Design and Development of New Enantioselective Organocatalytic Transformations, A Two-Step Synthesis of Carbohydrates, and Progress Toward the Total Synthesis of Callipeltoside C

Thesis by

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ABSTRACT

The LUMO-lowering activation of α, β-unsaturated ketones has been accomplished through the development of a new imidazolidinone organocatalyst. That new imidazolidinone catalyst provided the first enantioselective catalytic Diels-Alder reaction with simple ketone dienophiles. Significantly, that catalyst is able to activate both cyclic and acyclic α, β-unsaturated ketones in this cycloaddition process.

A new strategy for the synthesis of two privileged structural motifs, the polyketide and polyglycolate architectures, has been developed based on the direct aldehyde aldol reaction. Two different catalysts are presented that are capable of performing the enantioselective direct aldol cross coupling of two distinct aldehyde components. Imidazolidinones have been shown for the first time to initiate the HOMO-raising activation of both saturated and α, β-unsaturated aldehyde substrates. Using an imidazolidinone catalyst, the first direct enantioselective catalytic aldol coupling of two aldehydes is described and provides synthetically valuable β-hydroxy dimethylacetals. Later, proline was found to be an exceptionally effective catalyst for the direct aldehyde aldol reaction. In contrast to imidazolidinone catalysts, proline affords β-hydroxyaldehyde products that are primed for use directly in subsequent aldol reactions.

Utilizing those direct aldehyde aldol methodologies, a two-step synthesis of 2,4,6-*O*-protected carbohydrates has been developed. Importantly, this modular strategy is capable of producing highly enantioenriched differentially protected forms of glucose, mannose, allose, mannosamine, as well as unnatural hexose derivatives. Furthermore, this method for sugar synthesis has been applied to the construction of differentially protected $^{13}C_6$-labeled glucose, mannose, and allose in just four steps from labeled ethylene glycol.

The enantioselective catalytic direct aldehyde aldol reaction was further applied toward the total synthesis of the marine natural product callipeltoside C. Several key fragments have been successfully synthesized and coupled to form macrolactone precursors. Nozaki-Hiyama-Kishi ring closure across the *C*-9/*C*-10 bond, however, affords exclusively the undesired *C*-9 epimer. Therefore, completion of the total synthesis will require a revised order for fragment assembly.

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ABBREVIATIONS

Ac_2O	acetic anhydride
AcOH	acetic acid
Boc	*tert*-butyl carbamate
Cbz	carbobenzyloxy
COSY	correlation spectroscopy
Cp	cyclopentadienyl
DERA	2-deoxyribose-5-phosphate aldolase
DDQ	2,3-dichloro-5,6-dicyano-1,4-benzoquinone
DIBAL-H	diisobutylaluminum hydride
DIPT	diisopropyltartrate
DMF	dimethylformamide
DMPU	1,3-dimethyltetrahydro-2(1*H*)-pyrimidinone
DMSO	methylsulfoxide
DTBMP	2,6-di-*tert*-butyl-4-methylpyridine
EtOAc	ethyl acetate
GLC	gas liquid chromatography
h	hour
HOMO	highest occupied molecular orbital
HMQC	heteronuclear multiple quantum coherence
HPLC	high pressure liquid chromatography
HWE	Horner-Wadsworth-Emmons reaction
IC_{50}	concentration necessary for 50% inhibition
LA	Lewis acid
LiHMDS	lithium hexamethyldisilamide
LiTMP	lithium 2,2,6,6,-tetramethylpiperidine amide
LnLB	lanthanum (III) tris-lithium tris-binolate

LUMO	lowest unoccupied molecular orbital
MCA	monochloroacetic acid
MeOH	methanol
min	minutes
MOM	methoxymethyl
Ms	methanesulfonyl
MTPA	α-methoxy-α-(trifluoromethyl)phenyl acetyl
NHK	Nozaki-Hiyama-Kishi reaction
NMO	*N*-methylmorpholine-4-oxide
NMP	1-methyl pyrrolidin-2-one
NMR	nuclear magnetic resonance
NOE	Nuclear Overhauser effect
Nu	nucleophile
Phth	phthalimido
Piv	trimethylacetyl
PMB	*para*-methoxybenzyl
PMP	*para*-methoxyphenyl
***p*-TSA**	*para*-toluenesulfonic acid
Pyr	pyridine
TBDPS	*tert*-butyldiphenylsilyl
TBDPSCl	*tert*-butylchlorodiphenylsilane
TBHP	*tert*-butylhydroperoxide
TBS	*tert*-butyldimethylsilyl
TBSCl	*tert*-butylchlorodimethylsilane
TBSOTf	*tert*-butyldimethylsilyl trifluoromethanesulfonate
TCA	trichloroacetic acid
TES	triethylsilyl
TESCl	chlorotriethylsilane

TFA	trifluoroacetic acid
TfOH	trifluoromethanesulfonic acid
THF	tetrahydrofuran
TIPS	triisopropylsilyl
TLC	thin layer chromatography
TMS	trimethylsilyl
TMSCl	chlorotrimethylsilane
TPAP	tetrapropylammonium perruthenate
TROC	carbo-2,2,2-trichloroethoxy

To April

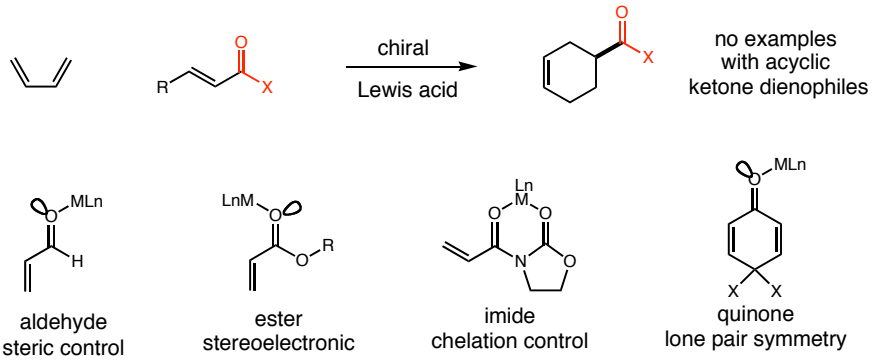
C h a p t e r 1

The Enantioselective Organocatalytic Ketone Diels-Alder Reaction*

Introduction

Simple monodentate α, β-unsaturated ketones have not been shown to be generally good substrates for Lewis acid catalysis—even for the most well studied transformations such as the Diels-Alder reaction. None of the more than 500 enantioselective catalytic variants of the Diels-Alder reaction[1] involve a monodentate ketone other than the quinone variants[2] developed by Mikami and Corey.[3]

Figure 1. Valuable Substrate Classes for Enantioselective Lewis Acid Catalysis



Lewis acid catalysts generally have a substrate-scope limited by the ability of the catalyst to selectively bind to one of the two lone pairs of a carbonyl compound to impart high levels of organizational control in the transition state (Figure 1). Whereas α, β-

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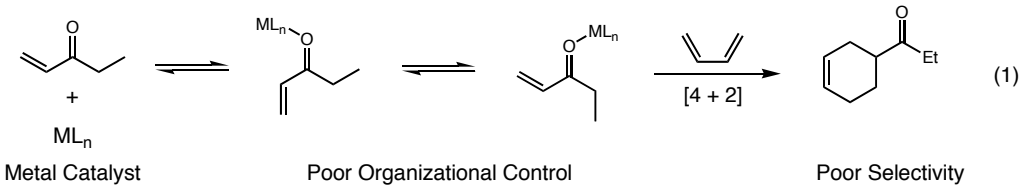
* A preliminary communication of this work has been published: Northrup, A. B.; MacMillan, D. W. C. *J. Am Chem. Soc.* **2002**, *124*, 2458.

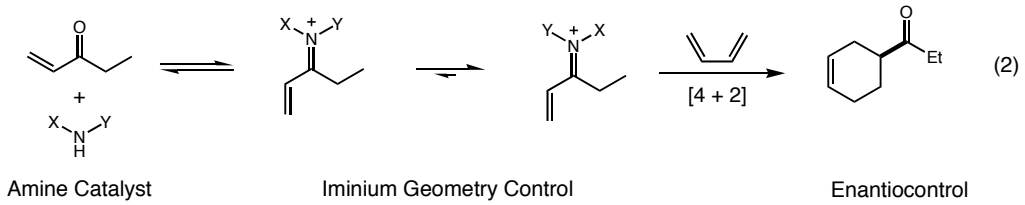
[1] Based on a survey of the CAS database, SciFinder 2000.

[2] (a) Mikami, K.; Terada, M.; Motoyama, Y.; Nakai, T. *Tetrahedron: Asymmetry* **1991**, *2*, 643. (b) Mikami, K.; Motoyama, Y.; Terada, M. *J. Am. Chem. Soc.* **1994**, *116*, 2812. (c) White, J. D.; Choi, Y. *Org. Lett.* **2000**, *2*, 2373. (d) Engler, T. A.; Letavic, M. A.; Lynch, K. O. Jr.; Takusagawa, F. *J. Org. Chem.* **1994**, *59*, 1179. (e) Engler, T. A.; Letavic, M. A.; Takusagawa, F. *Tetrahedron Lett.* **1992**, *33*, 6731. (f) Breuning, M.; Corey, E. J. *Org. Lett.* **2001**, *3*, 1559.

[3] After the completion and publication of this work, an enantioselective ketone Diels-Alder reaction based on alkene hydrogen bonding was reported: Ryu, D. H.; Lee, T. W.; Corey, E. J. *J. Am. Chem. Soc.* **2002**, *124*, 9992.

unsaturated aldehydes, esters, imides, and quinones have obvious modes of selectively partitioning lone pair binding, the same is not true for α, β-unsaturated ketones. In fact, the poor binding selectivity of Lewis acids for the nearly identical lone-pairs of a monodentate ketone, such as ethyl vinyl ketone (eq 1) has largely discouraged their use as substrates for enantioselective metal catalysis.



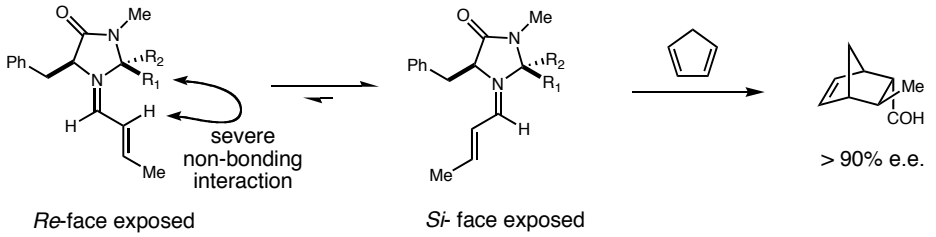


During our group's studies on LUMO-lowering organocatalysis, α, β-unsaturated aldehydes had been shown to be quite useful substrates in a broad range of transformations.[3-5] Central to the success of α, β-unsaturated aldehydes as substrates for imidazolidinone catalysts is their ability to reversibly form the reactive iminium ion intermediate with a high level of iminium geometry control (Figure 2). As the two iminium ion isomers expose opposite enantiofaces of the substrate toward cycloaddition, the observed enantiomer ratio should, in some measure, reflect the ratio of iminium ions. Therefore, the ability to perform substrate activation through π-bond formation with a secondary amine salt (eq 2) replaces the mechanistic requirement of selective lone-pair binding by a metal with the selective formation of a tetrasubstitued iminium ion[4] to

[4] Of the 7924 Bielstein examples of tetrasubstitued iminium ions, only those formed intramolecularly, hence unsuitable for catalysis, have been able to achieve geometric control.

achieve high levels of enantiocontrol (eq 2). As our catalyst system operates outside the mechanistic constraints of selective lone-pair coordination, we felt that it might be possible to develop an organic catalyst capable of imparting high levels of enantiocontrol using simple α, β-unsaturated ketones.

Figure 2: Iminium Geometry Control Is Essential for Enantioselectivity



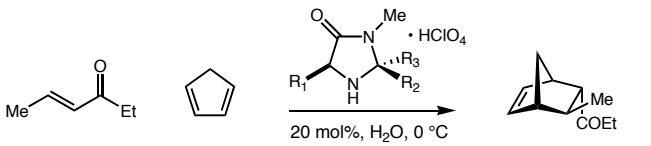
Catalyst Development

To test this hypothesis, we initially investigated the reaction between 4-hexen-3-one and cyclopentadiene catalyzed by amine salts **1-4** conducted as a biphasic mixture in water at 0 °C (Table 1).[5] The most effective organic catalysts we had previously identified[3, 4b] showed both poor reactivity and selectivity (entries 1 and 2, 20-27% yield, 0% ee). It seemed that the steric constraints designed for those catalysts to impart high levels of iminium geometry control with α, β-unsaturated aldehydes might prevent the formation of the tetrasubstituted iminium ions required for ketone catalysis. Surprisingly, replacing the bulky *t*-butyl group from **2** with a hydrogen to generate catalyst **3** showed no significant increase in catalytic efficiency. After examining a wide variety of different

[5] For many years the hydrophobic acceleration of the Diels-Alder reaction has been noted. Indeed, the rate of this Diels-Alder reaction is optimal in aqueous and protic solvents. For examples of other highly enantioselective reactions employing water as the main component of the solution se: (a) Anastas, P. T.; Williamson, T. C., Eds. *Green Chemistry*: ACS Symp. Ser. 626; American Chemical Society: Washington: D.C., 1996, and references therein. (b) Li, C. J.; Chan, T. H. *Organic Reactions in Aqueous Media*; Wiley: New York, 1997. (c) Grieco, P. A. Ed. *Organic Synthesis in Water*; Kluwer Academic Publishers: Drodrecht, The Netherlands, 1997. (d) Uozumi, Y.; Shibatomi, K. *J. Am. Chem. Soc.* **2001**, *123*, 2919. (e) Tokunaga, M.; Larrow, J. F.; Kakiuchi, F.; Jacobsen, E. N. *Science* **1997**, *277*, 936.

catalyst architectures, pseudo-*meso* catalyst **4** was identified as the first highly active catalyst for this transformation (88% yield, 21:1 *endo*:*exo*, 47% ee), albeit with only minimal selectivity.

Table 1. Effect of Amine Architecture on the Ketone Diels-Alder Reaction

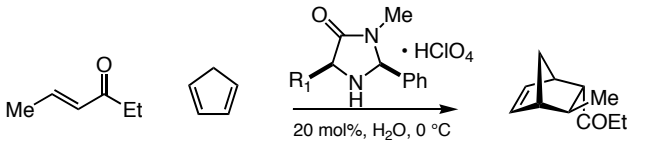


entry	catalyst	R_1	R_2 (R_3)	time (h)	% yield	*endo*:*exo*	% ee[a,b]
1	**1**	Bn	Me (Me)	48	20[c]	7:1	0
2	**2**	Bn	*t*-Bu (H)	48	27[c]	9:1	0
3	**3**	Bn	H (H)	48	25[c]	10:1	0
4	**4**	Ph	Ph (H)	22	88	21:1	47

[a]Product ratios determined by chiral GLC. [b]Absolute configuration assigned by chemical correlation to a known compound. [c]Reactions stopped with less than 30% consumption of starting material.

Varying the amino acid component of the imidazolidinone catalyst (Table 2) showed that the phenylalanine-derived catalyst (entry 4) afforded improved levels of enantioselectivity (82% ee) while maintaining reasonable reaction efficiency—in accord with previous studies utilizing α, β-unsaturated aldehydes.[6]

Table 2. Effect of Amine Architecture on the Ketone Diels-Alder Reaction



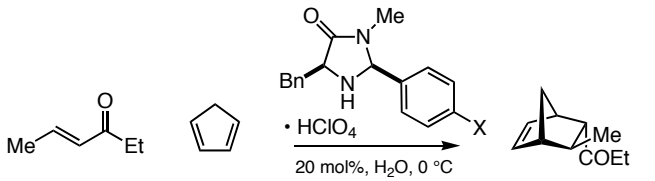
entry	catalyst	R_1	time (h)	% yield	*endo*:*exo*	% ee[a,b]
1	**4**	Ph	22	88	21:1	47
2	**5**	*i*-Pr	12	5[c]	4:1	0
3	**6**	CH_2-Indole	12	23[c]	11:1	40
4	**7**	Bn	42	83	23:1	82
5	**8**	*p*-NO_2Bn	12	42[c]	20:1	56
6	**9**	*p*-NMe_2Bn	12	49[c]	21:1	66

[a]Product ratios determined by chiral GLC. [b]Absolute configuration assigned by chemical correlation to a known compound. [c]Conversion

[6] Ahrendt, K. A., MacMillan, D. W. C. *Unpublished Results.*

Catalyst **3** (Table 1, entry 3, 0% ee) and catalyst **7** (Table 2, entry 4, 82% ee) differ only by the replacement of a *C*-2 hydrogen with a phenyl ring but have remarkably different properties. That observation begs the question of whether there is an electronic influence of the *C*-2 group on the imidazolidinone framework that could be used to generate a more active and more selective catalyst. To explore this possibility, a series of *para*-substituted *C*-2 phenyl imidazolidinone derivatives were studied. Both Table 3 and the Hammet correlation plot in Figure 3, indicate a significant electronic influence of the *C*-2 aryl group on both the reaction rate and enantioselectivity with optimal results arising from relatively electroneutral or slightly electron-deficient aryl groups. The sharp decrease in both rate and enantioselectivity observed with highly electron-withdrawing aryl groups (see Figure 3 and Table 3) can be rationalized by a change in the rate limiting step from the cycloaddition step to the iminium formation step due to the destabilizing influence of an electron-withdrawing group vicinal to the formal positive charge of the iminium ion.

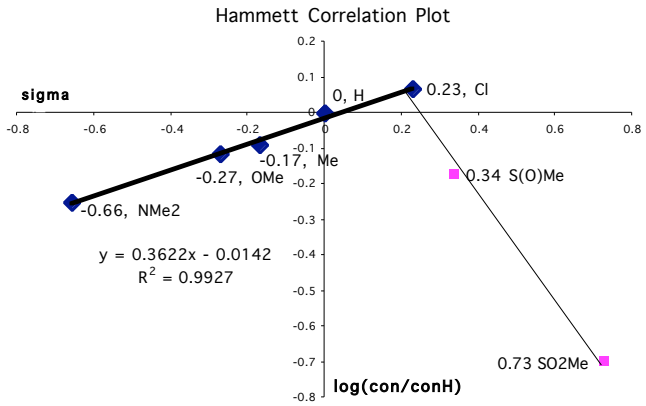
Table 3. Hammet Correlation Plot Data (*cf.* Figure 3)



entry	catalyst	X	σ_p	con/con$_H$	*endo*:*exo*	% ee[a,b]
1	**10**	NMe_2	– 0.66	0.6	17:1	55
2	**11**	OMe	– 0.27	0.7	17:1	72
3	**12**	Me	– 0.17	0.8	17:1	74
4	**7**	H	0	1	20:1	82
5	**13**	Cl	+ 0.23	1.2	22:1	74
6	**14**	S(O)Me	+ 0.34	0.5	17:1	68
7	**15**	SO_2Me	+ 0.73	0.2	17:1	42

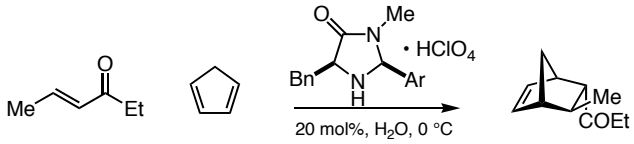
[a]Product ratios determined by chiral GLC. [b]Absolute configuration assigned by chemical correlation to a known compound.

Figure 3: Hammet Correlation Plot



Variation of the size of the *C*-2 aryl group revealed that sterically less demanding substituents afford both superior rates and enantioselectivities (Table 4) with the 5-methyl-2-furaldehyde derived catalyst **19** providing superior results (Table 4, entry 5, 89% yield, 25:1 *endo*:*exo*, 90% ee)

Table 4. Catalyst *C*-2 Aryl Group Steric Effects



entry	catalyst	Ar	time (h)	% yield	*endo*:*exo*	% ee[a,b]
1	**16**	Mesityl	48	0	–	–
2	**17**	α-Nap	16	28[c]	12:1	53
3	**18**	β-Nap	16	47[c]	19:1	61
4	**7**	Ph	42	83	23:1	82
5	**19**	2-(5-methylfuryl)	22	89	25:1	90

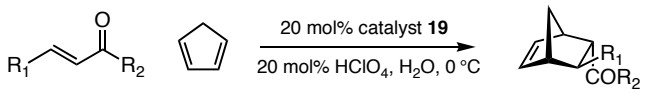
[a]Product ratios determined by chiral GLC. [b]Absolute configuration assigned by chemical correlation to a known compound. [c]Conversion

Substrate Scope

Having identified an optimal catalyst for this transformation, we next examined the range of ketones amenable to this new process (Table 5). With acyclic enones, the enantioselectivity is affected primarily by the steric contribution of the alkyl chain (entries 1-6, 5-25:1 *endo*:*exo*, 0-92% ee) and not the olefin substituent of the enone (*n*-Pr,

i-Pr, entries 7 and 8, 6-15:1 *endo*:*exo*, 90-92% ee). Medium-sized alkyl groups (Et, *n*-Bu, *i*-Am; entries 2-4) provide excellent levels of selectivity (20-25:1 *endo*:*exo*, 90-92% ee) and good yields (83-89% yield). However, sterically demanding alkyl ketones provide poor to moderate levels of selectivity (entries 5 and 6, 5:1 to 8:1 *endo*:*exo*, 0-51% ee) presumably due to the difficulty in forming such a sterically hindered tetrasubstituted iminium ion. Surprisingly, the methyl ketone (entry 1, 14:1 *endo*:*exo*, 61% ee, 85% yield) afforded only modest levels of enantioinduction.

Table 5. Amine-Catalyzed Reactions Between Acyclic Enones and Cyclopentadiene

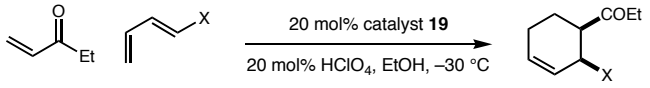


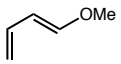
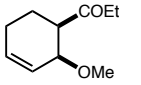
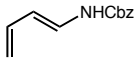
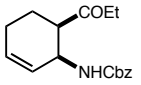
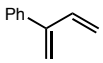
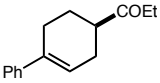
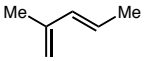
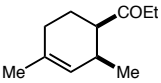
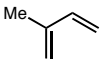
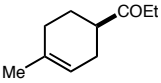
entry	R_1	R_2	% yield	*endo*:*exo*	% ee[a,b]
1	Me	Me	85	14:1	61
2	Me	Et	89	25:1	90
3	Me	*n*-Bu	83	22:1	92[c]
4	Me	*i*-Am	86	20:1	92
5	Me	*i*-Bu	79	5:1	51
6	Me	*i*-Pr	24	8:1	0
7	*n*-Pr	Et	84	15:1	92
8	*i*-Pr	Et	78	6:1	90

[a]Product ratios determined by chiral GLC. [b]Absolute configuration assigned by chemical correlation to a known compound. [c]Reaction performed in the absence of solvent.

This organocatalytic Diels–Alder reaction appears to be quite general with respect to diene structure, allowing enantioselective access to a broad range of alkyl, alkoxy, amino, and aryl substituted cyclohexenyl ketones. Of particular note is the fact that all entries in Table 6 produce a single regio- and diastereoisomer as determined by GLC (>200:1) or HPLC (>100:1) analysis. To highlight both the functional group tolerance and the preparative utility of this new strategy, entry 2 was performed on a 25 mmol scale to afford 5.71g (91% yield) of the Diels–Alder adduct in 98% ee. Aqueous extraction and flash chromatography provided a 91% recovery of the enantiopure catalyst.

Table 6. Amine-Catalyzed Reactions Between Ethyl Vinyl Ketone and Dienes



entry	diene	product	*endo*:*exo*	% yield	% ee[a,b]
1			>200:1	88	96
2			>100:1	91	98
3[c]			>200:1[d]	92	90
4			>200:1	90	90
5[e]			>200:1[d]	79	85

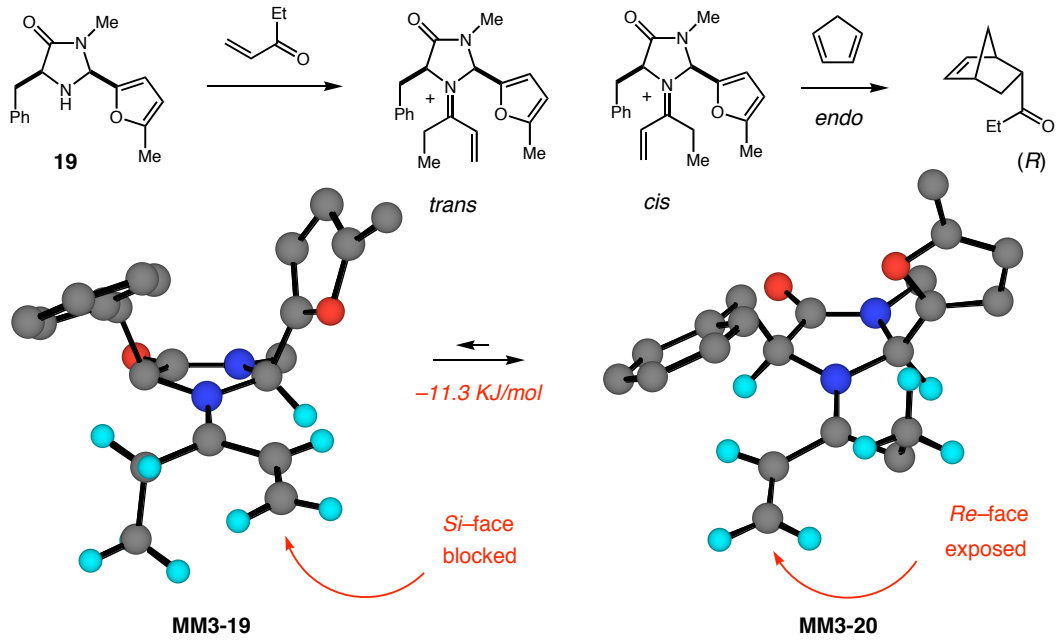
[a]Product ratios determined by chiral GLC. [b]Absolute configuration assigned by chemical correlation to a known compound. [c]Reaction conducted at –40ºC. [d]Regioselectivity [e] Reaction performed at –20ºC in the absence of solvent.

Explaining the Methyl Ketone

To attempt to expand the substrate scope, we sought to understand the reasons for the poor enantioselectivities exhibited by methyl ketones in this reaction (Table 5, entry 1, 61 % ee) in contrast to the excellent performance of ethyl and other alkyl ketones. With the help of computational models **MM3-19** and **MM3-20** in Figure 4,[7] we can begin to understand the differential selectivities for the methyl and *n*-alkyl ketones.

[7] Macromodel, v. 6.0 using an MM3 force-field.

Figure 4. MM3 Calculated Structures for the Iminium ions Formed by 19 and Ethyl Vinyl Ketone



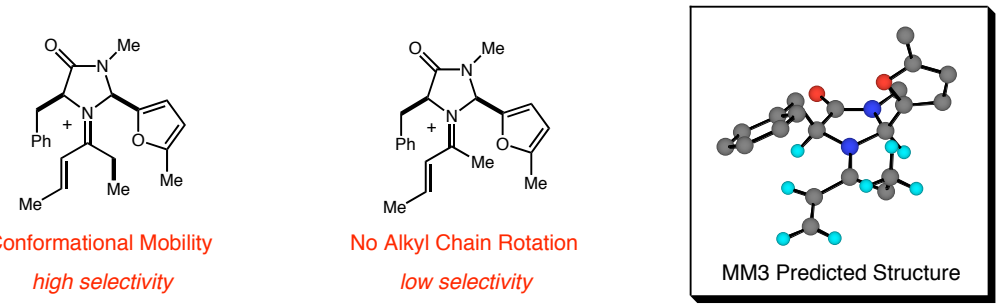
Analysis of the energy of each structure in Figure 4 shows that **MM3-20** is the lower energy iminium isomer.[8] The sense of asymmetric induction observed in all cases is consistent with the addition of the diene component to the *Si*-face of the *cis*-iminium isomer **MM3-20**. Examining the conformation of the two isomers reveals that both the *Si* and *Re* faces of the *trans*-**MM3-19** isomer are effectively shielded due to the rotation about the ketone's alkyl chain. In contrast, the *cis*-**MM3-20** isomer gains additional shielding of the *Re*-face due to the alkyl chain, leaving the *Si*-face completely exposed for cycloaddition. Therefore, alkyl ketones should exhibit high levels of enantioselectivity even if iminium geometry control is not complete because the more reactive intermediate **MM3-20** is afforded additional π-facial coverage by the alkyl chain. However, in the singular case of the methyl ketone, the two iminium isomers are enantiodivergent and

[8] Monte Carlo simulation using the Macromodel Force Field, Macromodel v. 6.5.

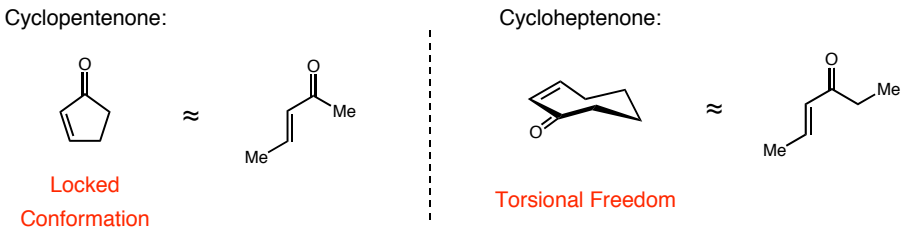
should be similarly reactive so the enantioselectivity should roughly reflect the relative population of the two iminium ion isomers.

To test the validity of the above model and the accompanying stereochemical analysis, the effect of the ring-size of a cyclic enone on the enantioselectivity of its reaction with cyclopentadiene catalyzed by **19** was examined. If the ring-size were small, there would not be sufficient torsional freedom for the alkyl chain to rotate to block either the *Si* or the *Re* faces (from Figure 4) toward cycloaddition, resulting in selectivities similar to the case of the methyl ketone. However, if the chain grew longer and more flexible, enantioselectivity should be restored (Figure 5).

Figure 5. Trends in Cyclic Ketone Dienophile Selectivity should Reflect Models



■ Cyclic Ketone Dienophiles Should Test This Feature of the Model



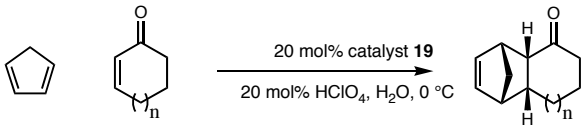
■ Small, inflexible cyclic enones (*e.g.*, cyclopentenone) should give low ee's

■ Larger, more flexible cyclic enones (*e.g.*, cycloheptenone) should give high ee's

As expected, Table 7 shows conformationally constrained enones (cyclopentenone and cyclohexenone) afford only modest selectivity (Table 7, entries 1 and 2, 48-63% ee) similar to the methyl ketone (Table 5, entry 1, 61% ee) while larger

ring ketones (cycloheptenone, cyclooctenone, and *trans*-cyclopentadecenone) afford enantioselectivities similar to the alkyl ketones (Table 7, entries 3-5, 90-93% ee).

Table 7. Amine-Catalyzed Reactions Between Cyclic Enones and Cyclopentadiene



entry	n	time (h)	% yield	*endo*:*exo*	% ee[a,b]
1	0	12	81	15:1	48
2	1	17	81	12:1	63
3	2	28	85	18:1	90
4	3	72	83	6:1	91
5[c]	10	72	88	5:1	93

[a]Product ratios determined by chiral GLC. [b]Absolute configuration assigned by chemical correlation to a known compound. [c]Reaction conducted with (*E*)-cyclopendadecen-2-one to provide the corresponding 1,2-*trans* tricyclo[15.2.1.0]eicos-18-en-3-one.

Conclusions

In summary we have documented the development of a new organic catalyst for the LUMO-lowering activation of α, β-unsaturated ketones in the context of the first enantioselective catalytic ketone Diels–Alder reaction. This work demonstrates the generality of the organocatalytic approach to LUMO-lowering catalysis. Future extension of this work will focus on broadening both the substrate and reaction scope of this new process to a similar extent that has been demonstrated with α, β-unsaturated aldehydes. For example, current studies by Dr. Stephane Oulette and Jamison Tuttle in our laboratory have revealed that catalyst **19** is highly effective at the enantioselective conjugate reduction of β-substituted enones.[9]

[9] Oulette, S. G.; Tuttle, J. B.; MacMillan, D. W. C. *Unpublished Results.*

Supporting Information

General Information. Commercial reagents were purified prior to use following the guidelines of Perrin and Armarego.[10] Non-aqueous reagents were transferred under nitrogen via syringe or cannula. Organic solutions were concentrated under reduced pressure on a Büchi rotary evaporator. Chromatographic purification of products was accomplished using forced-flow chromatography on ICN 60 32-64 mesh silica gel 63 according to the method of Still.[11] Thin-layer chromatography (TLC) was performed on EM Reagents 0.25 mm silica gel 60-F plates. Visualization of the developed chromatogram was performed by fluorescence quenching or by $KMnO_4$ stain.

^1H and ^{13}C NMR spectra were recorded on a Mercury 300 (300 MHz and 75 MHz) as noted, and are internally referenced to residual protio solvent signals. Data for ^1H NMR are reported as follows: chemical shift (δ ppm), multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet), integration, coupling constant (Hz) and assignment. Data for ^{13}C NMR are reported in terms of chemical shift. IR spectra were recorded on a Perkin Elmer Paragon 1000 spectrometer and are reported in terms of frequency of absorption (cm^{-1}). Mass spectra were obtained from the UC Irvine Mass Spectral facility. Gas liquid chromatography (GLC) was performed on Hewlett-Packard 6850 and 6890 Series gas chromatographs equipped with a split-mode capillary injection system and flame ionization detectors using a Bodman Chiraldex β-DM (30 m x 0.25 mm) column. High performance liquid chromatography (HPLC) was performed on

[10]Perrin, D. D.; Armarego, W. L. F. *Purification of Laboratory Chemicals;* 3rd ed., Pergamon Press, Oxford, 1988.

[11]Still, W. C.; Kahn, M.; Mitra, A. J. *J. Org. Chem.* **1978,** *43*, 2923.

Hewlett-Packard 1100 Series chromatographs using either a Chiralcel OD-H column (25 cm) and OD guard (5 cm) or a Chiralcel AD column (25 cm) and AD guard (5 cm) as noted.

The α, β-unsaturated ketones: 3-penten-2-one,[12] 4-octen-3-one,[13] 6-methylhept-4-en-3-one,[14] 2-methylhex-4-en-3-one,[15] 6-methylhept-2-en-4-one;[16] dienes: buta-1,3-dienyl-carbamic acid benzyl ester,[17] 1-(methyleneallyl)-benzene;[18] and (*5S*)-*5*-benzyl-3-methyl-imidazolidin-4-one[19] were prepared as described in the literature.

(2*R*, 5*R*)-3-Methyl-2,5-diphenyl-imidazolidin-4-one (4). A solution of (*R*)-phenylglycine methyl amide[20] (2.0 g, 12.2 mmol), benzaldehyde (990 μL, 9.7 mmol), and *p*-toluenesulfonic acid monohydrate (232 mg, 1.2 mmol) dissolved in 20 mL of methanol was heated to reflux for 16 hours. Concentration of the reaction mixture followed by flash chromatography (30-40% ethyl acetate in hexanes, linear gradient) afforded the title compound in 31% yield (750 mg, 3.0 mmol) and the more quickly eluting (2*S*, 5*R*) isomer in 58% yield (1.43g, 5.7 mmol). IR (film) 3478, 3324, 3086, 3063, 3031, 2958, 2917, 2863, 1959, 1890, 1814, 1698, 1603, 1477, 1456, 1428, 1400, 1343, 1281, 1204, 1107, 1069, 1027, 985.9, 935.2, 916.7, 868.6, 834.7, 732.9, 698.1 cm^{-1}; ^1H NMR (300

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[12] Chiu, P.; Wong, S. T. *Synth. Commun*. **1998**, *28*, 4513.

[13] Chamberlin; Le Goff *Synth. Commun*. **1978**, *8*, 579.

[14] Piers,E.; Phillips-Johnson,W. M. *Can. J. Chem*. **1975**, *53*, 1281.

[15] Bienvenue, A. *J. Am. Chem. Soc*. **1973**, *95*, 7345.

[16] Bienvenue, A.; Dubois, J. E. *Bull. Soc. Chim. Fr*. **1969**, 391.

[17] –Jessup, P. J.; Petty, C. B.; Roos, J.; Overman, L. E. *Org. Synth*. **1980**, *59*, 1.

[18] Marvel; Woolford *J. Org. Chem*. **1958**, *23*, 1658.

[19] Polonski, T. *Org. Magn. Reson*. **1984**, *22*, 176.

[20] Naef, R.; Seebach, D. *Helv. Chim. Acta* **1985**, *85*, 135.

MHz, $CDCl_3$) δ 7.41 (m, 10H, ArH), 5.33 (s, 1H, NCHN), 4.66 (s, 1H, CHCO), 2.65 (s, 3H, CH_3), 2.46 (s, 1H, NH); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.4, 139.0, 138.6, 129.8, 129.3, 128.9, 128.3, 128.0, 127.7, 77.3, 63.7, 28.0; HRMS (CI) exact mass calcd for ($C_{16}H_{16}N_2O$) requires *m/z* 252.1263, found *m/z* 252.1265. $[\alpha]_D$ = - 8.6 (c = 1.0, $CHCl_3$). The *cis* relative stereochemistry was confirmed by the presence of an NOE between the *C*-2 and *C*-5 protons in the lower R_f diastereomer that is absent in the higher R_f isomer.

(2*S*, 5*S*)-5-Benzyl-3-methyl-2-phenyl-imidazolidin-4-one (7). A solution of (*S*)-phenylalanine methyl amide (5.0 g, 28.1 mmol), benzaldehyde (3.14 mL, 30.9 mmol), and *p*-toluenesulfonic acid monohydrate (535 mg, 2.8 mmol) dissolved in 40 mL of methanol was heated to 50 ^oC for 24 hours. Concentration of the reaction mixture followed by flash chromatography (3:1 ethyl acetate:hexanes) afforded the title compound in 32% yield (2.38 g, 8.9 mmol) and the more quickly eluting (2*R*, 5*S*) isomer in 58% yield (4.32 g, 16.2 mmol). IR (film) 3479, 3331, 3085, 3061, 3030, 2921, 2861, 2242, 1959, 1891, 1815, 1696, 1603, 1494, 1475, 1436, 1370, 1335, 1282, 1206, 1098, 1028, 1002, 920.0, 760.0, 743.2, 700.7 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.25 (m, 8H, ArH), 6.82 (m, 2H, ArH), 5.10 (m, 1H, NCHN), 3.84 (dd, *J* = 4.5, 4.5 Hz, 1H, CHCO), 3.22 (dd, *J* = 14.1, 5.7 Hz, 1H, one of CH_2Ph), 3.11 (dd, *J* = 14.1, 4.5 Hz, 1H, one of CH_2Ph), 2.52 (s, 3H, CH_3), 1.87 (br s, 1H, NH); ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.6, 138.8, 137.1, 130.1, 129.7, 129.2, 129.1, 127.4, 127.1, 60.7, 37.2, 27.5; HRMS (CI) exact mass calcd for ($C_{17}H_{18}N_2O$) requires *m/z* 266.1419, found *m/z* 266.1421. $[\alpha]_D$ = - 101.8 (c = 1.0, $CHCl_3$). The enantiopurity of the catalyst was confirmed (>99% ee) by HPLC analysis (AD column, 10% isopropanol in hexanes, 1 mL/min, 254 nm); (2*S*, 5*S*) isomer

t_r = 17.1 min, (2*R*, 5*R*) isomer t_r = 15.5 min. The *cis* relative stereochemistry was confirmed by the presence of an NOE between the *C*-2 and *C*-5 protons in the lower R_f diastereomer that is absent in the higher R_f isomer. It should be noted that longer reaction times, higher temperatures, or an excess of benzaldehyde can lead to significant racemization of the catalyst.[21]

(2*S*, 5*S*)-5-Benzyl-3-methyl-2-(5-methyl-furan-2-yl)-imidazolidin-4-one (19). NOTE: *Attempts to utilize the above catalyst-forming procedures employing acidic methanol provided this catalyst in reduced enantiopurity, to forestall racemization of this catalyst it is essential to use the following procedure*. In an inert atmosphere glovebox, samarium (III) trifluoromethanesulfonate (1.20 g, 2.0 mmol) was added to a flame-dried 250 mL 3-neck round bottom flask fitted with a glass stopper, a septum, and a vacuum hose adapter followed by powdered 4Å molecular sieves (4.0 g). Following removal from the glove-box, the reaction was placed under nitrogen and (*S*)-phenylalanine methyl amide (8.91 g, 50 mmol) was added as a solution in 80 mL of tetrahydrofuran immediately followed by freshly distilled (77 ^{o}C, 14 mmHg, Vigreaux column) clear, colorless 5-methylfurfural (3.98 mL, 40 mmol). After stirring for 29 hours at room temperature, the reaction mixture was filtered through a plug of silica with dichloromethane, concentrated and purified by flash chromatography (1:1 ethyl acetate:hexanes) to afford the title compound as a clear, colorless oil in 46% yield (4.93 g, 18.2 mmol) and the faster eluting (2*R*, 5*S*) isomer as a pale yellow oil in 38% yield (4.10 g, 15.2 mmol). IR (film) 3482, 3325, 2922, 2862, 1695, 1563, 1495, 1477, 1453, 1402, 1326, 1267, 1218, 1098, 1021, 1006,

[21] For an insight into this racemization, see: Rios, A.; Crugeiras, J.; Amyes, T. L.; Richard, J. P. *J. Am. Chem. Soc.* **2001**, *123*, 7949-7950.

956.8, 938.9, 791.1, 734.4, 701.5 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.26 (m, 5H, PhH), 6.11 (m, 1H, C**H**CHCCH$_3$), 5.89 (m, 1H, CHC**H**CCH$_3$), 5.19 (s, 1H, NCHN), 3.79 (dd, *J* = 7.2, 4.5 Hz, 1H, CHCONMe), 3.26 (dd, *J* = 14.4, 4.5 Hz, 1H, one of CH_2Ph), 3.09 (dd, *J* = 14.1, 7.5 Hz, 1H, one of CH_2Ph), 2.64 (s, 3H, NCH_3), 2.21 (s, 3H, $ArCH_3$), 2.10 (br s, 1H, NH); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.9, 153.5, 148.5, 137.3, 129.6, 128.9, 127.0, 111.2, 106.6, 71.3, 60.5, 37.8, 27.4, 14.0; HRMS (CI) exact mass calcd for ($C_{16}H_{18}N_2O_2$) requires *m/z* 270.1368, found *m/z* 270.1368. $[\alpha]_D$ = – 156.5 (c = 1.0, $CHCl_3$). The enantiopurity of the catalyst was confirmed (>99% ee) by HPLC analysis (AD column, 5% isopropanol in hexanes, 1 mL/min, 254 nm); (2*S*, 5*S*) isomer t_r = 22.9 min, (2*R*, 5*R*) isomer t_r = 25.7 min. The *cis* relative stereochemistry was confirmed by the presence of an NOE between the *C*-2 and *C*-5 protons in the lower R_f diastereomer that is absent in the higher R_f isomer.

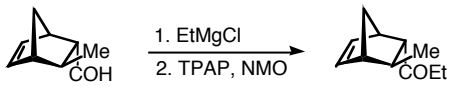
General Procedure (A: propenyl ketones): A 10-ml round bottomed flask equipped with a magnetic stir bar and containing (2*S*, 5*S*)-5-benzyl-3-methyl-2-(5-methyl-furan-2-yl)-imidazolidin-4-one (0.2 eq.) was either charged with H_2O (3-7*M*) or no solvent and cooled to 0 ^oC. To the resulting suspension, the α, β-unsaturated ketone (1.0 eq.) was added followed by 70% aqueous perchloric acid (0.2 eq.). After stirring for 5 minutes, freshly cracked, pre-chilled cyclopentadiene (1.5 eq.) was added dropwise. The resulting biphasic mixture was stirred at constant temperature until complete consumption of the α, β-unsaturated ketone was observed as determined by TLC or GLC analysis. The reaction mixture was then diluted with the appropriate eluent, loaded directly onto a column of silica gel and purified by flash chromatography.

General Procedure (B: ethyl vinyl ketone): (2*S*, 5*S*)-5-Benzyl-3-methyl-2-(5-methyl-furan-2-yl)-imidazolidin-4-one was dissolved in absolute ethanol (1-2*M*) and cooled to the appropriate temperature (–20 to –40 ^{o}C) with good stirring. Ethyl vinyl ketone (1.0 eq.) was added to that chilled solution, followed by dropwise addition of 70% aqueous perchloric acid down the side of the flask. After stirring for 5 minutes, the diene (1.25-1.5 eq.) was added and the resulting solution was stirred at constant temperature until complete consumption of the α, β-unsaturated ketone was observed as determined by TLC or GLC analysis. Reactions were purified as in procedure A.

1-[(1*R*, 2*R*, 3*S*, 4*R*)-3-Methylbicyclo[2.2.1]hept-5-en-2-yl]-ethanone (Table 5, entry 1). Prepared according to general procedure A from 3-penten-2-one (68 μL, 0.70 mmol), cyclopentadiene (69 μL, 0.84 mmol), 70% aqueous perchloric acid (12.1 μL, 0.14 mmol) and (2*S*, 5*S*)-5-benzyl-3-methyl-2-(5-methyl-furan-2-yl)-imidazolidin-4-one (37.8 mg, 0.14 mmol) in water (175 μL) for 2.5 hours at 0 ^{o}C. Purification by flash chromatography (9:1 pentane:ether) provided the title compound as a colorless oil in 85% yield (89 mg, 0.59 mmol); 14:1 *endo*:*exo*, *endo* 61% ee. IR (film) 3061, 2962, 2871, 1708, 1461, 1426, 1359, 1333, 1267, 1183, 1170, 114, 1095, 1055, 906.8, 797.8, 719.4, 654.5, 597.0 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.21 (dd, *J* = 6.0, 3.3 Hz, 1H, C**H**=CH), 5.90 (dd, *J* = 5.7, 2.7 Hz, 1H, CH=C**H**), 3.13 (m, 1H, C**H**CH=CH), 2.44 (m, 1H, C**H**CH=CH), 2.42 (dd, *J* = 4.8, 3.9 Hz, 1H, CHCO), 2.10 (s, 3H, CH_3CO), 1.86 (m, 1H, C**H**CH_3), 1.57 (m, 1H, one of CH_2), 1.43 (m, 1H, one of CH_2), 1.14 (d, *J* = 6.9 Hz, 3H, CHC**H$_3$**); ^{13}C NMR (75 MHz, $CDCl_3$) δ 209.2, 138.8, 132.6, 61.9, 49.3, 46.6, 46.5, 35.9, 29.5, 21.4; HRMS (CI) exact mass calcd for ($C_{10}H_{14}O$) requires *m/z* 150.1045, found *m/z*

150.1041. $[\alpha]_D$ = + 70.4 (c = 1.0, $CHCl_3$). Product ratios were determined by GLC analysis (120 °C, 23 psi); (1*R*, 2*R*, 3*S*, 4*R*) *endo* isomer t_r = 6.9 min, and (1*S*, 2*S*, 3*R*, 4*S*) *endo* isomer t_r = 6.3 min, *exo* isomers t_r = 5.7, 5.5 min.

1-[(1*R*, 2*R*, 3*S*, 4*R*)-3-Methylbicyclo[2.2.1]hept-5-en-2-yl]-propan-1-one (Table 5, entry 2). Prepared according to general procedure A from 4-hexen-3-one (70 μL, 0.61 mmol), cyclopentadiene (75 μL, 0.91 mmol), 70% aqueous perchloric acid (10.5 μL, 0.12 mmol) and (2*S*, 5*S*)-5-Benzyl-3-methyl-2-(5-methyl-furan-2-yl)-imidazolidin-4-one (30.7 mg, 0.12 mmol) in water (203 μL) for 22 hours at 0° C. Purification by flash chromatography (9:1 pentane:ether) provided the title compound as a colorless oil in 89% yield (88.7 mg, 0.54 mmol); 25:1 *endo*:*exo*, *endo* 90% ee. Product ratios were determined by GLC analysis (150 °C, 23 psi); (1*R*, 2*R*, 3*S*, 4*R*) *endo* isomer t_r = 3.7 min, and (1*S*, 2*S*, 3*R*, 4*S*) *endo* isomer t_r = 3.6 min, *exo* isomers t_r = 3.4, 3.5 min. ^{1}H NMR, ^{13}C NMR, and IR data were consistent with previously reported values.[22] $[\alpha]_D$ = + 101.7 (c = 1.0, $CHCl_3$).



Determination of the absolute stereochemistry of 1-[(1*R*, 2*R*, 3*S*, 4*R*)-3-methylbicyclo[2.2.1]hept-5-en-2-yl]-propan-1-one by correlation from (1*R*, 2*R*, 3*S*, 4*R*)-3-methylbicyclo[2.2.1]hex-5-ene-2-carboxaldehyde. (1*R*, 2*R*, 3*S*, 4*R*)-3-

[22] Zhu, Z.; Espenson, J. H.; *J. Am. Chem. Soc.* **1997**, *119*, 3507-3512.

Methylbicyclo[2.2.1]hex-5-ene-2-carboxaldehyde[23] was treated with ethylmagnesium chloride followed by tetrapropylammonium perruthenate and 4-methylmorpholine *N*-oxide to afford 1-[(1*R*, 2*R*, 3*S*, 4*R*)-3-methylbicyclo[2.2.1]hept-5-en-2-yl]-propan-1-one; $[\alpha]_D$ = + 105.5 (c = 1.0, $CHCl_3$).

1-[(1*R*, 2*R*, 3*S*, 4*R*)-3-Methylbicyclo[2.2.1]hept-5-en-2-yl]-pentan-1-one (Table 5, entry 3). Prepared according to general procedure A from oct-2-en-4-one (89 μL, 0.60 mmol), cyclopentadiene (74 μL, 0.90 mmol), 70% aqueous perchloric acid (10.3 μL, 0.12 mmol) and (2*S*, 5*S*)-5-benzyl-3-methyl-2-(5-methyl-furan-2-yl)-imidazolidin-4-one (32.4 mg, 0.12 mmol) neat for 34 hours at 0 °C. Purification by flash chromatography (19:1 hexanes:ethyl acetate) provided the title compound as a colorless oil in 83% yield (95.7 mg, 0.50 mmol); 22:1 *endo*:*exo*, *endo* 92% ee. IR (film) 3061, 2958, 2871, 1707, 1462, 1409, 1375, 1332, 1267, 1137, 1045, 904.4, 801.4, 715.9 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 6.19 (dd, *J* = 5.4, 3.0 Hz, 1H, C**H**=CH), 5.87 (dd, *J* = 5.7, 2.7 Hz, 1H, CH=C**H**), 3.10 (br s, 1H, C**H**CH=CH), 2.43 (m, 1H, C**H**CH=CH), 2.39 (m, 3H, CHCO and CH_2CO), 1.86 (m, 1H, C**H**CH_3), 1.57-1.20 (m, 6H, $COCH_2C\mathbf{H_2}C\mathbf{H_2}$, and CHC**H**$_2$CH), 1.12 (d, *J* = 6.9 Hz, 3H, CHC**H**$_3$), 0.87 (dd, *J* = 7.5, 7.5 Hz, 3H, $CH_2C\mathbf{H_3}$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 211.3, 138.6, 132.6, 61.2, 49.3, 46.6, 41.7, 35.9, 26.2, 22.8, 21.4, 14.3; HRMS (CI) exact mass calcd for ($C_{13}H_{20}O$) requires *m/z* 192.1514, found *m/z* 192.1509. $[\alpha]_D$ = + 89.3 (c = 1.0, $CHCl_3$). Product ratios were determined by GLC analysis (150 °C, 23 psi); (1*R*, 2*R*, 3*S*, 4*R*) *endo* isomer t_r = 6.1 min, and (1*S*, 2*S*, 3*R*, 4*S*) *endo* isomer t_r = 5.9 min, *exo* isomers t_r = 5.5, 5.6 min.

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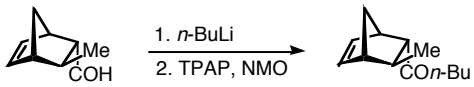
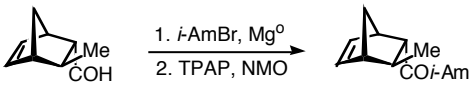
[23] Ahrendt, K. A.; Borths, C. J.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2000**, *122*, 4243-4244.



Determination of the absolute stereochemistry of 1-[(1*R*, 2*R*, 3*S*, 4*R*)-3-methylbicyclo[2.2.1]hept-5-en-2-yl]-pentan-1-one by correlation from (1*R*, 2*R*, 3*S*, 4*R*)-3-methylbicyclo[2.2.1]hex-5-ene-2-carboxaldehyde. (1*R*, 2*R*, 3*S*, 4*R*)-3-Methylbicyclo[2.2.1]hex-5-ene-2-carboxaldehyde[15] was treated with *n*-butyllithium followed by tetrapropylammonium perruthenate and 4-methylmorpholine *N*-oxide to afford 1-[(1*R*, 2*R*, 3*S*, 4*R*)-3-methylbicyclo[2.2.1]hept-5-en-2-yl]-pentan-1-one; $[\alpha]_D$ = + 87.4 (c = 1.0, $CHCl_3$).

4-Methyl-1-[(1*R*, 2*R*, 3*S*, 4*R*)-3-methylbicyclo[2.2.1]hept-5-en-2-yl]-pentan-1-one (Table 5, entry 4). Prepared according to general procedure A from 7-methyloct-2-en-4-one (82 μL, 0.50 mmol), cyclopentadiene (62 μL, 0.75 mmol), 70% aqueous perchloric acid (8.6 μL, 0.10 mmol) and (2*S*, 5*S*)-5-benzyl-3-methyl-2-(5-methyl-furan-2-yl)-imidazolidin-4-one (27 mg, 0.10 mmol) in water (167 μL) for 38 hours at 0 ^oC. Purification by flash chromatography (19:1 hexanes:ethyl acetate) provided the title compound as a colorless oil in 86% yield (89 mg, 0.43 mmol); 20:1 *endo*:*exo*, *endo* 92% ee. IR (film) 3061, 2957, 2870, 1708, 1462, 1367, 1332, 1269, 1141, 1107, 1064, 904.7, 799.8, 716.2 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 6.20 (dd, *J* = 5.7, 3.0 Hz, 1H, C**H**=CH), 5.87 (dd, *J* = 5.7, 2.7 Hz, 1H, CH=C**H**), 3.11 (m, 1H, C**H**CH=CH), 2.43 (m, 1H, C**H**CH=CH), 2.39 (m, 3H, CHCO and CH_2CO), 1.86 (m, 1H, C**H**CH_3), 1.58-1.37 (m,

5H, $COCH_2C\mathbf{H_2}C\mathbf{H}$, $CHC\mathbf{H_2}CH$), 1.13 (d, *J* = 6.9 Hz, 3H, $CH_2C\mathbf{H_3}$), 0.86 (d, *J* = 6.3 Hz, 6H, $CH(C\mathbf{H_3})_2$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 211.5, 138.6, 132.6, 61.2, 49.3, 46.6, 40.0, 35.9, 32.9, 28.1, 22.8, 22.7, 21.4; HRMS (CI) exact mass calcd for ($C_{14}H_{22}O$) requires *m/z* 206.1671, found *m/z* 206.1671. $[\alpha]_D$ = + 89.4 (c = 1.0, $CHCl_3$). Product ratios were determined by GLC analysis (150 °C, 23 psi); (1*R*, 2*R*, 3*S*, 4*R*) *endo* isomer t_r = 7.4 min, and (1*S*, 2*S*, 3*R*, 4*S*) *endo* isomer t_r = 7.1 min, *exo* isomers t_r = 6.6, 6.8 min.



Determination of the absolute stereochemistry of 4-methyl-1-[(1*R*, 2*R*, 3*S*, 4*R*)-3-methylbicyclo[2.2.1]hept-5-en-2-yl]-pentan-1-one by correlation from (1*R*, 2*R*, 3*S*, 4*R*)-3-methylbicyclo[2.2.1]hex-5-ene-2-carboxaldehyde. (1*R*, 2*R*, 3*S*, 4*R*)-3-Methylbicyclo[2.2.1]hex-5-ene-2-carboxaldehyde[15] was treated with (3-methyl-butyl)-magnesium followed by tetrapropylammonium perruthenate and 4-methylmorpholine *N*-oxide to afford 4-methyl-1-[(1*R*, 2*R*, 3*S*, 4*R*)-3-methylbicyclo[2.2.1]hept-5-en-2-yl]-pentan-1-one ; $[\alpha]_D$ = + 81.2 (c = 1.0, $CHCl_3$).

3-Methyl-1-[3-methylbicyclo[2.2.1]hept-5-en-2-yl]-butan-1-one (Table 5, entry 5). Prepared according to general procedure A from 6-methylhept-2-en-4-one (75 μL, 0.50 mmol), cyclopentadiene (62 μL, 0.75 mmol), 70% aqueous perchloric acid (8.6 μL, 0.10 mmol) and (2*S*, 5*S*)-5-benzyl-3-methyl-2-(5-methyl-furan-2-yl)-imidazolidin-4-one (27 mg, 0.10 mmol) in water (125 μL) for 3.5 days at 0 °C. Purification by flash chromatography (9:1 pentane:ether) provided the title compound as a colorless oil in 79%

yield (76 mg, 0.40 mmol); 5:1 *endo*:*exo*, *endo* 51% ee. IR (film) 3062, 2959, 2871, 1707, 1465, 1408, 1367, 1332, 1288, 1223, 1150, 1103, 1057, 1010, 907.9, 799.0, 718.4, 702.8 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 6.21 (dd, *J* = 5.7, 3.3 Hz, 1H, C**H**=CH), 5.88 (dd, *J* = 5.4, 2.7 Hz, 1H, CH=C**H**), 3.11 (m, 1H, C**H**CH=CH), 2.44 (m, 1H, C**H**CH=CH), 2.39 (dd, *J* = 3.6, 3.6 Hz, 1H, CHCO), 2.27 (m, 2H, CH_2CO), 2.12 (m, 1H, C**H**$(CH_3)_2$), 1.88 (m, 1H, C**H**CH_3), 1.56 (m, 1H, one of CH_2), 1.43 (m, 1H, one of CH_2), 1.13 (d, *J* = 7.2 Hz, 3H, CHC**H$_3$**), 0.88 (d, *J* = 6.6 Hz, 3H, one of (C**H$_3$**)$_2$CH), 0.87 (d, *J* = 6.6 Hz, 3H, one of (C**H$_3$**)$_2$CH); ^{13}C NMR (75 MHz, $CDCl_3$) δ 211.0, 138.6, 132.6, 61.6, 51.1, 49.3, 46.7, 46.6, 35.8, 24.7, 23.1, 23.0, 21.4; HRMS (CI) exact mass calcd for ($C_{13}H_{20}O$) requires *m/z* 192.1514, found *m/z* 192.1509. $[\alpha]_D$ = + 31.9 (c = 1.0, $CHCl_3$). Product ratios were determined by GLC analysis (140 °C, 23 psi); (1*R*, 2*R*, 3*S*, 4*R*) *endo* isomer t_r = 6.6 min, and (1*S*, 2*S*, 3*R*, 4*S*) *endo* isomer t_r = 6.3 min, *exo* isomers t_r = 5.9, 5.8 min.

2-Methyl-1-[3-methylbicyclo[2.2.1]hept-5-en-2-yl]-propan-1-one (Table 5, entry 6). Prepared according to general procedure A from 2-methylhex-4-en-3-one (66 μL, 0.50 mmol), cyclopentadiene (62 μL, 0.75 mmol), 70% aqueous perchloric acid (8.6 μL, 0.10 mmol) and (2*S*, 5*S*)-5-benzyl-3-methyl-2-(5-methyl-furan-2-yl)-imidazolidin-4-one (27 mg, 0.10 mmol) in water (125 μL) for 48 hours at 0 ^oC. Purification by flash chromatography (9:1 pentane:ether) provided the title compound as a colorless oil in 24% yield (22 mg, 0.12 mmol) as well as 29 mg recovered 2-methyl-hex-4-en-3-one; 8:1 *endo*:*exo*, *endo* 0% ee. IR (film) 3062, 2965, 2872, 1707, 1573, 1464, 1381, 1364, 1333, 1264, 1224, 1177, 1129, 1102, 1043, 1009, 908.1, 801.7, 724.5. 694.3 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 6.23 (dd, *J* = 6.0, 3.3 Hz, 1H, C**H**=CH), 5.84 (dd, *J* = 6.0, 2.7 Hz,

1H, CH=C**H**), 3.10 (m, 1H, C**H**CH=CH), 2.73 (dq, 1H, C**H**(CH_3)$_2$), 2.61 (dd, *J* = 4.5, 3.3, 1H, C**H**CO), 2.46 (m, 1H, C**H**CH=CH), 1.87 (ddq, *J* = 6.6, 1.8, 1.8 Hz, 1H, C**H**CHCO), 1.59 (m, 1H, one of CH_2), 1.44 (m, 1H, one of CH_2), 1.13 (d, *J* = 7.2 Hz, 3H, C**H$_3$**CHCHCO), 1.07 (d, *J* = 7.2 Hz, 3H, one of (C**H$_3$**)$_2$CH), 1.03 (d, *J* = 6.9 Hz, 3H, one of (C**H$_3$**)$_2$CH); ^{13}C NMR (75 MHz, $CDCl_3$) δ 215.3, 138.6, 132.5, 59.2, 49.4, 46.9, 46.8, 39.7, 35.9, 21.3, 19.4, 18.7; HRMS (CI) exact mass calcd for ($C_{12}H_{18}O$) requires *m/z* 178.1358, found *m/z* 178.1356. $[\alpha]_D$ = 0.0 (c = 1.0, $CHCl_3$). Product ratios were determined by GLC analysis (150 °C, 23 psi); *endo* isomers t_r = 3.8 min, 3.7 min, *exo* isomers t_r = 3.6, 3.5 min.

1-[(1*R*, 2*R*, 3*S*, 4*R*)-3-Propylbicyclo[2.2.1]hept-5-en-2-yl]-propan-1-one (Table 5, entry 7). Prepared according to general procedure A from oct-4-en-3-one (112 μL, 0.75 mmol), cyclopentadiene (93 μL, 1.13 mmol), 70% aqueous perchloric acid (12.9 μL, 0.15 mmol) and (2*S*, 5*S*)-5-benzyl-3-methyl-2-(5-methyl-furan-2-yl)-imidazolidin-4-one (40.5 mg, 0.15 mmol) in water (150 μL) for 32 hours at 0 ^{o}C. Purification by flash chromatography (15:1 pentane:ether) provided the title compound as a colorless oil in 84% yield (120 mg, 0.62 mmol); 15:1 *endo*:*exo*, *endo* 92% ee. IR (film) 3060, 2961, 2872, 1710, 1459, 1413, 1377, 1333, 1216, 1106, 1017, 935.7, 904.3, 716.7 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.22 (dd, *J* = 6.0, 3.3 Hz, 1H, C**H**=CH), 5.84 (dd, *J* = 5.4, 2.7 Hz, 1H, CH=C**H**), 3.12 (m, 1H, C**H**CH=CH), 2.57 (m, 1H, C**H**CH=CH), 2.45 (m, 3H, CH_2CO and CHCO), 1.83 (m, 1H, C**H**(nPr)), 1.59-1.19 (br m, 6H, CH_3C**H$_2$C H$_2$**, and CHC**H$_2$**CH), 1.02 (dd, *J* = 6.0, 6.0 Hz, 3H, one of CH_2C**H$_3$**), 0.89 (dd, *J* = 7.2, 7.2 Hz, 3H, one of CH_2C**H$_3$**); ^{13}C NMR (75 MHz, $CDCl_3$) δ 211.7, 138.8, 132.4, 59.5, 47.3, 47.2,

46.6, 41.4, 38.7, 35.1, 22.3, 14.7, 8.3; HRMS (CI) exact mass calcd for ($C_{13}H_{20}O$) requires *m/z* 192.1514, found *m/z* 192.1512. $[\alpha]_D$ = + 91.5 (c = 1.0, $CHCl_3$). Product ratios were determined by GLC analysis (150 °C, 23 psi); (1*R*, 2*R*, 3*S*, 4*R*) *endo* isomer t_r = 6.0 min, and (1*S*, 2*S*, 3*R*, 4*S*) *endo* isomer t_r = 5.6 min, *exo* isomers t_r = 5.1, 5.4 min.

1-[(1*R*, 2*R*, 3*S*, 4*R*)-3-Isopropylbicyclo[2.2.1]hept-5-en-2-yl]-propan-1-one (Table 5, entry 8). Prepared according to general procedure A from 6-methylhept-4-en-3-one (89 μL, 0.60 mmol), cyclopentadiene (99 μL, 1.2 mmol), 70% aqueous perchloric acid (10.3 μL, 0.12 mmol) and (2*S*, 5*S*)-5-benzyl-3-methyl-2-(5-methyl-furan-2-yl)-imidazolidin-4-one (32 mg, 0.12 mmol) in water (120 μL) for 2.5 days at 0 ^oC. Then, an additional 1.2 mmol of cyclopentadiene was added and the mixture was allowed to stir for an additional 3.5 days at 0 ^oC. Purification by flash chromatography (18:1 pentane:ether) provided the title compound as a colorless oil in 78% yield (90 mg, 0.47 mmol); 6:1 *endo*:*exo*, *endo* 90% ee. For the purpose of characterization, the more quickly eluting *exo* diastereomer was removed by flash chromatography as above. IR (film) 3057, 2961, 2869, 1709, 1460, 1367, 1334, 1136, 1028, 904.2, 716.6 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 6.26 (dd, *J* = 5.7, 3.3 Hz, 1H, C**H**=CH), 5.79 (dd, *J* = 5.7, 2.7 Hz, 1H, CH=C**H**), 3.14 (m, 1H, C**H**CH=CH), 2.77 (m, 1H, C**H**CH=CH), 2.63 (dd, *J* = 3.6, 3.6 Hz, 1H, CHCO), 2.49 (m, 2H, CH_2CO), 1.40 (m, 3H, C**H**$(CH_3)_2$ and CHC**H**$_2$CH), 1.05 (d, *J* = 7.5 Hz, 3H, one of CH(C**H$_3$**)$_2$), 0.99 (dd, *J* = 4.8, 4.8 Hz, 3H, CH_2C**H$_3$**), 0.84 (d, *J* = 7.5 Hz, 3H, one of CH(C**H$_3$**)$_2$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 211.6, 139.6, 131.9, 57.8, 49.1, 47.4, 47.2, 45.5, 35.2, 33.1, 22.7, 22.2, 8.5; HRMS (CI) exact mass calcd for ($C_{13}H_{20}O$) requires *m/z* 192.1514, found *m/z* 192.1513. $[\alpha]_D$ = + 20.1 (c = 1.0, $CHCl_3$). Product ratios were

determined by GLC analysis (162 °C, 23 psi); (1*R*, 2*R*, 3*S*, 4*R*) *endo* isomer t_r = 4.4 min, and (1*S*, 2*S*, 3*R*, 4*S*) *endo* isomer t_r = 4.2 min, *exo* isomers t_r = 3.9, 4.1 min.

(1*R*, 2*R*, 6*R*, 7*R*)-Tricyclo[5.2.1.0~2,6~]dec-8-en-3-one (Table 6, entry 1). Prepared according to general procedure A from 2-cyclopenten-1-one (50 μL, 0.60 mmol), cyclopentadiene (74 μL, 0.90 mmol), 70% aqueous perchloric acid (10.3 μL, 0.12 mmol) and (2*S*, 5*S*)-5-benzyl-3-methyl-2-(5-methyl-furan-2-yl)-imidazolidin-4-one (32.4 mg, 0.12 mmol) in water (150 μL) for 12 hours at 0 ^{o}C. Purification by flash chromatography (5:1 pentane:ether) provided the title compound as a volatile white powder in 81% yield (72 mg, 0.49 mmol); 15:1 *endo*:*exo*, *endo* 48% ee. IR (film) 3058, 2964, 2941, 2868, 1730, 1475, 1402, 1341, 1318, 1225, 1172, 1129, 1090, 1040, 936.0, 902.3, 840.8, 804.2, 732.8 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.22 (dd, *J* = 5.7, 2.7 Hz, 1H, C**H**=CH), 6.11 (dd, *J* = 5.7, 3.0 Hz, 1H, CH=C**H**), 3.19 (m, 1H, C**H**CH=CH), 3.00 (m, 1H, C**H**CH=CH), 2.97 (m, 1H, C**H**CO), 2.85 (m, 1H, one of CH_2CO), 2.02 (m, 4H, C**H**CH_2CH_2, one of CH_2CO, and CHC$\mathbf{H_2}$CH), 1.48 (m, 2H, C$\mathbf{H_2}CH_2CO$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 222.6, 136.3, 135.0, 54.7, 52.6, 47.8, 47.4, 41.6, 40.9, 23.1; HRMS (CI) exact mass calcd for ($C_{10}H_{12}O$) requires *m/z* 148.0888, found *m/z* 148.0887. $[\alpha]_D$ = + 122.3 (c = 1.0, $CHCl_3$). Product ratios were determined by GLC analysis (140 °C, 23 psi); (1*R*, 2*R*, 6*R*, 7*R*) *endo* isomer t_r = 7.1 min, and (1*S*, 2*S*, 6*S*, 7*S*) *endo* isomer t_r = 6.7 min, *exo* isomers t_r = 6.1 min.

(1*R*, 2*R*, 7*R*, 8*R*)-Tricyclo[6.2.1.0~2,7~]undec-9-en-3-one (Table 6, entry 2). Prepared according to general procedure A from 2-cyclohexen-1-one (58 μL, 0.60 mmol),

cyclopentadiene (74 μL, 0.90 mmol), 70% aqueous perchloric acid (10.3 μL, 0.12 mmol), and (2*S*, 5*S*)-5-benzyl-3-methyl-2-(5-methyl-furan-2-yl)-imidazolidin-4-one (32.4 mg, 0.15 mmol) in water (150 μL) for 17 hours at 0 ^{o}C. Purification by flash chromatography (5:1 pentane:ether) provided the title compound as a colorless oil in 81% yield (79 mg, 0.49 mmol); 12:1 *endo*:*exo*, *endo* 63% ee. For the purposes of characterization, the *endo* isomer was separated from the *exo* isomer by flash chromatography. IR (film) 3061, 2961, 2935, 2867, 1701, 1570, 1453, 1406, 1358, 1337, 1315, 1236, 1172, 1115, 1018, 910.6, 823.8, 779.2, 733.6, 561.5 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.15 (dd, *J* = 5.7, 3.0 Hz, 1H, C**H**=CH), 5.99 (dd, *J* = 5.7, 3.0 Hz, 1H, CH=C**H**), 3.24 (m, 1H, C**H**CH=CH), 2.85 (m, 1H, C**H**CH=CH), 2.66 (m, 2H, one of CH_2CO and CHCO), 2.30 (m, 1H, one of CH_2CO), 1.79 (m, 4H, CHC**H**CH_2, $COCH_2C$**H$_2$** and one of CHCHC**H$_2$**), 1.42 (ddd, *J* = 8.4, 1.8, 1.8 Hz, 1H, one of CHC**H$_2$**CH), 1.28 (m, 1H, one of CHC**H$_2$**CH), 0.73 (m, 1H, one of CHCHC**H$_2$**); ^{13}C NMR (75 MHz, $CDCl_3$) δ 215.7, 137.8, 135.1, 52.0, 48.7, 46.8, 45.5, 41.7, 39.7, 28.4, 22.2; HRMS (CI) exact mass calcd for ($C_{11}H_{14}O$) requires *m/z* 162.1045, found *m/z* 162.1049. $[\alpha]_D$ = + 120.6 (c = 1.0, $CHCl_3$). Product ratios were determined by GLC analysis (130 °C, 23 psi); (1*R*, 2*R*, 7*R*, 8*R*) *endo* isomer t_r = 13.4 min, and (1*S*, 2*S*, 7*S*, 8*S*) *endo* isomer t_r = 13.2 min, *exo* isomers t_r = 11.7, 12.3 min.

(1*R*, 2*R*, 8*R*, 9*R*)-Tricyclo[7.2.1.0~2,6~]dodec-10-en-3-one (Table 6, entry 3). Prepared according to general procedure A from 2-cyclohepten-1-one (67 μL, 0.60 mmol), cyclopentadiene (74 μL, 1.13 mmol), 70% aqueous perchloric acid (10.2 μL, 0.12 mmol) and (2*S*, 5*S*)-5-benzyl-3-methyl-2-(5-methyl-furan-2-yl)-imidazolidin-4-one (32.4

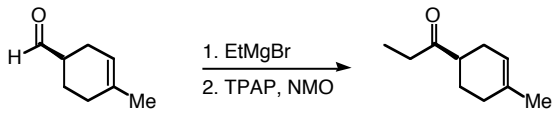
mg, 0.12 mmol) in water (150 μL) for 28 hours at 0 °C. Purification by flash chromatography (5:1 pentane:ether) provided the title compound as a colorless oil in 85% yield (90 mg, 0.51 mmol); 18:1 *endo*:*exo*, *endo* 90% ee. IR (film) 2958, 2930, 2862, 1700, 1455, 1405, 1335, 1289, 1246, 1166, 1125, 1066, 949.6, 912.0, 860.4, 776.5, 722.9, 580.5, 554.0 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 6.39 (dd, *J* = 5.4, 2.7 Hz, 1H, C**H**=CH), 5.91 (dd, *J* = 5.4, 3.0 Hz, 1H, CH=C**H**), 3.17 (dd, *J* = 10.2, 3.3 Hz, 1H, CHCO), 2.99 (m, 1H, C**H**CH=CH), 2.70 (m, 1H, C**H**CH=CH), 2.44 (m, 2H, CH_2CO), 2.21 (m, 1H, C**H**CHCO), 1.96-1.28 (br m, 7H, CHC**H₂**CH, $COCH_2C$**H₂C H₂**, and one of CHCHC**H₂**), 0.74 (m, 1H, one of CHCHC**H₂**); ^{13}C NMR (75 MHz, $CDCl_3$) δ 213.9, 137.7, 132.5, 58.6, 48.9, 48.1, 45.1, 43.0, 41.8, 30.8, 27.6, 23.2; HRMS (CI) exact mass calcd for ($C_{12}H_{16}O$) requires *m/z* 176.1201, found *m/z* 176.1201. $[\alpha]_D$ = + 9.1 (c = 1.0, $CHCl_3$). Product ratios were determined by GLC analysis (140 °C, 23 psi); (1*R*, 2*R*, 8*R*, 9*R*) *endo* isomer t_r = 13.2 min, and (1*S*, 2*S*, 8*S*, 9*S*) *endo* isomer t_r = 12.8 min, *exo* isomers t_r = 11.8, 15.0 min.

(1*R*, 2*R*, 9*R*, 10*R*)-Tricyclo[8.2.1.0~2,6~]tridec-11-en-3-one (Table 6, entry 4). Prepared according to general procedure A from 2-cycloocten-1-one (82 μL, 0.60 mmol), cyclopentadiene (74 μL, 1.13 mmol), 70% aqueous perchloric acid (10.2 μL, 0.12 mmol) and (2*S*, 5*S*)-5-benzyl-3-methyl-2-(5-methyl-furan-2-yl)-imidazolidin-4-one (32.4 mg, 0.12 mmol) in water (240 μL) for 72 hours at 0 °C. Purification by flash chromatography (19:1 pentane:ether) provided the title compound as a colorless oil in 83% yield (95 mg, 0.50 mmol); 6:1 *endo*:*exo*, *endo* 91% ee. IR (film) 3060, 2928, 2856, 1701. 1454, 1338, 1290, 1222, 1175, 1073, 1019, 895.9, 838.2, 716.9 cm-1; 1H NMR (300 MHz, $CDCl_3$) δ

6.49 (dd, J = 5.4, 2.7 Hz, 1H, CH=CH), 5.98 (dd, J = 5.4, 2.7 Hz, 1H, CH=CH), 3.29 (dd, J = 8.1, 3.3 Hz, 1H, CHCO), 2.90 (m, 1H, CHCH=CH), 2.72 (m, 1H, C**H**CH=CH), 2.49 (m, 2H, CH_2CO), 2.15 (m, 1H, CHCHCO), 1.82 (m, 2H, $COCH_2CH_2$), 1.63 (m, 1H, one of $COCH_2CH_2CH_2$), 1.32 (m, 3H, one of $COCH_2CH_2CH_2$, and $CHCH_2CH_2$), 1.08 (m, 1H, one of $CHCH_2$), 0.78 (m, 1H, one of $CHCH_2$); 13C NMR (75 MHz, $CDCl_3$) δ 215.9, 137.9, 132.0, 56.0, 50.9, 49.5, 48.3, 48.0, 47.4, 31.3, 30.9, 28.5, 23.6. $[\alpha]_D$ = – 69.9 (c = 1.0, $CHCl_3$). Product ratios were determined by GLC analysis (150 °C, 23 psi); (1*R*, 2*R*, 9*R*, 10*R*) *endo* isomer t_r = 12.8 min, and (1*S*, 2*S*, 9*S*, 10*S*) *endo* isomer t_r = 12.4 min, *exo* isomers t_r = 11.2, 10.6 min.

1-[(1*R*)-4-Methylcyclohex-3-en-1-yl]-propan-1-one (Table 6, entry 5). Prepared according to general procedure B from ethyl vinyl ketone (70 μL, 0.70 mmol), isoprene (140 μL, 1.40 mmol), 70% aqueous perchloric acid (12.1 μL, 0.14 mmol) and (2*S*, 5*S*)-5-benzyl-3-methyl-2-(5-methyl-furan-2-yl)-imidazolidin-4-one (38 mg, 0.14 mmol) neat for 3 days at -20 ^oC. Then, another portion of isoprene (100 μL, 1.00 mmol) was added and the solution was allowed to stir for an additional 3 days. Purification by flash chromatography (10:1 pentane:ether) provided the title compound as a single regioisomer (as judged by GLC analysis) in 79% yield (84 mg, 0.55 mmol) and 85% ee. IR (film) 2967, 2928, 2836, 1710, 1452, 1413, 1377, 1343, 1217, 1149, 1126, 952.6, 915.1, 871.9, 800.0 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.34 (m, 1H, C=CH), 2.46 (m, 3H, CH_2CO and CHCO), 2.09 (m, 2H, C**H₂**CH=C(CH_3)), 1.94 (m, 2H, C**H₂**C(CH_3)=CH), 1.86 (m, 1H, one of CH_2C**H₂**CH), 1.54 (m, 1H, one of CH_2C**H₂**CH), 0.99 (dd, *J* = 7.5, 7.5 Hz, 3H, CH_2C**H₃**); ^{13}C NMR (75 MHz, $CDCl_3$) δ 214.4, 133.8, 119.6, 46.6, 34.1, 29.9, 27.6, 25.4,

23.7, 8.1; HRMS (CI) exact mass calcd for ($C_{10}H_{16}O$) requires *m/z* 152.1201, found *m/z* 152.1201. $[\alpha]_D$ = + 37.8 (c = 1.0, $CHCl_3$). Product ratios were determined by GLC analysis (100 °C, 23 psi); (*R*) isomer t_r = 16.1 min, and (*S*) isomer t_r = 15.4 min.



Determination of the absolute stereochemistry of 1-[(1*R*)-4-methylcyclohex-3-en-1-yl]-propan-1-one by correlation from (1*R*)-4-methyl-3-cyclohexene-1-carboxaldehyde. (1*R*)-4-Methyl-3-cyclohexene-1-carboxaldehyde[15] was treated with ethylmagnesium bromide followed by tetrapropylammonium perruthenate and 4-methylmorpholine *N*-oxide to afford 1-[(1*R*)-4-methylcyclohex-3-en-1-yl]-propan-1-one; $[\alpha]_D$ = + 41.3 (c = 1.0, $CHCl_3$).

1-[(1*R*, 2*S*)-2-Methoxycyclohex-3-en-1-yl]-propan-1-one (Table 7, entry 1). Prepared according to general procedure B from ethyl vinyl ketone (59 μL, 0.59 mmol), 1-methoxybutadiene (75 μL, 0.74 mmol) added via syringe pump over 12 hours, 70% aqueous perchloric acid (10.2 μL, 0.12 mmol) and (2*S*, 5*S*)-5-benzyl-3-methyl-2-(5-methyl-furan-2-yl)-imidazolidin-4-one (32 mg, 0.12 mmol) in ethanol (590 μL) for 3.5 days at –30 ^{o}C. Purification by flash chromatography (9:1 pentane:ether) provided the title compound as a single diastereomer (as judged by GLC analysis) in 88% yield (88 mg, 0.52 mmol) and 92% ee. IR (film) 3027, 2975, 2937, 2879, 2821, 1715, 1452, 1432, 1375, 1211, 1191, 1129, 1108, 1084, 917.8, 889.2 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.95 (m, 2H, CH=CH), 4.06 (m, 1H, C**H**OCH_3), 3.30 (s, 1H, OCH_3), 2.53 (m, 3H,

CH_2CO and CHCO), 2.20 (m, 1H, one of C**H₂**CH=CH), 1.85 (m, 3H, C**H₂**CHCOEt and one of C**H₂**CH=CH), 1.05 (dd, *J* = 7.2, 7.2 Hz, 3H, CH_2C**H₃**); ^{13}C NMR (75 MHz, $CDCl_3$) δ 211.5, 133.2, 124.5, 73.0, 56.7, 51.8, 33.8, 25.6, 18.7, 8.1; HRMS (CI) exact mass calcd for $[M - CH_3OH]^+$ ($C_9H_{12}O_0$) requires *m/z* 136.0888, found *m/z* 136.0889. $[\alpha]_D$ = + 16.7 (c = 1.0, $CHCl_3$). Product ratios were determined by GLC analysis (100 °C, 23 psi); (1*R*, 2*S*) *endo* isomer t_r = 29.6 min, and (1*S*, 2*R*) *endo* isomer t_r = 32.6 min, *exo* isomers t_r = 19.1, 19.4 min.

Benzyl (1*S*, 6*R*)-6-propionylcyclohex-2-en-1-ylcarbamate (Table 7, entry 2). Concentrated (70% aqueous) perchloric acid (431 μL, 5.0 mmol) was added slowly to a stirring solution of ethyl vinyl ketone (2.49 mL, 25.0 mmol) and (2*S*, 5*S*)-5-benzyl-3-methyl-2-(5-methyl-furan-2-yl)-imidazolidin-4-one (1.35 g, 5.0 mmol) pre-chilled to -30 ^{o}C. Then, buta-1,3-dienyl-carbamic acid benzyl ester (4.47g, 31.3 mmol) was added dropwise over 15 minutes as a solution in 12.5 mL of absolute ethanol. After stirring for 3.5 days, the reaction was diluted with ether (150 mL), washed successively with 1N HCl (50 mL), water (50 mL) and brine (25 mL). The organic layer was then dried over anhydrous magnesium sulfate, filtered and concentrated *in vacuo* to afford a pale brown oil. Purification by flash chromatography (8:1 hexanes:ethyl acetate) afforded the title compound as a single diastereomer (as judged by HPLC analysis) in 91% yield (5.17g, 22.7 mmol) and 98% ee. The combined aqueous extracts were basified with solid K_2CO_3, extracted with 3 x 50 mL portions of $CHCl_3$, dried over anhydrous Na_2SO_4 and concentrated *in vacuo* to afford a 91% recovery of (2*S*, 5*S*)-5-benzyl-3-methyl-2-(5-methyl-furan-2-yl)-imidazolidin-4-one (1.23 g, 4.55 mmol) after flash chromatography.

IR (film) 3411, 3329, 3064, 3031, 2974, 2938, 2879, 2836, 1956, 1872, 1711, 1523, 1455, 1409, 1376, 1331, 1278, 1236, 1164, 1120, 1060, 1028, 988.9, 973.1, 775.6, 736.0, 697.9 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.33 (m, 5H, ArH), 5.82 (m, 1H, C**H**=CH), 5.70 (m, 1H, CH=C**H**), 5.04 (m, 3H, CH_2Ph and NH), 4.63 (m, 1H, C**H**NH), 2.86 (ddd, *J* = 10.2, 3.9, 3.9 Hz, 1H, CHCO), 2.70 (dq, *J* = 18.0, 7.2 Hz, 1H, one of CH_2CO), 2.43 (dq, *J* = 17.7, 7.2 Hz, 1H, one of CH_2CO), 2.10-1.65 (m, 4H, C$\mathbf{H_2}$C$\mathbf{H_2}$), 1.00 (dd, *J* = 6.9, 6.9 Hz, 3H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 212.0, 155.9, 136.6, 130.1, 128.7, 128.2, 128.1, 126.9, 67.0, 50.4, 46.9, 34.8, 24.2, 20.7, 8.0; HRMS (CI) exact mass calcd for ($C_{17}H_{21}NO_3$) requires *m/z* 287.1521, found *m/z* 287.1519. $[\alpha]_D$ = + 122.0 (c = 1.0, $CHCl_3$). Product ratios were determined by HPLC analysis (OD-H column, 3% ethanol in hexanes, 1 mL/min, 254 nm); (1*S*, 6*R*) *endo* isomer t_r = 12.5 min, and (1*R*, 6*S*) *endo* isomer t_r = 11.3 min, *exo* isomers t_r = 8.6, 9.2 min.

1-[(1*R*)-4-Phenylcyclohex-3-en-1-yl]-propan-1-one (Table 7, entry 3). Prepared according to general procedure B from ethyl vinyl ketone (48 μL, 0.48 mmol), 1-(methylene-allyl)-benzene (83 μL, 0.60 mmol), 70% aqueous perchloric acid (8.2 μL, 0.10 mmol), (2*S*, 5*S*)-5-benzyl-3-methyl-2-(5-methyl-furan-2-yl)-imidazolidin-4-one (26 mg, 0.10 mmol), and 14.4 mg of anhydrous calcium chloride (as desiccant) in ethanol (160 μL) for 4 days and 10 hours at -40 ^oC. Purification by flash chromatography (9:1 pentane:ether) provided the title compound as a single regioisomer (as judged by GLC analysis) in 92% yield (94 mg, 0.44 mmol) and 90% ee. IR (film) 3030, 2975, 2935, 2838, 1975, 1879, 1809, 1709, 1598, 1495, 1444, 1410, 1376, 1343, 1213, 1126, 1061, 1020, 958.4, 918.1, 868.1, 806.5, 743.2, 694.8 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.35

(m, 5H, ArH), 6.12 (m, 1H, C=CH), 2.54 (m, 7H, CH_2CO, CHCO, C**H$_2$**CH, and allylic C**H$_2$**CH_2), 2.12 (m, 1H, one of C**H$_2$**CH), 1.73 (m, 1H, one of C**H$_2$**CH), 1.08 (dd, *J* = 7.2, 7.2 Hz, 3H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 214.2, 141.9, 136.4, 128.5, 127.1, 125.2, 123.0, 46.4, 34.4, 28.2, 27.5, 25.7, 8.2; HRMS (CI) exact mass calcd for ($C_{15}H_{18}O$) requires *m/z* 214.1358, found *m/z* 214.1356. $[\alpha]_D$ = + 67.2 (c = 1.0, $CHCl_3$). Product ratios were determined by GLC analysis (150 °C, 23 psi); (*R*) isomer t_r = 62.4 min, and (*S*) isomer t_r = 60.8 min, regioisomers t_r = 49.6, 50.2 min.

1-[(1*R*, 2*S*)-2,4-Dimethylcyclohex-3-en-1-yl]-propan-1-one (Table 7, entry 4). Prepared according to general procedure B from ethyl vinyl ketone (59 μL, 0.59 mmol), *trans*-2-methyl-1,3-pentadiene (94 μL, 0.89 mmol), 70% aqueous perchloric acid (10.2 μL, 0.12 mmol) and (2*S*, 5*S*)-5-benzyl-3-methyl-2-(5-methyl-furan-2-yl)-imidazolidin-4-one (32 mg, 0.12 mmol) in ethanol (590 μL) for 4.5 days at –30 ^{o}C. Purification by flash chromatography (9:1 pentane:ether) provided the title compound as a single diastereomer (as judged by GLC analysis) in 90% yield (90 mg, 0.54 mmol) and 90% ee. IR (film) 2964, 2937, 2874, 2833, 1711, 1452, 1377, 1343, 1227, 1195, 1123, 1038, 984.2, 886.0, 841.6 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.37 (m, 1H, C**H**=CCH_3), 2.60 (m, 2H, CHCO and C**H**CH_3), 2.50 (dq, *J* = 17.4, 7.5 Hz, 1H, one of CH_2CO), 2.37 (dq, *J* = 17.4, 7.5 Hz, 1H, one of CH_2CO), 1.94 (m, 2H, allylic CH_2), 1.68 (m, 2H, C**H$_2$**CH), 1.64 (s, 3H, C**H$_3$**C=CH), 1.05 (dd, *J* = 7.5, 7.5 Hz, 3H, CH_2C**H$_3$**), 0.76 (dd, *J* = 6.9, 6.9 Hz, 3H, C**H$_3$**CH); ^{13}C NMR (75 MHz, $CDCl_3$) δ 214.0, 133.7, 126.3, 50.5, 34.6, 31.7, 30.2, 23.8, 19.0, 16.8, 8.1. $[\alpha]_D$ = + 16.7 (c = 1.0, $CHCl_3$). Product ratios were determined by GLC

analysis (100 °C, 23 psi); (1*R*, 2*S*) *endo* isomer t_r = 21.3 min, and (1*S*, 2*R*) *endo* isomer t_r = 20.4 min, *exo* isomers t_r = 15.4, 16.6 min.

(1*R*, 2*R*, 16*S*, 17*R*)-Tricyclo[15.2.1.0~2,16~]eicos-18-en-3-one (Table 7, entry 5). Prepared according to general procedure A from *trans*-2-cyclopentadecen-1-one (100 mg, 0.45 mmol), cyclopentadiene (56 μL, 0.67 mmol), 70% aqueous perchloric acid (7.8 μL, 0.09 mmol) and (2*S*, 5*S*)-5-benzyl-3-methyl-2-(5-methyl-furan-2-yl)-imidazolidin-4-one (24.3 mg, 0.09 mmol) in water (150 μL) for 72 hours at 0 ^{o}C. Purification by flash chromatography (9:1 ethyl acetate:hexanes) provided the title compound as a clear, colorless crystalline solid in 88% yield (114 mg, 0.50 mmol); 5:1 *endo*:*exo*, *endo* 93% ee. IR (film) 3052, 2922, 2854, 1698, 1456, 1368, 1331, 1225, 1126, 1084, 1016, 905.5, 884.9, 714.4 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.21 (dd, *J* = 5.4, 2.7 Hz, 1H, C**H**=CH), 5.86 (dd, *J* = 5.4, 2.7 Hz, 1H, CH=C**H**), 3.09 (m, 1H, C**H**CH=CH), 2.61 (m, 2H, CHCO and one of CH_2CO), 2.52 (m, 1H, C**H**CH=CH), 2.41 (m, 1H, one of CH_2CO), 2.27 (m, 1H, C**H**CHCO), 1.81-1.24 (br m, 22H, $(CH_2)_{11}$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 211.6, 138.5, 132.6, 59.6, 48.4, 47.2, 46.7, 41.5, 41.3, 36.3, 28.0, 27.9, 27.7, 27.2, 26.8, 26.8, 26.7, 26.7, 26.0, 23.6. $[\alpha]_D$ = + 22.2 (c = 1.0, $CHCl_3$). Product ratios were determined by GLC analysis (200 °C, 23 psi); (1*R*, 2*R*, 16*S*, 17*S*) *endo* isomer t_r = 20.1 min, and (1*S*, 2*S*, 16*R*, 17*R*) *endo* isomer t_r = 19.6 min, *exo* isomers t_r = 19.0, 18.6 min. The *trans* relative stereochemistry of C-16 and C-17 was confirmed by the presence of an NOE between the C-16 methine proton and the two C-19 protons.

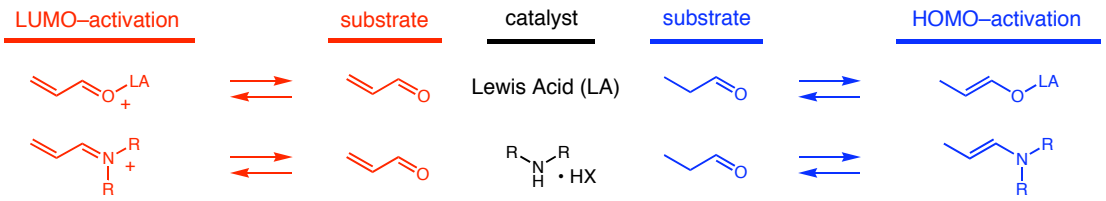
Chapter 2

Development of the Enantioselective Aldehyde Aldol Reaction

The HOMO-Raising Catalysis Concept

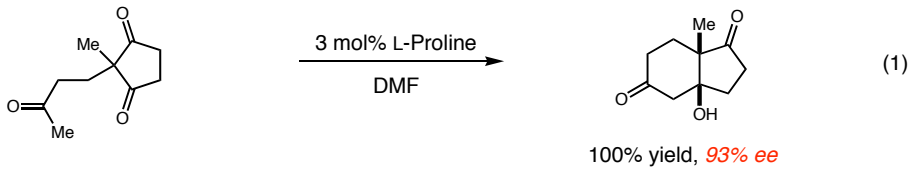
The LUMO-lowering organocatalysis concept has led to the development of several valuable enantioselective catalytic transformations.[1] Emulating the function of Lewis acids, iminium activation of conjugated olefins permits a broad spectrum of asymmetric cycloaddition and conjugate addition processes (Figure 1). Considering the inverse of LUMO-lowering—namely, HOMO-raising catalysis—unveils the possibility that enamine activation of carbonyl-containing compounds may allow their use as nucleophiles for a range of transformations (Figure 1).

Figure 1. Amines are Lewis Acid Equivalents in LUMO-Lowering and HOMO-Raising Processes



[1] For examples of enantioselective iminium ion catalysis, see: (a) Austin, J. F.; Kim, S-G.; Sinz, C. J.; Xiao, W-J.; MacMillan, D. W. C. *Proc. Nat. Acad. Sci. U.S.A.* **2004**, *101*, 5482. (b) Ahrendt, K. A.; Borths, C. J.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2000**, *122*, 4243. (c) Austin, J. F.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2002**, *124*, 1172. (d) Jen, W. S.; Wiener, J. J. M.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2000**, *122,* 9874. (e) Paras, N. A.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2001**, *123*, 4370. (f) Northrup, A. B.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2002**, *124*, 2458. (g) Paras, N. A.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2002**, *124*, 7894.

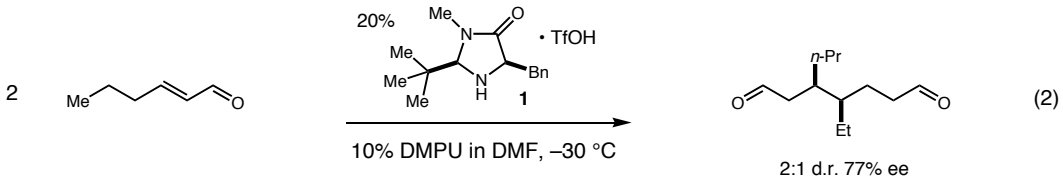
Several transformations such as the Hajos-Parrish reaction[2] (and the intermolecular variants and extensions probed by Barbas and List[3]) have generated enamines *in situ* from catalytic amounts of a secondary amine salt such as proline (eq 1).



Our group's study of HOMO-raising catalysis seeks to explore enamine catalysis as a broadly useful catalysis concept. That focus should lead to the invention of several novel enantioselective catalytic transformations of significant synthetic value.

Preliminary Results: The First Enantioselective Vinylogous Michael Reaction

Given our interest in HOMO-raising organocatalysis, the dimerization of hexenal to form a dialdehyde as a side-product of nitrone cycloadditions[4] appeared to be an interesting entry into enamine catalysis (eq 2).



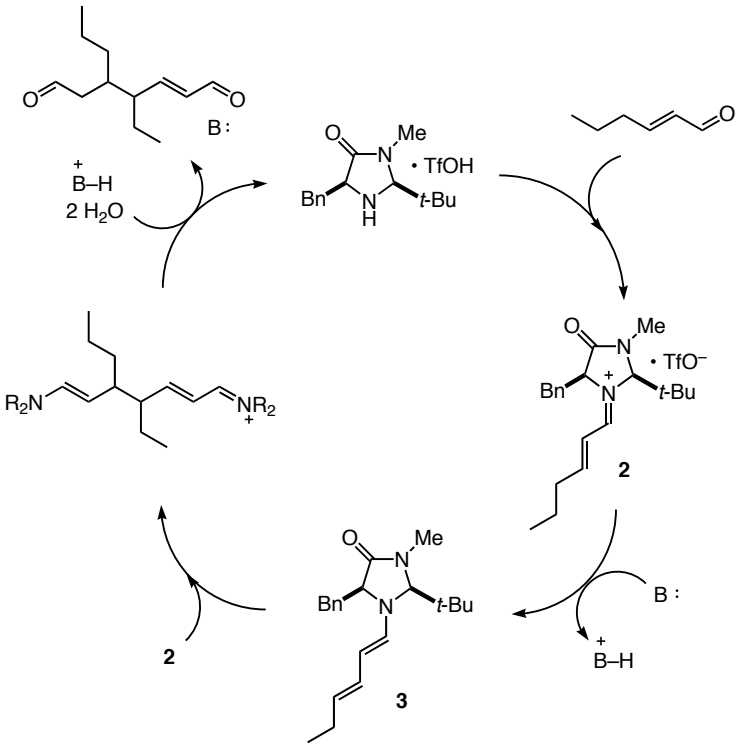
[2] (a) Hajos, Z. G.; Parrish, D. R. *J. Org. Chem.* **1974**, *39*, 1615. (b) Eder, U.; Sauer, G.; Wiechert, R. *Angew. Chem.* **1971**, *10*, 496. (c) Agami, C.; Platzer, N.; Sevestre, H. *Bull. Chim. Soc. Fr.* **1987**, *2*, 358.

[3] (a) Kandasamy, S.; Notz, W.; Bui, T.; Barbas, C. F., III *J. Am. Chem. Soc.* **2001**, *123*, 5260. (b) List, B.; Lerner, R. A.; Barbas, C. F., III *J. Am. Chem. Soc.* **2000**, *122*, 2395. (c) Notz, W.; List, B. *J. Am. Chem. Soc.* **2000**, *122*, 7386. (d) List, B.; Pojarliev, P.; Castello, C. *Org. Lett.* **2001**, *3*, 573. (e) Cordova, A.; Notz, W.; Barbas, C. F., III *J. Org. Chem.* **2002**, *67*, 301.

[4] First observed by Nicole C. Goodwin and Sean P. Brown. The original reaction conditions afforded nearly racemic products. After extensive optimization, significant enantioselectivities were observed. An alternative dimerization pathway observed by Julie Y. Park produced *o*-tolualdehyde from the imidazolidinone-catalyzed dimerization of crotonaldehyde.

To account for the observed vinylogous Michael product, a bifunctional catalysis mechanism was proposed wherein the imidazolidinone catalyst functions as both a LUMO-lowering and a HOMO-raising catalyst (Figure 2).

Figure 2. Proposed Bifunctional Catalysis Dimerization Mechanism



That mechanism postulates the requirement of two molecules of catalyst in the transition state for the enantiodetermining step. To verify that hypothesis, a study of the effect of varying catalyst ee on the observed product ee was undertaken. As Figure 3 illustrates, a non-linear relationship exists between the enantiopurity of the catalyst and that of the product. Following Kagan's analysis,[5] we can infer from that non-linear effect that more than one molecule of catalyst is involved in the enantiodetermining step as aggregation of the catalyst seems unlikely as an alternative explanation.

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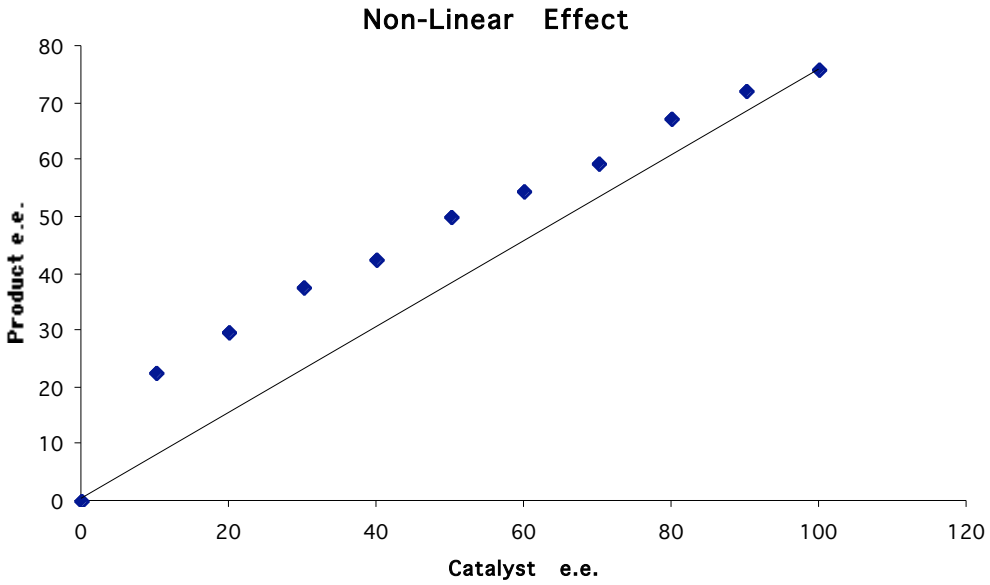
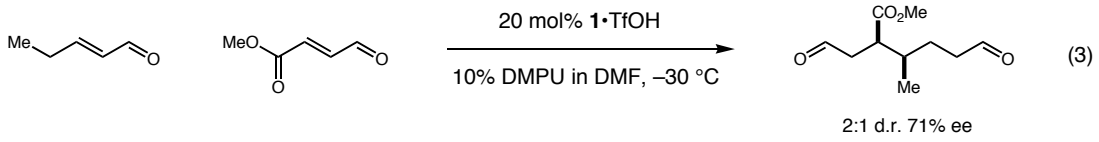
[5] For a detailed analysis of the non-linear effect first predicted and described by Kagan, see: Blackmond, Donna G. *Acc. Chem. Res.* **2000**, *33*, 402-411.

Figure 3: Observation of a Non-Linear Effect for the Dimerization of Hexenal



Cross-coupling by vinylogous Michael reaction proceeds with reaction efficiency similar to the dimerization process (eq 3, 84% conversion, 2:1 d.r., 71% ee) provided that the electrophilic α, β-unsaturated aldehyde bears no enolizable γ-protons.

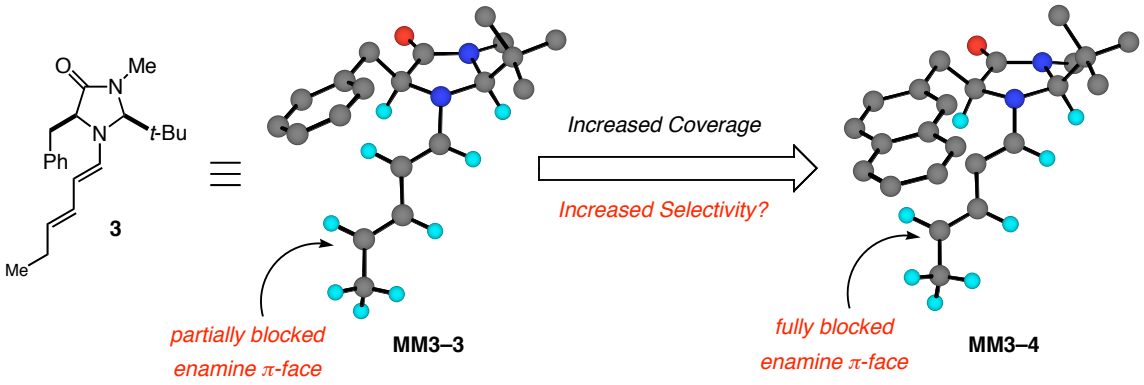


(3)

Increasing Selectivity in HOMO-Raising Organocatalysis

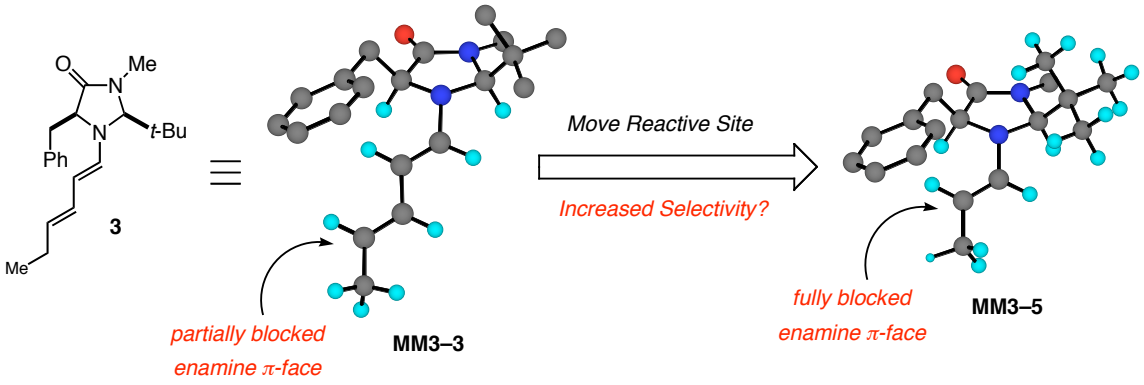
For the amine-catalyzed vinylogous Michael reaction to become synthetically useful, a drastic increase in enantioselectivity is required. As it has been demonstrated that α, β-unsaturated iminium ions formed between hexenal and catalyst **1** constitute an effective platform for enantioselective catalysis, it is believed that the low selectivity is primarily due to the structure of the dienamine component. As Figure 4 demonstrates, there appears to be only partial blockage of the nucleophilic π-face of dienamine **3**.

Figure 4. Increased π-Facial Coverage Is Needed for High Enantioselectivity



Consequently, it was envisioned that a new catalyst with extended π-facial coverage (*e.g.*, **MM3–4**) would be required to impart useful levels of selectivity with dienamine nucleophiles. However, rather than embarking on another round of catalyst design (*cf.* Chapter 1), a new direction for this line of research was pursued. Instead of extending the π-shielding to cover the dienamine π-face as in Figure 4, the reactive olefin could be positioned underneath the already present π-shielding (Figure 5).

Figure 5. Enamines Should Afford High Levels of Selectivity



By removing one of the olefins from the dienamine, a simple enamine, such as **MM3–5**, would be generated. As the reactive site is significantly closer to the catalyst framework, enamines should afford higher levels of enantiocontrol than dienamines. Therefore, imidazolidinone-derived enamines could potentially be used as intermediates in aldol,

mannich, α–oxidation, α-halogenation, α-alkylation, or other electrophilic substitution reactions.

The Aldehyde Aldol Reaction

Since its discovery in 1864, the aldol reaction has intrigued chemists due to its ability to simultaneously form a carbon-carbon bond and two vicinal stereocenters.[6] Since that time, several valuable aldol subtypes have been invented to achieve practical iterative aldol strategies for the construction of polyketide natural products. Perhaps the most well known strategy has been developed by Evans and co-workers and is outlined in Figure 6.[7] Over the past 20 years, that auxiliary-based strategy has represented the most powerful method for the synthesis of polyketides. However, a new movement toward direct aldol technology has sought to supplant Evans's technology as the premiere method for the construction of carbon-carbon bonds.

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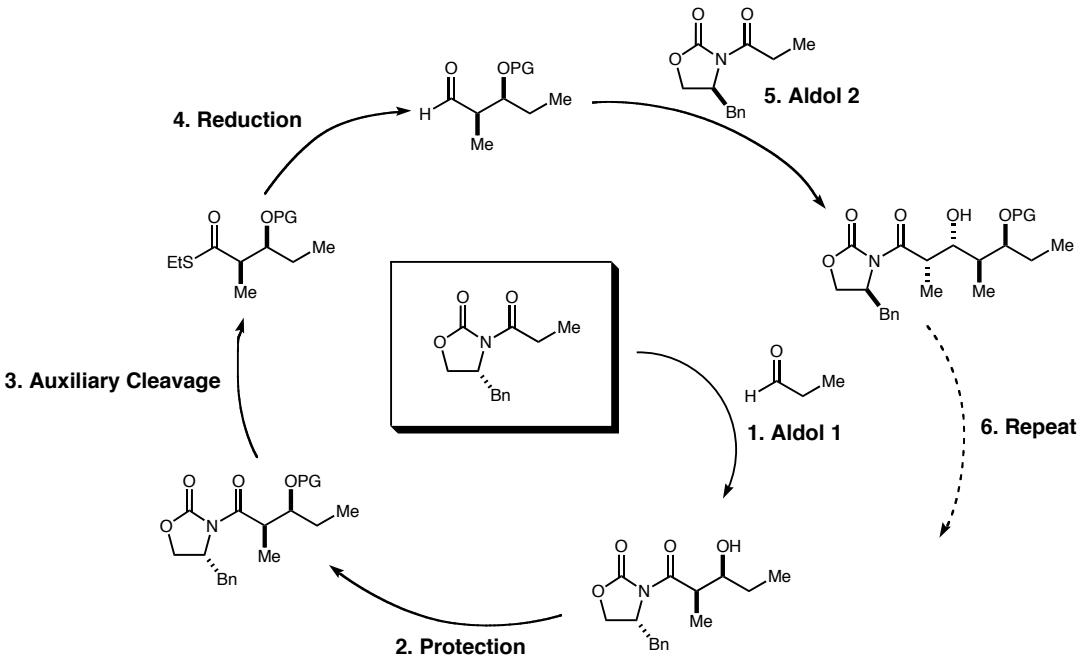
[6] For several excellent reviews of the aldol reaction, see: (a) Mahwald, R. *Chem. Rev.* **1999**, *99*, 1095. (b) Palomo, C.; Ojabride, M.; García, J. M. *Chem. Eur. J.* **2002**, *8*, 36. (c) Mukaiyama, T. "The Directed Aldol Reaction" in *Organic Reactions*, New York, 1982; Vol. 28, p 203. (d) Evans, D. A.; Nelson, J. V.; Taber, T. R. "Stereoselective Aldol Condensations," in *Topics in Stereochemistry* New York, 1982; Vol. 13, p. 2. (e) Machajewski, T. D.; Wong, C. –H. *Angew. Chem. Int. Ed.* **2000**, *39*, 1352.

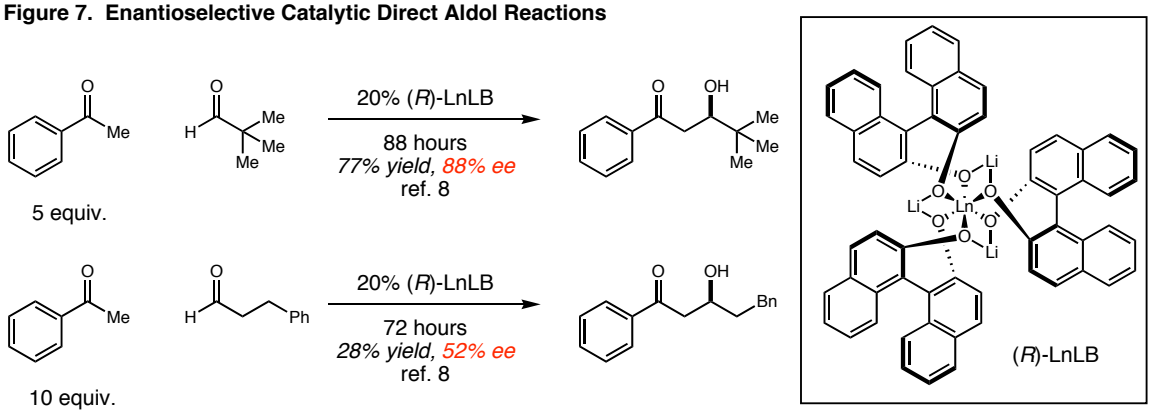
[7] Evans, D. A.; Bartroli, J.; Shih, T. L. *J. Am. Chem. Soc.* **1981**, *103*, 2127.

Figure 6. Evans's Iterative Aldol Strategy



While direct catalytic enantioselective aldol technologies have been developed by both Shibasaki[8] and Trost,[9] such reactions are typically limited to acetophenone and other acidic ketones as aldol donors, thus limiting the synthetic utility of those processes (Figure 7).

Figure 7. Enantioselective Catalytic Direct Aldol Reactions



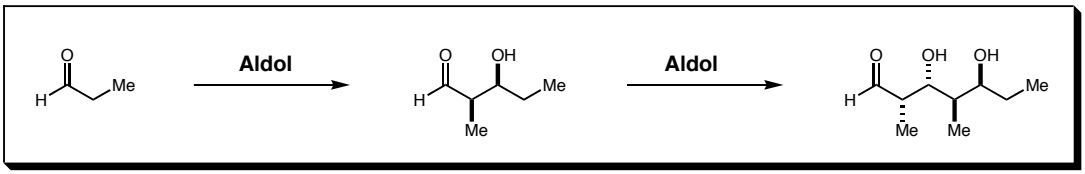
Furthermore, the use of enolizable aldehydes in such reactions has led to competing side-reactions that severely decrease reaction efficiencies (Figure 7). Moreover, the reliance on high-molecular weight organometallic complexes at relatively high catalyst loadings and

[8] Yoshikawa, N.; Yamada, Y. M. A.; Das, J.; Sasai, H.; Shibasaki, M. *J. Am. Chem. Soc.* **1999**, *121*, 4168.

[9] Trost, B. M.; Ito, H. *J. Am. Chem. Soc.* **2000**, *122*, 12003.

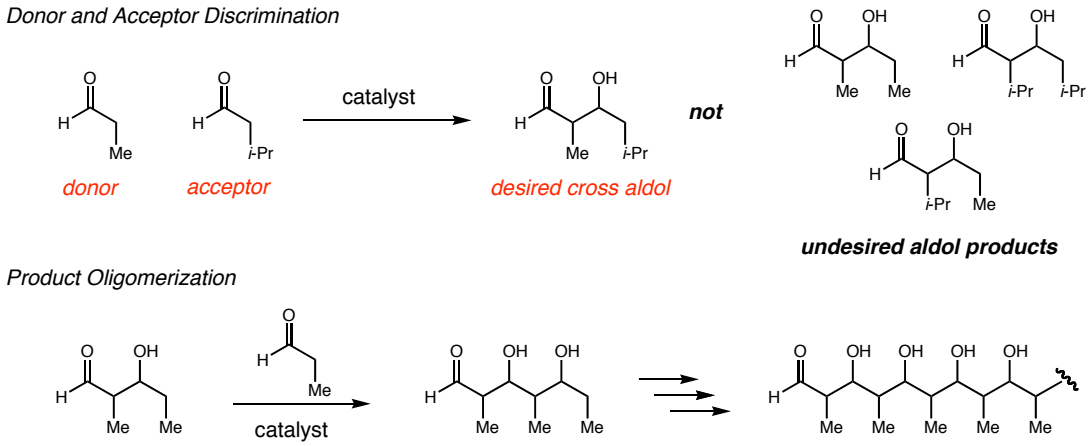
typically multiple equivalents of aldol donor put further restrictions on the general applicability of these methods. In contrast, a new strategy based on the direct aldehyde aldol reaction would offer significant advantages as both an atom economical and expedient strategy for polyketide synthesis (Figure 8). The use of the reactive aldehyde functionality in the aldol donor avoids the need for oxidation state adjustments and auxiliary cleavage steps in conventional iterative aldol technology, leading to a significant reduction in the number of steps required per iteration (*cf.* Figure 6).

Figure 8. The Iterative Aldehyde Aldol Strategy



While that aldol strategy in Figure 8 seems attractive due to its simplicity, the use of aldehydes as aldol donors raises several issues of chemoselectivity and stereoselectivity in a cross aldol event—*there is the potential to form four different products and a total of sixteen stereoisomers* (Figure 9).

Figure 9. Mechanistic Obstacles to the Aldehyde Aldol Reaction

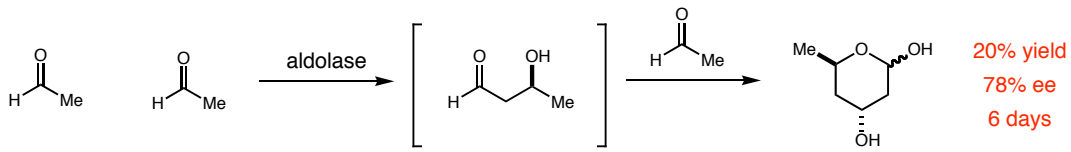


The primary challenge in this process is that the two aldehydes must selectively partition into two different mechanistic pathways: one aldehyde must become the nucleophilic aldol

donor while the other aldehyde must instead become the electrophilic aldol acceptor. A second challenge is the potential for the aldehyde product to undergo further aldolization to form an aldol oligomer or polymer.

While the aldehyde aldol reaction (*e.g.*, Figure 8) has not been accomplished in the realm of small-molecule catalysis, Wong *et al.* have demonstrated that mode of reactivity using both acetaldehyde and propionaldehyde dependent aldolase enzymes to produce enantioenriched tetrahydropyrans of defined stereochemistry through two sequential aldol events (Figure 10).[10] The enzyme DERA (2-deoxyribose-5-phosphate aldolase) is classified as a Type I aldolase enzyme due to its ability to perform aldol chemistry *via* an enamine intermediate, thereby affording a significant precedent for the use of enamine catalysis in the direct aldehyde aldol reaction.

Figure 10. Aldolase Enzymes Can Catalyze Aldehyde Trimerizations



However, Wong and co-workers proved that this reaction does not tolerate a variety of different aldol donors and acceptors. Furthermore, they were unable to isolate the presumed intermediate β-hydroxyaldehyde. While their work demonstrates the feasibility of utilizing aldehydes as aldol donors, it is not immediately obvious how such a result could be expanded into a general strategy for polyketide synthesis, particularly with respect to the generation of multiple stereochemical motifs.

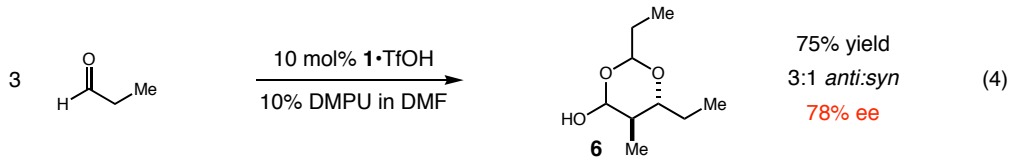
Based on the ability of the imidazolidinone catalyst to form reactive quantities of a dienamine (*vide supra*), it seemed reasonable that imidazolidinone catalysts might form

[10] (a) Machajewski, T. D.; Wong, C. –H. *Angew. Chem. Int. Ed.* **2000**, *39*, 1352 and references therein. (b) Gijsen, H. J. M.; Wong, C. –H. *J. Am. Chem. Soc.* **1994**, *116*, 8422.

enamines on saturated aldehydes to act as a small-molecule aldolase mimic. In so doing, the imidazolidinone might enable an enantioselective catalytic direct aldehyde aldol reaction—a highly sought-after process that had remained elusive.[11] Furthermore, the identification of this mode of reactivity should allow a new array of HOMO-raising processes to be invented using this catalyst.

Development of the Imidazolidinone-Catalyzed Direct Aldehyde Aldol Reaction

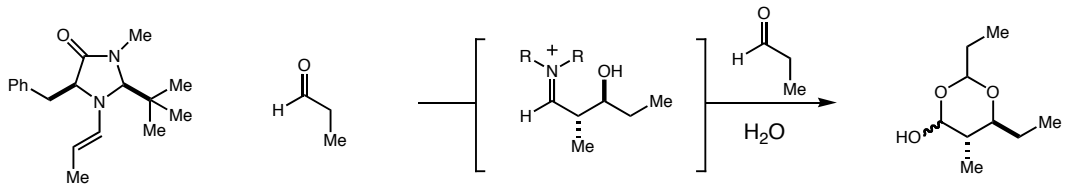
Initial studies focused on the reactions of propionaldehyde with imidazolidinone catalyst **1** under the previously optimized conditions for the vinylogous Michael chemistry (*vide supra)*. Trimeric structure **6** was formed during the course of these reactions and represents the first enantioselective catalytic direct aldehyde aldol reaction (eq 4).



(4)

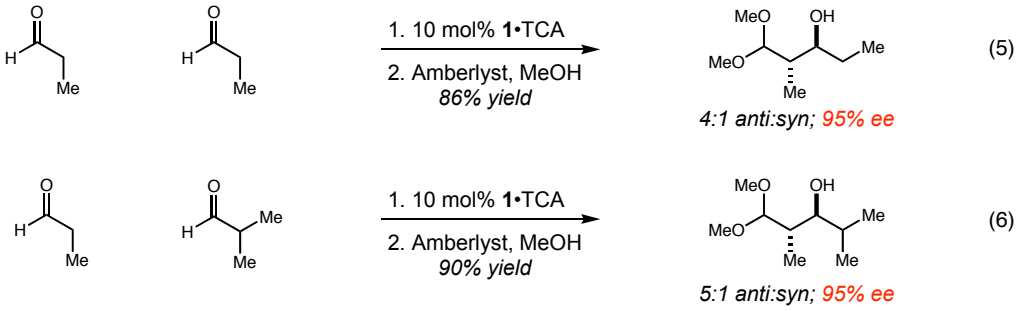
In this case, the oligomerization of the product through subsequent aldolizations was halted, presumably, by the interception of the iminium ion intermediate by a molecule of propionaldehyde (Figure 11). While modifications of the reaction conditions to directly form the β-hydroxyaldehyde products were unsuccessful, methanolysis smoothly provided the dimethyl acetal-protected aldol adducts.

Figure 11. Proposed Mechanism for Aldol Trimerization



[11] That goal has also been dubbed the "holy grail of aldol research" Movassaghi, M.; Jacobsen, E. N. *Science* **2002**, *298*, 1904.

Following those initial studies, Ian Mangion joined this project in our laboratory and completed the optimization and evaluation of the scope of this aldol trimerization reaction. Those studies produced a direct aldehyde aldol reaction capable of providing both aldol dimerization and cross-aldol adducts in high enantioselectivity and yields, and in modest to good diastereoselectivity (eqs 5 and 6).[12]



Stereochemical Rationale

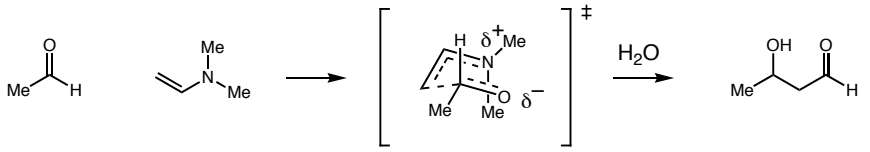
The sense of both diastereoselectivity and enantioselectivity can be rationalized in the context of a model produced by Houk in his calculation of the enamine aldol reaction between acetone and formaldehyde (Figure 12).[13] Their model predicts an envelope-type conformation wherein the forming positive charge on the nascent iminium ion is tightly paired with the developing negative charge on the aldol acceptor fragment in the calculated late transition state. They also suggest that the gas-phase transition state becomes barrierless by protonation of the nascent alkoxide with exogenous acid, further implicating the acid co-catalyst as being essential to the selectivity of the imidazolidinone-catalyzed aldol.

---

[12] Mangion, I. K.; Northrup, A. B.; MacMillan, D. W. C. manuscript in preparation.

[13] For a review of Houk's computational study of organocatalytic processes, see: Allemann, C.; Gordillo, R.; Clemente, F. R.; Cheong, H. –Y.; Houk, K. N. *Acc. Chem. Res.* **2004**, *37*, ASAP, 7/17/04. For his study of the aldol reaction, see: (a) Bahmanyar, S.; Houk, K. N. *J. Am. Chem. Soc.* **2001**, *123*, 12911. (b) Bahmanyar, S.; Houk, K. N.; Martin, H. J.; List, B. *J. Am. Chem. Soc.* **2003**, *125*, 2475. (c) Bahmanyar, S.; Houk, K. N. *J. Am. Chem. Soc.* **2001**, *123*, 11273.

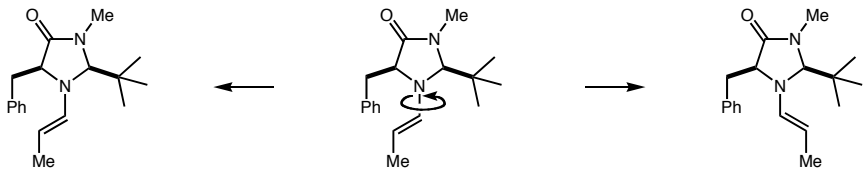
Figure 12. Calculated Transition State for Amine-Catalyzed Aldol Reactions



Due to the lateness of their calculated transition state, there is significant iminium ion formation, restricting rotation about the forming C–N π-bond. Therefore, enamine rotamer control (*e.g.*, *cis*–**5** *vs*. *trans*–**5**, Figure 13) is not essential for enantiocontrol in this reaction. Transition state iminium ion geometry control, however, should dictate the enantioselectivity of the aldol reaction as the *E* and *Z* transition state iminium isomers expose opposite olefin enantiofaces (Figure 13).

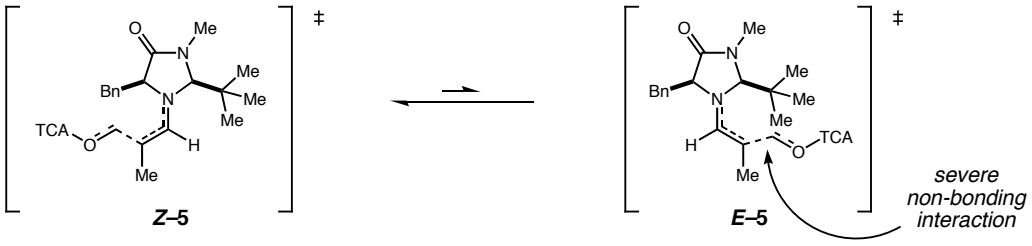
Figure 13. Transition State Iminium Ion Geometry Control Is Essential For Selectivity

Ground State Enamine Has Free Rotation:



***cis*–5** **5** ***trans*–5**

Transition State Iminium–Enamine Does Not:



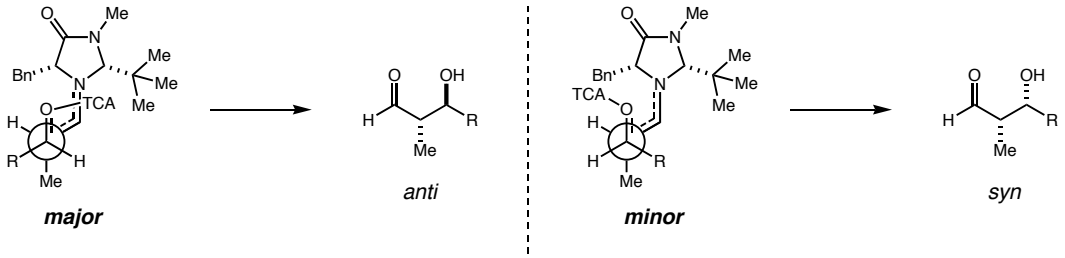
***Z*–5** ***E*–5**

Si-face exposed *Re*-face exposed

Fortunately, catalyst **1** was specifically designed to achieve iminium ion geometry control for LUMO-lowering catalysis and it appears that the control of iminium ion geometry in the transition state is exceptional in the aldehyde aldol reaction based on the observed high enantioselectivities.

Considering that the *E*–enamine geometry is fixed by allylic strain, the proposed open transition state also readily explains both the *anti*-aldol diastereoselectivity and the small variability in diastereoselectivity based on the nature of the steric bulk of the aldol acceptor or aldol donor (Figure 14). That fact is inconsistent with the proposal of a closed six-membered chair-like transition state *via* an enammonium intermediate as has been proposed by our group for proline-catalyzed processes (*vide infra*).[14]

Figure 14. Stereochemical Model for the Imidazolidinone-Catalyzed Aldol



Proline Is an Effective Aldol Catalyst

For over 30 years it has been recognized that proline is a highly efficient catalyst for the direct aldol reaction. In their seminal studies, Hajos, Parrish, Eder, Sauer, and Weichert[15] found that proline could effect a desymmetrization through an intramolecular aldol reaction in high enantioselectivity (eq 1). Later, Barbas, List, and Lerner realized that proline could be used in enantioselective catalytic direct intermolecular aldol reactions (eq 7).[16] Significantly, they observe exclusive regioselective enamine formation on the ketone instead of the aldehyde under their reaction conditions to provide a single aldol adduct in good enantioselectivity.

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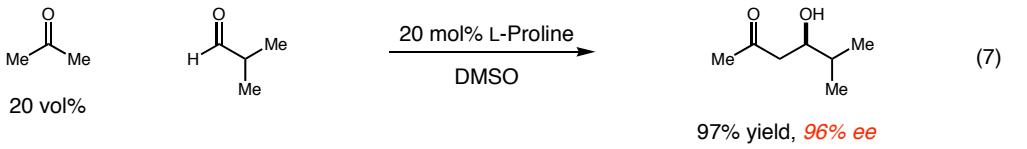
[14] For example, Brochu, M. P.; Brown, S. P.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2004**, *126*, 4108.

[15] (a) Hajos, Z. G.; Parrish, D. R. *J. Org. Chem.* **1974**, *39*, 1615. (b) Eder, U.; Sauer, G.; Weichert, R. *Angew. Chem. Int. Ed., Eng.* **1971**, *10*, 496.

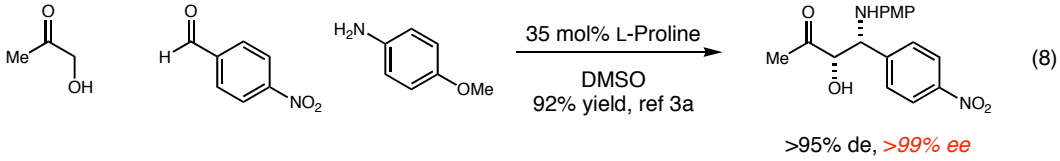
[16] List, B.; Lerner, R. A.; Barbas, C. F. III *J. Am. Chem. Soc.* **2000**, *122*, 2395.



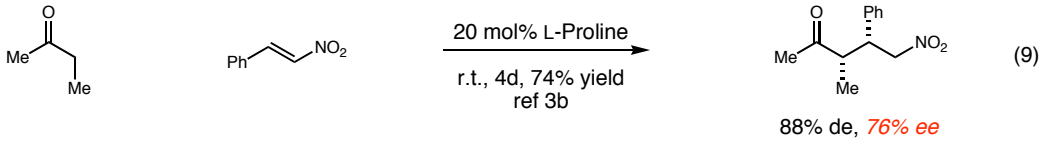
Those reports from the labs of Barbas and List have sparked a renaissance in the field of proline catalysis and have led to the intensive research efforts of many groups on the use of proline and derivatives as catalysts for a range of transformations (Figure 15).[17]

Figure 15. Proline and Derivatives Catalyze a Range of Transformations

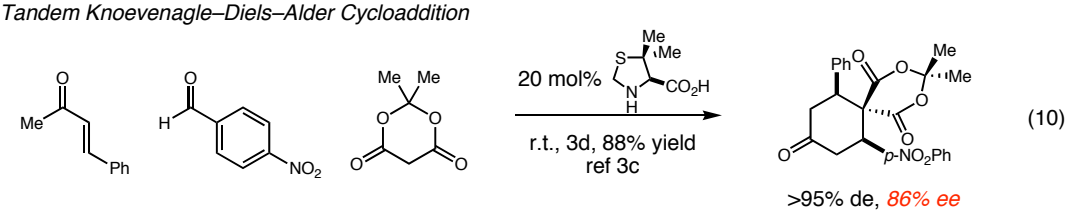
Mannich Reactions



Nitrostyrene Conjugate Additions



Tandem Knoevenagle–Diels–Alder Cycloaddition

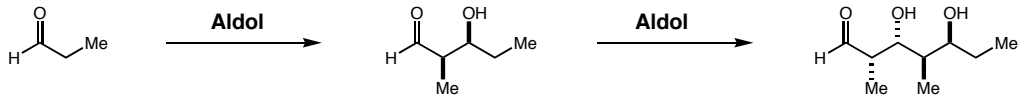


Proline Catalysis of the Aldehyde Aldol Reaction

As discussed above, the aldehyde aldol reaction is the cornerstone of an ideal iterative aldol strategy for use in polyketide synthesis (Figure 16).

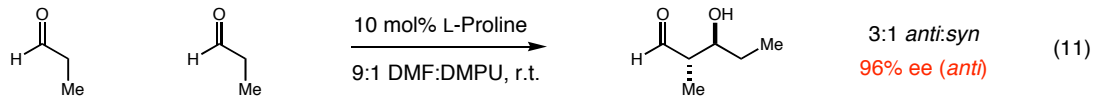
[17] (a) List, B.; Pojarliev, P.; Biller, W. T.; Martin, H. J. *J. Am. Chem. Soc.* **2002**, *124*, 827. (b) Enders, D.; Seki, A. *Synlett* **2001**, 26. (c) Ramachary, D. B.; Chowdari, N. S.; Barbas, C. F. III *Angew. Chem. Int. Ed.* **2003**, *42*, 4233.

Figure 16. The Iterative Aldehyde Aldol Strategy



While the use of imidazolidinones as aldol catalysts led to the production of synthetically valuable protected β-hydroxyaldehydes through such an aldehyde aldol reaction (eqs 4 to 6), the ideal aldehyde aldol transformation would allow direct access to β-hydroxyaldehydes (Figure 16).

To that end, amine architecture was examined to identify a catalyst capable of producing unprotected β-hydroxyaldehydes. Given the history of proline as an aldol catalyst (*vide supra*), it was the logical first choice. To our surprise and delight, it did not efficiently promote the trimerization of propionaldehyde in dimethylformamide; instead, proline smoothly effected an aldol dimerization of propionaldehyde in high enantioselectivity without any evidence of trimeric aldol products (eq 11).



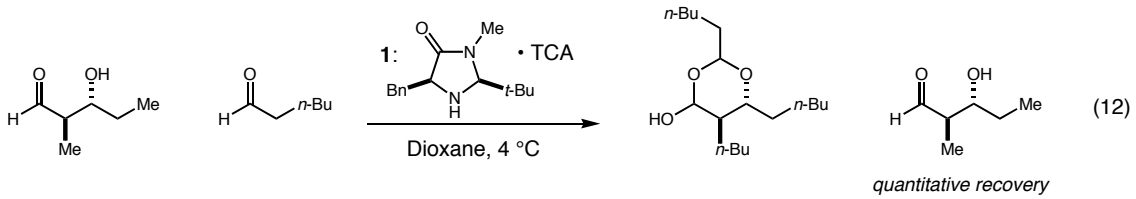
Despite the prior use of proline in other aldol reactions employing α-methylene aldehyde substrates,[18] this is the first example of a proline-catalyzed aldehyde mono-aldol reaction.

Chemoselectivity in Proline-Catalyzed Aldehyde Aldols

Why do proline and imidazolidinone catalysts afford different aldol products? The possibility exists under imidazolidinone-catalysis that β-hydroxyaldehydes are directly produced and then undergo protection by propionaldehyde to produce the

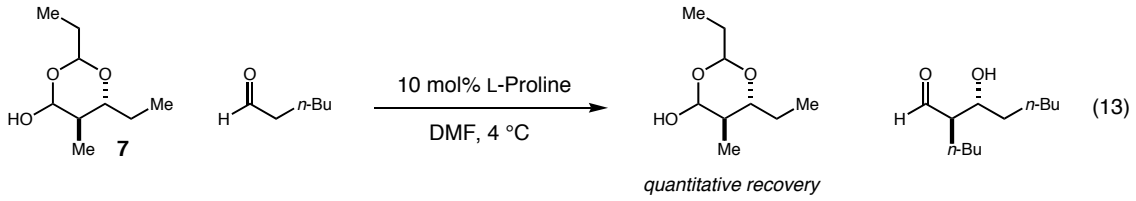
[18] List, B.; Pojarliev, P.; Martin, H. J. *Org. Lett.* **2001**, *3*, 2423.

observed aldol trimer (eq 6). To examine that chemoselectivity explanation, it was demonstrated that β-hydroxyaldehydes are not converted into aldol trimers when exposed to hexanal and imidazolidinone catalyst **1** (eq 12), therefore, β-hydroxyaldehydes are unlikely as intermediates in imidazolidinone-catalyzed aldehyde aldol reactions.



(12)

An alternative explanation for the divergent reactivity of proline and imidazolidinones is that proline produces an aldol trimer that is then deprotected *in situ* to afford the observed β-hydroxyaldehyde product. To test that theory, aldol trimer **7** was exposed to proline and hexanal in dimethylformamide (eq 13).

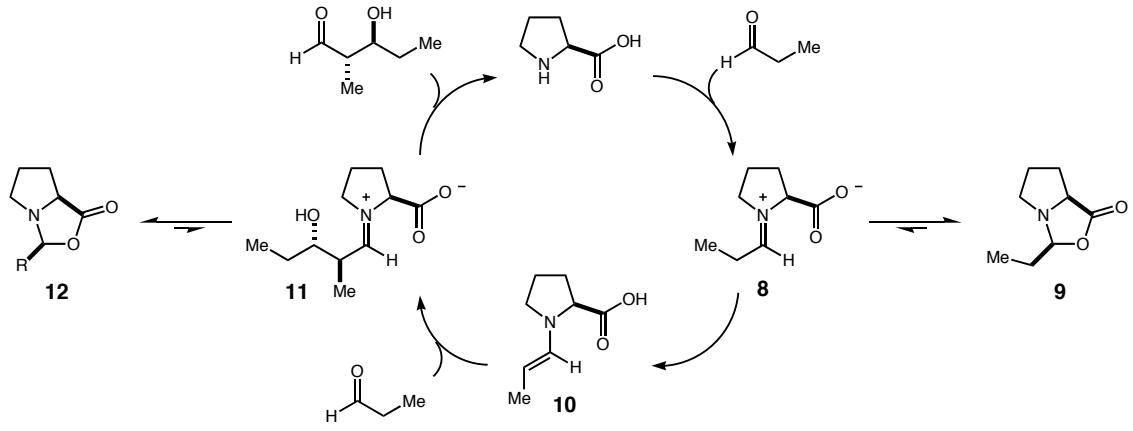


(13)

That experiment showed proline to be an inefficient catalyst for the deprotection of trimeric acetals. Therefore, it is unlikely that proline-catalysis produces such acetals as intermediates. In conclusion, it is most probable that imidazolidinones directly produce aldol trimers and proline directly affords β-hydroxyaldehydes.

The question now becomes: why are β-hydroxyaldehydes produced by proline whereas imidazolidinones provide trimeric structures? To help answer that question, the proline-catalyzed aldol dimerization reaction of propionaldehyde was studied by ^{1}H NMR. Neither enamine **10** nor iminium ion **8** were observed, however, an *N*, *O*–acetal of proline and propionaldehyde was observed (**9** in Figure 3).

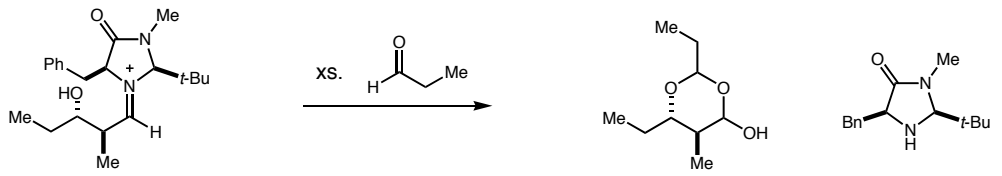
Figure 17. Proposed Catalytic Cycle for Proline-Catalyzed Aldehyde Aldol



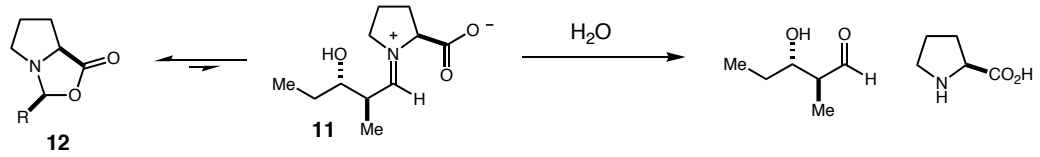
Presumably, acetal **9** represents the resting state of proline in the catalytic cycle that is in equilibrium with a miniscule amount of iminium ion **8**. Due to the relative stability of acetal **9** relative to iminium ion **8**, it is proposed that the nascent iminium ion aldol product **11** is converted into product acetal **12** by a side-equilibrium to the catalytic cycle. Liberation of proline from acetal **12** requires attack of a strong nucleophile, such as water, to compete with the carboxylate moiety on iminium ion **11**. In contrast, imidazolidinones lack the ability to form such acetals, therefore, even a weak nucleophile, such as propionaldehyde's carbonyl lone pair, can aid in catalyst turnover (Figure 18).

Figure 18. Influence of Iminium–Aldolate Structure on Product Distribution

Excess Propionaldehyde can Turnover Imidazolidinone Catalyst



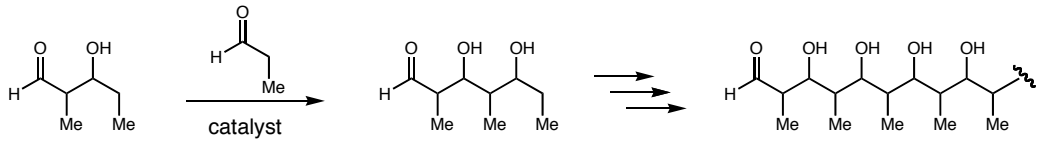
Proline Aldolate Requires Water for Turnover due to Acetal–Protection



Due to the large excess of propionaldehyde relative to the catalytic amount of water available in the imidazolidinone-catalyzed reaction, the trimeric product is observed. In the case of proline-catalysis, a similar equivalency is employed, however, the ability to form acetal **12** protects the product from attack by propionaldehyde, allowing the opportunity for water to turn over the catalyst.

Another question of chemoselectivity in the proline-catalyzed aldol dimerization is: why does the reaction stop after only a single aldol reaction instead of providing an aldol polymer (Figure 19)?

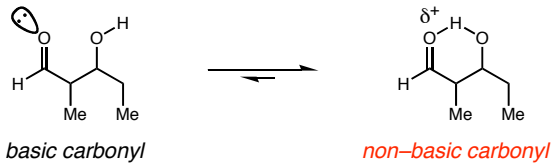
Figure 19. Aldol Product Has the Potential to Oligomerize



While it is true that propionaldehyde is sterically smaller than the dimeric aldol product, sterically demanding aldehydes are also excellent substrates for this reaction (*vide infra*), therefore, simple steric arguments cannot entirely explain the chemoselectivity. A more likely explanation incorporates the lower basicity of the product's carbonyl relative to

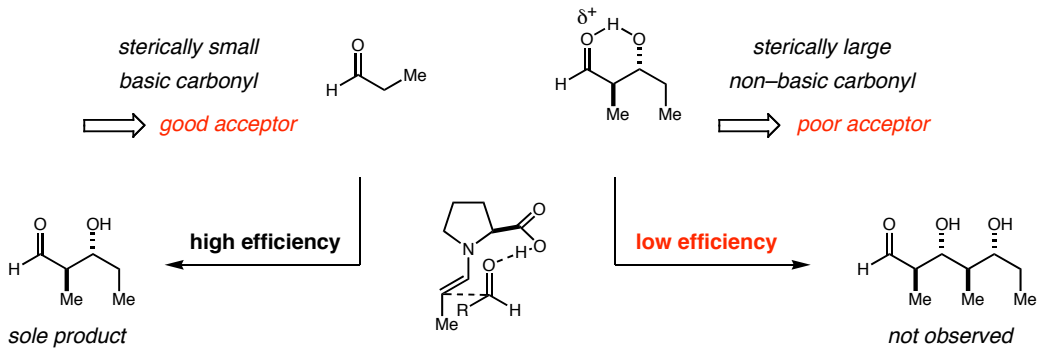
propionaldehyde due to the presence of an intramolecular hydrogen bond in the product (Figure 20).

Figure 20. Intramolecular Hydrogen Bond Decreases Product Carbonyl's Basicity



As it is believed that protonation of the electrophile by a proline enamine is essential for substrate activation, the relative basicity and steric demand of the competing aldol acceptors will determine the product ratios (Figure 21).

Figure 21. Basicity and Steric Size Determine Product Distribution



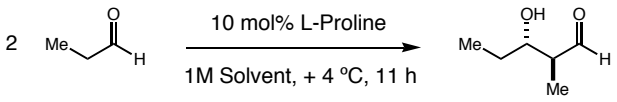
As the aldol dimer product is both larger and less basic than propionaldehyde, propionaldehyde outcompetes the dimeric product as an acceptor for the carboxylic acid's proton—accounting for the complete selectivity for dimerization over further oligomerization.

Optimization of Reaction Conditions

While equation 11 (above) certainly represents an outstanding first result, further studies were conducted to ensure that the optimal reaction conditions would be identified. Remarkably, the enantioselectivity of this aldol dimerization process remains quite high

in a wide range of solvents (Table 1, entries 1-9, ≥ 96% ee) from non-polar solvents such as benzene (entry 1, >99% ee) to highly polar solvents such as dimethylsulfoxide (entry 7, >99% ee). Aldol dimerization reactions conducted in dimethylformamide (entry 9, 91% conversion, 3:1 *anti*:*syn*, 99% ee) proceeded with optimal rate and selectivity, therefore, that solvent was selected for further study.

Table 1. Solvent Effects on the Proline–Catalyzed Dimerizatiol of Propionaldehyde



entry	solvent	conversion[a]	*anti*:*syn*[b]	ee (*anti*)[c, d]
1	Ph-H	32	5:1	>99
2	$CHCl_3$	29	4:1	98
3	EtOAc	41	5:1	99
4	THF	36	4:1	98
5	Dioxane	41	4:1	98
6	CH_3CN	42	3:1	96
7	DMSO	38	3:1	>99
8	NMP	62	3:1	98
9	DMF	91	3:1	99

[a]Determined by GLC analysis at an arbitrary 11h time point. [b]Relative stereochemistry determined by comparison to literature spectra. [c]Determined by chiral GLC analysis of the 2,2-dimethylpropylidine acetal. [d]Absolute configuration assigned by chemical correlation.

Unfortunately, further optimization of yield, rate, and diastereoselectivity was not achieved after studying a variety of different reaction parameters, such as temperature, concentration, and catalyst loading.

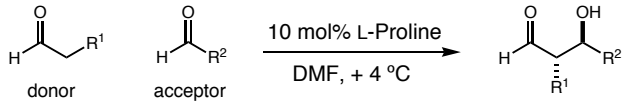
Cross Aldol Reactions

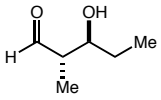
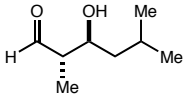
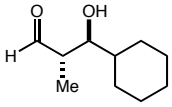
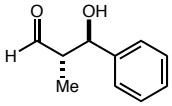
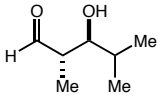
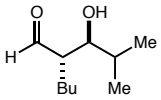
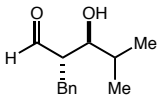
With a set of optimal conditions for the proline-catalyzed aldol dimerization, the possibility of effecting cross aldol reactions using catalytic amounts of proline was next examined. As in the case of the imidazolidinone-catalyzed aldol reactions, it was expected that syringe pump addition of the donor aldehyde, such as propionaldehyde, to a

stirring suspension of the acceptor aldehyde and proline would produce the desired cross aldol adducts. That expectation was based on the presumed second order kinetics of the aldol dimerization manifold relative to the first order nature of the cross aldol process with respect to the aldol donor. Based on that kinetic assumption it was realized that as the concentration of donor aldehyde decreases, the rate of homodimerization drops exponentially, whereas, the rate of cross aldol decreases only linearly. Therefore, the low donor aldehyde concentrations afforded by slow addition should bias the chemoselectivity of this process toward the desired cross aldol event.

As we had anticipated, syringe pump addition of propionaldehyde to a stirring suspension of proline, DMF, and a slight excess of the aldehyde aldol acceptor effectively suppressed propionaldehyde homodimerization, leading to useful amounts of the desired cross aldol products (Table 2, entries 1-5, 80 to 88% yield). Indeed, propionaldehyde can be used effectively as an aldol donor for a broad range of aldehyde aldol acceptors—including both alkyl (entries 1 to 3, 5, 80 to 88% yield, 97 to 99% ee) and aromatic aldehydes (entry 4, 81% yield, 99% ee). Of particular note is entry 2 as both aldol donor and aldol acceptor both bear two enolizable α-protons, yet only a single regioisomer of the cross-aldol reaction is detectable by ^{1}H NMR and is formed in 88% yield and 97% ee. The regiochemical course of that reaction is the likely result of the difference in steric demand of the two possible enamines. This cross aldol reaction can tolerate a range of differently substituted aldehyde aldol donors (entries 5 to 7, R_2 = Me, *n*-Bu, Bn, 95:5 to 96:4 *anti*:*syn*, 91 to >99% ee) while maintaining suitably high levels of regio- and enantiocontrol.

Table 2. Proline–Catalyzed Aldehyde Cross Aldol Reactions



entry	R^1	R^2	Product	% yield[a]	*anti*:*syn*[b]	% ee[c,d]
1	Me	Et		80	4:1	99
2	Me	*i*-Bu		88	3:1	97
3	Me	*c*-C_6H_{11}		87	14:1	99
4	Me	Ph		81	3:1	99
5	Me	*i*-Pr		82	24:1	>99
6[e]	*n*-Bu	*i*-Pr		80	24:1	98
7[e]	Bn	*i*-Pr		75	19:1	91

[a]Relative stereochemistry assigned by direct comparison to literature spectra or by analogy. [b]Determined by GLC analysis of the 2,2-dimethylpropylidine acetal or by HPLC analysis of the corresponding 1,3-diol. [c]Absolute stereochemistry determined by chemical correlation to a known compound or by analogy. [d]Reaction conducted at room temperature.

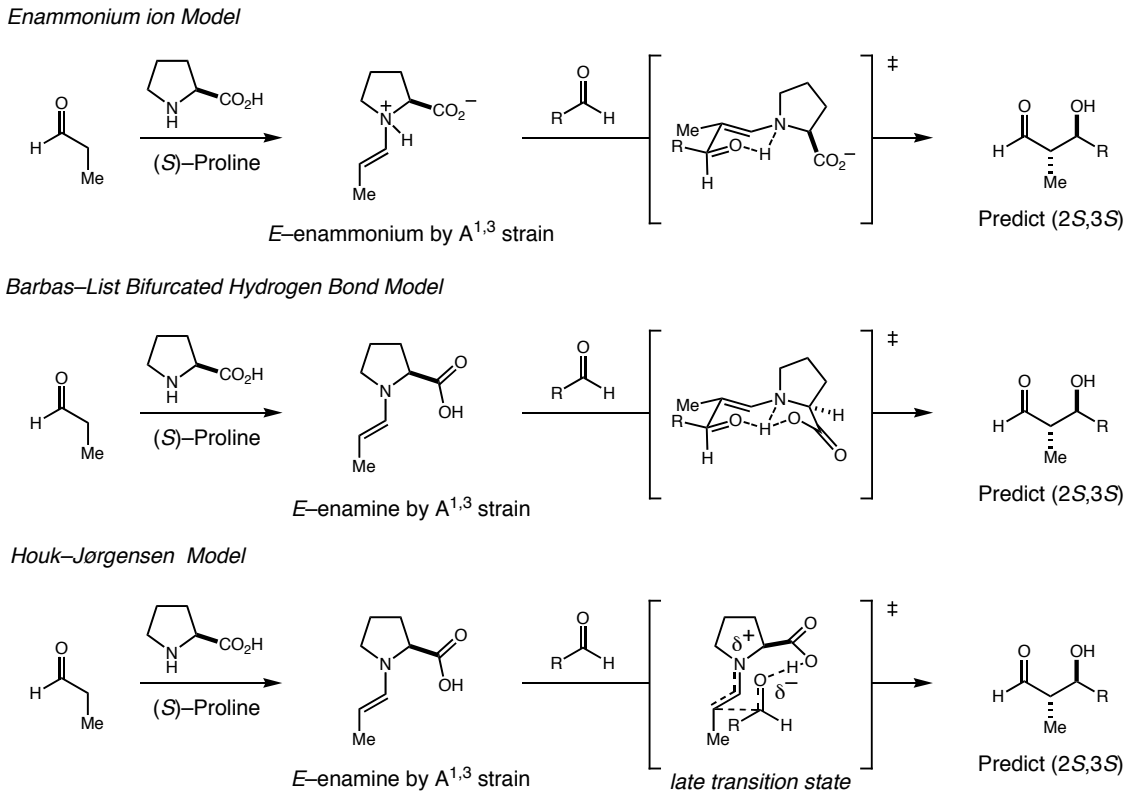
In contrast to previously reported proline-catalyzed aldol reactions, lower catalyst loadings (10 mol%) and shorter reaction times (11 to 26 hours) were possible while maintaining high levels of reaction efficiency. To illustrate the preparative utility of this new cross-aldol process, entry 5 of Table 2 was performed on a 25 mmol scale to afford

2.65g (82% yield) of (2*S,* 3*S*)-3-hydroxy-2, 4-dimethylpentanal in 96:4 *anti*:*syn* and >99% ee.

Stereochemical Rationale

The sense of both the absolute and the relative configurations of the products are in complete accord with the three proposed models for proline-catalyzed reactions (Figure 22).[19]

Figure 22. Predictive Stereochemical Models for Proline-Catalyzed Aldol Reaction



While the models in Figure 22 accurately predict both the relative and absolute stereochemistry observed in the proline-catalyzed aldehyde aldol reaction, they each

[19] Enammonium ion model: (a) Brown, S. P.; Brochu, M. P.; Sinz, C. J.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2003**, *125*, 10808. Barbas–List model: (b) List, B.; Lerner, R. A.; Barbas, C. F. III *J. Am. Chem. Soc.* **2000**, *122*, 2395. Houk–Jørgensen model: (c) Allemann, C.; Gordillo, R.; Clemente, F. R.; Cheong, P. H. –Y; Houk, K. N. *Acc. Chem. Res.* **2004**, *37*, ASAP, 7/17/04. (d) Bøgevig, A.; Kumaragurubaran, N.; Jørgensen, K. A. *Chem. Commun.* **2002**, 620.

imply different transition state structures. The primary difference between the three models concerns the bonding of acceptor-activating acidic proton in the transition state. The enammonium proposal from our group postulates full protonation of the enamine in the transition state with no interaction of the carboxylate moiety. Houk and Jørgensen invoke proton transfer to a nascent alkoxide from a carboxylic acid. Barbas and List provide an intermediate view of the proton's position in the transition state while still favoring a reactive enamine intermediate.

Conclusions and Future Directions

In summary, two new methods for the direct enantioselective catalytic aldol reaction using aldehydes as both the aldol donor and the aldol acceptor have been described. The first method utilizes an imidazolidinone catalyst to produce protected β-hydroxyaldehydes. Later, it was found that proline was also able to catalyze the aldehyde aldol reaction. The proline-catalyzed method is complementary to the imidazolidinone-catalyzed aldehyde aldol reaction in that it produces unprotected β-hydroxyaldehydes. Therefore, it is expected that proline-catalyzed aldol reactions will find many applications in polyketide synthesis as this key new aldol technology should allow the execution of a highly efficient iterative aldehyde aldol strategy. The following chapters will describe the invention of more aldehyde aldol technologies and their application to the synthesis of complex natural products.

Supporting Information

General Information. Commercial reagents were purified prior to use following the guidelines of Perrin and Armarego.[20] Dimethylformamide was obtained from EM Science in a DriSolv™ container and used as supplied. Non-aqueous reagents were transferred under nitrogen via syringe or cannula. Organic solutions were concentrated under reduced pressure on a Büchi rotary evaporator using an ice-water bath. Chromatographic purification of products was accomplished using forced-flow chromatography on ICN 60 32-64 mesh silica gel 63 according to the method of Still.[21] Thin-layer chromatography (TLC) was performed on EM Reagents 0.25 mm silica gel 60-F plates. Visualization of the developed chromatogram was performed by fluorescence quenching or by anisaldehyde stain.

^{1}H and ^{13}C NMR spectra were recorded on a Mercury 300 (300 MHz and 75 MHz) as noted, and are internally referenced to residual protio solvent signals. Data for ^{1}H NMR are reported as follows: chemical shift (δ ppm), multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet), integration, coupling constant (Hz) and assignment. Data for ^{13}C NMR are reported in terms of chemical shift. IR spectra were recorded on a Perkin Elmer Paragon 1000 spectrometer and are reported in terms of frequency of absorption (cm^{-1}). Mass spectra were obtained from the UC Irvine Mass Spectral facility. Gas liquid chromatography (GLC) was performed on Hewlett-Packard 6850 and 6890 Series gas chromatographs equipped with a split-mode capillary injection system and flame ionization detectors using a Bodman Chiraldex β-DM (30 m x 0.25

[20]Perrin, D. D.; Armarego, W. L. F. *Purification of Laboratory Chemicals;* 3rd ed., Pergamon Press, Oxford, 1988.

[21]Still, W. C.; Kahn, M.; Mitra, A. J. *J. Org. Chem.* **1978,** *43*, 2923.

mm) column or an ASTEC Chiraldex β-BP (30 m x 0.25 mm) as noted. High performance liquid chromatography (HPLC) was performed on Hewlett-Packard 1100 Series chromatographs using a Chiralcel AD column (25 cm) and AD guard (5 cm) or a Chiralcel OJ column (25 cm) and OJ guard (5 cm) as noted.

(2*S*, 3*S*)-3-Hydroxy-2-methylpentanal (Table 2, entry 1). A suspension of freshly distilled propionaldehyde (3.61 mL, 50 mmol) and L-proline in 25.0 mL of dimethylformamide was stirred at 4 ºC for 10 h. The resulting solution was diluted with diethyl ether and washed successively with water and brine. The combined aqueous layers were back-extracted with 3 portions of dichloromethane. The organic layers were combined, dried over anhydrous $MgSO_4$, and concentrated *in vacuo*. Flash chromatography (5:2 pentane : diethyl ether) afforded the title compound as a clear, colorless oil in 80% yield (2.31 g, 20 mmol), 99% ee, and 4:1 *anti*:*syn*. Analytical data for this compound are identical in every respect to the previously reported values, with the exception of optical rotation, which has not been reported.[22] $[\alpha]_D = -14.7$ (c = 1.0, $CHCl_3$). The product ratios were determined by GLC analysis of the acetal derived from 2,2-dimethylpropane-1,3-diol (obtained by the method of Yamamoto[23]) using a Bodman Chiraldex β-DM (30 m x 0.25 mm) column (110 ºC isotherm, 23 psi); (2*S*, 3*S*) *anti* isomer t_r = 24.6 min, (2*R*, 3*R*) *anti* isomer t_r = 25.5 min, (2*R*, 3*S*) and (2*S*, 3*R*) *syn* isomers t_r = 22.4 min.

[22] Mahrwald, R.; Costisella, B,; Guendogan, B. *Synthesis*, **1998**, 262.

[23] Furuta, K.; Shimizu, S.; Miwa, S.; Yamamoto, Y. *J. Org. Chem.* **1989**, *54*, 1481.

(2*S*, 3*S*)-3-Hydroxy-2,5-dimethylhexanal (Table 2, entry 2). A solution of freshly distilled propionaldehyde (144 μL, 2.0 mmol) in 500 μL dimethylformamide pre-cooled to 4 ºC was added slowly over the course of 2.5 h to a stirring suspension of isovaleraldehyde (107 μL, 1.0 mmol), L-proline (11.5 mg, 0.10 mmol) and 500 μL dimethylformamide at 4 ºC. After 16 h, the resulting solution was diluted with diethyl ether and washed successively with water and brine. The combined aqueous layers were back-extracted with 3 portions of dichloromethane. The organic layers were combined, dried over anhydrous $MgSO_4$, and concentrated *in vacuo*. Flash chromatography (20:7 pentane:diethyl ether) afforded the title compound as a clear, colorless oil in 88% yield (126 mg, 0.88 mmol), 97% ee and 3:1 *anti*:*syn*. IR (film) 3419, 2958, 2935, 2872, 1719, 1466, 1368, 1152, 1098, 1062, 1025, 976.5 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 9.75 (d, *J* = 1.5 Hz, 1H, CHO); 3.89 (ddd, 1H, *J* = 9.9, 6.6, 2.7 Hz, 1H, C**H**OH); 2.44 (m, 1H, C**H**CH_3); 1.83 (m, 1H, C**H**$(CH_3)_2$); 1.47 (m, 1H, CH_2); 1.26 (m, 1H, CH_2); 1.14 (d, 3H, *J* = 7.2 Hz, C**H$_3$**CHCHO); 0.97 (d, 3H, *J* = 5.1 Hz, (C**H$_3$**)$_2$CH); 0.92 (d, 3H, *J* = 6.6 Hz, (C**H$_3$**)$_2$CH); ^{13}C NMR (75 MHz, $CDCl_3$) δ 205.5, 70.9, 52.8, 44.0, 34.5, 24.1, 21.8, 11.1; HRMS (CI) exact mass calcd for $[M + H]^+$ ($C_8H_{17}O_2$) requires *m/z* 145.1228, found *m/z* 145.1225; $[\alpha]_D$ = – 33.6 (c = 1.0, $CHCl_3$). The product ratios were determined by GLC analysis of the acetal derived from 2,2-dimethylpropane-1,3-diol (obtained by the method of Yamamoto[14]) using a Bodman Chiraldex β-DM (30 m x 0.25 mm) column (100 ºC isotherm, 23 psi); (2*S*, 3*S*) *anti* isomer t_r = 50.8 min, (2*R*, 3*R*) *anti* isomer t_r = 53.2 min, (2*R*, 3*S*) and (2*S*, 3*R*) *syn* isomers t_r = 45.5 min.

(2*S*, 3*S*)-3-Cyclohexyl-3-hydroxy-2-methylpropanal (Table 2, entry 3). A solution of freshly distilled propionaldehyde (72 μL, 1.0 mmol) in 500 μL dimethylformamide pre-cooled to 4 ºC was added slowly over the course of 20 h to a stirring suspension of cyclohexane carboxaldehyde (242 μL, 2.0 mmol), L-proline (11.5 mg, 0.10 mmol) and 500 μL dimethylformamide at 4 ºC. After 22 hours, the resulting solution was diluted with diethyl ether and washed successively with water and brine. The combined aqueous layers were back-extracted with 3 portions dichloromethane. The organic layers were combined, dried over anhydrous $MgSO_4$, and concentrated *in vacuo*. Flash chromatography (20:7 pentane:diethyl ether) afforded the title compound as a clear, colorless oil in 87% yield (148 mg, 0.87 mmol), 99% ee and 93:7 *anti* : *syn*. IR (film) 3438, 2928, 2853, 1722, 1450, 1396, 1376, 1314, 1186, 1112, 1063, 975.8, 893.2, 847.5 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 9.75 (d, 1H, J = 2.1 Hz, CHO); 3.53 (dd, 1H, J = 7.2, 4.8 Hz, C**H**OH); 2.58 (m, 1H, C**H**CH_3); 1.8-1.0 (br m, 11H, cyclohexyl); 1.10 (d, 3H, J = 7.2 Hz, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 206.1, 77.1, 49.2, 40.7, 30.3, 26.73, 26.69, 26.68, 26.4, 11.4; HRMS (CI) exact mass calcd for $[M + H]^+$ ($C_{10}H_{19}O_2$) requires *m/z* 171.1385, found *m/z* 171.1386. $[\alpha]_D$ = –5.1 (c = 1.0, $CHCl_3$). The product ratios were determined by GLC analysis of the corresponding 4-cyclohexyl-2,2,5-trimethyl-[1,3]dioxane (obtained by $NaBH_4$ reduction followed by acetonide protection of the 1,3-diol according to the method of Goto *et al.*[24]) using a Bodman Chiraldex β-DM (30 m x 0.25 mm) column (110 ºC isotherm, 23 psi); (2*S*, 3*S*) *anti* isomer t_r = 17.8 min, (2*R*, 3*R*) *anti* isomer t_r = 18.7 min, (2*R*, 3*S*) and (2*S*, 3*R*) *syn* isomers t_r = 21.0, 22.2 min.

[24] Kitamura, M.; Isobe, Y.; Ichikawa, Y.; Goto, T. *J. Am. Chem. Soc.* **1984**, *106*, 3252.

Determination of the absolute stereochemistry of (2*S*, 3*S*)-3-Cyclohexyl-3-hydroxy-2-methylpropanal by correlation to (*2S*, 3*S*)-3-cyclohexyl-3-hydroxy-2-methylpropionic acid methyl ester. A stirring solution of (2*S,* 3*S*)-3-cyclohexyl-3-hydroxy-2-methylpropanal (77 mg, 0.45 mmol) in 3.0 mL of ethanol was treated sequentially with a solution of $AgNO_3$ (123 mg, 0.73 mmol) in 2.0 mL of water and a solution of NaOH (123 mg, 3.1 mmol) in 3.0 mL of 2:1 ethanol:water. After stirring for 4 hours, the mixture was filtered through celite, and the filter cake was rinsed with several portions of ethyl acetate. The filtrate was then washed with 1N HCl and the aqueous layer was back-extracted with ethyl acetate. The combined organic extracts were dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo*. The residue was then dissolved in 8.0 mL of methanol and trimethylsilyldiazomethane (2.0 M in hexane) was added until a yellow color persisted. Excess diazomethane was quenched by the dropwise addition of acetic acid. The resulting colorless solution was then diluted with ether, washed successively with 10% $NaHCO_3$ and brine, dried over anhydrous $MgSO_4$, and concentrated *in vacuo*. Flash chromatography (5–10% ethyl acetate in hexanes, linear gradient) afforded a 71% yield (63 mg, 0.32 mmol) of (*2S*, 3*S*)-3-cyclohexyl-3-hydroxy-2-methylpropionic acid methyl ester; $[\alpha]_D$ = + 5.1 (c = 1.05, $CHCl_3$) (lit.[25] $[\alpha]_D$ = – 8.1 (c = 1.05, $CHCl_3$) for (*2R*, 3*R*)-3-cyclohexyl-3-hydroxy-2-methylpropionic acid methyl ester).

(2*S*, 3*S*)-3-Hydroxy-2-methyl-3-phenyl-propionaldehyde (Table 2, entry 4). A solution of freshly distilled propionaldehyde (72 μL, 1.0 mmol) in 500 μL

[25] Meyers, A. I.; Yamamoto, Y. *J. Am. Chem. Soc.* **1981**, *103*, 4278.

dimethylformamide pre-cooled to 4 ºC was added slowly over the course of 16 h to a stirring suspension of benzaldehyde (1.02 mL, 10 mmol), L-proline (11.5 mg, 0.10 mmol) and 4.5 mL dimethylformamide at 4 ºC. After 16 hours, the resulting solution was diluted with ethyl acetate and washed successively with water and brine. The combined aqueous layers were back-extracted with 3 portions of dichloromethane. The organic layers were combined, dried over anhydrous Na_2SO_4, and then concentrated. Flash chromatography (4:1 hexanes:ethyl acetate) afforded the title compound as a clear, colorless oil in 81% yield (132 mg, 0.81 mmol), 99% ee and 3:1 *anti*:*syn*. Analytical data for this compound are identical in every respect to the previously reported with the exception of optical rotation which has not been reported.[9] $[\alpha]_D = +9.1$ (c = 1.0, $CHCl_3$). The product ratios were determined by HPLC analysis of the corresponding alcohol (obtained by $NaBH_4$ reduction) using a Chiracel AD and AD guard column (1.0 % isopropanol/hexanes, 1 mL/min); (2*S*, 3*S*) *anti* isomer t_r = 147.5 min, (2*R*, 3*R*) *anti* isomer t_r = 161.1 min, (2*R*, 3*S*) and (2*S*, 3*R*) *syn* isomers t_r = 173.0, 200.0 min.

(2*S*, 3*S*)-3-Hydroxy-2,4-dimethylpentanal (Table 2, entry 5). A solution of freshly distilled propionaldehyde (1.81 mL, 25.0 mmol) in 12.5 mL dimethylformamide pre-cooled to 4 ºC was added slowly over the course of 20 h to a stirring suspension of isobutyraldehyde (4.54 mL, 50 mmol), L-proline (288 mg, 2.5 mmol) and 12.5 mL dimethylformamide at 4 ºC. After 30 h, the resulting solution was diluted with diethyl ether and washed successively with water and brine. The combined aqueous layers were back-extracted with 3 portions of dichloromethane. The organic layers were combined, dried over anhydrous $MgSO_4$, and concentrated *in vacuo*. Flash chromatography (20:7

pentane:diethyl ether) afforded the title compound as a clear, colorless oil in 82% yield (2.65 g, 20.6 mmol), >99% ee and 96:4 *anti*:*syn*. Analytical data for this compound are identical in every respect to the previously reported values with the exception of optical rotation which has not been reported.[9] $[\alpha]_D = -17.9$ (c = 1.0, $CHCl_3$). The product ratios were determined by GLC analysis of the acetal derived from 2,2-dimethylpropane-1,3-diol (obtained by the method of Yamamoto[14]) using a Bodman Chiraldex β-DM (30 m x 0.25 mm) column (110 ºC isotherm, 23 psi); (2*S*, 3*S*) *anti* isomer t_r = 31.8 min, (2*R*, 3*R*) *anti* isomer t_r = 33.9 min, (2*R*, 3*S*) and (2*S*, 3*R*) *syn* isomers t_r = 29.4, 29.8 min.

Determination of the absolute stereochemistry of (2*S,* 3*S*)-3-Hydroxy-2,4-dimethylpentanal by correlation to (*2S*, 3*S*)-3-hydroxy-2,4-dimethylpentanoic acid methyl ester. A stirring solution of (2*S,* 3*S*)-3-hydroxy-2,4-dimethylpentanal (101 mg, 0.63 mmol) in 3.0 mL of ethanol was treated sequentially with a solution of $AgNO_3$ (170 mg, 1.0 mmol) in 2.0 mL of water and a solution of NaOH (171 mg, 4.3 mmol) in 3.0 mL of 2:1 ethanol:water. After stirring for 4 hours, the mixture was filtered through celite, and the filter cake was rinsed with several portions of ether. The filtrate was then washed with 1N HCl and the aqueous layer was back-extracted with ether. The combined organic extracts were dried over anhydrous $MgSO_4$, filtered, and concentrated *in vacuo*. The residue was then dissolved in 8.0 mL of methanol, and trimethylsilyldiazomethane (2.0 M in hexane) was added until a yellow color persisted. Excess diazomethane was quenched by the dropwise addition of acetic acid. The resulting colorless solution was then diluted with ether, washed successively with 10% $NaHCO_3$ and brine, dried over anhydrous $MgSO_4$, and concentrated *in vacuo*. Flash chromatography (5–25% ether in

pentane, linear gradient) afforded a 39% yield (47 mg, 0.25 mmol) of (*2S*, 3*S*)-3-hydroxy-2,4-dimethylpentanoic acid methyl ester; $[\alpha]_D$ = +7.6 (c = 0.85, $CHCl_3$) (lit.[26] $[\alpha]_D$ = +11.1 (c = 0.85, $CHCl_3$).

(2*S*)-2-[(1*S*)-1-hydroxy-2-methylpropyl]hexanal (Table 2, entry 6). A solution of freshly distilled hexanal (120 μL, 1.0 mmol) in 500 μL dimethylformamide was added slowly over the course of 24 h to a stirring suspension of isobutyraldehyde (272 μL, 3.0 mmol), L-proline (11.5 mg, 0.10 mmol) and 500 μL dimethylformamide at room temperature. After 24 h, the resulting solution was diluted with diethyl ether and washed successively with water and brine. The combined aqueous layers were back-extracted with 3 portions dichloromethane. The organic layers were combined, dried over anhydrous $MgSO_4$, and concentrated *in vacuo*. Flash chromatography (7:3 pentane:diethyl ether) afforded the title compound as a clear, colorless oil in 80% yield (127 mg, 0.80 mmol), 98% ee and 96:4 *anti* : *syn*. IR (film) 3458, 2960, 2934, 2874, 2725, 1720, 1467, 1328, 1220, 1146, 1024, 991.2, 959.9, 901.1, 775.6 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 9.75 (d, 1H, *J* = 3.3 Hz, CHO); 3.56 (dd (apparent q), 1H, *J* = 6.0, 5.7 Hz, C**H**OH); 2.46 (dddd, 1H, *J* = 8.4, 5.7, 5.7, 3.3 Hz, C**H**CH_2); 1.99 (d, 1H, *J* = 6.0 Hz, OH); 1.82 (m, 1H, C**H**$(CH_3)_2$); 1.70 (m, 1H, CHC$\mathbf{H_2}$); 1.58 (m, 1H, CHC$\mathbf{H_2}$); 1.30 (m, 4H, C$\mathbf{H_2}$C$\mathbf{H_2}$CH3); 0.97 (d, 3H, *J* = 6.6 Hz, CH(C$\mathbf{H_3}$)$_2$); 0.93 (d, 3H, *J* = 6.6 Hz, CH(C$\mathbf{H_3}$)$_2$); 0.90 (dd (apparent t), 3H, *J* = 6.6, 6.6 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 206.1, 76.7, 54.9, 31.3, 29.5, 26.7, 23.2, 20.0, 17.1, 14.2; HRMS (CI) exact mass calcd for $[M + H]^+$ ($C_{10}H_{21}O_2$) requires *m/z* 173.1541, found *m/z* 173.1540; $[\alpha]_D$ = –15.4 (c =

[26] Oppolzer, W.; Starkemann, C.; Rodriguez, I.; Bernardinelli, G. *Tet. Lett.* **1991**, *32*, 61.

1.0, $CHCl_3$). The product ratios were determined by GLC analysis of the acetal derived from 2,2-dimethylpropane-1,3-diol (obtained by the method of Yamamoto[14]) using a Bodman Chiraldex β-DM (30 m x 0.25 mm) column (110 ºC isotherm, 23 psi); (2*S*, 3*S*) *anti* isomer t_r = 97.8 min, (2*R*, 3*R*) *anti* isomer t_r = 102.7 min, (2*R*, 3*S*) and (2*S*, 3*R*) *syn* isomers t_r = 94.4, 96.5 min.

(2*S*, 3*S*)-2-Benzyl-3-hydroxy-4-methylpentanal (Table 2, entry 7). A solution of freshly distilled hydrocinnamaldehyde (132 μL, 1.0 mmol) in 500 μL dimethylformamide was added slowly over the course of 24 h to a stirring suspension of isobutyraldehyde (272 μL, 3.0 mmol), L-proline (11.5 mg, 0.10 mmol) and 500 μL dimethylformamide at room temperature. After 26 h, the resulting solution was diluted with ethyl acetate and washed successively with water and brine. The combined aqueous layers were back-extracted with 3 portions dichloromethane. The organic layers were combined, dried over anhydrous Na_2SO_4, and concentrated *in vacuo*. Flash chromatography (3:1 hexanes:ethyl acetate) afforded the title compound as a clear, colorless oil in 75% yield (155 mg, 0.75 mmol), 91% ee and 95:5 *anti* : *syn*. IR (film) 3466, 3086, 3063, 3028, 2962, 2932, 2834, 2733, 1950, 1875, 1806, 1722, 1604, 1496, 1454, 1390, 1368, 1244, 1180, 1136, 1049, 1031, 993.0, 964.3, 849.7, 800.6, 739.8, 700.2 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 9.83 (d, 1H, *J* = 2.1 Hz, CHO); 7.27 (m, 5H, Ar-H); 3.43 (ddd, 1H, *J* = 6.6, 6.6, 4.5 Hz, C**H**OH); 3.06 (dd, 1H, *J* = 13.2, 7.8 Hz, $PhCH_2$); 2.92 (dd, 1H, *J* = 13.2, 6.9 Hz, $PhCH_2$); 2.81 (m, 1H, C**H**CH_2); 2.15 (d, 1H, *J* = 6.0 Hz, OH); 1.90 (m, 1H, C**H**$(CH_3)_2$); 0.96 (d, 3H, *J* = 6.6 Hz, CH(C**H$_3$**)$_2$); 0.92 (d, 3H, *J* = 7.2 Hz, CH(C**H$_3$**)$_2$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 205.6, 129.2, 128.9, 128.6, 126.8, 76.9, 55.8, 33.4, 32.0, 19.7,

18.2; HRMS (CI) exact mass calcd for $[M + H]^+$ ($C_{13}H_{19}O_2$) requires *m/z* 207.1385, found *m/z* 207.1386; $[\alpha]_D = -7.9$ (c = 1.0, $CHCl_3$). The product ratios were determined by HPLC analysis of the corresponding alcohol (obtained by $NaBH_4$ reduction) using a Chiracel OJ and OJ guard column (1.0 % ethanol/hexanes, 1 mL/min); (2*S*, 3*S*) *anti* isomer t_r = 7.5 min, (2*R*, 3*R*) *anti* isomer t_r = 9.4 min, (2*R*, 3*S*) and (2*S*, 3*R*) *syn* isomers t_r = 6.3, 6.9 min.

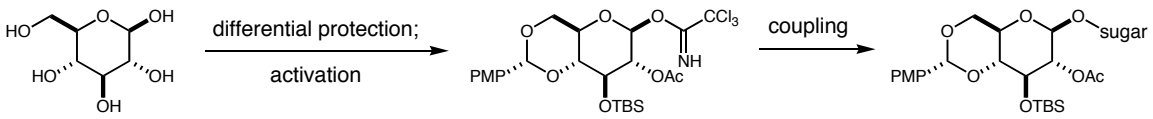
C h a p t e r 3

Proline-Catalyzed Aldol Reactions of Glycoaldehydes: Step One in a Two-Step Synthesis of Carbohydrates*

Introduction

Carbohydrates are the single largest class of natural products in the biosphere. Their chemical, structural, and functional diversity far outstrips proteins and it is, therefore, not surprising that there are no efficient, general enantioselective total syntheses of carbohydrates as efficient as those available for proteins and nucleic acids.[1] For over 100 years, the vast majority of carbohydrate syntheses begin with the selective protection of commercially available enantiopure carbohydrates to produce useful differentially protected monomers, generally requiring multiple chemical steps (Figure 1).[2]

Figure 1. Traditional Carbohydrate Synthesis Techniques



β-D-glucose

differentially-protected monosaccharide

Due to the inefficiency inherent in the traditional synthesis of carbohydrates (relative to proteins and nucleic acids) far less is known about the exact structure and biological function of carbohydrates than any other class of biomolecule. Therefore, the

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* For a preliminary communication of this work, see: Northrup, A. B.; Mangion, I. K.; Hettche, F.; MacMillan, D. W. C. *Angew. Chem. Int. Ed.* **2004**, *43*, 2152.

[1] Vogel, P. In *Glycoscience*; Fraser-Reid, B. O.; Tatsuta, K.; Thiem, J. Eds.; Springer: Berlin, 2001; Vol. 2, pp 1023-1174.

[2] *Glycoscience*; Fraser-Reid, B. O.; Tatsuta, K.; Thiem, J. Eds.; Springer: Berlin, 2001; Vol. 1.

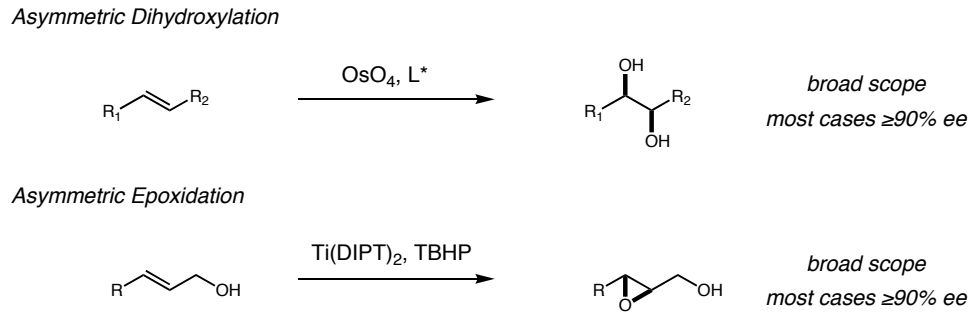
development of an efficient and general strategy for the synthesis of carbohydrates would greatly facilitate their study and would be a key enabling technology for glycobiology.

De Novo Carbohydrate Synthesis

The *de novo* total synthesis of carbohydrates from achiral precursors remains a significant synthetic challenge. Even simple hexopyranoses are densely functionalized, containing five contiguous stereocenters and only six carbon atoms. To date, there have been some impressively clever hexose syntheses developed since the base-promoted oligomerization of formaldehyde to form a mixture of hexoses was discovered in 1861.[3] Those hexose syntheses can be divided into several strategic classes—asymmetric oxidation, allylation/oxidation, hetero-Diels-Alder, and aldol.

Asymmetric olefin oxidation technology has been, perhaps, the most widely utilized of sugar-producing strategies due to the generality and consistently high enantioselectivity afforded by the chiral catalysts employed to set vicinal oxygen stereochemical relationships (Figure 2).[4]

Figure 2. Asymmetric Dihydroxylation and Epoxidation Strategies

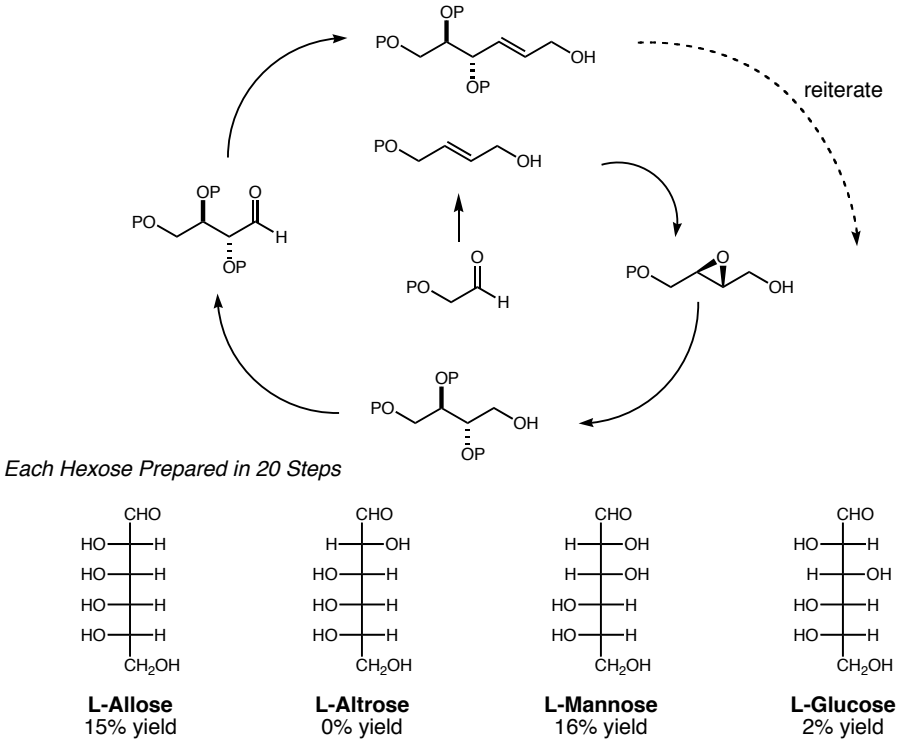


[3] Von Butlerow, A. *CR Séances Acad. Sci.* **1861**, *53*, 145.

[4] For a review of the asymmetric dihydroxylation reaction, see: (a) Kolb, H. C.; VanNieuwenhze, M. S.; Sharpless, K. B. *Chem. Rev.* **1994**, *94*, 2483. For reviews of asymmetric epoxidation reactions, see: (b) Yang, D. *Acc. Chem. Res.* **2004**, *37*, 497. (c) Aggarwal, V. K.; Winn, C. L. *Acc. Chem. Res.* **2004**, *37*, 611. (d) Jacobsen, E. N.; Wu, M. H. *Comprehensive Asymmetric Catalysis* **1999**, *2*, 649. (e) Katsuki, T. *Comprehensive Asymmetric Catalysis* **1999**, *2*, 621.

As Figure 3 illustrates, that strategy allows access to each of the aldohexoses due to the ability to use asymmetric catalysis or epimerization to set each of the stereocenters, albeit in a lengthy linear synthesis.[5] Furthermore, due to the requirement of acetonides as protecting groups for reasons of stereochemistry, this strategy is not amenable to the production of the highly differentially protected sugars necessary for polysaccharide synthesis.

Figure 3. Asymmetric Epoxidation Used to Synthesize the L-Hexoses



Due to the availability of enantiopure chiral allyl-metal reagents, the allylation of aldehydes has become a popular method for the construction of complex polyols, such as carbohydrates (Figure 4).[6]

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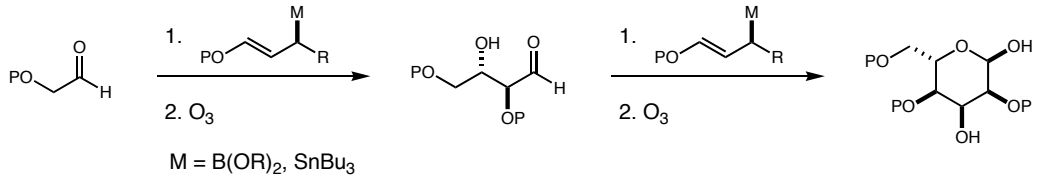
[5] Ko, S. Y.; Lee, A. W. M.; Masamune, S.; Reed, L. A. III; Sharpless, K. B.; Walker, F. J. *Science* **1983**, *220*, 949.

[6] Allylic stannanes: (a)Marshall, J. A. *Chem. Rev.* **1996**, *96*, 31. Allylic boronates: (b) Roush, W. R.; Hoong, L. K.; Palmer, M. A. J.; Straub, J. A.; Palkowitz, A. D. *J. Org. Chem.* **1990**, *55*, 4117. (c) Roush, W. R.; Straub, J. A.; Van Nieuwenhze, M. S. *J. Org. Chem.* **1991**, *56*, 1636. (d) Roush, W. R.; Lin, W.; Straub, J. A. *J. Org. Chem.* **1991**, *36*, 1649.

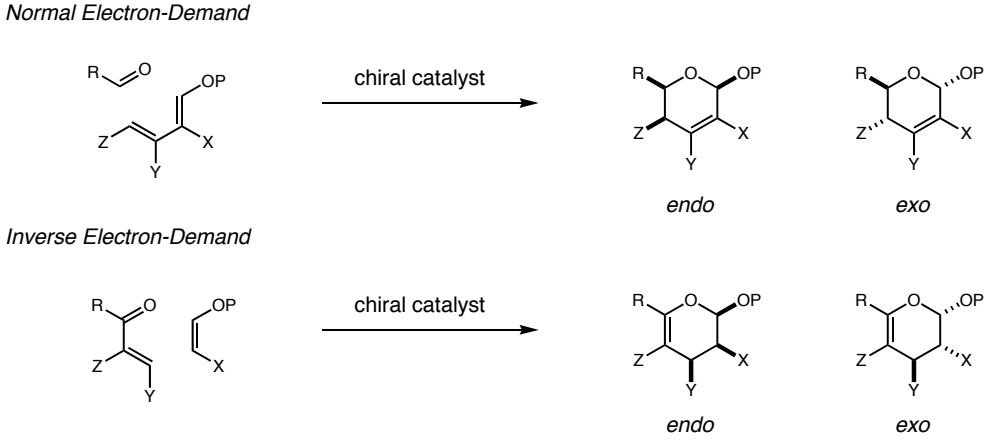
Figure 4. Allylmetal Reagents in Carbohydrate Synthesis



The primary disadvantages of that method are the lengthy syntheses required to produce the chiral metal reagents, their toxicity, waste, and their short shelf-lives. Furthermore, as with the oxidation-based methods above, the requirement for homologation-functionalization-protection sequences significantly decreases the efficiency of that strategy.

Hetero-Diels-Alder-based strategies represent a relatively expeditious method for the preparation of hexoses due to their high convergency (Figure 5).[7]

Figure 5. The Hetero-Diels-Alder Strategy for Carbohydrate Synthesis



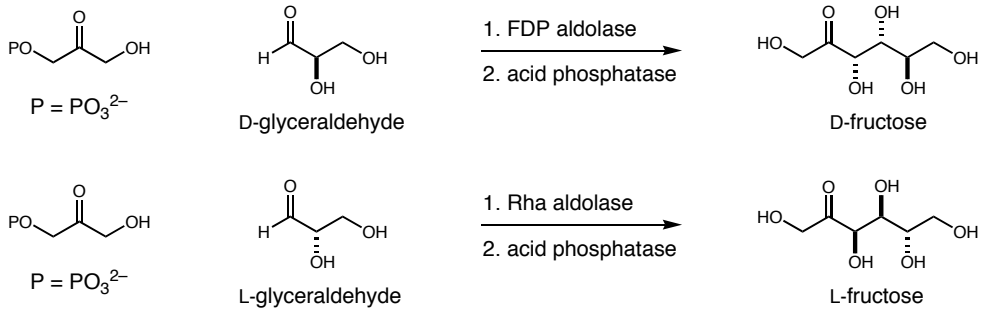
As Figure 5 explains, there are two potential Diels-Alder disconnections available for the production of unsaturated hexoses. A final oxidation provides a reasonably well differentially protected sugar. While the hetero-Diels-Alder approach constitutes an efficient strategy, the paucity of general methods for conducting the required

[7] For examples of hetero-Diels-Alder approaches to carbohydrates, see: (a) Bednarski, M.; Danishefsky, S. *J. Am. Chem. Soc.* **1986**, *108*, 7060. (b) Snider, B. B. *Acc. Chem. Res.* **1980**, *13*, 426. (c) Tietze, L. F.; Beifuss, U. *Angew. Chem. Int. Ed., Eng.* **1993**, *32*, 131. (d) Tietze, L. F.; Schneider, C.; Montenbruck, A. *Angew. Chem. Int. Ed., Eng.* **1994**, *33*, 980.

enantioselective hetero-Diels-Alder reaction severely limits its general application.[8] Furthermore, the large majority of Diels-Alder reactions afford only the *endo* diastereomer in high selectivity; therefore, this strategy cannot access all of the hexose stereochemistries.

The aldol reaction is a fundamentally important technology due to its ability to simultaneously form carbon-carbon bonds and vicinal stereocenters. Therefore, it is not surprising that the aldol reaction has found extensive use in hexose synthesis.[9] The most well documented approach utilizes kinase, aldolase, phosphatase, and isomerase enzymes with substrates, such as dihydroxyacetone, to produce a variety of ketoses and aldoses (Figure 6).[10]

Figure 6. Aldolase Enzymes Can Produce Sugars in an Efficient Manner



That powerful strategy allows the production of many useful monosaccharides for chemical synthesis, especially due to its ability to generate unnatural enantiomers of a few sugars. Unfortunately, that method cannot accommodate the use of protecting

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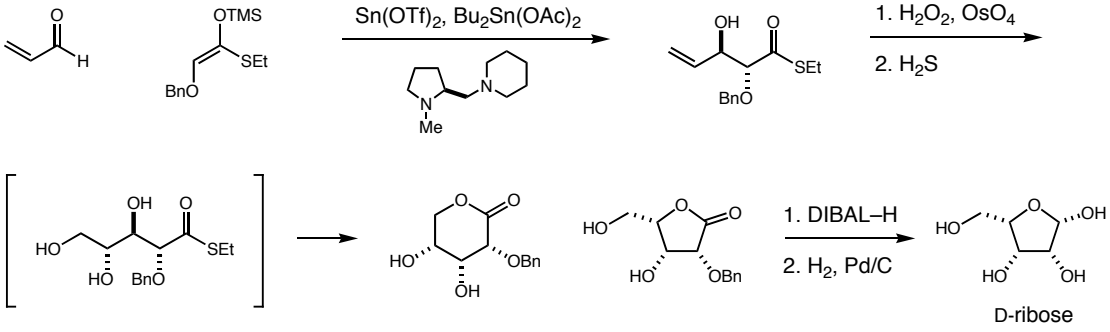
[8] For a review of the enantioselective hetero-Diels-Alder reaction, see: (a) Jørgensen, K. A. *Angew. Chem. Int. Ed.* **2000**, *39*, 3558.

[9] For recent examples of aldol reactions in the syntheses of carbohydrates, see: (a) Evans, D. A.; Hu, E.; Tedrow, J. S. *Org. Lett.* **2001**, *3*, 3133. (b) Davies, S. G.; Nicholson, R. L.; Smith, A. D. *Synlett* **2002**, *10*, 1637. (c) Sibi, M. P.; Lu, J.; Edwards, J. *J. Org. Chem.* **1997**, *62*, 5864.

[10] For a review on the use of aldolase enzymes, particularly in carbohydrate synthesis, see: (a) Machajewski, T. D.; Wong, C. –H. *Angew. Chem. Int. Ed.* **2000**, *39*, 1352. For specific examples of aldolase enzymes applied to carbohydrate synthesis, see: (b) Wong, C. –H.; Whitesides, G. M. *J. Org. Chem.* **1983**, *48*, 3199. (c) Wong, C. –H.; Mazenod, F. P.; Whitesides, G. M. *J. Org. Chem.* **1983**, *48*, 3493. (d) Durrwachter, J. R.; Drueckhammer, D. G.; Nozaki, K.; Sweers, H. M.; Wong, C. –H. *J. Am. Chem. Soc.* **1986**, *108*, 7812. (e) Whitesides, G. M.; Wong, C. –H. *Angew. Chem. Int. Ed., Eng.* **1985**, *24*, 617. (f) Wong, C. –H.; Halcomb, R. L.; Ichikawa, Y.; Kajimoto, T. *Angew. Chem. Int. Ed.* **1995**, *34*, 412.

groups due to the steric requirements of enzyme active sites. Therefore, differentially protected sugars are not accessible with enzyme-based methods. To circumvent that deficiency, other groups have employed standard metal-catalyzed aldol technology to produce sugars (Figure 7).[11]

Figure 7. Enantioselective Aldols in Carbohydrate Synthesis



As with the other *de novo* sugar syntheses, aldol methods are not as efficient as traditional selective protection strategies in terms of both expense and synthetic efficiency. Therefore, their use in polysaccharide synthesis has been limited.

In summary, while the construction of carbohydrates from achiral starting materials has been accomplished numerous times, there are still significant limitations on the aforementioned strategies. None of them are sufficiently general, efficient, and cost-effective to supplant the current practice of simply purchasing the sugar of interest and then achieving the required differentiation of the polyol. Therefore, traditional sugar chemistry protection and coupling strategies will remain the standard method for producing polysaccharides unless major advances are made in the *de novo* synthesis of protected carbohydrates.

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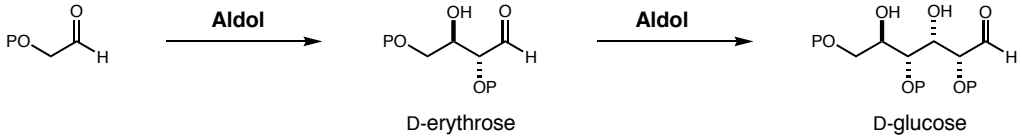
[11] For example: (a) Mukaiyama, T.; Shiina, I.; Kobayashi, S. *Chem Lett.* **1990**, 2201. (b) Kobayashi, S.; Kawasuji, T. *Synlett* **1993**, 911. and also see reference 9.

The Aldehyde Aldol Strategy for Carbohydrate Synthesis

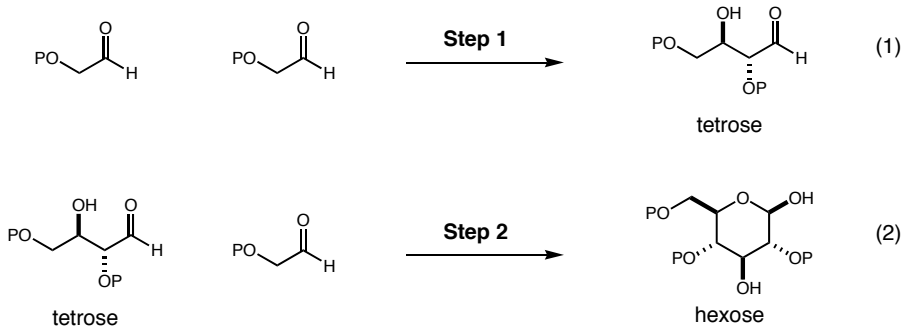
Traditional aldol techniques are inefficient for the synthesis of differentiated carbohydrates (*vide supra*). However, as discussed in the previous two chapters, the aldehyde aldol strategy erases those inefficiencies by minimizing the need for oxidation state and protecting group manipulations; therefore, the aldehyde aldol should constitute an effective strategy for the rapid synthesis of differentially protected carbohydrates (Figure 8).

Figure 8. The Iterative Aldehyde Aldol Strategy Should Constitute an Efficient Carbohydrate Synthesis



Moreover, the aldehyde aldol strategy should allow for a two-step synthesis of differentially protected aldohexoses from simple aldehyde starting materials. However, the successful invention of a two-step sugar synthesis will require the creation of two new aldehyde aldol reactions (Scheme 1). The first is the aldol coupling of two protected glycoaldehydes to form a tetrose (eq 1). The second is the cross coupling of an α-oxyaldehyde unit with a protected tetrose to form the desired differentially protected hexose product (eq 2).

Scheme 1. New Aldehyde Aldol Technologies Necessary for Two-Step Sugar Synthesis



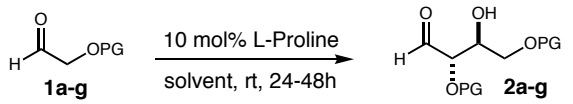
The first of those aldol steps is the subject of the research described in this chapter, and is the product of a collaborative effort with Dr. Frank Hettche and Ian Mangion in our laboratories. A discussion of the second step is deferred until Chapter 5.

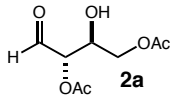
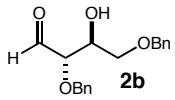
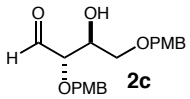
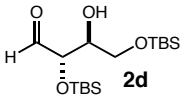
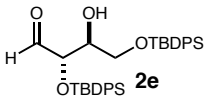
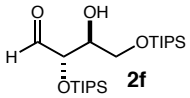
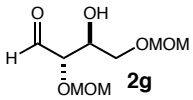
Proline-Catalyzed Aldol Dimerization of α-Oxygenated Aldehydes

Due to the ability of proline to efficiently catalyze the aldol dimerization of alkyl aldehydes (Chapter 3),[12] initial studies toward achieving a homodimerization of glycoaldehydes utilized proline as a catalyst. As Table 1 demonstrates, the choice of protecting group is essential to the efficacy of the aldol dimerization process. While unprotected glycoaldehyde was unchanged by proline (presumably due to its existence as a homodimeric acetal), a variety of protected glycoaldehydes are efficiently dimerized by proline. Aldehyde **1a**, possessing an electron-withdrawing protecting group, afforded no reaction under any conditions while aldehydes **1b** and **1c** bearing relatively electron-rich protecting groups provided increased yields (Entries 2 and 3, PG = Bn, PMB, 86% and 85% yield, respectively) and high enantioselectivity (>97% ee). Aldehydes **1e** and **1f**, bearing bulky silyl protecting groups, gave optimal results with the TIPS protected glycoaldehyde **1f** affording exceptional yield (92%), enantioselectivity (95% ee), and a chromatographically separable 4:1 mixture of *anti* and *syn* diastereomers.

[12] Northrup, A. B.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2002**, *124*, 6798.

Table 1. Proline–Catalyzed Aldol Dimerization of Glycoaldehydes



entry	product	solvent	% yield[a]	*anti*:*syn*[b]	% ee[c,d]
1	 **2a**	DMF	0	--	--
2	 **2b**	DMF	86[e]	4:1	98
3	 **2c**	DMF	85[e]	4:1	97
4[f]	 **2d**	CH_3CN	50	3:1	88
5[f]	 **2e**	DMF/ Dioxane	61	9:1	96
6	 **2f**	DMSO	92	4:1	95
7	 **2g**	DMF	42	4:1	96

[a]Yield represents the combined yield of diastereomers. [b]Relative stereochemistry assigned by correlation to a known compound. [c]Determined by chiral HPLC, see supporting information for details. [d]Absolute stereochemistry assigned by correlation to a known compound. [e]Based on recovered starting aldehyde. [f]20 mol% catalyst was employed.

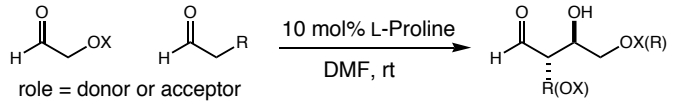
Significantly, the dimeric products from the reactions in Table 1 are protected forms of the naturally occurring sugar erythrose, a proven chiral building block in synthesis.[13] Furthermore, the ability to produce an array of differently protected erythroses will allow for the implementation of multiple different protecting group strategies on the target hexoses that will be necessary for polysaccharide synthesis.

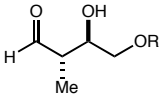
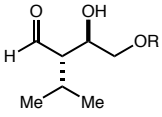
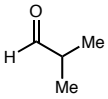
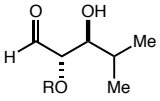
[13] For uses of erythrose in synthesis, see: (a) Pearson, W. H.; Hembre, E. J. *J. Org. Chem.* **1996**, *61*, 7217. (b) Ruiz, M.; Ojea, V.; Quintela, J. M. *Synlett* **1999**, *2*, 204. (c) Buchanan, J. G.; Edgar, A. R.; Hewitt, B. D. *J. Chem. Soc., Perkin 1* **1987**, 2371.

Cross Aldol Reactions with Glycoaldehydes

To explore the possibility of creating a variety of unnatural erythrose derivatives, we next explored the possibility of effecting cross aldol reactions employing catalytic amounts of proline as summarized in Table 2.

Table 2. Proline–Catalyzed Cross Aldol Reactions of Glycoaldehydes



entry	aldehyde α-alkyl	aldehyde OX	product	% yield[a]	*anti*:*syn*[b]	% ee[c,d]
1	 *donor*	OTIPS *acceptor*		75	4:1	99
2		OTBDPS *acceptor*		84	5:1	99
3	 *donor*	OTIPS *acceptor*		54	4:1	99
4		OBn *acceptor*		64	4:1	94
5	 *acceptor*	OTIPS *donor*		43	8:1	99
6		OBn *donor*		45	7:1	95

[a]Yield represents the combined yield of diastereomers. [b]Relative stereochemistry assigned by correlation to a known compound. [c]Determined by chiral HPLC, see supporting information for details. [d]Absolute stereochemistry assigned by correlation to a known compound.

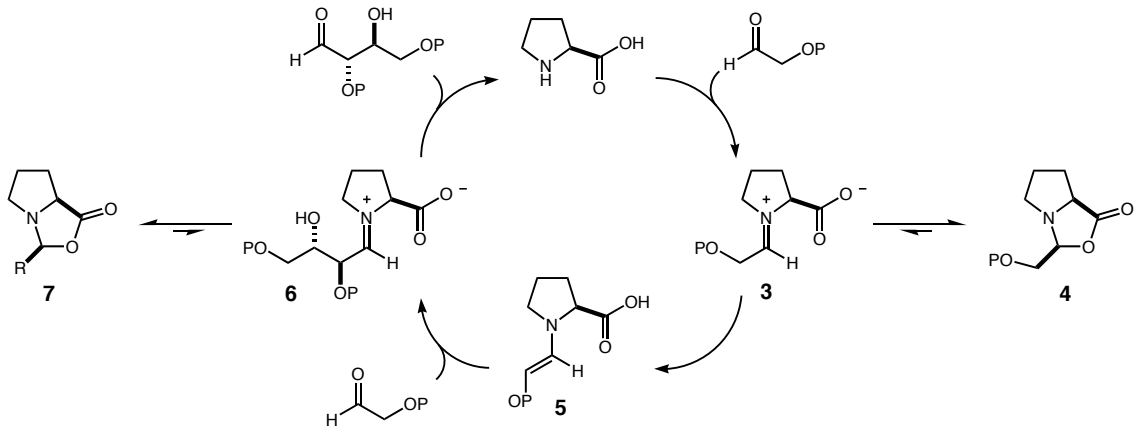
Surprisingly, the glycoaldehyde invariably acts as the electrophile in cross-aldol reactions with α-unbranched alkyl aldehydes (entries 1–4). Even the additional steric hindrance of an isopropyl-substituted nucleophile does not erode the regioselectivity of its addition to α-benzyloxyacetaldehyde (entries 3 and 4, 54–64% yield, 4:1 *anti*:*syn*, 94–99% ee). Based on the efficiency of the dimerization of aldehydes **1b** and **1f**, we explored their utility as aldol donors. However, they functioned with only moderate efficiency as aldol

donors with bulky aldehydes such as isobutyraldehyde (entries 5 and 6, 43–45% yield, 7:1–8:1 *anti*:*syn*, 95–99% ee) forming significant amounts of homodimers **2b** and **2f**.

On the Regioselectivity of Glycoaldehyde Cross Aldol Reactions

These organocatalytic results stand in marked contrast to metal-mediated direct aldol technologies[14] where the increased acidity and nucleophilicity afforded by α-oxygenated aldol donors greatly enhances their effectiveness relative to their all-alkyl counterparts. The divergent reactivity of metal and organic catalysts in aldol reactions with α-oxygenated substrates prompted us to probe the proposed mechanism of this reaction (Figure 9).

Figure 9. Proposed Catalytic Cycle for Proline–Catalyzed Aldehyde Aldol

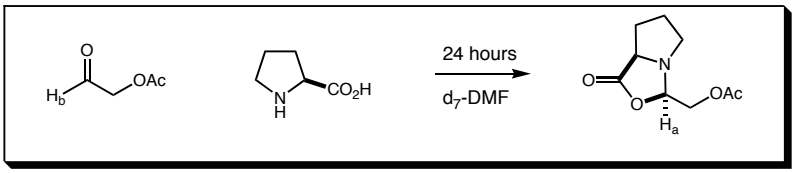


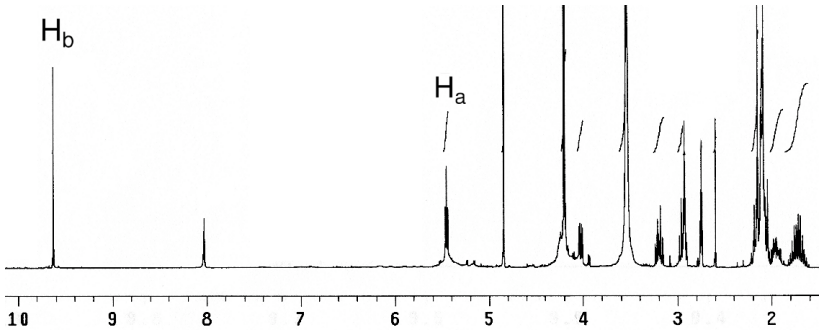
Initial investigations have implicated the importance of *N*,*O*–acetals **4** (detected by ^{1}H NMR in DMF-d_7 as ≥60% of the soluble proline) in determining the course of

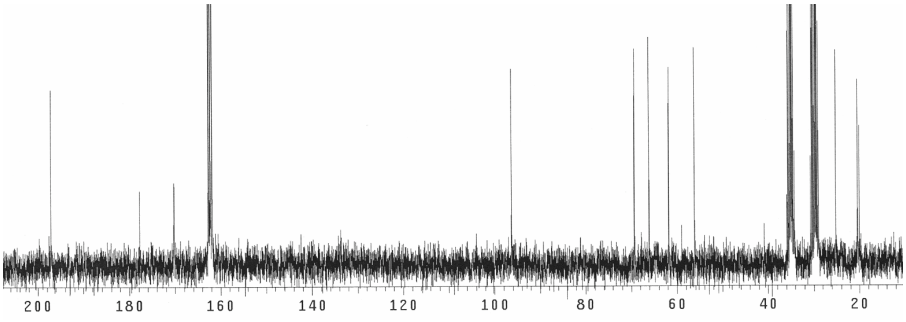
[14] For examples of metal-mediated direct aldol reactions see: (a) Yamada, Y. M. A.; Yoshikawa, N.; Sasai, H.; Shibasaki, M. *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 1871. (b) Yoshikawa, N.; Kumagai, N.; Matsunaga, S.; Moll, G.; Oshima, T.; Suzuki, T.; Shibasaki, M. *J. Am. Chem. Soc.* **2001**, *123*, 2466. (d) Kumagai, N.; Matsunaga, S.; Yoshikawa, N.; Oshima, T.; Shibasaki, M. *Org. Lett.* **2001**, *3*, 1539. (e) Trost, B. M.; Ito, H. *J. Am. Chem. Soc.* **2000**, *122*, 12003. (f) Trost, B. M.; Silcoff, E. R.; Ito, H. *Org. Lett.* **2001**, *3*, 2497. (g) Evans, D. A.; Tedrow, J. S.; Shaw, J. T.; Downey, C. W. *J. Am. Chem. Soc.* **2002**, *124*, 392. (h) Evans, D. A.; Downey, C. W.; Shaw, J. T.; Tedrow, J. S. *Org. Lett.* **2002**, *4*, 1127.

these aldol reactions (*cf.* Chapter 3). Surprisingly, no enamine or iminium ion content was detected at any point during the course of these studies. However, the electronic influence of substituents on the aldehyde undergoing dimerization strongly suggests the intermediacy of an iminium ion such as **3** (Figure 9) rather than a deprotonation of *N*,*O*–acetal **4** leading to enamine **5**. For glycoaldehydes bearing an electron-withdrawing protecting group (*e.g.*, Table 1, entry 1, PG = Ac, 0% yield), the propensity for the *N*,*O*-acetal **4a** to convert to iminium ion **3a** likely decreases due to electrostatic destabilization of iminium ion **3a**—driving the parasitic equilibrium toward **4a**. That supposition is strongly supported by the ^{1}H NMR and ^{13}C NMR observations of the clean conversion of aldehyde **1a** into acetal **4a** without any aldol dimer product observed (Figure 10).

Figure 10. NMR Investigation of Attempted Dimerization of Acetoxyacetaldehyde

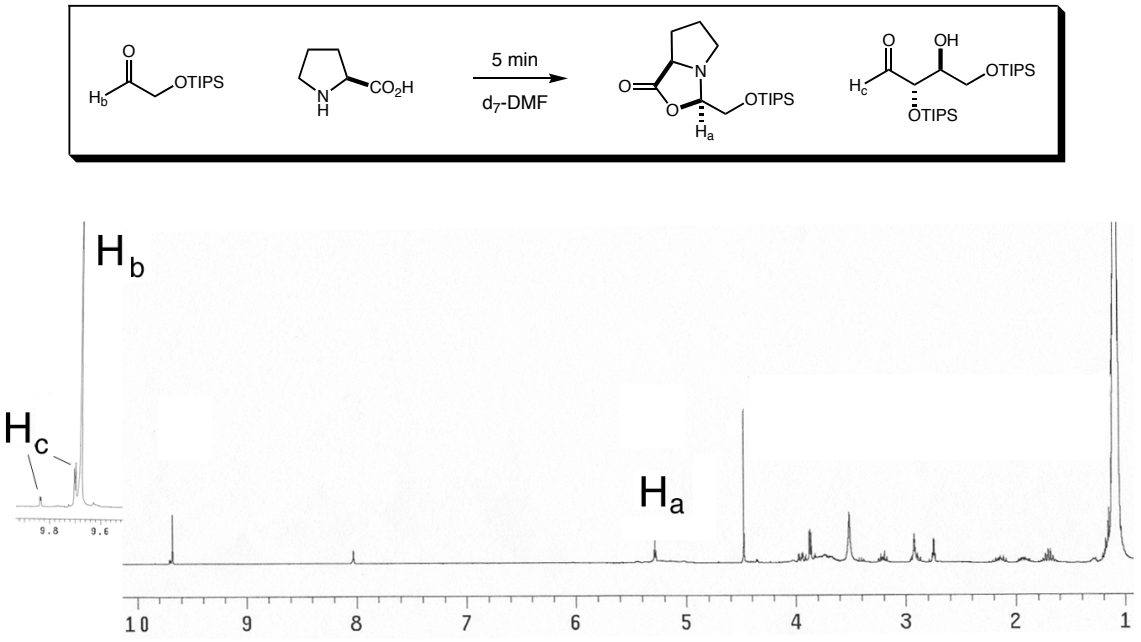






Conversely, relatively electron-releasing protecting groups, such as silicon protecting groups (Table 1, entries 4-6, 50-97% yield) should not greatly destabilize **3f** and allow the catalytic cycle to proceed. Indeed, ^{1}H NMR observation of the dimerization of aldehyde **1f** demonstrated the formation of acetal **4f** as well as the dimeric erythrose product **2f** (Figure 11).

Figure 11. NMR Investigation of the Aldol Dimerization of Triisopropylsiloxyacetaldehyde



The dimerization reactions of protected glycoaldehydes proceed less rapidly than their analogous alkyl-substituted counterparts. That fact can also be explained by the inductive destabilization of iminium ion **3** relative to the analogous iminium ion with alkyl aldehydes. The position of the acetal/iminium ion equilibrium for alkyl *vs*. α-oxyaldehydes also correctly predicts the regiochemical course of entries 1 through 4 of Table 2, resulting from preferential enamine formation of alkyl aldehydes. Furthermore, the parasitic equilibrium on the catalytic cycle completely explains the divergent reactivity of organic and metal-based catalyst systems.

Conclusions

In summary, we have documented the first direct enantioselective catalytic aldol reaction using α-oxygenated aldehydes as both the aldol donor and the aldol acceptor. Gratifyingly, the stereochemical course of these aldol reactions is in complete accord with the models previously discussed in Chapter 3, further establishing the predictability and reliability of organocatalytic transformations. Significantly, this method allows direct and enantioselective access to differentially protected tetroses and mono-protected *anti*-1,2 diols that are difficult to produce using standard metal-based methods. A study of the reaction mechanism through NMR analysis has revealed the existence of a parasitic equilibrium in the catalytic cycle. Consideration of the substrate-dependant position of that equilibrium allows a prediction of the regiochemical course of the cross aldol event. Importantly, this novel aldol variant represents the first step in a proposed two-step synthesis of fully differentiated carbohydrates. Completion of that synthetic strategy is described in the following chapter.

Supporting Information

General Information. Commercial reagents were purified prior to use following the guidelines of Perrin and Armarego.[15] Non-aqueous reagents were transferred under nitrogen via syringe or cannula. Organic solutions were concentrated under reduced pressure on a Büchi rotary evaporator using an ice-water bath. Chromatographic purification of products was accomplished using forced-flow chromatography on ICN 60 32-64 mesh silica gel 63 according to the method of Still.[16] Thin-layer chromatography (TLC) was performed on EM Reagents 0.25 mm silica gel 60-F plates. Visualization of the developed chromatogram was performed by fluorescence quenching or by anisaldehyde stain.

^{1}H and ^{13}C NMR spectra were recorded on a Mercury 300 (300 MHz and 75 MHz) as noted, and are internally referenced to residual protio solvent signals. Data for ^{1}H NMR are reported as follows: chemical shift (δ ppm), multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet), integration, coupling constant (Hz) and assignment. Data for ^{13}C NMR are reported in terms of chemical shift. IR spectra were recorded on a Perkin Elmer Paragon 1000 spectrometer and are reported in terms of frequency of absorption (cm^{-1}). Mass spectra were obtained from the California Institute of Technology Mass Spectral facility or from the UC Irvine Mass Spectral facility. Gas liquid chromatography (GLC) was performed on Hewlett-Packard 6850 and 6890 Series gas chromatographs equipped with a split-mode capillary injection system and flame ionization detectors using a Bodman Chiraldex β-DM (30 m x 0.25 mm) column or an

[15]Perrin, D. D.; Armarego, W. L. F. *Purification of Laboratory Chemicals;* 3rd ed., Pergamon Press, Oxford, 1988.

[16]Still, W. C.; Kahn, M.; Mitra, A. J. *J. Org. Chem.* **1978,** *43*, 2923.

ASTEC Chiraldex β-BP (30 m x 0.25 mm) as noted. High performance liquid chromatography (HPLC) was performed on Hewlett-Packard 1100 Series chromatographs using a Chiralcel AD column (25 cm) and AD guard (5 cm), a Chiralcel OJ column (25 cm) and OJ guard (5 cm) or a Chiralcel ODH column (25 cm) and ODH guard (5 cm) as noted.

(2*S*, 3*S*)-3-Hydroxy-2,3-bis-(benzylyloxy)-propionaldehyde (Table 1, entry 2). A suspension of benzyloxyacetaldehyde (1.0 g, 6.66 mmol) and L-proline (38.3 mg, 0.33 mmol) in dimethylformamide (13.3 mL) was stirred for 42 h at room temperature. The resulting solution was diluted with water, extracted with ethyl acetate and washed with brine, dried over anhydrous Na_2SO_4. Flash chromatography (1:19 ether: dichloromethane) afforded the title compound as a clear, colorless oil in 52% yield (518 mg, 0.31 mmol), 98% ee (*anti*), and 4:1 *anti*:*syn*. Recovered starting material (442 mg) was resubjected to the above conditions to afford and additional 21% yield (210 mg) for a combined yield of 73%. IR (film) 3438, 3064, 3031, 2868, 1957, 1879, 1813, 1732, 1497, 1454, 1094, 738.9, 698.7 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 9.72 (d, 1H, J = 1.8 Hz, CHO); 7.33 (m, 10H, Ar-H); 4.73 (d, 1H, J = 12.3 Hz, CH_2Ar); 4.56 (d, 1H, J = 12.3 Hz, CH_2Ar); 4.54 (d, 1H, J = 12.0 Hz, CH_2Ar); 4.49 (d, 1H, J = 12.0 Hz, CH_2Ar); 4.14 (m, 1H, C**H**OH); 3.93 (dd, 1H, J = 5.7, 1.8 Hz, C**H**CHO); 3.62 (m, 2H, CH_2OBn); 2.39 (d, 1H, J = 6.6 Hz, OH); ^{13}C NMR (75 MHz, $CDCl_3$): δ 202.1, 137.7, 137.1, 128.8, 128.7, 128.5, 128.4, 128.1, 128.0, 83.7, 73.7, 73.6, 71.1, 69.9; $[\alpha]_D$ = –30.6 (c = 0.47, $CHCl_3$); HRMS (CI) exact mass calcd for $[M+H]^+$ ($C_{19}H_{21}O_4$) requires *m/z* 301.1434, found *m/z* 301.1432. The enantiomeric purity was determined after reduction ($NaBH_4$)

by HPLC analysis using a Chiracel AD and AD guard column (10% ethanol/hexanes, 1 mL/min): (2*S*, 3*S*)-enantiomer: t_r = 23.7 min, (2*R*, 3*R*)-enantiomer: t_r = 32.3 min, *syn* isomers t_r = 27.2, 28.8 min. The diastereomer ratio was determined by ^{1}H NMR analysis of the crude title compound and verified by HPLC analysis after $NaBH_4$ reduction.

(2*S*, 3*S*)-3-Hydroxy-2,3-bis-(4-methoxybenzylyloxy)-propionaldehyde (Table 1, entry 3). A suspension of 4-methoxybenzyloxyacetaldehyde (180 mg, 1.0 mmol) and L-proline (5.8 mg, 0.05 mmol) in dimethylformamide (1.33 mL) was stirred for 48 h at room temperature. The resulting solution was diluted with water, extracted with ethyl acetate and washed with brine, dried over anhydrous Na_2SO_4. Flash chromatography (40% to 60% ethyl acetate: hexanes, linear gradient) afforded the title compound as a clear, colorless oil in 64% yield (116 mg, 0.32 mmol), 97% ee (*anti*), and 4:1 *anti*:*syn* along with 41 mg recovered starting material (83% yield based on recovered starting material). IR (film) 3445, 2915, 2838, 1723, 1613, 1514, 1250, 1174, 1098, 1033, 820.0, 516.5 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 9.67 (d, 1H, *J* = 1.5 Hz, CHO); 7.21 (m, 4H, Ar-H); 6.88 (m, 4H, Ar-H); 4.63 (d, 1H, *J* = 10.8 Hz, CH_2Ar); 4.48 (d, 1H, *J* = 11.4 Hz, CH_2Ar); 4.45 (d, 1H, *J* = 11.1 Hz, CH_2Ar); 4.41 (d, 1H, *J* = 11.4 Hz, CH_2Ar); 4.08 (m, 1H, C**H**OH); 3.88 (dd, 1H, *J* = 5.4, 2.1 Hz, C**H**CHO); 3.80 (s, 6H, OMe); 3.57 (m, 2H, CH_2OPMB); 2.47 (d, 1H, *J* = 6.6 Hz, OH); ^{13}C NMR (75 MHz, $CDCl_3$): δ 202.2, 159.5 (2), 132.1 (2), 130.1, 129.7, 114.2, 114.0, 83.3, 73.4, 73.2, 71.0, 69.5, 55.6 (2); $[\alpha]_D$ = –29.2 (c = 1.00, $CHCl_3$); HRMS (CI) exact mass calcd for $[M+NH_4]^+$ ($C_{20}H_{26}O_5N$) requires *m/z* 360.1811, found *m/z* 360.1827. The enantiomeric purity was determined after reduction ($NaBH_4$) by HPLC analysis using a Chiracel AD and AD guard column

(15% ethanol/hexanes, 1 mL/min): (2*S*, 3*S*)-enantiomer: t_r = 25.9 min, (2*R*, 3*R*)-enantiomer: t_r = 35.5 min, *syn* isomers t_r = 29.6, 29.6 min. The diastereomer ratio was determined by ^{1}H NMR analysis of the crude title compound and verified by HPLC analysis after $NaBH_4$ reduction.

(2*S*, 3*S*)-3-Hydroxy-2,3-bis-(*tert*-butyl-dimethyl-silanyloxy)-propionaldehyde (Table 1, entry 4). A suspension of (*tert*-butyl-dimethyl-silanoxy)-acetaldehyde (176 mg, 1.0 mmol) and L-proline (11.6 mg, 0.1 mmol) in 1,4-dioxane (2.0 mL) was stirred for 48 h at room temperature. The resulting solution was diluted with diethyl ether, passed through a plug of silica and concentrated. Flash chromatography (15:1 pentane: diethyl ether) afforded the title compound as a clear, colorless oil in 62% yield (109 mg, 0.31 mmol), 88% ee (*anti*), and 3:1 *anti*:*syn*. IR (film) 3455, 2956, 2930, 2897, 2886, 2859, 1736, 1473, 1362, 1256, 1117, 838, 780 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 9.63 (d, 1H, *J* = 1.6 Hz, CHO); 4.07 (dd, 1H, *J* = 5.5, 1.6 Hz, C**H**CHO); 3.95-3.84 (m, 1H, C**H**OH); 3.80-3.55 (m, 2H, CH_2OR); 2.39 (d, 1H, *J* = 7.1 Hz, OH); 0.94-0.86 (m, 18H, 2 $C(CH_3)_3$); 0.12-0.02 (m, 12H, 2 $Si(CH_3)_2$); (*syn*-isomer): δ 9.67 (d, 1H, *J* = 1.0 Hz, CHO); 4.19 (dd, 1H, *J* = 3.8, 1.1 Hz, C**H**CHO); 3.95-3.84 (m, 1H, C**H**OH); 3.80-3.55 (m, 2H, CH_2OR); 2.57 (d, 1H, *J* = 9.3 Hz, OH); 0.94-0.86 (m, 18H, 2 $C(CH_3)_3$); 0.12-0.02 (m, 12H, 2 $Si(CH_3)_2$); ^{13}C NMR (75 MHz, $CDCl_3$): δ 201.7, 78.2, 72.8, 62.2, 25.9 (3C), 25.8 (3 C), 18.3 (2C), –3.8, –4.4, –4.8 (2C); (*syn*-isomer): δ 203.3, 76.7, 73.1, 62.1, 25.9 (3C), 25.8 (3 C), 18.3 (2C), –3.9, –4.4, –4.7, –4.8; the optical rotation was determined after converting the product mixture into its 1,3-acetonide acetal (by $NaBH_4$-reduction followed by ketalization) and isolation of the *anti*-isomer by flash chromatography (60:1

pentane: diethyl ether): $[\alpha]_D = -33.6$ (c = 2.7, $CHCl_3$); HRMS (CI) exact mass calcd for $[M-CH_3]^+$ ($C_{18}H_{39}O_4Si_2$) requires *m/z* 375.2387, found *m/z* 375.2387. The enantiomeric purity of the acetal and thereby the title compound was determined by GLC analysis using a Bodman Chiraldex β-DM (30 m x 0.25 mm) column (110 ºC hold 120 min, ramp 1ºC/min to 150ºC, 23 psi): (2*S*, 3*S*)-enantiomer: t_r = 141.8 min, (2*R*, 3*R*)-enantiomer: t_r = 142.7 min. The diastereomer ratio was determined by ^{1}H NMR analysis of the crude title compound.

(2*S*, 3*S*)-3-Hydroxy-2,3-bis-(*tert*-butyl-diphenyl-silanyloxy)-propionaldehyde (Table 1, entry 5). A suspension of (*tert*-butyl-diphenyl-silanoxy)-acetaldehyde (298 mg, 1.0 mmol) and L-proline (11.5 mg, 0.1 mmol) in a mixture of 1,4-dioxane (1.0 mL) and DMF (1.0 mL) was stirred for 48 h at room temperature. The resulting solution was diluted with ethyl acetate and washed successively with water and brine. The organic layer was dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. Flash chromatography (10:1 pentane: diethyl ether) afforded the title compound as a clear, colorless oil in 61% yield (182 mg, 0.31 mmol), 93% ee (*anti*-diastereomer) and 9:1 *anti*:*syn*. IR (film) 3510, 2958, 2932, 2892, 2859, 1734, 1472, 1428, 1113, 823, 702 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) : δ 9.61 (d, 1H, *J* = 1.5 Hz, CHO); 7.70-7.56 (m, 8H, CH_{ar}); 7.48-7.30 (m, 12H, CH_{ar}); 4.23 (dd, 1H, *J* = 3.9, 1.2 Hz, C**H**CHO); 4.08-3.98 (m, 1H, C**H**OH); 3.80 (dd, *J* = 10.2, 6.9 Hz, 1H, CH_2OR); 3.62 (dd, 1H, *J* = 10.2, 6.3 Hz, CH_2OR); 2.13 (d, *J* = 5.4 Hz, 1H, OH); 1.10 (s, 9 H, $C(CH_3)_3$); 1.01 (s, 9H, $C(CH_3)_2$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 201.4, 135.7, 135.6, 135.4 (2C), 132.6, 132.5, 132.4 (2C), 130.0 (4C), 129.7 (4C), 127.8 (2C), 127.7 (6C), 79.5, 73.9, 63.2, 19.5, 19.2; HRMS (CI) exact mass calcd for $[M+NH_4]^+$

($C_{36}H_{48}NO_4Si_2$) requires *m/z* 614.3122, found *m/z* 614.3123; $[\alpha]_D$ = +0.5 (c = 1.1, $CHCl_3$). The enantiomeric purity was determined by HPLC analysis of the crude title compound using a Chiracel OD-H and OD-H guard column (3.0 % isopropanol/hexanes, 1 mL/min): (2*S*, 3*S*) *anti* isomer t_r = 14.5 min, (2*R*, 3*R*) *anti* isomer t_r = 12.1 min, (2*R*, 3*S*) and (2*S*, 3*R*) *syn* isomers t_r = 10.7, 20.0 min. The 1,3-acetonide-acetal was prepared and the *anti*-isomer was isolated by flash chromatography (40:1 pentane: diethyl ether) to obtain a optical rotation more suitable for comparison: $[\alpha]_D$ = –6.1 (c = 2.2, $CHCl_3$); HRMS (ESI) exact mass calcd for $[M+Na]^+$ ($C_{39}H_{50}NaO_4Si_2$) requires *m/z* 661.3145, found *m/z* 661.3134.

(2*S*, 3*S*)-3-Hydroxy-2,3-bis-triisopropylsilanoxy-propionaldehyde (Table 1, entry 6). A suspension of trisisopropylsilanoxy-acetaldehyde (224 mg, 1.0 mmol) and L-proline (11.7 mg, 0.1 mmol) in DMF (6.7 mL) was stirred for 24 h at room temperature. The resulting solution was diluted with diethyl ether and washed successively with water and brine. The organic layer was dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. Flash chromatography (40:1 pentane : diethyl ether) afforded the title compound as a clear, colorless oil in 75% yield (169 mg, 0.39 mmol), 95% ee (*anti*-diastereomer) and 4:1 *anti*:*syn*. Repeated chromatographic purification afforded a 51% yield (115 mg, 0.27 mmol) of the *anti*-isomer. IR (film) 3483, 2945, 2892, 2868, 1734, 1464, 1385, 1117, 1069, 883, 683 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 9.68 (d, 1H, *J* = 2.1 Hz, CHO); 4.25 (dd, 1H, *J* = 3.9, 2.1 Hz, C**H**CHO); 4.10-3.94 (m, 1H, C**H**OH); 3.84 (dd, 1H, *J* = 9.9, 6.6 Hz, CH_2OR); 3.79 (dd, 1H, *J* = 9.6, 6.3 Hz, CH_2OR); 2.40 (d, 1H, *J* = 5.4 Hz, OH); 1.16-1.00 (m, 42H, 6 $CH(CH_3)_2$); (*syn*-isomer): δ 9.74 (d, 1H, *J* = 1.5 Hz, CHO); 4.28

(dd, 1H, *J* = 4.9, 1.5 Hz, C**H**CHO); 3.97 (dd, 1H, *J* = 9.9, 2.7 Hz, CH_2OR); 3.89 (m, 1H, C**H**OH); 3.77 (dd, 1H, *J* = 9.9, 4.5 Hz, CH_2OR); 2.73 (d, 1H, *J* = 9.9 Hz, OH); 1.16-1.00 (m, 42H, 6 $CH(CH_3)_2$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 202.1, 78.9, 74.3, 62.7, 18.0 (12C), 12.4 (3C), 11.9 (3C); (*syn*-isomer): δ 203.8, 74.4, 62.2, 18.0 (12C), 12.3 (3C), 11.9 (3C), one signal obscured by solvent; HRMS (CI) exact mass calcd for $[M+H]^+$ ($C_{22}H_{49}O_4Si_2$) requires *m/z* 433.3169, found *m/z* 433.3176; $[\alpha]_D$ = –3.6 (c = 4.0, $CHCl_3$). The diastereomer ratio was determined by ^1H NMR of the crude product. The enantiomeric purity of the *anti*-diastereomer was determined after conversion of the isolated *anti*-isomer to the 1-hydroxy-3-*p*-nitrobenzoate-derivative as follows: To a solution of the title compound (40 mg, 0.09 mmol) in dichloromethane (0.6 mL), *p*-nitro-benzoylchloride (42.9 mg, 0.23 mmol), 4-dimethylaminopyridine (2.8 mg, 0.02 mmol) and triethylamine (0.06 mL, 0.46 mmol) were added at +4 ºC. The resulting mixture was stirred at +4 ºC for 3.5 h, before methanol (0.6 mL) and $NaBH_4$ (0.04g, 0.94 mmol) were added, which led to a vigorous gas evolution. After an additional 35 minutes, the mixture was warmed to room temperature and diluted with 5 mL dichloromethane. The resulting solution was washed with saturated $NaHCO_3$ solution, passed through a plug of silica and concentrated. HRMS (ESI) exact mass calcd for $[M + Na]^+$ ($C_{29}H_{53}NNaO_7Si_2$) requires *m/z* 606.3258, found *m/z* 606.3253. The product ratios were determined by HPLC using a Chiracel OD-H and OD-H guard column (0.16 % isopropanol/hexanes, 1 mL/min): (2*S*, 3*S*) enantiomer t_r = 46.5 min, (2*R*, 3*R*) enantiomer t_r = 41.4 min.

Triisopropylsilanoxy-acetaldehyde. (1f) A solution of (*Z*)-1,4-bis-triisopopylsilanoxy-but-2-ene (6.70 g, 16.7 mmol) and triethylamine (3.5 mL, 25.2 mmol) in

dichloromethane/methanol (100 mL/10 mL) was cooled to –78ºC. Ozone was bubbled through the solution until a pale blue color developed. At this time triphenylphosphine (5.70 g, 21.7 mmol) was added and the resulting mixture was stirred for 3 h allowing it to reach 0ºC. After concentration, the residue was treated with pentane (30 mL) causing precipitation of triphenylphosphine oxide. The resulting suspension was poured directly onto a wet column of silica gel (20:1 pentane:diethyl ether) . Flash chromatography (20:1 pentane:diethyl ether) afforded the title compound as a clear, colorless oil in 86% yield (6.2 g, 28.6 mmol). IR (film) 2945, 2893, 2868, 1741, 1464, 1133, 883, 685 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 9.73 (bs, 1H, CHO); 4.26 (d, J = 1.1 Hz, 2H, CH_2OR); 1.20-1.02 (m, 21H, 3 $CH(CH_3)_2$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 203.0, 69.7, 18.1 (6C), 12.1 (3C); HRMS (CI) exact mass calcd for $[M+H]^+$ ($C_{11}H_{25}O_2Si$) requires *m/z* 217.1624, found *m/z* 217.1615.

(2*S*, 3*S*)- 3-Hydroxy-2,4-bis-methoxymethoxy-butyraldehyde (Table 1, entry 7). A suspension of methoxymethoxyacetaldehyde (78 mg, 0.75 mmol) and L-proline (4.3 mg, 0.038 mmol) in dimethylformamide (0.75 mL) was stirred for 20 h at room temperature. The resulting solution was diluted with water, extracted with ether and washed with brine, dried over anhydrous Na_2SO_4. Flash chromatography (3:1 ether: pentane) afforded the title compound as a clear, colorless oil in 42% yield (33 mg, 0.16 mmol), 96% ee (*anti*), and 4:1 *anti*:*syn*. IR (film) 3364, 2978, 2938, 1715.9, 1555, 1446, 1379, 1343, 1101, 1039, 837.9, 713.8 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 9.70 (d, 1H, J = 1.8 Hz, CHO); 4.81-4.61 (m, 4H, 2 CH_2OMe); 4.12 (m, 1H, C**H**OH); 4.04 (dd, 1H, J = 5.1, 1.2 Hz, C**H**CHO); 3.69 (m, 2H, CH_2OMOM); 3.38 (s, 6H, 2 OMe); 3.15 (d, 1H, J = 7.2 Hz,

OH); ^{13}C NMR (75 MHz, $CDCl_3$): δ 200.9, 97.8, 97.3, 84.0, 71.0, 68.7, 56.6, 56.0; $[\alpha]_D$ = +2.4 (c = 1.00, $CHCl_3$); HRMS (CI) exact mass calcd for $[M+H]^+$ ($C_9H_{17}O_6$) requires *m/z* 209.1020, found *m/z* 209.1020. The enantiomeric purity was determined after reduction ($NaBH_4$) and 1,3 acetonide formation as below (see Table 1, entry 7) by GLC analysis using a Bodman Chiraldex β-DM (30 m x 0.25 mm) column (120 ºC, 23 psi): (2*S*, 3*S*)-enantiomer: t_r = 26.7 min, (2*R*, 3*R*)-enantiomer: t_r = 25.7 min, *syn* isomers t_r = 29.7, 29.8 min. The diastereomer ratio was determined by ^{1}H NMR analysis of the crude title compound.

Determination of the absolute stereochemistry of the silanoxy-acetaldehyde-dimers. Each dimer was converted into its 1,3-acetonide acetal as described above for Table 1, entry 7. Where necessary the isomers were separated (TBS, TBDPS). The isolated *anti*-isomer was then deprotected to furnish (4*S*, 5*R*)-4-hydroxymethyl-2,2-dimethyl-[1,3]dioxane-5-ol. This compound was purified by flash chromatography and compared to a sample, which had been prepared from β-D-glucose by a known procedure. HRMS (CI) exact mass calcd for $[M + H]^+$ ($C_7H_{15}O_4$) requires *m/z* 163.0970, found *m/z* 163.0976). In every case (TBS, TBDPS, TIPS), the ^{1}H- and ^{13}C-NMR spectra were identical to the natural sample and the specific optical rotation was identical in sign and close to the magnitude of the natural sample: $[\alpha]_D$ = –28.4 (c = 0.2, $CHCl_3$); TBS: $[\alpha]_D$ = –22.4 (c = 1.2, $CHCl_3$); TBDPS: $[\alpha]_D$ = –25.4 (c = 0.4, $CHCl_3$); TIPS: $[\alpha]_D$ = –26.3 (c = 1.0, $CHCl_3$).

(2*S*, 3*R*)-4-Triisopropyl-silanyloxy-3-hydroxy-2-methylbutanal (Table 2, entry 1). A solution of freshly distilled propionaldehyde (263 μL, 3.64 mmol) in 0.73 mL DMF pre-cooled to 4 ºC was added slowly over the course of 12 h to a stirring suspension of triisopropylsilanoxy-acetaldehyde (158 mg, 0.73 mmol), L-proline (8.2 mg, 0.073 mmol) and 0.73 mL DMF at 4 ºC. After 18 h, the resulting solution was diluted with diethyl ether and washed successively with water and brine. The combined aqueous layers were back-extracted with 3 portions of dichloromethane. The organic layers were combined, dried over anhydrous Na_2SO_4, and concentrated *in vacuo*. Flash chromatography (9:1 pentane:diethyl ether) afforded the title compound as a clear, colorless oil in 75% yield (150 mg, 0.55 mmol), 99% ee and 4:1 *anti*:*syn*. IR (film) 3435, 2943, 2867, 1725, 1463, 1384, 1107, 996.0, 882.2, 778.5, 682.7 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 9.82 (d, *J* = 2.1 Hz, 1H, C**H**O); 3.90-3.65 (m, 3H, C**H**OH, C**H$_2$**CHOH); 2.87 (d, 1H, *J* = 4.8 Hz, O**H**); 2.51 (m, 1H, C**H**CH_3); 1.18-0.95 (m, 24H, SiC**H**(C**H$_3$**)$_2$, CHC**H$_3$**); ^{13}C NMR (75 MHz, $CDCl_3$) δ 204.4, 73.0, 65.2, 49.0, 18.1, 12.1, 10.3; HRMS (CI) exact mass calcd for $[M + H]^+$ ($C_{14}H_{31}O_3Si$) requires *m/z* 275.2043, found *m/z* 275.2041; $[\alpha]_D$ = + 8.46 (c = 1.0, $CHCl_3$). The product ratios were determined by HPLC analysis following reduction to the corresponding alcohol (obtained by $NaBH_4$ reduction) and bis-acetylation with *p*-nitrobenzoyl chloride, using a Chiracel OD-H and OD-H guard column (2% isopropanol/hexanes, 1 mL/min) column; (2*R*, 3*S*) *anti* isomer t_r = 33.0 min, (2*S*, 3*R*) *anti* isomer t_r = 35.4 min, (2*R*, 3*R*) and (2*S*, 3*S*) *syn* isomers t_r = 41.0, 44.9 min.

(2*S*, 3*R*)-4-*tert*-Butyldiphenyl-silanyloxy-3-hydroxy-2-methylbutanal (Table 2, entry 2). A solution of freshly distilled propionaldehyde (361 μL, 5.0 mmol) in 1.0 mL dioxane pre-cooled to 4 ºC was added slowly over the course of 24 h to a stirring suspension of *tert*-butyl-diphenylsilanyloxyacetaldehyde (298 mg, 1.0 mmol), L-proline (11.5 mg, 0.10 mmol) and 1.0 mL dioxane at 4 ºC. After 25 h, the resulting solution was diluted with diethyl ether and washed successively with water and brine. The combined aqueous layers were back-extracted with 3 portions of dichloromethane. The organic layers were combined, dried over anhydrous Na_2SO_4, and concentrated *in vacuo*. Flash chromatography (9:1 hexanes:ethyl acetate) afforded the title compound as a clear, colorless oil in 84% yield (300 mg, 0.84 mmol), 99% ee and 5:1 *anti*:*syn*. IR (film) 3434, 3050, 2929, 2856, 1725, 1590, 1462, 1428, 1113, 996.6, 823.4, 740.3, 702.1 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 9.79 (d, *J* = 2.4 Hz, 1H, C**H**O); 7.65 (m, 4H, Ar-H); 7.42 (m, 6H, Ar-H); 3.88 (m, 1H, C**H**OH); 3.76 (dd, 1H, *J* = 10.0, 3.7 Hz, C$\mathbf{H_2}$CHOH); 3.65 (dd, 1H, *J* = 10.0, 6.0 Hz, C$\mathbf{H_2}$CHOH); 2.69 (d, 1H, *J* = 4.8 Hz, O**H**); 2.58 (m, 1H, C**H**CH_3); 1.06 (m, 12H, Si(C$\mathbf{H_3}$)$_3$, CHC$\mathbf{H_3}$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 204.5, 135.7, 132.9, 130.2, 128.0, 73.2, 49.0, 27.2, 19.6; HRMS (CI) exact mass calcd for $[M + H]^+$ ($C_{21}H_{29}O_3Si$) requires *m/z* 357.1886, found *m/z* 357.1870; $[\alpha]_D$ = + 8.78 (c = 1.0, $CHCl_3$). The product ratios were determined by HPLC analysis of the corresponding alcohol (obtained by $NaBH_4$ reduction) using a Chiracel OD-H and OD-H guard column (2% ethanol/hexanes, 1 mL/min) column; (2*R*, 3*S*) *anti* isomer t_r = 26.2 min, (2*S*, 3*R*) *anti* isomer t_r = 31.5 min, (2*R*, 3*R*) and (2*S*, 3*S*) *syn* isomers t_r = 35.4, 41.5 min.

(2*S*, 3*R*)-4-Triisopropylsilanoxy-3-hydroxy-2-isopropylbutanal (Table 2, entry 3). A solution of freshly distilled isovaleraldehyde (354 μL, 3.3 mmol) in 0.66 mL DMF pre-cooled to 4 ºC was added slowly over the course of 12 h to a stirring suspension of triisopropylsilanoxy-acetaldehyde (143 mg, 0.66 mmol), L-proline (7.5 mg, 0.066 mmol) and 0.66 mL DMF at 4 ºC. After 18 hours, the resulting solution was diluted with diethyl ether and washed successively with water and brine. The combined aqueous layers were back-extracted with 3 portions dichloromethane. The organic layers were combined, dried over anhydrous Na_2SO_4, and concentrated *in vacuo*. Flash chromatography (9:1 pentane:diethyl ether) afforded the title compound as a clear, colorless oil in 54% yield (107 mg, 0.36 mmol), 99% ee and 4:1 *anti* : *syn*. IR (film) 3480, 2960, 2868, 1722, 1464, 1388, 1115, 1013, 996.4, 882.5, 795.1, 682.6 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 9.80 (d, 1H, *J* = 3.9 Hz, C**H**O); 4.03 (m, 1H, C**H**OH); 3.73 (dd, 1H, *J* = 10.2, 4.2 Hz, C**H**$_2$OSi); 3.62 (dd, 1H, *J* = 10.2, 6.9 Hz, C**H**$_2$OSi); 2.71 (d, 1H, *J* = 5.1 Hz, CHO**H**); 2.24 (m, 1H, C**H**$(CH_3)_2$); 2.05 (ddd (apparent dt), 1H, *J* = 7.8, 3.9, 3.9 Hz, C**H**CHO); 1.17-0.95 (m, 27H, CH(C**H$_3$**)$_2$, SiC**H**(C**H$_3$**)$_2$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 206.2, 71.0, 66.2, 60.0, 26.6, 20.9, 20.4, 18.1, 12.0; HRMS (CI) exact mass calcd for $[M + H]^+$ ($C_{16}H_{35}O_3Si$) requires *m/z* 303.2356, found *m/z* 303.2348. $[\alpha]_D = -4.11$ (c = 1.0, $CHCl_3$). The product ratios were determined by HPLC analysis following reduction to the corresponding alcohol (obtained by $NaBH_4$ reduction) and bis-acetylation with *p*-nitrobenzoyl chloride, using a Chiracel OD-H and OD-H guard column (2% isopropanol/hexanes, 1 mL/min) column; (2*S*, 3*R*) *anti* isomer t_r = 24.8 min, (2*R*, 3*S*) *anti* isomer t_r = 33.7 min, (2*R*, 3*R*) and (2*S*, 3*S*) *syn* isomers t_r = 27.9, 30.7 min.

(2*S*, 3*R*)-4-Benzyloxy-3-hydroxy-2-isopropylbutanal (Table 2, entry 4). A solution of freshly distilled benzyloxyacetaldehyde (141 μL, 1.0 mmol) in 1.0 mL dimethylformamide pre-cooled to 4 ºC was added slowly over the course of 18 h to a stirring suspension of isovaleraldehyde (214 μL, 2.0 mmol), L-proline (11.5 mg, 0.10 mmol) and 1.0 mL dimethylformamide at 4 ºC. After 19 hours, the resulting solution was diluted with diethyl ether and washed successively with water and brine. The combined aqueous layers were back-extracted with 3 portions dichloromethane. The organic layers were combined, dried over anhydrous Na_2SO_4, and concentrated *in vacuo*. Flash chromatography (4:1 pentane:diethyl ether) afforded the title compound as a clear, colorless oil in 64% yield (151 mg, 0.64 mmol), 95% ee and 4:1 *anti* : *syn*. IR (film) 3456, 2961, 2929, 2871, 1721, 1468, 1453, 1390, 1370, 1101, 1028, 990.3, 946.0, 914.4, 738.2, 698.6 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 9.81 (d, 1H, *J* = 3.6 Hz, C**H**O); 7.33 (m, 5H, Ar-H); 4.54 (s, 2H, C**H$_2$**Ph); 4.18 (m, 1H, C**H**OH); 3.57 (dd, 1H, *J* = 6.6, 3.0 Hz, C**H**$_2$OBn); 3.45 (dd, 1H, *J* = 9.3, 6.6 Hz, C**H**$_2$OBn); 2.63 (d, 1H, *J* = 5.1 Hz, CHO**H**); 2.23 (m, 1H, C**H**$(CH_3)_2$); 2.07 (ddd (apparent dt), 1H, *J* = 7.8, 3.9, 3.9 Hz, C**H**CHO); 1.06 (d, 3H, *J* = 6.9 Hz, C**H$_3$**); 0.95 (d, 3H, *J* = 6.9 Hz, C**H$_3$**); ^{13}C NMR (75 MHz, $CDCl_3$) δ 206.2, 137.7, 128.7, 128.0, 73.8, 73.1, 69.7, 60.4, 26.6, 21.1, 20.6; HRMS (CI) exact mass calcd for $[M + H]^+$ ($C_{14}H_{21}O_3$) requires *m/z* 237.1491, found *m/z* 237.1492. $[\alpha]_D$ = –14.4 (c = 1.0, $CHCl_3$). The product ratios were determined by HPLC analysis of the corresponding alcohol (obtained by $NaBH_4$ reduction) using a Chiracel AD and AD guard column (4% isopropanol/hexanes, 1 mL/min) column; (2*R*, 3*S*) *anti* isomer t_r =

22.4 min, (2*S*, 3*R*) *anti* isomer t_r = 24.5 min, (2*R*, 3*R*) and (2*S*, 3*S*) *syn* isomers t_r = 29.3, 31.8 min.

(2*S*, 3*S*)-3-Hydroxy-4-methyl-2-triisopropylsilanyloxy-pentanal (Table 2, Entry 5). A solution of freshly distilled triisopropylsilanyloxyacetaldehyde (216 mg, 1.0 mmol) in 1.0 mL dimethylformamide pre-cooled to 4 ºC was added slowly over the course of 36 h to a stirring suspension of isobutyraldehyde (272 μL, 3.0 mmol), L-proline (22.6 mg, 0.2 mmol) and 1.0 mL dimethylformamide at 4 ºC. After 37 h, the resulting solution was diluted with diethyl ether and washed successively with water and brine. The combined aqueous layers were back-extracted with 3 portions of dichloromethane. The organic layers were combined, dried over anhydrous Na_2SO_4, and concentrated *in vacuo*. Flash chromatography (39:1 hexanes:ethyl acetate) afforded the title compound as a clear, colorless oil in 43% yield (124 mg, 0.43 mmol), 99% ee and 8:1 *anti*:*syn*. IR (film) 3464, 2947, 2864, 1735, 1464, 1379, 1316, 1254, 1109, 1064, 1016, 958.5, 917.0 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 9.70 (d, 1H, *J* = 2.1 Hz, CHO); 4.14 (dd (apparent t), 1H, *J* = 3.3 Hz, C**H**CHO); 3.48 (m, 1H, C**H**OH); 2.67 (d, 1H, *J* = 2.1 Hz, CHO**H**); 1.78 (m, 1H, C**H**$(CH_3)_2$); 1.16-1.01 (m, 24H, SiC**H**$(C\mathbf{H_3})_2$, CHC$\mathbf{H_3}$); 0.94 (d, 3H, *J* = 9.0 Hz, CH**CH$_3$**); ^{13}C NMR (75 MHz, $CDCl_3$) δ 203.6, 80.7, 78.9, 29.7, 19.6, 19.2, 18.3, 12.5; HRMS (CI) exact mass calcd for $[M + H]^+$ ($C_{15}H_{34}O_3Si$) requires *m/z* 289.2198, found *m/z* 289.2201. $[\alpha]_D$ = –2.47 (c = 1.0, $CHCl_3$). The product ratios were determined by GLC analysis of the acetonide derived from the corresponding alcohol (obtained by $NaBH_4$ reduction) and 2-methoxypropene (obtained by the method of Lipshutz[17]) using a

[17] Lipshutz, B. H.; Barton, J. C., *J. Org. Chem.* **1988**, *53*, 4495.

Bodman Chiraldex β-DM (30 m x 0.25 mm) column (110 ºC isotherm, 23 psi); (2*S*, 3*S*) *anti* isomer t_r = 88.4 min, (2*R*, 3*R*) *anti* isomer t_r = 90.5 min, (2*R*, 3*S*) and (2*S*, 3*R*) *syn* isomers t_r = 100.4, 102.2 min.

Determination of the absolute stereochemistry of (2*S*, 3*S*)-3-Hydroxy-4-methyl-2-triisopropylsilanyloxy-pentanal by correlation to (*2S*, 3*R*)-3-[(4-Methoxyphenyl)methoxy]-4-methyl-1,2-pentanediol. A stirring solution of (2*S*, 3*S*)-3-Hydroxy-4-methyl-2-triisopropylsilanyloxy-pentanal (70 mg, 0.24 mmol) in 10.0 mL of 4:1 dichloromethane:ethanol was treated with $NaBH_4$. After stirring for 5 minutes, the reaction was quenched with a saturated aqueous solution of $NaHCO_3$, and extracted with 3 portions of dichloromethane. The combined organic extracts were dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo*. The residue was then dissolved in 250 μL dimethylformamide, and treated with triisopropylsilyl chloride (55 μL, 0.26 mmol) and imidazole (35 mg, 0.52 mmol) according to the method of Cunico[18]. After stirring for 12 hours, the mixture was diluted in ether, and washed with saturated aqueous solutions of NH_4Cl and $NaHCO_3$, and water. The residue was then dissolved in 2.0 mL tetrahydrofuran, and treated sequentially with NaH (6.7 mg, 0.28 mmol), 4-methoxy-benzyl chloride (38 μL, 0.28 mmol) and tetrabutylammonium iodide (9 mg, 0.024 mmol). After stirring for 14 hours, the mixture was diluted in ether, and washed with saturated aqueous solutions of NH_4Cl and $NaHCO_3$, and water. The combined organic extracts were dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo*. Flash chromatography (0–2.5% ethyl acetate in hexanes, linear gradient) afforded a 51% yield

[18] Cunico, R.F.; Bedell, L., *J. Org. Chem.* **1980**, *45*, 4797.

(63 mg, 0.12 mmol) of (*2S*, 3*R*)-3-[(4-Methoxyphenyl)methoxy]-4-methyl-1,2-triisopropylsilanyloxy-pentane. To this compound was added tetrabutylammonium fluoride (174 μL, 1 M in tetrahydrofuran). After refluxing for 12 hours, the mixture was diluted in ether and washed with saturated aqueous solutions of NH_4Cl and $NaHCO_3$, and water. Flash chromatography (5:1 ethyl hexanes:ethyl acetate) afforded a 33% yield (10 mg, 0.04 mmol) of (*2S*, 3*R*)-3-[(4-Methoxyphenyl)methoxy]-4-methyl-1,2-pentanediol; $[\alpha]_D$ = -11.2 (c = 1.0, $CHCl_3$) (lit.[19] $[\alpha]_D$ = – 14.0 (c = 1.19, $CHCl_3$) for (*2S*, 3*R*)-3-[(4-methoxyphenyl)methoxy]-4-methyl-1,2-pentanediol).

(2*S*, 3*S*)-2-(Benzylyloxy)-3-hydroxy-4-methyl-pentanal (Table 2, entry 6). A solution of benzyloxyacetaldehyde (150.2 mg, 1.0 mmol) in dimethylformamide (1.0 mL) was added slowly over the course of 24 hours to a suspension of isobutryldehyde (914 μL, 10.0 mmol) and L-proline (23.0 mg, 0.20 mmol) in dimethylformamide (1.0 mL) at room temperature. The resulting solution was diluted with water, extracted with ethyl acetate and washed with brine, dried over anhydrous Na_2SO_4. Flash chromatography (1:3 ethyl acetate: hexanes) afforded the title compound as a clear, colorless oil in 33% yield (74 mg, 0.33 mmol), 96% ee (*anti*), and 7:1 *anti*:*syn*. IR (film) 3460, 3032, 2963, 2932, 2874, 1732, 1497, 1455, 1101, 1027, 738.5, 698.5 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 9.78 (d, 1H, *J* = 2.7 Hz, CHO); 7.36 (m, 5H, Ar-H); 4.72 (d, 1H, *J* = 12.0 Hz, CH_2Ar); 4.56 (d, 1H, *J* = 12.0 Hz, CH_2Ar); 3.81 (dd, 1H, *J* = 4.8, 2.4 Hz, C**H**CHO); 3.69 (m, 1H, C**H**OH); 2.28 (d, 1H, *J* = 4.5 Hz, OH); 1.92 (m, 1H, C**H**$(CH_3)_2$); 0.95 (d, 3H, *J* = 6.9 Hz, CH_3); 0.95 (d, 3H, *J* = 6.9 Hz, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$): δ 203.6, 137.1, 128.9, 128.6,

[19]Oikawa, M.; Ueno, T.; Oikawa, H.; Ichihara, A., *J. Org. Chem.* **1995**, *60*, 5048.

128.4, 84.3, 73.2, 29.8, 19.4, 17.7; $[\alpha]_D$ = –53.1 (c = 0.47, $CHCl_3$); HRMS (CI) exact mass calcd for $[M + H]^+$ ($C_{19}H_{21}O_4$) requires *m*/*z* 222.1256, found *m*/*z* 222.1259. The enantiomeric purity was determined after reduction ($NaBH_4$) by HPLC analysis using a Chiracel AD and AD guard column (5% ethanol/hexanes, 1 mL/min): (2*S*, 3*S*)-enantiomer: t_r = 14.7 min, (2*R*, 3*R*)-enantiomer: t_r = 17.3 min, *syn* isomers t_r = 24.7, 27.4 min. The diastereomer ratio was determined by ^1H NMR analysis of the crude title compound and verified by HPLC analysis after $NaBH_4$ reduction.

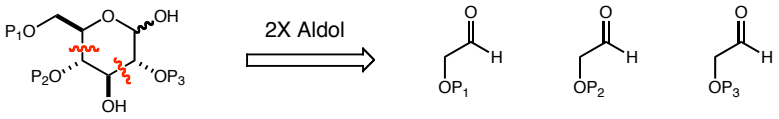
C h a p t e r 4

Completion of a Two-Step Synthesis of Carbohydrates*

Introduction

Hexoses are the most abundant class of natural products on Earth and play vital roles in biological processes as diverse as signal transduction, cognition, and the immune response; however, their study has lagged far behind that of proteins and nucleic acids. A paucity of general methods for the efficient synthesis of polysaccharides has led to such a deficiency in our understanding of those essential biological processes. For over one century, chemists have built suitably protected carbohydrate monomers by selective protection strategies.[1] While the inexpensive supply of enantiopure carbohydrate starting materials may have made those syntheses attractive, a *de novo* enantioselective synthesis of the hexoses should constitute a more efficient strategy. A retrosynthetic analysis of a fully differentiated hexose reveals the attractive proposal that it could arise from two aldol reactions between three protected glycoaldehyde units (Figure 1).

Figure 1. Retrosynthetic Analysis of a Protected Hexose



As discussed in the preceding chapter, the realization of the proposed two-step synthesis of differentiated hexoses requires the invention of two new aldehyde coupling technologies (Scheme 1).

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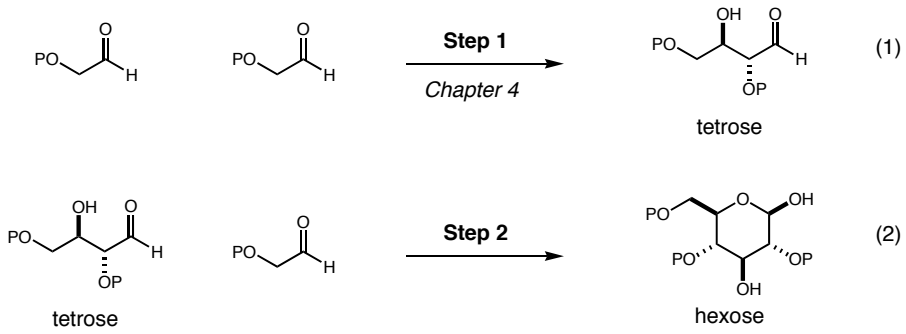
* For a preliminary communication of this work, see: Northrup, A. B.; MacMillan, D. W. C. *Science* **2004**, *accepted.*

[1] *Glycoscience*; Fraser-Reid, B. O.; Tatsuta, K.; Thiem, J. Eds.; Springer: Berlin, 2001; Vol. 1.

Scheme 1. New Aldehyde Aldol Technologies Necessary for Two-Step Sugar Synthesis

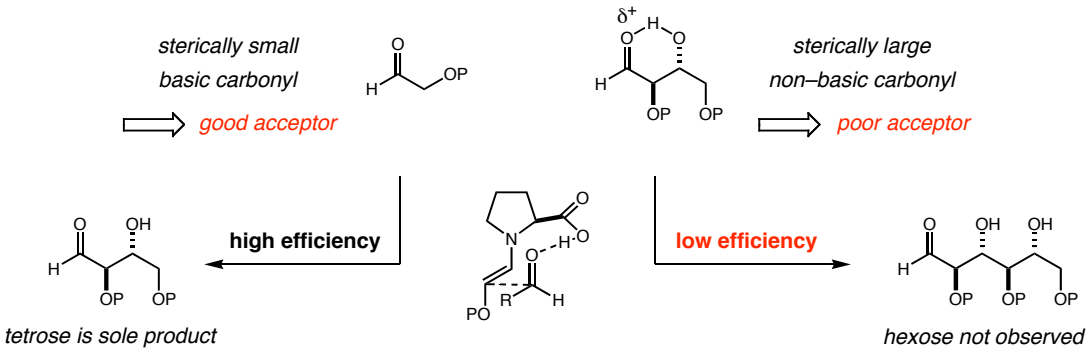


The first step, the aldol union of two glycoaldehyde fragments (eq 1), is described in Chapter 4 of this manuscript.[2] The completion of this strategy by invention of a cross aldol between a protected α-oxyaldehyde aldol donor with a tetrose aldol acceptor (eq 2) is the subject of the present discussion.

Direct Cross Aldol Approach to Hexoses

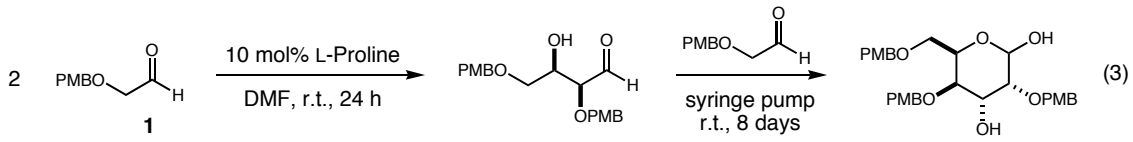
As we discussed in Chapter 3, due to the larger steric size and decreased basicity of an aldol dimer's carbonyl, proline-catalysis preferentially affords aldol dimers instead of aldol trimers such as hexoses (Figure 2).

Figure 2. Basicity and Steric Size Determine Product Distribution



[2] A preliminary communication of those results has been published: Northrup, A. B.; Mangion, I. K.; Hettche, F.; MacMillan, D. W. C. *Angew. Chem. Int. Ed.* **2004**, *43*, 2152.

However, one can envision that by allowing an initial homodimerization to occur, then adding a third equivalent of aldehyde *via* syringe pump, that one could perform such an aldol trimerization process.[3] Indeed, it was found that a catalytic amount of L-proline could effect such a reaction for *para*-methoxybenzyl-protected aldehyde **1** to form D-gulose **3** in a single step (eq 3). That reaction represents the first one-pot synthesis of an optically enriched aldohexose from achiral starting materials. Furthermore, that aldol trimerization reaction lends support to the hypothesis that this type of aldolization process is a viable pre-biotic route to carbohydrates.[4]



(3)

The remainder of the material isolated from the aldol trimerization reaction consisted of dimer **2** (21% yield), β-elimination of dimer **2** (19% yield), and a minor amount of unreacted **1**. Despite the extremely slow addition of aldehyde **1** to dimer **2**, that cross aldol process was quite inefficient due to the high propensity for homodimerization of aldehyde **1**. Interestingly, the trimerization produces a threose sugar, even though the dimerization affords a majority of erythrose products. The selectivity of the second aldol step can be rationalized due to the different basicities of the carbonyls of *syn*-**2** and *anti*-**2** (Figure 3).

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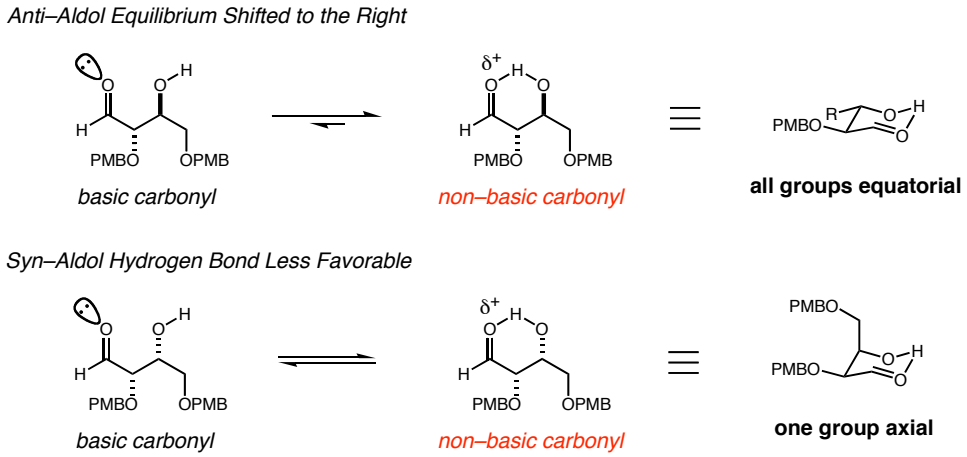
[3] A related alkyl aldehyde trimerization has been reported: Chowdari, N. S.; Ramachary, D. B.; Cordova, A.; Barbas, C. F. III *Tet. Lett.* **2002**, *43*, 9591.

[4] (a) Müller, D.; Pitsch, S.; Kittaka, A.; Wagner, E.; Wintner, C.; Eschenmoser, A. *Helv. Chim. Acta.* **1990**, *73*, 1410. (b) Pitsch, S.; Eschenmoser, A.; Gedulin, B.; Hui, S.; Arrhenius, G. *Orig. Life Evol. Biosph.* **1995**, *25*, 294. (c) Krishnamurthy, B.; Pitsch, S.; Arrhenius, G. *Orig. Life Evol. Biosph.* **1999**, *29*, 139.

Figure 3. Influence of Aldol Stereochemistry on Hydrogen Bond Equilibrium



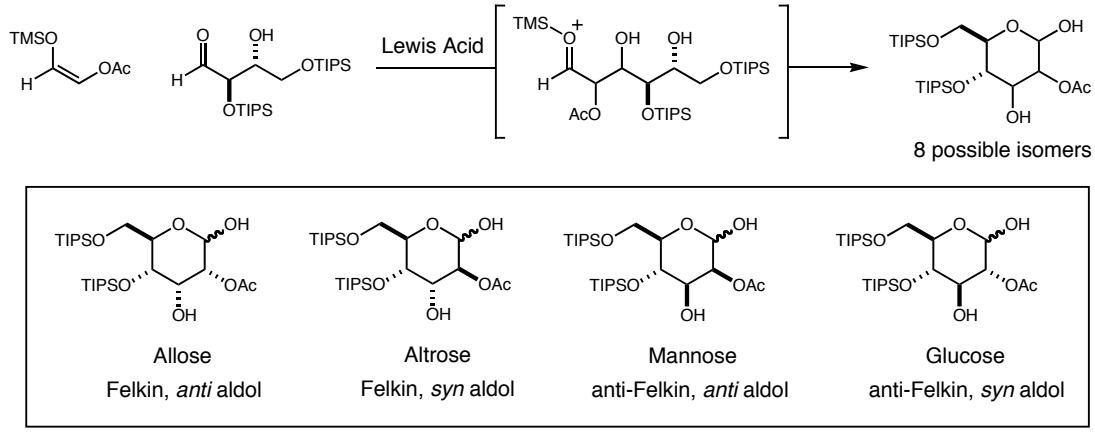
Both of those dimers exist as internally hydrogen-bound six-membered rings in equilibrium with an open-chain form. As *syn*-**2** requires one axial substituent in the lowest energy chair conformation, its equilibrium is shifted more toward the open-chain form. In contrast, all groups may occupy an equatorial position for hydrogen bonded *anti*-**2**. Due to that stereochemical difference, *syn*-**2** may have a significant fraction of the equilibrium mixture possessing the basic carbonyl necessary for reaction with a proline enamine. Therefore, one may predict that *syn*-**2** should be more reactive in proline-catalyzed aldol reactions than *anti*-**2** based on our current model for reactivity trends being reliant primarily on carbonyl basicity for aldol acceptors.

While that trimerization represents a significant advance in *de novo* carbohydrate synthesis, it has several limitations. For example, only the gulose stereochemistry is accessible due to a reliance on the same chiral catalyst for both aldol steps. Furthermore, this one-pot process suffered from only a modest amount of differentiation of the hexose product and a low yield. Therefore, this one-pot sugar synthesis, though viable, does not have the potential to become a truly general approach to the problem of hexose synthesis.

A Mukaiyama-Type Aldol Strategy

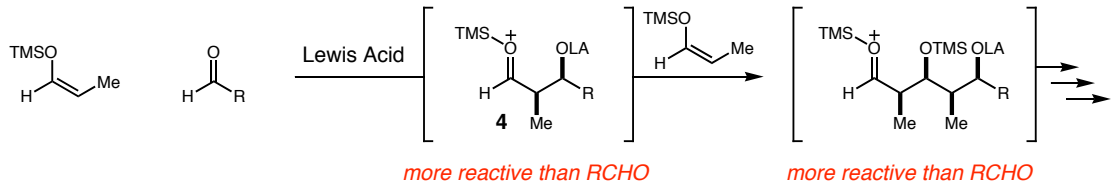
Based on those observations, an alternative strategy was designed whereby an initial enantioselective *anti*-selective aldol dimerization reaction followed by a second diastereoselective Mukaiyama-type aldol reaction would potentially enable the synthesis of each of the erythrohexoses (glucose, mannose, allose, and altrose) in a highly differentiated form (Scheme 2).

Scheme 2. Mukaiyama-Type Aldol Should Allow General Hexose Synthesis



While such a strategy seems attractive due to the potential to vary the Lewis acid to access each of the aldohexose diastereomers, Mukaiyama aldol reactions employing aldehyde-derived enolsilanes are without precedent.[5] The lack of aldehyde enolsilanes in the aldol literature likely stems from the reactivity of the intermediate silyloxycarbenium ion **4** (Figure 4).

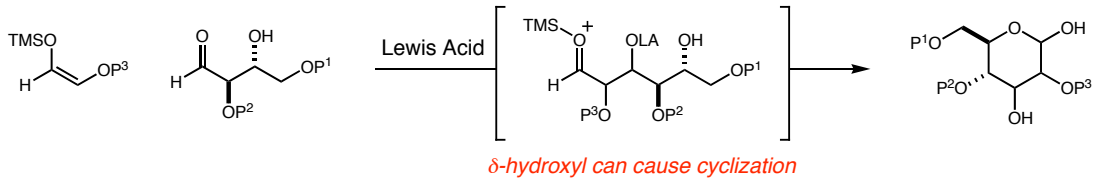
Figure 4. Aldols with Aldehyde Silylenolethers Should Lead to Oligomerization



[5] For a Lewis base catalyzed aldol reaction involving trichlorosilylenolethers, see: Denmark, S. E.; Ghosh, S. K. *Angew. Chem. Int. Ed.* **2001**, *40*, 4759.

As Figure 4 demonstrates, the initial aldehyde product **4** is more activated than the starting aldehyde and should undergo facile oligomerization. Therefore, the use aldehyde enolsilanes in this reaction necessitates suppression of the oligomerization pathway. Fortunately, the presence of a reactive alcohol δ to the nascent carbenium ion allows for an intramolecular cyclization that should out-compete the potential intermolecular aldol oligomerization (Figure 5).

Figure 5. Unprotected β-Hydroxyaldehdye Substrate Should Halt Oligomerization



That cyclization requires the use of an unprotected β-hydroxyaldehyde substrate for the Mukaiyama aldol reaction, which is another unprecedented feature of the proposed transformation. Therefore, the proposed strategy (Scheme 2) requires the development of a novel Mukaiyama-type aldol variant.

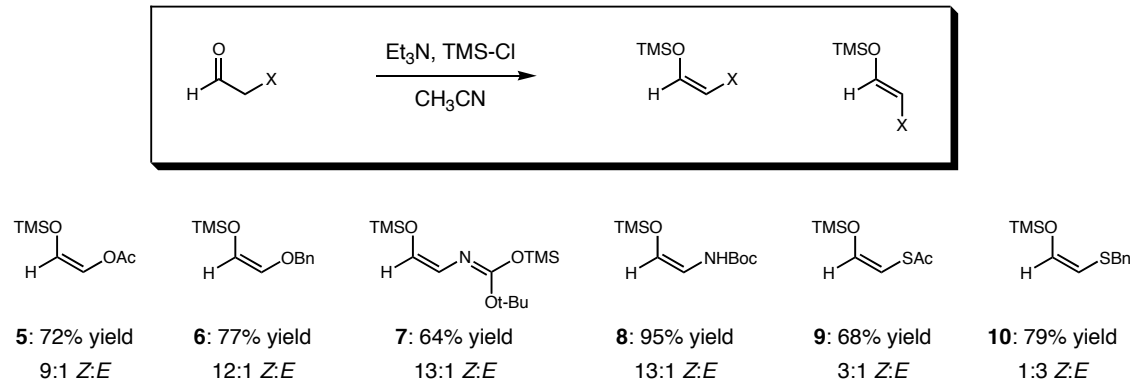
Synthesis of Aldehyde-Derived Enolsilanes

At the outset of this project, relatively few enolsilanes had been generated by the enolization of saturated aldehydes, presumably due to the propensity of aldehydes to undergo homo-aldolization reactions when exposed to bases. While it was found that the previously reported standard enolization conditions[6] failed to reproducibly afford high yields and sufficient purities of the required α-oxygenated enolsilanes, the use of excess triethylamine (4 equivalents) and chlorotrimethylsilane (2 equivalents) in acetonitrile (0.5

[6] Et_3N/TMSCl in DMF: (a) Stang. P. J. *et al. J. Am. Chem. Soc.* **1974**, *96*, 4562. TMSCl/Et_3N/NaI in CH_3CN/Pentane: (b) Cazeau, P.; Duboudin, F.; Moulines, F.; Babot, O.; Dunogues, J. *Tetrahedron* **1987**, *43*, 2075.

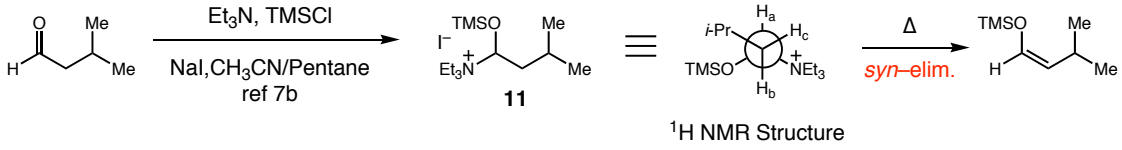
M) followed by a non-aqueous workup and distillation provided consistently high yields and moderate *Z*-selectivity for a range of aldehyde-derived enolsilanes (Figure 6).

Figure 6. Synthesis of Aldehyde Enolsilanes



A rationalization for the *Z*-selectivity of this enolization process has been proposed[7] by invoking a unimolecular decomposition of the observed quaternary ammonium ion intermediated **11** via a *syn*-elimination of triethylamine and H_c (Figure 7). However, an alternative explanation would be an E1-type mechanism wherein the initial silyloxycarbenium ion formation is followed immediately by selective deprotonation of H_b by the liberated triethylamine according to the principle of least motion.

Figure 7. *Z*–Selectivity Results from a *Syn*-Elimination Process

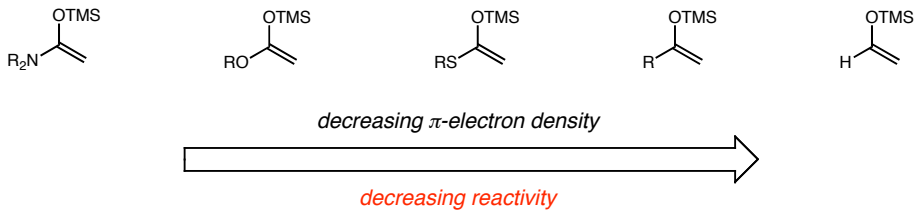


Titanium-Mediated Aldol Reactions

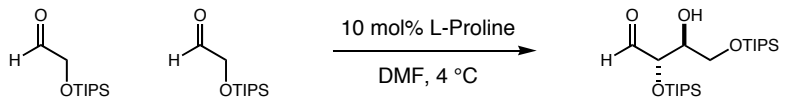
It was realized from the outset that aldehyde silylenolethers would be significantly less reactive than the more commonly employed ketone enolsilanes and silylketeneacetals due to their lower levels of π-electron density (Figure 8).

[7] See ref. 6b for a discussion of this elimination.

Figure 8. Aldehyde Enolsilanes are Less Reactive than Other Enolates



Therefore, initial studies toward the required carbohydrate-forming Mukaiyama-type aldol reaction were focused on strong activators of the Mukaiyama aldol reaction, such as titanium (IV) chloride ($TiCl_4$). The substrates for initial investigation were selected to maximize the orthogonality of the protecting groups on the sugar product. A silyloxyactealdehyde was chosen for the initial proline aldol dimerization step due to the well-known ability to selectively deprotect a 1° silyl group in the presence of a 2° silyl group.[8] As described in the preceding chapter, the dimerization of TIPS-aldehyde **12** in the presence of 10 mol% L-proline at room temperature smoothly affords a 92% yield of a highly enantioenriched (95% ee) protected L-erythrose **13** (eq 4).



(4)

Acetoxyacetaldehyde was chosen for the enolsilane component due to both the orthogonality of acetate to the TIPS protecting group and also for the well-known ability of an acetoxy group in the 2-position of the hexose ring to direct the stereochemistry of glycosidic coupling reactions.[1]

Based on those criteria, the reaction between acetoxyenolsilane **5** and TIPS-protected erythrose **13** promoted by $TiCl_4$•$(THF)_2$ was conducted in dichloromethane starting at –78 °C and warming until a reaction was detected by TLC analysis (eq 5).

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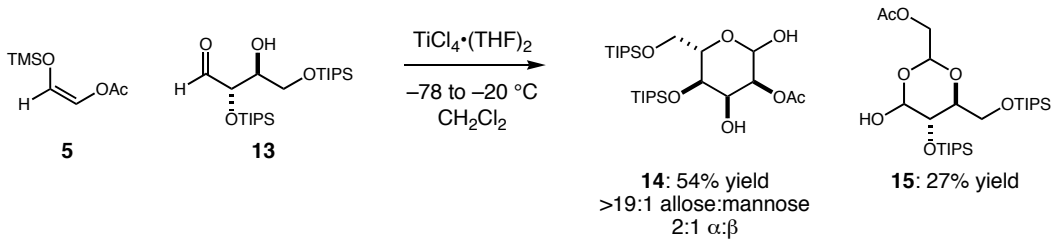
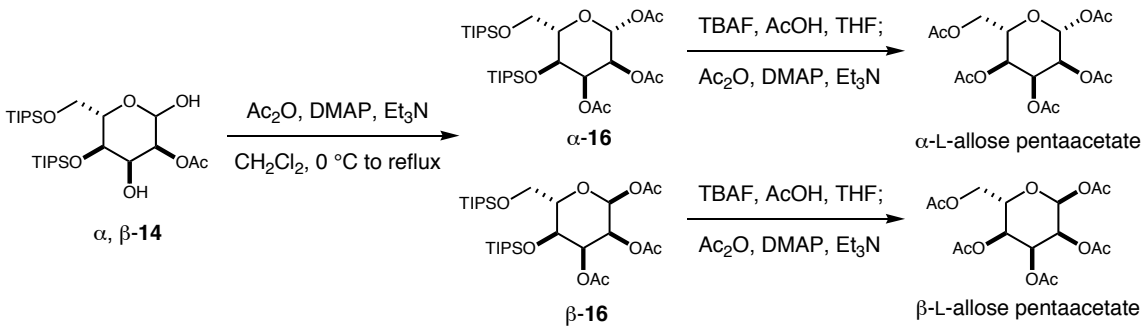
[8] For a review on selective silyl group deprotection strategies, see: Nelson, T. D.; Crouch, R. D. *Synthesis* **1996**, 1031.



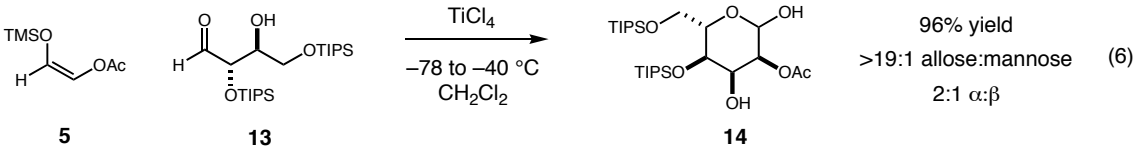
(5)

Gratifyingly, at –20 °C a smooth reaction occurred to form a two new hexose products, α, β-allose **14** along with an acetal side product **15**. The identities of the new hexose products were established by chemical correlation to the corresponding pentaacetates and comparison with authentic samples of each of the sixteen aldohexose pentaacetate isomers (Scheme 3).

Scheme 3. Chemical Correlation to the Sugar Pentaacetate Confirms Stereochemistry



Optimization of that lead result (eq 5) provided the observations that $TiCl_4$ was a superior Lewis acid to $TiCl_4$•$(THF)_2$ for this substrate and that switching to that more reactive titanium source allowed for decreased reaction temperatures, providing α, β-allose **14** as the sole hexose product in 96% yield (eq 6).

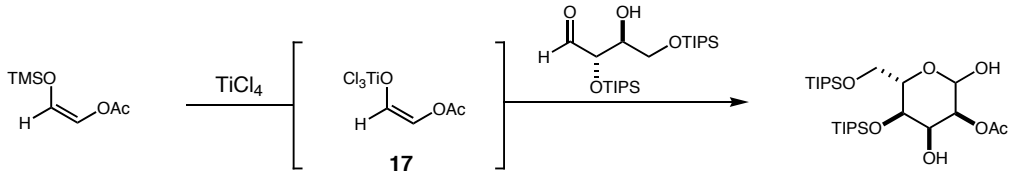


(6)

Rationalization of the observed allose stereochemistry (Felkin, *anti* aldol) could not be accomplished through a traditional Mukaiyama aldol stereochemical model, even by invoking a chelate between the aldehyde and β-hydroxyl of the substrate. A

preliminary indication this reaction may not be a Mukaiyama-type aldol reaction came from the observation that the addition of $TiCl_4$ to the reaction mixture immediately produced the intensely red color indicative of a titanium enolate. In fact, such transmetallations of ketone-derived silylenolethers with $TiCl_4$ have been previously reported,[9] although that type of transmetallation has not been reported with aldehyde enolsilanes (Figure 9).

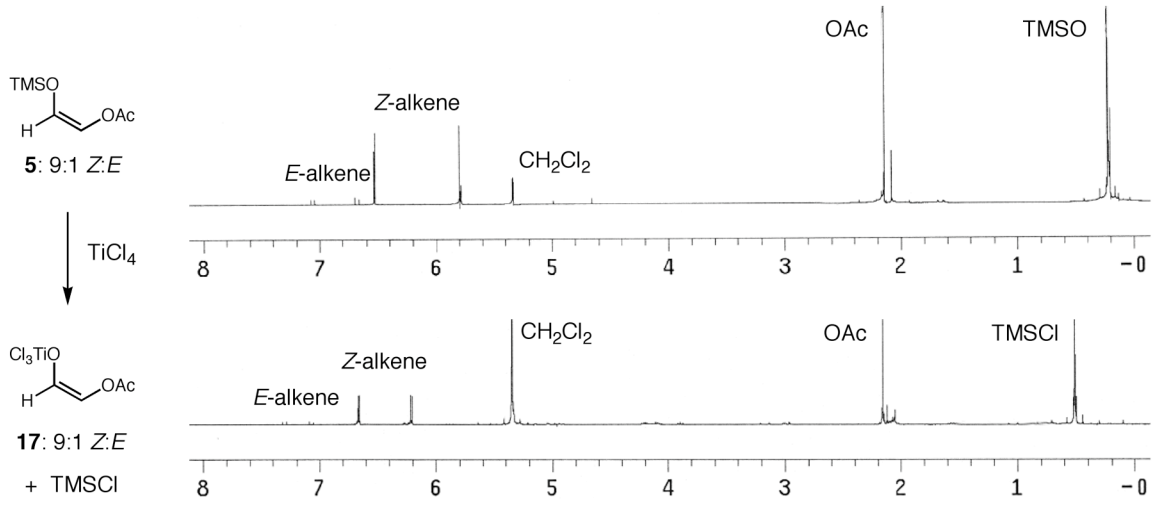
Figure 9. Do $TiCl_4$-Mediated Aldol Reactions Involve a Metalloenolate Intermediate?



To test the hypothesis that this reaction proceeds *via* titanium enolate intermediate **17**, a study of the purported transmetallation was undertaken using ^1H NMR. As Figure 10 demonstrates, in less than five minutes, the addition of $TiCl_4$ to a solution of enolsilane **5** in CD_2Cl_2 causes the liberation of TMSCl, complete consumption of silylenolether **5**, and the formation of a new enolate species assigned to trichlorotitanylenolate **17**.

[9] (a) Nakamura, E.; Shimada, J. Horiguchi, Y.; Kuwajima, I. *Tet. Lett.* **1987**, *28*, 3341. (b) Yamago, S.; Machii, D.; Nakamura, E. *J. Org. Chem.* **1991**, *56*, 2098.

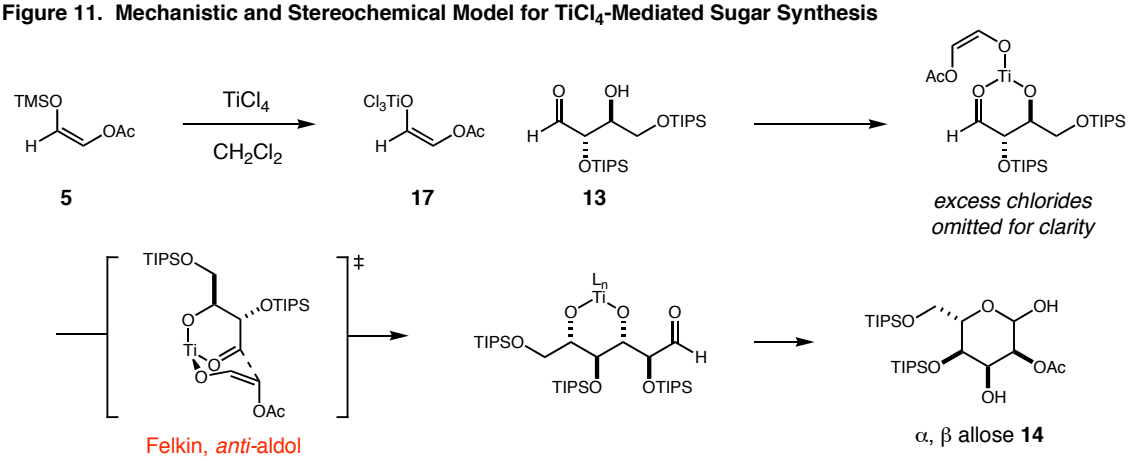
Figure 10. Enolate Transmetallation is Readily Observed by ^{1}H NMR Analysis



Therefore, there is strong support for the belief that a trichlorotitanylenolate is formed rapidly and completely before the addition of the aldol acceptor.

With that knowledge, a mechanism including a chelated bicyclic transition state model is proposed that accounts for the observed Felkin, *anti*-aldol selectivity that produces α, β-allose **14** (Figure 11).

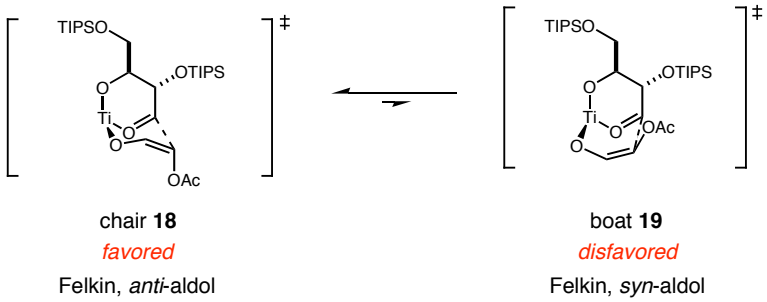
Figure 11. Mechanistic and Stereochemical Model for $TiCl_4$-Mediated Sugar Synthesis



Given the oxophilicity of titanium (IV) Lewis acids, that proposal invokes the coordination of titanium to three oxygen atoms—the enolate, aldehyde carbonyl, and β-hydroxyl. The Felkin face of attack of the aldehyde by the enolate is ensured by a steric

repulsion of the enolate with the α-silyloxy group on the anti-Felkin face. Transannular strain forces the transition state to adopt a chair-like arrangement of the enolate, aldehyde and Lewis acid (*cf.* boat **19** *vs.* chair **18**) that produces the observed *anti*-aldol selectivity (Figure 12).

Figure 12. Transannular Strain Enforces a Chair Conformer of the Bicyclic Transition State



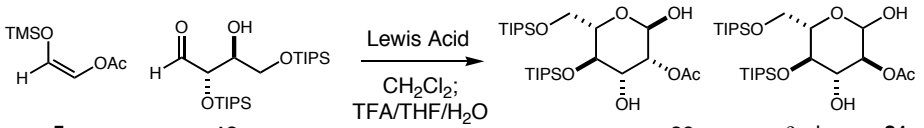
chair **18**
favored
Felkin, *anti*-aldol

boat **19**
disfavored
Felkin, *syn*-aldol

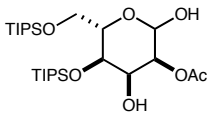
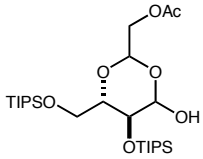
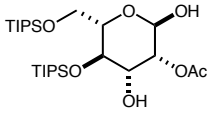
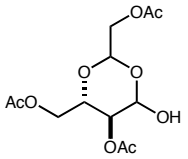
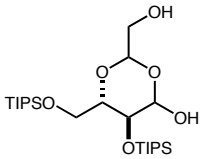
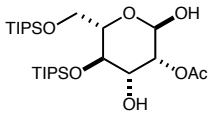
Magnesium-Mediated Aldol Reactions

Whereas $TiCl_4$ led to a transmetallation when exposed to an aldehyde enolsilane, it was believed that other Lewis acids would not readily form a reactive metal enolate capable of enabling a closed aldol transition state. The potential for accessing a mechanistically distinct Mukaiyama-type aldol reaction manifold should lead to hexose isomers inaccessible by $TiCl_4$ promotion. To that end, a brief survey of Lewis acids was undertaken in the reaction of acetoxyenolsilane **5** and TIPS-protected erythrose **13** conducted in dichloromethane (Table 1).

Table 1. Survey of Lewis Acid Promoters for Mukaiyama-Type Aldol Reaction



5 **13** α-mannose **20** α, β-glucose **21**

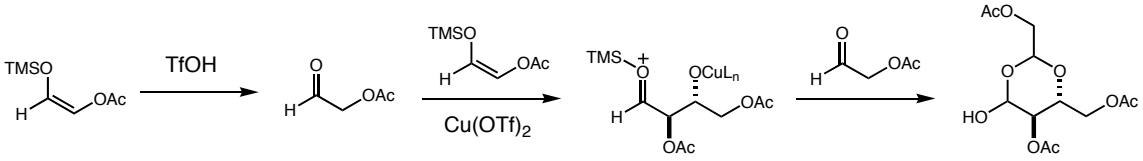
entry	Lewis Acid	major product	Temp (°C)[a]	conversion[b]	d.r. (**20:21**)[c]
1	$SnCl_4$		–40	45	>19:1[d]
2	$Yb(OTf)_3$		–20	93	--
3	$AlCl_3$		–20	25	2:1
4	$Cu(OTf)_2$		–20	73	>19:1[e]
5	$Sn(OTf)_2$		–60	52	--
6	$MgBr_2•Et_2O$		–20	90	>19:1

[a]Temperature refers to the final temperature of the reaction mixture after being warmed from –78 °C. [b]Conversion determined by ^1H NMR analysis of the crude reaction mixture. [c]Diastereoselectivity (d.r.) was determined by ^1H NMR integration of the crude reaction mixture and refers to the ratio of the combined anomers of each hexose product. [d]The d.r. refers to an allose:mannose ratio. [e]*Syn*/*anti*-aldol selectivity.

As Table 1 demonstrates, the chemoselectivity of the reaction between enolate **5** and aldehyde **13** is remarkably dependent on the choice of Lewis acid. While Lewis acids such as $BF_3•Et_2O$, $Ti(OiPr)_4$, and $Zn(OTf)_2$ were unreactive (data not shown), other promoters such as $Yb(OTf)_3$, and $Sn(OTf)_2$ afforded acetals as the major product (entries 2 and 5). Interestingly, $Cu(OTf)_2$ afforded a trimeric product entirely derived from the

enolsilane component. One can rationalize its formation *via* an initial acid-catalyzed enolate deprotection followed by Mukaiyama aldol and protection by another equivalent of aldehyde (Figure 13).

Figure 13. Triacetate is Formed by Aldol Followed by Protection



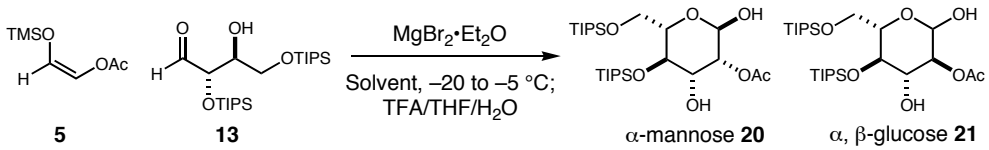
Other than tin (IV) chloride, which underwent a transmetallation similar to $TiCl_4$ to afford α, β-allose **14**,[10] each of the other Lewis acids in Table 1 afforded a mixture of α, β-glucose **21**, α-mannose **20**, and acetal **15**. Remarkably, reactions including $MgBr_2 \bullet Et_2O$ performed with superior reaction efficiencies and selectivities, affording α-mannose **20** as the sole hexose product[11] and only a minor amount of acetal **15**.

During an effort to optimize the mannose-forming reaction parameters, a surprising phenomenon was observed—*simply by changing the solvent from dichloromethane to ether or toluene provided a complete reversal in selectivity from mannose to glucose-selective* (Table 2).

[10] For the transmetallation of trimethylsilylenolethers with $SnCl_4$, see: Nakamura, E.; Kuwajima, I. *Tet. Lett.* **1983**, *24*, 3347.

[11] Absolute and relative stereochemistry determined by correlation to the corresponding pentaacetate.

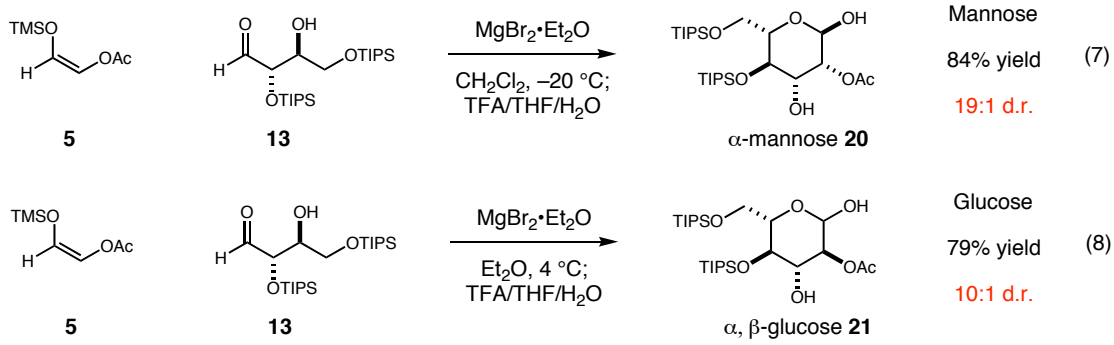
Table 2. Solvent Effects in Magnesium-Promoted Mukaiyama-Type Aldol Reactions



entry	solvent	dielectric constant	t(h)	conversion[a]	d.r. (**21**:**20**)[b]
1	Pentane	1.84	24	75	4:1
2	Hexanes	1.89	24	86	3:1
3	Toluene	2.38	24	100	8:1
4	Et_2O	4.20	48	85	9:1
5	$CHCl_3$	4.80	24	81	1:1
6	THF	7.58	72	0	--
7	CH_2Cl_2	8.90	24	81	1:19

[a]Conversion determined by ^{1}H NMR analysis of the crude reaction mixture. [b]Diastereoselectivity (d.r.) was determined by ^{1}H NMR integration of the crude reaction mixture and refers to the ratio of the combined anomers of each hexose product.

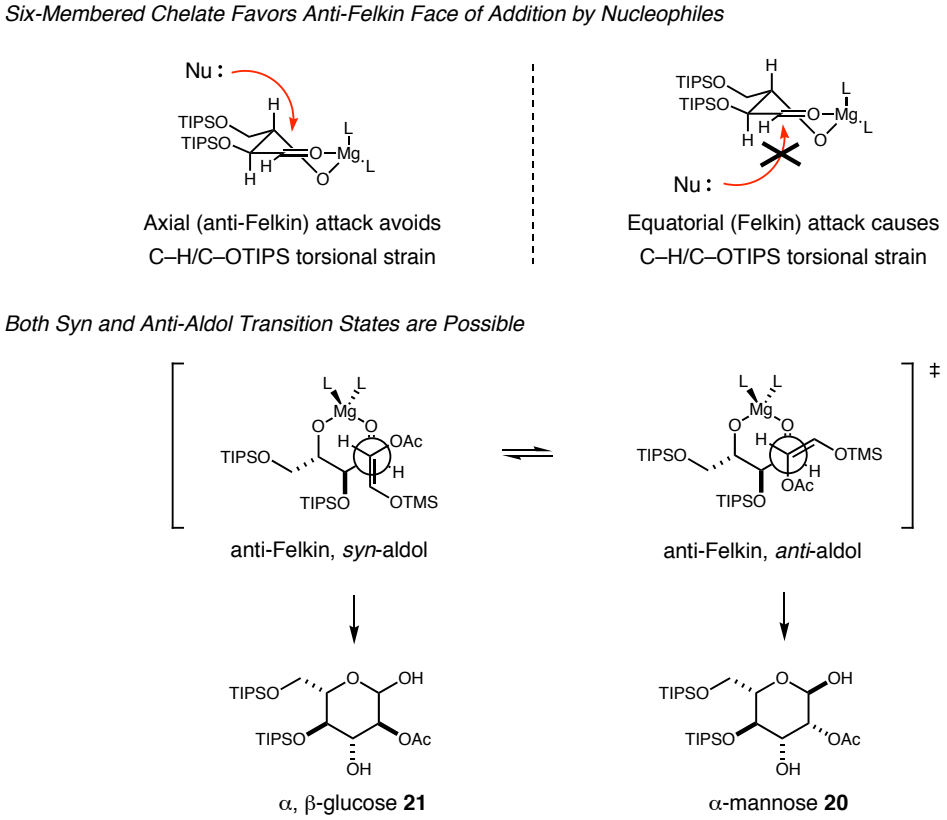
As Table 2 demonstrates, there is no apparent trend in either solvent polarity or Lewis basicity that readily accounts for the observed switch in diastereoselection due to solvent effects. However, employing that useful information, magnesium-promoted aldol reactions were fully optimized to afford good yields and diastereoselectivities of both α-mannose **20** (eq 7) and α, β-glucose **21** (eq 8).



The anti-Felkin stereochemistry of those magnesium-mediated aldol reactions is readily rationalized based on an open aldol transition state between the enolsilane and a magnesium-chelated β-hydroxyaldehyde. As Figure 14 demonstrates, nucleophilic attack

of the magnesium chelate occurs preferentially from the anti-Felkin face so that the reaction may proceed through a twist-chair transition state that minimizes torsional strain of the aldehydic proton eclipsing the bulky α-OTIPS moiety.

Figure 14. Stereochemical Rationale for Magnesium-Mediated Aldol Reactions

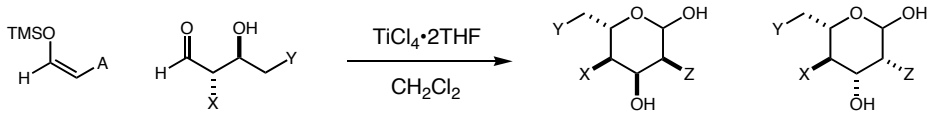


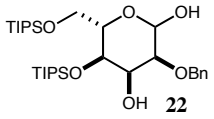
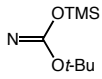
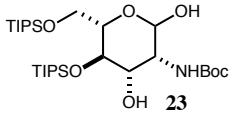
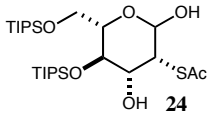
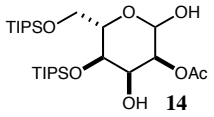
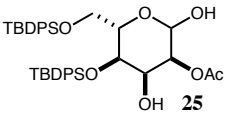
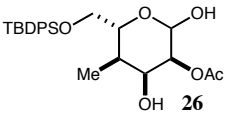
The origins of *syn*/*anti*-aldol selectivity switching based on solvent effects, however, are less readily understood. It is readily observed that there are low energy transition states leading to either the *syn* or *anti*-aldol products, although the reasons remain unclear why reactions conducted in ether, toluene, and pentane choose the *syn*-aldol pathway whereas reactions in dichloromethane prefer the *anti*-aldol manifold.

Substrate Scope Studies

To probe the generality of this approach to the synthesis of a wide variety of both natural and unnatural sugars, the possibility of applying the conditions identified above to a range of substrates was examined. As summarized in Table 3, $TiCl_4$ is both an excellent and general mediator for this aldol process.

Table 3. Representative Substrate Scope for the Titanium-Mediated Hexose Synthesis



entry	A	X	Y	product	Temp (°C)[a]	% yield[b]	d.r.[c]	%ee[d, e]
1	OBn	OTIPS	OTIPS	 **22**	–30	83	>19:1	95
2		OTIPS	OTIPS	 **23**	–40	74	10:1	95
3	SAc	OTIPS	OTIPS	 **24**	–20	71	>19:1	95
4[f]	OAc	OTIPS	OTIPS	 **14**	–40	96	>19:1	95
5	OAc	OTBDPS	OTBDPS	 **25**	–20	86	>19:1	96
6	OAc	Me	OTBDPS	 **26**	–30	68	>19:1	99

[a]Temperature refers to the final temperature of the reaction mixture after being warmed from –78 °C. [b]Yield refers to the combined yield of diastereomers. [c]Diastereoselectivity (d.r.) was determined by ^{1}H NMR integration of the crude reaction mixture and refers to the ratio of the combined anomers of each hexose product. [d]Enantioselectivity determined by chiral HPLC analysis. [e]Relative and absolute stereochemistries assigned by chemical correlation. [f]$TiCl_4$ was employed in place of its THF complex.

In addition to participating and non-participating protecting groups being readily accommodated at the 2-position of the sugar (entries 1 and 4, 83 to 96% yield, >19:1 d.r.), other heteroatoms such as nitrogen and sulfur may be incorporated without any loss in reaction efficiency (entries 2 and 3, 71 to 74% yield, 10:1 to >19:1 d.r.). That fact allows access to vitally important 2-deoxy, 2-amino sugars, unnatural 2-deoxy, 2-thio sugars, and, by desulfurization, 2-deoxy sugars. However, in the case of thio- and amino-substituted enolsilanes (entries 3 and 4), there is a reversal of the normal allose selectivity in favor of a mannose-selective process. The scope of this transformation is equally broad with respect to the aldol acceptor component. With this methodology, not only can differently-protected erythroses be employed (*cf.* entries 4 and 5) but also unnatural erythrose derivatives are good aldol acceptors allowing two-step access to enantioenriched 4-deoxy, 4-carbo sugars (entry 6, 68% yield, >19:1 d.r., 99% ee).

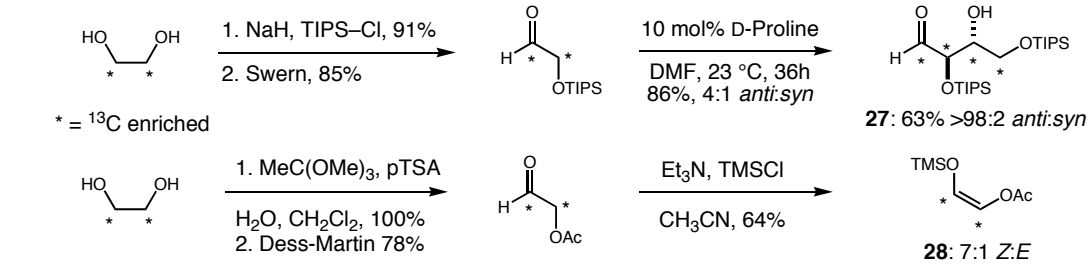
Synthesis of Isotopically-Labeled Hexoses

Isotopically enriched substances play a pivotal role in the elucidation of the mechanism of biological and chemical processes. However, the study of carbohydrate-involved biological pathways has been greatly retarded by the difficulty and expense of preparing labeled polysaccharides using standard sugar synthesis techniques. Due to the ability to produce three distinct differentially-protected hexoses (glucose **21**, mannose **20**, and allose **14**) in just two steps from the same two simple aldehyde starting materials, this technology seems ideally suited for the production of isotopically-enriched carbohydrates.

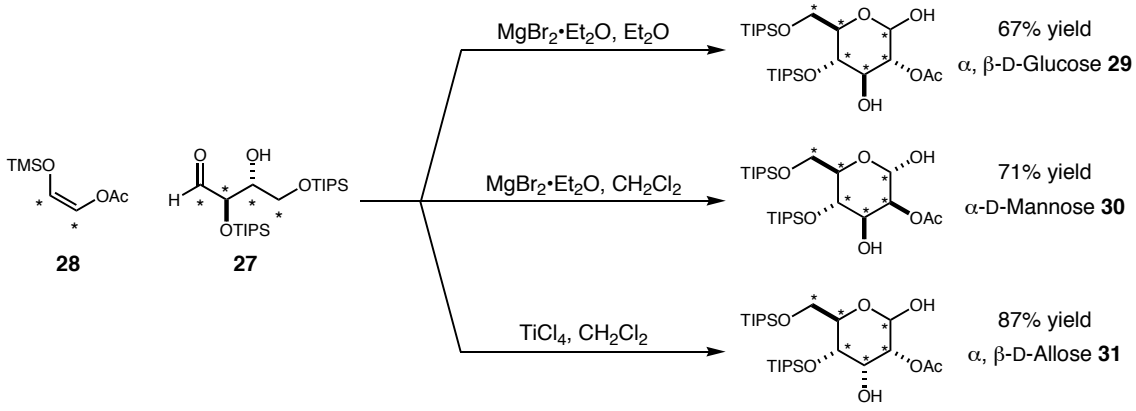
As an illustrative example of the power of this methodology for the production of labeled carbohydrates, a synthesis of differentially protected fully ^{13}C-labeled glucose, mannose, and allose was undertaken. A convenient starting material for these studies proved to be $^{13}C_2$-ethylene glycol. Due to the availability of multiple different isotopically enriched forms of ethylene glycol, this synthetic scheme should be applicable to deuterium, tritium, and ^{14}C labeling of the sugar ring (Scheme 4).

Scheme 4. Synthesis of Fully ^{13}C-Labeled Carbohydrates

Ethylene Glycol is a Convenient Common Starting Material



Common Intermediates Enable a Divergent Synthesis of Three Aldohexoses

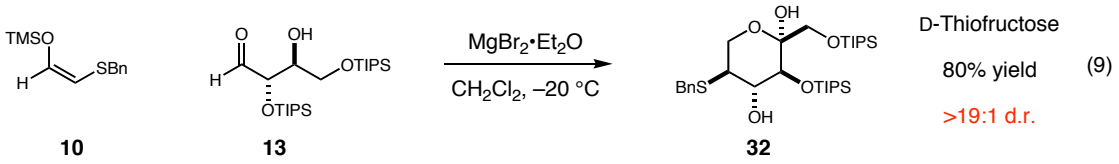


As Scheme 4 illustrates, in just four chemical steps from $^{13}C_2$-ethylene glycol, each of the hexose products α, β-glucose **29**, α-mannose **30**, and α, β-allose **31** were synthesized in 33%, 35%, and 43% yields, respectively. In contrast to the unlabeled work above, the natural D-enantiomer of each sugar was produced to highlight the stereochemical versatility of this approach. Importantly, the isotopic labeling did not significantly alter

the yield or stereochemical course of either selective aldehyde aldol reactions. It should also be noted that both the labeled enolsilane **28** and TIPS-protected erythrose **27** were available in gram quantities from only 1.00 g of ethylene glycol. It is hoped that applications of this methodology will enable a broader understanding of glycobiology.

An Unexpected Aldol-Tischenko Route to Ketohexoses

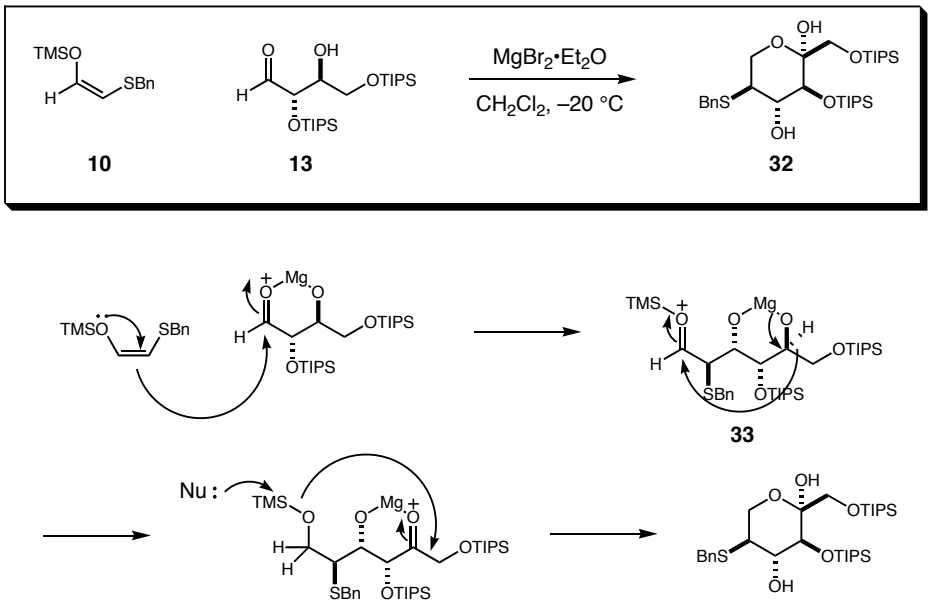
While aldehyde enolsilanes exhibit generally predictable reactivity, some enolsilanes display unusual and unexpected behavior. One such example occurred in the reaction of benzylthioenolsilane **10** with TIPS-protected dimer **13** promoted by $MgBr_2 \cdot Et_2O$ to afford thiofructose **32** as the sole hexose product (eq 9). The unusual reactivity of enolsilane **10** is in sharp contrast to that of acetylthioenolate **9** (*cf.* eq 9 and entry 3 of Table 3).



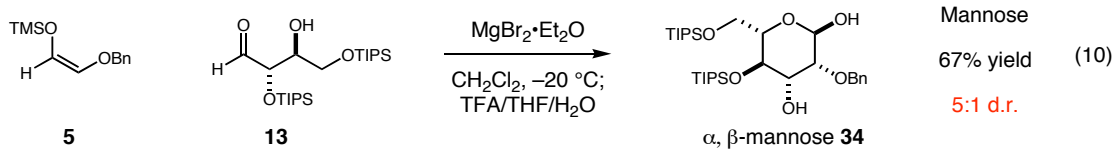
10 **13** **32**

The formation of fructose **32** can be rationalized *via* an aldol-Tischenko mechanistic pathway (Figure 15).

Figure 15. Proposed Mechanism for Thiofructose Formation



Interestingly, substituting benzyloxyenolsilane **6** under the exact conditions that led to the formation of ketohexose **32** produced the expected aldohexose α, β-mannose **34** in reasonable yield with no trace of fructose-derived products (eq 10).



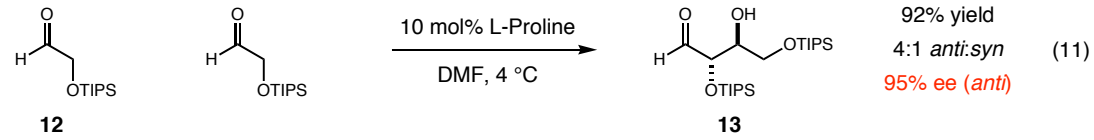
As the sole difference between equations 9 and 10 is a single sulfur atom, the exact reason for the divergent reactivity is unclear. However, it is possible that the presence of the sulfur atom sufficiently alters the reduction potential of the intermediate silyloxycarbenium ion **33** to undergo intramolecular hydride transfer faster than cyclization by attack of the alkoxide present in **33**. Alternatively, the sulfur atom could change the conformation of intermediate **33**, potentially by coordinating extra magnesium ions, to allow proper alignment of the hydride source and the carbonyl π*-orbital for the reduction to take place.

Summary and Conclusions

A new two-step method for the production of enantioenriched differentially-protected hexoses has been developed. That novel strategy stimulated the development of three new aldehyde aldol reaction variants: (1) the direct enantioselective aldol coupling of glycoaldehydes (eq 11); (2) a transmetallation-based diastereoselective indirect aldehyde aldol (eq 12); (3) the first Mukaiyama-type aldol reaction of aldehyde-derived enolsilanes (eqs 13 and 14). Those newly invented transformations have allowed enantioselective access to well-protected forms of glucose, mannose, allose, gulose, and also some unnatural sugar derivatives (Figure 16).

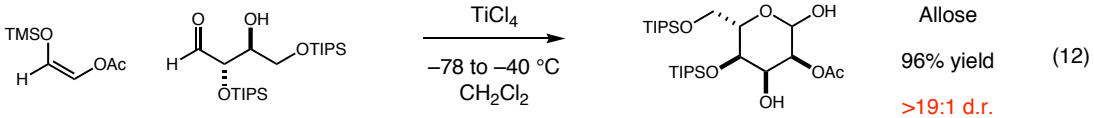
Figure 16. New Aldol Reactions Invented for Hexose Synthesis

Direct Enantioselective Catalytic Aldehyde Aldol Reaction



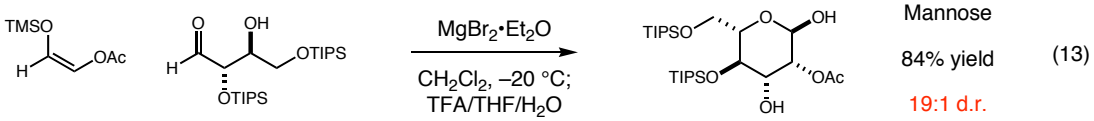
12 **13**

Transmetallation-Initiated Diastereoselective Aldehyde Aldol Reaction

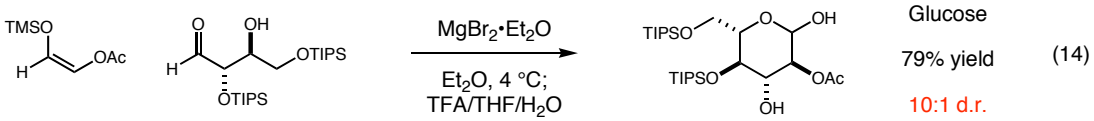


5 **13** α, β-allose **14**

Mukaiyama-Type Aldehyde Aldol Reaction



5 **13** α-mannose **20**



5 **13** α, β-glucose **21**

Significantly, that two-step *de novo* synthesis of carbohydrates is the first such approach to hexoses that is actually more efficient than simply protecting commercially

available sugars. Therefore, that aldehyde aldol strategy should enable practical total syntheses of biologically relevant polysaccharides from achiral starting materials in a more expedient fashion than possible from the chiral pool. Such a long-needed increase in carbohydrate synthetic efficiency should become an enabling technology for future developments in glycobiology.

Supporting Information

General Information. Commercial reagents were purifies prior to use following the guidelines of Perrin and Armarego.[12] All solvents were purified according to the method of Grubbs.[13] Non-aqueous reagents were transferred under nitrogen via syringe or cannula. Organic solutions were concentrated under reduced pressure on a Büchi rotary evaporator using an ice-water bath for volatile samples. Chromatographic purification of products was accomplished using forced-flow chromatography on ICN 60 32-64 mesh silica gel 63 according to the method of Still.[14] Thin-layer chromatography (TLC) was performed on EM Reagents 0.25 mm silica gel 60-F plates. Visualization of the developed chromatogram was performed by fluorescence quenching or by anisaldehyde, ceric ammonium molybdate, or $KMnO_4$ stain.

^1H and ^{13}C NMR spectra were recorded on a Mercury 300 (300 MHz and 75 MHz) or an Inova 500 (500 MHz and 125 MHz) as noted, and are internally referenced to residual protio solvent signals. Data for ^1H NMR are reported as follows: chemical shift (δ ppm), multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet), integration, coupling constant (Hz) and assignment. Data for ^{13}C NMR are reported in terms of chemical shift (δ ppm) for non-^{13}C labeled carbons or chemical shift (δ ppm), multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet), coupling constant (Hz) and assignment for ^{13}C labeled carbons. IR spectra were recorded on a Perkin Elmer Paragon 1000 spectrometer and are reported in terms of frequency of

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[12]Perrin, D. D.; Armarego, W. L. F. *Purification of Laboratory Chemicals;* 3rd ed., Pergamon Press, Oxford, 1988.

[13]Pangborn, A. B.; Giardello, M. A.; Grubbs, R. H.; Rosen, R. K.; Timmers, F. J. *Organometallics* **1996**, *15*, 1518.

[14]Still, W. C.; Kahn, M.; Mitra, A. J. *J. Org. Chem.* **1978**, *43*, 2923.

absorption (cm^{-1}). Mass spectra were obtained from the California Institute of Technology Mass Spectral facility. Gas liquid chromatography (GLC) was performed on Hewlett-Packard 6850 and 6890 Series gas chromatographs equipped with a split-mode capillary injection system and flame ionization detectors using a J&W Scientific DB-1701 (30 m x 0.25 mm) column as noted. High performance liquid chromatography (HPLC) was performed on Hewlett-Packard 1100 Series chromatographs using a Chiralcel OD-H column (25 cm) and OD-H guard (5 cm) as noted.

Preparation of Aldehyde Enolsilanes

(*Z*)-Acetic acid 2-(trimethylsilanyloxy)-vinyl ester (5). Acetoxyacetaldehyde[15] (4.13 mL, 49.0 mmol) was added in a single portion to a room temperature solution of chlorotrimethylsilane (12.43 mL, 98.0 mmol), triethylamine (27.31 mL, 195.9 mmol), and acetonitrile (100 mL). In less than five minutes, the solution became a hot white suspension that turned into a rust-colored suspension within fifteen minutes. Volatiles were removed *in vacuo* and the residue was extracted with three 50 mL portions of anhydrous diethyl ether. Distillation of the ethereal extracts afforded the title compound (6.13 g, 35.2 mmol, b.p. 64 °C (10 mmHg), 9:1 *Z*:*E*) in 72% yield as a clear, colorless liquid. IR (film) 3112, 2962, 2903, 1757, 1682, 1368, 1254, 1223, 1124, 1059, 961.3, 850.1, 754.5, 658.1 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) *Z* isomer: δ 6.56 (d, 1H, *J* = 3.3 Hz, CHOTMS); 5.77 (d, 1H, *J* = 3.3 Hz, CHOAc); 2.16 (s, 3H, $C(O)CH_3$); 0.23 (s, 9H, $Si(CH_3)_3$); *E* isomer: δ 7.11 (d, 1H, *J* = 10.5 Hz, CHOTMS); 6.66 (d, 1H, *J* = 10.5 Hz, CHOAc); 2.10 (s, 3H, $C(O)CH_3$); 0.20 (s, 9H, $Si(CH_3)_3$); ^{13}C NMR (75 MHz, $CDCl_3$) *Z*

[15] Brand, S.; Jones, M. F.; Rayner, C. M. *Tetrahedron Lett.* **1997**, *38*, 3595.

isomer: δ 168.2, 127.2, 121.2, 21.2, 0.0; HRMS (FAB+) exact mass calcd for $[M + H]^+$ ($C_7H_{15}O_3Si$) requires *m/z* 175.0791, found *m/z* 175.0788. The product ratios were determined by both ^1H NMR integrations and GLC analysis using a J&W Scientific DB-1701 column (50 ºC ramp 5 °C/min, 23 psi); *Z* isomer t_r = 10.46 min, *E* isomer t_r = 10.83 min.

(*Z*)-(2-Benzyloxy-vinyloxy)-trimethylsilane (6). Benzyloxyacetaldehyde (4.68 mL, 33.3 mmol) was added in a single portion to a room temperature solution of chlorotrimethylsilane (8.45 mL, 66.6 mmol), triethylamine (18.56 mL, 133 mmol), and acetonitrile (60 mL). In less than five minutes, the solution became a hot white suspension that turned into a rust-colored suspension within fifteen minutes. After stirring for 2 hours, volatiles were removed *in vacuo* and the residue was extracted with three 50 mL portions of anhydrous diethyl ether. Distillation of the ethereal extracts afforded the title compound (5.68 g, 25.5 mmol, b.p. 92 °C (0.08 mmHg), 12:1 *Z*:*E*) in 77% yield as a clear, colorless liquid. IR (film) 3034, 2959, 2901, 2872, 1667, 1497, 1455, 1397, 1362, 1298, 1252, 1129, 1026, 846.7, 734.0, 696.7 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.33 (m, 5H, Ph-H); 5.49 (d, 1H, *J* = 3.3 Hz, CHOTMS); 5.44 (d, 1H, *J* = 3.3 Hz, CHOBn); 4.81 (s, 2H, $PhCH_2$); 0.21 (s, 9H, $Si(CH_3)_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 137.7, 131.0, 128.6, 128.0, 127.7, 122.7, 74.1, –0.24; HRMS (FAB+) exact mass calcd for $[M + H]^+$ ($C_{12}H_{19}O_2Si$) requires *m/z* 223.1154, found *m/z* 223.1161. The product ratios were determined by ^1H NMR integration of the crude reaction mixture.

((*Z*)-[2-(Trimethylsilanyloxy)-vinyl]-carbamic acid *tert*-butyl ester)-trimethylsilyl-imidate (7). (2-Oxo-ethyl)-carbamic acid *tert*-butyl ester (3.0 g, 18.8 mmol) was added in a single portion as a solution in 10 mL of acetonitrile to a room temperature solution of chlorotrimethylsilane (4.78 mL, 37.7 mmol), triethylamine (10.51 mL, 75.4 mmol), and acetonitrile (30 mL). In less than five minutes, the solution became a hot white suspension that turned into a rust-colored suspension within fifteen minutes. After stirring for 3 hours, volatiles were removed *in vacuo* and the residue was extracted with three 50 mL portions of anhydrous diethyl ether. Distillation of the ethereal extracts afforded the title compound (3.67 g, 12.1 mmol, b.p. 66-68 °C, 0.25 mmHg, 13:1 *Z*:*E*) in 64% yield as a clear, colorless liquid. IR (film) 2977, 1709, 1689, 1482, 1392, 1367, 1313, 1251, 1170, 1086, 847.7, 784.3, 755.6 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.97 (d, 1H, *J* = 2.7 Hz, CHOTMS); 5.25 (d, 1H, *J* = 2.7 Hz, CHN); 1.49 (s, 9H, $C(CH_3)_3$); 0.24 (s, 9H, $Si(CH_3)_3$); 0.20 (s, 9H, $Si(CH_3)_3$); ^{13}C NMR (125 MHz, $CDCl_3$) δ 157.1, 134.7, 111.4, 80.1, 28.6, 0.74, –0.25; HRMS (FAB+) exact mass calcd for $[M + H]^+$ ($C_{13}H_{29}NO_3Si_2$) requires *m/z* 303.1686, found *m/z* 303.1695. The product ratios were determined by ^1H NMR integration of the crude reaction mixture.

(*E*)-Thioacetic acid *S*-(4-acetylsulfanyl-but-2-enyl) ester. Potassium thioacetate (10.0 g, 87.6 mmol) was added to a room temperature solution of (*E*)-1,4-dibromo-2-butene (8.61 g, 35.0 mmol) in dimethylformamide (50 mL). After stirring for 3 hours, the suspension was treated with 500 mL 10% $NaHCO_3$, extracted with 250 mL ethyl acetate, dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. Purification of the residue by flash chromatography (4:1 hexanes:ether) afforded the title compound (5.49 g,

26.9 mmol) as a white crystalline solid in 77% yield. IR (film) 3033, 2921, 1690, 1419, 1354, 1228, 1134, 960, 721.2, 683.4, 626.2 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.45 (m, 2H, CH=C); 3.30 (dd, 4H, *J* = 4.5, 1.8 Hz, CH_2); 2.14 (s, 6H, $C(O)CH_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 194.4, 128.5, 30.9, 30.7; HRMS (EI+) exact mass calcd for $[M\bullet]^+$ ($C_8H_{12}O_2S_2$) requires *m/z* 204.0279, found *m/z* 204.0278.

Thioacetic acid *S*-(2-oxo-ethyl) ester. A stream of ozone was passed through a solution of (*E*)-thioacetic acid *S*-(4-acetylsulfanyl-but-2-enyl) ester (5.49 g, 26.9 mmol) in dichloromethane (125 mL) at –78 °C for 1 hour until a light blue color developed. Then, the reaction was treated with methyl sulfide (9.87 mL, 134 mmol) and allowed to warm slowly to room temperature and stirred until a KI/starch paper test was negative, indicating complete decomposition of the ozonide intermediate. Distillation of the reaction mixture afforded the title compound (2.30 g, 19.5 mmol, b.p. 78 °C, 10 mmHg) in 36% yield as a clear, colorless liquid. A significant amount of decomposition products were observed in the pot residue. IR (film) 2919, 2840, 2725, 1727, 1691, 1356, 1136, 1032, 951.2, 626.4 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 9.48 (t, 1H, *J* = 2.1 Hz, CH=O); 3.66 (d, 2H, *J* = 2.1 Hz, CH_2); 2.42 (s, 3H, $C(O)CH_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 194.9, 194.0, 39.2, 30.6; HRMS (EI+) exact mass calcd for $[M\bullet]^+$ ($C_4H_6O_2S$) requires *m/z* 118.0089, found *m/z* 118.0086.

(*Z*)-Thioacetic acid *S*-[2-(trimethyl-silanyloxy)-vinyl] ester (9). Thioacetic acid *S*-(2-oxo-ethyl) ester (2.20 g, 18.6 mmol) was added in a single portion to a room temperature solution of chlorotrimethylsilane (4.72 mL, 37.2 mmol), triethylamine (10.4 mL, 74.5

mmol), and acetonitrile (40 mL). In less than five minutes, the solution became a hot white suspension that turned into a rust-colored suspension within fifteen minutes. After stirring for 1 hour, volatiles were removed *in vacuo* and the residue was extracted with three 50 mL portions of anhydrous diethyl ether. Distillation of the ethereal extracts afforded the title compound (2.40 g, 12.6 mmol, b.p. 66–68 °C, 3 mmHg, 3:1 *Z*:*E*) in 68% yield as a clear, colorless liquid. IR (film) 3076, 2960, 2901, 1700, 1624, 1419, 1353, 1255, 1227, 1183, 1125, 1083, 956.7, 891.8, 847.6, 754.6, 720.5, 619.3 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) *Z* isomer: δ 6.50 (d, 1H, *J* = 5.1 Hz, CHOTMS); 5.67 (d, 1H, *J* = 5.1 Hz, CHSAc); 2.34 (s, 3H, $C(O)CH_3$); 0.20 (s, 9H, $Si(CH_3)_3$); *E* isomer: δ 6.53 (d, 1H, *J* = 12.0 Hz, CHOTMS); 5.59 (d, 1H, *J* = 12.0 Hz, CHSAc); 2.30 (s, 3H, $C(O)CH_3$); 0.22 (s, 9H, $Si(CH_3)_3$); ^{13}C NMR (75 MHz, $CDCl_3$) *Z* isomer δ 192.5, 140.7, 96.5, 30.8, –0.09; *E* isomer δ 196.3, 149.4, 97.0, 30.2, –0.04; HRMS (EI+) exact mass calcd for $[M\bullet]^+$ ($C_7H_{14}O_2SiS$) requires *m/z* 190.0484, found *m/z* 190.0480. Product ratios were determined by ^1H NMR integrations of the crude reaction mixture.

(*E*)-(2-Benzylsulfanyl-vinyloxy)-trimethylsilane (10). Benzylsulfanylacetaldehyde[16] (2.00 g, 12.0 mmol) was added in a single portion to a room temperature solution of chlorotrimethylsilane (3.06 mL, 24.1 mmol), triethylamine (6.72 mL, 48.2 mmol), and acetonitrile (25 mL). In less than five minutes, the solution became a hot white suspension that turned into a rust-colored suspension within fifteen minutes. After stirring for 2 hours, volatiles were removed *in vacuo* and the residue was extracted with three portions of anhydrous diethyl ether. Distillation of the ethereal extracts afforded the

[16] Gawron; Glaid *J. Am. Chem. Soc.* **1949**, *71*, 3232.

title compound (2.27 g, 9.5 mmol, b.p. 79–81 °C, 0.025 mmHg, 1:3 *Z*:*E*) in 79% yield as a clear, colorless liquid. IR (film) 3028, 2958, 2920, 2828, 1608, 1495, 1453, 1254, 1169, 1088, 900.5, 846.1, 760.0, 689.3 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) *E* isomer: δ 7.28 (m, 5H, Ph-H); 6.45 (d, 1H, *J* = 11.7 Hz, CHOTMS); 5.43 (d, 1H, *J* = 11.7 Hz, CHSBn); 3.66 (s, 2H, $PhCH_2$); 0.14 (s, 9H, $Si(CH_3)_3$); *Z* isomer: δ 7.28 (m, 5H, Ph-H); 6.36 (d, 1H, *J* = 5.1 Hz, CHOTMS); 4.97 (d, 1H, *J* = 5.1 Hz, CHSBn); 3.84 (s, 2H, $PhCH_2$); 0.20 (s, 9H, $Si(CH_3)_3$); ^{13}C NMR (75 MHz, $CDCl_3$) *E* and *Z* isomers δ 149.2, 139.4, 138.5, 138.4, 129.2, 129.1, 128.6, 128.5, 127.2, 127.0, 103.2, 101.9, 40.6, 38.0, –0.02, –0.10; HRMS (CI+) exact mass calcd for $[M\bullet]^+$ ($C_{12}H_{18}OSSi$) requires *m/z* 238.0848, found *m/z* 238.0838. The product ratios were determined by ^1H NMR integration.

Preparation of ^{13}C–Labeled Sugar Precursors

1,2-bis-^{13}C-2-(Triisopropylsilanyloxy)-ethanol. The title compound was prepared according to the method of McDougal *et al.*[17] $^{13}C_2$-ethylene glycol (1.00 g, 15.6 mmol) was added dropwise to 60% sodium hydride in mineral oil (624 mg, 15.6 mmol) suspended in 30 mL of tetrahydrofuran. After 1 hour of vigorous stirring, chlorotriisopropylsilane (3.34 mL, 15.6 mmol) was added in a single portion and the solution was stirred for an additional 3.5 hours at room temperature. Then, the reaction was acidified with 250 mL saturated aqueous NH_4Cl, extracted with 250 mL ethyl acetate, washed with 100 mL 10% $NaHCO_3$, 100 mL brine, dried over anhydrous

[17] McDougal, P. G.; Rico, S. G.; Oh, Y. -I.; Condon, B. D. *J. Org. Chem.* **1986**, *51*, 3388.

Na_2SO_4, filtered and concentrated *in vacuo*. The oily residue was purified by flash chromatography (9:1 hexanes:ethyl acetate) to afford the title compound as a clear, colorless oil (2.83g, 12.8 mmol, 82%). IR (film) 3369, 2943, 2892, 2866, 1464, 1384, 1367, 1249, 1103, 1035, 923.6, 882.4, 734.0, 680.1 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 3.80 (m, 2H, $J_{13C–1H}$ = 138.9 Hz, CH_2OTIPS); 3.67 (m, 2H, $J_{13C–1H}$ = 145.5 Hz, C**H**$_2$OH); 2.18 (m, 1H, OH); 1.07 (m, 21H, TIPS); ^1H NMR (300 MHz, $CDCl_3$, ^{13}C decoupled) δ 3.80 (t, 2H, *J* = 5.1 Hz, CH_2OTIPS); 3.66 (q, 2H, *J* = 4.8 Hz, CH_2OH); 2.19 (t, 1H, *J* = 6.0 Hz, OH); 1.08 (m, 21H, TIPS); ^{13}C NMR (75 MHz, $CDCl_3$) δ 64.6 (d, $J_{13C–13C}$ = 39.6 Hz), 64.0 (d, $J_{13C–13C}$ = 39.6 Hz), 18.3, 12.3; HRMS (EI+) exact mass calcd for $[M + H]^+$ ($^{13}C_2{}^{12}C_9H_{27}O_2Si$) requires *m/z* 221.1843, found *m/z* 221.1837.

1,2-bis-^{13}*C*-(Triisopropylsilanyloxy)-acetaldehyde. Oxallyl chloride (2.16 mL, 24.8 mmol) was added dropwise to –78 °C solution of methyl sulfoxide (3.52 mL, 49.5 mmol) and triethylamine (8.63 mL, 61.9 mmol) dissolved in dichloromethane (115 mL). After stirring for 5 minutes, 1,2-bis-^{13}*C*-2-(triisopropylsilanyloxy)-ethanol (2.73 g, 12.4 mmol) was added via cannula as a solution in 10 mL of dichloromethane (8 mL followed by 2 mL rinse). After 30 minutes, the stirring solution was allowed to warm to 0 °C over the course of 1 hour. Then, 75 mL of dichloromethane was added and the reaction mixture was washed with 100 mL saturated aqueous NH_4Cl, 100 mL 10% $NaHCO_3$, 100 mL brine, dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. The oily residue was purified by flash chromatography (9:1 hexanes:ethyl acetate) to afford the title compound as a clear, colorless oil (2.31g, 10.6 mmol, 86%). IR (film) 2944, 2892, 2867, 1701, 1464, 1117, 1064.5, 882.1, 788.0, 683.3 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 9.74

(ddt, 1H, J_{13C-1H} = 175.2, 24.6 Hz, J_{1H-1H} = 1.2 Hz, CHO); 4.25 (ddd, 2H, J_{13C-1H} = 141.3, 4.2 Hz, J_{1H-1H} = 1.2 Hz, CH_2OTIPS); 1.08 (m, 21H, TIPS); ^{1}H NMR (300 MHz, $CDCl_3$, ^{13}C decoupled) δ 9.75 (s, 1H, CHO); 4.27 (s, 2H, CH_2OTIPS); 1.10 (m, 21H, TIPS); ^{13}C NMR (75 MHz, $CDCl_3$) δ 203.1 (d, $J_{13C-13C}$ = 44.2 Hz), 70.0 (d, $J_{13C-13C}$ = 44.1 Hz), 18.2, 12.2; HRMS (EI+) exact mass calcd for $[M + H]^+$ ($^{13}C_2{}^{12}C_9H_{25}O_2Si$) requires *m/z* 219.1691, found *m/z* 219.1684.

(2*R*, 3*R*)-1,2,3,4-tetra-^{13}C-3-Hydroxy-2,4-bis-(triisopropylsilanyloxy)-butyraldehyde (27). D-Proline (38.2 mg, 0.33 mmol) was added to a room temperature solution of 1,2-bis-^{13}*C*-(triisopropylsilanyloxy)-acetaldehyde (1.45 g, 6.64 mmol) dissolved in methyl sulfoxide (13.3 mL). After 28 hours, the solution was diluted with 150 mL ethyl acetate, washed with 100 mL water, 100 mL brine, dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. Crude ^{1}H NMR analysis indicated complete conversion to a 4:1 mixture of *anti* to *syn* isomers. The oily residue was purified by flash chromatography (49:1 pentane:THF) to afford the title compound as a single diastereomer of a low melting solid (908 mg, 2.1 mmol) as well as a faster eluting mixture of isomers that was principally composed of the *syn* isomer (366 mg, 0.84 mmol) in a combined yield of 88%. IR (film) 3488, 2943, 2892, 2867, 1695, 1464, 1384, 1248, 1098, 1065, 882.4, 683.3 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.67 (ddd, 1H, J_{13C-1H} = 178.5, 21.9 Hz, J_{1H-1H} = 1.8 Hz, CHO); 4.24 (m, 1H, C**H**CHO); 3.97 (m, 1H, C**H**OH); 3.87 (m, 2H, CH_2); 2.44 (m, 1H, OH); 1.09 (m, 42H, 2 TIPS); ^{1}H NMR (300 MHz, $CDCl_3$, ^{13}C decoupled) δ 9.68 (d, 1H, *J* = 6.6 Hz CHO); 4.25 (m, 1H, C**H**CHO); 3.97 (m, 1H, C**H**OH); 3.81 (m, 2H, CH_2); 2.44 (m, 1H, OH); 1.08 (m, 42H, 2 TIPS); ^{13}C NMR (75 MHz, $CDCl_3$) δ 202.3 (d,

$J_{13C–13C}$ = 43.8 Hz), 79.2 (dd, $J_{13C–13C}$ = 43.8, 40.1 Hz), 74.6 (dd, $J_{13C–13C}$ = 42.3, 40.4 Hz), 63.0 (d, $J_{13C–13C}$ = 42.3 Hz), 18.3 (2C), 12.7, 12.2; HRMS (FAB+) exact mass calcd for $[M + H]^+$ ($^{13}C_4{}^{12}C_{18}H_{49}O_4Si_2$) requires *m/z* 437.3304, found *m/z* 437.3304. $[\alpha]_D$ = 2.2 (c = 2.00, $CHCl_3$). The enantioselectivity of this sample was determined to be 95% ee by the method described for (*2S*, *3S*)-3-hydroxy-2,4-bis-(triisopropylsilanyloxy)-butyraldehyde.[18]

Acetic acid 1,2-bis-^{13}*C*-2-hydroxy-ethyl ester. The title compound was prepared according to the method of Kusumoto *et al.*[19] Trimethylorthoacetate (2.98 mL, 23.4 mmol) was added to a room temperature stirring solution of $^{13}C_2$-ethylene glycol (1.00 g, 15.6 mmol), *p*-toluenesulfonic acid monohydrate (148 mg, 0.78 mmol) and dichloromethane (150 mL). After stirring for 6 minutes, deionized water (422 μL, 23.4 mmol) was added in a single portion. After an additional 6 minutes of stirring, volatiles were removed *in vacuo* and the residue was passed through a short plug of silica gel with 9:1 diethyl ether:hexanes as eluent to afford the title compound in quantitative yield (1.66 g, 15.6 mmol) as a clear, colorless liquid. IR (film) 3400, 2947, 2870, 1733, 1456, 1380, 1251, 1061, 1036, 950.7, 872.8, 608.9 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.20 (m, 2H, $J_{13C–1H}$ = 144.9 Hz, CH_2OAc); 3.82 (m, 2H, $J_{13C–1H}$ = 141.3 Hz, CH_2OH); 2.10 (s, 3H, CH_3); ^{1}H NMR (300 MHz, $CDCl_3$, ^{13}C decoupled) δ 4.21 (t, 2H, *J* = 4.2 Hz, CH_2OAc); 3.84 (m, 2H, CH_2OH); 2.11 (s, 3H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.6, 66.4 (d, $J_{13C–13C}$ = 40.1 Hz), 61.4 (d, $J_{13C–13C}$ = 40.1 Hz), 21.3; HRMS (EI+) exact mass calcd for $[M + H]^+$ ($^{13}C_2{}^{12}C_2H_9O_3$) requires *m/z* 107.0619, found *m/z* 107.0617.

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[18] Northrup, A. B.; Mangion, I. K.; Hettche, F. *Angew. Chem. Int. Ed.* **2004**, *43*, 2152.

[19] Oikawa, M.; Wada, A.; Okazaki, F.; Kusumoto, S. *J. Org. Chem.* **1996**, *61*, 4469.

Acetic acid 1,2-bis-^{13}C-2-oxo-ethyl ester. Acetic acid 1,2-bis-^{13}C-2-hydroxy-ethyl ester (1.66 g, 15.6 mmol) was added as a solution in 5 mL of dichloromethane to a room temperature stirring solution of Dess-Martin periodinane (8.30 g, 19.6 mmol) dissolved in dichloromethane (80 mL). After 3 hours, volatiles were removed *in vacuo* on a rotary evaporator while cooling the suspension in an ice-water bath. The residue was extracted with 3x50 mL of pentane, then concentrated *in vacuo* at 50-55 °C and 30 mmHg for 30 minutes to remove a portion of the excess acetic acid. ^{1}H NMR analysis of the pot residue (2.73 g) indicated a 1:2 ratio of the title compound (1.27 g, 12.2 mmol, 78% yield) to acetic acid. A small sample was purified by flash chromatography (4:1 ethyl acetate:hexanes) for characterization purposes. IR (film) 2953, 1739, 1725, 1677, 1436, 1377, 1234, 1042 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.61 (dd, 1H, J_{13C-1H} = 179.1, 29.1 Hz, CHO); 4.67 (dd, 2H, J_{13C-1H} = 146.7, 3.9 Hz, CH_2OAc); 2.19 (s, 3H, CH_3); ^{1}H NMR (300 MHz, $CDCl_3$, ^{13}C decoupled) δ 9.59 (s, 1H, CHO); 4.66 (s, 2H, CH_2OAc); 2.18 (s, 3H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 195.7 (d, $J_{13C-13C}$ = 41.9 Hz), 170.6, 68.9 (d, $J_{13C-13C}$ = 41.9 Hz), 20.7; HRMS (EI+) exact mass calcd for $[M + H]^+$ ($^{13}C_2{}^{12}C_2H_7O_3$) requires *m/z* 105.0418, found *m/z* 105.0421.

(*Z*)-Acetic acid 1,2-bis-^{13}C-2-(trimethylsilanyloxy)-vinyl ester (28). The above described mixture of acetic acid and acetic acid 1,2-bis-^{13}C-2-oxo-ethyl ester (2.73 g, 12.2 mmol) was added as a solution in 3.0 mL acetonitrile in a single portion to a room temperature solution of chlorotrimethylsilane (6.19 mL, 48.8 mmol), triethylamine (10.2 mL, 73.2 mmol), and acetonitrile (22 mL). In less than five minutes, the solution became

a hot white suspension that turned into a rust-colored suspension within fifteen minutes. After stirring for 2 hours, volatiles were removed *in vacuo* and the residue was extracted with three 25 mL portions of anhydrous diethyl ether. Distillation of the ethereal extracts afforded the title compound (1.38 g, 7.8 mmol, b.p. 67-69 °C, 10 mmHg, 7:1 *Z*:*E*) in 64% yield as a clear, colorless liquid. IR (film) 3102, 3032, 2962, 2904, 1756, 1628, 1420, 1375, 1254, 1223, 1168, 1110, 1050, 953.9, 850.1, 754.1, 652.7 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 6.55 (ddd, 1H, $J_{13C–1H}$ = 175.8, 19.2, J_{1H-1H} = 3.9 Hz, CHOTMS); 5.77 (ddd, 1H, $J_{13C–1H}$ = 179.4, 23.7, J_{1H-1H} = 3.9 Hz, CHOAc); 2.16 (s, 3H, CH_3); 0.22 (s, 9H, TMS); ^1H NMR (300 MHz, $CDCl_3$, ^{13}C decoupled) identical to (*Z*)-acetic acid 2-(trimethyl-silanyloxy)-vinyl ester (*vide supra*); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.4, 126.9 (d, $J_{13C–13C}$ = 92.2 Hz), 120.9 (d, $J_{13C–13C}$ = 92.3 Hz), 21.1, –0.08; HRMS (EI+) exact mass calcd for $[M + H]^+$ ($^{13}C_2{}^{12}C_5H_{14}O_3Si$) requires *m/z* 176.0779, found *m/z* 176.0785. The product ratios were determined by both ^1H NMR integrations and GLC analysis using a J&W Scientific DB-1701 column (50 ºC ramp 5 °C/min, 23 psi); *Z* isomer t_r = 10.46 min, *E* isomer t_r = 10.83 min.

Aldol Reactions

2,4,6-tri-*O*-*para*-Methoxybenzyl-D-gulose (3). A solution of *para*-methoxybenzyloxyacetaldehyde (667 mg, 3.7 mmol), L-proline (63.8 mg, 0.55 mmol) and 3.7 mL of dimethylformamide was stirred at room temperature for 24 hours. Then, an additional aliquot of *para*-methoxybenzyloxyacetaldehyde (333 mg, 1.8 mmol) was added slowly over the course of 20 hours as a solution in 1.8 mL of dimethylformamide

via syringe pump. After stirring for an additional 7 days at room temperature, the solution was diluted with 100 mL ethyl acetate, washed with 100 mL water, 100 mL brine, dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. Flash chromatography (3:2 ethyl acetate:hexanes) of the oily residue afforded the title compound (211 mg, 0.39 mmol, >19:1 d.r., 3:1 α:β) as a clear, pale yellow oil in 21% yield and in 92% ee (based on Mosher ester analysis as described below). IR (film) 3432, 3000, 2934, 2837, 1713, 1612, 1514, 1464, 1302, 1250, 1087, 1034, 819.8 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) α- and β-isomers: δ 7.89 (m, 2H, Ar-H); 7.23 (m, 10H, Ar-H); 6.84 (m, 12H, Ar-H); 5.24 (br s, 1H, H1 α); 5.05 (d, 1H, J = 7.8 Hz, H1 β); 4.75-4.24 (m, 12H, 6 CH_2Ar); 4.13-3.13 (m, 30H, 6 CH3, H2 α,β, H3 α,β, H4 α,β, H5 α,β, H6 α,β); 3.35 (s, 1H, OH); 2.62 (s, 1H, OH); ^{13}C NMR (75 MHz, $CDCl_3$) α- and β-isomers: δ 159.6, 159.5, 159.4, 159.4, 159.3, 159.3, 131.9, 130.3, 130.2, 129.9, 129.8, 129.8, 129.7, 129.7, 94.5, 92.6, 78.1, 74.3, 73.4, 73.3, 73.3, 73.0, 72.7, 71.9, 71.5, 71.2, 70.5, 69.1, 68.8, 68.3, 67.2, 65.3, 55.7 (3), 55.5 (3); HRMS (FAB+) exact mass calcd for $[M+H]^+$ ($C_{30}H_{37}O_9$) requires m/z 541.2437, found m/z 541.2433; $[\alpha]_D$ = –12.7 (c = 2.00, $CHCl_3$, 3:1 α:β mixture). To determine the enantiopurity of the title compound, it was converted to both its (*R*) and (*S*) methoxytrifluoromethylphenylacetate esters according to the method of Mosher.[20] The acylation reactions were monitored by TLC analysis for complete consumption of the title compound. In both cases a 4:1 α:β ratio of acylated material was observed. The integrations of the following ^1H NMR shifts for the H1 protons for each anomer and diastereomer from the crude acylation reaction mixture were used to determine the enantiomer ratios. (*S*)-MTPA ester (from (*R*)-MTPA-Cl) ^1H NMR

[20] Dale, J. A.; Dull, D. L.; Mosher, H. S. *J. Org. Chem.* **1969**, *34*, 2543.

(500 MHz, $CDCl_3$) δ 6.10 (d, 1H, *J* = 8.5 Hz, H1 α); 6.15 (d, 1H, *J* = 8.0 Hz, H1 β). (*R*)-MTPA ester (from (*S*)-MTPA-Cl) ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.13 (d, 1H, *J* = 8.0 Hz, H1 α); 6.19 (d, 1H, *J* = 8.0 Hz, H1 β). A sample of the four different diastereomers (prepared by mixing the independently generated (*R*) and (*S*) MTPA esters) was dissolved in $CDCl_3$ to demonstrate the existence of baseline separation of the diagnostic peaks despite the small differences in chemical shift.

Determination of the Absolute and Relative Stereochemistry of 2,4,6-tri-*O-para*-Methoxybenzyl-D-gulose by Correlation to D-Gulose pentaacetate. Triethylamine (36 μL, 0.26 mmol), 4-dimethylaminopyridine (1.0 mg, 0.01 mmol), and acetic anhydride (20 μL, 0.21 mmol) were added to 2,4,6-tri-*O-para*-methoxybenzyl-L-gulose (28 mg, 0.05 mmol) dissolved in dichloromethane (100 μL) at room temperature and allowed to stir for 2 hours. The reaction was then acidified with 10 mL 1N HCl, extracted with 10 mL ethyl acetate, washed with 10 mL 10% $NaHCO_3$, 10 mL brine, dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo* to afford a mixture of two diastereomeric diacetates (33 mg, 0.05 mmol) in nearly quantitative yield. Treatment of the *para*-methoxybenzylated sugar (3 mg, 0.006 mmol) with iodotrimethylsilane (3.2 μL, 0.022 mmol) in 200 μL of $CHCl_3$ according to the method of Danishefsky[21], afforded 0.6 mg of the desired triol after flash chromatography (5% methanol in ethyl acetate). Trisacylation of the triol (0.6 mg, 0.002 mmol) by the action of triethylamine (10 μL, 0.09 mmol), 4-dimethylaminopyridine (1.0 mg, 0.01 mmol), acetic anhydride (10 μL, 0.11 mmol) and dichloromethane (100 μL) afforded two pentaacetate isomers. Comparison of those

[21] Gordon, D. M.; Danishefsky, S. J. *J. Am. Chem. Soc.* **1992**, *114*, 659.

above generated pentaacetate isomers to an authentic sample of α,β-D-gulose pentaacetate[22] showed the above generated pentaacetates to be identical by ^{1}H and ^{13}C NMR to α,β-D-gulose pentaacetate.

2-*O*-Acetyl-4,6-bis-*O*-triisopropylsilyl-α,β-L-allopyranose (14). Titanium (IV) chloride (125 μL, 1.13 mmol) was added dropwise to a stirring –78 °C solution of (2*S*, 3*S*)-3-hydroxy-2,3-bis-triisopropylsilanoxy-propionaldehyde (200 mg, 0.46 mmol), (*Z*)-acetic acid 2-(trimethyl-silanyloxy)-vinyl ester (241 mg, 1.39 mmol) and dichloromethane (9.2 mL). The resulting orange-red solution was stirred at –78 °C for 10 hours, then allowed to warm gradually over 3 hours to –40 °C. After stirring for an additional 4 hours at –40 °C, the reaction was acidified by the addition of 100 mL saturated aqueous NH_4Cl and extracted with ethyl acetate (2x50 mL). The combined organics were washed with 100 mL brine, dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. Crude ^{1}H NMR analysis indicated complete conversion to a >19:1 mixture of allose:mannose derived diastereomers as well as some minor acetal side-products. Flash chromatography (2:3 ether:hexanes) afforded the title compound as a clear, colorless oil (230 mg, 0.43 mmol, stains light green in anisaldehyde, 2:1 α:β, 93%) as well as the slower eluting 2-*O*-acetyl-4,6-bis-*O*-triisopropylsilyl-α-L-mannopyranose product (8 mg, 0.01 mmol, stains red/rust brown in anisaldehyde, 3%) in 96% combined yield. IR (film) 3406, 2944, 2867, 1742, 1464, 1374, 1236, 1050, 1014, 883.4, 681.6 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) α-isomer: δ 5.27 (d, 1H, *J* = 10.5 Hz, C1 OH); 5.16 (dd, 1H, *J* = 10.5, 3.5 Hz, H1); 4.68 (dd, 1H, *J* = 3.5, 3.0 Hz, H2); 4.32 (m, 1H, H3); 4.13 (dd, 1H, *J* = 9.5, 3.0

[22] α, β-D-gulose pentaacetate was prepared according to the method described in the following reference: Bonner *J. Am. Chem. Soc.* **1958**, *80*, 3372.

Hz, H4); 3.79 (ddd, 1H, 9.5, 2.5, 2.5 Hz, H5); 3.98 (m, 2H, H6); 3.09 (s, 1H, C3 OH); 2.19 (s, 3H, C(O)CH_3); 1.15-1.05 (m, 42H, 6 $CH(CH_3)_2$); β-isomer: δ 5.11 (dd, 1H, *J* = 8.5, 8.5 Hz, H1); 4.63 (dd, 1H, *J* = 8.0, 2.0 Hz, H2); 4.21 (apparent t, 1H, *J* = 3 Hz, H3); 4.02 (dd, 1H, *J* = 6.5, 3.0 Hz, H4); 3.72 (ddd, 1H, *J* = 9.0, 4.5, 2.0 Hz, H5); 3.87 (dd, 1H, *J* = 11.5, 5.0 Hz, one of H6); 3.97 (dd, 1H, *J* = 11.5, 3.0 Hz, one of H6); 3.23 (s, 1H, C1 OH); 2.57 (s, 1H, C3 OH); 2.18 (s, 3H, C(O)CH_3); 1.15-1.05 (m, 42H, 6 $CH(CH_3)_2$); ^{13}C NMR (125 MHz, $CDCl_3$) α-isomer: δ 170.5, 91.6 (C1), 72.0 (C3), 69.4 (C2), 68.1 (C5), 67.3 (C4), 62.4 (C6), 21.2, 18.3, 18.3, 18.2, 18.1, 12.8, 12.3; β-isomer: δ 171.4, 92.6 (C1), 75.4 (C5), 73.7 (C2), 70.7 (C3), 68.6 (C4), 63.1 (C6), 21.4, 18.3, 18.3, 18.2, 18.1, 12.8, 12.3; 500 MHz COSY and HMQC spectra support the above ^{1}H and ^{13}C NMR assignments; HRMS (FAB+) exact mass calcd for $[M+H]^+$ ($C_{26}H_{55}O_7Si_2$) requires *m/z* 535.3486, found *m/z* 535.3484; $[\alpha]_D = -26.6$ (c = 2.00, $CHCl_3$, 3.6:1 α:β mixture).

Determination of the Relative and Absolute Stereochemistry of 2-*O*-Acetyl-4,6-bis-*O*-triisopropylsilyl-α, β-L-allopyranose by Correlation to Allose Pentaacetate. Triethylamine (34 μL, 0.24 mmol), 4-dimethylaminopyridine (1.0 mg, 0.01 mmol), and acetic anhydride (17 μL, 0.18 mmol) were added to 2-*O*-acetyl-4,6-bis-*O*-triisopropylsilyl-α,β-L-allopyranose (15.1 mg, 0.03 mmol, 4:1 α:β) dissolved in dichloromethane (1.0 mL) at 0 °C. After being allowed to stir for 1 hour at 0 °C, the solution was warmed to room temperature over the course of 1 hour. Then, the solution was heated to reflux for 5 hours with the addition of an additional 34 μL of triethylamine and 17 μL of acetic anhydride. The reaction was then acidified with 10 mL 1N HCl, extracted with 10 mL ethyl acetate, washed with 10 mL 10% $NaHCO_3$, 10 mL brine,

dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. The residue was purified by flash chromatography (7:3 hexanes:ether) to afford the faster eluting β-anomer (7.7 mg, 0.01 mmol, 21%) as well as the slower eluting α-anomer (25 mg, 0.04 mmol, 67%) and an additional mixed fraction (4.8 mg, 0.01 mmol, 13%). The isolated triacetates were separately dissolved in THF (500 μL) along with tetrabutylammonium fluoride hydrate (4 equiv.) and acetic acid (4 equiv.) and heated to reflux for 3 hours. Then, triethylamine (100 μL, 0.72 mmol), 4-dimethylaminopyridine (2.0 mg, 0.02 mmol), and acetic anhydride (50 μL, 0.32 mmol) were added and the suspension was stirred for an additional hour at reflux. Then, the suspension was cooled to room temperature, acidified with 10 mL 1N HCl, extracted with 10 mL ethyl acetate, washed with 10 mL 10% $NaHCO_3$, 10 mL brine, dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. The residues were then purified by flash chromatography (2:3 ethyl acetate:hexanes) to afford 15.2 mg of the α-pentaacetate (96%, $[\alpha]_D = -2.6$ (c = 1.00, $CHCl_3$)) and 3.6 mg of the β-pentaacetate (82%, $[\alpha]_D = 15.0$ (c = 0.36, $CHCl_3$)). A comparison of the ^1H and ^{13}C NMR spectra of the above generated pentaacetates to spectra recorded from authentic samples of α-D-allose pentaacetate and β-D-allose pentaacetate prepared by the methods of Sims *et al.*[23] and Maurer *et al.*,[24] respectively, showed that the α-pentaacetate isomer was spectroscopically identical to α-D-allose pentaacetate and the β-pentaacetate isomer was spectroscopically identical to β-D-allose pentaacetate. Both generated pentaacetate isomers have optical rotations of opposite sign and similar magnitude to that reported in the literature, confirming the L-absolute

[23] Furneaux, R. H.; Rendle, P. M.; Sims, I. M. *J. Chem. Soc. Perkin Trans.1* **2000**, *11*, 2011.

[24] Weinges, K.; Haremsa, S.; Maurer, W. *Carb. Res.* **1987**, *164*, 453.

stereochemistry for each anomer: α-D-allose pentaacetate lit.[25] $[\alpha]_D$ = 3.0 (c = 0.70, $CHCl_3$); β-D-allose pentaacetate lit.[26] $[\alpha]_D$ = –14.8 (c = 1.00, $CHCl_3$)

1,2,3,4,5,6-hexa-^{13}C-2-*O*-Acetyl-4,6-bis-*O*-triisopropylsilyl-D-allopyranose (31). Prepared according to the method above for 2-*O*-acetyl-4,6-bis-*O*-triisopropylsilyl-L-allopyranose using (2*R*, 3*R*)-1,2,3,4-tetra-^{13}C-3-hydroxy-2,4-bis-(triisopropylsilanyloxy)-butyraldehyde (250 mg, 0.57 mmol), titanium (IV) chloride (157 μL, 1.43 mmol), (*Z*)-acetic acid 1,2-bis-^{13}*C*-2-(trimethylsilanyloxy)-vinyl ester (303 mg, 1.72 mmol) and 11.4 mL of dichloromethane. Crude ^{1}H and ^{13}C NMR analysis indicated complete conversion to a >19:1 mixture of allose:mannose derived diastereomers as well as some minor acetal side-products. Flash chromatography (2:3 ether:hexanes) afforded the title compound as a clear, colorless oil (269 mg, 0.50 mmol, stains light green in anisaldehyde, 2:1 α:β, 87%). IR (film) 3429, 2944, 2893, 2868, 1645, 1464, 1372, 1240, 1118, 1040, 883.2, 682.0 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) α-isomer: δ 5.27 (m, 1H, C1 OH); 5.16 (m, 1H, H1); 4.68 (m, 1H, H2); 4.32 (m, 1H, H3); 4.13 (m, 1H, H4); 3.79 (m, 1H, H5); 3.98 (m, 2H, H6); 3.10 (s, 1H, C3 OH); 2.18 (s, 3H, $C(O)CH_3$); 1.14-1.06 (m, 42H, 6 $CH(CH_3)_2$); β-isomer: δ 5.11 (m, 1H, H1); 4.63 (m, 1H, H2); 4.21 (m, 1H, H3); 4.02 (m, 1H, H4); 3.72 (m, 1H, H5); 3.87 (m, 1H, one of H6); 3.97 (m, 1H, one of H6); 3.23 (m, 1H, C1 OH); 2.56 (s, 1H, C3 OH); 2.17 (s, 3H, $C(O)CH_3$); 1.14-1.06 (m, 42H, 6 $CH(CH_3)_2$); ^{13}C NMR (125 MHz, $CDCl_3$) α-isomer: δ 170.5, 91.6 (d, $J_{13C\text{-}13C}$ = 44.1 Hz, C1), 72.0 (dd, $J_{13C\text{-}13C}$ = 35.6, 35.6 Hz, C3), 69.4 (dd, $J_{13C\text{-}13C}$ = 44.1, 39.5 Hz, C2), 68.1 (m, C5), 67.3 (m, C4), 62.4 (d, $J_{13C\text{-}13C}$ = 41.8 Hz, C6), 21.2, 18.3, 18.3, 18.2, 18.1, 12.8, 12.3; β-isomer:

[25] Jensen, S. R.; Mikkelsen, C. B.; Nielsen, B. J. *Phytochemistry* **1981**, *20*, 71.

[26] Zissis, L. M.; Richtmyer, J. D, *J. Org. Chem.* **1961**, *26*, 5244.

δ 171.4, 92.6 (d, $J_{13C\text{-}13C}$ = 47.1 Hz, C1), 75.4 (dd, $J_{13C\text{-}13C}$ = 44.0, 44.0 Hz, C5), 73.7 (dd, $J_{13C\text{-}13C}$ = 47.1, 39.6 Hz, C2), 70.7 (dd, $J_{13C\text{-}13C}$ = 38.0, 38.0 Hz, C3), 68.6 (dd, $J_{13C\text{-}13C}$ = 43.4, 37.3 Hz, C4), 63.1 (d, $J_{13C\text{-}13C}$ = 44.9 Hz, C6), 21.3, 18.3, 18.3, 18.2, 18.1, 12.8, 12.3; HRMS (EI+) exact mass calcd for $[M^{\bullet+} - OH]^+$ ($^{13}C_6{}^{12}C_{20}H_{53}O_6Si_2$) requires *m/z* 523.3582, found *m/z* 523.3592; $[\alpha]_D$ = 16.8 (c = 2.00, $CHCl_3$, 2:1 α:β mixture). ^{1}H NMR (500 MHz, $CDCl_3$, ^{13}C decoupled) was identical to that reported above for 2-*O*-acetyl-4,6-bis-*O*-triisopropylsilyl-L-allopyranose. Additional confirmation of the allose stereochemistry for these two anomeric products is the similarity in ^{13}C shifts to the unlabeled material above. The isotopic purity of >98% is estimated by the lack of any ^{13}C–^{13}C uncoupled resonances in the ^{13}C NMR spectrum and no observed ^{13}C–^1H uncoupled resonances in the ^{1}H NMR spectrum.

2-*O*-Acetyl-4,6-bis-*O*-triisopropylsilyl-α-L-mannopyranose (20). (2*S,* 3*S*)-3-Hydroxy-2,3-bis-triisopropylsilanoxy-propionaldehyde (200 mg, 0.46 mmol) was added as a solution in 4.6 mL of dichloromethane to a flame-dried flask charged with magnesium bromide diethyl etherate (358 mg, 1.39 mmol) and 4.6 mL of dichloromethane cooled to –20 °C. After stirring for 30 minutes at –20 °C, (*Z*)-acetic acid 2-(trimethyl-silanyloxy)-vinyl ester (242 mg, 1.39 mmol) was added. The –20 °C suspension was stirred for 2 hours, then allowed to warm to +4 °C over the course of 4 hours. After stirring for an additional 18 hours at +4 °C, the reaction was acidified by the addition of 100 mL saturated aqueous NH_4Cl and extracted with ethyl acetate (2x50 mL). The combined organics were washed with 100 mL brine, dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The residue was taken up in 5 mL of 7:2:1 THF:water:trifluoroacetic acid at 0

°C and stirred for 30 minutes before being basified with 50 mL 10% $NaHCO_3$, extracted with 100 mL ethyl acetate, dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. Crude ^{1}H NMR analysis indicated complete conversion to a >19:1 mixture of mannose:glucose derived diastereomers as well as some minor acetal side-products. Flash chromatography (2:3 ether:hexanes) afforded the title compound as a clear, colorless oil (207 mg, 0.39 mmol, stains red/rust brown in anisaldehyde, >19:1 α:β, 84%) as well as the faster eluting 2-*O*-acetyl-4,6-bis-*O*-triisopropylsilyl-α-L-glucoopyranose product (8.1 mg, 0.02 mmol, stains blue/green in anisaldehyde, 2:1 α:β, 3%) in 87% combined yield. IR (film) 3436, 2943, 2867, 1726, 1464, 1375, 1256, 1126, 1066, 883.2, 763.2, 681.6 cm^{-1}; While there is no detectable concentration effect on the ^{13}C NMR shifts, there is a significant concentration effect on the ^{1}H NMR shifts. Therefore, two ^{1}H NMR spectra have been provided: one at a high concentration (approx. 50 mg/mL), and one at a low concentration (approx. 2 mg/mL): ^{1}H NMR (500 MHz, $CDCl_3$) concentrated sample: δ 5.20 (m, 1H, H1); 5.09 (dd, 1H, *J* = 1.0, 1.0 Hz, H2); 4.17–3.91 (m, 4H, H3, H4, H6); 3.83 (m, 1H, H5); 3.61 (d, 1H, *J* = 1.0 Hz, C1 OH); 2.46 (d, 1H, *J* = 2.0 Hz, C3 OH); 2.10 (s, 3H, $C(O)CH_3$); 1.22-1.05 (m, 42H, 6 $CH(CH_3)_2$); dilute sample: δ 5.24 (dd, 1H, *J* = 4.0, 2.0 Hz, H1); 5.11 (dd, 1H, *J* = 2.5, 2.5 Hz, H2); 4.08 (m, 1H, H3); 4.11 (dd, 1H, *J* = 16.0, 8.0 Hz, H4); 3.79 (ddd, 1H, *J* = 8.0, 3.0, 3.0 Hz, H5); 3.99 (m, 2H, H6); 2.63 (d, 1H, *J* = 3.5 Hz, C1 OH); 2.11 (s, 3H, $C(O)CH_3$); 2.01 (d, 1H, *J* = 6.5 Hz, C3 OH); 1.27-1.09 (m, 42H, 6 $CH(CH_3)_2$); ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.3, 92.1, 74.7, 73.6, 70.8, 69.9, 63.3, 21.2, 18.5, 18.5, 18.2, 18.1, 13.2, 12.3; 500 MHz COSY spectra support the above ^{1}H NMR assignments; HRMS (FAB) exact mass calcd for $[M - H]^-$

($C_{26}H_{53}O_7Si_2$) requires *m/z* 533.3330, found *m/z* 533.3319; $[\alpha]_D$ = –17.3 (c = 2.00, $CHCl_3$).

Determination of the Relative and Absolute Stereochemistry of 2-*O*-Acetyl-4,6-bis-*O*-triisopropylsilyl-α-L-mannopyranose by Correlation to α-L-Mannose Pentaacetate. Triethylamine (20 μL, 0.14 mmol), 4-dimethylaminopyridine (1.0 mg, 0.01 mmol), and acetic anhydride (10 μL, 0.11 mmol) were added to 2-*O*-acetyl-4,6-bis-*O*-triisopropylsilyl-α-L-mannopyranose (19.5 mg, 0.036 mmol) dissolved in dichloromethane (360 μL) at 0 °C and allowed to stir for 30 minutes before being moved to room temperature for 3 hours. The reaction was then acidified with 10 mL 1N HCl, extracted with 10 mL ethyl acetate, washed with 10 mL 10% $NaHCO_3$, 10 mL brine, dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. The crude triacetate (23 mg, 0.04 mmol) was dissolved in THF (500 μL) along with tetrabutylammonium fluoride hydrate (39 mg, 0.15 mmol) and acetic acid (8.5 μL, 0.15 mmol) and heated to reflux for 3 hours. Then, triethylamine (100 μL, 0.72 mmol), 4-dimethylaminopyridine (2.0 mg, 0.02 mmol), and acetic anhydride (50 μL, 0.32 mmol) were added and the suspension was stirred for an additional hour at reflux. The suspension was then cooled to room temperature, acidified with 10 mL 1N HCl, extracted with 10 mL ethyl acetate, washed with 10 mL 10% $NaHCO_3$, 10 mL brine, dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. The residue was then purified by flash chromatography (1:1 ethyl acetate:hexanes) to afford a single pentaacetate in quantitative yield (13 mg, 0.04 mmol). A comparison of the ^1H and ^{13}C NMR spectra of the above generated pentaacetate to an authentic sample of α-D-mannose pentaacetate (generated by the

method of Bonner[27]) showed the two compounds to be spectroscopically identical. The optical rotation of the correlated sample $[\alpha]_D = -54.0$ (c = 1.00, $CHCl_3$) is opposite in sign and of similar magnitude to the reported value[28] for α-D-mannose pentaacetate $[\alpha]_D = 56.8$ (c = 1.00, $CHCl_3$). The correlated sample, therefore, posses the L absolute stereochemistry.

1,2,3,4,5,6-hexa-^{13}C-2-*O*-Acetyl-4,6-bis-*O*-triisopropylsilyl-α-D-mannopyranose (30). Prepared according to the method above for 2-*O*-acetyl-4,6-bis-*O*-triisopropylsilyl-α-L-mannopyranose using (2*R*, 3*R*)-1,2,3,4-tetra-^{13}C-3-hydroxy-2,4-bis-(triisopropylsilanyloxy)-butyraldehyde (250 mg, 0.57 mmol), magnesium bromide diethyl etherate (443 mg, 1.72 mmol), (*Z*)-acetic acid 1,2-bis-^{13}*C*-2-(trimethylsilanyloxy)-vinyl ester (303 mg, 1.72 mmol) and dichloromethane (11.4 mL). Crude ^{1}H and ^{13}C NMR analysis indicated complete conversion to a >19:1 mixture of mannose:glucose derived diastereomers as well as some minor acetal side-products. Flash chromatography (2:3 ether:hexanes) afforded the title compound as a clear, colorless oil (221 mg, 0.41 mmol, stains red/rust brown in anisaldehyde, >19:1 α:β, 71%). IR (film) 3445, 2944, 2893, 2867, 1728, 1464, 1374, 1253, 1107, 1060, 883.2, 747.7, 681.1 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) dilute sample: δ 5.22 (m, 1H, J_{13C-1H} = 171.0 Hz, H1); 5.10 (m, 1H, J_{13C-1H} = 153.0 Hz, H2); 4.23–3.56 (m, 5H, H3, H4, H5, H6); 2.91 (m, 1H, C1 OH); 2.11 (s, 3H, $C(O)CH_3$); 2.02 (m, 1H, C3 OH); 1.27-1.09 (m, 42H, 6 $CH(CH_3)_2$); ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.2, 92.2 (d, $J_{13C-13C}$ = 47.1 Hz), 74.8 (dd, $J_{13C-13C}$ = 41.8, 41.8 Hz), 73.4 (dd,

[27] Bonner, S. J.; *et al. J. Am. Chem. Soc.* **1958**, *80*, 3372.

[28] Bonner, S. J.; *et al. J. Am. Chem. Soc.* **1958**, *80*, 3372.

$J_{13C\text{-}13C}$ = 47.1, 36.5 Hz), 70.9 (dd, $J_{13C\text{-}13C}$ = 39.5, 39.5 Hz), 69.8 (dd, $J_{13C\text{-}13C}$ = 40.3, 40.3 Hz), 63.1 (d, $J_{13C\text{-}13C}$ = 44.1 Hz, C6), 21.1, 18.5, 18.5, 18.2, 18.1, 13.2, 12.3; HRMS (FAB+) exact mass calcd for $[M+H]^+$ ($^{13}C_6{}^{12}C_{20}H_{55}O_7Si_2$) requires *m/z* 541.3688, found *m/z* 541.3669; $[\alpha]_D$ = 16.2 (c = 2.00, $CHCl_3$). ^1H NMR (500 MHz, $CDCl_3$, ^{13}C decoupled) was identical to that reported above for a dilute sample of 2-*O*-acetyl-4,6-bis-*O*-triisopropylsilyl-α-L-mannopyranose. Additional confirmation of the mannose stereochemistry is the similarity in ^{13}C shifts to the unlabeled material above. The isotopic purity of >98% is estimated by the lack of any ^{13}C–^{13}C uncoupled resonances in the ^{13}C NMR spectrum and no observed ^{13}C–^1H uncoupled resonances in the ^1H NMR spectrum.

2-*O*-Acetyl-4,6-bis-*O*-triisopropylsilyl-α,β-L-glucopyranose (21). (2*S,* 3*S*)-3-Hydroxy-2,3-bis-triisopropylsilanoxy-propionaldehyde (200 mg, 0.46 mmol) was added as a solution in 2.3 mL of ethyl ether to a flame-dried flask charged with magnesium bromide diethyl etherate (358 mg, 1.39 mmol) and 2.3 mL of ethyl ether cooled to –20 °C. After stirring for 30 minutes at –20 °C, (*Z*)-acetic acid 2-(trimethyl-silanyloxy)-vinyl ester (169 μL, 0.92 mmol) was added. The suspension was stirred at –20 °C for 2 hours, then allowed to warm to +4 °C over the course of 4 hours. After stirring for an additional 24 hours at +4 °C, the reaction was acidified by the addition of 100 mL saturated aqueous NH_4Cl and extracted with ethyl acetate (2x50 mL). The combined organics were washed with 100 mL brine, dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The residue was taken up in 5 mL of 7:2:1 THF:water:trifluoroacetic acid at 0 °C and stirred for 30 minutes before being basified with 50 mL 10% $NaHCO_3$, extracted with 100 mL ethyl

acetate, dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. Crude ^1H NMR analysis indicated complete conversion to a 10:1 mixture of glucose:mannose derived diastereomers as well as some minor acetal side-products. Flash chromatography (1:1 ether:hexanes) afforded the title compound as a clear, colorless oil that solidified slowly upon standing at room temperature under reduced pressure (182 mg, 0.34 mmol, stains blue/green in anisaldehyde, 2:1 α:β, 74%) as well as the slower eluting 2-*O*-acetyl-4,6-bis-*O*-triisopropylsilyl-α-L-mannopyranose product (12 mg, 0.02 mmol, stains red/rust brown in anisaldehyde, 5%) in 79% combined yield. IR (film) 3447, 2944, 2892, 2867, 1725, 1464, 1381, 1251, 1125, 1056, 882.8, 786.3, 681.6 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) α-isomer: δ 5.36 (dd, 1H, *J* = 4.0, 4.0 Hz, H1); 4.61 (m, 1H, H2); 3.96 (m, 1H, H3); 3.75 (m, 1H, H4); 3.87 (m, 1H, H5); 3.98 (m, 2H, H6); 2.31 (d, 1H, *J* = 5.0 Hz, C3 OH); 2.13 (s, 3H, $C(O)CH_3$); 1.16-1.00 (m, 42H, 6 $CH(CH_3)_2$); β-isomer: δ 4.66 (dd, 1H, *J* = 8.0, 8.0 Hz, H1); 4.61 (m, 1H, H2); 3.60 (ddd, 1H, *J* = 9.0, 9.0, 5.0 Hz, H3); 3.77 (m, 1H, H4); 3.35 (ddd, 1H, *J* = 7.5, 5.0, 2.0 Hz, H5); 3.87 (m, 2H, H6); 2.50 (d, 1H, *J* = 4.5 Hz, C3 OH); 2.14 (s, 3H, $C(O)CH_3$); 1.16-1.00 (m, 42H, 6 $CH(CH_3)_2$); ^{13}C NMR (125 MHz, $CDCl_3$) α-isomer: δ 171.3, 90.2 (C1), 74.5 (C2), 73.4 (C4), 72.5 (C3), 72.3 (C5), 63.5 (C6), 21.2, 18.6, 18.5, 18.2, 18.1, 13.3, 12.2; β-isomer: δ 172.3, 95.2 (C1), 78.5 (C5), 76.9 (C2), 76.1 (C3), 72.4 (C4), 63.2 (C6), 21.2, 18.6, 18.5, 18.2, 18.1, 13.3, 12.2; 500 MHz COSY and HMQC spectra support the above ^1H and ^{13}C NMR assignments; HRMS (FAB+) exact mass calcd for $[M+H]^+$ ($C_{26}H_{55}O_7Si_2$) requires *m/z* 535.3486, found *m/z* 535.3487; $[\alpha]_D = -30.5$ (c = 2.00, $CHCl_3$, 2:1 α:β mixture).

Determination of the Relative Stereochemistry of 2-Acetoxy-4,6-bis-triisopropylsilanoxy-α, β-L-glucopyranose by Correlation to Glucose Pentaacetate. Triethylamine (16 μL, 0.11 mmol), 4-dimethylaminopyridine (2.0 mg, 0.02 mmol), and acetic anhydride (8 μL, 0.08 mmol) were added to 2-*O*-acetyl-4,6-bis-*O*-triisopropylsilyl-α,β-L-glucopyranose (15.1 mg, 0.03 mmol) dissolved in dichloromethane (100 μL) at 0 °C and allowed to stir for 30 minutes before being moved to room temperature for 4 hours. The reaction was then acidified with 10 mL 1N HCl, extracted with 10 mL ethyl acetate, washed with 10 mL 10% $NaHCO_3$, 10 mL brine, dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. The residue was purified by flash chromatography (3:1 hexanes:ether) to afford a mixture of two diastereomeric triacetates (16 mg, 0.03 mmol) in nearly quantitative yield. The triacetates (16 mg, 0.03 mmol) were dissolved in THF (500 μL) along with tetrabutylammonium fluoride hydrate (27 mg, 0.10 mmol) and acetic acid (6 μL, 0.10 mmol) and heated to reflux for 3 hours. Then, triethylamine (100 μL, 0.72 mmol), 4-dimethylaminopyridine (2.0 mg, 0.02 mmol), and acetic anhydride (50 μL, 0.32 mmol) were added and the resulting suspension was stirred for an additional hour at reflux. Then, the suspension was cooled to room temperature, acidified with 10 mL 1N HCl, extracted with 10 mL ethyl acetate, washed with 10 mL 10% $NaHCO_3$, 10 mL brine, dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. The residue was then purified by flash chromatography (1:1 ethyl acetate:hexanes) to afford a 2:1 mixture of pentaacetates in quantitative yield (10 mg, 0.03 mmol). A comparison of the ^{1}H and ^{13}C NMR spectra of the above generated pentaacetates to spectra recorded from commercially available (Aldrich Chemical Company) α-D-glucose pentaacetate and β-D-glucose pentaacetate showed that the major pentaacetate isomer was spectroscopically

identical to α-D-glucose pentaacetate and the minor pentaacetate isomer was spectroscopically identical to β-D-glucose pentaacetate.

1,2,3,4,5,6-hexa-^{13}C-2-*O*-Acetyl-4,6-bis-*O*-triisopropylsilyl-α, β-D-glucopyranose (29). Prepared according to the method above for 2-*O*-acetyl-4,6-bis-*O*-triisopropylsilyl-α,β-L-glucopyranose using (2*R*, 3*R*)-1,2,3,4-tetra-^{13}C-3-hydroxy-2,4-bis-(triisopropylsilanyloxy)-butyraldehyde (100 mg, 0.23 mmol), magnesium bromide diethyl etherate (177 mg, 0.69 mmol), (*Z*)-acetic acid 1,2-bis-^{13}*C*-2-(trimethylsilanyloxy)-vinyl ester (101 mg, 0.57 mmol) and 2.3 mL of diethyl ether. Crude ^{1}H and ^{13}C NMR analysis indicated complete conversion to a 8:1 mixture of glucose:mannose derived diastereomers as well as some minor acetal side-products. Flash chromatography (2:3 ether:hexanes + 1% triethylamine) afforded the title compound as a clear, colorless oil (83 mg, 0.15 mmol, stains blue/green in anisaldehyde, 2:1 α:β, 67%) as well as the slower eluting 2-acetoxy-4,6-bis-triisopropylsilanoxy-α-D-mannopyranose product (4.2 mg, 0.01 mmol, stains red/rust brown in anisaldehyde, 3%) in 70% combined yield. IR (film) 3446, 2944, 2892, 2867, 1727, 1464, 1375, 1249, 1120, 1039, 883.1, 778.6, 681.5 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) α-isomer: δ 5.39 (m, 1H, J_{13C-1H} = 171.5 Hz, H1); 4.64 (m, 1H, J_{13C-1H} = 150.1 Hz, H2); 3.96 (m, 1H, H3); 3.75 (m, 1H, H4); 3.87 (m, 1H, H5); 3.98 (m, 2H, H6); 2.28 (m, 1H, C3 OH); 2.15 (s, 3H, C(O)CH_3); 1.23-1.04 (m, 42H, 6 $CH(CH_3)_2$); β-isomer: δ 4.66 (m, 1H, H1); 4.61 (m, 1H, H2); 3.60 (m, 1H, H3); 3.77 (m, 1H, H4); 3.35 (m, 1H, H5); 3.87 (m, 2H, H6); 2.42 (m, 1H, C3 OH); 2.16 (s, 3H, C(O)CH_3); 1.23-1.04 (m, 42H, 6 $CH(CH_3)_2$); ^{13}C NMR (125 MHz, $CDCl_3$) α-isomer: δ 171.2, 90.2 (d, $J_{13C-13C}$ = 46.1 Hz, C1), 74.5 (m, C2), 73.5 (m, C4), 72.5 (C3), 72.3 (C5),

63.3 (d, $J_{13C\text{-}13C}$ = 43.8 Hz, C6), 21.2, 18.6, 18.6, 18.2, 18.1, 13.3, 12.3; β-isomer: δ 172.2, 95.2 (d, $J_{13C\text{-}13C}$ = 44.8 Hz, C1), 78.6 (dd, $J_{13C\text{-}13C}$ = 42.9, 42.9 Hz, C5), 77.0 (dd, $J_{13C\text{-}13C}$ = 40.9, 38.5 Hz, C2), 76.0 (dd, $J_{13C\text{-}13C}$ = 38.5, 38.5 Hz, C3), 72.4 (m, C4), 63.0 (d, $J_{13C\text{-}13C}$ = 44.5 Hz, C6), 21.2, 18.6, 18.6, 18.2, 18.1, 13.3, 12.3; 500 MHz COSY and HMQC spectra support the above ^{1}H and ^{13}C NMR assignments; HRMS (FAB) exact mass calcd for $[M - OH]^-$ ($^{13}C_6{}^{12}C_{20}H_{53}O_6Si_2$) requires *m/z* 523.3582, found *m/z* 523.3588; $[\alpha]_D$ = 35.0 (c = 2.00, $CHCl_3$, 2:1 α:β mixture). ^{1}H NMR (500 MHz, $CDCl_3$, ^{13}C decoupled) was identical to that reported above for 2-*O*-acetyl-4,6-bis-*O*-triisopropylsilyl-α,β-L-glucopyranose. Additional confirmation of the glucose stereochemistry for these two anomeric products is the similarity in ^{13}C shifts to the unlabeled material above. The isotopic purity of >98% is estimated by the lack of any ^{13}C–^{13}C uncoupled resonances in the ^{13}C NMR spectrum and no observed ^{13}C–^{1}H uncoupled resonances in the ^{1}H NMR spectrum.

2-*O*-Benzyl-4,6-bis-*O*-triisopropylsilyl-α-L-allopyranose (22). In an inert atmosphere glove-box, a 25 mL flame-dried flask was charged with titanium (IV) chloride tetrahydrofuran complex (1:2) (386 mg, 1.16 mmol) and a magnetic stir bar. After being removed from the glove-box and placed under an argon atmosphere, 4.6 mL of dichloromethane was added and the solution was cooled to –78 °C. Then, (*Z*)-acetic acid 2-(trimethyl-silanyloxy)-vinyl ester (308 mg, 1.39 mmol) was added dropwise followed by a solution of (2*S,* 3*S*)-3-hydroxy-2,3-bis-triisopropylsilanoxy-propionaldehyde (200 mg, 0.46 mmol) in 4.6 mL of dichloromethane. The resulting blood-red solution was stirred at –78 °C for 1 hour before being allowed to gradually warm to –30 °C over the

course of 3 hours. The reaction was then acidified by the addition of 100 mL saturated aqueous NH_4Cl, extracted with ethyl acetate (3x50 mL), washed with 100 mL 10% $NaHCO_3$, 100 mL brine, dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. Crude ^1H NMR analysis indicated complete conversion to a >19:1 mixture of allose:mannose derived diastereomers as well as some minor acetal side-products. Flash chromatography (3:7 ether:hexanes + 1% triethylamine) afforded the title compound as a clear, colorless oil (225 mg, 0.39 mmol, stains light green in anisaldehyde, 8:1 α:β, 83%). IR (film) 3293, 2943, 2866, 1464, 1388, 1248, 1138, 1089, 1068, 1016, 883.3, 680.5 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.34 (m, 5H, Ar-H); 5.31 (br s, 1H, C1 OH); 5.21 (s, 1H, H1); 4.79 (d, 1H, *J* = 12.0 Hz, one of CH_2Ar); 4.63 (d, 1H, *J* = 12.0 Hz, one of CH_2Ar); 3.34 (dd, 1H, *J* = 3.5, 3.5 Hz, H2); 4.27 (m, 1H, C3); 3.97 (m, 1H, H4); 3.80 (ddd, 1H, *J* = 9.0, 2.0, 2.0 Hz, H5); 3.97 (m, 2H, H6); 2.98 (s, 1H, C3 OH); 1.14-1.03 (m, 42H, 6 $CH(CH_3)_2$); ^{13}C NMR (125 MHz, $CDCl_3$) δ 137.8, 128.7, 128.3, 128.2, 92.0, 74.1, 72.3, 71.2, 68.2, 67.7, 62.7, 18.3, 18.3, 18.2, 18.1, 12.9, 12.4; 500 MHz COSY spectra support the above ^1H NMR assignments; HRMS (FAB+) exact mass calcd for $[M+H]^+$ ($C_{31}H_{59}O_6Si_2$) requires *m/z* 583.3850, found *m/z* 583.3834; $[\alpha]_D = -31.2$ (c = 2.00, $CHCl_3$, 8:1 α:β mixture).

Determination of the Relative Stereochemistry of 2-*O*-Benzyl-4,6-bis-*O*-triisopropylsilyl-α-L-allopyranose by Correlation to Allose Pentaacetate. Triethylamine (10 equiv.), 4-dimethylaminopyridine (0.1 equiv.), and acetic anhydride (5 equiv.) were added to 2-*O*-benzyl-4,6-bis-*O*-triisopropylsilyl-α-L-allopyranose dissolved in dichloromethane at 0 °C and allowed to stir for 30 minutes before being moved to

room temperature for 1 hour. Then, the solution was heated to reflux for 5 hours. The reaction was then acidified with 10 mL 1N HCl, extracted with 10 mL ethyl acetate, washed with 10 mL 10% $NaHCO_3$, 10 mL brine, dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. The crude diacetate was subjected to hydrogenolysis (50 psi H_2, 1:1 THF:EtOAc, 5 mg 10% Pd/C), followed by treatment with THF (500 μL) along with tetrabutylammonium fluoride hydrate (4 equiv.) and acetic acid (4 equiv.) and heated to reflux for 3 hours. Then, triethylamine (100 μL, 0.72 mmol), 4-dimethylaminopyridine (2.0 mg, 0.02 mmol), and acetic anhydride (50 μL, 0.32 mmol) were added and stirred for an additional hour at reflux. Then, the solution was cooled to room temperature, acidified with 10 mL 1N HCl, extracted with 10 mL ethyl acetate, washed with 10 mL 10% $NaHCO_3$, 10 mL brine, dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. The residue was then purified by flash chromatography (2:3 ethyl acetate:hexanes). A comparison of the ^1H and ^{13}C NMR spectra of the above generated pentaacetate to spectra recorded from an authentic samples of α-D-allose pentaacetate prepared by the methods of Sims *et al.*[29] showed that the α-pentaacetate isomer was spectroscopically identical to α-D-allose pentaacetate.

2-*tert*-Butylcarbamato-2-deoxy-4,6-bis-*O*-triisopropylsilyl-α. β-L-mannopyranose (23). Titanium (IV) chloride (38 μL, 0.35 mmol) was added dropwise to a stirring –78 °C solution of (2*S,* 3*S*)-3-hydroxy-2,3-bis-triisopropylsilanoxy-propionaldehyde (50 mg, 0.12 mmol), ((*Z*)-[2-(trimethylsilanyloxy)-vinyl]-carbamic acid *tert*-butyl ester)-

[29] Furneaux, R. H.; Rendle, P. M.; Sims, I. M. *J. Chem. Soc. Perkin Trans.1* **2000**, *11*, 2011.

trimethylsilyl-imidate (175 mg, 0.58 mmol) and dichloromethane (2.3 mL). The resulting blood red solution was stirred at –78 °C for 5 hours, then allowed to warm gradually over 5 hours to –40 °C. After stirring for an additional 48 hours at –40 °C, the reaction was acidified by the addition of 100 mL saturated aqueous NH_4Cl, extracted with ethyl acetate (3x50 mL), washed with 100 mL 10% $NaHCO_3$, 100 mL brine, dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. Crude ^1H and ^{13}C NMR analysis indicated complete conversion to a 10:1 mixture of mannose:allose derived diastereomers as well as some minor acetal side-products. Flash chromatography (1:3 ether:hexanes) afforded the title compound as a clear, colorless oil (51 mg, 0.09 mmol, 2:1 α:β, 74%). IR (film) 3436, 2943, 2893, 2867, 1699, 1510, 1464, 1368, 1248, 1151, 1122, 1066, 883.0, 763.3, 680.9 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 8.92 (d, 1H, *J* = 9.0 Hz, OH); 7.59 (br s, 1H, NH); 5.13 (d, 1H, *J* = 3.0 Hz, H1); 4.95 (m, 1H, H3); 3.95 (m, 1H, H2); 4.10 (m, 1H, H4); 3.85 (m, 1H, H5); 3.96 (m, 2H, H6); 1.47 (d, 1H, *J* = 3.0 Hz, C3 OH); 1.45 (s, 9H, $C(CH_3)_3$); 1.22-1.06 (m, 42H, 6 $CH(CH_3)_2$); ^{13}C NMR (125 MHz, $CDCl_3$) δ 163.1, 94.0, 80.5, 75.5, 71.2, 70.0 63.5, 54.5, 28.5, 18.5, 18.5, 18.2, 18.1, 13.0, 12.2; 500 MHz COSY spectra support the above ^1H NMR assignments; HRMS (EI+) exact mass calcd for $[M+H]^+$ ($C_{29}H_{62}NO_7Si_2$) requires *m/z* 592.4065, found *m/z* 592.4064; $[\alpha]_D$ = –27.1 (c = 2.00, $CHCl_3$, 2:1 α:β mixture).

Determination of the Relative and Stereochemistry of 2-*tert*-Butylcarbamato-2-deoxy-4,6-bis-*O*-triisopropylsilyl-α.β-L-mannopyranose by Correlation to 2-Acetamido-2-dexoy-1,3,4,6-tetra-*O*-acetyl-α-mannopyranose. Triethylamine (81 μL, 0.58 mmol), 4-dimethylaminopyridine (1.4 mg, 0.01 mmol), and acetic anhydride (28 μL,

0.29 mmol) were added to a solution of 2-*tert*-butylcarbamato-2-deoxy-4,6-bis-*O*-triisopropylsilyl-α.β-L-mannopyranose (34.6 mg, 0.058 mmol) in dichloromethane (300 μL) and allowed to stir for 10 hours. The reaction was then acidified with 10 mL 1N HCl, extracted with 10 mL ethyl acetate, washed with 10 mL 10% $NaHCO_3$, 10 mL brine, dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo* to afford 40 mg (3:1 α:β). The crude diacetate was subjected to tetrabutylammonium fluoride hydrate (62 mg, 0.24 mmol) and acetic acid (13.5 μL, 0.24 mmol) in THF (120 μL) at reflux for 4 hours. Then, triethylamine (100 μL, 0.72 mmol), 4-dimethylaminopyridine (2.0 mg, 0.02 mmol), and acetic anhydride (50 μL, 0.32 mmol) were added and stirred for an additional hour at reflux. Then, the solution was cooled to room temperature, acidified with 10 mL 1N HCl, extracted with 10 mL ethyl acetate, washed with 10 mL 10% $NaHCO_3$, 10 mL brine, dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. The crude tetraacetate was then dissolved in 5:1 dichloromethane:trifluoroacetic acid (1.0 mL) and stirred for 5 hours at room temperature. Then, the reaction was basified with 10 mL $NaHCO_3$, extracted with ethyl acetate (3x10 mL), dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. Then, the residue was dissolved in 200 μL of dichloromethane and triethylamine (100 μL, 0.72 mmol), 4-dimethylaminopyridine (2.0 mg, 0.02 mmol), and acetic anhydride (50 μL, 0.32 mmol) were added and the resulting solution was stirred for 5 hours at room temperature. The reaction was then acidified with 10 mL 1N HCl, extracted with 10 mL ethyl acetate, washed with 10 mL 10% $NaHCO_3$, 10 mL brine, dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. Purification by flash chromatography (3:1 ethyl acetate:hexanes) afforded a single α-pentaacetate isomer (7.8 mg, 0.020 mmol) in 35% overall yield. A comparison of the ^1H

and ^{13}C NMR spectra of the above generated pentaacetate to an authentic sample of α-D-mannosamine pentaacetate generated by the method of O'Niel[30] showed the two samples to be identical.

2-Deoxy-2-acetylmercapto-4,6-bis-*O*-triisopropylsilyl-α-L-allopyranose (24). In an inert atmosphere glove-box, a 2 dram flame-dried vial was charged with titanium (IV) chloride tetrahydrofuran complex (1:2) (231 mg, 0.69 mmol) and a magnetic stir bar. After removing the sealed vial from the glove-box and placing it under an argon atmosphere, 2.3 mL of dichloromethane was added and the solution was cooled to –20 °C. Then, a solution of (2*S,* 3*S*)-3-hydroxy-2,3-bis-triisopropylsilanoxy-propionaldehyde (100 mg, 0.23 mmol) in 2.3 mL of dichloromethane was added followed by dropwise addition of (*Z*)-thioacetic acid *S*-[2-(trimethyl-silanyloxy)-vinyl] ester (231 mg, 1.16 mmol, 3:1 *Z*:*E*). After 16 hours at –20 °C, an additional 100 mg of the enolsilane was added and the solution was stirred for an additional 34 hours. The reaction was then acidified by the addition of 100 mL saturated aqueous NH_4Cl, extracted with ethyl acetate (3x50 mL), washed with 100 mL 10% $NaHCO_3$, 100 mL brine, dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. Crude ^1H NMR analysis indicated a >19:1 mixture of allose:mannose derived diastereomers as well as some minor acetal side-products. Flash chromatography (1:4 ether:hexanes + 1% triethylamine) afforded the title compound as a clear, colorless oil (90 mg, 0.16 mmol, stains blue in anisaldehyde, 3:1 α:β, 71%). IR (film) 3446, 2944, 2892, 2867, 1697, 1464, 1248, 1113, 1066, 883.5, 770.9, 682.1 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) α-anomer: δ 5.04 (br s, 1H, H1); 4.14 (m,

[30] O'Neill, J. R. *Can. J. Chem.* **1959**, *37*, 1747.

2H, H3 and H4); 3.99 (m, 2H, H6); 3.85 (m, 1H, H5); 3.79 (m, 1H, H2); 3.12 (s, 1H, C1 OH); 2.41 (s, 1H, C3 OH); 2.39 (s, 1H, $C(O)CH_3$); 1.15-1.06 (m, 42H, 6 $CH(CH_3)_2$); ^{13}C NMR (125 MHz, $CDCl_3$) α-anomer: δ 194.8, 93.3 (C1), 72.3 (C3), 68.23 (C5), 68.16 (C4), 62.7 (C6), 45.9 (C2), 30.8, 18.3, 18.3, 18.2, 18.2, 12.9, 12.4; β-anomer: δ 194.8, 94.7, 75.7, 72.3, 69.0, 63.3, 50.0, 30.8, 18.3, 18.3, 18.2, 18.2, 12.9, 12.4; 500 MHz COSY and HMQC spectra support the above ^{1}H and ^{13}C NMR assignments; HRMS (CI+) exact mass calcd for $[M\bullet]^+$ ($C_{26}H_{54}O_6Si_2S$) requires *m/z* 550.3180, found *m/z* 550.3153; $[\alpha]_D = -8.1$ (c = 2.00, $CHCl_3$, 3:1 α:β mixture).

2-*O*-Acetyl-4,6-bis-*O*-*tert*-butyldiphenylsilyl-α-L-allopyranose (25). In an inert atmosphere glove-box, a 2 dram flame-dried vial was charged with titanium (IV) chloride tetrahydrofuran complex (1:2) (86.5 mg, 0.26 mmol) and a magnetic stir bar. After removing the sealed vial from the glove-box and placing it under an argon atmosphere, 0.865 mL of dichloromethane was added and the solution was cooled to –78 °C. Then, a solution of (2*S*, 3*S*)-3-hydroxy-2,3-bis-*tert*-butyl-diphenylsilanoxy-propionaldehyde (30.8 mg, 0.052 mmol) in 0.865 mL of dichloromethane was added followed by dropwise addition of (*Z*)-acetic acid 2-(trimethyl-silanyloxy)-vinyl ester (75.3 mg, 0.43 mmol). After 2 hours at –78 °C, the reaction was warmed to –40 °C over 1 hour and then warmed to –20 °C for 10 hours. The reaction was then acidified by the addition of 100 mL saturated aqueous NH_4Cl, extracted with ethyl acetate (3x50 mL), washed with 100 mL 10% $NaHCO_3$, 100 mL brine, dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. Crude ^{1}H NMR analysis indicated a >19:1 mixture of allose:mannose derived diastereomers as well as some minor acetal side-products. Flash chromatography (3:7

ethyl acetate:hexanes + 1% triethylamine) afforded the title compound as a clear, colorless oil (31.8 mg, 0.044 mmol, stains blue-green in anisaldehyde, 3:1 α:β, 86%). IR (film) 3406, 2944, 2867, 1742, 1464, 1374, 1236, 1050, 1014, 883.4, 681.6 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) α-isomer: δ 7.64–7.31 (m, 20H, Ar-H); 5.12 (dd, 1H, *J* = 10.5, 3.5 Hz, H1); 5.06 (d, 1H, *J* = 10.5 Hz, C1 OH); 4.48 (ddd, 1H, *J* = 2.5, 2.5, 1.0 Hz, H2); 4.08 (m, 1H, H3); 4.13 (dd, 1H, *J* = 9.5, 3.0 Hz, H4); 3.79 (ddd, 1H, 9.5, 2.5, 2.5 Hz, H5); 3.91 (m, 2H, H6); 2.80 (s, 1H, C3 OH); 2.13 (s, 3H, $C(O)CH_3$); 1.02 (s, 18H, $C(CH_3)_3$); ^{13}C NMR (125 MHz, $CDCl_3$) α-isomer: δ 170.3, 135.9, 134.1, 133.7, 132.8, 129.7, 128.4, 128.2, 127.7, 91.5, 71.5, 69.2, 69.1, 68.0, 63.7, 27.2, 21.2, 19.5; HRMS (FAB+) exact mass calcd for $[M+H]^+$ ($C_{40}H_{51}O_7Si_2$) requires *m/z* 699.3168, found *m/z* 699.3164; $[\alpha]_D = -20.3$ (c = 2.00, $CHCl_3$, 3:1 α:β mixture).

2-*O*-Acetyl-6-*O*-*tert*-butyldiphenylsilyl-4-methyl-α-L-allopyranose (26). In an inert atmosphere glove-box, a 2 dram flame-dried vial was charged with titanium (IV) chloride tetrahydrofuran complex (1:2) (140 mg, 0.42 mmol) and a magnetic stir bar. After removing the sealed vial from the glove-box and placing it under an argon atmosphere, 1.4 mL of dichloromethane was added and the solution was cooled to –78 °C. Then, a solution of (2*S,* 3*R*)-4-*tert*-butyldiphenyl-silanyloxy-3-hydroxy-2-methylbutanal (50 mg, 0.14 mmol) in 1.4 mL of dichloromethane was added followed by dropwise addition of (*Z*)-acetic acid 2-(trimethyl-silanyloxy)-vinyl ester (75.3 mg, 0.43 mmol). After 1 hour at –78 °C, the reaction was warmed slowly to –30 °C over 3 hours and then kept at –30 °C for 3 additional hours. The reaction was then acidified by the addition of 100 mL saturated aqueous NH_4Cl, extracted with ethyl acetate (3x50 mL), washed with 100 mL

10% $NaHCO_3$, 100 mL brine, dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. Crude ^1H NMR analysis indicated a >19:1 mixture of allose:mannose derived diastereomers as well as some minor acetal side-products. Flash chromatography (2:3 ethyl acetate:hexanes + 1% triethylamine) afforded the title compound as a clear, colorless oil (36.5 mg, 0.080 mmol, stains blue-green in anisaldehyde, 4:1 α:β, 68%). IR (film) 3436, 2932, 2858, 1743, 1428, 1373, 1273, 1113, 1057, 848.3, 823.1, 739.5, 702.7, 613.6, 504.3 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) α-isomer: δ 7.72 (m, 4H, Ar-H); 7.43 (m, 6H, Ar-H); 5.25 (dd, 1H, *J* = 8.0, 2.5 Hz, H2); 4.78 (dd (apparent t), 1H, *J* = 3.5, 3.5 Hz, H1); 4.48 (m, 1H, H3); 4.11 (br s, 1H, C1-OH); 3.85 (m, 3H, H5, H6); 2.24 (m, 1H, H4); (m, 2H, H6); 2.19 (s, 3H, $C(O)CH_3$); 1.08 (s, 9H, $C(CH_3)_3$); 1.00 (d, 3H, *J* = 7.0 Hz, C4-CH_3); ^{13}C NMR (125 MHz, $CDCl_3$) α-isomer: δ 170.4, 136.0, 135.9, 133.9, 133.6, 129.90, 129.87, 127.91, 127.85, 92.7, 72.5, 71.2, 69.1, 64.3, 35.3, 27.1, 21.3, 13.6; HRMS (FAB+) exact mass calcd for $[M+Na]^+$ ($C_{25}H_{34}O_6NaSi_2$) requires *m/z* 481.2022, found *m/z* 481.2007; $[\alpha]_D = -16.3$ (c = 2.00, $CHCl_3$, 4:1 α:β mixture).

5-Benzylsulfanyl-5-deoxy-1,3-bis-*O*-triisopropylsilyl-α-D-fructopyranose (32). (2*S*, 3*S*)-3-Hydroxy-2,3-bis-triisopropylsilanoxy-propionaldehyde (200 mg, 0.46 mmol) was added as a solution in 4.6 mL of dichloromethane to a flame-dried flask charged with magnesium bromide diethyl etherate (358 mg, 1.39 mmol) and 4.6 mL of dichloromethane cooled to –20 °C. After stirring for 30 minutes at –20 °C, (*E*)-(2-benzylsulfanyl-vinyloxy)-trimethylsilane (330 mg, 1.39 mmol, 3:1 *E*:*Z*) was added dropwise. The suspension was stirred at –20 °C for 22 hours, then the reaction was quenched by the addition of saturated aqueous NH_4Cl, extracted twice with ethyl acetate,

washed with brine, dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The residue was taken up in 5 mL of 7:2:1 THF:water:trifluoroacetic acid at 0 °C for 30 minutes before being quenched with 10% $NaHCO_3$, extracted with ethyl acetate, dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. Crude ^{1}H NMR analysis indicated complete conversion to a >19:1 mixture of fructopyranose:aldopyranose derived diastereomers. Flash chromatography (49:1 hexanes:ethyl acetate) afforded the title compound as a clear, colorless oil (221 mg, 0.37 mmol, >19:1 α:β, 80%). IR (film) 3535, 2942, 2890, 2866, 1464, 1384, 1250, 1114, 1070, 882.9, 681.6 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.33 (m, 5H, Ar-H); 3.82 (m, 1H, H3); 3.81 (m, 2H, CH_2Ar); 3.76 (dd, 1H, *J* = 12.0, 1.0 Hz, H6-equitorial); 3.69 (d, 1H, *J* = 9.5 Hz, one of H1); 3.65 (d, 1H, *J* = 9.5 Hz, one of H1); 3.60 (ddd, 1H, *J* = 10.5, 8.5, 2.0 Hz, H4); 3.56 (s, 1H, C2 OH); 3.48 (dd, 1H, *J* = 11.0, 5.0 Hz, H6-axial); 2.62 (ddd, 1H, *J* = 10.5, 10.5, 5.0 Hz, H5); 2.57 (d, 1H, *J* = 2.5 Hz, C3 OH); 1.24-1.06 (m, 42H, 6 $CH(CH_3)_2$); ^{13}C NMR (125 MHz, $CDCl_3$) δ 138.4, 128.9, 128.9, 127.6, 98.4 (C1), 73.8 (C3), 72.7 (C4), 66.0 (C1), 62.3 (C6), 48.7 (C5), 35.8 (CH_2Ar), 18.6, 18.5, 18.1, 18.0, 13.1, 12.2; 500 MHz COSY, DEPT, and HMQC spectra support the above ^{1}H and ^{13}C NMR assignments; HRMS (FAB+) exact mass calcd for $[M + H]^+$ ($C_{31}H_{57}O_4Si_2S$) requires *m/z* 581.3516, found *m/z* 581.3513; $[\alpha]_D$ = 12.1 (c = 2.00, $CHCl_3$). The assignment of the fructose relative stereochemistry is based on an analysis of the coupling constants as follows. The coupling between H4 and H5 is 10.5 Hz, and the H4–H3 coupling is 8.5 Hz, therefore, H3 and H4 must be trans-diaxial and H4 and H5 must also be trans-diaxial on the six-membered ring. The only stereochemistry consistent with those facts is the stereochemistry of fructose. The

fructose stereochemistry is also consistent with the sense of diastereoselectivity observed using oxygen in place of sulfur enolsilanes (*vide supra*).

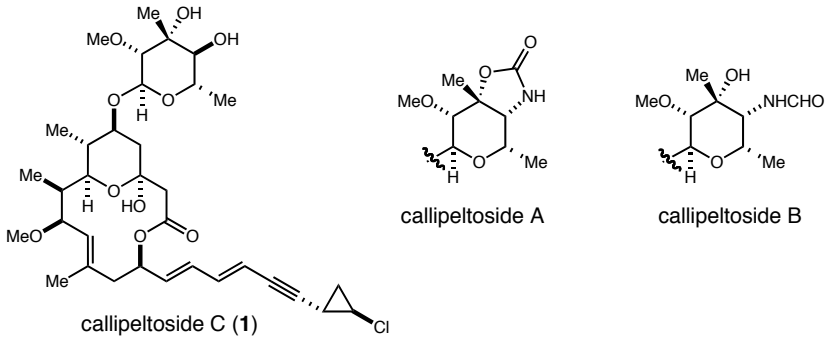
C h a p t e r 5

Progress Toward the Total Synthesis of Callipeltoside C

Isolation, Structure, and Biological Activity

Members of the callipeltoside class of natural products (Figure 1) were first isolated by Minale *et al.* from the lithistid sponge *Callipelta* sp. in the shallow waters off the eastern coast of New Caledonia.[1] Significantly, each of the callipeltosides exhibits cytotoxic behavior against the non-small-cell lung carcinoma NSCLC-N6 and P388 cell lines (IC_{50} = 11.3 to 30.0 μg/mL).

Figure 1. The Callipeltoside Family of Marine Natural Products



The exact mode of action could not be determined due to ≤ 3.5 mg of each callipeltoside having been isolated to date. Surprisingly, initial investigations have revealed that cell proliferation was halted by callipeltoside A at the G1 phase. Minale and co-workers proposed that the cessation of the cell cycle in G1 may be due to the induction of terminal cell differentiation. If their hypothesis is correct, then the callipeltosides may represent a mechanism-based lead for the development of a new class of cancer therapies.

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[1] Callipeltoside A: (a) Zampella, A.; D'Auria, M. V.; Minale, L.; Debitus, C.; Roussakis, C. *J. Am. Chem. Soc.* **1996**, *118*, 11085. Callipeltosides B and C: (b) Zampella, A.; D'Auria, M. V.; Minale, L. *Tetrahedron* **1997**, *53*, 3243.

While the stereochemistry of the macrocyclic core of all of the callipeltosides has been shown to be identical by extensive NMR studies, the major structural differences between the callipeltosides occur in the carbohydrate region. Unlike callipeltosides A and B, the structural assignment of callipeltoside C (**1**) is not complete due to only 0.8 mg of **1** having been isolated. It is not known whether D or L callipeltose C is the correct sugar stereochemistry due to a lack of spectroscopic data or chemical degradation studies relating the stereochemistry of the sugar to that of the macrocyclic core.

Previous Synthetic Efforts

Due to their unique fourteen-membered macrolactone with appended dienyne-chlorocyclopropyl side chain, unusual sugar moieties, low natural abundance, and intriguing biological activity, the callipeltosides represent an attractive target for total synthesis. Therefore, it is not surprising that this class of natural products has garnered significant attention from the synthetic community. While there have been three reported syntheses of callipeltoside A, there have been no reports of syntheses of either callipeltosides B or C. Therefore, the syntheses of callipeltoside A from the groups of Trost, Evans, and Patterson (as well as previous work by other members of our group) will be briefly reviewed to place our current efforts in the proper context.[2]

The first total synthesis of callipeltoside A was reported by Trost and co-workers.[3] Their retrosynthetic analysis begins with a disconnection of the sugar by glycolysis and

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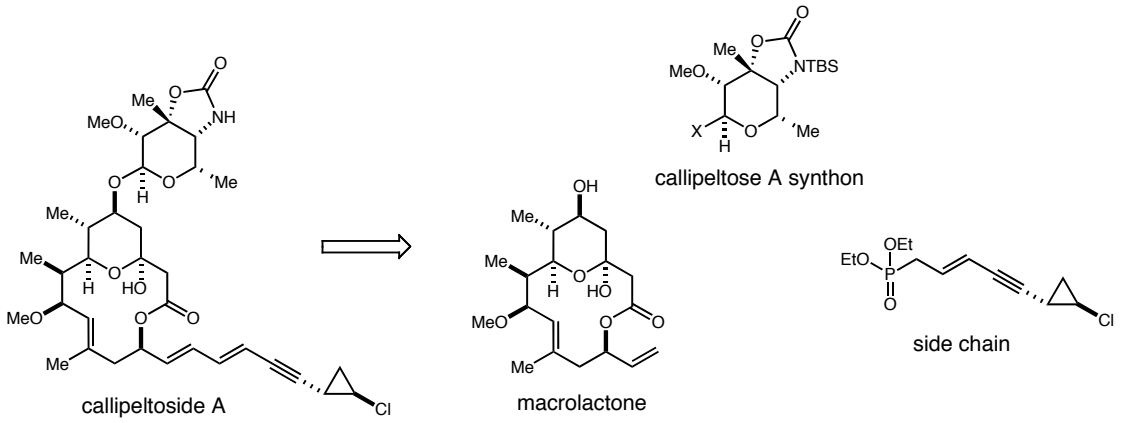
[2] A more extensive review has already been presented: Wiener, J. J. M. Ph.D. Thesis California Institute of Technology, Jan. 2004.

[3] (a) Trost, B. M.; Dirat, O.; Gunzner, J. L. *Angew. Chem. Int. Ed.* **2002**, *41*, 841. (b) Trost, B. M.; Gunzner, J. L.; Dirat, O.; Rhee, Y. H. *J. Am. Chem. Soc.* **2002**, *124*, 10396.

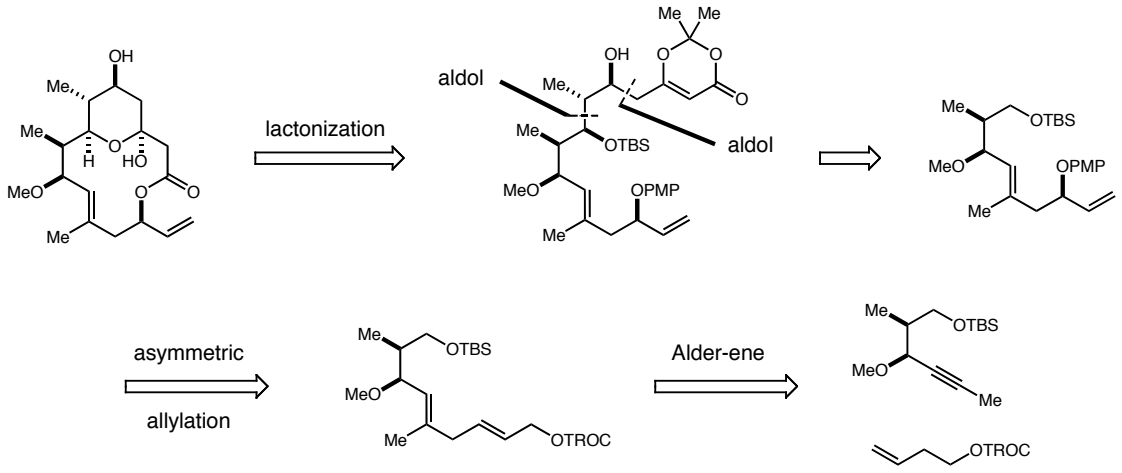
the side chain *via* either a Horner-Wadsworth-Emmons (HWE) coupling or olefin metathesis to reveal the macrolactone core (Figure 2).

Figure 2. Trost's Retrosynthesis of Callipeltoside A



Further analysis revealed to them the opportunity to employ their ruthenium-catalyzed Alder-ene coupling and asymmetric alkylation technology (Figure 3).

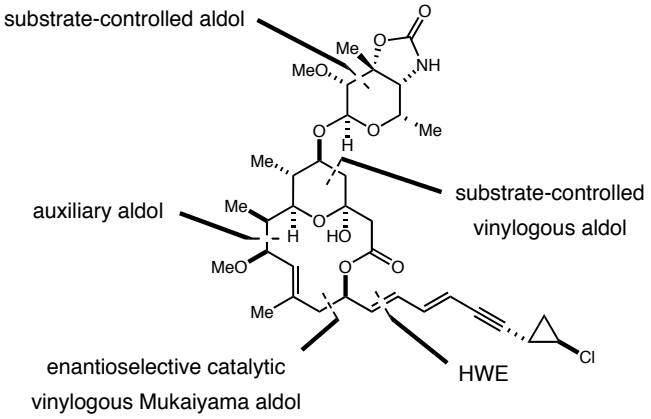
Figure 3. Trost's Retrosynthesis of the Callipeltoside Macrolactone



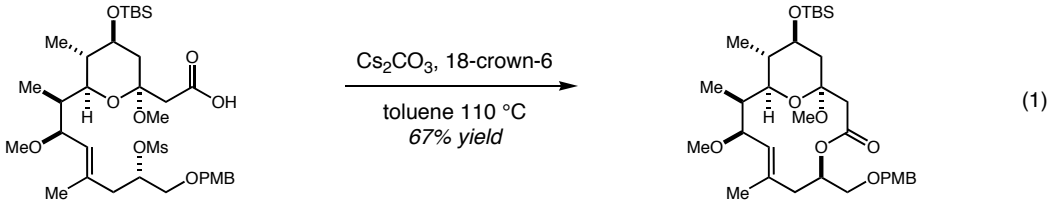
However, eight of the eleven stereocenters present in callipeltoside A are introduced by Trost from the chiral pool. Despite that reliance on the chiral pool and chiral reagents (such as a superstoichiometric CBS reduction), their synthesis is relatively efficient and completes the total synthesis in 22 linear steps (3.8% overall yield) and 46 total steps (0.05% overall yield).

Closely following Trost's report, Evans and co-workers disclosed a total synthesis of callipeltoside A.[4] Their synthetic strategy (Figure 4) utilizes highly selective auxiliary-based, diastereoselective and enantioselective catalytic aldol technologies to install six of the eleven callipeltoside stereocenters.

Figure 4. Evans's Strategy for Synthesizing Callipeltoside A



In contrast to the other approaches to callipeltoside A, Evans employs an alkylative macrolactonization strategy rather than the more conventional esterification route (eq 1).



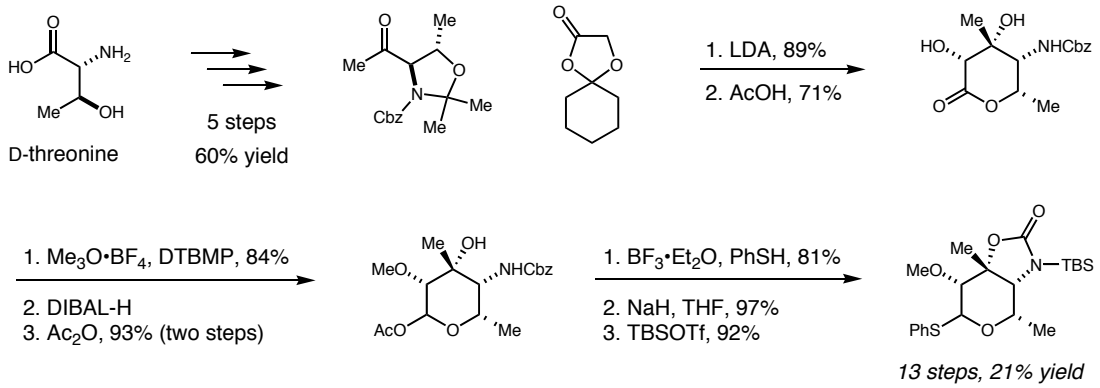
(1)

A further unique feature of their strategy is the synthesis of callipeltose A from non-carbohydrate precursors (Scheme 1).[5] Staring from D-threonine, they were able to construct an appropriately activated callipeltose synthon in only 13 steps and 21% overall yield.

[4] Evans, D. A.; Hu, E.; Burch, J. D.; Jaeschke, G. *J. Am. Chem. Soc.* **2002**, *124*, 5654.

[5] Evans, D. A.; Hu, E.; Tedrow, J. S. *Org. Lett.* **2001**, *3*, 3133.

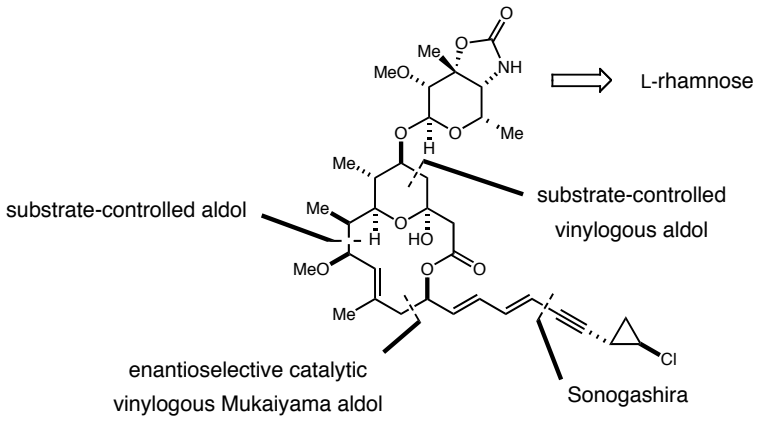
Scheme 1. Evans's Synthesis of Callipeltose A



Unlike either the syntheses from Trost's and Paterson's groups, Evans chose to delay installation of the potentially sensitive dienyne side chain until after glycosidation, completing their total synthesis in 26 steps (longest linear sequence).

Paterson *et al.* have reported the latest total synthesis of callipeltoside A,[6] although they had described the earliest synthesis of the aglycon.[7] As with Evans's synthesis, aldol chemistry is used with great effect to generate the majority of the complexity present in the macrolactone core (Figure 5).

Figure 5. Patersons's Strategy for Synthesizing Callipeltoside A

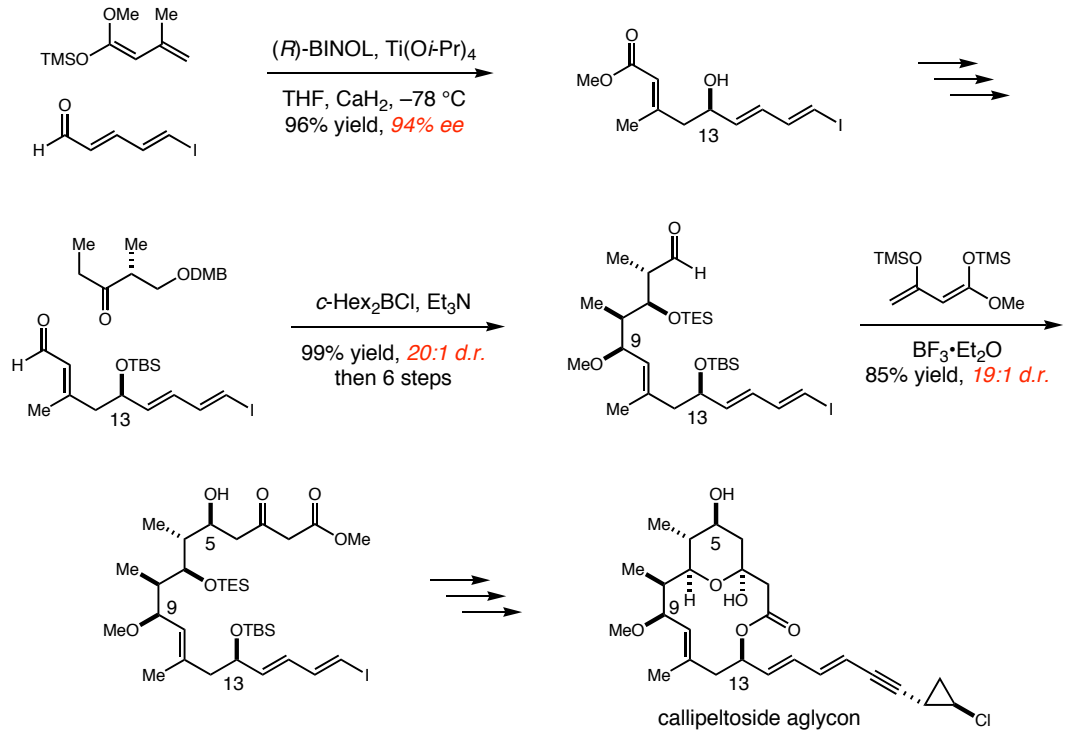


[6] Paterson, I.; Davies, R. D. M.; Heimann, A. C.; Marquez, R.; Meyer, A. *Org. Lett.* **2003**, *5*, 4477.

[7] Paterson, I.; Davies, R. D. M.; Marquez, R. *Angew. Chem. Int. Ed.* **2001**, *40*, 603.

Their total synthesis highlights a novel enantioselective catalytic vinylogous Mukaiyama aldol reaction, allowing them to set the *C*-13 stereocenter in 94% ee and 96% yield. Later in their sequence, diastereoselective aldol reactions are employed to set both the *C*-9 and *C*-5 carbinol stereocenters in ≥19:1 selectivity (Scheme 2).

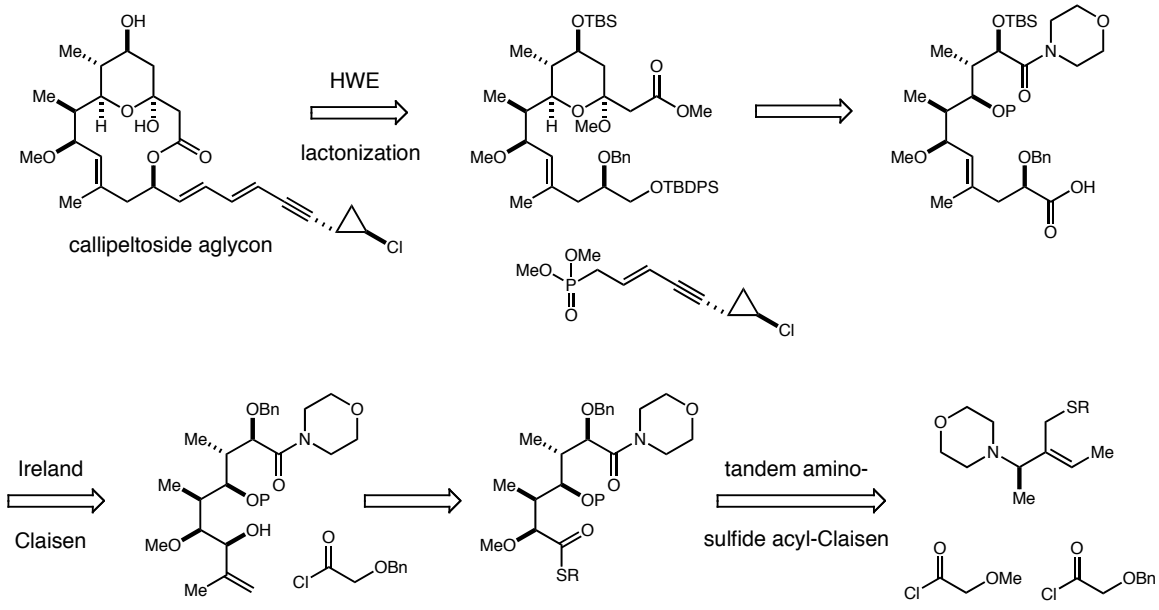
Scheme 2. Patersons's Total Synthesis of Callipeltoside Aglycon



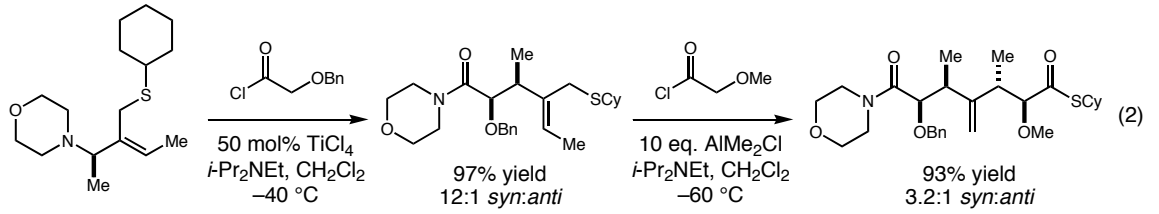
Significantly, they chose a Sonogashira disconnection of the side chain rather than the HWE or metathesis strategies that Trost and Evans employed. Impressively, they were able to carry the reactive dienyliodide moiety throughout the majority of their synthesis. Their synthesis is also notable for its efficiency as they completed the total synthesis in just 23 linear steps and in 4.8% overall yield.

Drs. Jake Wiener and Jeongbeob Seo in our group embarked upon an elegant route to the callipeltoside macrolactone,[8] taking advantage of the tandem amino-sulfide acyl-Claisen rearrangement developed in our group (Figure 6).[9]

Figure 6. MacMillan's Retrosynthesis of Callipeltoside Aglycon



That key rearrangement sequence furnished the entire stereochemical core of the callipeltosides in 90% yield and with useful selectivity over the two-step sequence (eq 2).



Elaboration of the stereochemical core set up a key Ireland Claisen rearrangement followed, after further functionalization, by a complex application of Marshall's alkoxycarbonylation reaction[10] to afford macrolactone precursor **2** (Scheme 3).

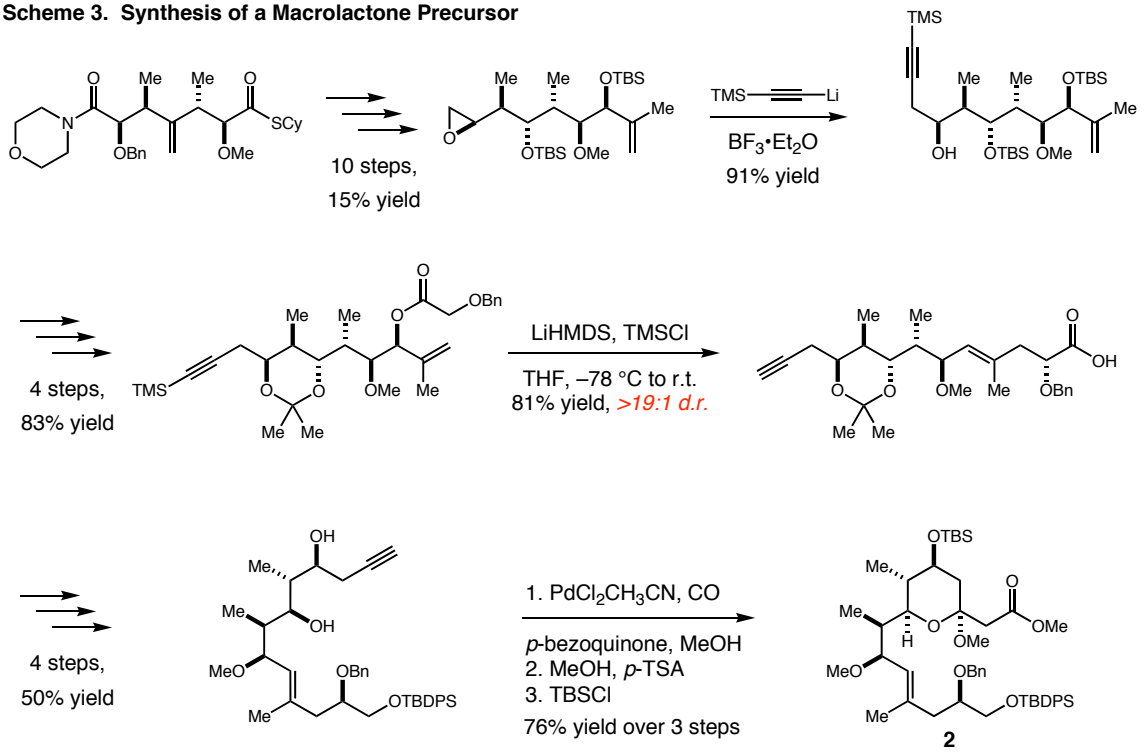
---

[8] Wiener, J. J. M. Ph.D. Thesis, California Institute of Technology, Jan. 2004.

[9] Seo, J.; Wiener, J. J. M.; Falsey, J. R.; Anker, N.; MacMillan, D. W. C. *unpublished results.*

[10] Marshall, J. A.; Yanik, M. M. *Tetrahedron Lett.* **2000**, *41*, 4717.

Scheme 3. Synthesis of a Macrolactone Precursor

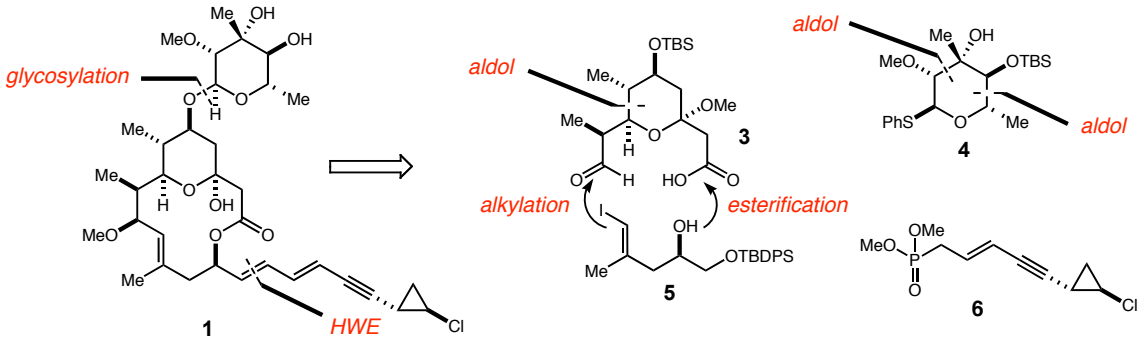


Unfortunately, all attempts at removal of the *C*-13 benzyl protecting group of **2** failed.

Retrosynthetic Analysis

Rather than pursuing a new protecting group strategy to complete the above Claisen-based route, a more efficient strategy toward the callipeltosides was envisioned utilizing the aldehyde aldol reaction (see Chapters 2 to 4) to build not only the stereochemical core of the macrolactone but also callipeltose C (Scheme 4).

Scheme 4. Retrosynthetic Analysis of Callipeltoside C

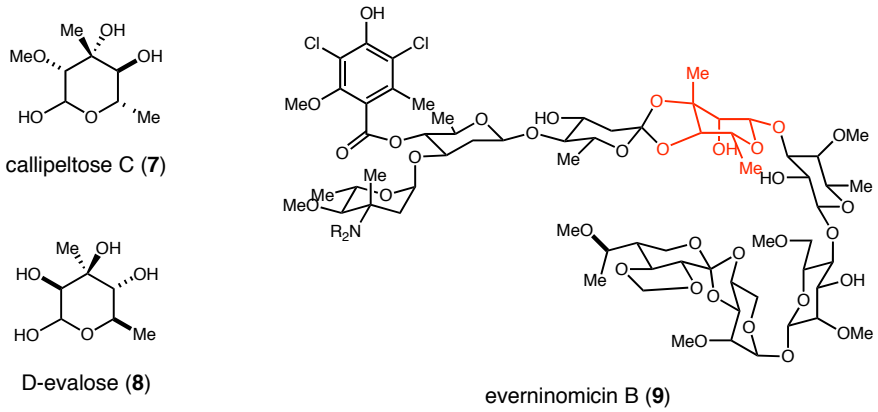


It was also envisioned that breaking the macrolactone portion into two fragments *via* alkylation and esterification transforms would lead to higher convergency. Due to the modularity of the above approach, fragment assembly (*i.e.*, attaching tetrahydropyran fragment **3**, sugar **4**, iodoalcohol **5**, and side chain **6**) could be performed in a variety of different orders to allow for flexibility of the synthesis plan. Due to the well-precedented use of esterification reactions for macrocylizations (*vide supra*), we chose to first explore the novel possibility of forming the macrocycle at the *C*-9/*C*-10 carbon-carbon bond through a ring-closing Nozaki-Hiyama-Kishi reaction (NHK).

Synthesis of Callipeltose C

Callipeltose C (2-*O*-methylevalose, **7**) is only found as the sugar component of callipeltoside C, although the related D-evalose (**8**) has been isolated as a component of the oligosaccharide antibiotic everninomicin B (**9**) (Figure 7).[11]

Figure 7. Callipeltose C and Related Sugars



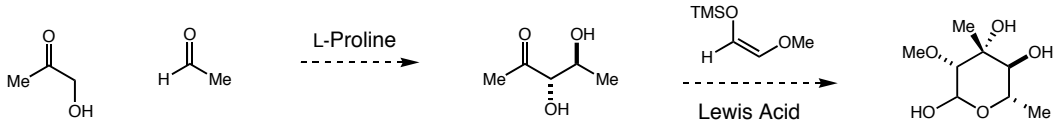
While the relative stereochemistry and gross structure of callipeltose C has been assigned by NMR structure elucidation, the stereochemistry of the sugar relative to the macrolactone has not been established. The L-configuration for callipeltose C has been

[11] Ganguly, K. A.; Saksena, K. A. *J.C.S. Chem. Comm.* **1973**, 531.

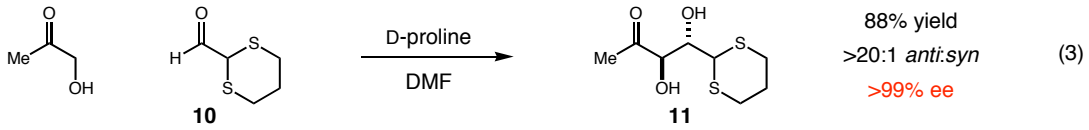
assumed by analogy to callipeltose A. Due to that stereochemical ambiguity, we felt that a synthesis capable of producing either enantiomer of callipeltose C would be necessary to help confirm the structural assignment—especially in light of only the D isomer of the structurally-related evalose having been previously isolated.

Initial efforts toward the total synthesis of callipeltose C focused on applying the two-step sugar synthesis methodology described in Chapters 3 and 4 (Scheme 5).

Scheme 5. Proposed Aldol Route to Protected Callipeltose C



As acetaldehyde performs poorly under proline-catalysis, an acetaldehyde equivalent was necessary for completion of the first step of that two-step sequence. Fortunately, Dr. R. Ian Storer in our group developed dithiane aldehyde **10** as a useful acetaldehyde equivalent and even performed the necessary aldol reaction during the course of those studies (eq 3).[12]



10 **11**

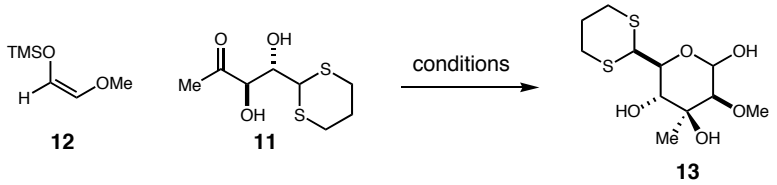
The second aldol step requires the diastereoselective addition of an aldehyde enolate to a ketone electrophile.[13] While a variety of aldehyde enolates were examined (Table 1), none of those enolates were capable of effecting the required transformation.

---

[12] Storer, R. I.; MacMillan, D. W. C. *Tetrahedron* **2004**, *60*, 7705.

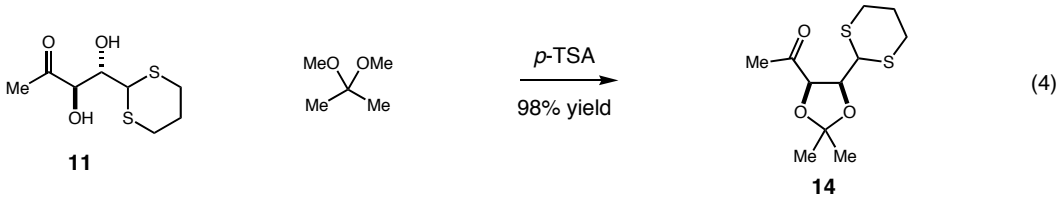
[13] For an example of a titanate-type aldehyde enolate addition to electrophilic ketones, see: Yachi, K.; Shinokubo, H.; Oshima, K. *J. Am. Chem. Soc.* **1999**, *121*, 9465.

Table 1. Attempted Aldehyde Aldol Route to Callipeltose C



conditions	results
$TiCl_4$, –78 °C to r.t.	no reaction
12/MeLi, then **11**	decomposition
TBAF	decomposition
12/MeLi, then Ti(O*n*-Bu)$_4$, then **11**	no reaction
11/Ti(O*n*-Bu)$_4$ 2 mmHg, then **12**/MeLi	decomposition

It was believed that the diol unit on the aldol accepter **11** was protonating the enolates in Table 1, thus generating methoxyacetaldehyde *in situ*—a more reactive aldol acceptor. Therefore, acetonide-protected keto-diol **14** was prepared in high yield as a protected equivalent of **11** for the second aldol step (eq 4).

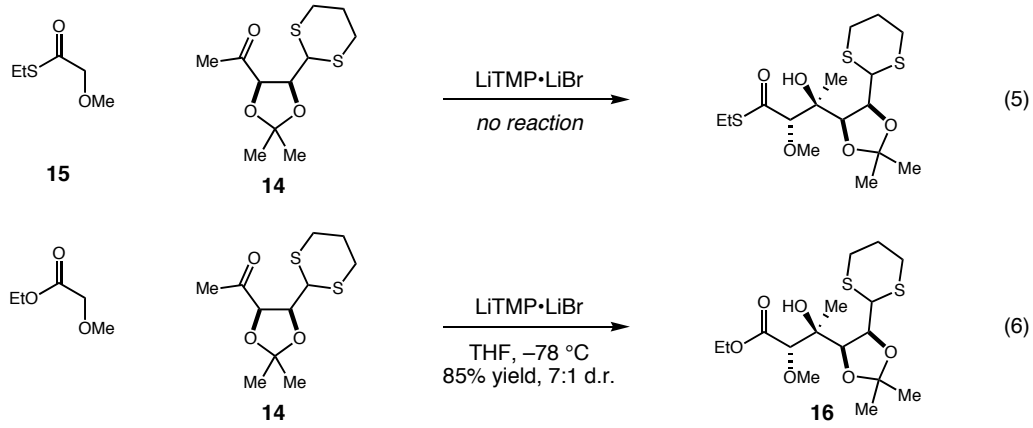


(4)

Unfortunately, further testing of the ability of our aldehyde enolates to undergo aldol addition to protected ketone **14** produced only recovered ketone **14** without any trace of the desired aldol adduct.

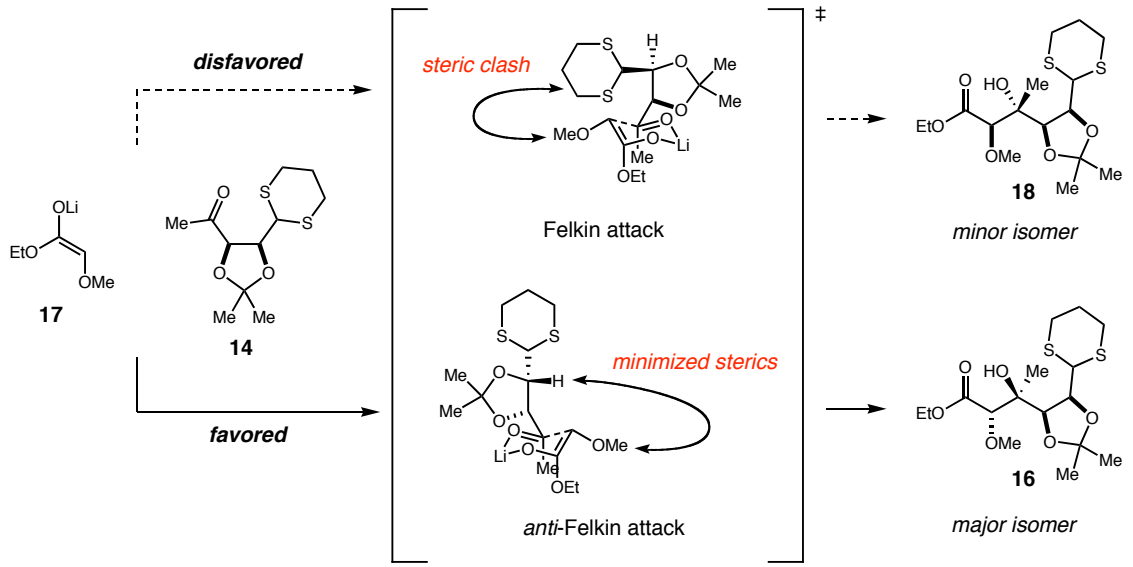
Considering the relatively weak nucleophilicity of aldehyde enolates (*cf.* Chapter 5), it was envisaged that more reactive enolates, such as esters or thiosesters, would be able to form the required C–C bond. While thioester **15** was found to be unreactive with keto-acetonide **14** (eq 5), reactions with ethyl methoxyacetate performed remarkably

well, affording the desired aldol adduct **16** in 85% yield as a 7:1 mixture of diastereomers (eq 6).



The diastereoselectivity of the reaction can be rationalized by invoking a closed six-membered chair-like transition state involving attack of the *E*-lithium enolate **17** on the anti-Felkin face of keto-acetonide **14** (Figure 8).[14]

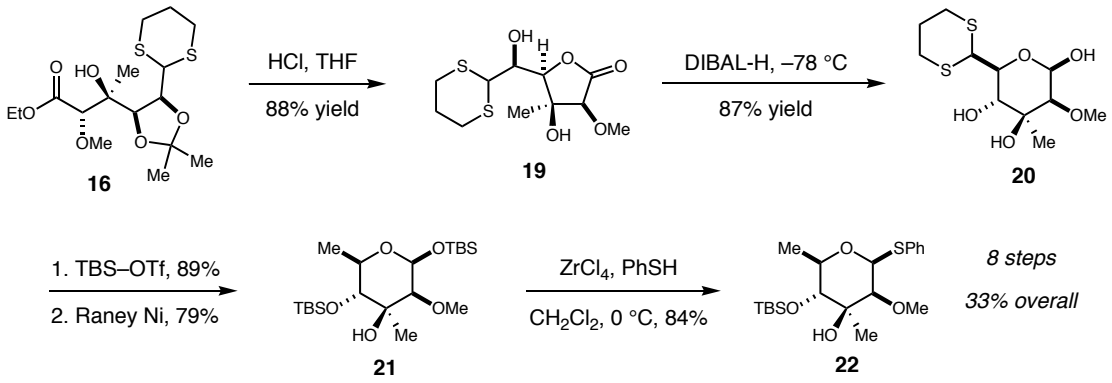
Figure 8. Stereochemical Model for Ester Aldol Reaction



[14] The stereochemistry of this aldol reaction is also in complete accord with the observations of Williams and co-workers with Grignard-type additions to similar erythrose-derived keto-acetonides conducted in THF: Williams, D. R.; Klinger, F. D. *J. Org. Chem.* **1988**, *53*, 2136.

With the carbon skeleton and stereochemistry of callipeltose C in place, completion of its total synthesis required deprotection and reduction of the ester and dithiane groups as well as activation of the sugar for coupling (Scheme 6).

Scheme 6. Completion of Activated Callipeltose C Synthesis



As we had anticipated, acidic hydrolysis of the acetonide **16** induced lactonization to form the δ-lactone **19**. NOE analysis of lactone **19** provided proof of the desired stereochemistry. Reduction of furanolactone **19** induced rearrangement to the more stable pyranose **20** in good yield. Selective bis-TBS protection of pyranose triol **20** proceeded efficiently with TBS-OTf, whereas TBSCl gave solely monoprotection. Finally, dithiane reduction with Raney nickel and coupling of 1-*O*-TBS-protected callipeltose C **21** with thiophenol under Priebe's conditions[15] afforded the activated callipeltose C **22** primed for coupling to the macrolactone in 8 steps and 33% overall yield. Significantly, not only is that the shortest enantioselective synthesis of a callipeltose, it is also the only one beginning with achiral starting materials.

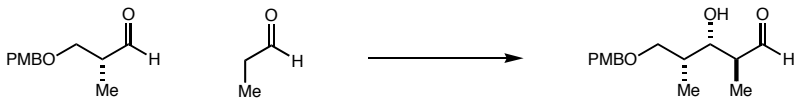
[15] Priebe, W.; Grynkiewicz, G.; Neamati, N. *Tetrahedron Lett.* **1991**, *32*, 2079.

Synthesis of the Tetrahydropyran Fragment

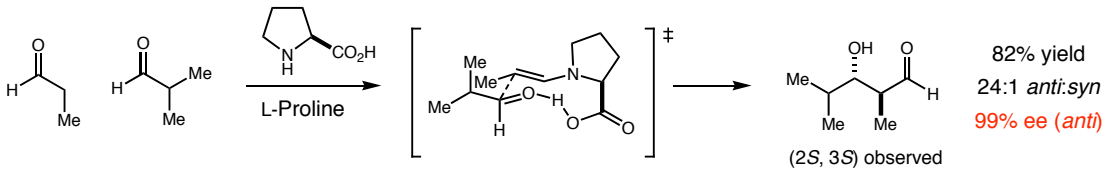
Synthesis of the tetrahydropyran fragment commenced with a double diastereodifferentiating aldehyde aldol reaction between propionaldehyde and Roche aldehyde **23** catalyzed by proline. Using the stereochemical model in Figure 9 (*cf.* Chapter 3), it was predicted that the L-proline-catalyzed reaction of **23** with propionaldehyde should represent the matched case and should afford β-hydroxyaldehyde **24** in high selectivity.

Figure 9. Double Stereodifferentiating Aldol Stereochemical Analysis

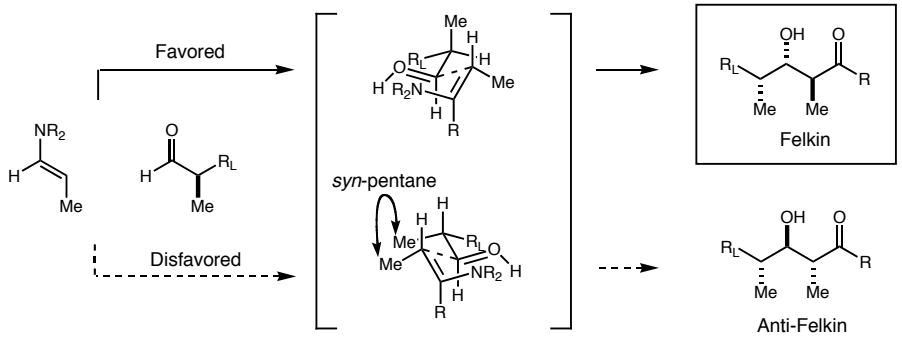
A Felkin, Anti-Aldol is Required for Callipeltoside Synthesis



L-Proline-Catalysis Should afford Desired Stereochemistry in Absence of Chiral Aldehyde



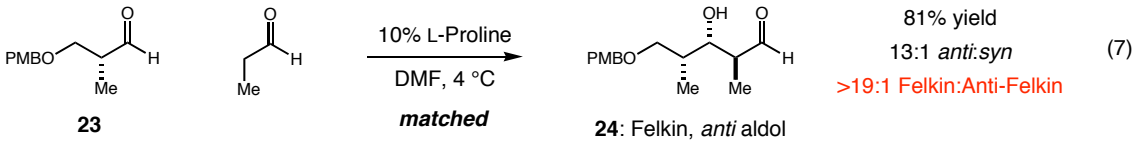
(E)-Enamines are Predicted to Give Felkin-Selective Aldols



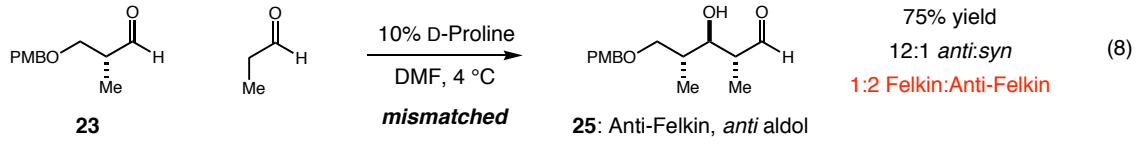
⇒ *Required stereochemistry for the callipeltosides should be the matched case with L-proline*

Equations 7 and 8 illustrate that the L-proline-catalyzed reaction represents the matched case (eq 7), whereas D-proline-catalysis is mismatched as expected (eq 8). Those reactions represent the first double stereodifferentiating organocatalytic aldol reactions.

As there is not an efficient achiral catalyst for the aldehyde aldol reaction, the inherent stereochemical bias of the Roche aldehyde substrate could not be evaluated for this reaction.



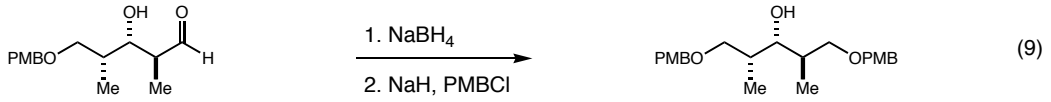
23 **24**: Felkin, *anti* aldol (7)



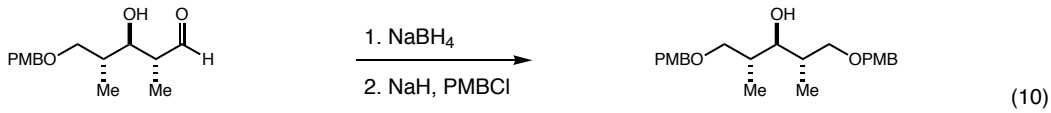
23 **25**: Anti-Felkin, *anti* aldol (8)

The above selectivities indicate that despite the high enantioselectivities usually afforded by proline catalysis of the aldehyde aldol reaction (>95% ee), the influence of the aldol acceptor's α-stereogenic centers can nearly override proline's stereochemical influence.

The relative stereochemistry of the aldol additions in equations 7 and 8 were proven by correlation to bis-PMB-protected alcohols **26** and **27** (eqs 9 and 10).



24: Felkin, *anti* aldol **26**: C_1–symmetric (9)



25: anti-Felkin, *anti* aldol **27**: *meso* (10)

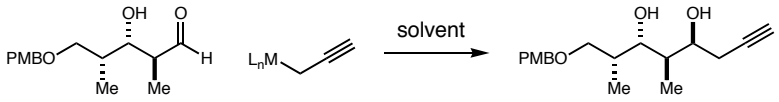
A simple analysis of the symmetry of the alcohols **26** and **27** by ^{1}H NMR allowed a determination of the relative methyl group stereochemistry. Further confirmation of stereochemistry for aldol product **24** derived from L-proline was obtained by comparison to the literature data for **24**.[16]

---

[16] Horita, K.; Inoue, T.; Tanaka, K.; Yonemitsu, O. *Tetrahedron* **1996**, *52*, 531.

Next, a chelation-controlled alkylation of β-hydroxyaldehyde **24** with propargyl Grignard was proposed to generate the required Felkin selectivity (Table 2). Surprisingly, Grignard reagents afforded only low levels of Felkin diastereoselectivity (entries 1 and 2, ≤ 1.5:1 d.r.). However, propargyl zinc reagents provided a nearly quantitative yield of the chelation-controlled addition product **28** in 6:1 d.r.

Table 2. Selectivity of Propargyl-Metal Additions to Aldehyde 24



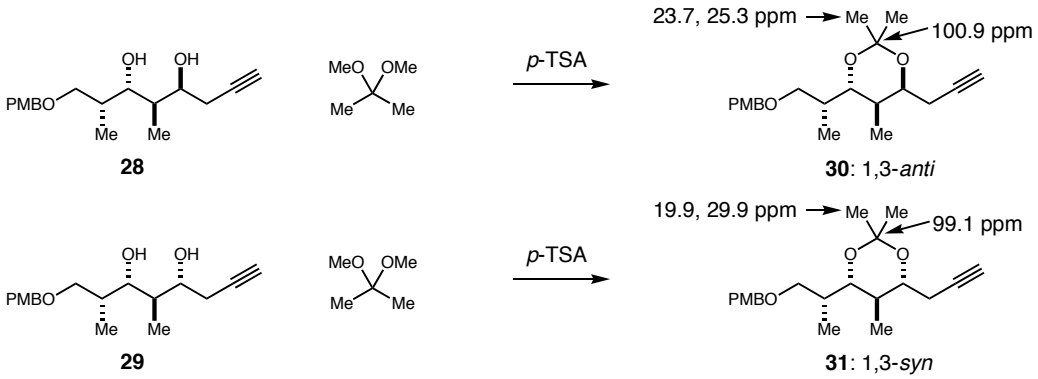
24 **28**

entry	ML_n	solvent	temp (°C)	yield %	d.r. (**28**:**29**)
1	MgBr	Et_2O	0	93	1.3:1
2	MgBr	Et_2O	–78	90	1.5:1
3	ZnBr	Et_2O	0	0	--
4	ZnBr	THF	–78	95	5:1
5	ZnBr	THF	–100	98	6:1

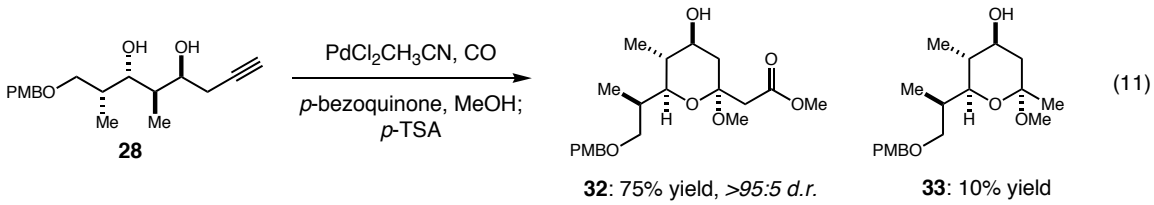
An analysis of the ^{13}C NMR spectra of the 1,3-acetonides **30** and **31** derived from diols **28** and **29** (according to the method of Rychnovsky)[17] provided proof that the major diastereomer **28** was the desired 1,3-*anti* configured diol and the minor isomer **29** was indeed 1,3-*syn* configured and not the product of epimerization of the β-hydroxyaldehyde **24** (Figure 10).

[17] Rychnovsky, S. D.; Rogers, B.; Yang, G. *J. Org. Chem.* **1993**, *58*, 3511.

Figure 10. Proof of Diol Stereochemistry by the Acetonide ^{13}C Method



Having established the required stereochemistry for the core of callipeltoside aglycon, the tetrahydropyran ring was constructed by palladium (II) catalyzed alkoxycarbonylation of the δ-hydroxyalkyne **28** (eq 11).[18]

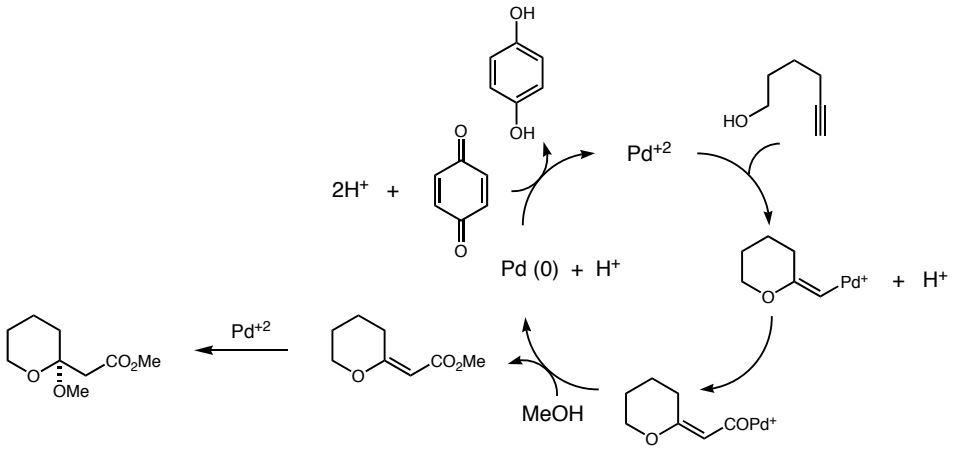


(11)

Critical to the yield of that process was the fact that the carbonylation was performed at 0 °C. Higher temperatures promoted an acid-catalyzed methanolysis of the PMB-protecting group. A major side-product of the reaction (**33**) resulted from an apparent protonolysis of an intermediate palladium (II) alkenyl species, in support of Marshall's proposed mechanism (Figure 11).

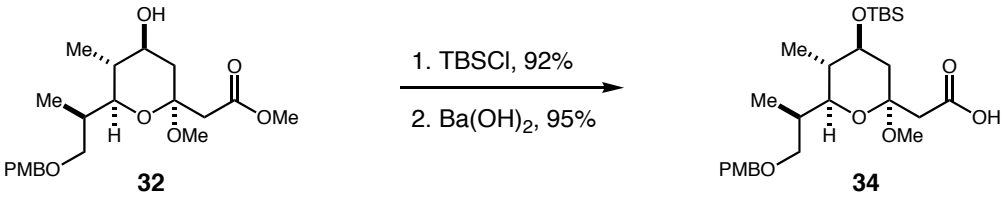
[18] Marshall, J. A.; Yanik, M. M. *Tetrahedron Lett.* **2000**, *41*, 4717.

Figure 11. Proposed Mechanism of the Palladium-Catalyzed Alkoxycarbonylation Reaction



Therefore, a further increase in the yield of this process may result from higher pressures of CO, although the already good yield, convenience, and safety of using only balloon pressure obviated those studies.

Completion of the tetrahydropyran fragment synthesis simply required TBS-protection of the *C*-5 hydroxyl and saponification of the methyl ester to afford THP **34** ready for coupling to the lower half of callipeltoside in just 5 steps and 53% overall yield (eq 12).



(12)

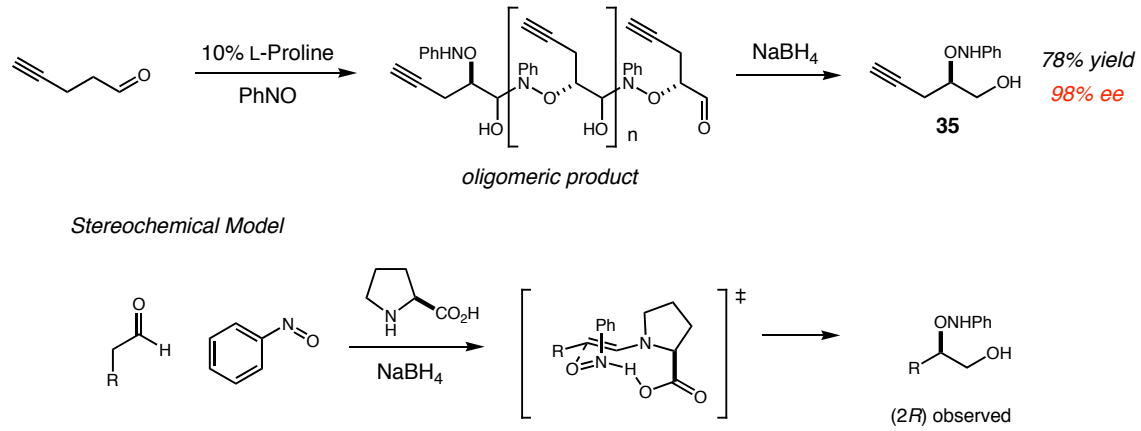
The Iodoalcohol Fragment

Synthesis of iodoalcohol **5** first required an enantioselective α-oxyamination[19] of 4-pentynal catalyzed by L-proline followed by *in situ* reduction of the oligomeric product

[19] Brown, S. P.; Brochu, M. P.; Sinz, C. J.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2003**, *125*, 10808.

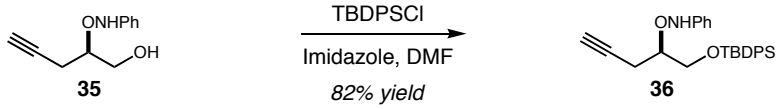
(Figure 12). That reaction performed admirably, affording the differentiated diol product **35** in 78% yield and 98% ee.

Figure 12. Proline-Catalyzed α-Oxyamination of Aldehydes



Unfortunately, the oxyaniline functionality proved to be unstable, leading to significant decomposition upon storage. Therefore, it was essential to conduct the following protection and O–N bond cleavage steps in rapid succession to obtain optimal yields.

Protection of the primary alcohol **35** with TBDPSCl proceeded smoothly to provide aniline **36** (eq 13).

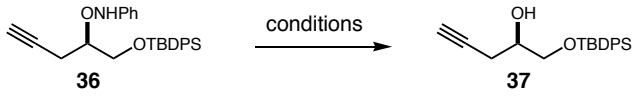


(13)

However, cleavage of the O–N bond of **36** proved to be challenging. The presence of an alkyne in **36** precluded the use of hydrogenation,[20] the most commonly employed method for O–N bond reduction. After a survey of other methods to effect the desired removal of the aniline, it was found that Na° in ethanol provided the desired alcohol **37** in good yield (Table 3).

[20] Brown, S. P.; Brochu, M. P.; Sinz, C. J.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2003**, *125*, 10808.

Table 3. Optimization of Aniline Cleavage Reaction

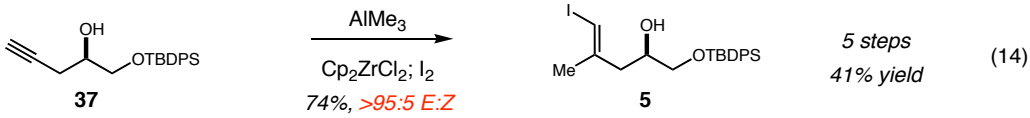


36 **37**

conditions	results
$CuSO_4$, MeOH	desilylation
Zn°, AcOH	desilylation
$LiAlH_4$, Et_2O	alkyne reduction
Na°, EtOH	86% yield

At this point, esterification of alkynol **37** with either enantiomer of Mosher's acid under DCC coupling conditions allowed the determination of the absolute configuration of the carbinol stereocenter as the desired (*R*)-configuration (see supporting information).

Synthesis of the iodoalcohol fragment was completed through the use of Negishi's carbometallation/iodination sequence[21] yielding iodoalcohol **5** in only 5 steps and 41% overall yield (eq 14).



37 **5** (14)

Fragment Coupling and Macrocyclization

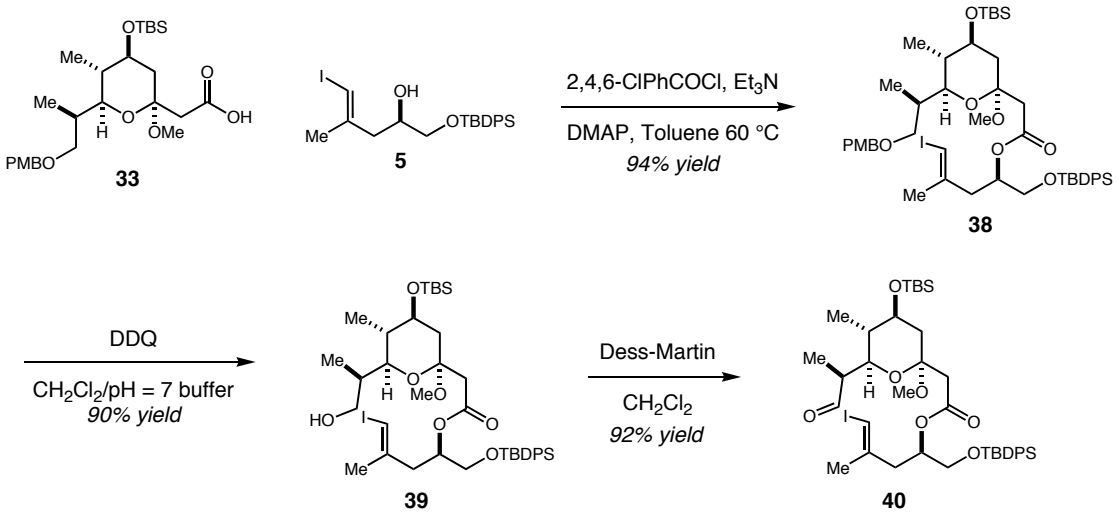
With both the THP and iodoalcohol fragments in hand, the completion of the macrolactone portion of callipeltoside C began with esterification of **33** with **5** under Yamaguchi conditions[22] to afford iodoester **38** in 94% yield (Scheme 7). Oxidative removal of the PMB-protecting group with DDQ, followed by Dess-Martin oxidation of

[21] Negishi, E.; Van Horn, D. E.; Yoshida, T. *J. Am. Chem. Soc.* **1985**, *107*, 6639.

[22] Inanaga, J.; Hirata, K.; Saeki, H.; Katsuki, T.; Yamaguchi, M. *Bull. Chem. Soc. Jpn.* **1979**, *52*, 1989.

the resulting primary alcohol **39** provided iodoaldehyde **40** ready for a ring-closing alkylation reaction.

Scheme 7. Fragment Coupling and Functionalization

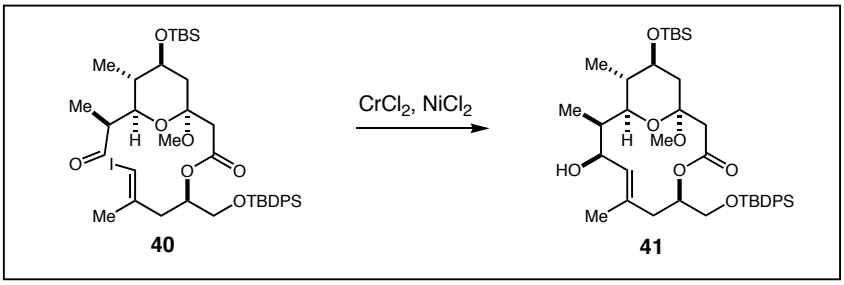


Due to the broad functional group tolerance of the NHK reaction and its proven ability to perform macrocyclization reactions, it was selected as the method of choice for inducing the desired ring-closure.[23] Furthermore, it was believed, based on MM3 calculations on the transition state model for the NHK presented by Overman and MacMillan[24] that such a cyclization should afford the desired diastereomer in high selectivity (Figure 13).

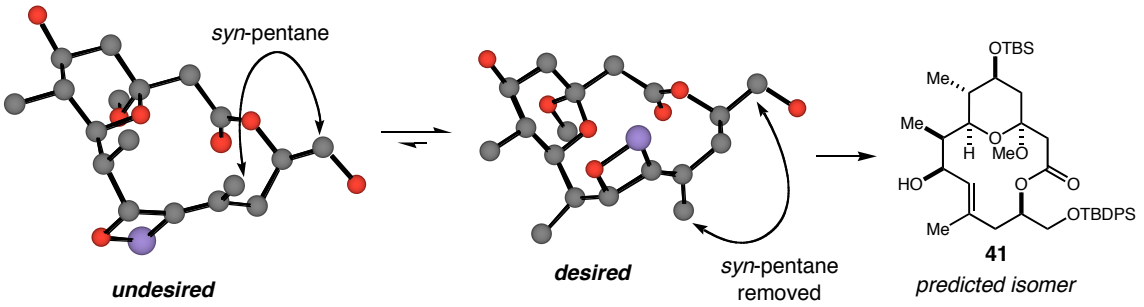
[23] For a review of the NHK reaction, see: Fürstner, A. *Chem. Rev.* **1999**, *99*, 991.

[24] MacMillan, D. W. C.; Overman, L. E. *J. Am. Chem. Soc.* **1995**, *117*, 10391.

Figure 13. MM3 Models Predict the NHK Should Proceed with the Desired Selectivity



Overman-MacMillan Model Relies on Developing Ring-Strain in Transition State

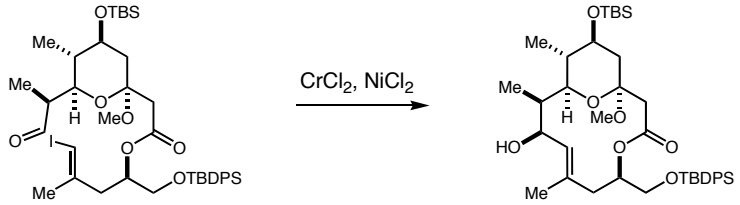


Silyl Groups and Hydrogens Omitted for Clarity

After a survey of the standard conditions for effecting such a transformation, it was found that $CrCl_2/NiCl_2$ in DMSO was superior, affording a single diastereomer of the macrolactone product **41** (Table 4). The yield of this transformation was optimized to 63% through a dilution of the reaction mixture to suppress competing intermolecular alkylation processes.

While the ring-closing NHK reaction produced a single diastereomer at *C*-9, the configuration of that stereocenter needed to be conclusively assigned. Unfortunately, attempted formation of the Mosher ester of alcohol **41** with either the acid chloride method or by DCC coupling of Mosher's acid afforded only decomposition products. Therefore, it was decided to proceed toward the aglycon to assign the stereochemistry at *C*-9.

Table 4. Optimization of the NHK Macrocyclization



40 **41**

entry	$CrCl_2$:$NiCl_2$ (equiv)	solvent	conc. (m*M*)	yield %	d.r.
1	9.8:0.2	DMF	2.5	0	--
2	9.8:0.2	DMF/THF	2.5	0	--
3	9.8:0.2	DMSO/THF	2.5	32	>19:1
4	9.8:0.2	DMSO	2.5	54	>19:1
5	9.8:0.2	DMSO	0.2	45	>19:1
6	98:2	DMSO	0.2	63	>19:1

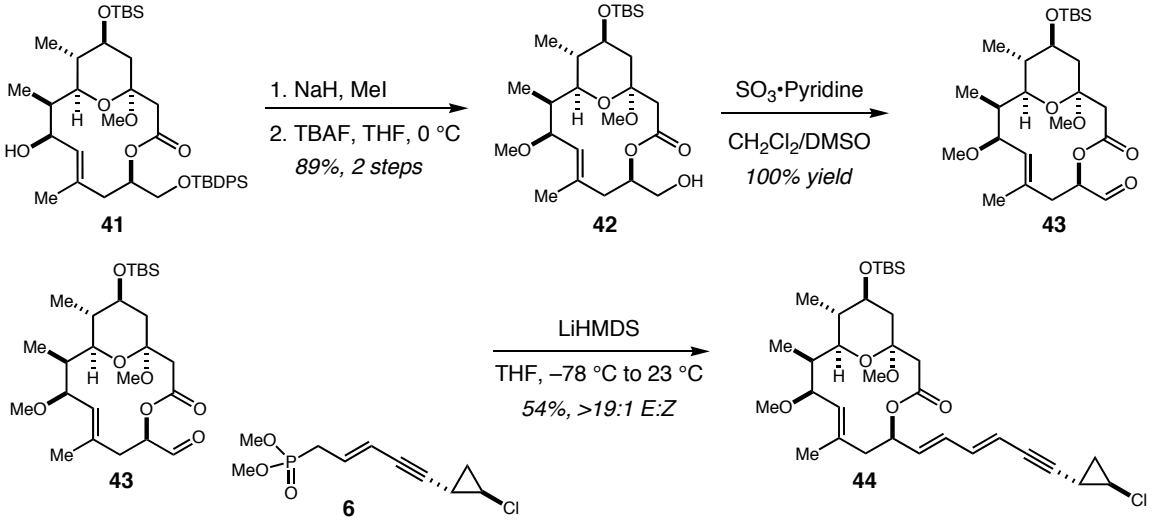
Elaboration toward the Aglycon: Interception of a Known Intermediate

Completion of the callipeltoside aglycon required simple methylation of the *C*-9 alcohol and appendage of the side chain (Scheme 8). After the spectrum of relatively mild methylation protocols employed in other syntheses of callipeltoside A showed only modest reactivity, it was found that classical anionic conditions with NaH and MeI in THF provided the methyl ether in good yield. Next, selective desilylation of the 1° TBDPS-group in the presence of a 2° TBS-group was accomplished using TBAF[25] to afford the acid-sensitive alcohol **42** that was prone to equilibration with a fifteen-membered lactone. That sensitive alcohol was, therefore, immediately oxidized to the aldehyde **43** to avoid that equilibration manifold. Perhaps due to the acid-sensitive nature of alcohol **42**, Dess–Martin oxidation afforded a complex mixture of products while

[25] For a review on selective silyl group deprotection strategies, see: Nelson, T. D.; Crouch, R. D. *Synthesis* **1996**, 1031.

oxidation under the mildly basic Parikh–Doering conditions[26] consistently gave a high yield of the macrolactone aldehyde **43** (Scheme 8). Next, HWE coupling of aldehyde **43** and known phosphonate **6**[27] proceeded in moderate yield to produce a single olefin isomer of the aglycon precursor **44** in contrast to the previously performed HWE reactions performed by Evans and Trost. That completes the entire carbon skeleton of callipeltoside C in only 13 steps (longest linear sequence).

Scheme 8. Functionalization of the Macrolactone to an Aglycon Precursor



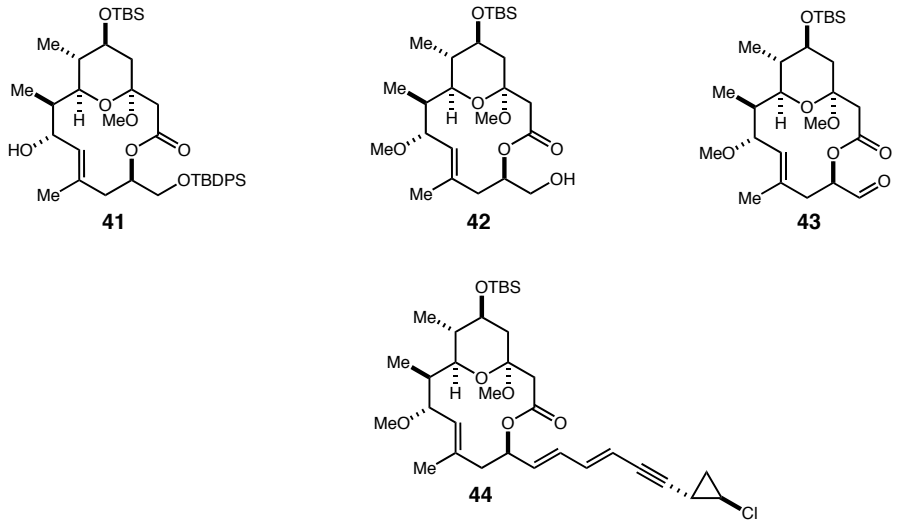
As advanced intermediate **44** should be identical to an intermediate in Paterson's total synthesis of callipeltoside A, comparison of their spectral properties allowed a determination of the stereochemistry of the NHK cyclization as each of the other stereocenters in **44** had already been proven by well-established means. To our surprise, comparison of **44** with Paterson's intermediate showed that the NHK macrocyclization afforded solely the undesired *C*-9 epimer in contrast to the predictions of the Overman-

[26] Parikh, J. R.; Doering, W. v. E. *J. Am. Chem. Soc.* **1967**, *89*, 5505.

[27] Evans, D. A.; Hu, E.; Burch, J. D.; Jaeschke, G. *J. Am. Chem. Soc.* **2002**, *124*, 5654.

MacMillan model. Therefore, the stereochemistry of **41**, **42**, **43**, and **44** at *C*-9 should be revised as shown in Figure 14.

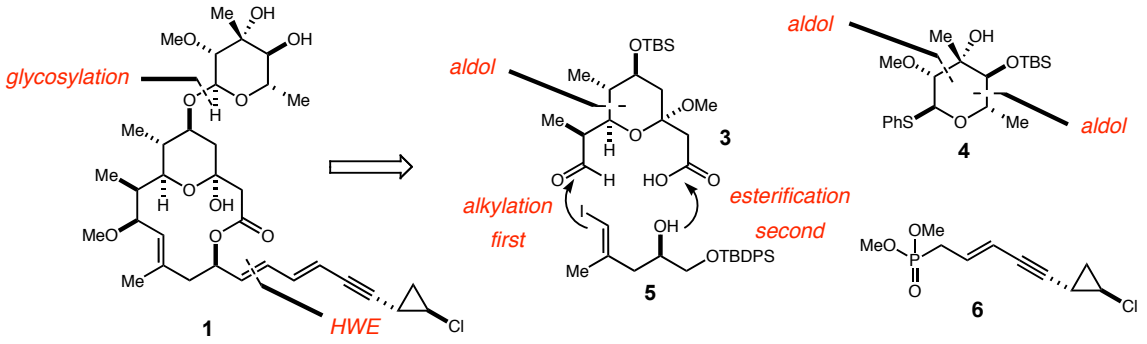
Figure 14. Stereochemical Revision of the NHK Macrocyclization



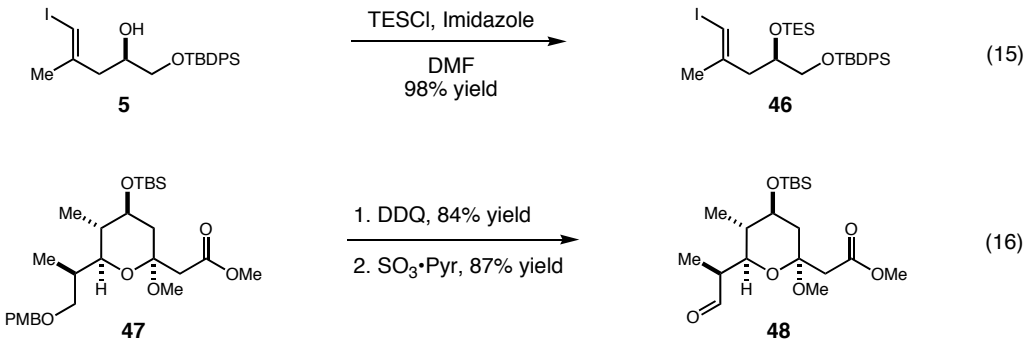
An Alternative Intermolecular Alkylation/Macrolactonization Strategy

Given the modular nature of our synthetic plan, an alternative route wherein formation of the *C*-9/*C*-10 bond precedes macrolactonization was envisioned (Scheme 9).

Scheme 9. Retrosynthetic Analysis of Callipeltoside C

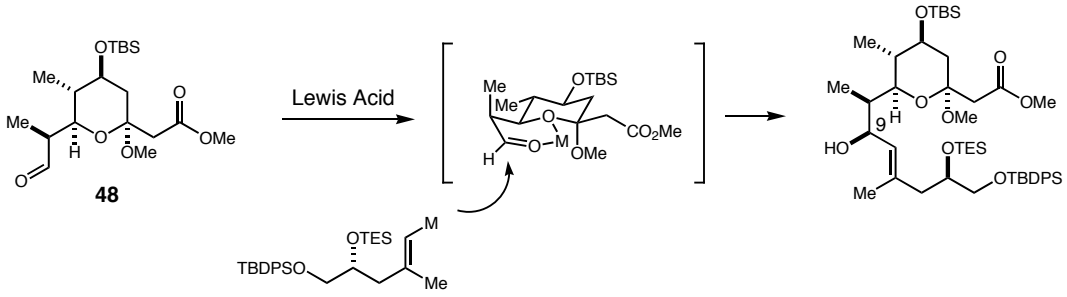


Therefore, an intermolecular alkylation of THP aldehyde **48** with an iodide such as **46** would be necessary. The synthesis of those two pieces was readily accomplished (eqs 15 and 16).



The desired stereochemistry at *C*-9 is envisioned to result from a β-chelation-controlled alkylation of THP aldehyde **48** with an alkenyl-metal derived from **46** as shown in Figure 15.

Figure 15. Chelation Control Should Give Desired Stereochemistry at *C*-9



Summary and Conclusions

In summary, the rapid and efficient synthesis of several key fragments for the total synthesis of callipeltoside C has been described. Enantioselective aldol reactions play a critical role in the production of the majority of the stereochemical complexity present in the callipeltosides. While a NHK ring-closing strategy provided the undesired *C*-9 epimer, despite the prediction otherwise by the Overman-MacMillan model for ring-closing NHK stereoselection, an alternative intermolecular alkylation route has been proposed to circumvent that issue. That new strategy should allow the most efficient synthesis of the callipeltoside aglycon to date.

Supporting Information

General Information. Commercial reagents were purified prior to use following the guidelines of Perrin and Armarego.[28] All solvents were purified according to the method of Grubbs.[29] Non-aqueous reagents were transferred under nitrogen via syringe or cannula. Organic solutions were concentrated under reduced pressure on a Büchi rotary evaporator using an ice-water bath for volatile samples. Chromatographic purification of products was accomplished using forced-flow chromatography on ICN 60 32-64 mesh silica gel 63 according to the method of Still.[30] Thin-layer chromatography (TLC) was performed on EM Reagents 0.25 mm silica gel 60-F plates. Visualization of the developed chromatogram was performed by fluorescence quenching or by anisaldehyde, ceric ammonium molybdate, or KMnO4 stain.

^{1}H and ^{13}C NMR spectra were recorded on a Mercury 300 (300 MHz and 75 MHz) or an Inova 500 (500 MHz and 125 MHz) as noted, and are internally referenced to residual protio solvent signals. Data for ^{1}H NMR are reported as follows: chemical shift (δ ppm), multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet), integration, coupling constant (Hz) and assignment referenced to the carbon numbering scheme for the natural product. IR spectra were recorded on a Perkin Elmer Paragon 1000 spectrometer and are reported in terms of frequency of absorption (cm^{-1}). Mass spectra were obtained from the California Institute of Technology Mass Spectral facility. Gas liquid chromatography (GLC) was performed on Hewlett-Packard 6850 and 6890

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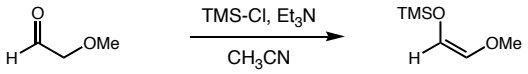
[28]Perrin, D. D.; Armarego, W. L. F. *Purification of Laboratory Chemicals;* 3rd ed., Pergamon Press, Oxford, 1988.

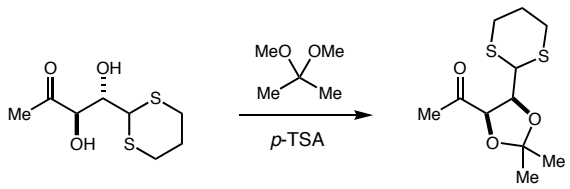
[29]Pangborn, A. B.; Giardello, M. A.; Grubbs, R. H.; Rosen, R. K.; Timmers, F. J. *Organometallics* **1996**, *15*, 1518.

[30]Still, W. C.; Kahn, M.; Mitra, A. J. *J. Org. Chem.* **1978,** *43*, 2923.

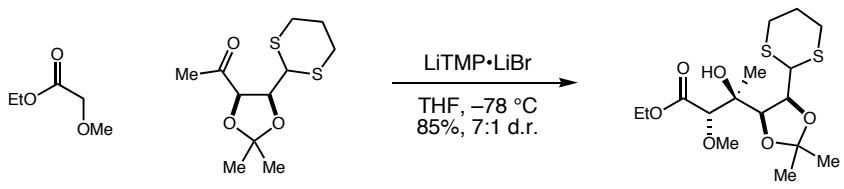
Series gas chromatographs equipped with a split-mode capillary injection system and flame ionization detectors using a J&W Scientific DB-1701 (30 m x 0.25 mm) column as noted. High performance liquid chromatography (HPLC) was performed on Hewlett-Packard 1100 Series chromatographs using a Chiralcel AD column (25 cm) and AD guard (5 cm) as noted.



(*Z*)-(2-Methoxy-vinyloxy)-trimethylsilane (12). Methoxyacetaldehyde (4.68 mL, 33.3 mmol) was added in a single portion to a room temperature solution of chlorotrimethylsilane (8.45 mL, 66.6 mmol), triethylamine (18.56 mL, 133 mmol), and acetonitrile (60 mL). In less than five minutes, the solution became a hot white suspension that turned into a rust-colored suspension within fifteen minutes. After stirring for 3 hours, volatiles were removed *in vacuo* and the residue was extracted with three 50 mL portions of anhydrous diethyl ether. Distillation of the ethereal extracts afforded the title compound (5.68 g, 25.5 mmol, b.p. 78–80 °C (125 mmHg), 12:1 *Z*:*E*) in 77% yield as a clear, colorless liquid. IR (film) 3034, 2959, 2901, 2872, 1667, 1497, 1455, 1397, 1362, 1298, 1252, 1129, 1026, 846.7, 734.0, 696.7 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.45 (d, 1H, J = 3.3 Hz, CHOTMS); 5.33 (d, 1H, J = 3.3 Hz, CHOMe); 3.60 (s, 3H, OCH_3); 0.20 (s, 9H, $Si(CH_3)_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 133.0, 121.8, 60.3, –0.28; HRMS (EI+) exact mass calcd for $[M•]^+$ ($C_6H_{14}O_2Si$) requires *m/z* 146.0763, found *m/z* 146.0764. The product ratios were determined by ^1H NMR integration of the crude reaction mixture.

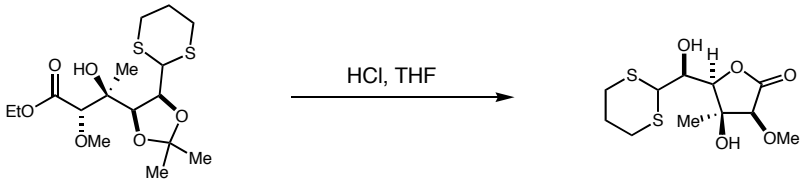


1-((4*R*,5*S*)-5-(1,3-dithian-2-yl)-2,2-dimethyl-1,3-dioxolan-4-yl)ethanone (14). Keto-diol **11** (100 mg, 0.45 mmol) was suspended in 2,2-dimethoxypropane (4.50 mL) with vigorous stirring followed by the addition of *para*-toluene sulfonic acid monohydrate (4.3 mg, 22 μmol). After 2.5 hours, the resulting clear, colorless solution was basified with 100 mL 10% $NaHCO_3$ and extracted with ethyl acetate (3x100 mL). The combined organic extracts were washed with 100 mL brine, dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. Purification by flash chromatography (1:4 ethyl acetate:hexanes) afforded the title compound as a clear, colorless oil (116.3 mg, 0.44 mmol, 99%). IR (film) 2871, 2935, 2899, 1708, 1422, 1381, 1210, 1082, 871.0, 514.2 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 4.64 (dd, 1H, J = 8.0, 2.5 Hz, C**H**CHS_2) 4.43 (d, 1H, J = 8.0 Hz, CHS_2); 4.19 (d, 1H, J = 2.5 Hz, CHCOMe); 2.95-2.66 (m, 4H, 2 CH_2S); 2.36 (s, 3H, CH_3CO); 2.06-2.01 (m, 1H, equatorial C**H$_2$**CH_2S); 1.92-1.84 (m, 1H, axial C**H$_2$**CH_2S); 1.62 (s, 3H, one of O_2CCH_3); 1.35 (s, 3H, one of O_2CCH_3); ^{13}C NMR (125 MHz, $CDCl_3$) δ 208.9, 110.7, 81.9, 81.6, 48.2, 30.8, 29.9, 29.0, 26.3, 25.6, 24.4; HRMS (EI+) exact mass calcd for $[M\bullet]^+$ ($C_{14}H_{14}O_3S_2$) requires *m/z* 262.0664, found *m/z* 262.0668; $[\alpha]_D$ = 67.1 (c = 2.00, $CHCl_3$).



(2*S*,3*S*)-ethyl 3-((4*R*,5*S*)-5-(1,3-dithian-2-yl)-2,2-dimethyl-1,3-dioxolan-4-yl)-3-hydroxy-2-methoxybutanoate (16). *n*-Butyllithium (2.10 mL,1.56*M* in hexane, 3.28 mmol) was added dropwise to a vigorously stirring suspension of 2,2,6,6-tetramethylpiperidinium hydrobromide (383 mg, 1.72 mmol) and 1,10-phenanthroline (0.7 mg) in 1.50 mL of THF at 0 °C. The concentration of the butyllithium reagent was determined by the appearance of a deep red color upon addition of just enough base to titrate 1.0 equivalent of HBr. After 30 minutes, the resulting deep red solution was cooled to –78 °C and ethyl methoxyacetate (192.2 µL, 1.64 mmol) was added. After stirring at –78 °C for a further 30 minutes, a solution of ketone **14** (172 mg, 0.656 mmol) was added dropwise *via* cannula as a solution in THF (1.0 mL, 0.5 mL rinse). After 4 h, the resulting clear, colorless solution was poured into 150 mL of saturated NH_4Cl, extracted with ethyl acetate (5 x 100 mL), dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. Purification by flash chromatography (3:7 ethyl acetate:hexanes) afforded the title compound as a clear, colorless oil as a 7:1 mixture of diastereomers (173.2 mg, 0.455 mmol, 85%). IR (film) 3480, 2986, 2925, 2903, 2830, 1747, 1732, 1452, 1370, 1257, 1212, 1112, 1040, 880.5, 799.7, 755.6 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 4.82 (d, 1H, J = 8.7 Hz, C**H**CHCHS$_2$); 4.47 (dd, 1H, J = 9.0, 6.3 Hz, C**H**CHS$_2$) 4.36 (d, 1H, J = 12.9 Hz, CHS$_2$); 4.26 (m, 2H, OC**H$_2$**CH$_3$); 3.88 (s, 1H, CHOMe); 3.41 (s, 3H, OCH$_3$); 3.17 (br s, 1H, OH); 2.90-2.83 (m, 4H, 2 CH$_2$S); 2.12-2.02 (m, 1H, equatorial C**H$_2$**CH$_2$S); 1.98-1.86 (m, 1H, axial C**H$_2$**CH$_2$S); 1.54 (s, 3H, one of O$_2$CCH$_3$);

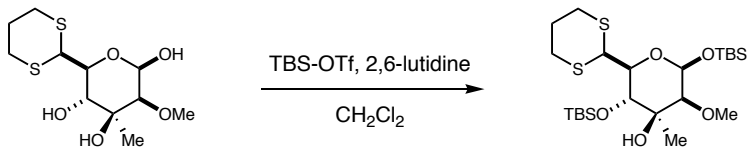
1.37 (s, 3H, one of O_2CCH_3); 1.32 (s, 3H, C3-CH_3); 1.32 (d, 3H, J =1.5 Hz, CH_3CH_2); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.3, 108.6, 84.5, 78.9, 77.6, 75.5, 61.2, 58.6, 46.0, 29.3, 28.9, 26.6, 25.8, 25.3, 20.4, 14.6; HRMS (EI+) exact mass calcd for $[M+H]^+$ ($C_{16}H_{29}O_6S_2$) requires *m/z* 381.1406, found *m/z* 381.1403; $[\alpha]_D$ = – 29.6 (c = 1.00, $CHCl_3$).



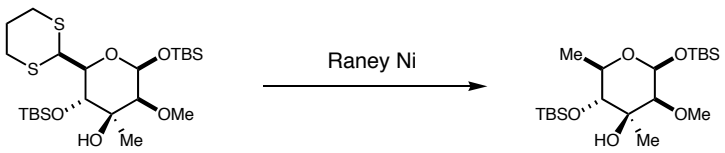
(3*S*,4*S*,5*R*)-5-((*S*)-(1,3-dithian-2-yl)(hydroxy)methyl)-dihydro-4-hydroxy-3-methoxy-4-methylfuran-2(3*H*)-one (19). Hydrochloric acid (5.0 mL, 1.0*M*, 5.0 mmol) was added to a stirring solution of ester **16** (142.6 mg, 0.37 mmol) in THF (5.0 mL). After 7 h, the reaction mixture was basified by the addition of 100 mL saturated $NaHCO_3$, extracted with ethyl acetate (5 x 50 mL), dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. Purification by flash chromatography (3:2 ethyl acetate:hexanes) afforded the title compound as a clear, colorless oil (83.2 mg, 0.28 mmol, 88%). IR (film) 3445, 3022, 2924, 1790, 1449, 1261, 1261, 1187, 1128, 1018, 908.8, 750.0 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.52 (d, 1H, J = 2.0 Hz, CHS_2); 4.32 (d, 1H, J = 10.0 Hz, C**H**CHCHS$_2$); 4.16 (s, 1H, CHOMe); 4.05 (ddd, 1H, J = 10.0, 3.5, 2.0 Hz, C**H**OH); 3.70 (s, 3H, OCH_3); 3.06-2.88 (m, 4H, 2 CH_2S); 2.62 (s, 1H, C3-OH); 2.53 (d, 1H, J = 4.0 Hz, C5-OH); 2.19-2.14 (m, 1H, equatorial C**H$_2$**CH$_2$S); 1.96-1.89 (m, 1H, axial C**H$_2$**CH$_2$S); 1.40 (s, 3H, C3-CH_3); ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.4, 83.7, 78.9, 77.9, 73.5, 59.8, 50.4, 30.5, 29.5,

25.9, 15.7; HRMS (FAB+) exact mass calcd for $[M\bullet]^+$ ($C_{11}H_{18}O_5S_2$) requires *m/z* 294.0596, found *m/z* 294.0601; $[\alpha]_D = 26.4$ (c = 0.50, $CHCl_3$). The stereochemistry was confirmed by NOE analysis.

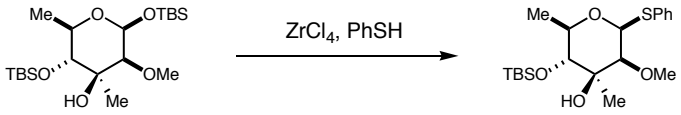
(2*R*,3*S*,4*S*,5*R*,6*S*)-6-(1,3-dithian-2-yl)-tetrahydro-3-methoxy-4-methyl-2*H*-pyran-2,4,5-triol (20). DIBAL-H (2.83 mL, 1.0*M* in hexanes, 2.83 mmol) was added to a –78 °C stirring solution of lactone **19** (83.2 mg, 0.28 mmol) in THF (14.0 mL). After 3 h, the reaction mixture was neutralized by the addition of 100 mL pH = 7.0 phosphate buffer, filtered through a pad of celite with ethyl acetate (5 x 20 mL), extracted with ethyl acetate (10 x 50 mL), dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. Purification by flash chromatography (4:1 ethyl acetate:hexanes) afforded the title compound as a clear, colorless oil (72.6 mg, 0.24 mmol, 2:1 α:β, 87%). IR (film) 3392, 2930, 2924, 1452, 1104, 1043, 979.5, 760.4 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) α-anomer: δ 5.30 (s, 1H, C1-H); 4.51 (d, 1H, *J* = 2.0 Hz, C6-H); 4.08 (dd, 1H, 10.0, 3.0 Hz, C5-H); 3.88 (d, 1H, *J* = 10.0 Hz, C4-H); 3.62 (s, 1H, C2-H); 3.45 (s, 3H, OCH_3); 3.18 (d, 1H, C1-OH); 3.04-2.80 (m, 4H, 2 CH_2S); 2.17-2.08 (m, 1H, equatorial C**H$_2$**CH_2S); 2.06 (s, 1H, C3-OH); 2.04-1.94 (m, 1H, axial C**H$_2$**CH_2S); 1.62 (br s, 1H, C4-OH); 1.39 (s, 3H, C3-CH_3); ^{13}C NMR (125 MHz, $CDCl_3$) α-anomer: δ 92.3, 81.2, 74.1, 72.4, 69.0, 59.2, 49.1, 30.8, 30.5, 26.4, 23.0; HRMS (FAB+) exact mass calcd for $[M\bullet]^+$ ($C_{11}H_{20}O_5S_2$) requires *m/z* 296.0752, found *m/z* 294.0742; $[\alpha]_D = 2.52$ (c = 0.50, $CHCl_3$).



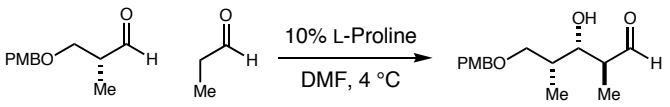
(2*R*,3*S*,4*S*,5*R*,6*S*)-6-(1,3-dithian-2-yl)-2,5-*O*-bis-(*tert*-butyldimethylsilyl)-tetrahydro-3-methoxy-4-methyl-2*H*-pyran-2,4,5-triol (49). TBS-OTf (85.7 μL, 0.37 mmol) was added to a –78 °C stirring solution of lactol **20** (55.3 mg, 0.19 mmol) and 2,6-lutidine (109 μL, 0.93 mmol) in CH_2Cl_2 (2.0 mL). After 1.5 h, the reaction mixture was warmed to 0 °C for 4 h before being basified by the addition of 100 mL saturated $NaHCO_3$, extracted with ethyl acetate, dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. Purification by flash chromatography (8:92 ethyl acetate:hexanes) afforded the title compound as a clear, colorless oil (87.2 mg, 0.24 mmol, >20:1 β:α, 89%). IR (film) 3506, 2930, 2910, 2860, 1462, 1256, 1105, 1041, 1002, 777.7, 543.1 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.28 (s, 1H, C1-H); 4.46 (br s, 1H, C6-H); 4.14 (d, 1H, 10.0, C5-H); 3.97 (s, 1H, C2-H); 3.93 (d, 1H, J = 9.0 Hz, C4-H); 3.42 (s, 3H, OCH_3); 3.00 (s, 1H, C3-OH); 2.95-2.80 (m, 4H, 2 CH_2S); 2.13-2.09 (m, 1H, equatorial C**H**$_2$$CH_2S$); 2.01-1.97 (m, 1H, axial C**H**$_2$$CH_2S$); 1.29 (s, 3H, C3-$CH_3$); 0.97 (s, 9H, $SiCMe_3$); 0.94 (s, 9H, $SiCMe_3$); 0.27 (s, 3H, SiMe); 0.24 (s, 3H, SiMe); 0.22 (s, 3H, SiMe); 0.18 (s, 3H, SiMe); ^{13}C NMR (125 MHz, $CDCl_3$) δ 92.7, 84.3, 73.6, 73.4, 70.9, 59.3, 49.0, 31.6, 30.5, 26.6, 26.4, 25.9, 24.0, 19.0, 18.2, –3.2, –3.5, –4.0, –5.4; HRMS (FAB+) exact mass calcd for $[M+H]^+$ ($C_{23}H_{49}O_5Si_2S_2$) requires *m/z* 525.2560, found *m/z* 525.2541; $[\alpha]_D$ = 24.3 (c = 0.25, $CHCl_3$).



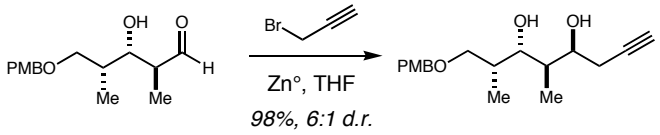
(2*R*,3*S*,4*S*,5*R*,6*R*)-2,5-*O*-bis-(*tert*-butyldimethylsilyl)-tetrahydro-3-methoxy-4,6-dimethyl-2*H*-pyran-2,4,5-triol (21). Raney nickel W-2 (225 mg) was added to a standing solution of dithiane **49** (44.9 mg, 86 μmol) in ethanol (4.50 mL). After 3 h, the reaction mixture was filtered through a pad of celite with ethyl acetate (10 x 1 mL) and concentrated *in vacuo*. Purification by flash chromatography (6:94 ethyl acetate:hexanes) afforded the title compound as a clear, colorless oil (28.4 mg, 68 μmol, 79%). IR (film) 3517, 2959, 2901, 2859, 1464, 1362, 1254, 1174, 1106, 1029, 1001, 837.4, 775.8, 669.5 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.13 (d, 1H, *J* = 1.5 Hz, C1-H); 3.98 (dq, 1H, *J* = 9.5, 6.5 Hz, C5-H); 3.89 (s, 1H, C3-OH); 3.46 (s, 3H, OCH_3); 3.41 (d, 1H, *J* = 9.5 Hz, C4-H); 3.03 (d, 1H, *J* = 1.5 Hz, C2-H); 1.27 (s, 3H, C3-CH_3); 1.25 (d, 3H, *J* = 6.5 Hz, C6-H); 0.95 (s, 9H, $SiCMe_3$); 0.94 (s, 9H, $SiCMe_3$); 0.18 (s, 3H, SiMe); 0.18 (s, 3H, SiMe); 0.13 (s, 6H, $SiMe_2$); ^{13}C NMR (125 MHz, $CDCl_3$) δ 93.1, 85.1, 75.9, 73.4, 65.5, 59.8, 26.5, 25.9, 23.8, 19.0, 18.7, 18.2, –3.1, –3.2, –4.4, –5.5; HRMS (FAB+) exact mass calcd for $[M+H]^+$ ($C_{20}H_{45}O_5Si_2$) requires *m/z* 421.2806, found *m/z* 421.2796; $[\alpha]_D$ = 19.5 (c = 1.00, $CHCl_3$).



1-Deoxy-1-phenylthio-4-*O*-(*tert*-butyldimethylsilyl)-callipeltose C (22). Thiophenol (2.4 μL, 23.8 μmol) was added to a stirring 0 °C suspension of sugar **21** (2.0 mg, 4.8 μmol) and zirconium (IV) chloride (2.2 mg, 9.5 μmol) in CH_2Cl_2 (0.50 mL). After 1 h, the reaction mixture was basified with saturated $NaHCO_3$, extracted with ethyl acetate, dried over anhydrous Na_2SO_4, and concentrated *in vacuo*. Purification by flash chromatography (1:9 ethyl acetate:hexanes) afforded the title compound as a clear, colorless oil (1.6 mg, 4.0 μmol, >19:1 α:β, 84%). IR (film) 3561, 2954, 2858, 1467, 1361, 1299, 1259, 1082, 878.0, 840.3, 775.9, 731.7 cm^{-1}; ^1H NMR (500 MHz, C_6D_6) δ 7.71 (m, 2H, Ar-H); 7.07 (m, 2H, Ar-H); 6.97 (m, 1H, Ar-H); 5.69 (s, 1H, C1-H); 4.60 (dq, 1H, *J* = 9.5, 6.5 Hz, C5-H); 3.61 (d, 1H, *J* = 9.5 Hz, C4-H); 3.54 (s, 1H, C3-OH); 2.93 (s, 3H, OCH_3); 2.49 (s, 1H, C2-H); 1.33 (s, 3H, C3-CH_3); 1.29 (d, 3H, *J* = 6.5 Hz, C6-H); 0.81 (s, 9H, $SiCMe_3$); –0.08 (s, 3H, SiMe); –0.12 (s, 3H, SiMe); ^{13}C NMR (125 MHz, C_6D_6) δ 130.2, 129.1, 128.2, 126.4, 86.2, 84.7, 76.5, 72.7, 66.3, 57.6, 26.0, 25.3, 19.0, 18.2, –3.67, –3.70; HRMS (FAB+) exact mass calcd for $[M\bullet]^+$ ($C_{20}H_{34}O_4SiS$) requires *m/z* 398.1947, found *m/z* 398.1942; $[\alpha]_D = 58.0$ (c = 0.25, $CHCl_3$).



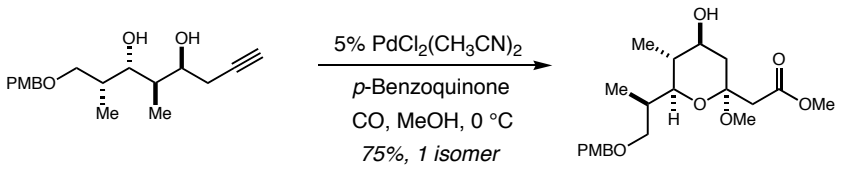
(2*S*, 3*S*, 4*R*)-5-(4-methoxybenzyloxy)-3-hydroxy-2,4-dimethylpentanal. (24) Propionaldehyde (0.485 mL, 6.72 mmol) was added slowly over 24 hours via syringe pump as a solution in DMF (1.18 mL) to a stirring suspension of L-proline (38.7 mg, 0.336 mmol) and (R)-3-(4-methoxybenzyloxy)-2-methylpropanal in DMF (1.18 mL). After the addition was complete, the resulting solution was diluted with ethyl acetate (100 mL), washed successively with water (100 mL) and brine (100 mL), dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. Purification by flash chromatography (3:7 ether:hexanes) afforded the title compound as a clear, colorless oil (585 mg, 2.20 mmol, 65%). Spectroscopic data were identical to that reported by Horita et al.[31]



(2*R*,3*S*,4*R*,5*S*)-1-(4-methoxybenzyloxy)-2,4-dimethyloct-7-yne-3,5-diol. (28) Zinc (5.00 g) was activated by stirring for 1 hour with 100 mL 1N HCl, washing with water (2x100 mL), drying *in vacuo* (2 mmHg, 150 °C), and grinding to a fine powder with a mortar and pestle. A portion of that activated zinc (515 mg, 7.88 mmol) was suspended in 4.0 mL THF and cooled to 0 °C. Then, a 69 wt% solution of propargyl bromide (1.43

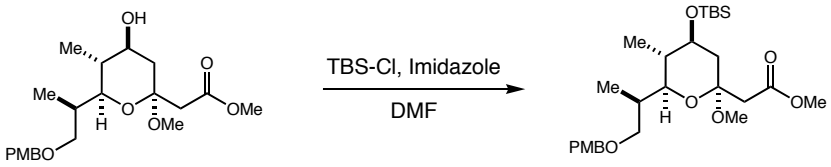
[31] Horita, K.; Inoue, T.; Tanaka, K.; Yonemitsu, O. *Tetrahedron*, **1996**, *52*, 531.

mL, 11.04 mmol) was added cautiously due to a vigorous exotherm. The resulting greenish grey solution was then cooled to –100 °C and β-hydroxyaldehyde **24** (385 mg, 1.58 mmol) was added dropwise via cannula as a solution in THF (2.5 mL + 1.0 ml + 0.50 mL rinse). After stirring for 1 hour at –100 °C, the reaction was acidified by the addition of 0.1*N* HCl (50 mL), warmed to room temperature and extracted with ethyl acetate (5 x 25 mL). The combined organic extracts were dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo*. Purification by flash chromatography (2:3 ethyl acetate:hexanes) afforded the title compound as a clear, colorless oil (434 mg, 1.42 mmol, 98%). IR (film) 3408, 3301, 2968, 2936, 2879, 1613, 1514, 1378, 1302, 1248, 1174, 1083, 1035, 978.1, 846.0, 820.3 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.25 (d, 2H, *J* = 8.5 Hz, Ar-H); 6.90 (d, 2H, *J* = 8.5 Hz, Ar-H); 4.47 (d, 1H, *J* = 12.0 Hz, one of CH_2Ar); 4.44 (d, 1H, *J* = 12.0 Hz, one of CH_2Ar); 4.10 (ddd, 1H, *J* = 8.0, 5.5, 2.5, $HOCHCH_2CCH$); 3.82 (s, 3H, OMe); 3.82 (dd, 1H, *J* = 13.0, 3.0 Hz, $PMBOCH_2CH(Me)CHOH$); 3.59 (dd, 1H, *J* = 9.0, 4.0 Hz, one of CH_2OPMB); 3.53 (dd, 1H, *J* = 9.0, 5.0 Hz, CH_2OPMB); 2.51 (ddd, 1H, *J* = 16.5, 8.5, 2.5 Hz, one of CH_2CCH); 2.37 (ddd, 1H, *J* = 16.5, 6.0, 3.0 Hz); 2.03 (t, 1H, *J* = 3.0 Hz, CCH); 1.96 (m, 1H, CHMe); 1.88 (m, 1H, CHMe); 1.01 (d, 1H, *J* = 7.5 Hz, CH3); 0.86 (d, 1H, *J* = 7.0 Hz); ^{13}C NMR (125 MHz, CDCl3) δ 159.6, 130.2, 129.5, 114.1, 82.2, 76.7, 75.4, 73.4, 72.3, 70.1, 55.5, 39.1, 35.5, 23.8, 11.8, 10.3; HRMS (EI+) exact mass calcd for $[M\bullet]^+$ ($C_{18}H_{26}O_4$) requires m/z 306.1831, found m/z 306.1844; $[\alpha]_D = -3.40$ (c = 1.00, $CHCl_3$).



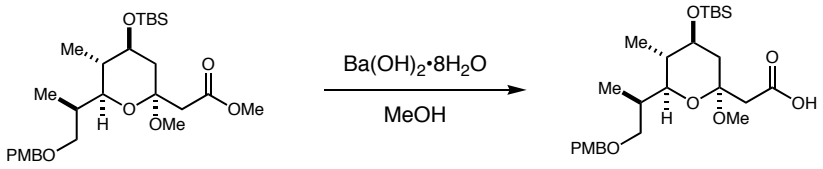
Methyl 2-((2*S*,4*S*,5*R*,6*S*)-6-((*R*)-1-(4-methoxybenzyloxy)propan-2-yl)-tetrahydro-4-hydroxy-2-methoxy-5-methyl-2H-pyran-2-yl)acetate (32). A 25 mL round bottom flask containing a solution of alkynyl diol **28** (402 mg, 1.31 mmol) in anhydrous methanol (8.75 mL) was purged with CO for 1 minute, and then cooled to 0 °C under 1 atm CO pressure. Then 1,4-benzoquinone (142 mg, 1.31 mmol) and bis(acetonitrile)dichloropalladium (II) (17.0 mg, 0.066 mmol) were added and the solution was re-purged with CO for 1 minute before stirring for an additional 3 hours at 0 °C. Then, para-toluenesulfonic acid monohydrate (25.0 mg, 0.131 mmol) was added and the solution was stirred for 30 minutes at 0 °C before warming to room temperature for 15 minutes. The reaction mixture was then diluted with 125 mL of ethyl acetate, washed with 100 mL 0.1M NaOH. The aqueous layer was then back-extracted with two 50 mL portions of ethyl acetate and the combined organics phases were dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. Purification by flash chromatography (2:3 ethyl acetate:hexanes) afforded the title compound as a clear, colorless oil (389 mg, 0.98 mmol, 75%). IR (film) 3386, 2967, 2934, 2879, 1731, 1613, 1514, 1456, 1440, 1378, 1320, 1303, 1248, 1095, 1030, 820.1 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.25 (d, 2H, *J* = 9.0 Hz, Ar-H); 6.89 (d, 2H, *J* = 8.0 Hz, Ar-H); 4.44 (d, 1H, *J* = 11.5 Hz, one of CH_2Ar); 4.40 (d, 1H, *J* = 11.5 Hz, one of CH_2Ar); 3.82 (s, 3H, $ArOCH_3$); 3.69 (s, 3H, CO_2CH_3); 3.67 (ddd, 1H, *J* = 11.5, 9.5, 5.0 Hz, C5-H); 3.54 (dd apparent t, 1H, *J* = 8.5, 8.5 Hz, one of C9-H); 3.50 (dd, 1H, *J* = 10.5, 1.5 Hz, C7-H); 3.33 (dd, 1H, *J* = 9.0, 6.0

Hz, one of C9-H); 3.18 (s, 3H, C3-OCH_3); 2.70 (d, 1H, *J* = 13.5 Hz, one of C2-H); 2.62 (d, 1H, *J* = 13.5 Hz, one of C2-H); 2.27 (dd, 1H, *J* = 13.0, 5.0 Hz, equatorial C4-H); 2.11 (m, 1H, C8-H); 1.67 (dd, 1H, *J* = 13.0, 11.5 Hz, axial C4-H); 1.43 (ddq apparent tq, 1H, *J* = 9.5, 9.5, 7.0 Hz, C6-H); 0.95 (d, 3H, *J* = 6.5 Hz, C8-CH3); 0.84 (d, 3H, *J* = 7.0 Hz, C6-CH3); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.0, 159.4, 130.8, 129.5, 114.0, 99.0, 73.1, 73.0, 72.9, 70.2, 55.5, 51.9, 48.0, 43.0, 42.0, 39.8, 33.9, 12.3, 9.6; HRMS (CI+) exact mass calcd for $[M+NH_4]^+$ ($C_{21}H_{36}O_7N$) requires m/z 414.2492, found m/z 414.2473; $[\alpha]_D$ = –38.6 (c = 1.00, CHCl3).



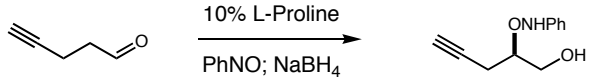
Methyl 2-((2*S*,4*S*,5*R*,6*S*)-6-((*R*)-1-(4-methoxybenzyloxy)propan-2-yl)-tetrahydro-4-tert-butyldimethylsilanoxy-2-methoxy-5-methyl-2H-pyran-2-yl)acetate (47). Imidazole (109 mg, 1.60 mmol) and tert-butyldimethylsilyl chloride (193 mg, 1.28 mmol) were added to a stirring solution of alcohol **32** (422.7 mg, 1.07 mmol) in DMF (4.25 mL) at room temperature. After stirring for 3 hours, the solution was diluted with 150 mL of ethyl acetate, washed with 100 mL 0.1*N* HCl, 100 mL 10% $NaHCO_3$, 100 mL brine, dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo* to afford the title compound as a clear, colorless oil (500.3 mg, 0.98 mmol, 92%). IR (film) 2956, 2932, 2857, 1743, 1716, 1640, 1613, 1587, 1514, 1464, 1249, 1072, 1037, 836.3, 775.6 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.26 (d, 2H, *J* = 8.5 Hz, Ar-H); 6.89 (d, 2H, *J* = 8.5 Hz, Ar-H); 4.44 (d, 1H, *J* = 11.0 Hz, one of CH_2Ar); 4.40 (d, 1H, *J* = 11.0 Hz, one of

CH_2Ar); 3.82 (s, 3H, $ArOCH_3$); 3.69 (s, 3H, CO_2CH_3); 3.65 (ddd, 1H, J = 10.5, 9.5, 5.0 Hz, C5-H); 3.54 (dd apparent t, 1H, J = 8.0, 8.0 Hz, one of C9-H); 3.48 (dd, 1H, J = 10.0, 1.5 Hz, C7-H); 3.33 (dd, 1H, J = 9.0, 6.5 Hz, one of C9-H); 3.17 (s, 3H, C3-OCH_3); 2.66 (d, 1H, J = 14.0 Hz, one of C2-H); 2.62 (d, 1H, J = 14.0 Hz, one of C2-H); 2.14 (dd, 1H, J = 13.0, 5.0 Hz, equatorial C4-H); 2.09 (m, 1H, C8-H); 1.69 (dd, 1H, J = 13.0, 10.5 Hz, axial C4-H); 1.45 (ddq apparent tq, 1H, J = 10.0, 10.0, 6.5 Hz, C6-H); 0.91 (s, 9H, $C(CH_3)_3$); 0.87 (d, 3H, J = 7.0 Hz, C6-CH_3); 0.84 (d, 3H, J = 7.0 Hz, C8-CH_3); 0.08 (s, 6H, $Si(CH_3)_2$); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.1, 159.3, 130.9, 129.5, 114.0, 99.0, 73.3, 73.1, 72.9, 70.9, 55.5, 51.8, 48.0, 43.4, 42.1, 40.1, 34.2, 26.1, 18.3, 12.7, 9.6, –3.8, –4.5; HRMS (CI+) exact mass calcd for $[M+H]^+–H_2$ ($C_{27}H_{45}O_7Si$) requires m/z 509.2935, found m/z 509.2917; $[\alpha]_D$ = –30.0 (c = 1.00, $CHCl_3$).



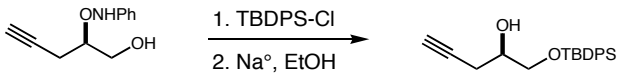
2-((2*S*,4*S*,5*R*,6*S*)-6-((*R*)-1-(4-methoxybenzyloxy)propan-2-yl)-tetrahydro-4-tert-butyldimethylsilanoxy-2-methoxy-5-methyl-2H-pyran-2-yl)acetic acid (34). Barium hydroxide octahydrate (2.162 g, 6.85 mmol) was added to a 0 °C stirring solution of methyl ester **47** (350 mg, 0.69 mmol) in methanol (13.8 mL). After stirring for 0.5 hours at 0 °C, the solution was allowed to come to room temperature over the course of 4 hours. The solution was then re-cooled to 0 °C and acidified by the dropwise addition of 0.5N HCl (27.5 mL) over 5 minutes. Then, an additional 100 mL of water was added and the resulting solution was extracted with diethyl ether (5x100 mL). The combined organic

extracts were then dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. Purification by flash chromatography (7:13 ethyl acetate:hexanes) afforded the title compound as a clear, colorless oil (323 mg, 0.65 mmol, 95%). IR (film) 2960 (br), 2958, 2931, 2857, 1713, 1613, 1514, 1464, 1250, 1071, 1036, 1007, 836.6, 775.4 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.25 (d, 2H, *J* = 8.5 Hz, Ar-H); 6.90 (d, 2H, *J* = 8.5 Hz, Ar-H); 4.45 (d, 1H, *J* = 1 Hz, one of CH_2Ar); 4.41 (d, 1H, *J* = 11.0 Hz, one of CH_2Ar); 3.82 (s, 3H, $ArOCH_3$); 3.67 (ddd apparent td, 1H, *J* = 10.0, 10.0, 4.5 Hz, C5-H); 3.60 (dd, 1H, *J* = 10.5, 2.0 Hz, C7-H); 3.53 (dd apparent t, 1H, *J* = 9.0, 9.0 Hz, one of C9-H); 3.35 (dd, 1H, *J* = 8.5, 6.0 Hz, one of C9-H); 3.19 (s, 3H, C3-OCH_3); 2.76 (d, 1H, *J* = 14.0 Hz, one of C2-H); 2.64 (d, 1H, *J* = 14.0 Hz, one of C2-H); 2.14 (dd, 1H, *J* = 13.0, 4.5 Hz, equatorial C4-H); 2.13 (m, 1H, C8-H); 1.65 (dd, 1H, *J* = 13.0, 10.5 Hz, axial C4-H); 1.50 (ddq apparent tq, 1H, *J* = 10.0, 10.0, 6.5 Hz, C6-H); 0.90 (s, 9H, $C(CH_3)_3$); 0.89 (d, 3H, *J* = 6.0 Hz, C6-CH_3); 0.84 (d, 3H, *J* = 7.5 Hz, C8-CH_3); 0.082 (s, 3H, $SiCH_3$); 0.076 (s, 3H, $SiCH_3$); ^{13}C NMR (125 MHz, $CDCl_3$) δ 173.0, 159.4, 130.7, 129.6, 114.0, 99.0, 73.8, 73.0, 72.9, 70.5, 55.5, 48.2, 43.2, 42.1, 40.1, 34.1, 26.1, 18.3, 12.6, 9.7, –3.8, –4.5; HRMS (FAB+) exact mass calcd for $[M+H]^+$ ($C_{26}H_{43}O_7Si$) requires m/z 495.2778, found m/z 495.2758; $[\alpha]_D$ = –36.7 (c = 2.00, $CHCl_3$).



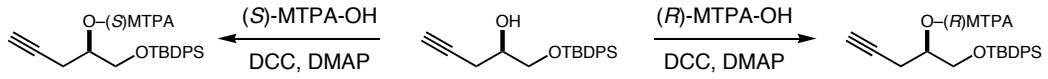
(*R*)-2-(N-Phenyl-aminoxy)-pent-4-yn-1-ol (35). A bright green solution of nitrosobenzene (1.294 g, 12.1 mmol) in chloroform (8.1 mL) was added dropwise to a stirring suspension of L-proline (139 mg, 1.21 mmol) and 4-pentynal (2.977 g, 36.2

mmol) in chloroform (10 mL) at 4 °C. After 3 hours, the color of the solution changed from bright green to orange. Then, the reaction was poured into a stirring 0 °C suspension of sodium borohydride (2.742 g, 72.5 mmol) in anhydrous ethanol (100 mL). After stirring for 3 hours, the reaction was warmed to room temperature, basified by the addition of 250 mL 10% $NaHCO_3$, and extracted with CH_2Cl_2 (5x100 mL). The combined organic phases were washed with 100 mL brine, dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. Purification by flash chromatography (3:17 ethyl acetate:hexanes to 3:7 ethyl acetate:hexanes, linear gradient) afforded the title compound as a clear, yellow oil (1.89 g, 9.88 mmol, 82%) in 98% ee. IR (film) 3399, 3288, 3051, 2927, 1708, 1602, 1494, 1421, 1349, 1240, 1029, 900.6, 770.3, 694.0, 647.5 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.30 (m, 2H, Ar-H); 7.14 (br s, 1H, NH); 7.02 (m, 3H, Ar-H); 4.12 (m, 1H, CHONHPh); 3.98 (dd, 1H, J = 12.0, 3.0 Hz, one of CH_2OH); 3.90 (dd, 1H, J = 12.5, 6.5 Hz, one of CH_2OH); 2.68 (ddd, 1H, J = 17.0, 5.5, 3.0 Hz, one of CH_2CCH); 2.61 (ddd, 1H, J = 16.5, 7.5, 2.0 Hz, one of CH_2CCH); 2.36 (br s, 1H, OH); 2.08 (t, 1H, J = 3.0 Hz, CCH); ^{13}C NMR (125 MHz, $CDCl_3$) δ 148.5, 129.3, 122.9, 115.0, 82.3, 80.4, 70.8, 63.8, 20.1; HRMS (FAB+) exact mass calcd for $[M+H]^+$ ($C_{11}H_{13}NO_2$) requires m/z 191.0946, found m/z 191.0944; $[\alpha]_D = -19.6$ (c = 1.00, $CHCl_3$). The product ratios were determined by HPLC using a Chiracel AD and AD guard column (5.0 % ethanol/hexanes, 1 mL/min): (*S*) enantiomer t_r = 51.0 min, (*R*) enantiomer t_r = 62.1 min.



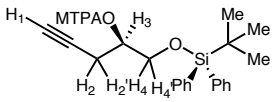
(*R*)-1-(tert-butyldiphenylsilanoxy)-pent-4-yn-2-ol (37). Imidazole (740 mg, 10.9 mmol) and tert-butyldiphenylsilyl chloride (2.70 mL, 10.4 mmol) were added to a stirring solution of alcohol **35** (1.89 g, 9.90 mmol) in DMF (20.0 mL) at room temperature. After stirring for 2 hours, the solution was diluted with 250 mL of diethyl ether, washed with 250 mL 0.1N HCl, 250 mL 10% $NaHCO_3$, 250 mL brine, dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo* to afford the unstable protected diol as a yellow oil. The crude yellow oil was then dissolved in anhydrous ethanol (40 mL), cooled to 0 °C and sodium (455 mg, 19.8 mmol) was added piecewise. After stirring for 8 hours, the reaction was warmed to room temperature, acidified with 250 mL 0.1N HCl, neutralized with 10% $NaHCO_3$ to pH = 8, and extracted with ethyl acetate (5x100 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. Purification by flash chromatography (3:47 ethyl acetate:hexanes) afforded the title compound as a clear, pale yellow oil (2.05 g, 6.06 mmol, 61% over two steps). IR (film) 3565, 3445, 3306, 3072, 2958, 2931, 2891, 2858, 1961, 1894, 1827, 1771, 1472, 1428, 1113, 823.3, 740.7, 702.2 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.67 (m, 4H, Ar-H); 7.41 (m, 6H, Ar-H); 3.89 (m, 1H, CHOH); 3.76 (dd, 1H, *J* = 10.5, 4.5 Hz, one of $CH_2OTBDPS$); 3.70 (dd, 1H, *J* = 10.0, 5.5 Hz, one of $CH_2OTBDPS$); 2.51 (br s, 1H, OH); 2.47 (dd, 2H, *J* = 5.5, 2.5 Hz, CH_2CCH); 1.98 (t, 1H, *J* = 2.5 Hz, CCH); 1.08 (s, 9H, $C(CH_3)_3$); ^{13}C NMR (125 MHz, $CDCl_3$) δ 135.8 (2), 133.2 (2), 130.1 (2), 128.1 (2), 80.6, 70.7, 70.4, 66.5, 27.1, 23.5, 19.5; HRMS (CI+) exact mass calcd for $[M+NH_4]^+$

($C_{21}H_{30}NO_2Si$) requires m/z 356.2046, found m/z 356.2047; $[\alpha]_D$ = –5.51 (c = 1.00, $CHCl_3$).



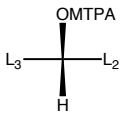
Determination of the Absolute Stereochemistry of (*R*)-1-(tert-butyldiphenyl-silanoxy)-pent-4-yn-2-ol by Mosher Ester Analysis. A solution of alcohol **37** (46.5 mg, 0.14 mmol), 4-dimethylaminopyridine (16.8 mg, 0.14 mmol), dicyclohexylcarbodiimide (85.0 mg, 0.41 mmol) and (*R*)-methoxytrifluromethylphenylacetic acid (64.3 mg, 0.27 mmol) in dichloromethane (0.50 mL) was stirred for 20 hours at room temperature. The resulting suspension was diluted with diethyl ether (10 mL), filtered through a cotton plug and concentrated *in vacuo*. Purification by flash chromatography (1:19 ethyl acetate:hexanes) afforded the (*R*)-MTPA ester as a colorless oil (65.5 mg, 0.12 mmol, 85%). Similarly, the (*S*)-MTPA ester was prepared from alcohol **37** (48.1 mg, 0.14 mmol), 4-dimethylaminopyridine (17.4 mg, 0.14 mmol), dicyclohexylcarbodiimide (88.0 mg, 0.43 mmol) and (*S*)-methoxytrifluromethylphenylacetic acid (66.5 mg, 0.28 mmol) in dichloromethane (0.50 mL) to afford the ester as a colorless oil (69.2 mg, 0.12 mmol, 86%). A comparison of the chemical shifts of the two diastereomeric esters by the method of Mosher revealed alcohol **37** to posses the (*R*) absolute configuration (see the below chart for details).

Mosher Ester Analysis for The α-Oxidation Product



δ_R = chemical shift ($CDCl_3$) with (R)-MTPA Ester
δ_S = chemical shift ($CDCl_3$) with (S)-MTPA Ester

Mosher's Model:

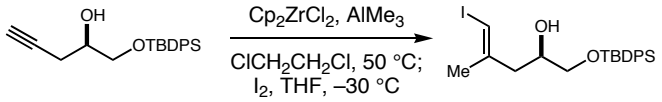


$\Delta\delta$ (L_3) < 0
$\Delta\delta$ (L_2) > 0

■ Proton NMR Comparison of the (*R*) and (*S*) Mosher Esters

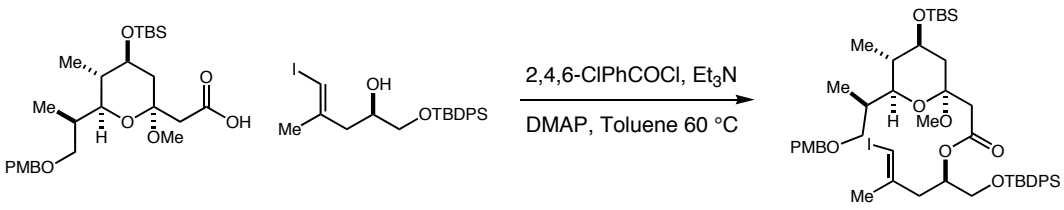
Proton	δ_S	δ_R	$\Delta\delta = \delta_S - \delta_R$	
H_1	1.99	1.89	+ 0.10	
H_2	2.76	2.61	+ 0.17	L_2 (positive by definition)
H_2'	2.65	2.58	+ 0.07	
H_3	5.29	5.31	– 0.02	
H_4	3.84	3.91	– 0.07	
H_4'	3.78	3.91	– 0.13	L_3 (negative by definition)
t-Bu	1.02	1.06	– 0.04	

■ Data proves the desired (*R*) absolute configuration for the α-oxidation reaction



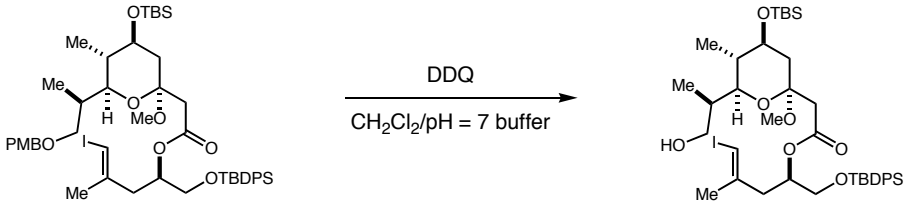
(*R*)-1-(tert-butyldiphenylsilanoxy)-5-iodo-4-methyl-pent-4-ene-2-ol (5). A 50 mL schlenk tube was charged with bis(cyclopentadienzyl)zirconium dichloride (864 mg, 2.95 mmol) and a magnetic stir-bar in an inert atmosphere glove-box. After removal from the box and placing the flask under an argon atmosphere, freshly distilled 1,2-dichloroethane (3.0 mL) was added followed by trimethylaluminum (850 μL, 8.86 mmol) with stirring. Within 5 minutes, all of the solids dissolved to form a lemon yellow solution. Then, alkynyl alcohol **37** (500 mg, 1.48 mmol) was added via cannula as a solution in 1,2-dichloroethane (2.0 mL plus 1.0 ml rinse). After stirring for 1 hour at room temperature,

the solution was heated to 50 °C for 16 hours. Then, the solution was cooled to –30 °C and iodine (562 mg, 2.22 mmol) was added via cannula as a solution in THF (4.0 mL plus 2.0 mL rinse). After stirring for 1 hour at –30 °C, the solution was allowed to warm to 0 °C over the course of 1 hour. Then, 10 mL of water was added cautiously due to vigorous gas evolution. Then, the reaction was neutralized by the addition of 150 mL sat. NH_4Cl and extracted with dichloromethane (5x100 mL). The combined organic extracts were washed with 100 mL 10% $Na_2S_2O_3$, 100 mL brine, dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. Purification by flash chromatography (1:19 ethyl acetate:hexanes on Et_3N-treated SiO_2) afforded the title compound as a clear, colorless oil (480 mg, 1.00 mmol, 68%). IR (film) 3422, 3070, 2957, 2930, 2857, 1472, 1113, 822.3, 739.9, 701.1 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.67 (m, 4H, Ar-H); 7.41 (m, 6H, Ar-H); 5.96 (q, 1H, J = 0.9 Hz, CHI); 3.85 (m, 1H, CHOH); 3.64 (dd, 1H, J = 9.9, 3.9 Hz, one of CH_2OTBDPS); 3.53 (dd, 1H, J = 9.9, 6.6 Hz, one of CH_2OTBDPS); 2.40 (d, 1H, J = 3.9 Hz, OH); 2.35 (dd, 2H, J = 6.0, 0.9 Hz, CH_2C=C); 1.84 (d, 1H, J = 0.9 Hz, C=CCH_3); 1.08 (s, 9H, C(CH_3)$_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 144.7, 135.8 (2), 133.2 (2), 130.2 (2), 128.1 (2), 77.4, 69.9, 67.4, 43.2, 27.1, 24.3, 19.5; HRMS (CI+) exact mass calcd for $[M+NH_4]^+$ ($C_{22}H_{33}NO_2SiI$) requires m/z 498.1326, found m/z 498.1318; $[\alpha]_D$ = 4.30 (c = 1.00, $CHCl_3$).



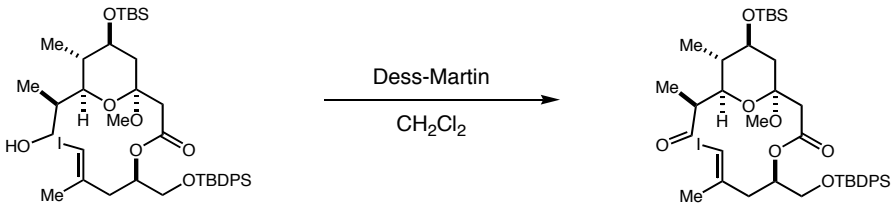
Iodoester (38). To a solution of acid **33** (263 mg, 0.53 mmol) in toluene (1.50 mL) was added 1.45 mL of a stock solution of 2,4,6-trichlorobenzoic acid (126 μL, 0.81 mmol) and triethylamine (122 μL, 0.88 mmol) in toluene (1.50 mL). After stirring for 1 hour at room temperature, the reaction was diluted with 1.80 mL of toluene and added slowly over the course of 1.5 hours via syringe pump to a solution of iodoalcohol **5** (254 mg, 0.53 mmol) and 4-dimethylaminopyridine (90.4 mg, 0.74 mmol) in toluene (6.0 mL). The resulting solution was then warmed to 60 °C for 2 hours. Then, the solution was cooled to room temperature, diluted with 250 mL of ethyl acetate, washed with 100 mL 10% $NaHCO_3$, 100 mL sat. NH_4Cl, 100 mL brine, dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. Purification by flash chromatography (2:23 ethyl acetate:hexanes) afforded the title compound as a clear, colorless oil (476.6 mg, 0.50 mmol, 94%). IR (film) 2931, 2857, 1739, 1612, 1514, 1249, 1090, 828.8, 772.2, 701.5 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.67 (m, 4H, Ph-H); 7.41 (m, 6H, Ph-H); 7.25 (d, 2H, J = 8.5 Hz, PMP-H); 6.90 (d, 2H, J = 8.5 Hz, PMP-H); 6.01 (s, 1H, C10-H); 5.12 (m, 1H, C13-H); 4.43 (d, 1H, J = 12.0 Hz, one of CH_2Ar); 4.39 (d, 1H, J = 12.0 Hz, one of CH_2Ar); 3.83 (s, 3H, $ArOCH_3$); 3.73 (dd, 1H, J = 11.0, 5.5 Hz, one of C14-H); 3.67 (m, 1H, C5-H); 3.64 (dd, 1H, J = 10.5, 5.5 Hz, one of C14-H); 3.52 (dd apparent t, 1H, J = 9.0, 9.0 Hz, one of C9-H); 3.48 (dd, 1H, J = 10.5, 2.0 Hz, C7-H); 3.30 (dd, 1H, J = 8.5, 6.5 Hz, one of C9-H); 3.14 (s, 3H, C3-OCH_3); 2.67 (d, 1H, J = 14.0 Hz, one of C2-H);

2.65 (dd, 1H, J = 13.5, 5.5 Hz, one of CH_2C=C); 2.50 (dd, 1H, J =13.5, 1.0 Hz, one of CH_2C=C); 2.49 (d, 1H, J = 14.0 Hz, one of C2-H); 2.18 (dd, 1H, J = 13.0, 5.0 Hz, equatorial C4-H); 2.08 (m, 1H, C8-H); 1.87 (d, 1H, J = 1.0 Hz, C11-CH_3); 1.58 (dd, 1H, J = 13.0, 11.0 Hz, axial C4-H); 1.44 (ddq apparent tq, 1H, J = 10.0, 10.0, 6.5 Hz, C6-H); 1.08 (s, 9H, $C(CH_3)_3$); 0.90 (s, 9H, $C(CH_3)_3$); 0.87 (d, 3H, J = 6.5 Hz, C6-CH_3); 0.81 (d, 3H, J = 6.5 Hz, C8-CH_3); 0.07 (s, 3H, $SiCH_3$); 0.05 (s, 3H, $SiCH_3$); ^{13}C NMR (125 MHz, $CDCl_3$) δ 168.7, 159.4, 143.8, 135.8 (2), 133.4 (2), 130.9, 130.1 (2), 129.5, 129.4, 128.1, 128.0, 98.9, 78.1, 73.3, 73.1, 72.9, 71.9, 70.9, 64.5, 55.5, 48.0, 43.5, 42.1, 40.7, 40.2, 34.2, 27.1, 26.1, 24.2, 19.5, 18.3, 12.7, 9.7, –3.7, –4.5; HRMS (FAB+) exact mass calcd for $[M\bullet]^+$ ($C_{48}H_{70}O_8Si_2I$) requires m/z 957.3654, found m/z 957.3642; $[\alpha]_D$ = –3.94 (c = 1.00, $CHCl_3$).



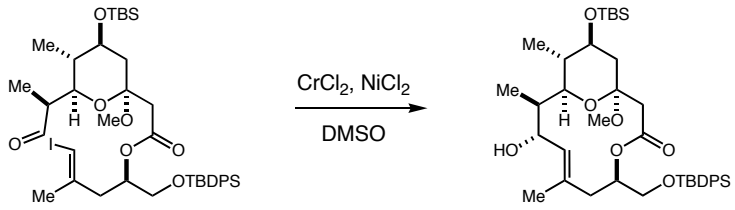
Iodoalcohol (39). DDQ (225 mg, 1.00 mmol) was added to a rapidly stirring suspension of iodoester **38** (476 mg, 0.50 mmol) in CH_2Cl_2 (4.50 mL) and pH = 7 phosphate buffer (450 μL) at room temperature. After stirring for 1.5 hours, the reaction was basified by the addition of 125 mL 10% $NaHCO_3$, extracted with dichloromethane (3x100 mL), dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. Purification by flash chromatography (1:4 ethyl acetate:hexanes on triethylamine-treated SiO_2) afforded the title compound as a clear, colorless oil (376 mg, 0.45 mmol, 90%). IR (film) 3468, 3072,

2958, 2931, 2858, 1738, 1472, 1428, 1251, 1114, 1033, 837.1, 775.4, 702.2 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.67 (m, 4H, Ph-H); 7.41 (m, 6H, Ph-H); 6.01 (s, 1H, C10-H); 5.12 (m, 1H, C13-H); 3.73 (dd, 1H, *J* = 10.5, 5.0 Hz, one of C14-H); 3.73 (m, 1H, one of C9-H); 3.65 (m, 1H, C5-H); 3.65 (m, 1H, one of C9-H); 3.64 (dd, 1H, *J* = 10.5, 5.0 Hz, one of C14-H); 3.51 (dd, 1H, *J* = 10.0, 2.0 Hz, C7-H); 3.20 (s, 3H, C3-OCH_3); 2.63 (d, 1H, *J* = 14.0 Hz, one of C2-H); 2.62 (dd, 1H, *J* = 14.0, 4.0 Hz, one of CH_2C=C); 2.51 (d, 1H, *J* = 14.0 Hz, one of C2-H); 2.49 (dd, 1H, *J* = 14.0, 8.0 Hz, one of CH_2C=C); 2.22 (d, 1H, *J* = 6.5 Hz, C9-OH); 2.18 (dd, 1H, *J* = 13.5, 4.5 Hz, equatorial C4-H); 1.89 (m, 1H, C8-H); 1.86 (d, 1H, *J* = 1.0 Hz, C11-CH_3); 1.59 (dd, 1H, *J* = 13.0, 11.0 Hz, axial C4-H); 1.46 (ddq apparent tq, 1H, *J* = 10.0, 10.0, 7.0 Hz, C6-H); 1.07 (s, 9H, $C(CH_3)_3$); 0.92 (d, 3H, *J* = 6.5 Hz, C6-CH_3); 0.90 (s, 9H, $C(CH_3)_3$); 0.88 (d, 3H, *J* = 6.5 Hz, C8-CH_3); 0.07 (s, 3H, $SiCH_3$); 0.06 (s, 3H, $SiCH_3$); ^{13}C NMR (125 MHz, $CDCl_3$) δ 168.5, 143.8, 135.9, 135.8, 133.4 (2), 130.1 (2), 128.0 (2), 99.3, 78.1, 76.6, 72.1, 70.5, 67.5, 64.5, 48.2, 43.3, 42.1, 40.7, 40.3, 35.6, 27.0, 26.1, 24.2, 19.5, 18.3, 12.7, 9.2, –3.7, –4.5; HRMS (FAB+) exact mass calcd for $[M\bullet]^+$ ($C_{40}H_{62}O_7Si_2I$) requires m/z 837.3079, found m/z 837.3075; $[\alpha]_D = -10.8$ (c = 2.00, $CHCl_3$).



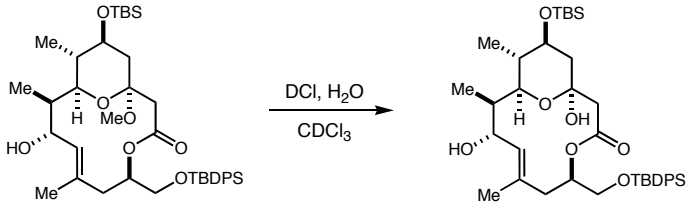
Iodoaldehyde (40). Dess-Martin periodinane (117 mg, 280 μmol) was added to a 0 °C stirring solution of iodoalcohol **39** (154 mg, 180 μmol) in dichloromethane (2.0 mL).

After stirring for 0.5 hours at 0 °C, the solution was allowed to come to room temperature over the course of 1 hour. Then, the reaction was neutralized by the addition of 100 mL 10% $NaHCO_3$ and extracted with diethyl ether (3x100 mL). The combined organic extracts were dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. Purification by flash chromatography (1:9 ethyl acetate:hexanes on triethylamine-treated SiO_2) afforded the title compound as a clear, colorless oil (142 mg, 170 μmol, 92%). IR (film) 3072, 2957, 2931, 2857, 1736, 1472, 1428, 1256, 1113, 837.1, 775.8, 702.2 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 9.72 (s, 1H, C9-H); 7.66 (m, 4H, Ph-H); 7.42 (m, 6H, Ph-H); 6.00 (q, 1H, *J* = 1.0 Hz, C10-H); 5.12 (m, 1H, C13-H); 3.90 (dd, 1H, *J* = 11.0, 2.5 Hz, C7-H); 3.71 (dd, 1H, *J* = 11.0, 5.0 Hz, one of C14-H); 3.71 (m, 1H, C5-H); 3.63 (dd, 1H, *J* = 10.5, 4.5 Hz, one of C14-H); 3.13 (s, 3H, C3-OCH_3); 2.65 (d, 1H, *J* = 15.0 Hz, one of C2-H); 2.61 (dd, 1H, *J* = 14.0, 5.0 Hz, one of CH_2C=C); 2.51 (m, 1H, C8-H); 2.47 (dd, 1H, *J* = 14.5, 7.0 Hz, one of CH_2C=C); 2.41 (d, 1H, *J* = 14.0 Hz, one of C2-H); 2.23 (dd, 1H, *J* = 13.0, 4.5 Hz, equatorial C4-H); 1.86 (d, 1H, *J* = 1.0 Hz, C11-CH_3); 1.57 (dd, 1H, *J* = 12.5, 11.0 Hz, axial C4-H); 1.50 (ddq apparent tq, 1H, *J* = 10.0, 10.0, 6.5 Hz, C6-H); 1.11 (d, 3H, *J* = 6.5 Hz, C8-CH_3); 1.07 (s, 9H, $C(CH_3)_3$); 0.92 (d, 3H, *J* = 6.5 Hz, C6-CH_3); 0.90 (s, 9H, $C(CH_3)_3$); 0.08 (s, 3H, $SiCH_3$); 0.06 (s, 3H, $SiCH_3$); ^{13}C NMR (125 MHz, $CDCl_3$) δ 204.2, 168.4, 143.7, 135.8 (2), 133.4, 133.3, 130.1 (2), 128.0 (2), 99.4, 78.1, 73.2, 71.9, 70.3, 64.5, 48.4, 47.5, 43.3, 41.7, 40.7, 40.0, 27.0, 26.1, 24.2, 19.5, 18.2, 12.9, 6.5, –3.7, –4.5; HRMS (FAB+) exact mass calcd for $[M\bullet]^+$ ($C_{40}H_{60}O_7Si_2I$) requires m/z 835.2923, found m/z 835.2905; $[\alpha]_D$ = –4.12 (c = 2.00, $CHCl_3$).



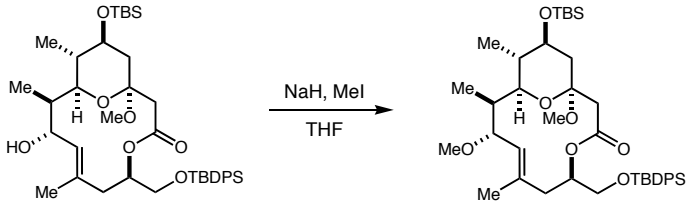
Macrolactone (41). A schlenk flask was charged with chromium (II) chloride (2.095 g, 17.05 mmol), nickel (II) chloride (45.1 mg, 348 μmol) and a magnetic stir-bar in an inert atmosphere glove-box. After removal from the glove-box, the flask was placed under an argon atmosphere and the solids were suspended in degassed (via 3 cycles of freeze-pump-thaw) anhydrous DMSO (60 mL, 1.2 ppm H_2O by Karl-Fischer titration) with vigorous stirring. Then, iodoaldehyde **40** (145.6 mg, 174 μmol) was added via cannula as a solution in degassed, anhydrous DMSO (15.0 mL plus 2 x 6.0 mL rinses). After stirring for 40 hours at room temperature, the charcoal grey suspension was poured into a mixture of 5% potassium DL-serinate (750 mL, adjusted to pH = 8 by adding K_2CO_3 to DL-serine dissolved in water), ethyl acetate (125 mL) and hexanes (125 mL). After stirring vigorously for 1 hour, the aqueous phase became purple in color and the mixture was allowed to warm to room temperature before separating the phases and back-extracting the aqueous layer with 1:1 ethyl acetate:hexanes (3 x 250 mL). The combined organic layers were then dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. Purification by flash chromatography (1:4 ethyl acetate:hexanes on triethylamine-treated SiO_2) afforded the title compound as a white foamy solid (78.2 mg, 110 μmol, 63%). IR (film) 3444, 2931, 2856, 1732, 1472, 1428, 1250, 1113, 1075, 998.4, 836.2, 702.3 cm^{-1}; ^1H NMR (500 MHz, C_6D_6) δ 7.76 (m, 4H, Ph-H); 7.21 (m, 6H, Ph-H); 5.48 (d, 1H, J = 9.0 Hz, C10-H); 5.40 (m, 1H, C13-H); 4.24 (dd, 1H, J = 9.0, 6.5 Hz, C9-H);

3.96 (br m, 1H, C7-H); 3.86 (dd, 1H, *J* = 11.0, 6.5 Hz, one of C14-H); 3.75 (dd, 1H, *J* = 10.5, 5.0 Hz, one of C14-H); 3.61 (ddd, 1H, *J* = 10.5, 10.5, 4.0 Hz, C5-H); 3.19 (s, 3H, C3-OCH_3); 2.53 (d, 1H, *J* = 12.5 Hz, one of C2-H); 2.49 (dd, 1H, *J* = 16.0, 1.0 Hz, one of CH_2C=C); 2.25 (d, 1H, *J* = 12.5 Hz, one of C2-H); 2.15 (dd, 1H, *J* = 16.0, 8.5 Hz, one of CH_2C=C); 2.07 (dd, 1H, *J* = 6.5, 6.5 Hz, C8-H); 2.02 (dd, 1H, *J* = 12.5, 4.0 Hz, equatorial C4-H); 1.56–1.40 (m, 2H, axial C4-H, C6-H); 1.50 (s, 3H, C11-CH_3); 1.16 (s, 9H, $C(CH_3)_3$); 0.96 (s, 9H, $C(CH_3)_3$); 0.94 (d, 3H, *J* = 6.5 Hz, C6-CH_3); 0.93 (d, 3H, *J* = 10.5 Hz, C8-CH_3); 0.03 (s, 3H, $SiCH_3$); 0.02 (s, 3H, $SiCH_3$); ^{13}C NMR (125 MHz, C_6D_6) δ 168.5, 135.9 (2), 133.8, 133.7, 130.0 (2), 128.2, 128.0 (2), 100.0, 71.0 (2), 65.7 (2), 46.6, 42.9, 40.1, 38.9, 26.9, 26.0 (2), 19.4, 18.5, 18.1, 13.2, 12.2, –4.1, –4.7; HRMS (FAB+) exact mass calcd for $[M+H]^+$ ($C_{40}H_{61}O_7Si_2$) requires m/z 709.3956, found m/z 709.3939; $[\alpha]_D$ = 17.6 (c = 1.00, EtOAc).



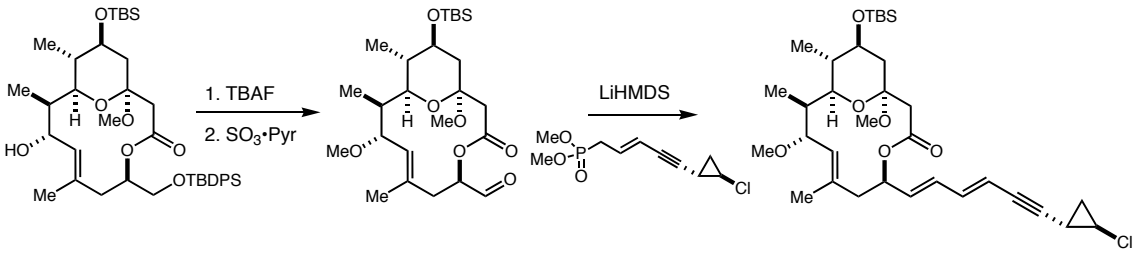
Lactol (50). A solution of macrolactone **41** (35 mg, 49 μmol) was allowed to stand in $CDCl_3$ for a period of 8 hours in an NMR tube placed inside an INOVA 500 MHz spectrometer before being diluted with ethyl acetate, washed with brine, and concentrated *in vacuo*. Purification by flash chromatography (1:4 ethyl acetate:hexanes on triethylamine-treated SiO_2) separated the faster eluting lactol ##, from the slower eluting macrolactone ## to afford the title compound as a clear, colorless oil (6.8 mg, 10 μmol,

20%). IR (film) 3471, 2959, 2931, 2858, 1704, 1472, 1428, 1322, 1251, 1113, 1073, 1027, 889.2, 836.6, 775.4, 702.1 cm^{-1}; ^1H NMR (500 MHz, C_6D_6) δ 7.67 (m, 4H, Ph-H); 7.42 (m, 6H, Ph-H); 5.36 (m, 1H, C13-H); 5.25 (d, 1H, *J* = 6.0 Hz, C10-H); 4.85 (br s, 1H, C3-OH); 4.43 (dd apparent t, 1H, *J* = 5.5 Hz, C9-H); 4.01 (dd, 1H, *J* = 10.0, 2.0 Hz, C7-H); 3.83 (ddd, 1H, *J* = 10.5, 10.5, 4.0 Hz, C5-H); 3.75 (dd, 1H, *J* = 10.5, 6.0 Hz, one of C14-H); 3.69 (dd, 1H, *J* = 10.5, 4.5 Hz, one of C14-H); 2.55 (d, 1H, *J* = 13.0 Hz, one of C2-H); 2.45 (d, 1H, *J* = 13.0 Hz, one of C2-H); 2.27 (m, 2H, CH_2C=C); 2.14 (m, 1H, C8-H); 2.04 (dd, 1H, *J* = 11.5, 4.5 Hz, equatorial C4-H); 1.71 (s, 3H, C11-CH3); 1.54 (br s, C9-OH); 1.46 (ddq apparent tq, 1H, *J* = 10.0, 10.0, 6.5 Hz, C6-H); 1.37 (dd apparent t, 1H, *J* = 11.0, 11.0 Hz, axial C4-H); 1.06 (s, 9H, $C(CH_3)_3$); 0.92 (s, 9H, $C(CH_3)_3$); 0.90 (d, 3H, *J* = 6.5 Hz, C6-CH_3); 0.83 (d, 3H, *J* = 7.5 Hz, C8-CH_3); 0.104 (s, 3H, $SiCH_3$); 0.095 (s, 3H, $SiCH_3$); ^{13}C NMR (125 MHz, C_6D_6, incomplete due to scarcity of sample) δ 135.9, 135.7, 129.7, 96.4, 71.9, 70.9, 70.8, 40.4, 39.7, 27.0 (2), 26.1 (2), 19.5, 10.2; HRMS (FAB+) exact mass calcd for $[M\text{-}OH]^+$ ($C_{39}H_{59}O_6Si_2$) requires m/z 679.3850, found m/z 679.3838; $[\alpha]_D$ = 16.4 (c = 0.50, $CHCl_3$).



Methyl Ether (51). Sodium hydride (9.0 mg, 226 μmol, 60% oil dispersion) was added to a 0 °C stirring solution of macrolactone **41** (64.2 mg, 90 μmol) and iodomethane (225 μL, 3.62 mmol) THF (9.0 mL). After stirring for 1 hour, an additional aliquot of sodium

hydride (18 mg, 452 μmol) was added and the solution was stirred for an additional 8 hours. Then, the reaction was acidified by the addition of 100 mL sat. NH_4Cl and extracted with ethyl acetate (3 x 100 mL). The combined organic extracts were washed with 100 mL 10% $NaHCO_3$, 100 mL brine, dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. Purification by flash chromatography (1:9 ethyl acetate:hexanes on triethylamine-treated SiO_2) afforded the title compound as a clear, colorless oil (55.3 mg, 76 μmol, 84%). IR (film) 2931, 2858, 1732, 1742, 1428, 1074, 836.1, 774.8, 702.2 cm^{-1}; ^1H NMR (500 MHz, C_6D_6) δ 7.77 (m, 4H, Ph-H); 7.21 (m, 6H, Ph-H); 5.56 (d, 1H, J = 9.5 Hz, C10-H); 5.31 (m, 1H, C13-H); 4.31 (dd apparent d, 1H, J = 10.0 Hz, C7-H); 3.96 (dd, 1H, J = 9.0, 7.0 Hz, one of C14-H); 3.81 (m, 2H, C9-H, one of C14-H); 3.69 (m, 1H, C5-H); 3.31 (s, 3H, C9-OCH_3); 3.14 (s, 3H, C3-OCH_3); 2.40–2.04 (m, 6H, C2-H, C12-H, equatorial C4-H, C8-H); 1.57 (m, 1H, C6-H); 1.46 (s, 3H, C11-CH_3); 1.20 (m, 1H, axial C4-H); 1.16 (s, 9H, $C(CH_3)_3$); 0.96 (m, 12H, $C(CH_3)_3$, C6-CH_3); 0.81 (d, 3H, J = 7.0 Hz, C8-CH_3); 0.01 (s, 6H, $Si(CH_3)_2$); ^{13}C NMR (125 MHz, C_6D_6) δ 168.9, 135.9 (2), 133.8, 133.7, 130.4, 130.0 (2), 129.7, 128.2, 128.0 (2), 100.2, 80.8, 74.7, 71.6, 71.0, 65.4, 55.7, 51.4, 43.5, 41.4, 40.5, 39.5, 38.9, 31.8, 26.9, 26.0 (2), 22.9, 19.4, 18.7, 18.1, 14.2, 13.2, 10.1, –4.7 (2); HRMS (FAB+) exact mass calcd for $[M–H]^+$ ($C_{41}H_{63}O_7Si_2$) requires m/z 723.4122, found m/z 723.4103; $[\alpha]_D$ = 36.9 (c = 1.00 EtOAc).



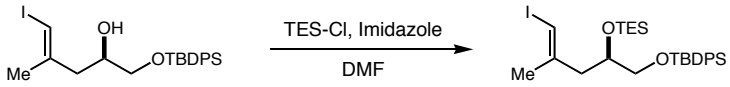
9-epi-5-(tert-Butyldimethylsilanoxy)-3-methoxy-callipeltoside aglycon (44). Tetrabutylammonium fluoride (31.5 μL, 1M THF, 31.5 μmol) was added dropwise to a 0 °C stirring solution of methyl ether **51** (15.2 mg, 21 μmol) in THF (2.10 mL). After stirring for 4 hours, the solution was diluted with 100 mL ethyl acetate, washed with 100 mL sat. NH_4Cl, 100 mL 10% $NaHCO_3$, 100 mL brine, dried over anhydrous Na_2SO_4, filtered and concentrate *in vacuo*. Purification by flash chromatography (2:3 to 1:1 ethyl acetate:hexanes, linear gradient, on triethylamine-treated SiO_2) afforded the title compound as a white solid (7.8 mg, 16 μmol, 76%). The unstable alcohol (6.6 mg, 13.6 μmol) was then dissolved immediately in dichloromethane (1.0 mL) and DMSO (0.40 mL) and cooled to 0 °C. Then, triethylamine (56.7 μL, 407 μmol) was added followed by a solution of sulfurtrioxide-pyridine complex (64.7 mg, 407 μmol) in DMSO (0.40 mL). After 1.5 hours at 0 °C, the solution was diluted with 100 mL brine, extracted with ethyl acetate (3 x 100 mL), dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. Purification by flash chromatography (3:7 to 2:3 ethyl acetate:hexanes, linear gradient, on triethylamine-treated SiO_2) afforded the title compound as an unstable white solid (6.7 mg, 13.6 μmol, 100%). The unstable aldehyde (5.0 mg, 10.3 μmol) was then added via cannula as a solution in THF (0.30 mL plus 0.20 mL rinse) to a –78 °C stirring solution of lithio-phosphonate **6**•Li (prepared by adding freshly prepared 0.5*M* LiHMDS (61.9 μL, 31.0 μmol) to a –78 °C stirring solution of phosphonate **6** (7.7 mg, 30.9 μmol) in THF (1.50 mL) and stirring for 10 minutes). After 2 hours at –78 °C, the solution was

allowed to warm to –40 °C for 30 minutes and then 30 minutes at room temperature before adding 100 mL water and 100 mL diethyl ether. The layers were separated and the aqueous phase was back-extracted with diethyl ether (2 x 50 mL). The combined organics were washed with 100 mL brine, dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. Purification by flash chromatography (1:9 ethyl acetate:hexanes on triethylamine-treated SiO_2) afforded the title compound as a clear, colorless oil (3.4 mg, 5.6 μmol, 54%, >19:1 *E*:*Z*). IR (film) 2929, 1732, 1463, 1374, 1322, 1251, 1184, 1074, 890.3, 836.6, 775.5, 688.0 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$, see table below); ^{13}C NMR (125 MHz, C_6D_6, see table below) δ 169.2, 141.0, 134.4, 129.8, 129.6, 129.3, 111.6, 100.4, 91.9, 81.2, 81.0, 77.9, 71.7, 71.5, 70.7, 43.6, 43.0, 41.0, 40.3, 38.7, 38.2, 34.3, 26.1, 19.5, 18.2, 13.3, 12.5, 12.2, 10.0, -4.5 (2); HRMS (FAB+) exact mass calcd for $[M+H]^+$ ($C_{33}H_{50}O_6SiCl$) requires m/z 605.3065, found m/z 605.3058; $[\alpha]_D$ = 15.6 (c = 0.329, $CHCl_3$).

^1H NMR signals (ppm) in $CDCl_3$		
atom	Patterson et al. (400 MHz)[32]	Compound ## (500 MHz)
C2-H	2.59, 2.44 (d, 1H each, *J* = 12.6 Hz)	2.65, 2.46 (2d, 1H, *J* = 12.0 Hz)
C3-OMe	3.28 (s, 3H)	3.22 (s, 3H)
C4-H(eq)	2.12 (dd, 1H, *J* = 13.2, 4.4 Hz)	2.18 (dd, 1H, *J* = 11.5, 4.5 Hz)
C4-	1.30-1.25 (m, 1H)	1.33-1.23 (m, 1H)
C5-H	3.47 (td, *J* = 10.8, 4.3 Hz)	3.54 (m, 1H)
C6-H	1.47-1.40 (m, 1H)	1.46-1.41 (m, 1H)
C6-Me	0.90 (obscured)	0.89 (obscured)
C7-H	3.54 (dd, 1H, *J* = 10.5, 1.5 Hz)	3.91 (dd, 1H, *J* = 10.5, 1.0 Hz)
C8-H	2.23-2.18 (m, 1H)	2.20-2.15 (m, 1H)
C8-Me	1.00 (d, 3H, *J* = 7.0 Hz)	0.82 (d, 3H, *J* = 6.5 Hz)
C9-H	3.89 (dd, 1H, *J* = 9.9, 2.6 Hz)	3.88 (dd, 1H, *J* = 10.0, 1.5 Hz)
C9-OMe	3.22 (s, 3H)	3.37 (s, 3H)
C10-H	5.30 (d, 1H, *J* = 9.3 Hz)	5.20 (d, 1H, *J* = 10.0 Hz)
C11-Me	1.65 (s, 3H)	1.61 (s, 3H)

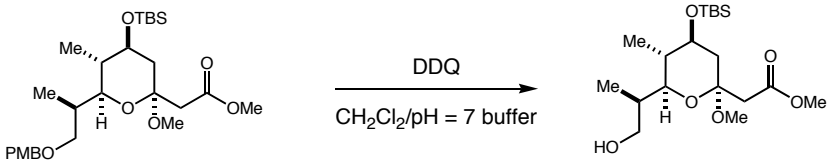
[32] Paterson, I.; Davies, R. D. M.; Heimann, A. C.; Marquez, R.; Meyer, A. *Org. Lett.* **2003**, *5*, 1216.

C12-H	2.42-2.36 (m, 1H); 2.27 (dd, 1H, *J* = 13.2, 2.9) Hz)	2.67 (m, 1H) and 2.18 (m, 1H)
C13-H	5.54-5.48 (m, 1H)	5.45 (m, 1H)
C14-H	5.73 (dd, 1H, *J* = 15.2, 6.7 Hz)	5.77 (dd, 1H, *J* = 15.5, 5.5 Hz)
C15-H	6.25 (dd, 1H, *J* = 15.3, 10.8 Hz)	6.27 (dd, 1H, *J* = 14.5, 11.5 Hz)
C16-H	6.46 (dd, 1H, *J* = 15.3, 10.8 Hz)	6.48 (dd, 1H, *J* = 15.5, 11.5 Hz)
C17-H	5.54 (dd, 1H, *J* = 15.4, 1.9 Hz)	5.54 (dd, 1H, *J* = 15.0, 1.5 Hz)
C20-H	1.82-1.77 (m, 1H)	1.82-1.78 (m, 1H)
C21-H	3.19-3.15 (m, 1H)	3.19-3.16 (m, 1H)
C-22-H	1.30-1.25 (m, 2H)	1.30-1.25 (m, 2H)
$SiCMe_3$	0.89 (s, 9H)	0.89 (s, 9H)
SiMe	0.07 (s, 3H)	0.07 (s, 3H)
SiMe	0.06 (s, 3H)	0.06 (s, 3H)



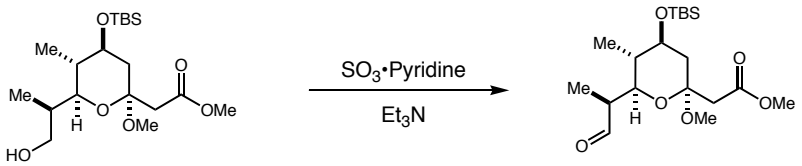
(*R*)-1-(*tert*-butyldiphenylsilanoxy)-2-(triethylsilanoxy)-5-iodo-4-methyl-pent-4-ene (46). Chlorotriethylsilane (103 μL, 0.61 mmol) was added to a stirring solution of iodoalcohol **5** (245.1 mg, 0.51 mmol), imidazole (52.1 mg, 0.77 mmol) and DMF (1.0 mL). After 2.5 hours, the solution was diluted with ethyl acetate (150 mL) and washed with 100 mL sat. NH_4Cl, 100 mL 10% $NaHCO_3$, 100 mL brine, dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. Purification by flash chromatography (1:49 ethyl acetate:hexanes on Et_3N-treated SiO_2) afforded the title compound as a clear, colorless oil (298 mg, 0.50 mmol, 98%). IR (film) 3072, 2956, 2876, 1590, 1472, 1428, 1113, 1077, 1007, 823.4, 738.3, 701.1 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.70 (m, 4H, Ar-H); 7.43 (m, 6H, Ar-H); 6.00 (q, 1H, *J* = 1.0 Hz); 3.81 (m, 1H, C**H**OTES); 3.60 (dd, 1H, *J* = 10.0, 7.0 Hz, one of C**H$_2$**OTBDPS); 3.48 (dd, 1H, *J* = 10.0, 7.0 Hz, one of C**H$_2$**OTBDPS); 2.70 (dd, 1H, *J* = 13.5, 3.5 Hz, one of CH_2C=C); 2.39 (dd, 2H, *J* = 13.5, 8.0 Hz, C**H$_2$**C=C); 1.91 (d, 1H, *J* = 1.0 Hz, C=CCH_3); 1.10 (s, 9H, $C(CH_3)_3$); 0.90 (t, 9H,

J = 7.5 Hz, 3 $CH_2C\mathbf{H_3}$); 0.50 (q, 6H, *J* = 7.5 Hz, 3 $C\mathbf{H_2}CH_3$); ^{13}C NMR (125 MHz, $CDCl_3$) δ 145.1, 135.8 (2), 133.8, 133.7, 130.0, 129.9, 128.0, 127.9, 77.6, 71.3, 67.4, 44.7, 27.1, 24.9, 19.5, 7.1, 5.1; HRMS (CI+) exact mass calcd for $[M\bullet]^+$ ($C_{28}H_{42}O_2Si_2I$) requires *m/z* 593.1768, found *m/z* 593.1782; $[\alpha]_D$ = 14.9 (c = 1.00, $CHCl_3$).



Methyl 2-((2*S*,4*S*,5*R*,6*S*)-6-((*R*)-propan-1-ol-2-yl)-tetrahydro-4-*tert*-butyldimethyl-silanoxy-2-methoxy-5-methyl-2*H*-pyran-2-yl)acetate (52). DDQ (167 mg, 0.73 mmol) was added to a 0 °C stirring suspension of tetrahydropyran **47** (250 mg, 0.49 mmol), dichloromethane (4.50 mL) and pH = 7 phosphate buffer (450 μL). After stirring for 1.5 hours, the reaction was basified by the addition of 125 mL 10% $NaHCO_3$, extracted with dichloromethane (3x100 mL), dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. Purification by flash chromatography (3:7 ethyl acetate:hexanes) afforded the title compound as a clear, colorless oil (159.8 mg, 0.41 mmol, 84%). IR (film) 3467, 2931, 2858, 1744, 1439, 1253, 1074, 1032, 836.7, 775.1 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 3.73 (dd, 1H, *J* = 11.0, 4.0 Hz, one of C_9-H); 3.68 (m, 1H, one of C_9-H); 3.68 (s, 3H, CO_2CH_3); 3.65 (ddd, 1H, *J* = 10.5, 9.5, 5.0 Hz, C_5-H); 3.50 (dd, 1H, *J* = 10.5, 2.5 Hz, C_7-H); 3.23 (s, 3H, C_3-OCH_3); 2.69 (d, 1H, *J* = 13.5 Hz, one of C_2-H); 2.57 (d, 1H, *J* = 13.5 Hz, one of C_2-H); 2.41, (d, 1H, *J* = 1.5 Hz, OH); 2.10 (dd, 1H, *J* = 13.5, 5.0 Hz, equatorial C_4-H); 1.87 (m, 1H, C_8-H); 1.71 (dd, 1H, *J* = 13.5, 11.0 Hz, axial C_4-H); 1.46 (ddq apparent tq, 1H, *J* = 10.0, 10.0, 6.5 Hz, C_6-H); 0.93 (d, 3H, *J* = 6.5 Hz, C_8-CH_3);

0.89 (s, 9H, $C(CH_3)_3$); 0.87 (d, 3H, J = 7.0 Hz, C_6-CH_3); 0.07 (s, 6H, $Si(CH_3)_2$); ^{13}C NMR (125 MHz, $CDCl_3$) δ 169.8, 99.4, 77.0, 70.5, 67.5, 51.9, 48.1, 43.2, 42.1, 40.2, 35.5, 26.1, 18.2, 12.7, 9.0, –3.8, –4.5; HRMS (EI+) exact mass calcd for $[M+H]^+$ ($C_{19}H_{39}O_6Si$) requires *m/z* 391.2510, found *m/z* 391.2506; $[\alpha]_D$ = –38.0 (c = 1.00, $CHCl_3$).



Methyl 2-((2*S*,4*S*,5*R*,6*S*)-6-((*R*)-propanal-2-yl)-tetrahydro-4-*tert*-butyldimethyl-silanoxy-2-methoxy-5-methyl-2*H*-pyran-2-yl)acetate (48). Alcohol **52** (159.8 mg, 0.41 mmol) was dissolved in a mixture of dichloromethane (2.25 mL) and DMSO (1.75 mL), then cooled to 0 °C. Then, triethylamine (171 μL, 1.23 mmol) was added followed by sulfurtrioxide-pyridine complex (195.3 mg, 1.23 mmol). After 45 minutes at 0 °C, the solution was diluted with 100 mL brine, extracted with ethyl acetate (3x100 mL), dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. Purification by flash chromatography (1:4 ethyl acetate:hexanes) afforded the title compound as a clear, colorless oil (139.1 mg, 0.36 mmol, 87%). IR (film) 2956, 2858, 1740, 1437, 1378, 1256, 1077, 837.9, 775.9 cm^{-1}; ^1H NMR (300 MHz, C_6D_6) δ 9.44 (s, 1H, C_9-H); 3.77 (ddd, 1H, J = 10.5, 9.5, 5.0 Hz, C_5-H); 3.72 (dd, 1H, J = 10.8, 2.4 Hz, C_7-H); 3.24 (s, 3H, CO_2CH_3); 2.98 (s, 3H, C_3-OCH_3); 2.45 (d, 1H, J = 14.1 Hz, one of C_2-H); 2.39 (dd, 1H, J = 12.9, 4.8 Hz, equatorial C_4-H); 2.32 (d, 1H, J = 14.1 Hz, one of C_2-H); 1.93 (dq, 1H, J = 7.2, 2.4 Hz, C_8-H); 1.78 (dd, 1H, J = 12.9, 10.8 Hz, axial C_4-H); 1.45 (ddq apparent tq,

1H, J = 10.8, 10.8, 6.6 Hz, C_6-H); 0.94 (d, 1H, J = 7.2 Hz, C_8-CH_3); 0.94 (s, 9H, $C(CH_3)_3$); 0.69 (d, 3H, J = 6.6 Hz, C_6-CH_3); 0.05 (s, 3H, $SiCH_3$); 0.04 (s, 3H, $SiCH_3$); ^{13}C NMR (75 MHz, C_6D_6) δ 202.2, 168.8, 99.5, 73.1, 70.5, 50.9, 47.9, 47.1, 43.5, 41.4, 39.8, 25.9, 18.1, 12.5, 6.1, –4.1, –4.8; HRMS (EI+) exact mass calcd for $[M+H]^+$ ($C_{19}H_{35}O_6Si$) requires *m/z* 387.2203, found *m/z* 387.2222; $[\alpha]_D$ = –25.3 (c = 1.00, EtOAc).

C h a p t e r 6

Summary of Doctoral Research

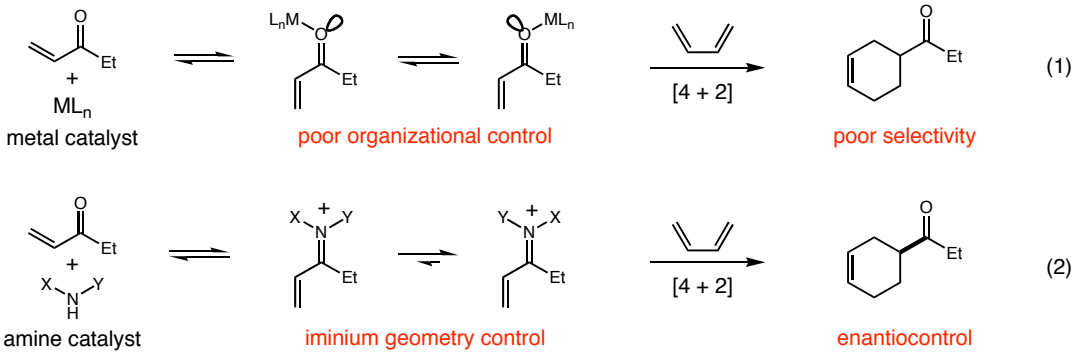
Introduction

The research described in this thesis has focused on the development of broadly useful and novel strategies for enantioselective catalysis and their application in the total synthesis of complex natural products. As nature provides the most challenging and rewarding intellectual challenges, the overarching theme of this research has been to study the structural problems that nature presents. These studies have been directed specifically at solving several of those issues by the enantioselective construction of key chemical motifs in naturally occurring substances. The particular structural motifs selected for study were: (1) enantiopure cyclohexane-containing ketones (especially as found in steroidal natural products); (2) the polyketide structural motif; and (3) polyglycolates such as carbohydrates. What follows in this chapter is a brief summary of the contributions of the methods described in this thesis to the efficient synthesis of archetypes of each of those structural classes.

LUMO-Lowering Activation of α, β-Unsaturated Ketones

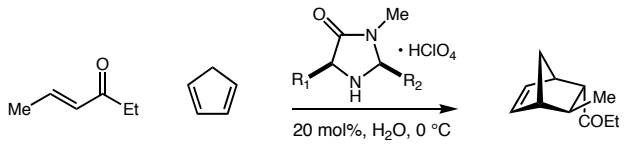
The development of a general strategy for enantioselective organocatalysis has been one of the defining features of research in our group. This work is predicated on the mechanistic observation of the functional equivalence of a Lewis acid and a secondary amine in the LUMO-lowering activation of α, β-unsaturated aldehydes. Further analysis of this concept revealed the attractive proposal that chiral secondary amines may

similarly activate α, β-unsaturated ketones for cycloaddition and conjugate addition processes—an area of asymmetric catalysis in which metal-based catalysts have typically underperformed. As amine catalysts operate outside the mechanistic requirement for selective lone-pair binding (eq 1), we felt that we had the potential to impart high levels of enantiocontrol through control of iminium geometry (eq 2).



Initial attempts with catalysts effective in LUMO-lowering activation of enals afforded no trace of product in the reaction between 4-hexen-3-one and cyclopentadiene (Table 1, entries 1 and 2) presumably due to the difficulty of forming a tetrasubstituted iminium ion intermediate with such sterically demanding catalysts. Less bulky catalysts were significantly more effective, with the 2-(5-methylfuryl) imidazolidinone catalyst **5** affording exceptional levels of enantioselectivity, diastereoselectivity as well as the highest reaction rate and, as such, catalyst **5** was selected for further study.

Table 1. Effect of Amine Architecture on the Ketone Diels-Alder Reaction

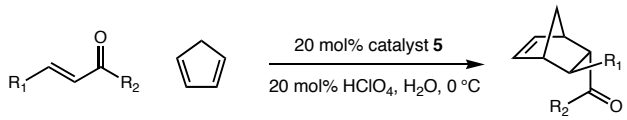


entry	catalyst	R_1	R_2	time (h)	% yield	*endo*:*exo*	% ee[a,b]
1	**1**	Bn	Me, Me	48	20[c]	7:1	0
2	**2**	Bn	*t*-Bu	48	27[c]	9:1	0
3	**3**	Ph	Ph	22	88	21:1	47
4	**4**	Bn	Ph	42	83	23:1	82
5	**5**	Bn	5-methylfuryl	22	89	25:1	90

[a] Product ratios determined by chiral GLC. [b] Absolute configuration assigned by chemical correlation. [c] Less than 30% conversion of starting materials after 48 h.

As Table 2 demonstrates, this catalyst system affords generally high levels of selectivity and reaction efficiency for a range of both linear and cyclic enones. A similarly broad scope was observed with respect to the diene component of the reaction.

Table 2. Representative Enone Scope for the Amine-Catalyzed Diels-Alder



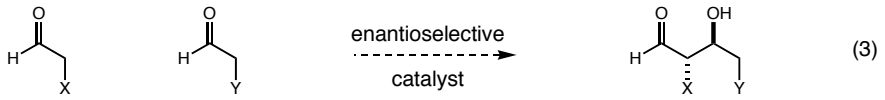
entry	R_1	R_2	% yield	*endo*:*exo*	% ee[a,b]
1	Me	Me	85	14:1	61
2	Me	Et	89	25:1	90
3	Me	*n*-Bu	83	22:1	92[c]
4	Me	*i*-Am	86	20:1	92
5	Me	*i*-Pr	24	8:1	0
6	*n*-Pr	Et	84	15:1	92
7	*i*-Pr	Et	78	6:1	90
8	$-CH_2CH_2CH_2-$		81	12:1	63
9	$-CH_2(CH_2)_2CH_2-$		85	18:1	90
10	$-CH_2(CH_2)_3CH_2-$		83	6:1	91
11	$-CH_2(CH_2)_{11}CH_2-$		88	5:1	93

[a] Product ratios determined by chiral GLC. [b] Absolute configuration assigned by chemical correlation or by analogy. [c] Reaction performed without solvent.

We are currently exploring the potential of catalyst **5** to become a generally useful and effective catalyst in a variety of cycloaddition and conjugate addition processes.

The Enantioselective Catalytic Direct Cross-Aldol Reaction of Aldehydes

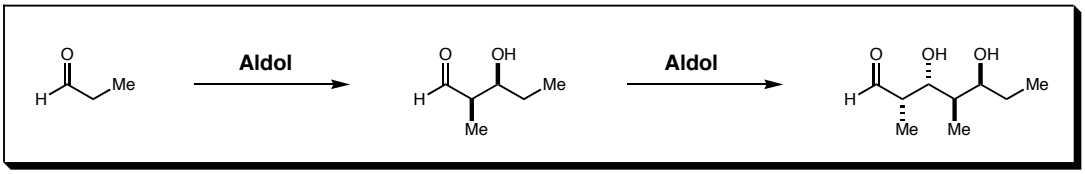
Over the past three decades, research on the aldol reaction has propelled it to the pinnacle of synthetically valuable transformations. While advances in aldol technology allow high levels of stereocontrol through the use of chiral auxiliaries and chiral catalysts, perhaps the most simple aldol reaction—the direct regioselective coupling of two discreet aldehyde components (eq 3)—had yet to be rendered enantioselective.



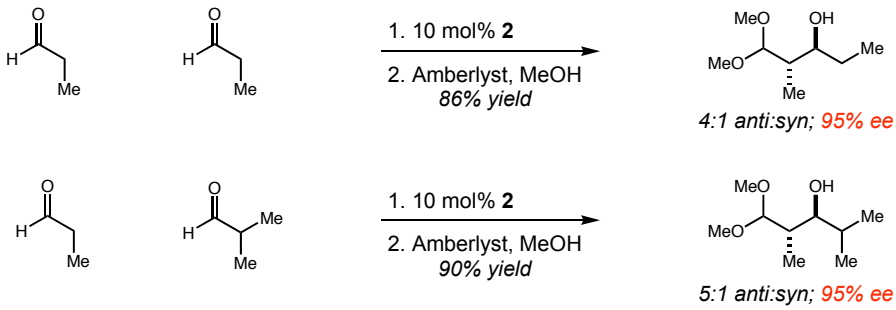
(3)

We felt, however, that such a reaction could be performed efficiently and enantioselectively using chiral enamine catalysis and would constitute an efficient strategy for polyketide natural product synthesis (Scheme 1).

Scheme 1. The Iterative Aldehyde Aldol Strategy



The principal issue in the direct aldehyde aldol reaction is that non-equivalent aldehydes must follow two different mechanistic pathways; one aldehyde must become a nucleophilic aldol donor while the other remains an electrophilic aldol acceptor. Imidazolidinone catalyst **2** was found to be a highly effective catalyst for that transformation, affording acetal-protected aldol adducts (after methanolysis) in a highly regio-, diastero- and enantioselective process for both homodimerization and cross-aldol reactions (eqs 4 and 5).

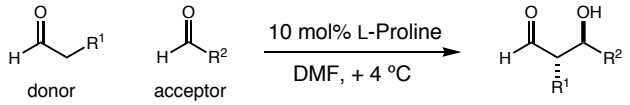


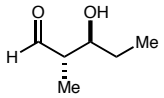
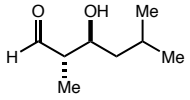
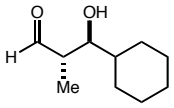
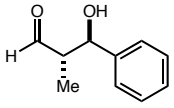
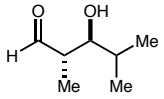
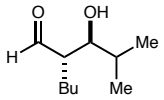
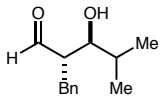
(4)

(5)

When propionaldehyde is instead exposed to a catalytic quantity of L-proline (10 mol%) in DMF, remarkably, the β-hydroxyaldehyde dimer product is directly formed (Table 3, entry 1, 80% yield, 4:1 *anti*:*syn*, 98% ee). Significantly, syringe pump addition (8 to 24h) of the aldehyde aldol donor to a solution of the acceptor effectively suppresses homodimerization and affords useful amounts of highly enantioenriched cross-aldol products (Table 3, entries 2-7, 75–88% yield, ≥97% ee). As entry 2 demonstrates, a highly regioselective cross-aldol reaction is possible between two different aldehydes bearing enolizable α-methylene protons (88% yield, 97% ee). In summary, two new methods for the construction of synthetically valuable diketides have been developed. Application of the aldehyde aldol strategy should lead to the efficient synthesis of polyketide natural products.

Table 3. Proline–Catalyzed Aldehyde Cross Aldol Reactions



entry	R^1	R^2	Product	% yield[a]	*anti*:*syn*[b]	% ee[c,d]
1	Me	Et		80	4:1	99
2	Me	*i*-Bu		88	3:1	97
3	Me	*c*-C_6H_{11}		87	14:1	99
4	Me	Ph		81	3:1	99
5	Me	*i*-Pr		82	24:1	>99
6[e]	*n*-Bu	*i*-Pr		80	24:1	98
7[e]	Bn	*i*-Pr		75	19:1	91

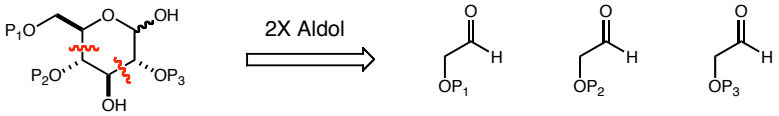
[a]Relative stereochemistry assigned by direct comparison to literature spectra or by analogy. [b]Determined by GLC analysis of the 2,2-dimethylpropylidine acetal or by HPLC analysis of the corresponding 1,3-diol. [c]Absolute stereochemistry determined by chemical correlation to a known compound or by analogy. [d]Reaction conducted at room temperature.

A Two-Step Enantioselective Total Synthesis of Differentiated Carbohydrates

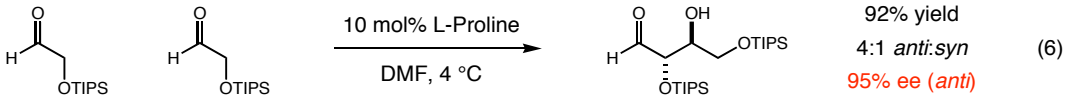
The aldohexoses caught our attention as a particularly valuable class of synthetic targets due to both the variety of natural isolates incorporating sugar moieties and a deficiency in methods for the efficient synthesis of polysaccharides. We felt that our

direct aldehyde aldol methodology would facilitate a two step enantioselective total synthesis of fully differentially protected forms of each erythrohexose from simple glycoaldehyde starting materials (Scheme 2).

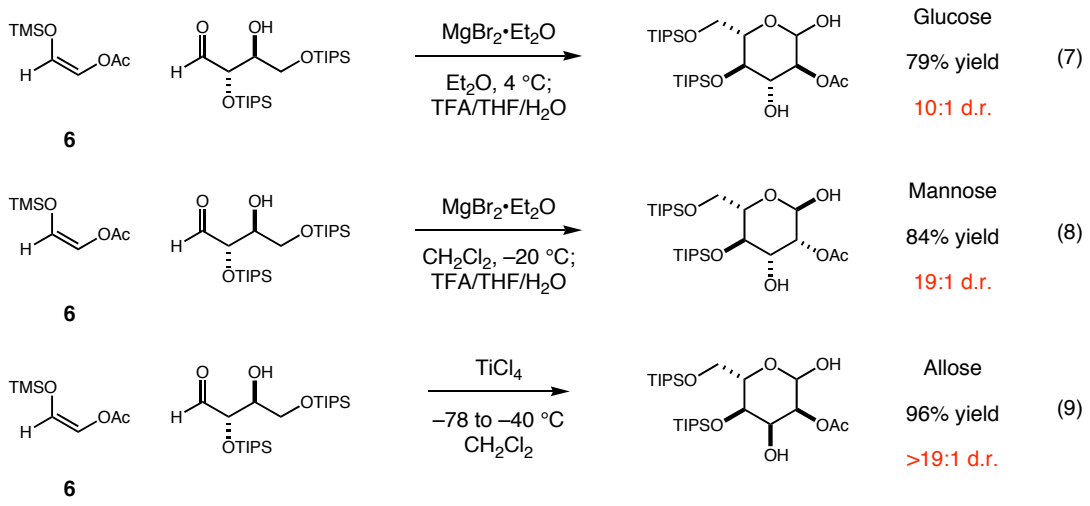
Scheme 2. Retrosynthetic Analysis of a Protected Hexose



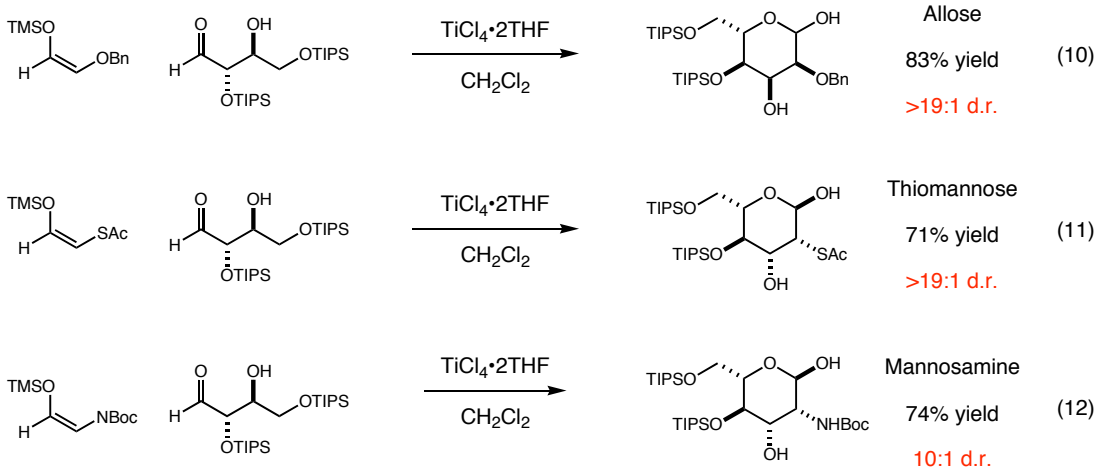
The first step required an aldol dimerization of protected α-oxyaldehydes. Silyloxyacetaldehydes were identified as ideal substrates for this process, due to their high yields, selectivities, and the well-known ability to differentiate primary from secondary silyl-ethers (eq 6).



The second aldol event has the potential to form each of the four erythrohexoses. Remarkably, the stereochemical outcome of the reaction between TIPS-protected aldol dimer above and enolsilane **6** (prepared in 78% yield from acetoxyacetaldehyde, Et_3N, and TMSCl) could be completely controlled by a judicious choice of Lewis acid and solvent combinations (eqs 7—9).



Importantly, a variety of aldehyde enolsilanes are substrates in this reaction allowing incorporation of not only participating (Ac) and non-participating (Bn) O-protecting groups at C-2 but also protected nitrogen and sulfur atoms (eqs 10–12).



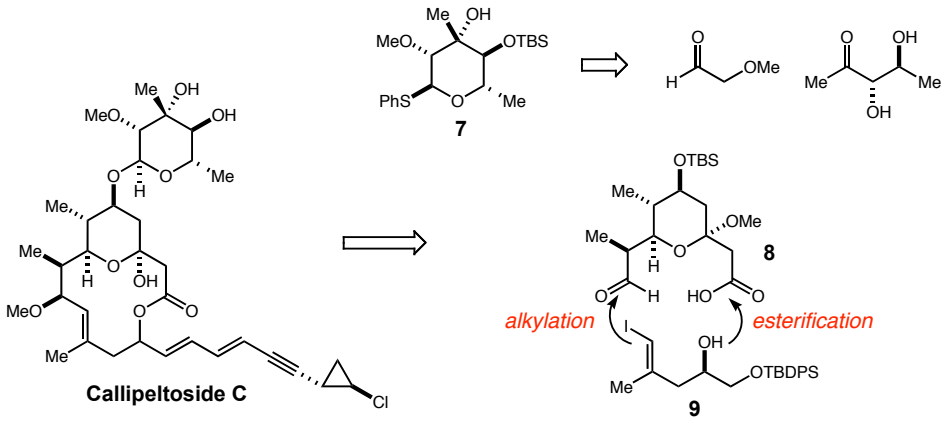
Progress Toward the Total Synthesis of Callipeltoside C

The callipeltosides are an architecturally complex class of natural products isolated from the lithistid sponge *Callipelta sp*., differing only in the identity of the sugar residue appended to the 14-membered macrolactone. While callipeltoside A is known to inhibit in vitro proliferation of NSCLC-N6 and P388 cells, callipeltosides B and C have

only been tested in a limited number of biological assays (due to short supply) and both exhibit similar cytotoxic activity to callipeltoside A.

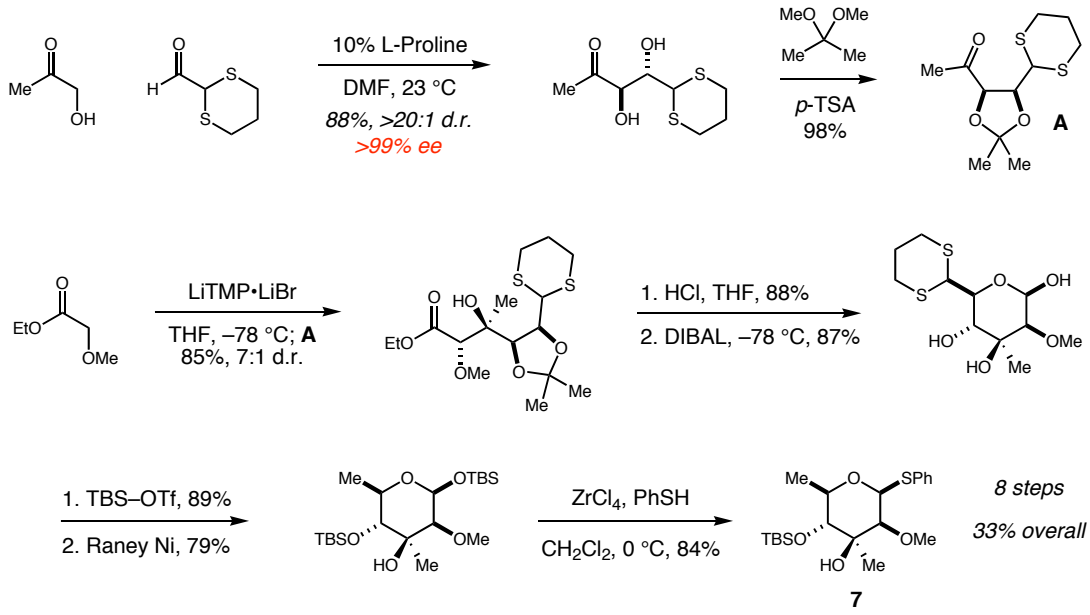
We envisioned accessing callipeltose C (**7**) using the above-described sugar-forming methodology. The macrolactone core of the callipeltosides could be assembled via ester coupling of fragments **8** and **9** followed by a ring-closing Nozaki-Hiyama-Kishi reaction (NHK) as shown in Scheme 3.

Scheme 3. Retrosynthetic Analysis of Callipeltoside C



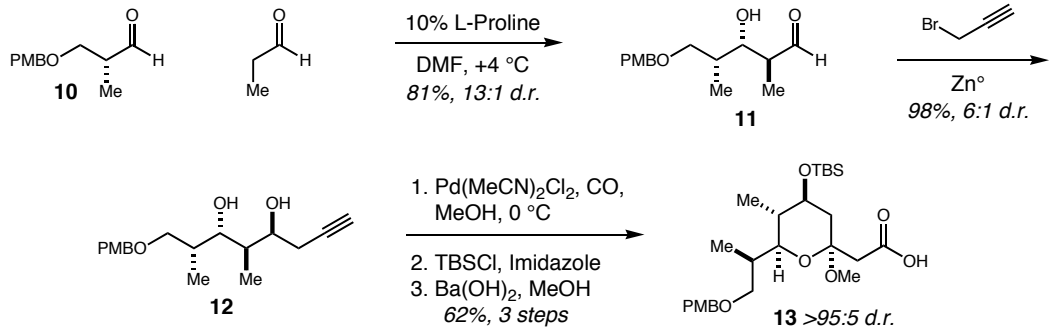
Synthesis of the sugar portion of callipeltoside C was readily achieved through an iterative aldol strategy and simple manipulations to achieve the required level of differential protection for coupling to the aglycon (Scheme 4).

Scheme 4. Synthesis of Protected Callipeltose C



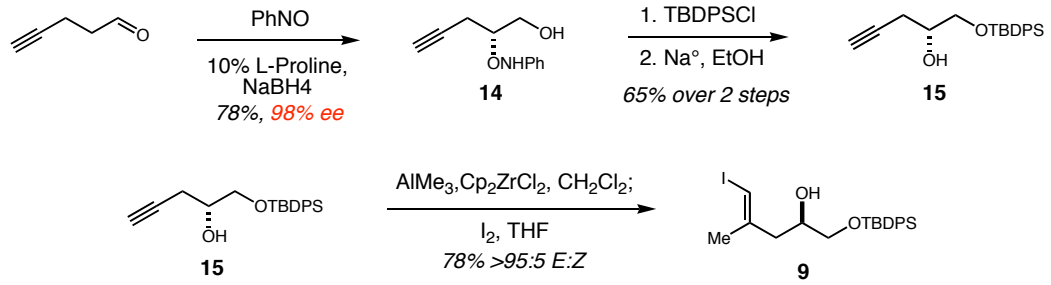
The synthesis of the upper tetrahydropyran fragment **8** commenced with a highly selective (13:1 d.r.) proline-catalyzed cross-aldol reaction between the Roche aldehyde **10** and propionaldehyde (Scheme 5). Addition of propargyl zinc to **11** proceeded in high yield to afford **12**, setting up a Pd (II)-catalyzed alkoxycarbonylation reaction which formed the THP ether in good yield (75%) as a single diastereomer. Protection of the secondary alcohol, followed by saponification afforded acid **13** primed for coupling to iodo-alcohol **9** in just five steps.

Scheme 5. Synthesis of the Upper THP Fragment



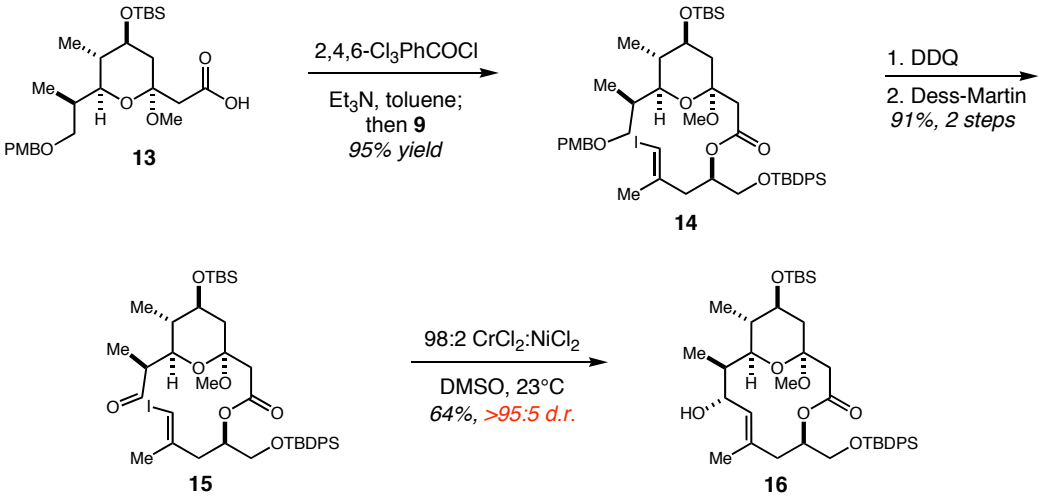
The requisite alcohol **9** was obtained by enantioselective oxidation of 4-pentynal, protection of the resulting primary alcohol **14**, sodium promoted cleavage of the O-N bond to afford **15**, and Negishi methyl-iodination of the terminal alkyne (Scheme 6).

Scheme 6. Synthesis of the Iodoalcohol Fragment



Under Yamaguchi esterification conditions, acid **13** and alcohol **9** were coupled in 95% yield; deprotection, followed by oxidation, provided iodo-aldehyde **15** in 91% yield (2 steps), setting up the penultimate Nozaki-Hiyama-Kishi macrocyclization. The key ring closure was best performed employing DMSO as the solvent with a 98:2 ratio of $CrCl_2$ to $NiCl_2$, providing macrolactone **16** as a single diastereomer (Scheme 7).

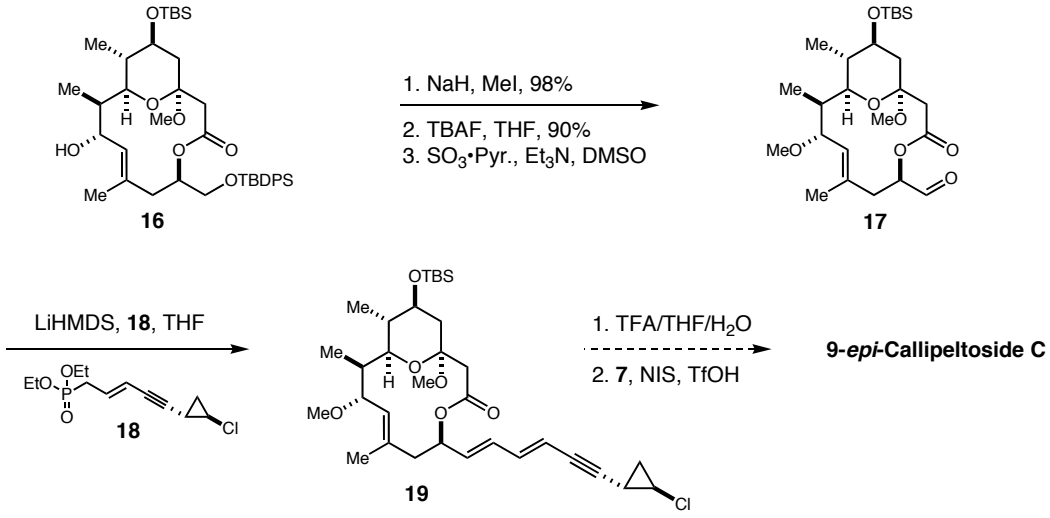
Scheme 7. Elaboration to the Key NHK Cyclization Reaction



Elaboration of macrolactone **16** toward callipeltoside C began with methylation of the C-9 alcohol, selective removal of the primary TBDPS ether in the presence of the secondary

TBS ether, and oxidation to aldehyde **17**. Horner-Wadsworth-Emmons coupling of known phosphonate **18** to aldehyde **17** allowed the determination that the NHK cyclization proceeded with the incorrect stereochemistry (Scheme 8). Therefore, the completion of this synthesis will require the construction of the proper *C*-9 epimer.

Scheme 8. Elaboration of the Macrolactone



Conclusions

The chemistry presented in thesis has demonstrated the power of organocatalytic strategies for the construction of key natural product architectures. Particularly, the development of the enantioselective aldehyde aldol strategy has led to a two-step synthesis of carbohydrates that should constitute a key enabling technology for future developments in glycobiology. Application of that strategy toward the total synthesis of callipeltoside C has also been demonstrated.