# Development of Organocatalytic Direct Aldol Transformations, Total Syntheses of Brasoside and Littoralisone, and Progress Toward the Total Synthesis of Diazonamide A

Thesis by

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# ABSTRACT

The enantioselective amine-catalyzed direct aldol reaction of aldehdyes has been accomplished for the first time using an imidazolidinone organocatalyst. That imidazolidinone catalyst, initially developed for LUMO-lowering activation of α, β-unsaturated aldehydes, provides new insight into amine-mediated aldol transition states. The concepts developed in this study have been applied toward the development of an unprecedented enantioselective Type II direct aldol. In the course of these studies the amino acid proline was also found to be a highly effective catalyst for this transformation. These catalyst systems form the basis for a novel approach to polyketide and polyglycolate architectures, structural motifs having broad representation amongst natural product isolates.

This enamine catalysis strategy was then applied towards the total synthesis of the iridoid natural products brasoside and littoralisone. Direct aldol chemistry was applied towards the synthesis of a substituted carbohydrate structure, and a recently developed enantioselective oxyamination reaction installed a key stereocenter. Stereocontrolled synthesis of the bicyclic core common to the iridoid class of natural products required the development of a new, kinetically controlled organocatalytic intramolecular Michael reaction. A [2+2] photocycloaddition completed the first total synthesis of littoralisone, and demonstrated a likely biosynthetic link to brasoside, which may well be a natural precursor.

An iminium-mediated addition-cyclization cascade reaction has been applied toward the total synthesis of the marine natural product diazonamide A. This strategy has provided stereoselective, catalytic access to the crucial *C*-10 quaternary carbon stereocenter for the first time. A novel intramolecular soft enolization aldol macrocyclization formed a precursor to the A-ring oxazole, which was subsequently completed in a newly discovered DAST-mediated cyclodehydration. Closure of the fourteen-membered biaryl macrocycle has been accessed through an unusual Suzuki macrocyclization, and completion of diazonamide A should be accessible in four further steps.

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# ABBREVIATIONS

| | |
|---|---|
| **$Ac_2O$** | acetic anhydride |
| **AcOH** | acetic acid |
| **Boc** | *tert*-butyl carbamate |
| **BOPCl** | bis(2-oxo-3-oxazolidinyl) phosphinic chloride |
| **Cbz** | carbobenzyloxy |
| **COSY** | correlation spectroscopy |
| **DAST** | diethylamino sulfur trifluoride |
| **DCC** | dicyclohexyl carbodiimide |
| **DDQ** | 2,3-dichloro-5,6-dicyano-1,4-benzoquinone |
| **DIBAL** | diisobutylaluminum hydride |
| **DMF** | dimethylformamide |
| **DMPU** | 1,3-dimethyltetrahydro-2(1*H*)-pyrimidinone |
| **DMSO** | dimethylsulfoxide |
| **DTBMP** | 2,6-di-*tert*-butyl-4-methylpyridine |
| **EtOAc** | ethyl acetate |
| **GLC** | gas liquid chromatography |
| **h** | Hour |
| **HATU** | *O*-7-azabenzotriazol-1-yl-tetramethyl uronium•$PF_6$ |
| **HOBt** | hydroxy benzotriazole |
| **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 |
| **LiHMDS** | lithium hexamethyldisilamide |
| **LUMO** | lowest unoccupied molecular orbital |

| | |
|---|---|
| **MeOH** | methanol |
| **Mes** | 2,4,6-trimethyl benzoate |
| **min** | minutes |
| **MOM** | methoxymethyl |
| **Ms** | methanesulfonyl |
| **MTPA** | α-methoxy-α-(trifluoromethyl)phenyl acetyl |
| **MVA** | mevalonic acid |
| **NMO** | *N*-methylmorpholine-4-oxide |
| **NMP** | 1-methyl pyrrolidin-2-one |
| **NMR** | nuclear magnetic resonance |
| **NOE** | Nuclear Overhauser effect |
| **Nu** | nucleophile |
| **Piv** | trimethylacetyl |
| **PMB** | *para*-methoxybenzyl |
| ***p*-TSA** | *para*-toluenesulfonic acid |
| **PyBroP** | bromo tripyrrolidinophosphonium•$PF_6$ |
| **PyClU** | chloro tetramethylformadinium•$PF_6$ |
| **Pyr** | pyridine |
| **TBDPS** | *Tert*-butyldiphenylsilyl |
| **TBDPSCl** | *tert*-butylchlorodiphenylsilane |
| **TBS** | *Tert*-butyldimethylsilyl |
| **TBSCl** | *Tert*-butylchlorodimethylsilane |
| **TBSOTf** | *Tert*-butyldimethylsilyl trifluoromethanesulfonate |
| **TBTU** | *O*-benzotriazol-1-yl-tetramethyl uronium•$BF_4$ |
| **TCA** | trichloroacetic acid |
| **TES** | triethylsilyl |
| **TESCl** | chlorotriethylsilane |
| **TFA** | trifluoroacetic acid |

| | |
|---|---|
| **Tf** | trifluoromethanesulfonyl |
| **TfOH** | trifluoromethanesulfonic acid |
| **THF** | tetrahydrofuran |
| **TIPS** | triisopropylsilyl |
| **TLC** | Thin layer chromatography |
| **TMS** | trimethylsilyl |
| **TMSCl** | chlorotrimethylsilane |
| **TPAP** | tetrapropylammonium perruthenate |

*To Erin*

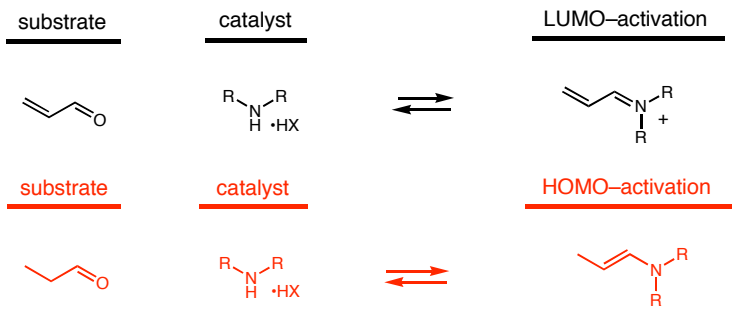
# C h a p t e r 1

## The Imidazolidinone-Catalyzed Direct Aldol Reaction*

### *Enantioselective Enamine-Based Catalysis*

Much of the early work accomplished in the MacMillan lab has focused on LUMO-lowering iminium activation of carbonyls.[1] In analogy to Lewis acid chemistry, the activation imparted by iminium formation provides the mechanistic basis for enantioselective amine catalysis of cycloaddition and conjugate addition processes (figure 1). In principle one could access a broad range of other enantioselective transformations by taking advantage of the enamine intermediate generated by the equilibrium between a secondary amine and a saturated aldehyde. Enamines are well known for their nucleophilic properties,[2] and have found use in reactions with a variety of electrophiles. In particular, they have been recently demonstrated in enantioselective aldol catalysis.[3]

**Figure 1: Iminium and Enamine Intermediates are Targets for Enantioselective Catalysis**

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For a communication of this work, see: Mangion, I. K.; Northrup, A. B.; MacMillan, D. W. C. *Angew. Chem. Int. Ed.* **2004**, *43*, 6722.

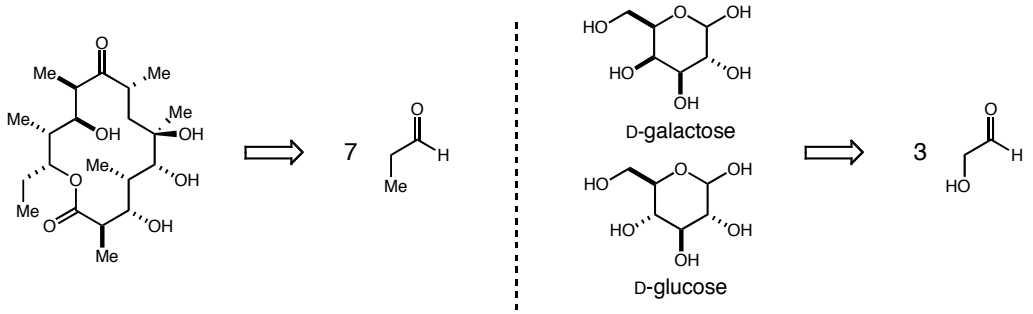
[1] Austin, J. F.; Kim, S-G.; Sinz, C. J.; Xiao, W-J.; MacMillan, D. W. C. *Proc. Nat. Acad. Sci. U.S.A.* **2004**, *101*, 5482, and references therein.

[2] For a comprehensive review see: Hickmott, P. W. *Tetrahedron* **1982**, *38*, 1975.

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

The MacMillan lab has focused on new methods for accessing structural motifs that have broad representation amongst natural products. Two such ubiquitous motifs are

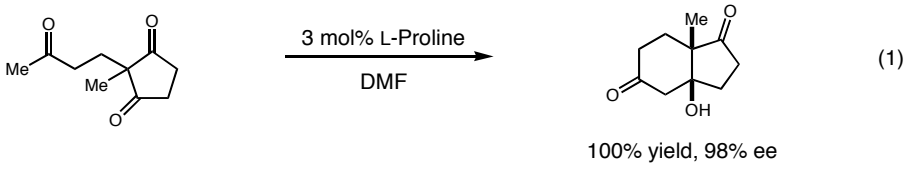
**Figure 2: Direct Aldehyde-Aldehyde Aldol Reaction Generates Common Motifs**




**Erythronolide B: polypropionate synthesis** **Hexoses: polyglycolate synthesis**

those of polypropionates and polyglycolates (figure 2). These structures can be reduced in a retrosynthetic sense as simply being the products of iterative, stereocontrolled aldol additions of aldehydes. In particular, one may think of carbohydrates as being the product of consecutive additions of hydroxyacetaldehydes. We hope to develop a direct aldehyde-aldehyde aldol reaction mediated by a chiral amine source to provide rapid access to these structures.

The basis for this work lies in literature precedent such as the Hajos-Parrish reaction,[4] in which a catalytic intramolecular aldol reaction presumably goes through an enamine intermediate (eq 1). Intermolecular aldol reactions between ketones and aldehydes have also been recently demonstrated by Barbas, List and Lerner.[3] A catalytic

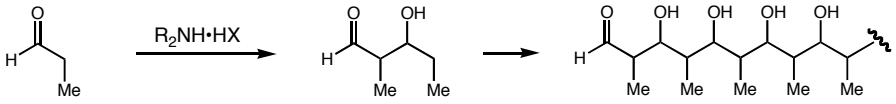



(1)

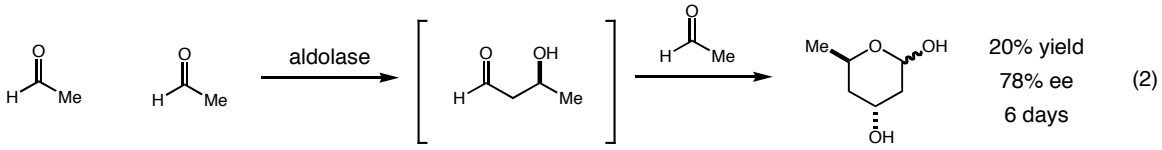
[4] (a) Hajos, Z. G.; Parrish, D. R. *J. Org. Chem.* **1974**, *39*, 1615. (b) Eder, U.; Sauer, G.; Wiechert, R. *Angew. Chem.* **1971**, *10*, 496. (c) Agami, C.; Platzer, N.; Sevestre, H. *Bull. Chim. Soc. Fr.* **1987**, *2*, 358.

enantioselective aldehyde-aldehyde aldol, however, remained unknown at the time these studies began. One reason we thought this might be is that the product of this reaction should be, like the starting materials, an aldehyde. Therefore chemoselectivity will be a critical issue in this aldol process in order to avoid oligomerization (figure 3).

**Figure 3: Chemoselectivity Will Be a Critical Issue in Direct Aldehyde Aldol**



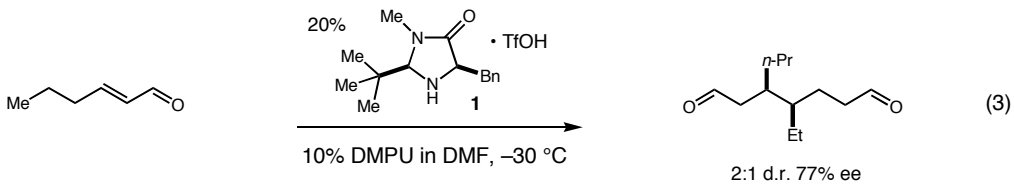

We were particularly interested in work developed in the Wong lab,[5] which demonstrated the ability of an aldolase enzyme to mediate a direct double aldol addition of acetaldehyde (eq 2). The sequential aldol process creates a cyclic acetal, which is inert towards further aldol reaction under the reported conditions. This shows that a second aldol event can provide a self-termination step that allows isolation of a useful, discrete product. Further, the aldolase in question was demonstrated by Wong to perform chemistry by an enamine mechanism. If this same enamine chemistry can apply to small molecule catalysis, then oligomerization should not be an issue in the direct aldehyde aldol.




It had been observed previously in the MacMillan lab[6] that exposure of hexenal to imidazolidinone catalyst **1** under certain conditions will lead to an apparent vinylogous Michael addition process (eq 3). It is envisioned that this product might arise from a dienamine conjugate addition. The moderate level of enantiocontrol is a promising entry

[5] Gijsen, H. J. M.; Wong, C.-H. *J. Am. Chem. Soc.* **1994**, *116*, 8422.

[6] Northrup, A. B.; Goodwin, N. C.; Brown, S. P.; MacMillan, D. W. C. *unpublished results*

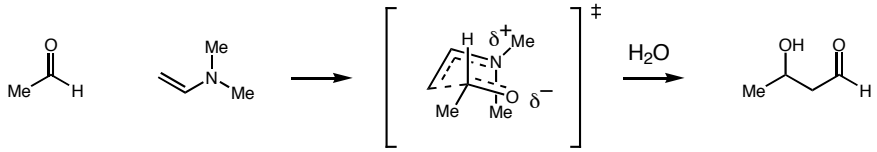



into enamine catalysis, and suggests that **1** can perhaps mediate the direct aldol event we wish to investigate, functioning as a small molecule aldolase.

### *Imidazolidinone Catalysis: Applications to Enamine-Based Reactions*

There was good reason to believe that the imidazolidinone catalyst architecture, which had been carefully optimized to provide enantiodiscrimination in reactions involving iminium ion intermediates, might prove effective as an enamine catalyst. In particular, computational work performed in the Houk group[7] demonstrated that in the transition state of aldol reactions mediated by enamines, formation of the iminium π-bond is very advanced relative to carbon-carbon bond formation (figure 4). Imidazolidinone catalyst **1**

**Figure 4: Houk's Calculated Transition State for Amine-Mediated Aldol Reactions**

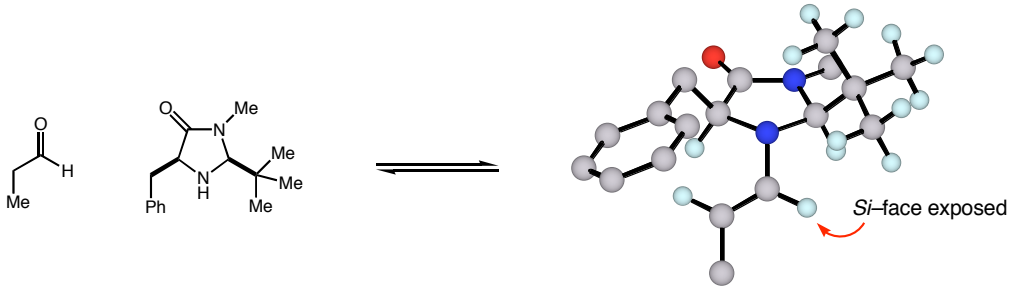



has been designed to provide steric control for iminium-like transition states, and in this instance may enforce a single enamine geometry and provide facial coverage for that olefin (figure 5). The *tert*-butyl group should enforce enamine geometry in this late transition state through nonbonding interactions (in the same fashion as for iminium ions), while the benzyl group should control selective facial blockage. If successful, this enamine catalysis

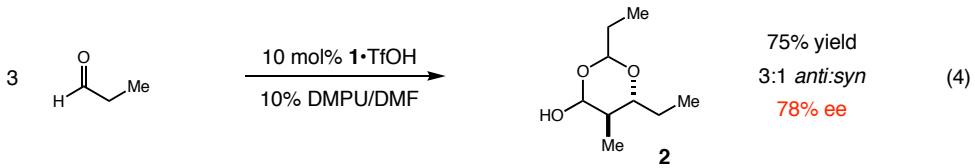
[7] Bahmanyar, S.; Houk, K. N. *J. Am. Chem. Soc.* **2001**, *123*, 11273.

would be a mechanistic platform from which other enantioselective reactions could be derived (e.g., α-oxidation, α-halogenation, etc.)

**Figure 5: Benzyl Group of Imidazolidinone Provides Clear Rationale for Stereocontrol**

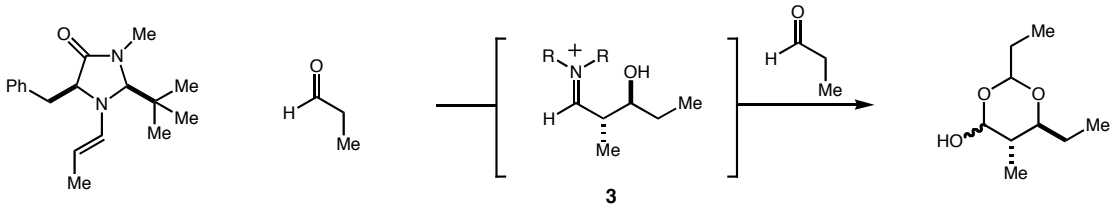



With these design parameters taken into account, propionaldehyde was subjected to a catalytic amount of **1** in conditions similar to those in which the vinylogous Michael reaction was first observed (eq 4). An unexpected product (**2**) was observed that results from a carbon-carbon bond forming event and that appears to contain a latent β-hydroxy aldehyde motif expected from an aldol event. However, a third equivalent of aldehyde has also incorporated itself into this product.



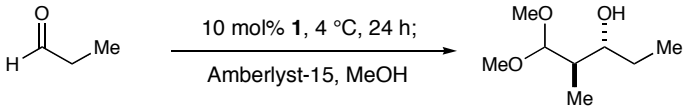

One can imagine this product arising from a transient iminium intermediate (**3**) that is activated towards attack by the excess of aldehyde in solution (figure 6). Cyclization completes the hemiacetal that is observed, providing the self-termination step that is required to avoid a oligomerization process. Unlike Wong's aldolase, the trapping event reported here occurs after a single aldol event.

**Figure 6: Interception of Iminium Intermediate Provides Self-Termination**




The promising enantioselectivity (78% ee) suggested this reaction warranted further development. Solvent was examined for its effect on enantio- and diastereoselectivity in the direct aldol reaction of propionaldehyde (table 1). To increase the utility of the aldol product, methanol and an acid resin (Amberlyst-15) are added to liberate the extraneous equivalent of aldehyde and protect the β-hydroxy aldehyde as its dimethyl acetal when conversion is complete. This creates a bench-stable product that is also simpler to analyze.

**Table 1: Effect of Solvent on Imidazolidinone-Catalyzed Direct Aldol**



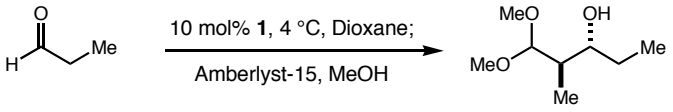

| entry | solvent | yield | *anti*:*syn* | %ee (*anti*) |
|---|---|---|---|---|
| 1 | Hexanes | 89 | 3:1 | 90 |
| 2 | $CH_2Cl_2$ | 66 | 4:1 | 93 |
| 3 | $CHCl_3$ | 42 | 4:1 | 91 |
| 4 | Toluene | 80 | 3:1 | 87 |
| 5 | EtOAc | 91 | 2:1 | 93 |
| 6 | THF | 22 | 2:1 | 90 |
| 7 | $Et_2O$ | 85 | 4:1 | 90 |
| 8 | Dioxane | 92 | 4:1 | 94 |

Dioxane was found to provide the optimal mix of reactivity and selectivity (table 1, entry 8) and was chosen for further study, though a range of solvents proved amenable to our direct aldol.

Further optimization studies focused on the effect of the acid co-catalyst on reactivity and selectivity (table 2). Ultimately, cocatalysts of intermediate ($pK_a$ ~0–1)

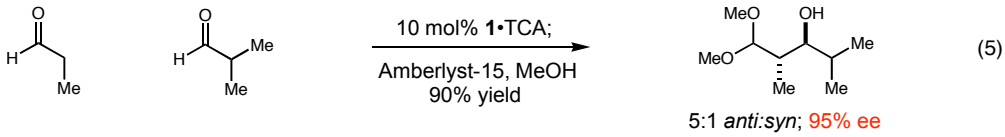
acidity proved to provide the best reactivity. Perhaps by out-competing background reaction this also had the effect of maximizing stereocontrol. Optimal rate should require balance between greater acidity that promotes iminium ion formation and lesser acidity that favors tautomerization to the corresponding enamine.

**Table 2: Effect of Cocatalyst on Imidazolidinone-Catalyzed Direct Aldol**




| acid | pKa ($H_2O$) | yield | *anti*:*syn* | %ee (*anti*) |
|---|---|---|---|---|
| TfOH | -10 | 0 | -- | -- |
| HCl | -6.1 | 0 | -- | -- |
| *p*TSA | -1.34 | 56 | 3:1 | 86 |
| TCA | 0.51 | 98 | 4:1 | 94 |
| TFA | 0.52 | 97 | 4:1 | 92 |
| DFA | 1.34 | 80 | 3:1 | 90 |
| DBA | 1.48 | 54 | 3:1 | 86 |
| Salicylic | 2.98 | 49 | 3:1 | 82 |
| AcOH | 4.76 | 0 | -- | -- |

The key issue in developing a truly useful direct aldol is the ability to perform cross aldol reactions (reactions between structurally discrete aldehydes) in a regioselective manner. Reaction between two different aldehydes could create as many as four regioisomeric products. To partition between these possible pathways, there must be a preference for one aldehyde to act as the nucleophilic aldol donor while the other aldehyde acts as the electrophilic aldol acceptor. This was first explored in the addition of propionaldehyde to isobutyraldehyde, where it was hoped that the increased steric encumbrance of the latter would force it to act as the aldol acceptor (eq 5). This proved to be true, though slow syringe pump addition of propionaldehyde was required to avoid competing homodimerization.



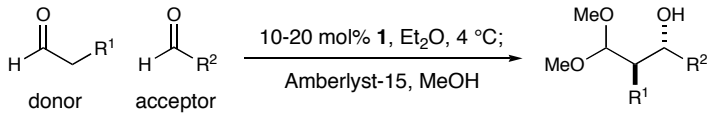

(5)

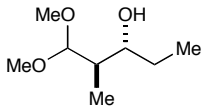
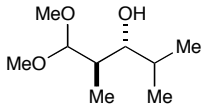
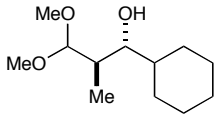
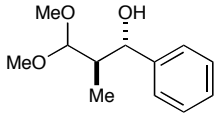
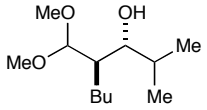
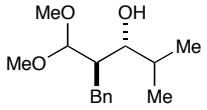
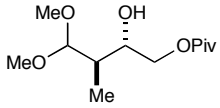
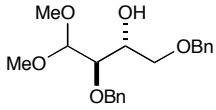
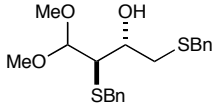
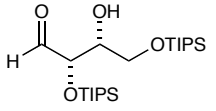
With optimal conditions in hand for cross aldol reactions, a scope study was undertaken to test the limitations of this new process (table 3). It was found that a range of different aldehydes could be applied with complete regiocontrol and high (>90%) enantiomeric excess.[8] In particular, α-alkyl, α-aromatic and α-oxy functionality can all be incorporated into the acceptor component (Entries 1-7, 90% to 97% ee). In an example of electronic rather than steric substrate differentiation, an α-oxy aldehyde was shown to act exclusively as the acceptor in a cross aldol with propionaldehyde (Entry 7, 90% ee). This is presumably because of its greater electrophilicity and also the greater instability of its corresponding iminium that may inhibit the catalyst from condensing with it.

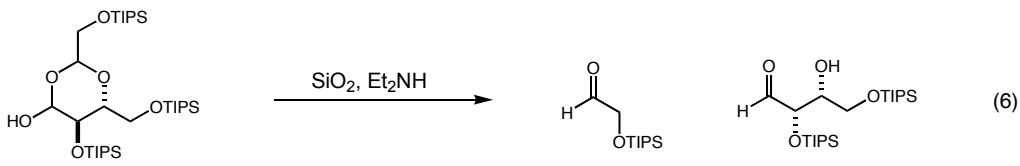
We next examined the capacity of imidazolidinone **1** to catalyze the homodimerization of α-heterosubstituted aldehydes. As shown in entries 8 and 9, exposure of **1** to α-benzyloxy and α-benzylsulfide aldehydes provides the erythrose aldol adduct with high levels of enantiocontrol (92%-97% ee). Silyl protecting groups proved not to be amenable to the acidic conditions of methanolysis, so a new method for opening the intermediate hemiacetals was required. It was observed that purification of the triisopropyl silyloxy hemiacetal on silica gel pretreated with triethylamine led to hydrolysis to the corresponding β-hydroxy aldehyde and one equivalent of free aldehyde. This result proved irreproducible, so further investigation (eq 6) proved that the active agent was actually

[8] Mangion, I. K.; Northrup, A. B.; MacMillan, D. W. C. *Angew. Chem. Int. Ed.* **2004**, *43*, 6722.

**Table 3: Imidazolidinone-Catalyzed Direct Aldol: Substrate Scope**




| entry | $R^1$ | $R^2$ | product | % yield | *anti*:*syn* | % ee |
|---|---|---|---|---|---|---|
| 1 | Me | Et |  | 86 | 4:1 | 94 |
| 2 | Me | *i*-Pr |  | 90 | 5:1 | 95 |
| 3 | Me | *c*-$C_6H_{11}$ |  | 81 | 5:1 | 97 |
| 4 | Me | Ph |  | 61 | 3:1 | 83 |
| 5 | *n*-Bu | *i*-Pr |  | 72 | 6:1 | 91 |
| 6 | Bn | *i*-Pr |  | 80 | 5:1 | 91 |
| 7 | Me | $CH_2OPiv$ |  | 58 | 4:1 | 90 |
| 8 | OBn | $CH_2OBn$ |  | 64 | 4:1 | 92 |
| 9 | SBn | $CH_2SBn$ |  | 84 | 11:1 | 97 |
| 10 | OTIPS | $CH_2OTIPS$ |  | 84 | 1:4 | 92 |




diethylamine (which likely existed in small amounts in the original sample of triethylamine). Interestingly, this opening occurred with epimerization to provide the threose aldol product (Entry 10, 4:1 *syn:anti*, 92% ee), which could well serve as a precursor to the threose hexoses (idose, gulose, galactose, and talose). Though this chemistry is without direct precedent, the hemiacetal hydrolysis is almost certainly an equilibrium process that is driven by chromatographic separation of the two aldehyde components. This fits well with the fact that silica gel and diethyl amine do not induce hydrolysis in solution, as well as with data from the Rychnovsky lab that show the reverse reaction (formation of hemiacetals from β-hydroxy aldehydes) is facile in the presence of an amine base.[9]

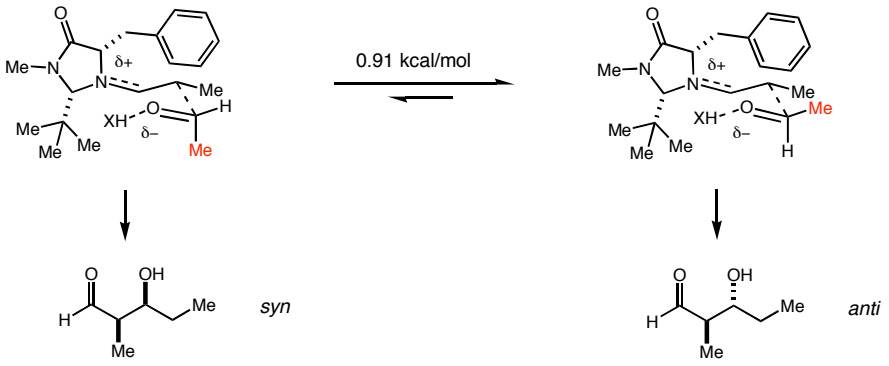
***Stereochemical Rationale***

Both the absolute and relative sense of stereochemistry can be rationalized by the stereochemical model shown in figure 5. Taking into account the theoretical work of Houk (figure 4), a computational approach was taken towards a locating a transition state. While Houk predicts this reaction to be barrierless in the gas phase, a transition state energy can be found for both *syn* and *anti* aldol products given the assumption of a solvated late

[9] Rychnovsky, S. D.; Vaidynathan, R.; Beauchamp, T.; Lin, R.; Farmer, P. J. *J. Org. Chem.* **1999**, *64*, 6849.

transition state (figure 7). These transition structures resemble the Houk model's envelope-type pseudo-cyclic orientation.[10] Though the transition state is nominally acyclic,

**Figure 7: Calculated Transition State for Imidazolidinone-Catalyzed Aldol**




the dipole attraction of the developing iminium ion for the developing alkoxide simulates a five-membered ring. Theoretical prediction is for a 0.91 kcal/mol preference for an *anti*-selective aldol, which matches well with experimental observation. This prediction does not vary much with increased steric bulk of the aldol acceptor, perhaps reflective of the torsional flexibility of this open (Type III)[11] transition state.

Absolute enantioselectivity can be predicted from facial coverage provided by the benzyl group. Control of the enamine geometry can be thought of as arising from allylic strain in the developing iminium ion (figure 8).[12] The steric bulk of the *tert*-butyl group of the imidazolidinone creates a strong non-bonding interaction that favors orientation of the enamine toward the benzyl group. This control is crucial to high enantiocontrol since exposure of the opposite face of the enamine leads to the opposite enantiomer.

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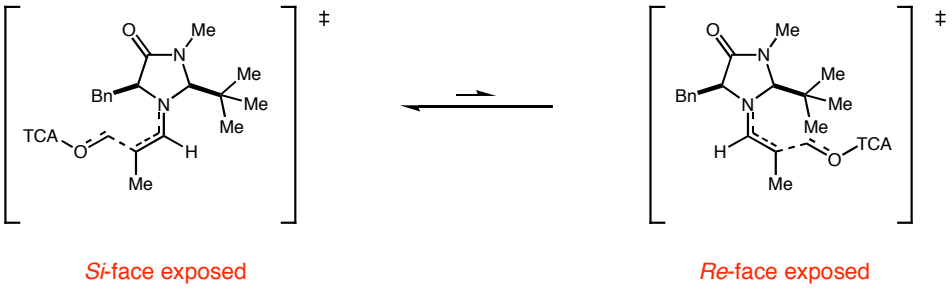
[10] Gaussian 03™ calculation, B3LYP/3-21G(d,p)

[11] Mahrwald, R. *Chem. Rev.* **1999**, *99*, 1095.

[12] Figure from Northrup, A. B.; "Design and Development of New Enantioselective Organocatalytic Transformations, A Two-Step Synthesis of Carbohydrates, and Progress Toward the Total Synthesis of Callipeltoside C", PhD thesis, California Institute of Technology, **2005**.

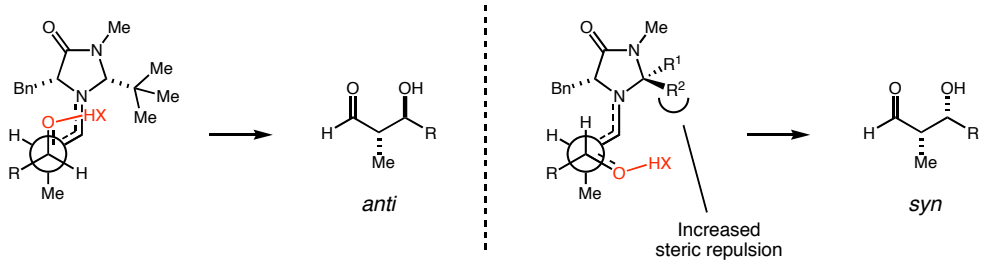
**Figure 8: Allylic Strain Predicts Control of Enamine Geometry**




## *Application Towards a* Syn-*Selective Direct Aldol*

Despite the wealth of aldol chemistry described in the literature,[13] there is no known enantioselective, *syn*-selective direct aldol reaction. This is presumably a consequence of the fact that known direct aldol chemistry[3, 14] typically proceeds via an *E*-enamine or *E*-enolate, and in the context of a chair or chair-like transition state this will favor *anti* selectivity. However, the open transition state postulated for the imidazolidinone-catalyzed aldehyde-aldehyde aldol suggests the possibility of perturbation into a *syn*-selective manifold. Increasing steric encumbrance around the catalyst might drive orientation of the incoming aldehyde such that the oxygen-cocatalyst complex will lie away from this added bulk (figure 9). Doing this will expose the opposite face of that aldehyde to attack, leading

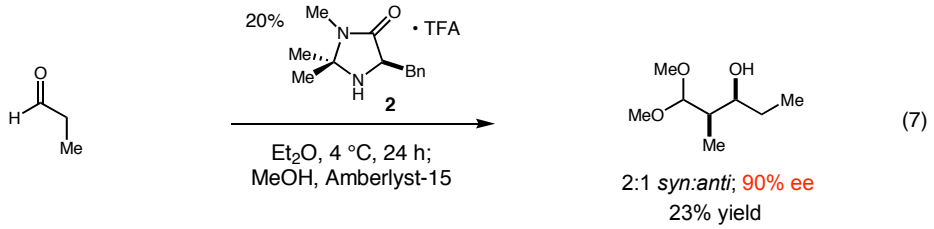
**Figure 9: Possible Model For a *Syn*-Selective Direct Aldol Reaction**




[13] Evans, D. A.; Nelson, J. V.; Taber, T. R. "Stereoselective Aldol Condensations," in *Topics in Stereochemistry* New York: Wileyy, 1982; vol. 13, p. 2.

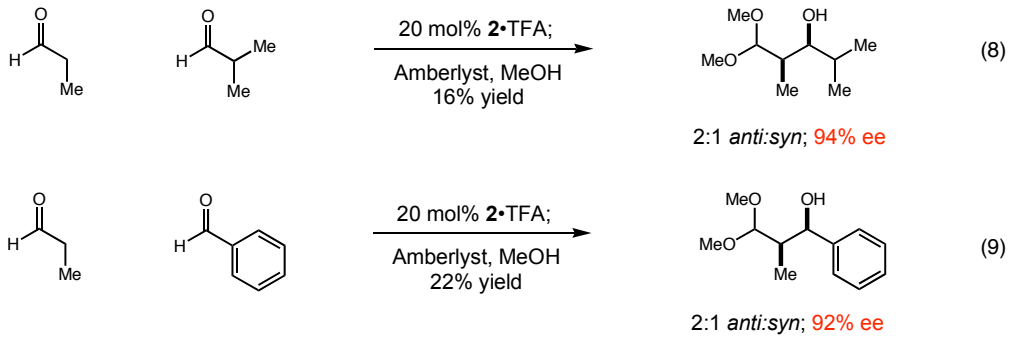
[14] (a) Yoshikawa, N.; Yamada, Y. M. A.; Das, J.; Sasai, H.; Shibasaki, M. *J. Am. Chem. Soc.* **1999**, *121*, 4168; (b) Trost, B. M.; Ito, H. *J. Am. Chem. Soc.* **2000**, *122*, 12003.

to the *syn* diastereomer. This was observed to a modest extent for imidazolidinone **2**, the first generation catalyst developed for iminium catalysis (eq 7). Use of this catalyst in a reaction with propionaldehyde led to aldol reactivity with a small *syn* preference (2:1) and modest yield but high enantioselectivity. This proved true for cross aldol reactions as well, with no loss in enantiocontrol (eq 8, 9).




(7)

Attempts to increase either diastereoselectivity or reaction efficiency by optimization of solvent, cocatalyst or temperature were unsuccessful. Efforts were then devoted toward optimization of the catalyst structure. In general, catalysts with the *gem*-disubstituted frameworks were the only ones that demonstrated any *syn* selectivity, but

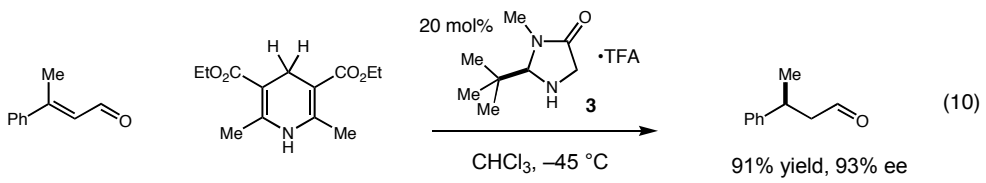



(8)

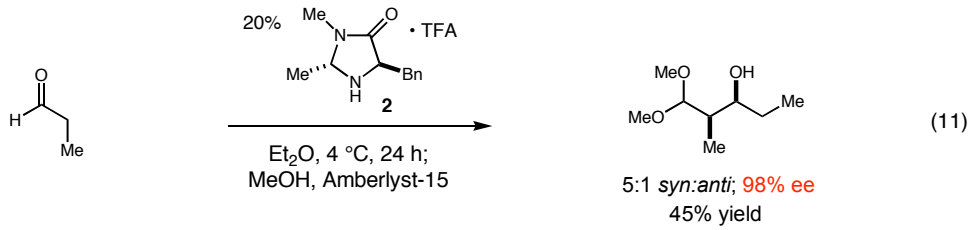
(9)

also tended to have only trace reactivity. At this point, catalyst **3** was demonstrated to be highly effective in the hydride reduction of enals (eq 10).[15] While it was only a marginal

[15] Ouellet, S. G.; Tuttle, J. B.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2005**, *127*, 32.




catalyst for the dimerization of propionaldehyde (83% ee, 3:1 *anti:syn*, 76% yield), it proved an inspiration for a catalyst structure (**4**)[16] that incorporates both the *tert*-butyl group and a *trans*-methyl substituent (as in first-generation **2**). On exposure of **4** to propionaldehyde, the aldol adduct was isolated in 45% yield as a 5:1 *syn:anti* mixture and 98% ee (eq 11).[17] While demonstrating that, in principle, high selectivities can be obtained in this new *syn* aldol process, this result proved to be the best in a series of optimization studies. Further, reactivity dropped off severely when tested in cross aldol




reactions. For these reasons studies were abandoned, but they may provide a suggestive lead as to how to approach a more general *syn*-selective direct aldol process.[18]

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[16] The synthesis of this catalyst has been reported: DeMico, A.; Margarita, R.; Parlanti, L.; Vescovi, A.; Piancatelli, G.; *J. Org. Chem.* **1997**, *62*, 6974; see also: Brown, S. B.; "Iminium and Enamine Activation: Methods for Enantioselective Orgnaocatalysis", PhD thesis, California Institute of Technology, **2005**.

[17] Work performed with Crystal Shih.

[18] For a *syn*-selective decarbonylative aldol reaction see: (a) Magdziak, D.; Lalic, G.; Lee, H. M.; Fortner, K. C.; Aloise, A. D.; Shair, M. D. *J. Am. Chem. Soc.* **2005**, *127*, 7284; for a *syn*-selective reductive aldol see: (b) Russell, A. E.; Fuller, N. O.; Taylor, S. J.; Aurisset, P.; Morken, J. P. *Org. Lett.* **2004**, *6*, 2309, and references therein.

***Conclusions and Future Directions***

The first method for the direct enantioselective aldol coupling of aldehydes has been reported using imidazolidinone catalyst **1**. This catalyst was optimized to provide enantiocontrol for reactions involving iminium ion intermediates, but that appears to be a design principle that is ideal for controlling the transition state of reactions involving nucleophilic enamines. This methodology has proven general for a range of substrates in regioselective cross aldol reactions, and provides a new concept for rapid polyketide or polyglycolate synthesis. These studies have also provided a foundation for development of an unprecedented *syn*-selective direct aldol methodology that would rapidly access valuable *threo* stereochemical motifs. The following chapters will detail the extension of this methodology in the context of proline catalysis, and the application of organocatalytic methods towards the synthesis of natural products.

***Supporting Information***

**General Information.** Commercial reagents were purified prior to use following the guidelines of Perrin and Armarego.[19] Dioxane and diethyl ether were obtained from EM Science 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.[20] 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 Varian Mercury 300 (300 MHz and 75 MHz) Spectrometer 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. 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 β-DM (30 m x 0.25 mm) column or an ASTEC Chiraldex γ-BP (30 m x

0.25 mm) or β-PH (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 (1.6 x 25 cm) and AD guard (1.6 x 5 cm), a Chiralcel OJ column (1.6 x 25 cm) and OJ guard (5 cm), or a Chiralcel ODH column (1.6 x 25 cm) and ODH guard (1.6 x 5 cm), as noted.

**(2*R*, 3*R*)-1,1-Dimethoxy-2-methyl-pentan-3-ol (table 3, entry 1).** Freshly distilled propionaldehyde (621 μL, 8.61 mmol) was added to a stirring 4 ºC solution of (2*S*, 5*S*)-5-benzyl-2-*tert*-butyl-3-methyl-imidazolidin-4-one (70.7 mg, 0.287 mmol) and trichloroacetic acid (46.9 mg, 0.287 mmol) in dioxane (8.6 mL). After 36 h methanol (14.4 mL) and Amberlyst-15 (359 mg) were added in one portion. The solution was stirred until the reaction was judged complete by TLC analysis (1 h). The Amberlyst-15 resin was removed by filtration through a fritted filter, and the filtrate was concentrated *in vacuo*. Flash chromatography (85:15 pentane:$Et_2O$) afforded the title compound as a clear, colorless oil in 86% yield (400 mg, 2.46 mmol), 94% ee and 4:1 *anti*:*syn*. IR (film) 3457, 2966, 2934, 2868, 1463, 1432, 1382, 1099, 1069, 977.5, 945.6 $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$) δ 4.28 (d, 1H, *J* = 6.3 Hz, C**H**$(OCH_3)_2$); 3.50 (m, 1H, C**H**OH); 3.42 (s, 3H, OC$\mathbf{H_3}$); 3.35 (s, 3H, OC$\mathbf{H_3}$); 1.84 (m, 1H, C**H**$CH_3$); 1.59 (m, 1H, C$\mathbf{H_2}CH_3$); 1.37 (m, 1H, C$\mathbf{H_2}CH_3$); 0.95 (t, 3H, *J* = 7.2 Hz, $CH_2C\mathbf{H_3}$); 0.86 (d, 3H, *J* = 6.6 Hz, CHC$\mathbf{H_3}$); $^{13}C$ NMR (75 MHz, $CDCl_3$) δ 109.0, 74.1, 55.9, 53.5, 40.6, 27.4, 12.0, 9.7; HRMS (CI) exact mass calculated for $[M + H]^+$ ($C_8H_{19}O_3$) requires *m/z* 163.1334, found *m/z* 163.1340. $[\alpha]_D$ = 34.06 (c = 1.0, $CHCl_3$). The product ratios were determined by GLC analysis of the *tert*-

butyl carbonate derived from the product alcohol by the method of Hassner[3] using a Bodman Chiraldex β-PH (30 m x 0.25 mm) column (80 ºC isotherm, 14 psi); (2*R*, 3*R*) *anti* isomer $t_r$ = 85.8 min, (2*S*, 3*S*) *anti* isomer $t_r$ = 90.8 min, (2*R*, 3*S*) and (2*S*, 3*R*) *syn* isomers $t_r$ = 82.9, 104.5 min.

**(2*R*, 3*R*)-1,1-Dimethoxy-2,4-dimethyl-pentan-3-ol (table 3, entry 2).** A 4 ºC solution of freshly distilled propionaldehyde (76.8 $\mu$L, 1.06 mmol) in 0.88 mL $Et_2O$ was added slowly over the course of 36 h to a stirring suspension of isobutyraldehyde (976 $\mu$L, 10.6 mmol), (2*S*, 5*S*)-5-benzyl-2-*tert*-butyl-3-methyl-imidazolidin-4-one (52.4 mg, 0.213 mmol) and trifluoroacetic acid (16.4 $\mu$L, 0.213 mmol) in $Et_2O$ (1.2 mL) at 4 ºC. After 37 h methanol (5.32 mL) and Amberlyst-15 (133 mg) were added in one portion. The solution was stirred until the reaction was judged complete by TLC analysis (4 h). The Amberlyst-15 resin was removed by filtration through a fritted filter, and the filtrate was concentrated *in vacuo*. Flash chromatography (4:1 pentane:$Et_2O$) afforded the title compound as a clear, colorless oil in 90% yield (181 mg, 0.961 mmol), 95% ee and 5:1 *anti*:*syn*. IR (film) 3504, 2961, 2923, 2871, 1457, 1387, 1105, 1073, 996.3 $cm^{-1}$; $^1$H NMR (300 MHz, $CDCl_3$) δ 4.30 (d, 1H, *J* = 5.7 Hz, C**H**$(OCH_3)_2$); 3.49 (d, 1H, *J* = 2.1 Hz, CH**OH**); 3.42 (s, 3H, OC**H$_3$**); 3.36 (m, 4H, C**H**OH, OC**H$_3$**); 1.88 (m, 1H, C**H**$CH_3$); 1.76 (m, 1H, C**H**$(CH_3)_2$); 0.98 (d, 3H, *J* = 6.6 Hz, C**H$_3$**); 0.85 (d, 6H, *J* = 7.8 Hz, CH(C**H$_3$**)**$_2$**); $^{13}$C NMR (75 MHz, $CDCl_3$) δ 109.3, 77.2, 56.2, 53.6, 38.8, 30.2, 20.6, 14.9, 11.9; HRMS (CI) exact mass calculated for $[M + H]^+$ ($C_9H_{21}O_3$) requires *m/z* 177.1492, found *m/z* 177.1487. $[\alpha]_D$ = 20.4 (c = 1.0, $CHCl_3$). The product ratios were determined by GLC analysis using a Bodman Chiraldex β-DM (30 m x 0.25 mm) column (70 ºC isotherm, 12

psi); (2*R*, 3*R*) *anti* isomer $t_r$ = 62.0 min, (2*S*, 3*S*) *anti* isomer $t_r$ = 59.0 min, (2*R*, 3*S*) and (2*S*, 3*R*) *syn* isomers $t_r$ = 65.0 min.

**(1*R*, 2*R*)-1-Cyclohexyl-3,3-dimethoxy-2-methyl-propan-1-ol (table 3, entry 3).** A 4 ºC solution of freshly distilled propionaldehyde (76.6 $\mu$L, 1.06 mmol) in 0.92 mL $Et_2O$ was added slowly over the course of 36 h to a stirring suspension of cyclohexanecarboxaldehyde (1.28 mL, 10.6 mmol), (2*S*, 5*S*)-5-benzyl-2-*tert*-butyl-3-methyl-imidazolidin-4-one (52.2 mg, 0.212 mmol) and trifluoroacetic acid (16.3 $\mu$L, 0.212 mmol) in $Et_2O$ (1.00 mL) at 4 ºC. After 44 h methanol (5.30 mL) and Amberlyst-15 (130 mg) were added in one portion. The solution was stirred until the reaction was judged complete by TLC analysis (6 h). The Amberlyst-15 resin was removed by filtration through a fritted filter, and the filtrate was concentrated *in vacuo*. Flash chromatography (97:3 pentane:$Et_2O$) afforded the title compound as a clear, colorless oil in 81% yield (186 mg, 0.860 mmol), 97% ee and 5:1 *anti*:*syn*. $^1$H NMR, $^{13}$C NMR, and IR data are consistent with those already reported.[21] $[\alpha]_D$ = 14.0 (c = 1.0, MeOH); lit: $[\alpha]_D$ = 0.5 (c = 1.12, MeOH); 19% ee. The product ratios were determined by GLC analysis of the acetate derived from the product alcohol by the method of Khorana[4] using a Bodman Chiraldex β-DM (30 m x 0.25 mm) column (105 ºC isotherm, 12 psi); (1*R*, 2*R*) *anti* isomer $t_r$ = 103.8 min, (1*S*, 2*S*) *anti* isomer $t_r$ = 103.4 min, (1*R*, 2*S*) and (1*S*, 2*R*) *syn* isomers $t_r$ = 106.0 min.

**(1*R*, 2*R*)-3,3-Dimethoxy-2-methyl-1-phenyl-propan-1-ol (table 3, entry 4).** A 4 ºC solution of freshly distilled propionaldehyde (66.7 $\mu$L, 0.925 mmol) in 0.83 mL $Et_2O$

was added slowly over the course of 36 h to a stirring suspension of benzaldehyde (940 $\mu$L, 9.25 mmol), (2*S*, 5*S*)-5-benzyl-2-*tert*-butyl-3-methyl-imidazolidin-4-one (45.6 mg, 0.185 mmol) and trichloroacetic acid (30.2 mg, 0.185 mmol) in $Et_2O$ (0.95 mL) at 4 ºC. After 48 h methanol (4.60 mL) and Amberlyst-15 (240 mg) were added in one portion. The solution was stirred until the reaction was judged complete by TLC analysis (1 h). The Amberlyst-15 resin was removed by filtration through a fritted filter, and the filtrate was concentrated *in vacuo*. Flash chromatography (4:1 pentane:$Et_2O$) afforded the title compound as a clear, colorless oil in 61% yield (109 mg, 0.518 mmol), 83% ee and 3:1 *anti*:*syn*. $^1$H NMR, $^{13}$C NMR, and IR data are consistent with those already reported.[21] $[\alpha]_D = -13.06$ (c = 1.0, MeOH); lit: $[\alpha]_D = -16.20$ (c = 1.06, MeOH). The product ratios were determined by GLC analysis using a Bodman Chiraldex β-DM (30 m x 0.25 mm) column (120 ºC isotherm, 12 psi); (1*R*, 2*R*) *anti* isomer $t_r$ = 75.6 min, (1*S*, 2*S*) *anti* isomer $t_r$ = 80.6 min, (2*R*, 3*S*) and (2*S*, 3*R*) *syn* isomers $t_r$ = 86.1 min.

**(3*R*, 4*R*)-4-Dimethoxymethyl-2-methyl-octan-3-ol (table 3, entry 5).** A 4 ºC solution of freshly distilled hexanal (165 $\mu$L, 1.37 mmol) in 0.80 mL $Et_2O$ was added slowly over the course of 36 h to a stirring suspension of isobutyraldehyde (1.18 mL, 13.7 mmol), (2*S*, 5*S*)-5-benzyl-2-*tert*-butyl-3-methyl-imidazolidin-4-one (67.5 mg, 0.274 mmol) and trifluoroacetic acid (21.1 $\mu$L, 0.274 mmol) in $Et_2O$ (1.0 mL) at 4 ºC. After 40 h methanol (6.9 mL) and Amberlyst-15 (171 mg) were added in one portion. The solution was stirred until the reaction was judged complete by TLC analysis (4 h). The Amberlyst-15 resin was removed by filtration through a fritted filter, and the filtrate was concentrated *in vacuo*. Flash chromatography (5:1 pentane:$Et_2O$) afforded the title

compound as a clear, colorless oil in 72% yield (202 mg, 0.801 mmol), 91% ee and 6:1 *anti*:*syn*. IR (film) 3520, 2956, 2932, 2872, 1467, 1379, 1365, 1200, 1188, 1101, 1074, 996.5 $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$) δ 4.42 (d, 1H, $J$ = 3.9 Hz, C**H**$(OCH_3)_2$); 3.42 (s, 3H, OC**H**$_3$); 3.40 (s, 3H, OC**H**$_3$); 3.34 (m, 2H, CH**OH**, C**H**OH); 1.76 (m, 2H, C**H**CH$(OCH_3)_2$, C**H**$(CH_3)_2$); 1.48-1.18 (m, 6H, CH(C**H**$_2$)$_3$CH$_3$); 0.94-0.85 (m, 9H, CH(**CH**$_3$)$_2$, $(CH_2)_3$C**H**$_3$); $^{13}C$ NMR (75 MHz, $CDCl_3$) δ 108.2, 76.2, 56.5, 55.0, 42.3, 31.3, 29.6, 25.9, 23.5, 20.2, 17.6, 14.4; HRMS (CI) exact mass calculated for $[M - H]^+$ ($C_{12}H_{25}O_3$) requires $m/z$ 217.1804, found $m/z$ 217.1805; $[\alpha]_D$ = 6.40 (c = 1.0, $CHCl_3$). The diastereomeric ratio was determined by $^1H$ NMR integration of the crude product (300 MHz, $CDCl_3$): δ 4.42 (d, 1H, major), 4.39 (d, 1H, minor). The enantiomeric purity was determined by conversion to the (*R*)-MTPA ester derivative and $^1H$ NMR integration (300 MHz, $CDCl_3$): δ 4.07 (d, 1H, major), 4.10 (d, 1H, minor).

**(2*R*, 3*R*)-2-Benzyl-1,1-dimethoxy-4-methyl-pentan-3-ol (table 3, entry 6).** A 4 ºC solution of freshly distilled hydrocinnamaldehyde (132 μL, 1.00 mmol) in 0.86 mL $Et_2O$ was added slowly over the course of 36 h to a stirring suspension of isobutyraldehyde (908 μL, 10.0 mmol), (2*S*, 5*S*)-5-benzyl-2-*tert*-butyl-3-methyl-imidazolidin-4-one (49.3 mg, 0.200 mmol) and trifluoroacetic acid (15.4 μL, 0.200 mmol) in $Et_2O$ (1.0 mL) at 4 ºC. After 40 h methanol (5.0 mL) and Amberlyst-15 (188 mg) were added in one portion. The solution was stirred until the reaction was judged complete by TLC analysis (4 h). The Amberlyst-15 resin was removed by filtration through a fritted filter, and the filtrate was concentrated *in vacuo*. Flash chromatography (4:1 pentane:$Et_2O$) afforded the title compound as a clear, colorless oil in 80% yield (202

mg, 0.801 mmol), 91% ee and 5:1 *anti*:*syn*. IR (film) 3517, 2958, 2873, 2834, 1495, 1453, 1366, 1207, 1111, 1068, 1032, 964.4, 747.5, 700.6 $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$) δ 7.31-7.16 (m, 5H, $C_6\mathbf{H_5}$); 4.30 (d, 1H, *J* = 3.3 Hz, C**H**$(OCH_3)_2$); 3.45 (s, 3H, OC$\mathbf{H_3}$); 3.39 (s, 3H, OC$\mathbf{H_3}$); 3.28 (m, 2H, CHO**H**, **CH**OH); 2.77 (d, 2H, *J* = 7.8 Hz, C$\mathbf{H_2}C_6H_5$); 2.16 (m, 1H, C**H**CH$(OCH_3)_2$); 1.78 (m, 1H, C**H**$(CH_3)_2$); 0.94 (d, 3H, *J* = 6.9 Hz, CH(C$\mathbf{H_3}$)$_2$); 0.86 (d, 3H, *J* = 6.9 Hz, CH(C$\mathbf{H_3}$)$_2$); $^{13}C$ NMR (75 MHz, $CDCl_3$) δ 129.3, 128.6, 128.5, 126.1, 107.9, 75.8, 57.0, 56.1, 44.6, 32.2, 31.7, 19.9, 18.0; HRMS (CI) exact mass calculated for $[M]^+$ ($C_{15}H_{24}O_3$) requires *m/z* 252.1726, found *m/z* 252.1724. $[\alpha]_D$ = –10.78 (c = 1.0, $CHCl_3$). The diastereomeric ratio was determined by $^1H$ NMR integration of the crude product (300 MHz, $CDCl_3$): δ 4.30 (d, 1H, major), 4.08 (d, 1H, minor). The enantiomeric purity was determined by conversion to the (*R*)-MTPA ester derivative and $^1H$ NMR integration (300 MHz, $CDCl_3$): δ 4.05 (d, 1H, major), 4.10 (d, 1H, minor).

**2,2-Dimethyl-propionic acid (2*S*, 3*R*)-2-hydroxy-4,4-dimethoxy-3-methyl-butyl ester (table 3, entry 7).** A 4 ºC solution of freshly distilled propionaldehyde (290 μL, 4.02 mmol) and 2,2-dimethyl-propionic acetoxyacetaldehyde (116 mg, 0.805 mmol) in 0.60 mL $Et_2O$ was added slowly over the course of 36 h to a stirring solution of (2*S*, 5*S*)-5-benzyl-2-*tert*-butyl-3-methyl-imidazolidin-4-one (40.0 mg, 0.161 mmol) and trifluoroacetic acid (12.4 μL, 0.161 mmol) in $Et_2O$ (0.60 mL). After 36 h methanol (4.0 mL) and Amberlyst-15 (200 mg) was added in one portion. The solution was stirred until the reaction was judged complete by TLC analysis (8 h). The Amberlyst-15 resin was removed by filtration through a fritted filter, and the filtrate was concentrated *in vacuo*.

Flash chromatography (95:5 hexanes:acetone) afforded the title compound as a clear, colorless oil in 58% yield (116 mg, 0.467 mmol), 90% ee and 4:1 *anti*:*syn*. IR (film) 3469, 2961, 2929, 1729, 1482, 1462, 1393, 1367, 1286, 1163, 1107, 1071, 945.4 $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$) δ 4.35 (d, 1H, *J* = 5.7 Hz, C**H**$(OCH_3)_2$); 4.22 (dd, 1H, *J* = 11.4, 3.3 Hz, C**H**$_2$OC(O)C$(CH_3)_3$); 4.09 (dd, 1H, *J* = 11.4, 5.4 Hz, C**H**$_2$OC(O)C$(CH_3)_3$); 3.81 (m, 1H, C**H**OH); 3.44 (s, 3H, OC**H**$_3$); 3.40 (s, 3H, OC**H**$_3$); 2.01 (m, 1H, C**H**$CH_3$); 1.21 (s, 9H, C(C**H**$_3)_3$); 0.93 (d, 3H, *J* = 7.2 Hz, $CH_2$C**H**$_3$); $^{13}C$ NMR (75 MHz, $CDCl_3$) δ 108.4, 71.8, 67.1, 56.3, 54.5, 39.1, 38.8, 27.6, 11.7; HRMS (CI) exact mass calculated for $[M + H]^+$ ($C_{12}H_{25}O_5$) requires *m/z* 249.1702, found *m/z* 249.1690. $[\alpha]_D$ = 4.20 (c = 1.0, $CHCl_3$). The product ratios were determined by GLC analysis of the product using a Bodman Chiraldex β-PH (30 m x 0.25 mm) column (120 ºC isotherm, 14 psi); (2*R*, 3*S*) *anti* isomer $t_r$ = 107.8 min, (2*S*, 3*R*) *anti* isomer $t_r$ = 114.7 min, (2*R*, 3*S*) and (2*S*, 3*R*) *syn* isomers $t_r$ = 127.3, 142.4 min.

**(2*R*, 3*R*)-1,3-Bis-benzyloxy-4,4-dimethoxy-butan-2-ol (table 3, entry 8).** Freshly distilled benzyloxyacetaldehyde (621 μL, 8.61 mmol) was added to a –20 ºC stirring solution of (2*S*, 5*S*)-5-benzyl-2-*tert*-butyl-3-methyl-imidazolidin-4-one (81.8 mg, 0.332 mmol) and trichloroacetic acid (54.2 mg, 0.332 mmol) in $Et_2O$ (0.35 mL). After 72 h methanol (2.8 mL) and Amberlyst-15 (138 mg) were added in one portion. The solution was stirred until the reaction was judged complete by TLC analysis (2 h). The Amberlyst-15 resin was removed by filtration through a fritted filter, and the filtrate was concentrated *in vacuo*. Flash chromatography (3:2-2:3 pentane:$Et_2O$, linear gradient) afforded the title compound as a clear, colorless oil in 64% yield (134 mg, 0.387 mmol),

91% ee and 4:1 *anti*:*syn*. IR (film) 3468, 2927, 2862, 1454, 1365, 1325, 1202, 1075, 736.6, 698.2 $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$) δ 7.43-7.22 (m, 10H, $C_6\mathbf{H_5}$); 4.82-4.43 (m, 5H, C**H**$(OCH_3)_2$, C$\mathbf{H_2}C_6H_5$); 4.00 (s, 1H, CHO**H**); 3.65-3.41 (m, 10H, OC$\mathbf{H_3}$, C**H**OH, C$\mathbf{H_2}$OBn, C**H**OBn); $^{13}C$ NMR (75 MHz, $CDCl_3$) δ 128.6, 128.4, 128.2, 128.1, 128.0, 127.9, 127.8, 106.2, 78.9, 78.3, 74.6, 73.6, 71.2, 69.7, 56.6, 56.2; HRMS (CI) exact mass calculated for $[M - H]^+$ ($C_{20}H_{25}O_5$) requires *m/z* 345.1702, found *m/z* 345.1691. $[\alpha]_D$ = –2.48 (c = 1.0, $CHCl_3$). The product ratios were determined by HPLC using a Chiracel OJ and OJ guard column (6% ethanol/hexanes, 1 mL/min): (2*R*, 3*R*) *anti* isomer $t_r$ = 41.7 min, (2*S*, 3*S*) *anti* isomer $t_r$ = 31.4 min, (2*R*, 3*S*) and (2*S*, 3*R*) *syn* isomers $t_r$ = 22.1, 24.8 min.

**Determination of the absolute stereochemistry of (2*R*, 3*R*)-1,3-Bis-benzyloxy-4,4-dimethoxy-butan-2-ol.** (2*S*, 3*S*)-3-Hydroxy-2,3-bis-(benzyloxy)-propionaldehyde (20 mg, 0.067 mmol) was prepared as reported previously[24] and dissolved in MeOH (0.33 mL). Amberlyst-15 (8 mg) was added in one portion with stirring. After 6 h, the Amberlyst-15 resin was removed by filtration through a fritted filter, and the filtrate was concentrated *in vacuo*. Flash chromatography (1:1 pentane:$Et_2O$) afforded (2*S*, 3*S*)-1,3-bis-benzyloxy-4,4-dimethoxy-butan-2-ol as a clear, colorless oil in 64% yield (14 mg, 0.043 mmol); $^1H$ NMR, $^{13}C$ NMR, and IR data match those reported above, but with an opposite rotation: $[\alpha]_D$ = 2.61 (c = 1.0, $CHCl_3$).

**(2*R*, 3*R*)-1,3-Bis-benzylsulfanyl-4,4-dimethoxy-butan-2-ol (table 3, entry 9).** Freshly distilled benzylsulfanylacetaldehyde (300 mg, 1.80 mmol) was added to a 4 ºC

stirring solution of (2*S*, 5*S*)-5-benzyl-2-*tert*-butyl-3-methyl-imidazolidin-4-one (14.8 mg, 0.060 mmol) and trifluoroacetic acid (4.6 $\mu$L, 0.060 mmol) in $Et_2O$ (0.60 mL). After 48 h methanol (2.8 mL) and Amberlyst-15 (138 mg) were added in one portion. The solution was stirred until the reaction was judged complete by TLC analysis (2 h). The Amberlyst-15 resin was removed by filtration through a fritted filter, and the filtrate was concentrated *in vacuo*. Flash chromatography (4:1 pentane:$Et_2O$) afforded the title compound as a clear, colorless oil in 84% yield (192 mg, 0.504 mmol), 97% ee and 11:1 *anti*:*syn*. IR (film) 3464, 3058, 3026, 2918, 2820, 1606, 1582, 1494, 1453, 1117, 1070, 1030, 765.8, 701.8 $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$) δ 7.40-7.18 (m, 10 H, $C_6\mathbf{H_5}$); 4.37 (d, 1H, *J* = 3.3 Hz, C**H**$(OCH_3)_2$); 3.93 (m, 1H, C**H**OH); 3.78 (s, 2H, $C\mathbf{H_2}C_6H_5$); 3.72 (s, 2H, $C\mathbf{H_2}C_6H_5$); 3.35 (s, 6H, $OC\mathbf{H_3}$); 3.18 (m, 1H, C**H**$CH(OCH_3)_2$); 2.87 (dd, 1H, *J* = 7.2, 4.2 Hz, $C\mathbf{H_2}$SBn); 2.54 (dd, 1H, *J* = 13.8, 7.2 Hz, $C\mathbf{H_2}$SBn) $^{13}C$ NMR (75 MHz, $CDCl_3$) δ 138.3, 138.2, 129.4, 129.2, 129.1, 128.7, 127.4, 127.2, 107.7, 70.4, 56.5, 56.4, 51.3, 37.5, 36.7; HRMS (CI) exact mass calculated for $[M - H]^+$ ($C_{20}H_{25}O_3S_2$) requires *m*/*z* 377.1245, found *m*/*z* 377.1253. $[\alpha]_D$ = 15.54 (c = 1.0, $CHCl_3$). The product ratios were determined by HPLC using a Chiracel AD and AD guard column (4% isopropanol/hexanes, 1 mL/min): (2*R*, 3*R*) *anti* isomer $t_r$ = 31.2 min, (2*S*, 3*S*) *anti* isomer $t_r$ = 27.1 min, (2*R*, 3*S*) and (2*S*, 3*R*) *syn* isomers $t_r$ = 43.5 min.

**(2*S*, 3*R*)-3-Hydroxy-2,3-bis-triisopropylsilanoxy-propionaldehyde (table 3, entry 10).** Freshly prepared triisopropylsilanoxy-acetaldehyde (900 mg, 4.17 mmol) was added to a 4 ºC stirring solution of (2*S*, 5*S*)-5-benzyl-2-*tert*-butyl-3-methyl-imidazolidin-4-one (34.2 mg, 0.138 mmol) and trifluoroacetic acid (10.8 $\mu$L, 0.138 mmol) in $Et_2O$

(1.38 mL). After 36 h, the reaction was diluted in $Et_2O$, and then successively washed with saturated aqueous solutions of $NH_4Cl$, $NaHCO_3$, and brine. The organic layer was dried over anhydrous $Na_2SO_4$ and concentrated *in vacuo*. Flash chromatography (40:1 pentane:$Et_2O$) was performed on a silica column prewashed with a solution of diethyl amine (150 mL) in pentane (900 mL), followed by 300 mL of the eluent to remove excess amine. The title compound was obtained from this column as a clear, colorless oil in 84% yield (504 mg, 1.17 mmol), 92% ee, 4:1 *syn:anti*. IR (film) 3559, 2944, 2867, 1729, 1464, 1384, 1248, 1119, 1068, 1015, 996.0, 882.3, 785.8, 683.1 $cm^{-1}$. $^1H$ NMR and $^{13}C$ NMR data are consistent with those already reported,[24] $[\alpha]_D = 0.60$ (c = 1.0, $CHCl_3$).

**Determination of the absolute stereochemistry of (2*S*, 3*R*)-3-Hydroxy-2,3-bis-triisopropylsilanoxy-propionaldehyde.** (2*S*, 3*R*)-3-Hydroxy-2,3-bis-triisopropylsilano-xy-propionaldehyde was reduced and converted to the corresponding benzylidene acetal as reported previously for stereochemical proof.[25] Removal of the silyl groups with TBAF furnished 1,3-(*R*)-O-benzylidine-D-threitol, whose IR, $^1H$ NMR and $^{13}C$ NMR data are consistent with those already reported.[25] $[\alpha]_D = -3.75$ (c = 0.7, MeOH); lit: $[\alpha]_D = -6$ (c = 1.0, MeOH)

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[21] Basel, Y.; Hassner, A., *J. Org. Chem.* **2000**, *65*, 6368.

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[24] Northrup, A. B.; Mangion, I. K.; Hettche, F.; MacMillan, D. W. C. *Angew. Chem., Int. Ed.* **2004**, *43*, 2152.

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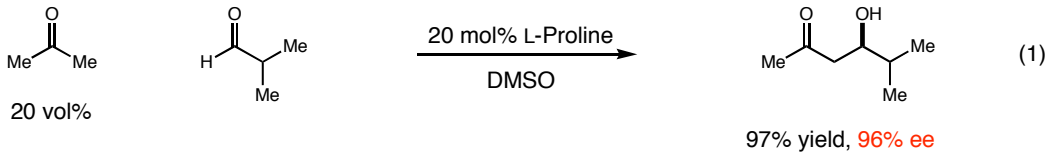
# C h a p t e r 2

## Proline-Catalyzed Direct Aldol Chemistry:

## Application to Carbohydrates*

### *Introduction*

Central to the growing interest in organocatalysis has been the renaissance of proline as an enantioselective catalyst. Beginning with the Hajos-Parrish reaction[1] (see Chapter 1), there has been a high standard for proline catalysis for thirty years. Remarkably, there had been few real advances in proline chemistry until recent work by Barbas, List, and Lerner that demonstrated high enantioselectivities in direct intermolecular aldol reactions between ketones and aldehydes (eq 1).[2] This strategy was




subsequently applied towards a variety of other reactions, including Mannich, conjugate addition, and cycloaddition processes.[3] Despite these advances, we noted that a direct aldehyde-aldehyde aldol had not been reported for proline. This seemed unusual given that proline has proven so effective for other direct aldol events.

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

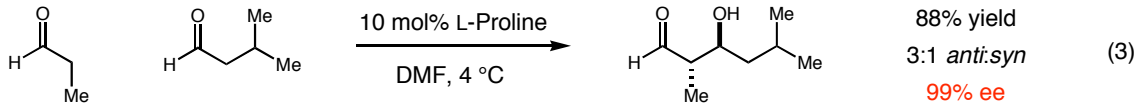
[1] (a) Hajos, Z. G.; Parrish, D. R. *J. Org. Chem.* **1974**, *39*, 1615. (b) Eder, U.; Sauer, G.; Weichert, R. *Angew. Chem. Int. Ed., Eng.* **1971**, *10*, 496.

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

[3] See: (a) List, B.; Pojarliev, P.; Biller, W. T.; Martin, H. J. *J. Am. Chem. Soc.* **2002**, *124*, 827; (b) Ramachary, D. B.; Chowdari, N. S.; Barbas, C. F. III *Angew. Chem. Int. Ed.* **2003**, *42*, 4233.

Given that imidazolidinone catalysts had proven successful in the direct aldehyde aldol, it was perhaps a logical effort to employ proline as a catalyst for the same transformation. A graduate student in our labs, Alan Northrup, attempted to do so using propionaldehyde as a substrate (eq 2). The initial result (96% ee) was exceptional, and


was improved yet further with slight modification of conditions (4:1 *anti:syn*, 99% ee).[4] This method proved amenable to regioselective cross aldol reactions, including the remarkable example shown below in which propionaldehyde can be effectively differentiated from isobutyraldehyde through careful syringe pump addition (eq 3).




Notably these proline-catalyzed reactions provided β-hydroxy aldehydes directly rather than the hemiacetal trimers observed for imidazolidinone catalysis.[5] There are few points of direct evidence to demonstrate why this is the case. However, Alan made the intriguing observation that the resting state of proline in the direct aldehdye aldol (as identified by $^1$H NMR) is *N, O*-acetal **5**[6] (figure 1).[7] He subsequently proposed that such an acetal is the product of a side equilibrium from the catalytic cycle of proline shown

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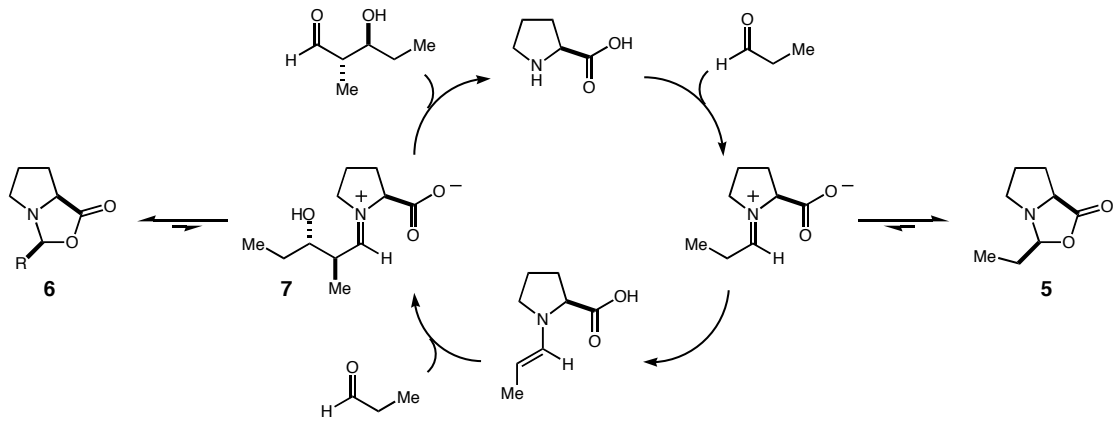
[4] Northrup, A. B.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2002**, *124*, 6798.

[5] Mangion, I. K.; Northrup, A. B.; MacMillan, D. W. C. *Angew. Chem. Int. Ed.* **2004**, *43*, 6722.

[6] Observation of a similar proline acetal has been reported: Orsini, F.; Pelizzoni, F.; Forte, M.; Sisti, M.; Bombieri, G.; Benetollo, F. *J. Heterocyclic Chem.* **1989**, *26*, 837.

[7] A more extensive review of this and other proline aldol work has already been presented: Northrup, A. B.; PhD thesis, California Institute of Technology, **2005**.

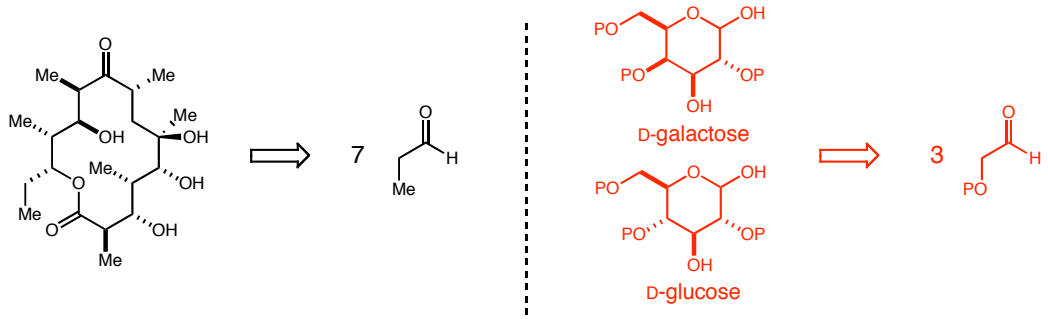
**Figure 1: Proposed Catalytic Cycle for Proline–Catalyzed Aldehyde Aldol**




here. Most of the cycle resembles that which is predicted for imidazolidinone catalysis (intermediacy of an enamine, etc.), but if one makes the assumption that a similar *N, O*-acetal (**6**) forms from product iminium **7**, then catalyst turnover will be dependent on the ability of a nucleophile to turn over **6** or the small equilibrium content of **7**. This acetal should be less reactive than a discrete iminium (as in the imidazolidinone aldol), and therefore might require a stronger nucleophile for turnover than an aldehyde (which would lead to the hemiacetal). Ambient water is assumed to provide that function, with hydrolysis of **6** leading to catalytic turnover.

The advantage of direct access to $\beta$-hydroxy aldehydes is that, in concept, they can be applied in further aldol reactions to try to build polypropionate arrays such as those present in the erythronolides (figure 2). In a similar fashion, one could build carbohydrates enantioselectively in a two-step fashion if protected hydroxyacetaldehydes could be used as substrates in a proline-catalyzed direct aldol. Herein is described studies on precisely such a methodology, performed in collaboration with Alan Northrup and Dr. Frank Hettche.

**Figure 2: Sequential Aldol Can Access Carbohydrates Enantioselectively**

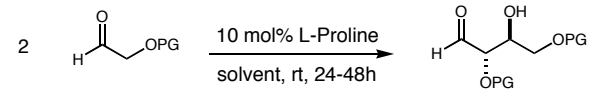


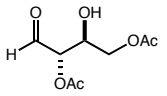
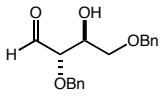
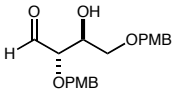
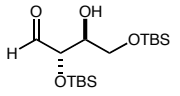
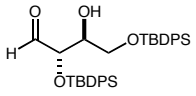
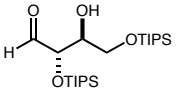
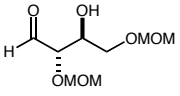

**Erythronolide B: polypropionate synthesis** **Hexoses: polyglycolate synthesis**

***Direct Synthesis of Protected Erythrose Derivatives***

Applying the optimal conditions derived from the previous proline aldol studies in the MacMillan lab,[4] we investigated a range of protected hydroxyacetaldehydes in dimerization reactions (table 1). Preliminary studies revealed that the proposed enantioselective aldol union is indeed possible, however, the electronic nature of the oxyaldehyde substituent has a pronounced effect on the overall efficacy of the process. For example, substrates that possess an electron-withdrawing substituent, such as α-acetoxyacetyaldehyde (Entry 1, 0% yield), do not participate in this transform, while aldehydes bearing relatively electron-rich oxyalkyl groups provide useful levels of enantiocontrol and reaction efficiency (Entry 2, R = Bn, 73% yield, 98% ee; Entry 3, R = PMB, 85% yield, 97% ee). Some of the best results were achieved with aldehydes bearing bulky α-silyloxy substituents (Entry 4, PG = TBS, 50% yield, 88% ee; Entry 5 R = TBDPS, 61% yield, 96% ee) with the TIPS protected glycoaldehyde (Entry 6) affording exceptional reaction efficiency (92%), enantioselectivity (95% ee), and a readily separable 4:1 mixture of *anti* and *syn* diastereomers. It should be noted that all of the dimeric aldol adducts shown in Table 1 constitute protected forms of the naturally occurring sugar erythrose, which we hope to apply as the basis for a two-step synthesis of

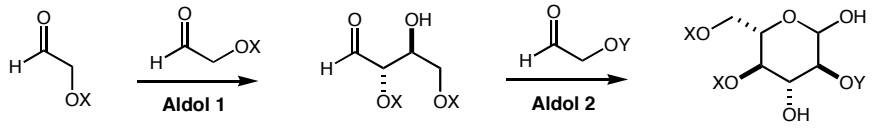
**Table 1. Proline–Catalyzed Aldol Dimerization of Glycoaldehydes**




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

*erythro* hexoses. More importantly, the α-oxyaldehyde products of this new aldol protocol are apparently inert to further proline-catalyzed enolization or enamine addition, a central requirement for controlled stereodifferentiation in the second step of our proposed two-step iterative-aldol carbohydrate synthesis (eq 4).

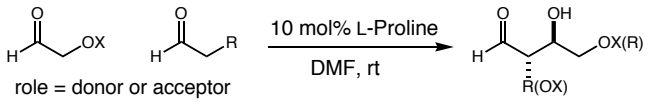


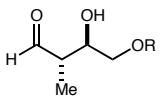
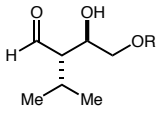
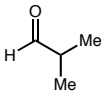
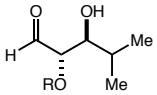

(4)

***Regioselectivity in Proline-Catalyzed Cross-Aldol Reactions***

If this aldol technology can be successfully applied toward carbohydrate synthesis, a key development would be the direct synthesis of unnatural erythrose derivatives by way of regioselective cross-aldols. When incorporated into hexose architectures, these novel structures could potentially serve as probes for biological studies focused on carbohydrates, or could enable the synthesis of unusual and elaborate sugars. As such, we examined the capacity of proline to catalyze the enantioselective cross-coupling of α-oxy- and α-alkyl-substituted aldehydes (table 2). As in the imidazolidinone aldol described in chapter 1, the principal issue in this reaction is that the

**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 |  | OTIPS *acceptor* |  | 75 | 4:1 | 99 |
| 2 | Me *donor* | OTBDPS *acceptor* | | 84 | 5:1 | 99 |
| 3 |  | OTIPS *acceptor* |  | 54 | 4:1 | 99 |
| 4 | *i*-Pr *donor* | OBn *acceptor* | | 64 | 4:1 | 94 |
| 5 |  | OTIPS *donor* |  | 43 | 8:1 | 99 |
| 6 | *acceptor* | 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.

non-equivalent aldehydes must selectively partition into two discrete components, a nucleophilic donor and an electrophilic acceptor. Given that most α-oxy- and α-alkyl

aldehydes we chose to employ bear enolizable protons, we anticipated that such catalyst-controlled substrate partitioning could only function on the basis of electronic, rather than steric, discrimination. Contrary to expectation, the glycoaldehyde invariably acts as the electrophile in the presence of alkyl aldehydes that contain α-methylene protons (Entries 1-4, 94% to 99% ee). Surprisingly, even the sterically demanding isovaleraldehyde assumes the role of nucleophile when exposed to proline and α-benzyloxyacetaldehyde or α-silyloxyacetaldehyde (Entries 3 and 4). However, both triisopropylsilyl and benzyl protected oxyaldehydes can function as aldol donors in the presence of aldehydes that do not readily participate in enamine formation (Entries 5 and 6, 7-8:1 *anti*:*syn*, 96% to 99% ee). It should be noted, however, that significant quantities of glycoaldehyde homodimers are generated in these cases, indicating that homodimerization is a competing process even with concentration control.

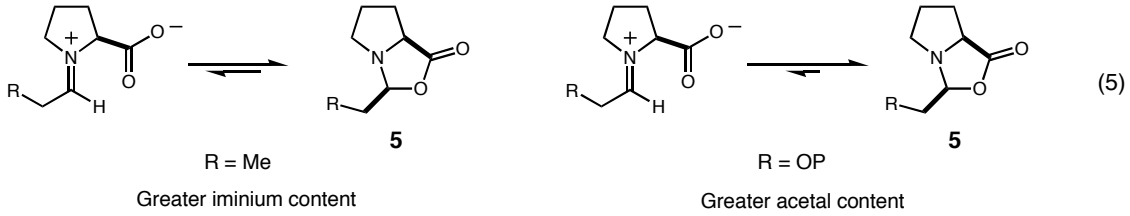
While the exquisite ability of proline to select alkyl aldehydes to act as aldol donors in these cross-aldol reactions was gratifying, it remained to determine the mechanistic origins of this selectivity. These organocatalytic results stand in marked contrast to metal-mediated direct aldol technologies where the increased acidity and nucleophilicity afforded by α-oxygenated aldol donors greatly enhances their reaction efficiency relative to their all-alkyl counterparts.[8] Based on these results one might expect the α-oxygenated aldehydes to act exclusively as the donor. But in general, the reactivity of these aldehydes generally proves to be slower than those of alkyl aldehydes:

---

[8] 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. (c) Trost, B. M.; Ito, H. *J. Am. Chem. Soc.* **2000**, *122*, 12003. (d) Evans, D. A.; Tedrow, J. S.; Shaw, J. T.; Downey, C. W. *J. Am. Chem. Soc.* **2002**, *124*, 392. (e) Evans, D. A.; Downey, C. W.; Shaw, J. T.; Tedrow, J. S. *Org. Lett.* **2002**, *4*, 1127.

the proline-catalyzed dimerization of benzyloxyacetaldehyde requires 42 hours and still fails to go to completion, while the dimerization of propionaldehyde requires only 11 hours.

To rationalize these observations, we returned to consideration of the catalytic cycle shown in figure 1 of this chapter. Qualitatively, one might expect the parasitic equilibrium that produces **5** would be driven further to the right if the aldehyde in question has an electron withdrawing group α to the carbonyl (eq 5). This effect should



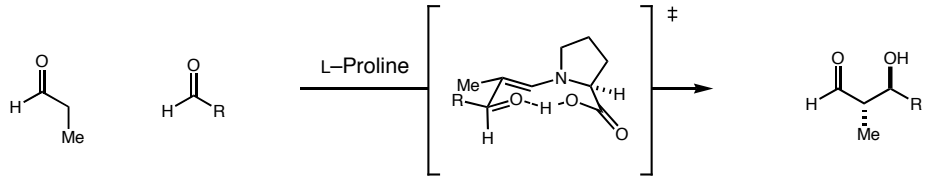

(5)

be especially pronounced for the case of R = OAc, and indeed the complete lack of aldol reactivity of acetoxyacetaldehyde on exposure to proline is consistent with trapping of the catalyst as **5**. We have since observed this acetal by $^1$H NMR in DMF-$d_7$ as a substantial (≥50%) fraction of soluble proline for a range of aldehydes.[6] One can then explain the poorer reactivity of glycoaldehydes as a consequence of the greater electronic instability of their corresponding iminium ions, and therefore greater propensity to exist in an inactive form. One might then predict that electron-releasing protecting groups such as silicon protecting groups might mitigate this destabilizing effect, and therefore allow for a greater iminium character which then leads to higher active enamine content. Their superior reactivity relative to other glycoaldehydes provides circumstantial evidence for this idea. In a similar way, one would predict a greater donor reactivity for the more electron-rich alkyl aldehydes, as is observed.

***Stereochemical Rationale for Proline Aldol***

There have been many models created for the purpose of predicting the stereochemical outcome of reactions mediated by proline. Because it is well supported through *ab initio* computation and matches experimental results closely, I have chosen the Houk model for presentation here (figure 3).[9] This model predicts a closed transition

**Figure 3: Stereochemical Model for Proline-Catalyzed Direct Aldehyde Aldol**




state linked through a nine-membered hydrogen bonding ring. The relative geometries of the enamine and aldehyde simulate a chair-type transition state that favors orientation of the R group of the aldol acceptor into a pseudo-equatorial conformation (pseudo-axial leading to the disfavored *syn* diastereomer). This model correctly predicts both absolute and relative stereochemistry in the aldol reaction, and highlights the remarkable ability of proline to dictate exceptional levels of stereocontrol through its lone chiral center by way of a hydrogen bond activation.

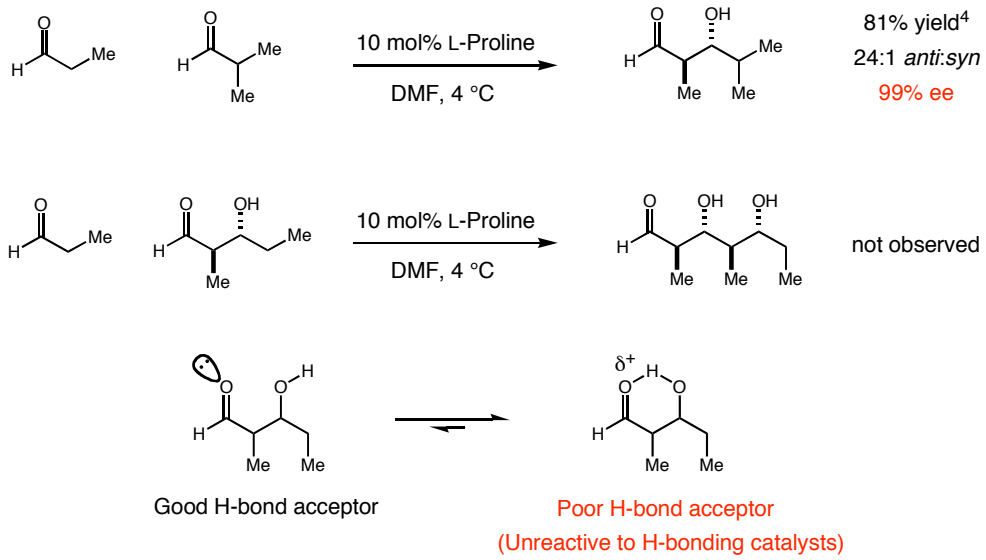
***Development of the Second Step of a Two-Step Carbohydrate Synthesis***

Having secured a direct enantioselective glycoaldehyde aldol reaction, the MacMillan lab began to pursue an iterative aldol approach to carbohydrates. As shown above in equation 4, this now requires the development of an aldol addition of a glycoaldehyde (or its equivalent) to a protected erythrose derivative. However, in the course of our proline studies we had observed only trace reactivity in attempts to add

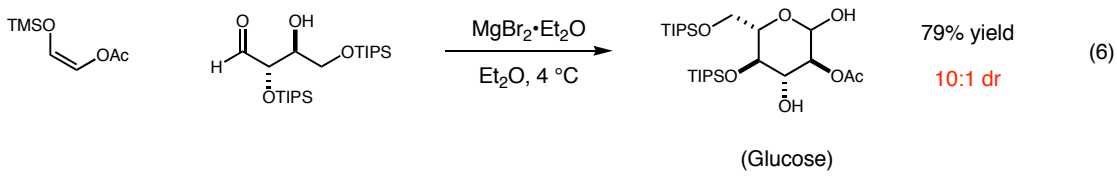
[9] Allemann, C.; Gordillo, R.; Clemente, F. R.; Cheong, P. H.-Y; Houk, K. N. *Acc. Chem. Res.* **2004**, *101*, 5482.

aldehydes directly to β-hydroxy aldehyde aldol products (figure 4). We supposed the poor reactivity of β-hydroxy aldehydes under conditions that seem well suited for α-branched aldehydes (i.e. isobutyraldehyde, Figure 4) meant that these aldol products might engage in an internal hydrogen bond that gives the carbonyl a partial positive charge and renders its free lone pair unreactive towards hydrogen-bond donors (i.e. proline). Given that proline's ability to use hydrogen bonding as an activation method is critical to its reactivity, these observations can make perfect sense.

**Figure 4: β-Hydroxy Aldehydes are Poor Substrates in Direct Aldol**




To overcome this limitation, a new method was envisioned for completing a sequential aldol approach. Alan Northrup developed the use of silyl enol ether equivalents of protected glycoaldehydes in a Lewis acid-mediated aldol reaction with the erythrose derivatives derived from our proline aldol method (eq 6). This approach not only overcomes the poorer reactivity of β-hydroxy aldehydes through metal activation, but also does so in a stereocontrolled fashion that allows selective synthesis of the glucose, mannose, and allose stereochemical arrays through judicious choice of reaction




(6)

conditions.[10] While this chemistry has not yet been successfully applied towards the synthesis of other stereochemical arrays, it demonstrates the possibility of eventually accessing all natural hexoses in a differentially protected form in two chemical steps.

### *Conclusions*

We have completed the development of a new proline-catalyzed direct aldehyde-aldehyde aldol method. This approach allows a one-step, enantioselective synthesis of protected erythrose derivatives from glycoaldehydes for the first time. Completely regioselective cross aldol reactions can also be performed between alkyl and oxygenated aldehydes taking advantage of a mechanism-based electronic differentiation imparted by proline. These erythroses can then be applied in a second, Lewis acid-mediated aldol reaction with silyl enol ether equivalents of aldehydes. This reaction produces differentially protected carbohydrates in a stereocontrolled fashion. Subsequent work shown in chapter 3 will detail efforts to take advantage of this and other applications of enamine catalysis toward the synthesis of natural products.

[10] Northrup, A. B.; MacMillan, D. W. C. *Science* **2004**, *305*, 1753.

***Supporting Information***

**General Information.** Commercial reagents were purified prior to use following the guidelines of Perrin and Armarego.[11] 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.[12] 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

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

[12]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, $CH_2$Ar); 4.48 (d, 1H, *J* = 11.4 Hz, $CH_2$Ar); 4.45 (d, 1H, *J* = 11.1 Hz, $CH_2$Ar); 4.41 (d, 1H, *J* = 11.4 Hz, $CH_2$Ar); 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, $CH_2$OPMB); 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**H$_2$**CHOH); 3.65 (dd, 1H, *J* = 10.0, 6.0 Hz, C**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**H$_3$**)$_3$, CHC**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**H₂**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**H₃**); 0.95 (d, 3H, *J* = 6.9 Hz, C**H₃**); $^{13}C$ 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[13]) using a

[13] 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.[14] 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%

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

yield (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.[15] $[\alpha]_D$ = – 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,

[15]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.

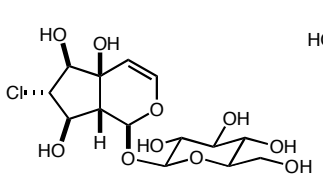
# C h a p t e r 3

## Total Synthesis of Brasoside and Littoralisone*

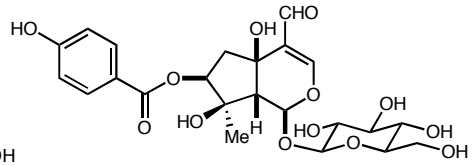
### *Isolation and Biological Activity*

Brasoside and littoralisone are members of a class of natural products commonly referred to as iridoids.[1] These compounds are generally characterized by a bicyclic cyclopentanoid-monoterpene core, around which a variety of oxidation states and substitution patterns have been observed (figure 1). Several hundred iridoids have already been isolated,[2] and they have been found to be ubiquitous in the vegetable kingdom, particularly amongst angiosperms of the superorder of *Sympetalae*.[3] Iridoids have found use as medicinal agents for a variety of folk medicines, and are now known for use as sedatives, analgesics, diuretics and antimicrobials.[4] Leaf extracts of *Verbena*

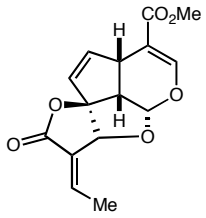
**Figure 1: Some Representative Iridoids**



**Thunbergioside**



**Tecomoside**



**Plumericin**

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* For a communication of this work, see: Mangion, I. K.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2005**, *127*, 3696.

[1] For reviews on the iridoid class of natural product, see: (a) Isoe, S. *Studies in Natural Products Chemistry,* vol. 16; Atta-ur-Rahman, ed., Elsevier Science, New York, **1995**; (b) Bianco, A. *Studies in Natural Products Chemistry,* Vol. 7; Atta-ur-Rahman, ed., Elsevier Science, New York, **1990**; (c) Franzyk, H. *Fortschritte der Chemie Org. Naturstoffe* **2000**, *79*, 1.

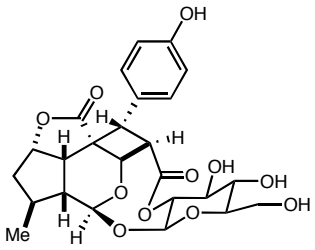
[2] For compilations of iridoid structures see: (a) El-Naggar, L. J.; Beal, J. L. *J. Nat. Prod.* **1980**, *43*, 649; (b) Boros, C. A.; Stermitz, F. R. *J. Nat. Prod.* **1991**, *53*, 1055; (c) Boros, C. A.; Stermitz, F. R. *J. Nat. Prod.* **1991**, *54*, 1173.

[3] Jensen, S. R.; Nielsen, B. J.; Dahlgren, R. *Botaniska Notisier* **1975**, *128*, 148.

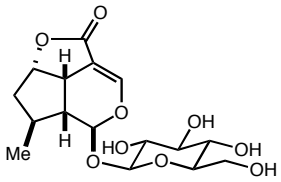
[4] For reviews on biological activities of irioid natural products, see: (a) Buzogany, K.; Cucu, V. *Farmacia*, **1983**, *31*, 129.; (b) Tietze, L.-F. *Angew. Chem. Int. Ed.* **1983**, *22*, 828.

*littoralis*, a plant used widely in traditional folk remedies for typhoid fever and tonsillitis, possess intriguing activity as enhancers for the neurotrophic properties of nerve growth factor (NGF).[5] Littoralisone (**1**, Figure 2), isolated by Ohizumi in 2001, was demonstrated to be the active agent for increased NGF-induced neurite outgrowth in PC12D cells.[6] As such, it is a prominent member of a small but growing class of natural non-peptidic neurotrophic agents with potential implications for the treatment of Alzheimer's disease.[7]

**Figure 2: Structures of Littoralisone and Brasoside**




**Littoralisone (1)**




**Brasoside (2)**

Littoralisone is also a uniquely complex member of the iridoid class of natural products. Synthetic challenges include the presence of four- and nine-membered rings as well as fourteen stereocenters, all within the context of a dense heptacyclic framework. Littoralisone shares several key structural features with brasoside[8] (**2**) and indeed may be biosynthetically derived from **2**, though no intermediates on such a pathway have been isolated. We sought to design a rapid organocatalytic approach to **1** that would also allow access to **2** from a common intermediate. This analysis began with a consideration of the biosynthesis of **1** and other iridoids.

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[5] Umana, E.; Castro, O. *Int. J. Crude Drug Res.* **1990**, *28*, 175.

[6] Li, Y.-S.; Matsunaga, K.; Ishibashi, M.; Ohizumi, Y. *J. Org. Chem.* **2001**, *66*, 2165.

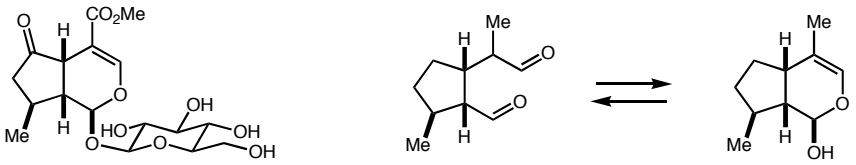
[7] Hefti, F. *Annu. Rev. Pharmacol. Toxicol.* **1997**, *37*, 239.

[8] (a) Schafer, B.; Rimpler, H. *Z. Naturforsch*, **1979**, *34*, 311; (b) Franke, A.; Rimpler, H. *Phytochemistry*, **1987**, *26*, 3015; (c) Jensen, S. R.; Kirk, O.; Nielsen, B. J.; Norrestam, R. *Phytochemistry* **1987**, *26*, 1725.

***Biosynthesis of Iridoid Natural Products***

The first known isolation of an iridoid is credited to Geiger as early as 1835,[9] with subsequent reisolation from *Verbena officinalis* in 1908 by Boudier,[10] who named it verbenalin (**3**). However, the name "iridoid" arose in 1956 from Cavill et al.,[11] who isolated a 1,5-dialdehydic compound they named iridodial (**4**) after the Australian ant from which it was derived (*Iridomyrmex detectus*). Iridodial represents the basic skeleton

**Figure 3: Verbenalin and Iridodial**




**Verbenalin (3)** **Iridodial (4)**

of the vast majority of iridoids, and it is noteworthy that it exists as an equilibrium mixture of lactol and dialdehyde forms. This observation led to the supposition that iridoids are only stable when the lactol is locked in a glycosidic or ether bond, a notion that has been borne out by total synthetic efforts.[12]

Several biosynthetic pathways have been proposed to explain the molecular origins of iridoids, though now the most commonly accepted is the mevalonic acid (MVA) pathway[13] (Scheme 1). On the basis of $^{14}C$ labeling, it was determined that mevalonic acid is incorporated into presumed iridodial precursor **5**. This labeling was

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[9] Geiger, P. L. *Ann.* **1835**, *14*, 206.

[10] Boudier, L. *Compt. Rend. Soc. Biol.* **1908**, *63*, 367.

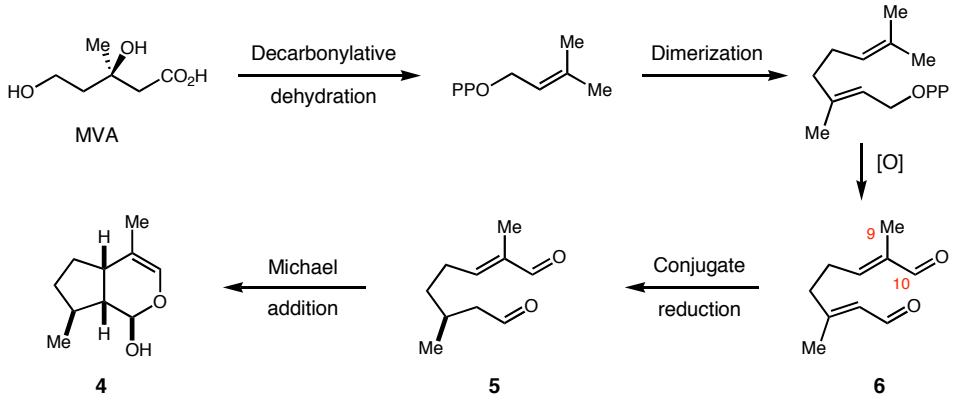
[11] Cavill, G. W. K.; Ford, D. L.; Locksley, H. D. *Aust. J. Chem.* **1956**, *9*, 288.

[12] For related iridoid syntheses see: (a) Büchi, G.; Carlson, J. A.; Powell, J. E.; Tietze, L.-F. *J. Am. Chem. Soc.* **1970**, *92*, 2165; (b) Callant, P.; Ongena, R.; Vandewalle, M. *Tetrahedron* **1981**, *37*, 2085; (c) Callant, P.; Storme, P.; Van der Eycken, E.; Vandewalle, M. *Tetrahedron Lett.* **1983**, *24*, 5797; (d) Trost, B. M.; Balkovec, J. M.; Mao, M. K.-T. *J. Am. Chem. Soc.* **1986**, *108*, 4974; (e) Laabassi, M.; Gree, R. *Tet. Lett.* **1988**, *29*, 611; (f) Piccinini, P.; Vidari, G.; Zanoni, G. *J. Am. Chem. Soc.* **2004**, *126*, 5088, and references therein.

[13] Inouye, H.; Uesato, S. *Prog. Chem. Org. Nat. Prod.* **1986**, *50*, 169.

also observed in iridodial itself, lending credence to the conclusion that **4** arises directly from **5**, perhaps by way of an enzyme-mediated Michael addition.[14] Iridodial may then serve as the synthetic precursor for a range of more complex iridoids through subsequent oxidations.

**Scheme 1: The Mevalonic Acid Pathway to Iridoids**




Further studies have suggested modified pathways, including a direct hydride reduction/Michael cyclization leading directly from 10-oxoneral (**6**) to **4**,[15] or oxidation to 9,10-dioxoneral with subsequent Michael addition.[16] Recent work from Pagnoni suggests that more than one pathway may be operative depending on the iridoid in question, and also on the plant source from which it is derived.[17]

Iridoids have also been identified through isotopic labeling studies as biosynthetic precursors to the non-tryptophan portions of indole alkaloids, such as catharanthine and aspidospermidine.[13] Heathcock and Ruggeri postulated the intermediacy of an iridoid, produced by an intramolecular enamine/enal cyclization mediated by a pyridoxal

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[14] (a) Coscia, C. J.; Guarnaccia, R. *J. Am. Chem. Soc.* **1967**, *89*, 1280; (b) Coscia, C. J.; Guarnaccia, R. *Biochemistry* **1969**, *8*, 5036.

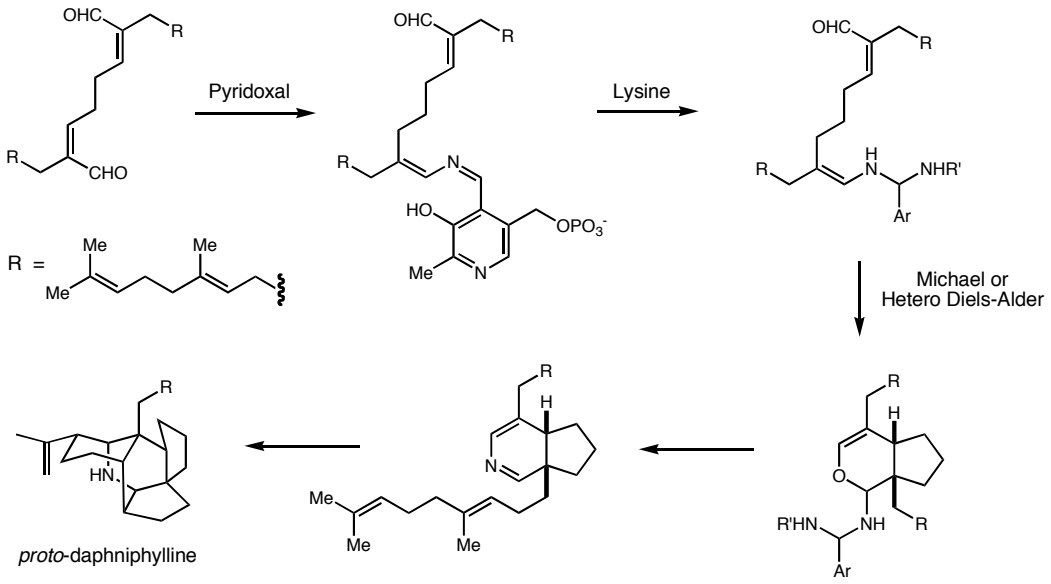
[15] Escher, S.; Loew, P.; Arigoni, D. *Chem. Comm.* **1970**, 823.

[16] Inouye, H.; Ueda, S.; Uesato, S. *Tet. Lett.* **1977**, *18*, 709.

[17] Bellesia, F.; Pagnoni, U. M.; Pinetti, A.; Trave, R. *Phytocehmistry* **1983**, *22*, 2197.

cofactor, in the biosynthesis of the *Daphniphyllum* alkaloids[18] (Scheme 2)–a strategy that was mimicked in Heathcock's total synthesis of (±)-*proto*-daphniphylline.[19]

**Scheme 2: Heathcock's Proposed Biosynthesis of *Daphniphyllum* Alkaloids**




Taking inspiration from the wealth of knowledge concerning iridoid natural products, we sought to design a rapid synthesis of littoralisone taking advantage of organocatalytic methodologies recently developed in the MacMillan lab. Our efforts toward this goal are described below.

### *Retrosynthetic Analysis*

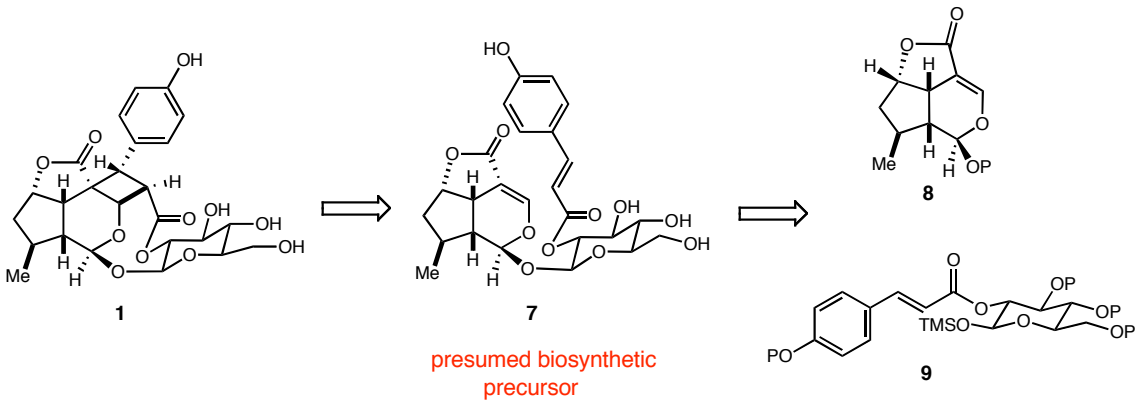
It was envisioned that littoralisone could be accessed from **7** by way of an intramolecular [2+2] photocycloaddition, in accord with the proposed biosynthetic pathway to **1** (Scheme 3). This transformation provides tremendous simplification, as it

[18] Ruggeri, R. B.; Heathcock, C. H. *Pure Appl. Chem.* **1989**, *61*, 289.

[19] Piettre, S.; Heathcock, C. H. *Science* **1990**, *248*, 1532.

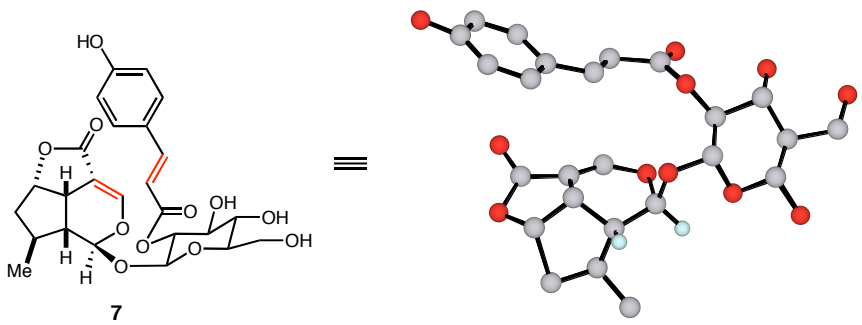
would implement several challenging synthetic features: an elaborate fully substituted cyclobutane, a nine-membered lactone, and a quaternary carbon stereocenter. However,

**Scheme 3: Initial Retrosynthetic Disconnections**




it was not immediately obvious that such a cycloaddition was necessarily accessible. In particular, we wondered as to whether the two reacting olefins could truly adopt a low energy conformation in which they could achieve overlap. Computational modeling,[20] on the other hand, provided some evidence that such a conformation was indeed accessible, and that cycloaddition might well proceed with high stereochemical control (figure 4).

**Figure 4: Computational Model of [2 + 2] Transition State**

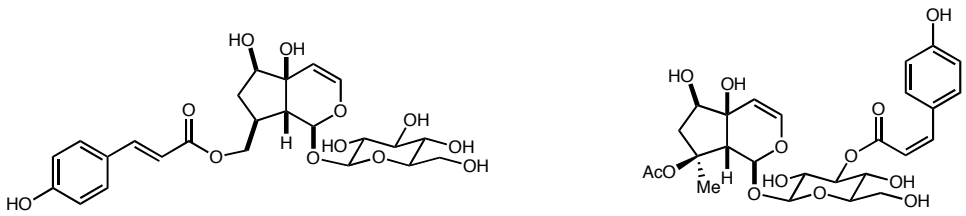



This information fits well with the biosynthetic proposal, but is also bolstered by the prevalence of iridoid natural products bearing a coumaroyl ester functionality as in **7**.[2] Such iridoids are diverse in their acylation pattern (figure 5), but one can imagine that the

[20] Gaussian 03™ calculation, B3LYP/3-21G(d,p).

2-substitution[21] of **7** might be vital for achieving an intramolecular reaction with the core pyran. The strong resemblance of **7** to brasoside (**2**) is suggestive of a role for **2** in the biosynthesis of **1** and implies that both are accessible from a common precursor (**8**).

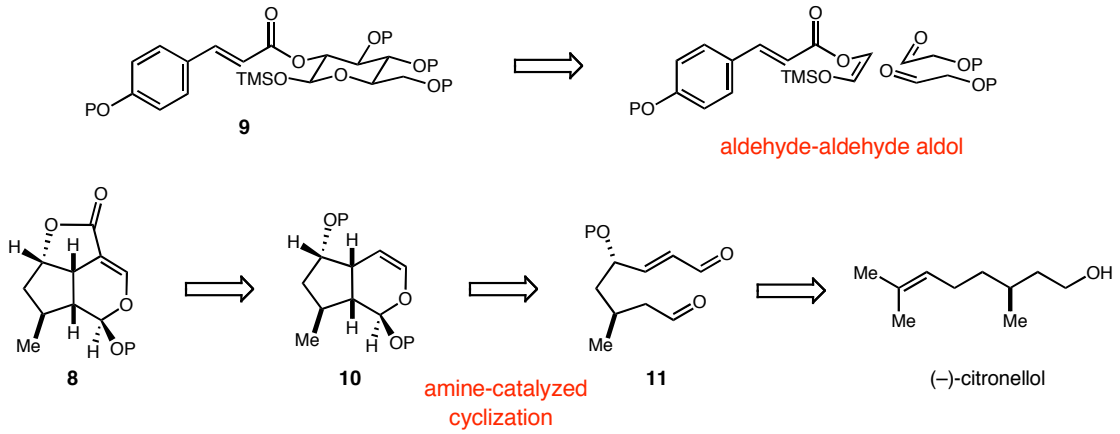
**Figure 5: Representative Coumaroyl-Substituted Iridoids**



**8-O-*p*-Coumaroylharpagide** **Decumbeside D**

Selectively substituted glucose **9** should be accessible by way of the iterative aldol technology developed and discussed in Chapter 2 (Scheme 4). This analysis leaves iridolactone **8** as the remaining target. We envisioned a late-stage introduction of the lactone, revealing bicyclic pyran **10** as the simplified intermediate. This compound we hoped to access by way of a linear precursor (**11**), perhaps through an amine-catalyzed cyclization reaction as has been implicated in the biosynthesis of iridoid natural products.

**Scheme 4: Approach to the Key Sugar and Iridolactone**



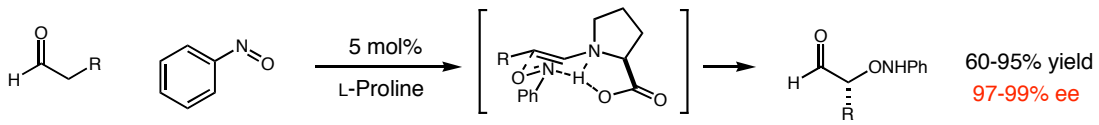

[21] Glucose numbering.

Dial **11** might then simply be produced from elaboration of commercially available material (i.e., (–)-citronellol).

***Synthesis of Iridolactone** 8*

Having recognized the utility of the carbon skeleton of (–)-citronellol in previous synthetic efforts toward iridoids,[12] we sought to elaborate this material toward dial **11**. Key to this approach was the recognition that proline-catalyzed enantioselective oxyamination technology recently developed in the MacMillan lab[22] might be used to introduce the chiral secondary alcohol of **11** in a diastereocontrolled fashion (figure 6).[23]

**Figure 6: Organocatalytic Nitrosobenzene Oxidation is Catalyst-Controlled and Highly Selective**



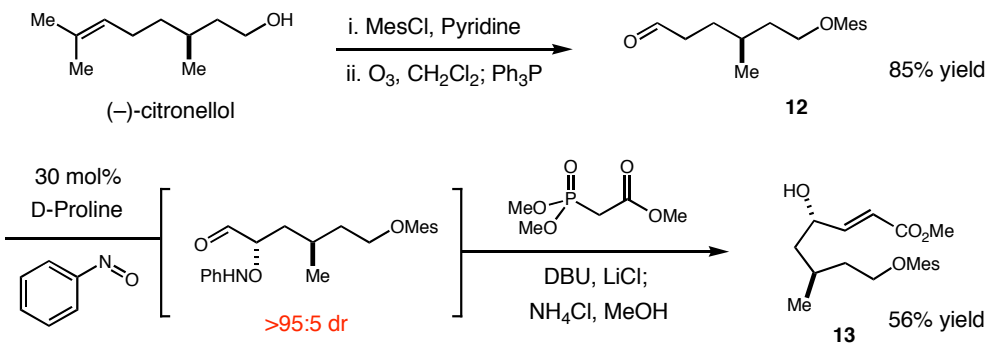

Synthesis of **11** was initiated by protection of commercially available (–)-citronellol as its mesitoate ester, followed by treatment with $O_3$ to furnish aldehyde **12** (figure 7). It was found that **12** could be treated with nitrosobenzene and D-proline to furnish the corresponding $\alpha$-oxyamino aldehyde with full catalyst control, in accord with reported stereochemical models.[24] Fortuitously, we realized that Horner-Wadsworth-Emmons olefination of this resultant aldehyde and cleavage of the aminoxy bond on standing in MeOH could furnish $\gamma$-chiral $\alpha$, $\beta$-unsaturated ester **13** in a single synthetic operation without purification. While this transformation could also be performed in a stepwise fashion, the yields were variable due to the instability of the aminoxy N-O bond, and a

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

[23] For other reports on proline-catalyzed oxidation of aldehydes, see: (a) Zhong, G. *Angew. Chem., Int. Ed.* **2003**, *42*, 4247; (b) Hayashi, Y.; Yamaguchi, J.; Hibino, K.; Shoji, M. *Tetrahedron Lett.* **2003**, *44*, 8293.

[24] Cheong, P. H.-Y.; Houk, K. N. *J. Am. Chem. Soc.* **2004**, *126*, 13912.

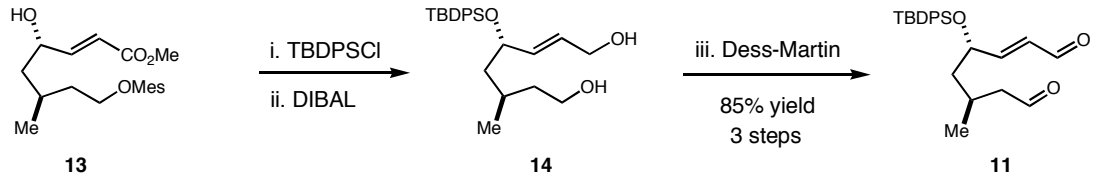
**Figure 7: Three Step Synthesis of Ester** 13




mild *in situ* cleavage seems the best approach.[25] This procedure allowed us remarkably rapid access to the carbon framework of the target iridolactone intermediate.[26,27]

At this point, we sought to access **11** to test the feasibility of the proposed amine-catalyzed cyclization. This was achieved by protection of the secondary alcohol as its TBDPS ether, treatment with DIBAL to reduce the esters to the corresponding alcohols, and Dess-Martin oxidation to the desired dialdehyde **11** (figure 8). There is good literature precedent for amine-mediated cyclization of aldehyde-enals such as **11**.[28] Work

**Figure 8: Completion of Dialdehyde** 11




performed in the Schreiber group demonstrated the ability of *N*-methyl aniline to effect cyclization to bicyclic aminopyrans with high diastereocontrol (figure 9).[28a] This

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[25] Methanolysis proved higher yielding for this substrate than other reported procedures, such as: $CuSO_4$/MeOH, Zn/AcOH, Na/EtOH, etc.

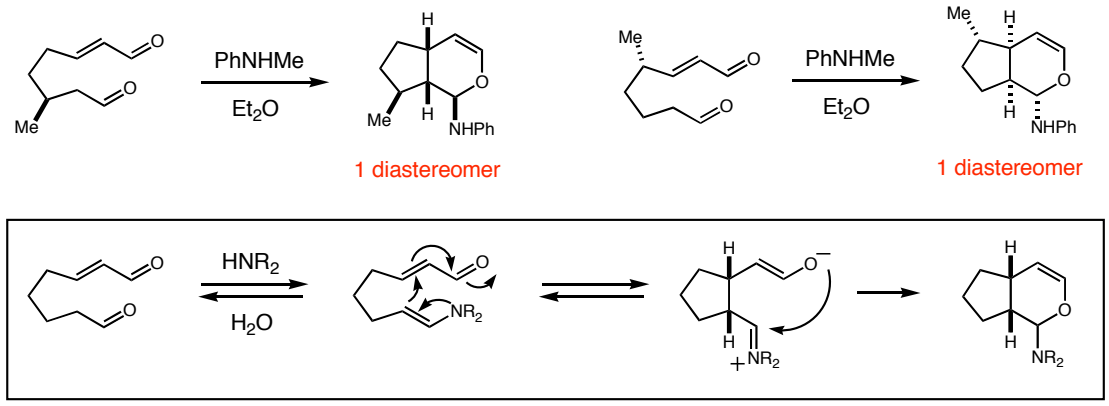
[26] For a related two-step approach, see: Zhong, G.; Yu, Y. *Org. Lett.* **2004**, *6*, 1637.

[27] To our surpise, conventional Wittig and Peterson olefinations provided no reactivity, while Takai olefination led to rapid, undesired side reactions.

[28] For a stoichiometric amine-mediated intramolecular Michael reaction see: (a) Schreiber, S. L.; Meyers, H. V.; Wiberg, K. B. *J. Am. Chem. Soc.* **1986**, *108*, 8274; For an imidazolidinone-catalyzed intramolecular Michael providing *trans*-cyclopentanes see: (b) Fonseca, M. T. H.; List, B. *Angew. Chem. Int. Ed.* **2004**, *43*, 395.

methodology facilitates precisely the type of cyclization we would like to perform in this synthesis, but suffers from the slight drawback that it requires a stoichiometric amount of the amine source. This requirement is likely a consequence of an irreversible catalyst trapping event – indeed, the original publication provides a separate method for acidic hydrolysis to liberate the amine after purification of the initial adduct.[28a] The mechanism shown in Figure 9 is speculative, but seems likely given the propensity of amines to condense with aldehydes and form enamines that can perform conjugate additions.[28b] While a hetero Diels-Alder reaction might provide the same product, for these purposes this is a formalism that will not be discussed here.[29]

**Figure 9: Schreiber's Anline-Mediated Cyclization**

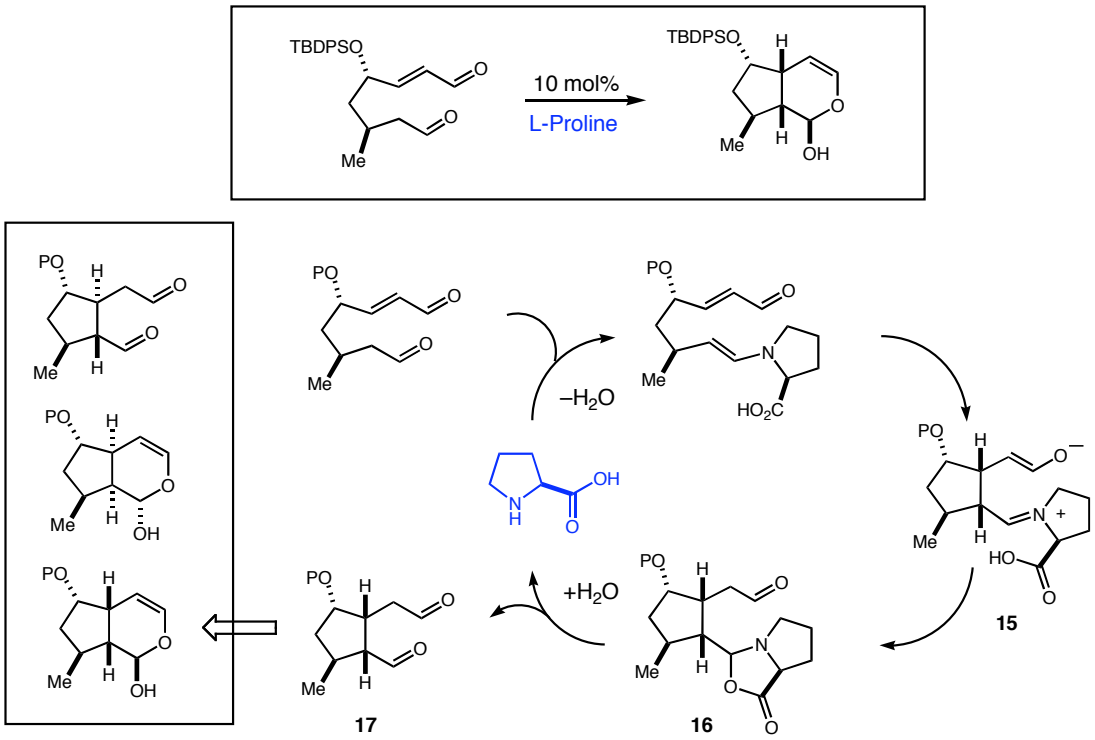



A key challenge we sought to address in this synthesis was the development of a catalytic, stereoselective variant of this Michael addition. It was envisioned that variation of the amine source might allow for interception of the amine trapping event and allow for catalytic turnover. In particular, proline might prove amenable to catalysis as its carboxylic acid might well trap forming iminiums, as was observed in the direct aldol

[29] For recent work on an amine-catalyzed hetero Diels-Alder reaction see: Juhl, K.; Jorgensen, K. A. *Angew. Chem. Int. Ed.* **2003**, *42*, 1498.

work described in Chapter 2 (Scheme 5). That is, carbon-carbon bond formation would lead to iminium **15**, which might then be trapped as *N,O*-acetal **16** rather than undergoing

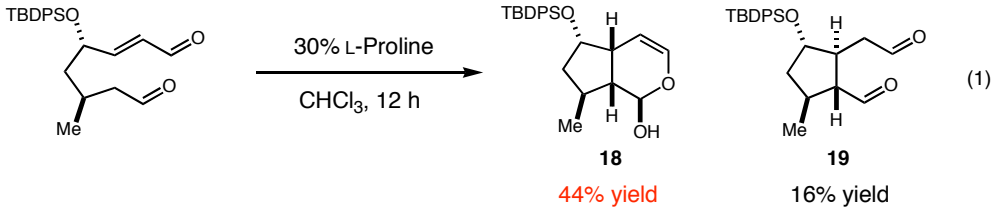
**Scheme 5: Possible Catalytic Cycle for Proline-Catalyzed Intramolecular Michael**

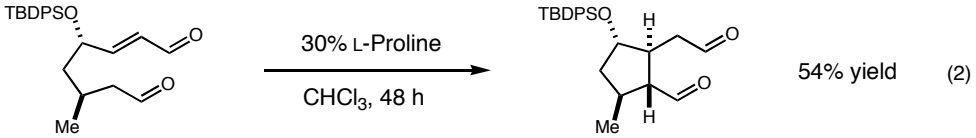



the catalyst trapping event depicted in Figure 9. As described earlier, such an acetal has been observed to be part of a productive catalytic cycle, and appears to hydrolyze under ambient reaction conditions. Hydrolysis would furnish dialdehyde **17**, which is simply a tautomer of the desired bicyclic pyran. However, the question was not only whether such a catalytic cycle would proceed, but also which of the possible diastereomers would be produced in the Michael addition and with what degree of stereocontrol. The precedent offered in Figure 9 is somewhat discouraging as it implies that the two stereocenters that exist in **11** might work in opposition to produce a mixture of two diastereomers. Here again proline might offer a solution – as a chiral catalyst, it might provide the steric

environment required to overcome the likely preference of **11** to produce an undesired diastereomer.

In the event, initial efforts with proline were met with some success (eq 1). Not only was catalytic turnover observed, but also some of the desired bicyclic pyran (**18**) was produced, albeit in modest yield as a 3:1 mixture of diastereomers. In an attempt to improve on this yield, the reaction time was extended (eq 2), with the surprising result that the only diastereomer observed (**19**) was the one in which all four substituents about the cyclopentane ring are oriented *trans* relative to each other. To examine this result



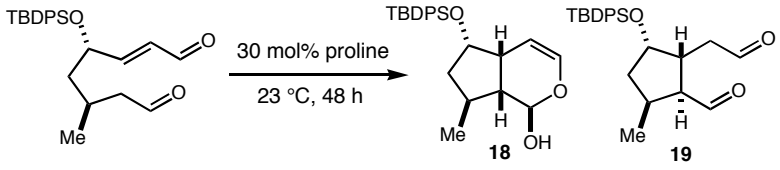


further, the desired pyran was resubjected to identical reaction conditions (eq 3), and a complete inversion in stereochemistry to the undesired diastereomer was observed. All these observations can perhaps be explained by a retro-Michael/Michael thermodynamic equilibration of the product, leading ultimately to the thermodynamically favored *trans* stereochemistry.

Since the problem could be reduced to favoring kinetic over thermodynamic selectivity, subsequent investigations focused on optimizing reaction conditions towards

a kinetic result (table 1). Changing the reaction medium had the surprising effect of drastically altering the distribution of diastereomers produced in the intramolecular Michael reaction. More polar solvents (MeOH and DMSO, entries 4-5) drove selectivity markedly toward **18** (7-10:1 selectivity). In the case of DMSO, this also proved to be an efficient (91% yield) reaction. To demonstrate that this phenomenon was not simply a dielectric effect, the enantiomer of the catalyst was varied under identical conditions, resulting in an inversion of selectivity (entries 5-7). It was further shown that the ratios observed in DMSO were kinetic rather than thermodynamic, as exposure of isolated **18** to

**Table 1: Examination of the Organocatalytic Intramolecular Michael**




| entry | catalyst | solvent | yield[a] | **18**:**19** |
|---|---|---|---|---|
| 1 | L-proline | $Et_2O$ | 11 | 2:1 |
| 2 | L-proline | $CH_2Cl_2$ | 54 | 3:1 |
| 3 | L-proline | $CHCl_3$ | 61 | 3:1 |
| 4 | L-proline | MeOH | 26 | 7:1 |
| 5[b] | L-proline | DMSO | 91 | 10:1 |
| 6[b] | (±)-proline | DMSO | 86 | 2:1 |
| 7[b] | D-proline | DMSO | 83 | 1:2 |

[a]Represents combined yield of diastereomers. [b] Run at 40 °C for 60 h

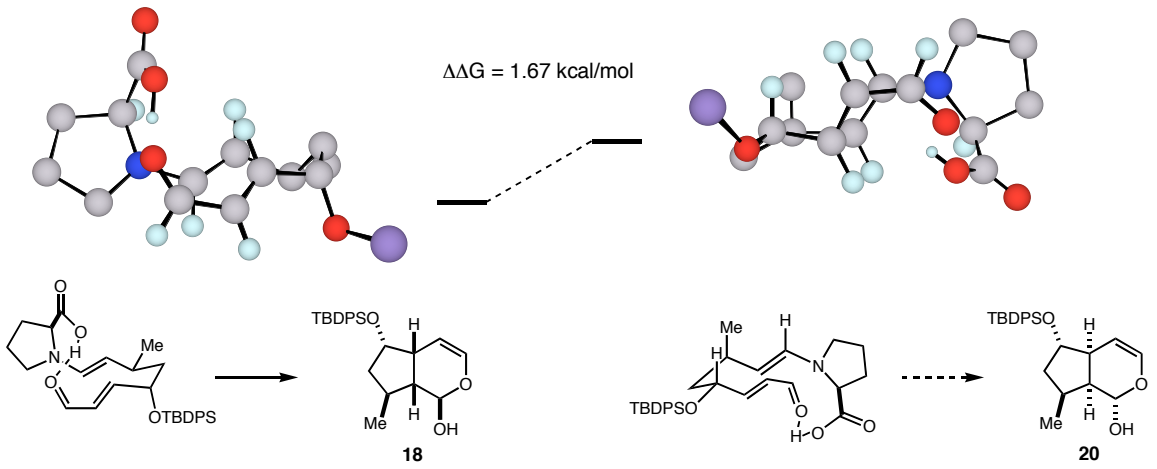
D- or L-proline for three days under identical reaction conditions led to no change in stereochemistry. $^1$H NMR studies in $d_6$-DMSO suggest that the rate-limiting step in that medium is catalyst turnover. This idea seems validated by the observation that the addition of $H_2O$ to DMSO greatly accelerates the Michael addition, with complete conversion at room temperature.[30] For the purposes of the synthesis, however, it was

[30] As little as 2% (v/v) $H_2O$ is sufficient to effect full conversion to **18** in 48 h at 23 °C in DMSO.

found to be more convenient to run the reaction in anhydrous DMSO, which allowed for *in situ* acetylation of the lactol once conversion was complete (eq 4, below).

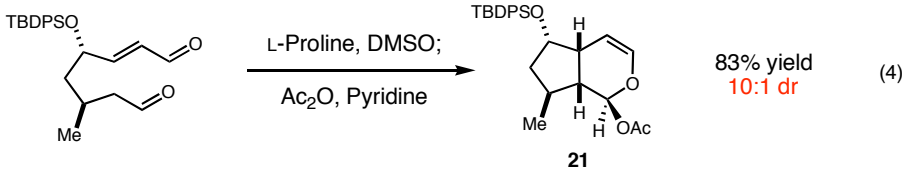
Initial computational studies[20] on the nature of catalyst stereocontrol in the Michael addition revealed a synergy between catalyst and subtrate (figure 10). The lowest-energy transition state observed predicts production of **18** through a closed, hydrogen-bonded transition state, in accord with proline studies cited in Chapters 1 and 2.

**Figure 10: Computational Model of Intramolecular Michael**

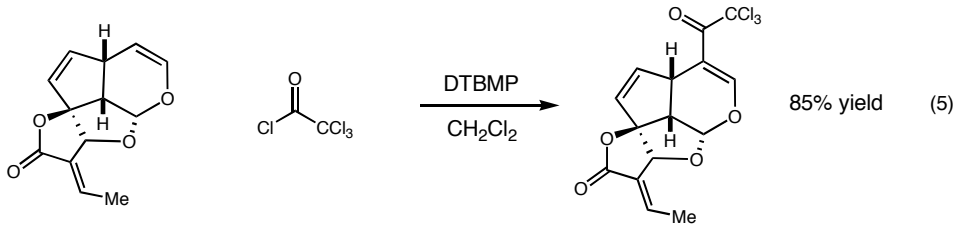



The closed transition state favors a *cis* orientation of the hydrogens of the forming cyclopentane, translating into the observed *cis* selectivity in the product. Another feature of this transition state is the pseudo-equatorial orientation of the chiral methyl substituent and the pseudo-axial alignment of the siloxy group. There is a seemingly accessible transition state in which the enal attacks from the opposite face of the enamine, activated by a similar hydrogen bond, to produce **20**. However, the methyl group is now oriented axially, and engages in an unfavorable transannular and allylic interactions with axial hydrogens. A calculated energetic penalty of 1.67 kcal/mol results, which may explain

why **20** has not been observed in the course of these studies. Thus the stereocontrol observed is a combination of catalyst diastereocontrol and substrate facial control.[31]




With a selective method for the production of **21** (after *in situ* acetylation), efforts could now be resumed toward iridolactone **8**. Attempts were made to acylate the enol ether of the pyran in order to introduce the desired lactone. Initial experiments[32] failed either for lack of reactivity or because of competing decomposition. While the lack of reactivity was disappointing in light of the successful acylation applied by the Trost lab in



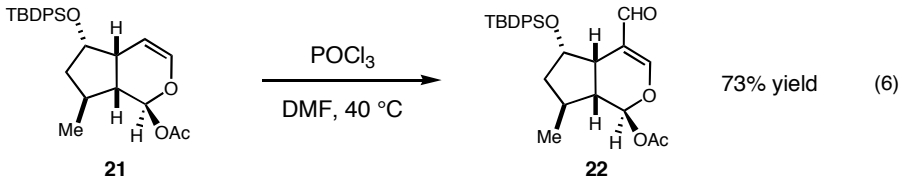

their synthesis of plumericin[12d] (eq 5), the presence of an electron-withdrawing acetoxy acetal could certainly be expected to contribute to failure. Similarly, decomposition can be expected in basic conditions because of this labile acetate, whereas acidic conditions have been well documented[1] to lead to ring-opening degradation of iridoids. However, the acetoxy acetal had been identified as a key activating functionality for the glycosyl couplings that would be needed in the future, so attempts were made to find a mild and effective acylation method.

---

[31] Use of achiral substrates with proline follows this prediction: high diasterecontrol (9-12:1 *cis*:*trans*), but poor enantiocontrol (<16% ee).

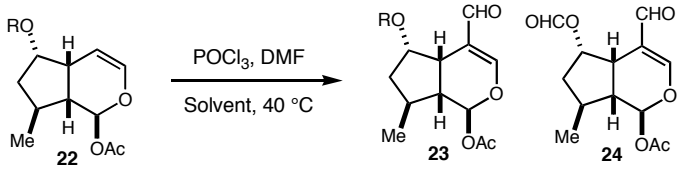
[32] Reagents attempted included, but are not restricted to: phosgene, trichloroacetyl chloride, chlorosulfonyl isocyanate, $Br_2$, $I_2$, NBS, and NIS.

Success was achieved through a Vilsmeier-Häack formylation, which installed an aldehyde at the *β*–position of the enol ether (eq 6).[33] However, this result was dependent




upon the nature of the protecting group on the secondary alcohol (table 2). Trace acid generated in the course of the reaction promotes deprotection of smaller silyl groups (entries 1-2) and subsequent formylation of the secondary alcohol. While this should be a workable result, yields were variable and problems were encountered trying to deprotect the formyl group in the presence of the labile acetate. Use of PMB and benzyl

**Table 2: Optimization of the Vilsmeier-Haack Formylation**




| entry | R | solvent | yield[a] | **23**:**24** |
|---|---|---|---|---|
| 1 | TBS | $CH_2Cl_2$ | 32 | 0:1 |
| 2 | TBS | DMF | 25 | 0:1 |
| 3[b] | PMB | $CH_2Cl_2$ | 0 | -- |
| 4[b] | Bn | $CH_2Cl_2$ | 0 | -- |
| 5 | TBDPS | $CH_2Cl_2$ | 42 | 3:1 |
| 6 | TBDPS | DMF | 73 | 11:1 |

[a]Represents yield of major product [b]Decomposition observed

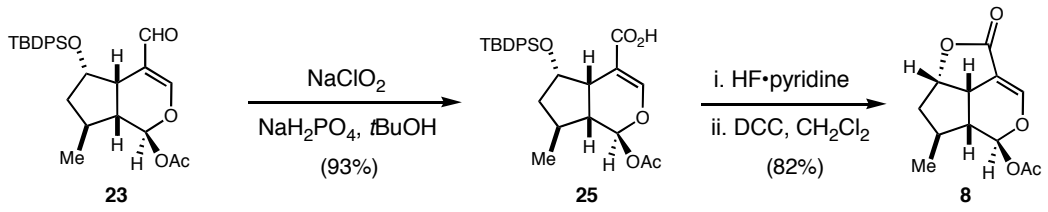
ether protecting groups failed as well, with decomposition of the starting material (entries 3-4).[34] The more acid-stable TBDPS protecting group proved optimal, with little *in situ* desilylation and improved overall efficiency when DMF was used as solvent (entry 6, 73% yield).

[33] For a related example see: Jensen, S. R.; Kirk, O.; Nielsen, B. J. *Tetrahedron* **1987**, *43*, 1949.

[34] This did not appear to be related to formylation of the protecting groups.

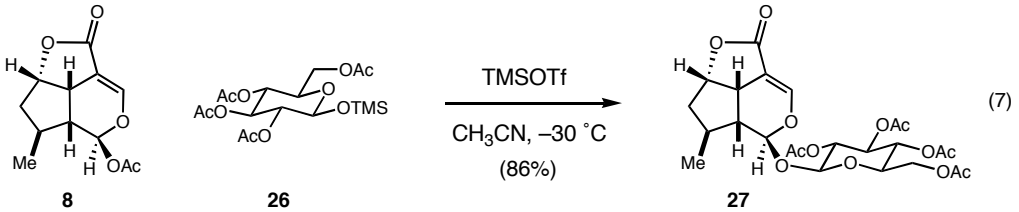
Following formylation, elaboration to iridolactone **8** was a straightforward matter (figure 11). Sodium hypochlorite oxidation converted the aldehyde to a carboxylic acid (**25**), at which point silyl deprotection was effected by HF•pyridine in THF. Closure of this hydroxy acid to lactone **8** is effectively mediated by DCC, furnishing the target iridolactone from **22** in 56% yield.

**Figure 11: Completion of Iridolactone** 8




***Total Synthesis of Brasoside***

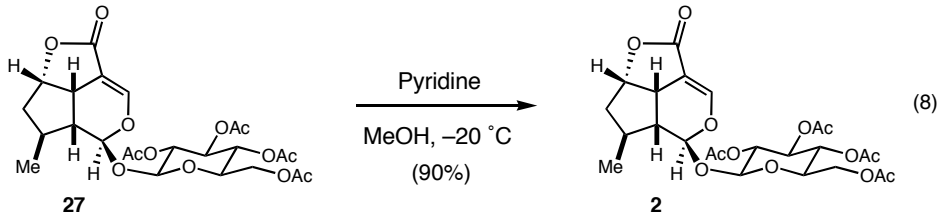
Completion of **1** and **2** would now require coupling of **8** with appropriately functionalized carbohydrates. Brasoside requires introduction of glucose, which in this case could come from TMS-protected glucose tetraacetate (**26)** (derived in two steps from the commercially available pentaacetate).[35] Exposure of **8** to TMSOTf in the presence of **26** led to efficient union of these two fragments (86% yield, Eq. 7). The product, brasoside tetraacetate (**27**), is a literature compound produced in the isolation of brasoside, and allows confirmation of the absolute stereochemistry of **8**.[8a] Careful deprotection of **27** completed the first total synthesis of brasoside, with synthetic material




(7)

[35] Allevi, P.; Anastasia, M.; Ciuffreda, P.; Bigatti, E.; MacDonald, P. *J. Org. Chem.* **1993**, *58*, 4175.

corresponding exactly to spectral data for the natural isolate (eq 8).

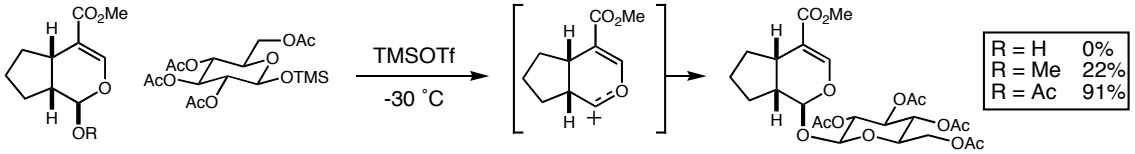



(8)

The TMSOTf-mediated carbohydrate coupling was based on methodology developed by Tietze,[36] who found existing coupling methods insufficient in his own iridoid syntheses. A traditional approach might involve reaction of a nucleophilic lactol with an electrophilic carbohydrate source, as in the well-known Koenigs-Knorr method.[37] However, there are few examples of such a method being successfully applied in iridoid chemistry, perhaps because of two related limitations: a pyran lactol is poorly nucleophilic and requires more forcing coupling conditions, and under these conditions anomeric stereochemical control with respect to the carbohydrate is poor.

Thus Tietze envisioned inverting the roles of the coupling partners by forcing the iridoid into the role of the acceptor (figure 12). The Lewis acid TMSOTf likely aids in

**Figure 12: Tietze's Iridoid-Carbohydrate Coupling Method**




ionizing the anomeric acetoxy group, which can then be attacked by the carbohydrate. Although the attacking alcohol is blocked by a silyl group, Tietze speculates that the ionized acetoxy group is associated with the pyran in a tight ion pair, and this anion attacks the TMS protecting group to liberate the nucleophilic alcohol and generate

[36] Tietze, L.-F.; Fischer, R.; Remberg, G. *Liebigs Ann. Chem.* **1987**, 971.

[37] Davis, B. G.; Fairbanks, A. J. *Carbohydrate Chemistry*; Oxford University Press, Oxford, UK, **2002**.

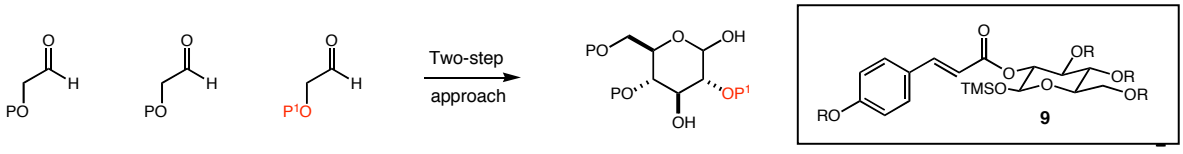
TMSOAc. The presence of TMSOAc was confirmed in Tietze's work, and this mechanism also accounts for the necessity of the TMS protecting group – in its absence the anomeric stereochemistry in the carbohydrate is lost, and a mixture of diastereomers is produced. In its presence the anomeric alcohol does not isomerize below –30 °C, and is revealed only in the course of nucleophilic attack. Further, the oxocarbenium intermediate is empirically verified by the improvement in yield observed by introducing more electron-withdrawing substituents on the iridoid lactol noted in Figure 12.

With a productive method for coupling a carbohydrate to iridolactone **8**, a key remaning task was the selective synthesis of a 2-coumarated glucose derivative. Coupling of such a carbohydrate with **8** would complete the carbon skeleton of littoralisone and permit investigation of the key intramolecular photocycloaddtion.

### *Synthesis of Carbohydrate 9 and Completion of Littoralisone*

Construction of a selectively substituted glucose such as **9** should certainly be possible using conventional sugar protecting group schemes. However, we wondered whether such a carbohydrate could be more efficiently and perhaps more rapidly produced by taking advantage of the two-step carbohydrate synthesis developed in the MacMillan lab, as described in Chapter 2 (figure 13).[38] In practice this approach proved

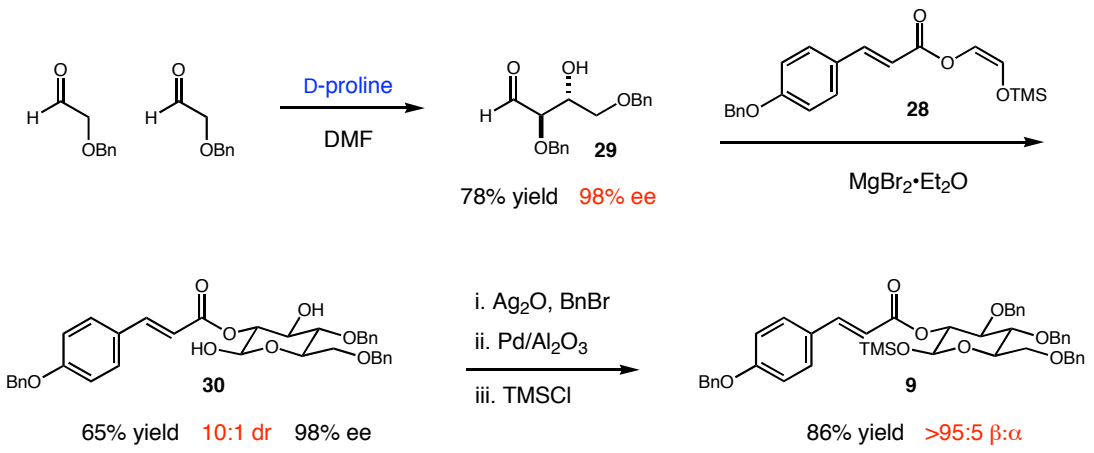
**Figure 13: Projected Two-Step Synthesis of Functionalized Glucose**




[38] (a) Northrup, A. B.; Mangion, I. K.; Hettche, F.; MacMillan, D. W. C. *Angew. Chem., Int. Ed.* **2004**, *43*, 2152; (b) Northrup, A. B.; MacMillan, D. W. C. *Science*, **2004**, *305*, 1752.

feasible, as reaction between enol silane **28**[39] and aldol dimer **29** (see Chapter 2) yielded the differentially functionalized carbohydrate core of **9** (**30**, Figure 14). From this stage, completion of **9** required a three step manipulation of protecting groups, providing the final product as a single anomer. While the available precedent[38b] for this aldol approach to carbohydrates provided only for silicon-based protecting group schemes, it was anticipated that such protecting groups might cause problems in the TMSOTf-mediating coupling, with deprotection or silyl scrambling being major concerns. Fortunately, this chemistry proved amenable to benzyl ether protecting groups with few modifications.[40]

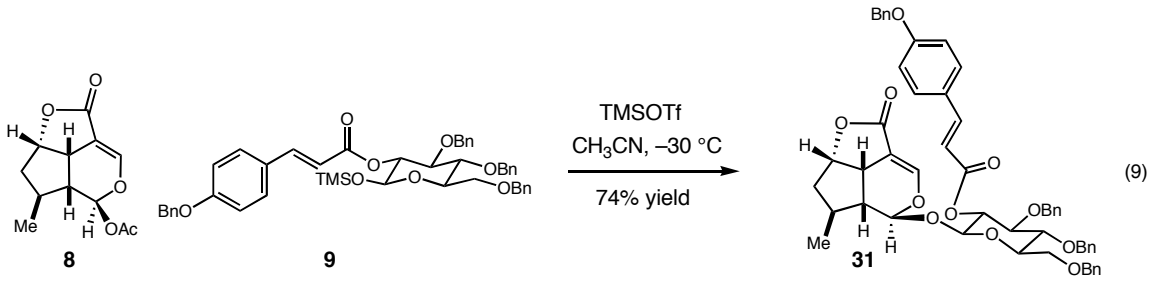
**Figure 14: Completion of Coumarated Glucose** 9




With an appropriately substituted carbohydrate now available, coupling of **9** with iridolactone **8** was now attempted (eq 9). Under conditions essentially identical to those used in the completion of brasoside an efficient (74% yield) union was observed, providing the total carbon skeleton of littoralisone (**31**). The key issue to be addressed was the proposed intramolecular photocycloaddition. While modeling studies had been suggestive of an accessibile [2 + 2] transition state, there remained the energetic penalties

[39] Synthesized in three steps – see supporting information.

[40] See supporting information for details.




one might expect to have to overcome, including the formation of a fully substituted cyclobutane including a quaternary carbon stereocenter, as well as an adjacent nine-membered lactone.

There is a wealth of literature concerning the photochemistry of enones, particularly for cycloadditions with other enones.[41] While a literature search failed to reveal an analogous 4,9-bicyclization, there is certainly encouragaing precedent for the formation strained or hindered systems. One of the most pressing challenges in these cycloadditions is stereochemical control, as *E/Z* geometric olefin isomerism generally occurs at a greater rate than carbon-carbon bond forming reactions for acylic enones. This was a concern in the projected completion of littoralisone, since olefin isomerization could lead to a mixture of cyclobutane diastereomers. However, it was anticipated that the *Z* isomer of coumarate **31** would be unreactive in cycloaddition due to nonbonding interactions with the iridolactone core.

Another issue was the choice of UV wavelength with which to attempt cycloaddition. Acrylates have a broad range of absorption in the ultraviolet spectrum (extending to at least the 360-70 nm wavelengths).[41a] As such, it was expected that optimal irradiation might come from a photobox with lamps tuned to 350 nm, with the

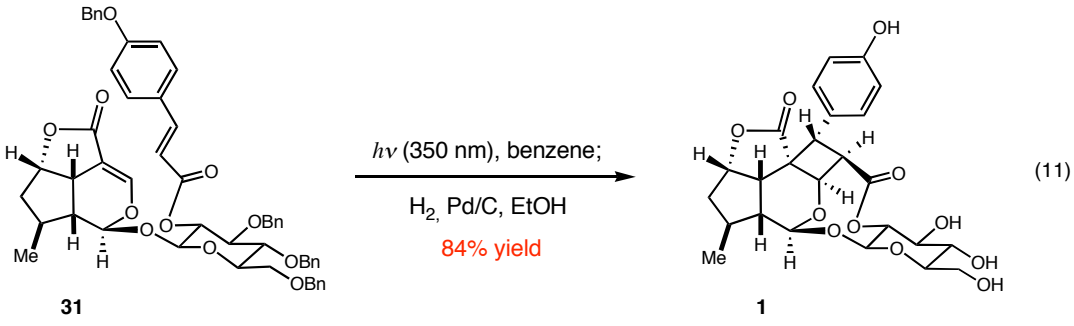
[41] (a) Patai, S.; Rappoport, Z., ed. *The Chemistry of Enones*, Wiley, New York, **1989**; (b) Kagan, J. *Organic Photochemistry: Principles and Applications*; Academic Press, London, **1993**; (c) Griesbeck, A. G.; Mattay, J., ed. *Synthetic Organic Photochemistry*; Marcel Dekker, New York, **2005**; (d) Crimmins, M. T. *Chem. Rev.* **1988**, *88*, 1453.

reaction carried out in a Pyrex flask.[42] The energy imparted to an organic molecule by absorption of a photon can be calculated as shown in Eq. 10.[43] By choosing the longest wavelength at which a desired functionality absorbs photons, one can lower the energy of absorption and avoid higher-energy side reactions.

$$E\ (\text{kcal/mol}) = \frac{2.86 \times 10^4}{\lambda\ (\text{nm})} \qquad (10)$$

for λ = 200 nm, E = 143 kcal  for λ = 310 nm, E = 92 kcal
for λ = 254 nm, E = 113 kcal  for λ = 350 nm, E = 82 kcal

Reaction medium can be critical for certain photochemical reactions, as the solvent can absorb photons depending on wavelength. In this way the solvent can sometimes act as a sensitizer or can suppress the reaction by absorbing available photons. Further, dielectric effects can partition molecules toward various excitation states. For enones, more polar solvents tend to stabilize n-π* transitions while less polar solvents favor π-π* transitions. For this synthesis, benzene was chosen both for its high transmittance at 350 nm and its ability to completely dissolve **31**. As shown in Eq. 11, irradiation of **31** in these conditions led to a quantitative conversion to the desired cyclobutane as a single diastereomer. *In situ* hydrogenolysis of the benzyl ethers completed the first total synthesis of littoralisone (**1**), a substance that was identical in all




(11)

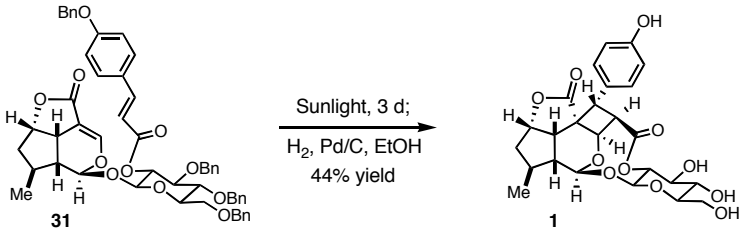
[42] Pyrex glass transmits above 310 nm, and increasingly absorbs at lower wavenumbers.

[43] From Evans, D. A.; Breit, B. *Chemistry 206, Lecture Number 34*; Harvard University, **2000**.

respects to the natural isolate. This synthesis was completed in 13 linear steps and 13% overall yield.

The surprising facility of the key intramolecular photocycloaddition provides some circumstantial support for the notion that this pathway is operative in the biosynthesis of littoralisone. Given that littoralisone was isolated from the leaf of *Verbena littoralis* (figure 15), one can easily imagine the exposure to natural UV light of littoralisone and its biosynthetic precursors. In an effort to probe this idea further, I subjected **31** to standing in natural sunlight for three days under otherwise identical reaction conditions (Pyrex flask, benzene), and obtained 44% yield of **1** after hydrogenolysis. This remarkable result supports the biosynthetic hypothesis even further, and raises the possibility that there may well be other cyclobutane-substituted iridoids that have yet to be identified.

**Figure 15: *Verbena Littoralis* and a Biomimetic Cycloaddition**




***Conclusions***

The first total syntheses of the iridoid natural products brasoside and littoralisone have been completed from a common intermediate. Each synthesis was achieved in 13 steps and 13% overall yield. This work highlights the use of organocatalysis in the stereoselective construction of complex natural product targets. Proline was used to perform a diastereoselective oxidation, overcome the inherent stereoinduction of enamine-Michael reactions, and enable the two-step asymmetric construction of a polyol differentiated glucose coupling partner. The synthetic route demonstrated here lends support to the proposed biochemical formation of littoralisone from brasoside.

***Supporting Information***

**General Information.** Commercial reagents were purified prior to use following the guidelines of Perrin and Armarego.[1] All solvents were purified according to the method of Grubbs.[2] $CH_3CN$ was stored under argon over activated molecular sieves. TMSOTf was doubly distilled from $CaH_2$ prior to use. Non-aqueous reagents were transferred under argon via syringe or cannula. Organic solutions were concentrated under reduced pressure on a Büchi rotary evaporator using a water bath. Chromatographic purification of products was accomplished using forced-flow chromatography on ICN 60 32-64 mesh silica gel or Iatrobeads® according to the method of Still.[3] 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.

$^1H$ and $^{13}C$ NMR spectra were recorded on a Varian Mercury 300 (300 MHz and 75 MHz) or 500 (500 MHz and 125 MHz) Spectrometer 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. Where appropriate, the notations H1, H2, H3, H4, H5, and H6 have been used to refer to protons residing on the denoted carbons in a sugar. 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. Optical rotations were measured on a Jasco P-1010 polarimeter, and $[\alpha]_D$ values are reported in $10^{-1}$ dg cm$^2$ g$^{-1}$.

**(*S*)-3,7-dimethyloct-6-enyl 2,4,6-trimethylbenzoate.** To a stirring solution of (–)-citronellol (8.8 mL, 48 mmol), pyridine (7.8 mL, 96 mmol), and DMAP (100 mg, 0.82 mmol) in $CH_2Cl_2$ (250 mL) was added 2,4,6-trimethylbenzoyl chloride (9.0 mL, 53 mmol). After 10 h the solution was diluted in 500 mL $Et_2O$ and washed with 150 mL saturated solutions of $NH_4Cl$, $NaHCO_3$, and NaCl. The organic layer was dried over $Na_2SO_4$ and concentrated *in vacuo*. Flash chromatography (95:5 pentane:$Et_2O$) afforded the title compound as a clear, colorless oil in 99% yield (14.4 g, 47.5 mmol). IR (film) 2956, 2921, 2852, 1778, 1726, 1613, 1453, 1436, 1376, 1264, 1214, 1170, 1083 cm$^{-1}$; $^1$H NMR (300 MHz, $CDCl_3$) δ 6.85 (s, 2H, Ar-**H**); 5.09 (m, 1H, $(CH_3)_2C$=C**H**); 4.35 (m, 2H, C**H$_2$**OMes); 2.29 (s, 9H, ArC**H$_3$**); 1.96 (m, 2H, C=CHC**H$_2$**); 1.82-1.26 (m, 11H, C=C(C**H$_3$**)**$_2$**, C**H$_2$**CHCH$_3$, C**H**CH$_3$); 1.02 (d, 3H, $J$ = 6.6 Hz, CHC**H$_3$**); $^{13}$C NMR (75 MHz, $CDCl_3$) δ 170.5, 151.1, 139.3, 135.2, 131.6, 131.4, 128.9, 128.6, 124.9, 63.5, 40.6, 37.2, 35.9, 29.7, 25.9, 25.7, 21.2, 20.0, 19.5, 17.8; HRMS (FAB+) exact mass calculated for $[M + H]^+$ ($C_{20}H_{31}O_2$) requires $m/z$ 303.2324, found $m/z$ 303.2333. $[\alpha]_D^{25}$ = –1.84 (c = 1.0, $CHCl_3$).

**(*S*)-5-formyl-3-methylpentyl 2,4,6-trimethylbenzoate (12).** A solution of (*S*)-3,7-dimethyloct-6-enyl 2,4,6-trimethylbenzoate (9.0 g, 30 mmol) and pyridine (2.6 mL, 45 mmol) in $CH_2Cl_2$/MeOH (140 mL/15 mL) was cooled to –78 °C. Ozone was bubbled through the solution until a dark blue color developed. At this time triphenylphosphine (8.6 g, 33 mmol) was added and the resulting mixture was stirred for 3 h allowing it to

reach 0 °C. After concentration, flash chromatography (19:1-10:1 pentane:$Et_2O$) afforded the title compound as a clear, colorless oil in 96% yield (7.96 g, 28.8 mmol). IR (film) 2959, 2926, 2873, 1724, 1612, 1458, 1435, 1380, 1266, 1170, 1085, 958.7, 853.1 $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$) δ 9.77 (t, 1H, *J* = 1.8 Hz, C**H**O); δ 6.85 (s, 2H, Ar-**H**); 4.36 (m, 2H, C$\mathbf{H_2}$OMes); 2.46 (m, 2H, C$\mathbf{H_2}$CHO); 2.28 (s, 9H, ArC$\mathbf{H_3}$); 1.83-1.46 (m, 5H, C$\mathbf{H_2}$CHC$H_3$, C**H**C$H_3$); 0.96 (d, 3H, *J* = 6.3 Hz, CHC$\mathbf{H_3}$); $^{13}C$ NMR (75 MHz, $CDCl_3$) δ 202.4, 170.3, 151.1, 139.4, 135.1, 131.4, 128.6, 128.5, 63.1, 41.6, 35.6, 29.6, 28.9, 21.3, 20.0, 19.2, 19.1; HRMS (EI+) exact mass calculated for $[M]^+$ ($C_{17}H_{24}O_3$) requires *m/z* 276.1728, found *m/z* 276.1726. $[\alpha]_D^{25} = -0.33$ (c = 1.0, $CHCl_3$).

**(*E*,3*R*,5*S*)-7-(methoxycarbonyl)-5-hydroxy-3-methylhept-6-enyl 2,4,6-trimethyl-benzoate (13).** D-Proline (530 mg, 4.6 mmol) was added to a stirring solution of **12** (3.12 g, 11.3 mmol) and nitrosobenzene (1.21 g, 11.3 mmol) in DMSO (45 mL). After 0.5 h the solution became a bright orange, at which time it was cooled to –15 °C. A premixed solution of methyl diethyl phosphonoacetate (6.0 mL, 34 mmol), 1,8-diazabicyclo[5.4.0]undec-7-ene (5.1 mL, 34 mmol) and lithium chloride (1.44 g, 34 mmol) in $CH_3CN$ (45 mL) was added over 5 min via cannula. After 15 min the solution was diluted with MeOH (150 mL) and $NH_4Cl$ (1.8 g, 34 mmol) was added. The resulting mixture was allowed to warm to room temperature and stand for 2 d. At this time the solution was diluted with $Et_2O$ (700 mL), and washed successively with 200 mL saturated solutions of $NH_4Cl$, $NaHCO_3$, and NaCl. The aqueous layers were extracted with 3 x 100 mL $CH_2Cl_2$, and the combined organic layers were dried over $Na_2SO_4$ and concentrated *in vacuo*. Flash chromatography (5:1-3:2 pentane:$Et_2O$) afforded the title

compound as a clear, colorless oil in 56% yield (2.2 g, 6.33 mmol). IR (film) 3479, 2958, 2925, 1723, 1612, 1455, 1436, 1267, 1170, 1085, 1036, 983.8, 853.0 $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$) δ 6.95 (dd, 1H, *J* = 15.6, 4.8 Hz, C=C**H**CHOH); 6.85 (s, 2H, Ar-**H**); 6.05 (dd, 1H, *J* = 15.6, 1.6 Hz, C=C**H**$CO_2$Me); 4.45-4.27 (m, 3H, C$\mathbf{H_2}$OMes, C**H**OH); 3.74 (s, 3H, OC$\mathbf{H_3}$); 2.28 (s, 9H, ArC$\mathbf{H_3}$); 1.98-1.24 (m, 5H, C$\mathbf{H_2}$$CHCH_3$, C**H**$CH_3$); 1.01 (d, 3H, *J* = 6.6 Hz, CHC$\mathbf{H_3}$); $^{13}C$ NMR (75 MHz, $CDCl_3$) δ 170.6, 167.3, 151.8, 139.4, 135.2, 135.0, 131.4, 128.6, 128.5, 119.4, 68.6, 63.2, 51.7, 43.8, 36.3, 26.6, 21.3, 20.0, 19.9 19.1; HRMS (EI+) exact mass calculated for $[M + H]^+$ ($C_{20}H_{29}O_5$) requires *m/z* 349.2015, found *m/z* 349.2023. $[\alpha]_D^{25} = -5.78$ (c = 1.0, $CHCl_3$).

**(*E*,3*R*,5*S*)-7-(methoxycarbonyl)-5-(*tert*-butyl-diphenyl-silanyloxy)-3-methylhept-6-enyl 2,4,6-trimethylbenzoate.** *tert*-Butylchlorodiphenylsilane (4.6 mL, 17.8 mmol) was added to a stirring solution of **13** (3.1 g, 8.9 mmol), imidazole (1.5 g, 22.2 mmol), and DMAP (100 mg, 0.82 mmol) in DMF (20 mL). After 12 h the solution was diluted in 250 mL $Et_2O$ and washed with 50 mL saturated solutions of $NH_4Cl$, $NaHCO_3$, and NaCl. The organic layer was dried over $Na_2SO_4$ and concentrated *in vacuo*. Flash chromatography (85:15 pentane:$Et_2O$) afforded the title compound as a clear, colorless oil in 97% yield (5.1 g, 8.63 mmol). IR (film) 3072, 3049, 2957, 2931, 2858, 1726, 1612, 1472, 1428, 1362, 1267, 1170, 1112, 1085, 1036, 852.6, 821.8, 740.9, 702.0, 607.9, 504.3 $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$) δ 7.81-7.34 (m, 10H, SiPh**H**); 6.90 (dd, 1H, *J* = 15.6, 5.4 Hz, C=C**H**CHOSi); 6.87 (s, 2H, Ar-**H**); 5.86 (d, 1H, *J* = 15.6 Hz, C=C**H**$CO_2$Me); 4.39 (m, 1H, C**H**OSi); 4.20 (m, 2H, C$\mathbf{H_2}$OMes); 3.72 (s, 3H, OC$\mathbf{H_3}$); 2.29 (s, 9H, ArC$\mathbf{H_3}$); 1.76-1.28 (m, 5H, C$\mathbf{H_2}$$CHCH_3$, C**H**$CH_3$); 1.10 (s, 9H, SiC(C$\mathbf{H_3}$)$_3$);

0.90 (d, 3H, $J$ = 6.6 Hz, CHC**H**$_3$); $^{13}$C NMR (75 MHz, $CDCl_3$) δ 170.5, 167.1, 150.6, 139.4, 136.2, 136.1, 136.0, 135.6, 135.5, 135.3, 135.1, 134.0, 130.5, 130.3, 130.1, 129.9, 128.6, 128.1, 128.0, 127.9, 127.8, 120.1, 71.3, 63.2, 51.8, 45.1, 35.8, 27.3, 26.8, 26.7, 26.4, 21.4, 20.0, 19.9, 19.6; HRMS (FAB+) exact mass calculated for $[M + H]^+$ ($C_{36}H_{47}O_5Si$) requires $m/z$ 587.3193, found $m/z$ 587.3192. $[\alpha]_D^{25}$ = –12.13 (c = 1.0, $CHCl_3$).

**(*E*,4*S*,6*R*)-6-methyl-4-(*tert*-butyl-diphenyl-silanyloxy)-oct-2-ene-1,8-diol (14).** A 1M solution of diisobutylaluminum hydride in hexanes (75 mL, 75 mmol) was slowly added to a stirred –78 °C solution of (*E*,3*R*,5*S*)-7-(methoxycarbonyl)-5-(*tert*-butyl-diphenyl-silanyloxy)-3-methylhept-6-enyl 2,4,6-trimethylbenzoate (7.4 g, 12.6 mmol) in $Et_2O$ (250 mL). After 30 min MeOH (3 mL) was slowly added, followed by dilution with 250 mL $Et_2O$ and warming to room temperature. Saturated Rochelle's salt (300 mL) was then added, followed by vigorous stirring overnight. The aqueous layer was then separated and extracted with 2 x 100 mL $CH_2Cl_2$ and $Et_2O$. The combined organic layers were dried over $Na_2SO_4$ and concentrated *in vacuo*. Flash chromatography (1:3 pentane:$Et_2O$) afforded the title compound as a clear, colorless oil in 96% yield (5.0 g, 12.1 mmol). IR (film) 3338, 3072, 3049, 2956, 2930, 2858, 1472, 1462, 1428, 1362, 1112, 1057, 972.6, 822.2, 739.1, 702.2, 612.4, 504.8 cm$^{-1}$; $^1$H NMR (300 MHz, $CDCl_3$) δ 7.70-7.32 (m, 10H, SiPh**H**); 5.56 (ddt, 1H, $J$ = 16.2, 7.5, 1.2 Hz, C=C**H**$CH_2OH$); 5.38 (ddt, 1H, $J$ = 16.2, 5.5, 0.6 Hz, C=C**H**CHOSi); 4.24 (m, 1H, C**H**OSi); 3.87 (d, 2H, $J$ = 5.5 Hz, CHC**H**$_2$OH); 3.56 (m, 2H, $CH_2$C**H**$_2$OH); 1.76-1.18 (m, 5H, C**H**$_2$$CHCH_3$, C**H**$CH_3$); 1.06 (s, 9H, SiC(C**H**$_3$)$_3$); 0.78 (d, 3H, $J$ = 6.9 Hz, CHC**H**$_3$); $^{13}$C NMR (75 MHz, $CDCl_3$) δ

136.4, 136.2, 135.0, 134.8, 129.9, 129.8, 129.6, 129.5, 128.0, 127.9, 127.8, 127.6, 72.5, 63.2, 61.0, 45.6, 39.9, 27.4, 27.3, 27.2, 25.7, 20.3, 19.6; HRMS (FAB+) exact mass calculated for $[M + H]^+$ ($C_{25}H_{37}O_3Si$) requires *m/z* 413.2512, found *m/z* 413.2513. $[\alpha]_D^{25}$ = –19.57 (c = 1.0, $CHCl_3$).

**(1*S*,4a*R*,5*S*,7*S*,7a*R*)-1,4a,5,6,7,7a-hexahydro-5-(*tert*-butyl-diphenyl-silanyloxy)-7-methylcyclopenta[*c*]pyran-1-yl acetate (21).** Dess-Martin periodinane (2.54 g, 6.1 mmol) was added to a stirred solution of (*E*,4*S*,6*R*)-6-methyl-4-(*tert*-butyl-diphenyl-silanyloxy)-oct-2-ene-1,8-diol (1.07 g, 2.60 mmol) in $CH_2Cl_2$ (26 mL). After 40 minutes the reaction was concentrated and extracted with 3 x 50 mL pentane. The combined organics were concentrated *in vacuo*, providing 1.0 g (94% yield, 2.44 mmol) of the corresponding dialdehyde, which was immediately redissolved in DMSO (61 mL). L-Proline (93 mg, 0.80 mmol) was added to this stirred solution in one portion. After 5 h, the reaction was warmed to 40 °C and stirred at this temperature for 60 h at which point TLC analysis showed completion. The reaction was then cooled to 0 °C, and acetic anhydride (2.3 mL, 24 mmol) was added, followed by pyridine (1.0 mL, 12 mmol) and DMAP (25 mg, 0.23 mmol). After 15 min the reaction was diluted with 200 mL $Et_2O$ and washed with 50 mL saturated solutions of $NH_4Cl$, $NaHCO_3$, and NaCl. The aqueous layers were then extracted with 2x50 mL $CH_2Cl_2$ and 2x50 mL $Et_2O$. The combined organic layers were dried over $Na_2SO_4$ and concentrated *in vacuo*. Flash chromatography (19:1 pentane:$Et_2O$) afforded the title compound as a clear, colorless oil in 83% yield (910 mg, 2.02 mmol). IR (film) 3072, 2956, 2931, 2858, 1761, 1652, 1472, 1428, 1362, 1211, 1112, 1026, 953.8, 702.3 $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$) δ 7.70-7.35 (m, 10H,

SiPh**H**); 6.35 (dd, 1H, *J* = 6.3, 2.4 Hz, OC**H**=CH); 6.08 (d, 1H, *J* = 6.6, C**H**OAc); 5.05 (dd, 1H, *J* = 6.3, 2.7 Hz, OCH=C**H**); 4.32 (dd, 1H, *J* = 12.0, 6.6 Hz, C**H**OSi); 2.59 (m, 1H, C=CHC**H**); 2.10 (s, 3H, OC(O)C**H$_3$**); 2.08-1.84 (m, 3H, C**H$_2$**CHCH$_3$, C**H**CH$_3$, C**H**CHOAc); 1.24 (m, 1H, C**H$_2$**CHCH$_3$); 1.08 (s, 9H, SiC(C**H$_3$**)$_3$); 0.94 (d, 3H, *J* = 6.9 Hz, CHC**H$_3$**); $^{13}$C NMR (75 MHz, $CDCl_3$) δ 170.0, 141.0, 136.1, 136.0, 135.9, 135.8, 130.0, 129.9, 129.8, 127.9, 127.8, 127.7, 101.3, 91.6, 75.3, 46.0, 40.9, 38.8, 31.6, 27.2, 21.5, 21.4, 19.5; HRMS (FAB+) exact mass calculated for $[M + H]^+$ ($C_{27}H_{35}O_4Si$) requires *m/z* 451.2305, found *m/z* 451.2305. $[\alpha]_D^{25} = -104.1$ (c = 1.0, $CHCl_3$).

**(1*S*,4a*S*,5*S*,7*S*,7a*R*)-4-formyl-1,4a,5,6,7,7a-hexahydro-5-(*tert*-butyl-diphenyl-silanyloxy)-7-methylcyclopenta[*c*]pyran-1-yl acetate (23).** DMF (6 mL) that had been stored over activated molecular sieves for at least 24 h was added to a flame-dried schlenk flask and cooled to –20 °C. Freshly distilled phosphorous oxychloride (0.84 mL, 9.0 mmol) was added dropwise with stirring. The mixture was allowed to slowly warm to room temperature over the course of 1 h, and then stirred at that temperature for an additional 1 h. A solution of **21** (580 mg, 1.3 mmol) in DMF (3 mL) was then added dropwise, and the resulting mixture was warmed to 40 °C. After 60 h the reaction was cooled to –20 °C, quenched by addition of 10 mL of a saturated solution of $NaHCO_3$, and extracted with 3x50 mL $Et_2O$. The combined organics were dried over $Na_2SO_4$ and concentrated *in vacuo*. Flash chromatography (5:1 pentane:$Et_2O$) afforded the title compound as a clear, colorless oil in 73% yield (451 mg, 0.94 mmol) and **24** in 6% yield (see below). IR (film) 3072, 2957, 2931, 2858, 1766, 1677, 1633, 1472, 1428, 1367, 1215, 1183, 1091, 1071, 821.6, 740.0, 704.5 cm$^{-1}$; $^1$H NMR (300 MHz, $CDCl_3$) δ 9.18 (s,

1H, C**H**O); 7.67-7.29 (m, 11H, SiPh**H,** OC**H**=C); 6.45 (d, 1H, *J* = 9.3, C**H**OAc); 4.60 (apparent t, 1H, *J* = 3.4 Hz, C**H**OSi); 2.83 (dd, 1H, *J* = 8.8, 3.4, Hz C=CC**H**); 2.22 (s, 3H, OC(O)C**H$_3$**); 2.13 (m, 1H, C**H**CHOAc); 1.85-1.71 (m, 2H, C**H$_2$**CHCH$_3$, C**H**CH$_3$); 1.20 (m, 1H, C**H$_2$**CHCH$_3$); 1.02 (s, 12H, SiC(C**H$_3$)$_3$**, CHC**H$_3$**); $^{13}$C NMR (75 MHz, $CDCl_3$) δ 190.0, 169.7, 162.7, 136.4, 136.3, 136.2, 136.1, 134.2, 133.2, 129.9, 129.8, 127.8, 127.7, 127.6, 119.1, 96.3, 76.1, 44.7, 43.5, 40.2, 34.2, 27.3, 27.2, 21.7, 21.2, 19.6; HRMS (FAB+) exact mass calculated for $[M + H]^+$ ($C_{28}H_{35}O_5Si$) requires *m/z* 479.2254, found *m/z* 479.2266. $[\alpha]_D^{25} = -13.82$ (c = 1.0, $CHCl_3$).

**(1*S*,4a*S*,5*S*,7*S*,7a*R*)-4-formyl-1,4a,5,6,7,7a-hexahydro-5-(formyl)-7-methylcyclopenta[*c*]pyran-1-yl acetate (24).** DMF (6 mL) that had been stored over activated molecular sieves for at least 24 h was added to a flame-dried schlenk flask and cooled to –20 °C. Freshly distilled phosphorous oxychloride (0.84 mL, 9.0 mmol) was added dropwise with stirring. The mixture was allowed to slowly warm to room temperature over the course of 1 h, and then stirred at that temperature for an additional 1 h. A solution of **21** (580 mg, 1.3 mmol) in DMF (3 mL) was then added dropwise, and the resulting mixture was warmed to 40 °C. After 60 h the reaction was cooled to –20 °C, quenched by addition of 10 mL of a saturated solution of $NaHCO_3$, and extracted with 3 x 50 mL $Et_2O$. The combined organics were dried over $Na_2SO_4$ and concentrated *in vacuo*. Flash chromatography (5:1 pentane:$Et_2O$) afforded the title compound as a clear, colorless oil in 6% yield (18 mg, 0.078 mmol) and **23** in 73% yield (see above). IR (film) 2958, 2924, 1763, 1724, 1673, 1633, 1368, 1216, 1180, 1092, 1066, 1018, 990.9, 963.5 cm$^{-1}$; $^1$H NMR (300 MHz, $CDCl_3$) δ 9.32 (s, 1H, C=CC**H**O); 7.93 (d, 1 H, OC**H**O,

*J* = 0.6 Hz); 7.36 (s, 1H, OC**H**=C); 5.98 (d, 1H, *J* = 9.0, C**H**OAc); 5.66 (apparent t, 1H, *J* = 4.2 Hz, C**H**OCHO); 3.11 (dd, 1H, *J* = 9.0, 4.2 Hz, C=CC**H**); 2.22 (s, 3H, OC(O)C$\mathbf{H_3}$); 2.13 (m, 1H, C**H**CHOAc); 1.97-159 (m, 2H, C$\mathbf{H_2}$CHCH$_3$, C**H**CH$_3$); 1.20 (m, 1H, C$\mathbf{H_2}$CHCH$_3$); 1.02 (d, 3H, *J* = 6.6 Hz, CHC$\mathbf{H_3}$); $^{13}$C NMR (75 MHz, $CDCl_3$) δ 189.7, 169.7, 162.4, 159.9, 117.9, 95.2, 76.1, 44.8, 40.7, 37.8, 34.4, 21.3, 21.1; HRMS (FAB+) exact mass calculated for $[M + H]^+$ ($C_{13}H_{16}O_6$) requires *m/z* 268.0947, found *m/z* 268.0954. $[\alpha]_D^{25} = -13.18$ (c = 1.0, $CHCl_3$).

**(1*S*,4a*S*,5*S*,7*S*,7a*R*)-1-acetoxy-1,4a,5,6,7,7a-hexahydro-5-(*tert*-butyl-diphenyl-silanyloxy)-7-methylcyclopenta[*c*]pyran-4-carboxylic acid (25).** Sodium hypochlorite (1.06 g, 9.4 mmol) was added to a stirred solution of $NaH_2PO_4$ (864 mg, 6.3 mmol) in $H_2O$ (3.2 mL). The resulting solution was added dropwise over 30 min to a stirred mixture of (1*S*,4a*S*,5*S*,7*S*,7a*R*)-4-formyl-1,4a,5,6,7,7a-hexahydro-5-(*tert*-butyl-diphenyl-silanyloxy)-7-methylcyclopenta[*c*]pyran-1-yl acetate (300 mg, 0.63 mmol) in 2-methyl butene (4.2 mL) and tBuOH (6.3 mL). The resulting solution was stirred for 24 h, at which time an additional portion of sodium hypochlorite (354 mg, 3.1 mmol) and $NaH_2PO_4$ (288 mg, 2.1 mmol) in $H_2O$ (1.0 mL) was added. After a further 24 h of stirring, the reaction was diluted with 10 mL $H_2O$, and extracted with 3x20 mL $CH_2Cl_2$ and 3x20 mL $Et_2O$. The combined organics were dried over $Na_2SO_4$ and concentrated *in vacuo*. Flash chromatography (5:1-1:6 pentane:$Et_2O$) afforded the title compound as a clear, colorless oil in 93% yield (288 mg, 0.58 mmol). IR (film) 3073, 2958, 2932, 2859, 1764, 1682, 1634, 1428, 1367, 1287, 1193, 1089, 960.2, 912.0, 737.0, 704.3 cm$^{-1}$; $^1$H NMR (300 MHz, $CDCl_3$) δ 7.76 (s, 1H, OC**H**=C); 7.69-7.29 (m, 10H, SiPh**H**); 6.40 (d,

1H, *J* = 8.7 Hz, C**H**OAc); 4.52 (m, 1H, C**H**OSi); 2.77 (dd, 1H, *J* = 8.4, 3.0 Hz, C=CC**H**); 2.22 (s, 3H, OCOC**H$_3$**); 2.15 (m, 1H, C**H**CHOAc); 1.86-1.73 (m, 2H, C**H$_2$**CHCH$_3$, C**H**CH$_3$); 1.24 (m, 1H, C**H$_2$**CHCH$_3$); 1.04 (s, 12H, SiC(C**H$_3$**)$_3$, CHC**H$_3$**); $^{13}$C NMR (75 MHz, $CDCl_3$) δ 172.9, 169.9, 156.2, 136.4, 136.3, 136.2, 136.1, 134.5, 133.1, 129.9, 129.8, 127.8, 127.7, 127.6, 105.7, 95.5, 76.4, 44.9, 43.1, 42.3, 34.2, 27.3, 27.2, 21.7, 21.2, 19.4; HRMS (FAB+) exact mass calculated for $[M + H]^+$ ($C_{28}H_{35}O_6Si$) requires *m/z* 495.2203, found *m/z* 495.2225. $[\alpha]_D^{25} = -13.82$ (c = 1.0, $CHCl_3$).

**Iridolactone (8).** A solution of HF•pyridine (2 mL, 70% HF) was added to a stirred solution of (1*S*,4a*S*,5*S*,7*S*,7a*R*)-1-acetoxy-1,4a,5,6,7,7a-hexahydro-5-(*tert*-butyl-diphenyl-silanyloxy)-7-methylcyclopenta[*c*]pyran-4-carboxylic acid (240 mg, 0.48 mmol) in THF (4 mL). After 10 h the reaction was diluted with 50 mL $Et_2O$, and washed with 20 mL of a saturated $NaHCO_3$ solution (Caution: violent bubbling). The aqueous layer was thoroughly extracted with 3x20 mL $CH_2Cl_2$ and $Et_2O$. The combined organics were dried over $Na_2SO_4$ and concentrated *in vacuo*. The resultant residue was then immediately dissolved in $CH_2Cl_2$ (10 mL), at which time 1,3-dicyclohexyl carbodiimide (150 mg, 0.73 mmol) was added in one portion. After 15 min, the reaction was concentrated *in vacuo*. Flash chromatography (5:1-1:4 pentane:$Et_2O$) afforded the title compound as a clear, colorless oil in 82% yield (95 mg, 0.40 mmol). IR (film) 2954, 2931, 2854, 1756, 1661, 1237, 1216, 1170, 1012, 972.2, 872.0 cm$^{-1}$; $^1$H NMR (300 MHz, $CDCl_3$) δ 7.31 (d, 1H, 2.7 Hz, OC**H**=C); 6.35 (s, 1H, C**H**OAc); 5.06 (apparent t, 1H, *J* = 4.6 Hz, C**H**OC(O)); 3.42 (m, 1H, C=CC**H**); 2.20-2.10 (m, 4H, OCOC**H$_3$**, C**H**CHOAc); 1.98 (m, 1H, C**H$_2$**CHCH$_3$); 1.66 (m, 1H, C**H**CH$_3$); 1.24 (m, 1H, C**H$_2$**CHCH$_3$); 1.07 (d,

3H, $J$ = 6.3 Hz, CHC**H$_3$**); $^{13}$C NMR (75 MHz, $CDCl_3$) δ 170.2, 169.2, 148.3, 103.6, 88.8, 81.1, 45.0, 42.0, 38.1, 31.8, 20.9, 17.6; HRMS (EI+) exact mass calculated for $[M]^+$ ($C_{12}H_{14}O_5$) requires $m/z$ 238.0841, found $m/z$ 238.0838. $[\alpha]_D^{25}$ = –229.2 (c = 1.0, $CHCl_3$).

**Brasoside Tetraacetate.** 1-*O*-(Trimethylsilyl)-2,3,4,6-tetra-*O*-acetyl-*β*-D-glucopyranose (31.5 mg, 0.075 mmol, prepared according to the method of Allevi[4]) and **8** (7.0 mg, 0.030 mmol) were added as benzene solutions to a schlenk flask under argon. The benzene was then frozen and sublimed. The remaining solid was redissolved in $CH_3CN$ (0.15 mL) and cooled to –30 °C. At this time TMSOTf (2.3 μL, 0.012 mmol) was added dropwise as a 5% solution in $CH_3CN$. After stirring at –30 °C for 3 d, the reaction was quenched with 1 mL pH 7 buffer and extracted with 3x10 mL $Et_2O$. The combined organics were dried over $Na_2SO_4$ and concentrated *in vacuo*. Flash chromatography (1:1-1:3 pentane:$Et_2O$) afforded the title compound as a clear, colorless oil in 86% yield (13.6 mg, 0.026 mmol). The spectral data ($^1$H and $^{13}$C) were in full accord with those reported for the natural isolate,[5,6] except for the IR and HRMS which have not been described: IR (film) 2955, 2920, 2858, 1756, 1660, 1367, 1219, 1216, 1038, 1013, 972.8, 862.2cm$^{-1}$; HRMS (EI+) exact mass calculated for $[M + H]^+$ ($C_{24}H_{31}O_{13}$) requires $m/z$ 527.1765, found $m/z$ 527.1764. $[\alpha]_D^{25}$ = –270.9 (c = 1.0, $CHCl_3$); lit: $[\alpha]_D$ = –229 (c = 0.9, $CHCl_3$).[5]

**Brasoside (2).** A solution of MeOH:$Et_3N$:$H_2O$ (0.08 mL, 8:1:1) was added slowly to a –15 °C solution of Brasoside tetraacetate (5.0 mg, 0.007 mmol) in $CH_2Cl_2$ (0.04 mL). After 3 h the reaction was quenched with 0.5 mL pH 7 buffer, and extracted

with 3x5 mL EtOAc. The combined organics were dried over $Na_2SO_4$ and concentrated *in vacuo*. Flash chromatography (9:1 EtOAc:MeOH) afforded the title compound as a white powder in 90% yield (2.3 mg, 0.0063 mmol). The spectral data ($^1H$ and $^{13}C$) were in full accord with those already reported (table 2),[5-7] except for the IR and HRMS which have not been described: IR (film) 2960, 2917, 2849, 1749, 1654, 1261, 1090, 1019, 799.0 $cm^{-1}$; HRMS (FAB+) exact mass calculated for $[M + H]^+$ ($C_{16}H_{23}O_9$) requires *m/z* 359.1342, found *m/z* 359.1332. $[\alpha]_D^{25} = -181.0$ (c = 0.41, EtOH); lit: $[\alpha]_D = -170$ (c = 0.97, EtOH)[5]; $[\alpha]_D = -283$ (c = 1.4, EtOH)[6].

**(*E*)-2-hydroxyethyl 3-(4-(benzyloxy)phenyl)acrylate.** Oxalyl chloride (8 mL, 2M solution in $CH_2Cl_2$) was added to a stirred solution of *p*-benzyloxycinammic acid (2.89 g, 11.3 mmol, prepared according to the method of Doherty[8]) in $CH_2Cl_2$ (45 mL) at 0 °C. A few drops of DMF were then added, and the resulting solution was stirred at 0°C for 1 h and at 23 °C for a further 1 h. At this stage the solution was added dropwise via cannula to a stirred mixture of ethylene glycol (12.6 mL, 226 mmol), triethylamine (4 mL, 28 mmol), and DMAP (100 mg, 0.82 mmol) in $CH_2Cl_2$ (110 mL) cooled to 0 °C. The resulting solution was stirred for 12 h, at which time the reaction was quenched with a saturated solution of $NaHCO_3$ (200 mL), and after extraction the organic layer was washed with brine, dried over $Na_2SO_4$ and concentrated *in vacuo*. Flash chromatography (4:1 $Et_2O$:pentane) afforded the title compound as a white solid in 93% yield (3.14 g, 10.5 mmol). IR (film) 3420, 2956, 2932, 2859, 1707, 1636, 1602, 1511, 1254, 1172, 984.1, 825.5 $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$) δ 7.68 (d, 1H, *J* = 16.2 Hz, ArC**H**=CH); 7.50-7.35 (m, 7H, Ar**H**); 6.98 (d, 2H, *J* = 9.0 Hz, Ar**H**); 6.34 (d, 1H, *J* = 16.2 Hz,

ArCH=C**H**); 5.10 (s, 2H, C**H**$_2$Ph); 4.35 (m, 2H, $CO_2C$**H**$_2CH_2$); 3.90 (dd, 2H, *J* = 9.0, 5.1 Hz, $CO_2CH_2C$**H**$_2$); $^{13}$C NMR (75 MHz, $CDCl_3$) δ 167.9, 160.9, 145.3, 136.7, 130.2, 128.9, 128.4, 127.7, 127.4, 115.5, 115.4, 70.3, 66.4, 61.5; HRMS (FAB+) exact mass calculated for $[M + H]^+$ ($C_{18}H_{19}O_4$) requires *m/z* 299.1283, found *m/z* 299.1276.

**Enolsilane (28).** Dess-Martin periodinane (2.15 g, 5.1 mmol) was added to a stirred solution of (*E*)-2-hydroxyethyl 3-(4-(benzyloxy)phenyl)acrylate (1.21 g, 4.06 mmol) in $CH_2Cl_2$ (20 mL). After 10 h the reaction was concentrated and extracted with 3x50 mL $Et_2O$. The combined organics were concentrated *in vacuo*, providing 1.15 g (95% yield, 5.8 mmol) of the corresponding aldehyde, which was immediately redissolved in $CH_3CN$ (5 mL). The resulting solution was added dropwise to a premixed solution of triethylamine (3.75 mL, 27 mmol) and chlorotrimethylsilane (2.44 mL, 19.2 mmol) in $CH_3CN$ (5 mL). This mixture was stirred for 2 h, at which time the reaction was concentrated *in vacuo*. Flash chromatography (3:1 pentane:$Et_2O$) on Iatrobeads afforded the title compound as a white solid in 82% yield (1.75 g, 4.8 mmol). IR (film) 3117, 3065, 3035, 2958, 2931, 2898, 2860, 1732, 1682, 1634, 1601, 1511, 1270, 1158, 1122, 985.2, 843.5 cm$^{-1}$; $^1$H NMR (300 MHz, $CDCl_3$) δ 7.74 (d, 1H, *J* = 16.2 Hz, ArC**H**=CH); 7.51-7.36 (m, 7H, Ar**H**); 6.98 (d, 2H, *J* = 8.7 Hz, Ar**H**); 6.74 (d, 1H, *J* = 3.6 Hz, C**H**=CHOTMS); 6.39 (d, 1H, *J* = 16.2 Hz, ArCH=C**H**); 5.84 (d, 1H, *J* = 3.6 Hz, CH=C**H**OTMS); 5.10 (s, 2H, C**H**$_2$Ph); 0.25 (s, 9H, Si(C**H**$_3$)$_3$); $^{13}$C NMR (75 MHz, $CDCl_3$) δ 164.3, 161.0, 146.1, 136.6, 130.2, 130.0, 128.9, 128.4, 127.7, 127.4, 121.2, 115.5, 114.7, 70.3, -0.2; HRMS (FAB+) exact mass calculated for $[M + H]^+$ ($C_{21}H_{25}O_4Si$) requires *m/z* 369.1522, found *m/z* 369.1517.

**2-*O*-Benzylcoumaroyl-4,6-bis-*O*-benzyloxy-α-D-glucopyranose (30).** (2*R*,3*R*)-3-Hydroxy-2,3-bis-(benzylyloxy)-propionaldehyde (**29**) (125 mg, 0.42 mmol, prepared according to the method of MacMillan[9] using D-proline) was added as a solution in 2.0 mL of toluene to a flame-dried schlenk flask charged with finely divided magnesium bromide diethyl etherate (322 mg, 1.25 mmol, freshly prepared from magnesium turnings and dibromoethane in $Et_2O$) and 2.0 mL of toluene cooled to –20 °C. After stirring for 30 minutes at –20 °C, **13** (230 mg, 0.63 mmol) was added as a solution in 0.5 mL toluene. 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 50 mL saturated aqueous $NH_4Cl$ and extracted with $Et_2O$ (3x50 mL). The combined organics were washed with 50 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 quenched with 50 mL 10% $NaHCO_3$, extracted with 2x100 mL $Et_2O$, dried over anhydrous $Na_2SO_4$, filtered and concentrated *in vacuo*. Crude $^1$H NMR analysis indicated an 10:1 mixture of glucose:mannose-derived diastereomers. Flash chromatography (1:1-4:1 $Et_2O$:pentane) afforded the title compound as a white solid (163 mg, 0.27 mmol) in 65% yield, 8:1 $\alpha$:$\beta$. IR (film) 3425, 3064, 3032, 2924, 2869, 1710, 1633, 1603, 1511, 1454, 1251, 1171, 1058, 910.58, 828.2, 743.8, 697.6 cm$^{-1}$; $^1$H NMR (300 MHz, $CDCl_3$) $\alpha$-isomer: δ 7.72 (d, 1H, *J* = 15.9 Hz, ArC**H**=CH); 7.47-7.20 (m, 17H, Ar**H**); 6.94 (d, 2H, *J* = 8.7 Hz, Ar**H**); 6.37 (d, 1H, *J* = 15.9 Hz, ArCH=C**H**); 5.48 (m, 1H, H1); 5.06 (m, 2H, C**H**$_2$Ph); 4.87 (dd, 1H, *J* = 10.2, 3.9 Hz, H2); 4.85 (d, 1H, *J* = 11.4 Hz, C**H**$_2$Ph); 4.64-4.50 (m, 3H, C**H**$_2$Ph);

4.24 (m, 1H, H6); 4.09 (m, 1H, H6); 3.72-3.53 (m, 3H, H3, H4, H5); $^{13}$C NMR (75 MHz, $CDCl_3$) $\alpha$-isomer: δ 167.4, 161.0, 146.0, 138.4, 138.0, 136.6, 130.2, 128.9, 128.8, 128.7, 128.4, 128.3, 128.2, 128.0, 127.7, 127.4, 115.4, 114.9, 90.7, 78.5, 75.0, 74.0, 73.7, 72.0, 70.3, 70.0, 68.9; HRMS (FAB+) exact mass calcd for $[M+H]^+$ ($C_{36}H_{37}O_8$) requires *m/z* 597.2488, found *m/z* 597.2512; $[\alpha]_D^{25} = 30.59$ (c = 1.0, $CHCl_3$, 8:1 $\alpha$:$\beta$ mixture).

**2-*O*-Benzylcoumaroyl-3,4,6-tris-*O*-benzyloxy-α-D-glucopyranose.** Benzyl bromide (0.132 mL, 1.1 mmol) was added to a solution of freshly prepared $Ag_2O$ (255 mg, 1.1 mmol) and **9** (131 mg, 0.22 mmol) in 2.3 mL of $CH_2Cl_2$ stirred in the dark. After stirring for 18 h, the reaction was filtered through a pad of celite and concentrated *in vacuo*. The resulting residue was redissolved in MeOH (3 mL), at which time ammonium formate (208 mg, 3.3 mmol) and 10% Pd on alumina (220 mg) were added. The suspension was stirred for 10 hours, then filtered and concentrated *in vacuo*. Flash chromatography (1:1-3:1 $Et_2O$:pentane) afforded the title compound as a white solid (103 mg, 0.15 mmol) in 68% yield, 12:1 $\alpha$:$\beta$. IR (film) 3424, 3063, 3030, 2892, 2868, 1713, 1631, 1602, 1510, 1453, 1249, 1172, 1060, 827.6, 736.4, 697.1 cm$^{-1}$; $^1$H NMR (300 MHz, $CDCl_3$) $\alpha$-isomer: δ 7.70 (d, 1H, *J* = 15.9 Hz, ArC**H**=CH); 7.48-7.18 (m, 22H, Ar**H**); 6.98 (d, 2H, *J* = 8.7 Hz, Ar**H**); 6.33 (d, 1H, *J* = 15.9 Hz, ArCH=C**H**); 5.50 (t, 1H, *J* = 3.6 Hz, H1); 5.08 (m, 2H, C**H$_2$**Ph); 4.88-4.83 (m, 3H, H2, C**H$_2$**Ph); 4.64-4.51 (m, 4H, C**H$_2$**Ph); 4.21-4.14 (m, 2H, H6); 3.86 (m, 1H, H3); 3.72-3.67 (m, 2H, H4, H5); $^{13}$C NMR (75 MHz, $CDCl_3$) $\alpha$-isomer: δ 166.8, 161.0, 145.7, 138.7, 138.3, 138.0, 136.7, 130.2, 128.9, 128.8, 128.7, 128.6, 128.4, 128.3, 128.2, 128.1, 128.0, 127.9, 127.8, 127.7, 127.5, 115.5, 115.2, 90.9, 80.2, 78.4, 77.8, 77.4, 76.9, 75.8, 75.4, 73.9, 73.7, 70.5, 70.3, 69.0;

HRMS (EI+) exact mass calcd for $[M]^+$ ($C_{43}H_{42}O_8$) requires *m/z* 686.2880, found *m/z* 686.2891; $[\alpha]_D^{25}$ = 38.62 (c = 1.0, $CHCl_3$, 12:1 $\alpha$:$\beta$ mixture).

**1-*O*-(Trimethylsilyl)-2-*O*-Benzylcoumaroyl-3,4,6-tris-*O*-benzyloxy-β-D-glucopyranose (9).** Chlorotrimethylsilane (27.8 μL, 0.22 mmol) was added dropwise over 20 min as a benzene (1 mL) solution to a refluxing mixture of triethylamine (0.202 mL, 1.46 mmol) and 2-*O*-benzylcoumaroyl-3,4,6-tris-*O*-benzyloxy-α-D-glucopyranose (100 mg, 0.146 mmol) in benzene (2.9 mL). After refluxing for 2 h, the reaction was filtered through a pad of celite and concentrated *in vacuo*. Flash chromatography (3:1 pentane: $Et_2O$) on Iatrobeads afforded the title compound as a clear oil that solidifies to a white solid on standing *in vacuo* (101 mg, 0.133 mmol) in 91% yield. IR (film) 3064, 3032, 2958, 2868, 1716, 1634, 1603, 1511, 1454, 1251, 1150, 1068, 846.6, 736.6, 697.3 $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$): δ 7.73 (d, 1H, *J* = 15.9 Hz, ArC**H**=CH); 7.55-7.25 (m, 22H, Ar**H**); 7.03 (d, 2H, *J* = 8.7 Hz, Ar**H**); 6.33 (d, 1H, *J* = 15.9 Hz, ArCH=C**H**); 5.20-5.15 (m, 3H, H1, C$\mathbf{H_2}$Ph); 4.92-4.61 (m, 7H, H2, C$\mathbf{H_2}$Ph); 3.85-3.76 (m, 4H, H3, H5, H6); 3.62 (m, 1H, H4); 0.24 (s, 9H, Si(C$\mathbf{H_3}$)$_3$); $^{13}C$ NMR (75 MHz, $CDCl_3$): δ 166.1, 160.9, 145.1, 138.6, 138.6, 138.4, 138.3, 136.8, 130.1, 129.0, 128.7, 128.6, 128.5, 128.4, 128.3, 128.2, 128.0, 127.9, 127.8, 127.7, 127.6, 115.8, 115.6, 96.3, 83.0, 78.4, 75.7, 75.4, 75.3, 75.2, 73.8, 70.4, 69.3, 0.48; HRMS (FAB+) exact mass calcd for $[M - H]^+$ ($C_{46}H_{49}O_8Si$) requires *m/z* 757.3197, found *m/z* 757.3174; $[\alpha]_D^{25}$ = 44.67 (c = 1.0, $CHCl_3$).

**2-*O*-Benzylcoumaroyl-3,4,6-tris-*O*-benzyloxy-brasoside (31). 9** (71 mg, 0.094 mmol) and **8** (15 mg, 0.063 mmol) were added as benzene solutions to a schlenk flask

under argon. The benzene was then frozen and evaporated. The remaining solid was redissolved in $CH_3CN$ (0.25 mL) and cooled to –30 °C. At this time TMSOTf (6.1 μL, 0.031 mmol) was added dropwise as a 10% solution in $CH_3CN$. After 5 d stirring at –30 °C the reaction was quenched with 2 mL pH 7 buffer, and extracted with 3x15 mL $Et_2O$. The combined organics were dried over $Na_2SO_4$ and concentrated *in vacuo*. Flash chromatography (50:1-25:1 $CH_2Cl_2$:$Et_2O$) afforded the title compound as a clear, colorless oil in 74% yield (40 mg, 0.047 mmol). IR (film) 3069, 3032, 2962, 2873, 1756, 1716, 1660, 1603, 1511, 1455, 1258, 1081, 800.0, 737.4, 698.4 $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$): δ 7.56 (d, 1H, *J* = 15.9 Hz, ArC**H**=CH); 7.49-7.15 (m, 23H, Ar**H**, OC**H**=C); 6.98 (d, 2H, *J* = 8.7 Hz, Ar**H**); 6.14 (d, 1H, *J* = 15.9 Hz, ArCH=C**H**); 5.52 (d, 1H, *J* = 0.9 Hz, OC**H**O-Glucose); 5.12-4.53 (m, 11H, H1, H2, C**H**$_2$Ph, C**H**OC(O)); 3.81-3.72 (m, 4H, H3, H5, H6); 3.58 (m, 1H, H4), 3.42 (dt, 1H, *J* = 6.9, 2.7 Hz, OC=CC**H**); 2.05 (m, 2H, C**H**$_2$CHCH$_3$, C**H**CHO-Glucose); 1.86 (m, 1H, C**H**CH$_3$); 1.54 (m, 1H, C**H**$_2$CHCH$_3$); 1.00 (d, 3H, *J* = 6.3 Hz, CHC**H**$_3$); $^{13}C$ NMR (75 MHz, $CDCl_3$): δ 170.4, 165.9, 160.8, 147.7, 145.5, 137.8, 136.5, 133.8, 130.0, 128.7, 128.6, 128.5, 128.4, 128.2, 128.1, 128.0, 127.9, 127.8, 127.7, 127.6, 127.5, 127.1, 115.3, 114.8, 106.7, 104.0, 96.3, 92.9, 82.5, 81.0, 77.7, 77.2, 75.4, 75.2, 75.1, 73.5, 72.7, 70.1, 68.4, 45.1, 42.1, 38.1, 31.4, 17.8; HRMS (FAB+) exact mass calcd for $[M + H]^+$ ($C_{53}H_{53}O_{11}$) requires *m/z* 865.3588, found *m/z* 865.3563; $[\alpha]_D^{25} = -37.42$ (c = 1.0, $CHCl_3$).

**Littoralisone (1).** **16** (10 mg, 0.012 mmol) was dissolved in degassed benzene (3.8 mL) in a Pyrex flask under argon. This solution was exposed to 350 nm UV light (Hitachi UVA lamps, Luzchem 10 lamp photoreactor) with stirring for 2 h. At this time

the reaction was concentrated *in vacuo*, then redissolved in EtOAc/MeOH (2:1), and 10% Pd/C (5 mg) was added with stirring. This suspension was degassed and backfilled with $H_2$ three times, at which point it was kept under a slight positive pressure of $H_2$. After 30 min, the reaction was filtered, and concentrated *in vacuo*. Flash chromatography (50:1-25:1 $CH_2Cl_2$:MeOH) afforded the title compound as a white powder in 84% yield (5.1 mg, 0.010 mmol). $^1H$ and $^{13}C$ NMR, IR and HRMS spectra confirm that synthetic and natural **1** are identical in all respects (table 1). IR (film) 3391, 1745, 1635, 1518, 1448, 1187, 1076, 972.4 $cm^{-1}$. Synthetic **1** $[\alpha]_D^{25}$= –46.1 (*c* = 0.4, MeOH), natural **1** $[\alpha]_D^{25}$ = –49.5 (*c* = 0.4, MeOH)[10]. HRMS (FAB+) exact mass calcd for $[M + H]^+$ ($C_{25}H_{29}O_{11}$) requires *m/z* 505.1710, found *m/z* 505.1699.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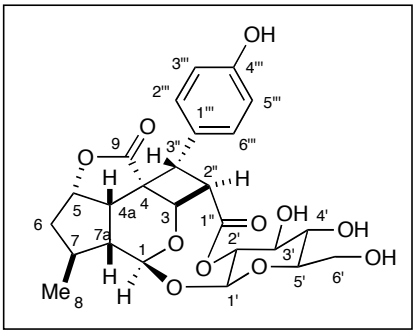
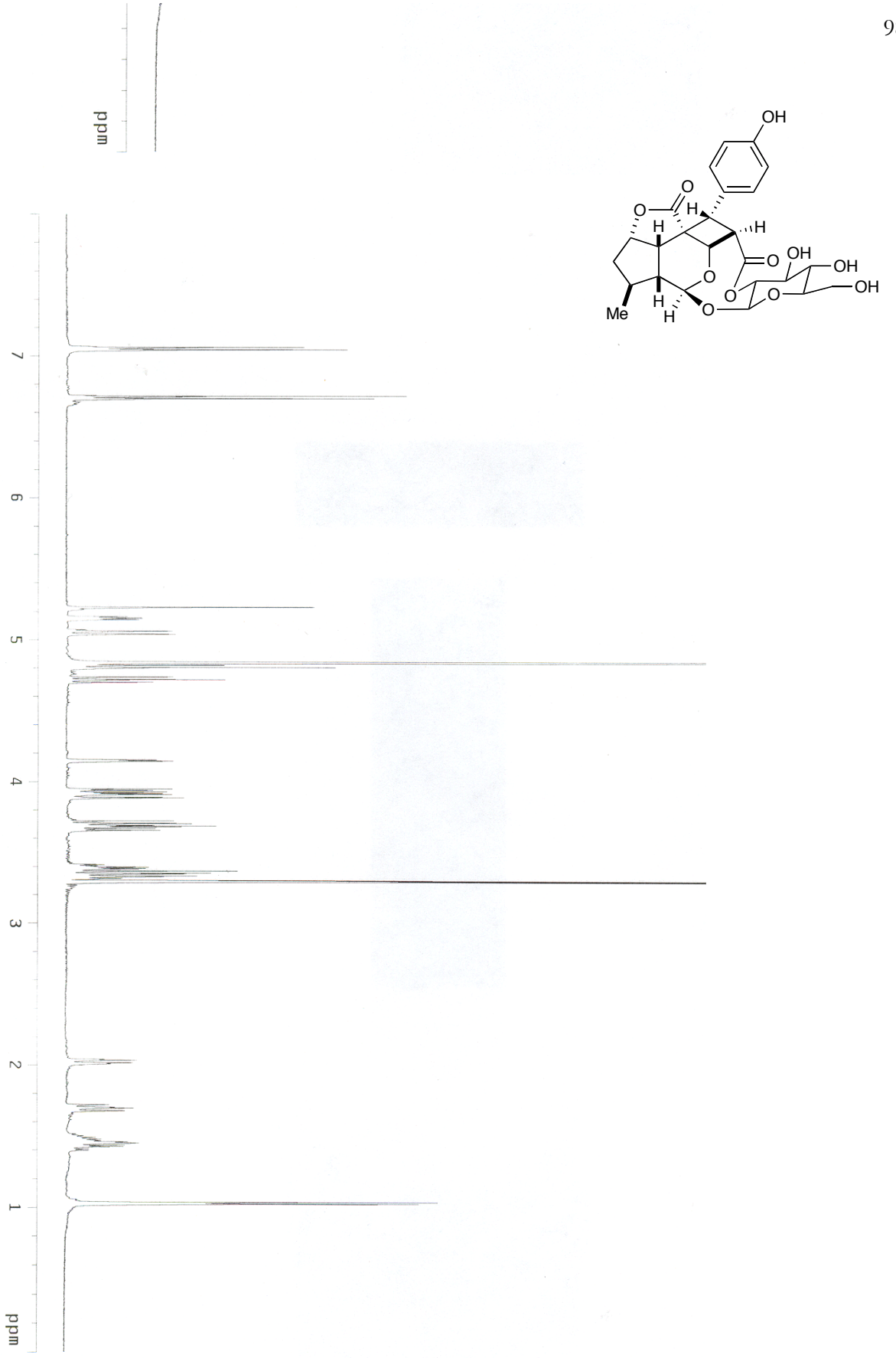


**Table 1. $^{1}H$ and $^{13}C$ NMR Data for Natural[10] and Synthetic 1[a]**

| position | Natural Littoralisone[b] | | Synthetic Littoralisone[c] | |
|---|---|---|---|---|
| | $^{13}C$ (δ) | $^{1}H$ (δ), m, J (Hz) | $^{13}C$ (δ) | $^{1}H$ (δ), m, J (Hz) |
| 1 | 96.45 | 5.23, s | 96.46 | 5.23, s |
| 3 | 66.84 | 5.06, d, 11.1 | 66.87 | 5.04, d, 10.8 |
| 4 | 48.13 | | 48.15 | |
| 4a | 43.87 | 3.35, dd, 9.2, 4.6 | 43.90 | 3.33, dd, 9.0, 4.5 |
| 5 | 83.47 | 5.16, dd, 5.0, 4.6 | 83.48 | 5.15, dd, 6.8, 4.4 |
| 6 | 43.23 | 2.03 (H-6α), dd, 12.6, 3.8<br>1.42 (H-6β), dd, 12.6, 5.0 | 43.26 | 2.02 (H-6α), dd, 12.6, 3.9<br>1.41 (H-6β), dd, 12.6, 5.3 |
| 7 | 33.21 | 1.49, m | 33.24 | 1.47, m |
| 7a | 46.98 | 1.70, dd, 11.8, 9.2 | 47.01 | 1.70, dd, 12.2, 9.0 |
| 8 | 16.58 | 1.03, d, 5.7 | 16.61 | 1.03, d, 5.7 |
| 9 | 176.94 | | 176.96 | |
| 1’ | 100.37 | 4.83, d, 8.4 | 100.39 | 4.81, d, 8.3 |
| 2’ | 80.49 | 4.73, dd, 9.9, 8.4 | 80.51 | 4.72, dd, 9.8, 8.4 |
| 3’ | 74.59 | 3.72, dd, 9.9, 8.4 | 74.62 | 3.70, dd, 9.8, 8.4 |
| 4’ | 71.93 | 3.37, dd, 9.9, 8.4 | 71.94 | 3.36, dd, 9.8, 8.4 |
| 5’ | 79.54 | 3.41, ddd, 9.9, 5.3, 2.3 | 79.57 | 3.40, ddd, 9.8, 5.3, 2.0 |
| 6’ | 62.63 | 3.68 (H-6’a), dd, 11.8, 5.3<br>3.90 (H-6’b), dd, 11.8, 2.3 | 62.66 | 3.67 (H-6’a), dd, 12.2, 5.3<br>3.89 (H-6’b), dd, 12.2, 2.0 |
| 1” | 175.13 | | 175.14 | 0.97, d, 6.6 |
| 2” | 50.14 | 3.94, dd, 11.1, 4.6 | 50.17 | 3.93, dd, 11.0, 4.6 |
| 3” | 49.65 | 4.15, d, 4.6 | 49.66 | 4.14, d, 4.4 |
| 1”’ | 128.37 | | 128.39 | |
| 2”’ | 130.32 | 7.06, dd, 6.5, 1.9 | 130.35 | 7.05, dd, 6.8, 1.9 |
| 3”’ | 116.19 | 6.72, dd, 6.5, 1.9 | 116.20 | 6.71, dd, 6.8, 1.9 |
| 4”’ | 157.79 | | 157.84 | |
| 5”’ | 116.19 | 6.72, dd, 6.5, 1.9 | 116.20 | 6.71, dd, 6.8, 1.9 |
| 6”’ | 130.32 | 7.06, dd, 6.5, 1.9 | 130.35 | 7.05, dd, 6.8, 1.9 |

[a]Spectra were measured in $CD_3OD$. [b]$^{1}H$ NMR (500 MHz); $^{13}C$ (125 MHz). [c]$^{1}H$ NMR (500 MHz);
$^{13}C$ (125 MHz).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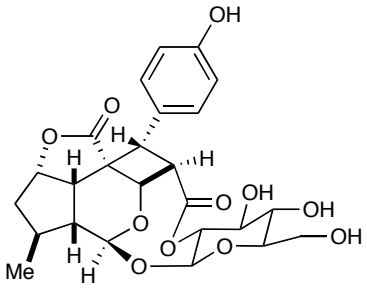
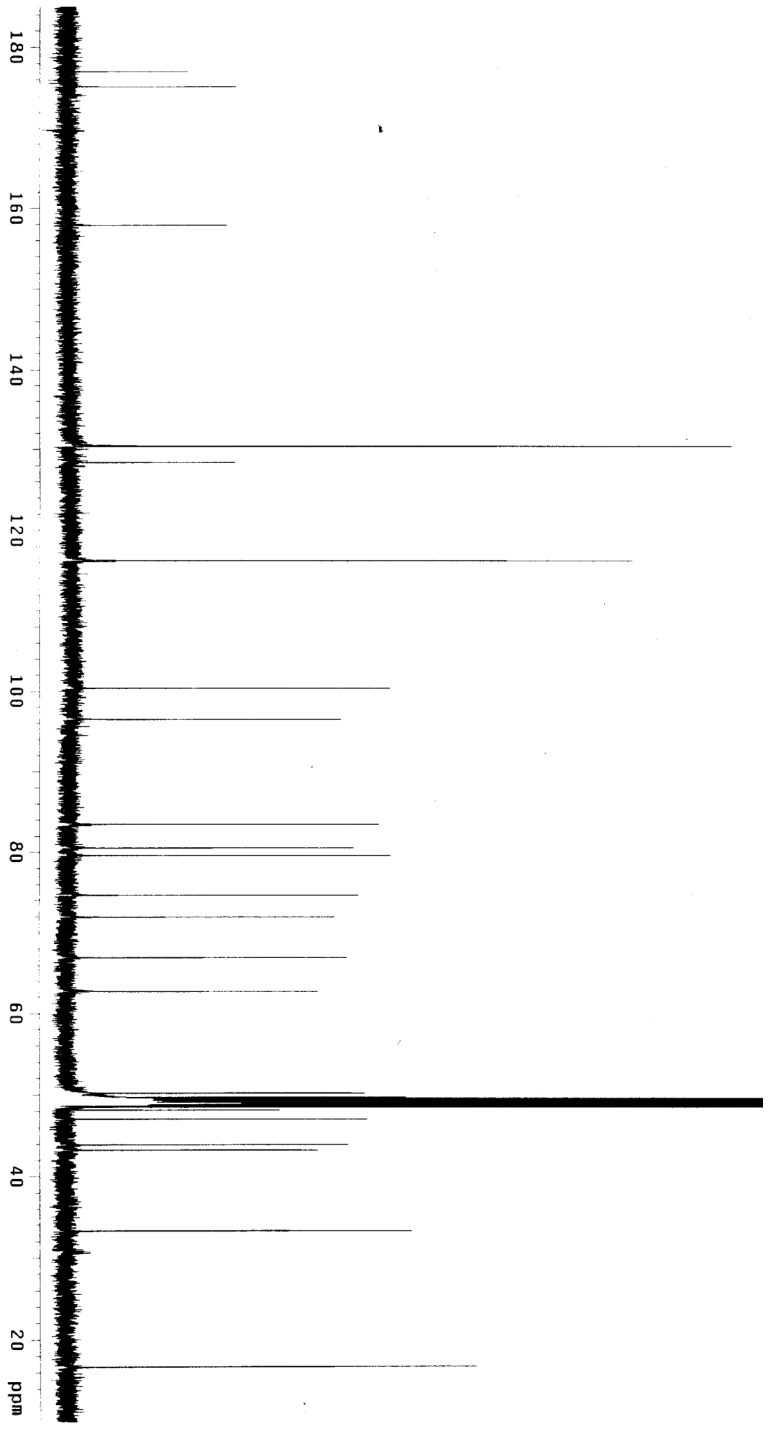
$^{13}C$ NMR of synthetic **1**



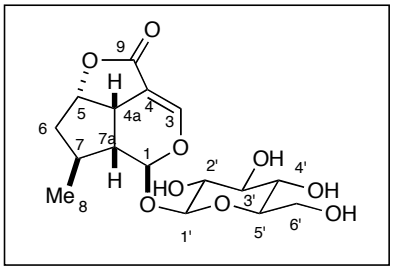
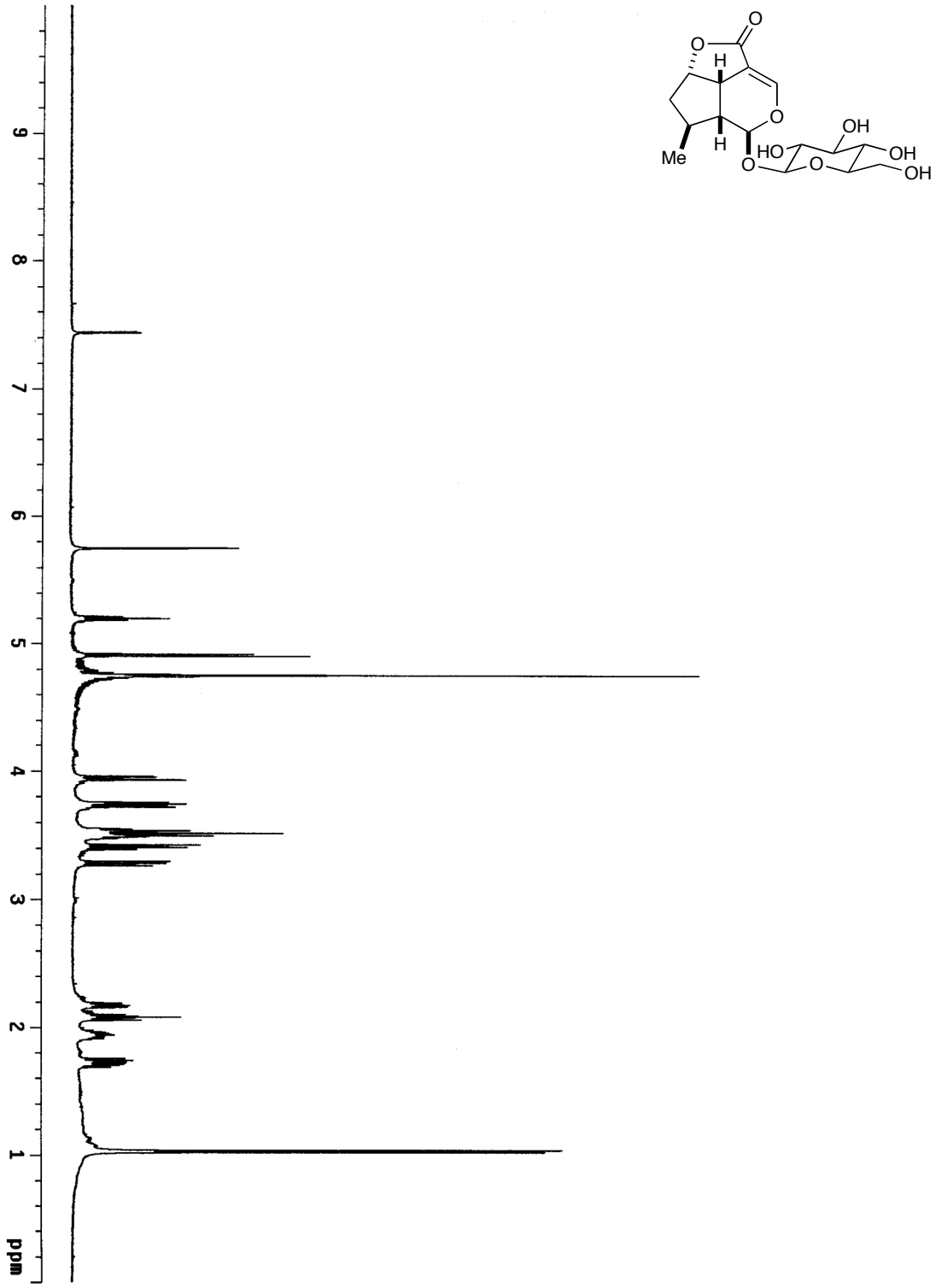


**Table 2. $^{1}H$ and $^{13}C$ NMR Data for Natural[5] and Synthetic 2[a]**

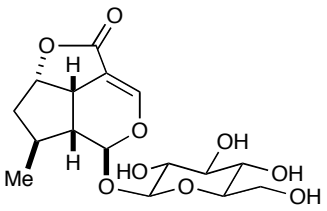
| | | | Natural Brasoside[b] | | | Synthetic Brasoside[c] | |
|---|---|---|---|---|---|---|---|
| position | | | $^{13}C$ (δ) | $^{1}H$ (δ), m, J (Hz) | | $^{13}C$ (δ) | $^{1}H$ (δ), m, J (Hz) |
| | 1 | | 95.3 | 5.75, s | | 95.5 | 5.75, s |
| | 3 | | 150.7 | 7.45, d, 2.6 | | 150.8 | 7.44, d, 2.5 |
| | 4 | | 104.1 | | | 104.2 | |
| | 4a | | 38.6 | 3.50, dt, 7.2, 2.5 | | 38.7 | 3.49, m |
| | 5 | | 84.4 | 5.20, t, 7.7 | | 84.6 | 5.20, t, 7.5 |
| | 6 | | 41.8 | 2.08 (H-6α), dd, 15.2, 7.6<br>1.73 (H-6β), ddd, 15.1, 11.4, 8.0 | | 41.8 | 2.07 (H-6α), dd, 15.0, 8.0<br>1.71 (H-6β), ddd, 15.0, 11.5, 8.0 |
| | 7 | | 32.3 | 1.94, m | | 32.3 | 1.93, m |
| | 7a | | 45.5 | 2.18, ddd, 11.0, 6.8, 0.8 | | 45.6 | 2.16, ddd, 11.0, 6.5, 0.7 |
| | 8 | | 17.5 | 1.03, d, 7.0 | | 17.5 | 1.02, d, 6.5 |
| | 9 | | 175.0 | | | 175.2 | |
| | 1’ | | 99.4 | 4.91, d, 8.0 | | 99.5 | 4.90, d, 8.0 |
| | 2’ | | 73.4 | -- | | 73.4 | 3.30, dd, 9.3, 8.2 |
| | 3’ | | 76.3 | -- | | 76.3 | 3.55-3.47, m |
| | 4’ | | 70.4 | -- | | 70.4 | 3.41, dd, 10.0, 9.3 |
| | 5’ | | 77.1 | -- | | 77.2 | 3.55-3.47, m |
| | 6’ | | 61.5 | -- | | 61.5 | 3.74 (H-6’a), dd, 12.4, 5.0<br>3.94 (H-6’b), dd, 12.4, 2.2 |

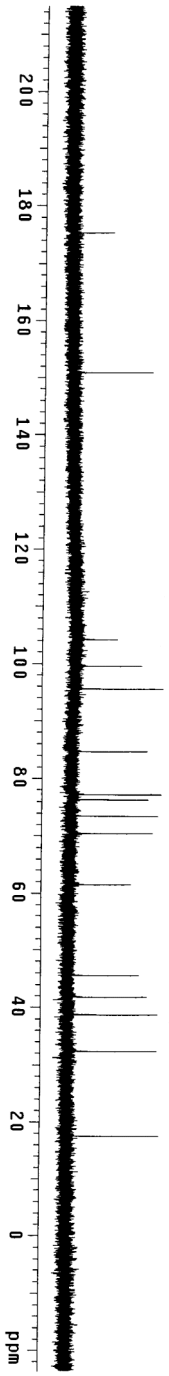
[a]Spectra were measured in $D_2O$. [b]$^{1}H$ NMR (500 MHz); $^{13}C$ (125 MHz). [c]$^{1}H$ NMR (500 MHz); $^{13}C$ (125 MHz).

$^1$H NMR of synthetic **2**



$^{13}C$ NMR of synthetic **2**



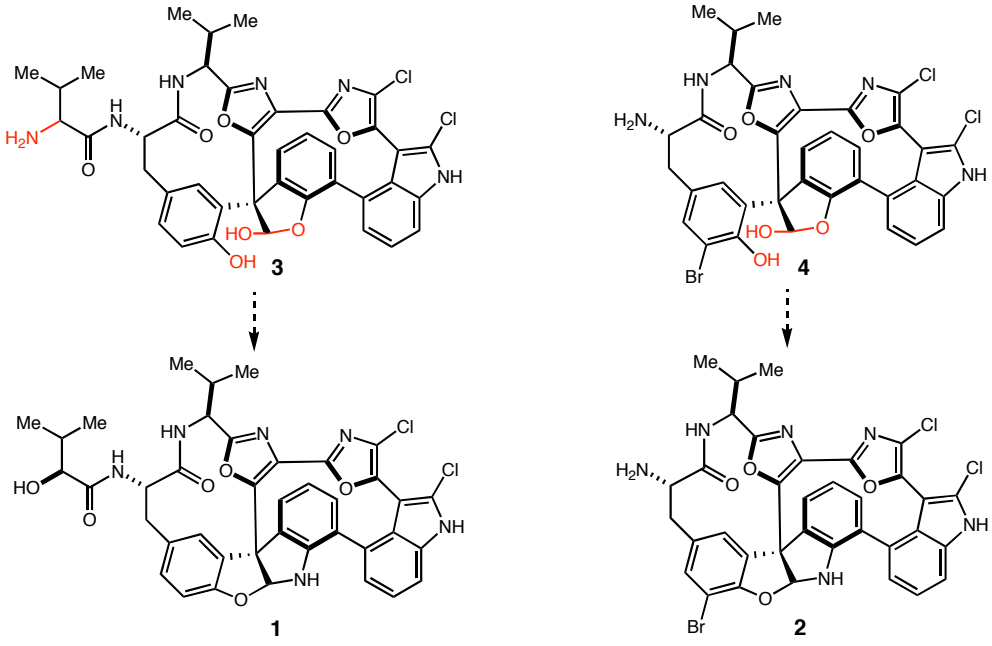
# Chapter 4

## Progress Toward the Total Synthesis of Diazonamide A*

### *Isolation, Biological Activity, and Structural Revision*

The diazonamides were isolated by Fenical and Clardy in 1991[1] from the methanol extracts of the marine ascidian *Diazona angluata*, originally misidentified as *Diazona chinensis*[2] (figure 1). From these extracts were obtained considerable quantities of each isolate: 54 mg of diazonamide A (**1**) and 132 mg of diazonamide B (**2**). However, the paucity of protons and abundance of heteroatoms in these structures made unambiguous structural assignment strictly through $^{1}H$-$^{13}C$ NMR correlation methods difficult. Instead, a single crystal X-ray structure of a *p*-bromobenzoyl derivative of **2** led

**Figure 1: Original and Revised Structures for the Diazonamides**




* A communication of this work is in preparation.

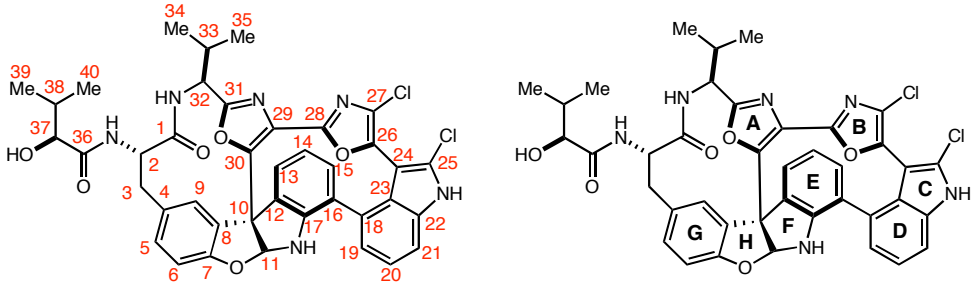
[1] Lindquist, N.; Fenical, W.; Van Duyne, G. D.; Clardy, J. *J. Am. Chem. Soc.* **1991**, *113*, 2303.

[2] Vervoort, H. C.; PhD thesis, University of California at San Diego, **1999**.

to the erroneous assignment of diazonamide B as **4**, with diazonamide A assigned as **3** based on $^{1}$H NMR and analogy to the crystal structure. Significantly, diazonamide A was found to be tremendously cytotoxic ($IC_{50}$ <15 nM) against HCT-116 and B-16 human cancer cell lines.[1] Subsequent studies at the National Cancer Institute showed even greater potency (4.9 nM) against CA46, MCF7, PC-3, and A549 cell lines.[3] Detailed biochemical studies have also indicated that **1** arrests cells at the $G_2$/M phase of the cell cycle through distortion of the microtubules constituting the mitotic spindle. Diazonamide A may also have a binding site on microtubules distinct from other tubulin-binding natural products (e.g., vinca alkaloids, dolastatins, epothilones).[4]

The excitement in the synthetic community for this novel, elaborate class of natural product was immediate. Numerous synthetic groups have reported progress toward the originally proposed structure **3**, but since this work has been thoroughly and precisely reviewed[5] I will focus strictly on the recent successful syntheses of **1** that can put our own efforts in proper context. In 2001, the Harran lab at the UT Southwestern Medical Center reported the first and only total synthesis of **3**. This feat was remarkable

**Figure 2: Accepted Carbon Numbering and Ring Labeling Terminology for** 1



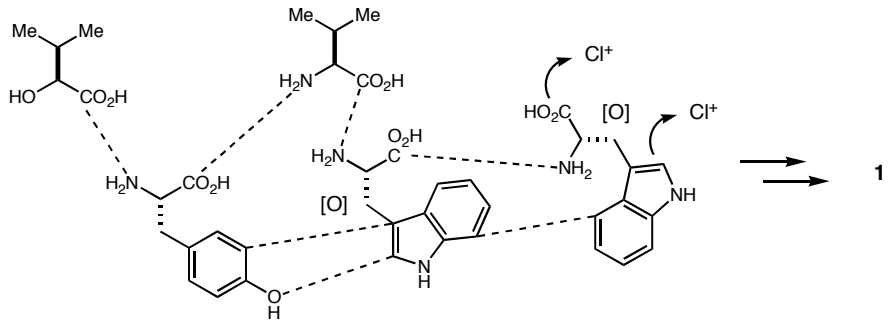

[3] Li, J.; Jeong, S.; Esser, L.; Harran, P. G. *Angew. Chem. Int. Ed.* **2001**, *40*, 4765.

[4] Cruz-Monserrate, Z.; Vervoort, H. C.; Bai, R.; Newman, D. J.; Howell, S. B.; Los, G.; Mullaney, J. T.; Williams, M. D.; Pettit, G. R.; Fenical, W.; Hamel, E. *Mol. Pharmacology* **2003**, *63*, 1273.

[5] (a) Fuerst, D, E.; PhD thesis, Yale University, **2004**; (b) Ritter, T.; Carreira, E. M. *Angew. Chem. Int. Ed.* **2002**, *41*, 2489.

in many respects, including highly creative chemistry. Most noteworthy was their revelation that synthetic **3** did not match natural diazonamide A in terms of spectral data, TLC mobility, biological activity and stability. Indeed, **3** turned out to be substantially less stable than the natural sample, and led the Harran lab to perform a detailed structural reassignment based on the available data. In back-to-back communications, Harran reported his synthesis of **3** and revised structures of the diazonamides (now **1** and **2**), and proposed a biosynthetic origin for **1** that is more concise than those envisioned for **3** (figure 3).[3,6] Armed with these new insights, synthetic chemists could finally hope to complete the synthesis of diazonamide A.

**Figure 3: Harran's Proposed Biosynthesis of** 1



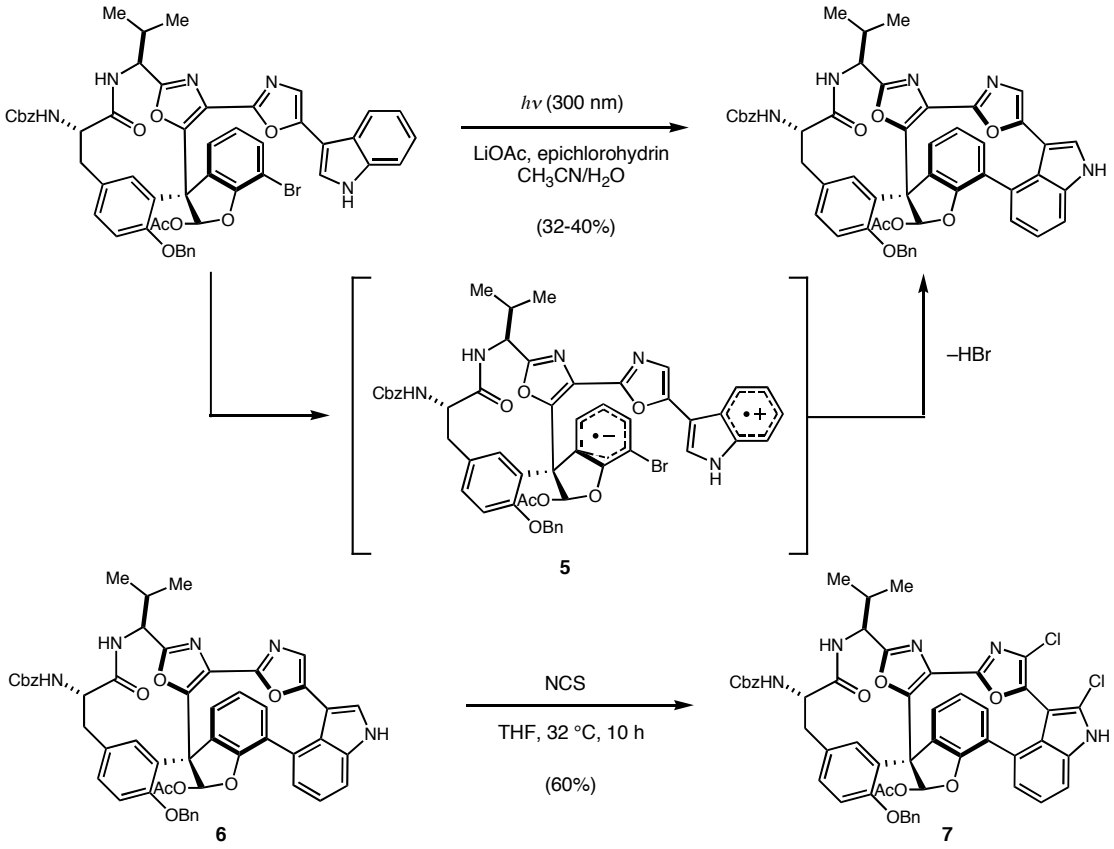

***Total Syntheses of Diazonamide A***

Although the Harran synthesis of **3** provided only the incorrect structure, this work provided at least two critical contributions to chemists confronted by diazonamide A's daunting features (scheme 1). First was a demonstration that the 14-membered right-hand macrocycle could be closed along its biaryl bond via a novel Witkop-type photocyclization. First reported in 1966,[7] the Witkop photocyclization has been documented to facilitate the closure of medium (7-9) rings at the 4-position of tryptophan

[6] Li, J.; Burgett, A. W. G.; Esser, L.; Amezcua, C.; Harran, P. G. *Angew. Chem. Int. Ed.* **2001**, *40*, 4770.

[7] Yonemitsu, O.; Cerutti, P.; Witkop, B. *J. Am. Chem. Soc.* **1966**, *88*, 3941.

**Scheme 1: Key Steps From Harran's Synthesis of** 3




derivatives (figure 4).[8] This method has found several applications in total synthesis,[9] but until Harran's work had been restricted to relatively simple indolic compounds and had not been demonstrated in the formation of either twelve-membered rings or biaryl bonds. Though the yields reported in this case were moderate (32%-40%), the ability to forge such a difficult ring closure in the presence of a wide array of sensitive functionalities identified this photocyclization as a viable technique for future work. Mechanistic studies are sparse, but Harran proposed a photoinduced electron transfer between the D and E rings to create a biradical intermediate (**5**) that collapses to form the key bond.

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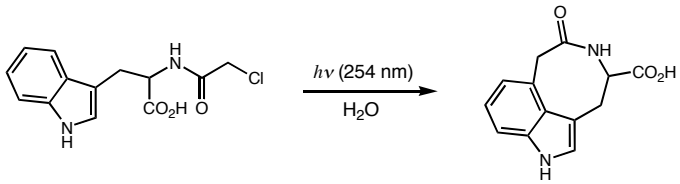
[8] (a) Mascal, M.; Moody, C. J. *J. Chem. Soc. Chem. Comm.* **1988**, 589; (b) Griesbeck, A. G.; Henz, A.; Hirt, J. *Synthesis* **1996**, 1261; (c) Ruchkina, E. L.; Blake, A. J.; Mascal, M. *Tet. Lett.* **1999**, *40*, 8443.

[9] For a recent example see: Feldman, K. S.; Ngernmeesri, P. *Org. Lett.* **2005**, *7*, 5449.

**Figure 4: Typical Application of the Witkop Photocyclization**




Secondly, Harran demonstrated that the sensitive chlorine substituents could be introduced onto an essentially fully elaborated core of **3** without an indolic protecting group (**6** to **7**, Scheme 1). This impressive late-stage transformation has enabled all subsequent approaches, allowing installation of these chlorines to be a relatively straightforward matter.

• *Nicolaou's Total Syntheses of **1***

Having already made substantial progress toward the originally reported structure for diazonamide A, the Nicolaou group was forced to alter its approach to account for the new structural features.[10] Two distinct synthetic plans arose from this work, the first of which was completed and published in 2002.[11] Some key elements of this strategy are shown in Scheme 2. Central to this effort was a rapid synthesis of oxindole **8** from simple precursors, allowing construction of the oxazole-substituted quaternary carbon stereocenter of **9** by way of an acid-mediated dehydration/Friedel-Crafts arylation. The yield (47%) was fairly impressive given the complexity of the product produced, but this reaction proceeded without stereocontrol and thus gave a 1:1 mix of diastereomers of the key stereocenter.

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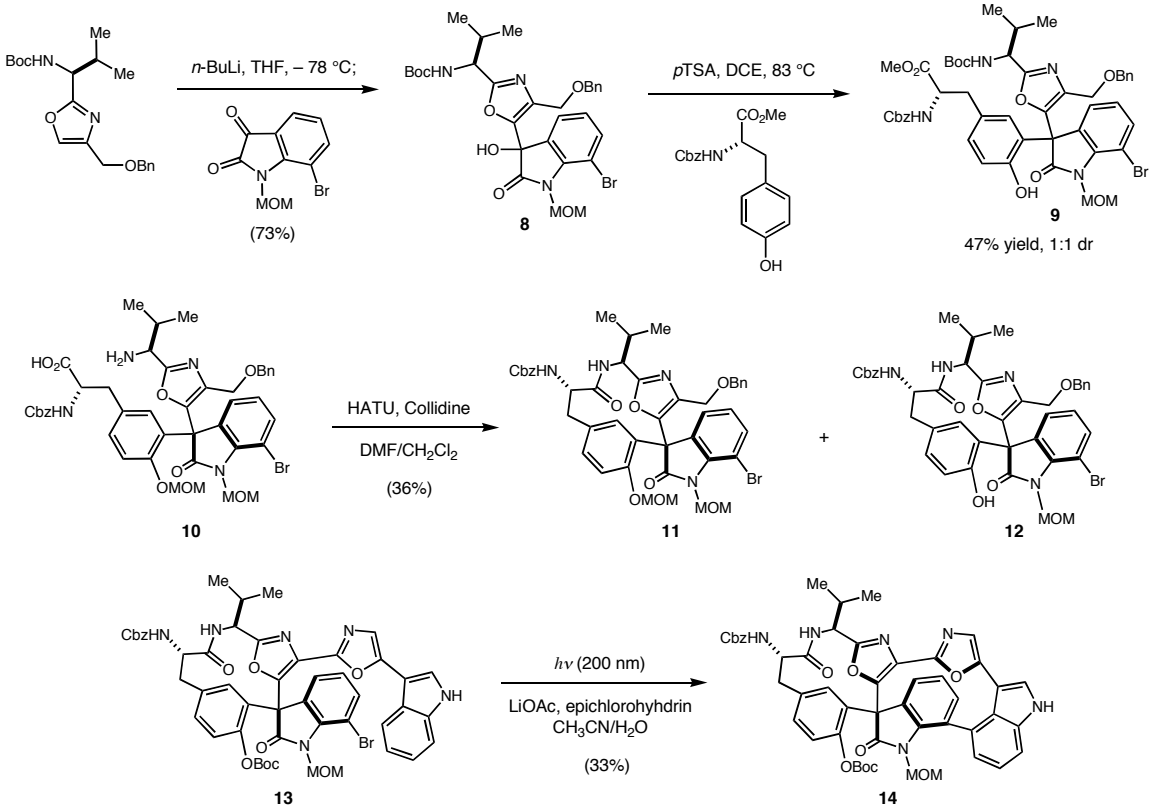
[10] For a complete review of this work see: Snyder, S. A.; PhD thesis, The Scripps Research Institute, **2004**.

[11] (a) Nicolaou, K. C.; Bella, M.; Chen, D. Y. K.; Huang, X. H.; Ling, T. T.; Snyder, S. A. *Angew. Chem. Int. Ed.* **2002**, *41*, 3495; (b) Nicolaou, K. C.; Chen, D. Y. K.; Huang, X. H.; Ling, T. T.; Bella, M.; Snyder, S. A. *J. Am. Chem. Soc.* **2004**, *126*, 12888.

**Scheme 2: Highlights of Nicolaou's First Synthesis of** 1



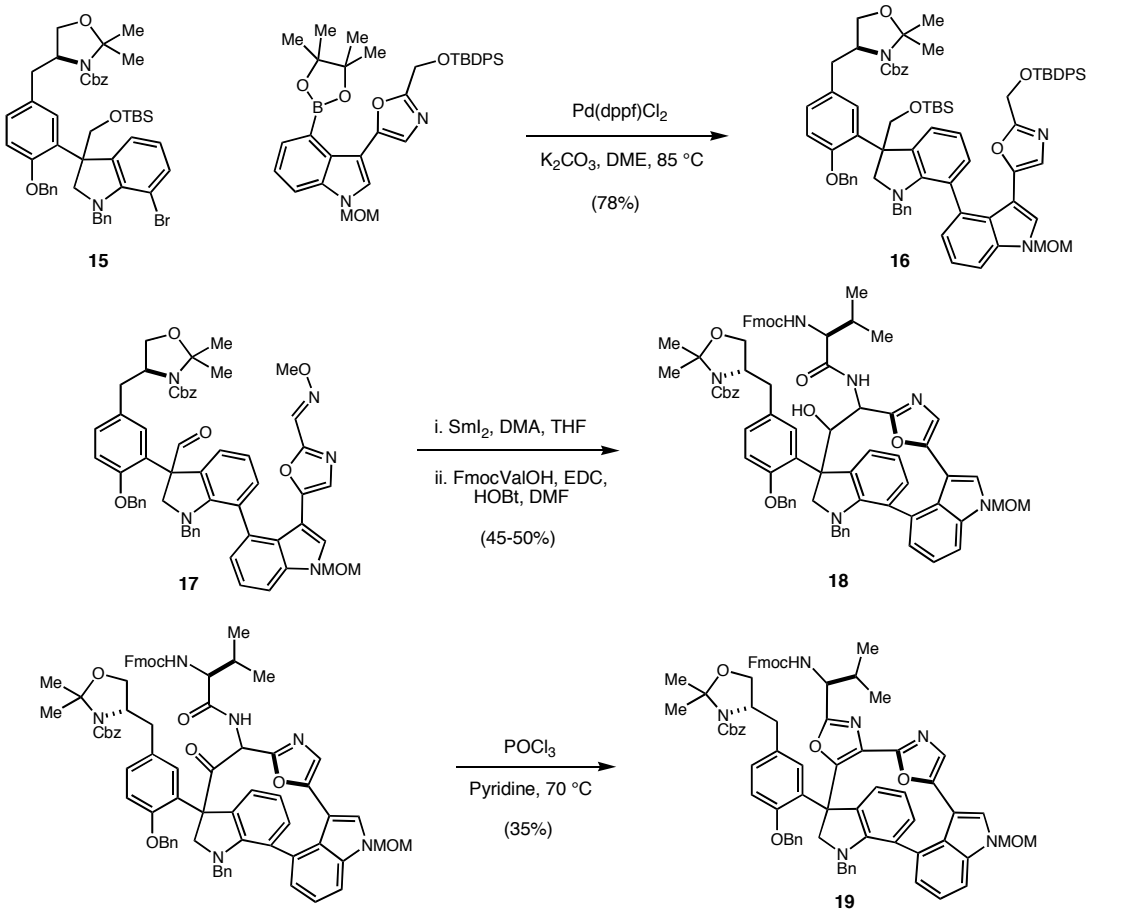

Elaboration to **10** allowed closure of the left-hand macrocycle using a standard uronium peptide coupling reagent, though the reaction suffered from competing dimerization or oligomerization processes, requiring high dilution and ultimately providing a modest 36% yield of a mixture of **11** and **12**. At this point, completion of **1** was greatly facilitated by the precedent from Harran, as closure of the right-hand biaryl macrocycle was accomplished under conditions closely resembling those reported in his synthesis of **3**. However, as in Harran's work, the yield for photocyclization of **13** was modest (33%), reflecting both the difficulty of this reaction and the instability of the product to the conditions.

Nicolaou's second synthesis of diazonamide A, first reported in 2003,[12] was based

[12] (a) Nicolaou, K. C.; Rao, P. B.; Hao, J. L.; Reddy, M. V.; Rassias, G.; Huang, X. H.; Chen, D. Y. K.; Snyder, S. A. *Angew. Chem. Int. Ed,* **2003**, *42*, 1753; (b) Nicolaou, K. C.; Hao, J. L.; Reddy, M. V.; Rao, P. B.; Rassias, G.;

on an alkylation strategy to produce the C-10 quaternary carbon stereocenter, again without stereocontrol. This strategy differed markedly from the first in the construction of the biaryl macrocycle (scheme 3). A Suzuki coupling introduced the biaryl bond as a mixture of atropisomers (**15** to **16**). Elaboration of **16** to oxime **17** set the stage for an unusual hetero pinacol coupling to close the twelve-membered ring. Without isolation, this macrocycle was coupled to valine to furnish advanced intermediate **18** in fairly impressive overall yield (45%-50%). Shortly thereafter, the A-ring oxazole **19** was completed via a modified Robinson-Gabriel dehydration developed in the Nicolaou lab.[12]

**Scheme 3: Highlights of Nicolaou's Second Approach**



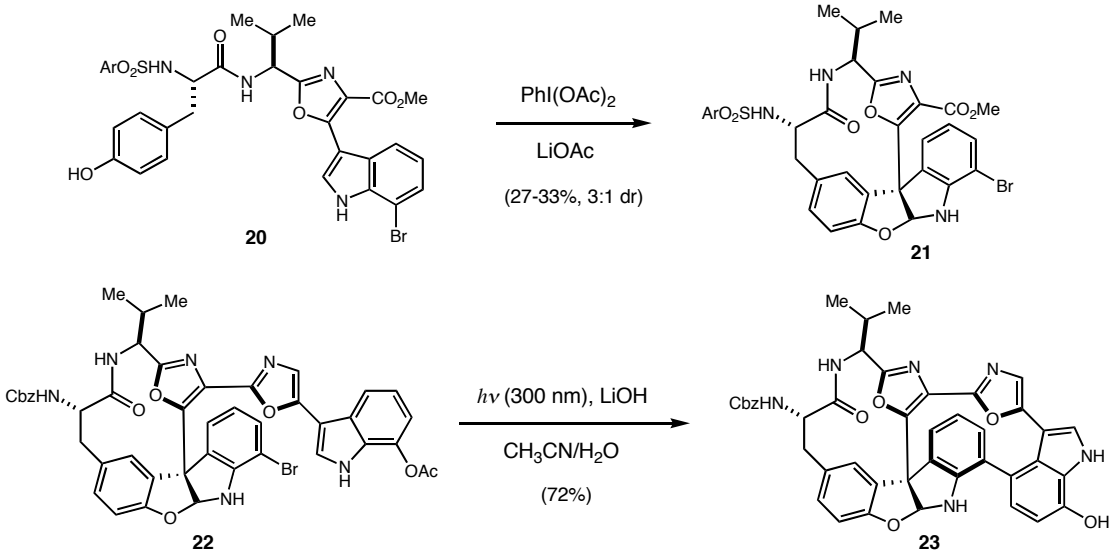

Snyder, S. A.; Huang, X. H.; Chen, D. Y. K.; Brenzovich, W. E.; Giuseppone, N.; Giannakakou, P.; O'Brate, A. *J. Am. Chem. Soc.* **2004**, *126*, 12897.

One significant drawback to this route not shown here is the macrolactamization used to produce the left-hand macrocycle, which ultimately proceeded in no better than 10%-15% yield.[13]

• *Harran's Total Synthesis of* ***1***

In 2003, Harran reported completion of his own synthesis of diazonamide A.[14] Central to his success was the execution of an oxidative macrocyclization/furanoindoline formation analogous to that mentioned in his biosynthetic proposal (**20** to **21**, Scheme 4). In this one reaction was introduced the F- and H-rings, the C-10 quaternary carbon stereocenter (in 3:1 dr, 27-33% yield), and the left-hand macrocycle. While mechanistic studies have yet to be disclosed, it is proposed that this reaction proceeds via oxidation of the phenol, facilitating Friedel-Crafts attack by the indole leading to cyclization. This

**Scheme 4: Highlights of Harran's Synthesis of** 1




[13] Some loss in yield can be accounted for by the resolution of the 1:1 mix of C-10 diastereomers that took place in this step.

[14] Burgett, A. W. G.; Li, Q.; Wei, Q.; Harran, P. G. *Angew. Chem. Int. Ed.* **2003**, *42*, 4961.

powerful transform enables rapid assembly of the natural product, taking advantage of the photocyclization chemistry developed earlier in the Harran lab (**22** to **23**). In this case, the yield was greatly improved (72%) by the inclusion of an electron-donating phenoxide at the 7-position of the indole that was revealed *in situ* by basic cleavage of the corresponding acetate. That this functionality improves reactivity is in full accord with Harran's photoinduced electron transfer hypothesis.

***Retrosynthetic Analysis***

The MacMillan lab commenced its own efforts toward the synthesis of diazonamide A in late 2002 after Nicolaou's first synthesis drew our attention to this target. We recognized in the C-10 quaternary stereocenter both a key challenge and a tremendous opportunity. Formation of this hindered center in a stereoselective, catalytic fashion became our primary goal, and all three syntheses published so far have served to verify our motivation since they have not addressed this problem in a comprehensive way. We were informed in our approach by recent work in our lab performed by Joel Austin and co-workers, who developed a method for the enantio- and diastereoselective synthesis of pyrroloindolines using our imidazolidinone organocatalyst (figure 5, see Chapter 1).[15] Most significant for our approach to **1** was the revelation that this reaction could be successfully applied to the synthesis of furanoindolines as well, with little loss in enantiocontrol (**24**, 82% ee, Figure 5). As **24** represents the E-H ring system of diazonamide A, we sought to expand on this methodology to forge the core of **1** in a stereoselective fashion.

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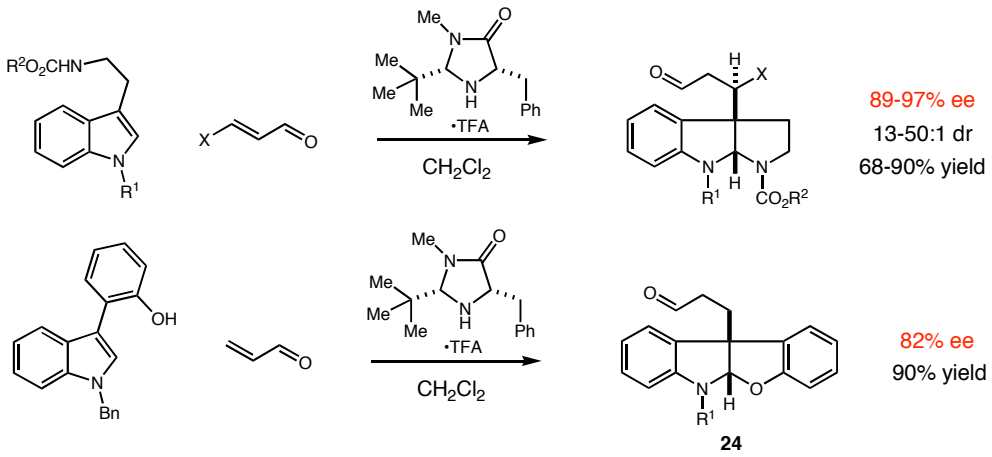
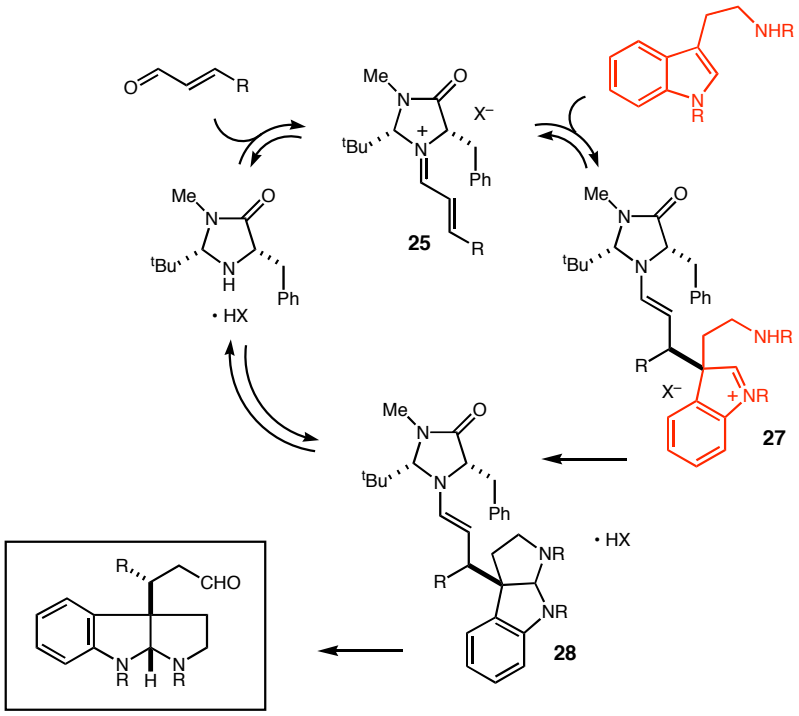
[15] Austin, J. F.; Kim, S. G.; Sinz, C. J.; Xiao, W. J.; MacMillan, D. W. C. *Proc. Nat. Acad. Sci. U.S.A.* **2004**, *101*, 5482.

**Figure 5: Organocatalytic Pyrroloindoline Formation**




Based on analogy to other enantioselective iminium-catalyzed reactions developed in our lab, the mechanism proposed for these reactions is a conjugate addition/cyclization cascade (scheme 5). Iminium formation leads to intermediate **25**, which is then activated towards Friedel-Crafts attack by the π-nucleophilic tryptamine. This creates an indolenium ion (**27**) that can be rapidly trapped by the pendant nitrogen,

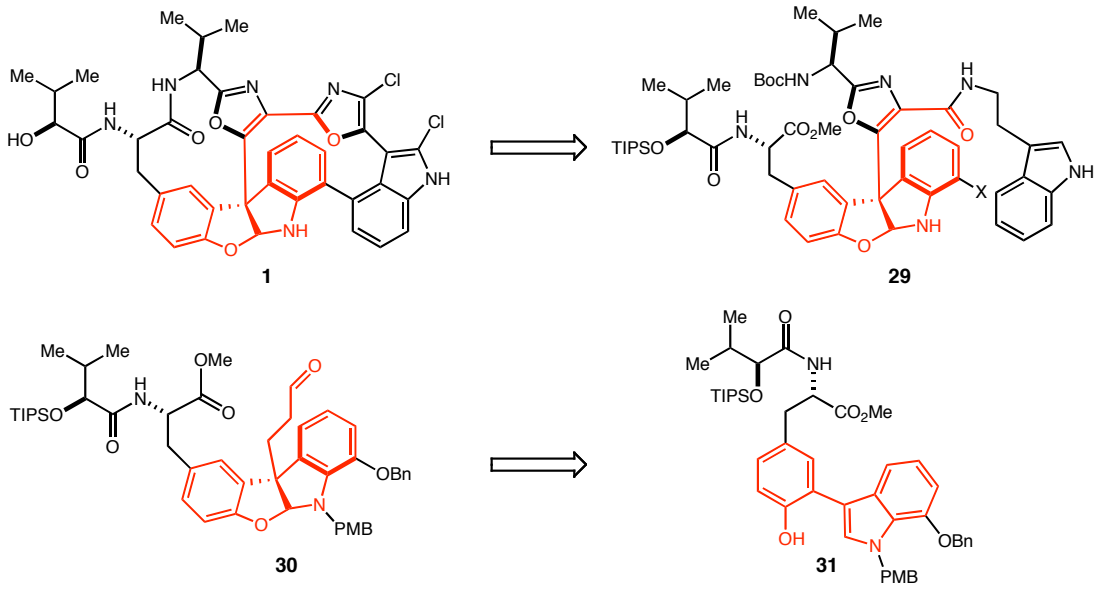
**Scheme 5: Proposed Catalytic Cycle of Organocatalytic Pyrroloindoline Synthesis**



quenching the charge and furnishing the pyrroloindoline core (**28**). Hydrolysis of the bound imidazolidinone provides the product and reintroduces the catalyst to the cycle.

Taking our lead from the work of Harran and Nicolaou, we began our retrosynthesis of **1** with excision of the chlorines and disconnection of the two macrocycles to arrive at **29**. Removal of the tryptamine and A-ring oxazole functionalities reveals **30**, a compound we hoped to access via an organocatalytic addition/cyclization cascade. Aldehyde **30** should be the product from such a reaction starting from phenol **31**, an intermediate we first targeted for initiation of our studies.

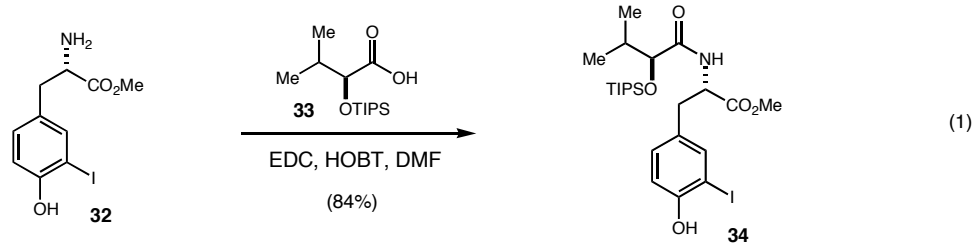
**Scheme 6: An Organocatalysis-Based Approach to** 1



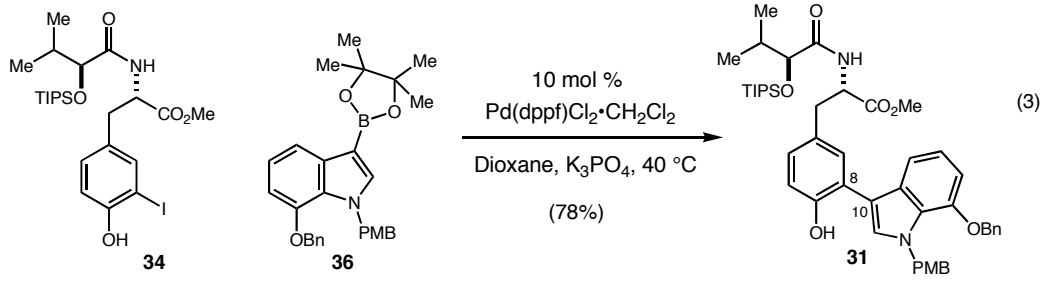

The following represents our combined efforts toward the synthesis of diazonamide A. This work was performed in conjunction with several co-workers, including Robert Knowles, Dr. Simon Blakey, Dr. Akio Kayano, and Dr. Christopher Sinz. The work produced in this project has been greater than the sum of individual efforts, and little presented here would have been accomplished without the involvement of all who contributed.

***Synthesis of Organocatalysis Product** 30*

Our construction of **30** began with the synthesis of two fragments representing the G- and E-F rings of diazonamide A (eqs. 1-2). Commercially available iodo-tyrosine methyl ester (**32**) was acylated with silylated hydroxy valeric acid **33**[16] to produce the first fragment. Commercial 7-benzyloxyindole was then functionalized via bromination and *in situ* protection as its *para*-methoxy benzyl amine (**35**). Lithiation of this indole was followed by trapping as the corresponding boronate ester (**36**).



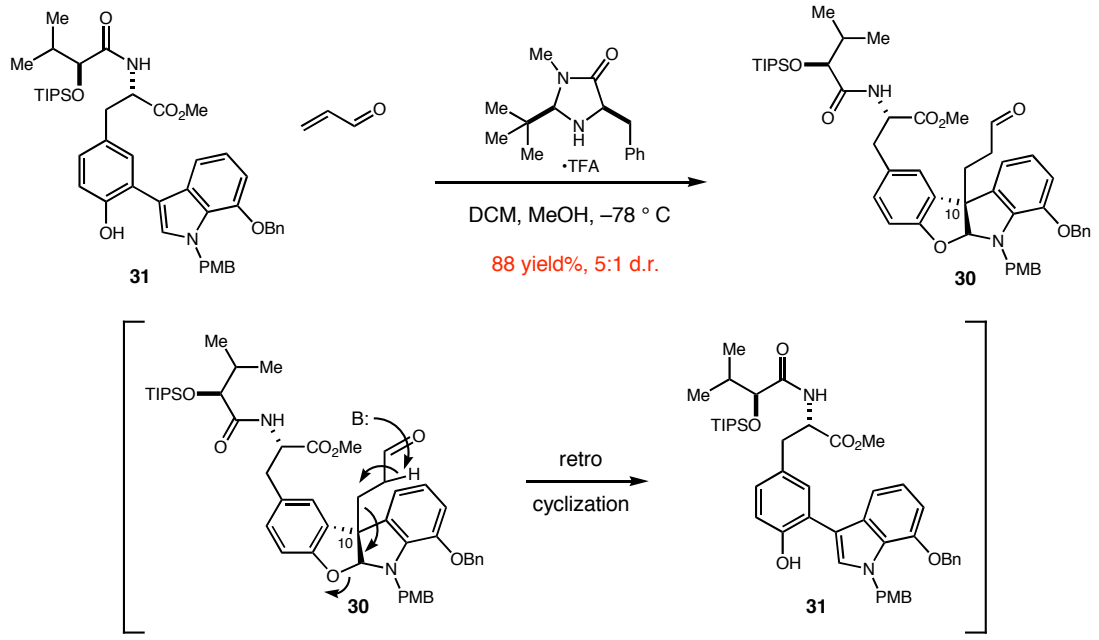

Fragments **34** and **36** could then be brought together in a convergent manner under typical Suzuki coupling conditions (78% yield, Eq. 3). This completed the synthesis of the key organocatalysis substrate (**31**) in three linear steps.




[16] See supporting information for the one-step synthesis of **33**.

Attempts to use **31** in the proposed addition/cyclization cascade with acrolein were met with success (88% yield, 5:1 dr), although for reproducibly high conversions on scale this reaction required the use of 50 mol% catalyst (figure 6). It was also found to be important to maintain temperature control, as the reverse reaction to produce **31** from **30** proves to be facile at higher temperatures in the presence of the imidazolidinone catalyst. Indeed, this retro-cyclization event proves to be a threat to **30** and related analogs, under a range of conditions involving base or nucleophile.[17] However, since our basic strategy of organocatalytic asymmetric construction of the C-10 quaternary carbon stereocenter had proven successful, we next sought to overcome the apparent fragility of the furanoindoline system to install the A-ring oxazole.

**Figure 6: Organocatalytic Construction of C-10 Quaternary Carbon Stereocenter**

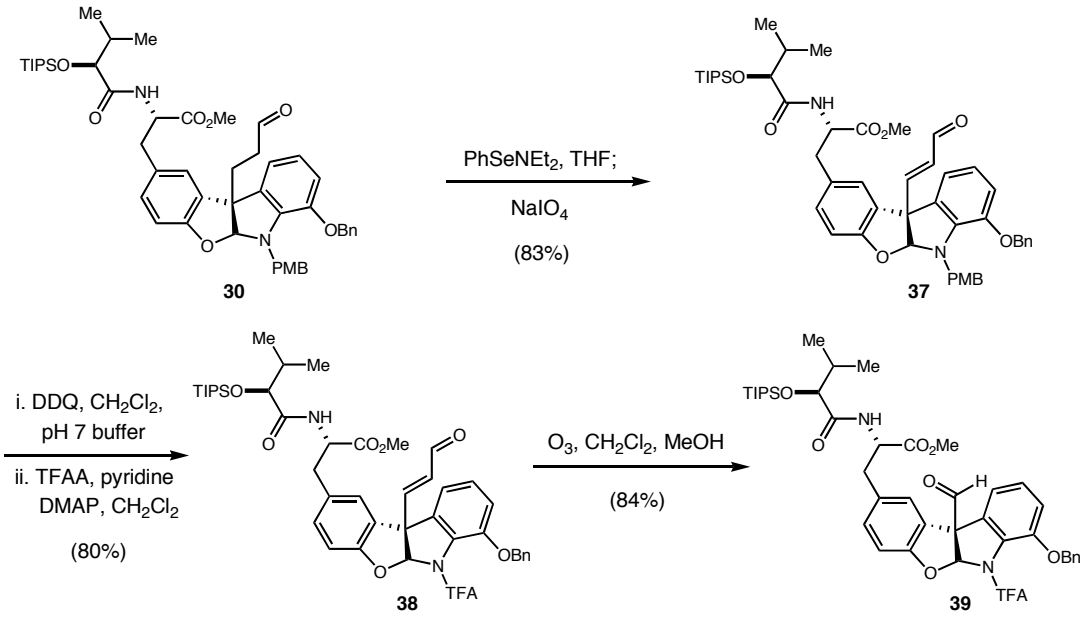



***Completion of the A-Ring Oxazole***

[17] A similar observation has been made previously: see reference 12b.

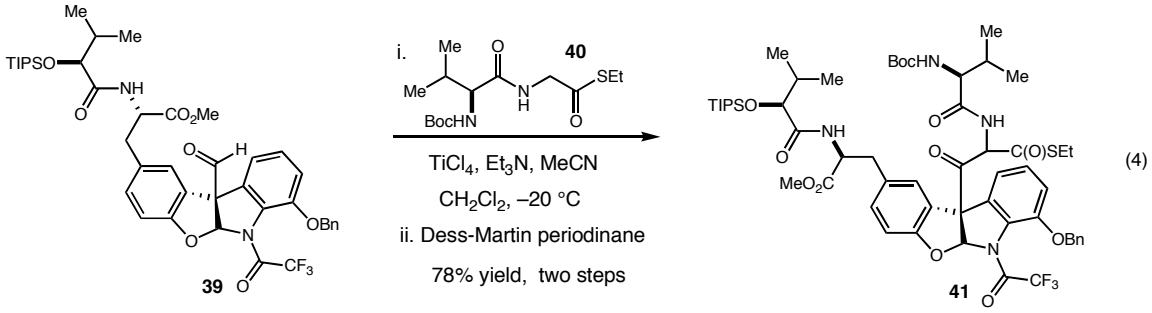
Considerable effort was devoted toward finding a method for advancing **30**, which contains some of the carbon skeleton necessary for the A-ring oxazole, toward that heterocycle. However, due to the instability of **30** noted earlier, a more roundabout way was ultimately devised that allows access to a more stable intermediate from which to build on the carbon skeleton of diazonamide A (figure 7). Selenation of aldehyde **30** was followed by a sodium periodate oxidation/elimination, producing unsaturated aldehyde **37**. We next wished to perform ozonolytic cleavage of this newly formed double bond, but this required exchange of the PMB protecting group for a trifluoroacetamide (**38**) that can better shield the indoline nitrogen from oxidation. Ozonolysis then provides aldehyde **39**, which proves to be considerably more stable than **30**.

**Figure 7: Elaboration to a More Stable Aldehyde**




While the above sequence has apparently accomplished little more than the removal of two carbons that map well onto the skeleton of the natural product, access to **39** let us perform chemistry that had been previously inaccessible. A considerable

remainder of the natural product structure can be directly introduced to **39** by way of an aldol reaction with thioester **40** (eq. 4). This soft-enolization aldol functions surprisingly




(4)

without competition from retro-cyclization, and the product appears stable to handling without retro-aldol degradation. While the reaction is relatively non-selective (3:3:1:1 mixture of diastereomers), this proves irrelevant since subsequent transformations eliminate the newly formed stereocenters. Interestingly, the addition of acetonitrile to the titanium enolate is necessary for reactivity, perhaps to break up titanium aggregates. Following this, Dess-Martin oxidation furnishes ketone **41** in an efficient manner. To our surprise, the Dess-Martin periodinane proved unique amongst oxidizing agents we used in its ability to perform this transformation, with others failing to react or resulting in degradation.[18]

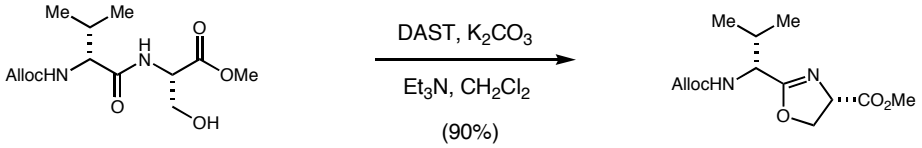
In **41** we now had a *β*-keto amide that we thought would serve as a viable precursor for the A-ring oxazole. In the event, however, dehydration of **41** proved to be a difficult task. Methods derived from the literature, such as Wipf's $PPh_3/I_2$ cyclodehydration[19] or Nicolaou's modified Robinson-Gabriel procedure[12] suffered from decomposition problems or poor reactivity. Searching for alternative procedures, we

[18] Other methods attempted include: Swern oxidation, TPAP, Pfitzner-Moffatt oxidation, PCC, Corey-Kim oxidation.

[19] Wipf, P.; Miller, C. P. *J. Org. Chem.* **1993**, *58*, 3604.

were intrigued by a recent report from the Wipf group on the synthesis of oxazolines from β-hydroxy amides using the relatively benign dehydrating agent diethylamino sulfur trifluoride (DAST, Scheme 7).[20] Although this manuscript might initially appear to have

**Scheme 7: Wipf's DAST-Mediated Oxazoline Synthesis**




only passing relevance to our attempted cyclodehydration of a β-keto amide, we noted two important features of DAST: the broad functional group tolerance demonstrated by Wipf, and its ability to react with ketones to produce difluorides noted in earlier reports.[21] Combining these observations, we postulated DAST might prove reactive toward the C-30 ketone and induce cyclization without causing decomposition. Attempting this transformation for the first time, we found to our delight that DAST mediates the cyclodehydration of **41** to produce oxazole **42** in 55% yield (figure 8). This method has no direct precedent in direct oxazole synthesis,[22] but there is some analogy in a recent report of microwave-assisted cyclodehydration of β-keto amides using the Burgess reagent.[23] We have performed no mechanistic studies to date, but one can envision a mechanism involving the known ketone fluorination followed by cyclization and elimination, as shown in Figure 8. We now sought to exploit oxazole **42** to complete the remaining heterocyclic ring structures of diazonamide A.

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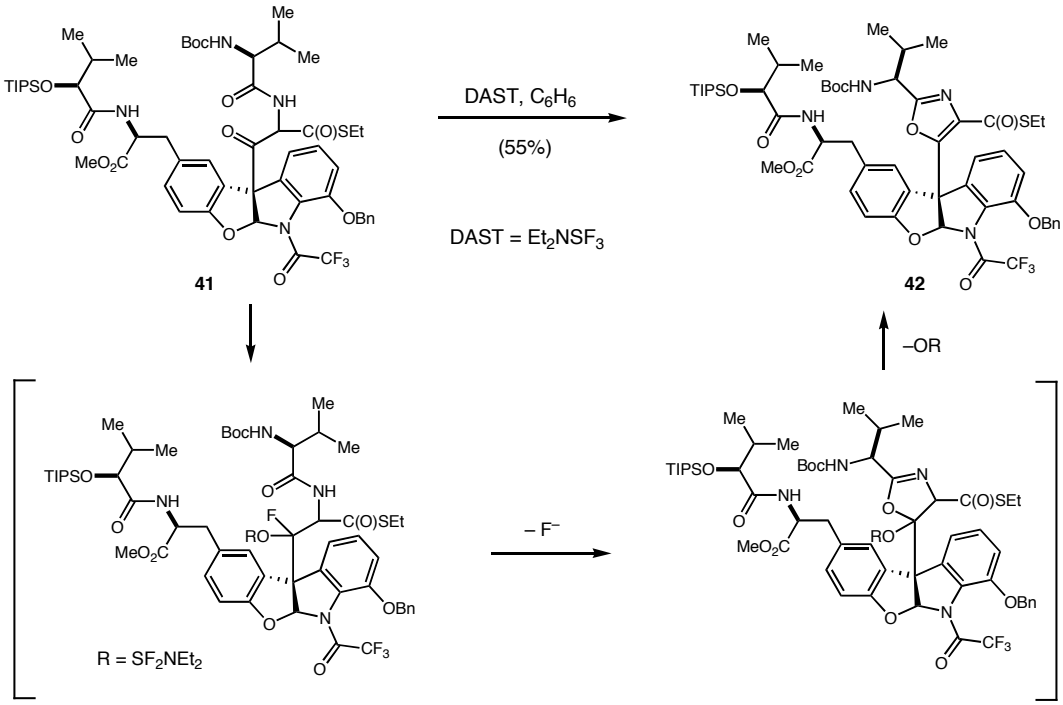
[20] Phillips, A. J.; Uto, Y.; Wipf, P.; Reno, M. J.; Williams, D. R. *Org. Lett.* **2000**, *2*, 1165.

[21] (a) Middleton, W. J. *J. Org. Chem.* **1975**, *40*, 574; (b) El-Laghdach, A.; Echarri, R.; Matheu, M. I.; Barrena, M. I.; Castillon, S. *J. Org. Chem.* **1991**, *56*, 4556.

[22] For a recent review on oxazoles in natural product synthesis, see: Yeh, V. S. C. *Tetrahedron* **2004**, *60*, 11995.

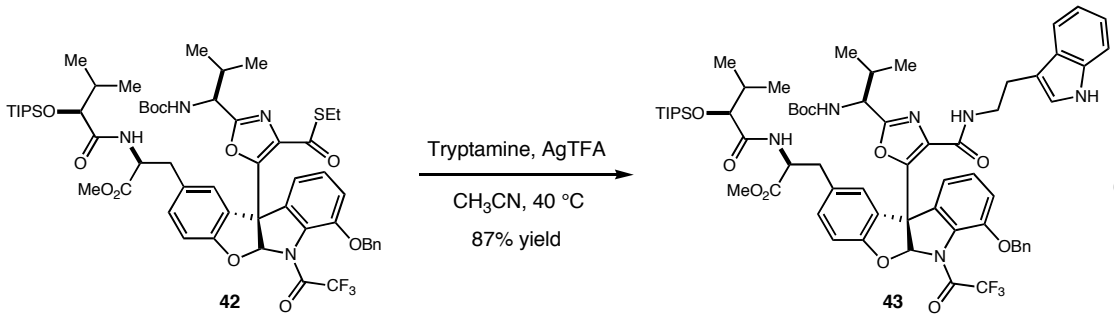
[23] Brain, C. T.; Paul, J. M. *Synthesis* **1999**, 1642.

**Figure 8: DAST-Mediated Cyclodehydration and Mechanistic Hypothesis**




### *Completion of the B-D Rings and Photochemical Macrocyclization*

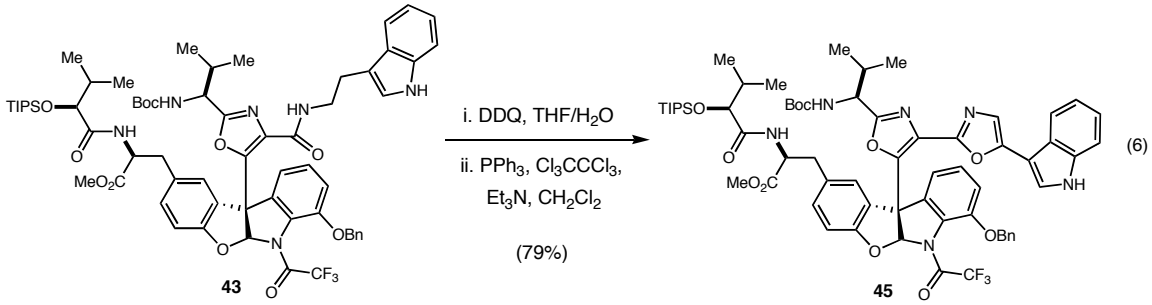
Introduction of the B-D ring oxazole and indole would be greatly simplified if tryptamine could be used to directly displace ethane thiol from thioester **42**. Fortunately Aggarwal has developed a method for precisely this kind of amine displacement, mediated by silver salts.[24] Treatment of **42** with AgTFA and tryptamine produced indole **43** in good (87%) yield (eq. 5). Remarkably, this reaction proceeds without displacement




(5)

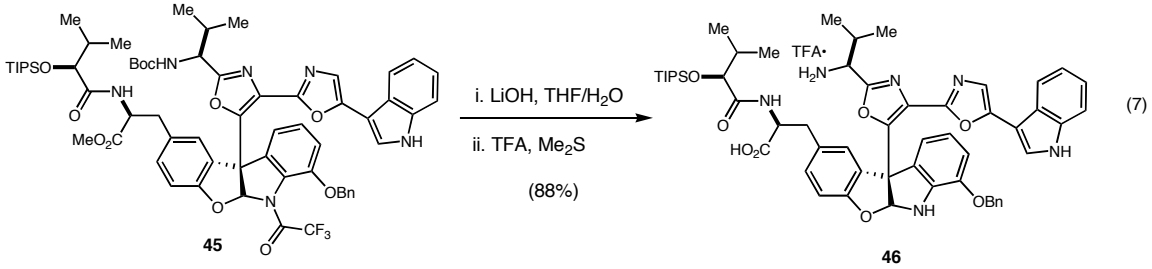
[24] Aggarwal, V. K.; Esquivel-Zamora, B. B. *J. Org., Chem.* **2002**, *67*, 8618.

of the labile TFA protecting group,[25] despite the fact that such deprotection occurs rapidly in the absence of silver. Closure of the B-ring oxazole could now follow established procedures in the diazonamide literature, with DDQ oxidation of **43** to the corresponding $\alpha$-keto indole (**44**) followed by Wipf cyclodehydration to produce bisoxazole **45** (eq. 6).




(6)

Attention was now turned toward the two key macrocyclizations. In each case, a twelve-membered ring requires closure, an endeavor that we thought could prove challenging but perhaps the closure of a second macrocycle might be entropically aided by completion of the other. Given this logic, the wealth of literature concerning cyclic peptide synthesis gave us hope that the left-handed macrolactam might prove easier to manage first.[26] To this end, **45** was converted into amino acid **46** in a high-yielding (88%) two-step process (eq. 7). Investigations into lactamization of **46** revealed some of

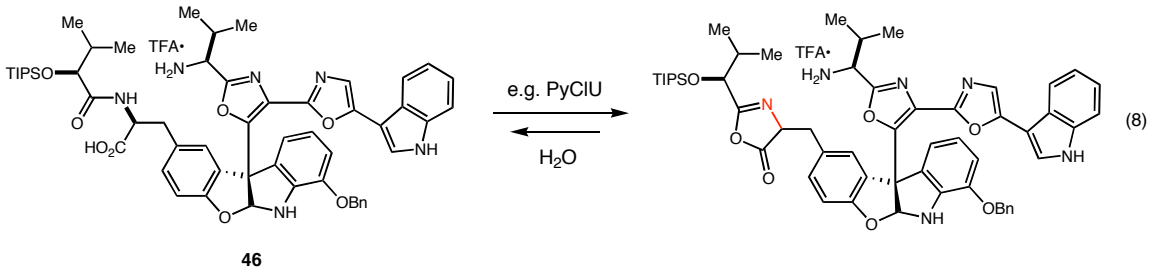



(7)

[25] Deprotection of the TFA protecting group can be induced through an excess of tryptamine relative to AgTFA.

[26] For lead reviews on reagents for peptide synthesis, see: (a) Chamberlin, R. A.; Humphey, J. M. *Chem. Rev.* **1997**, *97*, 2243; (b) Li, P.; Roller, P. P.; Xu, J. *Curr. Org. Chem.* **2002**, *6*, 411; (c) Han, S-Y.; Kim, Y.-H. *Tetrahedron* **2004**, *60*, 2447.

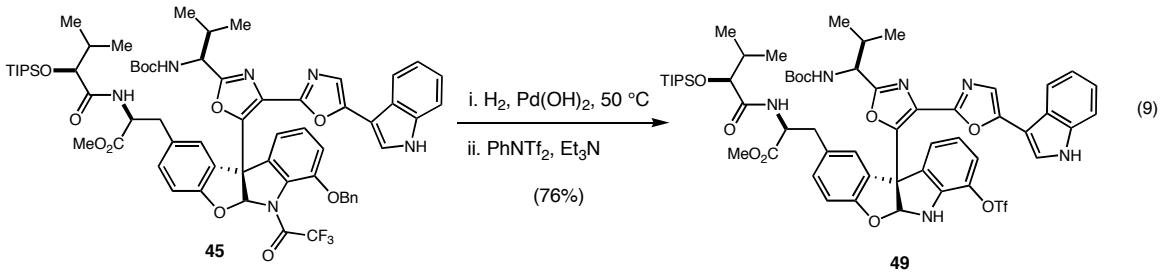
the challenges encountered in similar attempts in the Nicolaou lab.[11,12] The popular uronium-based coupling reagents (HATU, TBTU) provided only slow guanidation of the primary amine. More reactive coupling reagents (PyBroP, PyClU, BOPCl) resulted in formation of an unstable epimeric oxazolone (eq. 8), indicating a potential liability in the




46 (8)

inclusion of the hydroxy valeric acid side chain from the beginning of our synthesis rather than a protecting group that might not undergo this side reaction. It was thought that pre-activation of the carboxyl group as a pentafluorophenyl ester would circumvent oxazolone formation and facilitate closure. However, this resulted only in the formation of a macrolactam dimer, a problem that also plagued the Nicolaou syntheses.

We considered the possibility that formation of the biaryl macrocycle might prove easier to accomplish, in contrast to our earlier analysis. We sought to activate **45** toward biaryl bond formation, a task that was completed in a two-step procedure of hydrogenation of the benzyl ether and triflation of the resultant phenol (**45** to **49**, Eq. 9).

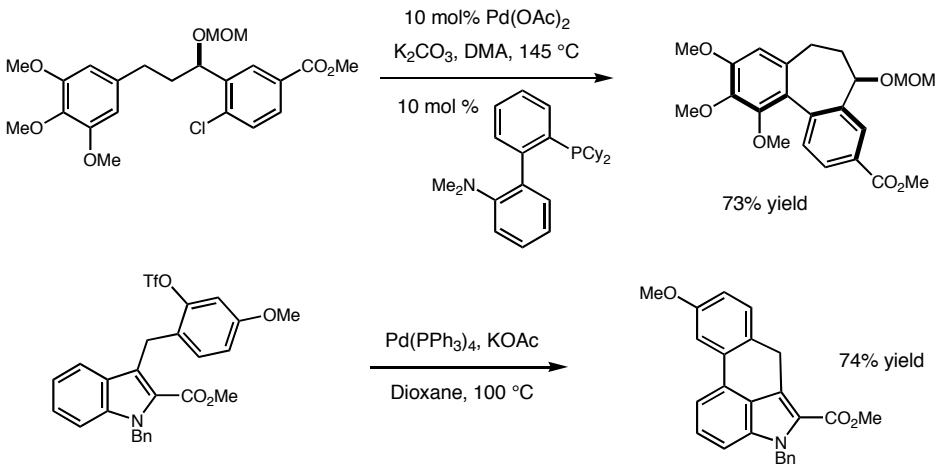



45 49 (9)

It was thought that **49** provided at least two pathways for closure of the right-hand macrocycle: the Witkop-type photocyclization pioneered by Harran, or the aryl Heck

methodology recently pioneered by Fagnou (figure 9).[27] While the photochemistry has the benefit of precedent in the diazonamide literature, it was unclear to us whether or not **49** could truly function as a substrate for electron transfer as triflates and other sulfonates

**Figure 9: Selected Examples of Intramolecular Aryl Heck Cyclization[27b,d]**




are known to be photolabile.[28] However, our efforts to perform the aryl Heck macrocyclization with **49** were met with failure, ranging from lack of reactivity to decomposition of starting material under more forcing conditions. Perhaps the generally high temperatures required in the Fagnou procedures are incompatible with **49**, despite the use of stoichiometric amounts of palladium.

We were encouraged, on the other hand, by work from the Albini lab which demonstrated that aryl sulfonates (as well as halides) can serve as sources for triplet cations when exposed to UV light (figure 10).[29] These cations react selectively with π-

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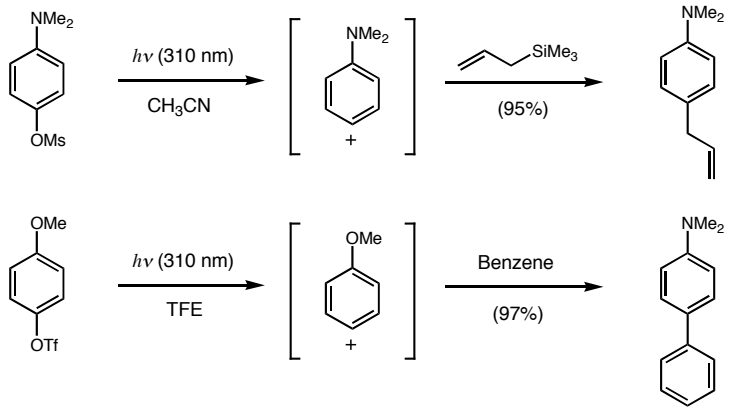
[27] Campeau, L.-C.; Parisien, M.; Leblanc, M.; Fagnou, K. *J. Am. Chem. Soc.* **2004**, *126*, 9186; (b) Leblanc, M.; Fagnou, K. *Org. Lett.* **2005**, *7*, 2849; (c) Campeau, L.-C.; Parisien, M.; Jean, A.; Fagnou, K. *J. Am. Chem. Soc.* **2006**, *128*, 581; see also: (d) Miki, Y.; Shirokoshi, H.; Asai, M.; Aoki, Y.; Matsukida, H. *Heterocycles* **2003**, *60*, 2095.

[28] (a) Tsuchiya, T.; Nakamura, F.; Umezawa, S. *Tet. Lett.* **1979**, *30*, 2805; (b) Liu, X.; Binkley, R. W. *J. Carbohydrate Chem.* **1992**, *11*, 183; (c) Liu, X.; Binkley, R. W.; Yeh, P. *J. Carbohydrate Chem.* **1992**, *11*, 1053.

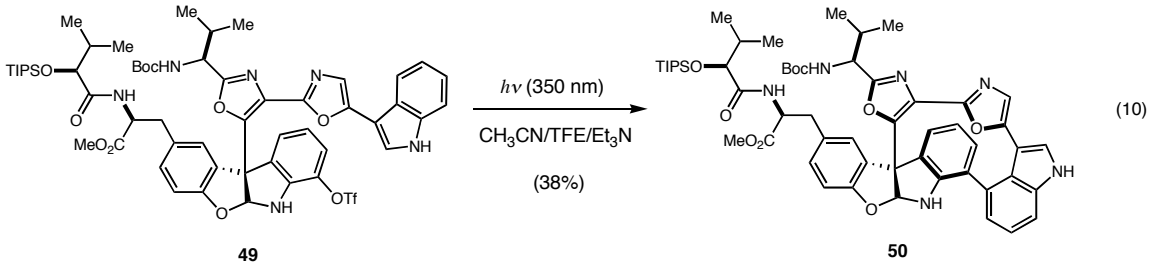
[29] (a) Freccero, M.; Fagnoni, M.; Albini, A. *J. Am. Chem. Soc.* **2003**, *125*, 13182; (b) De Carolis, M.; Protti, S.; Fagnoni, M.; Albini, M. *Angew. Chem. Int. Ed.* **2005**, *44*, 1232; (c) Fagnoni, M.; Albini, A. *Acc. Chem. Res.* **2005**, *38*, 713.

nucleophiles, a situation that should be amenable to biaryl bond formation in **49** between the aryl triflate and the π-nucleophilic indole. This mechanism is distinct from that proposed in Harran's Witkop-type cyclization (see Scheme 1, above), although we had little basis to suggest the likelihood of one mechanism over the other (or either) for our substrate. Rather, we found inspiration from this encouraging precedent.

**Figure 10: Photochemical Cross-Coupling Methodology[28b]**




To our delight, subjecting **49** to UV light in degassed solvent produced biaryl macrocycle **50** in modest (38%) yield as a single atropdiastereomer, in accord with Harran's work (eq. 10). The mass balance was typically a small amount of recovered **49**,




**49** **50** (10)

and substantial decomposition by undefined pathways. Further experimentation demonstrated that **50** is not stable to the reaction conditions, so the best results came from running the reaction to moderate conversion and recycling starting material. Optimal yield came with 350 nm irradiation, in contrast to Harran's conditions (300 nm)[3] or those

reported by Nicolaou (200 nm).[12] Examination of the UV-Vis spectrum of **49** showed a broad absorbance ranging as high as 370 nm,[30] so it is perhaps unsurprising that photocyclization can occur at a range of wavelengths. What is surprising is that three separate optimization efforts would arrive at such drastically different energies of irradiation to produce the best yield. We expected that a major side reaction for **49** would be solvent-assisted lysis of the triflate. However, this seemed to be a minor problem at best, and also appeared to be independent of the reaction medium.

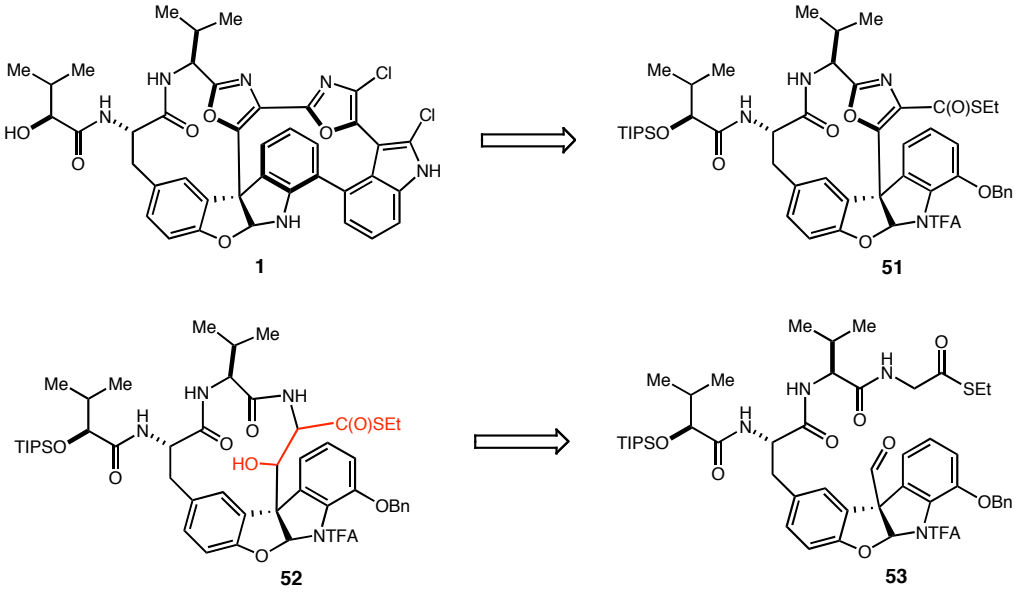
Despite the material throughput problems our photocyclization posed, we were optimistic at this point to be conceivably so close to the end of our synthesis. However, we were continually frustrated in our efforts to convert **50** to the bismacrocyclic core of diazonamide A. Attempts to close the macrolactam suffered from either lack of reactivity or competing dimerization as seen with **46**. The seemingly simple problem of amide bond formation had once again halted our efforts, and led us to reconsider our synthetic approach based on the thought that finding a new method to form the left-handed macrocycle would solve the last significant hurdle in our work.

### *A Second Generation Retrosynthesis: Aldol-Based Macrocyclization*

We devised a new strategy for the synthesis of diazonamide A that would allow us to take advantage of most of the chemistry we had already developed while addressing formation of the left-hand macrocycle at an earlier stage (scheme 8). Centered on the organocatalytic addition/cyclization we had developed in our previous approach, this plan posed the question as to whether the soft-enolization aldol that functioned so well in an

[30] In accord with this observation, no reaction occurred upon irradiation at 420 nm.

**Scheme 8: A Second Generation Approach to** 1



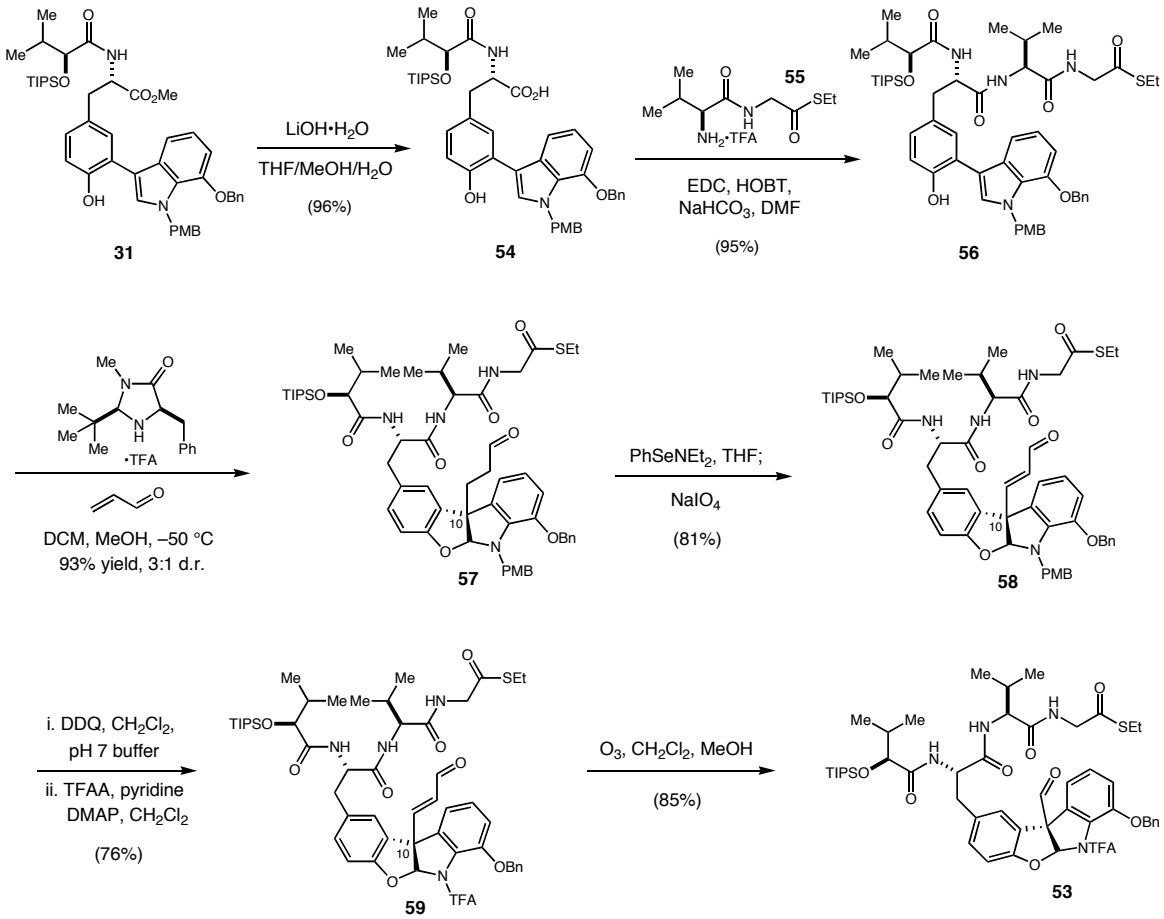

intermolecular sense might now work in an *intramolecular* fashion, closing the left-hand macrocycle in the process (**53** to **52**, Scheme 8). While examples of aldol macrocyclizations are rare,[31] we thought that our previous inability to macrolactamize might well have been due to the ring strain of the desired twelve-membered ring, and that some of the energetic penalty in our new approach would be delayed until formation of the A-ring oxazole (**52** to **51**). This cyclodehydration could be driven irreversibly by the loss of water, leaving us with only the task of completing the biaryl macrocycle. Given our previous success in formation of this bond, we thought this to be a feasible task. If so, our new strategy would place us remarkably close to our target.

### *Soft Enolization Aldol Macrocyclization and Synthesis of 51*

[31] For examples see: (a) Meng, D.; Bertinato, P.; Balog, A.; Su, D.; Kamenecka, T.; Sorensen, E.; Danishefsky, S. J. *J. Am. Chem. Soc.* **1997**, *119*, 10073; (b) Hayward, C. M.; Yohannes, D.; Danishefsky, S. J. *J. Am. Chem. Soc.* **1993**, *115*, 9345.

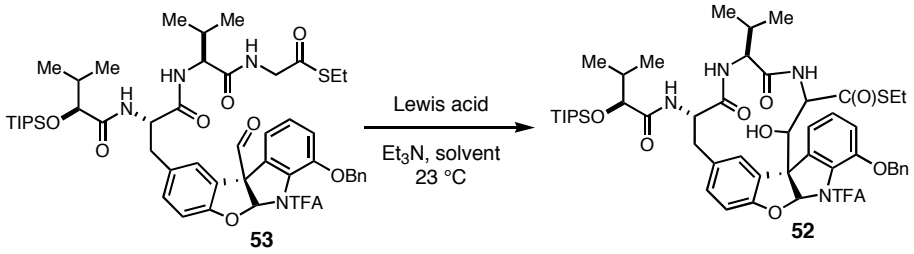
We sought to take advantage of most of the chemistry we had previously developed in our synthetic efforts to produce **53**. Starting from phenol **31** described earlier, elaboration to thioester **56** was a simple matter of methyl ester hydrolysis and amide bond formation (figure 11). Following this, organocatalytic addition/cyclization produced aldehyde **57** in excellent (93%) yield, in accord with our first-generation approach. Conversion of **57** into aldol macrocyclization precursor **53** followed without difficulty using the unsaturation/ozonolysis strategy we had applied earlier. Remarkably, the thioester functionality present in our system proved robust to $NaIO_4$ and DDQ oxidations as well as treatment with ozone (**57** to **53**, Figure 8).

**Figure 11: Synthesis of Macrocyclization Precursor** 53



We now sought to test the key element of our new strategy – the aldol macrocyclization. Our first efforts examined the conditions developed in our first generation synthesis, which involved $TiCl_4$ as a Lewis acid and a tertiary amine base for soft enolization (table 1). To our disappointment, these conditions furnished no discernible amount of the desired product. Increasing the amount of Lewis acid or other components of the reaction did not change this outcome, with degradation of starting material acting as a limiting process. We next chose to examine magnesium salts as promoters for this reaction since they generally display broader functional group tolerance.[32] To our delight, we obtained macrocycle **52** in our initial efforts using $MgBr_2$ (entry 2), a result that improved substantially on addition of TMSCl to prevent retro-aldolization (entry 3).[33] The reaction did not appear to proceed catalytically, and efforts

**Table 1: Optimization of the Intramoelcular Aldol Macrocyclization**




**53** **52**

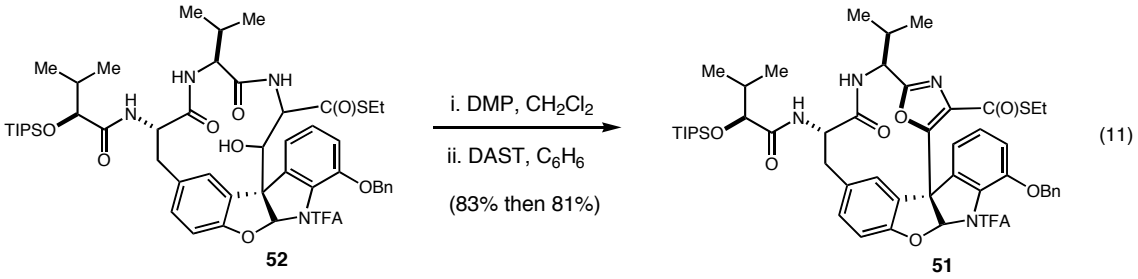
| entry | Lewis acid | equivalents | additive | solvent | yield |
|---|---|---|---|---|---|
| 1 | $TiCl_4$ | 3 | $CH_3CN$ | $CH_2Cl_2$ | 0 |
| 2 | $TiCl_4$ | 10 | $CH_3CN$ | $CH_2Cl_2$ | 0 |
| 3 | $MgBr_2$ | 3 | -- | EtOAc | 24 |
| 4 | $MgBr_2$ | 3 | TMSCl | THF | 67 |
| 5 | $MgBr_2$ | 0.3 | TMSCl | THF | 2 |
| 6 | $MgI_2$ | 3 | TMSCl | THF | 54 |
| 7 | $Mg(ClO_4)_2$ | 3 | TMSCl | THF | 57 |
| 8 | $Mg(OTf)_2$ | 3 | TMSCl | THF | 0 |

[32] For recent examples of magnesium-catalyzed aldol reactions see: (a) Evans, D. A.; Tedrow, J. S.; Shaw, J. T.; Downey, W. C. *J. Am. Chem. Soc.* **2002**, *124*, 392; (b) Evans, D. A.; Downey, W. C.; Shaw, J. T.; Tedrow, J. S. *Org. Lett.* **2002**, *4*, 1127.

[33] Evans, D. A.; Shaw, J. T. *Unpublished review.*

to improve the yield using other magnesium salts were met with little success. Interestingly, we found that **52** was produced as a single diastereomer (stereochemistry undetermined). While the stereocenters formed are destroyed in subsequent reactions, it is nonetheless an unexpected outcome. It is also noteworthy that this macrocyclization proceeds in good (67%) yield, a result that is substantially improved over those reported in the Harran and Nicolaou syntheses.

Having access to macrocycle **52**, we hoped to make use of the DAST-mediated cyclodehydration developed in our first generation approach to produce the A-ring oxazole. As this reaction has little substrate generality in our hands, we did not know what to expect from our second generation system in which the strain of cyclization might well be greater. However, as seen in equation 11, **52** proved even more amenable to cyclodehydration (following Dess-Martin oxidation to the corresponding ketone) than our original system. This completed our synthesis of **51** and left us to consider the task of introducing the remaining oxazole and indole ring systems.

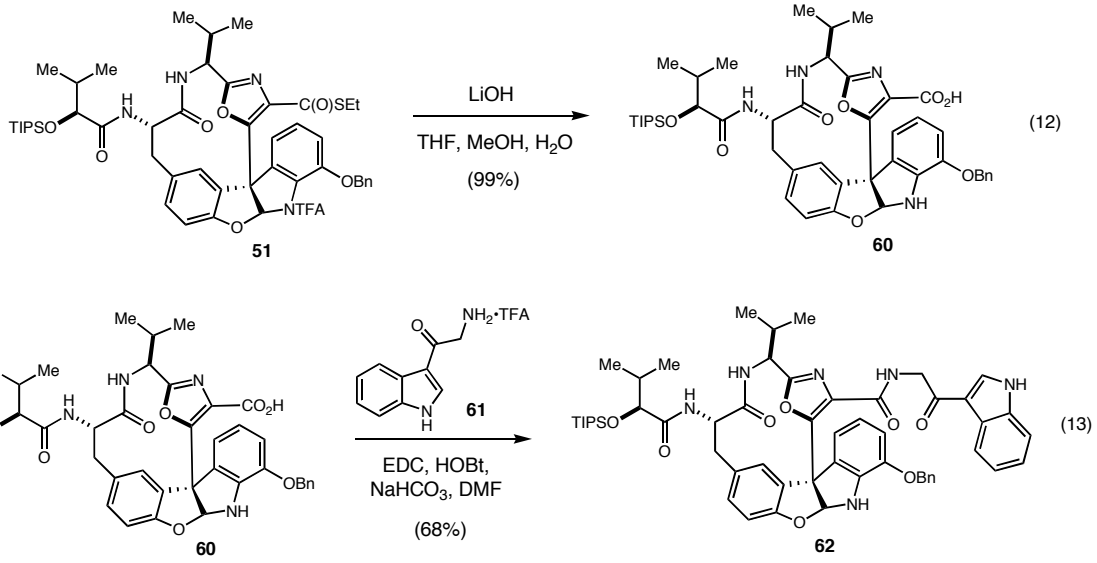



(11)

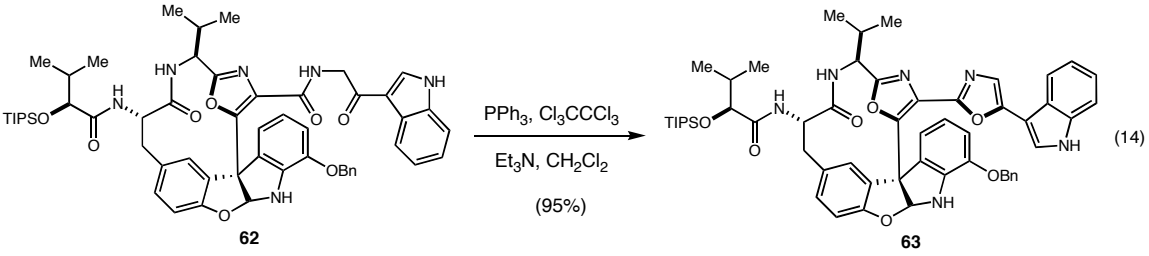
***Introduction of the B-D Rings and Attempts at Photocyclization***

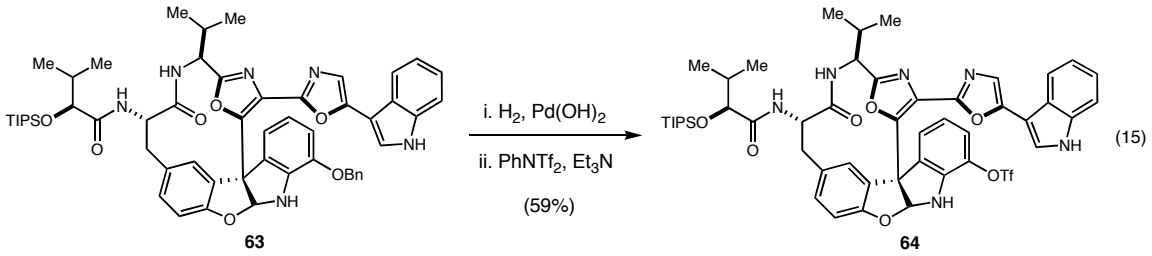
To maximize the efficiency of the necessary steps to complete the oxazole and indole ring systems (B-D), we slightly revised our first generation approach that involved thioester displacement followed by DDQ oxidation to create a $\beta$-keto amide B-ring

precursor. We felt that the DDQ oxidation produced variable yields, and avoiding it could enhance our overall efficiency. To this end, **51** was subjected to aqueous base in order to hydrolyze the thioester and trifluoroacetamide functionalities (eq. 12), producing carboxylic acid **60**. This could be coupled efficiently with known oxo-tryptamine **61**,[11] directly accessing $\beta$-keto amide **62** without an intervening oxidation step (eq. 13).




Completion of the B-ring oxazole was now a straightforward matter. Taking advantage of the cyclodehydration conditions that had worked successfully in our first generation approach, we converted **62** into **63** without difficulty (eq. 14). Subsequent elaboration of **63** into triflate **64** for investigations into a Witkop-type photocyclization also followed nicely with the precedent from our earlier work (eq. 15).






To our great disappointment, however, **64** proved a poor substrate for a photochemical biaryl bond formation, in contrast to what we had observed in our first approach. Considering the lower entropic barrier this new macrocyclization should face, and the precedent from the Harran and Nicolaou syntheses that seem to differ almost exclusively by the presence of an aryl bromide rather than an aryl triflate, we thought this reaction would prove even more successful than that which we had developed for our first-generation system. In a variety of solvents and wavelengths, we observed cleavage of the triflate to the phenol (as had been seen before), along with formation of unstable products that have not been identified. While the desired bismacrocyclic product had been seemingly observed by mass spectrometry, no authentic sample was ever isolated. These results led us to consider a modified endgame approach in which we would pursue a more conventional, metal-mediated biaryl bond formation.

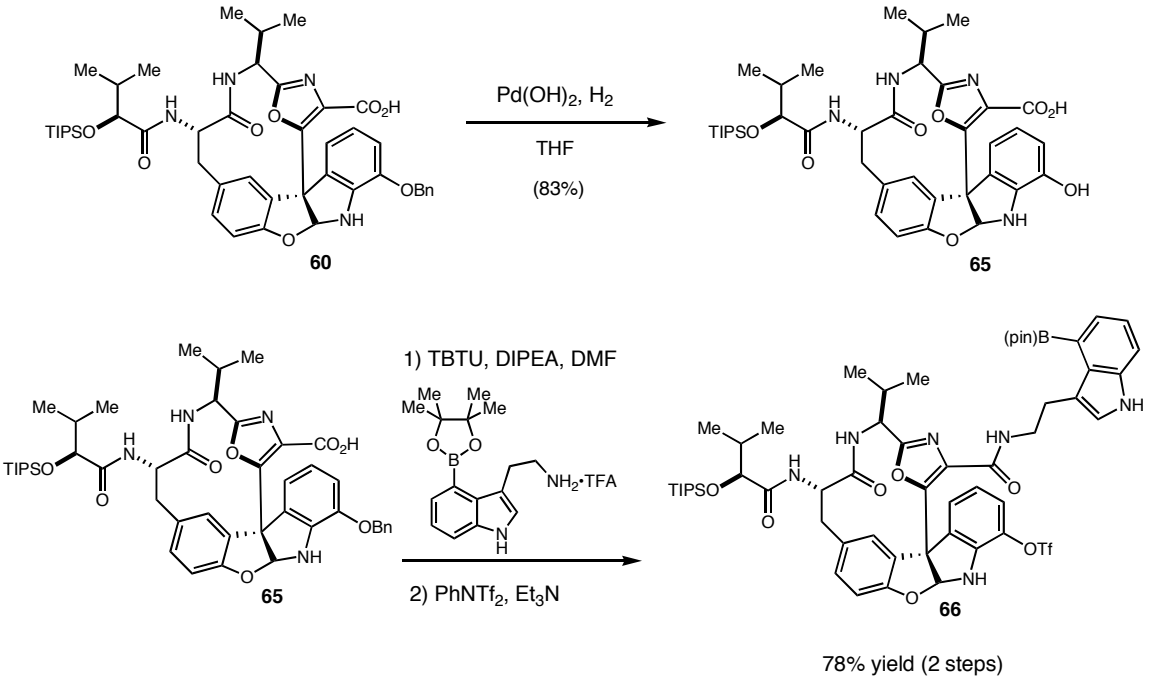
***Suzuki Macrocyclization: Completion of the Second Macrocycle***

We thought that a 4-functionalized tryptamine derivative, applied in an otherwise similar sequence to that described above, could provide an advanced intermediate (**66**) in which there was appropriate functionalization for a Suzuki biaryl macrocyclization (figure 12).[34] It seemed plausible that a subsequent palladium-catalyzed biaryl bond-

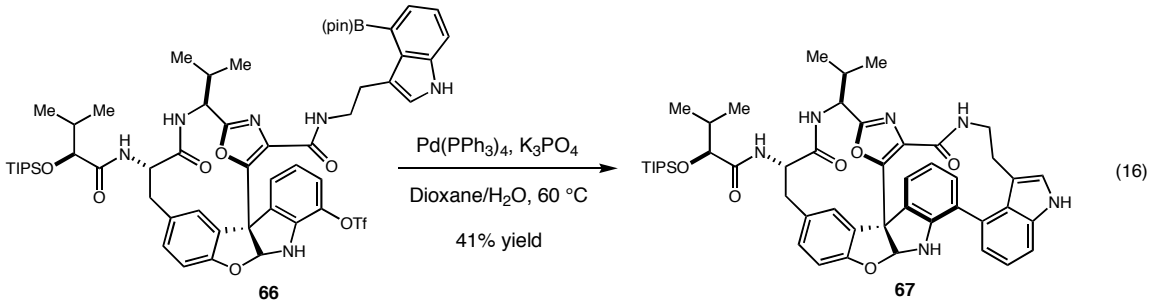
[34] Molander, G. A.; Dehmel, F. *J. Am. Chem. Soc.* **2004**, *126*, 10313.

forming reaction would be more easily controlled and optimized than the photochemistry used in our earlier efforts. Boronate **66** was accessed in a straightforward way from acid **60** in three steps, including the previously developed conversion of the benzyl ether to the corresponding triflate. Use of TBTU as the amide coupling reagent provided superior yields over those observed with DCC or other more conventional reagents.

**Figure 12: Synthesis of a Suzuki Macrocyclization Precursor**



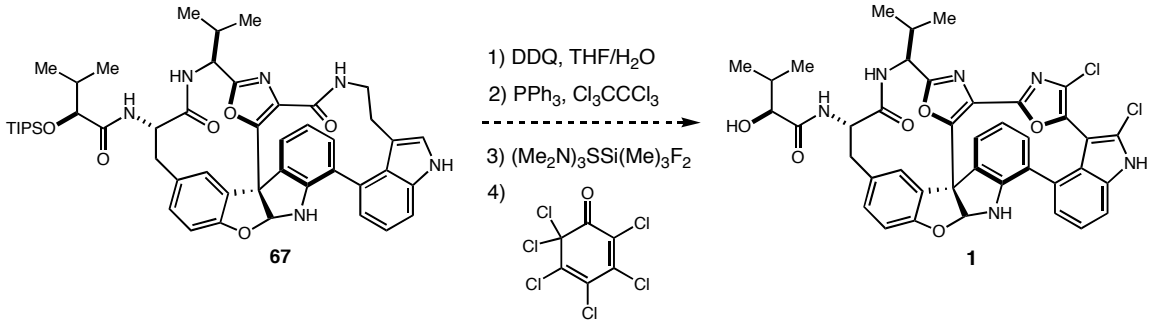

To our great delight, **66** proved amenable to a Suzuki coupling reaction to provide medium ring biaryl macrocycle **67** (eq. 16). Although the yield is perhaps modest (41%), it is an intriguing result all the same. Palladium couplings have not been utilized often in the late stages of complex syntheses and certainly less so in the context of challenging macrocyclizations. Furthermore, this reaction should be amenable to optimization through tuning of the phosphine ligands on the palladium source, including variations of steric bulk, electron-donating capacity, and phosphine to palladium ratios.



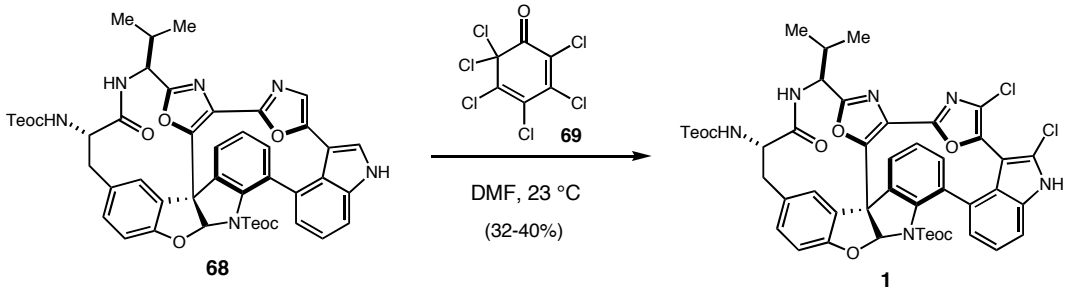

(16)

From bismacrocycle **67** the path toward diazonamide A appears feasible. The remaining challenges include an oxidation/cyclodehydration sequence to introduce the B-ring oxazole, removal of the silyl protecting group, and regioselective introduction of the chlorine substituents (figure 13). A plausible set of reagents to complete this sequence is detailed below. In particular, the bischlorination of the fully elaborated core of diazonamide A has some exceptional precedent in the form of Harran's synthesis of **1**.[14]

**Figure 13: Projected Sequence for the Completion of Diazonamide A**




As shown in equation 17, treatment of **68** with hexachloroquinone **69** provides a satisfactory (32-40%) yield of the selectively chlorinated product (**70**), essentially without need for protecting groups. This technique should translate onto our own system once more fully elaborated, but that will be a story for another chemist to tell.




(17)

***Summary and Future Work***

Two approaches toward the total synthesis of the marine natural product diazonamide A have been described. In each case, an iminium-mediated addition-cyclization cascade reaction has been applied to provide stereoselective, catalytic access to the crucial *C*-10 quaternary carbon stereocenter for the first time. In our first-generation approach, the Witkop-type photocyclization pioneered by Harran was exteneded in the context of an aryl triflate to forge the biaryl macrocycle. In our second-generation approach, a novel intramolecular soft enolization aldol macrocyclization formed a precursor to the A-ring oxazole, which was subsequently completed in a newly discovered DAST-mediated cyclodehydration. Closure of the fourteen-membered biaryl macrocycle has been accessed through an unusual Suzuki macrocyclization, and completion of diazonamide A should be accessible in four further steps. Efforts to this end are ongoing, and should be reported in due course.

***Supporting Information***

**General Information:** Commercial reagents were purified prior to use following the guidelines of Perrin and Armarego.[35] All solvents were purified according to the method of Grubbs.[36] Non-aqueous reagents were transferred under argon via syringe or cannula. Organic solutions were concentrated under reduced pressure on a Büchi rotary evaporator using a heated water bath. Chromatographic purification of products was accomplished using forced-flow chromatography on Silicycle 230-400 mesh silica gel 60 according to the method of Still.[37] Thin-layer chromatography (TLC) was performed on Silicycle 0.25 mm silica gel 60-F plates. Visualization of the developed chromatogram was performed by fluorescence quenching or by CAM stain.

$^{1}$H and $^{13}$C NMR spectra were recorded on a Varian Mercury 300 (300 MHz and 75 MHz) as noted, and are internally referenced to residual 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 1000 spectrometer and are reported in terms of frequency of absorption ($cm^{-1}$). Mass spectra were obtained from the Caltech Mass Spectral Facility. Optical rotations were measured on a Jasco P-1010 polarimeter, and $[\alpha]_D$ values are reported in $10^{-1}$ dg $cm^2$ $g^{-1}$.

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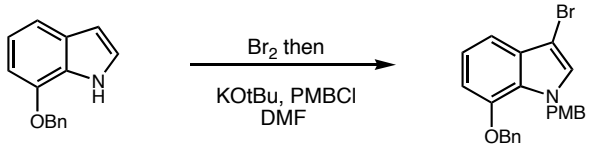
[35] Perrin, D. D.; Armarego, W. L. F. *Purification of Laboratory Chemicals;* 3rd ed., Pergamon Press, Oxford, 1988.

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

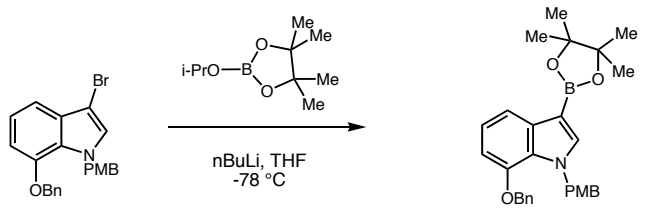
[37] Still, W. C.; Kahn, M.; Mitra, A. J. *J. Org. Chem.* **1978,** *43*, 2923.




**35**

**Bromoindole 35:** To a room temperature solution of 7-benzyloxyindole (5.0 g, 22.4 mmol) in 90 mL of DMF was added bromine (1.18 mL, 22.84 mmol) dropwise over the course of ten minutes. After 20 minutes the solution was cooled to 0 °C and KOtBu (5.78 g, 51.5 mmol) was added in a single portion. 30 minutes later PMBCl (3.65 mL, 26.88 mmol) was added dropwise over several minutes by syringe after which the reaction mixture was allowed to warm to room temperature. After 6 hours the reaction was judged complete by TLC and the reaction mixture was diluted with 300 mL of diethyl ether and washed with 100 mL of 1% $Na_2S_2O_3$. The organic portions were washed three times with water and then once with brine before being dried over sodium sulfate. The organic portion was then concentrated *in vacuo* to yield a viscous yellow oil. These crude extracts could then be recrystallized from a hot mixture of 10% ethyl acetate in hexanes to afford 7.27 g (77%) of the title compound as a white crystalline solid. IR (Film): 2931, 1611, 1574, 1512, 1497, 1453, 1422, 1383, 1322, 1248, 1209, 1175, 1080, 1056, 1033, 988, 875, 818, 774, 727, 695, 625 $cm^{-1}$; $^1H$ NMR: (300 MHz, $CDCl_3$) δ 7.38-7.25 (m, 5H, Ar**H**'s), 7.19 (dd, 1H, J = 0.9, 7.8 Hz, Ar**H**), 7.07 (t, 1H, J = 7.8 Hz, Ar**H**), 7.04 (s, 1H, C(2)-**H**), 6.95-6.88 (m, 2H, Ar**H**), 6.80-6.72 (m, 3H, Ar**H**), 5.51 (s, 2H, PhC$\mathbf{H}_2$), 5.12 (s, 2H, PMBC$\mathbf{H}_2$), 3.77 (s, 3H, **Me**O-Ar) $^{13}C$ NMR: (300 MHz, $CDCl_3$) δ 158.9, 146.6, 136.7, 130.9, 129.9, 128.6, 128.1, 127.8, 125.7, 120.8, 114.0, 112.3, 104,6, 90.4, 70.5,

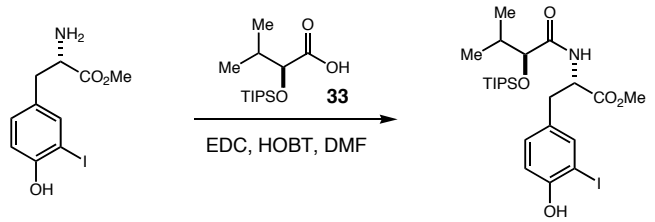
55.3, 52.2 HRMS (EI+) exact mass calculated for [M+•] ($C_{23}H_{20}NO_2Br$) requires *m/z* 421.0677, found *m/z* 421.0672.




**35** **36**

**Indole Boronic Ester 36**: To a solution of n-butyllithium (7.34 mL, 10.65 mmol, 1.2 eq, 1.45M in hexanes) in 80 mL of THF at –78 °C was added bromoindole **35** (3.75 g, 8.88 mmol, 1.0 eq) in 10 mL of THF dropwise via syringe over 10 minutes. After 15 minutes, 2-isopropoxy-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (3.62 mL, 17.76 mmol, 2.0 eq) was added via syringe. This reaction mixture was allowed to warm to ambient temperature over 3 hours. At this point, 100 mL of a saturated aqueous solution of $NH_4Cl$ was added to the reaction mixture and the layers were separated. The aqueous layer was washed 3 x 100 mL with EtOAc. The combined organic layer was washed with 100 mL of brine, dried over sodium sulfate, and concentrated *in vacuo*. The residual oil was then recrystallized from a hot solution of 10% EtOAc in hexanes to give the title compound as an off-white crystalline solid (3.40 g, 82% yield). The remaining mass was recovered as the debrominated starting material. IR (Film): 2976, 1613, 1573, 1539, 1513, 1495, 1454, 1379, 1290, 1267, 1247, 1206, 1144, 1107, 1059, 1009, 783, 735, 696, 681 $cm^{-1}$; $^1H$ NMR: (300 MHz, $CDCl_3$) δ 7.66 (dd, 1H, J = 0.6, 8.1 Hz, Ar**H**), 7.48 (s, 1H, C(2)-**H**), 7.35- 7.22 (m, 5H, Ar**H**), 7.03 (t, 1H, J = 8.1Hz, Ar**H**), 6.91-6.87 (m, 2H, Ar**H**), 6.78-6.65 (m, 3H, Ar**H**), 5.52 (s, 2H, PhC**H**$_2$), 5.09 (s, 2H, PMBC**H**$_2$), 3.75 (s, 3H, **Me**O-Ar),

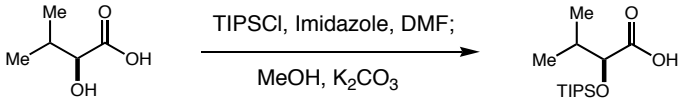
1.35 (s, 12H, 4x**Me**) $^{13}$C NMR: (300 MHz, $CDCl_3$) δ 158.7, 146.6, 138.8, 137.0, 135.3, 131.3, 128.5, 128.4, 128.1, 127.9, 127.8, 126.9, 120.8, 115.7, 113.8, 104.1, 82.8, 70.3, 55.3, 52.2, 25.0 HRMS (EI+) exact mass calculated for [M+•] ($C_{29}H_{32}BNO_4$) requires *m/z* 469.2424, found *m/z* 469.2416.




**32** **34**

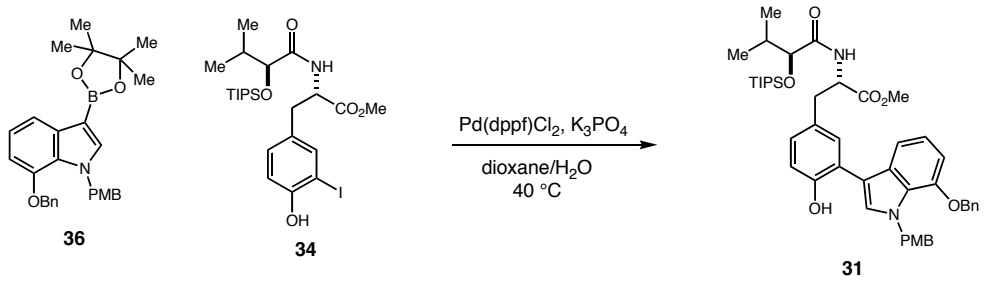
**Iodophenol 34:** Amine **32** (15.4 g, 47.95 mmol), acid **33** (11.96 g, 43.59 mmol), EDC (9.19 g, 47.95 mmol) and HOBT (6.47 g, 47.95 mmol) are combined in a 500 mL round bottom flask and 190 mL of DMF is added. After 12 hours the reaction mixture is diluted with 500 mL of ether and washed with 3 x 500 mL of water. The combined organic fractions are washed with brine and concentrated. The resulting oil is purified on silica gel (30% ethyl acetate in hexanes) to yield the title compound as a colorless oil (21.2 g, 84% yield). IR (Film): 3402, 2944, 2867, 1746, 1654, 1603, 1505, 1462, 1415, 1347, 1292, 1215, 1099, 1058, 882, 822, 684 $cm^{-1}$; $^1$H NMR: (300 MHz, $CDCl_3$) δ 7.44 (d, 1H, J = 2.1 Hz, Ar**H** ortho to iodide), 7.05 (br s, 1H, N**H**), 6.99 (dd, 1H, J = 2.1, 8.55 Hz, Ar**H** para to iodide), 6.87 (d, 1H, J = 8.5 Hz, Ar**H** meta to iodide), 5.82 (s, 1H, O**H**), 4.87 (m, 1H, NH**CH**), 4.15 (d, 1H, J = 3.3 Hz, C**H**OTIPS), 3.69 (s, 3H, $CO_2$**Me**), 2.91 (m, 2H, ArC**H$_2$**), 1.99 (m, 1H, C**H**$(CH_3)_2$), 1.1-1.0 (m, 21H, TIPS), 0.93 (d, 3H, J = 7.2 Hz, CH(C**H$_3$**)$_2$), 0.861 (d, 3H, J = 7.2 Hz, CH(C**H$_3$**)$_2$), $^{13}$C NMR: (75 MHz, $CDCl_3$) δ 172.88, 171.6, 154.5, 139.2, 131.0, 130.0, 115.3, 85.6, 78.3, 52.6, 52.4, 37.4, 34.2, 18.2,

18.1, 17.9, 17.5, 12.6 HRMS (FAB+) exact mass calculated for [M+H] ($C_{24}H_{41}NO_5SiI$) requires *m/z* 578.1799, found *m/z* 578.1791; $[\alpha]_D^{25}$ = -5.75 (c = 1.0 $CHCl_3$).



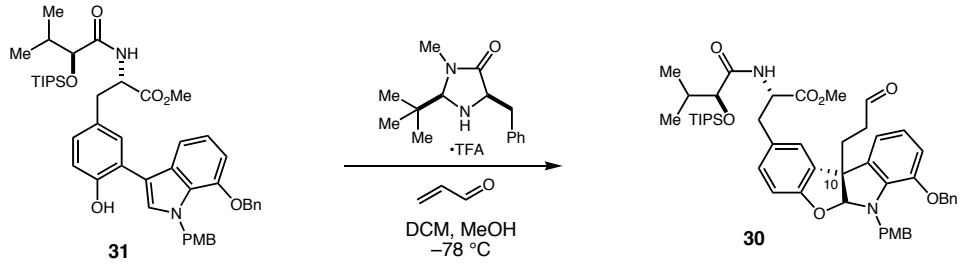

**33**

**TIPS hydroxy valeric acid 33:** To (S)–2-hydroxy valeric acid (5.0 g, 42.3 mmol) in a stirred solution of DMF (22 mL) was added triisopropylsilyl chloride (22 mL, 102 mmol) and imidazole (1.38 g, 204 mmol). After 24 hours, MeOH (210 mL) and 1M aqueous $K_2CO_3$ (64 mL) were added to this slurry, and after 4 h the resultant solution was diluted with 400 mL $H_2O$, acidified to pH = 4, and extracted 3x300 mL with EtOAc. The combined organic fractions are washed with brine and concentrated. The resulting oil is purified of remaining TIPSOH by vacuum distillation of this impurity (85 °C, min. 10 mTorr) to yield the title compound as a colorless oil (9.7 g, 82% yield). IR (Film): 2963, 2945, 2869, 1723, 1465, 1388, 1234, 1152, 1068, 997, 882, 825, 681 $cm^{-1}$; $^1$H NMR: (300 MHz, $CDCl_3$) δ 4.26 (d, 1H, J = 3.6 Hz, C**H**OTIPS), 2.06 (m, 1H, C**H**$(CH_3)_2$), 1.10-0.97 (m, 27H, TIPS, CH(C**H**$_3$)$_2$), $^{13}$C NMR: (75 MHz, $CDCl_3$) δ 173.2, 65.9, 33.7, 17.9, 17.8, 17.7, 17.0, 15.3, 12.2; HRMS (FAB+) exact mass calculated for [M+H] ($C_{14}H_{31}O_3Si$) requires *m/z* 275.2043, found *m/z* 275.2041; $[\alpha]_D^{25}$ = -16.81 (c = 1.0 $CHCl_3$).



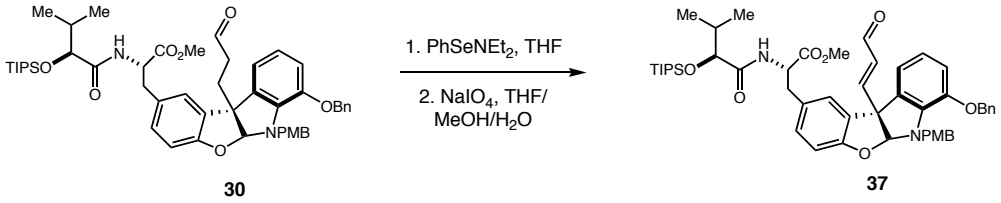

**Phenol 31**: A 100 mL round bottom flask with stirbar is charged with Pd(dppf)$Cl_2$ (0.633 g, 0.7755 mmol), $K_3PO_4$ (8.78 g, 41.36 mmol) and indole boronic ester **36** (8.74 g, 18.62 mmol) in a glove box. This flask was capped with a rubber septa and brought out of the box where in it was placed under a balloon of argon. To the flask is add aryl iodide **34** (5.976 g, 10.34 mmol) in a 60 mL of degassed 1,4 dioxane. To this solution is then added 6 mL of degassed water and the resulting solution is stirred at 40 °C for 2 hours. After the reaction was judged complete by TLC analysis, the reaction mixture was diluted with 200 mL of diethyl ether and washed sequentially with 100 mL portions of water, saturated $NH_4Cl$ solution and brine. The organic portion is dried over sodium sulfate and concentrated *in vacuo*. These crude extracts were purified by column chromatography (4% $Et_2O$/DCM) to yield the title compound (6.38 g, 78%) as a white amorphous solid. IR (Film): 3409, 2945, 2867, 2360, 1747, 1654, 1612, 1570, 1512, 1456, 1385, 1248, 1209, 1175, 1063, 882, 821 $cm^{-1}$; $^1H$ NMR: (300 MHz, $CDCl_3$) δ 7.34-6.68 (m, 17H, Ar**H** and N**H**); 5.59 (s, 2H, OC$\mathbf{H_2}$Ph), 5.34 (s, 1H, ArO**H**), 5.15 (s, 2H, OC$\mathbf{H}_2$-pMeOPh), 4.90 (ddd, 1H, J = 6.0, 6.3 and 8.4 Hz, C**H**$CO_2$Me), 4.14 (d, 1H, J = 3.3 Hz, C**H**OTIPS); 3.77 (s, 3H, ArO**Me**); 3.66 (s, 3H, $CO_2$**Me**); 3.05 (m, 2H, *C*$\mathbf{H}_2$Ar); 1.93 (ddq, 1H, J = 3.6, 7.2, and 7.9 Hz, C**H**$Me_2$); 1.10-0.98 (m, 21H, TIPS); 0.88 (d, 3H, J = 6.9 Hz, CH(**Me**)Me); 0.79 (d, 3H, J = 6.9 Hz, CH(**Me**)Me) $^{13}C$ NMR: (300 MHz, $CDCl_3$) δ 172.4, 171.8, 158.8, 152.5, 146.9, 136.7, 131.0, 129.2, 129.1, 128.6, 128.1, 128.0, 127.8, 127.5, 126.5, 121.1,

120.9, 115.4, 113.9, 112.7, 110.9, 104.6, 78.1, 76.6, 70.4, 55.2, 52.5, 52.2, 52.1, 37.7, 33.9, 18.0, 17.9, 17.7, 17.2, 12.3; HRMS (FAB+) exact mass calculated for [M+•] ($C_{47}H_{60}N_2O_7Si$) requires *m/z* 792.4170, found *m/z* 792.4175; $[\alpha]_D^{25}$: -9.39 (c = 1.03, $CHCl_3$).



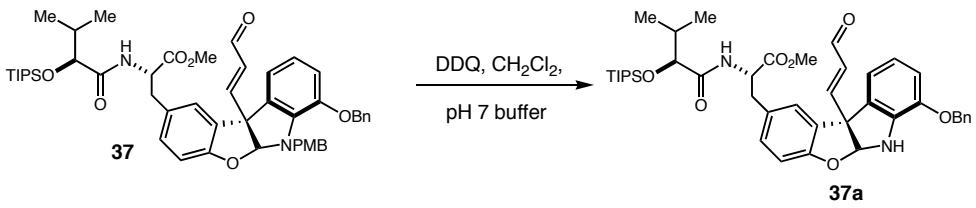

**Aldehyde 30**: (2*R*,5*R*)-2-*tert*-butyl-5-benzyl-3-methylimidazolidin-4-one•TFA (0.313 g, 0.87 mmol) and phenol **31** (2.30 g, 2.90 mmol) are dissolved in 13.75 mL of dichloromethane and 0.75 mL of MeOH. This mixture is cooled to -78 °C. To this cold solution is added freshly distilled acrolein (1.94 mL, 29.0 mmol) at –78 °C. The reaction is left at –78 °C for 48 hours before being diluted with 25 mL of pH 7 buffer. The layers were separated and the organic portions were washed with brine and dried over sodium sulfate. Following concentration *in vacuo*, the crude reaction extracts were purified by flash chromatography in 12:3:1 ratio of dichloromethane, hexanes, and diethyl ether to afford the title compound as an amorphous white solid (1.92 g, 85%) in a 3.5:1.0 mixture of diastereomers at the C(10) stereocenter. IR(Film): 3415, 2944, 2866, 1743, 1677, 1611, 1511, 1494, 1464, 1365, 1247, 1174, 1098, 882, 821, 734, 684 $cm^{-1}$; $^1H$ NMR: (300 MHz, $CDCl_3$) 9.49 (s, 1H, C**H**O), 7.33-6.68 (m, 12H, Ar**H** and N**H**); 5.82 (s, 1H, OC**H**N), 5.29 (d, 1H, J = 15.3 Hz, NCH(**H**)Ar), 5.02 (d, 2H, J = 5.7 Hz, OC$\mathbf{H_2}$Ph), 4.88 (m, 1H, NHC**H**), 4.49 (d, 1H, J = 15.3 Hz, NCH(**H**)Ar), 4.12 (d, 1H, J = 3.6 Hz,

C**H**OTIPS); 3.78 (s, 3H, ArO**Me**); 3.61 (s, 3H, $CO_2$**Me**); 3.01 (m, 2H, **C$H_2$**Ar); 2.15-1.80 (m, 5H, CHOC**$H_2$**C**$H_2$** and C**H**$(CH_3)_2$), 1.10-0.95 (m, 21H, TIPS); 0.88 (d, 3H, J = 7.2 Hz, CH(**Me**)Me); 0.79 (d, 3H, J = 7.2 Hz, CH(Me)**Me**) $^{13}$C NMR: (75 MHz, $CDCl_3$) δ 200.6, 172.3, 171.7, 158.8, 157.8, 144.4, 137.1, 136.8, 133.5, 131.9, 130.9, 129.5, 129.4, 128.5, 128.4, 127.9, 127.5, 123.7, 120.2, 115.7, 113.9, 113.4, 109.8, 105.8, 78.1, 70.9, 68.0, 57.9, 55.2, 52.6, 52.1, 50.4, 39.0, 38.1, 33.9, 29.2, 25.6, 18.0, 17.91, 17.87, 17.7, 17.3, 12.3 HRMS: (FAB+) exact mass calculated for [M+H] ($C_{50}H_{65}N_2O_8Si$) requires *m/z* 849.4354, found *m/z* 849.4386.



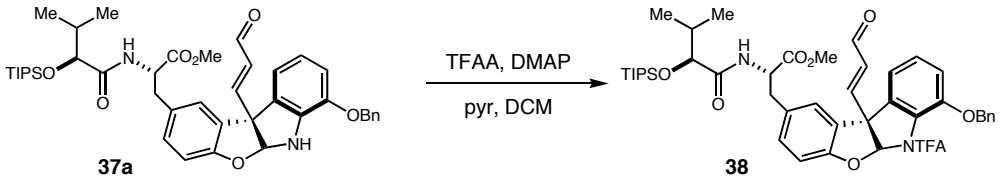

**Aldehyde 37**: To a solution of aldehyde **30** (6.1 g, 7.184 mmol) in 36 mL of dichloromethane at room temperature was added $PhSeNEt_2$ (1.80 mL, 9.34 mmol). After stirring for one hour the reaction was judged complete by TLC. The reaction mixture was concentrated *in vacuo* and the crude extracts were purified by flash chromatography (33% ethyl acetate in hexanes). The product was thus obtained as a yellow oil in a 3:3:1:1 mixture of diastereomers as judged by H-NMR. This product was then taken up in 60 mL of THF, 30 mL of methanol, and 30 mL of water and cooled to 0 °C. To this cold solution was added sodium periodate (7.21 g, 7.184 mmol) in a single portion. After 24 hours the reaction mixture was concentrated *in vacuo* to remove the methanol and THF, diluted with ethyl acetate and washed with water. After separation of the layers the organic portions were washed with brine and dried over sodium sulfate. Concentration of

the resulting solution gave a yellow oil which could be purified by column chromatography (20% – 35% ethyl acetate in hexanes) to give the title compound as an amorphous off-white solid (5.63 g, 88%). IR(Film): 3414, 2945, 2867, 2360, 1743, 1690, 1611, 1511, 1494, 1464, 1365, 1248, 1176, 1100, 882, 822, 749, 684 $cm^{-1}$; $^{1}H$ NMR: (300 MHz, $CDCl_3$) 9.45 (d, 1H, J = 7.5 Hz, C**H**O), 7.40-6.68 (m, 17H, Ar**H,** CHOCH=C**H** and N**H**); 5.97 (s, 1H, OC**H**N), 5.88 (dd, 1H, J = 7.8 and 15.6 Hz, CHOC**H**=CH) 5.23 (d, 1H, J = 15 Hz, NCH(**H**)Ar), 5.02 (d, 2H, J = 1.5 Hz, OC$\mathbf{H_2}$Ph), 4.89 (m, 1H, NHC**H**), 4.49 (d, 1H, J = 15 Hz, NCH(**H**)Ar), 4.12 (d, 1H, J = 3.3 Hz, C**H**OTIPS); 3.76 (s, 3H, ArO**Me**); 3.61 (s, 3H, $CO_2$**Me**); 3.02 (m, 2H, **C**$\mathbf{H_2}$Ar); 2.0-1.80 (m, 1H, C**H**$(CH_3)_2$), 1.10-0.95 (m, 21H, TIPS); 0.88 (d, 3H, J = 7.2 Hz, CH(**Me**)Me); 0.78 (d, 3H, J = 7.2 Hz, CH(Me)**Me**) $^{13}C$ NMR: (75 MHz, $CDCl_3$) δ 192.7, 172.3, 171.6, 158.9, 158.1, 154.9, 145.4, 137.4, 136.6, 133.1, 131.7, 130.3, 130.2, 129.7, 129.6, 129.2, 128.8, 128.5, 128.0, 127.5, 127.0, 124.8, 121.2, 117.0, 113.9, 113.7, 110.1, 106.8, 78.1, 77.2, 70.8, 61.6, 55.2, 52.7, 52.4, 52.1, 51.2, 38.0, 33.9, 21.0, 18.0, 17.91, 17.87, 17.7, 17.2, 14.2, 12.3 HRMS: (FAB+) exact mass calculated for [M+H] ($C_{50}H_{63}N_2O_8Si$) requires *m/z* 847.4354, found *m/z* 847.4313; $[\alpha]_D^{25}$ = -37.11 (c = 1.0 $CHCl_3$).



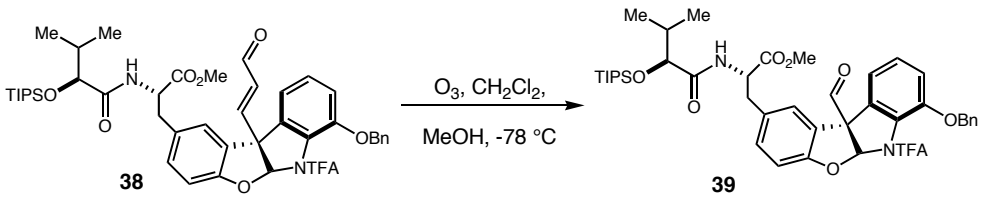

**Amine 37a**: To a vigorously stirred solution of aldehyde **37** (810 mg, 0.956 mmol) in a 1:1 mixture of dichloromethane and pH 7 buffer (16 mL each) at 0 °C was added freshly recrystallized DDQ (477 mg, 2.10 mmol). The resulting dark green heterogeneous

reaction mixture is allowed to warm to ambient temperature over the course of two hours after which time it is diluted with 100 mL of ethyl acetate and washed with 100 mL of a saturated solution of sodium bicarbonate. The layers were separated and the aqueous layer wash washed with three times with 50 mL of ethyl acetate. The combined organic layer was washed with brine and dried over sodium sulfate. Purification by flash chromatography on iatrobeads (25% - 35% ethyl acetate in hexanes) gave the desired product as an amorphous off-white solid as a 3.5:1 mixture of diastereomers in 89% yield (620 mg). IR(Film): 3413, 2945, 2867, 1743, 1689, 1620, 1497, 1464, 1348, 1250, 1207, 1098, 1057, 882, 822, 737, 684 $cm^{-1}$; $^1H$ NMR: (300 MHz, $CDCl_3$) 9.62 (d, 1H, J = 7.8 Hz, C**H**O), 7.40-6.68 (m, 12H, Ar**H,** CHOCH=C**H** and CON**H**); 6.27 (s, 1H, OC**H**N), 6.18 (dd, 1H, J = 7.8 and 16.2 Hz, C**H**OCH=CH), 5.13 (br s, 1H, OCHN**H**) 5.05 (s, 2H, OC**H**$_2$Ph), 4.91 (m, 1H, CONHC**H**), 4.13 (d, 1H, J = 3.6 Hz, C**H**OTIPS); 3.62 (s, 3H, $CO_2$**Me**); 3.04 (m, 2H, **CH**$_2$Ar); 2.00-1.85 (m, 1H, C**H**$(CH_3)_2$), 1.10-0.95 (m, 21H, TIPS); 0.89 (d, 3H, J = 6.9 Hz, CH(**Me**)Me); 0.79 (d, 3H, J = 6.9 Hz, CH(Me)**Me**) $^{13}C$ NMR: (75 MHz, $CDCl_3$) δ 192.9, 172.3, 171.6, 158.3, 155.0, 152.5, 144.2, 137.2, 136.7, 133.2, 131.3, 130.3, 129.4, 129.3, 129.1, 128.7, 128.6, 128.33, 128.29, 128.1, 127.9, 127.6, 124.7, 120.9, 116.5, 112.3, 110.2, 78.1, 77.2, 70.5, 63.7, 52.5, 52.1, 38.1, 33.9, 18.0, 17.91, 17.88, 17.7, 17.6, 17.3, 17.2, 12.3 HRMS: (FAB+) exact mass calculated for [M+H] ($C_{42}H_{55}N_2O_7Si$) requires *m/z* 727.3779, found *m/z* 727.3758; $[\alpha]_D^{25}$= -60.33 (c = 1.0 $CHCl_3$).



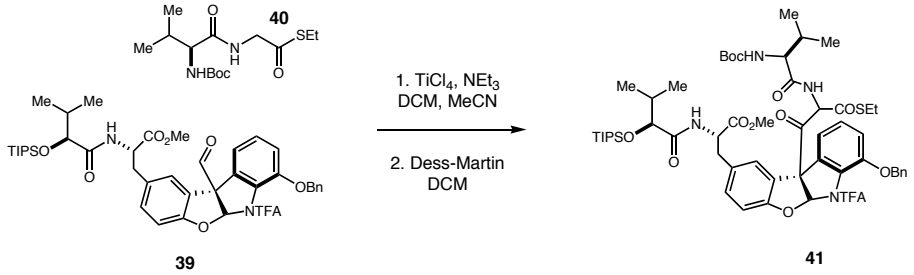

**Aldehyde 38**: To a solution of amino aldehyde **37a** (354 mg, 0.487 mmol), pyridine (0.1 mL, 1.2175 mmol) and DMAP (29.7 mg, 0.2435 mmol) in 5 mL of dichloromethane at 0 °C was added trifluoroacetic anhydride (0.172 mL, 1.22 mmol) dropwise by syringe under argon. After 30 minutes the reaction was diluted with 50 mL of ethyl acetate and washed with 30 mL of saturated sodium bicarbonate solution. The layers were separated and the organic fraction was washed with brine and dried over sodium sulfate. Purification by flask chromatography on silica gel (25% ethyl acetate in hexanes) gave the title compound product as an amorphous yellow solid in 89% yield (354 mg) in a 3.5:1 mixture of diastereomers. IR(Film): 3415, 2945, 2867, 1731, 1663, 1610, 1494, 1462, 1203, 1182, 1154, 948, 881, 822, 738 $cm^{-1}$; $^{1}H$ NMR: (300 MHz, $CDCl_3$) 9.67 (d, 1H, J = 7.2 Hz, C**H**O), 7.50-6.75 (m, 13H, Ar**H,** CHOCH=C**H** and CON**H**); 6.57 (d, 1H, J = 1.2 Hz, OC**H**N), 6.21 (dd, 1H, J = 7.5 and 15.9 Hz, C**H**OCH=CH), 5.20 (app q, 2H, OC$\mathbf{H_2}$PH), 4.92 (m, 1H, CONHC**H**), 4.13 (d, 1H, J = 3.3 Hz, C**H**OTIPS), 3.65 (s, 3H, $CO_2$**Me**), 3.06 (m, 2H, **C**$\mathbf{H_2}$Ar); 2.00-1.85 (m, 1H, C**H**$(CH_3)_2$), 1.10-0.95 (m, 21H, TIPS); 0.89 (d, 3H, J = 7.2 Hz, CH(**Me**)Me), 0.79 (d, 3H, J = 7.2 Hz, CH(Me)**Me**) $^{13}C$ NMR: (75 MHz, $CDCl_3$) δ 192.2, 172.5, 171.7, 157.5, 151.3, 149.9, 136.5, 135.4, 135.3, 135.1, 131.4, 130.8, 130.7, 129.3, 128.8, 128.5, 128.3, 128.2, 127.3, 124.7, 118.1, 116.7, 114.7, 114.3, 110.7, 100.6, 78.3, 71.0, 63.6, 60.6, 52.8, 52.5, 52.4, 38.3, 34.1, 21.2, 18.2, 18.1, 18.0, 17.7, 17.5, 17.3, 14.4, 12.6, 12.5 HRMS: (FAB+) exact mass calculated for [M+H]

($C_{44}H_{54}N_2O_8F_3Si$) requires *m/z* 823.3601, found *m/z* 823.3560; $[\alpha]_D^{25}$= -88.69 (c = 1.0 $CHCl_3$).



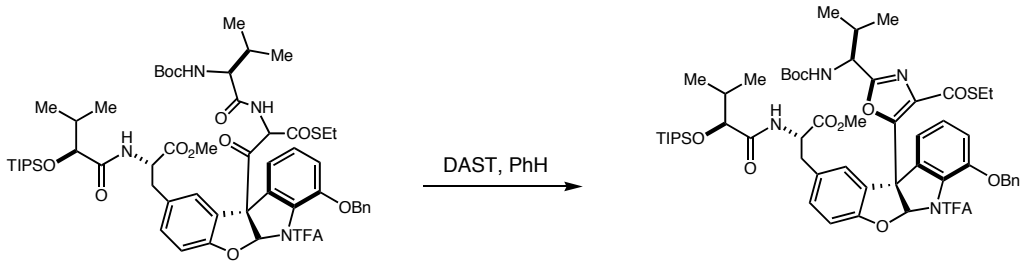

**Aldehyde 39**: A stream of ozone is passed through a solution of α,β-unsaturated aldehyde **38** (2.52 g, 3.06 mmol) in 40 mL of dichloromethane and 4 mL of methanol at –78 °C for 45 minutes. The solution was bubbled through with oxygen for ten minutes and then quenched by the addition of triphenylphospine (0.96 g, 3.67 mmol). After warming to room temperature overnight the reaction mixture was concentrated *in vacuo* and loaded directly onto a silica gel column. Elution with 35% ethyl acetate in hexanes gives 2.10 g of title product (87%) as an amorphous white solid in a 3.5:1 mixture of diastereomers. IR(Film): 3414, 2945, 2868, 1729, 1666, 1610, 1492, 1462, 1203, 1181, 1158, 986, 881, 822, 738, 681 $cm^{-1}$; $^1H$ NMR: (300 MHz, $CDCl_3$) 10.05 (s, 1H, C**H**O), 7.50-6.80 (m, 13H, Ar**H,** OC**H**NTFA and CON**H**), 5.19 (app q, 2H, OC**H**$_2$PH), 4.94 (m, 1H, CONHC**H**), 4.14 (d, 1H, J = 3.3 Hz, C**H**OTIPS), 3.65 (s, 3H, $CO_2$**Me**), 3.07 (m, 2H, **CH**$_2$Ar), 2.0-1.85 (m, 1H, C**H**$(CH_3)_2$), 1.10-0.95 (m, 21H, TIPS), 0.88 (d, 3H, J = 7.2 Hz, CH(**Me**)Me), 0.79 (d, 3H, J = 6.6 Hz, CH(Me)**Me**) $^{13}C$ NMR: (75 MHz, $CDCl_3$) δ 191.7, 173.0, 172.7, 171.8, 171.7, 157.0, 149.8, 136.9, 136.5, 135.0, 132.4, 131.7, 131.0, 130.9, 130.5, 129.6, 129.5, 129.2, 128.8, 128.7, 128.2, 128.0, 127.3, 125.2, 124.2, 118.0, 116.0, 115.3, 114.2, 110.9, 109.8, 99.1, 96.1, 78.3, 71.1, 70.8, 60.7, 56.1, 52.7, 52.4, 38.7, 38.2, 34.1, 33.9, 33.8, 21.3, 18.2, 18.1, 17.8, 17.7, 17.5, 17.4, 17.2, 14.4, 12.55, 12.51 HRMS:

(FAB+) exact mass calculated for [M+H] ($C_{42}H_{52}N_2O_8F_3Si$) requires *m/z* 797.3445, found *m/z* 797.3420; $[\alpha]_D^{25}$ = -112.22 (c = 1.0 $CHCl_3$).




**Ketoamide 41**: To a solution of thioester **40** (461 mg, 1.449 mmol) in 6.0 mL of DCM at –78 °C under an argon balloon was added $TiCl_4$ (0.334 mL, 3.029 mmol) and the resulting solution turned bright yellow. After 30 minutes triethylamine (0.423 mL, 3.029 mmol) was added turning the reaction mixture dark purple. After 30 minutes more MeCN (0.1375 mL, 2.634 mmol) was added. Ten minutes after aldehyde **39** (1.05 g, 1.317 mmol) was added dropwise as a solution in 1.5 mL of DCM. The dark purple reaction mixture was stirred at –78 °C for 1 hour then placed in a –30 °C refrigerator for 12 hours. At this time the reaction was diluted with DCM and quenched with a saturated solution of $NaHCO_3$. The layers were separated and the organic layer was washed with 2 x 50 mL of water then 50 mL of brine. The organic fractions were concentrated and purified by column chromatography (20%-25% ethyl acetate in hexanes) to afford the title compound as an amorphous yellow solid. This solid was immediately dissolved in 17.5 mL of DCM and Dess-Martin periodinane (1.11 g, 2.62 mmol) was added. After two hours the solution was diluted with ethyl acetate and washed with a saturated solution of $NaHCO_3$. The organic fractions were concentrated and the resulting oil purified by column chromatography to afford in 65% yield over the two steps the title compound (1.05 g) as

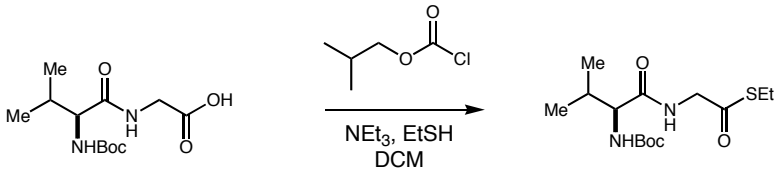
an off-yellow solid as a 3.5:3.5:1:1 mixture of inseparable diastereomers by $^1$H-NMR. This material was carried on without further purification. HRMS: (FAB+) exact mass calculated for [M+H] ($C_{56}H_{76}N_4O_{12}F_3SiS$) requires *m/z* 113.490, found *m/z* 113.491; $[\alpha]_D^{25}$ = -31.69 (c = 1.0 $CHCl_3$) (for ketoamide).




**41** **42**

**Oxazole 42**: To a solution of **41** (900 mg, 0.8 mmol) in benzene (15 mL) was added DAST (1.5 mL) dropwise by syringe. The solution was stirred at room temperature for one hour before being diluted with a saturated solution of $NaHCO_3$. The layers were separated and the organic was washed with ethyl acetate 3 x 50 mL. The combined organics were washed with brine and concentrated. The resulting oil was purified on silica gel (20%-25% ethyl acetate in hexanes) to yield the title compound (500 mg, 55%) as pale yellow solid. IR(Film): 3415, 2963, 2868, 2360, 2340, 1732, 1674, 1608, 1495, 1464, 1367, 1290, 1253, 1203, 1159, 1125, 1001, 878, 822, 738, 685, 668 $cm^{-1}$; $^1$H NMR: (300 MHz, $CDCl_3$): 7.80-6.80 (m, 13H, Ar-**H,** OC**H**NTFA and CON**H**), 5.59 (br d, 1H, J = 9.3 Hz, N**H**Boc), 5.17 (app q, 2H, OC$\mathbf{H}_2$Ph), 4.94 (m, 1H, CONHC**H**), 4.90 (m, 1H, C**H**NHBOC), 4.08 (d, 1H, J = 3.6 Hz, C**H**OTIPS), 3.59 (S, 3H, $CO_2$**Me**), 3.00 (M, 2H, C$\mathbf{H}_2$Ar), 2.76 (q, 2H, J = 7.5 Hz, C$\mathbf{H}_2CH_3$), 2.19 (m, 1H, NHCHC**H**$(CH_3)_2$), 1.85 (m, 1H, OCHC**H**$(CH_3)_2$), 1.47 (br s, 9H, Boc), 1.20 (t, 3H, J = 7.5 Hz, $CH_2C\mathbf{H}_3$), 0.99 (m, 27H, TIPS and NHCHCH(**C**$\mathbf{H}_3$)$_2$), 0.79 (d, 3H, J = 7.2 Hz, OCHCH(**Me**)Me); 0.75 (d, 3H, J =

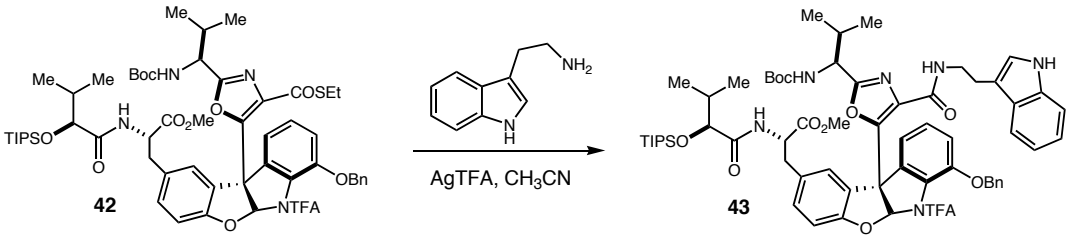
6.9 Hz, CH(Me)**Me**); $^{13}$C NMR: (75 MHz, $CDCl_3$) δ 186.8, 183.4, 180.6, 174.2, 172.2, 171.6, 163.5, 162.7, 161.8, 157.5, 155.6, 154.2, 153.7, 149.8, 149.4, 137.0, 136.4, 135.5, 135.0, 134.0, 133.1, 132.4, 131.0, 129.7, 128.5, 127.9, 127.7, 127.1, 125.1, 116.2, 115.5, 114.2, 110.1, 99.7, 94.6, 80.0, 78.1, 70.8, 60.1, 59.1, 54.4, 52.1, 47.9, 38.4, 33.7, 32.5, 28.3, 28.0, 22.9, 18.8, 18.2, 17.9, 17.8, 17.4, 17.1, 16.7, 16.0, 14.2, 13.6, 12.3; $^{19}$F NMR: (75 MHz, $CDCl_3$) δ –70.4 (s, 3F, $CF_3$); HRMS: (FAB+) exact mass calculated for [M–H] ($C_{56}H_{72}N_4O_{11}F_3SiS$) requires *m/z* 1093.464, found *m/z* 1093.464; $[\alpha]_D^{25}$ = -44.62 (c = 1.0 $CHCl_3$).




**40**

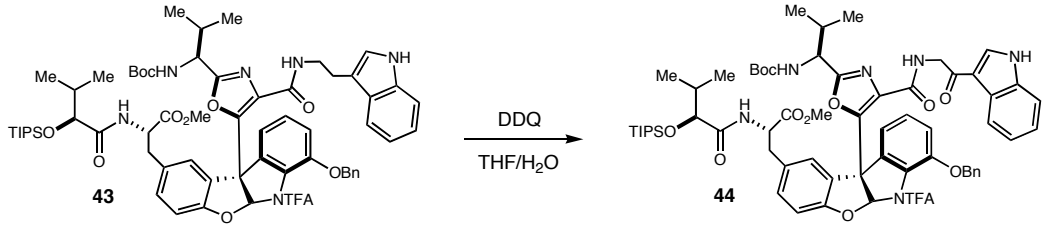
**Thioester 40**: To a 0 °C solution of carboxylic acid (2.96 g, 10.79 mmol) in 50 mL of DCM under argon was added $NEt_3$ (3.91 mL, 28.054 mmol) followed by isobutyl chloroformate (1.66 mL, 12.95 mL). After 1 hour at 0 °C was added ethanethiol (1.67 mL, 2.0 mmol) and the reaction was warmed to room temperature and stirred for ten hours. The reaction mixture was then diluted with $NaHCO_3$ and extracted 3 x 100 mL of DCM. The combined organic layer was washed with 200 mL of brine and concentrated. The resulting oil was recrystallized from a hot solution of 10% ethyl acetate in hexanes to give the title compound as a white crystalline solid in 85% yield (2.90 g). IR (Thin Film): 3310, 3077, 2968, 2932, 1688, 1663, 1525, 1392, 1366, 1298, 1247, 1170, 1094, 1043, 1016, 966 cm$^{-1}$; $^1$H NMR: (300 MHz, $CDCl_3$) δ 6.66 (br s, 1H, N**H**), 5.03 (br s, 1H, N**H**Boc), 4.19 (d, 2H, J = 5.4 Hz, NHC**H$_2$**), 4.00 (dd, 1H, J = 6.0, 8.4 Hz, C**H**NHBoc),

2.91 (q, 2H, J = 7.5 Hz, SC**H**$_2$), 2.21 (m, 1H, C**H**Me(Me)), 1.44 (s, 9H, O**tBu**), 1.25 (t, 3H, J = 7.5 Hz, SCH$_2$C**H**$_3$), 0.98 (d, 3H, J = 6.9 Hz, CH**Me**(Me)), 0.94 (d, 3H, J = 6.9 Hz, CHMe(**Me**)); $^{13}$C NMR: (75 MHz, $CDCl_3$) δ 196.9, 172.2, 156.2, 80.3, 60.1, 49.2, 30.9, 28.5, 23.4, 19.6, 17.9, 14.8; HRMS: (FAB+) exact mass calculated for [M+H] ($C_{14}H_{27}N_2O_4S$) requires *m/z* 319.1702, found *m/z* 319.1692; $[\alpha]_D^{25}$ = -17.01 (c = 1.0 $CHCl_3$).



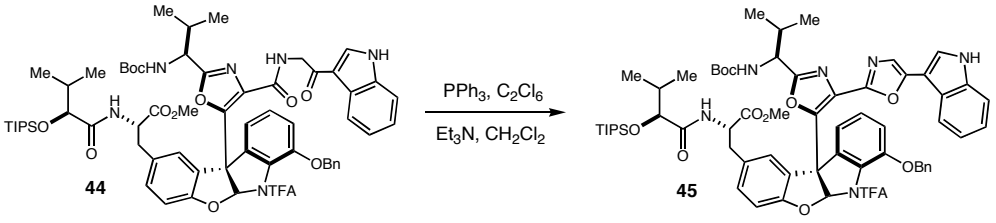

**Amide 43**: To **42** (100 mg, 0.091 mmol), tryptamine (51 mg, 0.318 mmol) and AgTFA (46 mg, 0.209 mmol) in a light-protected round-bottom flask was added degassed $CH_3CN$ (1.8 mL) with stirring. The solution was warmed to 40 °C and held for 45 min before being diluted with $Et_2O$ and passed through celite. After concentration, the resulting oil was purified on silica gel (40 -80 % $Et_2O$ in hexanes) to yield the title compound (87 mg, 87%) as pale yellow solid. IR(Film): 3410, 2961, 2868, 1724, 1672, 1607, 1494, 1458, 1367, 1288, 1204, 1159, 1011, 880, 821, 739, 684 cm$^{-1}$; $^1$H NMR: (300 MHz, $CDCl_3$): 8.14 (s, 1H, C=CN**H**), 7.78 (d, 1H, Ar-**H**, 1.2 Hz), 7.58-6.76 (m, 17H, Ar-**H,** OC**H**NTFA and CON**H**), 5.49 (br d, 1H, J = 9.3 Hz, N**H**Boc), 5.16 (m, 2H, OC**H**$_2$Ph), 4.95 (m, 1H, CONHC**H**), 4.75 (m, 1H, C**H**NHBOC), \ 4.09 (d, 1H, J = 3.6 Hz, C**H**OTIPS), 3.58 (m, 5H, $CO_2$**Me**, NHC**H**$_2$CH$_2$), 3.00 (m, 4H, C**H**$_2$Ar, NHC**H**$_2$C**H**$_2$), 2.14 (m, 1H, NHCHC**H**$(CH_3)_2$), 1.88 (m, 1H, OCHC**H**$(CH_3)_2$), 1.44 (br s, 9H, Boc), 0.99 (m, 27H, TIPS and NHCHCH(**CH**$_3$)$_2$), 0.78 (d, 3H, J = 7.2 Hz, OCHCH(**Me**)Me); 0.72 (d, 3H, J =

7.2 Hz, CH(Me)**Me**); $^{13}$C NMR: (75 MHz, $CDCl_3$) δ 172.3, 171.7, 162.0, 160.0, 157.5, 155.5, 150.0, 149.4, 136.5, 136.3, 135.6, 130.8, 130.3, 129.4, 128.5, 128.4, 128.3, 127.8, 127.4, 127.3, 127.0, 126.9, 124.8, 122.1, 122.0, 119.3, 118.6, 116.5, 114.0, 112.8, 111.2, 110.0, 100.1, 80.1, 78.1, 70.7, 60.0, 54.4, 52.2, 52.1, 39.3, 38.4, 33.9, 33.7, 32.3, 28.4, 25.2, 18.8, 18.2, 18.0, 17.9, 17.8, 17.4, 17.1, 12.3; $^{19}$F NMR: (75 MHz, $CDCl_3$) δ –70.4 (s, 3F, $CF_3$); HRMS: (FAB+) exact mass calculated for [M+H] ($C_{64}H_{78}N_6O_{11}F_3Si$) requires *m/z* 1192.551, found *m/z* 1192.547; $[\alpha]_D^{25}$ = -45.64 (c = 1.0 $CHCl_3$).



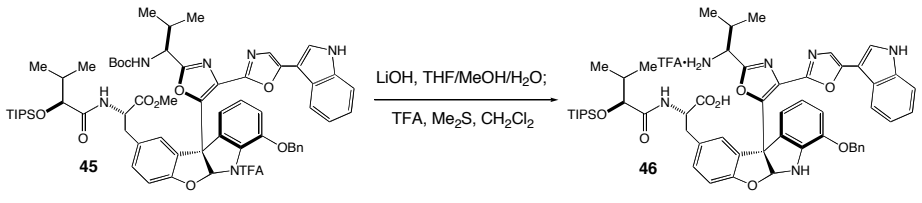

**Ketoindole 44**: To a solution of **43** (300 mg, 0.25 mmol) in THF/$H_2O$ (10:1, 5 mL) was added DDQ (122 mg, 0.75 mmol). The solution was stirred at room temperature for 15 min before being diluted with a saturated solution of $NaHCO_3$. The layers were separated and the aqueous was washed with ethyl acetate 3 x 50 mL. The combined organics were washed with brine and concentrated. The resulting oil was purified on silica gel (60%-80% $Et_2O$ in hexanes) to yield the title compound (228 mg, 75%) as pale yellow solid. IR (Film): 3406, 2962, 2868, 1732, 1674, 1608, 1511, 1495, 1455, 1367, 1288, 1247, 1204, 1159, 1126, 1009, 910, 881, 822, 736, 685, 648 $cm^{-1}$; $^1$H NMR: (300 MHz, $CDCl_3$): 9.63 (d, 1H, C=CN**H**, 2.1 Hz), 8.21 (d, 1H, Ar-**H**, 6.9 Hz), 7.98 (t, 1H, Ar-**H**, 4.8 Hz), 7.61-6.75 (m, 16H, Ar-**H,** OC**H**NTFA and CON**H**), 5.62 (br d, 1H, J = 9.0 Hz, N**H**Boc), 5.09 (m, 2H, OC$\mathbf{H}_2$Ph), 4.95 (m, 1H, CONHC**H**), 4.80 (m, 1H, C**H**NHBOC), 4.45 (t, 2H, J = 5.0 Hz, C$\mathbf{H}_2$CO), 4.09 (d, 1H, J = 3.6 Hz, C**H**OTIPS), 3.59 (s, 3H, $CO_2$**Me**), 3.03 (m, 2H,

C**H**$_2$Ar), 2.20 (m, 1H, NHCHC**H**$(CH_3)_2$), 1.87 (m, 1H, OCHC**H**$(CH_3)_2$), 1.47 (br s, 9H, Boc), 0.99 (m, 27H, TIPS and NHCHCH(**CH$_3$**)$_2$), 0.77 (d, 3H, J = 7.2 Hz, OCHCH(**Me**)Me); 0.71 (d, 3H, J = 7.2 Hz, CH(Me)**Me**); $^{13}$C NMR: (75 MHz, $CDCl_3$) δ 186.5, 172.3, 171.6, 162.4, 160.2, 157.5, 155.6, 155.5, 151.1, 149.3, 136.4, 136.3, 135.8, 132.0, 130.8, 130.3, 129.5, 128.7, 128.5, 128.2, 127.8, 127.0, 125.5, 125.3, 125.2, 123.7, 122.7, 121.8, 118.1, 116.2, 114.7, 114.3, 114.0, 111.9, 110.0, 100.3, 80.2, 78.2, 70.7, 65.9, 60.1, 54.5, 52.5, 52.1, 45.7, 38.3, 34.2, 33.8, 33.7, 32.6, 30.3, 28.4, 18.8, 18.2, 18.0, 17.9, 17.8, 17.4, 17.1, 15.3, 12.3; $^{19}$F NMR: (75 MHz, $CDCl_3$) δ –70.2 (s, 3F, $CF_3$); HRMS: (FAB+) exact mass calculated for [M–H] ($C_{64}H_{78}N_6O_{12}F_3Si$) requires *m/z* 1207.540, found *m/z* 1207.536; $[\alpha]_D^{25}$ = -40.21 (c = 1.0 $CHCl_3$).




**Bisoxazole 45**: To a solution of $PPh_3$ (186 mg, 0.71 mmol) in $CH_2Cl_2$ (6.6 mL) was added $C_2Cl_6$ (168 mg, 0.71 mmol). The solution was stirred at room temperature for 10 min at which time $Et_3N$ (0.20 mL, 1.42 mmol) was added dropwise. The resultant solution was stirred for 10 min at which time it was added dropwise via cannula to a stirred $CH_2Cl_2$ (2.8 mL) solution of **44** (171 mg, 0.142 mmol) held at -15 °C. After addition was complete, the reaction was warmed to 0 °C and held at this temperature for 10 min, at which point it was allowed to warm to room temperature and stirred for an additional 10 min. The solution was then diluted with a saturated solution of $NaHCO_3$. The layers were separated and the aqueous was washed with $CH_2Cl_2$ 3 x 20 mL. The

combined organics were washed with brine and concentrated. The resulting oil was purified on silica gel (50%-70% $Et_2O$ in hexanes) to yield the title compound (157 mg, 93%) as a pale off-white solid. IR(Film): 3406, 2962, 2868, 1733, 1674, 1610, 1495, 1458, 1367, 1288, 1256, 1203, 1156, 1124, 1057, 997, 882, 741, 668 $cm^{-1}$; $^1H$ NMR: (300 MHz, $CDCl_3$): 8.58 (s, 1H, C=CN**H**), 7.74-6.76 (m, 19H, Ar-**H,** OC**H**NTFA and CON**H**), 5.71 (br d, 1H, J = 9.0 Hz, N**H**Boc), 5.11 (app d, 2H, OC**H**$_2$Ph, J = 3.6 Hz), 4.92 (m, 1H, CONHC**H**), 4.82 (m, 1H, C**H**NHBOC), 4.09 (d, 1H, J = 3.3 Hz, C**H**OTIPS), 3.57 (s, 3H, $CO_2$**Me**), 2.98 (m, 2H, C**H**$_2$Ar), 2.20 (m, 1H, NHCHC**H**$(CH_3)_2$), 1.86 (m, 1H, OCHC**H**$(CH_3)_2$), 1.46 (br s, 9H, Boc), 0.99 (m, 27H, TIPS and NHCHCH(**CH**$_3$)$_2$), 0.77 (d, 3H, J = 6.9 Hz, OCHCH(**Me**)Me); 0.69 (d, 3H, J = 6.9 Hz, CH(Me)**Me**); $^{13}C$ NMR: (75 MHz, $CDCl_3$) δ 172.5, 171.8, 164.1, 163.3, 161.6, 161.5, 161.4, 161.3, 161.2, 157.6, 156.0, 155.8, 155.6, 151.7, 150.8, 149.4, 148.7, 147.5, 136.7, 136.4, 131.2, 130.2, 128.9, 128.8, 128.2, 128.1, 127.4, 125.8, 125.7, 124.0, 123.2, 123.1, 121.5, 121.1, 119.9, 118.3, 116.2, 114.3, 111.9, 110.4, 104.9, 100.3, 80.2, 78.4, 70.9, 60.6, 54.8, 52.5, 52.3, 38.6, 33.9, 33.1, 30.6, 28.6, 19.0, 18.5, 18.2, 18.1, 18.0, 17.7, 17.3, 12.5; $^{19}F$ NMR: (75 MHz, $CDCl_3$) δ –70.3 (s, 3F, $CF_3$); HRMS: (FAB+) exact mass calculated for [M–H] ($C_{64}H_{76}N_6O_{11}F_3Si$) requires *m/z* 1189.529, found *m/z* 1189.525; $[\alpha]_D^{25}$ = -21.03 (c = 1.0 $CHCl_3$).

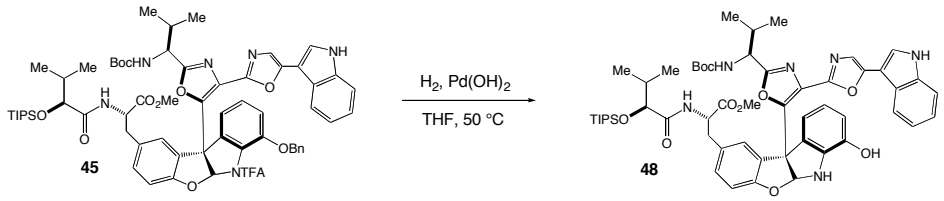


**Amino Acid 46**: To a solution of **45** (157 mg, 0.132 mmol) in THF/MeOH/$H_2O$ (10:2:1, 4.4 mL) was added LiOH•$H_2O$ (56 mg, 1.32 mmol). The solution was stirred at room temperature for 1 h at which time it was acidified with 1% aqueous HCl to pH 2. The aqueous layer was extracted 3x with EtOAc, the organics combined and dried over $Na_2SO_4$. Following concentration, the resultant carboxylic acid was redissolved in $CH_2Cl_2$ (2.4 mL). To this solution was then added $Me_2S$ (0.6 mL) and trifluoroacetic acid (1.2 mL) with stirring. After stirring for 25 min, the solvents were removed *in vacuo*, and the resulting solid redissolved in benzene and concentrated three successive times in order to remove residual trifluoroacetic acid. The resulting solid was purified on silica gel (5%-10% MeOH in $CH_2Cl_2$) to yield the title compound (125 mg, 88%) as a yellow solid. IR(Film): 3397, 2958, 2929, 2862, 1676, 1622, 1497, 1458, 1387, 1204, 1138, 1054, 996, 881, 801, 727 $cm^{-1}$; $^1$H NMR: (300 MHz, $CD_3OD$): 7.70-6.52 (m, 19H, Ar-**H,** OC**H**NH and CON**H**), 4.82 (app d, 2H, OC$\mathbf{H}_2$Ph, J = 11.7 Hz), 4.37 (d, 1H, CONHC**H**, J = 5.1 Hz), 4.29 (d, 1H, C**H**$NH_2$, J = 7.5 Hz), 4.01 (d, 1H, J = 4.2 Hz, C**H**OTIPS), 2.93 (m, 2H, C$\mathbf{H}_2$Ar), 2.30 (m, 1H, NHCHC**H**$(CH_3)_2$), 1.78 (m, 1H, OCHC**H**$(CH_3)_2$), 1.04 (m, 27H, TIPS and NHCHCH(**C**$\mathbf{H}_3$)$_2$), 0.74 (d, 3H, J = 6.9 Hz, OCHCH(**Me**)Me); 0.68 (d, 3H, J = 6.9 Hz, CH(Me)**Me**); $^{13}$C NMR: (75 MHz, $CD_3OD$) δ 173.2, 172.6, 158.8, 158.6, 152.6, 151.5, 149.9, 143.9, 138.2, 137.7, 136.7, 132.4, 132.3, 131.7, 131.6, 130.0, 129.2, 129.0, 128.8, 128.7, 128.5, 128.2, 128.0, 127.5, 127.4, 127.1, 127.0, 126.9, 126.2, 124.6, 123.7, 122.1, 120.2, 120.1, 119.3, 118.9, 118.5, 114.6, 112.2, 11.6, 109.5, 103.6, 103.2, 78.2, 69.6, 67.4, 60.3, 53.9, 53.7, 52.3, 37.0, 33.5, 31.2, 29.5, 25.1, 23.3, 18.9, 17.5, 17.1, 17.0, 16.9, 16.6, 16.5, 16.3, 12.1; HRMS: (FAB+) exact mass calculated for [M+H]

($C_{56}H_{67}N_6O_8Si$) requires *m/z* 979.4790, found *m/z* 979.4801; $[\alpha]_D^{25}$ = -42.16 (c = 1.0 MeOH).

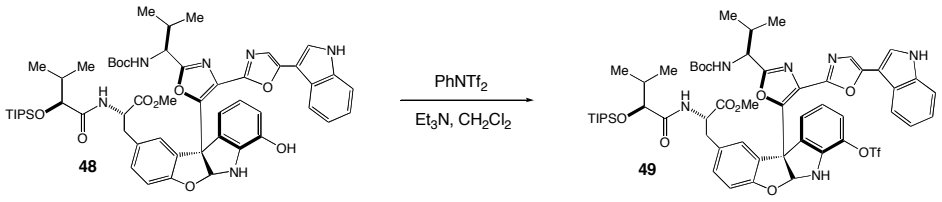
**Macrolactam dimer 47**: To a solution of **45** (50 mg, 0.042 mmol) in THF/MeOH/$H_2O$ (10:2:1, 1.4 mL) was added LiOH•$H_2O$ (18 mg, 0.420 mmol). The solution was stirred at room temperature for 1 h at which time it was acidified with 1% aqueous HCl to pH 2. The aqueous layer was extracted 3x with EtOAc, the organics combined and dried over $Na_2SO_4$. Following concentration, the resultant carboxylic acid was redissolved in EtOAc (1.4 mL). To this solution was then added DCC (21.7 mg, 0.105 mmol) and pentafluorophenol (19.3 mg, 0.105 mmol). This solution was stirred at room temperature for 20 min, at which time it was passed through celite and concentrated. The resulting pentafluorophenyl ester was dissolved in $CH_2Cl_2$ (1.2 mL). To this solution was then added $Me_2S$ (0.3 mL) and trifluoroacetic acid (0.6 mL) with stirring. After stirring for 25 min, the solvents were removed *in vacuo*, and the resulting solid redissolved in benzene and concentrated three successive times in order to remove residual trifluoroacetic acid. The resulting solid was redissolved in EtOAc (14 mL), and DIPEA (29 $\mu$L, 0.168 mmol) was added. After stirring at room temperature for 24 h, this solution was concentrated and the residue purified on silica gel (60% EtOAc in hexanes) to yield the title compound (28 mg, 71%) as a yellow oil. IR(Film): 3403, 2932, 2868, 1652, 1533, 1516, 1463, 1370, 1253, 1208, 1058, 1014, 996, 919, 882, 824, 742, 683 $cm^{-1}$; $^1H$ NMR: (300 MHz, $CDCl_3$): 7.83-6.40 (m, 36H, Ar-**H,** OC**H**NH and CON**H**), 5.15 (dd, 2H, CONHC**H**, J = 5.4, 3.3 Hz), 4.89 (app d, 4H, OC$\mathbf{H}_2$Ph, J = 12.0 Hz), 4.75 (m, 2H, CONHC**H**), 4.23 (d, 2H, J = 3.3 Hz, C**H**OTIPS), 3.18 (m, 4H, C$\mathbf{H}_2$Ar), 2.64 (m, 2H, NHCHC**H**$(CH_3)_2$), 2.30 (m, 2H,

OCHC**H**$(CH_3)_2$), 1.04 (m, 66H, TIPS and NHCHCH(**C**$\mathbf{H_3}$)$_2$, OCHCH(**Me**)Me, CH(Me)**Me**); $^{13}$C NMR: (75 MHz, $CDCl_3$) δ 172.8, 169.5, 161.2, 157.3, 157.1, 152.5, 150.3, 147.8, 143.3, 138.2, 137.1, 136.3, 136.1, 132.3, 129.5, 128.9, 128.6, 128.0, 127.4, 127.2, 126.3, 125.5, 125.4, 124.0, 123.0, 122.6, 121.5, 120.0, 119.7, 114.7, 112.6, 111.6, 105.3, 103.3, 78.1, 69.7, 60.0, 55.3, 52.0, 49.6, 39.7, 34.4, 34.2, 33.8, 33.7, 30.3, 29.7, 25.4, 24.8, 19.0, 18.8, 18.1, 18.0, 17.7, 17.3, 17.2, 12.5; HRMS: (FAB+) exact mass calculated for [M+H] ($C_{112}H_{130}N_{12}O_{14}Si_2$) requires *m/z* 1922.9968, found *m/z* 1922.9356; $[\alpha]_D^{25}$ = -8.49 (c = 1.0 $CHCl_3$).



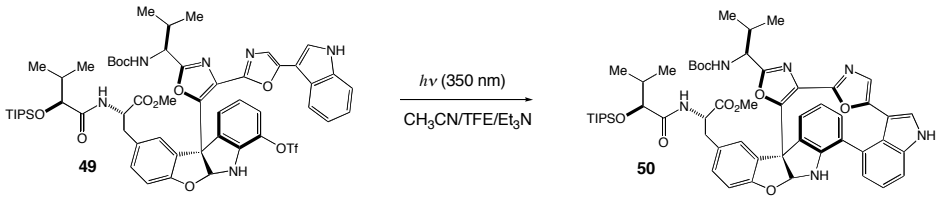

**Phenol 48**: To a solution of **45** (192 mg, 0.161 mmol) in THF (10 mL) was added $Pd(OH)_2$/C (80 mg). The solution was sparged with $H_2$ for 20 min and warmed to 50 °C under $H_2$ with stirring. After 18 h, the solution was then filtered through celite. After concentration, the resulting oil was purified on silica gel (70%-90% $Et_2O$ in hexanes) to yield the title compound (144 mg, 89%) as a pale off-white solid. IR(Film): 3327, 2962, 2868, 1748, 1671, 1633, 1611, 1500, 1463, 1367, 1292, 1250, 1172, 1058, 1014, 917, 881, 820, 736, 684 cm$^{-1}$; $^1$H NMR: (300 MHz, $CDCl_3$): 9.24 (s, 1H, C=CN**H**), 7.60-6.52 (m, 14H, Ar-**H,** OC**H**NH and CON**H**), 5.74 (br d, 1H, J = 9.0 Hz, N**H**Boc), 4.85 (m, 2H, CONHC**H**, C**H**NHBOC), 4.09 (d, 1H, J = 3.3 Hz, C**H**OTIPS), 3.50 (s, 3H, $CO_2$**Me**), 2.93 (m, 2H, C$\mathbf{H_2}$Ar), 2.16 (m, 1H, NHCHC**H**$(CH_3)_2$), 1.83 (m, 1H, OCHC**H**$(CH_3)_2$), 1.39 (br s, 9H, Boc), 0.98 (m, 27H, TIPS and NHCHCH(**C**$\mathbf{H_3}$)$_2$), 0.73 (d, 3H, J = 7.2 Hz,

OCHCH(**Me**)Me); 0.67 (d, 3H, J = 7.2 Hz, CH(Me)**Me**); $^{13}$C NMR: (75 MHz, $CDCl_3$) δ 172.7, 171.6, 163.2, 158.1, 156.0, 152.0, 148.8, 141.7, 136.5, 136.2, 130.4, 130.0, 129.4, 129.2, 128.9, 125.8, 125.2, 123.8, 123.7, 123.5, 122.6, 121.2, 120.6, 119.3, 116.0, 115.7, 111.8, 110.0, 104.3, 104.2, 103.3, 80.2, 78.2, 60.6, 54.6, 52.6, 52.1, 52.0, 38.4, 33.8, 32.6, 31.6, 29.7, 28.3, 18.9, 18.3, 18.1, 17.9, 17.5, 17.4, 12.3; HRMS: (FAB+) exact mass calculated for [M+H] ($C_{55}H_{71}N_6O_{10}Si$) requires *m/z* 1003.500, found *m/z* 1003.503; $[\alpha]_D^{25}$ = -12.89 (c = 0.073 $CHCl_3$).



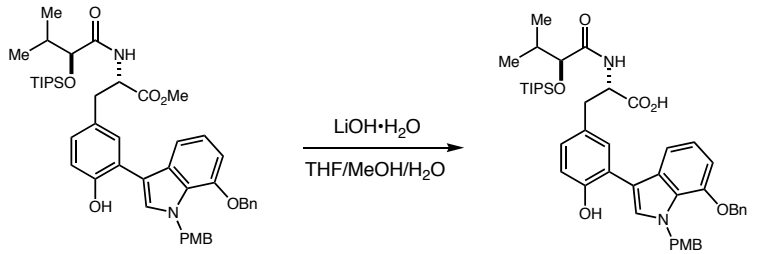

**Triflate 49**: To a solution of **48** (45 mg, 0.045 mmol) in $CH_2Cl_2$ (0.9 mL) was added $PhNTf_2$ (20 mg, 0.056 mmol) and $Et_3N$ (19 $\mu$L, 0.134 mmol). The solution was stirred under argon for 30 min and then diluted with saturated $NaHCO_3$. The aqueous layer was washed with EtOAc, and the combined organics were washed with $H_2O$ and dried over $Na_2SO_4$. After concentration of the solvents *in vacuo*, the resulting oil was purified on silica gel (20% EtOAc in hexanes) to yield the title compound (44 mg, 86%) as a pale off-white solid. IR(Film): 3307, 2963, 2868, 1672, 1630, 1497, 1424, 1367, 1211, 1140, 1058, 998, 908, 881, 815, 740, 684 cm$^{-1}$; $^1$H NMR: (300 MHz, $CDCl_3$): 8.55 (d, 1H, C=CN**H**, J = 1.8 Hz), 7.75-6.70 (m, 14H, Ar-**H,** OC**H**NH and CON**H**), 5.68 (br d, 1H, J = 9.0 Hz, N**H**Boc), 4.90, (m, 1H, CONHC**H),** 4.78 (m, 1H, C**H**NHBOC), 4.06 (d, 1H, J = 3.6 Hz, C**H**OTIPS), 3.52 (s, 3H, $CO_2$**Me**), 2.95 (m, 2H, C**H$_2$**Ar), 2.16 (m, 1H, NHCHC**H**$(CH_3)_2$), 1.83 (m, 1H, OCHC**H**$(CH_3)_2$), 1.45 (br s, 9H, Boc), 0.98 (m, 27H,

TIPS and NHCHCH($\mathbf{CH_3}$)$_2$), 0.74 (d, 3H, J = 6.9 Hz, OCHCH(**Me**)Me); 0.67 (d, 3H, J = 6.9 Hz, CH(Me)**Me**); $^{13}$C NMR: (75 MHz, $CDCl_3$) δ 172.6, 171.8, 163.6, 158.4, 155.9, 152.0, 149.4, 148.6, 141.3, 136.5, 133.5, 130.9, 130.0, 129.5, 128.0, 126.6, 125.6, 124.1, 123.1, 121.8, 121.6, 121.1, 121.0, 119.8, 116.7, 112.0, 110.7, 104.9, 103.1, 80.2, 78.4, 60.3, 54.8, 52.6, 52.3, 38.6, 33.9, 33.0, 31.8, 29.9, 28.6, 18.9, 18.6, 18.2, 18.1, 17.9, 12.5; $^{19}$F NMR: (75 MHz, $CDCl_3$) δ –73.5 (s, 3F, $CF_3$); HRMS: (FAB+) exact mass calculated for [M+H] ($C_{56}H_{70}N_6O_{12}F_3SiS$) requires *m/z* 1135.449, found *m/z* 1135.449; $[\alpha]_D^{25}$ = -10.74 (c = 0.94 $CHCl_3$).



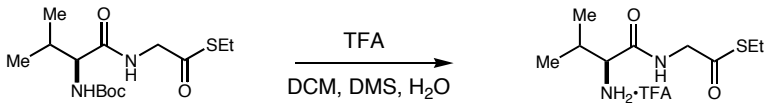

**Biaryl 50**: **49** (5 mg, 0.005 mmol) was dissolved in degassed $CH_3CN$/TFE/$Et_3N$ (3:1:0.1, 2.0 mL) in a Pyrex flask under argon. This solution was exposed to 350 nm UV light (Hitachi UVA lamps, Luzchem 10 lamp photoreactor) with stirring for 2 h. At this time the solvents were concentrated *in vacuo*, and the resulting oil was purified on silica gel (50% EtOAc in hexanes) to yield the title compound (1.9 mg, 38%) as a pale off-white solid. IR(Film): 3312, 2961, 2927, 2868, 1715, 1673, 1592, 1493, 1456, 1367, 1259, 1210, 1172, 1095, 1016, 914, 882, 803, 739, 685 cm$^{-1}$; $^1$H NMR: (300 MHz, $CDCl_3$): 8.71 (s, 1H, C=CN**H**), 7.71-6.75 (m, 12H, Ar-**H,** CON**H**), 6.32 (s, 1H, OC**H**NH), 5.71 (br d, 1H, J = 9.6 Hz, N**H**Boc), 5.03, (m, 1H, CONHC**H**), 4.78 (m, 1H, C**H**NHBOC), 4.11 (d, 1H, J = 3.6 Hz, C**H**OTIPS), 3.71 (s, 3H, $CO_2$**Me**), 3.15 (m, 2H, C$\mathbf{H_2}$Ar), 2.14 (m, 1H, NHCHC**H**$(CH_3)_2$), 1.81 (m, 1H, OCHC**H**$(CH_3)_2$), 1.48 (br s, 9H, Boc), 1.06-0.77 (m,

33H, TIPS, NHCHCH($\mathbf{CH_3}$)$_2$, and OCHCH(**Me**)**Me**); HRMS: (FAB+) exact mass calculated for [M+H] ($C_{55}H_{69}N_6O_9Si$) requires *m/z* 985.4895, found *m/z* 985.4897; $[\alpha]_D^{25}$ = -28.03 (c = 0.1, $CHCl_3$).



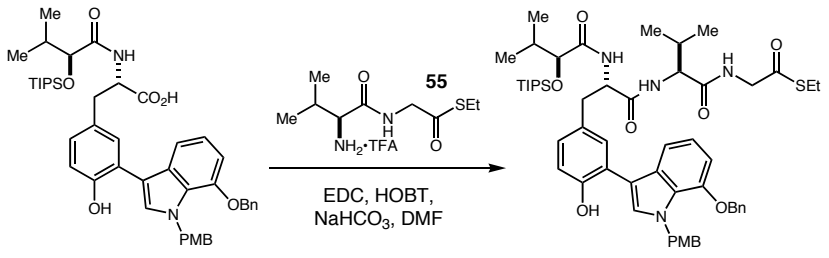

**Acid 54**: To a solution of **53** (9.50 g, 11.98 mmol) in THF/MeOH/$H_2O$ (130 mL, 10:2:1) was added LiOH•$H_2O$ (2.01 g, 47.9 mmol) with stirring. After the reaction was judged complete by TLC analysis (4 h), the reaction mixture was diluted with 300 mL of diethyl ether, acidified with 1N HCl to pH = 2, and washed with 100 mL of brine. The organic portion is dried over sodium sulfate and concentrated *in vacuo*. These crude extracts were purified by column chromatography (40% EtOAc/Hexanes with 1% AcOH) to yield the title compound (8.96 g, 96%) as a white amorphous solid. IR (Film): 3402, 2944, 2867, 1723, 1641, 1613, 1572, 1513, 1454, 1385, 1248, 1209, 1176, 1063, 909, 882, 821, 732 $cm^{-1}$; $^1$H NMR: (300 MHz, $CDCl_3$) δ 7.35-6.73 (m, 17H, Ar**H** and N**H**); 5.57 (s, 2H, OC$\mathbf{H_2}$Ph), 5.13 (s, 2H, OC$\mathbf{H}_2$-pMeOPh), 4.89 (dd, 1H, J = 7.2, 12.9 Hz, C**H**$CO_2$H), 4.16 (d, 1H, J = 3.3 Hz, C**H**OTIPS); 3.76 (s, 3H, ArO**Me**); 3.17 (dd, 1H, J = 5.4, 14.7 Hz, C$\mathbf{H}_2$Ar); 3.05 (dd, 1H, J = 7.2, 14.4 Hz, C$\mathbf{H}_2$Ar); 1.92 (m, 1H, C**H**$Me_2$); 1.04-0.98 (m, 21H, TIPS); 0.83 (d, 3H, J = 6.9 Hz, CH(**Me**)Me); 0.74 (d, 3H, J = 6.9 Hz, CH(**Me**)Me); $^{13}$C NMR: (300 MHz, $CDCl_3$) δ 175.8, 173.5, 158.8, 152.6, 146.9, 136.7, 131.3, 131.1, 129.2, 129.1, 128.6, 128.2, 128.0, 127.8, 127.2, 126.5, 121.3, 120.9, 115.6, 113.9, 112.7,

110.9, 104.5, 78.0, 70.4, 55.2, 52.6, 52.1, 37.0, 33.9, 18.0, 17.9, 17.6, 17.2, 12.3; HRMS (FAB+) exact mass calculated for [M+•] ($C_{46}H_{58}N_2O_7Si$) requires *m/z* 778.4013, found *m/z* 778.4034 $[\alpha]_D^{25}$ = -28.48 (c = 0.53, $CHCl_3$)



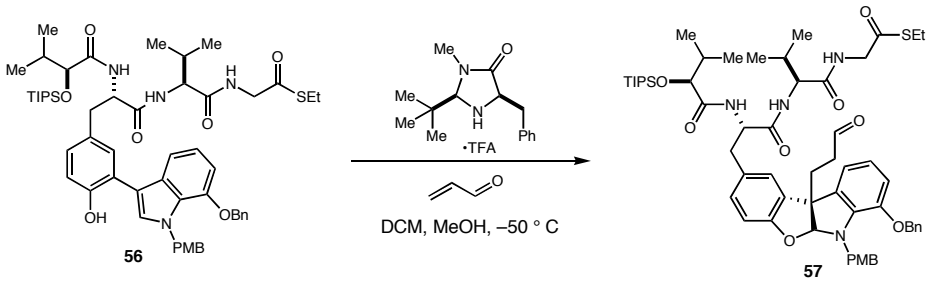

**40** **55**

**Thioester 55**: To a solution of 300 mL of 60:7:2:1 $CH_2Cl_2$/TFA/$Me_2S$/$H_2O$ under argon was added **40** (7.0 g, 22 mmol). After 12 h the solution was concentrated. The resulting oil was purified by column chromatography (10% MeOH/$CH_2Cl_2$) to yield the title compound as a white crystalline solid in 90% yield (6.24 g). IR(Thin Film): 2972, 2941, 1668, 1471, 1202, 1181, 1137, 971, 838, 799, 722 $cm^{-1}$; $^1H$ NMR: (300 MHz, $CD_3OD$) δ 4.28 (d, 1H, J = 17.4 Hz, NHC**H**$_2$), 4.06 (d, 1H, J = 17.4 Hz, NHC**H**$_2$), 3.77 (d, 1H, J = 5.7 Hz, C**H**$NH_2$), 2.91 (q, 2H, J = 7.5 Hz, SC**H$_2$**), 2.25 (m, 1H, C**H**Me(Me)), 1.23 (t, 3H, J = 7.5 Hz, $SCH_2$**C$H_3$**), 1.10 (d, 3H, J = 6.9 Hz, CH**Me**(Me)), 1.07 (d, 3H, J = 6.9 Hz, CHMe(**Me**)); $^{13}C$ NMR: (75 MHz, $CD_3OD$) δ 196.8, 169.0, 156.2, 58.5, 30.3, 22.7, 17.7, 16.6, 13.9; HRMS: (FAB+) exact mass calculated for [M+H] ($C_9H_{19}N_2O_2S$) requires *m/z* 219.1167, found *m/z* 219.1171; $[\alpha]_D^{25}$ = -0.95 (c = 1.0 MeOH)



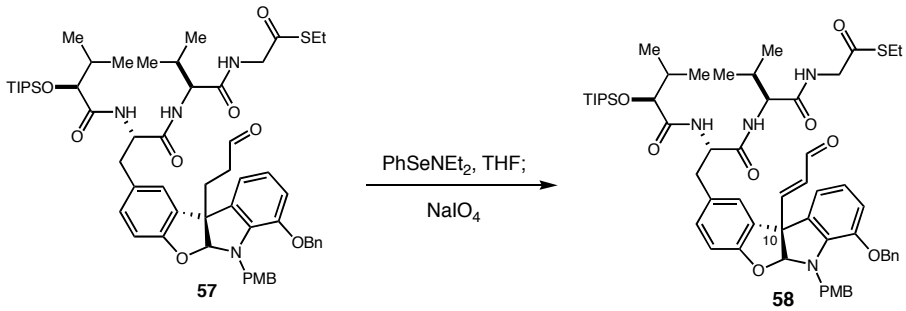

**54** **56**

**Thioester 56**: To a solution of **54** (8.96 g, 11.5 mmol) and **55** (4.71 g, 15.0 mmol) in DMF (120 mL) was added HOBt (2.02 g, 15.0 mmol), EDC•HCl (2.87 g, 15.0 mmol) and $NaHCO_3$ (3.86 g, 46.0 mmol) with stirring. After the reaction was judged complete by TLC analysis (7 h), the reaction mixture was diluted with 500 mL of diethyl ether and washed with 200 mL of saturated $NH_4Cl$, $H_2O$, and brine. The organic portion was dried over sodium sulfate and concentrated *in vacuo*. These crude extracts were purified by column chromatography (40% EtOAc/hexanes) to yield the title compound (10.7 g, 95% yield) as a white amorphous solid. IR (Film): 3288, 2962, 2943, 2868, 1642, 1612, 1513, 1455, 1385, 1262, 1248, 1209, 1176, 1064, 909, 882, 823, 732 $cm^{-1}$; $^1H$ NMR: (300 MHz, $CDCl_3$) δ 7.35-6.49 (m, 19H, Ar**H** and N**H**); 5.57 (s, 2H, OC**H**$_2$Ph); 5.15 (s, 2H, OC**H**$_2$-pMeOPh); 4.62 (dd, 1H, J = 7.2, 12.9 Hz, $CH_2$C**H**CONH); 4.30 (dd, 1H, J = 5.6, 8.6 Hz, NHC**H**CH$Me_2$); 4.16 (d, 1H, J = 3.0 Hz, C**H**OTIPS); 3.98 (t, 2H, J = 4.8 Hz, NHC**H**$_2$); 3.76 (s, 3H, ArO**Me**); 3.08 (m, 2H, C**H**$_2$Ar); 2.82 (q, 2H, J = 7.5 Hz, SC**H**$_2$); 2.21 (m, 1H, NHCHC**H**$Me_2$); 1.92 (m, 1H, OCHC**H**$Me_2$); 1.19 (t, 3H, J = 7.5 Hz, $SCH_2$**C**H$_3$); 1.04-0.98 (m, 21H, TIPS); 0.89-0.83 (m, 9H, OCHCH(**Me**)Me, NHCHCH(**Me**)**Me**); 0.74 (d, 3H, J = 6.9 Hz, OCHCH(**Me**)Me); $^{13}C$ NMR: (300 MHz, $CDCl_3$) δ 196.9, 173.8, 171.0, 170.9, 158.8, 152.5, 146.9, 136.7, 131.2, 131.0, 128.9, 128.6, 128.3, 128.1, 127.8, 127.7, 126.5, 121.7, 120.9, 115.7, 113.9, 112.7, 110.8, 104.6, 78.0, 70.4, 58.5, 55.2, 54.8, 52.2, 48.9, 37.2, 34.0, 29.8, 23.0, 19.4, 18.0, 17.5, 17.0, 14.5, 12.4; HRMS (FAB+) exact mass calculated for [M+•] ($C_{55}H_{74}N_4O_8SiS$) requires *m/z* 978.4996, found *m/z* 978.4966; $[\alpha]_D^{25}$ = –17.13 (c = 2.18, $CHCl_3$).



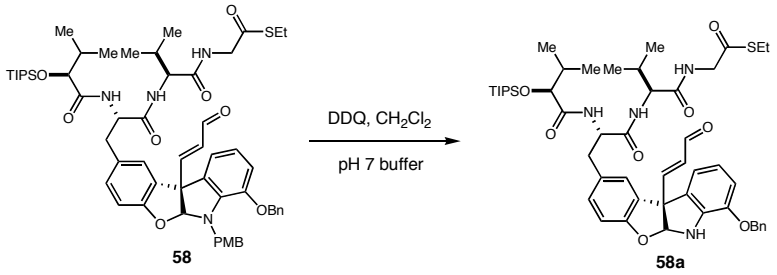

**Aldehyde 57**: (2*R,5R*)-2-*tert*-butyl-5-benzyl-3-methylimidazolidin-4-one•TFA (1.03 g, 2.86 mmol) and phenol **56** (8.0 g, 8.17 mmol) are dissolved in 40 mL of dichloromethane and 2 mL of MeOH. This mixture is cooled to -50 °C. To this cold solution is added freshly distilled acrolein (5.51 mL, 81.7 mmol). The reaction is left at –50 °C for 48 hours before being diluted with 50 mL of pH 7 buffer. The layers were separated and the organic portions were washed with brine and dried over sodium sulfate. Following concentration *in vacuo*, the crude reaction extracts were purified by flash chromatography (80% $Et_2O$ in pentane) to afford the title compound as an amorphous white solid (7.9 g, 93%). IR (Film): 3408, 3300, 2962, 2942, 2868, 1720, 1648, 1512, 1495, 1466, 1386, 1247, 1175, 1100, 1065, 915, 882, 822, 733, 683 $cm^{-1}$; $^1H$ NMR: (300 MHz, $CDCl_3$) δ 9.45 (s, 1H, C**H**O); 7.36-6.44 (m, 15H, Ar-**H**); 5.80 (s, 1H, OC**H**N); 5.33 (d, 1H, J = 15.6 Hz, NC$\mathbf{H_2}$-pMeOPh); 5.01 (m, 2H, OC$\mathbf{H_2}$Ph); 4.60 (m, 2H, C**H**NHCO); 4.47 (d, 1H, J = 15.6 Hz, NC$\mathbf{H_2}$-pMeOPh); 4.26-3.94 (m, 3H, C**H**OTIPS, NHC$\mathbf{H_2}$); 3.78 (s, 3H, ArO**Me**); 3.11-2.80 (m, 4H, C$\mathbf{H_2}$Ar, SC$\mathbf{H_2}$); 2.29-1.84 (m, 6H, NHCHC**H**$Me_2$, OCHC**H**$Me_2$, C$\mathbf{H_2}$C$\mathbf{H_2}$CHO); 1.21 (t, 3H, J = 7.5 Hz, $SCH_2\mathbf{CH_3}$); 1.09-0.68 (m, 33H, TIPS, OCHCH(**Me**)Me, NHCHCH(**Me**)**Me**); $^{13}C$ NMR: (300 MHz, $CDCl_3$) δ 201.0, 196.6, 173.9, 173.6, 170.9, 170.8, 170.7, 158.8, 157.8, 152.5, 146.9, 137.0, 136.7, 133.3, 132.5, 130.1, 130.8, 129.4, 129.3, 129.0, 128.8, 128.6, 128.5, 128.1, 128.0, 127.9, 127.5, 126.5, 123.6, 121.0, 120.4, 115.6, 114.0, 113.4, 110.7, 109.9, 105.8, 104.6, 78.0, 70.9, 58.5,

57.8, 55.3, 54.8, 50.4, 49.0, 39.0, 33.9, 29.9, 29.3, 23.1, 19.2, 18.1, 18.0, 17.6, 17.0, 14.6, 12.4; HRMS (FAB+) exact mass calculated for [M+H] ($C_{58}H_{78}N_4O_9SiS$) requires *m/z* 1034.526, found *m/z* 1034.528; $[\alpha]_D^{25}$ = -35.94 (c = 1.0, $CHCl_3$).



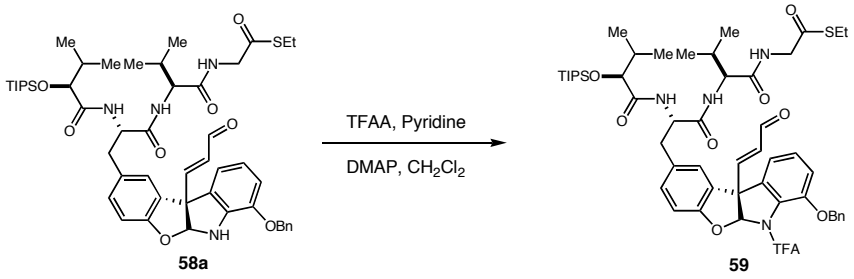

**Aldehyde 58**: To a solution of aldehyde **57** (5.73 g, 5.53 mmol) in 70 mL of THF at room temperature was added $PhSeNEt_2$ (1.47 mL, 7.65 mmol). After stirring for one hour the reaction was judged complete by TLC. The reaction mixture was concentrated *in vacuo* and the crude extracts were purified by flash chromatography (33% EtOAc in hexanes). The product was thus obtained as a yellow oil in a 3:3:1:1 mixture of diastereomers as judged by $^1$H-NMR. This product was then taken up in 42 mL of THF, 21 mL of methanol, and 21 mL of water. To this solution was added sodium periodate (2.06 g, 9.62 mmol) in a single portion. After 12 hours the reaction mixture was concentrated *in vacuo* to remove the methanol and THF, diluted with ethyl acetate and washed with water. After separation of the layers the organic portions were washed with brine and dried over sodium sulfate. Concentration of the resulting solution gave a yellow oil which could be purified by column chromatography (33% EtOAc in hexanes) to give the title compound as an amorphous off-white solid (4.81 g, 84%). IR (Film): 3409, 3300, 2962, 2942, 2868, 1692, 1648, 1512, 1494, 1466, 1385, 1248, 1175, 1100, 1064, 973, 911, 882, 822, 733, 683 $cm^{-1}$; $^1$H NMR: (300 MHz, $CDCl_3$) δ 9.45 (d, 1H, J = 7.5 Hz,

C**H**O); 7.33-6.72 (m, 16H, Ar-**H**, C**H**=**C**HCHO); 6.46 (d, 1H, J = 8.1 Hz, CON**H**); 5.93 (s, 1H, OC**H**N); 5.88 (dd, 1H, J = 15.9, 7.8 Hz, CH=**CH**CHO); 5.22 (d, 1H, J = 15.3 Hz, NC$\mathbf{H_2}$-pMeOPh); 5.01 (m, 2H, OC$\mathbf{H_2}$Ph); 4.59-4.46 (m, 3H, C**H**NHCO, NC$\mathbf{H_2}$-pMeOPh); 4.23 (dd, 1H, J = 8.2, 5.8 Hz, NHC$\mathbf{H_2}$); 4.15 (d, 1H, J = 3.3 Hz, C**H**OTIPS); 4.03 (dd, 1H, J = 5.8, 1.0 Hz, NHC$\mathbf{H_2}$); 3.76 (s, 3H, ArO**Me**); 3.11-2.82 (m, 4H, C$\mathbf{H_2}$Ar, SC$\mathbf{H_2}$); 2.18 (m, 1H, NHCHC**H**Me$_2$); 1.95 (m, 1H, OCHC**H**Me$_2$); 1.22 (t, 3H, J = 7.5 Hz, SCH$_2$C$\mathbf{H_3}$); 1.05 (m, 21H, TIPS); 0.90-0.83 (m, 9H, OCHCH(**Me**)Me, NHCHCH(**Me**)**Me**); 0.71 (d, 3H, J = 6.9 Hz, OCHCH(**Me**)Me); $^{13}$C NMR: (300 MHz, $CDCl_3$) δ 196.8, 196.6, 193.3, 173.8, 173.4, 171.0, 170.7, 158.9, 158.1, 155.3, 152.5, 146.9, 145.2, 137.3, 136.6, 136.5, 133.0, 131.8, 131.2, 130.3, 129.9, 129.7, 129.2, 129.0, 128.3, 128.0, 127.8, 127.5, 126.5, 121.7, 121.3, 121.0, 116.9, 115.7, 114.0, 113.9, 113.6, 112.7, 110.8, 110.3, 107.0, 104.6, 78.0, 70.8, 70.4, 61.6, 58.5, 55.2, 54.8, 51.1, 49.0, 37.5, 33.9, 30.3, 23.1, 19.3, 18.1, 17.5, 17.0, 14.6; HRMS (FAB+) exact mass calculated for [M+H] ($C_{58}H_{77}N_4O_9SiS$) requires *m/z* 1033.518, found *m/z* 1033.518; $[\alpha]_D^{25}$ = -46.19 (c = 1.20, $CHCl_3$).




**Amine 58a**: To a vigorously stirred solution of aldehyde **58** (4.8 g, 4.64 mmol) in a 1:1 mixture of dichloromethane and pH 7 buffer (75 mL each) at 0 °C was added freshly recrystallized DDQ (2.10 g, 9.29 mmol). The resulting dark heterogeneous reaction

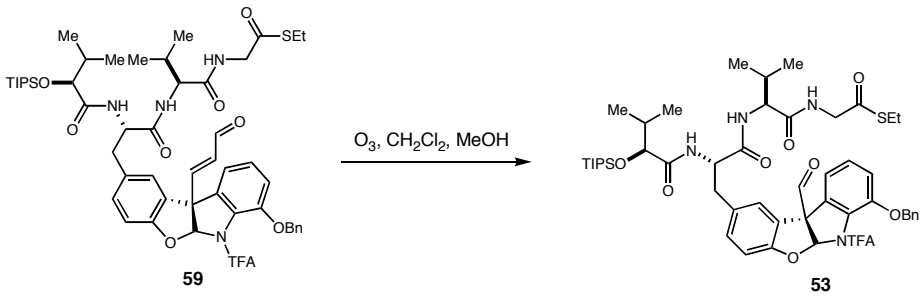
mixture is allowed to warm to ambient temperature over the course of two hours after which time it is diluted with ethyl acetate and washed with a saturated solution of $Na_2SO_3$, followed by a saturated solution of $NaHCO_3$ and brine. The layers were separated and the aqueous layer wash washed with three times with 50 mL of ethyl acetate. The combined organic layer was washed with brine and dried over sodium sulfate. Purification by flash chromatography on silica gel (35%-40% EtOAc in hexanes) gave the desired product as an amorphous off-white solid in 84% yield (3.54 g). IR (Film): 3301, 2962, 2942, 2868, 1691, 1648, 1498, 1466, 1387, 1206, 1058, 975, 882, 823, 749, 683 $cm^{-1}$; $^1H$ NMR: (300 MHz, $CDCl_3$) δ 9.61 (d, 1H, J = 7.5 Hz, C**H**O); 7.41-6.67 (m, 12H, Ar-**H**, C**H**=**C**HCHO); 6.56 (d, 1H, J = 8.7 Hz, CON**H**); 6.24 (d, 1H, J = 2.4 Hz, OC**H**N); 6.14 (dd, 1H, J = 15.6, 7.5 Hz, CH=**C**H**C**HO); 5.04 (s, 2H, OC$\mathbf{H_2}$Ph); 4.59 (m, 1H, CONHC**H**CH); 4.24 (dd, 1H, J = 8.6, 5.6 Hz, NHC$\mathbf{H_2}$); 4.14 (m, 1H, CONHC**H**$CH_2$); 4.03 (d, 1H, J = 5.7 Hz, C**H**OTIPS); 3.93 (m, 1H, NHC$\mathbf{H_2}$); 3.15-2.80 (m, 4H, C$\mathbf{H_2}$Ar, SC$\mathbf{H_2}$); 2.17 (m, 1H, NHCHC**H**$Me_2$); 1.92 (m, 1H, OCHC**H**$Me_2$); 1.22 (t, 3H, J = 7.5 Hz, $SCH_2$C$\mathbf{H_3}$); 1.05 (m, 21H, TIPS); 0.90-0.82 (m, 9H, OCHCH(**Me**)Me, NHCHCH(**Me**)**Me**); 0.72 (d, 3H, J = 6.9 Hz, OCHCH(**Me**)Me); $^{13}C$ NMR: (300 MHz, $CDCl_3$) δ 196.6, 193.5, 173.3, 170.7, 170.4, 158.2, 155.4, 137.1, 136.6, 133.1, 130.2, 129.7, 129.5, 129.4, 129.3, 129.2, 128.6, 128.1, 127.6, 125.0, 121.0, 116.4, 112.3, 110.4, 103.0, 78.0, 70.4, 63.7, 58.5, 54.6, 49.0, 37.5, 33.9, 30.3, 23.1, 19.0, 18.1, 18.0, 17.9, 17.5, 17.0, 14.6, 12.4; HRMS (FAB+) exact mass calculated for [M+H] ($C_{50}H_{69}N_4O_8SiS$) requires *m/z* 913.4605, found *m/z* 913.4632; $[\alpha]_D^{25}$ = -61.30 (c = 3.08, $CHCl_3$).




58a 59

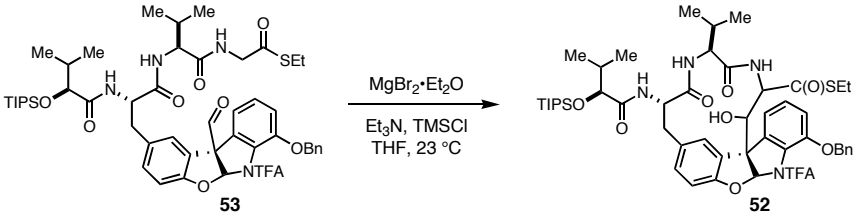
**Aldehyde 59**: To a solution of amino aldehyde **58a** (3.54 g, 3.87 mmol), pyridine (0.78 mL, 9.68 mmol) and DMAP (165 mg, 1.35 mmol) in 77 mL of dichloromethane at 0 °C was added trifluoroacetic anhydride (0.82 mL, 5.81 mmol) dropwise by syringe under argon. After 30 minutes the reaction was diluted with 200 mL of ethyl acetate and washed with 60 mL of saturated sodium bicarbonate solution. The layers were separated and the organic fraction was washed with brine and dried over sodium sulfate. Purification by flask chromatography on silica gel (40% ethyl acetate in hexanes) gave the title compound product as an amorphous yellow solid in 87% yield (354 mg). IR (Film): 3406, 3306, 2962, 2868, 1731, 1695, 1650, 1492, 1463, 1387, 1292, 1204, 1183, 1154, 1058, 981, 882, 823, 738, 684 $cm^{-1}$; $^{1}H$ NMR: (300 MHz, $CDCl_3$) δ 9.65 (d, 1H, J = 7.2 Hz, C**H**O); 7.47-6.54 (m, 13H, Ar-**H**, C**H**=**C**HCHO, OC**H**N); 6.24 (dd, 1H, J = 15.9, 7.2 Hz, CH=**C**H**C**HO); 5.19 (dd, 2H, J = 18.6, 6.4 Hz, OC$\mathbf{H_2}$Ph); 4.59 (m, 1H, CONHC**H**CH); 4.24-4.03 (m, 4H, NHC$\mathbf{H_2}$, C**H**OTIPS, CONHC**H**$CH_2$); 3.12-2.86 (m, 4H, C$\mathbf{H_2}$Ar, SC$\mathbf{H_2}$); 2.13 (m, 1H, NHCHC**H**$Me_2$); 1.95 (m, 1H, OCHC**H**$Me_2$); 1.23 (t, 3H, J = 7.5 Hz, $SCH_2\mathbf{CH_3}$); 1.05 (m, 21H, TIPS); 0.90-0.86 (m, 9H, OCHCH(**Me**)Me, NHCHCH(**Me**)**Me**); 0.75 (d, 3H, J = 6.6 Hz, OCHCH(**Me**)Me); $^{13}C$ NMR: (300 MHz, $CDCl_3$) δ 196.2, 192.7, 173.2, 170.5, 170.1, 157.3, 151.6, 149.6, 136.3, 135.2, 131.0, 130.8, 129.2, 128.6, 128.2, 128.0, 127.0, 124.9, 116.3, 114.4, 110.5, 100.4, 78.0, 70.8, 63.3, 58.5, 54.4, 49.0, 37.6, 33.9, 30.6, 23.1, 18.9, 18.1, 18.0, 17.5, 17.1, 14.6, 12.4; $^{19}F$

NMR: (75 MHz, $CDCl_3$) δ –70.0 (s, 3F, $CF_3$); HRMS (FAB+) exact mass calculated for [M+H] ($C_{52}H_{68}N_4O_9F_3SiS$) requires *m/z* 1009.443, found *m/z* 1009.444; $[\alpha]_D^{25}$ = -133.69 (c = 0.37, $CHCl_3$).



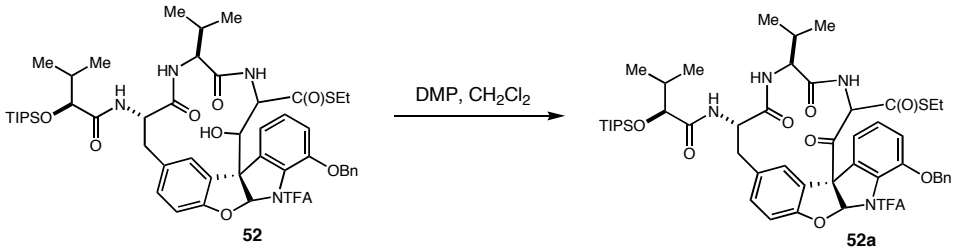

**Aldehyde 53**: A stream of ozone is passed through a solution of α, β-unsaturated aldehyde **59** (601 mg, 0.59 mmol) in 14 mL of dichloromethane and 1.4 mL of methanol at –78 °C for 45 minutes. The solution was bubbled through with oxygen for ten minutes and then quenched by the addition of triphenylphospine (0.44 g, 1.67 mmol). After warming to room temperature overnight the reaction mixture was concentrated *in vacuo* and loaded directly onto a silica gel column. Elution with 35% ethyl acetate in hexanes gives 517 mg of title product (88%) as an amorphous white solid. IR (Film): 3301, 2963, 2868, 1729, 1649, 1492, 1464, 1406, 1292, 1252, 1204, 1182, 1159, 985, 882, 823, 738, 684 $cm^{-1}$; $^1H$ NMR: (300 MHz, $CDCl_3$) δ 10.1 (s, 1H, C**H**O); 7.46-6.42 (m, 12H, Ar-**H**, OC**H**N); 5.18 (dd, 2H, J = 17.7, 12.0 Hz, OC$\mathbf{H_2}$Ph); 4.59 (m, 1H, CONHC**H**CH); 4.24-3.96 (m, 4H, NHC$\mathbf{H_2}$, C**H**OTIPS, CONHC**H**$CH_2$); 3.14-2.87 (m, 4H, C$\mathbf{H_2}$Ar, SC$\mathbf{H_2}$); 2.14 (m, 1H, NHCHC**H**$Me_2$); 1.92 (m, 1H, OCHC**H**$Me_2$); 1.24 (t, 3H, J = 7.5 Hz, $SCH_2\mathbf{CH_3}$); 1.04 (m, 21H, TIPS); 0.93-0.84 (m, 9H, OCHCH(**Me**)Me, NHCHCH(**Me**)**Me**); 0.69 (d, 3H, J = 6.6 Hz, OCHCH(**Me**)Me); $^{13}C$ NMR: (300 MHz, $CDCl_3$) δ 196.4, 191.7, 173.4, 170.6, 170.4, 156.7, 149.5, 136.2, 132.1, 131.4, 130.7,

129.0, 128.5, 128.0, 127.0, 125.2, 124.0, 115.7, 115.0, 114.0, 110.8, 100.0, 78.0, 70.8, 58.6, 54.4, 49.0, 37.5, 33.9, 30.4, 23.2, 19.2, 18.0, 17.9, 17.8, 17.5, 17.0, 14.6, 12.3; $^{19}$F NMR: (75 MHz, $CDCl_3$) δ –70.3 (s, 3F, $CF_3$); HRMS (FAB+) exact mass calculated for [M+H] ($C_{50}H_{66}N_4O_9F_3SiS$) requires *m/z* 983.4272, found *m/z* 983.4238; $[\alpha]_D^{25}$ = -93.42 (c = 0.47, $CHCl_3$).



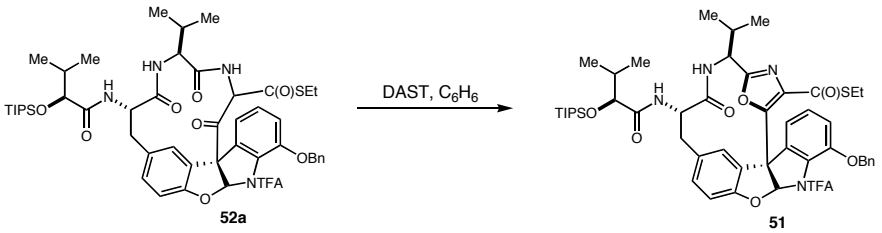

**Alcohol 52**: A flame-dried 1000 mL flask is charged with **53** (2.1 g, 2.14 mmol) and $MgBr_2$•$Et_2O$ (1.65 g, 6.41 mmol) under Ar. To this flask is added THF (425 mL) followed by $Et_3N$ (2.98 mL, 21.4 mmol) and TMSCl (0.68 mL, 5.34 mmol) with stirring. After 75 min 1N HCl (100 mL) is added and stirred for 10 min. The solution was diluted with EtOAc and pH 7 buffer, and washed with brine. The organic fractions were concentrated and the resulting oil purified by column chromatography to afford 1.49 g of the title compound (71%) as an off-white solid. IR (Film): 3401, 2962, 2868, 1732, 1681, 1644, 1490, 1462, 1288, 1204, 1181, 1160, 1125, 1099, 1057, 982, 881, 832, 752, 736, 684 $cm^{-1}$; $^1$H NMR: (300 MHz, $CDCl_3$) δ 7.50-6.86 (m, 10H, Ar-**H**); 6.77 (d, 1H, J = 8.4 Hz, Ar-**H**); 6.63 (s, 1H, OC**H**N); 5.36 (d, 1H, J = 10.2 Hz, CON**H**); 5.16 (dd, 2H, J = 17.7, 12.3 Hz, OC**H$_2$**Ph); 4.89 (d, 1H, J = 9.3 Hz, C**H**C(O)SEt); 4.48 (d, 1H, J = 6.0 Hz, C**H**OH); 4.36 (m, 1H, CONHC**H**CH); 4.18-4.10 (m, 2H, C**H**OTIPS, CONHC**H**$CH_2$); 3.04 (dd, 1H, J = 12.3, 4.6 Hz, C**H$_2$**Ar); 2.85 (q, 2H, J = 7.5 Hz, SC**H$_2$**$CH_3$); 2.65 (t, 1H, J = 12.3 Hz, C**H$_2$**Ar); 2.05 (m, 1H, NHCHC**H**$Me_2$); 1.92 (m, 1H, OCHC**H**$Me_2$); 1.20 (t,

3H, J = 7.5 Hz, $SCH_2\mathbf{CH_3}$); 1.06-0.94 (m, 30H, TIPS, OCHCH(**Me**)Me, NHCHCH(**Me**)**Me**); 0.84 (d, 3H, J = 6.6 Hz, OCHCH(**Me**)Me); $^{13}$C NMR: (300 MHz, $CDCl_3$) δ 199.8, 172.3, 170.4, 169.9, 158.6, 149.4, 136.7, 136.4, 129.8, 129.7, 128.5, 128.4, 128.3, 127.9, 127.3, 127.1, 126.4, 126.2, 117.9, 114.2, 110.9, 97.8, 77.9, 72.5, 70.8, 64.6, 58.9, 55.8, 40.2, 33.8, 30.1, 23.9, 19.3, 18.2, 18.0, 17.9, 17.8, 17.6, 17.5, 14.2, 12.2; $^{19}$F NMR: (75 MHz, $CDCl_3$) δ –69.7 (s, 3F, $CF_3$); HRMS (FAB+) exact mass calculated for [M+H] ($C_{50}H_{66}N_4O_9F_3SiS$) requires *m/z* 983.4272, found *m/z* 983.4243; $[\alpha]_D^{25} = -129.17$ (c = 0.27, $CHCl_3$).



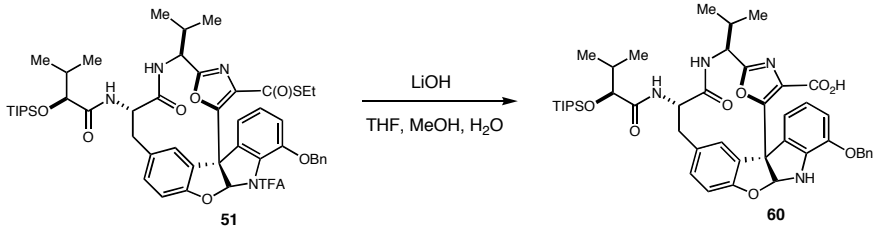

**Ketone 52a**: To a solution of **52** (46 mg, 0.047 mmol) in 1.0 mL of $CH_2Cl_2$ was added Dess-Martin periodinane (59 mg, 0.14 mmol). After 30 min the solution was diluted with EtOAc and washed with a saturated solution of $NaHCO_3$. The organic fractions were concentrated and the resulting oil purified by column chromatography to afford 37 mg of the title compound (80%) as an off-white solid. IR (Film): 3408, 3272, 2925, 2868, 1735, 1651, 1516, 1492, 1465, 1293, 1204, 1184, 1163, 1057, 967, 881, 737, 682 $cm^{-1}$; $^1$H NMR: (300 MHz, $CDCl_3$) δ 7.56-6.78 (m, 12H, Ar-**H**, OC**H**N); 5.76 (m, 2H, CON**H,** C**H**C(O)SEt); 5.16 (dd, 2H, J = 18.3, 12.3 Hz, $OC\mathbf{H_2}Ph$); 4.45 (m, 1H, CONHC**H**CH); 4.18 (d, 1H, J = 3.3 Hz, C**H**OTIPS); 4.02 (m, 1H, CONHC**H**$CH_2$); 2.95-2.75 (m, 4H, $C\mathbf{H_2}Ar$, $SC\mathbf{H_2}CH_3$); 2.05 (m, 1H, NHCHC**H**$Me_2$); 1.92 (m, 1H, OCHC**H**$Me_2$); 1.20 (t,

3H, J = 7.5 Hz, $SCH_2\mathbf{CH_3}$); 1.06 (m, 24H, TIPS, NHCHCH(Me)**Me**); 1.01-0.95 (m, 6H, OCHCH(**Me**)Me, NHCHCH(Me)**Me**); 0.88 (d, 3H, J = 6.3 Hz, OCHCH(**Me**)Me); $^{13}$C NMR: (300 MHz, $CDCl_3$) δ 196.3, 195.9, 172.4, 170.9, 169.8, 158.6, 149.0, 136.4, 132.2, 131.2, 130.3, 128.5, 128.4, 128.3, 128.2, 127.9, 127.0, 125.0, 124.2, 118.0, 114.5, 111.4, 96.7, 78.0, 73.7, 70.8, 61.8, 59.2, 55.2, 39.2, 33.8, 29.9, 23.8, 19.1, 18.4, 18.1, 18.0, 17.7, 17.5, 14.1, 12.4; $^{19}$F NMR: (75 MHz, $CDCl_3$) δ –70.0 (s, 3F, $CF_3$); HRMS (FAB+) exact mass calculated for [M+H] ($C_{50}H_{64}N_4O_9F_3SiS$) requires *m/z* 981.4115, found *m/z* 981.4107; $[\alpha]_D^{25}$ = -179.88 (c = 0.30, $CHCl_3$).



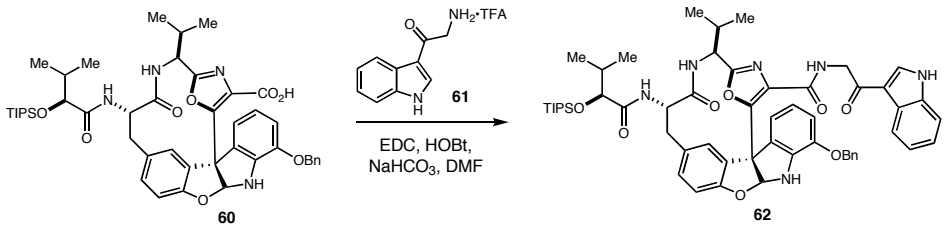

**Oxazole 51**: To a solution of **52a** (125 mg, 0.127 mmol) in benzene (11 mL) was added DAST (1.1 mL) dropwise by syringe. The solution was stirred at room temperature for 3 h before being diluted with EtOAc a saturated solution of $NaHCO_3$. The layers were separated and the aqueous layer was washed with ethyl acetate 3 x 50 mL. The combined organics were washed with brine and concentrated. The resulting oil was purified on silica gel (20% EtOAc in hexanes) to yield the title compound (99 mg, 81%) as a pale yellow solid. IR(Film): 3405, 3286, 2926, 2868, 1739, 1656, 1494, 1463, 1291, 1251, 1201, 1157, 990, 879 cm$^{-1}$; $^1$H NMR: (300 MHz, $CDCl_3$): δ 7.63 (d, 1H, J = 1.5 Hz, Ar-**H**), 7.40-7.26 (m, 5H, Ar-**H**), 7.18-7.08 (m, 2H, Ar-**H**), 6.99-6.93 (m, 2H, Ar-**H**), 6.84 (s, 1H, OC**H**N), 6.78 (d, 1H, J = 8.4 Hz, Ar-**H**), 5.26-5.11 (m, 3H, OC$\mathbf{H}_2$Ph, CONHC**H**CH),

4.71 (m, 1H, CONHC**H**$CH_2$), 3.96 (d, 1H, J = 3.0 Hz, C**H**OTIPS), 3.42 (t, 1H, J = 12.3 Hz, C**H**$_2$Ar), 2.99-2.75 (m, 2H, SC**H**$_2$$CH_3$), 2.64 (dd, 1H, J = 12.3, 3.3 Hz, C**H**$_2$Ar), 2.43 (m, 1H, NHCHC**H**$(CH_3)_2$), 1.72 (m, 1H, OCHC**H**$(CH_3)_2$), 1.18 (t, 3H, J = 7.5 Hz, $SCH_2$C**H**$_3$), 1.07 (m, 24H, TIPS and NHCHCH(**C**$H_3)_2$), 0.91-0.87 (m, 6H, NHCHCH(**C**$H_3)_2$, OCHCH(**Me**)Me), 0.63 (d, 3H, J = 7.2 Hz, OCHCH(**Me**)Me); $^{13}$C NMR: (75 MHz, $CDCl_3$) δ 186.2, 172.4, 171.7, 160.8, 156.8, 150.2, 149.7, 136.8, 136.2, 134.0, 130.4, 130.2, 129.4, 129.2, 128.8, 128.7, 128.6, 128.1, 127.6, 127.4, 115.0, 114.6, 110.7, 100.3, 77.9, 71.0, 60.9, 55.3, 53.5, 39.0, 34.0, 28.9, 23.0, 19.8, 18.3, 18.2, 18.0, 17.5, 17.0, 14.4, 12.6; HRMS: (FAB+) exact mass calculated for [M+H] ($C_{50}H_{62}F_3N_4O_8SiS$) requires *m/z* 963.4010, found *m/z* 963.3998; $[\alpha]_D^{25}$ = -61.01 (c = 0.55, $CHCl_3$).



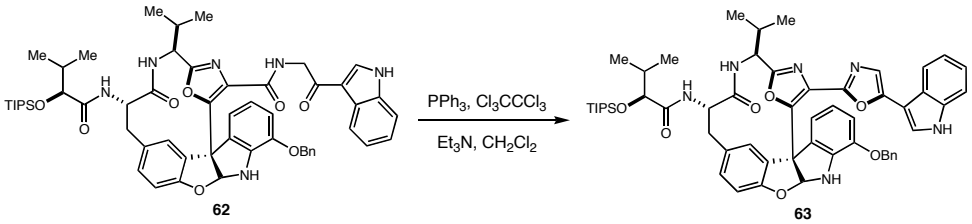

**Acid 60**: To a solution of **51** (84 mg, 0.087 mmol) in THF/MeOH/$H_2O$ (4.4 mL, 10:2:1) was added LiOH•$H_2O$ (36.5 mg, 0.87 mmol) with stirring. After the reaction was judged complete by TLC analysis (2 h), the reaction mixture was diluted with 50 mL of diethyl ether, acidified with 1N HCl to pH = 2, and washed with 20 mL of brine. The organic portion was dried over sodium sulfate and concentrated *in vacuo*. These crude extracts were purified by column chromatography (50% EtOAc/Hexanes to 10% MeOH in $CH_2Cl_2$) to yield the title compound (71 mg, 99%) as a white amorphous solid. IR (Film): 3405, 2917, 2849, 1654, 1498, 1464, 1289, 1251, 1209, 1068, 882, 754, 684 cm$^{-1}$; $^1$H NMR: (300 MHz, $CD_3OD$): δ 7.54-7.26 (m, 6H, Ar-**H**), 7.18 (dd, 1H, J = 8.2, 1.6 Hz, Ar-

**H**), 6.94 (s, 1H, OC**H**N), 6.87-6.65 (m, 4H, Ar-**H**), 5.08 (s, 2H, OC$\mathbf{H}_2$Ph), 4.93 (m, 1H, CONHC**H**CH), 4.53 (m, 1H, CONHC**H**$CH_2$), 4.16 (d, 1H, J = 3.9 Hz, C**H**OTIPS), 3.15 (t, 1H, J = 12.3 Hz, C$\mathbf{H}_2$Ar), 2.85 (dd, 1H, J = 12.3, 3.8 Hz, C$\mathbf{H}_2$Ar), 2.36 (m, 1H, NHCHC**H**$(CH_3)_2$), 2.05 (m, 1H, OCHC**H**$(CH_3)_2$), 1.09 (m, 24H, TIPS and NHCHCH(**C$\mathbf{H_3}$**)$_2$), 1.04-1.01 (m, 6H, NHCHCH(**C$\mathbf{H_3}$**)$_2$, OCHCH(**Me**)Me), 0.87 (d, 3H, J = 6.9 Hz, OCHCH(**Me**)Me); $^{13}$C NMR: (75 MHz, $CD_3OD$) δ 172.7, 172.6, 165.9, 160.0, 157.2, 154.0, 144.0, 138.3, 137.0, 133.0, 130.6, 130.1, 130.0, 128.7, 128.2, 127.9, 127.6, 127.4, 127.3, 120.3, 114.9, 112.1, 110.2, 103.9, 70.2, 61.5, 55.6, 53.8, 38.6, 33.8, 28.6, 19.1, 17.6, 17.5, 17.1, 17.0, 16.6, 12.2; HRMS: (FAB+) exact mass calculated for [M+Na] ($C_{46}H_{58}N_4O_8SiNa$) requires *m/z* 845.3921, found *m/z* 845.3914; $[\alpha]_D^{25}$ = -100.66 (c = 0.493, $CHCl_3$).



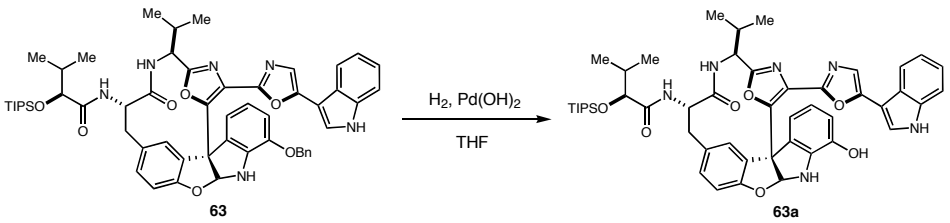

**Ketoindole 62**: To a solution of **60** (36.4 mg, 0.044 mmol) in DMF (2.2 mL) was added **61** (24 mg, 0.088 mmol), EDC•HCl (10.2 mg, 0.052 mmol), HOBt (7.2 mg, 0.052 mmol), and $NaHCO_3$ (14.8 mg, 0.18 mmol). The solution was stirred at room temperature for 12 h before being diluted with EtOAc and brine. The layers were separated and the aqueous was washed with ethyl acetate. The combined organics were washed with brine and concentrated. The resulting oil was purified on silica gel (40% EtOAc in hexanes) to yield the title compound (28 mg, 68%) as pale white solid. IR(Film): 3404, 3287, 2962, 2868, 1654, 1500, 1465, 1435, 1289, 1248, 1210, 1119, 1065, 913, 882, 843, 732, 685

$cm^{-1}$; $^1H$ NMR: (300 MHz, $CDCl_3$): δ 9.13 (d, 1H, J = 2.4 Hz, C=CN**H**), 8.24 (m, 1H, Ar-**H**), 7.90 (t, 1H, J = 4.6 Hz, Ar-**H**), 7.73 (d, 1H, J = 3.3 Hz, Ar-**H**), 7.58 (d, 1H, J = 1.8 Hz, Ar-**H**), 7.28-7.22 (m, 9H, Ar-**H**), 7.08 (dd, 1H, J = 8.2, 1.6 Hz, Ar-**H**), 6.89 (t, 1H, J = 4.4 Hz, Ar-**H**), 6.70 (m, 2H, Ar-**H**, OC**H**N), 6.31 (br d, 1H, J = 8.4 Hz, CON**H**), 5.62, (s, 1H, CON**H**), 5.16 (dd, 1H, J = 9.0, 5.6, CONHC**H**CH), 4.87 (dd, 2H, J = 24.6, 11.4 Hz, OC$\mathbf{H}_2$Ph), 4.54 (t, 2H, J = 4.8 Hz, C$\mathbf{H_2}$CO), 4.46 (m, 1H, CONHC**H**$CH_2$), 4.13 (d, 1H, J = 3.3 Hz, C**H**OTIPS), 3.36 (t, 1H, J = 12.0 Hz, C$\mathbf{H}_2$Ar), 2.74 (dd, 1H, J = 12.0, 3.3 Hz, C$\mathbf{H}_2$Ar), 2.44 (m, 1H, NHCHC**H**$(CH_3)_2$), 1.97 (m, 1H, OCHC**H**$(CH_3)_2$), 1.09 (m, 24H, TIPS and NHCHCH($\mathbf{CH_3}$)$_2$), 0.98-0.87 (m, 9H, NHCHCH($\mathbf{CH_3}$)$_2$, OCHCH(**Me**)$_2$); $^{13}C$ NMR: (75 MHz, $CDCl_3$) δ 188.4, 171.9, 160.8, 159.5, 157.2, 153.4, 144.0, 138.1, 136.8, 136.2, 131.4, 130.9, 130.6, 130.1, 129.6, 128.4, 128.2, 128.0, 127.8, 127.4, 125.1, 123.9, 122.9, 121.9, 120.6, 115.2, 115.1, 112.0, 111.7, 110.6, 103.7, 77.9, 77.2, 70.0, 61.4, 56.0, 53.1, 45.9, 38.7, 33.9, 28.5, 19.6, 18.1, 18.0, 17.7, 17.5, 17.2, 12.4; HRMS: (FAB+) exact mass calculated for [M+H] ($C_{56}H_{67}N_6O_8Si$) requires *m/z* 979.4789, found *m/z* 979.4765; $[\alpha]_D^{25}$ = -42.44 (c = 0.147, $CHCl_3$).

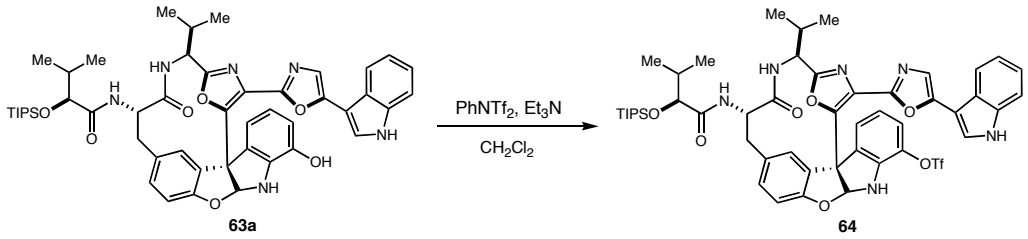



**Bisoxazole 63**: To a solution of $PPh_3$ (136 mg, 0.52 mmol) in $CH_2Cl_2$ (1.8 mL) was added $C_2Cl_6$ (123 mg, 0.52 mmol). The solution was stirred at room temperature for 10 min at which time $Et_3N$ (0.144 mL, 1.04 mmol) was added dropwise. The resultant solution was stirred for 10 min at which time it was added dropwise via cannula to a

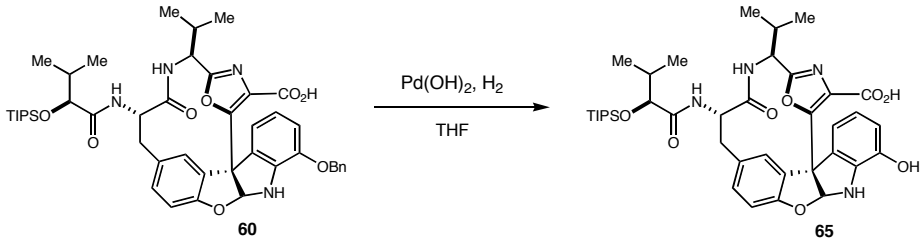
stirred $CH_2Cl_2$ (2.8 mL) solution of **62** (51 mg, 0.052 mmol) at 0 °C and held at this temperature for 10 min, at which point it was allowed to warm to room temperature and stirred for an additional 10 min. The solution was then diluted with a saturated solution of $NaHCO_3$. The layers were separated and the aqueous was washed with $CH_2Cl_2$ 3 x 5 mL. The combined organics were washed with brine and concentrated. The resulting oil was purified on silica gel (40% EtOAc in hexanes) to yield the title compound (47.7 mg, 95%) as a pale amorphous solid. IR(Film): 3405, 3289, 2961, 2868, 1655, 1498, 1460, 1288, 1254, 1207, 1116, 1096, 1061, 917, 882, 738, 685 $cm^{-1}$; $^1H$ NMR: (300 MHz, $CDCl_3$): δ 8.12 (s, 1H, C=CN**H**), 7.68-6.56 (m, 18H, Ar-**H**, OC**H**N), 5.41 (s, 1H, CON**H**), 5.06-4.86 (m, 3H, CONHC**H**CH, OC**H**$_2$Ph), 4.67 (m, 1H, CONHC**H**$CH_2$), 4.09 (d, 1H, J = 3.3 Hz, C**H**OTIPS), 3.34 (t, 1H, J = 12.0 Hz, C**H**$_2$Ar), 2.77 (dd, 1H, J = 12.0, 3.3 Hz, C**H**$_2$Ar), 2.38 (m, 1H, NHCHC**H**$(CH_3)_2$), 1.95 (m, 1H, OCHC**H**$(CH_3)_2$), 1.07 (m, 24H, TIPS and NHCHCH(**CH**$_3$)$_2$), 0.96 (d, 3H, J = 6.9 Hz, NHCHCH(**CH**$_3$)$_2$), 0.90 (d, 3H, J = 6.9 Hz, OCHCH(**Me**)Me), 0.84 (d, 3H, J = 6.9 Hz, OCHCH(**Me**)Me); $^{13}C$ NMR: (75 MHz, $CDCl_3$) δ 172.1, 172.0, 161.8, 157.5, 152.5, 149.9, 148.3, 143.7, 137.9, 137.4, 136.3, 130.4, 130.1, 129.7, 129.2, 129.0, 128.8, 128.5, 128.1, 127.6, 124.0, 123.1, 122.9, 121.6, 121.2, 121.1, 119.8, 115.9, 112.4, 111.8, 110.9, 105.3, 103.3, 78.1, 70.2, 62.1, 55.8, 54.4, 39.0, 34.1, 29.5, 19.8, 18.3, 18.2, 17.6, 17.5, 12.5; HRMS: (FAB+) exact mass calculated for [M+H] ($C_{56}H_{65}N_6O_7Si$) requires *m/z* 961.4687, found *m/z* 961.4682; $[\alpha]_D^{25}$ = –115.47 (c = 0.187, $CHCl_3$).



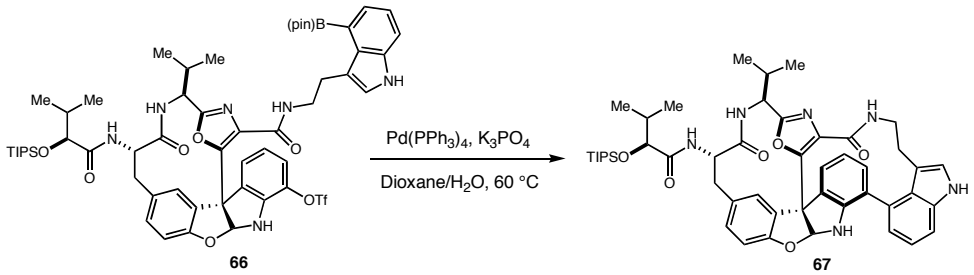

**Phenol 63a:** To a solution of **63** (47.5 mg, 0.049 mmol) in THF (5 mL) was added $Pd(OH)_2/C$ (120 mg). The solution was sparged with $H_2$ for 20 min and kept under a $H_2$ atmosphere for 7 h. At this time the solution was filtered through a silica plug, concentrated, and the resulting oil was purified on silica gel (40%-60% EtOAc in hexanes) to yield the title compound (38.0 mg, 88%) as a pale amorphous solid. IR(Film): 3287, 2962, 2868, 1652, 1496, 1458, 1292, 1254, 1191, 1099, 1061, 917, 882, 738, 683 $cm^{-1}$; $^1H$ NMR: (300 MHz, $CD_3OD$): δ 8.67 (d, 1H, J = 7.2 Hz, C=CN**H**), 7.64 (m, 1H, Ar-**H**), 7.49-7.41 (m, 3H, Ar-**H**), 7.21-7.13 (m, 4H, Ar-**H**), 7.04 (d, 1H, J = 1.8 Hz, Ar-**H**), 6.84-6.80 (m, 2H, Ar-**H**), 6.57 (dd, 1H, J = 6.0, 2.7 Hz, Ar-**H**), 6.39 (m, 2H, Ar-**H**, OC**H**N), 4.69 (t, 1H, J = 7.2 Hz, CONHC**H**CH), 4.55 (m, 1H, CONHC**H**$CH_2$), 4.15 (d, 1H, J = 3.9 Hz, C**H**OTIPS), 3.06 (t, 1H, J = 12.0 Hz, C**H**$_2$Ar), 2.85 (dd, 1H, J = 12.0, 4.0 Hz, C**H**$_2$Ar), 2.17-2.00 (m, 2H, NHCHC**H**$(CH_3)_2$, OCHC**H**$(CH_3)_2$), 1.10-0.96 (m, 33H, TIPS, NHCHCH(**CH$_3$**)$_2$, OCHCH(**Me**)$_2$); $^{13}C$ NMR: (75 MHz, $CD_3OD$) δ 172.8, 172.3, 162.6, 157.6, 151.7, 151.2, 149.6, 142.0, 137.0, 136.7, 131.2, 129.7, 129.0, 128.9, 128.4, 127.8, 123.7, 123.6, 121.9, 120.3, 120.0, 119.2, 118.8, 115.0, 113.4, 111.4, 110.1, 103.7, 103.2, 78.1, 61.9, 55.6, 55.5, 38.1, 33.8, 29.8, 18.4, 18.0, 17.2, 17.1, 16.7, 12.2; HRMS: (FAB+) exact mass calculated for [M+H] ($C_{49}H_{58}N_6O_7Si$) requires *m/z* 870.4136, found *m/z* 870.4132; $[\alpha]_D^{25}$ = -102.52 (c = 0.173, $CHCl_3$).




**Triflate 64:** To a solution of **63a** (38 mg, 0.044 mmol) in $CH_2Cl_2$ (4.3 mL) was added $PhNTf_2$ (39 mg, 0.109 mmol) and $Et_3N$ (30.4 $\mu$L, 0.218 mmol). The solution was stirred under argon for 30 min and then diluted with brine. The aqueous layer was washed with EtOAc, and the combined organics were dried over $Na_2SO_4$. After concentration of the solvents *in vacuo*, the resulting oil was purified on silica gel (30% EtOAc in hexanes) to yield the title compound (30 mg, 67%) as a pale yellow-orange amorphous solid. IR(Film): 3287, 2962, 2869, 1652, 1496, 1471, 1424, 1213, 1139, 1062, 916, 882, 812, 742, 668 $cm^{-1}$; $^1H$ NMR: (300 MHz, $CD_3OD$): δ 7.68 (m, 1H, Ar-**H**), 7.48-7.42 (m, 2H, Ar-**H**), 7.26-7.02 (m, 7H, Ar-**H)**, 6.85 (m, 2H, Ar-**H**, OC**H**N), 6.52 (dd, 1H, J = 7.5, 6.6 Hz, Ar-**H**), 4.69 (d, 1H, J = 7.2 Hz, CONHC**H**CH), 4.56 (dd, 1H, J = 14.2, 3.9 Hz, CONHC**H**$CH_2$), 4.16 (d, 1H, J = 3.9 Hz, C**H**OTIPS), 3.07 (t, 1H, J = 12.0 Hz, C**H**$_2$Ar), 2.87 (dd, 1H, J = 12.0, 3.9 Hz, C**H**$_2$Ar), 2.19-2.00 (m, 2H, NHCHC**H**$(CH_3)_2$, OCHC**H**$(CH_3)_2$), 1.12-0.99 (m, 33H, TIPS, NHCHCH(**CH$_3$**)$_2$, OCHCH(**Me**)$_2$); $^{13}C$ NMR: (75 MHz, $CD_3OD$) δ 172.7, 172.2, 162.8, 157.7, 151.4, 150.0, 149.5, 141.5, 136.8, 133.3, 131.8, 130.3, 129.9, 129.1, 128.8, 128.1, 123.7, 123.0, 122.2, 122.1, 121.2, 120.7, 120.1, 119.7, 119.2, 118.8, 116.5, 111.5, 110.4, 103.3, 103.2, 78.1, 61.2, 55.4, 38.0, 33.8, 29.8, 18.4, 18.0, 17.2, 17.1, 16.7, 12.2; $^{19}F$ NMR: (75 MHz, $CD_3OD$) δ –75.6 (s, 3F, $CF_3$); HRMS: (FAB+) exact mass calculated for [M+H] ($C_{50}H_{58}N_6O_9F_3SiS$) requires *m/z* 1003.371, found *m/z* 1003.369; $[\alpha]_D^{25}$ = -119.34 (c = 0.126 $CHCl_3$).




**Phenol 65:** To a solution of **60** (110 mg, 0.133 mmol) in THF (7 mL) was added $Pd(OH)_2/C$ (150 mg). The solution was sparged with $H_2$ for 20 min and kept under a $H_2$ atmosphere for 64 h. At this time the solution was filtered through a silica plug, concentrated, and the resulting oil was purified on silica gel (10% MeOH in $CH_2Cl_2$) to yield the title compound (82 mg, 83%) as a pale amorphous solid. IR (Film): 3406, 2962, 2868, 1652, 1601, 1493, 1414, 1295, 1251, 1184, 1097, 1063, 914, 882, 815, 758, 682 $cm^{-1}$; $^1H$ NMR: (300 MHz, $CD_3OD$): δ 7.52 (d, 1H, J = 8.7 Hz, Ar-**H**), 7.32 (s, 1H, Ar-**H**), 7.15 (dd, 1H, J = 8.4, 1.5 Hz, Ar-**H**), 7.02 (s, 1H, Ar-**H**), 6.78-6.54 (m, 4H, Ar-**H**, OC**H**N), 4.98 (m, 1H, CONHC**H**CH), 4.56 (m, 1H, CONHC**H**$CH_2$), 4.16 (d, 1H, J = 3.9 Hz, C**H**OTIPS), 3.15 (t, 1H, J = 12.0 Hz, C**H**$_2$Ar), 2.85 (dd, 1H, J = 12.3, 3.2 Hz, C**H**$_2$Ar), 2.40 (m, 1H, NHCHC**H**$(CH_3)_2$), 2.04 (m, 1H, OCHC**H**$(CH_3)_2$), 1.10 (m, 21H, TIPS), 1.02-0.98 (m, 9H, NHCHCH(**CH$_3$)$_2$**, OCHCH(**Me**)Me), 0.81 (d, 3H, J = 6.3 Hz, OCHCH(**Me**)Me); $^{13}C$ NMR: (75 MHz, $CD_3OD$) δ 172.8, 172.6, 171.6, 167.0, 159.8, 157.3, 153.2, 142.1, 137.0, 134.0, 131.2, 129.9, 129.8, 129.2, 127.8, 120.4, 114.7, 113.4, 110.0, 103.9, 78.0, 61.4, 60.1, 55.6, 53.7, 38.4, 33.8, 28.5, 18.8, 17.2, 17.1, 16.7, 16.3, 12.2; HRMS: (FAB+) exact mass calculated for [M+Na] ($C_{39}H_{52}N_4O_8SiNa$) requires *m/z* 755.3452, found *m/z* 755.3467; $[\alpha]_D^{25}$ = -112.44 (c = 0.285, $CH_3OH$).




**Bismacrocycle 67:** A Schlenk vial was charged with **66** (15 mg, 0.013 mmol), $K_3PO_4$ (5.5 mg, 0.0040 mmol) and $Pd(PPh_3)_4$ (4.6 mg, 0.0040 mmol). To this vial was added degassed dioxane/$H_2O$ (5:1, 3.3 mL). The resulting solution was warmed to 70 °C for 5 h. At this time the solution was diluted with EtOAc, and $Na_2SO_4$ was added to precipitate remaining palladium. This solution was filtered through florisil, concentrated, and the resulting oil was purified by prep TLC (100:25:4 $CH_2Cl_2$:Hexanes:MeOH) to yield the title compound (4.3 mg, 38%) as a pale amorphous solid. $^1$H NMR: (300 MHz, $CD_3OD$): δ 10.56 (s, 1H, C=CN**H**), 8.66 (d, 1H, J = 7.8 Hz, Ar-**H**), 7.54 (d, 1H, J = 9.0 Hz, Ar-**H**), 7.41 (d, 1H, J = 8.1 Hz, Ar-**H**), 7.24-7.15 (m, 4H, Ar-**H**), 6.99 (d, 1H, J = 7.2 Hz, Ar-**H**), 6.90 (t, 1H, J = 7.5 Hz, Ar-**H**), 6.75 (d, 1H, J = 8.1 Hz, Ar-**H**), 6.20 (s, 1H, OC**H**N), 4.73 (m, 1H, CONHC**H**CH), 4.59 (m, 1H, CONHC**H**$CH_2$), 4.16 (d, 1H, J = 3.9 Hz, C**H**OTIPS), 4.04 (m, 1H, $CH_2C\mathbf{H}_2$NHCO), 3.23 (t, 1H, J = 12.0 Hz, C$\mathbf{H}_2$Ar), 2.85 (m, 2H, C$\mathbf{H}_2$Ar, $CH_2C\mathbf{H}_2$NHCO), 2.68 (m, 1H, NHCHC**H**$(CH_3)_2$), 2.08 (m, 2H, OCHC**H**$(CH_3)_2$, C$\mathbf{H}_2CH_2$NHCO), 1.86 (dd, 1H, J = 15.3, 6.0 Hz, C$\mathbf{H}_2CH_2$NHCO), 1.11 (m, 21H, TIPS), 1.05-0.98 (m, 9H, NHCHCH(**C$\mathbf{H}_3$)$_2$**, OCHCH(**Me**)Me), 0.91 (d, 3H, J = 6.6 Hz, OCHCH(**Me**)Me); HRMS: (FAB+) exact mass calculated for [M+Na] ($C_{49}H_{61}N_6O_6Si$) requires *m/z* 857.4422, found *m/z* 857.4397.