Development of the Lewis Acid Catalyzed Allenoate-Claisen Rearrangement. Investigations of Enantioselective Catalysis of the Allenoate-Claisen Rearrangement. Studies Towards the Total Synthesis of Erythrolide E.

Thesis by

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For mom, dad, Ian, and Rebecca.

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Abstract

The development of a new Lewis acid catalyzed sigmatropic reaction is described. This process, termed the allenoate-Claisen rearrangement, involves the metal-catalyzed condensation of an allenic ester with a tertiary allylic amine. The zwitterionic intermediate resulting from this condensation undergoes facile [3,3] bond reorganization to provide □-amino-□,□,□,□-unsaturated-□,□-disubstituted ester products. The allenoate-Claisen reaction has been demonstrated to allow for the production of a diverse range of Claisen adducts in high yield and with very high diastereoselectivities. Perhaps most notably, this process is amenable to the rapid generation of quaternary carbon stereogenicity with nearly complete stereocontrol.

Investigations of an enantioselective catalytic variant of the allenoate-Claisen rearrangement have been initiated. Enantioselectivities of up to 49% have been achieved with the use of a titanium bis(binaphthyl) catalyst and a bidentate chelating allenic partner. The effects of solvent and method of catalyst preparation on enantioselectivity are described.

Progress towards the total synthesis of the briarane diterpene, erythrolide E, has been made. Using acyl-Claisen methodology developed in the MacMillan laboratories, both key fragments of the erythrolide framework have been prepared in racemic fashion. In addition, a highly enantioselective route to the core fragment has been developed using an enantioselective organocatalytic Diels-Alder reaction and Ireland-Claisen methodology.

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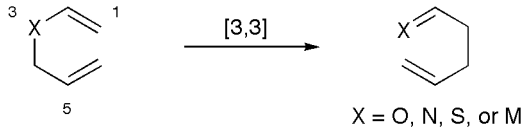
CHAPTER 1

The Claisen Rearrangement

Introduction

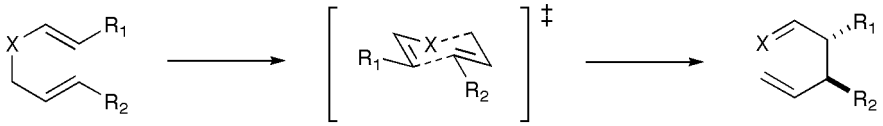
The Claisen rearrangement stands as one of the most powerful known methods for the generation of complex organic architecture.[1] Originally disclosed as the [3,3]-sigmatropic reorganization of allyl-aryl or allyl-vinyl ethers,[2] the term Claisen rearrangement has subsequently expanded to include any such process involving a 1,5-diene possessing a heteroatom in the 3-position (Figure 1). Thus, in addition to the traditional formulation in which X = O, aza-Claisen[3] (X = N), thio-Claisen[4] (X = S), and even metallo-Claisen[5] (X = M) rearrangements are well known.

Figure 1. The Claisen rearrangement.



The utility of the Claisen rearrangement lies in the highly predictable manner in which complex stereochemical motifs may be generated from relatively simple precursors. This predictability is a consequence of the propensity of Claisen substrates to proceed through highly ordered six-membered transition states (Figure 2). As such, the diastereomeric identity of Claisen rearrangement products is typically controlled by judicious choice of reactant olefin geometry.

Figure 2. Highly ordered six-membered transition state.

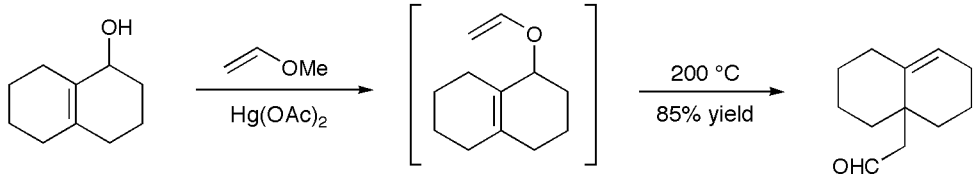


In general, the actual sigmatropic event is facile, often occurring at or just above ambient temperatures. Given this fact, Claisen rearrangement reports often focus on novel strategies to prepare the requisite allyl vinyl component in a geometrically defined manner. Indeed, it is the manner of substrate preparation that has traditionally defined the numerous Claisen variants.

Claisen Variants

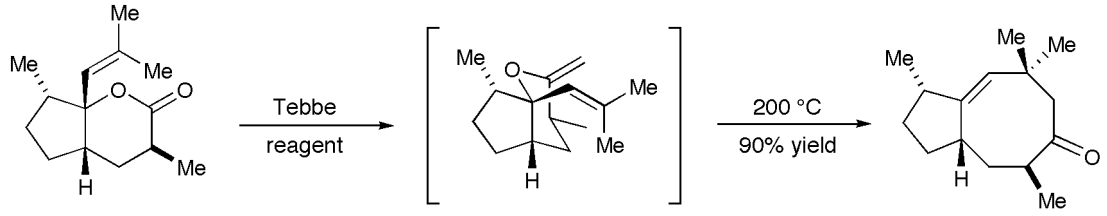
One of the earliest reported methods for the preparation of allyl vinyl ether Claisen substrates was the mercury-catalyzed interchange of allylic alcohols with alkyl vinyl ethers (Figure 3).[6] Once formed, simple allyl vinyl ethers typically require elevated temperatures to undergo rearrangement. Though it allows for straightforward access to an otherwise challenging functionality, the toxicity and low yields associated with mercury transetherification have limited the use of this procedure.

Figure 3. Mercury-catalyzed preparation of Claisen substrates.



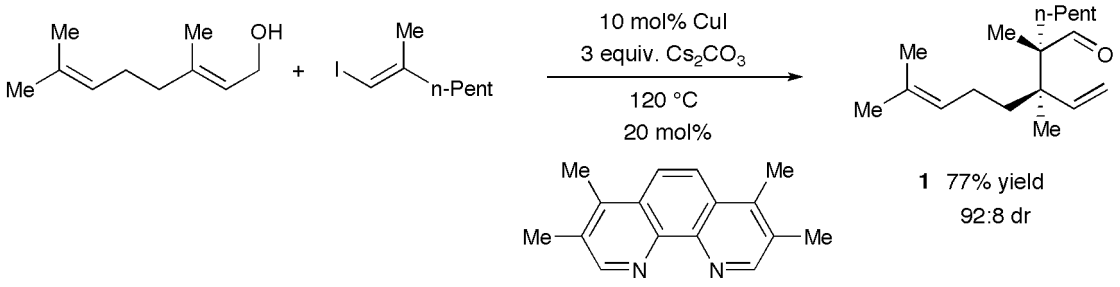
Numerous alternative methods have been reported to access the allyl vinyl ether motif. An important entry in this context is the olefination of ester or lactone carbonyls with the Tebbe reagent (Figure 4).[7] As an example, Paquette has successfully applied this strategy to the synthesis of precapnelladiene.

Figure 4. Allyl vinyl ether preparation via Tebbe olefination.



Very recently, Buchwald reported the facile preparation of allyl vinyl ethers via copper-catalyzed coupling of allylic alcohols with vinyl iodides (Figure 5).[8] The resulting coupling products undergo *in situ* rearrangement to provide Claisen products in good yields. Of particular note was the application of this methodology to the preparation of a range of adducts (i.e., **1**) incorporating vicinal quaternary carbon centers with high diastereoselectivities.

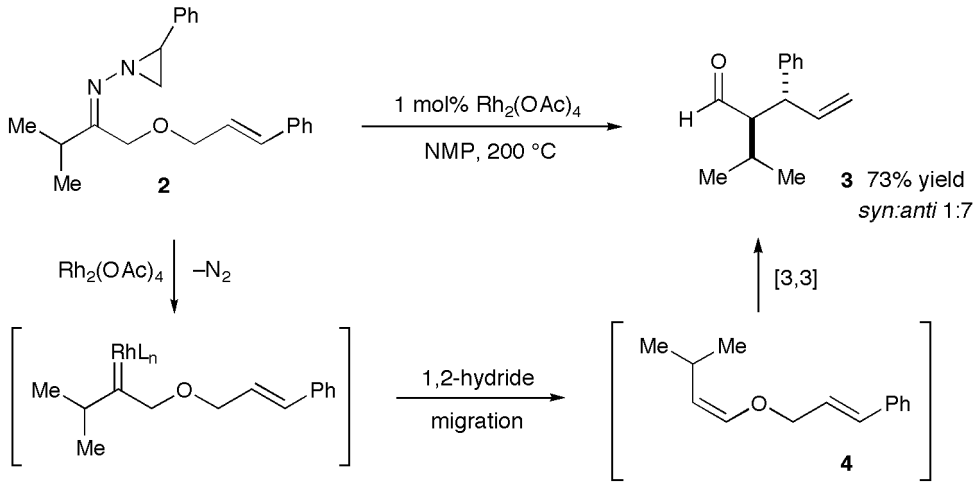
Figure 5. Domino Cu-catalyzed coupling / Claisen rearrangement.



Another clever strategy for accessing the allyl vinyl ether motif was recently reported by Stoltz and May.[9] Their protocol entails a tandem process in which β-allyloxy *N*-aziridinyl imines **2** are first converted via rhodium-catalyzed Bamford-Stevens reaction to allyl vinyl ethers **4**, which subsequently undergo thermal Claisen rearrangement to

furnish complex aldehyde products **3**. Importantly, the Bamford-Stevens reaction provides difficult to access (*Z*)-enol ethers with high stereoselectivity.

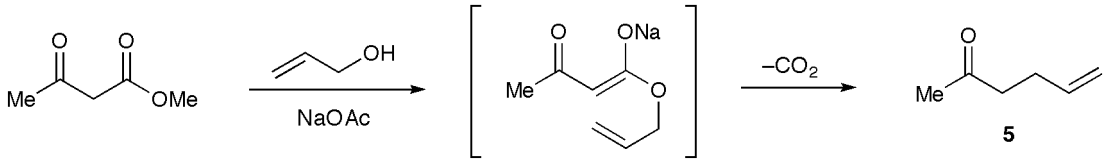
Figure 6. Tandem Rh-catalyzed Bamford-Stevens / Claisen rearrangement.



The common feature of these simple allyl vinyl ether Claisen rearrangements is the relatively high temperatures (100 to >200 °C) required to effect the pericyclic event. This fact, coupled with the higher degree of difficulty in accessing these substrates has led to a less widespread reliance on these traditional Claisen variants as compared to certain other, charge-accelerated protocols.

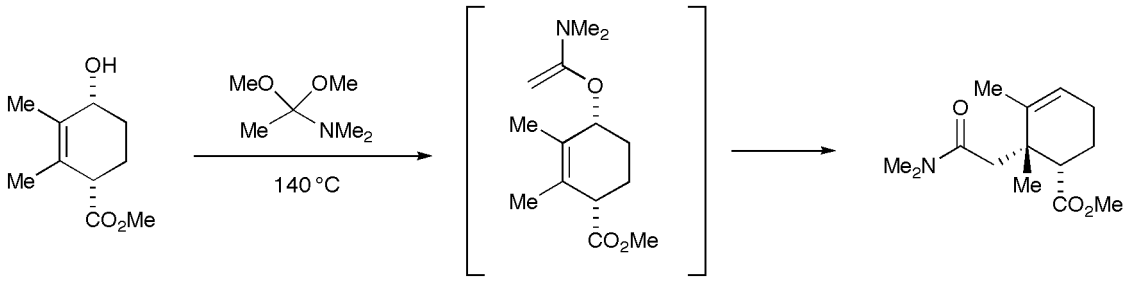
In 1940, as an alternative strategy for vinyl ether formation, Carroll reported the [3,3]-sigmatropic reaction of allylic β-ketoesters, a process now generally known as the Carroll-Claisen rearrangement (Figure 7).[10] In this process, preparation of the vinyl component of the Claisen substrate is greatly simplified, resulting from enol (or enolate) tautomerization of the ketoester. Upon rearrangement, the resulting β-ketoacid typically undergoes decarboxylation to yield a β,γ-unsaturated ketone (**5**).

Figure 7. Carroll-Claisen rearrangement.



Another significant advancement in Claisen technology came with a report by Eschenmoser and coworkers in 1964 who found that condensation of allylic alcohols with amide acetals results in the formation of an *N,O*-ketene acetals (Figure 8).[11] These acetals subsequently undergo facile *in situ* rearrangement to provide amide Claisen products.

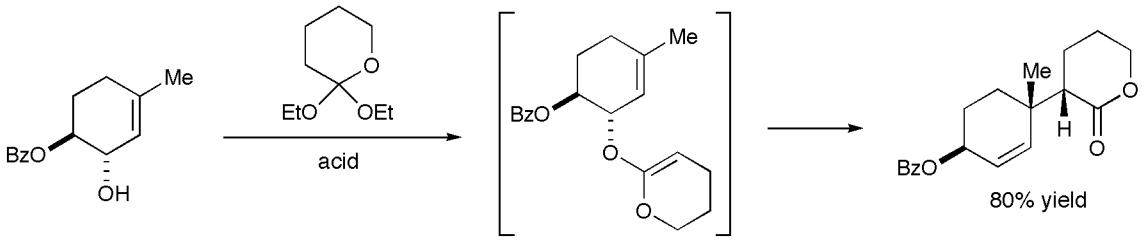
Figure 8. Eschenmoser-Claisen rearrangement.



In related work, Johnson found that treatment of allylic alcohols with ortho-esters and trace weak acid (such as propionic acid) results in the formation of ketene acetals (Figure 9).[12] Analogous to the Eschenmoser protocol, these Johnson ortho-ester intermediates undergo Claisen rearrangement to yield ester products. In contrast, however, the Johnson protocol does not generally provide geometrically defined ketene acetals, thereby limiting the utility of this protocol for the generation of □-stereogenicity.

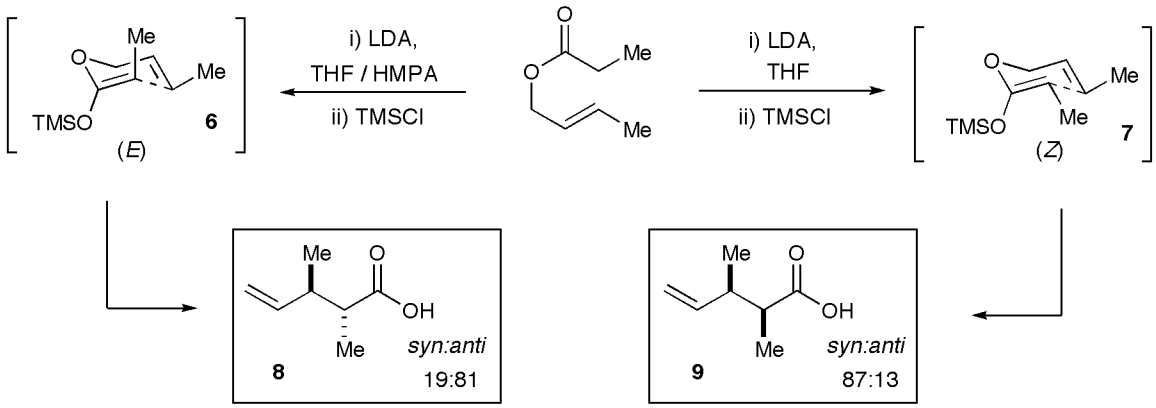
An exception to this limitation comes with the use of cyclic orthoesters, which of course provide complete control over olefin geometry (Figure 9).[13]

Figure 9. Johnson ortho ester rearrangement.



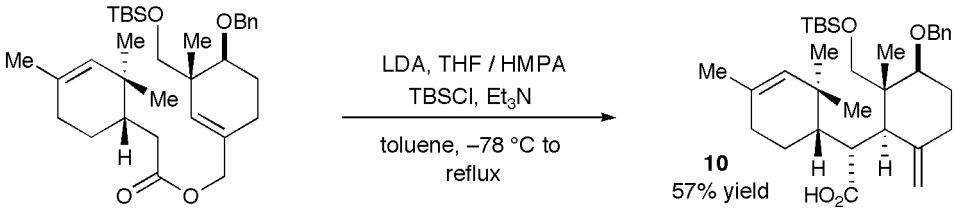
Perhaps the most significant advancement in the area of Claisen technology has come from the report by Ireland in 1972 that silyl ketene acetals readily undergo sigmatropic rearrangement at or below room temperature (Figure 10).[14] The silyl ketene acetals are typically generated at low temperature (–78 °C) by enolization of allylic esters with amide bases followed by silylative trapping. Simple warming of these intermediates to ambient temperature is often enough to facilitate rearrangement.

Figure 10. Ireland-Claisen rearrangement.



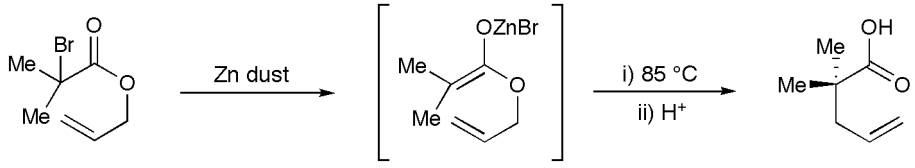
The utility of this protocol lies in the fact that silyl ketene acetal olefin geometry (**6** or **7**), and thus relative product stereochemistry (**8** or **9**), can be dictated by judicious choice of enolization conditions. This stereochemical control, coupled with exceedingly mild reaction conditions, has led to the extraordinarily broad application of the Ireland-Claisen rearrangement to complex molecular synthesis. A recent example of such is the application to the synthesis of the Taxol skeleton reported by Magnus and Westwood (Figure 11).[15] Remarkably, this transformation provides rearrangement product **10** in good yield despite the highly congested nature of the Claisen transition state.

Figure 11. Application of the Ireland-Claisen to the synthesis of the Taxol skeleton.



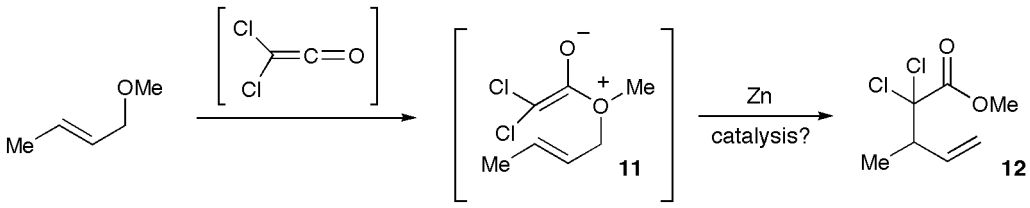
In a somewhat related process, the Reformatsky-Claisen reaction involves sigmatropic bond reorganization of ester enolates generated from zinc dehalogenation of allylic -halo esters (Figure 12).[16] The primary significance of this protocol is that it occurs under essentially neutral conditions.

Figure 12. Reformatsky-Claisen rearrangement.



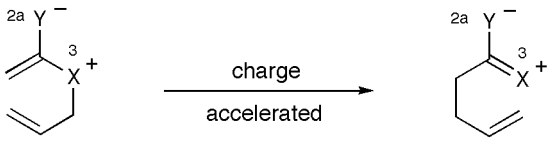
Bellus and Malherbe reported a Claisen protocol involving the addition of allyl ethers to ketenes (Figure 13).[17] The resulting zwitterionic intermediates **11** undergo rapid bond reorganization to yield charge-neutral ester products **12**. Although the authors reported that this ketene Claisen protocol was effective only with highly electrophilic ketenes, careful analysis of their report reveals that only those reactions involving ketenes generated by *in situ* zinc dehalogenation were productive. This raises the notion that successful ketene-Claisen rearrangements might have involved activation by $ZnCl_2$. Recognition of this possibility led to the development in the MacMillan laboratories of a Lewis acid catalyzed acyl-Claisen reaction (*vide infra*).

Figure 13. Bellus-Malherbe ketene-Claisen rearrangement.



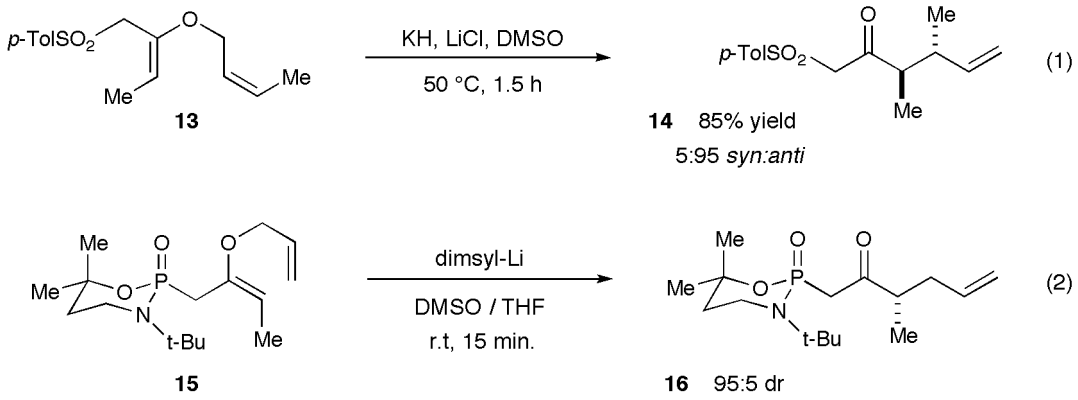
The zwitterionic nature of the ketene-Claisen intermediate underscores an important principle of charge-acceleration of the Claisen rearrangement. Specifically a substrate that incorporates positive charge at the 3 position[18] and/or negative charge at the 2a position[19] of the 1,5-diene undergoes rearrangement more readily than a charge-neutral substrate (Figure 14). These accelerating effects are usually attributed to a more advanced X(3)–C(4) bond breaking in the sigmatropic transition state. In this context, the Claisen rearrangement can be regarded as an intramolecular S_N2' reaction between the "nucleophilic" vinyl component and the "electrophilic" allyl component.

Figure 14. Charge acceleration of the Claisen rearrangement.



Although negative charge at the 2a position is usually manifested as an oxygen anion, Denmark and Harmata have reported two carbanion-accelerated Claisen protocols (Figure 15).[20,21] In one method, deprotonation of a pendant 2-sulfonylmethyl group results in Claisen rearrangement of allyl vinyl ether **13** to provide β-ketosulfone product **14** in high yield and high diastereoselectivity (Eq. 1).[20] In a similar manner, asymmetric induction was achieved by deprotonation and subsequent anion-accelerated rearrangement of chiral phosphorinane **15** (Eq. 2).[21] In both cases, orbital alignment of the carbanionic carbon and the vinyl π-system in the transition state is presumed.

Figure 15. Carbanion-accelerated Claisen rearrangements.



Stereocontrol of the Claisen Rearrangement

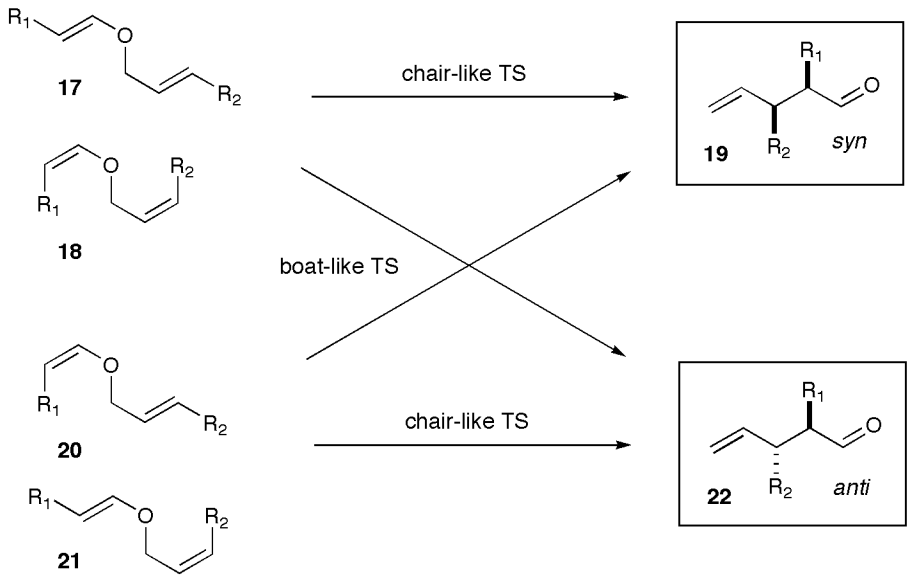
Besides the actual formation of bonds, the true power of the Claisen rearrangement lies in its ability to readily and predictably generate complex

stereochemical architecture. As noted earlier, Claisen rearrangements proceed through highly ordered six-membered transition states to produce as many as two stereocenters, often with high levels of stereoselectivity.

Analogous to the conformations of cyclohexyl rings, Claisen transition states may be chair-like or boat-like depending on substrate identity. Theses two conformationally distinct transition states lead to diastereomerically divergent products. Not surprisingly, olefin geometry is intimately linked to product stereochemistry.

As demonstrated in Figure 16, if the allyl and vinyl olefins of the Claisen substrate are both trans (**17**) or both cis (**18**), then a chair-like transition state will produce a product (**19**) with *syn* configuration. Alternatively, if the geometry of the olefinic components differ (**20** or **21**), then the *anti* product (**22**) will result from the chair-like transition state. In each case, a boat transition state produces the opposite diastereomer (in Figure 16, only relative stereochemistry is implied).

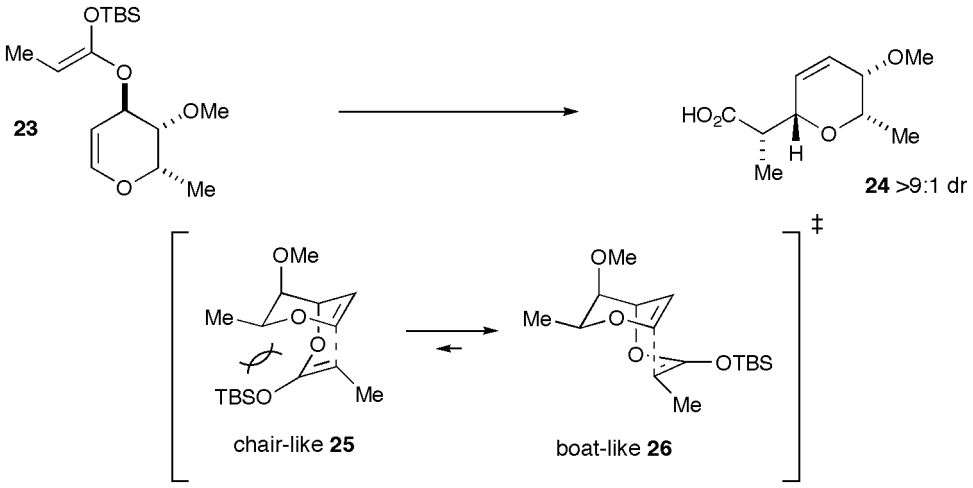
Figure 16. Sterechemical consequence of olefin geometry of Claisen reactants.



In reality, with acyclic substrates the chair-like transition state is nearly always preferred, a consequence of energetic minimization of torsional and transannular interactions.[1d] In contrast, Claisen rearrangements in which the allyl component is confined in a ring system often proceed through a boat-like transition state.[1d]

This conformational reversal is usually a result of an unfavorable interaction in the chair-like transition state **25** of the vinylic component with the allylic ring structure (Figure 17). Reaction through the boat-like conformation **26** avoids this interaction, and, indeed, boat selectivity can be quite high (e.g., greater than 9:1 in Figure 17). Such preference, however, is not a rigid rule and may vary from case to case.

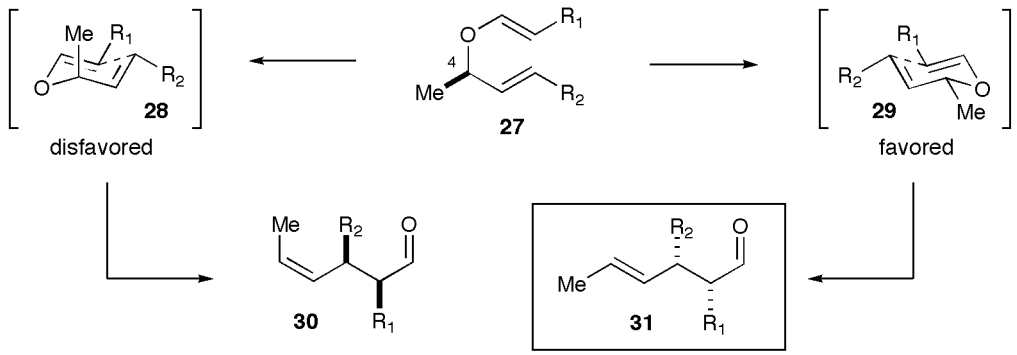
Figure 17. Boat-like transition state preference for cyclic substrates.



Another consequence of the highly ordered nature of Claisen transition states is that the transfer of stereochemistry from reactants to products is highly conservative.[1d] The most straightforward case to consider in this context is for a substrate that incorporates stereogenicity at C(4) (Figure 18). The rearrangement of substrates such as **27** could potentially proceed through either of two chair-like transition states, **28** or **29**.

One of these (**28**), however, is highly disfavored due to a pseudo-1,3-diaxial intereaction. Thus transition state **29**, which orients the C(4) substituent in a pseudo-equatorial position, is favored and hence dictates the product stereochemistry. A process such as this is termed "self-immolative" because the controlling stereocenter is destroyed in the reaction. Incidentally, another consequence of equatorial preference is that Claisen rearrangements of substrates with C(4) substitution give rise to products containing *E*-olefins (**31**).

Figure 18. Transfer of stereochemistry in the Claisen rearrangement.



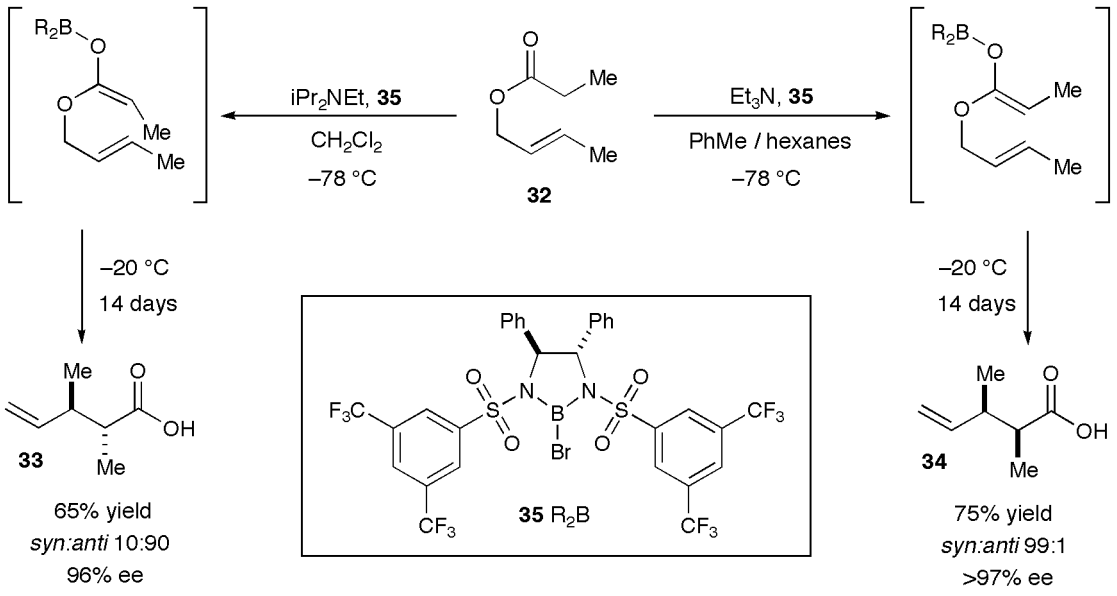
Numerous investigations have focused on the influence of stereogenic substitution at other positions of the 1,5-diene framework.[1g] These studies have led to a wide array of substrate and auxiliary-controlled methods for control of the absolute stereochemistry of Claisen products.

In contrast, relatively few strategies have been reported for asymmetric control of the Claisen rearrangement using an external chiral reagent.[1g,h] This paucity is particularly surprising in light of the inherent synthetic power of the Claisen rearrangement coupled with the explosive interest in the field of enantioselective catalysis over the last several decades. Indeed, while several notable stoichiometric methods for enantioselective

Lewis acid *promotion* of the Claisen rearrangement have been developed, to date only one enantioselective *catalytic* protocol has been reported.[22]

Corey has reported the first enantioselective promotion of the Claisen rearrangement of allylic ester enolates using a stilbenediamine-derived boron catalyst **35** (Figure 19).[23] With this method, both *anti* (**33**) and *syn* (**34**) Claisen products can be obtained with high enantioselectivity simply by altering enolization conditions. While the Corey procedure has been proven to be synthetically useful,[23b,c] this method suffers from extraordinary long reaction times (2 weeks) and an inherent need for stoichiometric amounts of the chiral promoter.

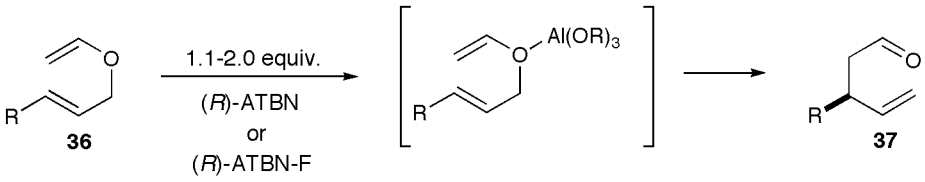
Figure 19. Corey's enantioselective Claisen rearrangement.

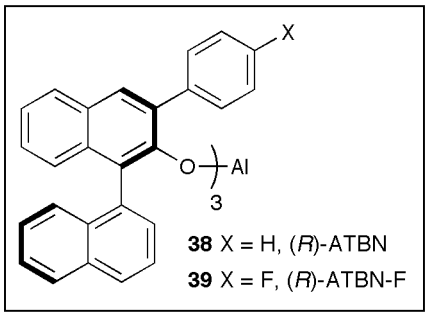


In 1995, Yamamoto disclosed a method for the enantioselective promotion of the Claisen rearrangement of allyl vinyl ethers **36** using chiral aluminum alkoxides (Figure 20).[24] By employing stoichiometric amounts of the tris(binaphthyl)aluminum derivatives

38 or **39**, cationic acceleration of the Claisen rearrangement of a limited substrate range can be achieved to provide Claisen products **37** in good to excellent yield and with generally modest enantioselectivity.

Figure 20. Yamamoto's cation-accelerated enantioselective Claisen rearrangement.

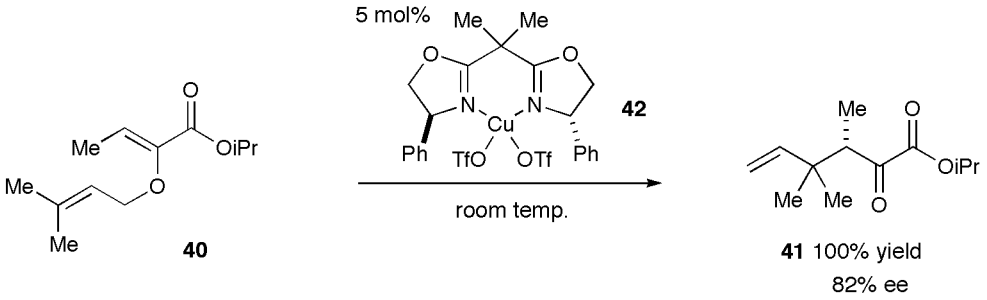




R	X	% yield	%ee
t-Bu	H	63	63
Cy	H	78	61
Ph	H	93	61
t-Bu	F	70	91
Cy	F	85	86
Ph	F	97	76

The first, and to date only, successful enantioselective catalytic Claisen rearrangement was described by Hiersemann in 2001 (Figure 21).[22] With this protocol, 5-10 mol% of copper bisoxazoline complex **42** effectively catalyzes the Claisen rearrangement of □-allyloxy alkenoate esters **40** to yield □-keto Claisen adducts **41** in very high yields and with modest enantioselectivities. Organizational control is undoubtedly bolstered by the bidentate nature of the reactant. Although the Hiersemann method represents a milestone in the Claisen rearrangement field, the modest enantioselectivities and rather specific substrates associated with this protocol leave much room for improvement.

Figure 21. Hiersemann's enantioselective catalytic Claisen rearrangement.

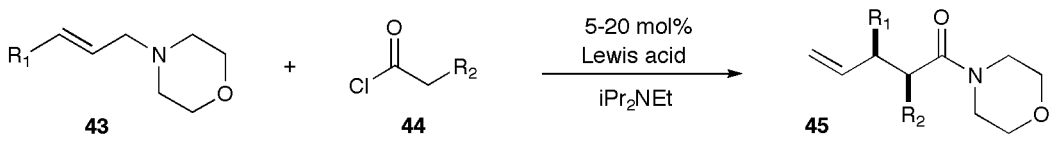


There has been an ongoing program in the MacMillan group aimed at the development of a broadly useful enantioselective Claisen rearrangement. In this context, a new sigmatropic variant, the acyl-Claisen rearrangement, was developed as a platform to achieve this goal.

The Acyl-Claisen Rearrangement

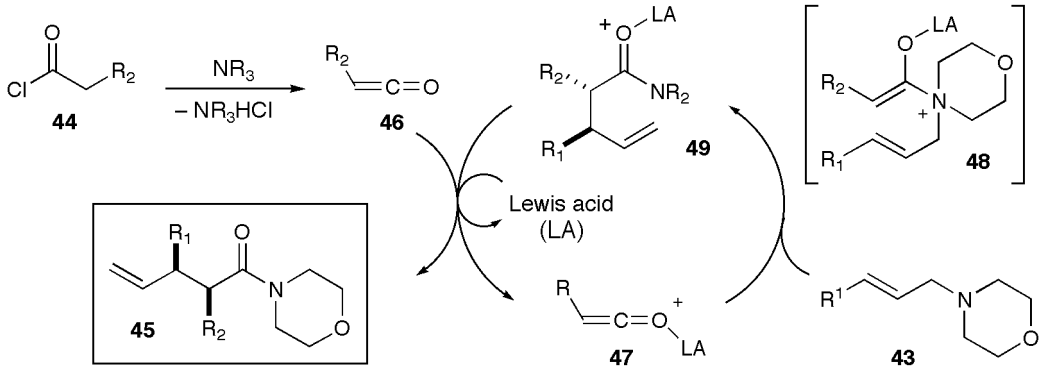
In 1999, the MacMillan group reported the development of the acyl-Claisen rearrangement.[25] In this process, the reaction of allyl morpholines **43** and acid chlorides **44** in the presence of catalytic amounts of Lewis acid and a tertiary amine base produces amide Claisen adducts **45** in high yields and with excellent diastereoselectivities (Figure 22).

Figure 22. The acyl-Claisen rearrangement.



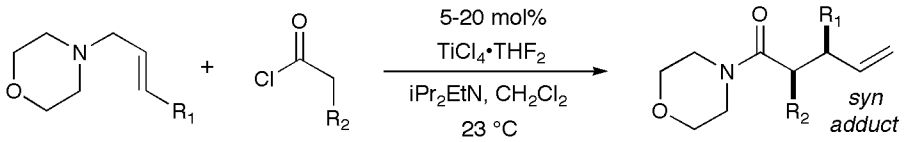
The inspiration for this work came from the recognition that the ketene-Claisen developed by Bellus and Mallherbe might be a Lewis acid-dependent process (see Figure 12).[17] It was reasoned that Lewis acid activated ketene (**47**) should be susceptible to addition of a tertiary allylic amine **43** (Figure 23). The resulting zwitterionic acyl-ammonium intermediate **48** should be suitably disposed to undergo facile bond reorganization. The product of this reorganization, a neutral amide (**49**), should readily dissociate from the Lewis acid to provide the Claisen product **45** and thereby allow for catalyst turnover.

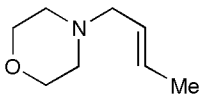
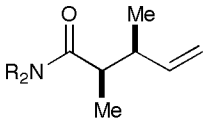
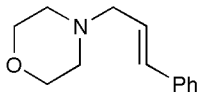
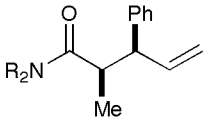
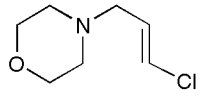
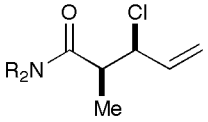
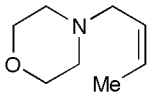
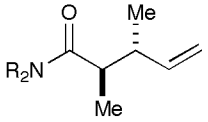
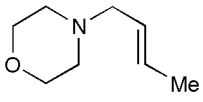
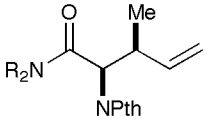
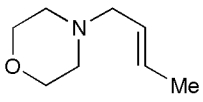
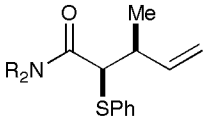
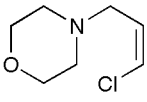
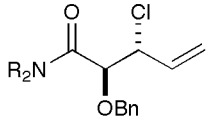
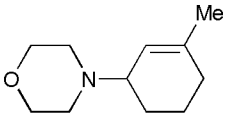
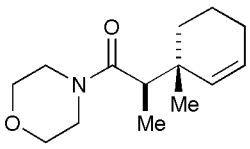
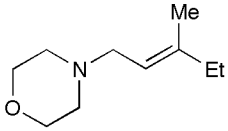
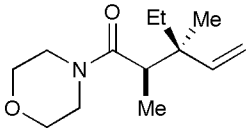
Figure 23. Catalytic cycle of the acyl-Claisen rearrangement.



This hypothesis was successfully realized with the development of the broadly useful acyl-Claisen rearrangement.[25] As can be seen in Table 1, a diverse range of allyl amine and acid chloride components can be utilitized in this transformation. Products thus obtained incorporate with high diastereoselectivity a wide variety of functionality, including alkyl, aryl, chloro, alkoxy, thio, and amino substituents (entries 1-7). In addition, the acyl-Claisen has been demonstrated to be highly effective for the generation of quaternary carbon centers in both cyclic and acyclic settings (entries 8 and 9).

Table 1. Substrate scope of the acyl-Claisen rearrangement.



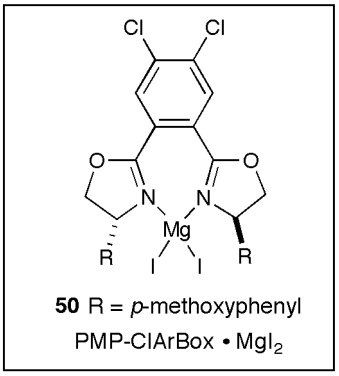
entry	amine	R_2	product	yield	*syn*:*anti*
1		Me		92	>99:1
2		Me		76	>99:1
3		Me		95	>99:1
4		Me		74	5:95
5		NPth		77	98:2
6		SPh		81	92:8
7		OBn		70	10:90
8		Me		75	95:5
9		Me		72	99:1

Importantly, relative product stereochemistry can be dictated by proper choice of olefin geometry of the allyl amine component. Thus, while trans allyl amines give rise to *syn* Claisen products (entries 1-3, 5, 6, 8, and 9), *anti* adducts may be obtained with the use of cis isomers (entries 4 and 7).

Two enantioselective variants of the acyl-Claisen rearrangement have subsequently been developed by Yoon in the MacMillan group.[27,28] The first method entails the reaction of allyl amines with □-benzyloxyacetyl chloride, promoted by three equivalents of magnesium bisoxazoline complex **50**.[27] As represented in Table 2, significant variety of the allyl component can be tolerated, providing access to Claisen products in high yields, diastereoselectivities, and enantioselectivities. At least one contributing factor to the requirement of multiple equivalents of chiral promoter is thought to be a chloride–iodide metathesis reaction of complex **50**, which renders this promoter ineffective.[25b]

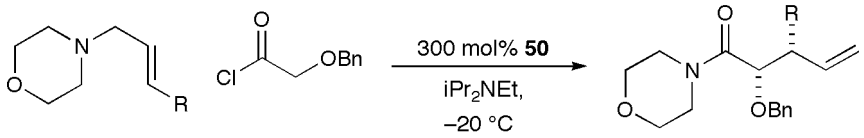
A second generation enantioselective acyl-Claisen strategy has been developed by Yoon and Kim for the reaction of allyl amines with propionyl chloride (Table 3).[25b, 28] In this protocol, two equivalents of the stilbene diamine-derived boron complex **51** are capable of providing acyl-Claisen products in good yield and with high levels of enantio- and diastereoselectivity. As with the first generation system, however, the use of substoichiometric quantities of promoter **51** results in drastically reduced enantioenrichment, again presumably due in part to inhibition of the Lewis acid by chloride ion.[25b]

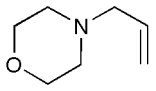
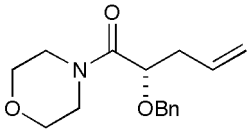
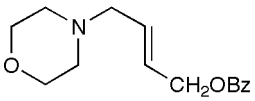
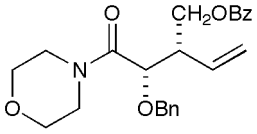
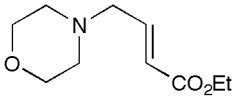
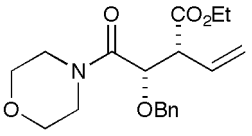
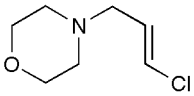
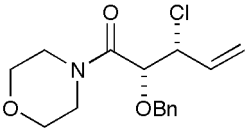
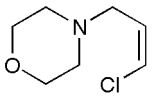
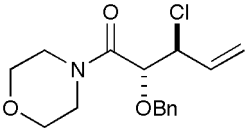
Table 2. First generation enantioselective acyl-Claisen rearrangement.



50 R = *p*-methoxyphenyl

PMP-ClArBox • MgI_2



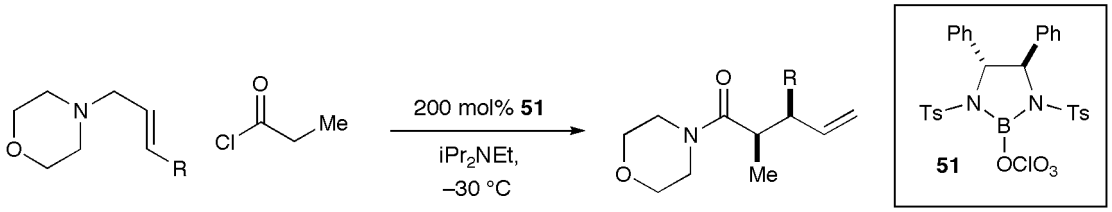
entry	amine	product	% yield	*syn*:*anti*	% ee
1			80	--	91
2			86	92:8	86
3			84	97:3	96
4			95	98:2	91
5			74	3:97	91

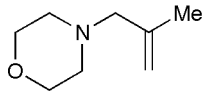
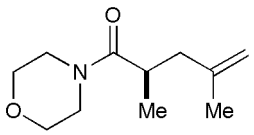
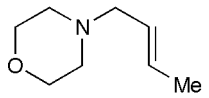
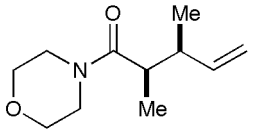
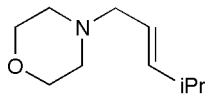
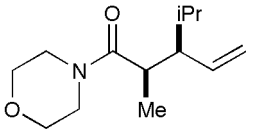
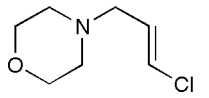
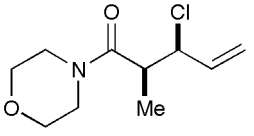
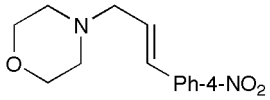
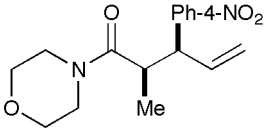
The acyl-Claisen rearrangement represents a powerful new technology for the generation of highly complex organic architecture in an operationally trivial manner. Within the MacMillan group, this reaction has led to many fruitful avenues of research,

including two new enantioselective Claisen variants. Yet the goal of achieving an enantioselective catalytic Claisen rearrangement has remained elusive.

To further our pursuit of this goal, we have investigated another novel Claisen methodology that possesses several attractive features in common with the acyl-Claisen reaction, yet offers significant alternatives in regard to bond construction and enantioselective catalysis. We have termed this new reaction the allenoate-Claisen rearrangement.

Table 3. Second generation enantioselective acyl-Claisen rearrangement.



entry	amine	product	% yield	*syn*:*anti*	% ee
1			66	--	86
2			81	>99:1	91
3			84	>99:1	92
4			77	>99:1	93
5			90	>99:1	90

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CHAPTER 2

Development of the Lewis Acid Catalyzed Allenoate-Claisen Rearrangement[1]

Chapter 1 describes the development of a new Lewis acid catalyzed sigmatropic rearrangement termed the acyl-Claisen rearrangement.[2] This chapter details our investigations of a conceptually related protocol that we have termed the allenoate-Claisen rearrangement.

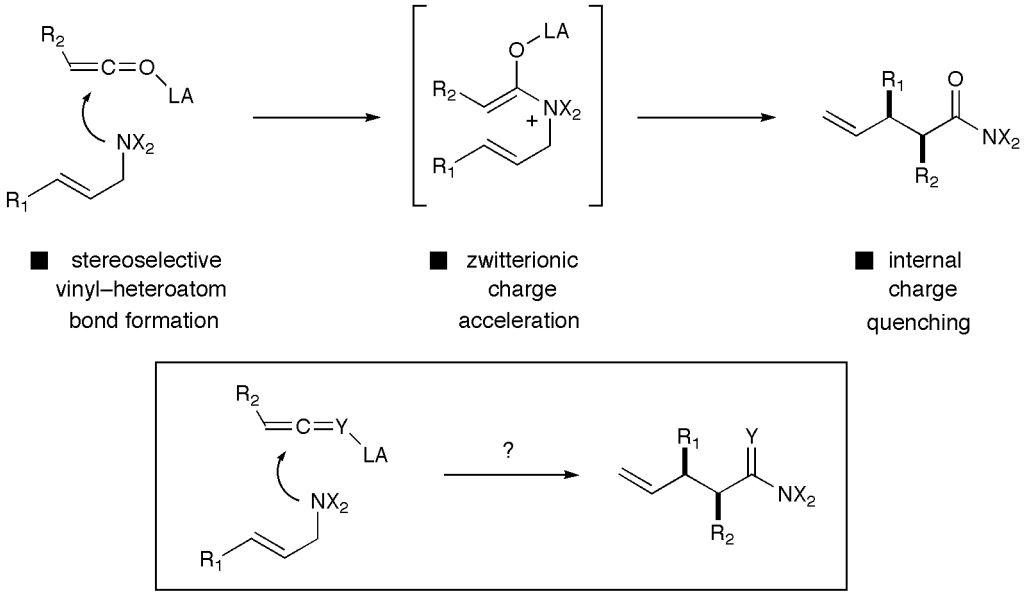
Reaction Design

Numerous mechanistic attributes render the acyl-Claisen rearrangement[2] a highly useful synthetic process. Prominent among these are (1) zwitterionic charge-acceleration of the sigmatropic event, (2) subsequent internal charge quenching, and (3) operationally trivial formation of the vinyl-heteroatom bond (Figure 1). Indeed, it was in pondering this last point that led to a consideration of whether analogous Claisen intermediates might be accessed via addition of allyl amines to cumulenic partners other than ketenes. Such alternatives would be expected to retain the above-mentioned positive characteristics while offering powerful new possibilities for bond construction and asymmetric catalysis.

In this context we recognized that allenic esters **1** might be subject to Lewis acid-activated 1,4-conjugate addition of allylic amines **2** (Figure 2). This type of coupling would result in a zwitterionic complex **3**, which would be suitably predisposed to undergo carbanion-accelerated Claisen rearrangement to provide □-amino-□,□,□,□-unsaturated-□,□-disubstituted ester products **4**.

Aside from the inherent synthetic utility of vinylogous carbamate Claisen products,[3] the proposed process would benefit from the advantage of employing stable, isolable allenic substrates rather than ketenes. As such, the use of exogenous tertiary amine base and the subsequent generation of stoichiometric quantities of ammonium chloride as dictated by the acyl-Claisen protocol would be forgone.[4] Moreover, variation of the nature of the allenic carbonyl (ester, amide, imide, etc.) should provide a tremendous breadth of functional handles with which to explore asymmetric catalysis.

Figure 1. Salient features of the acyl-Claisen reaction.

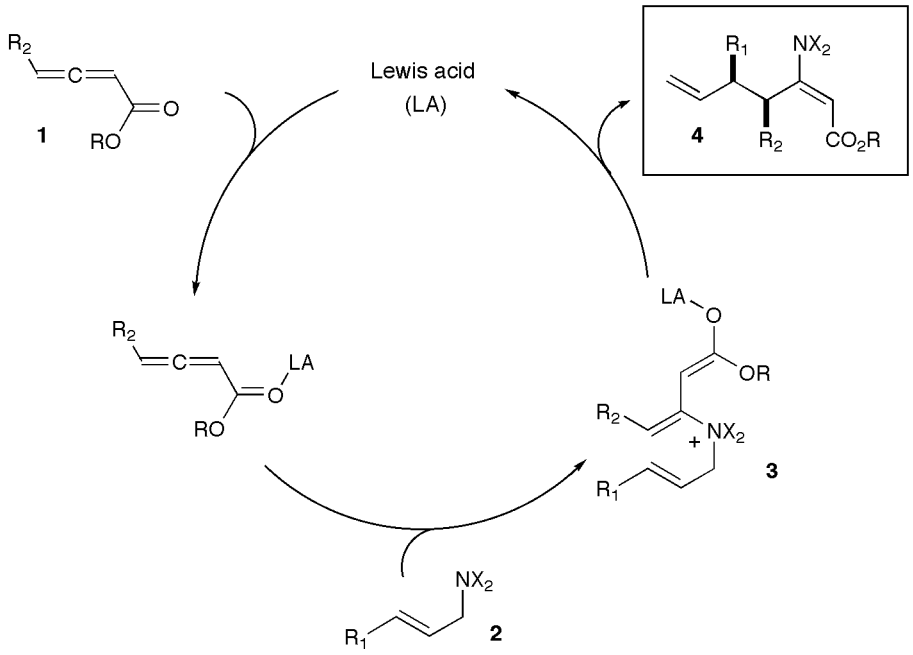


Results and Discussion

To facilitate our studies, we began by preparing the requisite allenic esters according to the procedure of Lang and Hansen.[5] In a straightforward manner, ester phosphoranylidenes **5** and acid chlorides **6** react in the presence of triethylamine to provide ester allene products **1** (Scheme 1). The operative reaction in this process is a Wittig olefination of *in situ*-generated ketene **7**. Although this protocol is invariably low-

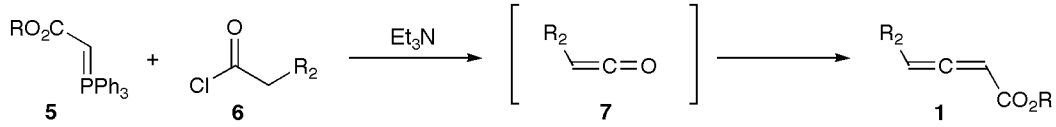
yielding (<50% yield), the operational simplicity and ready availability of starting materials served to make this our exclusive preparation of choice.

Figure 2. Proposed catalytic cycle for the allenoate-Claisen rearrangement.



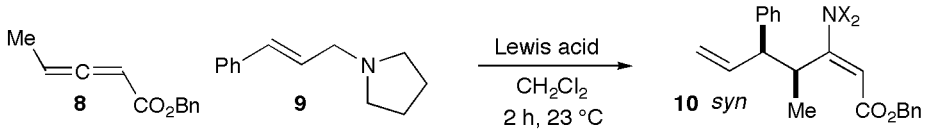
Our studies began with investigation of the reaction of benzyl 2,3-pentadienoate (**8**) and cinnamyl pyrrolidine (**9**) (Table 1). We were gratified to find that the production of Claisen adduct **10** was efficiently catalyzed by 5-10 mol% of a broad range of Lewis acids including, notably, $AlCl_3$, $Cu(OTf)_2$, $FeCl_3$, and $Zn(OTf)_2$. Importantly, high levels of reaction efficiency and diastereocontrol were observed in all metal-mediated cases (entries 2–9, 81–95% yields, >98:2 *syn:anti*), while rearrangement adducts were not detected in the absence of Lewis acid (entry 1). The superior catalytic efficiency exhibited by $Zn(OTf)_2$ prompted us to select this metal salt for further exploration.

Scheme 1. Preparation of allenic esters.



Our investigations into the scope of the allyl pyrrolidine component are summarized in Table 2. Allyl substituents of varying steric demand (R_1 = H, Me, iPr, and Ph, entries 1 and 3-5) can be incorporated in high yields and with high levels of stereocontrol (80-97% yield, >94:6 *syn:anti*). Importantly, in accord with established Claisen protocols,[6] the relative sense of stereoinduction can be dictated by appropriate choice of olefin geometry in the allyl component. Thus, while *trans*-allylic amines give rise to *syn* Claisen adducts with high levels of stereoselection (entries 1, 3, and 4, >94:6 *syn*:*anti*), the *anti*-Claisen products may be obtained with equally high selectivity by employing *cis*-allylic amines (entry 2, <2:98 *syn:anti*).

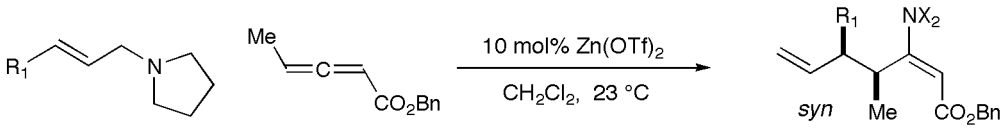
Table 1. Lewis acid catalyzed allenoate–Claisen rearrangement.

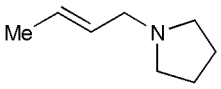
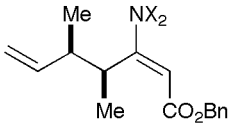
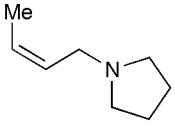
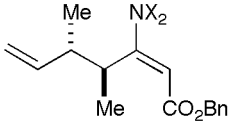
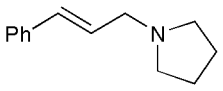
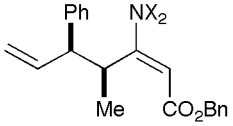
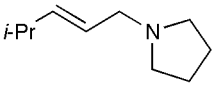
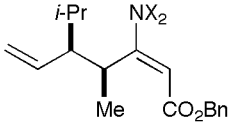
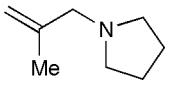
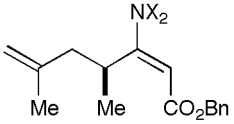


entry	Lewis acid	mol% cat	% yield	*syn*:*anti*[a,b]
1	--	--	NR	--
2	$Yb(OTf)_3$	5	82	>98:2
3	$Sn(OTf)_2$	5	86	>98:2
4	$Cu(OTf)_2$	10	87	>98:2
5	$AlCl_3$	10	83	>98:2
6	$MgBr_2 \cdot Et_2O$	10	81	>98:2
7	$FeCl_3$	10	83	>98:2
8	$Zn(OTf)_2$	10	95	>98:2
9	$Zn(OTf)_2$	5	93	>98:2

[a]Product ratios determined by ^{1}H NMR analysis. [b] NX_2 = pyrrolidine.

Table 2. Catalyzed allenoate–Claisen rearrangement between benzyl 2,3-pentadienoate and representative allyl pyrrolidines.

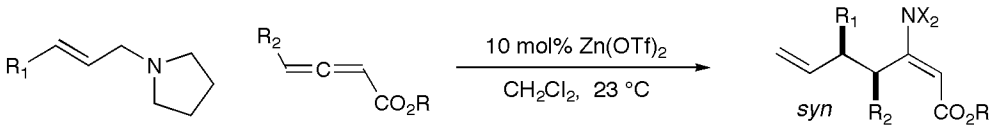


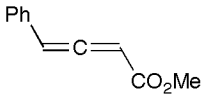
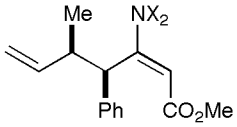
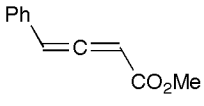
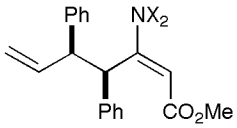
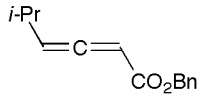
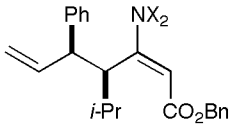
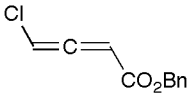
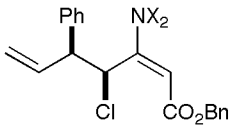
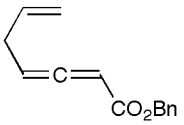
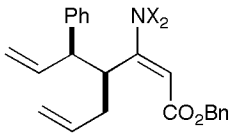
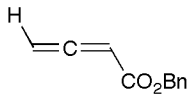
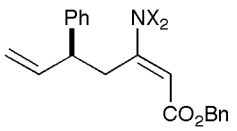
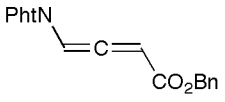
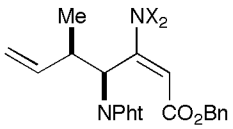
entry	amine	product[a]	yield	*syn*:*anti*[b,c]
1			95	>98:2
2			94	<2:98
3			97	94:6
4			81	> 98:2
5			80	--

[a]NX_2 = *N*-pyrrolidine, [b]Ratios determined by GLC or ^{1}H NMR analysis. [c]Relative configurations assigned by X-ray analysis.

Significant structural variation of the allenoate component is also well tolerated (Table 3). Substituents of disparate size and electronics (R_2 = H, allyl, iPr, Cl, and Ph, entries 1-6) may be incorporated in high yields (84-96%) and with high diastereoselectivities (≥93:7 *syn:anti*). Importantly, α-amino substitution can be achieved by employing a phthalimido-substituted allenic ester (entry 7, 75% yield, 91:9 *syn:anti*).

Table 3. Catalyzed allenoate–Claisen rearrangement between allyl pyrrolidines and representative allenic esters.



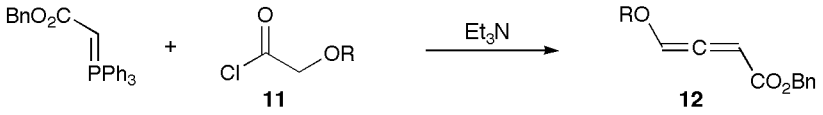
entry	R_1	allene	product[a]	yield	*syn*:*anti*[b,c]
1	Me			86	97:3
2	Ph			94	94:6
3	Ph			94	94:6
4	Ph			84	93:7
5	Ph			96	95:5
6	Ph			84	--
7	Me			75	91:9

[a]NX_2 = *N*-pyrrolidine. [b]Product ratios determined by GLC or ^1H NMR analysis. [c]Relative configurations assigned by X-ray analysis.

We were very mindful of the beneficial synthetic consequences that might be derived from the incorporation of oxygenation in an allenoate-Claisen product. This type of functionality, however, proved much more problematic to achieve. The primary

difficulty arose in the preparation of a β-oxy allenic ester **12**. Despite the suggestion of successful reaction by thin layer chromatography (TLC),[7] only complex mixtures of products were isolated when most β-oxy acid chlorides **11** were employed in the Lang and Hansen procedure (Table 4).[5] Indeed, only with the use of β-acetoxyacetyl chloride could any of the desired Claisen substrate be isolated in very low yield. It is not difficult to imagine several destructive pathways that an amphiphilic molecule such as **12** might follow.

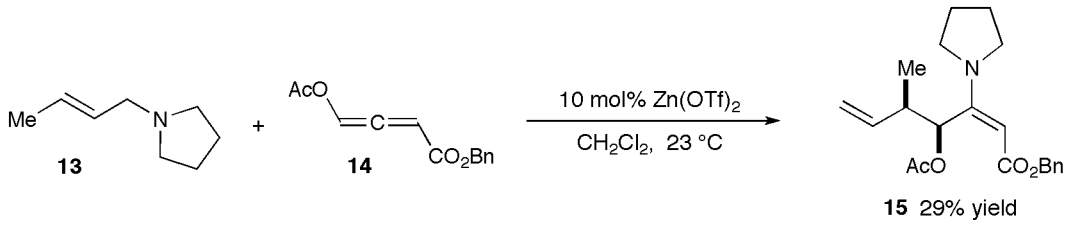
Table 4. Preparation of a β-oxy substituted allenic ester.



OR	% yield
OBn	--
OPh	--
OTBDPS	--
OPv	--
OAc	10

Although preparation of useful quantities of an oxygenated allenic ester was possible, the performance of this substrate in the allenoate-Claisen reaction proved problematic (Scheme 2). When allene **14** was added to a mixture of amine **13** and Lewis acid, TLC analysis indicated the presence of numerous species. Upon workup and purification, only a 29% yield of Claisen adduct **15** was obtained. It was hypothesized that Lewis acid mediated oligomerization of the allene was a significant contributing factor to the poor reaction efficiency, although syringe pump addition of the allene did not lead to any improvement in yield whatsoever.

Scheme 2. Allenoate-Claisen rearrangement of a β-oxy substituted allenic ester.

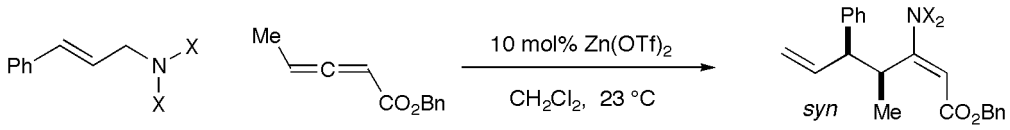


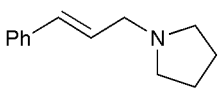
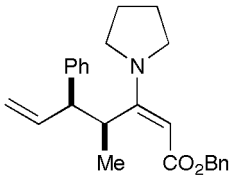
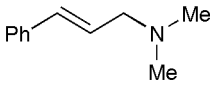
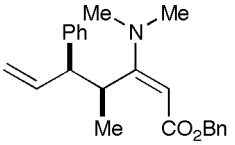
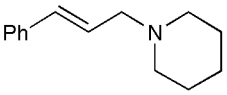
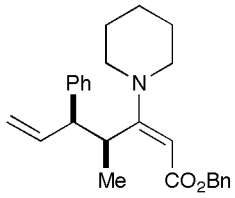
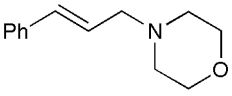
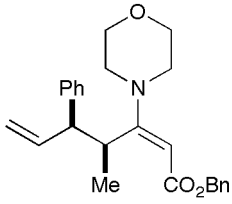
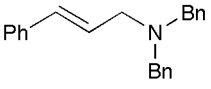
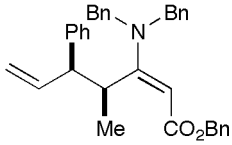
It seems apparent that the allenoate-Claisen rearrangement is not inherently unamenable to incorporation of oxygen substitution. Indeed, these results suggest that identification of a suitably stable oxyallene would readily facilitate this formulation. As evidence of this claim, one might note the successful reaction of the amino-substituted allene shown in entry 7 of Table 3. Although a similar instability of this heteroatom-substituted allene might be expected, incorporation of the nitrogen atom as an imide functionality reduces its electron donating ability to a sufficient extent that the desired reactivity is possible.

In addition to variation of the allyl moiety, it was found that alteration of the amine component was possible, although a significant correlation of substrate nucleophilicity to reaction efficiency was observed (Table 5). While pyrrolidino substitution seemed to be optimal both in terms of reaction rate and overall yield (entry 1), the dimethylamino substrate required a similar reaction time (entry 2). The yield in this case, however, was inexplicably reduced. The less nucleophilic cinnamyl piperidine was effective but required significantly longer reaction time (entry 3), while morpholino substitution reduced the nucleophilicity of the substrate to such an extent that higher catalyst loading (20 mol%) and much longer reaction time (48 h) was required to obtain

even a modest yield (entry 4). Dibenzyl cinnamyl amine provided no Claisen product whatsoever under the conditions screened (entry 5).

Table 5. Catalyzed allenoate-Claisen rearrangement between representative cinnamyl amines and benzyl 2,3-pentadienoate.

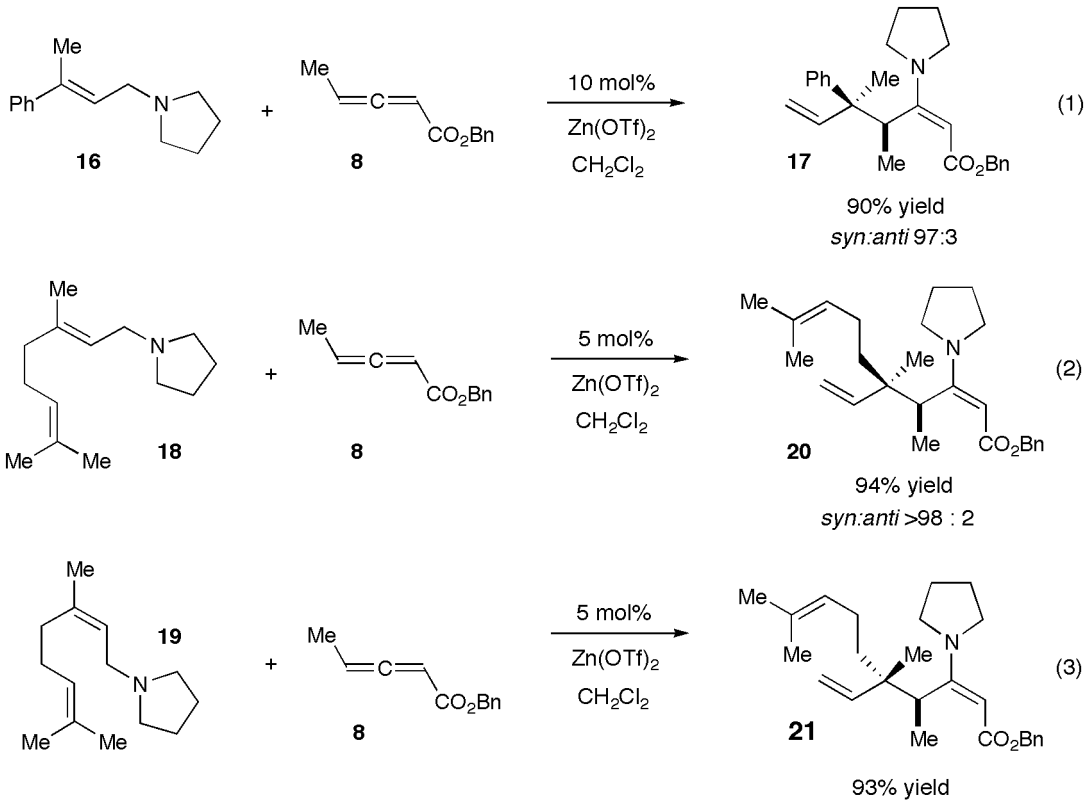


entry	amine	product	time (h)	yield	*syn*:*anti*[a,b]
1			2	97	94:6
2			2	81	94:6
3			12	87	94:6
4			48	55[c]	94:6
5			--	--	--

[a]Product ratios determined by ^{1}H NMR analysis. [b]Relative configurations assigned by X-ray analysis. [c]Reaction performed with 20 mol% Lewis acid.

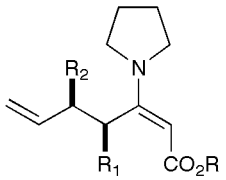
To further demonstrate the proficiency of the allenoate-Claisen reaction in generating complex stereochemical architecture, we examined the formation of quaternary carbon centers via the rearrangement of α-disubstituted allyl amines (Scheme 3).[8] Reaction of 3-methylcinnamyl pyrrolidine (**16**) with allenic ester **8** proceeded in the presence of 10 mol% Lewis acid to provide the Claisen adduct **17** in high yield and with high diastereocontrol (Eq. 1). Notably, this product incorporates a synthetically challenging benzylic quaternary carbon center.[9] Further, reaction of the same allene with isomeric substrates geranyl (**18**) and neryl pyrrolidine (**19**) in the presence only 5 mol% catalyst provided in high yield the Claisen adducts **20** and **21** in which the relative stereochemistry was completely dictated by the olefin geometry of the allylic amine substrates (eqs. 2 and 3). The complete differentiation of sterically similar substituents through transition state-controlled α-facial discrimination is noteworthy.

Scheme 3. Facile generation of quaternary carbon centers.

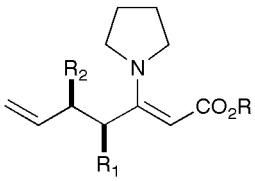


One subject that has thus far avoided note is that of enamine olefin geometry. Although depicted as *E*-isomers, allenoate-Claisen products are often isolated as a mixture of *E* (**22**) and *Z* (**23**) congeners (Table 6). Vinylogous carbamates are well-known to exist preferentially as *E*-isomers as a result of more efficient π-delocalization in this configuration.[10] Sufficient steric bulk at the β-position, however, can override this electronic preference to afford a mixture of products. As one can see from Table 6, the situation seems to be more complex than this, and apparently the product ratio is dependent on a number of steric and electronic factors.

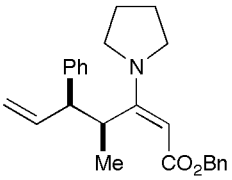
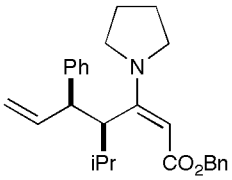
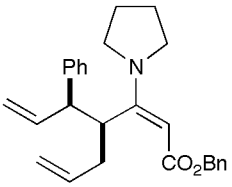
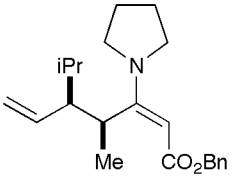
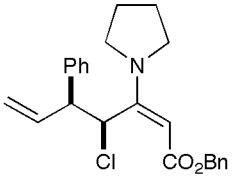
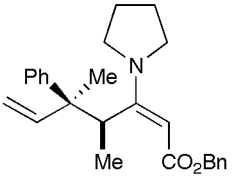
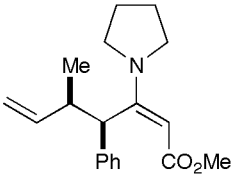
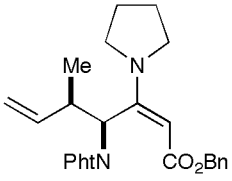
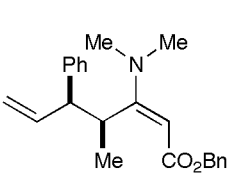
Table 6. Enamine olefin isomeric ratio of selected allenoate-Claisen products.[a]



E–adduct
22



Z–adduct
23

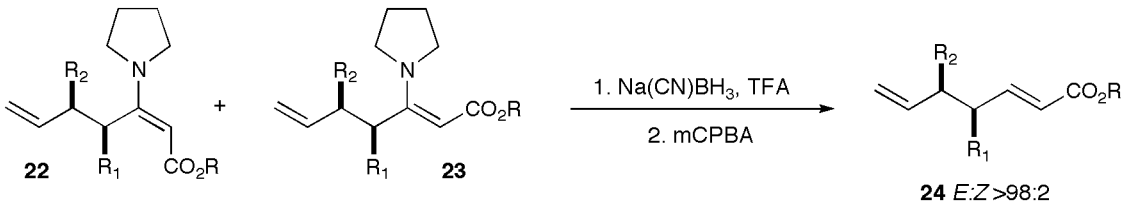
Adduct	*E*/*Z*	Adduct	*E*/*Z*	Adduct	*E*/*Z*
	3:1		7:1		2:1
	5:1		7:1		2:3
	10:1		1:1		6:1

a Product ratio was determined by ^{1}H NMR analysis.

Not surprisingly, the presence of two olefin isomers significantly complicates the determination of the diastereomeric ratio of the Claisen adducts. As such, we required a method to remove this complication. With some experimentation, it was found that hydrodeamination of the reaction products could be effected by a simple two-step procedure (Scheme 4).[3g]

First, selective reduction of the enamine moiety of both isomers **22** and **23** can be accomplished using standard reductive amination conditions [$Na(CN)BH_3$, TFA]. Then, treatment of the resulting amine with mCPBA results in *N*-oxidation and subsequent facile β-elimination to provide the α,β,γ,δ-unsaturated ester product **24** as a single *E*-olefin isomer. In addition to allowing for a straightforward determination of diastereoselection, this deamination procedure is unarguably a synthetically useful procedure in its own right, particularly when coupled with the allenoate-Claisen rearrangement.

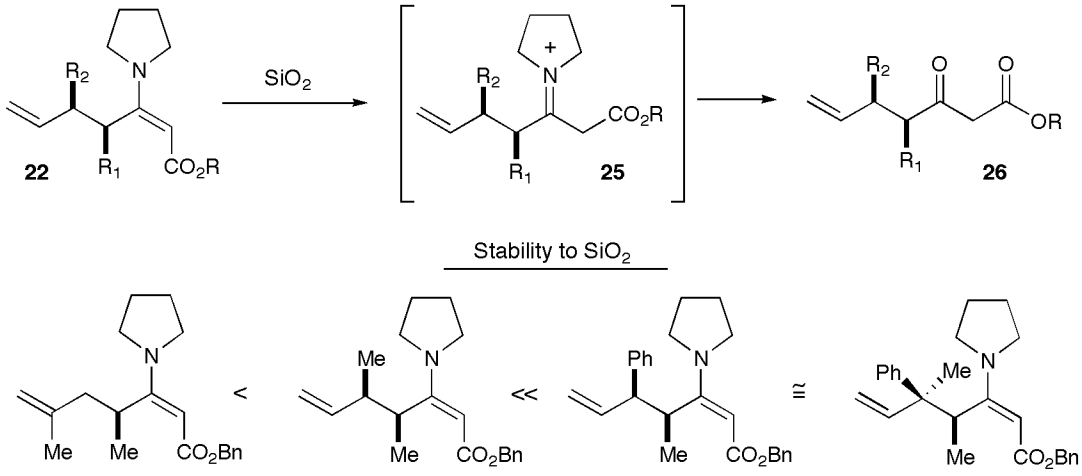
Scheme 4. Hydrodeamination of allenoate-Claisen products.



Another factor that served to complicate product isolation was the discovery that silica gel effects the hydrolysis of allenoate-Claisen products to the corresponding β-keto esters **26** (Scheme 5).[11] The susceptibility of substrates to this hydrolysis reaction was found to have a high correlation to the steric size of the α and β substituents. Thus adducts unsubstituted at either position undergo rapid hydrolysis upon exposure to silica

gel. Subtituents of modest size (i.e., methyl) at both positions render the Claisen substrate mildly susceptible to this reaction, while adducts that incorporate larger substitution patterns such as a phenyl ring at either position or a quaternary carbon center do not undergo any observable hydrolysis. Although β-ketoesters are highly valuable synthetic building blocks, this procedure provides a less than optimal means of access because extended exposure to silica gel results in α-epimerization of the ketoester products.

Scheme 5. Silica gel-promoted hydrolysis of allenoate-Claisen products.

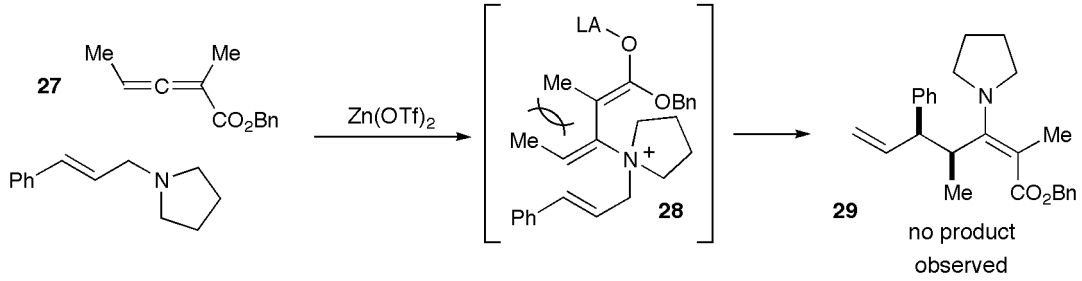


Limitations of the Methodology

Despite allowing for access to adducts bearing a wide scope of functionality, there are certain substitution patterns with which the allenoate-Claisen reaction has thus far not proven to be compatible. For example, attempted reaction of α-substituted allenic ester **27** resulted in no observed product **29** (Scheme 6). This result is easily rationalized by examination of the zwitterionic coupling intermediate **28**. If one assumes π-orbital alignment to be a requisite condition for carbanion-acceleration of the sigmatropic event,[13] one can readily see that Claisen rearrangement of intermediate **28** will be highly

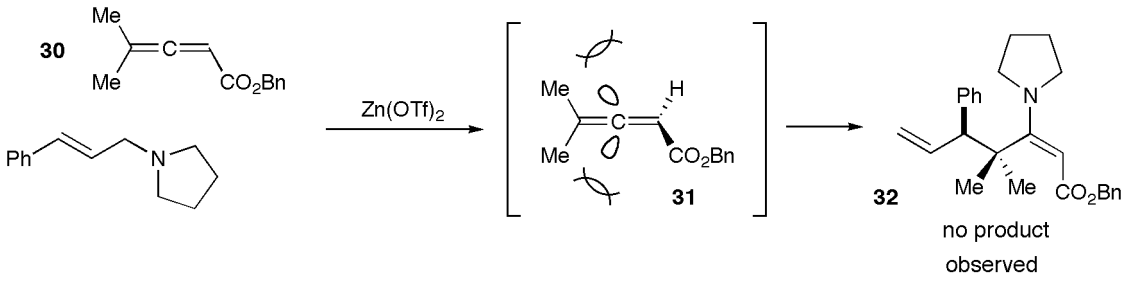
disfavored due to a severe $A^{1,3}$–interaction between the □-methyl group and the □-substituent (or between the □-methyl group and the quaternary ammonium moiety).

Scheme 6. Attempted allenoate-Claisen rearrangement of an □-substituted allenic ester.



Not surprisingly, □-disubstituted allenic ester **30** was also unreactive in the allenoate-Claisen reaction (Scheme 7). This lack of reactivity is attributed to steric blocking of both π* orbitals by the methyl groups (see structure **31**), thereby precluding amine addition.

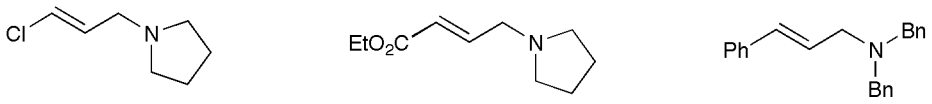
Scheme 7. Attempted Claisen rearrangement of a □-disubstituted allenic ester.



Finally, as alluded to previously, the allenoate-Claisen reaction displays a certain sensitivity to the nucleophilicity of the amine component (Figure 3). As such, allyl amines that possess highly electron-withdrawing substituents such as chloro or ester groups do not readily participate in this process. As mentioned, dibenzyl cinnamyl amine is also ineffective in the Claisen process, which is most readily attributed to the electron-withdrawing nature of the benzyl substituents. It is unclear to what extent these reactivity

issues might be overcome with the use of more forcing conditions such as catalyst variation, higher concentration, or heating.

Figure 3. Non-productive, weakly nucleophilic allylic amine components.



Concluding Remarks

We have developed a powerful new Lewis acid catalyzed variant of the Claisen rearrangement. This process employs simple allylic amines and allenic esters for the rapid generation of highly functionalized α-amino-β,γ,δ,ε-unsaturated-α,α-disubstituted ester products. Importantly, the allenoate-Claisen rearrangement allows for the stereoselective incorporation of a broad range of carbogenic and heteroatom substituents. Further, it has been found that relative product stereochemistry is strongly dictated by the geometric configuration of the allyl component. This protocol has proven to be particularly efficient for the production of quaternary carbon centers in a highly stereodefined manner. We feel confident that the operational simplicity and broad catalytic susceptibility of this chemistry provide a promising platform for the development of a highly enantioselective catalytic Claisen rearrangement.

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(1) Portions of the research described in this chapter have been published as a communcation: Lambert, T. H.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2002**, *124*, 13646.

(2) Yoon, T. P.; Dong, V. M.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **1999**, *121*, 9726.

(3) For some interesting examples, see: (a) Giuseppe, B.; Cimarelli, C.; Marcantoni, E.; Palmieri, G.; Petrini, M. *J. Org. Chem.* **1994**, *59*, 5328. (b) Schlessinger, R.; Lin, P.; Poss, M. *Heterocycles* **1987**, *25*, 315. (c) Corey, E. J.; Ueda, Y.; Ruden, R. A. *Tetrahedron Lett.* **1975**, 4347. (d) Michael, J. P.; Joseph, P.; Chang, S.-F.; Wilson, C. *Tetrahedron Lett.* **1993**, 8365. (e) Ishikawa, T.; Udeo, E.; Tani, R.; Sato, S. *J. Org. Chem.* **2001**, *66*, 186. (f) Ireland, R. E.; Brown, F. R. *J. Org. Chem.* **1980**, *45*, 1868. (g) Singaram, B.; Rangaishenvi, M. V.; Brown, H. C.; Goralski, C. T.; Hasha, D. L. *J. Org. Chem.* **1991**, *56*, 1543.

(4) Excess chloride ion is suspected to have a deleterious effect in the enantioselective acyl-Claisen protocols described in chapter 1.

(5) Lang, R. W.; Hansen, H.-J. *Org. Synth.* **1984**, *62*, 202.

(6) Wipf, P. In *Comprehensive Organic Synthesis*; Trost, B. M. and Flemming, I.; Eds.; Pergammon Press: Oxford, 1991; Vol. 5, Chapter 7.2.

(7) Allenic esters formed during the Lang/Hansen procedure typically appear as the sole high R_f spot by TLC as visualized by UV absorption and $KMnO_4$ stain.

(8) For excellent reviews on enantioselective quaternary carbon construction, see: (a) Corey, E. J.; Guzman-Perez, A. *Angew. Chem. Int. Ed.* **1998**, *37*, 388. (b) Christoffers, J.; Mann, A. *Angew. Chem. Int. Ed.* **2001**, *40*, 4700.

(9) For a discussion of the importance of benzylic stereogenicity, see: Paras, N. P.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2002**, *124*, 7894.

(10) For examples, see refs. 3a-g.

(11) See experimental details.

(12) For related Claisen rearrangements, see: (a) Denmark, S. E.; Harmata, M. A. *J. Am. Chem. Soc.* **1982**, *104*, 4972. (b) Denmark, S. E.; Harmata, M. A. *J. Org. Chem.* **1983**, *48*, 3369. (c) Denmark, S. E.; Harmata, M. A. *Tetrahedron Lett.* **1984**, *25*, 1543. (d) Denmark, S. E.; Harmata, M. A.; White, K. S. *J. Am. Chem. Soc.* **1989**, *111*, 8878.

Experimental Section

General Information. All reactions were performed using oven-dried glassware under an atmosphere of dry argon. Non-aqueous reagents were transferred under argon by syringe. Organic solutions were concentrated under reduced pressure using a Buchi rotary evaporator. Methylene chloride was distilled from CaH_2 or filtered through a column charged with Al_2O_3 (solvent purification system) immediately prior to use. Tetrahydrofuran and diethyl ether were distilled from sodium benzophenone ketyl immediately prior to use. Acid chlorides were distilled immediately prior to use. Allenic esters were prepared according to the procedure of Lang and Hansen.[1] All other commercial reagents were used as provided. Air sensitive solids were dispensed in an inert atmosphere glovebox. 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.[2] 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 $KMnO_4$ or p-anisaldehyde stain.

^1H and ^{13}C NMR were recorded on Mercury 300 (300 MHz and 75 MHz) as noted, and are internally referenced to residual protio solvent signals. Data for ^1H NMR are reported as follows: chemical shift (δ ppm), multiplicity (s = singlet, brs = broad 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 1600 Series spectrometer using NaCl salt plates, and reported in terms of frequency of absorption (cm^{-1}). Mass spectra were obtained

[1] Lang, R. W.; Hansen, H.-J. *Org. Syn* **1984**, *62*, 202.

from the UC Irvine Mass Spectral Facility. Gas chromatography was performed on Hewlett-Packard 6890 Series gas chromatograph equipped with split-mode capillary injection system and flame ionization detector using a C&C Column Technologies CC-1701 (30 m x 0.25 mm).

General Procedure A: The allylic amine and the allenic ester in CH_2Cl_2 were added sequentially to a 2 dram vial containing $Zn(OTf)_2$. The resulting solution was stirred until the allenic ester was completely consumed (0.25-24 h) as determined by TLC (20% EtOAc:hexanes). The solution was diluted with an equal volume of Et_2O and flushed through a short (8 x 30 mm) silica gel plug with an additional equal volume of Et_2O. The combined filtrates were concentrated and the resulting crude residue was purified by silica gel chromatography to afford the title compounds.

General Procedure B: The β-amino-α,β-unsaturated ester was taken up in 5% EtOAc:hexanes and silica gel was added. The resulting slurry was stirred until the starting material was completely consumed as determined by TLC (10% EtOAc:hexanes, p-anisaldehyde stain.) The slurry was filtered through a cotton plug and the silica gel was flushed with ether. The combined filtrates were concentrated to afford the pure β-keto esters products.

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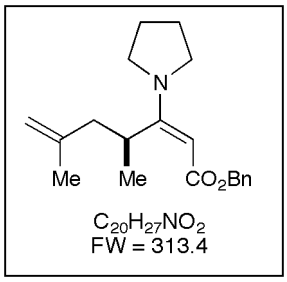
[2] Still, W. C.; Kahn, M.; Mitra, A. J. *J. Org. Chem.* **1978**, *43*, 2923.

General Procedure C: The β-amino-α,β-unsaturated esters were hydrodeaminated according to the procedure of Brown.[3] The β-amino-α,β-unsaturated ester (0.1 mmol) in THF (0.25 mL) was added to 9-BBN in a 2-dram vial, and the solution was stirred for 3h. Solvent was removed in vacuo and MeOH (0.5 mL) was added. The vial was heated briefly with a heat gun and then left at room temperature for 0.5h. Solvent was removed in vacuo and the resulting residue was dissolved in pentane (2 mL), washed with 1N HCl (0.5 mL) and H_2O (0.5 mL), dried (Na_2SO_4) and concentrated. The resulting residue was purified by silica gel chromatography to provide the α,β-unsaturated ester product.

General Procedure D: To the β-amino-α,β-unsaturated ester (0.2 mmol) in MeOH (3 mL) was added $NaCNBH_3$ (0.2 g, 3.2 mmol) followed by trifluoroacetic acid (0.3 mL). After 0.5 h the solution was basified to pH 12 with 1N NaOH, extracted with Et_2O (3 x 1 mL), dried (Na_2SO_4) and concentrated. The crude residue was taken up in THF (1 mL) and mCPBA (0.2 g, 1.2 mmol) was added. After 15 min the solution was diluted with Et_2O (2 mL) and washed with H_2O (3 x 1 mL), 20% $Na_2S_2O_3$ (1 mL), and 1N NaOH (2 mL), dried (Na_2SO_4) and concentrated. The crude residue was purified by silica gel chromatography to provide the α,β-unsaturated ester product.

Benzyl (*E*)-4,6-Dimethyl-3-pyrrolidinohepta-2,6-dienoate: Prepared according to general procedure A from methallyl pyrrolidine (144 mg, 1.14 mmol), benzyl penta-2,3-dienoate (108 mg, 0.58 mmol), and $Zn(OTf)_2$ (20 mg, 0.06 mmol). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.29-7.39 (m, 5H, Ar**H**), 5.08 (s, 2H, C**H**$_2$Ph), 4.73 (d, *J* = 1.5 Hz, 1H, C**H**$_2$=C),

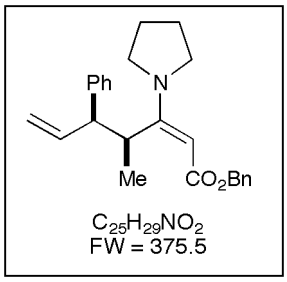
[3] Singaram, B.; Rangaishenvi, M. V.; Brown, H. C.; Goralski, C. T.; et al. *J. Org. Chem.* **1991**, *56*, 1543.



4.71 (s, 1H, C**H**$_2$=C), 4.48 (s, 1H, NC=C**H**), 3.34 (brs, 4H, N(C**H**$_2$CH$_2$)$_2$), 2.83 (brs, 1H, C**H**CH$_3$), 2.31 (brm, 2H, C(CH$_3$)C**H**$_2$), 1.88 (m, 4H, N(CH$_2$C**H**$_2$)$_2$), 1.77 (s, 3H, CH$_2$=CC**H**$_3$), 1.21 (brs, 3H, CHC**H**$_3$); LRMS (CI) *m/z* 313 (M)$^+$; HRMS (CI) exact mass calc'd for ($C_{20}H_{27}NO_2$) requires *m/z* 313.2042, found *m/z* 313.2037.

The yield was determined by enamine hydrolysis according to procedure B using 2 mL solvent and 0.8 g silica gel to provide the β-keto ester as a colorless oil in 80% yield (120 mg, 0.46 mmol). IR (thin film) 3072, 3034, 2972, 2936, 1746, 1714, 1649, 1623, 1456, 1376, 1310, 1262, 1225, 1154 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.34-7.36 (m, 5H, Ar**H**), 5.17 (s, 2, C**H**$_2$Ph), 4.78 (s, 1H C**H**$_2$=C), 4.68 (s, 1H C**H**$_2$=C), 3.54 (s, 2H, C(O)C**H**$_2$), 2.82 (dq, *J* = 7.2, 14.4, 1H, CH$_3$C**H**), 2.39 (dd, *J* = 6.0, 14.1 Hz, 1H, C(CH$_3$)C**H**$_2$), 2.00 (dd, *J* = 8.3, 14.3 Hz, 1H, C(CH$_3$)C**H**$_2$), 1.68 (s, 3H, CH$_2$=CC**H**$_3$), 1.08 (d, 3H, *J* = 7.2 Hz, CHC**H**$_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 205.8, 167.2, 142.5, 135.6, 128.8, 128.6, 128.5, 113.1, 67.3, 48.1, 44.8, 41.0, 22.5, 16.2; LRMS (CI) *m/z* 261 (MH)$^+$; HRMS (CI) exact mass calc'd for ($C_{16}H_{21}O_3$) requires *m/z* 261.1490, found *m/z* 261.1500.

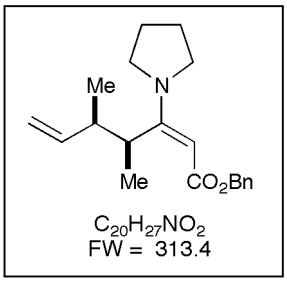
Benzyl (2*E*,4*R,5*S**)-4-Methyl-5-phenyl-3-pyrrolidinohepta-2,6-dienoate:** Prepared according to general procedure A from cinnamyl pyrrolidine (216 mg, 1.15 mmol), benzyl penta-2,3-dienoate (108 mg, 0.57 mmol), and Zn(OTf)$_2$ (20 mg, 0.06 mmol). The crude residue was purified by silica gel chromatography (10% EtOAc:hexanes) to afford the title compound as a light yellow oil in 97% yield (208 mg, 0.55 mmol), 94:6



syn:anti, 3:1 *E:Z*. *Syn, E* isomer: IR (thin film) 3062, 3029, 2972, 2873, 1676, 1560, 1455, 1400, 1345, 1128 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.29-7.43 (m, 10H, Ar**H**), 6.07 (ddd, *J* = 9.8, 9.8, 17.1, 1H, CH_2=C**H**), 5.44 (dq, *J* = 7.7, 11.6, 1H, C**H**CH_3), 5.19 (d, *J* = 12.6 Hz, 1H, C**H**$_2$Ph), 5.12 (d, *J* = 12.6 Hz, 1H, C**H**$_2$Ph), 4.90 (d, *J* = 7.8 Hz, 1H, C**H**$_2$=CH), 4.85 (s, 1H, C**H**$_2$=CH), 4.59 (s, 1H, NC=C**H**), 3.39-3.48 (m, 4H, N(C**H**$_2$$CH_2$)$_2$), 1.88-1.93 (m, 4H, N($CH_2$C**H**$_2$)$_2$), 1.01 (d, 3H, C**H**$_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.1, 167.3, 166.9, 165.4, 143.7, 141.5, 141.1, 138.0, 129.0, 128.8, 128.7, 128.6, 128.6, 128.3, 128.2, 128.1, 127.8, 127.7, 126.7, 126.5, 115.7, 114.0, 85.9, 84.1, 64.8, 64.7, 55.2, 51.1, 50.0, 49.6, 43.5, 37.1, 25.7, 25.6, 16.4, 15.1; LRMS (CI) *m/z* 375 $(M)^+$; HRMS (CI) exact mass calc'd for ($C_{25}H_{29}NO_2$) requires *m/z* 375.2198, found *m/z* 375.2199.

The diastereomer ratio was determined by derivitization of the product to benzyl (2*E*,4*R**,5*R**)-4-methyl-5-phenylhepta-2,6-dienoate according to general procedure C and analysis by ^1H NMR. ^1H NMR (300 MHz, $CDCl_3$) δ 7.15-7.39 (m, 10H, Ar**H**), 7.00 (dd, *J* = 8.2, 15.4 Hz, 1H, C**H**=$CHCO_2$), 5.90-6.01 (m, 1H, CH_2=C**H**), 5.86 (d, *J* = 15.4 Hz, 1H, CH=C**H**CO_2), 5.19 (s, 2H, C**H**$_2$Ph), 5.10 (d, *J* = 9.9 Hz, 1H, C**H**$_2$=CH), 5.01 (d, *J* = 17.6 Hz, 1H, C**H**$_2$=CH), 3.17 (dd, *J* = 8.2, 8.5 Hz, 1H, PhC**H**), 2.69 (dd, *J* = 6.6, 8.5 Hz, 1H, C**H**CH_3), 0.93 (d, *J* = 6.6 Hz, 3H, C**H**$_3$); LRMS (CI) *m/z* 307.2 $(MH)^+$; HRMS (CI) exact mass calc'd for ($C_{21}H_{23}O_2$) requires *m/z* 307.1698, found *m/z* 307.1695.

Benzyl (2*E*,4*R,5*S**)-4,5-Dimethyl-3-pyrrolidinohepta-2,6-dienoate:** Prepared according to general procedure A from (*E*)-crotyl pyrrolidine (144 mg, 1.14 mmol), benzyl penta-2,3-dienoate (108 mg, 0.58 mmol), and $Zn(OTf)_2$ (20 mg, 0.06 mmol) to



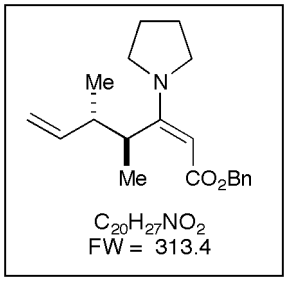
provide the crude enamine, >98:2 *syn:anti*. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.24-7.39 (m, 5H, Ar**H**), 5.67-5.76 (m, 1H, CH_2=C**H**), 5.11 (d, *J* = 12.9 Hz, 1H, C**H**$_2$Ph), 5.08 (d, *J* = 13.2 Hz, 1H, C**H**$_2$Ph), 4.74-4.94 (m, 3H, C**H**$_2$=CH and CC**H**CH_3), 4.47 (s, 1H, NC=C**H**), 3.31 (brs, 4H, N(C**H**$_2CH_2)_2$), 2.35 (m, 1H, CH_2=CHC**H**), 1.84 (brs, 4H, N(CH_2C**H**$_2)_2$), 1.22 (brs, 3H, CCHC**H**$_3$), 1.12 (d, *J* = 5.4 Hz, 3H, CH_2=CHCHC**H**$_3$); LRMS (CI) *m/z* 313 $(M)^+$; HRMS (CI) exact mass calc'd for ($C_{20}H_{27}NO_2$) requires *m/z* 313.2042, found *m/z* 313.2044.

The yield was determined by enamine hydrolysis according to procedure B using 3 mL solvent and 1.5 g silica gel to provide the beta keto ester as a colorless oil in 95% yield (142 mg, 0.55 mmol). IR (thin film) 3068, 3034, 2974, 1746, 1713, 1641, 1456, 1419, 1377, 1307, 1222, 1152 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.33-7.36 (m, 5H, Ar**H**), 5.71 (ddd, *J* = 7.1, 10.6, 16.9 Hz, 1H, CH_2=C**H**), 5.16 (s, 2H, C**H**$_2$Ph), 4.97-5.05 (m, 2H, C**H**$_2$=CH), 3.51 (s, 2H, C(O)C**H**$_2$), 2.44-2.65 (m, 2H, CH_2=CHC**H** and CC**H**CH_3), 1.04 (d, *J* = 7.1 Hz, 3H, CCHC**H**$_3$), 0.96 (d, *J* = 7.1 Hz, 3H, CH_2=CHCHC**H**$_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 205.7, 167.2, 141.5, 135.6, 128.8, 128.6, 128.5, 115.0, 67.3, 51.7, 49.0, 39.7, 16.0, 12.8; LRMS (CI) *m/z* 261 $(MH)^+$; HRMS (CI) exact mass calc'd for ($C_{16}H_{21}O_3$) requires *m/z* 261.1493, found *m/z* 261.1490.

The diastereomer ratio was determined by derivitization of the product to benzyl (2*E*,4*R**,5*R**)-4,5-dimethylhepta-2,6-dienoate according to general procedure C and analysis by ^{1}H NMR. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.33-7.39 (m, 5H, Ar**H**), 6.98 (dd, *J* = 7.8, 15.9 Hz, 1H, C**H**=$CHCO_2$), 5.84 (dd, *J* = 1.2, 15.9 Hz, 1H, CH=C**H**CO_2), 5.64-5.76 (m, 1H, CH_2=C**H**), 5.18 (s, 2H, C**H**$_2$Ph), 5.03 (s, 1H, C**H**$_2$=CH), 4.97-5.03 (m, 1H,

C**H**$_2$=CH), 2.18-2.37 (m, 2H, 2CH$_3$C**H**), 1.07 (d, *J* = 6.6 Hz, 3H, C**H**$_3$), 0.99 (d, *J* = 7.2 Hz, 3H, C**H**$_3$); ^{13}C NMR (75 MHz, $CDCl_3$) 166.7, 153.4, 141.4, 136.3, 128.7, 128.4, 128.4, 120.6, 114.9, 66.4, 42.7, 41.8, 17.2, 16.5; LRMS (CI) *m/z* 244.2 $(M)^+$; HRMS (CI) exact mass calc'd for ($C_{16}H_{20}O_2$) requires *m/z* 244.1463, found *m/z* 244.1469.

Benzyl (2E,4*R,5*R**)-4,5-Dimethyl-3-pyrrolidinohepta-2,6-dienoate:** Prepared



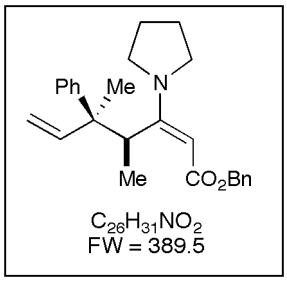
according to general procedure A from (*Z*)-crotyl pyrrolidine (144 mg, 1.14 mmol), benzyl penta-2,3-dienoate (108 mg, 0.58 mmol), and $Zn(OTf)_2$ (20 mg, 0.06 mmol) to provide the crude enamine, <2:98 *syn:anti*. ^{1}H NMR (300 MHz, $CDCl_3$) 7.25-7.39 (m, 5H, Ar**H**), 5.63-5.78 (m, 1H, CH_2=C**H**), 4.97-5.14 (m, 4H, C**H**$_2$Ph and C**H**$_2$=CH), 4.55 (s, 1H, NC=C**H**), 3.33-3.37 (m, 4H, N(C**H**$_2$CH$_2$)$_2$), 1.88 (brs, 4H, N(CH$_2$C**H**$_2$)$_2$), 1.15 (d, *J* = 7.2 Hz, 3H, CCHC**H**$_3$), 0.95 (d, *J* = 6.6 Hz, 3H, CH_2=CHCHC**H**$_3$); LRMS (CI) *m/z* 313 $(M)^+$; HRMS (CI) exact mass calc'd for ($C_{20}H_{27}NO_2$) requires *m/z* 313.2042, found *m/z* 313.2035.

The yield was determined by enamine hydrolysis according to procedure B using 3 mL solvent and 1.5 g silica gel to provide the beta keto ester as a colorless oil in 94% yield (140 mg, 0.54 mmol). IR (thin film) 3068, 3035, 2973, 1746, 1713, 1642, 1456, 1419, 1376, 1313, 1223, 1160 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) 7.34-7.38 (m, 5H, Ar**H**), 5.55-5.67 (m, 1H, CH_2=C**H**), 5.18 (s, 2H, C**H**$_2$Ph), 5.05 (d, *J* = 4.9 Hz, 1H, C**H**$_2$=CH), 5.00 (s, 1H, C**H**$_2$=CH), 3.53 (s, 2H, C(O)C**H**$_2$), 2.44-2.55 (m, 2H, CC**H**CH$_3$ and CH_2=CHC**H**CH$_3$), 1.04 (d, *J* = 6.6 Hz, 3H, CCHC**H**$_3$), 0.99 (d, *J* = 6.6 Hz, 3H, CH_2=CHCHC**H**$_3$); ^{13}C NMR (75 MHz, $CDCl_3$) 205.8, 167.1, 140.4, 135.6, 128.8, 128.6,

128.6, 115.7, 67.3, 51.9, 48.9, 40.5, 18.7, 14.2; LRMS (CI) *m/z* 260.2 $(M)^+$; HRMS (CI) exact mass calc'd for ($C_{16}H_{20}O_3$) requires *m/z* 260.1412, found *m/z* 260.1404.

The diastereomer ratio was determined by derivitization of the product to benzyl (2E,4*R**,5*S**)-4,5-dimethylhepta-2,6-dienoate according to general procedure C and analysis by ^{1}H NMR. ^{1}H NMR (300 MHz, $CDCl_3$) □ 7.33-7.39 (m, 5H, ArH), 6.94 (dd, *J* = 8.0, 15.7 Hz, 1H, C**H**=CHCO$_2$), 5.83 (d, *J* = 15.3 Hz, 1H, CH=C**H**CO$_2$), 5.61-5.73 (m, 1H, CH$_2$=C**H**), 5.18 (s, 2H, C**H**$_2$Ph), 5.02 (s, 1H, C**H**$_2$=CH), 4.97-4.99 (m, 1H, C**H**$_2$=CH), 2.12-2.28 (m, 2H, 2CH$_3$C**H**), 1.01 (d, *J* = 6.6 Hz, 3H, C**H**$_3$), 0.97 (d, *J* = 7.2 Hz, 3H, C**H**$_3$); LRMS (CI) *m/z* 245.2 $(MH)^+$; HRMS (CI) exact mass calc'd for ($C_{16}H_{21}O_2$) requires *m/z* 245.1541, found *m/z* 245.1544.

Benzyl (2*E/Z*,4*R,5*S**)-4,5-Dimethyl-5-phenyl-3-pyrrolidinohepta-2,6-dienoate:**

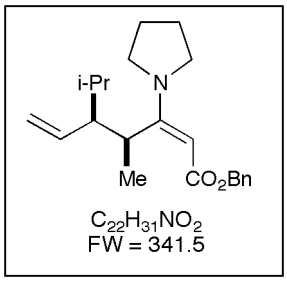


Prepared according to general procedure A from (*E*)-3-methyl cinnamyl pyrrolidine (69 mg, 0.34 mmol), benzyl penta-2,3-dienoate (54 mg, 0.29 mmol), and $Zn(OTf)_2$ (10 mg, 0.03 mmol). The crude residue was purified by silica gel chromatography (10% EtOAc:hexanes) to afford the title compound as a light yellow oil in 90% yield (100 mg, 0.26 mmol), 97:3 *syn:anti*, 40:60 *E:Z*. *Syn* isomer: IR (thin film) 3087, 3060, 3031, 2974, 2877, 1747, 1678, 1558, 1496, 1454, 1398, 1378, 1344, 1327, 1263, 1162, 1131, 1089, 1026, 919 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) □ 7.19-7.49 (m, 10H, Ar**H**), 6.41 (dd, *J* = 10.4, 16.5 Hz, 1H, CH$_2$=C**H,** *E* isomer), 6.32 (dd, *J* = 10.2, 16.8 Hz, 1H, CH$_2$=C**H** *Z* isomer), 5.50 (q, *J* = 7.7 Hz, 1H, C**H**CH$_3$ *E* isomer), 5.03-4.82 (m, 4H, C**H**$_2$Ph and C**H**$_2$=CH), 4.67 (s, 1H, NC=C**H** *E* isomer), 4.61 (s, 1H, NC=C**H** *Z* isomer),

3.44-3.52 (m, 2H, NC**H**$_2$ *Z* isomer), 3.12-3.24 (m, 3H, NC**H**$_2$ and C**H**CH$_3$ *Z* isomer), 2.96-3.03 (m, 2H, NC**H**$_2$ *E* isomer), 2.78-2.85 (m, 2H, NC**H**$_2$ *E* isomer), 1.59-1.81 (m, 4H, N(CH$_2$C**H**$_2$)$_2$) (*E* and *Z* isomer), 1.56 (s, 3H, CC**H**$_3$) (*E* isomer), 1.53 (s, 3H, CC**H**$_3$) (*Z* isomer), 1.14 (d, *J* = 7.7 Hz, 3H, CHC**H**$_3$) (*E* isomer), 0.97 (d, *J* = 7.1 Hz, 3H, CHC**H**$_3$ *Z* isomer); ^{13}C NMR (75 MHz, CDCl$_3$) □ 168.9, 166.0, 164.1, 163.5, 147.1, 145.9, 145.6, 144.5, 138.2, 138.0, 129.0, 128.8, 128.6, 128.6, 128.4, 128.3, 128.1, 128.1, 128.0, 127.8, 127.7, 127.7, 126.5, 126.2, 114.0. 112.8, 88.8, 84.9, 64.8, 64.7, 52.1, 50.5, 48.5, 48.4, 46.3, 40.5, 26.4, 25.8, 25.5, 25.1, 23.4, 22.0, 16.7, 14.5; LRMS (CI) *m*/*z* 388 (MH)$^+$; HRMS (CI) exact mass calc'd for (C$_{26}$H$_{30}$NO$_2$) requires *m*/*z* 388.2277, found *m*/*z* 388.2264.

The diastereomer ratio was determined by derivitization of the product to benzyl (2*E*,4*R**,5*R**)-4,5-dimethyl-5-phenylhepta-2,6-dienoate according to general procedure C and analysis by GLC with a CC-1701 column (100 °C, 20 °C/min gradient), t$_r$ 16.1 and 16.2 min. ^{1}H NMR (300 MHz, CDCl$_3$) □ 7.18-7.41 (m, 10H, Ar**H**), 7.01 (dd, *J* = 7.1, 15.9 Hz, 1H, C**H**=CHCO$_2$), 5.84 (d, *J* = 15.9 Hz, 1H, CH=C**H**CO$_2$), 5.19 (dd, *J* = 1.1, 11.0 Hz, 1H, C**H**$_2$=CH), 5.16 (s, 2H, C**H**$_2$Ph), 5.05 (d, *J* = 17.0 Hz, 1H, C**H**$_2$=CH), 2.90 (dq, *J* = 6.6, 7.1 Hz, 1H, C**H**CH$_3$), 1.38 (s, 3H, CC**H**$_3$), 0.91 (d, *J* = 6.6 Hz, 3H, CHC**H**$_3$); ^{13}C NMR (75 MHz, CDCl$_3$) □ 166.5, 152.2, 146.2, 144.4, 136.3, 128.7, 128.4, 128.3, 128.3, 126.9, 121.5, 114.3, 66.3, 47.7, 45.1, 21.4, 14.6; LRMS (CI) *m*/*z* 321.2 (MH)$^+$; HRMS (CI) exact mass calc'd for (C$_{22}$H$_{25}$O$_2$) requires *m*/*z* 321.1854, found *m*/*z* 321.1852.

Benzyl (2*E*,4*R,5*S**)-5-Isopropyl-4-methyl-3-pyrrolidinohepta-2,6-dienoate:** Prepared according to general procedure A from (*E*)-4-methyl-2-pentenyl pyrrolidine

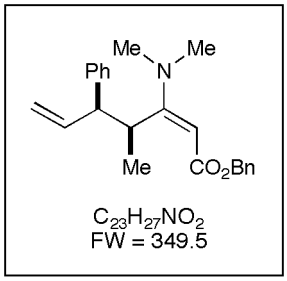


(176 mg, 1.15 mmol), benzyl penta-2,3-dienoate (108 mg, 0.57 mmol), and $Zn(OTf)_2$ (20 mg, 0.06 mmol) to provide the crude enamine as a yellow oil in 81% yield (159 mg, 0.47 mmol), >98:2 *syn:anti*, 5:1 *E:Z*. *Syn, E* isomer: IR (thin film) 3067, 3032, 2961, 2873, 1742, 1678, 1560, 1455, 1424, 1400, 1345, 1310, 1258, 1129, 1060, 1026 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.24-7.40 (m, 5H, Ar**H**), 5.60 (ddd, *J* = 10.2, 10.2, 17.3 Hz, 1H, CH_2=C**H**), 5.03-5.18 (m, 3H, CNC**H**CH_3 and C**H**$_2$Ph), 4.92 (dd, *J* = 2.2, 10.2 Hz, 1H, C**H**$_2$=CH), 4.79 (dd, *J* = 2.2, 17.0 Hz, 1H, C**H**$_2$=CH), 4.44 (s, 1H, NC=C**H**), 3.24-3.35 (m, 4H, N(C**H**$_2$)$_2$), 2.09 (ddd, *J* = 2.5, 10.7, 10.7 Hz, 1H, $(CH_3)_2$CHC**H**), 1.80-1.98 (m, 5H, $(CH_3)_2$C**H** and N(CH_2C**H**$_2$)$_2$), 1.22 (d, *J* = 7.1 Hz, 3H, CNCHC**H**$_3$), 0.94 (d, *J* = 7.1 Hz, 3H, (C**H**$_3$)$_2$CH), 0.89 (d, *J* = 6.6 Hz, 3H, (C**H**$_3$)$_2$CH); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.9, 166.6, 137.9, 128.5, 128.1, 115.5, 84.7, 64.5, 53.8, 49.7, 33.2, 28.6, 25.5, 22.5, 16.5, 16.4; LRMS (CI) *m/z* 342.2 $(MH)^+$; HRMS (CI) exact mass calc'd for ($C_{22}H_{33}NO_2$) requires *m/z* 342.2432, found *m/z* 342.2434.

The diastereomer ratio was determined by derivitization of the product to benzyl (2*E*,4*R**,5*R**)-5-isopropyl-4-methylhepta-2,6-dienoate according to general procedure C and analysis by ^1H NMR. ^1H NMR (300 MHz, $CDCl_3$) δ 7.29-7.40 (m, 5H, Ar**H**), 6.95 (dd, *J* = 8.4, 15.8 Hz, 1H, C**H**=CHCO_2), 5.83 (dd, *J* = 1.1, 15.6 Hz, 1H, CH=C**H**CO_2), 5.46 (ddd, *J* = 10.1, 10.1, 17.0 Hz, 1H, CH_2=C**H**), 5.18 (s, 2H, C**H**$_2$Ph), 5.09 (dd, *J* = 2.2, 10.1 Hz, 1H, C**H**$_2$=CH), 4.94 (dd, 2.2, 16.7 Hz, 1H, C**H**$_2$=CH), 2.53-2.64 (m, 1H, C**H**CH=CH), 1.62-1.74 (m, 2H, iPr-C**H** and C**H**$(CH_3)_2$), 1.02 (d, *J* = 7.0 Hz, 3H, C**H**$_3$), 0.92 (d, *J* = 6.1 Hz, 3H, C**H**$_3$), 0.82 (d, *J* = 6.6 Hz, 3H, C**H**$_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.7, 153.1, 137.5, 136.3, 128.7, 128.4, 128.3, 120.6, 117.8, 66.3, 57.1, 37.6, 28.9,

21.5, 20.2, 18.7; LRMS (CI) *m/z* 273.2 $(MH)^+$; HRMS (CI) exact mass calc'd for ($C_{18}H_{25}O_2$) requires *m/z* 273.1854, found *m/z* 273.1850.

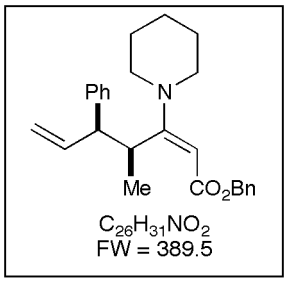
Benzyl (2*E*,4*R,5*S**)-3-Dimethylamino-4-methyl-5-phenylhepta-2,6-dienoate**:



Prepared according to general procedure A from (*E*)-cinnamyl-*N,N*-dimethylamine (185 mg, 1.15 mmol), benzyl penta-2,3-dienoate (108 mg, 0.57 mmol), and $Zn(OTf)_2$ (20 mg, 0.06 mmol). The crude residue was purified by silica gel chromatography (5% EtOAc:hexanes) to provide the title compound as white needles in 81% yield (162 mg, 0.46 mmol), 94:6 *syn:anti*, 6:1 *E:Z*. *Syn*, *E* isomer IR (thin film) 3063, 3029, 2971, 2936, 1678, 1569, 1494, 1454, 1397, 1372, 1316, 1130, 1041, 1024 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) □ 7.22-7.43 (m, 10H, Ar**H**), 6.03 (ddd, *J* = 9.4, 9.4, 17.7 Hz, 1H, CH_2=C**H**), 5.46 (dq, *J* = 7.0, 11.6 Hz, 1H, C**H**CH_3), 5.18 (d, *J* = 9.2 Hz, 1H, C**H**$_2$Ph), 5.13 (d, *J* = 9.2 Hz, 1H, C**H**$_2$Ph), 4.86-4.93 (m, 2H, C**H**$_2$=CH), 4.66 (s, 1H, NC=C**H**), 3.47 (dd, *J* = 10.3, 10.5 Hz, 1H, C**H**Ph), 3.00 (s, 6H, N(C**H**$_3$)$_2$), 1.02 (d, *J* = 7.5 Hz, 3H, CHC**H**$_3$); ^{13}C NMR (75 MHz, $CDCl_3$) □ 169.0, 167.9, 143.7, 141.5, 137.8, 129.0, 128.7, 128.3, 128.2, 127.9, 126.8, 114.1, 87.0, 64.9, 55.9, 41.9, 36.5, 16.8; LRMS (CI) *m/z* 350.2 $(MH)^+$; HRMS (CI) exact mass calc'd for ($C_{22}H_{28}NO_2$) requires *m/z* 350.2120, found *m/z* 350.2114.

The diastereomer ratio was determined by derivitization of the product to benzyl (2*E*,4*R**,5*S**)-4-methyl-5-phenylhepta-2,6-dienoate according to general procedure C and analysis by ^1H NMR.

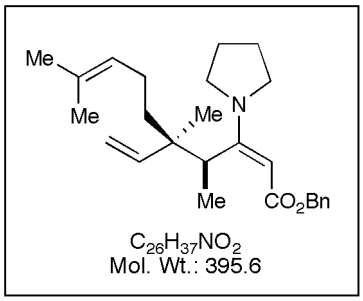
Benzyl (2*E*,4*R,5*S**)-3-Piperidino-4-methyl-5-phenylhepta-2,6-dienoate**: Prepared



according to general procedure A from (*E*)-cinnamyl piperidine (232 mg, 1.15 mmol), benzyl penta-2,3-dienoate (108 mg, 0.57 mmol), and $Zn(OTf)_2$ (20 mg, 0.06 mmol). The crude residue was purified by silica gel chromatography (5% EtOAc:hexanes) to provide the title compound as a yellow oil in 87% yield (194 mg, 0.50 mmol), 94:6 *syn:anti*, 6:1 *E:Z*. *Syn*, *E* isomer: IR (thin film) 3062, 3029, 2936, 2856, 1746, 1683, 1565, 1494, 1454, 1396, 1360, 1253, 1233, 1145, 1124, 1080, 1022 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) □ 7.18-7.45 (m, 10H, Ar**H**), 5.99-6.11 (m, 1H, CH_2=C**H**), 5.36 (brs, 1H, C**H**CH_3), 5.17 (s, 2H, C**H**$_2$Ph), 4.88-4.94 (m, 3H, C**H**$_2$=CH and NC=C**H**), 3.41-3.47 (m, 1H, PhC**H**), 3.29-3.31 (m, 4H, $N(CH_3)_2$), 1.64 (brs, 6H, piperdine), 1.01 (d, *J* = 7.5 Hz, 3H, C**H**$_3$); ^{13}C NMR (75 MHz, $CDCl_3$) □ 170.0, 166.5, 143.8, 141.6, 137.7, 128.9, 128.7, 128.4, 128.3, 127.9, 126.7, 114.5, 89.0, 65.0, 56.1, 49.9, 36.8, 27.5, 26.1, 24.7; LRMS (CI) *m/z* 390.2 $(MH)^+$; HRMS (CI) exact mass calc'd for ($C_{26}H_{31}NO_2$) requires *m/z* 389.2354, found *m/z* 390.2432.

The diastereomer ratio was determined by derivitization of the product to benzyl (2*E*,4*R**,5*R**)-4-methyl-5-phenylhepta-2,6-dienoate according to general procedure C and analysis by ^1H NMR.

Benzyl (2*E*,4*R,5*S**)-4,5,9-Trimethyl-3-pyrrolidinohepta-5-vinyldeca-2,8-dienoate:** Prepared according to general procedure A from geranyl pyrrolidine (178 mg, 0.86 mmol), benzyl penta-2,3-dienoate (108 mg, 0.57 mmol), and $Zn(OTf)_2$ (10 mg, 0.03 mmol). The crude residue was purified by silica gel chromatography (10%

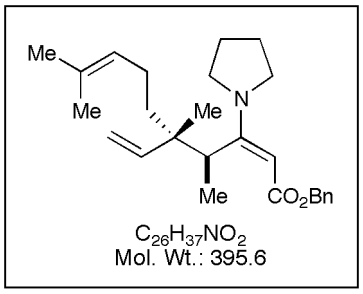


EtOAc:hexanes) to provide the title compound as a yellow oil in 94% yield (214 mg, 0.54 mmol), >98:2 *syn:anti*, 2:3 *E:Z*. *Syn* isomer: IR (thin film) 2971, 2876, 1681, 1561, 1454, 1414, 1397, 1378, 1345, 1320, 1263, 1161, 1129, 1093, 1026 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.25-7.40 (m, 5H, Ar**H**), 5.84 (dd, *J* = 11.0, 17.6, Hz, 1H, CH_2=C**H** *Z* isomer), 5.74 (dd, *J* = 11.0, 17.6 Hz, 1H, CH_2=C**H** *E* isomer), 4.91-5.17 (m, 6H, C**H**$_2$=CH, C**H**$_2$Ph, $(CH_3)_2$C=C**H** *E* and *Z* isomer; and C**H**CH_3 *Z* isomer), 4.63 (s, 1H, NC=C**H** *E* isomer), 4.57 (s, 1H, NC=C**H** *Z* isomer), 3.59-3.67 (m, 2H, N(C**H**$_3$)$_2$ *Z* isomer), 3.43-3.48 (m, 2H, N(C**H**$_3$)$_2$ *E* isomer), 3.24-3.29 (m, 2H, N(C**H**$_3$)$_2$ *Z* isomer), 3.10-3.18 (m, 2H, N(C**H**$_3$)$_2$ *E* isomer), 2.69 (q, *J* = 7.1 Hz, 1H, C**H**CH_3 *E* isomer), 1.74-1.95 (m, 6H, N(CH_2C**H**$_2$)$_2$ and CHC**H**$_2$ *E* and *Z* isomer), 1.67 (s, 3H, C**H**$_3$), 1.57 and 1.56 (s, 3H, C**H**$_3$), 1.37-1.49 (m, 2H, $CHCH_2$C**H**$_2$ *E* and *Z* isomer), 1.17 (d, *J* = 7.7 Hz, 3H, CHC**H**$_3$ *E* isomer), 1.12 (s, 3H, C**H**$_3$ *E* isomer), 1.05-1.07 (m, 6H, C**H**$_3$ *E* and *Z* isomer); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.8, 166.1, 164.9, 164.8, 144.9, 143.6, 138.2, 138.0, 131.5, 130.8, 128.6, 128.5, 128.0, 128.0, 127.7, 127.7, 125.6, 124.9, 113.8, 113.8, 88.4, 85.6, 64.7, 64.5, 52.3, 50.6, 45.0, 44.1, 44.0, 39.8, 39.2, 39.1, 26.1, 26.1, 26.0, 25.0, 23.7, 23.5, 20.9, 20.4, 18.1, 18.1, 16.3, 14.2; LRMS (CI) *m/z* 396.3 $(MH)^+$; HRMS (CI) exact mass calc'd for ($C_{26}H_{37}NO_2$) requires *m/z* 396.2902, found *m/z* 396.2899.

The diastereomer ratio was determined by derivitization of the product to benzyl (2*E*,4*R**,5*R**)-4,5,9-Trimethyl-5-vinyldeca-2,6-dienoate according to general procedure C and analysis by ^1H NMR. ^1H NMR (300 MHz, $CDCl_3$) δ 7.32-7.37 (m, 5H, Ar**H**), 7.01 (dd, *J* = 8.5, 15.6 Hz, 1H C**H**=$CHCO_2$), 5.83 (d, *J* = 15.4 Hz, 1H, CH=C**H**CO_2), 5.71 (dd,

J = 11.0, 17.6 Hz, 1H, CH_2=C**H**), 5.18 (s, 2H, C$\mathbf{H}_2$Ph), 5.04-5.13 (m, 2H, C$\mathbf{H}_2$=CH and $(CH_3)_2$=C**H**), 4.95 (d, *J* = 17.0 Hz, 1H, C$\mathbf{H}_2$=CH), 2.26 (dq, *J* = 7.1, 7.4 Hz, 1H, C**H**CH_3), 1.84-1.87 (m, 2H, C=CHC$\mathbf{H}_2$), 1.67 (s, 3H, C$\mathbf{H}_3$), 1.57 (s, 3H, C$\mathbf{H}_3$), 1.33 (t, *J* = 8.5 Hz, 2H, C=CHCH_2C$\mathbf{H}_2$), 1.00 and 0.97 (d and s, 6H, CHC$\mathbf{H}_3$ and CC$\mathbf{H}_3$); LRMS (CI) *m/z* 327.2 $(MH)^+$; HRMS (CI) exact mass calc'd for ($C_{22}H_{31}O_2$) requires *m/z* 327.2324, found *m/z* 327.2326.

Benzyl (2*E*,4*R,5*R**)-4,5,9-Trimethyl-3-pyrrolidinohepta-5-vinyldeca-2,8-dienoate:**

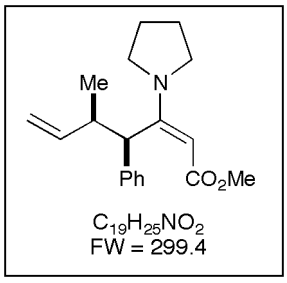


Prepared according to general procedure A from neryl pyrrolidine (178 mg, 0.86 mmol), benzyl penta-2,3-dienoate (108 mg, 0.57 mmol), and $Zn(OTf)_2$ (10 mg, 0.03 mmol). The crude residue was purified by silica gel chromatography (10% EtOAc:hexanes) to provide the title compound as a yellow oil in 93% yield (211 mg, 0.53 mmol), >98:2 *syn:anti*, 1:1. IR (thin film) 2970, 2876, 1680, 1560, 1455, 1413, 1398, 1376, 1344, 1319, 1264, 1161, 1130, 1091, 1026 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) 7.24-7.39 (m, 5H, Ar**H**), 5.95 (dd, *J* = 11.0, 17.6 Hz, 1H, CH_2=C**H**), 5.72 (dd, *J* = 11.0, 17.6 Hz, 1H, CH_2=C**H**), 4.91-5.19 (m, 6H, C$\mathbf{H}_2$=CH, C$\mathbf{H}_2$Ph, $(CH_3)_2$C=C**H** and C**H**CH_3), 4.61 (s, 1H, NC=C**H**), 4.59 (s, 1H, NC=C**H**), 3.09-3.62 (m, 4H, N(C$\mathbf{H}_3$)$_2$), 2.68 (q, *J* = 7.1 Hz, 1H, C**H**CH_3), 1.74-1.97 (m, 6H, N(CH_2C$\mathbf{H}_2$)$_2$ and CHC$\mathbf{H}_2$), 1.67 (s, 3H, C$\mathbf{H}_3$), 1.57 and 1.56 (s, 3H, C$\mathbf{H}_3$), 1.26-1.50 (m, 2H, $CHCH_2$C$\mathbf{H}_2$), 1.03-1.21 (m, 6H, 2C$\mathbf{H}_3$); ^{13}C NMR (75 MHz, $CDCl_3$) 168.8, 166.1, 165.2, 164.7, 145.4, 144.5, 138.3, 138.0, 131.4, 131.0, 128.5, 128.5, 128.1, 128.0, 127.7, 127.6, 125.3, 124.9, 114.3, 113.1, 87.5, 84.2, 64.6, 64.5, 52.3, 50.5, 45.2, 43.9,

42.8, 40.2, 40.1, 38.5, 26.1, 26.1, 26.0, 25.1, 23.3, 23.3, 19.9, 19.5, 18.1, 18.1, 16.3, 13.4; LRMS (CI) *m/z* 396.3 $(MH)^+$; HRMS (CI) exact mass calc'd for ($C_{26}H_{37}NO_2$) requires *m/z* 396.2902, found *m/z* 396.2901.

The diastereomer ratio was determined by derivitization of the product to benzyl (2*E*,4*R**,5*S**)-4,5,9-Trimethyl-5-vinyldeca-2,6-dienoate according to general procedure C and analysis by ^{1}H NMR. ^{1}H NMR (300 MHz, $CDCl_3$) □ 7.33-7.37 (m, 5H, Ar**H**), 6.98 (dd, *J* = 9.3, 15.9 Hz, 1H C**H**=CHCO$_2$), 5.85 (d, *J* = 15.9 Hz, 1H, CH=C**H**CO$_2$), 5.67 (dd, *J* = 11.0, 17.3 Hz, 1H, CH$_2$=C**H**), 5.18 (s, 2H, C**H**$_2$Ph), 5.12 (d, *J* = 11.0 Hz, 1H, C**H**$_2$=CH), 5.06 (t, *J* = 6.9 Hz, 1H, (CH$_3$)$_2$=C**H**), 4.95 (d, *J* = 17.6 Hz, 1H, C**H**$_2$=CH), 2.24 (dq, *J* = 7.1, 7.7 Hz, 1H, C**H**CH$_3$), 1.85 (dt, *J* = 7.4, 8.2 Hz, 2H, C=CHC**H**$_2$), 1.67 (s, 3H, C**H**$_3$), 1.57 (s, 3H, C**H**$_3$), 1.25-1.37 (m, 2H, C=CHCH$_2$C**H**$_2$), 0.97 and 0.95 (d and s, 6H, CHC**H**$_3$ and CC**H**$_3$); LRMS (CI) *m/z* 327.2 $(MH)^+$; HRMS (CI) exact mass calc'd for ($C_{22}H_{31}O_2$) requires *m/z* 327.2324, found *m/z* 327.2318.

Methyl (2*E*,4*R,5*R**)-4-Phenyl-5-methyl-3-pyrrolidinohepta-2,6-dienoate**: Prepared

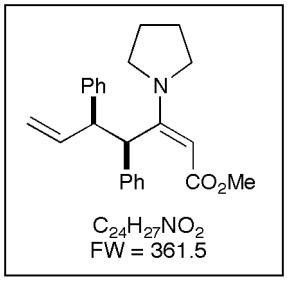


according to general procedure A from crotyl pyrrolidine (118 mg, 0.94 mmol), methyl 4-phenylbuta-2,3-dienoate (82 mg, 0.47 mmol), and Zn(OTf)$_2$ (17 mg, 0.05 mmol). The crude residue was purified by silica gel chromatography (5% EtOAc:hexanes) to afford the title compound as a crystalline solid in 86% yield (121 mg, 0.40 mmol), 97:3 *syn:anti*, 10:1 *E/Z*. *Syn*, *E* isomer: IR (thin film) 2973, 2869, 1675, 1561, 1496, 1449, 1422, 1385, 1345, 1281, 1141 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) □ 7.14-7.36 (m, 5H, ArH), 6.15 (brd, *J* = 9.9 Hz, 1H, CHPh), 5.85 (ddd 9.6, 9.6, 17.1 Hz, CH$_2$=CH), 4.96

(dd, J = 1.8, 17.1 Hz, 1H, CH_2=CH), 4.87 (dd, J = 2.0, 10.1 Hz, 1H, CH_2=CH), 4.57 (s, 1H, NC=CH), 3.67 (s, 3H, OCH_3), 2.90-3.21 (m, 5H, $CHCH_3$ and $N(CH_2CH_2)_2$), 1.61-1.71 (m, 4H, $N(CH_2CH_2)_2$), 1.28 (d, J = 6.3 Hz, 3H, $CHCH_3$); ^{13}C NMR (75 MHz, $CDCl_3$) □ 169.9, 164.0, 142.7, 139.4, 128.4, 128.4, 126.0, 112.8, 85.7, 50.4, 49.1, 47.0, 37.9, 25.3, 21.5; LRMS (CI) m/z 299 $(M)^+$; HRMS (CI) exact mass calc'd for ($C_{19}H_{25}NO_2$) requires m/z 299.1885, found m/z 299.1878.

The diastereomer ratio was determined by derivitization of the product to methyl (2*E*,4*R**,5*R**)-5-methyl-4-phenylhepta-2,6-dienoate according to general procedure C and analysis by ^{1}H NMR. ^{1}H NMR (300 MHz, $CDCl_3$) □ 7.10-7.35 (m, 6H, Ar**H** and C**H**=CHCO$_2$), 5.67-5.79 (m, 2H, CH=C**H**CO$_2$ and CH_2=C**H**), 5.07 (d, J = 5.5 Hz, 1H, C**H**$_2$=CH), 5.03 (s, 1H, C**H**$_2$=CH), 3.69 (s, 3H, $CO_2C\mathbf{H}_3$), 3.20 (t, J = 8.8 Hz, 1H, PhC**H**), 2.54-2.67 (m, 1H, CHC**H**$_3$), 0.89 (d, J = 6.6 Hz, 3H, CHC**H**$_3$); LRMS (CI) m/z 231.1 $(MH)^+$; HRMS (CI) exact mass calc'd for ($C_{15}H_{19}O_2$) requires m/z 231.1385, found m/z 231.1382.

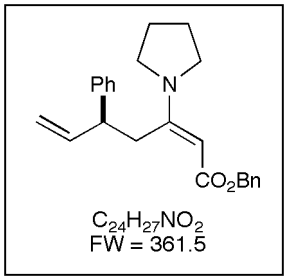
Methyl (2*E*,4*R,5*R**)-4,5-Diphenyl-3-pyrrolidinohepta-2,6-dienoate:** Prepared according to general procedure A from cinnamyl pyrrolidine (108 mg, 1.15 mmol), methyl 4-phenylbuta-2,3-dienoate (100 mg, 0.57 mmol), and $Zn(OTf)_2$ (20 mg, 0.06 mmol). The crude residue was purified by silica gel chromatography (5% EtOAc:hexanes) to afford the title compound as a colorless oil in 94% yield (196 mg, 0.54 mmol), 94:6 *syn:anti*. *Syn* isomer: IR (thin film) 2974, 2944, 1671, 1562, 1495, 1448, 1422, 1384, 1345, 1280, 1180, 1141 cm^{-1}; ^{1}H NMR (300 MHz,



$CDCl_3$) δ 7.02-7.59 (m, 11H, Ar**H** and NCC**H**Ph), 5.98 (ddd, *J* = 9.8, 9.8, 16.6 Hz, 1H, CH_2=C**H**), 4.95 (d, *J* = 17.1 Hz, 1H, C**H**$_2$=CH), 4.84 (dd, *J* = 1.2, 9.9 Hz, 1H, C**H**$_2$=CH), 4.72 (s, 1H, NC=C**H**), 4.14 (dd, *J* = 10.1, 10.0 Hz, 1H, CH_2=CHC**H**), 3.73 (s, 3H, OC**H**$_3$), 2.99-3.29 (m, 4H, N(CH_2C**H**$_2$)$_2$), 1.66-1.75 (m, 4H, N(CH_2C**H**$_2$)$_2$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.0, 163.1, 143.2, 141.7, 139.3, 129.1, 128.6, 128.2, 128.1, 126.6, 125.9, 113.1, 86.8, 51.2, 50.6, 49.3, 44.4, 25.4; LRMS (CI) *m/z* 361 $(M)^+$; HRMS (CI) exact mass calc'd for ($C_{24}H_{27}NO_2$) requires *m/z* 361.2042, found *m/z* 361.2041.

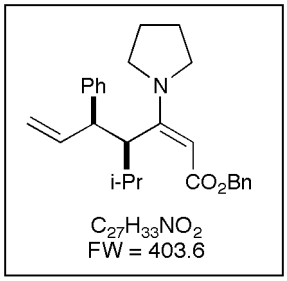
The diastereomer ratio was determined by derivitization of the product to methyl (2*E*,4*R**,5*R**)-4,5-diphenylhepta-2,6-dienoate according to general procedure C and analysis by ^{1}H NMR. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.02-7.28 (m, 11H, Ar**H** and C**H**=CHCO_2), 6.07 (ddd, *J* = 8.2, 10.4, 17.0 Hz, 1H, CH_2=C**H**), 5.82 (d, *J* = 15.9 Hz, 1H, CH=C**H**CO_2), 5.08-5.16 (m, 2H, C**H**$_2$=CH), 3.68-3.82 (m, 2H, 2C**H**Ph), 3.72 (s, 3H, C**H**$_3$); LRMS (CI) *m/z* 293.2 $(MH)^+$; HRMS (CI) exact mass calc'd for ($C_{20}H_{21}O_2$) requires *m/z* 293.1541, found *m/z* 293.1543.

(*E*)-Benzyl 5-Phenyl-3-Pyrrolidinohepta-2,6-dienoate: Prepared according to general procedure A from cinnamyl pyrrolidine (108 mg, 0.57 mmol), benzyl buta-2,3-dienoate (100 mg, 0.57 mmol), and $Zn(OTf)_2$ (10 mg, 0.03 mmol) to afford the title compound as a clear oil in 84% yield (174 mg, 0.48 mmol). The material was homogeneous by ^{1}H NMR and ^{13}C NMR analysis. IR (thin film) 3062, 3029, 2973, 2950, 2871, 1678, 1562, 1495, 1483, 1449, 1387, 1345, 1182, 1128, 1056, 1037, 916 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.18-7.42 (m, 10H, Ar**H**), 6.17 (ddd, *J* = 6.6,



10.4, 17.0, 1H, CH_2=C**H**), 5.09-5.18 (m, 4H, C**H**$_2$Ph, C**H**$_2$=CH), 4.58 (s, 1H, NC=C**H**), 3.76-3.80 (m, 2H, CHC**H**$_2$), 2.84-3.12 (brm, 5H, C**H**CH_2 and N(C**H**$_2CH_2)_2$), 1.73 (brs, 4H, N(CH_2C**H**$_2)_2$); ^{13}C NMR (75 MHz, $CDCl_3$) □ 168.3, 162.0, 143.6, 140.5, 138.1, 128.6, 128.5, 128.2, 128.2, 127.8, 126.7, 115,0, 84.0, 64.6, 49.2, 48.5, 36.5, 25.4; LRMS (CI) *m/z* 361 $(M)^+$; HRMS (CI) exact mass calc'd for ($C_{24}H_{27}NO_2$) requires *m/z* 361.2042, found *m/z* 361.2042.

B e n z y l (2*E*,4*R,5*S**)-4-Isopropyl-5-phenyl-3-pyrrolidinohepta-2,6-dienoate:**

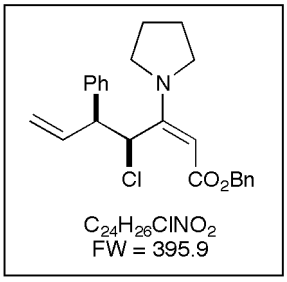


Prepared according to general procedure A from cinnamyl pyrrolidine (216 mg, 1.15 mmol), benzyl 5-methylhexa-2,3-dienoate (125 mg, 0.58 mmol), and $Zn(OTf)_2$ (20 mg, 0.06 mmol). The crude residue was purified by silica gel chromatography to afford the title compound as a yellow oil in 94% yield (219 mg, 0.54 mmol), 94:6 *syn/anti*, 7:1 *E/Z*. *Syn*, *E* isomer: IR (thin film) 3028, 2961, 2870, 1675, 1559, 1454, 1396, 1344, 1316, 1128, 1059, 1028 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) □ 7.14-7.52 (m, 10H, Ar**H**), 5.93 (ddd, *J* = 9.9, 9.9, 17.0 Hz, 1H, CH_2=C**H**), 5.31 (dd, *J* = 9.9, 9.9 Hz, 1H, C**H**$CH(CH_3)_2$), 5.21 (d, *J* = 12.6 Hz, 1H, C**H**$_2$Ph), 5.16 (d, *J* = 12.6 Hz, 1H, C**H**$_2$Ph), 4.85 (d, *J* = 17.0 Hz, 1H, C**H**$_2$=CH), 4.75 (dd, *J* = 1.4, 10.2 Hz, 1H C**H**$_2$=CH), 4.67 (s, 1H, NC=C**H**), 3.26-3.57 (m, 5H, PhC**H** and N(C**H**$_2)_2$), 1.80-2.01 (m, 5H, C**H**$(CH_3)_2$ and N($CH_2CH_2)_2$), 0.85 (d, *J* = 6.59 Hz, 3H, C**H**$_3$), 0.53 (d, *J* = 6.59 Hz, 3H, C**H**$_3$); ^{13}C NMR (75 MHz, $CDCl_3$) □ 169.2, 164.1, 146.0, 142.6, 138.0, 128.7, 128.6, 128.6, 128.2, 128.1, 127.8, 126.4, 112.1, 87.2, 64.7, 55.3,

50.1, 48.7, 31.7, 25.5, 23.9, 22.6; LRMS (CI) 404.3 $(MH)^+$; HRMS (CI) exact mass calc'd for ($C_{27}H_{34}NO_2$) requires *m/z* 404.2589, found *m/z* 404.2594.

The diastereomer ratio was determined by derivitization of the product to benzyl (2*E*,4*R**,5*R**)-4-isopropyl-5-phenylhepta-2,6-dienoate according to general procedure C and analysis by ^{1}H NMR. ^{1}H NMR (300 MHz, $CDCl_3$) □ 7.16-7.40 (m, 10H, Ar**H**), 6.88 (dd, *J* = 10.4, 15.4 Hz, 1H, C**H**=CHCO$_2$), 5.80-5.92 (m, 1H, CH$_2$=C**H**), 5.81 (d, *J* = 15.4 Hz, 1H, CH=C**H**CO$_2$), 5.20 (s, 2H, C**H**$_2$Ph), 5.00 (d, *J* = 4.4 Hz, 1H, C**H**$_2$=CH), 4.95 (d, *J* = 11.0 Hz, 1H, C**H**$_2$=CH), 3.44 (dd, *J* = 9.1, 9.1 Hz, 1H, C**H**Ph), 2.41 (ddd, *J* = 10.2, 4.1, 10.1 Hz, 1H, iPrC**H**), 1.54-1.64 (m, 1H, (CH$_3$)$_2$C**H**), 0.83 (d, *J* = 4.4 Hz, 3H, (C**H**$_3$)$_2$CH), 0.81 (d, *J* = 4.4 Hz, 3H, (C**H**$_3$)$_2$CH); LRMS (CI) 335.2 $(MH)^+$; HRMS (CI) exact mass calc'd for ($C_{23}H_{25}O_2$) requires *m/z* 335.2010, found *m/z* 335.2016.

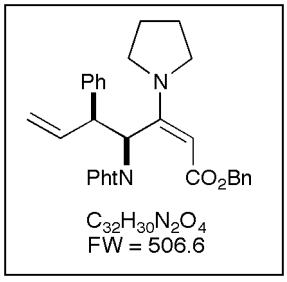
Benzyl (2*E*,4*S,5*S**)-4-Chloro-5-phenyl-3-pyrrolidinohepta-2,6-dienoate:** Prepared according to general procedure A from cinnamyl pyrrolidine (180 mg, 1.00 mmol), benzyl 4-chlorobuta-2,3-dienoate (100 mg, 0.48 mmol), and Zn(OTf)$_2$ (17 mg, 0.05 mmol). The crude residue was purified by silica gel chromatography to afford the title compound as a yellow oil in 84% yield (160 mg, 0.40 mmol), 93:7 *syn:anti*, 7:1 *E:Z*. *Syn*, *E* isomer: IR (thin film) 3503, 1670, 1570, 1456, 1395, 1345, 1133 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) □ 7.30-7.52 (m, 11H, Ar**H** and C**H**Cl), 6.02 (ddd, *J* = 9.1, 9.1, 17.6 Hz, 1H, CH$_2$=C**H**), 5.25 (d, *J* = 12.6 Hz, 1H, C**H**$_2$Ph), 5.19 (d, *J* = 12.0 Hz, 1H, C**H**$_2$Ph), 5.03 (d, *J* = 16.5 Hz, 1H, C**H**$_2$=CH), 5.02 (d, *J* = 9.9 Hz, 1H C**H**$_2$=CH), 4.71 (s, 1H, NC=C**H**), 3.92 (dd, *J* = 10.2, 10.2 Hz, 1H, PhC**H**), 3.72 (brs, 2H,



N(C**H**$_2$)$_2$), 3.41-3.44 (m, 2H, N(C**H**$_2$)$_2$, 1.90-1.97 (m, 4H, N(CH$_2$C**H**$_2$)$_2$); ^{13}C NMR (75 MHz, $CDCl_3$) □ 168.6, 157.4, 141.3, 138.1, 137.4, 129.1, 128.7, 128.3, 128.3, 128.1, 127.4, 116.6, 87.4, 65.3, 56.5, 56.1, 50.0, 25.6; LRMS (CI) 395.1 $(M)^+$; HRMS (CI) exact mass calc'd for ($C_{24}H_{24}ClNO_2$) $(M-H)^+$ requires *m/z* 394.1574, found *m/z* 394.1569.

The diastereomer ratio was determined by derivatization of the product to benzyl (2*E*,4*R**,5*S**)-4-chloro-5-phenylhepta-2,6-dienoate according to general procedure C and analysis by ^{1}H NMR. ^{1}H NMR (300 MHz, $CDCl_3$) □ 7.23-7.40 (m, 10H, Ar**H**), 7.00 (dd, *J* = 8.2, 15.4 Hz, 1H, C**H**=CHCO$_2$), 5.89-6.22 (m, 1H, CH$_2$=C**H**), 6.08 (d, ***J*** = 15.4 Hz, 1H, CH=C**H**CO$_2$), 5.09-5.25 (m, 2H, C**H**$_2$=CH), 5.21 (s, 2H, C**H**$_2$Ph), 4.73 (t, *J* = 7.7 Hz, 1H, C**H**Cl), 3.72 (t, *J* = 8.0 Hz, 1H, C**H**Ph). LRMS (CI) 327.0 $(MH)^+$; HRMS (CI) exact mass calc'd for ($C_{20}H_{20}ClO_2$) requires *m/z* 327.1152, found *m/z* 327.1148.

Benzyl (2*E*,4*S,5*S**)-5-Phenyl-4-phthalimido-3-pyrrolidinohepta-2,6-dienoate:**

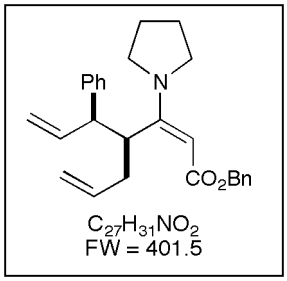


Prepared according to general procedure A from cinnamyl pyrrolidine (64 mg, 0.34 mmol), benzyl 4-phthalimidobuta-2,3-dienoate (91 mg, 0.28 mmol), and Zn(OTf)$_2$ (10 mg, 0.03 mmol). The crude residue was purified by silica gel chromatography (20% EtOAc:hexanes) to afford the title compound as a yellow solid in 75% yield (108 mg, 0.21 mmol) 91:9 *syn/anti*, 1:1 *E:Z.* The (*E*)-product isomer was recrystallized from EtOAc/hexanes. *Syn* isomer: IR (thin film) 3062, 3030, 2975, 2871, 1773, 1715, 1676, 1571, 1456, 1379, 1346, 1320, 1133 cm^{-1}; *E* isomer: ^{1}H NMR (300 MHz, $CDCl_3$) □ 7.93 (d, *J* = 11.5 Hz, 1H, C**H**N), 7.10-7.69 (m, 14H, Ar**H**), 6.04 (ddd, *J* = 9.3, 9.3, 16.9 Hz, 1H, CH$_2$=C**H**), 5.29 (s, 2H, C**H**$_2$Ph), 4.90-5.14 (m, 3H,

C**H**$_2$=CH and PhC**H**), 4.83 (s, 1H, NC=C**H**), 3.63-3.68 (m, 2H, N(C**H**$_2$)$_2$), 3.16-3.18 (m, 2H, N(C**H**$_2$)$_2$), 1.74-2.05 (m, 4H, N(CH$_2$C**H**$_2$)$_2$); ^{13}C NMR (75 MHz, $CDCl_3$) □ 168.7, 168.7, 168.3, 166.6, 158.5, 156.9, 141.6, 139.9, 139.5, 137.9, 137.7, 137.5, 134.5, 134.4, 134.1, 131.6, 131.4, 128.9, 128.8, 128.6, 128.5, 128.3, 128.2, 128.0, 127.8, 127.7, 127.2, 126.9, 123.4, 123.3, 118.4, 115.5, 89.2, 85.9, 65.2, 65.0, 56.3, 54.2, 52.4, 51.9, 50.1, 49.0, 26.2, 25.7. LRMS (CI) 506 $(M)^+$; HRMS (CI) exact mass calc'd for ($C_{32}H_{30}N_2O_4$) requires *m/z* 506.2206, found *m/z* 506.2206.

The diastereomer ratio was determined by derivitization of the product to benzyl (2*E*,4*R**,5*S**)-5-phenyl-4-phthalimidohepta-2,6-dienoate according to general procedure C and analysis by ^{1}H NMR. ^{1}H NMR (300 MHz, $CDCl_3$) □ 7.59-7.69 (m, 4H, phthalimide **H**), 7.28-7.42 (m, 6H, Ar**H** and C**H**=CHCO$_2$), 7.02-7.16 (m, 5H, Ar**H**), 5.91-6.03 (m, 2H, CH$_2$=C**H** and CH=C**H**CO$_2$), 5.15-5.26 (m, 5H, C**H**$_2$=CH and C**H**$_2$Ph and C**H**N), 4.38 (dd, *J* = 8.8, 11.5 Hz, 1H, C**H**Ph). LRMS (EI) 460.1 $(MNa)^+$; HRMS (EI) exact mass calc'd for ($C_{28}H_{23}NO_4Na$) requires *m/z* 460.1525, found *m/z* 460.1541.

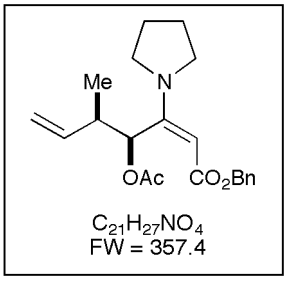
Benzyl (2*E*, 4*R, 5*S**)-4-Allyl-5-phenyl-3-pyrrolidinohepta-2,6-dienoate:** Prepared according to general procedure A from cinnamyl pyrrolidine (216 mg, 1.15 mmol), benzyl 2,3,6-heptatrienoate (122 mg, 0.58 mmol), and Zn(OTf)$_2$ (20 mg, 0.06 mmol). The crude residue was purified by silica gel chromatography (5% EtOAc:hexanes) to afford the title compound as a yellow oil in 96% yield (219 mg, 0.55 mmol), 95:5 *syn:anti*, 2:1 *E:Z*. *Syn* isomer: IR (thin film) 3064, 3029, 2974, 2869, 1676, 1561, 1493, 1483, 1454, 1400, 1345, 1128, 1081, 1067, 1039, 1027 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$)



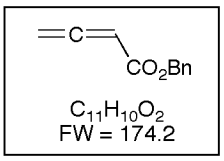
 7.17-7.49 (m, 10H, Ar**H**), 6.09 (ddd, *J* = 9.3, 10.0, 16.9 Hz, 1H, CH_2=C**H**CHPh, *E* isomer), 5.96 (ddd, *J* = 8.2, 10.4, 17.0 Hz, 1H, CH_2=C**H**CHPh**,** *Z* isomer), 5.56-5.69 (m, 2H, C**H**allyl and CH_2=C**H**CH_2), 5.19 (s, 2H, C$\mathbf{H}_2$Ph, *E* isomer), 5.17 (s, 2H, C$\mathbf{H}_2$Ph, *Z* isomer), 4.82-4.95 (m, 4H, C$\mathbf{H}_2$=CHCHPh and C$\mathbf{H}_2$=CHCH_2), 4.72 (s, 1H, NC=C**H**, *Z* isomer), 4.70 (s, 1H, NC=C**H**, *Z* isomer), 3.37-3.52 (m, 4H, N(C$\mathbf{H}_2)_2$), 3.07-3.13 (m, 1H, C**H**Ph), 2.09-2.28 (m, 2H, CH_2=CHC$\mathbf{H}_2$), 1.86-1.93 (m, 4H, N(CH_2C$\mathbf{H}_2)_2$; ^{13}C NMR (75 MHz, $CDCl_3$) 169.2, 167.3, 165.0, 162.9, 143.5, 143.2, 141.2, 140.8, 138.2, 138.0, 136.7, 136.7, 129.1, 129.0, 128.8, 128.7, 128.6, 128.3, 128.1, 128.0, 127.8, 127.7, 126.8, 126.6, 116.0, 115.9, 115.4, 114.1, 87.8, 84.4, 64.7, 64.7, 54.7, 50.8, 49.9, 49.8, 48.4, 42.5, 35.2, 34.4, 25.7, 25.6; LRMS (CI) 402.2 $(MH)^+$; HRMS (CI) exact mass calc'd for ($C_{27}H_{32}NO_2$) requires *m/z* 402.2433, found *m/z* 402.2428.

The diastereomer ratio was determined by derivitization of the product to benzyl (2*E*,4*S**,5*S**)-4-allyl-5-phenylhepta-2,6-dienoate according to general procedure C and analysis by ^{1}H NMR. ^{1}H NMR (300 MHz, $CDCl_3$) 7.19-7.41 (m, 10H, Ar**H**), 6.91 (dd, *J* = 9.3, 15.9 Hz, 1H, C**H**=C**H**CO_2), 5.96 (ddd, *J* = 8.8, 10.0, 17.1 Hz, 1H, CH_2=C**H**CHPh), 5.85 (d, *J* = 15.4 Hz, 1H, CH=C**H**CO_2), 5.61-5.75 (m, 1H, CH_2=C**H**CH_2), 5.21 (s, 2H, C$\mathbf{H}_2$Ph), 4.93-5.11 (m, 4H, 2C$\mathbf{H}_2$=CH), 3.37 (t, *J* = 8.5 Hz, 1H, C**H**Ph), 2.67 (ddd, *J* = 4.7, 8.8, 17.3 Hz, 1H, C**H**CH_2CH=CH_2), 1.98-2.23 (m, 2H, C$\mathbf{H}_2$CH=CH_2); LRMS (CI) 333.2 $(MH)^+$; HRMS (CI) exact mass calc'd for ($C_{23}H_{24}O_2$) requires *m/z* 333.1854, found *m/z* 333.1854.

Benzyl (4*S, 5*R**)-4-Acetoxy-5-methyl-3-pyrrolidinohepta-2,6-dienoate:** Prepared according to general procedure A from crotyl pyrrolidine (100 mg, 0.80 mmol), benzyl 4-acetoxybuta-2,3-dienoate (278 mg, 1.20 mmol), and $Zn(OTf)_2$ (29 mg, 0.08 mmol). The crude residue was purified by silica gel chromatography (10% EtOAc:hexanes) to afford the title compound as a yellow oil in 29% yield (83 mg, 0.23 mmol). IR (thin film) 1749, 1681, 1572, 1454, 1402, 1370, 1346, 1229, 1129, 1026 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.26-7.39 (m, 6H, Ar**H** and C**H**OAc), 5.71-5.83 (m, 1H, CH_2=C**H**), 5.10 (s, 2H, C**H**$_2$Ph), 4.91-4.98 (m, 2H, C**H**$_2$=CH), 4.57 (s, 1H, C**H**CO_2), 3.35 (brs, 4H, N(C**H**$_2$)$_2$), 2.04-2.10 (m, 1H, C**H**CH_3), 2.07 (s, 3H, C(O)C**H**$_3$), 1.81-1.93 (m, 4H, O(C**H**$_2$)$_2$), 1.15 (d, *J* = 6.6 Hz, 3H, CHC**H**$_3$); HRMS (FAB) $(MH)^+$ exact mass calc'd for ($C_{21}H_{28}NO_4$) requires *m/z* 358.2018, found *m/z* 358.2012.

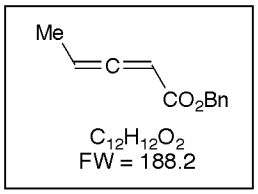


Benzyl Buta-2,3-dienoate: In a 500 mL round-bottomed flask, benzyl (triphenylphosphoranylidene)acetate (20.5 g, 50.0 mmol) was dissolved in CH_2Cl_2 (150 mL), and Et_3N (7.0 mL, 50 mmol) in CH_2Cl_2 (50 mL) was added over 5 min. Acetyl chloride (3.6 mL, 50 mmol) in CH_2Cl_2 (50 mL) was added over 15 min. After stirring for 1h at room temperature, the solvent was removed, and the remaining yellow slurry was triturated with Et_2O (400 mL) and filtered through a pad of Celite. The filtrate was concentrated, and the residue was purified by silica gel chromatography (7% EtOAc:hexanes) to afford the title compound as a clear colorless oil in 64% yield (5.6 g, 32 mmol.) IR (thin film) 3068, 3034, 2992,



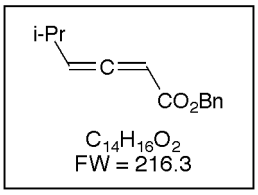
2956, 2893, 1970, 1941, 1720, 1259, 1155, 1082 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) 7.32-7.38 (m, 5H, Ar**H**), 5.69 (dt, *J* = 1.1, 6.6 Hz, 1H, C**H**CO_2), 5.25 (s, 1H, C**H**$_2$), 5.23 (s, 1H, C**H**$_2$), 5.20 (s, 2H, C**H**$_2$Ph); ^{13}C NMR (75 MHz, $CDCl_3$) 216.0, 165.7, 136.0, 128.7, 128.4, 128.3, 88.1, 79.8, 77.8, 76.9, 66.9; LRMS (CI) 173.1 $(M-H)^+$; HRMS (CI) exact mass calc'd for ($C_{11}H_9O_2$) $[M-H]^+$ requires *m/z* 173.0603, found *m/z* 173.0605.

Benzyl Penta-2,3-dienoate: Prepared according to the procedure given for the



preparation of benzyl buta-2,3-dienoate from benzyl (triphenylphosphoranylidene)acetate (13.0 g, 31.7 mmol), propionyl chloride (2.8 mL, 31.7 mmol), and Et_3N (4.4 mL, 31.7 mmol) to provide, after silica gel chromatography, the title compound as a clear, colorless oil in 43% yield (2.6 g, 13.7 mmol). IR (thin film) 3066, 3034, 2981, 2956, 2928, 1964, 1721, 1498, 1456, 1411, 1372, 1285, 1258, 1152, 1002 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) 7.32-7.38 (m, 5H, Ar**H**), 5.58-5.65 (m, 2H, C**H**=C=C**H**), 5.19 (s, 2H, C**H**$_2$Ph), 1.77-1.81 (m, 3H, C**H**$_3$); ^{13}C NMR (75 MHz, $CDCl_3$) 213.3, 166.1, 136.2, 128.8, 128.7, 128.4, 128.3, 90.7, 87.8, 66.7, 13.2; LRMS (CI) 189.1 $(MH)^+$; HRMS (CI) exact mass calc'd for ($C_{12}H_{11}O_2$) $(M-H)^+$ requires *m/z* 187.0759, found *m/z* 187.0752.

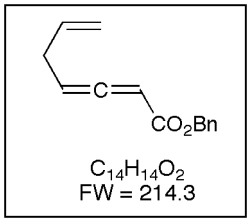
Benzyl 5-Methylhexa-2,3-dienoate: Prepared according to the procedure given for the



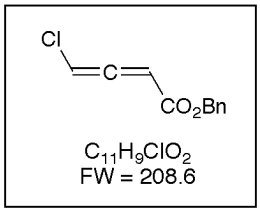
preparation of benzyl buta-2,3-dienoate from benzyl (triphenylphosphoranylidene)acetate (13.0 g, 31.7 mmol), isovaleryl chloride (3.9 mL, 31.7 mmol), and Et_3N (4.4 mL, 31.7 mmol) to provide, after silica gel chromatography, the title compound as a clear colorless

oil in 50% yield (3.5 g, 16.0 mmol). IR (thin film) 3034, 2963, 2872, 1958, 1722, 1498, 1456, 1414, 1383, 1320, 1251, 1150, 1003 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) 7.31-7.37 (m, 5H, Ar**H**), 5.63-5.69 (m, 2H, **H**C=C=C**H**), 5.22 (d, *J* = 12.6 Hz, 1H, C**H**$_2$), 5.14 (d, *J* = 12.6 Hz, 1H, C**H**$_2$), 2.42-2.54 (m, 1H, C**H**$(CH_3)_2$), 1.08 (d, *J* = 7.1 Hz, 6H, $(C\mathbf{H}_3)_2$); ; ^{13}C NMR (75 MHz, $CDCl_3$) 211.7, 166.2, 136.3, 128.7, 128.3, 128.2, 102.9, 89.4, 66.7, 28.1, 22.7, 22.6; LRMS (CI) 217.1 $(MH)^+$; HRMS (CI) exact mass calc'd for ($C_{14}H_{17}O_2$) requires *m/z* 217.1228, found *m/z* 217.1235.

Benzyl 2,3,6-heptatrienoate: Prepared according to the procedure given for the preparation of benzyl buta-2,3-dienoate from benzyl (triphenylphosphoranylidene)acetate (13.0 g, 31.7 mmol), 4-pentenoyl chloride (3.5 mL, 31.7 mmol), and Et_3N (4.4 mL, 31.7 mmol) to provide, after silica gel chromatography, the title compound as a clear colorless oil in 76% yield (5.1 g, 24.0 mmol). IR (thin film) 3034, 1961, 1721, 1640, 1498, 1456, 1419, 1374, 1259, 1151, 996 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) 7.31-7.38 (m, 5H, Ar**H**), 5.79-5.92 (m, 1H, CH_2=C**H**), 5.62-5.70 (m, 2H, C**H**=C=C**H**), 5.07-5.25 (m, 4H, C**H**$_2$Ph and C**H**$_2$=CH), 2.87-2.93 (m, 2H, CHC**H**$_2$); ^{13}C NMR (75 MHz, $CDCl_3$) 212.9, 165.9, 136.2, 134.9, 128.7, 128.4, 128.3, 116.8, 94.0, 88.8, 66.8, 32.0; LRMS (CI) 215.1 $(MH)^+$; HRMS (CI) exact mass calc'd for ($C_{14}H_{15}O_2$) requires *m/z* 215.1072, found *m/z* 215.1066.

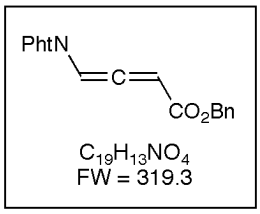


Benzyl 4-Chlorobuta-2,3-dienoate: Prepared according to the procedure given for the preparation of benzyl buta-2,3-dienoate from benzyl (triphenylphosphoranylidene)acetate



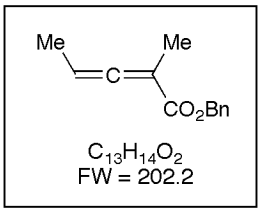
(5.0 g, 12.2 mmol), chloroacetyl chloride (1.0 mL, 12.2 mmol), and Et_3N (1.7 mL, 12.2 mmol). The crude residue was purified by silica gel chromatography (10% EtOAc:hexanes) to provide the title compound as a clear colorless oil in 32% yield (0.8 g, 4.0 mmol). IR (thin film) 3053, 1719, 1456, 1388, 1361, 1262, 1162 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) □ 7.34-7.40 (m, 5H, Ar**H**), 6.47 (d, *J* = 5.9 Hz, 1H, C**H**CO_2), 6.00 (d, *J* = 5.9 Hz, 1H, C**H**Cl), 5.25 (d, *J* = 12.6 Hz, 1H, C**H**$_2$Ph), 5.20 (d, *J* = 12.3 Hz, 1H, C**H**$_2$Ph); ^{13}C NMR (75 MHz, $CDCl_3$) □ 211.7, 163.3, 135.6, 128.8, 128.7, 128.5, 95.9, 93.3, 67.5. LRMS (CI) 209.3 $(MH)^+$; HRMS (CI) exact mass calc'd for ($C_{11}H_{10}ClO_2$) requires *m/z* 209.0369, found *m/z* 209.0366.

Benzyl 4-Phthalimidobuta-2,3-dienoate: Prepared according to the procedure given for the preparation of benzyl buta-2,3-dienoate from benzyl (triphenylphosphoranylidene)acetate (10.0 g, 24.4 mmol), phthalylglycyl chloride (5.5 g, 24.4 mmol), and Et_3N (3.4 mL, 24.4 mmol). The crude residue was purified by silica gel chromatography (35% EtOAc:hexanes) to provide the title compound as a yellow oil in 20% yield (1.6 g, 5.0 mmol). The compound was unstable and was used immediately after purification. IR (thin film) 3030, 2955, 1784, 1725, 1437, 1380, 1261, 1209, 1157 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) □ 7.85 (dd, *J* = 3.3, 5.5 Hz, 2H, NPhth**H**), 7.73 (dd, *J* = 3.3, 5.5 Hz, 2H, NPhth**H**), 7.29-7.38 (m, 6H, Ar**H** and C**H**CO_2), 6.30 (d, *J* = 6.0 Hz, 1H, C**H**CN), 5.24 (d, *J* = 12.6 Hz, 1H, C**H**$_2$Ph), 5.19 (d, *J* = 12.6 Hz, 1H, C**H**$_2$Ph); ^{13}C NMR



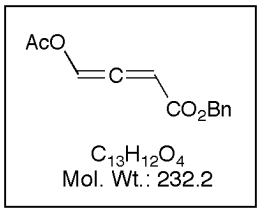
(75 MHz, $CDCl_3$) δ 210.4, 164.9, 164.1, 135.8, 134.9, 132.0, 128.7, 128.5, 128.4, 124.0, 97.2, 92.2, 67.3.

Benzyl 2,4-dimethylbuta-2,3-dienoate: Prepared according to the procedure given for



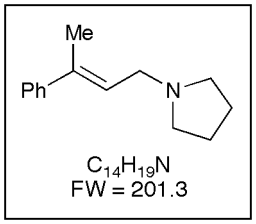
the preparation of benzyl buta-2,3-dienoate from benzyl 2-(triphenylphosphoranylidene)propionate (13.0 g, 23.5 mmol), propionyl chloride (2.2 g, 23.5 mmol), and Et_3N (6.6 mL, 47.0 mmol). The crude residue was purified by silica gel chromatography (5% EtOAc:hexanes) to provide the title compound as a colorless oil in 50% yield (2.36 g, 11.7 mmol). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.30-7.37 (m, 5H, Ar**H**), 5.40-5.50 (m, 1H, C=C**H**), 5.19 (s, 2H, C**H**$_2$Ph), 1.88 (d, *J* = 3.3 Hz, 3H, C**H**$_3$), 1.76 (d, *J* = 7.1 Hz, 3H, C**H**$_3$).

Benzyl 4-Acetoxybuta-2,3-dienoate: A solution of freshly distilled acetoxyacetyl



chloride in CH_2Cl_2 (1.2 M, 2.5 mL, 2.9 mmol) was added dropwise to a solution of benzyl (triphenylphosporanylidene)acetate (1.17 g, 2.9 mmol) and Et_3N (0.29 g, 2.9 mmol) in CH_2Cl_2 (11.5 mL) at 0 °C. After stirring for 30 min. hexanes (20 mL) was added and the mixture was filtered through a Celite plug. The filtrate was concentrated to an oily yellow solid. This crude material was triturated with hexanes (10 mL), filtered, and concentrated (three times) until only a clear, colorless oil remained. This material was unstable and was used without further purification (66 mg, 0.28 mmol, 10% yield).

(*E*)-3-Methyl Cinnamyl Pyrrolidine: (*E*)-3-phenyl-2-buten-1-ol was prepared using a modification of the procedure outlined by Corey and coworkers:[4] To a solution of copper(I)iodide (2.9 g, 15.4 mmol) and methyl lithium (23.0 mL of 1.3 M solution in Et_2O, 29.9 mmol) in Et_2O (10 mL) at 0 °C was added a solution of 3-iodo-3-phenyl-2-propen-1-ol (1.0 g, 3.8 mmol) in Et_2O (3 mL). The reaction mixture was stirred at 0 °C for 87 h and then washed with sat. aq. NH_4Cl (200 mL), dried (Na_2SO_4), and concentrated. The crude residue was purified by silica gel chromatography to provide (*E*)-3-phenyl-2-buten-1-ol in 69% yield (390 mg, 2.6 mmol). Spectroscopic data of this material were in complete agreement with reported literature values[5].



The allyl pyrrolidine was prepared using a modification of the procedure outlined by Froyen and coworkers.[6] To a solution of 3-phenyl-2-buten-1-ol (280 mg, 1.9 mmol) and PPh_3 (0.51 g, 1.9 mmol) in THF (3 mL) at 0 °C was added N-bromosuccinimide (0.35 g, 1.9 mmol) portionwise. After 15 min pyrrolidine (0.32 mL, 3.9 mL) was added at the reaction mixture was allowed to warm to room temperature. After 30 min 1N HCl (3 mL) was added and the layers were separated. The aqueous layer was extracted with Et_2O (3 x 2 mL) and then basified to pH = 10 with 1N NaOH (4 mL). The aqueous layer was extracted with Et_2O (3 x 2 mL) and the combined organic extracts were dried (Na_2SO_4) and concentrated. The crude residue was purified by silica gel chromatography to provide the title compound as a yellow oil in 53% yield (208 mg, 1.0 mmol). IR (thin film) 3082, 3057, 3030, 2966, 2874, 2780, 1599, 1494, 1458, 1445, 1376, 1348, 1315,

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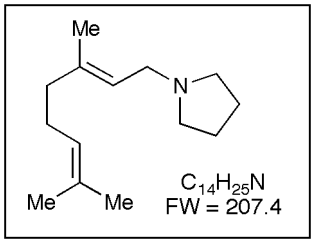
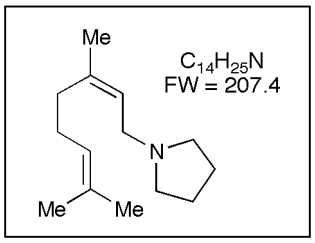
[4] Corey, E. J.; Chen, H. K. *Tetrahedron Lett.*, **1973**, *18*, 1611.
[5] Bussas, R.; Münsterer, H.; Kresze, G. *J. Org. Chem.*, **1983**, *48*, 2828.
[6] Froyen P.; Juvvik, P. *Tetrahedron Lett.* **1995**, *36*, 9555.

1290, 1276, 1242, 1200, 1140 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) □ 7.23-7.43 (m, 5H, Ar**H**), 5.97 (t, *J* = 7.4 Hz, 1H, C=C**H**), 3.30 (d, *J* = 6.6 Hz, 2H, CHC**H**$_2$), 2.56-2.61 (m, 4H, N(C**H**$_2$CH$_2$)$_2$), 2.08 (s, 3H, C**H**$_3$), 1.79-1.83 (m, 4H, N(CH$_2$C**H**$_2$)$_2$); ^{13}C NMR (75 MHz, $CDCl_3$) □ 143.6, 136.4, 128.4, 127.0, 125.9, 125.9, 54.5, 54.5, 23.9, 16.6; LRMS (CI) 201.2 $(M)^+$; HRMS (CI) exact mass calc'd for ($C_{14}H_{18}N$) $(M-H)^+$ requires *m/z* 200.1439, found *m/z* 200.1431.

Geranyl Pyrrolidine: Prepared from geraniol (4.3 mL, 25.0 mmol) according to the procedure outlined for the preparation of (*E*)-3-methyl cinnamyl pyrrolidine to provide the title compound as a yellow oil in 23% yield (1.2 g, 5.7 mmol). IR (thin film) 2967, 2927, 2778, 1445, 1377, 1348, 1140 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) □ 5.24 (t, *J* = 7.1, 1H, C**H**CH$_2$N), 5.01 (t, *J* = 6.0 Hz, 1H, (CH$_3$)$_2$C=C**H**), 2.99 (d, *J* = 7.1 Hz, 2H, CHC**H**$_2$N), 2.40-2.42 (m, 4H, N(C**H**$_2$CH$_2$)$_2$), 1.89-2.02 (m, 4H, CHC**H**$_2$C**H**$_2$), 1.69-1.71 (m, 4H, N(CH$_2$C**H**$_2$)$_2$), 1.59 (s, 3H, C**H**$_3$), 1.56 (s, 3H, C**H**$_3$), 1.51 (s, 3H, C**H**$_3$); ^{13}C NMR (75 MHz, $CDCl_3$) □ 137.4, 131.4, 124.3, 122.0, 54.2, 53.6, 40.0, 26.7, 26.0 23.7, 18.0, 16.6; LRMS (CI) 208.2 $(MH)^+$; HRMS (CI) exact mass calc'd for ($C_{14}H_{26}N$) requires *m/z* 208.2065, found *m/z* 208.2060.



Neryl Pyrrolidine: Prepared from nerol (4.5 mL, 25.0 mmol) according to the procedure outlined for the preparation of (*E*)-3-methyl cinnamyl pyrrolidine to provide the title compound as a yellow oil in 24% yield (1.3 g, 6.0 mmol). IR (thin film) 2966, 2928, 2778, 1447, 1377, 1344, 1140 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) □ 5.19-5.25 (m, 1H,



C**H**CH_2N), 5.00-5.04 (m, 1H, $(CH_3)_2$C=C**H**), 2.97 (d, *J* = 7.1 Hz, 2H, CHC**H**$_2$N), 2.38-2.42 (m, 4H, N(C**H**$_2CH_2)_2$), 1.97 (brs, 4H, N(CH_2C**H**$_2)_2$), 1.65-1.70 (m, 4H, CHC**H**$_2$C**H**$_2$), 1.62 (s, 3H, C**H**$_3$), 1.58 (s, 3H, C**H**$_3$), 1.51 (s, 3H, C**H**$_3$); ^{13}C NMR (75 MHz, $CDCl_3$) □ 137.4, 131.6, 124.2, 123.0, 54.3, 53.5, 32.4, 26.8, 26.0, 23.8, 23.7, 17.9; LRMS (CI) 208.2 $(MH)^+$; HRMS (CI) exact mass calc'd for ($C_{14}H_{26}N$) requires *m*/*z* 208.2065, found *m*/*z* 208.2061.

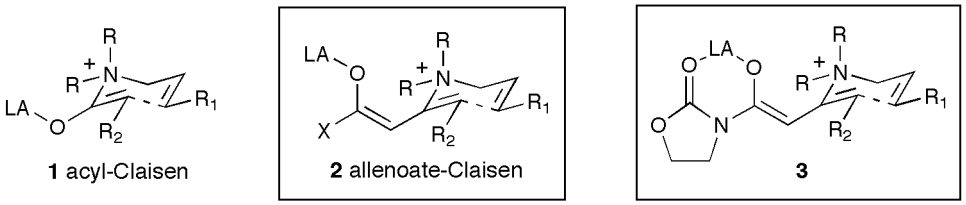
CHAPTER 3

Investigations of Enantioselective Catalysis of the Allenoate-Claisen Rearrangement

Reaction Design

In contemplating asymmetric catalysis of the allenoate-Claisen rearrangement, we recognized several unusual features of this protocol that we felt distinguished our endeavor from most other enantioselective catalytic investigations.[1] First, one readily recognizes that in the allenoate-Claisen transition state **2**, the Lewis acid binding site is significantly far removed from the sigmatropic event (Figure 1). As compared to the acyl-Claisen protocol (**1**), this binding point is further by two carbon atoms. Such an increase in distance obviously places significant demands on a chiral catalyst to impart asymmetry to the pro-stereogenic domain. Fortunately, however, variation of the allenic carbonyl component, particularly in regards to bidentate chelating moieties (for example **3**) should provide advantageous possibilities for organizational control.

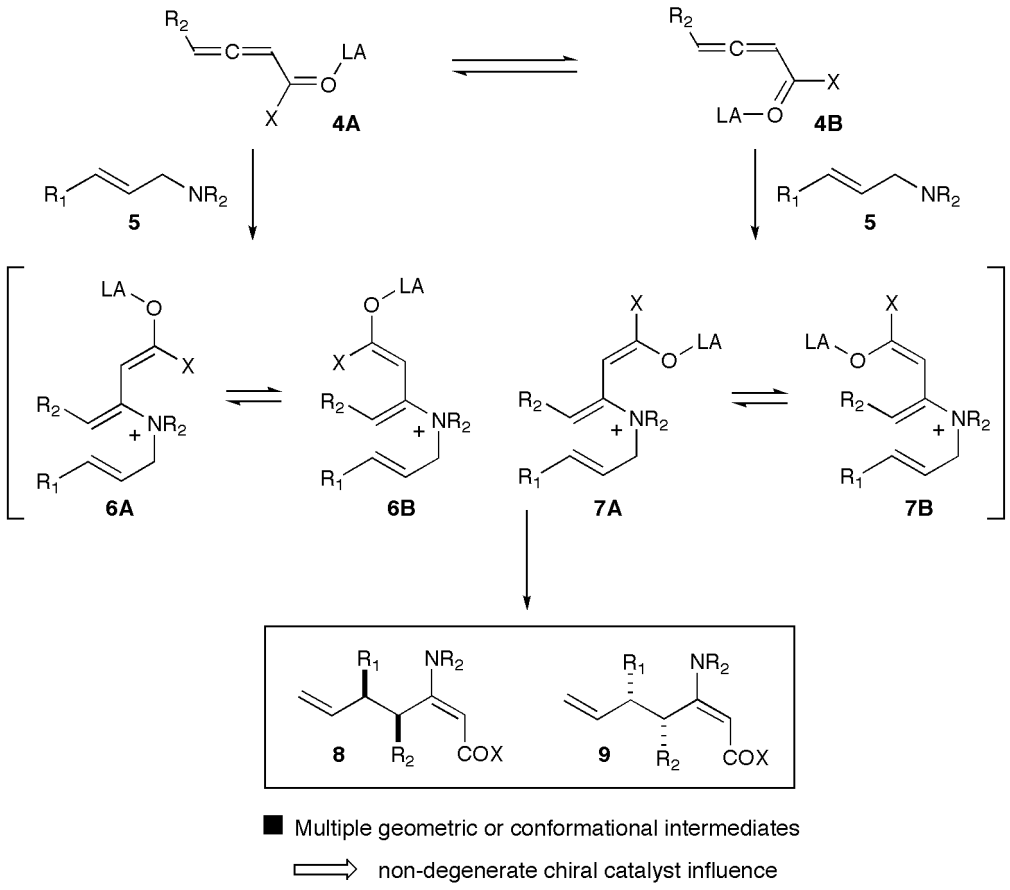
Figure 1. Lewis acid binding site considerations.



Second, we recognized that addition of allyl amine **5** to allene conformational isomers **4A** and **4B** could potentially result in either of two geometric enolate isomers **6**

and **7** (Figure 2). Further, each of these isomers could undergo Claisen rearrangement via either of two orbital-aligned conformational isomers **6A** and **6B** or **7A** and **7B**. Almost assuredly, the asymmetric influence of a chiral catalyst on these isomeric pairs would be nondegenerate. That is to say, these isomers would lead to opposite enantiomers **8** and **9**. Although it seems likely that one of the intermediate isomers will be favored, competitive rearrangement via an isomeric transition state could lead to significant degradation of reaction enantioselectivity.

Figure 2. Potential complication of conformational / geometric intermediate isomers.



Finally, we recognized that because we would be employing racemic allene starting material, the initial chiral Lewis acid-bound allenic substrate would be a diastereomeric complex (Figure 3). Although this should not have an effect on enantioselectivity since the cumulenic chirality is destroyed upon addition of the amine, conversion rates could be impacted if the diastereomeric complexes **10** and **11** react at significantly different rates.

Figure 3. Consequence of racemic allene.

■ Racemic allene results in diastereomeric chiral catalyst-bound substrates

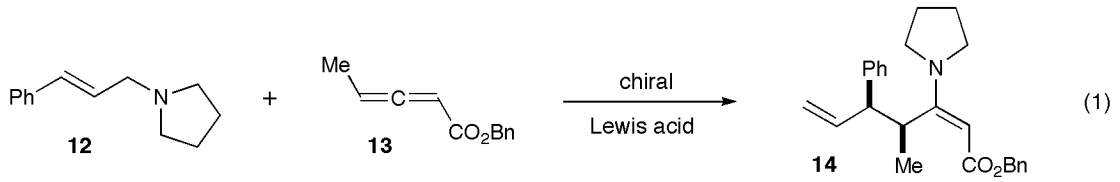
LA* = chiral Lewis acid

Despite these potentially complicating factors, we felt confident that an enantioselective catalytic allenoate-Claisen protocol could be devised.

Results and Discussion

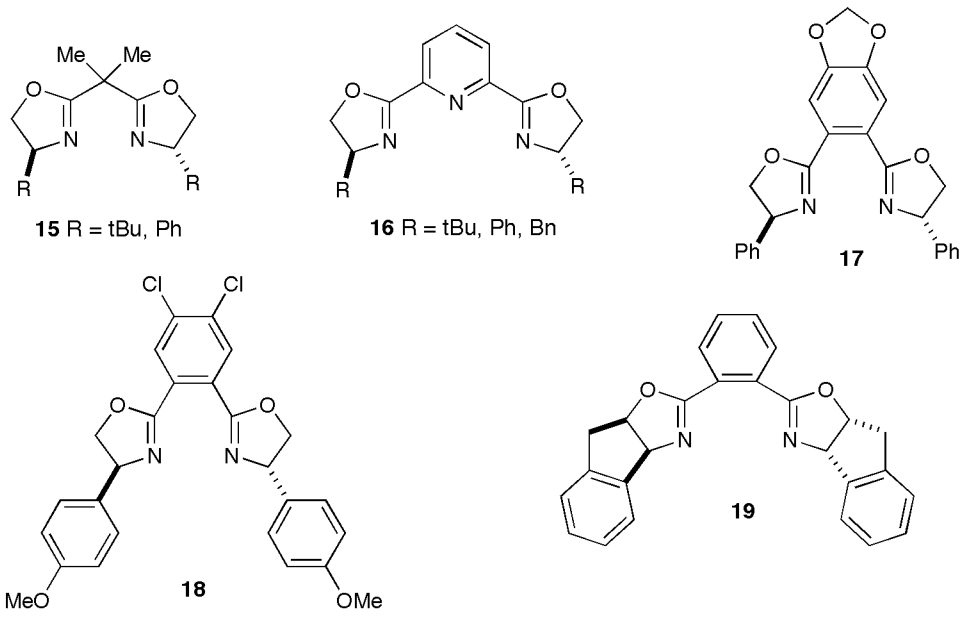
To begin our investigation, we chose for our catalyst screening the reaction of cinnamyl pyrrolidine (**12**) and benzyl 2,3-pentadienoate (**13**) (Scheme 1). This system was selected for its reasonable reaction rate and the high stability of Claisen product **14** towards silica gel hydrolysis.[2]

Scheme 1. System for initial enantioselective catalytic investigations.



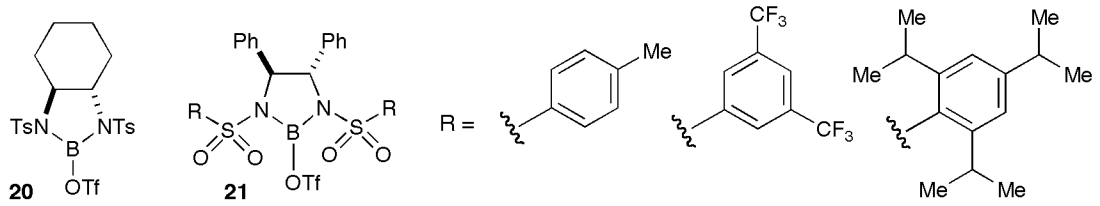
Our intitial studies involved a broad screen of chiral ligand and Lewis acid combinations. Notable among these were common bisoxazoline-based ligand systems such as Box (**15**) and PyBox (**16**) (Figure 4).[3] In addition, a number of arylBox systems (**17**, **18**, and **19**) such as those that were found to be effective for the enantioselective acyl-Claisen reaction were tested.[4] Regardless of the Lewis acid employed, none of these ligands provided an enantioselectivity for the reaction shown in Equation 1.

Figure 4. Bisoxazoline-based catalyst systems.



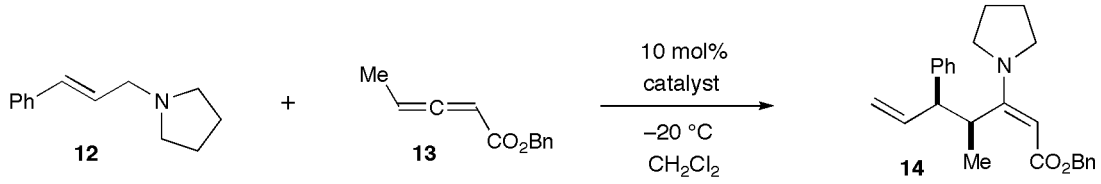
We also gave significant attention to the boron diamine catalyst systems (for example **20** and **21**) that were shown by Yoon in our laboratories to catalyze the acyl-Claisen rearrangement of non-bidentate chelating substrates (Figure 5).[5] Despite significant variation is steric size of these catalyst systems, in no case was any enantioselection observed.

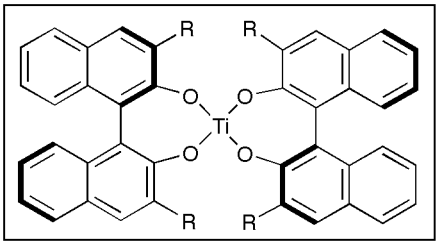
Figure 5. Boron diamine catalyst systems.



Our first enantioselective result came with the use of binaphthol (BINOL) based titanium catalysts (Table 1).[6,7] While the parent catalyst system, Ti(BINOL)$_2$ **22**, provided only barely detecTable enantioselectivity (entry 1, 9% ee), 3-phenyl Ti(BINOL)$_2$ **23** gave rise to product with significant enantioselectivity (entry 2, 25% ee). We hypothesized that substitution of the 3 position of the BINOL framework was required due to the large spatial separation of the catalyst binding site and the sigmatropic event. As such we anticipated that substituents that could provide further extension might have a greater impact on reaction selectivity. To test this theory, we employed 3-biphenyl Ti(BINOL)$_2$ **24** but, unfortunately, found no increase in enantioselectivity (entry 3, 19% ee).

Table 1. First enantioselective results using titanium BINOL catalysts.





entry	catalyst	%ee
1	$Ti(BINOL)_2$ **22** R = H	9
2	$Ti(3\text{-}PhBINOL)_2$ **23** R = Ph	25
3	$Ti(3\text{-}BiPhBINOL)_2$ **24** R = 4-biphenyl	19

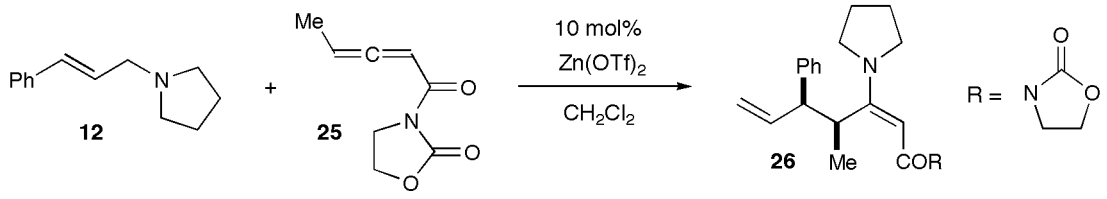
Although we were encouraged by this first enantioselective result, we were also wary of attempting to optimize a system of low enantiomeric excess with such a narrow catalyst requirement. As such, we decided to investigate the use of a bidentate chelating substrate.[8]

Bidentate Chelating Allene

It has been thoroughly established in the field of enantioselective catalysis that substrates that are capable of binding at two points to a metal center (bidentate) provide greatly enhanced organizational control over those that bind in a monodentate fashion. As such, substrates are often designed to incorporate an auxiliary capable of offering this two-point binding. We felt this strategy could be advantageous for the allenoate-Claisen reaction.

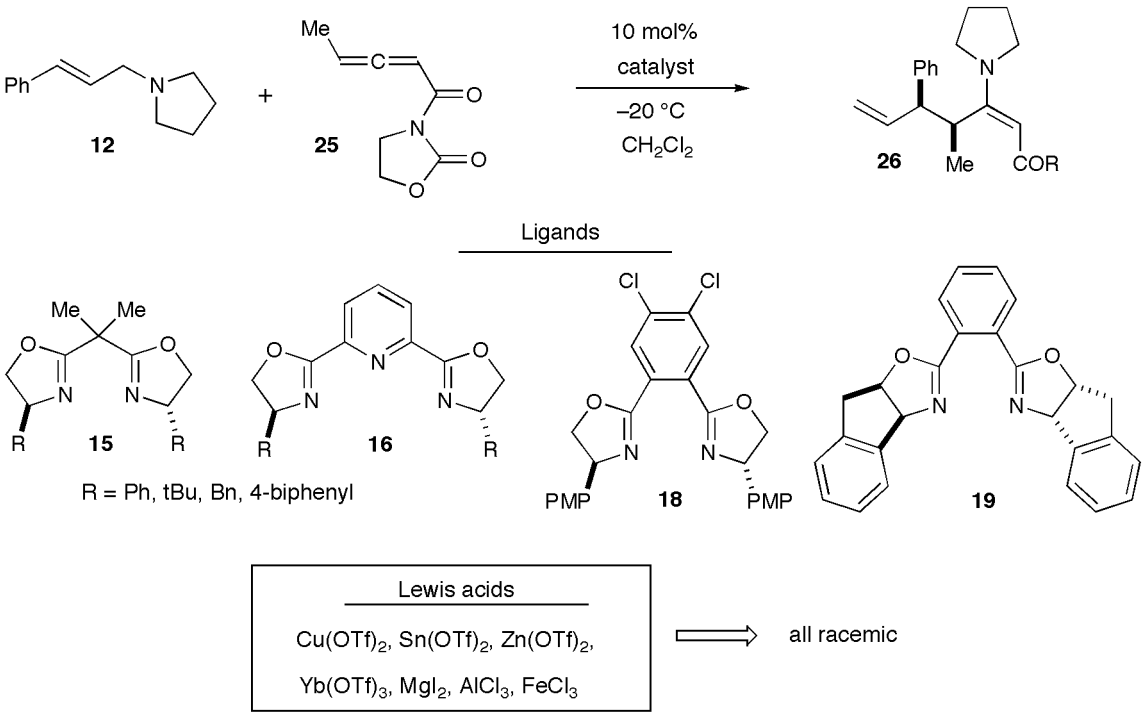
In this context we were pleased to find that the allenic oxazolidinone substrate **25** participated readily in the allenoate-Claisen process, providing Claisen adduct **26** in 76% yield with only 10 mol% $Zn(OTf)_2$ catalyst (Scheme 2).

Scheme 2. Allenoate-Claisen rearrangement of a bidentate chelating substrate.



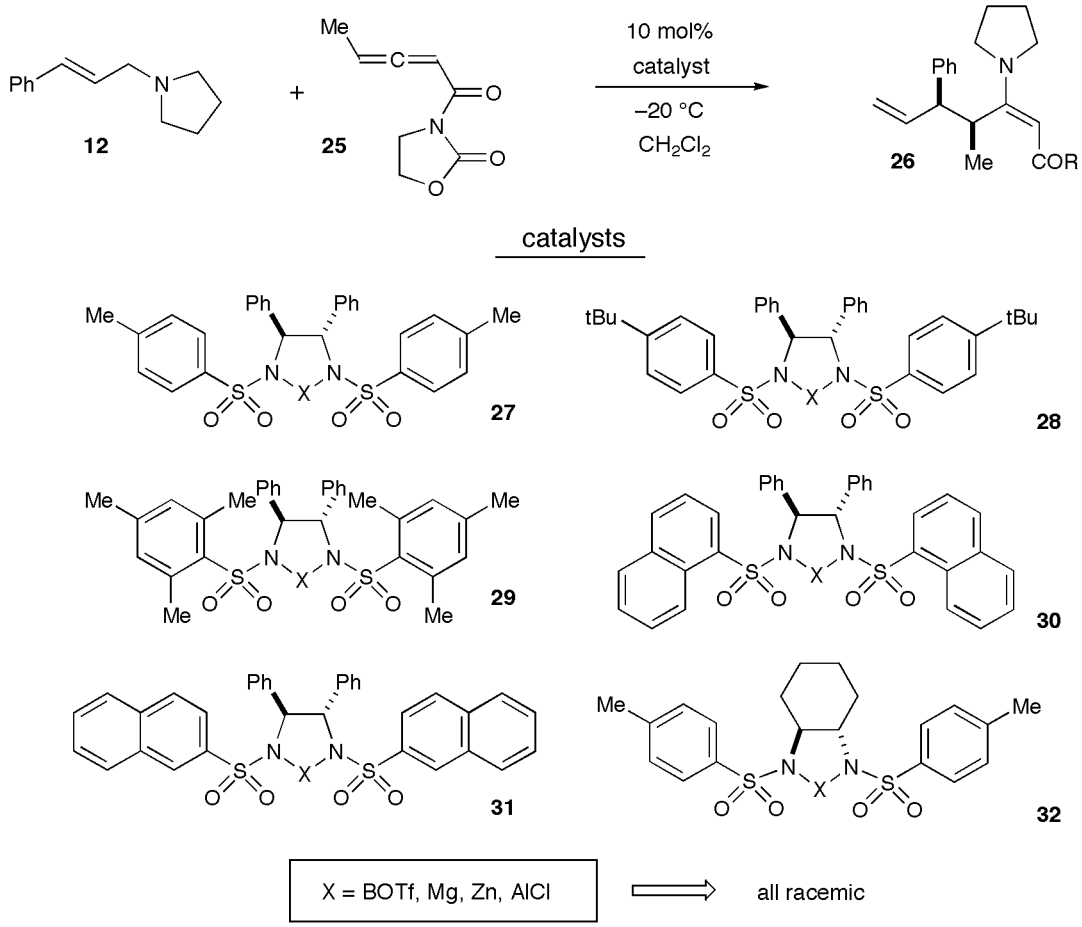
We began our catalyst screen for this reaction with bisoxazoline-based ligand systems as these have been proven to be very effective for a broad range of transformations using bidentate substrates. Unfortunately, although a diverse range of ligands (**15**-**19**) and Lewis acids were tested, no enantioselectivity was observed (Figure 6). Particularly noteworthy is the absence of enantioselection using the highly extended biphenylbisoxazoline ligand **15**.

Figure 6. Bisoxazoline-based catalyst systems.



Again we turned our attention to chiral diamine catalyst systems (**27**-**32**) (Figure 7). In this case we broadened our screen to include a wider range of sulfonamide substituents and Lewis acids (B, Mg, Zn, Al). However, as before, no enantioselectivity was observed in any case.

Figure 7. Boron diamine catalysts.

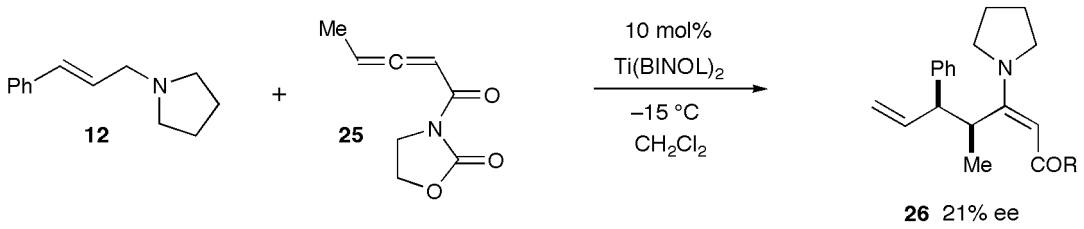


Many other catalyst systems not shown here were investigated for this transformation, however none of them resulted in any enantioselectivity. As with the ester allene, success using oxazolidinone allene **25** was found with BINOL-based titanium complexes. As shown in Scheme 3, 10 mol% of $Ti(BINOL)_2$ (**22**) at –15 °C

catalyzed the formation of Claisen adduct **26** with 21% ee. It was clear to us at this point that there was something unique about the titanium–BINOL system for our Claisen method, and we decided to focus our subsequent studies in this area.

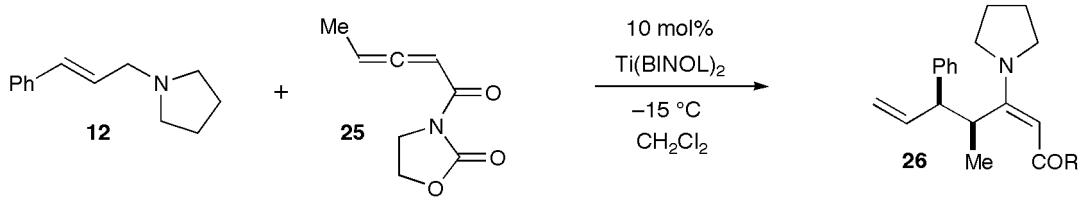
To begin with, we surveyed a range of solvents using 10 mol% $Ti(BINOL)_2$ as catalyst (Table 2). While chloroform (entry 2, 17% ee) and THF (entry 3, 17% ee) offered no advantage over CH_2Cl_2 (entry 1, 20% ee), we were encouraged to find that enantioselectivity could be increased somewhat in Et_2O and toluene (entries 4 and 5, 27% ee and 29% ee, respectively). Most significant was the reaction performed in chlorobenzene, which proceeded in 40% ee (entry 6). Reactions in highly polar solvents such as acetonitrile and DMF resulted in drastically reduced selectivities (entries 7 and 8, 11% ee and 9% ee, respectively). Based on this study, we chose chlorobenzene as the solvent in our subsequent experiments.

Scheme 3. $Ti(BINOL)_2$ catalyzed Claisen rearrangement.



In the course of our studies, we came to find that the 40% ee result shown in entry 6 of Table 2 was highly irreproducible. As this finding coincided with the use of a newly prepared batch of $Ti(BINOL)_2$, we assumed that catalyst purity was to blame.

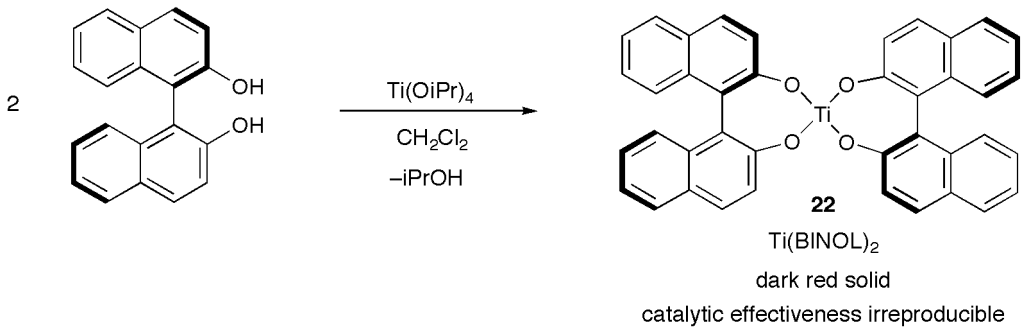
Table 2. Solvent screen with $Ti(BINOL)_2$.



entry	solvent	%ee	entry	solvent	%ee
1	CH_2Cl_2	20	5	PhMe	29
2	$CHCl_3$	17	6	PhCl	40
3	THF	17	7	CH_3CN	11
4	Et_2O	27	8	DMF	9

Titanium bisBINOL (**22**) is prepared by mixing two equivalents of BINOL with one equivalent of $Ti(OiPr)_4$ in CH_2Cl_2 and then azeotropically removing isopropanol (Scheme 4). We found it exceedingly difficult to remove all traces of iPrOH and we felt perhaps this was the cause of our irreproducible results. With this line of thinking, we decided that a study of catalyst preparation methods would be most worthwhile.

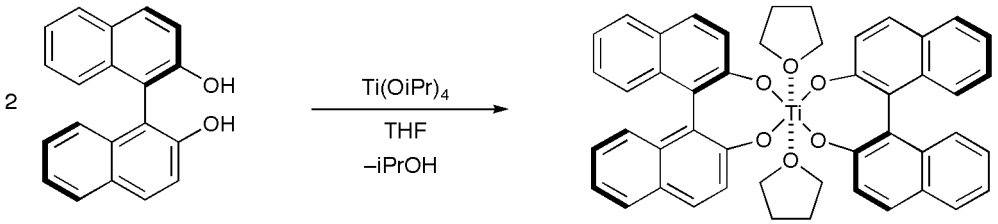
Scheme 4. Preparation of $Ti(BINOL)_2$.



It is a well-known aspect of titanium alkoxide complexes that the titanium center has a high preference for full occupation of its octahedral coordination sphere.[7a] This fact readily explains the difficulty of fully removing all isopropanol from our catalyst. We

reasoned, however, that if the $Ti(BINOL)_2$ was prepared in a coordinating solvent such as THF, then residual iPrOH might be readily displaced from the metal center and removed *in vacuo* (Scheme 5). Indeed this proved to be the case, and the catalyst could be isolated as the bis THF complex **33** with no trace of iPrOH.

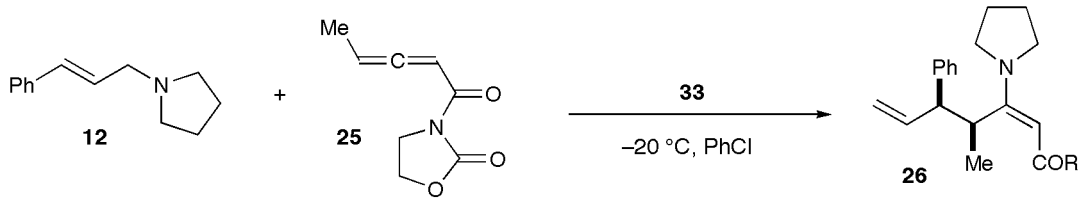
Scheme 5. Alternative catalyst preparation.



33
$Ti(BINOL)_2 \cdot 2THF$

The results of our investigation of the use of this catalyst complex are shown in Table 3. We were pleased to find that using stoichiometric **33** in PhCl, Claisen adduct **26** was obtained in 40% ee (entry 1). Unfortunately, however, while reducing the amount of catalyst to 50 mol% provided essentially the same result (entry 2), lower catalyst loadings of 20 and 10 mol% resulted in drastically reduced selectivities (entries 3 and 4, 25% ee and 15% ee, respectively). The same pattern was observed in other solvents such as CH_2Cl_2, toluene, and THF (entries 5-12). Notably, using100 mol% **33** in THF, a 48% ee was observed, our highest to date (entry 9). Unfortunately reducing catalyst loading produced an even more dramatic reduction in enantioselectivity that with other solvents. The reaction in THF was also more sluggish such that 10 mol% catalyst did not produce observable product (entry 12).

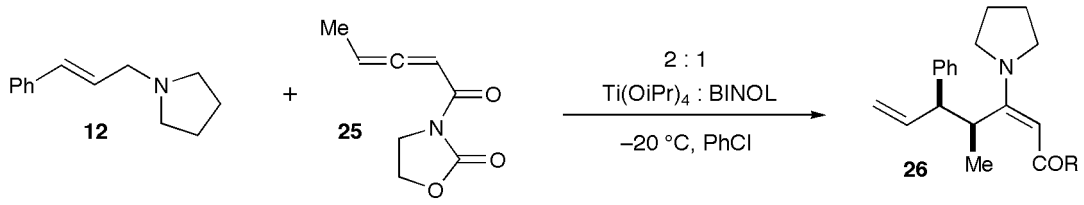
Table 3. Asymmetric Claisen using $Ti(BINOL)_2$•2THF.



entry	mol% **33**	solvent	%ee
1	100	PhCl	40
2	50	PhCl	39
3	20	PhCl	25
4	10	PhCl	15
5	100	CH_2Cl_2	40
6	20	CH_2Cl_2	24
7	100	PhMe	40
8	20	PhMe	21
9	100	THF	48
10	50	THF	29
11	20	THF	16
12	10	THF	--

The results shown in Table 3 supported our hypothesis that residual isopropanol had a detrimental effect on enantioselectivity. To be thorough, however, we wished to examine catalyst that did not have iPrOH removed. To accomplish this the catalyst complex was prepared *in situ* by mixing together BINOL and $Ti(OiPr)_4$ in a 2:1 ratio (Table 4). To our surprise, the enantioselectivity of reaction products using this protocol was not diminished. In fact, at stoichiometric catalyst loadings, a 48% ee was observed, matching our previous best (entry 1). Unfortunately, lower catalyst loadings resulted again in descreased selectivities, with 10 mol% producing only 13% ee (entry 3).

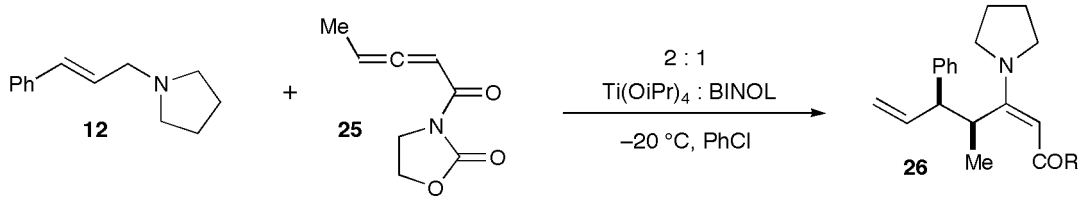
Table 4. In situ formation of $Ti(BINOL)_2$.



entry	mol% catalyst	%ee
1	100	48
2	50	39
3	10	13

In the course of further optimization studies of this *in situ* catalyst preparation protocol, we again found a disturbing lack of reproducibility of enantioselectivity. The fortuitous discovery was made, however, that allene starting material that was purified by silica gel chromatography *immediately* before use in the Claisen reaction provided consistently high selectivities. As shown in Table 5, allene that was not purified immediately beforehand resulted in 34% ee when employing stoichiometric catalyst (entry 1), while the same sample of allene, when purified, resulted in 47% ee (entry 2). Encouragingly, the same %ee was observed when only 50 mol% catalyst was employed (entry 3). Unfortunately, purified allene did not solve the problem of reduced enantioselectivity at lower catalyst loadings (entries 4 and 5).

Table 5. Effect of allene purification.

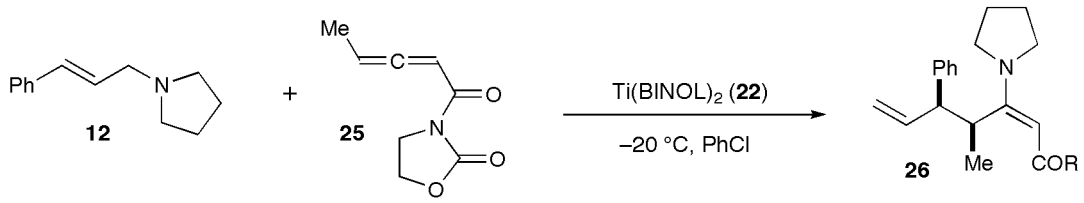


entry	mol% catalyst	%ee	
1	100	34	
2	100	47	allene purified immediately beforehand
3	50	48	
4	20	30	
5	10	13	

Confident we had discovered the root of our irreproducibility problems, we returned to the use of preformed $Ti(BINOL)_2$ (**22**) with newly purified allene (Table 6). Gratifyingly, stoichiometric use of this catalyst in chlorobenzene resulted in product with 45% ee, in line with our previous observations (entry 1). To our surprise, when 50 mol% catalyst was employed, our best result to date (50% ee) was observed (entry 2). Nonetheless, reducing catalyst loading to 20 mol% again led to a decrease in selectivity, down to 25% ee (entry 3).

It seems clear that there is some contaminant present with the allene or catalyst or both that has a detrimental effect on enantioselectivity. Although moisture might seem to be a likely culprit, rigorous exclusion of water has not correlated to improved results.[9] It is possible that the contaminant is a decomposition product of the allene formed in the reaction pot, although no such materials have yet been identified. It also remains to be seen if this contaminant is responsible for reduced selectivities at low catalyst loadings.

Table 6. Purified allene with $Ti(BINOL)_2$ catalyst.



entry	mol% **22**	%ee
1	100	45
2	50	50
3	20	25

Concluding Remarks

We have successfully identified a highly promising $Ti(BINOL)_2$ catalyst system for the enantioselective allenoate-Claisen rearrangement. Surprisingly, of the chiral Lewis acids investigated, the titanium bisbinaphtholate complexes are uniquely effective for imparting asymmetry in this reaction manifold. In a limited sense, we have achieved up to 40% ee using only 10 mol% $Ti(BINOL)_2$ for the reaction of a bidentate allenic partner. In a more reproducible manner, we have identified conditions for the allenoate-Claisen rearrangement with up to 50% ee using only 50 mol% catalyst. We feel confident that these studies have provided a strong platform for the successful development of a highly enantioselective catalytic Claisen rearrangement.

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(2) See chapter 2.

(3) For recent reviews of bisoxazoline ligands, see: (a) Pfaltz, A. *Acc. Chem. Res.* **1993**, *26*, 339. (b) Pfaltz, A. In *Encyclopedia of Reagents for Organic Synthesis*, Vol. 3; Wiley: New York, 1995; p. 2094. (c) Ghosh, A. K.; Packiarajan, M.; Cappiello, J. *Tetrahedron: Asymm.* **1998**, *9*, 1.

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(7) For examples of chiral titanium complexes in organic synthesis, see: (a) Duthaler, R. O.; Hafner, A. *Chem. Rev.* **1992**, *92*, 807, and ref. therein. (b) Balsells, J.; Davis, T. J.; Carroll, P.; Walsh, P. J. *J. Am. Chem. Soc.* **2002**, *124*, 10336. (c) Gao, Y.; Hanson, R. M.; Klunder, J. M.; Ko, S. Y.; Masamune, H.; Sharpless, K. B. *J. Am. Chem. Soc.* **1987**, *109*, 5765. (d) Kitamoto, D.; Imma, H.; Nakai, T. *Tetrahedron Lett.* **1995**, *36*, 1861. (e) Narasaka, K.; Iwasawa, N.; Inoue, M.; Yamada, T.; Nakashima, M.; Sugimori, J. *J. Am. Chem. Soc.* **1989**, *111*, 5340. (f) Keck, G. E.; Tarbet, K. H.; Geraci, L. S. *J. Am. Chem.*

Soc. **1993**, *115*, 8467. Mikami, K.; Terada, M.; Nakai, T. *J. Am. Chem. Soc*. **1989**, *111*, 1940.

(8) For instance: Johnson, J. S.; Evans, D. A. *Acc. Chem. Res*. **2000**, *33*, 325.

(9) For instance, reactions performed with distilled and undistilled chlorobenzene resulted in the same %ee, as did reactions performed with cinnamyl amine that had been freshly distilled from CaH_2 and cinnamyl amine that had not been purified for several months.

Experimental Section

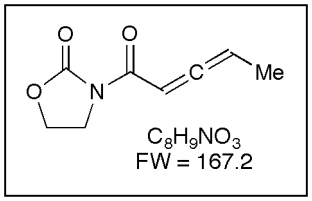
General Information. All reactions were performed using oven-dried glassware under an atmosphere of dry argon. Non-aqueous reagents were transferred under argon by syringe. Organic solutions were concentrated under reduced pressure using a Buchi rotary evaporator. Chlorobenzene was distilled from CaH_2 prior to use. Methylene chloride was distilled from CaH_2 or filtered through a column charged with Al_2O_3 (solvent purification system) immediately prior to use. Tetrahydrofuran and diethyl ether were distilled from sodium benzophenone ketyl immediately prior to use. Propionyl chloride was distilled immediately prior to use. All other commercial reagents were used as provided. Air sensitive solids were dispensed in an inert atmosphere glovebox. 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.[1] 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 $KMnO_4$ or p-anisaldehyde stain.

^1H and ^{13}C NMR were recorded on Mercury 300 (300 MHz and 75 MHz) as noted, and are internally referenced to residual protio solvent signals. Data for ^1H NMR are reported as follows: chemical shift (δ ppm), multiplicity (s = singlet, brs = broad 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 1600 Series spectrometer using NaCl salt plates, and are reported in terms of frequency of absorption (cm^{-1}). Mass spectra were obtained

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

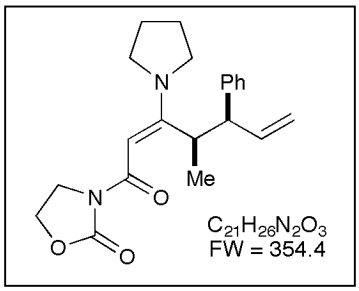
from the Caltech Mass Spectral Facility. Optical rotations were recorded on a Jasco P-1010 polarimeter (WI lamp, 589 nm, 25 °C). HPLC analysis was performed on Hewlett-Packard 1100 series HPLC at 254 nm a Chiralcel AS (25 cm) and AS guard (cm) column.

3-Penta-2,3-dienoyloxazolidin-2-one. To 3-[(triphenyl-phosphoranylidene)-acetyl]oxazolidin-2-one[2] (3.00 g, 7.7 mmol) in CH_2Cl_2 (50 mL) was added Et_3N (1.07 mL, 7.7 mmol) followed by a 1.0 M soln of freshly distilled propionyl chloride in CH_2Cl_2 (7.7 mL, 7.7 mmol) dropwise over 20 min. After stirring at room temperature for 1h, the solvent was removed in vacuo resulting in an orange solid. The crude residue was dissolved in a minimal amount of CH_2Cl_2 and then loaded onto a silica gel column. The column was run with 40% EtOAc : hexanes to provide the title compound as a mixture of the title compound and isomeric 3-pent-2-ynoyloxazolidin-2-one as a viscous yellow oil (0.52 g, 3.1 mmol, 40% yield). IR (thin film) 3630, 3532, 3059, 2984, 2924, 2860, 1960, 1774, 1708, 1676, 1522, 1478, 1412, 1388, 1317, 1264, 1227, 1111, 1037, 1016, 966 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.02-7.07 (m, 1H, C(O)C**H**=C), 5.63-5.72 (m, 1H, C=C**H**CH_3), 4.38-4.45 (m, 2H, OC**H**$_2$), 4.00-4.11 (m, 2H, NC**H**$_2$), 3.83-3.85 (m, 2H, C**H**$_2CH_3$), 1.77-1.83 (m, 3H, C**H**$_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 214.5, 168.4, 164.4, 153.8, 153.6, 90.7, 87.1, 80.2, 70.3, 62.6, 62.3, 43.0, 42.8, 27.5, 12.7, 3.8; HRMS (EI) *m/z* 167.0589 (M, 167.0582 calcd for $C_8H_9NO_3$).



[2] Cardillo, G.; Gentilucci, L.; Matteis, V. D. *J. Org. Chem.* **2002**, 5957.

3-(4(*R)-Methyl-5(*R**)-phenyl-3-pyrolidin-1-ylhepta-2,6-dienoyl)oxazolidin-2-one.**



To a 2 dram vial charged with $Zn(OTf)_2$ (18 mg, 0.05 mmol) was added 3-Penta-2,3-dienoyloxazolidin-2-one (84 mg, 0.5 mmol) in CH_2Cl_2 (2 mL) followed by cinnamyl pyrrolidine (0.16 g, 0.85 mmol) in CH_2Cl_2 (2 mL). After the allene was consumed as judged by TLC analysis (1 h), the reaction mixture was diluted with Et_2O and flushed through a short silica gel plug. The filtrate was concentrated and the crude residue was purified by silica gel chromatography using 35% EtOAc : hexanes to provide the title compound as a yellow foamy solid (135 mg, 0.38 mmol, 76% yield) as an approximately 3:1 *E:Z* enamine isomer ratio. IR (thin film) 3060, 2973, 2918, 2872, 1758, 1637, 1547, 1480, 1455, 1417, 1384, 1308, 1218, 1195, 1174 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) □ 7.15-7.41 (m, 5H, Ar**H**), 5.86-6.11 (m, 1H, C**H**CH_3), 6.00 (s, 1H, C=C**H**C(O)), 5.39-5.50 (m, 1H, CH_2=C**H**), 4.80-5.00 (m, 2H, C**H**$_2$=C), 4.25-4.30 (m, 2H, OC**H**$_2$), 4.03-4.09 (m, 2H, NC**H**$_2$), 3.34-3.54 (m, 5H, N(C**H**$_2$)$_2$ and C**H**Ph), 1.87-1.96 (m, 4H, O(C**H**$_2$)$_2$), 0.99 (d, *J* = 7.1 Hz, 3H, C**H**CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) □ 169.1, 167.8, 165.6, 163.2, 154.9, 154.6, 143.6, 143.2, 141.3, 141.0, 129.0, 128.8, 128.7, 128.3, 126.9, 126.8, 126.5, 126.2, 115.7, 114.1, 87.1, 85.0, 61.4, 61.3, 57.2, 54.9, 50.6, 50.3, 43.7, 43.6, 43.5, 37.9, 25.7, 25.3, 15.9, 14.2; HRMS (FAB) *m/z* 355.2016 (MH, 355.2022 calcd for $C_{21}H_{27}N_2O_3$).

General Procedure A: A 2 dram vial was charged with the appropriate amount of catalyst and the vial was placed under an atmosphere of argon. 3-Penta-2,3-dienoyloxazolidin-2-one (24 mg, 0.14 mmol) in solvent (1.0 mL) was added and the vial

was cooled to –40 °C. Cinnamyl amine (40 mg, 0.21 mmol) in solvent (1.0 mL) was added slowly over 5 min after which time the vial was allowed to warm to –20 °C. After the desired reaction time (typically 48 h) the reaction mixture was loaded rapidly onto a silica gel column (2 x 14 mm) and eluted with 35% EtOAc : hexanes. The fractions containing product (typically contaminated with ligand) were combined, concentrated, and then purified by silica gel chromatography using 35% EtOAc : hexanes to provide pure product.

Enantiomeric product ratios were determined by HPLC with a Chiralcel AS column and AS guard column (2.5% iPrOH/hexanes, 1 mL/min flow rate); t_r = 51.4 min. and 67.4 min. Material of 40% ee: $[\alpha]_D$ = +14.9 ° (c = 0.2, $CHCl_3$).

Preparation of Ti(BINOL)$_2$: A 20 mL Schlenk flask was charged with (*R*)-2-binaphthol (BINOL) (0.75 g, 2.6 mmol) in an inert atmosphere glovebox. Under positive argon pressure, degassed solvent (CH_2Cl_2, toluene, or THF) (13 mL) was added to the flask followed by freshly distilled $Ti(OiPr)_4$ (0.37 g, 1.3 mmol). The resulting dark red solution was stirred for 24 h after which time solvent was removed *in vacuo.* After remaining under high vacuum (1 mm Hg) for 24 h, solvent (13 mL) was added again to the flask and the mixture was stirred an additional 2 h. Solvent was again removed *in vacuo* and the flask was placed under high vacuum (1 mm Hg) for 48 h to provide the title material as a dark red solid. Catalyst prepared in this manner invariably contained small amounts of iPrOH as judged by ^{1}H NMR except with the use of THF as solvent, which instead contained approx. 2 equivalents of THF.

***In Situ* Preparation of Ti(BINOL)$_2$:** A 2 dram vial was charged with (*R*)-binaphthyl (BINOL) (2 eq.) under an inert atmosphere. Solvent (1 mL) was added followed by freshly distilled Ti(OiPr)$_4$ (1 eq.). The resulting dark red solution was allowed to stir at room temperature for 1 h before allene and amine were added in the manner described above.

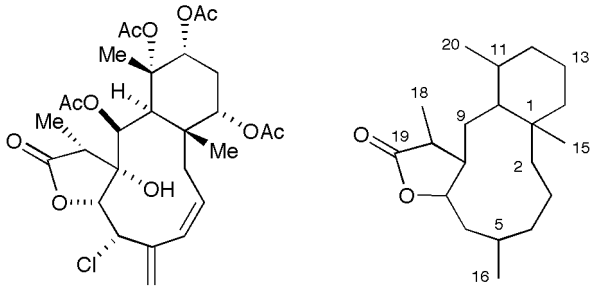
CHAPTER 4

Progress Towards the Total Synthesis of Erythrolide E

Briarane Diterpenes

Briarane diterpenes are a class of marine metabolites isolated from coelenterates of Mediterranean, Atlantic, and Pacific waters.[1] The first member of the family, briarane A (**1**), was isolated in 1977 by Burks et al., and its structure was determined by X-ray analysis (Figure 1).[2] Since this initial report, more than 200 members of the briarane family have been reported including excavatolides A-Z,[3] milolides A-N,[4] and erythrolides A-V.[5] The common distinguishing feature of the briaranes is a highly functionalized bicyclo[8.4.0] ring system (**2**).

Figure 1. Briarane A and common briarane structural features.

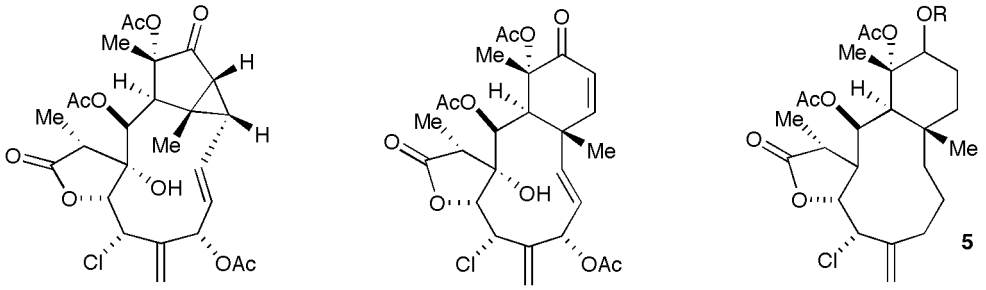


briarane A (**1**) common briarane skeleton **2**

As a subclass of the briarane family, the erythrolides are characterized by a highly oxidized tri- or tetracyclic framework. In 1984 Fenical, Clardy and coworkers isolated erythrolides A (**3**) and B (**4**) from *Erythropodium caribaeorum*, a gorgonian coral found off the coast of Belize (Figure 2).[5a] Erythrolide A was unique in that it was the first

natural product identified that presumably arises via a di-π-methane rearrangement. Erythrolide B, the most abundant metabolite of *E. caribaeorum* (comprising as much as 30% of the organic extract and 0.5% of the wet weight of the organism), was shown to posess the prototypical erythrolide framework described by structure **5**.

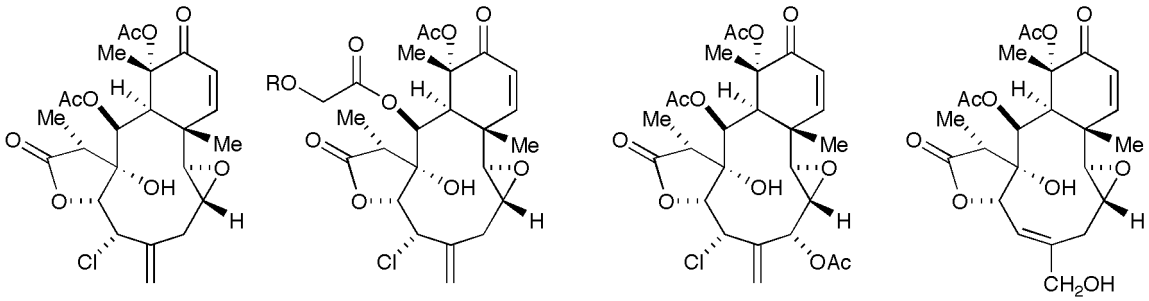
Figure 2. Erythrolides A and B and common erythrolide structural features.



In 1991 Schmitz, van der Helm, and coworkers isolated erythrolides C-I from *Erythropodium caribaeorum*.[5b] Subsequently, Mootoo and coworkers reported erythrolides J-Q[5c-e] and, recently, Roberge and Andersen et al. reported erythrolides R-V[5f] from the same species. The structures of these compounds were determined by X-ray analysis, mass spectrometry, NMR spectroscopy, and by comparison to the known erythrolides.

Of the new compounds, five were shown to possess 2,3-epoxy functionality (Figure 3). Erythrolides C (**6**), D (**7**), and U (**8**) vary only in the identity of the acyloxy group at C-9. Erythrolide T (**9**) possesses an additional acyloxy group at C-4 and is likely the direct epoxidation product of erythrolide B (**4**). Erythrolide H (**10**) lacks allylic chloride functionality and instead displays a primary allylic alcohol, the apparent result of an S_N2' displacement of erythrolide C (**6**) with hydroxide ion.

Figure 3. 2,3-Epoxy erythrolides: erythrolides C, D, H, T, and U.



erythrolide C (**6**)

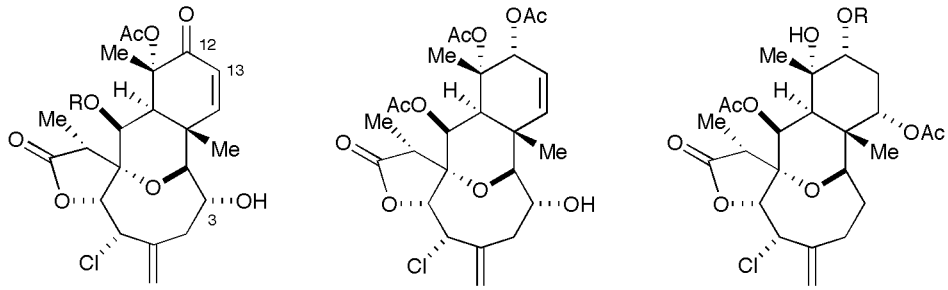
erythrolide D (**7**), R = Ac
erythrolide U (**8**), R = H

erythrolide T (**9**)

erythrolide H (**10**)

Six erythrolides have been shown to possess a bridging pyran ring (Figure 4). As with the epoxy compounds, three of the pyranyl erythrolides, E (**11**), F (**12**), and I (**13**), result only from variation of the C-9 acyl functionality. Erythrolides G (**14**), P (**15**), and Q (**16**) differ from the other pyranyl erythrolides in the oxidation pattern of C-12, C-13, or C-3. Although other briarane metabolites that incorporate cyclic ether functionality have been reported, the erythrolides are the only members that possess the C-2 to C-8 pyran linkage.[1]

Figure 4. Pyranyl erythrolide: erythrolides E, F, G, I, P, and Q.



erythrolide E (**11**) R = Ac

erythrolide F (**12**)
R = $(CO)CH_2O(CO)CH_3$

erythrolide I (**13**)
R = $(CO)CH_2OH$

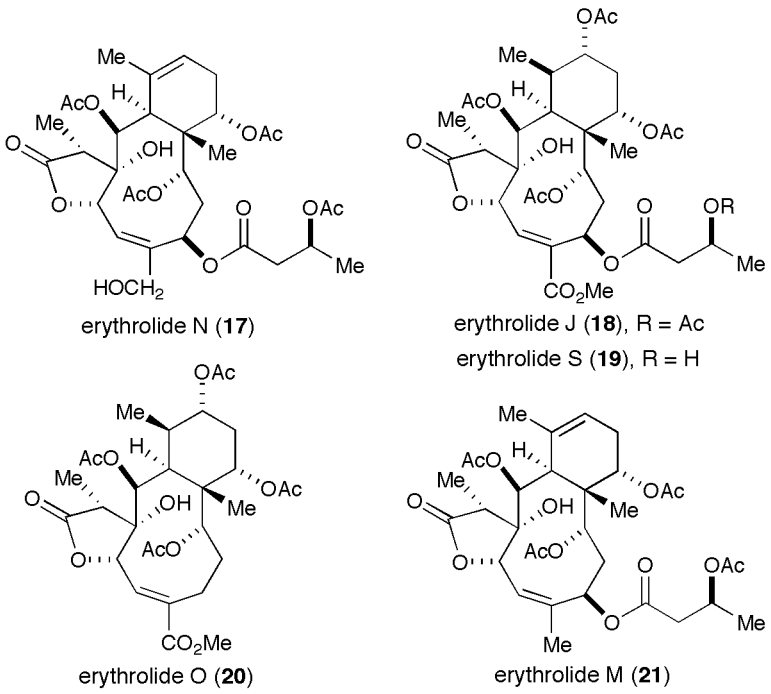
erythrolide G (**14**)

erythrolide P (**15**) R = H

erythrolide Q (**16**) R = Ac

In addition to erythrolide H (**10**), four other erythrolide members lack the allylic chloride functionality (Figure 5). Erythrolide N (**17**) possesses an allylic hydroxyl group, while C-16 of erythrolides J (**18**), S (**19**), and O (**20**) exists in the ester oxidation state. Although common among other briarane families, the C-16 methyl group of erythrolide M (**21**) is unique within the erythrolide class.

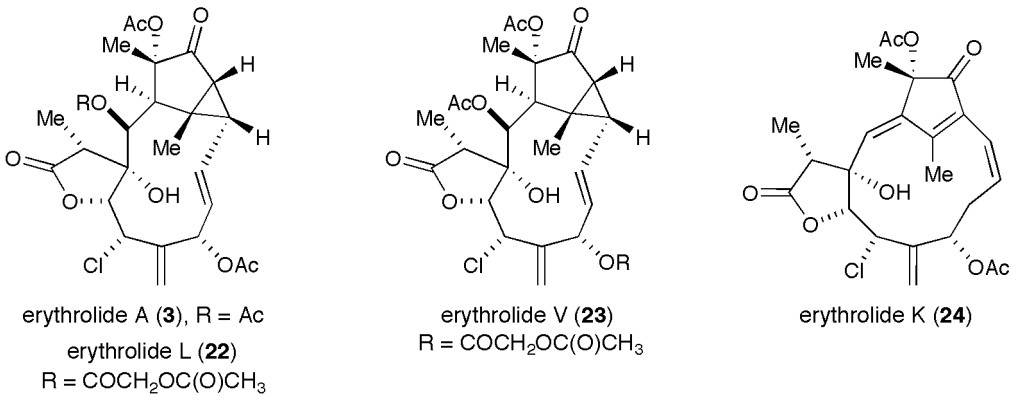
Figure 5. Deschloro erythrolides: erythrolides J, M, N, O, and S.



Four erythrolides possess skeletally rearranged carbon frameworks (Figure 6). As noted earlier, erythrolide A (**3**) contains a [3.1.0] bicyclic system that has been shown to arise from a di-π-methane rearrangement of erythrolide B (**4**). Erythrolide L (**22**) is a C-9 acyloxy analogue of erythrolide A(**3**), while erythrolide V (**23**) varies at C-4. Erythrolide K (**24**), which contains a bicyclo [9.2.1] system, is presumably derived from erythrolide

A (**3**) via [1,5]-sigmatropic hydrogen shift / acetic acid elimination and has, in fact, been synthesized by this route.[5d]

Figure 6. Skeletally rearranged erythrolides: erythrolides A, L, K, V.



erythrolide A (**3**), R = Ac
erythrolide L (**22**)
R = $COCH_2OC(O)CH_3$

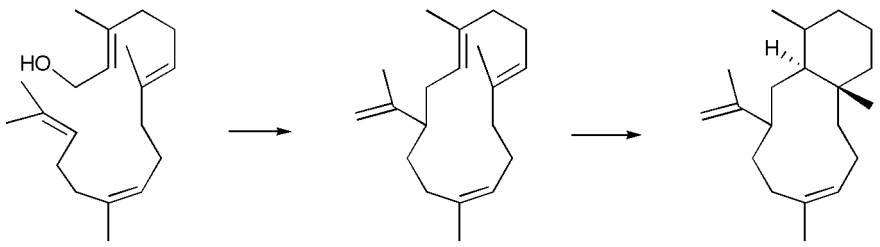
erythrolide V (**23**)
R = $COCH_2OC(O)CH_3$

erythrolide K (**24**)

Proposed Biosynthesis of the Erythrolides

Although a detailed study of the biosynthesis of the erythrolides has not been reported, several key steps have been proposed (Figure 7). The cembrene (**26**) skeleton, which arises from cyclization of geranyl geraniol (**25**), is the biosynthetic precursor to a number of natural product frameworks.[6] Ksebati and Schmitz have suggested that the briarane skeleton **27** results from 1,10 cyclization (briarane numbering) of cembrene (**26**).[7]

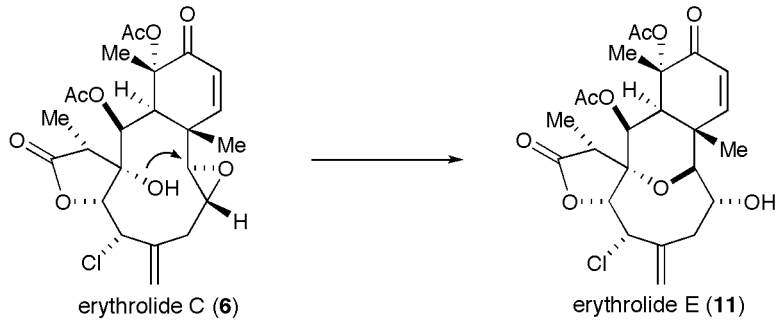
Figure 7. Proposed biosynthetic origin of the briarane skeleton.



geranyl geraniol (**25**) → cembrene (**26**) → briarane skeleton **27**

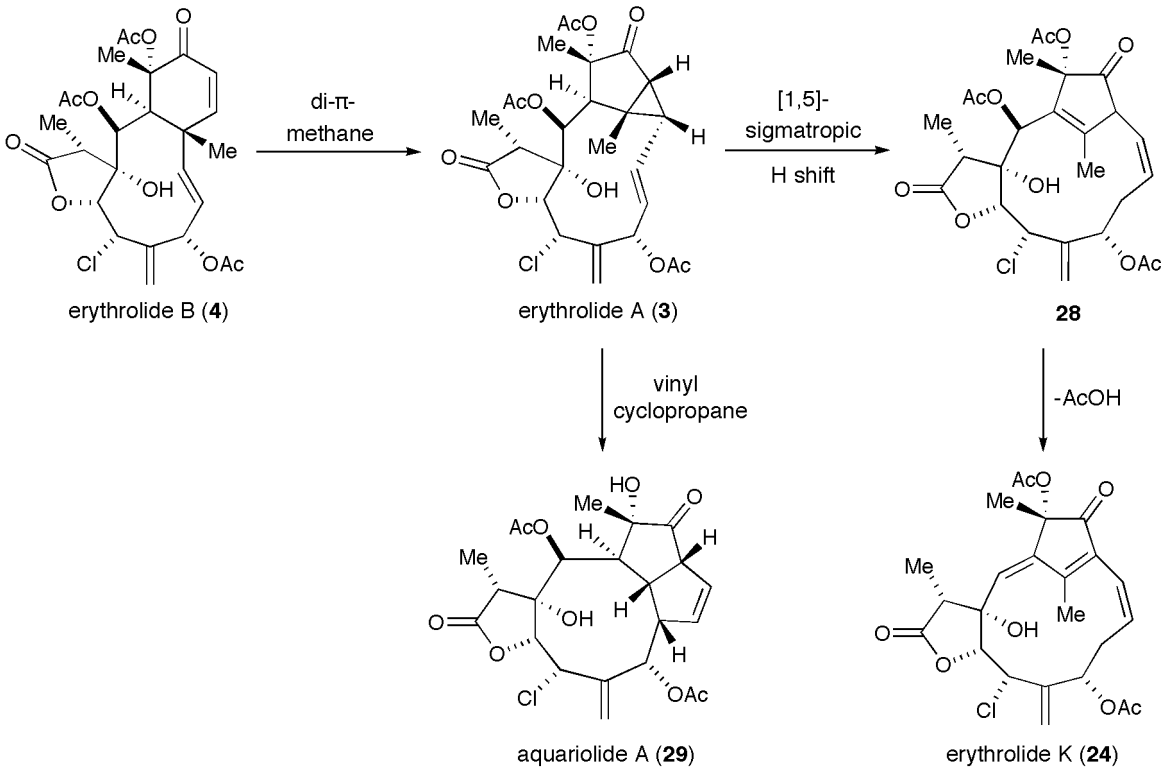
It seems most probable that the pyranyl erythrolides arise from internal ring opening of the 2,3-epoxy erythrolides (Figure 8).[8] Credence is lent to this claim by noting that the stereochemical configuration at C-2 of the 2,8-ether bridged compounds is opposite that present in the other members of the briarane family. Thus erythrolide E (**11**) is regarded as the direct biogenetic product of epoxide opening product of erythrolide C (**6**).

Figure 8. Biosynthetic origin of the pyranyl erythrolides.



As noted earlier, it has been shown that erythrolide A (**3**) can be obtained synthetically via photochemical di-π-methane rearrangement of erythrolide B (**4**), though this does not necessarily rule out an enzymatic bioorigin (Figure 9).[5a] Mootoo and coworkers have demonstrated that erythrolide A (**3**) is the progenitor of erythrolide K (**24**), having effected this conversion by way of a thermal [1,5]-sigmatropic hydrogen shift followed by silica gel promoted loss of acetic acid.[5d] Finally, a related compound, aquariolide A, presumably arise from the erythrolide A (**3**) skeleton by way of a vinyl cyclopropane rearrangement, although this proposal has yet to succumb to synthetic demonstration.[8]

Figure 9. Biosynthesis of erythrolides A and K and aquariolide A from erythrolide B.



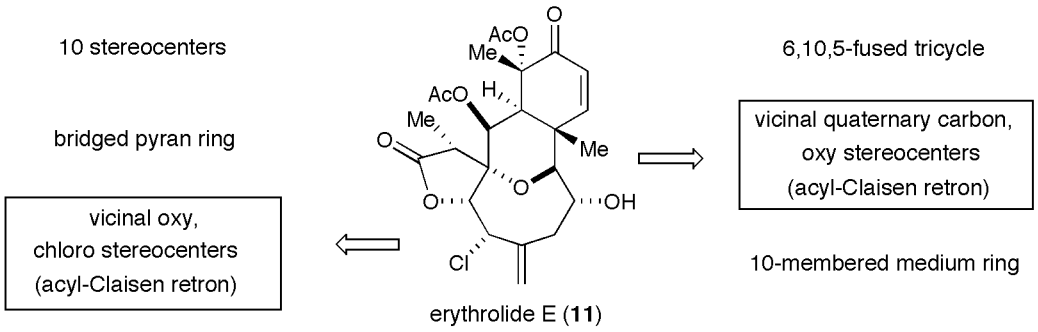
Biological Activity of the Erythrolides

A very limited biological activity study of several of the erythrolides has been disclosed by Roberge and Andersen et al.[5f] In an *in vitro* cytotoxicity assay against the MCF-7 human breast cancer cell line, erythrolides P (**15**) and J (**18**) were found to have IC_{50} values of less than 4 □g/mL. Erythrolide D (**7**) showed only modest activity (IC_{50} > 10 □g/mL), while erythrolide T (**9**) displayed absolutely no activity at the concentrations tested. The authors of the study have suggested that the fully reduced cyclohexane ring systems of erythrolides P (**15**) and J (**18**) might be an important motif for optimal cytotoxicity.

Erythrolide E

Our interest in the erythrolide diterpenes stemmed from identification of two key structural issues that we felt our acyl-Claisen rearrangement[9] technology would be particularly well suited to address. As shown in Figure 10, the vicinal oxy-chloro and vicinal quaternary carbon-oxy substitution patterns incorporate two structurally and stereochemically challenging acyl-Claisen retrons. Our chosen target, erythrolide E (**11**), also possesses significant additional elements of complexity including a total of ten stereocenters, a ten-membered medium ring, and a bridging pyran ring. Because of the distinct synthetic challenges posed by the erythrolide E (**11**) framework, we felt that a total synthetic effort toward this target would entail a suitable platform for the demonstration of the utility of the acyl-Claisen rearrangement.

Figure 10. Synthetically challenging structural features of erythrolide E.

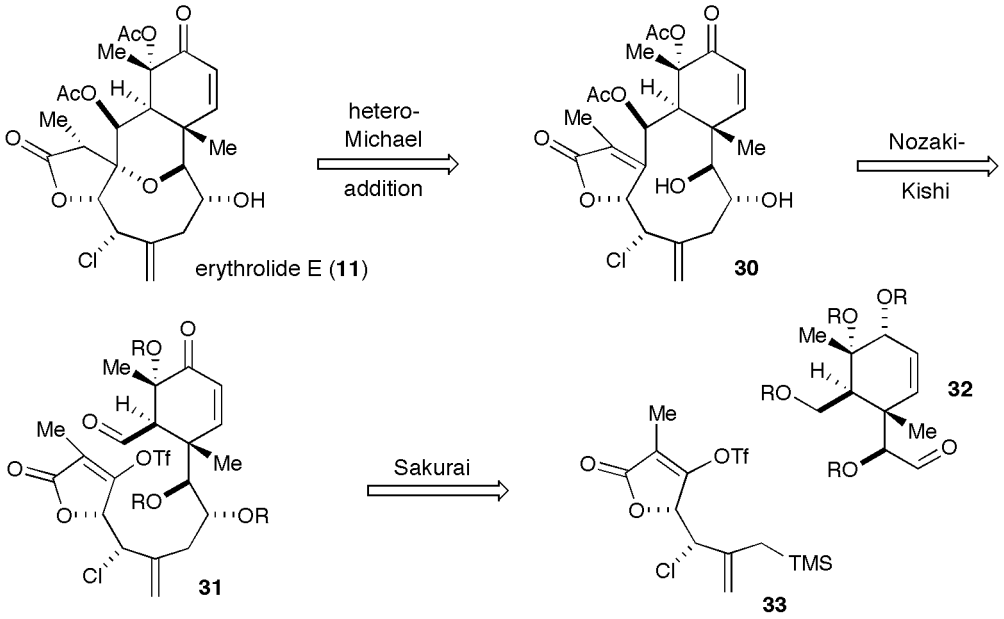


Synthetic Plan

Our strategy toward erythrolide E is shown in retrosynthetic format in Scheme 1. We reasoned that complex tricycle **30** could provide access to the target structure (**11**) via hetero-Michael addition. Medium ring **30** should be accessible by way of a Nozaki-Kishi[10] cyclization of tethered bicycle **31**. In turn, scission of the C(3)-C(4) bond of **31**

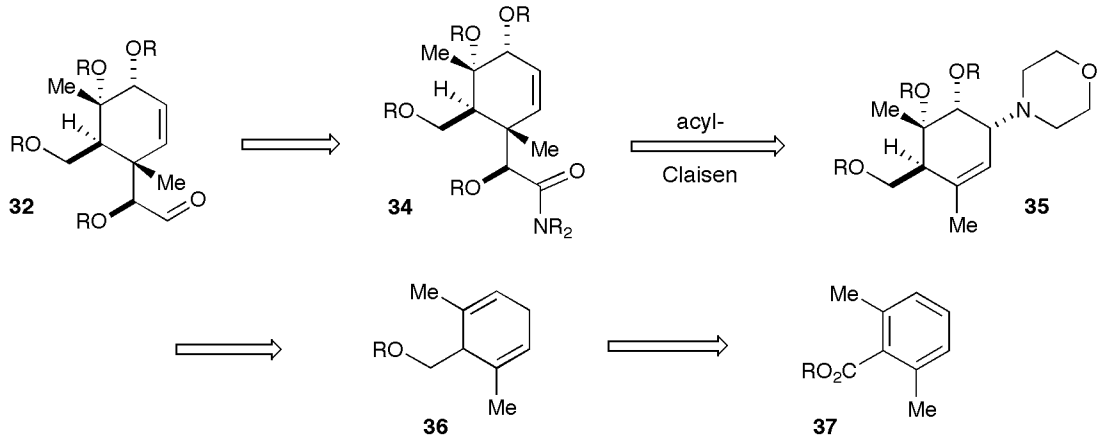
via Sakurai[11] disconnection reveals cyclohexenyl aldehyde **32** and methallyl silane-lactone **33**.

Scheme 1. Retrosynthetic analysis of erythrolide E.



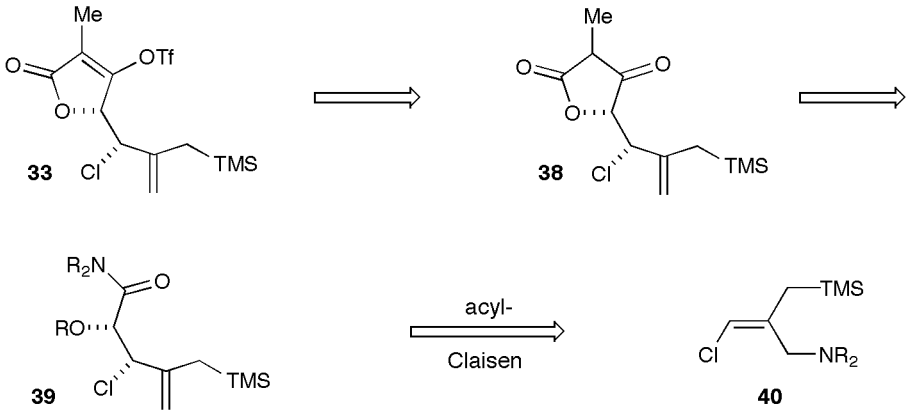
Our first generation retrosynthetic analysis of the core coupling fragment **32** is outlined in Scheme 2. Cyclohexenyl aldehyde **32** could be derived from morpholine amide **34**–an ideal Claisen rearrangement retron. Acyl-Claisen reaction of cyclohexenylamine **35** with an appropriate acid chloride should thus provide facile access to the complex core fragment **34**. We reasoned that amine **35** could be constructed by appropriate functionalization of 1,4-diene **36**, a substrate that should be readily derived from aromatic acid or ester **37** via Birch reduction.

Scheme 2. Retrosynthetic analysis of the core coupling fragment **32**.



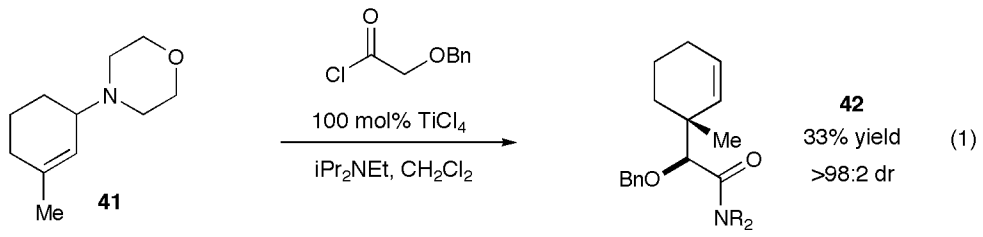
Our synthetic plan to construct the lactone coupling fragment **33** is shown in Scheme 3. The enol triflate moiety of fragment **33** should be readily prepared from the corresponding □-keto ester **38** by standard methods. Lactone **38** should be available by elaboration of amide **39** via addition of a propionate enolate equivalent followed by lactone ring closure. Vicinal oxy-chloro amide **39** represents our second acyl-Claisen rearrangement retron. Thus **39** could be prepared rapidly from the relatively simple allyl amine **40**.

Scheme 3. Retrosynthetic analysis of the acyclic fragment **33**.

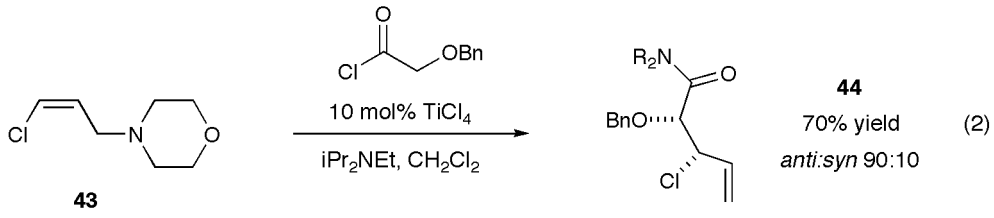


Model Studies

Before embarking on the total synthesis of erythrolide E, we wished to test the feasibility of our acyl-Claisen key steps. Shown in Equation 1 is our model study of the cyclohexenyl core rearrangement. Treatment of 3-methylcyclohexenylmorpholine **41** with benzyloxyacetyl chloride in the presence of iPr_2NEt and one equivalent of Lewis acid provided the rearrangement product **42** as a single diastereomer. Although the yield of this unoptimized reaction was low, we felt confident that our reaction technology allowed for the generation of the required functionality in the confines of a cyclic system.



Our model of the second fragment of erythrolide E is shown in Equation 2. In a reaction performed by Yoon and Dong,[9] (Z)-3-chloroallyl morpholine (**43**) was converted to the complex amide **44** in good yield and with high diastereoselectivity by treatment with benzyloxyacetyl chloride and catalytic Lewis acid in the presence of Hunig's base. Amide **44** displays the desired stereochemical architecture required by the erythrolide framework.



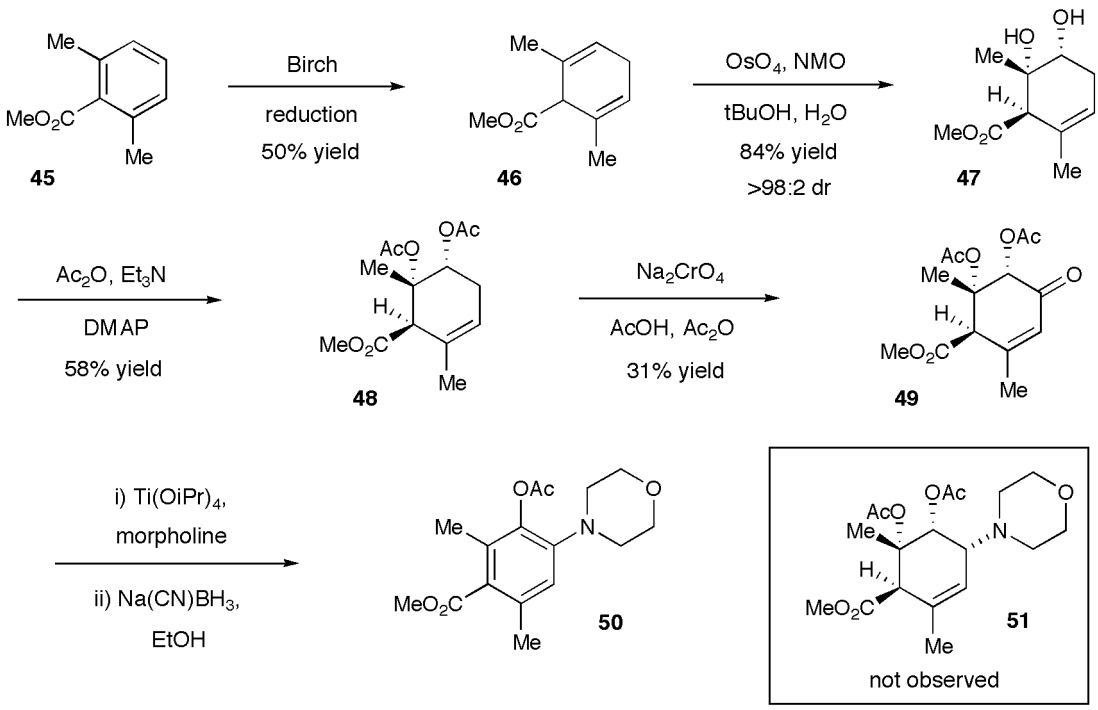
With the results of these successful model studies in hand, we turned our efforts towards construction of the appropriately functionalized fragments for our total synthetic effort.

Reductive Amination Route to the Cyclohexenyl Core

Our initial studies toward the cyclohexenyl core are shown in Scheme 4. Birch reduction[12] of commercially available methyl 2,6-dimethylbenzoate (**45**) proceeded in modest yield to provide the 1,4-diene **46**. Dihydroxylation of **46** with catalytic osmium tetroxide then provided the diol **47** in 84% yield as a single diastereomer in which the carbomethoxy substituent directed reaction exclusively from the opposite pi face. The diol **47** was bisacetylated using standard conditions[13] to provide bisacetate **48**.

At this stage we required the installation of functionality at the allylic methylene that would provide access to requisite acyl-Claisen substrate **51**. Very quickly we found that the allylic position could be oxidized with sodium chromate in AcOH / Ac_2O, albeit in low yield.[14] In analogy to our preparation of the model amine **41**, we anticipated that reductive amination of the ketone **49** would provide the desired acyl-Claisen rearrangement substrate **51**.

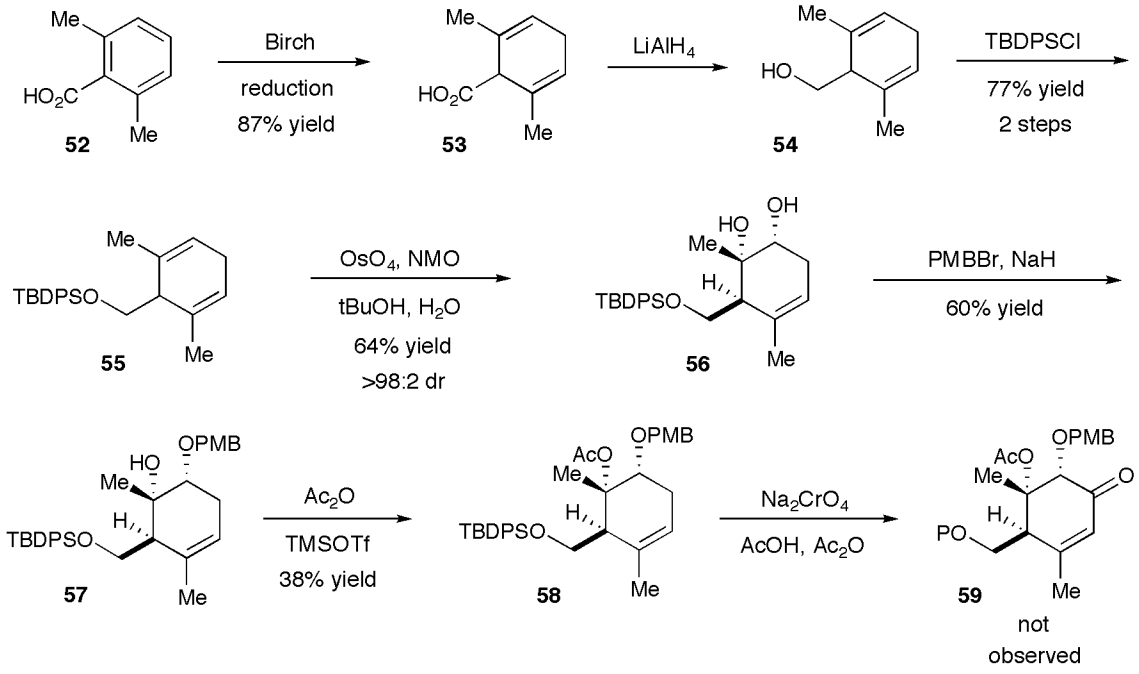
Scheme 4. Reductive amination route to the cyclohexenyl core.



Unfortunately, when ketone **49** was treated with morpholine and $Ti(OiPr)_4$ followed by $Na(CN)BH_3$ in EtOH,[15] no desired product was observed, nor was starting material recovered. Instead, a new compound was isolated that had a ^1H NMR spectrum consistent with aromatic compound **50**.

We rationalized that the C(2) substituted acetate as well as the carboxylate ester moiety rendered the C(2) and C(4) protons sufficiently acidic to undergo soft enolization under the reductive amination conditions. We therefore modified our strategy to diminish the capacity for soft enolization by replacing the carboxylate ester moiety and the acetate protecting group with functionality of a less electron-withdrawing nature.

Scheme 5. Modified reductive amination strategy.



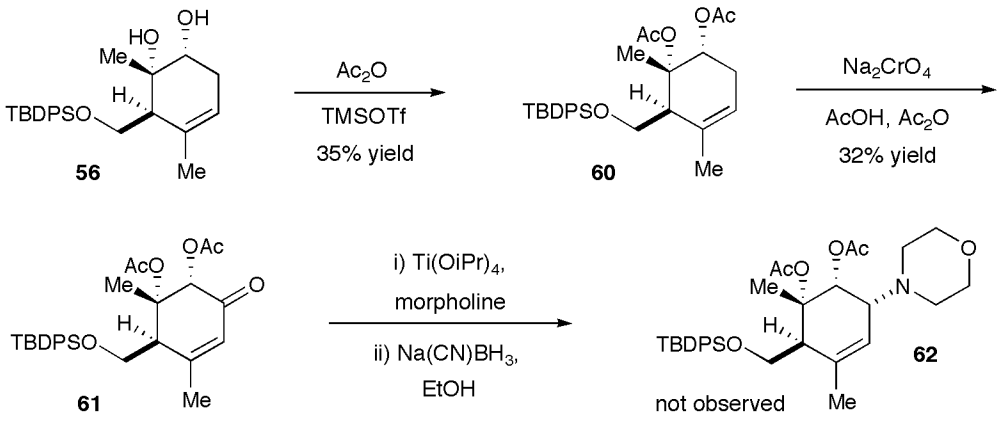
This modified strategy commenced with Birch reduction[16] of 2,6-dimethylbenzoic acid (**52**) using lithium metal to generate diene acid **53** in 87% yield (Scheme 5). Reduction of **53** with $LiAlH_4$ proceeded smoothly to give the alcohol **54** in similarly high yield, before protection with TBDPSCl furnished the silyloxy diene **55**. Treatment of **55** with NMO and catalytic OsO_4 then provided the vicinal diol **56** in 64% yield as a single diastereomer. Selective protection of the secondary alcohol moiety of **56** was achieved by treatment with NaH in THF followed by PMBBr to afford the benzylic ether **57**, which, upon exposure to Ac_2O and catalytic TMSOTf, provided the protected triol **58**.

Unfortunately, all attempts to access the desired ketone **59** by way of allylic oxidation resulted in removal of the PMB group and subsequent substrate decomposition.

Mindful that the bisacetate of **56** should be suitable for allylic oxidation, we decided to investigate whether the ketone derived from **56** (see **61** in Scheme 6) would

be stable to the reductive amination conditions. It was reasoned that the acidity of the allylic proton in this case should be relatively diminished and therefore less susceptible to soft enolization in comparison to **49**.

Scheme 6. Modified reductive amination strategy.



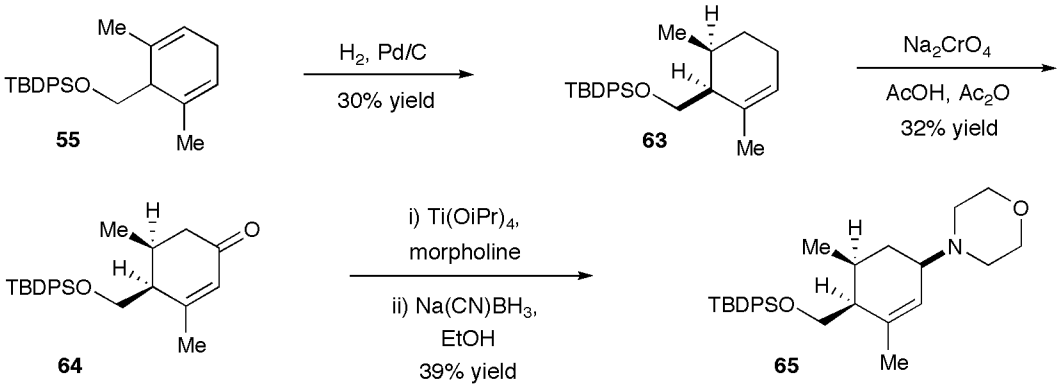
Treatment of the diol **56** with Ac_2O and catalytic TMSOTf provided the bisacetate **60**, and allylic oxidation with Na_2CrO_4 proceeded as expected to afford the ketone **61**. Unfortunately, treatment of **61** under the reductive amination conditions involving either morpholine or pyrrolidine resulted in a complex mixture of aromatic products. The desired amine **62** was not observed.

It was apparent that a reductive amination strategy involving a substrate with a □-leaving group would be untenable. We therefore decided to modify our approach by preparing a Claisen substrate lacking the offending acetoxy moiety.

Towards this end we began by hydrogenating the 1,4-diene **55** using palladium on carbon (Scheme 7). The yield of cyclohexene **63** was expectedly low, no doubt due to overhydrogenation. Allylic oxidation proceeded as expected to provide the ketone **64**. When subjected to our standard reductive amination conditions, **64** was converted to allyl

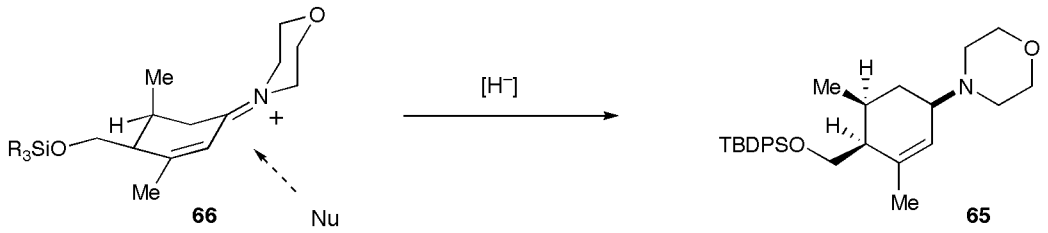
morpholine **65** in 39% yield as a single diastereomer. NOE coupling of the C(1) and C(3) protons, however, revealed that the stereochemistry at the amine bearing carbon was the opposite of what we desired.

Scheme 7. Hydrogenation route to the cyclohexenyl core.



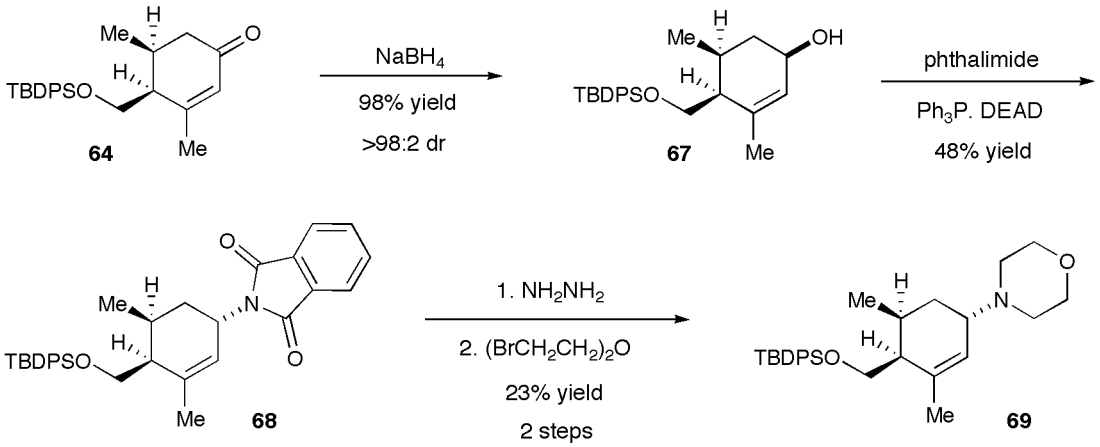
The rationale for the observed reduction stereoselectivity is straightforward (Figure 11). Iminium ion intermediate **66** is expected to exist predominantly in the conformation shown, which minimizes the number of unfavorable diaxial interactions. In this conformation the axial methyl group would block hydride attack from the top face resulting in the observed all *cis* product **65**.

Figure 11. Stereoselectivity of the reductive amination.



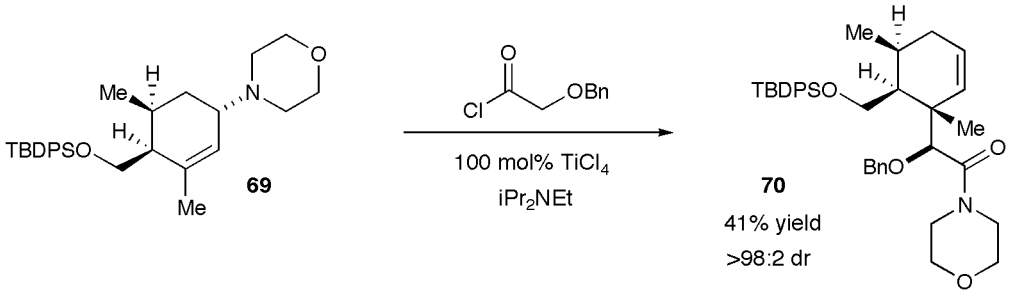
We decided to utilize this high diastereoselectivity to our advantage by employing a reduction/inversion strategy (Scheme 8). Ketone **64** was reduced with $NaBH_4$ in nearly quantitative yield to provide the allylic alcohol **67**. Complete diastereoselectivity was observed congruent with our reductive amination results. Mitsunobu inversion[17] of alcohol **67** with phthalimide resulted in the allylic phthalimide substrate **68**. Deprotection of the phthalimide group with hydrazine followed by morpholine ring formation (bromoethyl ether) then provided our desired acyl-Claisen substrate **69**.

Scheme 8. Reduction/inversion strategy.



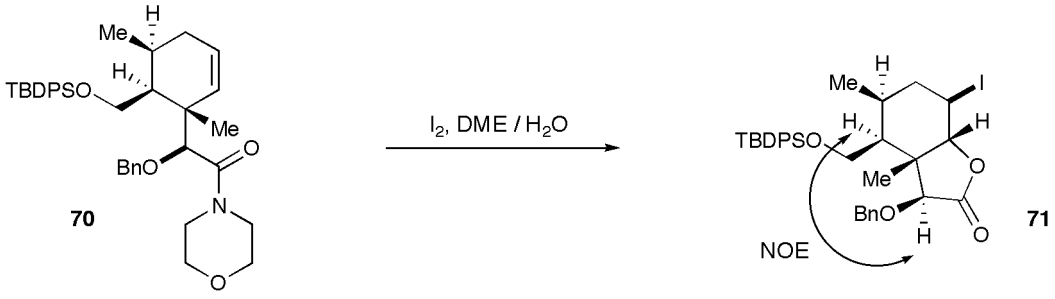
Acyl-Claisen rearrangement of amine **69** proved successful (Scheme 9). Treatment of **69** with benzyloxyacetyl chloride in the presence of Hunig's base and one equivalent of $TiCl_4$ produced Claisen rearrangement product **70** as a single diastereomer in 41% yield. Although our low yielding route to Claisen precursor **69** did not allow for sufficient optimization studies of the rearrangement step, we were confident a suitably high yield was possible. In any case we were highly encouraged by the successful reaction of this complex acyl-Claisen substrate.

Scheme 9. Acyl-Claisen rearrangement of cyclohexenyl amine **69**.



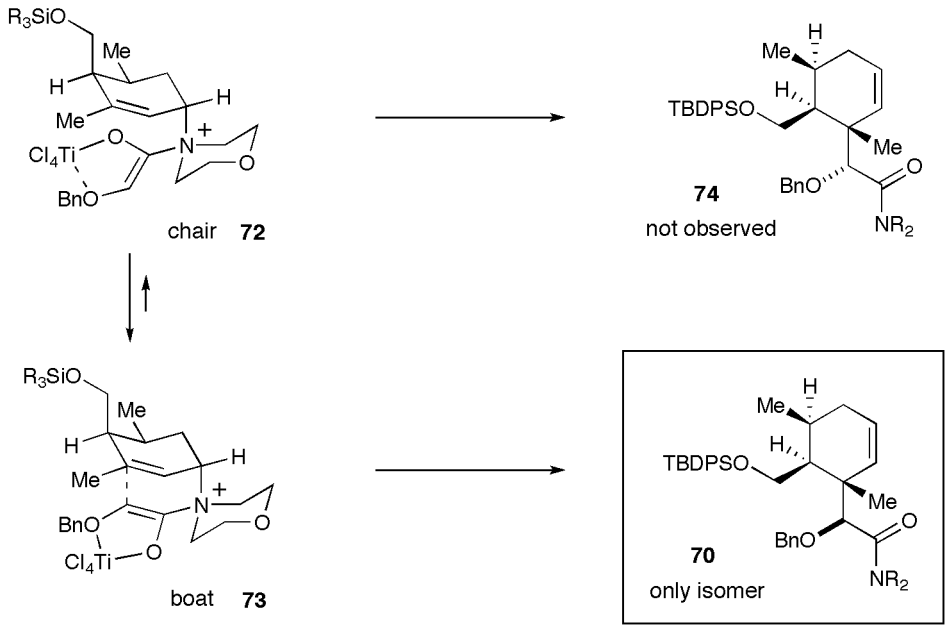
The stereochemistry of the Claisen product was determined by NOE analysis of the bicyclic lactone **71** obtained from iodolactonization of **70**.

Scheme 10. Iodolactonization of the acyl-Claisen rearrangement product **70**.



Our rationale for the observed diastereoselectivity of the acyl-Claisen reaction is based on well-established precedent of the Claisen rearrangement of cyclic substrates[18] (Figure 12). The acyl-Claisen rearrangement of amine **69** could proceed through either a chair-like (**72**) or boat-like (**73**) transition state to provide products epimeric at the □-position. In the chair conformation, however, the titanium-bound acyl-enolate moiety would experience an unfavorable steric interaction with the axial methine proton. In the boat conformation this interaction is absent, and, congruent with Claisen precedent, the observed product (**70**) is that resulting from the boat-like transition state.

Figure 12. Stereochemical rationale for the formation of **70**.



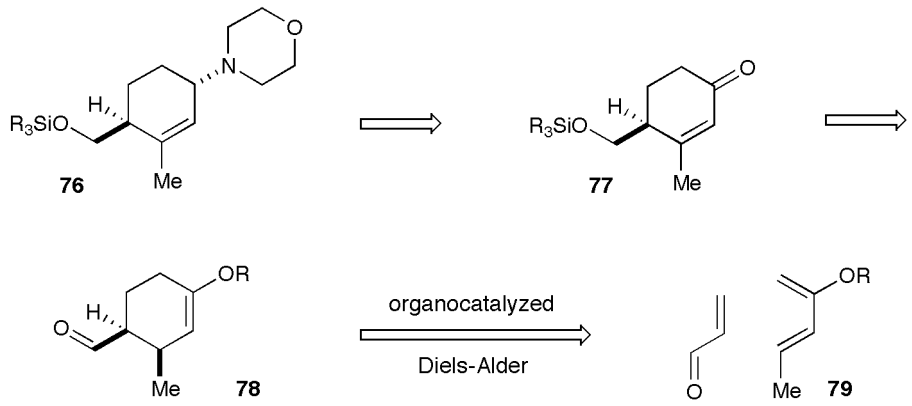
We next turned our attention to the development of a synthetic strategy that would allow facile production of significant quantities of the cyclohexenyl core bearing appropriate functionality.

Based on our rationale of the reduction of iminium **66**, we hypothesized that the reduction stereoselectivity might be reversed for a substrate such as iminium **75** in which the axial methyl group is absent (Figure 13).

Figure 13. Proposed substrate for reversal of reduction selectivity.

Our synthetic strategy incorporating this hypothesis is outlined in antithetic format in Scheme 11. Ketone **77**, which would serve as precursor to the acyl-Claisen substrate **76**, should be readily accessible from enol ether-aldehyde **78**. We were intrigued by the possibility of preparing **78** via another methodology developed in the MacMillan laboratories, namely the organocatalyzed Diels-Alder reaction.

Scheme 11. Retrosynthetic analysis of Claisen substrate **76**.

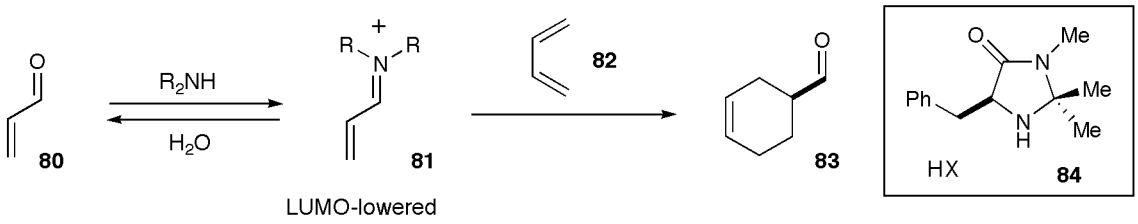


Organocatalysis

The MacMillan group has developed a research program directed at utilizing purely organic molecules as enantioselective reaction catalysts. With this aim, Ahrendt, Borths, and MacMillan reported the LUMO-lowering activation of α,β-unsaturated aldehydes **80** with chiral secondary amines in the first highly enantioselective organocatalytic Diels-Alder reaction[19a] (Figure 14). This organocatalytic protocol is predicated on (1) the reversibility of iminium ion formation **81** between an aldehyde and a secondary amine and (2) the selective reaction of the LUMO-lowered unsaturated iminium ion.

Indeed, the authors reported that imidazolidinone catalyst **84** was efficient at catalyzing the Diels-Alder reaction of a range of unsaturated aldehydes and dienes in a highly enantioselective fashion.

Figure 14. Organocatalyzed Diel-Alder reaction.



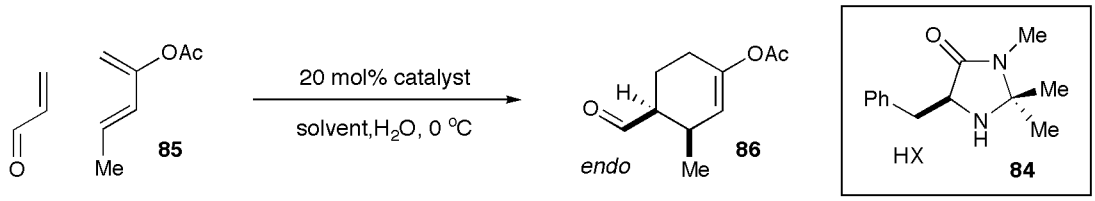
This LUMO-lowering catalysis strategy has since been extended to a number of different reaction technologies including [3+2]-nitrone cycloadditions,[19b] Friedel-Crafts alkylations,[19c,d] intramolecular Diels-Alder reactions,[19e] and Michael reactions.[19f]

Organocatalysis Strategy Towards the Cyclohexenyl Core

We were pleased to find that the organocatalyzed Diel-Alder methodology developed by Ahrendt and Borths proved suitable for our desired transformation. Shown in Table 1 is the condition screen that was performed to optimize this reaction. Thus cycloaddition of 2-acetoxy-1,3-pentadiene (**85**) with acrolein in the presence of 20 mol% imidazolidinone catalyst **84** at 0 °C proved facile with a range of solvents and acid cocatalysts. The optimal combination proved to be perchloric acid in THF which provided the cycloadduct as a 7.8 to 1 *endo:exo* mixture of diastereomers in 91% ee. In all cases the reactions proceeded to completion.

The organocatalytic preparation of aldehyde **86** can be performed on large-scale with no loss in selectivity (Scheme 12). Although the yield upon scale-up is somewhat low (44%) due to presumed polymerization of acrolein, the desired adduct **86** can be accessed readily on a 20 gram scale.

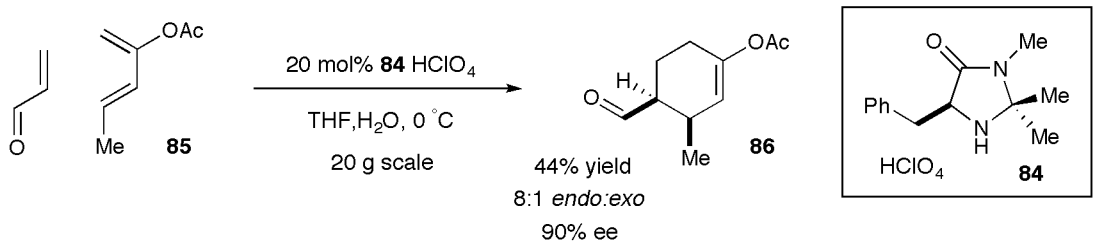
Table 1. Organocatalyzed Diels-Alder reaction towards the cyclohexenyl core.



Solvent	HX	*endo*:*exo*	%ee (*endo*)
THF	HCl	6.2:1	83
	$HClO_4$	7.8:1	91
CH_3CN	HCl	7.9:1	87
	$HClO_4$	8.0:1	84
CH_3NO_2	$HClO_4$	8.6:1	83
	TFA	8.7:1	87

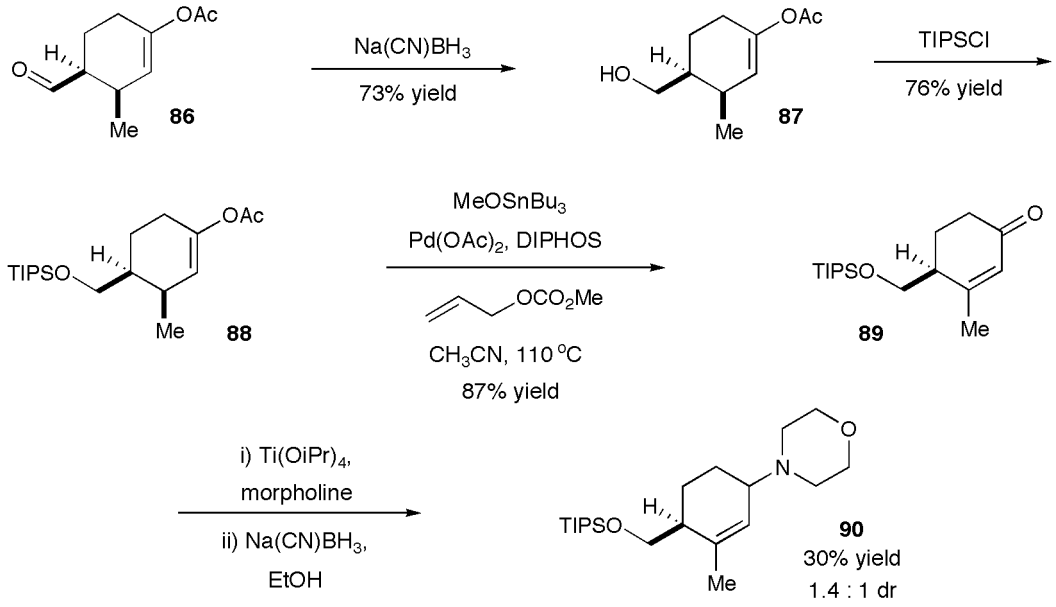
Our studies aimed at the elaboration of aldehyde **86** are presented in Scheme 13. While $NaBH_4$ proved too harsh for the reduction of **86** and resulted in cleavage of the vinyl acetate moiety, treatment of **86** with excess $Na(CN)BH_3$ provided the alcohol **87** cleanly in 73% yield. After protection with TIPSCl, vinyl acetate **88** was then converted to □,□-unsaturated ketone **89** via a Saegusa-type oxidation according to a modified procedure of Tsuji.[20]

Scheme 12. Large-scale organocatalyzed Diels-Alder reaction.



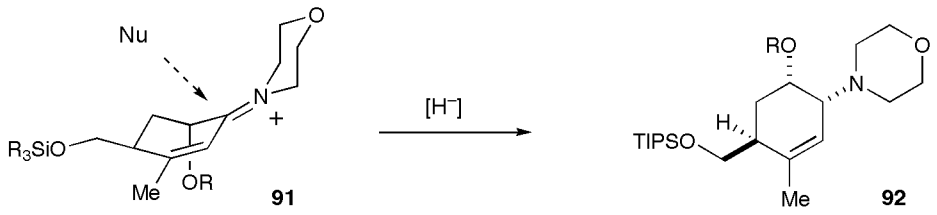
Unfortunately, when ketone **89** was subjected to the standard reduction amination conditions, allylic morpholine **90** was produced in low yield with almost no diastereoselectivity. Alteration of the reducing agent had no effect on this ratio.

Scheme 13. Elaboration of aldehyde **86**.



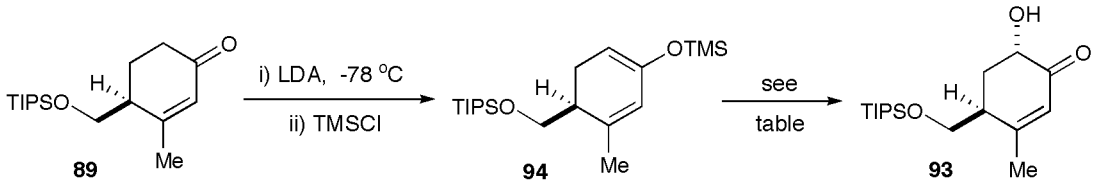
To address the issue of poor selectivity, we decided to install the C(2) oxygenation required of the erythrolide E framework. Our expectation was that this stereocenter would direct the facial selectivity of reduction in the desired sense (Figure 15).

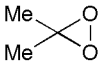
Figure 15. Proposed reduction selectivity with C(2) stereocenter.



To install the requisite oxygen stereocenter, we decided to utilize the well-known strategy of silyl enol ether oxidation[21] (Table 2). As such, ketone **89** was subjected to enolization with LDA at low temperature followed by TMSCl quench. Although used as a crude isolate, the intermediate siloxy diene **94** was pure as judged by ^{1}H NMR spectroscopy.

Table 2. Oxidation of ketone **89**.



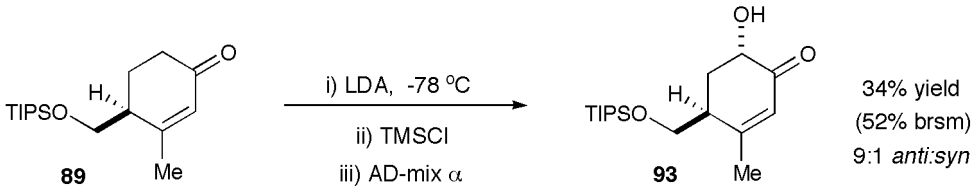
Reagent	trans:cis
mCPBA	2:1
	4:1
OsO_4, NMO	4:1
AD-mix α	9:1

A number of conditions for the oxidation of silyl enol ether **94** were screened including mCPBA, dimethyldioxirane, and OsO_4. However all of these reagents resulted in at best a 4:1 diastereoselectivity. To address this issue, we decided to employ

Sharpless' chiral dihydroxylating system,[22] the commercially available AD-mix β, which provided the desired hydroxy ketone **93** as a 9:1 *trans:cis* mixture of diastereomers.

We were somewhat disappointed with the low yield of this transformation (34%, 52% based on recovered starting material) (Scheme 14). We hypothesized that the low mass recovery might be a consequence of over oxidation since such highly polar products would tend to remain in the aqueous layer during workup. Nonetheless, this procedure allowed us to access sufficient quantities of hydroxyketone **93** with which to continue our investigations.

Scheme 14. Optimal hydroxylation procedure.

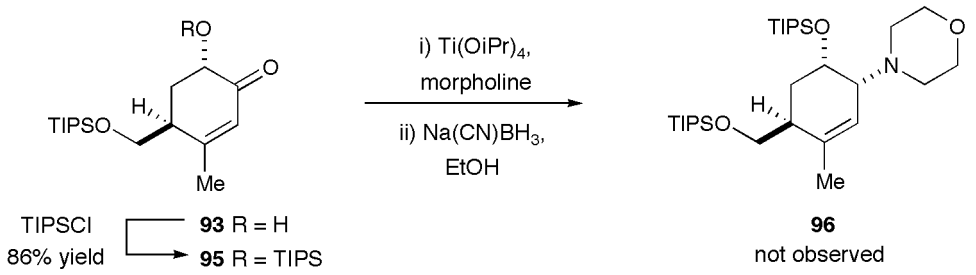


After protection of the newly formed hydroxyl group with TIPSCl to provide ketone **95**, we were ready for the reductive amination step (Scheme 15). Unfortunately **95** was completely unreactive to the reductive amination conditions and no products involving incorporation of morpholine were observed. The reason for the complete failure of this transformation is almost surely due to the very high steric demands of forming the tetrasubstituted iminium ion intermediate.

Given our inability to convert ketone **95** into the appropriate acyl-Claisen substrate, we decided to continue with our synthetic efforts by accessing the cyclohexenyl core fragment by way of an Ireland Claisen rearrangement[23] (Scheme 16). As such, ketone **95** was reduced with $NaBH_4$ to provide allylic alcohol **97** as a single

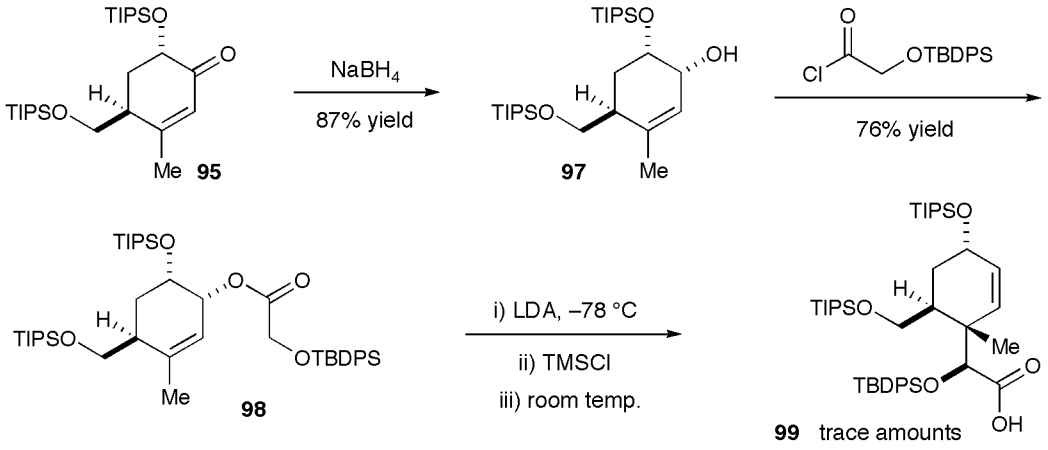
diastereomer. Acylation with *tert*-butyldiphenylsiloxyacetyl chloride then provided Ireland Claisen substrate **98**.

Scheme 15. Attempted reductive amination of ketone **95**.



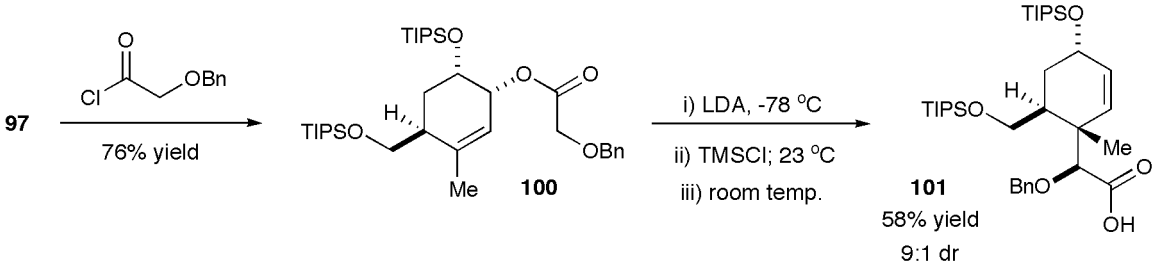
Unfortunately, when subjected to standard Ireland-Claisen conditions (LDA, TMSCl, -78 °C, then warming) substrate **98** failed to produce more than trace amounts of Claisen adduct **99**. We hypothesized that this lack of reactivity was due to the extraordinarily large size of the TBDPS protecting group. Therefore, we decided to prepare a less sterically demanding substrate.

Scheme 16. Preparation of Ireland-Claisen substrate **98**.



As shown in Scheme 17, allylic alcohol **97** was acylated with benzyloxyacetyl chloride to provide Ireland-Claisen substrate **100**. When subjected to the appropriate Ireland-Claisen conditions, **100** underwent reaction to provide the cyclohexenyl core acid **101** in 58% yield based on recovered starting material as a 9:1 mixture of diastereomers.

Scheme 17. Ireland-Claisen rearrangement of acyloxy substrate **100**.

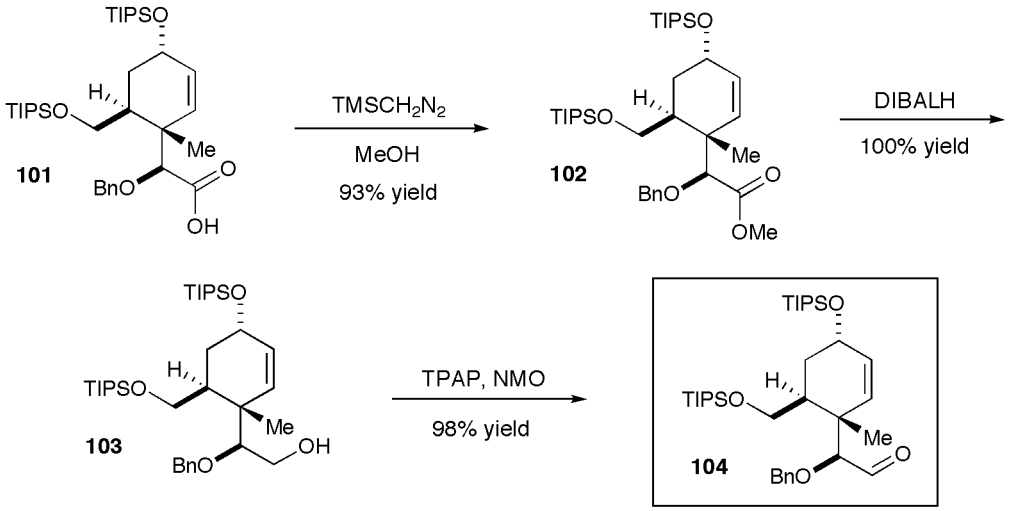


It should be noted that our acyl-Claisen methodology has been shown to provide much greater diastereoselectivity (>99:1) than the Ireland-Claisen rearrangement with similar substrates. The drawback to the acyl-Claisen approach is thus merely a lack of suitable reaction technology to prepare the appropriate acyl-Claisen substrate.

Although use of the Ireland-Claisen protocol was a departure from our outlined goals, it allowed us to access the desired core fragment with which to investigate the later stages of our synthetic plan.

In order to complete the synthesis of the requisite aldehyde coupling partner, acid **101** was methylated with $TMSCH_2N_2$, reduced (DIBALH), and oxidized (TPAP)[24] to provide the complex fragment **104** in 91% yield over 3 steps (Scheme 18).

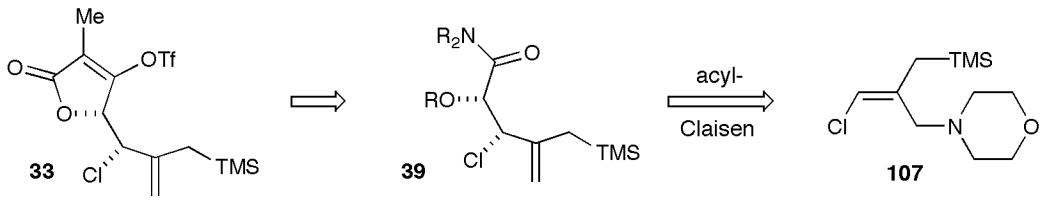
Scheme 18. Completion of the synthesis of coupling fragment **104**.



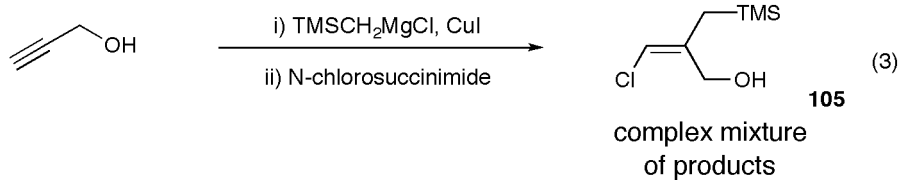
Synthesis of the Acyclic Fragment

With a suitable route in place to access core fragment **104**, we turned our attention to the synthesis of the second coupling partner, methallyl silane **33** (Scheme 19). To reiterate, we felt confident that compound **33** could be prepared from the complex amide **39**, which in turn should be readily prepared with our acyl-Claisen methodology. Thus to begin our studies of this phase of our total synthetic effort, we required a facile synthesis of the Claisen precursor, allyl amine **107**.

Scheme 19. Strategy for the preparation of coupling fragment **33**.

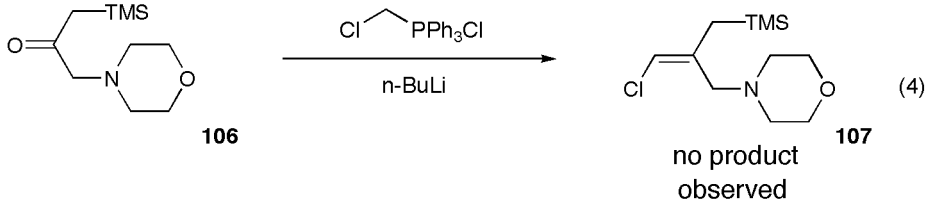


Although preparation of substrate **107** proved much more straightforward than the cyclohexenyl Claisen precursor, we investigated several unsuccessful routes before success was found. As most simple allyl morpholines used in the acyl-Claisen studies were prepared from the corresponding allylic alcohols, we intitially sought to prepare amine **107** by way of alcohol **105** (Eq. 3). Attempted trimethylsilylmethylation of propargyl alcohol followed by halogen quenching, however, provided only a complex mixture of products.



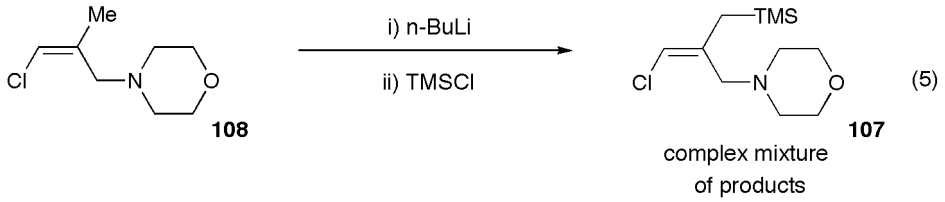
(3)

Alternatively, we investigated Wittig olefination of ketone **106** with chloromethyltriphenylphosphonium chloride. Unfortunately, this reaction was unsuccessful as well, resulting only in recovered starting material (Eq. 4).



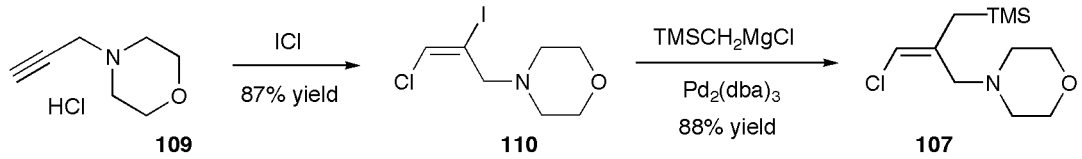
(4)

Finally, we were unsuccessful in functionalizing the methallyl position of amine **108**, undoubtedly due to the incompatibility of the vinyl halide moiety and the alkyl lithium species (Eq. 5).



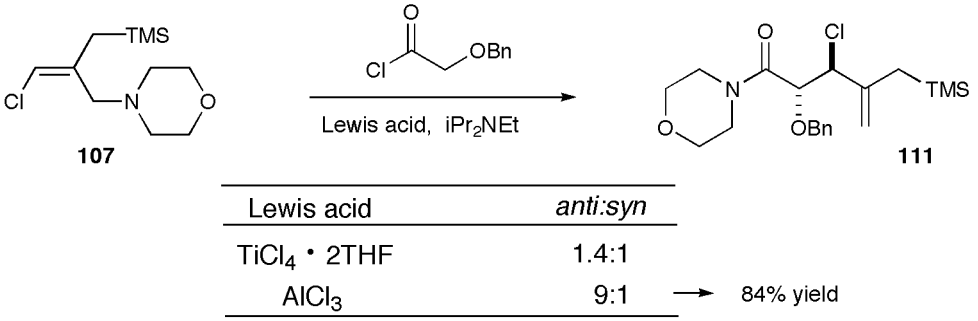
Success came by application of methodology reported by Lambert et al. (Scheme 20).[25] Treatment of propargyl morpholine hydrochloride with iodine monochloride in refluxing THF provided the bishalogenated substrate **110** in 87% yield as a readily separable 11:1 mixture of regioisomers. The regioselectivity of this reaction is due to the electron withdrawing nature of the ammonium chloride functionality. Completion of the synthesis of allyl amine **107** was accomplished by transition metal coupling of vinyl iodide **110** with $TMSCH_2MgCl$. A screen of palladium and nickel reagents identified $Pd_2(dba)_3$ as the optimal catalyst for this transformation, providing the amine **107** in 88% yield.

Scheme 20. Preparation of the acyclic acyl-Claisen substrate.



When allyl amine **107** was treated with benzyloxyacetyl chloride in the presence of iPr_2NEt and one equivalent of $TiCl_4$, Claisen product **111** was produced with a very poor diastereoselectivity (1.4:1 *anti:syn*) (Scheme 21). We were pleased to find, however that with the use of $AlCl_3$, the diastereoselectivity could be increased to 9:1 *anti:syn.*

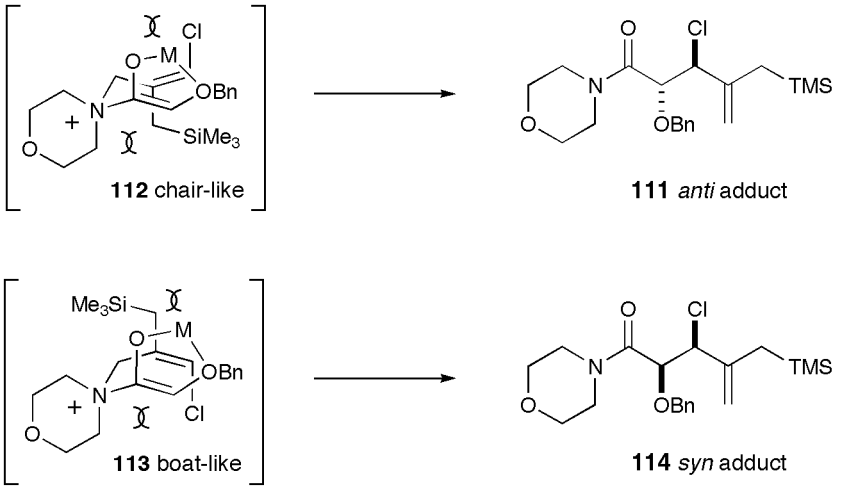
Scheme 21. Acyl-Claisen rearrangement of allyl amine **107**.



Lewis acid	*anti:syn*	
$TiCl_4$ • 2THF	1.4:1	
$AlCl_3$	9:1	→ 84% yield

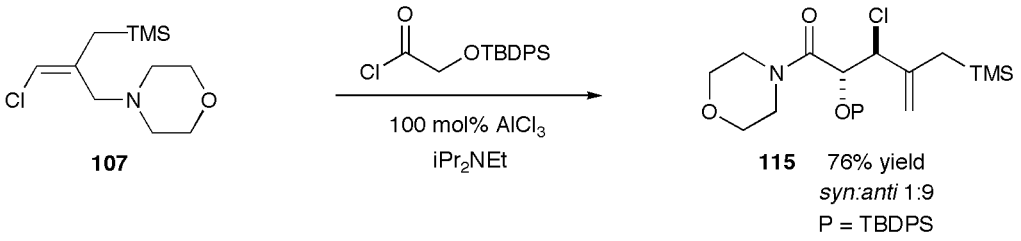
The reason for the disparity between the two Lewis acids in this reaction is unclear. Given the known high levels of (*Z*)-enolate formation in the addition of nucleophiles to ketenes and barring enolate equilibration, the two diastereomers must arise from competition between chair-like **112** and boat-like **113** transition states (Figure 16). In both transition states, however, several transannular interactions exist between the chloro, trimethylsilylmethyl, morpholine, and metal-bound enolate moieties. It might be proposed that dative bonding between the chloro group and the aluminum metal center enforces the chair-like transition state thus leading to the *anti* product **111**.

Figure 16. Transition states for acyl-Claisen rearrangement of amine **107**.



Notably, acyl-Claisen technology allowed for the facile preparation of adduct **115** that incorporates α-silyloxy substitution in good yield and with diastereoselectivity equal to the alkoxy substituted case (Scheme 22). This fact represents an important point of flexibility in anticipation of synthetic elaboration of this coupling fragment.

Scheme 22. Alternative acyl-Claisen rearrangement of allyl amine **107**.



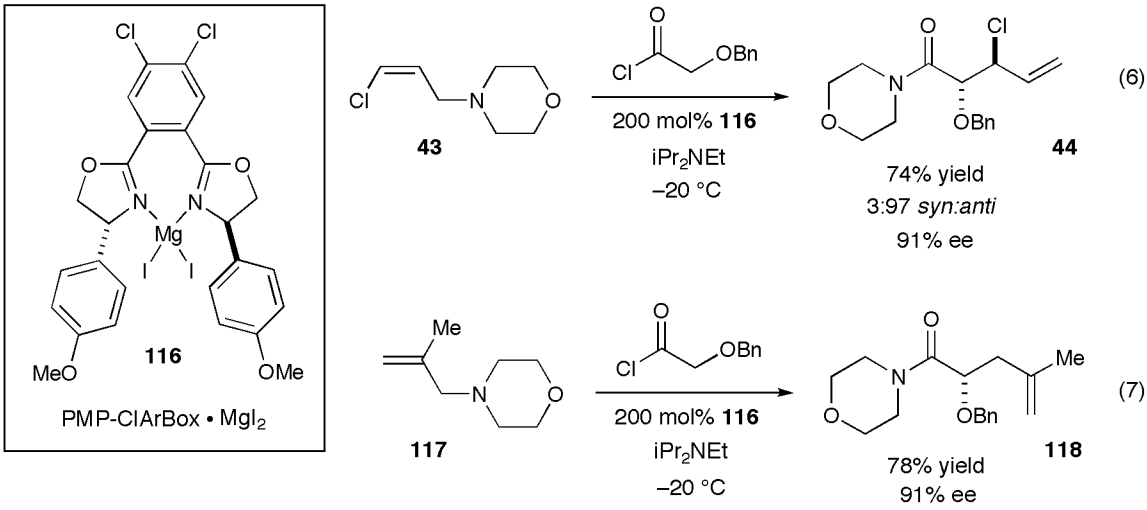
Asymmetric Synthesis of the Acyclic Fragment

Motivated by our success in accessing this complex fragment **111** of the erythrolide architecture in a racemic fashion, we turned our attention to preparing enantiomerically enriched material as required by our coupling strategy. To accomplish this goal, we anticipated employing the enantioselective acyl-Claisen protocol developed by Tehshik Yoon in our laboratories (see chapter 1).[26]

To restate, Yoon developed a protocol for the enantioselective acyl-Claisen rearrangement of allyl amines with α-benzyloxyacetyl chloride (Figure 17). By employing two equivalents of the magnesium aryl-Box complex **116**, a diverse range of Claisen adducts could be accessed in good yield and with excellent enantioselectivities. Of primary significance to our studies was the reaction of cis-chloro substrate **43** which, in the presence of **116**, produced the *anti* Claisen adduct **44** in 91% ee. Notably, amide **44** differs from our desired synthetic fragment **111** by only a trimethylsilylmethyl

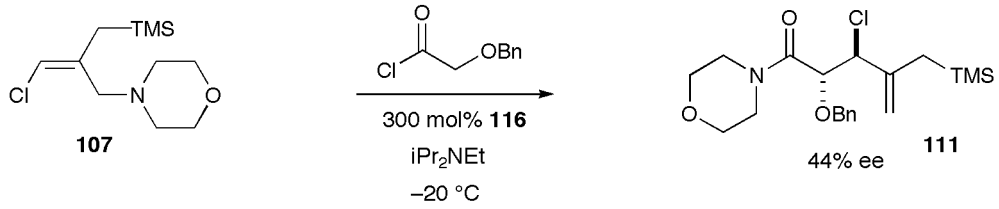
substituent. Further, it was shown that methallyl substitution was well tolerated in the asymmetric Claisen reaction, with methallyl morpholine (**117**) providing adduct **118** with similarly high enantioenrichment.

Figure 17. Enantioselective acyl-Claisen method.



Unfortunately, when allyl amine **107** was subjected to Yoon's optimal conditions using 300 mol% of chiral promoter **116**, the Claisen adduct **111** was produced in only 44% ee and with very low conversion (Scheme 23). It would seem that the demands imposed by incorporating both the cis electron- withdrawing chloro substituent and the bulky methallyl substituent are too severe.

Scheme 23. Asymmetric rearrangement of amine **107**.

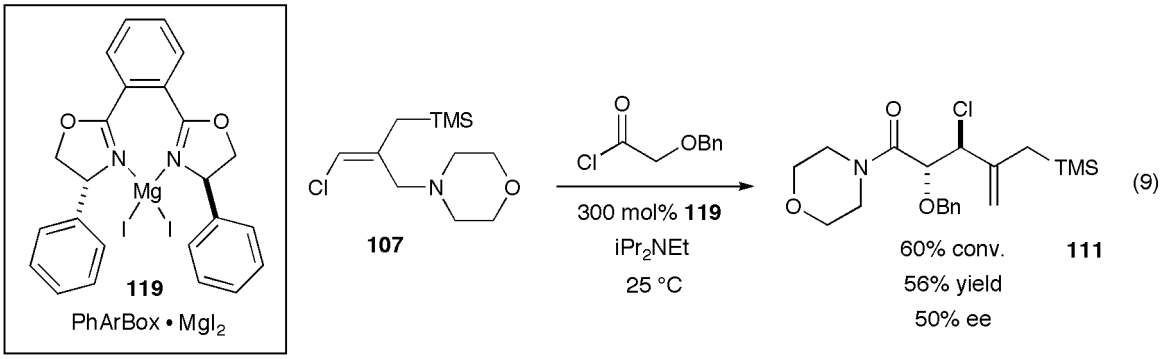


(8)

To address the problem of reactivity, we decided to employ a catalyst system that Yoon had found to be somewhat more reactive, namely, complex **119**. We were encouraged to find that with 300 mol% of **119** the Claisen adduct **111** could be obtained with 50% enantioselectivity and in 56% isolated yield at room temperature (Scheme 23).

The result shown in Equation 9 is our best to date. Though certainly not optimal, the 3:1 enantiomeric ratio achieved with chiral promoter **119** must be viewed as very promising.

Scheme 24. Asymmetric rearrangement of amine **107**.



(9)

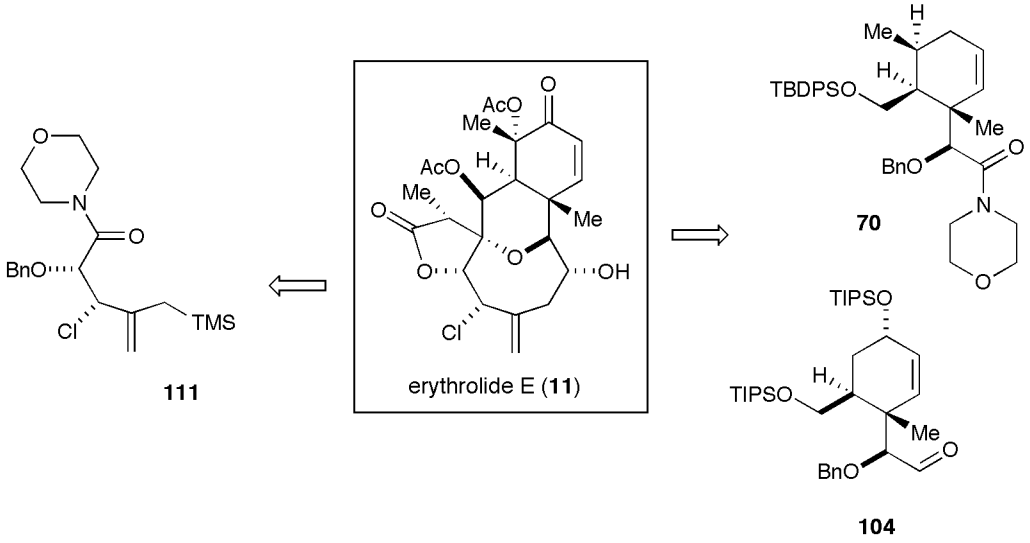
Concluding Remarks

Our principal goal of demonstrating the utility of the acyl-Claisen rearrangement for the rapid and selective generation of complex architecture in a natural product setting

has been achieved with the preparation of fragments **70** and **111** (Figure 18). Further, we have developed a concise route to access enantioenriched coupling fragment **104** using as key steps a novel organocatalytic Diels-Alder reaction and an Ireland-Claisen rearrangement.

Our broader goal of accomplishing a total synthesis of erythrolide E remains a challenge. In particular, suitable technologies for the asymmetric preparation of the core acyl-Claisen substrate must be developed. In addition, optimization of the enantioselective acyl-Claisen construction of fragment **111** is required. Finally, investigations of fragment coupling and subsequent elaboration parameters are requisite for a successful total synthetic achievement.

Figure 18. Summary of progress.



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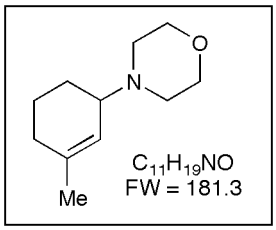
Experimental Section

General Information. All reactions were performed using oven-dried glassware under an atmosphere of dry argon. Non-aqueous reagents were transferred under argon or nitrogen by syringe. Organic solutions were concentrated under reduced pressure using a Buchi rotary evaporator. Methylene chloride (CH_2Cl_2), diisopropylethylamine (iPr_2NEt), and triethylamine (Et_3N) were distilled under N_2 from calcium hydride immediately prior to use. Tetrahydrofuran (THF) and ether were distilled under N_2 from sodium / benzophenone immediately prior to use. Acetic anhydride, 2-(benzyloxy)acetyl chloride, titanium (IV) tetraisopropoxide ($Ti(OiPr)_4$), and trimethylsilyltrifluoromethane-sulfonate (TMSOTf) were distilled under reduced pressure and stored under N_2 in sealed Schlenk flasks. Sodium and lithium metals were washed with hexane followed by THF immediately prior to use. All other commercial reagents were used as provided. Air sensitive solids were dispensed in an inert atmosphere glovebox. 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.[1] 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 $KMnO_4$ or p-anisaldehyde stain.

^1H and ^{13}C NMR were recorded on Mercury 300 (300 MHz and 75 MHz) or Bruker AMX-400 or AMX-300 spectrometers as noted, and are internally referenced to residual protio solvent signals. Data for ^1H NMR are reported as follows: chemical shift (ppm), multiplicity (s = singlet, brs = broad 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 1600 Series spectrometer using NaCl salt plates or with a ASI ReactIr system and are reported in terms of frequency of absorption (cm^{-1}). Mass spectra were obtained from the Mass Spectral Facility at the University of California at Berkeley or at Caltech. Gas chromatography was performed on Hewlett-Packard 6890 Series gas chromatograph equipped with split-mode capillary injection system and flame ionization detector using a C&C Column Technologies CC-1701 (30 m x 0.25 mm).

3-Methyl-1-morpholino-2-cyclohexene (41). A modified procedure of Mattson et al. was employed.[2] To a solution of 3-methyl-2-cyclohexen-1-one (1.50 g, 13.7 mmol) and morpholine (3.57 g, 41.0 mmol) in CH_2Cl_2 (120 mL) was added $Ti(OiPr)_4$ (14.59 g, 51.4 mmol) The reaction was monitored by react IR for disappearance of the ketone stretch. After 6 h the solution was concentrated, and EtOH (45 mL) was added, followed by $Na(CN)BH_3$ (1.81 g, 28.8 mmol). The solution was stirred for 1 h, before 1 N NaOH (30 mL) was added. The resulting mixture was extracted with EtOAc (3 x 50 mL), and the combined organic extracts were dried over Na_2SO_4 and concentrated. The crude residue was purified by silica gel chromatography using EtOAc to furnish amine **41** as a brown oil in 19% yield (0.47 g, 2.6 mmol). The spectral data for **41** were identical to that for the previously reported compound.[3]



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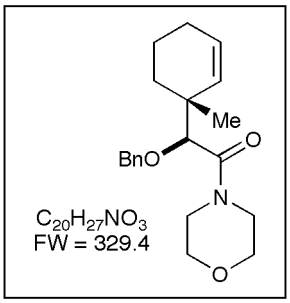
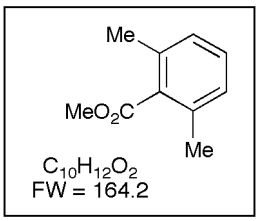
Morpholine-2-(1-methyl-2-cyclohexenyl)-2-benzyloxy-ethanamide (42). To amine **41**



(0.05 g, 0.3 mmol), iPr_2NEt (0.07 g, 0.6 mmol) and $TiCl_4 \cdot THF_2$ (0.09 g, 0.3 mmol) in CH_2Cl_2 (3 mL) was added 2-benzyloxyacetyl chloride (0.41 mL, 1.0 M in CH_2Cl_2) over 4 h by syringe pump. The resulting solution was diluted with Et_2O (10 mL) and 1 N NaOH (2 mL) was added. The resulting mixture was stirred for 5 min before the layers were separated and the organic layer was washed with brine, dried over Na_2SO_4, and concentrated. The crude residue was purified by silica gel chromatography using 35% EtOAc:hexanes to provide amide **42** as a yellow oil in 33% yield (0.03 g, 0.09 mmol). IR (CH_2Cl_2) 3053, 3030, 2968, 2926, 2864, 1644, 1455, 1436 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) □ 7.33 (m, 5H, Ar**H**), 5.69 (m, 2H, CC**H**C**H**CH_2), 4.64 (d, *J* = 12.1 Hz, 1H, OC**H**(H)Ph), 4.42 (d, *J* = 12.1 Hz, 1H, OC**H**(H)Ph), 4.00 (s, 1H, CC**H**(O)), 3.49-3.71 (m, 8H, N($C\mathbf{H}_2$)$_2$ and O($C\mathbf{H}_2$)$_2$), 1.38-1.96 (m, 6H, CHC$\mathbf{H}_2$C$\mathbf{H}_2$C$\mathbf{H}_2$C), 1.09 (s, 3H, C$\mathbf{H}_3$); ^{13}C NMR (100 MHz, $CDCl_3$) □ 169.0, 137.5, 132.6, 128.4, 127.9, 127.9, 127.3, 72.7, 67.2, 66.7, 50.2, 46.7, 42.6, 39.3, 32.4, 24.9, 24.5, 19.0; HRMS (FAB) *m/z* 330.2072 (MH, 330.2069 calcd for $C_{20}H_{27}NO_3H$).

Methyl 2,6-dimethylbenzoate (45). To 2,6-dimethylbenzoic acid (6.38 g, 42.5 mmol) in

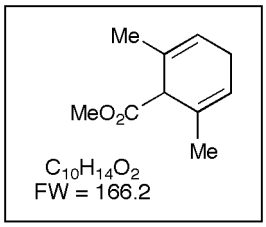


MeOH (100 mL) was added 1,3-dicyclohexylcarbodiimide (DCC) (8.76 g, 42.5 mmol). After stirring for 9 h solid was removed by filtration and H_2O (100 mL) was added to the filtrate to produce a white precipitate. The resulting mixture was filtered and the

[3] Birch, A. J. et al. *J. Chem. Soc. C* **1971**, 2409.

filtrate was extracted with CH_2Cl_2 (3 x 100 mL). The organic layer was dried over Na_2SO_4 and concentrated to give a yellow semi-solid. The residue was purified by silica gel chromatography using 20% EtOAc:hexane to provide methyl 2,6-dimethylbenzoate (**45**) as a colorless oil in 87% yield (6.04 g, 36.8 mmol). The spectral data for **45** was identical to that for the previously reported compound.[4]

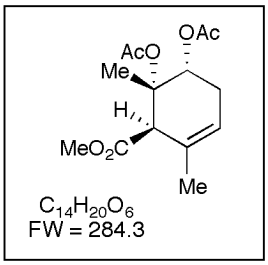
Methyl 2,6-dimethyl-2,5-cyclohexadiene-1-carboxylate (46). To methyl 2,6-dimethylbenzoate (**45**) (9.41 g, 57.4 mmol) and *tert*-BuOH (4.25 g, 57.4 mmol) in THF (30 mL) and NH_3 (60 mL) at –78 ºC was added sodium metal (8.0 g, 35 mmol) resulting in a yellow liquid covered by a brown oil. The mixture was stirred for 0.5 h before NH_4Cl (10 g) was added, and the flask was warmed to room temperature to remove NH_3. The resulting residue was dissolved in H_2O (100 mL) and extracted with Et_2O (3 x 50 mL). The organic extracts were dried over Na_2SO_4 and concentrated. The crude residue was purified by silica gel chromatography using 10% EtOAc:hexane to provide diene **46** as a clear, yellow oil in 50% yield (4.78 g, 28.8 mmol). The product was determined pure by ^{1}H NMR and TLC analysis and was used without further purification. IR (CH_2Cl_2) 2937, 2918, 2864, 1733, 1436 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) □ 5.56 (brs, 2H, CC**H**CH_2), 3.64 (s, 3H, C(O)OC**H**$_3$), 3.42 (t, *J* = 6.6 Hz, 1H, C**H**C(O)OCH_3), 2.76 (d, *J* = 16.0 Hz, 1H, CHC**H**(H)CH),), 2.62 (d, *J* = 16.0 Hz, 1H, CHC**H**(H)CH), 1.64 (s, 6H, C**H**$_3$); ^{13}C NMR (100 MHz, $CDCl_3$) □ 173.2, 128.6, 121.8, 52.3, 52.1, 27.5, 21.7; HRMS (EI) *m/z* 166.0994 (M, 166.0994 calcd for $C_{10}H_{14}O_2$).



[4] Jung, M. E.; Hagenah, J. A. *J. Org. Chem.* **1987**, *52*, 1889.

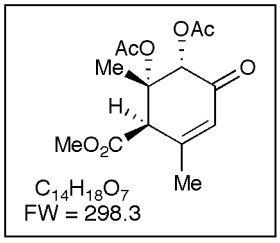
Methyl (1*R, 2*S**, 3*R**)-2,3-dihydroxy-2,6-dimethyl-5-cyclohexene-1-carboxylate (47).** To a mixture of *tert*-BuOH (140 mL) and H_2O (140 mL) was added AD-Mix (Aldrich Chemical Co.) (40.75 g). The mixture was stirred until two distinct layers were visible, with the bottom layer appearing bright orange. Methanesulfonamide (2.27 g, 23.9 mmol) was added, the flask was cooled to 0 ºC, and diene **46** (4.78 g, 23.9 mmol) was added with vigorous stirring. After stirring at 0 ºC for 67 h, Na_2SO_3 (36 g) was added and the flask was allowed to warm to room temperature. EtOAc (100 mL) was added and the layers were separated. The aqueous layer was extracted with EtOAc (3 x 100 mL) and the combined organic extracts were washed with 2 N KOH (200 mL), dried over Na_2SO_4, and concentrated. The crude residue was purified by silica gel chromatography using 85% EtOAc:hexane to provide diol **47** as a glassy solid in 85% yield (4.06 g, 20.3 mmol). IR (CH_2Cl_2) 3567, 3451, 2980, 2953, 2918, 2860, 1733, 1436, 1320 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) 5.42 (brs, 1H, CC**H**CH_2), 3.89 (dd, *J* = 6.0, 6.0 Hz, 1H, C**H**OH), 3.69 (s, 3H, C(O)OC**H**$_3$), 3.20 (s, 1H, C**H**C(O)OCH_3), 2.87 (brs, 2H, CHO**H** and CO**H**), 2.36 (d, *J* = 18.0 Hz, 1H, CHC**H**(H)CH), 2.11 (d, *J* = 18.0 Hz, 1H, CHC**H**(H)CH), 1.63 (s, 3H, CC**H**$_3$), 1.19 (s, 3H, C(OH)C**H**$_3$); ^{13}C NMR (100 MHz, $CDCl_3$) 172.9, 129.1, 121.7, 72.3, 70.4, 57.2, 52.0, 31.1, 22.4, 21.7; ; HRMS (FAB) *m/z* 201.1130 (MH, 201.1127 calcd for $C_{10}H_{16}O_4H$).

Methyl (1*R, 2*S**, 3*R**)-2,3-diacetoxy-2,6-dimethyl-5-cyclohexene-1-carboxylate (48).** To diol **47** (4.06 g, 20.3 mmol) and 4-(dimethylamino)pyridine (DMAP) in Et_3N (5 mL) was added acetic anhydride (6.22 g, 60.9 mmol). After stirring for 58 h the solution



was acidified with 2 N HCl to pH <2 and then diluted with Et_2O (10 mL). The layers were separated and the organic layer was washed with saturated $NaHCO_3$, dried over Na_2SO_4, and concentrated. The crude residue was purified by silica gel chromatography using 35% EtOAc:hexane to furnish bisacetate **48** as a white solid in 58% yield (3.33 g, 11.7 mmol). IR (CH_2Cl_2) 1737, 1436, 1370, 1239 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) □ 5.47 (m, 2H, CC**H**CH_2 and C**H**(OC(O)CH_3)), 4.11 (s, 1H, C**H**C(O)OCH_3), 3.71 (s, 3H, C(O)OC**H**$_3$), 2.42 (d, *J* = 17.4 Hz, 1H, C**H**(H)), 2.25 (d, *J* = 17.4 Hz, 1H, C**H**(H)), 2.07 (s, 3H, C(O)C**H**$_3$), 1.98 (s, 3H, C(O)C**H**$_3$), 1.62 (s, 3H CC**H**$_3$), 1.55 (s, 3H, C(OC(O)CH_3)C**H**$_3$); ^{13}C NMR (100 MHz, $CDCl_3$) □ 171.6, 170.3, 170.2, 128.5, 121.8, 80.2, 71.5, 53.2, 52.1, 28.1, 22.2, 21.7, 21.1, 19.4; HRMS (FAB) *m/z* 285.1338 (MH, 285.1338 calcd for $C_{14}H_{20}O_6H$).

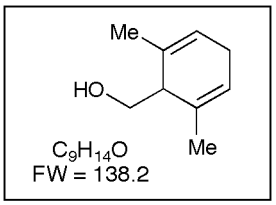
(1*R, 2*S**, 3*R**)-2,3-diacetoxy-3,5-dimethyl-4-methylcarboxylate-5-cyclohexen-1-one**



(49). To ester **48** (1.29 g, 4.5 mmol) in AcOH (10.6 mL) and acetic anhydride (6.4 mL) was added solid Na_2CrO_4 (2.93, 18.1 mmol). The mixture was observed to change from orange to dark green over the course of the reaction. After stirring for 65 h the solution was poured onto saturated $NaHCO_3$ (50 mL) overlaid with Et_2O (20 mL), stirred for 1 h, and then diluted with H_2O (20 mL). The aqueous layer was extracted with Et_2O (3 x 50 mL) and the combined extracts were dried over Na_2SO_4 and concentrated to a white solid. The residue was purified by silica gel chromatography using 35% EtOAc:hexane to furnish ketone **49** as a white solid in 23% yield (0.31 g, 1.0 mmol). IR

(CH_2Cl_2) 1741, 1702, 1498, 1436, 1374, 1227; ^{1}H NMR (400 MHz, $CDCl_3$) 6.02 (s, 1H, C**H**(OC(O)CH_3)), 5.96 (s, 1H, CC**H**CH_2), 4.67 (s, 1H, C**H**C(O)OCH_3), 3.78 (s, 3H, C(O)O**CH**$_3$), 2.22 (s, 3H, CH(O)C**H**$_3$), 1.95 (s, 3H, C(O)C**H**$_3$), 1.92 (s, 3H, CC**H**$_3$), 1.64 (s, 3H, C(OC(O)CH_3)C**H**$_3$); ^{13}C NMR (100 MHz, $CDCl_3$) 190.3, 170.4, 170.1, 168.9, 152.0, 126.7, 83.6, 76.0, 54.4, 53.1, 22.9, 22.1, 20.6, 19.6; LRMS (FAB) *m/z* 299 $(MH)^+$.

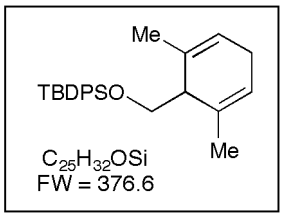
2,4-dimethyl-3-hydroxymethyl-1,4-cyclohexadiene (54). To a solution of 2,6-dimethylbenzoic acid (**52**) (20.40 g, 135.8 mmol) in NH_3 (1000 mL) and EtOH (134 mL) at –40 ºC (±5 ºC) was added lithium metal (4.70 g, 677 mmol). The deep blue solution was stirred for several minutes until a white suspension was observed. At this point NH_4Cl (50 g) was added and the flask was allowed warmed to room temperature to remove NH_3. The resulting solid residue was dissolved in H_2O (300 mL) and then acidified with 1 N HCl to pH <2. The resulting solution was extracted with EtOAc (3 x 250 mL), dried over Na_2SO_4, and concentrated to provide the acid **53** as a white solid in 87% yield (18.06 g). The spectral data for acid **53** was identical to that for the previously reported compound.[5] Acid **53** was used without further purification.



To a solution of $LiAlH_4$ (6.50 g, 171 mmol) in Et_2O (140 mL) at 0 ºC was added a solution of acid **53** (17.50 g, 115.0 mmol) in Et_2O (100 mL) and the flask was allowed to warm to 23 ºC over 1 h where it was maintained for a further 10 h. At this point the solution was adjusted to pH <2 with 1 N HCl and the layers were separated. The aqueous layer was extracted with Et_2O (3 x 100 mL) and the combined organic extracts were dried over Na_2SO_4 and concentrated to give alcohol **54** as a yellow oil in 87% yield (13.79 g,

99.8 mmol) which was determined to be pure by ^{1}H NMR and ^{13}C NMR analysis. Alcohol **54** was used without further purification. IR (CH_2Cl_2) 3570, 2968, 2937, 2918, 2887, 2860, 2826, 1447, 1386 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.71 (brs, 2H, CC**H**CH_2), 3.76 (brm, 2H, C**H**$_2$OH), 2.66 (m, 3H, CHC**H**$_2$CH and CC**H**(CH_2OH)C), 1.76 (s, 6H, CC**H**$_3$), 1.23 (t, *J* = 6.1 Hz, 1H, O**H**); ^{13}C NMR (75 MHz, $CDCl_3$) δ 131.7, 123.3, 60.8, 47.8, 28.0, 21.6; HRMS (EI) *m/z* 138.1042 (M, 138.1045 calcd for $C_9H_{14}O$).

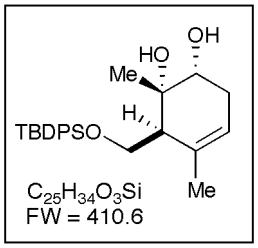
2,4-dimethyl-3-(*tert*-butyldiphenylsiloxy)methyl-1,3-cyclohexadiene (55). To a solution of alcohol **54** (7.00 g, 50.7 mmol), 4-(dimethylamino)pyridine (DMAP) (0.49 g, 4.0 mmol), and Et_3N (8.5 mL) in CH_2Cl_2 (100 mL) was added *tert*-butyldiphenylchlorosilane (TBDPSCl) (13.92 g, 50.7 mmol). After stirring for 20 h the resulting white precipitate was filtered off through a Celite pad and washed with CH_2Cl_2 (20 mL). The filtrate was then washed with saturated NH_4Cl (150 mL) followed by brine (150 mL), dried over Na_2SO_4, and then concentrated to provide the silyl ether **55** as a white solid in 88% yield (16.71 g, 44.4 mmol). Silyl ether **55** was determined pure by ^{1}H NMR and TLC analysis. IR (CH_2Cl_2) 2964, 2934, 2883, 2860, 1475, 1428 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.72 (d, *J* = 9.5 Hz, 4H, SiC(C**H**)$_2$), 7.45 (m, 6H, SiCCH(C**H**)$_2$ and SiCCHCHC**H**), 5.63 (brs, 2H, CC**H**CH_2), 3.76 (d, *J* = 3.8 Hz, 2 H, C**H**$_2$OSi), 2.72 (d, *J* = 16.2 Hz, 1H, CHC**H**(H)CH), 2.60 (d, *J* = 16.2 Hz, 1H, CHC**H**(H)CH), 2.58 (m, 1H, CC**H**(CH_2OSi)C), 1.76 (s, 6H, CC**H**$_3$), 1.07 (s, 9H, SiC(C**H**$_3$)$_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 135.7, 134.0, 133.3, 129.6, 127.6,



[5] Grossel, M. C. *J. Chem. Soc., Perkin Trans. 2* **1975**, 1544.

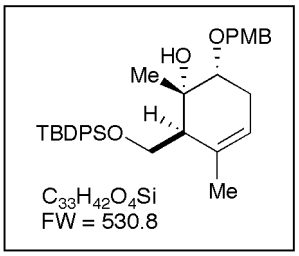
121.6, 64.0, 47.9, 27.8, 26.8, 22.1, 19.3; HRMS (FAB) *m/z* 383.2398 (M+Li, 383.2382 calcd for $C_{25}H_{32}OSiLi$).

(1*R, 2*S**, 3*R**)-3-(*tert*-butyldiphenylsiloxy)methyl-1,2-dihydroxy-2,4-dimethyl-4-cyclohexene (56).** To a mixture of OsO_4 in *tert*-BuOH (0.04 M, 18.0 mL) and N-methylmorpholine oxide monohydrate (NMO) (3.42 g, 25.3 mmol) in acetone (50 mL) and H_2O (11 mL) was added silyl ether **55** (0.79 g, 2.1 mmol). The flask was warmed with a heat gun until a homogeneous solution was observed. The resulting solution was maintained at 23 ºC for 13 h before a slurry of $NaHSO_3$ (0.06 g) and Florisil (7.25 g) in H_2O (100 mL) was added. The Florisil was removed by filtration and then washed with EtOAc (20 mL). The layers of the combined filtrates were separated, and the aqueous layer was neutralized with 1 N H_2SO_4 before NaCl (5 g) was added. The aqueous layer was then extracted with EtOAc (2 x 100 mL), and the combined organic extracts were dried over Na_2SO_4 and concentrated. The crude residue was purified by silica gel chromatography using a solvent gradient (10:90 EtOAc:hexane to 50:50 EtOAc:hexane) to furnish diol **56** as a viscous oil in 64% yield (0.55 g, 13.4 mmol). IR (CH_2Cl_2) 3567, 3486, 2964, 2934, 2891, 2860, 1471, 1428 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.71 (m, 4H, SiC(C**H**)$_2$), 7.45 (m, 6H, SiCCH(C**H**)$_2$ and SiCCHCHC**H**), 5.31 (brs, 1H, CC**H**CH_2), 4.25 (s, 1H, CHO**H**), 4.10 (dd, *J* = 10.6, 4.9 Hz, 1H, CH_2C**H**(OH)C), 3.80 (d, *J* = 10.1 Hz, 2H, CHC**H**$_2$OSi), 2.85 (bs, 1H, C(CH_3)O**H**), 2.72 (brs, 1H, C**H**CH_2OSi), 2.31 (d, *J* = 16.9 Hz, 1H, CHC**H**(H)CH(OH)), 2.20 (d, *J* = 16.9 Hz, 1H, CHC**H**(H)CH(OH)), 1.44 (s, 3H, CC**H**$_3$), 1.25 (s, 3H, C(OH)C**H**$_3$), 1.09 (s, 9H, SiC(C**H**$_3$)$_3$); ^{13}C NMR (100 MHz,



$CDCl_3$) □ 135.6, 135.5, 132.4, 130.8, 130.1, 128.0, 120.4, 74.5, 72.5, 63.7, 30.5, 26.8, 21.1, 21.0, 19.0; HRMS (FAB) *m/z* 411.2357 (MH, 411.2355 calcd for $C_{25}H_{34}O_3SiH$).

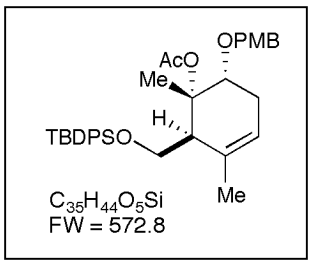
(1*R, 2*S**, 3*R**)-3-(*tert*-butyldiphenylsiloxy)methyl-2,4-dimethyl-2-hydroxy-1-(4-methoxy)benzyloxy-4-cyclohexene (57).** *para*-Methoxybenzyl bromide (PMBBr) was prepared immediately before use by mixing equal volumes (5 mL) of *p*-methoxybenzyl alcohol with 48% HBr. The mixture was stirred for 0.5 h before Et_2O (10 mL) was added. The layers were separated and the organic layer was washed with saturated $NaHCO_3$ (5 mL) followed by brine (5 mL), dried over Na_2SO_4 and concentrated to provide the PMBBr as a yellow oil which was >95% pure by ^1H NMR. The product was used immediately in the next step without purification.



To diol **56** (6.50 g, 15.9 mmol) in THF (60 mL) was added NaH (1.52 g, 63.4 mmol) followed by PMBBr (6.00 g, 29.9 mmol). After stirring for 5 h saturated NH_4Cl (50 mL) was added followed by Et_2O (50 mL). The layers were separated and the organic layer was dried over Na_2SO_4 and concentrated. The crude residue was purified by silica gel chromatography using 20% EtOAc:hexane to give alcohol **57** as a viscous oil in 60% yield (5.04 g, 9.5 mmol). IR (CH_2Cl_2) 3570, 2964, 2934, 2891, 2860, 1613, 1513, 1471, 1428 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) □ 7.69 (m, 4H, $SiC(CH)_2$), 7.43 (m, 6H, $SiCCH(CH)_2$ and SiCCHCHCH), 7.31 (d, *J* = 8.7 Hz, 2H, $CH_3OC(CH)_2$), 6.90 (d, *J* = 8.7 Hz, 2H, $CH_3OC(CH(CH))_2$), 5.45 (brs, 1H, $CCHCH_2$), 4.65 (d, *J* = 11.5, 1H, CHOCH(H)C), 4.53 (d, *J* = 11.5, 1H, CHOCH(H)C), 3.85 (m, 3H, $CHCH_2OSi$ and $CH_2CH(OCH_2)C$), 3.81 (s, 3H, $COCH_3$), 2.61 (s, 1H, $C(CH_3)OH$), 2.44 (d, *J* = 16.0 Hz,

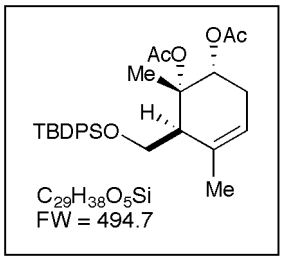
1H, CHC**H**(H)CH(OH)), 2.26 (brs, 1H, C**H**CH_2OSi), 2.24 (d, *J* = 16.0 Hz, 1H, CHC**H**(H)CH(OH)), 1.59 (s, 3H, CC$\mathbf{H}_3$), 1.38 (s, 3H, C(OH)C$\mathbf{H}_3$), 1.08 (s, 9H, SiC(C$\mathbf{H}_3$)$_3$); ^{13}C NMR (75 MHz, $CDCl_3$) □ 159.5, 136.1, 136.0, 133.7, 133.4, 132.4, 131.4, 130.1, 130.1, 129.6, 128.1, 128.0, 121.0, 114.1, 78.7, 74.1, 71.8, 62.3, 55.6 52.4, 29.4, 27.2, 23.5, 22.2, 19.6; HRMS (FAB) *m/z* 537.3013 (M+Li, 537.3012 calcd for $C_{33}H_{42}O_4SiLi$).

(1*R, 2*S**, 3*R**)-2-Acetoxy-3-(*tert*-butyldiphenylsiloxy)-methyl-2,4-dimethyl-1-(4-methoxy)benzyloxy-4-cyclohexene (58).** To alcohol **57** (0.20 g, 0.4 mmol) in CH_2Cl_2 (1.0 mL) was added acetic anhydride (0.19 g, 1.9 mmol) followed by a 1.0 M solution of trimethylsilyltrifluoromethanesulfonate (TMSOTf) in CH_2Cl_2 (20 □L). After stirring for 0.5 h MeOH (0.5 mL) was added and the solution was washed with saturated $NaHCO_3$ (3 mL). The organic layer was dried over Na_2SO_4 and concentrated. The crude residue was purified by silica gel chromatography using 10% EtOAc:hexane to provide acetate **58** as a colorless oil in 38% yield (0.08 g, 0.1 mmol). IR (CH_2Cl_2) 3073, 3049, 2961, 2934, 2860, 1722, 1613, 1513, 1370 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) □ 7.65 (m, 4H, SiC(C**H**)$_2$), 7.42 (m, 6H, SiCCH(C**H**)$_2$ and SiCCHCHC**H**), 7.27 (d, *J* = 6.4 Hz, 2H, CH_3OC(C**H**)$_2$), 6.86 (d, *J* = 8.6 Hz, 2H, CH_3OC(CH(C**H**))$_2$), 5.46 (brs, 1H, , CC**H**CH_2), 4.59 (d, *J* = 11.6 Hz, 1H, CHOC**H**(H)C), 4.49 (d, *J* = 11.6 Hz, 1H, CHOC**H**(H)C), 4.17 (t, *J* = 6.6 Hz, 1H, CH_2C**H**(OCH_2)C), 3.83 (m, 2H, CHC**H**$_2$OSi), 3.79 (s, 3H, COC$\mathbf{H}_3$), 3.11 (brs, 1H, C**H**CH_2OSi), 2.34 (brm, 2H, CHC**H**$_2$CH(OH)), 1.94 (s, 3H, C(O)C$\mathbf{H}_3$), 1.69 (s, 3H, CC$\mathbf{H}_3$), 1.58 (s, 3H, , C($OOCH_3$)C$\mathbf{H}_3$), 1.05 (s, 9H,

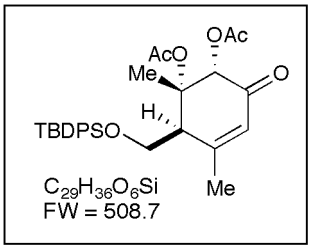


SiC(C**H**$_3$)$_3$); ^{13}C NMR (100 MHz, $CDCl_3$) □ 171.0, 159.1, 135.8, 135.7, 133.5, 133.2, 131.1, 129.7, 129.2, 127.7, 127.6, 113.7, 84.8, 71.8, 61.4, 55.3, 48.1, 31.6, 28.9, 26.9, 25.3, 22.7, 22.6, 21.8, 19.8, 19.3, 14.2; ; HRMS (FAB) *m/z* 579.3136 (M+Li, 579.3118 calcd for $C_{35}H_{44}O_5SiLi$).

(1*R, 2*S**, 3*R**)-3-(*tert*-butyldiphenylsiloxy)methyl-1,2-diacetoxy-2,4-dimethyl-4-cyclohexene (60).** To diol **56** (1.00 g, 2.4 mmol) in CH_2Cl_2 (5 mL) was added acetic anhydride (2.49 g, 24.4 mmol) followed by a 1.0 M solution of trimethylsilyltrifluoromethanesulfonate (TMSOTf) (240 □L) resulting in a red solution. After stirring for 2 h, MeOH (1 mL) was added and the solution was washed with saturated $NaHCO_3$ (5 mL). The organic layer was dried over Na_2SO_4 and concentrated. The crude residue was purified by silica gel chromatography using 10% EtOAc:hexane to furnish bisacetate **60** as a colorless oil in 35% yield (0.44 g, 0.9 mmol). IR (CH_2Cl_2) 2934, 2860, 1729, 1471, 1428, 1370 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) □ 7.67 (m, 4H, SiC(C**H**)$_2$), 7.39 (m, 6H, SiCCH(C**H**)$_2$ and SiCCHCHC**H**), 5.58 (t, *J* = 7.5 Hz, 1H, CH_2C**H**(OOCH_3)), 5.44 (s, 1H, CC**H**CH_2), 3.81 (dd, *J* = 11.3, 3.3 Hz, 1H, CHC**H**(H)OSi), 3.70 (dd, *J* = 11.3, 3.3 Hz, 1H, CHC**H**(H)OSi), 3.09 (brs, 1H, C**H**CH_2OSi), 2.42 (d, *J* = 16.8 Hz, 1H, CHC**H**(H)CH(OH)), 2.28 (d, *J* = 16.8 Hz, 1H, CHC**H**(H)CH(OH)), 2.12 (s, 3H, CH(OC(O)C**H**$_3$)), 1.96 (s, 3H, C(OC(O)C**H**$_3$)), 1.65 (s, 3H, CC**H**$_3$), 1.47 (s, 3H, C(OC(O)CH_3)C**H**$_3$), 1.06 (s, 9H, SiC(C**H**$_3$)$_3$); ^{13}C NMR (100 MHz, $CDCl_3$) □ 170.6, 170.5, 135.9, 135.8, 133.3, 133.0, 131.0, 129.7, 127.7, 127.6, 120.8, 83.1, 77.4, 73.2,

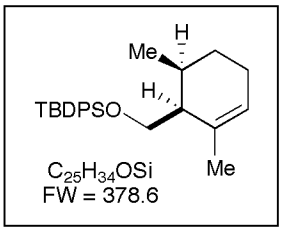


61.1, 48.4, 28.5, 26.7, 22.4, 21.7, 21.2, 19.5, 19.1; HRMS (FAB) *m/z* 501.2646 (M+Li, 501.2649 calcd for $C_{29}H_{38}O_5SiLi$).

(2*S, 3*S**, 4*S**)-4-(*tert*-butyldiphenylsiloxy)methyl-2,3-diacetoxy-3,5-dimethyl-5-cyclohexen-1-one (61).** 

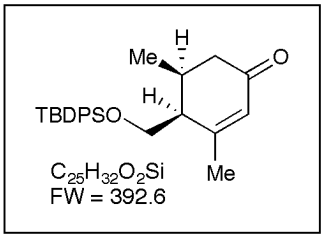
To bisacetate **60** (0.44 g, 0.8 mmol) in AcOH (2.4 mL) and acetic anhydride (1.6 mL) was added Na_2CrO_4 (0.54, 3.3 mmol). The mixture was observed to change from orange to dark green over the course of the reaction. After stirring for 14 h the mixture was diluted with Et_2O (2 mL) and basified with 1 N NaOH to pH >10. The aqueous layer was extracted with Et_2O (3 x 5 mL) and the combined organic extracts were dried over Na_2SO_4 and concentrated. The crude residue was purified by silica gel chromatography using 20% EtOAc:hexane to afford ketone **61** as a clear, colorless oil in 23% yield (0.11 g, 0.2 mmol). IR (CH_2Cl_2) 3073, 2953, 2891, 2860, 1749, 1733, 1691, 1471, 1428, 1374 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.64 (m, 4H, SiC(C**H**)$_2$), 7.41 (m, 6H, SiCCH(C**H**)$_2$ and SiCCHCHC**H**), 6.21 (s, 1H, C**H**(OOCH$_3$)), 6.06 (s, 1H, CC**H**C(O)), 4.06 (dd, *J* = 11.7, 2.9 Hz, 1H, CHC**H**(H)OSi), 3.89 (dd, *J* = 11.7, 2.9 Hz, 1H, CHC**H**(H)OSi), 3.53 (brs, 1H, C**H**CH$_2$OSi), 2.28 (s, 3H, CH(OC(O)C**H**$_3$)), 1.93 (s, 3H, C(OC(O)C**H**$_3$)), 1.75 (s, 3H, CC**H**$_3$), 1.62 (s, 3H, C(OC(O)CH$_3$)C**H**$_3$), 1.03 (s, 9H, SiC(C**H**$_3$)$_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 191.6, 170.8, 170.4, 157.3, 135.9, 135.7, 134.3, 132.5, 130.1, 130.0, 127.9, 127.8, 126.9, 86.3, 77.6, 60.9, 50.0, 26.7, 22.5, 22.2, 20.6, 19.6, 19.0; HRMS (FAB) *m/z* 515.2454 (M+Li, 515.2441 calcd for $C_{29}H_{36}O_6SiLi$).

(3*S, 4*S**)-3-(*tert*-butyldiphenylsiloxy)methyl-2,4-dimethyl-cyclohexene (63).** The



diene **55** (1.19 g, 3.2 mmol) and 10% Pd/C (1.3 g) in EtOH (10 mL) were stirred under an atmosphere of H_2 for 2 h. The reaction mixture was filtered through a silica gel plug with hexanes and the filtrate was concentrated. The crude residue was purified by silica gel chromatography using hexanes to provide the alkene **63** as a colorless oil (0.38 g, 1.0 mmol, 34% yield, 43% based on recovered starting material). IR (thin film) 3445, 3071, 3050, 2958, 2929, 2858, 1652, 1472, 1462, 1428, 1389, 1112, 1072, 998 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) 7.79-7.81 (m, 4H, Ar**H**), 7.45-7.48 (m, 6H, Ar**H**), 5.52 (s, 1H, C=C**H**), 3.79 (d, *J* = 3.8 Hz, 2H, C$\mathbf{H}_2$O), 1.52-2.16 (m, 6H, C$\mathbf{H}_2$C$\mathbf{H}_2$C**H**(CH_3)C**H**), 1.65 (s, 3H, CC$\mathbf{H}_3$), 1.15-1.17 (m, 12H, C(C$\mathbf{H}_3$)$_3$ and CHC$\mathbf{H}_3$); ^{13}C NMR (75 MHz, $CDCl_3$) 136.1, 136.0, 134.5, 129.8, 127.9, 123.8, 63.1, 46.6, 31.6, 27.5, 27.2, 25.5, 23.0, 19.5, 18.8; HRMS (FAB) *m/z* 377.2308 (M–H, 377.2301 calcd for $C_{25}H_{33}OSi$).

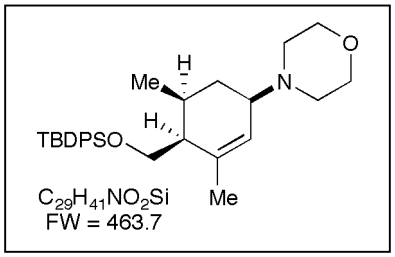
(4*S, 5*S**)-4-(*tert*-butyldiphenylsilyloxy)methyl-3,5-dimethyl-cyclohex-2-enone (64).**



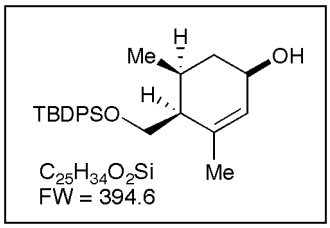
The alkene **63** (1.72 g, 4.6 mmol) in AcOH (10.7 mL) and Ac_2O (6.6 mL) was cooled to 0°C and Na_2CrO_4 was added. After stirring for 19 h at 23 °C, the dark green mixture was poured into a vigorously stirred 1:1 mixture of 1 N NaOH : Et_2O (100 mL). The layers were separated and the aqueous layer was extracted with Et_2O (3 x 100 mL). The combined organic extracts were dried (Na_2SO_4) and concentrated. The crude residue was purified by silica gel chromatography using 10% EtOAc : hexanes to provide ketone **64** as a colorless oil in 45% yield (0.82 g, 2.1 mmol). IR (thin film)

2958, 2931, 2857, 2361, 1663, 1428, 1112, 1088 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) 7.60-7.66 (m, 4H, Ar**H**), 7.34-7.43 (m, 6H, Ar**H**), 5.95 (s, 1H, C=C**H**), 3.91 (dd, *J* = 3.8, 11.0 Hz, 1H, C**H**$_2$O), 3.75 (dd, *J* = 4.4, 11.0 Hz, 1H, C**H**$_2$O), 2.58 (dd, *J* = 12.4, 16.2 Hz, 1H, C(O)C**H**$_2$), 2.33-2.42 (m, 1H, C**H**CH$_3$), 2.27 (dd, *J* = 4.4, 15.9 Hz, 1H, C**H**$_2$C(O)), 2.19 (dd, *J* = 4.4, 8.2 Hz, 1H, C**H**CH$_2$O), 1.81 (s, 3H, C=CC**H**$_3$), 1.10 (d, *J* = 6.6 Hz, 3H, CHC**H**$_3$), 1.00 (s, 9H, C(C**H**$_3$)$_3$); ^{13}C NMR (75 MHz, $CDCl_3$) 200.4, 163.1, 135.9, 135.8, 133.2, 133.0, 130.1, 130.1, 128.5, 128.0, 128.0, 61.7, 47.5, 42.8, 32.4, 27.0, 23.6, 19.3, 18.5; HRMS (FAB) *m/z* 377.1939 (M–CH_3, 377.1937 calcd for $C_{24}H_{29}O_2Si$).

(1*R* *, 4*S* *, 5*S)-4-(*tert*-butyldiphenylsiloxy)methyl-2,4-dimethyl-1-morpholino-cyclohex-2-ene (65).** To ketone **64** (50.0 mg, 0.13 mmol) in CH_2Cl_2 (1.5 mL) was added morpholine (33 mg, 0.38 mmol) followed by $Ti(OiPr)_4$ (136 mg, 0.48 mmol). After 2.5 h CH_2Cl_2 was removed in vacuo. The residue was dissolved in EtOH (1.0 mL) and $Na(CN)BH_3$ (17 mg, 0.27 mmol) was added. After stirring for 1 h 1 N NaOH (1.0 mL) was added and the mixture was filtered through a Celite plug. The filtrate was extracted with EtOAc (3 x 20 mL) and the combined organic extracts were dried (Na_2SO_4) and concentrated. The crude residue was purified by silica gel chromatography using 50% EtOAc : hexanes to provide amine **65** as a clear colorless oil in 30% yield (18 mg, 0.04 mmol).

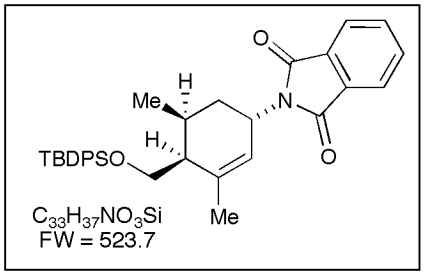


(1*R, 4*S**, 5*S**)-4-(*tert*-butyldiphenylsilyloxy)methyl-2,4-dimethyl-cyclohex-2-en-1-ol (67).** To ketone **64** (0.82 g, 2.1 mmol) in MeOH (40 mL) was added $NaBH_4$ (0.40 g, 10.5



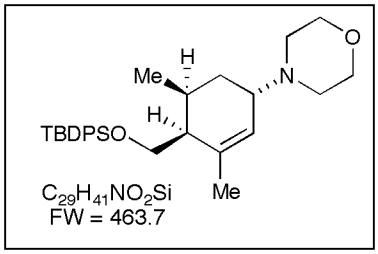
mmol). After 2.5 h MeOH was removed in vacuo. The residue was dissolved in CH_2Cl_2 (50 mL) and washed with H_2O (2 x 50 mL), dried (Na_2SO_4), and concentrated to provide alcohol as a clear oil in 98% yield (0.81 g, 2.1 mmol) that was homogeneous by TLC and ^{1}H NMR analysis. IR (thin film) 3332, 3071, 2959, 2930, 2858, 1659, 1472, 1428, 1112, 1084, 997, 824 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) 7.70-7.73 (m, 4H, Ar**H**), 7.38-7.47 (m, 6H, Ar**H**), 5.51 (s, 1H, C=C**H**), 4.20-4.25 (m, 1H, C**H**OH), 3.78 (dd, *J* = 4.9, 11.0 Hz, C**H**$_2$OSi), 3.71 (dd, *J* = 3.3, 10.0 Hz, 1H, C**H**$_2$OSi), 1.56-1.97 (m, 5H, O**H** and C(OH)C**H**$_2$ and C**H**C H$_3$ and C**H**C H$_2$OSi), 1.61 (s, 3H, C=CC**H**$_3$), 1.12, d, *J* = 6.6 Hz, CHC**H**$_3$), 1.09 (s, 9H, C(C**H**$_3$)$_3$); ^{13}C NMR (75 MHz, $CDCl_3$) 138.2, 136.0, 133.9, 129.9, 128.3, 127.9, 68.5, 62.5, 46.8, 37.3, 31.4, 27.2, 22.6, 19.6, 19.5; HRMS (FAB) *m/z* 393.2239 (M–H, 393.2250 calcd for $C_{25}H_{33}O_2Si$).

(1*S, 4*S* *, 5*S* *)-4-(*tert*-butyldiphenylsiloxy)methyl-2,4-dimethyl-1-phthalimido-cyclohex-2-ene (68).** To alcohol **67** (0.81 g, 2.1 mmol), PPh_3 (1.20 g, 4.5 mmol), and phthalimide (0.65 g, 4.4 mmol) in THF (30 mL) at 0 °C was added diethyldiazodicarboxylate (DEAD) in THF (1.0 M soln., 4.7 mL, 4.7 mmol) dropwise. The flask was warmed to room temperature and stirred for 1 h. Silica gel (1.0 g) was added and the solvent was removed in vacuo. The resulting solid was loaded onto a column using EtOAc and the crude product was eluted with EtOAc. Concentration of the combined eluents followed by purification by silica gel chromatography using 10% EtOAc :



hexanes provided the title compound as a white solid in 49% yield (0.53 g, 1.0 mmol). IR (thin film) 2958, 2930, 2857, 1771, 1713, 1468, 1428, 1390, 1369, 1112, 1085 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) 7.65-7.81 (m, 8H, Ar**H**), 7.39-7.45 (m, 6H, Ar**H**), 5.29 (s, 1H, C=C**H**), 4.91 (s, 1H, C**H**N), 3.84 (dd, *J* = 4.7, 10.2 Hz, 1H, C**H**$_2$O), 3.64 (dd, *J* = 7.7, 10.5 Hz, 1H, C**H**$_2$O), 2.54-2.55 (m, 1H, C**H**CH_3), 2.43 (brs, 1H, C**H**CH_2O), 1.93-2.04 (m, 2H, NCHC**H**$_2$), 1.62 (s, 3H, C=CC**H**$_3$), 1.06 (s, 12H, C(C**H**$_3$)$_3$ and CHC**H**$_3$); ^{13}C NMR (75 MHz, $CDCl_3$) 168.6, 138.1, 135.9, 135.8, 134.0, 132.4, 129.9, 127.9, 123.2, 121.4, 62.9, 45.9, 45.1, 33.9, 28.6, 27.1, 22.4, 19.4, 15.9; HRMS (FAB) *m/z* 524.2627 (M+H, 524.2621 calcd for $C_{33}H_{38}NO_3Si$).

(1*S, 4*S**, 5*S**)-4-(*tert*-butyldiphenylsiloxy)methyl-2,4-dimethyl-1-morpholino-cyclohex-2-ene (69).** To phthalimide **68** (0.43 g, 0.82 mmol) in MeOH (20 mL) was added $NH_2NH_2 \bullet H_2O$ (2.06 g, 41.1 mmol) and the resulting mixture was heated to 80-90 °C for 4h. MeOH was removed in vacuo to provide a white solid which was dissolved in CH_3CN (6 mL). Anhydrous K_2CO_3 (0.22 g, 1.6 mmol) was added and the mixture was stirred for 1 h. 2-Bromoethyl ether (0.23 g, 1.0 mmol) in CH_3CN (2 mL) was added and the resulting mixture was heated to 90 °C for 11 h. The mixture was diluted with CH_3CN (10 mL) and Na_2SO_4 (5 g) was added. The solution was filtered and concentrated. The crude residue was purified by silica gel chromatography using 35% EtOAc : hexanes to provide amine **69** as a yellow oil in 27% yield (102 mg, 0.22 mmol). IR (thin film) 2957, 2929, 2856, 1472, 1450, 1428, 1250, 1114, 1080, 998 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) 7.66-7.68 (m, 4H, Ar**H**), 7.36-7.42

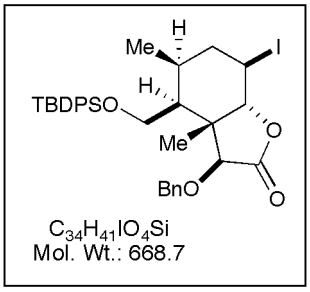


(m, 6H, Ar**H**), 5.45 (s, 1H, C=C**H**), 3.57-3.77 (m, 6H, (C**H**$_2$)$_2$N and C**H**$_2$OSi), 3.12 (brs, 1H, C**H**N), 2.50-2.64 (m, 4H, (C**H**$_2$)$_2$O), 2.08-2.17 (m, 3H, C**H**CH$_2$O and C**H**$_2$CHN), 1.66-1.69 (m, 1H, C**H**CH$_3$), 1.60 (s, 3H, C=CC**H**$_3$), 1.04 (s, 9H, C(C**H**$_3$)$_3$), 1.00 (d, *J* = 7.7 Hz, 3H, CHC**H**$_3$); ^{13}C NMR (75 MHz, $CDCl_3$) 138.5, 135.9, 135.8, 134.0, 133.9, 129.8, 127.8, 124.0, 67.7, 62.8, 58.4, 49.7, 45.9, 29.2, 29.2, 27.0, 22.8, 19.4, 16.9; HRMS (FAB) *m/z* 464.2965 (M+H, 464.2985 calcd for $C_{29}H_{41}NO_2Si$).

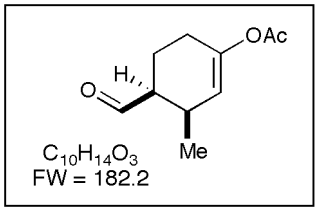
Morpholine 2(*S)-benzyloxy-[1(*R**),3(*S**)-dimethyl-2(*S**)-(*tert*-butyldiphenylsiloxy-methyl)-5-cyclohexenyl]ethanamide (70).** Amine **69** (50 mg, 0.11 mmol) in CH_2Cl_2 (1.25 mL) followed by iPr_2NEt (41 mg, 0.32 mmol) was added to $TiCl_4$•THF_2 (36 mg, 0.11 mmol). A 1.0 M solution of freshly distilled benzyloxyacetyl chloride in CH_2Cl_2 (0.21 mL, 0.21 mmol) was added via syringe pump over 2 h. The reaction mixture was diluted with Et_2O (3 mL) and then quenched with 1 N NaOH (2 mL). The layers were separated and the aqeous layer was extracted with Et_2O (3 x 2 mL). The combined organic extracts were washed with brine (2 mL), dried (Na_2SO_4), and concentrated. The crude residue was purified by silica gel chromatography using 35% EtOAc : hexanes to provide amide **70** as a clear colorless oil in 41% yield (27 mg, 0.04 mmol). IR (thin film) 3028, 2959, 2929, 2893, 2857, 1630, 1454, 1428, 1390, 1361, 1300, 1270, 1244, 1114 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) 7.61-7.64 (4H, m, Ar**H**), 7.24-7.41 (m, 11H, Ar**H**), 5.68 (dt, *J* = 3.9, 10.4 Hz, 1H, C=C**H**CH$_2$), 5.48 (d, *J* = 9.9 Hz, 1H, C(CH$_3$)C**H**=C), 4.53 (d, *J* = 11.5 Hz, 1H, C**H**$_2$Ph), 4.39 (d, *J* = 12.1 Hz, 1H, C**H**$_2$Ph), 4.22 (s, 1H, C**H**OCH$_2$Ph), 3.46-3.76 (m, 10H,

morpholine and C**H**$_2$OSi), 1.98-2.27 (m, 2H, C**H**CH$_2$OSi and C**H**CH$_3$), 1.54-1.67 (m, 2H, C=CHC**H**$_2$), 1.08 (s, 3H, CC**H**$_3$), 1.02 (s, 9H, tBu), 0.79 (d, *J* = 7.1 Hz, 3H, CHC**H**$_3$); ^{13}C NMR (75 MHz,$CDCl_3$) δ 169.2, 137.8, 136.0, 134.1, 133.9, 132.8, 129.8, 129.8, 128.6, 128.1, 128.0, 127.9, 127.8, 126.7, 86.9, 73.2, 67.5, 67.0, 61.9, 46.8, 44.8, 43.0, 31.4, 27.9, 27.1, 21.1, 19.4, 17.4; HRMS (FAB) *m/z* 612.3487 (M+H, 612.3509 calcd for $C_{38}H_{50}NO_4Si$).

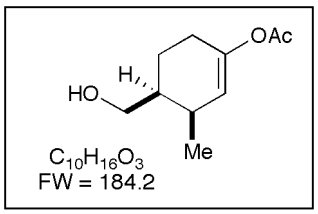
3(*S)-Benzyloxy-4(*S**)-(*tert*-butyldiphenylsilyloxymethyl)-7(*R**)-iodo-3a(*S**), 5(*S**)-dimethylhexahydrobenzofuran-2-one (71).** To amide **70** (27 mg, 0.04 mmol) in 1:1 DME:H_2O (2 mL) was added I_2 (12 mg, 0.1 mmol). After stirring for 4 h another portion of I_2 (13 mg) was added. After an additional 2 h the reaction mixture was diluted with Et_2O (3 mL), washed with 10% $Na_2S_2O_3$ (2 mL) and brine (2 mL), dried, and concentrated to provide the title compound **71** as a colorless oil in 81% yield (24 mg, 0.04 mmol) that was homogenous by TLC and ^{1}H NMR analysis. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.63-7.67 (m, 4H, Ar**H**), 7.23-7.46 (m, 11H, Ar**H**), 4.90 (d, *J* = 12.1 Hz, 1H, C**H**$_2$Ph), 4.72 (d, *J* = 9.9 Hz, 1H, C**H**OC(O)), 4.60 (d, *J* = 12.1 Hz, 1H, C**H**$_2$Ph), 4.30-4.40 (m, 1H, C**H**I), 3.93 (d, *J* = 11.5 Hz, 1H, C**H**$_2$OSi), 3.68 (dd, *J* = 3.3, 11.0 Hz, 1H, C**H**$_2$OSi), 3.41 (s, 1H, C**H**OCH$_2$Ph), 2.49-2.69 (m, 2H, C**H**$_2$CHI), 2.14-2.17 (m, 1H, C**H**CH$_2$OSi), 1.72 (brs, 1H, C**H**CH$_3$), 1.13 (s, 9H, tBu), 1.06 (s, 3H, CC**H**$_3$), 0.83 (d, *J* = 6.6 Hz, 3H, CHC**H**$_3$).



(3*S*, 4*S*)-1-acetoxy-4-formyl-3-methylcyclohex-1-ene (86). The reaction was divided between three 250 mL round bottom flasks to maximize yield. To a solution of (5*S*)-5-benzyl-2,2,3-trimethylimidazolin-4-one hydroperchlorate **84** (17.70 g, 50.1 mmol, 20 mol%) in THF (255 mL) at 0 °C was added acrolein (50.1 ml, 750 mmol) over 20 min (exotherm). Water (12.9 ml, 720 mmol) was added followed by (*E*)-2-acetoxy-1,3-pentadiene (31.50 g, 250 mmol) (Scheeren, JOC, 1985, 50, 1955). When the diene was consumed as determined by gas chromatography, the reaction mixture was diluted with Et_2O (300 mL) and washed with H_2O (300 mL). The layers were separated and the aqueous layer was extracted with Et_2O (3 x 200 mL). The combined organic extracts were dried (Na_2SO_4) and concentrated. The crude residue was purified by silica gel chromatography using 10% EtOAc : hexanes to provide aldehyde **86** as a colorless oil in 44% yield (20.00 g, 109.7 mmol); *endo:exo* 5.6:1 *endo* 90% ee. IR (thin film) 2963, 2938, 2875, 1753, 1723, 1367, 1213, 1127, 1094, 1018, 904 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 9.77 (s, 1H, C**H**O), 5.37-5.39 (m, 1H, C=C**H**), 2.85-2.90 (m, 1H, C**H**CHO), 2.53-2.60 (m, 1H, C**H**CH_3), 1.78-2.32 (m, 4H, C$\mathbf{H_2}$C$\mathbf{H_2}$), 2.08 (s, 3H, C(O)C$\mathbf{H_3}$), 0.99 (d, J = 6.6 Hz, 3H, CHC$\mathbf{H_3}$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 204.2, 169.5, 148.3, 118.9, 49.9, 29.1, 25.8, 21.2, 18.6, 17.1; HRMS (EI) *m/z* 182.0938 (M, 182.0943 calcd for $C_{10}H_{14}O_3$); $[\alpha]^{25}_D$ = –185.4, (*c* = 0.3, $CHCl_3$). The enantiomeric purity and diastereomer ratio was determined by GC with a Bodman β-TA Chiraldex column (70 °C with 3 °C/min, 2 mL/min); *exo* isomer, t_r = 33.0 min and 33.5 min; *endo* isomer t_r = 35.6 min and 36.6 min.

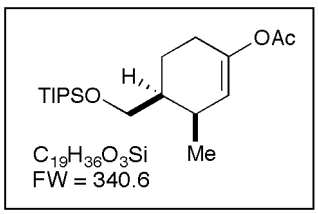


(3*S*, 4*S*)-1-acetoxy-4-(hydroxymethyl)-3-methylcyclohex-1-ene (87). To aldehyde **86**



(5.19 g, 28.5 mmol) in MeOH (150 mL) was added $Na(CN)BH_3$ (17.9 g, 285.0 mmol) portionwise over 10 min. After 6 h the reaction was judged to be complete by thin layer chromatography. MeOH was removed by rotary evaporation and the residue was taken up in CH_2Cl_2 (100 mL) and washed with H_2O (100 mL). The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (100 mL). The combined organic extracts were dried (Na_2SO_4) and concentrated. The crude residue was purified by silica gel chromatography using 35% EtOAc : hexanes to provide alcohol **87** as a colorless oil in 73% yield (3.81 g, 20.7 mmol). IR (thin film) 3419, 2960, 2933, 2875, 2360, 1755, 1689, 1455, 1435, 1371, 1222, 1127, 1091, 1040, 1012, 906 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) □ 5.32 (d, *J* = 5.0 Hz, 1H, C=C**H**), 3.50-3.63 (m, 2H, C**H**$_2$OH), 2.48-2.54 (m, 1H, C**H**CH_3), 1.47-2.30 (m, 5H, C**H**$_2$C**H**$_2$C**H**), 2.08 (s, 3H, C(O)C**H**$_3$), 0.90 (d, *J* = 7.1 Hz, 3H, CHC**H**$_3$); ^{13}C NMR (75 MHz, $CDCl_3$) □ 169.6, 148.0, 119.8, 64.5, 39.4, 29.9, 26.7, 21.4, 21.1, 15.6; HRMS (EI) *m/z* 184.1098 (M, 184.1100 calcd for $C_{10}H_{16}O_3$); $[□]^{25}_D = –238.6$, (*c* = 0.65, $CHCl_3$).

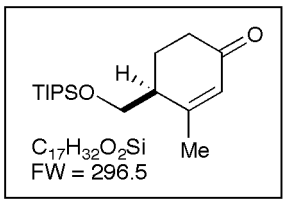
(3*S*, 4*S*)-1-acetoxy-3-methyl-4-(triisopropylsiloxymethyl)cyclohex-1-ene (88). Alcohol



87 (6.84 g, 37.2 mmol), TIPSCl (9.32 g, 48.3 mmol), and imidazole (6.96 g, 102.3 mmol) in DMF (150 mL) were stirred at 23 ºC for 2h after which time H_2O (200 mL) was added. The mixture was extracted with Et_2O (3 x 200 mL), and the combined organic extracts were washed with H_2O (200 mL) and brine (200 mL),

dried (Na_2SO_4), and concentrated. The crude residue was purified by silica gel chromatography using 2.5% EtOAc : hexanes to provide the title compound **88** as a colorless oil in 76% yield (9.62 g, 28.2 mmol). IR (thin film) 2943, 2866, 1760, 1690, 1463, 1366, 1216, 1104, 1067, 1015, 883 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) □ 5.33 (d, *J* = 4.9 Hz, 1H, C=C**H**), 3.61 (d, *J* = 4.9 Hz, 1H, C**H**$_2$O), 3.59 (d, *J* = 4.4 Hz, 1H, C**H**$_2$O), 2.53 (m, 1H, C=CHC**H**), 1.87-2.32 (m, 3H, C**H**$_2$C=CH and C**H**CH_2O), 2.10 (s, 3H, C(O)C**H**$_3$), 1.47-1.65 (m, 2H, C**H**$_2$CHCH_2O), 1.04-1.07 (m, 21H, TIPS), 0.91 (d, *J* = 7.1 Hz, 3H, CHC**H**$_3$); ^{13}C NMR (75 MHz, $CDCl_3$) □ 169.6, 148.1, 120.1, 64.8, 39.4, 29.7, 26.7, 21.3, 20.8, 18.3, 15.3, 12.2; HRMS (FAB) *m/z* 340.2434 (M+H, 340.5728 calcd for $C_{19}H_{37}O_3Si$); [□]$^{25}_D$ = –123.2, (*c* = 1.0, $CHCl_3$).

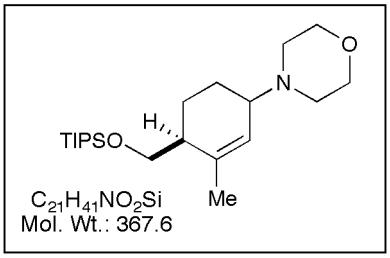
(4*S*)-3-methyl-4-(triisopropylsiloxymethyl)cyclohex-2-en-1-one (89). A modified procedure of Siegel et al. was used.[6] Vinyl acetate **88** (12.90 g, 37.9 mmol) was added to $Pd(OAc)_2$ (0.43 g, 1.9 mmol, 5 mol%), DIPHOS (0.76 g, 1.9 mmol, 5 mol%) and allyl methylcarbonate (11.0 g, 94.8 mmol) in CH_3CN (680 mL) in a 2L thick-walled jar with a screwcap. After stirring for 10 min the yellow mixture was homogeneous. Bu_3SnOMe (12.20 g, 37.9 mmol) was added and then the jar was sealed tightly and heated to 100 ºC for 6 h. After cooling to room temperature, brine (300 mL) was added and the mixture was filtered through a Celite pad with Et_2O (3 x 100 mL) washings. The filtrate layers were separated and the aqueous layer was extracted with Et_2O (2 x 100 mL). The combined organic filtrate and extracts were washed with sat. $NaHCO_3$ (100



[6] Siegel, C.; Gordon, P. M.; Uliss, D. B.; Handrick, G. R.; Dalzell, H. C.; Razdan, R. K. *J. Org. Chem.* **1991**, *56*, 6865.

mL) and brine (100 mL), dried (Na_2SO_4) and concentrated. The crude residue was purified by silica gel chromatography using 10% EtOAc : hexanes to provide ketone **89** as a colorless oil in 87% yield (9.72 g, 32.8 mmol). IR (thin film) 3425, 2944, 2867, 1674, 1627, 1463, 1382, 1249, 1202, 1110, 1069, 882 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) □ 5.85 (s, 1H, C=C**H**), 3.81 (d, *J* = 5.5 Hz, 2H, C**H**$_2$O), 2.36-2.52 (m, 2H, C(O)C**H**$_2$), 2.20-2.30 (m, 1H, C**H**CH$_2$O), 1.98-2.13 (m, 2H, C(O)CH$_2$C**H**$_2$), 1.96 (s, 21H, TIPS); ^{13}C NMR (75 MHz, $CDCl_3$) □ 199.7, 162.9, 128.4, 64.2, 42.9, 34.8, 25.7, 23.3, 18.2, 12.1; HRMS (FAB) *m/z* 297.2238 (M+H, 297.2250 calcd for $C_{17}H_{33}O_2Si$); [□]$^{25}_D$ = –130.3, (*c* = 1.1, $CHCl_3$).

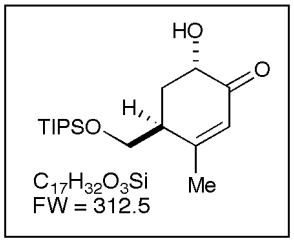
3-Methyl-1-morpholino-4(*S*)-(triisopropylsilyloxymethyl)cyclohex-2-ene (90). To



ketone **89** (1.00 g, 3.3 mmol) in CH_2Cl_2 (2 mL) in a React IR schlenk flask was added morpholine (0.29 mL, 3.3 mmol) followed by $Ti(OiPr)_4$ (1.2 mL, 4.2 mmol). After the ketone IR stretch had completely disappeared, EtOH (3.3 mL) and $NaCNBH_3$ (0.14 g, 2.2 mmol) were added. The reaction mixture was stirred for 20 h before H_2O (0.67 mL) was added. The resulting mixture was filtered through Celite with EtOH washes (3 x 20 mL). The combined filtrates were concentrated and the crude residue was purified by silica gel chromatography using 20 to 30% EtOAc : hexanes to provide amine **90** as a clear oil in 21% yield (0.27 g, 0.72 mmol); dr = 1.4 : 1. IR (thin film) 2943, 2865, 1463, 1450, 1382, 1325, 1287, 1249, 1119, 1069, 998 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) □ 5.41 (s, 1H, C=C**H**), 3.51-3.76 (m, 6H, N(C**H**$_2$)$_2$ and C**H**$_2$OSi), 3.07 (brs, 1H, C**H**N major isomer), 3.00 (brs, 1H, C**H**N minor isomer), 2.45-

2.58 (m, 4H, O(C**H**$_2$)$_2$), 1.97-2.07 (m, 2H, C**H**$_2$CHN), 1.69 (s, 3H, C=CC**H**$_3$), 1.53-1.55 (m, 2H, C**H**$_2$CH$_2$CHN), 1.00-1.06 (m, 21H, TIPS); ^{13}C NMR (75 MHz, $CDCl_3$) 138.1, 137.8, 126.0, 126.0, 67.7, 67.7, 65.4, 64.4, 61.3, 60.8, 49.6, 49.4, 42.5, 42.1, 25.4, 23.7, 22.9, 22.3, 22.0, 18.7, 18.2, 17.9, 12.2, 12.2; HRMS (FAB) *m/z* 366.2819 (M–H, 366.2828 calcd for $C_{21}H_{40}NO_2Si$).

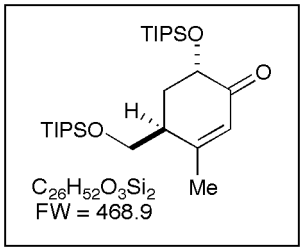
(4*S*, 6*S*)-6-hydroxy-3-methyl-4-(triisopropylsiloxymethyl)cyclohex-2-en-1-one (93).



To diisopropylamine (1.17 mL, 11.6 mmol) in THF (25 mL) at –78 °C was added a 1.7 M solution of n-BuLi in hexanes (6.9 mL, 11.6 mmol). After 10 min ketone **89** (3.15 g, 10.6 mmol) in THF (15 mL) was added and the mixture was stirred at –78 °C for 40 min. Freshly distilled TMSCl (2.8 mL, 22.1 mmol) was added rapidly and the flask was removed from the cold bath. The reaction mixture was stirred at room temperature for 2.5 h before pentane (5 mL) was added. The resultant mixture was washed with cold (0 °C) sat. $NaHCO_3$ (30 mL), and the organic layer was dried and concentrated to provide silyl enol ether **94**, which was pure as judged by ^{1}H NMR analysis. Silyl enol ether **94** in 27 mL *tert*-BuOH was added to a vigorously stirred mixture of AD-mix (15.0 g) and $MeSO_2NH_2$ (1.00 g, 10.6 mmol) in H_2O (54 mL) and *tert*-BuOH (27 mL) at 0 °C. The reaction mixture was stirred vigorously for 26 h at 0 °C before Na_2SO_3 (10.5 g) was added. After stirring for an additional 1 h, the reaction mixture was diluted with CH_2Cl_2 (100 mL), the layers were separated, and the aqueous layer was extracted further with EtOAc (3 x 100 mL). The combined organic extracts were dried and concentrated and the crude residue was purified by silica gel

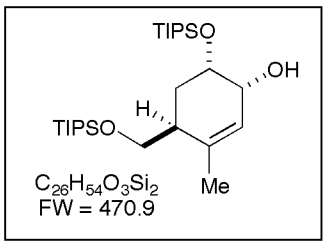
chromatography to provide starting material **89** (1.10 g) and hydroxy ketone **93** as a colorless oil (1.13 g, 3.6 mmol, 34% yield, 52% yield based on recovered starting material). IR (thin film) 3484, 2943, 2867, 1678, 1628, 1463, 1382, 1250, 1106, 1029, 1014, 998, 882 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) □ 5.95 (s, 1H, C=C**H**), 4.44-4.50 (m, 1H, C**H**OH), 3.95 (d, *J* = 5.5 Hz, 2H, C**H**$_2$OSi), 3.53 (d, *J* = 1.6 Hz, 1H, O**H**), 2.49-2.60 (m, 2H, C**H**$_2$CHOH), 1.94-2.05 (m, 1H, C**H**CH$_2$OSi), 2.01 (s, 3H, CC**H**$_3$), 0.96-1.15 (m, 21H, TIPS); ^{13}C NMR (75 MHz, $CDCl_3$) □ 200.2, 164.2, 125.4, 69.0, 64.9, 44.2, 34.8, 23.8, 18.2, 12.1; HRMS (FAB) *m/z* 313.2198 (M+H, 313.2199 calcd for $C_{17}H_{33}O_3Si$); $[\alpha]^{25}_D$ = –69.3, (*c* = 1.0, $CHCl_3$).

(4*S*, 6*S*)-3-methyl-6-triisopropylsiloxy-4-(triisopropylsiloxymethyl)cyclohex-2-en-1-one (95). To alcohol **93** (2.00 g, 6.4 mmol) and imidazole (1.20 g, 17.6 mmol) in DMF (28 mL) was added TIPSCl (2.7 mL, 12.8 mmol). When starting material was consumed as determined by TLC analysis (12 h), H_2O (30 mL) was added the resulting mixture was extracted with Et_2O (3 x 50 mL). The combined organic extracts were washed with brine (50 mL), dried, and concentrated. The crude residue was purified by silica gel chromatography to provide ketone **95** as a colorless oil in 86% yield (2.56 g, 5.5 mmol). IR (thin film) 2943, 2867, 1690, 1464, 1383, 1248, 1156, 1138, 1105, 1070, 1014, 997, 882 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) □ 5.80 (s, 1H, C=C**H**), 4.40 (dd, *J* = 4.7, 9.6 Hz, 1H, C**H**OSi), 3.81-3.91 (m, 2H, C**H**$_2$OSi), 2.55-2.60 (m, 1H, C**H**CHOSi), 2.29 (app dt, *J* = 4.7, 13.5 Hz, 1H, C**H**$_2$CHOSi), 2.11 (ddd, *J* = 5.2, 9.6, 13.5 Hz, C**H**$_2$CHOSi), 1.94 (s, 3H, CC**H**$_3$), 1.00-1.07 (m, 42H, TIPS); ^{13}C NMR (75 MHz,

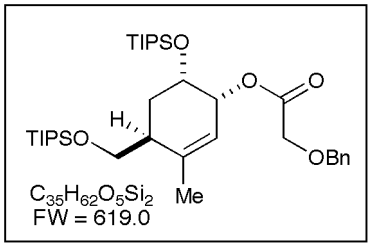


$CDCl_3$) □ 198.0, 161.1, 127.0, 71.1, 64.5, 42.5, 36.1, 22.8, 18.2, 18.2, 12.6, 12.2; HRMS (FAB) *m/z* 469.3530 (M+H, 469.3533 calcd for $C_{26}H_{53}O_3Si_2$); $[\square]^{22}_D$ = –39.6, (*c* = 1.0, $CHCl_3$).

(1*S*, 2*R*, 5*S*)-2-hydroxy-4-methyl-1-triisopropylsiloxy-5-(triisopropylsiloxymethyl)-cyclohex-3-ene (97). To ketone **95** (2.56 g, 5.5 mmol) in MeOH (60 mL) was added $CeCl_3 \bullet 7H_2O$ (8.20 g, 22.0 mmol). The mixture was stirred until homogeneous and then $NaBH_4$ (0.62 g, 16.4 mmol) was added cautiously. After stirring for 1 h, additional $NaBH_4$ (0.62 g, 16.4 mmol) was added. After 3 h H_2O (50 mL) was added and the resulting mixture was stirred until gas evolution ceased. The aqueous layer was extracted with EtOAc (3 x 100 mL) and the combined organic extracts were dried (Na_2SO_4) and concentrated to provide alcohol **97** as a colorless oil in 87% yield (2.25 g, 4.8 mmol) that was pure by TLC and ^{1}H NMR analysis. IR (thin film) 3456, 3206, 2943, 2867, 1464, 1383, 1248, 1106, 1068, 996, 883 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) □ 5.58-5.60 (m, 1H, C=C**H**), 4.08-4.15 (m, 1H, C**H**OH), 3.98 (brs, 1H, O**H**), 3.52-3.81 (m, 3H, C**H**$_2$OSi and C**H**OSi), 2.28-2.32 (m, 1H, C**H**CH_2OSi), 1.88-1.98 (m, 2H, C**H**$_2$CHOSi), 1.74 (s, 3H, C=CC**H**$_3$), 1.04-1.08 (m, 42H, TIPS); ^{13}C NMR (75 MHz, $CDCl_3$) □ 139.0, 124.2, 68.0, 66.6, 64.7, 43.5, 28.7, 22.5, 18.4, 18.4, 12.7, 12.4; HRMS (FAB) *m/z* 469.3533 (M–H, 469.3533 calcd for $C_{26}H_{53}O_3Si_2$); $[\square]^{25}_D$ = 92.5, (*c* = 1.0, $CHCl_3$).

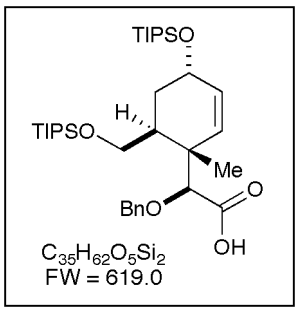


(1*S*, 2*R*, 5*S*)-2-(2-benzyloxyacetoxy)-4-methyl-1-triisopropylsiloxy-5-(triisopropyl-siloxymethyl)cyclohex-3-ene (100). To alcohol **97** (1.50 g, 3.2 mmol) in pyridine (21



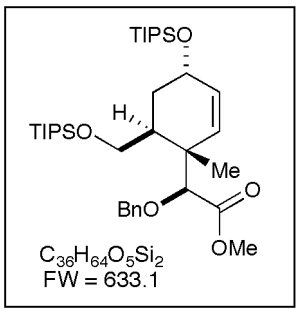
mL) was added freshly distilled benzyloxyacetyl chloride (0.88 g, 4.8 mmol) followed by DMAP (0.04 g, 0.3 mmol). After 1.5 h the reaction mixture was diluted with Et_2O (50 mL) and washed with saturated $NaHCO_3$ solution (50 mL) and brine (50 mL). The organic layer was dried (Na_2SO_4) and concentrated. The crude residue was purified by silica gel chromatography using 2.5% EtOAc : hexanes to provide ester **100** a colorless oil in 76% yield (1.48 g, 2.4 mmol). IR (thin film) 2943, 2866, 1753, 1464, 1384, 1248, 1197, 1118, 1070, 883 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) □ 7.27-7.40 (m, 5H, Ar**H**), 5.49 (d, *J* = 4.4 Hz, 1H, C=C**H**), 5.37-5.40 (m, 1H, C**H**OC(O)), 4.70 (d, *J* = 11.5 Hz, 1H, C**H**$_2$Ph), 4.63 (d, *J* = 11.5 Hz, 1H, C**H**$_2$Ph), 4.21 (dt, *J* = 3.9, 10.4 Hz, 1H, C**H**OSi), 4.12 (s, 2H, C(O)C**H**$_2$), 3.80 (dd, *J* = 3.9, 9.9 Hz, 1H, C**H**$_2$OSi), 3.60 (dd, *J* = 8.8, 9.5 Hz, 1H, C**H**$_2$OSi), 2.36 (brs, 1H, C=C(CH_3)C**H**), 1.87-2.05 (m, 2H, C**H**$_2$CHO), 1.74 (s, 3H, C**H**$_3$), 1.05-1.09 (m, 42H, TIPS); ^{13}C NMR (75 MHz, $CDCl_3$) □ 170.5, 141.3, 128.7, 128.6, 128.6, 128.3, 128.1, 121.2, 73.5, 70.3, 67.6, 66.2, 64.5, 43.2, 29.8, 22.2, 18.3, 18.2, 12.6, 12.2; HRMS (FAB) *m/z* 617.4057 (M–H, 617.4058 calcd for $C_{35}H_{61}O_5Si_2$); $[□]^{25}_D$ = 26.6, (*c* = 1.0, $CHCl_3$).

(2*S*)-2-benzyloxy-2-(1(*R*)-methyl-4(*S*)-triisopropylsiloxy-6(*S*)-triisopropylsiloxy-methylcyclohex-2-enyl)acetic acid (101). To diisopropylamine (0.72 mL, 5.1 mmol) in THF (8 mL) at –78 °C was added a 1.85 M solution of n-BuLi (2.8 mL, 5.1 mmol). After 10 min.ester **100** (1.58 g, 2.6 mmol) in THF (16 mL) was added, and after an additional 0.5 h TMSCl (1.41 g, 13.0 mmol) was added. The cold bath was



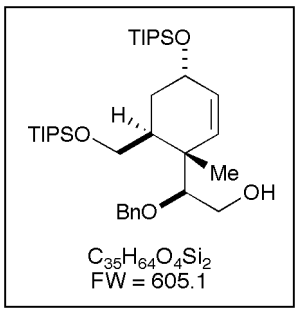
removed and the reaction mixture was allowed to stir at room temperature for 6h. The mixture was diluted with Et_2O (25 mL) and acidified with 1 N HCl (25 mL). After stirred for 0.5 h, the layers were separated and the aqueous layer was extracted with EtOAc (5 x 100 mL). The combined organic extracts were dried and concentrated. The crude residue was purified by silica gel chromatography (20% EtOAc:Hexanes) to provide starting material **100** (0.57 g) and acid **101** as a brown oil (0.34 g, 0.55 mmol, 22% yield, 58% yield based on recovered starting material). IR (thin film) 3416, 2943, 2866, 1714, 1463, 1110, 1066, 882 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) □ 8.83 (brs, 1H, CO_2**H**), 7.28-7.38 (m, 5H, Ar**H**), 5.84 (d, *J* = 10.4 Hz, 1H, C**H**=CHCHOSi), 5.76 (dd, *J* = 3.9, 10.4 Hz, 1H, CH=C**H**CHOSi), 4.75 (d, *J* = 12.1 Hz, 1H, C**H**$_2$Ph), 4.36 (d, *J* = 11.5 Hz, 1H, C**H**$_2$Ph), 4.23-4.26 (m, 1H, C**H**OSi), 4.20 (s, 1H, C**H**OCH_2Ph), 3.84 (dd, *J* = 7.7, 9.9 Hz, 1H, C**H**$_2$OSi), 3.55 (dd, *J* = 6.0, 9.9 Hz, 1H, C**H**$_2$OSi), 2.46-2.55 (brs, 1H, C**H**CH_2OSi), 1.64-1.68 (m, 2H, C**H**$_2$CHOSi), 0.98-1.16 (m, 45H, CC**H**$_3$ and TIPS); ^{13}C NMR (75 MHz, $CDCl_3$) □ 173.9, 137.5, 133.3, 129.3, 128.5, 128.2, 128.0, 84.0, 72.8, 65.1, 64.2, 42.1, 35.9, 31.9, 18.5, 18.4, 18.2, 12.7, 12.2; HRMS (FAB) *m/z* 617.4061 (M–H, 617.4058 calcd for $C_{35}H_{61}O_5Si_2$); $[\square]^{25}_D$ = 87.5, (*c* = 1.0, $CHCl_3$).

Methyl (2*S*)-2-benzyloxy-2-[1(*R*)-methyl-4(*S*)-triisopropylsiloxy-6(*S*)-triisopropylsiloxymethylcyclohex-2-enyl]acetate (102). To acid **101** (100 mg, 0.2 mmol) in CH_2Cl_2 (1.6 mL) and MeOH (0.3 mL) at room temperature was added a 2.0 M solution of $TMSCH_2N_2$ in hexanes (0.1 mL) dropwise resulting in gas evolution. After stirring for 0.5 h, AcOH was added dropwise



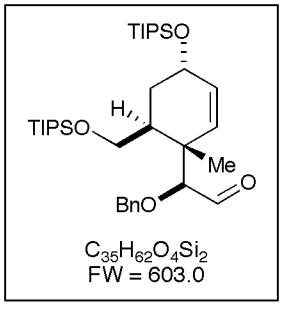
until the solution became colorless and gas evolution ceased. The reaction was concentrated and the crude residue was purified by silica gel chromatography to provide ester **102** as a colorless oil in 93% yield (95 mg, 0.2 mmol). IR (thin film) 3032, 2943, 2866, 1751, 1736, 1463, 1389, 1367, 1335, 1256, 1196, 1174, 1100, 1014, 920, 883 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) □ 7.27-7.37 (m, 5H, Ar**H**), 5.80 (d, *J* = 9.9 Hz, 1H, C**H**=CHCHOSi), 5.73 (dd, *J* = 3.9, 9.9 Hz, 1H, CH=C**H**CHOSi), 4.64 (d, *J* = 11.5 Hz, 1H, C**H**$_2$Ph), 4.33 (d, *J* = 11.5 Hz, 1H, C**H**$_2$Ph), 4.20-4.24 (m, 1H, C**H**OSi), 4.21 (s, 1H, C**H**OCH$_2$Ph), 3.82 (dd, *J* = 6.0, 9.6 Hz, 1H, C**H**$_2$OSi), 3.69 (s, 3H, $CO_2C\mathbf{H}_3$), 3.51 (dd, *J* = 9.6, 8.0 Hz, 1H, C**H**$_2$OSi), 2.27-2.36 (m, 1H, C**H**CH$_2$OSi), 1.53-1.81 (m, 2H, C**H**$_2$CHOSi), 1.02-1.07 (m, 45H, CC**H**$_3$ and TIPS); ^{13}C NMR (75 MHz, $CDCl_3$) □ 171.7, 137.9, 133.9, 128.6, 128.5, 128.1, 127.9, 84.2, 72.6, 64.3, 63.9, 51.5, 42.0, 35.5, 31.4, 18.3, 18.3, 18.3, 12.5, 12.2; HRMS (FAB) *m/z* 469.3530 (M–H, 469.3533 calcd for $C_{26}H_{53}O_3Si_2$); [□]$^{25}_D$ = 41.9, (*c* = 1.1, $CHCl_3$).

(2*S*)-2-Benzyloxy-2-[1(*R*)-methyl-4(*S*)-triisopropylsilyloxy-6(*S*)-triisopropylsilyloxy-methylcyclohex-2-enyl]ethanol (103). To ester **102** (107 mg, 0.17 mmol) in CH_2Cl_2 (1.0 mL) at –78 °C was added DIBAL-H (0.09 mL, 0.51 mmol) dropwise. The cold bath was removed, and the reaction was allowed to stir at room temperature for 1h after which time MeOH (0.1 mL) was added cautiously. After gas evolution ceased, the reaction mixture was diluted with CH_2Cl_2 (5.0 mL) and a saturated solution of Rochelle's salt (5.0 mL). After stirring vigorously for 12h the layers were separated and the aqueous layer was extracted with CH_2Cl_2 (3 x 10 mL). The



combined organic extracts were dried and concentrated to provide alcohol **103** as a colorless oil in 100% yield (102 mg, 0.17 mmol) that was homogeneous by TLC and ^{1}H NMR analysis. IR (thin film) 3566, 3453, 2942, 2866, 1463, 1388, 1367, 1335, 1248, 1210, 1084, 1065, 919, 883 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) 7.27-7.41 (m, 5H, Ar**H**), 5.88 (d, *J* = 9.9 Hz, 1H, C**H**=CHCHOSi), 5.79 (d, *J* = 4.4, 9.9 Hz, 1H, CH=C**H**CHOSi), 4.73 (d, *J* = 11.5 Hz, 1H, C**H**$_2$Ph), 4.66 (d, *J* = 11.5 Hz, 1H, C**H**$_2$Ph), 4.22-4.26 (m, 1H, C**H**OSi), 3.67-3.90 (m, 5H, C**H**$_2$O**H** and C**H**$_2$C**H**OSi and C**H**$_2$OSi), 3.53 (dd, *J* = 6.3, 10.2 Hz, 1H, C**H**$_2$OSi), 2.32-2.42 (m, 1H, C**H**CH$_2$OSi), 1.44-1.73 (m, 2H, C**H**$_2$CHOSi), 1.06-1.09 (m, 45H, CC**H**$_3$ and TIPS); ^{13}C NMR (75 MHz, $CDCl_3$) 139.0, 135.8, 128.6, 128.0, 127.9, 127.8, 85.4, 74.7, 65.5, 64.0, 62.9, 42.5, 35.2, 31.7, 18.3, 18.3, 18.2, 12.5, 12.2; HRMS (FAB) *m/z* 603.4247 (M-H, 603.4265 calcd for $C_{35}H_{63}O_4Si_2$); $[]^{25}_D$ = 16.4, (*c* = 1.0, $CHCl_3$).

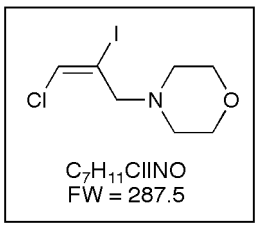
(2*S*)-2-Benzyloxy-2-[1(*R*)-methyl-4(*S*)-triisopropylsilyloxy-6(*S*)-triisopropylsilyloxy-



methylcyclohex-2-enyl]acetaldehyde (104). Alcohol **103** (95 mg, 0.16 mmol), *N*-methylmorpholine-*N*-oxide (NMO) (81 mg, 0.31 mmol), and 5Å mol sieves (20 mg) were stirred in CH_2Cl_2 (3.0 mL) for 15 min before tetrapropylammoniumperruthenate (TPAP) (8 mg, 0.02 mmol) was added. After 15 minutes the reaction was judged to be complete by thin layer chromatography. The reaction mixture was flushed through a silica plug with CH_2Cl_2 and the filtrate was concentrated to provide aldehyde **104** colorless oil in 98% yield (93 mg, 0.15 mmol) that was homogeneous by TLC and ^{1}H NMR analysis. IR (thin film) 2943, 2866, 1731, 1463, 1386, 1255, 1211,

1083, 1066, 1013, 997, 919, 883 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) 9.69 (d, *J* = 3.3 Hz, 1H, C**H**O), 7.27-7.35 (m, 5H, Ar**H**), 5.87 (d, *J* = 9.9 Hz, 1H, C**H**=CHCHO), 5.82 (dd, *J* = 3.9, 10.2 Hz, 1H, CH=C**H**CHO), 4.67 (d, *J* = 12.1 Hz, 1H, C**H**$_2$Ph), 4.41 (d, *J* = 11.5 Hz, 1H, C**H**$_2$Ph), 4.22-4.26 (m, 1H, C**H**OSi), 4.05 (d, *J* = 3.3 Hz, 1H, C**H**OCH$_2$Ph), 3.78 (dd, *J* = 7.1, 9.9 Hz, 1H, C**H**$_2$OSi), 3.54 (dd, *J* = 6.6, 9.9 Hz, 1H, C**H**$_2$OSi), 2.28-2.37 (m, 1H, C**H**CH$_2$OSi), 1.48-1.71 (m, 2H, C**H**$_2$CHOSi), 1.04-1.06 (m, 45H, CC**H**$_3$ and TIPS); ^{13}C NMR (75 MHz, $CDCl_3$) 203.1, 138.0, 133.5, 129.7, 128.6, 128.1, 128.0, 87.5, 73.1, 64.9, 63.8, 42.0, 35.5, 31.4, 18.3, 18.3, 17.6, 12.5, 12.1; HRMS (FAB) *m/z* 601.4103 (M-H, 601.4108 calcd for $C_{35}H_{61}O_4Si_2$); $[]^{25}_D$ = 29.3, (*c* = 1.0, $CHCl_3$).

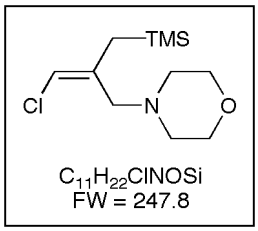
(*E*)-3-chloro-1-morpholino-2-iodoprop-2-ene (110). The procedure of Lambert was used.[7] To a solution of iodine monochloride (8.05 g, 49.5 mmol) in THF (190 mL) was added *N*-propargyl morpholine hydrochloride (**109**) (5.00 g, 31.0 mmol). The reaction mixture was heated to reflux for 2h, cooled to room temperature, and partitioned between 1 N NaOH (200 mL) and CH_2Cl_2 (200 mL). The organic layer was washed with 10% $Na_2S_2O_3$ aqueous solution (100 mL), dried (Na_2SO_4), and concentrated. ^1H NMR analysis revealed an 11:1 *E:Z* mixture of isomers. The desired isomer was easily separated by silica gel chromatography using 5% EtOAc : hexanes to provide vinyl iodide **110** as a yellow oil in 87% yield (7.76 g, 27.0 mmol). IR (thin film) 3073, 2959, 2856, 2813, 1606, 1452, 1346, 1331, 1292, 1268, 1236, 1115, 1070, 1032, 1008 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) 6.64-6.65 (m, 1H, ClC**H**=C), 3.67 (m, 4H, O((C**H**)$_2$)$_2$), 3.19-



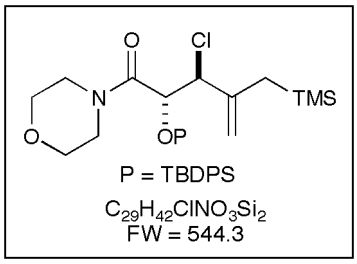
[7] Lambert, S. J.; Kabalka, G. W.; Knapp, Jr., F. F.; Srivastava, P. C. *J. Org. Chem.* **1991**, *56*, 3707.

3.20 (m, 2H, CC**H**$_2$), 2.43-2.46 (m, 4H, N(C**H**$_2$)$_2$); ^{13}C NMR (75 MHz, $CDCl_3$) 122.0, 100.8, 67.2, 61.6, 53.1; HRMS (FAB) *m/z* 287.9641 (M+H, 287.9652 calcd for $C_7H_{12}NOClI$).

(*E*)-3-chloro-1-morpholino-2-(trimethylsilylmethyl)prop-2-ene (107). To $Pd_2(dba)_3$ (80 mg, 0.09 mmol, 2.5 mol%) was added a freshly prepared 1 M trimethylsilylmethylmagnesium chloride solution in Et_2O (7.0 mL, 7 mmol) followed by vinyl iodide **110** (1.00 g, 3.5 mmol) in Et_2O (1.4 mL). After 22 h the reaction mixture was diluted with Et_2O (20 mL) and washed with saturated aqueous NH_4Cl (20 mL). The organic layer was separated, dried (Na_2SO_4), and concentrated. The crude residue was purified by silica gel chromatography using 5% EtOAc : hexanes to provide amine **107** as a clear, colorless oil in 88% yield (0.76 g, 3.1 mmol). IR (thin film) 3067, 2957, 2893, 2854, 2809, 1455, 1398, 1349, 1332, 1294, 1248, 1182, 1120, 1071, 1035, 1011, 992 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) 5.71 (s, 1H, ClC**H**=C), 3.65-3.68 (m, 4H, O(C**H**$_2$)$_2$), 3.03 (s, 2H, CC**H**$_2$), 2.37-2.40 (m, 4H, N(C**H**$_2$)$_2$), 1.67 (s, 2H, C**H**$_2$Si), 0.01 (s, 9H, Si(C**H**$_3$)$_3$); ^{13}C NMR (75 MHz, $CDCl_3$) 137.8, 111.6, 67.3, 58.3, 53.8, 23.9, -0.8; HRMS (FAB) *m/z* 246.1087 (M–H, 246.1081 calcd for $C_{11}H_{21}NOClSi$).

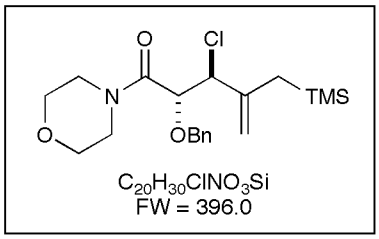


(2*R, 3 *R**)-Morpholine 2-(*tert*-butyldiphenylsiloxy)-3-chloro-4-trimethylsilyl-methyl)pent-4-enamide (115).** Amine **107** (1.18 g, 4.8 mmol) in CH_2Cl_2 (100 mL) was added to $AlCl_3$ (0.64 g, 4.8 mmol). The resulting mixture was treated with iPr_2NEt (3.1 mL, 19.1 mmol) followed by a 1.0 M solution of 2-(*tert*-butyldiphenylsilyloxy)acetyl



chloride in CH_2Cl_2 (14.3 mL, 14.3 mmol) via syringe pump over 15 h. The reaction mixture was diluted with Et_2O (100 mL) and 1 *N* NaOH (100 mL) and the layers were separated. The aqueous layer was extracted with EtOAc (3 x 100 mL) and the combined organic extracts were washed with brine (100 mL), dried, and concentrated. The crude residue was purified by silica gel chromatography (10% EtOAc : hexanes) to provide amide **115** as a yellow oil in 73% yield (1.90 g, 3.5 mmol); *syn:anti* 1:9. IR (thin film) 3073, 3050, 2958, 2932, 2896, 2858, 1655, 1461, 1428, 1361, 1248, 1113, 1031 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) 7.64-7.72 (m, 4H, Ar**H**), 7.33-7.44 (m, 6H, Ar**H**), 5.17 (s, 1H, C=C**H**$_2$), 4.95 (s, 1H, C=C**H**$_2$), 4.61 (d, *J* = 9.1 Hz, C**H**Cl or C**H**O), 4.57 (d, *J* = 9.1 Hz, 1H, C**H**Cl or C**H**O), 3.11-3.54 (m, 8H, morpholine), 1.36-1.49 (m, 2H, C**H**$_2$Si), 1.03 (s, 9H, tBu), 0.05 (s, 9H, TMS); ^{13}C NMR (75 MHz, $CDCl_3$) 168.9, 143.5, 136.4, 136.4, 132.6, 132.6, 130.4, 130.2, 127.9, 127.7, 115.0, 71.1, 66.7, 66.4, 66.1, 46.1, 42.4, 27.2, 23.5, 19.8, –0.7; HRMS (FAB) *m/z* 544.2464 (M+H, 544.2470 calcd for $C_{29}H_{43}NO_3ClSi_2$).

(2*R, 3*R**)-Morpholine 2-benzyloxy-3-chloro-4-(trimethylsilylmethyl)pent-4-enamide (111).** Amine **107** (1.00 g, 4.0 mmol) in CH_2Cl_2 (80 mL) was added to $AlCl_3$ (0.53 g, 4.0 mmol). The resulting mixture was treated with iPr_2NEt (2.1 mL, 12.0 mmol) followed by a 1.0 M solution of 2-benzyloxyacetyl chloride in CH_2Cl_2 (8.0 mL, 8.0 mmol) via syringe pump over 10 h. The reaction mixture was diluted with Et_2O (100 mL) and 1 *N* NaOH (100 mL) and the layers



were separated. The aqueous layer was extracted with EtOAc (3 x 100 mL) and the combined organic extracts were washed with brine (100 mL), dried, and concentrated. The crude residue was purified by silica gel chromatography (20% EtOAc : hexanes) to provide amide **111** as a yellow oil in 84% yield (1.33 g, 3.4 mmol); *syn:anti* 1:9. IR (thin film) 3088, 3031, 2957, 2898, 2859, 1744, 1654, 1600, 1455, 1438, 1248, 1116, 1030, 853 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) 7.27-7.36 (m, 5H, Ar**H**), 5.17 (s, 1H, C=C**H**$_2$), 4.97 (s, 1H, C=C**H**$_2$), 4.67 (d, *J* = 12.1 Hz, 1H, C**H**$_2$Ph), 4.59 (d, *J* = 13.2 Hz, 1H), 4.59 (d, *J* = 12.1 Hz, 1H, C**H**$_2$Ph), 4.46 (d, *J* = 10.4 Hz, 1H), 3.30-3.74 (m, 8H, morpholine), 1.61 (s, 2H, C**H**$_2$Si), 0.08 (s, 9H, TMS); ^{13}C NMR (75 MHz, $CDCl_3$) 167.8, 143.7, 137.0, 128.7, 128.4, 128.3, 114.7, 77.7, 71.9, 67.2, 66.8, 63.7, 46.3, 42.9, 22.8, –0.6; HRMS (FAB) *m/z* 396.1756 (M+H, 396.1762 calcd for $C_{20}H_{31}ClNO_3Si$).

Table 1. Crystal data and structure refinement for THL01 (CCDC 189664).

Empirical formula	$C_{19}H_{25}NO_2$
Formula weight	299.40
Crystallization Solvent	Hexanes
Crystal Habit	Block
Crystal size	0.24 x 0.20 x 0.19 mm^3
Crystal color	Colorless

Data Collection

Preliminary Photos	Rotation
Type of diffractometer	Bruker SMART 1000
Wavelength	0.71073 Å MoKα
Data Collection Temperature	98(2) K
θ range for 11109 reflections used in lattice determination	2.50 to 28.00°
Unit cell dimensions	a = 8.2333(6) Å b = 7.7870(6) Å β= 98.3330(10)° c = 26.445(2) Å
Volume	1677.6(2) $Å^3$
Z	4
Crystal system	Monoclinic
Space group	$P2_1/n$
Density (calculated)	1.185 Mg/m^3
F(000)	648
Data collection program	Bruker SMART v5.054
θ range for data collection	1.56 to 28.44°
Completeness to θ = 28.44°	93.2 %
Index ranges	$-10 \leq h \leq 10$, $-10 \leq k \leq 10$, $-34 \leq l \leq 35$
Data collection scan type	ω scans at 5 ϕ settings
Data reduction program	Bruker SAINT v6.022
Reflections collected	27787
Independent reflections	3936 [R_{int}= 0.0526]
Absorption coefficient	0.076 mm^{-1}
Absorption correction	None
Max. and min. transmission	0.9857 and 0.9820

Table 1 (cont.)

Structure solution and Refinement

Structure solution program	SHELXS-97 (Sheldrick, 1990)
Primary solution method	Direct methods
Secondary solution method	Difference Fourier map
Hydrogen placement	Difference Fourier map
Structure refinement program	SHELXL-97 (Sheldrick, 1997)
Refinement method	Full matrix least-squares on F^2
Data / restraints / parameters	3936 / 0 / 299
Treatment of hydrogen atoms	Unrestrained
Goodness-of-fit on F^2	1.978
Final R indices [$I>2\sigma(I)$, 3020 reflections]	R1 = 0.0412, *w*R2 = 0.0638
R indices (all data)	R1 = 0.0567, *w*R2 = 0.0651
Type of weighting scheme used	Sigma
Weighting scheme used	$w=1/\sigma^2(Fo^2)$
Max shift/error	0.001
Average shift/error	0.000
Largest diff. peak and hole	0.245 and -0.250 e.Å^{-3}

Special Refinement Details

Refinement of F^2 against ALL reflections. The weighted R-factor (*w*R) and goodness of fit (S) are based on F^2, conventional R-factors (R) are based on F, with F set to zero for negative F^2. The threshold expression of $F^2 > 2\sigma(F^2)$ is used only for calculating R-factors(gt) etc. and is not relevant to the choice of reflections for refinement. R-factors based on F^2 are statistically about twice as large as those based on F, and R-factors based on ALL data will be even larger.

All esds (except the esd in the dihedral angle between two l.s. planes) are estimated using the full covariance matrix. The cell esds are taken into account individually in the estimation of esds in distances, angles and torsion angles; correlations between esds in cell parameters are only used when they are defined by crystal symmetry. An approximate (isotropic) treatment of cell esds is used for estimating esds involving l.s. planes.

Methyl (2*E*,4*R,5*R**)-4-Phenyl-5-methyl-3-pyrrolidinohepta-2,6-dienoate**

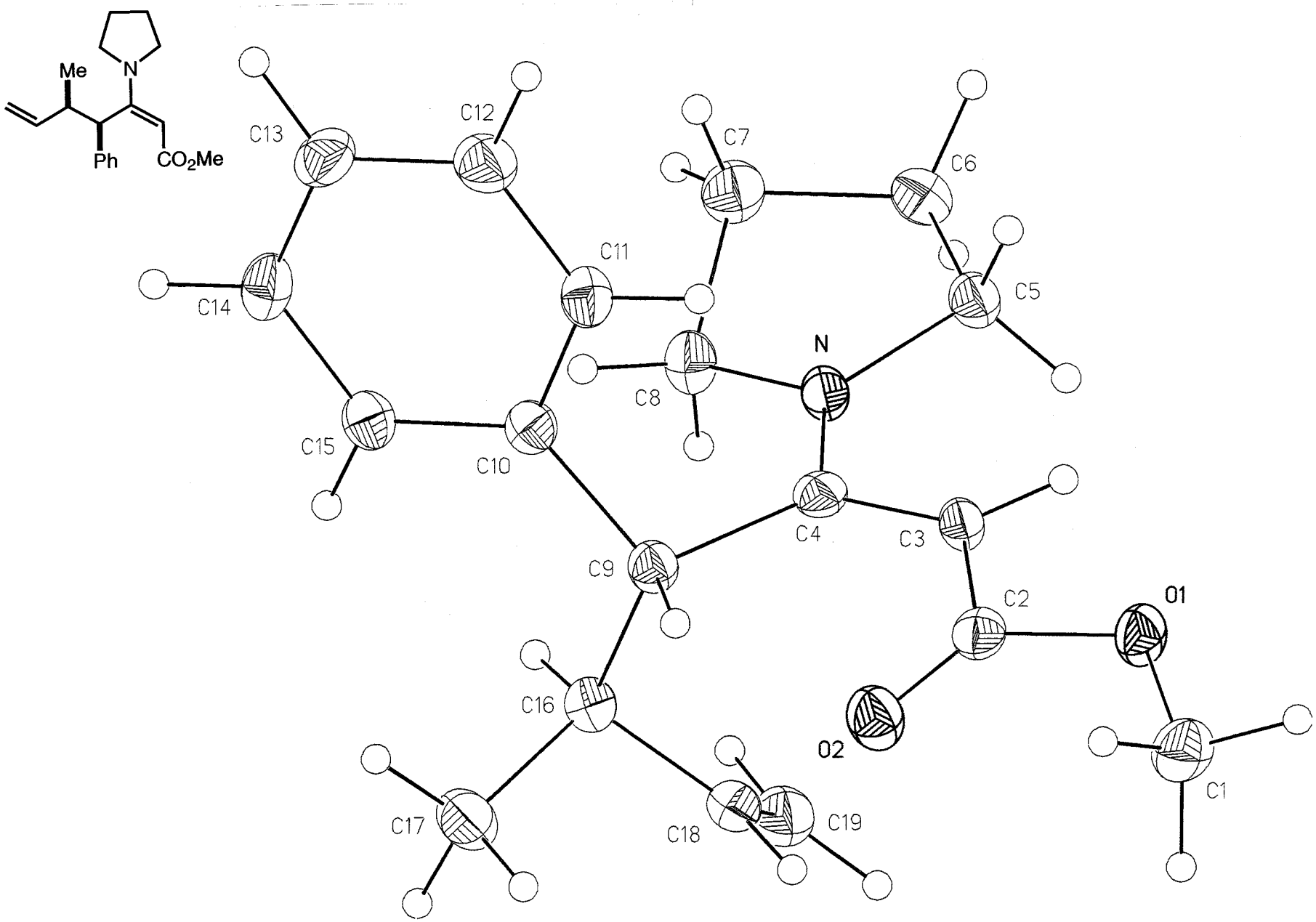


Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$x 10^3) for THL01 (CCDC 189664). U(eq) is defined as the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U_{eq}
O(1)	3163(1)	5676(1)	99(1)	23(1)
O(2)	1695(1)	5536(1)	751(1)	26(1)
N	3983(1)	10583(1)	1079(1)	19(1)
C(1)	2387(2)	4111(2)	-95(1)	27(1)
C(2)	2668(1)	6321(1)	530(1)	20(1)
C(3)	3445(1)	7955(1)	645(1)	18(1)
C(4)	3213(1)	9053(1)	1033(1)	18(1)
C(5)	5198(1)	11092(2)	753(1)	21(1)
C(6)	5808(2)	12845(2)	955(1)	25(1)
C(7)	5362(2)	12903(2)	1492(1)	27(1)
C(8)	3739(2)	11981(2)	1433(1)	23(1)
C(9)	2149(1)	8565(2)	1435(1)	18(1)
C(10)	3191(1)	8541(1)	1963(1)	19(1)
C(11)	4710(1)	7726(2)	2013(1)	23(1)
C(12)	5750(2)	7700(2)	2473(1)	27(1)
C(13)	5282(2)	8496(2)	2897(1)	27(1)
C(14)	3773(2)	9296(2)	2857(1)	24(1)
C(15)	2736(2)	9319(1)	2394(1)	21(1)
C(16)	510(1)	9571(2)	1385(1)	21(1)
C(17)	-768(2)	8578(2)	1634(1)	28(1)
C(18)	-141(1)	9885(2)	833(1)	22(1)
C(19)	-325(1)	11386(2)	609(1)	28(1)

Table 3. Bond lengths [Å] and angles [°] for THL01 (CCDC 189664).

O(1)-C(2)	1.3612(12)	C(4)-N-C(8)	127.36(9)
O(1)-C(1)	1.4362(14)	C(5)-N-C(8)	110.05(8)
O(2)-C(2)	1.2207(12)	O(1)-C(1)-H(1A)	110.7(7)
N-C(4)	1.3467(13)	O(1)-C(1)-H(1B)	105.4(7)
N-C(5)	1.4664(13)	H(1A)-C(1)-H(1B)	111.5(9)
N-C(8)	1.4686(13)	O(1)-C(1)-H(1C)	110.1(6)
C(1)-H(1A)	0.990(12)	H(1A)-C(1)-H(1C)	109.3(9)
C(1)-H(1B)	0.997(13)	H(1B)-C(1)-H(1C)	109.7(9)
C(1)-H(1C)	1.000(12)	O(2)-C(2)-O(1)	120.83(10)
C(2)-C(3)	1.4370(15)	O(2)-C(2)-C(3)	130.18(10)
C(3)-C(4)	1.3707(14)	O(1)-C(2)-C(3)	108.98(9)
C(3)-H(3)	0.935(10)	C(4)-C(3)-C(2)	127.20(10)
C(4)-C(9)	1.5188(14)	C(4)-C(3)-H(3)	119.9(6)
C(5)-C(6)	1.5241(16)	C(2)-C(3)-H(3)	112.6(6)
C(5)-H(5A)	0.992(10)	N-C(4)-C(3)	120.30(10)
C(5)-H(5B)	0.995(11)	N-C(4)-C(9)	118.05(9)
C(6)-C(7)	1.5171(17)	C(3)-C(4)-C(9)	121.61(10)
C(6)-H(6A)	1.001(11)	N-C(5)-C(6)	104.73(9)
C(6)-H(6B)	0.987(12)	N-C(5)-H(5A)	109.8(6)
C(7)-C(8)	1.5052(16)	C(6)-C(5)-H(5A)	112.4(6)
C(7)-H(7A)	1.006(12)	N-C(5)-H(5B)	108.1(6)
C(7)-H(7B)	1.004(12)	C(6)-C(5)-H(5B)	112.4(6)
C(8)-H(8A)	0.971(10)	H(5A)-C(5)-H(5B)	109.3(9)
C(8)-H(8B)	1.012(11)	C(7)-C(6)-C(5)	104.03(10)
C(9)-C(10)	1.5302(14)	C(7)-C(6)-H(6A)	109.1(6)
C(9)-C(16)	1.5493(15)	C(5)-C(6)-H(6A)	109.8(6)
C(9)-H(9)	0.966(10)	C(7)-C(6)-H(6B)	112.4(7)
C(10)-C(15)	1.3897(15)	C(5)-C(6)-H(6B)	111.9(6)
C(10)-C(11)	1.3916(15)	H(6A)-C(6)-H(6B)	109.5(9)
C(11)-C(12)	1.3833(16)	C(8)-C(7)-C(6)	102.80(10)
C(11)-H(11)	0.966(11)	C(8)-C(7)-H(7A)	107.5(7)
C(12)-C(13)	1.3837(16)	C(6)-C(7)-H(7A)	110.6(7)
C(12)-H(12)	0.958(11)	C(8)-C(7)-H(7B)	111.9(7)
C(13)-C(14)	1.3800(16)	C(6)-C(7)-H(7B)	114.0(6)
C(13)-H(13)	0.978(11)	H(7A)-C(7)-H(7B)	109.7(9)
C(14)-C(15)	1.3873(15)	N-C(8)-C(7)	102.57(9)
C(14)-H(14)	0.973(11)	N-C(8)-H(8A)	110.8(6)
C(15)-H(15)	0.960(10)	C(7)-C(8)-H(8A)	113.8(6)
C(16)-C(18)	1.5022(15)	N-C(8)-H(8B)	108.8(6)
C(16)-C(17)	1.5303(16)	C(7)-C(8)-H(8B)	110.2(6)
C(16)-H(16)	0.996(10)	H(8A)-C(8)-H(8B)	110.3(8)
C(17)-H(17A)	1.007(12)	C(4)-C(9)-C(10)	109.71(9)
C(17)-H(17B)	0.987(13)	C(4)-C(9)-C(16)	113.44(9)
C(17)-H(17C)	1.011(11)	C(10)-C(9)-C(16)	116.70(9)
C(18)-C(19)	1.3095(16)	C(4)-C(9)-H(9)	104.5(6)
C(18)-H(18)	0.971(11)	C(10)-C(9)-H(9)	106.8(6)
C(19)-H(19A)	1.021(12)	C(16)-C(9)-H(9)	104.6(6)
C(19)-H(19B)	0.969(12)	C(15)-C(10)-C(11)	117.82(10)
		C(15)-C(10)-C(9)	124.17(10)
C(2)-O(1)-C(1)	116.11(9)	C(11)-C(10)-C(9)	118.00(10)
C(4)-N-C(5)	122.57(9)	C(12)-C(11)-C(10)	121.53(11)

C(12)-C(11)-H(11)	119.0(7)	C(17)-C(16)-C(9)	110.66(9)
C(10)-C(11)-H(11)	119.5(7)	C(18)-C(16)-H(16)	107.3(6)
C(11)-C(12)-C(13)	119.82(12)	C(17)-C(16)-H(16)	109.0(6)
C(11)-C(12)-H(12)	119.8(7)	C(9)-C(16)-H(16)	110.1(6)
C(13)-C(12)-H(12)	120.4(7)	C(16)-C(17)-H(17A)	111.2(7)
C(14)-C(13)-C(12)	119.53(11)	C(16)-C(17)-H(17B)	113.4(7)
C(14)-C(13)-H(13)	120.7(6)	H(17A)-C(17)-H(17B)	108.7(10)
C(12)-C(13)-H(13)	119.8(6)	C(16)-C(17)-H(17C)	111.3(6)
C(13)-C(14)-C(15)	120.39(11)	H(17A)-C(17)-H(17C)	106.0(9)
C(13)-C(14)-H(14)	119.9(6)	H(17B)-C(17)-H(17C)	105.9(9)
C(15)-C(14)-H(14)	119.7(6)	C(19)-C(18)-C(16)	125.92(12)
C(14)-C(15)-C(10)	120.90(11)	C(19)-C(18)-H(18)	119.1(6)
C(14)-C(15)-H(15)	118.4(6)	C(16)-C(18)-H(18)	114.9(6)
C(10)-C(15)-H(15)	120.7(6)	C(18)-C(19)-H(19A)	123.0(7)
C(18)-C(16)-C(17)	109.30(10)	C(18)-C(19)-H(19B)	121.2(7)
C(18)-C(16)-C(9)	110.36(9)	H(19A)-C(19)-H(19B)	115.8(10)

Table 4. Anisotropic displacement parameters ($Å^2 x 10^4$) for THL01 (CCDC 189664). The anisotropic displacement factor exponent takes the form: $-2\pi^2 [h^2 a^{*2} U^{11} + ... + 2 h k a^* b^* U^{12}]$

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
O(1)	271(4)	223(4)	203(4)	-58(3)	63(3)	-9(4)
O(2)	279(5)	249(5)	263(4)	-24(4)	88(4)	-44(4)
N	201(5)	203(5)	174(5)	-13(4)	58(4)	-14(4)
C(1)	292(7)	240(7)	261(7)	-68(6)	30(6)	-7(6)
C(2)	178(6)	228(6)	175(6)	14(5)	2(5)	55(5)
C(3)	178(6)	226(6)	157(6)	13(5)	51(5)	8(5)
C(4)	150(6)	205(6)	174(6)	33(5)	-6(4)	20(5)
C(5)	202(6)	238(7)	199(6)	19(5)	54(5)	-1(5)
C(6)	212(7)	256(7)	280(7)	8(6)	58(5)	-30(6)
C(7)	294(7)	243(7)	273(7)	-38(6)	44(6)	-46(6)
C(8)	276(7)	215(7)	208(6)	-15(5)	73(5)	-9(5)
C(9)	191(6)	182(6)	181(6)	-4(5)	42(5)	-14(5)
C(10)	207(6)	172(6)	182(6)	28(5)	37(5)	-31(5)
C(11)	249(7)	245(7)	192(6)	14(5)	59(5)	6(5)
C(12)	219(7)	333(7)	260(7)	61(6)	26(5)	28(6)
C(13)	282(7)	317(7)	186(6)	42(5)	-16(5)	-50(6)
C(14)	330(7)	222(7)	179(6)	-2(5)	67(5)	-37(6)
C(15)	230(6)	207(6)	211(6)	22(5)	57(5)	1(5)
C(16)	200(6)	224(7)	196(6)	-9(5)	44(5)	4(5)
C(17)	221(7)	342(8)	282(7)	36(6)	73(6)	3(6)
C(18)	168(6)	282(7)	222(6)	-30(5)	36(5)	-1(5)
C(19)	226(7)	354(8)	253(7)	36(6)	33(6)	41(6)

Table 5. Hydrogen coordinates (x 10^4) and isotropic displacement parameters ($Å^2$x 10^3) for THL01 (CCDC 189664).

	x	y	z	U_{iso}
H(1A)	2384(14)	3257(15)	183(5)	36(4)
H(1B)	3039(14)	3701(15)	-361(5)	39(4)
H(1C)	1231(15)	4343(14)	-254(4)	30(3)
H(3)	4093(12)	8293(13)	400(4)	17(3)
H(5A)	4675(12)	11137(12)	391(4)	18(3)
H(5B)	6086(13)	10214(14)	791(4)	23(3)
H(6A)	5198(13)	13772(14)	745(4)	29(3)
H(6B)	6997(15)	12984(14)	952(4)	29(3)
H(7A)	6163(15)	12210(15)	1733(5)	39(4)
H(7B)	5280(13)	14096(16)	1630(4)	31(3)
H(8A)	3459(12)	11528(12)	1752(4)	14(3)
H(8B)	2835(13)	12759(13)	1265(4)	23(3)
H(9)	1828(12)	7391(13)	1354(4)	14(3)
H(11)	5062(13)	7187(13)	1718(4)	26(3)
H(12)	6777(14)	7106(14)	2499(4)	27(3)
H(13)	6024(13)	8492(13)	3221(4)	25(3)
H(14)	3436(12)	9854(13)	3154(4)	20(3)
H(15)	1714(13)	9925(13)	2375(4)	18(3)
H(16)	689(12)	10714(13)	1553(4)	14(3)
H(17A)	-1801(15)	9272(15)	1634(4)	36(3)
H(17B)	-367(14)	8215(15)	1988(5)	38(4)
H(17C)	-1111(13)	7490(14)	1439(4)	27(3)
H(18)	-451(12)	8857(14)	634(4)	24(3)
H(19A)	6(14)	12512(16)	794(5)	39(4)
H(19B)	-758(14)	11488(14)	249(5)	32(3)

Table 1. Crystal data and structure refinement for THL03 (CCDC 189743).

Empirical formula	$C_{23}H_{27}NO_2$
Formula weight	349.46
Crystallization Solvent	Ethylacetate/hexanes
Crystal Habit	Lozenge
Crystal size	0.30 x 0.22 x 0.15 mm^3
Crystal color	Colorless

Data Collection

Preliminary Photos	Rotation
Type of diffractometer	Bruker SMART 1000
Wavelength	0.71073 Å MoKα
Data Collection Temperature	98(2) K
θ range for 8464 reflections used in lattice determination	2.48 to 27.86°
Unit cell dimensions	a = 8.3194(7) Å b = 10.7382(9) Å β= 101.2320(10)° c = 11.0105(9) Å
Volume	964.79(14) $Å^3$
Z	2
Crystal system	Monoclinic
Space group	$P2_1$
Density (calculated)	1.203 Mg/m^3
F(000)	376
Data collection program	Bruker SMART v5.054
θ range for data collection	1.89 to 27.96°
Completeness to θ = 27.96°	95.1 %
Index ranges	$-10 \leq h \leq 10$, $-13 \leq k \leq 13$, $-14 \leq l \leq 14$
Data collection scan type	ω scans at 5 ϕ settings
Data reduction program	Bruker SAINT v6.022
Reflections collected	13823
Independent reflections	4301 [R_{int}= 0.0437]
Absorption coefficient	0.076 mm^{-1}
Absorption correction	None
Max. and min. transmission	0.9887 and 0.9776

Table 1 (cont.)

Structure solution and Refinement

Structure solution program	SHELXS-97 (Sheldrick, 1990)
Primary solution method	Direct methods
Secondary solution method	Difference Fourier map
Hydrogen placement	Difference Fourier map
Structure refinement program	SHELXL-97 (Sheldrick, 1997)
Refinement method	Full matrix least-squares on F^2
Data / restraints / parameters	4301 / 1 / 343
Treatment of hydrogen atoms	Unrestrained
Goodness-of-fit on F^2	1.699
Final R indices [$I>2\sigma(I)$, 3911 reflections]	R1 = 0.0361, *w*R2 = 0.0653
R indices (all data)	R1 = 0.0413, *w*R2 = 0.0662
Type of weighting scheme used	Sigma
Weighting scheme used	$w=1/\sigma^2(Fo^2)$
Max shift/error	0.001
Average shift/error	0.000
Absolute structure parameter	-0.4(8)
Largest diff. peak and hole	0.236 and -0.229 e.Å^{-3}

Special Refinement Details

Refinement of F^2 against ALL reflections. The weighted R-factor (*w*R) and goodness of fit (S) are based on F^2, conventional R-factors (R) are based on F, with F set to zero for negative F^2. The threshold expression of $F^2 > 2\sigma(F^2)$ is used only for calculating R-factors(gt) etc. and is not relevant to the choice of reflections for refinement. R-factors based on F^2 are statistically about twice as large as those based on F, and R-factors based on ALL data will be even larger.

All esds (except the esd in the dihedral angle between two l.s. planes) are estimated using the full covariance matrix. The cell esds are taken into account individually in the estimation of esds in distances, angles and torsion angles; correlations between esds in cell parameters are only used when they are defined by crystal symmetry. An approximate (isotropic) treatment of cell esds is used for estimating esds involving l.s. planes.

Benzyl (2*E*,4*R,5*S**)-3-Dimethylamino-4-methyl-5-phenylhepta-2,6-dienoate**

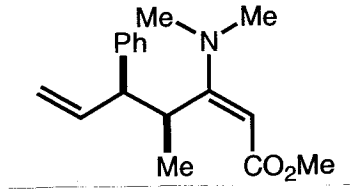


Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$x 10^3) for THL03 (CCDC 189743). U(eq) is defined as the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U_{eq}
O(1)	5689(1)	7542(1)	7882(1)	26(1)
O(2)	3584(1)	8078(1)	6354(1)	23(1)
N(1)	2346(1)	4378(1)	8084(1)	23(1)
C(1)	4388(2)	9244(1)	6221(2)	22(1)
C(2)	3108(2)	10214(1)	5774(1)	20(1)
C(3)	1687(2)	10287(2)	6256(1)	23(1)
C(4)	533(2)	11210(2)	5858(2)	27(1)
C(5)	792(2)	12068(1)	4978(1)	27(1)
C(6)	2213(2)	12012(2)	4509(1)	27(1)
C(7)	3361(2)	11085(1)	4901(1)	23(1)
C(8)	4347(2)	7283(1)	7267(1)	20(1)
C(9)	3304(2)	6219(1)	7309(1)	19(1)
C(10)	3542(2)	5239(1)	8131(1)	19(1)
C(11)	2449(2)	3224(2)	8792(2)	27(1)
C(12)	824(2)	4507(2)	7177(2)	26(1)
C(13)	5096(2)	5172(2)	9134(1)	21(1)
C(14)	4774(2)	5298(2)	10444(1)	24(1)
C(15)	6252(2)	4079(1)	8992(1)	22(1)
C(16)	7879(2)	4225(1)	9886(1)	19(1)
C(17)	8470(2)	3263(1)	10693(1)	21(1)
C(18)	9974(2)	3346(1)	11494(1)	24(1)
C(19)	10897(2)	4410(2)	11519(1)	25(1)
C(20)	10320(2)	5393(2)	10738(1)	25(1)
C(21)	8830(2)	5297(2)	9919(1)	23(1)
C(22)	6535(2)	3955(2)	7685(1)	25(1)
C(23)	6301(2)	2945(2)	7017(2)	37(1)

Table 3. Bond lengths [Å] and angles [°] for THL03 (CCDC 189743).

O(1)-C(8)	1.2190(17)	C(22)-H(22)	0.993(19)
O(2)-C(8)	1.3770(16)	C(23)-H(23A)	1.034(19)
O(2)-C(1)	1.4402(17)	C(23)-H(23B)	0.992(17)
N(1)-C(10)	1.3517(18)		
N(1)-C(11)	1.457(2)	C(8)-O(2)-C(1)	117.15(11)
N(1)-C(12)	1.4589(18)	C(10)-N(1)-C(11)	126.51(12)
C(1)-C(2)	1.502(2)	C(10)-N(1)-C(12)	119.72(12)
C(1)-H(1A)	0.983(14)	C(11)-N(1)-C(12)	113.54(12)
C(1)-H(1B)	0.979(14)	O(2)-C(1)-C(2)	108.81(11)
C(2)-C(3)	1.390(2)	O(2)-C(1)-H(1A)	109.2(9)
C(2)-C(7)	1.387(2)	C(2)-C(1)-H(1A)	111.2(8)
C(3)-C(4)	1.390(2)	O(2)-C(1)-H(1B)	108.4(8)
C(3)-H(3)	0.962(14)	C(2)-C(1)-H(1B)	110.9(8)
C(4)-C(5)	1.384(2)	H(1A)-C(1)-H(1B)	108.3(11)
C(4)-H(4)	0.971(16)	C(3)-C(2)-C(7)	118.84(13)
C(5)-C(6)	1.380(2)	C(3)-C(2)-C(1)	121.04(13)
C(5)-H(5)	0.952(17)	C(7)-C(2)-C(1)	120.08(13)
C(6)-C(7)	1.389(2)	C(2)-C(3)-C(4)	120.39(14)
C(6)-H(6)	0.980(16)	C(2)-C(3)-H(3)	119.9(8)
C(7)-H(7)	0.959(15)	C(4)-C(3)-H(3)	119.7(8)
C(8)-C(9)	1.441(2)	C(3)-C(4)-C(5)	120.25(15)
C(9)-C(10)	1.377(2)	C(3)-C(4)-H(4)	118.8(10)
C(9)-H(9)	0.978(14)	C(5)-C(4)-H(4)	121.0(10)
C(10)-C(13)	1.5295(19)	C(6)-C(5)-C(4)	119.66(15)
C(11)-H(11A)	0.993(18)	C(6)-C(5)-H(5)	120.6(10)
C(11)-H(11B)	0.975(18)	C(4)-C(5)-H(5)	119.7(10)
C(11)-H(11C)	0.967(16)	C(5)-C(6)-C(7)	120.13(15)
C(12)-H(12A)	0.934(16)	C(5)-C(6)-H(6)	120.2(9)
C(12)-H(12B)	0.984(19)	C(7)-C(6)-H(6)	119.7(9)
C(12)-H(12C)	0.982(16)	C(2)-C(7)-C(6)	120.72(15)
C(13)-C(14)	1.524(2)	C(2)-C(7)-H(7)	116.3(9)
C(13)-C(15)	1.545(2)	C(6)-C(7)-H(7)	123.0(9)
C(13)-H(13)	1.013(15)	O(1)-C(8)-O(2)	120.38(13)
C(14)-H(14A)	0.983(17)	O(1)-C(8)-C(9)	130.96(13)
C(14)-H(14B)	1.025(14)	O(2)-C(8)-C(9)	108.66(12)
C(14)-H(14C)	1.008(19)	C(10)-C(9)-C(8)	128.03(13)
C(15)-C(16)	1.5188(19)	C(10)-C(9)-H(9)	118.3(9)
C(15)-C(22)	1.509(2)	C(8)-C(9)-H(9)	113.5(9)
C(15)-H(15)	1.019(14)	N(1)-C(10)-C(9)	119.14(12)
C(16)-C(17)	1.389(2)	N(1)-C(10)-C(13)	120.51(13)
C(16)-C(21)	1.393(2)	C(9)-C(10)-C(13)	120.25(13)
C(17)-C(18)	1.386(2)	N(1)-C(11)-H(11A)	108.9(10)
C(17)-H(17)	0.946(17)	N(1)-C(11)-H(11B)	110.0(11)
C(18)-C(19)	1.374(2)	H(11A)-C(11)-H(11B)	103.1(14)
C(18)-H(18)	0.945(17)	N(1)-C(11)-H(11C)	112.7(10)
C(19)-C(20)	1.386(2)	H(11A)-C(11)-H(11C)	111.9(14)
C(19)-H(19)	0.982(17)	H(11B)-C(11)-H(11C)	109.8(14)
C(20)-C(21)	1.387(2)	N(1)-C(12)-H(12A)	111.0(9)
C(20)-H(20)	0.924(17)	N(1)-C(12)-H(12B)	108.7(10)
C(21)-H(21)	0.978(16)	H(12A)-C(12)-H(12B)	106.0(13)
C(22)-C(23)	1.304(2)	N(1)-C(12)-H(12C)	110.2(9)

H(12A)-C(12)-H(12C)	111.1(13)	C(21)-C(16)-C(15)	122.17(13)
H(12B)-C(12)-H(12C)	109.8(14)	C(18)-C(17)-C(16)	121.46(14)
C(10)-C(13)-C(14)	113.55(12)	C(18)-C(17)-H(17)	119.7(9)
C(10)-C(13)-C(15)	114.72(12)	C(16)-C(17)-H(17)	118.8(9)
C(14)-C(13)-C(15)	113.01(13)	C(19)-C(18)-C(17)	119.87(14)
C(10)-C(13)-H(13)	102.3(8)	C(19)-C(18)-H(18)	122.8(9)
C(14)-C(13)-H(13)	106.9(8)	C(17)-C(18)-H(18)	117.3(9)
C(15)-C(13)-H(13)	105.1(8)	C(18)-C(19)-C(20)	119.73(14)
C(13)-C(14)-H(14A)	111.9(9)	C(18)-C(19)-H(19)	121.6(10)
C(13)-C(14)-H(14B)	110.9(7)	C(20)-C(19)-H(19)	118.7(10)
H(14A)-C(14)-H(14B)	108.8(12)	C(19)-C(20)-C(21)	120.29(15)
C(13)-C(14)-H(14C)	113.3(10)	C(19)-C(20)-H(20)	122.0(10)
H(14A)-C(14)-H(14C)	102.0(13)	C(21)-C(20)-H(20)	117.7(10)
H(14B)-C(14)-H(14C)	109.6(12)	C(20)-C(21)-C(16)	120.60(14)
C(16)-C(15)-C(22)	110.01(12)	C(20)-C(21)-H(21)	116.9(9)
C(16)-C(15)-C(13)	110.49(12)	C(16)-C(21)-H(21)	122.5(9)
C(22)-C(15)-C(13)	112.28(12)	C(23)-C(22)-C(15)	125.27(17)
C(16)-C(15)-H(15)	107.4(7)	C(23)-C(22)-H(22)	120.6(11)
C(22)-C(15)-H(15)	109.1(8)	C(15)-C(22)-H(22)	113.8(11)
C(13)-C(15)-H(15)	107.3(8)	C(22)-C(23)-H(23A)	122.0(10)
C(17)-C(16)-C(21)	118.02(13)	C(22)-C(23)-H(23B)	123.3(10)
C(17)-C(16)-C(15)	119.81(13)	H(23A)-C(23)-H(23B)	114.6(14)

Table 4. Anisotropic displacement parameters ($Å^2 x 10^4$) for THL03 (CCDC 189743). The anisotropic displacement factor exponent takes the form: $-2\pi^2 [h^2 a^{*2} U^{11} + ... + 2 h k a^* b^* U^{12}]$

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
O(1)	185(5)	252(6)	316(6)	63(5)	-36(5)	-31(5)
O(2)	236(5)	178(5)	234(5)	40(4)	-23(4)	-23(4)
N(1)	201(6)	202(7)	265(7)	43(5)	23(5)	-4(6)
C(1)	225(8)	199(8)	224(8)	31(6)	23(7)	-29(6)
C(2)	203(8)	188(7)	191(7)	-28(6)	-11(6)	-36(6)
C(3)	278(8)	202(8)	212(8)	32(7)	46(6)	-16(7)
C(4)	252(8)	285(9)	285(9)	-42(7)	50(7)	7(7)
C(5)	289(9)	187(8)	286(8)	-26(7)	-93(7)	40(7)
C(6)	314(9)	222(8)	221(8)	41(7)	-46(7)	-57(7)
C(7)	216(8)	241(8)	207(8)	17(7)	1(6)	-38(7)
C(8)	214(8)	181(8)	193(7)	-6(6)	41(6)	45(6)
C(9)	159(7)	204(7)	193(8)	3(6)	-12(6)	16(6)
C(10)	184(7)	188(7)	212(7)	-21(7)	42(6)	25(6)
C(11)	278(9)	223(9)	287(9)	45(7)	19(8)	-22(7)
C(12)	213(8)	223(9)	318(10)	35(8)	-21(7)	-28(7)
C(13)	195(8)	218(8)	224(8)	11(7)	31(6)	-6(7)
C(14)	222(8)	237(8)	252(8)	-42(7)	-6(7)	30(8)
C(15)	198(8)	206(8)	256(8)	4(6)	18(6)	-5(6)
C(16)	167(7)	225(8)	194(8)	-41(6)	47(6)	29(6)
C(17)	257(8)	164(8)	236(8)	-12(6)	92(6)	3(7)
C(18)	278(9)	259(9)	202(8)	47(7)	65(7)	82(7)
C(19)	171(8)	352(10)	221(8)	1(7)	11(6)	56(7)
C(20)	200(8)	254(9)	300(8)	11(7)	49(6)	-37(7)
C(21)	206(8)	220(8)	251(8)	41(7)	30(6)	45(7)
C(22)	200(8)	309(9)	243(8)	26(7)	22(7)	81(7)
C(23)	417(10)	415(11)	275(9)	-37(9)	54(8)	12(9)

Table 5. Hydrogen coordinates (x 10^4) and isotropic displacement parameters ($Å^2$x 10^3) for THL03 (CCDC 189743).

	x	y	z	U_{iso}
H(1A)	5132(17)	9138(13)	5635(13)	16(4)
H(1B)	5044(16)	9474(13)	7027(13)	15(4)
H(3)	1496(17)	9693(13)	6867(13)	17(4)
H(4)	-440(20)	11252(15)	6223(13)	33(5)
H(5)	0(20)	12698(16)	4710(14)	29(4)
H(6)	2406(18)	12616(16)	3886(14)	29(4)
H(7)	4352(18)	11000(14)	4587(13)	24(4)
H(9)	2270(17)	6260(13)	6709(13)	16(4)
H(11A)	2510(20)	2513(17)	8227(16)	38(5)
H(11B)	1420(20)	3076(17)	9067(16)	44(5)
H(11C)	3349(19)	3222(16)	9496(15)	30(4)
H(12A)	290(18)	5249(16)	7295(13)	23(4)
H(12B)	80(20)	3832(18)	7308(16)	45(5)
H(12C)	1045(18)	4456(14)	6333(15)	26(4)
H(13)	5709(16)	5947(14)	8964(12)	19(4)
H(14A)	3946(19)	5938(16)	10498(14)	30(4)
H(14B)	5831(17)	5515(13)	11057(12)	14(3)
H(14C)	4260(20)	4532(18)	10739(16)	43(5)
H(15)	5717(16)	3285(13)	9229(12)	13(3)
H(17)	7804(19)	2553(16)	10715(14)	27(4)
H(18)	10310(18)	2656(15)	12014(15)	26(4)
H(19)	11960(20)	4498(16)	12084(15)	38(5)
H(20)	10880(19)	6139(16)	10764(14)	30(4)
H(21)	8494(17)	6009(15)	9376(13)	24(4)
H(22)	7040(20)	4700(18)	7384(16)	53(6)
H(23A)	5850(20)	2138(18)	7335(16)	45(5)
H(23B)	6497(19)	2894(16)	6158(16)	41(5)

Table 1. Crystal data and structure refinement for THL02 (CCDC 189742).

Empirical formula	$C_{24}H_{27}NO_2$
Formula weight	361.47
Crystallization Solvent	Hexanes/ether
Crystal Habit	Block
Crystal size	0.24 x 0.22 x 0.20 mm^3
Crystal color	Colorless

Data Collection

Preliminary Photos	Rotation
Type of diffractometer	Bruker SMART 1000
Wavelength	0.71073 Å MoKα
Data Collection Temperature	98(2) K
θ range for 13362 reflections used in lattice determination	2.23 to 28.84°
Unit cell dimensions	a = 10.4779(7) Å b = 10.6838(7) Å c = 17.4395(11) Å
Volume	1952.2(2) $Å^3$
Z	4
Crystal system	Orthorhombic
Space group	$P2_12_12_1$
Density (calculated)	1.230 Mg/m^3
F(000)	776
Data collection program	Bruker SMART v5.054
θ range for data collection	2.24 to 28.35°
Completeness to θ = 28.35°	96.2 %
Index ranges	$-13 \le h \le 13$, $-13 \le k \le 14$, $-22 \le l \le 22$
Data collection scan type	ω scans at 5 ϕ settings
Data reduction program	Bruker SAINT v6.022
Reflections collected	28772
Independent reflections	4606 [R_{int}= 0.0534]
Absorption coefficient	0.077 mm^{-1}
Absorption correction	None
Max. and min. transmission	0.9847 and 0.9817

Table 1 (cont.)

Structure solution and Refinement

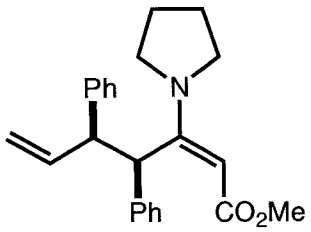
Structure solution program	SHELXS-97 (Sheldrick, 1990)
Primary solution method	Direct methods
Secondary solution method	Difference Fourier map
Hydrogen placement	Difference Fourier map
Structure refinement program	SHELXL-97 (Sheldrick, 1997)
Refinement method	Full matrix least-squares on F^2
Data / restraints / parameters	4606 / 0 / 352
Treatment of hydrogen atoms	Unrestrained
Goodness-of-fit on F^2	1.629
Final R indices [$I>2\sigma(I)$, 3972 reflections]	R1 = 0.0358, *w*R2 = 0.0532
R indices (all data)	R1 = 0.0444, *w*R2 = 0.0541
Type of weighting scheme used	Sigma
Weighting scheme used	$w=1/\sigma^2(Fo^2)$
Max shift/error	0.001
Average shift/error	0.000
Absolute structure parameter	-0.5(8)
Largest diff. peak and hole	0.200 and -0.238 e.Å^{-3}

Special Refinement Details

Refinement of F^2 against ALL reflections. The weighted R-factor (*w*R) and goodness of fit (S) are based on F^2, conventional R-factors (R) are based on F, with F set to zero for negative F^2. The threshold expression of $F^2 > 2\sigma(F^2)$ is used only for calculating R-factors(gt) etc. and is not relevant to the choice of reflections for refinement. R-factors based on F^2 are statistically about twice as large as those based on F, and R-factors based on ALL data will be even larger.

All esds (except the esd in the dihedral angle between two l.s. planes) are estimated using the full covariance matrix. The cell esds are taken into account individually in the estimation of esds in distances, angles and torsion angles; correlations between esds in cell parameters are only used when they are defined by crystal symmetry. An approximate (isotropic) treatment of cell esds is used for estimating esds involving l.s. planes.

Methyl (2*E*,4*R,5*R**)-4,5-Diphenyl-3-pyrrolidinohepta-2,6-dienoate**



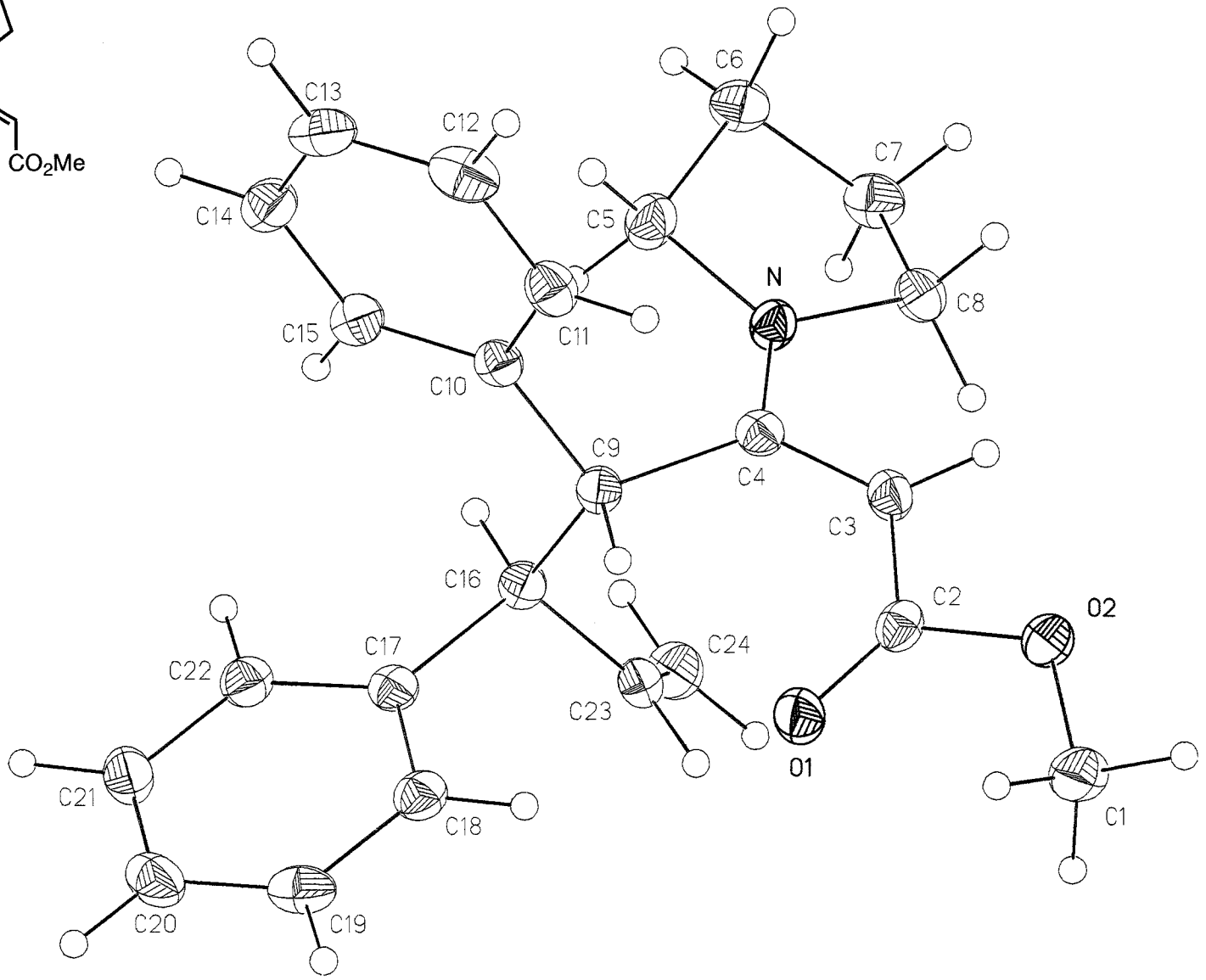


Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$x 10^3) for THL02 (CCDC 189742). U(eq) is defined as the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U_{eq}
O(1)	2744(1)	6191(1)	1802(1)	25(1)
O(2)	1295(1)	5324(1)	2593(1)	24(1)
N	1801(1)	9515(1)	3160(1)	19(1)
C(1)	1596(2)	4132(1)	2257(1)	28(1)
C(2)	1983(1)	6314(1)	2328(1)	19(1)
C(3)	1656(1)	7415(1)	2764(1)	19(1)
C(4)	2045(1)	8622(1)	2633(1)	17(1)
C(5)	1889(1)	10889(1)	3061(1)	24(1)
C(6)	1259(1)	11398(1)	3781(1)	23(1)
C(7)	1556(2)	10406(1)	4380(1)	24(1)
C(8)	1372(1)	9197(1)	3940(1)	22(1)
C(9)	2813(1)	8965(1)	1919(1)	17(1)
C(10)	2147(1)	9924(1)	1408(1)	18(1)
C(11)	956(1)	9626(1)	1112(1)	23(1)
C(12)	311(1)	10445(2)	631(1)	28(1)
C(13)	849(1)	11584(1)	444(1)	27(1)
C(14)	2029(1)	11898(1)	736(1)	25(1)
C(15)	2674(1)	11071(1)	1214(1)	21(1)
C(16)	4227(1)	9273(1)	2127(1)	18(1)
C(17)	5093(1)	9162(1)	1429(1)	18(1)
C(18)	5152(1)	8053(1)	1004(1)	22(1)
C(19)	5954(1)	7964(1)	374(1)	25(1)
C(20)	6710(1)	8963(1)	154(1)	28(1)
C(21)	6673(1)	10055(1)	578(1)	27(1)
C(22)	5879(1)	10148(1)	1215(1)	22(1)
C(23)	4696(1)	8421(1)	2754(1)	20(1)
C(24)	5094(1)	8803(2)	3427(1)	26(1)

Table 3. Bond lengths [Å] and angles [°] for THL02 (CCDC 189742).

O(1)-C(2)	1.2220(14)	C(22)-H(22)	0.968(12)
O(2)-C(2)	1.3613(14)	C(23)-C(24)	1.3099(18)
O(2)-C(1)	1.4365(16)	C(23)-H(23)	1.026(13)
N-C(4)	1.3487(15)	C(24)-H(24A)	0.980(14)
N-C(8)	1.4717(15)	C(24)-H(24B)	1.004(14)
N-C(5)	1.4805(16)		
C(1)-H(1A)	1.032(14)	C(2)-O(2)-C(1)	115.71(10)
C(1)-H(1B)	0.996(13)	C(4)-N-C(8)	121.58(10)
C(1)-H(1C)	0.990(16)	C(4)-N-C(5)	127.58(10)
C(2)-C(3)	1.4419(18)	C(8)-N-C(5)	110.84(10)
C(3)-C(4)	1.3718(18)	O(2)-C(1)-H(1A)	110.9(8)
C(3)-H(3)	0.938(11)	O(2)-C(1)-H(1B)	104.0(7)
C(4)-C(9)	1.5278(16)	H(1A)-C(1)-H(1B)	113.3(11)
C(5)-C(6)	1.5196(18)	O(2)-C(1)-H(1C)	109.8(9)
C(5)-H(5A)	1.003(13)	H(1A)-C(1)-H(1C)	106.9(12)
C(5)-H(5B)	0.998(13)	H(1B)-C(1)-H(1C)	111.9(11)
C(6)-C(7)	1.5202(19)	O(1)-C(2)-O(2)	121.11(11)
C(6)-H(6A)	0.971(12)	O(1)-C(2)-C(3)	129.68(12)
C(6)-H(6B)	0.991(12)	O(2)-C(2)-C(3)	109.21(10)
C(7)-C(8)	1.5148(19)	C(4)-C(3)-C(2)	127.50(12)
C(7)-H(7A)	0.975(13)	C(4)-C(3)-H(3)	117.5(7)
C(7)-H(7B)	0.968(14)	C(2)-C(3)-H(3)	114.9(7)
C(8)-H(8A)	1.018(12)	N-C(4)-C(3)	119.70(11)
C(8)-H(8B)	1.020(12)	N-C(4)-C(9)	119.08(11)
C(9)-C(10)	1.5262(16)	C(3)-C(4)-C(9)	121.14(11)
C(9)-C(16)	1.5597(17)	N-C(5)-C(6)	103.37(11)
C(9)-H(9)	0.975(12)	N-C(5)-H(5A)	110.7(7)
C(10)-C(15)	1.3860(17)	C(6)-C(5)-H(5A)	113.7(7)
C(10)-C(11)	1.3880(17)	N-C(5)-H(5B)	111.1(7)
C(11)-C(12)	1.3880(19)	C(6)-C(5)-H(5B)	109.9(7)
C(11)-H(11)	0.920(12)	H(5A)-C(5)-H(5B)	108.0(11)
C(12)-C(13)	1.380(2)	C(7)-C(6)-C(5)	103.28(11)
C(12)-H(12)	0.969(15)	C(7)-C(6)-H(6A)	115.2(7)
C(13)-C(14)	1.378(2)	C(5)-C(6)-H(6A)	111.1(7)
C(13)-H(13)	0.972(14)	C(7)-C(6)-H(6B)	108.2(7)
C(14)-C(15)	1.3906(17)	C(5)-C(6)-H(6B)	109.4(7)
C(14)-H(14)	0.989(13)	H(6A)-C(6)-H(6B)	109.4(10)
C(15)-H(15)	0.970(13)	C(6)-C(7)-C(8)	102.72(11)
C(16)-C(23)	1.5064(17)	C(6)-C(7)-H(7A)	113.2(7)
C(16)-C(17)	1.5228(17)	C(8)-C(7)-H(7A)	114.3(8)
C(16)-H(16)	1.027(11)	C(6)-C(7)-H(7B)	109.2(8)
C(17)-C(22)	1.3881(17)	C(8)-C(7)-H(7B)	110.7(8)
C(17)-C(18)	1.3991(17)	H(7A)-C(7)-H(7B)	106.8(10)
C(18)-C(19)	1.3862(18)	N-C(8)-C(7)	103.47(11)
C(18)-H(18)	0.988(13)	N-C(8)-H(8A)	109.3(7)
C(19)-C(20)	1.383(2)	C(7)-C(8)-H(8A)	113.9(7)
C(19)-H(19)	0.962(13)	N-C(8)-H(8B)	110.6(7)
C(20)-C(21)	1.383(2)	C(7)-C(8)-H(8B)	112.3(7)
C(20)-H(20)	0.963(13)	H(8A)-C(8)-H(8B)	107.2(10)
C(21)-C(22)	1.3908(18)	C(4)-C(9)-C(10)	113.31(10)
C(21)-H(21)	1.003(13)	C(4)-C(9)-C(16)	111.17(10)

C(10)-C(9)-C(16)	115.35(10)	C(17)-C(16)-H(16)	107.7(6)
C(4)-C(9)-H(9)	104.6(7)	C(9)-C(16)-H(16)	110.0(6)
C(10)-C(9)-H(9)	103.9(7)	C(22)-C(17)-C(18)	118.31(12)
C(16)-C(9)-H(9)	107.5(7)	C(22)-C(17)-C(16)	120.62(11)
C(15)-C(10)-C(11)	118.01(12)	C(18)-C(17)-C(16)	121.03(11)
C(15)-C(10)-C(9)	123.65(11)	C(19)-C(18)-C(17)	120.32(13)
C(11)-C(10)-C(9)	118.34(11)	C(19)-C(18)-H(18)	119.5(7)
C(12)-C(11)-C(10)	121.25(14)	C(17)-C(18)-H(18)	120.1(7)
C(12)-C(11)-H(11)	121.0(8)	C(18)-C(19)-C(20)	120.92(13)
C(10)-C(11)-H(11)	117.8(8)	C(18)-C(19)-H(19)	118.3(7)
C(13)-C(12)-C(11)	119.94(14)	C(20)-C(19)-H(19)	120.8(7)
C(13)-C(12)-H(12)	121.5(8)	C(21)-C(20)-C(19)	119.11(13)
C(11)-C(12)-H(12)	118.6(8)	C(21)-C(20)-H(20)	120.9(9)
C(14)-C(13)-C(12)	119.63(14)	C(19)-C(20)-H(20)	120.0(8)
C(14)-C(13)-H(13)	120.3(8)	C(20)-C(21)-C(22)	120.32(14)
C(12)-C(13)-H(13)	120.0(8)	C(20)-C(21)-H(21)	121.2(7)
C(13)-C(14)-C(15)	120.17(14)	C(22)-C(21)-H(21)	118.4(7)
C(13)-C(14)-H(14)	118.7(7)	C(17)-C(22)-C(21)	120.98(13)
C(15)-C(14)-H(14)	121.2(7)	C(17)-C(22)-H(22)	120.5(7)
C(10)-C(15)-C(14)	121.00(13)	C(21)-C(22)-H(22)	118.5(7)
C(10)-C(15)-H(15)	121.1(7)	C(24)-C(23)-C(16)	124.51(13)
C(14)-C(15)-H(15)	117.9(7)	C(24)-C(23)-H(23)	120.0(7)
C(23)-C(16)-C(17)	109.83(10)	C(16)-C(23)-H(23)	115.5(7)
C(23)-C(16)-C(9)	110.58(10)	C(23)-C(24)-H(24A)	119.7(8)
C(17)-C(16)-C(9)	111.35(10)	C(23)-C(24)-H(24B)	123.7(8)
C(23)-C(16)-H(16)	107.3(6)	H(24A)-C(24)-H(24B)	116.7(11)

Table 4. Anisotropic displacement parameters ($Å^2 x 10^4$) for THL02 (CCDC 189742). The anisotropic displacement factor exponent takes the form: $-2\pi^2 [h^2 a^{*2} U^{11} + ... + 2 h k a^* b^* U^{12}]$

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
O(1)	298(5)	205(5)	253(5)	-14(4)	76(4)	-7(4)
O(2)	249(5)	156(5)	311(5)	-19(4)	41(4)	-22(4)
N	230(6)	161(6)	173(5)	-2(5)	16(5)	-3(5)
C(1)	250(8)	169(8)	413(9)	-38(7)	30(7)	-26(7)
C(2)	191(7)	182(7)	199(6)	28(6)	-36(6)	-12(6)
C(3)	209(7)	201(7)	170(7)	8(5)	36(6)	-8(6)
C(4)	155(6)	204(7)	163(6)	6(5)	-19(5)	14(5)
C(5)	307(9)	177(7)	234(7)	-5(6)	35(7)	-6(6)
C(6)	242(8)	220(8)	234(7)	-55(6)	0(6)	16(7)
C(7)	261(8)	274(8)	197(7)	-42(6)	-7(6)	28(7)
C(8)	242(8)	243(8)	172(7)	-8(6)	30(6)	10(6)
C(9)	200(7)	157(6)	158(6)	-14(5)	17(6)	-7(5)
C(10)	211(7)	196(7)	123(6)	-24(5)	17(5)	25(6)
C(11)	225(7)	249(8)	203(7)	-25(6)	25(6)	-15(7)
C(12)	220(8)	392(9)	239(7)	-75(7)	-34(6)	49(7)
C(13)	317(8)	299(8)	185(7)	-20(6)	-21(6)	134(7)
C(14)	335(9)	213(7)	191(7)	-5(6)	21(6)	50(7)
C(15)	234(8)	216(7)	189(7)	-7(6)	-10(6)	13(6)
C(16)	203(7)	167(7)	160(6)	-12(5)	5(5)	0(6)
C(17)	169(7)	219(7)	151(6)	18(5)	-26(5)	32(6)
C(18)	213(8)	224(7)	214(7)	26(6)	-25(6)	34(6)
C(19)	259(8)	298(8)	205(7)	-48(6)	-42(6)	100(7)
C(20)	236(8)	411(9)	198(7)	48(7)	32(6)	85(7)
C(21)	223(7)	312(9)	264(7)	74(6)	29(6)	6(7)
C(22)	226(7)	214(8)	221(7)	13(6)	-3(6)	25(6)
C(23)	186(7)	223(7)	201(7)	33(6)	39(6)	6(6)
C(24)	258(8)	302(9)	221(7)	29(6)	-9(6)	23(7)

Table 5. Hydrogen coordinates (x 10^4) and isotropic displacement parameters ($Å^2$x 10^3) for THL02 (CCDC 189742).

	x	y	z	U_{iso}
H(1A)	1629(14)	4195(12)	1667(8)	38(4)
H(1B)	909(12)	3568(12)	2447(7)	25(4)
H(1C)	2451(15)	3856(14)	2429(9)	51(5)
H(3)	1156(11)	7265(11)	3200(6)	14(3)
H(5A)	1460(12)	11158(12)	2574(7)	26(4)
H(5B)	2797(12)	11167(12)	3039(7)	26(4)
H(6A)	1570(12)	12233(12)	3900(7)	21(4)
H(6B)	322(12)	11425(11)	3706(6)	13(3)
H(7A)	1029(12)	10477(12)	4839(7)	26(3)
H(7B)	2434(13)	10494(12)	4544(7)	29(4)
H(8A)	1903(12)	8471(11)	4142(6)	20(3)
H(8B)	444(12)	8912(11)	3935(7)	17(3)
H(9)	2817(12)	8203(11)	1611(7)	20(3)
H(11)	615(12)	8859(12)	1236(7)	17(3)
H(12)	-529(14)	10210(13)	447(8)	43(4)
H(13)	398(13)	12158(12)	108(8)	31(4)
H(14)	2393(12)	12725(12)	606(6)	22(4)
H(15)	3496(12)	11330(11)	1415(6)	15(3)
H(16)	4294(10)	10174(11)	2327(6)	8(3)
H(18)	4632(12)	7323(12)	1156(7)	22(4)
H(19)	5958(12)	7195(12)	86(7)	20(3)
H(20)	7242(13)	8896(13)	-294(8)	37(4)
H(21)	7189(12)	10806(12)	427(7)	26(4)
H(22)	5857(12)	10931(12)	1494(7)	22(3)
H(23)	4691(11)	7483(13)	2626(7)	25(4)
H(24A)	5087(12)	9698(13)	3548(7)	29(4)
H(24B)	5390(13)	8223(13)	3844(8)	35(4)