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CHELATION CONTROL IN THE INTRAMOLECULAR ADDITION OF ALLYLSILANES TO CARBONYL ELECTROPHILES

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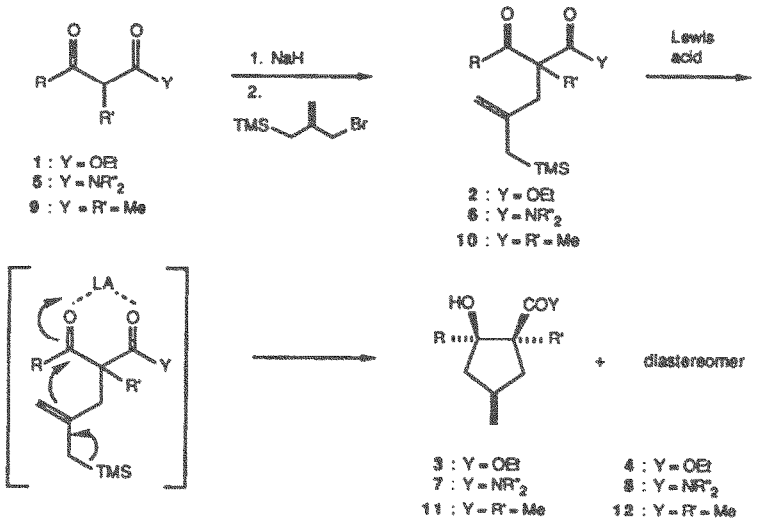
Abstract: Use of chelation control to direct the stereochemical outcome of intramolecular additions of allylsilanes to β-dicarbonyl substrates is described. Excellent diastereoselectivity is achieved by titanium tetrachloride promoted cyclization of a wide variety of β-dicarbonyl substrates, and these reactions also proceed in high yield. Cyclizations occur under mild conditions and are highly chemoselective, providing direct routes to highly functionalized five-, six- and seven-membered carbocycles.

Reactions of allylsilanes and allylstannanes with carbonyl electrophiles have become exceedingly useful for highly selective formation of carbon-carbon bonds. Although initial investigations focused primarily on the chemoselectivity of such additions,[2] more recently the unique stereoselectivity exhibited by these allylmetallics has received much attention. Studies have been reported on the erythro/threo selectivity that can be obtained in intermolecular additions of γ-substituted allylsilanes and allylstannanes to "simple" aldehydes and ketones,[3] as well as on use of chelation to direct addition of unsubstituted allylsilanes and allylstannanes to carbonyl substrates bearing Lewis basic substituents at the α or β position.[4] In many instances, these studies have demonstrated significant advantages over existing methodologies in both the sense and magnitude of stereoselectivity.[5]

The erythro/threo selectivity of allylsilanes and allylstannanes toward carbonyl electrophiles has also been demonstrated in intramolecular cases.[6] As with intermolecular examples, diastereoselectivity in these systems is quite high. Such investigations are particularly intriguing because the tolerance of allylsilanes, in particular, for a wide variety of chemical transformations[7] makes these latent nucleophiles ideal precursors for intramolecular carbon-carbon bond forming reactions. We were initially attracted to allylsilane cyclization reactions of this type because of the lack of studies on use of chelation to control stereochemistry in intramolecular carbonyl addition reactions. Thus, as part of a program to exploit chelation in the development of efficient, stereocontrolled approaches to functionalized carbocycles,[8] we have initiated a study aimed at delineating the application of this highly useful control element in intramolecular addition of allylsilanes to β-dicarbonyl substrates.

Results and Discussion

As a starting point, we targeted β-ketoesters **2** for study.[9] Related projects in our laboratory have demonstrated dicarbonyl substrates of this type to be effective templates for chelative cyclizations.[8b,d]



We postulated that an appropriate Lewis acid (LA) would be held in tight chelation by Lewis basic carbonyl groups, providing rigid control of the cyclization process. Such control would result in a transition state in which addition of the allylsilane would be directed exclusively to one face of the electrophilic carbonyl group, resulting in predictable formation of a single diastereomer. In addition, it was anticipated that chemoselectivity could be achieved in substrates containing two distinct carbonyl functionalities, e.g. ketones and esters, providing a direct route into highly functionalized carbocycles. Appropriately substituted β-dicarbonyl substrates were also attractive in that they proved readily accessible by simple alkylation of β-dicarbonyl precursors (**1**, **5**, or **9**) by 2-bromomethyl-3-trimethylsilylpropene.[10]

Selection of an appropriate Lewis acid was an important consideration for these processes. We proceeded by employing ethyl 2-acetyl-2-methyl-4-(trimethylsilyl)methyl-4-pentenoate (**2a**) as a model compound and set out to examine the effects of various Lewis acids on the cyclization process. Crude reaction mixtures were quantitated by obtaining GC yields based on an internal standard. While $SnCl_4$ and $FeCl_3$ either provided none of the desired products and/or poor diastereoselectivity, initial efforts with titanium tetrachloride proved most effective (Table I).

Table I. Cyclization of ethyl 2-acetyl-2-methyl-4-(trimethylsilyl)methyl-4-pentenoate (**2a**).

Promoter (equiv.)	Solvent	Temperature	% GC Yield	Ratio (**3a** : **4a**)
$TiCl_4$ (1.1)	CH_2Cl_2	-78°C	86	>200 : 1[a]
$TiCl_4$ (4)	CH_2Cl_2	-78°C	97	>200 : 1[a]
$TiCl_4$ (4)	CH_2Cl_2	-95°C	55	>200 : 1[a]
$BF_3{\cdot}Et_2O$ (4)	CH_2Cl_2	0°C	30	1 : 1.2
$BF_3{\cdot}Et_2O$ (4)	THF	0°C	22	1 : 1
Bu_4NF (1.1)	THF	80°C	48	2 : 1

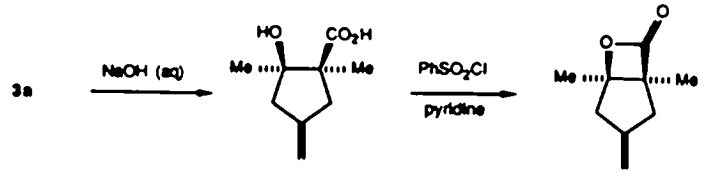
[a] Reflects inability to detect minor diastereomer by capillary GC.

Thus, treatment of **2a** with 4 equivalents of $TiCl_4$ at -78 °C for 15 minutes, followed by quenching with saturated potassium carbonate, extractive workup, and bulb to bulb distillation provided **3a** in an 88% isolated yield (Table II). Smaller excesses of the Lewis acid resulted in somewhat lower GC yields (though not lower diastereoselectivity), while larger excesses tended to complicate reaction workup. Lower reaction temperatures also seemed to decrease reaction efficiency.

Capillary GC analysis of the crude reaction mixture under these conditions showed no detectable amounts of diastereomer **4a**. It is also interesting to note that the order of addition is critical in obtaining this high diastereoselectivity. In the "normal" mode of addition, a solution of the allylsilane substrate is added dropwise to a solution of titanium tetrachloride. This sequence provides high selectivity as reported above. Inverse addition, i.e. addition of a solution of titanium tetrachloride to a solution of the substrate at -78 °C, results in substantially lower diastereoselectivity (e.g. 3 : 1 for substrate **2a**). Similar dramatic effects on diastereoselectivity have previously been observed in $TiCl_4$-promoted reactions of allylstannanes with aldehydes. Allyltitanium species have been implied as intermediates in some of these processes.[3k] Whether allyltitaniums are involved in the present examples or whether the results simply reflect a requirement for excess $TiCl_4$ to control stereochemistry in an effective fashion by providing a high concentration of the activated chelate is not known at this time.

The "non-chelation" generated diastereomer was absent from aliquots withdrawn from normal addition reaction mixtures over the period of several seconds to a few hours. The ratio of diastereomers generated by the inverse addition technique was also constant with time. Since these diastereomeric mixtures exhibited no apparent tendency to equilibrate under the reaction conditions, we believe that these selectivities reflect kinetic product ratios.[11]

The stereochemistry of **3a** was established by saponification to the carboxylic acid, followed by conversion to the corresponding β-lactone.[12] The corresponding carboxylic acid of diastereomer **4a** has been previously shown to resist such lactonization.[8b]



For comparison, we also performed the cyclization using boron trifluoride etherate, a non-chelating Lewis acid.[4c,13] In our hands such cyclizations proved largely unselective, providing approximately equal amounts of diastereomeric products in only a 30% combined yield.[14] The remainder of the material consisted of product arising from simple desilylation of the substrate. Fluoride-promoted cyclization was also relatively non-selective (Table I), favoring **3a** by a ratio of 2 : 1.

Encouraged by our preliminary success with the $TiCl_4$ promoted reactions, we examined substitution effects on the cyclization process using a series of substituted β-ketoesters **2b-i** (Table II). When subjected to optimal reaction conditions determined by our initial studies, these substrates were also readily cyclized. Reactions were generally complete within 2h at -78 °C. Diastereoselectivity of the cyclization process proved to be insensitive to substitution about the

ketone group, and in each case only the cyclized products arising from chelation control (3b-i) were detected in crude reaction mixtures. Products from these reactions were readily isolated by chromatography in good yields (57-88%). Although some correlation was observed between yield and increased steric bulk of substituents in the substrate, such effects were relatively small.

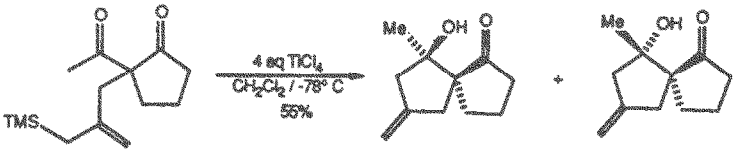
Table II. Titanium tetrachloride promoted cyclization of ethyl 2-alkyl-2-alkanoyl-4-(trimethylsilyl)methyl-4-pentenoates (2)

Substrate	R	R'	% Isolated Yield (3)
2a	Me	Me	88
2b	Me	Et	78
2c	Me	*i*-Pr	65
2d	Me	Ph	72
2e	Et	Me	78
2f	*i*-Pr	Me	66
2g	*t*-Bu	Me	74
2f	Ph	Me	74
2i	Me	H	57[a]

[a] Reaction was carried out at -20 °C.

As might be expected, more dramatic effects were observed in substitution of hydrogen for a methyl group at the α position (i.e. substrate 2i). Although this reaction is also completely diastereoselective, cyclization required higher reaction temperatures (-20°C) and product yield was somewhat attenuated. In this instance, the compound arising from simple desilylation of the starting material was isolated as the major byproduct of the reaction. We attribute these effects to competing enolization of the substrate, followed by protiodesilylation either during the reaction or possibly upon aqueous workup.

Titanium tetrachloride-promoted cyclization was also effective in generating the spirocyclic ring system **51**, with a 10 : 1 mixture of diastereomers isolated in 55% yield.



50 **51a** + **51b**

10 : 1

As anticipated, appropriately functionalized β-ketoamides proved to be suitable substrates for stereocontrolled cyclization (Table III). Although these cyclizations required somewhat more strenuous reaction conditions than corresponding β-ketoester substrates (generally 6 hours at -55 °C), again products arising from chelation control (**7a-e**) were formed to the exclusion of their diastereomers (**8a-e**). Isolated yields of these products further demonstrated the relative insensitivity of the cyclization process to steric encumbrance about the ketone group.

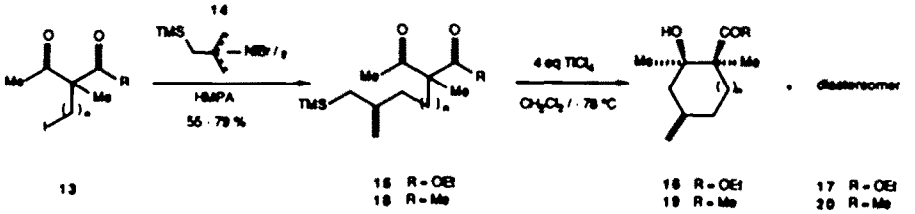
As in the β-ketoester series, substitution at the α position dramatically affects product yields. Substitution of a methyl group for a hydrogen at the α position in the β-ketoamides (6e) resulted in quantitative cyclization of the substrate under much milder conditions (15 min at -78 °C). It thus appears that competitive enolization and protiodesilylation can play a substantial role in attempted cyclization of both β-ketoamide and β-ketoester substrates.

Table III. Titanium tetrachloride promoted cyclizations of *N,N*-dialkyl-2-alkanoyl-4-(trimethylsilyl)methyl-4-pentenamides (6)

Substrate	R	R'	R"	% Isolated Yield (7)
6a	Me	H	Et	76
6b	Et	H	Me	57
6c	*i*-Pr	H	Me	56
6d	*t*-Bu	H	Me	75
6e	Me	Me	Et	100[a]

[a] Reaction was carried out at -78 °C.

On the basis of these studies and related processes previously reported, we anticipated that this methodology would provide effective entries into carbocycles containing larger rings.[15] To test this hypothesis, we prepared a homologous series of β-ketoesters (15a-c). The most convenient method for preparation of these compounds proved to involve coupling of appropriate iodides (13) with a π-allylnickel complex developed in our laboratory (14).[16] These coupling reactions proceeded in good yield (50-79%) to provide the desired substrates.



As postulated, substrates 15a and 15b were readily cyclized to six- (16a) and seven-membered ring alcohols (16b), respectively (Table IV). Excellent diastereoselectivity was observed in the cyclization process. Unfortunately, efforts to cyclize 15c to the corresponding eight-membered ring met with failure, providing only desilylated starting material. Carbocycles 16a and 16b were converted to the corresponding β-lactones according to the sequence described above, thus confirming their stereochemical assignment.

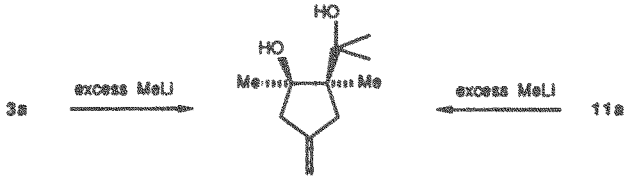
Symmetrical diketone substrates [10a (R = Me) and 18a] have also been effectively cyclized to five- and six-membered rings, respectively (Table IV). While 10a provided 11 as a single diastereomer, the homologous substrate (18a) gave 19 and 20 as a 13 : 1 ratio of diastereomers. We were unable to carry out cyclization of 18b to the corresponding seven-membered ring, isolating only desilylated starting material.

Table IV. Effect of chain length on cyclization.

Substrate	n	Ring Size	Product	% Isolated Yield
2a	0	5	**3a**	88
15a	1	6	**16a**	78
15b	2	7	**16b**	71[a]
15c	3	8	**16c**	0
10a	0	5	**11**	81
18a	1	6	**19a**	77[b]
18b	2	7	**19b**	0

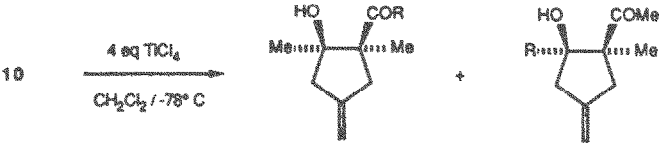
[a] A 23 : 1 ratio of diastereomers was generated in this case. [b] A 13 : 1 ratio of diastereomers was generated in this case.

Stereochemical assignments in this series were confirmed by treatment of **11** with excess methyllithium in THF.



The alcohol thus obtained was identical to that obtained from **3a** under similar conditions. The major and minor diastereomers **19** and **20** were correlated to **11** by comparison of their spectral characteristics.[17]

Extension of the chelation-controlled cyclization reaction to unsymmetrical diketones (**10b-e**) in some instances provided excellent selectivity between the two distinct ketone groups (Table V).



21 **22**

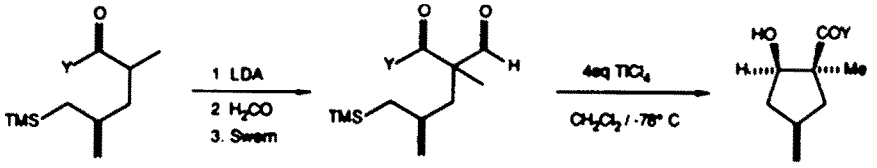
Indeed, for **10d** (R = *t*-Bu) and **10e** (R = Ph) only a single isomer, corresponding to chelation controlled cyclization at the least sterically encumbered methyl ketone (**21**), was detectable by ^{13}C NMR in each crude reaction mixture. Cyclization of **10c** (R = *i*-Pr) gave a ratio of 5.3 : 1 for the two isomers. A slight reversal of selectivity was observed for **10b** (R = Et), with addition to the ethyl ketone carbonyl favored by a ratio of 1.5 : 1. The corresponding *trans* diastereomers could not be detected by baseline ^{13}C NMR spectra obtained on crude reaction mixtures in any of these diketone examples.

Table V. Titanium tetrachloride promoted cyclizations of 3-alkanoyl-3-methyl-5-(trimethylsilyl)methyl-5-hexen-2-ones (10)

Substrate	R	% Isolated Yield (21 + 22)	Ratio (21 : 22)
10b	Et	71	1 : 1.5
10c	*i*-Pr	66	5.3 : 1
10d	*t*-Bu	71	>20 : 1[a]
10e	Ph	87	>20 : 1[a]

[a] Reflects inability to detect minor isomer by ^{13}C NMR.

This high selectivity led us to prepare β-formyl carbonyl compounds **23** and **25**. Hydroxymethylation of the appropriate carbonyl precursors with monomeric formaldehyde, followed by Swern oxidation provided the desired substrates.



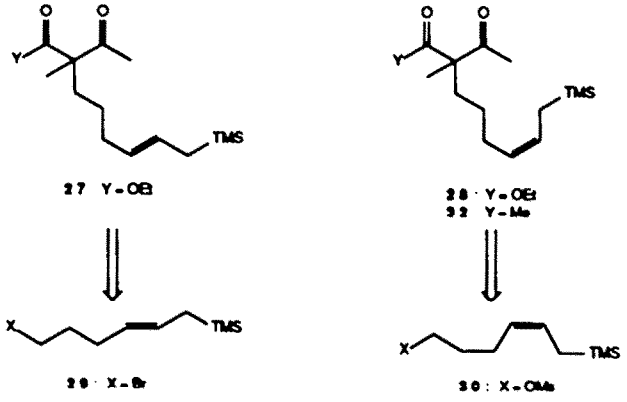
23 : Y = OEt
25 : Y = *t*-Bu

24 : Y = OEt
26 : Y = *t*-Bu

As expected, these substrates cyclized under standard reaction conditions, and the desired products (**24** and **26**) were isolated in excellent yields (91% and 85%, respectively). Careful GC/MS analysis of crude reaction mixtures in each instance indicated a diastereomeric ratio of > 90 : 1 for these transformations. As before, spectral and physical properties of these products were consistent with the expected chelation-controlled products.[17]

Keck and coworkers have reported use of chelation in intermolecular reactions to control diastereofacial addition of γ-substituted allylstannanes to α- and β-alkoxy aldehydes, generating three stereocenters in a single step.[4f,g] These reports and our own successes with intramolecular chelation control prompted us to explore intramolecular variants of this process, wherein three contiguous stereocenters could be established on the carbocyclic ring with a high degree of control.

We selected as target substrates isomeric β-ketoesters **27** and **28**.



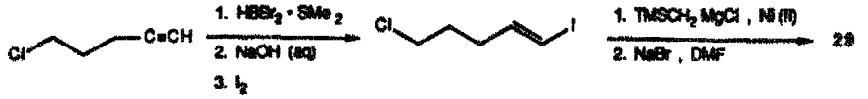
27 Y = OEt

28 : Y = OEt
32 Y = Me

29 : X = Br

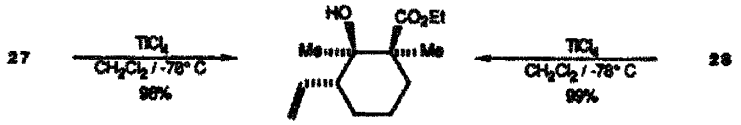
30 : X = OMs

The preparation of **30** had previously been described.[18] We prepared a diastereomeric compound by the following procedure. Hydroboration of 5-chloro-1-pentyne with dibromoborane dimethyl sulfide complex was followed by basic hydrolysis to provide the corresponding boronic acid. Treatment of this intermediate with molecular iodine afforded the desired alkenyl iodide.[19]



Coupling of the iodide with trimethylsilylmethylmagnesium chloride in the presence of a catalytic amount of nickel (II),[20] followed by a Finkelstein reaction afforded **29** in a 43% overall yield. Alkylation of ethyl 2-methylacetoacetate anion with mesylate **30** or bromide **29** proceeded in good yields (70-90%).

The non-stereospecificity of intermolecular Lewis acid catalyzed additions of linear allylsilanes and allylstannanes is well precedented,[5] and we anticipated that stereoselective cyclization would proceed through a synclinal transition state as delineated by Denmark and coworkers for intramolecular carbonyl addition.[6] If successful, such a process could be exploited to provide carbocycles containing three contiguous stereodefined centers; two determined by chelation control, and the third controlled by inherent stereoelectronic effects associated with the requisite synclinal transition state. As anticipated, treatment of *either* **27** or **28** with four equivalents of $TiCl_4$ at -78 °C provided **31** in nearly quantitative yield, with no detectable amounts of the other three possible diastereomers.

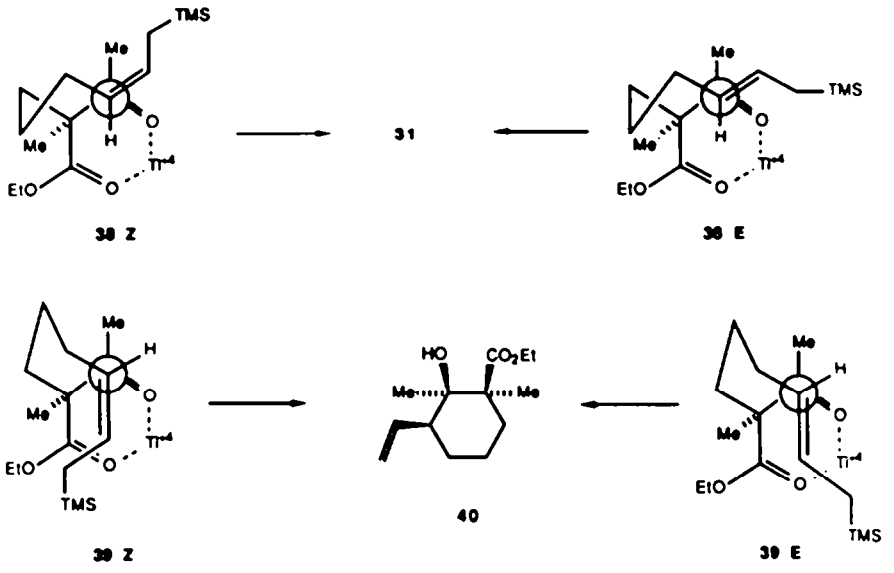


31

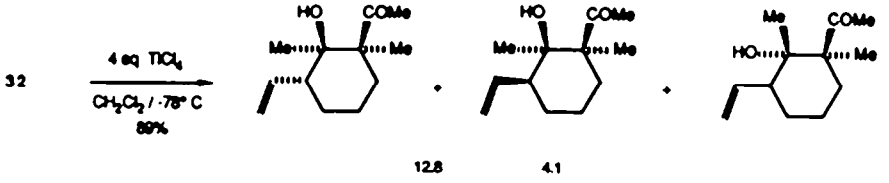
The relative stereochemistry of **31** was confirmed by saponification to the corresponding carboxylic acid, upon which a single-crystal X-ray structure was determined.

Logical transition structures for these processes are shown in the Figure below. Depicted are the possible synclinal orientations of the allylsilane moieties with respect to the electrophilic ketone group.[6] Antiperiplanar orientations appear to be excluded by geometric constraints of the system because when both carbonyl groups are held in tight chelation, meaningful overlap between the orbitals of the incoming allylsilane moiety and the electrophilic ketone group requires significant distortion of the "bicyclic" antiperiplanar transition structure. Of the synclinal transition structures shown, both **39E** and **39Z**, leading to the diastereomer epimeric about the vinyl group (**40**), are disfavored due to steric interactions between the approaching allylsilane and the chelated ring. No such interactions are present in structures **38E** and **38Z**. The lack of stereospecificity of the reaction, coupled with the degree of diastereoselectivity, suggests that the magnitude of the unfavorable interactions indicated by these empirical models must necessarily be large in comparison to differences in the distinct transition states leading to the diastereomeric products.[21]

Figure



An analogous diketone substrate provided useful mechanistic insights into this cyclization process. Under the reaction conditions, 32 cyclized to a mixture of three of the four possible diastereomeric products, in a ratio of 12.8 : 4 1 : 1.



The two major diastereomers, as expected, proved to be those generated by chelation control, epimeric about the vinyl substituted stereocenter. The stereochemistry of the major diastereomer was confirmed by treatment with methyllithium, which provided the same tertiary alcohol as that generated by reaction of 31 with excess methyllithium. The relative stereochemistry of the next most abundant diastereomer was assigned on the basis of comparative spectral data.[17] We were unable to assign stereochemistry about the vinyl substituted stereocenter in the least abundant diastereomer.

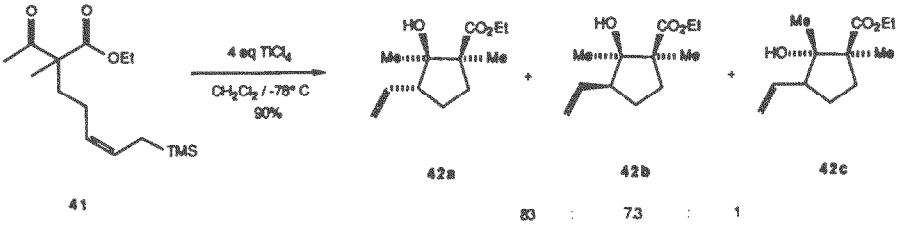
We attribute this dramatic erosion in diastereoselectivity for this substrate to decreased rigidity of the titanium (IV) chelate. It is logical to assume that substitution of the ester group in 32 with a less Lewis basic ketone group results in a weaker, and thus more flexible, chelate. In a less rigid chelate of this type, energy differences between the two synclinal transition states depicted in the Figure might not be as large, resulting in lower diastereoselectivity.

This proposal was also substantiated by results obtained in the cyclization of 28 using BF_3-OEt_2 as a catalyst. Under these non-chelating conditions[4c,13] a 1: 1.6 : 1.5 : 0.2 ratio of

diastereomers was obtained. While identity of the diastereomers other than **31** was not rigorously established in this case, it can be concluded from these results that the rigid template provided by chelation control is necessary to achieve good erythro/threo selectivity in these intramolecular systems.

1 : 1.8 : 1.5 : 0.2

Finally, we have accomplished similar cyclization of **41** to the corresponding carbocycle **42**, generating a mixture of three diastereomers in a ratio of 83 : 7.3 : 1.[22] This example again displays the same sense of stereochemical selectivity. The relative stereochemistry of the vinyl substituted stereocenter in the minor, non-chelated diastereomer was not established.



41

42a : 42b : 42c

83 : 7.3 : 1

Conclusions

Stereoselectivity in intramolecular additions of allylsilanes to carbonyl electrophiles can be effectively controlled by the use of chelation, mediated by titanium tetrachloride. This process has been successfully demonstrated for a variety of β-dicarbonyl compounds including ketoesters, ketoamides, ketolactones, diketones, formylesters and formylketones, and furthermore proves useful for the formation of five-, six-, and seven-membered rings. In most cases, the process is completely diastereoselective, favoring the chelation-controlled carbocycles in good to excellent yields. Cyclizations proceed under mild conditions and are also highly chemoselective, permitting efficient formation of functionalized ring systems. In some instances, excellent selectivity is observed between distinct ketone groups in β-diketone substrates.

The configuration of the allylsilane was also varied in this study. "Linear" allylsilane substrates permit one step creation of three contiguous stereocenters; two controlled by chelation and the third by simple erythro/threo selectivity. This process has proven to be highly diastereoselective for β-ketoester substrates in the formation of five- and six-membered rings. Stereochemical preference for the erythro isomer is independent of the olefin geometry of the allylsilane starting material. An empirical model for this process is proposed. Analogous cyclization of a β-diketone substrate shows much lower diastereoselectivity, and the mechanistic implications of this result are discussed.

Efforts continue in our lab to exploit chelation, as well as other stereochemical control elements, in intramolecular additions of allylsilanes and allylstannanes to carbon electrophiles.

Experimental Section

IR spectra were recorded on a Perkin-Elmer 727B infrared spectrophotometer and calibrated by comparison with a standard 0.05 mm thick polystyrene film. FT-IR spectra were performed on an IBM IR/30 Series or a Mattson Polaris FT-IR spectrometer. ^1H NMR were recorded using a JEOL FX-90Q, Magnachem A-200, or Bruker WM-250 spectrometer operating at 89.9 MHz, 200 MHz or 250 MHz, respectively, with $CDCl_3$ as solvent and $CHCl_3$ as internal standard (δ 7.24). ^{13}C NMR spectra were recorded using either a JEOL FX-90Q or Magnachem A-200 spectrometer operating at 22.5MHz or 50 MHz, respectively, with $CDCl_3$ as both solvent and internal standard (δ 77.0). Low resolution and exact mass spectra were recorded on a VG-7070 EQ-HF mass spectrometer employing perfluorokerosene as internal standard. All mass spectra were generated using a 70-ev ionization potential. Gas-liquid chromatographic analyses were conducted on a Hewlett Packard Model 5890A chromatograph equipped with a Hewlett Packard Model 3390 digital integrator utilizing either a 25 m x 320 μm 5% phenyl SE-54 fused silica or a 25m x 320 μm 10% fused silica Carbowax column. Flash chromatography was carried out utilizing standard procedures.

Reagents. Dichloromethane was stirred over concentrated H_2SO_4 overnight, then was washed with water and saturated potassium carbonate, fractionally distilled from calcium hydride under argon and stored in a brown bottle over 4 Å molecular sieves. Titanium tetrachloride was distilled prior to use and stored in a Teflon-stopcocked bottle under argon. Boron trifluoride diethyl etherate was distilled from calcium hydride and stored under argon. All reactions were conducted under an inert argon atmosphere employing standard bench-top techniques for handling of air sensitive materials.

Cyclization of β-oxoester and β-oxoketone substrates with $TiCl_4$. General Procedure. To a solution of titanium tetrachloride (4.0 mmol) in CH_2Cl_2 (7.5 mL) at -78 °C was slowly added a solution of the substrate (1.0 mmol) in CH_2Cl_2 (2.5 mL). The reaction mixture instantaneously turned deep red. The mixture was allowed to stir at -78 °C for the stated time before being quenched by rapid addition of saturated K_2CO_3 (5 mL). The reaction was then partitioned between ether (10 mL) and water (10 mL). The aqueous portion was further extracted with ether (3 x 10 mL), then the combined organic extracts were washed with brine (10 mL) and dried over K_2CO_3.

Cyclization of Ethyl 2-Acetyl-2-methyl-4-(trimethylsilyl)methyl-4-pentenoate (2a). Using the general procedure described above, **2a** (169 mg, 0.626 mmol) was cyclized over 15 min to provide **ethyl (1R*, 2S*)-1,2-dimethyl-2-hydroxy-4-methylenecyclopentanecarboxylate (3a)** (108 mg, 0.548 mmol), 88%, isolated by bulb to bulb distillation: bp 65-70 °C (0.03 mm Hg). ^1H NMR ($CDCl_3$): δ 4.94 (br m, 2H), 4.18 (q, J = 7.0 Hz, 2H), 3.25-3.08 (m, 2H), 2.50-2.05 (m, 3H), 1.41 (s, 3H), 1.28 (t, J = 7.0 Hz, 3H), 1.21 (s, 3H); ^{13}C NMR ($CDCl_3$): δ 176.45, 146.28, 109.15, 81.44, 60.69, 54.91, 45.61, 42.80, 22.64, 21.54, 14.31; FT-IR ($CHCl_3$): 3520, 2970, 2870, 1710, 1450, 1385, 1100, 1005 cm^{-1}. Exact mass calcd for $C_{11}H_{18}O_3$: 198.1256, found: 198.1267.

Cyclization of Ethyl 2-Acetyl-2-ethyl-4-(trimethylsilyl)methyl-4-pentenoate (2b). Using the general procedure described above, **2b** (607 mg, 2.13) was cyclized over 2 h to provide **ethyl (1R*, 2S*)-1-ethyl-2-methyl-2-hydroxy-4-methylenecyclopentanecarboxylate (3b)** (354 mg, 1.67 mmol), 78%, isolated by flash

chromatography (20% EtOAc in hexanes on silica gel). ^{1}H NMR ($CDCl_3$): δ 4.87 (m, 2H), 4.21 (q, J = 7.2 Hz, 2H), 3.11 (br s, 1H), 2.47 (m, 2H), 2.31-1.66 (m, 2H), 1.42-1.05 (m, 2H), 1.39 (s, 3H), 1.26 (t, J = 7.2 Hz, 3H), 0.82 (t, J = 7.0 Hz, 3H); ^{13}C NMR ($CDCl_3$): δ 174.73, 146.29, 107.66, 81.87, 60.64, 60.42, 46.82, 37.89, 26.51, 22.61, 14.05, 9.66; IR: (neat) 3480, 2975, 1710, 1460, 1370, 1325, 1245, 1135, 1035, 955 cm^{-1}. Exact mass calcd for $C_{12}H_{20}O_3$: 212.1412, found: 212.1419.

Cyclization of Ethyl 2-Acetyl-2-isopropyl-4-(trimethylsilyl)methyl-4-pentenoate (2c). Using the general procedure described above, **2c** (288 mg, 0.964 mmol) was cyclized over 2 h to provide **ethyl (1R*, 2R*)-1-isopropyl-2-methyl-2-hydroxy-4-methylenecyclopentanecarboxylate (3c)** (142 mg, 0.628 mmol), 65%, isolated by flash chromatography (14% EtOAc in hexanes on silica gel). ^{1}H NMR ($CDCl_3$): δ 4.83 (m, 2H), 4.17 (q, J = 7.0 Hz, 2H), 3.54 (br s, 1H), 3.25-1.85 (m, 3H), 2.46 (m, 2H), 1.37 (s, 3H), 1.27 (t, J = 7.0 Hz, 3H), 0.96 (d, J = 3.6 Hz, 3H), 0.88 (d, 3.9 Hz, 3H); ^{13}C NMR ($CDCl_3$): δ 175.65, 146.13, 107.17, 81.50, 62.59, 60.53, 48.56, 37.40, 31.66, 22.77, 22.55, 19.14, 14.16; IR ($CHCl_3$): 3475, 2980, 1715, 1450, 1375, 1250, 1040, 960 cm^{-1}. Exact mass calcd for $C_{13}H_{22}O_3$: 226.1569, found: 226.1563.

Cyclization of Ethyl 2-Acetyl-2-phenyl-4-(trimethylsilyl)methyl-4-pentenoate (2d). Using the general procedure described above, **2d** (311 mg, 0.935 mmol) was cyclized over 2 h to provide **ethyl (1R*, 2R*)-1-phenyl-2-methyl-2-hydroxy-4-methylenecyclopentanecarboxylate (3d)** (175 mg, 0.672), 72%, isolated by flash chromatography (17% EtOAc in hexanes on silica gel). ^{1}H NMR ($CDCl_3$): δ 7.35-7.21 (m, 5H), 5.07 (m, 1H), 4.99 (m, 1H), 4.27-4.00 (m, 3H), 3.20 (m, 1H), 3.13 (m, 1H), 2.49 (br m, 2H), 1.23 (t, J = 7.1 Hz, 3H), 1.15 (s, 3H); ^{13}C NMR ($CDCl_3$): δ 176.14, 145.96, 139.79, 128.19, 127.00, 107.82, 81.87, 62.91, 61.02, 45.53, 40.76, 23.99, 13.81; IR (neat): 3525, 3060, 2975, 2870, 1710, 1450, 1370, 1300, 1240, 1190, 1105, 1050, 940 cm^{-1}. Exact mass calcd for $C_{16}H_{20}O_3$: 260.1412, found: 260.1410.

Cyclization of Ethyl 2-Methyl-2-[2-(trimethylsilyl)methyl-2-propenyl]-3-oxopentanoate (2e). Using the general procedure described above, **2e** (657 mg, 2.31 mmol) was cyclized over 2 h to provide **ethyl (1R*, 2S*)-1-methyl-2-ethyl-2-hydroxy-4-methylenecyclopentanecarboxylate (3e)** (384 mg, 1.81 mmol), 78%, isolated by bulb to bulb distillation: bp 75-80 °C (0.1 mm Hg). ^{1}H NMR ($CDCl_3$): δ 4.91 (m, 2H), 4.15 (q, J = 7.3 Hz, 2H), 3.32 (br s, 1H), 3.15 (d, J = 16.1 Hz, 1H), 2.44 (br s, 2H), 2.30 (d, J = 16.1 Hz, 1H), 1.80-1.52 (m, 2H), 1.25 (t, J = 7.3 Hz, 3H), 1.15 (s, 3H), 0.93 (t, J = 7.4 Hz, 3H); ^{13}C NMR ($CDCl_3$): δ 176.07, 146.18, 107.47, 83.61, 60.13, 54.28, 43.25, 42.43, 27.73, 20.34, 13.61, 7.89; FT-IR ($CHCl_3$): 3450, 2975, 1695, 1475, 1390, 1370, 1300, 1275, 1215, 1150, 1120, 1025, 980 cm^{-1}. Exact mass calcd for $C_{12}H_{20}O_3$: 212.1412, found: 212.1425.

Cyclization of Ethyl 2,4-Dimethyl-2-[2-(trimethylsilyl)methyl-2-propenyl]-3-oxopentanoate (2f). Using the general procedure described above, **2f** (356 mg, 1.19mmol) was cyclized over 2 h to provide **ethyl (1R*, 2R*)-1-methyl-2-hydroxy-2-isopropyl-4-methylenecyclopentanecarboxylate (3f)** (177 mg, 0.782 mmol), 66%, isolated by flash chromatography (20% EtOAc in hexanes on silica gel). ^{1}H NMR ($CDCl_3$): δ 4.85 (br m, 2H), 4.11 (q, J = 7.0 Hz, 2H), 3.21-1.73 (m, 6H), 1.21 (t, J = 7.0 Hz, 3H), 1.09 (s, 3H), 0.87 (d, J = 8.9 Hz, 3H), 0.70 (d, J = 6.7 Hz, 3H); ^{13}C NMR ($CDCl_3$): δ 178.58, 146.97, 107.82, 86.86, 61.13, 52.16, 46.66, 44.52, 32.90, 19.13, 17.42, 16.53, 13.70; IR (neat): 3450, 2975,

1695, 1475, 1390, 1370, 1300, 1275, 1215, 1150, 1120, 1025 cm^{-1}. Exact mass calcd for $C_{13}H_{22}O_3$: 226.1569, found: 226.1575.

Cyclization of Ethyl 2,4,4-Trimethyl-2-[2-(trimethylsilyl)methyl-2-propenyl]-3-oxopentanoate (2g). Using the general procedure described above, **2g** (174 mg, 0.557 mmol) was cyclized over 2 h to provide **ethyl (1R*, 2R*)-1-methyl-2-*t*-butyl-2-hydroxy-4-methylenecyclopentanecarboxylate (3g)** (98.8 mg, 0.411 mmol), 74%, isolated by flash chromatography (8% EtOAc in hexanes on silica gel). ^1H NMR ($CDCl_3$): δ 5.24 (m, 1H), 4.90 (br m, 2H), 4.14 (q, J = 7.25 Hz, 2H), 3.28-1.38 (m, 4H), 1.25 (t, J = 7.2 Hz, 3H), 1.25 (s, 3H), 0.96 (s, 9H); ^{13}C NMR ($CDCl_3$): δ 178.96, 147.05, 107.93, 89.40, 61.40, 53.87, 48.45, 39.52, 38.59, 27.59, 21.96, 13.78; IR (neat): 3450, 2995, 1700, 1480, 1405, 1375, 1305, 1280, 1200, 1125, 1090, 1035, 990 cm^{-1}. Exact mass calcd for $C_{14}H_{24}O_3$: 240.1725, found: 240.1727.

Cyclization of Ethyl 2-Benzoyl-2-methyl-4-(trimethylsilyl)methyl-4-pentenoate (2h). Using the general procedure described above, **2h** (440 mg, 1.32 mmol) was cyclized over 2 h to provide **ethyl (1R*, 2R*)-1-methyl-2-hydroxy-2-phenyl-4-methylenecyclopentanecarboxylate (3h)** (255 mg, 0.979 mmol), 74%, isolated by flash chromatography (17% EtOAc in hexanes on silica gel).^1H NMR ($CDCl_3$): δ 7.44-7.22 (m, 5H), 5.05 (m, 2H), 4.79 (s, 1H), 4.14 (q, J = 7.2 Hz, 2H), 3.37-2.35 (m, 4H), 1.20 (t, J = 7.2 Hz, 3H), 1.12 (s, 3H); ^{13}C NMR ($CDCl_3$): δ 176.68, 146.21, 141.74, 127.49, 126.51, 108.58, 84.96, 60.99, 55.38, 44.60, 43.95, 21.10, 13.97; IR (neat): 3425, 3090, 2995, 1705, 1480, 1375, 1315, 1260, 1190, 1075, 1035, 980, 900 cm^{-1}. Exact mass calcd for $C_{16}H_{20}O_3$: 260.1412, found: 260.1412.

Cyclization of Ethyl 2-Acetyl-4-(trimethylsilyl)methyl-4-pentenoate (2i). Using the general procedure described above, **2i** (245 mg, 0.955) was cyclized over 6 h at -20 °C to provide **ethyl (1R*, 2S*)-2-hydroxy-2-methyl-4-methylenecyclopentanecarboxylate (3i)** (101 mg, 0.548 mmol), 57%, isolated by flash chromatography (17% EtOAc in hexanes on silica gel). ^1H NMR ($CDCl_3$): δ 4.91 (m, 2H), 4.17 (q, J = 7.2 Hz, 2H), 3.28, (br s, 1H), 2.80-2.25 (m, 5H), 1.39 (s, 3H), 1.26 (t, J = 7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$): δ 174.10, 147.07, 107.58, 78.68, 60.56, 52.54, 47.60, 34.71, 26.16, 14.06; IR (neat): 3560, 2950, 1720, 1700, 1480, 1310, 1250, 1120, 1040, 1010 cm^{-1}. Exact mass calcd for $C_{10}H_{16}O_3$: 184.1099, found: 184.1100.

Cyclization of 3-Acetyl-3-[2-(trimethylsilyl)methyl-2-propenyl] oxacyclopentan-1-one (50). Using the general procedure described above, **50** (101 mg, 0.431 mmol) was cyclized over 4 h to provide **(5R*, 6S*)-6-hydroxy-6-methyl-2-oxaspiro[4.4]nonan-1-one (51)** (43.1 mg, 0.237 mmol), 55%, isolated by flash chromatography (50% EtOAc in hexanes on silica gel). ^1H NMR ($CDCl_3$): δ 5.00 (m, 2H), 4.30 (m, 2H), 3.76 (m, 1H), 3.10-2.71 (m, 2H), 2.40 (m, 2H), 2.0 (m, 2H), 1.33 (s, 3H); ^{13}C NMR ($CDCl_3$): δ 180.70, 145.05, 109.22, 80.56, 65.42, 54.24, 45.85, 40.85, 31.68, 22.72; IR (neat): 3490, 2900, 1725, 1450, 1360, 1275, 1135, 1060, 1020 cm^{-1}. Exact mass calcd for $C_{10}H_{14}O_3$: 182.0943, found: 182.0938.

Cyclization of Ethyl 2-Acetyl-2-methyl-5-(trimethylsilyl)methyl-5-hexenoate (15a). Using the general procedure described above, **15a** (412 mg, 1.45 mmol) was cyclized over 2 h to provide **ethyl (1R*, 2S*)-1,2-dimethyl-2-hydroxy-4-methylenecyclohexanecarboxylate (16a)** (240 mg, 1.13 mmol), 78%, isolated by flash

chromatography (11% EtOAc in hexanes on silica gel). ^{1}H NMR ($CDCl_3$): δ 4.68 (m, 2H), 4.48 (br s, 1H), 4.17 (q, J = 7.1 Hz, 2H), 2.30 (m, 2H), 2.26-1.41 (m, 2H), 2.13 (m, 2H), 1.32 (q, J = 7.1 Hz, 3H), 1.26 (s, 3H), 1.12 (s, 3H); ^{13}C NMR ($CDCl_3$): δ 178.47, 145.13, 109.91, 73.91, 60.89, 49.74, 44.09, 32.05, 30.05, 29.65, 23.17, 18.41; IR ($CHCl_3$): 3500, 2950, 1750, 1460, 1380, 1270, 1220, 1180, 1105, 1020, 920 cm^{-1}. Exact mass calcd for $C_{12}H_{20}O_3$: 212.1412, found: 212.1413.

Cyclization of Ethyl 2-Acetyl-2-methyl-6-(trimethylsilyl)methyl-6-heptenoate (15b). Using the general procedure described above, **15b** (511 mg, 1.71 mmol) was cyclized over 2 h to provide **ethyl (1R*, 2S*)-1,2-dimethyl-2-hydroxy-4-methylenecycloheptanecarboxylate (16b)** (277 mg, 1.22 mmol), 71%, isolated by flash chromatography (17% EtOAc in hexanes on silica gel). ^{1}H NMR ($CDCl_3$): δ 4.76 (m, 2H), 4.17 (br s, 1H), 4.16 (q, J = 7.25 Hz, 2H), 2.78-2.05 (m, 5H), 1.70-1.31 (m, 3H), 1.26 (t, J = 7.25 Hz, 3H), 1.23 (s, 3H), 1.13 (s, 3H); ^{13}C NMR ($CDCl_3$): δ 178.09, 146.50, 113.40, 74.45, 60.42, 53.81, 48.18, 34.64 (2C), 25.26, 23.37, 20.28, 13.89; IR ($CHCl_3$): 3490, 2980, 1695, 1625, 1455, 1370, 1295, 1250, 1175, 1090, 1020, 940 cm^{-1}. Exact mass calcd for $C_{13}H_{22}O_3$: 226.1569, found: 226.1562.

Cyclization of 3-Acetyl-3-methyl-6-(trimethylsilyl)methyl-6-hepten-2-one (10a). Using the general procedure described above, **10a** (463 mg, 1.93 mmol) was cyclized over 2 h to provide **(1R*, 2S*)-1,2-dimethyl-2-acetyl-4-methylenecyclopentanol (11)** (265 mg, 1.57 mmol), 81%, isolated by bulb to bulb distillation: bp 65-70 °C (0.03 mm Hg). ^{1}H NMR ($CDCl_3$): δ 4.92 (m, 2H), 3.33 (m, 1H), 3.06 (d, J = 16 Hz, 1H), 2.44 (br m, 2H), 2.29 (d, J = 16 Hz, 1H), 2.15 (s, 3H), 1.36 (s, 3H), 1.17 (d, J = 0.7 Hz, 3H); ^{13}C NMR ($CDCl_3$): δ 215.39, 146.45, 108.10, 60.67, 55.13, 45.88, 42.97, 22.70, 28.31, 21.53; IR ($CHCl_3$): 3450, 2995, 1690, 1420, 1360, 1240, 1120, 1080, 990 cm^{-1}. Exact mass calcd for $C_{10}H_{16}O_2$: 168.1150, found: 168.1150.

Cyclization of 3-Acetyl-3-methyl-7-(trimethylsilyl)methyl-7-octen-2-one (18a). Using the general procedure described above, **18a** (127 mg, 0.499 mmol) was cyclized over 2 h to provide **(1R*, 2S*)-1,2-dimethyl-2-acetyl-5-methylenecyclohexanol (19a)** (70.2 mg, 3.85 mmol), 77%, isolated by flash chromatography (14% EtOAc in hexanes on silica gel). ^{1}H NMR ($CDCl_3$): δ 4.73 (br s, 1H), 4.68 (br s, 1H), 4.33 (s, 1H), 2.38-2.04 (m, 4H), 2.20 (s, 3H), 1.63-1.46 (m, 2H), 1.26 (s, 3H), 1.12 (s, 3H); ^{13}C NMR ($CDCl_3$): δ 214.89, 146.33, 109.12, 66.67, 55.13, 44.23, 42.12, 28.65, 22.70, 21.53, 18.45; IR ($CHCl_3$): 3460, 2995, 1685, 1640, 1420, 1360, 1240, 1130, 1020, 990 cm^{-1}. Exact mass calcd for $C_{11}H_{18}O_2$: 182.1307, found: 182.1316.

Cyclization of 3-Methyl-3-[2-(trimethylsilyl)methyl-2-propenyl]-2,4-pentanedione (10b). Using the general procedure described above, **10b** (235 mg, 0.923) was cyclized over 2 h to provide a 1:1.5 mixure of isomers (119 mg combined, 0.653 mmol), 71%, isolated by flash chromatography (9% EtOAc in hexanes on silica gel). Major isomer **(1R*, 2S*)-1-ethyl-2-acetyl-2-methyl-4-methylenecyclopentanol (22b)**: ^{1}H NMR ($CDCl_3$): δ 4.88 (br m, 2H), 3.09 (br s, 1H), 2.80-1.90 (m, 4H), 2.42 (q, J = 7.0 Hz, 2H), 1.03 (s, 3H), 1.07 (s, 3H), 1.02 (t, J = 7.0 Hz, 3H); ^{13}C NMR ($CDCl_3$): δ 214.87, 145.94, 108.18, 84.44, 59.63, 44.81, 42.85, 38.78, 28.27, 20.64, 18.36. Exact mass calcd for $C_{11}H_{16}O$ (M-18): 164.1201, found: 164.1189. Minor isomer **(1R*, 2S*)-1,2-dimethyl-2-propionyl-4-methylenecyclopentanol (21b)**: ^{1}H NMR ($CDCl_3$): δ 4.94 (br m, 2H), 3.33 (m, 1H), 3.15-

1.75 (m, 4H), 2.16 (s, 3H), 1.16 (s, 3H), 1.08-0.89 (m, 5H); ^{13}C NMR ($CDCl_3$): δ 216.88, 140.44, 115.57, 81.78, 59.34, 45.69, 43.33, 35.06, 27.79, 22.95, 17.59. FT-IR (mixture, $CHCl_3$): 3440, 2990, 1695, 1690, 1480, 1370, 1240, 1205, 1110, 1060, 1020, 1010, 990 cm^{-1}. Exact mass calcd for $C_{11}H_{16}O$ (M-18): 164.1201, found: 164.1193.

Cyclization of 3,5-Dimethyl-3-[2-(trimethylsilyl)methyl-2-propenyl]-2,4-pentanedione (10c). Using the general procedure described above, **10c** (268 mg, 0.998 mmol) was cyclized over 2 h to provide a 5.3:1 mixure of isomers (130 mg combined, 0.662 mmol), 66%, isolated by flash chromatography (8% EtOAc in hexanes on silica gel). Major isomer **(1R*, 2S*)-1,2-dimethyl-2-isobutyryl-4-methylenecyclopentanol (21c)**: ^{1}H NMR ($CDCl_3$): δ 4.92 (m, 2H), 3.50 (s, 1H), 3.01 (d, J = 16 Hz, 1H), 2.92 (m, 1H), 2.44 (br m, 2H), 2.34 (d, J = 16 Hz, 1H), 1.36 (s, 3H), 1.18 (s, 3H), 1.07 (d, J =8.2 Hz, 3H), 1.03 (d, J = 7.9 Hz, 3H); ^{13}C NMR ($CDCl_3$): δ 218.41, 145.88, 108.31, 81.61, 60.10, 45.63, 41.73, 36.60, 33.23, 23.07, 20.47, 19.76. Exact mass calcd for $C_{12}H_{18}O$ (M-18): 178.1358, found: 178.1371. Minor isomer **(1R*, 2R*)-1-isopropyl-2-acetyl-2-methyl-4-methylenecyclopentanol (22c)**: ^{1}H NMR ($CDCl_3$): δ 5.16 (s, 1H), 4.92 (m, 2H), 2.92 (d, J = 16 Hz, 1H), 2.45 (m, 2H), 2.32 (d, J = 16 Hz, 1H), 2.24 (s, 3H), 1.77 (m, 1H), 1.24 (s, 3H), 0.92 (m, 3H), 0.73 (m, 2H); ^{13}C NMR ($CDCl_3$): δ 216.88, 146.53, 108.13, 88.34, 57.09, 46.75, 45.28, 33.63, 28.85, 20.11, 18.40, 17.57. FT-IR (mixture, $CHCl_3$): 3470, 2995, 1710, 1690, 1610, 1470, 1385, 1360, 1265, 1235, 1105, 1000 cm^{-1}. Exact mass calcd for $C_{12}H_{18}O$ (M-18): 178.1358, found: 178.1364.

Cyclization of 3,5,5-Trimethyl-3-[2-(trimethylsilyl)methyl-2-propenyl]-2,4-pentanedione (10d). Using the general procedure described above, **10d** (796 mg, 2.82 mmol) was cyclized over 2 h to provide **(1R*, 2R*)-1,2-dimethyl-2-(dimethyl)propionyl-4-methylenecyclopentanol (21d)** (420 mg, 2.00 mmol), 71% isolated by flash chromatography (7% EtOAc in hexanes on silica gel). ^{1}H NMR ($CDCl_3$): δ 4.92 (m, 2H), 3.41 (br s, 1H), 3.15 (d, J = 15 Hz, 1H), 2.54 (d, J = 15 Hz, 1H), 2.46 (br m, 2H), 1.41 (s, 3H), 1.23 (s, 12H); ^{13}C NMR ($CDCl_3$): δ 197.38, 146.82, 108.07, 83.55, 61.05, 46.05, 44.45, 41.68, 28.74, 23.24, 21.41. FT-IR ($CHCl_3$): 3460, 2995, 1690, 1480, 1380, 1230, 1120, 995, 945, 910 cm^{-1}. Exact mass calcd for $C_{13}H_{20}O$ (M-18): 192.1514, found: 192.1516.

Cyclization of 3-Benzoyl-3-methyl-5-(trimethylsilyl)methyl-5-hexen-2-one (10e). Using the general procedure described above, **10e** (224 mg, 0.740) was cyclized over 2 h to provide **(1R*, 2S*)-1,2-dimethyl-2-benzoyl-4-methylenecyclopentanol (21e)** (149 mg, 0.647 mmol), 87%, isolated by flash chromatography (7% EtOAc in hexanes on silica gel). ^{1}H NMR ($CDCl_3$): δ 7.84-7.39 (m, 5H), 4.95 (m, 2H), 3.72 (m, 1H), 3.42-2.68 (m, 2H), 2.48 (br s, 2H), 1.49 (s, 3H), 1.36 (s, 3H); ^{13}C NMR ($CDCl_3$): δ 208.37, 146.53, 137.72, 131.72, 131.82, 128.10, 108.13, 83.26, 58.98, 44.98, 43.33, 22.89; FT-IR ($CHCl_3$): 3540, 3080, 3000, 2990, 1685, 1620, 1600, 1450, 1375, 1360, 1240, 980 cm^{-1}. Exact mass calcd for $C_{15}H_{16}O$ (M-18): 212.1201, found: 212.1189.

Cyclization of 2,2-Dimethyl-4-formyl-4-methyl-6-penten-3-one (23). Using the general procedure described above, **23** (149 mg, 0.555 mmol) was cyclized over 15 min to provide **(1R*, 2S*)-2-(dimethyl)propionyl-2-methyl-4-methylenecyclopentanol (24)** (98.1 mg, 0.500 mmol), 91%, isolated by flash chromatography (14% EtOAc in hexanes on silica gel). ^{1}H NMR ($CDCl_3$): δ 4.94 (m, 2H), 4.22 (m, 1H), 3.16-3.25 (m, 4H), 2.66 (br s, 1H),

1.20 (s, 9H), 1.08 (s, 3H); ^{13}C NMR ($CDCl_3$): δ 220.31, 147.83, 108.72, 79.42, 61.23, 45.52, 39.25, 37.36, 28.09, 21.94; FT-IR ($CHCl_3$): 3580, 2995, 1670, 1490, 1460, 1380, 1370, 1220, 1045, 990, 910 cm^{-1}. Exact mass calcd for $C_{12}H_{20}O_2$: 196.1463, found: 196.1449.

Cyclization of Ethyl 2-Formyl-2-methyl-4-(trimethylsilyl)methyl-4-pentenoate (25). Using the general procedure described above, **25** (148 mg, 0.577 mmol) was cyclized over 15 min to provide **ethyl (1R*, 2S*)-1-methyl-2-hydroxy-4-methylenecyclopentanecarboxylate (26)** (90.3 mg, 0.490 mmol), 85%, isolated by bulb to bulb distillation: bp 70-80 °C (0.3 mm Hg). ^1H NMR ($CDCl_3$): δ 4.93 (m, 2H), 4.16 (q, J = 7.0 Hz, 2H), 4.05 (m, 1H), 2.07-3.10 (m, 5H), 1.25 (t, J = 7.0 Hz, 3H), 1.17 (s, 3H); ^{13}C NMR ($CDCl_3$): δ 176.42, 146.70, 108.48, 78.42, 60.70, 53.61, 40.20, 38.96, 22.06, 14.09; FT-IR ($CHCl_3$): 3560, 2295, 1720, 1320, 1250, 1110, 1050, 1030 cm^{-1}. Exact mass calcd for $C_{10}H_{16}O_2$: 184.1099, found: 184.1090.

Preparation of (E)-1-Iodo-5-chloro-1-pentene. To a stirred solution of 5-chloro-1-pentyne (3.03g, 29.5 mmol) in CH_2Cl_2 (15 mL) at room temperature was added dibromoborane-methyl sulfide complex (7.04g, 30.2 mmol). The reaction was maintained at room temperature for 16 h, then the volatiles were removed under reduced pressure (20 mm Hg). The resulting thick, yellow oil was decanted, with rapid stirring, into ice-cold 3 N NaOH (50 mL, 150 mmol) affording the boronic acid as a white precipitate. After 30 min, the boronic acid was solubilized by addition of ethyl ether (30 mL) and then to this mixture was added dropwise, over ca. 45 min, a solution of molecular iodine (9.26 g, 36.5 mmol) in ethyl ether (50 mL). After an additional 30 min at 0 °C, saturated $Na_2S_2O_3$ (5 mL) was added, and the layers were separated. The aqueous portion was further extracted with ethyl ether (3 x 20 mL), then the combined organic layers were washed with brine (2 x 10 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo*. Distillation provided **(E)-1-iodo-5-chloro-1-pentene**, (3.38g, 14.7 mmol), 50%, as a clear, red liquid: bp 110-112 °C (16 mm Hg). ^1H NMR ($CDCl_3$): δ 6.40 (dt, J = 14.3, 6.7 Hz, 1H), 6.06 (d, J = 14.3 Hz, 1H), 3.53 (t, J = 6.3 Hz, 2H), 2.18 (m, 2H), 1.91 (m, 2H); ^{13}C NMR ($CDCl_3$): δ 144.23, 76.08, 43.68, 32.85, 30.73; IR (neat): 2990, 1675, 1175, 850 cm^{-1}.

Coupling of Trimethylsilylmethylmagnesium Chloride with (E)-1-Iodo-5-chloro-1-pentene. To a stirred suspension of magnesium ribbon (148 mg, 6.08 mmol) in refluxing ethyl ether (5 mL) was added chloromethyltrimethylsilane (624 mg, 5.09 mmol). The solution was maintained at reflux for 2.5 h then cooled to room temperature and the ethereal portion was slowly transferred *via* cannula into a stirred solution of (E)-1-iodo-5-chloro-1-pentene (1.10 g, 4.77 mmol) and 1,3-bis(diphenylphosphino)propanenickel(II) chloride (30 mgs, 0.055 mmol) in ethyl ether (5 mL) at 0 °C. The resulting mixture was allowed to warm to room temperature over 2 h, then heated to reflux for 2 h. After cooling to room temperature, the solution was diluted with ethyl ether (30 mL), washed with water (2 x 10 mL) and brine (1 x 5 mL), dried ($MgSO_4$), filtered, and concentrated *in vacuo*. Bulb to bulb distillation provided **(E)-1-trimethylsilyl-6-chloro-2-hexene**, (795 mg, 4.17 mmol), 87%, as a clear, colorless liquid: bp 95-105 °C (14 mm Hg). ^1H NMR ($CDCl_3$): δ 5.60-4.99 (m, 2H), 3.51 (t, J = 6.5 Hz, 2H), 2.08 (m, 2H), 1.78 (m, 2H), 1.39 (d, J = 7.01 Hz, 2H), -0.03 (s, 9H); ^{13}C NMR ($CDCl_3$): δ 127.87, 126.51, 44.33, 32.69, 29.81, 22.66, -2.03; IR (neat): 2990, 1665, 1235, 1120, 990 cm^{-1}.

Preparation of (E)-1-Trimethylsilyl-6-bromo-2-hexene (29). To a stirred solution of sodium bromide (2.14 g, 20.8 mmol) in DMF (20 mL) at room temperature was added (E)-1-trimethylsilyl-6-chloro-2-hexene (795 mg, 4.17 mmol). The mixture was heated to ca. 50°C for 36 hours, then cooled to room temperature, diluted with ethyl ether (40 mL), and washed with water (4 x 10 mL). The aqueous portions were back-extracted with ether (2 x 15 ml), then the combined organic layers were washed with brine (3 x 15 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo*. Bulb to bulb distillation provided **(E)-1-trimethylsilyl-6-bromo-2-hexene (29)**, (850 mg, 3.61 mmol), 87%, as a clear, colorless liquid: bp 97-107 °C (14 mm Hg). ^{1}H NMR ($CDCl_3$): δ 5.60-4.87 (m, 2H), 3.27 (t, J = 7.01 Hz, 2H), 2.12-1.74 (m, 4H), 1.39 (d, J = 7.5 Hz, 2H), -0.03 (s, 9H); ^{13}C NMR ($CDCl_3$): δ 128.73, 127.52, 45.76, 33.33, 29.75, 12.36, -2.03; IR (neat): 2995, 1665, 1235, 1115, 990 cm^{-1}. Exact mass calcd for $C_9H_{19}BrSi$: 234.0439, found: 234.0426.

Cyclization of Ethyl (*E*)-2-Acetyl-2-methyl-8-trimethylsilyl-6-octenoate (27). Using the general procedure described above, **27** (340 mg, 1.14 mmol) was cyclized over 2 h to provide **ethyl (1R*, 2S*, 3S*)-1,2-dimethyl-2-hydroxy-3-ethylenecyclohexanecarboxylate (31)** (247 mg, 1.09 mmol), 96%, isolated by bulb to bulb distillation: bp 50-60 °C (0.01 mm Hg). ^{1}H NMR ($CDCl_3$): δ 6.12 (ddd, J = 4.9, 10.7, 17.5 Hz, 1H), 5.07 (dt, J = 10.7, 1.7 Hz, 1H), 4.97 (dt, J = 17.5, 1.7 Hz, 1H), 4.62 (m, 1H), 4.17 (dq, J = 2.8, 7.1 Hz, 2H), 2.42 (m, 1H), 2.16 (m, 2H), 1.65 (m, 2H), 1.48-1.29 (m, 2H), 1.30 (t, J = 7.1 Hz, 3H), 1.27 (s, 3H), 1.02 (d, J = 0.6 Hz, 3H); ^{13}C NMR ($CDCl_3$): δ 179.20, 139.22, 114.54, 75.48, 60.64, 51.20, 48.39, 33.98, 27.88, 22.77, 20.82, 16.30, 13.92; FT-IR ($CHCl_3$): 3450, 2990, 1700, 1450, 1380, 1365, 1260, 1220, 1180, 1120, 1075, 1015 cm^{-1}. Exact mass calcd for $C_{13}H_{22}O_3$: 226.1569, found: 226.1573.

Cyclization of Ethyl (*Z*)-2-Acetyl-2-methyl-8-trimethylsilyl-6-octenoate (28). Using the general procedure described above, **28** (167 mg, 0.559 mmol) was cyclized over 2 h to provide **31** (126 mg, 0.557 mmol), 99%, isolated by bulb to bulb distillation.

Cyclization of (*E*)-3-Acetyl-3-methyl-9-trimethylsilyl-7-nonen-2-one (32). Using the general procedure described above, **32** (199 mg, 0.741 mmol) was cyclized over 2 h to provide a 1 : 4.1 : 12.8 ratio of diastereomers (131 mg, 0.667 mmol), 89%, isolated by bulb to bulb distillation, bp 50-60 °C (0.01 mm Hg). Major diastereomer **(1R*, 2S*, 6R*)-1,2-dimethyl-2-acetyl-6-ethenylcyclohexanol (33a)**: ^{1}H NMR ($CDCl_3$): δ 6.11 (ddd, J = 4.9, 10.7, 17.5 Hz, 1H), 5.08 (dt, J = 10.7, 1.7 Hz, 1H), 4.94 (dt, J = 17.5, 1.7 Hz, 1H), 4.55 (m, 1H), 2.51 (m, 1H), 2.32-1.10 (m, 6H), 2.20 (s, 3H), 1.13 (s, 3H), 0.99 (s, 3H); ^{13}C NMR ($CDCl_3$): δ 218.77, 139.14, 144.54, 76.61, 55.55, 47.47, 34.36, 31.43, 27.91, 23.15, 19.46, 17.08; FT-IR ($CHCl_3$): 3470, 3000, 2930, 1680, 1640, 1460, 1450, 1400, 1360, 1235, 1125, 995, 920 cm^{-1}. Exact mass calcd for $C_{12}H_{20}O_2$: 196.1463, found: 196.1455. Minor diastereomer **(1R*, 2S*, 6S*)-1,2-dimethyl-2-acetyl-6-ethenylcyclohexanol (33b)**: ^{1}H NMR ($CDCl_3$): δ 5.89 (ddd, J = 3.94, 8.66, 10.5 Hz, 1H), 5.00 (dt, J = 2.0, 3.9 Hz, 1H), 4.93 (dt, J = 2.0, 10.5 Hz, 1H), 4.34 (br s, 1H), 2.46 (s, 3H), 2.14-1.13 (m, 7H), 1.27 (s, 3H), 1.10 (s, 3H); FT-IR ($CHCl_3$): 3470, 3000, 2990, 1690, 1455, 1330, 11220, 1150, 990 cm^{-1}. Exact mass calcd for $C_{12}H_{20}O_2$: 196.1463, found: 196.1451.

Cyclization of Ethyl (*E*)-2-Acetyl-2-methyl-7-trimethylsilyl-5-heptenoate (41). Using the general procedure described above, **41** (268 mg, 0.942 mmol) was cyclized over 2 h to provide an 83 : 7.3 : 1 mixture of diastereomers **42** (190 mg combined, 0.895 mmol),

95%, isolated by flash chromatography (11% EtOAc in hexanes on silica). Major diastereomer **ethyl (1R*, 2S*, 3R*)-1,2-dimethyl-2-hydroxy-3-ethenylcyclopentanecarboxylate (42a)**: ^{1}H NMR ($CDCl_3$): δ 5.75 (m, 1H), 5.09 (m, 1H), 4.93 (m, 1H), 4.17 (q, J = 7.1 Hz, 2H), 3.56 (s, 1H), 2.8 -1.3 (m, 5H), 1.21 (t, J = 7.1 Hz, 3H), 1.23 (s, 3H), 1.15 (s, 3H); ^{13}C NMR ($CDCl_3$): δ 178.07, 138.91, 155.75, 83.61, 60.81, 55.08, 53.19, 33.05, 25.43, 19.70, 19.46, 14.09; FT-IR ($CHCl_3$): 3460, 2970, 1705, 1635, 1465, 1375, 1270, 1190, 1140, 1090, 1020, 910 cm^{-1}. Exact mass calcd for $C_{12}H_{20}O_3$: 212.1412, found: 212.1428.

Cyclization of 2-[2-(trimethylsilylmethyl)-2-propenyl]-β-ketoamides with $TiCl_4$. General Procedure. To a solution of titanium tetrachloride (4.0 mmol) in CH_2Cl_2 (7.5 mL) at -55 °C was slowly added a solution of the 2-[2-(trimethylsilyl)methyl-2-propenyl]-β-ketoamide (1.0 mmol) in CH_2Cl_2 (2.5 mL). The reaction mixture instantaneously turned deep red. The mixture was allowed to stir at -55°C for 6h before being quenched by rapid addition of saturated K_2CO_3 (5 mL). The reaction was then partitioned between ethyl acetate (10 mL) and water (10 mL). The aqueous portion was further extracted with ethyl acetate (4 x 10 mL), then the combined organic extracts were washed with brine (10 mL) and dried over K_2CO_3.

Cyclization of *N,N*-Diethyl-2-acetyl-4-(trimethylsilyl)methyl-4-pentenamide (6a). Using the general procedure described above, **6a** (96.7 mg, 0.341 mmol) was cyclized to provide **(1R*, 2S*)-*N,N*-diethyl-2-hydroxy-2-methyl-4-methylenecyclopentanecarboxamide (7a)** (55.2 mg, 0.261 mmol), 76%, isolated by bulb to bulb distillation: bp 85-90 °C (0.03mm Hg). ^{1}H NMR ($CDCl_3$): δ 6.04 (s, 1H), 4.91 (s, 2H), 3.34 (m, 4H), 2.80-2.15 (m, 5H), 1.31 (s, 3H), 1.10-1.23 (m, 6H); ^{13}C NMR ($CDCl_3$): δ 174.21, 147.98, 107.43, 78.93, 47.91, 47.64, 42.02, 40.25, 35.86, 26.09, 14.84; IR(neat): 3300, 2950, 1610, 1405, 1320, 1250, 1140 cm^{-1}. Exact mass calcd for $C_{12}H_{21}NO_2$: 211.1572, found: 211.1562.

Cyclization of *N,N*-Dimethyl-2-[2-(trimethylsilyl)methyl-2-propenyl]-3-oxopentanamide (6b). Using the general procedure described above, **6b** (130 mg, 0.482 mmol) was cyclized to provide **(1R*, 2S*)-*N,N*-dimethyl-2-ethyl-2-hydroxy-4-methylenecyclopentanecarboxamide (7b)** (54 mg, 0.274 mmol), 57%, isolated by flash chromatography (50% EtOAc in hexanes on silica gel). ^{1}H NMR ($CDCl_3$): δ 5.80 (s,1H), 4.83 (br s, 2H), 3.06 (s, 3H), 2.87 (s, 3H), 2.75-2.15 (m, 5H), 1.70-1.36 (m, 2H), 1.69 (t, J = 7.7 Hz, 3H); ^{13}C NMR ($CDCl_3$): δ 175.33, 147.86, 107.45, 81.88, 44.39, 44.77, 37.18, 35.23, 32.63, 8.91; IR(neat): 3300, 2950, 1610, 1405, 1320, 1250, 1140 cm^{-1}. Exact mass calcd for $C_{11}H_{19}NO_2$: 197.1416, found: 197.1428.

Cyclization of *N,N*-Dimethyl-2-[2-(trimethylsilyl)methyl-2-propenyl]-3-oxo-4-methylpentanamide (6c). Using the general procedure described above, **6c** (81.2 mg, 0.286 mmol) was cyclized to provide **(1R*, 2R*)-*N,N*-dimethyl-2-hydroxy-2-isopropyl-4-methylenecyclopentanecarboxamide (7c)** (33.8 mg, 0.160 mmol), 56%, isolated by flash chromatography (50% EtOAc in hexanes on silica gel). ^{1}H NMR ($CDCl_3$): δ 6.41 (s, 1H), 5.10 (br m, 2H), 3.06 (s, 3H), 2.87 (s, 3H), 3.02-2.10 (m, 6H), 0.97 (d, J = 6.7 Hz, 3H), 0.85 (d, J = 6.8 Hz, 3H); ^{13}C NMR ($CDCl_3$): δ 175.53, 147.47, 106.80, 84.14, 43.53, 42.78, 36.77, 36.01, 35.41, 34.84, 17.87, 17.43; IR (neat) 3320, 2900, 1620, 1485, 1330, 1215, 1010, 930 cm^{-1}. Exact mass calcd for $C_{12}H_{21}NO_2$: 211.1572, found: 211.1582.

Cyclization of *N,N*-Dimethyl-2-[2-(trimethylsilyl)methyl-2-propenyl]-3-oxo-4,4-dimethylpentanamide (6d). Using the general procedure described above, **6d** (310

mg, 1.04 mmol) was cyclized to provide **(1R*, 2R*)-*N,N*-dimethyl-2-*t*-butyl-2-hydroxy-4-methylenecyclopentanecarboxamide (7d)** (177 mg, 0.785 mmol), 75%, isolated by flash chromatography (50% EtOAc in hexanes on silica gel). ^{1}H NMR ($CDCl_3$): δ 6.29 (s, 1H), 4.77 (br s, 2H), 3.00 (s, 6H), 2.85 (s, 2H), 2.80-1.05 (m, 3H), 0.79 (s, 9H); ^{13}C NMR ($CHCl_3$): 176.68, 147.81,106.74, 86.91, 42.38, 40.38, 37.29, 37.02, 36.64, 35.28, 26.02; FT-IR ($CHCl_3$): 3305, 3000, 1620, 1480, 1420, 1345, 1210, 1165, 1010, 935 cm^{-1}. Exact mass calcd for $C_{13}H_{23}NO_2$: 225.1729, found: 225.1743.

Cyclization of *N,N*-Diethyl-2-acetyl-2-methyl-4-(trimethylsilyl)methyl-4-pentenamide (6e). Using the general procedure described above, **6e** (205 mg, 0.689 mmol) was cyclized over 15 min at -78 °C to provide **(1R*, 2S*)-*N,N*-diethyl-1,2-dimethyl-2-hydroxy-4-methylenecyclopentanecarboxamide (7e)** (155 mg, 0.688 mmol), 100%, isolated by bulb to bulb distillation: bp 90-95 °C (0.03 mm Hg). ^{1}H NMR ($CDCl_3$): δ 4.90 (m, 3H), 3.41 (m, 4H), 3.02 (d, J = 14.8 Hz, 1H), 2.44 (d, J = 14.8 Hz, 1H), 2.39 (m, 2H), 1.46 (s, 3H), 1.25- 1.05 (m, 6H), 1.22 (s, 3H); ^{13}C NMR ($CDCl_3$): δ 176.41, 147.15, 107.34, 83.50, 53.29, 44.23, 42.54, 41.14, 23.28, 22.81, 13.40; IR (neat): 3450, 3000, 1605, 1470, 1390, 1370, 1120, 1090 cm^{-1}. Exact mass calcd for $C_{13}H_{23}NO_2$: 225.1729, found: 225.1725.

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21. It has also been suggested that stereodefined allylsilanes and allylstannanes may rapidly equilibrate under Lewis acid conditions, providing substrates isomeric about the double bond. See refs. 3a,b and f. We found no evidence for this in our systems, as reaction mixtures quenched on partial reaction showed no evidence of double bond isomerized starting materials.

22. The stereochemistry of compounds **42a** and **42b** was confirmed by comparison of ^1H NMR and FT-IR spectra to authentic samples from our laboratory.[8b,17] GC/MS studies indicated that a minor diastereomer (**42c**) was also generated.