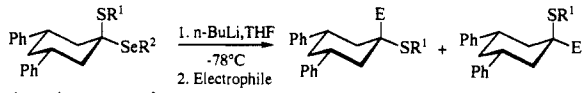
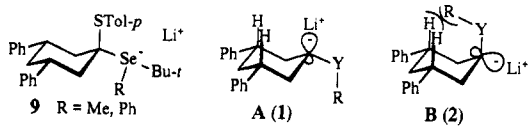
kinetically formed equatorial α-methylthio (**2b**) and α-tolylthio (**2c**) lithium reagents. The sequential experiment using **6a**[9] ((1) *n*-BuLi; (2) $EtCO_2H$) gave a 97/3 ratio of **7a**/**8a** (E = H), even when the electrophile was added less than 1 min after the *n*-butyllithium. Very similar ratios were also observed for cleavage



6a R^1 = Me R^2 = Ph
6b R^1 = *p*-Tol R^2 = Ph
6c R^1 = *p*-Tol R^2 = Me

7 Inversion **8** Retention

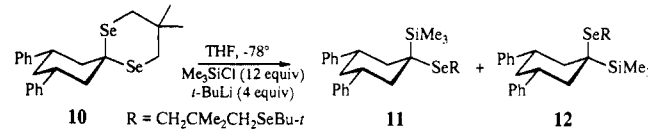
with *tert*-butyllithium and/or reaction with other electrophiles (Me_3SiCl, $EtMe_2SiCl$, $iPrMe_2SiCl$, Ph_2Se_2, Me_2SO_4). The behavior with in situ trimethylchlorosilane is summarized in Figure 1. As much as 96% of equatorial silane **8a** (E = $SiMe_3$) was formed, showing again that the Li-Se exchange occurred with retention of configuration at carbon. An interesting and significant difference was seen when the *p*-tolylthio compound **6b** was treated in a similar way. A maximum of 62% of the equatorially quenched product was obtained at high concentrations of silyl chloride. The shape of the curve suggests that equilibration of equatorial cleavage product to axial lithium reagent has two rate components. One is faster than reaction with trimethylchlorosilane; the second is competitive with the trapping rate. The nature of the fast component is not clear. It could represent a radical pathway in the Li-Se exchange, as for the Li/Br exchange,[12] or perhaps the exchange produces a transient aggregate or ion-pair structure that has a very low inversion barrier compared to the equilibrium structure of the lithium reagent. The ratio of products was identical within experimental error whether a phenylseleno (**6b**) or a methylseleno (**6c**[9]) was cleaved. These experiments argue against the direct reaction of possible intermediate ate complexes[1b] (**9**) giving retention products, since the two ate complexes should have different reactivities.



9 R = Me, Ph **A (1)** **B (2)**

Ordinary cyclohexyllithium reagents (e.g., (4-*tert*-butylcyclohexyl)lithium[13] and **1e**-**2e**) give predominantly equatorial products (>10/1). There must therefore be a significant stereoelectronic factor that stabilizes the axial lithium reagents studied here, and the same effect may operate to direct nucleophilic attack to the normally more hindered axial substituent in compounds **3a** and **3b**. We suggest that this effect involves steric inhibition of carbanion lone pair/S-C bond (n-σ*) hyperconjugation. In conformation A of the axial isomer **1**, the carbanion lone pair and S-C σ* orbitals are antiperiplanar and, hence, properly aligned for optimal n-σ* interaction.[14] However, in the equatorial α-lithio selenide or sulfide (**2**), there are severe steric interactions in the conformation (B) in which the n-σ* interaction is most effective.[15]

To test this explanation, we have examined the spiroselenoketal **10**, in which the above stereoelectronic effect is absent during the cleavage, since the key n-σ* interaction is now gauche (and unfavorable) for both seleniums. In, fact, the cleavage is much slower and there is a striking reversal of stereochemistry, which now occurs with a 30/1 preference for the *equatorial* selenium when an in situ quench was used (as judged by the formation of **12**). The isomerization of the equatorial lithium reagent **2d** to the more stable axial isomer **1d** was much slower than for **1a**, **1b**, or **1c**, so that equatorial products could be obtained even in a sequential experiment. The isomerization **2d** to **1d** occurred with a half-life of ~7 min at −78 °C and proceeded to a 24/1 ratio in favor of the axial isomer, just like the other systems examined. We feel that this provides support for the arguments represented by structures A and B.



10 R = $CH_2CMe_2CH_2SeBu$-*t* **11** **12**

in situ	1. Me_3SiCl 2. *t*-BuLi		3:97
sequential	1. *t*-BuLi 2. time 3. Me_3SiCl	(2 min)	20:89
		(8 min)	55:45
		(32 min)	91:9
		(60 min)	96:4

Summary. Cyclohexyl α-lithio sulfides and selenides **1** and **2** show a strong stereoelectronic preference for the axial lithium reagent. The equatorial α-thio and α-seleno reagents **2** can be produced and trapped with some stereospecificity, but they equilibrate to the more stable axial isomers **1** in 30 s or less (**1a**-**c**) or a few minutes (**1d**) at −78 °C. The spiroselenoketal **10**, in contrast to the noncyclic analogues **3a** and **3b**, cleaved the equatorial selenium with high stereoselectivity on treatment with *tert*-butyllithium.

Acknowledgment. We thank the National Science Foundation for generous support of our research and Mike Neeb for help with the preparative work.

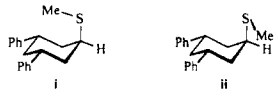
(11) The ratio of second-order rate constants for reaction of TolLi with Ph_2Se and Ph_2S to give TolYPh (THF, −78 °C) is 250/1: Reich, I. L., unpublished results.

(12) Ashby, E. C.; Pham, T. N. *J. Org. Chem.* **1987**, *52*, 1291. Bailey, W. F.; Nurmi, T. T.; Patricia, J. J.; Wang, W. *J. Am. Chem. Soc.* **1987**, *109*, 2442.

(13) Glaze, W. H.; Selman, C. M.; Ball, A. L., Jr.; Bray, L. E. *J. Org. Chem.* **1969**, *34*, 641.

(14) Lehn, J.-M.; Wipff, G. *J. Am. Chem. Soc.* **1976**, *98*, 7498. Epiotis, N. D.; Yates, R. L.; Bernardi, F.; Wolfe, S. *J. Am. Chem. Soc.* **1976**, *98*, 5435. Lehn, J.-M., Wipff, G.; Demuynck, J. *Helv. Chim. Acta* **1977**, *121*, 1239.

(15) The MM2 energy of conformation i is 4 kcal higher than that of the gauche conformation ii. The X-ray crystal structure of 4-*tert*-butyl-1-(methylseleno)-1-(phenylseleno)cyclohexane shows it to be in conformation ii.[6a]



Stereoselective Synthesis of Highly Substituted Tetrahydrofurans through Acid-Catalyzed Ring Closure of Selenyl Diols

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Despite extensive research efforts directed toward the stereocontrolled production of substituted tetrahydrofurans from olefinic precursors,[1] few studies have addressed the feasibility of directed ring closures of homoallylic alcohols.[2] Endo-cyclization modes, such as the one shown in the top line of Scheme I, are generally considered to be energetically unfavorable.[3] We envisioned the successful implementation of this strategy using an electrophilic selenium species which would be generated from epoxy alcohols II[4] as shown in Scheme I. Nucleophilic ring opening[5] leading to regioisomers III and III′ would then be followed by a stereoconvergent elimination of water to provide V via the intermediate IV. We report herein the stereoselective synthesis of tri- and tetrasubstituted tetrahydrofurans based on such a homoallylic precursor system.

Epoxy alcohols **1**-**4** (Chart I) were chosen to develop the methodology.[4,6] Ring opening of **1** with sodium phenyl selenide[5]

(1) (a) Cardillo, G.; Orena, M. *Tetrahedron* **1990**, *46*, 3321-3408. (b) Nicolaou, K. C.; Magolda, R. L.; Sipio, W. J.; Barnette, W. E.; Lysenko, Z.; Joullie, M. M. *J. Am. Chem. Soc.* **1980**, *102*, 3784-3793.

(2) Williams, D. R.; Grote, J.; Harigaya, Y. *Tetrahedron Lett.* **1984**, *25*, 5231-5234.

(3) Baldwin, J. *J. Chem. Soc., Chem. Commun.* **1976**, 734-736.

(4) Mihelich, E. D.; Daniels, K.; Eickhoff, D. J. *J. Am. Chem. Soc.* **1981**, *103*, 7690-7692.

(5) Sharpless, K. B.; Lauer, R. F. *J. Am. Chem. Soc.* **1973**, *95*, 2697-2699.

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Scheme I

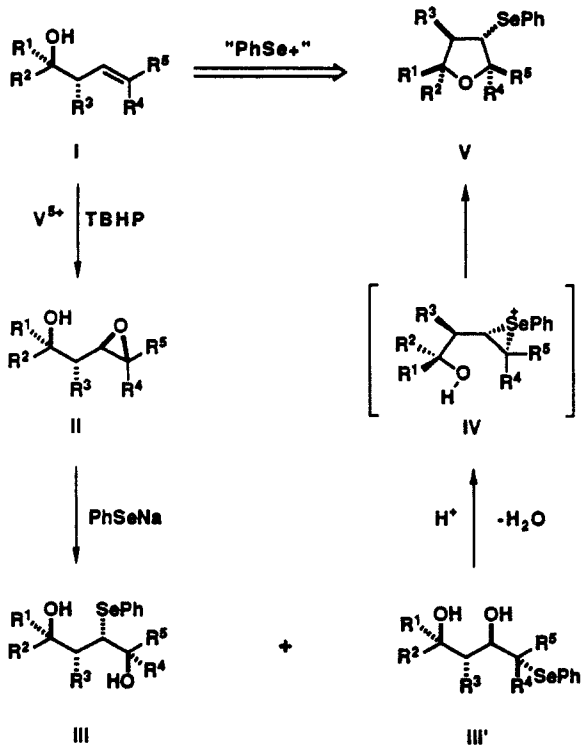
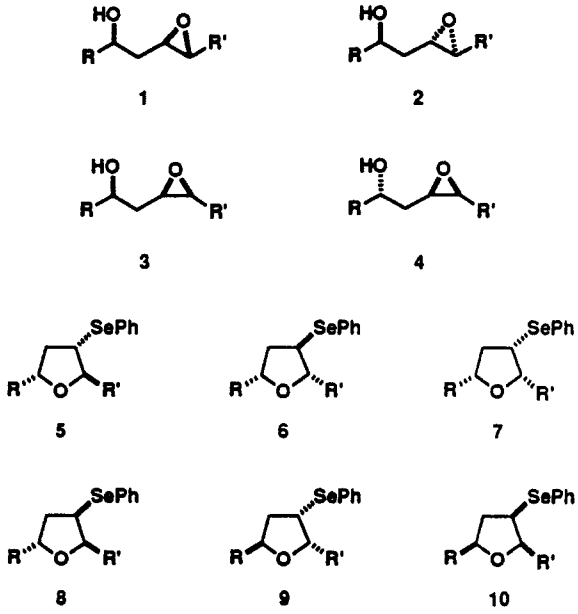


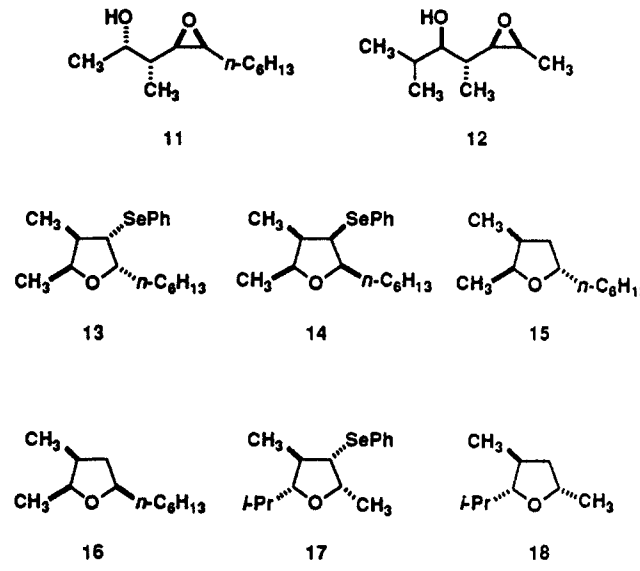
Chart I[a]



[a] R = $(CH_2)_5CH_3$, R′ = $(CH_2)_7CO_2CH_3$.

proceeded smoothly, affording the corresponding selenyl diols (91%),[7a] which, on treatment with perchloric acid in tetrahydrofuran, produced **5**[7b] in 86% yield.[8] Similarly, **2** underwent clean phenyl selenide ring opening (87%) and subsequent acid-induced closure ($HClO_4$, THF) to yield **6**[7b] (76%). Solvent choice was crucial to the successful outcome of these reactions. In dichloromethane, perchloric acid induces a rapid thermodynamic equilibration of **5** and **6** to a 40:60 mixture of the two, respectively.[9]

Chart II



With substrates **3** and **4**, alternative reaction modes became apparent. Epoxy alcohol **3** gave selenyl diols (90%) which, on treatment with perchloric acid, afforded **7**[7b] in either THF (24 h, 70%) or CH_2Cl_2 (0.25 h, 85%). Resubjecting **7** to reaction conditions in CH_2Cl_2 failed to generate **8**, but increasing the acid content 10-fold in the same solvent did lead to a 1:1 mixture of **7**:**8**.[7b] In contrast to the previous three examples, **4** yielded selenyl diols (58%) which underwent acid-induced ring closure ($HClO_4$, CH_2Cl_2) to give stereoisomer **10** (83%) containing only traces of **9**.[10]

The observed formation of all-syn tetrahydrofurans **7** and **10** from diastereomeric *cis*-epoxy alcohol precursors can be reconciled by an acid-induced conversion of intermediates III and III′ to olefin I, a well-known process for β-hydroxy selenides,[11] followed by an *unprecedented, highly stereoselective, and kinetically controlled* electrophilic cyclization. Indeed, this hypothesis is substantiated by the selective conversion of methyl ricinoleate [12(*R*)-hydroxy-9(*Z*)-octadecenoic acid methyl ester] to **7** by treatment with N-PSP[12] (CH_2Cl_2, 24 h, 47%).

These results suggested that an additional substituent at R^3 (Scheme I) would be well-tolerated and should lead to the predicted stereoisomer indicated in V. The known[4] epoxy alcohols **11** and **12** (Chart II)[13] were evaluated in this regard. Both compounds were attacked cleanly by phenyl selenide to form predominantly regioisomer III′. In the case of **11**, this product mixture underwent efficient ring closure ($HClO_4$, CH_2Cl_2, 2 h) to give a 96:4 mixture of **13**[7b]:**14** in 87% yield. Structures were confirmed by reduction (Bu_3SnH, AIBN, PhH) to the corresponding trisubstituted tetrahydrofurans **15** (78%) and **16** (50%). In like manner, the selenyl diol mixture derived from **12** gave, with acid treatment ($HClO_4$, CH_2Cl_2, 0.75 h), a single tetrahydrofuran, **17**,[7b] in 71% yield. Reduction as described above provided **18**.[14]

(6) Compounds **1** and **2** were separated by using medium-pressure liquid chromatography; compound **4** was prepared by a Mitsunobu procedure on **3**. The compounds of Chart I are single enantiomers.

(7) (a) All yields refer to isolated, chromatographed, and spectroscopically pure materials. (b) An elemental analysis was obtained on this compound.

(8) In a typical experiment, the selenyl diols (0.52 g) prepared from **1** in 50 mL of dry THF received 3 drops of 70% perchloric acid with stirring. After 6 h at ambient temperature, extractive isolation and chromatography on silica gave **5** (0.43 g). Stereochemistry was established by ^1H NMR as described by Williams et al.[18] Additionally, an authentic sample of *ent*-**5** was prepared by an alternative sequence.

(9) Kinetic ring closure of methyl ricinelaidate [12(*R*)-hydroxy-9(*E*)-octadecenoic acid methyl ester] with benzeneselenenyl chloride gave a 60:40 mixture of **5**:**6**.

(10) A few milligrams of **9** was isolated; the substance was identical with **8** with the exception of having an opposite sign of rotation.

(11) Remion, J.; Dumont, W.; Krief, A. *Tetrahedron Lett.* **1976**, 1385–1388.

(12) Nicolaou, K. C.; Claremon, D. A.; Barnette, W. E.; Seitz, S. P. *J. Am. Chem. Soc.* **1979**, *101*, 3704–3706.

(13) These materials are racemic mixtures.

(14) Each of the cyclizations performed on substrates derived from *cis*-epoxides has shown an intermediate spot on thin-layer analysis during the course of reaction consistent with the presence of the olefin. Preliminary experiments indicate that direct treatment of these olefins with standard selenating agents is sluggish and inefficient. These studies will be included in the full account of this work.

This constitutes the first report of stereoselective formation and ring closure of acyclic selenyl diols to highly substituted tetrahydrofurans. The synthetic potential of the selenium residue[15] retained on the ring should be emphasized. In addition to reductive removal, other synthetic transformations such as oxidative elimination to dihydrofurans and radical coupling processes are areas we are actively pursuing. Previous reports of similar cyclizations involving sulfur species[16] appear more limited in this regard.

Application of our method to a variety of important targets is indicated. The structural motif in **15** has been sought in ionophore synthesis[17] as have 2,5-cis-disubstituted tetrahydrofurans represented by **6**, **7**, and **18**. Further work in this and related areas will be reported in due course.

(15) Liotta, D.; Monahan, R. *Science* **1986**, *231*, 356-361.
(16) (a) Williams, D. R.; Phillips, J. G.; Barner, B. A. *J. Am. Chem. Soc.* **1981**, *103*, 7398-7399. (b) Williams, D. R.; Phillips, J. G. *Tetrahedron* **1986**, *42*, 3013-3019. (c) Aggarwal, V. K.; Coldham, I.; McIntyre, S.; Sansbury, F. H.; Villa, M.-J.; Warren, S. *Tetrahedron Lett.* **1988**, *29*, 4885-4888. (d) Warren, S.; McIntyre, S. *Tetrahedron Lett.* **1990**, *31*, 3457-3460.
(17) Ting, P. C.; Bartlett, P. A. *J. Am. Chem. Soc.* **1984**, *106*, 2668-2671.
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Total Synthesis of Glycinoeclepin A

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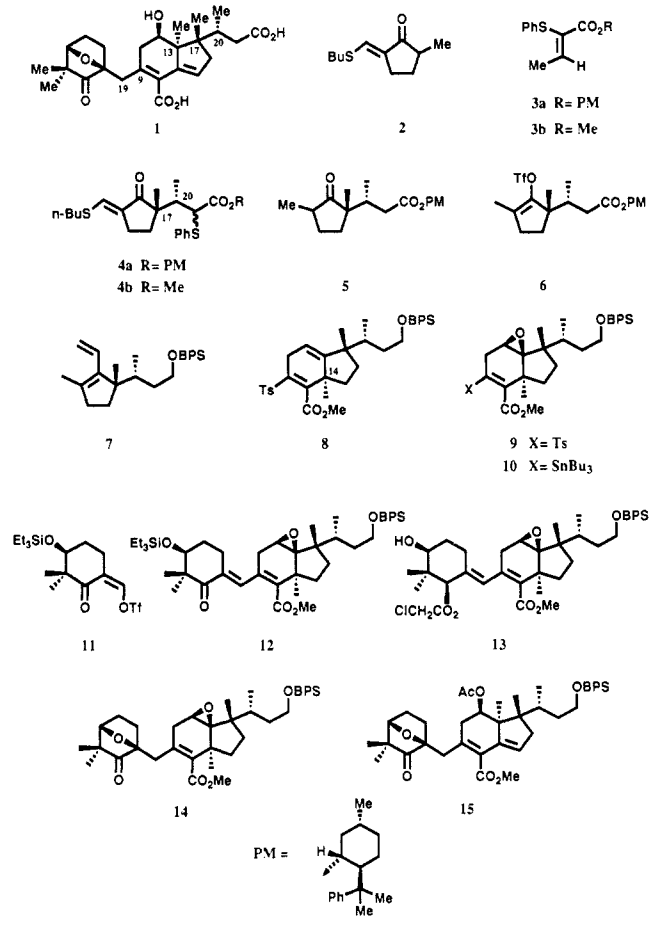
It is remarkable that glycinoeclepin A (**1**),[1] a product of the soybean plant (and various other beans) for which it may be a biochemical regulator, stimulates hatching (at 10^{-12} g/mL) of dormant eggs of the predatory nematode *Heterodera glycines*. In this paper we describe a total synthesis of glycinoeclepin A[2] which is direct and enantiocontrolled, and which depends on a number of unusual steps.

The construction of **1** (steroid numbering), which involved a coupling of mono and bicarbocyclic moieties at the C(9)-C(19) linkage, commenced with the enantioselective establishment of the C(17)-C(20) stereocenters as follows. Cyclopentanone **2**[3] was converted to the potassium enolate ($KN(SiMe_3)_2$ in 5:1 THF-toluene) which was allowed to react at -100 °C for 3 h with the ester (**3a**) of (*Z*)-2-(phenylthio)crotonic acid[4] and (-)-8-phenylmenthol[5,6] (PM) to give as the major product the adduct **4a** with 95:5 enantioselectivity and 5:1 C(17)-C(20) diastereoselectivity (89% total yield).[7] The corresponding reaction of the

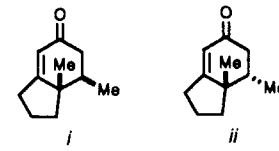
Chart I



potassium enolate of **2** with methyl ester **3b** (THF, 15 min at -78 °C) gave (±)-**4b** (82%) with 97:3 C(17)-C(20) diastereoselectivity.[8,9] Chiral adduct **4a** was separated from the minor C-(17)-C(20) diastereomer by silica gel chromatography (sgc) with use of 3:1 hexane-ether and converted by Raney nickel in ethanol at 23 °C for 1 h to keto ester **5** (85%) and thence sequentially with $KN(SiMe_3)_2$ and *N*-phenylbistrifluoromethanesulfonamide in THF at -78 °C to enol triflate **6** (oil), $[\alpha]^{26}_D$ +41.3° (*c* = 1.3, $CHCl_3$), which was obtained in pure form (84%) after sgc (13:1 hexane-ether). Vinylation[10] of **6** with vinyltributyltin-LiCl in the presence of 0.07 equiv of $(Ph_3P)_4Pd$ at 65 °C for 12 h afforded the desired diene ester (87%) which was reduced (*i*-Bu_2AlH, 0 °C, THF)[11] and protected (*tert*-butyldiphenylsilyl chloride (BPSCl)-imidazole-DMF, 25 °C, 15 min) to give diene **7** (oil,

(1) (a) Fukuzawa, A.; Furusaki, A.; Ikura, M.; Masamune, T. *J. Chem. Soc., Chem. Commun.* **1985**, 221-222, 748. (b) Masamune, T.; Anetai, M.; Takasugi, M.; Katsui, N. *Nature* **1982**, *297*, 495-496.
(2) Two syntheses of **1** have been reported previously. (a) Murai, A.; Tanimoto, N.; Sakamoto, N.; Masamune, T. *J. Am. Chem. Soc.* **1988**, *110*, 1985-1986. (b) Mori, K.; Watanabe, H. *Pure Appl. Chem.* **1989**, *61*, 543-546.
(3) Prepared from 2-methylcyclopentanone by the method of: Ireland, R. E.; Marshall, J. A. *J. Org. Chem.* **1962**, *27*, 1615-1629.
(4) Prepared from methyl 2-bromopropionate by the following sequence: (1) displacement with 1.1 equiv of thiophenol and 1.2 equiv of 1,8-diazabicyclo[5.4.0]undec-7-ene at 23 °C for 20 min to form methyl 2-(phenylthio)propionate (98%); (2) sequential treatment with 1.2 equiv of SO_2Cl_2 in CH_2Cl_2 at -10 °C for 10 min and Al_2O_3 in toluene at 75 °C for 12 h to form methyl (*Z*)-2-(phenylthio)crotonate (60%) (Cf. Trost, B. M.; Salzmann, T. M.; Hiroi, K. *J. Am. Chem. Soc.* **1976**, *98*, 4887-4902); and (3) saponification with 3 equiv of LiOH in 2:1 H_2O-dimethoxyethane at 23 °C for 16 h.
(5) Corey, E. J.; Ensley, H. E. *J. Am. Chem. Soc.* **1975**, *97*, 6908-6909. (-)-8-Phenylmenthol was conveniently purified by recrystallization of the chloroacetate ester after synthesis from (*R*)-(+)-pulegone.
(6) Ester **3a** was produced by reaction of (*Z*)-2-(phenylthio)crotonic acid and (-)-8-phenylmenthol with dicyclohexylcarbodiimide and 4-(dimethylamino)pyridine in THF at 26 °C for 6 h.

(7) Because of the additional complication of diastereomers α to the ester carbonyl, analysis was performed after conversion (Ni) to keto ester **5** (gas chromatography) or to **6** (HPLC).
(8) The opposite C(17)-C(20) diastereopreference was observed for the reaction of 1-((triethylsilyl)oxy)-2-methylcyclopentene with *N*-(*E*)-crotonylbenzoxazolidinone and ethylaluminum dichloride at -78 °C in CH_2Cl_2. Stereochemical assignments were made in the 2-methylcyclopentanone series by rigorous chemical correlation with diastereomeric enones *i* and *ii* (cf.: Scanio, C. J. V.; Starrett, R. M. *J. Am. Chem. Soc.* **1971**, *93*, 1539-1540).



i *ii*

(9) (a) For precedent and mechanistic rational for the stereoselective formation of adducts **4a** and **4b** see: Corey, E. J.; Peterson, R. T. *Tetrahedron Lett.* **1985**, *26*, 5025-5028. (b) For the use of methyl α-methylthioacrylate as a Michael acceptor, see: Cregge, R. J.; Herrmann, J. L.; Schlessinger, R. H. *Tetrahedron Lett.* **1973**, 2603-2606.
(10) Scott, W. J.; Stille, J. K. *J. Am. Chem. Soc.* **1986**, *108*, 3033-3040.
(11) 8-Phenylmenthol was recovered efficiently after sgc.

0002-7863/90/1512-8997$02.50/0