Pergamon

Tetrahedron Vol. 50, No. 19, pp. 5591-5614, 1994

0040-4020/94 $6.00+0.00

0040-4020(94)E0240-T

Asymmetric Induction in the Michael Initiated Ring Closure Reaction

Mary A. Amputch,[1] Regina Matamoros, and R. Daniel Little*

Department of Chemistry

University of California, Santa Barbara

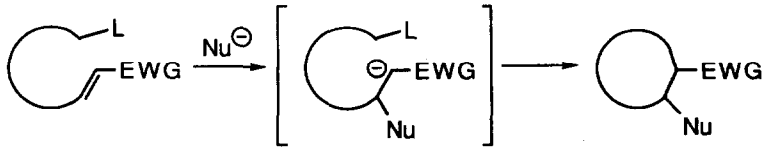
Santa Barbara, California 93106

Abstract: The Michael Initiated Ring Closure reaction has been explored with an eye toward achieving asymmetric induction. The formation of three, five and six-membered rings was examined using compounds **1**-**7** as substrates. In the case of cyclopropane formation, diastereoselectivity was studied over a range of temperatures, the best results being obtained between -68 and -72 °C using lithium *t*-butylthiolate as the nucleophile and a 10-dicyclohexylsulfamoyl-D-isoborneol-derived auxiliary (72-78% yield, 50-56% de; note equation 5). An isokinetic point is believed to occur between -41 and -68 °C. No improvement in de was observed when the Oppolzer sultam was used instead (compound **18**). The use of (-)-menthol and (-)-8-phenylmenthol derived auxiliaries led to substantially inferior results (2-6% de). Five and six-membered rings were formed in good to excellent yields (62-97%) with diastereomeric excesses reaching as high as 95% in the case of cyclohexyl ester formation, using lithium diisopropylamide as the nucleophile and the 10-dicyclohexylsulfamoyl-D-isoborneol-derived auxiliary. Note equations 7 and 8. As expected, cyclization affording the five-membered ring adducts proceeded substantially faster than those leading to the six. By conducting both reactions at low temperature, one can use this rate difference to assess the diastereomeric excess obtained in the conjugate addition of LDA to the six-membered ring precursor **7**. The de obtained in this manner (*ca.* 95%) agreed within experimental error with that obtained when the reaction was conducted at a temperature where cyclization occurred.

Introduction

The *M*ichael *I*nitiated *R*ing *C*losure reaction, simply referred to as the *MIRC* reaction, was defined in 1980 as "a general set of transformations which are initiated by a conjugate addition to an α,β-unsaturated ester or ketone to produce an enolate which subsequently undergoes intramolecular ring closure".[2]

... a MIRC reaction



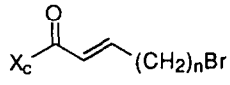
EWG = electron withdrawing group
$Nu^{\ominus}$ = nucleophile
L = leaving group

This definition was a consequence of a series of studies which led to the construction of three-, five-, six- and seven-membered rings from ω-halo α,β-unsaturated esters, using lithium *t*-butylthiolate and lithium diisopropylamide as nucleophiles.[2-4] The MIRC methodology was later extended to include ω-haloalkylidene malonates, permitting a wider variety of nucleophiles, counterions, and solvents to be utilized.[5] Apart from its simplicity, the MIRC reaction incorporates several valuable features, namely concomitant conjugate addition and formation of a C-*N*, -*S*, -*H*, -*C* or -*CN* bond depending on the choice of nucleophile and substrate, and formation of cyclic products which contain functional groups amenable to further elaboration.[1-5]

A report by Enders and co-workers describing their efforts to achieve diastereo- and enantioselective MIRC reactions appeared in 1991.[6] Impressive selectivities were obtained. For example, treatment of methyl (E)-6-bromohex-2-enoate with the anion derived from several SAMP/RAMP hydrazones afforded, after oxidative cleavage of the hydrazone, 43-78% yields of cyclopentyl keto esters with high diastereomeric (de ≥ 95-99%) and enantiomeric excesses (ee ≥ 95-97%). Enders' disclosure prompts us to describe our findings concerning the asymmetric MIRC reaction leading to the formation of three, five, and six-membered rings.

PREPARATION OF MIRC SUBSTRATES

We elected to use the simple and traditional chiral auxiliaries (X_c) derived from (-)-menthol and (-)-8-



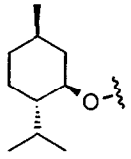
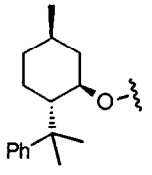
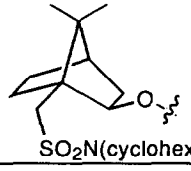
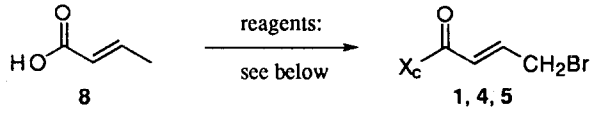
series	X_c	compound number (n)
a		**1** (n = 1), **2** (n = 3), **3** (n = 4)
b		**4** (n = 1)
c		**5** (n = 1), **6** (n = 3), **7** (n = 4)

Figure 1. MIRC substrates.

phenylmenthol, as well as 10-dicyclohexylsulfamoyl-D-isoborneol[7] in the preparation of the "a-", "b-", and "c"-series substrates illustrated in Figure 1. Throughout the remaining discussion, the expression "a-series" refers to the use of the (-)-menthol derived auxiliary, "b-series" to that derived from (-)-8-phenylmenthol, *etc.*

The synthetic pathway used to obtain each of the substrates **1-7** is illustrated in Scheme 1; details can be found in the Experimental Section.

Three-membered ring precursors



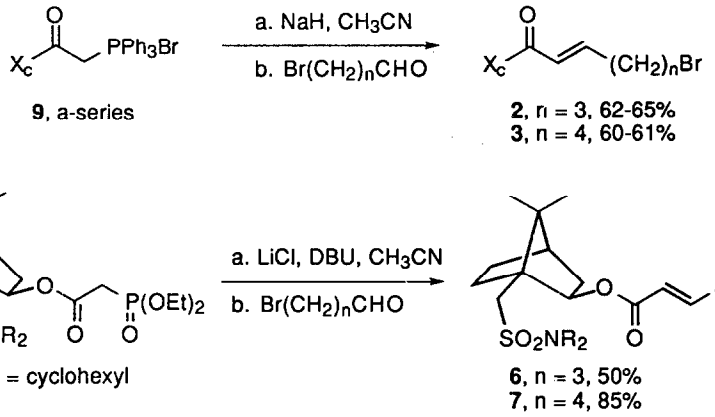
8 **1, 4, 5**

a-series (to **1**): i, (-)-menthol, HOTs-*p* (cat), $PhCH_3$, reflux, 7 h (86%); ii, NBS, AIBN, CCl_4, reflux (78%)

b-series (to **4**): i, (-)-8-phenylmenthol, DCC, DMAP, CH_2Cl_2, room temp (86-99%); ii, NBS, AIBN, CCl_4, reflux (70%)

c-series (from acid chloride to **5**): i, 10-dicyclohexylsulfamoyl-D-isoborneol, AgCN, PhH, reflux (81% trans, 9% cis); ii, NBS, AIBN, CCl_4 (43-77%)

Five- and six membered ring precursors



9, a-series

2, n = 3, 62-65%
3, n = 4, 60-61%

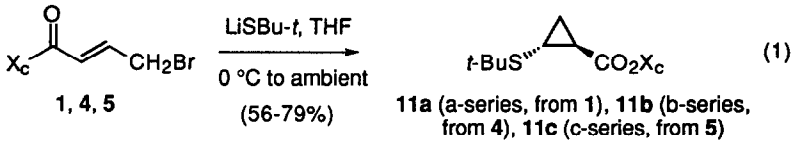
10, R = cyclohexyl

6, n = 3, 50%
7, n = 4, 85%

Scheme 1.

CYCLIZATIONS LEADING TO THREE-MEMBERED RINGS

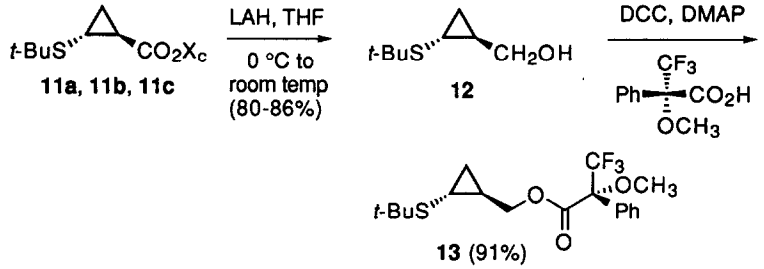
The MIRC reactions were carried out by application of the general procedure developed in these laboratories by Dawson.[2-4] An ice-bath-cooled solution of each of the bromoesters **1**, **4** and **5** in THF was treated with lithium *t*-butylthiolate (1.1 equiv, added dropwise over 20 min) and then gradually allowed to



(1)

warm to room temperature. Stirring was continued for 15-18 h. The cyclopropyl ester **11** was obtained as the major product in each case in yields ranging from 56 to 79%.

In their turn, each of the diastereomeric cyclopropyl esters **11a-c** was reduced with $LiAlH_4$ to afford the enantiomeric cyclopropyl alcohols **12**. The Mosher's ester **13** was then made by treatment of the alcohol **12** derived from each ester, with DCC, DMAP and S-(-)-α-methoxy-α-(trifluoromethyl)phenylacetic acid (Mosher's acid) in methylene chloride.[8] The percentage diastereomeric excess (de) in each case, was determined from the 500 MHz ^1H NMR spectrum of the Mosher's ester **13**.



(2)

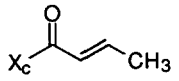
The results are summarized in Table 1. Clearly, the extent of asymmetric induction achieved was very low (2-6% de). However, these studies do show, that like the initial MIRC reactions with the methyl γ-bromocrotonate, the chiral auxiliary derived bromoesters **1**, **4** and **5** also afford the corresponding cyclopropyl esters **11a-c** in good yields.

Table 1. Summary of results for systems **1**, **4**, and **5**. Note equation 1.

Chiral auxiliary, X_c	Yield (%) of ester **11**	Yield (%) of alcohol **12**	Sign $[\alpha]^{24}$ °C, alcohol **12**	Yield (%), Mosher ester **13**	de (%), (ratio)
a-series	56-60	82	negative	96	2 (49:51)
b-series	78	80	negative	87	4 (48:52)
c-series	79	86	negative	89	6 (47:53)

Temperature-dependence

The possibility that the use of a lower temperature might improve the diastereoselectivity was considered and tested. Since the best results were obtained with 10-dicyclohexylsulfamoyl-D-isoborneol as the chiral auxiliary, it was chosen for use in these studies. Also, it was thought that subjecting sulfonamide ester **14** to the same conditions used for the MIRC reaction might provide



14 (c-series)

some insight into what was occurring at the initial conjugate addition stage of the sequence. Sulfonamide ester **14** does not have a leaving group and therefore, only conjugate addition can occur.

All reactions with sulfonamide bromoester **5** and sulfonamide ester **14** were conducted by the dropwise addition of lithium *t*-butylthiolate over 20 minutes, to a cooled solution of the appropriate ester in THF. When reactions were carried out at bath temperatures of 4 to 8 °C and -35 to -41 °C, introduction of the nucleophile to the cooled solution of the ester resulted in a cloudy *pale yellow* solution, whereas reactions conducted at -68 to -72 °C yielded a cloudy *pale blue-green* solution (electron transfer?).[9] In general, the outcome of the MIRC reaction with bromoester **5** and the conjugate addition reaction with sulfonamide ester **14** was found to be very sensitive to temperature, greatly hampering reproducibility.[9] Therefore, within each temperature range at least two reactions have been conducted, and the yield and de reported as a range rather than a single value. Note Tables 2 and 3.

Table 2. Results of temperature-dependence studies using compound **5** (c-series)

entry	bath temp (°C)	reaction time, h	yield (%), ester **11c**	yield (%) alcohol **12**	sign $[\alpha]^{24°C}$, **12**	yield (%), ester **13**	de (%), (ratio)
1	4 to 8	1.5	76-79	53-60	negative	74-78	34-38 (33:67-31:69)
2	-35 to -41	2	65-73	57-59	negative	74-78	12-14 (44:56-43:57)
3	-68 to -72	4-5	72-78	62-75	positive	83-86	50-56 (75:25-78:22)
4[a]	-93 to -97	8-9	52-53[b]	61-84	positive[a]	74-87[a]	38-44[a] (69:31-72:28)

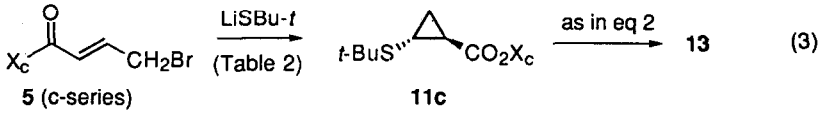
a, *Note commentary in reference 9.*

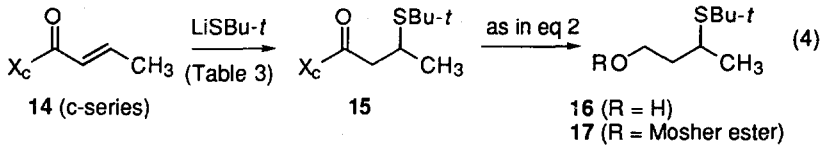
b, 76-82% yield based on recovered starting material.

Table 3. Results of temperature-dependence studies using compound **14**.

bath temp (°C)	reaction time, h	yield (%), thioester **15**	% de (ratio), **15**	yield (%) **16**	sign $[\alpha]^{24°C}$, **16**	yield (%), **17**	% de (ratio)
67	5	98	0 (50:50)	75	not applicable	85	0 (50:50)
4 to 8	5 to 10 min	89-98	38-40 (31:69-30:70)	76-78	negative	80-94	36 (32:68)
-35 to -41	1.5	88-94	16 (42:58)	73-78	negative	88	18 (41:59)
-68 to -72	1 to 3.5	97-98	16 (42:58)	61-78	positive	85-91	16-20 (58:42-60:40)

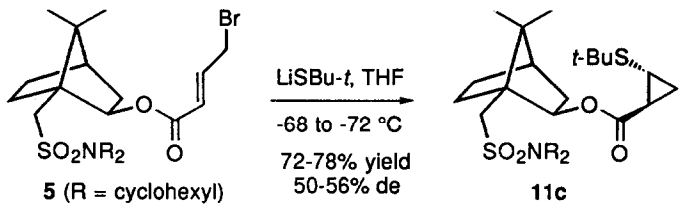
The de of the cyclopropyl esters obtained from the MIRC reaction was determined as previously indicated *i.e.*, using the Mosher's ester **13**. The de of the *t*-butylthioester **15** obtained from each trial, was determined in the same way *i.e.*, by conversion of the ester **15** to the *t*-butylthioalcohol **16**, with subsequent conversion to the t-butylthio Mosher's ester **17**.



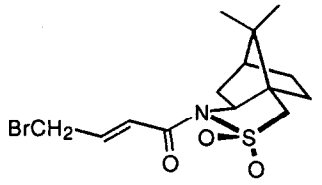


Also, because purification of the *t*-butylthioester **15** was easily accomplished by silica gel chromatography, and the ^{1}H NMR spectrum showed separation of several proton signals for each diastereomer, the de of the ester **15** could be determined at this stage and further confirmed from the ^{1}H NMR (500 MHz) spectrum of the Mosher's ester **17**.

The investigations involving bromoester **5** indicate that the cyclopropyl ester **11c** is obtained as the major product in satisfactory yields (57-79%) at all temperatures, and the highest level of asymmetric induction (50-56%) is observed in the temperature range -68 to -72 °C (Table 2). No improvement was observed when sultam **18** was subjected to the same conditions.[7]



5 (R = cyclohexyl) 11c (5)



18

It is interesting to note that the specific rotations of the enantiomeric mixture of alcohols **12**, derived from the cyclopropyl ester **11c** obtained at 4 to 8 °C and -35 to -41 °C, are *opposite in sign* to those derived from the cyclopropyl ester **11c** obtained at -68 to -72 °C. This change in sign is accompanied by a change in the cyclopropyl ester diastereomer favored. That is, based on the Mosher's ester of the two diastereomeric *trans*-cyclopropyl esters **11c** initially obtained, one diastereomer is favored at 4 to 8 °C and -35 to -41 °C, while the other is favored at -68 to -72 °C.[10] Compare entries 1 and 2 with 3 of Table 2. Also, as the temperature decreases from 4 to 8 °C to -35 to -41 °C, the de *decreases* from 34-38% to 12-14% favoring one diastereomer, and *then increases* to a maximum of 50-56% de at -68 to -72 °C and *favoring the opposite diastereomer*. These results clearly suggest the existence of an isokinetic point somewhere between -41 and -68 °C where the amount of each diastereomer is the same.[11]

Apart from the observation that the highest level of asymmetric induction (36% de) is achieved at 4 to 8 °C, the results obtained from the sulfonamide ester **14** (no leaving group; Table 3) exhibit several similarities to those obtained from the bromoester **5** (Table 2). The *t*-butylthioester **15** was obtained in satisfactory yield at all temperatures. The sign of the specific rotation for the enantiomeric mixture of alcohols **16** derived from *t*-butylthioester **15** at 4 to 8 °C and -35 to -41 °C is opposite to that of the alcohol derived from the t-butylthioester **15** at -68 to -72 °C, and this change in sign is again accompanied by a change in the diastereomeric ester favored in the initial conjugate addition reaction. Since the greatest induction was obtained in the highest temperature range, we wondered whether raising the temperature might not have a positive influence. In fact, raising the temperature from 4 to 8 °C to refluxing THF, a value which in retrospect is undoubtedly too high, results in no asymmetric induction.

The low to modest diastereoselectivity can be rationalized with the aid of the sequence illustrated in Figure 2. Let us assume that the α,β-unsaturated bromoester substrates **1**, **4** and **5** exist as an equilibrium mixture of *s-cis* and *s-trans* conformers.[12] Then, preferential addition of the nucleophile from the less hindered face of the carbon-carbon double bond establishes an absolute configuration which is exactly

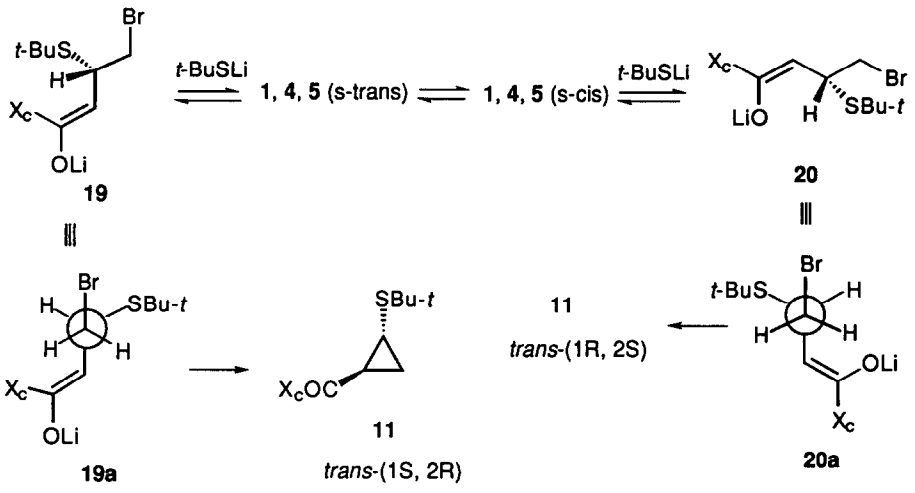


Figure 2. Possible rationale for low diastereoselectivity in the formation of cyclopropyl esters.

opposite in the enolates **19** and **20**. The conformations adopted by the *E* and *Z* enolates **19** and **20** to promote formation of the diastereomeric *trans*-(1*S*, 2*R*) and *trans*-(1*R*, 2*S*) cyclopropyl esters, approximate those shown in the Newman projections **19a** and **20a**. Since the rate of closure to three-membered rings is expected to be fast, especially at the temperature used (0 °C to room temp), the initially formed enolates **19** and **20** probably do not equilibrate with the substrate to an appreciable extent, and the product ratio therefore closely reflects the relative amounts of the *s-cis* and *s-trans* conformers present in the initial mixture of bromoester used. In other words, diastereoselection is determined by the relative amounts of *s-cis* and *s-trans* conformers of the substrate in solution. It follows then, that within the temperature range (0 °C to room temp) used, and despite the difference in chiral auxiliaries, the *s-cis* and *s-trans* conformers exist in approximately equal amounts, leading to the low de observed in each case.[13]

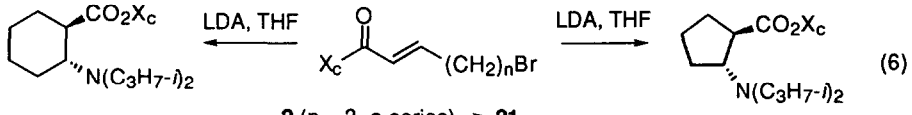
Since the absolute configuration of the chiral centers in the diastereomeric cyclopropyl esters **11** and the *t*-butylthioesters **15** have not been determined, it has not been possible to distinguish between the diastereomers in each set of esters, or indicate which is preferred at the lower or higher temperatures. In fact, at this time it is not clearly understood whether the observed trend in diastereoselectivity is entirely due to a temperature effect, an effect induced by a change in the solvent structure as the temperature is raised or lowered, or a result of a combination of these factors. However, several mechanistic points, though partly based on speculation, are worthy of discussion.

If, as indicated previously, the degree of asymmetric induction achieved is determined by the balance between the *s-cis* and *s-trans* conformers of the substrate esters **5** and **14**, then it follows that temperature must affect the ratio of *s-cis* to *s-trans* conformers, allowing one conformer to exist preferentially at the lower temperatures (-68 to -72 °C). This would in turn, account for the observed change-over in the diastereomer favored at the two temperature extremes.

For both the cyclopropyl ester **11c** and the *t*-butylthioester **15**, the trend observed is similar in that the diastereomer favored at 4 to 8 °C decreases in amount relative to the other diastereomer, which then becomes the favored product at -68 to -72 °C. It is interesting to note that within the temperature range 4 to 8 °C to -68 to -72°C, the reaction may pass through an isokinetic point, *i.e.*, a temperature at which equal amounts of both diastereomers are formed.

CYCLIZATIONS LEADING TO FIVE- AND SIX-MEMBERED RINGS

Cyclization of compounds **2**, **3**, **6** and **7** was accomplished by employing LDA as the nucleophile and THF as solvent.[1-5] Two procedures, one calling for the addition of the substrate to LDA, and the other for the reverse mode of addition, were utilized. Table 4 lists the yields and de values obtained in each case and under a variety of different conditions. Note especially entries 7 and 8 where de's as large as 95% are recorded.



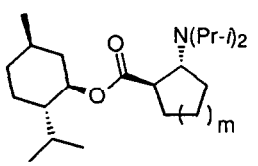
(6)

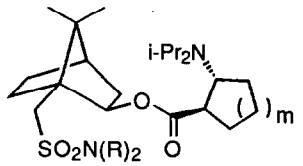
23 (a-series)
24 (c-series)

2 (n = 3, a-series) → **21**
6 (n = 3, c-series) → **22**
3 (n = 4, a-series) → **23**
7 (n = 4, c-series) → **24**

21 (a-series)
22 (c-series)

The same general sequence of transformations used to determine the de of the cyclopropyl esters **11a-c** (*i.e.*, conversion of cyclic ester to alcohol to Mosher's ester), was planned for use with the cyclopentyl esters **21** and **22** and cyclohexyl esters **23** and **24**. However, problems encountered with the reduction of these cyclic esters to the corresponding alcohols have not rendered this possible. Therefore, in the case of the cyclic menthyl esters **21** and **23**, the de reported was based on the relative ratios of each diastereomer as determined by ^{1}H NMR (500 MHz) spectroscopy and gas chromatography, whereas the de for the sulfonamide cyclic esters **22** and **24** was determined by ^{1}H NMR (500 MHz) spectroscopy (satisfactory GC traces could not be obtained from these sulfonamide cyclic esters).





21 (m = 1)
23 (m = 2)

22 (R = cyclohexyl, m = 1)
24 (R = cyclohexyl, m = 2)

The results obtained from the MIRC reaction of compounds **2**, **3**, **6** and **7** are summarized in Table 4. Addition of menthyl bromoester **2** and sulfonamide bromoester **6** to a solution of LDA/THF at approximately -68 to -72 °C, afforded the corresponding cyclopentyl esters **21** and **22** in yields of 83-93% and 71-74% respectively. In addition to the cyclopentyl esters **21** and **22**, one other product was consistently formed in

Table 4. Results from the MIRC reaction of compounds **2**, **3**, **6**, and **7**. Note equation 6.

entry	compound (series, n)	product (temp, °C)	yield (%)	% de by ^{1}H NMR analysis	% de by GC analysis
1	**2** (a, 3)	**21** (-68 to -72)	83-93[a]	34-38 (33:67-31:69)	34.8-38.2
2	**2** (a, 3)	**21** (-68 to -72)	92-94[b]	34 (33:67)	35.7
3	**3** (a, 4)	**23** (0)	63-65[b]	18 (41:59)	17.4-17.5
4	**3** (a, 4)	**26** (-68 to -72)	29-38[b] (51-69)[c]	16-18 (42:58-41:59)	—
5	**6** (c, 3)	**22** (-68 to -72)	71-74[a]	50-52 (25:75-24:76)	—
6	**6** (c, 3)	**22** (-68 to -72)	62-64[b]	60-62 (20:80-19:81)	—
7	**7** (c, 4)	**24** (-68 to -72, then 0, then ambient)	70-78[b]	*ca.* 95	—
8	**7** (c, 4)	**25** (-68 to -72)	91-97[b]	*ca.* 95	—

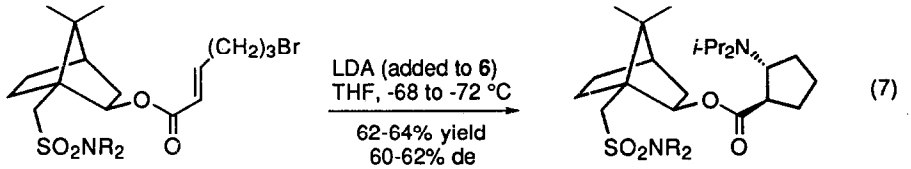
(a) Addition of substrate to LDA. (b) Addition of LDA to substrate. (c) Yield based on recovered substrate.

the MIRC reaction, but remains both unidentified and inseparable (by silica gel column chromatography) from the major cyclic products. Therefore, it is important to note that the yields reported are not for pure cyclopentyl esters only, but include this unidentified compound.

The conversion of bromoesters **2** and **6** to the corresponding *five-membered* cyclic esters **21** and **22** appeared to occur immediately, even at low temperatures. By TLC, the reaction appeared complete once all of the bromoester had been added. A higher de (50-52%) was observed using the sulfonamide bromoester **6** rather than the menthyl bromoester **2**; the latter afforded an approximately 34-38% de as determined by ^{1}H NMR spectroscopy and gas chromatography.

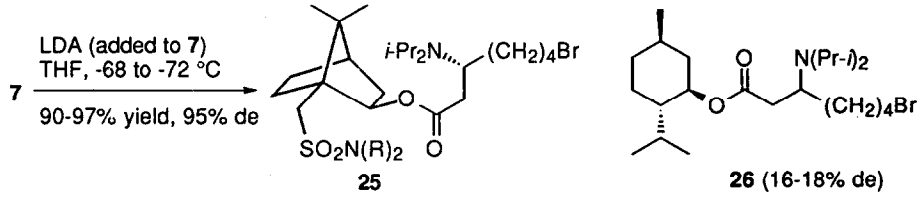
Since the cyclopentyl esters **21** and **22** contain acidic methine protons, and the order of addition employed (substrate to LDA) meant that LDA was always present in excess, there was a possibility that isomerization contributed to the observed de values; none of the cis-diastereomer was observed. Therefore,

reactions involving the *inverse order of addition, i.e.*, LDA to substrate, were also conducted. Note entries 2 and 6 of Table 4. The de obtained for the menthyl cyclopentyl ester **21** appears to be independent of the mode of addition of substrate and nucleophile (compare entries 1 and 2), whereas *the sulfonamide ester* **22** *displayed a 10% increase in de when the latter mode of addition was employed* (compare entry 5 with 6).



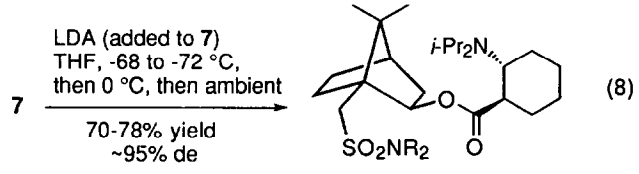
6 (R = cyclohexyl) **22**

Bromoesters **3** and **7** did not cyclize to the corresponding *cyclohexyl* esters **23** and **24** to an appreciable extent at -68 to -72 °C (addition of LDA to substrate, 2.5 h; additional reaction time, *ca.* 1.8 h). The ^{1}H NMR (500 MHz) spectrum of the product mixture isolated from the MIRC reaction of the sulfonamide bromoester **7**, revealed that approximately 3-10% of the mixture was due to the cyclized product **24**, and the other 90-97% was due to the β-adduct **25** (*ca.* 95% de). The MIRC reaction of menthyl bromoester **3** at this temperature resulted in isolation of only the β-adduct **26**, in 16-18% de. As expected, these results indicate that cyclization to form the six-membered ring is slower than that leading to the five.[14]



25 **26** (16-18% de)

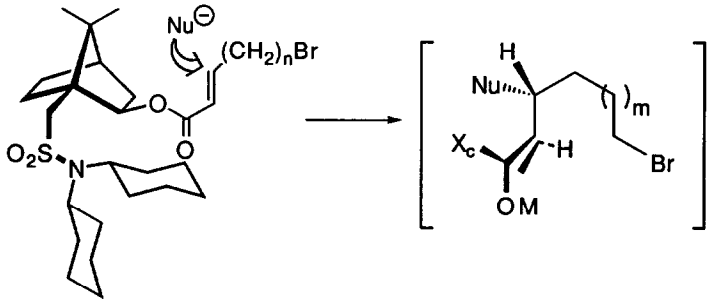
However, when the reaction mixture was allowed to reach approximately 0 °C for the menthyl bromoester **3** and ambient temperature for the sulfonamide bromoester **7**, cyclization was readily achieved. *The menthyl cyclohexyl ester* **23** *was obtained in 63-65% yield with a de of approximately 18%* (entry 3, Table



24

4), *whereas the sulfonamide cyclohexyl ester* **24** *was secured in 70-78% yield and approximately 95% de* (entry 7). It is interesting to note that the degree of asymmetric induction observed for the β-adducts **26** and **25** compares very closely with that obtained for the cyclohexyl esters **23** and **24**, respectively. This further supports the idea that the initial addition of the nucleophile to the *s-cis* or *s-trans* conformers of the substrate is a crucial factor in determining the level of asymmetric induction observed.[14]

Finally, it should be noted that we have not determined the absolute configuration for any of the MIRC adducts. However, we speculate, particularly for the c-series substrates, that conjugate addition occurs in accord with the Oppolzer model.[6,7] That is, the s-trans conformation of the starting material is assumed to be preferred so that attack of the nucleophile occurs preferentially from the *re*-face at the β-carbon.



CONCLUDING COMMENTS

This study has shown that three-membered rings can be prepared in 50-56% de, while five- and six-membered rings can be prepared in 60-62% de and approximately 95% de respectively, by employing the MIRC strategy. The most effective of the chiral auxiliaries examined was that derived from 10-dicyclohexylsulfamoyl-D-isoborneol.[6,7]

With regard to the three-membered rings, primary interest stems from the observation that different diastereomers are favored with a change in temperature. The factors which contribute to this result are not well understood. However, it was proposed that the ratio of *s-cis* and *s-trans* conformers of the substrate contribute significantly to the level of asymmetric induction achieved.

In the case of the six-membered rings, the rate of ring closure is slow relative to the three- and five-membered rings, allowing a greater amount of time for the equilibration of the Michael enolates and the substrate. When 10-dicyclohexylsulfamoyl-D-isoborneol was used as the chiral auxiliary, this equilibration was thought to perturb the balance of the initially formed enolates derived from the *s-cis* and the *s-trans* conformers of the substrate, in favor of one enolate, resulting in a higher de.

EXPERIMENTAL SECTION

Chemical shifts for ^{13}C NMR are reported in ppm relative to the central line of $CDCl_3$ (77.0 ppm). Fluorine-19 nuclear magnetic resonance (^{19}F NMR) spectra were recorded at 470.5 MHz; sweep width 70,572 Hz. Mass spectra were recorded using a ZAB 2F or VG 70-250 HF spectrometer. LRMS and HRMS refer to low and high resolution mass spectroscopy. Data are reported as the mass to charge (m/z) ratio of the observed fragment ion, and M refers to the molecular ion. IR bands which are deemed diagnostic for the functional groups present in the molecule are listed. Melting points are uncorrected.

(-)-Menthol [$[\alpha]^{20}_D$ -50° (*c* 10, C_2H_5OH)], (-)-8-phenylmenthol [$[\alpha]^{20}_D$ -26° (*c* 2, C_2H_5OH)], (+)-10-camphorsulfonyl chloride [$[\alpha]^{22}_D$ +33° (*c* 1, $CHCl_3$)], 10-dicyclohexylsulfamoyl-D-isoborneol [$[\alpha]^{20}_D$ -25° (*c*

0.76, C_2H_5OH)], (*S*)-(-)-α-methoxy-α-(trifluoromethyl)phenylacetic acid [$[\alpha]^{18}_D$ -72° (*c* 1.6, CH_3OH)] and all other chemicals [except diisobutylaluminium hydride (Alfa), triethylphosphite and silver cyanide (Mallinckrodt)] were purchased from Aldrich. Benzene, tetrahydrofuran and diethyl ether were distilled from sodium/benzophenone, and acetonitrile, methylene chloride, dimethylformamide and diisopropylamine distilled from calcium hydride immediately prior to use. HPLC grade or distilled reagent grade solvents were used for high performance liquid chromatography. Reagent grade solvents were used without purification for all other purposes. The petroleum ether (PE) used is the 30-60 °C boiling fraction. All reactions were conducted under a nitrogen atmosphere, and monitored by TLC. Note that compounds **8** (crotonic acid), **9**,[15] **10**,[19] **12**,[3,4] and **14**[17]are known materials, while **19** and **20** refer to enolates pictured in Figure 2.

(-)-Menthyl (*E*)-4-Bromobut-2-enoate (1). A solution of the known[15] (-)-menthyl 2-bromoacetate (5.5 g, 24.5 mmol), NBS (4.8 g, 26.9 mmol, 1.1 equiv), AIBN (37 mg, 0.23 mmol, 0.01 equiv) and CCl_4 (50 mL) was refluxed for 2 h. The reaction mixture was then filtered to remove the solid succinimide and the filtrate concentrated *in vacuo*. Chromatography of the crude product on silica gel (ICN) in a 3 cm x 34 cm column, using 1:9 ether/PE as the eluting solvent [TLC: Rf = 0.5; UV and *p*-anisaldehyde (stains blue) active], yielded 5.8 g (78%) of the product as a clear pale yellow liquid, $[\alpha]^{24}$ -40.18° (*c* 5.3, ether); ^{1}H NMR (500 MHz) δ 6.89 (td, 1 H, *J* = 15.2, 7.4 Hz, vinyl β to ester), 6.01 (d, 1 H, *J* = 15.2 Hz, vinyl α to ester), 4.75 (dt, 1 H, *J* = 10.9, 4.4 Hz, menthyl methine adjacent to ester), 4.01 (d, 2 H, *J* = 7.4 Hz, C*H*$_2$Br), 2.05-0.85 (several m, 9 H, menthyl ring), 0.91 and 0.89 (2 d, 3 H and 3 H, *J* = 6.4 Hz and *J* = 6.8 Hz, menthyl isopropyl), 0.77 (d, 3 H, *J* = 7.0 Hz, menthyl methyl); IR (neat) 1705, 1645 cm^{-1}; HRMS (PCI), m/z 304, 303 (M + 1), 302 (M), 301, 300, 223, 221, 139, 138, 137 (base), 136, 135, 123, 121, 107, 95, 93, 83, 81; HRMS (PCI), m/z 300.0729 (calcd for $C_{14}H_{21}O_2Br$, M - 2, 300.0725).

(-)-Menthyl (*E*)-6-Bromohex-2-enoate (2). Diisobutylaluminium hydride (6.1 mL, 6.67 mmol, 1.2 equiv, 20% w/w in hexane) was added dropwise by syringe pump to a solution of 4-bromobutyronitrile (823 g, 5.56 mmol, 1 equiv) in benzene (5 mL), during a 45 min period. Stirring was continued for 1 h. The reaction mixture was then poured into 5% aqueous H_2SO_4 (100 mL) and stirred for 10 min. After ensuring that the solution was acidic, it was extracted with ether (4 x 35 mL). The combined ether extracts were dried over anhydrous $MgSO_4$, concentrated *in vacuo* to a volume of 20-25 mL and used directly in the next reaction [TLC: 1:1 ether/PE; R_f = 0.51; *p*-anisaldehyde (stains yellow-green) active.

The known[15] phosphonium bromide **9** (3.0 g, 5.56 mmol, 1 equiv) was added to a slurry of NaH (60% dispersion in mineral oil, 245 mg, 6.11 mmol, 1.1 equiv) in CH_3CN (10 mL). The mixture was stirred at ambient temperature for 3 h and the added dropwise to an ice-bath-cooled solution of 4-bromobutanal in CH_3CN (10 mL). The resulting solution was allowed to gradually warm to room temperature and stirred for a further 8 h. The reaction mixture was then poured into NaCl solution (50 mL) and extracted with ether (4 x 50 mL). The combined ether extracts were dried over anhydrous $MgSO_4$ and concentrated *in vacuo*. Chromatography of the crude product on silica gel (ICN) in a 3 cm x 34 cm column, using 1:9 ether /PE as the eluting solvent [TLC: R_f = 0.4, UV and *p*-anisaldehyde (stains blue) active], yielded 1.2 g (65%) of product **2** as a clear colorless liquid, $[\alpha]^{24}$ -52.77° (*c* 2.2, ether); ^{1}H NMR (500 MHz) δ 6.90 (td, 1 H, *J* = 15.5, 7.0 Hz, vinyl β to ester), 5.86 (td, 1 H, *J* = 15.5, 1.5 Hz, vinyl α to ester), 4.74 (dt, 1 H, *J* = 10.9, 4.4 Hz, menthyl methine proton adjacent to ester), 3.42 (t, 2 H, *J* = 6.8 Hz, BrC*H*$_2$), 2.37 (m, 2 H, C*H*$_2$CH=CHCO$_2$), 2.20 (quintet, 2 H, *J* = 6.8 Hz, BrCH$_2$C*H*$_2$), 2.02-0.85 (several m, 9 H, menthyl ring), 0.91 and 0.89 (2 d, 3 H and 3

H, J = 5.2 Hz and J = 5.6 Hz, menthyl isopropyl), 0.76 (d, 3 H, J = 6.9 Hz, menthyl methyl); IR (neat) 1710, 1650 cm^{-1}; LRMS (PCI), m/z 333, 331 (M + 1), 329, 177, 175, 140, 139 (base), 138, 137, 123, 113, 97, 95, 83, 81, 69, 57; HRMS (EI), m/z 174.9741 (calcd for C_6H_8OBr, M - O-menthyl, 174.9758).

(-)-Menthyl (*E*)-7-Bromohept-2-enoate (3). The same procedure (*in all cases, this phrase refers to temperatures, times, quantities*) as that described in the preparation of **2** was used with the following variations: 5-bromovaleronitrile (901 mg, 5.56 mmol, 1 equiv). TLC (bromoaldehyde): 1:1 ether/PE; R_f = 0.6; *p*-anisaldehyde (stains yellow-green) active.

TLC: R_f (*cis*-**3**) = 0.55, R_f (*trans*-**3**) = 0.39; UV and *p*-anisaldehyde (stains dark blue) active], yielded 1.9 mg (1%) of the *cis* isomer and 1.17 g (61%) of the *trans* isomer as clear colorless liquids; *trans* Isomer — $[\alpha]^{24}$ -54.18° (*c* 3.2, ether): ^1H NMR (500 MHz) δ 6.92 (td, 1 H, J = 15.7, 7.0 Hz, vinyl β to ester), 5.82 (d, 1 H, J = 15.7 Hz, vinyl α to ester), 4.74 (dt, 1 H, J = 10.9, 4.4 Hz, menthyl methine adjacent to ester), 3.41 (t, 2 H, J = 6.6 Hz, BrCH_2), 2.23 (m, 2 H, CH_2CH=CHCO$_2$), 1.87 and 1.63 (2 m, overlapping with menthyl ring protons, 2 H and 2 H, BrCH$_2$CH_2CH_2), 2.01-0.85 (several m, 9 H, menthyl ring), 0.91 and 0.89 (2 d, 3 H and 3 H, J = 4.5 Hz, and J = 5.2 Hz, menthyl isopropyl), 0.76 (d, 3 H, J = 6.8 Hz, menthyl methyl); IR (neat) 1710, 1650 cm^{-1}; HRMS (EI), m/z 191, 189 (M - O-Menthyl), 139, 138 (base), 123, 96, 95, 83, 82, 81, 69, 67, 55, 43; HRMS (EI), m/z 188.9892 (calcd for $C_7H_{10}OBr$, M - O-menthyl, 188.9915).

cis Isomer: ^1H NMR (500 MHz) δ 6.17 (td, 1 H, J = 11.5, 7.5 Hz, vinyl β to ester), 5.78 (td, 1 H, J = 11.5, 1.5 Hz, vinyl α to ester), 4.72 (dt, 1 H, J = 10.9, 4.4 Hz, menthyl methine adjacent to ester), 3.43 (t, 2 H, J = 6.8 Hz, BrCH_2), 2.69 (m, 2 H, CH_2CH=CHCO$_2$), 1.89 and 1.61 (2 m overlapping with menthyl ring protons, 2 H and 2 H, BrCH$_2$CH_2CH_2), 2.02-0.85 (several m, 9 H, menthyl ring), 0.91 and 0.89 (2 d, 3 H and 3 H, J = 6.7 Hz and J = 7.1 Hz, menthyl isopropyl), 0.77 (d, 3 H, J = 6.9 Hz, menthyl methyl); IR (neat) 1710, 1640, 985, 920, 820 cm^{-1}; HRMS (EI), m/z 191, 189 (M - O-Menthyl), 139, 138 (base), 123, 97, 96, 95, 83, 82, 81, 69, 67 57, 55, 53, 43; HRMS (EI), m/z 188.9928 (calcd for $C_7H_{10}OBr$, M - O-menthyl, 188.9915).

(-)-8-Phenylmenthyl (*E*)-4-Bromobut-2-enoate (4). A solution of (-)-8-phenylmenthyl (*E*)-but-2-enoate, prepared as described in the literature[16] (900 mg, 3.0 mmol), NBS (533 mg, 3.0 mmol), AIBN (5.0 mg, 0.03 mmol, 0.01 equiv) and CCl_4 (15 mL) was refluxed for 45 min. [When an excess of NBS was used, or when the reflux conditions were too vigorous, the gem-dibrominated product was also formed]. The reaction mixture was filtered to remove the solid succinimide and the filtrate concentrated *in vacuo*. The crude product was chromatographed on silica gel (ICN) in a 3 cm x 34 cm column, using 1:9 ether/PE as the eluting solvent [TLC: R_f = 0.36; UV and *p*-anisaldehyde (stains blue) active], to afford 790 mg (70%) of the required product **4** as a viscous clear colorless liquid, $[\alpha]^{24}$ +4.95° (*c* 3.8, ether); Compound **4**: ^1H NMR (500 MHz) δ 7.17 (m, 5 H, phenyl), 6.41 (td, 1 H, J = 15.2, 7.5 Hz, vinyl β to ester), 5.37 (d, 1 H, J =15.2 Hz, vinyl α to ester), 4.84 (dt, 1 H, J = 10.8, 4.4 Hz, menthyl methine adjacent to ester), 3.83 (d, 2 H, J = 7.7 Hz, CH_2Br), 2.10-0.85 (several m, 8 H, menthyl ring), 1.29 and 1.20 (2 s, 3 H and 3 H, menthyl isopropyl), 0.85 (d, 3 H, J = 6.6 Hz, menthyl methyl); IR (neat) 3050, 3010, 1705, 1655, 1600, 970, 780, 760, 695 cm^{-1}; LRMS (PCI), m/z 381, 379 (M + 1), 281, 216, 215, 214, 213, 159, 145, 137, 133, 120, 119 (base), 118, 109, 106, 105, 95, 91, 81, 69. This material, being a simple relative of the menthyl ester **3**, was analyzed as the latter.

10-Dicyclohexyl sulfamoyl-D-isobornyl (*E*)-4-Bromobut-2-enoate (5). A solution of the known[17] ester **14** (300 mg, 0.64 mmol), NBS (172 mg, 0.97 mmol, 1.5 equiv), AIBN (1 mg, 0.006 mmol, 0.01 equiv)

and CCl_4 (10 mL) was refluxed for 4 h. The solid succinimide was removed by filtration and the filtrate concentrated *in vacuo*. Chromatography of the crude product on silica gel (ICN) in a 3 cm x 34 cm column, using 3:7 ether/PE as the eluting solvent [TLC: R_f = 0.36; UV and *p*-anisaldehyde (stains green-blue) active], yielded 200 mg (57%) of the product as a white solid, mp 138-144 °C and $[\alpha]^{24}$ -36.40° (*c* 0.5, ether); ^{1}H NMR (500 MHz) δ 7.0 (td, 1 H, *J* = 15.2, 7.3 Hz, vinyl β to ester), 6.02 (d, 1 H, *J* = 15.2 Hz, vinyl α to ester), 5.10 (dd, 1 H, *J* = 7.9, 3.0 Hz, isobornyl methine adjacent to ester), 3.99 (dd, 2 H, *J* = 7.3, 0.9 Hz, CH_2Br), 3.24 and 2.69 (2 d, 1 H and 1 H, *J* = 13.3 Hz and *J* = 13.3 Hz, CH_2SO_2), 3.21-1.02 (several m, 7 H, isobornyl ring and 22 H, cyclohexyl rings), 1.00 and 0.89 (2 s, 3 H and 3 H, isobornyl *gem* methyls); IR (KBr) 1710, 1650, 995, 890, 850, 825, 715 cm^{-1}, LRMS (PCI), m/z 465 [(M + 1) - Br], 380, 315, 298, 259, 246, 244, 228, 182, 181, 180, 179, 178, 146, 138, 137, 136, 135 (base), 121, 109, 107; HRMS (PCI), m/z 465.2918 (calcd for $C_{26}H_{43}NO_4S$, (M + 1) - Br, 465.2915).

10-Dicyclohexylsulfamoyl-D-isobornyl (*E*)-6-Bromohex-2-enoate (6) and 10-Dicyclohexylsulfamoyl-D-isobornyl (*E*)-3-Cyclopropylprop-2-enoate.[18] The known[19] phosphonate ester **10** (600 mg, 1.04 mmol) and DBU (0.16 mL, 1.04 mmol) were added to a solution of anhydrous LiCl (44 mg, 1.04 mmol) in dry CH_3CN (10 mL). This mixture was added dropwise to an ice-bath-cooled solution solution of 4-bromobutanal (157 mg, 1.04 mmol) in CH_3CN (5 mL). Stirring was continued at approximately 0 °C for 2 h. The reaction mixture was then poured into 10% aqueous HCl solution (50 mL) and extracted with ether (4 x 30 mL). The combined ether extracts were dried over anhydrous $MgSO_4$ and concentrated *in vacuo*. Chromatography of the crude product on silica gel (ICN) in a 3 cm x 34 cm column using 3:7 ether/PE as the eluting solvent [TLC: R_f (bromoester **6**) = 0.24 and R_f (cyclopropyl ester 10-dicyclohexylsulfamoyl-D-isobornyl (*E*)-3-cyclopropylprop-2-enoate) = 0.26; UV and *p*-anisaldehyde (stains green-blue) active], yielded 300 mg (50%) of the required bromoester **6** and 200 mg (39%) of the cyclopropyl ester as white solids; bromoester **6** — mp 197-199 °C and $[\alpha]^{24}$ -30.60 ° (*c* 0.5, ether): ^{1}H NMR (500 MHz) δ 6.92 (td, 1 H, *J* = 15.6, 7.0 Hz, vinyl β to ester), 5.82 (td, 1 H, *J* = 15.6, 1.3 Hz, vinyl α to ester), 5.06 (dd, 1 H, *J* = 7.9, 3.1 Hz, isobornyl methine adjacent to ester), 3.41 (t, 2 H, *J* = 6.5 Hz, CH_2Br), 3.27 and 2.68 (2 d, 1 H and 1 H, *J* = 13.3 Hz, CH_2SO_2), 3.21-1.02 (several m, 7 H, isobornyl ring), 2.35 (m, 2 H, CH_2CH=CHCO$_2$), 1.98 (m, 4 H, CH_2CH_2CH$_2$Br), 1.00 and 0.89 (2 s, 3 H and 3 H, isobornyl *gem* methyls); IR (solid film) 3010, 3000, 2880, 1715, 1650, 980, 910, 855, 775, 735 cm^{-1}; LRMS (PCI), m/z 573, 572, 571 (M), 381, 380, 298, 246, 244, 228, 181, 180, 179, 175, 138, 136, 135 (base), 107, 98, 97, 95, 93, 83, 81, 69, 67, 65; HRMS (PCI), m/z 571.2307 (calcd for $C_{28}H_{46}O_4BrNS$, M, 571.2331).

Cyclopropyl ester — mp 178-179 °C and $[\alpha]^{25}$ -35.8 ° (*c* 1.0, ether): ^{1}H NMR (500 MHz) δ 6.41 (dd, 1 H, *J* = 15.4, 10.1 Hz, vinyl β to ester), 5.86 (d, 1 H, *J* = 15.4 Hz, vinyl α to ester), 5.06 (dd, 1 H, *J* = 7.9, 3.3 Hz, isobornyl methine adjacent to ester), 3.27 and 2.68 (2 d, 1 H and 1 H, *J* = 13.3 Hz, CH_2SO_2), 3.23-1.08 (several m, 7 H, isobornyl ring), 1.75-1.60 (m overlapping with isobornyl ring protons, 1 H, C*H*CH=CHCO$_2$, cyclopropyl ring), 0.99 and 0.89 (2 s, 3 H and 3 H, isobornyl gem methyls), 0.88 9m, 2 H, cyclopropyl methylene), 0.62 (m, 2 H, cyclopropyl methylene); IR (KBr) 1720, 1650, 975, 895, 855, 775 cm^{-1}; LRMS (PCI), m/z 492 (M + 1), 491, 381, 380, 298, 246, 228, 182, 181, 180, 179, 138, 136, 113, 107, 98, 95 (base), 93, 83, 81, 79, 69, 67, 65; HRMS (EI), m/z 491.3059 (calcd for $C_{28}H_{45}ONBrS$, M, 491.3070).

10-Dicyclohexylsulfamoyl-D-isobornyl (*E*)-7-Bromohept-2-enoate (7).[18,19] The same procedure as that described in the preparation of **6** was used with the following variations: 2.0 g, 3.47 mmol of **10**; DBU

(0.52 mL, 3.47 mmol); anhydrous LiCl (147 mg, 3.47 mmol) in dry CH_3CN (35 mL). 5-Bromopentanal (573 mg, 3.46 mmol) was then introduced dropwise and the mixture stirred for 3 h. The reaction mixture was then poured into NaCl solution (50 mL) and extracted with ether (4 x 50 mL). The combined ether extracts were dried over anhydrous $MgSO_4$ and concentrated *in vacuo*. Chromatography of the crude product on silica gel (ICN) in a 3 cm x 34 cm column, using 1:1 ether /PE as the eluting solvent [TLC: R_f = 0.58; UV and *p*-anisaldehyde (stains green-blue) active], afforded 1.72 g (85%) of the required bromoester **7** as a white solid, mp 169-171 °C and $[\alpha]^{25}$ -40.13° (*c* 0.75, ether); ^{1}H NMR (500 MHz) δ 6.94 (td, 1 H, *J* = 15.6, 6.9 Hz, vinyl β to ester), 5.82 (td, 1 H, *J* = 15.6, 1.3 Hz, vinyl α to ester), 5.07 (dd, 1 H, *J* = 7.7, 3.1 Hz, isobornyl methine adjacent to ester), 3.41 (t, 2 H, *J* = 6.6 Hz, C*H*$_2$Br), 3.27 and 2.68 (2 d, 1 H and 1 H, *J* = 13.3 Hz, C*H*$_2$SO$_2$), 3.22-1.08 (several m, 7 H, isobornyl ring), 2.21 (m, 2 H, C*H*$_2$CH=CHCO$_2$), 1.88 and 1.61 (2 m, 2 H and 2 H, C*H*$_2$C*H*$_2$CH$_2$Br), 1.00 and 0.89 (2 s, 3 H and 3 H, isobornyl gem methyls); IR (KBr) 1720, 1650, 1450, 1400, 1320, 1255, 1170, 1145, 1110, 1050, 1030, 985, 890, 855, 825, 775 cm^{-1}; HRMS (EI), m/z 587, 585 (M), 298, 290, 244, 191, 189 (base), 181, 180, 179, 145, 138, 136, 135, 107, 98, 93, 91, 83, 82, 81, 79, 69, 68, 67, 56, 55, 44, 43; HRMS (EI), m/z 585.2499 (calcd for $C_{29}H_{48}O_4NBrS$, M, 585.2489).

(-)-Menthyl 2-[(1,1-Dimethylethyl)thio]cyclopropanecarboxylate (11a).[2-4] Lithium *t*-butylthiolate was prepared by adding *t*-butylthiol (0.37 mL, 3.3 mmol) to *n*-BuLi (2.1 mL, 3.3 mmol, 1.6 M in hexanes), at approximately 0 °C. Stirring was continued for 20 min, followed by addition of THF (2 mL).

Lithium *t*-butylthiolate (2.5 ml, 3.3 mmol) in THF (2 mL) was added dropwise over 20 min by syringe pump, to an ice-bath-cooled solution of the menthyl bromoester **1** (900 mg, 3.0 mmol) in THF (7.5 mL). [TLC analysis of the reaction mixture indicated that only a small quantity of starting material remained]. The reaction mixture was allowed to gradually warm to room temperature and stirred overnight. The mixture was then poured into water and extracted with ether (5 x 50 mL). The combined ether extracts were dried over anhydrous $MgSO_4$ and concentrated *in vacuo*. Chromatography of the crude product on silica gel (ICN) in a 3 cm x 34 cm column, using 1:9 ether/PE as the eluting solvent [TLC: R_f = 0.55; not UV active, *p*-anisaldehyde (stains blue) active], afforded 560 mg (60%) of the product **11a** as a pale yellow viscous liquid, $[\alpha]^{24}$ -30.25° (*c* 3.6, ether); ^{1}H NMR (500 MHz) δ 4.69 (dt for each diastereomer, 1 H and 1 H, *J* = 10.9, 1.4 Hz and *J* = 10.9, 1.4 Hz, menthyl methine adjacent to ester), 2.36 (ddd, 1 H, *J* = 11.9, 5.9, 3.1 Hz, C*H*S cyclopropyl ring). 2.01-0,82 (several m, 3H, cyclopropyl ring and 9 H, menthyl ring), 1.36 (s, 9 H, *t*-butyl, 0.91 and 0.89 (2 d, 3 H and 3 H, *J* = 6.4 Hz and *J* = 6.7 Hz, menthyl isopropyl), 0.77 and 0.75 (d, for each diastereomer, 3 H and 3 H, *J* = 3.7 Hz and *J* = 3.7 Hz, menthyl methyl); IR (neat) 1715, 1260, 1200, 1170, 1095, 1080, 1025, 980, 905, 840, 780, 765 cm^{-1}; LRMS (PCI), m/z 313 (M + 1), 311. 257, 255, 177, 176, 175 (base), 174, 139, 138, 137, 119, 118, 101, 83, 81; HRMS (PCI), m/z 313.2181 (calcd for $C_{18}H_{33}O_2S$, M + 1, 313.2202).

(-)-8-Phenylmenthyl 2-[(1,1-Dimethylethyl)thio]cyclopropanecarboxylate (11b).[2,3] The procedure was the same as that described above for **11a** with the following variations: lithium *t*-butylthiolate (1.7 mL, 2.3 mmol) in THF (1.5 mL); bromoester **4** (790 mg, 2.1 mmol) in THF (5 mL). TLC: R_f = 0.47; UV and *p*-anisaldehyde (stains blue) active; 630 mg (78%) of the product as a viscous pale yellow liquid, $[\alpha]^{24}$ -46.31° (*c* 0.95, ether); ^{1}H NMR (500 MHz) δ (m, 5 H, phenyl), 4.81 (dt, 1 H, *J* = 10.7, 4.3 Hz, menthyl methine proton adjacent to ester), 2.27 (ddd, 1 H, *J* = 8.3, 5.7, 4.0 Hz, C*H*S cyclopropyl ring), 2.01-0.80 (several m, 3 H, cyclopropyl ring and 8 H, menthyl ring), 1.35 (s, 9 H, *t*-butyl), 1.33 and 1.24 (2 s, 3 H and 3 H, menthyl isopropyl), 0.85 (d, 3 H, *J* = 6.5, menthyl methyl); IR (neat) 3090, 3060, 3010, 2960, 2930, 2865, 1715, 1600,

1285, 1260, 1200, 1175, 1160, 1130, 1090, 1025, 980, 910, 840, 760, 695 cm^{-1}; LRMS (EI), m/z 388 (M), 215, 214, 174, 120, 119, 118, 106, 105 (base), 101, 100, 95, 91, 83, 81, 79, 77, 69, 57, 55; HRMS (EI), m/z 388.2422 (calcd for $C_{24}H_{36}O_2S$, M, 388.2437).

10-Dicyclohexylsulfamoyl-D-isobornyl 2-[(1,1-Dimethylethyl)thio]cyclopropanecarboxylate (11c).[2-4] The procedure was the same as that described above for **11a** with the following variations: lithium *t*-butylthiolate (0.4 mL, 0.51 mmol, 1.1 equiv) in THF (0.5 mL); bromoester **5** (250 mg, 0.46 mmol) in THF (1 mL). The mixture was poured into water (20 mL) and extracted with ether (3 x 25 mL). Chromatography of the crude product on silica gel (ICN) in a 3 cm x 30 cm column, using 3:7 ether/PE as the eluting solvent [TLC: R_f = 0.44; not UV active, p-anisaldehyde (stains green-blue) active], yielded 200 mg (79%) of the required product as a white solid. This reaction was repeated at temperatures of 4 to 8 °C (reaction time ca. 1.5 h), -35 to -41 °C (reaction time ca. 2 h), -68 to -72 °C (reaction time ca. 4-5 h) and -93 to -97 °C (reaction time ca. 8-9 h); the reaction mixture was maintained at these temperatures for the duration of the reaction. These compounds could not be completely purified by silica gel chromatography and were therefore carried through to the next reaction and purified as the corresponding alcohol **12**; ^{1}H NMR (500 MHz) δ 4.97 (dd, 1 H, *J* = 7.9, 3.1 Hz, isobornyl methine adjacent to ester), 3.29 and 2.69 (2 d, 1 H and 1 H, *J* = 13.3 Hz, CH_2SO_2), 3.24-1.00 (several m, 3 H, cyclopropyl ring, 7 H, isobornyl ring and 22 H, cyclohexyl rings), 2.39 (m, 1 H, *J* = 3.7, CHS cyclopropyl ring), 1.36 (s, 9 H, *t*-butyl), 0.99 and 0.88 (2 s, 3 H and 3 H, isobornyl *gem* methyls).

2-[(1,1-Dimethylethyl)thio]cyclopropylmethanol (12). The following procedure is representative of the conversion of the cyclopropyl esters **11a-c** to the known cyclopropyl alcohol **12**.[3,4] Typically, 100-300 mg of each ester was used, and yields were in the range 53-86%.

The cyclopropyl ester **11** (120 mg, 0.38 mmol) in THF (1 mL) was added to an ice-bath-cooled slurry of $LiAlH_4$ (14.5 mg, 0.38 mmol) in THF (1 mL). The cooling bath was removed and the mixture stirred at ambient temperature for 1-2 h. (The reaction mixture may also be refluxed. This shortens the reaction time, but also results in loss of the slightly volatile alcohol **12** when dealing with small quantities). Water (10 mL) was then cautiously added to the cooled reaction mixture, followed by filtration and extraction of the filtrate with ethyl acetate (3 x 50 mL). The combined ethyl acetate extracts were dried over anhydrous $MgSO_4$ and concentrated *in vacuo*. Chromatography of the crude product on silica gel (INC) in a 3 cm x 34 cm column, using 1:1 ether /PE as the eluting solvent [TLC: R_f = 0.29; not UV active, *p*-anisaldehyde (stains yellow-brown) active], yielded 50 mg (82%) of the alcohol **12** as a pale yellow liquid.

The data which follows is presented in the order: temperature range, trial number, ester compound number, yield of alcohol **12** (%), optical rotation ($[\alpha]^{24}$ °C) for alcohol **12** at specified concentration. *0 °C to ambient*: **11a**, 82, -0.17° (*c* 2.3, ether); *0 °C to ambient*: **11b**, 80, -0.25° (*c* 2.0, ether); *0 °C to ambient*: **11c**, 86, -0.29° (*c* 3.0, ether). *4 to 8 °C*: trial 1, **11c**, 53, -1.79° (*c* 0.95, ether); trial 2, **11c**, 60, -1.88° (*c* 0.9, ether). *-35 to -41 °C*: trial 1, **11c**, 59, -1.60° (*c* 1.5, ether); trial 2, **11c**, 57, -1.55° (*c* 2.0, ether). *-68 to -72 °C*: trial 1, **11c**, 75, +5.99° (*c* 0.3, ether); trial 2, **11c**, 62, +5.67° (*c* 0.3, ether).

2-[(1,1-Dimethylethyl)thio]cyclopropylmethyl (*S*)-(-)-α-Methoxy-α-(trifluoro-methyl)phenyl acetate (13). The following procedure is representative of the conversion of the cyclopropane alcohols **12** to the Mosher's ester **13**.[8] Typically, 10-30 mg of each alcohol was used and yields ranged from 74-96%. The alcohol **12** (30 mg, 0.019 mmol) in CH_2Cl_2 (0.5 mL) was added to a solution of (*S*)-α-methoxy-α-

(trifluoromethyl)phenylacetic acid (Mosher's acid, 48 mg, 0.21 mmol, 1.1 equiv), and DMAP (4.6 mg, 0.37 mmol, 0.2 equiv) in CH_2Cl_2 (1 mL). The mixture was cooled to approximately 0 °C in an ice-bath and DCC (58 mg, 0.28 mmol, 1.5 equiv) was added. Stirring was continued for 3-4 h at ambient temperature. The reaction mixture was then filtered to remove the dicyclohexylurea and the filtrate concentrated *in vacuo*. The resulting viscous liquid was diluted with ether and washed with 5% aqueous HCl solution (2 x 20 mL) and water (1 x 30 mL). The ether layer was dried over anhydrous $MgSO_4$ and concentrated *in vacuo*. Chromatography of the crude product on silica gel (ICN) in a 3 cm x 34 cm column, using 1:9 ether/PE as the eluting solvent [TLC: $R_f = 0.44$; UV and *p*-anisaldehyde (stains yellow-brown) active], afforded 64 mg (91%) of product **13** as a pale yellow liquid; ^{1}H NMR (500 MHz) δ 7.46 (m, 5 H, phenyl), 4.35, 4.13 and 4.29, 4.22 (2-dd for each diastereomer, 2 H and 2 H, J = 11.5, 7.9 Hz and J = 11.5, 7.5 Hz, C*H*$_2$O), 3.57 and 3.56 (s for each diastereomer, 3 H, OC*H*$_3$), 1.83 (m, 1 H, C*H*S), 1.36 (m, 1 H, C*H*CH$_2$O), 1.31 and 1.29 (s for each diastereomer, 9 H, *t*-butyl), 0.91 and 0.83 (m, 1 H and 1 H, cyclopropyl ring methylene); IR (neat) 3070, 2950, 2895, 2880, 1745, 1450, 1360, 1260, 1165, 1130, 1075, 1020, 995, 765, 715, 695 cm^{-1}; LRMS (PCI), m/z 377 (M + 1), 189, 145, 144, 143 (base), 142, 109, 87; HRMS (PCI), m/z 376.1348 (calcd for $C_{18}H_{23}O_3F_3S$, M, 376.1321).

10-Dicyclohexylsulfamoyl-D-isobornyl 3-[(1,1-dimethylethyl)thio]butanoate (15). Lithium *t*-butylthiolate (0.75 mL, 1.0 mmol, 1.1 equiv) in THF was added dropwise over 20 min by syringe pump, to an ice-bath-cooled solution (4 to 8 °C) of the ester **14** (425 mg, 0.91 mmol) in THF (2 mL). The reaction mixture was stirred at 4 to 8 °C for 10 min, poured into cold saturated NaCl solution (50 mL) and extracted with ether (3 x 35 mL). The combined ether extracts were dried over anhydrous $MgSO_4$ and concentrated *in vacuo*. The crude product was chromatographed on silica del (ICN) in a 3 cm x 34 cm column, using 3:7 ether /PE as the eluting solvent [TLC: $R_f = 0.47$; not UV active, *p*-anisaldehyde (stains green-blue) active], to yield 500 mg (98%) of the product as a white solid. This reaction was repeated at temperatures of 67 °C (refluxing THF, reaction time ca. 5 min), -35 to -41°C (reaction time ca. 1.5 h) and -68 to -72 °C (reaction time 1-3 h); the reaction mixture was maintained at these temperatures for the duration of the experiment.

The following data is presented in the order: temperature range, trial number, yield (%), optical rotation ([α]^{24} °C) for ester **15** at specified concentration. *67 °C*: 98, -21.8°, (*c* 2.0, ether). *4 to 8 °C:* trial 1, 98, -23.35° (*c* 2.0, ether); trial 2, 89, -27.24° (*c* 2.0, ether). *-35 to -41 °C*: trial 1, 94, -20.63° (*c* 2.2, ether); trial 2, 88 -20.63° (*c* 2.2, ether). *-68 to -72 °C:* trial 1, 98, +5.90° (*c* 2.0, ether); trial 2, 97, +5.70° (*c* 2.0, ether).

^{1}H NMR (500 MHz) δ 4.94 (dd, 1 H, J = 7.8, 3.0 Hz, isobornyl methine adjacent to ester), 3.24 and 2.67 (2 d, 1 H and 1 H, J = 13.3 Hz, C*H*$_2$SO$_2$), 3.24 (m, 1 H, C*H*S), 3.29-1.08 (several m, 7 H, isobornyl ring and 22 H, cyclohexyl rings), 2.72 and 2.38 (2 dd, 1 H and 1 H, J = 15.4, 4.5 Hz and J = 15.4, 9.9 Hz, C*H*$_2$CO$_2$ for one diastereomer), 2.54 and 2.44 (2 dd, 1 H and 1 H, J = 15.4, 6.8 Hz and J = 15.4, 8.09 Hz, C*H*$_2$CO$_2$ for other diastereomer), 1.37 (d, 3 H, J = 6.9 Hz, C*H*3CH), 1.34 and 1.33 (s for each diastereomer, 9 H and 9 H, *t*-butyl), 0.98 (2 s, 3 H and 3 H, isobornyl *gem* methyls for one diastereomer), 0.88 (s, 6 H, isobornyl *gem* methyls for other diastereomer); IR (neat) 1725, 980, 890, 850, 820, 780 cm^{-1}; LRMS (EI), m/z 555 (M), 380, 228, 181, 180, 138, 136, 135, 107, 103, 98, 93, 91, 83, 81, 79, 69, 67, 57 (base), 56, 55, 43, 42; HRMS (PCI), m/z 555.3400 (calcd for $C_{30}H_{53}NO_4S_2$, (M), 555.3418).

3-[(1,1-Dimethylethyl)thio]butan-1-ol (16). The following procedure is representative of the conversion of the *t*-butylthioester **15** to the t-butylthio alcohols **16**. Typically, 95-300 mg of each ester was used and yields were in the range 73-94%.

The ester (2.63 mmol) in THF (3 mL) was added to an ice-bath-cooled slurry of $LiAiH_4$ (99.7 mg, 2.63 mmol) in THF (10 mL). The cooling bath was removed and the mixture stirred at ambient temperature for 3 h (reflux conditions may also be used). Water (25 mL) was cautiously added to the reaction mixture, followed by filtration and extraction of the filtrate with 7:3 CH_2Cl_2/ ether solution (4 x 50 mL). The combined organic extracts were dried over anhydrous $MgSO_4$ and concentrated *in vacuo*. Chromatography of the crude product on silica gel (ICN) in a 3 cm x 34 cm column, using 1:1 ether/PE as the eluting solvent [TLC: R_f = 0.39; not UV active, *p*-anisaldehyde (stains yellow-green) active], afforded 400 mg (94%) of the alcohol **16** as a clear colorless liquid.

The following data is presented in the order: temperature range, trial number, yield of alcohol **16** (%), optical rotation ($[\alpha]^{24\ °C}$) for alcohol **16** at specified concentration. *67 °C*: 75, no optical activity. *4 to 8 °C:* trial 1, 76, -15.09° (c 2.0, ether); trial 2, 78, -15.29° (c 2.0, ether). *-35 to -41 °C:* trial 1, 78, -8.50° (c 2.2, ether); trial 2, 73, -8.50° (c 2.2, ether). *-68 to -72 °C:* trial 1, 78, +5.90° (c 2.0, ether); trial 2, 61, +5.70° (c 2.0, ether).

^{1}H NMR (500 MHz) δ 3.81 (m, 2 H, C*H*$_2$OH), 2.92 (m, 1 H, *J* = 6.7 Hz, C*H*CH$_2$), 2.01 (t, 1 H, *J* = 5.1 Hz, CH$_2$O*H*), 1.77 (m, 2 H, C*H*$_2$CH$_2$OH), 1.37 and 1.35 (d, 3 H, *J* = 6.7 Hz, C*H*$_3$CH), 1.36 (s, 9 H, *t*-butyl); ^{13}C NMR (75 MHz, fully decoupled) δ 60.6 (*C*H$_2$OH), 43.0 *t*-butyl quaternary carbon), 40.7 (*C*HS), 34.7 (*C*H$_2$CH$_2$OH), 31.2 (*t*-butyl), 24.8 (C*H*$_3$CH); IR (neat) 3600-3100, 2960, 2920, 2860, 1450, 1360, 1160, 1040, 995, 845 cm^{-1}; LRMS (EI), m/z 162 (M), 106, 75, 72, 61, 59, 57 (base) 55, 43; HRMS (EI), m/z 162.1072 (calcd for $C_8H_{18}OS$, M, 162.1079).

3-[(1,1-Dimethylethyl)thio]butyl (*S*)-(-)-α-Methoxy-α-(trifluoromethyl)phenyl acetate (17). The following procedure is representative of the conversion of the *t*-butylthio alcohols **16** to the Mosher's ester **17**.[18] Typically, 10-15 mg of each alcohol was used and yields were in the range 85-94%.

The alcohol **16** (15 mg, 0.09 mmol) in CH_2Cl_2 (0.5 mL) was added to a solution of (S)-(-)-α-methoxy-α-(trifluoromethyl)phenylacetic acid (Mosher's acid, 22 mg, 0.09 mmol) and DMAP (2 mg, 0.02 mmol, 0.2 equiv) in CH_2Cl_2 (1 mL). The mixture was cooled to approximately 0 °C and DCC (29 mg, 0.14 mmol, 1,5 equiv) was added. Stirring was continued at ambient temperature for 1-1.5 h. The reaction mixture was then filtered to remove the dicyclohexylurea and the filtrate concentrated *in vacuo*. The resulting viscous liquid was diluted with ether (20 mL) and washed with 5% aqueous HCl solution (2 x 20 mL) and water (1 x 20 mL). The ether layer was dried over anhydrous $MgSO_4$ and concentrated *in vacuo*. Chromatography of the crude product on silica gel (ICN) in a 3 cm x 34 cm column, using a 1:9 ether/PE as the eluting solvent [TLC: R_f = 0.51; UV and p-anisaldehyde active], afforded 32 mg (94%) of product **17** as a pale yellow liquid; ^{1}H NMR (500 MHz) δ 7.45 (m, 5 H, phenyl), 4.47 (m, 2 H, C*H*$_2$O), 3.55 and 3.54 (s for each diastereomer, 3 H, OC*H*$_3$), 2.74 and 2.66 (m for each diastereomer, 1 H, *J* = 6.9 Hz and *J* = 6.8 Hz, C*H*CH$_2$), 1.84 (m, 2 H, C*H*$_2$CH$_2$O), 1.33, 1.32 and 1.29, 1.28 (d for each diastereomer, 3 H, *J* = 7.0 Hz and *J* = 6.8 Hz, C*H*$_3$CH), 1.27 and 1.26 (s for each diastereomer, 9 H, *t*-butyl); IR (neat) 3060, 2960, 2930, 2870, 1740, 1450, 1375, 1365, 1255, 1165, 1120, 1080, 1025, 985, 760, 735, 695 cm^{-1}; LRMS (EI), m/z 378 (M), 190, 189, 119, 105, 89, 88, 87, 77, 60, 59, 58, 57 (base), 55; HRMS (EI), m/z 378.1462 (calcd for $C_{18}H_{25}O_3F_3S$, 378.1477).

4-Bromo-N-[(E)-2-butenoyl]bornane-10,2-sultam (18). A solution of (+)-10,2-camphorsultam (2.17 mmol) was added dropwise to a stirred suspension of sodium hydride (2.39 mmol, 60% dispersion in mineral oil) in toluene (~4.34 mL). After stirring for 0.5 h at room temperature, a solution of γ-bromocrotonyl chloride (2.6 mmol) in toluene (1.05 mL) was added. After stirring for 4 h, water was added and the mixture extracted with ether. The organic layer was washed with brine, dried over $MgSO_4$, and concentrated in vacuo. Chromatography over silica gel using 40% ether in petroleum ether as eluent led to the isolation of a 65% yield of **18**.

^1H NMR ($CDCl_3$) δ 0.98 (s, 3H, methyl), 1.17 (s, 3H, methyl), 1.85-2 (m), 2.1-2.25 (m), 3.5 (dd, CH_2SO_2), 3.9 (dd, $CHNSO_2$), 4.05 (d, 2H, CH_2Br), 6.7 (apparent d, 1H, α-vinyl), 7.1 (dt, 1H, β-vinyl). ^{13}C NMR (APT; $CDCl_3$) δ 19.8 (down), 20.8 (down), 26.5 (up), 29.1 (up), 32.8 (up), 38.3, 44.6 (down), 47.8 (up), 48.6 (up), 53.1 (up), 65.2 (down), 123.5 (down), 142.6 (down), 162.9 (up). Calculated mass for $C_{14}H_{23}NO_3S^{81}Br$: 364.0405, for $C_{14}H_{23}NO_3S^{79}Br$: 362.0426. Found: 364.0429 and 362.0451, respectively.

(-)-Menthyl 2-[Bis(1-methylethyl)amino]cyclopentanecarboxylate (21).[2,4] *Procedure A:* Lithium diisopropylamide was prepared by adding *n*-BuLi (0.91 mL, 1.81 mmol, 2.0 equiv, 2.0 M in hexanes) to an ice-bath-cooled solution of diisopropylamine (0.25 mL, 1.81 mmol, 2 equiv) in THF (9.1 mL) and stirring for for 10 min. The bromoester **2** (300 mg, 0.91 mmol) in THF (9.1 mL) was added dropwise by syringe pump to to this solution of LDA at -68 to -72 °C, during 1.5 h. Stirring was continued at -68 to -72 °C for a further 0.5 h. The reaction mixture was then poured into saturated NaCl solution (50 mL) and extracted with ether (4 x 30 mL). The combined ether extracts were dried over anhydrous $MgSO_4$ and concentrated *in vacuo*. Chromatography of the crude product on silica gel (Fisher) in a 3 cm x 34 cm column, using 1:9 ether/PE as the eluting solvent [TLC: R_f = 0.45; UV and *p*-anisaldehyde (stains blue) active], yielded 295 mg (93%) of the cyclized product **21** as a pale-yellow liquid. *Procedure B:* Lithium diisopropylamide was prepared by adding *n*-BuLi (0.33 mL, 0.66 mmol, 2.0 M in hexanes) dropwise to an ice-bath-cooled solution of diisopropylamine (0.09 mL, 0.66 mmol, 1.1 equiv) in THF (6 mL) and stirring for 10 min. This solution was cooled to -68 to -72 °C and added dropwise in 1 mL portions, during 1.5 h, to a solution of the bromoester **2** (200 mg, 0.6 mmol) in THF (6 mL) at -68 to -72 °C. Stirring was continued at this temperature for a further 0.5 h. The reaction mixture was then poured into saturated NaCl solution (30 mL) and extracted with ether (4 x 25 mL). The combined ether extracts were dried over anhydrous $MgSO_4$ and concentrated *in vacuo*. Chtomatography of the crude product on silica gel (Fisher) in a 3 cm x 34 cm column, using 1:9 ether/PE as the eluting solvent [TLC: Rf = 0.45; UV and p-anisaldehyde (stains blue) active], yielded 192 mg (92%) of the cyclized product **21** as a pale yellow liquid. The analytical GC conditions for determining % de were: temperature 1, 120 °C, temperature 2, 300 °C, time 1, 2 min, time 2, 25 min, rate, 10 °C/min; retention time (min) cyclopentane, diastereomer 1, 14.16; diastereomer 2, 14.35.

^1H NMR (500 MHz) δ 4.66 (m, 1 H, menthyl methine adjacent to ester), 3.04 (m, 7 lines, 3 H, J = 6.5 Hz, $N(CH(CH_3)_2)_2$ and NCH cyclopentyl ring), 2.46 (2 dd overlapping, 1 H, J = 8.2, 5.8 Hz and J = 8.2, 5.3 Hz, $CHCO_2$ cyclopentyl ring), 2.00-0.88 (several m, 9 H, menthyl ring and 6 H, cyclopentyl methylenes), 1.00 (2 d overlapping, for one diastereomer, 12 H, J = 6.5 Hz, $N(CH(CH_3)_2)_2$), 0.96 (d, for other diastereomer, 12 H, J = 6.8 Hz, $N(CH(CH_3)_2)_2$), 0.89 (2 d, one for each diastereomer, 6 H and 6 H, J = 6.5 Hz and J = 7.0 Hz, menthyl isopropyl), 0.75 (2 d, one for each diastereomer, 3 H and 3 H, J = 7.1 Hz and J = 6.9 Hz, menthyl methyl); IR (neat) 2960, 2930, 2870, 1725, 1455, 1395, 1365, 1210, 1175, 1150, 1115, 1010, 990, 915 cm^{-1};

LRMS (EI), m/z 351 (M), 337, 336, 198, 154, 140, 138, 123, 98, 96, 95 (base), 84, 83, 82, 81, 80, 79, 78, 71, 70, 69, 67, 56, 55, 43, 42; HRMS (EI), m/z 351.3164 (calcd for $C_{22}H_{41}O_2N$, M, 351.3138).

10-Dicyclohexylsulfamoyl-D-isobornyl 2-[Bis(1-methylethyl)amino]cyclopentanecarboxylate (22). *Procedure A* is the same as that described above with the following variations: *n*-BuLi (0.14 mL, 0.28 mmol, 2 equiv, 2.0 M in hexanes); diisopropylamine (0.04 mL, 0.28 mmol, 2 equiv) in THF (1.5 mL); bromoester **6** (79 mg, 0.14 mmol) in THF (1.5 mL); 1.5 h. The reaction mixture was then poured into saturated NaCl solution (20 mL) and extracted with ether (4 x 20 mL). Chromatography of the crude product on silica gel (Fisher) in a 3 cm x 34 cm column, using 3:7 ether/PE as the eluting solvent [TLC: R_f = 0.4; UV and *p*-anisaldehyde (stains green-blue) active], yielded 60 mg (74%) of the cyclized product **22** as a white solid.

Procedure B is the same as that described above, with the following variation: *n*-BuLi (0.08 mL, 0.15 mmol. 1.1 equiv, 2.0 M in hexanes); diisopropylamine (0.02 mL, 0.15 mmol, 1.1 equiv) in THF (1.5 mL); added dropwise in 0.5 mL portions, during 1.5 h, to a solution of bromoester **6** (79 mg, 1.4 mmol) in THF (1.5 mL) at -68 to -72 °C. Stirring was continued at this temperature for a further 0.5 h. The reaction mixture was poured into saturated NaCl solution (20 mL) and extracted with ether (4 x 20 mL). The combined ether extracts were dried over anhydrous $MgSO_4$ and concentrated *in vacuo*. Chromatography of the crude product on silica gel (Fisher) in a 3 cm x 34 cm column, using 3:7 ether/PE as the eluting solvent [TLC: R_f = 0.4; UV and *p*-anisaldehyde (stains green-blue) active] yielded 50 mg (62%) of the cyclized product **22** as a white solid; ^{1}H NMR (500 MHz) δ 4.96 (dd for one diastereomer, 1 H, J = 7.9, 2.6 Hz, isobornyl methine adjacent to ester), 4.83 (dd for other diastereomer, 1 H, J = 7.8, 3.3 Hz, isobornyl methine adjacent to ester), 3.24-1.08 (several m, 7 H, isobornyl ring and 6 H, cyclopentyl methylenes), 3.27 and 2.63 (2 d, 1 H and 1 H, J = 13.2 Hz, CH_2SO_2), 3.02 (m, 7 lines, 3 H, J = 6.6 Hz, $N(CH(CH_3)_2)_2$ and NC*H* cyclopentyl ring), 2.44 (m, 1 H, J = 7.0 Hz, $CHCO_2$ cyclopentyl ring), 1.00 (s, 3 H, isobornyl gem methyl), 0.88 and 0.86 (2 s, one for each diastereomer, 3H and 3 H, isobornyl gem methyl); IR (solid film) 2940, 2870, 1725, 1455, 1395, 1355, 1330, 1280, 1260, 1215, 1170, 1150, 1110, 1050, 1030, 985, 915, 855, 825, 780, 735 cm^{-1};LRMS (PCI), m/z 593 (M + 1), 578, 577, 228, 214, 196, 180, 154 (base), 140, 135, 98, 95, 86, 83, 69, 67; HRMS (PCI, KVE), m/z 592.4232 (calcd for $C_{34}H_{60}O_4N_2S$, M, 592.4275).

(-)-Menthyl 2-[Bis(1-methylethyl)amino]cyclohexanecarboxylate (23).[2,4] Lithium diisopropylamide was prepared by adding *n*-BuLi (0.4 mL, 0.79 mmol, 1.1 equiv, 2.0 in hexanes) dropwise to an ice-bath-cooled solution of diisopropylamine (0.11 mL, 0.79 mmol, 1.1 equiv) in THF (4.0 mL) and stirring for approximately 10 min. This solution of LDA was cooled to -68 to -72 °C and added dropwise in 1 mL portions, during 1.5 h, to a solution of the bromoester **3** (250 mg, 0.72 mmol) in THF (7.5 mL) at -68 to 72 °C. The mixture was allowed to gradually warm to approximately 0 °C and maintained at this temperature for one hour. The reaction mixture was then poured into saturated NaCl solution (50 mL) and extracted with ether (4 x 30 mL). The combined ether extracts were dried over anhydrous $MgSO_4$ and concentrated *in vacuo*. Chromatography of the crude product on silica gel (Fisher) in a 3 cm x 34 cm column, using 1:9 ether/PE as the eluting solvent [TLC: R_f = 0.59; UV and *p*-anisaldehyde (stains blue) active], yielded 168 mg (65%) of the cyclized product **23** as a pale yellow liquid.

The analytical GC conditions for determining % de were: temperature 1, 130 °C, temperature 2, 300 °C, time 1, 2 min, time 2, 25 min; rate, 10 °C/min; retention time (min) Cyclohexane diastereomer 1, 14.32, diastereomer 2, 14.57.

^{1}H NMR (500 MHz) δ 4.64 (m, 1 H, menthyl methine adjacent to ester), 3.09 (m, 2 H, N(C*H*(CH$_3$)$_2$)$_2$), 2.89 (ddd, 1 H, *J* = 14,6, 7.3, 3.8 Hz, NC*H* cyclohexyl ring), 2.44 (ddd, 1 H, *J* = 15.2, 7.8, 3.8 Hz, C*H*CO$_2$ cyclohexyl ring), 2.05-0.85 (several m, 9 H, menthyl ring and 8 H, cyclohexyl methylenes), 1.02 (2 d overlapping, for one diastereomer, 12 H, *J* = 6.5 Hz, N(CH(C*H*$_3$)$_2$)$_2$), and 0.96 (d, for other diastereomer, 12 H, *J* = 6.7 Hz, N(CH(C*H*$_3$)$_2$)$_2$), 0.88 (2 d, one for each diastereomer, 6 H and 6 H, *J* = 6.4 Hz and *J* = 7.0 Hz, menthyl isopropyl), 0.75 (2 d, one for each diastereomer, 3 H and 3 H, *J* = 6.9 Hz and *J* = 6.8 Hz, menthyl methyl); IR (neat) 2940, 2870, 1730, 1450, 1390, 1365, 1305, 1255, 1215, 1190, 1170, 1140, 1120, 1010, 785 cm^{-1}; LRMS (EI), m/z 365 (M), 350, 212, 184, 141, 140 (base), 86, 85, 84, 83, 81, 70, 56, 55, 44, 43; HRMS (EI), m/z 365.3264 (calcd for $C_{23}H_{43}O_2N$, M, 365.3282).

10-Dicyclohexylsulfamoyl-D-isobornyl 2-[Bis(1-methylethyl)amino]cyclohexanecarboxylate (24).[2,4] The same procedure as that described for **23** was used, with the following variations: *n*-BuLi (0.19 mL, 0.37 mmol, 1.1 equiv); diisopropylamine (0.05, 0.37 mmol, 1.1 equiv) in THF (2 mL); LDA introduced dropwise in 0.5 mL portions, during 1.5 h, to a solution of the bromoester **7** ester (200 mg, 0.34 mmol) in THF (3.5 mL). Stirring was continued for a further 20-30 min (until all the starting material had disappeared by TLC). The mixture was allowed to gradually warm to approximately 0 °C and maintained at this temperature for a further 1.5 h and then at room temperature for 1 h. The reaction mixture was then poured into saturated NaCl solution (30 mL) and extracted with ether (4 x 25 mL). Chromatography of the crude product on silica gel (Fisher) in a 3 cm x 34 cm column, using 3:7 ether/PE as the eluting solvent [TLC: R_f = 0.49; UV and *p*-anisaldehyde (stains green-blue) active], yielded 160 mg (78%) of the cyclized product **24** as a white solid; ^{1}H NMR (500 MHz) δ 4.84 (dd, 1 H, *J* = 7.9, 3.5 Hz, isobornyl methine adjacent to ester), 3.24-1.08 (several m, 7 H, isobornyl ring and 8 H, cyclohexyl methylenes), 3.23 and 2.61 (2 d, 1 H and 1 H, *J* = 13.3 Hz, C*H*$_2$SO$_2$), 3.06 (m, 7 lines, 2 H, *J* = 6.6 Hz, N(C*H*(CH$_3$)$_2$)$_2$), 2.95 (dt, 1 H, *J* = 11.1, 3.3 Hz, NC*H* cyclohexyl ring), 2.35 (dt, 1 H, *J* = 11.4, 3.3 Hz, C*H*CO$_2$ cyclohexyl ring), 1.02 (s overlapping with diisopropyl methyls, 3 H, isobornyl gem methyl), 0.87 (s, 3 H, isobornyl *gem* methyl), 1.01 and 0.97 (2 d, 6 H and 6 H, *J* = 6.7 Hz, N(CH(C*H*$_3$)$_2$)$_2$); IR (solid film) 2930, 2880, 1725, 1450, 1390, 1325, 1305, 1260, 1190, 1135, 1050, 1030, 1005, 980, 910, 890, 855, 820, 770, 730 cm^{-1}; LRMS (PCI), m/z 607 (M + 1), 591, 380, 246, 228, 210, 182, 181, 180, 140 (base), 138, 136, 135, 109, 107, 98, 93, 83, 81; HRMS (PCI, KVE), m/z 606.4411 (calcd for $C_{35}H_{62}O_4N_2S$, M, 606.4413).

10-Dicyclohexylsulfamoyl-D-isobornyl 7-Bromo-3[(1-methylethyl)amino]heptanoate (25). Lithium diisopropylamide (from 0.28 mL *n*-BuLi, 1.1 equiv, 2.0 M in hexanes; 0.08 mL diisopropylamine in 3.0 mL THF) was cooled to -68 to -72 °C and introduced dropwise in 0.5 mL portions, during 2.5 h, to a solution of bromoester **7** (300 mg, 0.51 mmol) in THF (5.1 mL) at -68 to -72 °C. Stirring was continued at this temperature for a further 1 h and 50 min. The reaction mixture was then poured into saturated NaCl solution (50 mL) and extracted with ether (4 x 30 mL). The combined ether extracts were dried over anhydrous $MgSO_4$ and concentrated *in vacuo*. Chromatography of the crude product on silica gel (Fisher) in a 3 cm x 34 cm column, using 3:7 ether/PE as the eluting solvent [TLC: R_f = 0.47; UV and *p*-anisaldehyde (stains green-blue) active], yielded 341 mg (97%) of the β-adduct **25** as a white solid; ^{1}H NMR (500 MHz) δ 4.95 (dd, 1 H, *J* = 7.8, 3.3 Hz, isobornyl methine adjacent to ester), 3.24-1.08 (several m, 7 H, isobornyl ring and 6 H, C*H*$_2$C*H*$_2$C*H*$_2$Br), 3.23 and 2.66 (2 d, 1 H and 1 H, *J* = 13.2 Hz, C*H*$_2$SO$_2$), 3.17 (m, 1 H, NC*H*CH$_2$), 3.09 (m, 2 H, J = 6.6 Hz, N(C*H*(CH$_3$)$_2$)$_2$), 2.46 and 2.30 (2 dd, 1 H and 1 H, *J* = 13.8, 4.0 Hz and *J* = 13.8, 9.7

Hz, CH_2CO_2), 1.00 (2 d overlapping, 12 H, J = 6.0 Hz, $N(CH(CH_3)_2)_2$), 1.02 s overlapping with diisopropyl methyls, 3 H, isobornyl *gem* methyl), 0.88 (s, 3 H, isobornyl gem methyl);IR (KBr) 2940, 2880, 1730, 1450, 1390, 1330, 1280, 1260, 1210, 1170, 1140, 1150, 1050, 1030, 980, 895, 855, 820, 775 cm^{-1}; LRMS (EI), m/z 673, 671 (M - CH_3), 245, 244, 210, 182, 181, 180, 168, 140, 138 (base), 135, 125, 109, 107, 100, 98, 93, 83, 82, 81, 79, 69, 67, 57, 56, 55, 44, 43, 42; HRMS (EI, KVE), m/z 671.3382 (calcd for $C_{34}H_{60}O_4N_2SBr$, M - CH_3, 671.3440).

(-)-Menthyl 7-Bromo-3[(1-methylethyl)amino]heptanoate (26). The same procedure as that described for **25** was used, with the following variations: *n*-BuLi (0.48 mL, 0.96 mmol, 1.1 equiv, 2.0 M in hexanes), diisopropylamine (0.13 mL, 0.96 mmol, 1.1 equiv) in THF (5 mL); added dropwise in one 1 mL portions to a solution of the bromoester **3** (300 mg, 0.87 mmol) in THF (8.7 mL); chromatography using 1:9 ether/PE as the eluting solvent [TLC: R_f = 0.52; UV and *p*-anisaldehyde (stains blue) active]; 136 mg (45%) of **3** and 147 mg (38%, or 69 % based on recovered substrate) of the β-adduct **26** as a pale yellow liquid; ^1H NMR (500 MHz) δ 4.66 (m, 1 H, menthyl methine adjacent to ester), 3.39 (t, 2 H, J = 6.8 Hz, CH_2Br), 3.18 (m, 1 H, $NCHCH_2$), 3.10 (m, 7 lines, 2 H, J = 6.6 Hz, $N(CH(CH_3)_2)_2$), 2.50 and 2.47 (2 dd, for one diastereomer, appears as two triplets, 1 H and 1 H, J = 3.8 Hz, CH_2CO_2), 2.31 and 2.28 (2 dd, for other diastereomer, 1 H and 1 H, J = 9.5, 7.0 Hz and J = 9.5, 6.6 Hz, CH_2CO_2), 1.98-0.85 (several m, 9 H, menthyl ring, and 6 H, $BrCH_2CH_2CH_2$), 1.02 and 1.01 (2 d overlapping, 6 H and 6 H, J = 6.4 Hz and J = 6.2 Hz, $N(CH(CH_3)_2)_2$), 0.90 (d, 6 H, J = 6.6 Hz, menthyl isopropyl), 0.76 (2 d, one for each diastereomer, 3 H and 3 H, J = 7.0 Hz and J = 6.9 Hz, menthyl methyl); IR (neat) 2930, 2875, 1725, 1455, 1390, 1375, 1280, 1245, 1210, 1170, 1140, 1010, 990, 915, 845, 785 cm^{-1}; LRMS (EI), m/z 432, 430 (M - CH_3), 311, 310, 250, 249, 248, 172, 168, 167, 154, 152, 140, 138, 126, 124, 123, 112, 110, 98, 96, 95 (base), 86, 84, 83, 82, 81, 79, 71, 70, 69, 68, 67, 57,56, 55, 44, 43, 42; HRMS (EI), m/z 430.2327 (calcd for $C_{22}H_{41}O_2BrN$, 430.2309).

ACKNOWLEDGMENT. We are grateful to the National Science Foundation for its support of this research.

REFERENCES AND NOTES

(1.) Taken in part from the Ph. D. Thesis of Mary A. Amputch, University of California, Santa Barbara, 1989.

(2.) Little, R. D.; Dawson, J. R. *Tetrahedron Lett.* **1980**, *21*, 2609.

(3.) Little, R. D.; Dawson, J. R. *J. Am. Chem. Soc.* **1978**, 100, 4607.

(4.) Dawson, J. R. Ph. D. Thesis, University of California, Santa Barbara, 1980.

(5.) (a) Little, R. D.; Verhé, R.; Monte, W. T..: Nugent, S.; Dawson, J. R.; *J. Org. Chem.* **1982**, *47*, 362. (b) Monte, W. T. Ph.D Thesis, University of California, Santa Barbara, 1983. (c) Nugent, S. T. Ph.D. Thesis, University of California, Santa Barbara, 1983. For a similar type of reaction, refer to (d) Cooke, M. P., Jr. *J. Org. Chem.* **1984**, *49*, 1144. (e) Cooke, M. P., Jr.; Widener, R. K. *J. Org. Chem.* **1987**, *52*, 1381. (f) Cooke, M. P., Jr. *J. Org. Chem.* **1992**, 57, 1495. (g) See also Posner, G. H. *Chem. Rev.* **1986**, *86*, 831 for examples illustrating extensions of the methodology to sequential Michael reactions (MIMIRC/SMIRC).

(6.) (a) Enders, D.; Scherer, H. J.; Raabe, G. *Angew. Chem., Int. Ed. Engl.* **1991**, *30*, 1664 and the references cited therein. See also: Enders, D.; Papadopoulos, K.; Herdweck, E. *Tetrahedron*, **1993**, *49*, 1821. (b) For a general discussion of conjugate addition reactions including the asymmetric variety, refer to: Perlmutter, P.

Conjugate Addition Reactions in Organic Synthesis; Tetrahedron Organic Chemistry Series Volume 9; Pergamon Press: Oxford, 1992.

(7.) (a) Oppolzer, W.; Chapuis, C.; Bernardinelli, G. *Tetrahedron Lett.* **1984**, *25*, 5885. (b) Oppolzer, W.; Kelly, M. J.; Bernardinelli, G. *Tetrahedron Lett.* **1984**, *25*, 5889. (c) Oppolzer, W. *Tetrahedron*, **1987**, *43*, 1969. (d) Oppolzer, W. *Pure & Appl. Chem.* **1988**, *60*, 39. (e) Oppolzer, W. *Pure & Appl. Chem.* **1990**, *62*, 1241.

(8.) Dale, J. A.; Dull, D. L.; Mosher, H. S. *J. Org. Chem.* **1969**, *34*, 2543.

(9.) We also conducted these reactions in the temperature range of -93 to -97 °C, in hopes of further improving selectivity. However, we observed a *decrease* in de from 50-56% at -68 to -72 °C to 38-44% at -93 to -97 °C for the cyclopropyl ester **11c**. Perhaps this is due to a decreased rate of cyclization relative to the rate of cyclization at the higher temperatures, thereby permitting equilibration between the initially formed enolates and substrate. Equilibration could serve to decrease the quantity of the enolate leading to the favored diastereomer, resulting in an overall decrease in the de. Alternatively, two mechanisms may be operating. The extreme temperature sensitivity, as well as the change in color of the reaction solution from pale yellow at 4 to 8 °C and -31 to -41 °C, to pale blue-green at -68 to -72 °C and -93 to -97 °C suggests the possible participation of a mechanism other than the ionic mechanism, perhaps one involving electron transfer. Additional experiments are needed to address these issues.

(10.) For other examples where a switch in diastereomer preference accompanies a change in a reaction parameter, particularly in the assembly of cyclopropanes, see: (a) Inouye, Y.; Inamasu, S.; Ohno, M.; Sugita, T.; Walborsky, H. M. *J. Am. Chem. Soc.* **1961**, *83*, 2962. (b) Inouye, Y.; Inamasu, S.; Horiike, M.; Ohno, M.; Walborsky, H. M. *Tetrahedron* **1968**, *24*, 2907. (c). Inamasu, S.; Horiike, M.; Inouye, Y. *Bull. Chem. Soc. Jpn.* **1969**, *42*, 1393. (d) Tsuchihashi, G-i; Mitamura, S.; Ogura, K. *Tetrahedron Lett.* **1976**, 855.

(11.) For cases in which isokinetic (isoselective) points have been observed, see: (a) Stone, K. J.; Little, R. D. *J. Am. Chem. Soc.* **1985**, *107*, 2495; (b) Giese, B. *Acc. Chem. Res.* **1984**, *17*, 438 and the references in each.

(12.) Montaudo, G.; Librando, V.; Caccamese, S.; Maravigna, P. *J. Am. Chem. Soc.* **1973**, *95*, 6365.

(13.) For examples of cases where s-cis/s-trans equilbration hampered efforts to obtain asymmetric induction, refer to references 6b and 7, and: (a) Curran, D. P.; Heffner, T. A. *J. Org. Chem.* **1990**, *55*, 4585. (b) Curran, D. P.; Kim, B.H.; Piyasena, H. P.; Loncharich, R. J.; Houk, K. N. *J. Org. Chem.* **1987**, *52*, 2137. (c) Achmatowicz, O., Jr.; Szechner, B. *J. Org. Chem.* **1972**, *37*, 964. (d) Whitesell, J. K.; Bhattacharya, A.; Henke, K. *J. Chem. Soc., Chem. Commun.* **1982**, 988. (e) Whitesell, J. K.; Deyo, D. Bhattacharya, A. *J. Chem. Soc., Chem. Commun.* **1983**, 802.

(14.) Knipe, A. C.; Stirling, C. M. J. *J. Chem. Soc. B,* **1968**, *67*, 808.

(15.) Moeller, K. D. Ph. D. Thesis, University of California, Santa Barbara, 1985.

(16.) Oppolzer, W.; Loher, H. J. *Helv. Chim. Acta* **1981**, *64*, 2809.

(17.) Oppolzer, W.; Dudfield, P.; Stevenson, T.; Godel, T. *Helv. Chim. Acta* **1985**, *68*, 212.

(18.) Blanchette, M. A.; Choy, W.; Davis, J. T.; Essenfeld, A. P.; Masamune, S.; Roush, W. R.; Sakai, T. *Tetrahedron Lett.* **1984**, *25*, 2183.

(19.) Oppolzer, W.; Moretti, R.; Bernardinelli, G. *Tetrahedron Lett.* **1986**, *27*, 4713.

(*Received in USA* 4 *February* 1994; *accepted* 4 *March* 1994)