Pergamon

Tetrahedron Vol. 50, No. 13, pp. 3929-3942, 1994

0040-4020/94 $6.00+0.00

0040-4020(94)E0150-R

Highly Diastereoselective Formation of Bicyclic Compounds by Intramolecular Cycloaddition of Chiral Thiaalkenyl Nitrones

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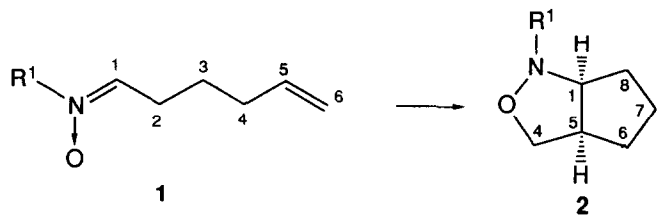
Abstract: Starting from chiral mercapto alcohols **5** in several reaction steps nitrones **7** were formed which underwent spontaneously intramolecular cycloaddition to give diastereomerically pure products **8**. However, during the reaction course partial racemization had occurred. In contrast, nitrones **9** in which the chiral center is adjacent to the nitrogen atom afforded a mixture of the two diastereomeric cycloadducts **10** and **11**. Compound **14** was synthesized from the homochiral amino diol **12** with retention of configuration at the two chiral centers. **14** was converted to the alcohol compounds **15**, **19** and **20**. These were subjected to Swern oxidation followed by treatment with N-alkyl or N-arylhydroxylamines. The nitrones formed in this way underwent spontaneously intramolecular cycloaddition to afford the diastereomerically and enantiomerically pure bicyclic products **17**, **21** and **22**, respectively.

The intramolecular cycloaddition of alkenyl-1-imine-N-oxides (alkenylnitrones) affords cycloadducts with at least two chiral centers. As is known since the pioneering work of Le Bel a mixture of cis- and trans-fused as well as bridged bicyclic compounds can arise from intramolecular cycloaddition of 6-heptenyl-1-imine-N-oxides [C-(5-hexenyl)nitrones]. In contrast, 5-hexenyl-1-imine-N-oxides [C-(4-pentenyl)nitrones] **1** form with very few exceptions cis-fused cycloadducts **2**, the 3-oxa-2-azabicyclo[3.3.0]octanes, in a highly regio- and stereoselective reaction.[1] Thus, in particular, the latter reaction has frequently been used for the formation of new chiral centers in the syntheses of natural products and other complex molecules.[1c,2] That is, a chiral center in the starting nitrone causes an asymmetric induction giving rise to the formation of new chiral centers with definite configuration in the cycloadduct.

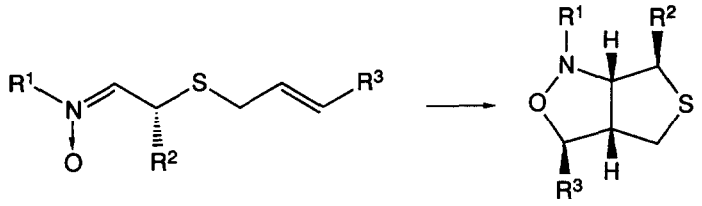
Starting from homochiral (enantiomerically pure) nitrones homochiral cycloadducts can be formed.[3] In particular, a chiral carbon atom at position 2 of the nitrone is very effective in asymmetric induction.[4]



1 **2**

The displacement of a methylene unit of nitrone **1** by a heteroatom gives rise to cycloadducts that contain an additional heteroatom besides oxygen and nitrogen. The intramolecular cycloaddition of such nitrones with additional oxygen,[3b,5] nitrogen[6] or sulfur atoms[7] has already been performed, in some cases even with homochiral educts.[3,5e,6c,7b,7c]

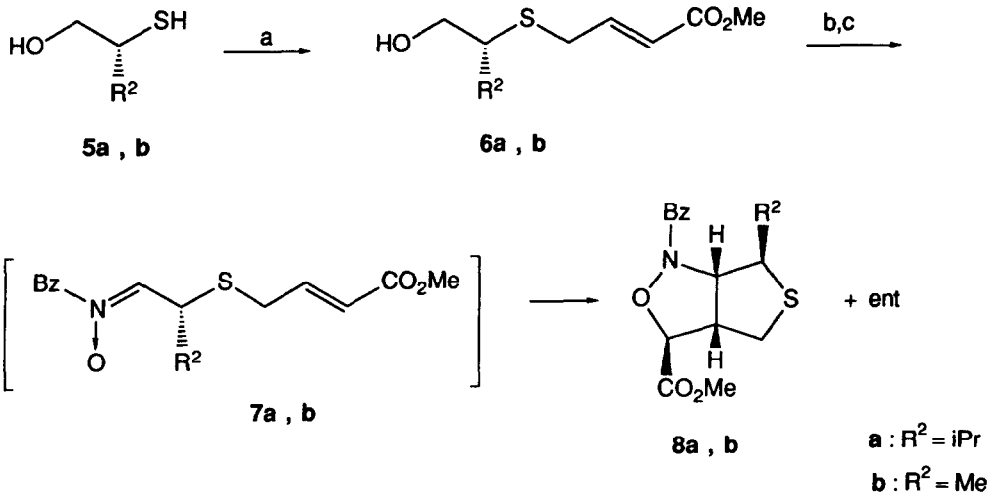
Our first goal was to synthesize homochiral nitrones of type **3**. Provided that the asymmetric induction by the chiral group is as high as for the corresponding oxa- and aza-nitrones,[5e,6c] 3-oxa-7-thia-2-azabicyclo[3.3.0]octanes **4** with four contiguous chiral centers should be formed. They should arise as homochiral compounds if neither one of the precursors of **3** nor the nitrone **3** itself undergo racemization.



3 **4**

Starting form (S)-valine the mercapto alcohol **5a** was prepared according to the procedure of Kurth et al.[8] However, partial racemization had occurred during the course of its preparation, the enantiomeric excess was found to be 81%. Mitsunobu reaction[9] of methyl (S)-lactate with mercapto acetic acid occurred with inversion yielding the methyl ester of (R)-2-acetylmercapto-propionic acid (ee = 96%).[10] Reduction of this compound with lithium aluminium hydride gave the mercapto alcohol **5b** (ee >90%).

Alcohols **6** were formed by reaction of **5** with methylester of 4-bromocrotonic acid. Swern oxidation[11] of **6** afforded the corresponding aldehydes. Without isolation these aldehydes were treated with N-benzylhydroxylamine to give nitrones **7** which spontaneously underwent intramolecular cycloaddition yielding the bicyclic compounds **8**.



5a , b **6a , b** **7a , b** **8a , b**

a : R^2 = iPr

b : R^2 = Me

a : Br—CH_2—CH=CH—CO_2Me-trans b : $(COCl)_2$, DMSO, Et_3N c : BzNHOH

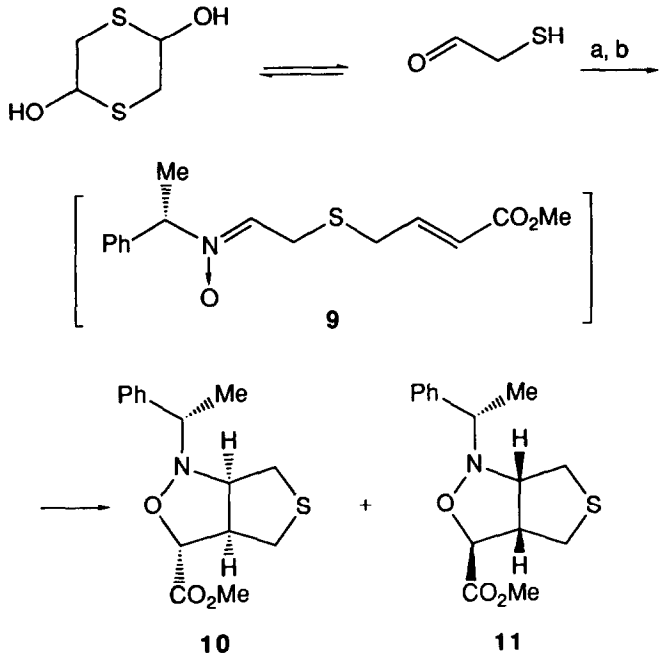
Compounds **8** arose diastereomerically pure as was shown by ^{1}H- and ^{13}C-NMR spectroscopy (de >96%), indicating that the intramolecular cycloaddition occurs with high asymmetric induction by the chiral

center. However, the products **8** were not enantiomerically pure as was found by reduction of their ester group to hydroxymethyl group and subsequent reaction with Mosher chloride.[12] In this way the enantiomeric excess of **8a** and **8b** was determined to 34% and approximately 10%, respectively.

Although it is known that α-mercaptocarbonic acids as well as their esters undergo easily racemization,[13] formation of **5**, in particular of **5b**, occurred with relatively slight loss of optical purity. That means that the major part of racemization occurs at the level of either the aldehydes or the nitrones **7**, which obviously are even more susceptible to racemization compared to carbonic acids and esters.

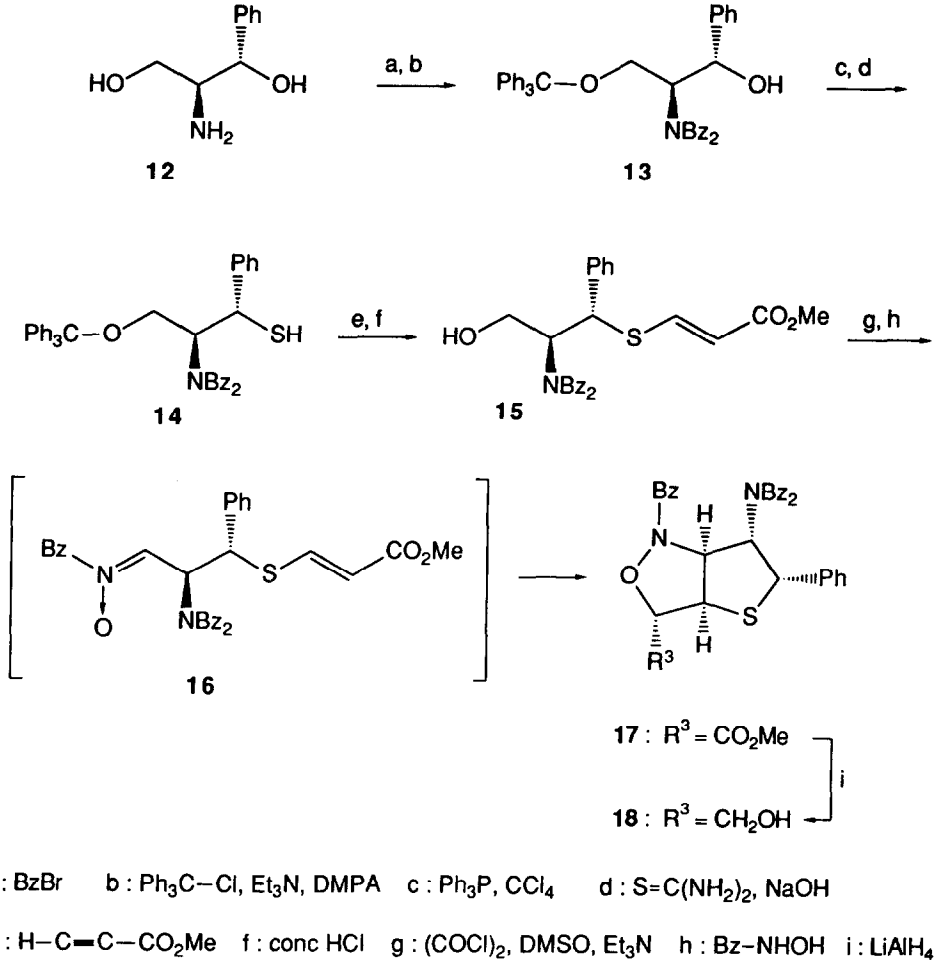
The risk of racemization of thiaalkenyl nitrones seemed to be far less, if the chiral center is attached to the nitrogen atom instead of being located between C-1 and the sulfur atom. However, in this case only 1.3-induction would occur in contrast to the 1.2-induction of the reaction **7** → **8**. On the other hand, good diastereoselectivity was achieved with the chiral (S)-α-methylbenzyl group at nitrogen in a very similar situation by Baldwin et al.[3b] Thus we attempted to prepare a homochiral product from intramolecular cycloaddition of nitrone **9**.

At first we treated 2.5-dihydroxy-1.4-dithiane, the dimer of mercaptoacetaldehyde, with methyl 4-bromocrotonate to give methyl 7-oxo-5-thia-2-heptenoate. Subsequent reaction with (S)-α-methylbenzyl-hydroxylamine yielded nitrone **9**, which underwent spontaneously intramolecular cycloaddition. From this reaction a mixture of diastereomers **10** and **11** in a 77:23 ratio was isolated. With reference to the results of Baldwin[3b] structure **10** was ascribed to the major isomer. In fact, the change from 1,2- to 1.3 induction caused a dramatic loss in diastereoselectivity.



a : Br–CH_2–CH=CH–CO_2Me - trans b : (S)–Ph(CH_3)CH–NHOH·$C_2H_2O_4$

Since in the preparation and intramolecular cycloaddition of homochiral 2-substituted nitrones with oxygen[5b] or nitrogen[6c] as heteroatom in position 3 no racemization was observed, the sulfur atom at position 3 of nitrones 7 seems to be responsible for the easy racemization in the formation of the bicyclic compounds **8**. In order to avoid the susceptibility to racemization by the sulfur atom at one hand taking advantage of the high asymmetric induction by a chiral center at carbon atom 2 on the other hand, we decided to shift the sulfur atom from position 3 to position 4 in the thiaalkenyl nitrones.



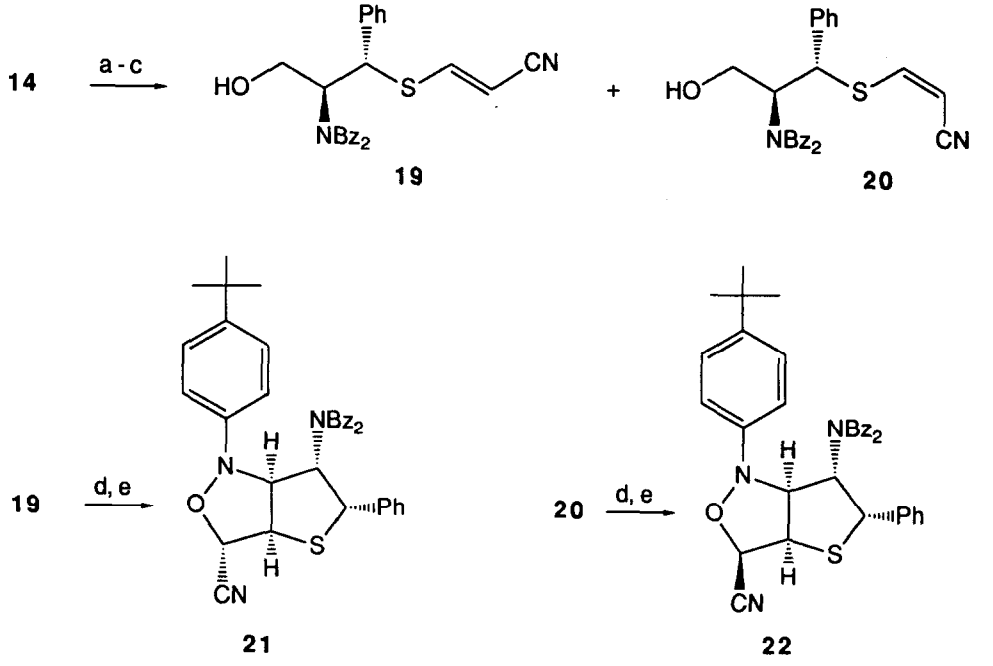
Thus we started from the homochiral aminodiol **12** which possesses even two chiral centers. After twofold benzylation of the amino group by benzyl bromide[14] the primary alcohol group was protected by tritylation with triphenylmethylchloride.[15] Subsequently the secondary alcohol group of **13** was converted to the mercapto group with double inversion maintaining the original S configuration at this chiral center of **14**.[16]

Addition of **14** to methyl propiolate occurred with formation of the trans product **15**. Detritylation by acid hydrolysis[17] and Swern oxidation followed by reaction with N-benzylhydroxylamine afforded nitrone **16** which underwent spontaneously an intramolecular cycloaddition to give the bicyclic compound **17** with five contiguous chiral centers.

Compound **17** was formed diastereomerically pure as was indicated by ^{1}H and ^{13}C-NMR spectroscopy.[18] Since racemization at one of the chiral centers would have led to the appearance of diastereomeric forms, it is confirmed that the formation and reaction of nitrone **16** had occurred without racemization. The optical active compound **17** was reduced by lithium aluminium hydride to give compound **18**.

In a similar way 4-cyanosubstituted 3-oxa-6-thia-2-azabicyclo[3.3.0]octanes were prepared. At first compound **14** was treated with 2-chloroacrylonitrile, subsequently hydrogen chloride was eliminated with 1.8-diazabicyclo[5.3.0]undecene-7.[19] After removal of the trityl group by hydrochloric acid[20] a 3:2 mixture of alcohols **19** and **20** was obtained. These could be separated by fractional crystallization from diethyl ether at -18°C.

Swern oxidation of **19** and **20** afforded the corresponding aldehydes which were treated with 4-tert-butylphenylhydroxylamine to yield the cycloadducts **21** and **22**, respectively, via the nitrone intermediates. Again no racemization took place, the cycloadducts were enantiomerically pure as was indicated by the absence of diastereomeric forms. In table 1 characteristic ^{1}H-NMR data of compounds **17**, **18**, **21** and **22** are given.



a : CH_2=C(Cl)CN, Et_3N b : DBU c : conc. HCl d : $(COCl)_2$, DMSO Et_3N e : 4-t-Bu - C_6H_4 - NHOH

Table 1. Characteristic ^{1}H-NMR data of bicyclic compounds (δ in ppm, J in Hertz, solvent $CDCl_3$)

	17	**18**	**21**	**22**
1-H (dd)	4.15	3.98[a)]	4.96	4.71
4-H (d)	4.58	4.16[b)]	4.87	5.22
5-H (dd)	4.52	4.28	4.73	4.58
7-H (d)	4.93	5.15	5.05	5.21
8-H (dd)	3.63	3.57[a)]	3.95	3.91
J1/5	7.75	8.2	7.1	7.85
J1/8	2.9	~0	3.3	2.5
J4/5	5.8	6.8	3.5	7.4
J7/8	6.6	6.3	6.4	6.2

a) only doublet, J1/8 = 0; b) ddd additional coupling with CH_2

Experimental Part

Elemental analyses were performed by the division Routine-Analytik, Fachbereich Chemie, University of Marburg. Spectra were recorded with following instruments: NMR: ^{1}H-NMR 300 MHz Bruker AC 300 if not quoted otherwise, or Bruker AM 400, Bruker AMX 500; ^{13}C-NMR 75 MHz Bruker AC 300. Solvent $CDCl_3$ internal standard residue of ^{1}H (δ = 7.25 ppm) or of ^{13}C (δ = 77.0 ppm) MS: Varian CH 7 (EI) and 711 (FD). - IR: Beckman IR 33 and Bruker IFS 88-FT-IR.

If not stated otherwise, the work up procedure was as follows: The reaction mixture was successively washed with saturated aqueous solutions of NH_4Cl and NaCl and then dried over $MgSO_4$. The solvent was removed and the crude product was purified by chromatography on silica gel if necessary.

(R)-2-Mercapto-1-propanol (**5b**) was prepared from ethyl (R)-2-(acetylthio)-propionate (ee >96%)[10] by reduction with lithium aluminium hydride in Et_2O. Light yellow oil, 65% yield, $[\alpha]_D^{25}$ = +45.5°. - MS (EI): m/e = 91 (16%, M^+). - IR (neat): 3556 cm^{-1}. - ^{1}H-NMR: δ = 1,20 (d, ^{3}J=6,92 Hz, 3H, CH_3); 1,49 (d, ^{3}J=7,26 Hz, 1H, S<u>H</u>); 2,91 (qddd, ^{3}J=7,26 Hz, ^{3}J= 6,92 Hz, ^{3}J=5,57 Hz, ^{3}J=7,05 Hz, 1H, 2-H); 3,30 (s, broad, 1H, O<u>H</u>); 3,35 (dd, ^{2}J=11,00 Hz, ^{3}J = 7,05 Hz, 1H, 1-H); 3,51 (dd, ^{2}J=11,00 Hz, ^{3}J = 5,57 Hz, 1H, 1'-H). - ^{13}C-NMR: δ = 20,8 (q,J=135,6 Hz, <u>C</u>H$_3$); 37,7 (d, J=140,2 Hz, C-2); 69,2 (t, J=144,9 Hz, C-1).

Preparation of alcohols 6: A solution of methyl 4-bromocrotonate (1.75 ml = 2.63 g, 8.40 mmol) in 50 ml of diethyl ether was added to a solution of **5** (8.33 mmol) and triethylamine (1.18 ml = 0.86 g, 8.38 mmol) in 50 ml of diethyl ether. The reaction mixture was stirred for 8 h. After the precipitated triethylammonium bromide had been filtered off the organic solution was worked up as described above.

Methyl (6R)-7-hydroxy-6-isopropyl-5-thia-2-heptenoate (6a) was isolated after chromatography (silicagel/Et_2O R_f = 0.45) as yellow brown oil in 79% yield. - MS (EI): m/e = 218 (7%, M^+). - IR (neat): 3492, 1732 cm^{-1}. - ^{1}H-NMR: δ = 0,79 (d, ^{3}J=6,84 Hz, 3H, CH(C<u>H</u>$_3$)$_2$); 0,87 (d, ^{3}J=6,84 Hz, 3H, CH(C<u>H</u>$_3$)$_2$); 1,86 (hept., ^{3}J=6,84 Hz, ^{3}J=4,84 Hz, 1H, C<u>H</u>(CH$_3$)$_2$); 2,38 (dt, ^{3}J=4,84, ^{3}J=4,70 Hz, 1H, 6-H); 3,00 (broad, 1H, OH); 3,14 (ddd, ^{2}J=13,47 Hz, ^{3}J=7,13 Hz, ^{4}J= 1,35 Hz, 2H, 4-H); 3,53 (d, ^{3}J=4,70 Hz, 2H, 7-H), 3,59 (s, 3H, $CO_2C\underline{H}_3$); 5,75 (dt, ^{3}J=15,45 Hz, ^{4}J=1,35 Hz, 1H; 2-H); 6,75 (dt, ^{3}J=15,45 Hz, ^{3}J=7,13 Hz, 1H, 3-H). - ^{13}C-NMR: δ = 18,7 (q, J=137,9 Hz, CH(C<u>H</u>$_3$)$_2$); 20,4 (q, J=138,9 Hz, CH(C<u>H</u>$_3$)$_2$); 29,0 (d, J=125,7 Hz, C<u>H</u>(CH$_3$)$_2$), 32,9 (t, J=141,4 Hz, C-4); 51,5 (q, J=146,9 Hz, $CO_2\underline{C}H_3$); 55,4 (d, J=142,4 Hz, C-6); 63,3 (t, J=143,0 Hz, C-7); 122,2 (d, J=163,1 Hz, C-2); 144,4 (d, J=160,5 Hz, C-3); 166,4 (s, <u>C</u>O$_2$CH$_3$).

Methyl (6R)-7-hydroxy-6-methyl-5-thia-2-heptenoate (6b): Yellow oil, silicagel/Et_2O R_f = 0.64, 60% yield, $[\alpha]_D^{25}$ = +44.1°. - MS (EI): m/e = 190 (9%, M^+). - IR (neat): 3531, 1729 cm^{-1}. - ^{1}H-NMR: δ = 1,16 (d, ^{3}J=6,90 Hz, 3H, C$\underline{H}_3$); 2,69 (qt, ^{3}J=6,90 Hz, ^{3}J=5,95 Hz, 1H, 6-H); 3,10 (broad, 1H, OH); 3,14 (ddd, ^{2}J=14,40 Hz, ^{3}J=7,62 Hz, ^{4}J=1,14 Hz, 1H, 4-H); 3,23 (ddd, ^{2}J=14,40 Hz, 7,62 Hz, ^{4}J=1,14 Hz, 1H, 4'-H); 3,45 (d, ^{3}J=5,95 Hz, 2H, 7-H/7'-H); 3,60 (s, 3H, $CO_2C\underline{H}_3$); 5,78 (dt, ^{3}J= 15,46 Hz, ^{4}J=1,14 Hz, 1H, 2-H); 6,78 (dt, ^{3}J= 15,46 Hz, ^{3}J=7,62 Hz, 1H, 3-H). - ^{13}C-NMR: δ = 17,6 (q, J=133,5 Hz, $\underline{C}H_3$); 31,5 (t, J=139,6 Hz, C-4); 42,3 (d, J=140,1 Hz, C-6); 51,3 (q, J=138,6 Hz, $CO_2\underline{C}H_3$); 66,1 (t, J=142,1 Hz, C-7); 121,7 (d, J=170,3 Hz, C-2); 142,2 (d, J=168,2 Hz, C-3); 166,6 (s, $\underline{C}O_2CH_3$).

(1S,2S)-2-Dibenzylamino-1-phenyl-3-triphenylmethoxy-1-propanol (13): (1S,2S)-2-Di-benzylamino-1-phenyl-1.3-propanediol was prepared according to the procedure described by X. Holdgrün.[21] Thus benzyl bromide (3.5 ml, 29 mmol) was dropped to a refluxing solution of 3.92 g (28.4 mmol) of potassium carbonate and 1.50 g (9.0 mmol) of (1S,2S)-2-amino-1-phenyl-1.3-propandiol (**12**) in 20 ml of water. Then refluxing was continued for 1 h. After addition of 20 ml of diethyl ether and separation of the two layers, the aqueous layer was extracted twice with diethyl ether. The combined organic solutions were washed and dried. After removal of the solvent, benzylalcohol formed as by-product was destilled off at 2 Torr. The residue was recrystallized from petroleum ether/diethyl ether to give white needles.

Triethylamine (0.45 ml = 0.33 g, 3.2 mmol), triphenylmethylchloride (0.9 g, 3.2 mmol) and a small quantity of 4-dimethylaminopyridine were added successively to a solution of 1 g (2.9 mmol) (1S,2S)-2-dibenzylamino-1-phenyl-1.3-propanediol in 50 ml of dichloromethane. The mixture was stirred for 8 h at room temperature. Removal of the solvent gave **13** as a white solid in 79% yield (1.35 g), mp. 103°C from Et_2O/petroleum ether $[\alpha]_D^{24}$ = +85.2°. - $C_{42}H_{39}NO_2$ (589,8) Calcd. C 85,53 H 6,67 N 2,37 Found C 84,87 H 6,50 N 2,63. - MS (FD): m/e = 589 (100%, M^+). - IR(KBr) :3492, 3178, cm^{-1}. - ^{1}H-NMR: δ = 3,27 (ddd, ^{3}J=9,82 Hz, ^{3}J=6,65 Hz, ^{3}J=3,13 Hz, 1H, 2-H); 3,35 (dd, ^{2}J=10,53 Hz, ^{3}J=3,13 Hz, 1H, 3-H); 3,41 (dd, ^{2}J=10,53 Hz, ^{3}J=6,65 Hz, 1H, 3'-H); 3,54 (d, ^{2}J=13,10 Hz, 2H, PhC$\underline{H}_2$N); 4,00 (d, ^{2}J=13,10 Hz, 2H, PhC$\underline{H}_2$N); 4,51 (d, ^{3}J=9,82 Hz, 1H,1-H); 5,10 (s, 1H, OH); 7,12-7,48 (m, 30H, aromatic H). - ^{13}C-NMR: δ = 54,5 (2t, J=137,9 Hz, Ph$\underline{C}H_2$N); 59,2 (d, J=143,7Hz, C-2); 64,7 (t, J=143,5 Hz, C-3); 70,8 (d, J=151,3 Hz, C-1); 87,4 (s, $Ph_3\underline{C}$); 127,0-147,1 (aromatic C).

(1S,2S)-2-Dibenzylamino-1-phenyl-3-triphenylmethoxy-propane-1-thiol (14): A mixture of **13** (10 g, 17 mmol), triphenylphosphine (4.9 g, 18.7 mmol) and tetrachloromethane (2 ml, 19 mmol) in dry tetrahydrofuran was refluxed under argon for 6 h. After removal of the solvent the crude product was separated from triphenylphosphine oxide by silica gel filtration and subsequently recrystallized from a 6:1 mixture of petroleum ether (40-60°) and Et_2O. Thus (1R,2S)-N-[(1-chloro-1-phenyl-3-triphenylmethoxy)propyl-2]dibenzylamine was isolated in 71% (7.34 g) yield, white solid, mp 79°C, $[\alpha]_D^{24}$ = +3.17°.

According to a general procedure by Speziale[22] a mixture of the chloro compound (10 g, 16.5 mmol) and thiourea in 150 ml of ethanol was refluxed for 8 h. Then the solvent was partially removed by distillation so that 50 ml are left. Subsequently, this solution was added to 100 ml of 6 N NaOH. This mixture was again refluxed for 2 h. The suspension formed in this way was cooled to 0 - 5° C. 2 N hydrochloric acid was cautiously added to adjust a pH of 6.0-6.5. The suspension was twice extracted by dichloromethane. The combined organic layers were worked up to afford **14** as a white solid in 59% (5.89 g) yield, mp 95°C from Et_2O. $[\alpha]_D^{24}$ = +68.43°. $C_{42}H_{39}NOS$ (605.8) Calcd. C 83,27 H 6,49 N 2,31 Found C 82,89 H 6,04 N 2,23 - MS(FD): m/e = 605 (100%, M^+) - ^{1}H-NMR: δ = 2,56 (broad, 1H, SH); 3,17 (ddd, ^{3}J=10,74 Hz, ^{3}J=5,41 Hz, ^{3}J=2,32 Hz, 1H, 2-H); 3,18 (d, ^{2}J=13,64 Hz, 2H, PhC$\underline{H}_2$N); 3,30 (dd, ^{2}J=12,63 Hz, ^{3}J=5,41 Hz, 1H, 3-H); 3,31 (dd, ^{2}J=12,63 Hz, ^{3}J=2,32 Hz, 1H, 3'-H); 3,91 (d, ^{2}J=13,64 Hz, 2H, PhC$\underline{H}_2$N); 4,58 (d, ^{3}J=10,74 Hz, 1H, 1-H); 7,16-7,50 (m, 30H, aromatic H); - ^{13}C-NMR: δ = 45,5 (d, J=145,2, C-1); 54,5 (t, J=138,1 Hz, Ph$\underline{C}H_2$N); 58,1 (d, J=142,7 Hz, C-2); 62,8 (t, J=148,9 Hz, C-3); 87,0 (s, $Ph_3\underline{C}$); 126,9-143,4 (aromatic C).

Methyl (5S,6S)-6-dibenzylamino-7-hydroxy-5-phenyl-4-thia-2-heptenoate (15): A solution of **14** (10 g, 16.5 mmol) and triethylamine (2.3 ml = 1.67 g, 16.5 mmol) in 50 ml of dichloromethane was dropped at 0° C to a solution of methyl propiolate

(1.47 ml, 1.42 g, 16.5 mmol) in 50 ml of dichloromethane. After stirring for 2 h, the reaction mixture was worked up. Chromatography on silica gel with Et_2O as solvent afforded methyl (5S,6S)-dibenzylamino-5-phenyl-7-triphenylmethoxy-4-thia-heptenoate in 77% yield (8.75 g) as white solid, mp 107°C from Et_2O/hexane, $R_f = 0.71$, $[\alpha]_D^{24} = +11.2°$. - $C_{46}H_{43}NO_3S$ (689,9) Calcd.: C 80,08 H 6,28 N 2,03 Found C 80,59 H 6,01 N 2,27 - MS(FD): m/e = 689 (70%; M^+). - IR(KBr): 1749 cm^{-1}.- ^{1}H-NMR: δ = 3,22 (dd, ^{2}J=10,37 Hz, ^{3}J=5,01 Hz, 1H, 7-H); 3,29 (d, ^{2}J=13,69 Hz, 2H, PhC$\underline{H}_2$N); 3,42 (ddd, ^{3}J=11,12 Hz, ^{3}J=5,50 Hz, ^{3}J=5,01 Hz, 1H, 6-H); 3,43 (dd, ^{2}J=10,37 Hz, ^{3}J=5,50 Hz, 1H, 7'-H); 3,64 (s, 3H, $CO_2C\underline{H}_3$); 3,96 (d ^{2}J=13,69 Hz, 2H, PhC$\underline{H}_2$N); 4,75 (d, ^{3}J=11,12 Hz, 1H, 5-H); 5,89 (d, ^{3}J=15,45 Hz, 1H, 2-H); 7,18-7,52 (m, 31H, 3-H, aromatic H). - ^{13}C-NMR: δ = 51,2 (q, J=146,0 Hz, $CO_2\underline{C}H_3$); 53,4 (d, J=131,0 Hz, C-6); 54,5 (t, J=142,1 Hz, Ph$\underline{C}H_2$N); 58,5 (t, J=143,0 Hz, C-7); 61,7 (d, J=135,4 Hz, C-5); 87,2 (s, $Ph_3\underline{C}$); 114,5 (d, J=165,0 Hz, C-2); 126,0-143,3 (aromatic C); 147,5 (d, J=169,7 Hz, C-3); 165,7(s, $\underline{C}O_2CH_3$).

To remove the triphenylmethyl group 4 ml of concentrated HCl were added to a solution of the triphenylmethyl-protected compound (10.0 g, 16 mmol) in dichloromethane. The mixture was vigorously stirred. The progress of the reaction was observed by thin layer chromatography. After 3 to 5 hours the reaction was finished. The residue was purified from triphenylmethanol by recrystallization from Et_2O at -18°C. **15** was isolated in 63% yield (4,50 g) as white solid, mp 97° from Et_2O/petroleum ether (40-60°), $[\alpha]_D^{25} = +47,7°$. - MS(FD): m/e = 447 (55%; M^+) - IR(KBr): 3450, 1756, cm^{-1}. - ^{1}H-NMR: δ = 2,10 (broad, 1H, OH); 3,20-3,41 (m, 3H, 6-H/7-H); 3,58 (s, 3H, $CO_2C\underline{H}_3$); 3,79 (d, ^{2}J=13,41 Hz, 2H, PhC$\underline{H}_2$N); 4,03 (d, ^{2}J=13,41 Hz, 2H, PhC$\underline{H}_2$N); 4,56 (d, ^{3}J=10,41 Hz, 1H, 5-H); 5,82 (d, ^{3}J=15,43 Hz, 1H, 2-H); 7,18-7,44 (m, 31H, 3-H, aromatic H); - ^{13}C-NMR: δ = 51,5 (q, J=145,1 Hz, $CO_2\underline{C}H_3$); 52,8 (d, J=134,7 Hz, C-6); 54,6 (t, J=143,2 Hz, Ph$\underline{C}H_2$N); 59,4 (t, J=144,0 Hz, C-7); 63,0 (d, J=134,1 Hz, C-5); 115,1 (d, J=167,6 Hz, C-2); 127-143,8 (aromatic C); 147,1 (d, J=173,5 Hz, C-3); 165,7 (s, $\underline{C}O_2CH_3$).

E-(5S,6S)-6-Dibenzylamino-7-hydroxy-5-phenyl-4-thia-2-heptenenitrile (19) and *Z-(5S,6S)-6-dibenzylamino-7-hydroxy-5-phenyl-4-thia-2-heptenenitrile (20)*: A solution of **14** (10.0 g, 16.5 mmol) and triethylamine (2.3 ml, 1.67 g, 16.5 mmol) in 50 ml of dichloromethane was dropped to a solution of 2-chloro acrylonitrile (1.32 ml, 1.45 g, 16.5 mmol) in 50 ml of dichloromethane at 0°C. The reaction mixture was stirred for 3 h at room temperature. The crude product was purified by chromatography on silica gel. In this way a mixture of the two diastereomers (2R,5S,6S)- and (2S,5S,6S)-2-chloro-6-dibenzylamino-5-phenyl-7-triphenylmethoxy-4-thia-heptanenitrile was formed in 69% yield (7.53 g) as a light-yellow solid from mp 94°C in the ratio of 5:4. MS(FD): m/e = 693 (64%; M^+). - IR(KBr): 2234 cm^{-1}. - 1. Diastereomer: ^{1}H-NMR: δ = 2,48 (dd, ^{2}J=14,53 Hz, ^{3}J=6,30 Hz, 1H,3-H); 2,74 (dd, ^{2}J=14,53 Hz, ^{3}J=8,11 Hz, 1H, 3'); 3,16-3,45 (m, 5H, 6-H/7-H/7'-H/PhC$\underline{H}_2$N), 3,96 (d,^{2}J=13,41 Hz, 2H, PhC$\underline{H}_2$N); 4,12 (dd,^{3}J=8,11 Hz, ^{3}J=6,30 Hz, 1H, 2-H); 4,55 (d, ^{3}J=10,88 Hz, 1H, 5-H); 7,20-7,60 (m, 30H, aromatic H); - ^{13}C-NMR: δ = 35,9 (t, J=135,7 Hz, C-3); 42,2 (d, J=147,4 Hz, C-5); 52,0 (d, J=142,1 Hz, C-2); 54,5 (2t, J=134,1 Hz, Ph$\underline{C}H_2$N); 59,1 (d, J=139,2 Hz, C-6); 62,3 (t, J=145,2 Hz, C-7); 87,2 (s, $Ph_3\underline{C}$); 116,5 (s, $\underline{C}N$); 126,8-143,4 (aromatic C). - 2. Diastereomer: ^{1}H-NMR: δ = 2,66 (dd, ^{2}J=14,55 Hz, ^{3}J=6,20 Hz, 1H, 3-H); 2,67 (dd, ^{2}J=14,55 Hz, ^{3}J=9,65 Hz, 1H, 3'-H); 3,17-3,49 (m, 5H, 6-H/7-H/7'-H/PhC$\underline{H}_2$N), 3,82 (dd, ^{3}J=9,65 Hz, ^{3}J=6,20 Hz, 1H, 2-H); 3,98 (d, ^{2}J=14,50 Hz, 2H, PhC$\underline{H}_2$N); 4,81 (d,^{3}J=11,10 Hz, 1H, 5-H); 7,21-7,62 (m, 30H, aromatic H). - ^{13}C-NMR: δ = 35,6 (t, J=132,9 Hz, C-3); 41,9 (d, J=148,4 Hz, C-2); 52,5 (d, J=143,0 Hz, C-5); 54,3 (2t, J=132,0 Hz, Ph$\underline{C}H_2$N); 58,6 (d, J=138,7 Hz, C-6); 61,9 (t, J=146,1 Hz, C-7); 87,1 (s, $Ph_3\underline{C}$); 117,1 (s, $\underline{C}N$); 126,9-144,0 (aromatic C).

The mixture of these diastereomers (10.0 g, 145 mmol) was dehydrohalogenated in dichloromethane by 1.8-diazabicyclo[5.4.0]undecene-7[19] (2.4 ml, 2.44 g, 16 mmol). The reaction mixture was stirred for 6 h. The crude product was purified by chromatography on silica gel. (Mixture of E and Z isomers in the ratio of 3:2). Separation of the diastereomers was possible by crystallization from Et_2O/petroleum ether at -18°C. The Z-isomer was enriched in the crystalline phase, whereas the E-isomer remained largely in the mother liquor. In this way *E-(5S,6S)-6-dibenzylamino-5-phenyl-7-triphenylmethoxy-4-thia-2-heptenenitrile* was isolated as a white solid in 56% yield (5.07 g), mp 83°C from Et_2O/petroleum ether 40-60, 1:6, $[\alpha]_D^{25} = +18.9°$

- MS(FD): m/e = 656 (71%; M^+). - IR(KBr): 2241 cm^{-1}. - ^{1}H-NMR: δ = 3,12 (m, 3H, 6-H/7-H/7'-H); 3,20 (d, ^{2}J=13,43 Hz, 2H, PhC$\underline{H}_2$N); 3,88 (d, ^{2}J=13,43 Hz, 2H, PhC$\underline{H}_2$N); 4,67 (d, ^{3}J=11,25 Hz, 1H, 5-H); 5,24 (d, ^{2}J=16,06 Hz, 1H, 2-H), 6,93 (d, ^{2}J=16,06 Hz, 1H, 3-H); 7,20-7,45 (m, 30H, aromatic H). - ^{13}C-NMR: δ = 53,8 (d, J=139,4 Hz, C-5), 54,5 (t, J=133,6 Hz, Ph$\underline{C}H_2$N); 58,3 (d, J=140,7 Hz, C-6); 61,7 (t, J=145,7 Hz, C-7), 87,3 (s, $Ph_3\underline{C}$); 92,5 (d, J=158,9 Hz, C-2); 117,7 (s, $\underline{C}$N); 127,1-143,5 (aromatic C), 153,0 (d, J=161,6 Hz, C-3).

Z-(5S,6S)-6-dibenzylamino-5-phenyl-7-triphenylmethoxy-4-thia-2-heptenenitrile was isolated in 32% yield (3.4 g) $[\alpha]_D^{25}$ = +24.9° - MS(FD): m/e = 656 (86%; M^+). - IR (KBr): 2214 cm^{-1}. - ^{1}H-NMR: δ = 3,20 (dd, ^{2}J=11,70 Hz, ^{3}J=4,60 Hz, 1H, 7-H); 3,24 (d, ^{2}J=13,56 Hz, 2H, PhC$\underline{H}_2$N); 3,41 (dd, ^{2}J=11,70 Hz, ^{3}J=2,35 Hz, 1H, 7'-H); 3,45 (ddd, ^{3}J=11,09 Hz, ^{3}J=4,60 Hz, ^{3}J=2,35 Hz, 1H, 6-H); 3,97 (d, ^{2}J=13,56 Hz, 2H, PhC$\underline{H}_2$N); 4,79 (d, ^{3}J=11,09 Hz, 1H, 5-H); 5,02 (d, ^{3}J=10,62 Hz, 2-H); 7,01 (d, ^{3}J=10,62 Hz, 1H, 3-H); 7,10-7,52 (m, 30H, aromatic H). - ^{13}C-NMR: δ = 54,2 (d, J=140,2 Hz, C-5); 54,7 (t, J=135,6 Hz, Ph$\underline{C}H_2$N); 58,5 (d, J=138,7 Hz, C-6); 61,8 (t, J=144,4 Hz, C-7); 87,5 (s, $Ph_3\underline{C}$); 92,7 (d, J=163,2 Hz, C-2); 116,5 (s, $\underline{C}$N); 127,4-147,0 (aromatic C), 152,5 (d, J=166,9 Hz, C-3).

The removal of the protecting triphenylmethyl group from a mixture of the E/Z-isomers was performed as described for the preparation of **15**. The product mixture was separated from triphenylmethanol by chromatography on silica gel. Separation of the E- and the Z-isomer occurred by fractionated recrystallization from Et_2O at -18°C. Whereas the E-isomer crystallized, the Z-isomer remained largely in mother liquor.

E-(5S,6S)-6-Dibenzylamino-7-hydroxy-5-phenyl-4-thia-2-heptenenitrile (19): white solid, mp 75°C from Et_2O/petroleum ether, $[\alpha]_D^{25}$ = +67.5°, yield 40% (2.65 g). - $C_{26}H_{26}N_2OS$ (414,6) Calcd. C 75,32 H 6,32 N 6,75 Found C 75,05 H 5,97 N 6,49. - MS(FD): m/e = 414 (100%; M^+). - IR (KBr): 3471, 2212 cm^{-1}. - ^{1}H-NMR: δ = 1,91 (broad, 1H, OH), 3,20 (ddd, ^{3}J=10,80 Hz, ^{3}J=2,62 Hz, ^{3}J=6,34 Hz, 1H, 6-H); 3,40 (dd, ^{2}J=11,34 Hz, ^{3}J=6,34Hz, 1H, 7-H); 3,63 (dd, ^{2}J=11,34 Hz, ^{3}J=2,62 Hz, 1H, 7'-H), 3,77 (d, ^{2}J=13,45 Hz, 1H, PhC$\underline{H}_2$N); 4,09 (d, ^{2}J=13,45 Hz, 1H, PhC$\underline{H}$N); 4,68 (d, ^{3}J=10,80 Hz, 1H, 5-H); 5,27 (d, ^{3}J=16,12 Hz, 1H, 2-H); 7,01 (d, ^{3}J=16,12 Hz, 3-H); 7,21-7,49 (m, 15H, aromatic H). - ^{13}C-NMR: δ = 53,0 (d, J=145,6 Hz, C-5); 54,7 (2t, J=134,7 Hz,Ph$\underline{C}H_2$N); 58,9 (d, J=143,5 Hz, C-6); 62,9 (t, J=147,2 Hz, C-7); 93,0 (d, J=159,6 Hz, C-2); 117,6 (s, $\underline{C}$N); 127,1-139,2 (aromatic C); 152,2 (d, J=164,4 Hz, C-3).

Z-(5S,6S)-6-Dibenzylamino-7-hydroxy-5-phenyl-4-thia-2-heptenenitrile (20): white solid, mp 81°C from Et_2O, $[\alpha]_D^{25}$ = +62.8°, yield 31% (2.12 g). - $C_{26}H_{26}N_2OS$ (414,6) Calcd. C 75,32 H 6,32 N 6,75 Found C 75,21 H 6,43 N 6,69 - MS(FD): m/e = 414 (100%; M^+).- IR(KBr): 3590, 2204 cm^{-1}. - ^{1}H-NMR: δ = 1,80 (broad, 1H, OH); 3,22 (ddd, ^{3}J=10,77 Hz,^{3}J=6,81 Hz, ^{3}J=3,23 Hz, 1H, 6-H); 3,34 (dd, ^{2}J=11,24 Hz, ^{3}J=6,81 Hz, 1H, 7-H); 3,49 (dd, ^{2}J=11,24 Hz, ^{3}J=3,22 Hz, 1H, 7'-H); 3,74 (d, ^{2}J=13,39 Hz, 1H,PhC$\underline{H}_2$N); 4,05 (d, ^{2}J=13,39 Hz, 1H, PhC$\underline{H}_2$N); 4,61 (d, ^{3}J=10,77 Hz, 1H, 5-H); 5,06 (d, ^{3}J=10,50 Hz, 1H, 2-H); 6,68 (d, ^{3}J=10,50 Hz, 1H, 3-H); 7,15-7,43 (m, 15H, aromatic H).- ^{13}C-NMR: δ = 53,4 (d, J=136,5 Hz, C-5); 54,5 (t, J=132,3 Hz,Ph$\underline{C}H_2$N); 59,1 (d, J=142,7 Hz, C-6); 62,7 (t, J=146,3 Hz, C-7); 93,2 (d, J=161,8 Hz, C-2); 115,9 (s, $\underline{C}$N); 127,2-139,0 (aromatic C); 151,3 (d, J=157,9 Hz, C-3).

Formation of the bicyclic compounds 8, 17, 21 and 22 from the corresponding alcohols by Swern oxidation to aldehydes and subsequent reaction with N-alkyl- or N-arylhydroxylamines: To a solution of 0.44 ml (0.64 g, 5 mmol) of oxalyl chloride in 50 ml of dichloromethane 0.60 ml (0.66 g, 8.6 mmol) of dimethyl sulfoxide dissolved in 5 ml of dichloromethane were dropped at -78°C. After the solution had been stirred for 15 min, 4.2 mmol of the alcohol in 20 ml of dichloromethane were added. The reaction mixture was stirred for 1 h then 2.26 ml (1.64 g, 16.2 mmol) of triethylamine were added and the mixture was stirred for further 5 min at -78°C. Subsequently, it is allowed to warm up to 0°C. Addition of 20 ml of water, 4.62 mmol of alkyl or arylhydroxylamine and 10 g of dry $MgSO_4$ was performed successively. The reaction mixture was stirred for another 12 h. The crude product could be purified by chromatography on silica gel.

2-Benzyl-8-isopropyl-4-methoxycarbonyl-3-oxa-7-thia-2-azabicyclo[3.3.0]octane (8a): Yellow-brown oil, from chromatography on silicagel, Et_2O/petroleum ether (40/60) 5:1, R_f = 0.76. - 57% yield. - MS(EI): m/e = 321 (6%; M^+). - IR (neat): 1758 cm^{-1}.- ^{1}H-NMR (500 MHz): δ = 0,74 (d, ^{3}J=6,67 Hz, 6H, CH(C<u>H</u>$_3$)$_2$) 1,59 (dq,^{3}J=6,67 Hz, ^{3}J=5,80 Hz, 1H, C<u>H</u>(CH$_3$)$_2$); 2,85 (dd, ^{2}J=12,0 Hz, ^{3}J=2,50 Hz, 1H, 6-H); 2,99 (dd, ^{3}J=5,80 Hz, ^{3}J=3,35, 1H, 8-H); 3,03 (dd, ^{2}J=12,0Hz, ^{3}J=6,20 Hz, 1H, 6'-H); 3,48 (dddd, ^{3}J=6,95Hz, ^{3}J=6,20 Hz, ^{3}J=6,55 Hz, ^{3}J=2,50 Hz, 1H, 5-H), 3,49 (dd, ^{3}J=6,95, ^{3}J=3,35, 1H, 1-H); 3,70 (s, 3H, $CO_2C\underline{H}_3$); 3,79 (d, ^{2}J=13,05 Hz, 1H, PhC<u>H</u>$_2$N); 4,17 (d,^{2}J=13,05 Hz, 1H, PhC<u>H</u>$_2$N); 4,34 (d, ^{3}J=6,55Hz, 1H, 4-H); 7,18-7,32 (m, 5H, aromatic H); ^{13}C-NMR: δ = 19,1 (q, J=143,6 Hz, CH(C<u>H</u>$_3$)$_2$); 21,2 (q, J=143,7Hz, CH(C<u>H</u>$_3$)$_2$); 29,1 (t, J=135,8 Hz, C-6); 32,4 (d, J=145,1 Hz, C<u>H</u>(CH$_3$)$_2$); 51,7 (d, J=147,9 HzC-8); 56,0 (t, J=139,4 Hz, PhC<u>H</u>N); 59,6 (q, J=143,8Hz, CO_2CH_3); 62,9 (d, J=148, 5 Hz, C-5), 78,3 (d, J=149,3 Hz, C-1); 81,1 (d, J=153,8 Hz, C-4); 124,2-141,0 (aromatic C); 171,6 (s, <u>C</u>O$_2$CH$_3$); enantiomeric excess of the (1S,4S,5S,8S)-isomer = 34%.

2-Benzyl-8-methyl-4-methoxycarbonyl-3-oxa-7-thia-2-azabicyclo[3.3.0]octane (8b): Colourless, viscous oil from chromatography on silica gel CH_2Cl_2/petroleum ether (40/60) 4:1, 48% yield.-.MS(EI): m/e = 293 (14%; M^+). - IR(neat): 1719 cm^{-1}. -^{1}H-NMR (400 MHz): δ = 1,04 (d, ^{3}J=7,00 Hz, 3H, C<u>H</u>$_3$); 2,87 (dd, ^{2}J=12,26 Hz, ^{3}J=2,72 Hz, 1H, 6-H); 2,93 (qd, ^{3}J=7,00 Hz, ^{3}J=3,74 Hz, 1H, 8-H); 3,12 (dd, ^{2}J=12,26 Hz, ^{3}J=6,97 Hz, 1H, 6'-H); 3,30 (dd, ^{3}J=7,70 Hz, ^{3}J=3,74 Hz, 1H, 1-H); 3,50 (dddd, ^{3}J=7,70 Hz, ^{3}J=6,97 Hz, ^{3}J=5,11 Hz, ^{3}J=2,72 Hz, 1H, 5-H); 3,73 (s, 3H, $CO_2C\underline{H}_3$); 3,79 (d, ^{2}J=12,67 Hz, 1H, PhC<u>H</u>$_2$N); 4,28 (d, ^{2}J=12,67 Hz, 1H, PhC<u>H</u>$_2$N); 4,31 (d, ^{3}J=5,11 Hz, 1H, 4-H); 7,10-7,30 (m, 5H, aromatic H) - ^{13}C-NMR: δ = 20,1 (q, J=133,4 Hz, <u>C</u>H$_3$); 33,6 (t, J=138,4 Hz, C-6); 46,7 (d, J=142,1 Hz,C-8); 52,4 (q, J=139,1 Hz, $CO_2\underline{C}H_3$); 55,6 (d, J=141,1 Hz, C-5); 63,1 (t, J=132,6 Hz, Ph<u>C</u>H$_2$N); 81,0 (d, J=141,9 Hz, C-1); 81,9 (d, J=150,3 Hz, C-4); 127,0-136,4 (aromatic C); 171,2 (s, <u>C</u>O$_2$CH$_3$); enantiomeric excess of the (1S,4S,5S,8R)-isomer = 10%.

(1S,4S,5R,7S,8S)-2-Benzyl-8-dibenzylamino-4-methoxycarbonyl-7-phenyl-3-oxa-6-thia-2-azabicyclo[3.3.0]octane (17): White solid from chromatography on silica gel, CH_2Cl_2 R_f = 0.72, mp 78°C from Et_2O/hexane $[\alpha]_D^{25}$ = -28.2°, de>98%.- 90% yield, $C_{34}H_{34}N_2O_3S$ (550,7) Calcd. C 74,15 H 6,22 N 5,09 Found C 74,55 H 6,46 N 4,63 - MS(FD): m/e = 550 (100%; M^+). - IR(KBr): 1747 cm^{-1}. - ^{1}H-NMR: δ = 3,34 (d, ^{2}J=13,84 Hz, 2H, PhC<u>H</u>$_2$N); 3,63 (dd,^{3}J=6,60 Hz, ^{3}J=2,90 Hz, 1H, 8α-H); 3,78 (s, 3H $CO_2C\underline{H}_3$); 3,89 (d, ^{2}J=13,84 Hz, 2H, PhC<u>H</u>$_2$N); 3,91 (d, ^{2}J=13,92 Hz, 1H, PhC<u>H</u>$_2$NO); 4,09 (d, ^{2}J=13,92 Hz, 1H, PhC<u>H</u>$_2$NO); 4,15 (dd, ^{3}J=7,75Hz, ^{3}J=2,90 Hz, 1H, 1ß-H); 4,52 (dd, ^{3}J=7,75 Hz, ^{3}J=5,78 Hz, 1H, 5ß-H); 4,58 (d, ^{3}J= 5,78 Hz, 1H, 4α-H); 4,93 (d, ^{3}J=6,60 Hz, 1H, 7α-H); 6,60-7,40 (m, 20H, aromatic H). - ^{13}C-NMR: δ = 52,6 (q, J=141,2 Hz, $CO_2\underline{C}H_3$); 54,8 (d, J=142,3 Hz, C-7); 55,5 (t[double intensity], J=132,1 Hz, Ph<u>C</u>H$_2$N); 55,6 (d, J=138,3 Hz, C-5); 61,7 (t, J=132,6Hz, Ph<u>C</u>H$_2$NO); 68,5 (d, J=137,4 Hz, C-8); 74,8 (d, J=141,8 Hz,C-1); 86,3 (d, J=156,2 Hz, C-4); 127,0-140,1 (aromatic C); 170,5 (s,<u>C</u>O$_2$CH$_3$).

(1S,4S,5R,7S,8S)-2-(4-tert-Butylphenyl)-4-cyano-8-dibenzylamino-7-phenyl-3-oxa-6-thia-2-azabicyclo[3.3.0]octane (21): Yellow solid, mp 67°C from Et_2O/petroleum ether, $[\alpha]_D^{25}$ = -37.6°, de>98%.- 43% yield, $C_{36}H_{37}N_3OS$ (559.8) Calcd. C 77.24 H 6.66 N 7.50 Found C 77.40 H 6.86 N 7.77 - MS(FD): m/e = 559 (100%; M^+). - IR(KBr): 2231 cm^{-1}. - ^{1}H-NMR: δ = 1,31 (s, 9H, C(C<u>H</u>$_3$)$_3$); 3,45 (d, ^{2}J=13,78 Hz, PhC<u>H</u>$_2$N); 3,86 (d, ^{2}J=13,78 Hz, 1H, PhC<u>H</u>$_2$N); 3,95 (dd,^{3}J=6,39 Hz, ^{3}J=3,30 Hz, 1H, 8α-H); 4,73 (dd,^{3}J=7,11 Hz, ^{3}J=3,53 Hz, 1H, 5ß-H); 4,87 (d, ^{3}J=3,53 Hz, 1H, 4α-H); 4,96 (dd, ^{3}J=7,11 Hz, ^{3}J=3,30 Hz, 1H, 1ß-H); 5,05 (d, ^{3}J=6,39 Hz, 1H, 7α-H); 7,10-7,51 (m, 19H, aromatic H); - ^{13}C-NMR: δ = 31,3 (q, J=138,4 Hz,C(<u>C</u>H$_3$)$_3$); 35,1 (s, <u>C</u>(CH$_3$)$_3$); 55,4 (t[double intensity], J=136,7 Hz,Ph<u>C</u>H$_2$N); 55,6 (d,J=144,2 Hz,C-5); 57,6 (d, J=142,1 Hz, C-7); 69,2 (d, J=139,5 Hz, C-8), 74,3 (d, J=146,8 Hz, C-1); 74,5 (d, J=152,1 Hz, C-4); 116,8 (s, <u>C</u>N); 121,1-157,3 (aromatic C).

(1S,4R,5R,7S,8S)-2-(4-tert-Butylphenyl)-4-cyano-8-dibenzylamino-7-phenyl-3-oxa-6-thia-2-azabicyclo[3.3.0]octane (22): Yellow-brown oil from chromatography on silica gel, CH_2Cl_2 R_f = 0.39, $[\alpha]_D^{25}$ = -37.6°, de>98%.- 37% yield. - MS(EI): m/e = 559 (6%; M^+) - IR(neat): 2214 cm^{-1} - ^{1}H-NMR: δ = 1,45 (s, 9H, tBu); 3.44 (d, ^{2}J=13,74 Hz, 2H, PhC<u>H</u>$_2$N); 3,91 (dd, ^{3}J=6,22

Hz, ^{3}J=2,50 Hz, 1H, 8α-H); 4,00 (d, ^{2}J=13,72 Hz, 2H, PhC$\underline{H}_2$N); 4,58dd, ^{3}J=7,84 Hz, ^{3}J=7,40 Hz, 1H, 5ß-H); 4,71 (dd,^{3}J=7,84 Hz, ^{3}J=2,50 Hz, 1H, 1ß-H); 5,21 (d, ^{3}J=6,22 Hz, 1H, 7α-H); 5,22 (d, ^{3}J=7,40 Hz, 1H, 4ß-H); 6,70-7,50 (m, 19H, aromatic H); - ^{13}C-NMR: δ = 31,2 (q, J=133,6 Hz, C($\underline{C}H_3)_3$); 34,7 (s, $\underline{C}(CH_3)_3$); 54,2 (d, J=139,1 Hz, C-7); 55,5 (t, J =137,2 Hz, Ph$\underline{C}H_2$N); 56,4 (d, J=141,2 Hz, C-5); 68,8 (d, J=145,2 Hz, C-8); 73,4 (d, J=140,8 Hz, C-1); 75,6 (d, J=149,4 Hz, C-4); 115,7 (s, CN); 120,1-150,0 (aromatic C).

2-(S)-α-Methylbenzyl-4-methoxycarbonyl-3-oxa-7-thia-2-azabicyclo[3.3.0]octane (10/11). (S)-α-Methylbenzylhydroxylamine oxalate[3a] (1.6 g, 6.65 mmol) and triethylamine (1 ml = 0.7 g, 6.7 mmol) were added successively to a solution of methyl 7-oxa-5-thia-2-heptenoate[5d] (1.1 g, 6.50 mmol) in dichloromethane. Then 10 g of dry $MgSO_4$ were added and the mixture was stirred at room temperature for 18 h. Yellow, viscous oil from chromatography on silica gel with Et_2O, yield 62%, mixture of diastereomers. 1R,2S,4R,5R and 1S,2S,4S,5S in the ratio of 77:23. - MS (EI): m/e = 293 (15%, M^+). - ^{13}C-NMR: δ = 21.3/21,7 (2q, PhCH$\underline{C}H_3$); 33,8/34,7 (2t, C-6); 34,6/37,0 (2t, broadened, C-8); 52,0/52,2 (2q, $CO_2\underline{C}H_3$); 55,4/56,3 (2d, C-1); 64,9/67,7 (2d, Ph$\underline{C}$HCH$_3$); 71,4/73,7 (2d,, C-5); 79,4/80,6 (2d, C-4); 121,1-142,2 (aromatic C); 170,6/171,3 (2s, $\underline{C}O_2$Me).- Major isomer: ^{1}H-NMR: δ = 1,50 (d, ^{3}J = 6,35 Hz, 3H, PhCHC$\underline{H}_3$); 2,34 (dd, broad, ^{2}J = 12,20 Hz, 1H, 8-H); 2.42 (dd, ^{2}J = 12,20 Hz, ^{3}J = 6,80 Hz, 1H, 8'-H); 2,84 (dd, ^{2}J = 12,30 Hz, ^{3}J = 4,60 Hz, 1H, 6-H); 2,86 (dd, ^{2}J = 12,30 Hz, 1H, 6'-H); 3,38 (dddd, ^{3}J = 7,60 Hz, ^{3}J = 7,60 Hz, 1H, 5-H); 3,71 (s, 3H, $CO_2C\underline{H}_3$); 3,72 (ddd, ^{3}J = 6,80 Hz, 1H, 1-H); 3,78 (q, ^{3}J = 6,35, 1H, PhC$\underline{H}$CH$_3$); 4,30 (d, ^{3}J = 7,60 Hz, 1H, 4-H); 7,1-7,3 (m, 5H, aromatic H). - Minor isomer: δ = 1,39 (d, ^{3}J = 6,74 Hz, 3H, PhCHC$\underline{H}_3$); 4,19 (d, ^{3}J = 10,35 Hz, 1H, 4-H).

Reduction of bicyclic esters 8 and 17. Lithium aluminium hydride (0.46 g, 12 mmol) was cautiously added to a solution of the ester (10 mmol) in carefully dried diethyl ether at 0°C. After the reaction mixture had been stirred for 2 h at room temperature, 10 ml of a saturated aqueous solution of ammonium chloride were added at 0°C. The aqueous layer was washed with several 10 ml-portions of diethyl ether. Then the joined organic phases were dried over $MgSO_4$.

(1S,4S,5R,7S,8S)-2-Benzyl-8-dibenzylamino-4-hydroxymethyl-7-phenyl-3-oxa-6-thia-2-azabicyclo[3.3.0]octane (18) was obtained from reduction of 17 in 80% yield after chromatography in Et_2O as light-yellow solid, mp 123°C from Et_2O/petroleum ether (40/60). $[\alpha]_D^{25}$ = +46.1° de>98%. - $C_{34}H_{34}N_2O_2S$ (522,7) Calcd. C 75,83 H 6,56 N 5,36 Found C 75,48 H 6,70 N 4,85. - MS(FD): m/e = 522 (100%, M^+); - ^{1}H-NMR: δ = 2,54 (s, broad, 1H, OH); 3,47 (d, ^{2}J=14,05 Hz, 2H, PhC$\underline{H}_2$N); 3,57 (d, ^{3}J=6,30 Hz, 1H, 8α-H); 3,72 (dd, ^{2}J=12,47 Hz, ^{3}J=3,70 Hz, 1H, C$\underline{H}_2$OH); 3,89 (d, ^{2}J=14,45 Hz, 1H, PhC$\underline{H}_2$N); 3,92 (dd, ^{2}J=12,47 Hz, ^{3}J=2,60 Hz 1H, C$\underline{H}_2$OH); 3,98 (d, ^{3}J=8,20 Hz, 1H, 1ß-H); 4,07 (d, ^{2}J=14,45 Hz, 1H, PhC$\underline{H}_2$N); 4,16 (ddd, ^{3}J=6,80 Hz, ^{3}J=3,70 Hz, ^{3}J=2,60 Hz, 1H, 4α-H); 4,20 (d, 14,05 Hz, 2H, PhC$\underline{H}_2$N); 4,28 (dd, ^{3}J=8,20 Hz, ^{3}J=6,80 Hz, 1H, 5ß-H); 5,15 (d, ^{3}J=6,30 Hz, 1H. 7α-H); 7,0-7,30 (m, 20H, aromatic H); - ^{13}C-NMR: δ = 53,0 (t, J=137,0 Hz, Ph$\underline{C}H_2$N); 55,9 (t[double intensity], J=138,8 Hz, Ph$\underline{C}H_2$N); 61,0 and 61,2 (2d, J=140,1 Hz/J=139,0 Hz, C-5 and C-7); 65,9 and 69,1 (2d, J=142,0 Hz / 143,9 Hz, C-1 and C-8); 76,4 (t, J=141,9 Hz, $\underline{C}H_2$OH); 88,1 (d, J=148,0 Hz, C-4); 126,6-139,3 (aromatic C).

2-Benzyl-4-hydroxymethyl-8-isopropyl-3-oxa-7-thia-2-azabicyclo[3.3.0]octane was isolated after chromatography as yellow oil in 76% yield from reduction of **8a**. MS (EI): m/e = 293 (12%, M^+).- IR (neat): 3468 cm^{-1}.

2-Benzyl-4-hydroxymethyl-8-methyl-3-oxa-7-thia-2-azabicyclo[3.3.0]octane was isolated after chromatography in Et_2O as yellow oil in 66% yield from reduction of **8b**. MS (FD): m/e = 265 (100%, M^+). - IR (neat): 3521 cm^{-1}.

Determination of the enantiomeric excess by formation of diastereomers.

Formation of an ester from *(S)-(+)-O-acetyl mandelic acid and 2-benzyl-4-hydroxymethyl-8-methyl-3-oxa-7-thia-2-azabicyclo[3.3.0]octane*: 1 Mmol of the bicyclic compound was dissolved in dichloromethane (20 ml) then 1.2 mmol of (S)-(+)-O-acetyl mandelic acid, 1.2 mmol N.N'-dicyclohexylcarbodiimide and a small quantity of N.N'-dimethyamino pyridine were successively added at 0°C. The solution was stirred at room temperature for 8 h. The N.N'-dicyclohexyl urea was filtered off, the

solution was washed and dried. After removal of the solvent the crude product was subjected to spectroscopic analysis without further purification. The ester was obtained as a light-yellow oil in 56% yield. Mixture of the diastereomers (αS-1S,4S,5S,8R) and (αS-1R,4R,5R,8R) in ratio of 5:4, de = 11%. - MS(EI): m/e= 441 (3% ; M^+); - IR(neat): 1778, 1745, cm^{-1}. - ^{1}H-NMR (400 MHz): δ 0,94 (d, ^{3}J=4,70 Hz, 3H, 8-C$\underline{H}_3$); 2,18 (s, 3H, CH_3CO_2); 2,48 (dd, ^{2}J=12,25 Hz, ^{3}J=2,25 Hz, 1H, 6-H); 2,73-2,85 (m, 3H, 8-H, 6'-H, 5-H); 2,98 (dd, ^{3}J=7,80 Hz, ^{3}J=2,55 Hz, 1H, 1-H); 3,64 (d, ^{2}J=12,75 Hz, 1H, PhC$\underline{H}_2$N); 3,85 (ddd, ^{3}J=5,0 Hz, ^{3}J=4,2 Hz, ^{3}J=7,7 Hz, 1H, 4-H); 3,97 (d, ^{2}J=12,75 Hz, 1H, PhC$\underline{H}_2$N); 4,16 (dd, ^{2}J=11,8 Hz, ^{3}J=4,2 Hz, C$\underline{H}_2$O); 4,26 (dd, ^{2}J=11,8 Hz, ^{3}J=5,0 Hz, 1H, C$\underline{H}_2$O); 5,86 (s, 1H, PhC$\underline{H}$ (OAc)); 7,12-7,43 (m, 10H, aromatic H). Additional signals of the minor diastereomer could be observed: 0,96 (d, ^{3}J=4,70 Hz, 3H, 8-C$\underline{H}_3$); 2,44 (dd, ^{2}J=12,0 Hz, ^{3}J=2,02 Hz, 1H, 6-H); 2,89 (dd, 1H, 1-H); 3,69 (d, ^{2}J=12,9 Hz, 1H, PhC$\underline{H}_2$N); 4,01 (d, ^{2}J=12,9 Hz, 1H, PhC$\underline{H}_2$N); 4,15 (dd, ^{2}J=11,82 Hz, ^{3}J=5,05 Hz, 1H, C$\underline{H}_2$O); 4,28 (dd, 1H, C$\underline{H}_2$O); - ^{13}C-NMR: δ = 20,2/20,5 (2q, 8-$\underline{C}H_3$ and $\underline{C}H_3CO$); 38,9 (t, C-6); 46,7 (d, C-8); 53,4 (d, C-5); 62,6 (t. Ph$\underline{C}H_2$N); 64,0 (t, $\underline{C}H_2O$); 74,3 (d, C-1); 79,9/82,2 (2d, C-4 and Ph$\underline{C}$H(OAc)); 127,0-136,2 (aromatic C); 168,4/170,2 (2s, $CH_3\underline{C}O$ and $\underline{C}O_2CH_2$). Additonal signals of the minor diastereomer could be observed: 53,6 (d,C-5); 62,7 (t,Ph$\underline{C}H_2$N); 63,9 (t,$\underline{C}H_2O$);74,2 (d, C-1); 80,0 / 82,1 (2d, C-4 and Ph$\underline{C}$H(OAc)); 168,5/170,0 (2s, $CH_3\underline{C}O$ and $\underline{C}O_2CH_2$).

[(2-Benzyl-8-isopropyl-3-oxa-7-thia-2-azabicyclo[3.3.0]octane-4)methyl] (αS)-α-methoxy-α-trifluormethyl-phenylacetate: Pyridine (0.135 ml) was dropped to a solution of 2-benzyl-4-hydroxymethyl-8-isopropyl-3-oxa-7-thia-2-azabicyclo[3.3.0]octane (0.2 mmol) in 10 ml of dichloromethane. Subsequently (S)-methoxy-trifluoromethyl-phenylacetylchloride (0.051 g 0.202 mmol) was added. The course of the reaction was controlled by thin layer chromatography. When it was finished 1.4 ml of water were added. The reaction mixture was extracted with 30 ml of ethyl acetate. The extract was successively treated with 1 ml of 1% hydrogen chloride, a saturated aqueous solution of $NaHCO_3$ and a saturated solution of sodium chloride. After the organic phase was dried over $MgSO_4$, the solvent was removed and the product was studied spectroscopically without further purification.

The ester was isolated in 59% yield as a colourless, viscous oil.- Mixture of the diastereomers (αS-1S,4S,5S,8R) and (αS-1R,4R,5R,8S) in the ratio 2:1, de = 34%. - MS(FD): m/e = 493 (89%; M^+). - IR(neat): 1756, 1521 cm^{-1}. - ^{1}H-NMR (400 MHz): δ = 0,85 (d, ^{3}J=6,70 Hz, 3H, $(C\underline{H}_3)_2CH$); 0,87 (d, ^{3}J=6,70 Hz, 3H, $(C\underline{H}_3)_2CH$); 1,67 (dhept, ^{3}J=6,70 Hz, ^{3}J=7,62 Hz, 1H, $(CH_3)_2C\underline{H}$); 2,64 (dd, ^{2}J=11,90 Hz, ^{3}J=3,05 Hz, 1H, 6-H); 2,90 (dd, ^{2}J=11,90 Hz, 7,20 Hz, 1H, 6'-H); 3,00 (dd, ^{3}J=7,62 Hz, ^{3}J=2,30 Hz, 1H, 8-H); 3,04 (dddd, ^{3}J=7,70 Hz, ^{3}J=7,20 Hz, ^{3}J=7,00 Hz, ^{3}J=3,05 Hz, 1H, 5-H); 3,36 (dd, ^{3}J=7,70 Hz, ^{3}J=2,30 Hz, 1H, 1-H); 3,48 (s, 3H, CH_3O); 3,89 (s,2H, PhC$\underline{H}_2$N); 4,08 (ddd, ^{3}J=7,00 Hz, ^{3}J=3,95 Hz, ^{3}J=5,70 Hz, 1H, 4-H); 4,40 (dd, ^{2}J= 11,80 Hz, ^{3}J=3,95 Hz, 1H, C$\underline{H}_2O_2C$); 4,46 (dd, ^{2}J=11,80 Hz, ^{3}J=5,70 Hz, 1H, C$\underline{H}_2O_2C$); 7,25-7,51 (m, 10H, aromatic H). Additional signals of the minor diastereomer : 3,34 (dd, ^{2}J=7,6 Hz, ^{3}J=2,3 Hz, 1H, 1-H); 3,52 (s, 3H, C$\underline{H}_3O$); 4,37 (dd, ^{2}J=11,9 Hz, ^{3}J=6,35 Hz, 1H, C$\underline{H}_2O_2C$); 4,49 (dd, ^{3}J=11,90 Hz, 3,60 Hz, 1H, C$\underline{H}_2O_2C$); - ^{13}C-NMR: δ = 19,3 (q, J=126,0 Hz, $(\underline{C}H_3)_2CH$); 21,2 (q, J=127,1 Hz, $(\underline{C}H_3)_2CH$); 32,4 (d, J=131,6 Hz$\underline{C}H(CH_3)_2$); 34,4 (t, J=140,1 Hz, C-6); 54,8 (q, J=144,7 Hz, $\underline{C}H_3O$); 55,5 (d, J=136,7 C-8); 59,7 (d, J=135,2 Hz, C-5); 62,2 (t, J=131,9 Hz, Ph$\underline{C}H_2$N); 65,4 (d, J=140,7 Hz, C-1); 65,8 (t, J=147,5 Hz, $\underline{C}H_2O$); 79,5 (d, J=145,3 Hz, C-4); 80,0 (s, $\underline{C}CF_3$); 126,0-137,2 (aromatic C; $\underline{C}F_3$); 173,4 (s, ester C). Additional signals of the minor diastereomer: ^{13}C-NMR: δ = 54,3 (q, $\underline{C}H_3O$); 59,6 (d,C-5); 62,3 (t, Ph$\underline{C}H_2$N);79,4 (d, C-4); 79,9 (s, $\underline{C}CF_3$).

Methyl (αS,6R)-6-methyl-7-[(α-methoxy-α-trifluoromethyl-phenyl)acetoxy]-5-thia-2-heptenoate was formed from **6b** and Mosher chloride in the same way. Yellow, viscous oil, yield 60%, $[\alpha]_D^{25}$ = +7.2° de>90%.- MS(FD): m/e = 406 (65 %; M^+). - IR(neat): 1743,cm^{-1} - ^{1}H-NMR: δ = 1,18 (d, ^{3}J=7,0 Hz, 3H, C$\underline{H}_3$); 2,86 (qdd, ^{3}J=7,01 Hz, ^{3}J=7,06 Hz, ^{3}J=5,76 Hz, 1H, 6-H); 3,14 (ddd, ^{2}J=13,90 Hz, ^{3}J=7,76 Hz, ^{4}J=1,05Hz, 1H, 4-H); 3,25 (ddd, ^{2}J=13,90 Hz, ^{3}J=7,96 Hz, ^{4}J= 0,98 Hz, 1H. 4'-H); 3,49 (s, 3H, C$\underline{H}_3$OC); 3,67 (s, 3H, $CO_2C\underline{H}_3$); 4,18 (dd, ^{2}J=11,10 Hz, ^{3}J=7,06 Hz, 1H, 7-H); 4,32 (dd, ^{2}J=11,10 Hz, ^{3}J=5,76 Hz, 1H, 7'-H); 5,77 (ddd, ^{3}J=15,49 Hz, ^{4}J=1,05, ^{4}J=0,98 Hz, 1H, 2-H); 6,81 (ddd, ^{3}J=15,49 Hz,^{3}J=7,76 Hz, ^{3}J=7,96 Hz, 1H, 3-H); 7,41 (m, aromatic H). An additional signal of the (αS, 6R) diastereomer could be observed: 6,02 (d, ^{3}J=15,30 Hz, 1H, 2-H). - ^{13}C-NMR: δ

= 17,8 (q, 6-$\underline{C}H_3$); 31,9 (t, C-4); 37,5 (d, C-6); 51,5 (q, $\underline{C}H_3O$); 55,4 (t, C-7), 62,1 (q, $CO_2\underline{C}H_3$); 69,7 (s, $\underline{C}CF_3$); 122,7 (d, C-2); 124,8-132,0 (aromatic C, $\underline{C}F_3$); 143,4 (d, C-3); 166,2/166,3 (2s, C-1 und $CF_3C(OMe)\underline{C}O_2$). Addional signals of the (αS,6R) diastereomer: 17,4 (q, 6-CH_3); 34,0 (t,C-4); 38,9 (d,C-6); 51,8 (q, CH_3O).

Acknowledgment: We would like to thank the Fonds der Chemischen Industrie for financial support.

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18. The high diastereoselectivity of this reaction is in contrast to the results of Baggiolini et al.[7b] who performed the intramolecular cycloaddition of an analogous nitrone with a NH-CO_2Me group at position 2 but unsubstituted at C-3 and C-7. They obtained a 65:35 ratio of the two diastereomers with different configuration at C-1 and C-5. Obviously the formation of an intramolecular hydrogen bridge affects the reaction course in favor of the product with cis-configuration at C-1 and C-8.
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(*Received in Germany* 21 *December* 1993; *accepted* 2 *February* 1994)