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SYNTHESIS OF CHIRAL SULFONYLMETHYL ISOCYANIDES, AND COMPARISON OF THEIR PROPENSITIES IN ASYMMETRIC INDUCTION REACTIONS WITH ACETOPHENONES[1]

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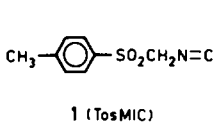
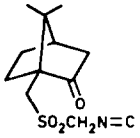
Summary. Seven chiral analogues of tosylmethyl isocyanide (TosMIC) were synthesized in order to investigate and compare their ability to achieve asymmetric induction in base mediated reactions with acetophenone and trifluoroacetophenone. Acid hydrolysis of the intermediate 2-oxazolines (10 and 11) gave optically active α-hydroxy aldehydes (12 and 13).

Asymmetric induction plays a vital role in the synthesis of chiral molecules. One of the most pertinent approaches is the use of a chiral synthon,[2] or chiron.[3] We are investigating ways to modify the highly successful, non-chiral synthon tosylmethyl isocyanide (TosMIC, 1)[4] into chiral analogues. In this paper the propensity is described of seven chiral analogues of TosMIC towards asymmetric induction, as determined by the conversion of acetophenones to chiral α-hydroxy aldehydes (12 and 13, Scheme 1). Furthermore, the synthesis is described of five new chiral TosMIC analogues (2, 3, 5b, c, d, Chart 1).

Chart 1



1 (TosMIC)



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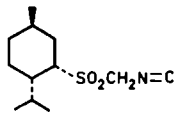

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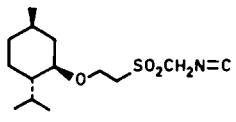

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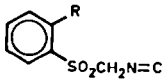
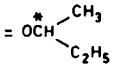
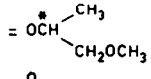
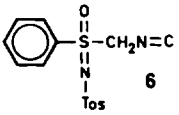


5a R = OCH_3

5b = 

5c = 

5d = 



6

Chiral analogues of TosMIC can be designed in two ways: (1) by replacing the p-tolyl group of TosMIC by a chiral entity as in compounds 2-5;[5] (2) by modifying the SO_2 group into a chiral

‡ Dedicated to Professor Hans Wynberg on the occasion of his sixty-fifth birthday.

functionality as in compound 6.[6] To avoid resolution of enantiomers, the synthesis of most of the chiral TosMIC analogues was based on commercially available and cheap optically pure starting materials: (-)-menthol, (+)-10-camphorsulfonic acid, and the lactic and malic acids. Only the synthesis of optically active S-phenyl-N-tosylsulfonimidoylmethyl isocyanide (6) requires a resolution step.[6]

Previously, reaction of TosMIC with ketones was shown to produce 2-oxazolines, from which racemic α-hydroxy aldehydes are obtained by acid hydrolysis, according to Scheme 1 with p-tolyl for R*.[7] When applied to the unsymmetric ketones, acetophenone and α,α,α-trifluoroacetophenone, this reaction leads to 2-oxazolines (10 and 11) with two asymmetric carbon atoms: C(4) and C(5). Of these two, C(5) is retained as the only chiral center in the hydrolysis product α-hydroxy aldehyde (12, 13).

Replacement of TosMIC by the chiral analogues 3-6 in the base mediated cycloadditions of Scheme 1 leads to the diastereomeric 2-oxazolines 10 and 11. The diastereomeric excess (d.e.) of 10 and 11, which is a measure of asymmetric induction, can be determined readily by ^{1}H and ^{19}F NMR. By acid hydrolysis α-hydroxy aldehydes 12 and 13 are formed in enantiomeric excess (e.e.) which appears to be the same as the d.e. of the precursor oxazolines 10 and 11, respectively, when optically pure isocyanides are used. Thus, ^{1}H and ^{19}F NMR can be used to determine the degree of asymmetric induction in the formation of the (intermediate) 2-oxazolines 10 and 11. As will be shown, this is true even when chiral derivatives of methyl isocyanide are used in racemic form.

Quite recently, Ito, Sawamura and Hayashi[8] have used a different approach to obtain optically active 2-oxazolines. Under influence of a chiral ferrocenylphosphine-gold (I) catalyst, methyl isocyanoacetate reacted with aldehydes in a highly enantio- and diastereoselective reaction to 5-alkyl-2-oxazoline-4-carboxylates, which were converted to β-hydroxy-α-amino acids.

TABLE I. Reactions of Chiral Isocyanides 3-5 with Acetophenone to Diastereomeric Oxazolines 10 and Hydrolysis to (R)-2-Hydroxy-2-phenylpropanal 12 According to Scheme 1

				Oxazolines 10[a]					α-Hydroxy aldehyde 12		
Entry	Isocyanide	e.e. (%)	Conditions[b] (temp. °C)	Yield (%)		^{1}H NMR[c]		d.e. (%)	Yield (%)	$[\alpha]_D^{20}$	o.p. (%)
1	3	93[d]	PTC, benzene (15)	10a	60	4.96	5.12	18	53	-40.8	16
2	4	100	PTC, benzene (15)	10b	74	5.22	5.45	33	47	-80.2	31
3	5b	50	1.1 eq. BuLi, THF (-78)	10c	76	5.76	5.87	40	50	-37.7	15
4	5b	racem.	2.2 eq. BuLi, THF[e](-78)	10c	52	5.76	5.87	15			
5	5b	"	PTC, benzene (15)	10c	98	5.76	5.87	40			
6	5c	"	PTC, benzene (15)	10d	80	5.75	5.95	17			
7	5c	"	1.1 eq. BuLi, THF (-78)	10d	57	5.75	5.95	33			
8	5c	"	2.2 eq. BuLi, THF[e](-78)	10d	54	5.75	5.95	17			
9	5c	"	PTC, toluene (15)	10d	94	5.75	5.95	20			
10	5d	"	PTC, benzene (15)	10e	100	5.76	5.79	7			
11	5d	"	PTC, toluene (15)	10e	66	5.76	5.79	20			
12	5d	"	1.1 eq. BuLi, THF (-78)	10e	89	5.76	5.79	40			
13	5d	"	MeMgI, Et_2O/THF (-78)	10e	75	5.76	5.79	19			
14	5d	47	1.1 eq. BuLi, THF (-78)	10e	70	5.76	5.79	38	43	-46.1	18

a. Structures of group R^* are depicted in Chart 1 for reagents 3-5: R^* in 10a = neomenthyl, in 10b = 2-menthoxyethyl, in 10c = o-sec-butoxyphenyl, in 10d = o-(1-methoxy-2-propoxy)phenyl, and in 10e = o-(3-tetrahydrofuranoxy)phenyl, respectively; b. PTC with 5 mol % BTEAC and 50% NaOH; c. δ C(4)-H, doublets; d. Determined on neomenthylthiol with $MeP(O)Cl_2$[41]; e. Same results with Et_2O.

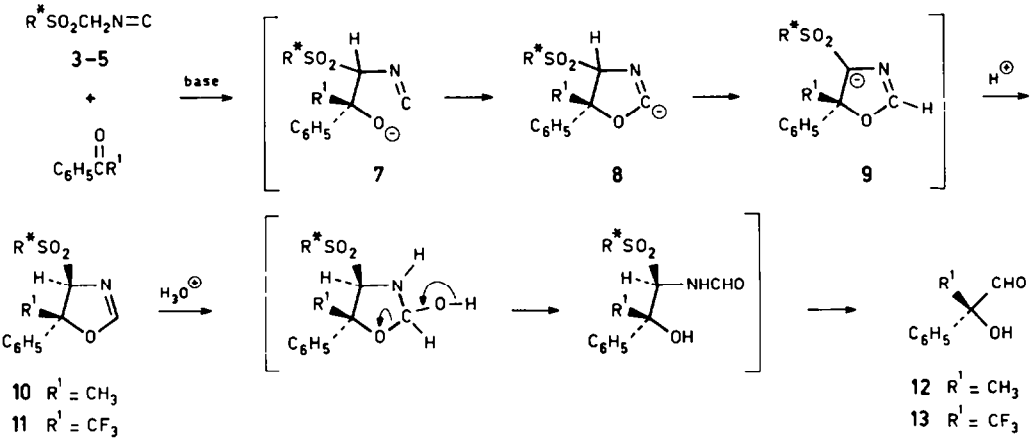
REACTION OF CHIRAL DERIVATIVES OF SULFONYLMETHYL ISOCYANIDES WITH ACETOPHENONES: RESULTS AND DISCUSSION

Results of reactions of chiral sulfonylmethyl isocyanides 3, 4, 5b, 5c and 5d with acetophenone, according to Scheme 1, are collected in Table I. Similar results of 3, 5d and 6 with

α,α,α-trifluoroacetophenone are compiled in Table II. The highest asymmetric induction (80%) was obtained with S-phenyl-N-tosylsulfonimidoylmethyl isocyanide (6, Table II, entries 20 and 21).

By way of example, we will first discuss the reaction of entry 2 (Table I). Enantiomerically pure (-)-(2-menthoxyethylsulfonyl)methyl isocyanide (4) reacted under phase transfer catalysis (PTC) conditions with acetophenone to give trans-4-(2-menthoxyethylsulfonyl)-5-methyl-5-phenyl-2-oxazoline (10b) as a viscous oil, which was converted, without being purified, by acid hydrolysis to (R)-(-)-2-hydroxy-2-phenylpropanal (12, Scheme 1). The optical purity (o.p.) of 12 was determined by comparison with data of Mukaiyama et al.[9] The e.e., or rather the o.p.,[10] of 31% found for 12 was the same, within experimental accuracy, as the d.e. of 33% observed for the precursor oxazoline 10b. The d.e. of (crude) 10b was determined by integration of the two diastereotopic C(4)-H doublets (long range coupling with C(2)-H, J = 2 Hz) at δ 5.22 and 5.45.

Scheme 1[a]



[a] For compound 6 R^*SO_2 is to be replaced by PhS*(O)NTos.

The proposed mechanism of Scheme 1 elucidates the correlation between d.e. of oxazoline 10 and e.e. of α-hydroxy aldehyde 12. Asymmetric induction determines the configuration at C(5) in 7, which eventually is carried on to 12. By ring closure to 8 and base induced epimerization at C(4) to the thermodynamically favoured trans-oxazoline,[11] 10b is formed as a mixture of two diastereomers only, which are represented by R^*SO_2-(R)C(4)-(R)C(5) (A) and R^*SO_2-(S)C(4)-(S)C(5) (B).

In entry 1, (+)-(neomenthylsulfonyl)methyl isocyanide 3 of 90% e.e. was used, which gives two pairs of enantiomerically related diastereomers of trans-10a. In addition to the main pair A and B, an enantiomeric pair $(R^*)'SO_2$-(S)C(4)-(S)C(5) (A') and $(R^*)'SO_2$-(R)C(4)-(R)C(5) (B') is formed. This obviously is of no consequence for the d.e. (18%) of 10a, as determined by ^1H NMR, but it lowers the e.e. of 12 from 18 to 16%, as observed. Similarly, (S)-(-)-(o-sec-butoxyphenylsulfonyl)-methyl isocyanide (5b, of 50% e.e., entry 3) gave trans-10c in 40% d.e., which ought to give 12 in 20% e.e. The observed e.e. was lowered to 15% by contamination of 12 with some acetophenone. We have thus confirmed experimentally that, according to expectations, the d.e. of the oxazolines 10 is a measure of asymmetric induction. Therefore, it is possible to investigate the induction power of chiral TosMIC analogues when they are only partially resolved (as in entries 1, 3, 14, 17 and 18), and even when they are racemic (entries 4-13, 19-21). Of course, in the latter case the e.e. of 12 (and 13) will be zero.

In entry 14 (as well as entry 22 of Table II) a reverse analysis was used to determine the e.e. of optically active 5d (and 6) from the e.e. of the final product α-hydroxy aldehyde 12 (and 13).

The data of Table I were collected to probe the influence of changes in R*, and in reaction conditions, on the d.e. of oxazolines 10. The chemical yields of 10 were quite satisfactory, except for the reaction of (+)-10-(camphorsulfonyl)methyl isocyanide (2). Under PTC conditions, as in entries 1 and 2, isocyanide 2 underwent intramolecular ring closure with participation of the camphor carbonyl group, rather than intermolecular reaction with acetophenone.[13]

Since asymmetric induction with isocyanide 3 was low (18%, entry 1), ether functions were introduced in 4 and 5 with the oxygen in position 5 with respect to the active methylene group. It was hoped to thus improve the asymmetric induction power by increasing the rigidity of the reacting species (i.e. $R^*SO_2\bar{C}HN{=}C$, $R^*SO_2CHM\bar{N}{=}C$ or $R^*SO_2CH_2N{=}C$) of Scheme 1, either by intramolecular chelation[14] or hydrogen bonding.[15] Whereas introduction of one ether oxygen (isocyanides 4 and 5b) gave a small increase in d.e. of 10 (33 and 40%, respectively, against 18%, entries 1-3, 5), introduction of a second ether oxygen (isocyanides 5c and 5d) gave no further improvement (entries 6-14). Application of two equivalents of BuLi (entries 4 and 8) to form dilithio reagents,[16] or use of a magnesium derivative (entry 13) resulted only in lower d.e.'s of 10. This approach was therefore abandoned for sulfonimidoylmethyl isocyanide 6 with a chiral center next to the reacting methylene group, which gave an asymmetric induction of 80% (Table II).

Table II. Reaction of TosMIC (1) and Chiral Analogs 3, 5d and 6 with α,α,α-Trifluoroacetophenone to Oxazolines 11 According to Scheme 1

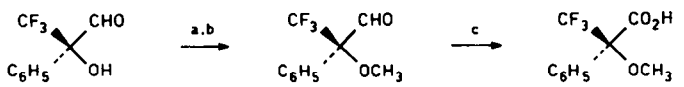
Entry	Isocyanide	e.e. (%)	Conditions[a]	Yield[b] (%)	^{1}H NMR[c]		cis/trans	d.e. (%)	^{19}F NMR[d]		cis/trans	d.e. (%)
15	1	-	A	11a 100	5.53	5.38	47:53	-	-79.4	-71.5	47:53	-
16	1	-	B	11a 96	5.53	5.38	34:66	-	-79.4	-71.5	35:65	-
17	3	90	A	11b 96	5.53	5.49	47:53	18	-80.5	-80.3	46:54	18
					5.35	5.33			-71.9	-71.7		
18	3	90	B	11b 90	5.53	5.49	34:66	18	-80.5	-80.3	35:65	18
					5.35	5.33			-71.9	-71.7		
19	5d	47	A	11c 98	6.33	6.26	40:60	41	-75.5	-75.0	38:62	45
					6.11	6.04			-73.7	-73.4		
20	6	racem.	A	11d 100	6.33	5.25	e	80	-79.3	-79.1	6:94	80
									-71.6	-71.4		
21	6	racem.	B	11d 92	6.33	5.25	e	80	-79.3	-79.1	5:95	80
									-71.6	-71.4		
22	6	34	B	11d 91	6.33	5.25	e	80	-79.3	-79.1	4:96	80
									-71.6	-71.4		

a. A = $Ti(OEt)_4$, N-Ethylpipiridine, CH_2Cl_2, 0°C. B = Triton B, THF, 20°C; b. Structures of group R^* are depicted in Chart 1 for reagents 1, 3, 5d and 6; R^* in 11a = p-tolyl, in 11b = neomenthyl, in 11c = o-(3-tetrahydrofuranoxy)phenyl, and R^*SO_2 in 11d = S-phenyl-N-tosylsulfonimidoyl, respectively; c. δ C(4)-H; d. δ CF_3; e. in ^{1}H NMR only two doublets were observed for C(4)-H (see text).

S-Phenyl-N-tosylsulfonimidoylmethyl isocyanide (6) failed to react with acetophenone. Under the reaction conditions given in Table I, 6 was decomposed. However, high yields of oxazoline 11d were obtained with the more reactive α,α,α-trifluoroacetophenone. This substrate needed a different set of reaction conditions to prevent the haloform reaction. Such conditions were tested first with TosMIC, which gave 5-phenyl-4-tosyl-5-trifluoromethyl-2-oxazoline (11a, Scheme 1, R* = p-tolyl) in quantitative yield when $Ti(OEt)_4$ was used with N-ethylpiperidine in CH_2Cl_2 (0°C, 4-5 h). Oxazoline 11a was obtained as a mixture of cis/trans 47:53[17] as determined both by ^{1}H and ^{19}F NMR (entry 15, Table II). Similar results were obtained with Triton B in THF at room temperature (entry 16).[18] The same high chemical yields of 11b were obtained with (+)-(neomenthylsulfonyl)methyl isocyanide (3) and trifluoroacetophenone, however, the d.e. (18%) was equally low as with acetophenone (entries 17 and 18). Oxazoline 11b was hydrolyzed to (R)-(+)-2-hydroxy-2-phenyl-3,3,3-trifluoropropanal (13, not reported previously) in 17% e.e. as shown by chemical correlation with (R)-(+)-2-methoxy-2-(trifluoromethyl)phenylacetic acid (15, "Mosher's acid", Scheme 2).[19,20] A comparable result was obtained with racemic [o-(3-tetrahydrofuranoxy)phenylsulfonyl]methyl isocyanide (5d, entry 19): 98%

yield of oxazoline 11e, with a d.e. (41%) not higher than with acetophenone (cf. entries 12 and 14).

Scheme 2



13 14 15

[a] NaH, Et_2O; [b] CH_3I; [c] $NaClO_2$.

By far the highest asymmetric induction (80%) was obtained with the sulfonimidoylmethyl isocyanide 6 and trifluoroacetophenone (entries 20-22). With both sets of reaction conditions oxazoline 11d (Scheme 1, with PhS*(O)NTos instead of R*SO_2) was obtained in nearly quantitative yield and with a d.e. of 80%, with racemic 6 as well as with partially resolved 6. In the latter case hydrolysis of 11d gave hydroxy aldehyde 13 (30% yield) of 27% o.p. It follows that 6 was 34% o.p. The cis/trans ratio of 11d was 95:5, as determined by ^{19}F NMR. In contrast to oxazolines 10, the oxazolines 11 did not epimerize to trans-diastereomers exclusively. Instead, partially resolved or racemic isocyanides and trifluoroacetophenone gave two pairs of enantiomerically related diastereoisomers for the trans-isomers (as described above), plus two pairs of enantiomerically related diastereoisomers for the cis-isomers. In this case the d.e. is determined by two pairs of doublets for C(4)-H, or, alternatively, by two pairs of singlets for CF_3. These results are mutually consistent (Table II).

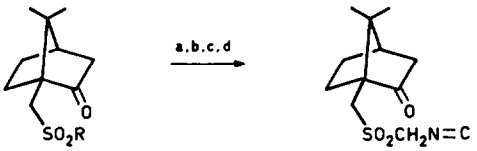
The above results show that a chiral center next to the reactive methylene as in 6 is more efficient[21] than the remote chirality in R*. Consequently, efforts are presently made towards a more efficient method to obtain enantiomerically enriched 6.

One peculiarity needs to be considered. [o-(3-Tetrahydrofuranoxy)phenylsulfonyl]methyl isocyanide (5d) gave with acetophenone oxazoline 10e, which initially showed only two ^1H NMR doublets (J = 2 Hz) for C(4)-H quite closely spaced at δ 5.76 and 5.79. After treatment with K_2CO_3 in MeOH for 4 h at 20°C two doublets with a normal shift difference of 0.2 ppm (compare entries 1-9) were obtained. We tentatively explain these results by assuming that initially only trans-R*SO_2-(R)C(4)-(R)C(5) (A) and cis-R*SO_2-(R)C(4)-(S)C(5) (C) (and their respective enantiomers) were formed, of which by a slow epimerization at C(4) C is converted to R*SO_2-(S)C(4)-(S)C(5) (B) (and its enantiomer). Of course, the d.e. of 10e was not affected by this slow epimerization step. Why the epimerization of 10e is slow remains to be explained.

CHIRAL DERIVATIVES OF METHYL ISOCYANIDE: SYNTHESIS AND DISCUSSION

(+)-(10-Camphorsulfonyl)methyl isocyanide (2) was prepared by straightforward chemistry from (+)-10-camphorsulfonic acid 16 in an overall yield of 28% (Scheme 3 and Experimental Section). An advantage of 16 is that the -SO_3H function can be transformed into the desired -$SO_2CH_2N{=}C$ group of 2 in just 4 steps. However, there are also two important disadvantages associated with 2: (1) the carbonyl group of 2, albeit of low reactivity, appears to interfere intramolecularly[7c,13]; (2) isocyanide 2 is of limited stability at room temperature, probably because the viscous oil failed to crystallize; the compound can be stored, however, at -40°C. Unfortunately, many different attempts to circumvent both disadvantages by replacing the C=O group of 2 have not met with success.[7c]

Scheme 3



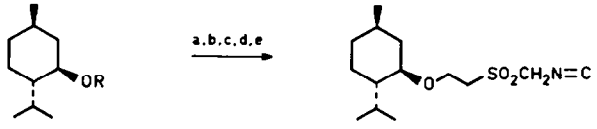
16 R = OH
17 R = Cl
18 R = H
19 R = CH_2NHCHO

2

[a] $SOCl_2$; [b] Na_2SO_3; [c] CH_2O, NH_2CHO; [d] $POCl_3$, Et_3N.

(+)-(Neomenthylsulfonyl)methyl isocyanide (3) was previously obtained in 6 steps and 26% overall yield from (-)-menthol as a stable crystalline compound.[5] The overall yield was increased to 39% mainly by replacing Et_3N by iPr_2NH in the final dehydratation step, following the recently improved method of Ugi et al.[22]

Scheme 4



20 R = H
21 R = $CH=CH_2$
22 R = CH_2CH_2SH
23 R = $CH_2CH_2SCH_2NHCHO$
24 R = $CH_2CH_2SO_2CH_2NHCHO$

4

[a] CH_2=CHOEt, $Hg(OAc)_2$; [b] $CH_3C(O)SH$, NaOH; [c] t-BuOK, $TosCH_2NHCHO$; [d] 2 equiv. mCPBA; [e] $POCl_3$, Et_3N.

(-)-(2-Menthoxyethylsulfonyl)methyl isocyanide (4) was prepared in 6 steps and 12% overall yield from (-)-menthol (20) according to Scheme 4. It was necessary to use carefully purified thiolacetic acid to prepare 22, which was converted to 23 by an exchange reaction with N-(tosylmethyl)formamide.[5] Oxidation (mCPBA) gave sulfone 24, at which stage a contamination of menthol could be readily removed by extraction with pentane. Dehydration[23] gave 4 as a colourless viscous oil of limited stability, in epimerically pure state (according to ^{13}C NMR) with $[\alpha]_{578}^{22}$ -51.6° (c 2.0, $CHCl_3$). The diastereotopic α-methylene group shows a well resolved AB quartet (J = 15 Hz) in ^1H NMR (Table III).

(S)-(-)-(o-sec-Butoxyphenylsulfonyl)methyl isocyanide (5b). Attempts to prepare the menthol derivative 5e were unsuccessful. Reaction of o-bromophenolate with the tosylate of (-)-menthol led to a mixture of 1- and 2-menthenes[24] only. Instead, the chiral isocyanides 5b, 5c and 5d were prepared, after the pilot synthesis of non-chiral 5a was carried out first (Scheme 6, and Experimental Section). The model compound 5a is a stable solid, which showed typical TosMIC reactivity in reactions with p-nitrobenzaldehyde and with acetophenone.

Stimulated by the results with 5a, isocyanide 5b was synthesized in 5 steps and 13% overall yield, both with racemic and with optically pure sec-butanol (Scheme 5). Reaction of the tosylate 26b of (R)-(+)-sec-butanol[26] (o.p. > 98%) with potassium o-bromophenolate gave 27b in 51% yield, with 50% e.e. as determined by ^1H NMR and $Eu(dcm)_3$. Apparently, some 50% racemization occurred during this displacement. Sulfinic acid 28b (66% yield from 27b by Grignard and SO_2) gave formamide 29b by a Mannich reaction (58% yield), followed by dehydratation[23] with $POCl_3$ and Et_3N (67% yield)

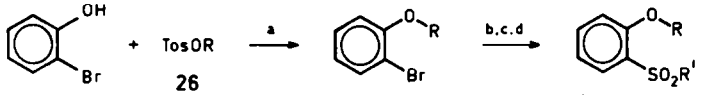
to give isocyanide **5b** with 50% e.e. Thus, no further racemization took place after the formation of **27b**. Partial racemization in step a towards **27b** was only slightly diminished, to 45%, by use of CsF in acetonitrile.

Table III. Some Characteristic Data of Chiral Methyl Isocyanide Derivatives **2-6** (Chart 1)

Isocyanide	mp[a] (°C)	$\nu_{N=C}$ (cm^{-1})	^1H NMR $\delta_{C(\alpha)H_2}$, AB q, (J, Hz)	^{13}C NMR $\delta_{N=C}$ (s), $C(\alpha)H_2$ (t)
2	oil	2180	4.47 and 5.21 (15)	-
3	67.7-68.4	2180	4.27 and 4.58 (15)	165.8, 59.8
4	oil	2180	4.55 and 4.83 (15)	165.6, 60.2
5a	93-94	2180	4.65[b]	164.6, 59.0
5b	oil	2180	4.86 and 4.93 (15)	164.1, 58.9
5c	oil	2150	5.15 and 5.25 (15)	-
5d	107.4-108.2	2150	4.87 and 4.94 (15)	165.3, 59.3
6	93.96 (decomp)	2165	5.11	-

a. Solids are stable shelf compounds, the oils are of limited stability at room temperature, but can be stored for long at -40°C; b. In ^1H NMR of non-chiral sulfonylmethyl isocyanide **5a**, $C(\alpha)H_2$ gave a doublet with J = 2 Hz.

Scheme 5



25 **27** **28** R' = H

29 R' = CH_2NHCHO

5 R' = $CH_2N{=}C$

b R = -$\overset{*}{C}$HMeEt

c R = -$\overset{*}{C}$H(Me)CH_2OCH_3

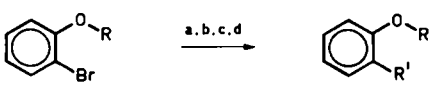
d R = 3-tetrahydrofuranyl

e R = menthyl)

[a] KOH or CsF; [b] Mg or BuLi, SO_2; [c] CH_2O, NH_2CHO; [d] $POCl_3$, Et_3N.

(±)-[o-(1-Methoxy-2-propoxy)phenylsulfonyl]methyl isocyanide (**5c**) was prepared analogously to **5b** from the tosylate of (±)-1-methoxy-2-propanol (**26c**).[27] The preparation of **28c** (step b) proceeded sluggishly via the Grignard of **27c** in only 5% yield, however, the yield was improved to 79% when BuLi was used instead of Mg.[28] After steps c and d, as for **5b**, **5c** was obtained in 29% overall yield, as an oil of limited stability at room temperature.

Scheme 6



27

a R = Me

d R = 3-tetrahydrofuranyl

30 R' = SH

31 R' = SCH_2NHCHO

32 R' = SO_2CH_2NHCHO

5 R' = $SO_2CH_2N{=}C$

[a] BuLi, S_8; [b] $TosCH_2NHCHO$, t-BuOK; [c] 2 equiv. mCPBA; [d] $POCl_3$, Et_3N or i-Pr_2NH.

(R)-(-)-[o-(3-Tetrahydrofuranoxy)phenylsulfonyl]methyl isocyanide (5d) was prepared in 35% overall yield according to Scheme 6 from both (±)-3-hydroxytetrahydrofuran[29] and (S)-(+)-3-hydroxytetrahydrofuran.[30] Thiol 30d was obtained in 73% yield from 27d with BuLi and sulfur[31] and was subsequently converted to 5d using the same type of reactions as for the synthesis of 4 (Scheme 4). In contrast to 5b and 5c, isocyanide 5d is a crystalline solid which is stable at room temperature. The e.e. of 5d could not be determined with chiral shift reagents, but was found to be 48%, as deduced from the o.p. of α-hydroxy aldehyde 12 (Table I, entry 14).

(-)-S-Phenyl-N-tosylsulfonimidoyl)methyl isocyanide (6). Racemic 6 was reported previously;[6] the overall yield of 60% was improved to 80% by the use of freshly distilled trimethylsilylmethyl isocyanide.[32] Optically active 6 was obtained with an e.e. of 34%, as deduced from the o.p. of 13 (Table II, entry 22), using partially resolved S-phenyl-N-tosylsulfonimidoyl fluoride.[6]

EXPERIMENTAL SECTION

General. All experiments were carried out under N_2. ^1H NMR spectra were recorded on a 60-MHz Hitachi Perkin-Elmer R-24B or 200-MHz Nicolet apparatus in δ units downfield from internal Me_4Si. Varian XL-100 or 200-MHz Nicolet machines were used for ^{13}C and ^{19}F NMR spectra. For reported multiplicity of ^{13}C NMR signals only $^1J_{C-H}$ values were taken into account. Optical activity was measured on a Perkin-Elmer 241 polarimeter using 10 cm cells. Elemental microanalyses were carried out in our Analytical Department under the supervision of Mr. A.F. Hamminga.

(+)-N-(10-Camphorsulfonylmethyl)formamide (19) was prepared by a Mannich condensation of 10-camphorsulfinic acid[33] (18; 23.2 g, 0.10 mol), formaldehyde (0.30 mol) and formamide (1.0 mol), according to the synthesis of N-(tosylmethyl)formamide,[23] for 1.5-2 h at 90-95°C. After cooling, the reaction mixture was poured in ice-water and extracted with $CHCl_3$. The $CHCl_3$ extracts were washed with ice-cold 5% aqueous $NaHCO_3$, dried ($MgSO_4$), and concentrated to give 16.4 g (60%) of 19 as a viscous oil: IR (neat) 3400 (NH), 1740 (C=O), 1690 and 1530 (NHCHO), 1325 and 1130 cm^{-1} (SO_2); ^1H NMR ($CDCl_3$) δ 0.90 (s, 3), 1.05 (s, 3), 1.2-2.7 (m, 7), 2.87 and 3.48 (AB q, J = 15 Hz, 2), 4.73 (d, 2), 7.81 (t, 1), 8.35 (s, 1); MS, m/e 273 (M^+); $[\alpha]_{578}^{25}$ +53° (c 2.50, $CHCl_3$).

(+)-(10-Camphorsulfonyl)methyl isocyanide (2). Formamide 19 (27.3 g, 0.10 mol) was dehydrated with $POCl_3$ using the procedure for the synthesis of TosMIC.[23] After the addition of $POCl_3$ was complete, the reaction mixture was stirred for 0.5 h at -5°C, poured in ice-water and extracted with $CHCl_3$. The combined $CHCl_3$ extracts were washed with a cold 5% aqueous $NaHCO_3$ solution and cold water, dried ($MgSO_4$) and concentrated. The resulting oil was rapidly chromatographed (neutral Al_2O_3, $CHCl_3$) to provide 15.3 g (60%) of 2 as a light-brown viscous oil: IR (neat) 2180 (N=C), 1740 (C=O), 1340 and 1140 cm^{-1} (SO_2); ^1H NMR ($CDCl_3$) δ 0.93 (s, 3), 1.08 (s, 3), 1.2-2.7 (m, 7), 3.01 and 3.69 (AB q , J = 15 Hz, 2), 4.47 and 5.21 (AB q, J = 15 Hz, 2); MS, m/e 255 (M^+); $[\alpha]_D^{25}$ +20.5° (c 0.82, $CHCl_3$).

Menthyl vinyl ether (21) was prepared according to the procedure reported by Chiellini[34] from (-)-menthol (20, 46.8 g, 0.30 mol), redistilled ethyl vinyl ether (240 g, 3.33 mol) and $Hg(OAc)_2$ (9.6 g, 0.03 mol) as a colourless oil: 41.03 g; bp 82-83°C (15 mm Hg) [Lit.[34] bp 100°C (22 mm Hg)]. The product was contaminated with ca. 20% of (-)-menthol (as evidenced by GLC) which could not be removed easily by distillation. This contamination was removed after formation of sulfone 24 (see below).

2-Menthoxyethanethiol (22) was prepared by addition of carefully distilled thiolacetic acid (6.0 g, 80 mmol) to a stirred mixture of 11.2 g of crude 21 (ca. 50 mmol) and benzoyl peroxide (200 mg, 0.80 mmol), during which the temperature rose to 32°C. The mixture was stirred for 1 h at room temperature, after which the crude thiolacetic acid adduct [IR (neat) 1700 cm^{-1}, C=O] was dissolved in a mixture of MeOH (100 mL) and 100 mL of 20% aqueous NaOH, and refluxed for 1 h. After cooling in ice, the solution was acidified (to pH 3) with ice-cold 6N HCl and water (200 mL) was added.

Extraction with $CHCl_3$ gave crude **22** which was distilled to give 10.0 g of **22** (which was still contaminated with ca. 20% of menthol) as a colourless oil: bp 82-84°C (0.2 mm Hg); MS, m/e 216.155 (M^+, calcd 216.155). Alternatively, 10.0 g (ca. 30 mmol) of the crude thiolacetic acid adduct was dissolved in 20 mL of ether and added, at room temperature, to a suspension of 1.14 g (30 mmol) of $LiAlH_4$ in 100 mL of ether. The mixture was refluxed for 2 h, cooled to 0°C and acidified (pH 3-4) with 6N HCl. Extraction with ether gave, after the usual work-up, 5.40 g (25 mmol, 83%) of **22**.

N-[(2-Menthoxyethylthio)methyl]formamide (23) was prepared analogously to N-[(neomenthylthio)-methyl]formamide,[5] from 4.33 g of crude **22** (ca. 17 mmol) and N-(tosylmethyl)formamide (4.26 g, 20 mmol).[23] Sulfide **23** was obtained as a colourless, viscous oil: 4.65 g (contaminated with ca. 20% of menthol); IR (neat) 3350 (NH), 1680 and 1530 cm^{-1} (NHCHO); ^1H NMR ($CDCl_3$) δ 0.5-2.6 (m), 2.6-4.0 (m, 5), 4.36 (d, 2), 7.35 (br, 1), 8.12 (s, br, 1); MS, m/e 273.172 (M^+, calcd 273.176).

N-[(2-Menthoxyethylsulfonyl)methyl]formamide (24) was prepared analogously to N-[(neomenthylsulfonyl)methyl]formamide,[5] from 4.09 g of crude **23** (ca. 13 mmol) and 5.17 g (30 mmol) of mCPBA (technical grade, 85%). Menthol was removed from the crude oily product by repeated extraction with n-pentane (8 x 30 mL). Column chromatography [CH_2Cl_2-$CHCl_3$ (1:1); neutral Al_2O_3] provided **24** as a colourless oil (1.82 g, 19% overall yield, calculated from (-)-menthol, **20**): IR (neat) 3400 (NH), 1685 and 1530 (NHCHO), 1325 and 1130 cm^{-1} (SO_2); ^1H NMR ($CDCl_3$) δ 0.5-2.5 (m, 18), 2.7-4.25 (m, 5), 4.3-5.1 (m, 2), 8.0 (br, 1), 8.2 (d, 1); MS, m/e 305.165 (M^+, calcd 305.166).

(-)-(2-Menthoxyethylsulfonyl)methyl isocyanide (4). Compound **24** (1.53 g, 5.0 mmol) was dehydrated with $POCl_3$ and Et_3N using the procedure for the synthesis of TosMIC.[23] The work-up was as follows: after the addition of $POCl_3$ was complete, the mixture was stirred for 0.5 h at 0°C and then poured in ice-water. Extraction with $CHCl_3$ gave crude **4** (1.24 g, 86%), which was chromatographed ($CHCl_3$; Florisil) to give **4** as a colourless oil (932 mg, 65%); IR (neat) 2180 (N≡C), 1340 and 1140 cm^{-1} (SO_2); ^1H NMR ($CDCl_3$) δ 0.5-2.5 (m, 18), 2.8-4.3 (m, 5), 4.55 and 4.83 (AB q, J = 15 Hz, 2); ^{13}C NMR ($CDCl_3$) δ 15.9 (q), 20.6 (q), 21.9 (q), 22.9 (t), 25.5 (d), 31.1 (d), 33.9 (t), 39.6 (t), 47.8 (d), 51.1 (t), 60.2 (t), 80.0 (d), 165.6 (s); $[\alpha]_{578}^{22}$ -51.6° (c 2.0, $CHCl_3$); MS, m/e 287.157 (M^+, calcd 287.155).

o-Methoxybenzenethiol (30a; commercially available from Ega Chemie). To a stirred solution of **27a** (1.12 g, 6.0 mmol) in Et_2O (30 mL) at -78°C was added dropwise 4.1 mL of BuLi (1.6 M solution in hexane, ca. 6.6 mmol). After 30 min freshly sublimed sulfur (0.19 g, 6.0 mmol)[31] was added all at once and the temperature was raised to 15°C in ca. 3 h. Then the mixture was poured in H_2O (30 mL). The organic layer was extracted with 2N NaOH (2 x 30 mL). The combined aqueous extracts were acidified with 20% aqueous H_2SO_4 and were extracted with ether (4 x 50 mL). The ether extracts were dried ($MgSO_4$) and concentrated to yield 0.75 g of crude **30a**, which was purified by distillation under reduced pressure (bp 115-118°C, 12 mm Hg) to give 0.681 g (81%) of **30a**; ^1H NMR ($CDCl_3$) δ 3.76 (s, 1), 3.82 (s, 3), 6.56-7.36 (m, 4); ^{13}C NMR ($CDCl_3$) δ 55.6 (q), 110.4 (d), 120.3 (s), 120.9 (d), 126.2 (d), 129.1 (d), 154.7 (s).

N-[(o-Methoxyphenylthio)methyl]formamide (31a). To an ice-cooled, stirred solution of **30a** (1.4 g, 0.01 mol) in a mixture of ether (10 mL) and Me_2SO (5 ml) was added, in 0.5 h, 1.23 g (0.011 mol) of solid t-BuOK. After stirring for 1 h at room temperature, N-(tosylmethyl)formamide[23] (2.13 g, 0.01 mol) was added at 0°C, in portions, during 0.5 h. The mixture was stirred for 5 h at room temperature, poured in ice-water (30 mL), and extracted with ether (3 x 15 mL). The combined extracts were washed with H_2O, with brine, dried ($MgSO_4$), and concentrated. The resulting oil was crystallized from benzene-hexane (1:3) to give 1.67 g (85%) of **31a**, mp 83-84°C. Analytically pure **31a** was obtained from the same solvent mixture: mp 85-86°C; IR (Nujol) 3360 (NH), 1660 and 1530 cm^{-1} (NHCHO); ^1H NMR ($CDCl_3$) δ 3.9 (s, 3), 4.55 and 4.65 (two s, 2), 6.0 (br, 1), 6.6-7.8 (m, 4), 8.0 (s, 1). Anal. Calcd for $C_9H_{11}NO_2S$: C, 54.82; H, 5.58; N, 7.10; S, 16.24. Found: C, 54.93; H, 5.56; N, 7.11; S, 16.18.

N-[(o-Methoxyphenylsulfonyl)methyl]formamide (32a). To an ice-cooled, stirred solution of sulfide **31a** (1.97 g, 0.01 mol) in CH_2Cl_2 (20 mL) was added in 0.5 h 3.45 g (0.02 mol) of mCPBA (technical

grade, 85%). The mixture was stirred for 5 h at room temperature, then filtered. The solid was extracted with CH_2Cl_2 (10 mL), combined with the filtrate, then washed with aqueous $NaHCO_3$ (10%, 20 mL), with water (20 mL), dried ($MgSO_4$) and concentrated. The resulting oil crystallized on cooling to give 1.71 g (75%) of **32a**. Analytically pure **32a** was obtained from CH_2Cl_2-hexane: mp 125-126°C; IR (Nujol) 3390 (NH), 1680 and 1530 (NHCHO), 1280 and 1120 cm^{-1} (SO_2); ^1H NMR ($CDCl_3$) δ 3.98 (s, 3), 4.70 and 4.90 (d of AB q, J = 8 and 15 Hz, 2), 6.50-7.80 (m, 4), 7.90 (s, 1). Anal. Calcd for $C_9H_{11}NO_4S$: C, 47.16; H, 4.80; N, 6.11; S, 13.97. Found: C, 47.05; H, 4.75; N, 6.22; S, 13.71.

(o-Methoxyphenylsulfonyl)methyl isocyanide (5a). Compound **32a** (1.14 g, 5.0 mmol) was dehydrated with $POCl_3$ and Et_3N by following the procedure used for TosMIC.[23] After the addition of $POCl_3$ was complete, the mixture was stirred for 0.5 h at 0°C and then poured in ice-water. A brown syrup, which crystallized on cooling, was collected and washed with ice-water. Two crystallizations from benzene-hexane gave colourless crystals of **5a**: yield 852 mg (85%), mp 93-94°C; IR (Nujol) 2180 (N≡C), 1335 and 1150 cm^{-1} (SO_2); ^1H NMR ($CDCl_3$) δ 3.98 (s, 3), 4.65 (d, J = 2 Hz, 2), 6.80-8.0 (m, 4); ^{13}C NMR ($CDCl_3$) δ 56.1 (q), 59.0 (t), 112.3 (d), 120.5 (d), 122.1 (s), 131.1 (d), 136.9 (d), 156.9 (s), 164.6 (s). Anal. Calcd for $C_9H_9NO_3S$: C, 51.18; H, 4.26; N, 6.63; S, 15.16. Found: C, 51.10; H, 4.34; N, 6.63; S, 15.08.

(R)-(+)-sec-Butyl tosylate (20b) was prepared according to the procedure of Cason et al:[26] $[\alpha]_D^{20}$ +11.3° (c 5.45, EtOH) [Lit.[35] $[\alpha]_{589}^{20}$ +5.80° (c 5.00, EtOH)].

(S)-(-)-o-Bromophenyl sec-butyl ether (27b). Method A. Compound **27b** was prepared according to the procedure of Niederl et al.[36] employing a slight modification. o-Bromophenol **25** (1.73 g, 0.01 mol) and finely powdered KOH (0.58 g, 10.35 mmol) were mixed together and heated on a low flame until the mixture liquified. The whole assembly was put in an oil bath preheated at 100°C. (R)-(+)-sec-Butyl tosylate (**26b**, 2.28 g, 0.01 mol) was added dropwise with stirring in 0.5 h. The reaction mixture was stirred at 90-100°C for 3 h. The cooled mixture was poured in water (10 mL) and extracted with Et_2O (3 x 25 mL). The combined extracts were washed twice with 10% aqueous NaOH (10 mL), with aqueous NaCl (10 mL), dried ($MgSO_4$), and concentrated. The resulting pale yellow oil was distilled to give 1.69 g (51%) of **27b**: bp 62-64°C (0.05 mm Hg); IR (neat) 1480, 1590 and 3000 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.98 (t, 3), 1.30 (d, 3), 1.45-2.0 (m, 2), 4.27 (m, 1), 6.5-7.5 (m, 4); $[\alpha]_D^{20}$ -32.5° (c 2.154, $CHCl_3$). The e.e. was determined to be 50% by ^1H NMR (200 MHz) with $Eu(dmc)_3$ in C_6D_6 using the integrated peaks of the two CH_3 doublets at δ 1.06 and 1.01. Anal. Calcd for $C_{10}H_{13}BrO$: C, 52.40; H, 5.67; Br, 34.93. Found: C, 52.68; H, 5.86; Br, 34.52. **Method B.** Compound **27b** was prepared also according to the procedure of Reinhoudt et al.[37] Thus a mixture of o-bromophenol (25, 435 mg, 2.5 mmol), (R)-(+)-sec-butyl tosylate (**26b**, 570 mg, 2.5 mmol), CsF (460 mg, ca. 3 mmol) and MeCN (20 mL) after refluxing for 24 h and kugelrohr distillation gave a colourless oil, 392 mg (69%) of **27b**: $[\alpha]_D^{20}$ -35.8° (c 2.0, $CHCl_3$), e.e. 55%.

(S)-(-)-o-sec-Butoxybenzenesulfinic acid (28b). In a flame dried flask were placed magnesium (320 mg, 0.013 mol), a few crystals of iodine and dry Et_2O (50 mL). To the stirred refluxing mixture was added dropwise a solution of (S)-o-bromophenyl sec-butyl ether **27b** (50% e.e.; 3.05 g, 0.013 mol) in Et_2O (10 mL). The mixture was refluxed with stirring for 3 h. The suspension was cooled to -50°C and dry SO_2 gas was bubbled into the solution keeping the temperature below -15°C. Completion of reaction was indicated by a continuous drop in temperature (after ca. 2 h). At room temperature the mixture was hydrolyzed with 10% ice-cooled H_2SO_4. The water layer was extracted with ether (10 x 25 mL). The combined ether solutions were extracted with saturated aqueous Na_2CO_3 (5 x 20 mL). The combined Na_2CO_3 extracts were acidified with cold 10% H_2SO_4 at 0°C and extracted with Et_2O (7 x 25 mL), dried ($MgSO_4$) and concentrated. The resulting colourless oil crystallized on cooling to give 1.98 g (66%) of **28b**; mp 48-50°; IR (CCl_4) 2550, 1280 and 1090 cm^{-1} (SO_2H); ^1H NMR ($CDCl_3$) δ 0.92 (t, 3), 1.25 (d, 3), 1.4-2.0 (m, 2), 4.3 (q, 1), 6.6-7.85 (m, 4), 8.10 (s, 1).

(S)-(-)-N-[(o-sec-Butoxyphenylsulfonyl)methyl]formamide (29b) was prepared from sulfinic acid **28b** (1.12 g, 5.0 mmol) with CH_2O and $HCONH_2$ by the procedure used for the synthesis of N-(tosylmethyl)formamide.[23] The colourless solid was crystallized from CH_2Cl_2-hexane to give 800 mg

(58%) of **29b**: mp 100-103°C. Analytically pure material was obtained by two more crystallizations from the same solvent mixture: mp 110-111°C; IR (Nujol): 3300 (NH), 1675 (NHCHO), 1280 and 1120 cm^{-1} (SO_2); ^1H NMR ($CDCl_3$) δ 1.04 (t, 3), 1.42 (d, 3), 1.55-2.20 (m, 2), 4.20-4.80 (m, 1), 4.85 and 4.95 (d of AB q, J = 15 Hz, 2), 6.7-7.9 (m, 5), 7.96 (s, 1); MS, m/e 271 (M^+); $[\alpha]_D^{20}$ -30.6° (c 1.1, $CHCl_3$). Anal. Calcd for $C_{12}H_{17}NO_4S$: C, 53.13; H, 6.27; N, 5.16; S, 11.80. Found: C, 52.96; H, 6.20; N, 5.25; S, 11.73.

(S)-(-)-(o-sec-Butoxyphenylsulfonyl)methyl isocyanide (5b). Sulfonylmethyl formamide **29b** (1.35 g, 5 mmol) was dehydrated with $POCl_3$ and Et_3N by the procedure used for the synthesis of TosMIC.[23] The work-up was as follows: After the addition of $POCl_3$ was complete, the mixture was stirred for 0.5 h at 0°C and then poured in ice-water. Extraction with benzene gave crude **5b**, which was chromatographed rapidly with $CHCl_3$ over Florisil to give 852 mg (67%) of a colourless viscous oil: IR (neat) 2180 (N≡C), 1340 and 1150 cm^{-1} (SO_2); ^1H NMR ($CDCl_3$) δ 1.0 (t, 3), 1.35 (d, 3), 1.5-2.0 (m, 2), 4.55 (q, 1), 4.86 and 4.93 (AB q, J = 15 Hz, 2), 6.6-8.0 (m, 4); ^{13}C NMR ($CDCl_3$) δ 9.4 (q), 18.5 (q), 28.4 (t), 58.9 (t), 76.5 (d), 113.6 (d), 120.2 (d), 131.7 (d), 136.8 (d), 122.3 (s), 155.7 (s), 164.1 (s); $[\alpha]_D^{22}$ -35.3° (c 1.16, $CHCl_3$). MS, m/e 253.076 (M^+, calcd 253.077). This material had the same e.e. of 50% as found for **28b** [determined with Eu(dcm)$_3$ in C_6D_6].

(±)-(1-Methoxy-2-propyl) tosylate (26c) was prepared in 79% yield, according to the procedure of Sanno,[38] from (±)-1-methoxy-2-propanol (purchased from ICN Pharmaceuticals).

(±)-o-Bromophenyl 1-methoxy-2-propyl ether (27c) was prepared analogously to 27b from 26c (9.76 g, 0.04 mol), o-bromophenol (25, 8.64 g, 0.048 mol) and KOH (2.8 g, 0.05 mol) as colourless oil (6.13 g, 63%): bp 52° (0.005 mm Hg); IR (neat) 1490, 1595, 3000 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.35 (d, 3), 3.35 (s, 3), 3.45 and 3.55 (d, 2), 4.45 (m, 1), 6.5-7.7 (m, 4); ^{13}C NMR ($CDCl_3$) δ 16.5 (q), 58.7 (q), 74.7 (d), 75.2 (t), 113.1 (s), 115.5 (d), 121.7 (d), 127.8 (d), 132.8 (d); MS, m/e 244.007 (M^+; calcd 244.010). Anal. Calcd for $C_{10}H_{13}BrO_2$: C, 48.97; H, 5.30; Br, 32.65. Found: C, 49.03; H, 5.32; Br, 32.47.

(±)-o-(1-Methoxy-2-propoxy)phenylsulfinic acid (28c). To a stirred solution of 27c (3.67 g, 15 mmol) in Et_2O (10 mL) at -78°C was added dropwise 10 mL of BuLi (1.6 M solution in hexane, ca. 16 mmol). After the addition was complete, the temperature was raised to 10°C (ca. 2 h). Dry SO_2 gas was introduced at -40°C for 1 h, to give a dense yellow precipitate. The reaction mixture was poured into 10 mL of 2 N H_2SO_4 and extracted with ether (8 x 10 mL). The ether layers were combined and extracted with saturated Na_2CO_3 solution (5 x 15 mL). The combined extracts were acidified with 10% aqueous H_2SO_4 and were extracted with ether (8 x 20 mL). The ether extracts were dried ($MgSO_4$) and concentrated to give 2.73 g (79%) of **28c** as a colourless viscous syrup; IR (neat) 1070-1120, 1240 and 1280 cm^{-1} (SO_2); ^1H NMR ($CDCl_3$) δ 1.35 (d, 3), 3.40 (s, 3), 3.60 (d, 2), 4.60 (m, 1), 6.7-8.0 (m, 4), 9.02 (s, 1).

(±)-N-[o-(1-Methoxy-2-propoxy)phenylsulfonylmethyl]formamide (29c). Sulfinic acid 28c (3.15 g, 13.7 mmol) was converted to **29c** with CH_2O and $HCONH_2$ according to the procedure used for the synthesis of N-(tosylmethyl)formamide.[23] The work-up was as follows: The oil, which separated after storing the reaction mixture at -20°C overnight, was extracted with CH_2Cl_2. The extract was washed with water, with brine, dried ($MgSO_4$) and concentrated to give 3.4 g (87%) of **29c** as colourless oil; IR (neat) 3450 (NH), 1680 and 1695 (NHCHO), 1280, 1320 cm^{-1} (SO_2); ^1H NMR ($CDCl_3$) δ 1.40 (d, 3), 3.35 (s, 3), 3.60 (d, 2), 4.7 (m, 3), 6.6-8.3 (m, 6); MS, m/e 287.084 (M^+, calcd 287.083).

(±)-[o-(1-Methoxy-2-propoxy)phenylsulfonyl]methyl isocyanide (5c). Sulfonylmethylformamide 29c (2.67 g, 9.3 mmol) was dehydrated with $POCl_3$ and Et_3N following the procedure used for the synthesis of TosMIC.[23] The work-up was as follows: After addition of $POCl_3$, the mixture was stirred for 0.5 h at 0°C and then poured in ice-water. The resulting brown oil was extracted with benzene; the combined organic layers were washed with H_2O, dried ($MgSO_4$) and concentrated to give a yellow oil, which was chromatographed with $CHCl_3$-benzene (1:1) over neutral Al_2O_3 to give **5c** as a pale yellow oil (1.7 g, 68%); IR (neat) 2150 (N≡C), 1145, 1280 and 1340 cm^{-1} (SO_2); ^1H NMR ($CDCl_3$) δ 1.35 (d, 3), 3.3 (s, 3), 3.5 (d, 2), 4.65 (m, 1), 5.25 and 5.15 (AB q, J = 15 Hz, 2), 6.7-8.1 (m,

4); MS, m/e 269.071 (M^+, calcd 269.072). Anal. Calcd for $C_{12}H_{15}NO_4S$: C, 53.52; H, 5.61; N, 5.20; S, 11.90. Found: C, 52.96; H, 5.80; N, 4.81; S, 11.24.

(S)-(+)-3-Tetrahydrofuranyl tosylate (26d) was prepared according to the procedure of Stuart and Ipson[39] from (S)-(+)-3-hydroxytetrahydrofuran[30] in 80% yield as colourless crystals, mp 34.5-35.5°C, $[\alpha]_D^{20}$ +18.4° (c 2.40, MeOH); ^1H NMR ($CDCl_3$) δ 1.96 (m, 2), 2.37 (s, 3), 3.68 (m, 4), 4.97 (m, 1), 7.33 and 7.50 (AB q, 4); ^{13}C NMR ($CDCl_3$) δ 20.5 (q), 32.1 (t), 65.7 (t), 71.7 (t), 81.2 (d), 126.8 (d), 129.3 (d), 133.0 (s), 144.3 (s). Anal. Calcd for $C_{11}H_{14}O_4S$: C, 54.53; H, 5.82; S, 13.23. Found: C, 54.44; H, 5.77; S, 13.22.

(R)-(-)-o-Bromophenyl 3-tetrahydrofuranyl ether (27d) was prepared analogously to **27b** from o-bromophenol (25, 2.16 g, 12.0 mmol), (S)-(+)-3-tetrahydrofuranyl tosylate (**27d**, 2.42 g, 10.0 mmol) and KOH (700 mg, 12.5 mmol) as a colourless oil (1.68 g, 69%): bp 115-117°C (0.15 mm Hg), $[\alpha]_D^{20}$ -35.8° (c 1.98, $CHCl_3$); IR (neat) 1485, 1590 cm^{-1}; ^1H NMR ($CDCl_3$) δ 21.5 (m, 2), 3.9 (m, 4), 4.85 (m, 1), 6.5-7.7 (m, 4); ^{13}C NMR ($CDCl_3$) δ 32.5 (t), 66.7 (t), 72.4 (t), 78.3 (d), 112.6 (s), 114.1 (d), 121.8 (d), 128.0 (d), 133.2 (d), 153.5 (s); MS, m/e 241.993 (M^+; calcd 241.994). Anal. Calcd for $C_{10}H_{11}BrO_2$: C, 49.38; H, 4.52; Br, 32.92. Found: C, 49.62; H, 4.59; Br, 32.81.

(R)-(-)-o-(3-Tetrahydrofuranoxy)benzenethiol (30d) was prepared analogously to **30a** from **27d** (1.21 g, 5.0 mmol) in 73% yield;[40] bp 105-108°C (0.2 mm Hg), $[\alpha]_D^{22}$ -30.6° (c 1.52, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 2.32 (m, 2), 3.95 (m, 4), 4.92 (m, 1), 6.6-7.8 (m, 5).

(R)-(-)-N-[o-(3-Tetrahydrofuranoxy)phenylsulfonylmethyl]formamide (32d) was prepared in 75% yield analogously to **32a** from crude **31d** [viscous oil; $[\alpha]_D^{20}$ -56.4° (c 1.4, $CHCl_3$); obtained from **30d** and N-(tosylmethyl)formamide[23] analogously to **31a** in 80% yield]. Two crystallizations from CH_2Cl_2-hexane gave colourless crystals: mp 107.5-110°C; $[\alpha]_D^{22}$ -28.8° (c 1.8, $CHCl_3$); IR (Nujol) 3250 (NH), 1640 cm^{-1} (NHCHO); ^1H NMR ($CDCl_3$) δ 2.30 (m, 2), 4.0 (m, 4), 4.90 (m, 3), 6.60-8.2 (m, 6); MS, m/e 285.067 (M^+; calcd 285.067).

(R)-(-)-[o-(3-Tetrahydrofuranoxy)phenylsulfonyl]methyl isocyanide (5d). Formamide **32d** (390 mg, 1.37 mmol) was dehydrated with $POCl_3$ and iPr_2NH according to the procedure of Ugi et al.[22] Pure **5d** was obtained as colourless needles after two crystallizations from benzene-hexane (2:1) in 66% yield; mp 107.4-108.2°C; $[\alpha]_D^{20}$ -40.8° (c 2.0, $CHCl_3$); IR (Nujol) 2150 (N≡C), 1235 and 1150 cm^{-1} (SO_2); ^1H NMR ($CDCl_3$) δ 2.30 (m, 2), 4.00 (m, 4), 4.87 and 4.94 (AB q, J = 15 Hz, 2), 5.18 (m, 1), 6.85-8.17 (m, 4); ^{13}C NMR ($CDCl_3$) δ 32.3 (t), 59.3 (t), 66.8 (t), 72.5 (t), 79.1 (d), 113.9 (d), 121.2 (d), 123.5 (s), 132.2 (d), 136.7 (d), 155.0 (s), 165.3 (s). Anal. Calcd for $C_{12}H_{13}NO_4S$: C, 53.93; H, 4.86; N, 5.24; S, 11.98. Found: C, 53.99; H, 4.88; N, 5.29; S, 11.87. The e.e. of **5d** could not be determined in a direct way be using chiral shift reagents. However, the e.e. was calculated to be 47% from the d.e. (38%) of **10e** and the o.p.[10] (18%) of **12** (Table 1, entry 14).

(-)-S-Phenyl-N-tosylsulfonimidoylmethyl isocyanide (6) was prepared from partially resolved S-phenyl-N-tosylsulfonimidoyl fluoride[6] ($[\alpha]_D^{20}$ +7.2°, c 1.1, $CHCl_3$), methyl isocyanide and 2.1 equiv. of BuLi in 35% yield; $[\alpha]_D^{21}$ -2.2° (c 1.4, $CHCl_3$). The e.e. of **6** was determined by conversion to oxazoline **11d** (Table II, entry 22) and subsequent hydrolysis to 2-hydroxy-2-phenyl-3,3,3-trifluoropropanal (**13**). This material was converted to (R)-(+)-2-methoxy-2-phenyl-3,3,3-trifluoropropionic acid (**15**) (according to Scheme 2, overall yield 16.5%); $[\alpha]_D^{20}$ +19.4° (c 1.4, $CHCl_3$), which corresponds to an o.p. of 27%.[20] The e.e. of (-)-**6** was calculated to be 34% from the o.p. (27%) of **15** and the d.e. (80%) of **11d**. This material was identical with racemic **6** by IR, ^1H NMR and mixed mp.

Trans-4-(2-Menthoxyethylsulfonyl)-5-methyl-5-phenyl-2-oxazoline (10b). Typical Procedure: PTC Conditions (entry 2). To a stirred solution of isocyanide **4** (430 mg, 1.5 mmol) and acetophenone (180 mg, 1.5 mmol) in benzene (15 mL) was added 18 mg (i.e. 5 mol %) of benzyltriethylammonium chloride (TEBACl) and 75 mL of 50% aqueous NaOH, and the mixture was stirred for 3 h at 10-15°C. The alkaline aqueous layer was twice extracted with ether (25 mL). The combined organic layers were

washed with ice-cold H_2O (10 mL), dried (Na_2SO_4) and concentrated to yield 451 mg (74%) of 10b as a yellow oil; IR (neat) 1620 (C=N), 1320, 1260 and 1140 cm^{-1} (SO_2); ^1H NMR ($CDCl_3$) δ 0.5-2.5 (m, 18), 2.06 (s, 3), 2.80-4.20 (m, 5), 5.22 and 5.45 (two d, J = 2 Hz, 1), 7.0-8.2 (m, 6). The d.e. (33%) was determined from the ratio (1:2) of the integrated doublets at δ 5.22 and 5.45.

Trans-4-(o-sec-Butoxyphenylsulfonyl)-5-methyl-5-phenyl-2-oxazoline (10c). Typical Procedure: BuLi/THF (entry 3). To a stirred solution of isocyanide 5b (50% e.e.; 126 mg, 0.5 mmol) in 5 mL of THF at -90°C was added 0.35 mL (1.6 M, 0.56 mmol) of BuLi in hexane diluted with THF (5 mL). The mixture was stirred for 15 min at -80°C. Then a solution of acetophenone (60 mg, 0.5 mmol) in THF (5 mL) was added dropwise to the reaction mixture. After stirring for 2 h between -50 and -60°C, the temperature was slowly raised to 0°C and saturated NH_4Cl solution (5 mL) was added. The mixture was extracted with CH_2Cl_2 (3 x 15 mL), dried ($MgSO_4$) and concentrated to give 141 mg (76%) of 10c as a yellow syrup; IR (neat) 1625 (C=N), 1320-1270 and 1150 cm^{-1} (SO_2); ^1H NMR ($CDCl_3$) δ 0.7-2.0 (m, 8), 2.17 (s, 3), 4.4 (m, 1), 5.76 and 5.87 (two d, J = 1 Hz and 2.1 Hz, 1), 6.6-8.2 (m, 10). The d.e. (40%) was determined from the ratio (3:7) of the integrated doublets at δ 5.76 and 5.87.

Trans-5-Methyl-4-(neomenthylsulfonyl)-5-phenyl-2-oxazoline (10a, entry 1). From (+)-(neomenthylsulfonyl)methyl isocyanide (3) and acetophenone. Yield 60%, semi-solid; IR (Nujol) 1620 (C=N), 1300 and 1120 cm^{-1} (SO_2); ^1H NMR ($CDCl_3$) δ 0.7-2.8 (m, 18), 2.06 (s, 3), 4.04 (br, 1), 4.96 and 5.12 (two d, J = 2 Hz, 1), 7.1-7.6 (m, 6); d.e. 18%.

Trans-4-[o-(1-Methoxy-2-propoxy)phenylsulfonyl]-5-methyl-5-phenyl-2-oxazoline (10d, entry 6). From (±)-5c and acetophenone. Yield 80%, yellow oil; IR (neat) 1620 (C=N), 1320-1260 and 1140 cm^{-1} (SO_2); ^1H NMR ($CDCl_3$) δ 1.35 (d, 3), 2.0 (s, 3), 3.3 (m, 5), 4.60 (m, 1), 5.75 and 5.95 (two d, J = 2 Hz, 1), 6.6-8.1 (m, 10); d.e. 17%.

Cis/trans-5-Methyl-5-phenyl-4-[o-(3-tetrahydrofuranoxy)phenylsulfonyl]-2-oxazoline (10e, entry 14). From (R)-(-)-5d of 47% o.p. and acetophenone. Yield 70%, pale yellow oil; IR (neat) 1620 (C=N), 1310, 1270 and 1145 cm^{-1} (SO_2); ^1H NMR ($CDCl_3$) δ 1.95 (m, 2), 2.00 (s, 3), 3.85 (m, 4), 5.05 (m, 1), 5.76 and 5.79 (two d, J = 2.1 Hz and J = 1.9 Hz, 1), 6.8-8.2 (m, 10); d.e. 38%.

Trans-4-(o-Methoxyphenylsulfonyl)-5-methyl-5-phenyl-2-oxazoline was prepared analogously to 10a from isocyanide 5a and acetophenone. Yield 92%; mp 170-171°C; IR (Nujol) 1615 (C=N), 1320-1280 and 1150 cm^{-1} (SO_2); ^1H NMR ($CDCl_3$) δ 2.14 (s, 3), 3.82 (s, 3), 5.74 (d, J = 2 Hz, 1), 6.8-8.0 (m, 10). Anal. Calcd for $C_{17}H_{17}NO_4S$: C, 61.63; H, 5.13; N, 4.22; S, 9.66. Found: C, 61.28; H, 5.08; N, 4.39; S, 9.62.

Cis/trans-4-Neomenthylsulfonyl-5-phenyl-5-trifluoromethyl-2-oxazoline (11b). Typical Procedure: Ti(OEt)$_4$/N-ethylpiperidine[42] (entry 17). To a stirred solution of titaniumtetraethoxide (0.456 g, 2.0 mmol) and N-ethylpiperidine (0.138 g, 1.2 mmol) in 2 mL of CH_2Cl_2 was added a solution of isocyanide 3 (0.24 g, 1 mmol) in CH_2Cl_2 (2 mL) at 0°C. After stirring the mixture for 30 min at 0°C a solution of α,α,α-trifluoroacetophenone (0.175 g, 1.0 mmol) in CH_2Cl_2 (2 mL) was added dropwise. After stirring for 1 h at 0°C the reaction mixture was quenched with saturated Na_2SO_4 solution (2 mL). After raising the temperature to 20°C, the resulting solid was removed by filtration (using Celite as filter aid). The filtrate was washed with H_2O (2 x 5 mL), with brine (5 mL), dried (Na_2SO_4) and concentrated to give 400 mg (96%) of 11b as a viscous oil; IR (neat) 1620 cm^{-1} (C=N); ^1H NMR ($CDCl_3$) δ 0.7-2.8 (m, 18), 4.09 (br, 1), 5.33, 5.35, 5.49 and 5.53 (four d, J = 2.1, 1.9, 2.1 and 1.9 Hz, respectively), 7.25-7.80 (m, 6); ^{19}F NMR ($CDCl_3$) δ -71.74, -71.92, -80.27 and -80.46; d.e. 18%.

Cis/trans-4-Tosyl-5-phenyl-5-trifluoromethyl-2-oxazoline (11a). Typical Procedure: Triton B (entry 16). To a stirred solution of TosMIC (1, 0.80 g, 4.1 mmol) and trifluoroacetophenone (0.71 g, 4.1 mmol) in 50 mL of THF (previously distilled from sodium and benzophenone) was added at room temperature 0.66 mL of a solution of Triton B (40% in MeOH). The mixture was stirred for 4 h, after which 62 μL of acetic acid and 0.6 mL of H_2O were added. After removal of the solvents, the residue was dissolved in 50 mL of CH_2Cl_2 and was washed with H_2O (3 x 20 mL), dried ($MgSO_4$) and concentrated to yield 1.45 g (3.93 mmol, 96%) of 11a; IR (Nujol) 1630 (C=N) cm^{-1}; ^1H NMR ($CDCl_3$) δ

2.36 (s, 3), 5.53 and 5.83 (two d, J = 1.9 Hz and J = 2.1 Hz, 1), 7.1-8.0 (m, 10); ^{19}F NMR ($CDCl_3$) δ -71.50 and -79.44.

Cis/trans-5-Phenyl-4-[o-(3-tetrahydrofuranoxy)phenylsulfonyl]-5-trifluoromethyl-2-oxazoline (11c, entry 19). From (R)-(-)-5d and trifluoroacetophenone. Yield 98%, viscous oil; ^{1}H NMR ($CDCl_3$) δ 2.16 (m, 2), 3.5-4.31 (m, 4), 4.84 (m, 1), 6.04, 6.11, 6.26 and 6.31 (four d, J = 2.1, 1.9, 2.1 and 1.9 Hz, 1), 6.7-8.22 (m, 10); ^{19}F NMR ($CDCl_3$) δ -73.41, -73.73, -75.03 and -75.47; d.e. 41%.

Cis/trans-5-Phenyl-4-(S-phenyl-N-tosylsulfonimidoyl)-5-trifluoromethyl-2-oxazoline (11d, entry 22). From (-)-6 and trifluoroacetophenone. Yield 91%, dark viscous oil; ^{1}H NMR ($CDCl_3$) δ 2.40 (br s, 3), 5.25 and 6.33 (two d, J = 2.1 Hz, 1), 6.98-8.10 (m, 15); ^{19}F NMR ($CDCl_3$) δ -71.4, -71.6, -79.1 and -79.3; d.e. 80%.

(R)-(-)-2-Hydroxy-2-phenylpropanal (12).[9] **Typical Procedure.** To a stirred solution of trans-4-(2-menthoxyethylsulfonyl)-5-methyl-5-phenyl-2-oxazoline (10b, 500 mg, 1.2 mmol) in THF (15 mL) was added 2 N HCl (3 mL). The mixture was stirred overnight at room temperature, then diluted with H_2O (10 mL), extracted with Et_2O (3 x 15 mL), dried ($MgSO_4$) and concentrated. Aldehyde 12 was obtained as a colourless liquid, 83 mg (47%) by kugelrohr distillation; bp 90-110°C (0.1 mm Hg) [Lit.[43] bp 108-110°C (0.3 mm Hg)]; IR (neat) 3440 (OH), 1720 cm^{-1} (C=O); ^{1}H NMR ($CDCl_3$) δ 1.60 (s, 3), 4.3 (br s, 1), 7.4 (br s, 5), 9.4 (s, 1); $[\alpha]_D^{20}$ -80.2° (c 1.73, $CHCl_3$), o.p. 31%.[9]

(R)-(+)-2-Hydroxy-2-phenyl-3,3,3-trifluoropropanal (13). **Typical Procedure.** To a solution of 4-neomenthylsulfonyl-5-phenyl-5-trifluoromethyl-2-oxazoline (11b, 1.5 g, 3.6 mmol) in THF (30 mL) was added 2 N HCl (10 mL). The mixture was stirred overnight at room temperature, then diluted with H_2O (150 mL) and extracted with Et_2O (3 x 50 mL). The combined extracts were washed with H_2O (3 x 20 mL), with brine (30 mL), dried (Na_2SO_4) and concentrated to give 0.37 g (51%) of crude 13 as a pale yellow oil, which was converted to 14 as such.

(R)-(+)-2-Methoxy-2-phenyl-3,3,3-trifluoropropanal (14). To a solution of crude aldehyde 13 (0.372 g) in Et_2O (30 mL) was added at room temperature 96 mg (4.0 mmol) of NaH (oil removed previously). After 1 h 0.6 g (4.0 mmol) MeI was added, after which the mixture was refluxed for 2 h. The mixture was poured in ice-water (100 mL) and extracted with ether (3 x 50 mL). The combined extracts were washed with H_2O (2 x 20 mL), dried (Na_2SO_4) and concentrated to give 0.39 g of crude product, which was distilled at reduced pressure (96-97°C, 12 mm Hg) to give 0.32 g (1.5 mmol, 42%) of 14; ^{1}H NMR ($CDCl_3$) δ 3.5 (s, 3), 7.0-7.6 (m, 5), 9.66 (q, $^4J_{FH}$ = 2 Hz, 1); ^{19}F NMR ($CDCl_3$) δ -70.92; ^{13}C NMR ($CDCl_3$) δ 54.66 (q), 84.72 (q, $^2J_{FC}$ = 37 Hz), 123.16 (q, $^1J_{FC}$ 286 Hz), 129.0 (d), 129.2 (s), 129.8 (d), 131.1 (d), 193.0 (d); $[\alpha]_D^{20}$ +7.2° (c 1.01, $CHCl_3$).

(R)-(+)-2-Methoxy-2-phenyl-3,3,3-trifluoropropionic acid (15).[20] A solution of sodium chlorite ($NaClO_2$, 0.14 g, 85%, 1.25 mmol)[44] in 1 mL of NaH_2PO_4 buffer (pH 3.5) was added dropwise to a rapidly stirred solution of purified methoxy aldehyde 14 (204 mg, 1.0 mmol) and 2-methyl-2-butene (1.06 mL, 10 mmol) in 50 mL of t-BuOH at 30°C and then stirred for 8 h . After addition of 6 N NaOH to pH ca. 10, t-BuOH was removed at reduced pressure. The residue was dissolved in H_2O (50 mL) and extracted with hexane (2 x 25 mL). The aqueous layer was acidified with 6 N HCl to pH ca. 3, and then extracted with Et_2O (2 x 50 mL). The organic layers were combined, washed with H_2O (25 mL), with brine (25 mL), dried (Na_2SO_4) and concentrated to give 0.190 g of crude material. Distillation at reduced pressure (106-108°C, 1 mm Hg) gave 0.17 g (0.73 mmol, 73%) of 15; ^{1}H NMR ($CDCl_3$) δ 3.5 (s, 3), 7.0-7.6 (m, 5), 11.13 (s, 1); ^{19}F NMR ($CDCl_3$) δ -71.46; ^{13}C NMR ($CDCl_3$) δ 55.4 (q), 84.4 (q, $^2J_{CF}$ = 28 Hz), 118.9 (q, $^1J_{CF}$ = 291 Hz), 127.3 (d), 128.6 (d), 129.9 (d), 131.0 (s), 171.7 (s); $[\alpha]_D^{21}$ +11.8° (c 1.5, $CHCl_3$), o.p. 17%.[20]

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References and Notes

1. Chemistry of Sulfonylmethyl Isocyanides 32. For part 30 see J. Moskal and A.M. van Leusen, J. Org. Chem. 51, 4131 (1986).
2. J.D. Morison and H.S. Mosher in "Asymmetric Organic Reactions", Prentice Hall, Engelwood Cliffs, N.Y. 1971.
3. S. Hanessian in "Total Synthesis of Natural Products. The Chiron Approach", Pergamon Press, New York 1984.
4. The chemistry of TosMIC has been reviewed: (a) A.M. van Leusen, Lect. Heterocycl. Chem. 5, S111 (1980); (b) A.M. van Leusen, in "Perspectives in the Organic Chemistry of Sulfur", B. Zwanenburg and A.J.H. Klunder, Eds., Elsevier, Amsterdam 1987, p. 119.
5. (+)-Neomenthylsulfonylmethyl isocyanide (3) was previously described. It has been used for the first synthesis of optically active 2-methylcyclobutanone: D. van Leusen, P.H.F.M. Rouwette and A.M. van Leusen, J. Org. Chem. 46, 5159 (1981).
6. D. van Leusen and A.M. van Leusen, Recl. Trav. Chim. Pays-Bas 103, 41 (1984).
7. See ref. 4a, and also: (a) O.H. Oldenziel and A.M. van Leusen, Tetrahedron Lett. 167 (1974); (b) O. Possel, Ph.D. Thesis, Groningen (1978); (c) P.H.F.M. Rouwette, Ph.D. Thesis, Groningen (1979).
8. Y. Ito, M. Sowamura and T. Hayashi, J. Am. Chem. Soc. 108, 6405 (1986).
9. T. Mukaiyama, Y. Sakito and M. Asami, Chem. Lett. 1253 (1978).
10. Throughout this paper, e.e. and o.p. are assumed to be equal.
11. ^{1}H NMR of the 4-tosyl-2-oxazolines indicates that only one isomer is formed, provided that the substituents at C(5) are sufficiently different in size. For 5-tert-butyl-5-methyl-4-tosyl-2-oxazoline the trans stereochemistry was established by NOE.
12. O.H. Oldenziel, Ph.D. Thesis, Groningen (1975).
13. To the intramolecular reaction product was tentatively assigned the structure 13,13-dimethyl-2-oxa-4-aza-6-thiatetracyclo[6.4.1^{8,11}.0^{1,5}.0^{1,8}]dodec-3-ene-6,6-dioxide. Intermolecular reaction products, however, were obtained from 2 and p-nitrobenzaldehyde or benzoyl chloride and base: 5-(p-nitrophenyl)oxazole (90%) and 4-(10-camphorsulfonyl)-5-phenyloxazole (70%), respectively, see ref. 7c, p. 22.
14. Chelation has been used previously with success in asymmetric induction, see f.e.: J.D. Morrison in "Asymmetric Synthesis", Vol. 3, Ch. 3 and 4, Academic Press, New York 1984.
15. W. Klyne in "Progress in Stereochemistry", Ch. 6, Butterworths, London, 1954.
16. S.P.J.M. van Nispen, C. Mensink and A.M. van Leusen, Tetrahedron Lett. 3723 (1980).
17. Trans is defined here for R*S(O)(X) and Ph at opposite sides of the oxazoline ring.
18. L. Colombo, G. Gennari, C. Scolastico, G. Guanti and E. Narisano, J. Chem. Soc. Perkin I, 1278 (1981).
19. Protection of the hydroxy group prior to oxidation is necessary since α-hydroxy acids are prone to oxidative cleavage, cf. P. Blumbergs, M.P. LaMontagne and J.L. Stevens, J. Org. Chem. 37, 1248 (1973).
20. J.A. Dale and H.S. Mosher, J. Am. Chem. Soc. 95, 512 (1973).
21. (a) C.R. Johnson, Aldrichimica Acta 18, 1 (1985) and references cited therein; (b) S.G. Pyne, J. Org. Chem. 51, 81 (1986).
22. R. Obrecht, R. Herrmann and I. Ugi, Synthesis, 400 (1985).
23. cf. B.E. Hoogenboom, O.H. Oldenziel and A.M. van Leusen, Org. Synth. 57, 102 (1977). As was shown for example, in the synthesis of 3 the use of iPr_2NH instead of Et_3N usually gives higher yields and/or purer products and is now recommended.
24. (a) W. Huckel, D. Maucher, O. Fechtig, J. Kurz, M. Heinzel and A. Hubele, Liebigs Ann. chem. 645, 115 (1961); (b) A similar mixture of menthenes was obtained in unsuccessful attempts to convert the tosylate of (-)-5-methyl-2-(2-phenyl-isopropyl)cyclohexanol (from (+)-pulegone)[25] into a 2-thiol, J. Boon, unpublished results.
25. E.J. Corey and H.E. Ensley, J. Am. Chem. Soc. 97, 6908 (1975).
26. J. Cason and J.S. Correia, J. Org. Chem. 26, 3645 (1961).
27. Enantiomerically pure 1,2-propanediol is available from lactic acid: (a) J. Gombos, E. Haslinger and U. Schmidt, Chem. Ber. 109, 2645 (1976); (b) C. Melchiorre, Chem. Ind. (London) 218 (1976).
28. The yield may vary considerably with minor changes in reaction conditions, cf. P. Beak and C-W. Chen, Tetrahedron Lett. 4979 (1985) and references therein.
29. H. Wynberg and A. Bantjes, Org. Synth. Coll. Vol. IV, 534 (1963).
30. V.K. Tandon, A.M. van Leusen and H. Wynberg, J. Org. Chem. 48, 2767 (1983).
31. (a) C.A. Hergrueter, P.D. Brewer, J. Tagat and P. Helquist, Tetrahedron Lett. 4145 (1977); (b) ibid, Tetrahedron Lett. 4573 (1977).
32. A.C. Brouwer and A.M. van Leusen, Synth. Comm. 865 (1986).
33. (a) S. Krishna and H. Singh, J. Am. Chem. Soc. 50, 792 (1928); (b) S. Smiles and T.P. Hilditch, J. Chem. Soc. 519 (1907).
34. E. Chiellini, Gazz. Chem. Ital. 102, 830 (1972).
35. J. Kenyon, H. Phillips and V.P. Pittman, J. Chem. Soc. 1072 (1935).
36. J.B. Niederl and S. Natelson, J. Am. Chem. Soc. 53, 1928 (1931).
37. D.N. Reinhoudt, F. de Jong and H.P.M. Tomassen, Tetrahedron Lett. 2067 (1979).
38. Y. Sanno, Yakugaku Zasshi 77, 626 (1957); Chem. Abstr. 51, 16431c (1957).
39. R. Stuart and T. Ipson, J. Org. Chem. 9, 235 (1944).
40. This compound is unstable at room temperature. Attempts to determine the e.e. by NMR techniques (i.e. chiral shift reagents or methylphosphonic dichloride[41]) were unsuccessful.
41. (a) B.L. Feringa, A. Smaardijk, H. Wynberg, B. Strijtveen and R.M. Kellogg, Tetrahedron Lett. 997 (1986); (b) B. Strijtveen, B.L. Feringa and R.M. Kellogg, Tetrahedron 43, 123 (1987).

42. Experimentally it was found to be crucial to use a combination of both bases. Other bases or base-combinations, which led either to destruction of the isocyanide or to decomposition of trifluoroacetophenone, were e.g. K_2CO_3, t-BuOK, $Ti(OEt)_4$- K_2CO_3 and $Ti(OEt)_4$-t-BuOK.
43. O.H. Oldenziel and A.M. van Leusen, Tetrahedron Lett. 167 (1974).
44. (a) J.E. Lynch and E.L. Eliel, Tetrahedron Lett. 2855 (1981); (b) ibid, J. Am. Chem. Soc. 106, 2943 (1984); (c) G.A. Kraus and B. Roth, J. Org. Chem. 45, 4825 (1980).