Synthesis of (+)-Neomenthanethiol and Some of Its Derivatives. A New Example of Asymmetric Induction in the Sulfoxide Synthesis

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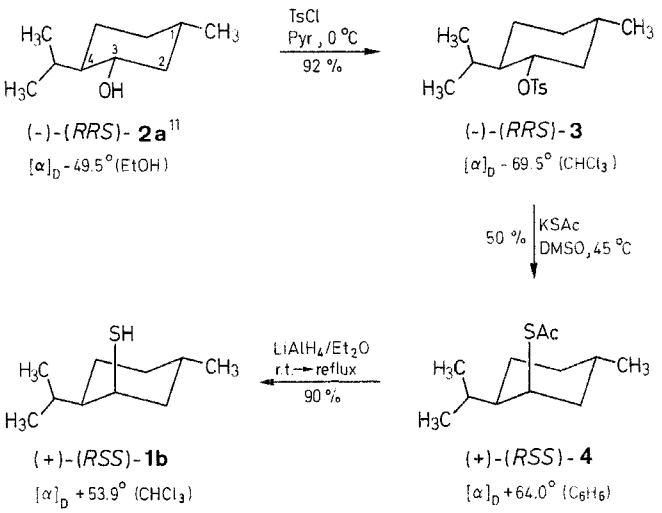
(+)-Neomenthanethiol **(1b)** with $[\alpha]_D^{20}$ +53.9° (c = 1.85, $CHCl_3$), is prepared from (−)-menthol **(2a)** in three steps in 42% overall yield. ^1H- and ^{31}P-NMR studies showed that the diastereomeric and optical purity of the product obtained is at least 95%. Methylation of (+)-**1b** leads to (+)-methyl neomenthyl sulfide **(11)** which undergoes oxidation to the corresponding sulfoxide (+)-**13** (a mixture of diastereomers in a 69:31 ratio) and sulfone (+)-**12**.

In the course of our studies on chiral enantiomeric trivalent phosphorus compounds,[2,3] it was necessary to prepare (+)-neomethanethiol **(1b)** as a chiral auxiliary reagent forming diastereomeric systems. A literature survey revealed that the synthetic approaches to optically active thiols are relatively few in number and for the most part their applicability is limited.[4-9] This is mainly due to moderate or low chemical yields and not full optical purity of the chiral thiols obtained, especially those having sterically hindered, chiral carbon atom bearing the SH-group. Thus, for example, the (+)-neomenthanethiol **(1b)** required in our investigations was obtained by Italian workers[8] from (−)-menthol in three steps in 14% yield only and with $[\alpha]_D^{25}$ +39.0° ($CHCl_3$). Van Leusen and coworkers,[10] using slightly modified procedure of Beretta et al,[8] obtained (+)-**1b** in 40% yield having $[\alpha]_D^{27}$ +47.8° ($CHCl_3$). However, no rigorous proof of its diastereomeric and optical purity was provided. In the paper by Mukaiyama et al[9] (+)-neomethanethiol **(1b)** was obtained from (−)-menthol *via* the corresponding *N,N*-dimethyldithiocarbamate. In this case, no data on its optical rotation, optical purity and chemical yield were given.

In this paper we report an efficient and highly stereoselective three-steps conversion (of (−)-menthol **(2a)** into (+)-neomenthanethiol **(1b)** which was obtained in 42% overall yield and with at least 95% (if not 100%) diastereomeric and enantiomeric purity. The synthesis of (+)-**1b** is outlined in Scheme A.

(−)-Menthol **(2a)** was reacted at first with *p*-toluenesufonyl chloride in pyridine to give the corresponding menthyl tosylate (−)-**3** in 92% yield. The latter on treatment with potassium thioacetate in a solution of dimethyl sulfoxide was transformed into (+)-neomenthyl thiolacetate **(4)** in 50% yield. This reaction, being a typical nucleophilic substitution of the S_N2-type, is accompanied by inversion of configuration at the carbom atom C-3. The last step of the synthesis of (+)-**1b** involves reduction

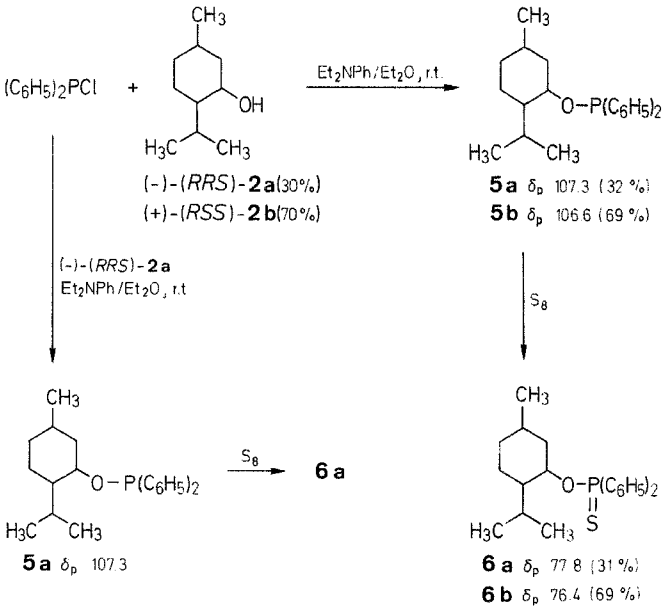


Scheme A

of (+)-**4** by lithium aluminium hydride affording the desired product in 90% yield having $[\alpha]_D^{20}$ +53.9° (c = 1.85, $CHCl_3$). The overall yield of conversion of (−)-**2a** to (+)-**1b** is 42%.

The most interesting fact is that the rotation value prepared as described above is still higher than that reported by van Leusen et al.[10] Since in our synthesis some extent of epimerization at C-3 could not be excluded in advance, it was desirable to determine the diastereomeric purity of our product i.e. to estimate the eventual presence of (−)-methanethiol **(1a)**. In the diastereomeric thiols **1a** and **1b** the SH-group is occupying an equatorial and axial position, respectively, and the six-membered ring exists in a rigid chair conformation. Therefore, it was quite reasonable to expect that even in the case of an achiral auxiliary reagent one should observe different chemical shifts for the axially and equatorially oriented derivatizing groups. We decided to use for that purpose diphenylchlorophosphine and ^{31}P-NMR spectroscopy as an analytical tool.[12]

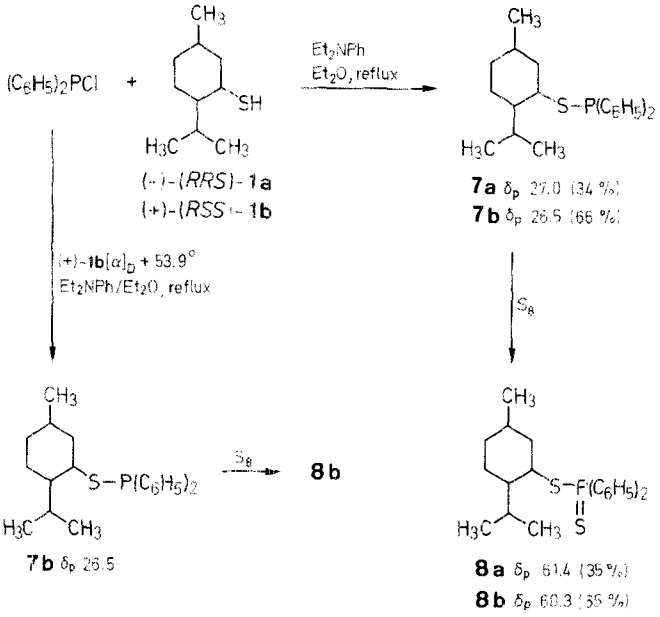
However, to confirm validity of the above reasoning diphenylchlorophosphine was initially treated with a mixture of (−)-menthol **(2a)** and (+)-neomenthol **(2b)** (30:70) in the presence of diethylaniline. The ^1H- and ^{31}P-NMR spectra of the condensation product **5** formed showed two singlets with the intensity



Scheme B

ratio of 31.5:68.5 due to the presence of two diastereomeric phosphinites **5a** and **5b**. Addition of elemental sulfur to this mixture gave the corresponding thiophosphinates **6a** and **6b** having also different chemical shifts (see Scheme **B**). As expected, condensation of (−)-menthol **(2a)** with diphenylchlorophosphine gave **5a** as the only product.

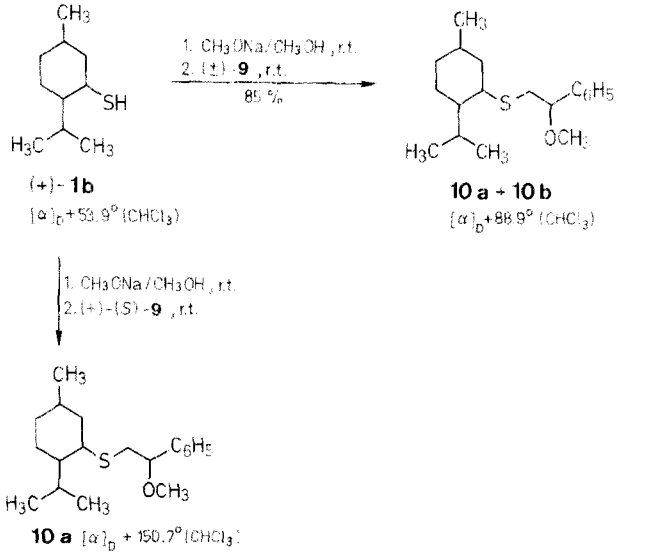
Similar set of experiments carried out in order to determine the diastereomeric purity of (+)-neomenthanethiol **1b** is depicted in Scheme **C**.



Scheme **C**

Since the ^{1}H- and ^{31}P-NMR spectra of the condensation product of diphenylchlorophosphine with (+)-neomenthanethiol **(1b)**, prepared in this work showed only one singlet at $\delta_P = 26.5$ and since both diastereomeric thiophosphinites **7** as well as dithiophosphinates **8** derived from (−)-methanethiol **(1a)** and (+)-neomenthanethiol **(1b)** differ in their ^{31}P-chemical shifts, it may be concluded that the diastereomeric purity of our product must be at least 95% if not higher.[13]

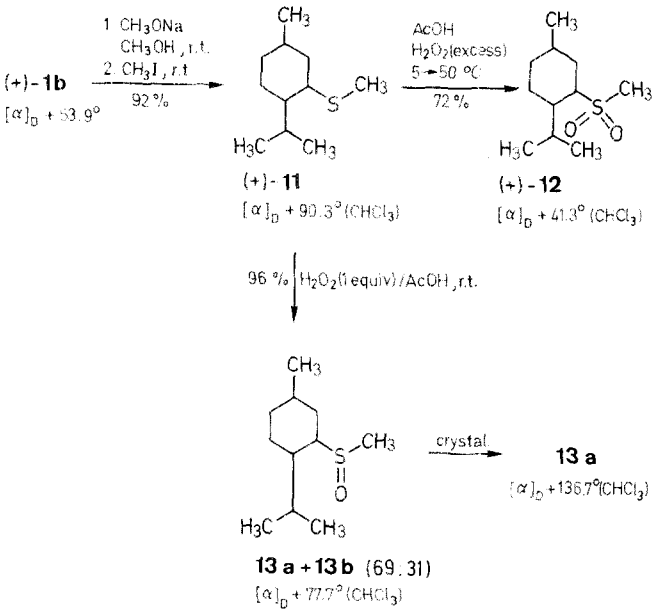
In order to determine the presence of eventual enantiomeric contaminant, the sample of (+)-**1b** obtained was condensed with optically active (+)-(*S*)-2-phenyl-2-methoxyethyl bromide



Scheme **D**

(9).[15] This reaction afforded the corresponding sulfide **10**, $[\alpha]_D^{20}$ + 150.7° (*c* = 3.8, $CHCl_3$), the ^{1}H-NMR spectrum of which showed one singlet at $\delta = 3.25$ for the methoxy protons. On the other hand, analogous reaction with racemic bromide (±)-**9** gave sulfide **10**, $[\alpha]_D^{20}$ + 88.9° (*c* = 3.6, $CHCl_3$) (Scheme **D**). Its ^{1}H-NMR spectrum showed two well separated ($\Delta\delta = 1.5$ Hz) methoxy-singlets of equal intensity corresponding to the two diastereomeric sulfides **10a** and **10b**. These observations may be taken as an indication that the enantiomeric purity of (+)-neomenthanethiol **(1b)** obtained is also high and lies in the range between 95 and 100%[13]

To characterize (+)-neomenthanethiol **(1b)** better, it was treated with methyl iodide to give the corresponding sulfide **11**, $[\alpha]_D^{20}$ + 90.3° (*c* = 3.52, $CHCl_3$). Oxidation of the latter with an excess of hydrogen peroxide in the presence of acetic acid gives (+)-methyl neomenthyl sulfone **(12)**, $[\alpha]_D^{21}$ + 41.3° ($CHCl_3$). The use of an equivalent amount of hydrogen peroxide allows to oxidize (+)-**11** selectively to the sulfoxide **13**, $[\alpha]_D^{22}$ + 77.7° (*c* = 1.43, $CHCl_3$). This product is a mixture of the two diastereomeric sulphoxides **13a** and **13b** which are formed in a 69:31 ratio[16] (Scheme **E**). Fractional crystallization of this mixture from petroleum ether-chloroform (20:1) affords the pure major diastereomer **13a**, m.p. 123.5–125 °C, $[\alpha]_D^{22}$ + 136.7° ($CHCl_3$).



Scheme **E**

The determination of the absolute configuration at sulfur in **13a** and other experiments aimed at rationalization of this new example of asymmetric oxidation are in progress.

All m.p.s. and b.p.s. are uncorrected. Solvents and commercial reagents were distilled before use; ether was distilled from lithium aluminium hydride. Natural menthol **(2a)** (BHD company) was used without purification. ^{1}H-NMR spectra were recorded at 80 MHz with a Tesla BS 847 C spectrometer using TMS as an internal standard. ^{31}P-NMR spectra were obtained on a Jeol JNM-C-60 Hz spectrometer using H_3PO_4 as an external standard. Optical activity measurements were made with a Perkin-Elmer 241 MC photopolarimeter (sensitivity 0.002°).

(−)-Menthone was obtained according to the procedure described in Organic Syntheses.[17] Reduction of (−)-menthone by tris(isopropoxy)-aluminum gave a mixture of (−)-menthol **(2a)** and (+)-neomenthol **(2b)** in a ratio 30:70, $[\alpha]_D^{20}$ − 0.82° (*c* = 2.51, 96% EtOH).

(−)-Menthyl *p*-Toluenesulfonate (3):[18]
Treatment of (−)-menthol (**2a**; 31.2 g, 0.2 mol) at 0 °C with *p*-toluenesulfonyl chloride (77 g, 0.4 mol) in dry pyridine (300 mL) gave, after the usual work-up,[18] the desired product **3**; yield: 57 g (92%); $[\alpha]_D^{22}$ −69.5° (*c* = 2.99, $CHCl_3$); m.p. 92.5–93.5 °C [Lit.[18] $[\alpha]_D^{24}$ −68.2° ($CHCl_3$); m.p. 93.5 °C].

(+)-Neomenthyl Thioacetate (4):
(−)-Menthyl *p*-toluenesulfonate (**3**; 52 g, 0.2 mol) is added to a solution of potassium thioacetate[19] (68.5 g, 0.6 mol) in dry DMSO (150 mL) and the mixture is stirred at 45 °C for 24 h. Water (200 mL) is added to the mixture and the product is extracted with $CHCl_3$ (5 × 50 mL). The $CHCl_3$ extract is dried ($MgSO_4$), evaporated and the residue distilled twice to give pure **4**; yield: 21.5 g (50%); b.p. 65–67 °C/0.07 mbar; $[\alpha]_D^{20}$ +64.0 (*c* = 2.66, $CHCl_3$).

$C_{12}H_{22}OS$	calc.	C 67.24	H 10.34	S 14.96
(214.4)	found	67.02	10.26	15.00

^{1}H-NMR ($CDCl_3$): δ = 0.63–2.0 (m, 18 H), 2.25 (s, 3 H, CH_3CO); 4.04 (m, 1 H).

MS: *m/e* (%) = 214(1.7), 171(6), 139(20), 138(100), 137(13), 123(19), 95(97), 86(39), 83(74), 81(76), 69(43), 67(31), 57(26), 55(64), 43(93), 27(20).

(+)-Neomenthanethiol (1b):
To a stirred suspension of $LiAlH_4$ (4.2 g, 0.11 mol) in dry ether (100 mL) a solution of (+)-neomenthyl thiolacetate (**4**; 21.4 g, 0.1 mol) in dry ether (50 mL) is added at room temperature under an argon atmosphere. After completion of the addition (ca. 45 min), the mixture is refluxed for 2 h, cooled to room temperature and treated with water (50 mL). Nascent gelatinous precipitate is dissolved in 10% H_2SO_4 (80 mL). The mixture separates into two layers and the aqueous phase is extracted with ether (3 × 40 mL). The ethereal extract is dried ($MgSO_4$), evaporated and the crude product distilled to give pure **1b**; yield: 15.4 g (90%); b.p. 65 °C/5.3 mbar; n_D^{20} = 1.4835, $[\alpha]_D^{20}$ +53.9° (*c* = 1.85, $CHCl_3$); [Lit.[8] b.p. 90–92 °C/13 mbar; n_D^{20} = 1.4738, $[\alpha]_D^{25}$ +39.0° ($CHCl_3$); Lit.[10] $[\alpha]_D^{?}$ +47.8° (*c* = 2.06, $CHCl_3$)].

$C_{10}H_{20}S$	calc.	C 69.70	H 11.70	S 18.61
(172.3)	found	69.74	11.70	18.54

^{1}H-NMR ($CDCl_3$): δ = 0.6–2.1 (m, 19 H); 3.5 (m, 1 H).

MS: *m/e* (%) = 174(0.8), 173(1.6); 172(15), 139(13), 138(38), 123(24), 96(23), 95(100), 83(48), 82(22), 81(53), 69(33), 67(28); 55(52), 43(23), 41(46), 29(14), 27(18).

Determination of Diastereomeric and Enantiomeric Purity of 1b by ^{1}H- and ^{31}P-NMR:

Reaction of Diphenylchlorophosphine with Menthyl and Neomenthyl Alcohols and Thiols; General Procedure:
To a solution of diphenylchlorophosphine (1.1 g, 0.005 mol) in dry ether (2 mL) placed in the NMR tube (∅ = 10 mm) a solution of menthyl (or neomenthyl) alcohol (or thiol) (0.005 mol) and *N,N*-diethylaniline (0.75 g, 0.005 mol) in dry ether (1 mL) is added at 0 °C under argon. The mixture is shaken at room temperature for 0.5 h. In the case of neomenthanethiol the mixture is heated to boiling for 3 h. After recording the ^{31}P-NMR spectrum for the tricoordinate phosphorus ester, the mixture is treated with an excess of elemental sulfur. After 0.5 hr the ^{31}P-NMR spectrum of the resulting tetracoordinate phosphorus ester is recorded. The chemical shifts and ratios of the diastereomeric esters **5,6,7** and **8** are shown in Schemes **B** and **C**.

(+)-Neomenthyl 2-Phenyl-2-Methoxyethyl Sulfides 10a and 10b:
To a solution of NaOMe [4.3 mmol, prepared from Na (0.1 g)] in methanol (20 mL) (+)-neomenthanethiol (**1b**; 0.69 g, 4 mmol) is added and the mixture is stirred for 0.5 h at room temperature. Racemic 2-phenyl-2-methoxyethyl bromide (**9**, 0.86 g, 4 mmol) is then added. After stirring overnight, the solvent is evaporated and the residue is treated with $CHCl_3$ (30 mL). The $CHCl_3$ solution is washed with water (3 × 10 mL), dried and evaporated to give the corresponding sulfide **10**; yield: 1 g (85%); $[\alpha]_D^{20}$ +88.9° (*c* = 3.6, $CHCl_3$). Its ^{1}H-NMR spectrum showed two singlets at δ = 3.25 and 3.22 for the methoxy-protons.

(+)-Neomenthyl 2-Phenyl-2-methoxyethyl Sulfide (10a):
The reaction of (+)-neomenthanethiol (**1b**) and (−)-(S)-**9**, according to the procedure described above, afforded sulfide **10a**; $[\alpha]_D^{20}$ +150.7° (*c* = 3.8, $CHCl_3$); its ^{1}H-NMR spectrum showed one singlet at δ = 3.25 for the methoxy-protons.

(+)-Methyl Neomenthyl Sulfide (11):
(+)-Neomenthanethiol (**1b**, 3.61 g, 0.021 mol) is added to a solution of NaOMe (0.21 mol, prepared from Na 0.49 g) in methanol (20 mL). After 0.5 h CH_3I (2.99 g, 0.021 mol) is added and the mixture is left for standing overnight. Methanol is removed unter vacuum, the residue is dissolved in $CHCl_3$ (25 mL), washed with water (2 × 10 mL) and dried ($MgSO_4$). Removal of the solvent affords the pure product **11**; yield: 3.6 g (92%); n_D^{20} = 1.4820; $[\alpha]_D^{20}$ +90.3° (*c* = 3.52, $CHCl_3$).

$C_{11}H_{22}S$	calc.	C 70.89	H 11.90	S 17.21
(186.4)	found	70.72	11.92	17.09

^{1}H-NMR ($CDCl_3$): δ = 0.6–2.05 (m, 18 H); 2.10 (s, 3 H, CH_3S); 3.15 (m, 1 H).

MS: *m/e* (%) = 188(1.8), 187(6.5), 186(40), 139(17), 138(49), 123(22), 96(23), 95(100), 83(81), 82(23), 69(44), 67(30), 61(13), 55(61), 43(23), 41(52), 29(13), 27(17).

(+)-Methyl Neomenthyl Sulfone (12):
A 30% H_2O_2 solution (16 mL) is added dropwise to a stirred solution of (+)-methyl neomenthyl sulfide (**11**; 3.0 g, 0.016 mol) in AcOH (32 mL) at 5 °C. The stirring is continued for 48 h at room temperature and then the mixture is heated at 50 °C for 2 h. AcOH is removed in vacuum and water (40 mL) is added. This solution is extracted with $CHCl_3$ (3 × 15 mL), the organic phase is washed with an aqueous solution of K_2CO_3 (3 × 15 mL), water (3 × 15 mL), dried (Na_2SO_4), and evaporated to give the crude sulfone **12**; yield: 2.5 g (72%); m.p. 78–79 °C (ether), $[\alpha]_D^{21}$ +41.3° (*c* = 1.27, $CHCl_3$).

$C_{11}H_{22}SO_2$	calc.	C 60.51	H 10.16	S 14.68
(218.4)	found	60.21	10.06	14.79

^{1}H-NMR ($CDCl_3$): δ = 0.5–2.45 (m, 18 H); 2.84 (s, 3 H); 3.43 (m, 1 H).

(+)-Methyl Neomenthyl Sulfoxide (13):
To (+)-methyl neomenthyl sulfide (**11**, 3.35 g, 0.018 mol) an equivalent amount of 30% H_2O_2 solution (2.04 g) is added in AcOH (1.1 g) and the mixture is stirred at room temperature for 48 h. Water (30 mL) is added and the aqueous phase is extracted with $CHCl_3$ (3 × 15 mL). The $CHCl_3$ solution is washed with water (3 × 15 mL), aqueous solution K_2CO_3 (2 × 15 mL) and again with water (2 × 10 mL). After drying Na_2SO_4 and removal of the solvent the pure sulfoxide **13** is obtained; yield: 3.5 g (96%); m.p. 103–105 °C; $[\alpha]_D^{22}$ +77.7° (*c* = 1.43, $CHCl_3$).

$C_{11}H_{22}SO$	calc.	C 65.29	H 10.96	S 15.84
(202.4)	found	65.51	10.86	15.49

^{1}H-NMR ($CDCl_3$): δ = 0.5–2.0 (m, 18 H); 2.55 (s, 3 H); 2.70 (m, 1 H).

The ^{1}H-NMR spectrum of the sulfoxide **13** obtained in the presence of (+)-2,2,2-trifluoro-1-phenylethanol revealed the presence of two diastereomeric sulfoxides **13a** and **13b** in a 69:31 ratio; δ = 2.25 and 2.20 (CH_3SO). Crystallization of **13** from a mixture of petroleum ether and $CHCl_3$ (20:1) gives the pure diastereomer **13a**; m.p. 123.5–125 °C, $[\alpha]_D^{22}$ +136.7° (*c* = 1.35, $CHCl_3$) δ = 2.25 (CH_3SO).

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