Synthesis of Chiral Sulfinic Acids: Sodium(1*S*-*exo*)-2-Bornanesulfinate

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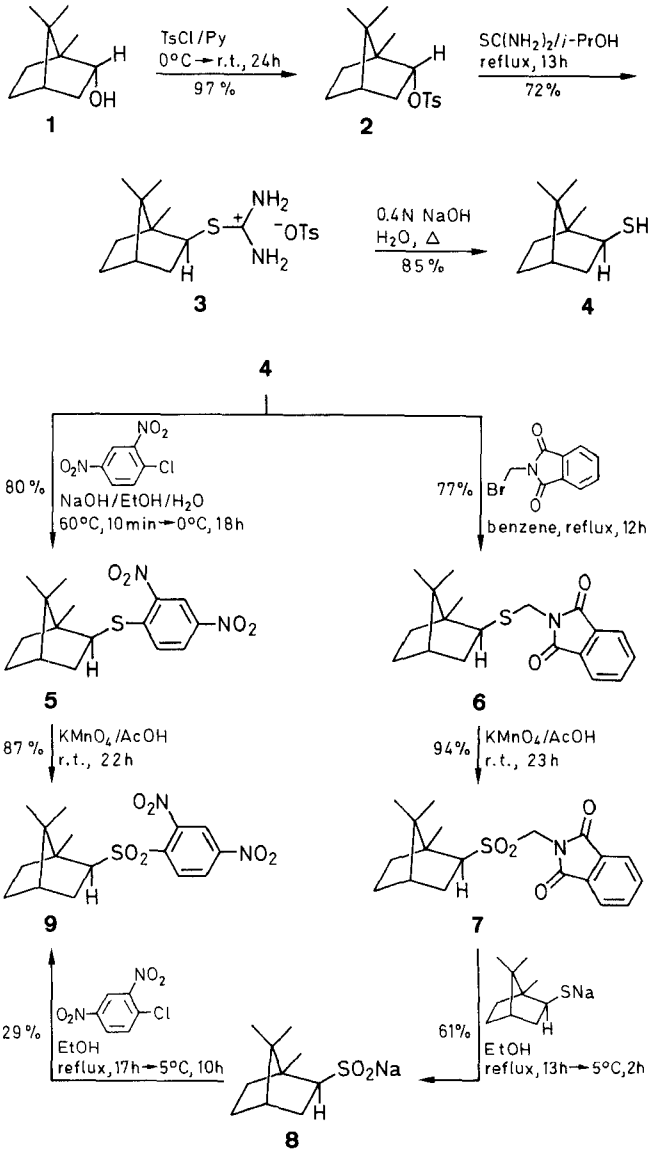
A convenient synthesis of the title compound from (−)-borneol, as a model applicable to that of other chiral, sensitive sulfinic acids, *via* the nucleophilic cleavage of the corresponding phthalimidomethyl sulfone, is described.

Chiral sulfonyl cyanides have been used to produce optically active 2-azabicyclo[2.2.1]hept-5-en-3-one, a key intermediate in the synthesis of carbocyclic analogues of nucleosides.[1] As sulfonyl cyanides are best produced from the sulfinic acid salts,[2] a reliable procedure for the preparation of chiral sulfinic acids (as their alkaline salts) was desirable. We have focused our attention on the preparation of sodium *exo*-2-bornane sulfinate as a good model compound, as chemical precursors with the bornane skeleton and either the 1*R* or the 1*S* configuration are available. Furthermore, as they are prone to rearrangement any reaction conditions that succeed should be readily applied to a wide variety of compounds.

Thus, many of the general methods for the preparation of aliphatic sulfinic acids,[3,4] such as the reaction of sulfur dioxide with magnesium or lithium derivatives or the reduction of sulfonyl chlorides, were unsuitable due to the chemical or stereochemical unstability of the synthetic intermediates. Direct oxidation of the corresponding thiol gives either the disulfide as the only product or a mixture composed mainly of sulfonic acids. Good results were obtained, however, by the nucleophilic cleavage of the phthalimidomethyl sulfone,[5] following the synthetic route outlined in the Scheme.

The starting material (−)-borneol [(1*S*,2*R*)-1,7,7-(trimethylbicyclo[2.2.1]heptan-2-ol, **1**] was almost quantitatively transformed into the tosylate **2**. Using the conditions quoted by Yoder[6] for a steroidal substrate, **2** was subsequently converted into the (1*S*-*exo*)-2-bornylisothiouronium salt **3**, $[\alpha]_D^{25}$ + 54.4° (*c* = 2.4, MeOH), in 72% yield. The only related reference found in the literature[7] deals mainly with a partially racemized *levo* isomer, for which an optical rotation of $[\alpha]_D^{25}$ − 54.4° when enantiomerically pure is estimated. The S_N2 substitution of the tosylate group by thiourea at C-2, should lead to an inversion of configuration, the stereochemistry of **3** was confirmed by examination of the chemical shift and coupling constants of H-2:

Alkaline cleavage of the salt **3** gave in good yield (85%) the desired (1*S*-*exo*)-2-bornanethiol (**4**). This compound is quoted in the literature as a racemate,[7,8] or as a nonisolated component of a mixture.[9] An older re-



Scheme

ference[10] discusses an optically active "thioborneol" of undefined stereochemistry, with mp 61–62 °C and $[\alpha]_D^{25}$ + 21.5° (*c* = 3.6, EtOAc). Our material had the ^{1}H-NMR spectral characteristics of a 2*exo*-substituted bornane and were almost coincident with those quoted by Dagonneau[8] for the racemic *exo*-thiol, [$[\alpha]_D^{25}$ + 48.3° (*c* = 11.8, MeOH)]. Compound **4** could be recrystallized from water, giving a low melting solid, which on standing or by recrystallization from other solvents raised its mp, probably due to the formation of the much higher melting disulfide.[11]

The structure of **4** was confirmed by conversion into the (1*S*-*exo*)-2-bornyl-2,4-dinitrophenyl sulfide (**5**), which is more stable, easier to purify and handle. The ^{1}H-NMR spectrum of **5** shows the signal corresponding to the H-2 as a double doublet, with *J* = 8.7 and 6.0 Hz, which were assigned[12] to the 2*endo*, 3*endo* and 2*endo*, 3*exo* couplings, respectively.

Reaction of **4** with *N*-bromomethylphthalimide by literature methods[13] to give (1*S*, *exo*)-2-bornyl phthalimidomethyl sulfide (**6**) and subsequent oxidation of **6** by potassium permanganate gave the sulfone **7** in good yield. Nucleophilic cleavage of **7** to the sodium sulfinate **8** was achieved with the sodium thiolate of **4**, which is a superior reagent in this case to sodium ethoxide. The purity of sulfinate **8** was shown to be 96 ± 2% by potassium permanganate titration.

To confirm the preservation of the stereochemistry in **8**, it was reacted with 2,4-dinitrochlorobenzene to yield a sulfone **9**, identical (mp, IR, NMR, $[\alpha]_D^{25}$) to the sample of (1*S*-*exo*)-2-bornyl 2,4-dinitrophenyl sulfone, obtained by direct oxidation of the sulfide **5**.

Melting points were determinated on a Kofler Thermopan Reichert apparatus and are uncorrected. Microanalyses were made with a Perkin-Elmer 240B element analyser. Observed rotations at the Na-D line were obtained at 25 °C using a Perkin-Elmer 141 polarimeter. IR spectra were recorded on a Perkin-Elmer 1600 FT spectrophotometer and ^{1}H-NMR spectra on a Bruker WN 250 spectrometer. 1*S*-Borneol, 2,4-dinitrochlorobenzene, *N*-bromomethylphthalimide, thiourea, and potassium permanganate were of commercial quality, purchased from Aldrich Chemical Co. Silica gel 230 mesh (Merck) was used for column chromatography. GC were carried out on a Hewlett Packard HP-5710A instrument with a FID detector and equipped with an HP-3380S integrator. Column: 10% OV-210 on Chromosorb W-HP (2 m × 1/8″), carrier gas: N_2, 20 mL/min, oven temperature: 120 °C.

(1*S*-*endo*)-2-Bornyl *p*-Toluenesulfonate (2):
p-Toluenesulfonyl chloride (9.00 g, 47.2 mmol) is added to a precooled (0 °C) solution of **1** (5.14 g, 33.3 mmol) in dry pyridine (15 mL) and the mixture stirred 24 h at r.t. 2 N HCl (100 mL) is added and the mixture is extracted with Et_2O (3 × 100 mL), washed with 10% $NaHCO_3$ (100 mL), H_2O (100 mL), and dried (Na_2SO_4). The solvent is evaporated *in vacuo* to leave a white solid; yield: 9.97 g (97%). A small amount of this material after two recrystallizations from hexane gives a sharp melting sample of **2** as colorless needles; mp 69–69.5 °C; $[\alpha]_D^{25}$ − 15.1° (*c* = 5.5, MeOH) [Lit.[14] mp 67 °C; $[\alpha]_D^{25}$ + 15.5° (EtOH) for the tosylate obtained from the (+)-borneol].

IR (KBr): *v* = 1600 (C=C_{arom}), 1350, 1190 cm^{-1} (SO_2).

^{1}H-NMR ($CDCl_3$/TMS): δ = 0.72 (s, 3 H, 1-CH_3), 0.80 and 0.83 (2s, 6 H, $C(CH_3)_2$), 1.14 (dd, 1 H, $J_{3endo,3exo}$ = − 14.1 Hz, $J_{3endo,2exo}$ = 3.3 Hz, H-3*endo*), 1.20–1.32 (m, 2 H, H-5*endo*,6*endo*), 1.63 (virtual t, 1 H, *J* = 4.5 Hz, H-4), 1.71 (m, 1 H, H-5*exo*), 1.91 (m, 1 H, H-6*exo*), 2.11 (m, 1 H, H-3*exo*), 2.45 (s, 3 H, Ar−CH_3), 4.61 (ddd, 1 H, $J_{2exo,3exo}$ = 9.9 Hz, $J_{2exo,3endo}$ = 3.3 Hz, $J_{2exo,6exo}$ = 2.0 Hz, H-2*exo*), 7.33 (virtual d, 2 H, *J* = 8.1 Hz, H_{arom}-3,5), 7.79 (virtual d, 2 H, *J* = 8.1 Hz, H_{arom}-2,6).

(1*S*-*exo*)-2-Bornylisothiouronium *p*-Toluenesulfonate (3):
A mixture of **2** (19.8 g, 64.2 mmol) and thiourea (10.0 g, 131 mmol) in *i*-PrOH (56 mL) is refluxed for 13 h. The solvent is removed *in vacuo* and the solid residue is ground, dispersed into cold H_2O (100 mL) and collected on a filter. The cake is then washed with acetone (50 mL) and vauum dried to give a white solid; yield: 17.8 g (72%). A small amount is recrystallized from H_2O to give an analytical sample of **3** as colorless needles, mp 162–163 °C; $[\alpha]_D^{25}$ + 54.4° (*c* = 2.4, MeOH) (Lit.[7] mp 163–167 °C; $[\alpha]_D^{25}$ − 33.8° (*c* = 3.3, MeOH) for its partially racemized enantiomer).

IR (KBr): *v* = 3250–2780 ($C^+(NH_2)_2$), 1670 (C=N), 1120, 1030 and 1005 (SO_2), 685 cm^{-1}(C−S).

^{1}H-NMR ($CDCl_3$/TMS): δ = 0.82, 0.90 and 0.95 (3s, 9 H, 1-CH_3 + $C(CH_3)_2$), 1.13–1.66 (m, 4 H, H-5,5,6,6), 1.76 (m, 1 H, H-4), 1.88 (m, 1 H, H-3*exo*), 2.15 (dd, 1 H, $J_{3endo,3exo}$ = − 13.3 Hz, $J_{3endo,2endo}$ = 8.9 Hz, H-3*endo*), 2.37 (s, 3 H, Ar−CH_3), 3.59 (dd, 1 H, $J_{2endo,3endo}$ = 8.9 Hz, $J_{2endo,3exo}$ = 5.3 Hz, H-2*endo*), 7.18 (virtual d, 2 H, *J* = 8.1 Hz, H_{arom}-3,5), 7.76 (virtual d, 2 H, *J* = 8.1 Hz, H_{arom}-2,6).

(1*S*-*exo*)-2-Bornanethiol (4):
A mixture of crude **3** from the preceding reaction (5.77 g, 15.0 mmol) and 0.40 N NaOH (40 mL) is heated and allowed to distill out while H_2O is being dropped in to keep the volume of the reacting mixture aprox. constant. When the distillate amounts to 500 mL, it is extracted with CH_2Cl_2 (5 × 50 mL), the combined organic extracts are dried (Na_2SO_4) and the solvent is removed *in vacuo* to leave virtually pure (98% by GC) **4**, as a colorless, low melting solid; yield: 2.18 g (85%). It recrystallizes readily only from H_2O, mp 24–26 °C; $[\alpha]_D^{25}$ + 48.3° (*c* = 11.8, MeOH).

$C_{10}H_{18}S$	calc.	C 70.52	H 10.65
(170.3)	found	70.68	10.53

^{1}H-NMR ($CDCl_3$/TMS): δ = 0.84, 0.98 and 1.02 (3s, 9 H, 1-CH_3 + $C(CH_3)_2$), 1.10–1.16 (m, 2 H, H-5*endo*,6*endo*), 1.66–1.75 (m, 3 H, H-4,5*exo*,6*exo*), 1.78 (d, 1 H, $J_{HS,2endo}$ = 7.0 Hz, slowly exchangeable with D_2O, SH), 1.83 (m, 1 H, H-3*exo*), 1.92 (dd, 1 H, $J_{3endo,3exo}$ = − 13.0 Hz, $J_{3endo,2endo}$ = 9.0 Hz, H-3*endo*), 2.98 (ddd, 1 H, $J_{2endo,3endo}$ = 9.0 Hz, $J_{2endo,SH}$ = 7.0 Hz, $J_{2endo,3exo}$ = 6.0 Hz, H-2*endo*).

(1*S*-*exo*)-2-Bornyl 2,4-Dinitrophenyl Sulfide (5):
To a solution of **4** (1.00 g, 5.87 mmol) in EtOH (10 mL) is added one of NaOH (0.23 g, 5.75 mmol) in EtOH (2 mL) and H_2O (1 mL) followed by another of 2,4-dinitrochlorobenzene (1.17 g, 5.78 mmol) in EtOH (11 mL). The mixture is stirred 10 min at 60 °C, then allowed to stand 18 h at 0 °C. The yellow crystalline product is isolated by suction and washed with cold EtOH; yield: 1.55 g (80%). One recystallization from heptane gives a analytical sample of **5**; mp 144–146 °C $[\alpha]_D^{25}$ + 110.8° (*c* = 5.0, acetone).

$C_{16}H_{20}N_2O_4S$	calc.	C 57.13	H 5.99	N 8.33
(336.4)	found	57.21	5.93	8.23

IR (KBr): *v* = 1600 and 1500 (arom), 670 cm^{-1} (C−S).

^{1}H-NMR ($CDCl_3$/TMS): δ = 0.91, 1.07 and 1.10 (3s, 9 H, 1-CH_3 + $C(CH_3)_2$), 1.31–1.42 (m, 2 H, H-5*endo*,6*endo*), 1.81–1.92 (m, 3 H, H-4,5*exo*,6*exo*), 2.05 (m, 1 H, H-3*exo*), 2.14 (dd, 1 H, $J_{3endo,3exo}$ = − 12.2 Hz, $J_{3endo,2endo}$ = 8.7 Hz, H-3*endo*), 3.41 (dd, 1 H, $J_{2endo,3endo}$ = 8.7 Hz, $J_{2endo,3exo}$ = 6.0 Hz, H-2*endo*), 7.68 (d, 1 H, J_{ortho} = 9.0 Hz, H_{arom}-6), 8.34 (dd, 1 H, J_{ortho} = 9.0 Hz, J_{meta} = 2.5 Hz, H_{arom}-5), 9.03 (d, 1 H, J_{meta} = 2.5 Hz, H_{arom}-3).

(1*S*-*exo*)-2-Bornyl Phthalimidomethyl Sulfide (6):
A mixture of *N*-(bromomethyl)phthalimide (2.13 g, 8.87 mmol) in benzene (15 mL) and **4** (1.50 g, 8.81 mmol) in benzene (10 mL) is refluxed with stirring for 12 h under argon. The solvent is removed *in vacuo* and the solid residue (3.02 g) is chromatographed on silica gel (80 g), eluent: hexane/EtOAc (80:20; 14 × 30 mL). Fractions 1–3 leave mostly (TLC) **4** (0.51 g), while fractions 4–8 afford pure

(TLC) **6**; yield: 2.24 g (77%). Two recrystallizations from hexane afford an analytical sample of **6**; mp 120–121.5°C; $[\alpha]_D^{25}$ +4.21° (c = 5.4, acetone).

$C_{19}H_{23}NO_2S$	calc.	C 69.27	H 7.04	N 4.25
(329.5)	found	69.36	6.98	4.20

IR (KBr): ν = 1773 and 1714 (C=O), 1608 and 1463 cm^{-1} (arom).

^{1}H-NMR ($CDCl_3$/TMS): δ = 0.80, 0.88 and 0.96 (3s, 9H, 1-CH_3 + $C(CH_3)_2$), 1.15–1.24 (m, 2H, H-5*endo*,6*endo*), 1.64–1.69 (m, 3H, H-4,5*exo*,6*exo*), 1.78 (m, 1H, H-3*exo*), 1.94 (dd, 1H, $J_{3endo,3exo}$ = −13.0 Hz, $J_{3endo,2endo}$ = 9.2 Hz, H-3*endo*), 3.05 (dd, 1H, $J_{2endo,3endo}$ = 9.2 Hz, $J_{2endo,3exo}$ = 5.7 Hz, H-2*endo*), 4.75 (s, 2H, SCH_2N), 7.74 (m, 2H, H_{arom}-4,5), 7.88 (m, 2H, H_{arom}-3,6).

(1*S*-*exo*)-2-Bornyl Phthalimidomethyl Sulfone (7):

Finely powdered $KMnO_4$ (1.61 g, 10.2 mmol) is added in portions to a stirred solution of **6** (2.79 g, 8.47 mmol) in AcOH (150 mL). Stirring is continued at r.t. till complete disappearence (TLC) of **6** (23 h). The solvent is evaporated at reduced pressure and the solid residue (4.7 g) is stirred with cold 0.8 N aq $NaHSO_3$ (200 mL), the dark insoluble manganic material is then separated by filtration and thoroughly washed with H_2O (2×100 mL). The combined filtrate and washings are extracted with CH_2Cl_2 (3×100 mL), the organic extracts are washed with H_2O (3×100 mL), dried ($NaSO_4$), and the solvent is removed at reduced pressure to leave a colorless solid; yield: 2.87 g (94%). This material, after three recrystallizations from toluene, gives an analytical sample of **7** as white needles, mp 200–201°C; $[\alpha]_D^{25}$ +64.8° (c = 2.5, acetone).

$C_{19}H_{23}NO_4S$	calc.	C 63.14	H 6.41	N 3.88
(361.5)	found	63.31	6.37	3.95

IR (KBr): ν = 1784 and 1725 (C=O), 1610 and 1466 (arom), 1351 and 1130 cm^{-1} (SO_2).

^{1}H-NMR ($CDCl_3$/TMS): δ = 0.88, 1.08 and 1.27 (3s, 9H, 1-CH_3 + $C(CH_3)_2$), 1.20–1.41 (m, 2H, H-5*endo*,6*endo*), 1.60–1.79 (m, 2H, H-5*exo*,6*exo*), 1.85 (m, 1H, H-4), 1.88 (dd, 1H, $J_{3endo,3exo}$ = −13.1 Hz, $J_{3endo,2endo}$ = 9.2 Hz, H-3*endo*), 2.32 (m, 1H, H-3*exo*), 3.26 (virtual t, 1H, J = 8.7 Hz, H-2*endo*), 4.88 (s, 2H, SCH_2N), 7.80 (m, 2H, H_{arom}-4,5), 7.94 (m, 2H, H_{arom}-3,6).

Sodium (1*S*-*exo*)-2-Bornanesulfinate (8):

The sulfone **7** (1.80 g, 4.98 mmol) is added to a stirred sodium thiolate solution prepared from clean cut Na metal (114 mg, 4.96 mmol) and the thiol **4** (848 mg, 4.98 mmol) in dry EtOH (17 mL). The mixture is refluxed with stirring for 13 h under argon and left 2 h in the cold (5°C). The precipitated sulfide **6** (0.60 g) is filtered off and the filtrate is evaporated to dryness. The residue left, mixture of the sulfinate **8** and some sulfide **6**, is dissolved in hot benzene (60 mL), the solution allowed to stand overnight at 0°C, and the precipitated sodium sulfinate **8** collected by filtration, washed with cold benzene (5 mL) and vacuum dried; yield: 0.68 g (61%).

$C_{10}H_{17}NaO_2S$	calc.	C 53.55	H 7.64	
(224.3)	found	53.30	7.50	

(1*S*-*exo*)-2-Bornyl 2,4-Dinitrophenyl Sulfone (9):

Method A: A mixture of the sulfinate **8** (231 mg, 1.03 mmol), obtained as described above, in EtOH (10 mL) and 2,4-dinitrochlorobenzene (210 mg, 1.03 mmol) in EtOH (13 mL) is refluxed for 17 h, then left in the cold (5°C) overnight and the precipitated product is isolated by suction; yield: 110 mg (29%). One recrystallization from EtOH gives an analytical sample, mp 207–208°C; $[\alpha]_D^{25}$ −70.3° (c = 2.5, acetone).

$C_{16}H_{20}N_2O_6S$	calc.	C 52.16	H 5.47	N 7.60
(368.4)	found	52.28	5.41	7.66

IR (KBr): ν = 1600, 1550 and 1525 (arom), 1345 and 1140 cm^{-1} (SO_2).

^{1}H-NMR ($CDCl_3$/TMS): δ = 0.92, 1.16 and 1.31 (3s, 9H, 1-CH_3 + $C(CH_3)_2$), 1.22–1.44 (m, 2H, H-5*endo*,6*endo*), 1.52 (dd, 1H, $J_{3endo,3exo}$ = −13.0 Hz, $J_{3endo,2endo}$ = 9.1 Hz, H-3*endo*), 1.64–1.88 (m, 3H, H-4,5*exo*,6*exo*), 2.24 (m, 1H, H-3*exo*), 3.93 (virtual t, 1H, J = 8.7 Hz, H-2*endo*), 8.29 (d, 1H, J_{ortho} = 8.2 Hz, H_{arom}-6), 8.54 (dd, 1H, J_{ortho} = 8.2 Hz, J_{meta} = 2.2 Hz, H_{arom}-5), 8.56 (virtual s, 1H, H_{arom}-3).

Method B: Finely powdered $KMnO_4$ (110 mg, 0.696 mmol) is added in portions to a stirred, cold solution of the sulfide **5** (200 mg, 0.595 mmol) in AcOH (11 mL) and the mixture kept stirring for 22 h. The solvent is evaporated at reduced pressure and the solid residue (0.4 g) is stirred with cold 0.8 N aq $NaHSO_3$ (30 mL), the dark insoluble manganic material is then separated by filtration and washed with H_2O (2×25 mL). The combined filtrate and washings are extracted with CH_2Cl_2 (3×30 mL), the organic extracts are washed with H_2O (3×40 mL), dried (Na_2SO_4), and the solvent is taken off *in vacuo* to leave a colorless solid; yield: 191 mg (87%). Only one recrystallization from benzene affords a material of mp 207–208°C; $[\alpha]_D^{25}$ −71.0° (c = 2.0, acetone).

IR and ^{1}H-NMR spectra of this material were superimposible with those of the product from the method A.

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