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Bithiocamphor : an interesting synthon for the synthesis of chiral ligands.

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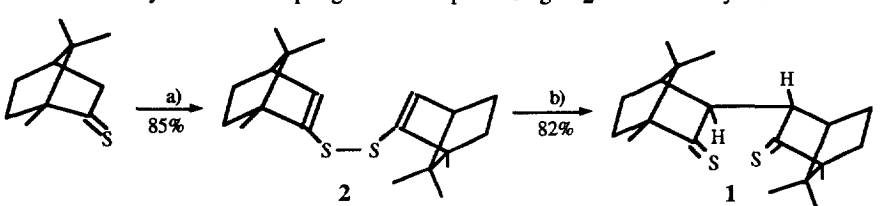
Abstract : Bithiocamphor **1** was studied; its reduction led to dithiols **3a** and **3b**, its oxidation led to bicamphor **8.**

As part of an ongoing program in the field of new chiral ligands for asymmetric catalysis, we report here our efforts to study the possibilities offered by bithiocamphor **1**. This compound was first reported by Ray[1] in 1936, prepared by Sen[2] in 1939, re-examined by Campbell[3] in 1973 and Barton[11] in 1981. The first obtained the disulfide intermediate **2** by radical coupling of thiocamphor using chloramine T in 46% yield[3]. The latest prepared intermediate **2** by oxidative coupling of thiocamphor using Ar_2TeO in 70 % yield[11].

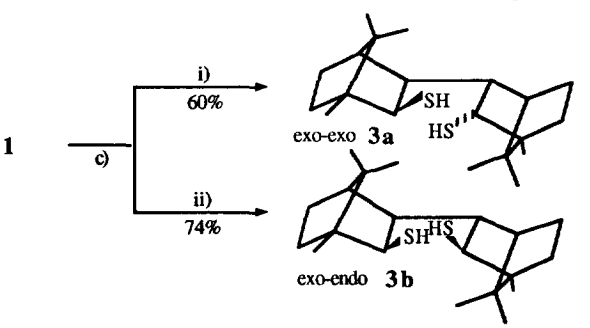


a) ^tBuOK, I_2 , toluene ; b) Isopropanol, 90°C

Scheme 1

We revisited the synthesis of **1** to simplify the procedure and to increase the yield (scheme 1); deprotonation of R(-)-thiocamphor with potassium tert-butoxide followed by oxidation with iodine furnished disulfide **2** in 85% yield. Sigmatropic rearrangement of **2** in isopropanol gave bithiocamphor **1** in 82% yield. We then studied the reduction and oxidation of **1.**

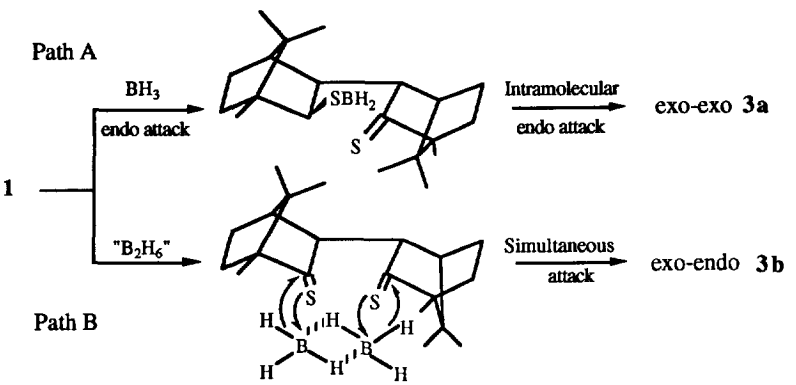
*REDUCTION OF 1:*This reaction was briefly mentioned by Sen[2] without any report of yield and selectivity. We used borane dimethylsulfide complex (BMS) as the reducing agent (scheme 2).



c) i) 1 eq BMS, Toluene 100°C; ii) 2 eq. BMS, reverse addition, Toluene, 100°C.

Scheme 2

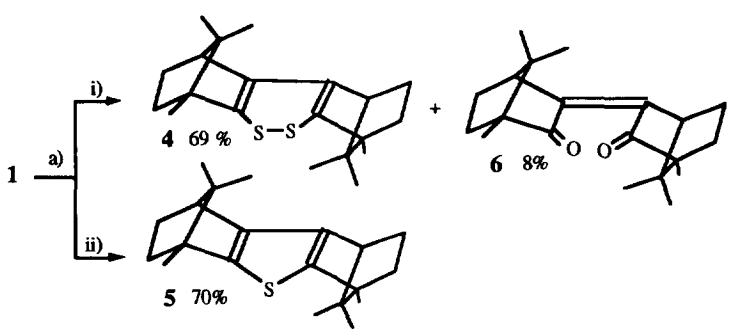
Under normal conditions, the reduction was slow with poor selectivity. After examination of different parameters, we optimized the reaction as followed to prepare diastereomers exo-exo **3a** or exo-endo **3b** selectively. **3a** was obtained in a 70 / 30 ratio by reaction of 1 eq. BMS with a toluene solution of **1**, at 100°C (scheme 2). On the other hand, when the reverse addition of bithiocamphor **1** to 2 eq BMS was carried out at 100°C, the ratio was 90 / 10 in favour of isomer **3b** (scheme 2). This result can be rationalized as follows (scheme 3).



Scheme 3

As shown by X-ray crystallography[4] and molecular modelling, it appears that steric repulsion of bridged methyl groups stabilizes the conformation of bithiocamphor **1**. In this conformation, the two camphor moieties are head to foot which explains the proximity of the thiocarbonyl groups. In path A, borane attacks in an endo fashion, then an intramolecular endo reduction leads to the exo-exo dithiol. In path B, with an excess of BMS, we assume a reduction by diborane and a simultaneous attack of the two thioketone in an intermolecular endo-exo process. The potential of these dithiols in asymmetric catalysis is under investigation.

OXIDATION OF 1: Conversion of thioketones into ketones is a well known transformation[5a]. However, mild literature procedures such as $NOBF_4$[5b], nBuHSO4-NaOH[5c], are efficient for thiocamphor but ineffective in our hands for the conversionof **1**. Depending on the conditions, $Hg(OAc)_2$ led to dithiin **4** (69%) or thiophen **5** (70%)[6], α–β unsaturated diketone **6** was also isolated as a by-product[7] (scheme 4).

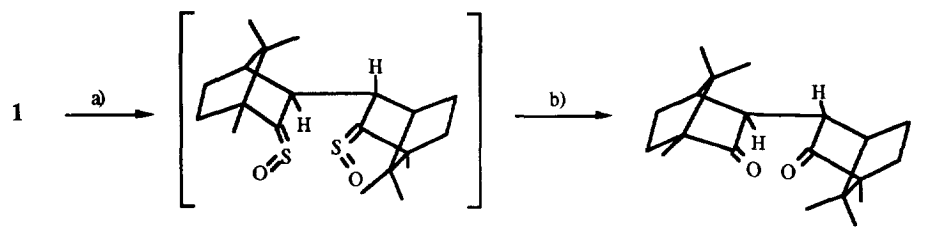


a) $Hg(OAc)_2$; i) Toluene, AcOH, 60°C; ii) AcOH, 90°C

Scheme 4

We finally succeeded in this transformation by using two steps. Metzner has described the oxidation of thioketone into sulfines using MCPBA *without formation of coupling products*[8]. Disulfine **7** was thus prepared without isolation, using Metzner's conditions; and then oxidized with the $RuCl_3$ / $NaIO_4$ system, well known for the transformation of sulfite to sulfate[9] (scheme 5).

Scheme 5



7 **8** 93%

a) MCPBA, 0°C, CH_2Cl_2; b) $RuCl_3$, $NaIO_4$, CCl_4, CH_3CN, 0°C-RT

Bicamphor **8** was thus obtained in 93% yield. This simple methodology is the first route to **8**, in an enantiomerically and diastereomerically pure form. Indeed, attempts to make this compound by oxidative coupling of camphor enolate led to a mixture of inseparable diastereomers[10]. Possibilities offered by this new C2 symmetric camphor derived diketone in the field of asymmetric catalysis are now under investigation.

EXPERIMENTAL

Apparatus and chemicals: All reactions were carried out under a nitrogen atmosphere. Toluene was distilled over Na before use. ^1H NMR and ^{13}C NMR spectra were performed on a Brucker AC 300 spectrometer, in deuterochloroform, using the solvent signal as internal reference. Mass spectra were obtained on a Varian MAT 311. Optical rotations were recorded on a Perkin Elmer 241 MC polarimeter. Melting points were determined on a Kofler hot stage apparatus. Silica gel (70-230 mesh) for flash column chromatogaphy was purchased from Merck.

Disulfide 2: To a solution of R(-)-thiocamphor (40 mmol, 6.7 g) in 350 ml of toluene, was added tBuOK (44 mmol 4.9 g). After 30 min. stirring, iodine (20 mmol, 5 g) was added. The reaction was then vigorously stirred for 2 hours at RT. The mixture was then washed with water (2 x 50 ml) and 1N sodium thiosulfate solution (30 ml). After drying (Na_2SO_4) the organic phase was filtered and the solvent removed. The residue was purified by flash column chromatography (eluant CCl_4). m = 5.7 g of a red solid. Yield = 85 %; mp = 59°C. Lit.[3] : 56-66°C; $[\alpha]_D^{20}$ = -291 (c = 1, $CHCl_3$). ^1H NMR ($CDCl_3$; 300 MHz) δ (ppm) : 5.98 (d, 2H, ^3J = 3,4 Hz); 2.35 (t, 2H, ^3J = 3,4 Hz); 1.88-1.81 (m, 2H); 1.54-1.46 (m, 2H); 1.11-0.88 (m, 4H); 1.07 (s, 6H); 0.79 (s, 6H); 0,76 (s, 6H). $M^{+\cdot}$: 334.1789; Found 334.1777.

Bithiocamphor 1: Product **2** (5.7 g 17 mmol) was refluxed for 5 h in 148 mL of isopropanol. The solution was then cooled. The orange precipitate was filtered. m = 4.7 g, Yield = 82 %; mp = 180°C Lit.[11] = 174-177°C. $[\alpha]_D^{20}$ = -333.1 (c = 1, C_6H_6) Lit.[2] $[\alpha]_D^{20}$ = -332.1 (C_6H_6). ^1H NMR ($CDCl_3$; 300 MHz) δ (ppm) : 2.52 (s, 2H); 2.36 (d, 2H, ^3J = 4 Hz); 2.10-2.00 (m, 2H); 1.80-1.73 (m, 2H); 1.57-1.48 (m, 2H); 1.39-1.30

(m, 2H); 1.08 (s, 6H); 1.00 (s, 6H); 0.68 (s, 6H); 67.9 (s); 49.3 (d) ; 49.1 (s); 32.0 (t) ; 29.3 (t); 21.3 (q); 20.7 (q); 14.2 (q). Anal. calcd for $C_{20}H_{30}S_2$: C, 71.79; H, 9.04; S, 19.16. Found : C, 71.8; H, 9.02; S, 19.07. M^+. : 334.1788; Found 334.1765.

Dithiol 3a: To a solution of bithiocamphor (3 mmol, 1 g) in 10 mL toluene was rapidly added BMS (3 mmol, 0.3 mL). After 10 min. stirring, the solution was refluxed for 1 h. The reaction was then cooled to RT, and 10 mL of 1N HCl were added. The mixture was stirred for 30 min. The layers were separated, and the organic layer was further washed with water (2x10 mL), dried (Na_2SO_4) and concentrated. The residue was purified by flash column chromatography on silica gel (eluant : toluene-cyclohexane, 15-85). m = 600 mg, Yield = 60 %. $[\alpha]_D^{20}$ = -84.56 (c = 1 $CHCl_3$). mp = 77-79°C. ^1H NMR ($CDCl_3$, 300 MHz) δ (ppm) : 3.47-3.36 (m, 2H, ^3J = 7,5 Hz); 2.43-2.34 (m, 2H, ^3J= 8,8 Hz); 1.91 (d, 2H, ^3J = 4,1 Hz); 1.61 (d, 2H, ^3J = 7,5 Hz); 1.82-1.60 (m, 4H); 1.35-1.12 (m, 4H); 1.00 (s, 6H); 0.99 (s, 6H); 0,80 (s, 6H). ^{13}C NMR ($CDCl_3$, 75,5 MHz) δ (ppm) : 54.9 (d); 51.0 (d); 50.1 (d); 49.7 (s); 48.3 (s); 38.0 (t); 29.8 (t); 22.1 (q); 21.8 (q); 15.0 (q). M^+. : 338.21018; Found 338.2105.

Dithiol 3b: To a 60 mL toluene solution of BMS (12 mmol, 1.2 mL) at 100°C, was added dropwise a 100 mL toluene solution of bithiocamphor (6 mmol, 2 g) in 2 h. At the end of the addition, the reaction was cooled at 40°C, and the excess of BMS was neutralized with 30 mL of EtOH. 50 mL of 1N HCl were then added at 40°C. The mixture was stirred for 1 h at 50°C. The aquous phase was separated, and the organic layer was washed with 2x20 mL water, dried (Na_2SO_4), and concentrated to give a white solid that was recrystallized from isopropanol. m = 1.5 g, Yield = 74 %. $[\alpha]_D^{20}$ = 85.5 (c = 0.97 $CHCl_3$). mp : 130-131°C. ^1H NMR ($CDCl_3$, 300 MHz) δ (ppm) : 3.53-3.47 (dd, 1H, ^3J = 7,2 Hz, ^3J = 9,1 Hz); 2.77-2.67 (td, 1H, ^3J = 7,4 Hz, ^3J = 7,1 Hz, ^4J = 2,4 Hz); 2.22-2.17 (t, 1H, ^3J = 6,5 Hz); 2.03 (d, 1H, ^3J = 7,2 Hz); 1.96 (d, 1H, ^3J = 4,5 Hz); 1.84 (d, 1H, ^3J = 4,8 Hz); 1.95-1.85 (m, 1H); 1.66 (dd, 1H, ^3J = 6,5 Hz, ^3J = 9.0 Hz); 1.78-1.64 (m, 2H); 1.63 (m, 1H); 1.44 (d, 1H, ^3J = 7,4 Hz); 1.25 (m, 1H); 1.23 (m, 1H); 1.10 (m, 2H); 0.98 (s, 3H); 0.91 (s, 3H); 0.89 (s, 3H); 0.83 (s, 3H); 0.80 (s, 3H); 0.78 (s, 3H). ^{13}C NMR ($CDCl_3$, 75,5 MHz) δ (ppm) : 59.8 (d); 58.8 (d); 54.5 (d); 53.5 (d); 51.4 (s); 50.1 (s); 49.8 (d); 49.0 (d); 47.7 (s); 47.4 (s); 38.1 (t); 29.8 (t); 29.7 (t); 27.5 (t); 21.7 (2 q); 21.1 (q); 20,0 (q); 15.1 (q); 13.5 (q). M^+. : 338,21018 Found 338,2105. Anal. calcd for : $C_{20}H_{34}S_2$ C, 70.94; H, 10.12; S, 18.94. Found C, 70.76; H, 10.21; S, 18,93.

Thiophene 5: To a mixture of bithiocamphor (1.48 mmoles ; 0.5 g) and mercuric acetate (2.96 mmol, 0.94 g) was added dropwise acetic acid (25 mL) over three minutes. The orange suspension turned grey. The reaction was heated at 90°C for 1h. The mixture was then cooled, filtered and volatiles were removed. The residue was purified by flash column chromatography (eluant : cyclohexane). m = 473 mg, Yield = 70 %. mp = 101°C (isopropanol). $[\alpha]_D^{20}$ = +222,2 (c = 1,1 $CHCl_3$). ^1H NMR ($CDCl_3$, 300 MHz) δ (ppm) : 2,78 (d, 2H, ^3J = 3,7 Hz); 2.00-1.89 (m, 2H); 1.82-1.71 (m, 2H); 1.23 (s, 6H); 1.02-0.82 (m, 4H); 0.89 (s, 6H); 0.78 (s, 6H). ^{13}C NMR ($CDCl_3$, 300 MHz) δ (ppm) : 148.38 (s); 143.56 (s); 60.15 (s); 54.64 (s); 50.78 (d); 34.13 (t); 27.52 (t); 20.09 (q); 19.77 (q); 12.85 (q). Anal. calcd for $C_{20}H_{28}S$: C, 79.94; H, 9.39; S 10.67. Found : C, 80.11; H, 9.28; S, 10.57. M^+. : 300.19116 Found 300. 1903.

Dithiin 4 and Diketone 6: To a suspension of bithiocamphor (2.96 mmol; 1 g) and mercuric acetate (5.92 mmol; 1.8 g) in 10 ml of toluene, was added acetic acid (50 ml) over 2 minutes. After being stirred for 20

minutes at RT, the mixture was heated for 20 min. at 60°C. The reaction was then cooled, filtered and volatiles were removed. The products were separated by flash column chromatography (eluant : cyclohexane).

Dithiin 4 : m = 685 mg, Yield = 69 %, mp = 122°C (isopropanol) lit.[4] 123°C. $[\alpha]_D^{20}$ = - 1530 (c = 0.1 $CHCl_3$) lit.[4] $[\alpha]_D^{20}$ = - 147.4 ($CHCl_3$). ^1H NMR ($CDCl_3$; 300 MHz) δ (ppm) : 2.41 (d, 2H, J^3 = 3,7 Hz); 1.97-1.81 (m, 2H); 1.70-1.59 (m, 2H); 1.48-1.37 (m, 2H); 1.17-1.08 (m, 2H); 1.00 (s, 6H); 0.83 (s, 6H); 0.79 (s, 6H). ^{13}C NMR ($CDCl_3$; 300 MHz) δ (ppm) : 144.1 (s); 130.1 (s); 57.4 (s); 56.3 (s); 52.7 (d); 33 (t); 26.0 (t); 19.6 (s); 19.0 (s); 11.4 (s). Anal. calcd for $C_{20}H_{28}S_2$: C, 72.23; H, 8.45; S, 19.28. Found C, 72.68; H, 8.59; S, 18.72.

Diketone 6 : m = 72 mg, yield = 8 %. $[\alpha]_D^{20}$ = 330 (c = 0.1 $CHCl_3$). mp = 100°C (isopropanol). ^1H NMR ($CDCl_3$, 300 MHz) δ (ppm) : 3.74 (d, 2H, ^3J = 4,3 Hz); 2.15-2.05 (m, 2H); 1.75-1.62 (m, 2H); 1.48-1.22 (m, 4H); 0.95 (s, 6H); 0.94 (s, 6H); 0.74 (s, 6H). ^{13}C NMR ($CDCl_3$, 300 MHz) δ (ppm) : 212.0 (s); 140.8 (s); 58.1 (s); 46.1 (s); 30.6 (t); 25.9 (t); 20.8 (s); 18.3 (s); 9.2 (s). Anal. calcd for $C_{20}H_{28}O_2$: C, 79.95; H, 9.39; O, 10.65. Found C, 79.23; H, 9.65; O, 11.12. M^+. : 300.2091; Found 300.2089.

Bicamphor 8: Bithiocamphor (9 mmol, 3 g), was dissolved in 75 mL CH_2Cl_2. MCPBA 65% (5 g, 18 mmol), was added portionwise at 0°C until decoloration (3 min.). The reaction was neutralized with a solution of saturated $NaHCO_3$. The aquous phase was extracted with CH_2Cl_2, and the organic layer was dried (Na_2SO_4). The solution was filtered through celite, and concentrated to 10 mL at low temperature. This residue was then diluted with 24 mL CH_3CN, 24 mL CCl_4, 45 mL H_2O. $RuCl_3$, 3 H_2O (130 mg, 0.62 mmol) was then added at 0°C, followed by addition of $NaIO_4$ (11,5 g; 54 mmol). The ice bath was removed after 5 min., and the reaction vigorously stirred 1 h at RT. The mixture was then diluted with H_2O, extracted with Et_2O, dried (Na_2SO_4) filtered through silica and evaporated. Flash column chromatography (Et_2O- C_6H_{12} 35-65) afforded **8**. m = 2.54 g, Yield = 93%. $[\alpha]_D^{20}$ = 135 (c = 1 $CHCl_3$). mp = 149°C. ^1H NMR ($CDCl_3$, 300 MHz) δ (ppm) : 2.12 (d, ^3J = 4.13 Hz, 2H); 2.05 (s, 2H); 2.03-1.95 (m, 2H); 1.65-1.5 (m, 4H); 1.37-1.18 (m, 2H); 0.94 (s, 6H); 0.91 (s, 6H); 0.76 (s, 6H). ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ (ppm) : 219.48 (s); 57.34 (s); 54.31 (t); 46.87 (s); 46.84 (d); 29.07 (t); 28.95 (t); 21.17 (q); 20.16 (q); 9.5 (q). IR : (cm^{-1}) 2955; 2850; 1740; 1400; 1053. M^+. : 302.2245; Found 302.2239.

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6) Dithiin **4** was previously synthesized by oxidation of the dienolate of **1** with $K_3Fe(CN)_6$ in 90% yield (ref 4). Oxydation of **1** with $Hg(OAc)_2$ was reported to give thiophene **5** in 35% yield (ref 4).

7) Reaction of dithiin **4** with $Hg(OAc)_2$ led to diketone **6** and thiophene **5** in a 50-50 ratio as shown by ^1H NMR.

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