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Registry No. 1, 3993-62-2; 2, 280-49-9; 3, 3310-59-6; 4, 703-35-5; 5, 703-36-6; 6, 670-79-1; 7, 704-53-0; DBO, 3310-62-1; 1-phenyl-DBO, 87373-48-6; tetramethylpiperidine-1-oxyl, 2564-83-2; 4-bromo-1-phenylcyclohexene, 110174-56-6; 4-bromocyclohexanol, 89599-47-3; 4-bromo-1-phenyl-1-cyclohexanol, 110174-57-7; perdeuterated 1,3-cyclohexadiene, 17647-18-6; perdeuterated 1,4-cyclohexadiene, 2102-12-7; deuterium, 7782-39-0; 1,3-cyclohexadiene, 592-57-4; 1,4-cyclohexadiene, 628-41-1; cyclopentadiene, 542-92-7; piperylene, 504-60-9; cyclopentene, 142-29-0; cyclohexene, 110-83-8; *cis*-2-butene, 590-18-1; 1-hexene, 592-41-6; 1-octene, 111-66-0; styrene, 100-42-5; *trans*-stilbene, 103-30-0; 1,1-diphenylethylene, 530-48-3; quadricyclene, 278-06-8; benzene, 71-43-2; *p*-dimethoxybenzene, 150-78-7; chlorobenzene, 108-90-7; benzotrichloride, 98-07-7; benzonitrile, 100-47-0; *p*-dicyanobenzene, 623-26-7; dimethyl phthalate, 131-11-3; 1,1-dimethylhydrazine, 57-14-7; 1,2-dimethylhydrazine, 540-73-8; carbon tetrabromide, 558-13-4; bromotrichloromethane, 75-62-7; tetranitromethane, 509-14-8; benzoyl peroxide, 94-36-0; di-*tert*-butyl peroxide, 110-05-4; *m*-dimethoxybenzene, 151-10-0; tetracyanoethylene, 670-54-2; tetramethyl-*p*-phenylenediamine, 100-22-1; benzophenone, 119-61-9; 1,4-dicyanonaphthalene, 3029-30-9; carbon tetrachloride, 56-23-5; biphenyl, 92-52-4; 4-chloro-1-phenylcyclohexene, 15619-36-0; 4-bromocyclohexanone, 22460-52-2; 1,4-cyclohexanediol, 556-48-9.

Notes

A Short, Efficient Synthesis of (1*S*,3*S*,5*R*)- and (1*S*,3*R*,5*R*)-1,3-Dimethyl-2,9-dioxabicyclo[3.3.1]nonane

Rosanna Bernardi and Dario Ghiringhelli*

Dipartimento di Chimica del Politecnico di Milano, Centro del CNR per lo Studio delle Sostanze Organiche Naturali, I-20133 Milano, Italy

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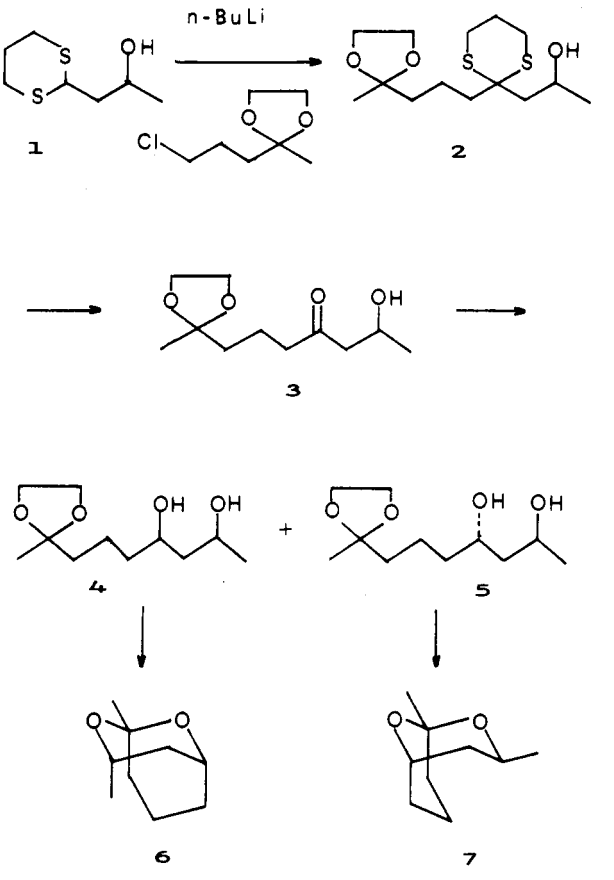
endo-1,3-Dimethyl-2,9-dioxabicyclo[3.3.1]nonane (**6**) is an interesting biologically active substance isolated from Norway spruce infested by *Trypodendron lineatum* Oliv.[1] The relative stereochemistry of the natural product was established by comparison of the NMR data of racemic synthetic *endo*-**6** and *exo*-**7** with that of the natural product.[2] The absolute stereochemistry is unknown, although all of the enantiomers were synthesized from glucose.[3]

In this paper we provide details of our syntheses of (1*S*,3*S*,5*R*)-**6** and (1*S*,3*R*,5*R*)-**7**, demonstrating the usefulness of (*R*)-1-(1,3-dithian-2-yl)-2-hydroxypropane [(*R*)-**1**, (*R*)-DHP] and (*S*)-1-(1,3-dithian-2-yl)-2-hydroxypropane [(*S*)-**1** (*S*)-DHP] as chiral building blocks in the synthesis of enantiomerically pure compounds (Scheme I). (*S*)-DHP[4] and (*R*)-DHP[5] are both available in high enantiomeric purity by microbial reduction of dithianylacetone. For this reason, we chose to synthesize the *endo*-(1*S*,3*S*,5*R*)-**6** from (*S*)-DHP and the *exo*-(1*S*,3*R*,5*R*)-**7** from (*R*)-DHP. The reaction of the dilithium salt of **1** with the commercially available 2-(3-chloropropyl)-2-methyl-1,3-dioxolane gave **2** in high yield. The conversion of **2** into the hydroxy ketone **3** requires very mild conditions to avoid the hydrolysis of the 1,3-dioxolanyl group. The right conditions were achieved by using a 4 M water solution of mercury perchlorate and controlling the pH with solid calcium carbonate. This hydrolytic procedure has the advantage of the methods using mercury oxide or lead dioxide with

Scheme I



boron trifluoride etherate (they are very fast) and of the method using mercury dichloride and calcium carbonate (it is very mild), and furthermore it needs only a slight excess of the mercury salt. The hydroxy ketone **3** obtained by this method is sufficiently pure to be used in the subsequent step. The reduction of the β-hydroxy ketone **3** with zinc borohydride provides the *syn*-diol **4** with good selectivity. The anti isomer **5** can be obtained only with a poor selectivity (2:1 = anti:syn) by reducing the hydroxy ketone **3** with sodium triacetoxyborohydride in acetic acid[6]

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or with sodium borohydride in methanol containing cerium trichloride.[7] The crude mixture of diols **4** and **5** is suitable for the cyclization that is easily performed by means of the acidic resin Amberlyst-15 in a high-dilution condition. The *endo*-**6** and *exo*-**7** are easily separated by flash chromatography. The *endo*-(1*S*,3*S*,5*R*)-**6** is obtained in a 50% overall yield, while the *exo*-(1*S*,3*R*,5*R*)-**7** is obtained in a 34% overall yield in spite of the low selectivity in the reduction of the hydroxy ketone **3** to the *anti*-diol **5**. Both isomers are of high chemical and enantiomeric purity as shown by VPC analyses and polarimetric measurements. The NMR data are in accord with published values.

Experimental Section

Infrared spectra were recorded with a Perkin-Elmer 177 spectrophotometer. ^{1}H nuclear magnetic resonance spectra were recorded in $CDCl_3$ at 90 MHz on a Varian XL 100/15 instrument with tetramethylsilane as the internal standard. Optical rotations were measured with the indicated solvent and at the indicated concentration in a 1-dm cell on a Jasco DIP-181 polarimeter. Gas chromatographic analyses were performed in the following ways: column A, 25 m × 0.32 mm (i.d.) glass capillary column, coated with OV-1 (d_f = 0.4 μm), using a C. Erba apparatus Model 4160 and on-column injection system, carrier gas H_2, μ = 60 cm/s; column B, 25 m × 0.32 mm (i.d.) fused silica capillary column, coated with OV-1701 (d_f = 0.2 μm), using a Dani apparatus Model 6500 and PTV injection system, carrier gas H_2, μ = 54 cm/s; column C, 2 m × 3 mm (i.d.) glass column, packed with 5% SP 1000 on 100/120 Supelcoport, using a Dani Model 3800 apparatus, carrier gas N_2, flow rate 25 mL/min. The (*S*)-DHP was more than 99% enantiomerically pure; the optical purity of the (*R*)-DHP was 98%.

(*S*)-2-Hydroxy-4-(1,3-dithian-2-yl)-8-(1,3-dioxolan-2-yl)-nonane [(*S*)-2]. *n*-BuLi (2.4 M, 10 mL) was added dropwise to a solution of (*S*)-DHP (1.78 g, 10 mmol) in THF (15 mL), stirred at −15 °C under argon. The resulting solution was allowed to warm to 0 °C over 3 h. Freshly distilled 2-(3-chloropropyl)-2-methyl-1,3-dioxolane (2.3 g, 14 mmol) and HMPA (1 mL) were added at 0 °C, and the reaction mixture was stirred overnight at room temperature. Water (50 mL) was added and the resultant mixture extracted twice with ether (100 mL). The combined ether extracts were washed with brine and dried over Na_2SO_4, and the ether was removed in vacuo. The residue was purified by flash chromatography with hexane/ethyl acetate (3:2) as eluent. A 0.15-g portion of unchanged (*S*)-DHP and 2.70 g (9 mmol) of the expected **2** were recovered. The title compound **2** is a dense oil, 98% pure by VPC on column A (4 min at 150 °C, 2.5 °C/min to 230 °C): RT 27.4 min; $[\alpha]^{20}_D$ +17.2° (*c* 1, $CHCl_3$); ^{1}H NMR δ 1.20 (d, *J* = 6 Hz, 3 H), 1.34 (s, 3 H), 1.65 (m, 4 H), 1.75–2.15 (brm, 6 H), 2.9 (m, 4 H), 3.46 (brs, 1 H), 3.98 (s, 4 H), 4.15 (m, 1 H).

(*R*)-2-Hydroxy-4-(1,3-dithian-2-yl)-8-(1,3-dioxolan-2-yl)-nonane [(*R*)-2]. This compound was obtained by the same procedure except from (*R*)-DHP: $[\alpha]^{20}_D$ −16.8 (*c* 1, $CHCl_3$).

(*S*)-2-Hydroxy-4-keto-8-(1,3-dioxolan-2-yl)nonane [(*S*)-3]. A solution of **2** (2.70 g, 9 mmol) in THF (30 mL) and water (6 mL) was stirred at room temperature in the presence of $CaCO_3$ (1.10 g), and $Hg(ClO_4)_2$ (2.5 mL of a 4 M water solution) was added in 10 min. After the resultant solution was stirred an additional 5 min, ether (150 mL) was added and the mixture filtered. The solvents were removed in vacuo to leave 1.72 g of the crude, liquid hydroxy ketone **3**, 93% pure by VPC on column B (1 min at 40 °C, 20 °C/min to 120 °C, 2 min at 120 °C, 2 °C/min to 200 °C): RT 20.0 min; IR (film) 1710 cm^{-1}; ^{1}H NMR δ 1.20 (d, *J* = 6 Hz, 3 H), 1.33 (s, 3 H), 1.66 (m, 4 H), 2.0–2.31 (m, 4 H), 2.5 (br s, 1 H), 3.98 (s, 4 H), 4.23 (m, 1 H).

(*R*)-2-Hydroxy-4-keto-8-(1,3-dioxolan-2-yl)nonane [(*R*)-3]. The compound, prepared by the preceding method, was 95% pure by VPC: $[\alpha]^{20}_D$ −41.7° (*c* 1, $CHCl_3$).

(1*S*,3*S*,5*R*)-1,3-Dimethyl-2,9-dioxabicyclo[3.3.1]nonane (6). The hydroxy ketone (*S*)-**3** (1.70 g) in ether (20 mL) was added to a 0.12 M solution of $Zn(BH_4)_2$ in ether (65 mL) under ice-cooling. The reduction was completed in 30 min. Water (4 mL) was added and the reaction mixture was stirred 30 min. Na_2SO_4 was added for drying, the resulting suspension filtered, and the solvent removed in vacuo. The residue was dissolved in methanol (20 mL) and the methanol evaporated in vacuo three times to liberate the diol from boric esters. The crude, oily diol weighed 1.70 g and was 81% pure, as determined by VPC on column B (same analytical conditions as for the hydroxy ketone **3**). The diol **5** (RT 31.8 min) and the diol **4** (RT 32.3 min) were in a 1 to 9 ratio. The crude mixture of the diols was dissolved in benzene (5 mL) and added in 4 h to a mixture of benzene (5 mL) and pentane (20 mL) with stirring at room temperature in the presence of 50 mg of Amberlyst-15. Stirring was continued for 1 h more, the resin was filtered off, the solvents were cautiously evaporated, and the residue was purified by flash chromatography with pentane/ether (6:1) as the eluent. The fractions containing the same compound were combined, the solvent was evaporated, and the residue was distilled (Kugelrohr) at 100 °C (5.3 kPa), affording 0.78 g (5 mmol) of the (1*S*,3*S*,5*R*)-**6**, 99% pure by VPC on column B [1 min at 40 °C, 20 °C/min to 80 °C, 2 min at 80 °C, 2.5 °C/min to 160 °C; RT 5.7 min] and on column C [8 min at 100 °C, 5 °C/min to 220 °C) RT 5.3 min]: $[\alpha]^{20}_D$ +45.7° (*c* 1, pentane) [lit.[3] $[\alpha]^{20}_D$ +37.5° (*c* 5.4, pentane)]; ^{1}H NMR δ 1.20 (d, *J* = 6 Hz, 3 H), 1.30 (s, 3 H), 1.33–2.30 (brm, 8 H), 3.97 (ddq, *J* = 3.8, 11.2, 6 Hz, 1 H), 4.30 (m, 1 H).

(1*S*,3*R*,5*R*)-1,3-Dimethyl-2,9-dioxabicyclo[3.3.1]nonane (7). $NaBH_4$ (265 mg, 7 mmol) was added portionwise, to an ice-cooled solution obtained by dissolving the hydroxy ketone (*R*)-**3** (1.70 g) in methanol (18 mL) containing $CeCl_3 \cdot 7H_2O$ (7.2 mmol). After the mixture was stirred for 30 min, water (30 mL) was added and the mixture extracted with ether (three 100-mL portions). The ether extracts were washed with brine and dried over Na_2SO_4, and the solvent was removed. The residue, after the methanol treatment as previously described, was a mixture of the diol **5** and the diol **4** in a 2 to 1 ratio as shown by VPC. The crude mixture was cyclized and purified as described before. The two isomers were isolated and distilled. (1*R*,3*R*,5*S*)-**6**: 250 mg (1.6 mmol); 95% pure by VPC; $[\alpha]^{20}_D$ −41° (*c* 1, pentane) [lit.[3] $[\alpha]^{20}_D$ −37.5° (*c* 0.9, pentane)]. (1*S*,3*R*,5*R*)-**7**: 530 mg (3.4 mmol); distilled (Kugelrohr) at 110 °C (5.3 kPa), 98% pure VPC (column B, RT 7.7 min; column C, RT 8.9 min) ; $[\alpha]^{20}_D$ +10.7° (*c* 3, pentane) [lit.[3] $[\alpha]^{20}_D$ +4.7° (*c* 3.2, pentane)]; ^{1}H NMR δ 1.17 (d, *J* = 6 Hz, 3 H), 1.32 (s, 3 H), 1.37–2.27 (brm, 8 H), 4.21 (m, 1 H), 4.60 (m, 1 H).

Registry No. (*S*)-**1**, 86146-06-7; (*R*)-**1**, 91888-93-6; (*S*)-**2**, 109927-88-0; (*R*)-**2**, 109927-89-1; (*S*)-**3**, 109927-90-4; (*R*)-**3**, 109927-91-5; **4** (isomer 1), 109927-92-6; **4** (isomer 2), 109927-93-7; **5** (isomer 1), 109927-94-8; **5** (isomer 2), 109927-95-9; (1*S*,3*S*,5*R*)-**6**, 76740-35-7; (1*R*,3*R*,5*S*)-**6**, 76740-34-6; (1*S*,3*R*,5*R*)-**7**, 76334-10-6; 2-(3-chloropropyl)-2-methyl-1,3-dioxolane, 5978-08-5.

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Room-Temperature Fluorination of 1-Phenylacetylenes with Cesium Fluoroxysulfate

Stojan Stavber and Marko Zupan*

"Jožef Stefan" Institute and Department of Chemistry, "Edvard Kardelj" University, Ljubljana, Yugoslavia

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It is of importance from a chemical and pharmaceutical point of view that only a limited number of reagents are able to introduce fluorine under mild conditions at room temperature.[1] It has been demonstrated that $CsSO_4F$ reacts with various organic molecules; however, the effectiveness of the fluorination is influenced by both the structure of the molecule and the appropriateness of the reaction conditions.[2-6]

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