Highly Efficient Conversion of (−)-Carvone to (+)-5β-Hydroxycarvone

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(−)-Carvone (2) has been efficiently transformed into (+)-5β-hydroxycarvone (1), which is expected to play an important role as a potential precursor or as a chiral template in the synthesis of natural products. Both hydroxy selenides 4 and 5, obtained by the reduction of selenenylcarvone 3, were stereoselectively converted to (+)-1, respectively. The sequence of reactions was performed with optical integrity, and the overall yield from (−)-2 to (+)-1 was ca. 44%.

trans-5-Hydroxycarvone (*trans*-5-hydroxy-*p*-mentha-6,8-dien-2-one) (1) has been isolated as a minor constituent of Scotch spearmint oil[1] and of American Midwest native spearmint oil (*Mentha spicata*)[2] although its absolute stereostructure has not been unequivocally established.

5β-Hydroxycarvone (1) seems to be a potential precursor and a versatile starting material for the synthesis of naturally occurring complex molecules provided that this compound is readily available from natural sources, such as carvone (2), in both of its enantiomeric forms.

In connection with the synthesis of picrotoxan sesquiterpenes,[3] we required multigrams of optically pure (+)-5β-hydroxycarvone (1) for use as our starting material and needed to develop an effective method to synthesize this compound. We report herein a highly efficient and stereoselective synthesis of (+)-5β-hydroxycarvone (1) starting from (−)-carvone (2).

Results and Discussion

It was clear from the outset that the regioselective oxidation of 2 at C(5) by allylic oxidants such as selenium(IV) oxide was not feasible,[4] and we envisaged a synthetic route employing stereoselective introduction of a β-hydroxyl group at C(5) using the conjugate addition of benzeneselenol (PhSeH) to 2. By the successful application of the conjugate addition of PhSeH to α,β-unsaturated carbonyl compounds recently developed by us (M.M. and A.Y.),[5] (−)-2 was readily converted to adduct 3, single isomer, in high yield. Since the product 3 was susceptible to silica gel,[6] the crude adduct was submitted to the following reduction without purification.

Thus when 3 was treated with lithium aluminum hydride in ether, the corresponding epimeric alcohols 4 and 5 were produced in 86% overall yield from (−)-2 in a ratio of 85:15. These alcohols were easily and cleanly separated by simple silica gel column chromatography even on a 40-g scale.

In order to gain further insight into the ratio of 4 and 5, we studied the reduction of 3 using a variety of reducing agents (Table I). As seen from Table I, both the yield and the ratio of products depended upon a reducing agent used, and the best yield was obtained when diisobutylaluminum hydride (DIBAH) was employed (94%). While lithium tri-*tert*-butoxyaluminohydride (LiAl(*t*-BuO)$_3$H) gave an excellent stereoselectivity (98:2), this reagent afforded a lower yield of products (62%) because of the attendant elimination of PhSeH from 3, resulting in formation of the starting material 2.

On the other hand, L-Selectride (Aldrich) did not produce any of the alcohol, presumably due to the participation between the selenium and the boron atoms.

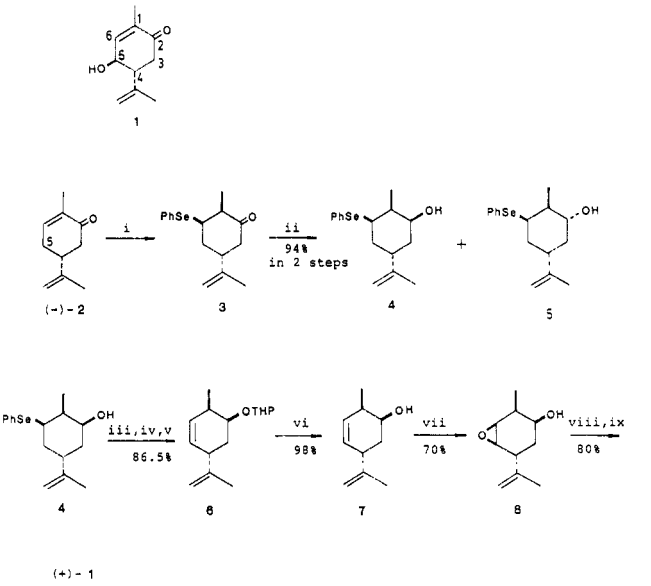
The stereochemistries of 3, 4, and 5 were tentatively assigned as shown in Scheme I on the basis of the following mechanistic rationale. The Michael addition of PhSeH to 2 should occur from the β-axial face at C(6) by stereoelectronic effects (A in eq 1), and subsequent proton-

Table I. Reduction of (2*S*,3*R*,5*S*)-2-Methyl-5-(1-methylethenyl)-3-(phenylseleno)-cyclohexanone (3)

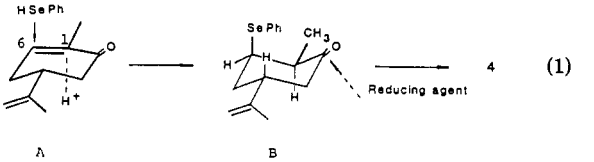
reducing agent	solvent	ratio of 4 and 5[a]	overall yield from 2, %[b]
$LiAlH_4$	ether	85:15	86
DIBAH	toluene	80:20	94
LiAl(*t*-BuO)$_3$H	THF	98:2	62
L-Selectride	THF		

[a] The ratio refers to isolated pure products. [b] Total yield of 4 + 5.

Scheme I[a]



[a] (i) PhSeNa, AcOH, EtOH; (ii) DIBAH, PhMe; (iii) DHP, PPTS, CH_2Cl_2; (iv) H_2O_2, py, CH_2Cl_2; (v) Δ, CCl_4; (vi) PPTS, EtOH; (vii) *t*-BuO_2H, $VO(acac)_2$, PhH; (viii) $CrO_3 \cdot 2py$, CH_2Cl_2 or CrO_3, aqueous H_2SO_4, $(CH_3)_2CO$; (ix) Al_2O_3.



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(2) Ichimura, N.; Matsuura, Y.; Kato, Y. "Abstracts of Papers", 25th Terupen, Seiyu oyobi Koryo ni kansuru Toronkai, Yamaguchi, Oct 1981; p 18.
(3) Miyashita, M.; Yoshikoshi, A. "Abstracts of Papers", 26th Tennen Yuki Kagobutsu Toronkai, Kyoto, Oct 1983: p 344.
(4) Büchi, G.; Wüest, H. *J. Org. Chem.* **1969**, *34*, 857.
(5) Miyashita, M.; Yoshikoshi, A. *Synthesis* **1980**, 664.
(6) Elimination of PhSeH occurs on contact with silica gel.

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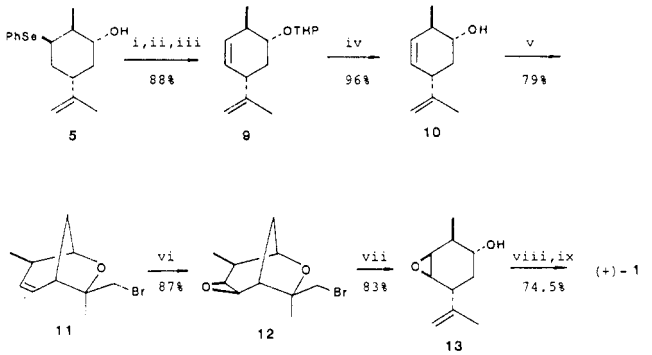
Scheme II[a]



[a] (i) DHP, PPTS, CH_2Cl_2; (ii) H_2O_2, py, CH_2Cl_2; (iii) Δ, CCl_4; (iv) PPTS, EtOH; (v) *N*-bromosuccinimide, CH_3CN; (vi) *m*-$ClC_6H_4CO_3H$, CH_2Cl_2; (vii) Zn(Cu), NH_4Cl, EtOH; (viii) CrO_3, aqueous H_2SO_4, $(CH_3)_2CO$; (ix) Al_2O_3.

ation at C(1) would take place from α-axial face, resulting in formation of B (i.e., **3**) as shown in eq 1. Consequently, one can expect that the reduction of **3** may produce the β-alcohol **4** predominantly by the attack of a reducing agent from the sterically less hindered α-face (B in eq 1).

This surmise was proven valid by experiment (vide infra). The conversion of the major hydroxy selenide **4** to the desired (+)-5β-hydroxycarvone (**1**) was straightforwardly performed as follows.

PPTS-catalyzed tetrahydropyranylation[7] of **4** followed by oxidation with hydrogen peroxide to the corresponding selenoxide and subsequent elimination of benzeneselenenic acid in refluxing carbon tetrachloride afforded exclusively diene **6** in 86% overall yield.[8,9] The formation of single isomer **6** with respect to a newly introduced double bond proved the structures of **4** and hence **3** since the syn elimination of selenoxide has been recognized.[10]

Deprotection of the tetrahydropyranyl group of **6** with PPTS in ethanol[7] gave homoallyl alcohol **7**, which was then converted to β-epoxy alcohol **8** by the Sharpless method.[11] Oxidation of **8** with Jones reagent followed by treatment of the resulting epoxy ketone with neutral alumina afforded the crystalline (+)-**1** in good yield; its spectral properties were in agreement with those of a natural specimen.[2,12] Thus we were successful in the stereoselective conversion of (−)-**2** to (+)-**1** employing the major alcohol **4**.

On the other hand, we could also accomplish the stereoselective transformation of the minor alcohol **5** into (+)-**1** as shown in Scheme II. By the same sequence of reactions described above, the minor alcohol **5** was easily transformed into epimeric homoallyl alcohol **10**, single isomer again, in high overall yield. On treatment with *N*-bromosuccinimide in acetonitrile, **10** afforded bromo ether **11**, which was then oxidized with *m*-chloroperoxybenzoic acid (MCPBA) in CH_2Cl_2 to give only the β-epoxide **12**, as was expected. Reduction of **12** with Zn(Cu) in ethanol followed by oxidation with Jones reagent resulted in formation of the same β-epoxy ketone obtained by Scheme I, which was readily transformed into (+)-**1** by treatment with neutral alumina.

As a consequence, (+)-**1** was obtained from (−)-**2** in ca. 44% overall yield in total. The synthetic method described herein was not only efficient but also highly stereoselective, and all operations could be performed with optical integrity.

Experimental Section

Melting points were determined with a Yamato melting point apparatus, Model MP-21, and are uncorrected. IR spectra were recorded on a Hitachi EP1-S2 or JASCO A-3 spectrophotometer. ^1H NMR spectra were recorded on a JEOL c-60HL (60 MHz) or a JEOL JNM-FX 90Q (90 MHz) spectrometer, except where noted, in CCl_4. ^{13}C NMR spectrum was recorded on a JEOL JNM-FX 90Q in $CDCl_3$. Chemical shifts are expressed in δ values relative to Me_4Si as internal standard. Coupling constants (*J*) are given in hertz. Solvent systems that developed the major reaction products in a moderate R_f range (0.4–0.6) are described for preparative, silica gel, thin-layer chromatography (TLC). Microanalyses were performed by the Microanalytical Laboratory in this institute.

(1*S*,2*S*,3*R*,5*S*)-2-Methyl-5-(1-methylethenyl)-3-(phenylseleno)cyclohexanol (4) and Its C(1) Epimer (5).[13] According to the procedure recently developed by us,[5] (−)-carvone (**2**) (30 g, 0.2 mol) was readily converted to crude selenenyl ketone **3** (^1H NMR 1.10 (d, 3 H, *J* = 7), 1.72 (br s, 3 H), 3.87 (dd, 1 H, *J* = 8.3), 4.67 (br s, 2 H), and 7.0–7.7 (m, 5 H)) in nearly quantitative yield, which was submitted to the following reduction without purification.[6]

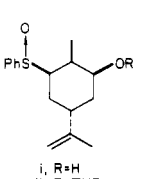
(a) Reduction of (2*S*,3*R*,5*S*)-2-Methyl-5-(1-methylethenyl)-3-(phenylseleno)cyclohexanone (3) with $LiAlH_4$. $LiAlH_4$ (38 mg, 1.0 mmol) was added to a solution of crude selenenyl ketone **3** (1.0 mmol) in dry ether (5 mL) at −5 °C under nitrogen, and the mixture was stirred for 30 min at the same temperature. Excess hydride was decomposed by adding wet ether, and the mixture was filtered.[14] Evaporation of the solvent gave an oil, which was purified using a silica gel column. Elution with *n*-hexane–ether (10:1 to 7:1) gave **4** (225 mg, 73%) as an oil, and further elution with *n*-hexane–ether (5:1) afforded **5** (40 mg, 13%) as crystals. **4**: IR (neat) 3430, 3050, 1642, 1576, 1475, 1440, 984, 885, 737, 690 cm^{-1}; ^1H NMR 1.22 (d, 3 H, *J* = 6.5), 1.72 (br s, 3 H), 1.25–2.33 (m, 6 H), 2.80 (br t, 1 H, *J* = 11), 3.38 (q, 1 H, *J* = 4), 3.85 (br, 1 H), 4.65 (br s, 2 H), 7.0–7.7 (m, 5 H). An analytical sample was prepared by distillation: bp 122–123 °C (bath temperature, 0.25 mmHg). Anal. Calcd for $C_{16}H_{22}OSe$: C, 62.13; H, 7.16. Found: C, 61.78; H, 6.80. **5**: colorless crystals; mp 97–98 °C (recrystallized from *n*-hexane); IR (KBr) 3430, 3050, 1642, 1575, 1435, 900, 738, 690 cm^{-1}; ^1H NMR 1.23 (d, 3 H, *J* = 6), 1.67 (br s, 3 H), 1.0–2.9 (m, 7 H), 3.2–3.8 (m, 2 H), 4.70 (br s, 2 H), 7.0–7.7 (m, 5 H). Anal. Calcd for $C_{16}H_{22}OSe$: C, 62.13; H, 7.16. Found: C, 62.01; H, 7.33.

(b) Reduction of 3 with DIBAH. DIBAH (1.7 M solution in toluene, 1.2 mL, 2 mmol) was added dropwise to a solution of

(7) Miyashita, M.; Yoshikoshi, A.; Grieco, P. A. *J. Org. Chem.* **1977**, *42*, 3772.

(8) Attempts to convert the hydroxy selenide **4** (or **5**) itself to **7** (or **10**) without protection of the hydroxyl group were totally fruitless.

(9) Thermolysis of the corresponding sulfoxides i or ii, prepared from **2** by the conjugate addition of NaSPh followed by reduction ($LiAlH_4$) and oxidation ($NaIO_4$), did not produce the desired product **7** or **6**.



(10) Clive, D. L. J. *J. Chem. Soc., Chem. Commun.* **1973**, 695. Sharpless, K. B.; Young, M. W.; Lauer, R. F. *Tetrahedron Lett.* **1973**, 1979. Reich, H. J.; Reich, I. L.; Renga, J. M. *J. Am. Chem. Soc.* **1973**, *95*, 5813.

(11) Sharpless, K. B.; Michaelson, R. C. *J. Am. Chem. Soc.* **1973**, *95*, 6136.

(12) The $[\alpha]_D$ value of a natural specimen has not been recorded.

(13) For experimental details for the preparation of **3**, see ref 5. Workup was conveniently modified as follows without extraction described in the original report.[5] The reaction mixture was diluted with *n*-hexane–ether (10:1) and the precipitate of NaOAc was filtered off through a pad of Celite with the aid of ether. Removal of the solvent gave crude **3**.

(14) It is pointed out that for a large-scale preparation oxygen should be bubbled into the mixture overnight prior to filtration in order to convert survival PhSeH, a malodorous and severe poison, into stable diphenyl diselenide.

crude **3** (1.0 mmol) in dry toluene (6 mL) at −78 °C under Ar. The mixture was stirred at −78 °C for 3 h and then gradually warmed to 0 °C overnight. Excess hydride was decomposed by adding a saturated ammonium chloride solution, and the supernatant organic layer was decanted. The inorganic residue was washed with ether. The combined organic solution was evaporated in vacuo, and the residue was purified by the same procedure described above to give **4** (232 mg, 75%) and **5** (60 mg, 19%) in 94% total yield.

(c) Reduction of 3 with LiAl(*t*-BuO)$_3$H. LiAl(*t*-BuO)$_3$H (1.017 g, 4.0 mmol) was added to a solution of crude **3** (1 mmol) in dry THF (5 mL) at 0 °C under Ar. The mixture was stirred at 0 °C overnight. After decomposition of excess hydride with wet ether, aqueous hydrochloric acid was added, and the product was extracted with ether. The extract was washed with water and saturated brine. Removal of the solvent left an oil, which was chromatographed on a silica gel column described above to give carvone (**2**) (42 mg), **4** (188 mg, 61%), and **5** (4 mg, 1.3%).

(1*S*,2*R*,5*S*)-2-Methyl-5-(1-methylethenyl)-1-((tetrahydropyran-2-yl)oxy)-3-cyclohexene (6). A mixture of **4** (3.09 g, 10 mmol), dihydropyran (1.68 g, 20 mmol), and PPTS[7] (251 mg, 1 mmol) in dry CH_2Cl_2 (80 mL) was stirred at room temperature for 16 h under N_2. The mixture was diluted with ether (200 mL) and washed with water and saturated brine. After removal of the solvent, the residual oil was dissolved in CH_2Cl_2 (30 mL) containing pyridine (1.6 mL, 20 mmol). Then 15% hydrogen peroxide (22.5 mL, 100 mmol) was added, and the resulting heterogeneous solution was vigorously stirred at room temperature for 1.5 h. The mixture was extracted with ether, and the extract was washed with water and saturated brine. Evaporation of the solvent gave an oil, the crude selenoxide, which was dissolved in CCl_4 (50 mL) containing pyridine (1.68 mL, 20 mmol), and the mixture was refluxed for 30 min. The solvent was removed in vacuo and the residual oil was purified with a silica gel column [*n*-hexane–ether (20:1) as solvent] to afford 2.04 g (86.5%) of **6**: IR (neat) 3070, 3020, 1642, 1022, 888 cm^{-1}; ^{1}H NMR 0.95 and 1.07 (2 d, 3 H in total, J = 7), 1.74 (br s, 3 H), 1.17–3.16 (m, 10 H), 3.17–4.16 (m, 3 H), 4.70 (br s, 2 H), 4.5–4.8 (m, 1 H), 5.47 (br s, 2 H). An analytical sample was prepared by distillation: bp 110 °C (bath temperature, 0.3 mmHg). Anal. Calcd for $C_{15}H_{24}O_2$: C, 76.22; H, 10.23. Found: C, 75.90; H, 10.41.

(1*S*,2*R*,5*S*)-2-Methyl-5-(1-methylethenyl)-3-cyclohexen-1-ol (7). A mixture of **6** (4.18 g, 17.7 mmol) and PPTS (451 mg, 1.8 mmol) in ethanol (80 mL) was stirred at 60 °C for 3 h. The solvent was evaporated in vacuo, and the residue was partitioned between ether and water. The organic layer was washed with water and saturated brine. Evaporation of the solvent left an oil, which was chromatographed [silica gel, *n*-hexane–ether (20:1) as solvent] to give 2.64 g (98%) of **7**: IR (neat) 3350, 3065, 3010, 1642, 992, 890 cm^{-1}; ^{1}H NMR 1.03 (d, 3 H, J = 7.5), 1.73 (br s, 3 H), 1.25–3.17 (m, 5 H), 3.85 (br, 1 H, $W_{1/2}$ = 12 Hz, C*H*OH), 4.70 (br s, 2 H), 5.45 (s, 2 H). An analytical sample was prepared by distillation: bp 70 °C (bath temperature, 0.3 mmHg). Anal. Calcd for $C_{10}H_{16}O$: C, 78.89; H, 10.59. Found: C, 78.64; H, 10.81.

(1*S*,2*S*,3*S*,4*R*,5*R*)-3,4-Epoxy-2-methyl-5-(1-methylethenyl)cyclohexanol (8). A mixture of **7** (152 mg, 1.0 mmol), *tert*-butyl hydroperoxide (72% solution in water, 138 μL, 1.1 mmol) and a catalytic amount of VO(acac)$_2$ in benzene (5 mL) was stirred at room temperature for 17 h under N_2.[11,15] The mixture was successively washed with aqueous $NaHCO_3$, water, and saturated brine. After removal of the solvent, the residual oil was purified by TLC [petroleum ether–ether (1:1) as solvent] to afford **8** (117 mg, 70%): IR (neat) 3450, 3060, 1645, 1196, 1055, 985, 956, 890, 831 cm^{-1}; ^{1}H NMR 1.25 (d, 3 H, J = 7), 1.83 (br s, 3 H), 1.0–2.2 (m, 3 H), 2.30 (br, 1 H, O*H*), 2.75 (dd, 1 H, J = 11, 6), 3.08 (s, 2 H), 3.58 (br, 1 H, $W_{1/2}$ = 13 Hz), 4.87 (br s, 2 H). An analytical sample was prepared by distillation: bp 24 °C (bath temperature, 0.4 mmHg). Anal. Calcd for $C_{10}H_{16}O_2$: C, 71.39; H, 9.59. Found: C, 71.60; H, 9.60.

(4*S*,5*R*)-2-Methyl-5-(1-methylethenyl)-4-hydroxy-2-cyclohexen-1-one ((+)-5β-Hydroxycarvone) (1). To a stirred mixture of dipyridine chromium(VI) oxide (Collins reagent, 696 mg, 2.70 mmol) in dry CH_2Cl_2 (5 mL) was added a solution of **8** (76 mg, 0.45 mmol) in CH_2Cl_2 (2 mL) at room temperature under N_2.[16] After being stirred for 10 min, the reaction mixture was diluted with ether (20 mL) and passed through a short silica gel column with the aid of ether. Evaporation of the solvent gave 77 mg of epoxy ketone [IR (neat) 3070, 1707, 1645, 946, 902, 822 cm^{-1}; ^{1}H NMR 1.25 (d, 3 H, J = 8), 1.80 (br s, 3 H), 1.92–2.83 (m, 3 H), 2.83–3.42 (m, 3 H), 4.85 (br m, 2 H)], which was adsorbed on a column of neutral alumina (Woelm activity III). Elution with petroleum ether–ether (1:1) afforded (+)-**1** (60 mg, 80%) as colorless crystals: mp 57–58 °C (recrystallized from *n*-hexane–ether); $[\alpha]^{15}_D$ + 225° (*c* 0.2, $CHCl_3$); IR (CCl_4) 3420, 3060, 1677, 1038, 980, 895 cm^{-1}; ^{1}H NMR ($CDCl_3$)[17] 1.78 (br s, 6 H), 2.2–2.9 (m, 4 H), 4.50 (dt, 1 H, J = 9.5, 2), 4.97 (br s, 2 H), 6.72 (t, 1 H, J = 1.8); ^{13}C NMR 198.3, 147.4, 143.0, 134.9, 114.4, 68.3, 52.6, 40.8, 19.0, 15.2. Anal. Calcd for $C_{10}H_{14}O_2$: C, 72.26; H, 8.49. Found: C, 72.12; H, 8.61.

(1*R*,2*R*,5*S*)-2-Methyl-5-(1-methylethenyl)-1-((tetrahydropyran-2-yl)oxy)-3-cyclohexene (9). By the same sequence of reactions employed in the conversion of **4** to **6**, the hydroxy selenide **5** (309 mg, 1.0 mmol) was transformed into **9** (208 mg) in 88% overall yield,: oil; IR (neat) 3070, 3020, 1643, 1038, 893, 745 cm^{-1}; ^{1}H NMR 1.01 and 1.12 (2 d, 3 H in total, J = 6), 1.66 (br s, 3 H), 1.3–2.5 (m, 9 H), 2.5–4.2 (m, 4 H), 4.70 (br s, 2 H), 4.4–4.8 (m, 1 H), 5.39 (br s, 2 H). An analytical sample was prepared by distillation: bp 103–104 °C (bath temperature, 0.25 mmHg). Anal. Calcd for $C_{15}H_{24}O_2$: C, 76.22; H, 10.23. Found: C, 75.85; H, 10.00.

(1*R*,2*R*,5*S*)-2-Methyl-5-(1-methylethenyl)-3-cyclohexen-1-ol (10). A mixture of **9** (236 mg, 1.0 mmol) and PPTS[7] (25 mg, 0.1 mmol) in ethanol (4 mL) was stirred at 65 °C for 2 h. The solvent was evaporated in vacuo and the residue was washed with water and saturated brine. Evaporation of the solvent left an oil, which was purified by TLC [petroleum ether–ether (10:1) as solvent] to afford 146 mg (96%) of **10** as an oil: IR (neat) 3325, 3060, 3010, 1641, 1053, 892, 737 cm^{-1}; ^{1}H NMR 1.10 (d, 3 H, J = 7), 1.66 (d, 3 H, J = 1), 1.17–2.33 (m, 4 H), 2.88 (m, 1 H), 3.33 (ddd, 1 H, J = 12, 9, 4, C*H*OH), 4.70 (br s, 2 H), 5.40 (s, 2 H). An analytical sample was prepared by distillation: bp 75 °C (bath temperature, 0.3 mmHg). Anal. Calcd for $C_{10}H_{16}O$: C, 78.89; H, 10.59. Found: C, 79.04; H, 10.89.

(1*S*,4*R*,7*R*)-7-(Bromomethyl)-4,7-dimethyl-6-oxabicyclo-[3.2.1]oct-2-ene (11). A mixture of **10** (152 mg, 1 mmol) and *N*-bromosuccinimide (232 mg, 1.3 mmol) in dry acetonitrile (8.5 mL) was stirred at 0 °C for 3 h under N_2. The reaction mixture was diluted with ether (50 mL) and washed successively with half-saturated brine, water, and saturated brine. Removal of the solvent left an oil, which was chromatographed on a silica gel column. Elution with pentane–ether (10:1) gave **11** (182 mg, 79%) as an oil: IR (neat) 3025, 1634, 1052, 722 cm^{-1}; ^{1}H NMR ($CDCl_3$)[17] 0.90 (d, 3 H, J = 7), 1.37 (s, 3 H), 1.77 (d, 1 H, J = 11), 1.8–2.6 (m, 3 H), 3.35 (d, 1 H, J = 9), 3.52 (d, 1 H, J = 9), 4.16 (dt, 1 H, J = 5.5, 1.8), 5.51 (dt, 1 H, J = 11, 3), 6.00 (m, 1 H). An analytical sample was prepared by distillation: bp 25 °C (bath temperature, 0.7 mmHg). Anal. Calcd for $C_{10}H_{15}OBr$: C, 51.95; H, 6.54; Br, 34.58. Found: C, 52.19; H, 6.28; Br, 34.41.

(1*S*,2*R*,4*S*,8*R*)-8-(Bromomethyl)-5,8-dimethyl-3,7-dioxatricyclo[4.2.1.0^{2,4}]nonane (12). A mixture of **11** (54 mg, 0.23 mmol) and MCPBA (80%, 61 mg, 0.28 mmol) in dry CH_2Cl_2 was stirred at 0 °C for 36 h. The reaction mixture was diluted with ether (30 mL) and washed successively with aqueous $NaHCO_3$, aqueous $Na_2S_2O_3$, water, and saturated brine. Evaporation of the solvent in vacuo gave 85 mg of an oil, which was purified by TLC [*n*-hexane–ethyl acetate (5:1) as solvent] to afford 50 mg (87%) of **12** as an oil: IR (neat) 1025, 901, 803 cm^{-1}; ^{1}H NMR ($CDCl_3$)[17] 1.00 (d, 3 H, J = 7), 1.42 (s, 3 H), 2.12 (d, 1 H, J = 12), 1.5–2.0 (m, 2 H), 2.57 (t, 1 H, J = 3.6), 3.06 (m, 1 H), 3.43 (d, 1 H, J = 10), 3.64 (d, 1 H, J = 10), 3.50 (d, 1 H, J = 4), 3.88 (dt, 1 H, J = 6, 2.5). An analytical sample was prepared by distillation: bp 33 °C (bath temperature, 1.0 mmHg). Anal. Calcd for $C_{10}H_{15}O_2Br$: C, 48.58; H, 6.12; Br, 32.35. Found: C, 48.81; H, 6.28; Br, 32.09.

(1*R*,2*S*,3*S*,4*R*,5*R*)-3,4-Epoxy-2-methyl-5-(1-methylethenyl)cyclohexanol (13). To a solution of **12** (126 mg, 0.51

(15) It is recommended for a large-scale preparation that the reaction mixture be heated at 65–70 °C for 3 h to shorten the reaction period.

(16) Jones oxidation was also effective, particularly for a large scale preparation (70–75%).

(17) ^{1}H NMR data were obtained at 90 MHz.

mmol) in ethanol (7.6 mL) was added a mixture of Zn(Cu) (329 mg, 2.55 mmol) and ammonium chloride (68 mg, 1.28 mmol) in water (0.2 mL), which was well agitated by a spatula in advance at room temperature. The mixture was then refluxed for 3 h. The cooled reaction mixture was diluted with *n*-hexane (20 mL) and inorganic precipitates were filtered off. After evaporation of the solvent the residual oil was purified by TLC [*n*-hexane–ethyl acetate (5:1) as solvent] to afford **13** (71 mg, 83%) as colorless crystals: mp 52.5 °C (recrystallized from *n*-hexane); IR ($CHCl_3$) 3585, 3430, 3060, 1645, 1047, 902, 820 cm^{-1}; ^1H NMR ($CDCl_3$)[17] 1.28 (d, 3 H, J = 7), 1.2–2.0 (m, 7 H), 2.62 (dd, 1 H, J = 12.5, 5.7), 3.05 (d, 1 H, J = 3.5), 3.14 (dd, 1 H, J = 3.5, 1.8), 3.42 (ddd, 1 H, J = 11.5, 9, 3.6, C*H*OH), 4.86 (br s, 2 H). Anal. Calcd for $C_{10}H_{16}O_2$: C, 71.39; H, 9.59. Found: C, 71.14; H, 9.35.

Conversion of 13 to (+)-1. To a solution of **13** (91 mg, 0.54 mmol) in acetone (5 mL) was added dropwise Jones reagent (0.35 mL) at 0 °C, and the resulting mixture was further stirred for 15 min at the same temperature. The reaction mixture was poured into cold water and extracted with CH_2Cl_2. The extract was washed with water and saturated brine. Evaporation of the solvent left crude epoxy ketone, which was adsorbed on a column of neutral alumina (Woelm activity III). Elution with ether gave 87 mg of an oil, which was purified by TLC [*n*-hexane–ether (1:1) as solvent] to afford 67 mg (74.5% e of **1** as colorless crystals.

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Carbon-13 Magnetic Resonance of Hydroaromatics. 3. Conformation of 1,2,3,4-Tetrahydrophenanthrene and 9,10-Dihydrophenanthrene and Their Methyl Derivatives[1,2]

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^{13}C chemical shift data have been obtained for 27 methylated 1,2,3,4-tetrahydro- and 9,10-dihydrophenanthrenes. It has been found that methyl-substituent parameters previously determined for the saturated ring of tetralin and 1,2,3,4-tetrahydroanthracene show a remarkable ability to predict the chemical shifts in spite of the significant structural differences in the basic structure of the hydrophenanthrenes, exemplified by the proximity of the C-4 and C-5 positions. Analogous to the tetralins, 1-methyltetrahydrophenanthrene was determined to prefer slightly the conformer with a pseudoaxial methyl, while, in contrast to the tetralins, the C-4 methyl derivatives were forced to exist entirely with the C-4 methyl pseudoaxial. The conformation of the cis-2,4 compound is ambiguous. Variable-temperature ^{13}C and ^1H NMR has provided $\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$ of 10.3 kcal mol^{-1} and −3.3 cal K^{-1} mol^{-1}, respectively, for the conformational inversion of *cis*-9,10-dimethyl-9,10-dihydrophenanthrene. It is hypothesized that significantly slower methyl group rotation in the transition state compared to the ground state is responsible for the negative $\Delta S^{\ddagger}$. The trans-9,10 compound is shown to exist exclusively as the diaxial conformer, and 9,9,10-trimethyldihydrophenanthrene is present as an equilibrium mixture where the conformer with the C-10 methyl axial dominates to better than 95%.

Introduction

The process of coal liquifaction requires the use of hydroaromatics as hydrogen donors.[3,4] As part of a continuing investigation[1,2] of hydroaromatic compounds, we recently analyzed[2] the ^{13}C chemical shifts of methylated tetralins and 1,2,3,4-tetrahydroanthracenes in terms of methyl substituent parameters, determined from a linear least-squares regression, to gain insight into the conformational characteristics of that ring system. It was found that substituent parameters for methyl groups at C-2 (or C-3) were nearly identical with those found for cyclohexane,[5] but C-1 (or C-4) methyls resulted in quite different substituent effects. In particular, it was shown that a large δ effect at C-4 of +1.0 ppm resulted from placement of a pseudoequatorial methyl at C-1. It was hypothesized that this was due to the high flexibility of the saturated ring, which also led to an inability to accurately predict the chemical shifts of the highly substituted derivatives.

The interaction of an equatorial C-1 methyl with the peri proton of the aromatic ring was also found to be severe enough to result in essentially equal populations of the pseudoequatorial and pseudoaxial conformers of 1-methyltetralin whereas 2-methyltetralin exists almost entirely in the equatorial conformation, similar to methylcyclohexane.

The tetrahydrophenanthrene system, while possessing a saturated six-membered ring fused to an aromatic ring, differs from tetrahydroanthracene through the severe steric congestion involving the C-4 and C-5 positions. This feature is anticipated to render those compounds with C-4 methyl groups conformationally immobile (i.e., the mole-

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