Calcd for $C_{20}H_{27}O_2N$: C, 76.64; H, 8.68; N, 4.47. Found: C, 76.70; H, 8.78; N, 4.23.

[16β-^{2}H]-5, was obtained by the similar treatment of **1** or **2** with KCN in D_2O (99 atom %)-pyridine as above. **5-*16-d***: mp 194–196 °C; MS, 2% d_0 and 98% d_1 (from **1**), 3% d_0 and 97% d_1 (from **2**).

17β-Cyano-16α,17α-epoxy-5α-androstan-3β-ol (6) was obtained in 75% yield from 16α-bromo-3β-hydroxy-5α-androstan-17-one (**3**)[1b] in a similar manner: mp 189–190 °C (colorless needles, from MeOH); IR 3400 (OH), 2250 (CN) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.83 (3 H, s, 19-Me), 0.97 (3 H, s, 18-Me), 3.50 (1 H, br m, 3α-H), 3.80 (1 H, s, 16β-H); $[\alpha]_D$ +47.8° (*c* 0.97, $CHCl_3$). Anal. Calcd for $C_{20}H_{29}O_2N$: C, 76.15; H, 9.27; N, 4.44. Found: C, 75.96; H, 9.48; N, 4.14.

17β-Cyano-16α,17α-epoxy-4-androsten-3-one (7). Compound **5** (100 mg, 0.32 mmol) was dissolved in 16 mL of acetone. To this solution was added dropwise slight excess of a 8 N CrO_3 solution with stirring below 5 °C, and then the solution was allowed to stand for 10 min. After this time, the mixture was poured into ice water (250 mL). The precipitate (95 mg) was collected by filtration, dried under vacuum, and then dissolved in 2 mL of hexane–AcOEt (9/1). The solution was passed through a column of Al_2O_3 (5 g, activity II–III) and set aside at room temperature overnight. After this time, the adsorbed streoid was eluted with the solvent and then repeatedly recrystallized from acetone to give **8** (50 mg, 50%) as colorless plates: mp 242–243 °C; IR 2250 (CN), 1650 (C=O) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.00 (3 H, s, 18-Me), 1.13 (3 H, s, 19-Me), 3.80 (1 H, s, 16β-H), 5.70 (1 H, s, 4-H); $[\alpha]_D$ +167.2° (*c* 0.40, $CHCl_3$). Anal. Calcd for $C_{20}H_{25}O_2N$: C, 77.14; H, 8.09; N, 4.50. Found: C, 76.96; H, 8.25; N, 4.23.

17β-Cyano-16α,17α-epoxy-5α-androstan-3-one (8). Oxidation of compound **6** with a 8 N $CrCO_3$ solution similarly as above gave **8** (65%): mp 180–181 °C (colorless needles, from MeOH); IR 2200 (CN), 1690 (C=O) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.97 (3 H, s, 18-Me), 1.03 (3 H, s, 19-Me), 3.80 (1 H, s, 16β-H); $[\alpha]_D$ +73.3° (*c* 0.43, $CHCl_3$). Anal. Calcd for $C_{20}H_{27}O_2N$: C, 76.64; H, 8.68; N, 4.47. Found: C, 76.37; H, 8.94; N, 4.12.

17β-Cyano-16α,17α-epoxy-1,3,5(10)-estratrien-3-ol (9). In a similar manner as described in the synthesis of compound **5**, 16α-bromo-3-hydroxy-1,3,5(10)-estratrien-17-one (**5**)[1c] gave **10** (61%): mp 212–216 °C (colorless needles, from ether); IR 3400 (OH), 2245 (C=O) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.00 (3 H, s, 18-Me), 3.97 (1 H, s, 16β-H), 6.67–7.23 (3 H, m, aromatic proton); $[\alpha]_D$ +24.4° (*c* 2.0, $CHCl_3$). Anal. Calcd for $C_{19}H_{21}O_2N$: C, 77.26; H, 7.17; N, 4.74. Found: C, 77.21; H, 7.22; N, 4.70.

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Registry No. **1**, 1093-91-0; **1-*16-d***, 100702-72-5; **2**, 74644-60-3; **2-*16-d***, 100702-73-6; **3**, 28507-02-0; **4**, 71765-95-2; **5**, 100702-67-8; [16β-^{2}H]-**5**, 100702-74-7; **6**, 100702-68-9; **7**, 100702-69-0; **8**, 100702-70-3; **9**, 100702-71-4.

Efficient Conversion of (1*R*,5*R*)-(+)-α-Pinene to (1*S*,5*R*)-(−)-Nopinone

Pierre Lavallée*[1] and Gilles Bouthillier

Department of Chemistry, Université de Sherbrooke, Sherbrooke, Québec, Canada J1K 2R1

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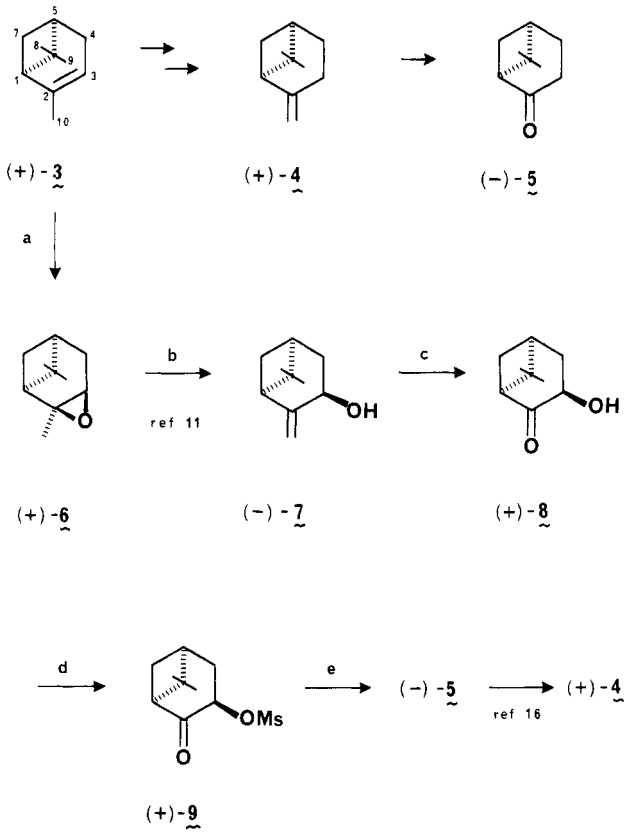
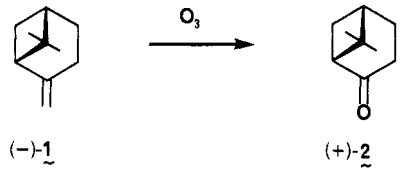
In connection with synthetic investigations in this laboratory, (1*R*,5*S*)-(+)- and (1*S*,5*R*)-(−)-nopinone were required as chiral starting materials. Since (1*S*,5*S*)-(−)-β-pinene (**1**) of high optical purity is available commercially,

Scheme I[a]



[a] Reagents and conditions: (a) *m*-CPBA, CH_2Cl_2, 0 °C, 93%. (b) Et_2NLi, Et_2O, reflux, 6–10 h, 95%. (c) 1°, O_3, MeOH, −78 °C; 2°, Me_2S, 100%. (d) MsCl, Et_3N, CH_2Cl_2, 0 °C, 91% crude. (e) $CrCl_2$, aqueous HCl–acetone, 1 h, 25 °C, CO_2 atm, 89%.

(1*R*,5*S*)-(+)-nopinone (**2**) is readily accessible by simple ozonolysis according to several procedures.[2]



Unfortunately, the enantiomer (1*R*,5*R*)-(+)-β-pinene (**4**) is scarcely produced by nature[3] and the acid, base, or neutral interconversion between α and β forms is in favor of the thermodynamically more stable α-pinene.[4,5] However, stepwise interconversions of (1*R*,5*R*)-(+)-α-pinene (**3**) to (+)-β-pinene (**4**) (Scheme I) have been reported with low to modest efficiency. A four-step sequence[6a] provided

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(+)-4 (80% optical purity) in 25% corrected overall yield. Cao et al.[6b] have also reported a two-step conversion (40–42% yield) of (1S,5S)-(−)-α-pinene to (−)-1, and after our work was completed, a two-step isomerization of (+)-3 to (+)-4 (50% yield, 65% optical purity) via an allylstannane intermediate was also communicated.[6c] Processes involving the thermal isomerization of hydroborated (+)-α-pinene (3) followed by displacement with a high-boiling olefin are known,[7] the latest report using 9-BBN[7d] gave (+)-4 in 51% overall yield (86% optical purity) after purification on silver nitrate impregnated silica gel. High optical purity (+)-β-pinene has also been obtained in two steps (6% yield) from (+)-10-camphenesulfonyl chloride.[8] Finally, nopinone has been prepared from camphor by two related seven-step sequences,[9a] but in low overall yield and from myrtenal[9b] (no optical rotation given). Few of these approaches seemed ideal for a convenient and preparative access to substantial quantities of (−)-nopinone 5.

Based on reports by Schultz et al.[10] that α-keto mesylates can be reduced efficiently to the parent ketone, we have developed the following five-step sequence for the conversion of commercially available (1R,5R)-(+)-α-pinene (3) to (1S,5R)-(−)-nopinone (5) (Scheme I). Following the excellent procedure for the base-induced rearrangement of epoxides described by Crandall et al.[11], (−)-*trans*-pinocarveol (7) was obtained very efficiently[12] (88% yield) from (+)-α-pinene (3) (91 ± 1% ee) via (+)-2,3-epoxypinane (6). Considering that the mesylate derived from 7 would be extremely prone to allylic (S_N2') displacement by various nucleophilic species to give back the α-pinene skeleton, the exocyclic methylene of 7 was first cleaved with ozone in methanol followed by the dimethyl sulfide workup[13] to give the low-melting and relatively unstable α-hydroxy ketone (+)-8 (quantitative). Mesylation (MsCl, Et_3N)[14] of crude (+)-8 afforded the crystalline α-keto mesylate (+)-9 (91% crude). Finally, the reduction of crude (+)-9 using an excess of chromous chloride[10] prepared in situ provided (−)-nopinone 5 (≥99% chemically pure by GLC) in 60% overall yield from (−)-7 after a simple vacuum distillation. Redistilled (1S,5R)-(−)-nopinone had $[\alpha]^{22}_D$ −16.6 ± 0.2° (neat) and $[\alpha]^{22}_D$ −35.7 ± 0.3° (*c* 4, MeOH), indicating 89.5% optical purity when compared to the evaluated optimum rotation value [$[\alpha]^{22}_D$ +39.9 ± 0.3° (*c* 4, MeOH)] for optically pure nopinone.[2a,d]

The efficient five-step sequence described here could be considered the first practical entry to high optical purity (1S,5R)-(−)-nopinone.[15] Its preparation can easily be scaled up to 50–100 g with an overall isolated yield of 53% from (+)-α-pinene, and without any special purification step being required all along the sequence. Furthermore, it also provides for a formal conversion of (+)-α-pinene to (+)-β-pinene since β-pinene has already been obtained from nopinone[16] (i.e., 5 + Ph_3PCH_2 → 4).

Experimental Section

General Methods. Melting points are uncorrected. Infrared spectra were recorded on a Perkin-Elmer Model 781 instrument. ^1H NMR spectra were recorded at 80 or 250 MHz and ^{13}C NMR spectra (BB, CW, and/or INEPT) at 62.9 MHz on Bruker instruments, and in $CDCl_3$ solutions. Chemical shifts are reported in δ units from Me_4Si as internal reference. Mass spectra were obtained on a ZAB-1F (medium-resolution) instrument. Optical rotations were measured in a thermostated 1-dm cell of 1-mL capacity on a Perkin-Elmer Model 141-B polarimeter. Ozonolysis reactions were carried out with a dilute concentration of ozone in oxygen, generated from a Welsbach ozonator. Capillary GLC analysis were performed on a Perkin-Elmer Model 8320 chromatograph equipped with a Durabond 1703 (30-m) column. Analytical TLC was performed with 0.25-mm-thickness precoated TLC plates and R_f determined by using 5 × 20 cm^2 plates and equilibrated solvent chamber. Column chromatography refers to the flash technique,[17] and E. Merck silica gel (230–400 mesh) was used. Spots were visualized under UV light, with iodine (by *dipping* into I_2-impregnated silica gel) and/or by spraying with an ethanolic solution of 30% H_2SO_4 or 10% phosphomolybdic acid. Reactants were of reagent grade, common solvents were distilled before use, and anhydrous solvents were obtained by distillation from the appropriate drying agent.[18] All manipulations of moisture-air-sensitive solvents and reagents and anhydrous reactions were conducted under a positive pressure (mercury bubbler) of argon using a double manifold (vacuum argon) as described or adapted from ref 19. All glassware, syringes, and needles were oven dried (130 °C) prior to use. Elemental analysis were performed by H. Séguin, National Research Council, Ottawa.

(1*S*,2*S*,3*R*,5*S*)-(+)-*trans*-2,3-Epoxypinane [(+)-6]. Prepared in 93% isolated yield from 138 g (1 mol) of (1R,5R)-(+)-α-pinene [(+)-3] [Aldrich, 98%, $[\alpha]^{22}_D$ +47° (neat), $[\alpha]^{25}_D$ +49.6° (*c*, 2, absolute EtOH), 91 ± 1% optical purity[20]] according to a literature procedure[11a] using *m*-CPBA as epoxidizing agent: bp 59–62 °C (10 mm); R_f 0.26 (benzene); $[\alpha]^{25}_D$ +100° (neat); $[\alpha]^{25}_D$ +96.24° (*c* 5, absolute EtOH); [lit.[22] bp 82 °C (20 mm); $[\alpha]^{28}_D$ −106.1° (neat), from the autooxidation of (1S,5S)-(−)-pinene; $[\alpha]^{27}_D$ −47.4° (neat)]; [lit.[23] bp 71–71.5 °C (12 mm); $[\alpha]^{20}_D$ +76.92° (neat), from (+)-3].

(1*R*,3*R*,5*S*)-(−)-*trans*-3-Hydroxypin-2(10)-ene [(−)-*trans*-Pinocarveol, (−)-7]. This compound was prepared from (+)-6 in 95% isolated yield on 50-g scale according to the procedure of Crandall:[11a] bp 90–95 °C (8 mm) as a colorless liquid; GLC

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analysis indicated ≥95% purity (R_t = 3.7 min; column temperature, 80–150 °C in 10 min); R_f 0.30 (5% EtOAc–hexanes); $[\alpha]^{25}_D$ −62.52° (neat); $[\alpha]^{25}_D$ −71.17° (*c* 3, absolute EtOH); [lit.[22] (+)-**7**, $[\alpha]_D$ +70.8° (*c* 3, EtOH); lit.[24a] (−)-**7** from (+)-**3**, $[\alpha]^{20}_D$ −62.6° (neat); lit.[24b] (−)-**7**, $[\alpha]_D$ −72° (neat)]. 3,5-Dinitrobenzoate derivative: mp 123–124 °C (from petroleum ether, 30–60 °C), $[\alpha]^{22}_D$ −30.7° (*c* 2, $CHCl_3$); [lit.[24a] mp 126–126.5 °C, $[\alpha]^{20}_D$ −29.4° (*c* 2, $CHCl_3$)].

(1*S*,3*R*,5*S*)-(+)-*trans*-3-Hydroxynorpinan-2-one [(+)-*trans*-3-Hydroxynopinone, (+)-8]. A solution of (−)-**7** (45 g, 0.3 mol) in 600 mL of dry MeOH[25] was treated with ozone at −78 °C until a characteristic blue color was obtained (ca. 8 h). Excess O_3 was flushed with oxygen and then argon, 100 mL (5 equiv) of Me_2S[13] was added, and the mixture was allowed to warm to 25 °C while stirring. *Caution*![27] After 5 h, a peroxide test (KI–starch *wet* paper and/or acidic aqueous KI) was found negative. The solvent was then evaporated under reduced pressure, the oily residue dissolved in CH_2Cl_2 (300 mL), and the solution washed successively with 10% $NaHSO_3$, saturated $NaHCO_3$, and saturated NaCl solutions (75 mL each). Drying (anhydrous $MgSO_4$) and concentration in vacuo afforded 45.8 g (quantitative yield) of (+)-**8**: GLC analysis indicated ≥90% homogeneity and suitability for use in the next step. Column chromatography of a sample using 10% EtOAc–CH_2Cl_2 as eluant (R_f 0.24) provided analytical material: mp 39–42 °C [recrystallized twice from petroleum ether (30–60 °C)]; $[\alpha]^{25}_D$ +67° (*c* 10, $CHCl_3$), $[\alpha]^{25}_D$ +29.1° (*c* 4, MeOH); IR (CH_2Cl_2) ν_{max} 3562, 3490 (OH), 1712 (C=O) cm^{-1}; ^1H NMR (250 MHz) δ 0.9, 1.36 (2 s, 6 H, 2 Me), 1.6 (m, 1 H, H-7′), 1.9 (ddd, 1 H, J_{gem} = 14 Hz, $J_{3,4'}$ = 3 Hz, $J_{4',5}$ = 2 Hz, H-4′), 2.27 (m, 1 H, H-5), 2.65 (dddd, 1 H, J_{gem} = 14 Hz, $J_{4,3}$ = 10 Hz, $J_{4,5}$ = $J_{4,7}$ = 2.5 Hz, H-4), 2.7 (m, 1 H, H-1), 2.74 (m, 1 H, H-7), 2.97 (d, 1 H, J = 2 Hz, OH, exchanges with D_2O), 4.18 (ddd, 1 H, $J_{3,OH}$ = 2 Hz, J_{vic} = 3, 10 Hz, H-3). ^{13}C NMR δ 23 (q, C_9), 25.9 (q, C_8), 27.6 (t, C_7), 32.4 (t, C_4), 40.5 (s, C_6), 40.6 (d, C_5), 57.5 (d, C_1), 69.1 (d, C_3), 213.6 (s, C_2); MS, *m/e* 154 (M^+), 139 (M^+ − Me), 136 (M^+ − H_2O), 121 (M^+ − Me − H_2O); exact mass for $C_9H_{14}O_2$ (M^+), Calcd 154.0994, found 154.0997. 3,5-Dinitrobenzoate derivative: mp 133–134 °C (MeOH); $[\alpha]^{22}_D$ +47.0° (*c* 2, $CHCl_3$). Anal. Calcd for $C_{16}H_{16}O_7N_2$: C, 55.17; H, 4.63; N, 8.04. Found: C, 55.01; H, 4.58; N, 7.95.

(1*S*,3*R*,5*S*)-(+)-*trans*-3-Hydroxy-3-*O*-(methanesulfonyl)norpinan-2-one [(+)-9]. To a cold (ice bath) solution of crude α-hydroxy ketone **8** (45.5 g, 0.29 mol) and dry Et_3N (45.5 g, 0.45 mol, 1.5 equiv, 63 mL) in 500 mL of dry CH_2Cl_2 were added dropwise 29 mL of methanesulfonyl chloride[14] (distilled from P_2O_5; 42.4 g, 0.37 mol, 1.25 equiv), and the mixture was allowed to stir for 2 h at 0–5 °C before it was quenched by the addition of water (100 mL) and saturated NH_4Cl (100 mL). The layers were separated, and the organic phase was washed successively with 10% citric acid, saturated $NaHCO_3$, and saturated NaCl aqueous solutions (75 mL each). After drying (anhydrous $MgSO_4$) and concentration in vacuo, 62.6 g (91%) of crude mesylate **9** was isolated as a yellow oil (≥80% homogeneous by GLC), which crystallized upon trituration with hexanes. A sample obtained from a different experiment was purified by column chromatography[28] (3% EtOAc–15% hexanes in CH_2Cl_2, R_f 0.26) to provide analytical material that was recrystallized twice from hexane, affording (+)-**9** as white needles: mp 82–83 °C; $[\alpha]^{25}_D$ +50.5° (*c* 3.5, $CHCl_3$); $[\alpha]^{25}_D$ +50.45° (*c* 4, MeOH); IR ($CHCl_3$) ν_{max} 1728 (C=O), 1360, 1176 (S=O) cm^{-1}; ^1H NMR (250 MHz) δ 0.89, 1.38 (2 s, 6 H, 2 Me), 1.70 (m, H-7′), 2.22 (m, 1 H, H-4′), 2.30 (m, 1 H, H-5), 2.65–2.77 (m, 3 H, H-1, H-4, H-7), 3.19 (s, 3 H, $MeSO_3$), 4.98 (dd, J_{vic} = 3 and 9 Hz, H-3). ^{13}C NMR δ 22.9 (q, C_9), 25.6 (q, C_8), 26.3 (t, C_7), 32.3 (t, C_4), 38.7 (q, $MeSO_3$), 39.7 (d, C_5), 41.0 (s, C_6), 57.5 (d, C_1), 76.2 (d, C_3), 205.7 (s, C_2); MS, *m/e* 233 (MH^+), 232 (M^+), 204 (M^+ − CO); exact mass for $C_{10}H_{16}O_4SH$ (MH^+), calcd 233.0847, found 233.0841. Anal. Calcd for $C_{10}H_{16}O_4S$: C, 51.71; H, 6.94; S, 13.80. Found: C, 51.98; H, 7.06; S, 13.67.

(1*S*,5*R*)-(−)-Nopinone [(−)-Norpinan-2-one, (−)-9]. **A.** A fresh solution of chromous chloride ($Cr^{II}Cl_2$) was prepared as follows according to the procedure of Djerassi et al.[29] and kept under a CO_2 atmosphere. A 5-L, three-neck flask equipped with a *mechanical* stirrer was charged with zinc powder (905 g, 13.8 mol), water (910 mL), and concentrated HCl (47 mL) followed, while stirring, by mercuric chloride (74 g, 0.27 mol) (EXOTHERMIC). After 15 min, the mixture was allowed to settle; the supernatant solution was decanted and discarded. Then, water (1820 mL) followed by concentrated HCl (180 mL) was added while stirring under a CO_2 atmosphere (constant bubbling *through* the solution *is* required). Solid chromic chloride ($CrCl_3 \cdot 6H_2O$; 456 g, 1.7 mol, 6.7 equiv)[30] was then added portionwise over 30 min to give a deep blue solution of chromous chloride (ca. 2 L).

B. Reduction of the α-keto mesylate **9** was achieved as follows: To a solution of crude (+)-**9** (61 g, 0.26 mol) in 1800 mL of acetone was added via cannula 1825 mL of the stock chromous chloride solution (ca. 6 equiv[30]). After 1 h at 25 °C, a large excess of acetone was removed under reduced pressure (i.e., until 60–65 mm were reached), and the combined aqueous distillate *and* residue were extracted with CH_2Cl_2 (3 × 500 mL). The combined organic phases were washed with saturated $NaHCO_3$ and brine solutions (300 mL each), dried (anh $MgSO_4$), and concentrated in vacuo to give 40.7 g (112%) of crude (−)-nopinone. Distillation using a short-path distillation head and a 12-cm Vigreux column gave 24.3 g [67% yield from crude **9**[31], 60% overall yield from starting pure (−)-**7**, and 53% overall yield from (+)-α-pinene] of (−)-nopinone (**5**): bp 50–52 °C (0.4 mm); ≥99% homogeneous by GLC [R_t 4.63 min; column temperature, 130 °C]; $[\alpha]^{25}_D$ −16.72° (neat); $[\alpha]^{22}_D$ −34.3° (*c* 4, MeOH). A sample of crude nopinone was purified by column chromatography with 25% EtOAc in hexanes as eluent (R_f 0.37) and distilled as mentioned above, affording analytical material: $[\alpha]^{25}_D$ −16.6° (neat); $[\alpha]^{22}_D$ −35.7° (*c* 4, MeOH); [lit.[2a] measured values: $[\alpha]^{22}_D$ +39.0° and 39.5° (*c* 4, MeOH); evaluated optimum rotation value: $[\alpha]^{22}_D$ +39.9 ± 0.3° (*c* 4, MeOH)]; IR ($CHCl_3$) ν_{max} 1712 cm^{-1} (C=O). The (−)-nopinone prepared by this procedure was identical in all respects (IR, TLC, GLC) with an authentic sample of (+)-nopinone obtained from (−)-β-pinene[2a] and by comparison with literature data: ^1H NMR[32a,b] and ^{13}C NMR.[32c] Anal. Calcd for $C_9H_{14}O$: C, 78.21;

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(25) On a different run, ozonolysis was conducted in anhydrous CH_2Cl_2 under identical conditions, and we observed that the decomposition of the ozonide by Me_2S took much longer time than in MeOH. In addition, the isolated crude product was contaminated with two unidentified side products. Further chemical transformation of this crude product (i.e., **8** → **9** → **5**) provided only 36% yield of (−)-nopinone after distillation (99% pure by GLC). For further information and discussion concerning the effects of the nature of the solvent (participating/nonparticipating; polar/nonpolar) on the structure and distribution of the products obtained in the course of the ozonolysis of olefins, see ref 26.

(26) Bailey, P. S. "Ozonation in Organic Chemistry"; Academic Press: New York, 1978; Vol. 1.

(27) The use of the dimethyl sulfide workup following the ozonolysis of (−)-β-pinene (80-g scale) has been reported to lead to *a serious explosion* on distillation of the product: McCreary, M. D.; Lewis, D. W.; Wernick, D. L.; Whitesides, G. M. *J. Am. Chem. Soc.* **1974**, *96*, 1038–1054, see ref 50 cited therein. Furthermore, stable and crystalline diperoxides of nopinone have been isolated from ozonolysis of β-pinene in *chloroform*: Overton, K. H.; Owen, P. *J. Chem. Soc., Perkin Trans. 1* **1973**, 226–227. We have also observed that when only 1–2 equiv of Me_2S are used (as recommended in the original work[13]) to destroy the ozonides and peroxides *of sterically hindered olefins* in nonpolar (see ref 25) as well as polar solvents (MeOH in this case) extended periods of time were required to produce a negative peroxide test (up to *70 h*) *compare to generally 5–10 h when 5–6 equiv of Me_2S was used.* We, and others,[2a] have experienced the Me_2S workup quite safely *but stress that a test for peroxides content should always be performed before concentrating and/or heating a crude solution after ozonolysis.*

(28) Attempted sublimation of the crude keto mesylate **9** under high vacuum produced extensive decomposition. Otherwise, this compound is quite stable when stored at 0–5 °C.

(29) Rosenkranz, G.; Mancera, O.; Gatica, J.; Djerassi, C. *J. Am. Chem. Soc.* **1950**, *72*, 4077–4080.

(30) Based on several runs conducted on a smaller scale, only 6 equiv of chromous chloride were found to be required for efficient and complete reduction of **9**, compared with ca. 8:1 and 35:1 Cr^{II} to substrate ratios used in ref 29 and 10a, respectively.

(31) A similar experiment conducted with 10 g of purified α-keto mesylate (+)-**9** provided 5.24g (88% yield) of ≥97% pure (−)-nopinone **5** after distillation.

(32) (a) Abraham, R. J.; Bottom, F. H.; Cooper, M. A.; Salmon, J. R.; Whittaker, D. *Org. Magn. Res.* **1969**, *1*, 51–56. (b) Edgar, M. T.; Barth, G.; Djerassi, C. *J. Org. Chem.* **1980**, *45*, 2680–2684. (c) Coxon, J. M.; Hydes, G. J.; Steel, P. J. *J. Chem. Soc., Perkin Trans. 2* **1984**, 1351–1355. Standard pinane numbering (see ref 5 and comments in ref 32c) has been used for the description of the chemical shifts reported in this work.

H, 10.21. Found: C, 78.04; H, 10.13.

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Cobalt(III)-Catalyzed Trifluoroacetoxylation of Benzene

Robert DiCosimo* and Hsiao-Chiung Szabo

Corporate Research, The Standard Oil Company, Cleveland, Ohio 44128

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The one-step oxidation of benzene directly to phenol has been the subject of much study. Hydroxylations have been performed using vanadium(V) peroxo complexes,[1] irradiation of powdered titanium dioxide,[2] aerial oxidation in the presence of Cu(I),[3] H_2O_2 in HF/BF_3,[4] Ni(II)–O_2 macrocyclic polyamine complexes,[5] and electroreduction of O_2 in the presence of Fe(II),[6] i),[6] $S_2O_8^{2-}$/Fe(II)/Cu(II),[7] Fenton's reagent (Fe(II)/H_2O_2),[8] and other Fe-based hydroxylation catalysts.[9] Further oxidation of the phenol product under these reaction conditions is often responsible for the low to moderate yields of phenol obtained, and the systems that generate hydroxyl radicals often also produce biphenyl as a byproduct. An alternate approach to that of hydroxylation is the acetoxylation or trifluoroacetoxylation of benzene, followed by hydrolysis; Co(III), Pb(IV), Mn(III), Ce(IV), Cu(II), and Tl(III) have been used as stoichiometric oxidants,[10] and Pd(II) and Ag(II) have been employed either stoichiometrically or as catalysts where product yields based on benzene reacted or oxidant consumed have been only fair.[10,11] We now report the production of phenol via the reaction of benzene and a peroxide or peracid oxidant (vide infra) with a cobalt(III) catalyst in trifluoroacetic acid/trifluoroacetic anhydride to produce phenyl trifluoroacetate; hydrolysis of this product yields phenol and solvent trifluoroacetic acid quantitatively.

Kochi and co-workers have previously reported the stoichiometric oxidation of benzene with cobalt(III) trifluoroacetate in trifluoroacetic acid/trifluoroacetic anhydride to produce phenyl trifluoroacetate (eq 1).[12] The

$$C_6H_6 + 2Co^{III}(O_2CCF_3)_3 \rightarrow C_6H_5O_2CCF_3 + 2Co^{II}(O_2CCF_3)_2 + CF_3CO_2H \quad (1)$$

yield of product was almost quantitative when the molar ratio of Co(III) to benzene was approximately 2. The reaction was proposed to proceed by a reversible one-electron transfer from benzene to Co(III) to produce a benzene radical cation, nucleophilic attack on the radical cation by solvent trifluoroacetic acid, and subsequent one-electron transfer to an additional 1 equiv of Co(III) to form phenyl trifluoroacetate. This mechanism was used to explain the high yields of product obtained, since the trifluoroacetate group deactivates phenyl trifluoroacetate toward oxidation by Co(III). The relative stability of the product to the strongly oxidizing reaction conditions prompted us to examine the possibility of using a peroxyacid or hydrogen peroxide as an oxidant to regenerate Co(III) from Co(II) for this same reaction (eq 2), eliminating the use of stoichiometric quantities of Co(III) trifluoroacetate.

$$ROOH + 2Co^{II}(O_2CCF_3)_2 + 2CF_3CO_2H \rightarrow ROH + 2Co^{III}(O_2CCF_3)_3 + H_2O \quad (2)$$

$$R = H, CF_3CO, CH_3CO$$

Results and Discussion

Table I lists representative examples of catalytic oxidations of benzene to phenyl trifluoroacetate using several different oxidants. Reactions were generally run in trifluoroacetic acid (TFA) containing 1–20% (v) trifluoroacetic anhydride (TFA-A), as it has been demonstrated that yields are higher under anhydrous conditions for stoichiometric oxidations of benzene by Co(III).[12] The highest product yields based on both converted benzene and added oxidant were obtained with trifluoroperacetic acid, which is readily prepared from hydrogen peroxide and trifluoroacetic anhydride in either dichloromethane[13] or trifluoroacetic acid. The presence of dichloromethane does not interfere with the course of the reaction; using either 10% (v) TFA-A in TFA or a 1:1 mixture of CH_2Cl_2 and 10% TFA-A in TFA as solvent for the stoichiometric oxidation of benzene by 2 equiv of cobalt(III) trifluoroacetate resulted in a 97% yield of phenyl trifluoroacetate.

Slow addition of the oxidant, either by the addition of aliquots of the oxidant sufficient to reoxidize the catalyst or by continuously adding the oxidant by syringe pump, resulted in higher product yields when using catalytic amounts of cobalt(II) acetate. For example, when 10 equiv (relative to cobalt) of trifluoroperacetic acid was added by syringe pump to a TFA/TFA-A solution 0.02 M in Co(II) and 0.1 M in benzene over a period of 20 h (Table I, entry 2), phenyl trifluoroacetate was produced in 96% yield based on benzene reacted, and oxidant selectivity was 70%; when this same reaction was repeated and all the oxidant was added at the start of the reaction, the product selectivity was only 3% at similar conversions and oxidant

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