gave 0.252 g of the nitrone as a white crystalline solid. IR (KBr, cm^{-1}): 1590, 1585, 1500, 1460, 1455, 1385, 1355, 1320, 1315, 1302, 1215, 1202, 1155, 1030, 950, 760, 750, 715, 695, 580. ^1H NMR: δ 5.06 (s, 2 H, $CH_2C_6H_5$), 7.35–7.53 (m, 9 H, aromatic and vinyl protons), 8.16–8.26 (m, 2 H, aromatic). ^{13}C NMR: δ 71.22, 128.42, 128.57, 128.95, 129.21, 130.35, 130.44, 133.16, 134.23.

***N*-[(4-Chlorophenyl)methylene]benzenamine *N*-Oxide.** Oxidation of 0.236 g of phenyl(4-chlorobenzyl)amine and removal of the solvent gave a pale yellow microcrystalline solid. Recrystallization of this solid from ethyl acetate–petroleum ether gave 0.244 g of cream-colored, shiny needles. IR (KBr, cm^{-1}): 3065, 1595, 1572, 1555, 1490, 1460, 1408, 1390, 1305, 1290, 1200 (NO), 1178, 1098, 1078, 1020, 920, 900, 848, 820, 770, 710, 702, 692, 532, 510. ^1H NMR: δ 7.43–7.55 (m, 6 H, aromatic), 7.74–7.82 (m, 2 H, aromatic), 7.93 (s, 1 H, CH=N), 8.36–8.46 (m, 2 H, aromatic). ^{13}C NMR: δ 121.67, 128.57, 128.95, 129.08, 129.85, 130.58, 134.52, 149.0. Mass spectrum (EI, 70 eV): m/z 231 (M^+, 11), 91 (base peak).

***N*-(Phenylmethylene)tricyclo[3.3.1.1^{3,7}]decan-1-amine *N*-Oxide.** Oxidation of 0.437 g of (1-adamantyl)benzylamine and removal of the solvent gave a white, flaky solid that was homogeneous in TLC analysis. This solid was dissolved in CH_2Cl_2, the solution was dried with anhydrous Na_2SO_4, and the solvent was evaporated to give 0.456 g of the white, flaky nitrone. IR (KBr, cm^{-1}): 1578, 1558 (C=N), 1545, 1445, 1415, 1350, 1312, 1190, 1140, 1115, 1058, 930, 800, 748, 695, 580, 510. ^1H NMR: δ 1.6–2.5 (m, 15 H, adamantane ring H), 7.41 (m, 3 H, aromatic), 7.48 (s, 1 H, CH=N), 8.30 (m, 2 H, aromatic). ^{13}C NMR: δ 29.71 (C-3,5,7), 35.96 (C-4,6,10), 40.87 (C-2,8,9), 70.74 (C-1), 128.37, 128.83, 129.51, 129.97, 130.98 (CH=N). Mass spectrum (EI, 70 eV): m/z 256 (M + 1), 255 (M^+), 135 (base peak). Calcd for $C_{17}H_{21}NO$: 255.34.

***N*,*N*′-1,2-Ethanediylidenebis(benzenamine) *N*,*N*′-Dioxide.** The general procedure was followed using 0.172 g of *N*-methylaniline. The reaction mixture turned yellow immediately upon addition of the solution of 1. After 5 min the reaction solution had turned dark orange. Removal of the solvent gave a dark orange crystalline solid (0.188 g). This solid was recrystallized from ethanol–petroleum ether to give orange needles. The needles were filtered off, washed with petroleum ether, and dried (0.110 g, 57% yield). IR (KBr, cm^{-1}): 3140, 3055, 1590, 1505, 1470, 1405, 1335, 1300, 1185, 1090, 1025, 1002, 815, 793, 772, 695, 660, 640, 635. ^1H NMR: δ 7.45–7.55 (m, 2 × 3 H, aromatic), 7.80–7.88 (m, 2 × 2 H, aromatic), 8.65 (s, 2 × 1 H, N=CHCH=N). ^{13}C NMR: δ 121.13, 128.04, 129.27, 130.94, 147.08. Mass spectrum (EI, 70 eV): 240 (M^+, 33), 242 (M + 2, 2), 241 (M + 1, 6).

***N*-[(4-Fluorophenyl)methylene]-2-methyl-2-propanamine *N*-Oxide.** Oxidation of 0.398 g of *tert*-butyl(4-fluorobenzyl)amine and removal of the solvent gave a white crystalline solid that was homogeneous in TLC analysis. The solid was dissolved in hexane and dried with anhydrous Na_2SO_4. Evaporation of the solvent gave 0.421 g of white needles. IR (KBr, cm^{-1}): 1605, 1595, 1565 (C=N), 1505, 1420, 1395, 1365, 1312, 1298, 1225, 1195, 1162, 1125, 1100, 1020, 915, 845, 815, 765, 715, 668, 525. ^1H NMR: δ 1.61 (s, 9 H, $C(CH_3)_3$), 7.10 (t, 2 H, J = 8.79 Hz, aromatic), 7.53 (s, 1 H, CH=N), 8.34 (dd, 2 H, J = 9.04, 9.03 Hz, aromatic). ^{13}C NMR: δ 28.23 ($C(CH_3)_3$), 70.70 ($C(CH_3)_3$), 115.42 (d, $^2J_{C-F}$ = 21.5 Hz, C-3), 127.37 (d, $^4J_{C-F}$ = 3.3 Hz, C-1), 128.70 (CH=N), 130.89 (d, $^3J_{C-F}$ = 8.0 Hz, C-2), 163.11 (d, $^1J_{C-F}$ = 251.4 Hz, C-4). Mass spectrum (EI, 70 eV): m/z 196 (M + 1, 1.5), 195 (M^+, 12.5), 57 (base peak).

Anal. Calcd for $C_{11}H_{14}FNO$: C, 67.67; H, 7.22; N, 7.17. Found: C, 67.92; H, 7.34; N, 7.25.

***N*-[(Methylphenyl)methylene]-2-methyl-2-propanamine *N*-Oxide.** Oxidation of 0.358 g of *tert*-butyl(4-methylbenzyl)-amine and removal of the solvent gave a colorless, viscous liquid that was homogeneous in TLC analysis. The liquid was dissolved in CH_2Cl_2 and the solution was dried with anhydrous Na_2SO_4. Evaporation of the solvent on the rotary evaporator gave a colorless, viscous liquid that solidified upon addition of hexane. The solid obtained (0.328 g) was recrystallized from hexane to give white cubes. IR (KBr, cm^{-1}): 1605, 1568 (C=N), 1560, 1510, 1480, 1455, 1415, 1362, 1325, 1302, 1255, 1238, 1202, 1186, 1125, 1115, 910, 846, 718, 665, 642, 525. ^1H NMR: δ 1.60 (s, 9 H, $C(CH_3)_3$), 2.37 (s, 3 H, 4-CH_3), 7.22 (d, 2 H, J = Hz, aromatic), 7.50 (s, 1 H, CH=N), 8.19 (d, 2 H, J = 8.49 Hz, aromatic). ^{13}C NMR: δ 21.57 (4-CH_3), 28.26 ($C(CH_3)_3$), 70.38 ($C(CH_3)_3$), 128.27, 128.76, 129.06, 129.85, 140.44 (C-4). Mass spectrum (EI, 70 eV): m/z 192 (M + 1, 3), 191 (M^+, 26), 57 (base peak). Calcd for $C_{12}H_{17}NO$: 191.26.

***N*-[(4-(1,1-Dimethylethyl)phenyl)methylene]-2-methyl-2-propanamine *N*-Oxide.** Oxidation of 0.422 g of *tert*-butyl-(4-*tert*-butylbenzyl)amine and removal of the solvent gave a white crystalline solid that was homogeneous in TLC analysis. The solid was dissolved in hexane, the solution was dried with anhydrous Na_2SO_4, and the solvent was evaporated to give 0.445 g of white needles. IR (KBr, cm^{-1}): 1610, 1578 (C=N), 1555, 1510, 1420, 1365, 1325, 1275, 1195, 1130, 1120, 1020, 915, 862, 565. ^1H NMR: δ 1.32 (s, 9 H, 4-$(CH_3)_3C$), 1.60 (s, 9 H, $NC(CH_3)_3$), 7.43 (d, 2 H, J = 8.68 Hz, aromatic), 7.51 (s, 1 H, CH=N), 8.22 (d, 2 H, J = 8.79 Hz, aromatic). ^{13}C NMR: δ 28.32 ($NC(CH_3)_3$), 31.11 (4-(C-$H_3)_3C$), 34.9 (4-$(CH_3)_3C$), 70.4 ($NC(CH_3)_3$), 125.31, 128.27, 128.63, 129.66, 153.52. Mass spectrum (EI, 70 eV): m/z 234 (M + 1, 3), (M^+, 17), 57 (base peak). Calcd for $C_{15}H_{23}NO$: 233.34.

Acknowledgment. This research was supported by the National Institute of Environmental Health Sciences through Grant No. ES01984. The varian XL-300 NMR spectrometer was purchased with support from the National Science Foundation.

Registry No. 1, 74087-85-7; *N*-(phenylmethylene)-2-methyl-2-propanamine *N*-oxide, 3376-24-7; *tert*-butylbenzylamine, 3378-72-1; *N*-[(4-chlorophenyl)methylene]-2-methyl-2-propanamine *N*-oxide, 40117-30-4; *tert*-butyl(4-chlorobenzyl)amine, 46234-01-9; *N*-[(4-methoxyphenyl)methylene]-2-methyl-2-propanamine *N*-oxide, 40117-28-0; *tert*-butyl(4-methoxybenzyl)amine, 22675-83-8; *N*-[(4-nitrophenyl)methylene]-2-methyl-2-propanamine *N*-oxide, 3585-88-4; *tert*-butyl(4-nitrobenzyl)amine, 3489-67-6; *N*-(phenylmethylene)benzenamine *N*-oxide, 1137-96-8; phenylbenzylamine, 103-32-2; *N*-(phenylmethylene)benzenemethanamine *N*-oxide, 3376-26-9; *N*,*N*-dibenzylhydroxylamine, 621-07-8; *N*-[(4-chlorophenyl)-methylene]benzenamine *N*-oxide, 5909-74-0; phenyl(4-chlorobenzyl)amine, 4750-61-2; *N*-(phenylmethylene)tricyclo-[3.3.1.1^{3,7}]decan-1-amine, 31463-28-2; (1-adamantyl)benzylamine, 3717-60-0; *N*,*N*′-1,2-ethanediylidenebis(benzenamine) *N*,*N*′-dioxide, 13532-81-5; *N*-methylaniline, 100-61-8; *N*-[(4-fluorophenyl)methylene]-2-methyl-2-propanamine *N*-oxide, 85623-70-7; *tert*-butyl (4-fluorobenzyl)amine, 125640-89-3; *N*-[(4-methylphenyl)methylene]-2-methyl-2-propanamine *N*-oxide, 40117-29-1; *tert*-butyl(4-methylbenzyl)amine, 55980-45-5; *N*-[(4-(1,1-dimethylethyl)phenyl)methylene]-2-methyl-2-propanamine *N*-oxide, 88888-33-9; *tert*-butyl(4-*tert*-butylbenzyl)amine, 125640-90-6; nitrosobenzene, 586-96-9.

Synthesis of Novel 6β,14-Epoxy-Bridged Opiates

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Received October 12, 1989

During the course of our research directed toward the development of selective opioid receptor antagonists, we discovered a novel opiate cyclization that makes the opiate C-ring rigid in a manner similar to the oripavines **1**.[1] These new compounds (**2a**, **2b**) have a 6,14β-epoxy linkage in place of the 6,14β-ethano bridge of Bently's[1] extremely potent thebaine-derived oripavines **1**. This was accomplished by an intramolecular ether-forming reaction of the relatively flexible C ring of 6α-(mesyloxy)opiates **4a** and **4b**, converting them into the rigid 1,4-epoxycyclohexane derivatives **2a** and **2b**.

(1) Bently, K. W.; Hardy, D. G. *Proc. Chem. Soc.* **1963**, 220.

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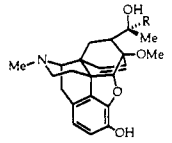


1, R = alkyl

Treatment of 6α-hydroxyopiates (**3a, 3b**)[2] with an excess of methanesulfonyl chloride in pyridine yielded the corresponding dimesylates (**4a, 4b**). Since the tertiary 14-hydroxyl group is not readily mesylated, and the secondary and phenolic hydroxyl groups reacted almost instantaneously, the preparation of **4a** and **4b** proceeded in high yield. The oxygen atom of the 14-hydroxyl group of **4** is in excellent position for intramolecular S_N2 displacement of the 6α-[(methylsulfonyl)oxy] group, yielding the 6,14β-epoxides **2**.[3] This ether-forming reaction may be favored over base-catalyzed E2 elimination due to the proximity and trajectory of the participating groups. No elimination products were detected in this clean "one-spot" reaction, despite the ability of the 14-alkoxide to function as an efficient intramolecular base for abstraction of the C-7β-hydrogen atom during enolization of related 6-keto systems.[4] This is consistent with evidence that the C ring of 6α-substituted opiates is in a boat conformation.[5] Moreover, the facility of the cyclization reaction may be promoted by participation of the neighboring basic nitrogen in removing the hydroxylic proton.[4]

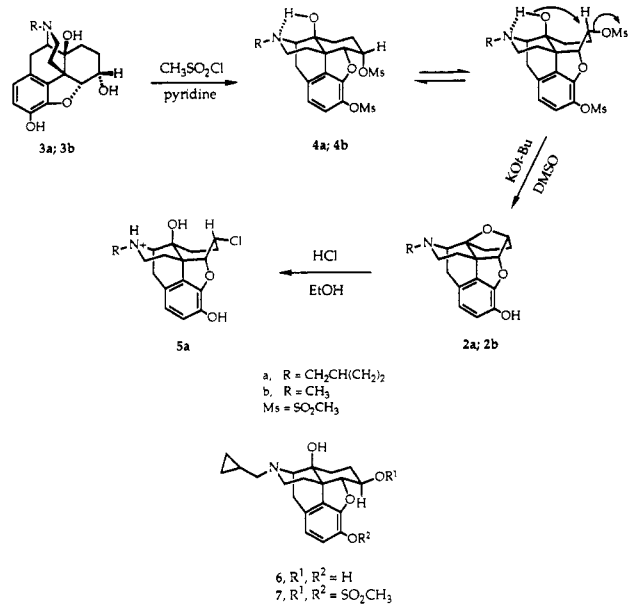
The C-6β isomers (**6** and **7**) also were readily prepared, but **7** would neither cyclize nor eliminate. Instead, nucleophilic attack at the sulfur atom of the mesylate **7** by *tert*-butoxide yielded **6**. The trajectory for S_N2 ether formation in **7** is clearly unfavorable. Also, apparently **7** is predominantly in the chair conformation,[5] lacking the requisite antiperiplanar hydrogen atom for E2 elimination.

As a consequence of the rigidity of these molecules, they exhibit a characteristic proton NMR peak at unusually high field. As shown in Figure 1, the C-8α proton is held directly over the aromatic ring. The ring current shields[6] this proton, thus its ^1H NMR signal is found at −0.2 ppm.

Despite the strain of this very rigid system, these molecules are quite stable, even in the presence of nonnucleophilic acids (e.g., refluxing methanolic H_2SO_4). However, in refluxing ethanolic HCl, the 6α-chloride **5a** is formed, possibly via chloride ion displacement of the protonated 6β,14-ether bridge, as the 6α-chloride was the only product detected.

Experimental Section

Dimethyl sulfoxide (DMSO) and pyridine were stored over 3-Å molecular sieves. Absolute ethanol was used as purchased. A rotary evaporator (bath temperature 40 °C) was used to remove solvents when evaporation is indicated. ^1H and ^{13}C NMR spectra were obtained on an IBM AC-300 spectrometer using $CDCl_3$ as solvent. Chemical shift data are reported with reference to the



a, R = $CH_2CH(CH_2)_2$
b, R = CH_3
Ms = SO_2CH_3

6, R^1, R^2 = H
7, R^1, R^2 = SO_2CH_3

$CHCl_3$ impurity in $CDCl_3$ (7.27 ppm) for ^1H and $CDCl_3$ (77.09 ppm) for ^{13}C spectra. Low and high resolution mass spectra were determined on an AEI MS-30 spectrometer. Merck silica gel 60 F-254 plates were used for preparative TLC.

17-Alkyl-3,6α-bis[(methylsulfonyl)oxy]-4,5α-epoxy-14-hydroxymorphinan (4). Methanesulfonyl chloride (0.90 mL, 11.6 mmol) was added to a stirred solution of α-naltrexol[2] (500 mg, 1.46 mmol) in dry pyridine (25 mL) at room temperature. After 10 min, the solution was evaporated and the residue was taken up in saturated aqueous $NaHCO_3$ (10 mL) and EtOAc (10 mL) and extracted with EtOAc (2 × 10 mL). The combined extract was washed with brine, dried (Na_2SO_4), and evaporated to yield 907 mg of a crude solid. This was chromatographed on a short column of silica gel (eluent EtOAc/EtOH/NH_4OH 94:5:1) to yield the title compound (693 mg, 95%). Compound **4b** was produced in 90% yield, using an identical procedure. ^1H NMR for **4a**: 7.05 (d, 1 H, J = 7.4 Hz), 6.69 (d, 1 H, J = 7.4 Hz), 5.21–5.13 (m, 1 H), 4.87 (d, 1 H, J = 5.4 Hz), 3.29 (s, 3 H), 3.19–3.07 (m, 2 H), 3.01 (s, 3 H), 2.75–2.57 (m, 2 H), 2.40–2.12 (m, 4 H), 2.01–1.90 (m, 1 H), 1.74–1.62 (m, 1 H), 1.60–1.49 (m, 4 H), 0.91–0.78 (m, 1 H), 0.60–0.51 (m, 2 H), 0.17–0.09 (m, 2 H). Mass spectrum (70 eV) for **4a**: m/z 499 (M^+), 420, 392, 324, 55.

17-Alkyl-4,5α:6β,14-diepoxy-3-hydroxymorphinan (2). Potassium *tert*-butoxide (20 mg, 0.18 mmol) was added to a stirred solution of **4a** (27 mg, 0.054 mmol) in dry DMSO (1 mL) at room temperature. The mixture was stirred for 24 h, poured into water (4 mL), and neutralized to pH 8 with 6 N HCl. The suspension was extracted with EtOAc (3 × 5 mL), and the combined extract was washed with water and brine, dried (Na_2SO_4), and evaporated. The residue was purified by preparative TLC (eluent EtOAc/EtOH/NH_4OH 94:5:1) to yield **2a** (13 mg, 74%). Compound **2b** was produced in 77% yield, using an identical procedure. ^1H NMR for **2a**: 6.72 (d, 1 H, J = 8.0 Hz), 6.54 (d, 1 H, J = 8.0 Hz), 4.99 (dd, 1 H, J = 4.8, 5.0 Hz), 4.66 (d, 1 H, J = 4.7 Hz), 3.79 (d, 1 H, J = 6.5 Hz), 3.38 (d, 1 H, J = 17.7 Hz), 2.90 (dd, 1 H, J = 5.2, 12.4 Hz), 2.72 (ddd, 1 H, J = 3.7, 13.0, 13.0 Hz), 2.60 (dd, 1 H, J = 5.9, 12.5 Hz), 2.47 (dd, 1 H, J = 4.5, 6.7 Hz), 2.41 (d, 1 H, J = 6.9 Hz), 2.22 (ddd, 1 H, J = 6.0, 13.2, 13.2 Hz), 1.75 (dd, 1 H, J = 2.5, 13.2 Hz), 1.65–1.41 (m, 2 H), 1.05 (ddd, 1 H, J = 5.2, 12.8, 12.8 Hz), 1.01–0.90 (m, 1 H), 0.59–0.47 (m, 2 H), 0.19–0.09 (m, 2 H), −0.11 to −0.23 (m, 1 H). ^{13}C NMR for **2a**: 149.04, 139.75, 134.95, 129.25, 122.48, 118.13, 92.12, 89.32, 86.47, 59.03, 57.25, 54.62, 42.73, 31.99, 31.69, 29.74, 21.31, 9.08, 4.37, 3.51. Mass spectrum (70 eV) for **2a**: m/z 325 (M^+), 282, 270, 254, 226, 161, 115, 77, 55. Exact mass calcd for $C_{20}H_{23}NO_3$ 325.1677, found 325.1674.

^1H NMR for **2b**: 6.70 (d, 1 H, J = 8.0 Hz), 6.52 (d, 1 H, J = 8.0 Hz), 4.96 (dd, 1 H, J = 4.5, 5.0 Hz), 4.62 (d, 1 H, J = 4.5 Hz), 3.44–3.38 (m, 2 H), 2.75–2.60 (m, 2 H), 2.45 (s, 3 H), 2.37 (d, 1 H, J = 6.8 Hz), 2.20 (ddd, 1 H, J = 3.8, 13.0, 13.0 Hz), 1.74 (dd, 1 H, J = 1.7, 13.0 Hz), 1.65–1.40 (m, 2 H), 1.01 (ddd, 1 H, J = 5.0, 13.3, 13.3 Hz), −0.11 to −0.23 (m, 1 H).

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(3) Compounds **2a** and **2b** were tested for activity in the mouse vas deferens (MVD) and the guinea pig illeum (GPI) preparations. Surprisingly, they had similar profiles despite the difference in cyclopropylmethyl and methyl substitution. They are both full agonists in the GPI. Compound **2a** was 4 times as potent as morphine, while **2b** was only one-tenth as potent as **2a**. In the MVD, both were inactive as agonists or antagonists.

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(6) See: Emsley, J. W.; Feeney, J.; Sutcliffe, L. H. *High Resolution Nuclear Magnetic Resonance Spectroscopy*; Pergamon: New York, 1975; Vol. 1.

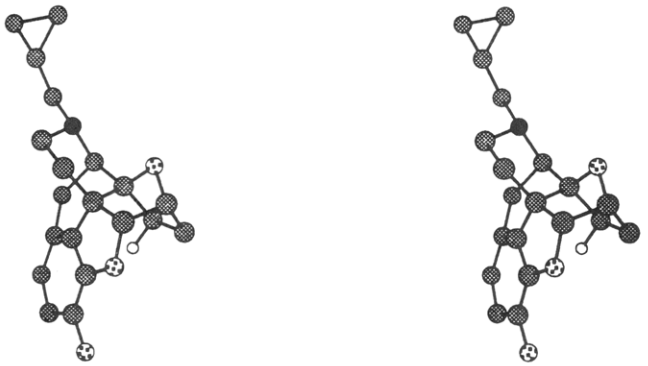

Figure 1. Stereoview of **2a** with the 7β-hydrogen atom shown eclipsed by the aromatic ring.

6α-Chloro-17-(cyclopropylmethyl)-3,14-dihydroxy-4,5α-epoxymorphinan (5a). To a stirred solution of **2a** (60 mg, 0.18 mmol) in ethanol (5 mL) at room temperature was added 5 drops of concentrated HCl. The mixture was heated to boiling, then cooled, and evaporated. Aqueous $NaHCO_3$ (5 mL) was added and the mixture was extracted with $CHCl_3$ (3 × 10 mL). The combined extract was dried (Na_2SO_4) and evaporated to a solid. The residue was purified by preparative TLC (eluent EtOAc/EtOH/NH_4OH 94:5:1) to yield 20 mg (31%) of the title compound and recovered **2a** (36 mg, 60%). ^1H NMR for **5a**: 6.73 (d, 1 H, J = 8.1 Hz), 6.57 (d, 1 H, J = 8.1 Hz), 4.69–4.60 (m, 2 H), 3.11 (d, 1 H, J = 6.8 Hz), 3.02 (d, 1 H, J = 18.1 Hz), 2.70–2.52 (m, 2 H), 2.43–2.20 (m, 4 H), 1.94–1.74 (m, 2 H), 1.60 (d, 1 H, J = 8.0 Hz), 1.50–1.38 (m, 2 H), 0.91–0.79 (m, 1 H), 0.59–0.50 (m, 2 H), 0.16–0.08 (m, 2 H). Mass spectrum (70 eV) for **5a**: m/z 361 (M^+), 326, 320, 306, 256, 229, 187, 110, 98, 84, 55, 28. Exact mass calcd for $C_{20}H_{24}NO_3Cl$ 361.1444, found 361.1438.

17-(Cyclopropylmethyl)-3,6β-bis[(methylsulfonyl)oxy]-4,5α-epoxy-14-hydroxymorphinan (7). Methanesulfonyl chloride (0.36 mL, 4.6 mmol) was added to a stirred solution of β-naltrexol[2] (200 mg, 0.58 mmol) in dry pyridine (5 mL) at room temperature. The solution rapidly changed color from colorless to deep blue to green to yellow to colorless over about 2 min. After 10 min, the solution was evaporated and the residue was taken up in saturated aqueous $NaHCO_3$ (10 mL) and EtOAc (10 mL) and extracted with EtOAc (2 × 10 mL). The combined extract was washed with brine, dried (Na_2SO_4), and evaporated to yield 300 mg of a crude solid. This solid was purified by preparative chromatography (eluent EtOAc/EtOH/NH_4OH 94:5:1) to yield the title compound (198 mg, 68%). ^1H NMR for **7**: 7.06 (d, 1 H, J = 7.4 Hz), 6.75 (d, 1 H, J = 7.4 Hz), 5.18–4.98 (m, 1 H), 4.76 (d, 1 H, J = 5.6 Hz), 4.43–4.34 (m, 1 H), 3.20 (s, 3 H), 3.24–3.01 (m, 2 H), 3.10 (s, 3 H), 2.71–2.54 (m, 2 H), 2.41–2.22 (m, 3 H), 2.10–1.90 (m, 2 H), 1.75–1.62 (m, 1 H), 1.60–1.40 (m, 3 H), 0.90–0.78 (m, 1 H), 0.61–0.50 (m, 2 H), 0.20–0.11 (m, 2 H).

Registry No. **2a**, 125902-95-6; **2b**, 125903-00-6; **3a**, 20410-98-4; **3b**, 2183-56-4; **4a**, 125902-96-7; **4b**, 125902-99-0; **5a**, 125902-97-8; **6**, 49625-89-0; **7**, 125902-98-9.

Synthetic Studies on Ingenol. Bridgehead Enolate Reactivity and ABC Ring Assembly

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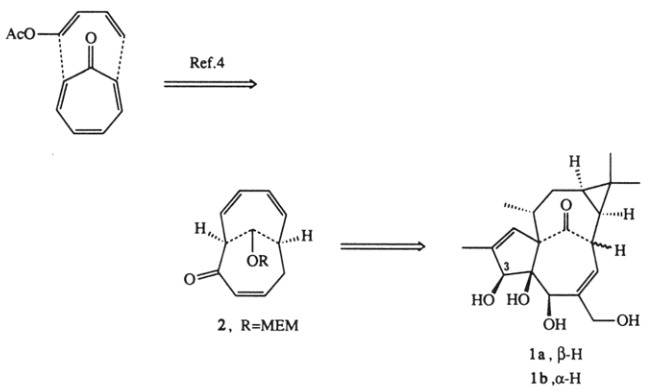
Received October 26, 1989

The architecturally complex and highly oxygenated diterpene ingenol (**1a**) has been the subject of intense synthetic investigation in recent years.[1] The relatively unusual bicyclo[4.4.1]undecane skeleton coupled with the stereochemical intricacies and high level of oxygenation which characterize this compound make for a particularly intriguing target for testing the prowess of modern organic synthesis. The importance of this substance is further magnified by the recognition that numerous fatty acid ester derivatives at the C_3 hydroxyl group are potent tumor-promoting species.[2] Recent work has suggested that the initial mode of action of these compounds may be associated with binding to, and activation of, protein kinase C.[3]

Scheme I



Our strategy for the construction of this natural product initially targets the less strained isoingenol (**1b**) by employing a thermally allowed [6 + 4] diene–tropone cycloaddition sequence for assembling the characteristic bicyclo[4.4.1]undecanone ring in a single operation.[4] Scheme I details the basic tenets of our approach. Our original entry into the ingenane skeleton featured an attempted intermolecular [6 + 4] cycloaddition employing a tropone addend bearing the elements of the five-membered ring already positioned at C_2. However, the proclivity of this substituted tropone for preferentially undergoing [4 + 2] cycloaddition when reacted with dienes rather than proceeding via the desired higher order cycloaddition pathway necessitated following a modified synthetic sequence which incorporated the elements of the A-ring unit subsequent to cycloaddition. As a consequence of this situation, the viability of the entire strategy depended critically on the successful alkylation of a bridgehead enolate in the bicyclo[4.4.1]undecane system.[5] The ease of alkylation and attendant high level regiocontrol observed during earlier studies in our laboratory on a bridgehead enolate in this ring system prompted a closer examination of the characteristics of this potenially important operation. The results of this study are detailed below.

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