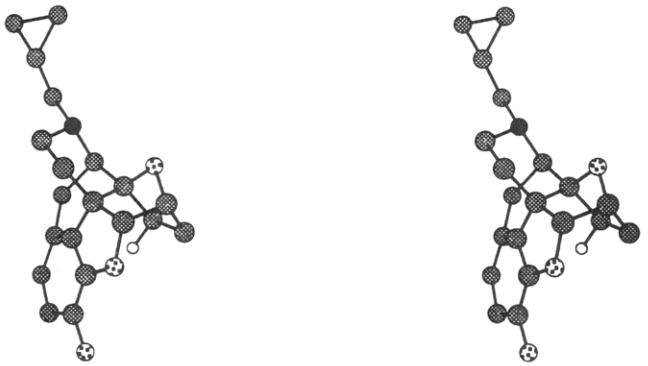

Figure 1. Stereoview of **2a** with the 7β-hydrogen atom shown eclipsed by the aromatic ring.

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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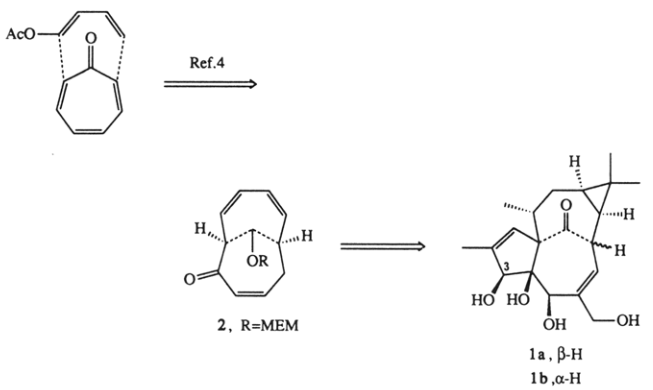
The architecturally complex and highly oxygenated diterpene ingenol (**1a**) has been the subject of intense synthetic investigation in recent years.[1] The relatively unusual bicyclo[4.4.1]undecane skeleton coupled with the stereochemical intricacies and high level of oxygenation which characterize 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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(2) Hecker, E. In *Carcinogenesis*; Slaga, T. S., Sivak, A., Boutwell, R. K., Eds.; Raven: New York, 1978; Vol. 2, Mechanism of Tumor Promotion and Carcinogenesis, p 11. (b) Evans, F. J.; Soper, C. J. *Lloydia* **1978**, *41*, 193. (c) Schmidt, R.; Adolf, W.; Marston, A.; Roeses, H.; Sorg, B.; Fujiki, H.; Moore, R. E.; Hecker, E. *Carcinogenesis* **1983**, *4*, 77.

(3) (a) Wender, P. A.; Koehler, K. F.; Sharkey, N. A.; Dell'Aquila, M. L.; Blumberg, P. M. *Proc. Natl. Acad. Sci. U.S.A.* **1986**, *83*, 4214. (b) Jeffery, A. M.; Liskamp, R. M. J. *Ibid.* **1986**, *83*, 241.

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(5) Efficient alkylation of bridgehead enolates is relatively rare: (a) Williams, R. M.; Armstrong, R. W.; Dung, J.-S. *J. Am. Chem. Soc.* **1985**, *107*, 3253. (b) Vedejs, E.; Rodgers, J. D.; Wittenberger, S. J. *Ibid.* **1988**, *110*, 4822. (c) Kende, A. S.; Kaldor, I.; Aslanian, R. *Ibid.* **1988**, *110*, 6265.

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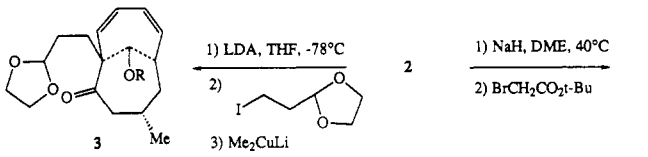
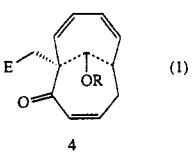
In typical fashion, enone **2**[4] can be conveniently converted into the requisite bridgehead enolate under conditions of kinetic control and regioselectively alkylated with 2-(2-iodoethyl)-1,3-dioxolane.[6] Subsequent stereoselective 1,4-addition of lithium dimethyl cuprate to the resultant enone provided **3** as a convenient model for an isoingenol

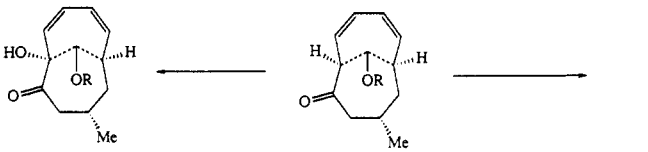


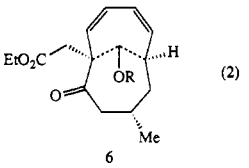


(1)

precursor in 60% overall yield. No evidence for β-elimination toward the one-carbon bridge has been observed in any of the examples studied to date. However, the epimeric series at C_9 (ingenol numbering) does experience some decomposition during bridgehead enolate formation. In an interesting development, exposure of enone **2** to conditions which would be expected to provide the thermodynamically favored enolate (NaH, DME, 40 °C, 24 h) followed by alkylation with *tert*-butyl α-bromoacetate gave only the bridgehead-substituted product **4** in 33% yield.

In a further dramatic illustration of preferential bridgehead enolate formation in this series, ketone **5**, derived from enone **2** via stereoselective addition of Me_2CuLi, was alkylated with ethyl α-bromoacetate. The enolate intermediate in this example was generated using kinetic control conditions and gave only the bridgehead product **6** in 75% yield upon reaction with the alkylating agent. None of the regioisomeric alkylation product at the less substituted position was observed! In addition, Rubottom oxidation[7] (TMSCl, mClPBA) of the "kinetic" enolate derived from **5** yielded exclusively the α-ketol **7** in 50% yield.

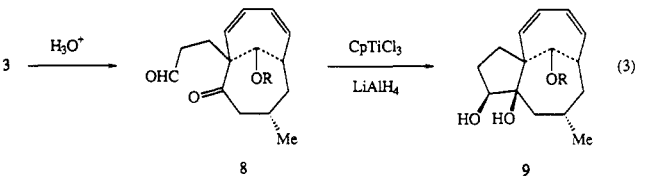




(2)

A rationalization of these intriguing results can be formulated by considering the apparent contributions of the C-ring diene system in compounds **2** and **5** to both the kinetic acidity of the bridgehead proton as well as to the stability of the resultant extended enolates. Models suggest that the diene system is well aligned relative to the bridgehead enolate for providing enhanced stabilization through an extended π-array. This interaction is reminiscent of the structurally similar bridged 1,6-methano-[10]annulene series.[8]

With a general and efficient method in hand for appending a wide variety of side chains onto the bridgehead position of the bicyclo[4.4.1]undecanone system, several methods have been developed in our laboratory for elaborating the ingenane A-ring unit. In this paper we disclose a particularly attractive protocol which effectively controls the crucial configuration at the tertiary alcohol center at C_4 in a potential isoingenol precursor. It was envisioned that an appropriate reductive coupling method for affecting cyclization to a 1,2-diol at C_3 and C_4 would be most useful in this context. The correct stereochemical outcome at the incipient C_4 stereogenic center was anticipated since the spatial disposition of the three-carbon side chain in the relatively rigid bicyclic array precludes bond formation from the β-face of the ketone carbonyl group. In the event, routine hydrolysis of the side-chain acetal in **3** provided the requisite keto aldehyde **8**, which was subjected to the Corey conditions for effecting pinacolic coupling ($CpTiCl_3/LiAlH_4$/50 °C).[9] This transformation provided tricyclic diol **9** as a single diastereomer in 43% overall yield from compound **3**. This sequence provides



(3)

8 9

rapid entry into the isoingenol ABC ring skeleton via a relatively well-functionalized intermediate. Furthermore, the methodology described in this paper is a useful complement to our previously reported aldol-mediated approach in terms of the elaboration of functionality characteristic of the southern periphery of the target molecule.[4]

Experimental Section

6-[2-(1,3-Dioxolan-2-yl)ethyl]-7-oxo-9α-methyl-11-[(2-methoxyethoxy)methoxy]bicyclo[4.4.1]undeca-2,4-diene (3). To a flask charged with diisopropylamine (2.2 mL, 15.6 mmol) in anhydrous tetrahydrofuran (50 mL) at 0 °C was added *n*-butyllithium (1.6 M in hexanes, 10.6 mL, 17 mmol). The resulting lithium diisopropylamide solution was cooled to −40 °C and stirred for 30 min. A solution of the MEM enone **2** (3.75 g, 14.2 mmol)[4] in tetrahydrofuran (50 mL) was added over 10 min and stirred for an additional 1 min at −40 °C. Hexamethylphosphoramide (HMPA, 30 mL) in tetrahydrofuran (20 mL) was added, and the solution was stirred for 5 min, at which time 2-(2-iodoethyl)-1,3-dioxolane (6.5 g, 28.4 mmol) in tetrahydrofuran (10 mL) was added and the reaction solution was allowed to warm to room temperature and stirred at that temperature for 1.5 h. The reaction mixture was poured into water (100 mL), extracted with diethyl ether (200 mL), washed with water (100 mL) and brine (100 mL), and concentrated in vacuo. Flash chromatography (4:1 petroleum ether–ethyl acetate) afforded 3.3 g (68%) of product: mp 50–51 °C; R_f 0.40 (2:1 petroleum ether–ethyl acetate); IR (film) ν 2936, 2888, 1662, 1456, 1136, 1106, 1031 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.60 (m 2 H), 1.88 (m, 1 H), 2.16 (m, 1 H), 2.52 (m, 2 H), 3.30 (m, 1 H), 3.37 (s, 3 H), 3.52 (m, 2 H), 3.68 (m, 2 H), 3.88 (m, 4 H), 3.98 (d, J = 2.3 Hz, 1 H), 4.74 (d, J = 7.3 Hz, 1 H), 4.78 (d, J = 7.3 Hz, 1 H), 4.86 (t, J = 4.5 Hz, 1 H), 5.21 (d, J = 12.0 Hz, 1 H), 5.80 (dd, J = 10.7, 6.4 Hz, 1 H), 6.02 (m, 2 H), 6.12 (dd, J = 12.1, 1.6 Hz, 1 H), 6.56 (m, 1 H); ^{13}C NMR ($CDCl_3$) δ 28.34, 28.38, 29.08, 42.74, 58.97, 63.83, 64.87, 67.78, 71.73, 80.08, 95.73, 104.72, 126.31, 127.61, 131.98, 135.57, 136.08, 141.87, 200.19; mass spectrum, m/e (%) 364 (0.3), 275 (3.6), 191 (17.9), 129 (10.1), 117 (9.5), 105 (17.8), 99 (14.6), 91 (16.9), 89 (48.6), 73 (41.5), 59 (100.0); high-resolution mass spectrum calcd for $C_{20}H_{28}O_6$ 364.18856 [exp − MEM] 275.1283, found 275.1287. Anal. Calcd for $C_{20}H_{28}O_6$: C, 65.90; H, 7.75. Found: C, 65.92; H, 7.73.

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(7) Rubottom, G. M.; Gruber, J. M. *J. Org. Chem.* **1978**, *43*, 1599.
(8) (a) Vogel, E. *Pure Appl. Chem.* **1982**, *54*, 1015. (b) Sondheimer, F. *Acc. Chem. Res.* **1972**, *5*, 81.
(9) Corey, E. J.; Danheiser, R. L.; Chandrasekaran, S. *J. Org. Chem.* **1976**, *41*, 260.

To a slurry of cuprous iodide (1.55 g, 81.5 mmol) in anhydrous diethyl ether (20 mL) at −20 °C was added methyllithium (1.5 M in diethyl ether, 10.9 mL, 16.3 mmol). The clear, tan solution was stirred for 15 min at −20 °C and then cooled to −78 °C, and the alkylated enone (1.0 g, 2.7 mmol) in diethyl ether (10 mL) was slowly added to the reaction mixture. The resultant yellow slurry was allowed to warm to room temperature, cooled to 0 °C, quenched with saturated aqueous ammonium chloride solution (20 mL), washed with saturated aqueous sodium bicarbonate solution (20 mL) and brine (20 mL), dried (anhydrous sodium sulfate), and concentrated in vacuo. Flash chromatography (1:1 petroleum ether–ethyl acetate) afforded 0.9 g (87%) of product as a yellow oil: R_f 0.45 (2:1 petroleum ether–ethyl acetate); IR (film) ν 2954, 2929, 2883, 1698, 1456, 1137, 1107, 1026 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.97 (d, J = 6.0 Hz, 3 H), 1.59 (m, 1 H), 1.72 (m, 1 H), 1.95 (m, 4 H), 2.26 (dd, J = 11.1, 2.2 Hz, 1 H), 2.64 (dd, J = 12.9, 11.1 Hz, 1 H), 3.19 (m, 1 H), 3.41 (s, 3 H), 3.57 (m, 2 H), 3.79 (m, 2 H), 3.90 (m, 4 H), 3.98 (s, 1 H), 4.82 (d, J = 7.1 Hz, 1 H), 4.85 (d, J = 7.1 Hz, 1 H), 4.88 (t, J = 4.4 Hz, 1 H), 5.43 (d, J = 11.4 Hz, 1 H), 5.56 (dd, J = 11.7, 5.6 Hz, 1 H), 5.82 (ddd, J = 11.7, 6.4, 1.1 Hz, 1 H), 5.93 (dd, J = 11.3, 6.7 Hz 1 H); ^{13}C NMR ($CDCl_3$) δ 23.77, 27.10, 28.20, 28.74, 36.74, 43.81, 49.78, 58.92, 62.79, 64.79, 67.99, 71.67, 79.58, 96.35, 104.37, 125.43, 126.84, 132.42, 132.81, 210.61; mass spectrum, m/e (%) 380 (5.1), 291 (27.0), 191 (16.9), 149 (12.6), 147 (15.9), 129 (26.2), 117 (11.6), 99 (17.9), 91 (31.8), 89 (67.9), 73 (33.9), 59 (100.0); high-resolution mass spectrum calcd for $C_{21}H_{32}O_6$ 380.2198, found 380.2195.

6-(1-*tert*-Butoxy-1-oxoeth-2-yl)-7-oxo-11-[(2-methoxyethoxy)methoxy]bicyclo[4.4.1]undeca-2,4,8-triene (4). Sodium hydride (60% dispersion in oil, 0.030 g, 0.76 mmol) was washed three times with pentane. Dry dimethoxyethane (1.0 mL) was added followed by addition of the MEM enone **2** (0.100 g, 0.38 mmol) in dimethoxyethane (1.5 mL). The orange-brown solution was stirred at 40 °C for 24 h with a slight liberation of hydrogen gas. *tert*-Butyl bromoacetate (0.074 mL, 0.46 mmol) was added, and the reaction mixture was allowed to stir overnight at room temperature. The reaction mixture was poured into ether, washed with saturated aqueous sodium bicarbonate solution and brine, dried (anhydrous sodium sulfate), and concentrated in vacuo. Chromatography (3:1 petroleum ether–ethyl acetate) afforded 0.047 g (33%) of ester **4**: R_f 0.60 (2:1 petroleum ether–ethyl acetate); IR (film) ν 2976, 2932, 2889, 1718, 1663, 1457, 1368, 1251, 1158, 1137, 1036 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.41 (s, 9 H), 2.45 (m, 1 H), 2.65 (m, 1 H), 2.71 (d, J = 14.5 Hz, 1 H), 2.98 (d, J = 14.5 Hz, 1 H), 3.83 (s, 3 H), 3.41 (m, 1 H), 3.53 (m, 2 H), 3.58 (m, 1 H), 3.77 (m, 1 H), 4.42 (d, J = 3.3 Hz, 1 H), 4.81 (s, 2 H), 5.41 (d, J = 14.0 Hz, 1 H), 5.90 (m, 3 H), 6.10 (dd, J = 14.0, 1.1 Hz, 1 H), 6.52 (m, 1 H); ^{13}C NMR ($CDCl_3$) δ 28.1, 28.7, 41.7, 43.5, 59.0, 63.2, 67.8, 71.7, 80.5, 81.1, 97.3, 125.8, 126.9, 129.9, 135.0, 135.3, 141.8, 170.8, 198.6 mass spectrum, m/e (%) (No M^+) 323 (8.8), 233 (13.2), 217 (14.6), 149 (46.5), 89 (100.0), 59 (75.9), 57 (31.8), 41 (16.0).

7-Oxo-9α-methyl-11-[(2-methoxyethoxy)methoxy]bicyclo[4.4.1]undeca-2,4-diene (5). To a slurry of copper(I) iodide (1.44 g, 7.57 mmol) in 15 mL of dry diethyl ether at −50 °C was added methyllithium (1.4 M, 10.8 mL, 15.14 mmol). The tan solution was stirred for 15 min at −50 °C and then cooled to −78 °C, followed by addition of enone **2** (1.0 g, 3.79 mmol) in 15 mL of diethyl ether. The resultant yellow slurry was stirred at −78 °C for 30 min, and then the reaction was warmed to 0 °C and quenched with 5 mL of a 1:1 mixture of aqueous ammonium hydroxide and saturated aqueous ammonium chloride solution. The reaction was extracted with ether, washed with a saturated aqueous solution of ammonium chloride (2 × 10 mL) and brine, and dried (anhydrous sodium sulfate). The ether solution was concentrated in vacuo, and flash chromatography of the residue (4:1 petroleum ether–ethyl acetate) yielded 0.92 g (87%) of ketone **5** as a yellow oil: R_f 0.65 (2:1 petroleum ether–ethyl acetate); IR (film) ν 2963, 2925, 2881, 1700, 1456, 1106, 1031 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.95 (d, J = 6.3 Hz, 3 H), 1.59 (m, 1 H), 1.95 (m, 2 H), 2.35 (dd, J = 14.7, 2.3 Hz, 1 H), 2.55 (dd, J = 14.7, 1.1 Hz, 1 H), 3.04 (m, 1 H), 3.36 (s, 3 H), 3.54 (dd, J = 9.0, 4.3 Hz, 2 H), 3.71 (dd, J = 9.1, 4.2 Hz, 2 H), 3.75 (m, 1 H), 4.10 (t, J = 4.3 Hz, 1 H), 4.75 (dd, J = 9.6, 7.2 Hz, 2 H), 5.62 (m, 2 H), 5.86 (m, 2 H); ^{13}C NMR ($CDCl_3$) δ 24.14, 25.62, 37.05, 44.56, 51.27, 58.99, 61.67, 67.22, 71.68, 76.10, 94.66, 125.25, 126.29, 126.84, 132.20, 213.28; mass spectrum, m/e (%) 191 (56.8), 175 (5), 131 (11.0), 91 (100.0), 69 (7), 59 (93); high-resolution mass spectrum calcd for $C_{16}H_{24}O_4$ 280.1674 [exp − MEM] 191.1072, found 191.1076.

6-(1-Ethoxy-1-oxoeth-2-yl)-7-oxo-9α-methyl-11-[(2-methoxyethoxy)methoxy]bicyclo[4.4.1]undeca-2,4-diene (6). To a solution of lithium diisopropylamide at −78 °C prepared from diisopropylamine (0.125 mL, 0.89 mmol) and *n*-butyllithium (2.5 M solution in hexanes, 0.34 mL, 0.85 mmol) in tetrahydrofuran (5 mL) was added the ketone **5** (0.20 g, 0.71 mmol) in tetrahydrofuran (5 mL). The yellow solution was stirred for 5 min at −78 °C, followed by addition of HMPA (2 mL) in tetrahydrofuran (1 mL). The dark yellow solution was stirred for an additional 5 min, and ethyl bromoacetate (0.20 mL, 1.78 mmol) was added. The dark yellow reaction mixture immediately paled in color. After 15 min the ice bath was removed and TLC analysis (4:1 ether–petroleum ether) indicated that starting material was gone. The reaction mixture was quenched with saturated aqueous ammonium chloride solution (1 mL) and poured into ether (100 mL), washed with water (30 mL) and brine (50 mL), dried (anhydrous sodium sulfate), and concentrated in vacuo. Chromatography (4:1 petroleum ether–ethyl acetate) afforded 0.197 g (75%) of keto ester: R_f 0.28 (4:1 petroleum ether–ethyl acetate); IR (film) ν 2960, 2930, 1740, 1705, 1450, 1370, 1260, 1175, 1100, 1030 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.94 (d, J = 6.5 Hz, 3 H), 1.22 (t, J = 7.1 Hz, 3 H), 1.54 (m, 1 H), 1.87 (m, 1 H), 1.99 (m, 1 H), 2.42 (m, 2 H), 2.76 (q, J = 5.5 Hz, 2 H), 3.17 (m, 1 H), 3.34 (s, 3 H), 3.51 (m, 2 H), 3.64 (m, 1 H), 3.75 (m, 1 H), 4.06 (q, J = 7.2 Hz, 3 H), 4.15 (d, J = 5.2 Hz, 1 H), 4.74 (q, J = 7.0 Hz, 3 H), 5.61 (m, 2 H), 5.85 (m, 2 H); ^{13}C NMR ($CDCl_3$) δ 14.03, 23.79, 25.93, 35.97, 40.31, 44.00, 50.22, 58.90, 60.24, 62.39, 68.03, 71.61, 79.78, 96.91, 125.30, 126.24, 130.89, 133.08, 171.27, 208.46; mass spectrum, m/e (%) 278 (13), 277 (76), 177 (63), 89 (76), 91 (30), 59 (100); high-resolution mass spectrum calcd for $C_{20}H_{30}O_6$, 366.2042 [exp − MEM] 277.1429, found 277.1440.

6-Hydroxy-7-oxo-9α-methyl-11-[(2-methoxyethoxy)methoxy]bicyclo[4.4.1]undeca-2,4-diene (7). To a solution of lithium diisopropylamide at −78 °C prepared from diisopropylamine (0.45 mL, 3.2 mmol) and *n*-butyllithium (2.5 M in hexane, 1.19 mL, 3.1 mmol) in tetrahydrofuran (10 mL) was added the ketone **5** (0.75 g, 2.7 mmol) in tetrahydrofuran (10 mL). After 5 min chlorotrimethylsilane (1.0 mL, 8.6 mmol) was rapidly introduced, and the resulting white slurry was allowed to warm to room temperature. The solvent was removed in vacuo, pentane was added, and the solution was filtered through a short column of anhydrous sodium sulfate with pentane as eluent. The organic phase was concentrated in vacuo to give 0.83 g of the silyl enol ether as a clear oil, R_f 0.9 (2:1 petroleum ether–ethyl acetate). To a solution of the silyl enol ether (0.83 g) in hexane (15 mL) at −15 °C was added metachloroperbenzoic acid (85%, 0.53 g, 2.6 mmol). The resultant white slurry was vigorously stirred at −15 °C for 15 min and then filtered through a short column of sodium sulfate with hexane as eluent and then concentrated in vacuo. The oil was dissolved in diethyl ether, washed with a saturated aqueous solution of sodium bicarbonate and brine, and concentrated in vacuo. Chromatography (4:1 petroleum ether–ethyl acetate) afforded 0.35 g (50%) of alcohol **7**: R_f = 0.42 (2:1 petroleum ether–ethyl acetate); IR (film) ν 3438, 3025, 2956, 2925, 2888, 1700, 1456, 1369, 1250, 1106, 1031 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.92 (d, J = 6.1 Hz, 3 H), 1.59 (m, 1 H), 1.77 (m, 1 H), 2.25 (m, 2 H), 2.64 (m, 1 H), 2.92 (m, 1 H) , 3.38 (s, 3 H), 3.53 (m, 2 H), 3.68 (m, 2 H), 4.06 (d, J = 3.9 Hz, 1 H), 4.75 (d, J = 7.1 Hz, 1 H), 4.84 (d, J = 7.1 Hz, 1 H), 4.89 (s, 1 H), 5.13 (d, J = 12.7 Hz, 1 H), 5.92 (m, 3 H); ^{13}C NMR ($CDCl_3$) δ 23.51, 23.98, 35.00, 41.63, 48.29, 58.86, 67.27, 71.56, 80.03, 85.89, 96.67, 124.81, 126.46, 127.89, 134.13, 207.86; mass spectrum, m/e (%) (No M^+) 297 (M + 1, 24), 222 (17.0), 221 (100.0), 220 (20), 207 (M − MEM, 14), 173 (38), 89 (43), 59 (44).

6-[3-(1-Oxopropyl)]-7-oxo-9a-methyl-11-[(2-methoxyethoxy)methoxy]bicyclo[4.4.1]undeca-2,4-diene (8). To a solution of acetal **3** (1.3 g, 3.4 mmol) in acetone (5 mL) was added a 15% aqueous solution of trifluoroacetic acid (2.6 mL). The reaction was stirred for 2 days and quenched with solid sodium bicarbonate, and the solvent was removed in vacuo. The crude product was dissolved in diethyl ether, washed with a saturated aqueous solution of sodium bicarbonate and brine, dried, and concentrated in vacuo to afford an oil, which was found by ^1H NMR spec-

troscopy to still contain starting material. The mixture was again dissolved in acetone (6.0 mL), a 15% aqueous solution of trifluoroacetic acid (2.6 mL) was added, and the reaction mixture was stirred for an additional 2 days. The reaction was worked up as above and chromatographed (4:1 petroleum ether–ethyl acetate) to afford 0.95 g (86%) of **8** as an oil: R_f 0.47 (2:1 petroleum ether–ethyl acetate); IR (film) ν 2953, 2938, 2877, 2725, 1724, 1699, 1455, 1105, 1023 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.96 (d, J = 6.0 Hz, 3 H), 1.57 (m, 1 H), 1.95 (m, 2 H), 2.05 (m, 1 H), 2.26 (m, 2 H), 2.41 (m, 1 H), 2.58 (m, 2 H), 3.16 (m, 1 H), 3.38 (s, 3 H), 3.55 (br t, J = 4.5 Hz, 2 H), 3.75 (dd, J = 8.4, 4.1 Hz, 2 H), 3.95 (d, J = 5.8 Hz, 1 H), 4.74 (d, J = 7.1 Hz, 1 H), 4.83 (d, J = 7.1 Hz, 1 H), 5.34 (d, J = 11.4 Hz, 1 H), 5.61 (dd, J = 11.6, 5.8 Hz, 1 H), 5.85 (ddd, J = 11.6, 6.7, 1.5 Hz, 1 H), 5.95 (dd, J = 11.5, 6.8 Hz, 1 H), 9.77 (s, 1 H); ^{13}C NMR ($CDCl_3$) δ 23.72, 26.81, 36.49, 38.71, 43.35, 50.01, 58.89, 62.47, 68.12, 71.62, 79.25, 95.83, 125.37, 127.36, 131.37, 133.15, 201.43, 210.30; mass spectrum, m/e (%) 336 (0.6), 247 (69), 231 (16), 147 (47), 105 (17), 91 (23), 89 (64), 59 (100.0); high-resolution mass spectrum calcd for $C_{19}H_{28}O_5$ 336.1936, [exp – MEM] 247.1334, found 247.1338.

12-(2-Methoxyethoxy)-2,3,8,9,10,11-hexahydro-10-methyl-3a,8-methano-3a*H*-cyclopentacyclodecene-1,11a-diol (9). The air-sensitive cyclopentadienyltitanium trichloride (Aldrich) and lithium aluminum hydride (Aldrich) were weighed and transferred, under N_2, in a glovebag. To a solution of cyclopentadienyltitanium trichloride (0.20 g, 9 mmol) in freshly distilled tetrahydrofuran (4.0 mL) was cautiously added lithium aluminum hydride (0.027 g, 0.675 mmol). The resultant black mixture was stirred at 50 °C for 1 h, and then a solution of the keto aldehyde **8** (0.05 g, 0.15 mmol) in tetrahydrofuran (2 mL) was introduced. The black mixture was stirred for 9 h at 50 °C, cooled to room temperature, treated with a saturated aqueous solution of potassium carbonate (0.5 mL), and stirred for an additional 0.25 h. The resultant dark blue mixture was filtered through Celite with a 1:1 mixture of diethyl ether and ethyl acetate. The filtrate was washed with brine, dried, and concentrated in vacuo to give a yellow oil. Flash chromatography (4:1 petroleum ether–ethyl acetate) afforded 0.024 g (48%) of diol **9**: R_f 0.24 (2:1 hexane–ethyl acetate); IR (film) ν 3447, 3021, 2951, 2929, 2887, 1457, 1368, 1219, 1202, 1128, 1106, 1090, 1020, 962 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.94 (d, J = 6.6 Hz, 3 H), 1.56 (m, 1 H), 1.66 (m, 4 H), 1.81 (m, 1 H), 2.01 (m, 1 H), 2.12 (m, 2 H), 2.36 (m, 1 H), 3.14 (m, 1 H), 3.18 (m, 1 H), 3.38 (s, 3 H), 3.55 (br t, J = 4.7 Hz, 2 H), 3.68 (m, 1 H), 3.78 (m, 2 H), 3.89 (d, J = 5.0 Hz, 1 H), 4.78 (d, J = 7.1 Hz, 1 H), 4.91 (d, J = 7.1 Hz, 1 H), 5.40 (m, 1 H), 5.56 (m, 1 H), 5.76 (m, 2 H); ^{13}C NMR ($CDCl_3$) δ 25.33, 30.67, 38.40, 39.13, 43.75, 44.10, 59.04, 60.09, 68.56, 71.71, 81.80, 83.26, 96.60, 122.72, 122.92, 134.74, 134.91. Anal. Calcd for $C_{19}H_{30}O_5$: C, 67.42; H, 8.94. Found: C, 67.34; H, 8.80.

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Registry No. (±)-**2**, 125902-33-2; (±)-**2**(dioxolanylethyl derivative), 125902-41-2; (±)-**3**, 125902-34-3; (±)-**4**, 125902-35-4; (±)-**5**, 125902-36-5; (±)-**5**(trimethylsilyl enol ether), 125902-42-3; (±)-**6**, 125902-37-6; (±)-**7**, 125902-38-7; (±)-**8**, 125902-39-8; (±)-**9**, 125902-40-1; $BrCH_2CO_2Bu$-*t*, 5292-43-3; $BrCH_2CO_2Et$, 105-36-2; 2-(2-iodoethyl)-1,3-dioxolane, 83665-55-8.

Unexpected Cis Openings of Cyclopentadiene Monoepoxide with Lithium Acetylides and Dialkylalkynylalanes[1a]

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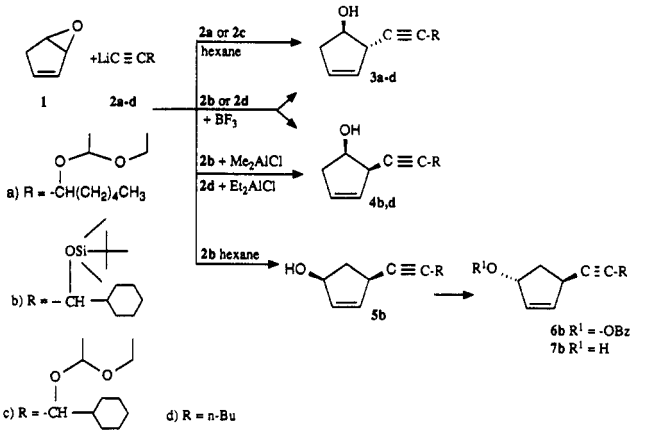
The reactions of vinyloxiranes with organometallic compounds have received considerable attention recently, with reliable methods now having been developed for syn-1,4 and anti-1,4 addition.[2] However, the reaction of alkynyl anions has been largely overlooked, there being only two applications in the literature.[3,4] We have previously applied the work of Stork[3] to prepare trans-cyclopentenol **3a**[5] by coupling the lithium acetylide **2a** with cyclopentadiene monoepoxide (**1**) for the preparation of prostacyclin analogues.[6] In an attempt to apply the same



conditions (*n*-BuLi/hexane) to the silyl-protected acetylide **2b**, we were surprised to obtain exclusively the cis-1,4-opening product **5b** (in 25% yield)[7] rather than the expected trans-1,2-opening product **3b**.

The 1,4-relationship in **5b** was readily ascertained from ^1H NMR decoupling experiments that showed the ring propargylic proton coupled to the downfield methylene proton but not the carbinol proton. The cis relationship of the substituents was initially deduced from the large chemical shift difference (0.9 ppm) of the two ring methylene protons arising from the cumulative shielding of one of these by the hydroxyl and acetylene moieties. To strengthen this assignment however, the trans isomer was needed for direct comparison. The presumed cis alcohol **5b** was therefore epimerized[9] by using the Mitsunobu reaction[10] to give the inverted benzoate **6b** (88%), followed by cleavage of the unstable benzoate with lithium aluminum hydride to give **7b** (92%). The much closer separation of the ring methylene proton resonances (0.1 ppm) in this epimer (trans) vindicated the original assignment.

To confirm that the origin of this effect (cis-1,4 versus trans-1,2 opening) lay in the nature of the protecting group

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(2) See: Marshall, J. A.; Trometer, J. D.; Blough, B. E.; Crute, T. D. *J. Org. Chem.* **1988**, *53*, 4274. Marshall, J. A.; Trometer, J. D.; Cleary, D. G. *Tetrahedron* **1989**, *45*, 391. Larock, R. C.; Ilkka, S. J. *Tetrahedron Lett.* **1986**, *27*, 2211. Tueting, D. R.; Echavarren, A. M.; Stille, J. K. *Tetrahedron* **1989**, *45*, 979. Marshall, J. A.; Trometer, J. D.; Blough, B. E.; Crute, T. D. *Tetrahedron Lett.* **1988**, *29*, 913. Marino, J. P.; Farina, J. S. *J. Org. Chem.* **1976**, *41*, 3213 and references therein.

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(5) For clarity, only one enantiomer or pair of diastereomers (for propargylic alcohols) are depicted. All compounds are racemic or mixtures of diastereomeric racemates.

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(7) Although the unoptimized yields in the reactions described are modest, no other significant products are obtained. The low yields probably reflect the known reluctance of acetylenes to add to epoxides[8] and loss or incomplete reaction of the sensitive epoxide **1**.

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