dition of water (0.3 mL), 15% aqueous sodium hydroxide (0.3 mL), and water (0.9 mL).

The resulting suspension was filtered through Celite being washed with ether. Removal of the solvent at reduced pressure and flash chromatography of the residue (3 × 25 cm column, 50% ethyl acetate in hexanes) gave the desired alcohol **19** (1.02 g, 68%): $[\alpha]^{22}_D$ +34.2° (*c* 0.96, $CHCl_3$); ^1H NMR (250 MHz, $CDCl_3$) δ 1.04 (s, 9 H, $C(CH_3)_3$), 1.28 and 1.26 (2 s, 6 H, $C(CH_3)_2$), 1.49 (quint, 2 H, H-19), 1.80 (m, 2 H, H-16), 2.12 (m, 2 H, J_{AB} = 14.5 Hz, H-13, H-13′), 3.59 (q, 2 H, *J* = 6.4 Hz, H-20), 3.78 (t, 1 H, *J* = 7.6 Hz, OCHC*H*H′O), 3.90 (m, 2 H, OCHCH*H*′O, and H-12), 3.78 (t, 1 H, *J* = 7.6 Hz, OCHC*H*H′O) 3.90 (m, 2 H, OCHCH*H*′O and H-12), 4.04 (dt, 1 H, *J* = 7.1 Hz, J^1 = 5.7 Hz, H-11), 5.34 (m, 2 H, H-14, H-15), 7.323–7.718 (m, 10 H, 2 Ph); high-resolution mass spectrum, *m/z* calcd for $C_{29}H_{41}O_4Si$ ($M^+ - CH_3$) 481.2774, found 481.2788.

11-*O*-Benzoyl-3-*O*-(*tert*-butyldiphenylsilyl)-1,2-bis-*O*-(1-methylethylidene)-5-undecene-1,2(*R*),3(*S*),11-triol (20). To a stirred solution of the alcohol **19** (980 mg, 2.0 mmol) in dichloromethane (15 mL) at 0 °C were added triethylamine (0.358 mL, 2.6 mmol) and benzoyl bromide (0.280 mL, 2.4 mmol) sequentially. The reaction mixture was partitioned, and the organic phase was dried over anhydrous sodium sulfate. Removal of the solvent at reduced pressure and flash chromatography of the residue (3 × 25 cm column, 10% ethyl acetate in hexanes) gave the benzoate **20** (998 mg, 85%): $[\alpha]^{22}_D$ +30.12° (*c* 0.83, $CHCl_3$); ^1H NMR (250 MHz, $CDCl_3$) δ 1.04 (s, 9 H, $C(CH_3)_3$), 1.28 and 1.30 (2 s, 6 H, $C(CH_3)_2$), 1.70 (quint, 2 H, *J* = 6.0 Hz, H-19), 1.82 (m, 2 H, H-16), 2.13 (m, 2 H, *J* = 14.5 Hz, H-13, H-13′), 3.77 (t, 1 H, *J* = 7.6 Hz, CC*H*H′O), 3.89 (m, 2 H, AB, CCH*H*′O and H-12), 4.05 (dt, 1 H, H-11), 4.27 (t, 1 H, *J* = 6.6 Hz, H-20), 5.34 (m, 2 H, H-14, H-15), 7.327–8.023 (m, 15 H, 3 Ph); high-resolution mass spectrum, *m/e* calcd for $C_{36}H_{45}O_5Si$ ($M^+ - CH_3$) 585.3036, found 585.3054.

Data for 12(*S*),20-dihydroxy-5(*Z*),8(*Z*),10(*E*),14(*Z*)-eicosatetraenoic acid (2): $[\alpha]^{22}_D$ +10.3° (*c* 1.36, acetone); ^1H NMR (acetone-d_6) δ 2.27 (t, 2 H, *J* = 7.3 Hz, H-2), 2.94 (t, 2 H, *J* = 6.2 Hz, H-7), 3.52 (t, 2 H, *J* = 6.45 Hz, H-20), 4.17 (q, 1 H, *J* = 6.6 Hz, H-12), 5.29–5.46 (m, 5 H, H-5, H-6, H-8, H-14, H-15), 5.72 (dd, 1 H, *J* = 6.1, 15.2 Hz, H-11), 5.98 (t, 1 H, *J* = 11.4 Hz, H-9), 6.59 (dd, *J* = 11.4, 15.2 Hz, H-10); high-resolution mass spectrum, *m/z* calcd for $C_{20}H_{32}O_4$ 336.2300, found 336.2338, *m/z* calcd for $C_{20}H_{30}O_3$ ($M^+ - H_2O$) 318.2195, found 318.2167.

Construction of the Taxane C-Ring Epoxy Alcohol Moiety and Examination of Its Possible Involvement in the Biogenesis of the Taxane 3-Oxetanol Structure

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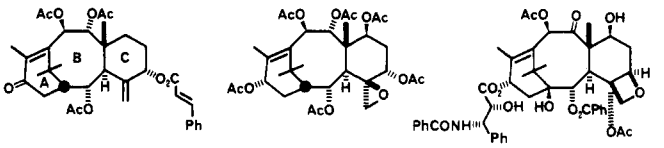
A stereospecific synthesis of a model compound containing the 2,3-epoxy alcohol moiety present in the C ring of several taxane diterpenes has been devised. Thus epoxide **8** was converted to allylic alcohol **9** which upon epoxidation to give **10** followed by treatment with hydroxide afforded **11**, the epoxy alcohol. Derived methanesulfonate **13** was found to yield **14** upon solvolysis in aqueous acetonitrile. Two possible mechanisms for this transformation are provided. This last experiment was designed to evaluate a described suggestion regarding the biogenesis of the taxane C-ring 3-oxetanol moiety.

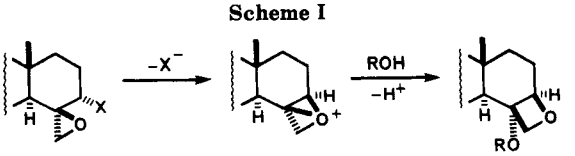
Among the structural complexities of the taxane diterpenes[2] which make these natural substances challenging synthetic[3] targets are the unique C-ring features. These allow organization of the taxanes into a group possessing an allylic oxygen function, as in taxinine,[4] **1**, a group in which the olefinic bond of the first has been oxidized to a β epoxide, as in **2**,[5] and a third group containing the fused 3-oxetanol function, as in taxol,[6] **3**. Although a plausible



1 (I) **2** (II) **3** (III)

biogenetic connection between the first two groups can be envisioned, their synthetic relationship is less obvious since any direct epoxidation of the C-ring allylically oxygenated system will lead to the incorrect epoxide stereochemistry. Experimental data on this point is available.[7] As part of

Scheme I



4 **5** **6**

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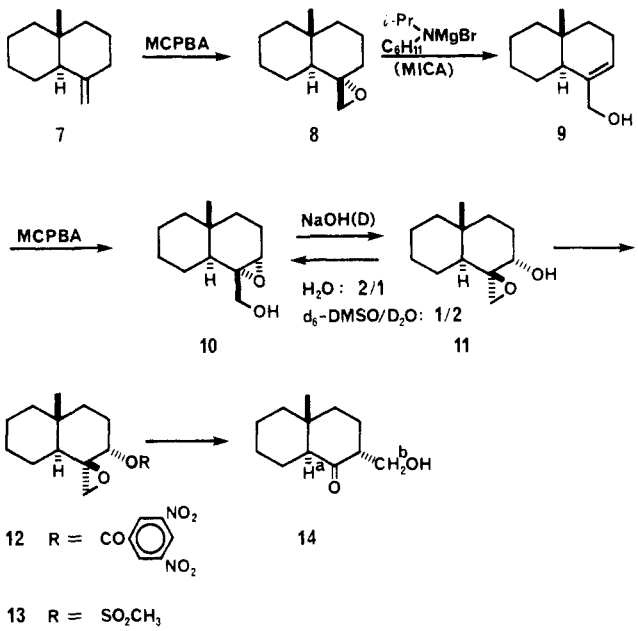
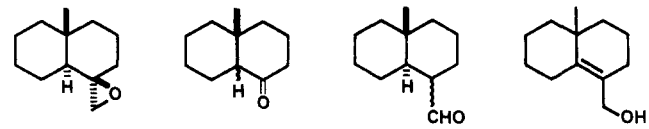
Scheme II



our interest in the preparation of members of this family, we sought a route to the epoxide system of group II. In addition, we were intrigued with the idea that such epoxides or derivatives thereof could be the biosynthetic precursors of the 3-oxygenated oxetanes of group III through the solvolytic process depicted in Scheme I.[8] Chemistry of this sort, if demonstrated in the laboratory, would also be of some preparative[9-13] value. We describe here our model studies which have produced a construction of the group II β epoxide structure and our investigation of its solvolytic chemistry.

To mimic both the chair conformation and the substitution pattern of possible taxane C-ring progenitors, we chose a cyclohexane ring incorporated in an angularly methylated *trans*-decalin structure. Conversion of the known olefin **7**[14] to epoxide **8** was followed by its isomerization to **9** upon treatment with MICA,[15] most plausibly through a syn elimination process[16] (Scheme II). Since it was not initially clear that the most efficient preparation of **9** would emanate from **8**, epoxide **15** was also constructed from **16**[14] and dimethylsulfoxonium methylide.[17] That the trans ring junction stereochemistry of **15** would be incorporated through the ylide procedure was suggested by the preparation of **7** from **16** and triphenylphosphonium methylide[14] and was borne out by the conversion of both **15** and **8** to mixtures of the same epimeric aldehydes **17** upon their treatment with boron trifluoride etherate. The interaction of **15** with MICA produced allylic alcohols **9** and **18** (1/2.5) but more slowly than in the reaction involving **8** and in poor yield. As far as we know, this is the first case in which a spiro epoxide well-constructed for trans diaxial E2 elimination but not for syn removal of an axial proton has been shown to be a poor substrate for metal amide-induced isomerization.[16]



15 16 17 18

Epoxidation of **9** predictably led to **10**. Our strategy in the construction of the group II epoxides involved subjection of **10** to a Payne rearrangement.[18] It has been appreciated for some time that although there are several different structural effects on the composition of the Payne equilibrium, in general, the epoxy alcohol which predominates is that one bearing least substitution on the hydroxylated carbon and greatest substitution on those carbons involved in the epoxide ring. We had hoped that this effect might be overcome at least partially in the case of **10**/**11** due to the less favorable half-chair conformation imposed on epoxy alcohol **10** vs. the minimal distortion of the chair conformation of **11**. In fact, this objective could be realized as indicated, although the solvent dependence of the equilibrium complicates this rationale. A variety of other basic conditions, including phase transfer, were unsuccessful in this transformation.

With epoxy alcohol **11** in hand, we turned our attention to its solvolytic chemistry. Although theory at the INDO level predicts that the epoxide moiety stabilizes an adjacent cationic center when the so-called bisected conformation obtains,[19] data on the translation of this effect into observed epoxycarbinyl solvolytic accelerations has been somewhat contradictory. Although Richey[9] suggests that his systems exhibit accelerations when compared to models lacking the epoxide ring, others[12,20,21] report minimal solvolytic accelerations at best. Clark[22] reports accelerations for bisected epoxycarbinyl substrates over similar perpendicular structures, but not necessarily rate enhancements over models. Likewise, several studies present a rich and somewhat confusing picture of product distribution as a function of reactant structure and reaction pathway. Richey[9] reports that his acyclic systems ionize with assistance from the epoxide oxygen leading to 3-oxetanol derivatives through the intervention of oxabicyclobutonium ions (cf. Scheme I). Santelli[12] describes an epoxycarbinyl rearrangement which might be consistent with a variation on the Richey mechanism involving nucleophilic attack on an oxabicyclobutonium ion at a non-

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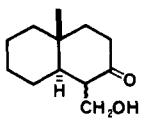
bridgehead carbon.[23] In addition, Morita and Oae[10] report the formation of 3-oxetanyl acetate in the acetolysis of epichlorohydrin, although this work has been questioned by Whalen,[24] and Thomas[11] and Santelli[12] describe examples of epoxycarbinyl to 3-oxetanol conversions which are, however, stereochemically inconsistent with the Richey mechanism. Indeed, Whalen[20,25] has failed to detect the epoxide oxygen assistance pathway in his extensive studies. Other acyclic epoxycarbinyl substrates appear to suffer migration of the epoxide carbon–carbon bond either in concert with ionization or after ionization[12] and undergo simple displacement at the leaving-group-bearing carbon with predominant inversion of stereochemistry.[20] Epoxycarbinyl systems having carbon atoms which are fused to another ring share the above ionization pathways except the first[22,25] and solvolyze to 2-oxahomoallyl cations,[22,25] undergo displacement at the leaving-group-bearing carbon with near random stereochemistry,[25] and exhibit elimination[25] and hydride migration[25] reactions. The Richey epoxide oxygen assistance pathway should have a stereoelectronic requirement for antiperiplanarity of the leaving group and epoxide oxygen which could be met by a derivative of the relatively conformationally inflexible **11**.

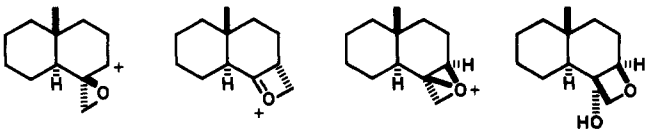
Epoxy alcohol **11** could be converted to 3,5-dinitrobenzoate **12** and also to mesylate **13**. Attempted solvolysis of **12** in aqueous acetonitrile led only to recovered starting material. Mesylate **13**, however, could be induced to undergo reaction under similar conditions to yield, in addition to recovered starting material, hydroxy ketone **14**. The trans ring junction stereochemistry and axial disposition of the hydroxy methylene side chain were supported by the observation of mutual NOE's involving α-keto methine proton A and hydroxy methylene protons B. Alternative regioisomer **19** could be ruled out since a 2D COSY ex-



19

periment on the solvolysis product indicated no coupling between the two methine protons.

The failure to observe 3-oxetanol-containing products in the face of the formation of **14** from the solvolysis of **13** obviates a definitive comment on the relevance of Scheme I to the biogenesis of the 3-oxetanol moiety in the taxanes. The pathway which does lead to **14** is problematic, however. Although **14** bears a superficial resemblance to the products of the processes described by Santelli,[12] the stereochemistry of its formation, rearrangement with retention at the leaving group bearing carbon, is without precedent. While further work will be required to determine the generality and mechanism of this chemistry, it is interesting to consider two possible pathways from **13** to **14**. In the first, cation **20** is formed from **13** and rearranges to cation **21** which is trapped by water to yield observed product **14**. In the second, oxabicyclobutonium ion **22** is indeed formed by epoxide oxygen assistance in the ionization. This intermediate then suffers rearrangement to **21** rather than nucleophilic trapping by water to give 3-oxetanol **23**. A labeling study[26] of the mechanistically related acid-catalyzed rearrangement of



20 **21** **22** **23**

a 3-oxetanol to a β-hydroxy ketone is consistent with the second proposal. In addition, the latter pathway does not rule out our biogenetic hypothesis outlined above, but implies that the enzyme involved might function to divert the oxabicyclobutonium ion into reaction with an oxygen nucleophile to provide the oxetane structure. Although the rearrangement of **22** to **21** is somewhat unusual since it appears to require the displacement of a pair of electrons in a carbon–oxygen bond by a migrating carbon–carbon bond far from antiperiplanarity with it, it may be regarded as occurring in a manner similar to the conceivable [$_\sigma 2_s$ + $_\sigma 2_a$] concerted rearrangement of bicyclobutane to cyclobutene which would experience analogous atom connectivity and stereochemical changes.[27] It is worth noting that the first pathway involving the rearrangement of **20** to **21** is also poorly set up stereoelectronically in the standard chair conformation for **20** since the epoxide carbon–carbon bond which migrates is poorly aligned with the linear axis of the empty p orbital on the cationic carbon. Rather severe conformational distortion of the *trans*-decalin structure of **20** prior to this process would be required. Finally, it is possible, of course, that **20** and **22** might be in equilibrium with each other, or represent two canonical structures of a bridged ion with but one minimum on the potential surface.

In conclusion, a stereospecific construction of the taxane group-II epoxy alcohol functionality has been developed. Although its suggested involvement in the biogenesis of the taxane group-III oxetane moiety remains to be proven, it is yet conceivable that such chemistry plays a role in the enzymic formation of this substructure. In principle, in vivo labeling studies could illuminate this question through the identification of the origin of the oxetane oxygen in taxol and related taxanes.

Experimental Section

Reactions requiring anhydrous conditions were performed in flame-dried glassware using anhydrous solvents under argon or nitrogen. Melting points were determined on a Thomas-Hoover capillary apparatus and are uncorrected. Infrared spectra were recorded on either Perkin-Elmer 283 or 287 spectrophotometers. ^{1}H Nuclear magnetic resonance spectra were determined in deuterated chloroform, unless noted otherwise, on a Nicolet NT-360 (360 MHz) fourier transform spectrometer with a 4000-Hz spectral window and 32K data points, on a Varian EM-390 (90 MHz) continuous wave spectrometer, or on a Varian T-60 (60 MHz) continuous wave spectrometer using tetramethylsilane (δ = 0 ppm) as an internal standard. ^{13}C nuclear magnetic resonance spectra were recorded in deuterated chloroform on a Varian CFT-20 (20 MHz) spectrometer with a 4000-Hz spectral window and 8K data points using tetramethylsilane (δ = 0 ppm) as internal standard. Mass spectra were obtained on a LKB-9000S gas chromatograph–mass spectrometer at 70 eV, on a Finnigan MAT 212 mass spectrometer–Varian 3700 GC with an open split interface using a 15 DB5 capillary column, or on an MM 7035 mass spectrometer interfaced with an HP 5710A gas chromatograph. Microanalyses were carried out at Merck Sharp & Dohme Research Laboratories, West Point, PA.

Preparation of Epoxide 8. To a solution of 8.3 g (51 mmol) **7** in 50 mL of methylene chloride at 0 °C was added dropwise a solution of 59 mmol of *m*-chloroperbenzoic acid in 120 mL of methylene chloride. Following the addition, the reaction mixture

(23) See the transformations of **6e** to **16E** and **6t** to **16Z** in ref 12.
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was warmed to room temperature for 2 h. At this time, the mixture was again cooled to 0 °C and 120 mL of 10% aqueous sodium sulfite added dropwise. The organic layer was washed successively with aqueous solutions of sodium bisulfite, sodium thiosulfate, sodium bicarbonate, and sodium chloride. After drying (sodium sulfate), removal of solvent left 8.8 g (97%) of **8** as an oil: ^{1}H NMR δ 0.8–2.0 (15 H, m, CH, CH_2), 0.88 (3 H, s, CH_3), 2.52 (1 H, d, J = 5, epoxide CH), 2.71 (1 H, dd, J = 1.5, 5, epoxide CH); ^{13}C NMR δ 59.2 (epoxide quaternary), 51.0 (epoxide CH_2), 47.8 (CH), 36.3 (quaternary), 17.0 (CH_3), 41.7, 41.6, 35.7, 26.4, 21.9, 21.1, 19.9 (CH_2); mass spectrum, m/z (relative intensity) 180 (M^+, 8), 165 (100); calcd for $C_{12}H_{20}O$ 180.1514, found 180.1509.

Preparation of Epoxide 15. A suspension of dimethylsulfoxonium methylide[17] was prepared from 6.8 g (31 mmol) of trimethylsulfoxonium iodide, 1.5 g (31 mmol) of sodium hydride (50% oil dispersion), and 30 mL of dimethyl sulfoxide. To this was added a solution of 3.48 g (21 mmol) of **16** (1/1 epimeric mixture) in 5 mL of dimethyl sulfoxide, and the reaction mixture was stirred at 45–50 °C for 1.75 h. After cooling to 0 °C, 10 mL of water was added dropwise, and after further dilution with water, the mixture was extracted with ether. The organic layer was washed with water and brine, dried (sodium sulfate), and evaporated. The residue was chromatographed on silica gel, eluting with hexane/ethyl acetate, to afford 1.72 g (45%) **15** as an oil: ^{1}H NMR δ 0.99 (3 H, s, CH_3), 1.0–2.0 (15 H, m, CH, CH_2), 2.25 (1 H, d, J = 5, epoxide CH), 2.73 (1 H, d, J = 5, epoxide CH); ^{13}C NMR δ 59.4 (epoxide quaternary), 47.8 (epoxide CH_2), 45.6 (CH), 35.5 (quaternary), 17.5 (CH_3), 42.3, 41.9, 35.2, 26.6, 21.5, 20.8, 19.6 (CH_2); mass spectrum, m/z (relative intensity) 180 (M^+, 18), 166 (50), 165 (100), 135 (100), 121 (50), 108 (55); calcd for $C_{12}H_{20}O$ 180.1514, found 180.1518.

Rearrangement of 8 and 15 to Aldehydes 17. To a solution of 320 mg (1.77 mmol) of **8** in 10 mL of benzene was added 3 drops of boron trifluoride etherate. After being stirred at room temperature for 1 h, the reaction mixture was evaporated, the residue taken up in ether, and the ether solution washed with aqueous sodium bicarbonate, dried (sodium sulfate), and evaporated. Flash chromatography of the residue, eluting with hexane/ether, gave **17** as a ca. 1/1 epimeric mixture.

Similar treatment of **15** again led to **17** as an epimeric mixture with the axial epimer predominating 3/1: IR (chloroform) 1720 (sh), 1705 cm^{-1}; ^{1}H NMR δ 0.78 (0.75 H, s, CH_3 of equatorial epimer), 0.88 (2.25 H, s, CH_3 of axial epimer), 1.0–1.8 (15 H, m, CH, CH_2), 2.1–2.3 (1 H, m, C*H*CHO), 9.45 (0.75 H, d, J = 4.5, CHO of axial epimer), 9.93 (0.25 H, apparent s, CHO of equatorial epimer); mass spectrum, m/z (relative intensity) 180 (M^+, 80), 179 (75), 177 (60), 162 (100), 151 (80), 136 (65), 95 (75), 94 (60); calcd for $C_{12}H_{20}O$ 180.1514, found 180.1506.

Rearrangement of 8 and 15 with MICA. To a solution of bromomagnesium isopropylcyclohexylamide (136 mmol) in 10 mL of ether and 48 mL of tetrahydrofuran was added a solution of 4.9 g (27 mmol) **8** in 5 mL of tetrahydrofuran. After the reaction mixture was stirred at room temperature for 5 days, it was cooled to 0 °C, diluted with 50 mL of ether, and treated with 20 mL of aqueous sodium dihydrogen phosphate. The resulting mixture was filtered and the filtrate washed with brine, dried (sodium sulfate), and evaporated. The residue was chromatographed on alumina (activity III), eluting with hexane/ethyl acetate, to yield 2.7 g (55%) of **9**: IR (neat) 3340, 1660 cm^{-1}; ^{1}H NMR δ 0.80 (3 H, s, CH_3), 0.8–2.2 (14 H, m, CH, CH_2, OH), 3.95 (1 H, d, J = 12, C*H*$_2$OH), 4.08 (1 H, d, J = 12, C*H*$_2$OH), 5.62 (1 H, br s, vinyl H); mass spectrum, m/z (relative intensity) 180 (M^+, 15), 162 (55), 149 (100), 147 (50), 109 (80), 81 (68), 67 (66); calcd for $C_{12}H_{20}O$ 180.1514, found 180.1517.

Similar treatment of **15** led to a 1/2.5 mixture of **9** and **18** in low yield. **18**: ^{1}H NMR δ 0.9–2.2 (14 H, m, CH, CH_2, OH), 1.08 (3 H, s, CH_3), 2.60 (1 H, br d, J = 13, allylic H), 4.02 (1 H, d, J = 11, C*H*$_2$OH), 4.14 (1 H, d, J = 11, C*H*$_2$OH); mass spectrum, m/z calcd for $C_{12}H_{20}O$ 180.1514, found 180.1512.

Preparation of Epoxide 10. To a solution of 2.95 g (16 mmol) of **9** in 30 mL of methylene chloride at 0 °C was added a solution of 23 mmol of *m*-chloroperbenzoic acid in 75 mL of methylene chloride. The reaction mixture was then stirred at room temperature for 3 h and filtered, and the filtrate was washed with aqueous sodium bicarbonate, water, and brine, dried (magnesium sulfate), and evaporated to give 3.0 g (95%) of **10** as an oil: ^{1}H NMR δ 0.80 (3 H, s, CH_3), 0.9–2.3 (13 H, m, CH, CH_2), 2.94 (1 H, br s, OH), 3.28 (1 H, t, J = 2, epoxide CH), 3.55 (1 H, $^1/_2$ AB q, J = 13.5, C*H*$_2$OH), 3.71 (1 H, $^1/_2$ AB q, J = 13.5, C*H*$_2$OH); mass spectrum, m/z (relative intensity) 196 (M^+, 10), 165 (80), 137 (80), 81 (55), 67 (70), 55 (65); calcd for $C_{12}H_{20}O_2$ 196.1463, found 196.1462.

Rearrangement of 10 to Epoxide 11. A suspension of 3.2 g (16 mmol) of **10** in 10 mL of 0.5 N sodium hydroxide was stirred at room temperature for 5 h. At this time, 6.5 g of ammonium sulfate was added, and the mixture was extracted with chloroform, dried (magnesium sulfate), and evaporated to provide an oil. ^{1}H NMR indicated the ratio of **10** to **11** to be 2/1. The oil was chromatographed on alumina (activity III), eluting with ether, to provide 800 mg of **11** and 650 mg of recovered **10** as well as mixed fractions. **11**: ^{1}H NMR δ 0.98 (3 H, s, CH_3), 1.1–2.2 (13 H, m, CH, CH_2), 1.60 (1 H, s, OH exchangeable with D_2O), 2.36 (1 H, d, J = 4.5, epoxide CH_2), 2.77 (1 H, d, J = 4.5, epoxide CH_2), 3.26 (1 H, t, J = 2, C*H*OH); mass spectrum, m/z (relative intensity) 196 (M^+, 12), 131 (40), 108 (45), 79 (40), 69 (100), 67 (60), 55 (55); calcd for $C_{12}H_{20}O_2$ 196.1463, found 196.1451.

To 33 mg of **10** in 0.5 mL of dimethyl-d_6 sulfoxide containing tetramethylsilane was added 2 drops of 10 N NaOD, and the reaction was allowed to proceed at room temperature. Periodic examination of the ^{1}H NMR spectrum indicated that after 2 h a 1/2 equilibrium mixture of **10** and **11**, respectively, had been established.

Preparation of 3,5-Dinitrobenzoate 12. To a solution of 110 mg (0.56 mmol) of **11** in 1.1 mL of pyridine was added 130 mg (0.56 mmol) of 3,5-dinitrobenzoyl chloride. After being stirred for 1 h, the reaction mixture was poured into ice–water and extracted with methylene chloride, and the organic layer was washed with aqueous copper sulfate, dried (sodium sulfate), and evaporated to provide 158 mg (72%) of **12**: ^{1}H NMR δ 1.07 (3 H, s, CH_3), 1.1–2.4 (13 H, m, CH, CH_2), 2.60 (1 H, d, J = 4.5, epoxide CH_2), 2.83 (1 H, d, J = 4.5, epoxide CH_2), 4.75 (1 H, t, J = 2, RCO_2CH), 9.16 (2 H, d, J = 2.5, C2′,C6′ H), 9.26 (1 H, t, J = 2.5, C4′ H); mass spectrum, m/z (relative intensity) 390 (M^+, weak), 345 (56), 195 (78), 163 (63), 148 (100), 133 (90), 91 (54), 67 (58); calcd for $C_{19}H_{22}N_2O_7$ 390.1427, found 390.1424.

Attempted Solvolyses of 12. A solution of 140 mg of **12** in 8 mL of 2-butanone/water (80/20) containing 45 μL of 2,6-lutidine was stirred at 90 °C for 24 h. Workup provided only recovered **12**.

A solution of 107 mg of **12** in 8 mL of acetonitrile/water (80/20) was refluxed for 10 days. Workup again provided only recovered **12**.

Preparation of Mesylate 13. To a solution containing 1.2 g (6.2 mmol) of **11** and 1.3 mL (9.5 mmol) of triethylamine in methylene chloride at −5 °C was added 720 μL of methanesulfonyl chloride dropwise. After 0.5 h, the reaction was added to ice–water, and the organic layer was washed with aqueous sodium bicarbonate, dried (sodium sulfate), and evaporated to afford 900 mg (53%) of **13**, mp 84–90 °C: ^{1}H NMR δ 0.98 (3 H, s, CH_3), 1.1–2.4 (13 H, m, CH, CH_2), 2.51 (1 H, $^1/_2$ AB q, J = 4.5, epoxide CH_2), 2.85 (1 H, $^1/_2$ AB q, J = 4.5, epoxide CH_2), 3.02 (3 H, s, OSO_2CH_3), 4.20 (1 H, t, J = 3, CH_3SO_3CH).

Anal. Calcd for $C_{13}H_{22}O_4S$: C, 56.91; H, 8.08. Found: C, 56.59; H, 8.24.

Mesylate **13** was also readily prepared from **10**/**11** mixtures since it could be easily crystallized from the mixture of isomeric mesylates in pure form.

Solvolysis of 13. A solution containing 664 mg (2.4 mmol) of **13** and 280 μL of 2,6-lutidine in 60 mL of acetonitrile/water (80/20) was stirred at 100 °C for 8 days. After concentration, the residue was taken up in methylene chloride and washed with aqueous copper sulfate, water, and brine and dried (sodium sulfate). Removal of solvent and chromatography of the residue on alumina (activity II), eluting with chloroform/methanol, gave, in addition to recovered **13**, 186 mg (44% based on recovered **13**) of **14**, mp 100–103 °C: IR (KBr) 3300, 1705 cm^{-1}; ^{1}H NMR δ 0.82 (3 H, s, CH_3), 1.1–1.9 (12 H, m, OH, CH_2), 2.0–2.2 (1 H, m, CH_2CHCH_2OH), 2.32 (1 H, dd, J = 3,9, CHCO), 2.58 (1 H, apparent q, J = 7, C*H*CH_2OH), 3.8–3.9 (1 H, m, C*H*$_2$OH), 3.9–4.0 (1 H, m, C*H*$_2$OH); mass spectrum, m/z (relative intensity) 196 (M^+, 15), 178 (20), 123 (100), 95 (100), 81 (60), 67 (100), 55 (65); calcd for $C_{12}H_{20}O_2$ 196.1463, found 196.1467.

Anal. Calcd for $C_{12}H_{20}O_2$: C, 73.43; H, 10.27. Found: C, 73.16; H, 10.57.

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Registry No. 7, 22628-06-4; 8, 100207-72-5; 9, 100207-75-8; 10, 100207-77-0; 11, 100207-78-1; 12, 100207-79-2; 13, 100207-80-5; 14, 100207-81-6; 15, 100296-06-8; *trans*-16, 937-99-5; *cis*-16, 937-98-4; 17 (isomer 1), 100207-73-6; 17 (isomer 2), 100207-74-7; 18, 100207-76-9; bromomagnesium isopropylcyclohexylamide, 100207-82-7.

Modified Taxols. 2.[1] Oxidation Products of Taxol

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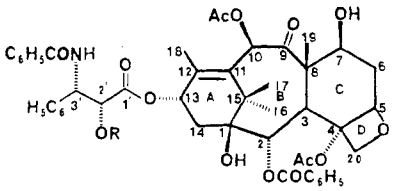
Oxidation of taxol (1) or substituted taxols with Jones' reagent under appropriate conditions yielded 7-oxotaxol (6), 2',7-dioxotaxol (9), or 2'-oxo-7-acetyltaxol (12). Treatment of 7-oxotaxol with DBU or silica gel yielded a *D*-secotaxol derivative 14. Hydrogenation of the 2'-acetate derivative of 14 yielded the unstable diketone 16, while hydrogenation of 14 itself followed by workup in methanol gave the lactone 17.

The complex diterpene taxol (1) was reported in 1971 as the major cytotoxic and antileukemic constituent of *Taxus brevifolia* Nutt.[2] It shows activity in several of the National Cancer Institute's in vivo screens, including the P-388, L-1210, and P-1534 mouse leukemias, the B-16 melanocarcinoma, the CX-1 colon xenograft, the LX-1 lung xenograft, and the MX-1 breast xenograft,[3] and it also shows strong cytotoxicity in KB cell culture.[2] Taxol blocks



1 R = H

4 R = $COCH_3$

7 R = $COOCH_2CCl_3$

cell replication in HeLa cells, predominantly in the mitotic phase of the cell cycle, and studies with purified microtubule protein have demonstrated that it promotes the assembly of unusually stable microtubles in vitro and in cells.[4] The ability to promote the assembly of microtubules in the absence of GTP is a unique feature of this drug,[5] and studies done in vitro with [^{3}H]taxol have indicated that at saturation the drug binds reversibly to polymerized tubulin with an approximate stoichiometry of 1 mol of taxol per mol of polymerized dimer.[6]

Because of its promising anticancer activity and its unusual structure and mechanism of action, taxol is currently undergoing clinical tests as a potential cancer chemotherapeutic agent. However, taxol is obtainable only in relatively low yield by extraction and isolation from *Taxus brevifolia*.[7] In an attempt to address this problem we have initiated a study of structure–activity relationships in the taxol area, in order to determine which parts of the molecule are essential for activity. The ultimate goal of this work (which may or may not be attainable) is to design a simpler analogue of taxol which would be accessible either by synthesis or by modification of such readily available taxanes as *O*-cinnamoyltaxicin-I triacetate (2)[9] or taxusin (3).[10]

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