The Total Synthesis of 12-HETE and 12,20-DiHETE

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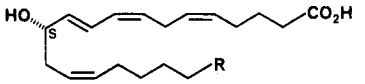
The total syntheses of 12-HETE (1) in racemic form and of both enantiomers in optically pure form are reported. The synthesis of a metabolite of 12(*S*)-HETE, 12,20-diHETE (2), in optically pure form is also reported.

As part of an ongoing research project into the lipoxygenase-derived metabolites of arachidonic acid, we became interested in 12-hydroxyeicosatetraenoic acid (12-HETE, 1). This natural product is generated from



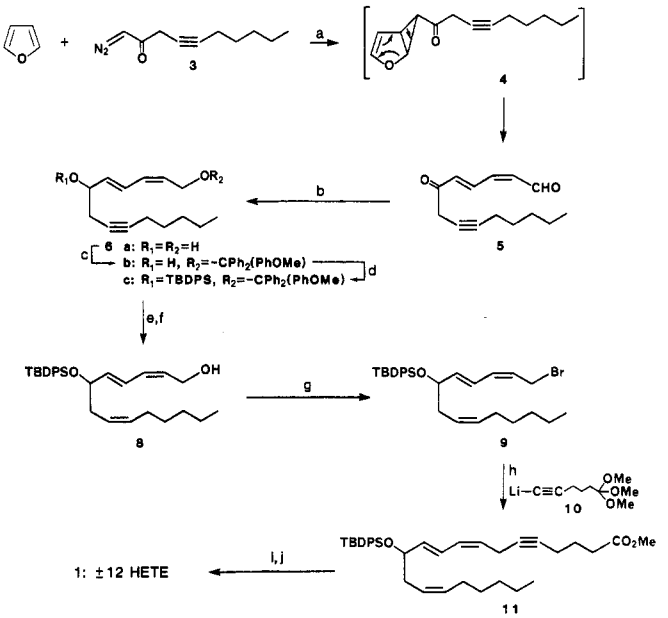
1: R=CH_3 12-HETE
2: R=CH_2OH 12,20-diHETE

arachidonic acid by a 12-lipoxygenase enzyme, which is found in platelets[1] and skin keratinocytes.[2] The 12-HETE is of particular interest since it has been detected in high concentrations in psoriatic lesions[3] and has been shown to possess both chemotactic and chemokinetic properties. The 12(*S*)-HETE is also the major lipoxygenase-derived arachidonic acid metabolite produced by the platelet and has been postulated as a mediator of the circulatory system. In the interest of fully evaluating the biological properties of 12-HETE it was desirable to obtain adequate supplies of both enantiomers of 12-HETE (1) and its metabolite 12,20-diHETE (2). 12,20-DiHETE is particularly interesting since the introduction of the 20-hydroxy function is performed in the leukocyte.[4] Therefore, this compound is an example of a product from the interaction of two different types of circulating cells.

In order to facilitate the study of the biological and biochemical properties of these arachidonic acid metabolites, 12-HETE and 12,20-diHETE have been synthetically prepared, and these syntheses are described herein. Two different approaches to 12-HETE were realized, and 12,20-diHETE was prepared by adaptation of one of the 12-HETE syntheses. The first synthesis of 12-HETE utilized the versatile cyclopropafuran–diene synthesis developed in these laboratories and yielded racemic 12-HETE. The second synthesis used D- and L-arabinose as the starting material and therefore gave optically pure 12(*S*)-HETE and 12(*R*)-HETE, respectively. The second synthesis was modified to give 12(*S*),20-diHETE.

The cyclopropafuran–diene synthesis is a convenient method for generation of the *cis,trans*-diene found in all of the HETE's,[5] as illustrated by the case of 12-HETE. This method allows the preparation of the *cis,trans*-diene backbone of the HETE's in a very straightforward manner without relying on the Wittig reaction. The Rh(II)-catalyzed addition of the diazo ketone **3**, prepared from the corresponding acid chloride by treatment with diazomethane, to furan gives the unstable cyclopropyafuran **4**, which undergoes an electrocyclic ring opening to give the *cis,trans*-diene aldehyde **5**, (Scheme I). Reduction of the dicarbonyl compound **5** by treatment with sodium borohydride and cerium(III) chloride in isopropyl alcohol gave the corresponding diol **6a**, which was converted to the alcohol **8** by selective protection and Lindlar reduction of the acetylenic function. Treatment of the alcohol **8** with CBr_4/DIPHOS gave the corresponding bromide **9**, which then was coupled with the lithium acetylide **10** in the presence of CuBr/DMS to yield, after aqueous workup, the ester **11**. Lindlar hydrogenation of the acetylene **11** and subsequent deprotection of the product of this reduction gave (±)-12-HETE [(±)-1].

Scheme I. Synthesis of (±)-12-HETE[a]



[a] (a) $Rh(OAc)_2$ dimer; (b) $NaBH_4/CeCl_3$, IPA/H_2O; (c) (*p*-(MeO)Ph)Ph_2CCl, pyr; (d) *t*-$BuPh_2SiCl$/imidazole, DMF; (e) Lindlar H_2; (f) 80% AcOH; (g) DIPHOS/CBr_4, CH_2Cl_2; (h) 10/CuI (1:1), THF/HMPA −78 °C → room temperature; (i) *n*-Bu_4NF, THF; (j) HO^-.

The second synthesis of 12-HETE utilized the thioacetal **12**,[6] which is readily available to 100-gm quantities from D-arabinose or its enantiomer prepared from L-arabinose to give the 12(*S*)- or 12(*R*)-HETE, respectively. This illustrates the advantage to the use of arabinose as a starting material. Since both enantiomers of this sugar are readily available and inexpensive, both enantiomers of the final product are also available if arabinose is used as the source of the asymmetric center(s) in the product. The reasoning behind the preparation of the 12(*R*)-HETE is that the

(1) Hamberg, M.; Svensson, J.; Samuelsson, B. *Proc. Natl. Acad. Sci. U.S.A.* **1974**, *71*, 3824–3828.

(2) Hammarstrom, S.; Lindgen, J. A.; Marcello, C.; Duell, E. A.; Anderson, T. F.; Voorhees, J. J. *J. Invest. Dermatol.* **1979**, *73*, 180–183.

(3) (a) Hammarstrom, S.; Hamberg, M.; Samuelsson, B.; Duell, E. A.; Stawiski, M.; Voorhees, J. J. *Proc. Natl. Acad. Sci. U.S.A.* **1975** *72*, 5130–5137. (b) The above reference identifies the 12-HETE in psoriatic lesions as the 12(*S*) isomer; however, a recent abstract (Woollard, P. *J. Invest. Dermatol.* **1985**, *84*, 455) reports that 12(*R*)-HETE is found in psoriatic scale.

(4) Marcus, A. J.; Safier, L. B.; Ullman, H. L.; Broekman, M. J.; Islam, N.; Oglesby, T. D.; Gorman, R. R. *Proc. Natl. Acad. Sci. U.S.A.* **1984**, *81*, 903–907.

(5) Rokach, J.; Adams, J.; Perry, R. *Tetrahedron Lett.* **1983**, *24*, 5185–5188.

(6) Wong, M. Y. H.; Gray, G. R. *J. Am. Chem. Soc.* **1978**, *100*, 3548–3553.

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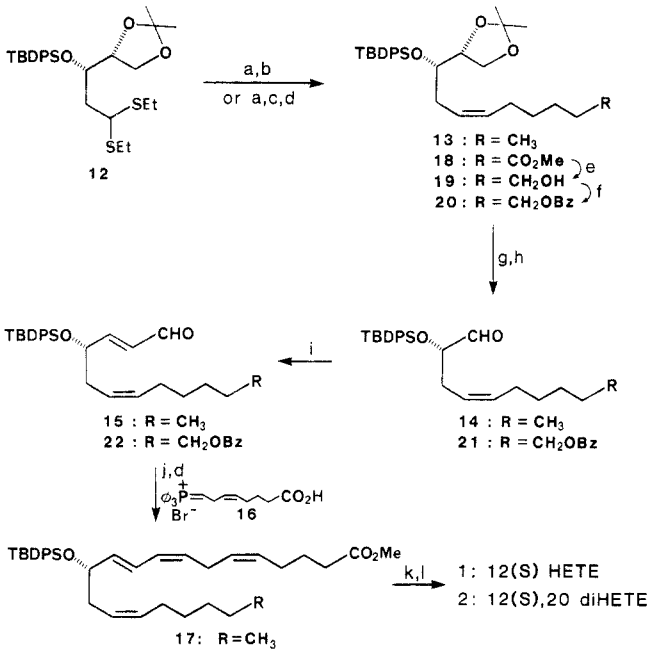
Scheme II



[a] (a) $NCS/AgNO_3$, CH_3CN/H_2O; (b) $Ph_3P{=}CH(CH_2)_4CH_3$, THF/HMPA, −78 °C → room temperature; (c) $Ph_3P{=}CH(CH_2)_4CO_2^-$; THF/HMPA, −78 °C → room temperature; (d) Me_2SO_4 (excess)/$NaHCO_3$; (e) $AlH_3{\cdot}Et_2O$, THF, 0 °C; (f) BzBr, CH_2Cl_2/Et_3N; (g) TFA, THF/H_2O; (h) $Pb(OAc)_4/Na_2CO_3$, CH_2Cl_2, −78 °C; (i) $Ph_3P{=}CHCHO$, $PhCH_3$, 80 °C; (j) **16**, THF/HMPA, −78 °C → room temperature; (k) n-Bu_4NF, THF; (l) HO^-.

kerotinocyte 12-lipoxygenase has been reported to be different than the platelet 12-lipoxygenase, and the absolute configuration of the kerotinocyte produced 12-HETE has not been determined.

Hydrolysis of the thioacetal **12** by treatment with *N*-chlorosuccinimide and silver(I) nitrate and condensation of the resulting aldehyde with (1-hexylidene)triphenylphosphorane gave the olefin **13** (Scheme II). Treatment of the acetonide **13** with aqueous TFA generated the corresponding diol and lead tetraacetate cleavage of this diol gave the aldehyde **14**. The aldehyde **14** was then homologated by treatment with (formylmethylidene)triphenylphosphorane to afford the α,β-unsaturated aldehyde **15**. Condensation of the aldehyde **15** with the phosphorane **16** gave, after deprotection optically pure ($[\alpha]^{22}_D$ +13° (*c* 1.5, acetone) methyl ester)[7,8] 12(*S*)-HETE (**1**). Starting with L-arabinose optically pure 12(*R*)-HETE was prepared by the same route ($[\alpha]^{22}_D$ −13° (*c* 1.6, acetone) methyl ester).

The 12(*S*),20-diHETE (**2**) was prepared by an analogous route. Hydrolysis of the thioacetal **12** and condensation of resulting aldehyde with the phosphorane generated from the phosphonium salt derived from 6-bromohexanoic acid gave, after quenching with dimethyl sulfate, the ester **18**. Reduction of the ester **18** by treatment with allene–ether complex gave the corresponding alcohol **19**, which was protected by treatment with benzoyl bromide and triethylamine to give the benzoate **20**. The benzoate **20** was converted into 12(*S*),20-diHETE (**2**) by the same transformations used to convert its CH_3 analogue **13** into 12-(*S*)-HETE in a similar yield.

In conclusion, 12-HETE (**1**) has been prepared in both racemic and optically pure forms (both enantiomers) and a metabolite 12(*S*),20-diHETE (**2**) has been synthesized optically pure. The biology of these compounds will be studied and reported at a later date.

Experimental Section

General. Tetrahydrofuran (THF) was distilled from sodium/benzophenone immediately prior to use. Oxalyl chloride and hexamethylphosphoramide (HMPA) were distilled from CaH_2 (HMPA at reduced pressure) and stored under a nitrogen atmosphere. All other solvents were of reagent grade from freshly opened bottles. Flash chromatography refers to the procedure described by Still et al.[7] NMR spectra were recorded on a Bruker AM 250 (250 MHz) or a Varian EM 390 (90 MHz) instrument. Numbers in the spectral assignments refer to the position of the carbon in the final product. IR spectra were obtained with a Perkin-Elmer 681 spectrophotometer. UV spectra were recorded on a Perkin-Elmer Lambda 5 instrument. Optical rotations were obtained with the indicated solvent and concentration in a 1-dm cell using a Perkin-Elmer 481 polarimeter. High-resolution mass spectra (HRMS) were performed by Mike Evans of l'Université de Montréal, Montreal, Quebec. All reactions were carried out under an inert atmosphere of nitrogen or argon and were monitored by thin-layer chromatography (TLC). TLC was performed with E. Merck 60F-254 precoated silica (0.2 cm) on glass.

1-Diazo-4-decyn-2-one (3). To a solution of 3-nonynoic acid[9] (9.5 g, 61.7 mmol) in benzene (50 mL) was added a solution of oxalyl chloride (8.1 mL, 1.5 equiv) in benzene (50 mL) and 1 drop of DMF. The resulting mixture was stirred at room temperature until the bubbling had ceased, and then the solvent was removed at reduced pressure to yield 9 g of a yellow oil. This oil was redissolved in dry benzene (40 mL) cooled to −10 °C and an excess of diazomethane in ether (~150 mmol) was added slowly. The resulting mixture was stirred at −10 °C for 1 h then −5 °C overnight. The solvent was then removed at reduced pressure, and the residue was filtered through SG-60 silica gel (2 × 10 cm) washing with ether. Removal of the solvent at reduced pressure gave the diazo ketone **3** as an orange oil (8.92 g; 81%): IR (neat) 3120, 2960, 2940, 2860, 2210, 2110, 1650, 1350, 1150, 1140 cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$) δ 1.2 (m 3 H, CH_2CH_3), 1.6 (m 6 H, $(CH_2)_3CH_3$), 2.5 (m, 2 H, $\equiv CCH_2CH_2$), 3.5 (t, 2 H, $C(O)CH_2C\equiv$, J = 3 Hz), 6.25 (br s, 1 H, $N_2CHC(O)$).

2,4-Tetradecadien-8-yne-1,6-diol (6a). A solution of the diazo ketone **3** (3.0 g, 17 mmol) in freshly distilled furan (90 mL) was added dropwise to a solution of $Rh(OAc)_2$ (15 mg) in furan (90 mL). The resulting mixture was stirred at room temperature for 1 h, and then the solvent was removed at reduced pressure. The residue was dissolved in 5:1 isopropyl alcohol/water (450 mL) containing ceric(III) chloride pentahydrate (17.1 g, 51 mmol). This solution was cooled to 0 °C, and then sodium borohydride (2.0 g, 51 mmol) was added over 30 min. The reaction mixture was then acidified to pH 6 with 1 N aqueous HCl and diluted with water (200 mL) and the resulting mixture extracted with ether (2 × 300 mL). The combined organic extracts were dried over anhydrous magnesium sulfate, and the solvent was removed at reduced pressure. Flash chromatography of the residue (2 × 20 cm column, 50% ethyl acetate in toluene containing 1% triethylamine) yielded the desired *cis,trans*-dienediol **6a** (1.5 g, 49%) as a 4:1 mixture with the undesired *cis/cis*-dienediol: ^1H NMR (250 MHz, acetone-d_6) δ 0.91 (t, 3 H, CH_2CH_3, J = 7.5 Hz), 2.12 (m, 2 H, $\equiv CCH_2CH_2$), 2.34 (m, 2 H, $CH(OH)CH_2C{=}$), 4.25 (t, 2 H, CH_2OH, J = 7.2 Hz), 4.65 (m, 1 H, CHOH), 5.49 (m, 1 H, $CH_2(OH)CH{=}$), 5.83 (dd, 1 H, $=CHCH(OH)$, J = 7.1 Hz, J = 14.3 Hz), 5.99 (dd, 1 H, $CH_2(OH)CH{=}CH$, $J = J$ = 9.8 Hz), 6.54

(7) Literature values. $[\alpha]^{25}_D$ +1.3° (*c* 0.3, $CHCl_3$): Corey, E. J.; Niwa, H.; Knolle, J. *J. Am. Chem. Soc.* **1978**, *100*, 1942–1943. $[\alpha]^{25}_D$ +1.5° (*c* 0.2, $CHCl_3$): Just, G.; Wang, Z. Y. *Tetrahedron Lett.* **1985**, *26*, 2993–2996. The authors found that in chloroform 12-HETE methyl ester did not have a measurable optical rotation in chloroform at concentrations as high as 20 mg/mL. However the optical rotation in acetone could be readily and reproducably determined and was of equal magnitude and opposite sign for the two enantiomers of 12-HETE prepared. The optical purity of 12-HETE's prepared from D- and L-arabinose was verified by the preparation of the "dehydroabietyl" urethane derivative[8] of the methyl ester and HPLC analysis of these derivatives (400:1:1 hexane/methanol/isopropyl alcohol, Waters 5 μ-Porasil column).

(8) Corey, E. J.; Hashimoto, S.-I. *Tetrahedron Lett.* **1981**, *22*, 299–302.

(9) Prepared by Jones oxidation of the commercially available 3-nonyn-1-ol.

(dd, 1 H, $CH_2(OH)CH{=}CHCH{=}$, J = 9.8 Hz, J = 14.3 Hz).

6-[(*tert*-Butyldiphenylsilyl)oxy]-1-[diphenyl(4-methoxyphenyl)methoxy]-2,4-tetradecadien-8-yne (6c). To a solution of the diol **6a** (1.3 g, 5.5 mmol) in pyridine (17 mL) at 0 °C was added chlorodiphenyl(*p*-methoxyphenyl)methane (2.37 g, 7.7 mmol), and the resulting solution was stirred at 0 °C overnight. The reaction mixture was then diluted with ether (200 mL), and the resulting mixture was washed with water (100 mL), saturated aqueous sodium bicarbonate (3 × 200 mL), and then saturated with aqueous sodium chloride (100 mL). The organic phase was then dried over anhydrous sodium sulfate, and the solvent was removed at reduced pressure. Flash chromatography of the residue (2 × 21 cm column, 33% ethyl acetate in hexanes) gave the desired tritylated material **6b** as a yellow oil. To a solution of the tritylated material in DMF (25 mL) at 0 °C were added imidazole (870 mg, 12.8 mmol) and *tert*-butylchlorodiphenylsilane (2.0 mL, 7.7 mmol). The resulting mixture was stirred at room temperature overnight, diluted with ether (200 mL), then washed with water (3 × 200 mL), and dried over anhydrous sodium sulfate. Removal of the solvent at reduced pressure and flash chromatography of the residue (2 × 20 cm column, 5% ethyl acetate in hexanes) yielded the desired silyl ether **6c** (2.14 g, 53%).

6-[(*tert*-Butyldiphenylsilyl)oxy]-1-[diphenyl(4-methoxyphenyl)methoxy]-2,4,8-tetradecatriene (7). To a solution of the acetylene **6c** (200 mg, 0.29 mmol) in hexane (20 mL) were added 120 mg of Lindlar catalyst and 200 μL of pyridine. The resulting mixture was stirred under an atmosphere of hydrogen (P = 1 atm) for 10 h and then filtered. Removal of the solvent at reduced pressure gave the desired olefin **7** (197 mg, 98%): ^{1}H NMR (250 MHz, acetone-d_6) δ 0.89 (br t, 3 H, CH_2CH_3), 1.3 (cm, 6 H, $(CH_2)_3$), 1.89 (m, 2 H, $=CCH_2CH_2$), 2.21, (cm, 2 H, $CH(O)CH_2C{\equiv}$), 3.83 (m, 2 H, $OCH_2CH{\equiv}$), 4.27 (br q, 1 H, $=CCH(OSi)$, $J \simeq$ 10 Hz), 5.38 (m, 2 H, $CH_2CH{=}CHCH_2$), 5.4–6.05 (diene protons).

6-[(*tert*-Butyldiphenylsilyl)oxy]-2,4,8-tetradecatrien-1-ol (8). The trityl ether **7** (500 mg, 0.68 mmol) was dissolved in 80% acetic acid (15 mL) and the resulting solution stirred at room temperature for 48 h. The reaction mixture was then diluted with ether (100 mL), the resulting mixture was washed with water (2 × 100 mL) and saturated aqueous sodium bicarbonate (2 × 100 mL) and dried over anhydrous sodium sulfate, and the solvent was removed at reduced pressure. HPLC of the residue (Waters μ-Porasil 7.9 mm × 30 cm column, 10% ethyl acetate in hexanes) gave the desired primary alcohol **8** (153 mg, 46%): ^{1}H NMR (250 MHz, acetone-d_6) δ 0.85 (br t, 3 H, CH_2C_3), 1.07 (s, 9 H, t-Bu), 1.85 (m, 2 H, $C{=}CCH_2CH_2$), 2.27 (cm, 2 H, $CH(OSi)CH_2C{=}$), 4.14 (t(dd), 2 H, CH_2OH, $J \simeq J$ = 6 Hz), 4.29 (q(dt), 1 H, $=CCH(OSi)CH_2$, $J = J$ = 7.0 Hz), 5.34 (m, 2 H, $CH_2CH{=}CHCH_2$), 5.49 (m, 1 H, $CH_2(OH)CH{=}$), 5.70 (dd, 1 H, $=CHCH(OSi)CH_2$, J = 7.0 Hz, J = 14.2 Hz), 5.93 (t(dd), 1 H, $(CH_2OH)CH{=}CH$, $J = J$ = 11.3 Hz), 6.29 (dd, 1 H, $CH_2(OH)CH{=}CHCH{=}$ J = 11.3 Hz, J = 14.2 Hz).

1-Bromo-6-[(*tert*-butyldiphenylsilyl)oxy]-2,4,8-tetradecatriene (9). To a solution of the alcohol **8** (52 mg, 0.11 mmol) in dichloromethane (2 mL) at 0 °C were added tetrabromomethane (1.1 eq) and bis(1,2-diphenylphosphino)ethane (DIPHOS) (44.8 mg, 0.12 mmol). The resulting mixture was stirred at room temperature for 30 min and passed through a 1 × 10 cm column of SG-60 silica washed with 10% ethyl acetate in hexanes. Removal of the solvent at reduced pressure yielded the desired bromide **9** (57 mg, 96%): ^{1}H NMR (250 MHz, acetone-d_6) δ 0.84 (br t, 3 H, CH_2CH_3), 1.08 (s, 9 H, t-Bu), 1.85 (m, 2 H $=CHCH_2CH_2$), 2.25 (cm, 2 H, $CH(OSi)CH_2CH{=}$), 4.03 (d, 2 H, CH_2Br, J = 9.4 Hz), 4.31 (br q (dt), 1 H, $CH(OSi)$, $J \simeq J$ = 6.6 Hz)8 5.35 (cm, 2 H, $CH_2CH{=}CHCH_2$), 5.64 (br q (dt), 1 H, $BrCH_2CH{=}$, $J \simeq J$ = 10 Hz), 5.87 (dd, 1 H, $=CHCH(OSi)$, J = 6.6 Hz, J = 15 Hz), 6.08 (t(dd), 1 H, $BrCH_2CH{=}CH$, $J = J$ = 11.3 Hz), 6.44 (dd, 1 H, $BrCH_2CH{=}CHCH{=}$, J = 11.3 Hz, J = 15 Hz).

Methyl 12-[(*tert*-Butyldiphenylsilyl)oxy]-8,10,14-eicosatrien-5-ynoate (11). To a stirred suspension of cupric iodide (28 mg, 0.15 mmol) in a solution of the ortho ester **10**[10] (25 mg, 0.15 mmol) in dry THF (0.3 mL) at −78 °C was added a solution of 1.55 M n-butyllithium in hexane (84 μL, 0.13 mmol). After 15 min a solution of the bromide **9** (70 mg, 0.13 mmol) was added and the resulting solution stirred at −78 °C for 15 min, and then HMPA (160 μL) was added and the reaction mixture allowed to warm to 0 °C for 1 h and room temperature for 1 h. The reaction mixture was then treated with saturated aqueous ammonium chloride (15 mL) and the resulting mixture extracted with ether (2 × 30 mL). The combined organic extracts were dried over anhydrous sodium sulfate, and the solvent was removed at reduced pressure. Flash chromatography of the residue (1 × 20 cm column, 5% ethyl acetate in hexanes) gave the desired coupled product **11** (28 mg, 48%): ^{1}H NMR (250 MHz, $CDCl_3$) δ 0.84 (t, 3 H, CH_2CH_3, J = 7.5 Hz), 1.01 (s, 9 H, t-Bu), 1.80 (m, 2 H, $=CHCH_2CH_2$), 2.22 (m, 4 H, $=CHCH_2CH(OSi)$ and $\equiv CCH_2CH_2$), 2.40 (t, 2 H, CH_2CO_2Me, J = 7.5 Hz), 2.85 (m, 2 H, $=CHCH_2C{\equiv}$), 3.66 (s, 3 H, CO_2CH_3), 4.18 (br q, 1 H, $CH(OSi)$), 5.29 (m, 3 H, $CH_2CH{=}CHCH_2$ and $\equiv CCH_2CH{=}$), 5.61 (dd, 1 H, $=CHCH(OSi)$, J = 6.8 Hz J^1 = 14.6 Hz), 5.88 (t(dd), 1 H, $\equiv CCH_2CH{=}CH$, $J \simeq J$ = 11.1 Hz), 6.10 (dd, 1 H, $CH{=}CHCH(OSi)$, J = 11.1 Hz, J^1 = 14.6 Hz).

12-Hydroxyeicosatetraenoic Acid ((±)-1). The acetylene **11** was semihydrogenated as described for the conversion of acetylene **6c** to olefin **7** to give the 12-*O*-silyl-12-HETE methyl ester in a 61% yield. This compound was deprotected as described for the conversion of the protected optically pure 12(*S*)-HETE **17** to 12(*S*)-HETE (**1**).

2-Deoxy-3-*O*-(*tert*-butyldiphenylsilyl)-4,5-bis-*O*-(1-methylethylidene)-D-*erythro*-pentose. To a stirred solution of silver(I) nitrate (9.92 g, 58.3 mmol) and *N*-chlorosuccinimide (7.64 g, 57.2 mmol) in 3:1 acetonitrile/water (210 mL) at −20 °C was added a solution of the thioacetal **12** (8.61 g, 16.6 mmol) in acetonitrile (48 mL). The resulting mixture was stirred at −20 °C for 10 min, and then Me_2SO (5 mL) was added. After a further 10 min at −20 °C, 100 mL of 25% aqueous ammonium acetate (100 mL) was added. The mixture was allowed to warm to 0 °C and then filtered through a pad of Celite being washed with water (50 mL) and dichloromethane (250 mL). The filtrate was partitioned and the aqueous phase extracted with dichloromethane (3 × 100 mL). The combined organic phases were washed with saturated aqueous sodium chloride and dried over anhydrous sodium sulfate, and the solvent was removed at reduced pressure. Flash chromatography of the residue (5 × 21 cm column, 20% ethyl acetate in hexanes) afforded the desired aldehyde (5.53 g, 77% yield): $[\alpha]^{23}_D$ −6.91° (c 0.54, $CHCl_3$); IR (neat) 3080, 3060, 2990, 2960, 2940, 2900, 2860, 2730, 1730, 1475, 1465, 1430, 1375, 1260, 1215, 1170, 1110, 1070, 860, 820, 740, 700 cm^{-1}; ^{1}H NMR (90 MHz, $CDCl_3$) δ 1.04 (s, 9 H, $(CH_3)_3CSi$), 1.26 (s, 6 H $(CH_3)_2$), 2.58 (m, 2 H, CH_2CHO), 9.58 (t, 1 H, CHO, J = 1.8 Hz).

3-*O*-(*tert*-Butyldiphenylsilyl)-1,2-bis-*O*-(1-methylethylidene)-5(*Z*)-undecene-1,2(*R*),3(*S*)-triol (13). To a stirred solution of 1-hexylidenetriphenylphosphorane (18.3 mmol), generated from the corresponding phosphonium salt (8.01 g, 18.3 mmol) and 1 equiv of *n*-BuLi in dry THF (50 mL), at −78 °C was added a solution of the above aldehyde (2.48 g, 6.0 mmol) in dry THF (40 mL) over 5 min. The resulting mixture was stirred at −78 °C for 10 min and then allowed to warm to room temperature. After 2 h the reaction was quenched by the addition of 25% aqueous ammonium acetate (100 mL) and the resulting mixture extracted with ether (2 × 200 mL).

The combined organic extracts were washed with saturated aqueous sodium chloride (200 mL) and dried over anhydrous magnesium sulfate, and the solvent was removed at reduced pressure. Flash chromatography of the residue (3 × 21 cm column, 5% ether in hexanes) gave the olefin **13** (2.59, 90%): $[\alpha]^{22}_D$ +36.2° (c 1.5, $CHCl_3$); IR (neat) 2960, 2940, 2900, 2860, 1590, 1470, 1460, 1430, 1390, 1380, 1365, 1250, 1210, 1110, 1070, 860, 820, 740, 700 cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$) δ 0.87 (t, 3 H, CH_2CH_3, J = 7 Hz), 1.07 (s, 9 H, $(CH_3)_3CSi$), 1.31 and 1.34 (2 s, 6 H, $(CH_3)_2C$), 1.80 (m, 2 H, $=CHCH_2CH_2$), 2.15 (m, 2 H, $CHCH_2HC{=}$), 3.80 (t, 1 H, $CHH'O$, $J = J$ = 15 Hz), 3.95 (t, 1 H, $CHH'O$, $J = J$ = 15 Hz), 3.98 (m, 1 H, $CHOSi$), 4.08 (m, 1 H, $CHOC$), 5.39 (m, 2 H, CH=CH).

3-*O*-(*tert*-Butyldiphenylsilyl)-5(*Z*)-undecene-1,2(*R*),3(*S*)-triol. To a stirred solution of the acetonide **13** (2.59 g, 5.39 mmol) in 4:1 THF/water (25 mL) at 0 °C was added trifluoroacetic acid (1 mL). The resulting solution was allowed to warm to room

(10) Just, G.; Luthe, C. *Tetrahedron Lett.* **1982**, *23*, 1331–1334.

temperature and left overnight. The reaction was then neutralized by the addition of concentrated ammonium hydroxide, and the THF was removed at reduced pressure. The residue was diluted with water (100 mL), and the resulting mixture was extracted with dichloromethane (2 × 100 mL). The combined organic extracts were dried over anhydrous sodium sulfate, and the solvent was removed at reduced pressure. Flash chromatography of the residue (3 × 25 cm column, 50% ethyl acetate in hexanes) yielded the desired diol (1.97 g, 83%): $[\alpha]^{22}_D$ +39.4 (*c* 1.8, $CHCl_3$); IR (neat) 3406, 3080, 3060, 3020, 2950, 2900, 2860, 1470, 1460, 1430, 1110, 1070, 935, 865, 820, 740, 700 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 0.86 (t, 3 H, CH_2CH_3, *J* = 7 Hz), 1.07 (s, 9 H, $(CH_3)_3C$), 1.76 (m, 2 H =$CHCH_2CH_2$), 2.24 (m, 2 H, $CHCH_2HC$=); 3.69, 3.80, and 3.92 (cm, 1, 1, and 2 H, CHOSi, CHOH, and CH_2OH), 5.30 (cm, 2 H, CH=CH).

2(*S*)-[(*tert*-Butyldiphenylsilyl)oxy]-4(*Z*)-decenal (14). To a stirred solution of the diol (1.97 g, 4.48 mmol) in dichloromethane (38 mL) at −78 °C were added sodium carbonate (1.51 g, 14.2 mmol) and then lead(IV) tetraacetate (2.92 g, 6.59 mmol). The resulting mixture was stirred at −78 °C for 15 min and then applied to the top of a flash chromatography column (2 × 25 cm, packed in hexanes), and the aldehyde was eluted with 20% ethyl acetate in hexanes to give the desired aldehyde **14** (1.69 g, 91%). This aldehyde was homogeneous by ^1H NMR and TLC and was used immediately without further purification: IR (neat) 3080, 3050, 3020, 2960, 2930, 2900, 2860, 2720, 1740, 1590, 1470, 1460, 1430, 1370, 1310, 1240, 1155, 1110, 1010, 1000, 830, 740, 700 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 0.83 (t, 3 H, CH_2CH_3, *J* = 7 Hz), 1.07 (s, 9 H, $(CH_3)_3$), 1.87 (m, 2 H, =$CHCH_2CH_2$), 2.34 (m, 2 H, $CHCH_2HC$=), 4.04 (dt, 1 H, CHCHO, *J* = 6.25 Hz, *J* = 1.5 Hz), 5.4 (m, 2 H, CH=CH), 9.52 (d, 1 H, CHO, *J* = 1.5 Hz).

[(*tert*-Butyldiphenylsilyl)oxy]-2(*E*),6(*Z*)-decadienal (15). To a stirred solution of the aldehyde **14** (881 mg, 2.16 mmol) in toluene 15 mL) was added (formylmethylidene)triphenylphosphorane (688 mg, 2.27 mmol) and the resulting mixture warmed to 80 °C and followed by TLC (20% ethyl acetate in hexanes). After 3 h the reaction mixture was cooled to room temperature, and the solvent was removed at reduced pressure. Flash chromatography of the residue (4 × 25 cm column, 8% ether in hexanes) gave the desired α,β-unsaturated aldehyde **15** (520 mg, 55%) plus recovered starting material (174 mg, 20%): $[\alpha]^{22}_D$ +15.6° (*c* 3, $CHCl_3$); IR (neat) 2960, 2935, 2860, 1685, 1110 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 1.01 (s, 9 H, $C(CH_3)_3$, 1.88 (m, 2 H, H-16), 2.3 3 (m, 2 H, H-13), 4.43 (m, 1 H, H-12), 5.18–5.51 (m, 2 H, H-14, H-15, 6.20 (dd, 1 H, *J* = 9.0 Hz, *J* = 17 Hz, H-10), 6.70 (dd, 1 H, *J* = 5 Hz, *J* = 17 Hz, H-11), 7.25–7.69 (m, 10 H, 2 Ph), 9.43 (d, 1 H, *J* = 9 Hz, H-9).

Methyl 12(*S*)-[(*tert*-Butyldiphenylsilyl)oxy]-5(*Z*),8(*Z*),10(*E*),14(*Z*)-eicosatetraenoate (17). The phosphorane **16** was generated as follows: To a stirred solution of the phosphonium salt (623 mg, 1.17 mmol) in (17) dry THF (3 mL) and HMPA (1.5 mL) at 0 °C was added a solution of lithium hexamethyldisilazide (LiHMDS) (2 mmol) in dry THF (3 mL) over 5 min. The resulting mixture was stirred at 0 °C until a clear orange solution was obtained (~1 h), and then the solution was cooled to −78 °C. A solution of the aldehyde **15** (298 mg, 0.69 mmol) in THF (3 mL) was then added over 5 min. The resulting mixture was stirred at −78 °C for 30 min and then at 0 °C for a further 30 min. At this time the reaction mixture was treated with sodium bicarbonate (253 mg, excess) and dimethyl sulfate (0.38 mL, 2 equiv), and after 10 min this mixture was allowed to warm to room temperature and the stirring continued until a clear solution was obtained (approximately 1 h). The reaction mixture was then diluted with 25% aqueous ammonium acetate (15 mL) and extracted with ether (2 × 50 mL). The combined ether extracts were washed with 25% aqueous ammonium acetate (3 × 20 mL) and dried over anhydrous sodium sulfate, and the solvent was removed at reduced pressure. Flash chromatography of the residue (3 × 25 cm column, 20% ethyl acetate in hexanes) afforded the Wittig adducts (323 mg, 81%) as a mixture of cis and trans isomers (19:1): IR (neat) 2965, 2930, 2860, 1735, 1420, 1110, 820, 740, 705 cm^{-1}; ^1H NMR (250 MHz, acetone-d_6) δ 0.85 (t, 3 H, *J* = 7 Hz, H-20), 1.03 (s, 9 H, $C(CH_3)_3$), 1.65 and 1.85 (2 m, 4 H, H-4 and H-16), 2.27 (t, 2 H, *J* = 7.4 Hz, H-2), 2.29 (m, 2 H, H-13), 2.80 (t, 2 H, *J* = 6 Hz, H-7), 3.58 (s, 3 H, CO_2Me), 4.31 (q, 1 H, *J* = 6.8 Hz, H-12), 5.25–5.42 (m, 5 H, H-5, H-6, H-8, H-14, H-15), 5.68 (dd, 1 H, *J* = 6.8, 15 Hz, H-11), 5.90 (dd, 1 H, *J* = 15 Hz, J^1 = 10.8 Hz, H-9), 6.33 (dd, 1 H, *J* = 11.0 Hz, J^1 = 15 Hz, H-10), 7.35–7.74 (m, 10 H, 2 Ph); high-resolution mass spectrum, *m/z* calcd for $C_{33}H_{43}SiO_3$ ($M^+ - C_4H_9$) 515.2932, found 515.3011.

Methyl 12(*S*)-Hydroxy-5(*Z*),8(*Z*),10(*E*),14(*Z*)-eicosatetraenoate. To a stirred solution of the 19:1 mixture of *cis*- and *trans*-**17** (55 mg, 0.096 mmol) in THF (0.5 mL) at 0 °C was added a solution of tetra-*n*-butylammonium fluoride in THF (1 M) (0.3 mL, 0.3 mmol); the resulting mixutre was allowed to warm to room temperature. After 2 h a further 3 equiv of tetra-*n*-butylammonium fluoride was added, and the reaction mixture was stirred overnight. Acetic acid (36 μL) was then added and the resulting solution filtered through a plug of SG-60 silica gel (0.5 × 10 cm, 20% ethyl acetate in hexanes). Concentration of the eluant and purification of the concentrate by standard phase HPLC (7.8 mm × 30 cm μ-Porasil column, 15% ethyl acetate in hexanes) gave the methyl ester of 12-HETE (23 mg, 74%): $[\alpha]^{22}_D$ +13° (*c* 1.5, acetone); IR (neat) 3380, 2960, 2930, 2860, 1740, 1425, 1110, 820, 740, 700 cm^{-1}; ^1H NMR (250 MHz, acetone-d_6) δ 0.85 (t, 3 H, *J* = 6 Hz, H-20), 1.67 and 2.06 (2 m, 4 H, H-4 and H-16), 2.27 (t, 2 H, *J* = 7.4 Hz, H-2), 2.22 (m, 2 H, H-13), 2.97 (t, 2 H, *J* = 6.8 Hz, H-7), 3.73 (s, 3 H, CO_2Me), 4.22 (m, 1 H, H-12), 5.33–5.53 (m, 5 H, H-5, H-6, H-8, H-14, H-15), 5.78 (dd, 1 H, *J* = 15, J^1 = 6.5 Hz, H-11), 5.99 (t, 1 H, *J* = 10.8 Hz; H-9), 6.59 (dd, 1 H, *J* = 15 Hz, *J* = 11 Hz, H-10); high-resolution mass spectrum, *m/z* calcd for $C_{21}H_{32}O_2$ ($M^+ - H_2O$) 316.2402, found 316.2395.

12(*S*)-Hydroxy-5(*Z*),8(*Z*),10(*E*),14(*Z*)-eicosatetraenoic Acid (1). To a solution of the 12-HETE methyl ester (30 mg, 0.09 mmol) in 5:1 DME/water (10 mL) was added lithium hydroxide (90 mg, excess); the resulting mixture was allowed to warm to room temperature and then stirred overnight. The mixture was then diluted with ether (30 mL) and cooled to 0 °C and the pH was adjusted to 3 by the addition of 1 N aqueous HCl. The resulting mixture was partitioned and the aqueous phase extracted with ether (30 mL). The combined partitioned and the aqueous phase extracted with ether (30 mL). The combined organic phases were washed with water (30 mL) and saturated aqueous sodium chloride (60 mL) and dried over anhydrous sodium sulfate, and the solvent was removed at reduced pressure to give 12-HETE (27 mg, 95%): IR (neat) 3480 b, 1710, 1460, 1400 cm^{-1}; ^1H NMR (250 MHz, acetone-d_6) δ 0.87 (t, 3 H, *J* = 6.3 Hz, H-20), 1.66 and 2.14 (2 m, H-4 and H-16), 2.22 (m, 2 H, H-13), 2.27 (t, 2 H, H-2, *J* = 7.4 Hz), 2.94 (t, 2 H, *J* = 6.1 Hz, H-7), 4.16 (q, 1 H, *J* = 6.3 Hz, H-12), 5.29 (m, 5 H, H-5, H-6, H-8, H-14, H-15), 5.72 (dd, 1 H, *J* = 15.3 Hz, J^1 = 6.2 Hz, H-11), 5.97 (t, 1 H, *J* = 11.0 Hz, H-9), 6.58 (dd, 1 H, *J* = 15.3 Hz, *J* = 11.0 Hz, H-10); ^{13}C NMR (benzene-d_6) 124.44, 125.96, 128.69, 128.88, 129.62, 129.98, 132.02, 137.77 (8 C, C=C), 174.35 (C, CO_2H) ppm; high-resolution mass spectrum, *m/z* calcd for $C_{20}H_{30}O_2$ ($M^+ - H_2O$) 302.2282, found 302.2242.

Methyl 9-*O*-(*tert*-Butyldiphenylsilyl)-10,11-bis-*O*-(1-methylethylidene)-9(*S*),10(*R*),11-trihydroxy-6(*Z*)-undecenoate (18). To a stirred solution of the ylide (6.11 mmol) generated by treatment of the bromide 6-(triphenylphosphonio)-hexanoic acid (**16**) (3.96 g, 8.65 mmol) with LiHMDS (14.8 mmol) in THF (53 mL) and HMPA (16 mL) at 0 °C for 1 h, at −78 °C, was added a solution of the aldehyde (2.12 g, 5.09 mmol) in THF (15 mL), obtained by hydrolysis of the thioacetal **12**, over 5 min. After being stirred at −78 °C for 30 min the reaction mixture was allowed to warm to room temperature. After a further 2 h sodium bicarbonate (3.13 g, 5.8 equiv) and dimethyl sulfate (2.8 mL, 5.8 equiv) were added and the resulting mixture was stirred until a clear solution was obtained (approximately 2 h). The resulting mixture was diluted with water (200 mL) and extracted with ether (2 × 200 mL), the combined organic phases were washed with saturated aqueous sodium chloride (2 × 100 mL) and dried over anhydrous sodium sulfate, and the solvent was removed at reduced pressure. Flash chromatography of the residue (2 × 25 cm column, 10% ethyl acetate in hexanes) gave the desired ester **18** (1.61 g, 59%).

3-*O*-(*tert*-Butyldiphenylsilyl)-1,2-bis-*O*-(1-methylethylidene)-5(*Z*)-undecene-1,2(*R*),3(*S*),11-tetrol (19). To a solution of the ester **18** (1.61 g, 3.06 mmol) in THF (30 mL) at 0 °C was cautiously added aluminium hydride ether complex (30.2 mg, 6.7 mmol), and the resulting mixture was stirred at 0 °C for 30 min. The reaction was then quenched by the sequential ad-

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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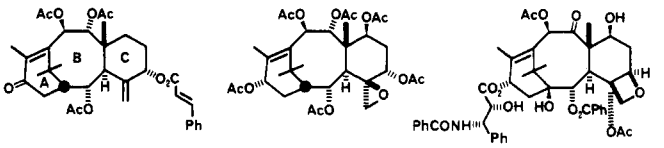
A stereospecific synthesis of a model compound containing the 2,3-epoxy alcohol moiety present in the C ring of several taxane diterpenes has been devised. Thus epoxide **8** was converted to allylic alcohol **9** which upon epoxidation to give **10** followed by treatment with hydroxide afforded **11**, 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.

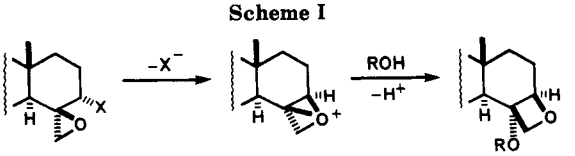
Among the structural complexities of the taxane diterpenes[2] which make these natural substances challenging synthetic[3] targets are the unique C-ring features. These allow organization of the taxanes into a group possessing an allylic oxygen function, as in taxinine,[4] **1**, a group in which the 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



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