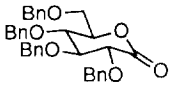
the region δ 4.2 - 5.2 indicative of the four benzyl and one oxetane methylene groups. The sterochemistry of **9** is assigned on the grounds that the anomeric radical **14** will react preferentially along the pseudoaxial direction[1,3,5b] and also that the upfield nature of H5 and 2 x H6, but not of H3, in the ^{1}H-NMR spectrum is best interpreted in terms of shielding by the oxetane phenyl group in the orientation indicated. The α-phenacyl mannoside (**6**) cleanly gave tetrabenzyl-1,5-mannonolactone (**10**) with less than 5% of any byproducts. The tetrahydropyranyl ether **7** was smoothly converted to δ-valerolactone (**11**) as evidenced by ^{1}H-NMR spectroscopy of the crude photolysate. Thus, each substrate cleanly underwent the anticipated Norrish II photochemistry to the exclusion of any significant side reactions.



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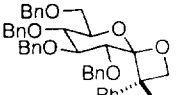

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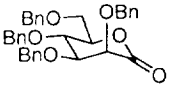

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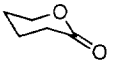


11

A mixture of **3** and **5** was prepared in benzene and the exact ratio of **3**:**5** determined by HPLC analysis. This mixture was then subjected to photolysis in the Rayonet reactor in the normal manner, with monitoring of the substrate ratio by HPLC, for 6.5 h . Examination of the crude photolysate by ^{1}H-NMR revealed that the reaction had proceeded to approximately 90% conversion and that no products were formed other than those described in the simple photolyses. Similar experiments were carried out with mixtures of **3** and **6**, and of **3** and **7**. The results of these experiments are presented in Fig. 1. Both glucose anomers are found to react at approximately the same rate. The α-glucosyl derivative **3** was consumed marginally faster than the corresponding mannose derivative **6**. The most striking difference in rate was between the glucose derivative **3** and the tetrahydropyran **7**, with the latter being consumed significantly more rapidly. If we make the reasonable assumption that the efficiency for excitation of the phenacyl chromophore is the same for each substrate then the above experiments represent differences in the rate of abstraction of the various anomeric hydrogen atoms.

The essentially identical photolysis rates of **3** and **5** indicate that, at least for this type of facile δ-intramolecular hydrogen atom abstraction, the difference in activation barriers for removal of an axial or equatorial hydrogen is insignificant. Going to a less readily accessible 7-membered cyclic transition state, as found by Descotes for **12** (in both the gluco- and manno-series), produces an imbalance in favor of abstraction of the axial hydrogen,[5] while the intermolecular reaction shows a significant preference for axial hydrogens.[2]

The slightly more rapid consumption of **3** than **6** is presumably due to a minor difference in conformation between the two precursors which is reflected in the different activation energies for hydrogen atom abstraction. Also of interest is the formation of spirooxetanes from **3** and **5**, but not from **6**. If we accept, notwithstanding their somewhat pyramidal σ-nature,[2,8] that 1-alkoxyglycosyl radicals adopt similar conformations to the corresponding simple anomeric radicals then hydrogen atom abstraction from **6** will lead to a chair[9] diradical **13** in which the single electron at the anomeric site benefits from overlap with the σ* C-O orbital at C-2 and the extended anomeric effect.[2c,10] Hydrogen abstraction from the anomeric position of **3** will lead initially to a chair conformer that does not benefit from the extended anomeric effect, and which will subsequently evolve to a boat like conformer **14**[9] in which it does. Thus, both **3** and **5** lead to radical **14**

which presumably has sufficient conformational mobility to enable the transition state for oxetane formation to be attained whereas **6** leads to the more rigid **13** from which coupling presumably cannot be achieved.

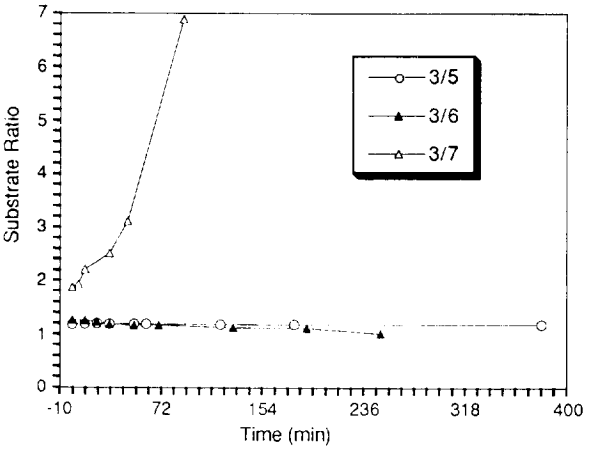
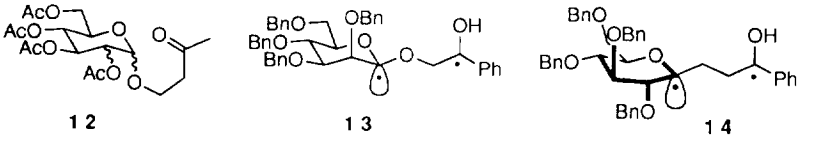


Figure 1



12 **13** **14**

The most striking difference in rate is between the tetrahydropyranyl derivative **7** and **3**, **5** and **6**. This difference, which may be attributed the lack of β-oxygen bonds which destabilize the polar transition state for hydrogen atom abstraction, parallels the work by Busfield and collaborators on the rates of hydrogen atom abstraction from acyclic and cyclic ethers, by the electrophilic t-butoxyl radical (Fig 2).[4e,f] ESR evidence suggests simple 1-alkoxy-1-glycosyl radicals to be chair like conformations with the single electron axial, thus it is reasonable to expect the diradical derived from **7**, to adopt a conformation **15** akin to that of **13** rather than **14** and so to show a similar reluctance to oxetane formation.

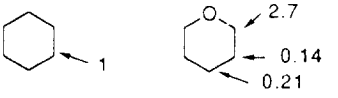
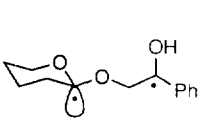


Figure 2. Relative Rates of Hydrogen Atom Abstraction by t-BuO•

Finally the observation that **7** is significantly more reactive toward intramolecular hydrogen atom abstraction than **3**, **5** or **6** would appear to shed some light on the earlier observations of Simpkins et al[1c]

whereby **16** provided moderate yields of spirocyclic ketals (**17**) on treatment with tributyltin hydride and AIBN but the glucose derivative **18** did not. Apparently, the benzyloxy groups in **18** are sufficient to prevent the intramolecular hydrogen atom abstraction, by the electrophilic vinyl radical,[11] by destabilization of the polar transition state.



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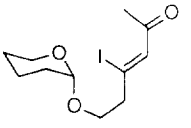

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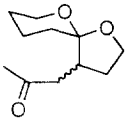

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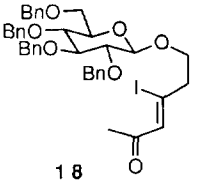

18

EXPERIMENTAL

General. M.p.s are uncorrected and were determined with a Hoover hot stage microscope. IR spectra were recorded with a Perkin Elmer 1605 spectrophotometer. ^{1}H- and ^{13}C-NMR spectra were recorded at 300 MHz. Chemical shifts (δ) are in ppm downfield from tetramethylsilane as internal standard, J-values are given in Hz. 70 eV EIMS mass spectra were recorded with an AEI MS-30 mass spectrometer. All solvents were dried and distilled by standard techniques. Tetrahydrofuran (THF) was distilled under nitrogen from sodium benzophenone ketyl before use. Ether refers to diethyl ether. Microanalyses were performed by Midwest Microanalytical, Indianapolis.

Phenacyl 2,3,4,6-Tetra-O-benzyl-α-D-glucopyranoside (3). To a stirred solution of 2,3,4,6-tetra-O-benzyl-D-glucose[12] (1.62 g, 3.0 mmol) and phenacyl bromide (3.0 g, 15.0 mmol) in freshly distilled DMF (10 mL) was added silver oxide (2.0 g, 8.6 mmol) portionwise over 1 h. Stirring was continued for 12 h, with shielding from the light, before the reaction mixture was diluted with chloroform until precipiataion was complete. The precipitate was filtered on Celite and thoroughly washed with chloroform and the combined filtrates and washings evaporated *in vacuo* to give a residue which, after chromatography on silica gel (eluent: hexane/ethyl acetate 7/1) gave recovered substrate (0.53 g, 33%) and the title compound (0.7 g, 35%) which crystallized from hexane/ethyl acetate as needles. M.p. 126-127 °C; $[\alpha]_D$ = + 83.4° (c = 1.25); ^{1}H-NMR, δ: 3.55-3.73 (m, 3H); 3.83-3.93 (m, 1H); 4.11 (t, J = 9.3, 1H), 4.40-4.62 (m, 3H), 4.75-4.90 (m, 4H), 4.90-5.09 (m, 4H), 5.16 (d, J = 3.6, 1H), 7.10-7.52 (m, 22H), 7.53-7.63 (m, 1H), 7.87-7.95 (m, 2H); ^{13}C-NMR, δ: 68.36, 68.55, 70.89, 72.62, 73.44, 75.00, 75.72, 77.47, 79.49, 81.69, 96.43, 127.65, 127.86, 127.92, 127.97, 128.12, 128.20, 128.46, 128.78, 128.85,133.63, 138.27, 138.39, 138.99, 195.49; υ_{max} (cm^{-1}): 1703, 1599, 1156, 1073. Anal. Calc. for $C_{42}H_{42}O_7$: C, 76.57; H, 6.43. Found: C, 76.50; H, 6.49.

2-Phenylallyl 2,3,4,6-Tetra-O-benzyl-β-D-glucopyranoside (4). Sodium hydride (80 mg, 3.3 mmol) was added to a solution of 2,3,4,6-tetra-O-benzylglucose (1.0 g, 1.85 mmol) in THF (10 mL) stirred under Ar at 0 °C. After stirring for 30 min 2-phenylallyl bromide[13] (0.95 g, 4.8 mmol) in THF (2 mL) was added and stirring continued for 6 h before the reaction mixture was pored into ice-water (30 mL) and extracted with ether. The extracts were washed with brine, dried ($MgSO_4$), concentrated, and purified by silica gel chromatography (eluent: hexane/ethyl acetate 7/1) to give **4** as an oil (0.714 g, 59%) which crystallized from ethanol. M.p. 79-80 °C; $[\alpha]_D$ = -3.4° (c = 0.29); ^{1}H-NMR, δ: 3.45-3.80 (m, 6H), 4.49-4.94 (m, 11H), 5.44 (bs, 1H), 5.58 (bs, 1H), 7.10-7.60 (m, 25H); ^{13}C-NMR, δ: 69.13, 70.84, 73.68, 74.89, 75.11, 75.15, 75.85, 78.09, 82.32, 84.92, 102.49, 115.34, 126.28, 127.70, 127.73, 127.78, 127.91, 128.00, 128.12, 128.33, 128.41, 128.55, 128.60, 138.32, 138.39, 138.51, 138.80, 143.57; υ_{max} (cm^{-1}): 2870, 1358, 1070. Anal. Calc. for $C_{43}H_{44}O_6$: C, 76.57; H, 6.43. Found: C, 76.50; H, 6.49.

Phenacyl 2,3,4,6-Tetra-O-benzyl-β-D-glucopyranoside (5). Sodium metaperiodate (54 mg, 0.26 mmol) was added portionwise over 10 min to a stirred solution of olefin **4** (80 mg, 0.12 mmol) and OsO_4 (1 small crystal) in dioxane (1.5 mL) and water (0.5 mL). After stirring for 7.5 h at room temperature the reaction mixture was diluted with water (2 mL), extracted with ether (3 x 2 mL), dried (Na_2SO_4) and concentrated *in vacuo* to give a crude product which was crystallized from ethanol to give **7** (78 mg, 97%). M.p. 103-104 °C; $[\alpha]_D$ = -4° (c = 0.8); ^{1}H-NMR, δ: 3.42-3.82 (m, 5H), 4.45-4.69 (m, 4H), 4.73-5.04 (m, 6H), 5.10-5.23 (m, 2H), 7.10-7.65 (m, 23 H), 7.95-8.10 (m, 2H); ^{13}C-NMR, δ: 68.68, 71.42, 73.47, 74.64, 74.98, 75.61,

77.63, 81.89, 84.46, 103.40, 127.53, 127.69, 127.82, 128.08, 128.25, 128.32, 128.33, 128.63, 133.42, 138.09, 138.43, 138.60, 194.82; υ_{max} (cm^{-1}): 1705, 1599, 1155, 1071. Anal. Calc. for $C_{42}H_{42}O_7$: C, 76.57; H, 6.43. Found: C, 76.68; H, 6.32.

Phenacyl 2,3,4,6-Tetra-O-benzyl-α-D-mannopyranoside (6). To a stirred solution of 2,3,4,6-tetra-O-benzyl-D-mannose[14] (0.30 g, 0.55 mmol) and phenacyl bromide (0.55 g, 2.75 mmol) in freshly distilled DMF (3 mL) was added silver oxide (0.35 g, 1.48 mmol) portionwise over 1 h. Stirring was continued for 12 h, with shielding from the light, before the reaction mixture was diluted with chloroform until precipiataion was complete. The precipitate was filtered on Celite and thoroughly washed with chloroform and the combined filtrates and washings evaporated *in vacuo* to give a residue which, after chromatography on silica gel (eluent: hexane/ethyl acetate 6/1) gave **6** as a syrup (0.13 g, 36%). $[\alpha]_D = +50^o$ (c = 0.09) ^{1}H-NMR, δ: 3.72-3.80 (m, 2H), 3.81-3.90 (m, 1H), 3.93-4.02 (m, 1H), 4.07-4.10 (m, 1H), 4.48-4.68 (m, 5H), 4.77 (s, 2H), 4.87-4.93 (m, 4H), 5.10 (d, J - 1.7, 1H),, 7.10-8.0 (m, 25H); ^{13}C-NMR, δ: 68.49, 69.38, 71.99, 72.39, 72.63, 73.34, 74.40, 74.78, 75.02, 79.90, 97.80, 127.44, 127.47, 127.54, 127.58, 127.67, 127.91, 128.27, 128.29, 128.44, 128.65, 128.75, 128.96, 133.60, 134.27, 134.75, 138.21, 138.35, 138.47, 195.36; υ_{max} (cm^{-1}): 1706, 1599, 1155, 1071. HRMS. Calc. for $C_{42}H_{42}O_7$: 658.2930. Found: 658.2898 ($M^{+\cdot}$).

Irradiation of 3. Isolation of 2,3,4,6-Tetra-O-benzyl-D-glucono-1,5-lactone (8) and of Byproduct 9. A solution of **3** (50 mg, 0.076 mmol) in benzene (5 mL) in a Pyrex flask under Ar was irradiated with 254 nm light in a Rayonet photoreactor for 5 h at room temperature with monitoring by HPLC (Sephadex C-18 reverse phase column, eluent: MeOH/H_2O 7/1, 1 mL/min, 254 nm detection). After completion and removal of the solvent under vacuum examination of the residue by ^{1}H-NMR revealed three products in the ratio 61/29/10. Preparative tlc on silica gel (eluent: hexane/ethyl acetate 3/1) enabled the isolation of **8**[15] as a colorless oil (23.5 mg, 57%). ^{1}H-NMR, δ: 3.65-3.85 (m, 2H), 3.90-4.05 (m, 2H), 4.12 (d, J = 6.7, 1H), 4.40-4.78 (m, 8H), 4.99 (d, J = 11.4, 1H), 7.00-7.50 (m, 20H); ^{13}C-NMR, δ: 68.16, 73.46, 73.64 (2C), 73.84, 75.96, 77.30, 78.07, 80.85, 127.76, 127.87, 127.91, 128.04, 128.33, 128.37, 128.39, 136.85, 137.42, 137.44, 137.51, 169.27; υ_{max} (cm^{-1}): 1773, 1419, 1091, and **9** also as a colorless oil (12 mg, 24%). ^{1}H-NMR, δ: 2.60 (ddd, J = 9.88, 2.83, 1.98, 1H), 2.94 (dd, J = 11.0, 1.98, 1H), 3.31 (dd, J = 11.0, 2.83, 1H), 3.67 (dd, J = 9.88, 8.95, 1H), 3.80 (d, J = 10.2, 1H), 4.00 (dd, J = 10.2, 8.95, 1H), 4.27 (d, J = 12.2, 1H), 3.98-4.60 (m, 3H), 4.65 (d, J = 6.4, 1H), 4.71 (d, J = 10.5, 1H), 4.85-5.00 (m, 3H), 5.11 (d, J = 10.5, 1H), 5.54 (s, 1H), 7.00-7.10 (m, 2H), 7.15-7.40 (m, 21H), 7.65-7.85 (m, 2H); ^{13}C-NMR, δ: 67.36, 71.97, 73.23, 75.02, 75.73, 77.14, 77.55, 81.80, 82.90, 86.23, 111.04, 126.33, 127.55, 127.69, 127.78, 128.01, 128.25, 128.35, 128.45, 128.68, 136.95, 137.31, 137.79, 137.98; υ_{max} (cm^{-1}): 3476, 2928, 1453, 1262, 1085. Thus far, we have been unable to obtain a molecular ion by EI or FAB MS for **9**. However, the high dilutions used in these experiments render the possibility of any dimeric species extremely unlikely. Isolation of the second byproduct was not possible owing to decomposition.

Irradiation of 5. Isolation of 2,3,4,6-Tetra-O-benzyl-D-glucono-1,5-lactone (8) and of Byproduct 9. A solution of **5** (50 mg, 0.076 mmol) in benzene (5 mL) under Ar was irradiated as described for **3**. Examination of the crude photolysate by ^{1}H-NMR revealed the same three products in the ratio 60/28/12 and preparative tlc enabled the isolation of **8** (23 mg, 56%) and **9** (10 mg, 20%).

Irradiation of 6. Isolation of 2,3,4,6-Tetra-O-benzyl-D-mannono-1,5-lactone (10). The phenacyl mannose derivative **6** (30 mg, 0.076 mmol) in benzene (1 mL) was irradiated through Pyrex under Ar in the Rayonet photoreactor for 24 h with monitoring by HPLC exactly as described for **3**. Analysis of the crude photolysate by ^{1}H-NMR showed greater than 95% conversion to **10** with < 5% of various unidentified byproducts. Pure **10**[16] (22 mg, 90%) was isolated as a syrup by preparative tlc on silica gel (eluent: hexane/ethyl acetate 2/1).^{1}H-NMR, δ: 3.64 (d, J = 4.5, 2H), 3.74-3.82 (m, 1H), 4.03-4.10 (m, 1H), 4.20-4.40 (m, 4H), 4.49-4.70 (m, 4H), 4.84 (d, J = 12.3, 1H), 5.06 (d, J = 11.9, 1H), 7.00-7.50 (m, 20H); ^{13}C-NMR, δ: 69.21, 71.88, 72.69, (2C), 73.51, 75.50, 76.11, 76.71, 78.64, 127.76, 127.83, 127.87, 128.11, 128.33, 128.43, 136.73, 137.16, 137.62 (2C), 169.29; υ_{max} (cm^{-1}): 1774, 1420, 1089.

Irradiation of Phenacyl Tetrahydropyranyl Ether (7). Isolation of δ-Valerolactone (11). A solution of **7** (20 mg, 0.09 mmol) in perdeuteriobenzene (3 mL) was irradiated as described for **3** for 24 h with monitoring by HPLC (Alltech SiO_2 normal phase column, eluent: hexane/ethyl acetate 10/1, 1 mL/min, 254 nm detection). After completion inspection by NMR showed essentially complete conversion to δ-valerolactone (**11**). ^{1}H-NMR, δ (C_6D_6): 0.75-1.05 (m, 4H), 1.95 (dd, J = 7.1, 6.8, 2H), 3.50 (dd, J = 5.7, 5.2, 2H); ^{13}C-NMR, δ (C_6D_6): 18.93, 22.10, 29.77, 68.18, 169.37; υ_{max} (cm^{-1}): 1742, 1265, 1236.

Irradiation of a Mixture of 3 and 5. A solution of **3** (11 mg, 0.017 mmol) and **5** (11 mg, 0.017 mmol) in benzene (3 mL) were irradiated in a Pyrex flask under Ar at room temperature. Consumption of the

substrates was monitored by HPLC (Sephadex C-18 reverse phase column, eluent: MeOH/H_2O 7/1, 1 mL/min, 254 nm detection, Table 1). After 7 h examination by ^{1}H-NMR revealed the presence of **8, 9** and the unidentified minor byproduct from **3**.

Irradiation of a Mixture of 3 and 6. A solution of **3** (10 mg, 0.015 mmol) and **6** (11 mg, 0.017 mmol) in benzene (3 mL) were irradiated in a Pyrex flask under Ar at room temperature. Consumption of the substrates was monitored by HPLC (Sephadex C-18 reverse phase column, eluent: MeOH/H_2O 7/1, 1 mL/min, 254 nm detection, Table 1). After 10 h examination by ^{1}H-NMR revealed the presence of **8, 9, 10** and the unidentified minor byproduct from **3**.

Irradiation of a Mixture of 3 and 7. A solution of **3** (12 mg, 0.018 mmol) and **7** (3.9 mg, 0.018 mmol) in benzene (3 mL) were irradiated in a Pyrex flask under Ar at room temperature. Consumption of the substrates was monitored by HPLC (Sephadex C-18 reverse phase column, eluent: MeOH/H_2O 7/1, 1 mL/min, 254 nm detection, Table 1). After 10 h examination by ^{1}H-NMR revealed the presence of **8, 9, 11** and the unidentified minor byproduct from **3**.

Table 1. Competitive Photolyses

Time (min)	Competition of **3** with **5** (3:5)	Competition of **3** with **6** (3:6)	Competition of **3** with **7** (3:7)	Time (min)	Competition of **3** with **5** (3:5)	Competition of **3** with **6** (3:6)	Competition of **3** with **7** (3:7)
0	1.175	1.254	1.863	70	-	1.164	-
5	-	-	1.922	90	-	-	6.883
10	1.190	1.248	2.208	120	1.179	-	-
20	1.192	1.227	-	130	-	1.122	-
30	1.185	1.184	2.504	180	1.174	-	-
45	-	-	3.107	190	-	1.111	-
50	1.190	1.170	-	250	-	1.006	-
60	1.182	-	-	380	1.177	-	-

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Rottnestol, A New Hemiketal from the Sponge *Haliclona* sp.

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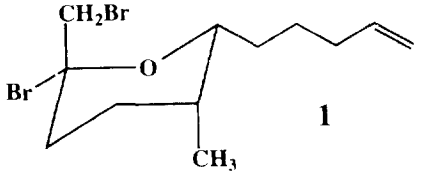
Summary: Rottnestol, a new hemiketal, was isolated from an Australian collection of the marine sponge *Haliclona* sp. Its structure was deduced as **3** from ^{1}H, ^{13}C, COSY, HMQC, HMBC and nOe NMR studies. Hemiketal **3** was readily converted to its epimer, **4**, and the methyl ketal of **4**.

Sponges of the genus *Haliclona* are well known sources of interesting secondary metabolites, with alkaloids representing the most common type of natural product isolated from this genus.[2-9] While investigating the organic extract of a Southwestern Australian (Rottnest Island) collection of *Haliclona* sp. (Haplosclerida: Haliclonidae) for cytotoxic metabolites, we isolated three inactive alkylated pyrans. Two of these, bromotetrahydropyrans **1** and **2**, were previously reported, perhaps from the same sponge species.[10] The third, hemiketal **3**, was a new compound and we report here its characterization.

The sponge extract was fractionated by vacuum-liquid chromatography (VLC) on Diol-60 columns. Tetrahydropyrans **1** and **2** were isolated from the hexane fraction by sequential silica gel VLC, reverse-phase thin-layer chromatography (RPTLC), and normal-phase silica gel TLC. Tetrahydropyrans **1** and **2** were identified by comparison of their spectral data with those published,[10] as well as by homonuclear (COSY) and heteronuclear (HMQC and HMBC) NMR analyses.



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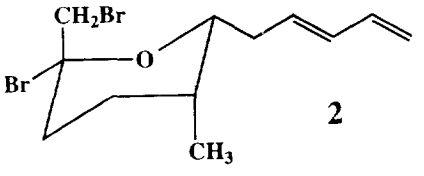

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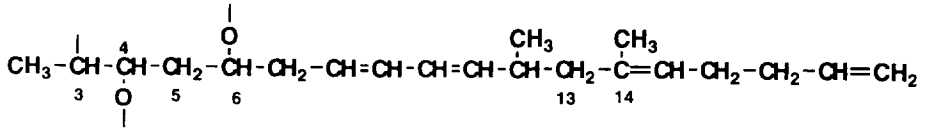
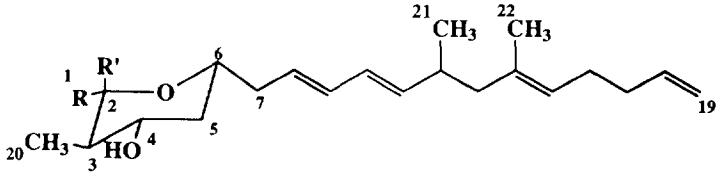
Hemiketal **3** (4% of the crude extract) was isolated from the dichloromethane fraction of the diol column by preparative silica gel TLC with 20% isopropanol-hexane. HREIMS established its molecular formula as $C_{22}H_{36}O_3$, signifying five sites of unsaturation. IR spectroscopy indicated the presence of alcohol (3386 cm^{-1}) and alkene (1641 cm^{-1}) groups. ^{1}H and ^{13}C NMR (Table 1), together with HMQC and HMBC experiments, identified two oxygen-bearing methines (δ 3.58, 69.7 and 3.84, 68.3); a hemiketal or ketal quaternary carbon (δ 98.9); eight olefinic carbons, one of which was quaternary (δ 133.8) and one of which was terminal (δ 114.8); five methylene groups, four of which were allylic; and four methyl groups, two of which were secondary, one tertiary, and one olefinic. An analysis of the

COSY and HMQC NMR spectra of **3** (Table 1) led to the following partial structure, with the C-13/C-14 connection made on the basis of the allylic nature of the C-13 methylene hydrogens:

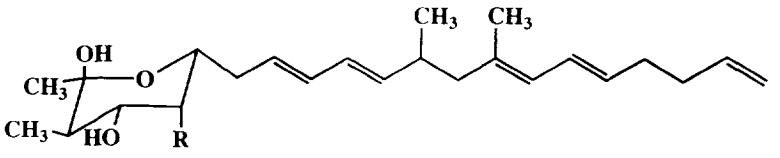


Remaining to be placed on this structure were one oxygen atom, the hemiketal/ketal quaternary carbon, and the tertiary methyl group. C-3 represented the only possible point of attachment for the quaternary hemiketal/ketal carbon. This required the placement of the tertiary methyl group on the hemiketal/ketal carbon as well. The one proton doublet at δ 0.78 was assigned as a hydroxyl group on C-4, because of its 5.4 Hz coupling to H-4 and lack of any observed HMQC correlation. This meant that the hemiketal bridge had to connect C-3 and C-6; this was supported by a weak HMBC correlation to the hemiketal hydroxyl group at δ 1.68 from C-3. Although the HMBC spectrum of **3** (Table 1) completely confirmed the entire carbon sequence, it failed to clarify the final oxide ring closure.

The observation of a cross peak between the secondary OH and the C-4 methine hydrogen in the COSY spectrum of methyl ketal **5** (*vide infra*), which was derived from **3**, made it possible to confirm the secondary OH at C-4. This left the C-6 oxygen as the only site for the hemiketal carbon-ether link and generated a six-membered ring as depicted in **3**. In support of this assignment, both the chemical shifts and the J-values for H-3 and H-4 were in much better agreement with those on an oxane ring than those on an oxetane ring.[11] The coupling constants for H-5 and H-6 also indicated that these protons were attached to carbons in a six-membered ring. Indeed, the relative stereochemistry shown for **3** rests upon the observed *trans*-diaxial vicinal couplings between H-3 and H-4 (10.8 Hz), H-4 and H-5a (12.2 Hz), and



3 R = CH_3, R' = OH
4 R = OH, R' = CH_3
5 R = OCH_3, R' = CH_3



6 R = H
7 R = CH_3