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DITERPENOIDS OF MIXED BIOGENESIS IN PHAEOPHYTA BIOGENETIC-TYPE INTERCONVERSIONS[1]

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Abstract—In the course of research into marine natural products, the diterpenoids taondiol **10** and atomaric acid **15**, were isolated from the brown seaweed *Taonia atomaria*. The similarities of these structures plus the fact that both compounds come from the same alga suggest that there may be a biogenetic relationship between the two. This speculated relationship is adumbrated in Scheme 1, where the cyclic and acyclic diterpenoids of mixed biogenesis isolated from Phaeophyta are interrelated. In the present work, the competitive cyclisation of the proposed olefinic intermediate **4** to the naturally occurring compounds taondiol **10**, isotaondiol **11**, epitaondiol **12** and stypodiol **13**, is reported. The stereoselective transformation of atomaric acid **15** into the compound **4** is also reported, which transformation occurs by intramolecular carbocyclisation of the olefinic aldehyde **7** followed by backbone rearrangement to the olefine **4**. This result prompted the proposal that atomaric acid **15** may arise in nature by means of a like rearrangement but operating in a reverse direction.

Biosynthetic speculation on organic natural products has paved the way for biochemists by providing them with work schemes whereby they can carry out true biosynthetic studies involving the use of isotopically-labelled compounds. Biogenetic considerations in marine natural products, particularly in those elaborated by macroalgae, cannot possibly be biochemically tested in the more or less immediate future; however, such speculative works are necessary, as researchers are often compelled thereby to reconsider proposed structures or to reinvestigate already studied extracts, so as to find hypothetical intermediate compounds which, due to their instability or their low concentration in the extracts, may have been overlooked in a first study. Until such time as one can successfully carry out true biosynthetic studies involving the use of isotopically-labelled compounds, the biogenetic-type syntheses and biomimetic interconversions between co-occurring metabolites must be considered as the best methods of gaining insight into biosynthetic routes, although the limitations of this research must be recognized.

In this proliferation of our knowledge of the metabolites of marine origin, biogenetic concepts play a useful and important role and it is the purpose of this paper to highlight this aspect by citing examples from diterpenoids of mixed biogenesis found in brown algae (Phaeophyta).

In the course of our research into marine natural products, the compounds taondiol **10**[2] and atomaric acid **15**[3] were isolated from the brown seaweed *Taonia atomaria*. The similarities in both structures, plus the fact that both compounds come from the same seaweed, suggest that there may be a biogenetic relationship between the two. This speculated relationship is adumbrated in Scheme 1, where the cyclic and acyclic diterpenoids of mixed biogenesis isolated from Phaeophyta are interrelated. It is presumed that they derive from the acyclic precursor 2 - geranylgeranyl - 6 - toluhydroquinone **1**, recently isolated in algae,[4] which is likely to be a basic substance of the diterpenoid-substituted toluquinones and toluhydroquinones distributed in many Sargassum species[5] and of which 2 - geranylgeranyl - 6 - toluquinone **8**[5a] and δ-tocotrienol epoxide **9**[5c] are two examples. The reported compounds from Dictyotaceae: taondiol **10**,[2,4] isotaondiol **11**,[6] epitaondiol **12**,[4] stypodiol **13**,[4] epistypodiol **14**[4] and atomaric acid **15**,[3,4] plus the fact that these compounds co-occur together with **1** and **8** in the seaweed *Stypopodium zonale*,[4] afforded structural evidence to the proposed biogenetic scheme (Scheme 1).

The published nonenzymic cyclisation **2** → **10**[7] and the here reported competitive acid cyclisations to **11**, **12** and **13**, are synthetic evidence that compounds **10–14** originate naturally according to the scheme presented here and quite possibly through the same intermediates **2**, **3**, **4** and **5**. In the present work we also report the stereoselective transformation of atomaric acid **15** via the aldehyde **7**, into the proposed olefinic intermediate **4**, which prompted the proposal that the former may arise in Nature from **4** by means of a like rearrangement but operating in the reverse direction.

The acid-catalyzed cyclisation of the previously described prenyl phenol **16**,[8] carried out in complete absence of air and in the dark, led to a mixture of at least three compounds from which 11′-desoxytaondiol methyl ether **17**[8] and 11′-desoxystypodiol methyl ether **18**[9] were isolated by fractional crystallisation. The proportion in which both products are formed and the total number of products formed, depend very much on the reaction conditions (see Table 1). Although **17** was prepared in yields of over 80%, conditions could not be found whereby **18** could be formed in yields above 7%.

Treatment of 11′-desoxytaondiol methyl ether **17** with HBr in refluxing AcOH gave a mixture of the compounds 11′-desoxytaondiol **22**, 11′-desoxyisotaondiol **27** and 11′-desoxyepitaondiol **28** in the ratio 8:1:4, which were separated by silica gel column chromatography and fractional crystallisation. Compounds **22** and **27** were identified by direct comparison with samples obtained from 10-methoxytaondiol **19**[2] {or 10-methoxyisotaondiol **23**[6]}, by removing the C-11′ hydroxy group by conversion

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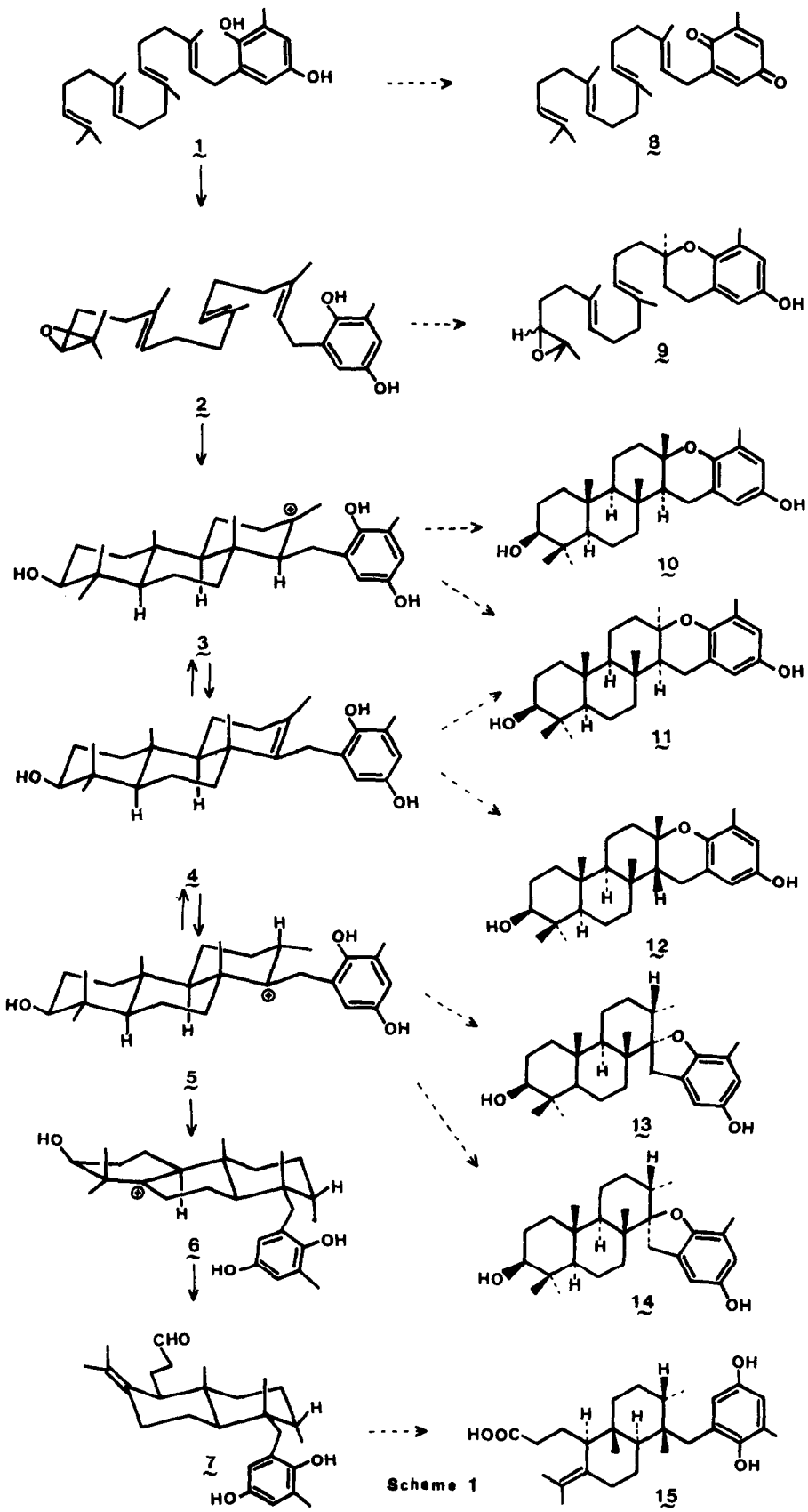


Scheme 1

Scheme 1.

Table 1. Acid-catalyzed cyclisation of **16** to the compounds **17** and **18**

Acid	Solvent	temp., °C	time, h	Compound 17[a] yield (%)	Compound 18[a] yield (%)
AcOH	—	50	48	9.8	0.87
HCO_2H	—	50	1	82.1	3.9
Picric	CH_3NO_2	25	7	30.2	6.6
$SnCl_4$	CH_2Cl_2	-70	0.5	16.9	1.9
$SnCl_4$	CH_2Cl_2	-15	1	69.6	3.3
$SnCl_4$	CH_2Cl_2	25	0.5	24.0	1.0
$SnCl_4$	C_6H_6	25	0.5	29.3	2.1
BF_3	CH_2Cl_2	0	2	40.0	1.2
BF_3	CH_2Cl_2	-70	0.25	--	---
Tos-OH	CH_2Cl_2	25	24	12.6	0.16
TFA	CH_2Cl_2	0	1	48.3	--
$HClO_4$	HCO_2H	50	1	33.4	5.1
H_2SO_4	HCO_2H	25	2	29.0	3.2

[a] Determined by GC analysis on a 12ft. x 0.125 in. column packed with 10% SE-30.

of **19** (or **23**) into the thioketal **21** (or **25**) *via* the ketone **20** (or **24**) to give **17** (or **26**), followed by demethylation with boron tribromide in methylene chloride to give **22** and **27**. It was not possible to correlate 11'-desoxyepitaondiol **28**, synthesized here from the natural product epitaondiol **11**, the latter being a very minor component of the alga.[4] The three diastereoisomers differ in their stereochemistry at C-2 and C-3 and while compound **22** occurs by simple demethylation of **16**, compounds **27** and **28** are undoubtedly *trans*-addition products of the olefinic and non-isolated intermediate **29**.[7b]

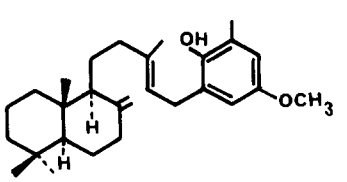
Treatment of **18** with HBr in refluxing AcOH gave the pentacarbocyclic quinone **30**, the reductive methylation of which gave **31**, which was shown to be identical with one of the products obtained by carbocyclisation followed by backbone rearrangement of atomaric acid (see further). In this case, the opening of the dihydrofuran ring occurred with 1,2-methyl shift and deprotonation on C-5', to give the olefin **32** as reasonable intermediate precursor of the carbocyclisation observed. This last reaction was carried out in order to prepare the C-11' deoxygenated equivalent of epistypodiol **14**, but the transformation of **18**–**30** was quantitative in the reaction conditions utilized.

In accordance with Scheme 1, atomaric acid **15** originates from **5** by a twofold hydrogen and methyl migration along the backbone of the molecule followed by a heterolytic cleavage of ring A giving the aldehyde **7** which is further oxidized to give **15**. The hydrogen atoms and methyl groups involved in the backbone rearrangement fulfil the axial antiparallel orientation required,[10] so such a process may occur through a nonstop sequence. The biogenetic pathway given in Scheme 1 shows that atomaric acid arises via the aldehyde **7** by a heterolytic cleavage on a 11' - hydroxy - precursor instead of a homolytic rupture on the 11' - keto - precursor as is commonly proposed to obtain most of the terpenic 3,4 - seco - 3 - acids.[11] The indicated C-11', C-12' heterolytic cleavage requires, to be concerted, a *cis*-relationship between the fragmented bond and the departing C-7' hydrogen. Thus the postulated rupture could not proceed in a concerted fashion and the carbenium ion **6** is required as a true intermediate.

Analysis of this biogenetic route reveals that the **5**–**6** rearrangement is opposed to all known rules for backbone rearrangements in acid medium, according to which the positive charge will always be directed to a site of tension in the molecule which will govern the rearrangement.[12] In the **5**–**6** rearrangement, however, the charge is directed towards ring A which lacks tension. This contradiction applies to the majority of biogenetic routes in most rearranged polycyclic terpenoids, where there are only a few instances of the *in vivo* and *in vitro* rearrangements being the same.[13]

The results obtained in attempts to transform atomaric acid **15**, *via* the aldehyde **7**, into the olefinic intermediate **4**, are now described. Two problems in particular had to be faced: (a) formation of ring A by intramolecular cyclisation of the olefinic aldehyde **7** and (b) backbone rearrangement to give **4**.

To avoid subsequent complications due to the facile oxidation to *p*-quinone of the aromatic entity of the molecule, acid **33** was converted with diazomethane into



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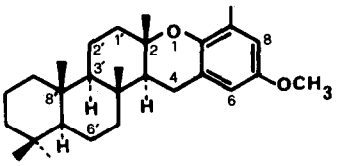

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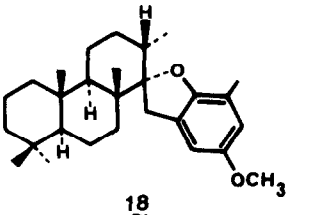

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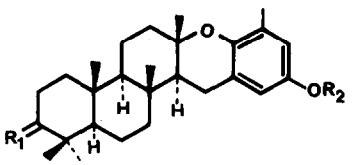
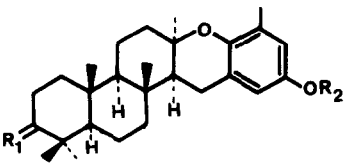


19 R_1 = OH, H R_2 = CH_3

20 R_1 = O R_2 = CH_3

21 R_1 = S, S R_2 = CH_3

22 R_1 = H_2 R_2 = H



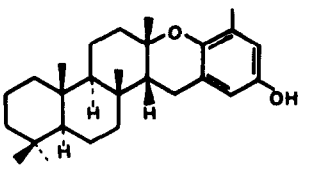
23 R_1 = OH, H R_2 = CH_3

24 R_1 = O R_2 = CH_3

25 R_1 = S, S R_2 = CH_3

26 R_1 = H_2 R_2 = CH_3

27 R_1 = H_2 R_2 = H



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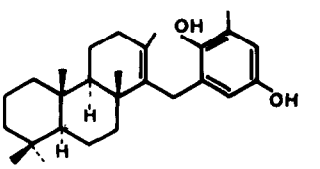

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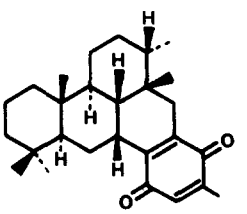

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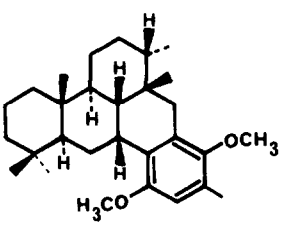

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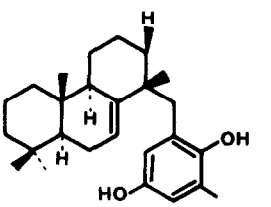

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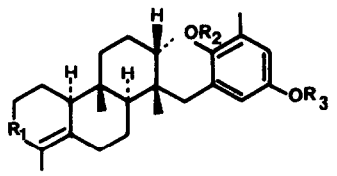
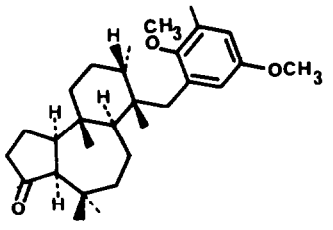
the crystalline methyl ester **34**, which was further methylated with dimethyl sulphate and potassium carbonate on refluxing in acetone to give **35**. On treatment with lithium aluminum hydride, compound **35** yielded the primary alcohol **36**, $C_{29}H_{46}O_3$, its IR spectrum indicating the absence of a carbonyl group and the presence of a hydroxy group (3.620 cm^{-1}). In the ^{1}H-NMR spectrum two methoxy groups at δ3.57 and 3.65 (s, 3H each) and two-proton multiplet at δ3.50 indicated a $-CH_2OH$ group which moves to δ3.98 on acetylation.

Oxidation of the alcohol **36** with pyridinium chlorochromate and sodium acetate suspended in anhydrous methylene chloride[14] gave the aldehyde **37**, $C_{29}H_{44}O_3$, carbonyl stretching frequency at 1730 cm^{-1}. The ^{1}H-NMR spectrum with a one-proton singlet at δ9.72 indicated a -CHO group. The cation-olefin cyclisation of compound **37** was carried out, either using stannic chloride or aqueous sulfuric acid, and both gave the same result as far as the nature of the products obtained was concerned, although the yield differed[15] (see Experimental). The reaction mixture chromatographed on a silica gel column gave the crystalline compounds **39** and **40** as the minor and less polar constituents. The spectroscopic data of the epimeric cyclopentanones **39** and **40** were virtually identical: IR spectra 1740 cm^{-1}, there being no ^{1}H-NMR signals due to olefinic protons or methyl groups on a double band. The only significant difference was in the chemical shifts of the signals due to the tertiary methyl groups: four three-proton singlets at δ0.82, 0.90, 0.95 and 1.02 in **39**, and 0.81, 0.89, 1.02 and 1.03 methyl singlets in **40**. The mass spectra indicated a molecular formula $C_{29}H_{40}O_3$ which is consistent with the formation of a new ring. Compounds **39** and **40** could have been generated by cyclisation at C-7′ to form **41** followed by a 1,2-alkyl migration. The most polar constituents isolated from the reaction mixture were the epimeric alcohols **42** and **43**. The ^{1}H-NMR spectra indicated the presence of an olefinic proton and four tertiary methyls. The geminal proton signal to the alcoholic group appeared in the β-isomer at δ3.48 and in the α-isomer at δ3.20 (m). Molecular formula $C_{29}H_{44}O_3$ indicated the formation of a new ring. Compounds **42** and **43** may be formed from **45** on losing a proton at C-6′.

Ketone **44** was obtained directly from acyclic alcohol



33 $R_1=CO_2H$ $R_2=H$ $R_3=CH_3$
34 $R_1=CO_2CH_3$ $R_2=H$ $R_3=CH_3$
35 $R_1=CO_2CH_3$ $R_2=R_3=CH_3$
36 $R_1=CH_2OH$ $R_2=R_3=CH_3$
37 $R_1=CHO$ $R_2=R_3=CH_3$
38 $R_1=CO_2H$ $R_2=R_3=CH_3$



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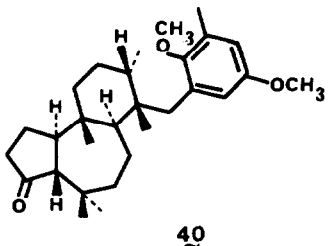

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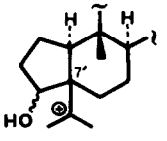

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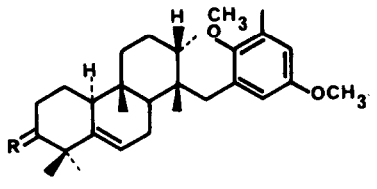
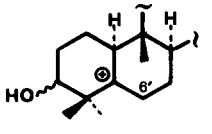


42 R = OH, H
43 R = OH, H
44 R = O



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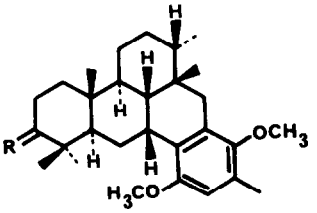
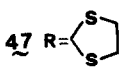
36 by oxidation with Jones' reagent as the least polar of the three reaction products and also as the principal constituent (72% yield).[16] A secondary ketone of the chromatography should have been an isomer of the former, but was only obtained in miniscule quantity and thus could not be identified. The most polar, and second more abundant product had acid characteristics, identified as compound **38**. Reduction of compound **44** with BH_4Na gave a mixture of the alcohols **42** and **43** in the proportion of 4:1.

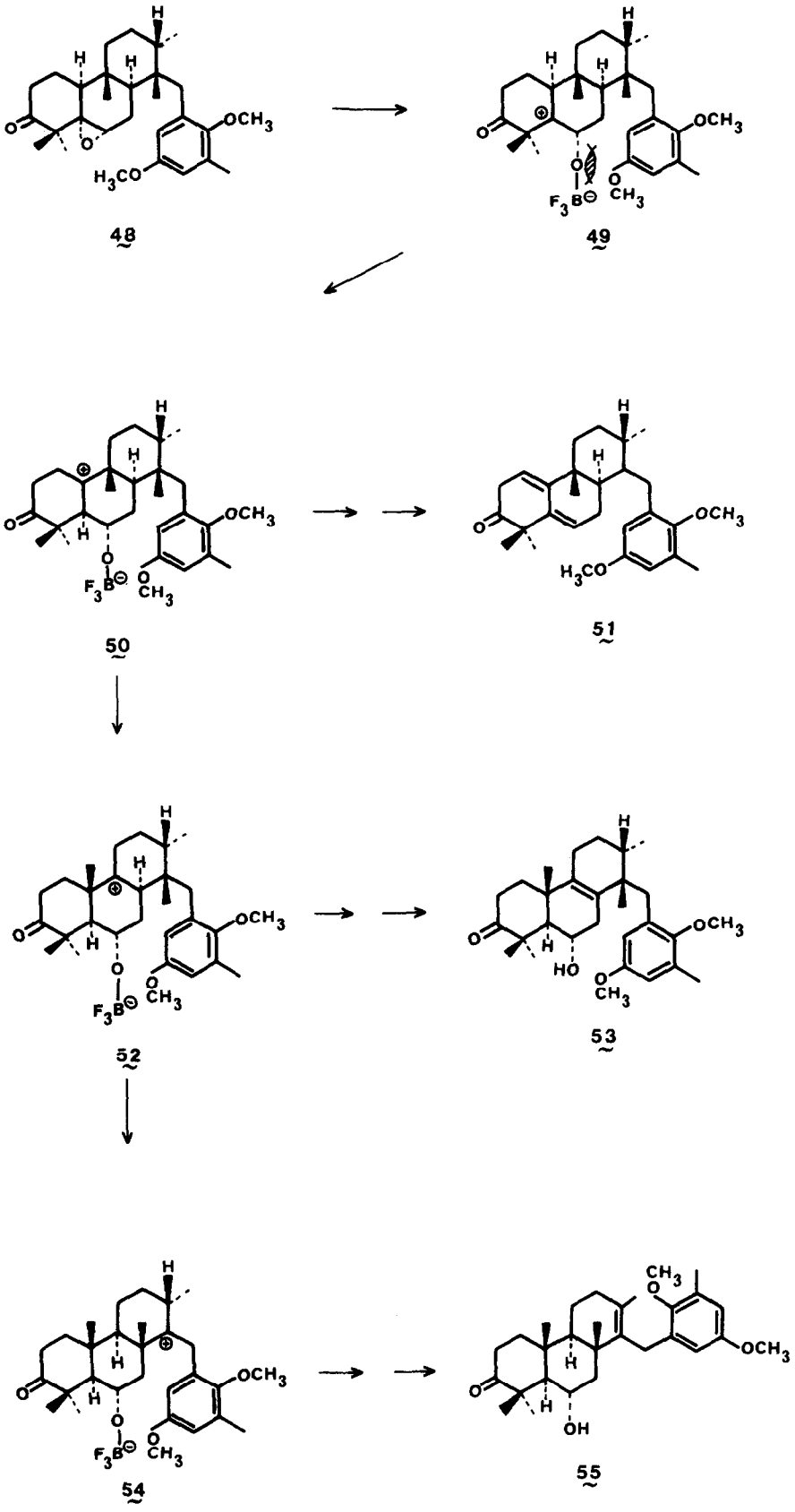
Ketone **44** was chosen as the substrate where a backbone rearrangement is induced in acid medium. Treatment of **44** with boron trifluoride-ether complex in benzene gave, as the only isolatable product, the pentacyclic ketone **46** in 65% yield. The ^{1}H-NMR spectrum indicated the presence of one aromatic proton at δ6.37, one-proton multiplet at δ3.20 and two one-proton doublets at δ2.65 and 2.20 (J = 14 Hz) assigned to hydrogens on carbons in α to the aromatic ring. There was a doublet at δ1.02 (3H) due to a secondary methyl group and four methyl singlets at δ1.04, 0.99, 0.85 and 0.81. The molecular weight, M^+ at *m/e* 438 (parent ion) which corresponds to the molecular formula $C_{29}H_{42}O_3$ indicated a pentacyclic skeleton. The mechanism for the formation of **46** presumably involves generation of a carbenium ion at C-7′ followed by three hydrogen methyl antiperiplanar migrations leading to the C-4′ ion, which after losing a proton from C-5′ further cycloalkylates in a non-concerted manner with the aromatic ring. The keto-group was removed *via* the thioketal **47** followed by Raney nickel desulfurization to give the previously described compound **31**. The thioketal **47** was formed directly and as the only product by treatment of ketone **44** with ethanodithiol-boron trifluoride ether complex. Ketone **46** is a partially rearranged product which demonstrates the good conditions of **44** as substrate to induce the desired backbone rearrangement, but clearly it must be modified so that the rearrangement may be complete.



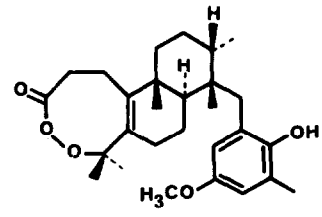
46 R = O
47 R = 

Treatment of **44** with *m*-chloroperbenzoic acid gave a mixture of epoxides of which the α-isomer, **48**, Scheme 2, was isolated with 65% yield by deactivated silica gel chromatography. The β-isomer was isolated with a yield of 25%. Treatment of **48** with BF_3 in dry ether led to a mixture of at least five compounds, from which the partially rearranged products **51** (26%), **53** (43%) and the totally rearranged keto-alcohol **55** (9%) were isolated (Scheme 2).

In an attempt to trace the natural formation of the proposed aldehyde intermediate **7** (Scheme 1), the alga *Taonia atomaria* was studied for its unstable and minor constituents. Freshly-gathered algae were extracted with cold acetone and subjected to a quick succession of chromatographies on silica gel. This study has given the isolation of nine new compounds among which the structures of the peroxylactone **56** and the hemilactal-triacetate **57** were determined.[9] Compound **56** was isolated by rapid silica gel column chromatography of the crude extract while the hemilactal-triacetate **57** was isolated by previous acetylation (Ac_2O/Py/25°) of the non-resolved and more polar chromatographic fractions.



Scheme 2.



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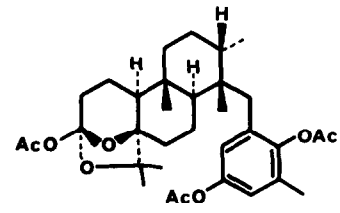

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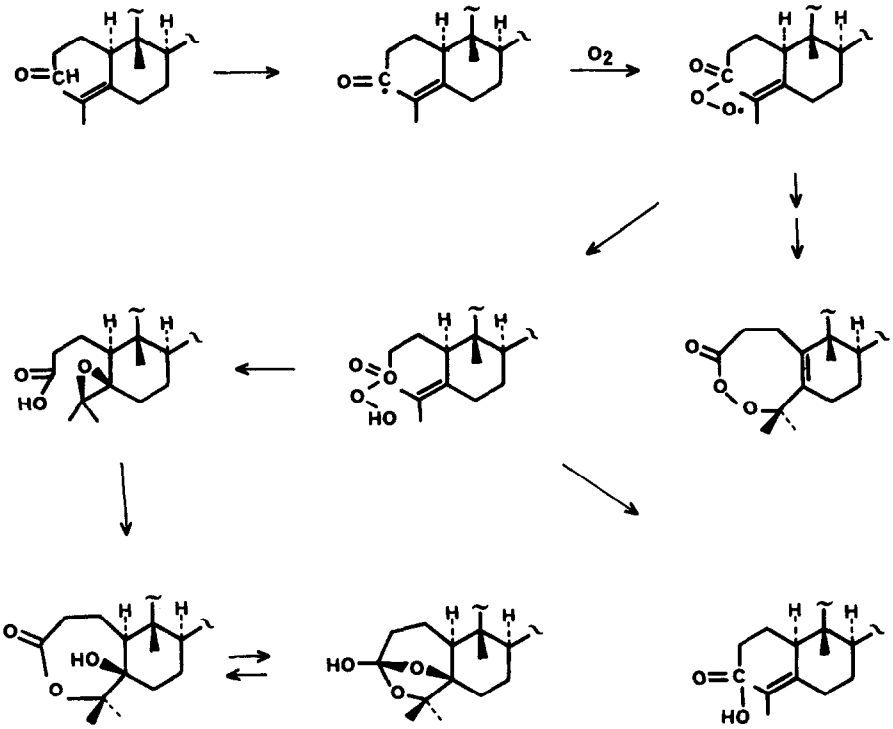

Scheme 3.

Although the aldehyde **7** was not isolated, compounds **56** and **57** are evidence that **7** may be a biogenetic precursor and that atomaric acid **15** accounts for the autoxidation of **7** (Scheme 3).

EXPERIMENTAL

M.p.s were determined on a Kofler block and are uncorrected. IR spectra were recorded on a Perkin–Elmer Model 237 spectrophotometer and untraviolet spectra recorded on a Perkin–Elmer Model 137 or a Unicam SP800. Optical rotations were determined for solutions in chloroform with a Perkin–Elmer 141 polarimeter. ^{1}H NMR spectra were recorded on Perkin–Elmer R-12B (60 MHz) or R-32 (90 MHz) spectrometers, chemical shifts are reported relative to Me_4Si (δ0) and coupling constants are given in hertz; $W_{1/2}$ refers to the width of a band at half height. Low-resolution mass spectra were obtained from a Hewlett-Packard 5930-A mass spectrometer and high-resolution from a VG-Micromass ZAB-2F. Column and dry column chromatography were performed in silica gel 0.2–0.5 and 0.005–0.2 mm, respectively, and tlc and plc on silica gel 6, all Merck products. Tlc plates were developed by spraying with 6*N*-sulphuric acid and heating. All solvents were purified by standard techniques. Anhydrous sodium sulphate was used for drying solutions.

Acid-catalysed cyclisation of **16**. The preparation of this stable "prenyl phenol" **16** has been adequately described in the earlier literature[2] and need not be repeated in detail here. However, it was discovered early in this work that it was best prepared when the solvent used was previously deoxygenated by passing argon through it for at least 0.5 hr, and the reaction was protected from light. A representative experiment of acid-catalysed cyclisation of **16** (line 4 in Table 1) was carried out as follows. To 10 ml of CH_2Cl_2 previously distilled in the absence of oxygen and moisture was added 0.096 ml of $SnCl_4$ (0.82 mmol). Of this solution 5 ml was poured into a round-bottom flask. The flask was tightly capped with a septum cap and cooled to −70° in the dark and under argon. A solution containing 16.4 mg (0.40 mmol) and 10 ml of CH_2Cl_2 was prepared in a test tube which was capped and cooled to −70°. After temperature equilibrium this solution was rapidly added by a prechilled pipette to the 5 ml of 0.82 mmol solution of $SnCl_4$ and the round-bottom flask capped again and shaken under argon for 30 min. The mixture was quenched with water and neutralised and the organic layer separated and dried over $MgSO_4$. After extraction, the organic layers were analysed using a Hewlett-Packard 5750 research chromatograph with a flame detector. The column used (12 ft × 0.125 in.) contained 10%

SE-30 silicone gum as a liquid phase and helium was the carrier gas. The reaction products were identified by peak enhancement using authentic samples.

11'-Desoxytaondiol methyl ether **17**. M.p. 158–160°, $\{\alpha\}_D - 69°$ (C, 0.40); IR (KBr) 1620, 1500, 1070, 860 cm^{-1}. ^1H NMR (60 MHz, $CDCl_3$) δ6.68 (1H, d, J = 3 Hz), 6.57 (1H, d, J = 3 Hz), 3.80 (3H, s), 2.61 (2H, d, J = 8 Hz), 2.15 (3H, s), 1.14 (3H, s) and 0.87 (12H, s). Mass spectrum: *m/e* (%) 410 (M^+, 100), 259 (92), 206 (30), 191 (50), 151 (84), 135 (30), 121 (30). (Found: C, 82.00; H, 9.97. Calc. for $C_{28}H_{42}O_2$: C, 81.95; H, 10.24%.)

11'-Desoxystypodiol methyl ether **18**. M.p. 187–188°, $\{\alpha\}_D + 18°$ (C, 0.52); IR (KBr) 1620, 1610, 1380, 1230, 1140, 1060 and 840 cm^{-1}; UV λ_{max} (EtOH) 235, 308 ϵ (6320, 5780). ^1H NMR (60 MHz, $CDCl_3$) δ6.47 (2H, bs), 3.69 (3H, s), 3.23 (1H, d, J = 17 Hz), 2.70 (1H, d, J = 17 Hz), 2.19 (3H, s), 0.92 (3H, s), 0.83 (3H, s), 0.78 (6H, s), 0.66 (3H, d, J = 6 Hz). Mass spectrum: *m/e* (%) 410 (M^+, 100), 259 (35), 191 (28), 163 (20), 151 (18), 135 (10), 123 (9), 121 (10). (Found: C, 81.93; H, 10.28. Calc. for $C_{28}H_{42}O_2$: C, 81.95; H, 10.24%.)

Treatment of 11'-desoxytaondiol methyl ether **17** *with* HBr. A soln of HBr (0.20 ml) in AcOH (5 ml) was added to a soln of 11'-desoxytaondiol methyl ether **17** (600 mg) in 10 ml of AcOH and the reaction mixture was heated at reflux for 3 hr. After cooling, water (30 ml) was added and then ether. The ether layer was extracted with 2*N* NaOH and the alkaline extract was then acidified with dil HCl. Extraction with ether gave 11'-desoxytaondiol **22** (323 mg, 54%), 11'-desoxyisotaondiol **27** (39 mg, 5.6%) and 11'-desoxyepitaondiol **28** (162 mg, 27%), which were separated by dry column chromatography. Compound **22**, m.p. 174–176°, $\{\alpha\}_D - 52°$ (C, 0.28); IR (KBr) 3460, 1600, 1230, 930 and 790 cm^{-1}; UV λ_{max} (EtOH) 301 nm (ϵ 3921). ^1H NMR (60 MHz, $CDCl_3$) δ6.45 (2H, bs), 2.55 (2H, bd, J = 8 Hz), 2.10 and 1.12 (s, 3H each), and δ0.85 (bs, 12H). Mass spectrum: m/e (%) 396 (M^+, 100), 312 (5), 259 (90), 192 (25), 175 (20), 164 (18), 149 (17), 137 (22), 121 (11). (Found: C, 81.79; H, 10.12. Calc. for $C_{27}H_{40}O_2$: C, 81.81; H, 10.10%.)

Compound **27**, m.p. 144–147°, $\{\alpha\}_D + 23°$ (c, 0.23); IR (KBr) 3465, 1602, 1235, 930 and 785 cm^{-1}; UV λ_{max} (EtOH) 299 nm (ϵ 3827). ^1H NMR (60 MHz, $CDCl_3$) δ6.45 and 6.39 (d, 1H each, J = 1.5 Hz), 2.62 (2H, m), 2.13, 1.16, 1.11, 0.98, 0.90 and 0.84 (s, 3H each). Mass spectrum: *m/e* (%) 396 (M^+, 100), 312 (8), 259 (82), 192 (29), 175 (18), 164 (30), 149 (22), 137 (31), 121 (18). (Found: C, 81.79; H, 10.09. Calc. for $C_{27}H_{40}O_2$: C, 81.81; H, 10.10%.)

Compound **28**, m.p. 125–128°, $\{\alpha\}_D + 5.7°$ (c, 0.42); IR (KBr) 3460, 1609, 1230, 1170, 990, 920, 850 and 790 cm^{-1}; UV λ_{max} (EtOH) 304 nm (ϵ 3790). ^1H NMR (60 MHz, $CDCl_3$) δ6.40 (2H, bs), 2.76 (2H, bd, J = 7 Hz), 2.07, 1.07, 0.82 (s, 3H each), 0.79 (s, 6H) and 0.65 (s, 3H). Mass spectrum: *m/e* (%) 396 (M^+, 100), 259 (98), 191 (25), 189 (23), 175 (26), 163 (30), 149 (18), 137 (31), 121 (20). (Found: C, 82.00; H, 10.14. Calc. for $C_{27}H_{40}O_2$: C, 81.81; H, 10.10%.)

Treatment of 11'-desoxytaondiol methyl ether **17** *with* BBr_3. A soln of BBr_3 (0.015 mole) in dry CH_2Cl_2 (15 ml of a soln containing 11.4 g BBr_3 in 40 ml CH_2Cl_2) was added to a soln of 11'-desoxytaondiol methyl ether (790 mg, 0.002 mol) in dry CH_2Cl_2 (15 ml) at room temp. After 2 hr, water (30 ml) was added and then ether (250 ml). The ether layer was extracted with 2*N* NaOH and the alkaline extract was then acidified with dil HCl. Extraction with ether gave 11'-desoxytaondiol (412 mg; 52%) which on crystallisation from benzene formed needles, m.p. 159–160°, $\{\alpha\}_D - 70°$ (c, 0.17).

11'-Desoxyisotaondiol **27** was obtained from its methyl ether **26** as prisms after crystallisation from methanol (43%), m.p. 146–147° $\{\alpha\}_D + 22.5°$ (c, 0.42).

Treatment of 11'-desoxystypodiol methyl ether **18** *with* HBr. A soln of HBr (0.10 ml) in AcOH (4 ml) was added to a soln of 11'-desoxystypodiol methyl ether **18** (280 mg) in 10 ml of AcOH and the reaction mixture was heated at reflux for 2.5 hr. After cooling, water (30 ml) was added and then ether. The ether layer was extracted with 2*N* NaOH and the extract was then acidified with dil HCl. Extraction with ether gave a red residue, which after crystallisation from methanol gave compound **30** as long needles (194 mg, 69%), m.p. 201–203° $\{\alpha\}_D - 81.8$ (c, 0.37); IR (KBr) 1643, 1609, 1250, 1180, 1170 and 885 cm^{-1}; UV λ_{max} (EtOH) 260, 360 nm (ϵ, 13984, 3940). ^1H NMR (60 MHz, $CDCl_3$) δ6.50 (1H, d, J = 1.5 Hz), 2.20 – 3.20 (3H, m), 2.00 (3H, d, J = 1.5 Hz), 0.95 (3H, d, J = 7 Hz), 0.85, 0.77, 0.72 and 0.61 (s, 3H each). Mass spectrum: *m/e* (%) 394 (M^+, 100), 375 (8), 298 (7), 268 (10), 241 (7), 189 (13), 137 (22). (Found: C, 82.28; H, 9.70. Calc. for $C_{27}H_{38}O_2$: C, 82.31; H, 9.66%.)

Reductive methylation of compound **30**. A soln of 142 mg of quinone **30** in MeOH (50 ml) was hydrogenated over Adams' catalyst until the soln was colourless. The mixture was left in the H_2 atmosphere at room temp. and during a period of 60 hr, a total of 8 ml of 30% NaOH aq and 6 ml of dimethyl sulphate was added to it in portions of 1 ml. The soln was shaken for 24 hr after the addition had been completed. The catalyst was filtered, 50 ml of water was added and the mixture was concentrated under reduced pressure to remove most of the MeOH. The residue was extracted with ether (100 ml) and the extract was washed with water, dried and passed through a column of silica gel (60 g). Elution of the column with benzene gave the *ether* **31** as a colourless, homogeneous (tlc) oil (94 mg, 66%) which slowly crystallises from MeOH as colourless needles, m.p. 140–142° $\{\alpha\}_D - 62°$ (c, 0.32); IR (KBr) 1595, 1450, 1090, 1080 and 990 cm^{-1}. ^1H NMR (60 MHz, CCl_4) δ6.35 (1H, s), 3.69 and 3.63 (s, 3H each), 3.40–2.30 (3H, m), 2.20 (3H, s), 0.88 (3H, d, J = 7 Hz), 0.84 (3H, s), 0.80 (6H, s) and 0.63 (3H, s). High-resolution mass spectrum (70 eV), *m/e* 424.3341 (M^+; 0.4 mamu deviation, $C_{29}H_{44}O_2$, 100%). (Found: C, 82.10; H, 10.47. Calc. for $C_{29}H_{44}O_2$: C, 82.02; H, 10.44%.)

Methylation of atomaric acid **33** *with diazomethane*. Atomaric acid **33** (200 mg) with CH_2N_2 in ether was allowed to stand overnight at room temp. Usual work-up gave the *methyl ester* **34**, m.p. 112–115°, $\{\alpha\}_D + 50°$ (c, 0.39); IR (CCl_4) 3620, 1740, 1620, 1490, 1240 and 860 cm^{-1}; UV λ_{max} (EtOH) 293 nm (ϵ, 3270). ^1H NMR (100 MHz, $CDCl_3$) δ6.68 and 6.49 (d, 1H each, J = 3 Hz), 4.34 (1H, bs, exchangeable with D_2O), 3.72, 3.64 (s, 3H each), 2.86 and 2.25 (2d, 1H each, J = 14 Hz), 2.22, 1.70, 1.68 (s, 3H each), 1.16 (3H, d, J = 7 Hz), 1.04 and 0.96 (s, 3H each). Mass spectrum: *m/e* (%) 456 (M^+, 12), 440 (6), 425 (22), 305 (52), 221 (31), 209 (29), 151 (100). (Found: C, 76.50; H, 9.86. Calc. for $C_{29}H_{44}O_4$: C, 76.31; H, 9.64%.)

Treatment of **34** *with* Me_2SO_4. A soln of **34** (300 mg) and dimethyl sulphate (2 ml) in dry acetone (50 ml) was refluxed over anhydrous potassium carbonate (2 g) for 20 hr. The solid was filtered off and the soln evaporated *in vacuo* and the residue taken up in water (40 ml) and extracted with ether (3 × 15 ml). The combined extracts were washed with 2*N*-sodium hydroxide (3 × 10 ml) and water (3 × 10 ml), dried, and evaporated *in vacuo*. Crystallization of the residue from methanol gave large needles (296 mmg, 98%) of the *dimethyl ether* **35**, m.p. 93–95°, $\{\alpha\}_D + 62°$ (c, 0.61), IR (CCl_4) 1740, 1620, 1490 and 860 cm^{-1}. ^1H NMR (60 MHz, CCl_4) δ6.56 and 6.43 (d, 1H each, J = 3 Hz), 3.45 (s, 3H), 3.57 (s, 6H), 2.21, 1.70, 1.66 (s, 3H each), 1.14 (d, 3H, J = 7 Hz), 1.02, 0.83 (s, 3H each). Mass spectrum: *m/e* (%) 470 (M^+, 9), 439 (17), 305 (45), 209 (32), 195 (28) and 165 (100). (Found: C, 76.60; H, 10.10. Calc. for $C_{30}H_{46}O_4$: C, 76.59; H, 9.8%.)

Reduction of **35** *with* $LiAlH_4$. A soln of ester **35** (820 mg) in dry ether (20 ml) was added dropwise during 15 min to a soln of LAS (500 mg) in dry ether (100 ml) at 0°. The mixture was stirred in an atmosphere of N_2 for 3 hr and then the excess of hydride was destroyed by treatment with EtOAc followed by MeOH. The mixture was then acidified with dil HCl and extracted with ether. Evaporation of the dried ($MgSO_4$) extract furnished a colourless oil (788 mg, 94%), which was dissolved in benzene and chromatographed in a silica gel (40 g) column. Compound **36**, oil, $\{\alpha\}_D + 44°$ (c, 0.28); IR (CCl_4) 3620, 1600, 865 cm^{-1}. ^1H NMR (60 MHz, CCl_4) δ6.56 and 6.42 (d, 1H each, J = 3 Hz), 3.65, 3.57 (s, 3H each), 3.50 (2H, bs), 2.84 (d, 1H, J = 14 Hz), 2.22 (s, 3H), 1.68 (s, 6H), 1.14 (d, 3H, J = 7 Hz), 1.01, 0.84 (s, 3H each). Mas spectrum: *m/e* (%), 442 (M^+, 42), 277 (29), 259 (35), 219 (18), 165 (100).

Oxidation of the alcohol **36** *with pyridinium chlorochromate*. Pyridinium chlorochromate (431 mg, 2.0 mmol) was added to a magnetically stirred solution of the alcohol **36** (442 mg, 1.0 mmol)

in 15 ml of dry CH_2Cl_2. After 2 hr 100 ml of dry ether was added and the supernatant decanted from the black gum. The insoluble residue was washed thoroughly 3 times with 10-ml portions of anhydrous ether whereupon it became a black granular solid. The combined organic solution was passed through a short pad of Florisil and the solvent was removed by distillation affording 312 mg (70%) of pure **37** homogeneous by glc, as an oil, $\{\alpha\}_D + 32°$ (c, 0.18); IR (KBr) 1735, 1610, 1490, 1225, 1070 and 1025 cm^{-1}; ^1H NMR (60 MHz, $CDCl_3$) 9.70 (1H, s), 6.62 and 6.46 (d, 1H each, J = 3 Hz), 3.69, 3.60, 2.25, 1.71, 1.68 (s, 3H each), 1.17 (3H, d, J = 7 Hz), 1.05 and 0.86 (s, 3H each). Mass spectrum: *m/e* (%), 440 (M^+, 60), 279 (100), 275 (75), 257 (98), 219 (20), 149 (99).

Acid-catalysed cyclisation of the unsaturated aldehyde **37**. (a) To a soln of **37** (200 mg) in AcOH (10 ml) at 0° was added H_2SO_4–AcOH (0.25 M; 2 ml). Isolation after 48 min by means of pentane gave a gum (187 mg) which was adsorbed onto silica gel (100 g). Elution with light petroleum gave the *ketones* **39** (36 mg) and **40** (24 mg) which crystallised from MeOH as needles. Compound **39**, m.p. 112–114°, $\{\alpha\}_D + 19°$ (c, 0.43); IR (KBr) 1740, 1480, 1150, 1070 and 1030 cm^{-1}. ^1H NMR (90 MHz, CCl_4) δ6.54 and 6.42 (d, 1H each, J = 3 Hz), 3.67 and 3.57 (s, 3H each), 2.86 (1H, d, J = 14 Hz), 2.21 (s, 3H), 2.14 (1H, d, J = 14 Hz), 1.11 (d, 3H, J = 7 Hz), 1.02, 0.95, 0.90 and 0.82 (s, 3H each). Mass spectrum: *m/e* (%) 440 (M^+, 10), 275 (18), 257 (16), 165 (100). (Found: C, 79.13; H, 9.98. Calc. for $C_{29}H_{44}O_3$: C, 79.09; H, 10.00%.)

Compound **40**, m.p. 132–135°, $\{\alpha\}_D - 6°$ (c, 0.17); IR (KBr) 1740, 1475, 1480, 1152, 1070 and 1030 cm^{-1}. ^1H NMR (60 MHz, $CDCl_3$) δ6.77 and 6.62 (d, 1H each, J = 3 Hz), 3.76 and 3.65 (s, 3H each), 2.98 (1H, d, J = 14 Hz), 2.29 (s, 3H), 2.27 (1H, d, J = 14 Hz), 1.13 (3H, d, J = 7 Hz), 1.03, 1.02, 0.89 and 0.81 (s, 3H, each). Mass spectrum: *m/e* (%) 440 (M^+, 6), 275 (24), 257 (26), 165 (100). (Found: C, 79.02; H, 10.12. Calc. for $C_{29}H_{44}O_3$: C, 79.09: H, 10.00%.)

Elution with light petroleum–benzene (1:1) gave the *alcohols* **42** (60 mg) and **43** (49 mg). Compound **42**, m.p. 160–162°, $\{\alpha\}_D - 9°$ (c, 0.82); IR (KBr) 3600, 1600, 1070, 1015, 875 and 840 cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$) δ6.61 and 6.56 (d, 1H each, J = 3 Hz), 5.68 (1H, bs, $W_{1/2}$ = 8 Hz), 3.73 and 3.64 (s, 3H each), 3.48 (1H, bs, $W_{1/2}$ = 7 Hz), 2.95 (1H, d, J = 14 Hz), 2.27 (3H, s), 1.18 (3H, d, J = 7 Hz), 1.16, 1.07, 0.91 and 0.86 (s, 3H each). Mass spectrum: *m/e* (%) 440 (M^+, 6), 290 (30), 265 (16), 166 (60), 165 (56), 149 (100). (Found: C, 78.97; H, 9.97. Calc. for $C_{29}H_{44}O_3$: C, 79.09; H, 10.00%.)

Compound **43**, oil, $\{\alpha\}_D + 6°$ (c, 0.52); IR (KBr) 3620, 1602, 1070, 1020, 880 and 840 cm^{-1}; ^1H NMR (60 MHz, $CDCl_3$) δ6.74 and 6.58 (d, 1H each, J = 3 Hz), 5.71 (1H, bs, $W_{1/2}$ = 8 Hz), 3.76 and 3.66 (s, 3H each), 3.30 (1H, m), 2.95 (1H, d, J = 14 Hz), 2.29 (s, 3H), 2.28 (1H, d, J = 14 Hz), 1.18 (3H, d, J = 7 Hz), 1.17 and 0.99 (s, 3H each and 0.86 (s, 6H). Mass spectrum: *m/e* (%) 440 (M^+, 10), 290 (32) 265 (14), 166 (81), 165 (92), 149 (100).

(b) Treatment of **37** with $SnCl_4$ in different solvents was found to give varying amounts of **42** and **43**. In the best run, to a soln of **37** (440 mg, 0.1 mol) in benzene (50 ml) at 10°, was added 0.1 mole of $SnCl_4$ in benzene (10 ml), the reaction mixture was kept at 10° for 10 min. Water (60 cm^3) was added and the organic layer was washed with 2N NaOH and dil HCl. Evaporation of the dried ($MgSO_4$) extract furnished a colourless oil (381 mg, 85%) comprising at least six compounds, from which compounds **39** (78 mg, 18%), **40** (51 mg, 12%), **42** (132 mg, 30%) and **43** (110 mg, 25%) were isolated by chromatography on silica gel (150 g), using *n*-hexane–ether gradient as eluent.

Oxidation of the alcohol **36** *with* CrO_3. Compound **36** (442 mg, 0.1 mole) in acetone (40 ml) was treated at room temp. with Jones reagent (0.23 ml). After 15 min the soln was poured into water and the product was extracted with ether. The ether solution was washed with water, aqueous $NaHCO_3$ and water. Evaporation *in vacuo* and separation by column chromatography on silica gel (100 g), with benzene as eluent, gave the *ketone* **44** (318 mg, 72%): m.p. 126–128°, $\{\alpha\}_D + 23°$ (c, 0.25); IR (CCl_4) 1710, 1595, 1590, 1210, 1060 and 1015 cm^{-1}; ^1H NMR (60 MHz, CCl_4) δ6.54 and 6.42 (d, 1H each, J = 3 Hz), 5.70 (1H, bs, $W_{1/2}$ = 10 Hz), 3.65, 3.58 (s, 3H each), 2.88 (1H, d, J = 14 Hz), 2.22 (s, 3H), 1.20 (6H, s), 1.14 (3H, d, J = 7 Hz), 0.86 and 0.84 (s, 3H each). Mass spectrum: *m/e* (%) 438 (M^+, 40), 273 (35), 204 (5), 189 (32), 177 (80), 166 (100). Anal. (Found: C, 79.51; H, 9.90. Calcd. for $C_{29}H_{42}O_3$: C, 79.41; H, 9.65%.)

Further elution (benzene–ethylacetate, 1:1) afforded the acid **38** (42 mg), identical with an authentic sample.

Reduction of **44** *with* $NaBH_4$. To a stirred soln of **44** (219 mg, 0.05 mole) in 40 ml of methanol was added $NaBH_4$ (0.3 mole) in small portions during 1.5 hr. The soln was then refluxed for 30 min, the reaction being monitored by tlc and glc. Water was then added and the mixture extracted with ether (3 × 25 ml); the organic soln was then washed with water, dried ($MgSO_4$), and conc. The products were fractionated by using a silica gel column (50 g) with *n*-hexane–ether as eluent. The two *alcohols* **42** (162 mg) and **43** (41 mg) were isolated and identified (m.m.p., tlc, IR, ^1H NMR, MS) with those obtained by acid-catalysed carbocyclisation of the aldehyde **37**.

Treatment of ketone **44** *with boron trifluoride—Ether complex.* Boron trifluoride–ether complex (0.5 ml) was added dropwise with swirling to a solution of the ketone **44** (200 mg) in dry benzene (50 ml). The soln was kept for 30 min and then potassium carbonate was added followed by water (50 ml). The mixture was extracted with benzene and the extract was evaporated. The residue was applied to one preparative plate and this was eluted 3 times with light petroleum–ether (20:1). The major band offered the *pentacarbocyclic ketone* **46** (128 mg, 65%): oil, $\{\alpha\}_D - 34°$ (c, 0.19; IR (KBr) 1695, 1600, and 855 cm^{-1}; ^1H NMR (60 MHz, CCl_4) δ6.38 (1H, s), 3.71, 3.61, 2.20, 1.04, 0.98 (s, 3H each), 0.95 (3H, d, J = 7 Hz), 0.86 and 0.82 (s, 3H each). High resolution mass spectrum (70 eV), *m/e* 438.3134 (M^+; 0.2 mamu deviation, $C_{29}H_{42}O_3$, 100%), further peaks at *m/e* (%) 423 (10), 311 (3), 217 (4).

Ethylene dithioacetal derivative of **46**. To a soln of **46** (78 mg) in glacial acetic acid (2 ml) were added ethanedithiol (0.1 ml) and boron trifluoride–ether (2 drops). After 2 hr at room temp., the soln was cooled to 0° and poured into cold 4*N* sodium hydroxide. The product was extracted with ether and the ether solution was washed several times with water, dried and evaporated *in vacuo*. The dithioacetal **47** was separated by plc as a crystalline solid, (46 mg, 60%), m.p. 127–128° (large needles from methanol); IR (CCl_4) 1610, 1470, 1390, 1080 and 840 cm^{-1}; ^1H NMR (60 MHz, CCl_4) δ6.36 (1H, s), 3.69, 3.61 (s, 3H each), 3.01 (4H, s), 2.20, 0.97 (s, 3H each), 0.89 (s, 6H), 0.79 (s, 3H). Mass spectrum: *m/e* (%), 514 (M^+, 80), 383 (100), 351 (2), 285 (8), 271 (2), 257 (4), 217 (20).

Reduction of the dithioacetal **47**. The dithioacetal **47** (36 mg) in absolute ethanol (15 ml) was refluxed with an excess of Raney nickel for 20 hr. The cooled mixture was filtered and evaporated *in vacuo*. Separation by plc gave the compound **31** (22 mg, 61%) which crystallised from methanol as needles, m.p. 142–143°, $\{\alpha\}_D - 61°$ (c, 0.08). (Found: C, 82.11; H, .10.45. Calc. for $C_{29}H_{44}O_2$: C, 82.02; H, 10.44%.)

Epoxidation of **44**. *m*-Chloro-perbenzoic acid in benzene (1.05 *M*; 5.2 ml) was added dropwise to the olefin **44** (1.5 g) in benzene (20 ml) with stirring. After 20 min, calcium hydroxide was added to remove the excess of peracid; the soln was then filtered and evaporated. The residue obtained was applied to 2 large preparative plates and these were eluted 4 times with light petroleum–ether (20:1). The major band afforded 6′α,7′α-epoxy-derivative **48** (960 mg, 64%), m.p. 194–196°, $\{\alpha\}_D + 92°$ (c, 0.33); IR (KBr) 1700, 920 and 830 cm^{-1}. ^1H NMR (60 MHz, CCl_4) δ6.59 and 6.47 (d, 1H each, J = 3 Hz), 3.67, 3.60 (s, 3H each), 3.09 (1H, bs, $W_{1/2}$ = 6 Hz), 2.23 (3H, s), 1.17 (3H, d, J = 7 Hz), 1.11, 0.93 (s, 3H each), 0.81 (6H, s). Mass spectrum: *m/e* (%), 454 (M^+, 78), 289 (20), 271 (98), 261 (22), 243 (12), 229 (10), 166 (100). (Found: C, 76.49; H, 9.31, Calc. for $C_{29}H_{42}O_4$: C, 76.61; H, 9.31%.)

A minor band afforded 6′β,7′β-epoxy-derivative (37 mg, 25%), m.p. 118–119°, $\{\alpha\}_D + 9°$ (c, 0.21); IR (KBr) 1710, 1320, 925 and 830 cm^{-1}. ^1H NMR (60 MHz, CCl_4) δ6.59 and 6.46 (d, 1H each, J = 3 Hz), 3.59, 3.50 (s, 3H each), 3.09 (1H, bs, $W_{1/2}$ = 9 Hz), 2.24, 1.27 (s, 3H each), 1.03 (3H, d, J = 6 Hz), 0.93, 0.84, 0.79 (s, 3H each). Mass spectrum: *m/e* (%) 454 (M^+, 69), 289 (17), 271 (90), 261 (23), 243 (19), 229 (25), 166 (100). (Found: C, 76.56; H, 9.29. Calc. for $C_{29}H_{42}O_4$: C, 76.61; H, 9.31%.)

Treatment of 6′α,7′α-*epoxy-derivative* **48** *with boron trifluoride—ether complex.* Compound **48** (300 mg) in dry benzene (5 ml) was treated with boron trifluoride–ether complex (0.5 ml)

in the manner described earlier. The oil obtained was applied to 2 small preparative plates and these were eluted 6 times with light petroleum–ether (20:1). The band with highest R_F afforded the diene **51** (78 mg, 26%) as prisms (from light petroleum), m.p. 185–186°, $\{\alpha\}_D$ + 134° (c, 0.25); IR (KBr) 3080, 1720, 1600, 1480, 1220, 1020, 860, 840, 810 cm^{-1}; UV λ_{max} (EtOH) 225, 246, 288 nm (ϵ, 26.600, 11.060, 4.108). ^1H NMR (60 MHz, CCl_4) δ6.60 and 6.45 (d, 1H each, J = 3 Hz), 5.75 (1H, bs, $W_{1/2}$ = 10 Hz), 5.45 (1H, bs, $W_{1/2}$ = 7 Hz), 3.68, 3.57 (s, 3H each), 2.25 (s, 3H), 1.19 (6H, s), 1.10 (d, 3H, J = 7 Hz), 1.02, 0.90 (s, 3H each). Mass spectrum: *m/e* (%) 436 (M^+, 30), 271 (36), 243 (2), 175 (62), 166 (100). (Found: C, 79.79; H, 9.14. Calc. for $C_{29}H_{40}O_3$: C, 79.81; H, 9.17%.)

The second band afforded the alcohol **53** (129 mg, 63%), m.p. 159–160°, $\{\alpha\}_D$ + 61° (c, 0.27); IR (KBr) 3650, 1710, 1600, 860 and 810 cm^{-1}. ^1H NMR (60 MHz, CCl_4) δ6.72 and 6.67 (d, 1H each, J = 3 Hz), 3.81 and 3.60 (s, 3H each), 2.88 (1H, d, J = 14 Hz), 2.50 (1H, d, J = 14 Hz), 2.35 (s, 3H), 1.39 (s, 6H), 1.14 (s, 3H), 1.09 (d, 3H, J = 7 Hz) and 0.96 (s, 3H). Mass spectrum: *m/e* (%) 454 (M^+, 4), 436 (2), 289 (62), 271 (100), 253 (10), 166 (32). (Found: C, 76.70; H, 9.18. Calc. for $C_{29}H_{42}O_4$: C, 76.65; H, 9.25%.)

The third band afforded the fully rearranged alcohol **55** (27 mg, 9%), m.p. 92–93°, $\{\alpha\}_d$ + 44° (c, 0.21); IR (CCl_4) 3635, 1710, 1600 and 860 cm^{-1}. ^1H NMR (60 MHz, CCl_4) δ 6.60 and 6.52 (d, 1H each, J = 3 Hz), 3.79 and 3.76 (s, 3H each), 3.46 (1H, bs, $W_{1/2}$ = 5 Hz), 2.34, 1.59 (s, 3H each), 1.31 (s, 6H), 1.09 and 0.80 (s, 3H each). Mass spectrum: *m/e* (%) 454 (M^+, 100), 436 (2), 421 (4), 405 (3), 271 (56), 218 (19), 185 (22), 165 (98). (Found: C, 76.66; H, 9.23. Calc. for $C_{29}H_{42}O_4$: C, 76.65; H, 9.25%.)

Acetate, oil, $\{\alpha\}_D$ + 62° (c, 0.42); IR (CCl_4) 1745, 1715 and 1600 cm^{-1}. ^1H NMR (60 MHz, CCl_4) δ6.45 and 6.30 (d, 1H each, J = 3 Hz), 4.85 (1H, m), 3.69, 3.66 (s, 3H each), 3.32 (1H, bs, $W_{1/2}$ = 4 Hz), 2.23, 1.90, 1.50 (s, 3H each), 1.14 (s, 6H), 0.99, 0.80 (s, 3H each).

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