Total Syntheses of Marine Sponge Metabolites. Part 3.[1] Stereoselective Total Synthesis of (±)-12-Deoxyscalaradial[2]

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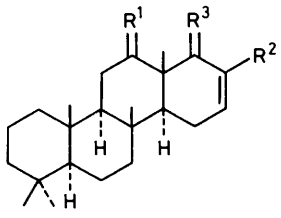
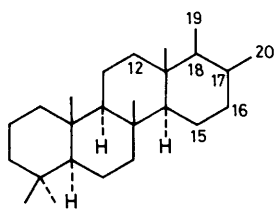
A highly efficient total synthesis of (±)-12-deoxyscalaradial (**1d**), a representative of the scalaradials from marine sponges, is described. (±)-Labda-8(20),13-dien-15-oic acid (**3**), chosen as the starting material, was transformed to the known tricyclic alcohol (**4a**) and the latter was oxidised with Swern's reagent to the aldehyde (**4b**). Isomerisation of compound (**4b**) with toluene-*p*-sulphonic acid in benzene afforded the conjugated aldehyde (**5**), which on Wittig reaction with methylenetriphenylphosphorane yielded the diene (**6**). On heating with dimethyl acetylenedicarboxylate the diene (**6**) afforded the Diels–Alder adduct (**7a**). Refluxing of compound (**7a**) with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) gave the isomeric conjugated diester (**8**), which on hydrogenation over 10% Pd–C led to the desired *trans*-fused olefin diester (**1e**). Reduction of compound (**1e**) with lithium aluminium hydride, followed by Swern's oxidation, provided the desired dialdehyde (**1d**).

The synthesis of the *trans*-fused olefin diester (**1e**) from compound (**7a**), *via* an alternative five-step sequence of reactions, is also reported.

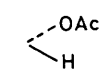
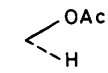
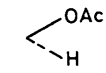
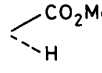
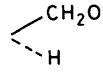
Terpenes are the most abundant non-steroidal secondary metabolites so far isolated from marine sponges. The occurrence of sesterterpenes has been rare in nature, but recently an increasing number of examples have been reported. Many of the examples have been obtained from sponges of the order Dictyoceratidae. The genera *Ircinia*, *Spongia*, *Hippospongia*, and *Cacospongia* have yielded an array of sesterterpenes.[3a–m] These compounds are members of a new class of sesterterpenes, originating from geranylfarnesol by a cyclisation[4] initiated at the isopropylidene group, which is typical of triterpenes. Three analogous tetracyclic sesterterpenes, scalaradial[5] (**1a**), 12-*epi*-scalaradial[3h] (**1b**), and 12,18-di-*epi*-scalaradial[3j] (**1c**), obtained from some species of the order Dictyoceratidae, possess the basic ring system represented by the scalarane hydrocarbon[3i] (**2**), and contain the enal-aldehyde entity present in molecules such as polygodial, warburganal, and related biologically active sesquiterpenes.[6] The compounds have received much attention not only from a chemical point of view but also due to their observed biological activity.[7] This paper describes the first total synthesis of the title compound (**1d**), a representative of the scalaradials from marine sponges.



(**1**)



(**2**)

	R^1	R^2	R^3
a;		CHO	
b;		CHO	
c;		CHO	
d;	H_2	CHO	
e;	H_2	CO_2Me	
f;	H_2	CH_2OH	

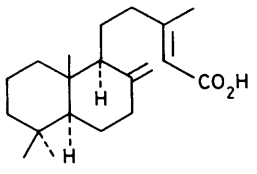
Results and Discussion

We have previously employed (±)-labda-8(20),13-dien-15-oic acid (**3**) as a starting material for the synthesis of (±)-isoagatholactone and its related diterpene metabolites,[8] and the same compound also served our present purpose.

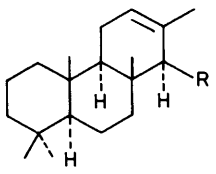
(±)-Labda-8(20),13-dien-15-oic acid (**3**) was transformed through a sequence of reactions previously reported,[8] into the known tricyclic alcohol† (**4a**). Oxidation of the alcohol (**4a**) with Swern's reagent[9] afforded the aldehyde (**4b**) (98%). On heating in the presence of toluene-*p*-sulphonic acid in benzene at 50 °C for 5 h, the aldehyde (**4b**) isomerised in 59% yield to the conjugated aldehyde (**5**). Wittig reaction[10] of compound (**5**) with methylenetriphenylphosphorane in tetrahydrofuran afforded the diene (**6**) (85%). Heating the diene (**6**) with dimethyl acetylenedicarboxylate at 105 °C for 24 h furnished the Diels–Alder adduct[11] (**7a**) (75%). The addition occurred stereoselectively from the less crowded α-face of the molecule, and no appreciable amount of the C-13 epimer was detected.

The next stage of the synthesis was the reduction of the Diels–Alder adduct (**7a**) to the *trans*-fused olefin diester (**1e**). We first attempted to effect this conversion according to the procedure reported by Ley *et al.*[12] The reductive/isomerising conditions

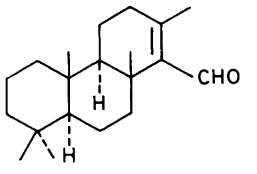
† All compounds synthesized are racemic modifications although only one enantiomer is depicted.



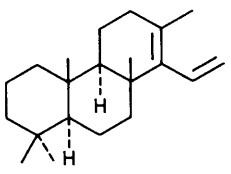
(3)



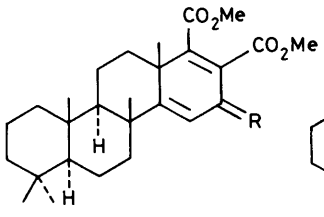
(4) a; R = CH_2OH
b; R = CHO

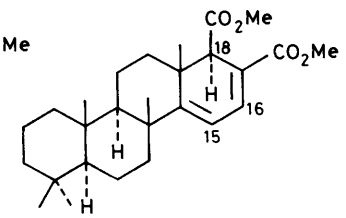


(5)



(6)





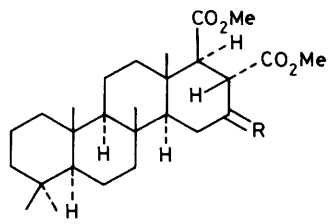
(7) a; R = H_2
b; R = O

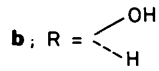
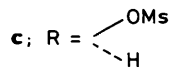
(8)

using 10% H_2–Pd–C in methanol in the presence of acid catalysts worked satisfactorily in their synthesis of (±)-polygodial. However, compound (**7a**) was found to be resistant to hydrogenation at atmospheric pressure and 23 °C with 10% Pd–C both in the presence and absence of mineral acids. The use of platinum oxide as the catalyst also resulted in the recovery of the starting material. At elevated pressures, however, compound (**7a**) was hydrogenated to a tetrahydro derivative.

We therefore turned to a two-step conversion of compound (**7a**) into (**1e**). This would involve kinetically controlled stereospecific protonation of the enolate derived from (**7a**) to afford (**8**), which on reduction with H_2–Pd–C would give (**1e**). A related conversion had previously been effected by Lallemand *et al.*[13] in the synthesis of drimane sesquiterpenes. When, however, compound (**7a**) was treated with lithium di-isopropylamide in tetrahydrofuran at −78 °C, followed by kinetic protonation with 0.5M-sulphuric acid at −78 °C, a mixture of unidentifiable products, which possessed no methoxy groups, was obtained.

Under these circumstances we were compelled to manipulate the following alternative five-step sequence of reactions to obtain compound (**1e**). Allylic oxidation of compound (**7a**) with chromium trioxide–pyridine complex[14] provided the dienone (**7b**) in 90% yield. Compound (**7b**) also resisted hydrogenation at atmospheric pressure and 23 °C with 10% Pd–C, but at 68 atm it was reduced to a tetrahydro derivative. In this case the hydrogenation took place exclusively from the less hindered α-side of the molecule and only a single product was obtained in 75% yield. This *trans*-fused ketone was formulated as (**9a**).* On reduction with sodium borohydride in ether–chloroform at 0 °C the ketone (**9a**) afforded the 16β-alcohol (**9b**) (38%). The stereochemistries of all substituents in ring D of compound (**9b**)



(9) a; R = O
b; R = 
c; R = 

were established from the ^1H n.m.r. spectrum, in which 16-, 17-, and 18-H absorbed at δ 4.23 (m, $W_{\frac{1}{2}}$ 18 Hz), 3.42 (dd, *J* 12, 9 Hz), and 3.06 (d, *J* 12 Hz), respectively. The large coupling constants between these three protons indicated that they are in a *trans*-diaxial relationship and hence the 16-hydroxy, 20-ester, and 19-ester groups are all equatorially oriented, possessing the β-, α-, and β-configuration, respectively. The alcohol (**9b**) was then treated with methanesulphonyl chloride and triethylamine and the resulting methanesulphonate (**9c**) heated under reflux in benzene with 1,8-diazabicyclo[5.4.0]undec-7-ene[15] (DBU) to afford the olefin diester (**1e**) in 75% overall yield.

After completion of the synthesis of compound (**1e**), a recent report by Mori *et al.*[16] was brought to our attention. They reported that on refluxing with DBU in tetrahydrofuran a bicyclic unconjugated diester, an equivalent of (**7a**), was isomerised smoothly to the conjugated diester, an equivalent of (**8**). The application of this procedure to compound (**7a**) furnished the isomeric conjugated diester (**8**) in 85% yield.† The configuration at C-18 of this compound was determined on the basis of the ^1H n.m.r. evidence. The 15- and 16-protons resonated at δ 5.71 (d) and 6.88 (dd), respectively, and they coupled with each other with a *J* value of 6 Hz. The 16-proton also coupled with the 18-proton at δ 3.28 (d) with a *J* value of 2.5 Hz. The observed value (2.5 Hz) of the coupling constant between 16- and 18-H confirmed the α-configuration of 18-H and hence the β-configuration of the 19-ester group. If, however, the 19-ester group were to adopt the α-configuration, the coupling constant between 18β-H and the 16-H would be zero.[13] On hydrogenation over 10% Pd–C at atmospheric pressure and 23 °C the conjugated diester (**8**) gave in 85% yield the olefin diester (**1e**), identical with that obtained earlier *via* a different route. Subsequent reduction of compound (**1e**) with lithium aluminium hydride in ether at 0 °C afforded in 100% yield the diol (**1f**). On Swern's oxidation the diol (**1f**) provided the desired dialdehyde (**1d**) (30%). In the ^1H n.m.r. spectrum the 19- and 20-CHO protons appeared at δ 9.42 (d, *J* 4 Hz) and 9.50 (s), respectively, and the observed value (4 Hz)‡ of the coupling constant between 18-H and the 19-CHO proton verified the β-configuration of the 19-CHO group.

Experimental

M.p.s were determined with a hot-stage microscope and are uncorrected. I.r. spectra were recorded on a Perkin-Elmer 337

* The 20-ester group in this β-keto ester is postulated to have been inverted to the more stable α(equatorial)-configuration, due to the equilibrium with the conjugated enol-form (see Experimental section).

† In this case, no appreciable amount of the C-18 epimer was formed (*cf.* D. Guillerm, M. Delarue, M. Jalali-Naini, P. Lemaitre, and J-Y. Lallemand, *Tetrahedron Lett.*, 1984, **25**, 1043).

‡ The coupling constant between the 19α(axial)-CHO proton and the 18-H is smaller (2.5 ~ 3 Hz) (see references 1, 3*h*, and 13).

spectrometer in KBr discs. N.m.r. spectra were measured on a Varian EM 3940 (90 MHz) spectrometer and chemical shifts are reported in p.p.m. downfield from internal $SiMe_4$. For column chromatography silica gel 60 (Merck, 70—230 mesh) was used. Thin layer chromatograms were prepared on silica gel G or silica gel GF_{254} 60 (Merck) and the spots were observed by exposure to iodine vapour or u.v. light. All organic extracts were dried over anhydrous sodium sulphate and evaporated under reduced pressure below 60 °C.

Oxidation of the Tricyclic Alcohol (**4a**).—A solution of dimethyl sulphoxide (1.2 ml, 15.2 mmol) in methylene dichloride (4 ml) was added dropwise to a stirred solution of oxalyl chloride (0.7 ml, 7.6 mmol) in methylene dichloride (25 ml) under dry nitrogen at −60 °C. After 3 min at −60 °C, a solution of the alcohol (**4a**) (2 g, 6.9 mmol) in methylene dichloride–dimethyl sulphoxide (3:1; 10 ml) was added dropwise over 5 min. The reaction mixture was stirred for a further 20 min, triethylamine (4.8 ml, 36.1 mmol) was added at −60 °C, and stirring was continued for a further 10 min. The cooling bath was removed, water was added at room temperature, and the product was extracted with ether. The ether was evaporated off and the remaining dimethyl sulphoxide was removed under reduced pressure, yielding a crude product as a gum. Chromatography on silica gel using 2% ether–hexane as eluant afforded the *aldehyde* (**4b**) (1.95 g), m.p. 60—62 °C (hexane–methanol); $\nu_{max.}$(neat) 1 710 (CHO) cm^{-1}; $\delta(CCl_4)$ 0.82, 0.87, 0.91, 1.02 (each 3 H, s, Me), 1.60 (3 H, m, =CMe), 2.52 (1 H, br s, 14-H), 5.60 (1 H, br s, 12-H), and 9.65 (1 H, d, *J* 4 Hz, CHO) (Found: C, 83.1; H, 11.35. $C_{20}H_{32}O$ requires C, 83.27; H, 11.18%).

Isomerisation of the Aldehyde (**4b**) *to the Conjugated Aldehyde* (**5**).—The aldehyde (**4b**) (1.95 g) in dry benzene (40 ml) was heated in the presence of a catalytic amount of toluene-*p*-sulphonic acid at 50 °C for 5 h. After filtration through a small column of silica gel the solution was evaporated and the residue subjected to chromatography on silica gel. Elution with 5% ether–hexane yielded the *conjugated aldehyde* (**5**) (1.15 g), m.p. 139—141 °C (hexane); $\nu_{max.}$ 1 660 cm^{-1} (CHO); $\delta(CCl_4)$ 0.82 (3 H, s, Me), 0.85 (6 H, s, 2 × Me), 1.15 (3 H, s, Me), 2.00 (3 H, s, =CMe), and 9.98 (1 H, s, CHO) (Found: C, 83.0; H, 11.45. $C_{20}H_{32}O$ requires C, 83.27; H, 11.18%).

Wittig Reaction of the Aldehyde (**5**).—A suspension of methyltriphenylphosphonium bromide (1.755 g, 4.9 mmol) in dry tetrahydrofuran (THF) (25 ml) was treated with a 1.4M solution of butyl-lithium (3.52 ml, 4.9 mmol) in hexane, and the mixture stirred under dry nitrogen for 1 h until all the solid had disappeared. A solution of the aldehyde (**5**) (0.118 g, 0.65 mmol) in dry THF (10 ml) was then added dropwise and stirring was continued for a further 1 h. Water was added and the solution was extracted with ether. After evaporation of the ether the crude product was subjected to chromatography on silica gel. Elution with hexane afforded the *diene* (**6**) (1.47 g), m.p. 54—56 °C (hexane); $\nu_{max.}$ 1 620 cm^{-1} (conjugated C=C); $\delta(CCl_4)$ 0.82 (3 H, s, Me), 0.85 (6 H, s, 2 × Me), 0.97 (3 H, s, Me), 1.60 (3 H, s, =CMe), 4.83 (1 H, dd, *J* 3, 18 Hz), and 5.16 (1 H, dd, *J* 3, 12 Hz, $=CH_2$), and 6.03 (1 H, ddm, *J* 12, 18 Hz, $CH{=}CH_2$) (Found: C, 88.35; H, 11.65. $C_{21}H_{34}$ requires C, 88.04; H, 11.96%).

Preparation of the Diels–Alder Adduct (**7a**).—The diene (**6**) (500 mg) was heated with freshly distilled dimethyl acetylenedicarboxylate (10 ml) under dry nitrogen at 105 °C for 24 h. The dimethyl acetylenedicarboxylate was removed by distillation under reduced pressure and the residue subjected to chromatography on silica gel. Elution with 25% ether–hexane yielded the *Diels–Alder adduct* (**7a**) (560 mg), m.p. 182—184 °C (ether–hexane); $\nu_{max.}$ 1 730 and 1 720 (CO_2Me), and 1 660 and 1 620 cm^{-1} (C=C); $\delta(CCl_4)$ 0.83, 0.87, 0.92, 1.07, 1.27 (each 3 H, s, Me), 2.70 (1 H, dd, *J* 3, 23 Hz, 16-H), 3.20 (1 H, dd, *J* 6, 23 Hz, 16-H), 3.70 (6 H, s, 2 × OMe), and 5.60 (1 H, dd, *J* 3, 6 Hz, 15-H) (Found: C, 75.35; H, 9.25. $C_{27}H_{40}O_4$ requires C, 75.66; H, 9.41%).

Oxidation of the Diels–Alder Adduct (**7a**).—A suspension of the chromium trioxide–pyridine complex (1.2 g) in methylene dichloride (3 ml) was added at room temperature to a stirred solution of compound (**7a**) (0.2 g) in methylene dichloride (10 ml). The reaction was monitored by t.l.c. After 5 h, stirring was discontinued and the reaction mixture, without work-up, was subjected to chromatography over silica gel. Elution with 40% ether–hexane afforded the *dienone* (**7b**) (1.86 g), m.p. 153—155 °C (ether–chloroform–hexane); $\nu_{max.}$ 1 730 (CO_2Me) and 1 665 cm^{-1} (conjugated CO); $\delta(CCl_4)$ 0.80, 0.83, 0.88, 1.13, 1.67 (each 3 H, s, Me), 3.72 (6 H, s, 2 × OMe), and 6.10 (1 H, s, 15-H) (Found: C, 73.45; H, 8.45. $C_{27}H_{38}O_5$ requires C, 73.27; H, 8.65%).

Hydrogenation of the Dienone (**7b**).—The dienone (**7b**) (200 mg) was dissolved in dioxane–methanol (1:4, 30 ml); 10% Pd–C (30 mg) was added to the solution and the mixture was stirred at 68 atm of hydrogen and 23 °C for 24 h. The mixture was then filtered through a Celite pad and the solvent evaporated to provide the *ketone* (**9a**) (0.15 g), m.p. 180—182 °C (chloroform–hexane); $\nu_{max.}$ 1 750 (CO_2Me), 1 680 (CO), and 1 645 cm^{-1} (CO of the conjugated chelate);[17] $\delta(CDCl_3)$ 0.79, 0.82 (each 6 H, s, 2 × Me), 0.88 (3 H, s, Me), 3.63, 3.69 (each 3 H, s, OMe), and 12.15 (1 H, s, chelated OH) (Found: C, 72.35; H, 9.25. $C_{27}H_{42}O_5$ requires C, 72.61; H, 9.48%).

Reduction of the Ketone (**9a**) *with Sodium Borohydride*.—Sodium borohydride (20 mg, 0.54 mmol) was added in small portions at 0 °C to a stirred solution of the ketone (**9b**) (160 mg, 0.36 mmol) in ethanol (6 ml) containing a small amount of chloroform (1.5 ml). After 3 h at 0 °C, stirring was discontinued and dilution with water and work-up gave a crude product which was subjected to chromatography on silica gel. Elution with 20% ether–hexane yielded the 16β-*alcohol* (**9b**) (40 mg), m.p. 178—180 °C (ether–hexane); $\nu_{max.}$ 3 460 (OH) and 1 740 cm^{-1} (CO_2Me); $\delta(CDCl_3)$ 0.82, 0.83, 0.92, 0.98, 1.03 (each 3 H, s, Me), 3.06 (1 H, d, *J* 12 Hz, 18α-H), 3.42 (1 H, dd, *J* 12, 9 Hz, 17β-H), 3.67, 3.70 (each 3 H, s, OMe), and 4.23 (1 H, m, $W_{\frac{1}{2}}$ 18 Hz, 16α-H) (Found: C, 72.5; H, 9.65. $C_{27}H_{44}O_5$ requires C, 72.28; H, 9.89%).

Further elution with 30% ether–hexane gave a mixture of products (20 mg), which was not identified. Increase in the amount of the reagent and the reaction time inevitably favoured the formation of these by-products.

Preparation of the Olefin Diester (**1e**).—Triethylamine (0.2 ml, 1.25 mmol) and methanesulphonyl chloride (0.03 ml, 0.36 mmol) were added to a stirred solution of the alcohol (**9b**) (80 mg, 0.18 mmol) in dry ether (4 ml) at 0 °C and the mixture was stirred at room temperature for 3 h. The product was extracted with ether and the ether extract was washed with 1.5% aqueous hydrochloric acid and then with water. Evaporation of the ether gave a crude product which was subjected to chromatography on silica gel. Elution with 50% ether–hexane yielded the methanesulphonate (**9c**) (70 mg), m.p. 128—130 °C (hexane); $\delta(CDCl_3)$ 0.78, 0.80, 0.83, 0.93, 1.08 (each 3 H, s, Me), 2.95 (3 H, s, SO_2Me), 3.20 (1 H, d, *J* 12 Hz, 18α-H), 3.52 (1 H, dd, *J* 12, 7 Hz, 17β-H), 3.69, 3.70 (each 3 H, s, OMe), and 5.30 (1 H, m, $W_{\frac{1}{2}}$ 12 Hz).

The methanesulphonate (**9c**) (70 mg, 0.14 mmol) was dissolved in dry benzene (5 ml), DBU (0.05 ml, 0.35 mmol) was

added, and the solution was refluxed gently under dry nitrogen. The reaction was monitored by t.l.c. After 30 min the solution was cooled and subjected to column chromatography on silica gel. Elution with benzene yielded the *olefin diester* (**1e**) (58 mg), m.p. 173—175 °C (hexane); $\nu_{max.}$ 1 740 and 1 680 cm^{-1} (CO_2Me); δ($CDCl_3$) 0.80, 0.83 (each 6 H, s, 2 × Me), 0.87 (3 H, s, Me), 2.35 (2 H, m, 15-H), 3.65 (1 H, m, 18α-H), 3.67, 3.71 (each 3 H, s, OMe), and 7.10 (1 H, m, 16-H) (Found: C, 75.0; H, 9.6. $C_{27}H_{42}O_4$ requires C, 75.31; H, 9.83%).

Isomerisation of the Diels–Alder Adduct (**7a**) *to the Conjugated Diester* (**8**).—The Diels–Alder adduct (**7a**) (200 mg) in dry THF (25 ml) was treated with DBU (3 drops), and the solution was gently refluxed under dry nitrogen for 5 h. The solution was filtered through a small column of silica gel and then evaporated under reduced pressure, yielding the *conjugated diester* (**8**) (170 mg), m.p. 148—150 °C (hexane); $\nu_{max.}$ 1 735 and 1 715 (CO_2Me); δ(CCl_4) 0.82, 0.83, 0.92 (each 3 H, s, Me), 1.13 (6 H, s, 2 × Me), 3.28 (1 H, d, *J* 2.5 Hz, 18α-H), 3.63, 3.66 (each 3 H, s, OMe), 5.71 (1 H, d, *J* 6 Hz, 15-H), and 6.88 (1 H, dd, *J* 2.5, 6 Hz, 16-H) (Found: C, 75.45; H, 9.25. $C_{27}H_{40}O_4$ requires C, 75.66; H, 9.41%).

Hydrogenation of the Conjugated Diester (**8**).—The conjugated diester (**8**) (170 mg) in methanol–dioxane (2:1; 9 ml) was hydrogenated in the presence of 10% Pd–C (30 mg) at 23 °C. The mixture was stirred overnight, and then filtered through Celite. Evaporation of the solvent yielded the olefin diester (**1e**) (145 mg), identical with that obtained earlier *via* a different route.

Reduction of the Olefin Diester (**1e**).—A solution of the olefin diester (**1e**) (125 mg, 0.29 mmol) in ether (5 ml) was added dropwise to a suspension of lithium aluminium hydride (50 mg, 1.3 mmol) in ether (10 ml) at 0 °C under dry nitrogen. Stirring was continued at room temperature for a further 3 h. The excess of reagent was decomposed by addition of water, and usual work-up gave the *olefin diol* (**1f**) (109 mg), m.p. 168—170 °C (ether); δ($CDCl_3$) 0.75 (3 H, s, Me), 0.81 (9 H, s, 3 × Me), 0.88 (3 H, s, Me), 3.3—4.5 (4 H, m, 2 × CH_2OH), and 5.76 (1 H, m, 16-H) (Found: C, 80.4; H, 11.1. $C_{25}H_{42}O_2$ requires C, 80.15; H, 11.30%).

Oxidation of the Olefin Diol (**1f**).—A solution of the olefin diol (**1f**) (100 mg, 0.27 mmol) in hexamethylphosphoramide (1.5 ml) was added to the Swern reagent [prepared by the addition of oxalyl chloride (0.1 ml, 1.1 mmol) in methylene dichloride (1.5 ml) to dimethyl sulphoxide (0.2 ml, 2.59 mmol) in methylene dichloride (0.5 ml) at −12 °C under dry nitrogen] dropwise under dry nitrogen at −12 °C. After 15 min triethylamine (0.56 ml, 0.8 mmol) was added at −12 °C, and stirring was continued for a further 5 min. The reaction mixture was worked up as usual. Chromatography of the product mixture on silica gel and elution with hexane–ether (1:1) gave the *dialdehyde* (**1d**) (30 mg), m.p. 216—218 °C (hexane–ether); $\nu_{max.}$ 1 710 and 1 670 cm^{-1} (CHO); δ($CDCl_3$) 0.80 (6 H, s, 2 × Me), 0.82, 0.83, 0.87 (each 3 H, s, Me), 2.50 (2 H, m, 15-H), 3.23 (1 H, m, 18α-H), 7.10 (1 H, m, 16-H), 9.42 (1 H, d, *J* 4 Hz, 19-CHO), and 9.50 (1 H, s, 20-CHO) (Found: C, 80.85; H, 10.1. $C_{25}H_{38}O_2$ requires C, 81.03; H, 10.34%).

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