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Chemistry of the Podocarpaceae. LXIII† Ring-C Oxidation of Totarol

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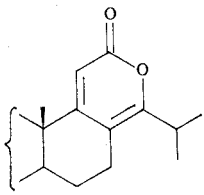
Abstract

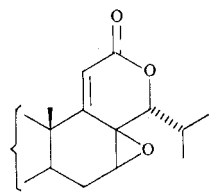
Methods for the conversion of totarol (1) into the catechol derivative (2) are described. Oxidative cleavage of the derived methyl ether (13) by ozonolysis affords a high-yielding route to a compound (34) with potential as a nagilactone precursor.

Introduction

The nor- and bisnor-diterpenoid lactones (nagilactones), obtained from various species of *Podocarpus*,[1,2] have been found to exhibit a wide range of biological properties including antitumour activity and activity as plant growth regulators.[3] They possess a totarane-like skeleton with a modified lactonic C-ring and a 6β,19-γ-lactone function bridging the A- and B-rings, and are classified into three major structural types (A–C) depending on the nature of the conjugated lactone system



type A



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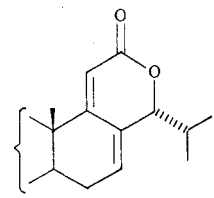


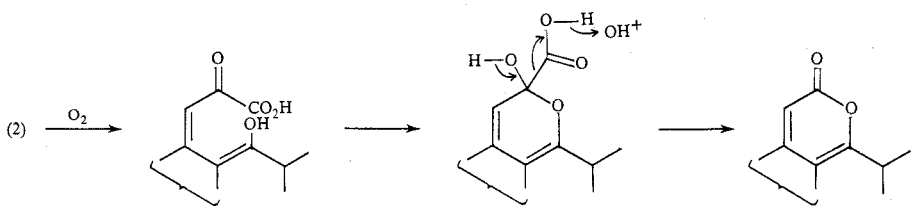
type C

in the B/C ring portion. Since totarol (1) and 12-hydroxytotarol (2) are reported to co-occur with nagilactones in *Podocarpus nagi*[4] it has been suggested[1,5] that the catechol (2) might be a biogenetic precursor of the nagilactones (Scheme 1). The proposal is supported by the fact that oxidative cleavage of aromatic nuclei by the action of an oxygenase enzyme and molecular oxygen is an important step in the

† Part LXII, *Aust. J. Chem.*, 1982, **35**, 863.

[1] Ito, S., and Kodama, M., *Heterocycles*, 1976, **4**, 595.
[2] Dorner, J. W., Cole, R. J., Springer, J. P., Cox, R. H., Cutler, H., and Wicklow, D. T., *Phytochemistry*, 1980, **19**, 1157.
[3] Hayashi, Y., Matsumoto, T., Uemura, M., and Koreeda, M., *Org. Magn. Reson.*, 1980, **14**, 86.
[4] Matsumoto, T., and Suetsuga, A., *Bull. Chem. Soc. Jpn*, 1979, **52**, 1450.
[5] Hayashi, Y., Takahashi, S., Ona, H., and Sakan, T., *Tetrahedron Lett.*, 1968, 2071.

biogenesis of many natural products.[6] For example, it is known that catechols undergo *in vivo* oxidative cleavage to α-pyrone derivatives by a *meta*-pyrocatechase type fission.[7] It has been suggested[8] that these oxidations may involve the enzymatic generation of a species which is equivalent to singlet oxygen in its oxidative powers, and studies with singlet oxygen[9] have simulated enzymatic aromatic ring cleavage. Other workers have studied the oxidation of copper-coordinated catechols as models for the catecholase enzyme system.[10]



Scheme 1

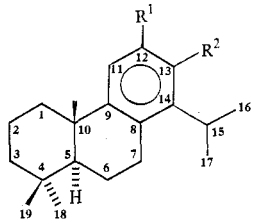
In an attempt to produce nagilactones from totarol (1) by a route modelled on the suggested biogenetic pathway, we have investigated methods for conversion of totarol into 12-hydroxytotarol (2) with a view to examining its subsequent cleavage by oxidative methods. The catechol (2) has been isolated previously as the dibenzoate (3) from the pyrolysis of maytenone,[11] and has also been prepared from totarol (1) through the 12-nitro and 12-amino derivatives (4) and (5).[12] However, in each case the compound (2) was obtained in low yield.

Discussion

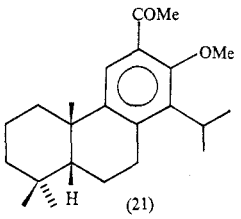
The first route investigated was by acylation of 13-methoxytotara-8,11,13-triene (6) at C 12 followed by Baeyer–Villiger oxidation and hydrolysis (Scheme 2). Friedel–Crafts acetylation of the methyl ether (6) with aluminium trichloride in 1,2-dichloroethane at 0° or 20°[13] gave only a moderate yield of the acetyl compound (7) but addition of titanium tetrachloride in 1,2-dichloroethane under carefully controlled conditions resulted in suppression of the formation of side products (cf. ref.[14])† and

† A singlet at δ 0·32 in the ^{1}H n.m.r. spectrum of the crude acetylated product obtained with aluminium trichloride indicated the presence of the A/B *cis*-fused isomer (21).

[6] Ribbons, D. W., *Annu. Rep. Prog. Chem.*, 1965, **62**, 445 (*Chem. Abstr.*, 1967, **66**, 44332).
[7] Senoh, S., and Sakan, T., in 'Biological and Chemical Aspects of Oxygenases' (Eds K. Block and O. Hayaishi) p. 93 (Maruzen: Japan 1966); Jefford, C. W., and Cadby, P. A., *Fortschr. Chem. Org. Naturst.*, 1981, **40**, 191.
[8] Baldwin, J. E., Basson, H. H., and Krauss, H., *J. Chem. Soc., Chem. Commun.*, 1968, 984.
[9] Matsuura, T., *Tetrahedron*, 1977, **33**, 2869.
[10] Brown, D. G., Beckmann, L., and Ashby, C. H., *Tetrahedron Lett.*, 1977, 1363; Rogić, M. M., and Demmin, T. R., *J. Am. Chem. Soc.*, 1978, **100**, 5472; Tsuji, J., and Takayanagi, H., *Tetrahedron Lett.*, 1976, 1365; Demmin, T. R., and Rogić, M. M., *J. Org. Chem.*, 1980, **45**, 1153, 2737, 4210; Funabiki, T., Sakamoto, H., Yoshida, S., and Tarama, K., *J. Chem. Soc., Chem. Commun.*, 1979, 754; Tsuji, J., and Takayanagi, H., *J. Am. Chem. Soc.*, 1974, **96**, 7349.
[11] Johnson, A. W., King, T. J., and Martin, R. J., *J. Chem. Soc.*, 1961, 4420.
[12] Elmore, N. F., and King, T. J., *J. Chem. Soc.*, 1961, 4425.
[13] Chuah, Y. S., and Ward, A. D., *Aust. J. Chem.*, 1969, **22**, 1333.
[14] Bennett, C. R., and Cambie, R. C., *Tetrahedron*, 1966, **22**, 2845.



	R^1	R^2
(1)	H	OH
(2)	OH	OH
(3)	OCOPh	OCOPh
(4)	NO_2	OH
(5)	NH_2	OH
(6)	H	OMe
(7)	COMe	OMe
(8)	OAc	OMe
(9)	OH	OMe
(10)	OMe	OH
(11)	NO_2	OMe
(12)	NH_2	OMe
(13)	OMe	OMe
(14)	COMe	H
(15)	COMe	OH
(16)	H	OAc
(17)	Br	OH
(18)	Br	OMe
(19)	MgBr	OMe
(20)	OBu^t	OMe



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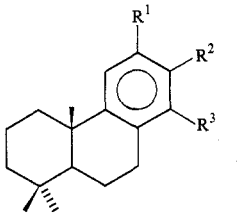
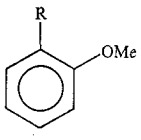
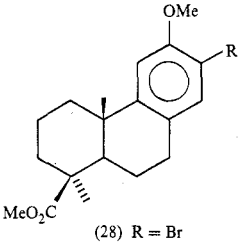


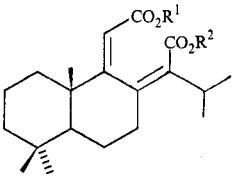
	R^1	R^2	R^3
(22)	NO_2	OMe	NO_2
(23)	NH_2	OMe	NH_2
(24)	H	OMe	H
(25)	COMe	H	NO_2



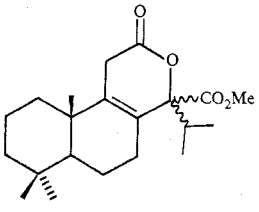
(26) R = Br
(27) R = OH



(28) R = Br
(29) R = H
(30) R = OH



	R^1	R^2
(31)	Me	Me
(32)	H	Me
(33)	Me	H



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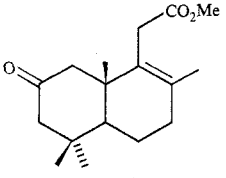

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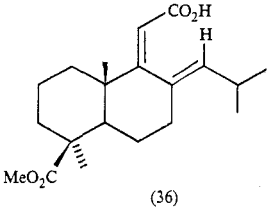

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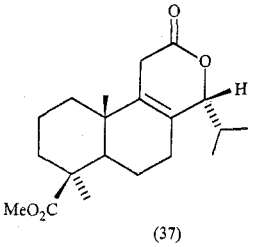

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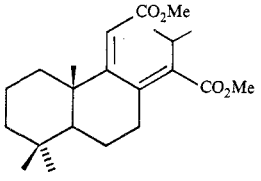

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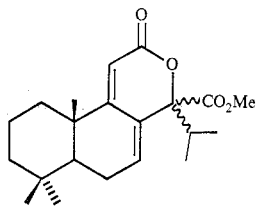

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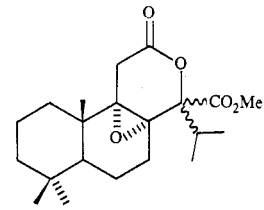
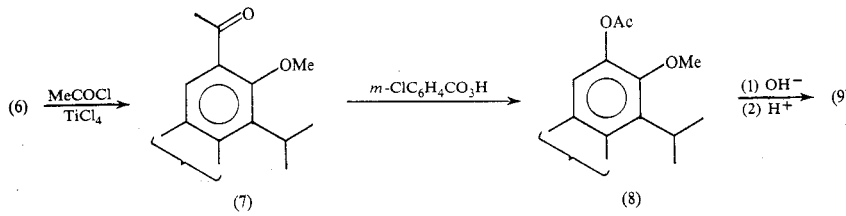


(40)

afforded the acetyl derivative (7) in 72% yield. Baeyer–Villiger oxidation of the latter compound with *m*-chloroperbenzoic acid gave the C 12 acetate (8) which on hydrolysis with methanolic potassium hydroxide afforded 13-methoxytotara-8,11,13-trien-12-ol (9) in 84% overall yield from the acetyl derivative (7). The phenol (9) has been isolated from *Maytenus dispermus* and given the name of dispermol.[15] The original erroneous structural assignment (10) of dispermol has recently been corrected[16] to (9) as the result of total syntheses of both compounds.



(7) (8)

Scheme 2

The phenol (9) was demethylated with pyridinium hydrochloride at 210° to give the catechol (2) which was converted without purification into the crystalline and more stable dibenzoate (3). Although the dibenzoate possessed a melting point somewhat higher than that reported by Elmore and King,[12] the structure followed readily from examination of the ^{1}H n.m.r. and mass spectra. Thus, the aromatic region of the ^{1}H n.m.r. spectrum contained signals which integrated for eleven protons, corresponding to two benzoyl groups and the C 11 proton, while the mass spectrum showed a molecular ion at *m/z* 510 and an intense base peak at *m/z* 105 ($Ph^+C{=}O$).

As indicated above, the catechol (2) can also be prepared through the C 12 nitro and amino derivatives (4) and (5).[12] Repetition of the published work gave only an 11% overall yield of totara-8,11,13-triene-12,13-diol (2) from totarol. In an attempt to improve the yield, the sequence was repeated by using the methyl ether (6) as starting material. Nitration of (6) with cupric acetate in acetic anhydride gave the nitro derivative (11) in 72% yield. Reduction of the latter compound with stannous chloride in hydrochloric acid was superior to catalytic hydrogenation, giving the amine (12) in 80% yield. Diazotization of the amine (12) in the presence of methanol gave a mixture of 12,13-dimethoxytotara-8,11,13-triene (13) (30%), 13-methoxytotara-8,11,13-trien-12-ol (9) (30%) and 13-methoxytotara-8,11,13-triene (6) (39%), the latter product arising by hydrogenolysis of the diazonium group.

[15] Martin, J. D., *Tetrahedron*, 1973, **29**, 2553.
[16] Matsumoto, T., Ohmura, T., and Usui, S., *Bull. Chem. Soc. Jpn*, 1979, **52**, 1957.

If the nitration of 13-methoxytotara-8,11,13-triene (6) was carried out under more vigorous conditions with concentrated nitric and sulfuric acids at low temperature the 12,14-dinitro derivative (22) was obtained in 77% yield. The deisopropylation occurring in this reaction suggests that the methoxy group *ortho* to the isopropyl group is sufficiently activating to enable nitrodealkylation to become the dominant reaction (cf. ref.[17]). Although reduction of the dinitro compound (22) with stannous chloride in concentrated hydrochloric acid gave the diamine (23) in 86% yield, all attempts to deaminate the latter compound to 13-methoxypodocarpa-8,11,13-triene (24) through a diazonium derivative were unsuccessful. The deactivating effect of a second diazonium group apparently makes deamination of the other group an unfavourable process. Nitrodeisopropylation of 12-acetyltotara-8,11,13-triene (14)[14] was also effected under the above nitration conditions to give a moderate yield of 12-acetyl-14-nitropodocarpa-8,11,13-triene (25), a compound of potential value for synthetic transformations.

Other methods for the formation of compound (2) were also examined. Attempted formation of the phenol (15) by a Fries rearrangement of the acetate (16) gave a complex mixture of products from which no pure compound was obtained.

In an alternative approach, a route to the compound (2) through 12-bromototarol (17)[18] was investigated. Of a number of bromination methods examined, treatment of 13-methoxytotara-8,11,13-triene with bromine and thallium(I) acetate in refluxing carbon tetrachloride[19] gave the bromide (18) as the sole product in the highest yield. Subsequent work showed that refluxing was unnecessary and that high yields (90–95%) of the bromide could be obtained when the reaction was carried out at room temperature provided that the rate of addition of the bromine solution was sufficiently slow that the concentration of free bromine in the reaction mixture remained low. The bromide (18) was also formed in high yield (75%) with *N*-bromosuccinimide in dimethylformamide, a reagent which hitherto has only been used for the bromination of activated systems such as phenols and anilines.[20]

Attempts to convert the bromide (18) into dispermol (9) by treatment of the Grignard derivative (19) with t-butyl perbenzoate[21,22] followed by cleavage of the resulting t-butyl aryl ether[22,23] could not be pursued since all attempts to form the Grignard derivative were unsuccessful. On the other hand, treatment of the bromide with 1 mol. equiv. of n-butyllithium in tetrahydrofuran resulted in a clean conversion into the aryllithium compound (cf. ref.[24]) as shown by the isolation of a high yield of 13-methoxytotara-8,11,13-triene (6) upon quenching the reaction with water. Attempts to form the t-butyl ether (20) by reaction of the aryllithium compound with t-butyl perbenzoate were unsuccessful, the methyl ether (6) being isolated as the major

[17] Cambie, R. C., and Franich, R. A., *Aust. J. Chem.*, 1971, **24**, 117.
[18] Short, W. F., and Wang, H., *J. Chem. Soc.*, 1951, 2979.
[19] McKillop, A., Bromley, D., and Taylor, E. C., *J. Org. Chem.*, 1972, **37**, 88; Uemura, S., Sohma, K., Okano, M., and Ichikawa, K., *Bull. Chem. Soc. Jpn*, 1971, **44**, 2490.
[20] Mitchell, R. H., Lai, Y.-H., and Williams, R. V., *J. Org. Chem.*, 1979, **44**, 4733.
[21] Lawesson, S.-O., and Yang, N. C., *J. Am. Chem. Soc.*, 1959, **81**, 4230.
[22] Frisell, C., and Lawesson, S.-O., *Org. Synth.*, 1961, **41**, 91; Lawesson, S.-O., and Frisell, C., *Ark. Kemi*, 1961, **17**, 393.
[23] Jakobsen, H. J., Larsen, E. H., and Lawesson, S.-O., *Recl Trav. Chim. Pays-Bas*, 1963, **82**, 791.
[24] Jones, R. G., and Gilman, H., *Org. React.*, 1951, **6**, 339; Langham, W., Brewster, R. Q., and Gilman, H., *J. Am. Chem. Soc.*, 1941, **63**, 545; Glaze, W. H., and Ranade, A. G., *J. Org. Chem.*, 1971, **36**, 3331.

product along with small amounts of the phenol (9) despite attempts to maintain an oxygen-free environment during these reactions. Monitoring of the reactions by t.l.c. indicated that the phenol (9) was present prior to workup and had not been produced by cleavage of an initially formed t-butyl ether but had been formed by reaction of the aryllithium compound with traces of molecular oxygen still in the system. Indeed, treatment of a solution of the aryllithium derivative with a stream of dry oxygen[25,26] gave the phenol (9) in 47% yield together with 13-methoxytotara-8,11,13-triene (6) (48%). Attempts to improve the yield of the phenol (9) by modifications of the procedure were unsuccessful and the same 1 : 1 ratio of (9) : (6) was produced in all cases even when an excess of n-butyllithium was used. That the methyl ether (6) was not formed by protonation of unchanged aryllithium compound during workup was confirmed when addition of deuterium oxide during this process did not result in any incorporation of deuterium into the products. The ether (6) must therefore be present prior to workup and could result from a competing aryl radical reaction.[26,27]

As a model for the diterpene system, *o*-bromoanisole (26) was allowed to react with n-butyllithium followed by a stream of oxygen to give guaiacol (27) in reproducible yields of 53%. No other compound could be detected in the acidic portion of the product although the neutral portion contained many products (cf. phenylmagnesium bromide with oxygen[28]). Treatment of methyl 13-bromo-12-methoxypodocarpa-8,11,13-trien-19-oate (28)[29] with n-butyllithium/oxygen afforded the corresponding products (29) and (30) in isolated yields of 28% and 64%, resepectively. The phenol (30) has been patented for its diuretic properties[30] and the present route to it through the bromide (28) is an improvement over the existing procedure.

Attempts were also made to increase the yield of the phenol (9) by using different sources of oxygen. In model studies, treatment of *o*-bromoanisole (26) in tetrahydrofuran with n-butyllithium and addition of the resulting solution to one of lithium t-butyl hydroperoxide (cf. ref.[21]) increased the yield of guaiacol (27) to 78%. However, when the same reagent system was used with the diterpenoid bromide (18) the phenol (9) was formed in only 36% yield with 13-methoxytotara-8,11,13-triene (6) comprising the remainder of the product. Treatment of *o*-bromoanisole with 1 mol. equiv. of n-butyllithium, followed by the molybdenum complex $[Mo(O_2)_2O]$ py,hmpt[31] as an alternative source of oxygen,[32] gave guaiacol in 76% yield. However, while treatment of methyl 13-bromo-12-methoxypodocarpa-8,11,13-trien-19-oate (28) with

[25] Kharasch, M. S., and Reinmuth, O., 'Grignard Reactions of Nonmetallic Compounds' (Constable: London 1954); Iwanow, D., *Bull. Soc. Chim. Fr.*, 1926, 47; Walling, C., and Buckler, S. A., *J. Am. Chem. Soc.*, 1955, **77**, 6032; Barluenga, J., Fananás, F. J., and Yus, M., *J. Org. Chem.*, 1979, **44**, 4798; Meyer, N., and Seebach, D., *Chem. Ber.*, 1980, **113**, 1304.

[26] Hock, H., Kropf, H., and Ernest, F., *Angew. Chem.*, 1959, **71**, 541.

[27] Bryce-Smith, D., *J. Chem. Soc.*, 1956, 1603; Barton, D. H. R., and Jones, D. W., *J. Chem. Soc.*, 1965, 3563; Fraenkel, G., and Geckle, M. J., *J. Chem. Soc., Chem. Commun.*, 1980, 55.

[28] Porter, C. W., and Steel, C., *J. Am. Chem. Soc.*, 1920, **42**, 2650.

[29] Bocks, S. M., Cambie, R. C., and Takahashi, T., *Tetrahedron*, 1963, **19**, 1109.

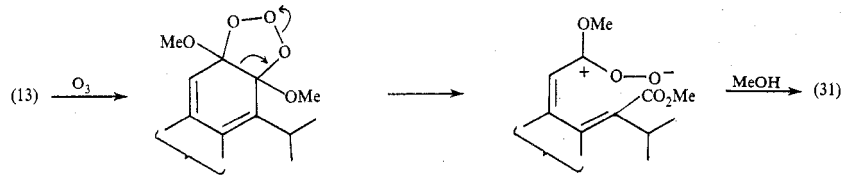
[30] G. D. Searle and Co., U.S. Pat. 3,038,930 (1962) (*Chem. Abstr.*, 1962, **57**, 16518).

[31] Mimoun, H., Seree de Roch, I., and Sajus, L., *Bull. Soc. Chim. Fr.*, 1969, 1481; *Tetrahedron*, 1970, **26**, 37.

[32] Vedejs, E., *J. Am. Chem. Soc.*, 1974, **96**, 5944; Vedejs, E., and Telschow, J. E., *J. Org. Chem.*, 1976, **41**, 740; Lewis, N. J., and Gabhe, S. Y., *Aust. J. Chem.*, 1978, **31**, 2091; Lewis, N. J., Gabhe, S. Y., and De la Mater, M. R., *J. Org. Chem.*, 1977, **42**, 1479.

the same reagent gave the phenol (30) (63%) and methyl 12-methoxypodocarpa-8,11,13-trien-19-oate (29) in 30% yield, the bromide (18) afforded a 47 : 53 mixture of the phenol (9) and the methyl ether (6) which were isolated in 40% and 49% yields respectively by p.l.c. Methylation of the phenol (9) with methyl iodide and potassium t-butoxide afforded the dimethyl ether (13) in 98% yield while demethylation again gave the dihydric phenol (2). The conversion of 13-methoxytotara-8,11,13-triene (6) into the dihydric phenol (2) by the bromination sequence corresponds to a 44% overall yield [or 90% based on recovered (6)] thereby providing a convenient alternative to the previous procedures.

Although the C-ring of the totarol nucleus has been reduced,[14] no successful oxidative degradation of the aromatic ring has been reported. Attempts to oxidize totarol (1) itself with peracids (cf. ref.[33]) gave no appreciable yield of oxidized products; the only compound isolated was totaryl acetate which, in a separate experiment, was shown to be inert to peracetic acid. Ozonolysis of totarol resulted in extensive degradation. However, although ozonolysis of the dimethyl ether (13) in aqueous acetic acid[34] or in ethyl acetate at 0°[35] resulted in the formation of a complex mixture of products, ozonolysis in the latter solvent at −78° resulted in a much cleaner reaction. The major product was isolated in 33% yield by p.l.c. and was identified as the muconic acid derivative (31) from the following evidence. The mass spectrum indicated a molecular weight of 362 corresponding to the addition of two oxygen atoms to the starting material and this was confirmed by a correct elemental analysis for $C_{22}H_{34}O_4$. In the ^1H n.m.r. spectrum the methyl ester groups appeared as two three-proton singlets at δ 3·56 and 3·63, while the C 11 vinylic proton resonated as a singlet at δ 5·48. A three-proton multiplet at δ 2·90 resulted from the C 7 protons and the C 15 proton of the isopropyl group, while the isopropyl methyl signals appeared as two doublets at δ 1·05 (J 6·5 Hz) and 1·12 (J 6·5 Hz). In contrast to the situation in totara-8,11,13-triene derivatives, these isopropyl methyl groups were now chemically non-equivalent as is the case with the nagilactones.[1] The i.r. spectrum showed strong ester absorption at 1705–1725 cm^{-1} together with double bond absorption at 1620 cm^{-1} and the u.v. spectrum of the product (31) was also in accord[34] with the proposed structure.



Scheme 3

When the ozonolysis was carried out in dichloromethane at −78° the diester (31) was again formed in similar yield while in the presence of a 1 : 1 mixture of dichloromethane and methanol, the isolated yields of (31) were 90–95%. Attack of ozone on the dimethyl ether (13) must occur at the C 12–C 13 bond in order to give rise to the observed product (Scheme 3), the course of this reaction closely resembling

[33] Birkinshaw, G. F., and Davis, B. R., *Tetrahedron*, 1967, **23**, 4147.
[34] Woodward, R. B., Cava, M. P., Ollis, W. D., Hunger, A., Daeniker, H. U., and Schenker, K., *Tetrahedron*, 1963, **19**, 247.
[35] Bernatek, E., and Vincze, A., *Acta Chem. Scand.*, 1965, **19**, 2007.

that proposed for the oxidative cleavage of *ortho*-substituted phenols with singlet oxygen.[8,9] Although initial reactions were carried out by using only a slight excess of ozone, later work indicated that both double bonds of the product (31) were unreactive towards ozone at −78° and subsequent reactions were carried out by using an excess of the reagent. The lack of reactivity of the double bonds of the diester (31) is probably the result of both electronic and steric factors, thus accounting for the particularly high yield of the product (31) obtained in the ozonolysis.

Saponification of the diester (31) in refluxing methanolic sodium hydroxide resulted in a slow but selective cleavage of the less sterically crowded ester group (cf. ref.[36]) to give a monocarboxylic acid (32). Even prolonged refluxing failed to effect any hydrolysis of the second ester group; a general decrease in the reactivity of both ester groups of the diester (31) as a result of conjugation probably enhances the selectivity of the hydrolysis. The structural assignment of the product (32) was confirmed when the phenol (9) was ozonized at −78° in methanol/dichloromethane. Although the reaction produced many products one of the major components of the mixture was identified by comparative t.l.c. and ^{1}H n.m.r. analysis as the same as that obtained from saponification of the diester (31). Furthermore, ozonolysis of the isomeric catechol monomethyl ether (10), which would be expected to result in formation of some of the other possible acid (33), produced a complex mixture in which none of the hydrolysis product could be detected. The monomethyl ether (10) for this experiment was prepared in 62% yield by selective demethylation of the dimethyl ether (13) with 1 equiv. of trimethylsilyl iodide.[37] The phenol (10) appeared to be less polar than the dimethoxy compound (13) since it was eluted before the latter during chromatography. This is probably because of steric buttressing of the hydroxy group by the *ortho*-methoxy and isopropyl substituents, since there was no evidence for either inter- or intra-molecular hydrogen bonding in the i.r. spectrum of this compound (ν_{max} 3540).[38] In contrast, the isomer (9) is more polar, and its i.r. spectrum did show evidence for hydrogen bonding (ν_{max} 3540, 3500–3200 cm^{-1}).

Heating the acid (32) at 250° for 1·5 h under a slight vacuum gave an 80% yield of an inseparable mixture of the C 14 epimers of the 8,9-enolide (34). The mass spectrum and elemental analysis of the product indicated that it was isomeric with the starting acid (32) but the ^{1}H n.m.r. spectrum showed no carboxyl proton resonance and the C 11 vinylic singlet of (32) at δ 5·48 had also disappeared. Two closely spaced singlets at δ 3·74 and 3·76 indicated that the methyl ester group (ν_{max} 1730 cm^{-1}) was still present and that the product was probably a mixture of two isomeric compounds. The multiplet resulting from the proton of the isopropyl group was still evident but had moved upfield to δ 2·54; this suggests that this proton was no longer in an allylic position. Irradiation of the signal collapsed the two sets of doublets of the isopropyl methyls into singlets, thereby confirming that the isopropyl group was still present. Of particular diagnostic importance was a two-proton multiplet centred at δ 3·05 which is characteristic of the H 11 protons of a 12-oxolabd-8-ene system [cf. δ 3·00 for (35)[39]]. The structural assignment was supported by the ^{13}C n.m.r. spectrum which showed that the product was a 3 : 2 mixture of C 14 epimers.

[36] Ingold, C. K., 'Structure and Mechanism in Organic Chemistry' p. 1134 (Bell: London 1969).
[37] Vickery, E. H., Pahler, L. F., and Eisenbraun, E. J., *J. Org. Chem.*, 1979, **44**, 4444.
[38] Goddu, R. F., *J. Am. Chem. Soc.*, 1960, **82**, 4533.
[39] Palmer, B. D., M.Sc. Thesis, University of Auckland, N.Z., 1979.

It was possible to partition the signals in the noise-decoupled spectrum (Table 1) between the two epimers on the basis of their intensities, and the assignments were confirmed by comparison with the spectrum of one of the pure epimers (34a) subsequently prepared by prolonged photolysis of the acid (32) (cf. ref.[40]). The ^{13}C n.m.r. spectrum also showed the presence of a tetrasubstituted double bond and of two carbonyl groups, the chemical shifts of the olefinic carbon atoms being similar to those of podocarp-8-enes[41] and pimar-8-enes.[42,43]† A singlet at *c.* δ 90 for each epimer was assigned to the quaternary carbon at C 14 which is flanked both by oxygen and a double bond, while C 11 resonated as a triplet with a particularly large residual coupling in the SFORD spectrum. The difference in chemical shifts between the two methyl carbons of the isopropyl group is of a similar magnitude to that observed in nagilactones.[3]

Table 1. ^{13}C n.m.r. of the epimers of (34)

Carbon	(34a)[A]	(34b)	Carbon	(34a)	(34b)
1	36·26	35·64	12	170·41	170·38
2	18·41	18·41	14	90·22	89·76
3	41·17	41·13	15[B]	30·84	31·78
4	33·18	33·21	16	15·97	15·58
5	50·84	50·68	17	19·35	19·54
6	18·76	18·60	18	33·11	32·89
7	26·00	25·81	19	21·56	21·56
8	124·08	124·08	20	16·72	16·72
9	139·56	140·28	CO_2Me	169·79	169·99
10	37·89	37·66	CO_2Me	52·66	52·65
11[B]	28·28	29·61			

[A] Major component of the mixture. [B] Assignment of these signals was confirmed by h.p.s.f. irradiation of the appropriate signal in the ^1H n.m.r. spectrum.

During a synthesis of nagilactone F from podocarpic acid, Hayashi *et al.*[40] carried out a photolysis of the diene-carboxylic acid (36) to obtain a single epimer (37) corresponding to the minor component of a 3 : 5 mixture of C 14 epimers obtained by pyrolysis of the acid (36). This is in contrast to the present case where the compound (34a) was the major component of the mixture from the pyrolytic reaction. Hayashi *et al.*[40] established a 14α-stereochemistry for the isopropyl group of the compound (37) by degradation to a compound of known stereochemistry at C 14. These workers rationalized the stereospecificity of the photolysis reaction by assuming that photochemical excitation of the 8,14-double bond permits free rotation about

† Assignments are reversed in refs 41 and 43. Those of ref. 43 have been used in the present work.

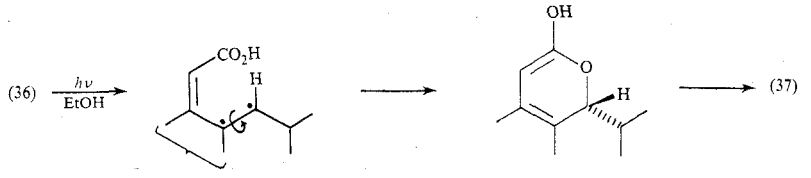
[40] Hayashi, Y., Matsumoto, T., Hyono, T., Nishikawa, N., Uemura, M., Nishizawa, M., Togami, M., and Sakan, T., *Tetrahedron Lett.*, 1979, 3311.

[41] Wahlberg, I., Almquist, S.-O., Nishida, T., and Enzell, C. R., *Acta Chem. Scand., Ser. B*, 1975, **29**, 1047.

[42] Delmond, B., Papillaud, B., Valade, J., Petraud, M., and Barbe, B., *Org. Magn. Reson.*, 1979, **12**, 209.

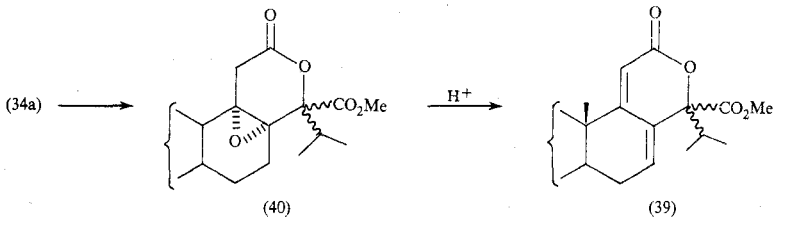
[43] Wenkert, E., and Buckwalter, B. L., *J. Am. Chem. Soc.*, 1972, **94**, 4367; Polonsky, J., Baskevitch, Z., Cagnoli-Bellavita, N., Ceccherelli, P., Buckwalter, B. L., and Wenkert, E., *J. Am. Chem. Soc.*, 1972, **94**, 4369.

this bond thereby allowing the isopropyl group to adopt a less hindered α-position prior to lactonization (Scheme 4). However, the present observation that the analogue of (36) with two bulky groups at C 14 (namely isopropyl and methoxycarbonyl) also gives only one epimer upon u.v. irradiation indicates that a more concerted, possibly electrocyclic process could be operating. Differences in the chemical shifts in the ^{13}C n.m.r. spectra of the epimers (34a) and (34b) were not sufficient to be diagnostic of the stereochemistry at C 14 (cf. ref.[3]) and thus assignment of stereochemistry at C 14 for the photolysis product (34a) remains uncertain.



Scheme 4

The mechanism by which thermal lactonization of the acid (32) occurs is also not clear. No isomerization of the pure epimer (34a) occurred when it was heated to 250° and no change in the ratio of epimers (34a) and (34b) occurred when the initial mixture from pyrolysis was reheated at 250° for several hours. These results indicate that the epimers are not thermally interconvertible and that they arise either by a non-stereoselective lactonization or from a prior thermal isomerization of the starting material followed by a cyclization of the resulting isomers. The latter possibility is supported since, when the diester (31) was heated at 220° for 30 min, ^1H n.m.r. analysis showed that it was converted into an inseparable mixture (1 : 1) of the diester (31) and what appeared to be an isomer, e.g. (38), resulting from *Z*/*E* isomerization of a double bond.



Scheme 5

In an attempt to convert the enolide (34a) into a 7,9(11)-dienolide (39) (Scheme 5) it was converted into the 8α,9α-epoxide (40). Although the enolide (34a) was recovered from treatment with *m*-chloroperbenzoic acid, it was converted into the epoxide (40) in 63% yield with trifluoroperacetic acid. The ^1H n.m.r. spectrum of the product was similar to that of the starting material but in the ^{13}C n.m.r. spectrum (Table 2) the singlets at δ 124·1 and 139·6 of (34a) were replaced by two higher field singlets at δ 64·8 and 86·6 corresponding to the C 8 and C 9 atoms respectively. The magnitude of the α-, β-, and γ-effects resulting from conversion of the enolide (34a) into the α-epoxide are comparable to those observed for epoxidation of pimar-8-enes.[42] In particular, an upfield shift of 8·3 ppm for the C 5 signal is similar to that for 8α,9α-epoxides (−9·1 ppm) but not for the corresponding β-epoxides (+1·4 ppm),

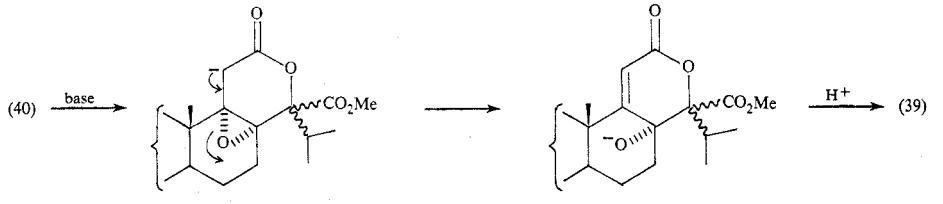
thereby confirming that epoxidation had occurred from the less hindered α-face. The assignments of C 11 and C 15 were confirmed by h.p.s.f. irradiation of the appropriate signals in the ^{1}H n.m.r. spectrum and the methyl signals in the latter spectrum were correlated with the corresponding signals in the ^{13}C n.m.r. spectrum (Table 2) by using selective irradiation in the ^{1}H n.m.r. spectrum. The positions of the doublets in the ^{1}H n.m.r. spectrum resulting from the two isopropyl methyl groups were established by irradiation of the C 15 isopropyl proton multiplet at δ 2·58, which caused clean decoupling to give two singlets.

Table 2. ^{13}C n.m.r. spectrum of epoxide (40)

Values in parentheses refer to correlations in the ^{1}H n.m.r. spectrum determined by selective decouplings

Carbon	δ	Carbon	δ
1	33·96	12	170·93
2	18·18	14	60·87
3	40·91	15	31·46 (2·58)
4	32·72	16	16·33 (1·06)
5	42·53	17	17·08 (0·94)
6	22·69	18	33·50 (0·87)
7	16·72	19	21·36 (0·82)
8	64·83	20	17·53 (0·97)
9	86·65	CO_2Me	168·85
10	35·84	CO_2Me	53·05
11	31·00 (2·94)		

Attempts to hydrolyse the epoxide with aqueous perchloric acid in refluxing tetrahydrofuran or with 50% aqueous sulfuric acid were unsuccessful while reaction with 80% aqueous sulfuric acid or lithium iodide in refluxing collidine[44] led to the formation of many products, none of which showed signals in the ^{1}H n.m.r. of the mixture expected for the dienolide (39). In an attempt to remove a proton from C 11 and effect a rearrangement as shown in Scheme 6, a solution of the β,γ-epoxylactone (40) in tetrahydrofuran was treated with 1 mol. equiv. of the non-nucleophilic base[45] lithium *N*-cyclohexylisopropylamide. The ^{1}H n.m.r. spectrum of the product showed signals at *c.* δ 5·5 indicative of 11-ene-unsaturation but attempts to separate a complex mixture of components resulted only in the isolation of starting material (40) (34%) and a small amount (8 mg, *c.* 14%) of an unidentified more polar product.



Scheme 6

[44] Herz, W., and Wahlborg, H. J., *J. Org. Chem.*, 1965, **30**, 1881.
[45] Rathke, M. W., and Lindert, A., *J. Am. Chem. Soc.*, 1971, **93**, 2318.

Despite the failure to isolate the compound (39) in the present work the conversion of totarol into the lactone (34) offers a potential route for its conversion into a compound with the ring system present in naturally occurring nagilactones.

Experimental

For general experimental details, see an earlier Part of this series.[46] Halogen–metal exchange reactions were carried out under an atmosphere of dried oxygen-free argon in a two-necked flask which was flame-dried and cooled under a stream of argon prior to use.

Acetylation of 13-Methoxytotara-8,11,13-triene (6)

(i) *With acetyl chloride/aluminium trichloride.*—A solution of aluminium trichloride (1·78 g, 13·3 mmol) and acetyl chloride (1·26 g, 16·0 mmol) in 1,2-dichloroethane (20 ml) was added dropwise to a stirred solution of the methyl ether (6)[47] (2·0 g, 6·6 mmol) in dry dichloroethane (20 ml) at 20°. The mixture was stirred for 24 h and poured into ice and dilute hydrochloric acid. The organic phase was washed with water, dried and concentrated to give an oily solid which was chromatographed on silica. Elution with hexane gave an oil (0·90 g) which contained a number of products and which darkened and became tarry on standing. Elution with benzene gave *12-acetyl-13-methoxytotara-8,11,13-triene* (7) (1·12 g, 49%) which crystallized from hexane/pentane as needles, m.p. 154–156°, $[\alpha]_D^{18}$ +48·6° (*c*, 1·13) (Found: C, 80·9; H, 9·8. $C_{23}H_{34}O_2$ requires C, 80·7; H, 10·0%). ν_{max} 1675 cm^{-1} (aryl CO). ^1H n.m.r. δ 0·97, s, *gem* 4,4-Me_2; 1·19, 1·29, 1·39, s and 2d, 10- and 15-Me_2; 2·57, s, COMe; 3·68, s, ArOMe; 7·28, s, H11. Mass spectrum: *m/z* 342 (M, 80%), 327 (100), 299 (7), 285 (14), 257 (44), 245 (41), 231 (64).

Similar yields were obtained when the reaction was carried out at 0°.

(ii) *With acetyl chloride/titanium tetrachloride.*—A solution of titanium tetrachloride (1·25 g, 6·6 mmol) in 1,2-dichloroethane (10 ml) was added dropwise to a stirred solution of acetyl chloride (0·56 g, 7·2 mmol) and the methyl ether (6) (1·0 g, 3·3 mmol) in dichloroethane (10 ml) at 0°. The mixture was stirred at 0° for 1 h and worked up as in (i). Chromatography on silica gave by-products (0·12 g) and then 12-acetyl-13-methoxytotara-8,11,13-triene (0·82 g, 72%), m.p. and mixed m.p. 152–154° (correct i.r. and ^1H n.m.r. spectra).

13-Methoxytotara-8,11,13-trien-12-yl Acetate (8)

A mixture of 12-acetyl-13-methoxytotara-8,11,13-triene (0·65 g, 1·9 mmol), *m*-chloroperbenzoic acid (0·40 g, 2·3 mmol) and toluene-*p*-sulfonic acid (0·05 g) in 1,2-dichloroethane (25 ml) was stood at 0–5° for 48 h. The mixture was washed successively with dilute aqueous sodium sulfite, sodium hydrogen carbonate solution and water. Removal of solvent from the dried organic layer gave *13-methoxytotara-8,11,13-trien-12-yl acetate* (0·57 g, 84%) which crystallized from methanol as needles, m.p. 136–140°, $[\alpha]_D^{18}$ +38·2° (*c*, 1·31) (Found: C, 76·8; H, 9·7. $C_{23}H_{34}O_3$ requires C, 77·0; H, 9·6%). ν_{max} 1760 cm^{-1} (aryl OAc). ^1H n.m.r. δ 0·89, 0·91, 2s, *gem* 4,4-Me_2; 1·15, s, 10-Me; 1·30, d, *J* 7 Hz, 15-Me_2; 2·28, s, OAc; 3·25, septet, *J* 7 Hz, H15; 3·73, s, ArOMe; 6·77, s, H11. Mass spectrum: *m/z* 358 (M, 60%), 353 (40), 316 (70), 301 (100), 286·7 (m*, 316→301), 278·9 (m*, 358 → 316), 231 (52), 219 (85), 205 (98).

13-Methoxytotara-8,11,13-trien-12-ol (9)

The acetate (8) was hydrolysed with methanolic potassium hydroxide in the usual manner to give 13-methoxytotara-8,11,13-trien-12-ol (100%) which crystallized from chloroform/pentane as needles, m.p. 165–167°, $[\alpha]_D^{18}$ +40·7° (*c*, 0·44) (lit.[16] 166·5–167·5°, $[\alpha]_D$ +43·5°; lit.[15] 164–166°, $[\alpha]_D$ +37°) (Found: C, 79·9; H, 10·2. Calc. for $C_{21}H_{32}O$: C, 79·7; H, 10·2%). ν_{max} 3540, 3350 br (OH), 1585 (aryl C=C), 990 (C–O), 860 cm^{-1}. ^1H n.m.r. δ 0·93, s, *gem* 4,4-Me_2; 1·17, s, 10-Me; 1·33, d, *J* 7 Hz, 15-Me_2; 2·80, m, 2H, H7; 3·31, septet, *J* 7 Hz, H15; 3·76, s, ArOMe; 5·18, s, OH, exchanged with D_2O; 6·76, s, H11. Mass spectrum: *m/z* 316 (M, 96%), 301 (82), 273 (8), 259 (12), 245 (11), 231 (56), 219 (72), 205 (100), 174 (40), 128 (35).

[46] Cambie, R. C., Pang, G. T. M., Parnell, J. C., Rodrigo, R., and Weston, R. J., *Aust. J. Chem.*, 1979, **32**, 2741.
[47] Cambie, R. C., and Mander, L. N., *Tetrahedron*, 1962, **18**, 465.

Demethylation of 13-Methoxytotara-8,11,13-trien-12-ol

A mixture of the monomethyl ether (9) (0·40 g, 1·3 mmol) and freshly prepared, dry pyridinium hydrochloride (5·0 g, 43 mmol) was heated at 210° under nitrogen for 40 min, and the cooled mixture was then diluted with 3 mol l^{-1} hydrochloric acid, and extracted with dichloromethane. Workup of the extract gave the crude catechol (2) as a brown oil which was dissolved immediately in benzoyl chloride (5·0 ml, 36 mmol) and an excess of 1 mol l^{-1} sodium hydroxide solution was added. The resulting suspension was shaken for 10 min, extracted with dichloromethane, and worked up to give an oil which was chromatographed on silica. Elution with n-hexane gave the dibenzoate (3) (0·40 g, 62%) which crystallized from chloroform/methanol as fine plates, m.p. 233–236°, $[\alpha]_D^{19}$ +46·0° (*c*, 0·78) (lit.[11] 227–228°). ν_{max} 1780, 1730 (OCOPh), 1600, 1592 (aryl C=C), 1265, 1220, 1175, 1115, 1080, 1060, 1022 cm^{-1}. ^1H n.m.r. δ 0·96, 0·98, 2s, *gem* 4,4-Me_2; 1·27, s, 10-Me; 1·29, d, *J* 7 Hz, 15-Me_2; 2·90, m, 2H, H7; 3·33, septet, *J* 7 Hz, H15; 7·19–8·23, m, 11H, H11 and ArH of benzoate. Mass spectrum: *m/z* 510 (M, 10%), 495 (2), 413 (2), 405 (1), 399 (1), 105 (100), 77 (17). Further elution with hexane gave starting material (9) (0·10 g).

Conversion of Totarol into Totara-8,11,13-triene-12,13-diol

Totarol (1) (2·5 g) was nitrated with cupric nitrate trihydrate (1·2 g) in acetic anhydride (20 ml) as described[12] to give 12-nitrototara-8,11,13-trien-13-ol (4) (1·0 g, 35%), m.p. 71–72° (lit.[12] 73–74·5°). The nitro derivative was hydrogenated over Adams catalyst to give 12-aminototara-8,11,13-trien-13-ol (5) (66%), m.p. 164–165° (lit.[12] 165–166°,[18] 166–167°). The amino derivative was diazotized with sodium nitrite in acetic acid containing sulfuric acid to give totara-8,11,13-triene-12,13-diol (2) (47%) as an oil which was characterized as the dibenzoate (3) as before.

12-Nitro-13-methoxytotara-8,11,13-triene (11)

Powdered cupric nitrate trihydrate (0·41 g, 1·7 mmol) was added in portions to a stirred solution of the methyl ether (6) (0·5 g, 1·6 mmol) in acetic anhydride (60 ml) and the solution was stirred at 20° for 30 min. The solution was poured onto ice and the precipitate was chromatographed on silica. Elution with hexane gave *12-nitro-13-methoxytotara-8,11,13-triene* (0·40 g, 72%) which crystallized from methanol as needles, m.p. 104–106° (Found: C, 73·2; H, 9·0; N, 4·2. $C_{21}H_{31}NO_3$ requires C, 73·0; H, 9·1; N, 4·1%). ν_{max} 1520, 1350 cm^{-1} ($ArNO_2$). ^1H n.m.r. δ 0·91, 0·94, 2s, *gem* 4,4-Me_2; 1·19, s, 10-Me; 1·32, d, *J* 7 Hz, 15-Me_2; 3·33, septet, *J* 7 Hz, H15; 3·75, s, ArOMe; 7·54, s, H11. Mass spectrum: *m/z* 340 (M, 86%), 325 (100), 315 (6), 302 (10), 288 (24), 274 (15), 260 (91), 248 (99), 234 (100), 220 (14), 141 (16), 115 (10).

13-Methoxytotara-8,11,13-trien-12-amine (12)

A solution of stannous chloride (25·0 g, 131 mmol) in hot concentrated hydrochloric acid (25 ml) was added dropwise to a solution of the nitro derivative (11) (5·6 g, 16 mmol) in boiling acetic acid (30 ml). The mixture was heated for a further 15 min, cooled, and poured into ice/water. The precipitated amine hydrochloride was filtered off and treated with 20% sodium hydroxide solution until alkaline to litmus and then extracted with ether. The ether layer was worked up to give a solid which was chromatographed on alumina. Elution with benzene gave *13-methoxytotara-8,11,13-trien-12-amine* (4·1 g, 80%) which crystallized from ether/pentane as needles, m.p. 136–138° (Found: C, 80·0; H, 10·4. $C_{21}H_{33}NO$ requires C, 79·9; H, 10·5%). ν_{max} 3480, 3340 cm^{-1} (NH_2). ^1H n.m.r. δ 0·92, s, *gem* 4,4-Me_2; 1·18, s, 10-Me; 1·30, d, *J* 7 Hz, 15-Me_2; 3·30, septet, *J* 7 Hz, H15; 3·49, br s, NH_2; 3·69, s, ArOMe; 6·50, s, H11. Mass spectrum: *m/z* 315 (M, 100%), 300 (99), 272 (20), 258 (76), 230 (43), 218 (40), 204 (93), 178 (51), 162 (29), 136 (12).

Diazotization of 13-Methoxytotara-8,11,13-trien-12-amine

Sodium nitrite (35 mg, 0·5 mmol) was added to a stirred solution of the amine (12) (0·12 g, 3·8 mmol) in methanol (25 ml) and concentrated sulfuric acid (25 drops) at 0°. The mixture was warmed slowly to 25° and then heated under reflux for 30 min. The solution was cooled, diluted with water, and extracted with ether. Workup of the extract gave a crystalline solid (0·17 g) which was separated into three components by p.l.c. (benzene).

The upper band gave 13-methoxytotara-8,11,13-triene (6) (45 mg, 39%) (identified by mixed m.p., ^1H n.m.r. and i.r. spectra). The middle band gave 12,13-dimethoxytotara-8,11,13-triene (13)

(41 mg, 30%), m.p. and mixed m.p. 86–87°. The lower band gave 13-methoxytotara-8,11,13-trien-12-ol (9) (10 mg, 30%), m.p. and mixed m.p. 162–164°.

13-Methoxy-12,14-dinitropodocarpa-8,11,13-triene (*22*)

Finely powdered methyl ether (6) (2·0 g, 6·6 mmol) was added in small portions to a stirred mixture of red fuming nitric acid (12·0 ml) and concentrated sulfuric acid (0·5 ml) at −40°. The mixture was warmed to 0° over 30 min and then poured into rapidly stirred ice/water. The precipitate was collected, dried and chromatographed on silica (dry column). Elution with hexane gave *13-methoxy-12,14-dinitropodocarpa-8,11,13-triene* (2·0 g, 77%) which crystallized from methanol as needles, m.p. 105–106° (Found: C, 62·1; H, 7·0; N, 8·1. $C_{18}H_{24}N_2O_5$ requires C, 62·1; H, 6·9; N, 8·0%). ν_{max} 1635 cm^{-1} ($ArNO_2$). ^1H n.m.r. δ 0·93, 0·94, 2s, *gem* 4,4-Me_2; 1·21, s, 10-Me; 2·80, m, H7; 3·91, s, ArOMe; 7·93, s, H11. Mass spectrum: *m/z* 348 (M, 42%), 333 (100), 305 (6), 291 (10), 277 (14), 263 (46), 251 (100), 238 (34), 221 (6), 128 (16), 115 (19).

13-Methoxypodocarpa-8,11,13-triene-12,14-diamine (*23*)

The dinitro compound (22) (2·0 g, 5·7 mmol) in acetic acid (20 ml) was reduced with stannous chloride (20·0 g, 100 mmol) in hot concentrated hydrochloric acid (20 ml) as for the nitro derivative (11). Workup gave *13-methoxypodocarpa-8,11,13-triene-12,14-diamine* (1·40 g, 86%) which crystallized from ether/hexane as needles, m.p. 188–190° (Found: C, 75·0; H, 9·6. $C_{18}H_{28}N_2O$ requires C, 75·0, H, 9·8%). ν_{max} 3480, 3400 cm^{-1} (NH_2). ^1H n.m.r. δ 0·90, 0·91, 2s, *gem* 4,4-Me_2; 1·12, s, 10-Me; 3·41, br s, $W_{h/2}$ 10 Hz, NH_2; 3·65, s, ArOMe; 5·99, s, H11.

Attempts to deaminate the diamine by diazotization and treatment with hypophosphorous acid or by reduction of the diazonium tetrafluoroborate salt with sodium borohydride were unsuccessful.

12-Acetyl-14-nitropodocarpa-8,11,13-triene (*25*)

Cold (0°) concentrated sulfuric acid (0·55 g, 5·6 mmol) was added to a cold (−50°) solution of the 12-acetyl compound (14)[14] (1·0 g, 4·0 mmol) in red fuming nitric acid (10 g, 160 mmol). The mixture was stirred at 0° for 30 min, poured into water and extracted with ether. Workup of the extract gave an oil which was chromatographed on alumina. Elution with benzene gave a yellow oil which was triturated with pentane to give *12-acetyl-14-nitropodocarpa-8,11,13-triene* (0·40 g, 40%) which crystallized from chloroform/pentane as needles, m.p. 190–194° (Found: C, 72·6; H, 7·9; N, 4·5. $C_{19}H_{25}NO_3$ requires C, 72·4; H, 8·0; N, 4·4%). ν_{max} 1710 (aryl CO), 1550, 1350 cm^{-1} ($ArNO_2$). ^1H n.m.r. δ 0·92, 0·96, 2s, *gem* 4,4-Me_2; 1·19, s, 10-Me; 2·58, s, COMe; 3·06, m, 2H, H7; 7·19, s, H11; 8·02, s, H13.

The pentane-soluble fraction contained a number of compounds which were not investigated further.

Bromination of 13-Methoxytotara-8,11,13-triene (*6*)

(i) *With bromine/thallium*(I) *acetate*.—A solution of bromine (0·93 ml, 17·0 mmol) in carbon tetrachloride (33 ml) was added over 2 h to a stirred suspension of the methyl ether (6) (3·60 g, 12·0 mmol) and thallium(I) acetate (5·04 g, 19·1 mmol) in carbon tetrachloride (33 ml) and the mixture was stirred at room temperature for a further 1 h. The thallium salts were filtered off and washed with carbon tetrachloride, and the combined organic solution was washed with aqueous solutions of sodium hydrogen sulfite and sodium hydrogen carbonate, and worked up to give an oil which was chromatographed on silica. Elution with hexane gave a forerun and then 12-bromo-13-methoxytotara-8,11,13-triene (18) (4·29 g, 94%) which crystallized from chloroform/methanol as needles, m.p. 127·5–129·5°, $[\alpha]_D^{18}$ +55·1° (*c*, 0·99) (lit.[18] 128·5–129·5°;[48] 134–135°, $[\alpha]_D$ +52·1°). ν_{max} 1035, 1012 cm^{-1} (C–O). ^1H n.m.r. δ 0·93, 0·95, 2s, *gem* 4,4-Me_2; 1·17, s, 10-Me; 1·32, d, *J* 7 Hz, 15-Me_2; 2·80, m, 2H, H7; 3·30, septet, *J* 7 Hz, H15; 3·83, s, ArOMe; 7·29, s, H11. Mass spectrum: *m/z* 380/378 (M, 82%), 365/363 (100), 295/293 (54), 283/281 (92), 269/267 (89), 69 (83).

(ii) *With N-bromosuccinimide/dimethylformamide*.—A solution of the methyl ether (6) (0·35 g, 1·17 mmol) in dry dimethylformamide (6 ml) was added to a solution of *N*-bromosuccinimide

[48] Cambie, R. C., Simpson, W. R. J., and Colebrook, L. D., *Tetrahedron*, 1963, **19**, 209.

(0·25 g, 1·40 mmol) in dry dimethylformamide (4 ml) and the mixture was stirred at 20° for 48 h. Water was added and the mixture was acidified and extracted with dichloromethane. The extract was washed with aqueous sodium metabisulfite and worked up to give an oil which was purified by p.l.c. (hexane). Removal of the top band gave the bromide (18) (0·33 g, 75%) (correct ^{1}H n.m.r. spectrum).

Reaction of o-*Bromoanisole (26) with n-Butyllithium and Oxygen*

n-Butyllithium (4·72 ml of a 1·36 mol l^{-1} solution in hexane) was added dropwise under argon to a stirred solution of *o*-bromoanisole,[49] b.p. 132°/25 mmHg, n_D^{21} 1·5718 (1·00 g, 5·35 mmol) in tetrahydrofuran (20 ml) at −78°. Stirring was continued for 30 s and a stream of dry oxygen was bubbled through the solution for 20 min as the latter was warmed to room temperature. Water was added and the mixture was acidified and extracted with ether. The extracts were washed with 3 mol l^{-1} sodium hydroxide solution and worked up to give a yellow oil (0·43 g) which contained many compounds (t.l.c. and ^{1}H n.m.r. analysis). The alkaline washings were acidified with dilute hydrochloric acid and steam distilled. The distillate was extracted with ether and the extracts were worked up to give guaiacol (27) (0·35 g, 53%) as a pale yellow oil with a characteristic, burnt odour (pure by t.l.c. and ^{1}H n.m.r.). ^{1}H n.m.r. δ (CCl_4) 3·71, s, ArOMe; 5·58, br s, OH; 6·59–6·76, m, 4H, ArH.

Reaction of 12-Bromo-13-methoxytotara-8,11,13-triene (18) with n-Butyllithium and Oxygen

A solution of the bromide (18) (2·16 g, 7·77 mmol) in tetrahydrofuran (25 ml) was treated with n-butyllithium (6·8 ml of a 1·26 mol l^{-1} solution in hexane) as above. The mixture was stirred at −78° for 10 min and then treated with a stream of dry oxygen for 20 min while it was warmed to room temperature. Workup as above gave a solid which was chromatographed on silica. Elution with hexane/ether (9 : 1) gave 13-methoxytotara-8,11,13-triene (6) which crystallized from methanol as cubes (0·82 g, 48%), m.p. and mixed m.p. 89–91° (correct ^{1}H n.m.r. spectrum). Elution with dichloromethane gave 13-methoxytotara-8,11,13-trien-12-ol (dispermol) (9) which crystallized from hexane/chloroform as small needles (0·85 g, 47%), m.p. and mixed m.p. 165–167° (correct i.r. and ^{1}H n.m.r. spectra).

Variation of the reaction time, temperature, or quantity of n-butyllithium did not improve the yield of (9).

Methyl 13-Bromo-12-methoxypodocarpa-8,11,13-trien-19-oate (28)

The bromide (28) prepared in 86% yield from the ether (29) by the method of Davis and Watkins,[50] had m.p. 141° (from hexane), $[\alpha]_D^{22}$ +126·3° (*c*, 2·16) (lit.[29] 144–145°, $[\alpha]_D$ +118°;[50] 134·5–136°). ν_{max} 1710 (CO_2Me), 1598 (aryl C=C), 1175, 1148, 1088, 1052, 1045 (C–O), 892, 852 cm^{-1}. ^{1}H n.m.r. δ 1·03, s, 10-Me; 1·27, s, 4α-Me; 2·75, m, 2H, H7; 3·67, s, CO_2Me; 3·83, s, ArOMe; 6·79, s, H11; 7·21, s, H14. Mass spectrum: *m/z* 382/380 (M, 58%), 367/365 (25), 355/353 (11), 307/305 (100), 226 (52).

Reaction of Methyl 13-Bromo-12-methoxypodocarpa-8,11,13-trien-19-oate with n-Butyllithium and Oxygen

A solution of the bromide (28) (0·75 g, 1·97 mmol) in tetrahydrofuran (9 ml) was treated with n-butyllithium (2·40 ml of a 1·26 mol l^{-1} solution in hexane) and oxygen as for the bromide (18). Workup gave an oil which was chromatographed on silica. Elution with hexane/ether (4 : 1) gave methyl 12-methoxypodocarpa-8,11,13-trien-19-oate (29) (0·17 g, 28%) as a solid (correct ^{1}H n.m.r. spectrum). Elution with hexane/ether (7 : 3) gave methyl 13-hydroxy-12-methoxypodocarpa-8,11,13-trien-19-oate (30) (0·40 g, 64%) which crystallized from aqueous methanol and then from hexane as cubes, m.p. 130–132°, $[\alpha]_D^{20}$ +136·4 (*c*, 0·86) (lit.[30] 132·5–135°, $[\alpha]_D$ +137°) (Found: C, 71·9; H, 8·6. Calc. for $C_{19}H_{26}O_4$: C, 71·7; H, 8·2%). ν_{max} 3540, 3500–3250 (OH), 1710 (CO_2Me), 1610, 1595 (aryl C=C), 1148, 1068, 1035 (C–O), 978, 910 cm^{-1}. ^{1}H n.m.r. δ 1·02, s, 10-Me; 1·27, s, 4α-Me; 1·38, m, 2H, H7; 3·67, s, CO_2Me; 3·85, s, ArOMe; 5·43, s, OH; 6·60, 6·76, 2s, H11 and H14. Mass spectrum: *m/z* 318 (M, 53%), 303 (62), 271 (12), 243 (100).

[49] Bigelow, L. A., *Org. Synth.*, 1944, Coll. Vol. I, 136.
[50] Davis, B. R., and Watkins, W. B., *Aust. J. Chem.*, 1968, **21**, 2769.

Treatment of o-*Bromoanisole* (*26*) *with n-Butyllithium and t-Butyl Hydroperoxide*

n-Butyllithium (5·50 ml of a 1·36 mol l^{-1} solution in hexane) was added at −78° under dry argon to a solution of t-butyl hydroperoxide (1·00 ml of a 64% solution in di-t-butyl ether) in tetrahydrofuran (6 ml) and the mixture was stirred at −78° for 5 min. It was then treated by means of a double-ended needle with a solution prepared by adding n-butyllithium (5·50 ml) at −78° under dry argon to a solution of *o*-bromoanisole (1·00 g, 5·35 mmol) in tetrahydrofuran (8 ml) and stirring at −78° for 30 s. The resulting mixture was stirred at −78° for 15 min and then at 20° for 2 h. Water was added and the mixture was acidified and extracted with ether. The ether portion was extracted with 3 mol l^{-1} sodium hydroxide solution and the extracts were acidified and steam-distilled. The distillate was extracted with ether and the extracts were worked up to give guaiacol (27) (0·52 g, 78%) as a pale yellow oil (correct t.l.c. behaviour and ^{1}H n.m.r. spectrum).

Treatment of 12-Bromo-13-methoxytotara-8,11,13-triene with n-Butyllithium and t-Butyl Hydroperoxide

A solution of the bromide (18) in tetrahydrofuran was treated with n-butyllithium and lithium t-butylperoxide as described above. T.l.c. and ^{1}H n.m.r. analyses of the resulting reaction mixture indicated that compounds (6) and (9) were the sole products and were present in the ratio 64 : 36. Inverse addition of the reagents and use of 2,2′-bipyridyl indicator[51] to confirm that sufficient n-butyllithium solution had been added to salt out the t-butyl hydroperoxide failed to improve the yield of (9).

Reactions of $[Mo(O_2)_2O]py,hmpt$

(i) *With* o-*bromoanisole* (*26*).—n-Butyllithium (1·20 ml of a 1·31 mol l^{-1} solution in hexane) was added dropwise under argon at −78° to a stirred solution of *o*-bromoanisole (0·25 g, 1·34 mmol) in tetrahydrofuran and the stirring was continued for 5 min. The molybdenum–oxygen complex ($[Mo(O_2)_2O]$py,hmpt)[31] (0·64 g) was added and the mixture was stirred at −78° under argon for 1·25 h and then at 20° for 1 h. Water was added and the solution was acidified and worked up as for previous reactions to give guaiacol (0·13 g, 76%) as a colourless oil (correct t.l.c. behaviour and ^{1}H n.m.r. spectrum).

(ii) *With 12-bromo-13-methoxytotara-8,11,13-triene* (*18*).—The bromide (18) (0·33 g, 1·00 mmol) was treated with n-butyllithium (0·75 ml) and the molybdenum–oxygen complex (0·57 g) as described above. Workup gave an oil which contained compounds (6) and (9) in the ratio 53 : 47 (^{1}H n.m.r. analysis). P.l.c. (hexane) gave 13-methoxytotara-8,11,13-triene (6) (0·13 g, 49%) and 13-methoxytotara-8,11,13-trien-12-ol (9) (0·11 g, 40%).

(iii) *Methyl 13-bromo-12-methoxypodocarpa-8,11,13-trien-19-oate* (*28*).—The bromide (28) (0·25 g, 0·66 mmol) was treated with n-butyllithium (0·55 ml) and the molybdenum–oxygen complex as described above. Workup gave an oil which was chromatographed on silica. Elution with hexane/ether (4 : 1) gave methyl 12-methoxypodocarpa-8,11,13-trien-19-oate (29) (59 mg, 30%). Elution with hexane/ether (7 : 3) gave methyl 13-hydroxy-12-methoxypodocarpa-8,11,13-trien-19-oate (30) (0·13 g, 63%).

12,13-Dimethoxytotara-8,11,13-triene (*13*)

Methyl iodide (2·94 g, 20·6 mmol) was added to a solution of the phenol (9) (0·90 g, 2·8 mmol) and potassium t-butoxide (1·76 g, 15·6 mmol) in dry t-butyl alcohol and the mixture was stirred at 20° for 48 h. The mixture was diluted with water, extracted with dichloromethane, and the extract was worked up to give an oil which was chromatographed on deactivated alumina. Elution with hexane gave 12,13-dimethoxytotara-8,11,13-triene (0·81 g, 86%) which crystallized from methanol as small cubes, m.p. 87–90°, $[\alpha]_D$ +47·2° (*c*, 2·57) (lit.[16] 89–91°, $[\alpha]_D$ +50·2°;[15] 89–90°, $[\alpha]_D$ +35°) (Found: C, 80·1; H, 10·4. Calc. for $C_{22}H_{34}O_2$: C, 80·0; H, 10·4%). ν_{max} 1595 (aryl C=C), 1130, 1122, 1080, 1038, 1018 cm^{-1} (C–O). ^{1}H n.m.r. δ 0·93, 0·95, 2s, *gem* 4,4-Me_2; 1·21, s, 10-Me; 1·31, d, *J* 7 Hz, 15-Me_2; 2·78, m, 2H, H 7; 3·23, septet, *J* 7 Hz, H 15; 3·81, s, 6H, ArOMe; 6·71, s, H 11. Mass spectrum: *m/z* 330 (M, 99%), 315 (100), 287 (5), 273 (8), 258 (9), 245 (37), 233 (26), 219 (80).

[51] House, H. O., 'Modern Synthetic Reactions' p. 551 (W. A. Benjamin: New York 1972).

Ozonolysis of 12,13-Dimethoxytotara-8,11,13-triene

A cooled (−78°) solution of the dimethyl ether (13) (0·25 g, 0·76 mmol) in a mixture (1 : 1) of chloroform and methanol (10 ml) was treated with a stream of ozonized oxygen until a blue colour developed in the solution. Excess of ozone was removed in a stream of nitrogen as the solution was warmed to room temperature, and the solvents were removed under vacuum to give an oil which was chromatographed on deactivated alumina. Elution with hexane/ether (9 : 1) gave *dimethyl 12,13-secototara-9(11),8(14)-diene-12,13-dioate* (31) which crystallized from aqueous acetone as rods (0·26 g, 95%), m.p. 77–78·5°, $[\alpha]_D^{22}$ −110·2° (*c*, 0·29) (Found: C, 73·1; H, 9·5. $C_{22}H_{34}O_4$ requires C, 72·9; H, 9·5%). λ_{max} (EtOH) 241 nm (log ε 3·93) with absorption below 300 nm. ν_{max} 1725–1705 (CO_2Me), 1620 (C=C), 1285, 1230, 1195 cm^{-1}. ^1H n.m.r. δ 0·90, s, *gem* 4,4-Me_2; 1·10, s, 10-Me; 1·05, 1·12, 2d, $J = J'$ 6·5 Hz, 6H, 15-Me_2; 2·90, m, $W_{h/2}$ 20 Hz, 3H, H 7,15; 3·56, 3·63, 2s, 6H, CO_2Me; 5·48, s, H 11. Mass spectrum: *m/z* 362 (M, 2%), 319 (22), 303 (100), 275 (8), 226 (9), 168 (7).

When the ozonolysis was carried out at −78° in ethyl acetate, the diester (31) was isolated in 33% yield by p.l.c. Ozonolysis at 0° resulted in cleavage of the double bonds of (31) and the formation of a complex mixture of products.

Hydrolysis of the Diester (31)

A solution of the diester (31) (0·53 g, 1·46 mmol) in methanol (40 ml) was heated under reflux with a solution of sodium hydroxide (1·18 g, 29·5 mmol) in water (4 ml) under nitrogen for 5 h. Water was added, the methanol was removed under vacuum, and the aqueous residue was washed with dichloromethane. The aqueous portion was then acidified, extracted with dichloromethane, and the extract was worked up to give *13-methyl hydrogen 12,13-secototara-9(11),8(14)-diene-12,13-dioate* (32) which crystallized from hexane as fine needles (0·48 g, 94%), m.p. 187–189° with decomp. above 170°, $[\alpha]_D^{20}$ −136·9° (*c*, 0·93) (Found: C, 72·5; H, 9·6. $C_{21}H_{32}O_4$ requires C, 72·4; H, 9·3%). λ_{max} (EtOH) 240 nm (log ε 3·86) with absorption below 300 nm. ν_{max} 3500, 3400–2400 (OH), 1710 (CO_2Me), 1690 (CO_2H), 1620 cm^{-1} (C=C). ^1H n.m.r. δ 0·90, s, *gem* 4,4-Me_2; 1·07, 1·19, 2d, $J = J'$ 7 Hz, 15-Me_2; 1·09, s, 10-Me; 2·86, m, $W_{h/2}$ 20 Hz, 3H, H 7,15; 3·57, s, CO_2Me; 5·49, s, H 11; 8·01, br s, CO_2H. Mass spectrum: *m/z* 348 (M, 3%) 333 (< 1), 315 (< 1), 305 (20), 303 (10), 289 (100).

Hydrolysis for 3 h gave the acid (32) (59%) and starting material (22%).

Selective Demethylation of 12,13-Dimethoxytotara-8,11,13-triene with Trimethylsilyl Iodide

Trimethylsilyl iodide (0·081 ml) was added to a solution of the dimethyl ether (13) (0·15 g, 0·45 mmol) in dry, ethanol-free chloroform (1·5 ml) under dry nitrogen, and the solution was stirred for 48 h. Methanol was added, followed by saturated sodium chloride solution, and the mixture was extracted with dichloromethane. The extract was washed with aqueous sodium hydrogen sulfite and worked up to give an oil which was chromatographed on silica. Elution with hexane/ether (19 : 1) gave 12-methoxytotara-8,11,13-trien-13-ol (10) (89 mg, 62%) which crystallized from methanol as cubes, m.p. 85–86°, $[\alpha]_D^{20}$ +47·8° (*c*, 0·56) (lit.[16] 87–88·5°, $[\alpha]_D$ +50·2°) (correct i.r. and ^1H n.m.r. spectra). Elution with hexane/ether (4 : 1) gave starting material (13) (17 mg, 11%) while elution with dichloromethane gave a bright yellow oil (34 mg) containing decomposition products of the catechol (2). Repetition of the demethylation by using the dimethyl ether (13) (0·15 g) and trimethylsilyl iodide (0·13 ml) (1·75 mol. equiv.) gave the phenol (23) (58 mg, 40%), starting material (3 mg, 2%) and decomposition products of the catechol (2) (69 mg).

Ozonolysis of 13-Methoxytotara-8,11,13-trien-12-ol (9)

A solution of the phenol (9) (0·10 g, 0·32 mmol) in a mixture (1 : 1) of dichloromethane and methanol (4 ml) was cooled to −78° and saturated with ozone. The solvent was removed under vacuum to give a yellow oil which contained the unsaturated acid (32) as a major component of a complex mixture (t.l.c. analysis). The ^1H n.m.r. spectrum of the product showed signals at δ 3·57 and 5·48 characteristic of the methoxycarbonyl and vinyl protons, respectively, of the acid (32).

When the isomeric phenol (10) was ozonized as above, a more complex mixture was formed in which none of the signals in the regions δ 3–4 and δ 5–6 corresponded with those of the acid (31).

Pyrolysis of the Unsaturated Acid (32)

The acid (32) (0·15 g, 0·43 mmol) was heated in a bulb-tube at 250° under a water-pump vacuum for 1·5 h. The vacuum was increased to 10 mm and the product was distilled out of the tube and purified by p.l.c. (hexane/ether, 1 : 1). The main band (R_F 0·5) gave a mixture (3 : 2) of the C14 epimers of *14-methoxycarbonyl-13-nor-12,14-secototara-8-ene-12,14-lactone* (34) (0·12 g, 80%) which was distilled at 115°/0·01 mm to give a clear oil (Found: C, 72·3; H, 9·5. $C_{21}H_{32}O_4$ requires C, 72·4; H, 9·3%). ν_{max} 1730 (CO_2Me), 1135, 1035 cm^{-1} (C–O). ^1H n.m.r. δ 0·85, 0·94, 2s, 3H and 6H, *gem* 4,4-Me_2 and 10-Me; 0·97, 1·02, 2d, $J = J'$ 7 Hz, 6H, epimeric 15-Me_2; 2·54, septet, J 7 Hz, H15; 3·05, m, $W_{h/2}$ 7 Hz, 2H, H11; 3·74, 3·76, 2s, epimeric CO_2Me. Mass spectrum: m/z 348 (M, 24%), 333 (10), 289 (100), 247 (53), 43 (64), 41 (49).

Photolysis of the Unsaturated Acid (32)

A solution of the acid (32) (0·32 g, 0·92 mmol) in 95% ethanol (30 ml) in a Pyrex flask† was irradiated under argon with a medium-pressure mercury lamp for 72 h, by which time t.l.c. indicated that no starting material was present. The solvent was removed under reduced pressure to give an oil which was chromatographed on silica. Elution with hexane/ether (1 : 1) gave *14ξ-methoxycarbonyl-13-nor-12,14-secototara-8-ene-12,14-lactone* (34a) (0·30 g, 94%) as a clear oil, which was distilled at 130°/0·08 mm, $[\alpha]_D^{20}$ +109·7° (c, 0·34) (Found: C, 72·3; H, 9·3. $C_{21}H_{32}O_4$ requires C, 72·4; H, 9·3%). ν_{max} 1730 (CO_2Me), 1138, 1035 cm^{-1} (C–O). ^1H n.m.r. δ 0·85, 0·94, 2s, 3H and 6H, *gem* 4,4-Me_2 and 10-Me; 1·02, d, J 7 Hz, 15-Me_2; 2·54, septet, J 7 Hz, H15; 3·05, m, $W_{h/2}$ 7 Hz, H11; 3·74, s, CO_2Me. Mass spectrum: m/z 348 (M, 22%), 333 (4), 289 (100), 275 (27), 247 (40), 43 (80), 41 (64).

Partial Isomerization of the Diester (31)

The diester (31) was heated to 220° for 30 min. T.l.c. analysis showed a single spot with the same R_F as the starting material. However, the ^1H n.m.r. spectrum indicated a 1 : 1 mixture of the starting material and an isomer, e.g. (38), ^1H n.m.r. δ 3·67 (CO_2Me) and 5·63 (H11), which could not be separated.

Epoxidation of the Enolide (34a)

Trifluoroacetic anhydride (0·52 ml) was added dropwise to a cooled (0°) solution of 90% hydrogen peroxide (0·11 ml) in dichloromethane (4 ml), and the solution was stirred at 0° for a further 20 min. The resulting solution of trifluoroperacetic acid was added dropwise at 0° to a solution of the enolide (34a) (0·65 g, 1·87 mmol) in dichloromethane (9 ml) and the mixture was stirred at 20° for 2 h. The solution was diluted with dichloromethane, washed with saturated sodium hydrogen carbonate solution, and worked up to give an oil which was chromatographed on silica. Elution with hexane/ether (1 : 1) gave *8α,9α-epoxy-14ξ-methoxycarbonyl-13-nor-12,14-secototarane-12,14-lactone* (40) (0·43 g, 63%) which crystallized from hexane as clusters of needles, m.p. 145–146°, $[\alpha]_D^{19}$ +39·0 (c, 0·54) (Found: C, 68·8; H, 8·95. $C_{21}H_{32}O_5$ requires C, 69·2; H, 8·85%). ν_{max} 1730 (CO_2Me), 1165, 1137, 1047, 1038, 1005 cm^{-1} (C–O). ^1H n.m.r. δ 0·82, s, 4β-Me; 0·87, s, 4α-Me; 0·97, s, 10-Me; 0·94, 1·06, 2d, J 7 Hz, 15-Me_2; 2·58, septet, J 7 Hz, H15; 2·94, br s, 2H, H11; 3·83, s, CO_2Me. Mass spectrum: m/z 364 (M, <1%), 348 (<1), 330 (54), 315 (54), 305 (29), 245 (29), 233 (42), 219 (68), 123 (38), 109 (30), 95 (42), 81 (49), 71 (98), 69 (74), 55 (56), 43 (100), 41 (83).

The epoxide (40) was isolated in 60% yield when the epoxidation was carried in dichloromethane under reflux.

Treatment of the epoxide (40) with lithium iodide in refluxing collidine[44] gave a product containing many compounds none of which corresponded with the expected dienolide (39). The ^1H n.m.r. spectrum of the crude product indicated that complete loss of the methyl ester group had occurred (cf. ref.[52]).

Treatment of the Epoxy Lactone (40) with Lithium N-*Cyclohexylisopropylamide*

n-Butyllithium (0·13 ml of a 1·29 mol l^{-1} solution) was added at 0° under argon to a solution of *N*-cyclohexylisopropylamine (0·029 ml) in tetrahydrofuran (1 ml) and the solution was stirred

† The flask was wrapped with an aluminium foil reflector and clamped *c.* 2 cm from the lamp.

[52] Liu, H.-J., and Browne, E. N. C., *Can. J. Chem.*, 1981, **59**, 601.

at 0° for 10 min and cooled to −78°. A solution of the epoxy lactone (40) (58 mg, 0·16 mmol) in tetrahydrofuran was added and the mixture was stirred at −78° under argon for 5 min and then at 20° for 30 min. Workup gave an oil which was chromatographed on silica. Elution with hexane/ether (1 : 1) gave a forerun (20 mg) containing several compounds. Further elution with hexane/ether (1 : 1) gave starting material (40) (12 mg). Elution with hexane/ether (3 : 7) gave an unidentified product (8 mg) as a yellow oil. ^{1}H n.m.r. δ 0·8–1·3, C–Me; 3·83, s, CO_2Me; 5·53, s, C=CHCO.

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