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Diterpenoids. XXXVIII.[1] Conversion of *l*-Abietic Acid into Steroidal Skeletons: Formation of the D-Ring (1)

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The steroidal D-rings (**31** and **37**), along with **32** and **38**, were synthesized by the use of a part or whole of the carbon units of the isopropyl group of *l*-abietic acid (**1**), *via* oxidation of **18** or **20** with $Tl(ONO_2)_3$, or addition reaction of **20** with 1,1-dichloroethylene, and modifications of the functionality, followed by Friedel-Crafts cyclization. Cyclization to the 14-position (formation of **31** or **37**) in **30** or **35** was always predominant over that to the 12-position (formation of **32** or **38**). In attempts for functionalization of the isopropyl group with $Pb(OAc)_4$, **9**, a hopeful intermediate to syntheseze quinoid diterpenes, was obtained *via* **3**, **4**, **5** and **6**. RuO_2 reduction of **6** and successive $Pb(OAc)_4$ oxidation to **17** is also described.

It is of interest to synthesize a steroidal D-ring by the use of a part or a whole of the carbon units of the isopropyl group of *l*-abietic acid (**1**), a major component of pine rosin. This objective has been achieved by oxidation with $Tl(ONO_2)_3$ or the addition reaction of 1,1-dichloroethylene, and by subsequent intramolecular Friedel-Crafts cyclization.[3]

Several workers[4] reported the synthesis of the steroidal D-ring from methyl 12-methoxypodocarpa-8,11,13-trien-16-oate or its derivatives by the intermolecular Friedel-Crafts reaction to introduce the carbon units at the 13-position and modifications of the functionality, followed by the intramolecular Friedel-Crafts cyclization. Cambie and his co-worker[5] reported the functionalization of the isopropyl group, but they could not achieve the formation of the steroidal D-ring. This paper is the first report on the synthesis of the steroidal D-ring by the use of a part or a whole of the carbon units of the ispropyl group of resin acid.

Now, we wish to report the respective synthesis of **31** and **37**, along with **32** and **38**, by the intramolecular Friedel-Crafts cyclization of **30** and **35**, *via* **21** and **22**, introduced from the oxidation products of **3** (**18** and **20**), by the action of $Tl(ONO_2)_3$[6] or *via* **33** from **20** by the action of 1,1-dichloroethylene.[7] We also wish to report other attempts on the functionalization of the isopropyl group.

Functionalization of the isopropyl group was attempted by the action of $Pb(OAc)_4$ with the 12-hydroxyl derivatives. Although it is well known that phenol derivatives are oxidized

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[1] Part XXXVII: H. Akita and A. Tahara (the late), *Chem. Pharm. Bull.* (Tokyo), 23, 2660 (1975).

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[3] A. Tahara, M. Shimagaki, M. Itoh, Y. Harigaya, and M. Onda, *Chem. Lett.*, **1974**, 651.

[4] R.H. Bible Jr., U.S. Patent 2759014 (1956) [*Chem. Abstr.*, **51**, 5838 (1957)]; B.R. Davis and W.B. Watkins, *Tetrahedron*, **24**, 2165 (1968); D.M.S. Wheeler and P.R. Witt, *J. Org. Chem.*, **37**, 4211 (1972). Also see B.R. Davis and W.B. Watkins, *Aust. J. Chem.*, **21**, 1611 (1968).

[5] R.C. Cambie and R.A. Franich, *Chem. Commun.*, **1969**, 725; *idem*, *Aust. J. Chem.*, **24**, 117 (1971).

[6] *a)* A. McKillop, J.D. Hunt, E.C. Taylor, and F. Kienzle, *Tetrahedron Letters*, **1970**, 5275; *b)* A. McKillop, B.P. Swann, and E.C. Taylor, *J. Am. Chem. Soc.*, **93**, 4919 (1971).

[7] K. Bott and H. Hellmann, *Angew. Chem.*, **78**, 932 (1966).

with $Pb(OAc)_4$ to give quinoid derivatives,[8] and also, in the diterpene fields, ferruginol and 7-hydroxy-C-aromatic hydrofluorene gave respective *o*-quinol acetate[9] and *p*-quinol derivative[10] in a low yield, it might have a possibility of attacking the isopropyl-methyl group which existed close to the hydroxyl group.

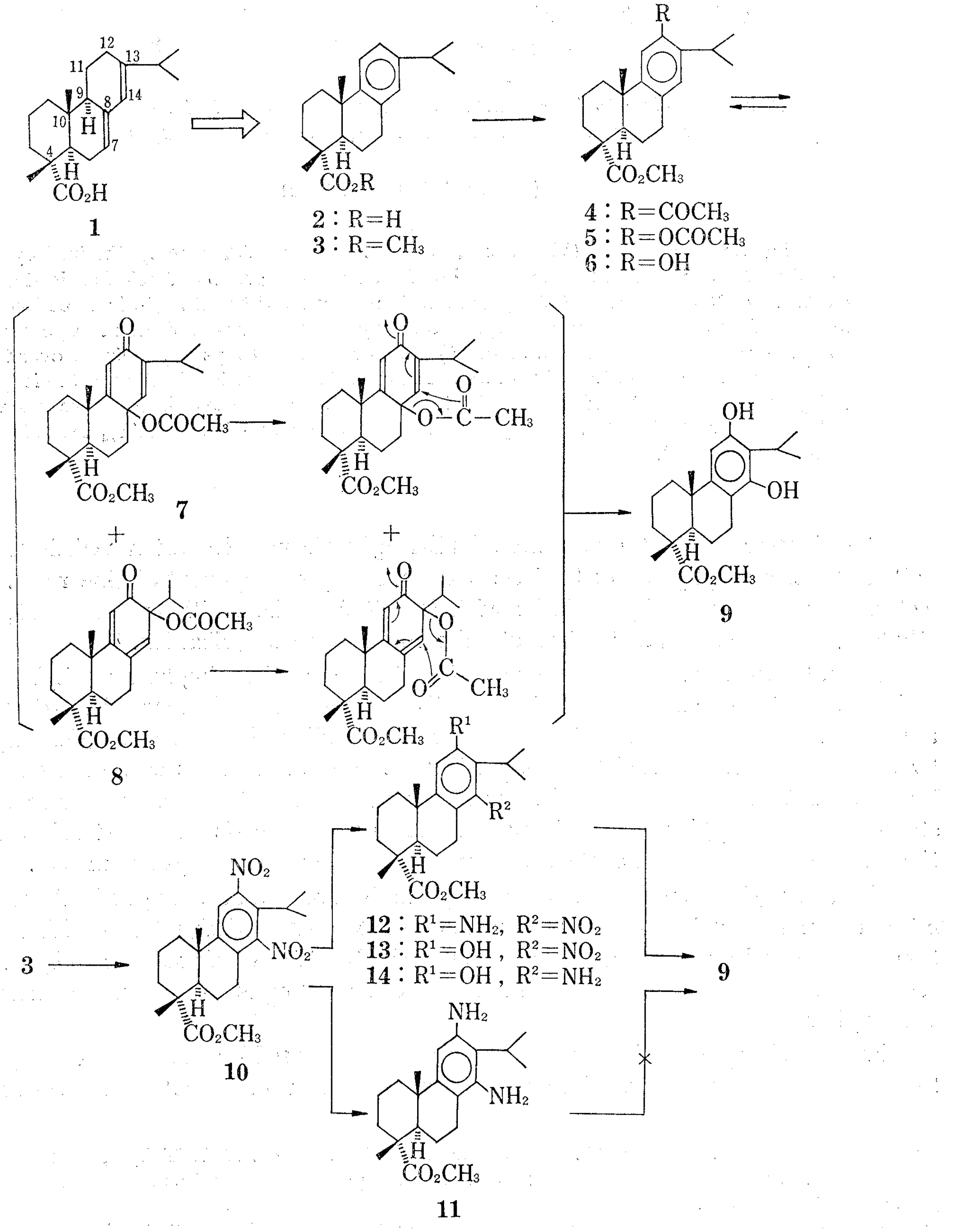

Chart 1

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[8] *e.g.* R. Criegee, "Oxidation in Organic Chemistry, "Part A, ed. by K.B. Wibergs, Academic Press, New York and London, 1965, p. 288.

[9] C.P. Falshaw, A.W. Johnson, and T.J. King, *J. Chem. Soc.*, **1963**, 2422.

[10] K. Hosaka, H. Nagaoka, and Y. Yamada, Abstr. Papers, 94th Annu. Meet. Pharm. Soc. Japan, Part II, 91 (1974).

Methyl 12-hydroxydehydroabietate (**6**) was used as a starting material. The phenol (**6**) was prepared (H_2SO_4, MeOH, H_2O) from methyl dehydroabietate (**3**), a methylated product of dehydroabietic acid (**2**), *via* methyl 12-acyldehydroabietate (**4**) (AcCl, $AlCl_3$, CS_2) and methyl 12-acetoxydehydroabietate (**5**) (AcOOH, AcOH, H_2SO_4), by slightly different ways reported by Cambie's group5) in nearly the same overall yield. The phenol (**6**) was treated with $Pb(OAc)_4$ to give a product, which was chromatographed on silica gel to give an unseparable mixture. The ultraviolet (UV) spectrum (EtOH) showed absorption bands at 245 and 322 mμ and the infrared (IR) spectrum (CCl_4) provided the bands at 1760, 1725 and 1670 cm^{-1}. These spectral data suggested a mixture of the *p*- and *o*-quinoid derivatives containing an acetoxyl group. Since the 11-position was sterically hindered, it seemed probably that the attack of $Pb(OAc)_4$ occurred at the 8- and 13-positions to afford a mixture of methyl 8-acetoxy-13-isopropyl-12-oxopodocarpa-9(11),13-dien-15-oate (**7**) and methyl 13-acetoxy-13-isopropyl-12-oxopodocarpa-8(14),9(11)-dien-15-oate (**8**). This mixture was changed back to **6** on catalytic hydrogenation over PtO_2 in 51% yield, and was also characterized by conversion into methyl 12,14-dihydroxydehydroabietate (**9**). This mixture (**7** and **8**) was treated with dienone-phenol rearrangement conditions11) with $(CF_3CO)_2O$ and successively hydrolyzed with H_2SO_4–MeOH–H_2O to give **9** in 35—90% overall yield from **6**. The IR spectrum ($CHCl_3$) showed absorption bands at 3615 and 1715 cm^{-1}. The nuclear magnetic resonance (NMR) spectrum provided signals at 1.33 (d, $J=8$ Hz) for the isopropyl-methyl groups, 4.64 (b.s) for the 12- and 14-hydroxyl groups and 6.24 (s) for the 11-proton. To confirm the position of the two hydroxyl groups,12) **9** was synthesized from methyl 12,14-dinitrodehydroabietate (**10**) by a different route. The dinitro derivative (**10**),13) derived from **3**, was reduced with Sn–HCl to methyl 12,14-diaminodehydroabietate (**11**),14) which was treated by diazotization conditions, followed by heating under acidic conditions, but it gave intractable product (s). Then **10** was partially reduced to methyl 12-amino-14-nitrodehydroabietate (**12**),15) which was converted by the usual manner to methyl 12-hydroxy-14-nitrodehydroabietate (**13**) in 54% yield. The hydroxy-nitro derivative (**13**) was reduced with Sn–HCl to methyl 14-amino-12-hydroxydehydroabietate (**14**) in 74% yield. The amino-hydroxyl derivative (**14**) was converted in the usual way to give **9** in 24% yield. The physical data were identical with those of the sample mentioned above. Although it could not achieve the attack of the hydroxyl group on the inactive carbon of the isopropyl group with $Pb(OAc)_4$, **9** could be a hopeful intermediate to synthesize quinoid diterpenes, royleanone,16*a*) horminone16*b*) and taxoquinone.16*a*,*c*)

The benzenoid ring of **6** was catalytically hydrogenated to fix the 12-hydroxyl and 13-isopropyl groups in the same side, the β-side. The phenol (**6**) was treated with $RuO_2$17) under 125 kg/cm^2 of H_2 at 80° to give methyl 12β-hydroxy-13β-isopropyl-8α-podocarpan-15-oate (**15**) in 63.5% yield. The physical data of **15**, except for the melting point, were identical with those of the authentic sample.18) The alcohol (**15**) was oxidized with Jones reagent to give methyl 13β-isopropyl-12-oxo-8α-podocarpan-15-oate (**16**) in 84% yield. The oxo derivative (**16**) was recovered unchanged on treatment with NaOMe in refluxing MeOH19) and changed back to **15**

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11) E. Hecker and E. Meyer, *Chem. Ber.*, **97**, 1926 (1964); E. Hecker, *ibid.*, **97**, 1940 (1964).

12) It was reported that thermal rearrangement of *o*-quinol acetate possessing an 13-acetoxyl group gave an 11-acetoxyl phenol.9)

13) E.S. Hansen and H.H. Zeiss, *J. Am. Chem. Soc.*, **77**, 1643 (1955).

14) E.R. Littmann, *J. Am. Chem. Soc.*, **60**, 1419 (1938).

15) E. Ochiai and M. Ohta, *Yakugaku Zassi*, **74**, 203 (1954).

16) *a*) O.E. Edwards, G. Feniak, and M. Los, *Can. J. Chem.*, **40**, 1540 (1962); *b*) M.M. Janot and P. Potier, *Ann. Pharm. France*, **22**, 387 (1964) [*Chem. Abstr.*, **61**, 13627 (1964)]; *c*) S.M. Kupchan, A. Karim, and C. Marcks, *J. Am. Chem. Soc.*, **90**, 5923 (1968).

17) *cf.* R.E. Ireland and P.W. Schiess, *J. Org. Chem.*, **28**, 6 (1963); R.B. Turner, K.H. Gänshirt, P.E. Shaw, and J.D. Tauber, *J. Am. Chem. Soc.*, **88**, 1776 (1966); R.A. Bell and M.B. Gravestock, *Can. J. Chem.*, **47**, 3661 (1969).

18) J.W. Huffmann, T. Kamiya, L.H. Wright, J.J. Schmid, and W. Herz, *J. Org. Chem.*, **31**, 4128 (1966).

19) W. Herz, H.J. Wahlborg, W.D. Lloyd, W.H. Shuller, and G.W. Hedrick, *J. Org. Chem.*, **30**, 3190 (1965).

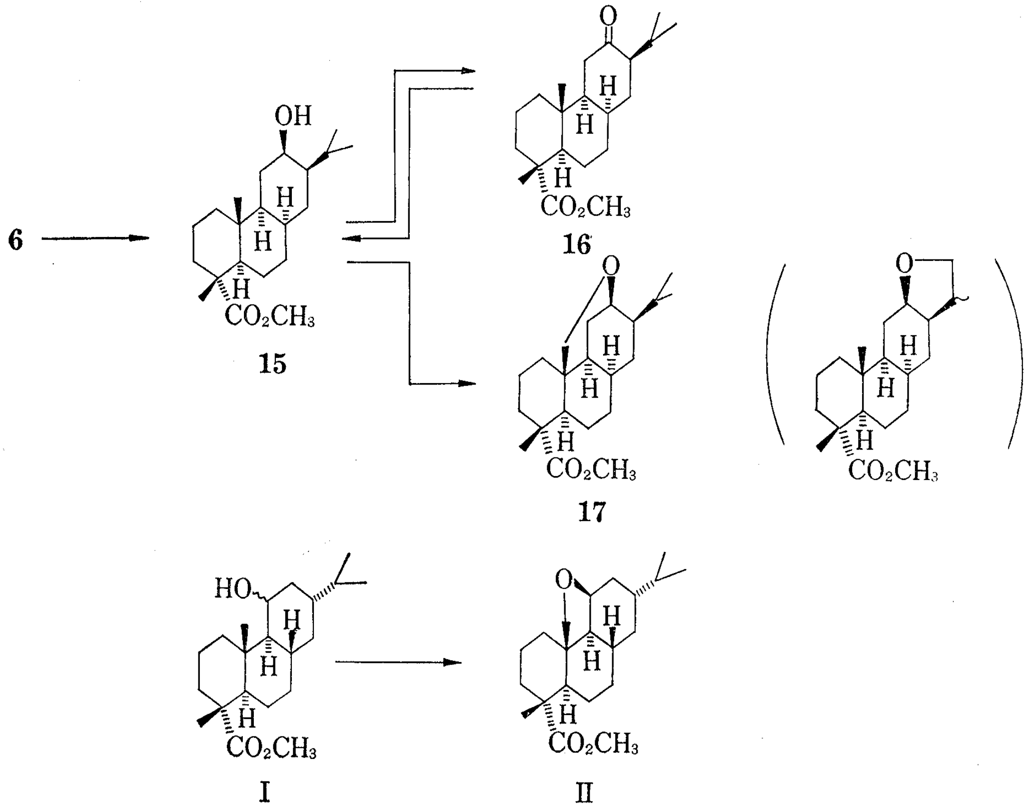

Chart 2

by treatment with NaBH$_4$.[18] The physical data, including the melting point, and these properties were identical with those of the authentic sample.[19] The alcohol (**15**) was treated with Pb(OAc)$_4$ to give a product, whose IR spectrum showed no absorption band for the hydroxyl group. The NMR spectrum showed the remainder of the isopropyl group (0.92 (d, J=6 Hz) and 0.95 (d, J=5.5 Hz)), the loss of one methyl group and the presence of one methyl group (1.02 (s)) and three protons adjacent to an oxygen function (3.7—4.2 (unidentified m)). These results showed that the attack of the oxygen of 12-hydroxyl group with Pb(OAc)$_4$ did not occur at the isopropyl-methyl groups, the desired position, but at the 4- or 10-methyl group, the undesired position. From the study of the molecular model of **15**, the oxygen in the 12-hydroxyl group could not make an ether bridge with the carbon in the 4-methyl group, because they were far distant from each other. Therefore, the attack performed at the 10-methyl group. This can be supported by the upfield shift of the 4-methyl group of the product by 0.18 ppm from the signal of the starting alcohol (**15**)[20] in its NMR spectrum. These results showed the structure not to be the desired five-membered ether, shown in parenthesis (Chart 2), but the undesired six-membered ether (**17**) as the Pb(OAc)$_4$ oxidation product, and its yield was 14%. This result could be explained by the fact that the 12-hydroxyl group was very close to the 10-methyl group, because the B—C ring juncture was *cis* with the α-hydrogens and the 13-isopropyl-methyl groups did not possess a rigid structure.

The oxidation products of the isopropyl group with CrO$_3$ were used for our next aim to form a steroidal skeleton. The initial materials were methyl 12-acyl-7-oxopodocarpa-8,11,13-trien-15-oate (**18**)[21] and methyl 13-isopropenyl-7-oxopodocarpa-8,11,13-trien-15-oate (**20**).[22]

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20) The 4-axial methyl group in I showed the upfield shift by 0.25 ppm from the signal of the starting alcohol (II), when an ether bridge was formed between the 11-hydroxyl and 10-methyl groups [W. Herz and D.H. White, *J. Org. Chem.*, **39**, 1 (1974)].

21) T.F. Sanderson, U.S. Patent 2750368 (1956) [*Chem. Abstr.*, **51**, 1278 (1957)].

22) P.F. Ritchie, T.F. Sanderson, and L.F. McBurney, *J. Am. Chem. Soc.*, **76**, 723 (1954).

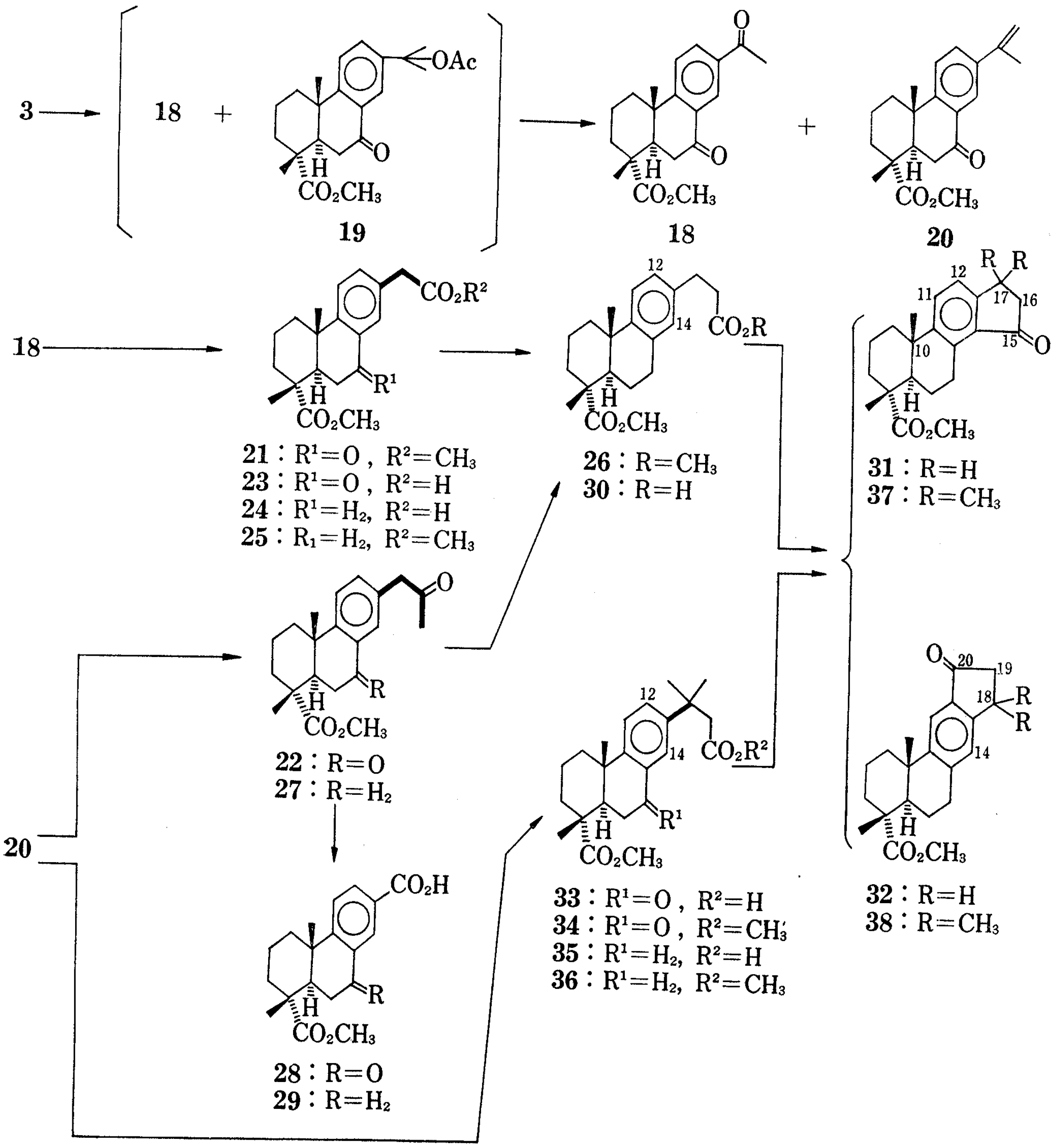

Chart 3

In order to improve the yield and separation of the products, a mixture of **18** and methyl 13-(1′-acetoxy-1′-methylethyl)-7-oxopodocarpa-8,11,13-trien-15-oate (**19**), obtained from **3** by the Sanderson's method,[21] was pyrolyzed at 205—210° without purification to give **18** and **20** in 24% and 28% yields, respectively.

The side chain at the 13-position in the both compounds (**18** and **20**) was conveniently changed for the formation of the steroidal D-ring. The dioxo ester (**18**) was selectively oxidized at the side chain with $Tl(ONO_2)_3$[6b] in MeOH in the presence of $HClO_4$ to give methyl 13-methoxycarbonylmethyl-7-oxopodocarpa-8,11,13-trien-15-oate (**21**) in a quantitative yield. The IR spectrum (CCl_4) showed absorption bands at 1730 and 1690 cm^{-1}. The NMR spectrum (100 MHz, CCl_4) provided signals at δ 3.54 (s, $W_{1/2}=2$ Hz) for the 1′-methylene group, 3.64 (s) for the 4- and 1′-methoxycarbonyl groups and no signal for an acyl group. The selective oxidation may be explained by the fact that $Tl(ONO_2)_3$ could only attack the side chain of **18** at room temperature, due to bulkiness of the reagent, even though both ketones could be enolyzed. The isopropenyl derivative (**20**) was also oxidized with $Tl(ONO_2)_3$[6a] in MeOH to give methyl

7-oxo-13-(2′-oxopropyl)-podocarpa-8,11,13-trien-15-oate (**22**) in 95% yield. The IR spectrum (CCl_4) showed absorption bands at 1730 and 1690 cm^{-1}. The NMR spectrum (100 MHz, CCl_4) provided signals at δ 2.10 (s) and 3.16 (s, $W_{1/2}=2$ Hz) for the 2′-oxopropyl group and no signal for an isopropenyl group.

The 7-oxo diester (**21**) was partially hydrolyzed with KOH–MeOH–H_2O to give methyl 13-carboxymethyl-7-oxopodocarpa-8,11,13-trien-15-oate (**23**) in 90% yield. Hydrogenolysis of **23** over Pd-C in AcOH gave methyl 13-carboxymethylpodocarpa-8,11,13-trien-15-oate (**24**) in a quantitative yield. The half ester (**24**) was characterized, by treatment with CH_2N_2, as the corresponding diester, methyl 13-methoxycarbonylmethylpodocarpa-8,11,13-trien-15-oate (**25**). The side chain of **24** was extended by one carbon unit by the Arndt-Eistert reaction. The half ester (**24**) was treated with $SOCl_2$ in abs. C_6H_6 in the presence of a trace of pyridine at room temperature and successively with CH_2N_2 to give a diazoketone, followed with Ag_2O in refluxing MeOH to give methyl 13-(2′-methoxycarbonylethyl)-podocarpa-8,11,13-trien-15-oate (**26**) in *ca.* 85% purity (monitored by gas–liquid chromatography (GLC)) in *ca.* 46% overall yield.

The diester (**26**) was also synthesezed from **22**. Methyl 13-(2′-oxopropyl)-podocarpa-8,11,13-trien-15-oate (**27**), derived from **22** on hydrogenolysis over Pd-C in AcOH (90% yield), was subjected to the Willgerodt reaction with $(NH_4)_2S_x$ in a sealed tube at 170° and successively hydrolyzed with NaOH–H_2O, followed by methylation with CH_2N_2 to give **26** in 17% yield.

Haloform reaction of **22** and **27**, on the other hand, gave methyl 13-carboxy-7-oxopodocarpa-8,11,13-trien-15-oate (**28**) and methyl 13-carboxypodocarpa-8,11,13-trien-15-oate (**29**) in 19% and 76% yields, respectively.

TABLE I. NMR Spectra ($CDCl_3$) of **31**, **37**, **32** and **38**

	Aromatic	4-CO_2CH_3	16-CH_2 in **31** and **37** 19-CH_2 in **32** and **38**	17-CH_3 in **37** 18-CH_3 in **38**	4,10-CH_3
31	7.24 d (12–H) 7.49 d (11–H) (*J* =8.5 Hz)	3.62	unidentified	—	1.20 1.26
37	7.26 d (12–H) 7.55 d (11–H) (*J* =8.5 Hz)	3.63	2.50 s	1.34 1.37	1.21 1.26
32	7.13 s (14–H) 7.68 s (11–H)	3.63	unidentified	—	1.19 1.27
38	7.12 s (14–H) 1.60 s (11–H)	3.64	2.51 s	1.36	1.17 1.25
	(7.12 7.61)	(3.64)	(2.51 s)	(1.38)	(1.19 1.28) a)

a) data from reference 5 (also see footnote 23)

In order to form a D-ring, methyl 13-carboxyethylpodocarpa-8,11,13-trien-15-oate (**30**), obtained from **26** by partial hydrolysis with KOH–MeOH–H_2O (98%), was treated with AcCl and $AlCl_3$ in CS_2 at room temperature to give two kinds of cyclized product (**31** and **32**) in 48% and 16% yields, respectively. The former (**31**) showed absorption bands at 1720 and 1695 cm^{-1} for carbonyl groups in its IR spectrum ($CHCl_3$) and signals at 1.20 and 1.26 for the 4- and 10-methyl groups, 3.62 for the 4-methoxycarbonyl group and 7.24 (d, $J=8.5$ Hz, 12-H) and 7.49 (d, $J=8.5$ Hz, 11-H) for the two aromatic protons in its NMR spectrum. The latter (**32**) showed absorption bands at 1725—1700 cm^{-1} for the carbonyl groups ($CHCl_3$) and signals at δ 1.19 and 1.27 for the 4- and 10-methyl groups, 3.63 for the 4-methoxycarbonyl group and 7.13 (s, 14-H) and 7.68 (s, 11-H) for the two aromatic protons in its NMR spectrum. The structure of **31** and **32** was determined by analyses of their NMR spectra due to aromatic protons (see Table I) and by comparison of the NMR data of the cyclized products (**37** and **38**) whose structures were confirmed by the nuclear Overhauser effect (NOE) as mentioned below. Therefore, the steroidal D-ring was synthesized by the use of two or three carbon units of the isopropyl group of **1**.

Although the conditions of acid chlorination, Lewis acid and the solvent were changed as shown in Table II, the yield of **31** did not increase in all the runs, as shown in parentheses, even though the total yield of **31** and **32** was increased in Run 5.

TABLE II. Cyclization Reaction of **30**[a]

$$\mathbf{30} \xrightarrow[\text{2) Friedel-Crafts reaction}]{\text{1) acid chlorination}} \mathbf{31} + \mathbf{32}$$

Run No.	Reagent of chlorination	Lewis acid	Solvent	Reaction time (hr)	Product ratio[b] of 31 : 32	Yield [%][c]
1	AcCl (*in situ*)	$AlCl_3$	CS_2	20	2.30:1	64.5(48[d])
2	AcCl (*in situ*)	$SnCl_4$	CS_2	25	—	Nil[e]
3	AcCl (*in situ*)	$SnCl_4$	C_6H_6	25	—	Nil[e]
4	$SOCl_2$, pyridine	$AlCl_3$	CS_2	18	1.37:1	46(26)
5	$SOCl_2$, pyridine	$AlCl_3$	C_6H_6	23	1.14:1	88.5(47)
6	$SOCl_2$, pyridine	$SnCl_4$	CS_2	23	3.75:1	33[f](26[f])
7	$SOCl_2$, pyridine	$SnCl_4$	C_6H_6	25	3.06:1	63(47.5)

a) All reactions were carried out at room temperature.
b) measured from the half-hight width × hight in the GLC chart
c) mixed yields of **31** and **32** after separation on alumina or Florisil chromatography, exept for Run 6 (parenseses are the yield of **31** calculated from the products ratio and mixed yields of **31** and **32**)
d) separated yield of **31**
e) checked by GLC
f) crude yield

On the other hand, 1,1-dichloroethylene added to the double bond of **20** in the presence of 8% BF_3·etherate–H_2SO_4 solution[7] to give methyl 13-(2′-carboxy-1′,1′-dimethylethyl)-7-oxo-podocarpa-8,11,13-trien-15-oate (**33**) ($\nu_{\max}^{\mathrm{CCl_4}}$ cm^{-1}: 3650—2300, 1730, 1710, 1690) in 77% yield, which was characterized, by treatment with CH_2N_2, as the corresponding diester, methyl 13-(1′,1′-dimethyl-2′-methoxycarbonylethyl)-7-oxopodocarpa-8,11,13-trien-15-oate (**34**). The IR spectrum (CCl_4) showed absorption bands at 1735, 1730, and 1685 cm^{-1}. The NMR spectrum (CCl_4) provided signals at δ 1.45 (s) for the 1′-methyl groups, 3.53 and 3.64 for the respective 2′- and 4-methoxycarbonyl groups and no signal for an isopropenyl group. Hydrogenolysis of **33** over Pd-C in AcOH gave methyl 13-(2′-carboxy-1′,1′-dimethylethyl)-podocarpa-8,11,13-trien-15-oate (**35**) in a quantitative yield. The half ester (**35**) was characterized, by treatment with CH_2N_2, as the corresponding diester, methyl 13-(1′,1′-dimethyl-2′-methoxycarbonyl-ethyl)-podocarpa-8,11,13-trien-15-oate (**36**). The half ester (**35**) was treated under the same conditions as those of **30** to give two kinds of cyclized product (**37** and **38**) in 51% and 15% yield, respectively. The former (**37**) showed absorption bands at 1720 and 1695 cm^{-1} for the carbonyl groups in its IR spectrum ($CHCl_3$) and signals at 1.21 and 1.26 for the 4- and 10-methyl groups, 1.34 and 1.37 for the 17-dimethyl groups, 2.50 (s) for the 16-methylene group, 3.63 for the 4-methoxycarbonyl group and 7.26 (d, J=8.5 Hz, 12-H) and 7.55 (d, J=8.5 Hz, 11-H) for the two aromatic protons in its NMR spectrum. Irradiations of the 17-dimethyl and 10-methyl signals resulted in 28% enhancement (NOE) of the 12-proton and 9% enhancement of the 11-proton, respectively. The latter (**38**)[23] showed absorption bands at 1725—1700 cm^{-1} for the carbonyl groups in its IR spectrum ($CHCl_3$) and signals at δ 1.17 and 1.25 for the 4- and 10-methyl groups, 1.36 (s) for the 18-dimethyl groups, 2.51 (s) for the 19-methylene group, 3.64

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[23] The physical constants of **38**, except for its melting point, were identical with those of the authentic sample.[5] The difference in the melting point can be considered as due to polymorphism or a crystal solvent.

for the 4-methoxycarbonyl group and 7.12 (s, $W_{1/2}$=2.5 Hz, 14-H) and 7.60 (s, $W_{1/2}$=2.5 Hz, 11-H) for the two aromatic protons in its NMR spectrum. A NOE was observed between the 18-methyl groups and 14-proton by 16%, when irradiated at the former. These results were reasonable for the given structures (**37** and **38**). Therefore, the steroidal D-ring was synthesized by the use of one carbon unit of the isopropyl group of **1**.

Though the cyclization reaction of **35** was performed in CF_3CO_2H in $(CF_3CO)_2O$, it could not give a better result.

It is noticeable that the cyclization to 14-position in **30** and **35** was always predominant over that to the 12-position (intramolecular Friedel-Crafts reaction), in contrast to the acylation of **3** which occurred almost exclusively at 12-position[24] (intermolecular Friedel-Crafts reaction), even though the 12-position was not blocked. The reason why the predominant acylation site differs between the intramolecular and intermolecular reactions is under investigation.

The main products (**31** and **37**) having a steroidal skeleton could be the key intermediates for the chemical conversion of a diterpene to steroids, by combination of the modification of the A-ring.[25]

Experimental

Boiling and melting points are uncorrected. Melting points were measured on a micro hot-stage. NMR spectra were measured at 60 MHz, when not mentioned, in CCl_4 or $CDCl_3$ *vs.* Me_4Si as internal reference. High-resolution mass spectra (high-MS) were taken with a JEOL JMS-01SG spectrometer. Retention times (t_R) of GLC were detected by using a glass column (1.5% OV-17 on Shimalite W (80—100 mesh), 4 mm × 2.0 m) and N_2 as carrier gas. Optical rotatory dispersion (ORD) were taken with a JASCO MODEL ORD/UV-5 spectrometer.

Methyl 12-Acyldehydroabietate (4)——Powdered $AlCl_3$ (43.3 g) was added cautiously to a stirred solution of methyl dehydroabietate (3) (10.00 g) and AcCl (25.3 g) in CS_2 (200 ml) under ice cooling, which was stirred at room temperature for one day. After cautious addition of water to the reaction mixture with stirring, the organic layer was separated. The water layer was extracted with ether. The combined organic layer was washed with brine and dried over Na_2SO_4. Evaporation of the solvent gave a crystal, which was recrystallized with $MeOH-H_2O$ to give 4[5] (10.89 g; 96%), IR $\nu_{max}^{CCl_4}$ cm^{-1}: 1730, 1685.

Methyl 12-Acetoxydehydroabietate (5)——To a stirred solution of **4** (5.00 g) in CH_2Cl_2 (11 ml) was added portionwise a solution of *ca.* 40% peracetic acid prepared from AcOH (7.06 g), conc. H_2SO_4 (0.08 ml) and 90% H_2O_2 solution[26] (6.44 ml) under ice cooling, which was stirred under dark at room temperature for 4 days. After addition of sat. $NaHCO_3$ solution to the reaction mixture with stirring under ice cooling, the organic layer was separated. The water layer was extracted with ether. The combined organic layer was washed with sat. $NaHCO_3$ solution and brine and dried over Na_2SO_4. Evaporation of the solvent gave a gum (5.31 g), which was recrystallized with $MeOH-H_2O$ to give **5** (3.45 g, 66%) as the first crop. The mother liquor was concentrated and the residue was recrystallized with $MeOH-H_2O$ to give **5** (0.38 g; 7%) as the second crop. The combined yield was 73%. Two more recrystallizations gave an analytical sample, mp 99—101° (lit.[5] mp 113—114°). IR $\nu_{max}^{CCl_4}$ cm^{-1}: 1740, 1725. NMR δ ($CDCl_3$): 1.19 (d, J=7 Hz, 6H, isopropyl), 1.22, 1.28 (each s, 3H × 2, CH_3 × 2), 2.32 (s, 3H, $OCOCH_3$), 3.68 (s, 3H, CO_2CH_3), 6.85 (s, 1H, 11-H), 6.96 (s, 1H, 14-H). *Anal.* Calcd. for $C_{23}H_{32}O_4$: C, 74.16; H, 8.66. Found: C, 74.29; H, 8.50.

Methyl 12-Hydroxydehydroabietate (6)——A) From **5**: A solution of **5** (3.20 g) in MeOH (320 ml) was refluxed with conc. H_2SO_4 (0.2 ml) for 2 hr. After evaporation of the solvent, the residue was dissolved in ether and it was washed with sat. $NaHCO_3$ solution and brine and dried over Na_2SO_4. Evaporation of the solvent gave a crystal, which was recrystallized with $MeOH-H_2O$ to give **6** (2.30 g; 79%) as the first crop. The mother liquor was concentrated, and the residue was recrystallized with $MeOH-H_2O$ to give **6** (0.31 g; 11%). The combined yield was 90%. Two more recrystallizations gave an analytical sample, mp 155—156° (lit. 156—157°,[27] mp 160—161°[5]). IR $\nu_{max}^{CCl_4}$ cm^{-1}: 3640, 1730. NMR δ ($CDCl_3$): 1.18, 1.27 (each s, 3H × 2,

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[24] It was reported that the Friedel-Crafts acylation of **3** with AcCl and $AlCl_3$ in $Cl_2CHCHCl_2$ or nitrobenzene gave a very low yield of methyl 14-acyldehydrobaietate in addition to **4**.[5] Also see L.F. Fieser and W.P. Campbell, *J. Am. Chem. Soc.*, **60**, 2631 (1938); *idem*, *ibid.*, **61**, 2528 (1939).

[25] *e.g.* A. Brossi, H. Gutmann, and O. Jeger, *Helv. Chim. Acta*, 33, 1730 (1950); H.H. Zeiss and W.B. Martin Jr., *J. Am. Chem. Soc.*, **75**, 5935 (1953); J.W. Huffmann, *J. Org. Chem.*, **35**, 478 (1970); R.C. Cambie, W.A. Denny, T.J. Fullerton, and R.C. Hayward, *Aust. J. Chem.*, **27**, 1317 (1974); Y. Harigaya, M. Onda, and A. Tahara, *Chem. Pharm. Bull.* (Tokyo), **23**, 1989 (1975); *idem, ibid.*, **23**, 1996 (1975)

[26] F.P. Greenspan, *J. Am. Chem. Soc.*, **68**, 907 (1946).

$CH_3 \times 2$), 1.22 (d, $J=7$ Hz, isopropyl), 3.64 (s, 3H, CO_2CH_3), 4.61 (b.s, 1H, OH), 6.63 (s, 1H, 11-H), 6.82 (s, 1H, 14-H). *Anal.* Calcd. for $C_{21}H_{30}O_3$: C, 76.63; H, 9.15. Found: C, 76.45; H, 8.94.

B) PtO_2 Reduction of $Pb(OAc)_4$ Oxidation Products of **6**: A mixture of **6** (82.1 mg) and $Pb(OAc)_4$ (175 mg) in abs. C_6H_6 (3 ml) was stirred at room temperature for 4 days. The reaction mixture was filtered, and the filtrate was washed with sat. $NaHCO_3$ solution and brine and dried over Na_2SO_4. Evaporation of the solvent gave a gum (102 mg), which was shaken in AcOEt (10 ml) with PtO_2 (30 mg) under H_2 atmosphere at room temperature for 1.5 hr. After removal of the catalyst by filtration, the filtrate was concentrated to give a crystal (91 mg), which was chromatographed on silica gel (9 g) with pet. ether–ether (10: 1) as eluant to give **6** (42 mg; 51%). The physical constants (GLC, IR, NMR) were identical with those of the sample mentioned above.

Methyl 12,14-Dihydroxydehydroabietate (9)——A) From **6**: A mixture of **6** (200 mg) and $Pb(OAc)_4$ (425 mg) in abs. C_6H_6 (8 ml) was stirred at room temperature for 4 days. The reaction mixture was filtered, and the filtrate was washed with sat. $NaHCO_3$ solution and brine and dried over Na_2SO_4. Evaporation of the solvent gave a gum, a crude mixture of methyl 8-acetoxy-13-isopropyl-12-oxopodocarpa-9(11),13-dien-15-oate (**7**) and methyl 13-acetoxy-13-isopropyl-12-oxopodocarpa-8(14),9(11)-dien-15-oate (**8**) (250 mg), IR $\nu_{\max}^{CCl_4}$ cm^{-1}: 1760, 1725, 1670. UV $\lambda_{\max}^{EtOH}$ mμ: 245, 322.

As it was known in a preliminary experiment that the mixture of **7** and **8** could not be separated by silica gel chromatography, the following experiment was performed without purification. A solution of the mixture of **7** and **8** in $(CF_3CO)_2O$ (1.4 ml) was left standing at room temperature for 36 hr and the solvent was removed at room temperature to give a gum (337 mg), IR $\nu_{\max}^{CCl_4}$: 3520 (b), 1795, 1725.

A solution of the gum (337 mg) in MeOH (20 ml) and water (0.8 ml) with trace of conc. H_2SO_4 was refluxed for 2 hr. After water was added, the mixture was acidified with conc. HCl and extracted with ether. The ethereal layer was washed with sat. $NaHCO_3$ solution and brine and dried over Na_2SO_4. Evaporation of the solvent gave a gum (242 mg), which was chromatographed on silica gel (25 g) with pet. ether–ether (10:1) as eluant to give **9** (188 mg; 90%), mp 167.5—168° (ether–pet. ether). GLC: $t_R=8.7$ min (250°). IR $\nu_{\max}^{CHCl_3}$ cm^{-1}: 3615, 1715. NMR δ ($CDCl_3$): 1.17, 1.25 (each s, $3H \times 2$, $CH_3 \times 2$), 1.33 (d, $J=8$ Hz, 6H, isopropyl), 3.64 (s, 3H, CO_2CH_3), 4.64 (b.s, 2H, 12,14-OH), 6.24 (s, 1H, 11-H). *Anal.* Calcd. for $C_{21}H_{30}O_4$: C, 72.80; H, 8.73. Found: C, 72.99; H, 8.77.

The yield (35—90%) was varied from batch to batch.

B) From **14**: To a solution of conc. H_2SO_4 (0.35 ml) in water (0.35 ml) was added $NaNO_2$ (7.9 mg) below 0°. The temperature of the mixture was raised to room one with stirring to dissolve $NaNO_2$. The mixture was cooled again below $-5°$, and a solution of **14** (34.4 mg) in pyridine (0.45 ml) was added slowly with stirring, and then a little ice water to stir easily. Stirring and cooling below 0° was continued for 60 min and water was added until the volume came to *ca.* 3.5 ml. Urea (20.0 mg) was added and it was stirred below 0° for 30 min. The mixture was added quickly to boiling water (*ca.* 5 ml) and it was boiled with stirring for 10 min. After cooling, the reaction mixture was extracted with ether. The extract was washed with brine and dried over Na_2SO_4. After evaporation of the solvent, the residue was chromatographed on silica gel (5 g) with pet. ether–ether (10: 1) to give **9** (8.1 mg; 24%) and then recover **14** (5.7 mg; 17%). The dihydroxyl derivative (**9**) was recrystallized twice with pet. ether–ether to give a sample, mp 167—168° (sintered at 164°). Mixed mp 167—168° (sintered at 164°). GLC: $t_R=8.7$ min (250°).

The retention time (t_R) of GLC and the IR and NMR spectra were identical with those of **9** prepared from **6** *via* a mixture of **7** and **8**.

Methyl 12,14-Diaminodehydroabietate (11)——A suspension of **10**[13] (300 mg) and Sn powder (600 mg) in MeOH (3.0 ml) was refluxed with stirring. Conc. HCl (2.5 ml) was added portionwise to the suspension in 6 hr, and it was refluxed with stirring for another 5 hr. After filtration, the filtrate was concentrated and alkalined with 10% KOH solution. The solution was extracted with ether. The extract was washed with brine and dried over Na_2SO_4. Evaporation of the solvent gave crude **11**[14] (215 mg), IR $\nu_{\max}^{CHCl_3}$: 3500(b), 3420 (b), 1715. NMR δ ($CDCl_3$): 1.18, 1.23 (each s, $3H \times 2$, $CH_3 \times 2$), 1.36 (d, $J=7.5$ Hz, 6H, isopropyl), 3.61 (b.s, 7H, CO_2CH_3 and 12,14-NH_2; D_2O treatment gave 3H as a singlet), 6.13 (s, 1H, 11-H).

The crude diamino derivative (**11**) was used, without purification, for the following reaction.

Treatment of 11 in Diazotization Conditions, followed in Hydrolysis Conditions——To a solution of conc. H_2SO_4 (0.5 ml) in water (0.5 ml) was added $NaNO_2$ (50.0 mg) below 0°. The temperature of the mixture was raised to room one with stirring to dissolve $NaNO_2$. The mixture was cooled again below $-5°$, and a solution of crude **11** (51.0 mg) in pyridine (0.5 ml) was added slowly with stirring, and then a little ice water to stir easily. Stirring and cooling below 0° was continued for 60 min and water was added until the volume came to *ca.* 10 ml. Urea (30.0 mg) was added and it was stirred below 0° for 30 min. The mixture was added quickly to boiling water (10 ml) and it was boiled with stirring for 10 min. After cooling, the reaction mixture was extracted with ether. The extract was washed with brine and dried over Na_2SO_4. Evaporation of a solvent gave a gum (43.4 mg), which was chromatographed on silica gel (5 g) with pet. ether–ether (10: 1—7: 1) as eluant but it gave intractable product(s).

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27) L.F. Fieser and W.P. Campbell, *J. Am. Chem. Soc.*, **61**, 2528 (1939).

Methyl 12-Amino-14-nitrodehydroabietate (12)——According to Ochiai and his co-worker's method,[15] **10** was partially reduced to **12**.

Methyl 12-Hydroxy-14-nitrodehydroabietate (13)——To a solution of conc. H_2SO_4 (3.0 ml) in water (3.0 ml) was added $NaNO_2$ (300 mg) below 0°. The temperature of the mixture was raised to room one with stirring to dissolve $NaNO_2$. The mixture was cooled again below $-5°$, and a solution of **12** (300 mg) in pyridine (4.0 ml) was added slowly with stirring, and then a little ice water to stir easily. Stirring and cooling below 0° was continued for 60 min and water was added until the volume came to *ca.* 30 ml. Urea (180 mg) was added and it was stirred below 0° for 30 min. The mixture was added quickly to boiling water (*ca.* 45 ml) and it was boiled with stirring for 10 min. After cooling, the reaction mixture was extracted with ether. The extract was washed with brine and dried over Na_2SO_4. After evaporation of the solvent, the residue was chromatographed on silica gel (30 g) with pet. ether–ether (8: 1) as eluant to give **13** (162 mg; 54%), mp 224—225.5° (ether–pet. ether). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3610, 3315 (b), 1720. NMR δ ($CDCl_3$): 1.19, 1.26 (each s, 3H × 2, $CH_3 \times 2$), 1.32 (d, $J=7.5$ Hz, 6H, isopropyl), 3.67 (s, 3H, CO_2CH_3), 5.31 (s, 1H, 12-OH), 6.72 (s, 1H, 11-H). *Anal.* Calcd. for $C_{21}H_{29}O_5N$: C, 67.18; H, 7.79; N, 3.73. Found: C, 67.54; H, 7.86; N, 3.93. More elution with pet. ether–ether (6: 1) recovered **12** (35 mg; 12%).

Methyl 14-Amino-12-hydroxydehydroabietate (14)——To a solution of **13** (74.0 mg) in MeOH (2.0 ml) was added Sn powder (151 mg) and conc. HCl (0.6 ml), and it was refluxed with stirring for 6 hr. After evaporation of the solvent, water was added to the residue and it was extracted with ether. The extract was washed with 10% Na_2CO_3 solution and brine and dried over Na_2SO_4. Evaporation of the solvent gave a crystal (69.4 mg), which was recrystallized from ether–*n*-hexane to give **14** (50.0 mg; 74%). Two more recrystallization gave an analytical sample, mp 165.5—167°. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3625, 3520 (b), 3420 (b), 1715. NMR δ ($CDCl_3$): 1.16, 1.25 (each s, 3H × 2, $CH_3 \times 2$), 1.35 (d, $J=7.5$ Hz, 6H, isopropyl), 3.64 (s, 3H, CO_2CH_3), 4.1 (b.s, 3H, 12-OH and 14-NH_2), 6.15 (s, 1H, 11-H). *Anal.* Calcd. for $C_{21}H_{31}O_3N$: C, 73.00; H, 9.05; N, 4.05. Found: C, 73.01; H, 9.02; N, 3.91.

Methyl 12β-Hydroxy-13β-isopropyl-8α-podocarpan-15-oate (15)——A) From **6**: The phenol (**6**) (300 mg) and RuO_2 (60 mg) in EtOH (50 ml) were shaken under 130 kg/cm^2 of H_2 pressure at 80° for 24 hr. After cooling, the catalyst was removed by filtration and washed with ether. Concentration of the combined organic filtrate gave an oil (315 mg), which was chromatographed on silica gel (30 g) with pet. ether–ether (10: 1) as eluant to give **15** (194 mg; 63.5%), mp 103—103.5° (*n*-hexane) (lit.[18] mp 110—111°). IR $\nu_{max}^{CCl_4}$ cm^{-1}: 3630, 1725. NMR δ ($CDCl_3$): 0.93, 0.96 (each d, $J=6$ Hz, 3H × 2, isopropyl), 1.12, 1.20 (each s, 3H × 2, $CH_3 \times 2$), 3.67 (s, 3H, CO_2CH_3), 4.04 (b.s, $W_{1/2}=10$ Hz, 12-H). *Anal.* Calcd. for $C_{21}H_{36}O_3$: C, 74.95; H, 10.78. Found: C, 75.08; H, 10.73.

B) From **16**[18]: A solution of **16** (200 mg) in MeOH (3 ml) was stirred with $NaBH_4$ (50 mg) at room temperature for 20 hr. The reaction mixture was diluted with ether and it was washed with water and dried over Na_2SO_4. Evaporation of the solvent gave **15** (200 mg). The physical constants (GLC, IR, NMR) were identical with those of the sample prepared from **6**.

Methyl 13β-Isopropyl-12-oxo-8α-podocarpan-15-oate (16)——Jones reagent (0.25 ml) was added to a stirred solution of **15** (100.0 mg) in acetone (10 ml) under ice cooling. The mixture was continued to stir under the same conditions for 60 min, and then MeOH (7.5 ml) was added. After evaporation of the solvent at room temperature, the residue was dissolved with ether, and it was washed with sat. $NaHCO_3$ solution and brine and dried over Na_2SO_4. Evaporation of the solvent gave a crystal, which was chromatographed on alumina (10 g) with pet. ether–ether (10: 1) as eluant to give **16** (83.7 mg; 84%), mp 115.5—116.5° (MeOH–H_2O) (lit.[19] 116°). IR $\nu_{max}^{CCl_4}$ cm^{-1}: 1725, 1705 and $\nu_{max}^{CHCl_3}$: 1715, 1700. NMR δ ($CDCl_3$): 0.83, 0.90 (each d, $J=6.5$ and 7 Hz, respectively, 3H × 2, isopropyl), 0.84, 1.15 (each s, 3H × 2, $CH_3 \times 2$), 3.66 (s, 3H, CO_2CH_3). ORD ($c=0.001$, dioxane) $[\alpha]^{22}$ (mμ): $+345°$ (304.5) (peak), 0° (280), $-95.5°$ (270) (trough). *Anal.* Calcd. for $C_{21}H_{34}O_3$: C, 75.40; H, 10.25. Found: C, 75.47; H, 10.18.

A solution of **15** (30 mg) in abs. MeOH (1 ml) was refluxed with NaOMe (prepared from Na (25 mg)) for 9 hr. The usual treatment recovered **15** (29.3 mg).[19]

A Six-membered Ether (17)——A suspension of **15** (335.0 mg), $CaCO_3$ (670 mg) and $Pb(OAc)_4$ (1.67 g) in abs. cyclohexane (135 ml) was refluxed with stirring for 24 hr. The reaction mixture was filtered and the filter paper was washed with ether. The combined organic filtrate was washed with sat. $NaHCO_3$ solution and brine and dried over Na_2SO_4. Evaporation of the solvent gave an oil (456.3 mg), which was chromatographed on Florisil (45 g) with pet. ether–ether (10: 1) as eluant to give **17** (46.4 mg; 14%), IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1720. NMR δ ($CDCl_3$): 0.92, 0.95 (each d, $J=5.5$ and 6 Hz, respectively, 3H × 2, isopropyl), 1.02 (s, 3H, CH_3), 3.64 (s, 3H, CO_2CH_3), 3.7—4.2 (unidentified m, 3H, 12-H and 17-CH_2).

A preparative thin-layer chromatography (TLC) (silica gel [Merck, PF_{254}]; 20 g, 20 cm × 20 cm) eluted three times with C_6H_6, and, successively, distillation gave an analytical sample, bp 130—140° (bath, 0.001 mmHg). *Anal.* Calcd. for $C_{21}H_{34}O_3$: C, 75.40; H, 10.25. Found: C, 75.48; H, 10.26. High-MS Calcd. (M^+; *m/e*): 334.2508. Found: 334.2478.

Methyl 13-Acyl-7-oxopodocarpa-8,11,13-trien-15-oate (18) and Methyl 13-Isopropenyl-7-oxopodocarpa-8,11,13-trien-15-oate (20) *via* a Mixture of 18 and Methyl 13-(1′-Acetoxy-1′-methylethyl)-podocarpa-8,11,13-trien-15-oate (19)——To a solution of **3** (43.9 g) in AcOH (300 ml) and Ac_2O (220 ml) was slowly added CrO_3

(60.5 g) in 4 hr with stirring at room temperature, which was stirred overnight in the same conditions. To the reaction mixture was added AcONa aq. solution (6.0 g/175 ml), MeOH (100 ml) and water, and it was extracted with C_6H_6. The extract was washed with water, 10% Na_2CO_3 solution and brine and dried over Na_2SO_4. Evaporation of the solvent gave a gum (46.0 g) which contained a mixture of **18** and **19**. The gum was heated, with addition of pieces of glass (10 g), at 205—210° for 5 hr under reduced pressure (aspirator). After cooling, C_6H_6 was added to the reaction mixture and it was filtered to separate the glass. The filtrate was concentrated to give a gum (38.0 g), which was chromatographed on alumina (800 g) with *n*-hexane–C_6H_6 (3: 1) as eluant to give **20** (12.8 g; 28%) and with *n*-hexane–C_6H_6 (1: 4) to give **18** (10.7 g; 24%). The physical constants (GLC, IR, NMR) of **18** and **20** were identical with those of the authentic samples.[21,22]

Methyl 13-Methoxycarbonylmethyl-7-oxopodocarpa-8,11,13-trien-15-oate (**21**)——To a solution of **18** (1.00 g) in MeOH (50 ml) was added 70% $HClO_4$ (10 ml) and then Tl $(ONO_2)_3 \cdot 3H_2O$[6b] (1.80 g) with stirring at room temperature. After stirring in the same conditions for 12 hr, water was added and the crystals were filtered off. The filtrate was extracted with ether and the extract was washed with sat. $NaHCO_3$ solution and brine and dried over Na_2SO_4. Evaporation of the solvent gave **21** (1.10 g), bp 151° (bath, 0.0033 mmHg). IR $\nu_{\max}^{\mathrm{CCl_4}}$ cm^{-1}: 1730, 1690. NMR δ (100 MHz, CCl_4): 1.24, 1.30 (each s, 3H × 2, CH_3 × 2), 3.54 (s, $W_{1/2}$= 2 Hz, 1′-H), 3.64 (s, 6H, 4,1′-CO_2CH_3), 7.25 (d, J=8 Hz, 1H, 11-H), 7.40 (d.d, J=2 and 8 Hz, 1H, 12-H), 7.77 (d, J=2 Hz, 1H, 14-H). *Anal.* Calcd. for $C_{21}H_{26}O_5$: C, 70.37; H, 7.31. Found: C, 70.28; H, 7.26. High-MS Calcd. (M^+; *m/e*): 358.1780. Found: 358.1752.

Methyl 7-Oxo-13-(2′-oxopropyl)-podocarpa-8,11,13-trien-15-oate (**22**)——To a solution of **20** (1.00 g) in MeOH (30 ml) was added Tl $(ONO_2)_3 \cdot 3H_2O$[6a] (1.30 g) with stirring at room temperature. After stirring under the same conditions for a few minutes, water was added and the crystals were filtered off. The filtrate was extracted with ether and the extract was washed with sat. $NaHCO_3$ solution and brine and dried over Na_2SO_4. Evaporation of the solvent gave **22** (1.00 g; 95%), mp 131—132° (MeOH). IR $\nu_{\max}^{\mathrm{CCl_4}}$ cm^{-1}: 1730, 1690. NMR δ (100 MHz, CCl_4): 1.26, 1.32 (each s, 3H × 2, CH_3 × 2), 2.10 (s, 3H, $COCH_3$), 3.16 (s, $W_{1/2}$=2 Hz, 1′-H), 3.65 (s, 3H, CO_2CH_3), 7.28 (s, $W_{1/2}$=3 Hz, 2H, 11,12-H), 7.72 (s, $W_{1/2}$=3 Hz, 1H, 14-H). *Anal.* Calcd. for $C_{21}H_{26}O_4$: C, 73.66; H, 7.66. Found: C, 73.68; H, 7.47. High-MS Calcd. (M^+; *m/e*): 342.1831. Found: 342.1810.

Methyl 13-Carboxymethyl-7-oxopodocarpa-8,11,13-trien-15-oate (**23**)——To a solution of **21** (2.44 g) in MeOH (100 ml) and H_2O (0.4 ml) was added KOH (2.20 g), and it was stirred for 2 hr at room temperature. Water was added to the reaction mixture, and it was washed with ether. The water layer was acidified with conc. HCl and extracted with ether. The extract was washed with brine and dried over Na_2SO_4. Evaporation of the solvent gave **23** (2.12 g; 90%), IR $\nu_{\max}^{\mathrm{CHCl_3}}$ cm^{-1}: 3650—2300, 1720, 1680. NMR δ ($CDCl_3$): 1.24, 1.33 (each s, 3H × 2, CH_3 × 2), 3.65 (s, 5H, CO_2CH_3, 1′-H), 7.31 (d, J=7 Hz, 11-H), 7.50 (d.d, J=2.5 and 7 Hz, 12-H), 7.90 (d, J=2.5 Hz, 14-H), 9.90 (b.s, 1H, CO_2H).

The ether washer was washed with brine and dried over Na_2SO_4. Evaporation of the solvent recovered **21** (0.17 g; 7%).

Methyl 13-Carboxymethylpodocarpa-8,11,13-trien-15-oate (**24**)——A mixture of **23** (2.12 g) and 10% Pd-C (0.80 g) in AcOH (100 ml) was shaken overnight at room temperature under H_2 atmosphere. After removal of the catalyst by filtration, the filtrate was concentrated to give **24** (quantitative), IR $\nu_{\max}^{\mathrm{CHCl_3}}$ cm^{-1}: 3630—2300, 1720. NMR δ ($CDCl_3$): 1.20, 1.28 (lach s, 3H × 2, CH_3 × 2), 3.57 (s, 2H, 1′-H), 3.67 (s, 3H, CO_2CH_3), 6.96—7.18 (m, 3H, 11,12,14-H), 9.30 (b.s, 1H, CO_2H).

The half ester (**24**) was treated with CH_2N_2 to give methyl 13-(methoxycarbonylmethyl)-podocarpa-8,11,13-trien-15-oate (**25**), bp 140—145° (bath, 0.01 mmHg). IR $\nu_{\max}^{\mathrm{CHCl_3}}$ cm^{-1}: 1720. NMR δ (100 MHz, CCl_4): 1.18, 1.22 (each s, 3H × 2, CH_3 × 2), 3.39 (s, $W_{1/2}$=2 Hz, 2H, 1′-H), 3.61 (s, 6H, 4,1′-CO_2CH_3), 6.84—7.12 (m, 3H, 11,12,14-H). *Anal.* Calcd. for $C_{21}H_{28}O_4$: C, 73.22; H, 8.19. Found: C, 73.24; H, 8.24. High-MS Calcd. (M^+; *m/e*): 344.1985. Found: 344.1987.

Methyl 13-(2′-Methoxycarbonylethyl)-podocarpa-8,11,13-trien-15-oate (**26**) ***via* Arndt-Eistert Reaction**——To a stirred suspension of **24** (2.19 g) in abs. C_6H_6 (15 ml) was added a solution of $SOCl_2$ (1.0 ml) in abs. C_6H_6 (4 ml) in the presence of a trace of pyridine at room temperature. The suspension was stirred at room temperature for 15 min to a homogeneous solution and the solution was continued to stir for 1 hr and 45 min under the same conditions. Evaporation of the solvent at 30° gave an acid chloride (the reaction without pyridine at room temperature gave none of the desired product or at refluxing temperature a complex mixture), IR $\nu_{\max}^{\mathrm{CHCl_3}}$ cm^{-1}: 1795, 1720.

A solution of the acid chloride in abs. C_6H_6 (10 ml) was added to a KOH-dried ethereal CH_2N_2 prepared from nitrosomethylurea (6.3 g) with vigorous stirring under ice cooling. The mixture was stirred under the same conditions for 30 min and then at room temperature for 2 hr. Evaporation of the excess CH_2N_2 and the solvent at room temperature (below 30°) gave a diazoketone, IR $\nu_{\max}^{\mathrm{CHCl_3}}$ cm^{-1}: 2125, 1720, 1635.

A suspension of Ag_2O (2.28 g) in MeOH (80 ml) was refluxed with stirring for 20 min. The diazoketone in MeOH (80 ml) was added to the above refluxing suspension with stirring and it was treated with the same conditions for 4 hr. Evaporation of the solvent without filtration gave a pasty suspension, which was chromatographed on Florisil (150 g) with pet. ether–ether (3: 1) as eluant to give **26** (1.27 g) as *ca.* 85% purity (monitored by GLC, then the yield was *ca.* 46% from **24**), IR $\nu_{\max}^{\mathrm{CHCl_3}}$ cm^{-1}: 1725. NMR δ ($CDCl_3$): 1.19, 1.27 (each s, 3H × 2, CH_3 × 2), 3.67 (s, 6H, 4,2′-CO_2CH_3), 6.89—7.14 (m, 3H, 11,12,14-H). High-MS Calcd. for

$C_{22}H_{30}O_4$ (M^+; m/e): 358.2144. Found: 358.2154.

Methyl 13-(2′-Oxopropyl)-podocarpa-8,11,13-trien-15-oate (27)——A mixture of **22** (33 mg) and 10% Pd-C (30 mg) in AcOH (5 ml) was shaken overnight at room temperature under H_2 atmosphere. After removal of the catalyst by filtration, the filtrate was concentrated to give **27** (28 mg; 90%), bp 120—125° (bath, 0.013 mmHg). IR $\nu_{\max}^{CCl_4}$ cm^{-1}: 1730, 1720. NMR δ (CCl_4): 1.20, 1.25 (each s, 3H×2, CH_3×2), 2.03 (s, 3H, $COCH_3$), 3.47 (s, 2H, 1′-H), 3.64 (s, 3H, CO_2CH_3), 6.77—7.20 (m, 3H, 11,12,14-H). *Anal.* Calcd. for $C_{21}H_{28}O_3$: C, 76.79; H, 8.59. Found: C, 76.65; H, 8.58. High-MS Calcd. (M^+; m/e): 328.2039. Found: 328.2045.

The Diester (26) from 27——A mixture of **27** (94.7 mg), sulfur (0.2 g) in dioxane (2.5 ml) and ammonium sulfide solution (2.0 ml; prepared from conc. NH_3 solution by saturation with H_2S) was heated in a sealed tube at 170° for 16 hr. After cooling, 15% NaOH solution (4 ml) was added and it was refluxed for 4.5 hr. After addition of water, the mixture was washed with ether. The water layer was acidified with conc. HCl and extracted with ether. The extract was washed with brine and dried over Na_2SO_4. Evaporation of the solvent gave an oil, which was, after esterification with CH_2N_2 chromatographed on Florisil (12.5 g) with pet. ether–ether (5: 1) as eluant to give **26** (17.4 mg; 17%). The physical constants (GLC, IR, NMR, MS) were identical with those of the sample prepared from **24** ***via*** Arndt-Eistert reaction.

Haloform Reaction of 22——A NaOBr solution was prepared by addition of Br_2 (0.246 ml) to a solution of NaOH (600 mg) in water (7.5 ml) with stirring under ice-salt cooling. A solution of **22** (500 mg) in tetrahydrofuran (THF) (30 ml) was added to the NaOBr solution with stirring under ice-salt cooling. After stirring under the same conditions for 3 hr, sat. $NaHCO_3$ solution and then 10% KOH solution were added, and it was washed with ether. The water layer was acidified with conc. HCl and extracted with ether. The extract was washed with brine and dried over Na_2SO_4. Evaporation of the solvent gave a crude methyl 13-carboxy-7-oxopodocarpa-8,11,13-trien-15-oate (**28**) (165.2 mg).

After esterification with CH_2N_2, the product was chromatographed on Florisil (8 g) with pet. ether–ether (1: 1) as eluant to give methyl 13-methoxycarbonyl-7-oxopodocarpa-8,11,13-trien-15-oate (95.2 mg; 19%). The physical constants (GLC, IR, NMR, MS) were identical with those of the authentic sample prepared from **18**.[28)]

Haloform Reaction of 27——A NaOBr solution was prepared from Br_2 (0.156 ml), NaOH (300 mg) and water (2.5 ml) as the same procedure mentioned above. A solution of **27** (50.0 mg) in THF (5 ml) was treated with the NaOBr solution to give methyl 13-carboxypodocarpa-8,11,13-trien-15-oate (**29**) (39.8 mg; 76%). The physical constants (GLC, IR, NMR) of the product by treatment with CH_2N_2 were identical with those of the sample prepared from **18**.[28)]

Methyl 13-(2′-Carboxyethyl)-podocarpa-8,11,13-trien-15-oate (30)——To a solution of **26** (108.2 mg) in MeOH (6.5 ml) and H_2O (2 drops) was added KOH (200 mg), and it was stirred for 12 hr at room temperature. Water was added to the reaction mixture, and it was washed with ether. The water layer was acidified with conc. HCl and extracted with ether. The extract was washed with brine and dried over Na_2SO_4. Evaporation of the solvent gave **30** (101.6 mg; 98%). IR $\nu_{\max}^{CHCl_3}$ cm^{-1}: 3550—2300, 1720, 1715. NMR δ ($CDCl_3$): 1.20, 1.27 (each s, 3H×2, CH_3×2), 3.67 (s, 3H, CO_2CH_3), 6.89—7.14 (m, 3H, 11,12,14-H), 9.67 (b.s, 1H, CO_2H).

Cyclization Reaction of 30 to Cyclized Products (31 and 32)——A) Run 1 in Table II: To a solution of **30** (101.0 mg) in CS_2 (14 ml) was added AcCl (5.6 ml) and then $AlCl_3$ (1.7 g) with stirring under ice cooling. The mixture was stirred at room temperature for 20 hr. Ice water was added to the reaction mixture, and it was extracted with ether. The extract was washed with brine, 5% NaOH solution and brine and dried over Na_2SO_4. Evaporation of the solvent gave an oil (123.0 mg; GLC: **31**: **32**=2.30: 1), which was chromatographed on Florisil (12 g) with pet. ether–ether (1: 1) as eluant to give **31** (46.2 mg; 48%) and then **32** (15.5 mg; 16%). The former (**31**) gave bp 185—190° (bath, 0.013 mmHg). IR $\nu_{\max}^{CHCl_3}$ cm^{-1}: 1720, 1695 and $\nu_{\max}^{CCl_4}$ cm^{-1}: 1725, 1705. NMR δ ($CDCl_3$): 1.20, 1.26 (each s, 3H×2, CH_3×2), 3.62 (s, 3H, CO_2CH_3), 7.24 (d, J=8.5 Hz, 1H, 12-H), 7.49 (d, J=8.5 Hz, 11-H). *Anal.* Calcd. for $C_{21}H_{26}O_3$: C, 77.27; H, 8.03. Found: C, 77.34; H, 8.16. High-MS Calcd. (M^+; m/e): 326.1882. Found: 326.1874.

The latter (**32**) gave bp 180—185° (bath, 0.012 mmHg). IR $\nu_{\max}^{CHCl_3}$ cm^{-1}: 1725—1700 and $\nu_{\max}^{CCl_4}$ cm^{-1}: 1725, 1710. NMR δ ($CDCl_3$): 1.19, 1.27 (each s, 3H×2, CH_3×2), 3.63 (s, 3H, CO_2CH_3), 7.13 (s, 1H, 14-H), 7.68 (s, 1H, 11-H). *Anal.* Calcd. for $C_{21}H_{26}O_3$: C, 77.27; H, 8.03. Found: C, 77.25; H, 8.07. High-MS Calcd. (M^+; m/e): 326.1882. Found: 326.1906.

The former (**31**) was not changed when left standing at room temperature, but the latter (**32**) was changed (it may be air-oxidized at the 7-position). This may cause the difference between the GLC's and separated products' ratios.

B) Run 2 in Table II: To a solution of **30** (13.5 mg) in CS_2 (0.5 ml) was added AcCl (0.5 ml) and then $SnCl_4$ (100 μl) with stirring under ice cooling. The mixture was stirred at room temperature for 25 hr. Ice water was added to the reaction mixture, and it was extracted with ether. The extract was washed with 1N NaOH solution and brine and dried over Na_2SO_4. Evaporation of the solvent gave an oil (7.8 mg), which gave no sign of **31** or **32** by its GLC.

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28) M. Ohta, *Pharm. Bull. Japan*, **4**, 273 (1956).

C) Run 3 in Table II: The same treatment, mentioned above, except for the change of the solvent from CS_2 to abs. C_6H_6, gave no sign of **31** or **32** by its GLC.

D) Run 4 in Table II: To a solution of **30** (69.5 mg) in abs. C_6H_6 (2 ml) was added a solution of $SOCl_2$ (0.1 ml) in abs. C_6H_6 (0.5 ml) with existence of a trace of dry pyridine with stirring at room temperature. The solution was stirred in the same conditions for 2 hr. Evaporation of the solvent at room temperature gave an acid chloride, IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1800, 1720.

To a solution of the acid chloride in CS_2 (10 ml) was added $AlCl_3$ (1.2 g) with stirring under ice cooling. The mixture was stirred at room temperature for 18 hr. Ice water was added to the reaction mixture, and it was extracted with ether. The extract was washed with brine, 5% NaOH solution and brine and dried over Na_2SO_4. Evaporation of the solvent gave an oil (58.1 mg; GLC: **31**: **32**=1.37: 1), which was chromatographed on Florisil (6 g) with pet. ether–ether (3: 1) as eluant to give a mixture of **31** and **32** (30.1 mg; 46%).

E) Run 5 in Table II: To a solution of the acid chloride, prepared as the same procedure mentioned above from **30** (51.0 mg) in abs. C_6H_6 (2 ml) and $SOCl_2$ (0.05 ml) in abs. C_6H_6 (0.5 ml), in abs. C_6H_6 (7.5 ml) was added $AlCl_3$ (0.88 g) with stirring under ice cooling and it was stirred at room temperature for 23 hr. The usual treatment gave an oil (60.4 mg; GLC: **31**: **32**=1.14: 1), which was chromatographed on Florisil (6 g) with *n*-hexane–ether (3: 1—1: 1) to give **31** (22.5 mg; 47%), a mixture of **31** and **32** (12.1 mg; 25%) and **32** (8.1 mg; 17%).

F) Run 6 in Table II: To a solution of the acid chloride, prepared from **30** (50.5 mg) in abs. C_6H_6 (2 ml) and $SOCl_2$ (0.05 ml) in abs. C_6H_6 (0.5 ml), in CS_2 (1.6 ml) was added $SnCl_4$ (1.6 ml) with stirring under ice cooling and it was stirred at room temperature for 23 hr. The usual treatment gave an oil (15.7 mg; GLC: **31**: **32**=3.75: 1).

G) Run 7 in Table II: To a solution of the acid chloride, prepared from **30** (31.9 mg) in abs. C_6H_6 (0.5 ml) and $SOCl_2$ (0.1 ml) in abs. C_6H_6 (0.5 ml), in abs. C_6H_6 (1 ml) was added $SnCl_4$ (1 ml) with stirring under ice cooling and it was stirred at room temperature for 25 hr. The usual treatment gave an oil (20.5 mg; GLC: **31**: **32**=3.06: 1), which was chromatographed on Florisil (3 g) with *n*-hexane–ether (3: 1) to give **31** (15.9 mg; 50%) and a mixture of **31** and **32** (4.2 mg; 13%).

Methyl 13-(2′-Carboxy-1′,1′-dimethylethyl)-7-oxopodocarpa-8,11,13-trien-15-oate (**33**)——To a solution of **20** (1.65 g) in 1,1-dichloroethylene (5 ml) was added 8 v/v-% BF_3·etherate–conc. H_2SO_4 solution (10 ml) with stirring below −5°. After stirring under the same conditions for 1.5 hr, the reaction mixture was poured onto ice-water (100 ml) and it was extracted with ether. The ether layer was washed with brine and extracted with 10% KOH solution. The alkaline extract was acidified with conc. HCl and extracted with ether. The extract was washed with brine and dried over Na_2SO_4. Evaporation of the solvent gave **33** (1.50 g; 77%), IR $\nu_{max}^{CCl_4}$ cm^{-1}: 3650—2300, 1730, 1710, 1690. NMR δ (CCl_4): 1.26, 1.33 (each s, 3H×2, 4,10-CH_3), 1.49 (s, 6H, 1′-CH_3), 3.65 (s, 3H, CO_2CH_3), 7.23 (d, J=8 Hz, 1H, 11-H), 7.50 (d.d, J=2 and 8 Hz, 1H, 12-H), 7.94 (d, J=2 Hz, 1H, 14-H), 10.57 (b.s, 1H, CO_2H).

The half ester (**33**) was treated with CH_2N_2 to give methyl 13-(1′,1′-dimethyl-2′-methoxycarbonylethyl)-7-oxopodocarpa-8,11,13-trien-15-oate (**34**), bp 170° (bath, 0.0029 mmHg). IR $\nu_{max}^{CCl_4}$ cm^{-1}: 1735, 1730, 1685. NMR δ (CCl_4): 1.26, 1.32 (each s, 3H×2, 4,10-CH_3), 1.45 (s, 6H, 1′-CH_3), 3.53 (s, 3H, 2′-CO_2CH_3), 3.64 (s, 3H, 4-CO_2CH_3), 7.20 (d, J=8 Hz, 1H, 11-H), 7.46 (d.d, J=2 and 8 Hz, 1H, 12-H), 7.88 (d, J=2 Hz, 1H, 14-H). *Anal.* Calcd. for $C_{24}H_{32}O_5$: C, 71.97; H, 8.05. Found: C, 71.73; H, 8.06. High-MS Calcd. (M^+; *m/e*): 400. 2250. Found: 400.2217.

Methyl 13-(2′-Carboxy-1′,1′-dimethylethyl)-podocarpa-8,11,13-trien-15-oate (**35**)——A mixture of **33** (866 mg) and 10% Pd-C (400 mg) in AcOH (50 ml) was shaken overnight at room temperature under H_2 atmosphere. After removal of the catalyst by filtration, the filtrate was concentrated to give **35** (853 mg; quantitative), IR $\nu_{max}^{CCl_4}$ cm^{-1}: 3600—2200, 1730, 1710. NMR δ (CCl_4): 1.20, 1.24 (each s, 3H×2, 4,10-CH_3), 1.43 (s, 6H, 1′-CH_3), 3.63 (s, 3H, CO_2CH_3), 6.90—7.05 (b.s, 3H, 11,12,14-H), 10.94 (b.s, 1H, CO_2H).

The half ester (**35**) was treated with CH_2N_2 to give methyl 13-(1′,1′-dimethyl-2′-methoxycarbonylethyl)-podocarpa-8,11,13-trien-15-oate (**36**), mp 74.5—76.5° (MeOH). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1720, and $\nu_{max}^{CCl_4}$ cm^{-1}: 1730. NMR δ (CCl_4): 1.20, 1.24 (each s, 3H×2, 4,10-CH_3), 1.39 (s, 6H, 1′-CH_3), 3.54 (s, 3H, 2′-CO_2CH_3), 3.65 (s, 3H, 4-CO_2CH_3), 6.93—7.06 (m, 3H, 11,12,14-H). *Anal.* Calcd. for $C_{24}H_{34}O_4$: C, 74.57; H, 8.87. Found: C, 74.35; H, 8.67. High-MS Calcd. (M^+; *m/e*): 386.2457. Found: 386.2451.

Cyclization Reaction of 35 to Cyclized Products (37 and 38)——A) By AcCl and $AlCl_3$ in CS_2: To a solution of **35** (244 mg) in CS_2 (35 ml) was added AcCl (14.5 ml) and then $AlCl_3$ (4.2 g) with stirring under ice cooling. The mixture was stirred overnight at room temperature. Ice water was added to the reaction mixture, and it was extracted with ether. The extract was washed with brine, 5% NaOH solution and brine and dried over Na_2SO_4. Evaporation of the solvent gave an oil (228 mg; GLC: **37**: **38**=3: 2), which was chromatographed on Florisil (40 g) with pet. ether–ether (5: 1) as eluant to give **37** (125 mg; 51%) and then **38** (38 mg; 15%). The former (**37**) gave mp 125—126° (MeOH–H_2O). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1720, 1695 and $\nu_{max}^{CCl_4}$ cm^{-1}: 1724, 1710. NMR δ ($CDCl_3$): 1.21, 1.26 (each s, 3H×2, 4,10-CH_3), 1.34, 1.37 (each s, 3H×2, 17-CH_3), 2.50 (s, 2H, 16-CH_2), 3.63 (s, 3H, CO_2CH_3), 7.26 (d, J=8.5 Hz, 12-H), 7.55 (d, J=8.5 Hz, 11-H). The NOE were detected between the 17-dimethyl groups and the 12-proton by 28%, when irradiated at the former and between the 10-methyl group and the 11-proton by 9%, when irradiated at the former. *Anal.* Calcd. for $C_{23}H_{30}O_3$: C, 77.93; H, 8.53. Found: C, 77.93; H, 8.39. High-MS Calcd. (M^+; *m/e*): 354.2195. Found: 354.2188.

The latter (**38**) gave mp 106—108° (MeOH–H_2O) (lit.[5]) 125—127° and 136—137°). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1725—1700 and $\nu_{max}^{CCl_4}$ cm^{-1}: 1730, 1705. NMR δ ($CDCl_3$): 1.17, 1.25 (each s, 3H × 2, 4,10-CH_3), 1.36 (s, 6H, 18-CH_3), 2.51 (s, 2H, 19-CH_2), 3.64 (s, 3H, CO_2CH_3), 7.12 (s, $W_{1/2}$=2.5 Hz, 1H, 14-H), 7.60 (s, $W_{1/2}$=2.5 Hz, 1H, 11-H). The NOE was detected between the 18-dimethyl groups and the 14-proton by 16%, when irradiated at the former. *Anal.* Calcd. for $C_{23}H_{30}O_3$: C, 77.93; H, 8.53. Found: C, 77.69; H, 8.48. High-MS Calcd. (M^+; *m/e*): 354.2195. Found: 354.2184.

The former (**37**) was not changed when left standing at room temperature, but the latter (**38**) was changed (it may be air-oxidized at the 7-position). This may cause the difference between the GLC's and separated products' ratios.

B) By $(CF_3CO)_2O$ in CF_3CO_2H: To a solution of **35** (206 mg) in CF_3CO_2H (1.0 ml) was added $(CF_3CO)_2O$ (1.0 ml), which was left standing at room temperature for 4 hr. The reaction mixture was poured onto ice water, and it was extracted with ether. The extract was washed with 5% NaOH solution and brine and dried over Na_2SO_4. Evaporation of the solvent gave a crystal (136 mg; GLC: **37**: **38**=3: 2), which was chromatographed on Florisil (25 g) with pet. ether–ether (3: 1) as eluant to give **37** (59 mg; 31%), a mixture of **37** and **38** (14 mg; 7.5%) and **38** (37.5 mg; 20%). The physical constants (GLC, IR, NMR) of **37** and **38** were identical with those of the sample mentioned above.