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THE SYNTHESIS OF CERTAIN 11,14-DIMETHOXYDEOXYPODOCARPIC ACID DERIVATIVES. AN APPLICATION TO THE SYNTHESIS OF (+)-WINTERIN FROM *DRIMYS WINTERI*

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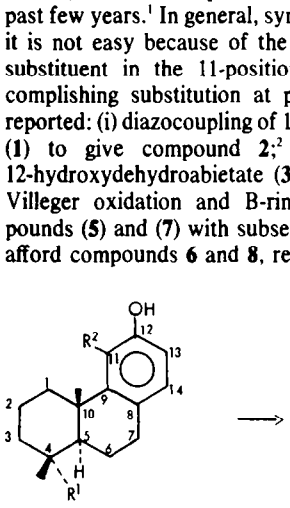
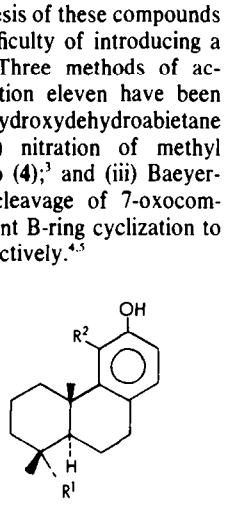
Abstract—This paper reports the synthesis of several 11,14-dimethoxydeoxypodocarpic acid derivatives from (+)-podocarpic acid. The synthesis of the naturally occurring sesquiterpene, (+)-winterin, from *Drimys winteri* illustrates a synthetic application of the 11,14-dimethoxy intermediates and establishes the absolute configuration for winterin.

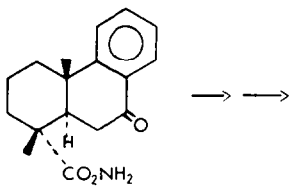
Many diterpenes bearing an oxygen function (hydroxyl or ketone) at the eleven position have been isolated over the past few years.[1] In general, synthesis of these compounds it is not easy because of the difficulty of introducing a substituent in the 11-position. Three methods of accomplishing substitution at position eleven have been reported: (i) diazocoupling of 12-hydroxydehydroabietane (**1**) to give compound **2**;[2] (ii) nitration of methyl 12-hydroxydehydroabietate (**3**) to (**4**);[3] and (iii) Baeyer-Villeger oxidation and B-ring cleavage of 7-oxocompounds (**5**) and (**7**) with subsequent B-ring cyclization to afford compounds **6** and **8**, respectively.[4,5]



1 $R^1 = CH_3$; $R^2 = H$
3 $R^1 = CO_2CH_3$



2 $R^1 = CH_3$; $R^2 = N_2C_6H_5$
4 $R^1 = CO_2CH_3$



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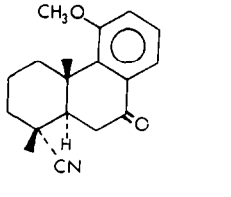

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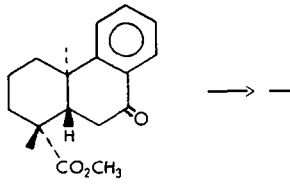

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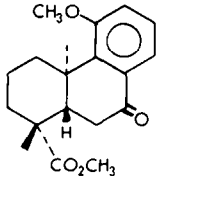

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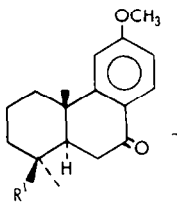
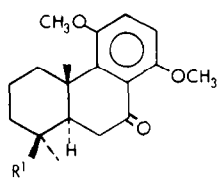
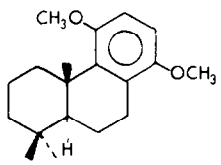
We have used method (iii) for the conversion of 7-oxo compounds (**9** and **10**) to the 11,14-dimethoxypodocarpic acid derivatives (**11**, **12**, **13**, **14** and **15**). These compounds are not only useful intermediates for the synthesis of 11-oxygenated natural products, but can be transformed to drimane-type sesquiterpenes (**16**) and to labdane-type diterpenes (**17**) via oxidative cleavage of ring C. The hydrogenated derivatives of **11** and **12** may also be converted to diterpenes and diterpenoid alkaloids bearing a D-ring by selective ring formation between the 8- and 12- positions (atisane skeleton: 18) or between the 8- and 13- positions (kaurane skeleton: 19; stachane skeleton: 20). As an example of the synthetic utility of the



9 $R^1 = CO_2CH_3$
10 $R^1 = CH_3$

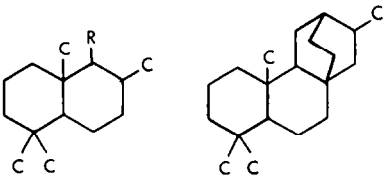


11 $R^1 = CO_2CH_3$
12 $R^1 = CH_3$



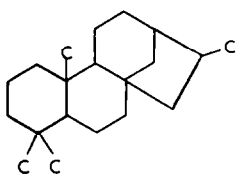
13 $R^1 = CO_2CH_3$
14 $R^1 = CH_2OH$
15 $R^1 = CH_3$

11,14-dimethoxy intermediates, we have synthesized (+)-winterin[6] (**21**), a bicyclofarnesol derivative present in the stem bark of *Drimys winteri*, from 11,14-dimethoxypodocarpa-8,11,13-triene (**15**). The detailed transformations involved in the synthesis of compounds **11–15** and winterin (**21**) are described below:



16 R = C_1 unit
17 R = C_6 unit

18



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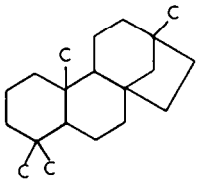

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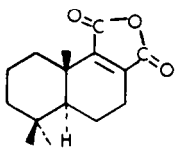

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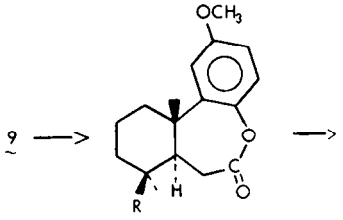
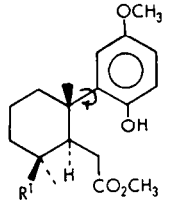
Oxidative cleavage and recyclization of ring-B of 7-oxo compounds **9** *and* **10**

The title compounds[7,8] were oxidized with *m*-chloroperbenzoic acid in chloroform to give lactones **22** and **23**, respectively in 80–88% yield. The IR and NMR spectra of **22** are consistent with the indicated structure, and the spectral data of **23** are identical with those reported.[9] Methanolysis of lactones **22** and **23** afforded the phenolic esters **24**, m.p. 154–154.5°, and **25**, m.p. 150–150.5°, respectively, in 85–98% yield. Methylation (dimethylsulfate–K_2CO_3 in acetone) and subsequent partial hydrolysis (10% aqueous KOH in MeOH) of **24** gave the methoxy monoester (**27**), m.p. 141.5–142°, in a yield of 84% via the oily dimethoxy diester **26**.

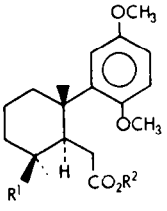
In the NMR spectra of methoxy diesters **24** and **26**, one of the methyl signals due to the methoxycarbonyl group was observed at an abnormally high magnetic field (**24**: δ 3.35 and **26**: δ 3.28). This signal was assigned to the C-6 methoxycarbonyl group by comparison of the chemical shift of the methoxycarbonyl group of methoxydiesters (**24** and **26**) with that of the corresponding methoxyesters



22 R = CO_2CH_3
23 R = CH_3



24 R^1 = CO_2CH_3
25 R^1 = CH_3



26 R^1 = CO_2CH_3; R^2 = CH_3
27 R^1 = CO_2CH_3; R^2 = H
28 R^1 = R^2 = CH_3

(**25**: δ 3.36 and **28**: δ 3.30) obtained as described later. A similar observation has been reported and explained in that the methyl of the methoxycarbonyl group is influenced by the diamagnetic effect of the aromatic C-ring.[4] This methoxy signal disappeared during hydrolysis (**26**→**27**).

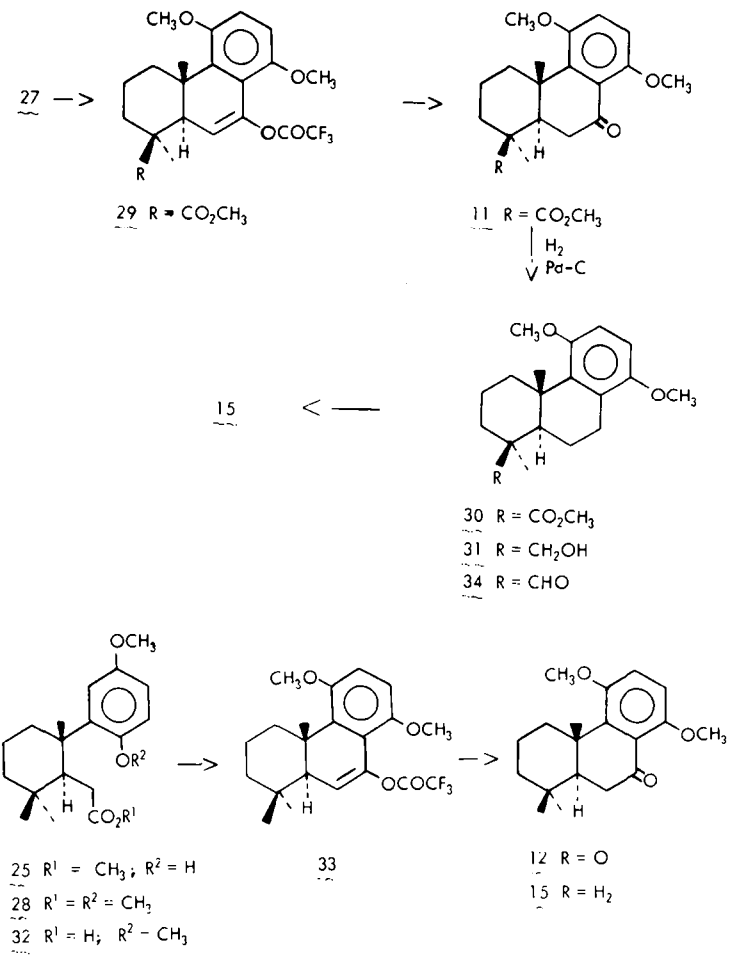
Treatment of dimethoxy monoester **27** with trifluoroacetic anhydride (room temperature) followed by 10% aqueous KOH in MeOH gave the desired dimethoxy oxo ester **11**, m.p. 138.5–139.5°, in 93–99% yield via trifluoroacetate **29**, ν_{max} CCl_4: 1800, 1730, 1675(w) cm^{-1}. An attempted oxidation of trifluoroacetate **29** with *m*-chloroperbenzoic acid in chloroform led to the recovery of starting material.

Hydrogenation (H_2, 10% Pd-C, AcOH-conc. H_2SO_4) of dimethoxy oxo-ester **11** afforded dimethoxy ester **30**, m.p. 118.5–119.5° in 93% yield, which on treatment with LAH was reduced to alcohol **31** in quantitative yield. The latter was transformed to 11,14-dimethoxypodocarpa-8,11,13-triene (**15**), m.p. 104.5–105°, by CrO_3-pyridine complex oxidation, thioacetalization and desulfurization (without characterization of intermediates) in an overall yield of 58%.

Phenolic hydroxy ester **25** was also converted into dimethoxy ketone **12**, m.p. 152.5–153°, in an overall yield of 88% by successive treatment with dimethylsulfate–K_2CO_3 in acetone, 10% KOH in MeOH, trifluoroacetic anhydride and 10% aqueous KOH in MeOH, via dimethoxy ester **28**, dimethoxy acid **32**, and trifluoroacetate **33**. Hydrogenolysis of the resulting dimethoxy ketone **12** gave **15** which was identical with the product obtained from 7-oxo ester **11**.

Structural determination of 11,14-*dimethoxy compounds.* The NMR spectrum of **11** was consistent with a dimethoxy oxo ester structure. The pattern in the aromatic region (δ 6.70 and 6.93 d, 1H each, J = 9.5 Hz; ortho-coupling) indicates clearly a 1,2,3,4-tetrasubstituted benzene ring. A substituent at position 14 is indicated by the 14-H signal which would be expected to appear at a lower magnetic field (e.g. δ: 7.70 in **8**[4] and δ: 8.05 in **9**) than that of the other aromatic proton because of the effect of the 7-oxo group, if position 14 is not substituted. Consequently, one of the methoxy groups must be located at the 11-position.

Further structural evidence for the dimethoxy compound was provided by NMR comparison between dimethoxy compounds **10**, **12**, **15**, **30**, **31** and **34**;



11-methoxy compounds **8**, **35** and **36**;[4] and podocarpic acid derivatives **9**, **37**, **38**, **39**, **10** and **40** (Table 1). It is known that substituents such as OMe or OH groups at the 12-, 13- and/or 14-positions have no effect on shifting the NMR signal of a 10 Me group. On the other hand, the NMR signal of the 10-Me group in the abietane series having a 11-OMe group is shifted *ca* 0.1–0.2 ppm downfield.[10] A similar phenomenon is also observed in the antipodal 11-methoxydeoxypodocarpic acid derivatives (*ca* 0.1–0.12 ppm).[4] In the dimethoxy compounds, the 4-methyl signals are not shifted, but the 10-Me signals are shifted 0.08–0.15 ppm downfield from the corresponding podocarpic acid derivatives (Table 1). Moreover, chemical shifts of the 4- and 10-Me groups in dimethoxy compounds **11**, **30** and **31** coincide with those of the corresponding 11-OMe compounds **8**, **35** and **36**), respectively. The above NMR data are consistent with the conclusion that all these compounds (**11**, **30**, **31**, **34**, **12** and **15**) have an 11-OMe group on a podocarpane skeleton, and, therefore, are 11,14-dimethoxydeoxypodocarpic acid derivatives.

Conformations of compounds **24**, **26** *and* **27** (Figs. 1 and 2). A study of Dreiding models suggests that conformation **A** having two axial substituents is more stable than conformation **B** having three axial substituents. The information from models was confirmed by NMR analysis. As described above, the Me signals of methoxycarbonyl groups in **24** (δ: 3.35) and **26** (δ: 3.28) were observed at an abnormally high magnetic field and disappeared during hydrolysis (**26** → **27**). This behavior is reasonable because the Me of the methoxycarbonyl group

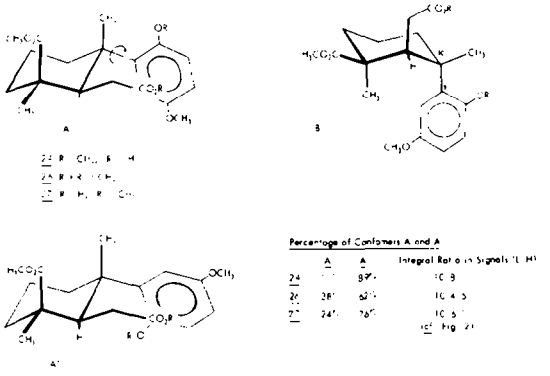


Fig. 1. Conformations of compounds **24**, **26** and **27**.

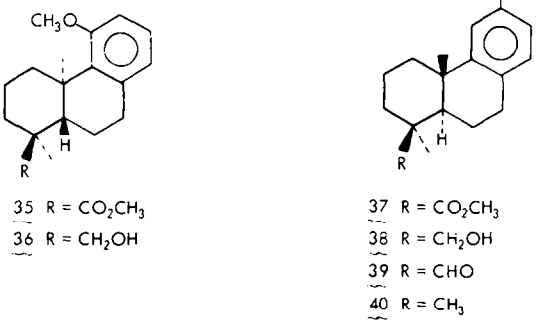
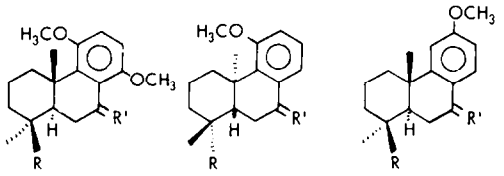


Table 1. Comparison of chemical shifts of 4- and 10-methyl groups (δ: ppm)



R = CO_2CH_3	10-CH_3	1.23	1.23	1.09
R' = O	4-CH_3	1.23	1.25	1.24
R = CO_2CH_3	10-CH_3	1.15	1.13	1.07
R' = H_2	4-CH_3	1.26	1.26	1.31
R = CH_2OH	10-CH_3	1.30	1.28	1.21
R' = H_2	4-CH_3	1.05	1.05	1.08
R = CHO	10-CH_3	1.18	-	1.06
R' = H_2	4-CH_3	1.08	-	1.10
R = CH_3	10-CH_3	1.36	-	1.21
R' = O	4-CH_3	0.93, 0.98	-	0.92, 0.98
R = CH_3	10-CH_3	1.33	-	1.18
R' = H_2	4-CH_3	0.93, 0.95	-	0.93, 0.93

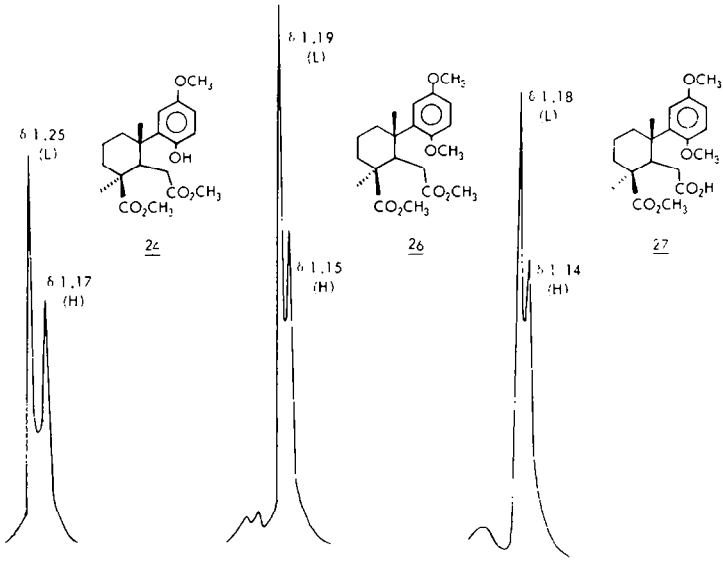


Fig. 2. NMR patterns of 4- and 10-methyl signals in compounds **24**, **26** and **27**.

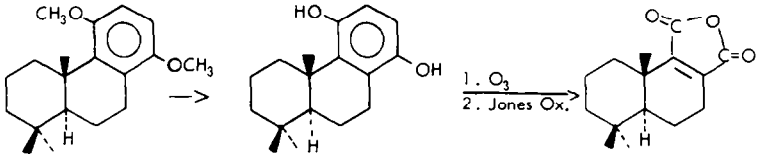
suffers a diamagnetic effect from the aromatic ring in conformation **A**.

The observation that these compounds (**24**, **26** and **27**) exhibited two broad singlets of unequal intensity for the 4- and 10-Me groups (the sum of the two singlets represented all six of the 4- and 10-Me groups) is expected where the possibility exists for more than one conformation **A**.[11] Inspection of molecular models shows the existence of two possible conformations (rotamer **A** and **A'** as shown in Fig. 1) caused by the rotation of the aromatic ring around the 9–10 bond. The 10-Me signal in conformation **A** appears at a slightly lower magnetic field than that in **A'** because the C(8)–O bond (OH or OMe group) on the aromatic ring in conformation **A** is positioned close to the 10-Me group in a 1,3-diaxial relationship. The preferred conformation is **A'** because of the steric effect between the 10-Me and OH (OMe) groups on the aromatic ring. On the basis of this idea, the percentage of each conformation

(A and A') present was estimated by integration (Fig. 2). It seems reasonable to assign the smaller signal at higher field to the 10-Me group in conformation A' and the larger one at lower field to the mixture of 4-Me in A' and 4- and 10-Me groups in A.

Synthesis of winterin (**21**). The total synthesis of (±)-winterin has been reported by Brieger[12] who used a Diels–Alder reaction to construct the B-ring. However, the yield in this key step was very poor (4%).

The dimethoxy derivative **15** was converted to the corresponding hydroquinone (**41**), m.p. 178.5–180° (dec), in a nearly quantitative yield by treatment with BBr_3 in methylene chloride. Ozonolysis of **41** was carried out in methanol–methylene chloride (1:1) at −78°, followed by Jones oxidation. TLC, NMR and IR spectra showed that the product obtained as neutral crystals in 64–72% yield



15 43 21 (+)-winterin

was almost pure. Purification by preparative TLC on silica gel[12] gave pure (+)-winterin (**21**), m.p. 157–157.5°, as colorless plates in a yield of 20–31%. The low yield appeared to result from partial hydrolysis of the anhydride during development. The physical data (m.p., IR and UV spectra, λ_{max} EtOH 257 nm, $[\alpha]_D^{25}$ + 100.1° (*c* 2.0 in $CHCl_3$) of **21** agree well with those reported in the literature (m.p. 158°, λ_{max} EtOH 257 nm, $[\alpha]_D^{25}$ + 109° (*c* 2.52 in $CHCl_3$)).[6] A comparison of the ^{13}C NMR spectrum of synthetic winterin with that of an authentic sample[6] proved identity. The optical rotation of winterin synthesized from (+)-podocarpic acid establishes the absolute configuration of naturally occurring winterin. The overall yield of (+)-winterin (**21**) from (+)-podocarpic acid derivative **9** in twelve steps is 11%, and from compound **10** in nine steps is 16.5%.

The transformation of a (+)-podocarpic acid derivative to the sesquiterpenes, drimenin and drimenol has been reported by Wenkert and Strike.[9] Their synthesis of drimenin was accomplished from methoxy ketone **10** in 18 steps in an overall yield of less than 6%. The 11,14-dimethoxy compounds described in this paper appear to be useful intermediates in the synthesis of sesquiterpenes.

EXPERIMENTAL

All m.ps were measured with a Büchi m.p. apparatus and are uncorrected. IR spectra were measured with Perkin-Elmer model 237B and model 257 spectrophotometers. NMR spectra were taken with Varian A-60 and T-60 spectrometers (60 MHz) in $CDCl_3$ (5–10% solution) with TMS as internal reference. UV spectra were taken in ethanol with a Varian model 202 spectrometer. Ozonolysis was carried out using a Welsbach T-408 ozonator.

Oxidation of methyl O-methyl-7-oxopodocarpate (**9**) *to lactone* **22**

A soln of **9** (5.00 g) in $CHCl_3$ (10 ml) was added to a soln of *m*-chloroperbenzoic acid (3.00 g) in $CHCl_3$ (90 ml) and the mixture was allowed to stand at room temp. After 2 days, *m*-chloroperbenzoic acid (2.50 g, total 2 equiv) was added and the mixture was stirred for an additional 3 days at room temp. The mixture was washed with sat Na_2CO_3 aq and filtered through a short column of silica gel. Evaporation of the eluent gave **22** (4.62 g) as an oil: ν_{max} (CCl_4): 1765, 1730 cm^{-1}; NMR: δ 1.23 (6H, s, 4- and 10-CH_3), 3.70 (3H, s, CO_2CH_3), 3.77 (3H, s, OCH_3). The crude product was used in the next experiment without further purification.

Methanolysis of lactone **22** *to hydroxy diester* **24**

A mixture of the crude **22** (4.200 g) obtained as described above and conc H_2SO_4 (2.1 ml) in MeOH (210 ml) was refluxed for 30 min and the solvent was removed under reduced pressure. The ether extract of the resulting residue was washed with sat Na_2CO_3 aq, water, and dried ($MgSO_4$). Evaporation of the solvent afforded **24** (3.920 g) as crystals which were used in the next reaction without further purification. Recrystallization of the crude product from MeOH gave colorless prisms (2.840 g), m.p. 154–154.5°; ν_{max} (KBr): 3345, 1720, 1710 cm^{-1}; NMR: δ 1.17 and 1.25 (total 6H, br.s, 4- and 10-CH_3), 3.35 (3H, s, 6-CO_2CH_3), 3.68 (3H, s, 4-CO_2CH_3), 3.73 (3H, s, OCH_3). (Found: C, 65.85; H, 7.77. Calc. for $C_{20}H_{28}O_6$: C, 65.91; H, 7.74%).

Methylation and successive partial hydrolysis of hydroxy diester **24** *to methoxy monoester* **27** *via methoxy diester* **26**

A mixture of **24** (2.700 g), Me_2SO_4 (25 ml) and K_2CO_3 (27.0 g) in acetone (270 ml) was refluxed for 20 hr. After the excess of Me_2SO_4 was decomposed by addition of water, the organic solvent was removed and the mixture was extracted with ether. The extract was washed with water and dried ($MgSO_4$). The solvent was evaporated to give an oily diester **26** (2.750 g): ν_{max} (CCl_4) 1735, 1727, 1230 cm^{-1}; NMR: δ 1.15 and 1.19 (total 6H, br.s, 4- and 10-CH_3), 3.28 (3H, s, 6-CO_2CH_3), 3.67 (3H, s, 4-CO_2CH_3), 3.72 and 3.81 (3H each, s, OCH_3), which was used in the next experiment without further purification.

A soln of **26** (2.750 g) in MeOH (110 ml) was heated under reflux for 2 hr with 10% KOH aq (110 ml). The organic solvent was removed under reduced pressure and the residue was washed with ether. The aqueous layer was acidified with conc HCl and extracted with ether. The extract was washed with water and dried ($MgSO_4$). Removal of the solvent gave the monoester as crystals **27** (2.650 g), which were used in the next experiment without further purification. A part of the crude product (200 mg) was purified by chromatography on silicic acid–celite (1:1) (20 g) with hexane–ether (9:1) as eluent to give crystals (175 mg). Recrystallization from ether–hexane yielded colorless prisms (117 mg); m.p. 141.5–142°; ν_{max} (CCl_4): 1725, 1705, 1227 cm^{-1}; NMR: δ 1.14 and 1.18 (total 6H, br.s, 4- and 10-CH_3), 3.67 (3H, s, 4-CO_2CH_3), 3.72 and 3.73 (3H each, s, OCH_3). (Found: C, 65.83; H, 7.75. Calc. for $C_{20}H_{28}O_6$: C, 65.91; H, 7.74%).

Cyclization of methoxy monoester **27** *to methyl* 11,14-*dimethoxy*-7-*oxodeoxypodocarpate* (**11**) *via trifluoroacetate* **29**

(a) A soln of **27** (349 mg) in trifluoroacetic anhydride (3.5 ml) was allowed to stand for 3.5 hr at room temp., and then was poured onto ice and extracted with ether. The ether extract was washed with cold, sat. Na_2CO_3 aq, water and dried (Na_2SO_4). Evaporation of the solvent gave a solid **29** (370 mg): ν_{max} (CCl_4): 1800, 1730, 1675(w) cm^{-1}; NMR: δ 1.03 (3H, s, 10-CH_3), 1.26 (3H, s, 4-CH_3), 2.05 (1H, d, *J* = 3.2 Hz, 5α-H), 3.66 (6H, s, 4-CO_2CH_3 and OCH_3), 3.70 (3H, s, OCH_3), 6.28 (1H, d, *J* = 3.2 Hz, 6-H), 6.63 and 6.82 (1H each, d, *J* = 9.5 Hz, 12- and 13-H). This product was treated with 10% KOH aq (3.7 ml) in MeOH (37 ml) for 60 min at room temp. The solvent was removed under reduced pressure and the residue was extracted with ether. The extract was washed with water and dried (Na_2SO_4). Removal of the solvent gave the crystalline oxo ester **11** (288 mg). Recrystallization from aqueous MeOH afforded colorless prisms: m.p. 138.5–139.5°; ν_{max} (KBr):

1720, 1680, 1585 cm^{-1}; NMR: δ 1.23 (6H, s, 4- and 10-CH_3), 3.61 (3H, s, 4-CO_2CH_3), 3.73 and 3.78 (3H each, s, OCH_3), 6.70 and 6.93 (1H each, d, J = 9.5, 12- and 13-H). (Found: C, 69.30; H, 7.60. Calc. for $C_{20}H_{26}O_5$: C, 69.34; H, 7.54%).

(b) Methoxy monoester **27** (1.145 g) was treated with trifluoroacetic anhydride (12 ml) for 3 hr at room temp. and the excess anhydride was removed under reduced pressure. The resulting residue was hydrolyzed with 10% KOH aq (6 ml) in MeOH (60 ml) for 60 min at room temp. The same work-up as described above gave crystalline **11** (950 mg), whose m.p., IR (CCl_4) and NMR spectra were identical with those of the product (**11**) prepared by method (a).

Hydrogenolysis of methyl 11,14-*dimethoxy*-7-*oxodeoxypodocarpate* (**11**) *to methyl* 11,14-*dimethoxydeoxypodocarpate* (**30**)

A soln of **11** (1.615 g) in AcOH (162 ml) was stirred at room temp. with 10% Pd–C (800 mg) in the presence of conc H_2SO_4 (16 drops) under H_2. After absorption of H_2 ceased (about 4 hr), the filtrate was evaporated under reduced pressure and the resulting residue was extracted with ether. The extract was washed with sat Na_2CO_3 aq, water and dried (Na_2SO_4). Evaporation of the solvent gave colorless crystals **30** (1.350 g) which were recrystallized from aqueous MeOH to yield colorless prisms: m.p. 118.5–119.5°; ν_{max} (KBr): 1725 cm^{-1}; NMR: δ 1.15 (3H, s, 10-CH_3), 1.26 (3H, s, 4-CH_3), 3.64 (3H, s, 4-CO_2CH_3), 3.72 and 3.74 (3H each, s, 11- and 14-OCH_3), 6.61 (2H, s, 12- and 13-H). (Found: C, 72.22; H, 8.53. Calc. for $C_{20}H_{28}O_4$: C, 72.26; H, 8.49%).

LAH reduction of methyl 11,14-*dimethoxydeoxypodocarpate* (**30**) *to* 11,14-*dimethoxydeoxypodocarpanol* (**31**)

Ester **30** (1.350 g) was reduced with LAH (1.700 g) in ether (250 ml) by refluxing for 17 hr. The usual work-up gave **31** (1.220 g) as a colorless oil: ν_{max} (CCl_4): 3625 cm^{-1}; NMR: δ 1.05 (3H, s, 4-CH_3), 1.30 (3H, s, 10-CH_3), 3.74 (6H, s, 11- and 14-OCH_3), 3.53 and *ca* 3.84 (1H each, d, J = 11.0 Hz, 4-CH_2OH), 6.67 (2H, s, 12- and 13-H).

A part of **31** (80 mg) was treated with *p*-nitrobenzoyl chloride (80 mg) in pyridine (2 ml) at room temp. overnight. The crude crystals (105 mg) obtained by usual work-up were recrystallized from ether–hexane to afford the *p*-nitrobenzoate (87 mg) as pale yellow prisms: m.p. 149–150°; ν_{max} (KBr): 1720, 1530 cm^{-1}. (Found: C, 68.78; H, 6.91; N, 3.19. Calc. for $C_{26}H_{31}NO_6$: C, 68.86; H, 6.89; N, 3.09%).

Conversion of 11,14-*dimethoxydeoxypodocarpanol* (**31**) *to* 11,14-*dimethoxypodocarpa*-8,11,13-*triene* (**15**) *via aldehyde* **34**

Dry CrO_3 (6.500 g) was added gradually to a mixture of CH_2Cl_2 (110 ml) and pyridine (11.0 ml) with stirring and the mixture was stirred for 30 min at room temp. After addition of a soln of **31** (1795 mg) in CH_2Cl_2 (16 ml), the mixture was stirred for 16 hr at room temp. and filtered through a short column of silica gel. The filtrate was evaporated to dryness to give the crude **34** (1720 mg) as a solid: NMR: δ 1.08 (3H, s, 4-CH_3), 1.18 (3H, s, 10-CH_3), 3.79 and 3.82 (3H each, s, 11- and 14-OCH_3), 6.78 (2H, s, 12- and 13-H), 10.02 (1H, s, CHO).

The crude aldehyde (1720 mg) was treated with ethanedithiol (2.0 ml) and BF_3-etherate (1.0 ml) in glacial AcOH (43 ml) at room temp. After 4 hr the mixture was poured onto ice and extracted with ether. The etheral extract was washed with sat Na_2CO_3 aq and dried ($MgSO_4$). Evaporation of the solvent gave an oil (2.30 g). A soln of the latter in EtOH (200 ml) was refluxed for 18 hr with Raney Ni (W-7 form prepared from 20 g of Ni–Al alloy) filtered and evaporated to dryness. The solid obtained (1.420 g) was purified by preparative TLC (silica gel, ether–hexane) to afford colorless crystals **15** (1037 mg) in 58% yield from **11**. Recrystallization from ether–hexane gave colorless needless: m.p. 101.5–102°, NMR: δ 0.93 and 0.95 (3H each, s, 4-CH_3), 1.33 (3H, s, 10-CH_3), 3.79 (6H, s, 11- and 14-OCH_3), 6.73 (2H, s, 12- and 13-H). (Found: C, 79.14; H, 9.81. Calc. for $C_{19}H_{28}O_2$: C, 79.12; H, 9.79%).

Oxidation of O-*methyl*-7-*oxopodocarpane* (**10**) *to lactone* **23**

To a solution of **10** (800 mg) in CH_2Cl_2 (28 ml) *m*-chloroperbenzoic acid (810 mg) was added and the mixture was stirred for 3 days at room temp. Additional *m*-chloroperbenzoic acid (800 mg) was added to the mixture which was stirred for a further 3 days at room temp. The same work-up as used for oxidation of **9** gave **23** (670 mg) as a neutral, pale brownish oil. The spectral data (IR and NMR) of the crude product were identical with those reported for **23** by Wenkert and Strike.[9] The crude lactone **23** was used in the next experiment without purification.

Methanolysis of lactone **23** *to phenolic hydroxy ester* **25**

Lactone **23** (670 mg) was treated with conc H_2SO_4 (0.40 ml) in MeOH (34 ml) and worked up under the same conditions as in the case of **22**. The neutral crystals obtained **25** (710 mg) were recrystallized from ether–hexane to give colorless prisms: m.p. 150–150.5°, ν_{max} ($CHCl_3$): 3570, 3420, 1713 cm^{-1}; NMR: δ 0.98 (6H, s, 4-CH_3), 1.35 (3H, s, 10-CH_3), 3.36 (3H, s, 6-CO_2CH_3), 3.76 (3H, s, OCH_3). (Found: C, 69.71; H, 8.63. Calc. for $C_{19}H_{28}O_4$: $\frac{1}{2}H_2O$; C, 69.27; H, 8.87%).

Transformation of phenolic hydroxy ester **25** *to* 11,14-*dimethoxy*-7-*oxopodocarpa*-8,11,13-*triene* (**12**) *via* **28**, **32** *and* **33**

Hydroxyester **25** (410 mg) was methylated with Me_2SO_4 (4.1 ml) and K_2CO_3 (4.10 g) in acetone (41 ml) under the same conditions as in the case of **24** to give a neutral oil **28** (425 mg): ν_{max} (CCl_4): 1730, 1583 cm^{-1}; NMR: δ 0.87 and 0.96 (3H each, s, 4-CH_3), 1.32 (3H, s, 10-CH_3), 3.30 (3H, s, CO_2CH_3), 3.70 and 3.82 (3H each, s, OCH_3).

The crude product (**28**) was hydrolysed with 10% KOH aq (21 ml) and MeOH (21 ml) under reflux for 2 hr. The same work-up used for **26** afforded a crude acid (400 mg), which was chromatographed on silicic acid–celite (1:1, 60 g) using hexane–ether (9:1) as eluant. The product was a colorless oil (**32**; 370 mg): ν_{max} (CCl_4): 1703, 1583 cm^{-1}; NMR: δ 0.89 and 0.98 (3H each, s, 4-CH_3), 1.31 (3H, s, 10-CH_3), 3.72 and 3.83 (3H each, s, OCH_3).

A part of the above acid (**32**; 270 mg) was treated with trifluoroacetic anhydride (3 ml) for 3.5 hr at room temp. and the solvent was evaporated to dryness to yield an oil (**33**; 340 mg): ν_{max} (CCl_4): 1790, 1665 cm^{-1}; NMR: δ 0.97 and 1.03 (3H each, s, 4-CH_3), 1.22 (3H, s, 10-CH_3), 2.30 (1H, d, J = 3.5 Hz, 5α-H), 3.73 and 3.77 (3H each, s, 11- and 14-OCH_3), 5.85 (1H, d, J = 3.5 Hz, 6-H), 6.77 and 7.00 (1H each, d, J = 9.0 Hz, 12- and 13-H).

The crude trifluoroacetate (**33**; 340 mg) was hydrolyzed with 10% KOH aq (3.4 ml) in MeOH (34 ml) for 60 min at room temp. The same treatment used for cyclization of **27** gave a neutral crystalline **12** (250 mg) which was recrystallized from CH_2Cl_2–hexane to afford colorless needles (**12**; 240 mg): 152.5–153°, ν_{max} (KBr): 1680, 1580 cm^{-1}; NMR: δ 0.93 and 0.98 (3H each, s, 4-CH_3), 1.36 (3H, s, 10-CH_3), 3.85 and 3.91 (3H each, s, 11- and 14-OCH_3), 6.92 and 7.16 (1H each, d, J = 9.0 Hz, 12- and 13-H). (Found: C, 75.18; H, 8.67. Calc. for $C_{19}H_{26}O_3$: C, 75.46; H, 8.67%).

Hydrogenolysis of 11,14-*dimethoxy*-7-*oxopodocarpa*-8,11,13-*triene* (**12**) *to* 11,14-*dimethoxypodocarpa*-8,11,13-*triene* (**15**)

Dimethoxy ketone **12** (140 mg) was hydrogenolyzed in AcOH (14 ml) containing conc H_2SO_4 (2 drops) in the presence of 10% Pd–C (70 mg). The work-up was as described for the hydrogenolysis of **11**. The crystalline product (136 mg) was recrystallized from hexane to yield colorless prisms **15** (98 mg): m.p. 104.5–105°, undepressed on admixture with **15** prepared from **30**. The spectral data (NMR and IR) are identical with those of **15** obtained from **30**.

Hydrolysis of 11,14-*dimethoxypodocarpa*-8,11,13-*triene* (**15**) *to* 11,14-*dihydroxypodocarpa*-8,11,13-*triene* (**41**)

A soln of **15** (1030 mg) in CH_2Cl_2 (11 ml) was treated with BBr_3 (2 ml) for 10 min in a dry ice–acetone bath and allowed to stand for 30 min at room temp. The mixture was poured onto ice and extracted with ether. The extract was washed with sat Na_2CO_3 aq, water and dried ($MgSO_4$). Removal of the solvent gave crystals of **41** (937 mg) which were used in the next experiment without further purification. Recrystallization from chloroform–hexane gave colorless plates (635 mg): m.p. 178.5–180° (dec), ν_{max} (KBr): 3495 cm^{-1}; NMR: δ (acetone-d_6) 0.97 and 0.98 (3H each, s, 4-CH_3), 1.38 (3H, s, 10-CH_3), 6.57 (2H, s, 12- and 13-H). (Found: C, 78.14; H, 9.28. Calc. for $C_{17}H_{24}O_2$: C, 78.42; H, 9.29%).

Ozonolysis followed by oxidation of 11,14-*dihydroxypodocarpa*-8,11,13-*triene* (**41**) *to winterin* (**21**)

Compound **41** (460 mg) in a mixture of MeOH and CH_2Cl_2 (1:1, 28 ml) was treated with ozonized O_2 at −78° until the soln was blue (10–15 min). Evaporation of the solvent afforded an amorphous product which was dissolved in acetone (28 ml) and treated with 4N Jones reagent (2.4 ml) for 30 min at 5–10°. The mixture was diluted with water and extracted with ether. The extract was washed with sat Na_2CO_3 aq. water and dried ($MgSO_4$). The solvent was evaporated to dryness to give crystalline **21** (314 mg) which was shown to be almost pure by IR (CCl_4) and NMR spectra. Purification by preparative TLC on silica gel (hexane–ether, 5:1) yielded crystalline **21** (134 mg). Recrystallization from ether gave colorless plates (64 mg): m.p. 157.0–157.5°, $[\alpha]_D^{25}$ + 100.1° (*c* 2.0, chloroform), ν_{max} (CCl_4): 1840, 1768, 1665 cm^{-1}; NMR: δ 0.93 and 0.98 (3H each, s, 4-CH_3), 1.25 (3H, s, 10-CH_3). (Found: C, 72.25; H, 8.20. Calc. for $C_{15}H_{20}O_3$: C, 72.55; H, 8.12%).

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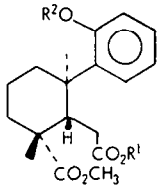
[11]A similar phenomenon was not observed in compounds **i**, **ii** and **iii** in which the NMR spectra showed two sharp singlets of equal intensity for 4- and 10-Me groups.[4]



i R^1 = Me; R^2 = H
ii $R^1 = R^2$ = Me
iii R^1 = H; R^2 = Me

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