IR comparison; mass spectrum (70 eV), M^+ 368, 370.

Deoxygenation of Nagilactone C (3) with Cr(II) Reagent. A solution of ethylenediamine (2 mL, 33.3 mmol) in purified DMF (170 mL) was carefully degassed and saturated with pure nitrogen. To this solution was added successively a $Cr(ClO_4)_2$ solution (10 mL, 14.2 mmol), prepared from 1.84 g of Cr metal and 25 mL of 20% $HClO_4$ at 70–80 °C under N_2, and then a DMF (10 mL) solution of nagilactone C (**3**, 1.00 g, 2.8 mmol) at 30 °C. After stirring for 4 h at 30 °C, the mixture was diluted with 300 mL of H_2O, acidified (pH ~2.0) with 6 N HCl, and extracted with $CHCl_3$. The $CHCl_3$ solution was worked up as usual to give 492 mg (52%) of the 1:2-deoxygenated product **33** as colorless crystals: mp 287–289 °C; UV (EtOH) 300 nm; IR (Nujol) 3500, 3300, 1750, 1695, 1630, 1550 cm^{-1}; ^1H NMR (py-d_5) δ 1.21 (3 H, d, J = 6.5 Hz, CH_3), 1.29 (3 H, d, J = 6.5 Hz, CH_3), 1.41 (3 H, s, CH_3), 1.98 (3 H, s, CH_3), 2.17 (1 H, d, J = 6.0 Hz, H-5), 3.48 (1 H, m, J = 6.5 Hz, H-15), 4.53 (1 H, d, J = 6.0 Hz, H-3), 5.02 (1 H, dd, J = 6.0, 8.5 Hz, H-6), 5.63 (1 H, d, J = 8.5 Hz, H-7), 6.17 (1 H, dd, J = 6.0, 9.5 Hz, H-2), 6.58 (1 H, s, H-11), 6.89 (1 H, d, J = 9.5 Hz, H-1); ^{13}C NMR (py-d_5) δ 20.2 (q, C-16), 20.8 (q, C-17), 25.9 (q, C-20), 27.0 (q, C-18), 29.7 (d, C-15), 38.2 (s, C-10), 48.4 (s, C-4), 54.8 (d, C-5), 60.5 (d, C-7), 69.3 (d, C-3), 74.0 (d, C-6), 105.5 (d, C-11), 111.7 (s, C-8), 129.6 (d, C-2), 136.9 (d, C-1), 162.2 (s, C-12), 163.1 (s, C-14), 170.7 (s, C-9), 178.8 (s, C-19).

Anal. Calcd for $C_{19}H_{22}O_6$: C, 65.88; H, 6.40. Found: C, 65.77; H, 6.44.

Acetylation of **33** by the usual method (Ac_2O/pyridine) gave diacetate **33a**: mp 248 °C; IR (Nujol) 1780, 1740, 1720, 1630, 1545 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.24 (3 H, d, J = 6.8 Hz, CH_3), 1.26 (3 H, d, J = 6.8 Hz, CH_3), 1.55 (6 H, s, 2 CH_3), 2.23 (1 H, d, J = 6.0 Hz, H-5), 3.00 (1 H, m, J = 6.8 Hz, H-15), 4.96 (1 H, dd, J = 6.0, 9.1 Hz, H-6), 5.88 (1 H, dd, J = 6.0, 9.8 Hz, H-2), 5.56 (1 H, d, J = 6.0 Hz, H-3), 6.22 (1 H, s, H-11), 6.36 (1 H, d, J = 9.1 Hz, H-7), 6.80 (1 H, d, J = 9.8 Hz, H-1).

Anal. Calcd for $C_{23}H_{26}O_8$: C, 64.17; H, 6.09. Found: C, 63.90; H, 5.97.

Hydrogenation of Allylic Alcohol 33. Catalytic hydrogenation of **33** was slow and gave a rather complicated mixture (3–4 spots on TLC). From the reduction of 130 mg of **33** (5% Pd/C 60 mg, EtOH 20 mL, 1 drop of 60% $HClO_4$, 25 °C, 1 atm of H_2, 2 h), 9 mg of a pure compound was obtained after repeated chromatography (ca. 55 mg of **33** was recovered). This product was assigned as the 2:3-unsaturated compound **35** from the following analytical data: mp 290 °C (sublime); IR (Nujol) 3440, 1760, 1695, 1635, 1550 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.25 (3 H, d, J = 6.5 Hz, CH_3), 1.34 (3 H, d, J = 6.5 Hz, CH_3), 1.38 (6 H, s, 2 CH_3), 2.00 (1 H, d, J = 5.5 Hz, H-5), 2.14 (2 H, br d, H-1), 3.24 (1 H, m, J = 6.5 Hz, H-15), 4.95 (1 H, dd, J = 5.5, 9.0 Hz, H-6), 5.30 (1 H, d, J = 9.0 Hz, H-7), 5.88 (3 H, br s, H-2, H-3, H-11).

Anal. Calcd for $C_{19}H_{22}O_5$: C, 69.07; H, 6.71. Found: C, 69.08; H, 6.82.

Epoxidation of Podolide (12) and 16-Hydroxypodolide (36). A solution of podolide (30 mg, 0.09 mmol) in dry $CHCl_3$ (7 mL) containing a catalytic amount of 4,4′-thiobis[6-*tert*-butyl-3-methylphenol] as a radical inhibitor was refluxed with 60 mg (0.35 mmol) of m-$ClC_6H_4CO_3H$ for 48 h. Evaporation of the solvent and purification of the residue by preparative TLC (SiO_2, 4:1 $CHCl_3$/acetone) gave 23 mg (73%) of the 2α:3α-epoxide **37** as colorless needles: mp 275 °C 4.0 Hz, UV (EtOH) 218 nm (ϵ 9800); IR (KBr) 1770, 1705 cm^{-1}; ^1H NMR (py-d_5) δ 1.01 (3 H, d, J = 7.0 Hz, CH_3), 1.11 (3 H, s, CH_3), 1.13 (3 H, d, J = 7.0 Hz, CH_3), 1.45 (3 H, s, CH_3), 1.59 (1 H, dd, J = 1.5, 14.0 Hz, H-1α), 1.86 (1 H, d, J = 5.0 Hz, H-5), 2.14 (1 H, dd, J = 6.5, 14.0 Hz, H-1β), 3.37 (1 H, m, H-2), 3.52 (1 H, d, J = 4.0 Hz, H-3), 4.20 (1 H, d, J = 1.5 Hz, H-7), 4.53 (1 H, d, J = 4.0, H-14), 5.11 (1 H, dd, J = 1.5, 5.0 Hz, H-6), 6.07 (1 H, s, H-11); ^{13}C NMR ($CDCl_3$) δ 16.5 (q, C-16), 19.5 (q, C-20), 21.4 (q, C-17), 24.5 (q, C-18), 26.9 (d, C-15), 32.5 (t, C-1), 35.5 (s, C-10), 41.7 (d, C-5), 43.5 (s, C-4), 52.2 (d, C-2), 53.7 (d, C-7), 54.0 (d, C-3), 57.4 (s, C-8), 72.2 (d, C-6), 82.7 (d, C-14), 118.1 (d, C-11), 156.8 (s, C-9), 163.2 (s, C-12), 177.1 (s, C-19); mass spectrum (20 eV), M^+ 346, 318, 303, 275, 247, 229.

Anal. Calcd for $C_{19}H_{22}O_6$: C, 65.88; H, 6.40. Found: C, 65.57; H, 6.39.

16-Hydroxypodolide (**36**), obtained from root bark of *Podocarpus nagi*, also gave a corresponding 2α,3α-epoxide **38** by the same procedure as described above; mp 272 °C dec; IR (KBr) 3540, 1777, 1700 cm^{-1}; ^1H NMR (py-d_5) δ 1.13 (3 H, s, CH_3), 1.30 (3 H, d, J = 7.0 Hz, CH_3), 1.46 (3 H, s, CH_3), 1.58 (1 H, dd, J = 1.5, 14.0 Hz, H-1α), 1.86 (1 H, d, J = 5.0 Hz, H-5), 2.12 (1 H, dd, J = 6.0, 14.0 Hz, H-1β), 3.38 (1 H, m, H-2), 3.52 (1 H, d, J = 3.5 Hz, H-3), 4.00 (1 H, dd, J = 7.0, 10.5 Hz, H-16), 4.11 (1 H, dd, J = 4.0, 10.5 Hz, H-16), 4.33 (1 H, d, J = 1.5 Hz, H-7), 4.82 (1 H, d, J = 5.0 Hz, H-14), 5.12 (1 H, dd, J = 1.5, 5.0 Hz, H-6), 6.16 (1 H, s, H-11); ^{13}C NMR (py-d_5) δ 16.1 (q, C-17), 19.5 (q, C-20), 23.7 (q, C-18), 32.3 (t, C-1), 34.7 (d, C-15), 35.8 (s, C-10), 41.7 (d, C-5), 43.7 (s, C-4), 52.5 (d, C-2), 54.4 (d, C-3), 54.9 (d, C-7), 57.8 (s, C-8), 62.5 (t, C-16), 72.7 (d, C-6), 82.2 (d, C-14), 118.1 (d, C-11), 157.3 (s, C-9), 163.6 (s, C-12), 177.8 (s, C-19); mass spectrum (20 eV), M^+ 362, 347, 332, 305.

Anal. Calcd for $C_{19}H_{22}O_7$: C, 62.97; H, 6.12. Found: C, 62.96; H, 6.19.

Registry No. 1, 19891-50-0; **1a**, 19891-54-4; **2**, 19891-51-1; **3**, 24338-53-2; **4**, 19891-53-3; **3a**, 82335-10-2; **4a**, 19891-65-7; **5**, 36895-12-2; dihydro-**5**, 39024-02-7; **5a**, 39024-01-6; **6**, 36912-00-2; **7**, 81348-87-0; **8**, 70469-56-6; **8a**, 70469-58-8; **9**, 65688-70-2; **10**, 65688-71-3; **12**, 55786-36-2; **13**, 73616-59-8; **14**, 73616-58-7; **15**, 82280-79-3; **16**, 71431-95-3; **16a**, 70469-57-7; **17**, 82335-11-3; **18**, 81362-33-6; **19**, 82280-80-6; **22**, 82280-81-7; **22a**, 82280-82-8; **23**, 82280-83-9; 1β-AcO-**23**, 82280-84-0; **24**, 19891-61-3; **25**, 33722-80-4; **27a**, 82280-85-1; **27b**, 82335-12-4; **28**, 82280-86-2; **29**, 82280-87-3; **29a**, 82280-88-4; **30**, 82280-89-5; **30a**, 82293-65-0; **30b**, 82293-66-1; **33**, 65688-75-7; **35**, 65688-77-9; **36**, 65688-72-4; **37**, 65688-73-5; **38**, 65688-74-6.

Total Synthesis of Nagilactone F, a Biologically Active Norditerpenoid Dilactone Isolated from *Podocarpus nagi*

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The details of the first total synthesis of nagilactone F (1), a member of the biologically active norditerpenoid dilactones isolated from *Podocarpus* plants, are described. The synthesis is accomplished by starting from a known resin acid, (4*S*)-(+)-podocarpic acid (4). Thus, the absolute configuration of the norditerpenoid is chemically established as represented by formula **1**.

Norditerpenoid dilactones isolated from various species of the *Podocarpus* genus[1] have attracted interest in natural product chemistry because of their wide variety of biological activity.[2] Even though more than 40 dilactone

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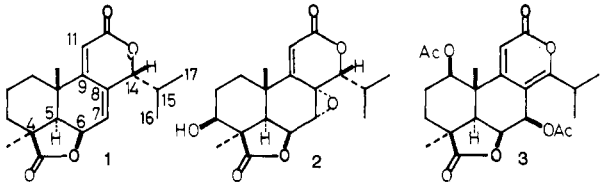
members have been found from plant sources since 1968, no synthetic works have appeared to date.[3] We have chosen nagilactone F[4] (1), a 7(8),9(11)-dienolide classified



as a type C dilactone,[5,6] as a synthetic target of this first total synthesis, since 1 is structurally the simplest but biologically the most active member of the dilactone congeners.[2]

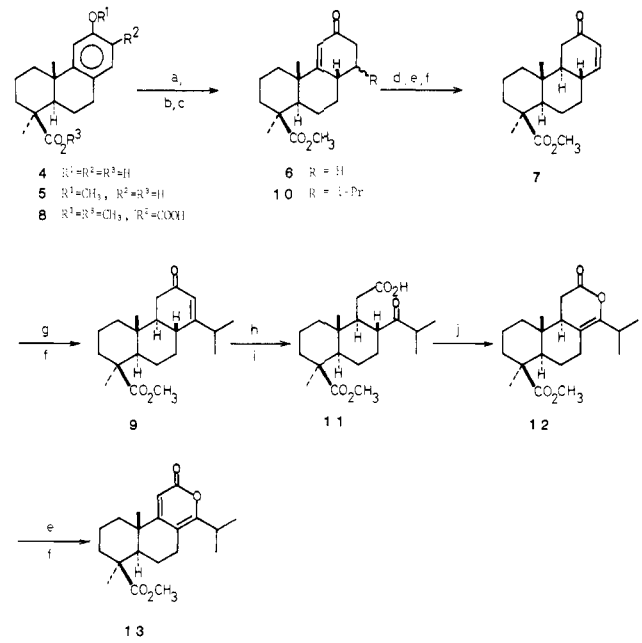
The synthesis[7] started from a resin acid, (*S*)-(+)-podocarpic acid (4), the structure and the absolute configuration of which have already been established.[8] The major problem of this synthesis was the transformation of the B/C ring part of the resin acid to the dienolide system by extrusion of the C_1 unit (C-13) and the stereocontrolled introduction of an isopropyl group of the C-14 position. For the latter purpose, a photochemical cyclization of the C_{19} dienoic acid **20**, derived from the C_{20} precursor **9**, was the key step, in which the desired stereochemistry at C-14 was furnished selectively (14α-isopropyl).

In the course of this synthesis, a series of reductive transformations of nagilactone F (1) to the synthetic intermediates became accessible. Several steps of the degradation have led 1 to two enolide esters, **21** and **23**, and a dienolide ester, **26**, which served as relay compounds of this total synthesis. Nagilactone F has been obtained from the plant in too small quantity to use for synthetic purpose. However, its successful derivation from nagilactone E (2, a 7α,8α-epoxy-9(11)-enolide classified as a type B dilactone[5,6]), the most abundant dilactone in root bark of *P. nagi*, solved this problem. Details of this derivation have been discussed.[6]

Results and Discussion

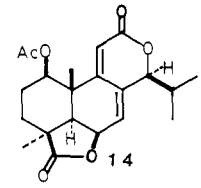
Birch reduction,[9] followed by acid treatment of *O*-methylpodocarpic acid (**5** Scheme I) produced the $\Delta^{9,11}$-enone **6** predominantly. The yield of **6** was dependent on the solvent system. A mixture of liquid ammonia and *tert*-butyl alcohol in 75:15 ratio gave an optimum yield. Conversion of **6** to the desired $\Delta^{13,14}$-enone **7** was done by

Scheme I



[a] $Li/NH_3/t$-BuOH. [b] H_3O^+. [c] CH_2N_2. [d] H_2/Pd-C. [e] $(i\text{-Pr})_2NLi$. [f] PhSeCl and then H_2O_2. [g] $(i\text{-Pr})_2CuLi$. [h] O_3/Me_2S. [i] $CrO_3/H_2SO_4/Me_2CO$. [j] $(CF_3CO)_2O$.

a modified Spencer's procedure.[9] A saturated ketone obtained by catalytic hydrogenation of **6** was treated with phenylselenenyl chloride in ethyl acetate and subsequently oxidized with hydrogen peroxide to give the expected $\Delta^{13,14}$-enone **7**[10] in a satisfactory yield. Enone **7** was reacted with 1.5 equiv of a lithium diisopropylcuprate–dimethyl sulfide complex, and the resulting enolate intermediate was directly trapped again by phenylselenenyl chloride, to form a 14-isopropyl-13-selenylated ketone, which was converted to the enone **9** by the usual oxidative elimination in 75% yield. Interception of the conjugate addition product (a saturated 14-isopropyl ketone) was not satisfactory. In the latter case, subsequent introduction of the double bond by a sequence of kinetic enolate formation, selenylation, and oxidative elimination gave a 1:1 mixture of **9** and the isomeric $\Delta^{9,11}$-enone **10**. Ozonolysis of **9**, followed by oxidation with Jones' reagent, gave keto carboxylic acid **11** as an amorphous solid. The acid **11** was transformed to the α-pyrone type compound **13** by enol lactonization with trifluoroacetic anhydride followed by the conventional selenylation–elimination sequence. Sodium borohydride reduction of a 7-acetoxylated type A dilactone,[6] e.g., nagilactone A diacetate (**3**), has been known to lead to a 7(8),9(11)-dienolide system, e.g., **14**.[4,11] Application of this



reaction to this synthesis was abandoned after fruitless attempts to introduce an acetoxyl or other related leaving

(1) Y. Hayashi, T. Matsumoto, and T. Sakan, *Heterocycles*, **10**, 123 (1978); J. A. Hembree, C.-jer Chang, J. L. McLaughlin, and J. M. Cassady, *Experientia*, **36**, 28 (1980); J. M. Sasse, K. S. Rowan, and M. N. Galbraith, *Phytochemistry* **20**, 2195 (1981), and references cited therein.

(2) Y. Hayashi, T. Matsumoto, and T. Tashiro, *Gann*, **70**, 365 (1979), and references cited therein.

(3) Synthesis of a 13,15,16,17-tetranorditerpenoid, an antifungal mold metabolite, is the only precedent for the synthetic work of this type of the dilactones: M. Adinolfi, L. Mangoni, G. Barone, and G. Laonigro, *Tetrahedron Lett.*, 695 (1972); *Gazz. Chim. Ital.*, **103**, 1271 (1973); S. C. Welch, C. P. Hagan, D. H. White, W. P. Fleming, and J. W. Trotter, *J. Am. Chem. Soc.*, **99**, 549 (1977).

(4) Y. Hayashi, J. Yokoi, Y. Watanabe, T. Sakan, Y. Masuda, and R. Yamamoto, *Chem. Lett.*, 759 (1972).

(5) Y. Hayashi and T. Sakan, *Proc. 8th Int. Conf. Plant Growth Substances*, 525 (1974).

(6) Y. Hayashi and T. Matsumoto, *J. Org. Chem.*, preceding article in this issue.

(7) The preliminary communication of this synthesis: Y. Hayashi, T. Matsumoto, T. Hyono, N. Nishikawa, M. Uemura, M. Nishizawa, M. Togami, and T. Sakan, *Tetrahedron Lett.*, 3311 (1979).

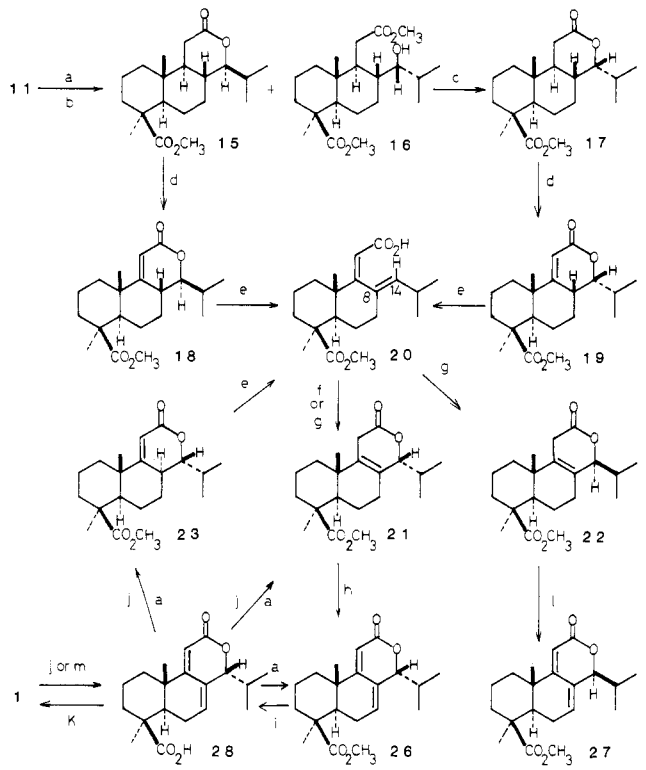
(8) E. Wenkert and T. Tahara, *J. Am. Chem. Soc.*, **82**, 3229 (1960); M. L. Meyer and K. K. Maheshwari, *Tetrahedron Lett.* 2175 (1964).

(9) T. A. Spencer, R. A. J. Smith, D. L. Storm, and R. M. Villarica, *J. Am. Chem. Soc.*, **93**, 4856 (1971).

(10) An alternative attempt to direct the preparation of **7**, Birch reduction of the 13-carboxy derivative **8** of *O*-methylpodocarpic acid followed by acid hydrolysis, gave no useful results.

(11) Y. Hayashi, S. Takahashi, H. Ona, and T. Sakan, *Tetrahedron Lett.*, 2071 (1968).

Scheme II

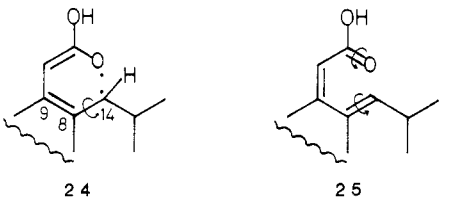


[a] CH_2N_2. [b] B_2H_6/THF. [c] TsOH/C_6H_6. [d] $(i\text{-Pr})_2NLi$/PhSeCl and then H_2O_2. [e] t-BuOK/Me_2SO. [f] $h\nu$/MeOH. [g] Δ. [h] DDQ/BF_3/dioxane. [i] H_2SO_4 and then H_2O. [j] H_2/PdC/HOAc/$HClO_4$. [k] $Pb(OAc)_4/h\nu$. [l] NBS and then Zn/THF. [m] H_2/PdC/n-BuOH/$NaHCO_3$.

group at C-7 of the intermediate **13**.

Reduction (diborane, 0 °C) of the ketone carbonyl group of **11**, after esterification with diazomethane, gave lactone **15** and hydroxy ester **16** (Scheme II), both of which were readily separated chromatographically. Hydroxy ester **16** was also lactonized under forcing conditions (refluxing in benzene with acid catalyst) to form the epimeric (C-14) lactone **17**. The stereochemistry at C-14 of the lactones **15** and **17** was found through the observed difference of the lactonization rate; readily formed **15** should form a more stable equatorial 14β-isopropyl group with the chair-type C ring, while **17** should form an axial 14α-isopropyl. The two saturated lactones **15** and **17** were transformed into 9(11)-unsaturated lactones **18** and **19**, respectively, by the selenylation (C-11) and subsequent oxidation process. The stereochemical relationship between H-8 and H-14 for the two unsaturated lactones were evidenced by ^{1}H NMR parameters, $J_{8,14} \approx 10.0$ Hz for **18** and 3.5 Hz for **19**, which also supported the above mentioned assignments of a C-14 configuration in **15** and **17**. On these $\Delta^{9,11}$-lactones, introduction of a functional group at C-8, which could serve to furnish a 7(8) double bond, was not successful. However, treatment of the both compounds with potassium *tert*-butoxide in dimethyl sulfoxide gave the same diene carboxylic acid, **20**, quantitatively by an internal elimination of the carboxyl group at C-8 and C-14. The acid **20** was also formed under the same conditions from another isomeric $\Delta^{9,11}$-lactone, **23**, which was derived from nagilactone F (**1**) through reductive degradation as mentioned below. The acid **20** from the three sources was identified and characterized by spectral (including the optical rotation) and elemental analysis. At this stage, the natural norditerpenoid dilactone was first correlated chemically with (4S)-(+)-podocarpic acid (**4**) with established stereochemistry. The configuration of the $\Delta^{8,14}$ double bond of **20** must be E, since this acid was formed under the base equilibrium conditions. The acid does not show a distinctive absorption maximum in the UV region, but shoulders around 220 and 260 nm are seen. This fact would indicate the lack of coplanarity of the diene system because of a steric reason.

The acid **20** decomposed on being heating above its melting point without coloration. After spectral inspection, the acid was found to be changed to a mixture (5:3) of two isomeric $\Delta^{8,9}$-lactones, **21** and **22**. On the other hand, irradiation in ethanol with a medium-pressure mercury lamp at 0 °C changed acid **20** exclusively into the single $\Delta^{8,9}$-lactone **21**, which was proved to be the minor component of the above pyrolysis mixture by the ^{13}C NMR comparison. The double bond in **21** was placed at the 8(9)-position, since **21** exhibited no appreciable UV absorption (no conjugation) and no olefinic proton signal in the ^{1}H NMR but two tetra-substituted olefinic carbon signals at 125.6 and 133.8 ppm in the ^{13}C NMR. The stereochemistry at C-14 was not obvious at this stage. The assignment for **21** as the desired 14α-isopropyl isomer is discussed in the following step. The exclusive formation of the desired isomer **21** in the above photoreaction could be understood by the favorable rotation of the C-8–C-14 bond during the lactonization to such direction that the large isopropyl group avoids the nonbonded interaction with the angular methyl group at C-10, in either a radical cyclization of a photochemically produced biradical at C-14 and the carbonyl oxygen (see **24**) or a concerted 6π-electrocyclic reaction involving the carbonyl system (see **25**).[12]



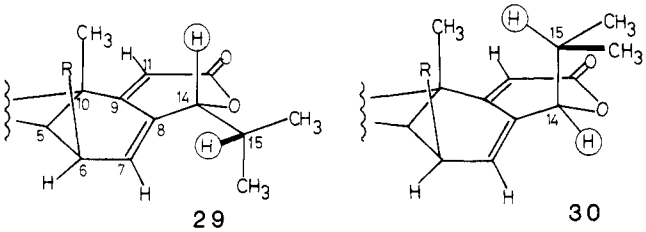
24 **25**

The $\Delta^{8,9}$-enolide **21** was dehydrogenated with dichlorodicyano-p-benzoquinone in refluxing dioxane in the presence of BF_3 to the $\Delta^{7(8),9(11)}$-dienolide **26**. The isomeric $\Delta^{8,9}$-enolide **22** gave another $\Delta^{7(8),9(11)}$-dienolide **27**, epimeric to **26** at C-14, by bromination with NBS (2.6 equiv) followed by elimination with zinc in DMF. Under the latter conditions, enolide **21** gave no useful results.

The configuration at C-14 of both of the epimeric $\Delta^{7(8),9(11)}$-dienolides **26** and **27** could be related to those of the dienolide-type dilactones **1** and **14**, respectively. The H-14β signal of **26** in the ^{1}H NMR spectrum appears in a narrow multiplet with fine splitting. The coupling parameters, $J_{14\beta,15}$ (vicinal), $J_{7,14\beta}$ (allylic), and $J_{6,14\beta}$ (homoallylic), have approximately the same magnitude (~2.5 Hz), which is characteristic to the natural nagilactone F (**1**). In contrast to this, the H-14α of **27** shows a clear doublet signal ($J_{14\alpha,15} \approx 8.0$ Hz) with small further splittings due to H-7/H-14α and H-6/H-14α interactions, also characteristic of the dienolide-type dilactone **14**.[11] These facts can be explained by the different orientation of H-14 to the nearby protons in both of the epimeric C-14 configurations: approximately 90° of the dihedral angle of the quasi-axial H-14β to the plane of the 7(8),9(11)-diene system for **26** and **1**, which should exhibit maximal magitude of the allylic (H-7/H-14) and the homoallylic (H-6/H-14) coupling (2.5 Hz), and approximately 30° of the

(12) O. L. Chapman and W. R. Adams, *J. Am. Chem. Soc.*, **90**, 2333 (1968).

corresponding angle of the quasi-equatorial H-14α for **27** and **14**, which should show smaller long-range coupling[13] as shown by **29** and **30**. The difference of $J_{14,15}$ values of



29 **30**

the epimeric dienolides is also explained in relation to the rotational conformation of the isopropyl group around the C-14–C-15 axis. **26** and **1** would exist in energetically the most favorable conformer **29** (minimal nonbonded interaction of two methyls of the isopropyl with nearby atoms), where the dihedral angle of H-14β/H-15 is 30–60° ($J_{14\beta,15} \approx 2.5$ Hz). On the other hand, the corresponding dihedral angle for the most stable conformer **30**, of the isomeric pair **27** and **14** with β-isopropyl group, would be 160–180° ($J_{14\alpha,15} \approx 8$ Hz).

The $\Delta^{7(8),9(11)}$-dienolide ester **26** was hydrolyzed to dienolide acid **28** in quantitative yield on treatment with concentrated sulfuric acid followed by quenching with ice. Attempts to hydrolyze **26** under basic SN_2 conditions,[14] usually applicable to sterically hindered methyl esters, gave no successful results.

Allylic lactonization of **28** was achieved by oxidation with lead(IV) acetate in benzene under irradiation. The product was identical with natural nagilactone F by IR, ^1H NMR, and melting point comparisons.[4]

Since nagilactone F (**1**) was successfully derived from nagilactone E (**2**),[6] the most abundant natural dilactone, the following degradative works of **1** have played an important role on this synthesis. Catalytic hydrogenation of **1** with Pd/C under acidic conditions ($HOAc/HClO_4$) gave the $\Delta^{7(8),9(11)}$-dienolide acid **28** in good yield with rapid incorporation of 1 mol of hydrogen. The acid **28** did not crystalize but gave, on treatment with diazomethane, the crystalline methyl ester **26**, which was characterized by elemental and spectral analyses. When the hydrogenation of **1** was prolonged until the second mole of hydrogen was absorbed, a mixture of the two unsaturated lactones **21** and **23** was obtained in an acceptable yield after esterification with diazomethane. So that this hydrogenation at the stage of the dienolide acid **28** could be stopped, alkaline conditions (n-$BuOH/NaHCO_3$) were more satisfactory since hydrogen incorporation practically ceased after the consumption of 1 equiv. The structures of **21** and **23** were deduced unambiguously by ^1H and ^{13}C NMR analysis. The three compounds **21**, **23**, and **26** were completely identical with those derived from podocarpic acid, including identical optical properties.

The structure and the absolute configuration of a type C dilactone (7(8),9(11)-dienolide) were established by this synthesis. Our next efforts are now directed to an idependent synthesis of more oxygenated type A (8(14),9-(11)-dienolides) or type B (7α,8α-epoxy-9(11)-enolides) dilactones, since no successful results have been obtained on the transformation of type C to the other two.[6]

Experimental Section

All melting points are uncorrected and were determined on a Yanagimoto Model MPJ-2 microapparatus. IR and UV spectra were recorded on a JASCO Model A-102 and a Hitachi Model 323 spectrometer, respectively. NMR spectra were measured on a JEOL Model PS-100 (CW, 100 MHz) and a Model FX-100 (FT, 100 MHz) spectrometer. Mass and CD spectra were determined with a JEOL Model D-300 high-resolution mass spectrometer and a JASCO Model J-20 automatic spectropolarimeter. Elemental analysis was performed with a Perkin-Elmer Model 240 automatic elemental analyzer. All organic solvents were purified by a standard procedure before use. Podocarpic acid was supplied by Aldrich Chemical Co. (Milwaukee, MN) and Koch-Light Laboratories (Colnbrook, Slough SL3 OBZ, England). Merck Kieselgel 60 (for column) and Kieselgel GF_{254} Type 60 (for TLC) were used for chromatographic adsorbents.

Synthesis of Nagilactone F (1) from (4*S*)-(+)-Podocarpic Acid (4). Preparation of $\Delta^{13,14}$-Enone 7. Enone **7** was prepared from (4*S*)-(+)-podocarpic acid by a modified procedure of Spencer's method.[9]

(a) Metal Reduction of *O*-Methylpodocarpic Acid (5). To a solution of *O*-methylpodocarpic acid (30 g, 0.104 mol), prepared from podocarpic acid [$(CH_3)_2SO_4/NaOH$], in 150 mL of anhydrous *tert*-butyl alcohol was introduced 750 mL of liquid NH_3. Lithium metal (7.2 g, 1.04 g-atom, 10 equiv) was added in small pieces under refluxing NH_3. After disappearance of the blue color of lithium metal (3 h), the mixture was decomposed by adding solid NH_4Cl (48 g) and worked up as usual manner. The crude product was treated with methanolic HCl (250 mL of MeOH, 34 mL of concentrated HCl, 20 mL of H_2O) and then esterified with CH_2N_2 in ether. The product was fractionated on SiO_2 with petroleum ether/ether solvent system. $\Delta^{9,11}$-Enone **6** was obtained in 40.6% average yield.

(b) Hydrogenation of $\Delta^{9,11}$-Enone 6. Enone **6** (4.08 g, 14.1 mmol) was hydrogenated with 5% Pd/C (300 mg) in 45 mL of EtOAc at 25 °C for 10 h. A saturated 12-ketone (4.09 g, quantitative) was obtained after filtration and evaporation of the solvent. The product was homogeneous on TLC and used directly for the following reaction.

(c) 13-Selenylation and Oxidative Elimination. The saturated ketone (5.75 g, 20 mmol) was treated with 4.6 g (24 mmol, 1.2 equiv) of phenylselenenyl chloride in EtOAc (100 mL) at 25 °C for 1 h. After addition of brine, the mixture was extracted with ether. The crude product, on evaporation of the solvent, was dissolved in THF (100 mL) and treated with 9 mL of 30% H_2O_2 (H_2O_2, 2.72 g, 80 mmol, 4 equiv) below 30 °C. After standing for 1 h at 25 °C, the mixture was diluted with water and worked up as usual. The product was chromatographed over silica gel (150 g) with hexane/ether (5:2) to give 4.81 g (82%) of $\Delta^{13,14}$-enone **7** as crystals: mp 131 °C (lit.[9] mp 130–131.5 °C); UV (EtOH) 232 nm; IR (CCl_4) 1722, 1684, 1163 cm^{-1}; ^1H NMR (CCl_4) δ 0.71 (3 H, s, CH_3), 1.16 (3 H, s, CH_3), 3.60 (3 H, s, OCH_3), 5.76 (1 H, dd, J = 4.0, 10.0 Hz, H-14), 6.51 (1 H, dd, J = 2.0, 10.0 Hz, H-13).

Methyl 13-Carboxy-*O*-methylpodocarpate (8). Methyl 13-acetyl-*O*-methylpodocarpate[15] (4.86 g, 14.1 mmol) was dissolved in dioxane (200 mL) and water (60 mL). To this mixture was added in 30 min at 5 °C a sodium hypobromite solution, prepared by adding 7.63 g (46.7 mmol) of bromine to a NaOH solution [NaOH (7.39 g, 185.7 mmol), H_2O (63 mL), dioxane (44 mL)] below 0 °C. The reaction mixture was kept at 5 °C for 3 h and quenched with Na_2SO_3 (1.75 g) in H_2O (18 mL). After acidification (HCl) and extraction (ether), the product **8** was obtained in quantitative yield, mp 168–169 °C.

Anal. Calcd for $C_{20}H_{26}O_5$: C, 69.34; H, 7.57. Found: C, 69.30; H, 7.65.

14-Isopropyl-$\Delta^{13,14}$-enone 9. A solution of enone **7** (980 mg, 3.38 mmol) in THF (8 mL) was added at −78 °C to a stirred solution of $LiCu(i\text{-}Pr)_2$, prepared from 0.52 M *i*-PrLi in THF (19.5 mL, 10.14 mmol, 3 equiv), $(CH_3)_2S$ (629 mg, 10.14 mmol) in THF (10 mL), and CuI (964, mg, 5.07 mmol, 1.5 equiv, at −78 °C for 10 min. The mixture was warmed to −30 °C in 1 h, and then PhSeCl (1.94 g, 10.14 mmol, 3 equiv) in THF (10 mL) was added at −78 °C in 10 min. After being quenched with aqueous NH_4Cl at 25 °C, the mixture was worked up as usual. The crude product was dissolved in THF (45 mL) and treated with 30% H_2O_2 (4 mL, H_2O_2, 1.19 g, 35 mmol). Dilution with water and extraction with

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ether gave a crude product, which was purified on silica gel (70 g) with petroleum ether/ether (5:2). 14-Isopropylenone **9** (843 mg, 75%) was obtained as crystals: mp 115 °C; UV (EtOH) 240 nm; IR (CCl_4) 1722, 1675, 1615 cm^{-1}; ^1H NMR (CCl_4) δ 0.72 (3 H, s, CH_3), 1.09 (3 H, d, J = 6.0 Hz, CH_3), 1.12 (3 H, d, J = 6.0 Hz, CH_3), 1.18 (3 H, s, CH_3), 3.64 (3 H, s, OCH_3), 5.76 (1 H, br s, H-13).

Anal. Calcd for $C_{21}H_{32}O_3$: C, 75.86; H, 9.70. Found: C, 75.72; H, 9.59.

Ozonolysis of Enone 9. A solution of **9** (298 mg, 0.90 mmol) in CH_2Cl_2 (3.5 mL) and MeOH (0.9 mL) was saturated with ozone at −78 °C (slight blue color). After removal of an excess of ozone by bubbling N_2 through for some time, the ozonide was decomposed by adding Me_2S (0.2 mL, 170 mg, 3 equiv) at −78 °C. The solvent was evaporated at 25 °C, and the residue was oxidized with Jones' reagent at 0 °C in acetone. After decomposition of an excess of the oxidant with *i*-PrOH, the mixture was worked up as usual. Keto acid **11** was obtained as a homogeneous amorphous solid: 228 mg (72.2%); IR ($CHCl_3$) 3400, 2500, 1708, 1700 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.67 (3 H, s, CH_3), 1.08 (6 H, d, J = 6.0 Hz, CH_3), 1.17 (3 H, s, CH_3), 3.67 (3 H, s, OCH_3), ~2.7 (1 H, m, $CHMe_2$); mass spectrum (20 eV), M^+ 352, $M^+ - H_2O$ 334, $M^+ - C_3H_7$ 309.

Acid **11** gave quantitatively a crystalline methyl ester (CH_2N_2 in ether): mp 103 °C; IR ($CHCl_3$) 1720, 1710 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.66 (3 H, s, CH_3), 1.07 (3 H, d, J = 7.0 Hz, CH_3), 1.08 (3 H, d, J = 7.0 Hz, CH_3), 1.18 (3 H, s, CH_3), 2.75 (1 H, m, J = 7.0 Hz, $CHMe_2$), 3.62 (3 H, s, OCH_3), 3.64 (3 H, s, OCH_3).

Anal. Calcd for $C_{21}H_{34}O_5$: C, 68.82; H, 9.35. Found: C, 68.80; H, 9.43.

Enol Lactone 12. Keto acid **11** (80 mg, 0.227 mmol) was treated with a large excess of $(CF_3CO)_2O$ at 25 °C for 3 h. The mixture was concentrated in vacuo and washed with aqueous $NaHCO_3$ as an ether solution. After purification by SiO_2 chromatography, enol lactone **12** was obtained as crystals: mp 174 °C; 65 mg (85.6%); IR ($CHCl_3$) 1735, 1715 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.61 (3 H, s, CH_3), 1.06 (6 H, d, J = 7.0 Hz, CH_3), 1.20 (3 H, s, CH_3), 2.90 (1 H, m, J = 7.0 Hz, $CHMe_2$), 3.63 (3 H, s, OCH_3); mass spectrum (20 eV), M^+ 334, 289, 273, 229.

Anal. Calcd for $C_{20}H_{30}O_4$: C, 71.82; H, 9.04. Found: C, 71.94; H, 9.03.

α-Pyrone 13. A solution of enol lactone **12** (34 mg, 0.10 mmol) in THF (0.1 mL) was added at −78 °C to a stirring solution of *i*-Pr_2NLi, prepared from *i*-Pr_2NH (30 mg, 0.275 mmol, 2.7 equiv), 1.5 M *n*-BuLi in hexane (165 μL, 0.25 mmol, 2.4 equiv), and THF (0.5 mL) at −78 °C. The mixture was then treated with a solution of PhSeCl (53 mg, 0.27 mmol, 2.7 equiv) in THF (0.5 mL) at −78 °C. After 30 min, the mixture was decomposed with aqueous NH_4Cl at 25 °C. The crude product was oxidized with 30% H_2O_2 (0.17 mL, 1.5 mmol). The product from this oxidation consisted of two components, which were separated on a SiO_2 column (10 g, petroleum/ether). The lower R_f component was the desired pyrone **13** (18 mg (53%)): mp 160 °C; UV (EtOH) 317 nm; IR ($CHCl_3$) 1715, 1705, 1610, 1524 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.06 (3 H, s, CH_3), 1.18 (3 H, d, J = 6.5 Hz, CH_3), 1.22 (3 H, d, J = 6.5 Hz, CH_3), 1.29 (3 H, s, CH_3), 3.70 (3 H, s, OCH_3), 6.09 (1 H, s, H-11); mass spectrum (20 eV), M^+ 332, 304, 289, 278. The higher R_f product was characterized as the 8,14-epoxide of enol lactone **12** (4 mg); mp 163–164 °C; IR ($CHCl_3$) 1737, 1715 cm^{-1}; ^{13}C NMR ($CDCl_3$) δ 12.9 (q, C-16), 15.9 (q, C-17), 17.9 (q, C-20), 19.3 (t, C-2), 23.3 (t, C-6), 28.1 (t, C-1), 28.8 (q, C-18), 30.3 (t, C-3), 30.6 (d, C-15), 37.9 (t, C-7), 39.6 (t, C-11), 39.9 (s, C-10), 44.0 (s, C-4), 48.0 (d, C-5), 51.5 (q, OCH_3), 55.0 (d, C-9), 65.2 (s, C-8), 93.1 (s, C-14), 169.1 (s, C-12), 177.1 (s, C-19).

Anal. Calcd for $C_{20}H_{30}O_5$: C, 68.54; H, 8.63. Found: C, 68.55; H, 8.67.

Diborane Reduction of the Methyl Ester of 11. A solution of the methyl ester (1.01 g, 2.73 mmol), prepared from **11** with CH_2N_2 in ether, in THF (20 mL) was treated with 1.1 M diborane in THF (27 mL, 30 mmol) at 0 °C for 1 h. The mixture was decomposed with H_2O and worked up as usual. Fractionation of the crude product over SiO_2 (60 g) with petroleum ether/ether (3:1) gave two pure compounds, **15** and **16**. Lactone **15** (421 mg (46%)): mp 181–182 °C; IR ($CHCl_3$) 1712, 1683 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.70 (3 H, s, CH_3), 0.92 (3 H, d, J = 8.0 Hz, CH_3), 1.12 (3 H, d, J = 8.0 Hz, CH_3), 1.22 (3 H, s, CH_3), 2.24 (1 H, dd, J = 11.0, 17.0 Hz, H-11β), 2.68 (1 H, dd, J = 7.0, 17.0 Hz H-11α), 3.74 (3 H, s, OCH_3), 3.88 (1 H, dd, J = 3.0, 8.0 Hz, H-14).

Anal. Calcd for $C_{20}H_{32}O_4$: C, 71.39; H, 9.59. Found, C, 71.14; H, 9.53.

Hydroxy ester **16** was obtained as an amorphous solid (410 mg (40%)): IR ($CHCl_3$) 3400, 1712 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.64 (3 H, s, CH_3), 0.80 (3 H, d, J = 7.0 Hz, CH_3), 1.04 (3 H, d, J = 7.0 Hz, CH_3), 1.21 (3 H, s, CH_3), 2.98 (1 H, d, J = 9.0 Hz, H-14), 3.71 (3 H, s, OCH_3), 3.76 (3 H, s, OCH_3). On refluxing (2 h) in benzene (3 mL) with TsOH (3 mg), hydroxy ester **16** (30 mg) was converted to lactone **17** (27 mg (95%)), isomeric to **15**; mp 117 °C; IR ($CHCl_3$) 1719, 1711 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.68 (3 H, s, CH_3), 1.02 (3 H, d, J = 8.0 Hz, CH_3), 1.09 (3 H, d, J = 8.0 Hz, CH_3), 1.23 (3 H, s, CH_3), 2.27 (1 H, dd, J = 10.0, 18.0 Hz, H-11β), 2.61 (1 H, dd, J = 7.0, 18.0 Hz, H-11α), 3.72 (3 H, s, OCH_3), 4.23 (1 H, dd, J = 5.0, 6.0 Hz, H-14).

Anal. Calcd for $C_{20}H_{34}O_4$: C, 71.39; H, 9.59. Found: C, 71.00; H, 9.42.

14β-Isopropyl-$\Delta^{9,11}$-enolide 18. The 14β-Isopropylenolide **18** was obtained from the corresponding saturated lactone **15** (16 mg) by the same procedure as described for the dehydrogenation of **12** to the pyrone **13** (*i*-Pr_2NLi/PhSeCl, then H_2O_2); 12 mg (75%); mp 126–8 °C; UV (EtOH) 223 nm; IR ($CHCl_3$) 1710, 1693 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.96 (3 H, s, CH_3), 0.98 (3 H, d, J = 7.0 Hz, CH_3), 1.12 (3 H, d, J = 7.0 Hz, CH_3), 1.23 (3 H, s, CH_3), 3.74 (3 H, s, OCH_3), 3.93 (1 H, dd, J = 3.0, 10.0 Hz, H-14), 5.92 (1 H, d, J = 2.0 Hz, H-11); mass spectrum (20 eV), M^+ 334.2142 (calcd for $C_{20}H_{30}O_4$, 334.2143), $M^+ - CH_3$ 319.1900 (calcd for $C_{19}H_{27}O_4$, 319.1909), $M^+ - CH_3O$ 303.1937 (calcd for $C_{19}H_{27}O_3$, 303.1960), $M^+ - C_3H_7$ 291.1562 (calcd for $C_{17}H_{23}O_4$, 291.1596).

14α-Isopropyl-$\Delta^{9,11}$-enolide 19. 14α-Isopropyllactone **17** (215 mg) was converted to enolide **19** by the same procedure as described above. The product, **19**, 140 mg (93%, on subtraction of 63 mg of **17** recovered) was obtained as an amorphous solid: UV (EtOH) 232 nm; IR ($CHCl_3$) 1718, 1698, 1612 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.98 (3 H, d, J = 7.0 Hz, CH_3), 1.04 (3 H, s, CH_3), 1.15 (3 H d, J = 7.0 Hz, CH_3), 1.20 (3 H, s, CH_3), 3.77 (3 H, s, OCH_3), 3.87 (1 H, dd, J = 3.5, 10.0 Hz, H-14), 5.85 (1 H, s, H-11); mass spectrum (20 eV), M^+ 334.2133 (calcd for $C_{20}H_{30}O_4$, 334.2143), $M^+ - C_3H_7$ 291.1582 (calcd for $C_{17}H_{23}O_4$, 291.1596), $M^+ - CO_2CH_3$ 275.2000 (calcd for $C_{18}H_{27}O_2$, 275.2010).

Dienoic Acid 20. (a) From 14α-Isopropyl-$\Delta^{9,11}$-enolide 18. $\Delta^{9,11}$-Enolide **18** (100 mg, 0.3 mmol) was dissolved in anhydrous Me_2SO (5 mL) and treated with 100 mg (3 equiv) of *t*-BuOK (purified by sublimation) at 25 °C for 12 h under N_2. After acidification with HCl, the product was taken up into $CHCl_3$ and purified by TLC. Dienoic acid **20**: 100 mg (quantitative); mp 145 °C; IR ($CHCl_3$) 3400–2500, 1715, 1697, 1623 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.81 (3 H, s, CH_3), 0.92 (3 H, d, J = 7.0 Hz, CH_3), 0.97 (3 H, d, J = 7.0 Hz, CH_3), 1.20 (3 H, s, CH_3), 3.65 (3 H, s, OCH_3), 5.00 (1 H, d, J = 9.5 Hz, H-14), 5.48 (1 H, s, H-11); ^{13}C NMR ($CDCl_3$) δ 18.5 (q, C-20), 20.0 (t, C-2), 21.9 (q, C-16), 23.3 (q, C-17), 24.5 (t, C-6), 27.1 (d, C-15), 29.0 (q, C-18), 30.0 (t, C-1), 37.3 (t, C-3), 38.2 (t, C-7), 42.5 (s, C-10), 44.8 (s, C-4), 51.5 (q, OCH_3), 54.8 (d, C-5), 111.1 (d, C-11), 133.6 (s, C-8), 135.2 (d, C-14), 170.4 (s, C-9), 173.4 (s, C-12), 177.4 (s, C-19); mass spectrum (10 eV), M^+ 334.2150 (calcd for $C_{20}H_{30}O_4$ 334.2144), $M^+ - H$ 333.2089 (calcd for $C_{20}H_{29}O_4$, 333.2064); $M^+ - C_3H_7$ 291.1590 (calcd for $C_{17}H_{23}O_4$; 291.1596), $M^+ - C_3H_7 - C_2H_4O_2$ 231.1385 (calcd for $C_{15}H_{19}O_2$, 231.1385); $[\alpha]^{14}_D$ − 86.8° (1.35 mg/mL, MeOH); CD (MeOH) $[\theta]_{244(max)}$ +4800, $[\theta]_{272(min)}$ −1800.

Anal. Calcd for $C_{20}H_{30}O_4$: C, 71.82; H, 9.04. Found: C, 71.99; H, 9.14.

(b) From 14α-Isopropyl-$\Delta^{9,11}$-enolide 19. Treatment of enolide **19** with 3 equiv of *t*-BuOK as described above gave the same dienoic acid, **20**, quantitatively as crystals.

(c) From an Isomeric 14α-Isopropyl-$\Delta^{9,11}$-enolide 23 Derived from Nagilactone F (1). Enolide **23** (50 mg, 0.15 mmol) was treated with *t*-BuOK (50 mg, 0.45 mmol, 3 equiv) in Me_2SO (3 mL) at 55 °C for 1.5 h. After working up as described above, a dienoic acid, 50 mg (quantitative), was obtained as crystals. This product was completely identical with **20** on the spectral comparison. The optical properties, $[\alpha]^{14}_D$ −87.2° (9.05 mg/mL, MeOH) and CD (MeOH) $[\theta]_{244(max)}$ +3850, $[\theta]_{272(min)}$ −3050, of this product were also consistent with those of acid **20** derived from (4*S*)-(+)-podocarpic acid as described in a.

14α-Isopropyl-$\Delta^{8,9}$-enolide 21. (a) By Photochemical Cyclization of Dienoic Acid 20. A solution of **20** (10 mg) in 95% EtOH (4 mL) was irradiated with a medium-pressure mercury lamp at 0 °C for 4 h under N_2. After evaporation of the solvent, the residue was purified over SiO_2 column (12:1:0.1 benzene/EtOAc/EtOH) to afford $\Delta^{8,9}$-enolide **21**, 9 mg (90%): mp 97 °C; $[\alpha]_D^{18}$ +121.7° (2.6 mg/mL, MeOH). All of the spectral data of this product were identical with those of the $\Delta^{8,9}$-enolide derived from nagilactone F as described below.

(b) By Thermal Cyclization of Dienoic Acid 20. When dienoic acid **20** (10 mg) was pyrolyzed at 210 °C for 1 min under N_2, a mixture of two enolides was produced as an amorphous solid in quantitative yield. Separation of the components was not successful, but ^1H and ^{13}C NMR spectra indicate it to be a mixture of two enolides in 5:3 ratio. Each skeletal carbon showed a close couple of signals in the ^{13}C NMR spectrum, in which one set of the signals due to the minor component was superimposable to the spectrum of the pure enolide **21** derived from nagilactone F. The major component is an isomer, **22**, at C-14, showing the following spectral data: IR ($CHCl_3$) 1718 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.83 (3 H, d, J = 7.0 Hz, CH_3), 0.85 (3 H, s, CH_3), 1.12 (3 H, d, J = 7.0 Hz, CH_3), 1.24 (3 H, s, CH_3), 2.93 (2 H, br s, H-11), 3.67 (3 H, s, OCH_3), 4.53 (1 H, br s); ^{13}C NMR ($CDCl_3$) δ 15.4, 16.7, 18.0, 19.4, 19.7, 20.3, 28.1, 28.4 (two peaks), 32.7, 36.3, 43.9, 51.4, 52.5, 86.5, 126.3, 133.6, 171.3, 177.6.

$\Delta^{7(8),9(11)}$-Dienolide Ester 26 by Dehydrogenation of $\Delta^{8,9}$-Enolide Ester 21. A mixture of $\Delta^{8,9}$-enolide **21** (16 mg, 0.048 mmol), dichlorodicyano-*p*-benzoquinone (DDQ) (35 mg, 0.154 mmol, 3.2 equiv), and BF_3 etherate (100 μL) in 8 mL of dioxane was refluxed for 48 h under N_2. The mixture was concentrated under vacuum and the residue purified by TLC (10:1 benzene/EtOAc) to give dienolide ester **26**, 6 mg (38%), mp 141 °C. The properties of this product were fully identical with those of compound **26** derived from natural nagilactone F as described below.

$\Delta^{7(8),9(11)}$-Dienolide 27, Isomeric to 26 at C-14. A mixture of two epimeric (C-14) enolides, **21** and **22** (8 mg, 0.024 mmol), produced by pyrolysis of dienoic acid **20** as described above, was dissolved in $CHCl_3$ (1 mL) and treated with purified NBS (11 mg, 0.062 mmol, 2.6 equiv) under refluxing for 30 min. After filtration and evaporation of the solvent, the residue was purified by TLC (1:1 petroleum ether/ether) to give 5 mg (42%) of a single bromide: ^1H NMR ($CDCl_3$) δ 3.66 (3 H, s, OCH_3), 4.76 (1 H, s, H-11), 4.94 (2 H, m, H-7, H-14). This bromide was mixed with 300 mg of Zn powder (activated with 2 N HCl) and 2 mL of DMF and stirred at 25 °C for 10 min under N_2. The reaction mixture was directly poured onto a SiO_2 (10 g) column and developed with petroleum ether/ether (1:1). Dienolide **27** (2 mg, 61%): UV (EtOH) 281 nm; IR ($CHCl_3$) 1710, 1690 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.88 (3 H, d, J = 6.5 Hz, CH_3), 0.93 (3 H, s, CH_3), 1.00 (3 H, d, J = 6.5 Hz, CH_3), 1.26 (3 H, s, CH_3), 3.69 (3 H, s, OCH_3), 4.48 (1 H, d, J = 8.0 Hz, H-14), 5.67 (1 H, s, H-11), 5.97 (1 H, m, H-7); mass spectrum (30 eV), M^+ 332.1951 (calcd for $C_{20}H_{28}O_4$, 332.1987), $M^+ - OCH_3 - H$ 300.1768 (calcd for $C_{19}H_{24}O_3$, 300.1725), $M^+ - C_3H_7 + H$ 290.1507 (calcd for $C_{17}H_{22}O_4$, 290.1518), $M^+ - C_3H_7$ 289.1436 (calcd for $C_{17}H_{21}O_4$, 289.1439), $M^+ - CO_2CH_3$ 273.1884 (calcd for $C_{18}H_{25}O_2$, 273.1855).

Hydrolysis of $\Delta^{7(8),9(11)}$-Dienolide Ester 26. Dienolide ester **26** (40 mg, 0.12 mmol) was dissolved in 0.3 mL of concentrated H_2SO_4 at 25 °C. After standing at 25 °C for 2 h, the mixture was decomposed with ice. A precipatated white solid was collected by filtration, giving 38 mg (quantitative) of dienolide carboxylic acid **28**. All of the properties of this product was identical with those of acid **28** derived from natural nagilactone F as described below.

Lead(IV) Acetate Oxidation of $\Delta^{7(8),9(11)}$-Dienolide Acid 28. A mixture of **28** (20 mg, 0.063 mmol) and lead(IV) acetate (50 mg, 0.113 mmol, 1.8 equiv) in dry benzene (5 mL) was stirred at 15 °C for 3 days under irradiation with a 15-W-fluorescent lamp. The mixture was directly developed on a SiO_2 column and eluted with CH_2Cl_2 to give 11 mg (55%) of the product, mp 225 °C, which was not distinguishable from natural nagilactone F in all respects.[4]

Hydrogenative Degradation of Nagilactone F (1). $\Delta^{7(8),9(11)}$-Dienolide Ester 26. (a) Nagilactone F (100 mg) was hydrogenated under 1 atm in HOAc (40 mL) containing 20% $HClO_4$ with 10% Pd/C (20 mg) at 25 °C. Hydrogenation was stopped after 20 min when 1 equiv of hydrogen was incorporated. The reaction mixture was worked up as usual to give 85 mg (85%) of $\Delta^{7(8),9(11)}$-dienolide acid **28** as a colorless, amorphous solid: UV (EtOH) 284 nm; IR ($CHCl_3$) 1692 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.98 (3 H, d, J = 7.0 Hz, CH_3), 1.03 (3 H, s, CH_3), 1.05 (3 H, d, J = 7.0 Hz, CH_3), 1.33 (3 H, s, CH_3), 4.75 (1 H, m, H-14), 5.77 (1 H, s, H-11), 6.13 (1 H, m, H-7). The acid was characterized as the methyl ester **26**, prepared with CH_2N_2 in ether; mp 141 °C; UV (EtOH) 283 nm; IR ($CHCl_3$) 1710, 1690 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.95 (3 H, s, CH_3), 0.98 (3 H, d, J = 7.0 Hz, CH_3), 1.04 (3 H, d, J = 7.0 Hz, CH_3), 1.26 (3 H, s, CH_3), 3.73 (3 H, s, OCH_3), 4.70 (1 H, m, H-14), 5.72 (1 H, br s, H-11), 6.09 (1 H, m, H-7); ^{13}C NMR ($CDCl_3$) δ 16.7 (q, C-16), 19.6 (t and q, C-2 and C-17), 20.1 (q, C-20), 25.1 (t, C-6), 28.5 (q, C-18), 33.7 (d, C-15), 36.6 (t, C-3), 37.5 (t, C-1), 38.1 (s, C-10), 44.0 (s, C-4), 49.6 (d, C-5), 51.7 (q, OCH_3), 84.3 (d, C-14), 110.1 (d, C-11), 127.7 (s, C-8), 132.3 (d, C-7), 162.4 (s, C-9), 165.7 (s, C-12), 177.1 (s, C-19); mass spectrum (30 eV), M^+ 332.1945 (calcd for $C_{20}H_{28}O_4$, 332.1987), $M^+ - C_3H_6$ 290.1560 (calcd for $C_{17}H_{22}O_4$, 290.1518), $M^+ - C_3H_7$ 289.1413 (calcd for $C_{17}H_{21}O_4$, 289.1440).

Anal. Calcd for $C_{20}H_{28}O_4$: C, 72.27; H, 8.49. Found: C, 71.96; H, 8.54.

(b) Nagilactone F (200 mg) was hydrogenated with 10% Pd/C (40 mg) in *n*-BuOH (30 mL) and 5% $NaHCO_3$ (30 mL) under 1 atm at 25 °C. The reaction proceeded smoothly with absorption of 1 equiv of H_2 and then stopped. After filtration of the catalyst and acidification with 2 N HCl, extraction with EtOAc gave 200 mg of the product. The crude material was purified by preparative TLC (SiO_2) to give dienolide acid **28** (170 mg, 85%), which was characterized as the crystalline methyl ester **26** (CH_2N_2) as described above.

$\Delta^{8,9}$-Enolide Ester 21 and $\Delta^{9,11}$-Enolide Ester 23. When hydrogenation of **1** under the acidic conditions (HOAc/$HClO_4$) was continued until 2 equiv of H_2 was consumed, a mixture of two compounds was produced. The crude product was esterified with CH_2N_2 and chromatographed on a SiO_2 (100 g) column with benzene/EtOAc/EtOH (15:1:0.1) to afford two pure components, **21** (320 mg, 61%) and **23** (75 mg, 14%). **21**: mp 97 °C; IR ($CHCl_3$) 1719 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.84 (3 H, d, J = 7.0 Hz, CH_3), 0.85 (3 H, s, CH_3), 1.12 (3 H, d, J = 7.0 Hz, CH_3), 1.25 (3 H, s, CH_3), 2.95 (2 H, br s, H-11), 3.67 (3 H, s, OCH_3), 4.53 (1 H, m, H-14); ^{13}C NMR ($CDCl_3$) δ 15.0 (q, C-16), 16.7 (q, C-17), 19.3 (t, C-2), 19.6 (q, C-20), 20.2 (t, C-6), 28.4 (q, C-18), 29.1 (d, C-15), 29.4 (t, C-7), 32.4 (t, C-1), 36.6 (t, C-3), 37.6 (t, C-11), 37.8 (s, C-10), 43.8 (s, C-4), 51.4 (q, OCH_3), 53.3 (d, C-5), 88.2 (d, C-14), 125.6 (s, C-8), 133.8 (s, C-9), 171.0 (s, C-12), 177.5 (s, C-19); $[\alpha]_D^{18}$ +121.6° (2.5 mg/mL, MeOH); mass spectrum (20 eV), M^+ 334.2119 (calcd for $C_{20}H_{30}O_4$, 334.2143), $M^+ - C_3H_7$ 291.1557 (calcd for $C_{17}H_{23}O_4$, 291.1596), $M^+ - CH_3O - CH_3 + H$ 289.1800 (calcd for $C_{18}H_{25}O_3$, 289.1803). **23**: mp 155 °C; UV (EtOH) 230 nm; IR ($CHCl_3$) 1717 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.98 (3 H, d, J = 7.0 Hz, CH_3), 1.04 (3 H, s, CH_3), 1.12 (3 H, d, J = 7.0 Hz, CH_3), 1.23 (3 H, s, CH_3), 3.66 (3 H, s, OCH_3), 3.81 (1 H, dd, J = 2.5, 11.0 Hz, H-14), 5.84 (1 H, d, J = 2.5 Hz H-11); ^{13}C NMR ($CDCl_3$) δ 15.0 (q, C-16), 19.2 (t, C-2), 19.8 (q, C-17), 19.8 (q, C-20), 22.0 (t, C-6), 28.6 (q, C-18), 28.6 (d, C-15), 30.8 (t, C-7), 36.3 (t, C-1), 36.5 (d, C-8), 37.5 (t, C-3), 40.5 (s, C-10), 44.2 (s, C-4), 51.4 (q, OCH_3), 53.3 (d, C-5), 85.8 (d, C-14), 111.3 (d, C-11), 166.2 (s, C-9), 171.1 (s, C-12), 177.0 (s, C-19).

Anal. Calcd for $C_{20}H_{30}O_4$: C, 71.82; H, 9.04. Found: C, 71.77, H, 9.12.

Registry No. 1, 36912-00-2; 4, 5947-49-9; 5, 10037-26-0; 6, 24402-17-3; dihydro-6, 19954-86-0; 7, 24402-16-2; 8, 82246-91-1; 9, 73616-45-2; 10, 73723-71-4; 11, 73616-47-4; 11 methyl ester, 73616-50-9; 12, 73616-48-5; 13, 73616-49-6; 15, 73616-52-1; 16, 82246-92-2; 17, 73650-96-1; 18, 73616-53-2; 19, 73650-97-2; 20, 73746-23-3; 21, 73616-55-4; 22, 73746-24-4; 23, 73650-98-3; 26, 73616-56-5; 27, 73746-25-5; 28, 73616-57-6.