A New Route toward 7-Oxo-13-hydroxy-8,11,13-podocarpatrienes from Labdane Diterpenes

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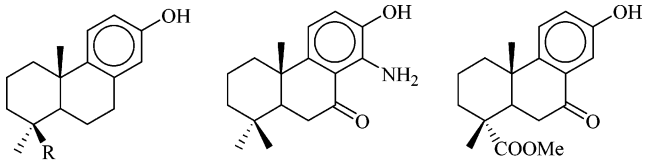
Trinorlabdane 1,5-diketones (**7**, **10a**,**b**, **13a**,**b**), which are easily prepared from labdane diterpenes, are directly converted into the corresponding 7-oxo-13-hydroxy-8,11,13-podocarpatrienes, immediate precursors of bioactive compounds, under basic treatment. Utilizing this strategy, the first enantiospecific synthesis of 13-hydroxy-8,11,13-podocarpatriene (**20**), a constituent of *Taiwania cryptomerioides*, was achieved starting from (−)-sclareol (**5**) after a seven-step sequence in 55% overall yield.

Podocarpane diterpenes do not occur extensively in nature but are present in several genera, such as *Azadirachta*,[1] *Humirianther*,[2] *Micrandropsis*,[3] and *Podocarpus*.[4] During recent years, some biologically active podocarpane phenols have been isolated. Representative examples are **1**, a highly fungistatic agent,[5,6] and the aminophenol **3**, a potent 5-lipoxygenase inhibitor.[7] Recently, some *nor*-dehydroabietic acid derivatives, such as **4**, have been patented as potential antiviral agents.[8]

Due to their natural scarcity, the synthesis of these terpenoids has become the object of increased interest. Some enantiospecific syntheses starting from diterpenes have been reported, but these usually involve many steps and low yields.[9,10] A synthesis based on the enantioselective cyclization of homogeranylbenzene derivatives was recently reported.[11]



1 R: COOH **3** **4**
2 R: Me

In this paper we report a short and efficient route to 7-oxo-13-hydroxy-8,11,13-podocarpatrienes from labdane diterpenes. The key step involves the intramolecular aldol condensation of a trinorlabdane 1,5-diketone, aromatization of the resulting β-enone, and benzylic oxidation.

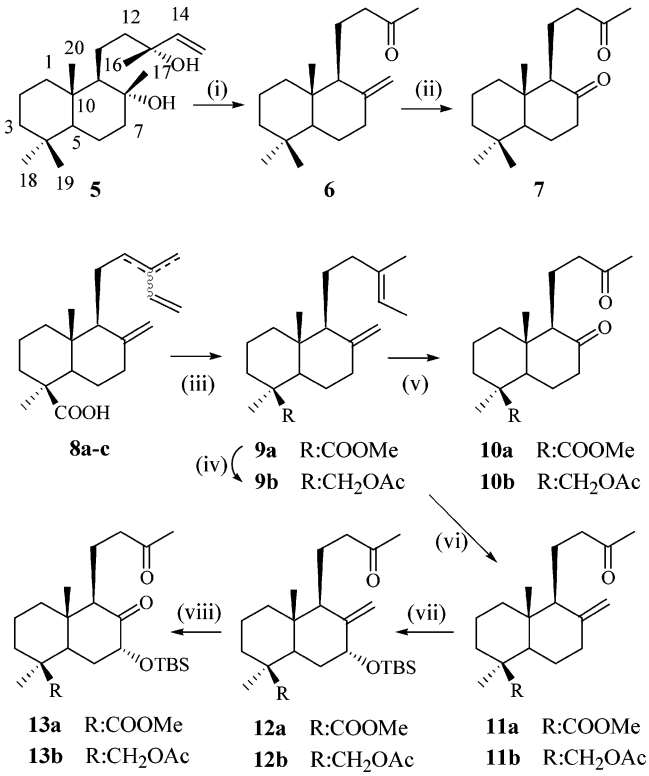
Results and Discussion

During our research into the C ring construction of pentacyclic quassinoids starting from communic acids (**8a**−**c**),[12] via aldol condensation of the corresponding 1,5-diketones, small quantities of phenol derivatives were obtained together with the required β-enones. To explore the synthetic usefulness of this side reaction and its utilization in preparing bioactive podocarpatriene derivatives, several diketones bearing different functionalities in the A- and B-rings were prepared. 1,5-Diketones **7**, **10a**,**b**, and **13a**,**b** were synthesized from (−)-sclareol (**5**), the main component of *Salvia sclarea*,[13] and communic acids (**8a**−**c**), widely found in species of the genus *Juniperus*,[14] respectively (Scheme 1). **7** was obtained by ozonolysis of enone **6**.[15] **10a**,**b** resulted from the ozonolysis of dienes **9a** and **9b**, prepared by 1,4-reduction of the conjugated diene in **8a**−**c**. **13a**,**b** were synthesized after allylic oxidation of **11a**,**b**.

Next, the reaction of these diketones to different basic reagents was investigated, and K_2CO_3 in refluxing MeOH was found to be the most favorable medium to obtain phenol derivatives (Table 1). All diketones gave the expected tricyclic β-enones resulting from the intramolecular aldol condensation, utilizing a diluted base solution for a short period of time. **13a**,**b** were transformed in good yields into phenols **19a**,**b** when a concentrated base and a prolonged reaction time were utilized. Aromatization and simultaneous benzylic oxidation took place when diketones **7** and **10 a**,**b**, lacking the oxygenated function on C-7, were the starting materials; thus, 7-oxophenols **17** and **18a**,**b** were obtained.

Variable quantities of the corresponding β-enones were obtained when the reaction of diketones, with a concentrated base, was quenched after a few hours. Further treatment of the α,β-unsaturated ketones with concentrated base led to the corresponding phenols. A possible mechanism consistent with these results is shown in Scheme 2. Cleavage of hydroperoxide **I** would provide the 1,4-diketone **II**, the dienolate **III** of which would be converted into

Scheme 1. Synthesis of 1,5-Diketones **7**, **10a**,**b**, and **13a**,**b**[a]



[a] (i) Ref 15. (ii) O_3, CH_2Cl_2, −78 °C, 1 h; PPh_3 (90%). (iii) Ref 12. (iv) $LiAlH_4$, THF, reflux, 3 h; Ac_2O, pyridine, DMAP, rt, 12 h (84%). (v) O_3, CH_2Cl_2, −78 °C, 1 h; PPh_3 (86/82%). (vi) Ref 12 for **11a**. OsO_4, $NaIO_4$, $^tBuOH-H_2O$, rt, 5 days (82%). (vii) Ref 12 for **12a**. SeO_2, ^tBuOOH, rt, 12 h; TBSCl, imidazole, DMF, 14 h (60%). (viii) O_3, CH_2Cl_2, −78 °C, 1 h; PPh_3 (89/85%).

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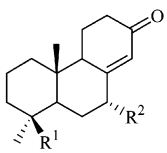
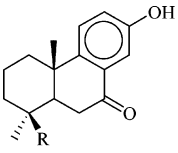
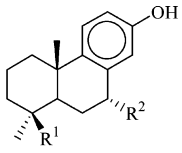


14 R^1: Me; R^2: H
15a R^1: COOMe; R^2: H
15b R^1: CH_2OH; R^2: H
16a R^1: COOMe; R^2: OTBS
16b R^1: CH_2OH; R^2: OTBS



17 R: Me
18a R: COOMe
18b R: CH_2OH



19a R^1: COOMe; R^2: OTBS
19b R^1: CH_2OH; R^2: OTBS

hydroperoxide **IV** by trapping a dioxygen, hence leading to the stable phenol **V**.

The above results permitted development of an efficient synthesis of 13-hydroxy-8,11,13-podocarpatriene (**20**), an antioxidative metabolite isolated from *Taiwania cryptomerioides*,[16] from (−)-sclareol (**5**), via 7-oxophenol **17**. Catalytic hydrogenation of this phenol in the presence of perchloric acid led to **20** in high yield (96%) (Scheme 3). The spectroscopic properties of this compound were identical to those reported. [16]

Experimental Section

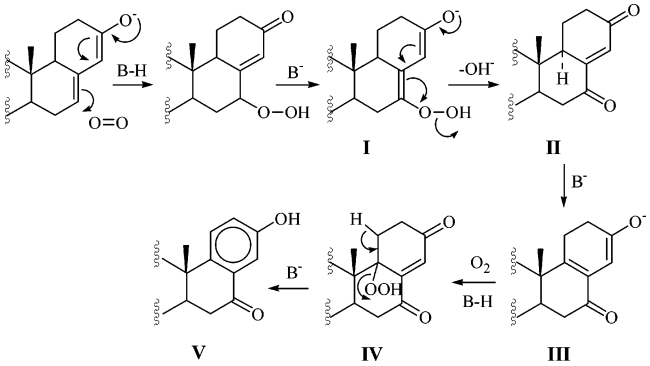
General Experimental Procedures. Melting points were determined with a Kofler hot-stage melting point apparatus and are uncorrected. IR spectra were obtained on Perkin-Elmer Models 782 and 983G spectrometers with samples between NaCl plates or as KBr pellets.

Table 1. Treatment of Diketones **7**, **10a**,**b**, and **13a**,**b** with K_2CO_3 in MeOH under Reflux

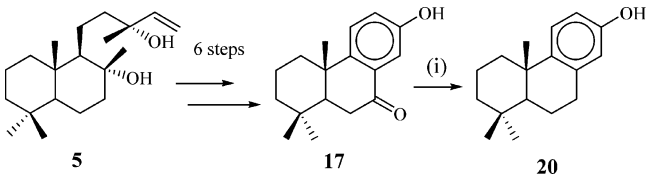
diketone	K_2CO_3 (equiv)	reaction time	product (%)
7	6	1 h	**14** (91)
7	12	2 days	**17** (85)
10a	6	1.2 h	**15a** (83)
10a	12	2 days	**18a** (80)
10b	6	1 h	**15b** (79)
10b	12	2 days	**15b**−**18b** (76)[a]
13a	6	1.5 h	**16a** (78)
13a	12	2 days	**19a** (82)
13b	6	1.1 h	**16b** (81)
13b	12	2 days	**19b** (71)

[a] Phenol **18b** was obtained as an admixture with enone **15b**.

Scheme 2. Mechanism of Formation of 7-Oxo Derivatives **17** and **18a**,**b**



Scheme 3. Synthesis of **20** from **5**[a]



[a] (i) H_2, Pd−C, 60% $HClO_4$, EtOAc, rt, 3 h (96%).

NMR spectra were recorded on Bruker AMX 300 (300 MHz) and Bruker ARX 400 (400 MHz) spectrometers using $CDCl_3$ as solvent and TMS or residual protic solvent $CHCl_3$ ($\delta_H = 7.25$ ppm) as internal reference. ^{13}C NMR spectra were run at 75 MHz on Bruker AMX 300 and at 100 MHz on Bruker ARX 400 instruments. Carbon substitution degrees were established by DEPT pulse sequence. MS were recorded on a Hewlett-Packard 5988A spectrometer using an ionizing voltage of 70 eV. HRMS were obtained on a trisector WG AutoSpecQ spectrometer. FAB spectra acquisition was performed with a 10 000 resolution and a relative error of 5 ppm. For analytical TLC Merck silica gel 60G in 0.25 mm thick layers was used. Chromatographic separations were carried out by conventional column on Merck silica gel 60 (70−230 mesh) and by flash column on Merck silica gel 60 (230−400 mesh) using hexane−MeO^{t}Bu (H−E) mixtures of increasing polarity. Routinely, dry organic solvents were stored under argon, over freshly activated molecular sieves. Ether, benzene, and THF were dried over sodium-benzophenone ketyl, HMPA from Na, CH_2Cl_2 over CaH_2, and MeOH from magnesium methoxide. Where necessary reactions were carried out under a nitrogen or argon atmosphere.

14,15,17-Trinorlabdan-8,13-dione (7). A solution of **6** (0.5 g, 1.90 mmol) in CH_2Cl_2 (12 mL) was slowly bubbled with a O_3−O_2 mixture at −78 °C for 1 h. The solution was flushed with argon, and then PPh_3 (0.6 g, 2.28 mmol) was added. The mixture was stirred at room temperature overnight and the solvent evaporated under vacuum, affording a crude mixture (0.53 g), which after flash column chromatography (hexane−ether, 7:3) gave 450 mg (90%) of **7**. [17]

Labda-8(17),13*E*/*Z*-dien-19-yl acetate (9b). A mixture of **9a** (5.0 g, 15.71 mmol), THF (75 mL), and $LiAlH_4$ (1.2 g, 31.4 mmol) was refluxed under argon for 3 h. The mixture was cooled to room temperature and diluted with MeO^{t}Bu (100 mL), acidified with a 10% HCl solution, and extracted with MeO^{t}Bu (3 × 30 mL). The organic phase was washed with 10% $NaHCO_3$ solution, dried over anhydrous Na_2SO_4, and evaporated to give a crude residue. A solution of this in CH_2Cl_2 (50 mL) was cooled at 0 °C, and then Ac_2O (2.0 mL), pyridine (1.0 mL), and DMAP (0.1 g, 0.8 mmol) were added and the mixture was further stirred at room temperature for 12 h. It was poured into ice and extracted with MeO^{t}Bu (3 × 40 mL), and the organic phase was successively extracted with 2 N HCl (3 × 30 mL), saturated $NaHCO_3$ (3 × 30 mL), and brine (3 × 30 mL), dried over anhydrous Na_2SO_4, filtered, and evaporated to give **9b** (4.4 g, 84%): IR (film, cm^{-1}) ν_{max} 2965, 2931, 2870, 2851, 1741, 1670, 1644, 1449, 1389, 1372,, 1140, 1032, 985, 940, 890, 852, 819; ^1H NMR ($CDCl_3$, 400 MHz) δ 0.70 (3H, s, Me-20), 0.98 (3H, s, Me-18), 1.00−2.35 (18H, m), 1.58 (3H, s, Me-16), 2.06 (3H, s, C-19-OCO*CH*$_3$), 3.88 (1H, d, J = 11.0 Hz, H-19), 4.25 (1H, d, J = 11.0 Hz, H-19), 4.56 (1H, s, H-17), 4.85 (1H, s, H-17), 5.19 (1H, c, J = 6.7 Hz, H-14); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 171.4 (C-19-O*CO*CH$_3$), 148.0 (C-8), 136.4 (C-13), 118.1 (C-14), 106.7 (C-17), 66.9 (C-19), 56.4 (C-9), 56.3 (C-5), 39.5 (C-9), 38.9 (C-12), 38.5 (C-1), 38.6 (C-3), 37.4 (C-4), 36.3 (C-7), 27.6 (C-18), 24.5 (C-11), 22.2 (C-6), 21.0 (C19-OCO*CH*$_3$), 19.0 (C-1), 15.3 (C-16), 13.4 (C-15), 12.5 (C-20); FAB-HRMS *m*/*z* calcd for $C_{22}H_{36}O_2$-Na (M^+ + Na) 355.2612, found 355.2613.

Methyl 8,13-dioxo-14,15,17-trinorlabdan-19-oate (10a). Ozonolysis of **9a** (3.2 g, 01.05 mmol), following the same procedure described for **6**, afforded **10a** (2.7 g, 86%): $[\alpha]^{25}_D$ +8.3 (*c* 1.8, CH_2Cl_2); IR (film, cm^{-1}) ν_{max} 2950, 2873, 2850, 1715, 1436, 1382, 1185, 1155, 1091, 1070, 1043, 1028, 973, 810; ^1H NMR ($CDCl_3$, 400 MHz) δ 0.53 (3H, s, Me-20), 1.08 (1H,dd, J = 13.4, 3.9 Hz), 1.24 (3H, s, Me-18), 1.27 (1H, ddd, J = 15.6, 13.4, 4.2 Hz), 1.51−1.61 (2H,m), 1.65 (1H, dd, J = 12.4, 2.6 Hz), 1.77 (1H, tt, J = 12.4, 2.9 Hz), 1.87 (1H, bd, J = 13.6 Hz), 2.07 (3H, s, Me-16), 2.09−2.30 (5H, m), 2.36−2.40 (1H, m), 2.56 (1H, ddd, J = 13.4, 8.0, 5.4 Hz), 2.63 (1H, dd, J = 10.87, 1.47 Hz), 3.60 (3H, s, C19-COO*Me*); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 211.9 (C-8), 209.3 (C-14), 177.2 (C-19), 62.2 (C-9), 54.9 (C-5), 51.4 (COO*CH*$_3$), 44.4 (C-10), 43.7 (C-4), 43.1 (C-7), 42.7 (C-13), 39.4 (C-1), 38.0 (C-3), 25.7 (C-6), 29.3 (C-15), 28.9 (C-18), 19.8 (C-2), 16.4 (C-12), 13.1 (C-10); FAB-HRMS *m*/*z* calcd for $C_{18}H_{28}O_4Na$ (M^+ + Na) 311.8853, found 311.8881.

8,13-Dioxo-14,15,17-trinorlabdan-19-yl acetate (10b). Ozonolysis of **9b** (2.4 g, 7.22 mmol), following the same procedure described for **6**, afforded **10b** (1.91 g, 82%): $[\alpha]^{25}_D$ −15.7 (*c* 0.85, CH_2Cl_2); IR (film, cm^{-1}) ν_{max} 2935, 2871, 1737, 1712, 1454, 1372, 1240, 1185, 1120, 1034, 973, 951; ^1H NMR ($CDCl_3$, 300 MHz) δ 0.73 (3H, s, Me-20), 1.04 (3H, s, Me-18), 1.04−1.13 (1H, m), 1.20−1.33 (1H, m), 1.45−

1.67 (5H, m), 1.67−1.90 (4H, m), 2.03 (3H, s, OCO*CH*$_3$), 2.08 (3H, s, Me-15), 2.10−2.30 (3H, m), 2.40 (1H, bd, J = 13.0 Hz), 2.57 (1H, ddd, J = 13.4, 7.8, 5.3 Hz), 3.89 (1H, d, J = 11.0 Hz, H-19), 4.17 (1H, d, J = 11.0, H-19); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 211.4 (C-8), 209.0 (C-13), 171.2 (O*CO*CH$_3$), 96.2 (C-4), 66.5 (C-19), 63.1 (C-9), 54.9 (C-5), 42.9 (C-7), 42.7 (C-14), 39.1 (C-1), 37.5 (C-10), 36.3 (C-3), 30.0 (C-16), 27.7 (C-18), 24.0 (C-6), 21.0 (OCO*CH*$_3$), 18.7 (C-2), 16.3 (C-12), 15.4 (C-20); FAB-HRMS *m*/*z* calcd for $C_{19}H_{30}O_4Na$ (M^+ + Na) 345.2042, found 345.2043.

13-Oxo-14,15-dinorlabdan-19-yl acetate (11b). A 0.2% aqueous OsO_4 solution (19 mL) was added to a solution of **9b** (6.0 g, 18.05 mmol) in ^{t}BuOH (30 mL) and H_2O (12.5 mL), and the mixture was stirred for 15 min. Then $NaIO_4$ (7.7 g, 36 mmol) was added, and the mixture was further stirred at room temperature for 5 days. After filtration, the solvent was evaporated and the residue was fractionated into MeO^{t}Bu (100 mL)−H_2O (40 mL). The organic phase was successively washed with 10% aqueous K_2CO_3 (2 × 30 mL) and brine (2 × 30 mL), dried over anhydrous Na_2SO_4, and evaporated to give **11b** (4.7 g, 82%): $[\alpha]^{25}_D$ +25.9 (*c* 0.85, CH_2Cl_2); IR (film, cm^{-1}) ν_{max} 3080, 2932, 2850, 1737, 1717, 1643, 1447, 1389, 1239, 1163, 1032, 983, 891, 852; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.67 (3H, s, Me-20), 0.93 (3H, s, Me-18), 0.96−1.15 (2H, m), 1.23 (1H, dd, J = 12.9, 2.24 Hz), 1.34 (1H, dc, J = 12.8, 4.2 Hz), 1.47−1.58 (4H, m), 1.71 (1H, bd, J = 13.7 Hz), 1.80−1.96 (4H, m), 2.02 (3H, s, OCO*CH*$_3$), 2.09 (3H, s, Me-16), 2.24−2.35 (1H, m), 2.37 (1H, dc, J = 12.6, 2.5 Hz) 2.56 (1H, ddd, J = 17.2, 8.3, 4.4 Hz), 3.83 (1H, d, J = 11.0 Hz, H-19), 4.19 (1H, d, J = 11.0 Hz, H-19), 4.43 (1H, bs, H-17), 4.81 (1H, bs, H-17); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 209.4 (C-13), 171.4 (O*CO*CH$_3$), 147.6 (C-8), 106.8 (C-17), 66.8 (C-19), 56.2 (C-9), 56.2 (C-5), 42.7 (C-14), 39.6 (C-10), 38.8 (C-7), 38.5 (C-1), 37.3 (C-4), 36.2 (C-3), 30.1 (C-16), 27.6 (C-18), 24.5 (C-6), 21.1 (OCO*CH*$_3$), 18.9 (C-2), 17.6 (C-12), 15.1 (C-20); FAB-HRMS *m*/*z* calcd for $C_{20}H_{32}O_3Na$ (M^+ + Na) 343.2249, found 343.2248.

7α-*tert*-Butyldimethylsilyloxy-13-oxo-14,15-dinorlabdan-19-yl acetate (12b). SeO_2 (346 mg, 3.09 mmol) and a 5.5 M solution of ^{t}BuOOH in undecane (1.36 mL, 7.48 mL) were added to a solution of methyl ketone **11b** (2.0 g, 6.24 mmol), and the mixture was stirred at room temperature for 12 h. The solvent was evaporated, and the residue was fractionated into MeO^{t}Bu (100 mL) and H_2O (40 mL). The organic extract was washed with H_2O, dried over anhydrous Na_2SO_4, and evaporated to give a crude residue. To a solution of this in DMF (60 mL) was added imidazole (1.5 g, 22.1 mmol) and TBDMSCl (4.6 g, 30.6 mmol). After being stirred for 14 h at room temperature, the mixture was extracted with MeO^{t}Bu (3 × 30 mL). The organic phase was successively washed with aqueous 2 N HCl (3 × 30 mL) and H_2O (3 × 30 mL), dried over anhydrous Na_2SO_4, and evaporated to yield **12b** as a colorless oil (1.68 g, 60%): $[\alpha]^{25}_D$ −16.0 (*c* 2.24, CH_2Cl_2); IR (film, cm^{-1}) ν_{max} 3077, 2951, 2930, 2887, 2856, 1740, 1718, 1648, 1467, 1072, 1034, 988, 954, 931, 902, 872; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.01 (3H, s, Si-*Me*), 0.07 (3H, s, Si-*Me*), 0.68 (3H, s, Me-20), 0.89 (9H, s, *(CH*$_3$*)*$_3$-C-Si), 0.92 (3H, s, Me-18), 0.97−1.29 (2H, m), 1.44−1.58 (5H, m), 1.72 (1H, bd, J = 13.7 Hz), 1.80−1.91 (4H, m), 2.05 (3H, s, OCO*CH*$_3$), 2.11 (3H, s, Me-16), 2.24−2.32 (1H, m), 2.52 (1H, ddd, J = 17.6, 9.1, 4.7 Hz), 3.84 (1H, d, J = 11.0 Hz, H-19), 4.20 (1H, d, J = 11.0 Hz, H-19), 4.29 (1H, t, J = 2.4 Hz, H-7), 4.50 (1H, s, H-17), 4.93 (1H, s, H-17); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 209.6 (C-13), 171.6 (O*CO*CH$_3$), 149.6 (C-8), 107.8 (C-17), 74.0 (C-7), 67.0 (C-19), 50.4 (C-9), 48.1 (C-5), 42.3 (C-12), 39.6 (C-10), 38.6 (C-1), 36.8 (C-4), 36.3 (C-3), 32.5 (C-6), 30.1 (C-16), 27.3 (C-18), 25.8 (*(CH*$_3$*)*$_3$-C-Si), 21.1 (OCO*CH*$_3$), 19.0 (C-2), 18.1 ((CH$_3$)$_3$-*C*-Si), 17.1 (C-11), 14.2 (C-20), −4.5 (Si-*CH*$_3$), −4.9 (Si-*CH*$_3$); FAB-HRMS *m*/*z* calcd for $C_{26}H_{46}O_4NaSi$ (M^+ + Na) 473.3063, found 473.3060.

Methyl 7α-*tert*-butyldimethylsilyloxy-8,13-dioxo-14,15,17-trinorlabdan-19-oate (13a). Ozonolysis of **12a** (2.5 g, 5.73 mmol), following the same procedure described for **6**, afforded **13a** (2.23 g, 89%): $[\alpha]^{25}_D$ −27.3 (*c* 1.15, CH_2Cl_2); IR (film, cm^{-1}) ν_{max} 2952, 2935, 2857, 1722, 1469, 1440, 1389, 1254, 1150, 1083, 981, 941, 866, 835; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.03 (3H, s, Si-*Me*), 0.10 (3H, s, Si-*Me*), 0.52 (3H, s, Me-20), 0.91 (9H, s, *(CH*$_3$*)*$_3$-C-Si), 0.92−1.20 (1H, m), 1.21 (3H, s, Me-18), 1.35 (1H, dt, J = 14.1, 4.1 Hz), 1.56 (1H, dt, J = 10.5, 2.1 Hz), 1.60−1.90 (3H, m), 2.09 (3H, s, Me-16), 2.1−2.30 (6H, m), 2.51 (1H, ddd, J = 17.5, 8.4, 5.2 Hz), 2.74 (1H, dd, J = 11.0, 2.7 Hz), 3.62 (3H, s, COO*CH*$_3$), 4.02 (1H, t, J = 3.1 Hz, H-7); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 211.7 (C-8), 208.6 (C-13), 177.4 (*CO*OCH$_3$), 75.5 (C-7), 56.7 (C-9), 47.7 (C-5), 51.4 (COO*CH*$_3$), 43.9 (C-10), 43.9 (C-4), 42.3 (C-12), 39.5 (C-1), 38.0 (C-3), 34.3 (C-6), 29.9 (C-16), 28.7 (C-18), 25.7 (*(CH*$_3$*)*$_3$-C-Si), 19.9 (C-2), 18.2 ((CH$_3$)$_3$-*C*-Si), 15.7 (C-11), 12.5 (C-20), −4.8 (Si-*CH*$_3$), −4.8 (Si-*CH*$_3$); FAB-HRMS *m*/*z* calcd for $C_{24}H_{42}O_5NaSi$ (M^+ + Na) 461.2699, found 461.2704.

7α-*tert*-Butyldimethylsilyloxy-8,13-dioxo-14,15,17-trinorlabdan-19-yl acetate (13b). Ozonolysis of **12b** (3.1 g, 6.9 mmol), following the same procedure described for **6**, afforded **13b** (2.6 g, 85%): $[\alpha]^{25}_D$ −43.6 (*c* 0.85, CH_2Cl_2); IR (film, cm^{-1}) ν_{max} 2951, 2932, 2857, 1740, 1718, 1467, 1164, 1085, 1055, 1034, 980, 956, 927, 876, 836; ^{1}H NMR ($CDCl_3$, 400 MHz) δ −0.06 (3H, s, Si-*Me*), 0.01 (3H, s, Si-*Me*), 0.63 (3H, s, Me-20), 0.82 (9H, s, *(CH*$_3$*)*$_3$-C-Si), 0.92 (3H, s, Me-18), 1.03−1.11 (1H, m), 1.23−1.31 (1H, m), 1.42−1.48 (2H, m), 1.52−1.60 (1H, m), 1.64−1.78 (4H, m), 1.93−2.1 (2H, m), 1.98 (3H, s, OCO*CH*$_3$), 2.02 (3H, s, Me-16), 2.52 (1H, ddd, J = 17.6, 8.4, 5.2 Hz), 2.63 (1H, dd, J = 10.9, 1.5 Hz), 3.81 (1H, d, J = 11.0 Hz, H-19), 3.92 (1H, t, J = 2.7 Hz, H-7), 4.09 (1H, d, J = 11.0 Hz, H-19); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 211.15 (C-8), 208.64 (C-13), 171.24 (O*CO*CH$_3$), 75.06 (C-7), 66.87 (H-18), 57.84 (C-1′), 47.41 (C-4a′), 43.29 (C-8a′), 42.21 (C-3), 39.04 (C-1), 36.83 (C-4), 36.25 (C-3), 32.56 (C-6), 29.94 (C-16), 27.40 (C-18), 25.70 (*(CH*$_3$*)*$_3$-C-Si), 21.02 (OCO*CH*$_3$), 18.76 (C-2), 18.20 ((CH$_3$)$_3$-*C*-Si), 15.55 (C-11), 14.69 (C-20), −4.78 (Si-*CH*$_3$), −4.89 (Si-*CH*$_3$); FAB-HRMS *m*/*z* calcd for $C_{25}H_{44}O_5NaSi$ (M^+ + Na) 475.2856, found 475.2856.

Treatment of 1,5-Diketones 7, 10a,b, and 13a,b with K_2CO_3 in MeOH under Reflux. K_2CO_3 (6 or 12 equiv) was added to a solution of diketone (3.7 mmol) in absolute MeOH (20 mL), and the mixture was stirred under reflux for the specified time. After evaporating the solvent, H_2O (20 mL) was added. The mixture was acidified by adding 2 N HCl and extracted with MeO^{t}Bu (2 × 30 mL). The organic phase was successively washed with 2 N HCl (3 × 30 mL) and brine (3 × 30 mL), dried over anhydrous Na_2SO_4, and evaporated to give a crude residue, which after chromatography column yielded the cyclization product.

Podocarp-8(14)-ene-13-one (14). The spectroscopic properties were similar to those reported in the literature.[18]

Methyl 13-oxo-podocarp-8(14)-en-19-oate (15a): $[\alpha]^{25}_D$ +11.0 (*c* 0.12, $CHCl_3$); IR (film, cm^{-1}) ν_{max} 2949, 2875, 2852, 1723, 1676, 1462, 1383, 1152, 1093, 1074, 1032, 983, 835; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.65 (3H, s, Me-20), 1.11 (1H, ddd, J = 17.4, 13.4, 3.9 Hz), 1.20−1.26 (2H, m), 1.25 (3H, s, Me-18), 1.40 (1H, dd, J = 12.7, 2.7 Hz), 1.55 (1H, dt, J = 10.5, 3.5 Hz), 1.75−1.92 (4H, m), 1.99−2.08 (2H, m), 2.18−2.27 (3H, m), 2.41 (1H, dt, J = 16.2, 4.5 Hz), 2.56 (1H, dd, J = 14.9, 2.0 Hz), 3.65 (3H, s, COO*Me*), 5.89 (1H, s, H-14); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 199.9 (C-13), 177.5 (C-19), 164.9 (C-8), 125.7 (C-14), 51.4 (COO*CH*$_3$), 55.2 (C-9), 50.6 (C-5), 44.2 (C-4), 40.7 (C-10), 39.5 (C-12), 38.0 (C-1), 36.7 (C-3), 36.5 (C-7), 23.8 (C-6), 29.0 (C-18), 19.5 (C-2), 20.7 (C-11), 14.2 (C-20); FAB-HRMS *m*/*z* calcd for $C_{18}H_{26}O_3Na$ (M^+ + Na) 313.1777, found 313.1779.

19-Hydroxypodocarp-8(14)-en-13-one (15b): $[\alpha]^{25}_D$ +16.3 (*c* 0.6, $CHCl_3$); IR (film, cm^{-1}) ν_{max} 3424, 2929, 2870, 1710, 1659, 1617, 1453, 1364, 1174, 1149, 1026, 962, 875; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.65−0.78 (1H, m), 0.79 (3H, s, Me-20), 0.89 (1H, d, J = 6.6 Hz), 1.03 (3H, s, Me-18), 1.05−1.30 (2H, m), 1.35 (1H, dt, J = 13.0, 2.3 Hz), 1.40−1.55 (2H, m), 1.60−1.95 (3H, m), 2.02 (1H, dc, J = 13.5, 5.4 Hz), 2.06−2.14 (1H, m), 2.15−2.32 (3H, m), 2.40 (1H, dt, J = 15.9, 4.2 Hz), 2.54 (1H, ddd, J = 15.5, 3.1, 1.6 Hz), 3.48 (1H, d, J = 10.8 Hz, H-19), 3.81 (1H, d, J = 10.8 Hz, H-19), 5.88 (1H, s, H-14); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 200.0 (C-13), 165.2 (C-8), 126.1 (C-14), 65.2 (C-19), 55.1 (C-9), 51.8 (C-5), 39.0 (C-4), 38.8 (C-10), 39.4 (C-12), 36.8 (C-1), 36.1 (C-3), 35.4 (C-7), 27.2 (C-18), 22.0 (C-6), 20.8 (C-11), 18.5 (C-2), 16.44 (C-20); FAB-HRMS *m*/*z* calcd for $C_{17}H_{26}O_2Na$ (M^+ + Na) 285.1830, found 285.1835.

Methyl 7α-*tert*-butyldimethylsilyloxy-13-oxo-podocarp-8(14)-en-19-oate (16a): $[\alpha]^{25}_D$ −12.6 (*c* 1.25, $CHCl_3$); IR (film, cm^{-1}) ν_{max} 2953, 2934, 2884, 2856, 1726, 1683, 1464, 1445, 1388, 1151, 1073, 985, 960, 867, 836; ^{1}H NMR ($CDCl_3$, 300 MHz) δ −0.11 (3H, s, Si-*Me*), 0.08 (3H, s, Si-*Me*), 0.64 (3H, s, Me-20), 0.88 (9H, s, *(CH*$_3$*)*$_3$-C-Si), 0.89−1.15 (2H, m), 1.18 (3H, s, Me-18), 1.50−1.60 (1H, m), 1.70−1.92 (3H, m), 1.98 (1H, dd, J = 5.5, 1.8 Hz), 2.02 (1H, dd, J = 6.0, 2.3 Hz), 2.05−2.12 (1H, m), 2.18−2.29 (2H, m), 2.30−2.45 (1H, m), 2.52 (2H, dt, J = 5.2, 2.1 Hz), 2.42 (1H, t, J = 6.30 Hz), 3.65 (3H, s, COO*Me*), 4.31 (1H, t, J = 2.6 Hz, H-7), 5.82 (1H, d, J = 2.0 Hz, H-14); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 200.6 (C-13), 177.7 (C-19), 164.0 (C-8), 125.4 (C-14), 72.4 (C-7), 51.4 (COO*CH*$_3$), 47.9 (C-9), 45.4 (C-5), 43.7 (C-4), 41.0 (C-10), 39.6 (C-12), 38.0 (C-1), 36.4

(C-3), 33.0 (C-6), 28.7 (C-18), 25.75 (*(CH$_3$)$_3$*-C-Si), 20.3 (C-11), 19.7 (C-2), 18.1 ((CH$_3$)$_3$-*C*-Si), 13.8 (C-20), −4.6 (Si-*C*H$_3$), −4.9 (Si-*C*H$_3$); FAB-HRMS *m*/*z* calcd for $C_{24}H_{40}O_4NaSi$ (M^+ + Na) 443.2593, found 443.2592.

7α-*tert*-Butyldimethylsilyloxy-19-hydroxypodocarp-8(14)-en-13-one (16b): $[\alpha]^{25}_D$ −31.9 (*c* 0.25, CH_2Cl_2); IR (film, cm^{-1}) ν_{max} 3449, 2953, 2930, 2888, 2856, 1717, 1676, 1468, 1389, 1365, 1161, 1131, 1071, 1029, 977, 940, 874, 834; ^{1}H NMR ($CDCl_3$, 400 MHz) δ −0.07 (3H, s, Si-*Me*), 0.01 (3H, s, Si-*Me*), 0.73 (3H, s, Me-20), 0.82 (9H, s, *(CH$_3$)$_3$*-C-Si), 0.94 (3H, s, Me-18), 0.9−1.20 (2H, m), 1.39−1.50 (1H, m), 1.59 (1H, dt, *J* = 13.6, 2.8), 1.69−2.03 (4H, m), 2.12−2.22 (2H, m), 2.34 (1H, dt, *J* = 16.1, 5.5 Hz), 2.42 (1H, t, *J* = 6.3 Hz), 3.39 (1H, d, *J* = 10.8 Hz, H-19), 3.73 (1H, d, *J* = 10.8 Hz, H-19), 4.23 (1H, t, *J* = 2.6 Hz, H-7), 5.82 (1H, d, *J* = 1.8 Hz, H-14); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 200.8 (C-13), 164.04 (C-8), 126.19 (C-14), 72.23 (C-7), 65.54 (C-19), 47.38 (C-9), 46.84 (C-5), 40.10 (C-10), 39.36 (C-12), 38.19 (C-4), 36.53 (C-1), 35.50 (C-3), 31.29 (C-6), 27.06 (C-18), 25.75 (*(CH$_3$)$_3$*-C-Si), 20.22 (C-2), 18.65 (C-11), 18.10 ((CH$_3$)$_3$-*C*-Si), 16.04 (C-20), −4.49 (Si-*Me*), −4.90 (Si-*Me*); FAB-HRMS *m*/*z* calcd for $C_{23}H_{40}O_3NaSi$ (M^+ + Na) 415.2644, found 415.2644.

13-Hydroxy-7-oxo-8,11,13-podocarpatriene (17): ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.90 (3H, s), 0.96 (3H,s), 1.24 (3H, s), 1.83 (1H, dd, *J* = 12.9, 4.5 Hz), 2.28 (1H, bd, *J* = 11.4 Hz), 2.58 (1H, dd, *J* = 17.8, 12.9 Hz), 2.69 (1H, dd, *J* = 17.8, 4.5 Hz), 7.03 (1H, dd, *J* = 8.6, 2.9 Hz), 7.21 (1H, D, *J* = 8.6 Hz), 7.48 (1H, d, *J* = 2.9 Hz).

Methyl 13-hydroxy-7-oxo-8,11,13-podocarpatrien-19-oate (18a): $[\alpha]^{25}_D$ +71.2 (*c* 0.24, CH_2Cl_2); IR (film, cm^{-1}) ν_{max} 3405, 2937, 2873, 1724, 1681, 1608, 1495, 1445, 1380, 1154, 1084, 1034, 983, 908, 888, 828; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.11 (3H, s, Me-20),1.16 (1H, dt,, *J* = 9.7, 4.0 Hz), 1.28 (3H, s, H-18), 1.51 (1H, dt, *J* = 13.4, 4.2 Hz), 1.72 (1H, dt, *J* = 14.1, 3.3 Hz), 2.00 (1H, dt, *J* = 13.9, 3.3 Hz), 2.07 (1H, dd, *J* = 14.5, 2.9 Hz, H-5), 2.30−2.4 (2H, m), 3.00 (1H, dd, *J* = 18.0, 3.1 Hz), 3.24 (1H, dd, *J* = 18.0, 14.5 Hz, H-6), 3.72 (3H, s, COO*Me*), 6.38 (1H, bs, 13-O*H*), 7.10 (1H, dd, *J* = 8.6, 2.8 Hz, H-12), 7.33 (1H, d, *J* = 8.6 Hz, H-11) 7.58 (1H, d, *J* = 2.8 Hz, H-14); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 199.5 (C-7), 177.2 (C-19), 154.5 (C-13), 147.1 (C-9), 131.6 (C-8), 126.7 (C-11), 122.3 (C-12), 112.4 (C-14), 51.7 (COO*CH$_3$*), 50.4 (C-5), 43.9 (C-4), 38.7 (C-1), 38.1 (C-10), 37.8 (C-6), 37.6 (C-3), 28.0 (C-18), 21.5 (C-20), 19.7 (C-2); FAB-HRMS *m*/*z* calcd for $C_{18}H_{23}O_4$ (M^+ + H) 303.1596, found 303.1595.

13,19-Dihydroxy-8,11,13-podocarpatrien-7-one (18b). In this case, an unsolvable mixture of phenol **18b** and *β*-enone **15b** was obtained, which complicated the spectroscopic assignment.

Methyl 7α-*tert*-butyldimethylsilyloxy-13-hydroxy-8,11,13-podocarpatrien-19-oate (19a): $[\alpha]^{25}_D$ +54.8 (*c* 0.20, CH_2Cl_2); IR (film, cm^{-1}) ν_{max} 3426, 2950, 2930, 2856, 1727, 1610, 1503, 1464, 1492, 1463, 1384, 1191, 1149, 1094, 1070, 894, 835; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.20 (3H, s, Si-*Me*), 0.22 (3H, s, Si-*Me*), 0.93 (9H, s, *(CH$_3$)$_3$*-C-Si), 1.05−1.25 (1H, m), 0.96 (3H, s, Me-20), 1.00−1.20 (1H, m), 1.23 (3H, s, H-18), 1.43 (1H, dt, *J* = 13.5, 4.4 Hz), 1.55−1.75 (2H, m), 2.00 (1H, dt, *J* = 13.8, 3.8 Hz), 2.05−2.25 (3H, m), 2.32 (1H, bd, *J* = 13.7 Hz), 3.69 (3H, s, COO*Me*), 6.65 (1H, d, *J* = 2.8 Hz, H-14), 6.75 (1H, dd, *J* = 8.6, 2.8 Hz, H-12), 7.16 (1H, d, *J* = 8.6 Hz, H-11); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 178.2 (C-19), 153.2 (C-13), 140.7 (C-9), 138.5 (C-8), 126.9 (C-11), 116.2 (C-12), 115.4 (C-14), 68.9 (C-7), 51.3 (COO*CH$_3$*), 45.5 (C-5), 43.8 (C-4), 39.3 (C-1), 38.1 (C-10), 37.7 (C-3), 30.8 (C-6), 28.6 (C-18), 26.1 (*(CH$_3$)$_3$*-C-Si), 22.0 (C-20), 20.1 (C-2), 18.10 ((CH$_3$)$_3$-*C*-Si), −3.9 (Si-*Me*), −4.0 (Si-*Me*); FAB-HRMS *m*/*z* calcd for $C_{24}H_{38}O_4NaSi$ (M^+ + Na) 441.2437, found 441.2429.

7α-*tert*-Butyldimethylsilyloxy-13,19-dihydroxy-8,11,13-podocarpatriene (19b): $[\alpha]^{25}_D$ −14.6 (*c* 1.75, CH_2Cl_2); IR (film, cm^{-1}) ν_{max} 3423, 2952, 2928, 2855, 1708, 1464, 1388, 1163, 1083, 1031, 957, 835; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.12 (3H, s, Si-*Me*), 0.13 (3H, s, Si-*Me*), 0.86 (9H, s, *(CH$_3$)$_3$*-C-Si), 0.90−1.10 (1H, m), 0.99 (3H, s, Me-20), 1.04 (3H, s, Me-18), 1.39 (1H, dt, *J* = 13.5, 4.0 Hz), 1.50−1.60 (1H, m), 1.64 (1H, dt, *J* = 13.7, 3.1 Hz), 1.75−1.95 (3H, m), 2.15−2.30 (2H, m), 3.49 (1H, d, *J* = 11.0 Hz, H-18), 3.79 (1H, d, *J* = 11.0 Hz, H-18), 4.67 (1H, t, *J* = 3.0 Hz, H-7), 5.87 (1H, bs, 13-OH), 6.60 (1H, d, *J* = 2.7 Hz, H-14), 6.65 (1H, dd, *J* = 8.6, 2.7 Hz, H-12), 7.05 (1H, d, *J* = 8.6 Hz, H-11); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 157.3 (C-13), 142.1 (C-9), 138.0 (C-8), 125.6 (C-11), 114.45 (C-12), 114.0 (C-14), 68.7 (C-7), 65.7 (C-19), 55.2 (13-*Me*O), 45.2 (C-5), 38.9 (C-1), 38.4 (C-10), 37.6 (C-4), 35.4 (C-3), 29.7 (C-6), 26.8 (C-18), 26.1 (*(CH$_3$)$_3$*-C-Si), 24.6 (C-20), 19.1 (C-2), 19.10 (*(CH$_3$)$_3$*-*C*-Si), −3.94 (Si-*CH$_3$*), −4.16 (Si-*CH$_3$*); FAB-HRMS *m*/*z* calcd for $C_{23}H_{39}O_4Si$ (M^+ + H) 407.2618, found 407.2629.

13-Hydroxy-8,11,13-podocarpatriene (20). 10% Pd/C (200 mg) and 60% $HClO_4$ (100 mg) were added to a solution of ketone **17** (0.35 g, 1.35 mmol) in EtOAc (20 mL), and the mixture was stirred under a hydrogen atmosphere for 3 h at room temperature. Then, it was filtered and washed with EtOAc (20 mL), and the filtrate was successively washed with H_2O (3 × 10 mL) and brine (3 × 10 mL), dried over anhydrous Na_2SO_4, and evaporated to give **20** (319 mg, 96%).

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