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Robert H. Burnell, Nathalie Dumont, and Nathalie Théberge

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SYNTHESIS OF *O*-METHYL NIMBINONE

ROBERT H. BURNELL,* NATHALIE DUMONT, and NATHALIE THÉBERGE

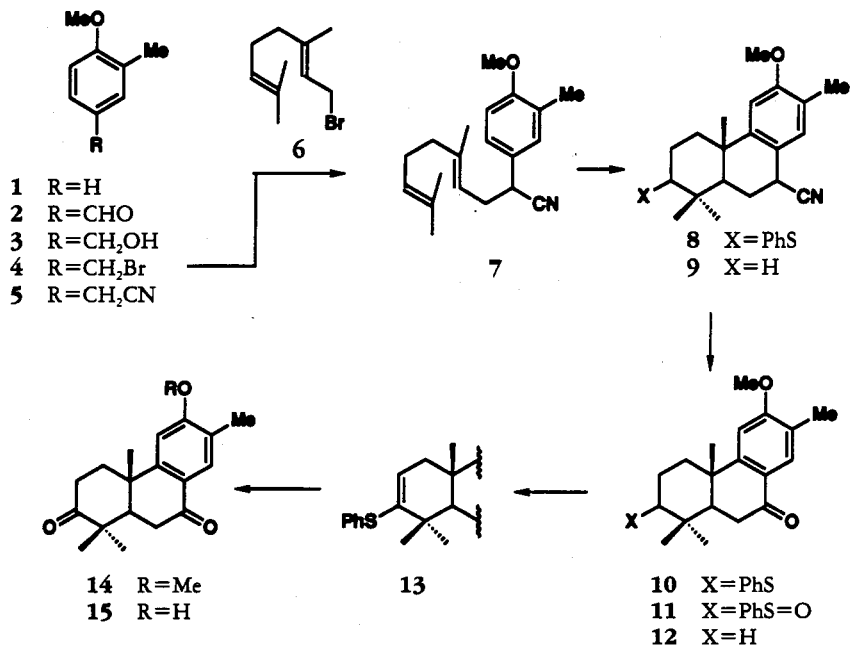
Département de Chimie, Université Laval, Québec, Québec, Canada G1K 7P4

ABSTRACT.—Two syntheses are described to confirm the structure **15** proposed for nimbinone. The first, which leads to racemic *O*-methyl nimbinone [**14**], involves the polycyclization of a geraniol-derived intermediate **7**. This same intermediate also afforded another preparation of (±)-methyl nimbiol [**12**]. The other synthesis starts from natural podocarpic acid and affords optically active *O*-methyl nimbinone [**14**].

Nimbinone [**15**] was recently described by Ira *et al.* (1) as one of the constituents of *Azadirachta indica*, the much studied "neem" tree. This skeleton is characterized by the methyl group at C-13, which suggests that the usual isopropyl residue has been degraded in the biosynthesis.

Although the method is impractical if the aromatic ring carries too many substituents (2), the synthetic approach we adapted from the Livinghouse cascade cyclization (3) should permit the ready construction of nimbinone (Scheme 1). The suitably substituted phenylacetonitrile **5** was prepared in good yield (almost 50% overall) from *o*-methyl anisole [**1**] via the 3-formyl derivative **2** (hexamethylenetetramine, CF_3COOH; 75%), the primary alcohol **3** ($NaBH_4$, MeOH, room temperature; 94%), the benzyl bromide **4** (PBr_3, pyridine, room temperature; 81%) and finally the nitrile **5** (18-cr-6, KCN, MeCN, 60°; 71%). The latter was readily alkylated with geranyl bromide [**6**] to afford the racemic diene **7**.

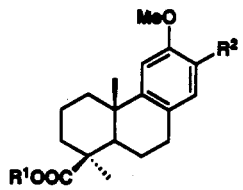
Cyclization of the long sidechain in the normal manner (PhSOMe, $BF_3/MeNO_2$) gave the trans-fused tricyclic **8**. Transformation of C-7 and then C-3 to carbonyl groups by methods found effective in our previous syntheses aimed at candelabrone (2) afforded a racemic diketone **14**, which showed identical spectral properties with the same *O*-methyl derivative of nimbinone described by Ira *et al.* (1).



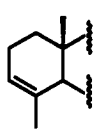
SCHEME 1

Compound **9** was obtained when the diene **7** was cyclized in the absence of methyl benzenesulfenate, but best results were achieved by deliberately aiming at recovering half of the starting material. Without the C-3 stereocenter (as in **8**) it was easier to see that the AB ring junction in the product was exclusively trans, but the reaction afforded both relative configurations at C-7 with the equatorial isomer (nitrile syn to C-10 methyl) predominant by the ratio 60/40. For the next step no separation was required, and oxidative decyanation at this position afforded **12** identical with methyl nimbiol (1) as judged by the comparison of spectral data.

O-Methyl nimbinone [**14**] was also synthesized in optically active form from methyl *O*-methyl podocarpate [**16**] derived from natural podocarpic acid following the methodology used previously to corroborate the structure of margocin (4). The key intermediate was the allylic alcohol **27**, which was prepared as follows. To establish the C-13 methyl group, an aldehyde residue was first introduced by the Duff reaction (5), affording **17**, and the latter was reduced to **18** with BF_3/Et_3SiH (6). The C-4 ester group was then hydrolyzed to the acid **19**, and the latter then decarboxylated with lead tetracetate. From the mixture of products, olefins **20**, **21**, and **22** and the tertiary acetate **23**, only the latter was obtained pure, and it was immediately pyrolyzed to give more **20**, **21**, and **22**. After epoxidation with *m*-CPBA the mixed olefinic products were easily separated affording



16 R^1=Me, R^2=H
17 R^1=Me, R^2=CHO
18 R^1=R^2=Me
19 R^1=H, R^2=Me



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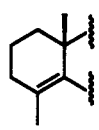

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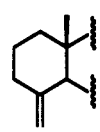

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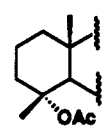

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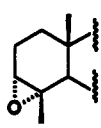

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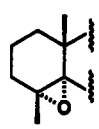

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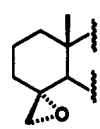

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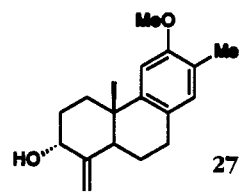

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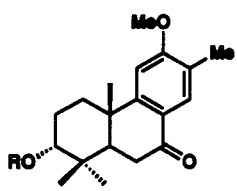

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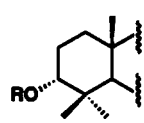
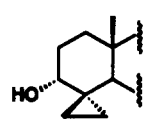
32 R=H



29 R=H
30 R=Ac



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some of the least reactive olefin **22** (13%), the epoxides **24** (36%), **25** (11%), and **26** (15%), and the alcohol **27** (10%). More of the latter was obtained by the SeO_2 oxidation of **22** and by the base-induced rearrangement of the epoxide **24**.

From all these sources the yield of this useful synthon **27** was over 20% from the methyl derivative **19**. Cambie *et al.* (7) published a more efficient route from podocarpic acid to the analogous olefin (**22** without the C-13 methyl group). In the present context it was found that **22** could be obtained in 36% yield from the acid **19** by this suite of four reactions, which involves formation of the acid chloride, its reaction with the sodium salt of pyridine-2-thiol *N*-oxide, rearrangement of the product by heating (110°), and, after *m*-CPBA oxidation, elimination to the olefin **22**.

Simmons-Smith cyclopropanation of the allylic alcohol **27** gave the spiro-cyclopropyl derivative **28**, which was hydrogenolyzed to the 4,4-dimethyl compound **29**. After protecting the secondary hydroxyl of the latter as the acetate **30**, the benzylic C-7 position was oxidized to afford the ketone **31**. Hydrolysis gave the C-3 hydroxy compound **32**, which was oxidized by the Jones reagent to the 3,7-diketone **14**, which was shown by spectral comparison to be identical with *O*-methyl nimbinone derived from the natural product.

EXPERIMENTAL

Unless otherwise stated, the conditions used to characterize the products were as follows: melting points, Electrothermal, uncorrected; uv spectra, EtOH solutions (ε in parentheses), Hewlett Packard 8450 A; ir spectra, CCl_4 solutions, Beckman 4250; 200 MHz ^1H and 50 MHz ^{13}C-nmr spectra, $CDCl_3$ solutions (multiplicity, integrated peak areas, coupling constants in Hz and where necessary assignments in parentheses; "dis. D_2O" signifies that the peak in question disappeared on shaking the solution with a small volume of D_2O), Varian XL-200. Assignments were from COSY, HETCOR, and APT experiments which are not described in the text. Ms, Hewlett Packard 5992, and exact mass measurements were performed at the Centre régional de spectrométrie de masse, Université de Montréal. Cc implies the use of Terochem Si gel (for flash chromatography) with the solvents determined by prior tlc using Whatman Al Sil G/UV precoated aluminium sheets. Reactions were carried out under N_2 or argon unless otherwise stated. Podocarpic acid (ex rimu resin) was supplied by Koch-Light, UK.

PREPARATION OF DIENE **7** FROM *O*-METHYLANISOLE [**1**].—*4-Methoxy-3-methylbenzaldehyde* [**2**].—Duff reaction: to *ortho*-methyl anisole (0.203 g) in CF_3COOH (11.5 ml) was added hexamethylenetetramine (0.886 g), and the mixture was refluxed for 1 h, then poured into H_2O, basified, and Et_2O extracted. Cc (petroleum ether/20% Et_2O) afforded aldehyde **2** (187 mg, 75%): ir 1685 cm^{-1}; ^1H nmr δ 2.19 (s, 3-Me), 3.84 (s, MeO), 6.85 (d, J=8.4 Hz, H-5), 7.60 (s, H-2), 7.63 (d, J=8.4 Hz, H-6), 9.78 (s, CHO); eims *m/z* $[M]^+$ 150 (61), 149 (100), 121 (12), 91 (29), 77 (18).

4-Methoxy-3-methylbenzyl alcohol [**3**].—Aldehyde **2** (157 mg) in MeOH (10 ml) was stirred with $NaBH_4$ (36 mg) for 15 min at room temperature. H_2O was added, and cc (petroleum ether/40% Et_2O) of the product obtained by Et_2O extraction gave alcohol **3** (148 mg, 94%): ^1H nmr δ 2.23 (s, 3-Me), 3.82 (s, MeO), 4.53 (s, 2H, CH_2OH), 6.78 (d, J=8.9 Hz, H-5), 7.11 (s, H-2), 7.13 (d, J=8.9 Hz, H-6); eims *m/z* $[M]^+$ 152 (100), 137 (90), 121 (25), 109 (24), 108 (31), 107 (17), 91 (52), 77 (35).

4-Methoxy-3-methylbenzyl bromide [**4**].—To a solution of **3** (2.09 g) in C_6H_6 (300 ml) at 0° was added pyridine (1.22 ml) and then PBr_3 (0.9 ml). After 4 h stirring, the mixture was poured into H_2O/dilute HCl, Et_2O extracted, and the residue chromatographed (petroleum ether/5% Et_2O) to give **4** (2.87 g, 97%): ^1H nmr δ 2.23 (s, 3-Me), 3.83 (s, MeO), 4.50 (s, 2H, CH_2Br), 6.78 (d, J=9.1 Hz, H-5), 7.19 (s, H-2), 7.21 (d, J=9.1 Hz, H-6): eims *m/z* 216, $[M]^+$ 214 (3), 135 (100), 91 (24).

4-Methoxy-3-methylphenylacetonitrile [**5**].—The mixture of bromide **4** (122 mg), 18-crown-6 (24 mg), and KCN (171 mg) in MeCN (1 ml) was stirred overnight at 60°, then diluted with Et_2O and washed (H_2O, saturated $NaHCO_3$, saturated NaCl). Cc afforded the nitrile **5** (65 mg, 71%): ir 2240 cm^{-1}; ^1H nmr δ 2.21 (s, 3-Me), 3.64 (s, 2H, CH_2CN), 3.82 (s, MeO), 6.79 (d, J=8.1 Hz, H-5), 7.07 (s, H-2), 7.09 (d, J=8.1 Hz, H-6); eims *m/z* $[M]^+$ 161 (90), 146 (100), 130 (11), 91 (56).

Alkylation with geranyl bromide [**6**].—To a suspension of NaH (468 mg) in THF (140 ml) was added geranyl bromide (2.02 g) and then the nitrile **5** (1.337 g). After refluxing for 20 h, excess NaH was destroyed (saturated NH_4Cl) and the product obtained by Et_2O extraction. Cc gave the alkylated product **7** [798 mg,

79% if the recovered starting material (780 mg) is subtracted]: ^{1}H nmr δ (product is numbered as a cyclized diterpene) 1.55, 1.59, and 1.68 (3s, 4-Me$_2$, 10-Me), 2.02 (m, 4H, H-1, H-2), 2.21 (s, 3H, MeAr), 2.55 (2dd, 2H, J=13.6 and 7.3 Hz, H-6), 3.67 (t, J=7.7 Hz, H-7), 3.82 (s, 3H, MeO), 5.06 (m, 1H, H-3), 5.16 (t, J=7.5 Hz, H-5), 6.78 (d, 1H, J=8.2 Hz, H-11), 7.08 (s, 1H, H-14), 7.10 (d, 1H, J=8.2 Hz, H-9); eims *m/z* [M]$^+$ 297 (1), 161 (100), 160 (30), 137 (17). It was found preferable to recover starting material to avoid forming the di-alkylated product.

CYCLIZATION WITH BF_3/$MeNO_2$.—Under N_2 at −30°, BF_3/$MeNO_2$ (2.28 M, 3.5 ml) was added to $MeNO_2$ (5 ml), and after 2 min diene **7** (108 mg) in $MeNO_2$ (1 ml) was introduced. Stirring was continued at −15° for 4 h, when saturated aqueous $NaHCO_3$ was added and the product extracted into Et_2O. Cc (petroleum ether/15% Et_2O) afforded product **9** (93 mg, 86%) as a 60:40 mixture of two stereoisomers which could be used as such for the next step. For characterization they were separated by further cc. The major component (C-7 nitrile and C-10 methyl syn): ^{1}H nmr δ 0.94, 0.96, and 1.25 (3s, 4-Me$_2$, 10-Me), 2.17 (s, MeAr), 3.80 (s, MeO), 3.97 (dd, 1H, J=11.7 and 6.9 Hz, H-7), 6.70 (s, H-11), 7.13 (s, H-14). Minor component: ^{1}H nmr δ 0.92, 1.03 and 1.18 (3s, 4-Me$_2$, 10-Me), 2.16 (s, MeAr), 3.80 (s, MeO), 4.01 (d, 1H, J=6.0 Hz, H-7), 6.70 (s, H-11), 6.98 (s, H-14). Both isomers showed ir 2220 cm^{-1}; eims *m/z* [M]$^+$ 297 (49), 212 (24), 200 (21), 187 (34), 186 (27), 185 (100), 173 (37), 167 (21), 128 (21); hrms *m/z* 297.2089 ($C_{20}H_{27}NO$ requires 297.2091).

OXYDECYANATION [(±)-METHYL NIMBIOL].—To diisopropylamine (0.04 ml) in THF (1.4 ml) at −78° under argon was added *n*-BuLi (0.12 ml of 2.5 M in hexane). The temperature was raised to 0° for 15 min, then lowered to −78° again before adding the nitrile **9** (52 mg) in THF (2.8 ml). After stirring for 5 min, a current of O_2 was passed into the flask during 1 h. The temperature was raised to 0°, and the mixture was stirred with a solution of $SnCl_2$ (0.6 ml, 1 M, in 2 M HCl) for 30 min. Extraction with Et_2O and cc (petroleum ether/10% Et_2O) gave (±)-ketone **12** (52 mg, 56%): ^{1}H nmr δ 0.92, 0.99, and 1.23 (3s, 4-Me$_2$, 10-Me), 1.85 (dd, 1H, J=12.2 and 5.5 Hz, H-5), 2.18 (s, MeAr), 2.29 (d, 1H, J=12.8 Hz, H$_\alpha$-1), 3.88 (s, MeO), 6.73 (s, H-11), 7.80 (s, H-14); ^{13}C nmr δ 38.0, 18.9, 41.3, 33.3, 49.7, 36.0, 198.5, 123.8, 156.8, 38.3, 104.0, 162.5, 124.9, 129.7, 15.6 (C-1 to C-15), 32.6 (10-Me), 21.3 and 23.3 (4-Me$_2$), 55.4 (OMe); eims *m/z* [M]$^+$ 286 (100), 271 (77), 229 (35), 203 (84), 201 (94), 189 (76), 175 (42), 149 (36), 128 (47), 115 (48); hrms *m/z* 286.1945 ($C_{19}H_{26}O_2$ requires 286.1931).

CYCLIZATION OF DIENE **7** WITH PhSOMe.—BF_3/$MeNO_2$ (3 ml of 1.95 M) was added to methyl benzenesulfenate (0.5 g) in $MeNO_2$ (50 ml) at −30°. After 2 min, diene **7** (0.998 g) was added in $MeNO_2$ (9 ml), and stirring was continued at −15° for 3 h. The mixture was then poured into saturated $NaHCO_3$ and extracted with Et_2O to give the clean cyclized product **8** (0.962 g, 71%): ir 2220 cm^{-1}; eims *m/z* [M]$^+$ 405 (100), 296 (46), 280 (93), 269 (21), 226 (29), 212 (41), 200 (74), 186 (27), 160 (89), 149 (22), 135 (42), 122 (24), 109 (41). Two diastereomers were discernible (60:40) from the nmr, and only the major (that with the C-7 nitrile equatorial and syn to the C-10 angular methyl) was obtained pure by further cc: ^{1}H nmr δ 1.04, 1.29, and 1.33 (3s, 4-Me$_2$, 10-Me), 2.18 (s, MeAr), 2.84 (m, 1H, H-3), 3.78 (s, MeO), 3.99 (dd, 1H, J=12.4 and 6.6 Hz, H-7), 6.65 (s, 1H, H-11), 7.15 (s, H-14), 7.2–7.4 (m, 5H, PhS); eims *m/z* [M]$^+$ 405 (100), 296 (46), 280 (93), 269 (21), 227 (24), 226 (28), 212 (41), 200 (74), 186 (27), 160 (89); hrms *m/z* 405.2135 ($C_{26}H_{31}NOS$ requires 405.2125). The ^{1}H-nmr spectrum of the minor product (from mixtures): δ 1.03, 1.33, and 1.40 (3s, 4-Me$_2$, 10-Me), 2.16 (s, MeAr), 2.95 (m, H-3), 3.77 (s, MeO), 4.02 (d, J=4.8 Hz, H-7), 6.98 (s, H-11), 7.2–7.5 (m, 6H, H-14 and Ph-S).

OXIDATIVE DECYANATION AT C-7.—To diisopropylamine (0.24 ml) in THF (8.2 ml) at −78° under argon, was added *n*-BuLi (0.67 ml of 2.5 M in hexane). The temperature was raised to 0° for 15 min, and after re-cooling to −78°, the nitrile **8** (394 mg) was added in THF (16.4 ml), and O_2 was passed through the flask for 1 h. A solution of $SnCl_2$ (3.3 ml of 1 M in 2 M HCl) was added at 0°, and after 30 min stirring the product was extracted into Et_2O and washed repeatedly with H_2O. Cc (petroleum ether/7% Et_2O) gave starting material (141 mg) and then ketone **10** (181 mg, 74%): ir 1668, 1605, 1486, 1270, 1140 cm^{-1}; ^{1}H nmr δ 1.09, 1.27, and 1.28 (3s, 10-Me, 4-Me$_2$), 1.62 (m, 1H, H-1), 1.95 (dd, 1H, J=11.7 and 6.2 Hz, H-5), 2.07 (dt, 1H, J=8.4, 8.4 and 2.9 Hz, H-2), 2.18 (s, MeAr), 2.32 (dt, 1H, J=12.8, 2.9, and 2.9 Hz, H-1), 2.69 (d, 1H, J=7.3 Hz, H-6), 2.73 (br s, 1H, H-6), 2.91 (dd, 1H, J=8.4 and 8.4 Hz, H-3), 3.85 (s, MeO), 6.66 (s, 1H, H-11), 7.28 (m, 3H, meta and para protons Ph-S), 7.42 (dd, 2H, J=8.3 and 1.6 Hz, H-ortho Ph-S), 7.80 (s, 1H, H-14); eims *m/z* [M]$^+$ 394 (81), 285 (64), 269 (74), 243 (33), 229 (12), 217 (64), 215 (51), 203 (35), 189 (100), 175 (27).

OXIDATION TO THE SULFOXIDE **11**.—To ketone **10** (40 mg) in CH_2Cl_2 (0.9 ml) at −78° was added *m*-CPBA (85 mg, 60%) suspended in CH_2Cl_2 (0.9 ml). After stirring for 1 h at −78°, the solution was allowed to warm slightly, saturated aqueous $NaHSO_3$ (3.5 ml) was added, and the product was obtained by Et_2O extraction. Cc (Et_2O) gave some starting material and then pure sulfoxide **11**: ^{1}H nmr δ 1.26, 1.34, and 1.40 (3s, 4-Me$_2$, 10-Me), 1.88 (dd, 1H, J=11.0 and 6.5 Hz, H-5), 2.15 (s, MeAr), 2.41 (br d, 1H, J=12.8 Hz,

H-1), 2.69 (d, J=11.0 Hz, H_β-6), 2.71 (d, J=6.5 Hz, H_α-6), 3.80 (s, MeO), 6.60 (s, H-11), 7.48 (m, 5H, PhSO), 7.77 (s, H-14); eims *m/z* no $[M]^+$, 285 (32) $[M-Ph-SO]^+$, 284 (36), 269 (18), 217 (31), 215 (25), 202 (100), 189 (59), 175 (24), 159 (21).

ENOL THIO ETHER **13**.—To sulfoxide **11** (56 mg) in CH_2Cl_2 (3.5 ml) at 0° was added trifluoroacetic anhydride (0.19 ml) and then pryidine (0.28 ml). After 5 h, H_2O (2 ml) was introduced slowly and the mixture was Et_2O-extracted. Cc (petroleum ether/7% Et_2O) gave thio ether **13** (24 mg, 49%): ^1H nmr δ 1.18, 1.21, and 1.37 (3s, 4-Me_2, 10-Me), 2.18 (s, MeAr), 2.29 (t, 1H, J=8.9 Hz, H-5), 2.40 (br d, 1H, J=17.2 Hz, H-1), 2.68 (d, 2H, J=9.2 Hz, H-6), 2.76 (dd, 1H, J=17.2 and 6.5 Hz, H-1), 3.87 (s, MeO), 5.90 (dd, 1H, J=6.5 and 2.1 Hz, H-2), 6.68 (s, H-11), 7.2–7.5 (5H, PhS), 7.82 (s, H-14); eims *m/z* $[M]^+$ 390 (100), 202 (12), 190 (62), 175 (28).

(±)-*O*-METHYL NIMBINONE [**14**].—To thio ether **13** (21.5 mg) in glacial HOAc (0.5 ml) was added $TiCl_4$ (0.02 ml), causing the color to change to orange. After 20 min, H_2O (0.7 ml) was added and the mixture refluxed for 1 h. It was then diluted with H_2O and Et_2O-extracted. Cc (petroleum ether/40% Et_2O) afforded the *O*-methyl nimbinone [**14**] (12 mg, 73%): mp 106°; ir 1710, 1667 cm^{-1}; ^1H nmr δ 1.12, 1.18, and 1.43 (3s, 4-Me_2, 10-Me), 2.17 (s, MeAr), 3.88 (s, MeO), 6.67 (s, H-11), 7.81 (s, H-14); ^{13}C nmr δ 36.9, 34.5, 214.4, 47.3, 49.7, 36.1, 196.9, 123.5, 154.1, 37.8, 104.4, 162.7, 125.8, 129.8, 15.7 (C-1 to C-15), 25.0 (10-Me), 22.6 and 21.4 (4-Me_2), 55.5 (OMe); eims *m/z* $[M]^+$ 300 (100), 285 (11), 243 (15), 229 (11), 215 (28), 204 (22), 201 (24), 189 (14); hrms *m/z* 300.1723 ($C_{19}H_{24}O_3$ requires 300.1724).

PREPARATION OF *O*-METHYL 13-METHYLPODOCARPIC ACID.—*Formylation of methyl O-methylpodocarpate* [**16**].—Duff reaction: To a solution of **16** (15.03 g) in TFA (160 ml) was added hexamethylenetetramine (25 g), and the mixture was refluxed for 3.5 h. After pouring into H_2O and neutralization ($NaHCO_3$), Et_2O extraction afforded the product **17**, methyl *O*-methyl-13-formyl-podocarpate (17.20 g, 100%): mp 120–124° (sufficiently pure for the next step); $[\alpha]^{26}D$ 147.6° (c=1.0, $CHCl_3$); ir 1725, 1680 cm^{-1}; ^1H nmr δ 1.03 (s, 3H, 10-Me), 1.06 (ddd, 1H, J=13.5, 13.5, and 4.4 Hz, H_α-3), 1.25 (s, 3H, 4-Me), 1.40 (ddd, 1H, J=13.6, 13.6, and 4.0 Hz, H_α-1), 1.49 (dd, 1H, J=12.1 and 1.8 Hz, H-5), 1.63 (m, 1H, H_β-2), 1.88 (m, 2H, H_β-6, H_α-2), 2.15 (m, 3H, H_α-6, H_β-1, H_β-3), 2.76 (m, 2H, H_2-7), 3.64 (s, 3H, MeOOC), 3.85 (s, 3H, MeOAr), 6.82 (s, 1H, H-11), 7.47 (s, 1H, H-14), 10.34 (s, 1H, CHO); eims *m/z* $[M]^+$ 330 (31), 255 (100), 227 (35), 199 (25), 189 (31), 171 (44), 164 (31), 158 (42), 128 (87); hrms *m/z* 330.1846 ($C_{20}H_{26}O_4$ requires 330.1831).

Reduction of the aldehyde **17**.—A current of BF_3 (bubbled through an H_2SO_4 solution of boric anhydride to remove the HF) was passed over CH_2Cl_2 (75 ml) at 0°. The aldehyde **17** (17.1 g) in CH_2Cl_2 (50 ml) wa added, and after 4 min triethylsilane was introduced (16.6 ml) and stirring was continued at 0° for 15 min. Saturated aqueous NaCl was added to stop the reaction, and the organic phase was washed with H_2O, saturated $NaHCO_3$, and saturated NaCl before drying and evaporating. Cc (petroleum ether/10% Et_2O) yielded some starting material (533 mg) and methyl *O*-methyl-13-methylpodocarpate [**18**] (12.31 g, 78%): mp 113–114°, $[\alpha]^{27}D$ 129.3 (c=1.0, $CHCl_3$): ir 1725 cm^{-1}; ^1H nmr δ 1.07 (s, 3H, 10-Me), 1.10 (ddd, 1H, J=13.6, 13.6, and 4.4 Hz, H_α-3), 1.29 (s, 3H, 4-Me), 1.43 (ddd, 1H, J=13.6, 13.6, and 4.4 Hz, H_α-1), 1.54 (dd, 1H, J=12.1 and 2.2 Hz, H-5), 1.65 (m, 1H, H_β-2), 1.97 (m, 2H, H_β-6, H_α-2), 2.25 (m, 3H, H_α-6, H_β-1, H_β-3), 2.17 (s, 3H, 13-Me), 2.80 (m, 2H, H_2-7), 3.68 (s, 3H, COOMe), 3.80 (s, 3H, MeOAr), 6.73 (s, 1H, H-11), 6.83 (s, 1H, H-14); eims *m/z* $[M]^+$ 316 (100), 301 (61), 269 (39), 242 (82), 241 (96), 187 (51), 185 (95), 175 (52), 161 (48), 135 (62), 128 (58); hrms *m/z* 316.2034 ($C_{20}H_{28}O_3$ requires 316.2038).

Hydrolysis of the ester.—A solution of the ester **18** (12.2 g) in 2,4,6-collidine containing LiI (38 g) was refluxed for 5 h and then poured into ice-H_2O, acidified (dilute HCl), and Et_2O-extracted to give the pure *O*-methyl 13-methylpodocarpic acid [**19**] (obtained via the sodium salt) (11.7 g, 100%): mp 178–183° (dec.); $[\alpha]^{28}D$ 124.1° (c=1.03, $CHCl_3$): ^1H nmr δ 1.12 (ddd, 1H, J=12.9, 12.9, and 3.7 Hz, H_α-3), 1.16 (s, 3H, 10-Me), 1.37 (s, 3H, 4-Me), 1.43 (ddd, 1H, J=13.6, 13.6, and 4.5 Hz, H_α-1), 1.58 (dd, 1H, J=11.7 and 2.1 Hz, H-5), 1.65 (m, 1H, H_β-2), 1.92–2.35 (m, 5H), 2.18 (s, 3H, 13-Me), 2.77 (m, 2H, H_2-7), 3.81 (s, 3H, MeO), 6.73 (s, 1H, H-11), 6.84 (s, 1H, H-14), 11.0 (br s, COOH); eims *m/z* $[M]^+$ 302 (96), 287 (42), 241 (100), 187 (31), 185 (63), 173 (35), 135 (52), 128 (48); hrms 302.1881 ($C_{19}H_{26}O_3$ requires 302.1882).

PREPARATION OF THE ALLYLIC ALCOHOL **27**.—*Decarboxylation of the acid*.—Pyridine (6 ml) was added to acid **19** (11.7 g) in C_6H_6 (120 ml) followed by $Pb(OAc)_4$ (24.34 g). After 4 h at reflux, the cooled solution was filtered, diluted with Et_2O, washed (dilute HCl, H_2O, saturated $NaHCO_3$, saturated NaCl), evaporated, and chromatographed (petroleum ether/10% Et_2O) to give the mixture of olefins **20–22** (4.14 g, 42%) and then the tertiary acetate **23** (2.23 g, 18%): ^1H nmr δ 1.24 (s, 10-Me), 1.58 (s, 4-Me), 2.02 (s, Ac), 2.20 (s, 13-Me), 3.83 (s, MeO), 6.73 (s, H-11), 6.85 (s, H-14).

Pyrolysis of the acetate.—Acetate **23** (2.23 g) was heated under a Vigreux column at 250° (sand bath) for 20 min, then taken up in Et_2O and washed (H_2O, $NaHCO_3$, NaCl). Cc of the residue (petroleum ether/3% Et_2O) gave more of the **20–22** olefin mixture (1.54 g, 86%).

Epoxidation.—To a solution of *m*-CPBA (3.43 g of 60%) in $CHCl_3$ (300 ml) at 0° was added the mixed olefins **20–22** (4.14 g), and stirring was continued for 2 h. The mixture was poured into saturated $NaHSO_3$ and the organic phase washed with H_2O. Cc of the residue (petroleum ether/10–30% Et_2O) gave exocyclic olefin **22** (524 mg, 13%), 3,4-epoxide **24** (1.569 g, 36%), 4,18-epoxide **26** (647 mg, 15%), 4,5-epoxide **25** (470 mg, 11%), and the allylic alcohol **27** (449 mg, 10%).

12-Methoxy-13-methyl-19-norpodocarpa-4(18),8,11,13-tetraene [**22**].—Mp 93–96°, $[\alpha]^{25}D$ 218.8 (c=0.95, $CHCl_3$); ir 1650 and 880 cm^{-1}; ^1H nmr δ 1.05 (s, 10-Me), 2.19 (s, 13-Me), 3.82 (s, MeO), 4.62 (dd, 1H, J=3.2 and 1.6 Hz, H-18), 4.87 (dd, 1H, J=3.2 and 1.6 Hz, H-18), 6.78 (s, H-11), 6.87 (s, H-14); eims m/z $[M]^+$ 256 (77), 241 (100), 213 (19), 185 (22), 173 (11), 135 (27), 128 (21); hrms m/z 256.1814 ($C_{18}H_{24}O$ requires 256.1827).

4α,5α-Epoxy-12-methoxy-13-methyl-18-norpodocarpa-8,11,13-triene [**25**].—$[\alpha]^{26}D$ 180.4° (c=1.18, $CHCl_3$): ^1H nmr δ 1.44, 1.46, 2.23 (3s, 10-Me, 4-Me, and 13-Me), 2.82 (m, 2H, H_2-7), 3.85 (s, MeO), 6.75 (s, H-11), 6.89 (s, H-14); eims m/z $[M]^+$ 272 (86), 214 (71), 201 (80), 199 (44), 187 (100), 173 (54), 159 (32), 141 (46), 128 (89); hrms m/z 272.1766 ($C_{18}H_{24}O_2$ requires 272.1776).

4α,18-Epoxy-12-methoxy-13-methyl-18-norpodocarpa-8,11,13-triene [**26**].—$[\alpha]^{27}D$ 99.6° (c=0.92, $CHCl_3$): ^1H nmr δ 1.18 (s, Me-10), 2.02 (dd, 1H, J=12.8 and 1.8 Hz, H-5), 2.18 (s, 13-Me), 2.66 (d, 1H, J=4.4 Hz, H-19), 3.82 (s, MeO), 6.76 (s, H-11), 6.86 (s, H-14); eims m/z $[M]^+$ 272 (100), 257 (47), 227 (28), 199 (27), 187 (42), 185 (36), 173 (83), 141 (49), 128 (82).

3α,4α-Epoxy-12-methoxy-13-methyl-18-norpodocarpa-8,11,13-triene [**24**].—Mp 87–95°, $[\alpha]^{27}D$ 158.1° (c=1.02, $CHCl_3$): ^1H nmr δ 1.14, 1.39, and 2.20 (3s, 10-Me, 4-Me, 13-Me), 2.82 (m, 2H, H_2-7), 3.06 (br s, 1H, H_β-3), 3.83 (s, MeO), 6.75 (s, H-11), 6.87 (s, H-14); eims m/z $[M]^+$ 272 (100), 257 (60), 239 (54), 201 (28), 187 (47), 173 (31), 159 (31), 141 (51), 135 (53), 128 (90); hrms m/z 272.1763 ($C_{18}H_{24}O_2$ requires 272.1776).

3α-Hydroxy-12-methoxy-13-methyl-19-norpodocarpa-4(18),8,11,13-tetraene [**27**].—Mp 48–52°; $[\alpha]^{26}D$ 135.7 (c=1.09, $CHCl_3$); ^1H nmr δ 1.03 (s, 10-Me), 1.70–2.10 (m, 7H), 2.20 (s, 13-Me), 274–2.90 (m, 3H), 3.83 (s, MeO), 4.37 (d, 1H, J=2.6 Hz, H_β-3), 4.76 (dd, 1H, J=1.8 Hz, H-18), 5.09 (dd, 1H, J=1.8 Hz, H-18), 6.78 (s, H-11), 6.88 (s, H-14); eims m/z $[M]^+$ 272 (68), 240 (17), 239 (100), 224 (12), 173 (12), 141 (11), 135 (23), 128 (18); hrms m/z 272.1781 ($C_{18}H_{24}O$ requires 272.1776).

Isomerization of epoxide **24**.—To a solution of diisopropylamine (1.3 ml) in Et_2O (4 ml) at −78° was added *n*-BuLi (1.0 ml, 2.5 M in hexanes) and the temperature allowed to rise to 0° for 15 min. The epoxide (251 mg) in Et_2O (3 ml) was added, and the mixture was refluxed for 4 h, cooled, diluted with Et_2O, and washed (dilute HCl, H_2O, saturated $NaHCO_3$, saturated NaCl). Cc of the oil (petroleum ether/30% Et_2O) gave allylic alcohol **27** (218 mg, 87%).

Allylic oxidation of exocyclic olefin **22**.—SeO_2 (62.8 mg) was added to a solution of **22** (203 mg) in 95% EtOH (12.5 ml), and the mixture was refluxed for 2 h, cooled, and filtered through Celite. Cc (petroleum ether/30% Et_2O) of the residue obtained by evaporating the solvent gave some starting material (86 mg) and the allylic alcohol **27** (109 mg, 51%, or 88% if recovered **22** is subtracted).

CYCLOPROPANATION OF THE ALLYLIC ALCOHOL **27**.—Under N_2, diethyl zinc (1.75 ml, 1.1 M in toluene) was added to **27** (150 mg) in CH_2Cl_2 (3 ml), and after stirring at room temperature for 5 min, the temperature was lowered to 0° and freshly distilled CH_2I_2 (0.25 ml) was added slowly. The cooling bath was removed, stirring continued for 35 min, and the mixture then poured into H_2O, acidified with dilute HCl, and Et_2O-extracted. Cc (petroleum ether/30% Et_2O) gave the cyclopropyl derivative **28** (112 mg, 71%) as a waxy solid: mp 45–53°; $[\alpha]^{24}D$ 42.5 (c=1.03, $CHCl_3$); ^1H nmr δ 0.15 (m, 1H, H-19), 0.41 (m, 1H, H-18), 0.65 (m, 2H, H-18 and H-19), 1.20 (s, 3H, 10-Me), 1.52 (s, OH), 1.80 to 2.20 (6H), 2.16 (s, 3H, MeAr), 2.37 (dd, 1H, J=10.3 and 5.1 Hz, H-5), 2.75 (m, 2H, H_2-7), 3.0 (br s, 1H, H-3), 3.81 (s, 3H, MeO), 6.76 (s, 1H, H-11), 6.82 (s, 1H, H-14); eims m/z $[M]^+$ 286 (100), 253 (60), 243 (40), 225 (41), 211 (30), 185 (33), 172 (38), 141 (41), 135 (67), 128 (54); hrms m/z 286.1925 ($C_{19}H_{26}O_2$ requires 286.1933).

HYDROGENATION OF **28** TO **29**.—Cyclopropyl compound **28** (112 mg) in glacial HOAc (20 ml) was stirred overnight with PtO_2 (23 mg) under H_2 (rubber balloon). After filtering (Celite) and diluting with Et_2O, the solution was well washed, evaporated, and chromatographed (petroleum ether/30% Et_2O) to recover starting material (25 mg), some fractions where the aromatic ring was also hydrogenated, and then gem-dimethyl compound **29** (47 mg, 54%): mp 117–120°, $[\alpha]^{27}D$ 43.7 (c=0.73, $CHCl_3$): ^1H nmr δ 0.96, 1.04, and 1.23 (3s, 4-Me_2, 10-Me), 1.61 (s, OH), 1.7–2.2 (7H), 2.16 (s, MeAr), 2.85 (m, H_2-7), 3.51 (dd,

J=2.8 Hz, H-3), 3.80 (s, MeO), 6.73 (s, H-11), 6.81 (s, H-14); eims *m/z* $[M]^+$ 288 (20), 255 (57), 188 (18), 173 (31), 158 (17), and 128 (27); hrms 288.2066 ($C_{19}H_{28}O_2$ requires 288.2089).

Acetylation (Ac_2O, pyridine) of **29** afforded acetate **30** (83%): ir 1730 and 1250 cm^{-1}; ^1H nmr δ 0.94, 1.01, 1.23, 1.99 (AcO), 2.16 and 3.80 (3H singlets), 4.74 (br s, H-3), 6.72 and 6.83 (arom); eims *m/z* $[M]^+$ 330 (28), 255 (100), 187 (18), 173 (21), 128 (23); hrms *m/z* 330.2217 ($C_{21}H_{30}O_3$ requires 330.2195).

BENZYLIC OXIDATION OF **30**.—To acetate **30** (38 mg) in C_6H_6 (3 ml) was added PCC (133 mg) and Celite (301 mg), and the mixture was refluxed overnight. After cooling and diluting with Et_2O, drying ($MgSO_4$), and filtering, evaporation left an oil which on cc gave the ketone **31** (20 mg, 51%): $[\alpha]^{26}D$ 11.9 (c=1.15, $CHCl_3$); ir 1730, 1670, 1245 cm^{-1}; ^1H nmr δ 0.92, 1.07, and 1.26 (3s, 4-Me_2, 10-Me), 2.0 (s, Ac), 2.19 (s, MeAr), 2.31 (dd, 1H, J=10.3 and 7.5 Hz, H-5), 2.60 (d, 1H, J=7.5 Hz, H-6), 2.61 (d, 1H, J=10.3 Hz, H-6), 3.89 (s, MeO), 4.77 (br s, H-3), 6.73 (s, H-11), 7.82 (s, H-14); eims *m/z* $[M]^+$ 344 (17), 269 (100), 202 (21), 189 (46), 159 (22), 128 (36); hrms *m/z* 344.1982 ($C_{21}H_{28}O_4$ requires 344.1988).

HYDROLYSIS OF THE ACETATE **31**.—Acetate **31** (37 mg) in MeOH (6 ml) was hydrolyzed with NaOH (4 ml, 5%) at room temperature overnight. Extraction and cc (petroleum ether/40% Et_2O) gave the alcohol **32** (28.3 mg, 87%): $[\alpha]^{24}D$ 35.4 (c=1.25, $CHCl_3$): ^1H nmr δ 1.01 (s, 6H, 4-Me_2), 1.24 (s, 10-Me), 1.64 (s, OH), 1.8 to 2.2 (4H), 2.17 (s, MeAr), 2.33 (dd, 1H, J=12.1 and 5.7 Hz, H-5), 2.58 (d, 1H, J=5.7 Hz, H-6), 2.60 (d, 1H, J=12.1 Hz, H-6), 3.56 (br s, 1H, H-3), 3.87 (s, MeO), 6.74 (s, H-11), 7.79 (s, H-14); eims *m/z* $[M]^+$ 302 (22), 269 (45), 201 (20), 189 (14), 159 (16), 128 (24); hrms *m/z* 302.1889 ($C_{19}H_{26}O_3$ requires 302.1882).

O-METHYL NIMBINONE **14** (OXIDATION OF **32**).—Alcohol **32** (25 mg) in Me_2CO (2.5 ml) at 0° was treated with excess Jones reagent for 10 min. Dilution with H_2O, Et_2O extraction, and cc gave *O*-methyl nimbinone (25 mg, quant): mp 150–154°, $[\alpha]^{25}D$ 19.7 (c=1.0, $CHCl_3$); uv λ max 227 (14,700), 279 (11,300) nm; ir 1710, 1670 cm^{-1}; ^1H nmr δ 1.13, 1.19, and 1.44 (3s, 4-Me_2, 10-Me), 2.03 (ddd, 1H, J=13.0, 13.0 and 5.5 Hz, H_α-1), 2.18 (s, 3H, MeAr), 2.31 (dd, J=13.2 and 4.0 Hz, H-5), 2.5–3.0 (5H), 3.89 (s, 3H, MeO), 6.68 (s, 1H, H-11), 7.82 (s, 1H, H-14); eims *m/z* $[M]^+$ 300 (13), 201 (16), 189 (11), 175 (10), 159 (12), 141 (12), 128; hrms *m/z* 300.1716 ($C_{19}H_{24}O_3$ requires 300.1725).

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