A Simple Total Synthesis of (+)-Ferruginol, (+)-Sempervirol, and (+)-Podocarpa-8(14)-en-13-one

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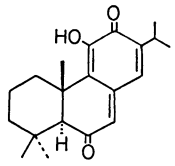
The Wittig reaction of (*R*)-(−)-α-cyclocitral with (3-isopropyl-4-methoxybenzyl)-, (4-isopropyl-3-methoxybenzyl)-, and (3-methoxybenzyl)triphenylphosphonium chloride afforded the styryl derivatives which were partially hydrogenated to the corresponding dihydro derivatives (**18**, **26**, and **27**). Intramolecular cyclization of **18** and **26** with anhydrous aluminium chloride followed by demethylation with boron tribromide gave (+)-ferruginol and (+)-sempervirol. The similar cyclization of **27** gave (+)-13-methoxypodocarpa-8, 11, 13-triene. This was reduced with lithium in liquid ammonia in the presence of ethanol and then treated with dilute hydrochloric acid to give (+)-podocarpa-8(14)-en-13-one, a versatile intermediate for natural diterpene synthesis.

In previous papers,[1-3] we have reported the syntheses of highly-oxygenated tricyclic diterpenes, *i.e.* taxodione (**1**), royleanone (**2**), 7-oxoroyleanone (**3**), taxoquinone (**4**), horminone (**5**), 7α-acetoxyroyleanone (**6**), dehydroroyleanone (**7**), cryptojaponol (**8**), and inuroyleanol (**9**), using ferruginol (**10**) as an useful key intermediate. We also reported the synthesis of sempervirol (**11**), which is a rare tricyclic diterpene phenol possessing an isopropyl group at the C-12 position. All these syntheses started from natural (−)-abietic acid (**12**). To complete these previous works, we planned to devise a more efficient and general synthetic method for the optically active tricyclic diterpenes to achieve the total syntheses of the above natural products. This paper will describe the simple total syntheses of (+)-ferruginol (**10**), (+)-sempervirol (**11**), and (+)-13-methoxypodocarpa-8,11,13-triene (**13**),[4] which was easily converted into (+)-podocarpa-8(14)-en-13-one (**14**),[5-9] a versatile intermediate for naturally-occurring diterpenes.



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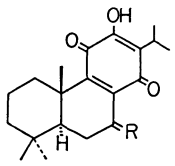
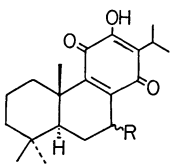
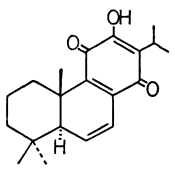


2 R = H_2
3 R = O



4 R = β-OH
5 R = α-OH
6 R = α-OAc



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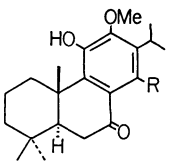
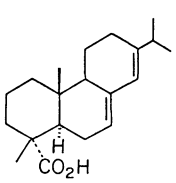


8 R = H
9 R = OH



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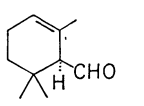
(*R*)-(−)-α-Cyclocitral (**15**)[10] prepared from (±)-α-cyclogeranic acid was chosen as a starting material. The Wittig reaction of **15** with (3-isopropyl-4-methoxybenzyl)triphenylphosphonium chloride (**16**) in hexane in the presence of butyllithium gave 3-(3-isopropyl-4-ethoxystyryl)-2,4,4-trimethyl-1-cyclohexene (**17**). The stereochemistry of the newly formed double bond in **17** was assigned as the *trans*-configuration because of the vicinal coupling constant (J=15 Hz) between the olefinic protons in the NMR spectrum. The compound **17** in ethanol was submitted to partial catalytic hydrogenation over Pd–C at room temperature to give the corresponding phenethyl derivative (**18**). This was treated with anhydrous aluminium chloride in benzene and gave a mixture of two intramolecular cyclization products. The chromatographic purification of the mixture afforded ferruginyl methyl ether (**19**) and its *cis*-isomer (**20**) in a ratio of 1:1. The *cis*-configuration of the A/B ring junction in **20** was supported by its NMR spectrum, which showed a signal due to the $C_{4\beta}$ methyl group in the high field, δ 0.40 ppm, because of the shielding effect of the aromatic ring. The demethylation of **19** with boron tribromide in dichloromethane gave ferruginol (**10**). However, since the optical rotation ($[\alpha]_D$+33.2°) was somewhat lower than that of the natural product,[2] this was further purified *via* the benzoate (**21**) to give the optically pure compound (**10**), $[\alpha]_D$+55.0°.



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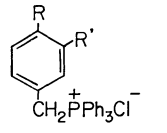
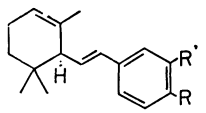
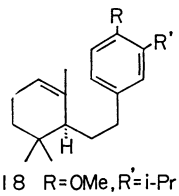


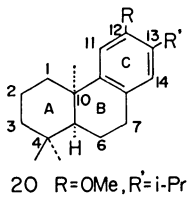
16 R=OMe, R'=i-Pr
22 R=i-Pr, R'=OMe
23 R=H, R'=OMe



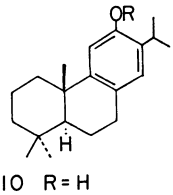
17 R=OMe, R'=i-Pr
24 R=i-Pr, R'=OMe
25 R=H, R'=OMe



18 R=OMe, R'=i-Pr
26 R=i-Pr, R'=OMe
27 R=H, R'=OMe

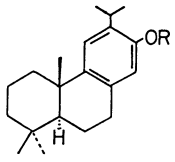


20 R=OMe, R'=i-Pr
29 R=i-Pr, R'=OMe
31 R=H, R'=OMe

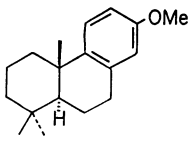


10 R = H
19 R = Me
21 R=COPh

Similarly, **15** was condensed respectively with (4-isopropyl-3-methoxybenzyl)triphenylphosphonium chlo-



11 R=H
28 R=Me
30 R=Ac



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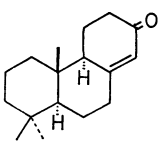

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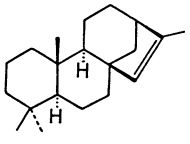
ride (**22**) and (3-methoxybenzyl)triphenylphosphonium chloride (**23**) in the presence of butyllithium to afford the styryl derivatives (**24** and **25**), which were then hydrogenated in the presence of Pd–C to yield the corresponding phenethyl derivatives, **26** and **27**, respectively. The intramolecular cyclization of **26** with anhydrous aluminium chloride gave semperviryl methyl ether (**28**) and its *cis*-isomer (**29**).[3] The *trans*-compound (**28**) was demethylated with boron tribromide to give sempervirol (**11**), $[\alpha]_D$+38.0°. The purification of **11** *via* the acetate (**30**) gave the optically pure sample (**11**), $[\alpha]_D$+60.2°. The compound **27** was also cyclized with anhydrous aluminium chloride to give 13-methoxypodocarpa-8,11,13-triene (**13**),[4] which was purified by crystallization along with its *cis*-isomer (**31**). The conversion of racemic **13** into racemic podocarpa-8(14)-en-13-one (**14**) has already been reported by Barltrop and Rogers[11] and Church *et al.*[12] The synthetic optically-active **13** was similarly reduced with lithium in liquid ammonia in the presence of ethanol and then treated with dilute hydrochloric acid to give the α,β-unsaturated ketone (**14**), mp 61.5—62.5 °C, $[\alpha]_D$+40.4°, a degradation product of natural diterpenes, *e.g.* isophyllocladene (**32**)[5] and manool (**33**).[5,6,9] The optically-active ketone (**14**) has already been transformed into isophyllocladene (**32**),[13] manool (**33**),[7] phyllocladene (**34**),[13] hibaone (**35**),[14] sclareol (**36**),[7] manoyl oxide (**37**),[7] anticopalic acid (**38**),[15,16] *trans*-abienol (**39**),[17] and isoabienol (**40**).[17] Therefore, the present work can be regarded as the total syntheses of the above natural diterpenes.



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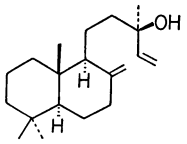

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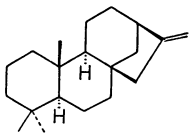

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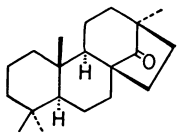

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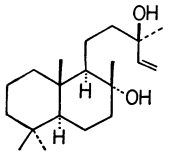

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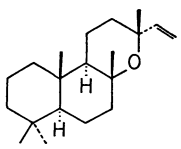

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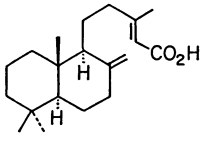

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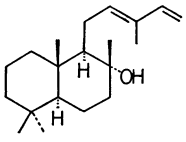

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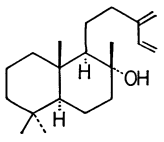

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Experimental

All melting points are uncorrected. The IR spectra and optical rotations were measured in chloroform, and the NMR spectra in carbon tetrachloride at 60 MHz, with tetramethylsilane as the internal standard, unless otherwise stated. The chemical shifts are presented in terms of δ values; s: singlet, bs: broad singlet, d: doublet, bd: broad doublet, dd: double doublet, t: triplet, m: multiplet. Column chromatography was performed using Merck silica gel (0.063 mm).

*(R)-(−)-α-Cyclocitral (**15**).*[10] (−)-α-Cyclogeraniol[10,18] (4.11 g, $[\alpha]_D$ −117° (EtOH)) prepared from (±)-α-cyclogeranic acid, and dicyclohexylcarbodiimide[19] (16.5 g) were dissolved in dimethyl sulfoxide (15 ml) and benzene (15 ml). Anhydrous phosphoric acid[20] (7 ml, 1 M solution in dimethyl sulfoxide) was added at 5 °C, and the mixture was stirred at this temperature for 4 h. Dry ether (50 ml) was added, followed by a solution of oxalic acid (6.72 g) in methanol (7 ml). After 30 min, the *N,N'*-dicyclohexylurea was removed by filtration and washed with ether. The filtrate was washed with water, dried over sodium sulfate, and then evaporated. The crude product was purified by column chromatography on silica gel using hexane–benzene (1:4) as the eluent to yield **15** (2.90 g: 72%), $[\alpha]_D$ −711° (EtOH), NMR: 0.89 and 0.97 (each 3H and s, $-\dot{C}(CH_3)_2$), 1.60 (3H, d, J=1.5 Hz, $=\dot{C}CH_3$), 5.69 (1H, bs, $-CH=\dot{C}-$), 9.34 (1H, d, J=5 Hz, −CHO).

*(3-Isopropyl-4-methoxybenzyl)triphenylphosphonium Chloride (**16**).* A solution of 3-isopropyl-4-methoxybenzyl chloride[21] (5.71 g) and triphenylphosphine (7.54 g) in dry benzene (10 ml) was refluxed for 5 h and the precipitate (**16**) (7.80 g, mp 253—259 °C) was collected. The filtrate was further refluxed for 3 h to give some additional salt (1.20 g, mp 251—254 °C).

*3-(3-Isopropyl-4-methoxystyryl)-2,4,4-trimethyl-1-cyclohexene (**17**).* A solution of butyllithium in hexane (15%; 2.9 ml) was added at room temperature to a suspension of **16** (2.660 g) in hexane (13 ml) under a stream of nitrogen. The mixture was stirred for 1 h and a solution of **15** (549 mg) in hexane (2.0 ml) was added at 5 °C. After stirring at 5—10 °C for 4 h, the mixture was acidified with dilute hydrochloric acid, extracted with ether, and the extract was washed with brine, dried over sodium sulfate, and then evaporated. The residue was triturated with hexane, and the precipitated triphenylphosphine oxide was removed by filtration. The filtrate was evaporated and the residue (1.208 g) was purified by column chromatography on silica gel (50 g) using hexane as the eluent to give **17** (852 mg: 79%) as an oil, $[\alpha]_D$ −273°, NMR: 0.90 and 0.94 (each 3H and s, $-\dot{C}(CH_3)_2$), 1.21 (6H, d, J=7 Hz, $-CH(C\underline{H}_3)_2$), 1.63 (3H, bs, $=\dot{C}CH_3$), 3.27 (1H, m, $-C\underline{H}(CH_3)_2$), 3.79 (3H, s, $-OCH_3$), 5.40 (1H, m, $-CH=\dot{C}-$), 5.76 (1H, dd, J=8 and 15 Hz, $-\dot{C}H-C\underline{H}=CH-$), 6.25 (1H, d, J=15 Hz, $-\dot{C}H-CH=C\underline{H}-$), 6.63 (1H, d, J=9 Hz), 7.04 (1H, d, J=2 Hz), and 7.04 (1H, dd, J=2 and 9 Hz) (aromatic protons). Found: C, 84.62; H, 10.10%. Calcd for $C_{21}H_{30}O$: C, 84.51; H, 10.13%.

*3-(3-Isopropyl-4-methoxyphenethyl)-2,4,4-trimethyl-1-cyclohexene (**18**).* A suspension of **17** (852 mg) and 5% Pd–C (300 mg) in ethanol (8.0 ml) was stirred at room temperature in an atmosphere of hydrogen. After one equivalent of hydrogen had been absorbed (*ca.* 80 min), the mixture was filtered. The filtrate was evaporated and the residue (828 mg) was purified by column chromatography on silica

gel (80 g) using hexane as the eluent to afford **18** (790 mg: 92%) as an oil, $[\alpha]_D$ −89.3°, NMR: 0.88 and 0.99 (each 3H and s, $-\dot{C}(CH_3)_2$), 1.19 (6H, d, J=7 Hz, $-CH(C\underline{H}_3)_2$), 1.68 (3H, bs, $=\dot{C}CH_3$), 3.26 (1H, m, $-C\underline{H}(CH_3)_2$), 3.77 (3H, s, $-OCH_3$), 5.28 (1H, m, $-CH=\dot{C}-$), 6.59 (1H, d, J=9 Hz), 6.83 (1H, dd, J=2 and 9 Hz), and 6.88 (1H, d, J=2 Hz) (aromatic protons). Found: C, 83.66; H, 10.73%. Calcd for $C_{21}H_{32}O$: C, 83.94; H, 10.73%.

Intramolecular Cyclization of ***18***. Anhydrous aluminium chloride (370 mg) was added at 30 °C to a solution of **18** (814 mg) in dry benzene (8.0 ml). The mixture was stirred at 30—33 °C for 30 min, decomposed with dilute hydrochloric acid, and then extracted with ether. The ether extract was washed with brine, dried over sodium sulfate, and evaporated. The crude product was chromatographed on silica gel (80 g) using hexane as the eluent to give the *cis*-isomer (**20**) (363 mg: 45%) as an oil, $[\alpha]_D$ −28.0°, NMR: 0.40 (3H, s, $C_{4\beta}$–CH_3), 0.93 (3H, s, $C_{4\alpha}$–CH_3), 1.14 (3H, s, C_{10}–CH_3), 1.16 (6H, d, J=7 Hz, $-CH(C\underline{H}_3)_2$), 3.19 (1H, m, $-C\underline{H}(CH_3)_2$), 3.78 (3H, s, $-OCH_3$), 6.63 and 6.69 (each 1H and s, C_{11}–H and C_{14}–H). Found: C, 84.21; H, 10.85%. Calcd for $C_{21}H_{32}O$: C, 83.94; H, 10.73%. Further elution gave the *trans*-isomer (**19**) (352 mg: 43%) as an oil, $[\alpha]_D$ +35.9°, NMR: 0.95 (6H, s, $-\dot{C}(CH_3)_2$), 1.16 (6H, d, J=7 Hz, $-CH(C\underline{H}_3)_2$), 1.19 (3H, s, C_{10}–CH_3), 3.18 (1H, m, $-C\underline{H}(CH_3)_2$), 3.74 (3H, s, $-OCH_3$), 6.55 and 6.67 (each 1H and s, C_{11}–H and C_{14}–H). Found: C, 84.24; H, 10.96%. Calcd for $C_{21}H_{32}O$: C, 83.94; H, 10.73%.

*Ferruginyl Benzoate (****21****).* A solution of **19** (384 mg) and boron tribromide (0.30 ml) in dichloromethane (4.0 ml) was allowed to stand at 0—5 °C for 2 h. The solution was then poured into water and extracted with ether. The extract was washed with brine, dried, and then evaporated to dryness. The crude product was purified by column chromatography on silica gel (40 g) using hexane–benzene (1:1) as the eluent to give ferruginol (**10**) (349 mg: 95%), $[\alpha]_D$ +33.2°, as an oil. The IR and NMR spectra were identical with those of an authentic sample.[2]

The above ferruginol (349 mg) was benzoylated at 50—55 °C for 3 h with benzoyl chloride (0.3 ml) in pyridine (3.5 ml). After the usual work-up, the crude product was chromatographed on silica gel (40 g) using hexane–benzene (1:1) as the eluent to give ferruginyl benzoate (**21**) (409 mg) which was recrystallized from ethanol, mp 154.5—156 °C, $[\alpha]_D$ +60.1°, IR: 1728 cm^{-1}, NMR: 0.96 (6H, s, $-\dot{C}(CH_3)_2$), 1.18 (6H, d, J=7 Hz, $-CH(C\underline{H}_3)_2$), 1.21 (3H, s, C_{10}–CH_3), 6.86 and 6.89 (each 1H and s, C_{11}–H and C_{14}–H), 7.3—7.7 (3H, m) and 8.1—8.3 (2H, m) (aromatic protons). The IR and NMR spectra were identical with those of authentic benzoate which was prepared from natural ferruginol. Found: C, 83.32; H, 9.02%. Calcd for $C_{27}H_{34}O_2$: C, 83.03; H, 8.78%.

*Ferruginol (****10****).* A mixture of **21** (134 mg) and lithium aluminium hydride (15 mg) in dry ether (2.0 ml) was refluxed for 1 h. After the usual work-up, the product was purified by column chromatography on silica gel (10 g) using hexane–benzene (1:1) as the eluent to give ferruginol (**10**) (93 mg: 94%) as an oil, $[\alpha]_D$ +55.0° (lit,[2] $[\alpha]_D$ +57.5°); IR: 3605, 3350 cm^{-1}; NMR: 0.91 (6H, s, $-\dot{C}(CH_3)_2$), 1.10 (3H, s, C_{10}–CH_3), 1.19 (6H, d, J=7 Hz, $-CH(C\underline{H}_3)_2$), 3.09 (1H, m, $-C\underline{H}(CH_3)_2$), 4.73 (1H, bs, –OH), 6.41 and 6.68 (each 1H and s, C_{11}–H and C_{14}–H). Found: C, 84.13; H, 10.49%. Calcd for $C_{20}H_{30}O$: C, 83.86; H, 10.56%.

*(4-Isopropyl-3-methoxybenzyl)triphenylphosphonium Chloride (****22****).* A solution of 4-isopropyl-3-methoxybenzyl chloride[22] (3.34 g) and triphenylphosphine (4.41 g) in dry benzene (5 ml) was refluxed for 6 h. The precipitate was collected and recrystallized from chloroform–benzene to give crystals (6.40 g: 82%), mp 222—225 °C.

*3-(4-Isopropyl-3-methoxystyryl)-2,4,4-trimethyl-1-cyclohexene (****24****).* A suspension of **22** (4.460 g) in hexane (22 ml) was treated with a solution of butyllithium in hexane (15%; 4.8 ml) under a stream of nitrogen and then with a solution of **15** (921 mg) in hexane (2.0 ml), as described for the preparation of **17**. The crude product was chromatographed on silica gel (100 g) using hexane as the eluent to give **24** (956 mg: 53%), $[\alpha]_D$ −320°, NMR: 0.89 and 0.95 (each 3H and s, $-\dot{C}(CH_3)_2$), 1.17 (6H, d, J=7 Hz, $-CH(C\underline{H}_3)_2$), 1.63 (3H, bs, $=\dot{C}CH_3$), 3.25 (1H, m, $-C\underline{H}(CH_3)_2$), 5.42 (1H, m, $-CH=\dot{C}-$), 5.83 (1H, dd, J=8 and 15 Hz, $-\dot{C}H-C\underline{H}=CH-$), 6.28 (1H, d, J=15 Hz, $-\dot{C}H-CH=C\underline{H}-$), 6.69 (1H, overlap), 6.75 (1H, dd, J=2 and 8 Hz), and 7.02 (1H, d, J=8 Hz) (aromatic protons). Found: C, 84.71; H, 10.10%. Calcd for $C_{21}H_{30}O$: C, 84.51; H, 10.13%.

*3-(4-Isopropyl-3-methoxyphenethyl)-2,4,4-trimethyl-1-cyclohexene (****26****).* A mixture of **24** (956 mg), 5% Pd–C (300 mg), and ethanol (10 ml) was subjected to catalytic hydrogenation at room temperature for *ca.* 60 min as described for the preparation of **18**. After the usual work-up, the crude product was purified by column chromatography on silica gel (90 g) using hexane as the eluent, to afford **26** (765 mg: 80%) as an oil, $[\alpha]_D$ −98.7°, NMR: 0.88 and 0.99 (each 3H and s, $-\dot{C}(CH_3)_2$), 1.16 (6H, d, J=7 Hz, $-CH(C\underline{H}_3)_2$), 1.69 (3H, bs, $=\dot{C}CH_3$), 3.22 (1H, m, $-C\underline{H}(CH_3)_2$), 3.78 (3H, s, $-OCH_3$), 5.27 (1H, m, $-CH=\dot{C}-$), 6.50 (1H, overlap), 6.58 (1H, dd, J=2 and 8 Hz), and 6.97 (1H, d, J=8 Hz) (aromatic protons). Found: C, 84.22; H, 10.66%. Calcd for $C_{21}H_{32}O$: C, 83.94; H, 10.73%.

Intramolecular Cyclization of ***26***. A mixture of **26** (395 mg), anhydrous aluminium chloride (180 mg), and dry benzene (4.0 ml) was treated at 30 °C for 30 min. After the usual work-up, the crude product was chromatographed on silica gel (40 g) using hexane as the eluent, to give the *cis*-isomer (**29**) (188 mg: 48%), $[\alpha]_D$ −24.7°, NMR: 0.37 (3H, s, $C_{4\beta}$–CH_3), 0.92 (3H, s, $C_{4\alpha}$–CH_3), 1.11 (3H, s, C_{10}–CH_3), 1.17 (6H, d, J=7 Hz, $-CH(C\underline{H}_3)_2$), 3.22 (1H, m, $-C\underline{H}(CH_3)_2$), 3.74 (3H, s, $-OCH_3$), 6.32 and 6.96 (each 1H and s, C_{14}–H and C_{11}–H). Found: C, 83.67; H, 10.84%. Calcd for $C_{21}H_{32}O$: C, 83.94; H, 10.73%.

Further elution gave semperviryl methyl ether (**28**) (151 mg: 38%), $[\alpha]_D$ +35.0°, NMR: 0.95 (6H, s, $-\dot{C}(CH_3)_2$), 1.15 (3H, s, C_{10}–CH_3), 1.16 (6H, d, J=7 Hz, $-CH(C\underline{H}_3)_2$), 3.19 (1H, m, $-C\underline{H}(CH_3)_2$), 3.73 (3H, s, $-OCH_3$), 6.32 and 6.94 (each 1H and s, C_{14}–H and C_{11}–H). Found: C, 83.92; H, 10.79%. Calcd for $C_{21}H_{32}O$: C, 83.94; H, 10.73%.

*Semperviryl Acetate (****30****).* A solution of **28** (283 mg) and boron tribromide (0.20 ml) in dichloromethane (3.0 ml) was allowed to stand at 0 °C for 2 h. The crude product was purified by column chromatography on silica gel (30 g) to give sempervirol (**11**) (249 mg: 92%), $[\alpha]_D$ +38.0°, which was treated at 50 °C for 2 h with acetic anhydride (0.20 ml) and pyridine (2.5 ml). The product was chromatographed on silica gel (25 g) using hexane–benzene (1:1) as the eluent and then recrystallized from ethanol to give the acetate (**30**), mp 92—94 °C, $[\alpha]_D$ +55.4° (lit,[23] mp 92—93 °C, $[\alpha]_D$ +51°), IR: 1750 cm^{-1}, NMR: 0.93 (6H, s, $-\dot{C}(CH_3)_2$), 1.15 (6H, d, J=7 Hz, $-CH(C\underline{H}_3)_2$), 1.18 (3H, s, C_{10}–CH_3),

2.21 (3H, s, $-OCOCH_3$), 6.52 (1H, bs, C_{14}–H), 7.04 (1H, s, C_{11}–H). Found: C, 80.41; H, 9.90%. Calcd for $C_{22}H_{32}O_2$: C, 80.44; H, 9.83%.

*Sempervirol (**11**).* A mixture of **30** (105 mg) and lithium aluminium hydride (15 mg) in dry ether (2.0 ml) was refluxed for 1 h. After the usual work-up, the product was purified by column chromatography on silica gel (10 g) using hexane–benzene (1:1) as the eluent, to afford sempervirol (**11**) (90 mg: 98%), $[\alpha]_D$ +60.2°; IR: 3605, 3340 cm^{-1}; NMR: 0.92 (6H, s, $-\dot{C}(CH_3)_2$), 1.13 (3H, s, C_{10}–CH_3), 1.19 (6H, d, J=7 Hz, $-CH(C\underline{H}_3)_2$), 3.10 (1H, m, $-C\underline{H}(CH_3)_2$), 4.59 (1H, bs, –OH), 6.18 (1H, s, C_{14}–H), 6.92 (1H, s, C_{11}–H). Found: C, 83.78; H, 10.50%. Calcd for $C_{20}H_{30}O$: C, 83.86; H, 10.56%.

*3-(3-Methoxystyryl)-2,4,4-trimethyl-1-cyclohexene (**25**).* A solution of butyllithium in hexane (15%; 2.8 ml) was added to a suspension of (3-methoxybenzyl)triphenylphosphonium chloride (**23**)[24] (mp 159—165 °C, 2.39 g) in dry benzene (20 ml) under a stream of nitrogen and stirred at room temperature for 15 min. After the addition of a solution of **15** (434 mg) in dry benzene (2.0 ml), the mixture was stirred for 6 more hours and then treated as described for the preparation of **17**. The crude product was purified by column chromatography on silica gel (40 g) using hexane–benzene (4:1) as the eluent to give **25** (411 mg: 56%) as an oil, $[\alpha]_D$ −345°, NMR: 0.89 and 0.94 (each 3H and s, $-\dot{C}(CH_3)_2$), 1.63 (3H, bs, $=\dot{C}CH_3$), 3.76 (3H, s, $-OCH_3$), 5.42 (1H, m, $-CH=\dot{C}-$), 5.92 (1H, dd, J=8 and 15 Hz, $-\dot{C}H-C\underline{H}=CH-$), 6.32 (1H, d, J=15 Hz, $-\dot{C}H-CH=C\underline{H}-$). Found: C, 84.03; H, 9.29%. Calcd for $C_{18}H_{24}O$: C, 84.32; H, 9.44%.

*3-(3-Methoxyphenethyl)-2,4,4-trimethyl-1-cyclohexene (**27**).* A mixture of **25** (1090 mg), 5% Pd–C (600 mg), and ethanol (10 ml) was subjected to catalytic hydrogenation as described for the preparation of **18**. After the usual work-up, the product was purified by column chromatography on silica gel (100 g) using hexane–benzene (95:5) as the eluent to give **27** (785 mg: 71%) as an oil, $[\alpha]_D$ −113°, NMR: 0.88 and 0.99 (each 3H and s, $-\dot{C}(CH_3)_2$), 1.68 (3H, bs, $=\dot{C}CH_3$), 3.73 (3H, s, $-OCH_3$), 5.28 (1H, m, $-CH=\dot{C}-$). Found: C, 83.72; H, 10.19%. Calcd for $C_{18}H_{26}O$: C, 83.66; H, 10.14%.

*Intramolecular Cyclization of **27**.* A mixture of **27** (780 mg), anhydrous aluminium chloride (450 mg), and dry benzene (10 ml) was stirred at 30 °C for 30 min. After the treatment by a method similar to that used for **18**, the crude product was chromatographed on silica gel (80 g) using hexane–benzene (9:1) as the eluent to give the *cis*-isomer (**31**) (285 mg: 36%) as an oil, $[\alpha]_D$ −21.9°, NMR: 0.38 (3H, s, $C_{4\beta}$–CH_3), 0.92 (3H, s, $C_{4\alpha}$–CH_3), 1.11 (3H, s, C_{10}–CH_3), 3.70 (3H, s, $-OCH_3$), 6.44 (1H, overlap, C_{14}–H), 6.53 (1H, dd, J=2.5 and 8.5 Hz, C_{12}–H), 7.06 (1H, d, J=8.5 Hz, C_{11}–H). Found: C, 83.37; H, 10.23%. Calcd for $C_{18}H_{26}O$: C, 83.66; H, 10.14%.

Further elution gave the *trans*-isomer (**13**) (291 mg: 37%), $[\alpha]_D$ +41.4°, which was recrystallized from methanol to afford an optically pure sample (138 mg), mp 84.5—86 °C, $[\alpha]_D$ +53.9° (lit,[4] mp 86—88 °C, $[\alpha]_D$ +54°), NMR: 0.93 (6H, s, $-\dot{C}(CH_3)_2$), 1.13 (3H, s, C_{10}–CH_3), 3.67 (3H, s, $-OCH_3$), 6.40 (1H, overlap, C_{14}–H), 6.51 (1H, dd, J=3 and 8 Hz, C_{12}–H), 7.01 (1H, d, J=8 Hz, C_{11}–H). Found: C, 83.42; H, 10.18%. Calcd for $C_{18}H_{26}O$: C, 83.66; H, 10.14%.

*(+)-Podocarpa-8(14)-en-13-one (**14**).* According to the method of Church *et al.*,[12] the compound **13** (138 mg) in dry ether (7.0 ml) was reduced with lithium (110 mg) in liquid ammonia (*ca.* 20 ml) in the presence of ethanol (5.0 ml) and then treated with dilute hydrochloric acid. The crude product was purified by column chromatography on silica gel (5.0 g) using ether–benzene (3:97) as the eluent, followed by recrystallization from petroleum ether to afford the enone (**14**), mp 61.5—62.5 °C, $[\alpha]_D$ +40.4° (lit,[8] mp 62—65 °C, $[\alpha]_D$ +41°); IR: 1656, 1617 cm^{-1}; NMR: 0.83, 0.90, and 0.94 (each 3H and s, $-\dot{C}(CH_3)_2$ and C_{10}–CH_3), 5.73 (1H, bs, C_{14}–H). Found: C, 83.00; H, 10.78%. Calcd for $C_{17}H_{26}O$: C, 82.87; H, 10.64%.

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