

Synthesis based on cyclohexadienes Part 36:¹ an efficient methodology for the construction of spiro[4.5]decanes: a formal synthesis of acorone

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Dedicated to Professor Sukh Dev on his 80th birthday

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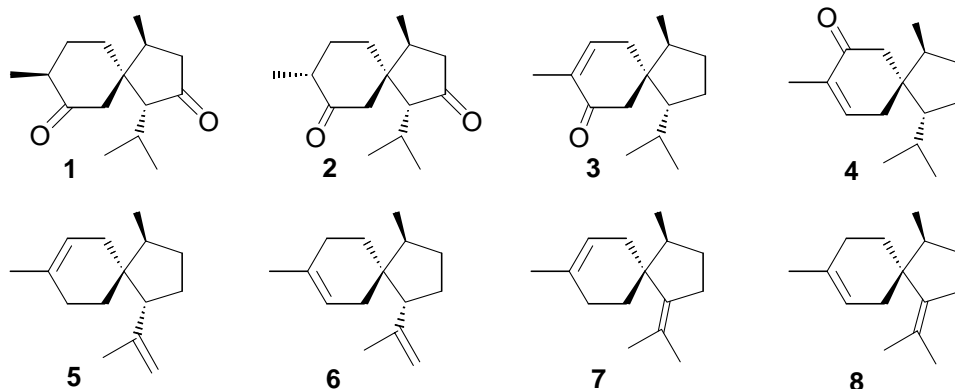
Abstract

An efficient strategy for the construction of spiro[4.5]decanes is described and involves a bridgehead substitution of a methoxyl group by a methyl group followed by an oxidative cleavage of the tricyclo[5.2.2.0^{1,5}]undecane **25** to produce the spiro[4.5]decanes **31** & **32** which are intermediates in the synthesis of acorone. A novel one-pot conversion of α -methoxy carboxylic acid to α -methyl carboxylic acid is described.

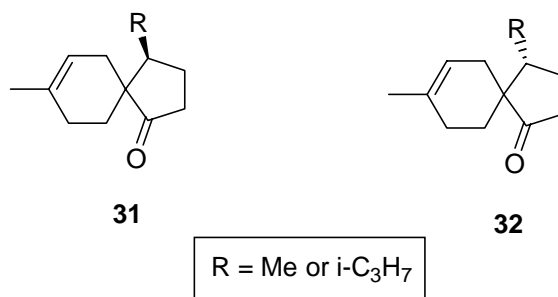
Keywords: Spiro[4.5]decane synthesis; bridgehead substitution; reductive alkylation

Introduction

A large number of sesquiterpenes, possessing the spiro[4.5]decane framework, have been isolated² from natural sources. Among them, the acoranones and the enantiomerically isomeric alaskanones constitute a major group in the spiro[4.5]decanes. These compounds are represented by acorone **1**, isoacorone **2** and acorenone **3**, isolated from the oil of sweet flag,³ *Acorus calamus* L., acorenone B⁴ **4**, α -acoradiene⁵ **5**, β -acoradiene⁶ **6**, γ -acoradiene⁷ (α -alaskene) **7**, and δ -acoradiene (β -alaskene)⁷ **8**. The absolute stereochemistry of acorone³ was assigned on the basis of X-ray study of a derivative and also on the basis of ORD studies. Because of their structural simplicity and commercial importance, these spirocyclic sesquiterpenes attracted⁸ the attention of many synthetic groups and in particular several syntheses⁹ of acorone **1** and its congeners have been reported in the literature.



The main challenges towards the synthesis of this class of natural products are i) stereospecific construction of the spiro quaternary carbon relative to the chiral centers, and ii) arranging the relative stereochemistry of isopropyl and methyl groups in the cyclopentane ring. The methoxycyclohexadienes, readily available from the Birch reduction of anisole derivatives are versatile intermediates in organic synthesis.¹⁰ We have extensively employed them for the synthesis of several bicyclic and tricyclic structures, which culminated in the total synthesis of several natural terpenoids.¹¹ As part of our continued interest on the use of dihydrobenzenes in organic synthesis, we describe herein an efficient strategy for the construction of spiro[4.5]decanes, which led to the

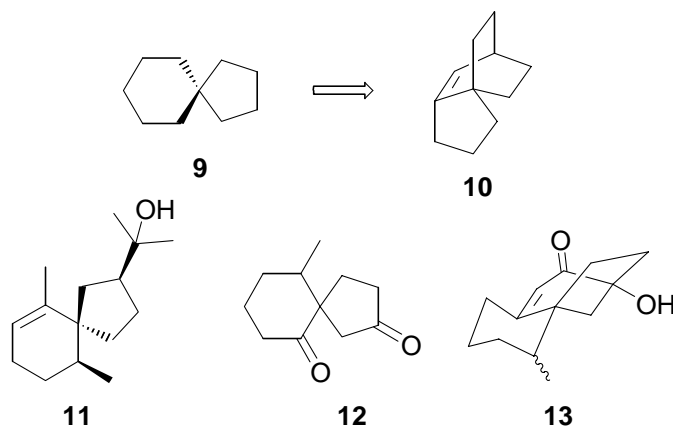


formal synthesis of acorone. The intermediates, 4,8-dimethylspiro[4.5]dec-7-en-1-one **31a** and 4-isopropyl-8-methylspiro[4.5]dec-7-en-1-one **31b** have been identified as the targets for the synthesis of acorone and acoradienes and a detailed account of the preparation of these synthons is presented in this paper. A preliminary account¹² of this work has been reported.

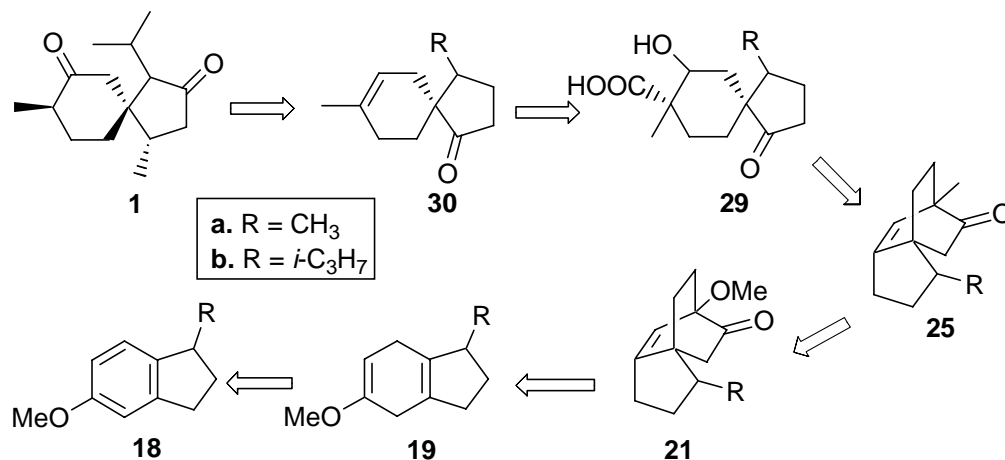
Results and Discussion

We envisioned that the spiro[4.5]decane **9** can be readily generated by the oxidative cleavage of the C₅-C₆ double bond of the tricyclo[5.2.2.0^{1,5}]undecene **10**, a strategy adopted¹³ by us for the total synthesis of (±) hinesol **11** from 9-hydroxytricyclo[7.2.1.0^{1,6}]dodec-6-ene-8-one **13** through the intermediate **12**. The advantage of this oxidative cleavage method will be the stereospecific

generation of the spirocentre, which scores over other synthetic strategies towards spiro compounds. Thus, oxidative cleavage of the tricyclic ketone **25a** should result in the formation of the desired spiro[4.5]decane having a well defined geometry at the spiro center that can be readily converted into acorone **1** and isoacorone **2**.



The retrosynthetic analysis of the spiro[4.5]decanes, exemplified for acorone **1**, as shown in *Scheme 1*, indicated that the ketone **30** can be obtained from the spiro-hydroxyacid **29**, which in

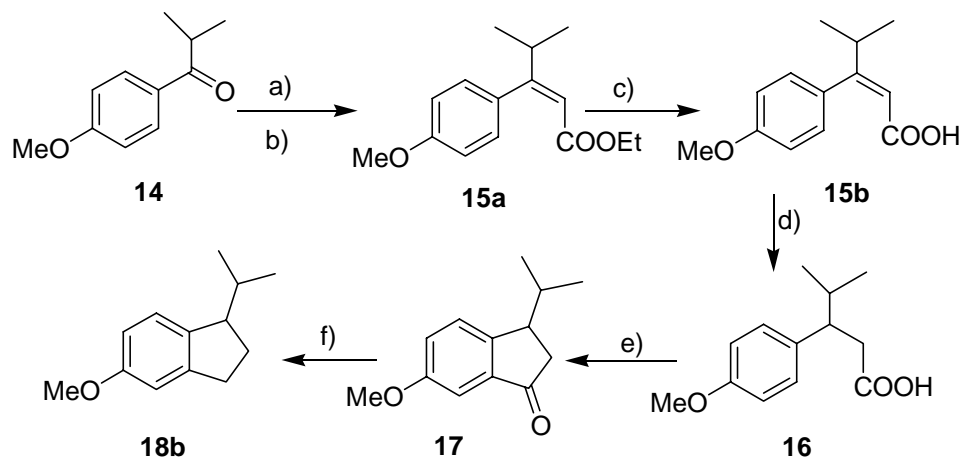


Scheme 1

turn can be prepared from the tricyclic ketone **25** through an oxidative cleavage of the C₅-C₆ double bond. The tricyclic ketone **25** can be obtained from the corresponding ketone **21** by replacing the methoxyl group with the methyl group by the strategy developed^{14,15} in our laboratory. The tricyclic ketones **21** can be prepared from the corresponding indanes **18** by the Birch reduction and Diels-Alder reaction protocol. Thus, the indanes **18** have been identified as the starting materials.

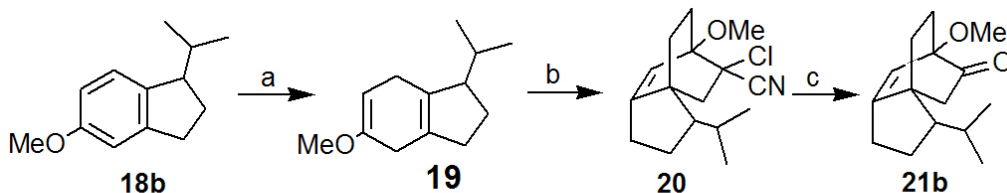
Preparation of the tricyclic ketones (21a) & (21b)

The tricyclic ketone **21a** was prepared from 5-methoxyindane **18a** according to the reported procedure¹⁶ and was obtained in very good yield. The tricyclic ketone **21b** was obtained from 1-isopropyl-6-methoxyindane **18b** which was in turn made from 4-methoxyisobutyrophenone **14**. Thus, reaction of anisole with isobutyroyl chloride in the presence of anhydrous AlCl₃ afforded 4-methoxyisobutyrophenone **14**. Reformatsky reaction of **14** with ethyl bromoacetate followed by dehydration gave the cinnamate ester **15a**, which was hydrolyzed to the acid **15b**, and reduced with sodium in liquid ammonia to the acid **16** in good yield. Cyclization of the acid **16** with SOCl₂/AlCl₃ afforded the indanone **17**, which was subjected to Wolf-Kishner reduction to give 1-isopropyl-5-methoxyindane **18b**.



a) Zn, BrCH₂COOEt, C₆H₆, reflux, 2h; b) p-TSA, C₆H₆, reflux, 5h; c) i) 15% aq. NaOH, MeOH, reflux, 12h; ii) H⁺; d) Na, Liq.NH₃; e) i) SOCl₂, reflux; ii) AlCl₃, CH₂Cl₂, 10°C, 12h; f) NH₂NH₂·H₂O, KOH, diethylene glycol, reflux, 12h.

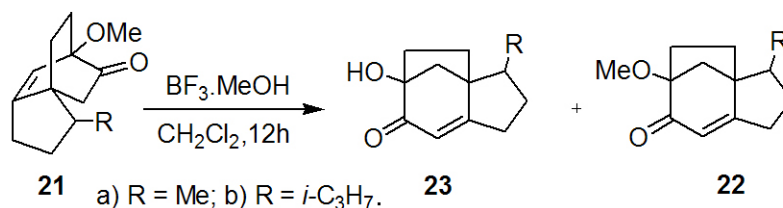
Birch reduction of the indane **18b** with Li and liquid ammonia in the presence of absolute ethanol afforded 1-isopropyl-5-methoxy-4,7-dihydroindane **19** in quantitative yield. The diene **19b** had the absorption bands at 1690 and 1650cm⁻¹ characteristic of an unconjugated diene system. The ¹H NMR spectrum showed a broad singlet at δ 2.70 for the C₄ and C₇ methylene protons and a broad singlet at δ 4.64 for the olefinic proton of the enol ether, and did not show any absorption beyond δ 5 indicating absence of aromatic protons. Cycloaddition of 1-isopropyl-



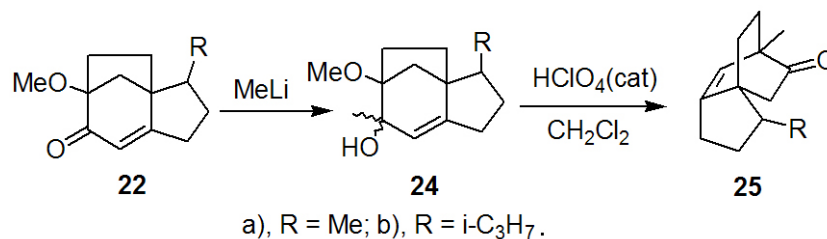
a) Li/NH₃/EtOH; b) CH₂=C(Cl)CN; c) 25% KOH, DMSO, 55 °C, 48h.

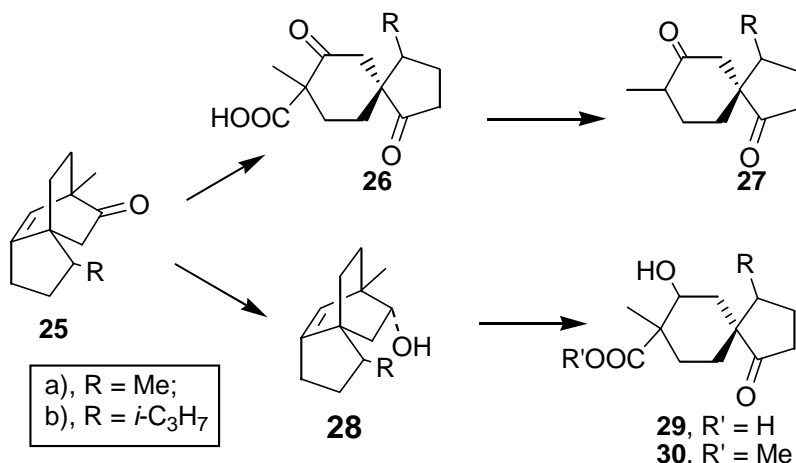
5-methoxy-4,7-dihydroindane **19** with 2-chloroacrylonitrile in refluxing benzene gave after chromatographic purification, the adduct **20**, as a colourless liquid. The structure of the adduct **20** was deduced from its IR and ^1H NMR spectra. Hydrolysis of the adduct **20** with aq. KOH in dimethyl sulphoxide¹⁷ at 55 °C furnished the tricyclic ketone **21b** in 72% yield, whose structure was deduced from its spectral data.

We have described earlier¹⁵ a method for substituting the methoxyl group by a methyl group at the bridgehead position in bi- and tricyclic systems. The same strategy was now adopted for the conversion of the ketones **21a** and **21b** into **25a** and **25b**, respectively. Thus, acid catalysed rearrangement of the ketone **21a** in presence of $\text{BF}_3\cdot\text{MeOH}$ in dry methylene chloride, furnished a 8:1 mixture of methoxy-enone **22a** and the hydroxy-enone **23a** in 94% yield.

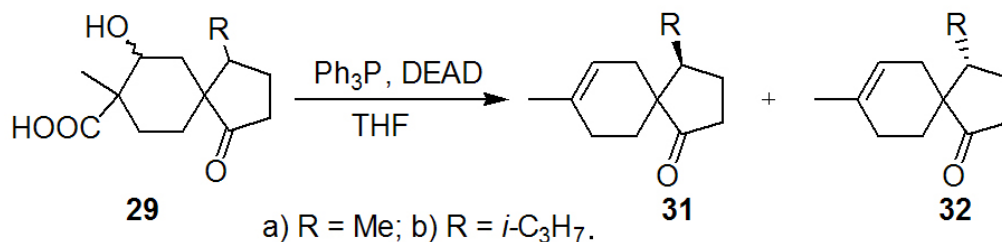


However reaction of **21a** with PTSA gave a 3:1 mixture of **22a** and **23a**. This mixture was easily separated by column chromatography on silica gel and the structures of the enones were deduced from their spectral characteristics. Treatment of the enone **22a** with methyl lithium furnished the allylic alcohol **24a** whose IR spectrum showed the presence of a hydroxyl group. Acid catalyzed rearrangement of the alcohol **24a** in the presence of perchloric acid afforded exclusively the ketone **25a**. At this juncture it was envisaged that the spirodiketone **27** could be obtained from the tricyclic ketone **25** through an oxidative cleavage of the double bond, followed by decarboxylation of the resulting β -ketocarboxylic acid **28**. A chemoselective reduction of the six membered ketone should result in the alcohol, which can be easily converted to (\pm)-acorone. However, ozonolysis of **25** followed by oxidative workup did not provide the diketone. Reduction of **25a** with DIBALH afforded a 1:10 mixture of *exo* and *endo* alcohols **28a**, which was separated by chromatography and characterised. Ozonolysis of this mixture **28a** followed by oxidative work up with hydrogen peroxide afforded the spirohydroxy acid **29a** as a colourless low melting solid, characterized as its methyl ester **30a**. Several attempts¹⁸ to convert the spirohydroxyacid **29a** into the spiroketones **31a** and **32a** through a dehydrative-decarboxylative elimination reaction failed. The attempted methods were essentially heating the acid **29a** with

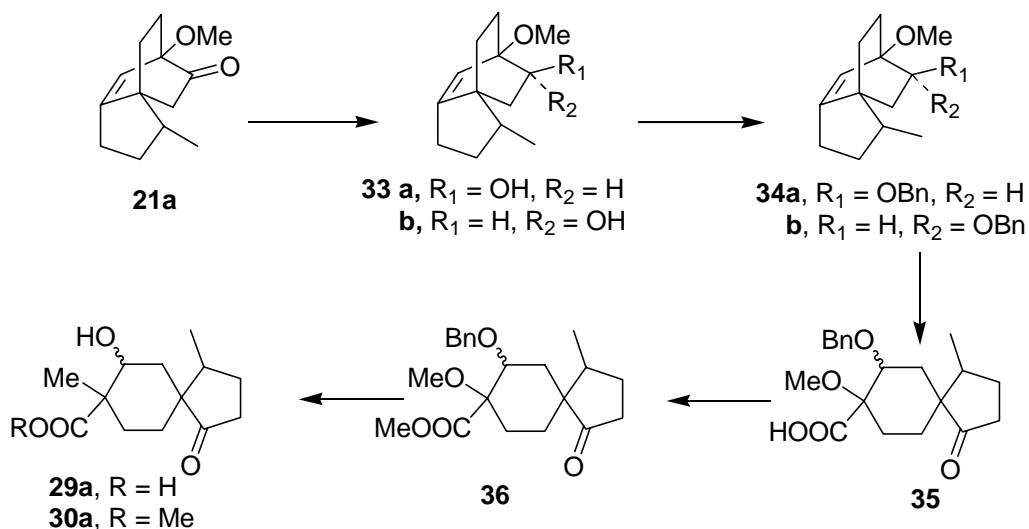




N,N-dimethylformamide dimethyl acetal, to form the β -lactone for initiating the elimination process. In all these cases extensive decomposition of the product was noticed. However, treatment of the spirohydroxy acid **29a** with Ph₃P/DEAD¹⁹ in anhydrous THF afforded the desired ketones **31a** and **32a** as a 1:1 epimeric mixture. The structure of the ketones was deduced from their spectra data and finally by comparison²⁰ with an authentic sample, kindly provided by Professor Marx. The ketone **31a** has been converted²⁰ earlier into acorone and other related compounds, thus completing a formal synthesis of these spiro[4.5]decane sesquiterpenes.



We have previously identified the spiroketones **31b** and **32b** as the precursors for the synthesis of acoradienes, **5**, **6**, **7** and **8**. The spiroketones **31b** and **32b** have been synthesized from the tricyclic ketones **21b** and **25b** by essentially iterating the same reaction sequence described for **31a** and **32a**. Thus, treatment of ketone **21b** with BF₃·MeOH in dry CH₂Cl₂, gave a 8:1 mixture of enones **22b** and **23b**, which was readily separated by chromatography. Reaction of **22b** with MeLi gave the allylic alcohol **24b**, which smoothly rearranged to the tricyclic ketone **25b** upon treatment with a catalytic amount of perchloric acid. Reduction of the ketone **25b** with DIBALH afforded a 10:1 mixture of *endo* and *exo* alcohols **28b**, which was separated by chromatography. This mixture **28b** was subjected to ozonolytic cleavage followed by an oxidative workup with H₂O₂ in aqueous glacial acetic acid to afford the spirohydroxy acid **29b**, which was characterized as its methyl ester **30b**. Reaction of the acid **29b** with PPh₃/DEAD in anhydrous THF afforded a 1:1 epimeric mixture of the spiro-ketones **31b** and **32b** in 53% yield. These spiroketones are useful intermediates for the synthesis of acoradienes.



In an alternative approach²¹ to the synthesis of the spiroketones **31a** and **32a**, the tricyclic ketone **21a** was reduced with sodium borohydride to give a 1:1 mixture of *endo* and *exo* alcohols **33**, which was benzylated with sodium hydride and benzyl bromide to the product **34**. Ozonolysis of **34** followed by oxidative work up with Jones reagent afforded the spiro acid **35** characterized as its methyl ester **36**. Several methods have been investigated to convert the methoxycarboxylic acid **35** into the methylcarboxylic acid **29a**. However, the best method appears to be a new one pot reductive cleavage²² of the methoxyl group of an α -methoxycarboxylic acid with metal-ammonia solutions, followed by quenching the intermediate with methyl iodide to afford the desired product having the tertiary methyl group. Thus, reaction of the acid **35** with sodium in liquid ammonia followed by quenching the enolate with methyl iodide afforded the acid **29a** whose methyl ester **30a** showed identical spectral data with the same compound obtained through the bridgehead substitution strategy.

In conclusion, we have demonstrated an efficient method for the construction of the spiro[4.5]decane from readily available cyclohexadienes, which includes the synthetic exploitation of bridgehead substitution strategy and oxidative cleavage of the tricyclo[5.2.2.0^{1,5}]undecane system. During the course of the synthesis we have developed a novel method for the conversion of α -methoxy carboxylic acid to α -methyl carboxylic acid.

Experimental Section

General Procedures. Mps were recorded on a Mettler FP1 instrument and are uncorrected. IR spectra were recorded as neat liquids or in nujol mull for solids on a Perkin 780 and JASCO FT/IR-410 spectrophotometers. NMR spectra were recorded in CDCl₃ solution using TMS as internal standard, on a JEOL FX 90Q, Bruker ACF-200 and JEOL JNM λ -300 spectrometers. Mass spectra were recorded on a JEOL MS-DX 303 with direct-inlet system, and relative intensities of the ions are given in parenthesis. Microanalysis was carried out using a Carlo Erba

1106 instrument. Analytical and preparative TLC were performed on glass plates coated with Acme silica gel G containing 13% calcium sulphate as the binder. Spot visualization was accomplished by exposure to iodine vapour. Acme's silica gel (60-120) mesh was used for column chromatography. Liquid ammonia was distilled over sodamide before use. All reactions were performed under a blanket of nitrogen or argon filled balloons.

3-(4-Methoxyphenyl)-4-methylpent-2-enoic acid (15b). To a mixture of 4-methoxyisobutyrophenone **14** (31g, 0.1741mol), zinc dust (14.23g, 0.217mol) and dry benzene (200ml) was added slowly a solution of ethyl bromoacetate (19.3ml, 0.1741mol) in dry benzene (60ml) and the mixture was warmed to initiate the reaction. The reaction mixture was heated to reflux for 2h. After cooling, the reaction mixture was poured into ice cold 10% sulphuric acid (300ml), the aqueous layer was extracted with benzene (3 x 100ml) and the combined extract was washed with water, 10% Na₂CO₃ (2 x 50ml), brine, dried and concentrated to furnish a red coloured liquid, which was refluxed with p-TSA (1g) in dry benzene (300ml) for 5h. The benzene extract was washed with water, dried and the solvent was removed to yield **15a** (82%).

The compound **15a** (10g, 0.04mol) in methanol (50ml) was hydrolysed with 15% aqueous NaOH (40.2ml). After heating for 8h at 80°C, methanol was removed at reduced pressure. The residue was diluted with water and extracted with ether (3 x 100ml) to remove the organic impurities. The aqueous layer was acidified with conc. HCl and the precipitate was filtered, washed with ice-cold water and dried to give the acid **15b** (75%, 3 steps), which was recrystallised from hexane-CH₂Cl₂. mp: 106.9°C; IR: ν_{\max} 2930, 1680 and 1600 cm⁻¹; ¹H NMR: δ 1.02 (6H, d, *J* 7.7Hz, 2 x Me), 2.4-2.8 (1H, m, -CH), 3.77 (3H, s, -OMe), 5.75 (1H, s, olefinic), 6.80 (2H, d, *J* 11.5Hz, Ar H), 7.00 (2H, d, *J* 11.5Hz, Ar H); ¹³C NMR: δ 21.0 (2 C), 37.4, 54.9, 113.0 (2 C), 114.5, 128.4 (2 C), 131.6, 159.0, 167.4 and 172.1; Mass: m/z 220 (M⁺, 100%), 203 (58.7), 161 (24), and 115 (10); HRMS: Calcd. for C₁₃H₁₆O₃: M⁺, 220.1096. Found: 220.1092. Anal. Calcd. for C₁₃H₁₆O₃: C, 70.89; H, 7.32. Found: C, 70.95; H, 7.36.

3-(4-Methoxyphenyl)-4-methylpentanoic acid (16). Sodium (2.74g, 0.119mol) was added in small pieces to a solution of the acid **15b** (10.5g, 0.0477mol) in liquid ammonia (200ml) while stirring. The resulting blue coloured solution was stirred vigorously for 1h. Solid NH₄Cl was added slowly to destroy the excess sodium and the ammonia was allowed to evaporate. Water was then cautiously added and the mixture was extracted with ether to remove any neutral products. The aqueous extract was acidified with 5N HCl. The precipitated acid was filtered, washed with ice-cold water, dried and recrystallised from hexane-CH₂Cl₂ to give the acid **16** (10g, 95%), mp 103.1°C; IR: ν_{\max} 2880, 1700 and 1600cm⁻¹; ¹H NMR: δ 0.75 (3H, d, *J* 7.7Hz, Me), 0.85 (3H, d, *J* 7.7Hz, Me), 1.60-2.0 (1H, m, -CH), 2.40-3.00 (3H, m), 3.80 (3H, s, -OMe), 6.80 (2H, d, *J* 10.2Hz, Ar H), 7.08 (2H, d, *J* 10.2Hz, Ar H); ¹³C NMR: δ 19.9, 20.4, 33.0, 38.2, 47.5, 54.5, 113.4, 113.4, 128.9, 128.9, 134.4, 158.0 and 179.2; Mass: m/z 222 (M⁺, 40%), 179 (100), 163 (10) and 137 (77.5); HRMS: Calcd. for C₁₃H₁₈O₃: M⁺ 222.1260, Found: 222.1264; Anal. calcd. for C₁₃H₁₈O₃: C, 70.25; H, 8.16. Found: C, 70.83; H, 8.37.

3-Isopropyl-6-methoxyindan-1-one (17). To an ice cooled solution of the acid chloride [prepared from the acid **16** (9.7g, 0.0436mmol) and thionyl chloride (3.82ml, 0.052mol)] in dry

methylene chloride (300ml), anhydrous AlCl_3 (5.9g, 0.0443mol) was added over 1h with stirring. The resulting orange-red solution was stirred at room temperature for 12h and poured onto ice-cold water. The organic layer was separated and the aqueous layer was extracted with methylene chloride. The combined extracts were washed with water, brine and dried over anh. Na_2SO_4 . Removal of the solvent gave a residue which was purified by column chromatography over silica gel [ethyl acetate-hexane (1:4) as eluent] to afford the ketone **17** (6.5g, 74%) as a yellow liquid, IR: ν_{max} 2940, 1690 and 1600cm^{-1} ; ^1H NMR: δ 0.64 (3H, d, J 7.7Hz, Me), 0.95 (3H, d, J 7.7Hz, Me), 1.90-2.70 (3H, m), 3.15-3.40 (1H, m, benzylic H), 3.60 (3H, s, -OMe), 7.05-7.50 (3H, m, Ar Hs); ^{13}C NMR: δ 15.7, 20.0, 30.5, 38.2, 42.5, 54.3, 103.7, 122.3, 125.7, 137.7, 149.2, 158.5 and 204.6; Mass: m/z 204 (M^+ , 36%), 161 (100), 133 (34), and 90 (10); HRMS calcd. for $\text{C}_{13}\text{H}_{16}\text{O}_2$: M^+ 204.1156; Found: 204.1162.

1-Isopropyl-5-methoxyindane (18b). A mixture of **17** (7.8g, 0.038mol), KOH (4.9g, 0.087mol) and hydrazine hydrate (4.6ml, 0.0956mol) in diethylene glycol (50ml) was heated to reflux for 24h. The mixture was cooled, diluted with water and extracted with ether. Combined organic extracts were washed with water, brine and dried over anh. Na_2SO_4 . Solvent was evaporated and the resultant liquid was distilled under reduced pressure to give **18b** (5.8g, 80%) as a colourless liquid, IR: ν_{max} 2950, 1605 & 1490cm^{-1} ; ^1H NMR: δ 0.76 (3H, d, J 7.7Hz, Me), 0.95 (3H, d, J 7.7Hz, Me), 1.50-2.40 (3H, m), 2.60-3.20 (3H, m, benzylic H), 3.71 (3H, s, -OMe), 6.60-7.30 (3H, m, Ar H); ^{13}C NMR: δ 18.1, 21.3, 27.5, 31.4, 32.2, 50.7, 55.1, 109.9, 112.2, 124.9, 138.4, 146.1 and 159.1; Mass: m/z 190 (M^+ , 18.7%), 147 (100), 115 (10), and 91 (12); HRMS: Calcd. for $\text{C}_{13}\text{H}_{18}\text{O}$: M^+ 190.1354. Found: 190.1350.

1-Isopropyl-5-methoxy-4,7-dihydroindane (19). A solution of 1-isopropyl-5-methoxyindane **18b** (10g, 0.053mol) in dry ether (45ml) was added to distilled dry ammonia (400ml) while stirring. To this mixture was added lithium (1.6g, 0.23mol) in small pieces followed by ethanol (17.3ml, 0.29mol) for 1h. Solid NH_4Cl was added to the reaction mixture until the blue colour was discharged. The residue obtained after the evaporation of the ammonia was cautiously treated with ice-cold water and the mixture was extracted with ether (4 x 100ml). The organic extract was washed with brine and dried over anhydrous Na_2SO_4 . Removal of the solvent gave the diene **19** (9.92g, 97%), IR: ν_{max} 1690 and 1650cm^{-1} ; ^1H NMR: δ 0.72 (3H, d, J 7.71Hz, Me), 0.93 (3H, d, J 7.71Hz, Me), 1.20-2.50 (6H, m), 2.70 (4H, br s, two doubly allylic CH_2), 3.55 (3H, s, -OMe), 4.64 (1H, s, olefinic).

8-Chloro-8-cyano-2-isopropyl-7-methoxytricyclo[5.2.2.0^{1,5}]undec-5-ene (20). A mixture of the diene **19** (9.5g, 0.049mol), 2-chloroacrylonitrile (10ml, 0.12mol) and a catalytic amount of hydroquinone (10mg) in dry benzene (20ml) was refluxed with stirring for 48h under N_2 atmosphere. The reaction mixture was concentrated in vacuum and purified by chromatography over alumina. Elution with 5% ethyl acetate-hexane afforded the adduct **20** (10.29g, 74%) as colourless oil, IR: ν_{max} 2950, 2220, 1600 & 1460cm^{-1} ; ^1H NMR: δ 0.94 (3H, d, J 11.7Hz, Me), 0.95 (3H, d, J 11.7Hz, Me), 1.20-2.60 (12H, m), 3.51 & 3.52 (3H, 2 x s, -OMe), 5.86 & 6.04 (1H, 2 x br s, olefinic); Anal. calcd. for $\text{C}_{16}\text{H}_{22}\text{ClNO}$: C, 68.68; H, 7.93; N, 5.01; Found: C, 68.80; H, 7.81; N, 5.12.

2-Isopropyl-7-methoxytricyclo[5.2.2.0^{1,5}]undec-5-en-8-one (21b). The tricyclic adduct **20** (5g, 17.8 mmol) was dissolved in DMSO (35 ml) and treated with a solution of 25% aqueous KOH (17.5 ml). The resultant dark brown solution was stirred vigorously at 55°C for 48h. The reaction mixture was cooled, diluted with excess ice-cold water and extracted with ether. The combined ether extracts were washed with water, brine and dried (Na₂SO₄). Evaporation of the solvent gave a residue which was purified by chromatography over silica gel [ethyl acetate-hexane (1:19)] to afford the ketone **21b** (3g, 72%), IR: ν_{\max} 2960, 1720 and 1460 cm⁻¹; ¹H: NMR δ 0.96 (3H, d, *J* 6.6Hz, Me), 0.98 (3H, d, *J* 6.6Hz, Me), 1.15-2.40 (9H, m), 1.93 (1H, dd, *J*_I = 18.3Hz, *J*_W = 2.7Hz, H_{9-endo}), 2.44 (1H, d, *J* 18.3Hz, H_{9-exo}), 2.46 (1H, d, *J* 16.2Hz, C_{4-H}), 3.52 (3H, s, -OMe), 5.86 (1H, d, *J* 3Hz, olefinic); ¹³C NMR: δ 22.3, 22.3, 23.9, 26.1, 28.6, 28.6, 30.6, 46.7, 46.9, 52.7, 54.8, 84.6, 115.6, 156.0 and 209.9; Mass: *m/z* 234 (M⁺, 12.5%), 192 (48), 149 (100), and 91 (12); HRMS: Calcd. for C₁₅H₂₂O₂: M⁺, 234.1618. Found: 234.1616.

7-Methoxy-2-methyltricyclo[5.2.2.0^{1,5}]undec-5-en-8-one (21a). This compound was prepared from 5-methoxy-1-methylindane according to the literature procedure.¹⁶

8-Methoxy-2-methyltricyclo[6.2.1.0^{1,5}]undec-5-en-7-one (22a) and 8-hydroxy-2-methyltricyclo[6.2.1.0^{1,5}]undec-5-en-7-one (23a). To a solution of the ketone **21a** (1.533g, 7.44mmol) in CH₂Cl₂ (30 ml) BF₃-MeOH was added. The mixture was stirred at room temperature for 12 h after which it was diluted with water and worked up with CH₂Cl₂ to yield a residue, which was chromatographed over silica gel. Elution with ethyl acetate-hexane (1:7) afforded the enone **23a** (147mg, 10%), IR: ν_{\max} 3440, 1660 and 1620 cm⁻¹; ¹H NMR: δ 0.99 (3H, d, *J* 7Hz, Me), 1.10-2.30 (9H, m), 2.44-2.76 (2H, m, allylic CH₂) and 5.90 (1H, m, olefinic); Further elution with the same solvent system gave the enone **22a** (1.22g, 80%), IR: ν_{\max} 1665, 1625 and 1450 cm⁻¹; ¹H NMR δ 1.01 (3H, d, *J* 7Hz, Me), 1.16-2.30 (9H, m), 2.42-2.72 (2H, m, allylic CH₂), 3.40 (3H, s, OMe), and 5.81 (1H, m, olefinic); ¹³C NMR: δ 12.6, 16.0, 24.6, 29.1, 29.6, 30.3, 30.7, 31.6, 34.1, 38.7, 39.8, 42.6, 44.5, 53.2, 56.3, 56.8, 87.6, 88.7, 119.2, 179.3 and 199.6; Mass: *m/z* 206 (M⁺, 54%), 177 (100), 164 (45) and 135 (60); HRMS: Calcd. for C₁₃H₁₈O₂: M⁺ 206.1307. Found: 206.1309.

2,7-Dimethyl-8-methoxytricyclo[6.2.1.0^{1,5}]undec-5-en-7-ol (24a). To a solution of the enone **22a** (127mg, 0.617mmol) in dry ether at 0°C was added MeLi (1M solution in ether; 1ml, 1mmol). The mixture was stirred at 0°C for 1h and quenched by the addition of saturated aqueous NH₄Cl and worked up with ether to afford the alcohol **24a** (110mg, 91%), which was directly used without purification. IR: ν_{\max} 3420 and 1445 cm⁻¹; ¹H NMR: δ 0.95 (3H, d, *J* 7.0Hz, Me) 1.20-2.40 (11H, m), 1.37 (3H, s, Me), 3.36 (3H, s, OMe) and 5.06 (1H, m, olefinic); Mass: *m/z* 222 (M⁺, 2.5%), 207 (7), 147 (100), 135 (42) and 43 (60); HRMS: Calcd. for C₁₄H₂₂O₂: M⁺ 222.1620. Found: 222.1605.

2,7-Dimethyltricyclo[5.2.2.0^{1,5}]undec-5-en-8-one (25a). A solution of the allylic alcohol **24a** (1.26g, 5.69mmol) in CH₂Cl₂ (50ml) was stirred with HClO₄ (70%, 0.2 ml) at room temperature. After 30min, the reaction mixture was diluted with CH₂Cl₂, washed with water, saturated aqueous NaHCO₃ and brine, dried over Na₂SO₄ and evaporated. Chromatography of the crude product over silica gel and elution with ethyl acetate - hexane (1:30) afforded the ketone **25a**

(894 mg, 83%) as a colourless liquid. IR: ν_{\max} 1710 and 1440 cm^{-1} ; ^1H NMR: δ 1.01 (3H, d, J 7.2Hz, Me), 1.20 and 1.23 (3H, s, Me), 1.24-2.48 (11H, m), 5.47 (1H, m, olefinic); ^{13}C NMR: δ 13.7, 14.2, 17.6, 25.4, 28.7, 29.0, 30.1, 31.9, 32.2, 34.0, 34.4, 40.0, 40.8, 41.6, 45.6, 48.3, 49.1, 120.8, 121.3, 156.0, 156.7, 213.6 and 214.0; Mass: m/z 190 (M^+ , 4%), 148 (90), 133 (100), 105 (18), and 91 (16); HRMS: Calcd. for $\text{C}_{13}\text{H}_{18}\text{O}$: M^+ 190.1339. Found: 190.1337.

The 2,4-dinitrophenylhydrazone derivative crystallized from ethanol, mp 145.6°C; Anal. calcd. for $\text{C}_{19}\text{H}_{22}\text{N}_4\text{O}_4$: C, 61.6, H, 6.0; N, 15.1. Found: C, 61.55, H, 6.1; N, 15.1.

(endo) 2,7-Dimethyltricyclo[5.2.2.0^{1,5}]undec-5-en-8-ol (28a). A solution of the ketone **25a** (1g, 5.26mmol) in anhydrous THF (15 ml) was cooled to -78°C under argon. A 1.0M solution of DIBALH (5.789 ml, 5.78mmol) in toluene was added drop wise into it over a period of 15 min, and slowly warmed to room temperature over 15min. After being attained the room temperature, the reaction mixture was quenched with methanol (3 ml). The resulting solution was treated with a saturated solution of sodium potassium tartrate (50 ml). The clear solution thus obtained was worked up to give a mixture, which was chromatographed to afford the alcohol **28a** (90% overall yield, *endo* and *exo* ratio, 8:1); IR: ν_{\max} 3430 and 1640 cm^{-1} ; ^1H NMR δ 0.98 (3H, d, J 6.4 Hz, Me), 1.1 & 1.16 (3H, 2 x s, Me), 1.20-2.48 (11H, m), 3.40 (1H, br d, J 11.5Hz, $-\text{HC}-\text{OH}$), 5.44 (1H, br s, olefinic); Mass: m/z 192 (M^+ , 5%), 175 (81), 148 (69), 133 (100), 105 (16.5) and 91 (16); HRMS: Calcd. for $\text{C}_{13}\text{H}_{20}\text{O}$: M^+ 192.1489. Found: 192.1464; Anal. calcd. for $\text{C}_{13}\text{H}_{20}\text{O}$: C, 81.20; H, 10.48. Found: C, 81.13; H, 10.30.

4,8-Dimethyl-7-hydroxy-1-oxospiro[4.5]decan-8-carboxylic acid (29a) and its methyl ester (30a). Ozone was bubbled through a pre-cooled (-78°C) solution of the mixture of the olefinic alcohol **28a** (192 mg, 1mmol) in dry ethyl acetate (10ml) until the solution turned blue. Excess ozone was removed by bubbling nitrogen through the reaction mixture. The ozonide was stirred with glacial acetic acid (10ml), H_2O_2 (2 ml), and water (5 ml), for 12h, after which the solution was concentrated under reduced pressure and the residue was diluted with ethyl acetate (50ml), washed with water, brine and dried over Na_2SO_4 . Removal of the solvent produced the acid **29a** (200mg, 83%). IR: ν_{\max} 3430-3300, 1735, 1700 cm^{-1} ; Mass: m/z 240 (M^+ , 2%), 223 (16), 193 (15), 177 (14), 149 (28), 124 (46), 11 (52), 55 (68) and 43 (100);

The above acid **29a** (50mg) was esterified with ethereal diazomethane affording the methyl ester **30a** as a viscous liquid. IR: ν_{\max} 3430 and 1735 cm^{-1} ; ^1H NMR: δ 1.04 and 1.08 (3H, 2 x d, J 6Hz and 6.3Hz, Me), 1.16 and 1.19 (3H, 2 x s, Me), 1.20-2.50 (11H, m), 3.32 (1H, m, $-\text{CHOH}$) and 3.77 and 3.80 (3H, 2 x s, $-\text{COOMe}$); Anal Calcd. $\text{C}_{14}\text{H}_{22}\text{O}_4$: C, 66.12; H, 8.72. Found: C, 66.58; H, 8.83.

4,8-Dimethylspiro[4.5]dec-7-en-1-one (31a) and (32a). The stirred solution of the β -hydroxyacid **29a** (500mg, 2.08mmol) and triphenylphosphine (545mg, 2.08mmol) in anhydrous THF (3ml) under N_2 atmosphere was treated drop-wise with a solution of DEAD (0.26 ml, 2.08 mmol) in anhydrous THF (2ml). The slight warming of the mixture and the instantaneous decolourisation of the DEAD indicated the rapid progress of the reaction. The reaction mixture was stirred for 0.5h and extracted with ether (3x50 ml) to yield a residue, which was chromatographed over silica gel. Elution with ethyl acetate-hexane (1:9) gave the mixture of ketones **31a**

and **32a** (200mg, 55%) as an inseparable mixture (1:1). IR: ν_{\max} 2930, 1735 cm^{-1} ; $^1\text{H NMR}$: δ 0.90 & 0.95 (3H, 2 x d, J 6.4Hz, epimeric Me), 1.60 (3H, s, Me), 1.60-2.40 (11H, m), and 5.21 (1H, br s, olefinic); Mass: m/z 178 (M^+ , 21%), 160 (12), 149 (26), 11 (27), 83 (100), and 47 (18); Anal. Calcd. $\text{C}_{12}\text{H}_{18}\text{O}$: C, 80.85; H, 10.18. Found: C, 80.50; H, 10.01. This mixture was identical in all respects with the sample²⁰ kindly provided by Prof. J. N. Marx.

2-Isopropyl-8-methoxytricyclo[6.2.1.0^{1,5}]undec-5-en-7-one (22b) and 8-Hydroxy-2-isopropyltricyclo[6.2.1.0^{1,5}]undec-5-en-7-one (23b). To a solution of the ketone **21b** (5g, 21mmol) in CH_2Cl_2 (100ml), $\text{BF}_3\cdot\text{MeOH}$ (20% 11.7ml, 24mmol) was added. The mixture was stirred at room temperature for 12h after which it was diluted with water and worked up with CH_2Cl_2 to yield a residue, which was chromatographed over silica gel. Elution with ethyl acetate-hexane (1:7) afforded the enone **23b** (500mg, 10%), IR: ν_{\max} 3440, 1660 & 1610 cm^{-1} ; $^1\text{H NMR}$: δ 0.90 (3H, d, J 7.7Hz, Me), 1.10 (3H, d, J 7.7Hz, Me) 1.20 –2.80 (12H, m), 4.00 (1H, br s, -OH), 5.83 (1H, s, olefinic); Further elution with the same solvent system gave the enone **22b** (4g, 81.4%), IR: ν_{\max} 2920, 1660, 1620 & 1450 cm^{-1} ; $^1\text{H NMR}$: δ 0.89 (3H, d, J 6.4Hz, Me), 1.00 (3H, d, J 6.4Hz, Me), 1.20-2.30 (10 H, m), 2.35-2.70 (2H, m, allylic), 3.39 (3H, s, -OMe), 5.70 (1H, s, olefinic); $^{13}\text{C NMR}$: δ 21.6, 22.1, 24.8, 28.4, 28.7, 28.7, 29.1, 31.3, 49.9, 50.8, 56.0, 80.7, 116.1, 183.1 and 201.20; Mass m/z 234 (M^+ , 6%), 220 (16), 191 (33), 177 (63), 135 (100), 121 (17) and 91 (20); HRMS: Calcd. for $\text{C}_{15}\text{H}_{22}\text{O}_2$: M^+ 234.1604. Found: 234.1602.

2-Isopropyl-8-methoxy-7-methyltricyclo[6.2.1.0^{1,5}]undec-5-en-7-ol (24b). To a solution of the enone **22b** (1g, 4.2mmol) in dry ether at 0°C was added MeLi (1M solution in ether; 5.1ml, 5.1mmol). The mixture was stirred at 0°C for 1h after which excess MeLi was quenched by the addition of saturated aqueous NH_4Cl solution. The mixture was worked up with ether to afford the alcohol **24b** (0.979g, 92%), IR: ν_{\max} 3430 and 1445 cm^{-1} .

2-Isopropyl-7-methyltricyclo[5.2.2.0^{1,5}]undec-5-en-8-one (25b). A solution of the allylic alcohol **24b** (1.26g, 5.04mmol) in CH_2Cl_2 (50ml) was stirred with HClO_4 (70%, 0.2ml) at room temperature. After 30min, the reaction mixture was diluted with CH_2Cl_2 , washed with water, saturated aqueous NaHCO_3 , brine, dried over Na_2SO_4 and the solvent was evaporated. Chromatography of the crude product over silica gel [ethyl acetate-hexane (1:30)] as eluent gave the ketone **25b** (0.950 mg, 81%) which crystallised from hexane- CH_2Cl_2 , mp 71.5°C; IR: ν_{\max} 2950, 1710 and 1450 cm^{-1} ; $^1\text{H NMR}$: δ 0.97 (3H, d, J 6.6Hz, Me), 0.98 (3H, d, J 6.6Hz, Me), 1.19 (3H, s, Me), 1.20-2.30 (9H, m), 1.92 (1H, dd, J_I 18.2 Hz, J_W 2.7 Hz, $\text{H}_9\text{-endo}$), 2.37 (1H, d, J 18.2Hz, $\text{H}_9\text{-exo}$), 2.41 (1H, dd, J 7.2 and 15.9Hz, C_4H), 5.52 (1H, s, olefinic); $^{13}\text{C NMR}$: δ 17.7, 22.9, 22.9, 25.1, 29.0, 29.0 30.1, 31.1, 47.6, 48.3, 49.0, 55.5, 120.1, 156.9 and 214.1; Mass: m/z 218 (M^+ , 4%), 176 (44), 133 (100), 105 (12), and 91 (12); HRMS: calcd. for $\text{C}_{15}\text{H}_{22}\text{O}$ M^+ 218.1683. Found: 218.1671.

2-Isopropyl-7-methyltricyclo[5.2.2.0^{1,5}]undec-5-en-8-ol (28b). A solution of the ketone **25b** (1g, 4.58mmol) in anhydrous THF (15 ml) was cooled to -78°C under argon. A 1.0M solution of DIBALH (5.0ml, 5.0mmol) in toluene was added drop-wise over a period of 15 min, and slowly warmed to room temperature over 15min. The reaction mixture was then quenched with methanol (3ml). The resulting solution was treated with a saturated solution of sodium potassium

tartrate (50 ml). The clear solution thus obtained was worked up to give a mixture, which was chromatographed over silica gel to afford the alcohol **28b** (90% yield, *endo* & *exo* ratio, 10:1). IR: ν_{\max} 3360 and 1460 cm^{-1} ; $^1\text{H NMR}$: δ 0.91 (3H, d, J 9Hz, Me), 0.97 (3H, d, J 6.3Hz, Me), 1.13 & 1.18 (3H, 2 x s, bridgehead Me), 1.20-2.20 (10H, m), 2.25-2.40 (2H, m, allylic CH_2), 3.47 (1H, br d, J 9.9Hz, CH-OH), 5.41 and 5.45 (1H, 2 x s, olefinic); Mass: m/z 220 (M^+ , 12%), 203 (16), 177 (100), 149 (15), 133 (100), 105 (24) and 91 (45); Anal. calcd. for $\text{C}_{15}\text{H}_{24}\text{O}$: C, 81.76; H, 10.97. Found: C, 81.98; H, 10.12.

4-Isopropyl-7-hydroxy-8-methyl-1-oxo-spiro[4.5]decan-8-carboxylic acid (29b) and its methyl ester (30b). Ozone was bubbled through a pre-cooled (-78°C) solution of the mixture of the olefinic alcohols **28b** (220 mg, 1mmol) in dry ethyl acetate (10ml) until the solution turned blue. Excess ozone was removed by bubbling nitrogen through the reaction mixture. The ozonide was then stirred with glacial acetic acid (10ml), H_2O_2 (2 ml), and water (5 ml), for 12h, after which the solution was concentrated under reduced pressure and the residue was diluted with ethyl acetate (50ml), washed with water, brine and dried over Na_2SO_4 . Removal of the solvent afforded the acid **29b** (200mg, 74%) as a white gummy solid, which resisted crystallization. IR: ν_{\max} 3300, 2930, 1730 and 1460 cm^{-1} ; Mass: m/z 268 (M^+ , 2%), 251 (3), 225 (30), 207 (23), 179 (18), 137 (35) and 43 (100); HRMS: Calcd. for $\text{C}_{15}\text{H}_{24}\text{O}_4\text{-OH}$ ($\text{C}_{15}\text{H}_{23}\text{O}_3$): M^+ 251.1663. Found: 251.1679.

The above acid **29b** (50mg, 18mmol) was esterified with ethereal diazomethane (10mg), which afforded the methyl ester **30b** as a viscous liquid, IR: ν_{\max} 3340 & 1730 cm^{-1} ; $^1\text{H NMR}$: δ 0.80-1.10 (6H, m, 2 x Me), 1.15 and 1.20 (3H, 2 x s, Me), 1.20-2.50 (12H, m), 3.40 (1H, m, -CHOH), 3.60 and 3.63 (3H, 2 x s, -OMe); Anal. calcd. for $\text{C}_{16}\text{H}_{26}\text{O}_4$: C, 68.05; H, 9.28; Found: C, 68.24; H, 9.56.

4-Isopropyl-8-methylspiro[4.5]dec-7-en-1-one (31b) and (32b). To a stirred solution of the β -hydroxyacid **29b** (500mg, 1.86mmol) and triphenylphosphine (487mg, 1.86mmol) in anhydrous THF (3ml) under nitrogen was added drop-wise a solution of DEAD (0.26 ml, 1.86mmol) in anhydrous THF (2ml). The slight warming of the mixture and decolourisation indicated that the reaction commenced. The reaction mixture was stirred for 0.5h, extracted with ether (3 x 50 ml) and worked up to yield a residue, which was chromatographed over silica gel. Elution with ethyl acetate-hexane (1:9) gave the ketone (204mg, 53%) as an inseparable mixture of **31b** and **32b**, IR: ν_{\max} 2930, 1735 and 1650 cm^{-1} ; $^1\text{H NMR}$: δ 0.83 and 0.98 (6H, 2 x d, J 7.7Hz, 2 x Me), 1.70 (3H, d, J 3.85, Me), 1.70-2.40 (12H, m), 5.31(1H, s, olefinic); Anal. calcd. for $\text{C}_{14}\text{H}_{22}\text{O}$: C, 81.49; H, 10.74. Found: C, 81.48; H, 10.72.

endo- and exo 7-Methoxy-2-methyltricyclo[5.2.2.0^{1,5}]undec-5-en-8-ol (33). To the ketone **21a** (3.2g) in methanol (30ml), sodiumborohydride (1.5g) was added in portions while stirring at room temperature. After 2 h, methanol was distilled and the residue was dissolved in water and extracted with ether (4 x 75 ml). The organic extract was worked up to afford a viscous liquid (3.17g). TLC indicated that this liquid is a mixture of two compounds, which was separated by chromatography on silica gel. Elution with hexane-ethyl acetate (9:1) gave the pure sample of *exo*-alcohol **33a** (1g, 32%); IR: ν_{\max} 3400, 3040, 2950, 1660 cm^{-1} ; $^1\text{H NMR}$: δ 0.92 (3H, d, J 7

Hz, CH₃), 1.0-2.45 (11H, complex), 3.3 (3H, s, OMe), 3.73 (1H, bm, -CHOH), 5.68 (1H, bs, olefinic); Mass: m/z 208 (65), 162 (100); Anal. Calcd. for C₁₃H₂₀O₂: C, 74.96; H, 9.68; Found: C, 74.89; H, 9.61. Further elution with the same solvent gave a mixture of *exo*- and *endo*-alcohols followed by pure *endo* alcohol **33b** (1.8g, 56%); ν_{\max} 3440, 3040, 2950, 1640 cm⁻¹; ¹H NMR: δ 0.9 (3H, d, *J* 7Hz, CH₃), 1.0-2.45 (11H, complex), 3.28 (3H, s, OMe), 3.8 (1H, bm, CHOH), 5.79 (1H, bs, olefinic); Mass: m/z 208 (M⁺, 60), 162 (100); Anal. Calcd. for C₁₃H₂₀O₂: C, 74.96, H, 9.68; Found: C, 74.92, H, 9.81.

Benylation of (33a) and (33b). The alcohol mixture **33a** and **33b** (2g) was stirred with dry sodium hydride (600 mg), obtained by washing the 50% dispersion with hexane. The resulting alkoxide and benzyl bromide (1.75g) in THF was refluxed for 3h and reaction mixture worked up to afford a mixture of benzylation compounds **34a** and **34b** (2.8g, 93%); IR: ν_{\max} 3020, 2950, 1655, 1595, 1500, 1100 cm⁻¹; ¹H NMR: δ 0.93 (3H, d, *J* 7Hz, CH₃), 1.0-2.5 (11H, complex), 3.3 (3H, s, OMe), 3.67 (1H, m, -CH-O), 4.52 (2H, bm, OCH₂Ph), 5.8 (1H, bm, olefinic H), 7.2 (5H, Ar H); Anal. Calcd. for C₂₀H₂₆O₂: C, 80.5; H, 8.78. Found: C, 80.45; H, 8.62.

7-Benzyloxy-8-methoxy-4-methyl-1-oxo-spiro[4.5]decane-8-carboxylic acid (36). Ozone was bubbled through the cooled mixture of **33a** and **33b** (3g) in CH₂Cl₂ (30ml) at -65°C for 2 h. Nitrogen was flushed through the reaction mixture to replace the excess ozone and the solvent was removed at low temperature. The crude ozonide in acetone (30 ml) was cooled to 0°C and treated with Jones reagent. After 5 minutes, the reaction mixture was worked up by removing the acetone, the resulting gummy material was dissolved in ether and extracted with 5% sodium hydroxide solution. The aqueous layer was acidified with conc. HCl and the mixture was extracted with chloroform. The organic layer was washed with water, brine and dried over anhydrous sodium sulphate. Evaporation of the solvent afforded a gummy acid **35** (2.82 g), which resisted crystallization. A small portion (300 mg) of this acid was treated with ethereal diazomethane. The crude ester was purified by chromatography over silica gel. Elution with hexane-ethyl acetate (9:1) afforded the keto-ester **36** as an epimeric mixture (240 mg); bp 139-141°/0.1mm; IR: ν_{\max} 1735, 1595, 1500 cm⁻¹; ¹H NMR: δ 0.92 and 0.93 (3H, 2 x d, *J* 6.5 and 6.9 Hz, CH₃), 1.15-2.8 (11H, complex), 3.21 and 3.27 (3H, 2 x s, OMe), 3.66 and 3.67 (3H, 2 x s, OMe), 4.5 (2H, m, -OCH₂Ph), 7.28 (5H, m, Ar H); Anal. Calcd. for C₂₁H₂₈O₅: C, 69.98; H, 7.83. Found: C, 69.74; H, 8.17.

4,8-Dimethyl-7-hydroxy-1-oxospiro[4.5]decane-8-carboxylic acid (29a). The keto-acid **35** (2.5 g), in dry THF (20 ml) was injected to a mixture of sodium (1.2 g) in liquid ammonia (100 ml) while stirring. After 15 minutes of vigorous stirring, methyl iodide (5ml) was injected all at once and stirred the solution for additional 30 min. Ammonia was allowed to evaporate and the reaction was quenched with saturated NH₄Cl solution. The mixture was diluted with water and extracted with ether (2 x 50 ml) to remove neutral impurities. This aqueous extract was acidified with HCl and the mixture was extracted with ethyl acetate. The organic extract was washed with water and dried over anhydrous Evaporation of the solvent afforded a gummy material (1.82g, 97%). A small portion of this gummy acid **29a** (300mg) in dry ether (5ml) was treated with ethereal solution of diazomethane and allowed to stand overnight. Excess of the diazomethane

was destroyed by adding a drop of glacial acetic acid and the ethereal solution was washed with water, brine and dried over anhydrous Na_2SO_4 . Evaporation of the solvent gave a viscous liquid, which was chromatographed on silica gel. Elution with benzene-ethyl acetate (85:15) gave the hydroxy-ester **30a** (234 mg). IR: ν_{max} 3450, 1735, 1220 cm^{-1} ; $^1\text{H NMR}$: δ 1.04 and 1.08 (3H, 2 x d, J 6 Hz and 6.3 Hz, CH_3), 1.16 and 1.19 (3H, 2 x s, CH_3), 1.2-2.5 (11H, complex), 3.32 (1H, m, $-\text{CHOH}$), 3.77 and 3.8 (3H, 2 x s, $-\text{COOCH}_3$); Anal. Calcd. for $\text{C}_{14}\text{H}_{22}\text{O}_4$: C, 66.12; H, 8.72. Found: C, 66.58; H, 8.23.

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