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

P. John Biju, K. Pramod and G. S. R. Subba Rao*

Department of Organic Chemistry, Indian Institute of Science, Bangalore 560 012, India.
E-mail: gsrs@orgchem.iisc.ernet.in

Dedicated to Professor Sukh Dev on his 80th birthday
(received 03 Jan 03; accepted 24 Feb 03; published on the web 27 Feb 03)

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[5.2.2.01,5]undecane²⁵ 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 acoranes and the enantiomerically isomeric alaskanes 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 ⁴ ⁴, α-acoradiene⁵ ⁵, β-acoradiene⁶ ⁶, γ-acoradiene⁷ (α-alaskene) ⁷, and δ-acoradiene (β-alaskene)⁸ 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 methoxy cyclohexadienes, readily available from the Birch reduction of anisole derivatives are versatile intermediates in organic synthesis.\textsuperscript{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.\textsuperscript{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 31\textsubscript{a} and 4-isopropyl-8-methylspiro[4.5]dec-7-en-1-one 31\textsubscript{b} 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 account\textsuperscript{12} 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 C\textsubscript{5}-C\textsubscript{6} double bond of the tricyclo[5.2.2.0\textsuperscript{1,5}]undecene 10, a strategy adopted\textsuperscript{13} by us for the total synthesis of (±) hinesol 11 from 9-hydroxytricyclo[7.2.1.0\textsuperscript{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.

\[ \text{OH} \]
\[ \text{OH} \]
\[ \text{O} \]
\[ \text{O} \]
\[ \text{9} \]
\[ \text{10} \]
\[ \text{11} \]
\[ \text{12} \]
\[ \text{13} \]

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 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\textsuperscript{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.

Scheme 1
Preparation of the tricyclic ketones (21a) & (21b)
The tricyclic ketone 21a was prepared from 5-methoxyindane 18a according to the reported procedure\(^\text{16}\) 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 AlCl\(_3\) 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 SOCl\(_2/\)AlCl\(_3\) afforded the indanone 17, which was subjected to Wolf-Kishner reduction to give 1-isopropyl-5-methoxyindane 18b.

\[
\begin{align*}
14 & \xrightarrow{a)} \text{MeO} & \xrightarrow{b)} \text{MeO} & \xrightarrow{c)} \text{MeO} & \xrightarrow{d)} \text{MeO} \\
15a & \xrightarrow{15b} & \text{COOH} & \text{COOH} & \\
15 & & \text{COOH} & \text{COOH} & \\
17 & \xrightarrow{e)} \text{MeO} & \xrightarrow{f)} \text{MeO} & \\
16 & & \text{MeO} & \\
18b & & & \\
\end{align*}
\]

- a) Zn, BrCH\(_2\)COOEt, C\(_6\)H\(_6\), reflux, 2h; b) p-TSA, C\(_6\)H\(_6\), reflux, 5h; c) i) 15% aq. NaOH, MeOH, reflux, 12h; ii) H\(^+\); d) Na, Liq.NH\(_3\); e) i) SOCl\(_2\), reflux; ii) AlCl\(_3\), CH\(_2\)Cl\(_2\), 10\(^\circ\)C, 12h; f) NH\(_2\)NH\(_2\).H\(_2\)O, 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 1650 cm\(^{-1}\) characteristic of an unconjugated diene system. The \(^1\)H NMR spectrum showed a broad singlet at \(\delta\) 2.70 for the C\(_4\) and C\(_7\) methylene protons and a broad singlet at \(\delta\) 4.64 for the olefinic proton of the enol ether, and did not show any absorption beyond \(\delta\) 5 indicating absence of aromatic protons. Cycloaddition of 1-isopropyl-
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 sulphoxide\textsuperscript{17} at 55 °C furnished the tricyclic ketone 21b in 72% yield, whose structure was deduced from its spectral data.

We have described earlier\textsuperscript{15} 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 BF\textsubscript{3}-MeOH in dry methylene chloride, furnished a 8:1 mixture of methoxy-enone 22a and the hydroxy-enone 23a in 94% yield.

![Chemical structure](image)

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 methyllithium 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 (±)-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 \textit{exo} and \textit{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 attempts\textsuperscript{18} 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

![Chemical structure](image)
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 approach\textsuperscript{21} 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 \textit{endo} and \textit{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 cleavage\textsuperscript{22} of the methoxyl group of an $\alpha$-methoxy-carboxylic 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\texttextsuperscript{1,5}]undecane system. During the course of the synthesis we have developed a novel method for the conversion of $\alpha$-methoxy carboxylic acid to $\alpha$-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 spectropho-meters. NMR spectra were recorded in CDCl\textsubscript{3} solution using TMS as internal standard, on a JEOL FX 90Q, Brucker ACF-200 and JEOL JNM $\lambda$-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% Na$_2$CO$_3$ (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-CH$_2$Cl$_2$. mp: 106.9°C; IR: $\nu_{max}$ 2930, 1680 and 1600 cm$^{-1}$; $^1$H NMR: $\delta$ 1.02 (6H, d, $J_\text{7.7Hz}$, 2 x Me), 2.4-2.8 (1H, m, -C$_2$H), 3.77 (3H, s, -OMe), 5.75 (1H, s, olefinic), 6.80 (2H, d, $J_\text{11.5Hz}$, Ar H), 7.00 (2H, d, $J_\text{11.5Hz}$, Ar H); $^{13}$C NMR: $\delta$ 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 C$_{13}$H$_{16}$O$_3$: M$^+$, 220.1096. Found: 220.1092.

Anal. Calcd. for C$_{13}$H$_{16}$O$_3$: C, 70.89; H, 7.32. Found: C, 70.95; H, 7.36.

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 AlCl₃ (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. Na₂SO₄. 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: νmax 2940, 1690 and 1600 cm⁻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); ¹³C 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 C₁₃H₁₆O₂: 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. Na₂SO₄. Solvent was evaporated and the resultant liquid was distilled under reduced pressure to give 18b (5.8g, 80%) as a colourless liquid, IR: νmax 2950, 1605 & 1490 cm⁻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); ¹³C 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 C₁₃H₁₈O: 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 NH₄Cl 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 Na₂SO₄. Removal of the solvent gave the diene 19 (9.92g, 97%), IR: νmax 2950, 1600 & 1460 cm⁻¹; ¹H NMR: δ 0.72 (3H, d, J 11.7Hz, Me), 0.93 (3H, d, J 7.7Hz, Me), 1.20-2.50 (6H, m), 2.70 (4H, br s, two doubly allylic CH₂), 3.55 (3H, s, -OMe), 4.64 (1H, s, olefinic).

8-Chloro-8-cyano-2-isopropyl-7-methoxytricyclo[5.2.2.0₁₅]undec-5-ene (20). A mixture of the diene 19 (9.5g, 0.049mol), 2-choroacrylonitrile (10ml, 0.12mol) and a catalytic amount of hydroquinone (10mg) in dry benzene (20ml) was refluxed with stirring for 48h under N₂ 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: νmax 2950, 2220, 1600 & 1460 cm⁻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 C₁₆H₂₂ClNO: 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: v_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_1 = 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 C_{15}H_{22}O_2: 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.

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 CH_2Cl_2 (30 ml) BF_3-MeOH was added. The mixture was stirred at room temperature for 12 h after which it was diluted with water and worked up with CH_2Cl_2 to yield a residue, which was chromographed over silica gel. Elution with ethyl acetate-hexane (1:7) afforded the enone 23a (147mg, 10%), IR: v_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 CH_2) and 5.90 (1H, m, olefinic); Further elution with the same solvent system gave the enone 22a (1.22g, 80%), IR: v_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 CH_2), 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 C_{13}H_{18}O_2: 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 NH_4Cl and worked up with ether to afford the alcohol 24a (110mg, 91%), which was directly used without purification. IR: v_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 C_{14}H_{22}O_2: 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 CH_2Cl_2 (50ml) was stirred with HClO_4 (70%, 0.2 ml) at room temperature. After 30min, the reaction mixture was diluted with CH_2Cl_2, washed with water, saturated aqueous NaHCO_3 and brine, dried over Na_2SO_4 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: \( \nu_{\text{max}} \) 1710 and 1440 cm\(^{-1}\); \(^1\)H NMR: \( \delta \) 1.01 (3H, d, \( J \) 7.2 Hz, Me), 1.20 and 1.23 (3H, s, Me), 1.24-2.48 (11H, m), 5.47 (1H, m, olefinic); \(^{13}\)C NMR: \( \delta \) 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 C\(_{13}\)H\(_{18}\)O: M\(^{+}\) 190.1339. Found: 190.1337.

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

\((\text{endo})\) 2,7-Dimethyltricyclo[5.2.2.0\text{1,5}]t\text{e}ndec-5-en-8-ol (28a). A solution of the ketone 25a (1g, 5.26mmol) in anhydrous THF (15 ml) was cooled to –78\(^\circ\)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, \( \text{endo} \) and \( \text{exo} \) ratio, 8:1); IR: \( \nu_{\text{max}} \) 3430 and 1640 cm\(^{-1}\); \(^1\)H: NMR \( \delta \) 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, -\( \text{C-H} \)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 C\(_{13}\)H\(_{20}\)O: M\(^{+}\) 192.1489. Found: 192.1464; Anal. calcd. for C\(_{13}\)H\(_{20}\)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\(^\circ\)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\(_2\)O\(_2\) (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\(_2\)SO\(_4\). Removal of the solvent produced the acid 29a (200mg, 83%). IR: \( \nu_{\text{max}} \) 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: \( \nu_{\text{max}} \) 3430 and 1735 cm\(^{-1}\); \(^1\)H NMR: \( \delta \) 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, -\( \text{C-H} \)OH) and 3.77 and 3.80 (3H, 2 x s, -COOMe); Anal Calcd. C\(_{14}\)H\(_{22}\)O\(_{4}\): C, 66.12; H, 8.72. Found: C, 66.58; H, 8.83.

4,8-Dimethylspi\text{ro}[4.5]dec-7-en-1-one (31a) and (32a). The stirred solution of the \( \beta \)-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 (3×50 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: \( \nu_{\text{max}} \) 2930, 1735 cm\(^{-1}\); \(^1\)H NMR: \( \delta \) 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. C\(_{12}\)H\(_{18}\)O: C, 80.85; H, 10.18. Found: C, 80.50; H, 10.01. This mixture was identical in all respects with the sample\(^\text{20}\) 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\(_2\)Cl\(_2\) (100ml), BF\(_3\).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\(_2\)Cl\(_2\) to yield a residue, which was chromatographed over silica gel. Elution with ethyl acetate-hexane (1:7) afforded the enone 23b (500mg, 10%), IR: \( \nu_{\text{max}} \) 3440, 1660 \& 1610 cm\(^{-1}\); \(^1\)H NMR: \( \delta \) 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: \( \nu_{\text{max}} \) 2920, 1660, 1620 \& 1450 cm\(^{-1}\); \(^1\)H NMR: \( \delta \) 0.89 (3H, d, \( J \) 6.4Hz, Me), 1.00 (3H, d, \( J \) 6.4Hz, Me), 1.20-2.30 (10H, m), 2.35-2.70 (2H, m, allylic), 3.39 (3H, s, -OMe), 5.70 (1H, s, olefinic); \(^13\)C NMR: \( \delta \) 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 C\(_{15}\)H\(_{22}\)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\(_4\)Cl solution. The mixture was worked up with ether to afford the alcohol 24b (0.979g, 92%), IR: \( \nu_{\text{max}} \) 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\(_2\)Cl\(_2\) (50ml) was stirred with HClO\(_4\) (70%, 0.2ml) at room temperature. After 30min, the reaction mixture was diluted with CH\(_2\)Cl\(_2\), washed with water, saturated aqueous NaHCO\(_3\), brine, dried over Na\(_2\)SO\(_4\) 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\(_2\)Cl\(_2\), mp 71.5°C; IR: \( \nu_{\text{max}} \) 2950, 1710 and 1450 cm\(^{-1}\); \(^1\)H NMR: \( \delta \) 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, \( J \) 18.2 Hz, \( J_w \) 2.7 Hz, H\(_9\)-endo), 2.37 (1H, d, \( J \) 18.2Hz, H\(_9\)-exo), 2.41 (1H, dd, \( J \) 7.2 and 15.9Hz, C\(_4\) H), 5.52 (1H, s, olefinic); \(^13\)C NMR: \( \delta \) 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 C\(_{15}\)H\(_{22}\)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: \( \nu_{\text{max}} \) 3360 and 1460 cm\(^{-1}\); \(^1\)H NMR: \( \delta \) 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 9Hz, \( \text{CH-OH} \)), 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 C\(_{15}\)H\(_{24}\)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\(^\circ\)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\(_2\)O\(_2\) (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\(_2\)SO\(_4\). Removal of the solvent afforded the acid 29b (200mg, 74%) as a white gummy solid, which resisted crystallization. IR: \( \nu_{\text{max}} \) 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 C\(_{15}\)H\(_{24}\)O\(_4\)-OH (C\(_{15}\)H\(_{23}\)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: \( \nu_{\text{max}} \) 3340 & 1730 cm\(^{-1}\); \(^1\)H NMR: \( \delta \) 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, -C\(_\text{H-OH} \)), 3.60 and 3.63 (3H, 2 x s, -OMe); Anal. calcd. for C\(_{16}\)H\(_{26}\)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 \( \beta \)-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 \times 50 ml) and worked up to yield a residue, which was chromatographed over silica gel. Elution with ethyl acetate–hexane (1:9) gave the mixture of ketone (204mg, 53%) as an inseparable mixture of 31b and 32b, IR: \( \nu_{\text{max}} \) 2930, 1735 and 1650 cm\(^{-1}\); \(^1\)H NMR: \( \delta \) 0.83 and 0.98 (6H, 2 x d, J 7.7Hz, 2 x Me), 1.70-2.40 (12H, m), 3.40 (1H, m, -CH\(_\text{OH} \)), 3.60 and 3.63 (3H, 2 x s, -OMe); Anal. calcd. for C\(_{14}\)H\(_{22}\)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\(^1\)5.1]undec-5-en-8-ol (33). To the ketone 21a (3.2g) in methanol (30ml), sodiumborohydride (1.5g) was added in protins while stirring at room temperature. After 2 h, methanol was distilled and the residue was dissolved in water and extracted with ether (4 \times 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: \( \nu_{\text{max}} \) 3400, 3040, 2950, 1660 cm\(^{-1}\); \(^1\)H NMR: \( \delta \) 0.92 (3H, d, J 7
Hz, CH₃), 1.0-2.45 (11H, complex), 3.3 (3H, s, OMe), 3.73 (1H, bm, -CH₂OH), 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, OCHOH), 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.

**Benzylation 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 benzylated 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 6.5 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), 4.52 (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-Benzylxy-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-oxo-spiro[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$_2$SO$_4$. 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: $\nu_{\text{max}}$ 3450, 1735, 1220 cm$^{-1}$; $^1$H NMR: $\delta$ 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, -CH$_2$OH), 3.77 and 3.8 (3H, 2 x s, -COOCH$_3$); Anal. Calcd. for C$_{14}$H$_{22}$O$_4$: C, 66.12; H, 8.72. Found: C, 66.58; H, 8.23.

Acknowledgements

We thank the CSIR, New Delhi for financial assistance (SRF to PJB & Emeritus Scientist award to GSRS) and Prof. J. N. Marx for providing us with the authentic sample and spectra.

References