Synthesis based on cyclohexadienes. Part 21.[1] Total synthesis of (±)-hinesol and (±)-10-*epi*-hinesol

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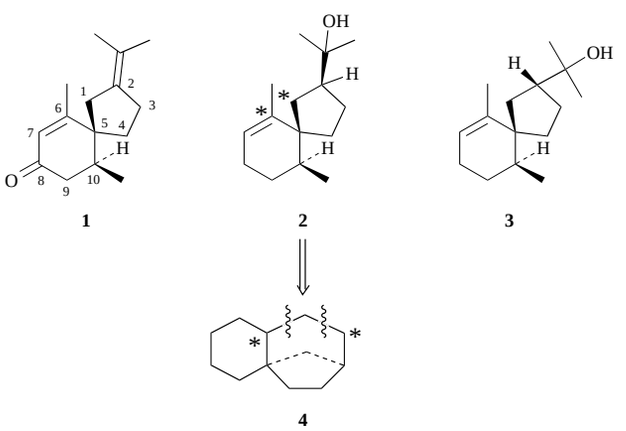
An efficient strategy for the construction of the spiro[4.5]decane and eremane systems is described which involves an acid-catalysed rearrangement of an *endo* alcohol, followed by an oxidative cleavage resulting in the generation of a spiro-system, as the key step. This methodology is extended to the total synthesis of (±)-hinesol and (±)-10-*epi*-hinesol 2.

Introduction

Spirovetivanes are a group of sesquiterpenes having a spiro-[4.5]decane carbon framework with a 10-methyl group and a 2-isopropyl group. A number of sesquiterpenes belonging to the spirovetivane family are known[2] in nature and they include β-vetivone **1**,[3] hinesol **2**[4] and agaspirol **3**.[5] Owing to their novel structure and interesting biogenesis, several syntheses[6] of these sesquiterpenes have been reported. A convenient synthesis of these sesquiterpenes must address the construction of a stereogenic spirocentre. In continuation of our interest in the total synthesis of spirosystems[7] of the β-vetivone family, we describe herein an efficient total synthesis of (±)-hinesol and its 10-epimer. A preliminary account of this work has been reported[8] earlier.

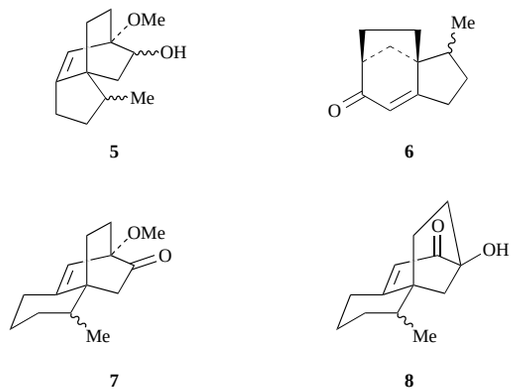


1 **2** **3** **4**

Results and discussion

Careful examination of the structure of hinesol **2** showed that the isopropyl side chain and the vinylic carbon of the cyclohexene ring are *cis* orientated. This *cis* relationship of these groups indicated the possibility of obtaining hinesol from the cyclic structure of the type **4**. Scission of the bonds shown in the structure **4** would generate the spirodecane framework having the substituents at appropriate positions which can be further elaborated into hinesol **2**.

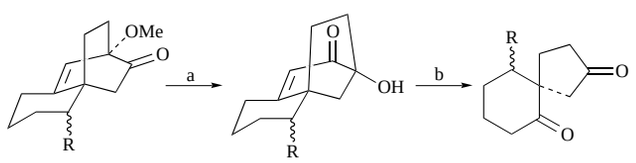
Analysis of the structure **4** indicated that it possessed a bicyclo[3.2.1] carbon framework fused to a cyclohexane ring. Earlier, we reported[9] the formation of 2-methyltricyclo-[6.2.1.0^{1,5}]undec-5-en-7-one **6** from 7-methoxy-2-methyltricyclo[5.2.2.0^{1,5}]undec-5-en-8-ol **5**, by an acid-catalysed rearrangement and visualised that the analogous compound **7** should rearrange to the unsaturated ketone **8**, which is structurally similar to the carbocyclic framework **4**.



5 **6** **7** **8**

Scheme 1

Before attempting the synthesis of hinesol from **7**, model experiments were carried out using the known tricyclic ketone **10**.[10] Thus the ketone **10** was rearranged[11] smoothly to the hydroxy enone **11** with 98% formic acid in good yield. The enone **11** was oxidatively cleaved[12] with $RuCl_3/NaIO_4$ to afford the dione **12**. The IR spectrum of the dione **12** exhibited two absorption bands at 1740 and 1715 cm^{-1} for the cyclohexanone and cyclopentanone carbonyl moieties respectively. The structure was further confirmed from its ^{13}C NMR spectrum and analytical data.

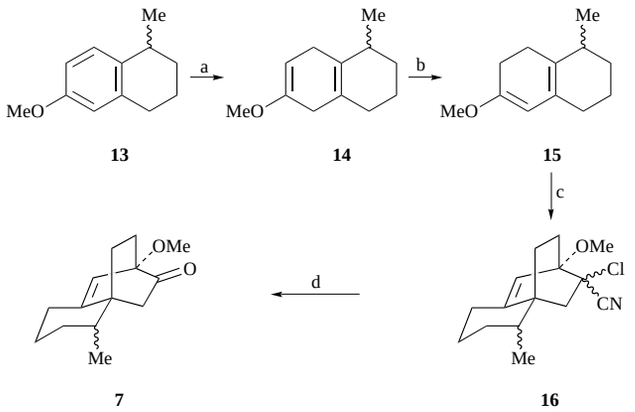


7 R = Me, **10** R = H; **8** R = Me, **11** R = H; **9** R = Me, **12** R = H

Scheme 2 *Reagents and conditions:* a, 98% HCOOH, RT, 1 h; b, $RuCl_3$, $NaIO_4$, CCl_4, CH_3CN, H_2O; RT, 4 h

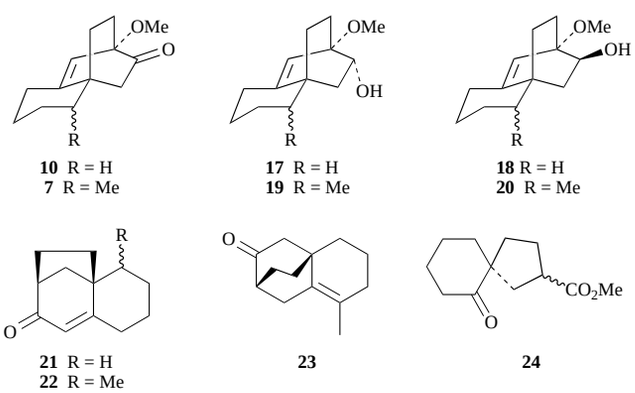
Having succeeded in the stereoselective synthesis of the spiro[4.5]decane moeity on a model system, we turned our attention towards the synthesis of the tricyclic ketone **7** from 1-methyl-6-methoxytetralin **13**. Birch reduction of **13** with sodium-*tert*-butyl alcohol in liquid ammonia gave the diene **14** which was isomerised[13] to the conjugated diene **15** with KNH_2 in ammonia in high yield. Cycloaddition of the diene **15** with α-chloroacrylonitrile at 90 °C for 48 h in a sealed tube furnished an inseparable mixture of adducts **16**. Hydrolysis of the adducts **16** with aq. KOH in dimethyl sulfoxide (DMSO) afforded the tricyclic ketone **7** (60%). The ^1H NMR spectrum exhibited two doublets at δ 0.87 and 0.94 for the methyl group

indicating that it is an epimeric mixture. Rearrangement of the tricyclic ketone **7** with 90% formic acid gave the enone **8** which upon oxidation with $RuCl_3/NaIO_4$ afforded the spiro-dione **9**.



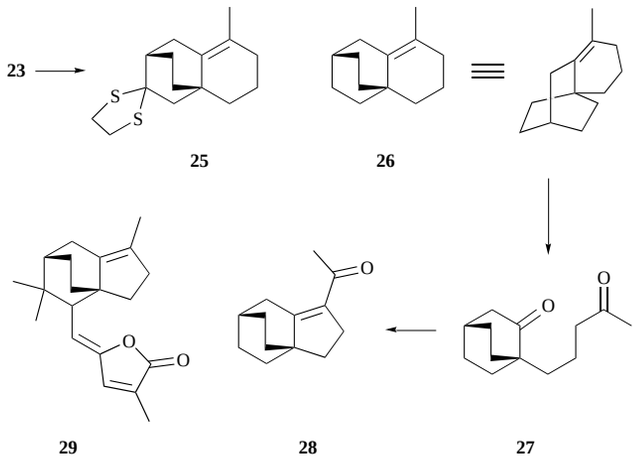
Scheme 3 *Reagents and conditions:* a, Na, liq. NH_3, Bu^{t}OH; b, KNH_2, NH_3; c, $CH_2C(Cl)CN$, 90 °C, 48 h; d, aq. KOH, DMSO, 55 °C, 48 h

The compounds **12** and **9** possessed the spiro[4.5]decane carbon skeleton present in the spirovetivanes. Although a carbonyl group at C-2 in **12** could be transformed into an isopropyl group, we envisioned that the tricyclic system of type **21**, which lacked the bridgehead hydroxy group, would produce the spiro system on oxidation, having a carboxyl group at C–2 which could be later elaborated into the isopropyl functionality. Thus, oxidation of the enone **21**, obtained [14] through the analogous skeletal rearrangement of the *endo* alcohol **17**, prepared from the ketone **10**, with $RuCl_3/NaIO_4$ afforded the acid, which was characterised as its methyl ester **24**. The stereochemistry of the C–2 substituent in the ester **24** with respect to the spiro carbon is the same as that present in β-vetivanes as it is derived from the tricyclic system **21** wherein the stereochemistry of the ethano bridge has been well defined. In order to accomplish the total synthesis of (±)-hinesol, a 10-methyl group had to be introduced which has been successfully accomplished as detailed in Scheme 4.



Scheme 4

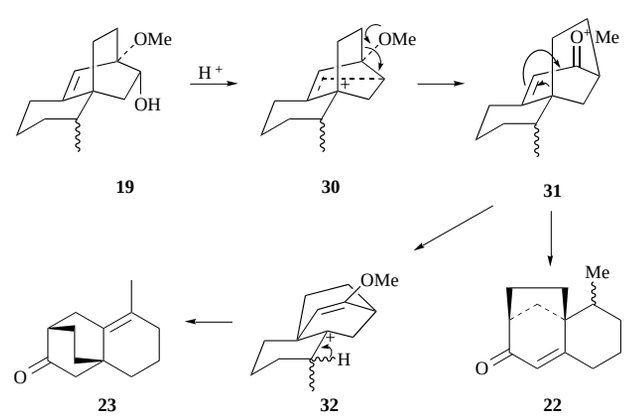
Reduction of the ketone **7** with $NaBH_4$ afforded a mixture of *endo* and *exo* alcohols **19** and **20**, respectively, in a ratio of 3:1. The *endo* alcohol **19** when heated with a catalytic amount of $BF_3{\cdot}OEt_2$ in refluxing benzene for 38 h furnished a mixture of the enone **22** and the ketone **23** in 3:2 ratio. The IR spectrum of the enone **22** had absorptions at 1680 and 1600 cm^{-1}. The ^1H NMR spectrum exhibited signals at δ 0.92 and 1.00 for the methyl group indicating the presence of epimers. The bridgehead proton appeared at δ 2.75 and the olefinic proton at 5.7. On the other hand, the ketone **23** had IR absorption at 1720 cm^{-1} for the six-membered carbonyl functionality. The ^1H NMR spectrum showed a singlet at δ 1.67 integrating for three protons and indicating the presence of the methyl group on a double bond.



Scheme 5

To confirm the structure of the isomeric ketone **23** unambiguously, a series of chemical transformations were carried out. The ketone **23** was converted through its dithioketal **25** into the olefin **26**. The ^{13}C NMR spectrum of the olefin **26** was informative as it had only 11 lines as against the expected 13 carbons, since the molecule has a plane of symmetry. The olefin **26** was oxidised with $RuCl_3/NaIO_4$ to afford the diketone **27**, which upon aldol condensation with mild alkali yielded the enone **28**. The formation of the enone **28** conclusively established the structure of the ketone as **23**. Compound **28** possessed the structural features of the eremane skeleton and hence compound **23** can be elaborated into isoeremolactone **29**.[15]

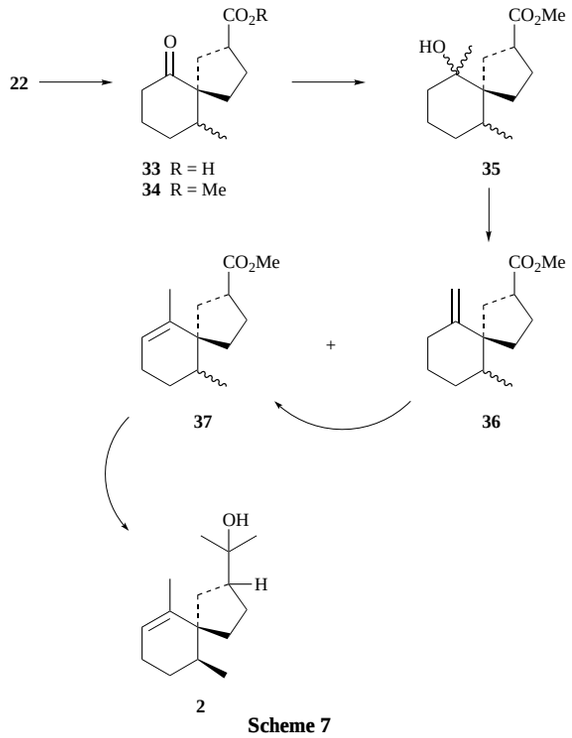
Although the enone **22** upon treatment with $BF_3{\cdot}OEt_2$ is unchanged even after a prolonged period of time, the attempted ketalisation with ethylene glycol resulted in compound **23**. The mechanism of this novel rearrangement of the *endo* alcohol **19** into the enone **22** and the ketone **23** appeared to be as depicted in Scheme 6. The isomerisation of the enone **22** to the ketone **23**



Scheme 6

during ketalisation involved a rearrangement of the bicyclo[3.2.1] system **31** through the bicyclo[2.2.2] moiety, **32**. In conclusion, the transformation of the *endo* alcohol **19** to the ketone **23** featured a novel rearrangement of a bicyclo[2.2.2] carbon framework to a new bicyclo[2.2.2] system through the intermediacy of a bicyclo[3.2.1] system.

The enone **22**, obtained from the *endo* alcohol **19**, was converted into (±)-hinesol as follows. Oxidation of the enone **22**



Scheme 7

with $RuCl_3/NaIO_4$ furnished the keto acid **33**, characterised as its methyl ester **34**. The spiro acid **33** possessed the functional groups at appropriate places with defined stereochemistry, having the vinylic carbon and the ester group in a *cis* relationship, for its conversion into hinesol **2**. Reaction of the spiro acid **33** with methylmagnesium iodide afforded the tertiary alcohol which gave the ester **35** with ethereal diazomethane. Dehydration of the hydroxy ester **35** was accomplished with $POCl_3$ in pyridine to give a mixture of *endo* and *exo* cyclic olefins **36** and **37**, respectively, in 1:1 ratio. These were separated on a $AgNO_3$-impregnated silica gel column. The exocyclic olefin **36** had resonances in its ^1H NMR spectrum at δ 4.6 for the olefinic proton in addition to the methoxycarbonyl protons at δ 3.58. The endocyclic olefin **37** had a broad singlet at δ 5.27 for the olefinic proton along with a singlet at δ 1.61 for the methyl group situated on the olefin. The exocyclic olefin **36** was readily converted into the endocyclic olefin **37** on treatment with toluene-*p*-sulfonic acid in benzene. Addition of methylmagnesium iodide to the ester **37** resulted in (±)-hinesol **2** and its 10-epimer in 95% yield. The spectral data of the synthetic sample **2** was comparable to the reported[16] data, thus completing the total synthesis of these spiro sesquiterpenes. The salient features of our synthesis are (i) the construction of the bicyclo[2.2.2] system from the readily available cyclohexadienes, (ii) the rearrangement of the bicyclo[2.2.2] system to a bicyclo[3.2.1] system and (iii) a high degree of stereocontrol in the preparation of the keto acid **33**, a key intermediate required for the synthesis of hinesol, from the enone **22** wherein the carbonyl carbon and the carboxy group are *cis* orientated in a spiro system.

In conclusion, we have demonstrated an efficient method for the construction of the spiro[4.5]decanes from easily available cyclohexadienes which represents an acid-catalysed rearrangement of a bicyclo[2.2.2] carbon skeleton to a bicyclo[3.2.1]carbon framework. In addition, the basic carbon skeleton of the eremane group of natural products was generated, which can be exploited for the synthesis of isoeremolactone.

Experimental

Mps (measured on Mettler FPI) and bps are uncorrected. IR Spectra were recorded on a Perkin-Elmer 781 spectrometer as either neat samples or solutions in $CHCl_3$. ^1H and ^{13}C NMR spectra were recorded as solutions in $CDCl_3$ (unless otherwise stated) with $SiMe_4$ as internal standard using JEOL FX-90Q, Bruker WH-270 and Brucker AMX 400 spectrometers. Chemical shifts are reported in δ units, and J values are given in Hz. Work-up involved dilution of the reaction mixture with water, extraction with diethyl ether, washing of the organic extract with water and brine, followed by drying over Na_2SO_4 and evaporation at aspirator pressure. Column chromatography was performed on silica gel (60-120 mesh). Liquid ammonia was distilled over sodium amide prior to its use.

9-Hydroxytricyclo[7.2.1.0^{1,6}]dodec-6-en-8-one 11

A solution of the ketone **10** (412 mg, 2 mmol) in 98% formic acid (2 cm^3) was stirred at room temperature for 1 h. The reaction mixture, after work-up, afforded the keto alcohol **11** as a solid which crystallised from diethyl ether–light petroleum (300 mg, 78%), mp 94-95 °C; ν_{max}/cm^{-1} 3440, 1680 and 1600 cm^{-1}; δ_H 1.4-2.0 (m, 12 H), 2.2 (br m, 2 H, allylic H), 3.95 (s, 1 H, OH, exchangeable with D_2O) and 5.8 (s, 1 H, olefinic); δ_C 201.9 (s), 173.2 (s), 120.2 (d), 82 (s), 51.2 (t), 46.9 (s), 34.8 (t), 34.1 (t), 33.8 (t), 30.5 (t), 24 (t) and 21 (t) (Found: C, 75.21; H, 8.47. $C_{12}H_{16}O_2$ requires C, 75.0; H, 8.4%).

Spiro[4.5]decane-2,6-dione 12

The ketone **11** (192 mg, 1 mmol) was dissolved in a mixture of carbon tetrachloride (2 cm^3), acetonitrile (2 cm^3) and water (3 cm^3). To this mixture was added sodium periodate (877 mg, 4.1 equiv.) and $RuCl_3 \cdot 3H_2O$ (2.2%, 5 mg) in water (3 cm^3) and stirred vigorously for 4 h. The reaction mixture was worked up and the residue in diethyl ether was purified by chromatography on silica gel. Elution with light petroleum–ethyl acetate (1:1) furnished the dione **12** (150 mg, 90%), bp 141–42 °C (1 mmHg); ν_{max}/cm^{-1} 1740 and 1715; δ_H 1.6-2.8 (m, 14 H); δ_C 215.7 (s), 211.8 (s), 53.0 (s), 46.5 (t), 37.8 (2t), 35.6 (t), 30.7 (t), 26.3 (t) and 21.1 (t) (Found: C, 72.31; H, 8.4. $C_{10}H_{14}O_2$ requires C, 72.26; H, 8.49%).

6-Methoxy-1-methyl-1,2,3,4,5,8-hexahydronaphthalene 14

6-Methoxy-1-methyltetralin **13** (5 g, 0.028 mol) in a mixture of dry THF (10 cm^3) and *tert*-butyl alcohol (20 cm^3) was added with stirring to distilled liquid ammonia (500 cm^3). Sodium (3.1 g) was added as small pieces to the mixture and the resulting deep blue solution was stirred for 3 h. The reaction mixture was quenched with solid NH_4Cl. Ammonia was allowed to evaporate and the residue was diluted with water and extracted with light petroleum (3 × 100 cm^3). Evaporation of the combined extracts under reduced pressure gave the dihydro compound **14** (4.8 g, 95%); ν_{max}/cm^{-1} 1690 and 1660; δ_H 1.0 (d, *J* 7, 3 H, Me), 1.4-1.9 (m, 7 H), 2.5 (m, 4 H, doubly allylic), 3.45 (s, H, OMe) and 4.5 (br m, 1 H, olefinic). Since the dihydro aromatic compounds are known to aromatise with time, the compound was used immediately for the next reaction.

6-Methoxy-1-methyl-1,2,3,4,7,8-hexahydronaphthalene 15

Anhydrous ferric chloride (15 mg) was added to a stirred mixture of potassium (1.5 g) in freshly distilled ammonia (400 cm^3). A solution of the diene **14** (4.8 g) in dry diethyl ether (10 cm^3) was added dropwise to the above freshly prepared potassium amide in liquid ammonia and the mixture was stirred for 40 min. It was then quenched with solid ammonium chloride and the residue was diluted with water and extracted with light petroleum (4 × 75 cm^3). Evaporation of the solvent afforded the diene **15** as a liquid (90%); ν_{max}/cm^{-1} 1660 and 1610; δ_H 1.0 (d, *J* 7, 3 H, Me), 1.5-2.5 (m, 11 H), 3.5 (s, 3 H, OMe) and 4.6 (s, 1 H, olefinic).

9-Chloro-9-cyano-8-methoxy-2-methyltricyclo[6.2.2.0^{1,6}]dodec-6-ene 16

A mixture of the diene **15** (4 g, 0.022 mmol), α-chloro-

acrylonitrile (4 g, 0.045 mol) and hydroquinone (10 mg) was heated in a sealed tube at 90 °C for 48 h. Excess of the chloroacrylonitrile was removed under reduced pressure and the crude product was purified by chromatography on silica gel column. Elution with ethyl acetate–light petroleum (1:9) afforded a mixture of *exo* and *endo* adducts **16** (3 g, 50%) in a ratio of 1:2 (by ^{1}H NMR); bp 165–166 °C (1 mmHg); ν_{max}/cm^{-1} 3030, 2940 and 2220; δ_H 0.9 (d, *J* 7, 3 H, Me), 1.2–2.7 (m, 13 H), 3.5 (s, H, OMe) and 5.85 and 6.01 (2 br s, 1 H, olefinic) (Found: C, 67.8; H, 7.62. $C_{14}H_{20}ONCl$ requires C, 67.78; H, 7.58%).

8-Methoxy-2-methyltricyclo[6.2.2.0^{1,6}]dodec-6-en-9-one 7

To a solution of the mixture of adducts **16** (1.5 g, 5.6 mmol) in dimethyl sulfoxide (7 cm^3) was added 50% aq. KOH (5 cm^3). The reaction mixture was then stirred and heated to 55 °C for 48 h. After cooling, the reaction mixture was diluted with water and extracted with diethyl ether (4 × 50 ml). Work-up afforded the crude product which was chromatographed on silica gel. Elution with light petroleum–ethyl acetate (9:1) furnished the ketone **7** (740 mg, 60%); bp 139–141 °C (1 mmHg); ν_{max}/cm^{-1} 3040, 2950 and 1720; δ_H 0.87, 0.94 (2 d, *J* 5.2, 3 H, Me), 1.2-2.4 (m, 13 H), 3.52 (s, 3 H, OMe) and 5.85 (s, 1 H, olefinic); δ_C 209.4 (s), 149.8 (s), 119.4 (d), 84.3 (s), 84.05 (s), 52.7 (q), 44.6 (t), 42 (s), 38.2 (t), 32.9 (t), 29.7 (t), 27.3 (t), 27.1 (t), 26.7 (t), 26.5 (t), 26.3 (t), 26.05 (t), 23.3 (t), 20.2 (q) and 15.3 (q) (Found: C, 76.3; H, 9.12. $C_{14}H_{20}O_2$ requires C, 76.3; H, 9.15%).

9-Hydroxy-2-methyltricyclo[7.2.1.0^{1,6}]dodec-6-en-8-one 8

A solution of the ketone **7** (200 mg, 0.9 mmol) in 98% formic acid (2 cm^3) was stirred at room temperature for 1 h. The reaction mixture was diluted with water and extracted with diethyl ether (3 × 25 cm^3). The crude product obtained after removal of the solvent was chromatographed on silica gel and eluted with light petroleum–ethyl acetate (4:1) which furnished the hydroxy enone **8** (135 mg, 77%); ν_{max}/cm^{-1} 3440, 1680 and 1600; δ_H 0.94, 1.0 (2 d, *J* 6.6, 3 H, Me), 1.2–2.4 (m, 13 H), 3.45 (br s, 1 H, OH) and 5.65 (m, 1 H, olefinic) (Found: C, 75.63; H, 9.72. $C_{13}H_{18}O_2$ requires C, 75.73; H, 8.74%).

10-Methylspirol[4.5]decane-2,6-dione 9

A mixture of compound **8** (206 mg, 1 mmol), sodium periodate (877 mg, 4.1 equiv.), carbon tetrachloride (2 cm^3), acetonitrile (2 cm^3) and water (3 cm^3) was stirred vigorously. To this biphasic solution was added $RuCl_3 \cdot 3H_2O$ (5 mg, 2.2%) and the mixture stirred for 4 h at room temperature. Dichloromethane (10 cm^3) was added to the mixture and the aqueous phase was extracted with dichloromethane (3 × 50 cm^3). The combined organic extract was worked up to afford a residue which was diluted with diethyl ether (10 cm^3), filtered through a Celite pad and evaporated to yield the product **9** (150 mg, 83%) which was distilled (bulb–bulb) at 148 °C (1 mmHg); ν_{max}/cm^{-1} 1740 and 1710; δ_H 0.92, 0.98 (2 d, *J* 4.5, 3 H, Me) and 1.8–3.0 (m, 13 H); δ_C 216.7 (s), 216.1 (s), 213.2 (s), 212.5 (s), 58.1 (s), 57.5 (s), 45.6 (t), 43.9 (t), 41.2 (2d), 37.3 (t), 37.1 (t), 36.9 (t), 36.3 (t), 31.9 (t), 29.3 (t), 28.0 (t), 26.4 (t), 23.9 (t), 22.1 (t), 16.1 (q) and 15.4 (q) (Found: C, 73.25; H, 9.07. $C_{11}H_{16}O_2$ requires C, 73.3; H, 8.95%).

Methyl 6-oxospiro[4.5]decane-2-carboxylate 24

The ketone **21** (176 mg, 1 mmol) was dissolved in a mixture of carbon tetrachloride (2 cm^3), acetonitrile (2 cm^3) and water (3 cm^3). To this mixture was added a solution of sodium periodate (8.77 mg, 4.1 mmol) and $RuCl_3 \cdot 3H_2O$ (5 mg, 2.2%) in water. The reaction mixture was stirred for 4 h and then diluted and extracted with dichloromethane (3 × 25 cm^3). The residue, obtained after removal of the solvent from the combined extracts, was dissolved in diethyl ether and passed through a Celite pad. The acid (152 mg, 78%), obtained after removal of the solvent, was esterified with ethereal diazomethane. The crude ester was purified by chromatography on silica gel and eluted with light petroleum–ethyl acetate (7:3) to afford the spiro ester **24** (150 mg); bp 155 °C (2 mmHg); ν_{max}/cm^{-1} 1735 and 1710; δ_H 1.2–2.4 (m, 14 H), 2.9 (quintet, 1 H, $CHCO_2Me$) and 3.65 (s, 3 H, CO_2Me); δ_C 211.8 (s), 174.5 (s), 55.5 (s), 50.6 (q), 42 (d), 38.7 (t), 38.3 (t), 36.8 (t), 27.7 (t), 26.2 (t) and 21.6 (t) (Found: C, 68.52; H, 8.63. $C_{12}H_{18}O_3$ requires C, 68.54; H, 8.3%).

8-Methoxy-2-methyltricyclo[6.2.2.0^{1,6}]dodec-6-en-9-ol 19 and 20

To a stirred solution of ketone **7** (1.5 g, 6.8 mmol) in dry methanol (50 cm^3) was added sodium borohydride (500 mg, 0.013 mol) at 0 °C. After the reaction mixture had been allowed to attain room temperature it was treated with acetone (10 cm^3) to quench the excess of borohydride. After 10 min, methanol was removed under reduced pressure and the residue was treated with saturated aqueous ammonium chloride and diethyl ether. The aqueous layer was extracted with diethyl ether (3 × 50 cm^3) and the combined ethereal extracts were worked up to yield a mixture which showed two closely separable spots on TLC due to the *exo* and *endo* alcohols. This mixture was chromatographed on silica gel. Careful elution with light petroleum–ethyl acetate (9:1) furnished the *exo* alcohol **20** (385 mg); ν_{max}/cm^{-1} 3440 and 1640; δ_H 0.85 (d, *J* 6.2, 3 H, Me), 1.0–2.2 (m, 13 H), 3.36 (s, 3 H, OMe), 3.8 (br m, 1 H, CHOH) and 5.83 (br s, 1 H). Further elution with the same solvent mixture gave the *endo* alcohol **19** (1 g), ν_{max}/cm^{-1} 3440 and 1650; δ_H 0.85 (d, *J* 6.2, 3 H, Me), 1.0–2.3 (m, 13 H), 3.38 (s, 3 H, OMe), 3.84 (br m, 1 H, CHOH) and 5.75 (br s, 1 H, olefinic) (Found: C, 75.44; H, 9.80. $C_{14}H_{22}O_2$ requires C, 75.63; H, 9.97%).

2-Methyltricyclo[7.2.1.0^{1,6}]dodec-6-en-8-one and 5-methyltricyclo[6.2.2.0^{1,6}]dodec-5-en-9-one 22 and 23

A mixture of the *endo* alcohol **19** (1 g, 4.5 mmol) and $BF_3 \cdot OEt_2$ (0.5 cm^3) in dry benzene (50 cm^3) was refluxed for 48 h. After cooling, the reaction mixture was diluted with benzene (20 cm^3), washed with aq. $NaHCO_3$ and water and dried. After work-up the crude material was purified by chromatography on silica gel. Elution with light petroleum–ethyl acetate (9:1) gave the ketone **23** (248 mg); ν_{max}/cm^{-1} 1720; δ_H 1.67 (br s, 3 H, Me), 1.2-2.1 (m, 14 H) and 2.3 (br s, 1 H); δ_C 215.9 (s), 128.8 (s), 125.9 (s), 49.6 (d), 43.5 (s), 35.7 (t), 33.7 (t), 31.2 (t), 30.5 (t), 29.8 (t), 22.9 (t), 18.6 (t) and 17.7 (q) (Found: C, 82.2; H, 9.47. $C_{13}H_{18}O$ requires C, 82.06; H, 9.54%). Further elution with the same solvent mixture afforded the enone **22** (372 mg), λ_{max} 242 nm (ε 10 000); ν_{max}/cm^{-1} 1680 and 1600; δ_H 0.92, 1.0 (2 d, *J* 7, 3 H, Me), 1.4–2.4 (13 H), 2.75 (m, 1 H, bridgehead H) and 5.7 (m, 1 H, olefinic); *m*/*z* 190 (M^+, 100%), 175 (31), 162 (29), 147 (45), 121 (30) and 91 (60) (Found: C, 81.9; H, 9.4. $C_{13}H_{18}O$ requires C, 82.0; H, 9.5%).

Rearrangement of compound 22

To a solution of the enone **22** (100 mg) in benzene (10 cm^3) was added ethylene glycol (2 cm^3) and $BF_3 \cdot Et_2O$ (0.2 cm^3). The mixture was refluxed for 24 h. After cooling, the mixture was diluted with benzene, washed successively with aq. $NaHCO_3$, water and brine and dried. Removal of the solvent afforded the ketal which was dissolved in dichloromethane (3 cm^3) and treated with aqueous HCl (10%, 7 cm^3). After being stirred for 12 h, the mixture was diluted with dichloromethane (10 cm^3), washed with water and brine and dried and evaporated to afford an oil. This on purification by chromatography on silica gel and elution with light petroleum–ethyl acetate (9:1) yielded the pure ketone **23** (40 mg).

5-Methyltricyclo[6.2.2.0^{1,6}]dodec-5-ene 26

$BF_3 \cdot OEt_2$ (0.2 cm^3) was added to a mixture of the ketone **23** (200 mg, 1.05 mmol) and ethane-1,2-dithiol (0.1 cm^3, 1.26

mmol) in dry dichloromethane (5 cm^3) which was then stirred for 30 min at 0 °C and for 3 h at room temperature. The mixture was then diluted with ice-water and extracted with dichloromethane (3 × 50 cm^3). Evaporation of the dried extract afforded the thioketal **25** (220 mg, 79%); ν_{max}/cm^{-1} 3020, 2950, 1630 and 1110.

A mixture of the above thioketal **25** (200 mg), absolute ethanol (10 cm^3) and Raney nickel (2.5 mg) was heated under reflux for 12 h. After cooling, the reaction mixture was filtered, diluted with water and extracted with pentane (3 × 25 cm^3). The pentane layer was washed with water and brine, dried and evaporated to furnish the hydrocarbon **26** (125 mg, 95%); ν_{max}/cm^{-1} 3040, 2950 and 1630; δ_H 1.67 (br s, 1 H, Me), 1.1–1.5 (m, 15 H) and 2.1 (br s, 2 H, allylic H); δ_C 134.3 (s), 123.9 (s), 46.6 (s), 35.8 (d), 33.5 (t, 2 C), 31.7 (t), 26.8 (t, 2 C), 20.0 (t) and 18.4 (q).

1-(4′-Oxopentyl)bicyclo[2.2.2]octan-2-one 27

Oxidation of compound **26** (110 mg, 0.63 mmol) with sodium periodate (548 mg, 4.1 equiv.), water (1.9 cm^3), carbon tetrachloride (1.3 cm^3), acetonitrile (1.3 cm^3) and $RuCl_3 \cdot 3H_2O$ (3 mg, 2.2%) afforded the dione **27** (84.5 mg, 65%); ν_{max}/cm^{-1} 1710; δ_H 2.1 (s, 3 H, COMe) and 1.4–2.4 (m, 17 H); δ_C 217.1, 208.7, 44.7, 44.5, 44.1, 33.0, 29.5, 27.9, 27.5, 25.0 and 18.1 (Found: C, 74.91; H, 9.63. $C_{13}H_{20}O_2$ requires C, 74.96; H, 9.68%).

4-Acetyltricyclo[5.2.2.0^{1,5}]undec-4-ene 28

A mixture containing compound **27** (50 mg), KOH (100 mg), water (1 cm^3) and methanol (3 cm^3) was refluxed for 4 h. After removal of the methanol, the residue was diluted with water and extracted with diethyl ether (3 × 20 cm^3). After work-up, the crude product was purified by chromatography on silica gel. Elution with light petroleum–ethyl acetate (4:1) furnished the product **28** (35 mg, 77%); ν_{max}/cm^{-1} 1670 and 1625; δ_H 2.2 (s, 3 H, COMe), 1.4–1.8 (m, 12 H) and 2.62 (m, 3 H) (Found: C, 82.12; H, 9.49. $C_{13}H_{18}O$ requires C, 82.06; H, 9.54%). The 2,4-dinitrophenylhydrozone had mp 198 °C (Found: M^+, 370.1654. $C_{19}H_{22}O_4N_4$ requires *M*, 370.1641).

10-Methyl-6-oxospiro[4.5]decane-2-carboxylic acid and its methyl ester 33 and 34

To a stirred solution of the enone **22** (280 mg, 2 mmol) in carbon tetrachloride (4 cm^3), acetonitrile (4 cm^3) and water (6 cm^3) was added sodium periodate (1.754 g, 8.2 equiv.) and $RuCl_3 \cdot 3H_2O$ (10 mg, 2.2%). The resulting mixture was stirred vigorously for 4 h. Work-up furnished the spiro acid **33** (230 mg, 75%). The spiro acid (100 mg) in diethyl ether (5 cm^3) was treated with an ethereal solution of diazomethane at −10 °C and left for 4 h. Excess of diazomethane was destroyed by adding a drop of glacial acetic acid to the diethyl ether solution which was then washed with water and brine, and evaporated to give a viscous liquid. This was chromatographed on silica gel. Elution with light petroleum–ethyl acetate (7:3) afforded the spiro ester **34** (80 mg); bp 134 °C (1 mmHg); ν_{max}/cm^{-1} 1735 and 1700; δ_H 0.9 and 0.93 (2 d, *J* 7, 3 H, Me), 1.25–2.6 (m, 13 H), 2.72 (br s, 1 H, C*H*CO_2Me) and 3.65 and 3.67 (2 s, 3 H, CO_2Me); δ_C 213.3, 175.3, 60.5, 51.4, 43.8, 43.6, 42.2, 41.0, 37.9 (2C), 37.2, 33.4, 33.0, 31.4, 30.2, 29.7, 29.4, 28.9, 23.9, 23.3, 15.8 and 15.5 (Found: C, 69.46; H, 8.85. $C_{13}H_{20}O_3$ requires C, 69.61; H, 8.98%).

Methyl 6-hydroxy-6,10-dimethylspiro[4.5]decane-2-carboxylate 35

The spiro acid **33** (120 mg) in dry diethyl ether (10 cm^3) was added dropwise to a freshly prepared solution of MeMgI in diethyl ether (8 equiv.) at °C which was then stirred for 30 min at room temperature. Work-up gave a crude material which was esterified with ethereal diazomethane. The ester was purified by passage through a column of neutral alumina and elution with light petroleum–ethyl acetate (4:1) to furnish the alcohol **35** (115 mg, 87% overall); ν_{max}/cm^{-1} 3500 and 1735; δ_H 0.89, 0.95 (2 d, *J* 5, 3 H, Me), 1.2 (2 s, 3 H, Me), 3.3 (br s, 1 H, OH, exchangeable with D_2O) and 3.62 (s, 3 H, CO_2Me).

Methyl 10-methyl-6-methylenespirol[4.5]decane-2-carboxylate and methyl 6,10-dimethylspiro[4.5]dec-6-ene-2-carboxylate 36 and 37

To a stirred solution of compound **35** (100 mg, 0.42 mmol) in dry pyridine (1 cm^3) was added dropwise freshly distilled $POCl_3$ (184 mg, 1.2 mmol) at °C. The mixture was stirred at 0 °C for 24 h after which it was diluted with diethyl ether (10 cm^3) and slowly quenched with ice–water (2 cm^3) and extracted with diethyl ether (3 × 25 cm^3). The combined extracts were washed with dilute hydrochloric acid (20%), water and brine, dried and evaporated to afford the crude olefin. This was passed though a column of silver nitrate impregnated silica gel. Elution with light petroleum–ethyl acetate (15:1) furnished the *endo* olefin **37** (40 mg); ν_{max}/cm^{-1} 1735, 1640, 1450 and 1370; δ_H 0.84, 0.86 (2 d, *J* 4.8, 3 H, Me), 1.61 (s, 3 H, Me), 2.7 (br m, 1 H, C*H*CO_2Me), 3.6 (s, 3 H, CO_2Me) and 5.27 (br s, 1 H, olefinic) (Found: C, 75.51; H, 9.88. $C_{14}H_{22}O_2$ requires C, 75.63; H, 9.97%). Further elution with same solvent mixture furnished the *exo* olefin **36** (38 mg); δ_H 3.58 (s, 3 H, CO_2Me) and 4.6 (m, 2 H, $=CH_2$).

Isomerisation of 36 to 37

A mixture of the *exo* olefin **36** (35 mg) in benzene (5 cm^3) and toluene-*p*-sulfonic acid (5 mg) was refluxed for 5 h. After cooling, the reaction mixture was worked up with benzene to give the *endo* olefin **37** (32 mg, 90%).

(±) Hinesol and 10-*epi*-hinesol 2

The olefin **37** (25 mg) in dry diethyl ether (5 cm^3) was added dropwise to an ice-cold solution of methylmagnesium iodide (10 equiv.) in dry ether (15 cm^3). The mixture was stirred for 30 min at 0 °C and then at room temperature for 3 h. The crude product obtained after work-up, was chromatographed on silica gel. Elution with light petroleum–ethyl acetate (9:1) furnished **2** (23 mg, 95%); ν_{max}/cm^{-1} 3350, 1640 and 1380; δ_H 0.9, 0.92 (2 d, *J* 6.5, 3 H, Me), 1.21 (s, 6 H, Me at C-12 and C-13), 1.64 (s, 3 H, 6–Me) and 5.3 (m, 1 H, olefinic); δ_H (reported) 0.9 (d, 3 H, *J* 6), 1.25 (s, 6 H, 2 × Me), 1.64 (s, 3 H, Me) and 5.3 (m, 1 H, olefinic) (Found: M^+, 222.1992. $C_{15}H_{26}O$ requires *M*, 222.1980).

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