Synthesis based on cyclohexadienes. Part 25.[1] Total synthesis of (±)-*allo*-cedrol (khusiol)

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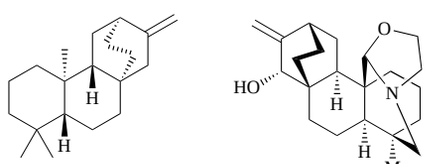
The first stereoselective total synthesis of (±)-*allo*-cedrol 20, an enantiomer of khusiol and a complex sesquiterpene having a novel tricyclo[5.2.2.0^{1,5}]undecane framework, is reported from 8-methoxytricyclo[6.2.2.0^{1,6}]dodec-6-en-9-one 6c. The methodology involves preparation of 9-methoxytricyclo[7.2.1.0^{1,6}]dodec-6-en-8-one 12 from 6c and its conversion through the compounds 8-benzyloxy-7,7-dimethyl-9-methoxytricyclo[7.2.1.0^{1,6}]dodec-5-ene 38, 7-benzyloxy-8-methoxy-2,6,6-trimethyltricyclo[6.2.1.0^{1,5}]undecane 48 into 8-methoxy-2,6,6-trimethyltricyclo[6.2.1.0^{1,5}]undecan-7-one 49. Wittig reaction of 49 affords the olefin 50 which has been smoothly rearranged into khusione 51. Metal–ammonia reduction of khusione under specific conditions affords (±)-*allo*-cedrol. Thus, bridgehead substitution of a methoxy group by a methyl group is the key reaction in this synthesis. In an alternative strategy, attempted conversion of 8-methoxy-2-methyltricyclo[6.2.1.0^{1,5}]undec-5-en-7-one 16 into khusione 37 results in an inseparable mixture of the isomers. A notable observation in this synthesis is the unusual formation of a γ-alkylated product 27 during Woodward methylation of 16.

Introduction

A number of terpenoids such as atiserene **1**, atisine **2**, isoishwarone **3** and isorhodolaureol **4** contain the tricyclo-



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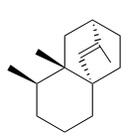

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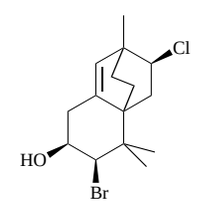

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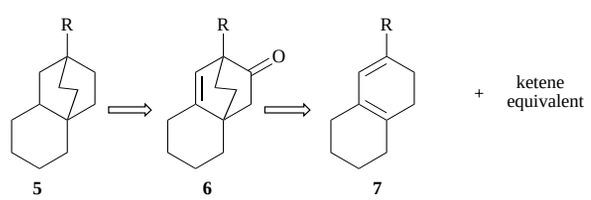
[6.2.2.0^{1,6}]dodecane **5** framework as a structural subunit having a hydrogen or a methyl group at the bridgehead position. These tricyclic compounds **5a** and **5b** can be readily prepared from the ketones **6a** and **6b** which, in turn, can be obtained by the cycloaddition of the dienes **7a** and **7b**, with a ketene equivalent (Scheme 1). However preparation of the pure dienes **7a** and **7b**



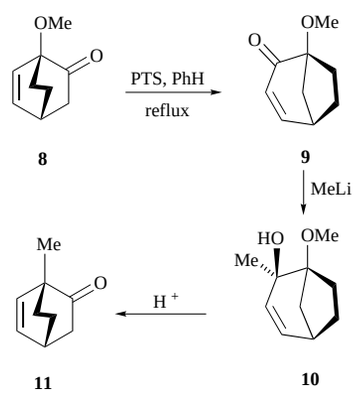
5 **6** **7**

a R = Me; **b** R = H; **c** R = OMe

Scheme 1

by any of the conventional methods was cumbersome and difficult. On the other hand, the diene **7c** can be readily obtained from 6-methoxy-1,2,3,4-tetrahydronaphthalene which affords the adduct **6c** exclusively. Methodology involving the substitution of the bridgehead methoxy group of **6c** with methyl or hydrogen will lead to the desired ketones **6a** and **6b**.

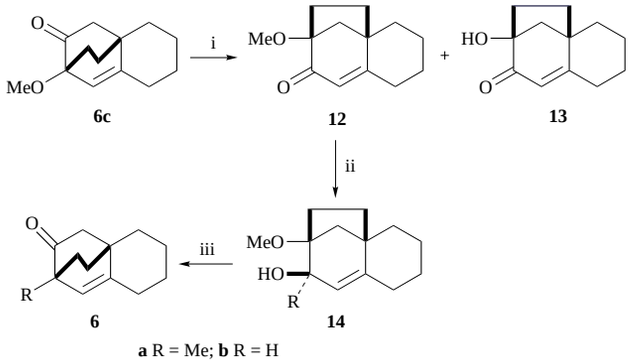
Rogers *et al.*[2] reported a novel bridgehead substitution method involving two successive rearrangements. Thus, treatment of the bicyclooctenone **8** with toluene-*p*-sulfonic acid (PTS) in benzene under refluxing conditions afforded 1-methoxybicyclo[3.2.1]oct-3-en-2-one **9** along with a small amount of the 1-hydroxybicyclo[3.2.1]octenone. Treatment of the enone **9** with methyllithium gave the allylic alcohol **10** which underwent an acid-catalysed rearrangement to afford the ketone **11** (Scheme 2). Thus, substitution at the bridgehead position has



8 **9** **10** **11**

Scheme 2

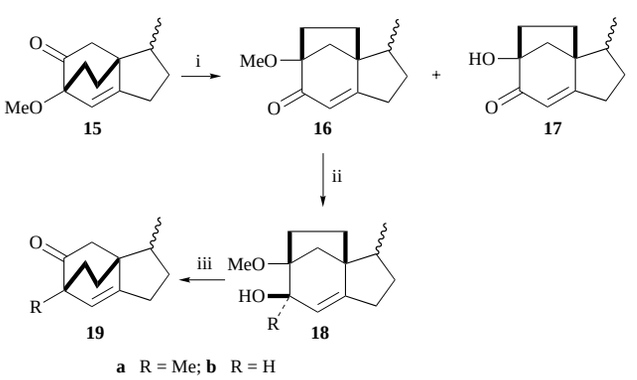
been successfully accomplished from **8** to **11**. Later Uyehara *et al.*[3] described a similar strategy for the bridgehead substitution of the methoxy group of a bicyclooctenone with hydrogen and alkyl groups. They observed that only the ethano bridge had migrated during the back rearrangement indicating that the acid-catalysed dehydration and the bridge migration were not concerted. A stable intermediate such as an allyl cation might have been involved in this process. With this background, the preparation of the ketones **6** and **19** was investigated through the bridgehead substitution of the intermediates **6c** and **15** for its application in the total synthesis of the sesquiterpene *allo*-cedrol and the results are described in this paper. A preliminary account of this work has been reported.[4]



Scheme 3 *Reagents and conditions:* i, PTS, PhH, reflux; ii, MeLi, Et_2O or $NaBH_4$, $CeCl_3 \cdot 7H_2O$, MeOH; iii, cat. H^+, CH_2Cl_2

Results and discussion

When the ketone **6c**[5] was refluxed with anhydrous PTS in benzene it gave a mixture (3:1) of the enones **12** and **13** which were readily separated by column chromatography (Scheme 3). Reaction of **13** with methyllithium gave the allylic alcohol **14a** which smoothly rearranged to the ketone **6a** upon treatment with a catalytic amount of perchloric acid. The structure of the ketone **6a** was established from its mass spectrum which showed a base peak at 148 corresponding to the diene **7a** due to the retro-Diels–Alder fragmentation. Treatment of the enone **12** with $NaBH_4$–$CeCl_3$ afforded the allylic alcohol **14b** which was similarly transformed into the ketone **6b** under acidic conditions. The ketones **6a** and **6b** were isolated exclusively even when these transformations were performed on the mixture of the enones **12** and **13**. Similarly, refluxing the known[6] ketone **15** with PTS in benzene afforded a 3:1 mixture of the epimeric enones **16** and **17** (Scheme 4). However in the presence of



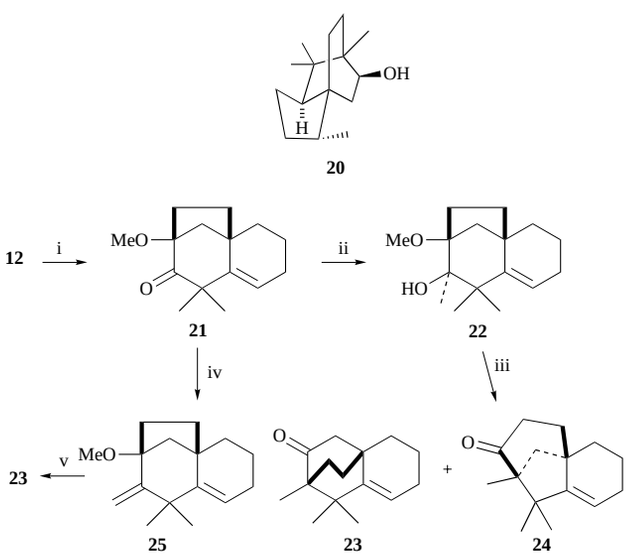
Scheme 4 *Reagents and conditions.* Same as in Scheme 3

$BF_3 \cdot$MeOH, more of **16** was formed (**16**:**17** = 8:1). The enone **16** was separated and converted into the epimeric ketones **19a** and **19b** as per the procedure described above.

Having established the procedure for the bridgehead substitution method, we attempted the synthesis of *allo*-cedrol **20** which possessed a novel tricyclo[5.2.2.0^{1,5}]undecane framework. The sesquiterpene *allo*-cedrol **20**, isolated[7] from *Juniperus rigida* Sieb et Zucc., which is enantiomeric with khusiol, isolated[8] from *Vetiveria zizanioides* has been chosen as our target compound since it can be readily obtained from the ketone **19a**. The synthesis of 2-*epi*-*allo*-cedrol has been reported.[9] We have investigated two different approaches for the synthesis of this natural sesquiterpene and the results are reported in this paper.

First approach

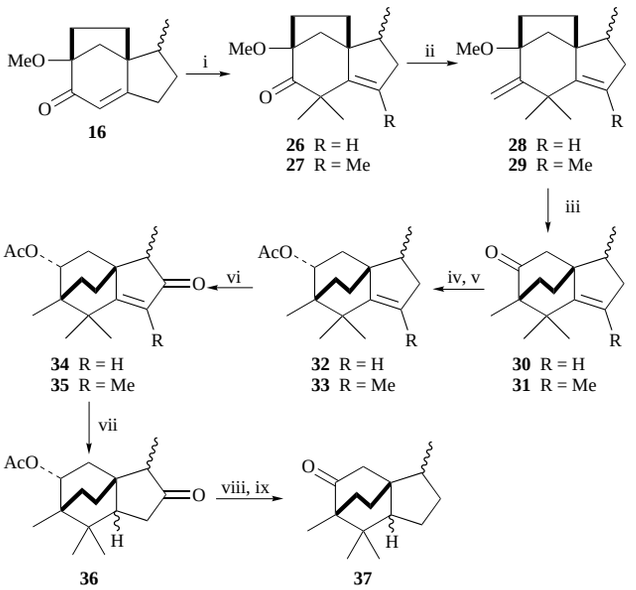
In order to transform the ketone **19a** into *allo*-cedrol the geminal methyl groups at C-6 position had to be introduced which can be carried out on the enone **16** using potassium *tert*-butoxide and methyl iodide. During the alkylation of the enone **16** the C-5, C-6 double bond will migrate into the adjacent five-membered ring which will serve as a latent functionality for the epimerisation of the C-2 secondary methyl group. This operation might impede the preferential migration of the ethano bridge over the methano bridge during the backward rearrangement which had to be worked out. These transformations were explored on the enone **12** rather than the enone **16** which might result in the epimeric mixture of products and will be difficult to separate and characterise. Thus, alkylation of the enone **12** with KOBu′–MeI gave the dialkylated ketone **21** which upon treatment with methyllithium gave the alcohol **22** as a crystalline product (Scheme 5). Treatment of this alcohol



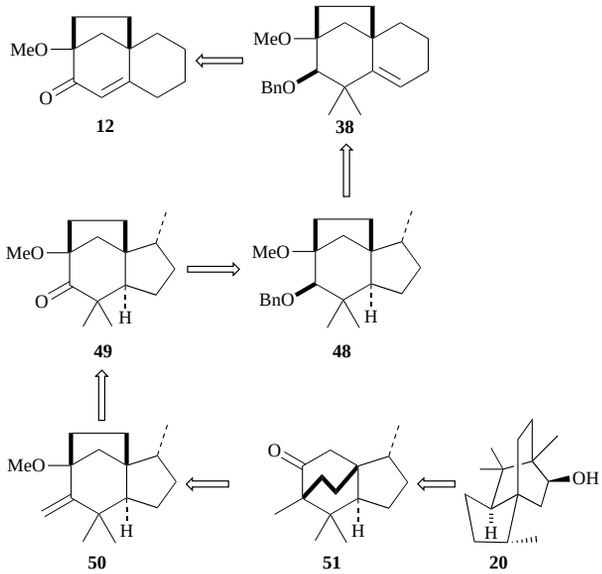
Scheme 5 *Reagents and conditions:* i, Bu′OK, Bu′OH, MeI, PhH (68%); ii, MeLi, Et_2O (74%); iii, Cat. $BF_3 \cdot OEt_2$ CH_2Cl_2, 20 min (83%); iv, Ph_3PMeI, Pent′OK, PhH, ref, (86%); v, $BF_3 \cdot OEt_2$, CH_2Cl_2, 24 h, (70%)

with $BF_3 \cdot OEt_2$ complex afforded an inseparable (2:1) mixture of the ketones **23** and **24**. Acid-catalyzed rearrangement of the alcohol **22** even with formic or perchloric acids afforded a similar ratio of the products **23** and **24**. It is clear from the above that both the ethano- and methano-bridges migrated during the backward rearrangement of the alcohol **22** under acidic conditions.

At this stage the acid-catalyzed rearrangement of the diene **25** was investigated, it being hoped that the exocyclic methylene of the diene would preferentially complex with $BF_3 \cdot OEt_2$, away from the ethano bridge and hence might favour the migration of the ethano bridge leading to the ketone **23**. This diene **25** was prepared by the Wittig reaction of the ketone **21** with methyl(triphenyl)phosphonium iodide under refluxing conditions. Treatment of this diene with $BF_3 \cdot OEt_2$ gave exclusively the ketone **23** as expected. Having successfully established the procedure for the bridgehead substitution, we carried out similar transformations on the enone, **16**. However, when the enone **16** was subjected to Woodward alkylation conditions using KOBu′/MeI, it produced an inseparable mixture of the ketones **26** and **27** whose structures were deduced from their spectral data (Scheme 6). GCMS analysis of the product indicated that it is a mixture of two components, one with a molecular ion peak at *m*/*z* 234 and the other at *m*/*z* 248. Both these components showed a similar fragmentation pattern. Based on this and other spectral data the product was assumed to be a mixture of the ketones **26** and **27**. Since this mixture could not be separated, further transformations were carried out on the mixture itself. Thus, Wittig reaction of the ketone mixture **26** and **27** gave a mixture of the dienes **28** and **29** which upon treatment with $BF_3 \cdot OEt_2$ rearranged to the ketones **30** and **31**. The ketone **30**



Scheme 6 *Reagents and conditions:* i, Bu^{t}OK, Bu^{t}OH, MeI, PhH; ii, Ph_3PMeI, Pent^{t}OK, PhH, ref; iii, $BF_3{\cdot}OEt_2$, CH_2Cl_2, 24 h; iv, $NaBH_4$, MeOH; v, Ac_2O, Py, 12 h, RT; vi, PDC, Bu^{t}OOH, (70% aq.), 24 h; vii, H_2, Pd–C, EtOAc, 40 psi, 5 h (86%); viii, $NH_2NH_2{\cdot}H_2O$, K_2CO_3, diethylene glycol; ix, PDC, CH_2Cl_2



Scheme 7 Retrosynthesis of *allo*-cedrol (khusiol)

possessed the complete carbon framework present in *allo*-cedrol. The ketone mixture **30** and **31** was reduced with $NaBH_4$ and acetylated to afford a mixture of the acetates **32** and **33** which upon allylic oxidation[10] afforded the enones **34** and **35**. This enone mixture was easily separated and the enone **34** was subjected to further transformations. Attempted equilibration of the epimeric centre at C-2 of the enone **34** under a variety of acidic or basic conditions failed. Hence, the double bond of the enone was first reduced by catalytic hydrogenation and then subjected for equilibration. Even at this stage epimerisation could not be achieved. Finally, the keto acetate **36** was subjected to Wolff–Kishner reduction and the resulting alcohol was oxidised with pyridinium dichromate (PDC) to afford the ketone **37** as a mixture of diastereoisomers at C-2 and C-5. Although this synthetic strategy provided the tricyclic core of *allo*-cedrol in a few steps, the major limitations are the unusual γ-alkylation of the enone **16** which lead to an inseparable mixture of products and the failure to control the stereochemistry at C-2 and C-5. An alternative strategy for the total synthesis of *allo*-cedrol **20** was successfully accomplished by overcoming the above problems through stereoselective transformations.

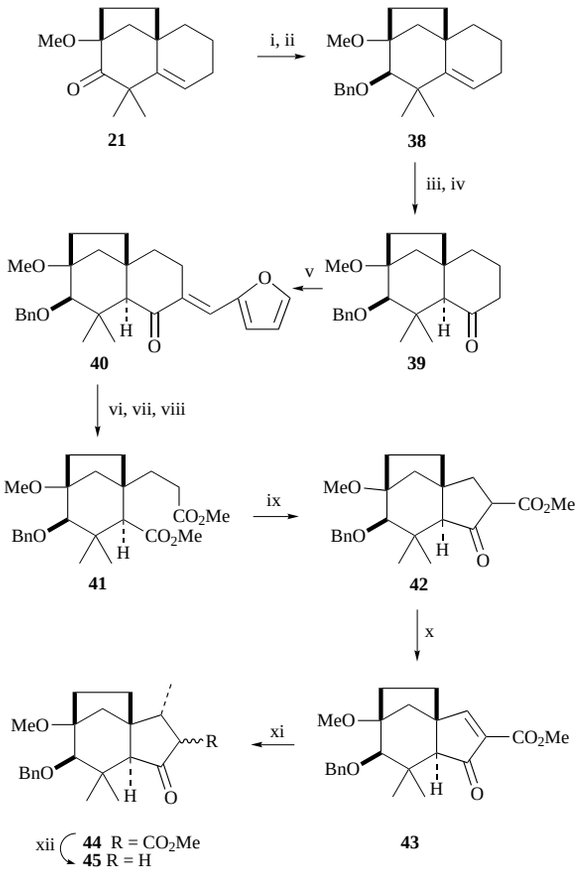
Second approach

The retrosynthetic analysis of *allo*-cedrol **20** is indicated in Scheme 7. Thus, the penultimate ketone, khusione **51**, can be obtained from the olefin **50** through the acid-catalyzed rearrangement as described before. The key steps are the preparation of the compound **38** having the tricyclo[7.2.1.$0^{1,6}$]-dodecane framework and its conversion into the tricyclo-[6.2.1.$0^{1,5}$]undecane structure, **48** having an equatorial methyl group at C-2. We have earlier developed[11] a novel methodology for this type of conversion which culminated in the total synthesis of zizaene group of sesquiterpenes. Thus, compound **48** can be readily converted into the olefin **50** through subsequent transformations.

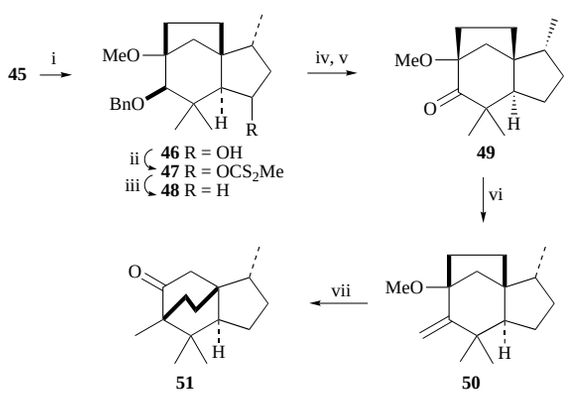
The conversion of the enone **12** into the dialkylated ketone **21** was described earlier. The next task was to convert the cyclohexene ring of the ketone **21** into the cyclopentane ring having a methyl group (Scheme 8). Thus, the ketone **21** was reduced with sodium borohydride to the alcohol and protected as its benzyl ether **38**. Hydroboration of **38** followed by oxidation gave the ketone **39** as a single isomer. During hydroboration it is expected that addition of borane occurs from the α-face of the molecule opposite to the ethano bridge and hence the C-6 hydrogen will have the α-configuration. Condensation of the ketone **39** with furfural gave the furfurylidene derivative **40** which upon ozonolysis followed by oxidative work-up and esterification gave the diester **41**. Dieckman cyclisation of this diester **41** gave exclusively the keto ester **42**. No trace of the other possible Dieckman product could be detected. This may be rationalised in terms of thermodynamic control since the observed product is an enolisable β-keto ester. The next task in the synthesis was to introduce the secondary methyl group at C-2 in a stereoselective manner. This can be achieved from the keto ester **42** by a sequential dehydrogenation and conjugate addition reactions. Thus, phenylselenylation[12] of **42** followed by oxidation with hydrogen peroxide resulted in the selenoxide which on elimination afforded the enone **43**. Treatment of the unsaturated keto ester **43** with lithium dimethyl cuprate at −100 °C gave the keto ester **44**. The stereochemistry of the methyl group at C-2 was assumed to be α-equatorial since the delivery of the methyl group will occur from the α-side of the molecule opposite to the ethano bridge as observed earlier.[11] Decarboxylation[13] of the keto ester **44** with DABCO gave the ketone **45** as a single isomer. Thus, starting from the enone **12** the ketone **45** was obtained in an overall yield of 16.5%.

The ketone **45** was converted into compound **48** under Wolff–Kishner conditions which resulted in an epimeric mixture of products. Hence, the deoxygenation was attempted using Barton's protocol.[14] Thus, the alcohol **46**, obtained by the reduction of the ketone **45** with $LiBH_4$, upon treatment with BuLi, CS_2 and MeI sequentially gave the corresponding xanthate **47** which when refluxed in dioxane with hypophosphorous acid[15] gave the benzyl ether **48** (Scheme 9). Treatment of the benzyl ether **48** with lithium in liquid ammonia followed by oxidation afforded the ketone **49**. Wittig reaction of this ketone **49** under refluxing conditions gave the olefin **50** which was smoothly rearranged with $BF_3{\cdot}OEt_2$ to the ketone **51** whose spectral data were identical with khusione.[8] Although it is known[8] that reduction of khusione with LAH in ether gave a 1:9 mixture of khusiol **20** and 8-*epi*-khusiol **52**, respectively, the reduction of the ketone **51** was attempted with LAH, $NaBH_4$ and $LiBH_4$ which afforded 8-*epi*-khusiol **52** exclusively. Hence reduction of khusione **51** under metal–ammonia conditions was examined.

There are several reports[16] in the literature describing anomalous dissolving metal reductions of cyclic ketones. Grieco *et al.*[17] observed that the stereochemistry of the alcohol, resulting from the metal–ammonia reduction of a cyclic ketone, will depend upon whether the reaction was carried under



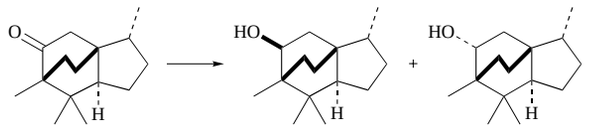
Scheme 8 *Reagents and conditions:* i, $NaBH_4$, MeOH (95%); ii, NaH, BnBr, THF, TBAI, 70 °C (88%); iii, BH_3, THF, H_2O_2, NaOH; iv, PCC, CH_2Cl_2 (86%); v, NaOH, 2-furfuraldehyde, EtOH; vi, O_3, EtOAc, −78 °C; vii, H_2O_2, AcOH; viii, CH_2N_2, Et_2O (74%); ix, NaH, THF (80%); x, NaH, PhSeCl, H_2O_2 (85%); xi, Me_2CuLi, Et_2O, −100 °C (77%); xii, DABCO, toluene, 95 °C (87%)



Scheme 9 *Reagents and conditions:* i, $LiBH_4$, THF (90%); ii, BuLi, CS_2, MeI, THF (94%); iii, H_3PO_2, Et_3N, dioxane, 120 °C (79%); iv, Li, liq NH_3; v, PCC, CH_2Cl_2 (78%); vi, Ph_3PMeI, Pent′OK, toluene, 120 °C (80%); vii, $BF_3{\cdot}OEt_2$, CH_2Cl_2 (66%)

anhydrous conditions or in the presence of a proton source. Based on this observation, reduction of the ketone **51** was attempted with lithium in liquid ammonia in the presence of NH_4Cl as the proton donor which gave (±)-*allo*-cedrol **20** (80%) along with a small amount of 8-*epi*-*allo*-cedrol **52** (20%) (Scheme 10). However, Li–NH_3 reduction of the ketone **51**, in the presence of *tert*-butyl alcohol afforded the alcohols **20** and **52** in 5 : 3 ratio. The structure of these two alcohols, which were separated by preparative thin layer chromatography, were confirmed by comparing the spectral data for the compounds with those of authentic samples.[8]

Thus, in this first stereoselective total synthesis of (±)-*allo*-cedrol, we have unambiguously established the structure



Scheme 10

proposed for the natural product by chemical transformations and spectroscopic analysis. Some of the salient features of the synthesis were (i) stereoselective conjugate addition, (ii) construction of the tricyclo[5.2.2.$0^{1,5}$]undecane skeleton by Lewis acid-catalysed rearrangement of a bicyclo[3.2.1]octane system to a bicyclo[2.2.2.]octane system and (iii) metal–ammonia reduction of the ketone **51** to (±)-*allo*-cedrol in the presence of a proton donor.

Recently Dr Klaus P. Adam of the University of Saarlandes, Germany has isolated[18] *allo*-cedrol as a secondary metabolite from liverworts (*Bryophytes*), the spectral data of which were identical with our sample.

Experimental

Mps and bps are uncorrected. IR spectra were recorded as liquid films or Nujol mulls on a Perkin–Elmer model 781 and Hitachi 750-50 spectrometers. ^1H NMR and ^{13}C NMR spectra were recorded on solutions in $CDCl_3$ with $SiMe_4$ as internal standard. Chemical shifts are reported in δ units and J values are given in Hz. Low-resolution and high-resolution mass spectra were recorded on a JEOL MS-DX-303 instrument with a built-in direct inlet system. Microanalyses were carried out using a Carlo Erba 1106 instrument. Analytical TLC was performed on glass plates coated with Acme silica gel G (containing 13% calcium sulfate as the binder). Acme silica gel (60–120 mesh) was used for column chromatography. The work-up procedure involved dilution of the reaction mixture with water, extraction with ether (or ethyl acetate or benzene or CH_2Cl_2), washing of the organic extract with water and brine, drying (anhydrous Na_2SO_4) and evaporation of the solvent at aspirator pressure.

9-Methoxytricyclo[7.2.1.$0^{1,6}$]dodec-6-en-8-one 12 and 9-hydroxytricyclo[7.2.1.$0^{1,6}$]dodec-6-en-8-one 13

A mixture of the ketone **6c**[5] (3.570 g, 17.33 mmol) and PTS (3 g) in dry benzene (150 cm^3) was refluxed for 2 h. After removal of benzene under reduced pressure, the reaction mixture was dissolved in CH_2Cl_2, and the solution washed with water (2 times) and saturated aqueous $NaHCO_3$ (2 times). The aqueous layer was further extracted with CH_2Cl_2. The combined organic extracts were washed with water and brine, dried (Na_2SO_4) and the residue was chromatographed (silica gel, ethyl acetate–hexane, 1 : 7) to afford the hydroxy enone **13** (685 mg, 21%), mp 95–96 °C (hexane) (lit.,[9] mp 90–91 °C); δ_H(90 MHz) 1.2–2.3 (12H, m), 2.3–2.6 (2H, m, allylic CH_2), 4.0 (1H, s, OH) and 5.82 (1H, s, =C*H*H) (Found: C, 75.0; H, 8.5. Calc. for $C_{12}H_{16}O_2$: C, 75.0; H, 8.4%).

Further elution with the same solvent system gave the methoxy enone **12** (2.106 g, 61%), mp 72 °C (hexane); ν_{max}/cm^{-1} 1670, 1600 and 1450 cm^{-1}; δ_H(90 MHz) 1.2–2.6 (14H, m), 3.42 (3H, s, OMe) and 5.74 (1H, s, =C*H*H); δ_C(22.5 MHz) 22.0, 24.6, 30.7, 32.9, 34.6, 35.5, 47.7, 48.6, 53.7, 88.6, 123.7, 170.8 and 200.7; *m*/*z* 206 (M^+, 55%), 177 (70) and 164 (100) (Found: C, 75.9; H, 8.9. $C_{13}H_{18}O_2$ requires C, 75.7; H, 8.8%).

9-Methoxy-8-methyltricyclo[7.2.1.$0^{1,6}$]dodec-6-en-8β-ol 14a

To a solution of the enone **12** (127 mg, 0.617 mmol) in dry ether at 0 °C was added MeLi (of 1 M solution in ether; 1 cm^3, 1 mmol). The mixture was stirred at 0 °C for 1 h after which excess of MeLi was quenched by the addition of saturated aqueous NH_4Cl. The mixture was worked-up with ether to

afford the alcohol **14a** (110 mg, 91%); ν_{max}/cm^{-1} 3400 and 1430; δ_H(90 MHz) 1.1–2.4 (14H, m), 1.4 (3H, s, Me), 3.35 (3H, s, OMe) and 4.96 (1H, s, =C*H*H); *m*/*z* 222 (M^+, 2%), 165 (27) and 147 (100) (Found: M^+, 222.1627. $C_{14}H_{22}O_2$ requires M, 222.1620).

General procedure for rearrangement of the allylic alcohols

A solution of the allylic alcohol (1 mmol) in CH_2Cl_2 (10 cm^3) was stirred with $HClO_4$ (70% 3 drops) at room temperature. After 30 min, the reaction mixture was diluted with CH_2Cl_2, washed with water, saturated aqueous $NaHCO_3$ and brine, dried (Na_2SO_4) and evaporated. Chromatography of the crude product over silica gel [ethyl acetate–hexane (1 : 30) as eluent] gave the ketone.

8-Methyltricyclo[6.2.2.0^{1,6}]dodec-6-en-9-one 6a

Rearrangement of the alcohol **14a** (110 mg, 0.5 mmol) yielded the ketone **6a** (85 mg, 90%); ν_{max}/cm^{-1} 1722 and 1449; δ_H(90 MHz) 1.2 (3H, s, Me), 1.3–1.84 (10H, m), 1.84–2.04 (2H, m, CH_2CO), 2.08–2.38 (2H, m, allylic CH_2) and 5.42 (1H, s, =C*H*H); δ_C(22.5 MHz) 17.5 (q), 18.8 (t), 21.1 (t), 26.3 (t), 31.3 (t, 2C), 32.7 (t), 39.7 (s), 45.9 (t), 49.0 (s), 124.4 (d), 149.4 (s) and 213.1 (s); *m*/*z* 190 (M^+, 4%) and 148 (100). The 2,4-DNP derivative had mp 174 °C (Found: C, 60.9; H, 5.95; N, 14.8. $C_{19}H_{22}O_4N_4$ requires C, 61.6; H, 6.0; N, 15.1%).

9-Methoxytricyclo[7.2.1.0^{1,6}]dodec-6-en-8-ol 14b

To a mixture of the enone **12** (245 mg, 1.189 mmol) and $CeCl_3 \cdot 7H_2O$ (447 mg, 1.2 mmol) in methanol (8 cm^3) at 0 °C was added $NaBH_4$ (23 mg, 0.6 mmol). The mixture was stirred for 1 h, after which methanol was removed under reduced pressure and the residue was treated with saturated aqueous NH_4Cl. Work-up with ether afforded the alcohol **14b** (236 mg, 95%) which was used as such without further purification; ν_{max}/cm^{-1} 3380 and 1440; δ_H(90 MHz) 1–2.4 (14H, m), 3.3 (3H, s, OMe), 4.68 (1H, br s, C*H*OH) and 5.06 (1H, br s, =C*H*H); *m*/*z* 208 (M^+, 22%), 176 (100), 147 (64), 134 (66) and 91 (75).

Tricyclo[6.2.2.0^{1,6}]dodec-6-en-9-one 6b

The allylic alcohol **14b** (200 mg, 0.96 mmol) upon rearrangement afforded the ketone **6b** (107 mg, 63%); ν_{max}/cm^{-1} 1710 and 1440; δ_H(90 MHz) 1.3–2.48 (14H, m), 3.02 (m, 1H, bridgehead H) and 5.76 (1H, br d, =CH*H*); δ_C(22.5 MHz) 19.0 (t), 21.3 (t), 23.5 (t), 26.5 (t), 31.1 (t), 31.5 (t), 40.1 (s), 45.9 (t), 48.8 (d), 118.9 (d), 150.1 (s) and 213.3 (s). The 2,4-DNP derivative had mp 126 °C (Found: C, 60.2; H, 5.6; N, 15.3. $C_{18}H_{20}O_4N_4$ requires C, 60.7; H, 5.7; N, 15.7%).

8-Methoxy-2-methyltricyclo[6.2.1.0^{1,5}]undec-5-en-7-one 16 and 8-hydroxy-2-methyltricyclo[6.2.1.0^{1,5}]undec-5-en-7-one 17

To a solution of the ketone **15**[5] (1.533 g, 7.44 mmol) in CH_2Cl_2 (30 cm^3) $BF_3 \cdot MeOH$ (0.75 cm^3) 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 chromatographed over silica gel. Elution with ethyl acetate–hexane (1 : 7) afforded the enone **17** (147 mg, 10%); ν_{max}/cm^{-1} 3440, 1660 and 1620; δ_H(90 MHz) 0.93 and 1.06 (3H, d, *J* 7, Me), 1.1–2.3 (9H, m), 2.44–2.76 (2H, m, allylic CH_2) and 5.9 (1H, m, =C*H*H).

Further elution with the same solvent system gave the enone **16** (1.22 g, 80%), ν_{max}/cm^{-1} 1665, 1625 and 1450; δ_H(90 MHz) 0.96 and 1.06 (3H, d, *J* 7, Me), 1.16–2.3 (9H, m), 2.42–2.72 (2H, m, allylic CH_2), 3.4 (3H,s, OMe) and 5.81 (1H, m, =C*H*H); δ_C(22.5 MHz) 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; *m*/*z* 206 (M^+, 54%), 177 (100), 164 (45) and 135 (60) (Found: M^+, 206.1309. $C_{13}H_{18}O_2$ requires *M*, 206.1307).

8-Methoxy-2,7-dimethyltricyclo[6.2.1.0^{1,5}]undec-5-en-7-ol 18a

Treatment of the enone **16** (1.232 g, 5.98 mmol) with MeLi as described above for **12** gave the alcohol **18a** (1.263 g, 95%) which was used as such without further purification; ν_{max}/cm^{-1} 3420 and 1445; δ_H(90 MHz) 0.95 (3H, d, *J* 7, Me), 1.2–2.4 (11H, m), 1.37 (3H, s, Me), 3.36 (3H,s, OMe) and 5.06 (1H, m, =CH*H*); *m*/*z* 222 (M^+, 2.5%), 207 (7), 147 (100), 135 (42) and 43 (60) (Found: M^+, 222.1605. $C_{14}H_{22}O_2$ requires *M*, 222.1620).

2,7-Dimethyltricyclo[5.2.2.0^{1,5}]undec-5-en-8-one 19a

The alcohol **18a** (1.263 g, 5.69 mmol) was subjected to rearrangement to furnish the ketone **19a** (894 mg, 83%) as a colourless liquid; ν_{max}/cm^{-1} 1710 and 1440 cm^{-1}; δ_H(90 MHz) 0.98 and 1.04 (3H, d, *J* 7.2, Me), 1.2 and 1.23 (3H, s, Me), 1.24–2.48 (11H, m), 5.47 (1H, m, =C*H*H); δ_C(22.5 MHz) 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; mp of 2,4-DNP derivative 145.6 °C (Found: C, 61.55; H, 6.1; N, 15.1. $C_{19}H_{22}N_4O_4$ requires C, 61.6; H, 6.0; N, 15.1%).

8-Methoxy-2-methyltricyclo[6.2.1.0^{1,5}]undec-5-en-7β-ol 18b

The enone **16** (211 mg, 1.024 mmol) was reduced with $NaBH_4$ as described earlier for the preparation of **14b** to yield the alcohol **18b** (205 mg, 96%); ν_{max}/cm^{-1} 3420, 1455 and 1100; δ_H(90 MHz) 0.88 and 0.96 (3H, d, *J* 7, Me), 1.1–2.5 (11H, m), 3.32 (3H, s, OMe), 4.72 (1H, m, C*H*OH) and 5.18 (1H, m, =C*H*H); *m*/*z* 208 (M^+, 12%), 193 (10), 177(36) and 147 (100) (Found: M^+, 208.1446. $C_{13}H_{20}O_2$ requires *M*, 208.1463).

2-Methyltricyclo[5.2.2.0^{1,5}]undec-5-en-8-one 19b

The alcohol **18b** (149 mg, 0.716 mmol) was rearranged to yield the ketone **19b** (78 mg, 62%) as a colourless liquid, ν_{max}/cm^{-1} 1715 and 1455; δ_H(90 MHz) 0.98 and 1.04 (3H, d, *J* 7, Me), 1.2–2.68 (11H, m), 2.93–3.16 (1H, m, bridgehead H) and 5.68–5.92 (1H, br d, =C*H*H); δ_C(22.5 MHz) 13.8, 14.2, 22.1, 23.8, 24.3, 28.9, 29.1, 30.4, 34.2, 34.5, 40.1, 41.0, 41.7, 45.7, 48.6, 115.4, 116.0, 156.6, 157.1, 213.4 and 213.9; *m*/*z* 176 (M^+, 6%), 148 (9), 134 (100) and 119 (66) (Found: M^+, 176.1206. $C_{12}H_{16}O$ requires *M*, 176.1201).

7,7-Dimethyl-9-methoxytricyclo[7.2.1.0^{1,6}]dodec-5-en-8-one 21

To a solution of Bu^{t}OK in Bu^{t}OH prepared from potassium (371 mg, 9.5 mmol) and Bu^{t}OH (15 cm^3) was added the enone **12** (647 mg, 3.14 mmol) in dry benzene (10 cm^3). The mixture was stirred for 30 min, after which it was cooled to 0 °C and treated with methyl iodide (1.25 cm^3). The mixture was then stirred at room temperature for 8 h after which it was worked-up with benzene. Chromatography of the residue (silica gel, ethyl acetate–hexane, 1 : 11) yielded the ketone **21** (497 mg, 68%); ν_{max}/cm^{-1} 1716, 1452 and 993; δ_H(90 MHz) 1.3 (3H, s, Me), 1.32 (3H, s, Me), 1.4–2.2 (12H m), 3.34 (3H, s, OMe) and 5.5 (1H, t, *J* 4, =C*H*H); δ_C(22.5 MHz) 19.3, 25.3, 30.4, 31.6, 33.5, 35.8, 36.5, 42.3, 44.3, 47.9, 53.8, 88.6, 119.9, 148.0 and 214.9; *m*/*z* 234 (M^+, 2%), 221 (30), 178 (49) and 123 (100) (Found: M^+, 234.1594. $C_{15}H_{22}O_2$ requires *M*, 234.1620).

9-Methoxy-7,7,8-trimethyltricyclo[7.2.1.0^{1,6}]dodec-5-en-8β-ol 22

To a solution of ketone **21** (120 mg, 0.513 mmol) in dry ether under a nitrogen atmosphere at 0 °C was added MeLi (1 M solution in ether; 1.2 cm^3, 1.2 mmol). The mixture was stirred at room temperature for 12 h after which excess of MeLi was destroyed by the addition of saturated aqueous NH_4Cl. The mixture was worked-up with ether and the residue chromatographed (silica gel, ethyl acetate–hexane, 1 : 13) to afford the pure alcohol **22** (95 mg, 74%) as a white crystalline material, mp 48.2 °C (hexane); ν_{max}/cm^{-1} 3500 and 1090; δ_H(90 MHz) 1.13 (3H, s, Me), 1.2 (3H, s, Me), 1.28 (3H, s, Me), 1.32–2.3 (12H, m), 3.28 (3H, s, OMe) and 5.52 (1H, t, *J* 4, =C*H*H); δ_C(22.5 MHz) 20.8, 22.1, 25.1, 26.6, 27.4, 29.1, 36.5, 38.5, 42.3, 43.8, 44.3, 49.9, 79.7, 87.7, 118.6 and 149.4; *m*/*z* 250 (M^+, 8%), 207

(100), 191 (12), 175 (45) and 123 (78) (Found: M^+, 250.1952. $C_{16}H_{26}O_2$ requires *M*, 250.1933).

7,7,8-Trimethyltricyclo[6.2.2.0^{1,6}]dodec-5-en-9-one 23 and 7,7,8-trimethyltricyclo[6.3.1.0^{1,6}]dodec-5-en-9-one 24

To a solution of the alcohol **22** (33 mg, 0.132 mmol) in CH_2Cl_2 (2 cm^3), $BF_3{\cdot}OEt_2$ (2 drops) was added. The mixture was stirred at room temperature for 20 min after which work-up with ether and chromatography of the crude product (silica gel, ethyl acetate–hexane, 1:30) gave an inseparable mixture of the ketones **23** and **24** (24 mg, 83%); ν_{max}/cm^{-1} 1710, 1440 and 1370; δ_H(200 MHz) 0.88, 0.92, 0.93, 0.95, 0.96 and 1.1 (18H, s, 6 × Me), 5.49 (1H, t, *J* 4, =C*H*H) and 5.61 (1H, t, *J* 4, =CH*H*).

7,7-Dimethyl-9-methoxy-8-methylenetricyclo[7.2.1.0^{1,6}]dodec-5-ene 25

A solution of Pent^{t}OK [prepared from potassium (195 mg, 5 mmol) and Pent^{t}OH (5 cm^3)] in benzene was added to triphenyl(methyl)phosphonium iodide (2 g, 5 mmol) in benzene (10 cm^3) under nitrogen, *via* a cannula. The resulting pale-yellow solution was stirred at room temperature for 20 min after which the ketone **21** (608 mg, 2.6 mmol) in dry benzene (10 cm^3) was added to it. After this had been refluxed at 90 °C for 24 h, the reaction mixture was allowed to cool and then worked-up with ether. Chromatography of the residue (silica gel, ethyl acetate–hexane, 1:30) furnished the olefin **25** (521 mg, 86%) as an oil; ν_{max}/cm^{-1} 1610, 1435, 1090 and 895; δ_H(60 MHz) 1.32 (3H, s, Me), 1.36 (3H, s, Me), 1.4–2.2 (12H, m), 3.21 (3H, s, OMe), 5.04 (1H, s, =C*H*H), 5.19 (1H, s, =C*H*H) and 5.42 (1H, t, *J* 4, =C*H*H); δ_C(22.5 MHz) 19.7, 26.0, 35.4, 35.6, 36.5, 37.8, 40.0 (2C), 42.5, 43.3, 52.1, 85.5, 106.0, 117.5, 151.6 and 159.6; *m*/*z* 232 (M^+, 58%), 204 (42), 189 (100), 161 (57) and 149 (73) (Found: M^+, 232.1845. $C_{16}H_{24}O$ requires *M*, 232.1827).

7,7,8-Trimethyltricyclo[6.2.2.0^{1,6}]dodec-5-en-9-one 23

A solution of the above diene **25** (363 mg, 1.55 mmol) in CH_2Cl_2 (10 cm^3) was treated with $BF_3{\cdot}OEt_2$ (0.39 cm^3, 3.2 mmol). After being stirred for 24 h at room temperature, the reaction mixture was worked-up with ether and the residue chromatographed (silica gel, ethyl acetate–hexane, 1:30) to furnish the ketone **23** (240 mg, 70%); ν_{max}/cm^{-1} 1710, 1440, 1385 and 1070; δ_H(200 MHz) 0.88 (3H, s, Me), 0.92 (3H, s, Me), 1.1 (3H, s, Me), 1.4–2.1 (10H, m), 2.14 (1H, s, CH_2CO), 2.16 (1H, d, *J* 2.3, CH_2CO) and 5.6 (1H, t, *J* 4, =C*H*H); δ_C(22.5 MHz) 14.0 (q), 19.1 (t), 24.3 (t), 25.6 (q), 27.7 (t + q), 32.4 (t), 35.0 (t), 36.1 (s), 39.0 (s), 49.2 (t), 50.6 (s), 119.0 (d), 149.0 (s) and 215.6 (s); *m*/*z* 218 (M^+, 65%), 203 (28), 175 (19), 161 (100), 147 (23) and 133 (50). The 2,4-DNP derivative had mp 181.2 °C (Found: C, 63.05; H, 6.5; N, 13.6. $C_{21}H_{26}O_4N_4$ requires C, 63.3; H, 6.6; N, 14.1%).

8-Methoxy-2,6,6-trimethyltricyclo[6.2.1.0^{1,5}]undec-4-en-7-one 26 and 8-methoxy-2,4,6,6-tetramethyltricyclo[6.2.1.0^{1,5}]undec-4-en-7-one 27

To a solution of Bu^{t}OK prepared from potassium (3.9 g, 100 mmol) and Bu^{t}OH (80 cm^3), the enone **16** (6.327 g, 31 mmol) in dry benzene (20 cm^3) was added. The mixture was stirred for 30 min after which it was cooled to 0 °C and treated with methyl iodide (10 cm^3), slowly added over a period of 15 min. After warming to room temperature, the mixture was stirred for 8 h and then worked-up with benzene. Chromatography (silica gel, ethyl acetate–hexane 1:11) of the residue yielded an inseparable mixture (2.6 g) of the ketones **26** and **27**; ν_{max}/cm^{-1} 1710, 1445, 1040 and 990; δ_H(270 MHz) 0.97, 1.01 and 1.06 (3H, d, *J* 7, Me), 1.29, 1.35, 1.36 and 1.42 (6H, s, 2 × Me), 2.44 (1H, ddd, *J* 3, 7.8 and 15, allylic CH_2), 2.66 (1H, ddd, *J* 2, 7.6 and 16.3, allylic CH_2), 3.34 and 3.35 (3H, s, OMe), 5.35 and 5.45 (1H, t, *J* 2, =C*H*H); GCMS data for **26**; *m*/*z* 234 (M^+, 15%), 206 (100), 191 (100), 163 (85) and 120 (100) (Found: M^+, 234.1622. $C_{15}H_{22}O_2$ requires *M*, 234.1620); GCMS data for **27**: *m*/*z* 248 (M^+, 29%), 220 (100), 205 (40), 177 (55) and 134 (100).

8-Methoxy-7-methylene-2,6,6-trimethyltricyclo[6.2.1.0^{1,5}]undec-4-ene 28 and 8-methoxy-7-methylene-2,4,6,6-tetramethyltricyclo[6.2.1.0^{1,5}]undec-4-ene 29

The ketone mixture **26** and **27** (2.5 g) when subjected to Wittig reaction as described before for the ketone **21** furnished the olefinic mixture **28** and **29** (2.18 g as an oil; ν_{max}/cm^{-1} 1445, 1090, 895 and 690; δ_H(200 MHz) 0.92, 0.96, and 1.01 (3H, d, *J* 7, Me), 1.32, 1.36, 1.40 and 1.43 (6H, s, 2 × Me), 3.25 and 3.26 (3H, s, OMe), 4.99 (1H, s, =C*H*H), 5.16 (1H, s, =C*H*H), 5.25 and 5.34 (1H, t, *J* 2.4, =C*H*H); *m*/*z* 246 (M^+, 65%), 232 (100), 217 (45), 203 (62) and 189 (65).

2,6,6,7-Tetramethyltricyclo[5.2.2.0^{1,5}]undec-4-en-8-one 30 and 2,4,6,6,7-pentamethyltricyclo[5.2.2.0^{1,5}]undec-4-en-8-one 31

The olefinic mixture **28** and **29** (2.18 g) and $BF_3{\cdot}OEt_2$ (4 cm^3) in CH_2Cl_2 (30 cm^3) was stirred at room temperature for 24 h and worked-up as described above for the diene **25** to afford a mixture of the ketones **30** and **31** (980 mg); ν_{max}/cm^{-1} 1705 and 1445; *m*/*z* 232 (43), 218 (100), 203 (16), 189 (25), 175 (75), 161 (86), 147 (48), 133 (67), 119 (55) and 41 (53) (Found: M^+, 232.1830. $C_{16}H_{24}O$ requires *M*, 232.1827). (Found: M^+, 218.1670. $C_{15}H_{22}O$ requires *M*, 218.1670).

8-Acetoxy-2,6,6,7-tetramethyltricyclo[5.2.2.0^{1,5}]undec-4-en-3-one 34 and 8-acetoxy-2,4,6,6,7-pentamethyltricyclo[5.2.2.0^{1,5}]-undec-4-en-3-one 35

The above ketone mixture **30** and **31** (980 mg) was reduced with $NaBH_4$ and the resulting crude alcohol was stirred at room temperature with Ac_2O (4 cm^3) and pyridine (2 cm^3) for 12 h. The reaction mixture was heated on a water-bath for 1 h, after which it was cooled and worked up with ether. Chromatography of the residue (silica gel, ethyl acetate–hexane, 1:19) gave the acetate mixture **32** and **33** (1.041 g) which, mixed with PDC (4.512 g, 12 mmol) and Celite (3 g), was dissolved in CH_2Cl_2 (30 cm^3). Bu^{t}OOH (70% aqueous solution; 1.8 cm^3, 12 mmol) was added to the reaction mixture which was then stirred at room temperature for 24 h. Solvent was removed from the reaction mixture under reduced pressure, after which the residue was diluted with ether and filtered through a pad of Celite. Evaporation of the filtrate followed by chromatography of the residue (silica gel, ethyl acetate–hexane, 1:19) afforded the unchanged starting material (150 mg). Elution with ethyl acetate–hexane (1:7) then gave the enone **35** (175 mg), mp 101 °C (hexane), λ_{max}/nm 243 (ε 15 000); ν_{max}/cm^{-1} 1730, 1690, 1625 and 1245; δ_H(270 MHz) 0.91 (3H, s, Me), 1.01 (3H, d, *J* 7.5, Me), 1.1–2.2 (6H, m), 1.24 (3H, s, Me), 1.38 (3H, s, Me), 1.83 (3H, s, allylic Me), 2.03 (3H, s, OCOMe), 2.56 (1H, dd, *J* 13.6 and 10.5) and 4.8 (1H, dd, *J* 10 and 5, C*H*OAc); *m*/*z* 290 (M^+, 7%), 248 (8), 230 (100) and 43 (83) (Found: C, 74.6; H, 9.2. $C_{18}H_{26}O_3$ requires C, 74.4; H, 9.0%).

Further elution with the same solvent system gave the enone **34** (170 mg), mp 118 °C (hexane); λ_{max}/nm 237 (ε 10 400); ν_{max}/cm^{-1} 1730, 1690, 1610, 1445, 1370, 1360 and 1240; δ_H(270 MHz) 0.91 and 0.92 (3H, s, Me), 1.03 (3H, d, *J* 7.5, Me), 1.1–2.1 (6H, m), 1.16 and 1.19 (3H, s, Me), 1.32 (3H, s, Me), 2.04 and 2.05 (3H, s, OCOMe), 2.44 and 2.59 (1H, dd, *J* 13.8 and 10.2), 4.7–4.94 (1H, m, C*H*OAc) and 5.86 (1H, s, =C*H*H); *m*/*z* 276 (M^+, 19%), 246 (7), 234 (27), 216 (94) and 43 (100) (Found: M^+, 276.1707. $C_{17}H_{24}O_3$ requires *M*, 276.1725).

8-Acetoxy-2,6,6,7-tetramethyltricyclo[5.2.2.0^{1,5}]undecan-3-one 36

The enone **34** (35 mg) in ethyl acetate (5 cm^3) was hydrogenated at 40 psi in the presence Pd–C (10 mg) as catalyst to afford the saturated ester **36** (32 mg, 86%); ν_{max}/cm^{-1} 1730, 1440, 1360 and 1240; δ_H(270 MHz) 0.82, 0.87, 0.88, 0.89, 0.91, 0.98 and 1.19 (12H, 4 × Me), 2.03 and 2.08 (3H, s, OCOMe) and 4.7–4.87

(1H, m, C*H*OAc); *m*/*z* 278 (M^+, 7%), 230 (12), 218 (68), 203 (40), 121 (91) and 43 (100) (Found: M^+, 278.1899. $C_{17}H_{26}O_3$ requires *M*, 278.1882).

2,6,6,7-Tetramethyltricyclo[5.2.2.0^{1,5}]undecan-8-one 37

The acetate **36** (10 mg), hydrazine hydrate (2 drops) and anhyd. potassium carbonate (100 mg) in diethylene glycol (1 cm^3) were refluxed at 150 °C for 5 h and then further at 200 °C for 3 h. After cooling, the reaction mixture was worked up with ether and the residue was chromatographed (silica gel, ethyl acetate–hexane, 1 : 19) to afford an alcohol (5 mg) which was mixed with PDC (25 mg) and silica gel (30 mg) in CH_2Cl_2 (2 cm^3) and stirred at room temperature for 2 h. CH_2Cl_2 was then removed from the mixture and the residue was chromatographed (silica gel, ethyl acetate–hexane, 1 : 30) to afford the pure ketone **37** (4 mg) as a diastereoisomeric mixture at C-2 and C-5; ν_{max}/cm^{-1} 1710 and 1450; *m*/*z* 220 (M^+, 88%), 205 (10), 177 (62), 150 (43), 135 (100), 121 (43), 109 (65) and 41 (70) (Found: M^+, 220.1846. $C_{15}H_{24}O$ requires *M*, 220.1827).

8-Benzyloxy-9-methoxy-7,7-dimethyltricyclo[7.2.1.0^{1,6}]dodec-5-ene 38

To a solution of the ketone **21** (1.120 g, 4.79 mmol) in methanol (10 cm^3), was added $NaBH_4$ (300 mg) at 0 °C. The mixture was stirred at room temperature for 1 h, after which the methanol was removed under reduced pressure and saturated aqueous NH_4Cl was added to the residue. Work-up with ether and chromatography of the crude product (silica gel, ethyl acetate–hexane, 1 : 9) provided the corresponding alcohol (1.09 g, 95%); ν_{max}/cm^{-1} 3450, 1450 and 1100. This alcohol (1.126 g, 4.77 mmol) and tetrabutyl ammonium iodide (20 mg) in dry THF (10 cm^3) was added to a suspension of NaH (60% dispersion in mineral oil; 286 mg, 7.15 mmol) in dry THF under nitrogen. The mixture was stirred for 30 min after which it was treated with benzyl bromide (0.57 cm^3, 4.8 mmol) and refluxed for 6 h at 70 °C. After cooling of the reaction mixture it was worked up with ether and the residue chromatographed (silica gel, ethyl acetate–hexane, 1 : 19) to furnish the benzyl ether **38** (1.367 g, 88%) as a viscous liquid; ν_{max}/cm^{-1} 1495, 1450, 1350, 1090, 1030, 735 and 700; δ_H(60 MHz) 1.18 (6H, s, 2 × Me), 3.31 (3H, s, OMe), 3.42 (1H, br s, C*H*OBn), 4.59 and 5.07 (2H, AB_q, *J* 12, benzylic CH_2), 5.46 (1H, t, *J* 4, =C*H*H) and 7.1–7.48 (5H, m, ArH); δ_C(100 MHz) 20.6, 26.1, 26.5, 28.5, 31.8, 36.6, 38.3, 42.3, 43.7, 45.4, 50.6, 76.1, 86.6, 89.2, 118.1, 127.1, 127.3 (2C), 128.3 (2C), 140.3 and 150.9 (Found: C, 80.65; H, 9.1. $C_{22}H_{30}O_2$ requires C, 80.9; H, 9.3%).

8-Benzyloxy-7,7-dimethyl-9-methoxytricyclo[7.2.1.0^{1,6}]dodecan-5-one 39

To the benzyl ether **38** (2.096 g, 6.429 mmol) in THF (20 cm^3), diborane (0.8 M solution in THF; 12.5 cm^3, 10 mmol) was added at 0 °C. The mixture was stirred at room temperature under argon for 5 h after which excess of diborane was destroyed by dropwise addition of water and aqueous NaOH (3 M solution; 3 cm^3). 30% H_2O_2 (3 cm^3) was added dropwise to the reaction mixture which was then stirred at room temperature for 3 h. After solvent removal under reduced pressure, the mixture was worked up with ether to afford the crude alcohol. This was dissolved in CH_2Cl_2 (30 cm^3) and the stirred solution treated with PCC (1.663 g, 7.715 mmol) and silica gel (2 g) at room temperature for 30 min. CH_2Cl_2 was removed under reduced pressure from the mixture and the residue was dissolved in ether and the solution filtered through a pad of Celite. Removal of the solvent from the filtrate followed by chromatography of the residue (silica gel, ethyl acetate–hexane, 1 : 9) gave the ketone **39** (1.891 g, 86%); ν_{max}/cm^{-1} 1695 and 1100; δ_H(90 MHz) 1.25 (3H, s, Me), 1.37 (3H, s, Me), 1.4–2.4 (13H, m), 3.28 (1H, br s, C*H*OBn), 3.35 (3H, s, OMe), 4.59 and 5.03 (2H, AB_q, *J* 11, benzylic CH_2) and 7.16–7.48 (5H, m, ArH); δ_C(100 MHz) 16.3, 21.8, 26.9, 31.2, 33.2, 39.1, 40.3, 42.9, 47.1, 49.2, 51.4, 64.8, 76.3, 85.2, 90.3, 127.2 (3C), 128.2 (2C), 139.9 and 209.3; *m*/*z* 342 (M^+, 15%), 221 (11), 123 (100) and 91 (58) (Found: M^+, 342.2210. $C_{22}H_{30}O_3$ requires *M*, 342.2195).

8-Benzyloxy-7,7-dimethyl-4-furfurylidene-9-methoxytricyclo-[7.2.1.0^{1,6}]dodecan-5-one 40

To a stirred solution of the ketone **39** (789 mg, 2.307 mmol) in ethanol (20 cm^3) at 0 °C, NaOH (20% solution; 0.5 cm^3, 2.5 mmol) was added. This was followed after 30 min by 2-furfuraldehyde (0.2 cm^3, 2.42 mmol) in ethanol (2 cm^3). The mixture was then stirred at room temperature for 8 h, after which work-up with ether afforded the adduct **40** as a yellow crystalline compound in quantitative yield, mp 129.6 °C (hexane); ν_{max}/cm^{-1} 1655, 1580, 1535 and 1460; δ_H(90 MHz) 1.1 (3H, s, Me), 1.24–2.24 (9H, m), 1.52 (3H, s, Me), 2.62–2.98 (2H, m, allylic CH_2), 3.34 (3H, s, OMe), 3.42 (1H, br s, C*H*OBn), 4.62 and 5.06 (2H, AB_q, *J* 11, benzylic CH_2), 6.42–6.68 (2H, m, furan-H) and 7.12–7.62 (7H, m, ArH, =C*H*H and furan-H) (Found: C, 77.4; H, 7.8. $C_{27}H_{32}O_4$ requires C, 77.1; H, 7.7%).

Methyl 3-(4-benzyloxy-3,3-dimethyl-5-methoxy-2-methoxycarbonylbicyclo[3.2.1]octan-1-yl)propionate 41

Ozone was bubbled through a solution of the furfurylidene derivative **40** in ethyl acetate (20 cm^3) at −78 °C until disappearance of the starting material as indicated by TLC. Excess of ozone was removed by bubbling nitrogen through the reaction mixture which was then treated with acetic acid (20 cm^3) and 30% hydrogen peroxide (15 cm^3) and stirred at room temperature for 12 h. Work-up with ethyl acetate provided the diacid which upon esterification with ethereal diazomethane gave the crude diester. This was chromatographed (silica gel, ethyl acetate–hexane, 1 : 7) to afford the pure diester **41** (714 mg, 74%) as a viscous liquid; ν_{max}/cm^{-1} 1725; δ_H(60 MHz) 1.07 (3H, s, Me), 1.14 (3H, s, Me), 3.3 (3H, s, OMe), 3.37 (1H, br s, C*H*OBn), 3.66 (6H, s, 2 × CO_2Me), 4.57 and 5.04 (2H, AB_q, *J* 11.5, benzylic CH_2) and 7.16–7.48 (5H, m, ArH); δ_C(100 MHz) 19.6, 26.3, 29.8, 30.1, 33.6, 34.0, 39.4, 44.5, 44.7, 51.0 (2C), 51.7, 59.3, 76.3, 86.2, 89.1, 127.2, 127.3 (2C), 128.2 (2C), 139.6, 172.8 and 174.0 (Found: C, 69.0; H, 8.4. $C_{24}H_{34}O_6$ requires C, 68.9; H, 8.2 %).

Methyl 7-benzyloxy-6,6-dimethyl-8-methoxy-4-oxotricyclo-[6.2.1.0^{1,5}]undecane-3-carboxylate 42

To a suspension of NaH (60% dispersion in mineral oil; 120 mg, 3 mmol) freed from mineral oil in THF (5 cm^3) under nitrogen, the diester **41** (871 mg, 2.084 mmol) in THF (15 cm^3) was added dropwise. The mixture was refluxed at 70 °C for 5 h after which it was allowed to cool to room temperature, when the excess of NaH was destroyed by dropwise addition to it of water. After acidification with dilute aq. HCl, the mixture was worked-up with ether. Chromatography of the residue (silica gel, ethyl acetate–hexane, 1 : 6) gave the keto ester **42** (647 mg, 80%) as a gum which solidified with time, mp 106 °C (hexane); ν_{max}/cm^{-1} 1740, 1720 and 1100; δ_H(90 MHz) 1.16 (3H, s, Me), 1.25 (3H, s, Me), 1.32–2.48 (9H, m), 3.26 (1H, dd, *J* 8 and 11, C*H*CO_2Me), 3.35 (3H, s, OMe), 3.41 (1H, br s, C*H*OBn), 3.75 (3H, s, CO_2Me), 4.58 and 5.02 (2H, AB_q, *J* 11, benzylic CH_2) and 7.12–7.52 (5H, m, ArH); δ_C(22.5 MHz) 15.8, 26.1, 30.5, 32.4, 35.5, 37.6, 44.5, 45.2, 50.8, 52.0, 54.6, 65.8, 75.8, 86.5, 88.8, 126.9 (3C), 128.0 (2C), 139.4, 169.4 and 207.3 (Found: C, 71.4; H, 7.85. $C_{23}H_{30}O_5$ requires C, 71.5; H, 7.8%).

Methyl 7-benzyloxy-6,6-dimethyl-8-methoxy-4-oxotricyclo-[6.2.1.0^{1,5}]undec-2-ene-3-carboxylate 43

A solution of the keto ester **42** (422 mg, 1.09 mmol) in THF (5 cm^3) was added to a stirred suspension of NaH (60% dispersion in mineral oil; 65 mg, 1.625 mmol) free of mineral oil, in dry THF (5 cm^3) under nitrogen at 0 °C. After 10 min, a solution of PhSeCl (220 mg, 1.149 mmol) in THF was added rapidly to the reaction mixture which was then slowly added to ether (50 cm^3)

containing saturated Na_2CO_3 (15 cm^3). Work-up of the mixture with ether gave the crude selenide which was dissolved in CH_2Cl_2 (15 cm^3), and the solution cooled to 5 °C. 30% H_2O_2 (0.25 cm^3) was then added dropwise to the solution during 5 min. After being stirred for an additional 15 min, the reaction mixture was diluted with CH_2Cl_2, washed with aqueous Na_2CO_3 and brine, dried (Na_2SO_4) and evaporated. The residue was chromatographed (silica gel, ethyl acetate–hexane, 1:3) to yield the enone **43** (358 mg, 85%) as a gum; ν_{max}/cm^{-1} 1740 and 1720; δ_H(90 MHz) 1.25 (3H, s, Me), 1.33 (3H, s, Me), 1.36–2.6 (7H, m), 3.38 (3H, s, OMe), 3.43 (1H, s, C*H*OBn), 3.83 (3H, s, CO_2Me), 4.62 and 5.04 (2H, AB_q, *J* 11, benzylic CH_2), 7.12–7.56 (5H, m, ArH) and 8.14 (1H, s, =C*H*H); δ_C(22.5 MHz) 16.1, 25.1, 32.4, 33.7, 37.8, 42.8, 49.9, 51.1, 51.7, 65.3, 76.2, 88.5, 88.8, 127.0 (3C), 128.1 (2C), 134.8, 139.4, 162.3, 170.6 and 198.2; *m*/*z* 384 (M^+, 3%), 105 (92) and 91 (100); (Found: M^+, 384.1957. $C_{23}H_{28}O_5$ requires 384.1938).

7-Benzyloxy-8-methoxy-2,6,6-trimethyltricyclo[6.2.1.0^{1,5}]-undecan-4-one 45

To a suspension of CuI (292 mg, 1.53 mmol) in dry ether under argon at 0 °C, MeLi (1.007 M in ether; 3 cm^3, 3.06 mmol) was added and the mixture stirred at 0 °C for 10 min. The resultant solution of Me_2CuLi was cooled to −100 °C and a solution of the enone **43** (490 mg, 1.276 mmol) in dry ether (20 cm^3) was added to it. After being stirred at −100 °C for 20 min, the reaction mixture was quenched with water and transferred into a separatory funnel. The reaction flask was rinsed with NH_4OH (2 cm^3) and transferred into the same separatory funnel to which solid NH_4Cl (2 g) was then also added. After agitation, the organic layer was separated and the aqueous layer was worked-up with ether and chromatographed (silica gel, ethyl acetate–hexane, 1:7) to yield the pure keto ester **44** (393 mg, 77%); ν_{max}/cm^{-1} 1740 and 1715.

A solution of the keto ester **44** (491 mg, 1.228 mmol) and DABCO (687 mg, 6.13 mmol) in toluene (20 cm^3) was heated at 90 °C for 4 h. After dilution of the reaction mixture with ether, it was washed with dilute aq. HCl (2 times), water and brine, dried (Na_2SO_4) and evaporated. Chromatography of the residue (silica gel, ethyl acetate–hexane; 1:9) yielded the ketone **45** (364 mg, 87%) as a white crystalline compound, mp 71 °C (hexane); ν_{max}/cm^{-1} 1730, 1450 and 1115; δ_H(90 MHz) 1.05 (3H, d, *J* 7.2, Me), 1.19 (3H, s, Me), 1.29 (3H, s, Me), 1.32–2.68 (10H, m), 3.39 (4H, s, OMe and C*H*OBn), 4.6 and 5.02 (2H, AB_q, *J* 11, benzylic CH_2) and 7.2–7.52 (5H, m, ArH); δ_C(22.5 MHz) 16.4, 17.5, 26.1, 33.0, 36.4, 37.4, 42.0, 46.1, 50.4, 51.0, 60.7, 76.1, 86.9, 89.5, 127.0 (3C), 128.1 (2C), 139.5 and 215.6.

7-Benzyloxy-8-methoxy-2,6,6-trimethyltricyclo[6.2.1.0^{1,5}]-undecan-4-ol 46

A solution of the ketone **45** (252 mg, 0.737 mmol) in dry THF was added to $LiBH_4$ (15 mg) at 0 °C and the mixture stirred at room temperature for 24 h. It was then worked-up with ether and the residue chromatographed (silica gel, ethyl acetate–hexane, 1:9) to afford the starting ketone **45** (58 mg, 23%). Further elution afforded the alcohol **46** (170 mg, 67%); ν_{max}/cm^{-1} 3400, 1450 and 1100; δ_H(90 MHz) 1.01 (3H, d, *J* 7.2, Me), 1.16 (3H, s, Me), 1.21 (3H, s, Me), 1.22–2.62 (10H, m), 3.34 (3H, s, OMe), 3.38 (1H, s, C*H*OBn), 4.24 (1H, m, C*H*OH), 4.58 and 5.02 (2H, AB_q, *J* 11, benzylic CH_2) and 7.16–7.52 (5H, m, ArH); δ_C(100 MHz) 17.6, 20.2, 25.9, 33.9, 34.1, 38.1, 38.6, 42.2, 43.1, 51.1, 51.7, 59.0, 72.7, 76.3, 87.1, 89.9, 127.1, 127.3 (2C), 128.2 (2C) and 140.1; *m*/*z* 344 (M^+, 4%), 137 (58), 124 (100), 99 (63) and 91 (70) (Found: M^+, 344.2353. $C_{22}H_{32}O_3$ requires *M*, 344.2353).

7-Benzyloxy-8-methoxy-2,6,6-trimethyltricyclo[6.2.1.0^{1,5}]-undecane 48

To a solution of the alcohol **46** (42 mg, 0.122 mmol) in dry THF at 0 °C under argon was added BuLi (0.8315 M solution in hexane; 0.29 cm^3, 0.244 mmol) and the mixture stirred at 0 °C for 45 min. After addition of carbon disulphide (0.1 cm^3) to the mixture at 0 °C it was stirred at 25 °C for 3 h. Again it was cooled to 0 °C and methyl iodide (0.2 cm^3) was added to it and stirring continued at 25 °C for 2 h. Work-up of the mixture with ether followed by chromatography of the residue (silica gel, ethyl acetate–hexane, 1:19) gave the xanthate **47** (50 mg, 94%) as a pale yellow solid.

The above xanthate **47** (97 mg, 0.2235 mmol), hypophosphorous acid (30% aqueous solution; 0.2 cm^3), Et_3N (0.2 cm^3) and AIBN (20 mg) in dioxane (10 cm^3) were refluxed at 120 °C for 4 h. After cooling, the reaction mixture was worked-up with ether and the residue was chromatographed (neutral alumina, ethyl acetate–hexane, 1:30) to yield the benzyl ether **48** (58 mg, 79%); ν_{max}/cm^{-1} 1450, 1100, 735 and 695; δ_H(300 MHz) 0.9 (3H, d, *J* 7, Me), 0.95–2.03 (12H, m), 1.04 (3H, s, Me), 1.05 (3H, s, Me), 3.36 (3H, s, OMe), 3.4 (1H, br s, C*H*OBn), 4.6 and 5.04 (2H, AB_q, *J* 11, benzylic CH_2) and 7.16–7.43 (5H, m, ArH); δ_C(75 MHz) 17.4, 19.6, 22.7, 25.9, 32.0, 32.6, 33.8, 38.0, 40.5, 42.0, 50.9, 51.9, 53.7, 75.8, 87.2, 89.6, 126.8, 127.1 (2C), 127.9 (2C) and 140.0; *m*/*z* 328 (M^+, 47%), 237 (25), 137 (100), 124 (58) and 91 (50) (Found: M^+, 328.2388. $C_{22}H_{32}O_2$ requires *M*, 328.2402).

8-Methoxy-2,6,6-trimethyltricyclo[6.2.1.0^{1,5}]undecan-7-one 49

A solution of the benzyl ether **48** (55 mg, 0.168 mmol) in dry ether (3 cm^3) was added to lithium (25 mg) in liquid ammonia (15 cm^3) and the mixture stirred for 45 min. Excess of lithium was destroyed by addition of solid NH_4Cl to the mixture after which the ammonia was allowed to evaporate. Work-up of the mixture with ether and chromatography of the crude product (silica gel, ethyl acetate–hexane, 1:11) gave the alcohol (33 mg, 83%). This was mixed with PDC (126 mg, 0.34 mmol) and silica gel (100 mg) in CH_2Cl_2 (2 cm^3) and the mixture stirred at room temperature for 2 h. After removal of CH_2Cl_2 under reduced pressure from the mixture, the residue was chromatographed (silica gel, ethyl acetate–hexane, 1:19) to afford the ketone **49** (31 mg, 95%) as a colourless liquid; ν_{max}/cm^{-1} 1710 and 1460; δ_H(90 MHz) 0.91 (3H, d, *J* 7.2, Me), 1.13 (6H, s, 2 × Me) and 3.37 (3H, s, OMe); δ_C(100 MHz) 19.7, 22.6, 24.2, 29.1, 31.3, 31.5, 32.8, 40.9, 41.5, 45.5, 53.0, 54.2, 89.7 and 215.6.

8-Methoxy-7-methylene-2,6,6-trimethyltricyclo[6.2.1.0^{1,5}]-undecane 50

In a two-necked round bottomed flask, triphenyl(methyl)phosphonium iodide (120 mg, 0.3 mmol) in toluene (2 cm^3) under argon was treated with Pent^{t}OK [prepared from potassium (15 mg) and Pent^{t}OH (0.5 cm^3)] in toluene. After 10 min, the ketone **49** (20 mg, 0.0847 mmol) in toluene (2 cm^3) was added and refluxed at 120 °C for 8 h. The reaction mixture was cooled and worked up with ether and the residue was chromatographed (silica gel, ethyl acetate–hexane, 1:49) to provide the olefin **50** (16 mg, 80%) as an oil; ν_{max}/cm^{-1} 1465, 1110 and 910; δ_H(90 MHz) 0.88 (3H, d, *J* 7.2, Me), 1.12 (3H, s, Me), 1.18 (3H, s, Me), 1.22–2.22 (12H, m), 3.34 (3H, s, OMe), 4.94 (1H, br s, =C*H*H) and 5.1 (1H, br s, =C*H*H); δ_C(100 MHz) 19.8,. 23.0, 27.6, 31.1, 31.8, 33.2, 35.2, 37.2, 41.2, 43.7, 52.5, 52.7, 54.5, 87.3, 104.4 and 159.8; *m*/*z* 234 (M^+, 49%), 163 (75) and 123 (100) (Found: M^+, 234.1988. $C_{16}H_{26}O$ requires *M*, 234.1985).

(±)-Khusione 51

The olefin **50** (16 mg, 0.068 mmol) and $BF_3{\cdot}OEt_2$ (0.1 cm^3) in CH_2Cl_2 (2 cm^3) were stirred at room temperature for 24 h. Work-up of the mixture with ether followed by chromatography of the crude product (silica gel, ethyl acetate–hexane, 1:30) afforded the ketone **51** (10 mg, 66%); ν_{max}/cm^{-1} 1710 and 1450; δ_H(300 MHz) 0.76 (3H, s, Me), 0.8 (3H, d, *J* 7.2, Me), 0.85 (3H, s, Me), 0.9 (3H, s, Me), 0.95–1.12 (1H, m), 1.2–

1.75 (8H, m) and 1.96–2.17 (3H, m); δ_C(75 MHz) 13.9, 18.1, 19.7, 24.2, 27.8, 28.6, 29.3, 33.9, 34.4, 39.0, 44.0, 46.8, 50.1, 54.1 and 218.7.

(±)-8-*epi*-*allo*-Cedrol 52

A solution of the ketone **51** (4 mg) in dry ether (1 cm^3) was added to a suspension of LAH (10 mg) in dry ether (1 cm^3) at 0 °C and the mixture stirred at room temperature for 3 h. The reaction mixture was quenched with moist ether and filtered through a column of silica gel with ethyl acetate–hexane (1 : 9) as eluent to yield the (±)-8-*epi*-*allo*-cedrol **52** (3.5 mg); ν_{max}/cm^{-1} 3400, 1460, 1040 and 985; δ_H(90 MHz) 0.82 (3H, d, *J* 7, Me), 0.84 (3H, s, Me), 0.89 (3H, s, Me), 0.96–2.16 (12H, m), 1.11 (3H, s, Me) and 3.68 (1H, dd, *J* 9 and 2, C*H*OH).

(±)-8-*epi*-*allo*-Cedrol 52 and (±)-*allo*-cedrol 20

To a mixture of anhydrous liquid ammonia (10 cm^3) containing NH_4Cl (40 mg) and the ketone **46** (8 mg) in dry THF (3 cm^3), lithium (25 mg) was added in small pieces. The resulting blue solution was stirred for 1 h after which excess lithium was destroyed by the addition to it of solid NH_4Cl. The residue was worked-up with ether. GC analysis of the crude product indicated that the alcohols **52** and **20** were present in the ratio of (1 : 5.3) which were separated by preparative thin layer chromatography (silica gel, ethyl acetate–hexane, 1 : 9). The less-polar fraction (1 mg) was found to be identical with (±)-8-*epi*-*allo*-cedrol **52**. The more-polar fraction (5 mg) was identified as (±)-*allo*-cedrol **20**; ν_{max}/cm^{-1} 3380, 1460, 1030 and 1000; δ_H(300 MHz) 0.74 (3H, s, Me), 0.79 (3H, d, *J* 7.2, Me), 0.84 (3H, s, Me), 0.87 (3H, s, Me), 0.9–1.63 (10H, m), 1.86–1.97 (1H, m), 2.0–2.1 (1H, m) and 3.95 (1H, ddd, *J* 2.3, 5.7 and 9.6, C*H*OH); *m*/*z* 222 (M^+, 43%), 207 (15), 177 (100) and 122 (40) (Found: M^+, 222.1993. $C_{15}H_{26}O$ requires *M*, 222.1985).

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