Tetrahedron. Vol. 27, pp 1481 to 1490. Pergamon Press 1971. Printed in Great Britain

A STEREOSPECIFIC TOTAL SYNTHESIS OF ZIZANOIC AND ISOZIZANOIC ACIDS

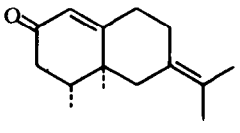
D. F. MACSWEENEY and R. RAMAGE

The Robert Robinson Laboratories, University of Liverpool

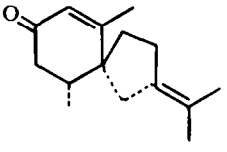
(*Received in the UK* 30 *December* 1970; *Accepted for publication* 11 *January* 1971)

Abstract—The total syntheses of zizanoic and isozizanoic acids, **5a** and **37a** respectively have been achieved starting from D(+)-camphor and utilising rearrangement of a tricyclo [6.2.1.$0^{1,6}$] undecane system to form the desired tricyclo [6.2.1.$0^{1,5}$] undecane skeleton of the tricyclovetivane class of sesquiterpenes. An intermediate (**33**) has also been synthesised which can be transformed into epizizanoic acid (**36a**).

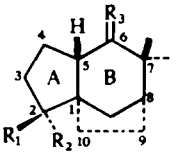
OIL OF vetiver contains sesquiterpenes of varied structural type, e.g. α-vetivone (**1**),[1] β-vetivone (**2**)[2] and tricyclovetivene (**3**).[3] A consideration of the kinship of these and their possible biogenesis led us to propose that the tricyclovetivane skeleton could be formed by rearrangement of the tricyclo[6.2.1.$0^{1,6}$]undecane derivative **4**. In order to test the credibility of such a scheme, it was decided to synthesise zizanoic acid (**5a**)* by a route, which utilised a similar rearrangement to construct the novel ring system of the tricyclic vetiver sesquiterpenes. For ease of synthesis the key intermediate chosen was the diol **6**, rather than **4**, since it would be expected that **6** could be induced to undergo a modified pinacol-type rearrangement to the ketone **32** having the tricyclo[6.2.1.$0^{1,5}$]undecane system of zizanoic acid (**5a**).



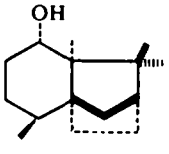
1



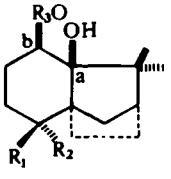
2



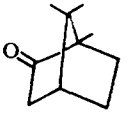
3 R_1 = Me; R_2 = H; R_3 = CH_2
5 R_1 = COOMe; R_2 = H; R_3 = CH_2
32 R_1 = COOMe; R_2 = H; R_3 = O
33 R_1 = H; R_2 = COOMe; R_3 = O
36 R_1 = H; R_2 = COOMe; R_3 = CH_2
38 R_1 = CH_2OH; R_2 = H; R_3 = CH_2



4



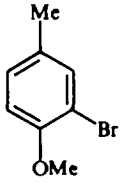
6 R_1 = COOMe; R_2 = H; R_3 = H
27 R_1 = H; R_2 = COOMe; R_3 = H
34 R_1 = COOMe; R_2 = H; R_3 = $MeSO_2$—
35 R_1 = H; R_2 = COOMe; R_3 = $MeSO_2$—



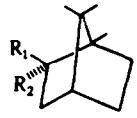
7

* Suffix *a* represents the corresponding acid.

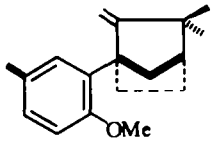
D(+)-camphor (7) was chosen as starting material because of its ready availability and also, because it was hoped that subsequent rearrangement would afford the bicyclo-[2.2.1]-heptyl system present in **6**, correct in stereochemical detail. Reaction of the Grignard derivative of 3-bromo-4-methoxytoluene with **7** gave a mixture of epimeric alcohols **9** and **10**, in which the former predominated. Although it had been shown[5] that **9** rearranged smoothly to **11**, on treatment with silica, it was found that separation of the epimeric mixture was unnecessary. Silica chromatography of the crude Grignard product gave the arylcamphene **11** in 30% yield starting from D(+)-camphor (7). The low yield from the Grignard step is due to competitive enolisation of **7** preventing nucleophilic attack at the carbonyl group.[6]



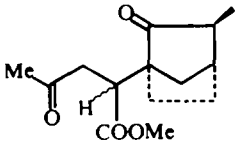
8



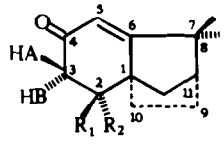
9 R_1 = OH; R_2 = Ar
10 R_1 = Ar; R_2 = OH



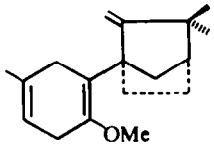
11



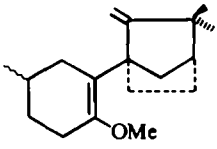
12



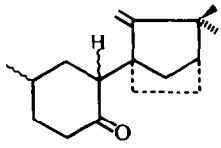
13 R_1 = COOMe; R_2 = Hx
14 R_1 = Hx; R_2 = COOMe



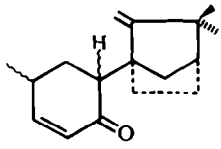
15



16



17

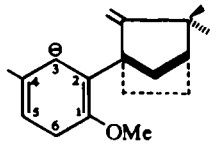


18

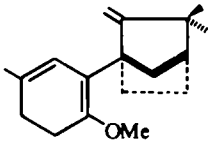
Having found an efficient route to **11**, methods were sought to transform this, initially, to the diketo-ester **12** and thence to the tricyclo[6.2.1.$0^{1,6}$]undecane system of **13** and **14**. Birch reduction using Li in liquid NH_3, in the presence of isopropanol, converted the arylcamphene **11** to an inseparable 1 : 1 mixture of the desired product **15** and the over-reduced material **16**. This was evident from the hydrolysis of the mixture of **15** and **16**, which gave the corresponding saturated and unsaturated ketones **17** and **18**, having *m/e* 246 and 244 respectively.

The first stage in metal-NH_3 reductions is thought[7] to be electron capture by the anisole ring system to give a radical-anion, which has maximum separation of the non-bonding electrons in the least substituted 2 and 5 positions of the ring system.

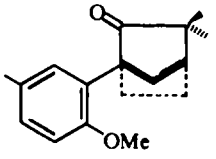
This is followed by protonation at the position α- to the OMe grouping to give a radical, which then proceeds to take up another electron to produce a carbanion, e.g. **19**, which is the case here. Over reduction during the Birch reaction is a consequence of both steric and electronic factors involved in the final protonation of **19** leading to the non-conjugated cyclohexadiene system **15**. It would not be surprising, therefore, to expect steric hindrance to protonation at C-3 in **19** due to the adjacent bulky bicyclo[2.2.1]heptyl system and, to a lesser extent, the CH_3 substituent at C-4. The alternative position of protonation, C-5, would lead to the conjugated cyclohexadiene **20**, which would be liable to further reduction to **16** by the metal-NH_3 system. Analogous cases[8,9] have been found where compounds, which are reduced with difficulty under Birch conditions due to steric effects, give rise to over-reduced products.



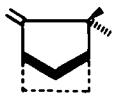
19



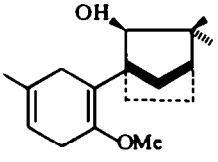
20



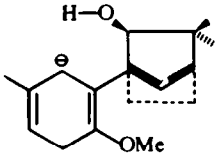
21



22



23



24

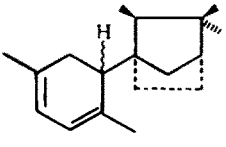
If steric and electronic factors are important influences on protonation of **19** and so produce undesirable side reactions, it was decided to circumvent this by directing the position of protonation by an intramolecular proton transfer. Since the *exo*-methylene grouping in **11** must eventually be oxidatively cleaved to yield **12**, this step was advanced to precede the reduction of the aromatic ring. OsO_4-$NaIO_4$ treatment[10] of **11** afforded the camphenilone **21**, which showed absorption at 1732 cm^{-1} and no evidence for an *exo*-methylene grouping in the IR. Ozonolysis of **11** also gave **21**, but in poor yield and accompanied by other products, which is not surprising since ozonolysis of camphene **22** is not a simple process.[11] Birch reduction of the 1-arylcamphenilone **21** gave an almost quantitative yield of **23**, with no attendant over-reduction. Assuming rapid reduction of the carbonyl function to the *exo*-alcohol,[12] the reduction can be envisaged as involving protonation of the intermediate **24** by an intramolecular process, greatly facilitated by a six-membered transition state.

In order to convert the dihydrobenzene system in **23** to the acyclic residue of **12**, it was necessary to rearrange **23** to the conjugated diene **25**. The isomerisation was accomplished using $(Ph_3P)_3RhCl$[13] as catalyst in refluxing $CHCl_3$, under carefully controlled conditions. Transformation of **23** to **25** was supported by spectroscopic evidence, most important of which was the appearance of two olefinic protons in the NMR of the product (**25**) compared with the sole olefinic proton of the starting

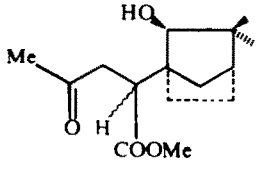
material (**23**). Due to the facile aereal oxidation of **23** and **25**, neither of these compounds were submitted to rigorous purification. Ozonolysis of **25** in EtOAc solution gave **26**, which afforded the desired diketo-ester (**12**) after Jones oxidation.[14] The overall yield of the cumulative steps from **21** to **12** was 40%. The NMR spectrum of **12** suggested the presence of two epimers at C-1, as evidenced by two Me—CO— resonances at 7·84–7·85 τ. This is predictable, since there is no stereospecificity expected in the rearrangement of **23** to **25**.

Base catalysed cyclisation of **12** gave a mixture of **13** and **14** in the ratio 2:3. This epimeric mixture could be conveniently separated by column chromatography on silica to give **14** as a crystalline compound m.p. 95° and **13** as an oil. The IR absorptions of both epimers at 1725 and 1660 cm^{-1} are consistent with structures **13** and **14**, as is the UV maximum at λ 245 nm (ε, 9000) exhibited by these cyclised products. Stereochemical assignment of structures **13** and **14** was possible from a consideration of the NMR spectra. If the molecule is conformationally rigid, due to the planar conjugated enone system then, in **14**, Hx is unsymmetrically disposed with respect to HA and HB. The protons at C-2 and C-3 would thus constitute a complex ABX system in the NMR spectrum of **14**. By contrast, the protons at C-2 and C-3 in **13** should give rise to an AA^1X system due to a symmetrical arrangement of HA and HB with respect to HX. This proved to be the case on both counts. The NMR spectrum of the crystalline isomer **14** contained a complex pattern between 6·5 and 7·7 τ, whereas the oil **13** showed a triplet at 7·0 τ (Hx; J = 3·5 H_2) and a doublet at 7·6 τ (HA, HB; J = 3·5 cps). Equilibration of **13** with t-BuOK in refluxing t-BuOH gave a mixture of **13** and **14** in the ratio 2:3. A similar result was obtained by base treatment of **14** and gives a method for the epimerisation of the α-carbomethoxy group to the more useful β-series corresponding to zizanoic acid (**5a**).

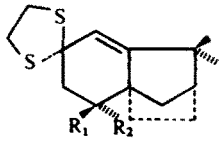
In order to convert **13** to **6** or **14** to **27** it was necessary to remove the ketonic function prior to hydroxylation. This was effected by formation of the thioketals **28** and **29** in both series using ethanedithiol in the presence of $BF_3.Et_2O$. Treatment of **28** and **29** with Raney-Ni in refluxing EtOH led to the smooth formation of the desired olefins **30** and **31** respectively. Hydroxylation of **30** and **31** with OsO_4 in refluxing ether, containing pyridine, resulted in the *cis* diols **6** and **27** required for the rearrangement to the tricyclo[6.2.1.$0^{1,5}$]undecan-6-ones **32** and **33**. For such a rearrangement to take place in a concerted manner, bonds *a* and *b* in structures **6** and **27** should be *trans* and coplanar. Dreiding models show that this is so for either the β-diol system or the α-diol, hence the choice of OsO_4 as hydroxylating agent. The approach of such a bulky reagent would be expected to be from the least hindered *exo*-face producing the β-diol systems **6** and **27**.



25

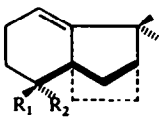


26

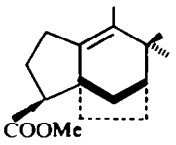


28 R_1 = COOMe; R_2 = H
29 R_1 = H; R_2 = COOMe

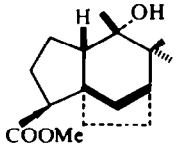
In order to facilitate the rearrangement to **32** and **33**, the diols were converted to the mesylates **34** and **35**. The conditions required for this transformation were a matter of some concern due to the fact that the products **32** and **33** have two epimerisable centres at C-2 and C-5. Concerted rearrangement of **34** and **35** would cause inversion at the site vacated by the departing methane sulphonate ion and, in fact, set up the correct stereochemistry at C-5 in **32** and **33**. It was therefore important to protect the stereochemical integrity of the products **32** and **33** from post-rearrangement epimerisation by using mild basic reaction conditions. It was found that **35** rearranged smoothly in triethylamine–pyridine during 1·5 hr under reflux to give the keto-ester **33** and that prolonged exposure to these conditions did not cause epimerisations. The keto ester **33** exhibited the expected IR absorptions at 1725 (ester) and 1700 (ketone) cm^{-1}, together with an ORD positive Cotton effect[15] indicating a trans A/B ring juncture. Independent work by Yoshikoshi[16] and coworkers on the transformation of **35** to **33**, in which strong base (t-BuOK) was used, substantiated our fears of epimerisation. Nevertheless, these workers were able to isolate and convert **33** to epizizanoic acid **36a**, thus our synthesis of **33** from **11** constitutes a stereospecific synthesis of epizizanoic acid (**36a**).



30 R_1 = COOMe; R_2 = H
31 R_1 = H; R_2 = COOMe



37



39

Having accomplished the rearrangement of **35** we turned to the more rewarding epimer **34** which has the correct stereochemistry at C-2 corresponding to zizanoic acid (**5a**), isozizanoic acid (**37a**) khusimol (**38**)[17] and tricyclovetivene (**3**). Treatment of **34** with pyridine–triethylamine (7 hr at reflux temperature) gave the desired product (**32**). The slower rate being due, presumably, to steric hindrance by the β-carbomethoxy grouping since in **34** all three functional groupings in ring A are *cis* to each other. Comparison of the rearrangement product (**32**) with authentic material, prepared by degradation[18] of the Me ester of zizanoic acid (**5**), showed these to be identical in every respect confirming the stereochemistry at C-5 in **32**. Predictably, treatment of **32** with t-BuOK afforded a mixture of products by glc analysis.

Thus, the desired tricyclo[6.2.1.$0^{1,5}$]undecane ring system had been synthesised with complete control of stereochemistry and the final stage was the introduction of the last substituent at C-6. Before this could be attempted the ester had to be converted to the carboxylic acid to prevent subsequent reaction at this centre or epimerisation at C-2. The transformation of **32** to the acid (**32a**) was effected by reduction with LAH followed by Jones oxidation. A check on epimerisation at C-2 and C-5 during this sequence was made by conversion to (**32**) using CH_2N_2 followed by comparison with authentic material by IR, NMR and glc. The keto acid (**32a**) was efficiently (85%) converted to the hydroxy-acid (**39a**) by reaction with MeMgBr in ether. Although *exo* attack by the Grignard reagent would be expected as shown, the

stereochemistry at C-6 is of little moment since the final stage will remove any asymmetry at this centre. The direct conversion of **32a** to **5a** by means of a Wittig reaction failed in our hands, presumably due to steric hindrance to attack at C-6. In the synthesis of epizizanoic acid (**36a**), however, Yoshikoshi reported[16] a successful Wittig reaction on **33a**, albeit in low yield.

Dehydration of **39a** by means of silica (Grace, 200–300 mesh) in refluxing C_6H_6 gave a quantitative yield of isozizanoiç acid (**37a**). CH_2N_2 treatment gave **37**, which was identical in all respects with the Me ester of naturally occurring isozizanoic acid (**37a**).[19] $POCl_3$ in pyridine at 86° converted **39** to a 3:2 mixture of **37** and **5**, which were separated by chromatography over silica impregnated with 40% $AgNO_3$. Both dehydration products were identical in all respects with methylisozizanoate (**37**) and methyl zizanoate (**5**) obtained from naturally occurring materials. Since **5** has been converted into khusimol (**38**)[18] and tricyclovetivene (**3**),[3] this also constitutes a total stereospecific synthesis of these tricyclic vetiver sesquiterpenes. We are presently actively engaged on the synthesis and rearrangement of **4** with a view to testing our biogenetic proposals.[4]

EXPERIMENTAL

All m.p.s are uncorrected. UV spectra were measured in EtOH on a Unicam SP 800 spectrometer. IR spectra were determined using a Unicam SP 200 spectrometer. Reference NMR spectra were taken on Varian A56-60A or HA-100 spectrometers (TMS) and routine spectra on a Perkin–Elmer R. 12 machine. Mass spectra were determined on an AEI MS 9 spectrometer. Analytical g/c was carried out with a Perkin–Elmer F. 11 gas chromatograph. Optical rotation measurements are for $CHCl_3$ solutions using a Bendix–Ericsson ETL-NPL automatic polarimeter type 143 A.

The silica gel used for column chromatography was Grace 200–300 mesh and Merck (kiesel gel) 70–325 mesh. The alumina used was Merck neutral. Petroleum ether refers to the fraction b.p. 40–60°C. D(+)-Camphor was supplied by B.D.H. Ltd.

1-(2-Methoxy-5-methylphenyl)camphene (**11**). A solution of 3-bromo-4-methoxytoluene (80 g) in anhyd. ether (100 ml) was added slowly with stirring to Mg filings (9·8 g) covered with anhyd. ether (100 ml). After the addition, and subsequent reflux for 1·5 hr to complete the formation of the Grignard reagent, the solution was cooled to 0°. D(+)-Camphor (61 g) in ether (100 ml) was added slowly to the ice-cooled Grignard reagent, and the mixture refluxed for 1·5 hr. The complex was decomposed at 0° by a saturated NH_4Cl aq. The ethereal layer was separated, dried over Na_2SO_4 and the solvent removed *in vacuo* to give an oil (107 g) as crude product. Steam distillation of this material gave a viscous oil (42·5 g) as the non-steam volatile fraction.

Chromatography of the viscous oil (42·5 g) over silica (1 kg, Grace), on elution with 40% C_6H_6 in petroleum ether, gave the 1-arylcamphene (**11**)[5] (30 g) m.p. 66–67°, crystallised from MeOH.

Birch reduction of 1-(2-methoxy-5-methylphenyl)camphene (**11**). To a solution of Li (1·5 g, 0·21 g atom) in liquid NH_3 (150 ml) was added 1-(2-methoxy-5-methylphenyl)camphene (**11**) (1·0 g, 4 m.mole) in anhyd. THF (5 ml). After 1 hr anhyd. t-BuOH (15 ml) was added, followed immediately by Li metal (1·0 g, 0·14 g atom). After 1·5 hr at −33°C, the mixture became white and the NH_3 was removed at 0°C. Saturated NH_4Cl aq and ether were added carefully to the residue and stirred for 30 min at room temperature. The organic layer was separated, dried (Na_2SO_4) followed by removal of the solvent *in vacuo* to give an oil (1·0 g) which showed IR absorption at 1657 (double bond) and 890 (exomethylene) cm^{-1} but no absorptions attributable to an aromatic ring.

Hydrolysis of the crude reduction product (1·0 g) was effected in ether (75 ml)—aqueous oxalic acid (2M, 60 ml) for 22 hr with vigorous stirring at room temperature under N_2. The ethereal layer was washed with $NaHCO_3$, H_2O then dried (Na_2SO_4). Removal of solvent gave crude product (1·0 g). IR ν_{max} 1710, 1650 cm^{-1}. Base catalysed (tBuOK) isomerisation gave a mixture of two compounds IR ν_{max} 1710, 1680 cm^{-1}. Mass spectral parent ions observed at *m/e* 244 and 246.

1-(2-Methoxy-5-methylphenyl)camphenilone (**21**). Method (a): 1-(2-Methoxy-5-methylphenyl)camphene (**11**) (1·0 g) in dry MeOH (45 ml) and CH_2Cl_2 (30 ml) was ozonised at −70°C for 70 min. N_2 was then bubbled

through the solution for 15 min, then triethylphosphite (1·5 ml) was added at −70° and the mixture stirred for 10 min before allowing to warm to room temperature. Removal of the solvent *in vacuo* 40° gave a crude product which was dissolved in pentane washed with H_2O, and the organic layer dried (Na_2SO_4). Removal of the solvent, followed by chromatography of the residue on grade III neutral alumina (30 g), on elution with 25% C_6H_6 in petroleum ether, afforded the arylcamphenilone (**21**) (362 mg; 39%) m.p. 94°C (crystallised from EtOH) $[\alpha]_D^{20}$ + 61° (C. 5%); IR ν_{max} 1732 cm^{-1}; NMR (CCl_4) τ 6·4 (s, 3H), 7·75 (s, 3H), 8·85 (s, 3H), 8·95 (s, 3H). Mass spectral parent ion at *m/e* 258. (Found: C, 78·96; H, 8·69; $C_{17}H_{22}O_2$ requires C, 79·03; H, 8·58%).

Method (b): To arylcamphene (**11**) (15 g) in ether (75 ml), 80% AcOH aq (30 ml) was added OsO_4 (300 mg). After stirring at room temperature for 30 min, $NaIO_4$ (21 g) dissolved in 70% AcOH aq (450 ml) was added slowly to the reaction mixture, which was stirred at room temperature for 14 days. NaI was filtered and the solvent removed *in vacuo*. The crude product was dissolved in ether and H_2S passed through the solution for 30 min. After filtration, the ethereal solution was washed with H_2O and dried (Na_2SO_4). Removal of solvent afforded crude product, which was chromatographed on Grade III neutral alumina (450 g) and eluted with 25% C_6H_6 in petroleum ether to give the arylcamphenilone (**21**) (12·2 g; 81%), fully characterised as the required product of ozonolysis of **11**.

1-(1-*Carbomethoxy-3-oxobutyl*)-*camphenilone* (**12**). A solution of the arylcamphenilone (**21**) (10 g) in a mixture of isopropanol (150 ml) and ether (120 ml) was added to anhyd. liquid NH_3 (1 litre) cooled to −70°C. The solution was rendered homogeneous by addition of more ether (130 ml). Li metal (15 g), as thin strips, was added to the well stirred reaction mixture. After the blue colour had been discharged, the NH_3 was distilled off at 0°. Distilled H_2O was added to the residue and the whole stirred, under N_2, for 20 min. The organic layer was separated and the aqueous layer extracted with ether (2 × 100 ml). The combined ethereal solutions were dried (Na_2SO_4). Removal of the solvent *in vacuo* yielded the crude reduced product (**23**) (10 g). (IR ν_{max} 3500, 1665 cm^{-1}; NMR ($CHCl_3$) τ 4·62 (m, H olefinic), 6·55 (s, 3H), 7·1–7·4 (m, 4H allylic), 8·35 (d, J = lcps, 3H), 9·02 (s, 3H), 9·08 (s, 3H).

This material was dissolved in AR $CHCl_3$ (500 ml) and *tris*triphenylphosphinerhodium chloride (250 mg) added. After refluxing the solution under O_2-free N_2 for 25 min, the solvent was removed *in vacuo* to give crude (**25**) (10 g) as an oil IR ν_{max} 3500, 1658, 1612 cm^{-1}; NMR ($CHCl_3$) τ 4·5 (m, H olefinic) 4·97 (m, H olefinic), 6·45 (s, 3H), 7·5–7·9 (m, 3H allylic), 8·25 (d, J = lcps, 3H), 9·06 (s, 3H), 9·14 (s, 3H). λ_{max} 276 nm.

The conjugated diene **25** was immediately dissolved in dry MeOH (100 ml) and treated with ozone for 4 hr at −70°. After most of the MeOH had been removed *in vacuo* 50% AcOH aq (50 ml) was added to the residue and this mixture stirred at room temperature for 2 hr. The solvent was then removed *in vacuo* and the residue taken up in ether, which was then washed with H_2O and dried (Na_2SO_4). Removal of the solvent gave a residue which was dissolved in acetone (50 ml) and to this well-stirred solution was added Jones reagent[14] (15 ml). After 10 min at room temperature, the solvent was removed *in vacuo* and the crude product of oxidation dissolved in ether, washed with H_2O, then dried (Na_2SO_4). After removal of the solvent the residue was esterified with ethereal CH_2N_2, followed by decomposition of the excess reagent with ethereal AcOH. Removal of solvent gave an oil, which after chromatography over kieselgel (300 g) on elution with 20% EtOAc in C_6H_6 afforded the diketoester (**26**) (4·5 g; 43%) m.p. 118–120° (from heptane). IR ν_{max} 1720 cm^{-1} NMR ($CHCl_3$) τ 6·3 (s, broad, 3H), 7·85 (2s, 3H), 8·95 (s, 6H), 6·6–7·4 (m, 3H). Mass spectral parent ion at *m/e* 266. (Found: C, 67·82; H, 8·37. $C_{15}H_{22}O_4$ requires C, 67·64; H, 8·33%).

2β- *and* 2α-*Carbomethoxy-7:7-dimethyl-4-oxotricyclo*[6.2.1.0^{1,6}] *undec-5:6-ene* (**13**) *and* (**14**). t-BuOK (8·0 g) was added to a solution of the diketo-ester (**26**) (4·2 g) in dry t-BuOH (350 ml) and the reaction mixture refluxed for 5·5 hr under N_2. The solvent was removed *in vacuo* and H_2O added to the residue. The mixture was neutralised with 4N HCl and extracted with ether. The ethereal layer was dried (Na_2SO_4) and the solvent removed *in vacuo*. The crude product was reacted with excess ethereal CH_2N_2 for 15 min at room temperature. After decomposition of the excess CH_2N_2 with ethereal AcOH, the solvent was evaporated to give a crude product (4·0 g), which was carefully chromatographed over kieselgel (150 g).

Elution with 20% EtOAc in C_6H_6 gave the 2α-epimer (**14**) (1·56 g; 40%) m.p. 95° (from hexane) $[\alpha]_D^{20}$ (C, 4·6%) + 204°; IR ($CHCl_3$) ν_{max} 1725, 1660 cm^{-1} UV λ_{max} 243 nm (9650); NMR (CCl_4) τ 4·4 (s, H), 6·30 (s, 3H), 6·93 (m, H), 7·55 (q, 2H), 8·85 (s, 6H). Mass spectral parent ion at *m/e* 248; glc (carbowax packed capillary 25 ft, 20% 30 psi, 220°) R_t 49·4 min. (Found: C, 72·61; H, 8·18 $C_{15}H_{20}O_3$ requires C, 72·55; H, 8·12%).

Further elution with 20% EtOAc in C_6H_6 afforded the 2β-epimer (**13**) (1·10 g) as an oil. $[\alpha]_D^{20}$ (C, 4·8%) + 118°; IR ($CHCl_3$) ν_{max} 1725, 1660 cm^{-1}; UV λ_{max} 246 nm (9070); NMR (CCl_4) τ 4·45 (s, H), 6·40 (s, 3H), 7·00 (t, J = 3·5 cps, H), 7·60 (d, J = 5 cps, 2H), 8·85 (s, 3H), 8·90 (s, 3H); glc (carbowax packed capillary,

20% 25 ft, 30 psi, 220°) R_t 53·5 min. Accurate mass: found 248·142022; $C_{15}H_{20}O_3$ requires 248·141235.

Ethylene thioketal (**29**). To a solution of 2α-carbomethoxy-7,7-dimethyltricyclo [6.2.1.0^{1,6}]undec-5-en-4-one (**14**) (416 mg) in ether (10 ml) was added ethanedithiol (2 ml) followed by freshly distilled BF_3Et_2O etherate (2 ml). The reaction mixture was stirred at room temperature for 1 hr. After removal of solvent, the residue was chromatographed twice over kieselgel (15 g). Elution with 20% EtOAc in C_6H_6 afforded the thioketal (**29**) (512 mg, 94%) m.p. 120–125° (EtOH aq). IR ν_{max} ($CHCl_3$) 1723 cm^{-1}. NMR (CCl_4) τ 4·7 (s, H), 6·33 (s, 3H), 6·62 (m, 4H), 8·95 (s, 6H). Mass spectral parent ion at *m/e* 324. (Found: C, 62·94; H, 7·27; s, 19·63. $C_{17}H_{24}O_2S_2$ requires C, 62·95; H, 7·46; s, 19·73).

Ethylene thioketal (**28**). Prepared as above from 2β-carbomethoxy-7,7-dimethyltricyclo[6.2.1.0^{1,6}]undec-5-en-4-one (**13**) (9·4 g), $BF_3.Et_2O$ (15 ml), ethanedithiol (15 ml) in ether (100 ml). This gave the desired thioketal (**28**) (7·0 g; 60%) as a viscous oil IR ν_{max} 1735 cm^{-1}; NMR (CCl_4) τ 4·55 (s, H), 6·40 (s, 3H), 6·75 (s, 4H), 8·93 (s, 3H) 8·98 (s, 3H). Accurate mass of parent ion at *m/e* 324·122126; $C_{17}H_{24}O_2S_2$ requires 324·121766.

2α-*Carbomethoxy-7,7-dimethyltricyclo*[6.2.1.0^{1,6}]*undec-5-ene* (**31**). The ethylene thioketal (**29**) (512 mg) in absolute EtOH (50 ml) was reflexed under N_2 for 15 min. Raney Ni W.2 slurry (4 ml) was added and the mixture refluxed with continuous stirring under N_2 for 1·5 hr. The solution was filtered and solvent removed to give a crude product, which was chromatographed over kieselgel (15 g). Elution with 10% EtOAc in C_6H_6 gave the olefine (**31**) (332 mg, 90%) as an oil b.p. 70°/0·01 mm; m.p. 30°; IR ($CHCl_3$) 1722 cm^{-1}; NMR (CCl_4) τ 4·78 (t, J = 3 cps, H), 6·35 (s, 3H), 8·98 (s, 6H). Accurate mass of parent ion at *m/e* 234·160009; $C_{15}H_{22}O_2$ requires 234·161971. (Found: C, 76·58; H, 9·46. $C_{15}H_{22}O_2$ requires C, 76·88; H, 9·46%).

2β-*Carbomethoxy-7,7-dimethyltricyclo*[6.2.1.0^{1,6}]*undec-5-ene* (**30**). Prepared as above from thioketal (**28**) (6·0 g), Raney Ni W.2 slurry (40 ml) in abs. EtOH (300 ml). This gave the olefine (**30**) (3·7 g, 90%) as an oil b.p. 180°/0·07 mm. IR ($CHCl_3$) ν_{max} 1727 cm^{-1}; NMR (CCl_4) τ 4·75 (t, J = 3·5, H), 6·40 (s, 3H), 7·30 (t, J = 3·5 cps, H), 8·97 (s, 3H) 9·00 (s, 3H). Accurate mass of parent ion at *m/e* 234·162199 $C_{15}H_{22}O_2$ requires 234·161917.

2α-*Carbomethoxy-5,6-dihydroxy-7,7-dimethyltricyclo*[6.2.1.0^{1,6}]*undecane* (**27**). OsO_4 (400 mg) was added to a solution of the olefine (**31**) (380 mg) in ether (50 ml). After addition of pyridine (0·6 ml), the solution was refluxed gently for 80 hr. The solvent was removed and a solution containing pyridine (6 ml), H_2O (8 ml) and sodium metabisulphite (150 g) was added. After stirring for 2 hr at room temperature H_2O was added and the reaction mixture extraced with ether. The ether layer was dried (Na_2SO_4) and the solvent removed to give a crude product, chromatographed over kieselgel. Elution with 50% EtOAc in C_6H_6 gave the diol (**27**) (344 mg, 86%) IR ($CHCl_3$) ν_{max} 3570 (broad), 1720 cm^{-1}; NMR (CCl_4) τ 5·80 (m, H), 6·38 (s, 3H), 6·92 (m, H), 7·60 (broad s, 2H removed by D_2O), 8·92 (s, 3H), 9·00 (s, 3H). Mass spectral parent ion at *m/e* 268. (Found: C, 67·29; H, 9·23. $C_{15}H_{24}O_4$ requires C, 67·13; H, 9·02%).

The diol (**27**) (28 mg) in pyridine (6 ml) and triethylamine (3 ml) was treated with methanesulphonyl chloride (460 mg). After 72 hr at room temperature under N_2, the solvent was removed and H_2O added. The ether extract was washed with H_2O and dried (Na_2SO_4). Removal of the solvent afforded a crude mesylate, which was chromatographed over kieselgel (15 g). Elution with 20% EtOAc in C_6H_6 yielded the mesylate (**35**) (304 mg, 84%) m.p. 114–116° (hexane) which proved to be fairly unstable. IR ($CHXl_3$) ν_{max} 3500, 1722, 1365, 1185 cm^{-1}; NMR ($CDCl_3$) τ 4·66 (m, H), 6·30 (s, 3H), 6·92 (s, 3H), 7·72 (s, H removed by D_2O), 8·87 (s, 3H), 8·94 (s, 3H). Mass spectrum did not give a parent ion at *m/e* 346 but an ion at *m/e* 250, corresponding to loss of the methanesulphonyl group. (Found: C, 55·15; H, 7·75; $C_{16}H_{26}O_6S$ requires C, 55·48; H, 7·57%).

2β-*Carbethoxy-5,6-dihydroxy-7,7-dimethyltricyclo*[6.2.1.0^{1,6}]*undecane* (**6**). Prepared as above from the olefine (**30**) (3·7 g) using OsO_4 (4·2 g), pyridine (8 ml) in ether (200 ml). After 80 hr reflux the complex was decomposed by water (80 ml), pyridine (50 ml) containing sodium metabisulphite (11 g). Isolation of the product as for **27** afforded the required diol (**6**) (3·3 g, 80%) m.p. 111–112° (hexane) IR ($CHCl_3$) ν_{max} 3550, 1725 cm^{-1}; NMR ($CDCl_3$) τ 6·35 (s, 3H), 7·65 (s, 3H removed by D_2O), 8·80 (s, 3H), 9·05 (s, 3H). Mass spectral parent ion at *m/e* 268. (Found: C, 67·39; H, 9·23. $C_{15}H_{24}O_4$ requires C, 67·13; H, 9·02%).

The diol (**6**) (3.3 g) was converted into the mesylate (**34**) on treatment with methanesulphonyl chloride in pyridine (50 ml) and triethylamine (25 ml) at room temperature. Isolation of the product, as for **35**, afforded the required monomesylate **34** (3.60 g, 85%). IR ($CHCl_3$) ν_{max} 3600; 1723, 1375, 1175 cm^{-1}; NMR ($CDCl_3$) τ 4·97 (m, H), 6·35 (s, 3H), 6·95 (s, 3H), 7·37 (m, H), 7·85 (s, H, removed by D_2O), 8·80 (s, 3H), 9·03 (s, 3H). Mass spectrum did not give a parent ion at *m/e* 346 but an ion at *m/e* 250, corresponding to loss of the methanesulphonyl group.

2α-Carbomethoxy-7,7-dimethyltricyclo[6.2.1.0^{1,6}]*undecan-6-one* (**33**). A solution of the mesylate (**35**) (65 mg) in a mixture of pyridine (3 ml) and triethylamine (1·5 ml) was refluxed under N_2 for 1·5 hr. The solvent was removed and the residue extracted with ether, washed with H_2O then dried (Na_2SO_4). Removal of solvent followed by chromatography of the residue over kieselgel (15 g) and elution with 5% EtOAc in C_6H_6 gave the rearranged ketone **33** (44 mg, 93%) m.p. 85° (subl.) $[\alpha]^{20}$ (C, 2·7%)—47°, ORD in diethyl ether (C O. 1%) $[\phi]_{314}$ +5250°, $[\phi]_{259}$ −6874°; I.R. ($CHCl_3$) ν_{max} 1725, 1700 cm^{-1}; NMR ($CDCl_3$) τ 6·36 (s, 3H), 7·14–7·52 (m, 2H), 8·85 (s, 3H), 8·93 (s, 3H); Mass spectral parent ion at *m/e* 250; glc (carbowax packed capillary 20%, 25 ft, 30 psi, 220°) R_t 27·08 min. (Found: C, 71·96%; H, 8·85. $C_{15}H_{22}O_3$ requires C, 71·97; H, 8·86%). Lit.,[16,20] m.p. 78–78·5°; ORD ϕ 314 + 6925°, ϕ_{259} − 9425°; IR (KBr) ν_{max} 1737, 1713 cm^{-1}; NMR (CCl_4) τ 6·38 (s, 3H), 8·82 (s, 3H), 9·00 (s, 3H).

Base treatment of **33**, using t-BuOK in refluxing t-BuOH, afforded a mixture consisting of four main products by glc analysis (carbowax packed capillary, 20%, 25 ft, 30 psi, 220°) R_t 23·5 (**32**), 26·7 (**33**), 50·0 and 54·5 min.

2β-Carbomethoxy-7,7-dimethyltricyclo[6.2.1.0^{1,5}]*undecan-6-one* (**32**). The mesylate (**34**) (440 mg) was rearranged in refluxing pyridine (10 ml) and triethylamine (5 ml) for 7 hr under N_2. The solvent was removed and H_2O added. Ether extraction followed by chromatography of the crude product over kieselgel (30 g) gave, on elution with 5% EtOAc in C_6H_6, the desired ketone (**32**) (290 mg, 91%) m.p. 100–102° (from hexane); $[\alpha]_D^{20}$ (C. 5·6%) + 126°; ORD in diethyl ether (C. 1%) $[\phi]_{315}$ + 7750°, $[\phi]_{273}$ − 5500°, a + 132·5, $[\phi]_{305-308}$ + 5625 (sh.), $[\phi]_{230}$ + 870°; IR ($CHCl_3$) ν_{max} 1720, 1703 cm^{-1}; NMR ($CDCl_3$) τ 6·28 (s, 3H) 6·87 (m, H), 7·30 (m, H), 8·82 (s, 3H), 8·96 (s, 3H); Mass spectral parent ion at *m/e* 250; glc (carbowax packed capillary 20%, 25 ft, 30 psi, 220°) R_t 23·75 min. (Found: C, 72·18; H, 9·08. $C_{15}H_{22}O_3$ requires C, 71·97; H, 8·86%).

This synthetic product was identical in every respect with authentic material, prepared from zizanoic acid (**5a**) kindly supplied by Dr. E. Klein, DRAGOCO, Holzminden, W. Germany. [Lit.,[18] m.p. 103° $[\alpha]_D^{20}$ (dioxane, c. 1%) + 129·8°; ORD $[\phi]_{312·5}$ + 7200°, $[\phi]_{273·5}$ − 6100°, a + 133.]

Base treatment of **32**, using t-BuOK in refluxing t-BuOH, afforded a mixture consisting of four main products by glc analysis (carbowax packed capillary, 20%, 25 ft, 30 psi, 220°) R_t 23·6 (32), 27·4 (**33**), 49·4 and 52·8 min.

2β-Carboxy-7,7-dimethyltricyclo[6.2.1.0^{1,5}]*undecan-6-one* (**32a**). LAH (231 mg) was added to a solution of (**32**) (157 mg) in anhyd. ether (30 ml) and the reaction mixture stirred at room temperature for 4 hr. A saturated aqueous solution of sodium potassium tartrate (30 ml) was carefully added then the mixture filtered through celite. The ethereal extract was dried (Na_2SO_4) and solvent removed to give the required 7,7-dimethyl-2β-hydroxymethyltricyclo[6.2.1.0^{1,5}]undecan-6-ol. IR ($CHCl_3$) ν_{max} 3650, 3470 cm^{-1}. NMR ($CDCl_3$) τ 6·10–6·70 (m, 3H), 8·13 (s, 2H removed by D_2O), 8·97 (s, 3H), 9·07 (s, 3H).

This crude diol was dissolved in acetone (10 ml) and Jones' reagent (0·9 ml) added rapidly with stirring. After 15 min the solvent was removed and H_2O added to the residue. The aqueous solution was extracted with EtOAc and the organic layer dried (Na_2SO_4). Removal of solvent gave crude product, was taken up in ether and extracted with saturated $NaHCO_3$aq. The extracts were combined and acidified with 2N HCl. This solution was extracted with EtOAc. After washing with H_2O, drying (Na_2SO_4) and removal of solvent, afforded the desired acid (**32a**) (132 mg, 96%). IR ($CHCl_3$) ν_{max} 1700 cm^{-1}; NMR ($CDCl_3$) τ − 1·25 (s, H), 6·85 (m, H), 7·25 (m, H), 8·80 (s, 3H), 8·95 (s, 3H); mass spectral parent ion at *m/e* 236.

A portion of this acid was esterified with ethereal CH_2N_2 to give the corresponding ester, which was identical in all respect to authentic **32**.

2β-Carboxy-6β-7,7-trimethyltricyclo[6.2.1.0^{1,5}]*undecan-6α-ol* (**39a**). A solution of MeMgBr in ether (3 ml) was prepared from Mg (200 mg) and MeI (0·4 ml). To this solution, at room temperature, was added the acid **32a** (95 mg) in ether (3 ml). After the initial exothermic, the mixture was stirred for 12 hr under reflux. The complex was decomposed, at 0°, by saturated NH_4Claq. The organic layer was separated, the aqueous layer acidified and extracted with EtOAc. The organic extracts were combined and dried (Na_2SO_4). Removal of solvent gave a crude product, taken up in ether and extracted with saturated $NaHCO_3$. The extracts were combined and acidified, followed by EtOAc extraction, yielding the desired acid (**39a**) (85 mg, 85%). IR ($CHCl_3$) ν_{max} 3500, 1700 cm^{-1}; NMR ($CDCl_3$)τ 7·40 (m, H), 8·95 (s, 3H), 9·03 (s, 3H), 9·08 (s, 3H). Accurate mass of parent ion at *m/e* 252·173045; $C_{15}H_{24}O_3$ requires 252·172534.

Methylisozizanoate (**37**). To a solution of **39a** (45 mg) in C_6H_6 (20 ml) was added silica (10 g, Grace) and the slurry stirred under reflux for 5 hr. The silica was filtered, washed with EtOAc. Removal of the solvent from the combined filtrates afforded a crude product (41 mg), which was esterified using ethereal CH_2N_2. The crude ester was purified by chromatography over kieselgel to give methylisozizanoate (**37**) (40 mg,

95%) $[\alpha]_D^{20}$ (C. 3·8%) + 37·5°; IR ($CHCl_3$) ν_{max} 1720 cm^{-1}; NMR ($CDCl_3$) τ 6·38 (s, 3H), 7·29 (m, H), 8·53 (t, 3H), 9·00 (s, 3H), 9·01 (s, 3H); glc (carbowax coated capillary 50 ft, 15 psi, 150°) R_t 11·52 min, (SE 30 packed capillary, 25 ft, 5%, 30 psi, 220°) R_t 21·04 min. This synthetic product proved to be identical in all respects with authentic methyl isozizanoate (**37**)[19] prepared from methyl zizanoate (**5**) by acid treatment.[21]

Methyl zizanoate (**5**). The acid **39a** (169 mg) was esterified using ethereal CH_2N_2. To a solution of the ester **39** in pyridine (5 ml) was added $POCl_3$ (1 ml). The reaction mixture was heated at 86° for 24 hr and decomposed with ice. The ether extracts were combined and the solvent removed. The crude product was chromatographed over silica impregnated with 30% w/w $AgNO_3$ nitrate (30 g). Elution with C_6H_6 gave methyl isozizanoate (58 mg, 37%) identical with authentic material. Further elution with C_6H_6 afforded methyl zizanoate (**5**) (40 mg, 26%) $[\alpha]_D^{20}$ (C. 2·1%) + 47°; IR ($CHCl_3$) ν_{max} 1720, 912 (*exo* methylene) cm^{-1}; NMR ($CDCl_3$) τ 5·27 (t, H), 5·40 (t, H), 6·33 (s, 3H), 7·36 (m, 2H) 8·94 (s, 3H), 8·95 (s, 3H); glc (carbowax coated capillary, 50 ft, 15 psi, 150°) R_t 14·08 min, (SE 30 packed capillary, 25 ft, 5%, 30 psi, 220°) R_t 22·48 min. This synthetic product proved to be identical in all respects with authentic methyl zizanoate (**5**) prepared from zizanoic acid (**5a**) and CH_2N_2.

Acknowledgements—We thank the University of Liverpool for a research award to D. F. Mac. S. The skilled technical assistance of Mr. D. Harrison and Mr. J. Roberts are gratefully acknowledged. We also thank Professor W. Parker (Stirling University) for ORD measurements performed at the University of Ulster.

REFERENCES

[1] K. Endo and P. De Mayo, *Chem. Comm.* 89 (1967)
[2] J. A. Marshall, N. H. Anderson and P. C. Johnson, *J. Amer. Chem. Soc.* **89**, 2748 (1967)
[3] R. Sakuma and A. Yoshikosi, *Chem. Comm.* 41 (1968)
[4] D. F. MacSweeney, R. Ramage and A. Sattar, *Tetrahedron Letters* 557 (1970)
[5] C. R. Hughes, D. F. MacSweeney and R. Ramage, *Tetrahedron*, in press
[6] D. C. Kleinfelter, R. W. Aaron, T. J. Gerreisen, J. M. Miller and T. B. Bennett, *J. Org. Chem.* **32**, 3521 (1967)
[7] A. J. Birch, *Quart. Rev.* **4**, 69 (1950)
[8] A. L. Wilds, N. A. Nelson, *J. Amer. Chem. Soc.* **75**, 5360 (1953)
[9] H. L. Dryden, G. M. Webber, R. R. Burtner and J. A. Cella, *J. Org. Chem.* **26**, 3137 (1961)
[10] R. Pappo, D. S. Allen, R. V. Lemieux and W. S. Johnson, *Ibid.* **21**, 478 (1956)
[11] P. S. Bailey, *Br. Dtsch. Chem. Ges.* **88**, 795 (1955)
[12] G. Ourisson and A. Rassat, *Tetrahedron Letters* 16 (1960)
[13] A. J. Birch and G. S. R. Subba Rao, *Ibid.* 3797 (1968)
[14] K. Bowden, I. M. Heilbron, E. R. H. Jones and B. C. L. Weedon, *J. Chem. Soc.* 39 (1946)
[15] F. Kido, H. Uda and A. Yoshikoshi, *Tetrahedron Letters* 1247 (1968)
[16] F. Kido, H. Uda and A. Yoshikoshi, *Chem. Comm.* 1335 (1969)
[17] R. M. Coates, R. F. Farney, S. M. Johnson and I. C. Paul, *Ibid.* 999 (1969)
[18] F. Kido, H. Uda and A. Yoshikoshi, *Tetrahedron Letters* 2815 (1967)
[19] H. Komae and I. C. Nigam, *J. Org. Chem.* **33**, 1771 (1968)
[20] N. Hanayama, F. Kido, R. Sakuma, H. Uda and A. Yoshikoshi, *Tetrahedron Letters* 6099 (1968)
[21] H. Komae and I. C. Nigam, *J. Pharm. Sci.* **56**, 1299 (1967)