Tetrahedron. Vol. 31, pp. 689 to 694. Pergamon Press 1975. Printed in Great Britain

STEREOCHEMICAL STUDIES OF TRICYCLO[6.2.1.0.^{1,6}]UNDECANES—II

STEREOCHEMISTRY OF ISOLONGIFOLENE EPOXIDE

C. W. GREENGRASS and R. RAMAGE*

The Robert Robinson Laboratories, University of Liverpool, Liverpool L69 3BX

(*Received in the UK* 17 *June* 1974; *Accepted for publication* 16 *August* 1974)

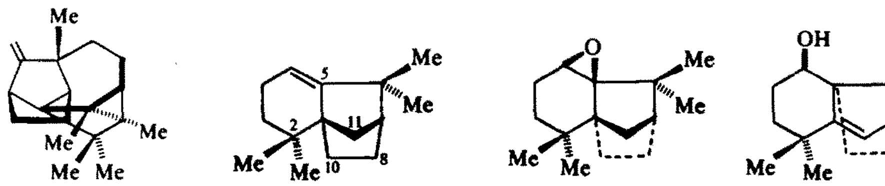
Abstract—The stereochemistry of epoxidation and hydroboration of isolongifolene has been elucidated by comparison with the chemistry of the C_2-desmethyl epoxides and their transformation products. The main factors controlling the stereochemistry of epoxidation of isolongifolene are the bicycloheptyl moiety and the C-2β methyl substituent.

Acid-catalysed isomerisation of the sesquiterpene longifolene (1) produces partially racemic isolongifolene (2) having the tricyclo[6.2.1.0.^{1,6}]undecane skeleton.[1] There has been considerable controversy concerning the stereochemistry of isolongifolene epoxide and subsequent rearrangement products. The original β-epoxide structure (3) was derived mainly on the basis of the acid-catalysed rearrangement to the olefinic alcohol (4) since it was assumed that the rearrangement would be concerted and require a *trans* relationship of the groups involved. This assignment was contested[3] on the basis of NMR chemical shift data of epimeric alcohols (8 and 9) produced by the route shown in Scheme I. The question of isolongifolene epoxide has now been settled in favour of 5 by X-ray crystallography.[5] Our stereochemical studies of tricyclo-[6.2.1.0.^{1,6}]undecane derivatives independently support this assignment since we have shown that olefins **10** and **14** undergo preferential *endo* epoxidation and that, further, acid-catalysed rearrangement of the *endo* epoxides gave the analogous rearrangement product **13** to that found in the case of isolongifolene epoxide. In the desmethyl series the final deprotonation proceeds to give the tetrasubstituted double bond which is precluded in rearrangement of isolongifolene epoxide (5). Thus the *cis* relationship of the groups participating in the rearrangement can be explained by a non-concerted process and is due to stereoelectronic factors involving overlap of the migrating group with the vacant p-orbital of the carbonium ion in the intermediate (17) produced by cleavage of the epoxide ring. An analogous rearrangement was observed when isolongifolene (2) was treated with NBS in aqueous dimethoxyethane (DME). The product (19) was the result of *endo* attack by Br^+ on the olefin followed by rearrangement of the postulated intermediate (18).

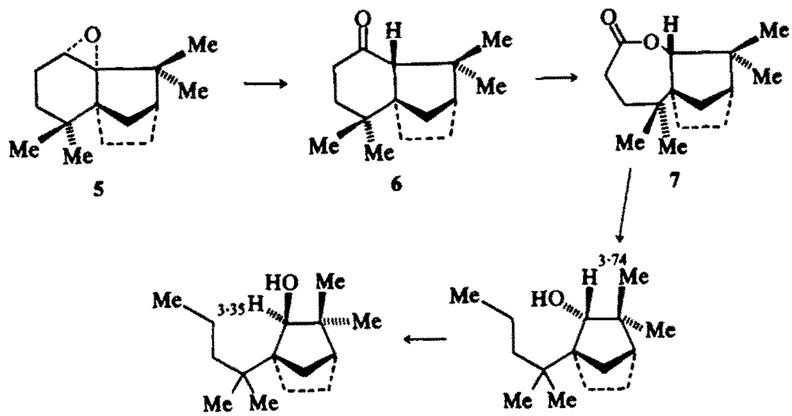
Other approaches to the problem of isolongifolene epoxide stereochemistry utilised reactions, and hence the stereochemistry, of the ketone [νmax (CCl_4) 1710 cm^{-1}] produced by kinetically controlled acid-catalysed rearrangement of the epoxide. This ketone could be epimerised to the more thermodynamically stable ketone [νmax (CCl_4) 1695 cm^{-1}] which could also be prepared by hydroboration of isolongifolene (2) followed by oxidation under conditions which would not epimerise the ketone produced. Previous work[6] in the tricyclo-[6.2.1.0.^{1,6}]undecane series suggested that B_2H_6 would attack isolongifolene from the *endo* face to give the alcohol (**20**) and then the ketone (**21**). Thus the kinetic product should have the structure **6** consistent with rearrangement of *endo* epoxide. These alternative structures **6** and **21** could be differentiated by comparison of the NMR and IR data of the partially racemic isolongifolene ketones with the optically active ketones (**23–26**) belonging to the desmethyl series derived from the olefins (**10** and **14**).

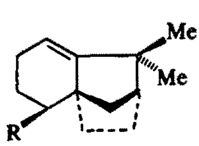
Comparison of the NMR of the Me signals of the desmethyl series (**10 and 14**) with isolongifolene (2) using the easily identifiable secondary Me resonances as a probe allows an assignment to be made of the two quaternary 2α-Me and 2β-Me groups in siolongifolene. (Table 1). The $C_7\alpha$ and $C_7\beta$ quaternary Me groups may be differentiated tentatively on the basis that the *endo*-Me group of the bicyclo[2.2.1]heptyl system should experience a slight shielding effect relative to the corresponding *exo*-Me group.[7] An important requirement for this comparison is that the cyclohexene ring has the same conformation in all three olefins.† Table 2 shows the NMR and IR data of the desmethylisolongifolene ketones of known absolute stereochemistry and the two ketones derived from isolongifolene epoxide. The IR CO frequency of the 5β-H ketones (**24, 26**) is found at 1712 cm^{-1} whereas the 5α-H ketones (**23, 25**) have a CO frequency

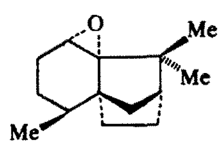
†It has been shown[8] that the esters 11 and 15 have the COOMe group axial and equatorial respectively indicating that the cyclohexene ring has the half-chair conformation in both. Conformational change to the half-boat form would place the C_2-β substituent in a pseudo-equatorial conformation but would introduce eclipsing of the C_2-β group with the C-11 methylene.

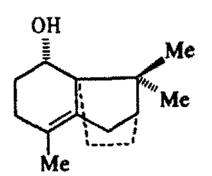

1 2 3 4

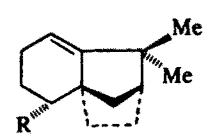
Scheme 1.

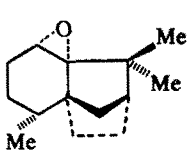

5 6 7 8 9

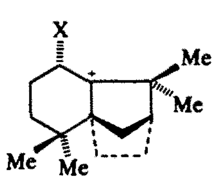

10; R = Me
11; R = COOMe

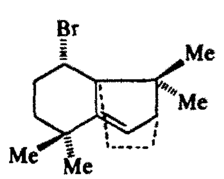

12

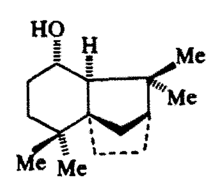

13

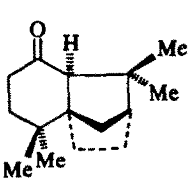

14; R = Me
15; R = COOMe

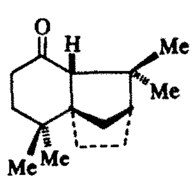

16


17; X = OH
18; X = Br


19


20

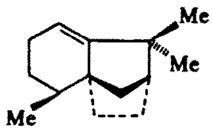
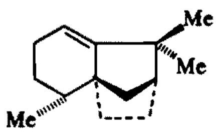
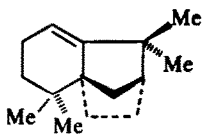

21


6

at 1700 and 1695 cm^{-1} respectively. These CO frequencies compare well with those found for the kinetic and thermodynamic products. In the NMR of the 5α-H ketones (23, 25) the 7β-Me, which is in the deshielding zone of the CO group, should be deshielded relative to 7α-Me whereas the reverse holds for the 5β-H series (24, 26). Comparison of the Me resonances of 23 with 24 and 25 with 26 shows this deshielding effect to be 0·22 ppm. Epimerisation of 24 to 23 is accompanied by an upfield shift of the C_2-β Me resonance. This effect is observed on equilibration of the ketone produced from isolongifolene epoxide under kinetically controlled conditions supporting structure 6 for the less stable epimer and the *endo* epoxide structure 5 for isolongifolene epoxide.

Further evidence for the *endo* epoxide came from consideration of the NMR of the Me signals of the tertiary

Table 1.

	Me resonance (ppm)		
	$C_2\beta$	$C_2\alpha$	$C_7\alpha/C_7\beta$
 10	0·86 (d, J = 7 Hz)		0·96/1·02
 14		0·96 (d, J = 7 Hz)	1·01/1·05
 2	0·83	0·95	0·95/1·03

alcohol **29** derived from isolongifolene epoxide along with the tertiary alcohols **27** and **28** (Table 3). Comparison of **27** and **28** shows the effect of *cis* 1-3 diaxial relationship of Me and OH groups on the Me resonance. Because of the secondary Me (d, 7 Hz) this deshielding (0·15 ppm) can be clearly observed. The NMR of the Me signals found for the tertiary alcohol **29** derived from isolongifolene epoxide was in very good agreement with the data predicted for structure **29** by comparison of the NMR signals for **27** and **28**.

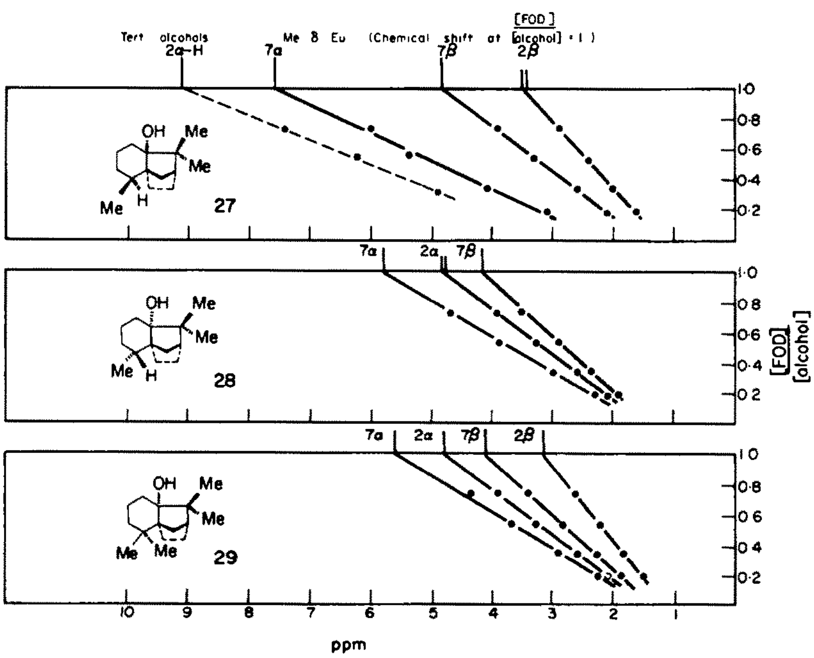
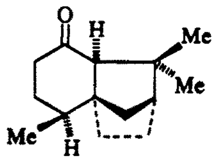
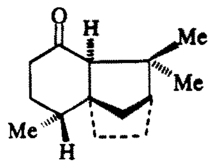
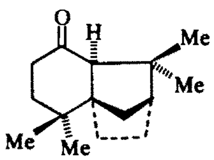
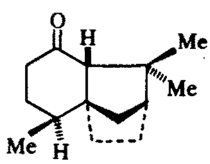
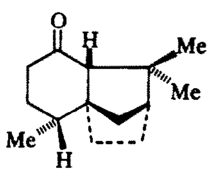
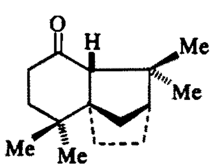


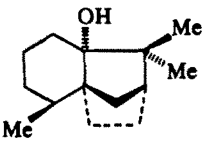
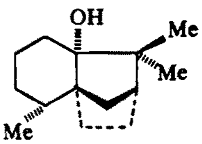
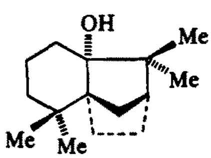
Fig 1.

Table 2.

Compound	CH$_3$ resonance (ppm)				Carbonyl IR frequency (cm^{-1})
 23	1·17 $_7\beta$-Me	•0·98 (d, J = 7 Hz) $_2\beta$-Me	0·96 $_7\alpha$-Me		1700
 25	1·15 $_7\beta$-Me	0·98 (d, J = 7 Hz) $_2\alpha$-Me	0·93 $_7\alpha$-Me		1695
 21 Thermodynamic Product	1·19 $_7\beta$-Me	0·98 $_7\alpha$-Me	0·92 $_2\alpha/\beta$-Me	0·92	1695
 24	1·20 $_7\alpha$-Me	1·16 (d, J = 7 Hz) $_2\beta$-Me	0·98 $_7\beta$-Me		1712
 26	1·22 $_7\alpha$-Me	1·00 $_7\beta$-Me	0·99 (d, J = Hz) $_2\alpha$-Me		1712
 6 Kinetic Product	1·20 $_2\beta$-Me	1·20 $_7\alpha$-Me	1·02 $_2\beta$-Me	0·98 $_7\beta$-Me	1710

The stereochemical assignment for **29** and the close relationship with **28** was confirmed by NMR spectra shifted by four different concentrations of tris - (111,22,33- heptaflour - 7,7 - dimethyloctane - 4,6 - dionato) - europium 111 [Eu(FOD)$_3$] up to a maximum ratio of shift reagent to alcohol of 0·75 : 1. The chemical shifts of the resolved resonances were plotted against the ratio of shift reagent to alcohol. Extrapolation to equimolar ratios of shift reagent to alcohol gave δ Eu values for the Me groups (Fig 1). In the case of the C$_2$-β Me tertiary alcohol **27** the axial C$_2$-α H is *cis* 1-3 diaxial to the OH which complexes with the shift reagent and shows a large δ Eu value (9·1 ppm) not observed for the C$_2$-α Me tertiary alcohol **28**. The C$_2$-αH was assigned by spin decoupling on irradiation at the frequency of the C$_2$-β Me group. In the qualitative application of the McConnell

Table 3.

	$C_2\alpha$ Me	$C_7\alpha/\beta$ Me	$C_2\beta$ Me
 27		0·91/0·91	0·87 d, J = 7
 28	1·02 d, J = 7	0·91/0·87	
 29	1·02	0·91/0·87 Predicted	0·87
	0·98	0·91/0·88 Found	0·85

$\Delta\delta$ ($C_2\alpha$-Me—$C_2\beta$—Me) = 0·15 ppm.

relationship[11] describing dipolar pseudocontact lanthanide shifted NMR spectra the dominant term is the distance between the Eu atom and the group whose shift is under consideration. This would predict the magnitude of the δ Eu values for the Me resonances in the series **27**, **28** and **29** to be $7\alpha > 2\alpha > 7\beta > 2\beta$. As before the doublet Me resonances of the 2α-Me and 2β-Me groups in **27** and **28** simplify the spectral assignments. From Fig 1 it may be seen that the three Me groups in **29** which have the greatest δ Eu values are in very good agreement with those observed in the C_2-α Me series (**28**). The fourth Me in **29** is therefore the C_2-β Me and, as expected, suffers the smallest induced shift. In the case of the C_2-β Me alcohol (**27**) the absence of 1-3 diaxial interaction of Me with the OH results in more efficient complex formation compared with **28** and **29** as evidenced by greater shifts of the 7α and 7β-Me signals. As before the C_2-β Me is least effected by the shift reagent and exhibits a δ Eu value close to that found in **29**.

Thus the good correlation of (a) isolongifolene ketones with the known desmethyl analogues and (b) the tertiary alcohol formed by reduction of isolongifolene epoxide with the known desmethyl alcohol (**28**) clearly shows isolongifolene epoxide to be **5** resulting from preferred *endo* attack by peracid.

EXPERIMENTAL

The general experimental conditions are as reported in the previous publication. Isolongifolene, isolongifolene epoxide and isolongifolene ketones (**6** and **21**) were supplied by Bush Boake Allen Ltd. Tris (111,22,33 - heptafluor - 7,7 - dimethyloctane - 4,6 - dianato) - europium III [$Eu(FOD)_3$] was supplied by Fluorochem Ltd.

5 - Oxo - 6αH - isolongifolane (**21**)

(a) *Via hydroboration.* Reaction carried out under N_2.1MB_2H_6 in THF (2 ml, 2 mmole) was added to **2** (300 mg, 1·4 mmole) in anhyd THF (6 ml). The soln was stirred at room temp for 16 h then the excess hydride was decomposed by H_2O. 3N NaOH (2 ml) was added followed by slow addition of 30% H_2O_2 (1 ml) and the mixture was stirred 2 h before being diluted with brine. The aqueous layer was extracted with Et_2O after which the combined organic layer was washed with brine and dried ($MgSO_4$). Removal of the solvent followed by chromatography over silica (10 g) gave **20** (243 mg, 72%) on elution with 20% Et_2O in petrol, νmax ($CHCl_3$) 3600, 3450 cm^{-1} (NMR (CCl_4) δ 0·85 (3H, S), 0·89 (3H,S), 1·02 (3H,S), 1·08 (3H,S), 3·40 (H,m).

The alcohol **20** (107 mg, 0·46 mmole) in Et_2O (4 ml) was stirred for 2·5 h with 1 M chromic acid (0·3 ml) then diluted with Et_2O. The Et_2O layer was washed with $NaHCO_3$ aq, brine and dried ($MgSO_4$). Removal of the solvent followed by chromatography over silica (5 g) gave the known **21** (75 mg, 70%) on elution with 10% Et_2O in petrol. The product was identical with authentic material by IR, NMR and GLC comparison, νmax (CCl_4) 1695 cm^{-1}, NMR (CCl_4) δ 0·92 (6H,S), 0·98 (3H,S), 1·19 (3H,S), GLC 10, 10% carbowax, 200°, 25 psi, Rt 9 min.

(b) *Via epimerisation of* **6**. 70% $HClO_4$ aq (2 drops) was added to **6** (20 mg) in CCl_4 (1 ml) and stirred for 2 h then the soln was diluted with pentane, washed $NaHCO_3$ aq and brine. The soln was dried ($MgSO_4$) and the solvent removed to give **21** (20 mg). GLC analysis indicated 5% of the starting 6βH epimer **6**.

6α-Hydroxyisolongifolane (**29**). Isolongifolene epoxide **5** (728 mg, 3·3 mmole) in anhyd Et_2O (10 ml) was added to a stirred soln of LAH (400 mg, 10·5 mmole) in anhyd Et_2O (15 ml). The soln was stirred under reflux for 4·5 h then cooled to room temp and the excess hydride decomposed using saturated Rochelle salt soln. The Et_2O soln was filtered through celite and dried ($MgSO_4$). Removal of the solvent followed by chromatography of the crude product over silica (40 g) gave, on elution with 10% Et_2O in pentane, the tert alcohol **29** (400 mg, 55%). Recrystallisation from pentane gave **29** as colourless plates, m.p. 68·5–69·5°; νmax ($CHCl_3$) 3600, 3450 cm^{-1}; NMR (CCl_4) δ 0·85 (3H,S), 0·88 (3H,S), 0·91 (3H,S), 0·98 (3H,S); mass spec m/e 222 (M^+), 208, 204; GLC 9, 7% carbowax, 150°, 20 psi Rt 8 min. (Found C, 81·19; H, 11·86. $C_{15}H_{26}O$ requires: C, 81·02; H, 11·79%).

2α - Bromo - 5,5 - dimethyl - 11,11 - dimethyltricyclo-[6.2.1.0[1,6]]undec - 6 - ene (**19**) NBS (360 mg, 2·02 mmole) was added over 15 min to a stirred soln of **2** (408 mg, 2 mmole) in DME (4·5 ml)/H_2O (0·6 ml). The mixture was stirred under N_2 for 19 h in the dark. Brine and Et_2O were added and the Et_2O layer was washed with brine and dried ($MgSO_4$). Removal of the solvent gave a partially crystalline residue which was triturated with pentane and filtered. The filtrate concentrated *in vacuo* to give a yellow oil (630 mg) which was chromatographed over silica (15 g). Elution with petrol gave a colourless oil (425 mg, 75%) which was identified as the rearranged bromide, b.p. 110°/0·1 mm; νmax ($CHCl_3$) 1000, 970, 950, 900, 880, 860, 840 cm^{-1}; NMR (CCl_4) δ 0·83 (3H,S), 0·94 (3H,S), 1·04 (3H,S), 1·09 (3H,S), 4·24 (H, q; J = 8, 8·5 Hz), 5·60 (H, d J = 3·5 Hz); mass spec m/e 288·0902 (2·7%, M^+), $C_{15}H_{23}{}^{81}Br$ (−22); 282·0924 (1·8), $C_{15}H_{23}{}^{79}Br$ (−21) 203·1842 (100). $C_{15}H_{23}$ (−20). (Found C, 63·42; H, 8·36. $C_{15}H_{23}Br$ required C, 63·70; H, 8·18%).

Acknowledgements—We wish to thank S. R. C. for a postgraduate award to C. W. G. and are indebted to Dr. P. Scopes, Westfield

College for C. D. measurements. We also thank Mr. A. J. Curtis and Dr. R. Ansari (Bush Boake Allen Ltd.) for samples and exchange spectral data.

REFERENCES

[1]R. Ranganathan, V. R. Nayak, S. T. Santhanakrishnan and Sukh Dev, *Tetrahedron* **26**, 621 (1970)

[2]L. K. Lala, *J. Org. Chem.* **36** 2560 (1971)

[3]E. H. Eshinasi, G. W. Shaffer and A. P. Bartels, *Tetrahedron Letters* 3523 (1970)

[4]G. Mehta and S. K. Kapoor, *Ibid.* 497 (1973)

[5]J. A. McMillan, I. C. Paul, V. R. NAyak and Sukh Dev, *Ibid.* 419 (1974)

[6]C. W. Greengreass, R. Ramage, A. F. Cameron and H. J. Hair, *Tetrahedron* **31**, 679 (1975)

[7]L. M. Jackman and S. Sternhell, *Applications of Nuclear Magnetic Resonances Spectroscopy in Organic Chemistry* (2nd Ed.) p. 78. Pergamon Press, Braunschweig (1969)

[8]D. F. MacSweeney and R. Ramage, *Tetrahedron* **27**, 1481 (1971)

[9]L. M. Jackman and S. Sternhell, *Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry* (2nd Ed) p. 88. Pergamon Press, Braunschweig (1969)

[10]R. F. Zurcher, *Helv. Chim. Acta* **46**, 2054 (1963)

[11]H. M. McConnell, R. E. Robertson, *J. Chem. Phys.* **29**, 1361 (1958)