# Studies on Terpenes. Part II.[1] Elaboration of 9-Methyl-6-*p*-tolyl-7-oxatricyclo[4,3,0,$0^{3,9}$]nonane into (+)-(1*R*,3*S*)-3-Isopropenyl-1-*p*-tolylcyclopentane-1-carboxylic Acid, a Model for Sesquiterpene Synthesis

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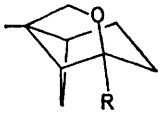
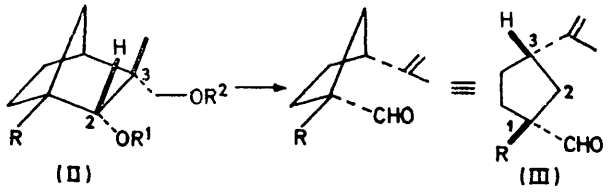
The non-enolisable ketone 3-methyl-2-oxo-1-*p*-tolylnorbornan-3α-ylmethyl toluene-*p*-sulphonate (IX) undergoes fragmentation on treatment with base to the title cyclopentanecarboxylic acid derivative (XI), a model for the synthesis of spiro[4,5]decane sesquiterpenes [(IV)—(VII)].

PREVIOUSLY we described the rearrangement of 7-oxatricyclo[4,3,0,$0^{3,9}$]nonanes (I) into 8-substituted 1,3,3-trimethylnorbornane derivatives (II).[1] In effect this transformation converts a masked 1,4-diol (tetrahydrofuran derivative) into a 1,3-diol system. The 1,3-diol system of functionality maybe used in a fragmentation reaction to break the C(2)–C(3) bond in structure (II) (Scheme). The resulting cyclopentane (III) contains



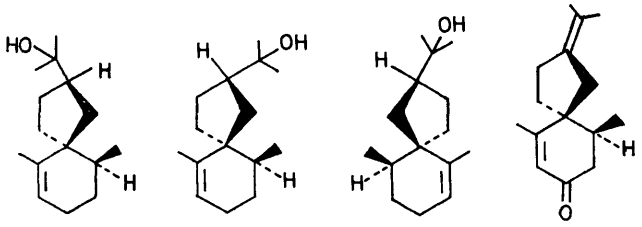
(I)



(II) (III)

SCHEME

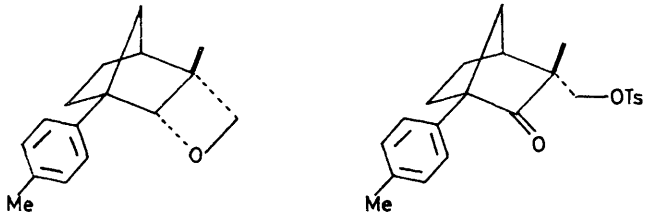
two chiral centres of defined absolute configuration [derived from (—)-pin-2(10)-ene], the tetrasubstituted centre C-1 being particularly difficult to construct by conventional synthetic methods. Its stereochemical relationship to the spiro[4,5]decane sesquiterpenes [2]



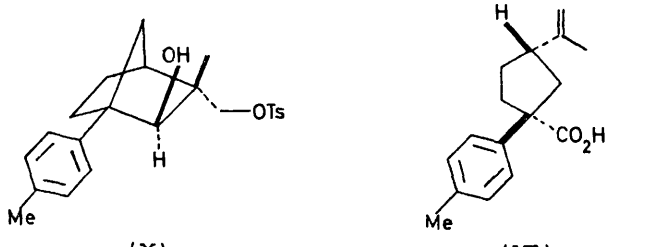
(IV) (V) (VI) (VII)

(—)-hinesol (IV), agarospirol (V), and (+)-β-vetivone (VII) is as follows. If R in structure (III) contained the methyl group attached to an $sp^3$-hybridised carbon atom and the aldehyde were converted into a methyl group attached to an $sp^2$ carbon system then the resulting structure (after formation of the cyclohexene ring) would correspond to (VI), which is the mirror image of (—)-hinesol (IV). Interchanging the $sp^3$-methyl and $sp^2$-methyl groups in (VI) gives agarospirol (V), which is epimeric with (—)-hinesol. Conversions of structures (IV) and (V) by known procedures would result in (+)-β-vetivone (VII) (the antipode of the natural isomer), whereas a similar conversion of structure (VI) would give (—)-β-vetivone.[3] These stereochemical correlations are reversed for the system corresponding to (III) derived from (+)-pin-2(10)-ene.

The key transformation for the utilisation of 8-substituted 1,3,3-trimethylnorbornane derivatives (II) in



(VIII) (IX)



(X) (XI)

the synthesis of spiro[4,5]decanes (IV)—(VII) is the cleavage of the C(2)–C(3) bond in (II). To study this transformation we chose the compound (I; R = $C_6H_4Me$-*p*) since it rearranged [1] to (II; R = $C_6H_4Me$-*p*, $R^1 = R^2$ = Ac) in 95% yield and all the intermediates in its preparation were crystalline compounds. Treatment of compound (II; R = $C_6H_4Me$-*p*, $R^1 = R^2$ = Ac) with lithium aluminium hydride in tetrahydrofuran gave the diol (II; R = $C_6H_4Me$-*p*, $R^1 = R^2$ = H), which readily forms an acetonide. Tosylation of this diol gave the primary monotosyl derivative (II; R =

[1] N. Bosworth and P. D. Magnus, *J.C.S. Perkin I*, 1972, 943.

[2] Leading references to this series of sesquiterpenes are: (*a*) J. A. Marshall and S. F. Brady, *J. Org. Chem.*, 1970, **35**, 4068 and references quoted therein; (*b*) J. A. Marshall and S. F. Brady, *Tetrahedron Letters*, 1969, 1387; (*c*) J. A. Marshall and P. C. Johnson, *Chem. Comm.*, 1968, 391; (*d*) I. Yosioka and T. Kimura, *Chem. and Pharm. Bull. (Japan)*, 1965, **13**, 1430; (*e*) W. Z. Chow, O. Motl, and G. Sorm, *Coll. Czech. Chem. Comm.*, 1962, **27**, 1914; (*f*) M. Mongrain, J. Lafontaine, A. Belanger, and P. Deslongchamps, *Canad. J. Chem.*, 1970, **48**, 3273.

[3] 'The Terpenes,' vol. III, 2nd edn., ed. J. Simonsen and D. H. R. Barton, Cambridge University Press, 1952, p. 224.

$C_6H_4Me$-*p*, $R^1 = H$, $R^2 = Ts$) (91%), treatment of which with potassium t-butoxide gave, as expected, the oxetan (VIII) (100%), thus exemplifying the stereochemical requirements of β-fragmentation.[4] Oxidation of the tosylate (II; $R = C_6H_4Me$-*p*, $R^1 = H$, $R^2 = Ts$) by use of Collins' procedure[5] ($CrO_3$–pyridine–$CH_2Cl_2$) gave the ketone (IX) (93%), $\nu_{max.}$ 1730 $cm^{-1}$. Reduction of this ketone with lithium aluminium hydride and the usual more bulky modified hydride reducing agents gave only the starting *endo*-alcohol (II; $R = C_6H_4Me$-*p*, $R^1 = H$, $R^2 = Ts$), whereas use of sodium borohydride in tetrahydrofuran gave a 3 : 2 mixture of *endo*- and *exo*-alcohols (n.m.r.). Although this was not satisfactory as a synthetic step we investigated the β-fragmentation of the *exo*-alcohol (X). An inseparable mixture of the *exo*- and *endo*-alcohols (X) and (II; $R = C_6H_4Me$-*p*, $R^1 = H$, $R^2 = Ts$) was treated with potassium t-butoxide–t-butyl alcohol to give the oxetan (VIII) and the aldehyde (III; $R = C_6H_4Me$-*p*) in the ratio 3 : 2 (no other products were formed). The aldehyde (III; $R = C_6H_4Me$-*p*), $\nu_{max.}$ 1730 and 1650 $cm^{-1}$, was isolated and purified as its *p*-tolylsulphonylhydrazone. Modified borohydride reducing agents did not improve the ratio of *endo*- to *exo*-alcohol; consequently although β-fragmentation of the *exo*-alcohol (X) is feasible, as a step in a synthesis it is precluded.

The keto-tosylate (IX) was treated with potassium t-butoxide in dimethyl sulphoxide–water[6] at room temperature, and the isopropenyl acid (XI) was isolated as a crystalline compound (≥98% yield), $\nu_{max.}$ 3300—2800, 1695, 1640, and 900 $cm^{-1}$. No isomerisation of the double-bond had taken place during the exposure to the strongly basic reaction conditions.

Cleavage of the non-enolisable ketone (IX) by base is thus the method of choice for generating (+)-(1*R*,3*S*)-3-isopropenyl-1-*p*-tolylcyclopentane-1-carboxylic acid (XI). Modification of R in structure (I) and subsequent transformations *via* β-fragmentation appear to offer a simple route to optically active spiro[4,5]decanes (IV)—(VII) and simpler analogues with no substituents in the cyclohexane ring.

## EXPERIMENTAL

M.p.s were determined on a Kofler hot-stage apparatus. I.r. spectra were measured for Nujol mulls or thin films unless otherwise stated. N.m.r. spectra were recorded with Varian A60 and HA100 instruments for solutions in [$^2$H]-chloroform with tetramethylsilane as internal standard.

All solvents were purified prior to use by standard techniques. Light petroleum refers to the fraction of b.p. 40—60 °C.

The preparation of 9-methyl-6-*p*-tolyl-7-oxatricyclo-[4,3,0,$0^{3,9}$]nonane (I; $R = C_6H_4Me$-*p*) and its conversion into 3α-acetoxymethyl-3-methyl-1-*p*-tolylnorbornan-2α-yl acetate (II; $R = C_6H_4Me$-*p*, $R^1 = R^2 = Ac$) has been described before.[1]

*3α-Hydroxymethyl-3-methyl-1-p-tolylnorbornan-2α-ol* (II; $R = C_6H_4Me$-*p*, $R^1 = R^2 = H$).—The diacetate (II; $R = C_6H_4Me$-*p*, $R^1 = R^2 = Ac$) (1·17 g) in dry tetrahydrofuran (20 ml) was treated with lithium aluminium hydride (0·4 g). The mixture was heated at reflux for 0·5 h and quenched with ether–water–ammonium chloride. The ether layer was dried ($Na_2SO_4$) and evaporated to yield the *diol* (II; $R = C_6H_4Me$-*p*, $R^1 = R^2 = H$), m.p. 109—112° (from light petroleum–ethyl acetate) $\nu_{max.}$ ($CHCl_3$) 3500 $cm^{-1}$, τ 8·85 (3H, s), 7·7 (3H, s), 6·30 (2H, ABq, *J* 11 Hz), 7·1 (1H, s), and 2·8 (4H, s)* (Found: C, 77·8; H, 9·0. $C_{16}H_{22}O_2$ requires C, 78·0; H, 9·0%).

Treatment of the diol (II; $R = C_6H_4Me$-*p*, $R^1 = R^2 = H$) (50 mg) in acetone (5 ml) with a trace of anhydrous copper(II) sulphate gave *OO'-isopropylidene-3α-hydroxymethyl-3-methyl-1-p-tolylnorbornan-2α-ol* (II; $R = C_6H_4Me$-*p*, $R^1R^2 = CMe_2$), b.p. 70° at 5 × $10^{-3}$ mmHg, $\nu_{max.}$ 1390 1230, and 1100 $cm^{-1}$, $[\alpha]_D^{28}$ +39·9° (*c* 0·12 in $CHCl_3$), τ 8·6 (3H, s), 8·4 (3H, s), 8·35 (3H, s), 7·65 (3H, s), 6·4 (2H, ABq, *J* 11 Hz), 6·45 (1H, s), and 2·8 (2H, $A_2B_2q$, *J* 8 Hz) (Found: C, 79·6; H, 9·0. $C_{19}H_{26}O_2$ requires C, 79·7; H, 9·2%).

*2α-Hydroxy-3-methyl-1-p-tolylnorbornan-3α-ylmethyl Toluene-p-sulphonate* (II; $R = C_6H_4Me$-*p*, $R^1 = H$, $R^2 = Ts$).—The diol (II; $R = C_6H_4Me$-*p*, $R^1 = R^2 = H$) (0·5 g) in pyridine (10 ml) at −20° was treated with toluene-*p*-sulphonyl chloride (0·8 g) in pyridine (10 ml). After 48 h at −5° the mixture was poured into water and extracted with ether. The extract was washed with 3N hydrochloric acid, saturated aqueous sodium hydrogen carbonate, and water. The dried ($Na_2SO_4$) extract was evaporated to give the *tosylate*[7] (II; $R = C_6H_4Me$-*p*, $R^1 = H$, $R^2 = Ts$) (0·74 g, 91%), m.p. 114—115° (from light petroleum–ether), $[\alpha]_D^{28}$ +34·4° (*c* 0·08 in $CHCl_3$), $\nu_{max.}$ ($CHCl_3$) 1600, 1360, and 980 $cm^{-1}$, τ 8·8 (3H, s), 7·8 (3H, s), 7·55 (3H, s), 7·5 (1H, s, exchanged by $D_2O$), 6·45 (1H, d, *J* 4 Hz), 5·95 (2H, ABq, *J* 10 Hz), 2·85 (4H, s), and 2·4 (4H, $A_2B_2q$, *J* 9 Hz) (Found: C, 68·8; H, 7·0; S, 8·2. $C_{23}H_{28}O_4S$ requires C, 69·0; H, 7·0; S, 8·0%).

*Treatment of the Tosylate* (II; $R = C_6H_4Me$-*p*, $R^1 = H$, $R^2 = Ts$) *with Potassium t-Butoxide in t-Butyl Alcohol.*—The tosylate (II; $R = C_6H_4Me$-*p*, $R^1 = H$, $R^2 = Ts$) (50 mg) in t-butyl alcohol (3 ml) under nitrogen was treated with potassium t-butoxide (50 mg). After 0·5 h at reflux the mixture was poured into water and extracted with chloroform. Evaporation of the dried ($Na_2SO_4$) extract and distillation of the residue (50° at $10^{-3}$ mmHg) gave *5-methyl-1-p-tolyl-3-oxatricyclo*[4,2,1,$0^{2,5}$]*nonane*[7] (VIII) (98%), m.p. 43°, $[\alpha]_D^{28}$ +15·9° (*c* 0·10 in $CHCl_3$), $\nu_{max.}$ 970 $cm^{-1}$, τ 8·72 (3H, s), 7·80 (3H, s), 5·54 (2H, ABq, *J* 7 Hz), 5·54 (1H, s), and 2·85 (4H, s) (Found: C, 84·2; H, 9·2. $C_{16}H_{20}O$ requires C, 84·2; H, 8·8%).

*3-Methyl-2-oxo-1-p-tolylnorbornan-3α-ylmethyl Toluene-p-sulphonate* (IX).—To chromium trioxide (0·6 g) in dichloromethane (16 ml) was added pyridine (0·95 g). After 15 min at room temperature the monotosylate (II; $R = C_6H_4Me$-*p*, $R^1 = H$, $R^2 = Ts$) (0·425 g) in dichloromethane (5 ml) was added. The dichloromethane was decanted after 15 min and the residue was washed with ether (2 × 25 ml). The combined organic solutions were washed with aqueous 3N-sodium hydroxide (10 ml), 2N-hydrochloric acid (10 ml),

* The methylene signals occurred at τ 7·5—9·0; only diagnostic n.m.r. signals are mentioned here and in subsequent cases.

[4] (*a*) C. A. Grob and P. W. Schiess, *Angew. Chem. Internat. Edn.*, 1967, **1**, 6; (*b*) C. A. Grob, *ibid.*, 1969, **8**, 535.

[5] J. C. Collins, W. W. Hess, and F. J. Frank, *Tetrahedron Letters*, 1968, 3363.

[6] P. G. Gassman and F. V. Zalar, *Tetrahedron Letters*, 1964, 3031, 3251.

[7] N. Bosworth and P. D. Magnus, *Chem. Comm.*, 1972, 257.

saturated aqueous sodium hydrogen carbonate (10 ml), and aqueous sodium chloride (10 ml). The dried ($K_2CO_3$–$Na_2SO_4$) extract was evaporated to give the *ketone* (IX) (0·393 g, 93%), m.p. 101—104° (from ether–hexane), $[\alpha]_D^{28}$ −66·3° (*c* 0·06 in $CHCl_3$), $\nu_{max.}$ 1730, 1380, and 990 $cm^{-1}$, τ 8·85 (3H, s), 7·7 (3H, s), 7·55 (3H, s), 5·97 (2H, ABq, *J* 10 Hz), 2·85 (4H, s), and 2·4 (4H, $A_2B_2q$, *J* 9 Hz) (Found: C, 69·3; H, 6·7; S, 8·1. $C_{23}H_{26}O_4S$ requires C, 69·3; H, 6·6; S, 8·0%).

*Reduction of the Keto-tosylate* (IX) *with Sodium Borohydride and* β-*Fragmentation.*—The keto-tosylate (IX) (300 mg) in dry tetrahydrofuran (20 ml) was treated with sodium borohydride (150 mg) in methanol (2 ml). After 4 h at 0° work-up with dilute hydrochloric acid and extraction with ether (25 ml) gave a mixture (296 mg) of the epimeric alcohols (II; R = $C_6H_4Me$-*p*, $R^1$ = H, $R^2$ = Ts) and (X), τ (tertiary Me) 8·8 and 8·9 (ratio 3 : 2).

The mixture in t-butyl alcohol (20 ml) under nitrogen was treated with potassium t-butoxide (300 mg). After 0·5 h at reflux the mixture was worked up in the usual way. Two products only were formed, (VIII) and (III; R = $C_6H_4Me$-*p*) in the ratio 3 : 2, $\nu_{max.}$ 1730, 1650, and 970 $cm^{-1}$, τ [for (III; R = $C_6H_4Me$-*p*)] 8·3 (3H, d, *J* 1 Hz), 7·7 (3H, s), 5·35 (2H, m), 2·95 (4H, s), and 0·7 (1H, s).

Treatment of the mixture of (VIII) and (III; R = $C_6H_4Me$-*p*) with toluene-*p*-sulphonohydrazide (100 mg) in tetrahydrofuran (5 ml) gave 3-*isopropenyl*-1-p-*tolylcyclopentane*-1-*carbaldehyde* (III; R = $C_6H_4Me$-*p*) p-*tolylsulphonylhydrazone* as an oil (purified by p.l.c.), $\nu_{max.}$ 3200, 1645, 1380, 1160, and 890 $cm^{-1}$, τ 8·74 (3H, s), 7·9br (3H, s), 7·7 (3H, s), 5·5 (2H, m), 3·2 (4H, s), 2·75 (4H, $A_2B_2q$, *J* 9 Hz), 3·0 (1H, s), and 1·7 (1H, s), *m/e* 212 ($M^+$ − 184; loss of toluene-*p*-sulphonohydrazide residue) and 184 (no $M^+$).

(+)-(1R,3S)-3-*Isopropenyl*-1-p-*tolylcyclopentane*-1-*carboxylic Acid* (XI).—The keto-tosylate (IX) (300 mg) in dimethyl sulphoxide (5 ml) under nitrogen at room temperature was treated with potassium t-butoxide (0·8 g) and water (0·360 g). After 2 h the mixture was poured into water (30 ml). Acidification with 6N-hydrochloric acid (5 ml) and extraction with chloroform (2 × 15 ml), drying ($Na_2SO_4$), and evaporation gave the *acid* (XI), purified by short column distillation at 100° and $10^{-5}$ mmHg (≥98% yield); m.p. 57°, $[\alpha]_D^{28}$ +10·7° (*c* 0·07 in $CHCl_3$), $\nu_{max.}$ 1695, 1640, 900, and 3300—2800 $cm^{-1}$, τ 8·35 (3H, s), 7·8 (3H, s), 5·4br (2H, d, *J* 5 Hz), 2·95 (4H, $A_2B_2q$, *J* 7 Hz), and 0·1br (1H, s, exchanged by $D_2O$) (Found: C, 78·4; H, 8·0. $C_{16}H_{20}O_2$ requires C, 78·7; H, 8·3%).

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