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A SHORT, EFFICIENT SYNTHESIS OF (±)VALERANE

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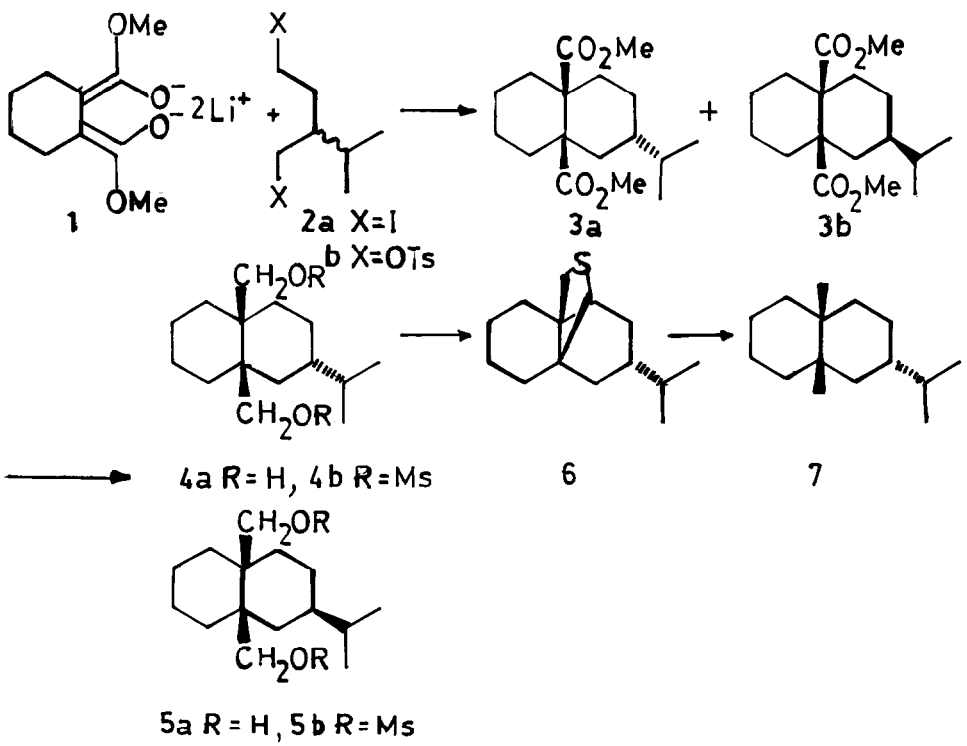
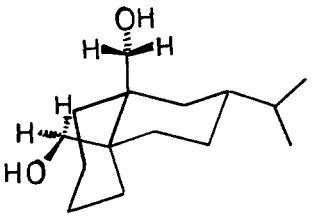
Summary: (±)Valerane has been prepared in 5 steps from dilithium dimethyl 1,2-cyclohexanedioate in 14% overall yield.

The cis-9,10-dimethyldecalins provide an interesting synthetic challenge which has been met in a number of syntheses of valeranone[1] and valerane (7).[2] We now provide a short, efficient route to (±)valerane using the vicinal diester dianion route we have introduced earlier.[3]

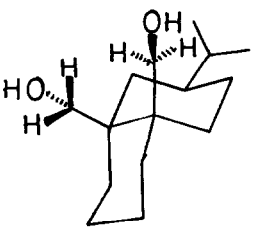
Addition of a solution of dilithiated dimethyl 1,2-cyclohexanedioate (1) (10 mmol) in THF over 30 min through a cannula to a solution of the diiodide 2a (10 mmol)[4] in THF at -78 °C gave a 2.6 : 1 mixture of the diesters 3a,b in 47% yield.[5] These esters could be separated by HPLC but it proved better to carry out the separation at the next step of the reaction sequence.[6,7]



The 3a,b mixture was reduced with $LiAlH_4$ in Et_2O to give a mixture of diols 4a, 5a in 85% yield that could be separated by fractional precipitation. The ^1H NMR spectra[7] of 4a and 5a differ in the pattern of signals attributed to the diastereotopic CH_2O protons, 4a having a 'triplet' at high field and two doublets at low field, whereas 5a has two doublets at high field and a 'triplet' at low field.[8] We interpret this difference as being due to the different conformational preference of the two isomers, 4a adopting the 'steroidal' conformation and 5a the 'nonsteroidal' conformation,[9] and with the subsequent transformation of 4a to valerane described below, the spectra becomes diagnostic for the two configurations.



4a



5a

The major isomer 4a[6,7], mp 95-96 °C, was treated with mesyl chloride in pyridine to give the dimesylate 4b, mp 107-110 °C, in 83% yield.[6,7,10] Reaction of 4b with KSEt in benzene[11] gave the cyclic sulphide 6 in 83% yield.[6,7,12] Desulphurisation of 6 with Raney nickel in boiling ethanol under N_2 gave (±)valerane (7) in 70% yield. 2-D Analysis of the 200 MHz ^1H NMR spectrum [δ 2.02 - 1.01 (m, 16H, CH, CH_2), 0.88 - 0.84 (m, 12H, Me, i-Pr)] resolved the high field band into two singlets and a doublet (J = 6.5 Hz) and this region conformed to the spectral pattern described by Rao.[9] At 400 MHz, the high field band was resolved into singlets at δ0.86 and 0.84, and a doublet centered at δ 0.859. The ^{13}C NMR spectrum [δ 39.5, 37.2, 37.0, 35.4, 34.8, 33.1, 25.0, 24.7, 23.6, 22.5, 21.9, 20.1, 19.8] confirmed that only one isomer had been prepared.

We had hoped that addition of 1 to 2 would proceed preferentially to give the valerane cis-trans arrangement of the esters and isopropyl group rather than the isovalerane all-cis arrangement. Our assumptions were that the transition state would be exo rather than endo, that reaction would occur at the least hindered iodide first, and that there would be a preference for the isopropyl group to be on the opposite side to the incoming nucleophile. Our model of the transition state leading to the valerane arrangements of groups is illustrated in 8. Besides the non-equivalent formation of the two esters 3a,b, some support for these arguments is given by the isolation of a monoalkylated materials when 1 reacts with the ditosylate 2b, alkylation having occurred at the less hindered site. Our findings encourage the view that reaction with the appropriate enantiomer of 2a may lead to natural (-)valerane.[13]

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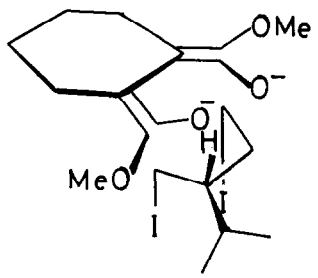

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References and Notes

1. J.A. Marshall, G.L. Bundy, and W.I. Fanta, *J. Org. Chem.*, 33, 3913 (1968); E. Wenkert and D.A. Berges, *J. Am. Chem. Soc.*, 89, 2507 (1967); E. Wenkert, D.A. Berges, and N.F. Golob, *ibid*, 100, 1263 (1978); P.G. Sammes and L.J. Street, *J. Chem. Soc., Chem. Commun.*, 666 (1983).

2. See, for example S.W. Baldwin and R.E. Gawley, *Tetrahedron Lett.*, 3969 (1975); G.H. Posner, J.J. Sterling, C.E. Whitten, C.M. Lentz, and D.J. Brunelle, *J. Am. Chem. Soc.*, 97, 107 (1975).

3. See K.G. Bilyard, P.J. Garratt, R. Hunter, and E. Lete, *J. Org. Chem.*, 47, 4731 (1984); P.J. Garratt and J.R. Porter, *J. Org. Chem.*, in press, and refs therein.

4. Prepared from the corresponding diol; K. Freudenberg and W. Lwowski, *Ann.*, 587, 213 (1954); M. Le Moal, A. Foucaud, R. Carné, J. Hamelin, and C. Sévellec, *Bull. Chim. Soc. France*, 579 (1964).

5. Reaction of 1 and 2 at 0 °C gave a 60% yield of the diesters but the isomer ratio was only 1.7 : 1.

6. Satisfactory analytical and/or mass spectral data were obtained for all new compounds.

7. 3a: ^{1}H NMR, δ 3.63 (s, 3H, CO_2CH_3), 3.62 (s, 3H, CO_2CH_3), 2.48 - 2.67 (m, 2H, CH), 1.87 - 0.98 (m, 14H, CH_2), 0.81 (d, 6H, J = 6.8 Hz); ^{13}C NMR, δ 177.4, 177.3, 51.55, 51.5, 48.5, 47.4, 39.7, 34.3, 32.5, 32.4, 32.3, 30.55, 24.7, 22.1, 21.3, 19.75, 19.55.

4a: ^{1}H NMR, δ 4.09 (d, 1H, J = 11.7 Hz, CH_2O), 4.06 (d, 1H, J = 11.6 Hz, CH_2O), 3.29 (d, 1H, J = 12.9 Hz, CH_2O), 3.22 (d, 1H, J = 12.0 Hz, CH_2O), 2.75 (br s, 2H, OH), 2.10 - 1.02 (m, 16H), 0.86 (d, 6H, J = 6.5 Hz); ^{13}C NMR, δ 68.5, 67.9, 39.55, 38.9 38.7, 34.5, 33.15, 30.5, 30.3, 30.15, 24.3, 21.9, 21.1, 20.0, 19.6.

5a: mp 86 - 88 °C; ^{1}H NMR, δ 4.09 (d, 1H, J = 12 Hz, CH_2O), 4.03 (d, 1H, J = 11.5 Hz, CH_2O), 3.27 (d, 1H, J = 11.4 Hz, CH_2O), 3.24 (d, 1H, J = 11.1 Hz, CH_2O), 2.08 (br s, 2H, OH), 2.12 - 0.96 (m, 16H), 0.87 (d, 3H, J = 6.4Hz) 0.88 (d, 3H, J = 6.4 Hz); ^{13}C NMR, δ 68.05, 67.9, 39.55, 38.8, 38.2, 34.1, 33.15, 31.85, 30.8, 29.75, 25.1, 21.95, 21.1, 20.2, 19.8.

4b: ^{1}H NMR, δ 4.39 (d, 1H, J = 9.7 Hz, CH_2O), 4.31 (d, 1H, J = 9.6 Hz, CH_2O), 4.13 (d, J = 9.7 Hz, CH_2O), 4.11 (d, 1H, J = 9.6 Hz, CH_2O), 3.03 (s, 6H), 1.96 -1.14 (m, 16H), 0.88 (d, 6H, J = 6.6 Hz); ^{13}C NMR, δ 73.3, 73.0, 39.25, 38.55, 38.4, 37.2, 37.15, 32.8, 31.25, 31.05, 31.0, 26.95, 23.95, 21.15, 20.5, 19.75, 19.65.

5b: mp 158 - 159 °C; ^{1}H NMR, δ 4.38 (d, 1H, J = 9.8 Hz, CH_2O), 4.30 (d, 1H, J = 9.8 Hz, CH_2O), 4.14 (d, J = 9.7 Hz, 1H, CH_2O), 4.10 (d, 1H, J = 9.6 Hz, CH_2O), 3.05 (s, 3H), 3.03 (s, 3H), 2.09 - 1.06 (m, 16H), 0.88 (d, 6H, J = 6.1 Hz).

6: ^{1}H NMR, δ 3.34 (d, 1H, J = 10.5 Hz), 3.31 (d, 1H, J = 10.5 Hz), 2.28 (d, 1H, J = 10.7 Hz), 2.27 (d, 1H, J = 10.3 Hz), 1.88 - 1.57 (m, 2H), 1.51 - 1.08 (m, 14H), 0.88 (d, 6H, J = 6.3 Hz); ^{13}C NMR, δ 46.5, 45.75, 42.2, 41.05, 39.0, 34.9, 34.75, 33.0, 32.2, 28.05, 24.9, 21.7, 21.55, 20.1, 19.9.

8. The 'triplets' are partially resolved into two doublets in the 400 MHz spectrum. Decoupling experiments show that in each case the low field doublet of the low field band is coupled to the low field doublet of the high field band.

9. P.N. Rao, *J. Org. Chem.*, 36, 2426 (1971).

10. The minor isomer 5a was converted to the corresponding mesylate 5b under the same conditions.

11. G. Stork, E.E. van Tamelen, L.J. Friedman, and A.W. Burgstahler, *J. Am. Chem. Soc.*, 75, 384 (1953).

12. In initial experiments with a mixture of mesylates 5a,b we obtained both the cyclic sulphide and cyclic oxide on treatment with KSEt. Only the cyclic sulphide was obtained when thoroughly dried reagents and equipment were used.

13. It remains possible that 3b arises from the endo transition state with the isopropyl group on the opposite side to the incoming nucleophile. It seems very unlikely, however, that any 3a arises from an endo transition state since this would require the isopropyl group to be on the same side as the incoming nucleophile, in close proximity to the cyclohexane ring.

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