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SYNTHESIS OF DITERPENOID ACIDS—XI[1]
CYCLIZATIONS WITH MALONIC ESTER

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Abstract– The dimesylate of one of the epimeric 1-methyl-1-(3'-hydroxypropyl)-2-cyclohexanols reacts with malonic ester to give *cis*-1,1-dicarboalkoxy-4-methyldecalin. Similarly, the dimesylate of one of the epimeric 1-methyl-1-(3'-hydroxypropyl)-1,2,3,4-tetrahydro-2-naphthols condenses with malonic ester to give *cis*-1,1-dicarbomethoxy-4a-methyl-1,2,3,4,4a,9,10,10a-octahydrophenanthrene. This product on heating with palladized charcoal gave the *trans* isomer. A number of derivatives of the *cis*-fused products have been prepared. A study of the NMR spectra of the cyclization products and some of their derivatives and other data shows that the trisubstituted bicyclic compounds exist mainly in a conformation in which the angular methyl group is in a 1,3-diaxial relation to an ester group, while with the trisubstituted tricyclic compounds the major conformation is one in which there is no 1,3-diaxial relation between the angular methyl and an ester.

OUR MAIN attempts at synthesizing diterpenoid acids have involved formation of a decalin (precursor of rings A and B) through an initial Diels–Alder reaction,[2–4] followed by insertion of the quaternary Me groups. In another approach we tried condensing compounds related to the Windaus acid (as a model for **1a**) with suitable 3C atom fragments to obtain the diterpene AB system with the *gem* methyl carboxyl at C_4.[5,6] In this work, we carried out a successful cyclization of the ditosylate of the diol derived from the Windaus acid using cyanoacetic ester[7] and we now discuss cyclizations with malonic ester to give bi- and tricyclic compounds with *cis* AB ring fusions.

Bicyclic series. Compound **1a**[8] was reduced with LAH to give a mixture of **1b** and **1c** in 98% yield. Inspection of the NMR spectrum of the mixture indicates that the epimers were present in approximately a 1:2 ratio (stereochemistries not specified). As we were not able to separate the isomers, the mixture was treated with mesyl chloride in pyridine to give a mixture of the epimeric dimesylates (**1d** and **1e** in approximately a 1:2 ratio) in 82% yield. Condensation of the mesylates with sodium ethyl malonate was carried out in dioxane under reflux for 22 hr. After purification (by distillation and chromatography) an oil (32%), which appeared to contain 2 compounds, was obtained. The chemical shift of the angular Me ($\delta = 0{\cdot}86$ ppm), the absence of signals corresponding to vinyl protons, and the low intensity of a signal corresponding to $\underline{H}$—$C(COOC_2H_5)_2$ indicated that the main product was **2a** (or its *trans* fused isomer), and the minor component was a monocondensation product **1h**. To confirm that the ring closure had taken place, the product was hydrolysed with an excess of alcoholic potassium hydroxide. After acidification and decarboxylation a crystalline acid m.p. 153–154°, **2b**, was isolated. This material has a mass spectrum (Fig 1) that accords well with the structure (ignoring stereochemistry) we assign. The crude product from the decarboxylation still contained a small amount of ester (as shown by the NMR spectrum) and this suggested the ester groups in **2a** might be hydrolysed

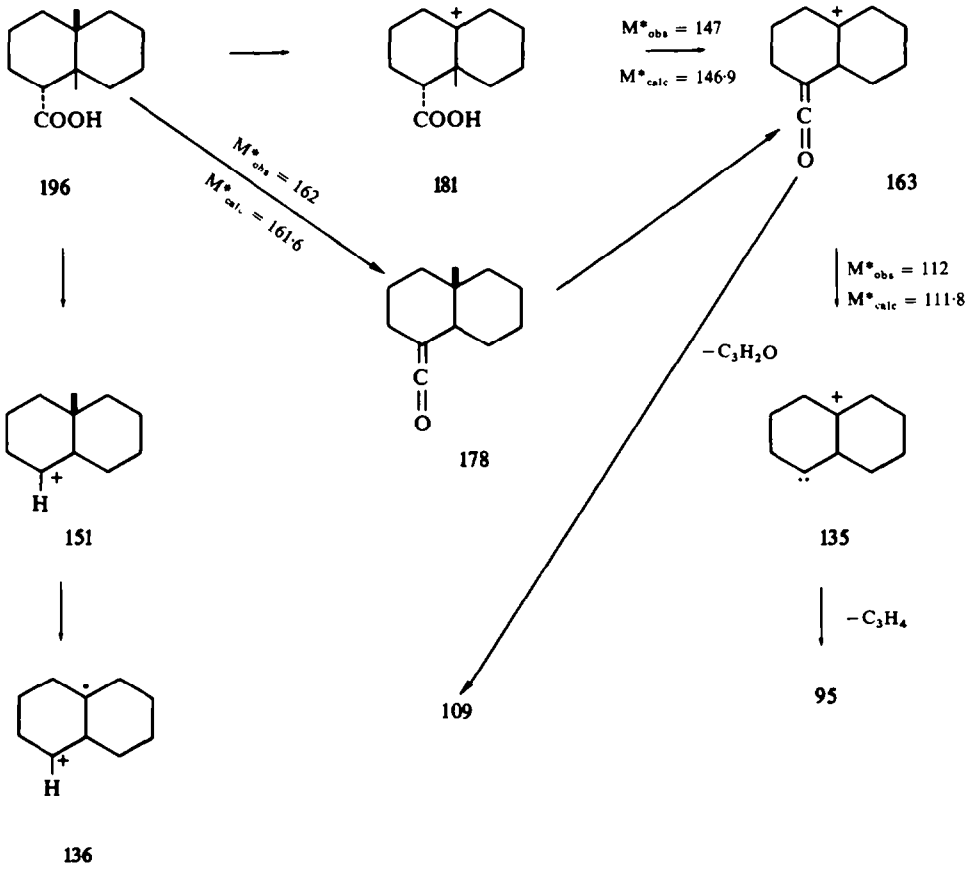


FIG 1.

Major Peaks in Mass Spectrum of 2b

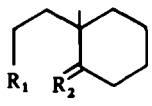
at different rates. Hydrolysis of the diester, **2a**, with sodium hydroxide in aqueous ethanol followed by decarboxylation gave an appreciable amount of the monoester **2c** as well as the acid, **2b**. Hydrolysis of **2c** gave **2b**.

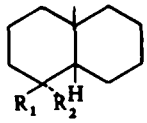
To simplify the NMR spectrum of the product obtained on cyclization, and in the hope of obtaining a crystalline material, we carried out the reaction of the mixture of **1d** and **1e** with sodium methyl malonate instead of the ethyl ester. After refluxing for 19 hr in dioxane and purification, the dimethyl ester, **2d**, was obtained crystalline (m.p. 91°) in 33% yield.

We tried to convert the gem dicarbomethoxy substituents to the gem methyl carboxyl group which is present in diterpenoid acids. The key step is the hydrolysis of **2d** to the monoacid monoester (**2e**). Originally we were able to hydrolyse one ester group selectively by refluxing **2d** with slightly more than 1 mole of sodium hydroxide in methanol for 17 hr. Excellent yields of semiester **2e** were obtained twice, but subsequently mainly **2d** was recovered. However, **2e** was obtained in 62% yield when the

hydrolysis was done in ethanol for 3 hr with a small quantity of water; the recovered material contained **2d** mixed with the transesterification product (**2f**). Decarboxylation of ester **2e** gave the monoester **2g** which on hydrolysis gave **2b**.

The conversion of the carboxyl group in **2e** into a hydroxymethyl group was done by the method of Paquette and Nelson[9] *via* the acid chloride **2i** which was reduced with $NaBH_4$ to **2h**. Reduction of the mesylate from **2h** with LAH gave no clear result. Oxidation of **2h** with CrO_3 pyridine complex gave the aldehyde, **2j**. Reduction of **2j**

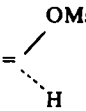




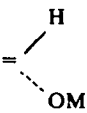
1a: $R_1 = COOC_2H_5$; $R_2 = O$

1b: $R_1 = CH_2OH$; $R_2 =$

1c: $R_1 = CH_2OH$; $R_2 =$



1d: $R_1 = CH_2OMs$; $R_2 =$



1e: $R_1 = CH_2OMs$; $R_2 =$

1f: $R_1 = CH_2CH(COOCH_3)_2$; $R_2 =$

1g: $R_1 = CH_2CH(COOCH_3)_2$; $R_2 =$

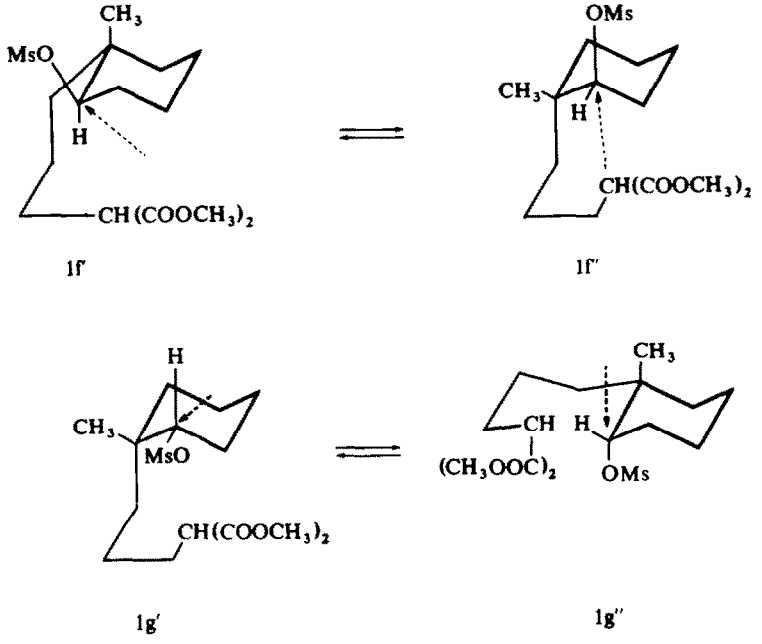
1h: $R_1 = CH_2CH(COOC_2H_5)_2$; $R_2 =$

2a: $R_1 = R_2 = COOC_2H_5$
2b: $R_1 = H$; $R_2 = COOH$
2c: $R_1 = H$; $R_2 = COOC_2H_5$
2d: $R_1 = R_2 = COOCH_3$
2e: $R_1 = COOCH_3$; $R_2 = COOH$
2f: $R_1 = COOCH_3$; $R_2 = COOC_2H_5$
2g: $R_1 = H$; $R_2 = COOCH_3$
2h: $R_1 = COOCH_3$; $R_2 = CH_2OH$
2i: $R_1 = COOCH_3$; $R_2 = COCl$
2j: $R_1 = COOCH_3$; $R_2 = CHO$
2k: $R_1 = COOH$; $R_2 = H$
2l: $R_1 = COOCH_3$; $R_2 = CH_3$

by the Wolff–Kishner (Huang–Minlon) method gave a mixture of the acid **2b** and its C_4 epimer **2k**. The structures of these bicyclic compounds are based on their spectra.

Bicyclic series, discussion. The reaction of sodium methyl malonate with **1d** and **1e** should give initially the monocondensation products **1f** and **1g** respectively. Compound **1f** will exist in 2 conformations **1f'** (predominately) and **1f''**, while **1g** exists similarly as **1g'** (predominating) and **1g''**. Cyclization of **1f** and **1g** occurs through attack of the

monomalonate anion on C_2 with inversion at that center. Inspection of models shows that this reaction can take place easily in conformation **1f''** (but not **1f'**) leading to **2d**; that cyclization is improbable with **1g'** and although it could take place with **1g''**, the approach of the anion to the backside of the mesyl group is blocked by the Me group. On the basis of these arguments it appears that the product we obtained is **2d** (from **1f''**) and the monocondensation product is **1g'**. This assignment means that all the compounds in our bicyclic series, **2a–2k**, are *cis* fused.



1f' 1f''

1g' 1g''

(Dotted arrows indicate required direction of attack by anion for cyclization to occur)

There are two apparent inconsistencies with the assignment of *cis* structures to our compounds. Firstly, the only 9-methyldecalin-1-carboxylic acid previously reported[10] had a m.p. of 150° (*cf* **2b** m.p. 153–154°), and was assigned the *trans* structure, **6**, on the grounds that the hydrogen at the ring fusion had been introduced by catalytic hydrogenation under acid conditions, and its methyl ester was not methylated (at the 1 position) when treated with methyl iodide and base. Secondly, one would expect the *cis* compounds **2a** and **2d** to exist in 2 conformations and so selective hydrolysis of one of their ester groups should be difficult.

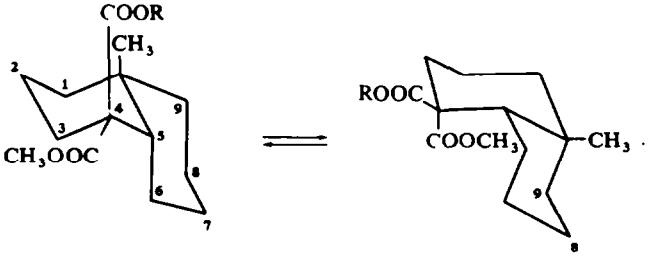
To decide definitely whether our bicyclic compounds are *cis* or *trans* fused we considered their NMR spectra (Table I). The shifts observed for the Me group in *cis*- and *trans*-9-methyldecalin are 0·97 and 0·84 ppm downfield from TMS.[11] Whether the monosubstituted compounds **2b**, **2c** and **2g**, are *cis* or *trans*, the substituent should be equatorial and should not affect the position of the signal for the angular Me group. This is confirmed by the fact that the shift is not changed on going from the esters (**2c** and **2g**) to the acid (**2b**). The position of the peak in these compounds (1·02 ppm) clearly indicates *cis*—(0·97) rather than *trans*—(0·84) compounds. With

TABLE 1. CHEMICAL SHIFTS[a] OF C_{10}—CH_3[b] IN BI- AND TRICYCLIC SERIES

Compound	$CDCl_3$	C_6H_6	$CDCl_3 - C_6H_6$	C_5H_5N
2a	0·86	0·94	−0·08	
2d	0·83	0·88	−0·05	0·87
2e	0·83			
2h	0·78	0·85	−0·07	
2c	1·02	0·90	+0·12	
2g	1·025	0·91	+0·115	
2b	1·02	0·83	+0·19	0·98
5a	1·27	1·22	+0·05	
5b	1·27			
5c	1·22	1·25	−0·03	
5d	1·25			1·17
7c	1·05			

[a] Peaks given in ppm downfield from tetramethylsilane.
[b] Steroid numbering.

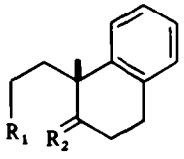
the disubstituted compounds, **2a**, **2d**, **2e** and **2h**, which all contain at least one ester group, the methyl signal is shifted upfield by 0·17–0·23 ppm, which indicates the presence of a 1,3-diaxial interaction between an ester group and the Me group, (similar to that in podocarpic ester).[12] These interactions are confirmed by the deshielding observed when the solvent is changed from $CDCl_3$ to C_6H_6.[13] The similarity in the position of the signal for **2e** and **2h** to that in the diesters **2a** and **2d** confirms that in **2e** and **2h** the ester is *cis* to the angular Me. These results not only confirm that the compounds are *cis* but that they exist mainly in conformation **2d'** rather than **2d''**. Apparently this latter fact accounts for the selectivity of hydrolysis though in contrast to the esters of podocarpic acid, the axial ester can be hydrolysed under sufficiently strong conditions. It is not clear if this easier hydrolysis is the result of steric factors or of the presence of the α-substituted carboxylate ion (instead of a Me group in podocarpic ester). The structures proposed for the monosubstituted compounds (**2b**, **2c**, and **2g** rather than their C_4 epimers) are based on the predominant conformation of the disubstituted compounds and on earlier work with **1**-substituted decalins (as opposed to the 9-methyldecalins considered here).[14]



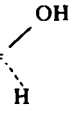
2d': R = CH_3
5a': C_8—C_9 aromatic bond; R = CH_3
5b': C_8—C_9 aromatic bond; R = H

2d'': R = CH_3
5a'': C_8—C_9 aromatic bond; R = CH_3
5b'': C_8—C_9 aromatic bond; R = H

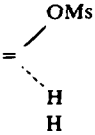
Tricyclic series. The Michael addition of 1-methyl-2-tetralone to ethyl acrylate gave **3a**. Reduction of **3a** with LAH gave an 87% yield of a mixture of **3b** and **3c** in approximately 1:4 ratio (the assignment of stereochemistry is discussed below). When the mixture was treated with boiling ether, **3c** could be filtered off as a crystalline material, and evaporation of the filtrate gave a mixture of **3b** and **3c**. The mixture of **3b** and **3c** was converted to a mixture of the dimesylates **3d** and **3e**, and the pure isomer **3c** to the oily dimesylate **3e**.

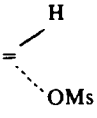


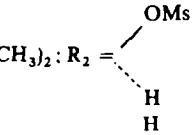
3a: $R_1 = COOC_2H_5$; $R_2 = O$

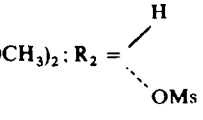
3b: $R_1 = CH_2OH$; $R_2 =$ 

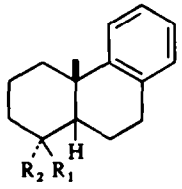
3c: $R_1 = CH_2OH$; $R_2 =$ 

3d: $R_1 = CH_2OMs$; $R_2 =$ 

3e: $R_1 = CH_2OMs$; $R_2 =$ 

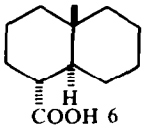
3f: $R_1 = CH_2CH(COOCH_3)_2$; $R_2 =$ 

3g: $R_1 = CH_2CH(COOCH_3)_2$; $R_2 =$ 



5a: $R_1 = R_2 = COOCH_3$
5b: $R_1 = COOH$; $R_2 = COOCH_3$
5c: $R_1 = COOCH_3$; $R_2 = H$
5d: $R_1 = COOH$; $R_2 = H$
5e: $R_1 = CH_3$; $R_2 = COOCH_3$
5f: $R_1 = COOCH_3$; $R_2 = CH_3$

4



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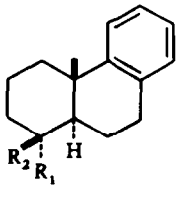

7a: $R_1 = COOH$; $R_2 = H$
7b: $R_1 =$ Any substituent; $R_2 = CH_3$
7c: $R_1 = R_2 = COOCH_3$

Condensation of **3e** with sodium methyl malonate in refluxing xylene for 18 hours gave an oil containing 2 components: one of these was probably the alkene **4**, the other appeared to be a product which no longer contained the quaternary Me group and in which the ring had closed. No structure can be proposed for this latter product.

Condensation of a mixture of **3d** and **3e** with sodium methyl malonate in refluxing dioxane for 21 hr gave the tricyclic compound **5a** as well as **3g**. Running the reaction in refluxing xylene also gave **5a** (as crystals m.p. 108°) but in lower yield than from the reaction in dioxane.

Hydrolysis of **5a** with 1 mole of NaOH in ethanol with a trace of water gave the semi-ester **5b**; decarboxylation of this gave the ester **5c**, which was hydrolysed to **5d**, m.p. 200°. The same acid was obtained directly by hydrolysis of **5a** with excess of alcoholic KOH followed by decarboxylation. The structures of these compounds were assigned from their NMR spectra. The structure of **5d** is also consistent with its mass spectrum, which shows fragmentations similar to those observed for **2b** (Fig 1) and those generally shown by tricyclic diterpenoids.[15]

Tricyclic series, discussion. The discussion of the possible conformations of **1f** and **1g** and their ease of cyclization can be applied directly to the corresponding compounds **3f** and **3g**. Again we expect that **3f** (from **3d**) should cyclize to the tricyclic compound **5a**, and **3e** should give mainly the monocondensation product **3g**. On this basis, the structure of the pure diol is **3e**. An additional point is that using refluxing xylene rather than refluxing dioxane leads to elimination, particularly with **3g**.

From these considerations we expect **5a** and the related compounds **5b–5d** to be *cis*. Wenkert and Jackson[16] synthesized **7a** (m.p. 153–154°) of unequivocal stereochemistry. The difference in m.p. (50°) between their compound (**7a**) and ours (**5d**) suggests that the compounds are different and hence ours is *cis*. Unfortunately the sample of **7a** available was not sufficient for a comparison with **5d**.*

The chemical shifts for the angular Me group in compounds **5a–5d** are given in Table I. The shifts for the angular Me group in compounds of the type **7b**, when the Me is not affected by other substituents, is 1·18–1·22 ppm. Insertion of an ester group at 4β position of the *trans* compounds introduces a shielding effect of 0·15 ppm.[12] The fact that the shifts for **5a** and **5b** are close to the values for **5c** and **5d** and are between those for isopodocarpic ester (**5f**, 1·22 ppm) and isodehydroabietic ester (**5e**, 1·36 ppm) shows clearly that **5a** and **5b** (and hence **5c** and **5d**) are *cis*-fused and that **5a** and **5b** exist predominantly in the conformations **5a″** and **5b″** respectively (corresponding to the conformation **2d″**, though probably with ring B a half boat[12]) rather than the conformation corresponding to **2d′**. The difference in the preferred conformations in the bicyclic and tricyclic series is not surprising: the double bond at C_{8-9} (steroid numbering) in **5a** and **5b** removes several unfavourable interactions present in **2d″**, *viz* the C_8–H to C_{10}-methyl, the C_9–H to $COOCH_3$ and the C_9–H to C_2–H interactions. The removal of these interactions is sufficient to reverse completely the conformational preference of **5a** and **5b** in comparison with that of **2a**, **2d**, **2e**, and **2h**. Assuming that relative stabilities of the conformations of the monosubstituted tricyclic compounds are similar to those of the disubstituted compounds we assign the structures **5c** and **5d** rather than the corresponding C_4 epimers.

Dutta *et al.*[17] discovered that *cis*-dehydrodeisopropylabietic acid and other related

* We thank Professor Wenkert for sending us all his sample of **7a**.

A/B *cis* tricyclic compounds are isomerized to the *trans* compounds when heated with Pd–C. We heated **5a** with Pd–C at 235–240° and obtained a product m.p. 129–131° to which we assign the structure **7c**. As expected the chemical shift of the angular Me group is at 1·03 ppm, which is the same as in methyl podocarpate. Further, the shifts for the OMe peaks differ by 0·15 ppm in **5a** (probably in conformation **5a**″ the shift of the OMe of the axial ester group is affected by the benzene ring), but only by 0·03 ppm in **7c**.

The mass spectra of **5a** and **7c** are rather similar and show peaks (e.g. 117, 141 and 241) analogous to those observed in diterpenoids.[15] The spectrum of **5a** shows strong peaks at 284 (M-32), 62% and 256 (M-60) 100%; these peaks, which are much weaker (8 and 17%) in the spectrum of **7c**, are characteristic of 4α-carbomethoxy-*cis*-fused tricyclic diterpenoids.[15] This evidence confirms convincingly our assignment of *cis* structures to **5a**–**5d** and a *trans* structure to **7c**.

CONCLUSION

Our work provides an easy route to 4,4-disubstituted (steroid numbering) *cis*-decalins and tricyclic compounds. The tricyclic compounds will provide starting points for the synthesis of diterpenoid acids and for studies of conformational problems involving *cis* fused compounds.

EXPERIMENTAL*

Epimeric 1-(3′-*hydroxypropyl*)-1-*methyl*-2-*cyclohexanols* (**1b** *and* **1c**)

An ethereal soln of **1a** (20 g, 0·094 mole) was added dropwise to a stirred suspension of LAH (4 g, 0·105 mole) in ether (150 ml) so that the ether refluxed gently. The mixture was refluxed for 5 hr, water (20 ml) was added dropwise to the cooled (ice/NaCl bath) soln and then 5N HCl until the salts dissolved. The mixture was extracted 3 times with ether, the combined ethereal solns were washed until neutral with sat NaCl aq and dried ($MgSO_4$). After removal of the ether by evaporation, the residue was distilled in a bulb tube and the fraction with b.p. 200–230° (0·7 mm) obtained as a colourless viscous glassy mass, was a mixture of **1b** and **1c** (16 g, 98%).(Found: C, 69·76; H, 11·93. $C_{10}H_{20}O_2$ requires: C, 69·72; H, 11·70%): ν_{max} 3625 and 3350 cm^{-1} (no C=O absorption); NMR peaks at δ: 0·89 and 0·95 (2s, 3H, ratio of peaks about 35:65), 1·08–2·17 (m, 12H), 2·95 (s, 2H, position of peak variable), and 3·25–3·80 (m, 3H) ppm: in C_5H_5N the methyl singlets were no longer resolved and were at 1·03 ppm.

Epimeric 1-(3′-*hydroxypropyl*)-1-*methyl*-2-*cyclohexanol dimesylates* (**1d** *and* **1e**)

Methane sulphonyl chloride (35 g, 0·305 mole) followed by a soln of the epimers **1b** and **1c** (16 g, 0·093 mole) in pyridine (100 ml) were added to cooled (ice/NaCl bath) pyridine (250 ml). The mixture was kept for 6 hr at −10°, poured onto ice and then acidified with 5N HCl (with cooling). The mixture was extracted several times with $CHCl_3$, the combined $CHCl_3$ solns were washed with H_2O, dried, and concentrated. The residue was chromatographed on Florisil and the fraction eluted in ether gave **1d** and **1e** as a light yellow oil (25 g, 82%): ν_{max} 1362, 1190 and 1180 cm^{-1} (no OH absorption); NMR peaks at δ: 0·98 and 1·02 (2s, 3H, ratio of peaks about 35:65), 1·15–2·20 (m, 14H), 3·05 (s, 6H), 4·25 (t, 2H, J = 6 Hz) and 4·36–4·65 (q (?), 1H) ppm.

Condensation of mesylates **1d** *and* **1e** *with ethyl malonate*

Ethyl malonate (8·5 g) was added to a dispersion of NaH in mineral oil (2·18 g, 51·8%) in dioxane (80 ml) under N_2. The mixture was heated until the sodium ethyl malonate was in soln, the heating was stopped,

* Unless otherwise specified IR spectra were determined for CCl_4 solns and NMR spectra for $CDCl_3$ solns. The NMR data (obtained on A-60 and A–60D spectrometers) are given in ppm downfield from TMS. Mass spectra were determined on a Hitachi RMU-6D spectrometer at an ionization potential of 70 ev. Samples were introduced through the direct inlet. M.ps are uncorrected.

the mixture of epimeric mesylates (**1d** and **1e**, 5·5 g) in dioxane (30 ml) was added all at once, and the mixture was refluxed with stirring for 22 hr. After concentration *in vacuo* ether was added, and the ethereal soln was washed several times with water and dried (Na_2SO_4). The ether and excess malonate were removed *in vacuo*, and the residue was distilled. (The oil-bath temp must be kept below 160° to avoid decomposition of mesylate). The fraction with b.p. 126° (0·1 mm) was chromatographed on alumina. Mineral oil was eluted in light petroleum. The fraction eluted in ether was distilled and the fraction with b.p. 125° (0·25 mm) gave **2a** (1·6 g, 32%, contaminated with a trace of **1b**) as a colourless oil: ν_{max} 1735 cm^{-1}: NMR peaks at δ: 0·86 (s, 3H), 1·00–2·60 (m, 21H, includes 3 sets of t): 3·07–3·45 (q, *ca* 0·2 of 4H), 3·90–4·50 (m, 0·8 of 4H, 3 overlapping quartets), 5·30–5·60 (m, very slight intensity) ppm: in C_6H_6 the Me singlet shifted to 0·94 ppm.

cis-4a-*Methyldecahydronaphthalene*-1-*carboxylic acid* (**2b**)

(a) A soln of the diester **2a** (880 mg) and KOH (2 g) in EtOH (20 ml) was refluxed for 17 hr. The EtOH was removed *in vacuo*, water (25 ml) was added and the mixture was extracted with ether. The aqueous soln was added slowly to stirred conc HCl aq (25 ml). The acidic soln was extracted three times with ether, the ethereal solns were dried ($MgSO_4$) and evaporated. The residue was decarboxylated at 170–190° and the crude **2b** (455 mg) was mixed with light petroleum (b.p. 30–60°) and kept at 0°. The resultant crystalline product sublimed at 150–160° (0·7 mm) to give **2b** (120 mg) m.p. 147–150°. After several recrystallisations from light petroleum (b.p. 30–60°) **2b** had m.p. 153–154°. (Found: C, 73·36; H, 10·36. $C_{12}H_{20}O_2$ requires: C, 73·43; H, 10·27%): NMR peaks at δ: 1·02 (s, 3H), 1·10–2·00 (m, 15H), 2·58–3·07 (m, 1H), and 10·75–11·12 (m, 1H) ppm: in C_6H_6 peaks were at 0·83 (s, 3H) 2·50–2·95 (m, 1H), and 12·77 (s, 1H): and in C_5H_5N a singlet was at 0·98 ppm: mass spectrum *m/e* (rel.intensity):196 (30), 181 (27), 163 (100), 151 (12), 136 (49), 135 (52), 109 (34), 107 (13), 96 (34), 95 (30), 94 (18), 93 (24), 91 (14), 82 (13), 81 (12), 79 (29), 77 (18), 73 (18), 69 (18), 68 (17), 67 (17), 55 (54) and 53 (24); metastable peaks at 162 and 112.

(b) The monoester, **2c**, (70 mg) in ethanol with KOH (200 mg) was refluxed for 2 hr, and the mixture was worked-up as described for (a). Sublimation of the crude product at 130–140° (0·4 mm) and recrystallization of the sublimate from light petroleum (b.p. 30–60°) gave **2b** (24 mg) m.p. 152–152·5° not depressed on mixing with product from (a).

Ethyl cis-4a-*methyldecahydronaphthalene*-1-*carboxylate* (**2c**)

A soln of **2a**, (720 mg) in 10 N NaOH (10 ml) and EtOH (6 ml) was refluxed for 17 hr and treated similarly to part (a) in the preparation of **2b**. The product from the decarboxylation (234 mg) in acetone (3 ml) was added to hot conc Na_2CO_3 aq (20 ml). The cooled mixture was extracted with ether and the ethereal soln was dried and evaporated to give the monoester **2c** (70 mg): NMR peaks at δ: 1·02 (s, 3H), 1·08–3·00 (m, 19H, includes t, J = 7Hz at 1·25) and 3·97–4·32 (q, 2H) ppm: in C_6H_6 the singlet shifted to 0·90 and the triplet to 1·00 ppm.

cis-1,1-*Dimethoxycarbonyl*-4a-*methyldecahydronaphthalene* (**2d**)

Methyl malonate (40 g) was added to a dispersion of NaH in mineral oil (51·8%, 10 g) in dioxane (300 ml) under N_2. The mixture was heated until the sodium methyl malonate was in soln, and then the mixture of dimesylates, **1d** and **1e** (20 g) in dioxane (50 ml) was added all at once and the mixture was refluxed for 19 hr. The work-up was the same as that used in the preparation of **2a**. The product which distilled at 131° (0·7 mm) was chromatographed on alumina. The material eluted in ether was kept at 0° overnight with hexane to give **2d** as crystals m.p. 88–90° (3·81 g). Chromatography of the hexane filtrate (mainly mineral oil) on alumina (Woelm neutral, activity 1) yielded further **2d** m.p. 87–89° (1·52 g; total yield on whole amount of mesylate 33%). After several recrystallizations from hexane **2d** had m.p. 91°. (Found: C, 67·35; H, 9·20. $C_{15}H_{24}O_4$ requires: C, 67·13; H, 9·02%): ν_{max}^{KBr} 1745 and 1720 cm^{-1}; NMR peaks at δ: 0·83 (s, 3H), 1·00–2·70 (m, 15H), 3·68 (s, 3H) and 3·75 (s, 3H) ppm: in C_6H_6 singlets appeared at: δ 0·88, 3·32 and 3·43 ppm; in C_5H_5N singlets at 0·87, 3·61, and 3·67 ppm.

cis-1β-*Methoxycarbonyl*-4a-*methyldecahydronaphthalene*-1α-*carboxylic acid* (**2e**)

(a) A mixture of **2d** (100 mg, 0·000373 mole), NaOH (20 mg, 0·0005 mole), EtOH (5 ml) and water (50 µl) was refluxed for 3 hr. The solvent was removed by evaporation and water (10 ml) was added to the residue. The aqueous mixture was extracted twice with ether and a neutral material (23 mg, indicated by NMR to be a mixture of **2d** and the transesterification product **2f**) was recovered from the combined ethereal solns. The aqueous soln was added slowly with stirring to a cooled (ice/NaCl bath) mixture of conc HCl aq (20 ml) and ice (20 g). The acidified mixture was extracted 3 times with ether and the combined ethereal solns were

dried ($MgSO_4$) and evaporated *in vacuo* at room temp to yield a residue which on treatment with hexane and cooling gave the semi-ester (**2e**) as crystals m.p. 138° (with decarboxylation) (58 mg, 62%); NMR peaks at δ; 0·83 (s, 3H), 1·15–2·65 (m, 15H), 3·78 (s, 3H) and 8·90 (s, 1H) ppm.

The NMR of the unhydrolysed material was similar to that of **2d** except the peak at 3·68 ppm had almost disappeared and been replaced by a quartet centered at 4·15 and a triplet at 1·12 ppm. The ratio of **2f** to **2d** appeared to be about 7:1.

(b) The hydrolysis was also done by refluxing a soln of **2d** (500 mg, 0·0019 mole) and NaOH (100 mg, 0·0025 mole) in MeOH (25 ml) and water (150 µl) for 17 hr. Work-up by the method described in (a) twice gave **2e** (67%) and recovered **2d** (15%). In later experiments up to 80–90% of **2d** was recovered when the hydrolysis was done in MeOH.

Decarboxylation of **2e** gave **2g**, NMR peaks at δ: 1·02 (s, 3H), 1·15–2·20 (m, 15H), 2·40–3·05 (m, 1H), and 3·72 (s, 3H) ppm: in C_6H_6 the singlets were at 0·90 and 3·40 ppm: the peak at 0·90 has a small singlet beside it, probably due to a C_4 epimer of **2g**.

cis-1β-*Methoxycarbonyl*-1α-*hydroxymethyl*-4a-*methyldecahydronaphthalene* (**2h**)

A mixture of **2e** (291 mg, 0·00115 mole) and oxalyl chloride (2 ml) was kept at room temp for 2 hr and at 50° for 1 hr. The excess oxalyl chloride was removed *in vacuo* at 20–30°. Benzene (5 ml) was added to the residue and the evaporation *in vacuo* at 20–30° was repeated. The residue in dioxane (10 ml) was added dropwise to a stirred suspension of $NaBH_4$ (200 mg) in dioxane (5 ml). The mixture was refluxed for 4½ hr, cooled, and poured slowly into water (20 ml). The cooled aq soln was acidified with HCl aq and then extracted 3 times with ether. The ethereal solns were dried and evaporated. The residue (249 mg) was chromatographed on alumina (Woelm neutral, activity 3) and the crude hydroxymethyl compound (137 mg) was eluted in ether. Recrystallization from light petroleum (b.p. 30–60°) at 0° gave **2h** m.p. 101–102° (120 mg, 43%), raised by further recrystallizations to 102–103° (62 mg) (Found: C, 69·85; H, 10·10. $C_{14}H_{24}O_3$ requires: C, 69·96; H, 10·07%); ν_{max}^{KBr} 3425 and 1725 cm^{-1}; NMR peaks at δ: 0·78 (s, 3H), 1·00–2·30 (m, 15H), 3·20–3·65 (q, 2H, J = 10 Hz), 3·72 (s, 3H) ppm; in C_6H_6 the singlets were at 0·85 and 3·37 ppm

Attempted preparation of cis-1β-*methoxycarbonyl*-1α,4a-*dimethyldecahydronaphthalene* (**2i**)

A soln of **2h** (88 mg, 0·000366 mole) in pyridine (1 ml) was stirred for 30 min with CrO_3.Py complex (from CrO_3 200 mg, 0·002 mole, and pyridine 2 ml), kept for 18 hr and then poured into ice-water. The product was extracted with ether and the ethereal soln was washed with dil $NaHCO_3$ aq, water and dried. Evaporation of the ether gave **2j** as an oil (64 mg, 0·00027 mole positive DNP) which was subjected to Wolff–Kishner reduction (Huang-Minlon conditions; KOH 250 mg; triethylene glycol, 3 ml; hydrazine hydrate, 64% 0·4 ml). Examination of the NMR of the crude product from the reduction indicated it was a mixture of the epimeric acids **2b** and **2k**.

Ethyl β-(1-*methyl*-2-*oxo*-1,2,3,4-*tetrahydronaphthyl*)*propionate* (**3a**)

Ethyl acrylate (8·3 g, 0·083 mole) was added to a soln of 1-methyl-2-oxo-1,2,3,4-tetrahydronaphthalene (15 g, 0·084 mole, 90% technical Aldrich) and tBuOK [prepared from 330 mg K (0·084 g atom)] in tBuOH (150 ml) kept at 30°. The mixture was stirred overnight at room temp, diluted with 2N H_2SO_4 and extracted with ether. The ethereal soln was washed with water, dried and concentrated. Distillation of the residue afforded **3a** as a light yellow oil, b.p. 141–145° (0·3 mm) (16·17 g, 77%). (Found: C, 73·75; H, 7·63. $C_{16}H_{20}O_3$ requires: C, 73·82; H, 7·74%); ν_{max} 1733 and 1715 cm^{-1}; NMR peaks at δ: 1·18 (t, 3H, J = 7Hz), 1·45 (s, 3H), 1·70–3·30 (m, 8H), 3·80–4·28 (q, 2H, J = 7Hz) and 7·10–7·40 (m, 4H) ppm.

Epimeric 1-(3′-*Hydroxypropyl*)-1-*methyl*-1,2,3,4-*tetrahydro*-2-*naphthols* (**3b** *and* **3c**)

A soln of **3a** (13·75 g, 0·0527 mole) in ether (150 ml) was added dropwise to a stirred mixture of LAH (3 g, 0·079 mole) in ether (100 ml) and the mixture was refluxed for 8 hr. The work-up was the same as that used in the preparation of **1b** and **1c**. Xylene was added to the crude product (13·70 g) and the mixture was kept for 2 days at 0° to give a crystalline mixture of **3b** and **3c** (10·12 g, 87%).

The mixture of products (10·12 g) was refluxed with ether (150 ml) for 5 min and filtered hot. The crystals of **3c** after washing with boiling ether had m.p. 119–124° (5·05 g) and on recrystallization from xylene had m.p. 121–123°, (Found: C, 76·10; H, 9·17. $C_{14}H_{20}O_2$ requires: C, 76·32; H, 9·15%): ν_{max}^{KBr} 3250 cm^{-1} (no C=O absorption), NMR peaks at δ: 1·25 (s, 3H), 1·50–2·20 (m, 6H), 2·40 (s, 2H), 2·65–3·15 (m, 2H), 3·43–3·70 (m, (q?), 2H), 3·85 (t, 1H, J = 5·5 Hz) and 7·00–7·35 (m, 4H) ppm: in C_5D_5N peaks were at δ: 1·45 (s, 3H), 1·60–3·20 (m, 8H), 3·65–4·25 (m, 3H), 5·90 (broad s, 2H, disappears on addition of D_2O) and 7·00–7·60 (m, 4(?)H) ppm.

The filtrate remaining after the isolation of **3c** was concentrated to give a crystalline mixture of **3b** and **3c** which was used without further purification: NMR similar to that of **3c** except an additional singlet at 1·22 ppm, more intense than that at 1·25 ppm.

Inspection of the NMR spectrum of the original crystalline mixture of **3b** and **3c** shows that **3c** is predominant (approximately 4:1).

1-(3'-Hydroxypropyl)-1-methyl-1,2,3,4-tetrahydro-2-naphthol dimesylates (**3d** *and* **3e**)

(a) *Compound* **3e**. A soln of **3c** (5·06 g, 0·0229 mole) in pyridine (70 ml) was added to methane sulphonyl chloride (8 g, 0·07 mole) in pyridine (80 ml) as described for the preparation of **1d** and **1e**. The further treatment was the same as for that preparation and **3e** was obtained as a light yellow oil (7·8 g, 90%), NMR peaks at δ: 1·37 (s, 3H), 1·67–2·90 (m, 8H), 2·97 (s, 3H), 3·05 (s, 3H), 4·20 (m, 2H), 4·95 (d of d, J = 4 and J = 7Hz, 1H) and 7·00–7·33 (m, 4H) ppm.

(b) *Compounds* **3d** *and* **3e**. The same procedure was used on a mixture of **3b** and **3c** (5 g, 0·023 mole) and gave a mixture of **3d** and **3e** (6·5 g, 76%). NMR peaks in the same positions as for **3e** above except that the multiplets at 4·20 and 4·95 are broader and the peak at 1·37 is two overlapping singlets.

Condensation of **3d** *and* **3e** *with methyl malonate*

(a) A mixture of **3d** and **3e** (7·8 g, 0·0207 mole, approximately 7% **3d** and 93% **3e**) in dioxane (60 ml) was added to a soln of sodium methyl malonate prepared from NaH in mineral oil (3·16 g, 51·8%, 0·068 mole) and methyl malonate (15 g) in dioxane (130 ml) and the mixture was refluxed for 21 hr. After the same work-up as used in the preparation of **2d** the crude product was distilled and the product with b.p. at 160–170° (0·4 mm) (accompanied by some decomposition of mesylate) was chromatographed (neutral alumina, activity 1). The diester was obtained on elution with ether as colourless crystals m.p. 104–107° (211 mg, 48% based on **3d**), NMR identical with product from (b).

(b) Methyl malonate (25 g) was added slowly to a dispersion of Na (1·5 g, 0·065 g. atom) in xylene (200 ml) and the mixture was refluxed until the sodium methyl malonate was in soln. A mixture of dimesylates (**3d** and **3e**, 6 g, approximately 4:3, 0·016 mole) in xylene (60 ml) was added at once and the mixture was refluxed for 18 hr. Water was added to the cooled mixture until the sodium mesylate dissolved. The aqueous soln was extracted with xylene, the combined xylene solns were washed several times with water, dried and concentrated *in vacuo*. The excess of malonate was removed under high vacuum (*ca* 1 mm). The residue was chromatographed on alumina (Woelm neutral, activity 1). Elution with ether gave a material which with hexane at 0° gave **5a** as crystals m.p. 107–109° (578 mg, 20% based on **3d**). (Found: C, 71·90; H, 7·55. $C_{19}H_{24}O_4$ requires: C, 72·12; H, 7·65%); ν_{max}^{KBr} 1748 and 1718 cm^{-1}; NMR peaks at δ: 1·27 (s, 3H), 1·50–2·33 (m, 8H), 2·67–3·08 (m, 3H), 3·58 (s, 3H), 3·73 (s, 3H) and 7·00 to 7·33 (m, 4H) ppm; in C_6H_6 the singlets are at δ: 1·22, 3·22 and 3·38 ppm. Mass spectrum, *m/e* (rel. intensity): 316(41), 284(62), 256(100), 241(83), 225(29), 197(90), 181(76), 155(41), 152(28), 142(38), 141(55), 129(31), 128(48), 115(26), 104(41), and 91(31); metastable peaks at 231·5 and 262.

The oil (1·55 g) remaining after crystallisation of **5a** is probably a mixture of **4**, **5a** and possibly an unknown product: NMR peaks at δ: 1·25 (s, 1H), 1·33 (s, 3H), 1·40–3·10 (m, 19H), 3·20–3·50 (m, 3H), 3·50–3·80 (4s, 12H), 5·35–6·10 (m, 2H) and 7·00–7·40 (m, 8H) ppm. The peaks at 1·33, 3·20–3·50 and 5·35–6·10 are attributed to **4**: and the low intensity singlet at 1·25 to **5a**: in C_6H_6 the singlets are at 1·20 and 1·25 ppm.

(c) The condensation was carried out in a manner similar to (b) by using sodium (3 g), methyl malonate (15 g) in xylene (100 ml) and **3e** (3 g) in xylene (30 ml). The product (1·60 g) after chromatography was a mixture with an NMR spectrum similar to the byproduct from (b) except that the singlet at 1·25 and one of the 4 OMe singlets, that at 3·58, had almost disappeared, (indicating almost complete absence of **5a**) The mixture is therefore **4** and an unknown product.

Selective hydrolysis of **5a**

A mixture of **5a** (100 mg, 0·00032 mole), NaOH (15 mg, 0·00038 mole), water (100 µl), and EtOH (5 ml) was refluxed for 2 hr. The mixture was worked up as in the preparation of **2e** and the semiester **5c** was obtained as a viscous oil (63 mg, 66%): NMR peaks at δ: 1·27 (s, 3H), 1·50–2·33 (m, 8H), 2·53–3·03 (m, 3H), 3·78 (s, 3H), 6·92–7·33 (m, 4H) and 9·40 (s, 1H) ppm.

Thermal decarboxylation of **5b** gave the monoester **5c**: NMR peaks at δ: 1·22 (s, 3H), 1·30–3·20 (m, 12H), 3·67 (s, 3H), and 7·00–7·40 (m, 4H) ppm: there is a small singlet at 3·70 ppm, so the material is probably a mixture of C_4 epimers: in C_6H_6 singlets are at 1·25 and 3·39 (with small singlet at 3·42) ppm.

Acid **5d**

(a) Hydrolysis of **5c** with an excess of KOH yielded the acid **5d** m.p. 198–201° which after sublimation at 150–160° (0·4 mm) and recrystallization from light petroleum (b.p. 30–60°) had m.p. 200–202° ν_{max}^{KBr} 3500 and 1700 cm^{-1}: NMR peaks at δ: 1·25 (s, 3H), 1·40–3·10 (m, 12H), 7·00–7·45 (m, 4H) and 11·33 (broad s, 1H) ppm: in C_5H_5N the Me singlet appears at 1·17 ppm; mass spectrum *m/e* (rel. intensity): 244(34), 229(72), 183(10), 143(30), 141(29), 117(23), 115(23), and 91(23); metastable peaks at 146·5 and 194·5(?) (M^*_{calc} 229 → 183 = 146·2).

(b) The same acid **5d** (m.p. 200–201°) was obtained by refluxing a mixture of **5a** (100 mg), KOH (300 mg), water (0·5 ml) and EtOH (4 ml) for 14 hr followed by work-up and decarboxylation.

Epimerisation of **5a** *with* Pd/C

A mixture of **5a** (70 mg) and Pd–C (70 mg, 10%) was heated at 235–240° for 1 hr (as described by Dutta).[17] Chromatography of the product on alumina (Woelm neutral, activity 1) and elution with ether gave an oil which when treated with pentane gave crystals of **7c** m.p. 129–131° (10 mg); ν_{max}^{KBr} 1733 cm^{-1}; NMR peaks at δ: 1·05 (s, 3H), 1·17–3·00 (m, 11H), 3·74 and 3·75 (2 overlapping s, 6H); 6·97–7·40 (m, 4H) ppm; mass spectrum *m/e* (rel. intensity): 316(17), 256(17), 241(100), 236(28), 205(23), 197(19), 181(31), 177(19), 143(23), 141(21), 129(19), 128(20), 115(19), and 91(19).

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