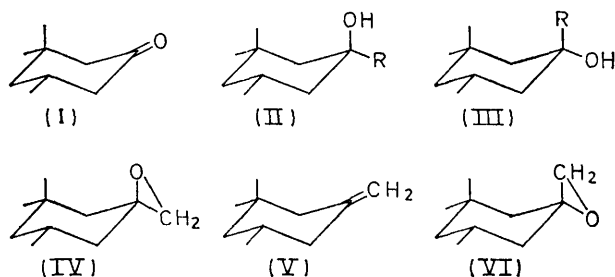


## Asymmetric Synthesis. Part VI.<sup>1</sup> Reactions of 3,3,5-Trimethylcyclohexanone with Grignard Reagents and Configurational Interrelationships of 1-Alkyl(alkenyl and alkynyl)-3,3,5-trimethylcyclohexanols and Compounds Derived from 1-Hydroxy-3,3,5-trimethylcyclohexanecarbonitriles

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The reactions of 3,3,5-trimethylcyclohexanone (I) with methyl-, ethyl-, vinyl-, allyl-, prop-2-ynyl-, isopropyl-, and t-butyl-magnesium halides and with methyl-, ethyl-, isopropyl-, and t-butyl-lithium gave one product in each case. Chemical correlations and n.m.r. data showed that all had the same relative configuration (*trans*-1-OH,5-Me). The epimeric cyanohydrins from 3,3,5-trimethylcyclohexanone provided a route to the epimeric methyl 1-hydroxy-3,3,5-trimethylcyclohexanecarboxylates; configurational interrelationships with the 1-alkyl analogues are reported. Contrary to a previous report, reactions of the ketone (I) with both dimethylxosulphonium methylide and dimethylsulphonium methylide gave the same oxiran, which on reduction gave the *trans*-compound. Epoxidation of 1,1,3-trimethyl-5-methylenecyclohexane and reduction of the resulting oxiran gave the elusive 1,3,3-*cis*-5-tetramethylcyclohexanol, the configuration being supported by n.m.r. data for the oxiran precursor.

THE reduction of 3,3,5-trimethylcyclohexanone (I) with a variety of reducing agents was recently examined and a theory of flexible form participation was advanced.<sup>2</sup> As an extension of that investigation the reactions of organometallic compounds, sulphur ylides, and hydrogen cyanide with the same ketone (I) were investigated. Since this formed part of a wider study of the addition reactions of cyclic ketones,<sup>3-14</sup> it was considered necessary to interrelate unambiguously the configurations of all the products and to assign their configurations wherever possible.



(II) and (III): R = (a) H, (b) Me, (c) CN, (d) CO<sub>2</sub>H, (e) CO<sub>2</sub>Me  
 (II): R = (f) Et, (g) CH=CH<sub>2</sub>, (h) C≡CH, (i) Pr<sup>n</sup>, (j) CH<sub>2</sub>-CH=CH<sub>2</sub>,  
 (k) CH<sub>2</sub>-C≡CH, (l) Pr<sup>i</sup>, (m) Bu<sup>t</sup>, (n) CH<sub>2</sub>-SMe

The reactions of methyl-, ethyl-, vinyl-, ethynyl-, propyl-, allyl-, prop-2-ynyl-, isopropyl-, and t-butyl-magnesium halides with the ketone (I) gave crude alcohols (II) which were analysed by g.l.c. and isolated by

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<sup>1</sup> Part V, S. R. Landor, B. J. Miller, and A. R. Tatchell, *J. Chem. Soc. (C)*, 1971, 2339.

<sup>2</sup> S. R. Landor and J. P. Regan, *J. Chem. Soc. (C)*, 1967, 1159.

<sup>3</sup> A. V. Kamernitzky and A. A. Akhrem, *Tetrahedron*, 1962, **18**, 705 and references cited therein.

<sup>4</sup> G. D. Meakins, R. K. Percy, E. E. Richards, and R. N. Young, *J. Chem. Soc. (C)*, 1968, 1106.

<sup>5</sup> M. R. Harnden, *J. Chem. Soc. (C)*, 1969, 960.

<sup>6</sup> J. McKenna, R.I.C. Lecture Series, 1966, No. 1 and references cited therein.

<sup>7</sup> M. Cherest and H. Felkin, *Tetrahedron Letters*, 1968, 2205.

<sup>8</sup> M. Perry and Y. Maroni-Barnaud, *Bull. Soc. chim. France*, 1969, 2372.

<sup>9</sup> F. Rocquet, J. P. Battioni, M. L. Capmau, and W. Chodkiewicz, *Compt. rend.*, 1969, 1449.

crystallisation and preparative g.l.c. Reactions with methyl-, vinyl-, ethynyl-, allyl-, and prop-2-ynyl-magnesium halides each gave only one major product, contaminants accounting for less than 2% of the total product. We obtained no evidence that these contaminants contained any of the expected epimeric products. In the other cases the tertiary alcohol was accompanied by varying amounts of the secondary alcohols, (IIa) and (IIIa), resulting from the competing reduction of the ketone by the Grignard reagent. Pure tertiary alcohols were obtained in these latter cases either by the reaction of the ketone (I) with the appropriate alkyl-lithium compound, followed in some instances by preparative g.l.c., or by indirect methods involving reduction of the unsaturated analogues.

The reactions of the ketone (I) with vinylmagnesium chloride,<sup>15</sup> sodium acetylide,<sup>16</sup> and methylmagnesium halide<sup>17</sup> had been previously reported, and the m.p., i.r., and n.m.r. data of our products are in agreement with the literature values. Only in the case of the 1-vinyl analogue had the configuration (IIg) been assigned, and this was based on i.r. data. Neither the preparation of epimers nor configurational interrelationships have been recorded and a definite assignment of configurations has been hampered by the inadequate number of compounds studied.

As a first step in the configurational interrelationship studies, the 1-ethynyl- and 1-vinyl-3,3,5-trimethylcyclohexanols from the Grignard reactions were reduced to 1-ethyl-3,3,5-trimethylcyclohexanol. In each case

<sup>10</sup> J.-C. Richer and C. Lamarre, *Canad. J. Chem.*, 1969, **47**, 2349.

<sup>11</sup> J.-C. Richer and D. Eugene, *Canad. J. Chem.*, 1969, **47**, 2387.

<sup>12</sup> D. C. Ayres and R. Sawdaye, *J. Chem. Soc. (B)*, 1967, 581.

<sup>13</sup> J. Klein, E. Dunkelblum, E. L. Eliel, and Y. Senda, *Tetrahedron Letters*, 1968, 6127.

<sup>14</sup> G. Chauviere, Z. Welvart, D. Eugene, and J.-C. Richer, *Canad. J. Chem.*, 1969, **47**, 3285.

<sup>15</sup> S. Watanabe, K. Suga, Y. Suematsu, and T. Suzuki, *Austral. J. Chem.*, 1968, **21**, 531.

<sup>16</sup> D. Papa, F. Villani, and H. Ginsburg, *J. Amer. Chem. Soc.*, 1954, **76**, 4446.

<sup>17</sup> E. J. Corey and M. Chaykovsky, *J. Amer. Chem. Soc.*, 1965, **87**, 1353.

the same epimer was obtained; this had also been prepared directly from ethylmagnesium bromide and the ketone (I) and hence all these materials have the same configuration and are tentatively formulated as the *trans*-isomers (IIh, g, and f). Similarly reduction of the 1-prop-2-ynyl and 1-allyl analogues in each case gave a compound identical with the 1-propyl analogue obtained directly from the Grignard reaction with propylmagnesium bromide; these must also all have the same configuration, and are tentatively formulated as the *trans*-isomers (IIk, j, and i).

The n.m.r. spectra of all these tertiary alcohols exhibit a common recognisable pattern of signals which may be assigned to the 3- and 5-methyl groups (Table). The chemical shift values are similar to those previously noted for the secondary *trans*-alcohol (IIa)<sup>12</sup> obtained by reduction of the ketone (I), and this provides circumstantial evidence for the *trans*-configurations (IIb) of the tertiary alcohols. However direct chemical evidence is desirable.

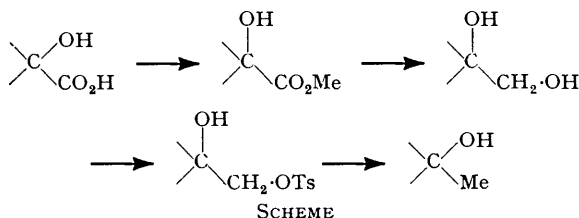
However, the cyanohydrin prepared from the ketone (I), potassium cyanide, and hydrochloric acid at  $-10^\circ$ , on hydrolysis and esterification gave a two-component mixture of esters (g.l.c.). The major component was the ester (IIe); the minor component (9%), isolated by preparative g.l.c., was the epimeric ester (IIIe) (i.r. and n.m.r. data, elemental analysis). Insufficient pure epimer (IIIe) was available from the preparative g.l.c. for conversion into the tetramethylcyclohexanol (IIb) by the reactions outlined in the Scheme. The mixed ester fraction [91% (IIe), 9% (IIIe)] gave only one tosylate, which on reduction gave the 1,3,3,5-tetramethylcyclohexanol (IIb) which had previously been obtained from ketone (I) and methylmagnesium iodide. No trace of the epimeric product was detected on g.l.c.

An alternative route to the epimeric tetramethylcyclohexanols (IIb) and (IIIb) had been reported<sup>17</sup> previously. Ketone (I) with dimethyloxosulphonium methylide gave the oxiran (IV), and with dimethylsulphonium methylide it gave a 45:55 mixture of the

N.m.r. and g.l.c. data for the products from the addition reactions of 3,3,5-trimethylcyclohexanone with Grignard reagents and organolithium compounds

R	G.l.c.		N.m.r.							Ring positions and OH			
	$t_R$ / min	Col.	$^\circ\text{C}$	$\delta_{eq}\text{-Me}$ $\tau$	$J/\text{Hz}$	$\delta_{3eq}\text{-Me}$ $\tau$	$\delta_{3ax}\text{-Me}$ $\tau$	$\delta_{1eq}\text{-R}$ $\tau$	$J/\text{Hz}$	$\tau$			
(IIb) Me	6.5	B	120	9.13(d)	6.5	9.12(s)	8.9(s)	8.81(s)			7.7—9.5	7.7—9.6	8.83(s)
(IIg) $\text{CH}=\text{CH}_2$	37.2	D	100	9.11(d)	6.5	9.11(s)	8.86(s)	5.02(dd)	10.4 <i>cis</i> 2.0 <i>gem</i> 4.84(dd) 17.9 <i>trans</i> 2.0 <i>gem</i> 4.09 (dd) 17.9 <i>trans</i> 10.4 <i>cis</i>		7.7—9.5		8.83(s)
(IIh) $\text{C}\equiv\text{CH}$	47.4	D	120	9.10(d)	7.0	9.10(s)	8.91(s)	7.6(s)			7.9—9.3		8.30(s)
(IIj) $\text{CH}_2=\text{CH}=\text{CH}_2$	18.8	B	100	9.13(d)	6.5	9.12(s)	8.90(s)	7.86(m) 4.9—6.5(m)			7.8—9.4		8.67(s)
(IIk) $\text{CH}_2-\text{C}\equiv\text{CH}$	42.5	B	100	9.08(s)	6.0	9.08(s)	8.87(s)	7.90(t) 7.68(d)	2.5 2.5		8.1—9.5		8.36(s)
(IIl) $\text{Bu}^t$				9.12(d)	6.0	9.12(s)	8.93(s)	9.08(s)				8.2—9.4	
(IIe) $\text{CO}_2\text{Me}$	8.7	B	150	9.08(d)	6.0	9.06(s)	8.86(s)	6.21(s)			7.6—9.3		7.06(s)

The configuration of the ethynyl compound (IIh), and hence also of the vinyl compound (IIg) and the ethyl compound (IIf) was related to that of the methyl analogue (IIb) by oxidation of the ethynyl compound (IIh) to the acid (IIId), which was converted into the methyl compound (IIb) as shown in the Scheme. The same



hydroxy-acid (IIId) was obtained from the ketone (I) with potassium cyanide and aqueous sodium hydrogen sulphite at  $25^\circ$  after hydrolysis, and this had already been ascribed the *trans*-configuration on the basis of n.m.r. and dissociation constant data.<sup>15</sup> Esterification with diazomethane gave an ester which was shown to be one single epimer (IIe) by g.l.c.

oxirans (IV) and (VI). The mixed oxirans had been reduced and it was claimed that the epimeric compounds (IIb) and (IIIb) had been isolated; apart from the m.p. no other physical data for (IIIb) were reported. In our hands both sulphur ylides gave completely stereoselective formation of the same oxiran, which on reduction gave the tetramethylcyclohexanol (IIb).

We considered that if a methylene insertion reaction at the carbonyl group of compound (I) gives the oxiran (IV) by equatorial attack, then an epoxidation reaction with (V) should give the oxiran (VI), which would provide a route to (IIIb). Furthermore the n.m.r. spectra of compounds (IV) and (VI) in the region corresponding to the methylene group of the oxiran ring should show a significant difference, since the methylene hydrogen atoms are non-equivalent in structure (VI) but equivalent in (IV). After this work had been completed a similar sequence with 4-*t*-butyl-2,2-dimethylcyclohexanone was published.<sup>10</sup> Accordingly the ketone (I) was converted into the methylene compound (V) by a Wittig reaction and the product was characterised by elemental analysis and i.r. and n.m.r. spectra. Epoxidation of

(V) was accomplished with *m*-chloroperbenzoic acid and the oxiran was purified by preparative g.l.c. That the oxiran is correctly formulated as (VI) was shown by an AB quartet in the n.m.r. spectrum arising from the non-equivalence of the oxiran CH<sub>2</sub> group. The oxiran isolated from the reaction of (I) with dimethyloxosulphonium methylide gave a singlet for the corresponding CH<sub>2</sub> group and hence is correctly formulated as (IV). Reduction of compound (VI) gave the 1,3,3,5-tetramethylcyclohexanol (IIIb), in the n.m.r. spectrum of which the signals of the 3- and 5-methyl groups are similar to those exhibited by (IIIa) and distinct from those of the group having the configurations given by (IIa—m).

Finally the configuration of compound (IIj) [and hence of (IIIi and k)] was related to that of (IIf) as follows. *O*-Methylation of (IIj) and ozonolysis of the product gave an aldehyde which was purified *via* the thioacetal derivative formed by treatment with 4,5-dimethyl-1,2-phenylenedimethanethiol.<sup>18</sup> Desulphurisation yielded a compound identical (by g.l.c.) with the *O*-methyl derivative of (IIf).

Direct chemical correlation of the isopropyl and *t*-butyl analogues with the tetramethylcyclohexanol (IIb) is so far lacking, but from a consideration of the reaction conditions, the n.m.r. spectra, and the chemical correlations reported here, there can be little doubt that the configurations are given by (III) and (IIm), respectively.

#### EXPERIMENTAL

G.l.c. analyses were carried out on a Pye 104 gas chromatograph fitted with a flame-ionisation detector (nitrogen as carrier gas at 40 ml min<sup>-1</sup>) and glass columns: (A) 5 ft silicone oil (10%) on Chromosorb W (80—100 mesh), (B) 5 ft Carbowax 20M (10%) on Chromosorb W (80—100 mesh), (C) 5 ft diglycerol (25%) on Chromosorb W (80—100 mesh), (D) 5 ft Carbowax 6000 (5%) on Hylon P (80—100 mesh), (E) 7 ft Carbowax 6000 (5%) on Hylon P (80—100 mesh), (F) 7 ft Carbowax 20M (25%) on Chromosorb W (60—80 mesh), and (G) 7 ft poly(ethylene glycol) (15%) on siliconised Diatomite C (60—70 mesh). Ether and tetrahydrofuran were dried over sodium. Ether, chloroform, and light petroleum extracts were dried over MgSO<sub>4</sub> or as otherwise stated, and evaporated under reduced pressure. N.m.r. spectra were obtained for solutions in deuteriochloroform with a Varian A60 (60 MHz) or a Varian HA-100D (100 MHz) instrument with tetramethylsilane as internal reference;  $\tau$  values obtained with the latter instrument are marked with an asterisk. N.m.r. and g.l.c. data are given in the Table.

*Reactions of 3,5,5-Trimethylcyclohexanone (I) with Grignard Reagents.*—(i) *Methylmagnesium iodide.* To an ethereal solution (80 ml) of methylmagnesium iodide (0.03 mol) [from magnesium turnings (0.73 g) and methyl iodide (4.3 g)] a solution of the ketone (I) (1.4 g, 0.01 mol) in ether (20 ml) was added with stirring. The mixture was stirred for a further 2 h and cooled to 0°, and the magnesium complex was decomposed with saturated ammonium chloride solution (20 ml). The ethereal layer was separated, the aqueous layer extracted with ether (3 × 50 ml), and the

combined ethereal extracts dried and evaporated. The crude product (1.5 g) solidified spontaneously to give 1,3,3-*trans*-5-tetramethylcyclohexanol (IIb) (1.4 g, 90%), m.p. 80—81° [from light petroleum (b.p. 60—80°)] (lit.,<sup>19</sup> 80—81°);  $\nu_{\max}$  3400 cm<sup>-1</sup> (OH).

(ii) *Ethylmagnesium bromide.* The reaction of ketone (I) (1.4 g) with ethylmagnesium bromide (0.03 mol) in ether solution (80 ml) [from ethyl bromide (3.3 g) and magnesium (0.73 g)] was carried out as in (i). The crude product (1.5 g) slowly solidified to give 1-ethyl-3,3,5-trimethylcyclohexanol (IIf) (1.3 g, 81%), m.p. 66—67° [from light petroleum (b.p. 60—80°)] (Found: C, 77.9; H, 12.8. C<sub>11</sub>H<sub>22</sub>O requires C, 77.6; H, 13.2%),  $\tau^*$  6.5—9.0 (22H, m);  $\nu_{\max}$  3480 cm<sup>-1</sup> (OH);  $t_R$  (col. C; 100°) 3.9,  $t_R$  (col. B; 120°) 9.6,  $t_R$  (col. D; 100°) 21 min; only the first column specified separated the tertiary alcohol from traces of contaminating secondary alcohols in the crude product: *trans*-(IIa),  $t_R$  9.6, *cis*-(IIIa),  $t_R$  11.4 min.

(iii) *Vinylmagnesium bromide.* A solution of vinyl bromide (8.69 g, 0.08 mol) in tetrahydrofuran (20 ml) was cooled to -30° and added dropwise to a suspension of magnesium (1.9 g, 0.08 g atom) in tetrahydrofuran (60 ml). After the reaction had subsided, the solution was heated under reflux for 30 min and a solution of ketone (I) (5.6 g, 0.04 mol) in tetrahydrofuran (20 ml) was added. The mixture was stirred for 2 h, cooled, and decomposed with saturated ammonium chloride solution (25 ml), and the tetrahydrofuran layer was separated. The aqueous layer was extracted with tetrahydrofuran (3 × 25 ml). The combined tetrahydrofuran extracts were evaporated and the residue was dissolved in ether (100 ml). The solution was dried and evaporated to give a yellow solid (6 g) which afforded 3,3,5-trimethyl-1-vinylcyclohexanol (IIg) (4.2 g, 63%), m.p. 65—66° (from benzene) (lit.,<sup>15</sup> 66°);  $\nu_{\max}$  3420 (OH) and 1860 and 1650 cm<sup>-1</sup> (-CH=CH<sub>2</sub>). Catalytic hydrogenation (PtO<sub>2</sub>) of pure olefin (IIg) (1 g) in ethyl acetate (100 ml) gave a solid product which on g.l.c. analysis (col. E; 100°) showed one symmetrical peak corresponding to (IIf). After recrystallisation this product had i.r. and n.m.r. spectra identical with those of (IIf).

(iv) *Ethynylmagnesium bromide.* A solution of ethylmagnesium bromide (0.15 mol) was prepared by adding ethylmagnesium bromide (0.15 mol) in tetrahydrofuran (100 ml) [from ethyl bromide (16.4 g) and magnesium, (3.7 g)] dropwise during 2 h to tetrahydrofuran (60 ml) saturated with dry acetone-free acetylene. A rapid stream of acetylene was passed through the mixture during the addition. The mixture was cooled to 0° and the ketone (I) (7.0 g, 0.05 mol) in tetrahydrofuran (20 ml) was added dropwise with slow passage of acetylene. The mixture was stirred for 1 h and poured into ice-ammonium chloride. The tetrahydrofuran layer was separated and the aqueous layer extracted with tetrahydrofuran (3 × 25 ml). The combined tetrahydrofuran extracts were evaporated and the residue was dissolved in ether (100 ml); the solution was dried and evaporated. The product (7.2 g) was a yellow oil, which was distilled to give 1-ethynyl-3,3,5-trimethylcyclohexanol (IIh) (5.6 g, 70%), b.p. 78—79° at 8 mmHg (lit.,<sup>16</sup> 89—91° at 15 mmHg), which slowly crystallised; m.p. 26—27° (lit.,<sup>16</sup> 28°);  $\nu_{\max}$  3450 (OH), 3300 (C≡CH), and 2100 cm<sup>-1</sup> (C≡C); catalytic hydrogenation (PtO<sub>2</sub>) of pure (IIh) (0.5 g) in ethyl acetate solution (100 ml)

<sup>18</sup> I. Shahak and E. D. Bergmann, *J. Chem. Soc. (C)*, 1966, 1005.

<sup>19</sup> H. Barbier, *Helv. Chim. Acta*, 1840, **23**, 519.

followed by appropriate isolation gave a solid crude product which on g.l.c. (col. D; 100°) gave a symmetrical peak corresponding to (IIf). The i.r. and n.m.r. spectra of recrystallised product were identical with those of (IIf).

(v) *Propylmagnesium bromide*. To an ethereal solution (80 ml) of propylmagnesium bromide (0.06 mol) prepared by the general procedure described in (i) [from propyl bromide (7.4 g) and magnesium (1.45 g)], a solution of ketone (I) (4.2 g, 0.03 mol) in ether (60 ml) was added dropwise with stirring. The mixture was stirred for 2 h and worked up as previously described. The crude product (4.6 g) was a mixture of the tertiary alcohol (IIi) and the secondary alcohols (IIa) and (IIIa), identified by i.r. and n.m.r. spectroscopy and g.l.c.

(vi) *Allylmagnesium bromide*. The Grignard reagent was prepared in ether solution (100 ml) by the slow addition (2 h) of allyl bromide (36.3 g, 0.3 mol) to a vigorously stirred suspension of magnesium (29.2 g, 1.2 g atom). The ketone (I) (21 g, 0.15 mol) in ether (25 ml) was added dropwise and with continued stirring during a 2 h period. The crude liquid product (26 g) was isolated in the usual manner and distilled (b.p. 73° at 3 mmHg) to give 1-allyl-3,3,trans-5-trimethylcyclohexanol (IIj) (17.8 g, 66%) (Found: C, 78.9; H, 12.2.  $C_{12}H_{22}O$  requires C, 79.1; H, 12.2%),  $\nu_{\max}$  3460 (OH) and 1840  $cm^{-1}$  ( $-CH=CH_2$ ). G.l.c. analysis (col. B; 100°) of the crude product showed that it consisted substantially of one component; catalytic hydrogenation of (IIj) as described in (iii) and (iv) gave a crude product which on g.l.c. gave one symmetrical peak corresponding to (IIi). Preparative g.l.c. (col. F) gave pure 3,3,trans-5-trimethyl-1-propylcyclohexanol (Found: C, 77.9; H, 13.2.  $C_{12}H_{24}O$  requires C, 78.2; H, 13.1%),  $\nu_{\max}$  3420  $cm^{-1}$  (OH).

(vii) *Prop-2-ynylmagnesium bromide*. To an ethereal solution (100 ml) of prop-2-ynylmagnesium bromide (0.3 mol) [from prop-2-ynyl bromide (35.7 g) and magnesium (7.3 g) in the presence of mercuric chloride] was added in the usual way a solution of the ketone (I) (21 g, 0.15 mol) in ether (25 ml). Standard isolation procedures gave a crude liquid product (25.7 g) which g.l.c. analysis (col. B; 100°) showed to be substantially homogeneous. Distillation (b.p. 72° at 3 mmHg) gave pure 3,3,trans-5-trimethyl-1-prop-2-ynylcyclohexanol (IIk) (12.1 g, 45%) (Found: C, 79.7; H, 11.3.  $C_{12}H_{20}O$  requires C, 79.9; H, 11.2%),  $\nu_{\max}$  3460 (OH), 3320 ( $C\equiv CH$ ), and 2120  $cm^{-1}$  ( $C\equiv C$ ). Catalytic hydrogenation gave a crude product which g.l.c. analysis showed to consist only of (IIi).

(viii) *Isopropylmagnesium chloride*. A solution of ketone (I) (1.4 g, 0.01 mol) in ether (25 ml) was added to an ethereal solution (80 ml) of isopropylmagnesium chloride (0.03 mol) as in the general procedure already described. The crude product was isolated as an oil (1.4 g) which was shown by g.l.c. analysis (col. D; 100°) to consist of (IIi) ( $t_R$  27.3 min) accompanied by (IIa) and (IIIa).

(ix) *t-Butylmagnesium chloride*. Ketone (I) (1.4 g, 0.01 mol) in ether (25 ml) was added to an ethereal solution (80 ml) of t-butylmagnesium chloride (0.03 mol) by the general procedure already described. The crude product was isolated as an oil (1.4 g) which was shown by g.l.c. analysis (col. D; 100°) to consist of (IIm) ( $t_R$  31.7 min) accompanied by (IIa) and (IIIa).

*Reactions of 3,3,5-Trimethylcyclohexanone (I) with Alkyl-lithium Compounds.*—(i) *Methyl-lithium*. A solution of the ketone (I) (1.4 g, 0.01 mol) in ether (20 ml) was added dropwise with stirring during 20 min to an ethereal solution (80 ml) of methyl-lithium (0.03 mol) [from lithium (0.69 g)

and methyl iodide (4.3 g); excess of lithium had previously been filtered off under nitrogen]. The mixture was heated under reflux with stirring for a further 2 h, and then decomposed with water (50 ml). The product (1.3 g, 84%), m.p. 80–81°, isolated in the usual way was identical with the Grignard reaction product (IIb). G.l.c. analysis of the crude material revealed no other products.

(ii) *Ethyl-lithium*. A solution of ketone (I) (1.4 g, 0.01 mol) in ether (20 ml) was added dropwise with stirring to an ethereal solution of ethyl-lithium (0.03 mol) [from lithium (0.69 g) and ethyl bromide (3.3 g)] as in (i). After isolation, g.l.c. of the crude solid product (1.5 g) showed the presence of compound (IIf) only.

(iii) *Isopropyl-lithium*. An ethereal solution (60 ml) of isopropyl-lithium (0.04 mol) was prepared by addition of isopropyl chloride (3.2 g) in ether (20 ml) to a stirred suspension of finely divided lithium (0.69 g), the mixture being kept at  $-60^\circ$  under nitrogen. After 1 h the solution was filtered through glass-wool in an atmosphere of nitrogen. A solution of the ketone (I) (1.4 g, 0.01 mol) in ether (20 ml) was added to the foregoing solution at  $-60^\circ$ ; the mixture was allowed to warm to room temperature and then stirred for 3 h. Isolation gave a crude product (1.6 g); g.l.c. analysis (col. E; 100°) revealed substantial quantities of unchanged ketone. Preparative g.l.c. (col. F; 140°) gave pure 1-isopropyl-3,3,trans-5-trimethylcyclohexanol (IIi) (Found: C, 78.0; H, 12.9.  $C_{12}H_{24}O$  requires C, 78.2; H, 13.1%), identical with that obtained by the appropriate Grignard reaction,  $\tau^*$  6.3–9.3 (24H, m);  $\nu_{\max}$  3450  $cm^{-1}$  (OH).

(iv) *t-Butyl-lithium*. The alkyl-lithium was prepared as in (iii) from t-butyl chloride (3.7 g 0.04 mol) and lithium (0.69 g, 0.1 g atom) in ether (80 ml). Addition of the ketone (I) (1.4 g, 0.01 mol) in ether (20 ml) to the filtered ethereal solution of t-butyl-lithium as already described gave, on isolation, a crude product (1.5 g) which consisted largely of unchanged (I) (ca. 90%) (g.l.c. analysis on col. D; 100°). 3,3,trans-5-Trimethyl-1-t-butylcyclohexanol (IIm) was obtained by preparative g.l.c. (col. F; 140°) (Found: C, 78.9; H, 12.9.  $C_{13}H_{26}O$  requires C, 78.7; H, 13.2%).

1-Hydroxy-3,3,5-trimethylcyclohexanecarbonitrile [(IIc) + (IIc)].—(i) The ketone (I) (14 g, 0.1 mol) was added to sodium cyanide (4.9 g, 0.1 mol) in water (20 ml); sulphuric acid (33.4 g; 30%) was then added dropwise with stirring while the temperature was maintained below 15° by addition of ice. After being stirred for a further 15 min, the solution was extracted with ether; the combined extracts were dried and evaporated. The crude product, which decomposed on distillation under reduced pressure, had an i.r. spectrum consistent with it containing about 50% of the mixed cyanohydrins.

(ii) To a cooled ( $-10^\circ$ ) stirred suspension of potassium cyanide (10 g) in a solution of ketone (I) (14 g, 0.1 mol) in ether (30 ml), concentrated hydrochloric acid (25 ml) was added dropwise during 1 h. The mixture was kept at 0° for a further 6 h; the ether layer was then separated, the aqueous layer was extracted with ether ( $3 \times 35$  ml), and the combined extracts were washed, dried, and evaporated. The crude product,  $\nu_{\max}$  2240 (CN) and 3400  $cm^{-1}$  (OH), was hydrolysed as described later without further purification.

(iii) A solution of sodium hydrogen sulphite (13.5 g, 0.13 mol) in water (40 ml) was added during 30 min to a stirred mixture of ketone (I) (14 g, 0.1 mol), potassium cyanide (8.5 g, 0.13 mol), and water (25 ml) maintained at 25°. The mixture was stirred for a further 2 h and extracted with

ether; the extracts were dried and evaporated. The crude product was hydrolysed without further purification.

*Hydrolysis and Subsequent Esterification of Epimeric Mixtures of Cyanohydrins.*—(a) The cyanohydrin obtained in either (i) or (iii) of the foregoing preparations was kept in a mixture of glacial acetic acid (50 ml) and concentrated hydrochloric acid (50 ml) at room temperature for 3 days; the mixture was then heated under reflux for 50 h. The solution was concentrated under reduced pressure, the residue basified with aqueous sodium hydroxide, and the mixture extracted with ether (3 × 50 ml) (the extract being discarded). The aqueous layer was acidified with concentrated hydrochloric acid and extracted with ether (6 × 50 ml), and the combined extracts were dried and evaporated. The residue (II<sub>d</sub>) (7 g) crystallised [m.p. 133—134° (from hexane) (lit.,<sup>4</sup> 134—136°)] and was dissolved in ether (50 ml) and esterified with an excess of diazomethane in ether. Next day unchanged diazomethane was destroyed with glacial acetic acid; the ether solution was washed with aqueous sodium hydrogen carbonate, dried, and evaporated to give an oily residue (5.0 g). G.l.c. analysis revealed the presence of only one component. Preparative g.l.c. (col. F; 140°) gave pure *methyl 1-hydroxy-3,3,cis-5-trimethylcyclohexane-1-carboxylate* (II<sub>e</sub>) (Found: C, 65.9; H, 10.3. C<sub>11</sub>H<sub>20</sub>O requires C, 65.9; H, 10.1%);  $\nu_{\max}$ . 3530 (OH) and 1730 cm<sup>-1</sup> (C=O).

(b) The cyanohydrin (9 g) obtained in preparation (ii) was hydrolysed and the product esterified as described in (a). G.l.c. of the oily residue (5.0 g) (col. B; 150°) revealed the presence of two components. The major component,  $t_R$  8.7 min, was identical with (II<sub>e</sub>). The minor component (9%),  $t_R$  14.9 min was isolated as an oil by preparative g.l.c. (col. F; 140°) and was identified as *methyl 1-hydroxy-3,3,trans-5-trimethylcyclohexane-1-carboxylate* (III<sub>e</sub>) (Found: C, 65.8; H, 10.2. C<sub>11</sub>H<sub>20</sub>O<sub>3</sub> requires C, 65.9; H, 10.1%);  $\tau$  9.23 (3H, s, 3*ax*-Me), 9.06 (3H, s, 3*eq*-Me), 9.04 (3H, d,  $J$  5.1 Hz, 5*eq*-Me), 7.63 (1H, s, OH-*eq*), 6.26 (3H, s, CO<sub>2</sub>Me-*ax*), and 7.6—9.5 (7H, m, ring protons);  $\nu_{\max}$ . 3480 (OH) and 1750 cm<sup>-1</sup> (C=O).

*Oxidation of Compound (IIh).*—To a solution of the ethynyl alcohol (IIh) (1 g) in acetone (10 ml), potassium permanganate (1.25 g) in water (25 ml) was added during 1 h with stirring. The temperature was maintained below 20°. Stirring at room temperature was then continued for 1 h and the solution was heated under reflux for a further 1 h, cooled, filtered, decolourised by the passage of sulphur dioxide, and acidified with hydrochloric acid. The acid (II<sub>d</sub>) (0.7 g, 58%) was filtered off and recrystallised [from light petroleum (b.p. 60—80°)]; m.p. and mixed m.p. 134—135°. Its identity was confirmed by g.l.c. analysis of the methyl ester.

*Reduction of the Mixed Esters (II<sub>e</sub>) and (III<sub>e</sub>).* The mixed esters (5 g) obtained by hydrolysis and esterification of the mixed cyanohydrins were dissolved in ether (20 ml) and added dropwise to a stirred suspension of lithium aluminium hydride (1 g) in ether (50 ml). After being heated under reflux for 2 h the mixture was decomposed and the crude product isolated in the usual way. Distillation gave a major fraction (3.0 g), b.p. 76—80° at 2 × 10<sup>-3</sup> mmHg,  $\nu_{\max}$ . 3450 cm<sup>-1</sup> (OH). The product (1.1 g) was converted into the monotonoluen-*p*-sulphonate by dissolving in dry pyridine (20 ml), cooling to 0°, and adding toluene-*p*-sulphonyl chloride (1.4 g). The mixture was stored in a refrigerator for 2 days then worked up by standard procedures. Repeated recrystallisation [light petroleum (b.p. 40—60°)]

gave the pure *derivative*, m.p. 68—68.5° (Found: C, 62.9; H, 7.7; S, 9.8. C<sub>16</sub>H<sub>24</sub>O<sub>4</sub> requires C, 62.5; H, 8.0; S, 9.8%),  $\tau$  9.14 (3H, d,  $J$  6.5 Hz, 5*eq*-Me), 9.13 (3H, s, 3*eq*-Me), 8.93 (3H, s, 3*ax*-Me), 8.30 (1H, s, OH), 7.57 (3H, s, ArCH<sub>3</sub>), 6.27 (2H, s, TsO·CH<sub>2</sub>), 2.17 (2H, d,  $J$  8.5 Hz, aromatic), 2.64 (2H, d,  $J$  8.5 Hz, aromatic), and 7.8—9.5 (7H, m, ring protons). Conversion of the tosylate into the methyl derivative was accomplished by adding a solution of the crude product (0.5 g) in ether (20 ml) to a stirred suspension of lithium aluminium hydride (0.5 g) in ether (20 ml). After heating under reflux for 2 h the product (II<sub>b</sub>) (0.2 g) was isolated in the usual manner; m.p. and mixed m.p. 80—81°. Identity was confirmed by g.l.c., which also demonstrated that the crude reduction product consisted of only one epimer.

*Reaction of Ketone (I) with Dimethylloxosulphonium Methylide.*—The ylide reagent (0.1 mol) was prepared in tetrahydrofuran solution (50 ml) by heating under reflux in a flow of nitrogen for 2 h a suspension of sodium hydride (2.5 g; from a 50% mineral oil dispersion) with trimethyl-oxosulphonium iodide (22 g, 0.1 mol). A solution of the ketone (I) (7.0 g, 0.05 mol) in tetrahydrofuran (25 ml) was added dropwise with stirring and the mixture was heated under reflux for a further 24 h. The solvent was evaporated off and water (50 ml) was added to the residue. The mixture was extracted with light petroleum (b.p. 40—60°; 3 × 50 ml) and the combined extracts were dried and evaporated. The oily residue was distilled to give 5,5,7-trimethyl-1-oxaspiro[2,5]octane (IV) (4.5 g, 57%), b.p. 52—54° at 7 mmHg (lit.,<sup>17</sup> 90° at 13 mmHg),  $t_R$  22.6 min (col. A; 80°);  $\tau$  9.09 (3H, d,  $J$  6.5 Hz, 7*eq*-Me), 9.08 (3H, s, 5*eq*-Me), 8.96 (3H, s, 5*ax*-Me), 7.55 (2H, s, CH<sub>2</sub>O), and 8.0—9.3 (7H, m, ring protons);  $\nu_{\max}$ . 3040 cm<sup>-1</sup> (epoxide). The configuration was established by the reduction of this compound (1.54 g) in ether solution (30 ml) with lithium aluminium hydride (0.38 g). The product (II<sub>b</sub>) (1.3 g, 84%) had m.p. and mixed m.p. 80—81° [from light petroleum (b.p. 60—80°)]. G.l.c. of the crude material gave no indication of the presence of (III<sub>b</sub>).

*Reaction of Ketone (I) with Dimethylsulphonium Methylide.*—The ylide reagent (0.2 mol) was prepared by addition of an ethereal solution (75 ml) of butyl-lithium (0.22 mol) [from lithium (3.03 g) and butyl bromide (30.1 g)] under the usual conditions to a suspension of trimethylsulphonium iodide (40.8 g, 0.2 mol) in dry tetrahydrofuran (100 ml).<sup>17</sup> The mixture was stirred under nitrogen and was maintained at -5° during the addition (15 min). After a further 15 min stirring, a solution of ketone (I) (14 g, 0.1 mol) was added dropwise, and the mixture was stirred for a further 30 min at 0°. It was then warmed to room temperature, stirred for 1 h, and evaporated. Water (50 ml) was added and the organic material was extracted with light petroleum (b.p. 40—60°; 3 × 50 ml); the combined extracts were dried and evaporated. The crude product exhibited i.r. absorption indicating the presence of hydroxy-, epoxy-, and carbonyl groups. Careful distillation gave three fractions: (i) b.p. 74—78° at 20 mmHg (1.5 g), (ii) b.p. 78—79° at 20 mmHg (5.2 g), and (iii) b.p. 86—87° at 0.5 mmHg (5.5 g). G.l.c. analysis (col. A; 80°) of the first two fractions demonstrated that they consisted only of (I) and (IV). Fraction (iii) exhibited hydroxy-absorption (i.r.); the n.m.r. spectrum was consistent with this compound being (II<sub>n</sub>). The crude product (1.3 g) from a similar reaction was reduced with lithium aluminium hydride by the procedure already described to give a crude mixture; g.l.c. showed that this

consisted of (IIb) and the two epimeric 3,3,5-trimethylcyclohexanols, but gave no indication of the presence of (IIIb).

*1,1,3-Trimethyl-5-methylenecyclohexane* (V).—To an ethereal solution of phenyl-lithium (136 ml; 0.0011 mol per ml; 0.149 mol) were added successive small portions of triphenylphosphine methiodide (60 g, 0.15 mol). The suspension was stirred for 4 h; the ketone (I) (21 g, 0.15 mol) was then added with vigorous stirring and the mixture was heated under reflux overnight. After the addition of water (25 ml) the precipitate was filtered off and washed with ether, and the combined ethereal extracts were evaporated. The residue was fractionated from a thermostatically controlled oil-bath and the fraction b.p. 144–147° at 662 mmHg was refractionated to furnish pure *olefin* (V) (11.3 g, 53%), b.p. 144–146° at 662 mmHg (Found: C, 87.0; H, 13.1.  $C_{10}H_{18}$  requires C, 86.9; H, 13.1%);  $t_R$  3.0 min (col. B; 80°);  $\tau$  5.39 (2H, d,  $J$  4.5 Hz, C=CH<sub>2</sub>), and 7.7–9.3 (16H, ring protons and methyl groups),  $\nu_{max}$  3075 and 1610 cm<sup>-1</sup> (C=CH<sub>2</sub>).

*Epoxidation of the Olefin* (V).—To a dichloromethane solution (100 ml) of *m*-chloroperbenzoic acid (8.6 g, 0.05 mol), a solution of the olefin (V) (6.9 g, 0.05 mol) in dichloromethane was added dropwise with stirring. The temperature of the mixture was maintained below 25° during the following 2 h; the dichloromethane was then evaporated off and the residue filtered through a short column of Grade II alumina (petroleum as eluant). The petroleum was evaporated off and the residue distilled. The fraction b.p. 74–80° at 14 mmHg was refractionated to yield impure epoxide (VI) (3.1 g), b.p. 62–63° at 5 mmHg. The epoxide was contaminated by a carbonyl compound and this was removed by careful preparative g.l.c. (col. G; 120°) to give pure *epoxide*,  $\nu_{max}$  (neat) 3020 cm<sup>-1</sup> (epoxide),  $\tau$  7.25 and 7.35 (2H, q, CH<sub>2</sub>·O) and 8.15–9.30 (16H, m, ring protons and methyl groups),  $t_R$  44 min (col. G; 120°) (Found: C, 77.65; H, 11.9.  $C_{10}H_{18}O$  requires C, 77.85; H, 11.75%).

*1,3,3-cis-5-Tetramethylcyclohexanol* (IIIb).—Reduction of the epoxide (VI) (1 g) with lithium aluminium hydride in ether followed by standard isolation procedures gave a crude product which was purified by preparative g.l.c. (col. F; 140°). The *alcohol* (IIIb) was isolated as an oil (Found: C, 76.9; H, 12.9.  $C_{10}H_{20}O$  requires C, 76.8; H, 12.9%);  $t_R$  9.1 min (col. B; 100°) [*cf.*  $t_R$  7.0 min for the epimer (IIb) under the same conditions],  $\tau$  8.04 (1H, s, OH) and 8.0–9.4 (19H, m, ring protons and methyl groups);  $\nu_{max}$  3370 cm<sup>-1</sup> (OH).

*Methylation of the Alcohol* (IIj). A solution of (IIj) (13.4 g, 0.07 mol) in dry dimethylformamide (50 ml) was added to sodium hydride (from 4.5 g of the 50% mineral oil dispersion) followed by methyl iodide (31 g, 0.22 mol), which was added dropwise with stirring during 30 min. The mixture was heated under reflux overnight; water (50 ml) was then added

and the mixture was extracted with ether (3 × 50 ml). The ether layer was washed successively with 2.5N-hydrochloric acid (6 × 50 ml) and water (2 × 50 ml) and then dried. Distillation (80–86° at 9 mmHg) gave the *O-methyl ether* (5.7 g, 40%), which was shown to be pure by g.l.c.,  $t_R$  (col. B; 100°) 8 min (Found: C, 79.8; H, 12.2.  $C_{13}H_{24}O$  requires C, 79.5; H, 12.3).

*Ozonolysis of the O-Methyl Ether of (IIj)*.—The foregoing compound (2.9 g, 0.015 mol) was dissolved in chloroform (50 ml), cooled to -20°, and subjected to a stream of ozonised oxygen. A sample was tested at 10 min intervals with bromine water and the reaction was stopped when the addition of the ozonised solution no longer discoloured the reagent. The ozonide was decomposed with water (25 ml) and zinc dust (2 g) and the mixture was stirred for 2 h. The zinc was filtered off and the organic layer separated. The aqueous layer was extracted with chloroform (3 × 25 ml) and the combined extracts dried and evaporated under reduced pressure to give a crude aldehyde (2.0 g),  $\nu_{max}$  2740, 2840, and 1730 cm<sup>-1</sup> (CHO).

*Thioacetal Formation from 2-(1-Methoxy-3,3,5-trimethylcyclohexyl)ethanal*.—The crude aldehyde (2 g) from the foregoing experiment was dissolved in methanol (10 ml) and added to a solution of 4,5-dimethyl-1,2-phenylenedimethanethiol (2.8 g) in methanol (30 ml). After addition of concentrated hydrochloric acid (1 ml) the mixture was left for 3 h. Water (50 ml) was added, the solution was extracted with ether (3 × 50 ml), and the ether layer was washed with water (2 × 50 ml), dried, and evaporated. The oily product (3 g) was shown to be a mixture of three major and several minor components by t.l.c.; a sample (1.6 g) purified by dry column chromatography on alumina (100 g) deactivated by water (1 g) (methylene chloride as solvent) and recrystallisation from aqueous ethanol gave the pure *thioacetal* (100 mg), m.p. 120° (Found: C, 69.7; H, 8.9; S, 16.8.  $C_{22}H_{34}S_2O$  requires C, 69.8; H, 9.0; S, 16.9%).

*Reductive Desulphurisation of the Thioacetal*.—The thioacetal (50 mg) in ethanol (50 ml) was refluxed with Raney nickel (1 g) for 6 h. The solution was filtered and evaporated and a solution of the residue in ether (50 ml) was dried and evaporated. The crude product (30 mg) was shown to consist of one major component, the *O-methyl ether of (IIg)*, by g.l.c. [ $t_R$  (col. B; 80°) 5.6 min].

*Methylation of the Alcohol* (IIf).—The reaction of (IIf) (6.3 g, 0.04 mol) with sodium hydride (2.2 g of dispersion) in dry dimethylformamide (50 ml) and methyl iodide (15.4 g, 0.11 mol) was carried out as already described. The crude *product* (5.2 g) was purified by preparative g.l.c. (col. E; 120°) (Found: C, 78.3; H, 13.4.  $C_{12}H_{24}O$  requires C, 78.2; H, 13.1) and characterised by n.m.r. and i.r. spectroscopy.

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