

## Metacyclophane and Related Compounds. Part 11. Reaction of 8,16-Bis(bromomethyl)[2.2]metacyclophane and 8,16-Bis(bromomethyl)-5,13-di-*t*-butyl[2.2]metacyclophane with Grignard Reagents<sup>1</sup>

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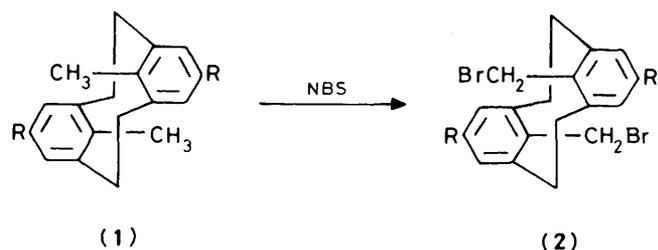
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Reaction of 8,16-bis(bromomethyl)- (2a) and 8,16-bis(bromomethyl)-5,13-di-*t*-butyl[2.2]metacyclophane (2b) with Grignard reagents (3a-f) afforded the corresponding 8,16-dialkyl derivatives (4a-j) together with the spiro compound (5a) and (5b), respectively.

The yield of (4) was dependent upon the reaction time and the steric bulk and quantity of Grignard reagent used.

Reaction of 8-bromomethyl-16-methyl[2.2]MCP (13c) with Grignard reagents afforded the corresponding 8-alkyl-16-methylMCP (15) together with the reduction product, 8,16-dimethyl[2.2]MCP (1a), and the bis[2.2]MCP (16a). However, 8-bromomethyl-16-methyl-5,13-di-*t*-butyl[2.2]MCP (13d) gave only the corresponding 8-alkyl-16-methyl MCP in good yield.

Recently, we have reported that 8,16-bis(bromomethyl)[2.2]-metacyclophanes (2) could be easily prepared by treatment of the corresponding 8,16-dimethyl derivatives (1) with *N*-bromosuccinimide (NBS) (Scheme 1).<sup>2</sup>



a; R = H  
b; R = Bu<sup>t</sup>

Scheme 1.

Benzyl halides are very reactive with many kinds of nucleophiles. Therefore, compound (2) seems to be a key synthetic intermediate leading to various 8,16-disubstituted [2.2]metacyclophanes.

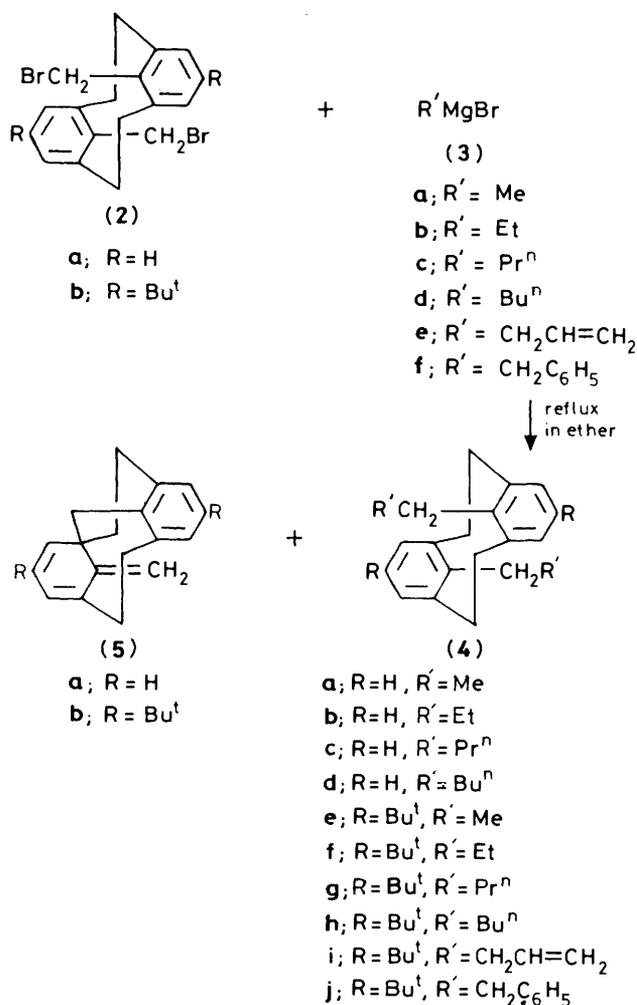
It is expected that substituents at the internal positions of metacyclophanes (MCPs) might have different chemical properties from similar benzenoid substituents since the former substituents are positioned over the face of the opposing aromatic ring. Nevertheless, there are a few reports about the chemical nature of internal substituents on MCPs.<sup>3</sup>

We undertook the present work in order to obtain information on the chemical nature of the title compounds as part of an investigation concerning the chemistry of MCPs.

### Results and Discussion

Reaction of 8,16-bis(bromomethyl)[2.2]MCP (2a) and 8,16-bis(bromomethyl)5,13-di-*t*-butyl[2.2]MCP (2b) with several Grignard reagents (3) was carried out under various conditions. The results are summarized in Table 1 and Scheme 2.

When (2a) was treated with (3a) in refluxing ether for 1 h, the expected product (4a) was obtained in only 1.9% yield together with a trace amount of the unexpected alkene (5a). However, the prolonged reaction of (2a) with (3a) afforded (4a) and (5a)



Scheme 2.

in 47 and 41% yields, respectively. The yield of (4a) increased with increasing amounts of (3a) used.

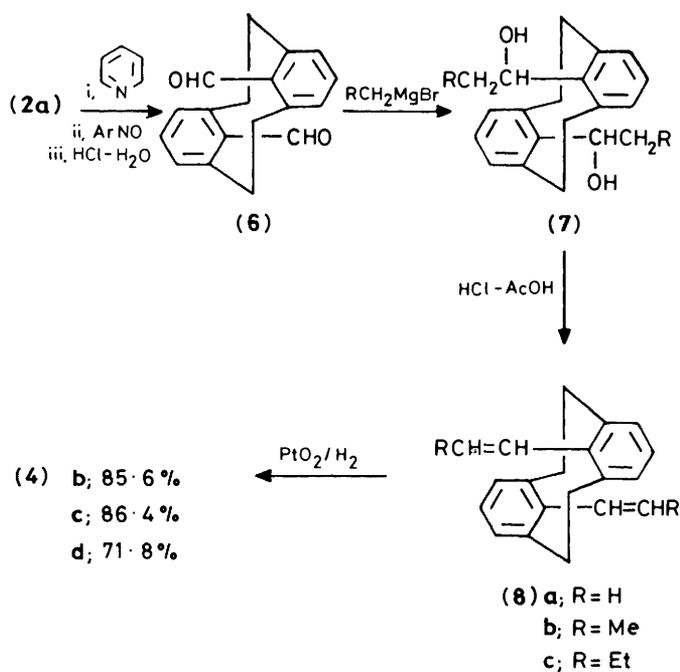
In contrast with (3a) Grignard reagents (3b-d) having larger alkyl groups than methyl afforded poor yields of the corresponding compounds (4) but high yields of (5a).

**Table 1.** Reaction of 8,16-bis (bromomethyl)[2.2]MCP (**2a**) and -5,13-di-*t*-butyl[2.2]MCP (**2b**) with Grignard reagents<sup>a</sup>

Run	MCP	Grignard reagent	(3)/(2) (molar ratio)	Product (%) <sup>b</sup>
1 <sup>c</sup>	(2a)	(3a)	20	(4a) (1.9), (5a) (+) <sup>d</sup>
2	(2a)	(3a)	20	(4a) (47), (5a) (41)
3	(2a)	(3a)	50	(4a) (53), (5a) (26)
4	(2a)	(3a)	100	(4a) (76), (5a) (+) <sup>d</sup>
5	(2a)	(3b)	20	(4b) (4), (5a) (85)
6	(2a)	(3b)	100	(4b) (16), (5a) (43)
7	(2a)	(3c)	20	(4c) (+), <sup>d</sup> (5a) (90)
8	(2a)	(3d)	20	(4d) (+), <sup>d</sup> (5a) (94)
9 <sup>e</sup>	(2b)	(3a)	20	(4e) (54), (5b) (4)
10	(2b)	(3a)	20	(4e) (96), (5b) (3)
11	(2b)	(3b)	3	(4f) (5), (5b) (92)
12	(2b)	(3b)	20	(4f) (81), (5b) (6)
13	(2b)	(3c)	20	(4g) (41), (5b) (40)
14	(2b)	(3d)	20	(4h) (24), (5b) (62)
15	(2b)	(3d)	50	(4h) (60), (5b) (11)
16	(2b)	(3e)	50	(4i) (82), (5b) (10)
17 <sup>f</sup>	(2b)	(3f)	100	(4j) (38), (5b) (25)

<sup>a</sup> The reaction mixture was refluxed in ether for 12 h unless otherwise indicated. <sup>b</sup> The isolated yields are shown. <sup>c</sup> The reaction time was 1 h, and (**1a**) was recovered in 89% yield. <sup>d</sup> Plus sign means that the yield of product was less than 1%. <sup>e</sup> The reaction time was 1 h, and (**1b**) was recovered in 39% yield. <sup>f</sup> A small amount of diphenylethane was detected.

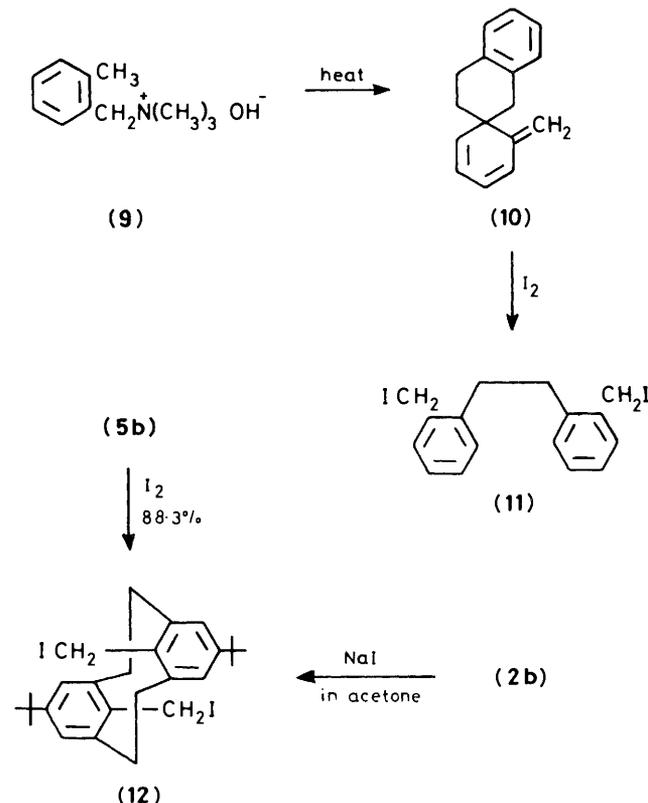
For identification and comparison compounds (**4b–d**) were prepared by the alternative route shown in Scheme 3. The preparative route from (**2a**) to (**8**) via (**6**) and (**7**) was reported previously.<sup>4</sup> The hydrogenation of (**8**) in the presence of PtO<sub>2</sub> catalyst gave the corresponding dialkyl MCP (**4**) in good yield.



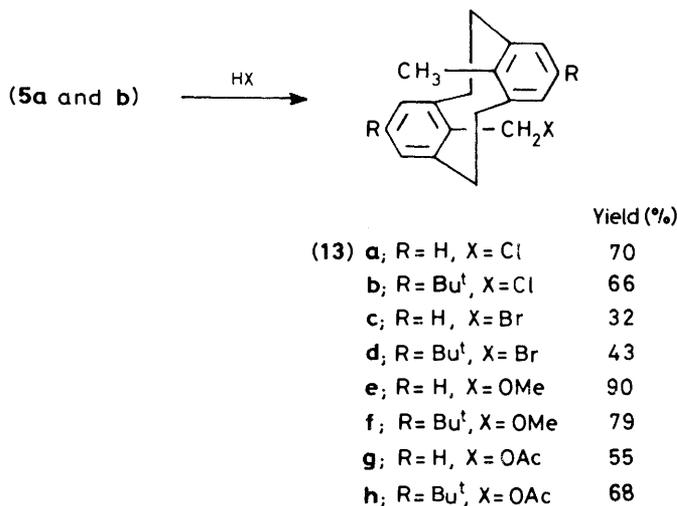
In contrast with (**2a**), compound (**2b**) reacted easily with an excess of a Grignard reagent (**3**) having a larger alkyl group than methyl to give the corresponding (**4**) as the main product in good yield. Unexpectedly, compound (**5b**) was obtained in good

yield in the reaction of (**2b**) with (**3b**) when the molar ratio of (**2b**):(**3b**) was 1:3 (Run 11).

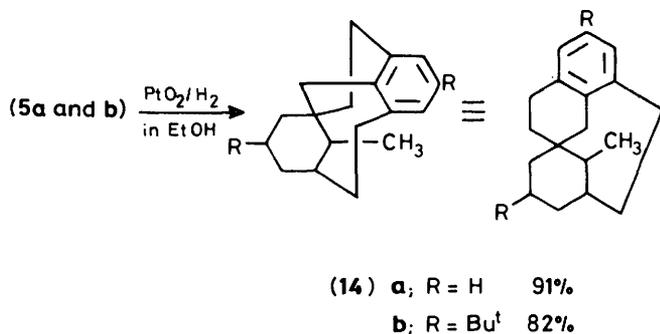
Errede reported<sup>5</sup> that the thermolysis of *o*-methylbenzyl-(trimethyl)ammonium hydroxide (**9**) afforded 3',4'-dihydro-6-methylenespiro[cyclohexa-2,4-diene-1,2'(1'*H*)-naphthalene] (**10**). Compound (**5b**) was converted into the iodide (**11**) the bis(iodomethyl)MCP (**12**) which<sup>3</sup> was previously obtained by a halogen exchange reaction of (**2b**) (Scheme 4).



It was also found that the treatment of (**5a** and **b**) with hydrochloric acid or hydrobromic acid in methanol in the presence of sulphuric or acetic acid afforded the corresponding 8,16-unsymmetrically disubstituted MCPs (**13a–d**) (Scheme 5).

**Scheme 5.**

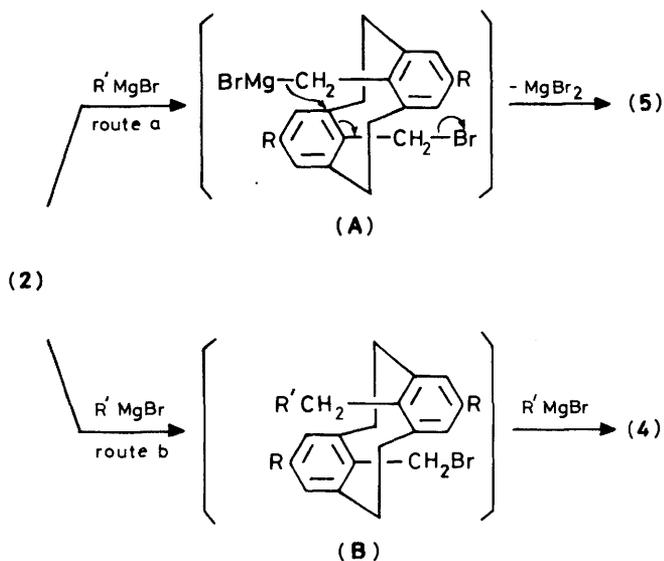
When (**5a** and **b**) were hydrogenated in the presence of  $\text{PtO}_2$ , the corresponding hexahydro derivatives (**14a** and **b**) were obtained in good yield (Scheme 6).



Scheme 6.

Based on the above chemical conversions and spectral data, (**5a** and **b**) were confirmed as 3',4'-dihydro-2-methylene-3,8'-ethanspiro[cyclohexa-3,5-diene-1,2'(1'*H*)-naphthalene] and as 5,6-di-*t*-butyl-3',4'-dihydro-2-methylene-3,8'-ethanspiro[cyclohexa-3,5-diene-1,2'(1'*H*)-naphthalene], respectively.

From the results described above, it is concluded that (**4**) and (**5**) must be formed competitively, and Scheme 7 is proposed.

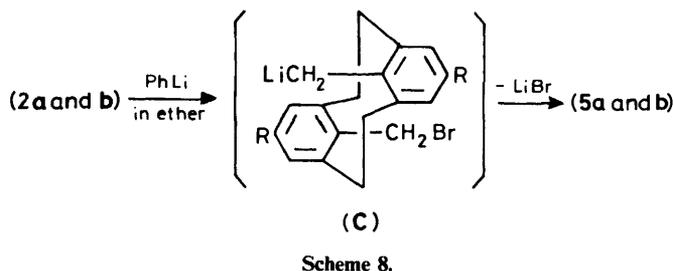


Scheme 7.

Route a, an exchange reaction, should be more favourable than route b, because the former route has less steric hindrance than the latter course. An excess of Grignard reagents, therefore, was required to give (**4**) in good yield. The preferred formation of the C-C-coupling product (**4**) in the reaction with (**2b**) can be explained by the destabilization of the intermediate (**A**) by the electron-donating *t*-butyl groups.

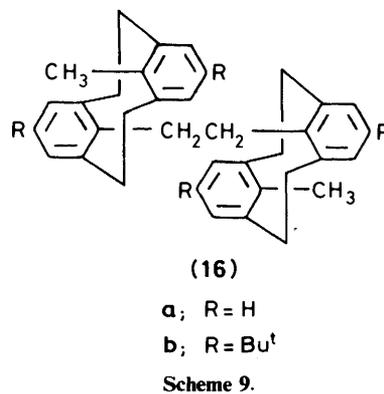
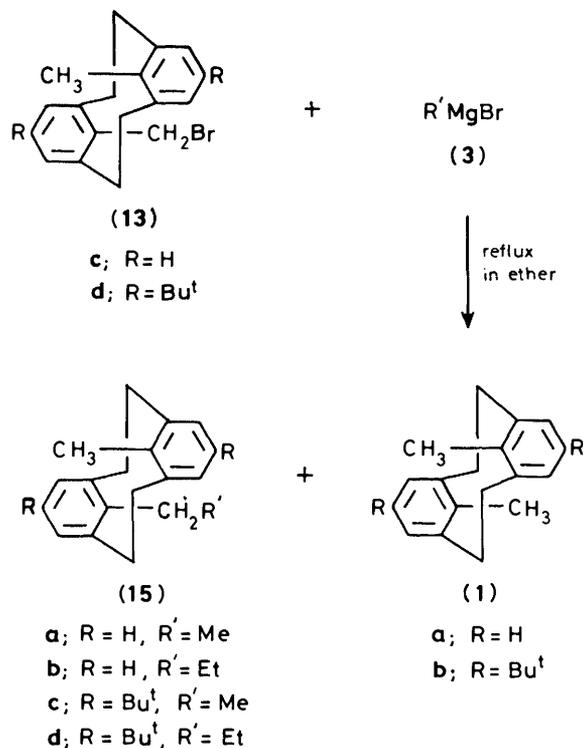
It was also found that treatment of (**2a** and **b**) with phenyllithium in ether afforded (**5a** and **b**) respectively, in almost quantitative yield (Scheme 8). This result strongly supports route a proposed above as (**5a** and **b**) are very likely formed through intermediate (**C**), which resembles intermediate (**A**).

It might be expected that the reaction of 8-bromomethyl-16-methyl- (**13c**) or 8-bromomethyl-5,13-di-*t*-butyl-16-methyl-



[2.2]MCP (**13d**) with (**3**) would afford the corresponding 8-alkyl-16-methyl[2.2]MCP (**15**) in good yield (Scheme 9). However, the expected (**15a**) was obtained in good yield only when (**13c**) was allowed to react with excess of (**3a**) for prolonged periods. However, at shorter reaction times, 8,16-dimethyl-[2.2]MCP (**1a**) was obtained in the reaction of (**13c**) with (**3b**).

In contrast to (**13c**), compound (**13d**), like (**2b**), reacted easily with Grignard reagents (**3**) to give the corresponding products (**15**) in good yield (Table 2).

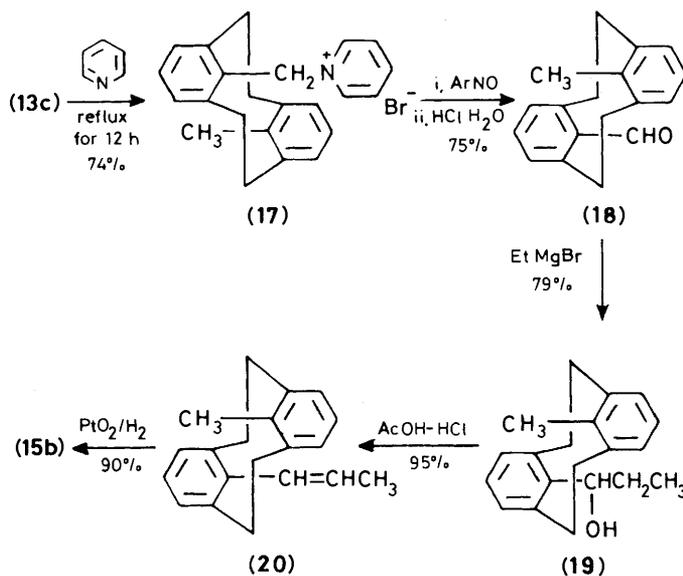


**Table 2.** Reaction of 8-bromomethyl-16-methyl- (13c) and 8-bromomethyl-5,13-di-*t*-butyl-16-methyl-[2.2]MCP (13d) with Grignard reagents<sup>a</sup>

Run	MCP	Grignard reagent	(3)/(13) molar ratio	Time (h)	Product (%) <sup>b</sup>
1	(13c)	(3a)	3	1	(1a) (60), (15a) (9), (16a) (18)
2	(13c)	(3a)	10	12	(1a) (40), (15a) (7), (16a) (50)
3	(13c)	(3a)	50	12	(1a) (+), <sup>c</sup> (15a) (80), (16a) (4)
4	(13c)	(3b)	3	1	(1a) (73), (15b) (11), (16a) (8)
5	(13c)	(3b)	10	1	(1a) (63), (15b) (21), (16a) (4)
6	(13c)	(3b)	10	12	(1a) (38), (15b) (21), (16a) (17)
7	(13c)	(3b)	50	12	(1a) (19), (15b) (59), (16a) (3)
8	(13d)	(3a)	10	1	(15c) (92)
9	(13d)	(3b)	10	1	(15d) (84)

<sup>a</sup> The reaction mixture was refluxed in ether. <sup>b</sup> The isolated yields of (16) and (15c and d) are shown. The other yields were determined by g.l.c. <sup>c</sup> Plus sign means that the yield of product was less than 1%.

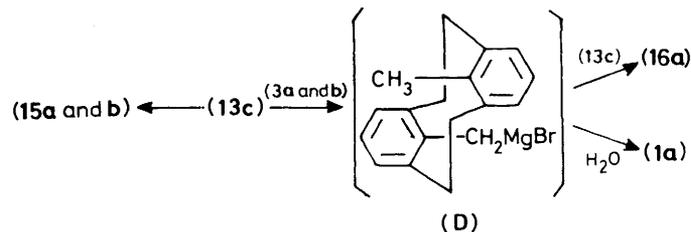
The separation of (1a) and (15b) was so difficult that their yields were determined only by g.l.c. The necessary authentic sample of (15b) for the g.l.c. analysis was prepared by the route outlined in Scheme 10.



**Scheme 10.**

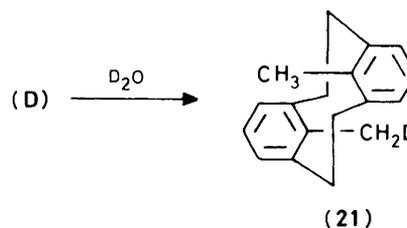
Compound (16a and b) were also prepared in good yield by treatment of (1a and b) with phenyl-lithium in ether. The <sup>1</sup>H n.m.r. spectra of (16a and b) show the protons of the central ethano-bridge at  $\delta$  0.50 and 0.33, respectively, indicating that they are shielded by the ring current of the opposing aromatic rings.

The formation of (1a) in the reaction of (13c) with (3a and b) suggests the occurrence of an exchange reaction between (13c) and (2) (Scheme 11). The intermediate (D) could react with (13c) to afford (16a). The exchange reaction would occur competitively with the C-C-coupling reaction of (13c) with (3a) or (3b), which would give the product (15a) or (15b). The intermediate (D) is so stable in the reaction mixture that compound (1a) might be generated when the reaction mixture is quenched with water. Indeed, when the reaction mixture obtained from



**Scheme 11.**

(13c) and (3b) (Run 4) was quenched with D<sub>2</sub>O, the 8-monodeuteriated methyl-16-methyl[2.2]MCP (21) was obtained in good yield and in high isotopic purity (90%).



### Experimental

All m.p.s and b.p.s were uncorrected. N.m.r. spectra were determined at 100 MHz with a Nippon Denshi JEOL-100 NMR spectrometer with Me<sub>4</sub>Si as internal reference, and i.r. spectra were measured as KBr pellets or as a liquid film on NaCl plates in a Nippon Bunko IR-A-102 spectrophotometer. Mass spectra were obtained on a Nippon Denshi JMS-01SA-2 spectrometer at 75 eV using a direct inlet system.

**Analytical Procedure.**—Analyses were carried out by g.l.c. using a JGC-20KFP Nippon Denshi gas chromatograph, Silicon OV-1 30%, 0.75 m, column temperature 220 °C, carrier gas nitrogen, 50 ml min<sup>-1</sup>.

**Reaction of 8,16-Bis(bromomethyl)- (2a) and 8,16-Bis(bromomethyl)-5,13-di-*t*-butyl[2.2]MCP (2b) with Grignard Reagents (3). General Procedure.**—To a solution of the Grignard reagent in refluxing ether (30 ml) was added (2) (1 mmol). After the reaction mixture had been refluxed for 12 h, it was quenched with 10% aqueous ammonium chloride and extracted with methylene dichloride. The extract was dried (Na<sub>2</sub>SO<sub>4</sub>) and evaporated under reduced pressure to leave a residue which, on column chromatography (silica gel) with hexane and benzene as eluants, afforded (4) and (5) respectively.

**Compound (4a)**, prisms (from hexane), m.p. 210–212 °C;  $\nu_{\max}$  (KBr) 3 040, 2 940, 1 575, 1 445, 1 180, 1 050, 870, 800, 760, and 735 cm<sup>-1</sup>;  $\delta_{\text{H}}$  (CDCl<sub>3</sub>) 0.31 (6 H, t, *J* 7 Hz), 1.06 (4 H, q, *J* 7 Hz), 2.60–3.08 (8 H, m), and 6.73–7.18 (6 H, m); *m/z* 264 (*M*<sup>+</sup>) (Found: C, 90.8; H, 9.2. C<sub>20</sub>H<sub>24</sub> requires C, 90.85; H, 9.15%).

**Compound (4e)**, prisms (from hexane), m.p. 262–264 °C (lit.,<sup>2</sup> 262–264 °C).

**Compound (4f)**, prisms (from hexane), m.p. 205–206 °C (lit.,<sup>2</sup> 205–206 °C).

**Compound (4g)**, prisms (from hexane), m.p. 166–168 °C (lit.,<sup>2</sup> 166–168 °C).

**Compound (4h)**, prisms (from hexane), m.p. 113–115 °C;  $\nu_{\max}$  (KBr) 3 020, 2 950, 2 900, 1 460, 1 355, 1 270, 1 180, 880, 860, and 715 cm<sup>-1</sup>;  $\delta_{\text{H}}$  (CDCl<sub>3</sub>) 0.72 (6 H, t, *J* 6 Hz), 0.55–1.10 (16 H, m), 1.28 (18 H, s), 2.76–2.86 (8 H, m), and 7.00 (4 H, s); *m/z* 460 (*M*<sup>+</sup>) (Found: C, 88.8; H, 11.05. C<sub>34</sub>H<sub>52</sub> requires C, 88.62; H, 11.38%).

**Compound (4i)**, prisms (from hexane), m.p. 187–189 °C;  $\nu_{\max}$  (KBr) 3 040, 2 960, 1 590, 1 450, 1 360, 1 275, 1 180, 990, 910, 880, 860, and 660  $\text{cm}^{-1}$ ;  $\delta_{\text{H}}$  ( $\text{CDCl}_3$ ) 1.00–1.52 (8 H, m), 1.26 (18 H, s), 2.72–2.94 (8 H, m), 4.55–4.64 (2 H, m), 4.72–4.75 (2 H, m), 5.16–5.55 (2 H, m), and 7.02 (4 H, s);  $m/z$  428 ( $M^+$ ) (Found: C, 89.7; H, 10.2.  $\text{C}_{22}\text{H}_{44}$  requires C, 89.65; H, 10.35%).

**Compound (4j)**, plates (from hexane), m.p. 239–242 °C;  $\nu_{\max}$  (KBr) 3 040, 2 950, 2 860, 1 595, 1 490, 1 445, 1 360, 1 275, 1 180, 885, 860, 750, and 700  $\text{cm}^{-1}$ ;  $\delta_{\text{H}}$  ( $\text{CDCl}_3$ ) 1.09 (18 H, s), 1.18–1.36 (4 H, m), 1.84–2.01 (4 H, m), 2.85–3.10 (8 H, s), 6.72–6.81 (4 H, m), 6.99 (4 H, s), and 6.98–7.16 (6 H, m);  $m/z$  528 ( $M^+$ ) (Found: C, 90.8; H, 9.15.  $\text{C}_{40}\text{H}_{48}$  requires C, 90.85; H, 9.15%).

**Compound (5a)**, prisms (from hexane), m.p. 101–102 °C;  $\nu_{\max}$  (KBr) 3 020, 2 940, 1 540, 1 200, 880, 775, 760, 725, 704, 695, and 680  $\text{cm}^{-1}$ ;  $\delta_{\text{H}}$  ( $\text{CDCl}_3$ ) 1.86–3.27 (12 H, m), 3.96 (1 H, d,  $J$  1 Hz), 4.05 (1 H, s), 5.78–6.12 (3 H, m), and 6.80–7.10 (3 H, m);  $\delta_{\text{C}}$  ( $\text{CDCl}_3$ ) 27.29 (t), 28.80 (t), 34.55 (t), 36.21 (t), 41.18 (t), 45.81 (s), 107.89 (t), 118.36 (d), 125.19 (d), 125.33 (d), 126.11 (d), 126.36 (d), 138.40 (s), 139.90 (s), 140.20 (s), 140.87 (d), 151.94 (s), and 169.14 p.p.m. (s);  $m/z$  234 ( $M^+$ );  $\lambda_{\max}$  (cyclohexane) (log  $\epsilon$ ) 290 (3.48), 272 (3.46), and 225 nm (3.92) (Found: C, 92.0; H, 7.9.  $\text{C}_{18}\text{H}_{18}$  requires C, 92.26; H, 7.74%).

**Compound (5b)**, prisms (from hexane), m.p. 252–254 °C;  $\nu_{\max}$  (KBr) 3 040, 2 950, 2 860, 1 475, 1 460, 1 360, 1 200, 870, 815, 780, and 710  $\text{cm}^{-1}$ ;  $\delta_{\text{H}}$  ( $\text{CDCl}_3$ ) 1.07 (9 H, s), 1.27 (9 H, s), 1.82–3.15 (10 H, m), 3.86 (1 H, d,  $J$  1 Hz), 3.96 (1 H, s), 5.73 (1 H, d,  $J$  1 Hz), 5.92 (1 H, s), 6.84 (1 H, d,  $J$  1 Hz), and 6.90 (1 H, d,  $J$  1 Hz);  $\delta_{\text{C}}$  ( $\text{CDCl}_3$ ) 28.12 (t), 29.34 (t), 29.34 (t), 31.58 (q), 33.67 (s), 34.26 (s), 35.18 (t), 36.55 (t), 41.47 (t), 46.20 (s), 106.62 (t), 118.95 (d), 122.36 (d), 122.90 (d), 130.05 (d), 135.95 (s), 138.60 (s), 139.46 (s), 146.33 (s), and 150.24 p.p.m. (s);  $m/z$  346 ( $M^+$ );  $\lambda_{\max}$  (cyclohexane) (log  $\epsilon$ ) 289 (3.39), 268 (2.43), and 225 nm (4.08) (Found: C, 90.0; H, 9.8.  $\text{C}_{26}\text{H}_{34}$  requires C, 90.11; H, 9.87%).

**Hydrogenation of Compounds (8) in the Presence of  $\text{PtO}_2$  Catalyst. Typical Procedure.**—A mixture of (**8a**) (28.8 mg, 0.1 mmol), platinum dioxide (10 mg, 0.038 mmol), and ethanol (20 ml) was stirred for 4 h at room temperature under hydrogen. The reaction mixture was filtered and the filtrate was evaporated under reduced pressure to leave a residue which was recrystallized from methanol to give (**4b**) (25 mg, 85.6%) as prisms, m.p. 172–174 °C;  $\nu_{\max}$  (KBr) 3 040, 2 950, 2 900, 2 850, 1 460, 1 445, 1 370, 1 260, 1 180, 1 085, 1 060, 775, and 735  $\text{cm}^{-1}$ ;  $\delta_{\text{H}}$  ( $\text{CDCl}_3$ ) 0.42 (6 H, t,  $J$  6 Hz), 0.54–1.12 (8 H, m), 2.70–2.97 (8 H, m), and 6.74–7.09 (6 H, m);  $m/z$  292 ( $M^+$ ) (Found: C, 90.6; H, 9.6.  $\text{C}_{22}\text{H}_{28}$  requires C, 90.35; 9.65%).

Compounds (**4c**) and (**4d**) were also obtained in this manner, from (**8b**) and (**8c**), respectively.

**Compound (4c)**, prisms (from methanol), m.p. 72–74 °C;  $\nu_{\max}$  (KBr) 3 050, 2 960, 2 920, 2 850, 1 580, 1 440, 1 420, 1 180, 885, 800, 765, and 730  $\text{cm}^{-1}$ ;  $\delta_{\text{H}}$  ( $\text{CDCl}_3$ ) 0.62 (6 H, t,  $J$  7 Hz), 0.72–1.16 (12 H, m), 2.60–3.04 (8 H, m), and 6.75–7.09 (6 H, m);  $m/z$  320 ( $M^+$ ) (Found: C, 90.7; H, 10.05.  $\text{C}_{24}\text{H}_{32}$  requires C, 89.94; H, 10.06%).

**Compound (4d)**, prisms (from methanol), m.p. 51–52 °C;  $\nu_{\max}$  (KBr) 3 060, 2 970, 2 930, 2 860, 1 580, 1 445, 1 180, 1 100, 890, 780, 740, and 720  $\text{cm}^{-1}$ ;  $\delta_{\text{H}}$  ( $\text{CDCl}_3$ ) 0.72 (6 H, t,  $J$  6 Hz), 0.48–1.18 (16 H, m), 2.70–2.97 (8 H, m), and 6.75–7.10 (6 H, m);  $m/z$  348 ( $M^+$ ) (Found: C, 89.2; H, 10.1.  $\text{C}_{26}\text{H}_{36}$  requires C, 89.59; H, 10.41%).

**Reaction of Compound (5b) with Iodine.**—To a solution of (**5b**) (150 mg, 0.434 mmol) in carbon tetrachloride (20 ml) was added dropwise a solution of iodine (116.9 mg, 0.460 mmol) in carbon tetrachloride (5 ml) at room temperature. After 20 h, the

reaction mixture was concentrated under reduced pressure to leave a residue, to which was added a small amount of hexane to give compound (**12**) (230 mg, 88.3%) as prisms (from benzene), m.p. 300 °C (lit.,<sup>2</sup> 300 °C).

**Reaction of the Spin Compounds (5a and b) with Hydrogen Chloride.**—To a magnetically stirred solution of (**5a**) (150 mg, 0.641 mmol) in dry ether (20 ml) was passed hydrogen chloride at room temperature for 15 min. The reaction mixture was refluxed for 48 h and concentrated under reduced pressure to leave a residue which was extracted with methylene dichloride; the extract was washed with water, dried ( $\text{Na}_2\text{SO}_4$ ), and evaporated under reduced pressure to leave a residue which was recrystallized from hexane to give (**13a**) (121 mg, 70%) as prisms, m.p. 202–205 °C (decomp.);  $\nu_{\max}$  (KBr) 3 030, 2 930, 1 570, 1 440, 1 180, 1 045, 880, 800, 765, 715, 680, and 660  $\text{cm}^{-1}$ ;  $\delta_{\text{H}}$  ( $\text{CDCl}_3$ ) 0.57 (3 H, s), 2.64–3.12 (8 H, m), 3.05 (2 H, s), and 6.84–7.22 (6 H, m);  $m/z$  270 and 272 ( $M^+$ ) (Found: C, 79.4; H, 7.2.  $\text{C}_{18}\text{H}_{19}\text{Cl}$  requires C, 79.84; H, 7.07%).

Compound (**13b**) was similarly obtained from (**5b**).

**Compound (13b)**, prisms (from hexane), m.p. 271–273 °C (decomp.);  $\nu_{\max}$  (KBr) 3 030, 2 940, 1 580, 1 450, 1 350, 1 270, 1 180, 880, 855, 735, and 675  $\text{cm}^{-1}$ ;  $\delta_{\text{H}}$  ( $\text{CDCl}_3$ ) 0.58 (3 H, s), 1.28 (9 H, s), 1.32 (9 H, s), 2.75–3.03 (8 H, m), 3.07 (2 H, s), 7.06 (2 H, s), and 7.15 (2 H, s);  $m/z$  382 and 384 ( $M^+$ ) (Found: C, 80.7; H, 9.2.  $\text{C}_{26}\text{H}_{35}\text{Cl}$  requires: C, 81.53; H, 9.21%).

**Reaction of Compounds (5g and b) with Hydrogen Bromide.**—To a magnetically stirred solution of (**5a**) (150 mg, 0.641 mmol) in dry ether (20 ml) was passed hydrogen bromide at room temperature for 15 min. The reaction mixture was refluxed for 12 h and concentrated under reduced pressure to leave a residue which was extracted with methylene dichloride; the extract was washed with water, dried ( $\text{Na}_2\text{SO}_4$ ), and evaporated under reduced pressure to leave a residue which was recrystallized from hexane to give (**13c**) (65 mg, 32.2%) as prisms, m.p. 215–217 °C (decomp.);  $\nu_{\max}$  (KBr) 3 040, 2 920, 2 850, 1 570, 1 210, 1 180, 880, 765, 740, and 720  $\text{cm}^{-1}$ ;  $\delta_{\text{H}}$  ( $\text{CDCl}_3$ ) 0.59 (3 H, s), 2.68–3.14 (8 H, m), 3.00 (2 H, s), and 6.84–7.22 (6 H, m);  $m/z$  314 and 316 ( $M^+$ ) (Found: C, 68.7; H, 5.8.  $\text{C}_{18}\text{H}_{19}\text{Br}$  requires C, 68.58; H, 6.08%).

Compound (**13d**) was similarly obtained from (**5b**).

**Compound (13d)**, prisms (from hexane), m.p. 272–275 °C (decomp.);  $\nu_{\max}$  (KBr) 3 020, 2 940, 1 580, 1 445, 1 350, 1 270, 1 215, 1 180, 880, 855, and 730  $\text{cm}^{-1}$ ;  $\delta_{\text{H}}$  ( $\text{CDCl}_3$ ) 0.58 (3 H, s), 1.28 (9 H, s), 2.76–3.02 (8 H, m), 3.07 (2 H, s), 7.06 (2 H, s), and 7.12 (2 H, s);  $m/z$  426 and 428 ( $M^+$ ) (Found: C, 72.3; H, 8.2.  $\text{C}_{26}\text{H}_{35}\text{Br}$  requires C, 73.05; H, 8.25%).

**Reaction of Compounds (5a and b) with Methanol in the Presence of Sulphuric Acid.**—To a solution of (**5a**) of (102 mg, 0.434 mmol) in absolute methanol (30 ml) were added two drops of conc.  $\text{H}_2\text{SO}_4$  at room temperature. After the reaction mixture had been refluxed for 24 h, the solvent was removed under reduced pressure to leave a residue which was extracted with methylene dichloride; the extract was washed with water, dried ( $\text{Na}_2\text{SO}_4$ ), and evaporated under reduced pressure to leave a residue which was recrystallized from methanol to give (**13e**) (104 mg, 90.1%) as prisms, m.p. 146–149 °C;  $\nu_{\max}$  (KBr) 3 070, 2 950, 1 580, 1 450, 1 180, 1 100, 1 060, 770, 735, and 720  $\text{cm}^{-1}$ ;  $\delta_{\text{H}}$  ( $\text{CDCl}_3$ ) 0.57 (3 H, s), 2.70 (2 H, s), 2.77 (3 H, s), 2.66–3.08 (8 H, m), and 6.82–7.19 (6 H, m);  $m/z$  266 ( $M^+$ ) (Found: C, 85.5; H, 8.3.  $\text{C}_{19}\text{H}_{22}\text{O}$  requires C, 85.67; H, 8.33%).

Compound (**13f**) was similarly obtained from (**5b**).

**Compound (13f)**, prisms (from methanol), m.p. 183–184 °C;  $\nu_{\max}$  (KBr) 3 050, 2 980, 2 880, 1 595, 1 480, 1 455, 1 360, 1 280, 1 190, 1 105, 1 100, 960, 885, 860, 770, and 730  $\text{cm}^{-1}$ ;  $\delta_{\text{H}}$  ( $\text{CDCl}_3$ ) 0.58 (3 H, s), 1.27 (9 H, s), 1.33 (9 H, s), 2.70 (2 H, s), 2.87 (3 H,

s), 2.66—3.06 (8 H, m), 7.04 (2 H, s), and 7.14 (2 H, s);  $m/z$  378 ( $M^+$ ) (Found: C, 85.7; H, 10.6.  $C_{27}H_{38}O$  requires C, 85.66; H, 10.12%).

**Reaction of Compounds (5a and b) with Acetic Acid.**—A solution of (5a) (102 mg, 0.434 mmol) in glacial acetic acid (50 ml) was refluxed for 6 h. After the reaction mixture had cooled, the solvent was removed under reduced pressure to leave a residue which was extracted with methylene dichloride; the extract was washed with water, dried ( $Na_2SO_4$ ), and evaporated under reduced pressure to leave a residue which crystallized from methanol to give (13g) (70 mg, 54.9%) as prisms, m.p. 98—101 °C;  $v_{max}$  (KBr) 3 040, 2 930, 1 720, 1 450, 1 370, 1 220, 1 180, 1 020, 960, 880, 775, and 720  $cm^{-1}$ ;  $\delta_H(CDCl_3)$  0.58 (3 H, s), 1.74 (6 H, s), 2.68—3.06 (8 H, m), 3.41 (2 H, s), and 6.88—7.22 (6 H, m);  $m/z$  294 ( $M^+$ ) (Found: C, 81.5; H, 7.6.  $C_{20}H_{22}O_2$  requires C, 81.60; H, 7.53%).

Compound (13h) was similarly obtained from (5b).

**Compound (13h)**, prisms (from methanol), m.p. 178—180 °C;  $v_{max}$  (KBr) 3 040, 2 960, 2 850, 1 725, 1 590, 1 475, 1 370, 1 355, 1 240, 1 220, 1 180, 1 015, 960, 880, 850, 760, and 720  $cm^{-1}$ ;  $\delta_H(CDCl_3)$  0.59 (3 H, s), 1.28 (9 H, s), 1.33 (9 H, s), 1.76 (3 H, s), 2.72—3.06 (8 H, m), 3.43 (2 H, s), 7.08 (2 H, s), and 7.16 (2 H, s);  $m/z$  406 ( $M^+$ ) (Found: C, 82.4; H, 9.4.  $C_{28}H_{38}O_2$  requires C, 82.71; H, 9.42%).

**Hydrogenation of Compounds (5a and b) in the Presence of  $PtO_2$  Catalyst.**—A mixture of (5a) (81.2 mg, 0.347 mmol), platinum dioxide (40 mg, 0.114 mmol), and ethanol (80 ml) was stirred for 15 min at room temperature under hydrogen. The reaction mixture was filtered and the filtrate was evaporated under reduced pressure to leave a residue which was recrystallized from methanol to give (14a) (75 mg, 90.7%) as prisms, m.p. 43—44 °C;  $v_{max}$  (KBr) 3 040, 2 940, 2 850, 2 730, 1 590, 1 460, 1 375, 1 150, 760, 730, and 680  $cm^{-1}$ ;  $\delta_H(CDCl_3)$  0.80—3.40 (21 H, m) and 6.70—7.00 (3 H, m);  $\delta_C(CDCl_3)$  13.21, 19.37, 19.73, 25.30, 28.71, 29.36, 33.23, 33.41, 37.69, 38.34, 39.57, 40.04, 124.64, 125.34, 125.81, 140.02, 140.55, and 140.73 p.p.m.;  $m/z$  240 ( $M^+$ );  $\lambda_{max}$  (cyclohexane) (log  $\epsilon$ ) 272 (2.63) and 217 nm (4.20) (Found: C, 89.7; H, 10.0.  $C_{18}H_{24}$  requires C, 89.93; H, 10.06%).

Compound (14b) was similarly obtained from (5b).

**Compound (14b)**, needles (from methanol), m.p. 154—158 °C;  $v_{max}$  (KBr) 3 040, 2 960, 1 605, 1 585, 1 480, 1 460, 1 360, 1 240, 1 200, 870, and 850  $cm^{-1}$ ;  $\delta_H(CDCl_3)$  0.60—4.16 (37 H, m), 6.84 (1 H, s), and 6.91 (1 H, s);  $m/z$  352 ( $M^+$ );  $\lambda_{max}$  (cyclohexane) (log  $\epsilon$ ) 270 (2.60) and 215 nm (4.17) (Found: C, 88.7; H, 11.3.  $C_{26}H_{40}$  requires C, 88.56; H, 11.44%).

**Reaction of Compounds (2a) and (2b) with Phenyl-lithium.**—To a refluxing solution of PhLi [prepared from phenyl bromide (3.93 g, 25 mmol) and lithium (347 mg, 50 mg-atom)] in ether (30 ml) was added (2a) (394 mg, 1 mmol). After the reaction mixture had been refluxed for 12 h, it was quenched with 10% aqueous ammonium chloride and extracted with methylene dichloride. The extract was dried ( $Na_2SO_4$ ) and evaporated under reduced pressure to leave a residue which was recrystallized from hexane to give (5a) (210 mg, 90%).

Compound (5b) was similarly obtained.

**Reaction of 8-Bromomethyl-16-methyl[2.2]MCP (13c) with Grignard Reagents. Typical Procedure.**—To a refluxing solution of MeMgBr [prepared from methyl bromide (5.7 g, 60 mmol) and magnesium (1.2 g, 50 mg-atom)] in ether (20 ml) was added a solution of (13c) (315 mg, 1 mmol) in ether (10 ml). After the reaction mixture had been refluxed for 12 h, it was quenched with 10% aqueous ammonium chloride and extracted with methylene dichloride; the extract was dried ( $Na_2SO_4$ ) and evaporated under reduced pressure to leave a residue. The

benzene-insoluble solid was filtered off to give the dimer (16a) (10 mg, 4.3%); the filtrate was concentrated to give a mixture of (1a) (trace) and (15a) (80% yield) (the yields were determined by g.l.c. analyses). The mixture was recrystallized from methanol to afford (15a) (180 mg, 72%). Thus obtained were compound (1a), prisms (from hexane), m.p. 205—206 °C (lit.,<sup>6</sup> 205—206 °C).

**Compound (15a)**, prisms (from methanol), m.p. 185—186 °C;  $v_{max}$  (KBr) 3 060, 2 960, 1 580, 1 440, 1 430, 1 180, 1 050, 880, 800, 765, 740, and 720  $cm^{-1}$ ;  $\delta_H(CDCl_3)$  0.32 (3 H, t,  $J$  7 Hz), 0.57 (3 H, s), 1.10 (2 H, q,  $J$  7 Hz), 2.60—3.08 (8 H, m), and 6.72—7.15 (6 H, m);  $m/z$  250 ( $M^+$ ) (Found: C, 91.2; H, 9.0.  $C_{19}H_{22}$  requires C, 91.14; H, 8.86%).

**Compound (16a)**, prisms (from  $CH_2Cl_2$ ), m.p. > 300 °C;  $v_{max}$  (KBr) 3 050, 2 940, 2 860, 1 450, 1 420, 1 180, 1 060, 890, 765, 740, and 720  $cm^{-1}$ ;  $\delta_H(CDCl_3)$  0.40 (6 H, s), 0.50 (4 H, s), 2.12—2.90 (16 H, m), and 6.60—6.90 (12 H, m);  $m/z$  470 ( $M^+$ ) (Found: C, 92.0; H, 8.0.  $C_{36}H_{38}$  requires C, 91.86; H, 8.14%).

**Reaction of 8-Bromomethyl-5,13-di-*t*-butyl-16-methyl[2.2]MCP (13d) with Grignard Reagents. Typical Procedure.**—To a solution of MeMgBr [prepared from methyl bromide (392.4 mg, 36 mmol) and magnesium (72 mg, 3 mg-atom)] in refluxing ether (6 ml) was added a solution of (13d) (128.1 mg, 0.3 mmol) in ether (30 ml). After the reaction mixture had been refluxed for 1 h it was quenched with 10% aqueous ammonium chloride and extracted with methylene dichloride; the extract was dried ( $Na_2SO_4$ ) and evaporated under reduced pressure to leave a residue, which was recrystallized from hexane to give (15c) (100 mg, 92.1%) as prisms, m.p. 226—228 °C (lit.,<sup>2</sup> 226—228 °C).

Compound (15d) was also obtained in this manner, from ethylmagnesium bromide, as plates (from methanol), m.p. 112—114 °C (lit.,<sup>2</sup> 112—114 °C).

**Preparation of 8-Methyl-16-pyridiniomethyl[2.2]MCP Bromide (17).**—A mixture of (13c)<sup>+</sup> (250 mg, 0.794 mmol) and pyridine (10 ml) was boiled under reflux for 12 h. After the reaction mixture had cooled, hexane (10 ml) was added to give a solid which was washed with hexane to give the salt (17) (230 mg, 73.6%) as prisms, m.p. 240—242 °C;  $v_{max}$  (KBr) 3 040, 2 950, 1 620, 1 480, 1 450, 1 180, 1 150, 1 050, 800, 770, 760, 735, 720, and 670  $cm^{-1}$ ;  $\delta_H(CDCl_3)$  0.63 (3 H, s), 2.40—3.30 (8 H, m), 4.24 (2 H, s), 6.92—7.47 (6 H, m), 7.86 (2 H, dd,  $J_{b,a}$  6,  $J_{b,c}$  8 Hz,  $H_b$ ), 8.20 (2 H, dd,  $J_{a,b}$  6,  $J_{a,c}$  1 Hz,  $H_a$ ), and 8.35 (1 H, dd,  $J_{c,b}$  8,  $J_{c,a}$  1 Hz,  $H_c$ );  $m/z$  314 and 316 ( $M - C_5H_5N$ ) (Found: C, 65.85; H, 5.9; N 3.75.  $C_{23}H_{24}BrN \cdot \frac{4}{3}H_2O$  requires C, 66.03; H, 6.43; N, 3.35%).

**Preparation of 8-Formyl-16-methyl[2.2]MCP (18).**—To a magnetically stirred solution of (17) (900 mg, 2.28 mmol) and *p*-nitrosodimethylaniline (342 mg, 2.28 mmol) in ethanol (25 ml) was added aqueous sodium hydroxide solution [900 mg in water (2 ml)] at room temperature. After 5 min, the green solution turned to pale yellow and a pale yellow solid precipitated. To the stirred reaction mixture was then added 10% aqueous HCl (20 ml) at room temperature. After a few min, the pale yellow suspension turned to reddish brown and a pale yellow solid precipitated. The reaction mixture was extracted with methylene dichloride; the extract was dried ( $Na_2SO_4$ ) and evaporated under reduced pressure to leave a residue which was purified by column chromatography (silica gel) with hexane-benzene (1:1) as eluant to afford aldehyde (18) (430 mg, 75.3%) as pale yellow prisms (from hexane), m.p. 213—215 °C;  $v_{max}$  (KBr) 3 070, 2 950, 2 800, 1 680, 1 580, 1 450, 1 180, 1 160, 810, 780, 740, 720, and 700  $cm^{-1}$ ;  $\delta_H(CDCl_3)$  0.64 (3 H, s), 2.64—3.16 (6 H, m), 3.36—3.71 (2 H, m), 6.80—7.28 (6 H, m), and 8.54 (1 H, s);  $m/z$  250 ( $M^+$ ) (Found: C, 86.3; H, 7.3.  $C_{18}H_{18}O$  requires C, 86.36; H, 7.25%).

**Reaction of Compound (18) with Ethylmagnesium Bromide.**—To a solution of EtMgBr [prepared from ethyl bromide (654 mg, 6 mmol) and magnesium (122 mg, 5 mg-atom)] in refluxing ether (20 ml) was added dropwise a solution of (18) (250 mg, 1 mmol) in ether (10 ml). After the reaction mixture had been refluxed for 12 h it was extracted with methylene dichloride; the extract was dried ( $\text{Na}_2\text{SO}_4$ ) and evaporated under reduced pressure to leave a residue which was purified by column chromatography (silica gel) with benzene–chloroform (1:1) as eluant to afford the alcohol (19) (220 mg, 78.6%) as prisms (from hexane), 144–146 °C;  $\nu_{\text{max}}$ (KBr) 3 550, 3 050, 2 950, 1 440, 1 320, 1 180, 1 040, 980, 770, 740, and 720  $\text{cm}^{-1}$ ;  $\delta_{\text{H}}$ ( $\text{CDCl}_3$ ) 0.44 (3 H, t,  $J$  7 Hz), 0.65 (3 H, s), 0.78–1.10 (2 H, m), 1.14 (1 H, br s, exchanged by  $\text{D}_2\text{O}$ ), 2.68–3.03 (7 H, m), 3.60–3.94 (2 H, m), and 6.73–7.17 (6 H, m);  $m/z$  222 ( $M^+$  –  $\text{C}_3\text{H}_6\text{O}$ ) (Found: C, 85.4; H, 8.8.  $\text{C}_{20}\text{H}_{24}\text{O}$  requires C, 85.67; H, 8.63%).

**Dehydration of the Alcohol (19) to give the Alkene (20).**—A suspension of (19) (140 mg, 0.5 mmol) in a mixture of acetic acid (8 ml) and conc. hydrochloric acid (2 ml) was heated on the water-bath for 30 min. After being cooled the reaction mixture was extracted with methylene dichloride and the extract was washed successively with 10% aqueous sodium hydrogen carbonate and water, dried ( $\text{Na}_2\text{SO}_4$ ), and evaporated under reduced pressure to leave a residue which was recrystallized from methanol to give the alkene (20) (125 mg, 95.4%) as prisms, m.p. 115–117 °C;  $\nu_{\text{max}}$ (KBr) 3 050, 2 940, 1 575, 1 440, 1 175, 970, 765, 730, and 715  $\text{cm}^{-1}$ ;  $\delta_{\text{H}}$ ( $\text{CDCl}_3$ ) 0.63 (3 H, s), 1.41 (3 H, dd,  $J_{c,b}$  6.5,  $J_{c,a}$  1.5 Hz,  $\text{H}_c$ ), 2.52–2.98 (8 H, m), 4.38 (1 H, dd,  $J_{a,b}$  16,  $J_{a,c}$  1.5 Hz,  $\text{H}_a$ ), 4.85 (1 H, dq,  $J_{b,c}$  6.5,  $J_{b,a}$  16 Hz,  $\text{H}_b$ ), and 6.73–7.13 (6 H, m);  $m/z$  262 ( $M^+$ ) (Found: C, 91.35; H, 8.5.  $\text{C}_{20}\text{H}_{22}$  requires C, 91.55; H, 8.45%).

**Hydrogenation of Compound (20) in the Presence of  $\text{PtO}_2$  Catalyst.**—A mixture of (20) (26.2 mg, 0.1 mmol), platinum dioxide (10 mg, 0.038 mmol), and ethanol (20 ml) was stirred for 4 h at room temperature under hydrogen. The reaction mixture was filtered and the filtrate was evaporated under reduced pressure, to leave a residue which was recrystallized from methanol to give (15b) (23.8 mg, 90%) as prisms, m.p. 130–132 °C;  $\nu_{\text{max}}$ (KBr) 3 050, 2 950, 1 580, 1 445, 1 180, 1 055, 760, 730, and 715  $\text{cm}^{-1}$ ;  $\delta_{\text{H}}$ ( $\text{CDCl}_3$ ) 0.41 (3 H, t,  $J$  7 Hz), 0.56 (3 H, s), 0.52–1.14 (4 H, m), 2.60–3.02 (8 H, m), and 6.71–7.12 (6 H, m);  $m/z$  264 ( $M^+$ ) (Found: C, 90.9; H, 9.2.  $\text{C}_{20}\text{H}_{24}$  requires C, 90.85; H, 9.15%).

**Reaction of Compounds (13c) and (13d) with Phenyl-lithium.**—To a refluxing solution of PhLi [prepared from phenyl bromide (1.97 g, 12.5 mmol) and lithium (173.5 mg, 25 mg-atom) in ether (10 ml)] was added a solution of (13c) (315 mg, 1 mmol) in ether (20 ml). After the reaction mixture had been refluxed for 12 h it was quenched with 10% aqueous ammonium chloride and extracted with methylene dichloride; the extract was dried ( $\text{Na}_2\text{SO}_4$ ) and evaporated under reduced pressure to leave a residue which was recrystallized from  $\text{CH}_2\text{Cl}_2$  to give (16a) (193.9 mg, 82.5%).

Compound (16b) was also obtained in this manner, using (13d), as prisms [hexane–benzene (2:1)], m.p. > 300 °C;  $\nu_{\text{max}}$ (KBr) 3 050, 2 970, 1 595, 1 470, 1 430, 1 390, 1 360, 1 280, 1 180, 930, 880, 860, 735, 730, and 710  $\text{cm}^{-1}$ ;  $\delta_{\text{H}}$ ( $\text{CDCl}_3$ ) 0.33 (4 H, s), 0.44 (6 H, s), 0.93 (18 H, s), 1.26 (18 H, s), 2.50–2.84 (16 H, s), 6.75 (4 H, s), and 6.92 (4 H, s);  $m/z$  694 ( $M^+$ ) (Found: C, 90.1; H, 10.1.  $\text{C}_{52}\text{H}_{70}$  requires C, 89.85; H, 10.15%).

**Preparation of 8-Monodeuteriated Methyl-16-methyl[2.2]-MCP (21).**—To a refluxing solution of EtMgBr [prepared from ethyl bromide (117.8 mg, 1.08 mmol) and magnesium (21.6 mg, 0.9 mg-atom)] in ether (6 ml) was added a solution of (13c) (94.5 mg, 0.3 mmol) in ether (3 ml). After the reaction mixture had been refluxed for 1 h it was quenched with  $\text{D}_2\text{O}$  (5 mol) and extracted with methylene dichloride. The extract was dried ( $\text{Na}_2\text{SO}_4$ ) and evaporated under reduced pressure to leave a residue, which was recrystallized from hexane to give compound (21) (39 mg, 55%) as prisms, m.p. 205–206 °C;  $\nu_{\text{max}}$ (KBr) 3 050, 2 950, 1 580, 1 445, 1 180, 1 055, 880, 800, 760, and 705  $\text{cm}^{-1}$ ;  $\delta_{\text{H}}$ ( $\text{CDCl}_3$ ) 0.59 (5 H, s), 2.64–3.04 (8 H, m), and 6.74–7.12 (6 H, m);  $m/z$  236 ( $M^+$ ).

The yields of the products are summarized in the Tables and Schemes described above.

## References

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