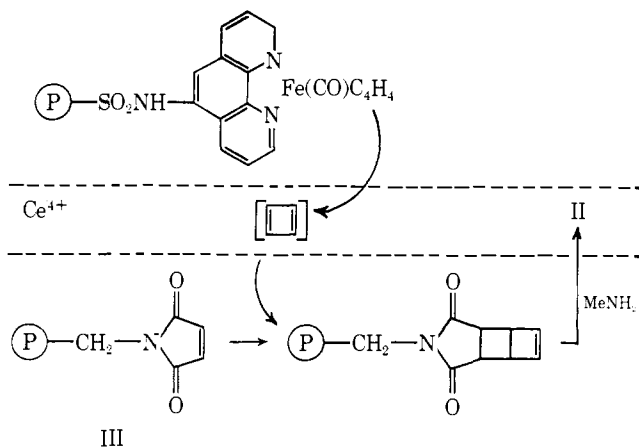


## Scheme IV



mediates, and measurements of lifetimes through separation of the resins to increasing distances are underway.

**Acknowledgments.** We are pleased to acknowledge encouragement and advice from Professors H. D. Kaesz and J. I. Zink and F. A. L. Anet. Financial support was provided through the Fulbright Commission's Program of Cultural Cooperation between the U. S. A. and Spain, the Eli Lilly Co., and the Research Corporation.

(14) Visiting Fulbright Scholar on leave from the University of Valencia, Spain.

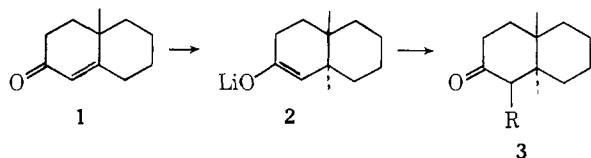
J. Rebek,\* F. Gaviña<sup>14</sup>

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University of California  
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Received June 17, 1974

### Condensation of Formaldehyde with Regiospecifically Generated Anions

Sir:

Sophisticated synthesis design has been greatly helped by the demonstration<sup>1</sup> that enolate ions can be regiospecifically generated, *e.g.*, from enones, and that if these enolates are *lithium* enolates they can, in many cases, be alkylated without loss of structural integrity (*cf.* **1** → **2** → **3**).<sup>1,2</sup>



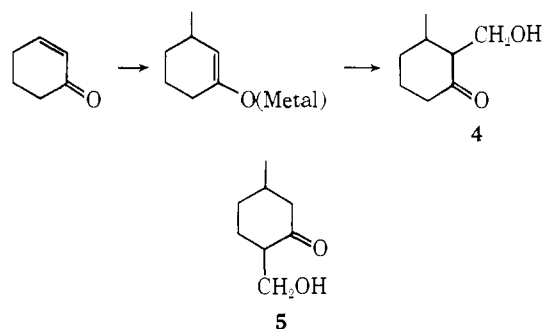
These important methods for regiospecific formation of carbon-carbon bonds have been extended recently to the Michael condensation with  $\alpha$ -silyl vinyl ketones (and

(1) G. Stork, P. Rosen, and N. L. Goldman, *J. Amer. Chem. Soc.*, **83**, 2965 (1961); G. Stork, P. Rosen, N. L. Goldman, R. V. Coombs, and J. Tsuji, *ibid.*, **87**, 275 (1965).

(2) For other methods of kinetic generation of enolates *cf.* (a) M. J. Weiss, R. E. Schaub, G. R. Allen, Jr., J. F. Poletto, C. Pidacks, R. B. Conrow, and C. J. Coscia, *Tetrahedron*, **20**, 357 (1964); (b) D. Caine, *J. Org. Chem.*, **29**, 1868 (1964); (c) G. Stork and P. F. Hudrlík, *J. Amer. Chem. Soc.*, **90**, 4462, 4464 (1968); (d) H. O. House, L. J. Czuba, M. Gall, and H. D. Olmstead, *J. Org. Chem.*, **34**, 2324 (1969); (e) R. M. Coates and L. Ofenshain Sandefur, *ibid.*, **39**, 275 (1974), and references therein cited.

esters)<sup>3</sup> and to directed aldol condensations between methyl ketones and aldehydes.<sup>4</sup> We report here on the successful trapping of regiospecifically generated enolate ions from cyclic ketones with formaldehyde,<sup>5</sup> a method which promises to be of considerable importance because the derived hydroxymethyl ketones are well-known intermediates in a number of useful constructions. They, for instance, are precursors of  $\alpha$ -methylene ketones which can be used, *inter alia*, for Michael additions, *e.g.*, annelation with  $\beta$ -ketoesters (*vide infra*), for chain extension *via* addition alkyl cuprates or dialkylaluminum acetylenes,<sup>6</sup> and for Diels-Alder additions.<sup>7</sup> In spite of their potential importance,  $\alpha$ -hydroxymethyl ketones of predictable structures have remained difficultly accessible. The base-catalyzed condensation of formaldehyde with ketones is usually unsatisfactory,<sup>8</sup> and introduction of a hydroxymethyl group has previously been accomplished by a variety of multistep processes.<sup>9</sup>

Our initial experiments were conducted with the enolates resulting from 1,4-addition of organometallic reagents to enones. Addition of methylmagnesium bromide, catalyzed with 1%  $\text{CuI} \cdot \text{Bu}_3\text{P}$ , to cyclohexenone in ether in the usual manner, was followed by passage at  $-10^\circ$  of anhydrous gaseous formaldehyde<sup>10</sup> in a stream of nitrogen (8.8 g of formaldehyde absorbed, starting with 0.3 mol of cyclohexenone), and by acidification (ammonium chloride at  $0^\circ$ ). Distillation gave, in  $\sim 70\%$  yield, 2-hydroxymethyl-3-methylcyclohexanone which was obtained as a mixture of stereoisomers, bp  $73-76^\circ$  (0.5 mm),  $R_f$  (major) 0.55, (minor) 0.40 (60:40 benzene:ethyl acetate on silica); ratio of methyl doublets at  $\delta$  ( $\text{CCl}_4$ ) 0.83 and 1.13 is  $\sim 1:5$ . The carbinols **4** formed *via* trapping were different (tlc) from



the single regioisomer **5** formed in 20% yield by base-catalyzed condensation of 3-methylcyclohexanone with formaldehyde.<sup>11</sup> The identity of **4** was established by

(3) (a) G. Stork and B. Ganem, *J. Amer. Chem. Soc.*, **95**, 6152 (1973); (b) G. Stork and J. Singh, *ibid.*, **96**, 6181 (1974); (c) R. K. Boeckman, Jr., *ibid.*, **95**, 6867 (1973); (d) R. K. Boeckman, Jr., *ibid.*, **96**, 6179 (1974).

(4) G. Stork, G. Kraus and G. García, in press.

(5) A recent interesting example of reaction of an enolate with formaldehyde in aprotic media has been described by P. A. Grieco and K. Hiroi, *J. Chem. Soc., Chem. Commun.*, 1317 (1972). In that case, however, the problem of regiospecific control does not arise.

(6) J. Hooz and R. B. Layton, *J. Amer. Chem. Soc.*, **93**, 7320 (1971).

(7) *Cf.* A. Tanaka, H. Uda, and A. Yoshikoshi, *Chem. Commun.*, 188 (1967).

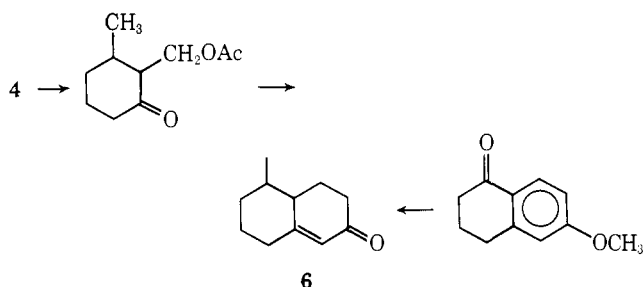
(8) *Cf.* E. J. Corey and D. E. Cane, *J. Org. Chem.*, **36**, 3070 (1971).

(9) *Cf.* D. Stauffacher and H. Schinz, *Helv. Chim. Acta*, **37**, 1227 (1954).

(10) The formaldehyde was generated by the thermal depolymerization of paraformaldehyde (dried over phosphorus pentoxide, under vacuum) at  $150^\circ$ . Higher temperatures must be avoided because small amounts of protic impurities (methanol?) can then be carried into the reaction mixture. See also footnote 16.

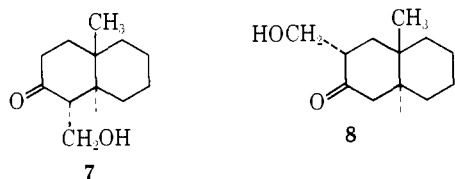
(11) J. Colonge, J. Dreux, and H. Delplace, *Bull. Soc. Chim. Fr.*, 1635 (1956).

reaction of its acetate with 1 equiv of ethyl acetoacetate<sup>12</sup> (5% sodium ethoxide in ethanol, room temperature, 24 hr; followed by 2 hr of reflux with 5% aqueous potassium hydroxide). The methyl octalone **6**<sup>13</sup> thus formed



was identical with a sample unambiguously synthesized from 6-methoxy-1-tetralone.<sup>14</sup>

We were encouraged by this result to examine the much more critical regiospecific trapping of enolates derived from the reduction of  $\alpha,\beta$ -unsaturated ketones. The need of using a proton donor more acidic than ammonia in order to achieve complete reduction of the unsaturated ketone is a source of potential difficulties, as we indeed observed in our initial attempt at trapping the enolate ion **2** derived from **1**. When the generation of **2** was conducted in liquid ammonia by simultaneous addition of an ether solution of **1** and of *tert*-butyl alcohol, the enolate ion present after complete removal of ammonia was indeed **2**, as shown by its isolation in very high yields (*vide infra*) as the corresponding trimethylsilyl enol ether **9**. Nevertheless, passage of anhydrous formaldehyde into an ether "solution" of this enolate at  $-78^\circ$  (20 min, followed by acetic acid at  $-78^\circ$ ) gave, in 64% yield, a mixture of the two regioisomers **7** and **8**, in which the *latter* predominated.



Equilibration evidently had taken place during the addition of formaldehyde. We believe that this equilibration was caused by small amounts of *tert*-butyl alcohol formed by proton transfer between the formaldehyde-ketone reaction product and the lithium *tert*-butoxide in solution. After some experimentation, we were able to suppress this equilibration completely by using aniline, instead of *tert*-butyl alcohol, as a proton donor in the reduction step; the aniline which might be formed by the exchange referred to above is not, in contrast to *tert*-butyl alcohol, a strong enough acid to protonate the unreacted enolate **2**. Under these conditions, **7** could be isolated in 60% yield.<sup>15</sup> The best results were finally obtained by trapping the enolate ion as its trimethyl silyl ether.<sup>2c,d</sup> Complete removal of ammonia (finally at room temperature at 0.5 mm) from

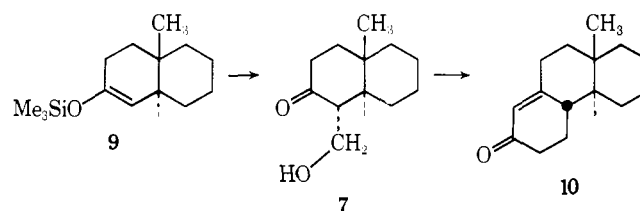
(12) Cf. C. Mannich, W. Koch, and F. Borkowsky, *Ber.*, 70, 355 (1937).

(13) The initial mixture of  $\alpha,\beta$ - and  $\beta,\gamma$ -compounds was isomerized to the  $\alpha,\beta$ -isomer with 2 *N* hydrochloric acid.

(14) G. Stork and M. Jung, *J. Amer. Chem. Soc.*, 96, 3682 (1974).

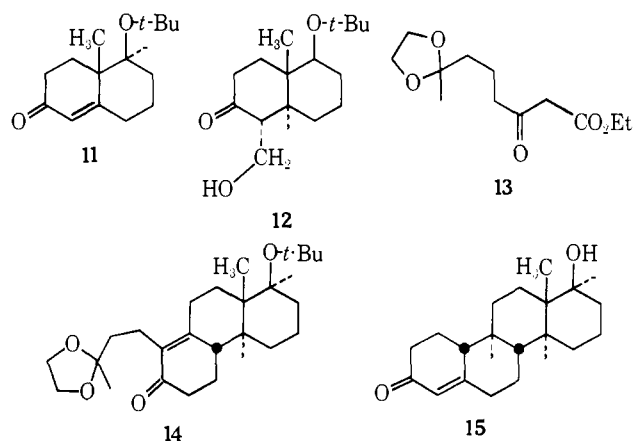
(15) Reaction of formaldehyde with the enolate obtained by reduction in liquid ammonia, in the absence of a more acidic proton donor, also gave, as expected, the unrearranged hydroxymethyl ketone **7**, but the yield was only 25%.

the lithium enolate **2** obtained (*vide supra*) by reduction in the presence of 0.8 equiv<sup>16</sup> of *tert*-butyl alcohol and 25% excess of lithium (excess lithium destroyed with isoprene) followed by addition of dry tetrahydrofuran and 2.5 equiv of trimethylchlorosilane<sup>2b</sup> gave the silyl enol ether **9** (work-up with cold saturated bicarbonate solution and ether extraction) in 90% yield, after short path distillation,  $\nu$  (film) 1660  $\text{cm}^{-1}$ . Regeneration of the lithium enolate **2** with 1 equiv of methyl lithium (1 hr, room temperature), followed by anhydrous formaldehyde at  $-78^\circ$  for 20 min, gave the crystalline carbinol **7** in 90% yield: mp  $68.5\text{--}69^\circ$  (from pentane);  $\delta(\text{CCl}_4)$  1.08 (s,  $\text{CH}_3$ ), 3.6 (b, m  $\text{CH}_2\text{OH}$ ).<sup>17</sup> The structure was proved, as in the case of **4** above, by reaction of the corresponding acetate with ethyl acetoacetate,<sup>12, 18</sup> followed by hydrolysis to the known tricyclic enone **10**, mp  $122\text{--}124^\circ$ , identical with an authentic sample.<sup>1</sup>



In the same manner, using the aniline procedure, the octalone **11** gave the hydroxymethyldecalone **12**: mp  $85\text{--}86^\circ$  (from hexane),  $\nu$  (mull) 3400, 1700  $\text{cm}^{-1}$ ;  $\delta(\text{CCl}_4)$  3.8 (2 H, m), 1.18 (3 H, s), 1.18 (9 H, s).<sup>17</sup>

The structure was confirmed by reaction of the mesylate of **12** with the  $\beta$ -keto ester **13**<sup>18, 19</sup> to give **14**.<sup>20</sup> A mixture of the crude mesylate from 200 mg of crystalline ketol **12** in 7 ml of *tert*-amyl alcohol and 290 mg of the  $\beta$ -ketoester **13** was treated (under nitrogen in deoxygenated solvents) with sodium *tert*-amylate (from 65 mg of 50% sodium hydride in oil) and kept  $\sim 3$  hr at  $0^\circ$  and 48 hr at room temperature. Addition of 70 mg of potassium hydroxide in 0.3 ml of water and refluxing for 2 hr gave crystalline **14**, in  $\sim 85\%$  yield from **12**.



(16) The ease with which enolate equilibration takes place makes it essential to avoid any excess of *t*-butyl alcohol. See also footnote 10.

(17) The substance gave correct carbon and hydrogen analyses.

(18) Z. G. Hajos and D. R. Parrish, *J. Org. Chem.*, 38, 3244 (1973), have used this type of annelation to form steroids systems from hydroxymethylketones obtained by a different route.

(19) We prepared this compound by alkylation of the dianion of ethyl acetoacetate with 2(2-bromoethyl)-2-methyl-1,3-dioxolane.

(20) This variation on the experimental conditions used by Hajos and Parrish (ref 18) in a related case is described in detail since it gives considerably better yields (85% vs. 31%).

The pure compound, recrystallized from hexane, had mp 121–122°: nmr  $\delta$  (CCl<sub>4</sub>) 3.86 (4 H, s), 1.28 (3 H, s), 1.17 (9 H, s) 0.93 (s, 2 H).

Further transformation of **14** by catalytic hydrogenation (Pd-on-charcoal, triethylamine), followed by refluxing with 2 *N* hydrochloric acid in methanol to ( $\pm$ )-D-homo-19-nor-testosterone **15**, mp 140.5–142°, undepressed on admixture with an authentic sample.<sup>21</sup>

It is apparent that  $\alpha$ -hydroxymethyl ketones can be produced regiospecifically in high yields. They should prove valuable intermediates in synthesis.<sup>22</sup>

(21) G. Stork and J. E. McMurry, *J. Amer. Chem. Soc.*, **89**, 5464 (1967).

(22) We thank the National Institutes of Health and the National Science Foundation for their support of this work.

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#### Four-Carbon Carboranes. Synthesis of Tetra-C-methyltetracarbadodecaborane(12) and Its Metallocarborane Derivatives

Sir:

Addition of two electrons to the icosahedral carborane C<sub>2</sub>B<sub>10</sub>H<sub>12</sub>, a filled-shell electronic system, is expected to open or otherwise distort the polyhedral cage. Several isomeric C<sub>2</sub>B<sub>10</sub>H<sub>12</sub><sup>2-</sup> ions and protonated C<sub>2</sub>B<sub>10</sub>H<sub>13</sub><sup>-</sup> analogs are known,<sup>1–7</sup> but the only X-ray determined structure<sup>8</sup> is that of a C, C'-diphenyl derivative, (C<sub>6</sub>H<sub>5</sub>)<sub>2</sub>C<sub>2</sub>B<sub>10</sub>H<sub>11</sub><sup>-</sup>, which is an icosahedral fragment containing a bridging C<sub>6</sub>H<sub>5</sub>CH group on the edge of the open face. The isoelectronic neutral species C<sub>4</sub>B<sub>8</sub>H<sub>12</sub> is unknown, and in fact the only previously reported carborane having four carbon atoms in the same cage is the C<sub>4</sub>B<sub>8</sub>H<sub>8</sub> system.<sup>9–11</sup> We report here a new carborane, tetra-C-methyltetracarbadodecaborane (12), (CH<sub>3</sub>)<sub>4</sub>C<sub>4</sub>B<sub>8</sub>H<sub>8</sub> (I), a derivative of C<sub>4</sub>B<sub>8</sub>H<sub>12</sub>, which exhibits structural dynamics of a type novel to carborane chemistry and also functions as a face-bonding ligand in metallocarborane formation. Compound I is a colorless, air-stable, sublimable crystalline solid, mp 138°, which has been obtained in 35–40% yield as an adjunct of the synthesis of the red bis(dicarbonylhexaboranyl)cobalt and -iron metallocarboranes [2,3-(CH<sub>3</sub>)<sub>2</sub>C<sub>2</sub>B<sub>4</sub>H<sub>4</sub>]<sub>2</sub>Co<sup>11</sup>H and [2,3-(CH<sub>3</sub>)<sub>2</sub>C<sub>2</sub>B<sub>4</sub>H<sub>4</sub>]<sub>2</sub>Fe<sup>11</sup>H<sub>2</sub> from Na<sup>+</sup>[2,3-(CH<sub>3</sub>)<sub>2</sub>C<sub>2</sub>B<sub>4</sub>H<sub>5</sub>]<sup>-</sup> and CoCl<sub>2</sub> or FeCl<sub>2</sub> in tetrahydrofuran (THF). The metal complexes *per se* are not directly germane to this report and will be de-

(1) D. Grafstein and J. Dvorak, *Inorg. Chem.*, **2**, 1128 (1963).

(2) L. I. Zakharkin, V. N. Kalinin, and L. S. Podvisotskaya, *Izv. Akad. Nauk SSSR, Ser. Khim.*, 1495 (1966); 2310 (1967).

(3) L. I. Zakharkin and L. S. Podvisotskaya, *Zh. Obshch. Khim.*, **37** 506 (1967).

(4) V. Stanko, Yu. V. Gol'tyapin, and V. Brattsev, *Zh. Obshch. Khim.*, **39**, 1175 (1969).

(5) L. I. Zakharkin and V. N. Kalinin, *Izv. Akad. Nauk SSSR, Ser. Khim.*, 194 (1969).

(6) G. B. Dunks, R. J. Wiersema, and M. F. Hawthorne, *J. Amer. Chem. Soc.*, **95**, 3174 (1973).

(7) G. B. Dunks, R. J. Wiersema, and M. F. Hawthorne, *J. Chem. Soc., Chem. Commun.*, 899 (1972).

(8) E. I. Tolpin and W. N. Lipscomb, *Inorg. Chem.*, **12**, 2257 (1973).

(9) P. Binger, *Tetrahedron Lett.*, 2675 (1966).

(10) T. P. Onak and G. T. F. Wong, *J. Amer. Chem. Soc.*, **92**, 5226 (1970).

(11) V. R. Miller and R. N. Grimes, *Inorg. Chem.*, **11**, 862 (1972).

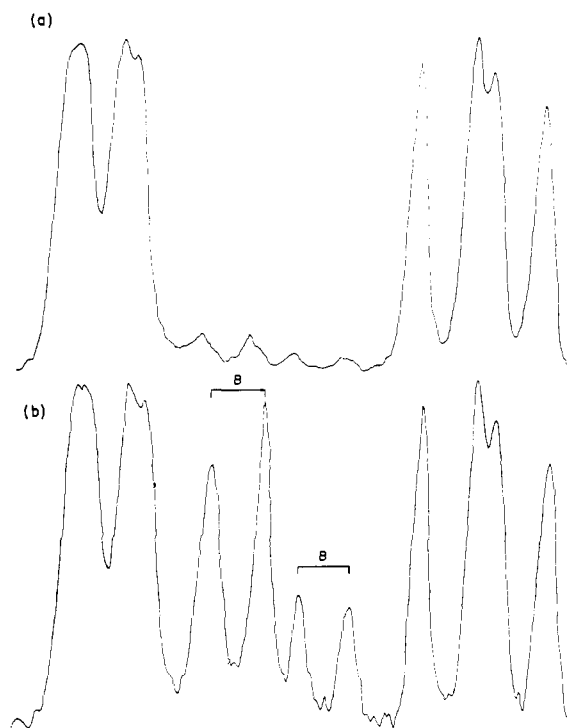


Figure 1. The 32.1-MHz <sup>11</sup>B nmr spectra of I in CCl<sub>4</sub> at ambient temperature: (a) 3 min after preparation of solution (large peaks are BH doublets of isomer A; small peaks in center are due to traces of isomer B ( $\delta$  and  $J$  values given in text)), (b) same solution 12 min later (bracketed doublets are due to isomer B; the spectrum did not undergo further significant change other than slight increase in the area of the B resonances).

scribed elsewhere. We have determined that I forms *via* decomposition of the metal complexes and does not appear to be produced directly from the (CH<sub>3</sub>)<sub>2</sub>C<sub>2</sub>B<sub>4</sub>H<sub>5</sub><sup>-</sup> ion.

The mass spectrum of I exhibits intense parent-group peaks with little cage fragmentation (calcd mass for <sup>12</sup>C<sub>8</sub><sup>11</sup>B<sub>8</sub><sup>1</sup>H<sub>20</sub><sup>+</sup>, 204.2310; found, 204.2310); the ir spectrum contains strong CH<sub>3</sub> and BH stretching bands but has no appreciable B–H–B absorptions. The compound is thermally stable, but the isomer which is initially evident in solution and presumably exists in the solid state (A) undergoes reversible rearrangement in solution to a second isomer (B); an essentially solvent-independent equilibrium [B]/[A] ratio of ~0.5 (measured from <sup>11</sup>B and <sup>1</sup>H nmr peak areas) is reached within a few minutes at ambient temperature, and thereafter no further noticeable change occurs. The isomerization takes place in CCl<sub>4</sub>, CH<sub>2</sub>Cl<sub>2</sub>, C<sub>2</sub>H<sub>5</sub>OH, THF, CH<sub>3</sub>CN, CDCl<sub>3</sub>, and C<sub>6</sub>H<sub>6</sub> and is completely reversible, since on evaporation of the solvent followed by redissolving, the original nmr spectra (containing only A initially) are regenerated. The <sup>11</sup>B nmr spectrum of A in CCl<sub>4</sub> (Figure 1a) contains four B–H doublets of equal area of  $\delta$  ~-9.2, ~-8.4, +22.4, and 29.5 ppm relative to BF<sub>3</sub>·O(C<sub>2</sub>H<sub>5</sub>)<sub>2</sub> ( $J$  = 155 ± 20 Hz); the two low-field doublets are heavily overlapped but distinguishable. On proton decoupling, all doublets collapse to singlet resonances. The <sup>11</sup>B spectrum of B (see Figure 1b) contains doublets at  $\delta$  +2.4 ( $J$  = 150 Hz) and +11.0 (148) with a 6:2 area ratio, which also collapse to singlets on decoupling; since the area 6 doublet is asymmetric (Figure 1b) and since in any case