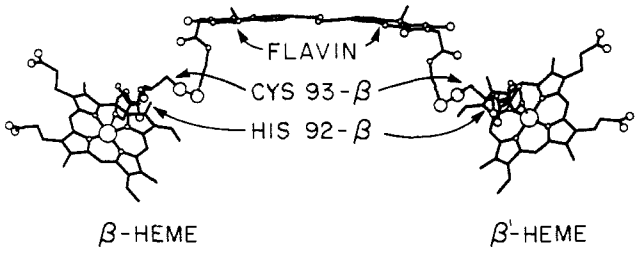

Figure 3. The interaction of the symmetry-related flavins and heme groups of the two β-chains in a tetrameric molecule. The cyano groups are roughly 3 Å apart. The long axes of the isoalloxazine rings are not colinear; they are approximately parallel but displaced by about 1.4 Å in the plane of the rings.

donated by NAD(P)H to one flavin may also be transferred to the second flavin and subsequently to the second β-heme.

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Ring Enlargement of Boracyclanes via Sequential One-Carbon Homologation. The First Synthesis of Boracyclanes in the Strained Medium Ring Range

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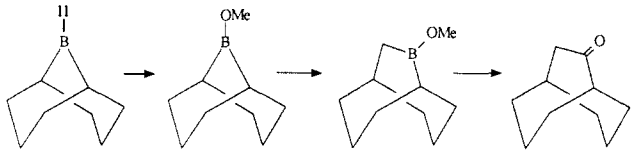
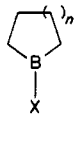
Previous attempts to achieve the synthesis of boracyclanes, $HB(CH_2)_{n-1}$ in the medium ring range (n = 9-12) have failed. However, the homologation of *B*-methoxyboracyclanes with in situ generated (chloromethyl)lithium, $LiCH_2Cl$, proceeds smoothly to furnish the next higher homologue. In this way we have successfully achieved the conversions: $MeOB(CH_2)_5 \rightarrow MeOB(CH_2)_6 \rightarrow MeOB(CH_2)_7 \rightarrow MeOB(CH_2)_8 \rightarrow MeOB(CH_2)_9 \rightarrow MeOB(CH_2)_{10} \rightarrow MeOB(CH_2)_{11}$. The yields achieved are in the range of 75-85%, and no decrease in the yield was observed in synthesizing the more strained members. Consequently, there appears to be no limit to the applicability of this procedure for the synthesis of many membered boracyclanes.

Numerous previous attempts to achieve the synthesis of medium ring boracyclanes by cyclic hydroboration of α,ω-dienes with various hydroborating agents like diborane,[1] thexylborane,[2] BH_2Cl,[3] and 9-BBN[4] have failed. Such cyclic hydroboration works well for the synthesis of five, six, and seven-membered derivatives but in general fails with higher members. In one case it was possible to achieve the formation of the eight-membered ring derivative in impure form.[3] One of the major difficulties with the synthesis of pure boracyclanes via cyclic hydroboration arises from the attack of the borane at the internal position of the diene, leading to the formation of polymeric species which upon thermal depolymerization undergo isomerization to give isomeric boracyclanes.

This long string of failures in our efforts to synthesize medium ring systems containing a boron hetero atom as part of the ring implied that the strains in these medium ring boracyclanes were too large for the relatively labile boron-carbon bonds.[5] Our present success in synthesizing and isolating such compounds and in successfully transforming them without observable molecular rearrangement opens up a major new area for the application of borane chemistry to facilitate organic synthesis. This development also opens up the possibility of increasing the size of a ring in bi- and polycyclic systems.



We recently have had considerable success in applying the Matteson homologation procedure[6] in lengthening the chain of optically active derivatives.[7] We decided to explore this procedure as a means of enlarging the size of the ring in *B*-methoxyboracyclanes. Two procedures were explored:[8] (dichloromethyl)lithium, $LiCHCl_2$ generated in situ, followed by potassium (triisopropoxy)borohydride (KIPBH) reduction, and by (chloromethyl)lithium, $LiCH_2Cl$, generated in situ. Both procedures worked entirely satisfactorily for the conversion of borinane to borepane, However, the fact that the $LiCH_2Cl$ procedure involves only a single step persuaded us to adopt this route. Indeed it worked quite satisfactorily to go stepwise from the six-membered boracyclane to the 12-membered boracyclane structure.



		ring size	
1	$n = 1$, X = H	5	borolane, boracyclopentane
2	$n = 2$, X = H	6	borinane, boracyclohexane
3	$n = 3$, X = H	7	borepane, boracycloheptane
4	$n = 4$, X = H	8	borocane, boracyclooctane
5	$n = 5$, X = H	9	boronane, boracyclononane
6	$n = 6$, X = H	10	borecane, boracyclodecane
7	$n = 7$, X = H	11	boracycloundecane
8	$n = 8$, X = H	12	boracyclododecane

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Table I. Physical Constants and Spectral Data for the Medium Ring Boracycles Prepared by One-Carbon Homologation of *B*-Methoxyboracycles[c]

starting boracyclane	yield of the homologated product[a] (%)	product boracyclane	bp of boracyclane (°C/mm)	monoethanol amine adduct[b] mp (°C)	monoethanol amine adduct[b] mass ion	DCME reaction product	DCME reaction %
B-methoxyborinane				154–55	142	cyclohexanone	73
B-methoxyborinane	85	*B*-methoxyborepane	70–71/35	140–41	156	cycloheptanone	70
B-methoxyborepane	82	*B*-methoxyborocane	89–90/30	140–41	170	cyclooctanone	74
B-methoxyborocane	80	*B*-methoxyboronane	34–35/3	95–96	184	cyclononanone	75
B-methoxyboronane	80	*B*-methoxyborecane	60–61/2	127	198	cyclodecanone	79
B-methoxyborecane	75	*B*-methoxyboracycloundecane	80–81/3	139	212	cycloundecanone	77
B-methoxyboracycloundecane	82	*B*-methoxyboracyclododecane	80–81/1	165	226	cyclododecanone	75

[a] Determined by oxidizing the boracycle to the corresponding diol and analyzing the diol by GLC[9] as its bis(trimethylsilyl) ether with a proper choice of an internal standard. [b] Gave correct elemental analysis for C, H, N, and B. [c] All these reactions were run on a 50-mmol scale.

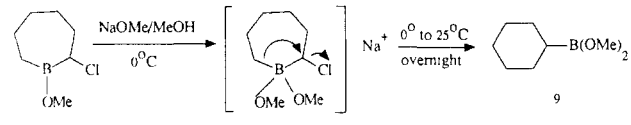
B-Methoxyborinane, $(CH_2)_5BOMe$ (**2**: X = OMe), was prepared in accordance with the literature procedure by reacting borinane with an equivalent of methanol.[4] Homologation of *B*-methoxyborinane with $LiCH_2Cl$[8,9] generated in situ by reacting chloroiodomethane and/or bromochloromethane with *n*-BuLi in THF at −78 °C is representative. To a solution of *B*-methoxyborinane (10 mmol) in THF (20 mL) was added chloroiodomethane (11 mmol), and the solution was cooled to −78 °C. To this was slowly added *n*-BuLi (11 mmol) dropwise from the side of the flask over a period of 0.25 h. The reaction mixture was allowed to stir at −78 °C for 1 h and then warmed to room temperature over a period of 14 h. The completion of the reaction was monitored by ^{11}B NMR (δ 51 ppm). *B*-Methoxyborepane was then purified by fractional distillation under reduced pressure (bp 70–71 °C/35 mm), yield 85%. Oxidation of a small aliquot furnished 1,6-hexanediol identified by GLC analysis[10] of its bis(trimethylsilyl) derivative.

For the present study we chose as the starting material *B*-methoxyborepane (**3**, X = OMe), prepared either via homologation of **2** or by methanolysis of borepane prepared via hydroboration of 1,5-hexadiene with 9-BBN.[4c] One-carbon homologation of *B*-methoxyborepane with $LiCH_2Cl$ furnished the eight-membered boracycle, borocane (**4**, X = OMe), in 82% yield. Oxidation of **4** with alkaline H_2O_2 furnished 1,7-heptanediol which was analyzed by GLC[10] as its bis(trimethylsilyl) ether. By following similar successive one-carbon homologation with $LiCH_2Cl$, generated in situ, all the *B*-methoxyboracycles through the 12-membered derivative have been prepared (Table I).

The formation of these medium ring boracycles was ascertained by converting them to the corresponding diols via oxidation and analyzing the product diols by GLC as their bis(trimethylsilyl) ethers prepared by treating the product diols with bis(trimethylsilyl)acetamide (BSA).[10] These boracycles could be conveniently purified by distillation under reduced pressure indicating their thermal stability. These boracyclanes were also converted to the corresponding cycloalkanones via the DCME (α,α-dichlorodimethyl ether) reaction.[11] The structure of these cycloalkanones was ascertained by IR, PMR and mass spectral data, and direct comparison of an authentic sample by GLC. These medium ring boracycles were converted to the corresponding ethanolamine adducts[12] and characterized by ^{11}B NMR, ^1H NMR, and mass spectral data. These adducts gave satisfactory elemental analyses (Table I).

Because of the potential synthetic importance of α-chloroborinate esters[12] we thought it worthwhile to undertake one-carbon homologation of *B*-methoxyboracyclanes with (dichloromethyl)-lithium, $LiCHCl_2$, generated in situ in THF at −78 °C.[8] One-carbon homologation of *B*-methoxyborecane, from **6** to **7**, utilizing $LiCHCl_2$ generated in situ by reacting dichloromethane with *sec*-BuLi in THF at −78 °C is representative. To a solution of *B*-methoxyborecane (10 mmol) in THF (20 mL) was added dichloromethane (11 mmol), and the solution was cooled to −78 °C. To this was slowly added *sec*-BuLi (11 mmol) dropwise over a period of 0.5 h, The reaction mixture was stirred at −78 °C for 0.25 h, and KIPBH (15 mmol) was added at −78 °C and warmed to room temperature over a period of 14 h. GLC analysis of the oxidation product[10] indicated the presence of 1,10-decanediol and cyclodecanol in the ratio of 23:1. If KIPBH was added at higher temperatures the amount of cyclodecanol increases, at 0 °C the yield of cyclodecanol was about 25%. The formation of cyclodecanol indicated the presence of *B*-chloro-*B*-methoxyborane presumably via the ionization of the C–Cl bond with the transfer of the α-carbon. Also, if NaOMe/MeOH is added instead of KIPBH, cyclic boronates can be obtained in good yields.

These observations suggested the possibility for preparing the higher cycloalkylboronic acids by a slight modification of the present procedure. Indeed, treatment of the intermediate, α-chloro-*B*-methoxyborepane with NaOMe/MeOH furnished methyl cyclohexylboronate in 70% yield. The reaction essentially proceeds via the formation of an ate-complex followed by ring contraction to furnish the carbocyclic boronate ester **9**. By



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following this procedure various cycloalkylboronic acids which are otherwise difficult to prepare via hydroboration could be prepared in good yields. The importance of such boronic esters in asymmetric synthesis is well recognized.[13]

This is the first report in the literature for the preparation of medium ring boracyclane structures without any contamination by isomeric boracycles. Cycloalkanones which are otherwise difficult to prepare via known synthetic transformations can be conveniently prepared in good yields via the DCME reaction of these boracycles. Intermediate α-haloboracycles are versatile intermediates for the synthesis of α-substituted cycloalkanones via treatment with the appropriate alkyl- or aryllithium as well as for the synthesis of cycloalkylboronic esters which are otherwise difficult to prepare via hydroboration because of the inavailability of the necessary cycloalkene.

It is evident that considerable progress has been made in developing a convenient simple method for the synthesis of strained medium ring boracycles. This development has opened up a number of fascinating theoretical questions for exploration.

Acknowledgment. We are grateful to the National Science Foundation for the support under Grant CHE-8706102.

(10) The bis(trimethylsilyl) ether of the diol was prepared by using BSA and analyzed on a Hewlett-Packard 5890A gas chromatograph with a 0.125 in. × 12 ft column packed with 5% SP-2100 on Chromosorb W (100–200 mesh) at 50–170 °C, programming with a 10 °C rise in temperature/min.

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