A New Strategy for the Synthesis of Macrocycles. The Polyhomologation of Boracyclanes

K. J. Shea,* S. Y. Lee, and B. B. Busch

Department of Chemistry, University of California, Irvine, California 92697-2025

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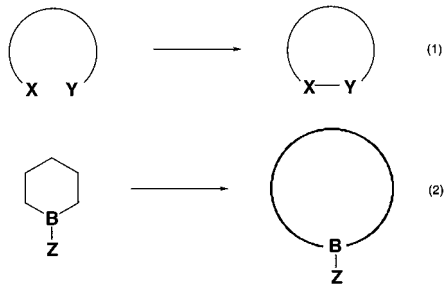
General strategies for the synthesis of macrocycles are quite limited. Aside from several very specialized reactions that include fragmentation of bicyclic rings, the basic approach relies on ring closure of an α,ω-difunctional linear precursor under conditions of high dilution (eq 1).[1] We report a new strategy for the synthesis of macrocycles. The approach draws upon our discovery of the polyhomologation of trialkylboranes.[2] Polyhomologation results in repetitive methylene insertions into the carbon−boron bond. When applied to boracyclanes, the reaction generates macrocyclic rings (eq 2). These macrocyclic organoboranes can be elaborated to carbocyclic rings and other derivatives.



The polyhomologation reaction employs the ylide dimethylsulfoxonium methylide (**1**)[3] as monomer, and the polymerization is initiated by trialkylboranes. For simple trialkylboranes, all three alkyl groups on boron participate, giving rise to a star polymethylene organoborane **2** (Scheme 1). These oligomeric and polymeric organoboranes (**2**) are amenable to synthetic transformations that can be used to terminate the polymethylene chain with functionality.[4] For example, peroxide cleavage of the carbon−boron bonds in star **2** results in hydroxyl terminated linear polymethylene **3** in yields over 90% (Scheme 1).[2]

The synthesis of macrocycles by the polyhomologation reaction requires boracycles as starting materials. These compounds are readily prepared by hydroboration of dienes. Since all three boron−carbon bonds undergo polyhomologation, we chose thexylborane[5] as the hydroborating agent. The thexyl group has been shown to exhibit a low migratory aptitude in rearrangements of organoboranes.[6] The suppressed tendency toward migration should permit exclusive

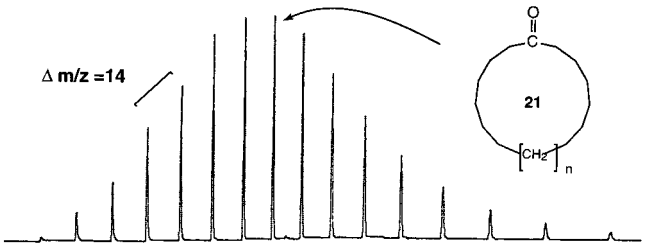
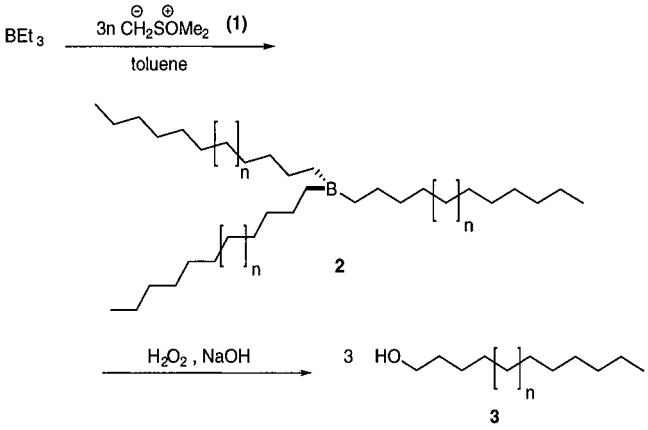
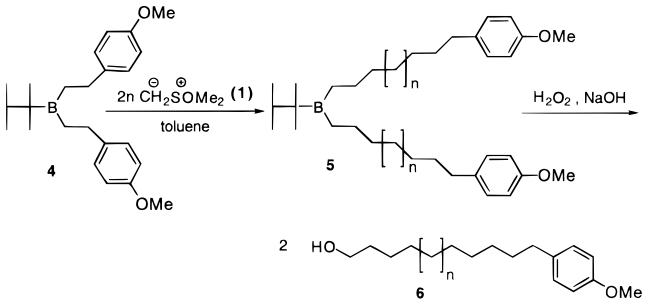


Figure 1. Gas chromatograph of the distribution of macrocyclic ketones resulting from the reaction in eq 3. HRMS found the most abundant ion at t_R = 19.4 to be 322.3222, the calculated M^+ for n = 21 is 322.3235.

Scheme 1



Scheme 2



ring expansion, simplifying product characterization and enhancing the overall efficiency (eq 2).

To verify the use of the thexyl group as a blocking ligand, thexylbis(methoxyphenethyl) borane **4** was added to 50 molar equiv of dimethylsulfoxonium methylide (**1**) at 0 °C (Scheme 2). Following ylide consumption (<10 min), oxidation (NaOH, H_2O_2) provided α-hydroxy-ω-(*p*-methoxybenzene)polymethylene **6** in 85% yield.[7] The product was free of thexyl-terminated polymethylene. Its absence confirms the low migratory aptitude of the thexyl group.

Incorporation of a nonmigrating thexyl substituent as the third ligand in a *boracycle* allows for selective ring enlargement. *B*-Thexylborocane **7** was prepared by the hydroboration of 1,5-hexadiene with thexylborane in THF at −10 °C (Scheme 3). The polyhomologation reaction was run in

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(7) The average degree of polymerization (DP = *n*) for polymethylene **6**, based on ^{1}H NMR integration, was 33, while the calculated DP based on initial ylide to borane **4** ratio was 25.

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Scheme 3

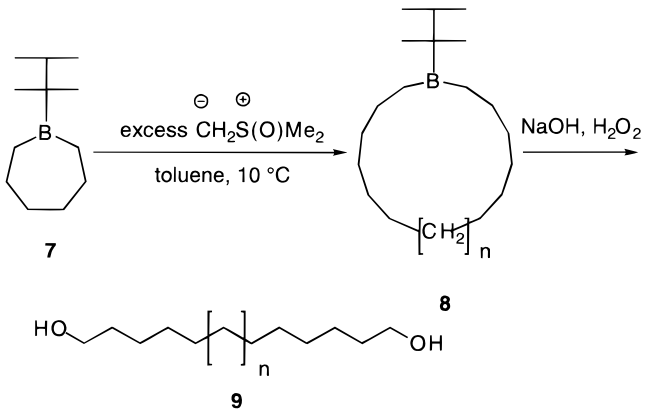


Table 1. Molecular Weight and Degree of Polymerization for α,ω-Dihydroxylpolymethylene 9

entry	$\overline{DP}^a$	$\overline{MW}^a$	$\overline{M_n}^b$	$\overline{DP}^b$	$\bar{M}_w/\bar{M}_n{}^c$	calcd[d] ratio of MW	found[e] (NMR)	found[f] (GPC)
1	26	399				2.0	1.5	
2	38	651	658	38	1.05			
3	40	680	705	42	1.07	2.0	1.8	1.8
4	71	1114	1180	76	1.29			
5			1139	73	1.21	2.0		1.9
6			2023	136	1.63			
7	25	469			1.60	3.0	2.9	
8	72	1127	1133	72				

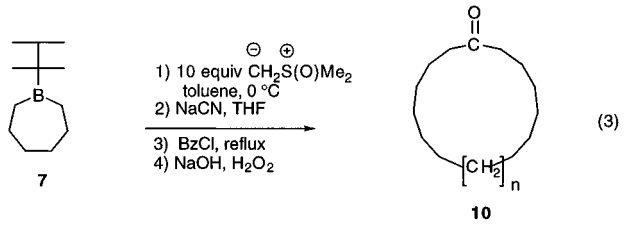
[a] Degree of polymerization and derived average molecular weight from NMR end group analysis. [b] Number average molecular weight and degree of polymerization from gel permeation chromatography. [c] PDI from gel permeation chromatography. [d] Calculated ratio of molecular weight between entries based upon ratio of **1**:**9**. [e] Experimentally determined ratio of molecular weight between entries (NMR). [f] Experimentally determined ratio of molecular weights between entries (GPC).

toluene at ~5−10 °C. Verification of exclusive ring expansion to boracycle **8** was obtained by oxidization to the α,ω-dihydroxypolymethylene **9**. No thexyl-containing polyhomologated product was observed, and the combined yield of **9** was >90%.

This important observation allows control of ring size of boracycle **8**. This was established from analysis of the molecular weights of α,ω-dihydroxypolymethylene **9** (Table 1). Molecular weights were determined by a combination of GPC and NMR end group analysis. The sets of entries in the table correspond to experiments employing different ratios of ylide **1** to boracyclane **7**. The expected ratios of molecular weights (between entries) based upon the ratios of reagents and the experimentally found ratio from the molecular weight data are given in the last three columns. For example, doubling the molar ratio of ylide **1** to thexylboracycle **7** doubles the molecular weight of **9** (entries 5 and 6).

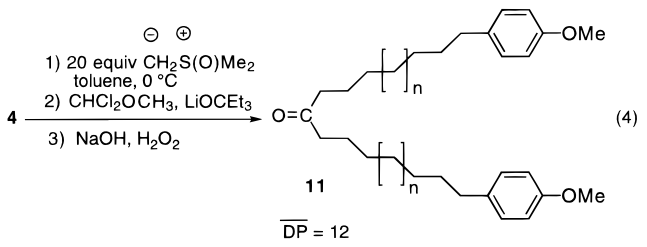
The polyhomologation reactions summarized in Table 1 produced *B*-thexylboracyclanes with average ring sizes that ranged from 30 to 140.

The macrocyclic organoboranes may be transformed directly to carbocyclic rings.[9] We demonstrate the utility of this new chemistry by synthesis of a distribution of macrocyclic ketones. The molecular weights incorporate members of the musk odorant class.[10] In one experiment, *B*-thexylborocane **7** was added to 10 equiv of ylide in THF at room temperature. After ylide consumption, the expanded boracycle was treated as indicated in eq 3. The yield of cyclic



ketone **10** was ~30%. The spectral properties of chromatographed product were consistent with the assigned structure. On the basis of the ratio of integrated intensities of methylenes α to the carbonyl to those of the ring methylenes, $\overline{DP} = 20$. The distribution of ketone macrocycles is shown in the gas chromatograph of the reaction mixture (Figure 1). The identity of the individual peaks was established by high-resolution GC mass spectrometry. The most abundant molecular ion (M^+ 322.3222) corresponds to a 21-membered cyclic ketone (322.3235). The molecular ions of the surrounding peaks were separated by approximately 14.03 *m*/*z*. The molecular weights, calculated from the mass spectral data, are $M_n = 290$ and $M_w = 295$ (PDI = 1.02).

Thexylborane **4** may also be converted to linear polymethylene ketones. This was achieved by polyhomologation of **4** followed by treatment with α,α-dichloromethyl methyl ether and lithium triethylcarboxide in toluene.[9] The reaction mixture was then oxidized. Bis(*p*-methoxyphenyl)-polymethylene ketone **11** was isolated in 30% yield. In one example, a 20:1 ratio (calculated DP = 10) gave ketone **11** with a DP = 12. Mass spectral analysis of the product gave $M_n = 635$ and $M_w = 640$ (PDI = 1.01).[11]



The scope of the polyhomologation has been extended to include synthesis of macrocyclic rings and symmetrical polymethylene ketones. The thexyl substituent has proven to be effective for restricting the number of growing polymethylene chains on boron from 3 to 2. The ring size of these macrocycles is controlled by the molar ratio of ylide to organoborane. Preparation of large rings via polyhomologation represents a fundamentally new approach to the synthesis of macrocycles.

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Supporting Information Available: Experimental procedure (1 page).

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(11) The main side product was found to be α-hydroxy-ω-(*p*-methoxybenzene)polymethylene **2**, a compound which results from incomplete polymethylene chain migration onto the methyl ether reagent.