Novel Conversion of Aldehydes to Boronic Esters. Simultaneous IGOR2 Computer Generation and Experimental Observation of an Unusual Rearrangement of α-Aminoboranes

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Abstract: Utilization of the IGOR2 (Interactive Generation of Organic Reactions 2) program to study the addition of the boron–hydrogen bond to various carbon–carbon and carbon–heteroatom double bonds is reported. The IGOR2 program not only generated a number of hydroboration reactions but also indicated an unusual rearrangement of α-aminomonoalkylboranes to the corresponding *B*-(dialkylamino)monoalkylboranes. Independent and simultaneous experimental observation of these IGOR2-generated rearrangements was made during the hydroboration of β,β-disubstituted morpholino and piperidino enamines. Thus, the hydroboration of 2-ethyl-1-morpholino-1-butene using borane–methyl sulfide (BMS) gave *B*-morpholinoborane as a byproduct. Additionally, upon oxidation, 2-ethyl-1-butanol was isolated from the reaction mixture. These results are explained in terms of unusual rearrangements of the α-(dialkylamino)monoalkylborane intermediate. The use of BH_3·THF–BF_3·OEt_2 or $NaBH_4$–BF_3·OEt_2 for the hydroboration permits the utilization of any β,β-disubstituted enamine in this rearrangement reaction and vastly improves the yields of the rearrangement products. Nonoxidative workup of the rearrangement reaction mixture affords excellent yields of the corresponding boronic acids, which were isolated as 2-alkyl-1,3,2-dioxaborinanes.

Introduction

During the last 15 years, the extraordinary improvements in all areas of computer hardware have allowed programmers to design software of remarkable power and sophistication. The use of numerical programs such as MM2(85),[2] AM1,[3] PM3,[4] and GAUSSIAN[5] has become almost as routine as NMR. Nonnumerical programs such as SECS (Simulation and Evaluation of Chemical Synthesis)[6] and REACCS (Reaction Access System)[7] are heavily used in the chemical industry to generate routes to desired compounds. SECS provides an unbiased analysis of possible synthesis pathways and their feasibility. REACCS provides rapid access to literature precedents for individual reactions and thus to specific reaction conditions. Together, they enable the chemist to optimize the synthesis plan before committing time and resources to attempting the actual synthesis of the target molecule in the laboratory. In an increasing number of cases, the syntheses so generated have proven to be both original and productive.[8] For chemists primarily interested in developing new reactions, there is a useful IBM PC program, IGOR2.[9] From a set of constraints and a reaction matrix that represents an electron redistribution pattern, IGOR2 generates a comprehensive set of possible chemical reactions. As a part of another program, we investigated the hydroboration reaction using the IGOR2 software. The general reaction scheme that we investigated is shown in Figure 1.

Results and Discussion

The application of IGOR2 to this scheme resulted in the generation of 212 different reactions. The detailed problem specification and complete set of reactions generated are included as supplementary material. For X, Y = C and Z = N (enamines), numerous rearranged products were generated without mechanistic implications (IGOR2 does not consider electronegativity or thermodynamics). Among the many reactions generated by the IGOR2 program, two reactions dealing with the hydroboration of enamines caught our attention. These reactions are shown in Figure 2.

According to the reactions generated by the IGOR2 program, hydroboration of enamines can give both the α- and the β-adducts. Additionally, IGOR2 indicated that the α-borane adduct could undergo rearrangement to give the corresponding *B*-aminomonoalkylborane and the β-borane adduct could undergo an elimination reaction to afford the aminoborane. We were intrigued, however, by the IGOR2 program's generation of α-borane adducts in the hydroboration of enamines. Until our investigation of the hydroboration of β,β-disubstituted enamines,[10] hydroboration of enamines leading to such α-adducts had been postulated only once before.[11,12] Additionally, the electronic structure of enamines clearly indicates that the β-adducts are the normal,

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(1) The Dow Chemical Company.
(2) Allinger, N. L.; Kok, R. A.; Imam, M. R. *J. Comput. Chem.* **1988**, *9*, 591.
(3) Dewar, M. J. S.; Zoebisch, E. G.; Healy, E. F. *J. Am. Chem. Soc.* **1985**, *107*, 3902.
(4) (a) Stewart, J. J. P. *J. Comput. Chem.* **1989**, *10*, 209. (b) Stewart, J. J. P. *J. Comput. Chem.* **1989**, *10*, 221.
(5) (a) Hehre, W. J.; Radom, L.; Schleyer, P. v. R.; Pople, J. A. *Ab Initio Molecular Theory*; Wiley: New York, 1986. (b) Frisch, M. J.; Brinkley, J. S.; Schelgel, H. B.; Rhaghavachari, K.; Melius, C. F.; Martin, R. L.; Stewart, J. J. P.; Bobrowica, F. W.; Rohlfing, C. M.; Kahn, L. R.; Defrees, D. J.; Fluder, E. M.; Pople, J. A. *GAUSSIAN 86*; Carnegie-Mellon Quantum Chemistry Publications Unit: Pittsburgh, PA, 1984.
(6) (a) Wipke, W. T.; Dyott, T. M. *J. Am. Chem. Soc.* **1974**, *96*, 4825. (b) Wipke, W. T. In *Computer-Assisted Three-Dimensional Synthetic Analysis*; Wipke, W. T.; Heller, S. R., Feldmann, R., Hyde, E., Eds.; John Wiley: New York, 1974; 147–174.
(7) (a) *Chem. Eng. News* **1982**, *60*, 92. (b) Wipke, W. T.; Dill, J.; Hounshell, D.; Moock, T.; Grier, D. In *Modern Approaches to Chemical Reaction Searching*; Barnard, J. M., Ed.; Gower Publishing Co., Ltd.: Hampshire, England, 1986, 92–117.
(8) Andose, J. D.; Grabowski, E. J. J.; Gund, P.; Rhodes, J. B.; Smith, G. M.; Wipke, W. T. *Computer-Assisted Drug Design*; ACS Symposium Series 12; American Chemical Society: Washington, DC, 1979; 527–551.
(9) (a) Bauer, J.; Herges, R.; Fountain, E.; Ugi, I. *Chimia* **1985**, *39*, 43. (b) Bauer, J.; Forstmeyer, D.; Fountain, E.; Ugi, I. *Tetrahedron Comput. Methodol.* **1988**, *1*, 129. (c) Bauer, J. *Tetrahedron Comput. Methodol.* **1989**, *2*, 269 (disk 21 contains the executable program for the IBM PC computer).
(10) Singaram, B.; Goralski, C. T.; Fisher, G. B. *J. Org. Chem.* **1991**, *56*, 5691.
(11) Lewis, J. W.; Pearce, A. A. *J. Chem. Soc. B* **1969**, 863.
(12) α-Borane adducts have been observed previously during the hydroboration of enol ethers, enol acetates, vinyl sulphides, and vinyl chlorides. (a) Pasto, D. J.; Snyder, R. *J. Org. Chem.* **1966**, *31*, 2773. (b) Pasto, D. J.; Hickman, J. *J. Am. Chem. Soc.* **1967**, *89*, 5608, (c) Pasto, D. J.; Cumbo, C. C. *J. Am. Chem. Soc.* **1964**, *86*, 4343. (d) Pasto, D. J.; Miesel, J. L. *J. Am. Chem. Soc.* **1963**, *85*, 2118. (e) Brown, H. C.; Sharp, R. L. *J. Am. Chem. Soc.* **1968**, *90*, 2915.

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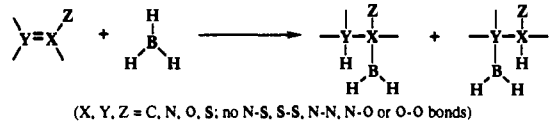


Figure 1. Model system used in this study for the generation of reactions with the IGOR2 program. Charged structures were not permitted.

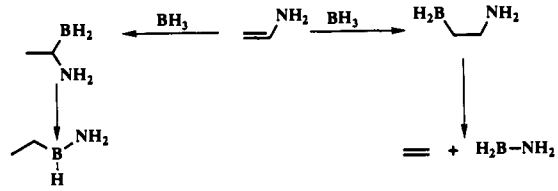


Figure 2. Hydroboration of enamines as generated by the IGOR2 program.

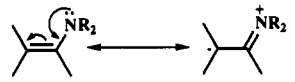
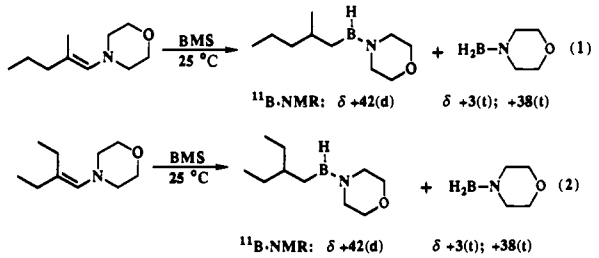


Figure 3. Electronic structure of enamines predicts that only β-adducts will result during hydroboration.

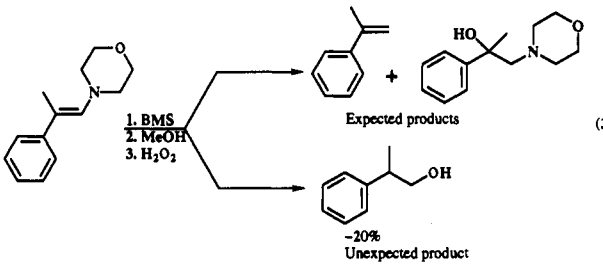
expected products from the hydroboration of enamines (Figure 3).[13]

Moreover, β-borane adducts are remarkably stable[10,13] and undergo elimination to the corresponding alkenes only under special and rather drastic experimental conditions.[10,14]

What is even more remarkable is that we observed the formation of the *B*-aminomonoalkylboranes and the aminoboranes as by-products during our comprehensive investigation of the hydroboration of β,β-disubstituted enamines (eqs 1 and 2).



Additionally, during the hydroboration–oxidation of 2-phenyl-1-morpholino-1-propene, we observed the formation of not only the expected alkene and amino alcohol but also an unexpected byproduct, 2-phenyl-1-propanol (eq 3).[10]



These results led us to believe that we were experimentally observing the rearrangement reactions of α-aminoboranes suggested by the IGOR2 program. This unusual rearrangement of α-aminoboranes has been invoked previously, without any mechanistic implications, to explain some unexpected results in the hydroboration–protonolysis of enamines.[11] Consequently, we undertook a detailed study of the hydroboration of β,β-disubstituted enamines in order to better understand these rearrangement reactions and to increase the yield of the rearranged products.

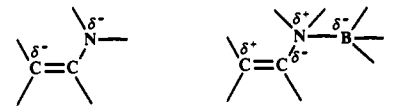
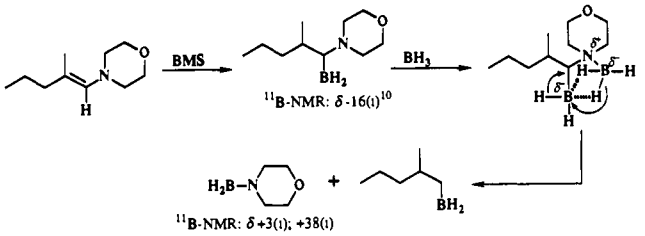
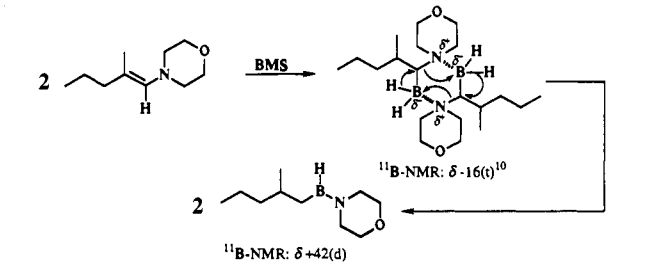


Figure 4. Reversal of the normal electronic effect of the enamine dialkylamino group due to coordination of BH_3 or BF_3 with the enamine nitrogen.

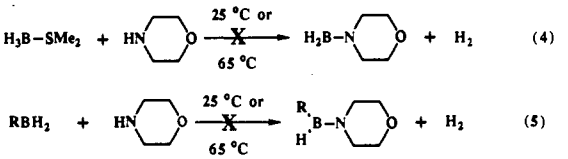
Scheme I



Scheme II



We found that simple secondary amines do not react with either borane–methyl sulfide (BMS) or monoalkylboranes (RBH_2) to form *B*-(dialkylamino)boranes or *B*-(dialkylamino)monoalkylboranes, respectively (eqs 4 and 5). Therefore, these aminoborane



byproducts must be formed by some other route. We observed these byproducts (~30%) only in the hydroboration of β,β-disubstituted enamines derived from morpholine and piperidine. In earlier work, we had shown that morpholine and piperidine moieties direct borane predominantly to the α-position in the hydroboration of β,β-disubstituted enamines.[10] We therefore assumed that it was these α-aminoorganoboranes that undergo rearrangement to afford the unusual side products that we observed.

There are at least two possible mechanisms which can account for the observed products. In the first pathway, the α-aminoborane coordinates with borane, making the amine moiety a better leaving group. A hydride then migrates intramolecularly to displace the aminoborane product (Scheme I).

In the second possible route, the α-aminoborane is visualized to form a dimer, thereby making the amino moiety a better leaving group. Intramolecular hydride transfer then completes the rearrangement (Scheme II).

In both schemes, the key step is the formation of the tetravalent boron atom and the positively charged nitrogen atom. We speculated that the use of a better Lewis acid, such as BF_3, might facilitate the reaction by forming a better adduct with the amino group. Additionally, coordination of the Lewis acid to the enamine is expected to change the normal polarity of the enamine[10,11] and direct the borane to the α-position regardless of the amine moiety of the enamine (Figure 4). Consequently, the use of $BF_3{\cdot}Et_2O$ should promote the IGOR rearrangement in enamines regardless of the amino group.

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Table I. Oxidation Product Obtained from the IGOR Rearrangement of Enamines[a]

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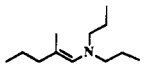
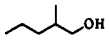
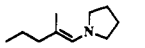
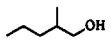
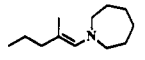
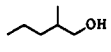
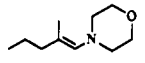
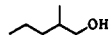
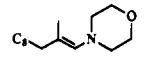
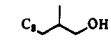
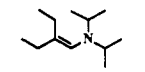
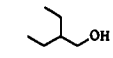
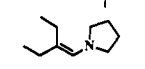
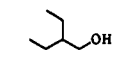
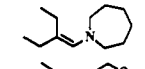
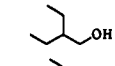
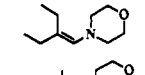
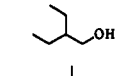
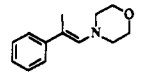
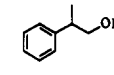
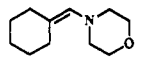
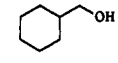
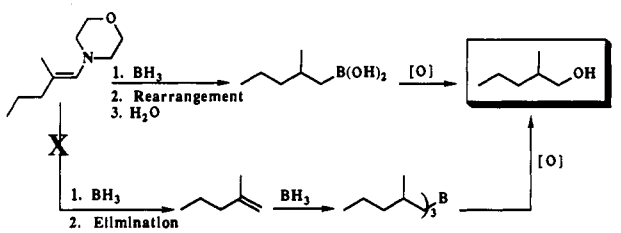
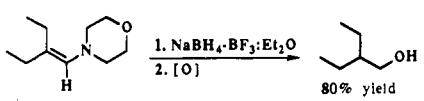
		40	0
		54	0
		48	10
		75	20
		75	25
		35	15
		52	0
		48	15
		80	30
		60	20
		60	15

[a] Hydroboration of β,β-disubstituted enamines was carried out in THF at 25 °C for 3 h. [b] Product obtained after the oxidation using alkaline hydrogen peroxide. [c] Isolated yield.

Scheme III



As expected, we found that hydroboration of a morpholino or piperidino enamine in the presence of 1 equiv of $BF_3{\cdot}Et_2O$ significantly improved the product yield.[15a] Moreover, we also observed the rearrangement with enamines having other amine moieties. Finally, the use of $BH_3{\cdot}THF$ generated in situ from sodium borohydride and $BF_3{\cdot}Et_2O$ afforded the rearranged products in high yield. Following oxidation, the products are isolated as the corresponding primary alcohols (Table I, eq 6).



(6)

When these reactions were quenched with water, the ^{11}B-NMR spectrum of the reaction mixture showed the presence of boronic acids. Trialkylboranes were completely absent from the reaction products. This clearly showed that the primary alcohols are not produced by an initial elimination reaction of the β-aminoorganoborane followed by a hydroboration–oxidation reaction of the product alkenes; if this were the case, then the trialkylboranes would be the predominant intermediates (Scheme III). Exclusive formation of boronic acids in this reaction lends further support

(15) (a) Fisher, G. B.; Juarez-Brambila, J.; Singaram, B. Unpublished results. (b) The reaction of *B*-pyrrolidinodihydridoborane with 1-octene also produced no reaction after 24 h. Fisher, G. B.; Singaram, B. Unpublished results.

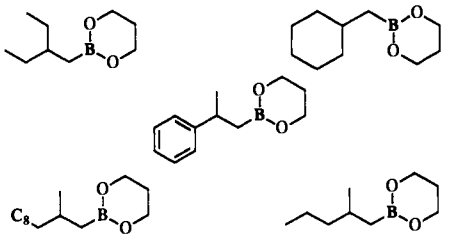


Figure 5. Boronic esters prepared from the corresponding aldehyde enamines.

Scheme IV

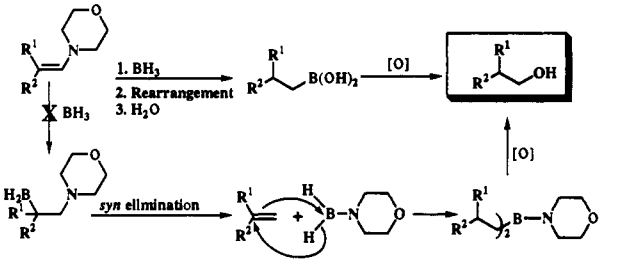


Table II. Alkylboronic Esters Obtained from the Corresponding Aldehyde Enamines

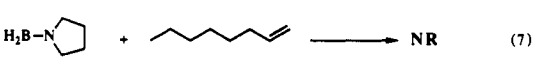
boronic ester	yield, %[a]	bp, °C (Torr)[b]	^{11}B-NMR chemical shift[c]
2-(2-ethyl-1-butyl)-1,3,2-dioxaborinane	83	90–92 (10)	+32
2-(2-methyl-1-pentyl)-1,3,2-dioxaborinane	80	88–90 (12)	+32
2-(2-methyl-1-undecyl)-1,3,2-dioxaborinane	75	*d*	+31
2-(cyclohexylmethyl)-1,3,2-dioxaborinane	76	70–72 (0.5)	+32
2-(2-phenyl-1-propyl)-1,3,2-dioxaborinane	75	*d*	+30

[a] Isolated yields. [b] Boiling points are uncorrected. [c] Relative to $BF_3{\cdot}Et_2O$. [d] Isolated as a thick oil.

to the mechanisms proposed above. Additionally, the β-addition–elimination–rehydroboration has been considered before as an unlikely pathway to the formation of some unexpected products of the hydroboration–protonolysis of enamines.[11]

Another alternative to our proposed mechanism invokes a syn elimination of the β-aminoorganoborane to yield the corresponding aminoborane and alkene. Such eliminations have been reported recently.[14] The aminoborane then hydroborates the alkene to form the *B*-(dialkylamino)dialkylborane, which, upon oxidation, yields the rearranged alcohol (Scheme IV).

To test this hypothesis, we synthesized *B*-morpholinodihydridoborane and monitored its reaction with 1-hexene by ^{11}B-NMR over a 24-h period (eq 7).[15b]



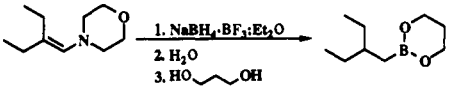
(7)

However, there was no spectroscopic evidence for the formation of the *B*-(dialkylamino)dialkylborane predicted by the alternative mechanism shown in Scheme IV. This conclusively demonstrates that the aminoborane does not form an organoborane intermediate that is subsequently oxidized to the primary alcohol that we isolated.

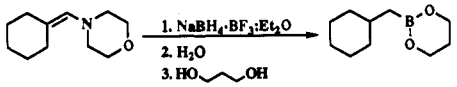
As pointed out earlier, boronic acid derivatives were formed as intermediates in these reactions as evidenced by ^{11}B-NMR spectroscopy. Alkylboronic acid derivatives are esthetically appealing reagents for carbon–carbon bond-forming reactions.[16,17] There are major advantages in using boronic esters in organic synthesis. Unlike the trialkylboranes, the single organic group

(16) Brown, H. C.; Singaram, B. *Acc. Chem. Res.* **1988**, *21*, 287.
(17) Matteson, D. S. *Tetrahedron* **1989**, *45*, 1859.

in the boronic ester can be quantitatively incorporated into organic molecules. Additionally, in the past, boronic esters have been converted into compounds containing a wide variety of functional groups, such as aldehydes, ketones, acids, amines, nitriles, alkenes, and acetylenes.[16] Consequently, we checked the possibility of isolating these boronic acid intermediates. We found that a nonoxidative workup of the reaction mixture afforded the corresponding boronic acid derivatives in good yields (eqs 8 and 9).



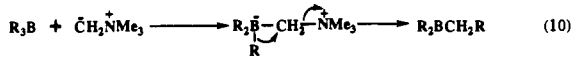
(8)



(9)

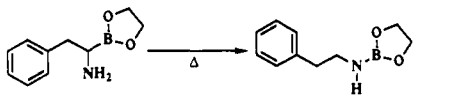
Using the general procedure, the following boronic esters were prepared from the corresponding aldehyde enamines (Figure 5, Table II).

It should be pointed out that the reactions described in this manuscript belong to a broader class of reactions known as "α-transfer" reactions.[12] Previously known "α-transfer" reactions involved the halogens and methoxy moieties as leaving groups. The reactions described in this paper involve an "α-transfer" reaction with an ammonium moiety as the leaving group. A similar reaction involving an alkyl group migration from boron to carbon, displacing an ammonium group, has been reported earlier (eq 10).[17]



(10)

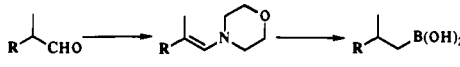
However, in the present study, we are reporting, for the first time, a reaction involving a hydride migration from boron to carbon with concurrent displacement of an ammonium moiety. Recently, Matteson and co-workers reported a related, but different, reaction of α-aminoboronate esters (eq 11).[18]



(11)

Conclusion

The present study describes the use of the IGOR2 program to generate new hydroboration reactions. Use of the IGOR2 program also led to the study of an unusual rearrangement reaction in the hydroboration of β,β-disubstituted enamines. Thus, the hydroboration of 2-ethyl-1-morpholino-1-butene followed by oxidation gave 2-ethyl-1-butanol. This result is explained in terms of two rearrangements of the α-(dialkylamino)alkylborane intermediate. A nonoxidative workup of the reaction mixture affords the corresponding boronic acids. This constitutes a novel method of converting β-substituted aldehydes into the corresponding boronic acid derivatives, which are valuable synthetic reagents (eq 12).[16,17]



(12)

Experimental Section

All operations were carried out under a nitrogen atmosphere. All glassware, syringes, and needles were oven-dried at 110 °C and cooled to room temperature with nitrogen gas before use. Tetrahydrofuran (THF) was freshly distilled from sodium and benzophenone ketyl. Anhydrous diethyl ether (EE) was purchased from Fisher and was used directly. Borane–dimethyl sulfide (BMS, 10.2 M) and all of the amines and aldehydes were purchased from the Aldrich Chemical Company, stored under nitrogen, and used without further purification. ^{11}B-NMR were obtained on a General Electric GN 300 wide bore 300-MHz NMR, and the chemical shifts are in δ relative to EE·BF_3 with chemical shifts downfield from EE·BF_3 assigned as positive. ^{1}H-NMR and ^{13}C-NMR were obtained on a General Electric GN 300 wide bore 300-MHz NMR or a Bruker ACF dual probe 250-MHz NMR. Chemical shifts are in δ relative to internal Me_4Si. Mass spectra were obtained on a Finnegan 4000 mass spectrometer with the Super Incos Data System.

Synthesis of β,β-Disubstituted Enamines. All enamines used in this study were synthesized using literature methods.[10,20]

Hydroboration of 2-Ethyl-1-morpholino-1-butene using $NaBH_4$·BF_3. The following procedure is representative. To a suspension of $NaBH_4$ (0.92 g, 24 mmol) in THF (40 mL), BF_3·OEt_2 (3.4 mL, 3.92 g, 28 mmol) was added dropwise at 25 °C with gentle stirring. After 1 h, 2-ethyl-1-morpholino-1-butene (3.8 mL, 3.38 g, 20 mmol) was added and the stirring was continued for an additional 3 h at 25 °C. The reaction was quenched with methanol (1.6 mL, 40 mmol) slowly to avoid excessive foaming. NaOH (3 M, 20 mL, 60 mmol) was added and the solvent, THF, removed by vacuum (25 °C, 12 Torr). The alkaline aqueous layer was cooled to 0 °C and acidified using concentrated HCl (12 M, 8 mL, 96 mmol). The boronic acid was extracted with ether (3 × 10 mL), washed with water (2 × 10 mL), and dried over anhydrous $MgSO_4$. Evaporation of the ether under reduced pressure afforded (2-ethyl-1-butyl)boronic acid (1.82 g, 70% yield). The boronic acid was suspended in *n*-pentane (30 mL), 1,3-propanediol (20 mmol) was added, and the reaction mixture was stirred until all of the boronic acid had dissolved (4 h). The clear pentane layer was separated and dried over anhydrous $MgSO_4$. Air filtration and evaporation of the *n*-pentane gave pure 2-(2-ethyl-1-butyl)-1,3,2-dioxaborinane (2 g, 83% yield): bp 90–92 °C (10 Torr); ^{11}B-NMR (THF) δ +32 (s).

2-(2-Methyl-1-pentyl)-1,3,2-dioxaborinane: 1.7 g, 80% yield; bp 88–90 °C (12 Torr); ^{11}B-NMR (THF) δ +32 (s); (*m*/*z*) calcd for $C_9H_{19}BO_2$ 170.0579, found 170.1478.

2-(2-Methyl-1-undecyl)-1,3,2-dioxaborinane: 3.26 g, 75% yield; ^{11}B-NMR (THF) δ +31 (s); (*m*/*z*) calcd for $C_{15}H_{31}BO_2$ 254.2187, found 254.2483.

2-(Cyclohexylmethyl)-1,3,2-dioxaborinane: 2.35 g, 76% yield; bp 70–72 °C (0.5 Torr); ^{11}B-NMR (THF) δ +32 (s); (*m*/*z*) calcd for $C_{10}H_{19}BO_2$ 182.0689, found 182.135.

2-(2-Phenyl-1-propyl)-1,3,2-dioxaborinane: 2.45 g, 75% yield; ^{11}B-NMR (THF) δ +30 (s).

Synthesis of Primary Alcohols from the Corresponding Alkylboronic Acid. The following procedure is representative. To a suspension of $NaBH_4$ (0.92 g, 24 mmol) in THF (40 mL), BF_3·OEt_2 (3.4 mL, 3.92 g, 28 mmol) was added dropwise at 25 °C with gentle stirring. After 1 h, 2-ethyl-1-morpholino-1-butene (3.8 mL, 3.38 g, 20 mmol) was added and the stirring was continued for an additional 3 h at 25 °C. The reaction was quenched with methanol (1.6 mL, 40 mmol) slowly to avoid excessive foaming. NaOH (3 M, 20 mL, 60 mmol) was added and the solvent, THF, removed by vacuum (25 °C, 12 Torr). The residue obtained from 20 mmol of enamine was layered with ether (30 mL) and oxidized with 30% H_2O_2 at 25 °C for 3 h. The organic phase was extracted with ether (2 × 15 mL), washed successively with 3 M HCl (2 × 5 mL) and water (2 × 10 mL), and dried. Evaporation of the solvent gave 2-ethyl-1-butanol (1.65 g, 80% yield), which was further purified by distillation: bp 50–52 °C (20 Torr) (lit.[21a] 144–146 °C, 760 Torr); ^{1}H-NMR ($CDCl_3$) δ 0.79 (t, J = 7 Hz, 6 H), 1.24 (m, 5 H), 3.6 (d, J = 7 Hz, 2 H); ^{13}C-NMR ($CDCl_3$) δ 11.0, 23.1, 42.6, 64.7.

2-Methyl-1-pentanol: 1.53 g, 75% yield; bp 86–88 °C (80 Torr); ^{1}H-NMR ($CDCl_3$) δ 0.81 (d, J = 7 Hz, 3 H), 0.82 (t, J = 7 Hz, 3 H), 1.2–1.5 (m, 5 H), 3.52 (dd, J = 6, 14 Hz, 2 H); ^{13}C-NMR ($CDCl_3$) δ 14.2, 16.5, 20.0, 35.4, 42.3, 67.9.

2-Methyl-1-undecanol: 2.80 g, 75% yield; bp 50–52 °C (20 Torr); ^{1}H-NMR ($CDCl_3$) δ 0.8 (t, 3 H), 1.1 (d, 3 H), 1.2 (br m, 16 H), 3.6 (br m, 2 H); ^{13}C-NMR ($CDCl_3$) δ 14, 17, 22.7, 27.2, 29.3, 29.7, 29.9, 31.9, 33.7, 35, 36, 68.3.

Cyclohexylmethanol: 1.37 g, 60% yield; bp 104–106 °C (20 Torr) (lit.[21b] 199–200 °C, 740 Torr); ^{1}H-NMR ($CDCl_3$) δ 0.75–1.8 (m, 11 H), 3.07 (br s, 1 H), 3.30 (d, J = 7 Hz, 2 H); ^{13}C-NMR ($CDCl_3$) δ 25.8, 26.6, 29.6, 40.4, 67.8.

2-Phenyl-1-propanol: 1.63 g, 60% yield; bp 100–102 °C (5 Torr) (lit.[21c] 112–114 °C, 14 Torr); ^{1}H-NMR ($CDCl_3$) δ 1.28 (d, J = 7 Hz, 3 H), 3.0 (sextet, J = 7 Hz, 1 H), 3.6 (m, 2 H), 7.3 (m, 5 H); ^{13}C-NMR ($CDCl_3$) δ 17.8, 42.4, 68.5, 126.6, 128.6, 143.1.

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Supplementary Material Available: Problem specification with constraints that were used in the IGOR2 exploration of hydroboration and the complete set of reactions generated (35 pages). Ordering information is given on any current masthead page.

A General Synthetic Strategy toward Aminocyclopentitol Glycosidase Inhibitors. Application of Palladium Catalysis to the Synthesis of Allosamizoline and Mannostatin A

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Abstract: A general strategy for the synthesis of aminocyclopentitol glycosidase inhibitors has been applied to the synthesis of allosamizoline and mannostatin A. These cyclic pseudosugars are members of a growing family of highly potent and selective glycosidase inhibitors. A palladium-catalyzed ionization/cyclization reaction for preparing oxazolidinones from *meso*-alkenediols forms the cornerstone for this approach toward the synthesis of highly functionalized cyclopentane rings.

Glycosidase inhibitors are aiding in developing an understanding of glycoprotein processing in which glycoconjugates present on the surface of mammalian cells constitute functional domains for carbohydrate protein interactions involved in recognition, adhesion, transport, etc.[1] Possible applications in immunology, diabetes, virology, and cancer stimulates general interest into structures with specific biological function.[2] Inhibitors of glycoside-processing enzymes have traditionally been molecules which share direct structural homology with the natural enzymatic substrate—often polyhydroxylated six-membered heterocyclic rings.[3-5] The reported isolation of allosamidin in 1986[6] opened the way to recognition that aminohydroxy-substituted five-membered carbocyclic rings can have powerful and specific inhibitory activity against glycosidases which normally accept six-membered pyranoside substrates. Since this initial report, four other such aminohydroxycyclopentanes have been reported—the mannostatins,[7] the trehalase inhibitors trehalostatin[8] and trehazolin,[9] and Merrell Dow's cyclopentylamine[10] (Figure 1).[11] The intensitive synthetic investigations of aminohydroxycyclopentanes are a result not just of the challenging density and juxtaposition of functionality but of their biological activity as glycosidase inhibitors. The compounds in Figure 1 are the most potent and specific known competitive inhibitors for their respective enzymes. The superiority of five-membered ring inhibitors over six-membered ring analogs (which more closely resemble the enzymatic substrates) may be related to the energetic costs associated with distortion of the natural chair conformation of six-membered rings to match the enzymatic transition state. The potential therapeutic applications of this newly emerging class of glycosidase inhibitors demands a general and flexible approach to their synthesis.

A Unified Approach to Aminocyclopentitols Involving Palladium Catalysis

Pd(0) catalyzed reactions provide selective entry to amino alcohols of varying regio- and stereoselectivity. The *cis*-vicinal amino alcohols may derive either from epoxides in a single step as in eq 1, path a[12] or their synthetic equivalents such as 2-alkene-1,4-diols as illustrated in the one-pot sequence of eq 1, path b,[12,13] wherein the bisurethane is generated in situ. In both cases, the regio- and diastereoselectivity is assured by covalent tethering of the nitrogen nucleophile to the substrate. An asymmetric synthesis of the amino alcohol via the vinyl epoxide requires an asymmetric synthesis of the latter. On the other hand, the use of *meso*-2-alkene-1,4-diols permits asymmetric induction by differentiation of the enantiotopic leaving groups.

Two approaches for dissymmetrization of the *meso*-diols are feasible. Enzymatic hydrolysis of a diester[14] or transacylation[15] (eq 2) may provide the enantiomeric monoesters which then may

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