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(+)-1(*S*), 5(*R*), 8(*S*)-8-PHENYL-2-AZABICYCLO[3.3.0]OCTAN-8-OL N,O-METHYLBORONATE (2) AND ITS ENANTIOMER, CHIRAL CHEMZYMES WHICH SERVE AS CATALYSTS FOR THEIR OWN ENANTIOSELECTIVE SYNTHESIS

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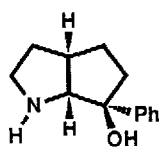
Summary: An efficient synthesis of (+)-1*(S)*, 5*(R)*, 8*(S)*-8-phenyl-2-azabicyclo[3.3.0]octan-8-ol (**1**) and its enantiomer is described. The B-methyloxazaborolidine derivatives (**2**) of these amino alcohols are excellent catalysts (chemzymes) for the enantioselective reduction of a variety of achiral ketones to chiral secondary alcohols, e.g. acetophenone, 98% ee; pinacolone, 98% ee; α-tetralone, 97% ee; and 2-bromo-2-cyclohexen-1-one, 98% ee. The oxazaborolidine **2** is a catalyst for the enantioselective synthesis of **14**, a starting material for the synthesis of chiral **2** itself.

This note describes the synthesis of the rigid bicyclic amino alcohol **1**, (+)-1*(S)*, 5*(R)*, 8*(S)*-8-phenyl-2-azabicyclo[3.3.0]octan-8-ol, and the condensation product with methylboronic acid, oxazaborolidine **2**, and the performance of the latter as a catalyst in the borane reduction of several test achiral ketones to form the corresponding chiral secondary alcohols. We expected on the basis of previous studies[1] that **2**, or its enantiomer, would be highly effective catalysts for such enantioselective reductions (CBS reduction).[1] Previous studies have demonstrated the great utility of the CBS reduction process in multistep synthesis, for example, of ginkgolides,[2,3] forskolin,[4] anti-PAF 2,5-diaryltetrahydrofurans,[5] and fluoxetine.[6]

The synthesis of (±)-**1** was accomplished by a direct and stereoselective route starting from commercially available (±)-(2-cyclopentenyl)-acetic acid (**3**). This acid was converted via the acid chloride (1.5 equiv of oxalyl chloride in CH_2Cl_2 with a catalytic amount of dimethylformamide at 23°C for 3 h) to the corresponding benzylamide **4** (1.2 equiv of benzylamine and 2.5 equiv of triethylamine in THF at 23°C for 0.5 h, 80% overall) which after reduction with lithium aluminum hydride in THF at reflux for 4 h provided secondary amine **5** (93%). Treatment of amine **5** with 1.5 equiv of *N*-bromosuccinimide in ether at 0°C for 1 h transformed it into the corresponding *N*-bromo amine which was isolated simply by filtration to remove succinimide and removal of ether in vacuo, and used directly in the next step. Upon exposure of the bromo



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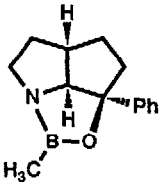

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amine in CH_2Cl_2 to a catalytic amount of cuprous bromide (2 mg/g of bromo amine) at 0°C for 2 h, stereoselective (30 : 1) cyclization occurred to generate the desired bicyclic amine **6** (85%) along with only a few percent of diastereomer **7**. The mixture was heated at reflux for 1 h with 1 : 1 2M aqueous lithium hydroxide-dimethoxyethane to afford amino alcohol **8** (formed from **6** via ammonium ion **9**) and unreacted **7** which is totally inert to these conditions. After separation of **8** and **7** by chromatography on a short silica gel column (tlc R_f values using silica plates and 1 : 1 ether-hexane : 0.3 for amino alcohol **8** and 0.6 for bromo amine **7**), amino alcohol **8** was easily obtained in pure form (83%).

Swern oxidation of alcohol **8** to ketone **10** was accomplished by addition over 5 min to 1.13 equiv of oxalyl chloride and 2 equiv dimethyl sulfoxide in CH_2Cl_2 at -78°C, further reaction at -78°C for 15 min, addition of triethylamine (5 equiv) and reaction at -78°C for 30 min. Extractive isolation and chromatography on silica gel (4 : 1 hexane-ether) afforded **10** (93%) as a colorless oil; Mass, m/e: calcd, 215.13; found, 215.12; IR_{max} (neat): 1740 cm^{-1}. Reaction of **10** with phenyllithium in THF at -78°C for 1 h provided amino alcohol **11** (93%) which was debenzylated using 10% palladium hydroxide on carbon catalyst and hydrogen (1 atm) in methanol containing 1.5 equiv of acetic acid at 23°C for 2 h to give (±)-**1** (99%), as colorless crystals; TLC, R_f 0.2 (silica gel, ether); mp 66 - 66.5; IR (neat) 3600-3200, 2952, 2867, 1445, 700 cm^{-1}; ^1H NMR ($CDCl_3$) 7.47 - 7.46 (m, 2H), 7.33 - 7.30 (m, 2H), 7.20 (t, 1H, J=7.3 Hz), 5.7 - 5.0 (br, 1H), 3.78 (d, 1H, J=9.5 Hz), 3.12 - 3.02 (m, 2H), 2.88 - 2.80 (m, 1H), 2.18 - 2.0 (m, 2H), 2.0 - 1.85 (m, 2H), 2.0 - 1.3 (br, 1H), 1.7 - 1.6 (m, 2H); mass, m/e: calcd, 203.13; found, 203.10.

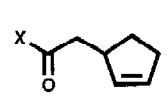
The racemic alcohol **1** was resolved by recrystallization of the salt obtained with 1 equiv of 2,3 : 4,6-di-O-isopropylidine-2-keto-L-gulonic acid (**12**, DIKG, Aldrich Co.). The crystalline salt obtained by slow crystallization from ethanol contained levorotatory **1** of 95% optical purity (determined by HPLC analysis of the MTPA (Mosher) amide[7]). A second recrystallization from ethanol afforded salt from which the free base (-)-**1** of 99.2% optical purity was obtained having mp 69.5 - 70°C, $[\alpha]^{23}_D$ - 51.2° (c=1, $CHCl_3$). Optically pure (-)-**1** can be obtained by a third recrystallization of the DIKG salt from ethanol. Two recrystallizations from CH_2Cl_2 of the DIKG salt obtained by concentration of the ethanol mother liquors, and conversion of salt to free base, gave (+)-**1** of 99% optical purity, $[\alpha]^{23}_D$ + 51.0° (c=1, $CHCl_3$), mp 69.5 - 70°C. The absolute configurations of (+)-**1** and (-)-**1** are assigned on the basis of the absolute configurations of the chiral alcohols produced by CBS reduction of various achiral ketones (see below).

The amino alcohol **8** could be resolved by recrystallization of the 1 : 1 salt with mandelic acid using isopropyl alcohol-ethyl acetate-hexane as solvent. *(R)*-(-)-Mandelic acid afforded crystals containing levorotatory **8** (99% optical purity after 3 recryst), which corresponds to the absolute configuration shown since it was converted to dextrorotatory **1** by the above described sequence. Specifically, (-)-**8**, $[\alpha]^{23}_D$ - 31.1° (c=1, $CHCl_3$), gave **10**, $[\alpha]^{23}_D$ + 35.9° (c=1, $CHCl_3$), and thence dextrorotatory **1**, $[\alpha]^{23}_D$ + 51.0° (c=1, $CHCl_3$). The chiral ketone **10** was used to synthesize several analogs of **1**, **13a** - **c**.[8]

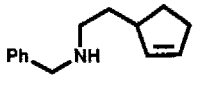
Conversion of (+)-**1** to the oxazaborolidine **2** was effected by heating for 3 h with 1 equiv of methylboronic acid in toluene at reflux using a Soxhlet extractor containing 4A molecular sieves to remove water. The ^{11}B NMR spectrum of **2** (colorless oil) in THF solution showed a broadened peak at 34.1 ppm (downfield from external $BF_3 \bullet Et_2O$ as reference), and addition of 1 equiv of BH_3 in THF resulted in a BH_3 complex with ring ^{11}B-CH_3 peak at 38.2 ppm and N-BH_3 peak at -15.4 ppm, consistent with previous data on other CBS complexes.[1]

Oxazaborolidine **2** was shown to be a highly effective catalyst for the borane reduction of a variety of achiral ketones to chiral secondary alcohols, as summarized on the next page. Reductions were performed with either 0.1 or 0.2 equiv of catalyst by slow addition of ketone to a mixture of catalyst and BH_3 (0.6 equiv) in THF at the temperature indicated; for reactions at 0°C addition and subsequent reaction times were 10 and 15 min, and at -22°C these reaction times were 20 and 40 min. The resulting secondary alcohols (100% yield by GC analysis) could be isolated in >90% yield by addition of a small amount of 10% aqueous HCl, removal of THF in vacuo, extraction with ether, drying, and removal of ether. Basification of the aqueous layer and extraction with ethyl acetate allowed efficient recovery of amino alcohol **1**. Values of enantiomeric excess and absolute configurations were determined by gas chromatographic analysis of the Mosher esters[1,7] using authentic reference samples. Since alcohols of *R* absolute configuration were obtained in high enantiomeric excess starting with catalyst derived from dextrorotatory **1**, it follows from previous results on the stereochemistry of CBS reduction[1] that the (+)-amino alcohol has the absolute configuration **1**.

Catalytic reduction of 2-bromo-2-cyclopentenone with 0.6 equiv of BH_3 and 0.1 equiv of **1** afforded the *R*-alcohol **14** (95% ee) which after acetylation (Ac_2O-C_5H_5N) and debromination (Bu_3SnH) gave the *R*-acetate **15**. Claisen rearrangement in THF at reflux of the enol TBDMS ether of **15** produced *R*-**3**, a chiral starting material for the synthesis of chiral amino alcohol **1** and catalyst **2**. To our knowledge this is the first instance in which an enzyme-like recoverable chiral catalyst (chemzyme) has been used to generate a chiral starting material for its own synthesis.[9]



3 X=OH
4 X=NHCH$_2$Ph



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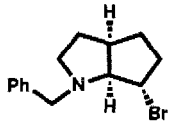

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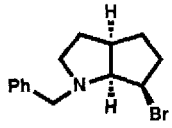

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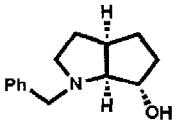

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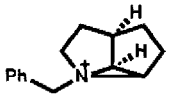

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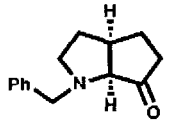

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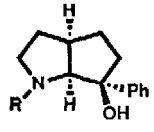
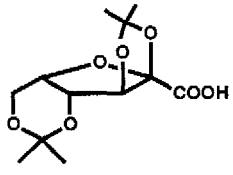


11 R=PhCH$_2$
1 R=H



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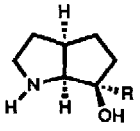
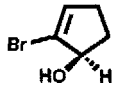


13a R= β-napthyl
13b R= *o*-MeO-C$_6$H$_4$
13c R= *t*-Bu



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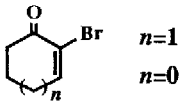
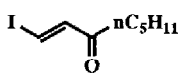
Reduction of Ketones by BH_3 with Chiral Catalyst 2 (Derived from (+)-1)

$$R_1R_2CO + BH_3{\bullet}THF \xrightarrow{2,\ THF} (R_1R_2CH\text{-}O)_2BH \longrightarrow R_1R_2CHOH$$

ketone	equiv BH_3 • THF	equiv cat	reaction temp, °C	config of product (% ee)
$C_6H_5COCH_3$	0.6	0.1	0	*R* (97.5)
t-$BuCOCH_3$	0.6	0.1	0	*R* (98.3)
α-tetralone	0.6	0.1	-22	*R* (95.3)
α-tetralone	0.6	0.2	-22	*R* (97.0)
c-$C_6H_{11}COCH_3$	0.6	0.1	-22	*R* (91.8)
 *n*=1	0.6	0.1	-23	*R* (97.5)
n=0	0.6	0.1	+23	*R* (95.0)
	0.6	0.1	-23	*R* (87.6)

References and Notes

1. (a) E. J. Corey, R. K. Bakshi, and S. Shibata, *J. Am. Chem. Soc.*, **109**, 5551 (1987); (b) E. J. Corey, R. K. Bakshi, S. Shibata, C.-P. Chen, and V. K. Singh, *J. Am. Chem. Soc.*, **109**, 7925 (1987); (c) E. J. Corey, S. Shibata, and R. K. Bakshi, *J. Org. Chem.*, **53**, 2861 (1988); (d) E. J. Corey, Proceedings of the 31st National Organic Symposium, American Chemical Society, p. 1 (1989).
2. E. J. Corey, *Chem. Soc. Rev.*, **17**, 111 (1988).
3. E. J. Corey and A. V. Gavai, *Tetrahedron Letters*, **29**, 3201 (1988).
4. E. J. Corey, P. D. S. Jardine, and T. Mohri, *Tetrahedron Letters*, **29**, 6409 (1988).
5. E. J. Corey, C.-P. Chen, and M. J. Parry, *Tetrahedron Letters*, **29**, 2899 (1988).
6. E. J. Corey and G. A. Reichard, *Tetrahedron Letters*, submitted.
7. See J. A. Dale and H. S. Mosher, *J. Am. Chem. Soc.*, **95**, 512 (1973).
8. The oxazaborolidine derived from **13a** was almost as good a catalyst as **2** for the enantioselective reduction of ketones by BH_3; **13b** and **13c** furnished catalysts which were decidedly inferior to **2**.

9. This research was assisted financially by grants from the National Institutes of Health and the National Science Foundation.

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