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Synthesis of Novel, Optically Active, Heterocyclic Amino Alcohols Through Desymmetrization of a C_2-Symmetric Cyclic Sulfate

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Abstract: A general and efficient method for the synthesis of optically active *cis*-4-amino-3-hydroxy-substituted heterocycles (**1-4**) has been developed through desymmetrization of a C_2-symmetric cyclic sulfate chiron prepared from catalytic asymmetric dihydroxylation of 1,4-dichloro-*trans*-2-butene.

Vicinal amino alcohols embedded in heterocycles are of a particular interest, since they can serve as novel building blocks for biologically active molecules.[1] Tetrahydrofuran, tetrahydrothiophene, and sulfolane derivatives containing 4-amino-3-hydroxy substituents (**1**, **2**, and **3**, respectively) can serve as both monosaccharide mimetic structures[1b,1c] and amino acid surrogates.[1d-1f] Pyrrolidine derivatives (**4**) are useful intermediates for quinolone derivatives[1g] and for agents possessing antidepressant[1h] and secretory phospholipase A_2 (sPLA$_2$) inhibitory activities.[1c] However, few general synthetic methods for optically active amino alcohols of such heterocyclic structures have been available.[1,2]

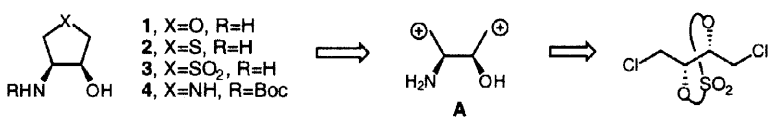
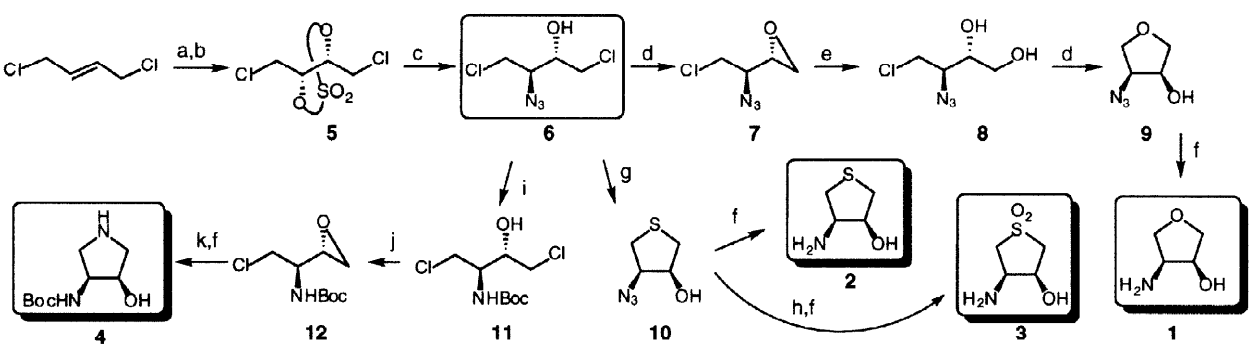


Figure 1.

Desymmetrization has been extensively utilized for the generation of useful chiral synthons and a number of successful applications have been reported.[3] Desymmetrization of the cyclic sulfate[4] prepared from the diol obtained through catalytic asymmetric dihydroxylation (AD)[5] of 1,4-dichoro-*trans*-2-butene can effectively generate a useful 'chiron'[6] featuring 3-amino-2-hydroxybutane equipped with electrophilic functionalities at C(1) and C(4) (structure **A**, Figure 1). Herein, we report on the efficient method for the preparation of optically active 4-amino-3-hydroxy-substituted 5-membered heterocycles **1–4** from such desymmetrization.

Scheme 1. Synthesis of heterocyclic aminoalcohols **1 - 4** from the common chiral synthon **6.**



a. AD-mix-β, $NaHCO_3$, *t*BuOH-H_2O, 0 °C. b. SO_2Cl_2, imidazole, 0 °C or i) $SOCl_2$, CCl_4, reflux; ii) $RuCl_3 \cdot H_2O$, $NaIO_4$, H_2O-CH_3CN-CCl_4, 0 °C. c. LiN_3, THF, rt; cat. conc H_2SO_4, 1 eq H_2O, THF. d. K_2CO_3, MeOH, rt. e. 60 % $HClO_4$, DMSO-H_2O, rt. f. H_2, Pd/C, EtOAc, rt. g. $Na_2S \cdot 9H_2O$, EtOH, rt. h. cat OsO_4, NMO, acetone-water. i. H_2, Pd/C, $(Boc)_2O$, EtOAc. j. Cs_2CO_3, EtOH, rt. k. NaN_3, NH_4Cl, MeOH-water, 40 °C.

Detailed synthesis of four amino alcohols (**1–4**) is described in Scheme 1.[7] The C_2-symmetric cyclic sulfate **5** was prepared from 2(*R*),3(*R*)-1,4-dichlorobutanediol through AD of 1,4-dichloro-*trans*-2-butene under

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Sharpless' buffered conditions[8] followed by cyclic sulfate formation according to known procedures.[4] Between one-step procedure employing sulfuryl chloride[9] and two-step method involving thionyl chloride and oxidation using ruthenium catalyst,[4a,b] the latter proved to give better yields of **5** (93%). Opening of the cyclic sulfate **5** with LiN_3 in THF provided *the common intermediate*, chlorohydrin **6** in 95% yield. For the tetrahydrofuran structure **1**, the chlorohydrin **6** was treated with K_2CO_3 in methanol to provide epoxide **7**. Acid-catalyzed hydrolysis of **7** with 60% $HClO_4$ in aqueous DMSO provided diol **8** in 74% yield from **7**. Treating diol **8** with K_2CO_3/MeOH gave the tetrahydrofuran structure **9** (73%) ($[\alpha]_D^{23}$=22.1 (*c* 1.07, $CHCl_3$), lit. for **ent-9**,[2a] $[\alpha]_D^{25}$=–14.7 (*c* 0.71, $CHCl_3$)). Hydrogenation of the azide group in **9** furnished 4(*S*)-amino-3(*S*)-hydroxytetrahydrofuran (**1**) in 77% yield ($[\alpha]_D^{23}$=–5.6 (*c* 1.06, MeOH), lit. for **ent-1**,[2a] $[\alpha]_D^{25}$=4.8, (*c* 1.08, MeOH)). The tetrahydrothiophene ring system **10** was constructed by treatment of **6** with $Na_2S{\bullet}9H_2O$ (85%). Hydrogenation of the resulting sulfide **10** gave 4(*S*)-amino-3(*S*)-hydroxytetrahydrothiophene (**2**) in 86% yield ($[\alpha]_D^{19}$=–21.0 (*c* 0.83, MeOH)). Oxidation of sulfide **11** followed by hydrogenation provided the corresponding sulfolane derivative **3** (83% from **10**, $[\alpha]_D^{26}$=–11.5 (*c* 0.22, MeOH)). For pyrrolidine ring structure, compound **6** was converted to *t*-Boc-protected amino alcohol **11**, which was treated with cesium carbonate to furnish epoxide **12** (74% yield from **6**). Opening of the epoxide **12** with sodium azide and catalytic hydrogenation proceeded with spontaneous cyclization to furnish the 4(*S*)-(*tert*-butyloxycarbonyl)amino-3(*R*)-hydroxypyrrolidine (**4**), ($[\alpha]_D^{24}$=–13.6, (*c* 1.13, MeOH)) in 77% yield.

In conclusion, through desymmetrization of the C_2-symmetric chiral synthon **5**, a general and highly efficient synthetic strategy for novel, optically active amino alcohols **1**-**4** has been developed. By a judicious choice of alkaloid reagent in the AD step, one should be able to prepare both enantiomers of the four heterocyclic amino alcohols. Further investigation on the synthetic utility of this useful methodology and incorporation of the amino alcohol derivatives into biologically active molecules is in progress.

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