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Stereoselective Synthesis of *anti*-1,3-Aminoalcohols *via* Reductive Opening of 4-Amidotetrahydropyrans Derived from the Prins/Ritter Sequence

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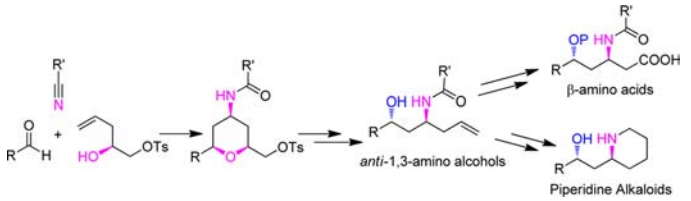
ABSTRACT



A novel method has been devised for *anti*-1,3-aminoalcohols through reductive elimination of iodomethyltetrahydropyrans which are in turn derived from a Prins/Ritter reaction sequence. The synthetic versatility of this method has been explored in the total synthesis of piperidine alkaloids and *β*-amino acids.

Chiral 1,3-aminoalcohols with two stereogenic centers are key structural motifs in many biologically active molecules such as HIV-protease inhibitors[1] (ritonavir and lopinavir), μ-opioid receptor antagonists,[2] antibiotics (negamycin[3]), serotonin reuptake inhibitors, and antidepressants.[4] In addition, 1,3-aminoalcohols are very useful in the study of mutagenic behavior of deoxyguanosine oligonucleotides[5] and are often found in natural products such as *Sedum* alkaloids, paliclavine, and the micronesian marine sponge toxin, dysiherbain.[6] Moreover, 1,3-aminoalcohols have also been recognized as ligands, chiral auxiliaries, resolving agents, and phase transfer catalysts in asymmetric synthesis.[7]

Considering their potential applications in biology and pharmaceuticals, several elegant processes have been developed for the construction of 1,3-aminoalcohols. However, only a few methods are reported for their stereoselective synthesis.[8] Of these, the substrate controlled

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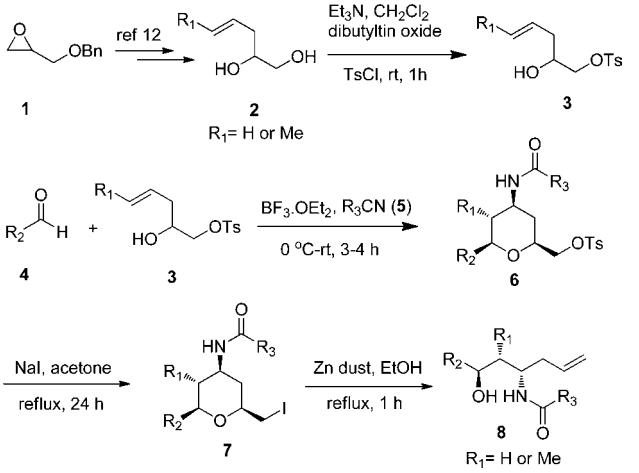
diastereoselective reduction of enantiopure substrate is the most commonly used for chiral 1,3-aminoalcohols and chiral amines.[9] More recently, an organocatalytic iterative approach has been reported for the enantiopure synthesis of *syn*/*anti*-1,3-aminoalcohols.[9h] Another interesting strategy for the construction of 1,3-aminoalcohols involves the ring opening of substituted chiral piperidines.[10] However, many of these procedures involve the use of costly reagents or precursors and toxic heavy metal catalysts such as Sm, Ti, Pd, Rh, etc. Inspired by their unique biological properties and natural prevalence, we were interested to develop a new protocol for the synthesis of *anti*-1,3-aminoalcohols.

Recently, the Prins cyclization has emerged as a powerful synthetic tool for the construction of tetrahydropyran scaffolds.[11] In our earlier reports, we have successfully demonstrated the scope of Prins cyclization in the total synthesis of polyketide natural products containing *anti*-1,3-diol units through the reductive ring opening of iodomethyltetrahydropyrans.[12]

Recently, we needed to generate 1,3-aminoalcohol libraries for our ongoing project on drug discovery. As a consequence, we found an elegant process to produce *anti*-1,3-aminoalcohols by reductive opening of iodomethyl-4-amidotetrahydropyrans which are prepared easily by Prins/Ritter amidation.[13,14] Following our interest on Prins cyclization and its subsequent application to the synthesis of bioactive natural products,[15] we herein report a novel method for the synthesis of *anti*-1,3-aminoalcohols through a sequential Prins−Ritter reaction followed by reductive opening of the resulting iodomethyl-4-amidotetrahydropyran ring (Scheme 1).

Scheme 1. General Strategy for the Synthesis of *anti*-1,3-Aminoalcohols



The starting chiral homoallylic alcohols were synthesized from the corresponding epoxides by Jacobsen's hydrolytic kinetic resolution (HKR).[12,16] Chemoselective protection of homoallylic diol **2** with TsCl in the presence of dibutyltin oxide and triethyl amine gave the desired homoallylic alcohol (**3**).[17] Three-component coupling of homoallylic alcohol **3**, aldehyde **4**, and nitrile **5** in the presence of 20 mol % $BF_3 \cdot OEt_2$ afforded the substituted 4-amidotetrahydropyran **6** in good yields with high diastereoselectivity (Table 1). The reaction proceeds through a cascade of the Prins/Ritter reaction affording the *cis*-diastereomer predominantly which is consistent with earlier reports.[14] The structure and stereochemistry were established by NOE experiments in which all substituents exist in equatorial positions. Substituents introduced into a cyclic building block with stereocontrol translate their stereochemistry when the tetrahydropyran ring is opened.[10,12] After establishing the 4-amidotetrahydropyran structure, the tosylate **6** was converted into the corresponding iodide **7** using NaI in acetone under reflux conditions. Reductive ring opening of iodide **7** using Zn dust in refluxing ethanol gave the corresponding *anti*-1,3-aminoalcohol **8** in good yield (Table 1).

Next we examined the scope of this methodology using various aldehydes and homoallyl alcohols in the presence of different nitriles. The reaction shows a wide substrate

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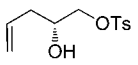
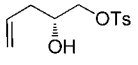
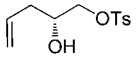
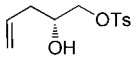
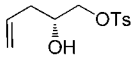
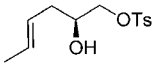
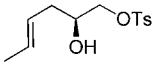
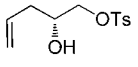
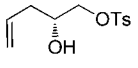
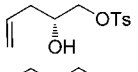
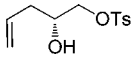
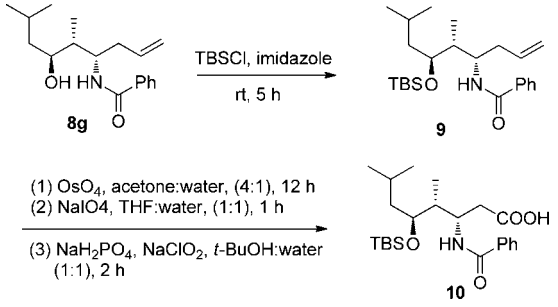
Table 1. Synthesis of *anti*-1,3-Amino Alcohols via Prins/Ritter Amidation Followed by Reductive Ring-Opening Sequence[a]

entry	(3)	R_2	R_3	yield % (6)	yield % (7)	yield % (8)	(8) dr
a		Ph	Me	63	82	89	--
b		n-Butyl	Me	62	84	85	99:1[a]
c		*n*-Hexyl	Ph	56	81	88	96:3
d		4-$MeOC_6H_4$	Ph	58	88	87	97:3
e		*trans*-PhCH=CH	Me	60	83	84	95:5
f		4-MeC_6H_4	Me	62	87	86	98:2
g		*iso*-Butyl	Ph	56	84	85	99:1
h		Cyclohexyl	Me	64	85	87	98:2[a]
i		Ph	Ph	58	83	83	99:1
j		$PhCH_2$	Ph	56	85	83	98:1
k		Naphthyl	Me	62	86	87	99:1

[a] Diastereomeric ratio was determined by ^1H NMR.

Scheme 2. Synthesis of β-Amino Acid Derivatives



scope as shown in Table 1. Remarkably, *anti*-1,3-aminoalcohols were formed with an excellent diastereoselectivity (dr 97:3 to 99:1) which was measured by HPLC, and the results are presented in Table 1.

Considering the significance of β-amino acids in natural product synthesis and therapeutic agents,[18] we were interested in extending this approach to the synthesis of a highly functionalized β-amino acid derivative. Thus obtained *anti*-1,3-amino alcohol **8g** was converted into the corresponding

(18) For a review on the biology and synthesis of β-amino acids, see: *Enantioselective Synthesis of β-Amino Acids*; Juaristi, E., Ed.; Wiley-VCH: New York, 1997.

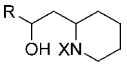
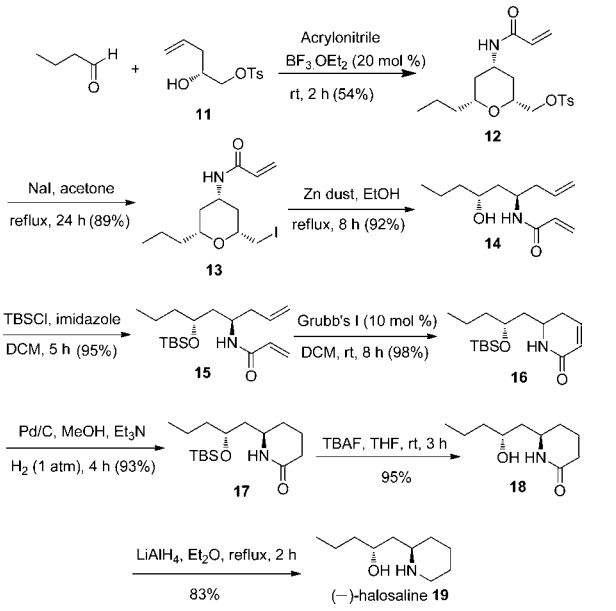


Figure 1. 2-(2-Hydroxyalkyl)piperidine alkaloids.

Scheme 3. Synthesis of (−)-Halosaline



β-amino acid **10** by a sequence of reactions as depicted in Scheme 2.

The 2-(2-hydroxyalkyl)piperidine core is often found in the *Sedum* and *Lobelia inflata* family of alkaloids (Figure 1). These piperidine alkaloids exhibit a broad range of biological activities, which are being used for the treatment of nicotine drug abuse and neurological disorders such as asthma, anxiety, Alzheimer's, and Parkinson's.[19] These alkaloids generally differ by the R group and also stereochemistry at amine and hydroxyl groups (Figure 1). Consequently, several approaches have been reported for the stereoselective synthesis of these piperdine alkaloids through 1,3-aminoalcohols.[20] Having established the protocol for the stereoselective synthesis of *anti*-1,3-aminoalcohols *via* Prins/Ritter reaction, we would like to demonstrate the versatility of this method in the total synthesis of two of the piperidine alkaloids, namely, (−)-halosaline and (+)-norallosedamine, as these alkaloids possess an *anti*-1,3-aminoalcohol core.

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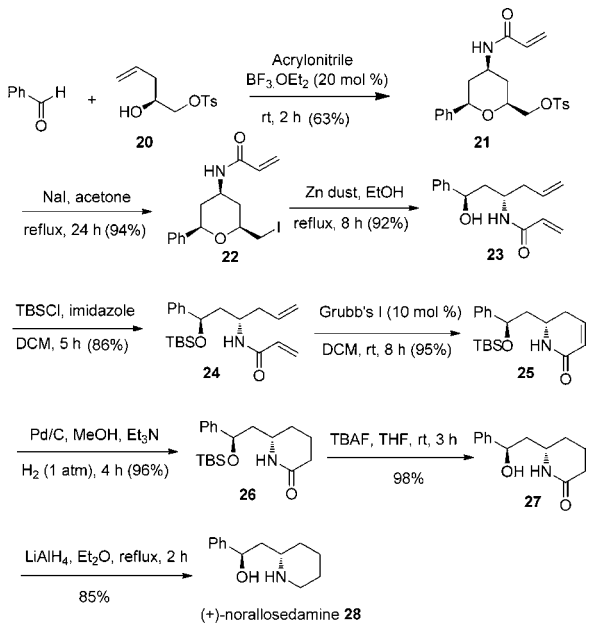
Scheme 4. Synthesis of (+)-Norallosedamine



Accordingly, we commenced the synthesis of (−)-halosaline from the chiral homoallylic alcohol **11**. As shown in Scheme 3, the primary tosylate **11** was treated with butyraldehyde in acrylonitrile in the presence of 20 mol % $BF_3 \cdot OEt_2$ under Prins−Ritter conditions to afford the trisubstituted tetrahydropyran **12** in 54% yield. Treatment of compound **12** with NaI in refluxing acetone gave the corresponding iodide **13** in 89% yield. Reductive ring opening of **13** using Zn in refluxing ethanol afforded the desired *anti*-1,3-aminoalcohol **14** in 92% yield, which is a key intermediate for the synthesis of (−)-halosaline. The hydroxyl group of **14** was then protected as its TBS ether **15** in 95% yield using TBS chloride in the presence of imidazole. Compound **15** was then subjected to ring closing metathesis using Grubb's I catalyst (10 mol %) in DCM to furnish the α,β-unsaturated-δ-lactam **16** in 98% yield. Reduction of olefin in compound **16** using palladium on carbon in methanol gave the δ-lactam **17** in 93% yield. Deprotection of silyl ether **17** with TBAF in THF gave the desilylated δ-lactam **18** in 95% yield. Finally, the reduction of δ-lactam **18** with $LiAlH_4$ in refluxing Et_2O gave the target molecule (−)-halosaline **19** in 83% yield and an overall yield of 24% starting from compound **11**. The data of synthetic (−)-halosaline were in good agreement with the data reported in the literature.[21a,b]

Next, we examined the scope of the reported methodology in the total synthesis of (+)-norallosedamine. As shown in Scheme 4, we began the synthesis of (+)-norallosedamine from the chiral homoallyl alcohol **20** following the above sequence of reactions as described in Scheme 3. The target (+)-norallosedamine was obtained in a 34% overall yield from compound **20**. The data of synthetic (+)-norallosedamine **28** were in good agreement with reported values.[21c−g]

In conclusion, we have demonstrated a novel strategy for the synthesis of *anti*-1,3-aminoalcohols through a highly stereoselective Prins/Ritter amidation followed by the reductive opening of the iodomethyltetrahydropyran system. To demonstrate its synthetic utility, this method was successfully applied to the total synthesis of (−)-halosaline and (+)-norallosedamine alkaloids. Further applications of this methodology are in progress, and the results will be disclosed in due course.

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Supporting Information Available. Full experimental procedures and characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

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