Current Topics

Reversal or Control of the Innate Reactivity of Functional Groups

Communication to the Editor

Concise, Protecting-Group-Free Synthesis of (+)-Nemonapride *via* $Eu(OTf)_3$-Catalyzed Aminolysis of 3,4-Epoxy Alcohol

Shun-ichiro Uesugi, Yusuke Sasano, Shogo Matsui, Naoki Kanoh, and Yoshiharu Iwabuchi*

Department of Organic Chemistry, Graduate School of Pharmaceutical Sciences, Tohoku University; 6–3 Aoba, Aramaki, Aoba-ku, Sendai 980–8578, Japan.
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A concise, protecting-group-free synthesis of the antipsychotic agent (+)-nemonapride has been achieved featuring a europium(III) trifluoromethanesulfonate ($Eu(OTf)_3$)-catalyzed C4 selective aminolysis of a 3,4-epoxy alcohol by benzylamine and an expedient use of the resulting 4-benzylamino-1,3-diol product for constructing the pyrrolidine skeleton.

Key words chemoselectivity; aminolysis; 3,4-epoxy alcohol; Lewis acid catalysis; protecting-group-free; nemonapride

A nucleophilic ring opening of a chiral epoxide substrate in a regio- and stereocontrolled manner has enabled the construction of numerous molecules with contiguous stereogenic centers.[1,2] Along with expanding the scope of catalytic enantioselective epoxidation reactions, the structural diversity of chiral epoxides is increased,[3–8] inspiring chemists to develop methods that conduct a selective nucleophilic ring opening of the epoxide.[9–13] To date, a number of reagents and conditions that lead to the regio- and stereocontrolled installation of various nucleophiles have been developed employing Lewis acid catalysis.[14] Among potential nucleophiles, *N*-nucleophiles,[15] such as amines, azides, amides, carbamates, and so on, have received considerable attention because the reaction allows access to *β*-amino alcohols,[16,17] which are versatile intermediates for biologically active compounds, chiral ligands, and catalysts. Due to the substantial issue of acid-base interaction, however, amines have rather limited use in a Lewis acid-promoted or catalyzed nucleophilic ring opening of epoxides: other than a few particular exceptions,[18–22] regio- and stereoselective aminolysis of epoxides could be operative in the case when either aromatic amines[23–28] or activated substrates[27,29] (benzylic or allylic epoxides) or a large amount[30,31] of Lewis acid are applied. Thus, state-of-the-art aminolysis of epoxides with an aliphatic amine is still under development in modern synthetic chemistry.

Previously, our group showed[32] that europium(III) trifluoromethanesulfonate ($Eu(OTf)_3$) catalyzes a highly C3-selective alcoholysis of various 2,3-epoxy alcohols in the presence of catalytic amounts of 2,6-di-*tert*-butyl-4-methylpyridine (DTBMP) to give 3-substituted 1,2-diols, together with the following unprecedented results in terms of chemo- and regioselectivity: (1) $Eu(OTf)_3$ enabled the highly C3-selective aminolysis of a 2,3-epoxy alcohol with aliphatic amines; (2) the $Eu(OTf)_3$/DTBMP system could be applicable to alcoholysis of a 3,4-epoxy alcohol to give the corresponding C4-adduct selectively. These serendipitous findings prompted us to examine a $Eu(OTf)_3$-catalyzed aminolysis of a 3,4-epoxy alcohol[27] using an aliphatic 1° amine, the product of which we expected would be promising feedstock for the expedient synthesis of chiral *β*-hydroxy-pyrrolidines.[33] Reported herein is a protecting-group-free, enantioselective synthesis of the antipsychotic agent (+)-nemonapride[34–38] (**1**) featuring a $Eu(OTf)_3$-catalyzed C4-selective ring opening of a 3,4-epoxy alcohol by benzylamine, and an expedient use of the resulting 4-benzylamino-1,3-diol product for constructing the *β*-hydroxy-pyrrolidine skeleton.

On the condition that the $Eu(OTf)_3$-catalyzed aminolysis of a 3,4-epoxy alcohol proceeds *via* the inversion of the configuration, (2*R*,3*R*)-(+)-nemonapride (**1**) was retrosynthetically disconnected, as shown in Chart 1, in which several critical issues are indicated. First, a Lewis acid-catalyzed C4-selective ring opening of the 3,4-epoxy alcohol by an aliphatic 1° amine has to be achieved as a practically acceptable level (**4** to **3**). Second, highly chemoselective activation of the amino diol must be realized in order to conduct the intended intramolecular S_N2 reaction, giving the *β*-hydroxy-pyrrolidine skeleton efficiently (**3** to **2**).

The synthesis began with an enantioselective epoxidation of an (*E*)-homoallyl alcohol by a Shi oxidation.[6] Treatment of (*E*)-3-penten-1-ol **5** with Oxone® in the presence of Shi's ketone[6] (30 mol%), *n*-Bu_4NHSO_4 (1.6 mol%) and K_2CO_3 (5.8 eq) in dimethoxymethane (DMM)/MeCN/aqueous buffer (pH 9.3) at −15°C gave 3,4-epoxy alcohol **4** in 76% yield and 90% enantiomeric excess (ee) (Chart 2). The first key reaction, which represents an unprecedented Lewis acid-catalyzed ring opening of 3,4-epoxy alcohols using an aliphatic 1° amine as the nucleophile, was found to proceed smoothly in the presence of 10 mol% $Eu(OTf)_3$ and 2.0 eq of benzylamine in toluene at 60°C to give a 2.9 : 1 regioisomeric mixture of amino

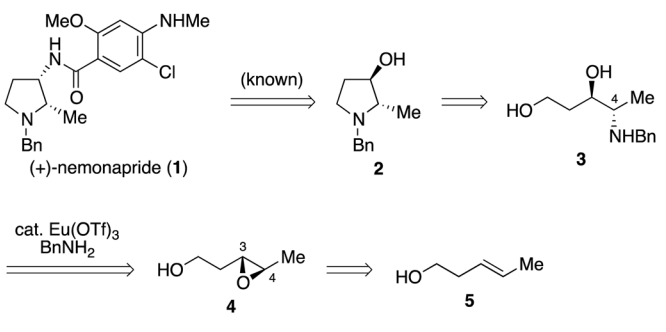

Chart 1. Retrosynthesis of (+)-Nemonapride (**1**)

* To whom correspondence should be addressed. e-mail: y-iwabuchi@m.tohoku.ac.jp

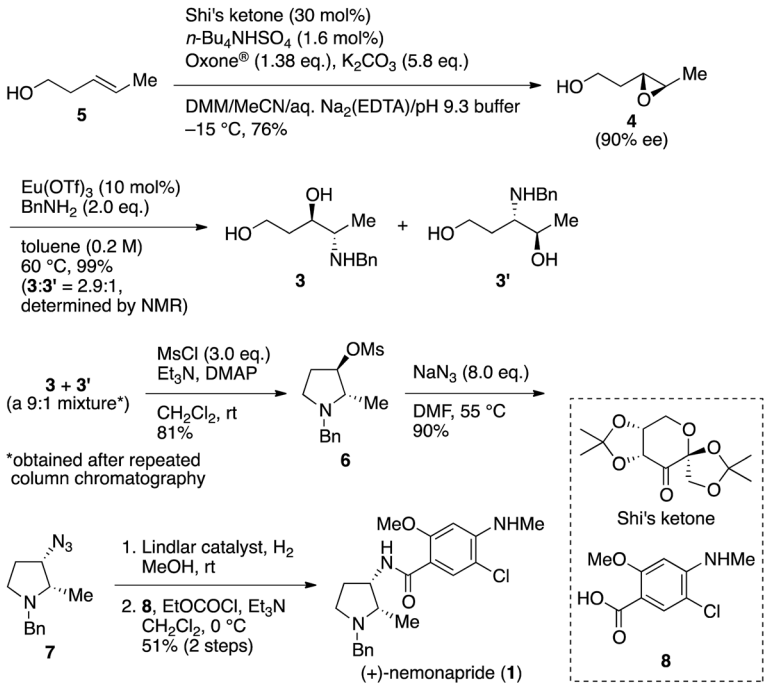

Chart 2. Synthesis of (+)-Nemonapride (**1**)

diols in preference to 4-amino-1,3-diol **3** in 99% yield. After chromatographic purification, a 9 : 1 mixture of **3** and **3′** was eventually obtained. Note that the addition of DTBMP is not necessary, but heating was essential to promote the aminolysis reaction. It should be pointed out that other Lewis acids, such as $W(OEt)_6$,[26] $Ni(ClO_4)_2 \cdot 6H_2O$,[27] and LiOTf,[31] which were reported to promote a highly regioselective nucleophilic ring opening of 2,3-epoxy alcohols and 3,4-epoxy alcohols with various nucleophiles, resulted in unsatisfactory results in terms of efficiency and regioselectivity.[39] The second key reaction, that is, the alcohol-selective installation of sulfonyl groups in the presence of 2° amine functionality, proceeded smoothly on treatment of the mixture with 3.0 eq of MsCl in the presence of Et_3N and *N*,*N*-dimethyl-4-aminopyridine (DMAP) in CH_2Cl_2 at 0°C, with a concomitant 5-exo-*tet*-type intramolecular S_N2 reaction to construct the pyrrolidine ring to give the known pyrrolidene **6** in 81% yield as a readily separable product.[40] Protecting-group-free synthesis of nemonapride (**1**) was completed in 46% yield by following Wei's protocol[37] involving azidation, Lindlar reduction of the azide, and condensation with aromatic carboxylic acid **8**.

In conclusion, we have demonstrated the synthetic use of $Eu(OTf)_3$-catalyzed C4-selective aminolysis with an aliphatic amine by illustrating an enatioselective and protecting-group-free synthesis of (+)-nemonapride. The synthetic sequence developed in this study could be applicable to the rapid construction of various chiral 2-substituted 3-hydroxypyrrolidines.

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Conflict of Interest The authors declare no conflict of interest.

Supplementary Materials The online version of this article contains supplementary materials.

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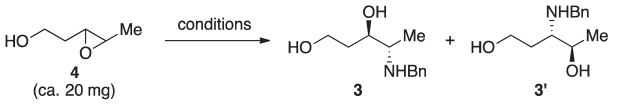
39) The superiority of $Eu(OTf)_3$ in the catalytic aminolysis of 3,4-epoxy-alcohol **4** was confirmed by comparison with other conventional catalysts.



entry	Lewis acid (mol%)	$BnNH_2$ (eq.)	solvent (M)	NMR yield (%)[a]	**3** : **3'**
1[b]	$Eu(OTf)_3$ (10)	2.0	toluene (0.2)	99	2.9 : 1
2	LiOTf (150)	2.0	MeCN (0.2)	94	1.2 : 1
3	$Ni(ClO_4)\cdot 6H_2O$ (10)	1.5	*t*-BuOH (0.1)	11	3.6 : 1
4	$W(OEt)_6$ (10)	2.0	MeCN (0.2)	0	---

(a) 1,3,5-trimethoxybenzene was used as the internal standard.
(b) One gram of **4** was used.

40) To gain insight into the origin of the chemoselectivity observed in the mesylation of amonidiol **3**, we conducted a set of competitive experiments using simple substrates. *N*-Mesylation proceeded preferentially in the case of primary amine and sterically less-hindered secondary amine over the *O*-mesylation of primary alcohols (**9** *vs.* **11**; **13** *vs.* **15**). The selectivity reversed in the case of sterically congested secondary amines: *O*-mesylation of **13** proceeded preferentially over the *N*-mesylation of secondary amine **17**, indicating that the innate *N*-selectivity would be overridden by steric factors.