An Efficient and Highly Stereoselective Method to Synthesize 3-(1-Hydroxyalkyl)pyrrolidinone

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Three contiguous stereocenters with syn–anti structure on the 3-(1-hydroxyalkyl)pyrrolidinone were constructed in one step with high yields and high diastereoselectivity by an Et_2AlCl-catalyzed group transfer radical cyclization reaction from *N*-alkenyl-β-hydroxyalkanamides with 125-W UV lamp irradiation. The relative stereochemistry was confirmed by X-ray analysis.

In recent years, pyrrolidine derivatives have increasingly attracted the attention of pharmaceutical companies because of their ability to modulate chemokine receptors and selectively inhibit phosphodiesterase PDE4. As such, they are promising drug candidates for the prevention or treatment of HIV infection, inflammatory, and immunoregulatory diseases.[1] Studies have also demonstrated that the absolute stereochemistry of pyrrolidine derivatives contributes significantly to their biological activity. For example, with regards to selective PDE4 inhibitors, the syn–anti structure shows lower PDE4 IC50 and less CNS side effects than the anti–anti structure.[1a] This syn–anti structure with a *N*-containing five-membered ring particularly attracted our attention since the usual synthetic route via butyrolactam reduction leads to the "anti–anti" structure as the major product.[2]

In recent years, radical reaction was frequently used to construct cyclic compounds.[3] β-Hydroxy esters were used as a cyclic precursor for stereoselective construction of mono- or bicyclic carbon cycles in the present of Et_2AlCl.[4] Here, we reported our work on constructing the "syn–anti" structure **4** from β-hydroxyalkanamide in one step with high regio- and diastereoselectivity (Figure 1), which can be easily transferred to **1** by further functionization of SePh group and a simple reduction of keto group.

We used the bulky *tert*-butyl group as N-protecting group,[5] so that the compounds **3a**–**3d** adopt the conformer as shown in Table 1, which favors the cyclization reaction. Different Lewis acids were screened for the cyclization of **3a** into **4a** (Table 1).[6] Because **4a** contains four stereocenters, the crude products were converted directly into olefins (**5a** and **6a**) by peroxide-mediated oxidation and elimination in THF, so as to simplify the stereochemistry analysis of products.

Initially, the substrate **3a** was irradiated with UV light in CH_2Cl_2 at room temperature. Cyclic products were formed in moderate yield, and the selectivity between **5a** and **6a**[7] was poor. $Yb(OTf)_3$ and $Mg(ClO_4)_2$ were used, but the yield and the selectivity were not improved. When strong Lewis acid ($AlCl_3$ and $ZnCl_2$) was used, few cyclization products were obtained (Entries 2 and 3), most of the substrates decomposed. When 2 equiv. of Et_2AlCl[8] was used under the same conditions, a high yield (82%) and high selectivity (**5a**:**6a** = 12:1) were obtained (Table 2). The stereochemistry of the major product **5a** was confirmed by X-ray analysis (Figure 2).[9]

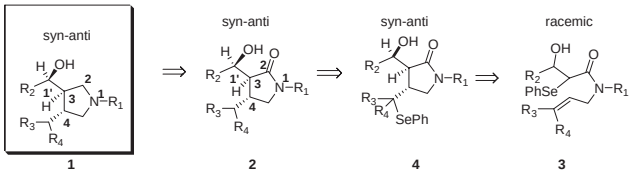
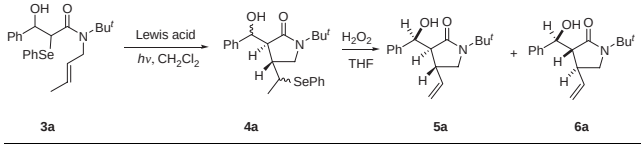


Figure 1. Retro-synthesis.

Table 1. Screening of Lewis acids on the stereoselective phenylseleno group transfer radical cyclization reaction of **3a**[a]



Entry	Lewis acid/equiv.	Time/h	Yield/% (**5a**:**6a**)[b]
1	—	10	42 (1:1)
2	$AlCl_3$ (1.0)	10	<5
3	$ZnCl_2$ (1.0)	36	<5
4	$Mg(ClO_4)_2$ (1.0)	10	50 (1:1)
5	$Yb(OTf)_3$ (1.0)	10	51 (1:1)
6	Et_2AlCl (2.0)	12	82 (12:1)

[a]Unless otherwise indicated, all reactions were carried out at 25–30 °C with 0.4–0.5 mmol of substrates (0.05 M in CH_2Cl_2). [b]Two steps yields, ratio of **5a** and **6a** was determined by ^{1}H NMR analysis of crude products after filtration through Celite.

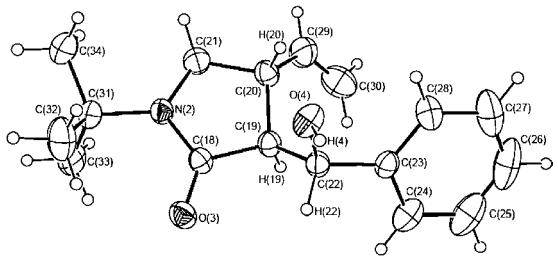


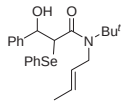
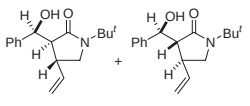
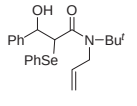
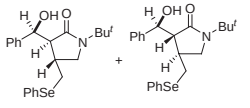
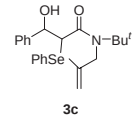
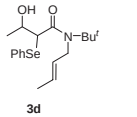
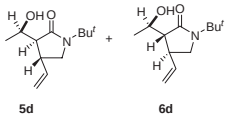
Figure 2. ORTEP drawing of compound **5a**.

We applied this method to compounds **3b**–**3d**. Compounds **3b** and **3d** also gave the cyclization products in high yields and with high selectivity as determined by ^{1}H NMR. However, the cyclization of **3c** did not proceed and 66% of **3c** was recovered (Entry 3).

Given the highly reactive nature of radical intermediates, the excellent diastereoselectivity of this substrate-induced stereoselective cyclization is impressive (Scheme 1). Reaction of the aluminum-complexed β-hydroxy amide radical intermediate[10] can proceed via two possible transition states. TS2 (which will cyclize into the "anti–anti" structure) is relatively disfavored owing to steric interactions between the R group and the *N*-allylic group. Thus, the reaction proceeds via TS1 to obtain the syn–

Table 2. Phenylseleno group transfer radical cyclization of *N*-alkenyl α-phenylseleno-β-hydroxyalkanamides[a]

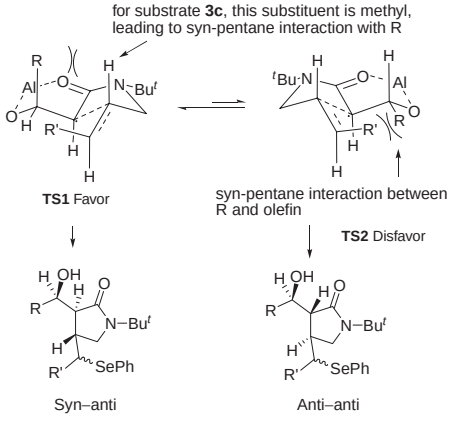
3a-3d $\xrightarrow[h\nu,\ CH_2Cl_2]{Et_2AlCl}$ **4a-4d** $\xrightarrow[THF]{H_2O_2}$ **5a-5d** + **6a-6d**

Entry	Substrate	Product	Yield/%
1	 **3a**	 **5a** + **6a**	82 (12:1)[c]
2	 **3b**	 **4b-1** + **4b-2**	95[b] (8.1:1)[c]
3	 **3c**	**3c** (66%) was recovered	—
4	 **3d**	 **5d** + **6d**	63 (17:1)[c]

[a]Unless otherwise indicated, all reactions were carried out at 25–30 °C with 0.4–0.5 mmol of substrates (0.05 M in CH_2Cl_2) and the yields are two-step yields of cyclization and oxidation. [b]One-step yield of cyclization. [c]Ratio determined by ^{1}H NMR analysis of crude products after filtration through Celite.

anti structure. According to this model, syn–pentane interactions would be unavoidable during the cyclization of substrate **3c**, which is consistent with its observed lack of reactivity. Taken together, these results indicate that steric effects play an important role in determining both the efficiency and diastereoselectivity of this reaction.

In conclusion, three contiguous stereocenters on 3-(1-Hydroxyalkyl)pyrrolidinone with "syn–anti" structure were constructed in one step by Et_2AlCl-catalyzed group transfer radical cyclization in high yields and in high regio- and diastereo-selectivity. Et_2AlCl showed great advantage over other Lewis acids in this substrate-induced asymmetric radical cyclization. In these reactions, the free hydroxy group need not be protected and in fact appears to play a key role in organizing the transition state via aluminum complexation. Compared with the known synthetic route for the pyrrolidine derivatives,[11] our method shows impressive efficiency and high stereoselectivity; its further synthetic application is in progress in our laboratory and will be reported in due course.



Scheme 1.

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References and Notes

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5 For deprotection of *t*-butyl group see: a) H. Rosenberg, H. Rapoport, *J. Org. Chem.* **1985**, *50*, 3979. b) G. Stork, R. Mah, *Heterocycles* **1989**, *28*, 723.

6 A typical experimental procedure was as followed: Compound **3a** (200 mg, 0.47 mmol) was dissolved in dry CH_2Cl_2 (20 mL) and the solution was degassed with nitrogen for 15 min. Et_2AlCl (1 M in *n*-hexane, 0.94 mL, 0.94 mmol) was added at room temperature. Ten min later, the mixture was irradiated with a 125-W UV light at 25–30 °C. The reaction was monitored by TLC. To the reaction mixture was added saturated aqueous Na_2CO_3 (10 mL), extracted with CH_2Cl_2, and then dried over Na_2SO_4. After removal of the solvent, the residue went through Celite to give crude product of **4a**.

7 The stereochemistry of **6a** was confirmed by NOESY and our unpublished related work.

8 The extra amount of Et_2AlCl was used to compensate any Lewis acid that might be hydrolyzed by trace of moisture.

9 The product **5a** was recrystallized from Et_2O. Crystal data: $[C_{17}H_{23}NO_2]$; $M_r = 273.36$, Triclinic, $P\bar{1}$ (No. 2), $a = 10.712(2)$ Å, $b = 12.517(3)$ Å, $c = 12.698(3)$ Å, $\alpha = 99.61(3)°$, $\beta = 94.62(3)°$, $\gamma = 104.17(3)°$, $V = 1614.4(6)$ Å^3, $Z = 4$, $D_{calcd} = 1.125$ g cm^{-3}, $T = 253$ K. X-ray intensities were measured on a graphite monochromatized Mo Kα radiation ($\lambda = 0.71073$ Å). The final R factors was 0.0467 and $wR_2 = 0.1089$.

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