References

1. (a) Chandrasekhar, S. *Liquid Crystals*, 2nd Ed.; Cambridge; New York, 1992. (b) Bahadur, B. *Liquid Crystals-Applications and Uses*; World Scientific, Singapore, 1991.
2. Fayer, M. D. *IEEE J. Quantum Electron.* **1986**, *QE-22*, 1437.
3. (a) Khoo, I. C.; Shepard, S. *J. Appl. Phys.* **1983**, *54*, 5491. (b) Eyring, G.; Fayer, M. D. *J. Chem. Phys.* **1984**, *81*, 4314. (c) Khoo, I. C.; Normandin, R. *IEEE J. Quantum. Electron.* **1985**, *QE-21*, 329.
4. Kim, S. H.; Kim, S. K. (*in preparation*).
5. (a) Chen, A. G.; Brady, D. J. *Opt. Lett.* **1992**, *17*, 441. (b) Khoo, I. C.; Wu, S. T. *Optics and nonlinear optics of liquid crystals*; World Scientific; Singapore, 1993; ch. 1.
6. (a) Ross, D. L.; Blanc, J. In *Photochromism*; Brown, G. H. Ed.; Wiely; New York, 1971; ch. 5. (b) Lee, G. J.; Kim, D.; Lee, M. Appl. Opt. 1995, 34, 138.
7. Hervert, H.; Urbach, W.; Rondelez, F. *J. Chem. Phys.* **1978**, *68*, 2725.
8. Urbach, W.; Hervert, H.; Rondelez, F. *J. Chem. Phys.* **1985**, *83*, 1877.
9. Stephen, M. J.; Straley, J. P. *Rev. Mod. Phys.* **1974**, *46*, 617.
10. Zupancic, I.; Pirs, J.; Luzar, M.; Blinc, R. *Solid State Commum.* **1974**, *15*, 227.
11. Khoo, I. C. *Liquid Crystals*; Wiley; New York, 1995.
12. Agranovich, V. M.; Hochstrasser, R. M. *Spectroscopy and Excitation Dynamics of Condensed Molecular Systems*; North-Holland, Amsterdam, 1983.

A Stereoselective Synthesis of *syn*-β-Amino Alcohols *via* Iodocyclization

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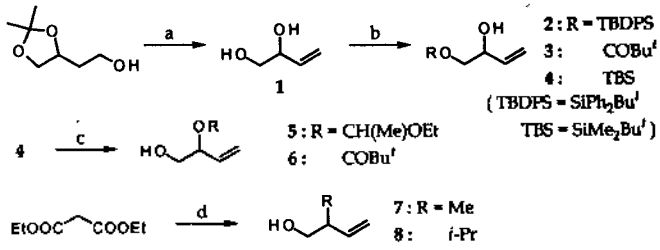
In recent years the stereoselective synthesis of β-amino alcohols is an increasingly important area in organic synthesis. They are indispensable peptide isosteres for the development of HIV protease,[1] renin[2] and ACE inhibitors.[3] Besides their utility as such therapeutic agents, β-amino alcohols have been employed as chiral auxiliaries,[4] and they are also expected to serve as chiral building blocks for the construction of glycosidase inhibitors.[5]

Several approaches to optically active β-amino alcohols have been explored such as the addition reaction of organometallics to α-amino aldehydes,[6] the reduction of α-amino ketones,[7] nitroaldol reaction,[8] the hydroboration of enamines[9] and the ring opening of epoxy alcohols with amine.[10] Alternatively we sought to exploit a practical asymmetric synthetic route to them, based on the electrophile promoted cyclization of allylic or homoallylic alcohols which comprise a nucleophilic nitrogen tethered through the alcoholic oxygen. Although Cardillo *et al.* pioneered this strategy,[11] we elected to reinvestigate the cyclization reaction in a more systematic manner to attain a facile procedure to β-amino alcohols with superior stereoinduction. This paper describes our stereocontrolled pathway to *syn*-β-amino alcohols *via* iodocyclization of homoallylic trichloroacetimidates derived from 3-buten-1,2-diols.



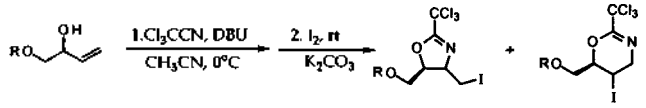
Scheme 1. Reagents : a. I_2/Ph_3P/imidazole/THF/0 ℃; *t*-BuOK/DMSO/rt; 6 N HCl/MeOH/rt. b. For **2** : TBDPSCl/imidazole/DMF/−60 ℃. For **3** : *t*-BuCOCl/Et_3N/CH_2Cl_2/0 ℃. For **4** : TBSCl/imidazole/DMF/−60 ℃. c. For **5** : CH_2=CHOEt/PPTS/CH_2Cl_2/0 ℃; *n*-Bu_4NF/aq. THF/rt. For **6** : *t*-BuCOCl/Py/CH_2Cl_2/0 ℃; 40% HF/CH_3CN/0 ℃. d. For **8** : NaH/*i*-PrI/18-crown-6/THF/65 ℃; LAH/Et_2O/0 ℃; TBSCl/imidazole/DMF/−55 ℃; Swern ox.; $Ph_3P^+CH_3I^-$/*n*-BuLi/THF/0 ℃; 40% HF/CH_3CN/0 ℃.

Allylic and homoallylic substrates **1-6** were prepared from 1,2-isopropylidenebutane-1,2,4-triol,[12] which was converted into iodide, eliminated and deprotected in sequence to furnish 3-buten-1,2-diol **1** in 71% overall yield (Scheme 1). Diol **1** reacted with TBDPSCl, pivaloyl chloride and TBSCl to produce TBDPS ether **2** (90%), pivalate **3** (57%) and TBS ether **4** (81%), respectively. The hydroxyl group of **4** was protected with ethyl vinyl ether and pivaloyl chloride, and then desilylated to yield ethoxyethyl ether **5** (82%) and pivalate **6** (86%), respectively. While 2-methyl-3-buten-1-ol **7** is commercially available, 2-isopropyl-3-buten-1-ol **8** was obtained from diethyl malonate over 6 steps in 40% overall yield.

After treatment of allylic alcohols **2** and **3** with trichloroacetonitrile in the presence of DBU in acetonitrile at 0 ℃, the resulting trichloroacetimidates were cyclized *in situ* using iodine and potassium carbonate at room temperature. The results are summarized in Table 1. While a 1 : 1 mixture of oxazolines **9** and dihydro-1,3-oxazines **10** was formed from TBDPS ether **2**, only oxazolines **11** could be isolated from pivalate **3**. Although stereochemical outcomes were not so excellent, it was noted that the identical aziridine could be generated from *trans*-**9**, *trans*-**10** and *trans*-**11** (*vide infra*). In addition better stereoselectivity was observed from **2** in favor of *trans*-isomers.

Homoallylic alcohols **1, 5-8**, containing a chiral substituent at the allylic position, were functionalized into trichloroacetimidates, of which *in situ* iodoamination was performed with iodine and sodium bicarbonate at 0 ℃. The experimental data are shown in Table 2. A relatively low stereoselectivity was resulted from **7** (entry 1). Although satisfactory stereoin-

Table 1. Iodocyclization of trichloroacetimidates from allylic alcohols **2** and **3**



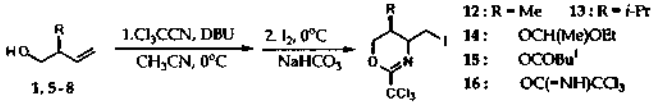
2: R = TBDPS
3: COBu^t

9: R = TBDPS
11: COBu^t

10: R = TBDPS

entry	substrate	isomeric ratio	% yield
1	**2**	*trans*-**9** : *cis*-**9** = 7 : 1	48
		trans-**10** : *cis*-**10** = 7 : 1	46
2	**3**	*trans*-**11** : *cis*-**11** = 4 : 1	87

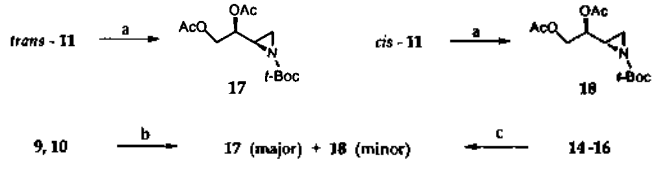
Table 2. Iodocyclization of trichloroacetimidates from homoallylic alcohols **1**, **5-8**



1, 5-8

12 : R = Me 13 : R = *i*-Pr
14 : OCH(Me)OEt
15 : OCOBu^t
16 : OC(=NH)CCl3

entry	substrate	isomeric ratio	% yield
1	**7**	*cis*-**12** : *trans*-**12** = 4 : 1	94
2	**8**	*cis*-**13** : *trans*-**13** = >100 : 1	85
3	**5**	*cis*-**14** : *trans*-**14** = 9 : 1	85
4	**6**	*cis*-**15** : *trans*-**15** = 25 : 1	93
5	**1**	*cis*-**16** : *trans*-**16** = 28 : 1	91

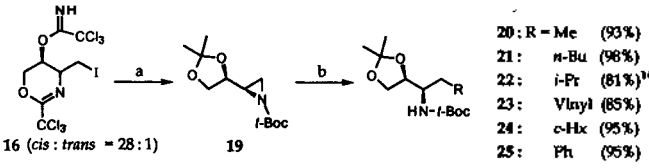


Scheme 2. **Reagents** : a. conc. HCl/MeOH/60 ℃; *t*-Boc_2O/$NaHCO_3$/MeOH/rt; Ac_2O/Et_3N/CH_2Cl_2/rt. b. CF_3COOH/aq. MeOH/rt; *t*-Boc_2O/aq. $NaHCO_3$/MeOH/rt; *n*-Bu_4NF/aq. THF/rt; Ac_2O/Et_3N/CH_2Cl_2/rt (66% from **9** and **10**, respectively). c. 6 N HCl/MeOH/rt (60 ℃ for **15**); *t*-Boc_2O/$NaHCO_3$/MeOH/rt; Ac_2O/Et_3N/CH_2Cl_2/rt (72% from **14**, 65% from **15** and 72% from **16**).

duction was achieved from the other substrates (entries 1-5), evidently the formation of *cis*-**16** from **1** is the most efficient process for a precursor of *syn*-β-amino alcohols (entry 5).

It is apposite to mention how the stereochemistries of **9-16** were determined. The stereochemistries of **9**, **11-13** were assigned by nOe experiments. However, those of **10**, **14-16** could not be corroborated unambiguously. Accordingly *trans*-**11** and *cis*-**11** were converted into the corresponding aziridines **17** and **18**, respectively. Also **9**, **10**, **14-16** were derivatized into a mixture of the aziridines respectively (Scheme 2). The spectroscopic comparison of the mixtures with **17** and **18** identified their stereochemistries as depicted in Table 1 and 2.[13]

Finally, as an effort to elaborate **16** (*cis* : *trans* = 28 : 1) to



Scheme 3. **Reagents** : a. CF_3COOH/aq. MeOH/rt; *t*-Boc_2O/$NaHCO_3$/MeOH/−15 ℃; $Me_2C(OMe)_2$/*p*-TsOH/acetone/0 ℃; NaH/THF/0 ℃/chromatographic separation. b. For **20** : Me_2CuLi/THF/−30~−20 ℃. For **21** : *n*-BuMgBr/CuCN/THF/−60~−20 ℃. For **22** : *i*-PrMgCl/CuCN/THF/Et_2O/−60~−20 ℃. For **23** : CH_2=CHMgBr/CuI/THF/−60~−30 ℃. For **24** : *c*-HxMgBr/CuCN/THF/−60~−20 ℃. For **25** : PhMgBr/CuBr·SMe_2/$PhCH_3$/−30~−20 ℃.

syn-β-amino alcohols, they were deprotected completely, and the generated amino and dihydroxyl groups were protected as *t*-butyl carbamate and acetonide sequentially (Scheme 3). The resulting iodides were cyclized and separated to furnish aziridine **19** in 80% overall yield from **16**. Further subjection of **19** to various cuprate reagents completed a facile stereoselective synthesis of *syn*-β-amino alcohols **20-25**.[15]

Acknowledgment. This work was supported by the Korea Advanced Institute of Science and Technology, and the Organic Chemistry Research Center sponsored by the Korea Science and Engineering Foundation.

References

1. (a) Kempf, D. J.; Sowin, T. J.; Doherty, E. M.; Hannick, S. M.; Codavoci, L.; Henry, R. F.; Green, B. E.; Spanton, S. G.; Norbeck, D. W. *J. Org. Chem.* **1992**, *57*, 5692-5700. (b) Lyle, T. A.; Wiscount, C. M.; Guare, J. P.; Thompson, W. J.; Anderson, P. S.; Darke, P. L.; Zugay, J. A.; Emini, E. A.; Schleif, W. A.; Quintero, J. C.; Dixon, R. A.; Sigal, I. S.; Huff, J. R. *J. Med. Chem.* **1991**, *34*, 1228-1230.
2. Ocain, T. D.; Abou-Gharbia, M. *Drugs of the Future* **1991**, *16*, 37-51.
3. Gordon, E. M.; Godfrey, J. D.; Plusec, J.; Von Langen, D.; Natarajan, S. *Biochem. Biophys. Res. Commun.* **1985**, *126*, 419-426.
4. (a) Noyori, R.; Kitamura, M. *Angew. Chem. Int. Ed. Engl.* **1991**, *30*, 49-69. (b) Tomioka, K. *Synthesis* **1990**, 541-549.
5. Robinson, K. M.; Rhinehart, B. L.; Ducep, J. B.; Danzin, C. *Drugs of the Future* **1992**, *17*, 705-720.
6. (a) Jurczak, J.; Prokopowicz, P.; Golebiowski, A. *Tetrahedron Lett.* **1993**, *34*, 7107-7110. (b) Coleman, R. S.; Carpenter, A. J. *ibid.* **1992**, *33*, 1697-1700.
7. (a) Cho, B. T.; Chun, Y. S. *Tetrahedron : Asymmetry* **1992**, *3*, 341-342. (b) Kitamura, M.; Ohkuma, T.; Inoue, S.; Sayo, N.; Kumobayashi, H.; Akutagawa, S.; Ohta, T.; Takaya, H.; Noyori, R. *J. Am. Chem. Soc.* **1988**, *110*, 629-631.
8. Sasai, H.; Itoh, N.; Suzuki, T.; Shibasaki, M. *Tetrahedron Lett.* **1993**, *34*, 855-858.
9. Fisher, G. B.; Goralski, C. T.; Nicholson, L. W.; Singaram, B. *ibid.* **1993**, *34*, 7693-7696.
10. Poch, M.; Alcon, M.; Moyano, A.; Pericas, M. A.; Riera, A. *ibid.* **1993**, *34*, 7781-7784.
11. Cardillo, G.; Orena, M. *Tetrahedron* **1990**, *46*, 3321-3408.

12. A 9 : 1 mixture of 1,2- and 2,4-isopropylidenebutane-1,2,4-triol was used. Meyers, A. I.; Lawson, J. P. *Tetrahedron Lett.* **1982**, *23*, 4883-4886.
13. The isomeric ratios of oxazolines and dihydro-1,3-oxazines were the same as those of aziridines.
14. The product generated from the hydride attack to aziridine **19** was formed in 10% yield (*i.e.* R=H).
15. All new compounds showed satisfactory spectral data.

Chemoselective Reduction of Carbonyl Compounds with Diisobutylethoxyalane

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Very recently, we reported that diisobutylchloroalane (i-Bu_2AlCl) is a highly selective reducing agent for the competitive reduction between carbonyl compounds[1] and for the 1,2-reduction of α,β-unsaturated carbonyl compounds.[2] In continuation of our efforts to explore new reducing systems for such transformations, we prepared a series of diisobutylalkoxyalane (i-Bu_2AlOR) and examined the reducing action toward general organic functional groups. In the course of this systematic investigation, we found that the ethoxy derivative, diisobutylethoxyalane (i-Bu_2AlOEt), reduces aldehydes in a fast rate but ketones only slowly. Accordingly, we applied this reagent for the competitive reduction between carbonyl compounds. Herein, we report the results for such selective reduction by i-Bu_2AlOEt in ethyl ether.

The reagent can be readily prepared by alcoholysis of diisobutylaluminum hydride (i-Bu_2AlH) in ether solution (Eq. 1). The reagent is effective for the reduction of aldehydes and ketones at 25°. As in the case of i-Bu_2AlCl,[1,2] the reduction with i-Bu_2AlOEt involves hydride shift from the β-carbon atom of isobutyl group.

$$i\text{-}Bu_2AlH + EtOH \xrightarrow[0°]{Et_2O} i\text{-}Bu_2AlOEt + H_2\uparrow \quad (1)$$

The reduction of representative aldehydes and ketones with 10% excess reagent at 25° in ethyl ether is listed in Table 1. Aldehydes are reduced readily in less than 1 or 3 h, while ketones are reduced slowly requiring 48 hrs for completion.

The chemoselectivity of this reagent was tested with twenty-four representative pairs in competition experiments. Equimolar amounts of two compounds were allowed to compete for a limited quantity of i-Bu_2AlOEt (1 equivalent). A standard solution of the reagent (*ca.* 1 M) in ethyl ether was added to the equimolar mixture of two compounds (*ca.* 1 M in each compound) in ethyl ether maintained at 25°.

Table 1. Reduction of Representative Aldehydes and Ketones with Diisobutylethoxyalane in Ethyl Ether at 25 °C[a]

Compound	Product	Time (h)	Yield (%)[b]
Butanal	1-Butanol	1.0	96
		3.0	100
Benzaldehyde	Benzyl alcohol	0.5	98
		1.0	100
2-Butanone	2-Butanol	24	90
		48	100
Acetophenone	1-Phenyl ethanol	24	95
		48	100

[a]Ten % excess reagent was utilized. Reaction mixtures were *ca.* 1 M in substrates. [b]Determined by GC using internal standard.

Table 2. Chemoselective Reduction of Carbonyl Compounds with Diisobutylethoxyalane in Ethyl Ether at 25 °C[a]

Entry	Starting mixture	Time (h)	Ratio of redn products[b]
1	Butanal/Hexanal	12	60 : 40
2	Butanal/Benzaldehyde	3	5 : 95
3	Butanal/Anisaldehyde	6	95 : 5
4	Hexanal/Benzaldehyde	3	2 : 98
5	Hexanal/Anisaldehyde	6	92 : 8
6	Benzaldehyde/Anisaldehyde	3	99.5 : 0.5
7	Butanal/Cyclohexanone	6	100 : 0
8	Hexanal/Cyclohexanone	6	100 : 0
9	Hexanal/2-Heptanone	6	100 : 0
10	Hexanal/Acetophenone	6	100 : 0
11	Hexanal/Benzophenone	6	100 : 0
12	Anisaldehyde/Cyclohexanone	12	99 : 1
13	Cyclohexanone/2-Heptanone	24	100 : 0
14	Cyclohexanone/Acetophenone	24	95 : 5
15	Cyclohexanone/Benzophenone	24	100 : 0
16	Acetophenone/2-Heptanone	48	100 : 0
17	2-Heptanone/Benzophenone	96	95 : 5
18	Acetophenone/Benzophenone	48	100 : 0
19	Cyclohexanone/Cyclopentanone	24	90 : 10
20	Hexanal/Hexanoyl Chloride	6	100 : 0
21	Hexanal/Benzoyl Chloride	6	100 : 0
22	2-Heptanone/Benzoyl Chloride	96	99 : 1
23	Hexanal/Hexanenitrile	6	100 : 0
24	Hexanal/Ethyl Hexanoate	6	100 : 0

[a]Reaction mixtures were *ca.* 1 M in substrates. One equivalent of reagent was utilized for competitive reduction of equimolar mixture of two carbonyl compounds. [b]Normalized ratio determined by GC with appropriate internal standard; the total yields of product alcohols were ≥ 99%.

After appropriate time intervals, the mixture was hydrolyzed with 3 N HCl. The results obtained by GC analysis of the reaction mixture with an internal standard are summarized in Table 2.

Both aliphatic and aromatic aldehydes examined are selec-