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A stereocontrolled synthetic route to *anti*-β-amino alcohols

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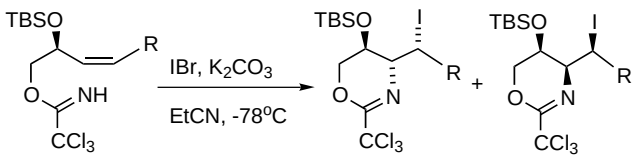
Abstract—A physiologically indispensable β-amino hydroxy functionality has been constructed with complete *anti*-stereoselectivity by intramolecular iodoamidation of (*Z*)-olefinic homoallylic trichloroacetimidates **4–6**, **18**, **20**, **30** and **32**, which comprise bulky substituents at the vinylic positions. © 2001 Elsevier Science Ltd. All rights reserved.

A plethora of pharmaceutically and biologically valuable compounds comprise 1,2-amino hydroxy functional groups. The substances are usually involved in exhibiting a variety of biological activities. The representatives are the glycosidase inhibitors (−)-swainsonine,[1] (+)-castanospermine[2] and azasugars,[3] and (−)-statine as the key constituent of the aspartic protease inhibitor pepstatin.[4] In addition, others include the neurotrophic agent (+)-lactacystin,[5] the antibiotic (+)-furanomycin,[6] the antifungal agent (−)-anisomycin[7] and so forth. The stereoselective installation of the β-amino hydroxy functionality has been implemented via the intramolecular Michael addition of allylic and homoallylic carbamates,[8] the halocyclization of aminoalkenes[9] and thiocarbamidates,[10] the organometallic addition reaction and the hetero-Diels–Alder reaction of α-amino aldehydes,[11] the aldol reaction of the chiral oxazolidinones,[12] the epoxide opening reaction with nitrogen nucleophiles,[13] the diastereoselective hydroxylation of allylic carbamates,[14] the reduction of α-amino ketones,[11a,15] and the apposite functionalization of carbohydrates.[16] Remarkably, β-amino alcohols also have been enantioselectively synthesized by employing chiral catalysts in the amino hydroxylation,[17] the nitroaldol reaction,[18] the Mannich-type reaction of aldimines[19]and the aldol reaction of β-amino enol ether.[20]

In this context, we established the stereoselective synthesis of *syn*-β-amino alcohols via the electrophile-promoted intramolecular amidation of (*Z*)-olefinic allylic[21] and terminal olefinic homoallylic trichloroacetimidates.[22] Since it is ideal and complementary to generate *anti*-β-amino alcohols diastereoselectively by the same protocol, we have been engaged in developing the conceived synthetic methodology. In this paper, we describe a diastereoselective synthesis of *anti*-β-amino alcohols via the intramolecular iodoamidation of (*Z*)-olefinic homoallylic trichloroacetimidates, which have bulky substituents at the terminal olefinic positions to induce the conformational change by introducing $A^{1,3}$-strain. In the involved transition state, it was envisioned

Table 1. Iodoamidation of trichloroacetimidates **1–6**



1 - 6 | **7a - 9a, 10 - 12** (*anti*) | **7s - 9s** (*syn*)

Entry	R	Substrate	Stereo-selectivity	Yield (%)
1	Me	**1**	**7a**:**7s** = 4:1	88
2	Et	**2**	**8a**:**8s** = 8:1	97
3	$CHMe_2$	**3**	**9a**:**9s** = 11:1	96
4	CMe_3	**4**	**10** only	95
5	TMS	**5**	**11** only	98
6	$C(OH)Me_2$	**6**	**12** only	92

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that the steric effect between the allylic and the vinylic substituents would be more predominant than the electronic effect caused by the eclipsing stabilization[23] between the allylic heteroatomic substituent and the olefinic double bond to dictate the formation of *anti*-β-amino alcohols.

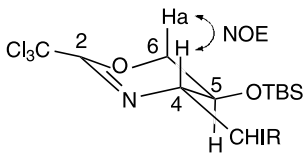
Substrates **1**–**6** with various sizes of substituents at the vinylic positions were prepared from D-glyceraldehyde acetonide in 40–57% overall yields. Iodoamidation of **1**–**6** was conducted with IBr in the presence of K_2CO_3 in propionitrile at −78°C. The cyclization reactions proceeded efficiently as described in Table 1. When the size of the R group becomes bulkier, the stereoselectivity increases. The complete *anti*-stereoselectivity was observed with the substrates having the tertiary R groups (entries 4–6). The stereochemistry of products **7**–**12** was determined by the coupling constant data and NOE experiments, as summarized in Table 2. On the other hand, the triol precursory to **6** was treated with trichloroacetonitrile in the presence of DBU in EtCN and the resulting bis(imidate) was cyclized under identical conditions to those in Table 1 to afford *anti*-β-amino alcohol **13** in 79% yield along with 14% of *syn*-isomer **14** (Fig. 1).

The other type of substrates which comprise substituents not only at the vinylic positions but also homoallylic positions was employed to explore the iodoamidation because the stereoselectively generated amino alcohols could be more versatile for further functionalization. While imidates **17**–**20** were prepared from aldehyde **15**[24] in 57–73% yields, imidates **29**–**32** were rendered from aldehyde **16**[25] in 52–75% yields (Fig. 2). Subjection of **17**–**20** to iodoamidation was performed under the aforementioned conditions and the results are presented in Table 3. While **17** and **19** provided a mixture of *anti*, *syn*-β-amino alcohols and oxazepines in favor of *anti*-isomers (entries 1 and 3), **18** and **20** gave *anti*-isomers exclusively (entries 2 and 4). The structural proof of products **21**–**24** is explained in Scheme 1. Since **ent-25** ($[\alpha]_D^{25}$ −14.9, *c* 0.9, MeOH) could be procured from L-glutamic acid, **21a** and **21s** were converted into carbamates **25** ($[\alpha]_D^{23}$ +14.3, *c* 1.0, MeOH) and **ent-25** ($[\alpha]_D^{25}$ −14.8, *c* 0.5, MeOH), respectively, for comparison. Analogous derivatization of **23a**, **23s** and **23o** produced carbamates **27** ($[\alpha]_D^{21}$ +30.7, *c* 0.8, MeOH), **ent-27** ($[\alpha]_D^{25}$ −31.4, *c* 0.6, MeOH) and **ent-27** ($[\alpha]_D^{25}$ −30.6, *c* 0.4, MeOH), respectively. Their stereochemistry was also assigned by comparing their $[\alpha]_D$ values with that of **ent-27** ($[\alpha]_D^{26}$ −32.3, *c* 1.1, MeOH) derived from L-aspartic acid. On the other hand, the structures of **22**, **21o** and **24** were determined by NOE experiments and the coupling constant data of **22**, **26** and **28**, of which the latter two were derived from **21o** and **24**, respectively.

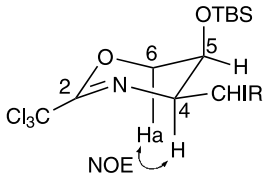
Intramolecular iodocyclization of **29**–**32** was also carried out under the described iodoamidation conditions and the experimental data are shown in Table 4. A mixture of *anti*- and *syn*-amino alcohols was produced from **29** and **31** without any appreciable formation of seven-membered oxazepines (entries 1 and 3). On the other hand, only *anti*-isomers were obtained from **30** and **32** (entries 2 and 4).

While the structures of **30a**, **33s** and **34** were concluded by the coupling constant data and NOEs, those of **35a** and **35s** were deduced by their chemical conversion into **ent-27** ($[\alpha]_D^{25}$ −31.3, *c* 0.5, MeOH) and **27** ($[\alpha]_D^{25}$ +30.8, *c* 0.4, MeOH), and also supported by the coupling constant data (Scheme 2). The stereochemistry of **36** was confirmed by the coupling constant data and NOEs of **37**, which was prepared from **36** via reductive elimination.

Table 2. The coupling constants and NOEs of **7**–**12**

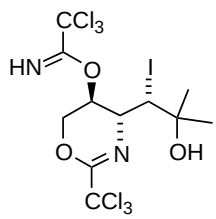


7a - 9a, 10 - 12



7s - 9s

Compound	$J_{5H,\ 6Ha}$ (Hz)	Compound	$J_{5H,\ 6Ha}$ (Hz)
7a	10.0	**12**	10.1
8a	11.4	**7s**	1.1
9a	10.4	**8s**	1.5
10	9.8	**9s**	1.2
11	10.0		



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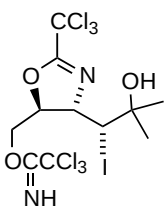

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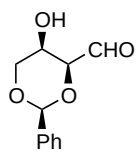
Figure 1.



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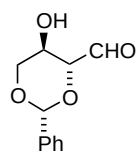

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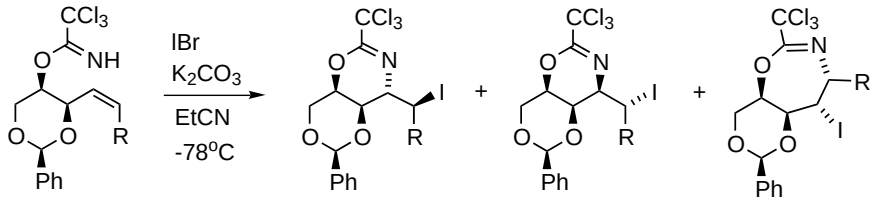
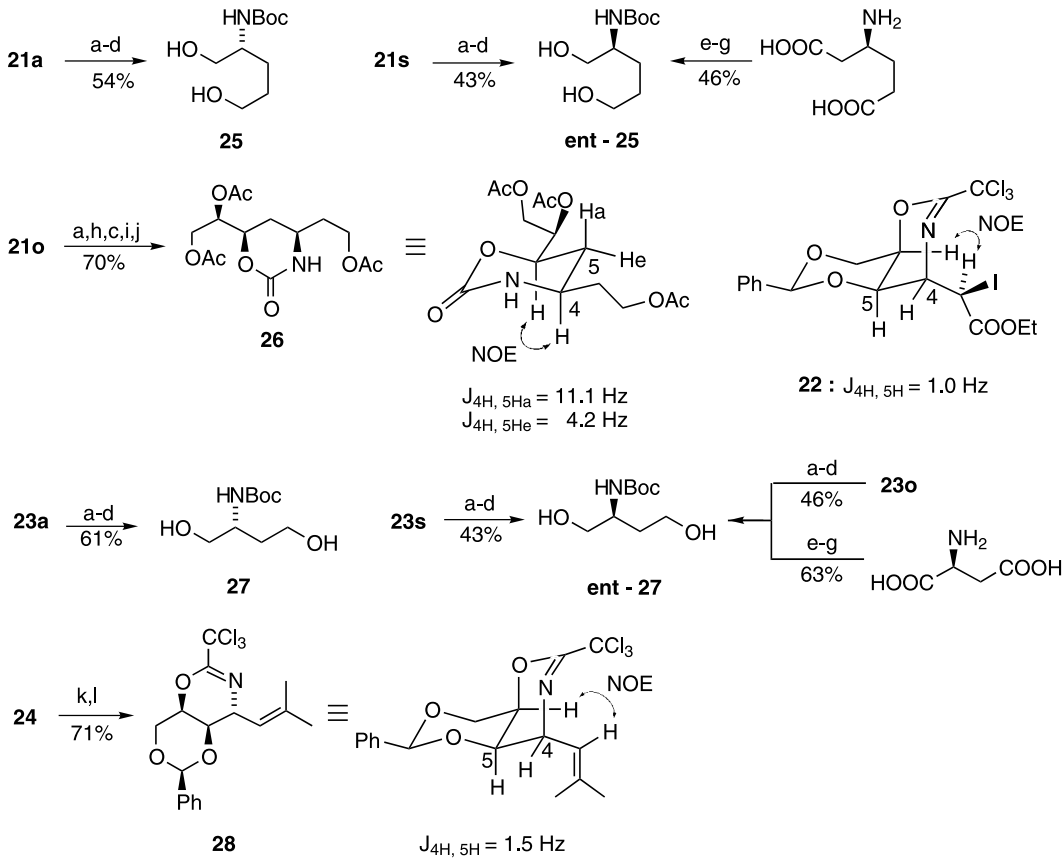
Figure 2.

Table 3. Iodoamidation of trichloroacetimidates **17–20**



Entry	R	Substrate	Stereoselectivity	Yield (%)
1	$(CH_2)_2OTBDPS$	**17**	**21a**:**21s**:**21o** = 6.8:1.8:1	96
2	COOEt	**18**	**22** only	64
3	$CH_2OTBDPS$	**19**	**23a**:**23s**:**23o** = 1.8:1.1:1	95
4	$C(OH)Me_2$	**20**	**24** only	89



Scheme 1. (a) 6N HCl, MeOH, 55°C; (b) Boc_2O, $NaHCO_3$, MeOH, 0°C to rt; (c) *n*-Bu_3SnH, Et_3B, THF, 0°C; (d) $NaIO_4$, MeOH, H_2O, 0°C, then $NaBH_4$, 0°C; (e) Boc_2O, NaOH, H_2O, dioxane, rt; (f) CH_2N_2, Et_2O, 0°C; (g) $LiBH_4$, THF, rt; (h) CbzCl, $NaHCO_3$, MeOH, rt; (i) NaH, THF, 0°C; (j) Ac_2O, DMAP, pyridine, rt; (k) TFAA, Et_3N, CH_2Cl_2, 0°C; (l) NaI, DMF, 0°C.

In summary, we have developed a stereoselective synthetic route to *anti*-β-amino alcohols via the intramolecular iodoamidation of (*Z*)-olefinic homoallyic trichloroacetimidates, which is complementary to our previously reported synthesis of *syn*-β-amino alcohols.[21,22]

Acknowledgements

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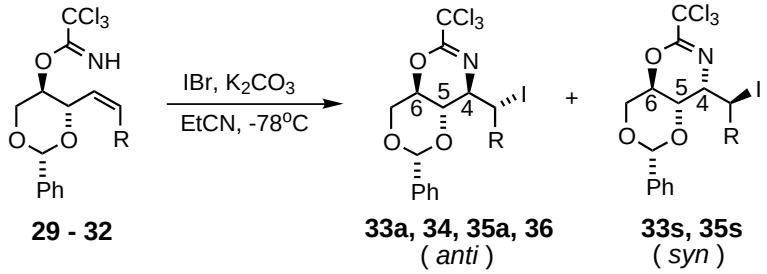
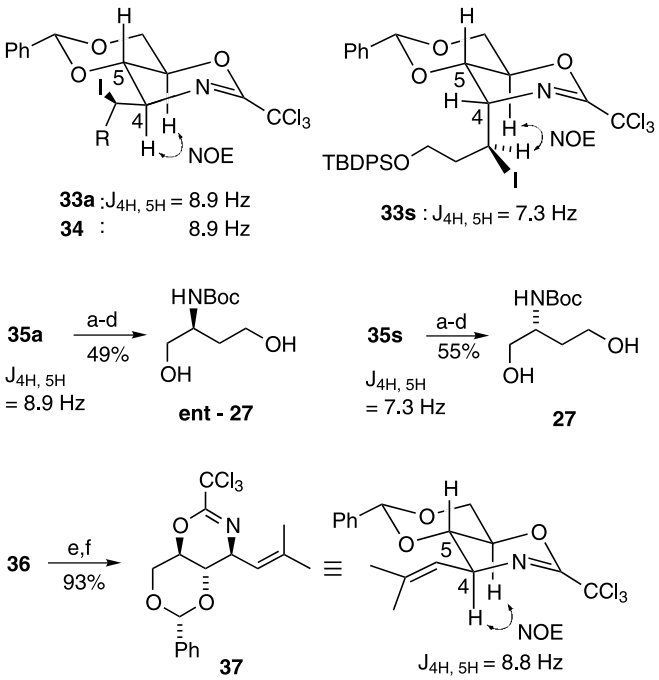
Table 4. Iodoamidation of trichloroacetimidates **29–32**



29 - 32 **33a, 34, 35a, 36** (*anti*) **33s, 35s** (*syn*)

Entry	R	Substrate	Stereoselectivity	Yield (%)
1	$(CH_2)_2OTBDPS$	**29**	**33a**:**33s** = 3.8:1	95
2	COOEt	**30**	**34** only	95
3	$CH_2OTBDPS$	**31**	**35a**:**35s** = 4.7:1	98
4	$C(OH)Me_2$	**32**	**36** only	96



Scheme 2. (a) 6N HCl, MeOH, 55°C; (b) Boc_2O, $NaHCO_3$, MeOH, 0°C to rt; (c) *n*-Bu_3SnH, Et_3B, THF, 0°C; (d) $NaIO_4$, MeOH, H_2O, 0°C, then $NaBH_4$, 0°C; (e) TFAA, Et_3N, CH_2Cl_2, 0°C; (f) NaI, DMF, 0°C.

References

1. (a) Guengerich, F. P.; DiMari, S. J.; Broquist, H. P. *J. Am. Chem. Soc.* **1973**, *95*, 2055; (b) Molyneux, R. J.; James, L. F. *Science* **1982**, *216*, 190.
2. (a) Hohenschutz, L. D.; Bell, E. A.; Jewess, P. J.; Leworthy, D. P.; Pryce, R. J.; Anold, E.; Clardy, J. *Phytochemistry* **1981**, *20*, 811; (b) Gruters, R. A.; Neefjes, J. J.; Tersmette, M.; de Goede, R. E. Y.; Tulp, A.; Huisman, H. G.; Miedema, F.; Ploegh, H. L. *Nature* **1987**, *330*, 74.
3. (a) Sinnott, M. L. *Chem. Rev.* **1990**, *90*, 1171; (b) Hughes, A. B.; Rudge, A. J. *Nat. Prod. Rep.* **1994**, *11*, 135.
4. Umezawa, H.; Aoyagi, T.; Morishima, H.; Matsuzaki, M.; Hamada, H.; Takeuchi, T. *J. Antibiot.* **1970**, *23*, 259.
5. Omura, S.; Fujimoto, T.; Otogurro, K.; Matsuzaki, K.; Moriguchi, R.; Tanaka, H.; Sasaki, Y. *J. Antibiot. Chem.* **1991**, *44*, 113.
6. Category, K.; Tori, K.; Kimura, Y.; Yoshida, T.; Nagasaki, T.; Minato, H. *J. Med. Chem.* **1967**, *10*, 1147.
7. (a) Grollman, A. P. *J. Biol. Chem.* **1967**, *242*, 3226; (b) Jimenez, A.; Vazquez, D. In *Antibiotics*; Hahn, F. E., Ed.; Springer Verlag: Berlin, 1979; pp. 1–19.
8. (a) Hirama, M.; Shigemoto, T.; Yamazaki, Y.; Ito, S. *J. Am. Chem. Soc.* **1985**, *107*, 1797; (b) Hirama, M.; Hioki, H.; Ito, S.; Kabuto, C. *Tetrahedron Lett.* **1988**, *29*, 3121.
9. Tamaru, Y.; Kawamura, S.-i.; Bando, T.; Tanaka, K.; Hojo, M.; Yoshida, Z.-i. *J. Org. Chem.* **1988**, *53*, 5491.
10. Knapp, S.; Patel, V. *J. Am. Chem. Soc.* **1983**, *105*, 6985.
11. (a) Reetz, M. T. *Angew. Chem., Int. Ed. Engl.* **1991**, *30*, 1531; (b) Golebiowski, A.; Jurczak, J. *Synlett* **1993**, 241.
12. Evans, D. A.; Weber, A. E. *J. Am. Chem. Soc.* **1987**, *109*, 7151.
13. (a) Saito, S.; Bunya, N.; Inaba, M.; Morowake, T.; Torii, S. *Tetrahedron Lett.* **1985**, *26*, 5309; (b) Boger, D. L.; Ledeboer, M. W.; Kume, M. *J. Am. Chem. Soc.* **1999**, *121*, 1098.
14. Ohfune, Y. *Acc. Chem. Res.* **1992**, *25*, 360.
15. (a) 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; (b) Cho, B. T.; Chun, Y. S. *Tetrahedron: Asymmetry* **1992**, *3*, 341.
16. Cintas, P. *Tetrahedron* **1991**, *47*, 6079.
17. Bruncko, M.; Schlingloff, G.; Sharpless, K. B. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 1483.
18. (a) Sasai, H.; Suzuki, T.; Itoh, N.; Tanaka, K.; Date, T.; Okamura, K.; Shibasaki, M. *J. Am. Chem. Soc.* **1993**, *115*, 10372; (b) Arai, T.; Yamada, Y. M. A.; Yamamoto, N.; Sasai, H.; Shibasaki, M. *Chem. Eur. J.* **1996**, *2*, 1368.
19. Kobayashi, S.; Ishitani, H.; Ueno, M. *J. Am. Chem. Soc.* **1998**, *120*, 431.
20. Horikawa, M.; Busch-Peterson, J.; Corey, E. J. *Tetrahedron Lett.* **1999**, *40*, 3843.

21. (a) Kang, S. H.; Kim, G. T. *Tetrahedron Lett*. **1995**, *36*, 5049; (b) Kang, S. H.; Kim, G. T.; Yoo, Y. S. *Tetrahedron Lett*. **1997**, *38*, 603; (c) Kang, S. H.; Kim, J. S. *Chem. Commun*. **1998**, 1353; (d) Kang, S. H.; Jun, H.-S.; Youn, J.-H. *Synlett* **1998**, 1045.
22. (a) Kang, S. H.; Ryu, D. H. *Bioorg. Med. Chem. Lett*. **1995**, *5*, 2959; (b) Kang, S. H.; Ryu, D. H. *Chem. Commun*. **1996**, 355; (c) Kang, S. H.; Lee, S. B. *Chem. Commun*. **1998**, 761.
23. Chamberline, A. R.; Mulholland, Jr., R. L.; Kahn, S. D.; Hehre, W. J. *J. Am. Chem. Soc*. **1987**, *109*, 672.
24. Schmidt, R. R.; Zimmermann, P. *Tetrahedron Lett*. **1986**, *27*, 481.
25. Baker, S. R.; Clissold, D. W.; McKillop, A. *Tetrahedron Lett*. **1988**, *29*, 991.