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A STEREOCONTROLLED SYNTHESIS OF (-)-BESTATIN FROM AN ACYCLIC ALLYLAMINE BY IODOCYCLOCARBAMATION

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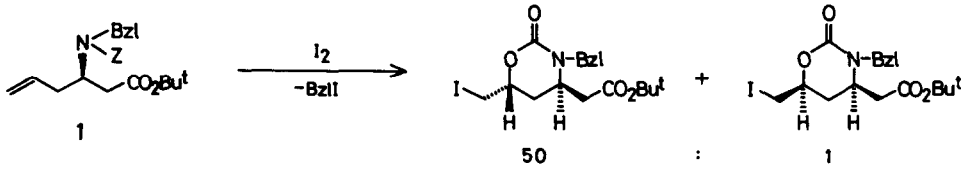
Abstract: 1,2-Asymmetric induction of iodocyclocarbamation is described by using allylamines **2** and **6** and the method has been successfully applied to a stereocontrolled synthesis of bestatin.

Halocyclocarbamation recently developed by several groups[1] efficiently gives important functional groups such as amino alcohol frequently seen in biologically interesting compounds. Fraser-Reid and his co-workers first made a significant advance toward the amino sugars by using the reaction for cyclic systems[1]. We also developed an enantioselective total synthesis of (+)-negamycin in which a remarkable 1,3-asymmetric induction was realized by taking advantage of iodocyclocarbamation for an acyclic homoallylamine **1**[2]. However, the stereochemical course of the halocyclocarbamation has not been explored yet in detail when compared with that of halolactonization[3] which seems to be mechanistically closely related.

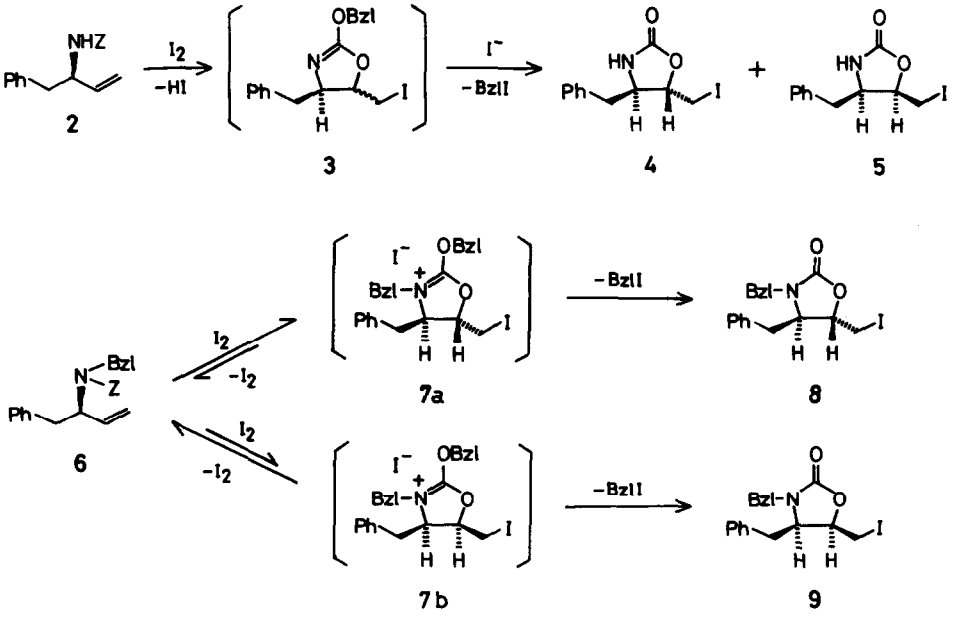


1 **50** : **1**

In this paper, we wish to describe 1,2-asymmetric induction of iodocyclocarbamation in acyclic allylamines and the application to the synthesis of bestatin, an important immuno-potentiator[4]. The chiral allylamine **2** [mp 92.5-93.0°C, $[\alpha]_D^{20}$ -33.3° (c 2.0, $CHCl_3$), Rf 0.33 (Et_2O: hexane=1:2) was obtained in 64% overall yields from Z-D-phenylalanine ethyl ester by known two step procedures [(1) DIBAH in toluene[5], and (2) $Ph_3P^+CH_3I^-$, KH in toluene and THF]. Treatment of **2** with iodine (3 equiv) in methylene chloride at 0°C for 7hr afforded a mixture of trans- and cis-iodocyclocarbamates in 69% yield, but the ratio was about 1.5:1 slightly in favor of the desired trans isomer **4**.

Bartlett observed the similar poor 1,2-asymmetric induction in the halolactonization of γ,δ-unsaturated carboxylic acid but achieved high 1,2-

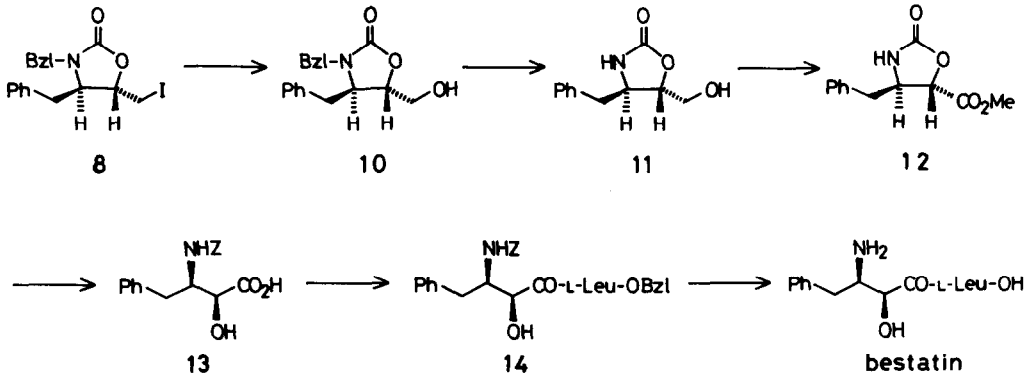
asymmetric induction by employing the condition where an equilibration of a cyclic intermediate lead to the thermodynamically more favored trans isomer[6]. The low selectivity in our case might be due to the irreversible formation of the cyclic imino acetal **3**.



Therefore, N-benzyl derivative **6** was prepared ($PhCH_2Br$, KH in DMF and benzene, 95%, **6**; oil, MS m/e 372(M^++1), $[\alpha]_D^{20}$-80.4°(c 2.7, $CHCl_3$),Rf 0.44 (Et_2O:hexane =1:4)) in order to perform iodocyclocarbamation under thermodynamic control by the equilibration through the iminium intermediate **7**. Iodocyclocarbamation of N-benzyl derivative **6** was carried out in a similar manner to afford the trans isomer **8** and the cis isomer **9** in 80% and 12% yields, respectively ((6.7:1 ratio). **8**; mp 110~111°C, $[\alpha]_D^{20}$+34.2°(c 2.4, $CHCl_3$), Rf 0.27 (Et_2O :hexane=1:1). **9**; mp 118~118.5°C,$[\alpha]_D^{22}$-1.0°(c 3.1, $CHCl_3$), Rf 0.30 (Et_2O :hexane=1:1)). The stereochemistry of iodocarbamates **8** and **9** was assumed as shown on the basis of ^1H-NMR[7] ($J_{4,5}$=5.0Hz for **8** and 7.0Hz for **9**), and eventually established by correlating to bestatin. The relatively high stereoselection could be reasonably explained by the thermodynamic process mentioned above and the substituent on the nitrogen was found to play an important role in the iodocyclocarbamation.[3] This point seems to be essentially different from halolactonization where stereochemical control is possible by proper choice of the condition[8] (the presence or the absence of base).

The stereocontrol for bestatin was thus accomplished and the functional group transformation to bestatin was achieved by rather conventional procedures. The conversion of the iodide **8** into the alcohol **10** was best carried out in two steps [(93% yield); (1) AgOAc[9] in DMF and AcOH, (2) 1N NaOH in MeOH-H_2O. **10**; mp 97.0~97.5°C, $[\alpha]_D^{20}$+45.3°(c 1.1, $CHCl_3$) . Removal of the

benzyl group by Birch reduction[10] (Na in NH_3, **10**→**11** 82%), followed by Jones oxidation and treatment with CH_2N_2 afforded methyl ester **12** in 54% yield (recrystallized yield)(**12**; mp 91.0~91.5°C, $[\alpha]^{20}$+66.3° (c 1.2, $CHCl_3$)]. The key part of bestatin **13**, (2S, 3R)-3-benzyloxycarbonylamino-2-hydroxy-4-phenylbutanoic acid, was obtained by alkaline hydrolysis (2N LiOH in MeOH-H_2O) of the oxazolidone **12** and reprotection of the amino group (ZCl, 1N NaOH in Et_2O and H_2O, **12**→**13** 72%). **13**; mp 161.0~161.5°C, $[\alpha]^{20}$+82.9° (c 1.1, AcOH)[4]. The total synthesis of bestatin was completed by condensation with L-leucine (L-LeuOBzl·p-TsOH, DCC, HOBt, Et_3N in CH_2Cl_2-THF, 95%, **13**→**14**) followed by hydrogenolysis (Pd black, H_2 in MeOH-H_2O **14**→bestatin). The synthetic material (mp 232-233°C, $[\alpha]^{20}$-15.4° (c 1.40, 1N HCl)) was confirmed to be identical with natural bestatin[4a] (mp 233~236°C, $[\alpha]^{20}$-15.5°(c 1.0, 1N HCl) in all respects.[11]



REFERENCES AND NOTES

1. (a) M.Georges, D.MacKay, and B.Fraser-Reid, J. Am. Chem. Soc., **104**, 1101 (1982) and references cited therein. (b) P.A.Bartlett, D.J.Tanzella, and J.F.Barstow, Tetrahedron Lett., **23**, 619 (1982). (c) S.Takano and S.Hatakeyama, Heterocycles, **19**, 1243 (1982). (d) L.E.Overman and R.J.McCready, Tetrahedron Lett., **23**, 4887 (1982). (e) K.A.Parker and R.O'Fee, J. Am. Chem. Soc., **105**, 654 (1983).

2. (a) Y.F.Wang, T.Izawa, S.Kobayashi, and M.Ohno, J. Am. Chem. Soc., **104**, 6465 (1982). (b) M.Ohno, S.Kobayashi, T.Izawa, and Y.F.Wang, J. Chem. Soc. Japan, Chem. & Ind. Chem., **12**, 99 (1983) (in Japanese).

3. (a) M.D.Dowle and D.I.Davies, Chem. Soc. Revs., **2**, 171 (1979). (b) P.A.Bartlett, Tetrahedron, **36**, 2 (1980).

4. Isolation; (a) H.Umezawa, T.Aoyagi, H.Suda, M.Hamada, and T.Takeuchi, J.Antibiot., **29**, 97 (1976). (b) M.Ishizuka, T.Masuda, N.Kanbayashi, S.Fukasawa, T.Takeuchi, T.Aoyagi, and H.Umezawa, J. Antibiot., **33**, 642 (1980) references cited therein.
Synthesis; (c) H.Suda, T.Takita, T.Aoyagi, and H.Umezawa, J.Antibiot., **29**, 600 (1976). (d) K.Kato, T.Saino, R.Nishizawa, T.Takita, and H.Umezawa, J. Chem. Soc. Perkin I, 1618 (1980) (e) R.Nishizawa, T.Saino, M.Suzuki, T.Fujii, T.Shirai, T.Aoyagi, and H.Umezawa, J. Antibiot., **36**, 695 (1983) (f) K.B.Sharpless, C.H.Behrens, T.Katsuki, A.W.M.Lee, V.S.Martin, M.Takatani, S.M.Viti, F.J.Walker, and S.S.Woodard, Pure and Applied Chemistry, **55**, 589 (1983).

5. A.Ito, R.Takahashi, and Y.Baba, Chem. Pharm. Bull., **23**, 3081 (1975).

6. P.A.Bartlett and J.Myerson, J. Am. Chem. Soc., **100**, 3950 (1978).

7. Stereochemistry of 4,5-disubstituted 2-oxazolidone could be determined by ^{1}H NMR analysis. The signal due to H_4 in trans isomer generally appears at higher field with smaller coupling constant ($J_{4,5}$) than that of the corresponding cis isomer. (a) T.A.Foglia and D.Swern, J. Org. Chem., **34**, 1680 (1969). (b) S.Futagawa, T.Inui, and T.Shiba, Bull. Chem. Soc. Jpn., **46**, 3308 (1973).

8. In sharp contrast to Bartlett's procedure,[6] which afforded thermodynamically more stable 3,4-trans-δ-lactone, Chamberlin reported that the iodolactonization of some acyclic hydroxy olefinic acids proceeds under kinetic condition with high degree of asymmetric induction, giving thermodynamically less stable 3,4-cis-iodolactones. A.R.Chamberlin, M.Dezube, and P.Dussault, Tetrahedron Lett., **22**, 4611 (1981).

9. The use of sodium or potassium acetate instead of silver salt was unsuccessful. Alternatively, silver trifluoroacetate [1b] was also effective for this transformation.

10. N-Benzyl group was found to resist to catalytic hydrogenolysis at the final step of bestatin synthesis. So the debenzylation of **10** was carried out considering the convenience in separation and purification of the intermediates.

11. All compounds describes here were well characterized by spectroscopic analysis (IR, ^{1}H NMR and MS) and elemental analysis.

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