Asymmetric Synthesis of Orthogonally Protected (2*S*,4*R*)- and (2*S*,4*S*)-4-Hydroxyornithine

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Abstract: Synthesis of orthogonally protected (2*S*, 4*R*)- and (2*S*, 4*S*)-4-hydroxyornithine was reported featuring an asymmetric alkylation of *N*-(diphenylmethylene)glycine *tert*-butyl ester (**6**) by (5*S*)-*N*-benzyloxycarbonyl-5-iodomethyl oxazolidine (**7**). Double stereoselection was examined using chiral ammonium salts as phase transfer catalysts and a substrate-directed chiral induction is documented.

Key words: amino acid, asymmetric alkylation, double stereoselection, glycine template, 4-hydroxyornithine, phase transfer catalyst

The (2*S*,4*R*)- (**1**) and (2*S*,4*S*)-4-hydroxyornithine (**2**) are key structural units found in macrocyclic antibiotic biphenomycin A and B **3**,[1] and β-lactam antibiotic clavalanine (**4**),[2] respectively (Figure 1). The related 4-hydroxylated α-amino acids such as (2*S*,4*S*,6*R*)-4-hydroxy-5-phenylsulfinylnorvaline (**5**) has also been identified as a key component of ustiloxin A and B,[3] a family of cyclic peptides with potent antimitotic activity. A number of synthetic routes including stereoselective approaches have been developed for the preparation of these non-proteinogenic amino acids.[4–9]

Enantioselective alkylation of *N*-(diphenylmethylene)glycine *tert*-butyl ester (**6**) using phase transfer catalysts has recently been developed into a powerful method for the synthesis of chiral non-racemic amino acids.[10–13] However, the stereochemistry of the alkylation of **6** with chiral electrophiles has not been addressed. In examples reported in the literature, the existing asymmetric center is generally too far away from the newly created chiral center to exert any chiral directing effect.[14,15] In connection with our interest in the total synthesis of biphenomycin,[16] we thought that alkylation of glycine template **6** by (5*S*)-*N*-benzyloxycarbonyl-5-iodomethyl oxazolidine (**7**) could potentially constitute a rapid access to (2*S*,4*R*)-4-hydroxyornithine (**1**). Moreover, such an approach would give us the opportunity to examine in detail the effect of the vicinal chiral center on the stereochemical course of the alkylation process. The result of this study is the subject of the present communication.

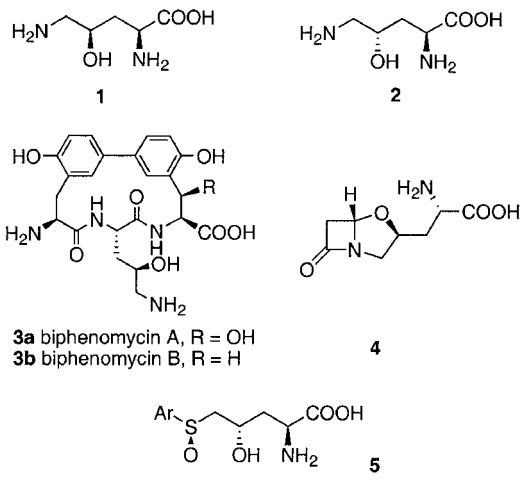
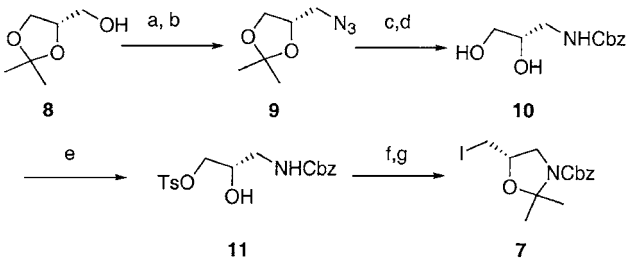


Figure 1



Scheme 1 *Reagents and Conditions*: a) TsCl, pyridine, r.t., 93%; b) NaN_3, DMSO, 100 °C, 99%; c) H_2, Pd/C, MeOH–HCl (10%); d) CbzOSu, $NaHCO_3$, H_2O–dioxane, r.t., 94%; e) TsCl, pyridine, r.t., 85%; f) dimethoxypropane, acetone, $BF_3{\cdot}OEt_2$, r.t., 73%; g) NaI, acetone, reflux, 85%.

The (5*S*)-*N*-benzyloxycarbonyl-5-iodomethyl oxazolidine (**7**) was synthesized as shown in Scheme 1. Tosylation of (*S*)-1,2-*O*-isopropylideneglycerol (**8**) followed by nucleophilic displacement of tosylate with sodium azide provided azido derivative **9**. Hydrogenolysis under acidic conditions provided an amino diol that was chemoselectively *N*-acylated to give carbamate **10**. Regioselective tosylation of the primary hydroxy group afforded **11**, which was subsequently converted into iodide **7** via a classical two-step sequence.

Alkylation of **6** with iodide **7** was examined under a set of conditions varying the temperature, the base, and the catalyst (Scheme 2). The results are summarized in Table 1. The first experiment was carried out using *O*-(9)-allyl-*N*-(9-anthracenylmethyl)cinchonidinium bromide (**14**, Figure 2) as catalyst under Corey's conditions (CsOH,

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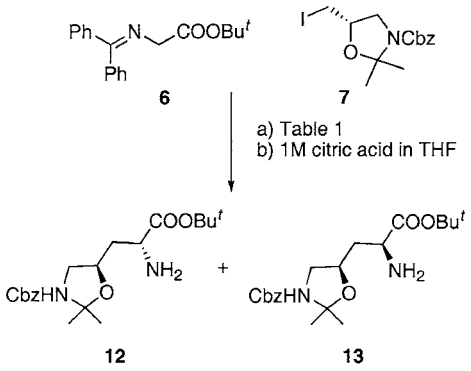


Scheme 2

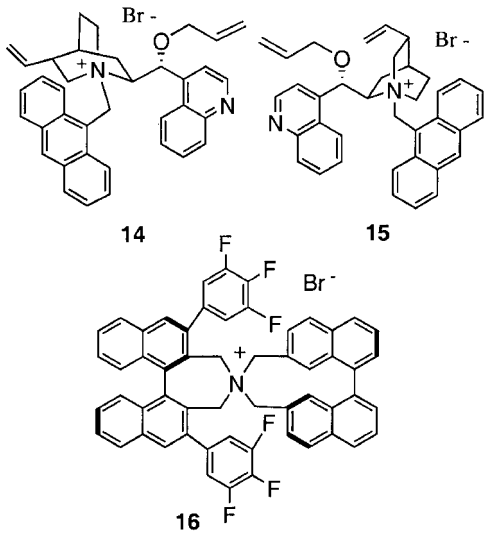


Figure 2

0.56 M in CH_2Cl_2). When the reaction was performed at –50 °C, no alkylation product was observed in accord with the lower reactivity of alkyl halides relative to benzyl and allyl halides (entry 1). By performing the reaction at –20 °C, two diastereomers **12** and **13** were obtained in a ratio of 7/3 (41% yield) in favor of the (2*R*,4*R*) stereomer **12** (entry 2). The yield was further increased without modifying the selectivity when the reaction was carried out at room temperature under otherwise identical conditions (entry 3). The relative stereochemistry of **12** and **13** was determined by conversion to their known derivatives (vide infra).

The formation of **12** with a 2*R* absolute configuration as a major isomer was unexpected since the 2*S* configuration was anticipated on the basis of Corey's empirical model. To gain more information about this reaction, catalyst **15** derived from cinchonine was synthesized. Using **15** as catalyst was thought to modify the stereoselectivity since it is a pseudo-enantiomer of **14**. However, as can be seen (entry 4), the two diastereomers **12** and **13** were produced in essentially the same ratio as in the case of catalyst **14**, although the yield was lower. To further tune the structure of the catalysts, Maruoka's axially chiral C_2-symmetric spiro ammonium salt **16** was employed. As is seen, the same diastereoselectivity was once again observed (entry 6). Overall, these results might indicate that the asymmetric induction during the alkylation of **6** by iodide **7** was dictated by the substrate rather than by the catalyst, regardless of the structure and the chirality of the latter (matched or mismatched).[17,18] This consideration prompted us to examine the alkylation using achiral ammonium salt as phase transfer catalyst. Indeed, the same diastereoselectivity was observed when tetrabutylammonium bromide was used (TBAB) under otherwise identical conditions (entry 7). Alkylation performed in the absence

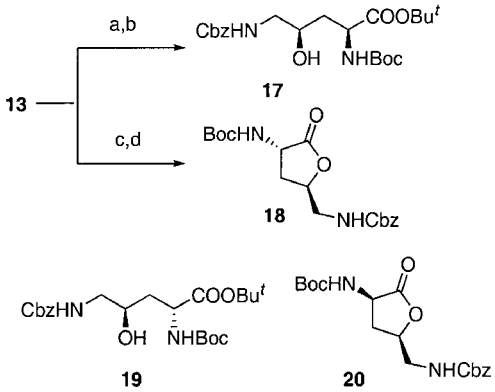
Table 1 Conditions for the Alkylation of **6** with Iodide **7**[a]

Entry	Catalyst	Base	Temp (°C)	Yield (%)[b]	Ratio (**12**/**13**)[c]
1	**14**	CsOH·H_2O	–50	0	
2	**14**	CsOH·H_2O	–50 then –20	41	7/3
3	**14**	CsOH·H_2O	–50 then r.t.	68	7/3
4	**15**	CsOH·H_2O	–50 then r.t.	32	7/3
5	**16**	NaOH	r.t.	0	
6	**16**	CsOH·H_2O	–50 then r.t.	55	7/3
7	TBAB[d]	CsOH·H_2O	–50 then r.t.	68	7/3
8	TBAHS[d]	NaOH	r.t.	0	
9	no	CsOH·H_2O	–50 then r.t.	40	7/3

[a] Concentration of substrate: 0.56 M in CH_2Cl_2.
[b] Isolated yield of **12** and **13** after acidic hydrolysis.
[c] Diastereomerical ratio was deduced from the ^{1}H NMR spectra. The diastereomers were separated by preparative TLC.
[d] Abbreviations: TBAB = tetrabutylammonium bromide; TBAHS = tetrabutylammonium hydrogensulfate.

of quaternary ammonium salt was found to give two diastereomers in a similar ratio, but with lower chemical yields (entry 9).[19]

The amino ester **12** and **13** are suitably functionalized for their use in the synthesis of biphenomycin and analogues thereof. Their relative stereochemistry was determined by subsequent transformation into the known compounds. Thus, selective hydrolysis of oxazolidine function of **13** with *p*-TsOH followed by *N*-Boc formation led to ester **17**.[8] On the other hand, treatment of **13** with 5 N HCl provided the γ-lactone that was *N*-protected to afford **18** in 72% yield.[20] Compound **12** was similarly converted into products **19** and **20** (Scheme 3).[21]



Scheme 3 *Reagents and Conditions*: a) catalytic *p*-TsOH, MeOH, r.t.; b) Boc_2O, K_2CO_3, H_2O–dioxane; 55% for two steps; c) 5 N HCl, $CHCl_3$, r.t., Boc_2O, K_2CO_3, H_2O–dioxane; 72% for two steps.

In conclusion, we have developed a new access to the protected (2*S*,4*R*)- and (2*S*,4*S*)-4-hydroxyornithine. Although the stereoselectivity of the alkylation step was only moderate, the present study did provide an interesting example of substrate-controlled stereoselective alkylation of glycine template in the presence of external chiral sources and urged the development of novel catalyst that can improve the double stereoselection.[22] Previously, low selectivity of Sharpless asymmetric dihydroxylation of olefins with stereocenters proximal to the reaction site has been observed that provided impetus for the development of new asymmetric process.[23]

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References

(1) (a) Ezaki, M.; Iwami, M.; Yamashita, M.; Hashimoto, S.; Komori, T.; Umehara, K.; Mine, Y.; Kohsaka, M.; Aoiki, H.; Imanaka, H. *J. Antibiot.* **1985**, *38*, 1453. (b) Uchida, I.; Shigematsu, N.; Ezaki, M.; Hashimoto, M. *J. Antibiot.* **1985**, *38*, 1462. (c) Uchida, I.; Ezaki, M.; Shigematsu, N.; Hashimoto, M. *J. Org. Chem.* **1985**, *50*, 1341. (d) Kannan, R.; Williams, D. H. *J. Org. Chem.* **1987**, *52*, 5435. (e) Hempel, J. C.; Brown, F. K. *J. Am. Chem. Soc.* **1989**, *111*, 7323. (f) Brown, F. K.; Hempel, J. C.; Dixon, J. S.; Amato, S.; Mueller, L.; Jeffs, P. W. *J. Am. Chem. Soc.* **1989**, *111*, 7328.

(2) (a) Pruess, D. L.; Kellett, M. *J. Antibiot.* **1983**, *36*, 208. (b) Evans, R. H. Jr.; Ax, H.; Jacoby, A.; Williams, T. H.; Jenkis, E.; Scannell, J. P. *J. Antibiot.* **1983**, *36*, 213. (c) Müller, J.-C.; Toome, V.; Pruess, D. L.; Blount, J. F.; Weigele, M. *J. Antibiot.* **1983**, *36*, 217.

(3) (a) Koiso, Y.; Natori, M.; Iwasaki, S.; Sato, S.; Sonoda, R.; Fujita, Y.; Yaegashi, H.; Sato, Z. *Tetrahedron Lett.* **1992**, *33*, 4157. (b) Koiso, Y.; Morisaki, N.; Yamashita, Y.; Mitsui, Y.; Shirai, R.; Hashimoto, Y.; Iwasaki, S. *J. Antibiot.* **1998**, *51*, 418. (c) Koiso, Y.; Li, Y.; Iwasaki, S.; Hanaoka, K.; Kobayashi, T.; Sonoda, R.; Fujita, Y.; Yaegashi, H.; Sato, Z. *J. Antibiot.* **1994**, *47*, 765. (d) Morisaki, N.; Mitsui, Y.; Yamashita, Y.; Koiso, Y.; Shirai, R.; Hashimoto, Y.; Iwasaki, S. *J. Antibiot.* **1998**, *51*, 423.

(4) (a) Talbot, G.; Gaudry, R.; Berlinguet, L. *Can. J. Chem.* **1956**, *34*, 911. (b) Mizusaki, K.; Makisumi, S. *Bull. Chem. Soc. Jpn.* **1981**, *54*, 470. (c) Hausler, J. *Liebigs Ann. Chem.* **1992**, 1231. (d) Jacob, M.; Roumestant, M. L.; Viallefont, P.; Martinez, J. *Synlett* **1997**, 691.

(5) (a) De Bernardo, S.; Tengi, J. P.; Sasso, G. J.; Weigele, M. *J. Org. Chem.* **1985**, *50*, 3457. (b) Girard, A.; Greck, C.; Genêt, J. P. *Tetrahedron Lett.* **1998**, *39*, 4259. (c) Mues, H.; Kazmaier, U. *Synthesis* **2001**, 487.

(6) Schmidt, U.; Meyer, R.; Leitenberger, V.; Stäbler, F.; Lieberknecht, A. *Synthesis* **1991**, 409.

(7) Jackson, R. F. W.; Rettie, A. B.; Wood, A.; Wythes, M. J. *J. Chem. Soc., Perkin Trans. 1* **1994**, 1719.

(8) Rudolph, J.; Hannig, F.; Theis, H.; Wischnat, R. *Org. Lett.* **2001**, *3*, 3153.

(9) Hutton, C. A.; White, J. M. *Tetrahedron Lett.* **1997**, *38*, 1643.

(10) Corey, E. J.; Xu, F.; Noe, M. C. *J. Am. Chem. Soc.* **1997**, *119*, 12414.

(11) Lygo, B.; Wainwright, P. G. *Tetrahedron Lett.* **1997**, *38*, 8595.

(12) (a) Ooi, T.; Kameda, M.; Maruoka, K. *J. Am. Chem. Soc.* **1999**, *121*, 6519. (b) Ooi, T.; Takeuchi, M.; Kameda, M.; Maruoka, K. *J. Am. Chem. Soc.* **2000**, *122*, 5228. (c) Kita, T.; Georgieva, A.; Hashimoto, Y.; Nakata, T.; Nagasawa, K. *Angew. Chem. Int. Ed.* **2002**, *41*, 2832.

(13) O'Donnell, M. J. *Aldrichimica Acta* **2001**, *34*, 3.

(14) (a) Lygo, B.; Crosby, J.; Peterson, J. A. *Tetrahedron Lett.* **1999**, *40*, 1385. (b) Lygo, B. *Tetrahedron Lett.* **1999**, *40*, 1389.

(15) Boisnard, S.; Carbonnelle, A.-C.; Zhu, J. *Org. Lett.* **2001**, *3*, 2061.

(16) Carbonnelle, A.-C.; Zhu, J. *Org. Lett.* **2000**, *2*, 3477.

(17) Substrate-directed transformation, see: Hoveyda, A. H.; Evans, D. A.; Fu, G. C. *Chem. Rev.* **1993**, *93*, 1307.

(18) Double asymmetric induction: (a) Horeau, A.; Kagan, H. B.; Vigneron, J. P. *Bull. Soc. Chim. Fr.* **1968**, 3795. (b) Masamune, S.; Choy, W.; Petersen, J. S.; Sita, L. R. *Angew. Chem., Int. Ed. Engl.* **1985**, *24*, 1.

(19) We thank one of the reviews for pointing out this control experiment. This result was not unexpected, but it didn't allow us to conclude whether the observed stereoselectivity in the presence of chiral ammonium salt was intrinsic to our substrate or was the consequence of the lack of the catalyst assistance.

(20) Estiarte, M. A.; Diez, A.; Rubiralta, M.; Jackson, R. F. W. *Tetrahedron* **2001**, *57*, 157.

(21) Compound **17**. R_f = 0.5 (eluent: ethyl acetate/heptane = 1/4); IR ($CHCl_3$) 3444, 3024, 2982, 1712, 1507 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$, 293 K) δ 1.44 (s, 9 H) Hz, 1.46 (s, 9 H), 1.65–1.82 (m, 1 H), 1.93–1.98 (m, 1 H), 3.08–3.17 (ddd, 1 H, J_1 = 13.3 Hz, J_2 = 7.8 Hz, J_3 = 6 Hz), 3.36–3.42 (m, 1 H), 3.91 (m, 1 H), 4.22 (m, 1 H), 5.10 (s, 2 H), 5.26 (m,1 H), 5,39 (m, 1 H), 7,35 (m, 5 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 28.0, 28.3, 38.0, 46.8, 52.1, 66.9, 69.1, 82.3, 82.5, 128.1, 128.2, 128.5, 136.4, 156, 157.1, 171.6; MS (ESI) *m/z* 461 (M + Na); $[\alpha]_D$ = +9.3 (*c* 0.9 $CHCl_3$). Compound **18**. R_f = 0.41 (eluant: ethyl acetate/heptane = 1/1); IR ($CHCl_3$) 3445, 1783, 1717 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$, 293 K) δ 1.45 (s, 1 H), 2.32 (m, 1 H), 2.46–2.53 (m, 1 H), 3.30 (dt, 1 H, J_1 = 15 Hz, J_2 = 6.3 Hz), 3.52–3.56 (m, 1 H), 4.23 (br d, 1 H, *J* = 6.8 Hz), 4.75 (br s, 1 H), 5.12–5.18 (m, 4 H), 7.36 (m, 5 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 28.2, 31.4, 44.6, 49.5, 67.1, 77.2, 80.7, 128.1, 128.2, 128.6, 136.2, 155.3, 156.7, 175.1; MS (EI) *m/z* 387 (M + Na), 403 (M + K); $[\alpha]_D$ = –18.1 (*c* 0.57 $CHCl_3$); $[\alpha]_D$ = –22.4 (*c* 0.5 $CHCl_3$).[20]

(22) Double stereoselection using matched and mismatched chiral ammonium catalyst in the alkylation of a Gly-L-Phe derivative has been documented very recently, see: (a) Ooi, T.; Tayama, E.; Maruoka, K. *Angew. Chem. Int. Ed.* **2003**, *42*, 579. (b) For an earlier example of an achiral quarternary ammonium salt catalyzed alkylation of a dipeptide, see: O'Donnell, M. J.; Zhou, C.; Scott, W. L. *J. Am. Chem. Soc.* **1996**, *118*, 6070.

(23) (a) Morikawa, K.; Sharpless, K. B. *Tetrahedron Lett.* **1993**, *34*, 5575. (b) Guzman-Perez, A.; Corey, E. J. *Tetrahedron Lett.* **1997**, *34*, 5941.