Stereoselective Synthesis of *trans*-(2*R*,3*S*)- and *cis*-(2*R*,3*R*)-Disubstituted Pyrrolidines

Young-Ah Kim, Sang-Mi Oh, and So-Yeop Han*

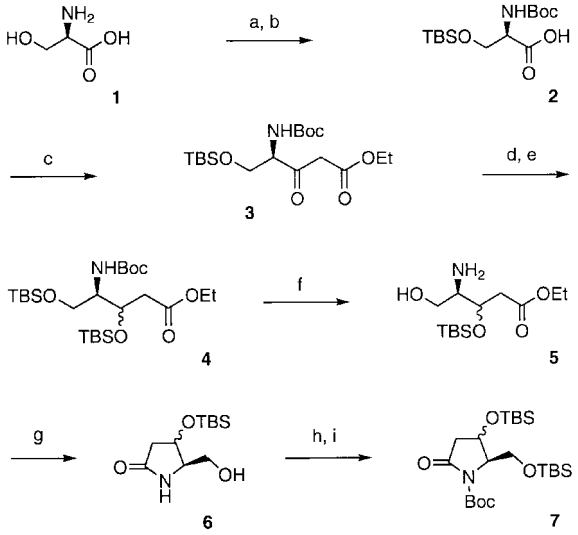
Department of Chemistry and Division of Molecular Life Sciences, Ewha Womans University, Seoul 120-750, Korea
Received January 5, 2001

Keywords : Pyrrolidines, *D*-Serine, BOP-Cl, β-Oxo ester, β-Keto ester.

Pyrrolidines, the 5-membered aza-heterocycles, are known to constitute major frameworks of alkaloids, which display diverse and potent biological activities.[1] Numerous strategies for the synthesis of pyrrolidines have been developed including 1,3-dipolar cycloaddition with azomethine ylide,[2] nucleophilic opening of aziridine,[3] internal displacement in aminocarbohydrate,[4] intramolecular cyclization involving radical,[5] acylnitrilium ion,[6] β-oxo ester[7] and organometallic complex.[8] Synthesis of 2,3-disubstituted pyrrolidines attracts much interest because they carry a basic nitrogen atom and a diol that potentially allow extension of the side chain or ring closure. We wish to report herein that *trans*-(2*R*,3*S*)- and *cis*-(2*R*,3*R*)-disubstituted pyrrolidines could be efficiently synthesized from *D*-serine by use of an appropriate coupling reagent.

trans-(2*R*,3*S*)-Disubstituted pyrrolidine was prepared as outlined in Scheme 1 and Scheme 2. *D*-Serine was treated with di-*tert*-butyl dicarbonate and *tert*-butyldimethylsilyl chloride sequentially to afforded compound **2** in a quantitative yield. Monosilylation on the hydroxyl group was achieved while the carboxylic acid was intact, and thus the cleavage of silyl ester was not necessary as previously reported.[7] This may be due to the enhanced nucleophilicity of hydroxyl oxygen by hydrogen bonding with DMF. β-Keto ester **3** was obtained by careful treatment of acid **2** with 1,1′-carbonyldiimidazole followed by ethyl lithioacetate in 61% yield. After reduction of β-keto ester with KBH_4 in ethanol,[9] the resulting diastereomeric mixture was protected to silyl ether **4** without separation. The 5-membered aza-heterocycle formation reaction was challenging to us. Since selective removal of the Boc group under various conditions was difficult, both Boc and the silyl group on the primary alcohol were removed using *B*-bromocatechol borane to afford **5** which was cyclized to **6** in ammonia-saturated methanol. The 2,3-disubstituted pyrrolidinone **7** was obtained after reprotection of compound **6** in low yield.

A much better approach toward intramolecular lactamization was studied as shown in Scheme 2. Hydrolysis of compound **4** was carried out using lithium hydroxide in aqueous ethanol. Intramolecular cyclization of the resulting acid with Boc-protected amine to form the five-membered lactam was first attempted with DPPA without success. The cyclization

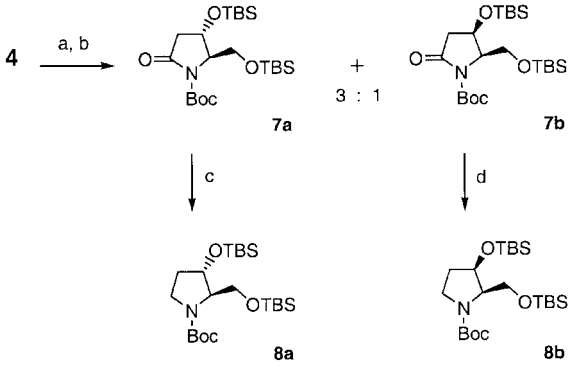


Scheme 1. (a) $(Boc)_2O$, NaOH, H_2O, 18 h; (b) TBDMS-Cl, imidazole, DMF, 18 h; (c) (1) 1,1'-carbonyldiimidazole, THF, 0 °C, 1.5 h; (2) LDA, EtOAc, THF, -78 °C, 61% from **2**; (d) KBH_4, EtOH, 2.5 h, 98%; (e) TBDMS-OTf, 2,6-lutidine, CH_2Cl_2, 0 °C, 10 min, 95%; (f) *B*-bromocatechol borane, CH_2Cl_2, 30 min; (g) dry NH_3/MeOH, 30 min, two steps 71%; (h) TBDMS-OTf, 2,6-lutidine, CH_2Cl_2, 0 °C, 10 min, 57%; (i) $(Boc)_2O$, DMAP, NEt_3, CH_2Cl_2, 30 min, 40%.

was achieved by using BOP-Cl as the coupling reagent to afford compounds **7a** and **7b** in a combined yield of 69%. These two diastereomers were chromatographically separable and the desired *trans* isomer **7a** was obtained as the major product (*trans* : *cis* = 3 : 1). The ^1H NMR analysis performed on the minor diastereomer **7b** permitted the assignment of the relative configuration of the stereocenter created, corresponding to the *cis* relationship of compound **7b**.[7a] Coupling constant ($J_{C2H\text{-}C3H}$) determined by the ^1H NMR decoupling experiment for the *trans* isomer **7a** is almost 0 Hz whereas the *cis* isomer **7b** is 8.0 Hz. Borane reduction of the *trans* isomer **7a** to afford compound **8a** required shorter reaction period and lower temperature compared with the *cis* isomer **7b** to afford compound **8b**. Thus, the two diastereomers **8a** and **8b** were synthesized in eight steps from *D*-serine.

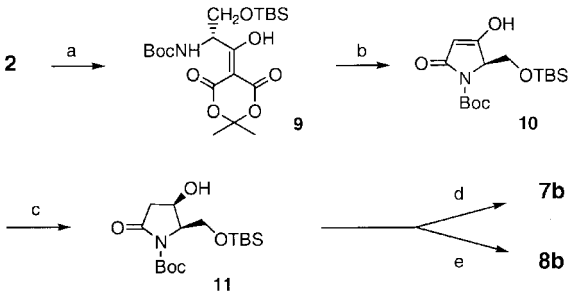
The synthetic route of *cis*-(2*R*,3*R*)-disubstituted pyrrolidine is shown in Scheme 3. This compound was prepared by using a modified procedure of Jouin and Joullié.[7] Conver-

*To whom correspondence should be addressed: Tel: +82-2-3277-2377, Fax: +82-2-3277-2384, e-mail: syhan@mm.ewha.ac.kr



Scheme 2. (a) LiOH·H_2O, H_2O/EtOH, 4 h, 70%; (b) BOP-Cl, DMAP, NEt_3, CH_2Cl_2, 0 °C, 6 h, 69%; (c) BH_3·SMe_2, THF, 65-70 °C, 10 min, 83%; (d) BH_3·SMe_2, THF, 70-75 °C, 30 min, 90%.

sion of compound **2** to the β-oxo ester **9** with less expensive BOP-Cl instead of isopropenyl chloroformate as the carboxyl activator required considerable experimentation. It is noteworthy to mention that the pre-activation of the acid **2** with BOP-Cl or longer reaction time caused appreciable racemization. The best result for the coupling reaction toward compound **9** was obtained under the condition using 1.2 equiv. of BOP-Cl, 1.2 equiv. of Meldrum's acid, 2.0 equiv. of Et_3N and 2.0 equiv. of DMAP for 3 h at 0 °C under argon atmosphere. Intramolecular cyclization to compound **10** at reflux followed by $NaBH_4$ reduction at the least hindered site produced optically pure **11** in 53% overall yield from *D*-serine. The *cis*-disposition of compound **11** as the single diastereomer was determined by the value of the ^{1}H NMR coupling constant ($J_{C2H\text{-}C3H}$ = 8.0 Hz, decoupling experiment) as well as the optical rotation value.[7a] Thus, the synthesis of pyrrolidinone **11** was carried out without purification of intermediates in a 5-step sequence from *D*-serine. Compound **11** was easily transformed to either disilylated pyrrolidinone **7b** or *cis*-(2*R*,3*R*)-disilylated pyrrolidine **8b**. The obscure splitting pattern in the ^{1}H NMR spectrum of compound **8b** implies the interconversion of *cis-trans* amide rotamers.[10] Therefore, we were able to optimize the reaction condition[7] utilizing readily available BOP-Cl as the coupling reagent. The products **7b** and **8b** provided the same physical



Scheme 3. (a) BOP-Cl, Meldrum's acid, DMAP, NEt_3, CH_2Cl_2, 0 °C, 3 h; (b) EtOAc reflux, 90-95 °C, 1.5 h; (c) $NaBH_4$, CH_2Cl_2, 0 °C, 5 h, overall 53% from **1**; (d) TBDMS-OTf, 2,6-lutidine, CH_2Cl_2, 0 °C, 10 min, 73%; (e) (1) BH_3·SMe_2, THF, 80 °C, 3 h, 88%; (2) TBDMS-OTf, 2,6-lutidine, CH_2Cl_2, 0 °C, 10 min, 94%.

properties with the minor products produced by β-keto ester pathway as shown in Scheme 2. From this result, we could confirm the stereochemistry of the major products to be *trans*-(2*R*,3*S*)-disubstituted pyrrolidines **7a** and **8a** in Scheme 2.

In conclusion, we were able to find the suitable conditions to synthesize *trans*-(2*R*,3*S*)- and *cis*-(2*R*,3*R*)-disubstituted pyrrolidines from *D*-serine which served as a chiral template. The pathway utilizing β-keto ester **3** afforded *trans*-(2*R*,3*S*)-disubstituted pyrrolidine **8a** as the major product in eight steps from *D*-serine and 17% overall yield and *cis*-(2*R*,3*R*)-disubstituted pyrrolidine **8b** as the minor product in 6% yield. The pathway utilizing β-oxo ester **9** resulted in *cis*-(2*R*,3*R*)-disubstituted pyrrolidine **8b** as a single diastereomer in seven steps and overall 44% yield. In both strategies utilizing β-keto ester and β-oxo ester, and BOP-Cl served as the common coupling reagent. These two diastereomers as well as synthetic intermediates were characterized by ^{1}H- and ^{13}C-NMR, IR, HRMS and/or elemental analysis.[11] There 2,3-disubstituted pyrrolidines could be widely applicable to the synthesis of natural products as their chiral intermediates.

Acknowledgment. Financial support from the Korea Research Foundation (1999-015-DI0072) and the Brain Korea 21 program (Y.-A. Kim) are gratefully acknowledged.

References

1. (a) Kato, A.; Adachi, I.; Miyauchi, M.; Ikeda, K.; Komae, T.; Kizu, H.; Kameda, Y.; Watson, A. A.; Nash, R. J.; Wormald, M. R.; Fleet, G. W. J.; Asano, N. *Carbohydr. Res.* **1999**, *316*, 95. (b) Shibano, M.; Kitagawa, S.; Kusano, G. *Chem. Pharm. Bull.* **1997**, *45*, 505. (c) Auvin, C.; Lezenven, F.; Blond, A.; Augeven-Bour, I.; Pousset, J.-L.; Bodo, B. *J. Nat. Prod.* **1996**, *59*, 676. (d) Cui, C.-B.; Kakeya, H.; Osada, H. *Tetrahedron* **1996**, *52*, 12651.
2. Fokas, D.; Ryan, W. J.; Casebler, D. S.; Coffen, D. L. *Tetrahedron Lett.* **1998**, *39*, 2235.
3. (a) Fort, S.; McCort, I.; Duréault, A.; Depezay, J.-C. *Synlett* **1997**, 1235. (b) Ungureanu, I.; Bologa, C.; Chayer, S.; Mann, A. *Tetrahedron Lett.* **1999**, *40*, 5315.
4. Han, S.-Y.; Liddell, P. A.; Joullié, M. M. *Synth. Commun.* **1988**, *18*, 275.
5. (a) Aurrecoechea, J. M.; Fernández, A.; Gorgojo, J. M.; Saornil, C. *Tetrahedron* **1999**, *55*, 7345. (b) Gilbert, B. C.; Kalz, W.; Lindsay, C. I.; McGrail, P. T.; Parsons, A. F.; Whittaker, T. E. *Tetrahedron Lett.* **1999**, *40*, 6095. (c) Bachi, M. D.; Melman, A. *Pure & Appl. Chem.* **1998**, *70*, 259.
6. Kercher, T.; Livinghouse, T. *J. Org. Chem.* **1997**, *62*, 805.
7. (a) Ewing, W. R.; Joullié, M. M. *Heterocycles* **1988**, *27*, 2843. (b) Jouin, P.; Castro, B.; Nisato, D. *J. Chem. Soc., Perkin I* **1987**, 1177.
8. (a) Daley, V.; d'Angelo, J.; Cavé, C.; Mahuteau, J.; Chiaroni, A.; Riche, C. *Tetrahedron Lett.* **1999**, *40*, 1657. (b) Arredondo, V. M.; Tian, S.; McDonald, F. E.; Marks, T. J. *J. Am. Chem. Soc.* **1999**, *121*, 3633. (c) Sato, Y.; Saito, N.; Mori, M. *Tetrahedron* **1998**, *54*, 1153. (d) Okamoto, S.; Iwakubo, M.; Kobayashi, K.; Sato, F. *J. Am. Chem. Soc.*

1997, *119*, 6984.
9. Harris, B. D.; Joullié, M. M. *Tetrahedron* **1988**, *44*, 3489.
10. Nakatsuka, M.; Ragan, J. A.; Sammakia, T.; Smith, D. B.; Uehling, D. E.; Schreiber, S. L. *J. Am. Chem. Soc.* **1990**, *112*, 5583.
11. The spectral and analytical data of representative compounds are shown as follows. **3**: $[\alpha]^{25}_{D}$ = -31 (*c* 0.84, $CHCl_3$); ^{1}H NMR (250 MHz, $CDCl_3$) δ 0.02 (6H, s), 0.84 (9H, s), 1.25 (3H, t), 1.42 (9H, s), 3.57 (2H, d), 3.79 (1H, dd, J_1 = 4.4 Hz, J_2 = 10.4 Hz), 4.05 (1H, dd, J_1 = 3.1 Hz, J_2 = 10.4 Hz), 4.17 (2H, q), 4.38 (1H, t), 5.41 (1H, d); ^{13}C NMR (63 MHz, $CDCl_3$) δ -5.64, 14.06, 18.15, 25.73, 28.29, 47.12, 61.27, 61.39, 63.12, 80.08, 155.24, 166.74, 201.09; HRMS (EI) *m/z* calcd for $C_{14}H_{26}NO_5Si$ (M-$OCMe_3$) 316.1581, found 316.1580. **7a**: mp 75-76 ^{o}C; $[\alpha]^{25}_{D}$ = -30 (*c* 0.98, $CHCl_3$); ^{1}H NMR (250 MHz, $CDCl_3$) δ 0.00 (6H, d, *J* = 4.0 Hz), 0.04 (6H, d, *J* = 1.4 Hz), 0.83 (18H, s), 1.50 (9H, s), 2.26 (1H, d, *J* = 17.6 Hz), 2.81 (1H, dd, J_1 = 17.6 Hz, J_2 = 5.7 Hz), 3.75 (2H, m), 3.92 (1H, m), 4.25 (1H, d, *J* = 5.7 Hz); ^{13}C NMR (63 MHz, $CDCl_3$) δ -5.66, -4.77, 17.91, 18.13, 25.64, 25.77, 28.03, 42.84, 62.07, 67.60, 68.75, 82.79, 150.06, 173.21; Anal. Calcd for $C_{22}H_{45}NO_5Si_2$: C, 57.47; H, 9.87; N, 3.05; Found: C, 57.62; H, 9.98; N, 2.74. **8a**: $[\alpha]^{25}_{D}$ = -14 (*c* 0.69, $CHCl_3$); ^{1}H NMR (250 MHz, $CDCl_3$) δ 0.01 (6H, s), 0.04 (6H, s), 0.84 (9H, s), 0.86 (9H, s), 1.43 (9H, s), 1.70 (1H, m), 1.96 (1H, m), 3.49 (5H, m), 4.34 (1H, m); ^{13}C NMR (63 MHz, $CDCl_3$) δ -5.44, -4.73, 17.98, 18.19, 25.76, 25.86, 28.54, 31.91, 33.01, 44.71, 45.21, 61.81, 62.58, 67.60, 67.77, 73.54, 73.89, 78.88, 79.22, 154.74, 154.91 (signals from rotamer shown in NMR); HRMS (CI) *m/z* calcd for $C_{22}H_{48}NO_4Si_2$ (MH^+) 446.3123, found 446.3121.