Efficient Synthesis of *N*-Benzyloxycarbonyl- and *N*-*tert*-Butoxycarbonyl-(*S*)-Isoserine and their Derivatives

Ryszard Andruszkiewicz,* Monika Wyszogrodzka

Department of Pharmaceutical Technology and Biochemistry, Gdańsk University of Technology, 80-952 Gdańsk, Poland
Fax +48(58)3471144; E-mail: ryszarda@chem.pg.gda.pl

Received 23 September 2002

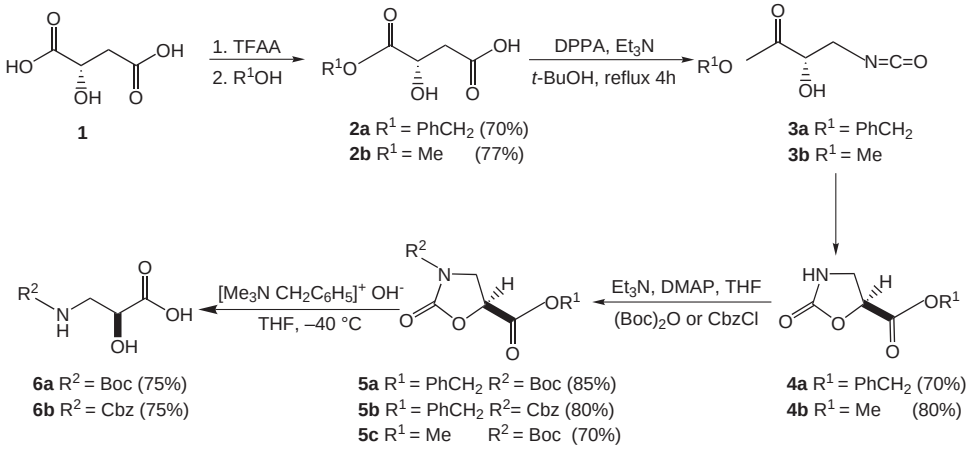
Abstract: A mild and efficient synthesis of N-protected (*S*)-isoserine from (*S*)-malic acid monoester via an oxazolidin-2-one is described.

Key words: amino acids, asymmetric synthesis, oxazolidin-2-ones, ring opening, protecting groups

(*S*)-Isoserine, i.e. (*S*)-3-amino-2-hydroxypropanoic acid is an amino acid component of biologically active peptides produced by the *Bacillus brevis* V_m[4] strain: edeine antibiotics and tatumine.[1] It has also been found in a group of keramamides F-K[2], cytotoxic peptides isolated from *Theonella* sp sponges. These marine organisms are also known to produce a variety of cyclic glycopeptides including theopalauamide,[3] theonellamides A-F,[4] and theonegramide,[5] all containing (*S*)-isoserine. This non-protein amino acid has also been applied in a semisynthetic aminoglycoside antibiotic derivatives (e.g. gentamycin and butyrosin).[6] Recently, polyamides containing (*S*)-isoserine have been used in DNA recognition studies.[7] Several practical methods for the synthesis of optically active isoserines using malic acid, substituted imidazolin-2-ones, or chiral cyanohydrins as starting materials have been reported.[8]

In connection with our program centered on edeine antibiotic analogues[9] and glucosamine-6-phosphate synthase inhibitors[10] we needed an N-protected (*S*)-isoserine and its constrained analogue to be built into peptide conjugates or to serve as a chiral synthon for further synthesis. Therefore, we report here a simple synthetic approach to N-protected isoserine and its cyclic derivative, which starts from cheap starting materials, proceeds in good yields, and allows easy scale-up to multigram scale.

The preparation of the title compounds was carried out from enantiomerically pure 1-monoesters of (*S*)-malic acid, which are easily accessible from (*S*)-malic acid **1** by adopting a literature reported procedure,[11] in which treatment of malic acid with trifluoroacetic acid anhydride furnished the corresponding trifluoroacetate of (*S*)-malic anhydride (Scheme 1). Regioselective opening of the anhydride with one equivalent of anhydrous benzyl or methyl alcohol provided optically active 1-monoesters. The 1-monoesters **2a** and **2b** were then converted to the corresponding oxazolidin-2-ones **4a** and **4b**. Oxazolidin-2-ones were effectively formed by refluxing **2a** and **2b** with diphenylphosphoryl azide (DPPA) and triethylamine (Et_3N) in *t*-BuOH. The isocyanates **3a** and **3b** transiently formed underwent internal cyclization to **4a** and **4b** with good yields.[12] However, due to the good solubility of **4b** in aqueous phase, the extraction process was ineffective, therefore, pure **4b** was obtained by using column chromatography. For further synthetic use, there is no need to use column chromatography and compound **4b** may also be used without isolation for the next reaction. Owing to the



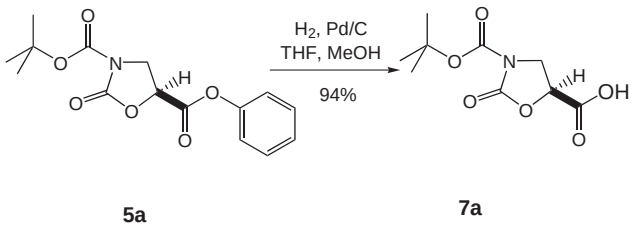
Scheme 1

Synlett 2002, No. 12, Print: 02 12 2002.
Art Id.1437-2096,E;2002,0,12,2101,2103,ftx,en;G27902st.pdf.

ISSN 0936-5214

low reactivity of the nitrogen atom in a heterocyclic ring, the nitrogen in **4a** was proteced using di-*tert*-butyl dicarbonate $(Boc)_2O$, Et_3N and a catalytic amount of DMAP in THF at –20 °C,[13] thus obtaining the desired *N*-Boc derivative **5a** in good yield. Under the same reaction conditions, compound **5c** was obtained from **4b**. On the other hand, the reaction of **4a** with an excess of benzyloxycarbonyl chloride (Cbz-Cl) in a THF/Et_3N solution at –20 °C and DMAP furnished the *N*-Cbz derivative **5b**.[14] The critical ring opening in the protected oxazolidin-2-ones **5a**, **5b** and **5c** was performed using benzyltrimethylammonium hydroxide in THF at –40 °C.[15] In all cases, hydrolysis of the esters was also observed. The low temperature conditions for base induced opening of the oxazolidin-2-ones were essential to avoid the formation of undesired by-products. We also found that the treatment of protected oxazolidin-2-ones with NaOH or LiOH in THF solutions, even at low temperature gave rise to N-deprotected and other non identified products. Hydrolysis of **5a** and **5c** yielded the same products **6a** with the same melting point and optical rotation.

Finally, catalytic hydrogenation (Scheme 2) of **5a** in methyl alcohol afforded the Boc protected acid **7a** in good yield.[16] Hydrogenolysis did not damage the heterocyclic ring.



5a **7a**

Scheme 2

In conclusion, we have developed a new, mild and efficient route to N-protected isoserines and isoserine cyclic derivative from 1-monoesters of (*S*)-malic acid via oxazolidin-2-ones.

Acknowledgment

The authors are indebted to the Faculty of Chemistry, Gdańsk University of Technology for financial support.

References

(1) (a) Hettinger, T. P.; Craig, L. C. *Biochemistry* **1970**, *9*, 1224. (b) Heaney-Kieras, J.; Kurylo-Borowska, Z. *J. Antibiot.* **1980**, *33*, 359.

(2) (a) Sowinski, J. F.; Toogood, P. L. *Tetrahedron Lett.* **1995**, *68*, 67. (b) Kobayashi, J.; Itagaki, F.; Shigemori, I.; Takao, T.; Shimonishi, Y. *Tetrahedron* **1995**, *51*, 2525. (c) Sowinski, J. F.; Toogood, P. L. *Chem. Commun.* **1999**, 981. (d) Uemoto, H.; Yahiro, Y.; Shigemori, H.; Tsuda, M.; Takao, T.; Shimonishi, Y.; Kobayashi, J. *Tetrahedron* **1998**, *54*, 6719. (e) Dohren, H.; von Kleinkauf, H. *Biotechnology* **1999-2001**, *7*, 313.

(3) (a) Schmidt, E. W.; Bewley, C. A.; Faulkner, D. J. *J. Org. Chem.* **1998**, *63*, 1254. (b) Moore, B. S. *Nat. Prod. Rep.* **1999**, *16*, 653.

(4) (a) Matsunaga, S.; Fusetani, N. *J. Org. Chem.* **1995**, *60*, 1177. (b) Taylor, C. M. *Tetrahedron* **1998**, *54*, 11317.

(5) Bewley, C.; Faulkner, D. J. *J. Org. Chem.* **1994**, *59*, 4849.

(6) (a) Wright, J. J.; Cooper, A.; Daniels, P. J. L.; Nagabhushan, T. L.; Rane, D.; Turner, W. N.; Weinstein, J. *J. Antibiot.* **1976**, *29*, 714. (b) Haskell, T. H.; Rodebaugh, R.; Plessas, N.; Watson, D.; Westland, R. D. *Carbohydr. Res.* **1973**, *28*, 263.

(7) Floreancig, P. E.; Swalley, S. E.; Trauger, J. W.; Dervan, P. B. *J. Am. Chem. Soc.* **2000**, *122*, 6342.

(8) For a review see: Andruszkiewicz, R. *Pol. J. Chem.* **1998**, *72*, 1.

(9) (a) Andruszkiewicz, R.; Walkowiak, A. *Org. Prep. Proc. Int.* **2001**, *33*, 379. (b) Czajgucki, Z.; Sowinski, P.; Andruszkiewicz, R. *Amino Acids* **2002**, in press.

(10) (a) Andruszkiewicz, R.; Milewski, S.; Borowski, E. *J. Enzyme Inhib.* **1995**, *9*, 123. (b) Andruszkiewicz, R.; Jedrzejczak, R.; Zieniawa, T.; Wojciechowski, M.; Borowski, E. *J. Enzyme Inhib.* **2000**, *15*, 429.

(11) Cammas, S.; Renard, I.; Boutault, K.; Guerin, P. *Tetrahedron: Asymmetry* **1993**, *4*, 1925.

(12) **Typical Procedure for the Preparation of 4a and 4b:** The appropriate substrate **2a**,**b** (5 mmol), and DPPA (1.18 mL, 5.5 mmol) were dissolved in *t*-BuOH (20 mL). The reaction flask was flushed with argon, and Et_3N (0.75 mL, 5.5 mmol) was added. The reaction mixture was refluxed for 4 h and cooled to r.t. The solvent was removed under reduced pressure, the residue dissolved in EtOAc (50 mL). In the case of **4a**, the solution was washed with sat. $NaHCO_3$ solution, water and finally dried over anhyd $MgSO_4$. After evaporation of the solvent, the solid residue was crystallized from EtOAc and hexane to yield **4a** (0.77 g, 70%). Mp: 128–129 °C; $[\alpha]_D$ +10.0 (*c* 1, EtOAc). ^{1}H NMR (200 MHz, $CDCl_3$): δ = 3.66–3,74 (dd, $J_{4a,4b}$ = 9.5 Hz, $J_{4a,5a}$ = 5.6 Hz, 1 H CH*CH*$_2$, 4H$_a$), 3.85–3.95 (dd, $J_{4b,4a}$ = 9.5 Hz, 1 H, CH*CH*$_2$, 4 H$_b$), 5.05–5.10 (dd, $J_{5a,4b}$ = 9.5 Hz, $J_{5a,4a}$ = 5.6 Hz, 1 H, *CH*CH$_2$, 5 H$_a$), 5.28 (s, 2 H, *CH*$_2$C$_6$H$_5$), 5.9 (br s, 1 H, *NH*), 7.40(s, 5 H, *C*$_6$*H*$_5$). Anal. Calcd for $C_{11}H_{11}NO_4$: C, 59.73; H, 5.01; N, 6.33. Found: C, 59.58; H, 5.12; N, 6.38. In the case of **4b**, after evaporation of the solvent, the product was purified by column chromatography (silica gel, hexane–ethyl acetate 2:3) furnishing **4b** (0.58g, 80%) which was crystallized from ethyl acetate and hexane. Mp: 95–97 °C; $[\alpha]_D$ +20.1 (*c* 1, EtOAc). ^{1}H NMR (200 MHz, $CDCl_3$): δ = 3.65–3.75(dd, $J_{4a,4b}$ = 9.6 Hz, $J_{4a,5a}$ = 5.5 Hz, 1 H, CH*CH*$_2$, 4 H$_a$), 3.85 (s, 3 H, *CH*$_3$), 3.86–3.96 (dd, $J_{4a,4b}$ = 9.6, $J_{4b,5a}$ = 5.5 Hz, 1 H, CH*CH*$_2$, 4 H$_b$), 5.01–5.09 (dd, $J_{5a,4b}$ = 9.6 Hz, $J_{5a,4b}$ = 5.5 Hz, 1 H, *CH*CH$_2$, 5 H$_a$), 6.24 (br s, 1 H, *NH*). Anal. Calcd for $C_5H_7NO_4$: C, 41.38; H, 4.86; N, 9.65. Found: C, 41.22; H, 4.74; N, 9.60.

(13) **Typical Procedure, 4a,b to 5a–5c:** Compound **4a** or **4b** (9 mmol), DMAP (25 mg) and Et_3N (1.5 mL, 11 mmol) were dissolved in dry THF (25 mL) and cooled in an ice bath. A solution of $(Boc)_2O$ (2.05 g, 9.4 mmol) in THF (8 mL) was added to a stirred reaction mixture over 20 min. The temperature of the reaction was kept between 5 °C and 10 °C overnight. Then, equimolar amounts of $NaHSO_4$ (1.32 g, 11 mmol) in water (10 mL) were added. After evaporation of the solvent under reduced pressure, the white suspension was dissolved in EtOAc (50 mL), and the solution was washed with dilute $NaHSO_4$ solution, water and finally dried ($MgSO_4$) and evaporated. The solid was crystallized from diethyl ethyl ether and hexane to give **5a** (2.5 g, 85%). Mp: 130–131 °C; $[\alpha]_D$ +24.0 (*c* 1, EtOAc). ^{1}H NMR (200 MHz,

$CDCl_3$): δ = 1.56 [s, 9 H (*CH_3*)C],. 4.00–4.07 (dd, $J_{4a,4b}$ = 10.7, $J_{4a,5a}$ = 5.5 Hz, 1 H, CH*CH_2*, 4 H_a), 4.14–4.24 (dd, $J_{5a,4b}$ = 9.5 Hz, $J_{4a,4b}$ = 10.7 Hz, 1 H, CH*CH_2*, 4 H_b), 4.91–4.99 (dd, $J_{5a,4b}$ = 9.5 Hz, $J_{5a,4a}$ = 5.5 Hz, 1 H, *CH*CH_2), 5.29 (s, 2 H, *CH_2*C_6H_5), 7.40 (s, 5 H, *C_6H_5*). Anal. Calcd for $C_{16}H_{19}NO_6$: C, 59.18; H, 5.96; N, 4.36. Found: C, 59.34; H, 5.92; N, 4.22. In the same manner compound **5c** was obtained (1.54 g, 70%). Mp: 76–78 °C; $[\alpha]_D$ +36.8 (*c* 2.5, MeOH). ^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.55 [s, 9 H (*CH_3*)C], 3.87 (s, 3 H, CH_3), 4.00–4.08 (dd, $J_{4a,4b}$ = 10.7, $J_{4a,5a}$ = 5.5 Hz, 1 H, CH*CH_2*, 4H_a), 4.14–4.25 (dd, $J_{5a,4b}$ = 9.5 Hz, $J_{4a,4b}$ = 10.7 Hz, 1 H, CH*CH_2*, 4 H_b), 4.89–4.97 (dd, $J_{5a,4b}$ = 9.5 Hz, $J_{5a,4a}$ = 5.5 Hz, 1 H, *CH*CH_2). Anal. Calcd for $C_{10}H_{15}NO_6$: C, 48.98; H, 6.17; N, 5.71. Found: C, 49.17; H, 6.22; N, 5.58.

(14) **Synthesis of 5b:** (5*S*)-5-Benzyloxycarbonyl-2-oxazolidinone **4a** (1.99 g, 9 mmol) was dissolved in THF (30 mL) and Et_3N (10 mL). The reaction mixture was cooled to –20 °C. A solution of benzyl chloroformate (2.6 mL, 18 mmol) in THF (3.3 mL) was slowly added over 20 min. The stirred reaction mixture was then kept at –10 °C overnight. The reaction mixture was quickly neutralized with a stoichiometric amount of cold 10% aq solution of $NaHSO_4$ and extracted with EtOAc (2 × 50 mL). The extracts were washed with water, dried ($MgSO_4$) and evaporated. The solid residue was dissolved in a small volume of hot EtOAc and diluted with a large volume of diethyl ether. Crystals were collected to give **5b** (2.4g, 80%). Mp: 112–114 °C; $[\alpha]_D$ +24.0 (*c* 2.5, EtOAc). ^{1}H NMR (200 MHz, $CDCl_3$): δ = 4.04–4.12 (dd, $J_{4a,4b}$ = 10.6, $J_{4a,5a}$ = 5.5 Hz, 1 H, CH*CH_2*, 4H_a), 4.18–4.28 (dd, $J_{5a,4b}$ = 9.5 Hz, $J_{4a,4b}$ = 10.6 Hz, 1 H, CH*CH_2*, 4 H_b), 4.93–5.01 (dd, $J_{5a,4b}$ = 9.5 Hz, $J_{5a,4a}$ = 5.5 Hz, 1 H, *CH*CH_2), 5.27 (s, 2 H, *CH_2*C_6H_5-benzyl ester), 5.31 (s, 2 H, *CH_2*C_6H_5-benzyloxycarbonyl group), 7.35–7.45 (br s, 10 H, 2 × *C_6H_5*). Anal. Calcd for $C_{19}H_{17}NO_6$: C, 64.22; H, 4.82; N, 3.94. Found: C, 64.34; H, 4.68; N, 3.88.

(15) (a) **Representative Experimental Procedure:** Compound **5a**–**5c** (5 mmol) was quickly dissolved in dry THF (50 mL) and cooled under argon to –40 °C. Benzyltrimethylammonium hydroxide (5.5 mL of 40% solution in methanol, 10.5 mmol) was added over 20 min to the solution of **5a**–**5c** and stirred for an additional 1 h. HOAc (1.1 mL) and water (2.5 mL) were then added and the reaction mixture was warmed to r.t. and the solvent was evaporated under reduced pressure. The residue was extracted with EtOAc (2 × 50 mL). The extracts were washed, dried over $MgSO_4$ and evaporated. The solid residue was crystallized from a mixture of EtOAc and hexane to yield **6a** (0.77 g, 75%). Mp: 93–94 °C; $[\alpha]_D$ +6.4 (*c* 2.5, MeOH). Similarily, **6b** was also obtained (0.89 g, 75%). Mp: 117–119 °C; $[\alpha]_D$ +3.2 (*c* 2.5, MeOH). Physical and spectral data for **6a** and **6b** are in agreement with literature values, see ref.[15b] (b) Burger, K.; Windeisen, E.; Pires, R. *J. Org. Chem.* **1995**, *60*, 7641.

(16) **Preparation of 7a:** Compound **5a** (0.64 g, 2 mmol) was dissolved in a mixture of THF (10 mL) and MeOH (15 mL) and palladium on activated carbon (5%, 50 mg) was added. The reaction flask was flushed with hydrogen and the hydrogenation was performed at atmospheric pressure for 1 h at r.t. The catalyst was filtered off and the solvents were evaporated. The residue was crystallized from a mixture of EtOAc and hexane to give **7a** (0.43g, 94%). Mp: 99–100 °C; $[\alpha]_D$ +28.2 (*c* 1, MeOH). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.56 [s, 9 H (*CH_3*)C],. 4.08–4.11 (dd, $J_{4a,4b}$ = 10.7, $J_{4a,5a}$ = 5.4 Hz, 1 H, CH*CH_2*, 4 H_a), 4.21–4.25 (dd, $J_{5a,4b}$ = 9.8 Hz, $J_{4a,4b}$ = 10.7 Hz, 1 H, CH*CH_2*, 4 H_b), 4.95–4.98 (dd, $J_{5a,4b}$ = 9.8 Hz, $J_{5a,4a}$ = 5.4 Hz, 1 H, *CH*CH_2). Anal. Calcd for $C_9H_{13}NO_6$: C, 46.75; H, 5.67; N, 6.06. Found: C, 46.78; H, 5.52; N, 5.98.