Orthogonally Protected, Enantiopure *syn*-2-Amino-1,3,4-butanetriol: A General Building Block for *syn*-Amino Alcohols

Soon Ji Kwon and Soo Y. Ko*

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

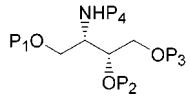
sooyko@mm.ewha.ac.kr

Received July 3, 2001

Amino alcohols are often found in various bioactive compounds, and their stereoselective synthesis is of interest.[1] Our interest in this area has led to the discovery of cyclic iminocarbonate rearrangement (CIR).[2] Coupled with Sharpless's asymmetric dihydroxylation (AD), this process affords *syn*-amino alcohols in high enantiomeric purity, a unique and quite useful feature in light that the AD provides only syn diastereomers of vicinal diols, from which *anti*-amino alcohols are perhaps more easily derived.[3] Also, the regiochemistry of the rearrangement is complementary to that of Sharpless's asymmetric aminohydroxylation (AA) process in that, with β-alkyl-substituted α,β-dihydroxy ester substrates, α-amino-β-hydroxy compounds are obtained.[4] With β-aryl compounds, on the other hand, the rearrangement conditions have been devised so as to afford either α-amino-β-hydroxy or β-amino-α-hydroxy regioisomers selectively.[5] The efficacy of this flexible regiocontrol has been demonstrated in the syntheses of several natural products.[6]

Despite this versatility in regiocontrol, the synthetic utility of CIR is still limited to such targets as ones having either carbonyl- or aryl-activating groups next to the nitrogen function. When one bears in mind the AA's own limitations in regiochemical control, a *general* solution for the synthesis of *syn*-amino alcohols seems still lacking.[7]

We propose protected *syn*-2-amino-1,3,4-butanetriol (compound type **1**) to be a general building block for *syn*-amino alcohols. The protecting groups should be orthogonal with one another so that regioselective transformations to desired target molecules may be possible. An earlier report for compound type **1** employed a single, cyclic ketal-type protecting group for both C-1 and C-4 hydroxyl groups, wherein the C-1/C-4 regioselection was achieved via a clever protecting group migration.[8] We describe herein a selective synthesis of compound type **1**.



1

Results and Discussion

Our synthesis of the compound type **1** starts from a tartrate diester **2** (Scheme 1). The availability of both enantiomers of the ubiquitous chiral building block obviates the use of AD or any other asymmetric reaction.[9] The *syn*-amino alcohol functionality was then introduced via our CIR as previously reported (84%). Due to the C_2-symmetric nature of the substrate, the issue of regioselection was nonexistent in this step. With the *syn*-amino alcohol functionality in hand in compound **3**, the next task was to differentiate the two ester groups. This was achieved via chelate-controlled regioselective reduction. Thus, the *N*-benzoyl group was removed ($BF_3{\cdot}OEt_2$, *i*-PrOH, 89%), providing an anchoring site for a Lewis acid. The resulting oxazolidinone **4** was then treated with $BF_3{\cdot}OEt_2$ followed by $NaBH_4$. A clean reduction took place at the ester function adjacent to the nitrogen (**5**, 92%); no regioisomeric product was observed.[10] To the desired compound type **1**, the remaining steps were now straightforward functional group transformations. Thus, the hydroxyl group of **5** was benzyl-protected under acidic conditions (90%);[11] the remaining ester function of **6** was reduced ($NaBH_4$, 93%); the resulting C-4 hydroxyl group of **7** was silyl-protected (TBDMS-Cl, 82%). To complete the job, the oxazolidinone ring in **8** needed to be cleaved to unveil the desired *syn*-amino alcohol functions, which then needed to be independently protected by more amenable protecting groups. These multiple tasks were achieved efficiently in a two-step sequence. *N*-Boc protection was performed on **8** (94%) in order to render the oxazolidinone ring more easily cleavable. Treatment of **9** with PhLi (2 equiv, −78 °C) resulted in a cleavage of the five-membered ring (78%) to afford the *N*-Boc-*O(3)*-benzoyl-protected amino alcohol **1a**,[12] whose O(1),O(4) groups have already been protected as benzyl and TBDMS, respectively.

(1) (a) Juaristi, E. *Enantioselective Synthesis of* α*-Amino Acids*; Wiley-VCH: New York, 1997 and references therein. (b) Cole, D. C. *Tetrahedron* **1994**, *50*, 9517. (c) Juraristi, E.; Quintana, D.; Escalante, J. *Aldrichim. Acta* **1994**, *27*, 3. (d) Cardillo, G.; Tomasini, C. *Chem. Soc. Rev*. **1996**, *25*, 117.

(2) Cho, G. Y.; Ko, S. Y. *J. Org. Chem*. **1999**, *64*, 8745.

(3) (a) Kolb, H. C.; VanNieuwenhze, M. S.; Sharpless, K. B. *Chem. Rev*. **1994**, *94*, 2483. (b) Wang, L.; Sharpless, K. B. *J. Am. Chem. Soc.* **1992**, *114*, 7568. (c) Ko, S. Y.; Malik, M.; Dickinson, A. F. *J. Org. Chem*. **1994**, *59*, 2570.

(4) (a) Reiser, O. *Angew. Chem., Int. Ed. Engl*. **1996**, *35*, 1308. (b) O'Brien, P. *Angew. Chem., Int. Ed. Engl*. **1999**, *38*, 326, and references therein.

(5) Cho, G. Y.; Park, J. N.; Ko, S. Y. *Tetrahedron Lett*. **2000**, *41*, 1789.

(6) (a) Park, J. N.; Ko, S. Y.; Koh, H. Y. *Tetrahedron Lett*. **2000**, *41*, 5553. (b) Cho, G. Y.; An, K. M.; Ko, S. Y. *Bull. Korean Chem. Soc.* **2001**, *22*, 432.

(7) (a) Tao, B.; Schlingloff, G.; Sharpless, K. B. *Tetrahedron Lett*. **1998**, *39*, 2507. (b) Morgan, A. J.; Masse, D. E.; Panek, J. *Org. Lett*. **1999**, *1*, 1949.

(8) (a) Inaba, T.; Yamada, Y.; Abe, H.; Sagawa, S.; Cho, H. *J. Org. Chem*. **2000**, *65*, 1623. (b) Sagawa, S.; Abe, H.; Hase, Y.; Inaba, T. *J. Org. Chem*. **1999**, *64*, 4962. (c) Inaba, T.; Birchler, A. G.; Yamada, Y.; Sagawa, S.; Yokota, K.; Ando, K.; Uchida I. *J. Org. Chem*. **1998**, *63*, 7582.

(9) (a) Gawronski, J.; Gawronska, K. *Tartaric and Malic acids in Synthesis*; John Wiley & Sons: 1999. (b) Seebach, D.; Hungerbühler, E. In *Modern Synthetic Methods*; Scheffold, E., Ed.; Frankfurt-Aarau: Otto Salle-Sauerländer, 1980; Vol. 2, p 91.

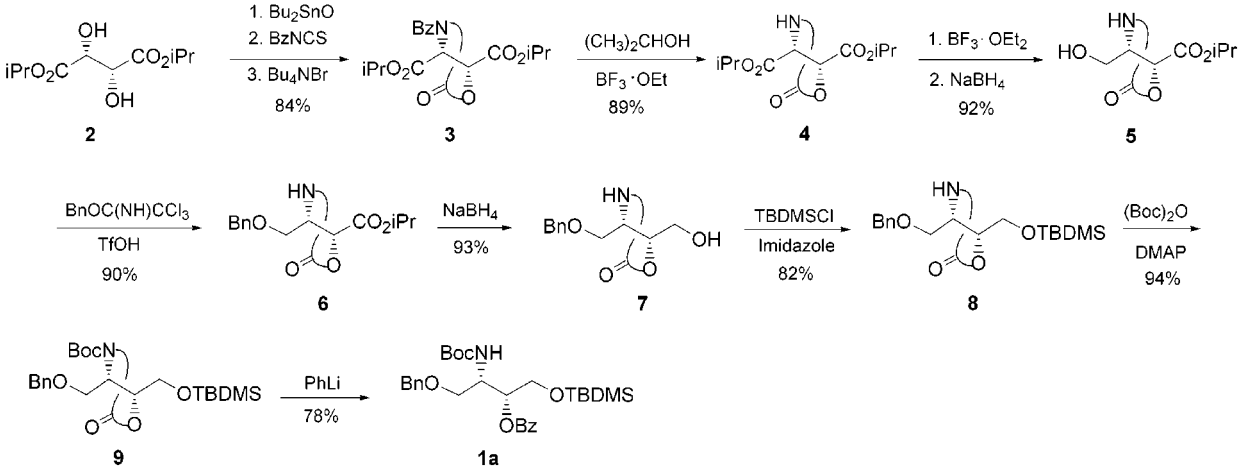
(10) For related examples of chelate-controlled regioselective reductions, see: (a) Claffey, M. M.; Hayes, C. J.; Heathcock, C. H. *J. Org. Chem*. **1999**, *64*, 8267. (b) Saito, S.; Ishikawa, T.; Kuroda, A.; Koga, K.; Moriwake, T. *Tetrahedron* **1992**, *48*, 4067.

(11) (a) Eckenberg, P.; Groth, U.; Huhn, T.; Richter, N. Schmeck, C. *Tetraheron* **1993**, *49*, 1619. (b) Wessel, H. P.; Lversen, T.; Bundle, D. R. *J. Chem. Soc., Perkin Trans. 1* **1985**, 2247.

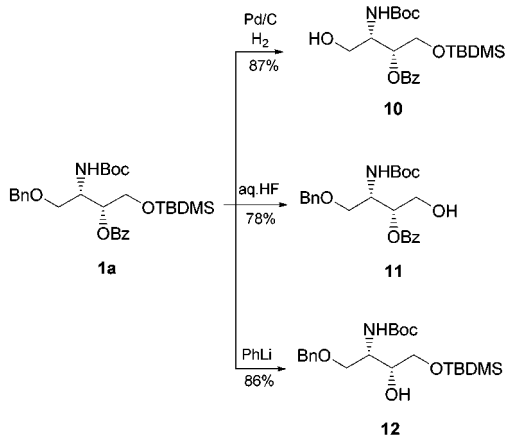
(12) Nicolaou, K. C.; Renaud, J.; Nantermet, P. G.; Couladouros, E. A.; Guy, R. K.; Wrasidlo, W. *J. Am. Chem. Soc.* **1995**, *117*, 2409.

10.1021/jo015886j CCC: $20.00
Published on Web 09/01/2001

Scheme 1



Scheme 2



O(1)-Benzyl-*N*(2)-Boc-*O*(3)-benzoyl-*O*(4)-TBDMS-protected *syn*-2-amino-1,3,4-butanetriol thus prepared in enantiomerically pure form should serve as a general building block for *syn*-amino alcohol compounds. The orthogonality of the protection strategy employed in the synthesis was confirmed by regioselective unmaskings of O(1), O(3), O(4) protecting groups as shown in Scheme 2. No migration of the remaining protecting groups to the just released free hydroxyl was observed when the O(1), O(3), and O(4) deprotections were conducted under catalytic hydrogenolysis, PhLi, and aqueous HF[13] conditions, respectively.

In conclusion, we have prepared *O*(1)-Benzyl-*N*(2)-Boc-*O*(3)-benzoyl-*O*(4)-TBDMS-protected 2-amino-1,3,4-butanetriol (**1a**) in enantiomerically pure form starting from diisopropyl tartrate. Its orthogonal protecting groups enable one to regioselectively transform the four-carbon unit to desired target compounds. Therefore, the compound **1a** may serve as a general building block for *syn*-amino alcohol compounds.

Experimental Section

Conversion of Diisopropyl L-Tartrate (2) to (4*R*,5*R*)-4,5-Diisopropyloxycarbonyl-3-benzoyloxazolidin-2-one (3). Diisopropyl L-tartrate (16 g, 50 mmol) was dissolved in dichloroethane (300 mL). Dibutyltin oxide (15 g, 60 mmol) was added and the mixture heated to reflux for 4 h under nitrogen with a concomitant removal of water (Dean−Stark trap). Benzoyl isothiocyanate (9.2 mL, 70 mmol) and triethylamine (8.34 mL, 60 mmol) were added, and the mixture was heated to reflux. After 1 h, tetrabutylammonium bromide (16 g, 50 mmol) was added, and heating was continued for a further 2 h. The reaction mixture was partitioned between ethyl acetate and water. The organic phase was separated, washed with brine, and dried (Na_2SO_4). The concentrated crude product was chromatographed on a silica column (hexane/EtOAc = 2.2:1) to yield the pure product **3** (15.2 g, 84%): $[\alpha]_D$ −47.7 (*c* 0.80, EtOH); mp 115−116 °C; ^{1}H NMR ($CDCl_3$) δ 7.70 (2H, d, J = 7.0 Hz), 7.61−7.55 (1H, m), 7.48−7.42 (2H, m), 5.23−5.12 (2H, m), 5.02 (1H, d, J = 3.7 Hz), 4.87 (1H, d, J = 3.6 Hz), 1.55−1.30 (12H, m); IR 2993 (s), 1809 (s), 1741 (s), 1688 (s), 1387 (m) cm^{-1} ; MS *m/e* 364 (MH$^+$). Anal. Calcd for $C_{18}H_{21}NO_7$: C, 59.50; H, 5.83; N, 3.85. Found: C, 59.71; H, 5.85; N, 3.80.

(4*R*,5*R*)-4, 5-Diisopropyloxycarbonyloxazolidin-2-one (4). Compound **3** (12.7 g, 35 mmol) was dissolved in 2-propanol (200 mL). BF_3·OEt_2 (13.4 mL, 70 mmol) was added, and the mixture was heated to reflux overnight. The reaction mixture was partitioned between ethyl acetate and 0.2 M aqueous H_2SO_4. The organic phase was separated, washed with brine, and dried (Na_2SO_4). The concentrated crude product was chromatographed on a silica column (hexane/EtOAc = 3:2) to yield the pure product **4** (7.8 g, 89%): $[\alpha]_D$ −50.9 (*c* 0.43, EtOH); ^{1}H NMR ($CDCl_3$) δ 5.54 (1H, br s), 5.20−5.07 (2H, m), 5.07 (1H, d, J = 3.9 Hz), 4.46 (1H, d, J = 3.9 Hz), 1.34−1.23 (12H, m); IR 2925 (m), 1723 (b), 1426 (s), 1262 (s) cm^{-1} ; MS *m/e* 260 (MH$^+$).

(4*S*,5*R*)-4-Hydroxymethyl-5-isopropyloxycarbonyloxazolidin-2-one (5). Compound **4** (4.6 g, 18 mmol) was dissolved in anhydrous THF (150 mL), and BF_3·OEt_2 (3.4 mL, 18 mmol) was added dropwise. After 4 h, $NaBH_4$ (672 mg, 18 mmol) was added and the mixture was stirred at room temperature for 5 day. The reaction mixture was partitioned between ethyl acetate and 1 N aqueous HCl. The organic phase was separated, washed with brine, and dried (Na_2SO_4). The concentrated crude product was chromatographed on a silica column (EtOAc) to yield the pure product **5** (3.3 g, 92%): $[\alpha]_D$ −34.5 (*c* 0.41, EtOH); mp 105−107 °C; ^{1}H NMR ($CDCl_3$) δ 6.50 (1H, br s), 5.14 (1H, m), 4.82 (1H, q, J = 4.8 Hz), 3.97 (1H, m), 3.86 (1H, m), 3.69(1H, br s), 1.31 (6H, m); IR 3278 (b), 2984 (m), 2872 (m), 1734 (s) cm^{-1} ; MS *m/e* 204 (MH$^+$). Anal. Calcd for $C_8H_{13}NO_5$: C, 47.38; H, 6.43; N, 6.62. Found: C, 47.27; H, 6.45; N, 6.90.

(4*S*,5*R*)-4-Benzyloxymethyl-5-isopropyloxycarbonyloxazolidin-2-one (6). Compound **5** (2.4 g, 12 mmol) was dissolved in 5:1 mixture of CH_2Cl_2−THF (120 mL). Benzyl 2,2,2-trichloroacetimidate (4.4 mL, 24 mmol) and triflic acid (0.5 mL, 6 mmol) were added, and the mixture was stirred at room temperature for 2 days. The reaction mixture was partitioned between ethyl acetate and 10% aqueous NaOH. The organic phase was separated, washed with brine, and dried (Na_2SO_4). The concentrated crude product was chromatographed on a silica column (hexane/EtOAc = 1:2) to yield the pure product **6** (3.1 g, 90%): $[\alpha]_D$ −27.9 (*c* 0.63, $CHCl_3$); mp 78−81 °C; ^{1}H NMR ($CDCl_3$) δ

(13) When the O(4)-deprotection was conducted using tetrabutylammonium fluoride, a benzoyl migration from the O(3) to the just unmasked O(4) was observed.

7.39−7.32 (5H, m), 5.53 (1H, br s), 5.15 (1H, sept, J = 6.2 Hz), 4.64 (1H, d, J = 4.8 Hz), 4.57 (2H, s), 4.06−4.00 (1H, m), 3.63−3.48 (2H, m); IR 3300 (b), 2983 (s), 2875 (s), 1754 (m) cm^{-1} ; MS *m/e* 294 (MH^+). Anal. Calcd for $C_{15}H_{19}NO_5$: C, 61.13; H, 6.56; N, 4.73. Found: C, 61.41; H, 6.53; N, 4.78.

(4*S*,5*R*)-4-Benzyloxymethyl-5-hydroxymethyloxazolidin-2-one (7). Compound **6** (2.6 g, 9 mmol) was dissolved in THF (100 mL). $NaBH_4$ (354 mg, 9 mmol) was added, and the mixture was stirred at room temperature for 1 day. The reaction mixture was partitioned between ethyl acetate and 1 N aqueous HCl. The organic phase was separated, washed with brine, and dried (Na_2SO_4). The concentrated crude product was chromatographed on a silica column (EtOAc) to yield the pure product **7** (2.0 g, 93%): $[\alpha]_D$ −40.2 (*c* 0.36, EtOH); ^1H NMR ($CDCl_3$) δ 7.36−7.19 (5H, m), 6.13 (1H, s), 4.52 (2H, s), 4.35−4.33 (1H, m), 3.82 (1H, dd, J = 2.5, 10 Hz), 4.62 (1H, dd, J = 2.5, 10 Hz), 3.47 (2H, d, J = 5.5 Hz), 3.49 (1H, br s); IR 3325 (b), 2868 (s), 1738 (s), 1243 (m) cm^{-1} ; MS *m/e* 238 (MH^+).

(4*S*,5*R*)-4-Benzyloxymethyl-5-(*tert*-butyldimethylsilyoxymethyl)oxazolidin-2-one (8). Compound **7** (1.7 g, 7.6 mmol) was dissolved in DMF (50 mL). TBDMS-Cl (1.3 g, 9.1 mmol) and imidazole (1.0 g, 15 mmol) were added. The mixture was stirred at room temperature overnight. Evaporation of DMF under reduced pressure was followed by aqueous workup (water−EtOAc). The organic phase was dried (Na_2SO_4) and concentrated. The crude product thus obtained was chromatographed on a silica column (hexane/EtOAc = 1:1) to yield the product **8** (2.2 g, 82%): $[\alpha]_D$ −32.3 (*c* 0.25, EtOH); ^1H NMR ($CDCl_3$) δ 7.27 (5H, m), 5.43 (1H, brs), 4.47 (2H, s), 4.22−4.16 (1H, m), 3.90−3.83 (1H, m), 3.71−3.67 (2H, m), 3.42−3.39 (2H, m), 0.81 (9H, s), 0.06 (6H, s); IR 3283 (s), 2927 (m), 1758 (s) cm^{-1} ; MS *m/e* 352 (MH^+).

(4*S*,5*R*)-4-Benzyloxymethyl-3-(*tert*-butoxycarbonyl)-5-(*tert*-butyldimethylsilyoxymethyl)oxazolidin-2-one (9). Compound **8** (1.2 g, 3.5 mmol) was dissolved in THF. Di-*tert*-butyl dicarbonate (1.5 g, 7 mmol) and DMAP (427 mg, 3.5 mmol) were added. The mixture was stirred at room temperature for 1 h. Aqueous workup was followed by a silica column chromatography (hexane/EtOAc = 2:1) to yield the product **9** (1.5 g, 94%): $[\alpha]_D$ −6.25 (*c* 0.22, EtOH); ^1H NMR ($CDCl_3$) δ 7.31−7.24 (5H, m), 4.49 (2H, s), 4.37 (1H, m), 4.22 (1H, m), 3.77 (1H, dd, J = 2.5 Hz, J = 11.4 Hz), 3.59 (1H, m), 1.43 (9H, s), 0.80 (9H, s), 0.06 (6H, s); IR 2983 (s), 1816 (m), 1721 (s) cm^{-1} ; MS *m/e* 452 (MH^+).

(2*S*,3*R*)-*O*(1)-Benzyl-*N*(2)-Boc-*O*(3)-benzoyl-*O*(4)-TBDMS-Protected 2-Amino-1,3,4-butanetriol (1a). Compound **9** (1.3 g, 3 mmol) was dissolved in anhydrous THF (50 mL). The solution was cooled to −78 °C, and then PhLi (3.3 mL of a 1.8M solution in THF, 6 mmol) was added dropwise. The mixture was stirred at −78 °C for 10 min. The reaction mixture was partitioned between ethyl acetate and saturated aqueous NH_4Cl. The organic phase was separated, washed with brine, and dried (Na_2SO_4). The concentrated crude product was chromatographed on a silica column (hexane/EtOAc = 5:1) to yield the pure product 1a (1.2 g, 78%): $[\alpha]_D$ +14.1 (*c* 0.32, EtOH); ^1H NMR ($CDCl_3$) δ 8.0 (2H, d, J = 7.5 Hz), 7.56−7.50 (1H, m), 7.43−7.37 (2H, m), 7.27 (5H, m), 5.38−5.32 (1H, m), 5.01 (1H, d, J = 9.5 Hz), 4.48 (2H, d, J = 2.5 Hz), 4.27 (1H, m), 3.82 (2H, m), 3.56−3.50 (2H, m), 1.35 (9H, s), 0.83 (9H, s), 0.01 (6H, s); IR 3454 (m), 2922 (s), 1721 (s), 1498 (s) cm^{-1}; MS *m/e* 530 (MH^+). Anal. Calcd for $C_{29}H_{43}NO_6Si$: C, 65.71; H, 8.21; N, 2.56. Found: C, 65.75; H, 8.19; N, 2.65.

Acknowledgment. This work was supported by the KRF (2000-015-DP0271). S.J.K. is grateful to the Brain Korea 21 project for a graduate fellowship.

Supporting Information Available: Experimental procedure for the reactions of Scheme 2 and the spectral data for compounds **10**−**12**. This material is available free of charge via the Internet at http://pubs.acs.org.

JO015886J