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TETRAHEDRON: *ASYMMETRY*

A convenient synthesis of (1*S*)-*tert*-butyl-1,2-ethylenediamine

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Abstract

A practical four-step synthesis of (1*S*)-*tert*-butyl-1,2-ethylenediamine has been developed. The sequence proceeds in good overall yield via crystalline intermediates and provides the title compound in 99.3% ee.

1. Introduction

Chiral diamines and their derivatives now form an important class of ligands in asymmetric catalysis.[1] These compounds have found use in epoxidations,[2] Diels–Alder cyclizations,[3] alkene dihydroxylations,[4] cyclopropanations[5] and aziridinations[6] to name only a few applications. In the course of our research into various palladium-catalyzed processes, we required multigram quantities of enantiomerically pure (1*S*)-*tert*-butyl-1,2-ethylenediamine, **1**. A survey of the literature[7–9] revealed several syntheses of **1**, yet none proved to be entirely satisfactory for our purposes. The synthesis of **1** has been reported in racemic form,[7] although the yield was not given and potential racemization issues were not addressed. A second method[8] utilized a racemic four-step synthesis followed by a classical resolution, yet the overall yield was less than 10%. A more recent method[9] required an enzyme-catalyzed hydrocyanation followed by tosylation, azide formation and reduction to furnish **1** in 84.9% ee. Related diamines have also been prepared via ammonolysis of esters followed by reduction,[10c] yet reaction times were in excess of 4 days. We have found that treatment of *tert*-Leu methyl ester under these conditions furnished less than 5% of the amide after 1 week. Thus, the combination of long reaction times, low overall yields, low optical purity, and the prospect of handling both toxic HCN and azides at elevated temperatures for prolonged periods prompted us to develop a more practical route to this important hindered diamine.[10]

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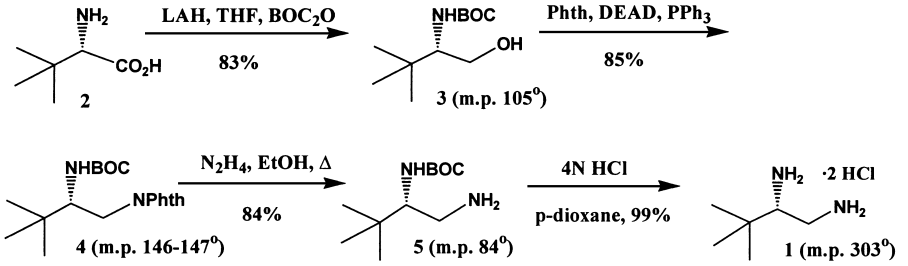
2. Results and discussion

As shown in Scheme 1, LAH reduction of (*S*)-*tert*-leucine **2** with in situ BOC protection furnished the known[11] hydroxycarbamate **3** in 83% yield. Mitsunobu amination[12] of this alcohol with phthalimide proceeded smoothly to give phthalimidocarbamate **4** in 85% yield. Hydrazinolysis of the phthalimide (84%) and BOC deprotection/salt formation (99%) then completed the synthesis of the title diamine dihydrochloride, **1**.



Scheme 1. Synthesis of (1*S*)-*tert*-butyl-1,2-ethylenediamine dihydrochloride, **1**

This robust four-step sequence proceeds in 59% overall yield, and each chemical intermediate is crystalline. In order to quantify the optical purity of the product, the sequence shown was repeated using racemic *tert*-leucine and the diamine thus obtained converted to the benzaldehyde-derived bisimine. Baseline resolution of the enantiomers was achieved using a Chiralpak AD chiral HPLC method.[13] Analysis of diamine **1** prepared as described above was then shown to be 99.3% ee using this analytical method. The four-step sequence thus proceeds with no erosion of optical activity from the starting (*S*)-*tert*-leucine.

In summary, an operationally simple four-step synthesis of (1*S*)-*tert*-butyl-1,2-ethylenediamine dihydrochloride has been developed which proceeds in good overall yield, through crystalline intermediates, and furnishes the title compound in enantiomerically pure form.

3. Experimental

3.1. General

^{1}H NMR spectra were obtained with a Bruker DPX 400 MHz spectrometer. ^{1}H chemical shifts are reported in δ ppm relative to $CHCl_3$ (7.27 ppm). ^{13}C NMR spectra were obtained at 100 MHz, and chemical shifts are reported in δ ppm relative to the center of the $CDCl_3$ triplet (77.0 ppm). Microanalyses were carried out by Quantitative Technologies Inc., of Whitehouse, NJ. Column chromatography was performed using EM Silica Gel 60 (230–400 mesh) and all solvents were used as received.

3.2. Phthalimidocarbamate *4*

A flask was charged with 1.24 g phthalimide (8.49 mmol, 1.5 equiv.), 60 mL dry THF, 4.45 g PPh_3 (17.0 mmol, 3 equiv.), and 1.23 g of hydroxycarbamate **3** (5.66 mmol, 1 equiv.) in the order given. The resulting colorless solution was cooled to 0°C under N_2, then 2.23 mL DEAD (14.2

mmol, 2.5 equiv.) was slowly added. The yellow solution was allowed to slowly warm to ambient temperature. After 3 h, the reaction mixture was concentrated in vacuo and the residue chromatographed on silica gel eluting with 3:1 hexane:EtOAc to give 1.65 g (85%) of **4** as a colorless solid, m.p. 146–147°C; $[\alpha]_D = +48.7$ (c 0.46, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ: 7.82 (dd, $J = 5.4$, 3.0 Hz, 2H), 7.67 (dd, $J = 5.5$, 3.1 Hz, 2H), 4.46 (br d, $J = 10.6$ Hz, 1H), 3.84 (dd, $J = 12.2$, 2.9 Hz, 1H), 3.79 (dd, $J = 10.7$, 3.0 Hz, 1H), 3.62 (m, 1H), 1.10 (s, 9H), 1.02 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 168.86 (s), 156.42 (s), 134.14 (d), 132.58 (s), 123.53 (d), 79.32 (s), 57.90 (d), 39.04 (t), 34.06 (s), 28.20 (q), 26.85 (q). Anal. calcd for $C_{19}H_{26}N_2O_4$: C, 65.88; H, 7.56; N, 8.09. Found: C, 65.96; H, 7.53; N, 8.00.

3.3. BOC-diamine 5

A flask with reflux condenser was charged with 1.60 g **4** (4.62 mmol, 1 equiv.), 40 mL EtOH and 1.31 mL N_2H_4 hydrate (CAUTION: toxic; 23.1 mmol, 5 equiv.) in the order given. The mixture was refluxed for 45 min, cooled and filtered, and the solids washed well with Et_2O. The filtrate was washed with H_2O, dried (K_2CO_3) and concentrated in vacuo to a light orange solid. Recrystallization (hexane) afforded 840 mg (84%) of **5** as a colorless solid, m.p. 84°C; $[\alpha]_D = +9.8$ (c 0.48, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ: 4.59 (br d, $J = 10.2$ Hz, 1H), 3.23 (br t, $J = 9.0$ Hz, 1H), 2.85 (d, $J = 13.3$ Hz, 1H), 2.30 (br t, $J = 12.1$ Hz, 1H), 1.35 (s, 9H), 0.81 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 156.78 (s), 78.86 (s), 62.40 (d), 42.26 (t), 34.10 (s), 28.32 (q), 26.50 (q). Anal. calcd for $C_{11}H_{24}N_2O_2$: C, 61.07; H, 11.18; N, 12.95. Found: C, 61.22; H, 11.26; N, 12.91.

3.4. Diamine dihydrochloride 1

Compound **5** (690 mg, 3.19 mmol, 1 equiv.) was dissolved in 12 mL MeOH, then 3.19 mL 4N HCl/*p*-dioxane (12.8 mmol, 4 equiv.) was added and the resulting mixture stirred for 5 h at ambient temperature under N_2. The reaction mixture was concentrated in vacuo, and the resulting solids filtered under N_2 washing well with Et_2O to give 620 mg (99%) of **1** as a colorless solid, m.p. 303°C (dec.); $[\alpha]_D = +14.6$ (c 1.07, H_2O); ^1H NMR (400 MHz, $CDCl_3$) δ: 8.61 (br s, 6H), 3.20 (d, $J = 9.2$ Hz, 1H), 3.19 (d, $J = 14.9$ Hz, 1H), 2.94 (dd, $J = 14.3$, 9.2 Hz, 1H), 0.96 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 58.36 (d), 39.35 (t), 33.44 (s), 26.22 (q). Anal. calcd for $C_6H_{18}Cl_2N_2$: C, 38.10; H, 9.58; Cl, 37.49; N, 14.81. Found: C, 38.13; H, 9.77; Cl, 37.41; N, 14.81.

References

1. For an excellent diamine review, see: Le Gall, T.; Mioskowski, C.; Lucet, D. *Angew. Chem., Int. Ed. Engl.* **1998**, *37*, 2580–2627.
2. Katsuki, T. *Coord. Chem. Rev.* **1995**, *140*, 189–214.
3. (a) Evans, D. A.; Lectka, T.; Miller, S. J. *Tetrahedron Lett.* **1993**, *34*, 7027. (b) Corey, E. J.; Sarshar, S.; Bordner, J. *J. Am. Chem. Soc.* **1992**, *114*, 7938.
4. (a) Sharpless, K. B.; Kolb, H. C.; VanNieuwenhze, M. S. *Chem. Rev.* **1994**, *94*, 2483. (b) Corey, E. J.; Jardine, P. D.; Vigil, S.; Yuen, P.-W.; Connel, R. D. *J. Am. Chem. Soc.* **1989**, *111*, 9243.
5. Kobayashi, S.; Takahashi, H.; Yoshioka, M.; Shibasaki, M.; Ohno, M.; Imai, N. *Tetrahedron* **1995**, *51*, 12013.
6. Jacobsen, E. J.; Li, Z.; Conser, K. R. *J. Am. Chem. Soc.* **1993**, *115*, 5326.
7. (a) Duchateau, A. L. L.; Guns, J. J.; Kubben, R. G. R.; van Tilburg, A. F. P. *J. Chromatography A*, **1994**, *664*, 169–176. (b) Garbarino, J. A. *Ann. Chim. (Rome)* **1969**, *59*, 841–846.
8. (a) Hawkins, C. J.; Peachey, R. M. *Aust. J. Chem.* **1976**, *29*, 33–48. (b) Yanagihara, Y.; Yano, T.; Kobayashi, H.; Ueno, K. *Bull. Chem. Soc. Jpn.* **1972**, *45*, 554–557.

9. (a) Effenberger, F.; Kremser, A.; Stelzer, U. *Tetrahedron: Asymmetry* **1996**, *7*, 607–618. See also: (b) Effenberger, F.; Stelzer, U. *Angew. Chem., Int. Ed. Engl.* **1991**, *30*, 873–874. (c) Effenberger, F.; Ziegler, T.; Forster, S. *Angew. Chem., Int. Ed. Engl.* **1987**, *26*, 458–460. (d) Effenberger, F.; Stelzer, U. *Chem. Ber.* **1993**, *126*, 779–786.
10. Asymmetric cyclopropanation: (a) Imai, N.; Nokami, J.; Sakamoto, K.; Maeda, M.; Kouge, K.; Yoshizane, K. *Tetrahedron Lett.* **1997**, *38*, 1423–1426. Asymmetric deprotonation: (b) Singh, V. K.; Bhuniya, D.; DattaGupta, A. *J. Org. Chem.* **1996**, *61*, 6108–6113. (c) Brunner, H.; Schmidt, M.; Unger, G.; Schonenberger, H. *Eur. J. Med. Chem. Chim. Ther.* **1985**, *20*, 509–512.
11. Ali, S. M.; Jayasinghe, L. R.; Hoemann, M. Z.; Aube, J.; Mitscher, L. A.; Georg, G. I.; McCall, R. *J. Med. Chem.* **1995**, *38*, 3821–3828.
12. Suzuki, T.; Imanishi, N.; Itahana, H.; Watanuki, S.; Miyata, K. *Chem. Pharm. Bull.* **1998**, *46*, 1116–1124.
13. Chiralpak AD, 250×4.6 mm; Mobile phase: hexane, 1.5 ml/min; sample dissolved in 90:10:0.1 hexane:IPA:Et_2NH; c = 0.15 mg/ml, 10 μl injection; 254 nm observation; (*S*): rt 7.33 min.; (*R*): rt 12.74 min.