Preparation of (3*S*)-*N*,*N*-1,7-Bis-*tert*-butoxycarbonyl-3-hydroxyspermidine in High Enantiomeric Purity

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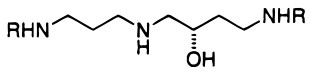
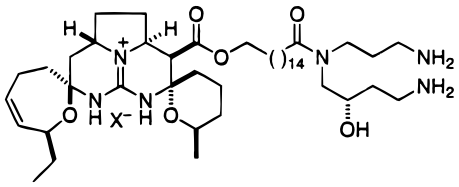
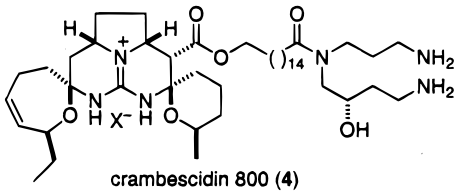
Although polyamines are structural features of many natural products,[1] 3-hydroxyspermidine (**1**) is rare, being found only in the crambescidin family of guanidinium alkaloids.[2] During our recent total syntheses of 13,14,-15-isocrambescidin 800 (**3**)[3] and crambescidin 800 (**4**),[4] we required a practical way to prepare suitably protected 3-hydroxyspermidines in high enantiopurity. Ponasik and Ganem had previously reported the only synthesis of the 3-hydroxyspermidine unit, albeit in racemic form.[5] Herein we describe a convenient, high-yielding procedure for preparing (3*S*)-*N*,*N*-1,7-bis-*tert*-butoxycarbonyl-3-hydroxyspermidine (**2**).



1: R = H
2: R = BOC



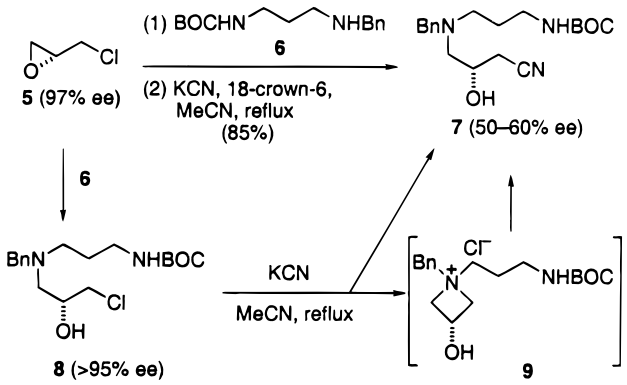
13,14,15-isocrambescidin 800 (**3**)



crambescidin 800 (**4**)

(*R*)-Epichlorohydrin (**5**) is an obvious starting material for preparing the (*S*)-1,4-diamino-2-butanol fragment of **2** (Scheme 1), since Bergeron and co-workers had previously used this precursor to fashion the diaminobutanol unit of (+)-hypusine.[6] Reaction of [*N*-(*tert*-butoxycarbonyl)-3-aminopropyl]benzylamine (**6**)[7] and **5** (97% ee) at room temperature for 24 h and then heating the resulting crude chlorohydrin at reflux in acetonitrile in the presence of KCN and 18-crown-6[6a] provided *β*-hydroxy nitrile **7** in 85% yield. However, ^{19}F NMR analysis of the (*R*)-α-methoxy-α-(trifluoromethyl)phenylacetate [(*R*)-MTPA][8] derivative revealed that **7** had been generated in only 50−60% ee. To confirm that racemization had occurred in the second step, chlorohydrin **8** was isolated and shown to have high enantiopurity (>95% ee).[8] Thus, competitive formation of achiral azetidinium salt **9** in refluxing acetonitrile during the second step was undoubtedly the cause of the partial epimerization observed in forming **7**.[6c,9,10]

Scheme 1



In their synthesis of hypusine, Bergeron and co-workers solved the racemization problem by preparing the *N*-benzyloxycarbonyl derivative of the chlorohydrin intermediate prior to reaction with cyanide.[6c] An alternate solution would be to avoid formation of azetidinium salt **9** during the conversion of **8** → **7**. We reasoned that simply switching to a nonpolar solvent for the cyanide displacement step would accomplish this goal. To this end, a solution of [*N*-(*tert*-butoxycarbonyl)-3-aminopropyl]-benzylamine (**6**) and (*R*)-epichlorohydrin (**5**) was maintained at room temperature for 24 h, and the resulting crude chlorohydrin was heated at 70 °C in toluene with a slight excess of tetrabutylammonium cyanide for 5 h to give **7** in 80% yield (Scheme 2). Gratifyingly, the enantiomeric purity of **7** formed in this way was ∼97% ee.[8] Selective reduction of the nitrile group of **7** with

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(4) Coffey, D. S.; McDonald, A. I.; Overman, L. E.; Rabinowitz, M. H.; Renhowe, P. A. To be submitted for publication.

(5) Ponasik, J. A.; Ganem, B. *Tetrahedron Lett.* **1995**, *36*, 9109−9112.

(6) (a) Bergeron, R. J.; Xia, M. X. B.; Phanstiel IV, O. *J. Org. Chem.* **1993**, *58*, 6804−6806. (b) Bergeron, R. J.; Ludin, C.; Müller, R.; Smith, R. E., Phanstiel IV, O. *J. Org. Chem.* **1997**, *62*, 3285−3290. (c) Bergeron, R. J.; Weimar, W. R.; Müller, R.; Zimmerman, C. O.; McCosar, B. H.; Yao, H.; Smith, R. E. *J. Med. Chem.* **1998**, *41*, 3888−3900.

(7) Bergeron, R. J.; Garlich, J. R.; Stolowich, N. J. *J. Org. Chem.* **1984**, *49*, 2997−3001.

(8) (a) Dale, J. A.; Mosher, H. S. *J. Am. Chem. Soc.* **1973**, *95*, 512−519. (b) MTPA esters were prepared by the method of Ward: Ward, D. E.; Rhee, C. K. *Tetrahedron Lett.* **1991**, *32*, 7165−7166.

(9) The intermediacy of azetidinium salts in reactions of 1-chloro-3-dialkylamino-2-propanol derivatives with nucleophiles, including cyanide, is well-known.[10]

(10) (a) Gaertner, V. R. *J. Org. Chem.* **1968**, *33*, 523−530. (b) Gaertner, V. R. *Tetrahedron Lett.* **1967**, 343−347. (c) Beaulieu, P. L.; Wernic, D. *J. Org. Chem.* **1996**, *61*, 3635−3645. (c) For a review of azetidines and azetidinium cations, see: Cromwell, N. H.; Phillips, B. *Chem. Rev.* **1979**, *79*, 331−358.

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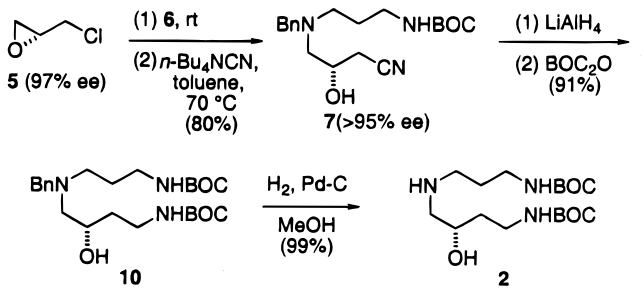
Scheme 2



lithium aluminum hydride at 0 °C, followed by treatment of the resulting primary amine with di-*tert*-butyl dicarbonate (BOC_2O), provided **10** in 91% yield. Standard hydrogenolysis of the benzyl group of **10** then delivered **2** in nearly quantitative yield.

In summary, a convenient procedure for preparing bis-BOC derivative **2** of (*S*)-3-hydroxyspermidine in high enantiopurity from commercially available (*R*)-epichlorohydrin (**5**) has been developed. This first enantiospecific synthesis of the (*S*)-3-hydroxyspermidine unit proceeds in 72% yield from **5** by way of two isolated and purified intermediates. Partial racemization in generating β-hydroxy nitrile intermediate **7** was prevented by carrying out the displacement reaction of 1-chloro-3-dialkylamino-2-propanol **8** with cyanide in toluene. Since epichlorohydrin is a common precursor of diverse 1-dialkylamino-2-propanol derivatives, performing the nucleophilic displacement of 1-chloro-3-dialkylamino-2-propanol intermediates in a nonpolar solvent should be a useful tactic for enantiospecific synthesis of other epichlorohydrin-derived amino alcohols.

Experimental Section

General Methids. (*R*)- and (*S*)-epichlorohydrin (97% ee) were purchased from Aldrich Chemical Co. Dry THF, Et_2O, and CH_2Cl_2 were filtered through a column charged with Al_2O_3.[11] Triethylamine (Et_3N), pyridine, diisopropylethylamine, diisopropylamine, and acetonitrile were distilled from CaH_2 at atmospheric pressure. Silica gel (0.040−0.063) by Merck was used for flash chromatography. Microanalyses were performed by Atlantic Microlabs, Atlanta, GA. Other general experimental details have been described.[12]

(3*S*)-4-*N*-Benzyl-*N*-[3-(*tert*-butoxycarbonyl)aminopropyl]amine-3-hydroxybutyronitrile (7). (*R*)-Epichlorohydrin (**5**, 310 μL, 4.0 mmol) and [*N*-(*tert*-butoxycarbonyl)-3-aminopropyl]-benzylamine (**6**, 1.00 g, 3.78 mmol) were mixed and maintained at room temperature for 24 h. Tetra-*n*-butylammonium cyanide (1.22 g, 4.54 mmol) and toluene (19 mL) were then added, and the resulting solution was heated at 70 °C for 5 h. The solution was allowed to cool to room temperature and then partitioned between EtOAc (100 mL) and brine (40 mL). The organic phase was dried ($MgSO_4$), filtered and concentrated. The resulting crude oil was purified by flash chromatography (7:3 hexanes−EtOAc → 6:4 hexanes−EtOAc) to give 1.05 g (80%) of nitrile **7** as a clear oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.23−7.32 (m, 5 H), 4.81 (s, 1H), 3.84−3.89 (m, 1 H), 3.69 (d, J = 13.4 Hz, 1 H), 3.49 (d, J = 13.4 Hz, 1 H), 3.09−3.11 (m, 2 H) 2.38−2.60 (m, 7 H), 1.61−1.67 (m, 2 H), 1.41 (s, 9 H); ^{13}C NMR (125 MHz, $CDCl_3$) 155.9, 138.0, 128.8, 128.4, 127.3, 117.3, 79.0, 64.0, 59.0, 58.9, 51.7, 38.3, 28.3, 27.1, 23.2 ppm; IR (film) 3371, 2252, 1694 cm^{-1}; $[\alpha]^{25}_D$ +41.7, $[\alpha]^{25}_{577}$ +43.4, $[\alpha]^{25}_{546}$ +49.5, $[\alpha]^{25}_{435}$ +85.0, $[\alpha]^{25}_{405}$ +102 (*c* 1.6, $CHCl_3$). Anal. Calcd for $C_{19}H_{29}O_3N_3$: C, 65.68; H, 8.41; N, 12.09. Found: C, 65.57; H, 8.49; N, 12.03.

Following the general procedure of Ward,[8b] **7** was treated with (*S*)-α-methoxy-α-(trifluoromethyl)phenylacetic acid chloride [(*S*)-MTPACl] to give the corresponding (*R*)-MTPA ester. Analysis by ^{19}F NMR showed a ratio of approximately 74:1 of **7**-(*R*)-MTPA and *ent*-**7**-(*R*)-MTPA[13] corresponding to 97% ee. Diagnostic ^{19}F NMR (400 MHz, $CDCl_3$) signals:[14] **7**-(*R*)-MTPA, δ −71.4; *ent*-**7**-(*R*)-MTPA, δ −71.6.

(2*S*)-1-[*N*-Benzyl-*N*-[3-(*tert*-butoxycarbonyl)aminopropyl]-amino]-4-(*tert*-(butoxycarbonyl)aminobutan-2-ol (10). A solution of **7** (400 mg, 1.15 mmol) and Et_2O (5 mL) was added dropwise to a stirring suspension of $LiAlH_4$ (180 mg, 4.74 mmol) and Et_2O (15 mL) at 0 °C. After 1 h, H_2O (180 μL), 3 N NaOH (180 μL), and H_2O (540 μL) were added sequentially to the reaction mixture. The resulting mixture was filtered through a pad of Celite and concentrated, and the resulting colorless oil was used without further purification.

A mixture of this crude primary amine, BOC_2O (310 mg, 1.4 mmol), CH_2Cl_2 (5 mL), and saturated aqueous $NaHCO_3$ (5 mL) was stirred at room temperature for 1 h. The reaction mixture was then poured into Et_2O (20 mL), and the layers were separated. The organic layer was washed with brine (5 mL), dried ($MgSO_4$), and concentrated. The residual oil was purified by flash chromatography (1:1 hexanes−EtOAc) to provide 470 mg (91%) of **10** as a colorless oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.20−7.29 (m, 5 H), 5.15 (s, 1 H), 4.88 (s, 1 H), 3.66−3.74 (m, 2 H), 3.58 (s, 1 H), 3.30−3.39 (m, 2 H), 3.06−3.15 (m, 3 H), 2.53−2.59 (m, 1 H), 2.35−2.42 (m, 3 H), 1.52−1.62 (m, 4 H), 1.34 (s, 18 H); ^{13}C NMR (75 MHz, $CDCl_3$) 156.2, 155.9, 138.4, 128.9, 128.3, 127.2, 78.8, 66.2, 60.2, 58.8, 51.4, 38.5, 37.9, 34.4, 28.3, 27.1 ppm; IR (film) 3354, 1694 cm^{-1}; $[\alpha]^{25}_D$ +42.3, $[\alpha]^{25}_{577}$ +44.3, $[\alpha]^{25}_{546}$ +49.7, $[\alpha]^{25}_{435}$ +88.2 (*c* 3.5, $CHCl_3$). Anal. Calcd for $C_{24}H_{41}O_5N_3$: C, 63.83; H, 9.15; N, 9.30. Found: C, 63.87; H, 9.22; N, 9.22.

(2*S*)-1-[*N*-[3-(*tert*-butoxycarbonyl)aminopropyl]amino]-4-(*tert*-butoxycarbonyl)aminobutan-2-ol (2). A mixture of **10** (120 mg, 0.27 mmol), 10% Pd/C (20 mg), and MeOH (5 mL) was maintained at room temperature under 1 atm of H_2 for 5 h. The mixture was then filtered through a plug of Celite, the plug was washed with MeOH (20 mL), and the eluent was concentrated to yield 96 mg (99%) of **2** as a colorless oil that was sufficiently pure to be employed directly in our syntheses of **3** and **4**.[3,4] For characterization purposes, a sample of **2** was purified by flash chromatography (9:1 $CHCl_3$−MeOH) to give a colorless oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.16 (s, 1 H), 5.06 (s, 1 H), 3.69−3.71 (m, 1 H), 3.34−3.36 (m, 1 H), 3.10−3.20 (m, 3 H), 2.96 (br s, 2 H), 2.59−2.69 (m, 3 H), 2.47−2.51 (m, 1 H), 1.53−1.64 (m, 3 H), 1.39−1.50 (m, 19 H); ^{13}C NMR (125 MHz, $CDCl_3$) 156.6, 156.2, 79.1, 79.0, 67.4, 55.2, 46.8, 38.5, 37.4, 35.0, 29.9, 28.3 ppm; IR (film) 3344, 1694 cm^{-1}; HRMS (FAB) (MH) *m/z* 362.2653 (362.2655 calcd for $C_{17}H_{36}N_3O_5$); $[\alpha]^{25}_D$ +9.8, $[\alpha]^{25}_{577}$ +10.2, $[\alpha]^{25}_{546}$ +11.4, $[\alpha]^{25}_{435}$ +18.2, $[\alpha]^{25}_{405}$ +21.1 (*c* 2.0, $CHCl_3$).

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(14) ^{19}F NMR spectra were calibrated using fluorobenzene (δ −113.1) as an internal standard.