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Practical Synthesis of *trans-tert*-Butyl-2-aminocyclopentylcarbamate and Resolution of Enantiomers

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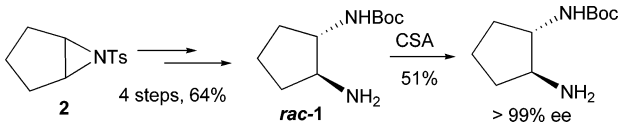

Optically active *trans-tert*-butyl-2-aminocyclopentylcarbamate (**1**) has potential utility as a scaffold for chiral ligands and as a modified backbone unit for peptide nucleic acids (PNAs). We have developed a short and practical synthesis of **1** via aziridine opening of tosyl-activated cyclopentene aziridine **2** and optical resolution of racemic **1** with 10-camphorsulfonic acid (CSA). The route provides ready access to multigram quantities of both enantiomers without the need for chromatography.

Optically active 1,2-diamines are important components of many biologically active natural products and medicinal agents.[1] Bidentate C_2-symmetric ligands based on 1,2-diamine functionality have also found widespread applications in asymmetric catalysis.[2] For example, chiral salen ligands derived from *trans*-1,2-diaminocyclohexane effect remarkable enantioselectivity for a broad range of transformations.[3] In contrast, the use of *trans*-1,2-diaminocyclopentane as a chiral scaffold has received less attention due to the limited availability of both enantiomers.[4] In connection with our research on peptide nucleic acids (PNAs),[5] we felt that *trans-tert*-butyl-2-aminocyclopentylcarbamate (**1**) would be a versatile synthetic precursor and that resolution of racemic **1** should be feasible. In our experience, compound **1** is air stable[6] and can be easily converted to *trans*-1,2-diaminocyclopentane. More importantly, **1** allows the stepwise functionalization of amino groups to generate non-C_2-type chiral ligands or medicinal agents.[7]

Recently, we reported that incorporating *trans*-1,2-diaminocyclopentane into aminoethylglycine peptide nucleic acids (aegPNAs) significantly increases binding affinity and sequence specificity to complementary DNA.[5] Related to this, we developed an asymmetric synthetic route to (*S*,*S*)-**1** relying on Curtius rearrangement and multistep functional group transformations.[5] The route was only serviceable for initial evaluation of **1** as a building block. Its long sequence and low yield (10 steps, 10% yield) hindered its further application.

Our ongoing interest in design and application of *trans*-cyclopentane-constrained PNA prompted us to develop a more efficient and practical process, which can provide multigram quantities of both enantiomers of **1**.[8] We envisioned that a straightforward approach to prepare such diamines would be ring-opening of an appropriate aziridine with an azide nucleophile in the presence of a promoter.[9] In this way, two amine groups or its equivalents are installed in one step, thus circumventing the tedious functional group transformations.

Our synthesis begins with ring opening of tosyl-activated aziridine **2** (Scheme 1, Table 1), which is readily accessible in one step from commercially available cyclopentene.[10] A literature search revealed four examples of ring-opening of **2** with azides.[11−14] However, our examination of these methods revealed that none of them gave satisfactory results, especially for large-scale (4 mmol scale) synthesis. For instance, attempted opening of **2** with NaN_3 using Oxone in aqueous acetonitrile failed to provide any ring-opening products.[11] The use of ceric ammonium nitrate (CAN) instead of Oxone led to 15% convension and 13% yield of **3**.[12] Similar results were observed when $TMSN_3$ in DMF was used.[13] Fortunately, adding 5% TBAF to $TMSN_3$ significantly promoted the transformation (entry 4, 80% conversion, 76% yield).[14] However, the operation requires laborious column chromatography to separate azido amine product **3** from unreacted **2**, which has an R_f value close to that of **3**. Complete conversion was achieved by increasing the amount of TBAF to 20% (entry 5). If 1 equiv of TBAF is

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SCHEME 1

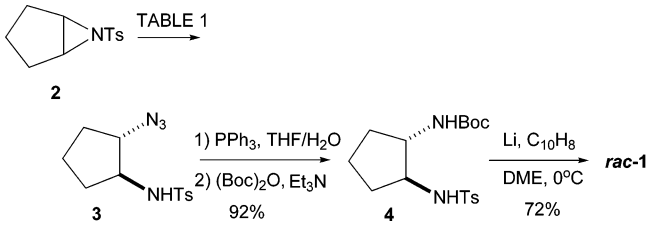


TABLE 1. Ring Opening of Aziridine 2 with Azides[a]

entry	reagents	solvent	*T* (°C)	time (h)	conv[b] (%)	yield[c] (%)
1	NaN_3, Oxone	CH_3CN/H_2O	23	5	0	0
2	NaN_3, 10% CAN	CH_3CN/H_2O	23	20	15	13
3	$TMSN_3$	DMF	40	16	34	30
4	$TMSN_3$, 5% TBAF	THF	40	16	81	76
5	$TMSN_3$, 20% TBAF	THF	40	16	100	93
6	$TMSN_3$, 100% TBAF	THF	40	4	100	96
7	30% $TMSN_3$, 30% TBAF, 100% NaN_3	THF	40	20	100	95

[a] All reactions were conducted at 4 mmol scale, and entries 5−7 were also conducted at ∼85 mmol scale. [b] Determined by ^1H NMR. [c] Isolated yield.

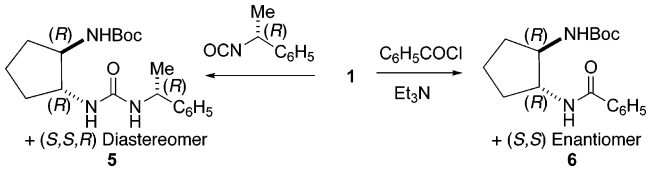
used, the reaction time can be shortened to 4 h and **3** can be obtained in 96% yield (entry 6). Similar results can be obtained, although with longer reaction times, by using 30% $TMSN_3$, 30% TBAF, and 100% NaN_3 (entry 7). For our purposes, these final conditions prove to be the most cost-effective and reliable for preparation of **3**.

Without further purification, **3** was reduced to the corresponding amine by Pd-catalyzed hydrogenation or Staudinger reduction (PPh_3, THF/H_2O).[15] Subsequent Boc protection of the resulting amine yielded **4** in 92% yield for two steps.

The major drawback of tosyl-activated aziridine chemistry is that harsh conditions are required for the cleavage of the sulfonamide bond at a later stage of the synthesis.[9b] Recently, milder conditions have been developed in this context, and magnesium in methanol under ultrasonic conditions has been successfully applied to a variety of substrates.[16] Under these conditions, **4** underwent clean but very sluggish conversion. After considerable experimentation, the detosylation was achieved with lithium and naphthalene in dimethoxyethane (DME) or THF.[17] The reaction was temperature-dependent: at low (−78 °C) or room temperature, either very slow conversion (10%) was observed or low yield (40%) resulted. The reaction was best performed at 0 °C for 5 h to afford **1** in 72% yield.

The resolution of primary amines with similar structures to **1** have been typically performed with tartaric acid or mandelic acid.[18] Our initial attempts to resolve **1** with these two acids did not give precipitate under various conditions. Therefore, 20 other chiral resolving acids were screened. The resolution results

SCHEME 2



were rapidly examined by a ^1H NMR method as follows (Scheme 2): the precipitated salts were converted to amine **1** and subsequently treated with optically pure (*R*)-(+)-1-phenylethyl isocyanate in $CDCl_3$ to give corresponding urea disastereomers **5**.[19] The Boc groups of the two disastereomers **5** showed separated peaks at 1.30 and 1.44 ppm in the ^1H NMR. Among the different chiral acids that were screened, di-*p*-toluoyltartaric acid, 2-phenylpropionic acid, and menthyloxyacetic acid showed partial resolution. Fortunately, optimal results were obtained when 10-camphorsulfonic acid (CSA) was used as a resolving agent. The precipitate from *rac*-**1** and CSA (1:1 or 1:0.5) in acetone showed approximately 60% ee. After crystallizations from acetonitrile, the optical purity of **1** was enhanced to over 99% ee, as determined by HPLC analysis (on a chiral stationary phase) of the benzoylated derivative **6** (experimental section). The configuration of **1** obtained from the resolution was assigned based on the comparison of HPLC data of **6** (obtained on a chiral stationary phase) to material obtained from previous syntheses performed in our laboratory.[5]

In conclusion, we have developed a short synthetic route to optically enriched **1**, a versatile building block for chiral ligands and modified PNAs. The synthesis does not require column chromatography and is amenable to large-scale preparation (10 g scale for *rac*-**1**), which can provide gram quantities of both enantiomers.

Experimental Section

2-Azido-*N*-tosylcyclopentanamine (3). To a mixture of 6-tosyl-6-azabicyclo[3.1.0]hexane **2**[10] (20.0 g, 84.4 mmol) and NaN_3 (5.5 g, 84.4 mmol) in dry THF (300 mL) was added $TMSN_3$ (2.9 g, 3.3 mL, 25.3 mmol), followed by the addition of TBAF (25.3 mL, 1 M in THF, 25.3 mmol). The solution was stirred at 40 °C for 20 h. The reaction solution was cooled to room temperature, and saturated $NaHCO_3$ aqueous solution (200 mL) was added. The aqueous layer was extracted with diethyl ether (100 mL × 3). Combined organic layers were washed with brine (100 mL), dried over Na_2SO_4, filtered, and concentrated under vacuum. The oil residue was filtered through a pad of silica gel and washed with a mixture of ethyl acetate/hexanes (1:2, 2000 mL). Solvents were removed under vacuum to afford **3** (22.4 g, 95%) as a colorless oil. Spectroscopic data of **3** were consistent with the literature data for this compound.[14]

***tert*-Butyl 2-(Tosylamino)cyclopentylcarbamate (4).** Triphenylphosphine (40.3 g, 153.8 mmol) was added to a solution of **3** (21.5 g, 76.9 mmol) in THF/H_2O (600/50 mL). The mixture was stirred at room temperature for 16 h. HCl (1 M) solution (200 mL) was added. The aqueous layer was separated, extracted with diethyl

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ether (200 mL × 3), and basified with 2 N NaOH solution to pH 12−14. The aqueous solution was extracted with ethyl acetate (200 mL × 5). Combined organic layers were washed with brine (100 mL), dried over Na_2SO_4, filtered, and concentrated under vacuum to afford a light yellow oil (18.9 g, 97%). Without further purification, the resulting oil was dissolved in dry methylene chloride (360 mL), and di-*tert*-butyl dicarbonate (15.6 g, 71.6 mmol) and triethylamine (10 mL) were added. The solution was stirred at room temperature for 16 h. Most of the solvent was removed under vacuum, and ethyl acetate (300 mL) was added. The mixture was washed with 1 N HCl solution (50 mL × 3), dried over Na_2SO_4, and concentrated to afford a white solid which crystallized from diethyl ether to give white needles (24.9 g, 92% for two steps). R_f = 0.36 (hexanes/EtOAc 2:1). Mp: 129−130 °C. IR (film): 3680, 2973, 2844, 2866, 1685, 1346, 1160, 1055, 1012 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 7.75 (d, 2H), 7.26 (d, 2H), 6.19 (s, br, 1H), 4.55 (s, br, 1H), 3.70 (m, 1H), 3.03 (m, 1H), 2.42 (s, 3H), 2.02 (m, 2H), 1.65 (m, 3H), 1.42 (s, 9H), 1.30 (m, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 156.9, 143.1, 137.4, 129.6, 127.2, 80.1, 61.7, 57.1, 31.3, 29.4, 28.4, 21.6, 20.2. HRMS (EI): *m*/*z* calcd for $C_{17}H_{27}N_2O_4S$ $[M + 1]^+$ 353.1535, found 353.1554.

***tert*-Butyl 2-Aminocyclopentylcarbamate (1).** A mixture of lithium granules (1.52 g, 226.6 mmol) and naphthalene (10.9 g, 85.0 mmol) in dry dimethoxyethane (350 mL) was stirred at room temperature for 2 h. The deep blue solution was then cooled to 0 °C, and a solution of **4** (10.0 g, 28.33 mmol) in dry dimethoxyethane (40 mL) was added dropwise over 20 min. The mixture was stirred at 0 °C for 5 h. The undissolved lithium was filtered off, and 1 N HCl solution (60 mL) was added to the filtrate. The organic layer was separated and extracted with 1 N HCl (50 mL × 2). The aqueous layers were combined, extracted with diethyl ether (50 mL × 3), and then basified with 2 N NaOH solution to pH 12−14. The aqueous solution was extracted with ethyl acetate (50 mL × 5). Organic layers were combined and dried over Na_2SO_4, and solvent was removed under vacuum to afford *rac*-**1** as a colorless oil, which solidified under vacuum to a white solid (4.08 g, 72%). R_f = 0.31 (hexanes/EtOAc 2:1). Mp: 60−62 °C. IR (film): 3301, 2967, 1689, 1526, 1453, 1390, 1365, 1250, 1170, 1045, 1020, 870, 781 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 4.48 (s, br, 1H), 3.48 (m, 1H), 2.99 (m, 1H), 2.14 (m, 1H), 1.98 (m, 1H), 1.70 (m, 2H), 1.45 (s, 9H), 1.38 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 156.1, 78.9, 60.5, 59.4, 33.0, 30.9, 28.4, 20.7. HRMS (EI): *m*/*z* calcd for $C_{10}H_{21}N_2O_2$ $[M + 1]^+$ 201.1603, found 201.1632.

Optical Resolution of *tert*-Butyl 2-Aminocyclopentylcarbamate (1) Using (*S*)-(+)-10-Camphorsulfonic Acid. (*S*)-(+)-10-Camphorsulfonic acid (8.24 g, 35.5 mmol) in acetone (HPLC grade, 20 mL) was added to a solution of *rac*-**1** (7.1 g, 35.5 mmol) in acetone (HPLC grade, 20 mL). The mixture was stirred for 6 h, and the resulting white precipitate was collected by filtration. The precipitate was recrystallized in acetonitrile twice. The white precipitate was taken up in a mixture of ethyl acetate and 2 N NaOH solution. The aqueous layer was extracted with ethyl acetate (30 mL × 3). The organic layers were combined and dried over Na_2SO_4. The solvent was removed under vacuum to give a colorless oil (2.34 g, 11.7 mmol), which was dissolved in acetone and treated with a solution of (*S*)-(+)-10-camphorsulfonic acid (2.71 g, 11.7 mmol) in acetone (HPLC grade, 20 mL). After the mixture was stirred for 2 h, solvent was evaporated and solid was crystallized from acetonitrile. The same workup procedure described above to make the free base gave a colorless oil which solidified under vacuum to give a white solid (*S*,*S*-**1**: 1.90 g, 51% based on one enantiomer). $[\alpha]^{23}_D$: +15.8 (*c* 1.0, EtOH). Mother liquid was basified and extracted with ethyl acetate, resolved with (*R*)-(−)-10-camphorsulfonic acid following the procedure described above to afford (*R*,*R*)-**1** (1.58 g, 46% based on one enantiomer): $[\alpha]^{23}_D$ −16.0 (*c* 1.0, EtOH).

HPLC Analysis of *tert*-Butyl 2-(Benzamido)cyclopentylcarbamate (6). Benzoyl chloride (20 mg, 0.016 mL, 0.14 mmol) was added to a solution of nonracemic **1** (28 mg, 0.14 mmol) and triethylamine (28 mg, 0.038 mL, 0.28 mmol) in dry methylene chloride (2 mL). The solution was stirred for 16 h and then washed with 1 M HCl solution (1 mL × 3). The organic layer was dried over Na_2SO_4, solvent was removed under vacuum, and the residue was purified by preparative TLC (solvent: hexanes/EtOAc 2:1) to afford **5** (38 mg, 85%) as a white solid. R_f = 0.29 (hexanes/EtOAc 2:1). Mp: 190−192 °C. IR (film): 3314, 2974, 1638, 1621, 1541, 1302, 1170, 1033 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 7.75 (m, 2H), 7.34 (m, 3H), 4.75 (s, br, 1H), 3.85 (s, br, 2H), 2.33 (m, 1H), 2.04 (m, 1H), 1.72 (m, 2H), 1.39 (m, 2H), 1.34 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 168.0, 157.1, 134.3, 131.4, 128.5, 127.1, 80.0, 59.2, 56.5, 30.1, 29.8, 28.8, 28.4, 19.6. HRMS (EI): *m*/*z* calcd for $C_{17}H_{27}N_2O_4S$ $[M + 1]^+$ 327.1685, found 327.1689.

Compound **6** was dissolved in 2-propanol/hexanes (1:1) for HPLC analysis. HPLC conditions: column: (*S*,*S*)-Whelk-O1, 250 mm × 4.6 mm, 10 μm; mobile phase: hexanes/2-propanol (95:5); flow rate: 1.5 mL/min; absorbance 0.04; sample concentration: 1 mg/mL; injection volumn: 20 μL; retention time: (*S*,*S*)-**1**, 7.07 min; (*R*,*R*)-**1**, 9.53 min.

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Supporting Information Available: ^1H and ^{13}C NMR data for compounds **1**, **4**, and **6**. HPLC data (obtained on a chiral stationary phase) for **6**. This material is available free of charge via the Internet at http://pubs.acs.org.

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