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Application of aziridinium ring opening for preparation of optically active diamine and triamine analogues: Highly efficient synthesis and evaluation of DTPA-based MRI contrast enhancement agents

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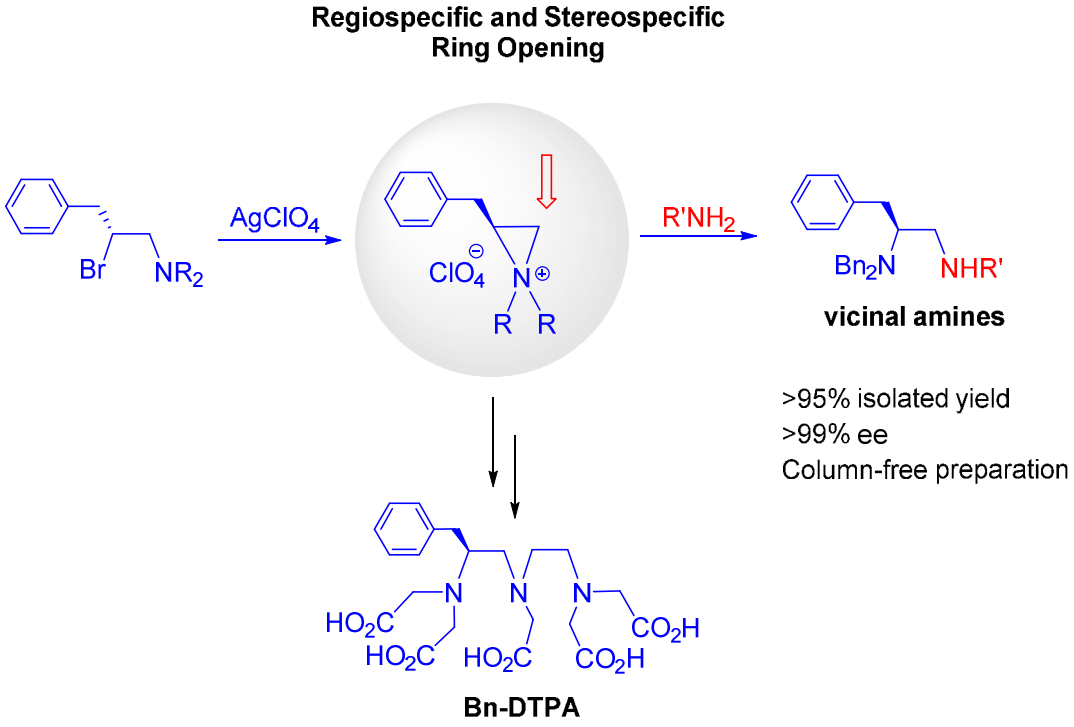
Graphical Abstract



Abstract

Ring opening of aziridinium ions with nitrogen nucleophiles was applied to highly efficient synthesis of optically active vicinal diamines and diethylene triamine pentaacetic acid (DTPA) analogues as potential magnetic resonance imaging (MRI) contrast enhancement agents. The synthetic method features a column-free isolation of the regiospecific and stereospecific nucleophilic substitution products of enantiomerically enriched aziridinium ions in excellent yield.

Introduction

Acyclic DTPA (diethylenetriamine pentaacetic acid) analogues containing polyaminocarboxylate groups have been employed as chelating agents of lanthanides and transition metals such as Y(III), Lu(III), Cu(II), and Gd(III) for numerous therapeutic and diagnostic techniques including magnetic resonance imaging (MRI), positron emission tomography (PET) imaging, and targeted radiation therapy.[1-3] Particularly, research effort has been made to development of Gd(III) complexes of DTPA analogues for sensitive MRI.[4-8] Paramagnetic Gd(III) complexes of DTPA analogues including Gd(DTPA) (Magnevist®) are clinically available MRI contrast enhancement agents for non-invasive and high resolution imaging of various diseases.[1] The extracellular MRI contrast agents have limitations of low relaxivity, low tissue specificity, and rapid clearance.[1] As one of the approaches to address such limitations, DTPA backbone has been modified to possess a functional group for conjugation to a targeting moiety.[1] For example, Gd(III) complexes of functionalized DTPA analogues, Gd(BOP-DTPA) (Multihance®) and Gd(EOB-DTPA) (Eovist®), are the clinically approved hepatobiliary agents that are known to selectively target albumin and cytosolic protein in the hepatocytes.[9,10] Conjugation of the Gd(III) complexes to a targeting moiety or a macromolecule including antibody, peptide, and dendrimer was also shown to result in a substantial increase in relaxivity.[1,7-8,11-12] It should be noted that substitution of a functional group onto the carbon backbone of DTPA will lead to generation of a stereocenter, and the stereochemistry in chelating agents was demonstrated to affect stability and biological activity of their metal complexes.[4,13-15]

A general method to prepare *C*-substituted DTPA analogues containing a functional group involves condensation of *C*-substituted β-amino ester with ethylenediamine and subsequent reduction of amide group and *N*-alkylation of the diethylenetriamine (DETA) backbone as the key steps.[4-6] However, *N*-alkylation of a triamine analogue typically produces polyalkylated byproducts along with the desired penta-alkylated DTPA analogues in low yield, and isolation of the alkylated DTPA analogues requires complicated and tedious chromatographic purification.[4-6] Development of more efficient method for preparation of optically active DTPA analogues and other polyamine-based chelating agents is a compelling research goal.

Recently, we reported the synthesis and characterization of optically active β-haloamines and aziridinium ions derived from β-aminoalcohol and demonstrated utility of aziridinium ions as the substrates of intramolecular Friedel-Crafts reaction to generate optically active tetrahydroisoquinoline (THIQ) analogues.[16] With our continued research interest in aziridinium ion chemistry, we chose to investigate nucleophilic ring opening of aziridinium ions with nitrogen nucleophiles. We report here stereoselective and regioselective ring opening of aziridinium ions for preparation of optically active vicinal diamines and *C*-benzyl substituted DTPA analogues (Bn-DTPA) as MRI contrast enhancement agents. Gd(III) complexes of the optically active Bn-DTPA analogues as MRI contrast enhancement were also prepared and evaluated for T1 and T2 relaxivities.

Result and Discussion

To understand regiochemistry and stereochemistry in ring opening of *C*-benzyl substituted aziridinium ions, we investigated nucleophilic reactions of aziridinium ion **4a**

(Scheme 1) as a model system. The *C*-benzyl substituted aziridinium ion **4a** was prepared starting from primary β-amino alcohols **1a**[17] (Scheme 1). Bromination of **1a** using NBS/PPh_3 proceeded via formation of phosphonium bromide followed by intramolecular rearrangement to aziridinium ion **2a** which further reacted with the bromide counter anion to provide β-bromoamines **3a** (86% isolated yield). The reaction was complete in 4 h at room temperature as evidenced by TLC analysis, and no byproduct was shown to be formed. However, β-bromoamines **3a** was obtained in less than quantitative yield. Relatively labile **3a** could be further hydrolyzed during silica gel column chromatography. However, no hydrolysis product was isolated by the column chromatographic purification. It seems that some of aziridinium ion **2a** was decomposed in situ prior to reaction with the bromide counter anion. The formation of **3a** with inverted stereochemistry was expected from regiospecific and stereospecific nucleophilic substitution reaction of aziridinium ion **2a** with the bromide occurred at the more hindered carbon in a S_N2 pathway. β-bromoamine **3a** was characterized by ^1H and ^{13}C NMR and optical rotation and remained stable with no noticeable change in optical activity over several months when stored at low temperature (–20 ^oC). Aziridinium ion **4a** was prepared from reaction of **3a** with silver perchlorate ($AgClO_4$) as a halosequestering agent. Reaction of **4a** with $AgClO_4$ was completed in 15 min to furnish aziridinium ion **4a** which was characterized by ^1H and ^{13}C NMR and optical rotation. Aziridinium ion **4a** generated from β-bromoamine **3a** in situ was further studied for convenient synthesis of vicinal diamines in high stereoselectivity and reacted with benzyl amine and diethyl amine as the representative nucleophiles to provide nucleophilic addition product **5** and **6** in excellent isolated yield (>93%) and enantiomeric excess

(>99% ee as determined by chiral HPLC analysis**)**. The regiospecific ring opening of **4a** by the nitrogen nucleophile at the less hindered methylene carbon led to the formation of **5** or **6** with retained stereochemistry in the methane carbon (C2). The regiochemistry in the ring opening reaction seems to be kinetically controlled by steric hindrance of bulky and strongly nucleophilic amines. It should be noted that the ring opening products **5** and **6** were obtained in high purity from simple work-up without column chromatographic purification. Vicinal diamines **7**[19] and **10**[21] were readily obtained from removal of *N*-benzyl groups in compounds **5** and **6** by hydrogenolysis, respectively. To further confirm regiochemistry and stereochemistry in the ring opening products **5**, the known *N*-methyl vicinal amine **9**[20] was prepared from **5** (Scheme 2). Reaction of **5** with dimethyl sulfate provided compound **8,** and *N*-benzyl groups in **8** were selectively removed by reaction of ammonium formate in the presence of Pd/C to produce **9**. The stereochemistry and regiochemistry in compounds **5** and **6** was confirmed by comparative analysis of NMR spectral and optical rotation data of the known compounds **7**, **9**, and **10**. The data suggest that aziridinium ion **4a** formed by intramolecular rearrangement of β-bromoamine **3a** in a S_N2 displacement reacted with the primary and secondary amine at the less hindered carbon leading to formation of **5** and **6** in almost absolute stereoselectivity, respectively.

With the excellent stereoselectivity observed in the aziridinium ring opening reactions with the nitrogen nucleophiles, we pursued to apply the efficient aziridinium opening to preparation of optically active DTPA analogues (Schemes 2-5). Bn-DTPA analogues contain a benzyl group substituted to the parent DTPA backbone, and the benzyl group is expected to enhance rigidity and liphophilicity of the DTPA chelating backbone system which can improve complex stability and cell permeability of the Bn-DTPA analogues

bound to Gd(III). Chirality in chelating agents was also known to affect complex stability and biological activity of metal complexes *in vivo*. Synthesis of β-bromoamine **3b** and aziridinium ions **4b** as the precursor molecules for synthesis of optically active *C*-benzyl substituted DTPA analogues is shown in Scheme 2. Reaction of *N*,*N*-bisubstituted amino alcohols[18] (*R*)-**1b** and (*S*)-**1b** with NBS and PPh_3 formed aziridinium ion **2b** with retained stereochemistry in the methane carbon (C2). The regiospecific and stereospecific ring opening of aziridinium ion (*S*)-**2b** and (*R*)-**2b** with the counter anion bromide provided β-bromoamines (*R*)-**3b** and (*S*)-**3b** with inverted stereochemistry at the methine (C2) carbon (~70% isolated yield), respectively. β-bromoamines (*R*)-**3b** and (*S*)-**3b** were reacted with halo-sequestering agent ($AgBF_4$) to afford azirdinium ion (*S*)-**4b** and (*R*)-**4b,** respectively. Complete conversion of β-bromoamine **3b** with bulky *N*-substitution groups to aziridinium ion **4b** took longer than that of **3a** with *N*-Bn groups to **4a** (45 min vs 15 min). Aziridinium ion **4a** was characterized by ^{1}H and ^{13}C NMR and optical rotation

(*R*)-**3b** was studied for nucleophilic substitution reactions with the nitrogen nucleophiles (Scheme 3). As expected, ring opening of (*S*)-**4b** by the amines occurred at the less hindered methylene carbon (C3). When (*R*)-**3b** was reacted with diethyl amine in DMSO and the absence of silver sequestering agent ($AgClO_4$) for 5 h, the reaction provided (*S*)-**11** in relatively low isolated yield (30%) along with the byproduct (**12**) formed from elimination of aziridinium ion (*S*)-**2b**. The same reaction in CH_3CN was slightly more efficient in providing the product (*S*)-**11** (53%). Later, (*R*)-**3b** was subjected to the reaction with $AgClO^4$ for formation of aziridinium ion (*S*)-**4b'** that was reacted with different amines in the regiospecific and stereospecific manner. The ring opening reaction of (*S*)-**4b'** at the less hindered carbon (C3) with the amines at room temperature for 2 h

afforded the substitution vicinal amine analogues **11**, **13**, and **14** in excellent isolated yield (>92%).

Synthesis of Bn-DTPA chelating agents is outlined in Scheme 4. The optically active and racemic aziridinium ions **4b′** generated from β-bromoamines **3b** were subjected to nucleophilic substitution reactions with pre-alkyated amine. First, (*rac*)-**3b**[18] was reacted with **15**[22] to provide penta-alkylated triamines (*rac*)-**16** as the regiospecific isomer. As expected, ring opening reaction of aziridnium ion (*rac*)-**4b′** with **15** occurred at the less hindered methylene carbon in (*rac*)-**4b′**. Simple work-up furnished (*rac*)-**16** in high purity and almost quantitative yield (94%). Removal of *tert*-Butyl groups in (*rac*)-**16** using HCl(g) provided (*rac*)-Bn-DTPA. Similarly, the stereoisomers (*R*)-**16** (93%) and (*S*)-**16** (91%) in excellent isolated yield were produced by the same procedure. (*R*)-Bn-DTPA,[23] and (*S*)-Bn-DTPA[23] were obtained from removal of *tert*-butyl groups in the respective stereoisomers of (*R*)-**16** and (*S*)-**16** using HCl(g).

To confirm stereochemistry and regiochemistry in the ring opening of aziridinium ion **4b,** (*S*)-Bn-DTPA was independently prepared using the standard synthetic method based on polyalkylation of triamines (Scheme 5). Condensation of β-amino ester **17** with ethylene diamine afforded compound **18**, which was further converted to **19** via reduction using BH_3/THF. Base-promoted alkylation of **19** with *tert*-butyl bromoacetate provided compound (*S*)-**16**. Removal of *tert*-butyl groups in (*S*)-**16** using HCl (aq) gave (*S*)-Bn-DTPA. ^{1}H and ^{13}C NMR data of compounds (*S*)-**16** and (*S*)-Bn-DTPA prepared via the two independent synthetic routes (Schemes 4 and 5) were essentially identical, and the optical rotation data of (*S*)-**16** and (*S*)-Bn-DTPA confirmed that intramolecular rearrangement of β-bromoamine (*R*)-**3a** produced aziridinium ion (*S*)-**4b** with inversion

of stereochemistry at the more hindered carbon (C2), and subsequent regiospecific ring opening of (*S*)-**4b′** by **15** at the less hindered carbon (C3) provided (*S*)-**16**.

The Gd(III) complexes of the new Bn-DTPA chelates were prepared, characterized, and evaluated for T_1 relaxivity as previously reported.[24] The Bn-DTPA analogues were complexed with Gd(III), and the corresponding Gd(III) complexes were evaluated as potential MRI contrast agents. Gd(III) complexes of (rac)-Bn-DTPA, (*R*)-Bn-DTPA, and (*S*)-Bn-DTPA were synthesized by mixing each chelator with $GdCl_3$ in a molar ratio of 1 to 0.9, and the resulting mixture at pH 7 was heated to 90 ^{o}C and stirred until no free Gd(III) ions were detected using an ArsenazoIII (AAIII) assay.[24] The Gd(III) complexes were purified by semi-prep HPLC, and a serial samples of pure Gd(III) complexes (H_2O, pH 7) in different concentration were measured for relaxivity, and concentration of each sample of Gd(III) complexes was measured by ICP-MS (Figure 2 and Supporting Information). Relaxivities of the Gd(III) complexes at 60 MHz and 37 ^{o}C were measured and compared to the clinically available MRI contrast enhancement agents, Gd(DTPA)[25] as previously reported.

The Gd(III) complexes of all Bn-DTPA complexes displayed slightly higher T_1 relaxivities relative to Gd(DTPA) (3.8 $mM^{-1}s^{-1}$). (*S*)-Bn-DTPA and (*R*)-Bn-DTPA, and (*rac*)-Bn-DTPA provided T_1 relaxivities (4.05, 4.05, and 3.93 $mM^{-1}s^{-1}$, respectively). The introduction of the benzyl group into the DTPA backbone lead to an increase in the T_1 relaxivities, probably due to an increase in the rotational correlation time with a concomitant increase in the molecular weight.

Conclusion

We have shown that nucleophilic reactions of aziridinium ions with nitrogen nucleophiles provided vicinal diamine analogues in excellent and enantioselectivity (>99% ee) as the regiospecific ring opening products. The convenient ring opening of aziridinium ions was successfully applied for the synthesis of optically active polyaminocarboxylate-based DTPA analogues centered on isolation of the ring opening products via a simple work-up without complicated column purification. Gd(III) complexes of the enantiomerically enriched Bn-DTPA analogues were favorably compared to the MRI contrast agent in clinical use for T_1 relaxivities.

Experimental

Instrument and methods. ^{1}H and ^{13}C NMR spectra were obtained using a Bruker 300 instrument, and chemical shifts are reported in ppm on the δ scale relative to TMS or solvent. Fast atom bombardment (FAB) high resolution mass spectra (HRMS) were obtained on JEOL double sector JMS-AX505HA mass spectrometer (University of Notre Dame, IN). Analytical HPLC was performed on Agilent 1200 (Agilent, Santa Clara, CA) equipped with a diode array detector (λ = 254 and 280 nm), thermostat set at 35 ^{o}C and a Zorbax Eclipse XDB-C18 column (4.6 x 150 mm, 80Å, Agilent, Santa Clara, CA). The mobile phase of a binary gradient (0-100%B/40 min; solvent A = 0.05 M AcOH/Et_3N, pH 6.0; solvent B = CH_3CN for method 1). Enantiomeric excess of optically active compounds (20 μL, 1 mg of sample in 1 mL of hexanes) was determined by chiral HPLC (Chiralpak® AD-H, 4.6 x 150 mm, 80Å) using the following chromatographic conditions: method 2 (binary isocratic, 1% i-PrOH/Hexanes, 15 min, λ = 230 nm, flow rate = 1.0 mL/min) or method 3 (binary isocratic, 30% i-PrOH/Hexanes, 20 min, λ=230nm, flow rate = 1.0 mL/min). Optical rotation of chiral molecules was determined using JASCO P-2000 polarimeter.

(*S*)-2-Dibenzylamino-3-phenylpropan-1-ol ((*S*)-1a).[17] To a solution of (S)-phenylalaniol (1.50 g, 10.0 mmol) and K_2CO_3 (3.05 g, 22.0 mmol) in CH_3CN (20 mL) at 0 ^{o}C was added dropwise a solution of benzyl bromide (3.76 g, 22.0 mmol) in CH_3CN (2 mL) over 20 min. The reaction mixture was filtered, and the filtrate was concentrated *in vacuo*. The residue was purified via chromatography on silica gel (60-230 mesh) eluted with 5% ethyl acetate in hexanes to afford **(*S*)-1a** (3.29 g, 99%) as a colorless oil. HRMS

(ESI) Calcd for $C_{23}H_{26}NO$ $[M + H]^+$ *m/z* 332.2014. Found: $[M + H]^+$ *m/z* 332.2036. $[\alpha]^{26}_D = +46.7°$ (*c* = 1.0, $CHCl_3$). [lit.[17] $[\alpha]^{26}_D = +42.4°$ (c = 1.45, CH_2C1_2]

General Synthesis of β-bromoamines 3. To a solution of *N*,*N*-dialkylated alcohol **1** (1 equiv) and PPh_3 (1.2 equiv) in $CHCl_3$ was portionwise added N-bromosuccinimide (1.2 equiv) at 0 °C over 10 min. The resulting mixture was stirred for 4 h while being maintained at 0 °C. The ice bath was removed, and the reaction mixture was warmed to room temperature and stirred for 1 h and evaporated to dryness. The residue was purified via column chromatography on silica gel (60-230 mesh) eluting with 5% ethyl acetate in hexanes.

Dibenzyl[(2*R*)-2-bromo-3-phenylpropyl]amine ((*R*)-3a).[26] To a solution of **(*S*)-1a**[17] (139 mg, 0.42 mmol) and PPh_3 (165.2 mg, 0.63 mmol) in $CHCl_3$ (5 mL) at 0 ^oC was added NBS (112.1 mg, 0.63 mmol) portionwise at 0 °C over 20 min. After the work-up, the residue was purified by silica gel column chromatography eluted with 5% ethyl acetate in hexanes to afford **(*R*)-3a** (142 mg, 85.8%) as a colorless oil. ^1H NMR ($CDCl_3$, 300 MHz) δ 2.71 (dd, *J* = 14.2, 9.8 Hz, 1H), 2.90-2.96 (m, 2H), 3.46 (dd, *J* = 14.5, 3.1Hz, 1H), 3.66 (dd, *J* = 37.2, 13.3 Hz, 4H), 4.07-4.14 (m, 1H), 7.06-7.40 (m, 15H); ^{13}C NMR ($CDCl_3$, 300 MHz) δ 42.7 (t), 54.8 (d), 59.4 (t), 61.5 (t), 126.6 (d), 127.2 (d), 128.3 (d), 129.1 (d), 129.2 (d), 138.9 (s), 139.0 (s). $[\alpha]^{26}_D = -11.7^o$ (*c* = 1.0, $CHCl_3$). HRMS (ESI) Calcd for $C_{23}H_{26}NO$ $[M - Br + H_2O]^+$ m/z 332.2009. Found: $[M - Br + H_2O]^+$ m/z 332.2034.

***tert*-butyl-2-{[(2*R*)-2-bromo-3-phenylpropyl][2-(*tert*-butoxy)-2-oxoethyl]amino}acetate ((*R*)-3b)**. To a solution of **(*S*)-1b**[18] (400 mg, 1.05 mmol) and PPh_3 (332 mg, 1.27 mmol) in $CHCl_3$ (50 mL) at 0 ^oC was added NBS (225 mg, 1.27 mmol). The residue

was purified by silica gel column chromatography eluted with 5% ethyl acetate in hexanes to afford **(*R*)-3b** (322 mg, 70%) as yellow oil. $[\alpha]^{26}_{D}$ = + 1.10 (*c* = 1.0, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.46 (s, 18H), 2.92-3.09 (m, 2H), 3.27 (dd, *J* = 14.1, 6.3 Hz, 1H), 3.41-3.59 (m, 5H), 4.19-4.32 (m, 1H), 7.17-7.38 (m, 5H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 28.2 (q), 42.4 (t), 55.4 (d), 57.2 (t), 62.1 (t), 81.3 (s), 126.6 (d), 128.3 (d), 129.3 (d), 138.7 (s), 170.6 (s). HRMS (positive ion FAB) Calcd for $C_{21}H_{33}NO_4Br$ $[M + H]^+$ m/z 442.1593.

***tert*-butyl-2-{[(2*R*)-2-bromo-3-phenylpropyl][2-(*tert*-butoxy)-2-oxoethyl]amino}acetate ((*S*)-3b)**. To a solution of **(*R*)-1b**[18] (400 mg, 1.05 mmol) and PPh_3 (332 mg, 1.27 mmol) in $CHCl_3$ (20 mL) at 0 ^{o}C was added NBS (225 mg, 1.27 mmol). The residue was purified by silica gel column chromatography eluted with 5% ethyl acetate in hexanes to afford **(*S*)-3b** (328 mg, 71%) as a yellow oil. $[\alpha]^{26}_{D}$ = − 2.13 (*c* = 1.0, $CHCl_3$). Calcd for $C_{21}H_{33}NO_4Br$ $[M + H]^+$ m/z 442.1593. Found: $[M + H]^+$ m/z 442.1596. ^{1}H and ^{13}C NMR data were essentially identical to (*R*)-**3b** as previously above.

General synthesis of isolable aziridinium ions 4. To a stirred solution of β-amino halide in $CDCl_3$ (0.5 mL) at –5 °C was added silver perchlorate (5 eq) or silver borotetrabromide (5 eq). The resulting mixture was continuously stirred at –5 °C, while the reaction progress was monitored using TLC. After completion of the reaction, silver bromide was filtered, and the resulting solution was immediately characterized by ^{1}H and ^{13}C NMR and optical rotation.

(*S*)-1,1,2-Tribenzylaziridinium perchlorate ((*S*)-4a). The general procedure was followed for the reaction of **(*R*)-3a**[24] (50 mg, 0.13 mmol) and $AgClO_4$ (131.2 mg, 0.63 mmol) in $CDCl_3$ (1 mL) for 15 min. ^{1}H NMR ($CDCl_3$, 300 MHz) *δ* 3.13 (d, *J* = 4.6 Hz,

1H), 3.34 (dd, *J* = 14.4, 6.5 Hz, 1H), 3.49-3.75 (m, 3H), 3.99 (d, *J* = 13.5 Hz, 1H), 4.38-4.42 (m, 3H), 7.02 (d, *J* = 7.5 Hz, 2H), 7.15-7.47 (m, 13H); ^{13}C NMR ($CDCl_3$, 300 MHz) δ 32.1 (t), 42.4 (t), 51.7 (d), 57.0 (t), 61.1 (t), 127.5 (d), 127.9 (s), 129.0 (d), 129.1 (d), 129.4 (d), 129.7 (d), 130.3 (d), 130.4 (d), 130.9 (d), 134.5 (s). $[\alpha]^{26}_{D}$ = + 9.3° (*c* = 0.6, $CDCl_3$).

(2*S*)-2-benzyl-1,1-bis[2-(tert-butoxy)-2-oxoethyl]aziridin-1-ium tetrafluoroborate ((*S*)-4b). The general procedure was followed for the reaction of **(*R*)-3b** (100 mg, 0.23 mmol) and $AgBF_4$ (44 mg, 0.23 mmol) in $CDCl_3$ (1 mL) for 40 min. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.47 (s, 9H), 1.50 (s, 9H), 3.11 (dd, *J* = 13.5, 9.6 Hz, 1H), 3.39-3.57 (m, 3H), 3.68-3.82 (m, 1H), 3.98-4.21 (m, 4H), 7.17-7.33 (m, 5H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 27.9 (q), 32.1 (t), 47.3 (t), 53.7 (t), 55.8 (d), 60.4 (t), 85.6 (s), 85.7 (s), 127.4 (d), 128.8 (d), 129.2 (d), 133.4 (s), 163.9 (s), 163.9 (s). $[\alpha]^{26}_{D}$ = + 11.1° (*c* = 1.0, $CDCl_3$)

(2*R*)-2-benzyl-1,1-bis[2-(tert-butoxy)-2-oxoethyl]aziridin-1-ium tetrafluoroborate ((*R*)-4b). The general procedure was followed for the reaction of **(*S*)-3b** (50 mg, 0.11 mmol) and $AgBF_4$ (22 mg, 0.11 mmol) in $CDCl_3$ (0.5 mL) for 40 min. The NMR data are identical to those of **(*S*)-4b**. $[\alpha]^{26}_{D}$ = −10.6° (*c* = 1.0, $CDCl_3$)

Dibenzyl[(2*S*)-1-(benzylamino)-3-phenylpropan-2-yl]amine ((*S*)-5). To a stirred solution of (*R*)-**3a** (150.0 mg, 0.38 mmol) in CH_3CN (6 mL) was added silver perchlorate (394.3 mg, 1.90 mmol), and the reaction mixture was stirred at –5 °C for 15 min. After which, benzyl amine (122.3 mg, 1.14 mmol) was added and the resulting mixture was stirred at room temperature for 2 h. The resulting mixture was filtered and concentrated *in vacuo*. The residue was treated with 0.1M HCl (20 mL) and then extracted with CH_2Cl_2 (4 × 15 mL). The combined organic layer was evaporated. The residue was

treated with 0.1M aqueous NaOH (20 mL) and then extracted with CH_2Cl_2 (4 × 15 mL). The combined organic layer was dried over $MgSO_4$, filtered, and concentrated *in vacuo* to provide technically pure **(*S*)-5** (158.8 mg, 99.5%) as yellow oil which was further purified by column chromatography on silica gel (60-220 mesh) eluting with 2% methanol in dichloromethane to afford pure **(*S*)-5** (155.5 mg, 94.9%) as a yellow oil. $[\alpha]^{26}_{D} = -1.7^{\circ}$ (*c* = 1.0, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.02 (s, 1H), 2.45-2.60 (m, 2H), 2.81 (dd, *J* = 12.3, 9.6 Hz, 1H), 3.11-3.24 (m, 2H), 3.34-3.44 (m, 1H), 3.53-3.66 (m, 3H), 3.91 (d, *J* = 13.5 Hz, 2H), 7.04-7.49 (m, 20H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 33.3 (t), 49.0 (t), 53.3 (t), 53.7 (t), 59.2 (d), 126.0 (d), 126.7 (d), 127.1 (d), 128.1 (d), 128.3 (d), 128.4 (d), 128.5 (d), 128.9 (d), 129.3 (d), 140.0 (s), 140.2 (s), 140.6 (s). HRMS (Positive ion ESI) Calcd for $C_{30}H_{33}N_2$ $[M + H]^+$ m/z 421.2638. Found: $[M + H]^+$ m/z 421.2630. Chiral HPLC (method 2): binary isocratic, 1% i-PrOH/Hexanes, 15 min, λ = 230 nm, flow rate = 1.0 mL/min t_R = 8.1 min (S, minor) and 9.6 min (R, major), >99% ee.

Dibenzyl[1-(benzylamino)-3-phenylpropan-2-yl]amine ((*rac*)-5). To a stirred solution of (*rac*)-**3a**[18] (59 mg, 0.150 mmol) in CH_3CN (3.0 mL) was added silver perchlorate (155.11 mg, 0.748 mmol), and the reaction mixture was stirred at – 5 ^{o}C for 15 min. After which, benzyl amine (48.09 mg, 0.449 mmol) was added and the resulting mixture was stirred at room temperature for 2 h. The resulting mixture was filtered and concentrated *in vacuo*. The residue was treated with 0.1M HCl (20 mL) and then extracted with CH_2Cl_2 (4 × 15 mL). The combined organic layer was evaporated. The residue was treated with 0.1M aqueous NaOH (20 mL) and then extracted with CH_2Cl_2 (4 × 15 mL). The combined organic layer was dried over $MgSO_4$, filtered, and concentrated *in vacuo*

to provide pure (**rac**)-**5** (54.2 mg, 86%) as a yellow oil. ^{1}H and ^{13}C NMR are identical to those of (*S*)-**5** as reported above.

Dibenzyl[(2*S*)-1-(diethylamino)-3-phenylpropan-2-yl]amine ((*S*)-6). To a stirred solution of (R)-**3a** (150.0 mg, 0.38 mmol) in CH_3CN (6 mL) was added silver perchlorate (394.3 mg, 1.90 mmol), and the reaction mixture was stirred at –5 ^{o}C for 15 min. After which, diethylamine (83.4 mg, 1.14 mmol) was added and the resulting mixture was stirred at room temperature for 2 h. The resulting mixture was filtered and concentrated *in vacuo*. The residue was treated with 0.1M HCl (20 mL) and then extracted with CH_2Cl_2 (4 × 15 mL). The combined organic layer was evaporated. The residue was treated with 0.1M aqueous NaOH (20 mL) and then extracted with CH_2Cl_2 (4 × 15 mL). The combined organic layer was dried over $MgSO_4$, filtered, and concentrated *in vacuo* to provide technically pure (*S*)-**6** (141.3 mg, 96.2%) as a yellow oil which was purified by column chromatography on silica gel (60-220 mesh) eluting with 2% methanol in dichloromethane to afford pure (*S*)-**6** (139.1 mg, 94.7%) as a yellow oil. $[\alpha]^{26}_{D} = -23.7^{\circ}$ (*c* = 1.0, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.97 (t, *J* = 6.9 Hz, 6H), 2.35 (dd, *J* = 12.6, 7.8 Hz, 1H), 2.43 (q, *J* = 6.9 Hz, 4H), 2.72-2.96 (m, 3H), 2.97-3.09 (m, 1H), 3.69 (d, *J* = 14.1 Hz, 2H), 3.76 (d, *J* = 13.8 Hz, 2H), 7.04-7.35 (m, 15H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 11.9 (q), 36.6 (t), 47.3 (t), 53.4 (t), 53.5 (t), 57.6 (d), 125.6 (d), 126.6 (d), 128.0 (d), 128.6 (d), 129.6 (d), 140.5 (s), 141.4 (s). HRMS (Positive ion ESI) Calcd for $C_{27}H_{35}N_2$ $[M + H]^+$ m/z 387.2795. Found: $[M + H]^+$ m/z 387.2790. Chiral HPLC (method 3): binary isocratic, 30% i-PrOH/Hexanes, 20 min, λ=230nm, flow rate = 1.0 mL/min t_R = 2.28 min (R, minor) and 2.35 min (S, major), >99% ee.

Dibenzyl[1-(diethylamino)-3-phenylpropan-2-yl]amine (*rac*-6). To a stirred solution of (*rac*)-**3a**[18] (50 mg, 0.13 mmol) in CH_3CN (3.0 mL) was added silver perchlorate (131.4 mg, 0.63 mmol), and the reaction mixture was stirred at –5 ^oC for 15 min. After which, diethylamine (27.82 mg, 0.38 mmol) was added and the resulting mixture was stirred at room temperature for 2 h. The resulting mixture was filtered and concentrated *in vacuo*. The residue was treated with 0.1M HCl (20 mL) and then extracted with CH_2Cl_2 (4 × 15 mL). The combined organic layer was evaporated. The residue was treated with 0.1M aqueous NaOH (20 mL) and then extracted with CH_2Cl_2 (4 × 15 mL). The combined organic layer was dried over $MgSO_4$, filtered, and concentrated *in vacuo* to provide pure (*rac*)-**6** (45.8 mg, 91%) as a yellow oil. ^1H and ^{13}C NMR are identical to those of (*S*)-**6** as reported above.

(2*S*)-3-phenylpropane-1,2-diamine (7).[19] To a round-bottomed flask containing **5** (69 mg, 0.164 mmol) in ethanol (10 mL) at room temperature was added wet 10% Pd/C (20 mg). The reaction mixture was placed under hydrogenation apparatus (20 psi) for 3 days. The resulting mixture was filtered via celite bed and washed thoroughly with methanol. The filtrate was added 3 drops concentrated HCl and concentrated to provide **7** (20.2 mg, 82%) as a white solid. ^1H NMR (D_2O, 300 MHz) δ 2.90 (dd, J = 14.1, 8.7 Hz, 1H), 3.09 (dd, J = 14.4, 6.3 Hz, 1H), 3.28 (d, J = 6.0 Hz, 2H), 3.75-3.88 (m, 1H), 7.21-7.39 (m, 5H); ^{13}C NMR (D_2O, 75 MHz) δ 36.1 (t), 40.6 (t), 50.6 (d), 128.1 (d), 129.4 (d), 133.9 (s). $[\alpha]^{26}_D = +10.12^{\circ}$ (c = 2.0, $CHCl_3$). (Lit.[19] $[\alpha]^{26}_D = +8.2$ (c = 2.0, $CHCl_3$).

Dibenzyl[(2*S*)-1-[benzyl(methyl)amino]-3-phenylpropan-2-yl]amine (8). To a solution of **5** (200 mg, 0.476 mmol) in CH_3CN (2 mL) was added dimethyl sulfate (60 mg, 0.0476 mmol) and triethyl amine (57.6 mg, 0.57 mmol). The resulting mixture was heated to

reflux for 3 h and evaporated to dryness. The residue was purified by column chromatography eluting with 5% ethyl acetate in hexane to provide pure product **8** (151.6 mg, 73.3%). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.14 (s, 3H), 2.44 (dd, J = 12.3, 7.5 Hz, 1H), 2.82 (dd, J = 12.3, 5.4 Hz, 1H), 2.88-3.00 (m, 2H), 3.16-3.28 (m, 1H), 3.46 (d, J = 13.2 Hz, 1H), 3.56 (d, J = 12.9 Hz, 1H), 3.74 (d, J = 14.4 Hz, 2H), 3.79 (d, J = 14.1 Hz, 2H), 7.14 (d, J = 6.3 Hz, 2H), 7.20-7.41 (m, 18H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 36.6 (t), 42.9 (q), 53.5 (t), 57.2 (d), 58.1 (t), 63.1 (t), 125.7 (d), 126.7 (d), 126.9 (d), 128.1 (d), 128.2 (d), 128.7 (d), 129.1 (d), 129.6 (d), 139.6 (s), 140.4 (s), 141.4 (s). $[\alpha]^{26}_{D} = -22.4^{\circ}$ (c = 1.0, $CHCl_3$). HRMS (ESI) Calcd for $C_{31}H_{35}N_2$ $[M + H]^+$ *m/z* 435.2795. Found: $[M + H]^+$ *m/z* 435.2794.

[(2*S*)-2-Amino-3-phenylpropyl](methyl)amine ((*S*)-9).[20] To a solution of **8** (126 mg, 0.29 mmol) in anhydrous MeOH (3 mL), 10% Pd/C (126 mg) and ammonium formate (182.9 mg, 2.9 mmol) were added. The resulting mixture was heated to reflux for 1 h and then was filtered over celite pad. The filtrate was evaporated to dryness. The residue was dissolved in $CHCl_3$ (10 mL) and filtered to provide pure product **9** (35 mg, 73.5%). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.47 (s, 3H), 2.54 (dd, J = 12.0, 8.7 Hz, 2H), 2.67-2.83 (m, 2H), 2.89 (s, br, 3H), 3.15-3.24 (m, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 35.8 (q), 42.6 (t), 51.6 (d), 57.1 (t), 126.5 (d), 128.6 (d), 129.3 (d), 138.5 (s). $[\alpha]^{26}_{D} = -5.9^{\circ}$ (c = 1.0, $CHCl_3$). [Lit.[20] $[\alpha]^{26}_{D} = -6.2$ (c = 1.12, $CHCl_3$)].

[(2*S*)-2-amino-3-phenylpropyl]diethylamine (10).[21] To **6** (50 mg, 0.129 mmol) in ethanol (10 mL) at room temperature was added wet 10% Pd/C (20 mg). The reaction mixture was placed under hydrogenation apparatus (20 Psi) for 2 days. The resulting mixture was filtered via Celite bed and washed thoroughly with methanol. The filtrate

was added 3 drops concentrated HCl and concentrated to provide **10** (23 mg, 86.2%) as a light yellow oil. ^{1}H NMR (D_2O, 300 MHz) δ 0.88 (t, J = 6.9 Hz, 3H), 1.09 (t, J = 7.2 Hz, 3H), 2.87-2.97 (m, 3H), 3.03-3.30 (m, 5H), 3.85-3.89 (m, 1 H), 7.13-7.30 (m, 5H); ^{13}C NMR (D_2O, 75 MHz) δ 7.0 (q), 8.1 (q), 36.8 (d), , 47.0 (d), 48.4(d), 48.8(d), 53.2(t), 128.2 (d), 129.4 (d), 129.5 (d),133.6 (s). $[\alpha]^{26}_{D} = +37.8^{\circ}$ (c = 1.0, CH_3OH). [Lit.[21] $[\alpha]^{20}_{D} = +40.7^{\circ}$ (c = 1.0, CH_3OH)].

***tert*-butyl-2-{[(2S)-1-(diethylamino)-3-phenylpropan-2-yl][2-(tert-butoxy)-2-oxoethyl]amino}acetate ((*S*)-11) and di-tert-butyl 2,2'-(cinnamylazanediyl)diacetate (12).**

From reaction of (*R*)-3b in DMSO and the absence of $AgClO_4$. To a stirred solution of (*R*)-**3b** (50.0 mg, 0.11 mmol) in DMSO (1 mL) was added diethylamine (24.8 mg, 0.34 mmol), and the reaction mixture was stirred at room temperature for 6 h. After completion of the reaction by TLC, the reaction mixture was treated with water (15 mL) and then extracted with ether (3 × 15 mL). The combined organic layer was dried over $MgSO_4$, filtered, and concentrated *in* vacuo. The residue was purified by column chromatography on silica gel (60-220 mesh) eluting with 1% methanol in dichloromethane to afford pure **12** (0.6 mg, 1.5%) as a colorless oil and continued elution with 10% methanol in dichloromethane to afford pure **(*S*)-11** (14.8 mg, 30.1%) as a yellow oil.

From reaction of (*R*)-3b in CH_3CN and the absence of $AgClO_4$. To a stirred solution of (*R*)-**3b** (50.0 mg, 0.11 mmol) in CH_3CN (1 mL) was added diethylamine (24.8 mg, 0.34 mmol), and the reaction mixture was stirred at room temperature for 6 h. After completion of the reaction by TLC, the reaction mixture was concentrated and purified by

column chromatography on silica gel (60-220 mesh) eluting with 1% methanol in dichloromethane to afford pure **12** (0.9 mg, 2.2%) as a colorless oil and continued elution with 10% methanol in dichloromethane to afford pure **(*S*)-11** (25.8 mg, 52.5%) as a yellow oil.

Compound **11**. $[\alpha]^{26}_{D} = -16.4^{\circ}$ (c = 1.0, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.90 (t, J = 7.1 Hz, 6H), 1.44 (s, 18H), 2.28 (dd, J = 13.2, 6.6 Hz, 1H), 2.42-2.50 (m, 4H), 2.58 (dd, J = 13.2, 6.6 Hz, 1H), 2.65-2.85 (m, 2H), 3.13-3.19 (m, 1H), 3.41-3.55 (m, 4H), 7.13-7.27 (m, 5H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 11.6 (q), 28.1 (q), 37.6 (t), 47.1 (t), 53.8 (t), 54.7 (t), 62.2 (d), 80.5 (s), 125.7 (d), 128.1 (d), 129.3 (d), 140.8 (s), 171.5 (s). HRMS (positive ion ESI) Calcd for $C_{25}H_{43}N_2O_4$ $[M + H]^+$ m/z 435.3217. Found: $[M + H]^+$ m/z 435.3237.

Compound 12. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.45 (s, 18H), 3.48 (s, 4H), 3.53 (d, J = 6.9 Hz, 2H), 6.25-6.35 (m, 1H), 6.53 (d, J = 16.2 Hz, 1H), 7.20-7.39 (m, 5H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 28.2 (q), 55.2 (t), 56.6 (t), 80.9 (s), 126.4 (d), 127.3 (d), 127.5 (d), 128.5 (s), 133.0 (d), 137.0 (d), 170.6 (s). HRMS (Positive ion ESI) Calcd for $C_{21}H_{32}NO_4$ $[M + H]^+$ m/z 362.2331. Found: $[M + H]^+$ m/z 362.2327.

***tert*-butyl 2-{[2-(*tert*-butoxy)-2-oxoethyl][(2S)-1-(diethylamino)-3-phenyl pro-pan-2-yl] amino}acetate ((*S*)-11).**

From reaction of (*R*)-3b in the presence of $AgClO_4$. To a stirred solution of *(R)*-**3b** (50.0 mg, 0.11 mmol) in CH_3CN (1.5 mL) was added silver perchlorate (117 mg, 0.57 mmol), and the reaction mixture was stirred at –5 ^{o}C for 25 min. After which, diethylamine (24.8 mg, 0.34 mmol) was added dropwise and the resulting mixture was stirred at room temperature for 1 h. The resulting mixture was filtered and concentrated

in vacuo. The residue was treated with 0.1M HCl (20 mL) and then extracted with CH_2Cl_2 (4 × 15 mL). The combined organic layer was evaporated. The residue was treated with 0.1 M aqueous NaOH (20 mL) and then extracted with CH_2Cl_2 (4 × 15 mL). The combined organic layer was dried over $MgSO_4$, filtered, and concentrated *in vacuo*. After the work-up, a technically pure (*S*)-**11** (46 mg, 94%) was obtained as a yellow oil which was further purified by column chromatography on silica gel (60-220 mesh) eluting with 10% methanol in dichloromethane to afford pure (45.3 mg, 92%) as a yellow oil. ^{1}H and ^{13}C NMR are identical to those of (*S*)-**11** as reported above.

***tert*-butyl 2-{[(2S)-1-(benzylamino)-3-phenylpropan-2-yl][2-(*tert*-butoxy)-2-oxoethyl] amino}acetate ((*S*)-13).** To a stirred solution of (*R*)-**3b** (50.0 mg, 0.11 mmol) in CH_3CN (3 mL) was added silver perchlorate (117.2 mg, 0.57 mmol), and the reaction mixture was stirred at –5 ^{o}C for 15 min. After which, benzylamine (36.3 mg, 0.34 mmol) was added and the resulting mixture was stirred at room temperature for 2 h. The resulting mixture was filtered and concentrated *in vacuo*. The residue was treated with 0.1M HCl (20 mL) and then extracted with CH_2Cl_2 (3 × 15 mL). The combined organic layer was evaporated. The residue was treated with 0.1M NaOH (20 mL) and then extracted with CH_2Cl_2 (3 × 15 mL). The combined organic layer was dried over $MgSO_4$, filtered, and concentrated *in vacuo* to provide technically pure (*S*)-**13** (50.8 mg, 96.2%) as a yellow oil which was further purified by column chromatography on silica gel (60-220 mesh) eluting with 5% methanol in dichloromethane to 30% methanol in dichloromethane containing 1% Et_3N to afford pure (*S*)-**13** (49.4 mg, 93.4%) as a yellow oil. $[\alpha]^{26}_{D} = -19.3^{\circ}$ (*c* = 1.0, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.45 (s, 18H), 2.36-2.55 (m, 3H), 2.60-2.79 (m, 1H), 2.99 (dd, *J* = 13.2, 4.5 Hz, 1H), 3.10-3.24 (m, 1H), 3.27-3.52 (m, 5H),

3.70 (dd, J = 39.3, 13.2 Hz, 2H), 7.08-7.36 (m, 10H); ^{13}C NMR ($CDCl_3$, 75 MHz)) δ 28.1 (q), 36.6 (t), 50.1 (t), 53.6 (t), 53.8 (t), 64.9 (d), 80.9 (s), 126.1 (d), 126.7 (d), 128.2 (d), 128.3 (d), 128.4 (d), 129.1 (d), 139.5 (s), 140.4 (s), 171.5 (s). HRMS (Positive ion ESI) Calcd for $C_{28}H_{41}N_2O_4$ $[M + H]^+$ m/z 469.3061. Found: $[M + H]^+$ m/z 469.3066.

***tert*-butyl 2-{[2-(*tert*-butoxy)-2-oxoethyl][(2S)-1-phenyl-3-(piperidin-1-yl)-propan-2-yl]amino}acetate ((*S*)-14).** To a stirred solution of (*R*)-**3b** (50.0 mg, 0.11 mmol) in CH_3CN (3 mL) was added silver perchlorate (117.2 mg, 0.57 mmol), and the reaction mixture was stirred at –5 ^oC for 15 min. After which, piperidine (28.9 mg, 0.34 mmol) was added and the resulting mixture was stirred at room temperature for 2 h. The resulting mixture was filtered and concentrated *in vacuo*. The residue was treated with 0.1M HCl (20 mL) and then extracted with CH_2Cl_2 (3 × 15 mL). The combined organic layer was evaporated. The residue was treated with 0.1M NaOH (20 mL) and then extracted with CH_2Cl_2 (3 × 15 mL). The combined organic layer was dried over $MgSO_4$, filtered, and concentrated *in vacuo* to provide technically pure (*S*)-**14** (47.6 mg, 94.3%) as a yellow oil which was further purified by column chromatography on silica gel (60-220 mesh) eluting with 5% methanol in dichloromethane to 30% methanol in dichloromethane containing 1% Et_3N to afford pure (*S*)-**14** (47.4 mg, 93.9%) as a yellow oil. $[\alpha]^{21}_D = -6.5^\circ$ (c = 1.0, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.36-1.45 (m, 24H), 2.18-2.28 (m, 5H), 2.43-2.49 (m, 1H), 2.62 (dd, J = 13.5, 7.2 Hz, 1H), 2.86 (dd, J = 13.5, 5.4 Hz, 1H), 3.24 (t, J = 6.3 Hz, 1H), 3.48 (dd, J = 23.7, 16.8 Hz, 4H), 7.14-7.28 (m, 5H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 24.4 (t), 26.1 (t), 28.1 (q), 37.8 (t), 54.0 (t), 54.9 (t), 60.7 (t), 60.9 (d), 80.6 (s), 125.7 (d), 128.1 (d), 129.3 (d), 140.5 (s), 171.6 (s). HRMS (Positive ion ESI) Calcd for $C_{26}H_{43}N_2O_4$ $[M + H]^+$ m/z 447.3223. Found: $[M + H]^+$ m/z 447.3219.

***tert*-butyl 2-[(2-{bis[2-(tert-butoxy)-2-oxoethyl]amino}ethyl)amino]acetate (15).**[22] *N*-Bn protected precursor compound[27] was prepared via a modification of literature procedure and subjected to *N*-Bn deprotection to provide compound **15** as described below. To a solution of *N*-Bn protected precursor compound[27] (780 mg, 18.2 mmol) in ethanol (100 mL) was added wet 10% Pd/C (400 mg) under argon gas. The reaction mixture was placed into a hydrogenation apparatus for 26 h at room temperature. The resulting mixture was filtered via celite bed and washed thoroughly with ethanol. The filtrate was concentrated *in vacuo* to provide **15** (615 mg, 96%) as a yellow solid. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.44 (s, 18H), 1.45 (s, 9H), 2.41 (s, br, 1H), 2.66 (t, J = 5.7 Hz, 2H), 2.86 (t, J = 5.7 Hz, 2H), 3.30 (s, 2H), 3.43 (s, 4H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 28.1 (q), 28.2 (q), 47.1 (t), 51.5 (t), 53.8 (t), 56.0 (t), 81.0 (s), 170.9 (s), 171.5 (s). ^{1}H and ^{13}C NMR data are identical to those as previously reported.[22]

***tert*-butyl 2-[(2-{bis[2-(tert-butoxy)-2-oxoethyl]amino}-3-phenylpropyl)(2-{bis[2-(tert-butoxy)-2-oxoethyl]amino}ethyl)amino]acetate (16).** To a solution of (*rac*)-**3b**[18] (100 mg, 0.226 mmol) in CH_3CN (2 mL), $AgClO_4$ (46.8 mg, 0.226 mmol) was added at -5^{o}C and stirred for 40 min until aziridinium ion **4b′** was completely formed. Compound **15** (90.9 mg, 0.226 mmol) and DIPEA (87.5 mg, 0.678 mmol) were added at the same temperature. The reaction mixture was stirred for overnight at room temperature and then was filtered and evaporated to dryness. The residue was treated with 1.0 M HCl solution (10 mL) and extracted with ethyl ether (4 × 15 mL). The combined organic layers were concentrated to dryness. The residue was washed with 1M NaOH (4 × 15 mL). The organic layer was dried over $MgSO_4$, evaporated, dried under vacuum to afford relatively pure product (*rac*)-**16** (169.5 mg, 98.2%) which was purified by column chromatography

eluting 10% ethyl acetate in hexane to provide pure product (*rac*)-**16** (161.3 mg, 93.5%). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.39 (s, 9H), 1.43 (s, 18H), 1.44 (s, 18H), 2.50 (dd, J = 13.5, 6.3 Hz, 1H), 2.59-2.77 (m, 5H), 2.78-2.91 (m, 2H), 3.07-3.14 (m, 1H), 3.29-3.53 (m, 10H), 7.11-7.26 (m, 5H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 28.1 (q), 28.2 (q), 37.2 (t), 52.5 (t), 52.8 (t), 53.5 (t), 55.7 (t), 55.8 (t), 56.0 (t), 63.1 (d), 80.7 (s), 81.0 (s), 125.7 (d), 128.2 (d), 129.3 (d), 140.6 (s), 170.7 (s), 171.3 (s), 171.4 (s). HRMS (ESI) Calcd for $C_{41}H_{70}O_{10}N_3$ $[M + H]^+$ *m/z* 764.5056. Found: $[M + H]^+$ *m/z* 764.5099.

tert*-butyl 2-{[(2S)-1-[(2-{bis[2-(tert-butoxy)-2-oxoethyl]amino}ethyl)[2-(tert-butoxy)-2-oxoethyl]amino]-3-phenylpropan-2-yl][2-(tert-butoxy)-2-oxoethyl]amino}acetate ((*R*)-16).** To a solution of **(*S*)-3b** (100 mg, 0.226 mmol) in CH_3CN (2 mL), $AgClO_4$ (46.8 mg, 0.226 mmol) was added at -5^{o}C and stirred for 40 min until intermediate **(*R*)-4b′** was completely formed. Compound **15** (90.9 mg, 0.226 mmol) and DIPEA (87.5 mg, 0.678 mmol) were added at the same temperature. The reaction mixture was stirred for overnight at room temperature. The same work-up procedure for the preparation of (rac)-**12** as described above was followed to afford pure **(*R*)-16** (169.4 mg, 98.2%) which was purified by column chromatography eluting 10% ethyl acetate in hexane to provide pure product (R***)-**16** (159.8 mg, 92.6%). ^{1}H and ^{13}C NMR are identical to those of (*rac*)-**16** as reported above. $[\alpha]^{26}_D$ = + 4.3 (c = 1.0, $CHCl_3$). HRMS (ESI) Calcd for $C_{41}H_{70}O_{10}N_3$ $[M + H]^+$ m/z 764.5056. Found: $[M + H]^+$ m/z 764.5088.

***tert*-butyl 2-{[(2S)-1-[(2-{bis[2-(tert-butoxy)-2-oxoethyl]amino}ethyl)[2-(tert-butoxy)-2-oxoethyl]amino]-3-phenylpropan-2-yl][2-(tert-butoxy)-2-oxoethyl]amino}acetate ((*S*)-16).** To a solution of **(*R*)-3b** (100 mg, 0.226 mmol) in CH_3CN (2 mL), $AgClO_4$ (46.8 mg, 0.226 mmol) was added at -5^{o}C and stirred for 40 min

until intermediate (S)-**4b′** was completely formed. Compound **15** (90.9 mg, 0.226 mmol) and DIPEA (87.5 mg, 0.678 mmol) were added at the same temperature. The reaction mixture was stirred for overnight at room temperature. The same work-up procedure for the preparation of (*rac*)-**16** as described above was followed to afford pure product (*S*)-**16** (163.9 mg, 95%) which was purified by column chromatography eluting 10% ethyl acetate in hexane to provide pure product (***S***)-**16** (157.0 mg, 91%). ^{1}H and ^{13}C NMR are identical to those of (*rac*)-**16** as reported above. $[\alpha]^{26}_{D}$= – 4.6 (c = 1.0, $CHCl_3$). HRMS (ESI) Calcd for $C_{41}H_{70}O_{10}N_3$ $[M + H]^+$ m/z 764.5056. Found: $[M + H]^+$ m/z 764.5095.

2-({2-[bis(carboxymethyl)amino]-3-phenylpropyl}({2-[bis(carboxymethyl)amino]ethyl})amino)acetic acid ((*rac*)-Bn-DTPA). To a flask containing compound (*rac*)-**16** (42.5 mg, 0.056 mmol) was added 6M HCl aqueous solution (10 mL). The resulting mixture was heated to reflux for 15 min. After which time period, the reaction mixture was cooled to room temperature and washed with $CHCl_3$ (2 × 10 mL). The aqueous solution was concentrated in *vacuo* to provide compound (*rac*)-**Bn-DTPA** (36 mg, 98.1%) as a light yellow solid. ^{1}H NMR (D_2O, 300 MHz) δ 2.63 (dd, J = 12.3, 9.6 Hz, 1H), 2.92-3.47 (m, 7H), 3.49-3.65 (m, 2H), 3.65-3.89 (m, 5H), 3.90-3.99 (m, 3H), 4.12-4.25 (m, 1H), 7.13-7.34 (m, 5H); ^{13}C NMR (D_2O, 75 MHz) δ 32.4 (t), 49.5 (t), 51.5 (t), 52.7 (t), 53.9 (t), 54.8 (t), 55.2 (t), 62.7 (d), 127.5 (d), 129.2 (d), 129.3 (d), 135.8 (s), 169.6 (s), 171.1 (s), 172.4 (s). HRMS (ESI) Calcd for $C_{21}H_{30}O_{10}N_3$ $[M + H]^+$ *m/z* 484.1926. Found: $[M + H]^+$ *m/z* 484.1924.

Analytical HPLC (method 1, t_R = ~ 8.3 min)

2-{[(2R)-1-({2-[bis(carboxymethyl)amino]ethyl}(carboxymethyl)amino)-3-phenylpropan-2-yl](carboxymethyl)amino}acetic acid [(*R*)-Bn-DTPA)].[23]

To a flask containing compound (*R*)-**16** (50 mg, 0.065 mmol) was added 6M HCl aqueous solution (10 mL). The resulting mixture was heated to reflux for 15 min. After which time period, the reaction mixture was cooled to room temperature and washed with $CHCl_3$ (10 mL × 2). The aqueous solution was concentrated in *vacuo* to provide compound **(*R*)-Bn-DTPA** (37.9 mg, 98.5%) as a light yellow solid. ^1H and ^{13}C NMR are identical to (*rac*)-**Bn-DTPA.** $[\alpha]^{26}_D$ = − 9.2º (c = 1.0, H_2O). HRMS (ESI) Calcd for $C_{21}H_{30}O_{10}N_3$ $[M + H]^+$ *m/z* 484.1926. Found: $[M + H]^+$ *m/z* 484.1927.

Analytical HPLC (method 1, t_R = ~ 8.3 min)

2-{[(2S)-1-({2-[bis(carboxymethyl)amino]ethyl}(carboxymethyl)amino)-3-phenylpropan-2-yl](carboxymethyl)amino}acetic acid [(S)-Bn-DTPA)].[23] To a flask containing compound (S)-**16** (44.6 mg, 0.058 mmol) was added 6M HCl aqueous solution (10 mL). The resulting mixture was heated to reflux for 15 min. After which time period, the reaction mixture was cooled to room temperature and washed with $CHCl_3$ (10 mL × 2). The aqueous solution was concentrated in *vacuo* to provide compound (*S*)-**Bn-DTPA** (33.8 mg, 98.4%) as a light yellow solid. ^1H and ^{13}C NMR are identical to (*rac*)-**Bn-DTPA.** $[\alpha]^{26}_D$= + 9.7º (*c* = 1.0, H_2O). HRMS (ESI) Calcd for $C_{21}H_{30}O_{10}N_3$ $[M + H]^+$ *m/z* 484.1926. Found: $[M + H]^+$ *m/z* 484.1923.

Analytical HPLC (method 1, t_R = ~ 8.3 min)

(2*S*)-2-amino-*N*-(2-aminoethyl)-3-phenylpropanamide (18). To a solution of **17** (1 g, 5.57 mmol) in CH_3OH (5 mL) was added ethylenediamine (10 mL) dropwise and stirred for 18 h. Then the resulting mixture was evaporated at 50 ^oC until a constant weight was obtained. The residue was washed by toluene (30 mL × 2). The resulting residue was treated with CH_2Cl_2 (30 mL) and filtered. The filtrate was evaporated to dryness to afford

pure compound **18** (1.07 g, 92.8%). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.26-2.42 (m, 2H), 2.70 (dd, J = 12.9, 8.4 Hz, 1H), 2.80-2.97 (m, 2H), 3.02-3.14 (m, 1H), 3.46 (dd, J = 8.4, 6.3 Hz, 1H), 7.07-7.30 (m, 5H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 39.5 (t), 40.8 (t), 41.5 (t), 56.6 (d), 127.0 (d), 128.7 (d), 129.3 (d), 137.1 (s), 176.6 (s). $[\alpha]^{26}_{D}$ = – 15.4 (c = 1.0, $CHCl_3$). HRMS HRMS (ESI) Calcd for $C_{11}H_{18}ON_3$ $[M + H]^+$ *m/z* 208.1444. Found: $[M + H]^+$ *m/z* 208.1479.

[(2S)-2-amino-3-phenylpropyl](2-aminoethyl)amine (19). To the solution of **18** (597.8 mg, 2.89 mmol) in THF (10 mL) at 0 ^{o}C was added dropwise 1M BH_3 Me_2S in THF (10 mL) over 30 min. The resulting mixture was warmed to room temperature and stirred for 2 h and heated to reflux overnight. Then the reaction mixture was concentrated to dryness. The residue was treated with CH_3OH (10 mL) and concentrated to dryness. The quenching process was repeated two more times. The residue was dried in *vacuo* and treated with 6M HCl (10 mL). The resulting mixture was stirred at room temperature for 1h and heated to reflux for 2 h. The aqueous solution was cooled down to room temperature and adjusted to pH 7 by using 5M NaOH and then extracted with $CHCl_3$ (30 mL × 2). The aqueous solution was further adjusted to pH 10 and pH 13. At each pH, the aqueous solution was extracted with $CHCl_3$ (30 mL × 2). The organic layers extracted at pH 10 and pH 13 were combined, dried over $MgSO_4$, filtered, and concentrated to provide pure **19** (244.3 mg, 43.8%). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.28 (s, br, 5H), 2.45 (td, J = 21.6, 8.4 Hz, 2H), 2.58-2.81 (m, 6H), 3.00-3.12 (m, 1H) 7.12-7.32 (m, 5H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 41.9 (t), 42.9 (t), 52.7 (d), 52.7 (t), 56.0 (t), 126.2 (d), 128.4 (d), 129.2 (d), 139.2 (s). $[\alpha]^{26}_{D}$ = – 9.7 (c = 1.0, $CHCl_3$). HRMS (ESI) Calcd for $C_{11}H_{20}N_3$ $[M + H]^+$ *m/z* 194.1652. Found: $[M + H]^+$ *m/z* 194.1614.

***tert*-butyl 2-{[(2*S*)-1-[(2-{bis[2-(tert-butoxy)-2-oxoethyl]amino}ethyl)[2-(tert-butoxy)-2-oxoethyl]amino]-3-phenylpropan-2-yl][2-(tert-butoxy)-2-oxoethyl]amino}acetate ((*S*)-16, Scheme 5).** To a solution of **19** (124 mg, 0.64 mmol) and KI (127.5 mg, 0.77 mmol) in DMF (3 mL) was added *tert*-butyl bromoacetate (688.3 mg, 3.53 mmol) and DIPEA (830.0 mg, 6.43 mmol) dropwise at 0 ^{o}C. The resulting mixture was warmed to room temperature and stirred for 48 h. Then the mixture was concentrated to dryness and the residue was purified by silica gel (60~230 mesh) column chromatography eluted with 10 % ethyl acetate in hexanes to provided pure (*S*)-**16** (327.1 mg, 66.9%). The ^{1}H and ^{13}C NMR data of (*S*)-**16** was essentially identical to those of (*S*)-**16** that was prepared from the reaction of (*R*)-**3b** with **15** (Scheme 4). $[\alpha]^{26}_{D}$= – 5.13 (c = 1.0, $CHCl_3$).

2-{[(2S)-1-({2-[bis(carboxymethyl)amino]ethyl}(carboxymethyl)amino)-3-phenylpropan-2-yl](carboxymethyl)amino}acetic acid ((S)-Bn-DTPA), Scheme 5). (S)-**16** (200 mg, 0.263 mmol) was dissolved in 6M HCl (10 mL) and the resulting solution was heated to reflux for 15 min. Then the mixture was washed by diethyl ether (10 mL × 2) and the resulting aqueous layer was evaporated to dryness to provide (*S*)-**Bn-DTPA** (196.2 mg, 96.6%). Analytical HPLC (method 1, t_R = ~ 8.3 min)

$[\alpha]^{26}_{D}$ = + 10.3º (*c* = 1.0, H_2O). The ^{1}H and ^{13}C NMR data of (*S*)-**Bn-DTPA** was essentially identical to those of (*S*)-**Bn-DTPA** that was prepared from removal of *tert*-butyl groups in (*S*)-**16** obtained from the reaction of (*R*)-**3b** with **15** (Scheme 4).

Preparation of Gd(III) Complexes of Bn-DTPA chelates. The Gd^{3+} Complexes were prepared by reacting the aqueous solution of the appropriate ligand (7.8 mM, 1 mL, Bn-DTPA, (S)-Bn-DTPA, or (R)-Bn-DTPA) and $GdCl_3$ (7.8 mM, 0.9 mL) at a 1:0.9 mol

ratio. The pH was adjusted to ~7 using 1 M NaOH, and the reaction was done at 90 ^{o}C for 24 h. No unbound Gd(III) was detected in the reaction mixture as evidenced by AAIII assay. The Gd^{3+} complexes were purified using semi-prep HPLC (0-50% B/30 min; solvent A, H_2O; solvent B, MeOH). Fractions centered at 6.5-8min were collected to provide Gd(III) complexes of Bn-DTPA, (S)-Bn-DTPA and (R)-Bn-DTPA, respectively. The collected fractions were concentrated and dried *in vacuo* to provide the corresponding Gd(III) complexes of Bn-DTPA analogues that was characterized by analytical HPLC (method 1, t_R = ~7.7 min).

Procedure for detection of free Gd(III) using AAIII assay.[24] A solution of AAIII (10 μM) was prepared in the acetate buffer (NH_4OAc, 0.15 M, pH 7). AAIII solution (100 μL) was arranged in a 96 well plate, and a droplet of reaction mixture (5 μL, 2 mM) was added to AAIII solution in each well. The presence of free Gd(III) was indicated by the immediate color change from pink to green.

ICP-MS measurement.[24,25] The concentration of Gd(III) in each complex was determined by ICP-MS (Dr. Thomas J. Meade lab, Northwestern University). To verify the concentration of Gadolinum ICP-MS was performed using a computer-controlled Thermo Elemental (Now Thermo Fisher) PQ ExCell Inductively Coupled Plasma Mass Spectrometer. Samples were prepared by nitric acid digestion (9:1 nitric acid:sample) in a 65°C water bath. The digested samples were diluted into 15mL conical vials with a final concentration of 3% (v/v) nitric acid. Gd standards were prepared in 3% (v/v) nitric acid with values 0.1, 0.25, 0.5, 1, 5, 10, 25, and 50 ng/mL Gd. Indium was spiked into every sample (including standards) for a final indium concentration of 5ng/mL. Isotopes ^{157}Gd and ^{115}In were used for determination.

Relaxivity Measurements.[24,25] Relaxivity measurements were acquired by taking the slope of a plot of $1/T_1$ (s^{-1}) versus concentration (mM). The longitudinal water proton relaxation times (T_1) were determined using a Bruker mq60 NMR (Bruker Canada, Milton, ON, Canada) analyzer operating at 59.97 MHz and 37°C. The agent was added to Millipore water and serially diluted by 0.5 to give a series of 5 concentrations (500 μL total volume) for each relaxivity trial. The T_1 was determined using an inversion recovery pulse sequence with 10 different pulse separations per sample, 4 repetitions per echo time, phase cycling, and a recycle delay that is ≥5 times the T_1 of each given sample. All curves were fit using a monoexponential curve fitting formula.

Acknowledgement

This work was partly supported by National Institutes of Health (2R01CA112503 to H. S. Chong).

Supporting Information: NMR spectra of all new compounds and chiral HPLC chromatograms of compounds **5** and **6** and relaxity and ICP-MS data of Gd(III)-Bn-DTPA complexes.

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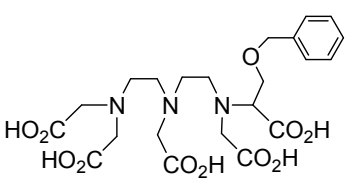
Figure 1. DTPA analogues as MRI contrast agents in clinical and preclinical use



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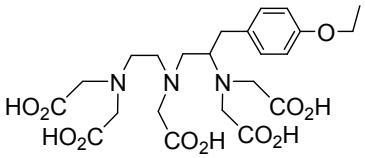

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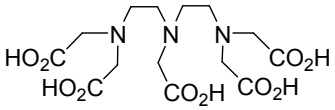
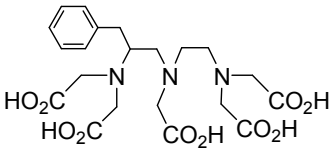
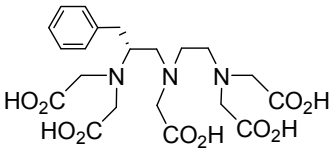


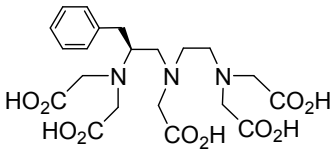
DTPA



Bn-DTPA

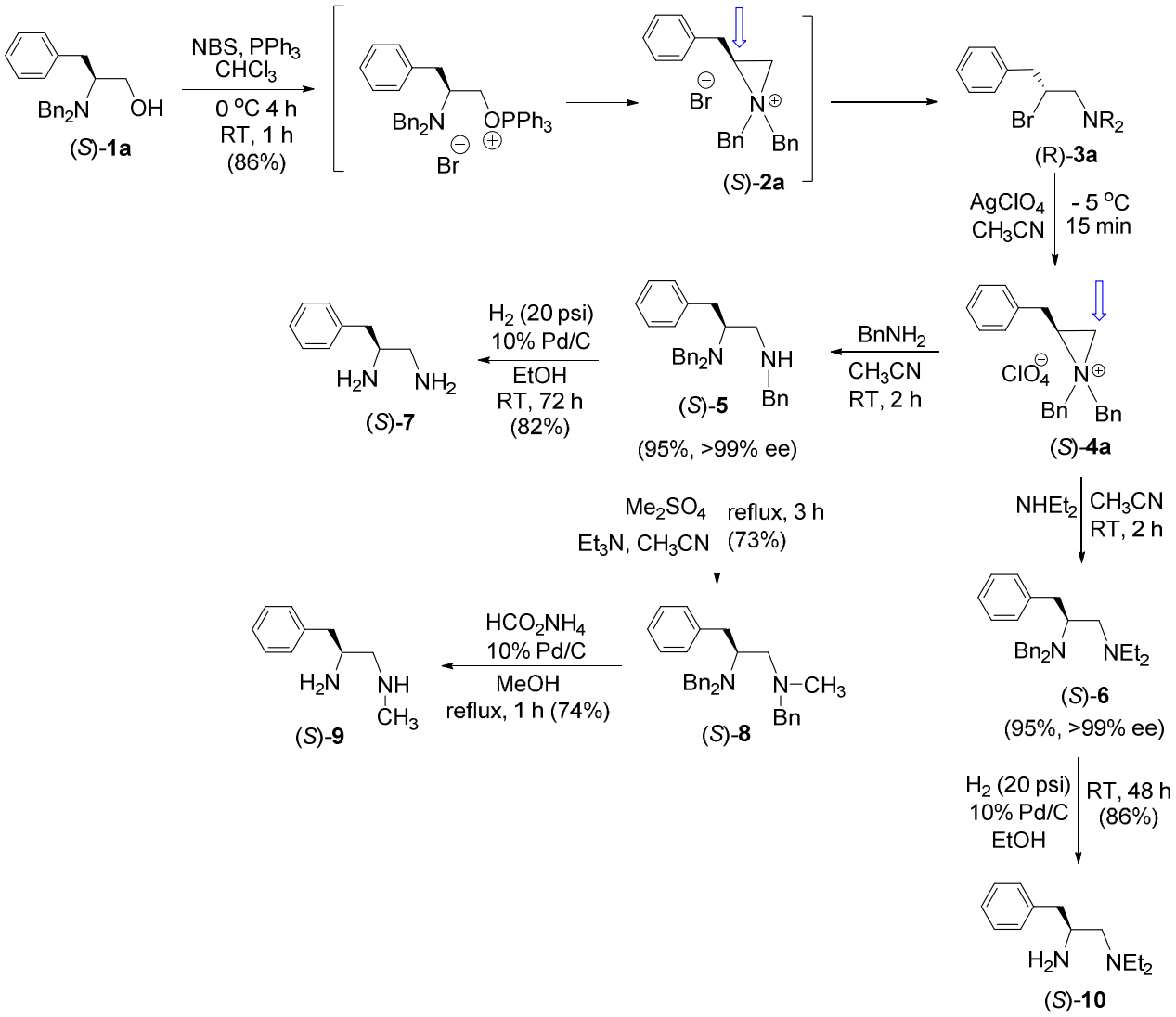


(S)-Bn-DTPA

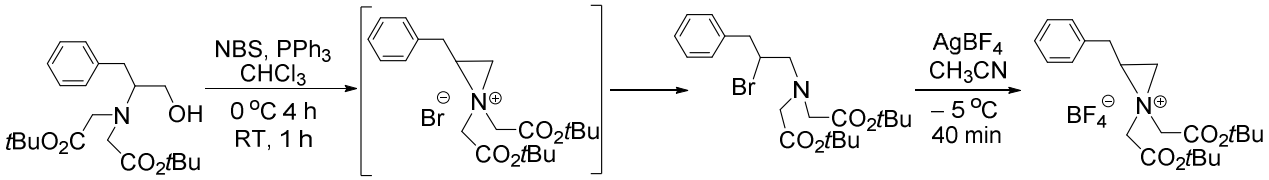


(R)-Bn-DTPA

Scheme 1. Regioselective and stereoselective ring opening of aziridinium ions: Synthesis of substituted chiral vicinal amines



Scheme 2. Synthesis of optically active b-bromoamines 3b and aziridinium ions 4b



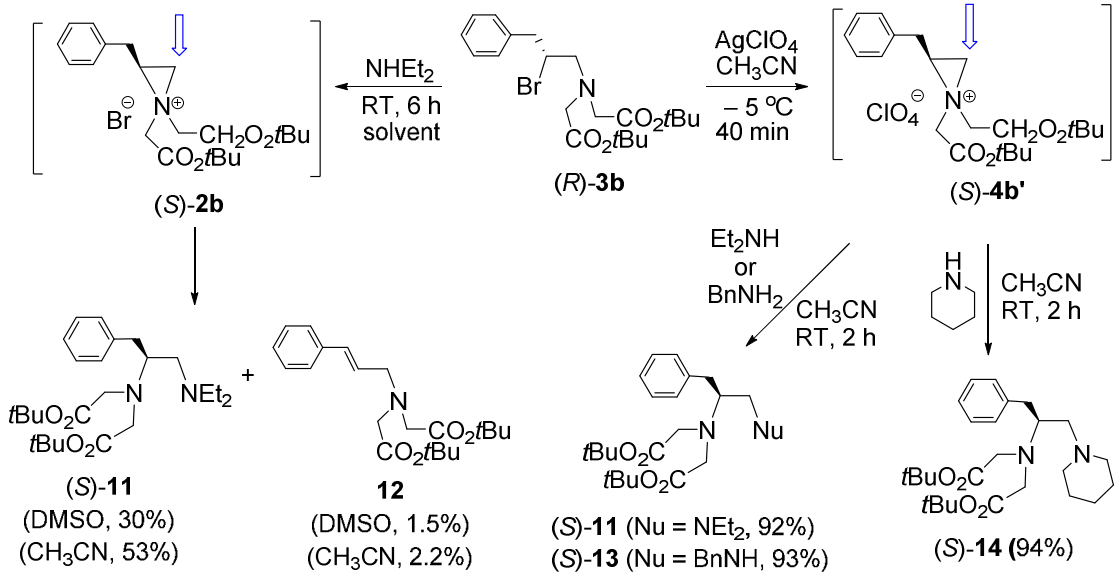
(*R*)-**1b**
(*S*)-**1b**

(*R*)-**2b**
(*S*)-**2b**

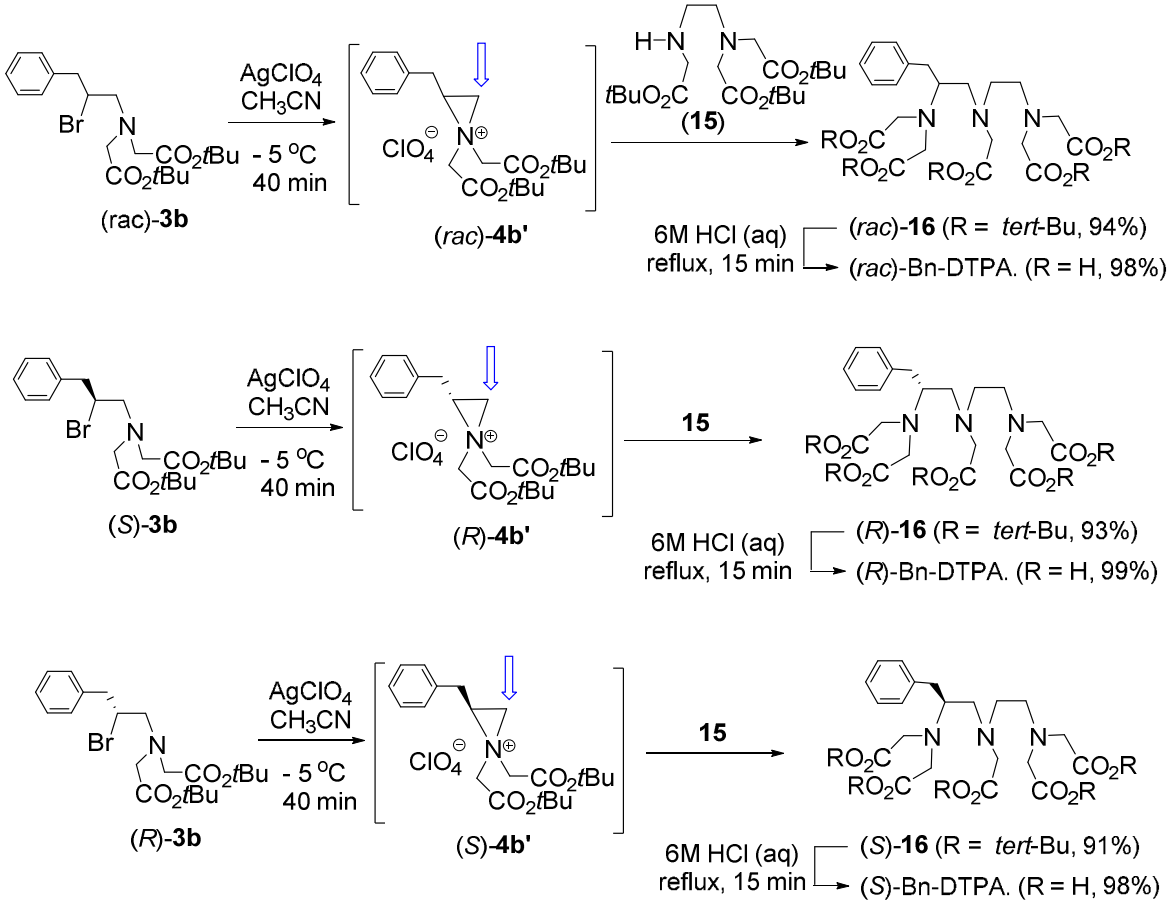
(*R*)-**3b** (71%)
(*S*)-**3b** (70%)

(*R*)-**4b**
(*S*)-**4b**

Scheme 3. Conversion of b-bromoamine (*R*)-3b to aziridinium ions for regiospecific and stereospecific ring opening with amine nucleophiles



Scheme 4. Regiospecific and Stereospecific ring opening of aziridinium ions: Synthesis of Bn-DTPA analogues



Scheme 5. Synthesis of (*S*)-Bn-DTPA for confirmation of regiochemistry and stereochemistry

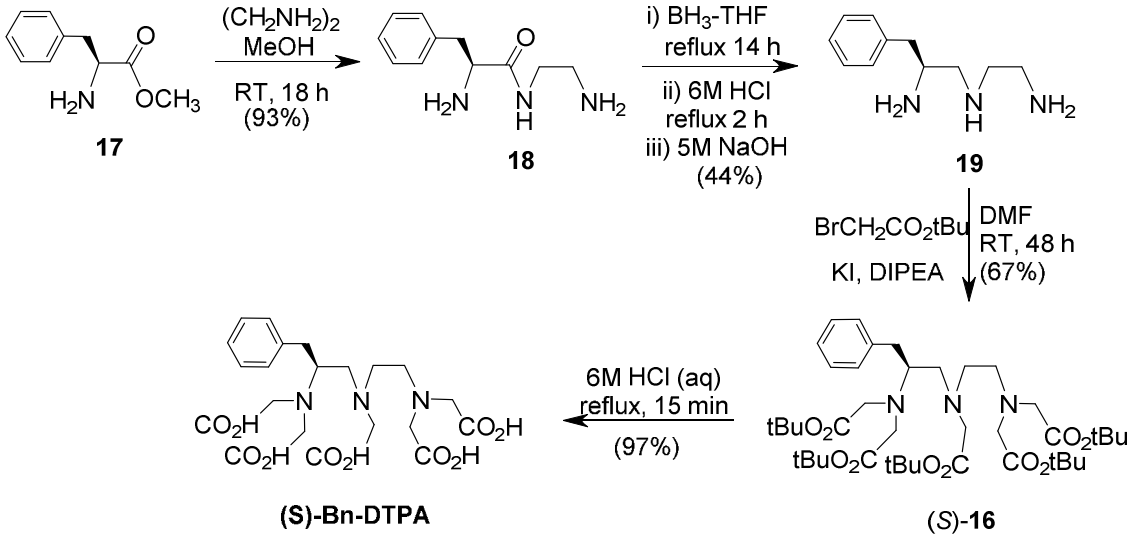
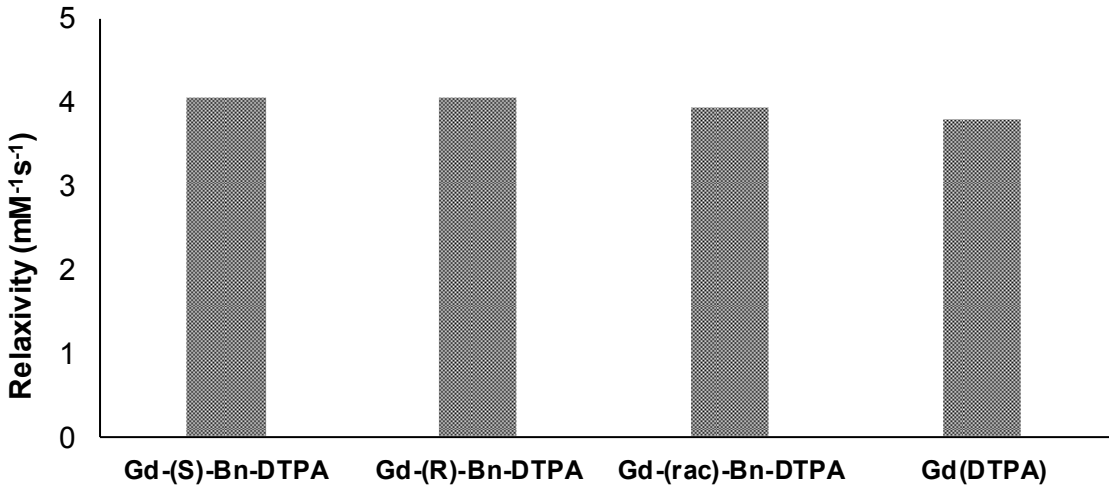


Figure 2. T_1 Relaxivity of Gd(III)-Bn-DTPA analogues and Gd(DTPA), a clinically available MRI contrast agent (60 MHz, 37°C). T_1 relaxivity of Gd(DTPA) was cited for comparison.[25]



Graphical Abstract