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Stereoselective synthesis of enantiomerically pure D-*threo*-PDMP; manipulation of a core 2,3-diamino alcohol unit

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Abstract

The C(3)–*N* bond of various non-activated enantiomerically pure aziridine-2-methanols was regioselectively cleaved by nitrogen nucleophiles to provide a variety of β-aminoalanine derivatives in high yields.

1. Introduction

Enantiomerically pure and polyfunctionalized small molecules can be used as chiral building blocks in the asymmetric synthesis of biologically active compounds and the synthesis of these molecules is an important area in organic chemistry.[1] Among such compounds vicinal diamine and amino alcohol units can be found in a wide range of biologically important molecules.[2] Preparations of enantiomerically pure 2,3-amino alcohols and also vicinal diamines from a variety of sources have been well documented.[3] One of the most efficient processes for the synthesis of enantiomerically pure vicinal diamines is the ring opening of the corresponding aziridine with nitrogen nucleophiles. Though aziridines are readily accessible synthetic intermediates, they have been compared with epoxides due to their low reactivity in ring-opening reactions with nucleophiles.[4] Regioselective ring-openings of activated and non-activated aziridines by azide[5] and amine[6] nucleophiles have been reported. The ready access to chiral aziridines and the development of new synthetic transformations have made the aziridine approach more attractive to synthetic chemists.[7] We would like to report the highly regioselective C(3)–*N* bond cleavage of non-activated aziridine-2-methanols by azide and amine nucleophiles based on our previously reported work.[8]

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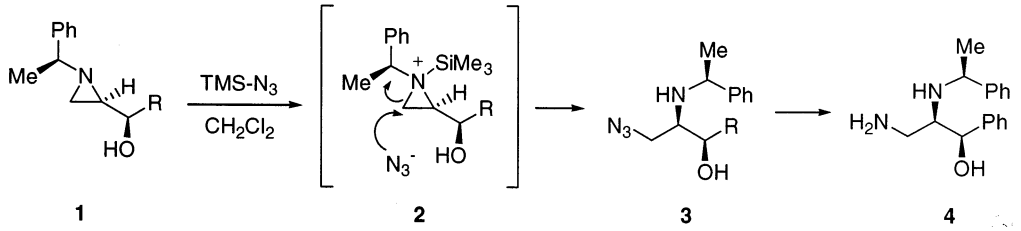
2. Results and discussion

Regioselective ring opening reactions of aziridine-2-methanols **1** by the azide TMS–N_3 provides **3**, through the aziridinium intermediate **2** as the major product (Scheme 1). Sodium azide, NaN_3, was used as a nitrogen source for most of ring-opening reactions of activated aziridines.[6] However, the presence of the α-methylbenzyl substituent on the ring nitrogen requires the activation of the basic nitrogen prior to the ring opening of **1**. Therefore, azido trimethylsilane, TMS–N_3, was used for the activation of the basic ring nitrogen of the *N*-α-methylbenzyl aziridines and also as the source of the nitrogen nucleophile to attack the less substituted C(3) position of the aziridines.[9]



Scheme 1.

The reaction of *N*-[(*S*)-α-methylbenzyl]aziridine-2(*R*)-[1′(*R*)-alkyl(or aryl)]methanol **1** with two equivalents of TMS–N_3 in CH_2Cl_2 at room temperature provides the ring-opening products **3a–k** in 80–97% yields after chromatographic purification depending on the substrate (Table 1). The azido group of **3d** was readily reduced by $LiAlH_4$ to provide the corresponding diamino alcohol **4d** in 94% yield (Fig. 1).

Table 1
The results of the ring-opening reactions of **1** with TMS–N_3

Entry	R	Yield **3** (% isolated)
a	Methyl	85
b	*n*-Butyl	84
c	*tert*-Butyl	82
d	Phenyl	88
e	2-Methoxyphenyl	80
f	4-Chlorophenyl	97
g	1-Hexynyl	91
h	4-Fluorophenyl	89
i	3-Methylphenyl	91
j	2-Thiazolyl	88
k	2-Propenyl	91

Glycosylceramide synthase inhibitor PDMP (**5**, D-*threo*-1-phenyl-2-decanoylamino-3-morpholino-1-propanol) and several 5a-carba-sugar analogues (*E* and *Z* isomers) of glycosylceramides, which have enantiomerically pure 2,3-diamino alcohol units, have been synthesized and extensively studied.[10–15] Recently, modifications of the morpholine[13] **6** or phenyl[17] **7** moieties have been carried out by other groups for the study, evaluation, and also promotion of the activity of these compounds. However, there have been some limitations in the syntheses reported by other research groups [16,17] regarding stereochemical control, and the modification of the structure.

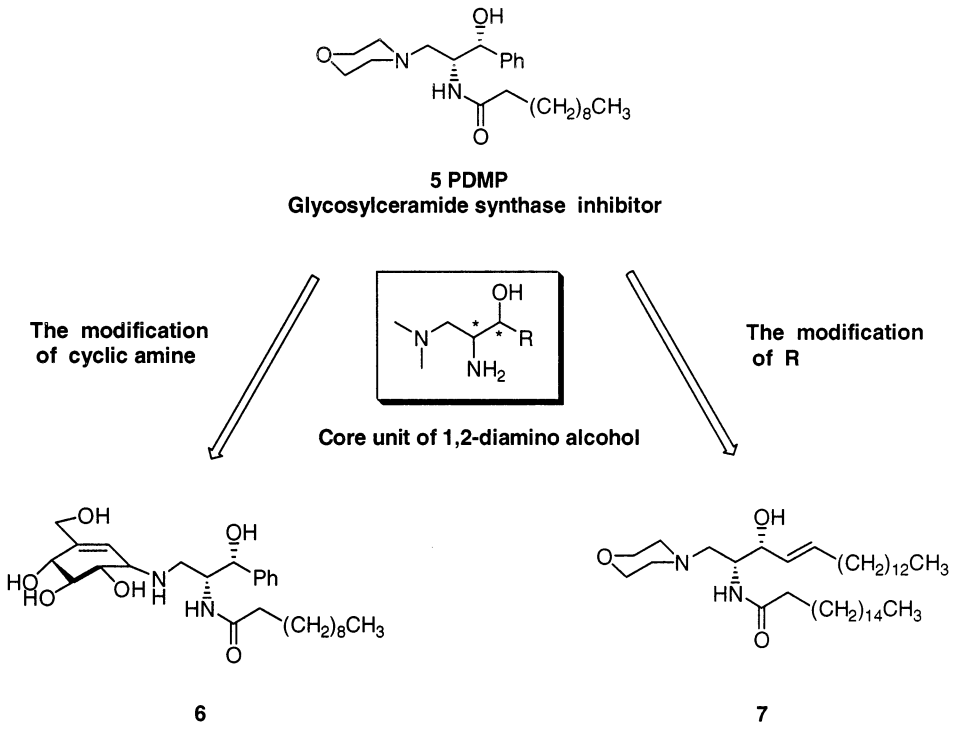
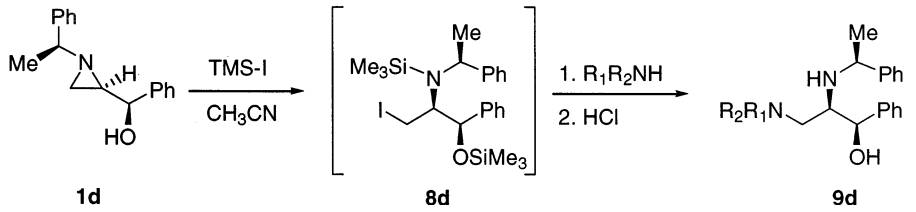


Figure 1.

We used various cyclic secondary amines as nucleophiles in the ring opening reactions of **1d** to obtain D-*threo*-PDMP **5** and its analogues by regioselective ring openings of aziridine. Since the aziridine ring is not prone to react with amine nucleophiles, compound **1d** was treated with iodotrimethylsilane (TMS-I) prior to the reaction with cyclic secondary amines. The aziridine ring readily opens up regioselectively upon treating with iodotrimethylsilane to provide an alkyl iodide intermediate **8d** which then reacts with amine nucleophiles to give alkylation products **9d** in high yields (Scheme 2Table 2).

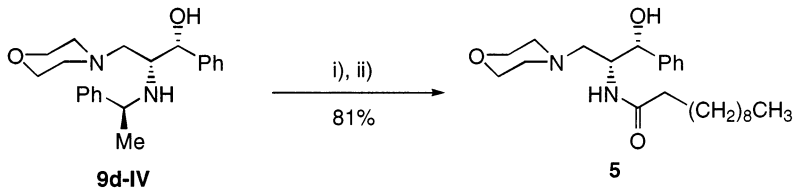


Scheme 2.

Table 2
The results of ring openings of aziridine-2-methanol **1d** by amine nucleophiles

Entry	R_1R_2NH	Yield **9d** (% isolated)
I	Pyrrolidine	95
II	Piperidine	87
III	Hexamethyleneimine	98
IV	Morpholine	99

The transformation of **9d-IV** into D-*threo*-PDMP **5** was accomplished by catalytic hydrogenation in the presence of AcOH to activate the basic nitrogen. After stirring for 4 hours under a balloon pressure of hydrogen, the palladium catalyst was filtered, the reaction solvent was concentrated, and then the solvent was changed to THF. Without purification, the residue was sequentially treated with aqueous sodium hydroxide and decanoyl chloride. We obtained the product **5** as a light brown oil in high yield and ^{1}H, ^{13}C NMR, specific rotation, and elemental analysis data of the product agreed with the known data[16] (Scheme 3).



Scheme 3. (i) $Pd(OH)_2$, H_2, AcOH, MeOH, 40°C; (ii) 10% NaOH, decanoyl chloride

3. Conclusion

According to the above results, the manipulation of a variety of non-activated aziridine-2-methanols which we had previously reported[8] enables us to modify efficiently either the alkyl or cyclic amine portions. In addition to the readiness of the structural modification, the utilization of the enantiomer of the aziridine **1** allows control over the stereochemistry and achieves the synthesis of L-*threo*-PDMP efficiently.

4. Experimental

4.1. General method

Flash chromatography was performed on a Tokyo Rikagikai EF-10 with Merck 230–400 mesh silica gel. Melting points were determined on a Thomas–Hoover capillary melting point apparatus and all melting points were not corrected. ^{1}H NMR spectra were obtained on a Varian Gemini 200 (200 MHz), Varian Gemini 300 (300 MHz) and Varian Gemini 500 (500 MHz) spectrometer. NMR spectra were recorded in ppm(δ) related to tetramethylsilane ($\delta = 0.00$) as an internal standard unless stated otherwise and are reported as follows; chemical shift, multiplicity (br = broad, s = singlet, t = triplet, q = quartet, m = multiplet), coupling constant and integration. Elemental analysis was performed by Carlo Erba EA 1180 elemental analyzer. Optical rotations were obtained on Rudolph Autopol III digital polarimeter. Data are reported as follow: $[\alpha]_D^{25}$(concentration g/100 mL solvent). Solvents and liquid reagents were transferred using hypodermic syringes. All other reagents and solvents used were grade. All glassware was dried in an oven at 150°C prior to use. Methylene chloride and triethylamine were

dried from calcium hydride prior to use. Small and medium scale purifications were performed by flash chromatography.

4.2. Representative procedure for the ring opening reaction of **1a** with azidotrimethylsilane

To a solution of **1a** (201 mg, 0.951 mmol) in methylene chloride (CH_2Cl_2, 3.2 mL) was added TMS–N_3 (0.25 mL, 1.90 mmol). The mixture was stirred for 12 h at room temperature and the mixture was treated with aqueous 1N HCl solution and then stirred for an additional 1 h. After the solution was basified with sat. $NaHCO_3$ and the aqueous layer was extracted with CH_2Cl_2 (1.0 mL×3). The combined organic extracts were dried over anhydrous $MgSO_4$, filtered, and concentrated in vacuo. Purification by silica gel flash chromatography (EtOAc/hexane 30:70) gave 154 mg (85%) of **3a** as an oil.

4.2.1. 2(R)-N-[(S)-α-Methylbenzyl]amino-3-azido-1(R)-methylpropanol **3a**

R_f 0.21 (EtOAc/hexane 20:80). $[\alpha]_D^{26} = -146.3$ (*c* 2.00, $CHCl_3$). ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.38–7.25 (m, 5H), 3.96 (q, $J = 6.5$ Hz, 1H), 3.64 (m, 2H), 3.35 (dd, $J = 12.8$, 3.0 Hz, 1H), 2.25 (m, 1H), 1.40 (d, $J = 6.4$ Hz, 3H), 1.09 (d, $J = 6.2$ Hz, 3H). ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 144.6, 128.8. 127.5, 127.0, 67.0, 59.6, 54.8, 50.1, 25.0, 19.1. *Anal*. calcd for $C_{12}H_{18}N_4O$: C, 61.52; H, 7.74; N, 23.91. Found: C, 61.88; H, 7.75; N, 23.71.

4.2.2. 2(R)-N-[(S)-α-Methylbenzyl]amino-3-azido-1(R)-n-butylpropanol **3b**

R_f 0.24 (EtOAc/hexane 20:80). $[\alpha]_D^{27} = -98.6$ (*c* 1.00, $CHCl_3$). ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.33–7.24 (m, 5H), 3.95 (q, $J = 6.5$ Hz, 1H), 3.63 (dd, $J = 12.6$, 4.6 Hz, 1H), 3.39 (m, 2H), 2.33 (m, 2H), 1.38 (d, $J = 6.5$ Hz, 3H), 1.23 (m, 5H), 0.86 (m, 3H). ^{13}C NMR (50.3 MHz, $CDCl_3$) δ 144.8, 128.6, 127.3, 126.9, 71.2, 58.1, 55.4, 51.3, 33.5, 27.8, 25.1, 22.7, 13.9. *Anal*. calcd for $C_{15}H_{24}N_4O$: C, 65.19; H, 8.75; N, 20.27. Found: C, 65.16; H, 8.97; N, 20.32.

4.2.3. 2(R)-N-[(S)-α-Methylbenzyl]amino-3-azido-1(R)-tert-butylpropanol **3c**

R_f 0.46 (EtOAc/hexane 20:80). $[\alpha]_D^{26} = -99.2$ (*c* 1.00, $CHCl_3$). ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.33–7.24 (m, 5H), 3.97 (q, $J = 6.6$ Hz, 1H), 3.64 (dd, $J = 12.6$, 4.6 Hz, 1H), 3.32 (dd, $J = 12.6$, 4.8 Hz, 1H), 2.98 (d, $J = 4.9$ Hz, 1H), 2.77 (m, 2H), 2.62 (q, $J = 4.8$ Hz, 1H), 1.42 (d, $J = 6.5$ Hz, 3H), 0.70 (s, 9H). ^{13}C NMR (50.3 MHz, $CDCl_3$) δ 144.1, 128.7, 127.6, 127.3, 76.4, 55.7, 54.5, 53.2, 34.9, 25.7, 24.2. *Anal*. calcd for $C_{15}H_{24}N_4O$: C, 65.19; H, 8.75; N, 20.27. Found: C, 65.21; H, 8.98; N, 20.12.

4.2.4. 2(R)-N-[(S)-α-Methylbenzyl]amino-3-azido-1(R)-phenylpropanol **3d**

R_f 0.24 (EtOAc/hexane 20:80). $[\alpha]_D^{28} = -134.2$ (*c* 0.50, $CHCl_3$). ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.38–7.17 (m, 10H), 4.43 (d, $J = 8.5$ Hz, 1H), 3.52 (dd, $J = 12.8$, 4.0 Hz, 1H), 3.02 (dd, $J = 12.8$, 2.9 Hz, 1H), 2.56 (m, 1H), 1.41 (d, $J = 6.5$ Hz, 3H). ^{13}C NMR (50.3 MHz, $CDCl_3$) δ 144.1, 128.7, 127.3, 76.4, 55.7, 54.5, 53.2, 34.9, 25.7, 24.2. *Anal*. calcd for $C_{17}H_{20}N_4O$: C, 68.90; H, 6.80; N, 18.90. Found: C, 69.11; H, 6.92; N, 18.61.

4.2.5. 2(R)-N-[(S)-α-Methylbenzyl]amino-3-azido-1(R)-(2-methoxyphenyl)propanol **3e**

R_f 0.12 (EtOAc/hexane 20:80). $[\alpha]_D^{26} = -141.0$ (*c* 1.00, $CHCl_3$). ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.30–7.17 (m, 7H), 6.94–6.78 (m, 2H), 4.83 (d, $J = 7.4$ Hz, 1H), 3.83 (q, $J = 7.4$ Hz, 1H), 3.83

(q, $J=6.4$ Hz, 1H), 3.69 (s, 3H), 3.51 (dd, $J=12.6$, 4.6 Hz, 1H), 3.07 (dd, $J=12.8$, 3.5 Hz, 1H), 2.72 (m, 1H), 1.37 (d, $J=6.6$ Hz, 3H). ^{13}C NMR (50.3 MHz, $CDCl_3$) δ 128.7, 128.5, 128.0, 127.1, 126.7, 120.9, 110.6, 69.0, 58.9, 55.4, 55.3, 51.1, 24.7. *Anal*. calcd for $C_{18}H_{22}N_4O_2$: C, 66.24; H, 6.79; N, 17.16. Found: C, 66.38; H, 6.96; N, 17.08.

*4.2.6. 2(*R*)-N-[(*S*)-α-Methylbenzyl]amino-3-azido-1(*R*)-(4-chlorophenyl)propanol* ***3f***

R_f 0.26 (EtOAc/hexane 20:80). $[\alpha]_D^{26}=-114.6$ (c 1.00, $CHCl_3$). ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.38–7.11 (m, 9H), 4.42 (d, $J=8.3$ Hz, 1H), 3.92 (q, $J=6.5$ Hz, 1H), 3.57 (dd, $J=12.9$, 4.1 Hz, 1H), 3.04 (dd, $J=12.8$, 2.8 Hz, 1H), 1.42 (d, $J=6.5$ Hz, 3H). ^{13}C NMR (50.3 MHz, $CDCl_3$) δ 144.1, 139.7, 133.7, 128.8, 128.6, 128.3, 127.5, 126.8, 73.0, 60.3, 55.2, 49.9, 25.0. *Anal*. calcd for $C_{17}H_{19}ClN_4O$: C, 61.72; H, 5.79; N, 16.94. Found: C, 62.00; H, 5.87; N, 16.66.

*4.2.7. (*R*)-N-[(*S*)-α-Methylbenzyl]amino-3-azido-1(*R*)-(1-hexynyl)propanol* ***3g***

R_f 0.28 (EtOAc/hexane 20:80). $[\alpha]_D^{26}=-88.0$ (c 1.00, $CHCl_3$). ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.35–7.23 (m, 5H), 4.22 (m, 1H), 3.96 (q, $J=6.4$ Hz, 1H), 3.65 (dd, $J=12.6$, 4.4 Hz, 1H), 3.52 (dd, $J=12.5$, 3.5 Hz, 1H), 2.60 (m, 1H), 2.18 (m, 2H), 1.39 (m, 7H), 0.88 (t, $J=7.0$ Hz, 3H). ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 144.6, 128.7, 127.3, 87.3, 78.3, 63.0, 59.2, 55.3, 50.8, 30.6, 24.8, 22.0, 18.4, 13.5. *Anal*. calcd for $C_{17}H_{24}N_4O$: C, 67.97; H, 8.05; N, 18.65. Found: C, 68.11; H, 7.87; N, 18.69.

*4.2.8. 2(*R*)-N-[(*S*)-α-Methylbenzyl]amino-3-azido-1(*R*)-(4-fluorophenyl)propanol* ***3h***

R_f 0.22 (EtOAc/hexane 20:80). $[\alpha]_D^{28}=-136.0$ (c 0.50, $CHCl_3$). ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.38–6.92 (m, 9H), 4.42 (d, $J=8.4$ Hz, 1H), 3.93 (q, $J=6.3$ Hz, 1H), 3.57 (dd, $J=13.0$, 3.8 Hz, 1H), 3.01 (dd, $J=12.8$, 2.4 Hz, 1H), 2.48 (m, 1H), 1.42 (d, $J=6.2$ Hz, 3H). ^{13}C NMR (50.3 MHz, $CDCl_3$) δ 128.7, 128.5, 127.5, 126.8, 116.9, 115.5, 115.1, 73.1, 60.4, 55.2, 49.9, 25.1. *Anal*. calcd for $C_{17}H_{19}FN_4O$: C, 64.95; H, 6.09; N, 17.82. Found: C, 65.07; H, 5.76; N, 17.65.

*4.2.9. 2(*R*)-N-[(*S*)-α-Methylbenzyl]amino-3-azido-1(*R*)-(3-methylphenyl)propanol* ***3i***

R_f 0.29 (EtOAc/hexane 20:80). $[\alpha]_D^{27}=-128.0$ (c 1.00, $CHCl_3$). ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.37–6.99 (m, 9H), 4.40 (d, $J=8.4$ Hz, 1H), 3.91 (q, $J=6.5$ Hz, 1H), 3.54 (dd, $J=12.8$, 4.0 Hz, 1H), 3.03 (dd, $J=12.8$, 2.7 Hz, 1H), 2.54 (m, 1H), 2.28 (s, 3H), 1.40 (d, $J=6.5$ Hz, 3H). ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 144.5, 141.2, 138.3, 128.9, 128.5, 127.7, 127.5, 127.0, 124.3, 73.6, 60.1, 55.0, 49.7, 24.9, 21.2. *Anal*. calcd for $C_{18}H_{22}N_4O$: C, 69.65; H, 7.14; N, 18.05. Found: C, 69.96; H, 7.15; N, 17.75.

*4.2.10. 2(*R*)-N-[(*S*)-α-Methylbenzyl]amino-3-azido-1(*R*)-(2-thiazolyl)propanol* ***3j***

Mp 68–70°C, R_f 0.27 (EtOAc/hexane 30:70). $[\alpha]_D^{26}=-81.2$ (c 0.50, $CHCl_3$). ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.68 (d, $J=3.3$ Hz, 1H), 7.32–7.16 (m, 6H), 4.79 (d, $J=6.4$ Hz, 1H), 3.83 (q, $J=6.6$ Hz, 1H), 3.68 (dd, $J=12.6$, 4.7 Hz, 1H), 3.59 (dd, $J=12.6$, 4.3 Hz, 1H), 2.85 (m, 1H), 1.38 (d, $J=6.5$ Hz, 3H). ^{13}C NMR (50.3 MHz, $CDCl_3$) δ 172.9, 144.2, 142.4, 128.7, 127.4, 126.7, 119.2, 71.1, 59.2, 55.6, 50.9, 24.6. *Anal*. calcd for $C_{14}H_{17}N_5OS$: C, 55.43; H, 5.65; N, 23.08; S, 10.57. Found: C, 55.53; H, 5.87; N, 22.90; S, 10.26.

*4.2.11. 2(*R*)-N-[(*S*)-α-Methylbenzyl]amino-3-azido-1(*R*)-(2-propenyl)propanol* ***3k***

R_f 0.38 (EtOAc/hexane 30:70). $[\alpha]_D^{26}=-158.2$ (c 1.00, $CHCl_3$). ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.38–7.25 (m, 5H), 4.96 (d, $J=13.9$ Hz, 2H), 3.92 (m, 2H), 3.60 (dd, $J=12.5$, 4.5 Hz, 1H), 3.30

(dd, $J=12.5$, 3.2 Hz, 1H), 1.45 (s, 3H), 1.40 (d, $J=6.5$ Hz, 3H). ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 144.6, 144.5, 128.8, 127.5, 126.9, 114.5, 75.0, 55.4, 54.9, 50.2, 24.7, 16.7. *Anal.* calcd for $C_{14}H_{20}N_4O$: C, 64.59; H, 7.74; N, 21.52. Found: C, 64.68; H, 7.76; N, 21.30.

4.3. Representative procedure for the ring opening reactions of ***1d*** *by amine nucleophiles*

To a solution of the substrate **1d** (60 mg, 0.237 mmol) in 0.79 mL of acetonitrile (CH_3CN) was added sodium iodide (107 mg, 0.711 mmol) and trimethylsilyl chloride (90 μL, 0.711 mmol) at room temperature. After the solution was stirred for 1 h 50 min, pyrrolidine was added to the mixture. The solution was heated to the boiling point of the solvent for 2 h. The dark brown reaction mixture was quenched with aqueous 1.2N hydrochloric acid solution and then was treated with sat. $NaHCO_3$. The organic layer was separated and the aqueous layer was extracted with methylene chloride (10 mL×3). The combined organic extracts were washed with 20 mL of brine, dried over anhydrous $MgSO_4$, filtered and concentrated in vacuo. Purification by silica gel flash chromatography (MeOH/EtOAc 30:70) gave 73 mg (95%) of **9a** as brown oil.

*4.3.1. 2(*R*)-*N*-[(*S*)-α-Methylbenzyl]amino-3-pyrrolidino-1(*R*)-phenylpropanol* ***9d-I***

R_f 0.26 (MeOH/EtOAc 30:70). $[\alpha]_D^{26}=-19.4$ (*c* 1.00, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.10–7.36 (m, 10H), 4.80 (d, $J=3.9$ Hz, 1H), 3.76–3.80 (q, 1H), 2.87 (m, 1H), 2.61–2.72 (m, 6H), 1.79–1.81 (m, 4H), 1.24–1.25 (d, $J=6.35$ Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 145.4, 142.1, 127.9, 126.9, 128.8, 126.5, 76.0, 56.7, 55.2, 55.1, 24.5, 23.5. *Anal.* calcd for $C_{21}H_{28}N_2O$: C, 77.74; H, 8.70; N, 8.63. Found: C, 77.70; H, 8.93; N, 8.67.

*4.3.2. 2(*R*)-*N*-[(*S*)-α-Methylbenzyl]amino-3-piperidino-1(*R*)-phenylpropanol* ***9d-II***

R_f 0.21 (MeOH/EtOAc 10:90). $[\alpha]_D^{26}=-35.5$ (*c* 1.00, $CHCl_3$). ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.14–7.33 (m, 10H), 4.74–1.80 (d, $J=4.0$ Hz, 1H), 3.71–3.81 (q, 1H), 2.92–3.00 (m, 1H), 2.39–2.47 (m, 1H), 1.44–1.80 (m, 6H), 1.21–1.24 (d, $J=6.6$ Hz). ^{13}C NMR (125 MHz, $CDCl_3$) δ 145.60, 142.24, 128.33, 127.82, 126.83, 126.80, 126.52, 126.49, 76.05, 59.76, 55.39, 55.36, 55.06, 26.08, 24.46, 24.08. *Anal.* calcd for $C_{22}H_{30}N_2O$: C, 78.06; H, 8.93; N, 8.28. Found: C, 78.23; H, 8.93; N, 8.21.

*4.3.3. 2(*R*)-*N*-[(*S*)-α-Methylbenzyl]amino-3-hexamethyleneimino-1(*R*)-phenylpropanol* ***9d-III***

R_f 0.67 (MeOH/EtOAc 10:90). $[\alpha]_D^{26}=-33.7$ (*c* 1.00, $CHCl_3$). ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.17–7.33 (m, 10H), 4.70 (d, 1H), 2.83–3.00 (m, 1H), 2.55–2.83 (m, 7H), 1.55–1.94 (b, 8H), 1.21–1.24 (d, $J=6.6$ Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 145.62, 142.47, 128.27, 127.74, 126.74, 126.48, 76.39, 75.74, 59.58, 56.84, 56.15, 56.37, 28.07, 26.61, 24.42. Anal. calcd for $C_{23}H_{32}N_2O$: C, 78.37; H, 9.15; N, 7.95. Found: C, 78.320; H, 9.397; N, 7.946.

*4.3.4. 2(*R*)-*N*-[(*S*)-α-Methylbenzyl]amino-3-morpholino-1(*R*)-phenylpropanol* ***9d-IV***

R_f 0.33 (EtOAc). $[\alpha]_D^{26}=-32.2$ (*c* 1.00, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.08–7.33 (m, 10H), 4.66 (d, $J=4.1$ Hz, 1H), 3.68–3.73 (m, 5H), 2.40–2.59 (m, 6H), 1.20 (d, $J=6.9$ Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 145.09, 142.17, 128.24, 127.84, 126.75, 126.31, 126.71, 75.22, 66.76, 59.76, 55.93, 54.24, 24.26. *Anal.* calcd for $C_{21}H_{28}N_2O_2$: C, 74.08; H, 8.29; N, 8.23. Found: C, 74.257; H, 8.239; N, 7.917.

4.4. Preparation of PDMP **5** (D-threo-1-phenyl-2-decanoylamino-3-morpholino-1-propanol)

To a solution of **9d-IV** (230 mg, 0.676 mmol) in methanol (3.4 mL) were added acetic acid (77 μL, 1.35 mmol), and $Pd(OH)_2$ (25 wt%, 69 mg). The mixture was stirred under a balloon pressure of hydrogen for 4 hours at 40°C. The catalyst was filtered and the reaction solvent was removed under reduced pressure and the residue was dissolved in 3.0 mL of tetrahydrofuran. The solution was treated with 10% aqueous NaOH (0.8 mL, 1.8 mmol) and was sequentially treated with decanoyl chloride (0.13 mL, 0.607 mmol). Upon completion of reaction, as judged by TLC, the mixture was treated with water. The organic layer was separated, dried over anhydrous $MgSO_4$, filtered, and concentrated in vacuo. Purification by silica gel flash column chromatography (EtOAc only) gave 212 mg (two step yield: 81%) of the product as a light brown oil. R_f 0.40 (EtOAc). $[\alpha]_D^{25} = +8.02$ (*c* 0.30, $CHCl_3$, Lit. [16] $[\alpha]_D^{25} = +8.05$) ^1H NMR (500 MHz, $CDCl_3$) δ 7.31 (m, 5H), 5.84 (d, $J = 6.83$ HZ, 1H), 4.96 (d, $J = 3.90$ Hz, 1H), 4.28 (m, 1H), 3.72 (t, $J = 4.88$, 4.39 Hz, 4H), 2.47–2.62 (m, 6H), 2.10 (t, $J = 7.32$, 7.81 Hz, 2H), 1.50 (m, 2H), 1.23–1.31 (m, 12H), 0.88 (t, $J = 6.83$ Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 173.6, 140.9, 128.2, 127.5, 125.9, 75.1, 66.8, 59.6, 54.2, 51.1, 36.6, 31.7, 29.3, 29.2, 29.1, 29.0, 25.5, 22.5, 14.0. *Anal*. calcd for $C_{23}H_{38}N_2O_3$: C, 70.73; H, 9.81; N, 7.17. Found: C, 70.69; H, 9.81; N, 7.20.

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