Glycosyltransferase Inhibitors: Synthesis of D-*threo*-PDMP, L-*threo*-PDMP, and Other Brain Glucosylceramide Synthase Inhibitors from D- or L-Serine

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The synthesis of enantiomerically pure (1*S*,2*S*)-1-phenyl-2-decanoylamino-3-*N*-morpholino-1-propanol (L-*threo*-PDMP) (**1a**) from L-serine, and the enantiomer (1*R*,2*R*)-1-phenyl-2-decanoylamino-3-morpholino-1-propanol (D-*threo*-PDMP] (**1b**) from D-serine is reported. Reductive alkylation of the fully protected O'Donnell's Schiff base (**3b**) derived from D-serine provided the β-amino alcohol **5b** in high yield and excellent selectivity, which yielded optically pure **1b** in high yield after six steps. Three other D-*threo*-PDMP analogues with various amine groups have been synthesized using the same methodology, including the more potent pyrrolidine compound D-*threo*-PDPP (**1e**). A key feature of the synthesis is the isolation of tosylate (**8b**), which allows for the divergent synthesis of many analogues from a common advanced intermediate. The synthesis is amenable to large-scale production of D-*threo*-PDMP, L-*threo*-PDMP, and similar compounds.

The regulation of glycosphingolipids (GSLs) is critical for normal cellular function and is an important means of regulating cell−cell communication, cell adhesion and proliferation, neuronal growth, cell transformation, tumor progression, and immune response.[1] Biochemical tools (potent and selective enzyme inhibitors) are required for the exploration of GSL function as well as for new therapeutic approaches. Since its discovery by Vunnam and Radin in 1980,[2] the drug D-*threo*-PDMP (**1b**) (D-*threo*-1-phenyl-2-decanoylamino-3-morpholino-1-propanol) has been shown to be a potent inhibitor of the glucosyltransferase responsible for attachment of the first sugar to ceramide, glucosylceramide synthase.[3] The syntheses reported by Inokuchi and Radin[4] in 1987, Ganem and colleagues[5] in 1994, and Ogawa et al.[6] in 1997 all have significant limitations. This compound and its congeners have broad clinical application not only as glycosphingolipid modulation agents,[7] but also as antitumor agents.[8]

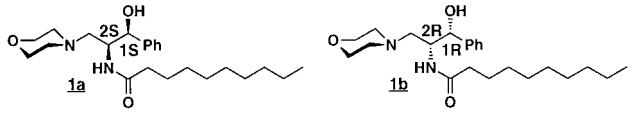

Figure 1.

The administration of D-*threo*-PDMP, **1b**, has interesting developmental consequences caused by inhibition of the biosynthesis of gangliosides.[9] More recently, D-*threo*-PPMP, the hexadecanoyl analogue of **1b**, has been demonstrated to reverse multidrug resistance in cancer cells.[10] The best-studied analogue, D-*threo*-PDMP (**1b**), inhibits glucosylceramide synthase, resulting in the *decreased* de novo synthesis of glucosylceramide and down-regulation of ganglioside biosynthesis.[11] Interestingly enough, the enantiomer L-*threo*-PDMP (**1a**) *increased* the biosynthesis of gangliosides, leading to enhanced synapse formation and increased memory retention in rats.[12] Although it seems likely that one or more sphingosine-, sphingomyelin-, ceramide-, or glycosphingolipid-processing enzymes is affected by the L-compounds, the precise molecular target or targets of **1a** remain murky. These facts dictate that an enantio-

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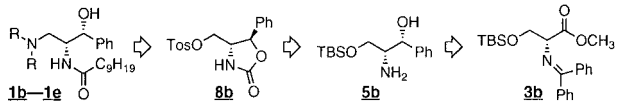
Scheme 1



merically pure synthesis of **1a**, **1b**, and related analogues is required. Ideally, a single advanced intermediate should provide for the synthesis of numerous structural analogues without reworking the entire synthetic approach for each analogue.

Our strategy focuses on the stereoselective reductive alkylation of a serine-derived Schiff base ester such as **3b** (Scheme 1). This provides the (1*R*,2*R*) diastereomer in high yield without racemization, and with good threo-diastereoselectivity.[13,14] Easy separation of the desired threo isomers on SiO_2 has been shown to be general.[15,16] Our hope was that the PDMP molecule could be generated from the carbamate tosylate, **8b**,[17] which could be obtained from the corresponding β-amino diol, **5b**. Thus, diverse cyclic secondary amines and fatty acids could be introduced at either end to produce the various PDMP analogues from a single advanced intermediate.

Initially, the Schiff base derived from L-serine was taken through to the less-studied isomer L-*threo*-PDMP **1a** without isolation of the tosylate intermediate **8a**. Subsequently, the D-form of *threo*-PDMP (**1b**), as well as a series of D-threo analogues **1c**, **1d**, and **1e**, were synthesized from the enantiomeric intermediate **8b**, which was easily purified by crystallization.

Imino ester **3a**, obtained in three steps from L-serine,[13,14b] was sequentially treated with *i*-Bu_5Al_2H (1:1 mixture of *i*-Bu_2AlH and *i*-Bu_3Al in hexanes) followed by PhMgBr (3.0 M in Et_2O) in CH_2Cl_2 at −78 °C to yield the threo imino alcohol **4a** as an oil in 69% yield and 8:1 selectivity. Because of imine−oxazoline tautomerization,[16] the minor erythro product was easily removed by flash chromatography[17] along with small amounts of over-reduced primary alcohol (Scheme 2).

Treatment of **4a** with pyridinium *p*-toluenesulfonate in THF:H_2O (10:1) cleanly removed the Schiff base to afford threo β-amino alcohol **5a** in 72% yield. The carbamate moiety was necessary to protect the amine, since attempts to displace the primary tosylates and mesylates of several threo-ceramides led to intramolecular attack of the amide on the tosylate, resulting in formation of cyclic imino ethers. Thus, the carbamate "ties back" the amide carbonyl, preventing intramolecular displacement of the tosylate (oxazoline formation[15]), while protecting the benzylic alcohol at the same time.[18] Treatment with either carbonyl diimidazole or triphosgene [$Cl_3CO(CO)OCCl_3$] afforded the silyl carbamate **6a** in 70% yield as a waxy solid. Removal of the silyl group was achieved with 10% aqueous HF in acetonitrile (10:1 CH_3CN/49% HF in H_2O) to yield crystalline carbamate alcohol **7a** in 92% yield. Although chlorides have been generated under similar conditions,[19] tosylation of the primary alcohol using tosyl chloride in pyridine and DMAP cleanly furnished **8a** in 97% yield as a white crystalline solid (mp 116−117 °C).

For L-*threo*-PDMP, **1a**, tosylate formation and subsequent displacement with 10 equivalents of morpholine in THF at reflux for 28 h was done in the same pot to yield the morpholino carbamate **9a** as an oil in 90% yield. Thus, isolation of the tosylate **8a** is not necessary. Removal of the carbamate was achieved by treatment with 1 M KOH in a 4:1 mixture of MeOH:H_2O at 65 °C for 36 h, affording the morpholino amino alcohol **10a** in 80% yield as a colorless oil. The fatty amide chain was then introduced using either *p*-nitrophenyl decanoate or pentafluorophenyl decanoate as the acylating agent and 10 mole-% HOBt in dry pyridine. After extraction with 1 N NaOH to remove *p*-nitrophenol or pentafluorophenol, and flash chromatography, the desired drug enantiomer **1a** was obtained as an oil in 90% yield (Scheme 3).

Starting with D-serine, the synthesis was repeated to produce enantiomeric Schiff base **3b**, which in turn provided the enantiomeric tosylate **8b** in crystalline form. Displacement of the tosylate with cyclic amines provided the carbamate amines **9b**−**9e** (Scheme 4). Similarly, each of the other alkylated amines was deprotected and acylated as before to provide the isomeric D-*threo*-PDMP **1b**, as well as the depicted structural analogues. Analogue **1e** is of particular note because reported studies (with enantiomeric mixtures) suggest that this compound has four times the activity of **1b** against glycosylceramide synthase.[9b]

Now that an efficient enantioselective synthesis has been established, diverse analogues of D-*threo*-PDMP can be easily prepared to explore the nature of the interaction with glucosylceramide synthase and other sphingosine- and ceramide-processing enzymes. Because a number of the intermediates are crystalline and the protecting group manipulations are straightforward, it is expected that this route could also be optimized for large-scale synthesis of these compounds. Our ongoing work will involve the introduction of more complex secondary amines at the glycosphingosine-like headgroup, changes in the fatty acid amide chain of the ceramide, and variation of the carbanion source during reductive alkylation to produce alterations in the sphingosine moiety.

Experimental Section

General Information. All air- and moisture-sensitive reactions were performed under an argon atmosphere in flame-dried reaction flasks. THF was dried and deoxygenated over $Ph_2C{=}O/K°$. CH_2Cl_2 (dichloromethane) was dried over P_2O_5, CH_3CN (acetonitrile) was dried over CaH_2, and all solvents were freshly distilled under an argon atmosphere before use. For flash chromatography, 400−230 mesh silica gel 60 (E. Merck no. 9385) was used. All compounds described were >95% pure by ^1H and ^{13}C NMR, and purity was confirmed by high-resolution fast atom bombardment (FAB) mass spectrometry in most cases, and by CHN analysis for one of the final products. The ^1H and ^{13}C NMR spectra were obtained on either a Bruker WM 250 MHz or a Bruker 500 MHz spectrometer. For ^{13}C, spectra were taken at 62.9 MHz in the form

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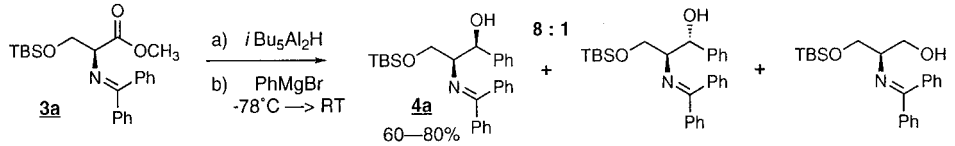
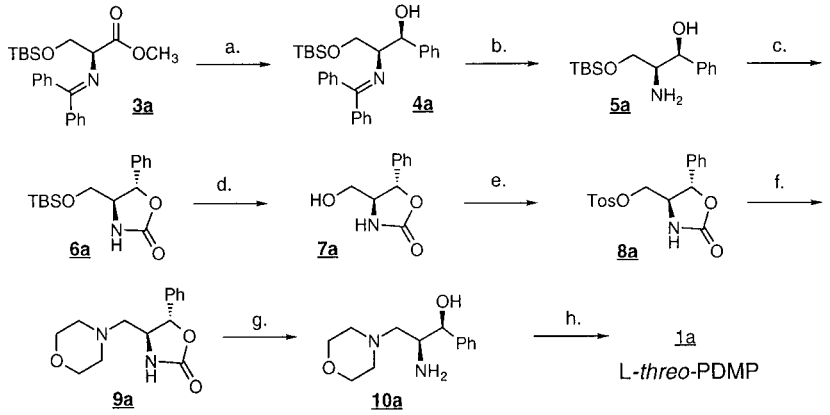
Scheme 2

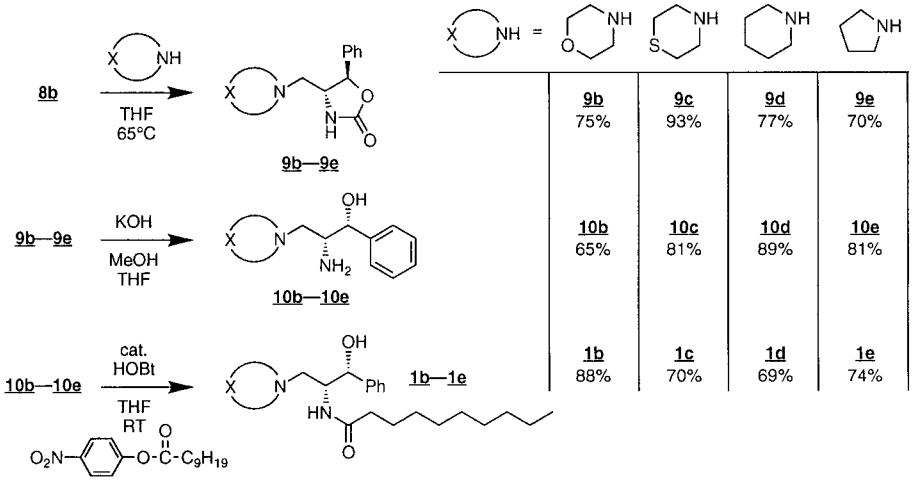


Scheme 3



a) i. $iBu_2AlH{\bullet}iBu_3Al$ / hexanes / -78°C **ii.** C_6H_5MgBr **b)** pyridine•HOTs / THF / H_2O **c)** $Cl_3COCOOCCl_3$ / THF **d)** HF / H_2O / CH_3CN **e)** TosCl / pyridine **f)** Morpholine / THF / Δ **g)** KOH (aq.)/Δ **h)** NO_2-C_6H_4-O_2C-C_9H_{19}

Scheme 4



of APTs (attached proton test spectra). Chemical shifts are reported in δ vs Me_4Si in ^1H spectra and vs $CDCl_3$ in ^{13}C spectra. Infrared spectra were taken on a Nicolet Impact-400D FT-IR. Optical rotations were taken on a Jasco DIP-1000 polarimeter using the Na^D-line. All melting points were taken on a Hoover capillary melting point apparatus and are uncorreced. Elemental analyses were performed by Desert Analytics of Tucson, Arizona.

Methyl-*O*-(*tert*-butyldimethylsilyl)-*N*-(diphenylmethylene)-D-serinate (3b). Methyl-*N*-(diphenylmethylene)-D-serinate (28.00 g, 0.099 mol) was dried over P_2O_5 in vacuo and added to a RB-flask and dry dimethyl formamide (DMF) (90 mL) was added. TBDMS−Cl (23.83 g, 0.16 mol) and imidazole (17.5 g, 0.257 mol) were added in one portion and stirred at room temperature (RT) under argon for 24 h. The sample was then poured over ether (200 mL) and washed 2× with 1% $NaHCO_3$. The organic layer was pooled, washed with brine, dried over $MgSO_4$, and concentrated in vacuo. The resultant oil solidified on standing to give 33.60 g of a crystalline mass in 86% yield. MP: 56−58 °C. $[\alpha]^{25}_D = +100.68°$ (c = 0.76, $CHCl_3$). ^1H NMR (250 MHz, $CDCl_3$): δ 7.66−7.20 (Ar−*H*, m, 10H), 4.32 (αC*H*, dd, J = 7.58, 5.4 Hz, 1H), 4.13 (βH, dd, J = 9.75, 5.4 Hz, 1H), 3.94 ($\beta'H$, dd, J = 9.73, 7.63 Hz, 1H), 3.70 (OCH_3, s, 3H), 0.84 [$(CH_3)_3C$−, s, 9H], 0.02 (CH_3−Si−, s, 3H), −0.0044 (CH_3'−Si−, s, 3H). ^{13}C NMR (62.5 MHz, $CDCl_3$): δ 171.5, 171.0, 139.5, 136.1, 130.2, 128.8, 128.6, 128.3, 128.27, 127.9, 67.7, 51.9, 25.7, 18.2, −5.4, −5.5. IR (CH_2Cl_2): 3060, 2952, 1740, 1625 cm^{-1}.

(1*R*,2*R*)-(−)-2-Amino-*N*-(diphenylmethylene)-3-*O*-(*tert*-butyldimethylsilyl)-1-phenylpropane-1,3-diol (4b). Fully protected D-serine **3b** (20.0 g, 0.05 mol) was added to CH_2Cl_2 (500 mL) in a long-necked addition flask under argon and cooled to −78 °C. To this solution was added *i*-$Bu_2AlH{\bullet}$*i*-Bu_3Al (0.05 mol of each in 100.60 mL of hexanes) at −78 °C over 90 min. The solution turned yellow upon addition and was allowed to stir for 60 min. Next, PhMgBr in ether (50.3 mL, 3 equiv, 0.15 mol) was added dropwise at −78 °C over 130 min and the resulting solution was allowed to stir overnight and slowly warm from −78 to 0 °C, turning a deep orange-yellow color. After completion of reaction the flask was cooled to 0 °C and concentrated $NaHCO_3$ (~10 mL) was added dropwise slowly to quench the reaction. The reaction turned a light milky yellow upon quenching, and the solution was diluted with CH_2Cl_2 (400 mL), the phases separated, and the crude was washed 3× with concentrated $NaHCO_3$, followed by brine and dried over $MgSO_4$. Silica gel flash chromatography (5% EtOAc:hexanes, R_f = 0.63) yielded 15.60 g of pure threo product as a colorless oil in 70% yield. $[\alpha]^{25}_D = -109°$

(c = 1.70, $CHCl_3$). ^1H NMR (250 MHz, $CDCl_3$): δ 7.83−7.14 (Ar−*H*, m, 15H), 4.94 (C*H*−O, d, J = 6.23 Hz, 1H), 3.86 (βH, dd, J = 10.73, 3.05 Hz, 1H), 3.64 ($\beta' H$, dd, J = 12.08, 1.43 Hz, 1H), 3.14 (αC*H*, dt, J = 8.25 Hz, 1H), 0.85 [(CH_3)$_3$C−, s, 9H], 0.08 (CH_3−Si−, s, 3H), 0.04 (CH_3'−Si−, s, 3H). ^{13}C NMR (62.5 MHz, $CDCl_3$): δ 145.6, 145.3, 140.4, 128.44, 128.33, 128.12, 128.07, 127.8, 127.6, 127.5, 127.3, 126.9, 126.6, 125.9, 125.7, 100.1, 81.9, 68.3, 59.1, 25.7, 18.1, −5.5. IR (CH_2Cl_2): 3061, 2953, 1450 cm^{-1}.

(1*R*,2*R*)-(+)-2-amino-3-*O*-(*tert*-butyldimethylsilyl)-1-phenylpropane-1,3-diol (5b). Threo product **4b** (12.90 g, 2.89 mmol) was dissolved in THF (200 mL) and H_2O (20 mL). Pyridinium *p*-toluenesulfonate (14.55 g, 5.79 mmol, 2 equiv) was added and reacted for 4.5 h, the solvent was removed in vacuo, and the residue was redissolved in CH_2Cl_2 (150 mL) and washed with concentrated $NaHCO_3$ (3 × 50 mL), brine, and dried over K_2CO_3. The crude product was then chromatographed on silica gel (9:1, CH_2Cl_2:MeOH, R_f = 0.5) yielding 6.54 g as a colorless oil in 80% yield. $[\alpha]^{25}_D$ = +3.14° (c = 1.34, $CHCl_3$). ^1H NMR (250 MHz, $CDCl_3$): δ 7.36−7.27 (Ar−*H*, m, 5H), 4.64 (C*H*−OH, d, J = 5.26 Hz, 1H), 3.65 (βH, dd, J = 10.07, 4.12 Hz, 1H), 3.58 ($\beta' H$, dd, J = 10.11, 5.00 Hz, 1H), 2.21 (O*H*, bs, 1H), 0.91 [(CH_3)$_3$C−, s, 9H] 0.06 [(CH_3)$_2$−Si−, s, 6H]. ^{13}C NMR (62.5 MHz, $CDCl_3$): δ 142.4, 128.2, 127.3, 126.2, 73.9, 65.0, 58.3, 25.8, 18.1, −5.60. IR (neat): 3444, 2956, 912, 740 cm^{-1}.

(4*R*,5*R*)-(+)-4-(*tert*-Butyldimethylsilyloxymethyl)-5-phenyloxazolidin-2-one (6b). Amino alcohol **5b** (1.92 g, 6.82 mmol) was dissolved in 20 mL of dry CH_2Cl_2 under argon and cooled to 0 °C. Triethylamine was then added in one portion (2.87 mL, 20.6 mmol) at 0 °C. A solution of triphosgene (682.5 mg, 2.3 mmol, 0.33 equiv) in CH_2Cl_2 (20 mL) was added dropwise over 60 min. After 4 h the reaction was complete, and all solvent was removed in vacuo. The residue was then redissolved in Et_2O, filtered, and washed with concentrated $NaHCO_3$ (3 × 100 mL) and dried over $MgSO_4$. Flash chromatography (3:2 hexanes:EtOAc, R_f = 0.57) yielded 1.52 g as a waxy solid in 72.8% yield. MP: 88−90 °C. $[\alpha]^{25}_D$ = +31.1° (c = 0.405, $CHCl_3$). ^1H NMR (250 MHz, $CDCl_3$): δ 7.42−7.34 (Ar−*H*, m, 5H), 6.58 (N*H*, bs, 1H), 5.35 (C*H*−OH, d, J = 4.63 Hz, 1H), 3.79 (C*H*−NH, p, J = 5.78, 4.98 Hz, 1H), 3.74 (βCH_2, d, J = 4.75 Hz, 2H), 0.91 [(CH_3)$_3$C−Si, s, 9H], 0.094 (CH_3−Si, s, 6H). ^{13}C NMR (62.5 MHz, $CDCl_3$): δ 159.7, 139.0, 128.6, 128.4, 125.3, 79.8, 64.0, 61.5, 25.6, 18.0, −5.6. IR (CH_2Cl_2): 3416, 2955, 1757 cm^{-1}. HRMS $C_{16}H_{26}NO_3Si$ [M + H] calcd. 308.1681, found 308.1682.

(4*R*,5*R*)-(+)-4-(Hydroxymethyl)-5-phenyloxazolidin-2-one (7b). Carbamate **6b** (1.00 g, 3.25 mmol) was dissolved in 20 mL of acetonitrile and HF (49% aqueous, 0.5 mL, 12.25 mmol, 3.8 equiv) was added via syringe at RT and stirred for 75 min. After TLC showed full conversion, solvent was removed in vacuo. The crude product was redissolved in 9:1 CH_2Cl_2:MeOH and passed through a plug of silica gel (R_f = 0.44). Isolation and concentration yielded 0.60 g as white crystals in 95% yield. MP: 96−97 °C. $[\alpha]^{25}_D$ = +44.0° (c = 0.345, MeOH). ^1H NMR (250 MHz, CD_3OD + D_2O): δ 7.37 (Ar−*H*, m, 5H), 5.37 (C*H*−OD, d, J = 5.6 Hz, 1H), 3.83 (βCH_2, dt, J = 9.41, 3.21 Hz, 2H), 3.67 (C*H*−ND$_2$, dd, J = 12.61, 5.46 Hz, 1H). ^{13}C NMR (62.5 MHz, CD_3OD): δ 159.9, 138.3, 128.9, 125.7, 79.8, 62.7, 61.8. IR (CH_2Cl_2): 3292, 3057, 1707, 1268 cm^{-1}. MS (FAB) [M + H] for $C_{10}H_{12}NO_3$; HRMS calcd. 194.0817, found 194.0814.

(4*R*,5*R*)-(+)-4-(4′-*p*-Toluenesulfonyloxymethyl)-5-phenyloxazolidin-2-one (8b). Alcohol **7b** (330.8 mg, 1.71 mmol) was dissolved in dry pyridine (2.0 mL) and tosyl chloride (502.5 mg, 2.635 mmol, 1.5 equiv) was added in one portion. The resulting mixture was reacted at RT for 4 h, the solvent was removed in vacuo and the crude was purified by flash chromatography (EtOAc:hexanes 1:1, R_f = 0.33), yielding 585.5 mg as a white crystalline solid in 98.5% yield. MP: 116−117 °C. $[\alpha]^{25}_D$ = +39.6° (c = 0.75, $CHCl_3$). ^1H NMR (250 MHz, $CDCl_3$): δ 7.80 (Ar−*H*, 2H, d, J = 8.3 Hz), 7.41−7.27 (Ar−*H*, m, 7H), 6.28 (N*H*, bs, 1H), 5.23 (C*H*−OPh, d, J = 5.45 Hz, 1H), 4.15 (CH_2−OTos, dd, J = 5.22, 5.41 Hz, 2H), 3.96 (C*H*−NH, dd, J = 5.32, 5.24 Hz, 1H), 2.46 (CH_3, s, 3H). ^{13}C NMR (62.5 MHz, $CDCl_3$): δ 158.5, 145.6, 137.4, 131.9, 130.1, 129.2, 129.0, 127.9, 125.5, 79.3, 68.9, 58.8, 21.6. IR (CH_2Cl_2): 3018, 1771, 1221, 758 cm^{-1}. MS (FAB) [M + H] for $C_{17}H_{18}O_5NS$; HRMS calcd. 348.0906, found 348.0913.

(4*R*,5*R*)-(+)-4-[(*N*-Morpholino)methyl]-5-phenyloxazolidin-2-one (9b). Tosylate **8b** (585.5 mg, 1.69 mmol) was dissolved in THF (5.0 mL) and morpholine (0.44 mL, 5.0 mmol, 3 equiv) was added, and the resultant mixture was heated to reflux for 34 h. THF was removed in vacuo, the residue was dissolved in CH_2Cl_2 and extracted with $NaHCO_3$, and flash chromatography (CH_2Cl_2:MeOH 20:1, R_f = 0.34) yielded 335 mg as a colorless oil in 75.2% yield. $[\alpha]^{25}_D$ = +36.5° (c = 0.325, $CHCl_3$). ^1H NMR (250 MHz, $CDCl_3$): δ 7.38 (Ar−*H*, m, 5H), 6.24 (N*H*, bs, 1H), 5.22 (C*H*−OPh, d, J = 5.65 Hz, 1H), 3.84 (C*H*−NH, dd, J = 6.74, 6.26 Hz, 1H), 3.67 (CH_2−O$_{MOR}$, t, 4.59 Hz, 4H), 2.74 (βCH_2−N, ddd, 4.74, 3.46 Hz, 2H), 2.46 (CH_2−N$_{MOR}$, tq, 13.2, 4,6 Hz, 4H). ^{13}C NMR (62.5 MHz, $CDCl_3$): δ 159.0, 138.5, 128.5, 125.4, 81.4, 66.4, 62.1, 57.4, 53.6. IR (neat): 3434, 3018, 1759 cm^{-1}. HRMS $C_{14}H_{19}N_2O_3$ [M + H] calcd. 263.1396, found 263.1396.

(4*R*,5*R*)-(+)-4-[(*N*-Thiomorpholino)methyl]-5-phenyloxazolidin-2-one (9c). Tosylate **8b** (235.5 mg, 0.68 mmol) was dissolved in THF (5.0 mL) and thiomorpholine (0.52 mL, 5.2 mmol, 7.7 equiv) was added, and the resultant mixture was heated to reflux for 47 h. THF was removed in vacuo, the residue was dissolved in CH_2Cl_2 and extracted with $NaHCO_3$, and flash chromatography (CH_2Cl_2:MeOH 20:1, R_f = 0.55) yielded 175 mg as a colorless oil in 93.1% yield. $[\alpha]^{25}_D$ = +30.9° (c = 0.25, $CHCl_3$). ^1H NMR (250 MHz, $CDCl_3$): δ 7.42−7.35 (Ar−*H*, m, 5H), 5.60 (N*H*, bs, 1H), 5.17 (C*H*−OPh, d, J = 5.53 Hz, 1H), 3.82 (C*H*−NH, q, J = 7.65 Hz, 1H), 2.81−2.77 (m, 2H), 2.72−2.68 (m, 2H), 2.66−2.56 (m, 6H). ^{13}C NMR (62.5 MHz, $CDCl_3$): δ 159.1, 138.6, 128.7, 125.5, 81.5, 62.6, 57.7, 55.3, 27.7. IR (neat): 3426, 2923, 1754, 1657 cm^{-1}. HRMS $C_{14}H_{19}N_2O_2S$ [M + H] calcd. 279.1167, found 279.1179.

(4*R*,5*R*)-(+)-4-[(*N*-Piperidino)methyl]-5-phenyloxazolidin-2-one (9d). Tosylate **8b** (330 mg, 0.95 mmol) was dissolved in THF (5.0 mL) and piperidine (0.94 mL, 9.5 mmol, 10 equiv) was added, and the resultant mixture was heated to reflux for 16 h. THF was removed in vacuo, the residue was dissolved in CH_2Cl_2 and extracted with $NaHCO_3$, and flash chromatography (CH_2Cl_2:MeOH 20:1, R_f = 0.35) yielded 196 mg as a colorless oil in 76.7% yield. $[\alpha]^{25}_D$ = +40.7° (c = 0.245, $CHCl_3$). ^1H NMR (250 MHz, $CDCl_3$): δ 7.38 (Ar−*H*, m, 5H), 6.24 (N*H*, bs, 1H), 5.22 (C*H*−OPh, d, J = 5.65 Hz, 1H), 3.84 (C*H*−NH, dd, J = 6.74, 6.26 Hz, 1H), 3.67 (CH_2−O$_{MOR}$, t, 4.59 Hz, 4H), 2.74 (βCH_2−N, ddd, 4.74, 3.46 Hz, 2H), 2.46 (CH_2−N$_{MOR}$, tq, 13.2, 4.6 Hz, 4H). ^{13}C NMR (62.5 MHz, $CDCl_3$): δ 159.0, 138.5, 128.5, 125.4, 81.4, 66.4, 62.1, 57.4, 53.6. IR (neat): 3419, 3066, 2935, 1755, 1655 cm^{-1}. HRMS $C_{15}H_{21}N_2O_2$ [M + H] calcd. 261.1603, found 261.1606.

(4*R*,5*R*)-(+)-4-[(*N*-Pyrrolidino)methyl]-5-phenyloxazolidin-2-one (9e). Tosylate **8b** (187.6 g, 0.54 mmol) was dissolved in THF (5.0 mL) and pyrrolidine (0.45 mL, 5.4 mmol, 10 equiv) was added and heated to reflux for 11 h. THF was removed in vacuo, the residue was dissolved in CH_2Cl_2 and extracted with $NaHCO_3$, and flash chromatography (CH_2Cl_2:MeOH 20:1, R_f = 0.35) yielded 87.9 mg as a colorless oil in 70.1% yield. $[\alpha]^{25}_D$ = +43.8° (c = 0.665, $CHCl_3$). ^1H NMR (250 MHz, $CDCl_3$): δ 7.42−7.35 (Ar−*H*, m, 5H), 5.59 (N*H*, bs, 1H), 5.19 (C*H*−OPh, d, J = 5.73 Hz, 1H), 3.80 (C*H*−NH, dt, J = 6.74, 8.55 Hz, 1H), 2.84 (βH, dd, J = 12.02, 8.95 Hz, 1H), 2.65 ($\beta' H$, dd, J = 12.13, 4.97 Hz, 1H), 2.59 (αCH_{2PYR}, m, 2H), 2.51 (α′CH_{2PYR}, m, 2H), 1.78 (βCH_{2PYR}, m, 4H). ^{13}C NMR (62.5 MHz, $CDCl_3$): δ 158.9, 138.7, 128.7, 128.6, 125.6, 81.4, 59.9, 59.3, 54.2, 23.4. IR (neat): 3390, 2960, 1755 cm^{-1}. HRMS $C_{14}H_{19}N_2O_2$ [M + H] calcd. 247.1447, found 247.1447.

(1*R*,2*R*)-(+)-2-Amino-3-(*N*-morpholino)-1-phenyl-1-ol (10b). Carbamate **9b** (330 g, 1.26 mmol) was dissolved in MeOH:H_2O (4:1) and treated with) 2 M KOH (5.0 mL) and heated under reflux conditions at 70 °C, and the reaction progress was monitored by TLC. After 16 h the sample was concentrated in vacuo and redissolved in CH_2Cl_2 and washed with concentrated $NaHCO_3$. Passing the sample through silica gel using 20% MeOH:CH_2Cl_2 yielded 192.4 mg as a colorless

oil in 65.4% yield. $[\alpha]^{25}_D = +5.86°$ ($c = 0.25$, $CHCl_3$). ^1H NMR (250 MHz, $CDCl_3$): δ 7.38−7.25 (Ar−*H*, m, 5H), 4.55 (C*H*−OH, d, $J = 3.29$ Hz, 1H), 3.70 (CH_2-O_{MOR}, t, $J = 4.6$ Hz, 4H), 3.21 (C*H*−NH_2, ddd, $J = 6.57$, 5.33 Hz, 1H), 2.56 (βH, dd, $J = 11.28$, 4.23 Hz, 1H), 2.36 ($\beta' H$, dd, $J = 12.58$, 5.44 Hz, 1H), 2.45 (CH_2-N_{MOR}, m, 4H). ^{13}C NMR (62.5 MHz, $CDCl_3$): δ 142.5, 128.2, 127.2, 125.9, 75.1, 66.9, 61.9, 53.9, 52.7. IR (neat): 3450, 3018, 1641 cm^{-1}. HRMS $C_{13}H_{21}N_2O_2$ [M + H] calcd. 237.1603, found 237.1603.

(1*R*,2*R*)-(+)-2-Amino-1-phenyl-3-(*N*-thiomorpholino)-1-ol (10c). Carbamate **9c** (105.4 mg, 0.399 mmol) was dissolved in MeOH:H_2O (4:1) and treated with) 2 M KOH (5.0 mL) and heated under reflux conditions at 70 °C, and the reaction progress was monitored by TLC. After 18 h the sample was concentrated in vacuo and redissolved in CH_2Cl_2 and washed with concentrated $NaHCO_3$. Passing the sample through silica gel using 20% MeOH:CH_2Cl_2 yielded 100.6 mg as a colorless oil in 81.3% yield. $[\alpha]^{25}_D = +5.23°$ ($c = 0.32$, $CHCl_3$). ^1H NMR (250 MHz, $CDCl_3$ + D_2O): δ 7.37−7.26 (Ar−*H*, m, 5H), 4.54 (C*H*−OH, d, $J = 3.17$ Hz 1H), 3.22 (C*H*−NH_2, dt, $J = 3.4$, 6.87 Hz 1H), 2.82 (CH_2-N_{TM}, m, 2H), 2.71 ($CH_2'-N_{TM}$, m, 2H), 2.67 (CH_2-S_{TM}, m, 4H), 2.44 (βCH_2, d, $J = 6.66$ Hz). ^{13}C NMR (62.5 MHz, $CDCl_3$): δ 142.5, 128.2, 127.2, 125.9, 75.1, 62.2, 55.4, 52.9, 27.9.

(1*R*,2*R*)-(+)-2-Amino-1-phenyl-3-(*N*-piperidino)-1-ol(10d). Carbamate **9d** (167 mg, 0.64 mmol) was dissolved in MeOH:H_2O (4:1) and treated with) 2 M KOH (5.0 mL) and heated under reflux conditions at 70 °C, and the reaction progress was monitored by TLC. After 16 h the sample was concentrated in vacuo and redissolved in CH_2Cl_2 and washed with concentrated $NaHCO_3$. Passing the sample through silica gel using 20% MeOH:CH_2Cl_2 yielded 150 mg as a colorless oil in 99.7% yield. $[\alpha]^{25}_D = -6.35°$ ($c = 0.29$, $CHCl_3$). ^1H NMR (250 MHz, $CDCl_3$ + D_2O): δ 7.29−7.14 (Ar−*H*, m, 5H), 4.55 (C*H*−OH, d, $J = 3.37$ Hz 1H), 3.16 (C*H*−NH_2, dt, 6.72, 3.36 Hz 1H), 2.36 (αCH_{2PIP}, m, 4H), 2.32 (βH, dd, $J = 12.8$, 6.95 Hz, 1H), 2.22 ($\beta' H$, dd, $J = 12.7$, 6.63 Hz, 1H), 1.50 (βCH_{2PIP}, p, $J = 5.6$ Hz, 4H), 1.36 (γCH_{2PIP}, bp, $J = 4.975$ Hz, 2H). ^{13}C NMR (62.5 MHz, $CDCl_3$): δ 142.3, 127.9, 126.9, 126.2, 76.0, 62.4, 55.1, 52.3, 25.9, 24.1. IR (neat): 3373, 3017, 2933, 1452 cm^{-1}. HRMS $C_{14}H_{23}N_2O$ [M + H] calcd. 235.1810, found 235.1812.

(1*R*,2*R*)-(+)-2-Amino-1-phenyl-3-(*N*-pyrrolidino)-1-ol (10e). Carbamate **9e** (88 mg, 0.036 mmol) was dissolved in MeOH:H_2O (4:1) and treated with) 2 M KOH (5.0 mL) and heated to 70 °C under reflux conditions and the reaction progress was monitored by TLC. After 16 h the sample was concentrated in vacuo and redissolved in CH_2Cl_2 and washed with concentrated $NaHCO_3$. Passing the sample through silica gel using 20% MeOH:CH_2Cl_2 yielded 79 mg as a colorless oil in 80.7% yield. $[\alpha]^{25}_D = +3.51°$ ($c = 0.91$, $CHCl_3$). ^1H NMR (250 MHz, $CDCl_3$ + D_2O): δ 7.38−7.26 (Ar−*H*, m, 5H), 4.68 (C*H*−OH, d, $J = 3.35$ Hz, 1H), 3.19 (C*H*−NH_2, dt, $J = 6.38$, 3.38 Hz, 1H), 2.74 (βH, dd, $J = 12.7$, 6.6 Hz, 1H), 2.53 ($\beta' H$, dd, $J = 12.4$, 5.8 Hz, 1H), 2.63 (αCH_{2PYR}, m, 4H), 1.75 (βCH_{2PYR}, m, 4H). ^{13}C NMR (62.5 MHz, $CDCl_3$): δ 142.5, 128.2, 127.2, 125.9, 75.1, 66.9, 61.9, 53.9, 52.7. IR (neat): 3362, 3296, 3086, 2926, 1451 cm^{-1}. HRMS $C_{13}H_{21}N_2O$ [M + H] calcd. 221.1654, found 221.1649.

(1*R*,2*R*)-(+)-1-Phenyl-2-decanoylamino-3-(*N*-morpholino)-1-propanol [D-*threo*-PDMP] (1b). Compound **10b** (192.4 mg, 0.814 mmol) was dissolved in pyridine (dried over sieves) and was sequentially treated with *p*-nitrophenyl decanoate (239 mg, 0.814 mmol) and 1-hydroxybenzotriazole (10 mol %, 12.5 mg, 0.0814 mmol). Upon completion judged by TLC, the solvent was removed, and the residue was dissolved in CH_2Cl_2 and extracted with NaOH (5 × 20 mL, 1 M). The crude was chromatographed (4:1 CH_2Cl_2:MeOH, $R_f = 0.42$) to give 280 mg of **1b** as a light brown oil in 88% yield. $[\alpha]^{25}_D = 8.05°$ ($c = 0.3$, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$): δ 7.36−7.25 (Ar−*H*, m, 5H), 5.89 (N*H*, bd, $J = 6.75$ Hz, 1H), 4.96 (C*H*−OH, d, $J = 3.73$ Hz, 1H), 4.29 (C*H*−NH, ddd, $J = 6.30$, 6.9 Hz, 1H), 3.73 (CH_2-O_{MOR}, t, $J = 4.53$ Hz, 4H), 2.64 (βH, dd, $J = 6.63$, 13.05 Hz, 1H), 2.58 (CH_2-N_{MOR}, t, $J = 5.53$ Hz, 4H), 2.51 ($\beta' H$, dd, $J = 6.63$, 13.05 Hz, 1H), 2.10 (αCH_2, t, $J = 7.52$ Hz, 2H), 1.49 (βCH_2, p, $J = 6.90$ Hz, 2H), 1.23 [$(CH_2)_6$, m, 12H], 0.87 (CH_3, t, 6.61 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 173.6, 140.9, 128.2, 127.5, 125.9, 75.0, 66.8, 59.6, 54.2, 51.1, 36.6, 31.8, 29.3, 29.2, 29.0, 25.6, 22.6, 14.0. IR (neat): 3428, 3017, 2956, 1656, 1509 cm^{-1}. MS (FAB) [M + H] for $C_{23}H_{39}O_3N_2$; HRMS calcd. 391.2961, found 391.2980.

D-*threo*-PDMP (150 mg, 0.384 mmol) was dissolved in MeOH (5.0 mL), cooled to 0 °C, and acidified to pH 4.0 with HCl (3 M). The resulting mixture was concentrated in vacuo to afford a white crystalline compound. The crystalline product was recrystallized ($CHCl_3$:Et_2O) to give D-*threo*-PDMP·HCl·H_2O (126.5 mg, 0.296 mmol) in 77% yield. MP: 94−96 °C; $[\alpha]^{25}_D = -12.1°$ ($c = 0.40$, $CHCl_3$). IR (CH_2Cl_2): 3442, 2932, 1635 cm^{-1}. Elemental analysis (C, H, N): $C_{23}H_{38}N_2O_3$·HCl·H_2O calcd. 62.08% C, 9.29% H, and 6.30% N; found 61.76% C, 9.19% H, and 6.25% N.

(1*R*,2*R*)-(+)-1-Phenyl-2-decanoylamino-3-(*N*-thiomorpholino)-1-propanol [D-*threo*-PDTMP] (1c). Compound **10c** (81.4 mg, 0.323 mmol) was dissolved in pyridine (dried over sieves) and was sequentially treated with *p*-nitrophenyl decanoate (95 mg, 0.322 mmol) and 1-hydroxybenzotriazole (10 mol %, 5.0 mg, 0.032 mmol). Upon completion judged by TLC, the solvent was removed, and the residue was dissolved in CH_2Cl_2 and extracted with NaOH (5 × 20 mL, 1 M). The crude was chromatographed (20:1 CH_2Cl_2:MeOH, $R_f = 0.48$) to give 90 mg of **1b** as a light brown oil in 81.3% yield. $[\alpha]^{25}_D = +2.83°$ ($c = 1.17$, $CHCl_3$). ^1H NMR (250 MHz, $CDCl_3$): δ 7.36−7.25 (Ar−*H*, m, 5H), 5.82 (N*H*, d, $J = 7.03$ Hz, 1H), 4.93 (C*H*−OH, d, $J = 3.69$ Hz, 1H), 4.25 (C*H*−NH, ddd, $J = 10.77$, 6.63, 3.94 Hz, 1H), 2.82 (CH_2-N_{TM}, m, 4H), 2.69 (CH_2-S_{TM}, t, $J = 5.18$ Hz, 4H), 2.59 (βH, dd, $J = 13.17$, 6.60 Hz, 1H), 2.48 ($\beta' H$, dd, $J = 13.15$, 5.59 Hz, 1H), 2.09 (αCH_2, t, $J = 7.44$ Hz, 2H), 1.50 (βCH_2, p, $J = 7.51$ Hz, 2H), 1.24 [$(CH_2)_6$, m, 12H], 0.88 (CH_3, t, $J = 6.82$ Hz, 3H). ^{13}C NMR: (62.5 MHz, $CDCl_3$): δ 173.6, 140.9, 128.3, 127.5, 126.0, 75.1, 59.8, 55.7, 51.2, 36.7, 31.8, 29.3, 29.2, 29.18, 29.04, 27.9, 25.6, 22.6, 14.0. IR (neat): 3309, 2952, 1642, 1534 cm^{-1}. MS (FAB) [M + H] for $C_{23}H_{39}N_2O_2S$; HRMS calcd. 407.2732, found 407.2724.

(1*R*,2*R*)-(+)-1-Phenyl-2-decanoylamino-3-(*N*-piperidino)-1-propanol [D-*threo*-PDPiP] (1d). Compound **10d** (144.5 mg, 0.617 mmol) was dissolved in pyridine (dried over sieves) and was sequentially treated with *p*-nitrophenyl decanoate (181 mg, 0.617 mmol) and 1-hydroxybenzotriazole (10 mol %, 10 mg, 0.062 mmol). Upon completion judged by TLC, the solvent was removed, and the residue was dissolved in CH_2Cl_2 and extracted with NaOH (5 × 20 mL, 1 M). The crude was chromatographed (9:1 CH_2Cl_2:MeOH, $R_f = 0.58$) to give 164 mg of **1b** as a light brown oil in 68.8% yield. $[\alpha]^{25}_D = +6.33°$ ($c = 0.215$, $CHCl_3$). ^1H NMR (250 MHz, $CDCl_3$): δ 7.37−7.22 (Ar−*H*, m, 5H), 5.91 (N*H*, d, $J = 7.19$ Hz, 1H), 4.96 (C*H*−OH, d, $J = 3.56$ Hz, 1H), 4.31 (C*H*−NH, dt, $J = 11.25$ Hz, 1H), 2.62 (βH, dd, $J = 13.24$, 6.37 Hz, 1H), 2.50 ($\beta' H$, dd, $J = 13.49$, 5.26 Hz, 1H), 2.54 (αCH_{2PIP}, m, 4H), 2.08 (αCH_2, t, $J = 7.28$ Hz, 2H), 1.63 (βCH_{2PIP}, bp, $J = 5.28$ Hz, 4H), 1.49 (γCH_{2PIP}, m, 4H), 1.23 [$(CH_2)_6$, m, 12H], 0.87 (CH_3, t, $J = 6.38$ Hz, 3H). ^{13}C NMR (62.5 MHz, $CDCl_3$): δ 173.4, 140.9, 128.1, 127.3, 126.0, 75.5, 59.9, 55.4, 50.6, 36.6, 31.7, 29.3, 29.2, 29.16, 28.9, 25.9, 25.5, 23.7, 22.5, 14.0. IR (neat): 3308, 2926, 1644, 1537 cm^{-1}. MS (FAB) [M + H] for $C_{24}H_{41}O_2N_2$; HRMS calcd. 389.3168, found 389.3170.

(1*R*,2*R*)-(+)-1-Phenyl-2-decanoylamino-3-(*N*-pyrrolidino)-1-propanol [D-*threo*-PDPP] (1e). Compound **10b** (33 mg, 0.015 mmol) was dissolved in pyridine (dried over sieves) and was sequentially treated with *p*-nitrophenyl decanoate (43 mg, 0.015 mmol) and 1-hydroxybenzotriazole (10 mol %, 2.5 mg, 0.0015 mmol). Upon completion judged by TLC, the solvent was removed, and the residue was dissolved in CH_2Cl_2 and extracted with NaOH (5 × 20 mL, 1 M). The crude was chromatographed (9:1 CH_2Cl_2:MeOH, $R_f = 0.23$) to give 41 mg of **1b** as a light brown oil in 74.2% yield. $[\alpha]^{25}_D = +2.26°$ ($c = 0.96$, $CHCl_3$). ^1H NMR (250 MHz, $CDCl_3$): δ 7.29−7.17 (Ar−*H*, m, 5H), 5.84 (N*H*, d, $J = 7.05$ Hz, 1H), 4.99 (C*H*−OH, d, $J = 3.2$ Hz, 1H), 4.19 (C*H*−NH, ddd, 8.04, 4.98, 4.92 Hz, 1H), 2.81 (βCH_2, d, $J = 5.12$ Hz, 2H), 2.68 (αCH_{2PYR}, m, 2H), 2.64 (βCH_{2PYR}, m, 2H), 1.99 ($\alpha' CH_2$, m, $J = 11.63$, 4.63 Hz, 2H), 1.75 (m, 4H), 1.40 ($\beta' CH_2$, p, $J = 7.29$ Hz, 2H), 1.27−1.09

[(CH_2)$_6$, m, 12H], 0.812 (CH_3, t, J = 7.12 Hz, 3H). ^{13}C NMR (62.5 MHz, $CDCl_3$): δ 173.5, 140.9, 128.2, 127.4, 125.8, 75.3, 57.7, 55.2, 52.3, 36.7, 31.8, 29.7, 29.4, 29.3, 29.0, 25.6, 23.6, 22.6, 14.0. IR (neat): 3352, 2924, 1645, 1536 cm^{-1}. MS (FAB) [M + H] for $C_{23}H_{39}N_2O_2$; HRMS calcd. 375.3012, found 375.3005.

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Supporting Information Available: ^{1}H and ^{13}C data for compounds **1b**−**e**, **4b**, **5b**, **8b**, **9b**−**e**, and **10b**−**e** (29 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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