New Highly Efficient Stereoselective Synthesis of D-*threo*-PDMP

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Dedicated to Prof. Alberto Brandi on the occasion of his 60th birthday.

Abstract: Starting from a suitably functionalized aziridine, a highly efficient stereoselective synthesis of (1*R*,2*R*)-phenyl-2-decanoylamino-3-morpholinopropan-1-ol (D-*threo*-PDMP) is described. The approach, based on the ring expansion of the aziridine ring to oxazoline, could be applicable to the synthesis of many analogues with different amide chains and sugar mimic portions.

Key words: regioselectivity, ring opening, glycosidases, inhibitors, ring expansion

Glycosphingolipids (GSLs) play an important role in the regulation of numerous cellular processes; they affect membrane physical properties, cell-cell interactions, cell adhesion, cellular immune responses and differentiation,[1] and they have also been implicated in cancer cell metabolism.[2] The GSLs are formed by a glucosyltransferase-catalyzed transfer of glucose from UDP-glucose (UDP-Glc) to C-1 of ceramide, whereas glucocerebrosidase catalyzes the hydrolysis of GSLs to ceramide and glucose. Any alteration of this crucial equilibrium may cause serious pathologies; for example a deficiency of the latter enzyme is responsible for the Gaucher's disease, the most common of the lysosomal storage diseases, characterized by an accumulation of glucocere-brosides in the spleen, liver, kidneys, lungs, brain, and bone marrow.

There are currently two therapies available for the treatment of Gaucher's disease, which are both aimed at reducing GSLs storage.[3] The first-line treatment is based on the administration of recombinant form of glucocerebrosidase, to supplement the defective hydrolytic enzyme, whereas a second strategy uses inhibitors of glucosylceramide synthase, responsible for the glucosylation of ceramide.

In this context, different ceramide analogues have been developed and, among them, D-*threo*-PDMP [D-*threo*-(1*R*,2*R*)-phenyl-2-decanoylamino-3-morpholinopropan-1-ol] has shown to be a potent inhibitor of glucosylceramide synthase (Figure 1).[4] Surprisingly, the enantiomer L-*threo*-PDMP increased the biosynthesis of gangliosides, leading to enhanced synapse formation.[5] Because of the opposite bioactivity of the two, their enantiomerically pure synthesis is strongly required. Among the synthesis already reported,[6] generally L- or D-serine were used as source of chirality, except for an example regarding the regioselective elaboration of a nonactivated aziridine ring.[7]

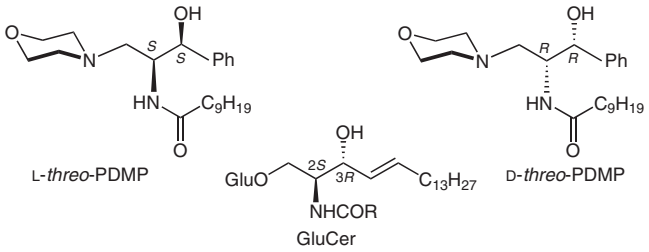

Figure 1 *threo*-PDMP enantiomers and glucosylceramide

This paper reports an expeditious synthesis of D-*threo* PDMP based on a straightforward ring expansion of a suitable phenyl-functionalized aziridine, consisting in the formation of a *syn*-vicinal amino alcohol starting from a *trans*-phenylaziridine. Over the last years, we have focused our attention on the use of the aziridine ring to prepare functionalized fragments through regio- and stereocontrolled ring-opening reactions;[8] in particular, very recently we were involved on the control of the $MgBr_2$-mediated opening of 2,3-three membered heterocyclic amines.[9] As delineated in Scheme 1, the nucleophilic attack of the bromine occurred preferentially at the C-3 position, as expected for chelation-controlled ring-opening reactions.

In the light of these results, the preparation of D-*threo*-PDMP was planned first starting from the suitable *N*-Boc-aziridine **1** (Scheme 2), having already the morpholine residue in the required position. The *syn* relationship of the amino alcohol fragment would be introduced following the above reported stereocontrolled opening of aziridine by halide and subsequent hydrolysis with silver nitrate in acetone.[10]

As shown in Scheme 3, the preparation of optically active aziridine amine **1** started from the Sharpless asymmetric epoxidation of the commercially available cinnamyl alcohol **2**. The morpholine residue was readily introduced via mesylate derivative **4**, affording the epoxyamine **5** with an overall yield of 83% from **3**. At this point, **5** was easily

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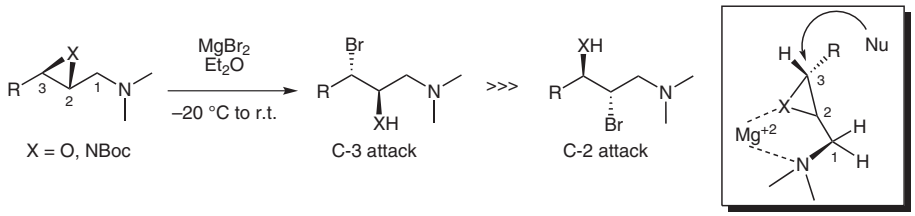
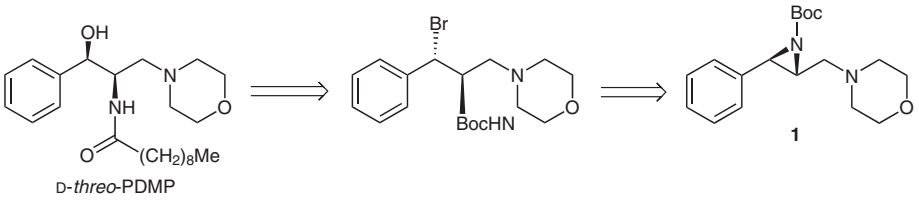
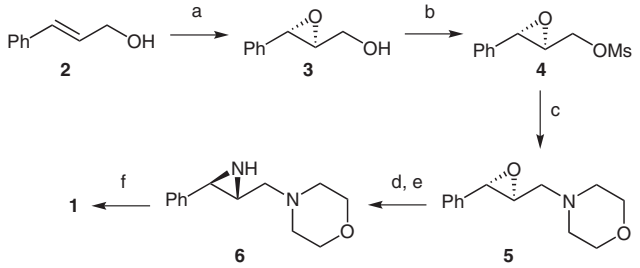


Scheme 1 Regio- and stereoselective ring opening 2,3-three membered heterocyclic amines by $MgBr_2$

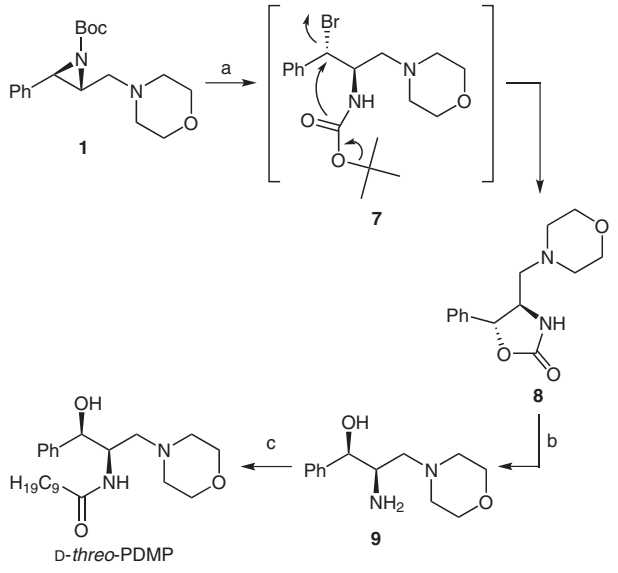


Scheme 2 Retrosynthesis of D-*threo*-PDMP

transformed in the corresponding aziridine amine **6** in the usual manner[11]and finally the reaction with di-*tert*-butyl dicarbonate gave **1** in satisfactory chemical yield.



Scheme 3 *Reagents and conditions*: a) L-(+) DIPT, Ti(O*i*-Pr)$_4$, TBHP, CH_2Cl_2, –20 °C, 75%; b) MsCl, Et_3N, DMAP, CH_2Cl_2, –20 °C; c) morpholine, pyridine, r.t., 6 h, 83% from **3**; d) NaN_3, NH_4Cl, MeOH, reflux; e) PPh_3, MeCN, reflux; f) Boc_2O, DMAP, CH_2Cl_2, r.t., 63% (overall yield from **5**).



Scheme 4 *Reagents and conditions*: a) $MgBr_2$, Et_2O, –40 °C, 78%; b) KOH, MeOH–H_2O (4:1), 70 °C, 66%; c) 4-$NO_2C_6H_4O(C{=}O)C_9H_{19}$, HOBt, pyridine, r.t., 88%.

The *N*-Boc-aziridine amine **1** was then treated with $MgBr_2$ in Et_2O at low temperature affording the expected 3-bromo derivative **7**. Unexpectedly, this compound underwent a slow spontaneous rearrangement (4–5 h) to the known oxazolidinone **8**, probably due to an intramolecular nucleophilic substitution of the bromine in benzylic position (Scheme 4).

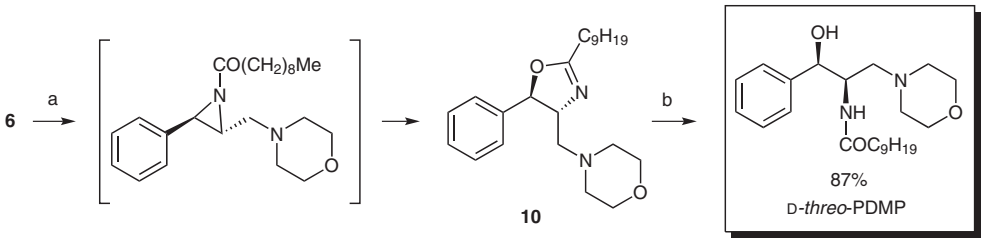
The oxazolidinone **8** was already described in the D-*threo*-PDMP synthesis by Polt;[6b] according to the authors, **8** was transformed to D-*threo*-PDMP in two steps.[6b]

Although the synthesis described above represented an efficient route to D-*threo*-PDMP, it was felt that an even more straightforward synthesis based on a regio- and stereocontrolled transformation of a suitable *trans N*-acylaziridine was possible. In fact, it is known that the aziridine nitrogen activation with an acyl group causes the ring expansion of the aziridine to the corresponding oxazoline,[12] which can be easily hydrolyzed to *syn*-hydroxyamino alcohol.

To this purpose, the aziridine **6** was treated with decanoyl chloride to give the *N*-decanoyl derivative, which spontaneously furnished the *trans*-oxazoline **10** in a regio- and stereocontrolled fashion. The *trans*-stereochemistry of the oxazoline **10** was unequivocally established on the basis of the $J_{4,5}$ value ($J_{4,5}$ = 6.6 Hz),[13] whereas the regiochemistry was confirmed by ^{1}H NMR spectroscopy by employing a spin-spin decoupling technique.

Finally, the hydrolysis of oxazoline **10** with Amberlyst 15 in the presence of a trace of water in acetone, complete in few hours, afforded nearly quantitatively the desired D-*threo*-PDMP (Scheme 5), as confirmed by the ^{1}H NMR, ^{13}C NMR, HR mass spectra, and specific rotation identical to those already obtained following the Scheme 4.

In conclusion, the efficient, but little used ring expansion of *N*-acylaziridines to the corresponding oxazolines was exploited to provide a highly stereo- and regioselective synthesis of D-*threo*-PDMP and has been developed starting from the cheap commercial cinnamyl alcohol in few steps (many of which did not need of any purification)[14]



Scheme 5 *Reagents and conditions*: a) $Me(CH_2)_8COCl$, Et_3N, CH_2Cl_2, –40 °C, 85%; b) Amberlyst 15, acetone, r.t., 90%.

with an overall yield of near to 35%. Moreover, this flexible synthetic route allows the preparation of different D-*threo*-PDMP analogues (or L-*threo*-PDMP analogues), by changing the length of the amide chain and the sugar mimic portion.

^1H and ^{13}C NMR spectra were recorded at 200 and 50.3 MHz, respectively. Reactions were monitored by TLC using Merck silica gel 60 F-254 plates with UV indicator; spots were also visualized with phosphomolybdic acid (10% solution in EtOH). Flash column chromatography on silica gel was normally used for purification of the reaction mixtures. ESI-MS analyses were performed using a commercial API 365 triple-quadrupole mass spectrometer from PerkinElmer Sciex Instruments, equipped with an ESI source and a syringe pump. The experiments were conducted in the positive ion mode. Optical rotations were recorded at the sodium D line with a polarimeter at r.t. All commercial reagents were purchased from Aldrich, Lancaster, Acros, or Carlo Erba unless otherwise noted. Petroleum ether (PE) used refers to the fraction boiling in the range of 40–60 °C.

(2′*S*,3′*S*)-4-(3′-Phenyloxiranylmethyl)morpholine (5)

To a solution of **3**[15] (235 mg, 1 mmol) in CH_2Cl_2 (1.6 mL) were added Et_3N (0.27 mL, 2 mmol) and a catalytic amount of DMAP. After stirring at 0 °C, $MeSO_2Cl$ (0.08 mL, 1 mmol) was added dropwise. After 2 h (TLC monitoring, eluent: PE–EtOAc, 8:2), the reaction was quenched with ice cold water (5 mL), and the mixture was extracted with CH_2Cl_2 (3 × 8 mL). The combined organic extracts were washed with ice cold aq 1 N HCl (10 mL), sat. aq $NaHCO_3$ (10 mL) and brine (10 mL), dried (Na_2SO_4), and then evaporated in vacuo. The crude mesylate **4** was then dissolved in pyridine (1 mL) and morpholine (2 mmol (0.20 mL) was added. The reaction mixture was stirred at r.t. overnight. The mixture was diluted with EtOAc (8 mL), washed with H_2O (6 mL) and brine (6 mL), dried (Na_2SO_4), and concentrated in vacuo. The crude mixture was purified by flash chromatography affording **5** (227.9 mg, 83% from **3**); $[\alpha]_D^{25}$ –40.7 (*c* 1.6, $CHCl_3$).

IR (neat): 3010, 2843, 1090 cm^{-1}.

^1H NMR (200 MHz, $CDCl_3$): δ = 7.40–7.14 (m, 5 H), 3.67 (t, *J* = 4.8 Hz, 4 H, CH_2O), 3.61 (d, *J* = 1.4 Hz, 1 H, PhC*H*O), 3.19–3.10 (m, 1 H, CHO), 2.74 (dd, *J* = 13.2, 3.6 Hz, 1 H, CH_AN), 2.66–2.42 (m, 5 H, CH_BN, 2 CH_2N).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 136.7, 128.1, 127.8, 125.2, 66.5, 60.3, 60.1, 56.3, 53.7.

HRMS: *m*/*z* calcd for $C_{13}H_{17}NO_2 + H^+$: 220.1338; found: 220.1340.

(2*R*,3*R*)-4-(1-*tert*-Butoxycarbonyl-3-phenylaziridine-2-ylmethyl)morpholine (1)

To a solution **5** (219.28 mg, 1 mmol) in MeOH (10 mL) were added NaN_3 (325 mg, 5 mmol) and NH_4Cl (106 mg, 2 mmol). The mixture was refluxed for 24 h, cooled to r.t. and concentrated in vacuo. The residue was diluted with EtOAc (15 mL), and the EtOAc layer was washed with H_2O (10 mL) and brine (10 mL). The organic layer was dried (Na_2SO_4) and concentrated to give the azido alcohol derivative as a mixture of regioisomers. The crude mixture was dissolved in MeCN (10 mL) and PPh_3 (314.13 mg, 1.2 mmol) was added. After 4 h at r.t., the mixture was refluxed for 6 h, and then concentrated in vacuo to give the crude aziridine amine **6**. To a solution of the crude aziridine amine **6**, (217 mg, 1 mmol) in anhyd CH_2Cl_2 (22 mL) at r.t. were added Boc_2O (248 mg, 1.1 mmol) and DMAP (cat.). The reaction mixture was stirred for 24 h. Upon completion of reaction (TLC monitoring, eluent: PE–EtOAc, 2:8), it was filtered through a Celite pad and the pad was washed with Et_2O (5 mL). The filtrate was washed with H_2O until neutral, and the organic layer was dried (Na_2SO_4) and concentrated in vacuo. The residue was then chromatographed on silica gel ($CHCl_3$–MeOH, 95:5) affording **1** (235 mg, 63% from **5**); $[\alpha]_D^{25}$ –10.7 (*c* 2.3, $CHCl_3$).

IR (neat): 3012, 2952,1620, 1220 cm^{-1}.

^1H NMR (200 MHz, $CDCl_3$): δ = 7.38–7.19 (m, 5 H), 3.72 (t, *J* = 4.4 Hz, 4 H, CH_2O), 3.26 (d, *J* = 2.9 Hz, 1 H, PhC*H*N), 2.95–2.81 (m, 2 H), 2.62–2.35 (m, 5 H), 1.30 (s, 9 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 159.5, 132.0, 128.2, 127.9, 126.9, 81.1, 66.7, 59.2, 53.6, 45.0, 42.4, 27.7.

HRMS: *m*/*z* calcd for $C_{18}H_{26}N_2O_3 + H^+$: 319.2022; found: 319.2025.

(1*S*,2*R*)-1-Phenyl-2-*tert*-butoxycarbonylamino-3-(*N*-morpholino)-1-bromopropane (7)

To a cold (–40 °C) stirred solution of **1** (400 mg, 1 mmol) in anhyd Et_2O (10 mL) was added $MgBr_2{\cdot}Et_2O$ (516.5 mg, 2 mmol). The mixture was stirred for 6 h (TLC monitoring, eluent: PE–EtOAc, 2:8) and then filtered through a pad of Celite. The filtrate was diluted with EtOAc (5 mL), washed with brine (5 mL), dried (Na_2SO_4), and then evaporated in vacuum. The crude mixture was analyzed spectroscopically without any purification.

^1H NMR (200 MHz, $CDCl_3$): δ = 7.35–7.18 (m, 5 H), 5.38 (br d, *J* = 4.4 Hz, 1 H, NH), 4.86 (d, *J* = 2.9 Hz, 1 H, CHBr), 4.31–4.11 (m, 1 H, CHN), 3.70 (t, *J* = 4.4 Hz, 4 H, CH_2O_{morph}), 2.66–2.26 (m, 6 H, CH_2N_{morph} + CH_2N).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 158.5, 137.4, 128.9, 128.5, 127.7, 80.41, 66.4, 60.2, 59.2, 53.8, 53.1, 28.1.

(4*R*,5*R*)-4-[(*N*-morpholino)methyl]-5-phenyloxazolidin-2-one (8)

Compound **7** was stirred for 6 h at r.t. in $CHCl_3$ (5 mL) and only **8** was isolated; $[\alpha]_D^{25}$ +32.0 (*c* 2.7, $CHCl_3$, lit.[6b] $[\alpha]_D^{20}$ +36.5).

IR (neat): 3430, 3016, 1751 cm^{-1}.

^1H NMR (200 MHz, $CDCl_3$): δ = 7.51–7.28 (m, 5 H), 5.96 (br s, 1 H, NH), 5.22 (d, *J* = 5.9 Hz, 1 H, CHO), 3.84 (dd, *J* = 5.9, 6.6 Hz, 1 H, C*H*NH), 3.67 (t, *J* = 4.4 Hz, 4 H, CH_2O_{morph}), 2.66–2.34 (m, 6 H, CH_2N_{morph} + CH_2N).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 158.8, 138.5, 128.8, 125.6, 81.5, 66.7, 62.5, 57.5, 53.9.

HRMS: *m*/*z* calcd for $C_{14}H_{19}N_2O_3$ + H^+: 263.1396; found: 263.1392.

(1*R*,2*R*)-2-Amino-3-(*N*-morpholino)-1-phenylpropan-1-ol (9)

To a stirred solution of **8** (263 mg, 1 mmol) in MeOH–H_2O (4:1, 8 mL) was added aq 2 M KOH (4 mL). The solution was heated to 70 °C for 16 h (TLC monitoring, eluent: PE–EtOAc, 1:9) and then concentrated in vacuo. The residue was dissolved in CH_2Cl_2 (10 mL), washed with sat. aq $NaHCO_3$ (7 mL), dried (Na_2SO_4), and evaporated in vacuum to give **9** (156 mg, 66%); $[\alpha]_D^{25}$ +5.8 (*c* 2.5, $CHCl_3$, lit.[6b] $[\alpha]_D^{20}$ +5.86).

IR (neat): 3430, 3016, 1640 cm^{-1}.

^1H NMR (200 MHz, $CDCl_3$): δ = 7.51–7.22 (m, 5 H, C_6H_5), 4.55 (d, *J* = 3.9 Hz, 1 H, C*H*OH), 3.69 (t, *J* = 4.4 Hz, CH_2O_{morph}), 3.23 (ddd, *J* = 8.8, 5.1 Hz, 1 H, C*H*NH_2), 2.77 (br d, 3 H, OH + NH_2), 2.56 (dd, *J* = 11.3, 4.3 Hz, 1 H, CH_A), 2.32 (dd, *J* = 12.5, 5.3 Hz, 1 H, CH_B), 2.48–2.39 (m, 4 H, CH_2N_{morph}).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 142.6, 128.2, 127.2, 126.0, 75.1, 66.9, 62.0, 54.0, 52.8.

HRMS: *m*/*z* calcd for $C_{13}H_{21}N_2O_2$ + H^+: 237.1603; found: 237.1602.

(1*R*,2*R*)-1-Phenyl-2-decanoylamino-3-(*N*-morpholino)propan-1-ol (D-*threo*-PDMP)

Compound **9** (236 mg, 1 mmol) was dissolved in pyridine (1 mL, dried over molecular sieves) and was sequentially treated with 4-nitrophenyl decanoate (293.6 mg, 1 mmol) and 1-hydroxybenzotriazole (10 mol%, 15.3 mg, 0.01 mmol). Upon completion of the reaction as judged by TLC (eluent: $CHCl_3$–MeOH, 9:1), the solvent was removed, and the residue was dissolved in CH_2Cl_2 (20 mL) and washed with aq 1 M NaOH (5 × 20 mL). The crude product obtained after evaporation of CH_2Cl_2 was chromatographed to give D-*threo*-PDMP (344 mg, 88%); $[\alpha]_D^{20}$ +7.7 (*c* 1.12, $CHCl_3$, lit.[7] $[\alpha]_D^{20}$ +8.05).

IR (neat): 3430, 3016, 2936, 1650, 1510 cm^{-1}.

^1H NMR (200 MHz, $CDCl_3$): δ = 7.38–7.22, (m, 5 H), 5.96 (br d, *J* = 7.3 Hz, 1 H, NH), 4.96 (d, *J* = 3.7 Hz, 1 H, C*H*OH), 4.35–4.18 (m, 1 H, C*H*NH), 3.73 (t, *J* = 4.4 Hz, 4 H, CH_2O_{morph}), 3.68 (m, 4 H), 2.65–2.37 (m, 6 H), 2.13–2.00 (m, 2 H), 1.57–1.37 (m, 12 H), 0.89 (t, *J* = 5.9 Hz, 3 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 173.7, 140.8, 128.3, 127.6, 126.0, 75.1, 66.7, 59.6, 54.2, 51.1, 36.6, 31.7, 29.3, 29.1, 29.0, 25.5, 22.6, 14.0.

HRMS: *m*/*z* calcd for $C_{23}H_{38}N_2O_3$ + H^+: 391.2958; found: 391.2961.

(4*R*,5*R*)-4-(2-Nonyl-5-phenyl-4,5-dihydrooxazol-4-ylmethyl)morpholine (10)

To a solution of crude aziridine amine **6** (217 mg, 1 mmol) in CH_2Cl_2 (5 mL) at –40 °C were added Et_3N (0.17 mL, 1.2 mmol) and decanoyl chloride (0.25 mL, 1.2 mmol). The reaction mixture was stirred for 24 h. Upon completion of reaction (TLC monitoring, eluent: PE–EtOAc, 3:7), it was filtered through a Celite pad and the pad was washed with Et_2O (10 mL). The filtrate was washed with H_2O until neutral, and the organic layer was dried (Na_2SO_4), and concentrated in vacuo. The residue was purified by flash chromatography (PE–Et_2O, 6:4) affording **10** (317 mg, 85%); $[\alpha]_D^{25}$ +5.8 (*c* 2, $CHCl_3$).

IR (neat): 3010, 1661, 1310 cm^{-1}.

^1H NMR (200 MHz, $CDCl_3$): δ = 7.39–7.15 (m, 5 H), 5.18 (d, *J* = 6.6 Hz, 1 H, PhC*H*NCO), 4.10–3.93 (m, 1 H, CHNCO), 3.64 (t, *J* = 4.8 Hz, 4 H, CH_2O_{morph}), 2.66 (dd, *J* = 12.4, 5.1 Hz, 1 H, CH_AN), 2.45–2.34 (m, 6 H, CH_2N + CH_2), 2.34 (dd, *J* = 2.4, 8.0 Hz, 1 H, CH_BN), 1.74–1.56 (m, 2 $H_{decanoyl}$), 1.40–1.05 (m, 12 $H_{decanoyl}$), 0.82 (t, *J* = 5.9 Hz, 3 H, CH_3).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 167.8, 141.1, 128.5, 127.8, 125.4, 84.9, 72.6, 66.7, 63.4, 54.0, 31.7, 29.3, 29.1, 28.2, 26.0, 22.5, 13.9.

HRMS: *m*/*z* calcd for $C_{23}H_{36}N_2O_2$ + H^+: 373.2856; found: 373.2855.

(1*R*,2*R*)-1-Phenyl-2-decanoylamino-3-(*N*-morpholino)propan-1-ol (D-*threo*-PDMP)

To a stirred solution of **10** (373 mg, 1 mmol) in acetone (10 mL) was added Amberlyst 15 (217 mg, 1 mmol). The mixture was stirred for 6 h (TLC monitoring, eluent: $CHCl_3$–MeOH, 9:1), filtered, and diluted with EtOAc (15 mL). The organic layer was washed with brine (10 mL), dried (Na_2SO_4), and concentrated in vacuo. The crude mixture was purified by flash chromatography (EtOAc–PE, 8:2) affording D-*threo*-PDMP as a light brown oil (340 mg, 87%); $[\alpha]_D^{20}$ +7.7 (*c* 1.12, $CHCl_3$, lit.[6b,7] $[\alpha]_D^{20}$ +8.05).

The analytical data were identical with those reported above for the D-*threo*-PDMP prepared from **9**.

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