Supporting Information

Lipase-catalyzed synthesis of chiral poly(ester amide)s with alternating sequence of hydroxy acid and L/D-aspartate units

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1. Synthesis of N-(6-hydroxyhexanoyl) aspartate diesters.

The methods to obtain 2, 3, 4 and 5 were adapted from the literature with some modifications.1-3

(1) Synthesis of 6-(tert-Butyldimethyl)siloxyhexanoic acid 2:

\[
\text{HO-} \quad \text{C} \quad \text{OH} \quad \xrightarrow{\text{TBDMSI}} \quad \text{TBDMS-} \quad \text{O-} \quad \text{C} \quad \text{OH}
\]

tert-Butyldimethylsilylchloride (0.11 mol) was added to a mixture of 1 (0.1 mol) and imidazole (0.2 mol) in DMF (90 mL). The reaction mixture was stirred overnight at 50 °C under nitrogen atmosphere and poured into a separatory funnel containing 200 mL of brine and extracted 4 times with 200 mL of diethyl ether. The organic fractions were combined, dried over MgSO₄, filtered and concentrated under reduced pressure to give the crude product which was further purified via flash chromatography eluting with 1:1 hexanes:ethyl acetate to give 2 as a clear colorless oil (80% yield); ¹H NMR (400 MHz, CDCl₃): δ 3.53-3.56 (t, CH₂OSi, 2H), 2.14-2.17 (t, CH₂COOH, 2H), 1.27-1.50 (m, SiOCH₂[CH₃]₃CH₂COOH, 6H), 0.82 (s, (CH₃)₃CSi, 9H), 0.01 (s, (CH₃)₂Si, 6H).

(2) Synthesis of 4:

\[
\text{TBDMS-} \quad \text{O-} \quad \text{C} \quad \text{OH} \quad \xrightarrow{\text{DCC, HOBT}} \quad \text{TBDMS-} \quad \text{O-} \quad \text{C} \quad \text{NH} \quad \text{O} \quad \text{O} \quad \text{R}^1 \quad \text{O} \quad \text{R}^2
\]

Under the ice bath condition, a solution of 3 (10 mmol) in 10 mL CH₂Cl₂ was added dropwise to a mixture of 2 (10 mmol), 1,3-Dicyclohexylcarbodiimide (DCC, 11 mmol) and 1-Hydroxybenzotriazole (HOBT, 12 mmol) in 30 mL CH₂Cl₂. The reaction mixture was then stirred overnight at 0 °C, concentrated under reduced pressure and 200 mL diethyl ether added followed by filtration. The filtrate was poured into a separatory funnel and washed with 200 mL of sat. NaHCO₃, 5 wt% citric acid and brine. After dried over MgSO₄ and filtered, the filtrate was concentrated under reduced pressure to get the crude product. The crude product was then purified via flash chromatography using 1:1 hexanes:ethyl acetate as eluent to give 4 as a clear colorless oil (70% yield); ¹H NMR (400 MHz, CDCl₃): 7.22-7.28 (m, PhCH₂O, 5H), 6.58-6.60 (d, CONH, 1H), 5.05-5.13 (q, J=12 Hz, PhCH₂O, 2H), 4.81-4.93 (m, NH(CH)COOR, 1H), 3.51-3.54 (m, COOCH₃ and SiOCH₂, 5H), 2.92-2.97 (dd, J=4.4, 17.2 Hz, CHCH₂COOCH₃, 1H),
2.73-2.78 (dd, J=4.4, 17.2 Hz, CHCH$_2$COOCH$_3$, 1H), 2.14-2.17 (t, J=7.6 Hz, CH$_2$COONH, 2H), 1.45-1.27 (m, SiOCH$_2$(CH$_2$)$_2$CH$_2$CONH, 6H), 0.82 (s, (CH$_3$)$_3$CSi, 9H), 0.00 (s, (CH$_3$)$_2$Si, 6H).

4b–4d were synthesized through the similar method as 4a, starting from different Asp derivatives.

(3) Synthesis of 5:

A mixture of glacial acetic acid (20 mmol) and tetrabutylammonium fluoride (TBAF) (20 mmol, 1.0 M solution in THF) was added to a solution of 4a (10 mmol) in 20 mL THF. The reaction mixture was stirred overnight at 50 °C and then poured into a separatory funnel containing 200 mL of CH$_2$Cl$_2$ and 200 mL of H$_2$O. The organic layer was then washed with sat. NaHCO$_3$, 5 wt% citric acid and H$_2$O, dried over MgSO$_4$, filtered and concentrated under reduced pressure. The crude product was purified via flash chromatography using 1:1 hexanes:ethyl acetate as eluent to give 5a as a transparent waxy solid (90% yield).

5b–5d were synthesized through the similar method as 5a, only with the different Asp derivatives 4b–4d as starting materials.
2. Copies of $^1$H NMR, $^{13}$C NMR and HR-MS of 5a-5d.

![Figure S1](image_url)

**Fig. S1** $^1$H NMR (a), $^{13}$C NMR (b) and HR-MS (c) of $N$-(6-hydroxyhexanoyl)-L/D-$\alpha$-benzyl-$\beta$-methyl-aspartate 5a/b
Fig. S2  $^1$H NMR (a), $^{13}$C NMR (b) and HR-MS (c) of N-(6-hydroxyhexanoyl)-L/D-$\alpha$-methyl-$\beta$-benzyl-aspartate 5c/d
3. Copies of $^1$H NMR, $^{13}$C NMR and FTIR of PA-PD.

(a)

(b)
Fig. S3  $^1$H NMR (a), $^{13}$C NMR (b) and FTIR (c) spectra of PA.
Fig. S4 $^1$H NMR (a), $^{13}$C NMR (b) and FTIR (c) spectra of PB
Fig. S5  $^1$H NMR (a), $^{13}$C NMR (b) and FTIR (c) spectra of PC.
Fig. S6  $^1$H NMR (a), $^{13}$C NMR (b) and FTIR (c) spectra of PD.
4. Copies of 2D-NMR of PA.

![2D-NMR diagram of PA](image)
Fig. S7  2D-NMR of PA in CDCl$_3$: $^1$H, $^1$H-COSY spectrum (a), $^{13}$C, $^1$H-HSQC spectrum (b) and $^{13}$C, $^1$H-HMBC spectrum (c).
5. Copies of SEC of PA-PD

Fig. S8  SEC of PA in DMF.

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Fig. S9  SEC of PB in THF.

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Fig. S10  SEC of PC in THF.

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Fig. S11  SEC of PD in THF.

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6. DSC curves of PB-PD

**Fig. S12** DSC curves of PB.

**Fig. S13** DSC curves of PC.
DSC curves of PD

$T_g$: -14.90 °C

Fig. S14  DSC curves of PD.

References