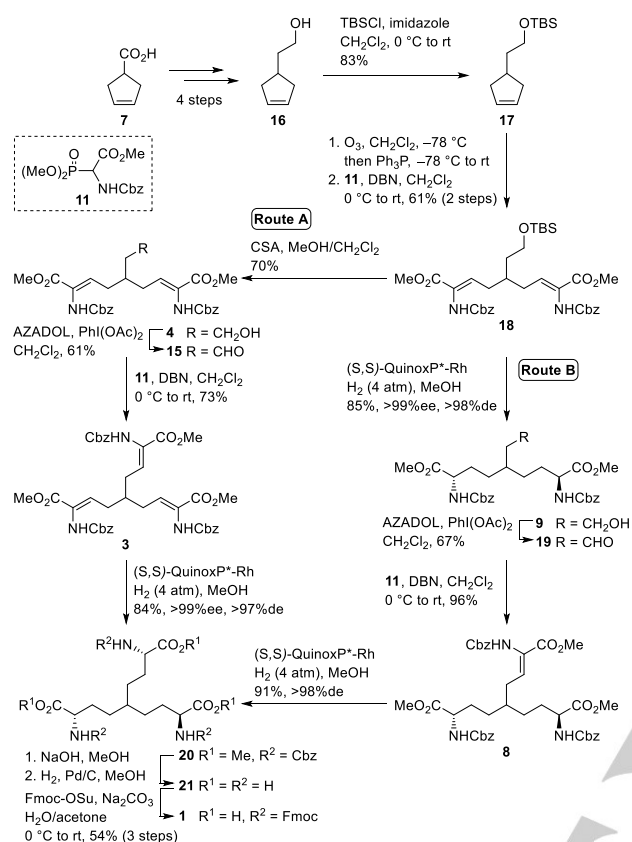


FULL PAPER

catalyst gave protected *t*ButA **20** in 84% yield. The enantiomeric excess and diastereomeric ratio of **20** were >99%ee and >97%de, respectively.



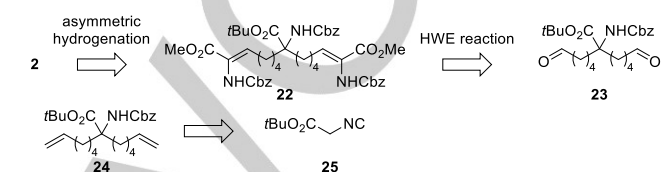
We also investigated stepwise route B. The two alkene functionalities of **18** were hydrogenated asymmetrically under the same conditions as route A using a (S,S)-QuinoxP*-Rh catalyst to produce protected bis- α -amino acid **9** in 85% yield (>99%ee and >98%de). The TBS group of **18** was removed during hydrogenation, which may be because methanol, which served as the solvent, also acted as a nucleophile. After AZADO oxidation of the primary alcohol of **9**, the HWE reaction of **19** gave compound **8** in 64% overall yield. Asymmetric hydrogenation of **8** using (S,S)-QuinoxP*-Rh catalyst gave protected *t*ButA **20** in 91% yield (>98%de).

With protected *t*ButA (**20**) in hand, the protecting group manipulation was performed to access Fmoc-protected *t*ButA (**1**), which can be used in solid-phase peptide synthesis. Hydrolysis of **20** under basic conditions and subsequent removal of the benzyloxycarbonyl (Cbz) groups, gave *t*ButA **21**. Although the hydrophilic property of the three free amino acid moieties prevented extraction of **21** from water, the ¹H and ¹³C NMR spectra (D₂O) confirmed its structure. Fmoc groups were introduced to the primary amino groups of **21** to produce **1** in 54% yield from **20**. Since both ¹H and ¹³C NMR analyses showed that the corresponding signals of each homoalanine (-

CH₂CH₂CHNHR²(CO₂R¹)) moiety of **20** and **21** were equivalent, the C₃-symmetric structure of the product was confirmed.

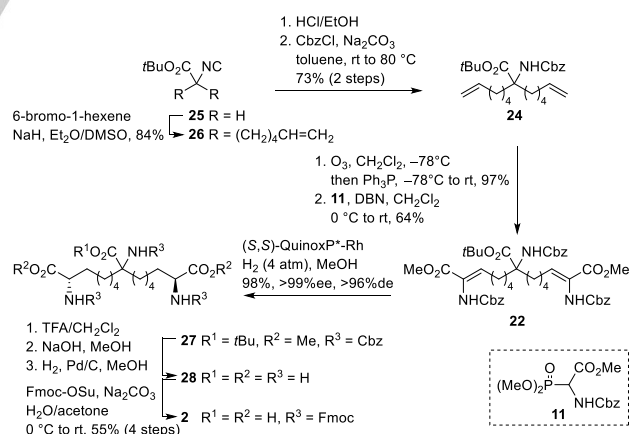
Synthesis of Fmoc-(S,S)- α,α -di-L-homonorleucyl-L-glycine (Fmoc-di-hNor-Gly, **2**)

We then focused on the synthesis of Fmoc-di-hNor-Gly (**2**), which is a linear tris- α -amino acid for trimer peptide models. Scheme 4 depicts our envisioned retrosynthesis. The terminal amino acid moieties of Fmoc-di-hNor-Gly (**2**) would be introduced via the HWE reaction of dialdehyde **23** and subsequent asymmetric hydrogenation of **22**. Compound **23** would be derived from bisolefin **24**, which would be prepared from isocyanide **25**.



Scheme 4. Retrosynthetic analysis of Fmoc-(S,S)- α,α -di-L-homonorleucyl-L-glycine (**2**).

Compound **25** was dialkylated by following Schöllkopf and Hoppe's procedure^[19] to give isocyanide **26** in 84% yield (Scheme 5). Hydrolysis of the isocyanide group of **26** and subsequent treatment of CbzCl and Na₂CO₃ in toluene at 80 °C produced Cbz-protected amino acid **24** in 73% yield. The terminal olefins of **24** were cleaved by ozonolysis and then treated with triphenylphosphine. The resultant dialdehyde was immediately converted to compound **22** by the HWE reaction. Asymmetric hydrogenation of **22** using the (S,S)-QuinoxP*-Rh catalyst gave protected di-hNor-Gly (**27**) in 98% yield. The enantiomeric excess and diastereomeric ratio of **27** were >99%ee and >96%de, respectively.



Scheme 5. Synthesis of Fmoc-(S,S)- α,α -di-L-homonorleucyl-L-glycine (**2**). DMSO = dimethyl sulfoxide, TFA = trifluoroacetic acid.

Acidic hydrolysis of the *tert*-butyl ester, alkaline hydrolysis of the methyl ester, and subsequent hydrogenolysis of the Cbz groups gave di-hNor-Gly (**28**). Finally, the Fmoc groups were

FULL PAPER

introduced to the primary amino groups of **28** to produce **2** in 55% yield from **27**. Although the tetrasubstituted carbons of **27**, **28**, and **2** have the same two side chains, these compounds are chiral because the side chains contain a chiral center (namely, pseudo σ -symmetry). Hence, the two chains are not equivalent. As expected, the signals derived from each carbon in ^{13}C NMR spectra were observed independently.

Conclusion

Here, we established an enantioselective synthetic route toward two new C_3 -symmetric and linear tris- α -amino acids containing alkyl spacers, (*S,S,S*)-*t*-ButA (**21**) and (*S,S*)-di-*h*Nor-Gly (**28**). Both compounds were converted into the corresponding Fmoc-protected amino acids. These synthetic routes should allow the syntheses of various derivatives with modified protecting groups and configurations. They should realize powerful tools to synthesize various cross-linked trimer models of pathogenic aggregative peptides using a solid-phase Fmoc strategy, as exemplified in the synthesis of the trimer models of A β 40.^[12] Currently we are trying to synthesize these trimer models, including C_3 -symmetric and β -sheet peptides. These results, which consider the structure–activity relationships, will be reported in due course.

Experimental Section

General: All non-aqueous reactions, except hydrogenation reactions, were carried out under a nitrogen or argon atmosphere in dried glassware. Analytical thin-layer chromatography was performed with TLC Silica gel 60 F254 (Merck, Darmstadt, Germany). Silica gel column chromatography was performed with Wakogel C-200 (Wako Pure Chemical Industries, Osaka, Japan) or Chromatorex BW-300 (Fuji Silica Chemical, Aichi, Japan). Flash column chromatography was performed with a Model 800E with a Model prep UV-10V UV detector (Yamazen, Osaka, Japan), and YMC*GEL ODS-A (YMC, Kyoto, Japan) was used as the carrier. HPLC was performed with Model 600E with a Model 2487 UV detector (Waters, Milford, MA, USA). Proton nuclear magnetic resonance (^1H NMR) spectra were recorded on an AVANCE III 400 (Bruker, Germany) at 400 MHz or an AVANCE III 500 (Bruker, Germany) at 500 MHz. Chemical shifts were reported relative to Me_4Si (δ 0.0) in CDCl_3 , and residual solvent of CD_3OD (δ 3.31) and D_2O (δ 4.79). Multiplicity is indicated by one or more of the following: s (singlet); d (doublet); t (triplet); q (quartet); m (multiplet); br (broad). Carbon nuclear magnetic resonance (^{13}C NMR) spectra were recorded on an AVANCE III 400 (Bruker, Germany) at 101 MHz or an AVANCE III 500 (Bruker, Germany) at 126 MHz. Chemical shifts were reported relative to CDCl_3 (δ 77.0) and CD_3OD (δ 49.0). Infrared spectra were recorded on a FT/IR-470 Plus Fourier-transform infrared spectrometer (Jasco, Tokyo, Japan). Specific rotations were recorded on a P-2200 digital polarimeter (Jasco, Tokyo, Japan). Low- and high-resolution mass spectra were recorded on a JMS700 mass spectrometer (JEOL, Tokyo, Japan) for FAB-MS (matrix, *m*-nitrobenzyl-alcohol) or timsTOF (Bruker, Germany) for ESI-MS and APCI-MS.

Compound 12: A solution of **10** (605 mg, 2.85 mmol) in CH_2Cl_2 (30 mL) was cooled to -78°C . The solution was bubbled with O_3 until it turned blue. Excess O_3 was removed from the reaction mixture by purging with O_2 . To the mixture was added Me_2S (3 mL) at -78°C , and the reaction mixture was stirred for 25 minutes. Then the reaction mixture was washed with water, and the aqueous layer was extracted with CH_2Cl_2 . The organic layers were washed with brine. The combined organic layers were dried over Na_2SO_4 . Filtration and concentration afforded a crude dialdehyde. To a solution of (Z)- α -phosphonoglycine trimethyl ester (1.98 g, 5.99 mmol) in CH_2Cl_2 (10 mL) was added DBN (0.750 g, 6.04 mmol). The mixture was

stirred at 0°C for 15 minutes. The dialdehyde in CH_2Cl_2 (5 mL) was added slowly at 0°C . The reaction mixture was gradually warmed to room temperature while stirring overnight. The reaction mixture was washed with 1 M aqueous HCl solution. The aqueous layer was further extracted with ethyl acetate. The combined organic layers were washed with brine, dried over Na_2SO_4 , filtered, and concentrated. The crude product was purified by silica gel column chromatography (hexane/ethyl acetate = 1/0 to 3/7) to afford **12** (577 mg, 31% for 2 steps) as colorless oil. R_f = 0.62 (hexane/ethyl acetate = 1/1); ^1H NMR (400 MHz, CDCl_3): δ 7.36–7.28 (m, 10H), 6.55 (t, J = 7.6 Hz, 2H), 6.50 (br s, 2H), 5.12 (s, 4H), 3.74 (s, 6H), 3.48 (d, J = 5.4 Hz, 2H), 2.31–2.18 (m, 4H), 1.95–1.85 (m, 1H), 0.86 (s, 9H), 0.03 ppm (s, 6H); ^{13}C NMR (101 MHz, CDCl_3): δ 164.8 (2C), 154.1 (2C), 136.0 (2C), 134.2 (2C), 128.5 (4C), 128.24 (2C), 128.21 (4C), 127.0 (2C), 67.4 (2C), 65.2, 52.4 (2C), 40.0, 29.8 (2C), 25.9 (3C), 18.3, -5.4 ppm (2C); IR (neat on KBr plate): $\bar{\nu}$ 3316, 3033, 2952, 2856, 1725, 1659, 1500, 1226, 1049, 837, 777, 698 cm^{-1} ; HRMS (FAB): m/z calcd for $\text{C}_{34}\text{H}_{47}\text{N}_2\text{O}_9\text{Si}$: 655.3051 [$\text{M}+\text{H}$] $^+$; found: 655.3054.

Compound 13: To a solution of **12** (44.7 mg, 68.3 μmol) in $\text{MeOH}/\text{CH}_2\text{Cl}_2$ (1.5 mL/1.5 mL) was added (\pm)-10-camphorsulfonic Acid (CSA, 3.2 mg, 13.8 μmol) at room temperature. The reaction mixture was stirred overnight at room temperature and then was added triethylamine (9.10 mL). The mixture was evaporated and purified by silica gel column chromatography (hexane/ethyl acetate, 1/1 to 1/4) to afford **13** (31.4 g, 85%) as colorless oil. R_f = 0.30 (hexane/ethyl acetate = 3/7); ^1H NMR (400 MHz, CDCl_3): δ 7.38–7.29 (m, 10H), 6.71 (br s, 2H), 6.56 (t, J = 7.4 Hz, 2H), 5.14 (s, 4H), 3.74 (s, 6H), 3.50–3.48 (m, 2H), 3.05 (br s, 1H), 2.42–2.34 (m, 2H), 2.22–2.15 (m, 2H), 1.94–1.85 ppm (m, 1H); ^{13}C NMR (101 MHz, CDCl_3): δ 164.9 (2C), 154.4 (2C), 135.9 (2C), 134.7 (2C), 128.5 (4C), 128.3 (2C), 128.2 (4C), 127.0 (2C), 67.5 (2C), 63.3, 52.4 (2C), 39.8, 30.1 ppm (2C); IR (neat on KBr plate): $\bar{\nu}$ 3307, 3032, 2952, 1717, 1655, 1508, 1238, 1054, 753, 698 cm^{-1} ; HRMS (FAB): m/z calcd for $\text{C}_{28}\text{H}_{33}\text{N}_2\text{O}_9$: 541.2186 [$\text{M}+\text{H}$] $^+$; found: 541.2191.

Compound 17: A solution of **16** (722 mg, 6.43 mmol) in dry CH_2Cl_2 (20 mL) was cooled to 0°C under a nitrogen atmosphere. To this solution were added TBSCl (1.13 g, 7.51 mmol) and imidazole (861 mg, 12.6 mmol). The reaction mixture was warmed to room temperature and stirred overnight. Water (10 mL) was then added, and the two layers were separated. The aqueous layer was further extracted with CH_2Cl_2 3 times, and the organic layers were washed with brine. The combined organic layers were dried over Na_2SO_4 , filtered and concentrated. The crude product was purified by silica gel column chromatography (hexane/ethyl acetate = 1/0 to 9/1) to afford **17** (1.21 g, 83%) as colorless oil. R_f = 0.21 (hexane/ethyl acetate = 1/0); ^1H NMR (500 MHz, CDCl_3): δ 5.69–5.64 (m, 2H), 3.63 (t, J = 6.7 Hz, 2H), 2.52–2.44 (m, 2H), 2.37–2.28 (m, 1H), 2.02–1.95 (m, 2H), 1.64 (dd, J = 13.9, 6.9 Hz, 2H), 0.90 (s, 9H), 0.05 ppm (s, 6H); ^{13}C NMR (126 MHz, CDCl_3): δ 129.9 (2C), 62.3, 39.6, 38.9 (2C), 34.2, 26.0 (3C), 18.3, -5.3 ppm (2C); IR (neat on KBr plate): $\bar{\nu}$ 3055, 2928, 2857, 1472, 1255, 1102, 835, 775 cm^{-1} ; HRMS (APCI): m/z calcd for $\text{C}_{13}\text{H}_{27}\text{OSi}$: 227.1826 [$\text{M}+\text{H}$] $^+$; found: 227.1824.

Compound 18: A solution of **17** (688 mg, 3.04 mmol) in CH_2Cl_2 (30 mL) was cooled to -78°C . The solution was bubbled with O_3 until the color of it turned blue (6 minutes). Excess O_3 was removed from the reaction mixture by purging with O_2 for 3 minutes. To the mixture was added Ph_3P (4.08 g, 15.6 mmol) at -78°C , and the reaction mixture was stirred at -78°C for 10 minutes and warmed to room temperature with stirring for an additional 20 minutes. Then the reaction mixture was washed with water, and the aqueous layer was extracted with ethyl acetate twice. The organic layers were washed with brine. The combined organic layers were dried over Na_2SO_4 , filtered and concentrated. The crude product was purified by silica gel column chromatography (hexane/ethyl acetate = 1/0 to 3/7) to afford the dialdehyde as colorless oil. To a solution of (Z)- α -phosphonoglycine trimethyl ester (2.18 g, 6.59 mmol) in dry CH_2Cl_2 (20 mL) was added DBN (0.800 g, 6.44 mmol) under a nitrogen atmosphere. The mixture was stirred at 0°C and allowed to gradually warm to room temperature with stirring for 2.5 h. The dialdehyde in dry CH_2Cl_2 (4 mL) was added slowly by cannula at 0°C . The reaction mixture was gradually warmed to room temperature while stirring overnight. The reaction mixture was washed with 1 M aqueous HCl solution. The aqueous layer was further extracted with ethyl acetate twice. The organic layers were washed

FULL PAPER

with water, saturated aqueous NaHCO_3 solution, and brine. The combined organic layers were dried over Na_2SO_4 , filtered and concentrated. The crude product was purified by silica gel column chromatography (hexane/ethyl acetate = 1/0 to 1/1) to afford **18** (1.25 g, 61% for 2 steps) as colorless oil. R_f = 0.26 (hexane/ethyl acetate = 7/3); ^1H NMR (500 MHz, CDCl_3): δ 7.38–7.30 (m, 10H), 6.63 (t, J = 7.3 Hz, 2H), 6.32 (br s, 2H), 5.14 (s, 4H), 3.74 (s, 6H), 3.64 (t, J = 6.3 Hz, 2H), 2.29–2.18 (m, 4H), 2.01–1.94 (m, 1H), 1.55–1.51 (m, 2H), 0.89 (s, 9H), 0.04 ppm (s, 6H); ^{13}C NMR (126 MHz, CDCl_3): δ 164.8 (2C), 154.1 (2C), 136.0 (2C), 135.9 (2C), 128.5 (4C), 128.2 (2C), 128.1 (4C), 126.5 (2C), 67.4 (2C), 60.7, 52.3 (2C), 37.0, 34.2, 32.8 (2C), 25.9 (3C), 18.3, –5.4 ppm (2C); IR (neat on KBr plate): $\bar{\nu}$ 3321, 3033, 2952, 2856, 1726, 1658, 1502, 1256, 1051, 837, 776, 698 cm^{-1} ; HRMS (FAB): m/z calcd for $\text{C}_{35}\text{H}_{49}\text{N}_2\text{O}_9\text{Si}$: 669.3207 $[\text{M}+\text{H}]^+$; found: 669.3217.

Compound 4: To a solution of **18** (51.8 mg, 77.4 μmol) in $\text{MeOH}/\text{CH}_2\text{Cl}_2$ (0.5 mL/0.5 mL) was added CSA (2.0 mg, 8.6 μmol) at room temperature. The reaction mixture was stirred at room temperature for 70 minutes and then was added triethylamine (1.50 mL). The mixture was evaporated and purified by silica gel column chromatography (hexane/ethyl acetate = 1/0 to 3/7) to afford **4** (29.7 g, 70%) as colorless oil. R_f = 0.25 (hexane/ethyl acetate = 3/7); ^1H NMR (400 MHz, CDCl_3): δ 7.38–7.28 (m, 10H), 6.61 (t, J = 7.4 Hz, 2H), 6.54 (s, 2H), 5.13 (s, 4H), 3.73 (s, 6H), 3.64–3.61 (m, 2H), 2.32–2.16 (m, 4H), 2.05 (br s, 1H), 2.00–1.94 (m, 1H), 1.55–1.51 ppm (m, 2H); ^{13}C NMR (101 MHz, CDCl_3): δ 164.9 (2C), 154.3 (2C), 135.9 (2C), 135.4 (2C), 128.5 (4C), 128.2 (2C), 128.1 (4C), 126.6 (2C), 67.4 (2C), 60.2, 52.4 (2C), 36.3, 34.3, 32.6 ppm (2C); IR (neat on KBr plate): $\bar{\nu}$ 3310, 3033, 2952, 1714, 1658, 1505, 1240, 1053, 754, 699 cm^{-1} ; HRMS (ESI): m/z calcd for $\text{C}_{29}\text{H}_{33}\text{N}_2\text{O}_9$: 553.2192 $[\text{M}-\text{H}]^-$; found: 553.2191.

Compound 15: To a solution of **4** (63.8 mg, 115 μmol) in CH_2Cl_2 (5 mL) were added $\text{PhI}(\text{OAc})_2$ (52.9 mg, 184 μmol) and AZADOL (2.6 mg, 17 μmol). The mixture was stirred overnight at room temperature. The reaction mixture was diluted with ethyl acetate, washed with water, extracted with ethyl acetate (3 times), and washed with brine. The combined organic layers were dried over Na_2SO_4 , filtered and concentrated. The crude product was purified by silica gel column chromatography (hexane/ethyl acetate = 1/0 to 1/1) to afford **15** (38.7 mg, 61%) as colorless oil. R_f = 0.30 (hexane/ethyl acetate = 2/3); ^1H NMR (400 MHz, CDCl_3): δ 9.69 (s, 1H), 7.37–7.28 (m, 10H), 6.56 (t, J = 7.4 Hz, 2H), 6.43 (br s, 2H), 5.13 (s, 4H), 3.74 (s, 6H), 2.45–2.34 (m, 3H), 2.27–2.24 ppm (m, 4H); ^{13}C NMR (101 MHz, CDCl_3): δ 201.4, 164.6 (2C), 154.1 (2C), 135.8 (2C), 134.1 (2C), 128.5 (4C), 128.3 (2C), 128.1 (4C), 127.0 (2C), 67.4 (2C), 52.5 (2C), 47.9, 32.7 (2C), 32.1 ppm; IR (neat on KBr plate): $\bar{\nu}$ 3312, 3033, 2952, 2732, 1721, 1659, 1500, 1233, 1049, 754, 699 cm^{-1} ; HRMS (ESI): m/z calcd for $\text{C}_{29}\text{H}_{32}\text{N}_2\text{O}_9\text{Na}$: 575.2000 $[\text{M}+\text{Na}]^+$; found: 575.1990.

Compound 3: To a solution of (Z)- α -phosphonoglycine trimethyl ester (25.5 mg, 77.0 μmol) in dry CH_2Cl_2 (1 mL) was added DBN (10.6 mg, 85.4 μmol) under an argon atmosphere. The mixture was stirred at 0 $^\circ\text{C}$ for 15 minutes. A solution of **15** (33.8 mg, 61.2 μmol) in dry CH_2Cl_2 (4 mL) was then added slowly by cannula at 0 $^\circ\text{C}$. The reaction mixture was gradually warmed to room temperature with stirring overnight. The reaction mixture was washed with 1 M aqueous HCl solution. The aqueous layer was further extracted with ethyl acetate twice. The organic layers were washed with brine. The combined organic layers were dried over Na_2SO_4 , filtered and concentrated. The crude product was purified by silica gel column chromatography (hexane/ethyl acetate = 1/0 to 1/1) to afford **3** (33.7 mg, 73%) as colorless oil. R_f = 0.34 (hexane/ethyl acetate = 2/3); ^1H NMR (400 MHz, CDCl_3): δ 7.36–7.27 (m, 15H), 6.58 (t, J = 7.3 Hz, 3H), 6.40 (br s, 3H), 5.12 (s, 6H), 3.71 (s, 9H), 2.24–2.21 (m, 6H), 2.05–2.00 ppm (m, 1H); ^{13}C NMR (101 MHz, CDCl_3): δ 164.7 (3C), 154.2 (3C), 135.9 (3C), 135.2 (3C), 128.6 (6C), 128.3 (3C), 128.2 (6C), 126.6 (3C), 67.5 (3C), 52.4 (3C), 37.4, 33.1 ppm (3C); IR (neat on KBr plate): $\bar{\nu}$ 3311, 3032, 2952, 1724, 1659, 1504, 1235, 1053, 755, 699 cm^{-1} ; HRMS (APCI): m/z calcd for $\text{C}_{40}\text{H}_{44}\text{N}_3\text{O}_{12}$: 758.2920 $[\text{M}+\text{H}]^+$; found: 758.2925.

Compound 9: Compound **18** (933 mg, 1.40 mmol) and $[\text{Rh}((\text{S,S})\text{-QuinoxP}^*)(\text{cod})]\text{SbF}_6$ (21.6 mg, 27.6 μmol) were charged in a hydrogenation bottle. After the bottle was evacuated and filled with hydrogen several times, degassed MeOH (3 mL) was added. The hydrogen pressure was adjusted to 4 atm, and the mixture was stirred

vigorously overnight at room temperature. The reaction mixture was concentrated, and the crude product was purified by silica gel column chromatography (hexane/ethyl acetate = 1/0 to 1/4) to afford **9** (665 mg, 85%) as orange oil. Ee and de were determined by HPLC (Daicel CHIRAL CEL OX-RH, λ = 254 nm, $\text{CH}_3\text{CN}/\text{H}_2\text{O}$ = 9/11, 0.5 mL/minutes, >99% ee, >98% de). R_f = 0.12 (hexane/ethyl acetate = 3/7); $[\alpha]_D^{27}$ = +13.4 (c = 1.64 in CHCl_3); ^1H NMR (500 MHz, CDCl_3): δ 7.37–7.29 (m, 10H), 5.41 (d, J = 8.1 Hz, 1H), 5.37 (d, J = 8.0 Hz, 1H), 5.10 (s, 4H), 4.37–4.33 (m, 2H), 3.74 (s, 3H), 3.73 (s, 3H), 3.60–3.58 (m, 2H), 1.86–1.20 ppm (m, 11H); ^{13}C NMR (126 MHz, CDCl_3): δ 172.8 (2C), 156.0, 155.9, 136.29, 136.26, 128.5 (4C), 128.2 (2C), 128.1 (4C), 67.1, 67.0, 60.4, 54.0, 53.7, 52.3 (2C), 36.2, 33.0, 29.8, 29.4, 28.7, 28.6 ppm; IR (neat on KBr plate): $\bar{\nu}$ 3335, 3033, 2952, 1714, 1531, 1455, 1215, 1051, 742, 698 cm^{-1} ; HRMS (FAB): m/z calcd for $\text{C}_{29}\text{H}_{39}\text{N}_2\text{O}_9$: 559.2656 $[\text{M}+\text{H}]^+$; found: 559.2662.

Compound 19: To a solution of **9** (515 mg, 922 μmol) in CH_2Cl_2 (10 mL) were added $\text{PhI}(\text{OAc})_2$ (444 mg, 1.38 mmol) and AZADOL (14.2 mg, 92.7 μmol). The mixture was stirred overnight at room temperature. The reaction mixture was diluted with ethyl acetate and washed with water and brine. The combined organic layers were dried over Na_2SO_4 , filtered and concentrated. The crude product was purified by silica gel column chromatography (hexane/ethyl acetate = 1/0 to 1/1) to afford **19** (342 mg, 67%) as pale yellow oil. R_f = 0.23 (hexane/ethyl acetate = 1/1); $[\alpha]_D^{27}$ = +17.5 (c = 1.20 in CHCl_3); ^1H NMR (500 MHz, CDCl_3): δ 9.71 (s, 1H), 7.37–7.29 (m, 10H), 5.37 (d, J = 7.5 Hz, 1H), 5.33 (d, J = 7.8 Hz, 1H), 5.10 (s, 4H), 4.37–4.33 (m, 2H), 3.74 (s, 6H), 2.34 (d, J = 5.4 Hz, 2H), 2.03–1.96 (m, 1H), 1.85–1.77 (m, 2H), 1.67–1.57 (m, 2H), 1.44–1.24 ppm (m, 4H); ^{13}C NMR (126 MHz, CDCl_3): δ 201.5, 172.5 (2C), 155.8 (2C), 136.2 (2C), 128.5 (4C), 128.2 (2C), 128.1 (4C), 67.1 (2C), 53.8 (2C), 52.4 (2C), 48.0, 31.8, 29.8, 29.6, 29.2, 29.1 ppm; IR (neat on KBr plate): $\bar{\nu}$ 3342, 3033, 2953, 1729, 1714, 1531, 1455, 1215, 1047, 753, 699 cm^{-1} ; HRMS (FAB): m/z calcd for $\text{C}_{29}\text{H}_{37}\text{N}_2\text{O}_9$: 557.2499 $[\text{M}+\text{H}]^+$; found: 557.2506.

Compound 8: To a solution of (Z)- α -phosphonoglycine trimethyl ester (86.6 mg, 261 μmol) in dry CH_2Cl_2 (3 mL) was added DBN (36.0 mg, 290 μmol) under a nitrogen atmosphere. The mixture was stirred at 0 $^\circ\text{C}$ for 15 minutes. A solution of **19** (126.7 mg, 228 μmol) in dry CH_2Cl_2 (3 mL) was then added slowly by cannula at 0 $^\circ\text{C}$. The reaction mixture was gradually warmed to room temperature with stirring for 5.5 h. The reaction mixture was washed with 1 M aqueous HCl solution. The aqueous layer was further extracted with ethyl acetate twice. The organic layers were washed with water, saturated aqueous NaHCO_3 solution, and brine. The combined organic layers were dried over Na_2SO_4 , filtered and concentrated. The crude product was purified by silica gel column chromatography (hexane/ethyl acetate = 1/0 to 2/3) to afford **8** (166 mg, 96%) as colorless oil. R_f = 0.36 (hexane/ethyl acetate = 1/1); $[\alpha]_D^{27}$ = +15.5 (c = 1.24 in CHCl_3); ^1H NMR (500 MHz, CDCl_3): δ 7.36–7.28 (m, 15H), 6.60 (t, J = 6.7 Hz, 1H), 6.36 (br s, 1H), 5.46–5.42 (m, 2H), 5.13–5.05 (m, 6H), 4.33–4.29 (m, 2H), 3.72 (s, 9H), 2.18–2.15 (m, 2H), 1.83–1.74 (m, 2H), 1.67–1.52 (m, 3H), 1.38–1.21 ppm (m, 4H); ^{13}C NMR (126 MHz, CDCl_3): δ 172.6 (2C), 164.7, 155.9 (2C), 154.2, 136.23 (2C), 136.18, 136.0, 128.48 (2C), 128.47 (4C), 128.2 (2C), 128.1 (4C), 128.05 (2C), 127.96, 126.6, 67.4, 67.0 (2C), 53.9 (2C), 52.3 (3C), 36.4, 31.8, 29.51, 29.48, 29.0, 28.8 ppm; IR (neat on KBr plate): $\bar{\nu}$ 3334, 3033, 2952, 1714, 1519, 1455, 1218, 1052, 753, 699 cm^{-1} ; HRMS (FAB): m/z calcd for $\text{C}_{40}\text{H}_{48}\text{N}_3\text{O}_{12}$: 762.3238 $[\text{M}+\text{H}]^+$; found: 762.3229.

Compound 20: Method A: A solution of $[\text{Rh}(\text{cod})_2]\text{BF}_4$ (2.4 mg, 5.9 μmol) and (S,S)-QuinoxP* (2.6 mg, 7.8 μmol) in degassed MeOH (0.5 mL) was stirred vigorously at room temperature under nitrogen atmosphere. After 45 minutes, additional degassed MeOH (0.5 mL) was added to the mixture. Compound **3** (25.8 mg, 34.0 μmol) was charged in a hydrogenation bottle. After the bottle was evacuated and filled with hydrogen several times, the catalyst solution was added. The hydrogen pressure was adjusted to 4 atm, and the mixture was stirred vigorously overnight at room temperature. The reaction mixture was concentrated, and the crude product was purified by silica gel column chromatography (hexane/ethyl acetate = 1/0 to 1/1) to afford **20** (21.9 mg, 84%) as pale yellow oil. Ee and de were determined by HPLC (Daicel CHIRAL CEL OX-RH, λ = 254 nm, $\text{CH}_3\text{CN}/\text{H}_2\text{O}$ = 3/2, 0.5 mL/minutes, >99% ee, >97% de). Method B: Compound **8** (193 mg, 254 μmol) and $[\text{Rh}((\text{S,S})\text{-QuinoxP}^*)(\text{cod})]\text{SbF}_6$ (2.0 mg, 2.6 μmol) were charged in a hydrogenation bottle. After the bottle was evacuated and filled

FULL PAPER

with hydrogen several times, degassed MeOH (1 mL) was added. The hydrogen pressure was adjusted to 4 atm, and the mixture was stirred vigorously overnight at room temperature. The suspended reaction mixture was dissolved in CHCl_3 and concentrated. The crude product was purified by silica gel column chromatography (hexane/ethyl acetate = 1/0 to 1/1) to afford **20** (177 mg, 91%) as colorless oil. De was determined by HPLC (Daicel CHIRAL CEL OJ-RH, λ = 254 nm, $\text{CH}_3\text{CN}/\text{H}_2\text{O}$ = 1/1, 0.5 mL/minutes, >98%de). R_f = 0.24 (hexane/ethyl acetate = 1/1); $[\alpha]_D^{27}$ = +22.3 (c = 1.35 in CHCl_3); ^1H NMR (400 MHz, CDCl_3): δ 7.37–7.28 (m, 15H), 5.39 (d, J = 6.9 Hz, 3H), 5.13–5.06 (m, 6H), 4.34–4.29 (m, 3H), 3.73 (s, 9H), 1.79–1.68 (m, 3H), 1.64–1.53 (m, 3H), 1.37–1.17 ppm (m, 7H); ^{13}C NMR (101 MHz, CDCl_3): δ 172.8 (3C), 155.9 (3C), 136.2 (3C), 128.5 (6C), 128.22 (3C), 128.16 (6C), 67.1 (3C), 53.9 (3C), 52.4 (3C), 36.1, 29.5 (3C), 28.4 ppm (3C); IR (neat on KBr plate): $\bar{\nu}$ 3340, 3033, 2952, 1714, 1531, 1455, 1215, 1050, 753, 698 cm^{-1} ; HRMS (FAB): m/z calcd for $\text{C}_{40}\text{H}_{50}\text{N}_3\text{O}_{12}$: 764.3394 $[\text{M}+\text{H}]^+$; found: 764.3401.

Compound 1: To a solution of **20** (147 mg, 193 μmol) in MeOH (8 mL) was added 2 M aqueous NaOH solution (1.49 mL). The reaction mixture was stirred at room temperature for 75 minutes. The volatile in the reaction mixture was removed under reduced pressure. The residual water layer was adjusted to pH 2 using 1 M aqueous HCl solution and extracted with ethyl acetate 3 times. The organic layers were washed with brine. The combined organic layers were dried over Na_2SO_4 . Filtration and concentration afforded a crude tricarboxylic acid. To a solution of the tricarboxylic acid in deoxygenated MeOH (5 mL) was added Pd/C (10 wt%, 35.6 mg), and the reaction mixture was stirred overnight under a hydrogen atmosphere at room temperature. The reaction mixture was filtered through celite and washed with MeOH/ H_2O (1/1 to 0/1) to afford triamino acid **21** as a white solid: ^1H NMR (400 MHz, D_2O): δ 3.75 (t, J = 5.9 Hz, 3H), 1.93–1.79 (m, 6H), 1.56–1.30 ppm (m, 7H); ^{13}C NMR (101 MHz, D_2O): δ 174.7 (3C), 54.9 (3C), 35.9, 27.32 (3C), 27.28 ppm (3C).

To a suspension of the **21** in H_2O /acetone (3 mL/3 mL) were added Fmoc-OSu (214 mg, 636 μmol) and Na_2CO_3 (137 mg, 1.29 mmol). The reaction mixture was stirred at room temperature for 4 days. The reaction mixture was adjusted to pH 2 using 1 M aqueous HCl solution and extracted with ethyl acetate 9 times. The organic layers were washed with brine. The combined organic layers were dried over Na_2SO_4 , filtered and concentrated. The crude product was purified by silica gel column chromatography (hexane/ethyl acetate = 1/0 to 1/4, 1% acetic acid), ODS flash column chromatography ($\text{CH}_3\text{CN}/\text{H}_2\text{O}$ = 3/7 to 7/3, 0.1% TFA), and HPLC (YMC Pack ODS-A No.2015000608, λ = 254 nm, $\text{CH}_3\text{CN}/\text{H}_2\text{O}$ = 7/3, 0.1% TFA, 8.0 mL/minutes, retention time 19.0 minutes) to afford **1** (103 mg, 54%) as a white solid. R_f = 0.04 (hexane/ethyl acetate = 0/1, 1% AcOH); $[\alpha]_D^{27}$ = +26.6 (c = 1.31 in CHCl_3); ^1H NMR (400 MHz, CDCl_3 , 313 K): δ 7.63 (d, J = 7.5 Hz, 6H), 7.58–7.34 (m, 6H), 7.27 (t, J = 7.5 Hz, 6H), 7.18 (t, J = 7.3 Hz, 6H), 6.79 (br s, 1H), 5.81 (br s, 2H), 4.83–3.87 (m, 12 H), 2.00–1.44 (m, 6H), 1.44–0.97 ppm (m, 7H); ^{13}C NMR (101 MHz, CDCl_3 , 313 K): δ 176.4 (3C), 156.5 (3C), 143.6 (6C), 141.3 (6C), 127.7 (6C), 127.1 (6C), 125.0 (6C), 112.0 (6C), 67.4 (3C), 53.8 (3C), 47.0 (3C), 35.8, 29.1 (3C), 28.2 ppm (3C) (The signals derived from a minor conformation were also observed); IR (neat on KBr plate): $\bar{\nu}$ 3321, 3066, 2952, 2869, 2603, 1715, 1520, 1450, 1219, 1050, 741 cm^{-1} ; HRMS (ESI): m/z calcd for $\text{C}_{58}\text{H}_{55}\text{N}_3\text{O}_{12}\text{Na}$: 1008.3678 $[\text{M}+\text{Na}]^+$; found: 1008.3677.

Compound 26: To a suspension of NaH (60%) (1.30 g, 32.4 mmol) in dry Et_2O /dry DMSO (100 mL/5 mL) was added **25** (1.53 g, 10.8 mmol) dropwise under a nitrogen atmosphere at room temperature. The mixture was stirred for 30 minutes. 6-Bromo-1-hexene (5.14 g, 31.5 mmol) was added and the reaction mixture was stirred at room temperature for 1 h. 10 mL of H_2O was added dropwise to the reaction mixture at room temperature. The two layers were separated, and the aqueous layer was extracted with Et_2O 3 times. The organic layers were washed with brine. The combined organic layers were dried over Na_2SO_4 , filtered and concentrated. The crude product was purified by silica gel column chromatography (hexane/ethyl acetate = 1/0 to 19/1) to afford **26** (2.78 g, 84%) as colorless oil. R_f = 0.44 (hexane/ethyl acetate = 9/1); ^1H NMR (400 MHz, CDCl_3): δ 5.83–5.73 (m, 2H), 5.04–4.94 (m, 4H), 2.10–2.04 (m, 4H), 1.91–1.83 (m, 2H), 1.76–1.68 (m, 2H), 1.65–1.54 (m, 2H), 1.49 (s, 9H), 1.46–1.37 (m, 4H), 1.34–1.23 ppm (m, 2H); ^{13}C NMR (101 MHz, CDCl_3): δ 167.8, 158.2, 138.2 (2C), 114.8 (2C), 83.4, 68.9, 39.1 (2C), 33.3 (2C), 28.4 (2C),

27.8 (3C), 23.4 ppm (2C); IR (neat on KBr plate): $\bar{\nu}$ 3077, 2933, 2863, 2137, 1748, 1641, 1370, 1254, 1153, 911, 844 cm^{-1} ; HRMS (APCI): m/z calcd for $\text{C}_{19}\text{H}_{32}\text{NO}_2$: 306.2428 $[\text{M}+\text{H}]^+$; found: 306.2427.

Compound 24: Isocyanide **26** (2.77 g, 9.08 mmol) was dissolved in EtOH (10 mL) containing 12 M aqueous HCl solution (398 μL) and the resulting mixture was stirred overnight at room temperature. Additional 12 M aqueous HCl solution (390 μL) was added and the mixture was stirred for 40 minutes. The solvent was removed under reduced pressure and the remaining oil was taken up in toluene (100 mL). The mixture was cooled to 0 $^\circ\text{C}$, and CbzCl (1.80 g, 10.6 mmol) and 1 M aqueous Na_2CO_3 solution (18.5 mL) were added. The reaction mixture was stirred at room temperature for 2 h and at 80 $^\circ\text{C}$ for 1.5 h. Additional CbzCl (1.52 g, 8.93 mmol) and 1 M aqueous Na_2CO_3 solution (18.2 mL) were added and the mixture was stirred at 80 $^\circ\text{C}$ for 35 minutes. The two layers were separated, and the aqueous layer was extracted with ethyl acetate twice. The organic layers were washed with 0.1 M aqueous HCl solution and saturated aqueous NaHCO_3 solution. The combined organic layers were dried over Na_2SO_4 , filtered and concentrated. The crude product was purified by silica gel column chromatography (hexane/ Et_2O = 1/0 to 49/1) to afford **24** (2.84 g, 73% for 2 steps) as colorless oil. R_f = 0.30 (hexane/ Et_2O = 9/1); ^1H NMR (400 MHz, CDCl_3): δ 7.40–7.28 (m, 5H), 5.88 (br s, 1H), 5.80–5.70 (m, 2H), 5.06 (s, 2H), 5.00–4.90 (m, 4H), 2.34–2.27 (m, 2H), 2.02–1.97 (m, 4H), 1.71–1.63 (m, 2H), 1.45 (s, 9H), 1.41–1.22 (m, 6H), 1.06–0.94 ppm (m, 2H); ^{13}C NMR (101 MHz, CDCl_3): δ 172.9, 153.9, 138.7 (2C), 136.9, 128.4 (2C), 127.9, 127.8 (2C), 114.4 (2C), 82.2, 66.0, 64.1, 35.5 (2C), 33.5 (2C), 28.7 (2C), 27.9 (3C), 23.4 ppm (2C); IR (neat on KBr plate): $\bar{\nu}$ 3418, 3075, 2928, 2859, 1717, 1640, 1496, 1253, 1158, 1067, 911, 697 cm^{-1} ; HRMS (FAB): m/z calcd for $\text{C}_{26}\text{H}_{40}\text{NO}_4$: 430.2957 $[\text{M}+\text{H}]^+$; found: 430.2963.

Compound 23: A solution of **24** (685 mg, 1.60 mmol) in CH_2Cl_2 (15 mL) was cooled to -78 $^\circ\text{C}$. The solution was bubbled with O_3 until the color of it turned blue (10 minutes). Excess O_3 was removed from the reaction mixture by purging with O_2 for 2 minutes. To the mixture was added Ph_3P (1.64 g, 6.26 mmol) at -78 $^\circ\text{C}$, and the reaction mixture was stirred at -78 $^\circ\text{C}$ for 10 minutes and warmed to room temperature with stirring for an additional 30 minutes. Then the reaction mixture was washed with water, and the aqueous layer was extracted with CH_2Cl_2 3 times. The organic layers were washed with brine. The combined organic layers were dried over Na_2SO_4 , filtered and concentrated. The crude product was purified by silica gel column chromatography (hexane/ethyl acetate = 4/1 to 3/2) to afford **23** (672 mg, 97%) as colorless oil. R_f = 0.38 (hexane/ethyl acetate = 3/2); ^1H NMR (400 MHz, CDCl_3): δ 9.71 (t, J = 1.6 Hz, 2H), 7.38–7.28 (m, 5H), 5.88 (br s, 1H), 5.06 (s, 2H), 2.43–2.29 (m, 6H), 1.72–1.65 (m, 2H), 1.62–1.54 (m, 4H), 1.46 (s, 9H), 1.33–1.21 (m, 2H), 1.09–1.98 ppm (m, 2H); ^{13}C NMR (101 MHz, CDCl_3): δ 202.2 (2C), 172.5, 153.9, 136.8, 128.5 (2C), 128.0, 127.9 (2C), 82.7, 66.1, 63.8, 43.6 (2C), 35.3 (2C), 27.9 (3C), 23.5 (2C), 21.8 ppm (2C); IR (neat on KBr plate): $\bar{\nu}$ 3416, 3033, 2938, 2865, 2721, 1718, 1497, 1252, 1157, 1070, 847, 742, 698 cm^{-1} .

Compound 22: To a solution of (Z)- α -phosphonoglycine trimethyl ester (712 mg, 2.15 mmol) in dry CH_2Cl_2 (4 mL) was added DBN (280 mg, 2.25 mmol) under an argon atmosphere. The mixture was stirred at 0 $^\circ\text{C}$ for 20 minutes. A solution of **23** (443 mg, 1.02 mmol) in dry CH_2Cl_2 (6 mL) was then added slowly by cannula at 0 $^\circ\text{C}$. The reaction mixture was gradually warmed to room temperature with stirring overnight. The reaction mixture was washed with 1 M aqueous HCl solution. The aqueous layer was further extracted with ethyl acetate twice. The organic layers were washed with brine. The combined organic layers were dried over Na_2SO_4 , filtered and concentrated. The crude product was purified by silica gel column chromatography (hexane/ethyl acetate = 1/0 to 3/2) to afford **22** (552 mg, 64%) as colorless oil. R_f = 0.35 (hexane/ethyl acetate = 1/1); ^1H NMR (400 MHz, CDCl_3): δ 7.38–7.28 (m, 15H), 6.57 (t, J = 7.3 Hz, 2H), 6.31 (br s, 2H), 5.88 (s, 1H), 5.14 (s, 4H), 5.04 (s, 2H), 3.72 (s, 6H), 2.34–2.27 (m, 2H), 2.23–2.12 (m, 4H), 1.68–1.60 (m, 2H), 1.44–1.39 (m, 13H), 1.31–1.20 (m, 2H), 1.06–0.95 ppm (m, 2H); ^{13}C NMR (101 MHz, CDCl_3): δ 172.6, 165.0 (2C), 154.2 (2C), 154.0, 138.1 (2C), 136.7, 136.1 (2C), 128.5 (4C), 128.4 (2C), 128.2 (2C), 128.1 (4C), 128.0, 127.8 (2C), 125.5 (2C), 82.5, 67.3 (2C), 66.2, 64.0, 52.3 (2C), 35.2 (2C), 27.93 (2C), 27.88 (2C), 27.8 (3C), 23.5 ppm (2C); IR (neat on KBr plate): $\bar{\nu}$ 3410, 3326, 3033, 2951, 2861, 1714, 1659, 1504, 1227, 1063, 754, 698 cm^{-1} ; HRMS (FAB): m/z calcd for $\text{C}_{46}\text{H}_{57}\text{N}_3\text{O}_{12}\text{Na}$: 866.3840 $[\text{M}+\text{Na}]^+$; found: 866.3838.

FULL PAPER

Compound 27: A solution of $[\text{Rh}(\text{cod})_2]\text{BF}_4$ (3.9 mg, 9.6 μmol) and (S,S)-QuinoxP* (4.1 mg, 12.3 μmol) in degassed MeOH (0.5 mL) was stirred vigorously at room temperature under nitrogen atmosphere. After 50 minutes, additional degassed MeOH (1.5 mL) was added to the mixture. Compound **22** (421 mg, 499 μmol) was charged in a hydrogenation bottle. After the bottle was evacuated and filled with hydrogen several times, the catalyst solution was added. The hydrogen pressure was adjusted to 4 atm, and the mixture was stirred vigorously overnight at room temperature. The reaction mixture was concentrated, and the crude product was purified by silica gel column chromatography (hexane/ethyl acetate = 1/0 to 1/1) to afford **27** (412 mg, 98%) as colorless oil. Ee and de were determined by HPLC (Daicel CHIRAL CEL OX-RH, λ = 254 nm, $\text{CH}_3\text{CN}/\text{H}_2\text{O}$ = 7/3, 0.5 mL/minutes, >99%ee, >96%de). R_f = 0.39 (hexane/ethyl acetate = 1/1); $[\alpha]_D^{27}$ = +8.67 (c = 0.92 in CHCl_3); ^1H NMR (400 MHz, CDCl_3): δ 7.36–7.27 (m, 15H), 5.87 (s, 1H), 5.34 (d, J = 7.9 Hz, 1H), 5.26 (d, J = 8.3 Hz, 1H), 5.12 (s, 2H), 5.10 (s, 2H), 5.06 (s, 2H), 4.37–4.30 (m, 2H), 3.73 (s, 3H), 3.72 (s, 3H), 2.30–2.23 (m, 2H), 1.78–1.72 (m, 2H), 1.67–1.54 (m, 4H), 1.44 (s, 9H), 1.32–1.19 (m, 10H), 1.00–1.91 ppm (m, 2H); ^{13}C NMR (101 MHz, CDCl_3): δ 173.0, 172.9, 172.7, 155.9, 155.8, 153.9, 136.8, 136.25, 136.20, 128.5 (4C), 128.4 (2C), 128.14, 128.11, 128.07 (2C), 128.0 (2C), 127.9, 127.8 (2C), 82.3, 66.9 (2C), 66.0, 64.0, 53.81, 53.77, 52.3 (2C), 35.5, 35.3, 32.5, 32.3, 29.0, 28.8, 27.9 (3C), 25.0, 24.8, 23.7, 23.4 ppm. IR (neat on KBr plate): $\tilde{\nu}$ 3412, 3353, 3033, 2950, 2861, 1716, 1499, 1214, 1066, 698 cm^{-1} ; HRMS (FAB): m/z calcd for $\text{C}_{46}\text{H}_{61}\text{N}_3\text{O}_{12}\text{Na}$: 870.4153 $[\text{M}+\text{Na}]^+$; found: 870.4154.

Compound 2: To a solution of **27** (285 mg, 336 μmol) in CH_2Cl_2 (5 mL) was added TFA (5 mL) at room temperature. The mixture was stirred for 1.5 h. The volatile in the reaction mixture was removed under reduced pressure. The residue was reconstituted in Et_2O (30 mL) and washed with saturated aqueous NH_4Cl solution 3 times. The organic layer was dried over Na_2SO_4 , filtered and concentrated. Residual solvent was removed by azeotropic drying with pentane to afford monocarboxylic acid as colorless oil. To a solution of the monocarboxylic acid in MeOH (7 mL) was added 2 M aqueous NaOH solution (1.65 mL). The reaction mixture was stirred at room temperature for 1 h. The volatile in the reaction mixture was removed under reduced pressure. The residual water layer was adjusted to pH 1 using 1 M aqueous HCl solution and extracted with ethyl acetate 3 times. The organic layers were washed with and brine. The combined organic layers were dried over Na_2SO_4 . Filtration and concentration afforded a crude tricarboxylic acid as a white solid. 5 mL of MeOH was added to the tricarboxylic acid and Pd/C (10 wt%, 62.0 mg). The reaction mixture was stirred overnight under a hydrogen atmosphere at room temperature. The reaction mixture was filtered through celite and washed with H_2O to afford triamino acid **28** as a white solid: ^1H NMR (400 MHz, D_2O): δ 3.79–3.76 (m, 2H), 1.91–1.73 (m, 8H), 1.48–1.33 (m, 10H), 1.29–1.19 ppm (m, 2H); ^{13}C NMR (101 MHz, D_2O): δ 175.9, 174.5 (2C), 65.1, 54.5 (2C), 35.8, 35.9, 30.1, 30.0, 28.23, 28.18, 23.9, 23.7, 22.6, 22.5 ppm.

To a suspension of the **28** in H_2O /acetone (3 mL/3 mL) were added Fmoc-OSu (349 mg, 1.04 mmol) and Na_2CO_3 (209 mg, 1.97 mmol) at 0 °C. The reaction mixture was gradually warmed to room temperature with stirring 1.5 days. The reaction mixture was adjusted to pH 1 using 1 M aqueous HCl solution and extracted with ethyl acetate 3 times. The organic layers were washed with brine. The combined organic layers were dried over Na_2SO_4 , filtered and concentrated. The crude product was purified by silica gel column chromatography (hexane/ethyl acetate = 1/0 to 0/1, 1% acetic acid) and HPLC (YMC Pack ODS-A No.2015000608, λ = 254 nm, $\text{CH}_3\text{CN}/\text{H}_2\text{O}$ = 7/3, 0.1% TFA, 8.0 mL/minutes, retention time 26.9 minutes) to afford **2** (186 mg, 55% for 4 steps) as a white solid. R_f = 0.37 (hexane/ethyl acetate = 0/1, 1% acetic acid); $[\alpha]_D^{27}$ = +1.58 (c = 0.92 in MeOH); ^1H NMR (400 MHz, CD_3OD): δ 7.74–7.71 (m, 6H), 7.64–7.58 (m, 6H), 7.36–7.24 (m, 12H), 4.43–4.25 (m, 6H), 4.20–4.10 (m, 5H), 2.17–2.04 (m, 2H), 1.83–1.69 (m, 4H), 1.68–1.56 (m, 2H), 1.47–1.11 (m, 10H), 0.97–0.71 ppm (m, 2H); ^{13}C NMR (126 MHz, CD_3OD): δ 176.9, 176.1 (2C), 158.6 (2C), 156.1, 145.33 (2C), 145.27, 145.24, 145.16 (2C), 142.6 (6C), 128.8 (6C), 128.1 (6C), 126.3 (4C), 126.1 (2C), 120.9 (6C), 67.9 (2C), 67.2, 64.4, 55.3 (2C), 48.4 (3C), 36.0, 35.9, 32.6, 32.5, 30.1, 30.0, 26.7, 26.6, 24.8, 24.6 ppm; IR (neat on KBr plate): $\tilde{\nu}$ 3405, 3066, 2940, 2861, 2604, 1693, 1514, 1449, 1207, 740 cm^{-1} ; HRMS (ESI): m/z calcd for $\text{C}_{61}\text{H}_{61}\text{N}_3\text{O}_{12}\text{Na}$: 1050.4147 $[\text{M}+\text{Na}]^+$; found: 1050.4146.

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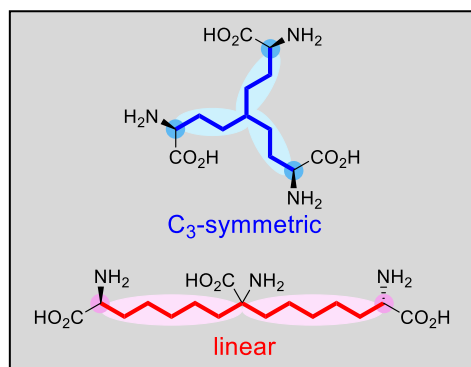
Keywords: amino acids • amyloid beta-peptides • trimer

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FULL PAPER

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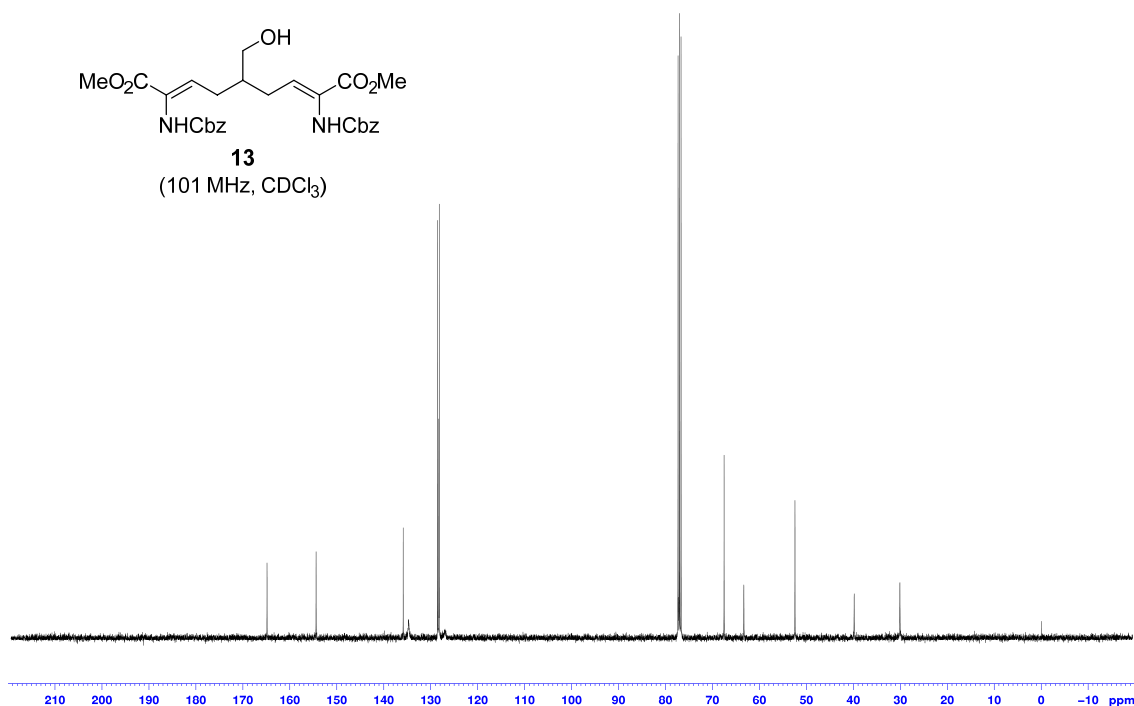
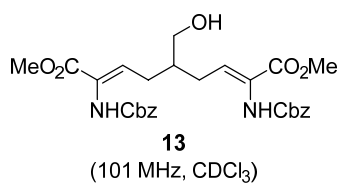
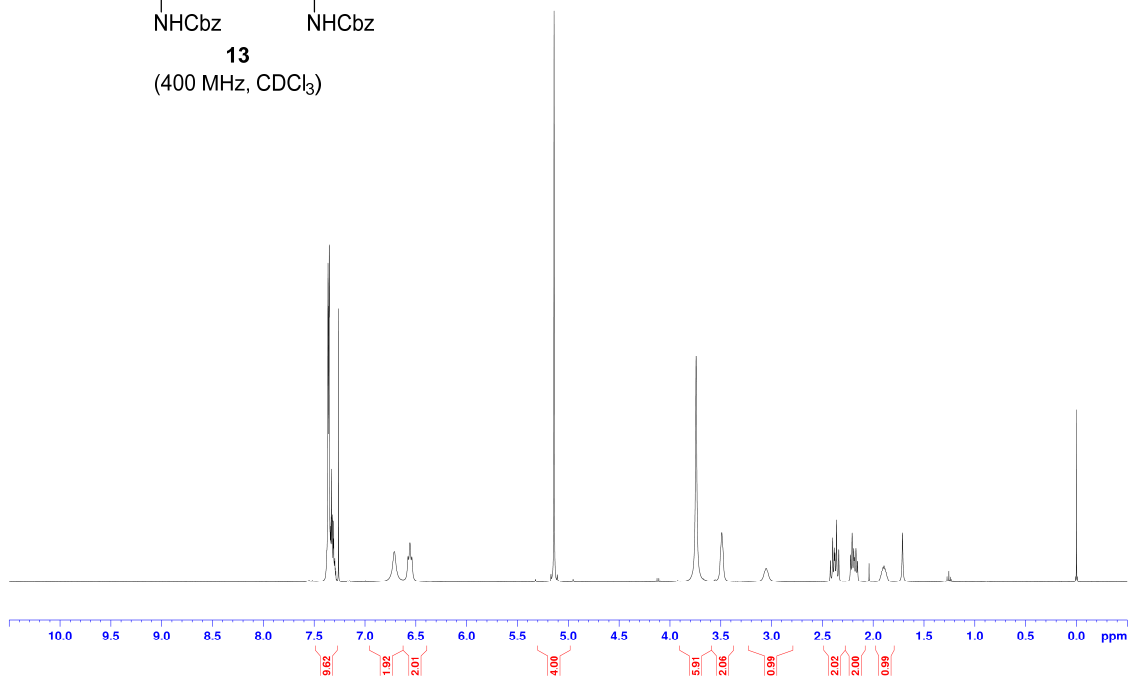
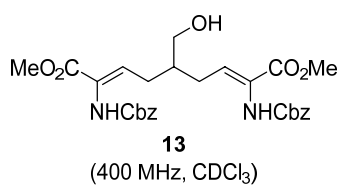


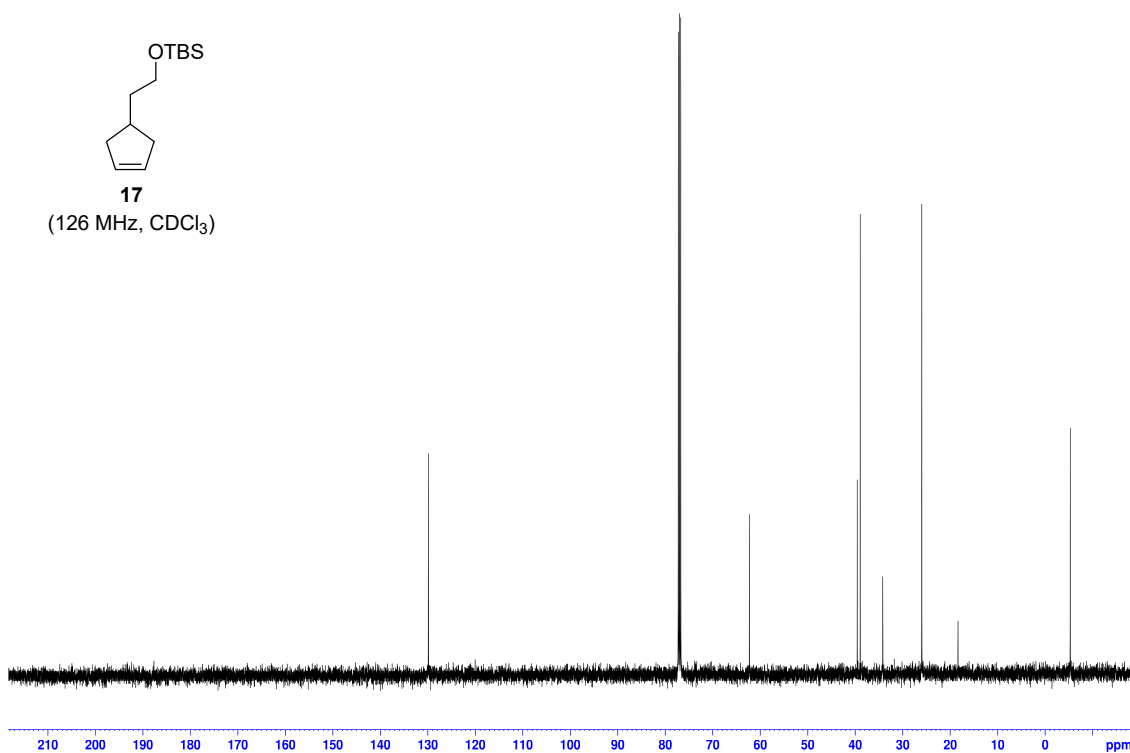
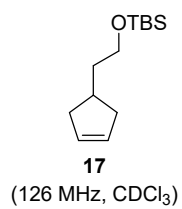
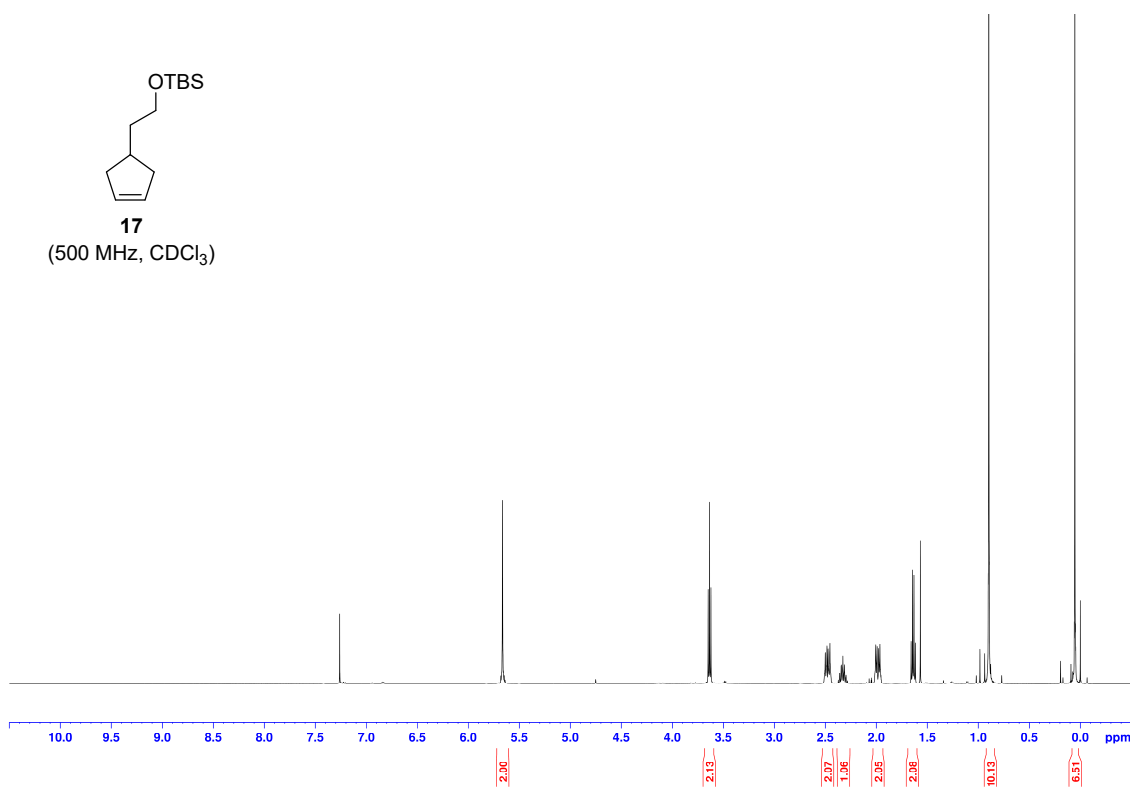
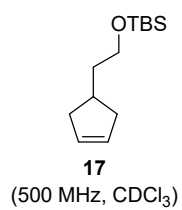
The lack of suitable trivalent linkers has limited trimer peptide models. This study designed and synthesized two new alkyl bridged-tris-α-amino acids with Fmoc protecting groups as flexible linkers, which are characterized by C₃-symmetric and linear structures, respectively.

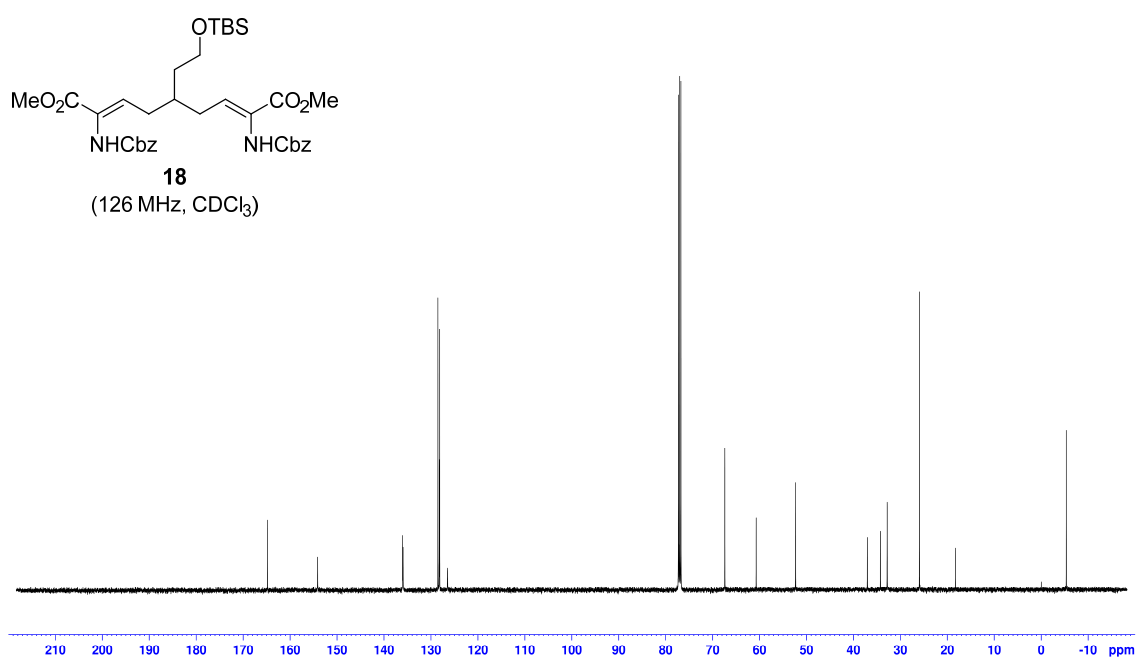
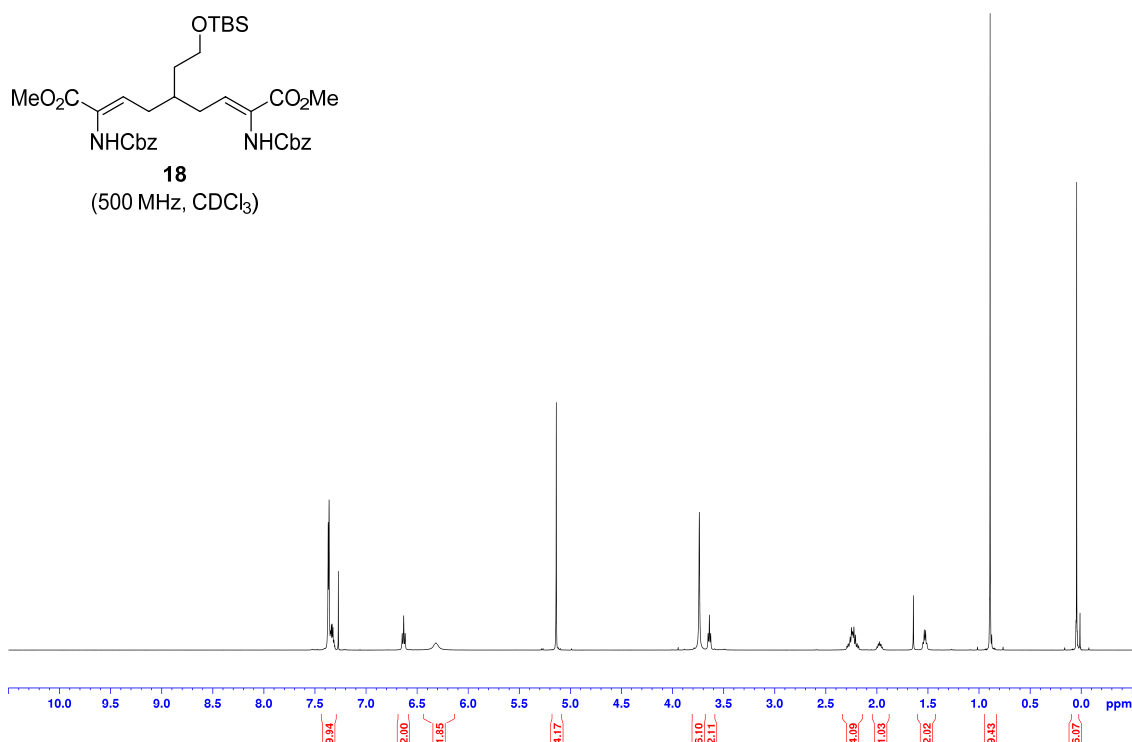
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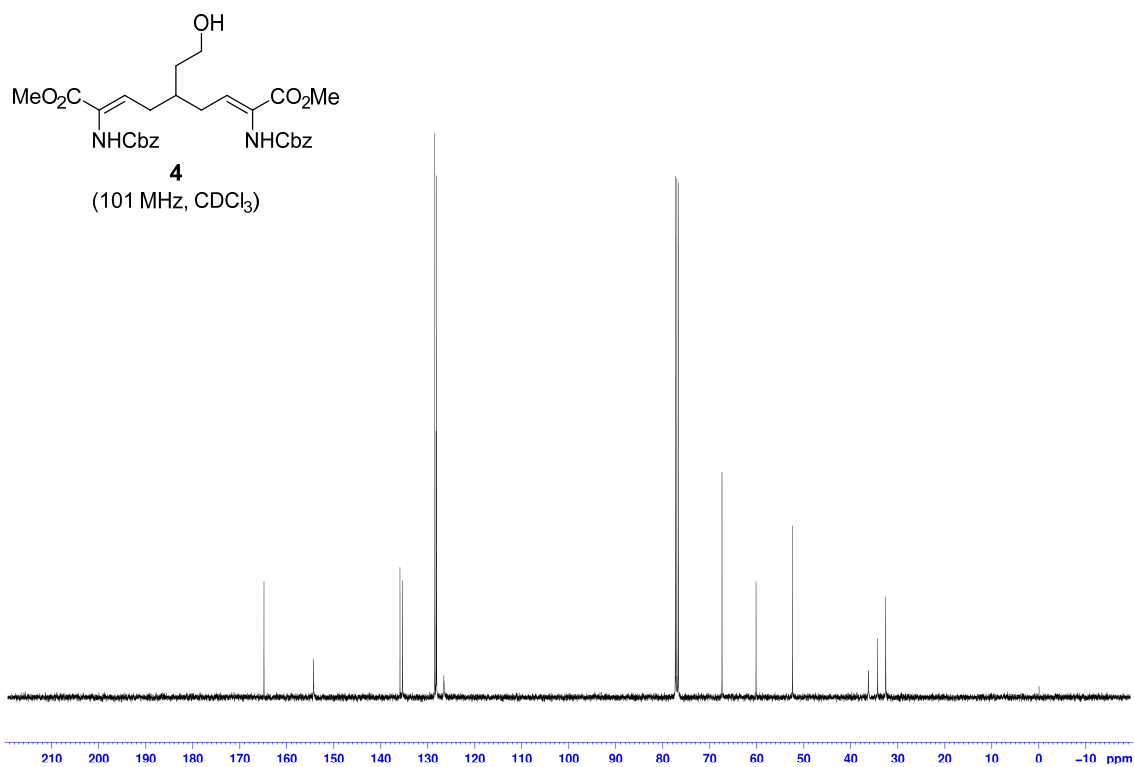
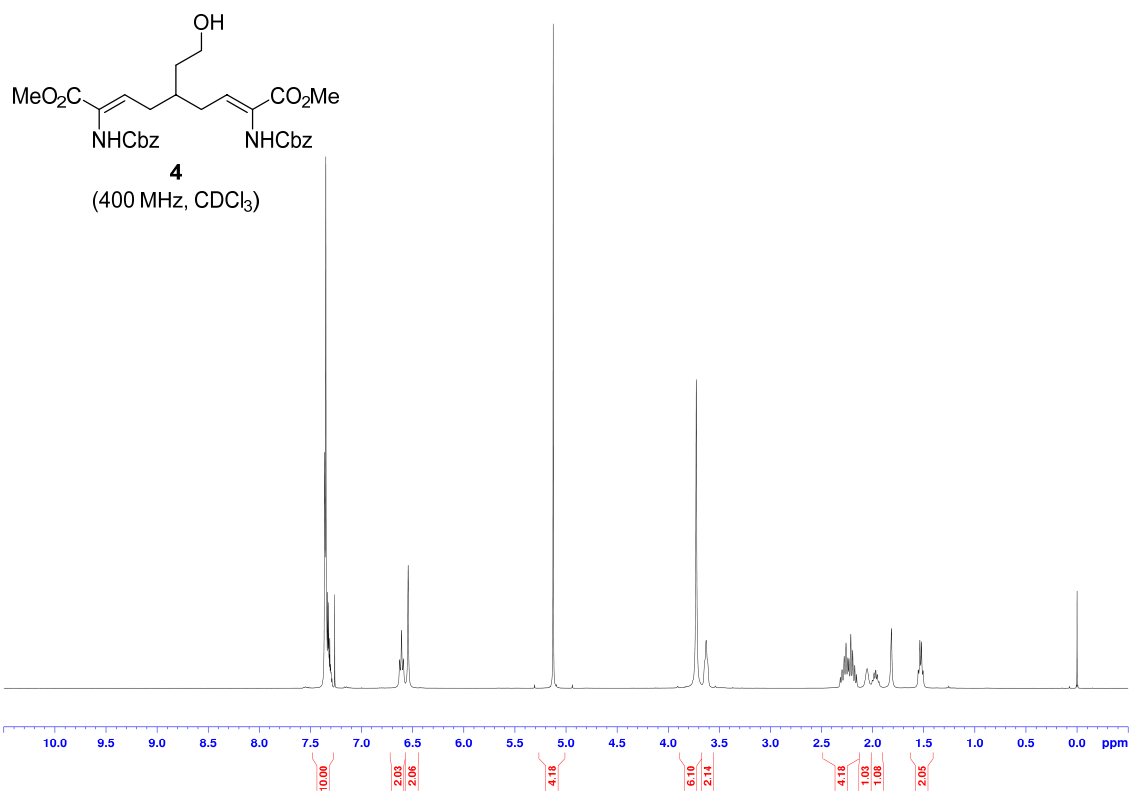
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- II. Experimental procedure of synthesis of stereoisomers of **9**, **20**, and **27**
- III. Copy of HPLC chart of compounds **9**, **20**, and **27**

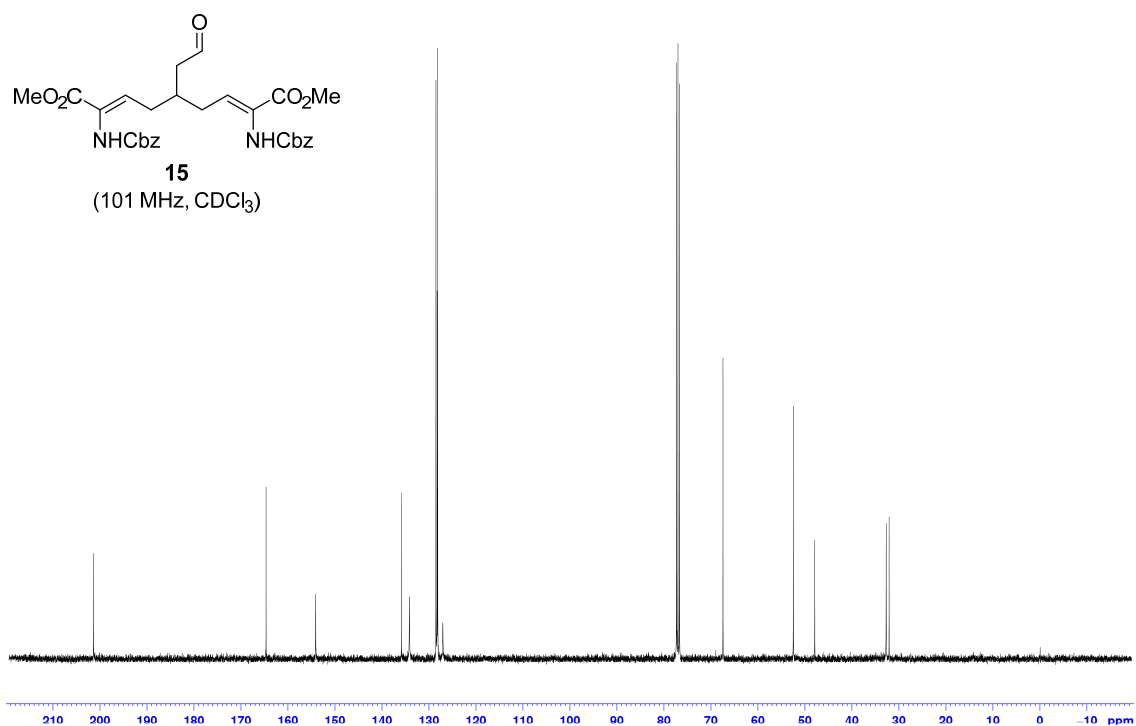
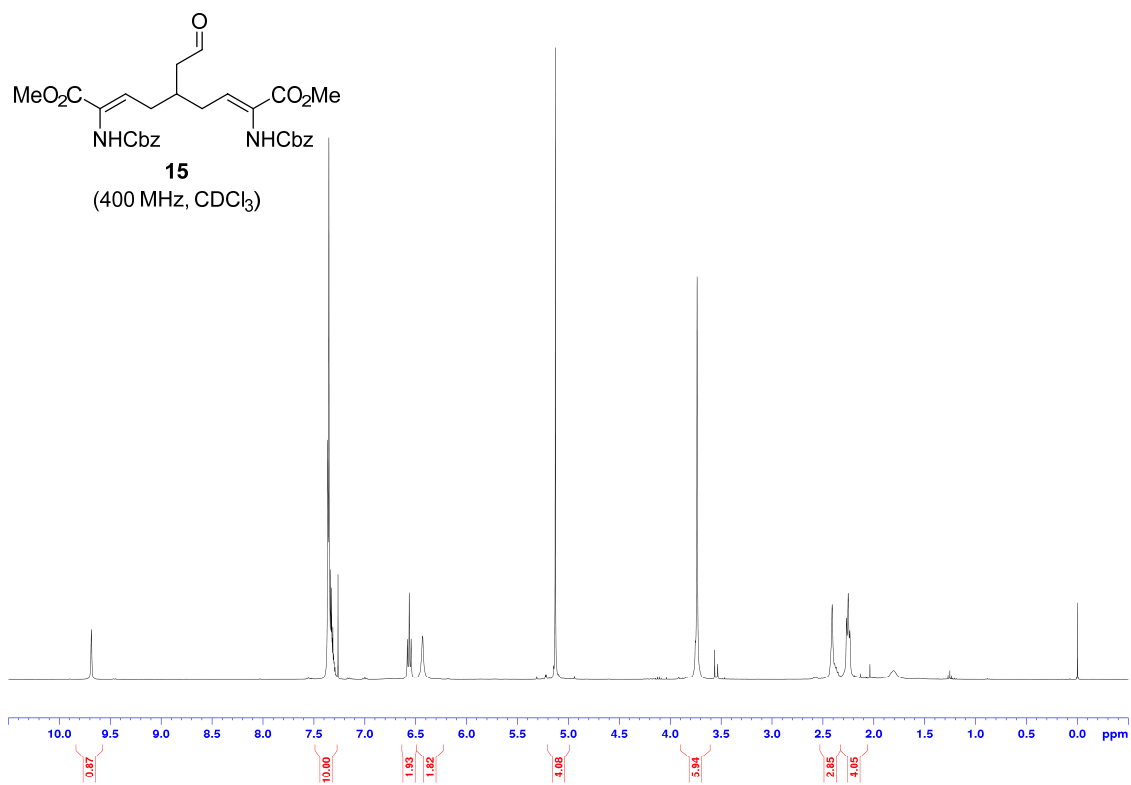
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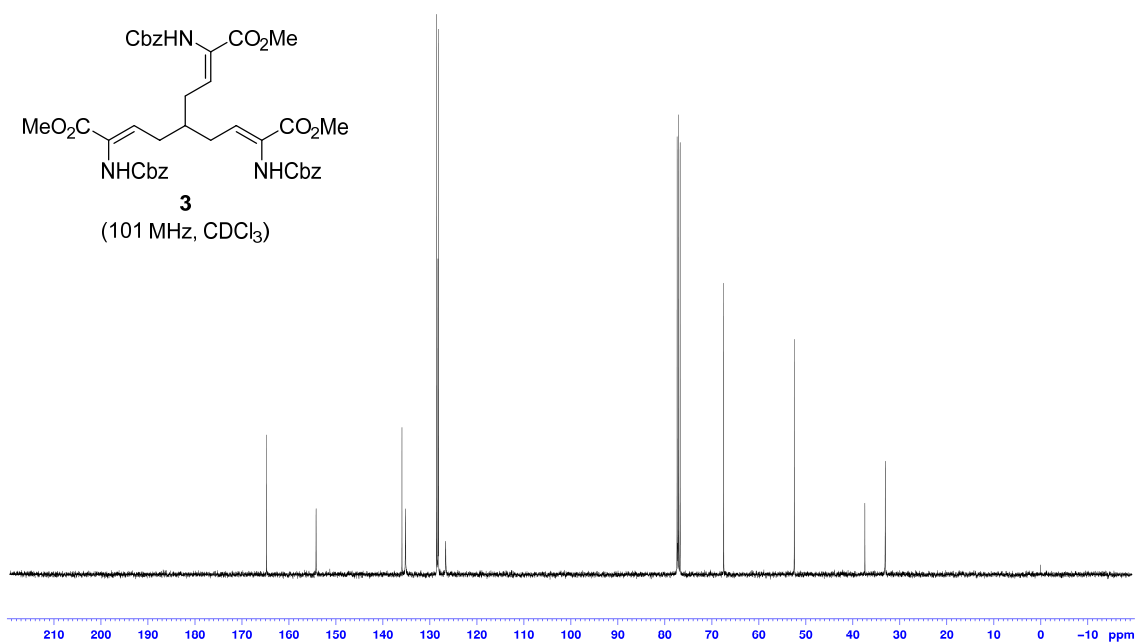
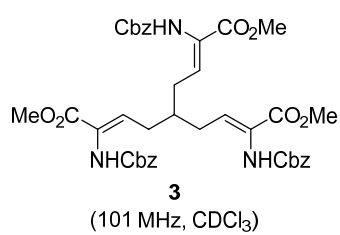
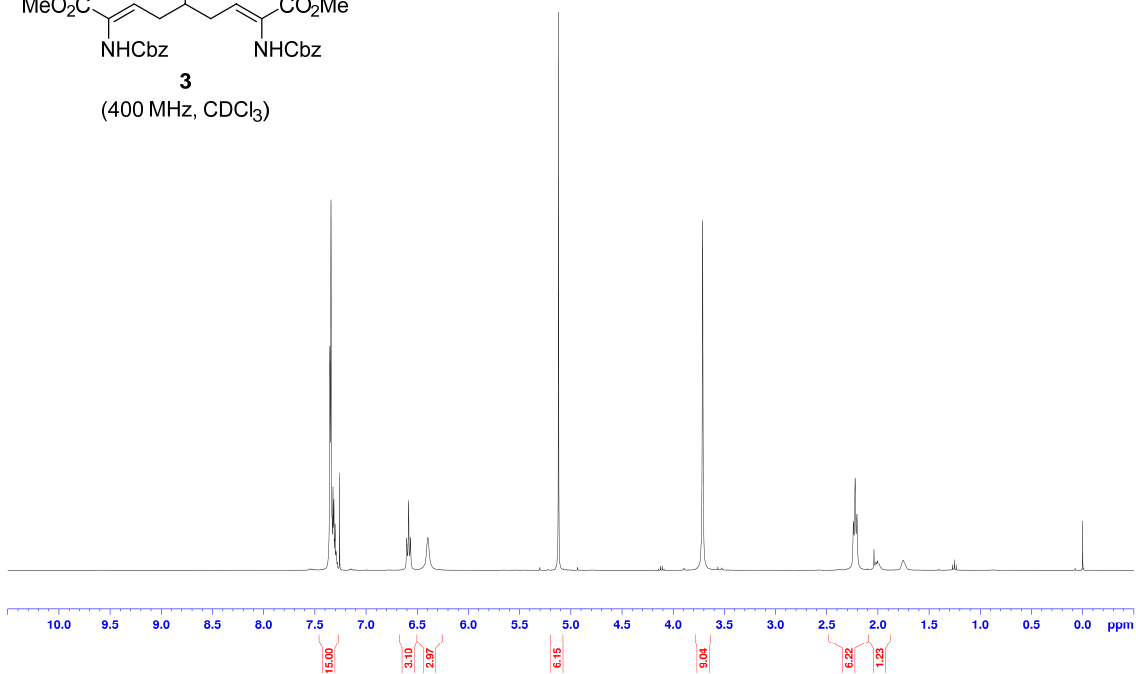
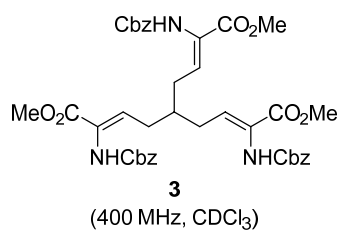


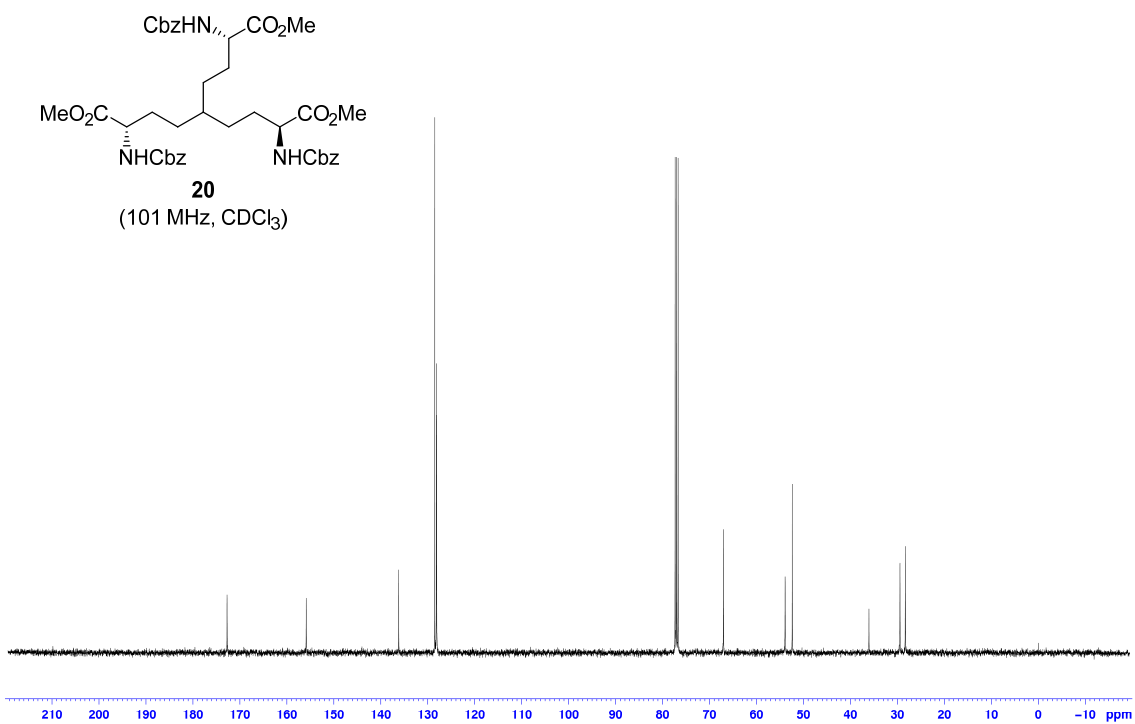
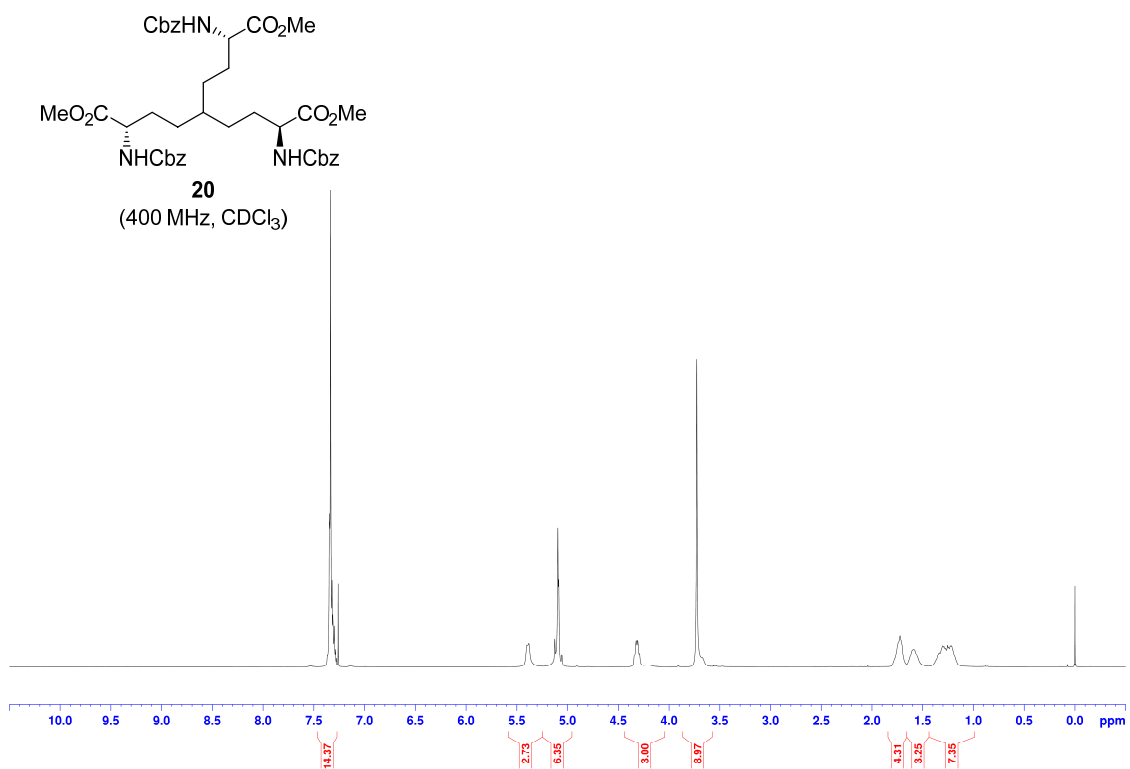


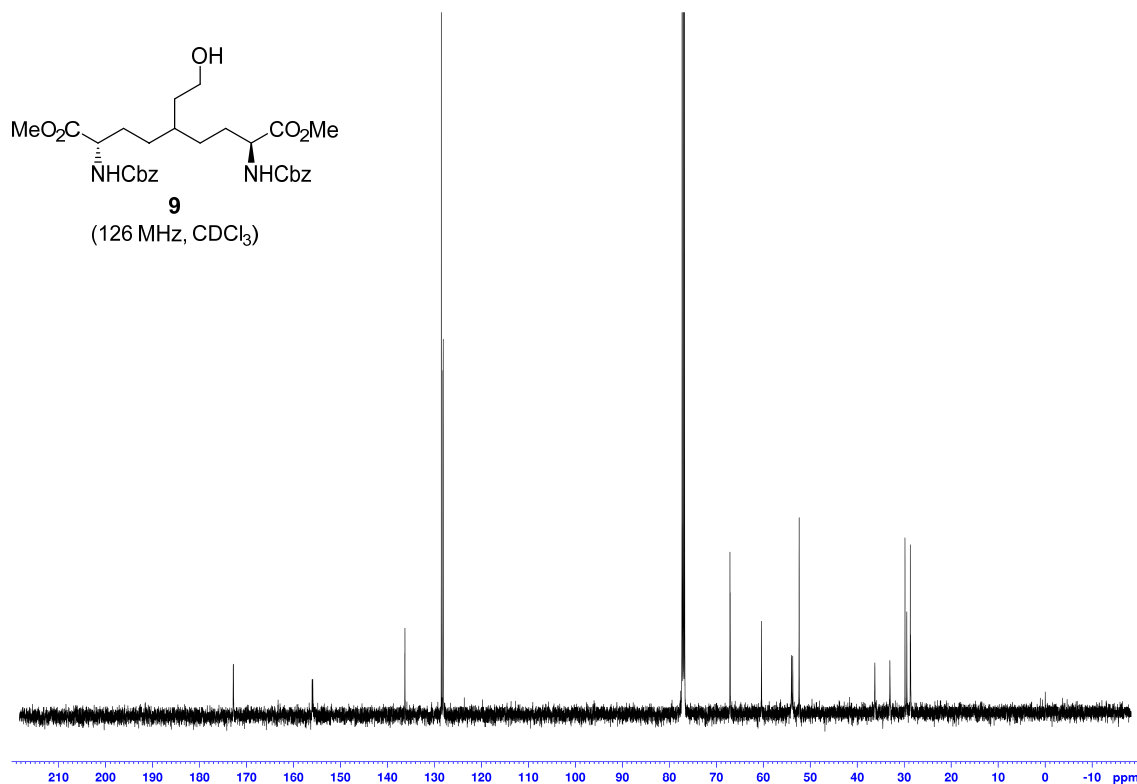
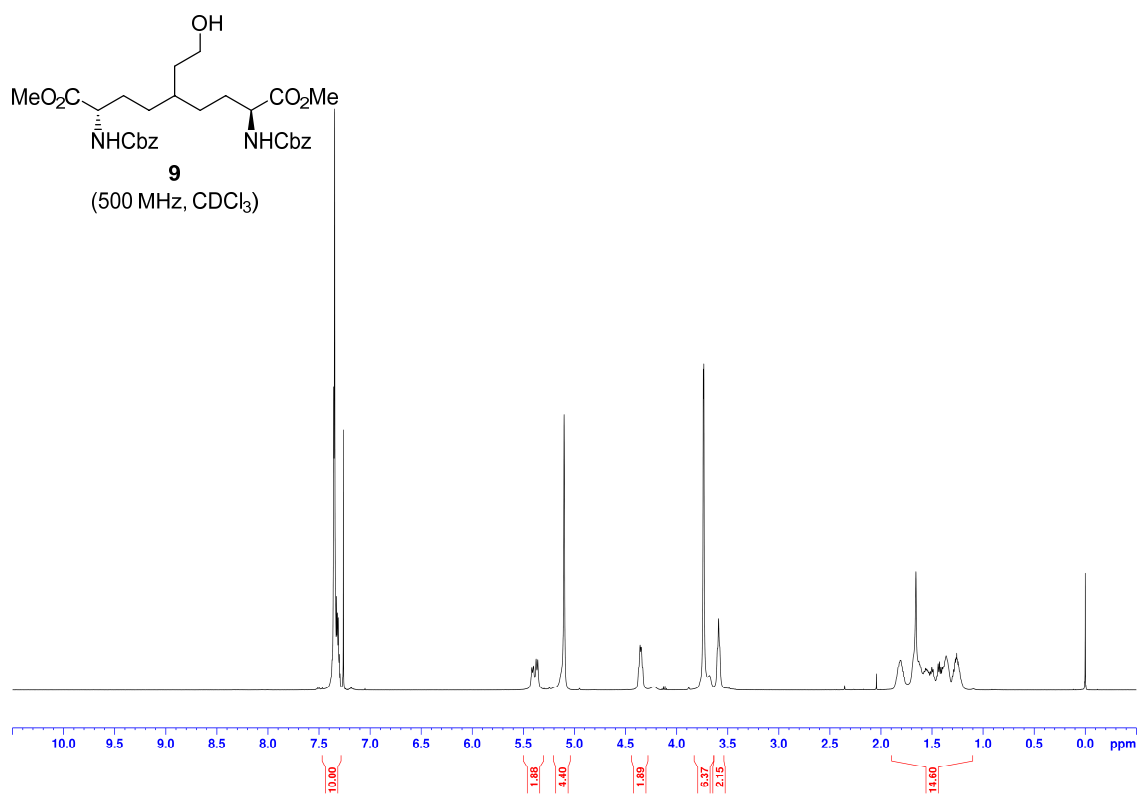


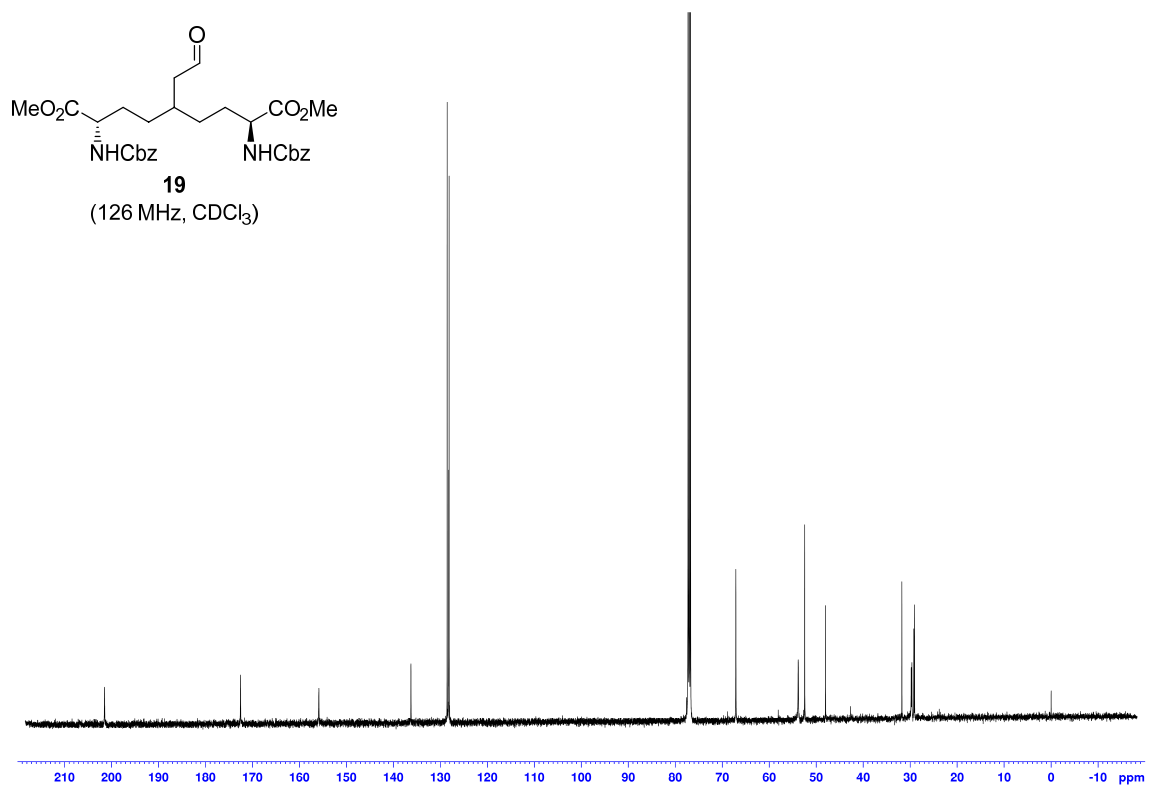
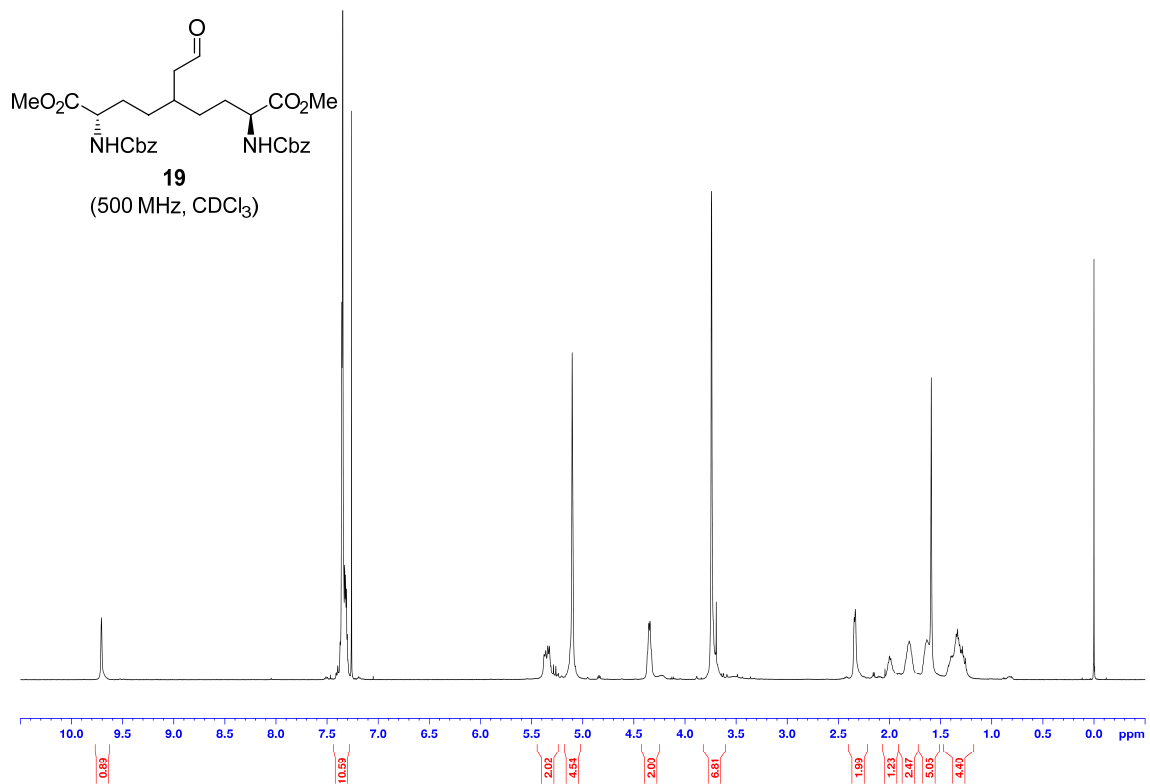


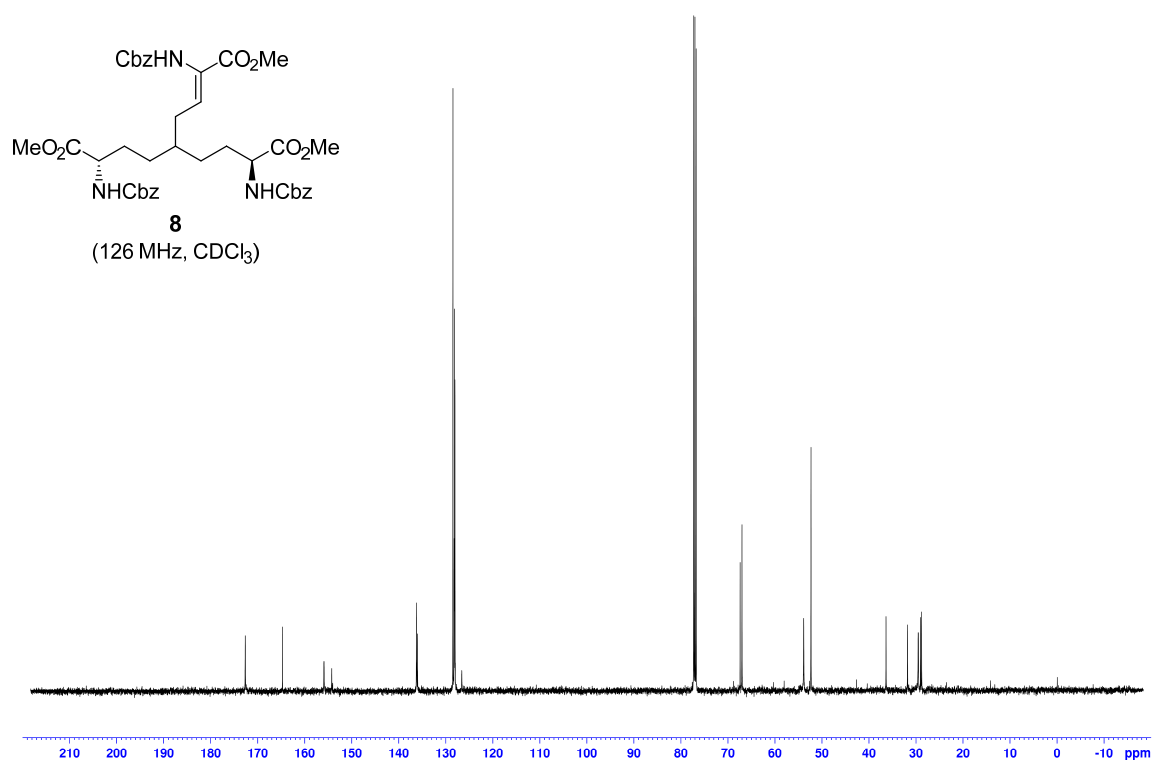
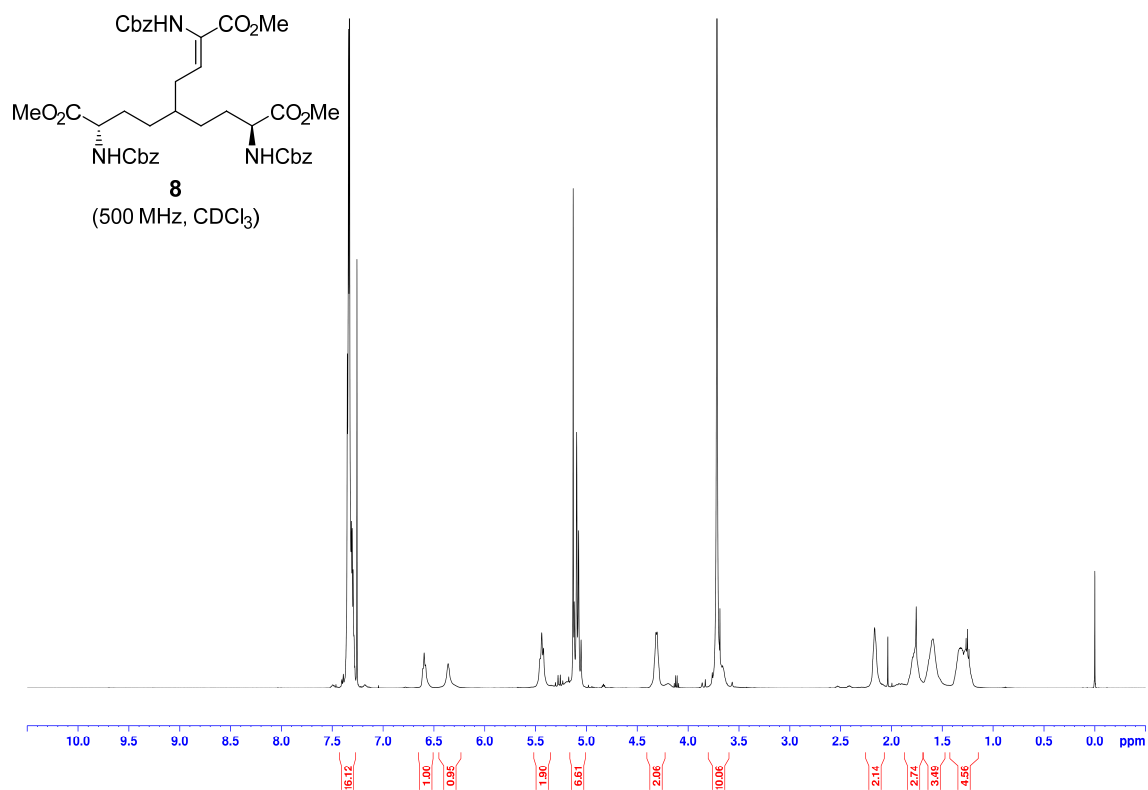


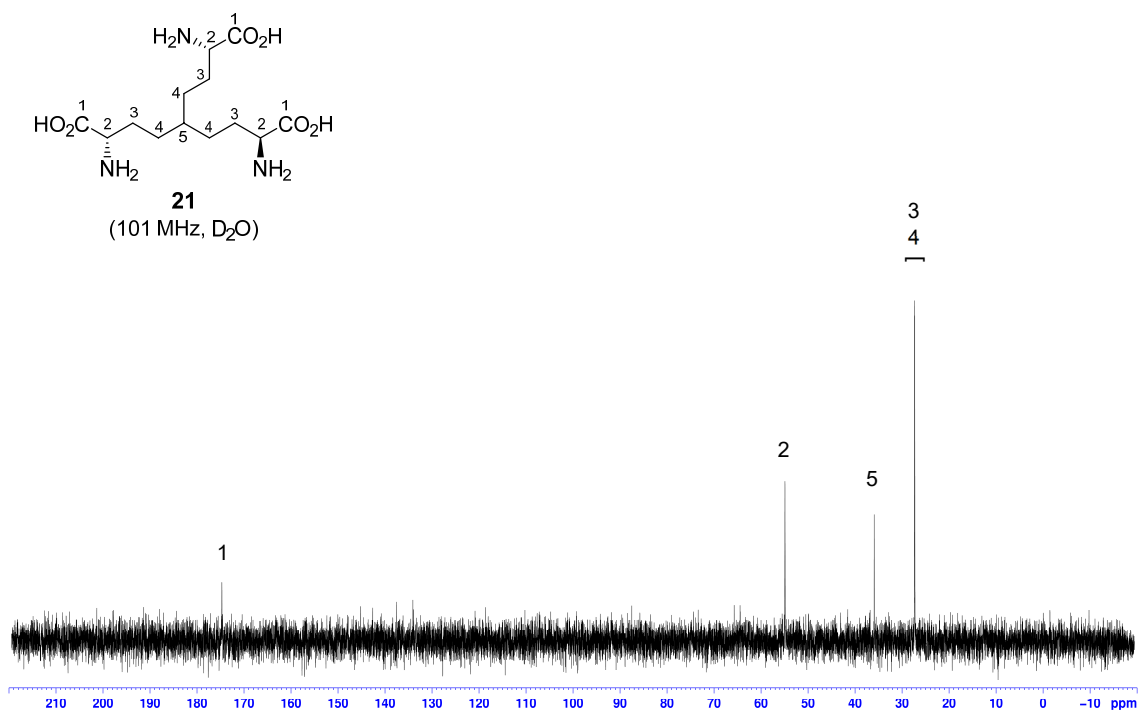
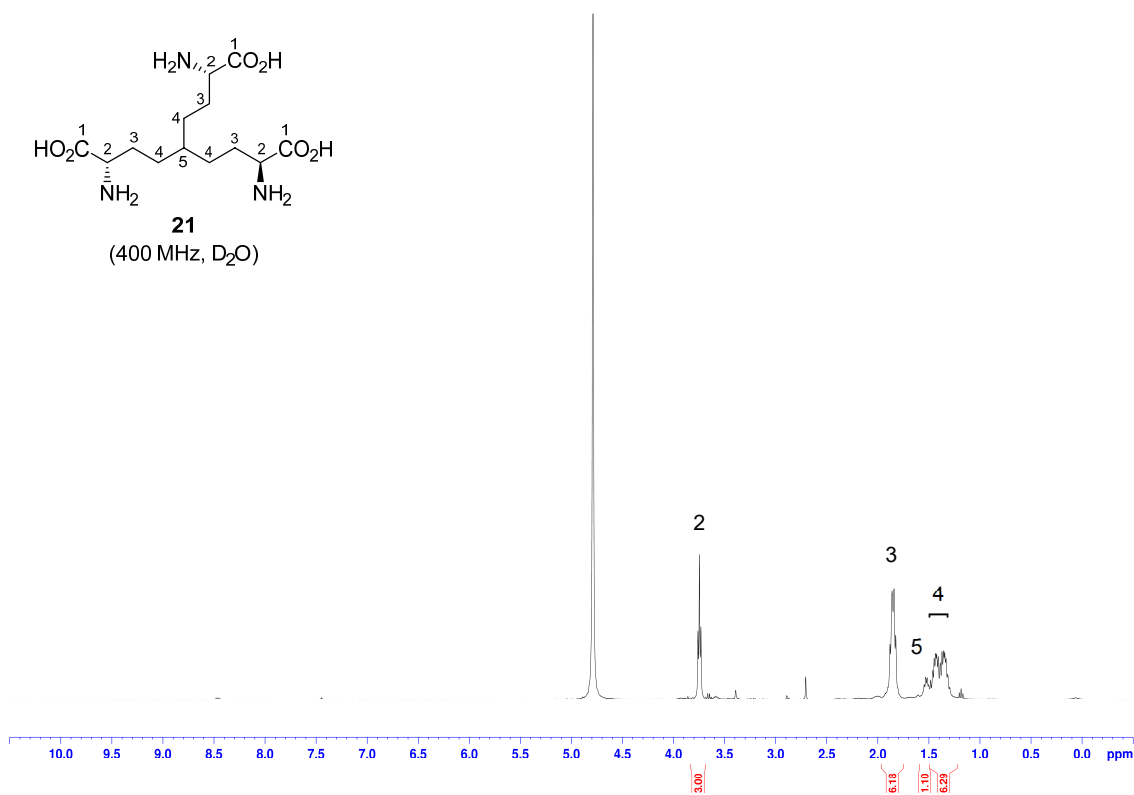


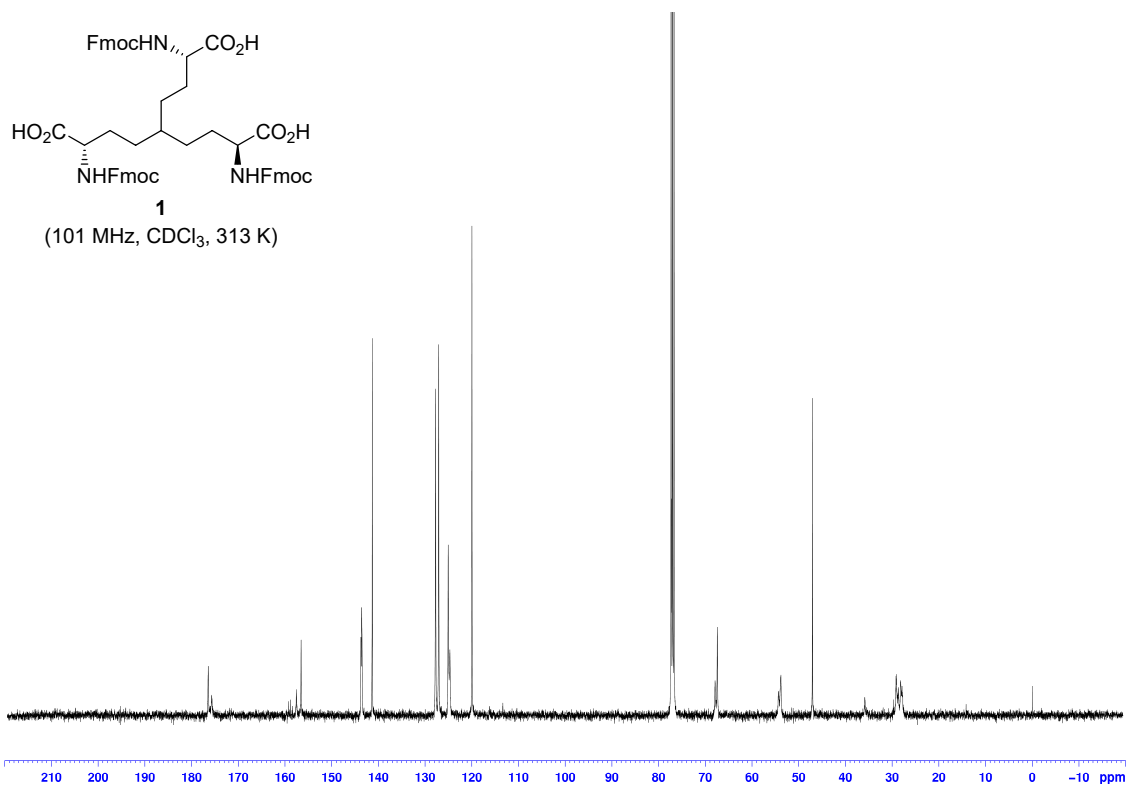
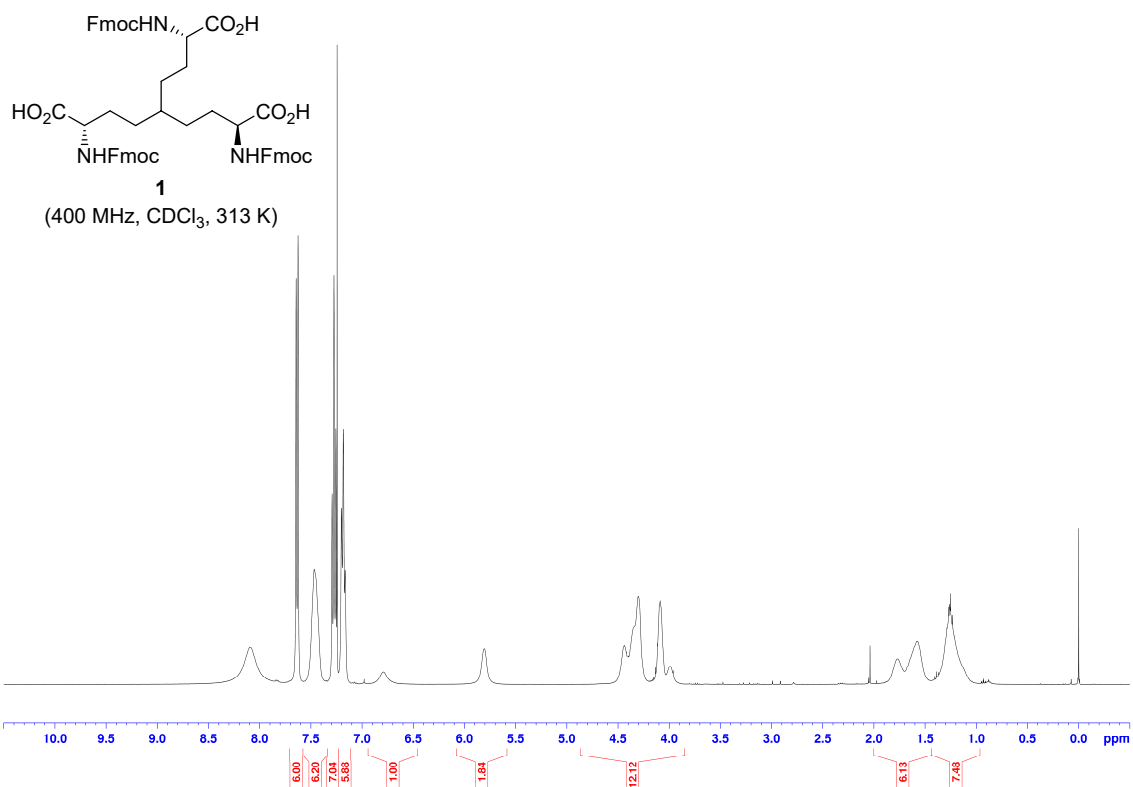


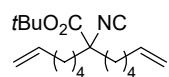




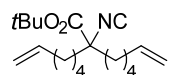
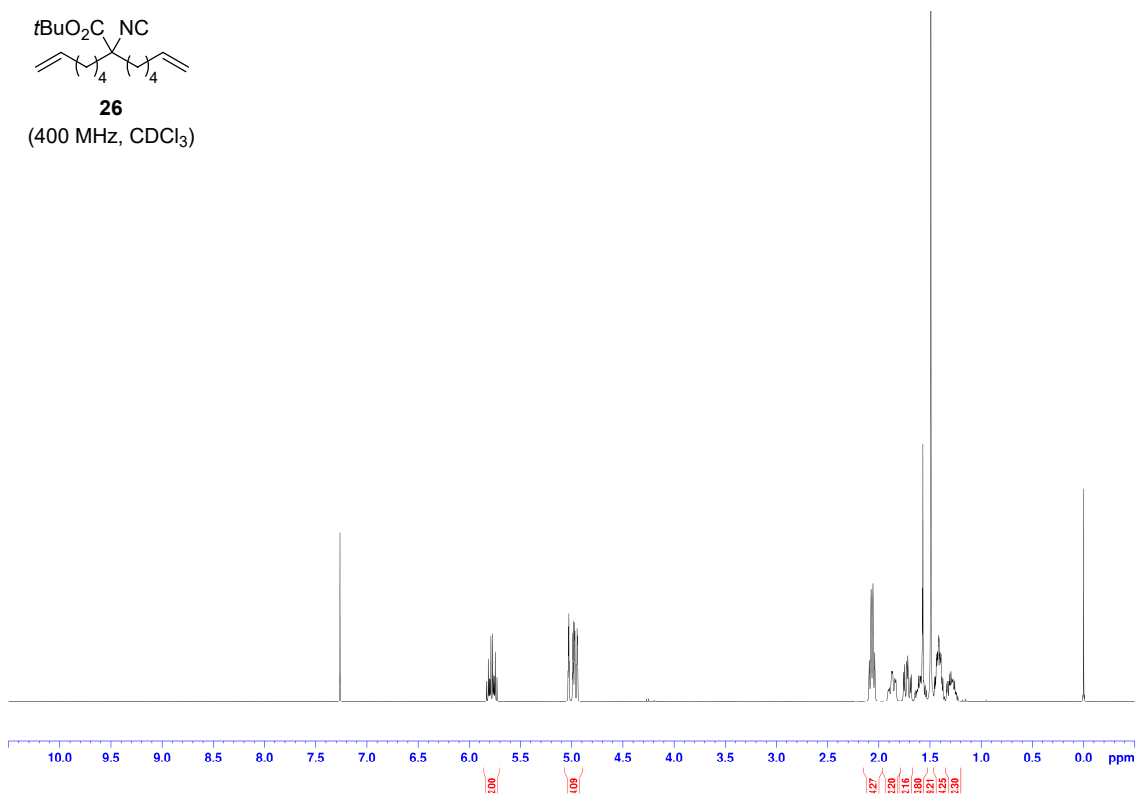




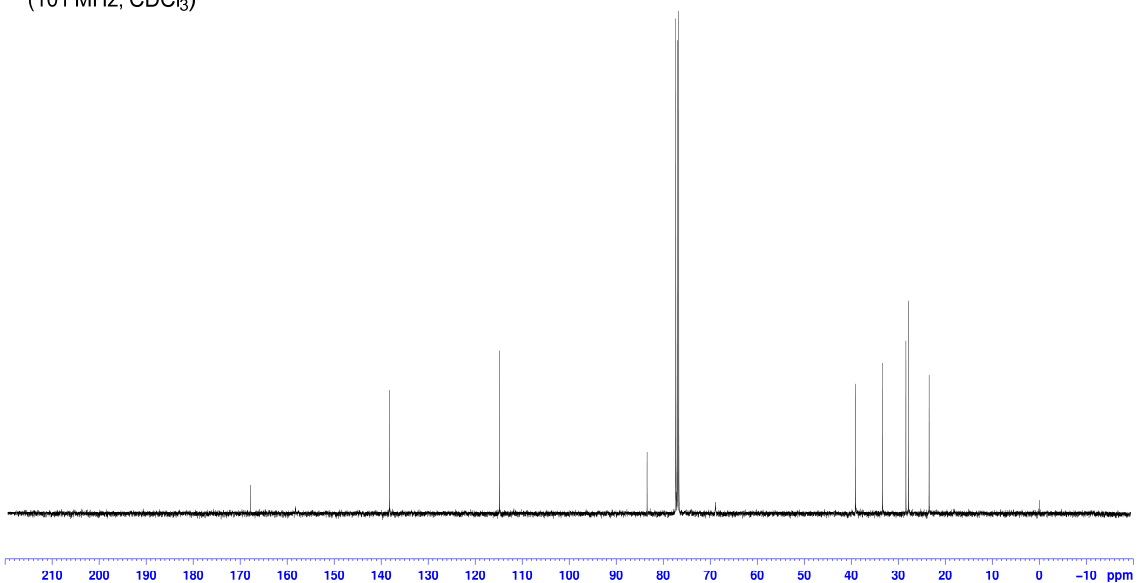


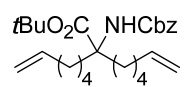


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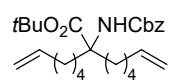
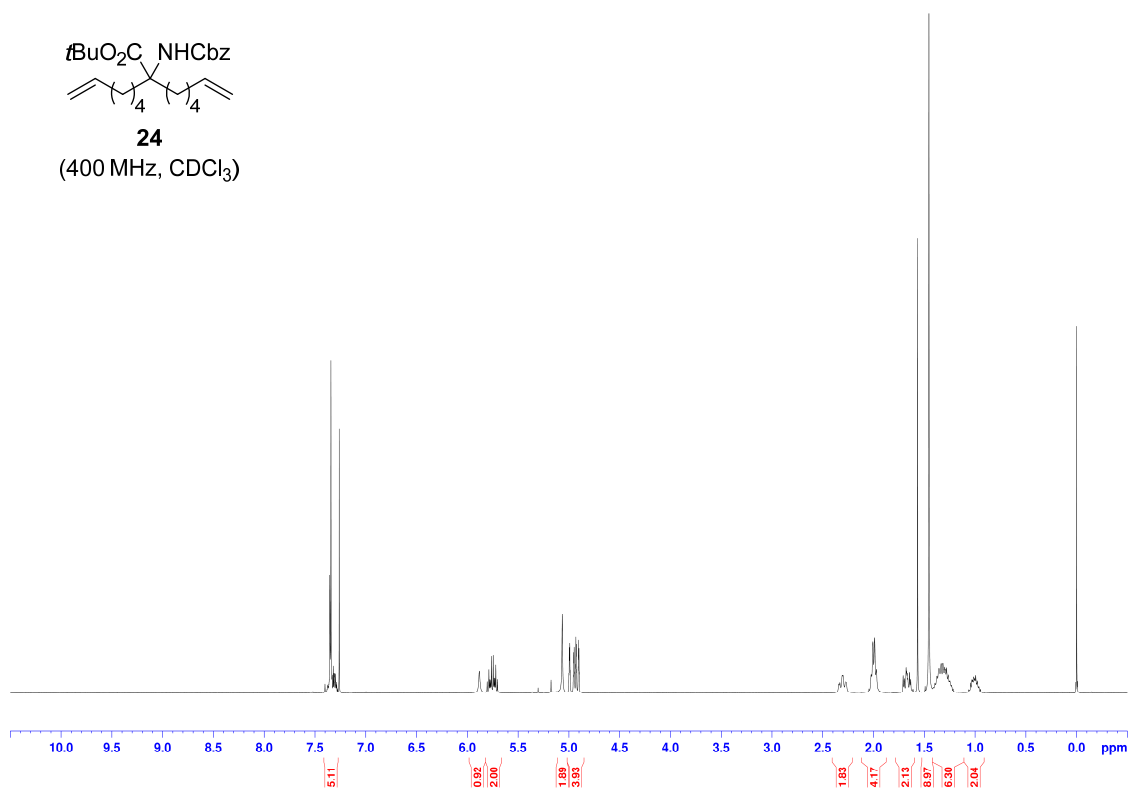
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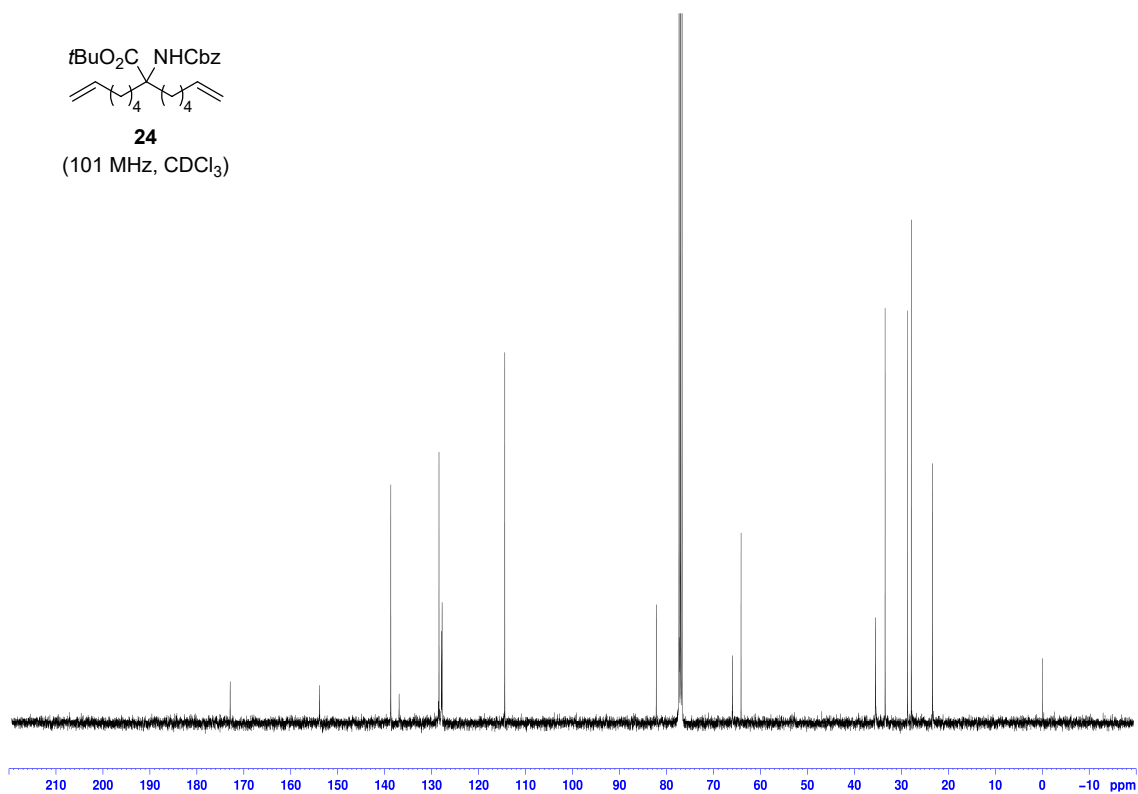
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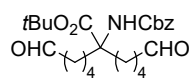
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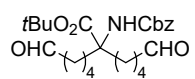
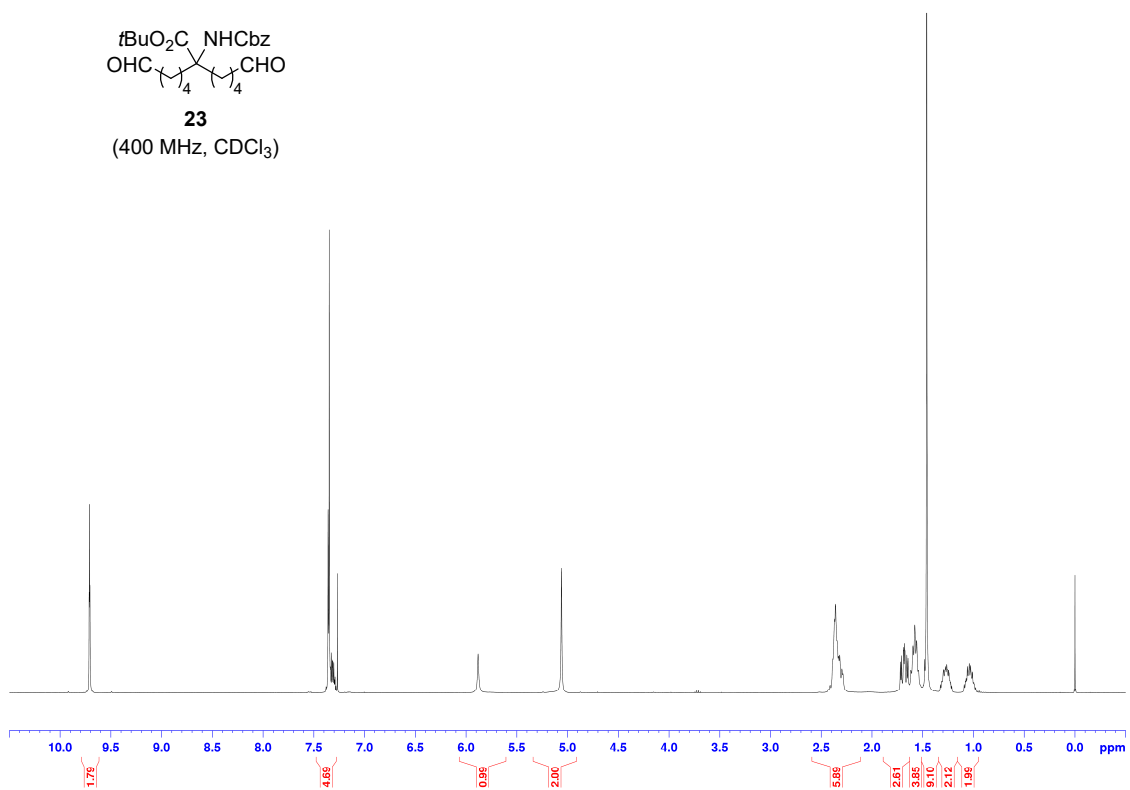
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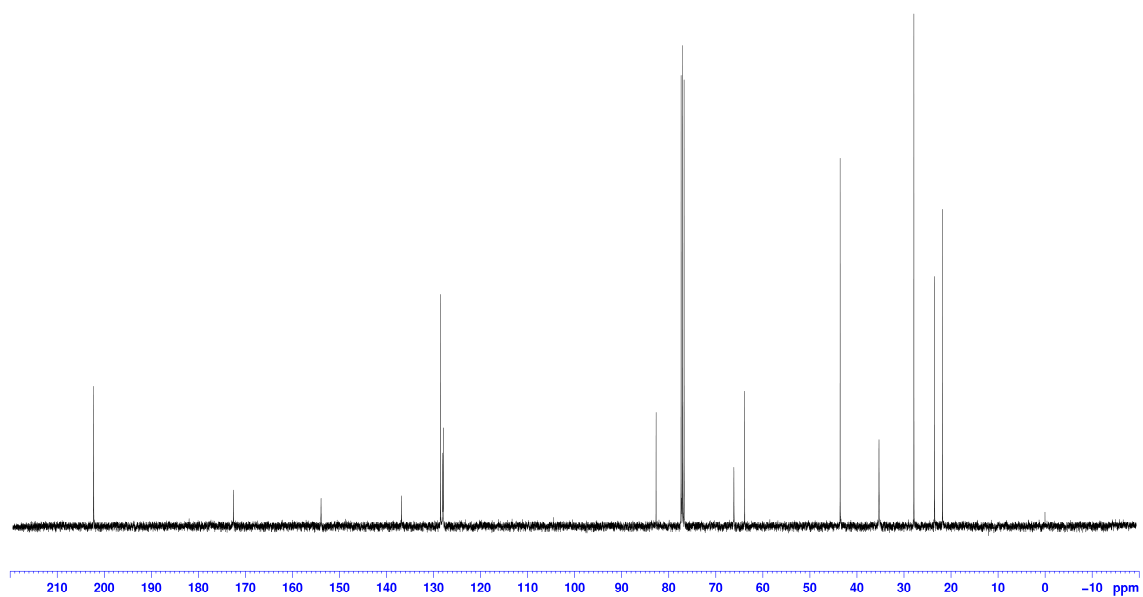


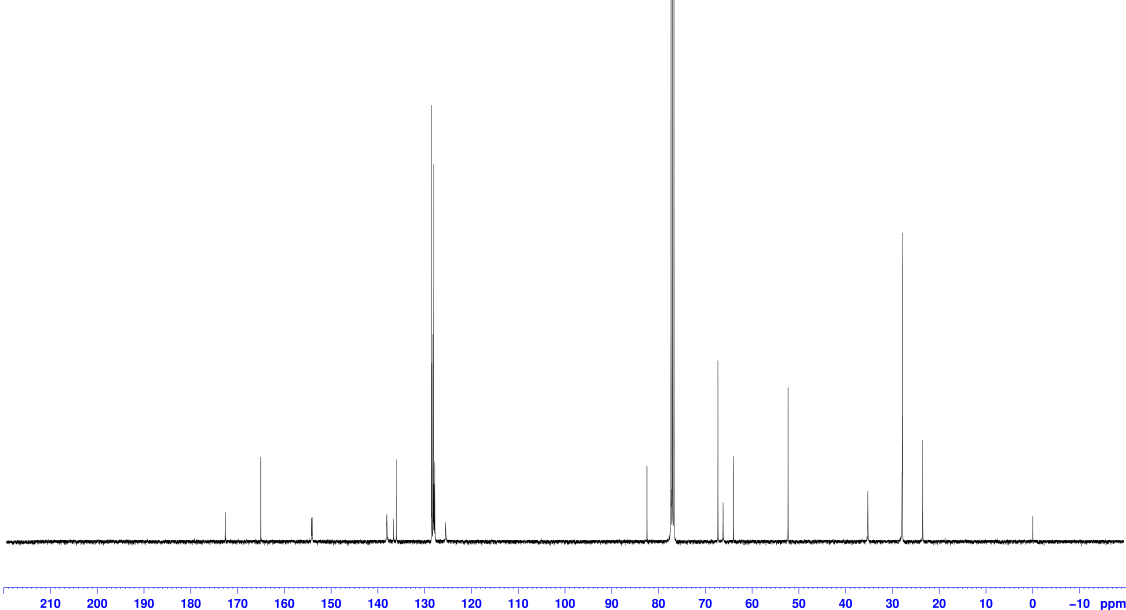
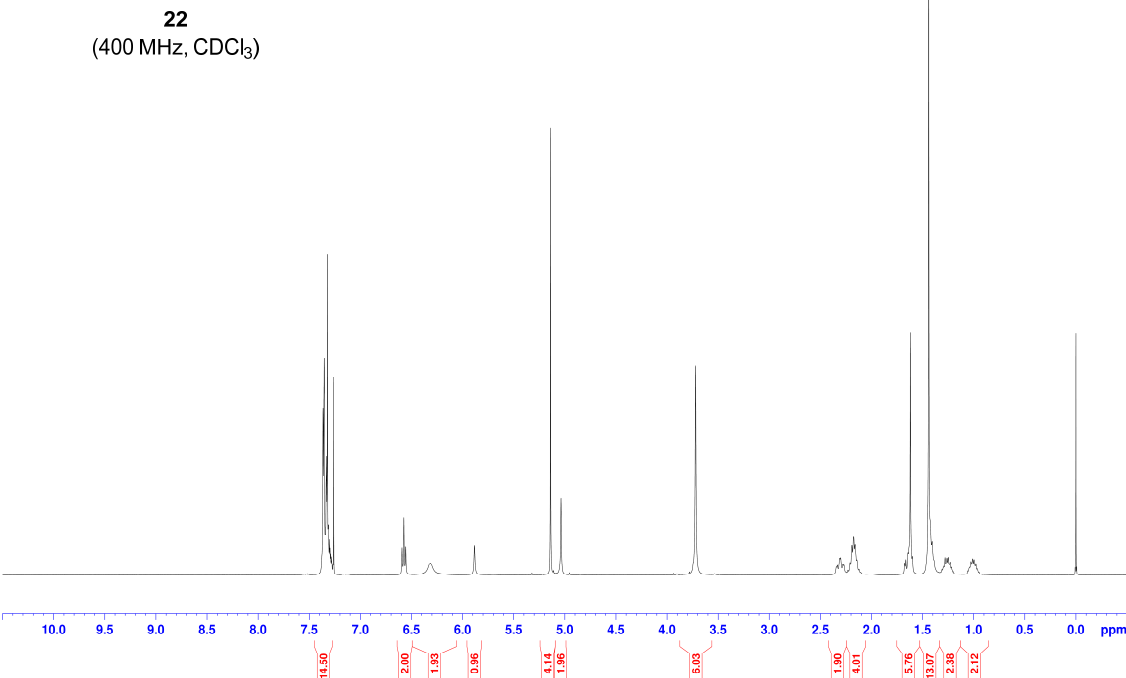


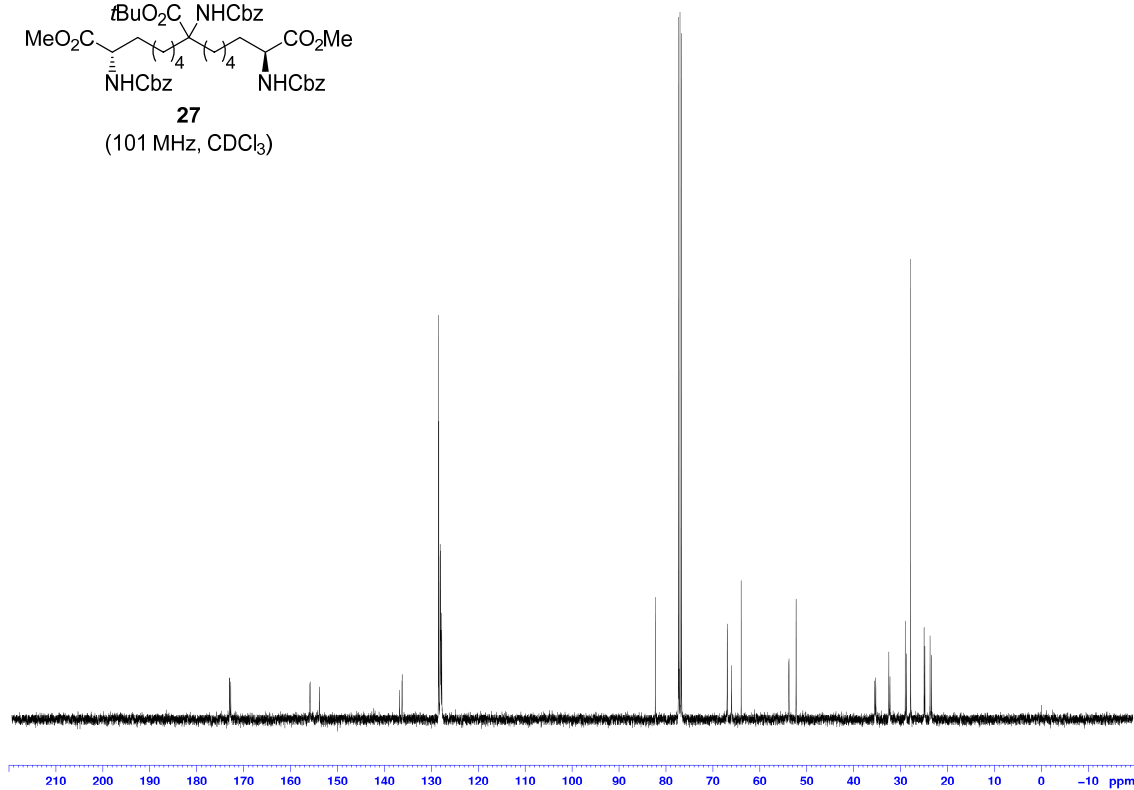
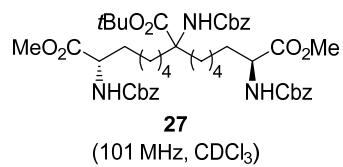
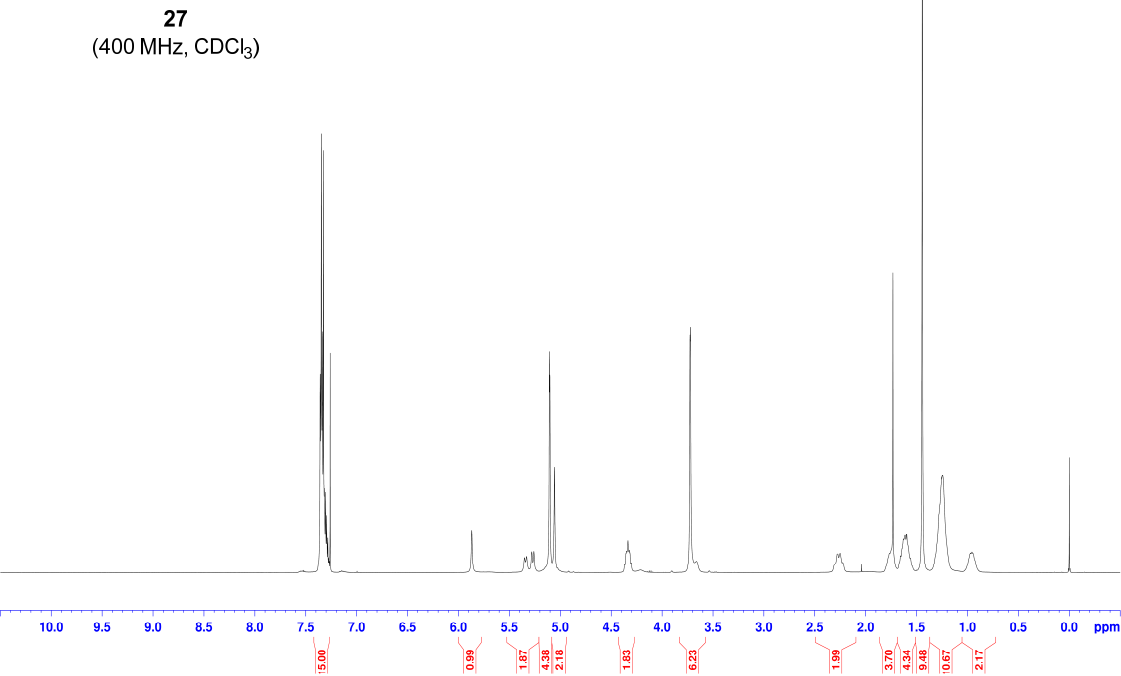
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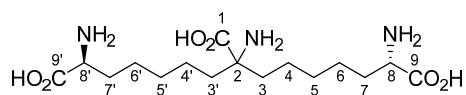
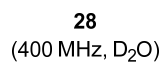


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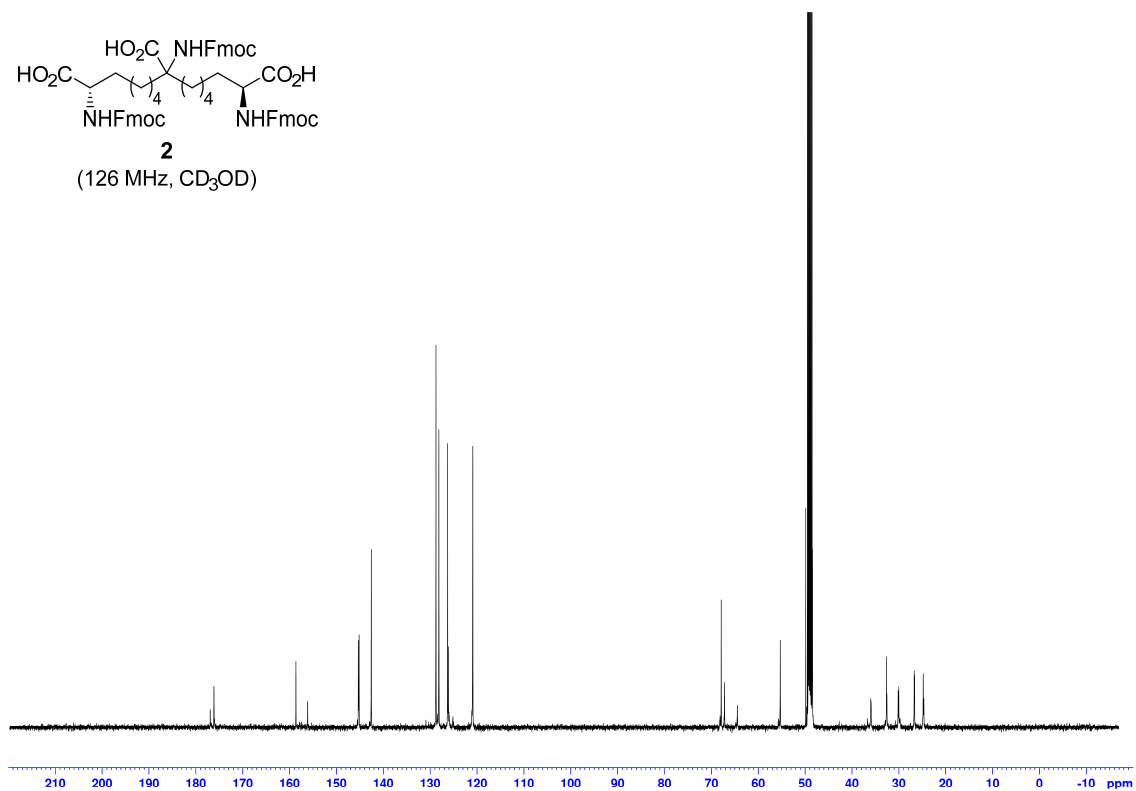
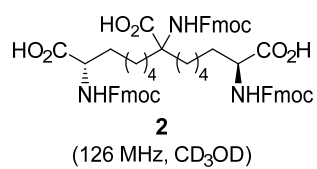
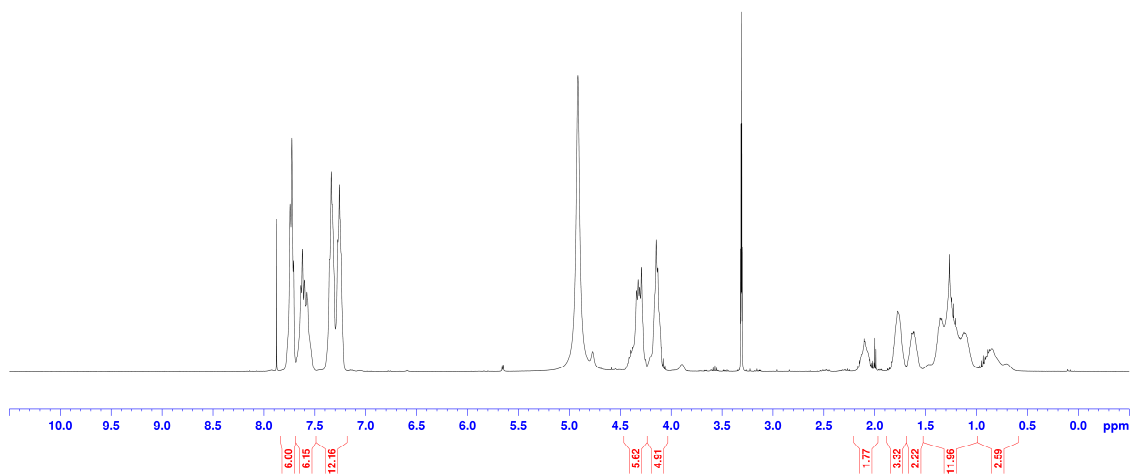
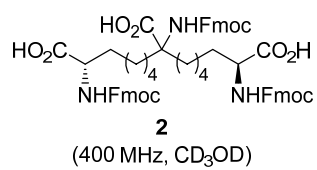




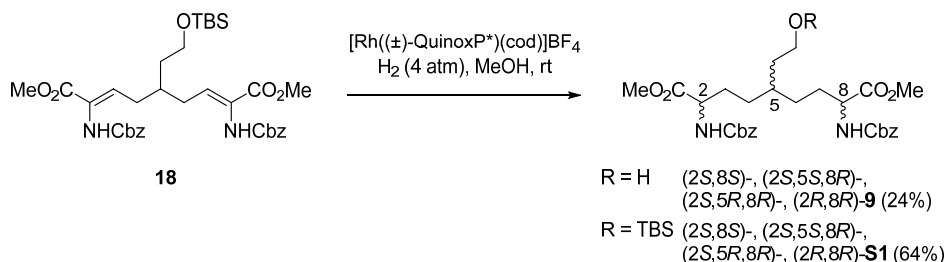


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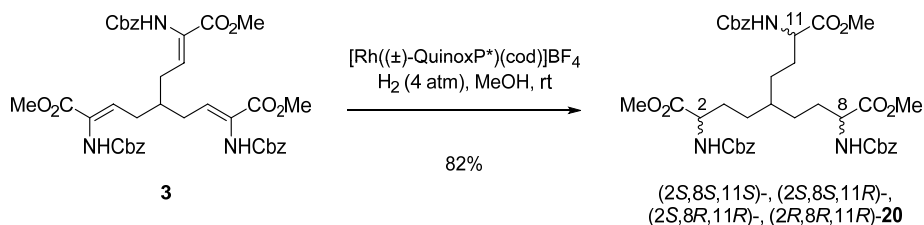




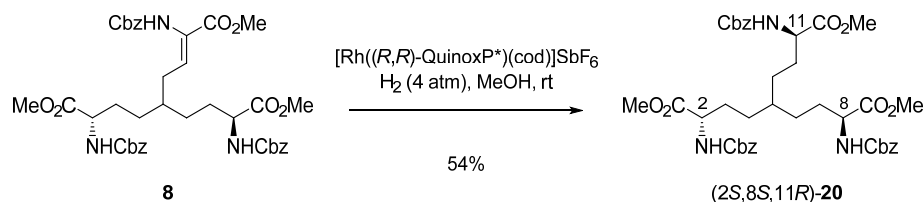
II. Experimental procedure of synthesis of stereoisomers of 9, 20, and 27



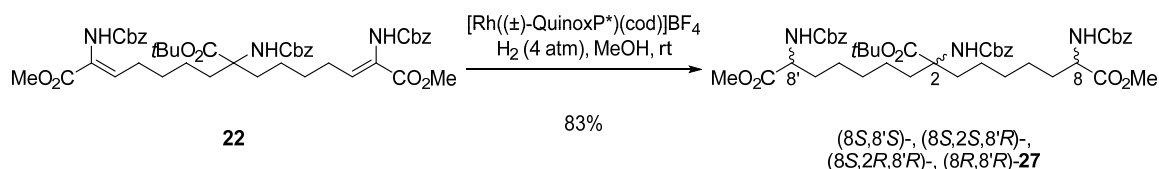
A solution of $[\text{Rh}(\text{cod})_2]\text{BF}_4$ (4.0 mg, 9.9 μmol), (*S,S*)-QuinoxP* (2.2 mg, 6.6 μmol) and (*R,R*)-QuinoxP* (2.2 mg, 6.6 μmol) in degassed MeOH (0.5 mL) was stirred vigorously at room temperature under nitrogen atmosphere. After 40 minutes, additional degassed MeOH (2.5 mL) was added to the mixture. Compound **18** (97.5 mg, 146 μmol) was charged in a hydrogenation bottle. After the bottle was evacuated and filled with hydrogen several times, the catalyst solution was added. The hydrogen pressure was adjusted to 4 atm, and the mixture was stirred vigorously overnight at room temperature. The reaction mixture was concentrated, and the crude product was purified by silica gel column chromatography (hexane/ethyl acetate = 1/0 to 1/9) to afford a mixture of (2*S*,8*S*)-, (2*S*,5*S*,8*R*)-, (2*S*,5*R*,8*R*)-, (2*R*,8*R*)-**9** (19.5 mg, 24%) and a mixture of (2*S*,8*S*)-, (2*S*,5*S*,8*R*)-, (2*S*,5*R*,8*R*)-, (2*R*,8*R*)-**S1** (63.2 mg, 64%) as colorless oil. ((2*S*,8*S*)-**9**:(2*S*,5*S*,8*R*)-**9** and (2*S*,5*R*,8*R*)-**9**:(2*R*,8*R*)-**9** = 1.0:2.3:1.3)



A solution of $[\text{Rh}(\text{cod})_2]\text{BF}_4$ (1.9 mg, 4.7 μmol), (*S,S*)-QuinoxP* (1.4 mg, 4.2 μmol) and (*R,R*)-QuinoxP* (1.4 mg, 4.2 μmol) in degassed MeOH (0.5 mL) was stirred vigorously at room temperature under nitrogen atmosphere. After 4 h, additional degassed MeOH (1.5 mL) was added to the mixture. Compound **3** (6.5 mg, 8.6 μmol) was charged in a hydrogenation bottle. After the bottle was evacuated and filled with hydrogen several times, the catalyst solution was added. The hydrogen pressure was adjusted to 4 atm, and the mixture was stirred vigorously overnight at room temperature. The reaction mixture was concentrated, and the crude product was purified by silica gel column chromatography (hexane/ethyl acetate = 1/0 to 3/7) to afford a mixture of (2*S*,8*S*,11*S*)-, (2*S*,8*S*,11*R*)-, (2*S*,8*R*,11*R*)-, (2*R*,8*R*,11*R*)-**20** (5.4 mg, 82%) as colorless oil. ((2*S*,8*S*,11*S*)-**20**:(2*S*,8*S*,11*R*)-**20** and (2*S*,8*R*,11*R*)-**20**:(2*R*,8*R*,11*R*)-**20** = 1.0:3.8:0.4)

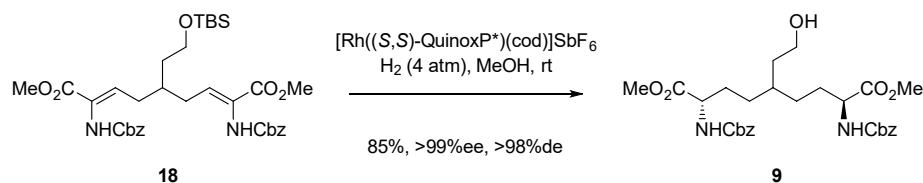


A solution of $[\text{Rh}(\text{cod})_2]\text{SbF}_6$ (2.7 mg, 4.9 μmol) and (R,R) -QuinoxP* (2.9 mg, 8.7 μmol) in degassed MeOH (0.7 mL) was stirred vigorously at room temperature under nitrogen atmosphere. After 50 minutes, additional degassed MeOH (1.3 mL) was added to the mixture. Compound **8** (97.5 mg, 146 μmol) was charged in a hydrogenation bottle. After the bottle was evacuated and filled with hydrogen several times, the catalyst solution was added. The hydrogen pressure was adjusted to 4 atm, and the mixture was stirred vigorously overnight at room temperature. The reaction mixture was concentrated, and the crude product was purified by silica gel column chromatography (hexane/ethyl acetate = 1/0 to 2/3) to afford a mixture of starting material **8** and the product. The mixture was hydrogenated by the same procedure as above using $[\text{Rh}(\text{cod})_2]\text{SbF}_6$ (3.5 mg, 6.3 μmol) and (R,R) -QuinoxP* (3.2 mg, 9.6 μmol). After completion of the reaction, the reaction mixture was concentrated, and the crude product was purified by silica gel column chromatography (hexane/ethyl acetate = 1/0 to 2/3) to afford (2S,8S,11R)-**20** (44.4 mg, 54%) as colorless oil.

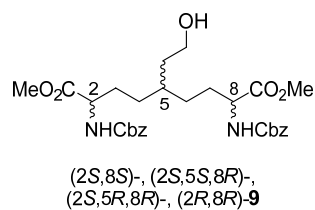
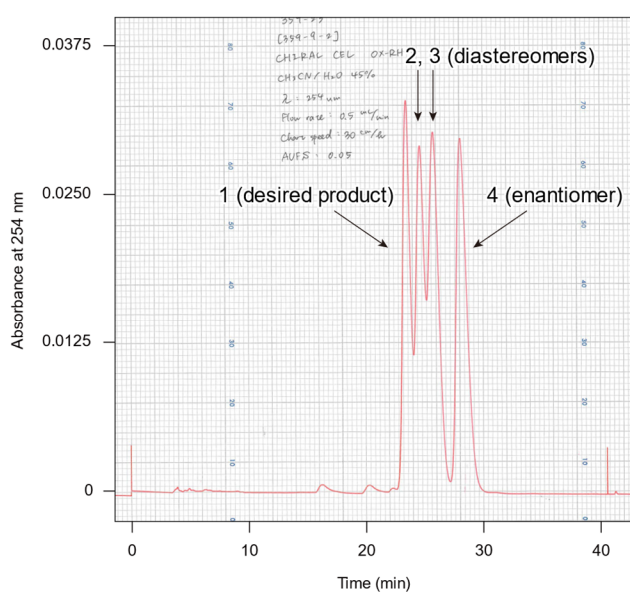


A solution of $[\text{Rh}(\text{cod})_2]\text{BF}_4$ (2.2 mg, 5.4 μmol), (S,S) -QuinoxP* (1.3 mg, 3.9 μmol) and (R,R) -QuinoxP* (1.3 mg, 3.9 μmol) in degassed MeOH (0.5 mL) was stirred vigorously at room temperature under nitrogen atmosphere. After 60 minutes, additional degassed MeOH (0.5 mL) was added to the mixture. Compound **22** (43.0 mg, 50.9 μmol) was charged in a hydrogenation bottle. After the bottle was evacuated and filled with hydrogen several times, the catalyst solution was added. The hydrogen pressure was adjusted to 4 atm, and the mixture was stirred vigorously overnight at room temperature. The reaction mixture was concentrated, and the crude product was purified by silica gel column chromatography (hexane/ethyl acetate = 1/0 to 1/1) to afford a mixture of (8S,8'S)-, (8S,2S,8'R)-, (8S,2R,8'R)-, (8R,8'R)-**27** (36.0 mg, 83%) as colorless oil. ((8S,8'S)-**27**:(8S,2S,8'R)-**27** and (8S,2R,8'R)-**27**:(8R,8'R)-**27** = 1.0:2.7:1.7)

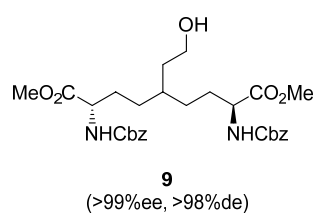
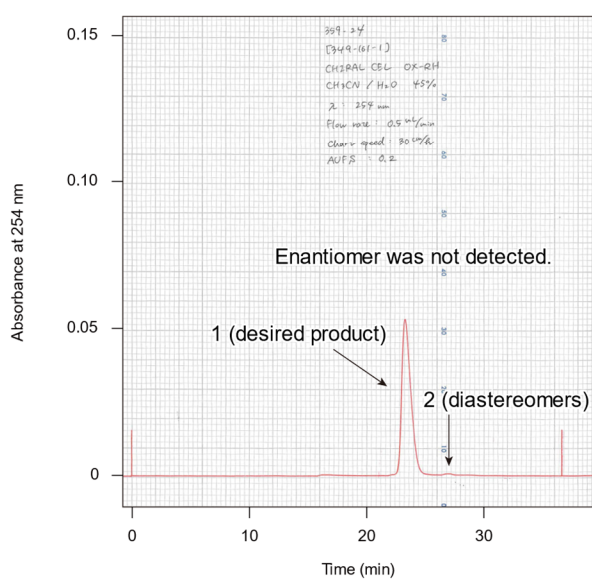
III. Copy of HPLC chart of compounds 9, 20, and 27



Ee and de were calculated from the peak area of each stereoisomer in HPLC (Daicel CHIRAL CEL OX-RH, $\lambda = 254 \text{ nm}$, $\text{CH}_3\text{CN}/\text{H}_2\text{O} = 9/11$, 0.5 mL/minutes) by weighing each peak.

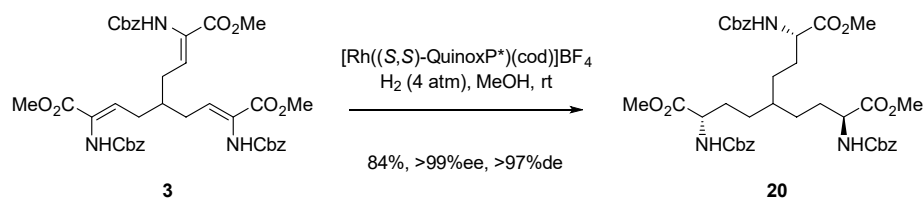


peak No.	ret. time (min)	wight of paper (mg)	wight of paper (%)
1	23.5	39.7	21.8
2, 3	24.6, 25.8	90.3	49.5
4	28.0	52.3	28.7

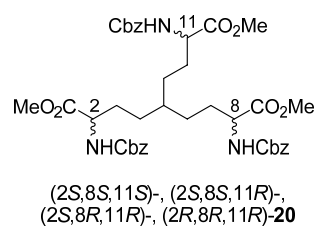
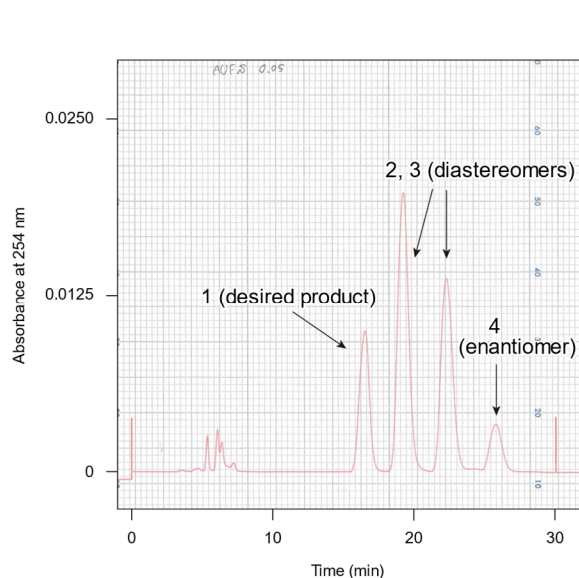


Peak No.	ret. time (min)	wight of paper (mg)	wight of paper (%)
1	23.3	40.1	99.3
2	27.0	0.3	0.7

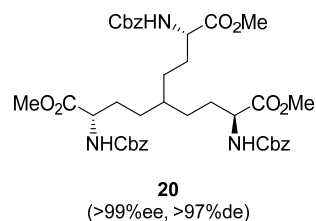
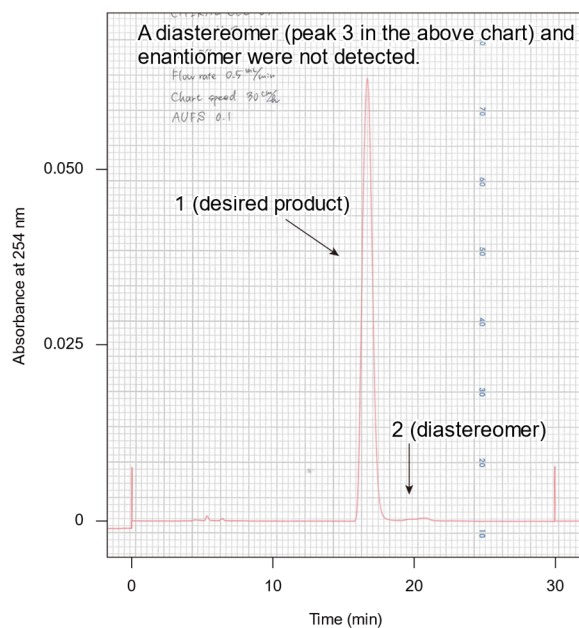
Enantiomer was not detected.



Ee and de were calculated from the peak area of each stereoisomer in HPLC (Daicel CHIRAL CEL OX-RH, $\lambda = 254 \text{ nm}$, $\text{CH}_3\text{CN}/\text{H}_2\text{O} = 3/2$, 0.5 mL/minutes) by weighing each peak.

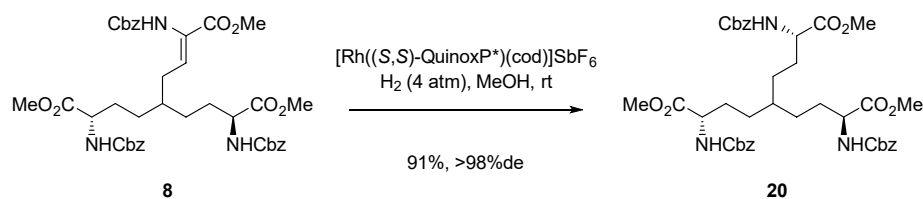


peak No.	ret. time (min)	wight of paper (mg)	wight of paper (%)
1	16.6	13.6	19.3
2, 3	19.3, 22.4	51.3	72.8
4	25.8	5.6	7.9

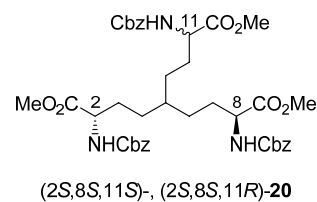
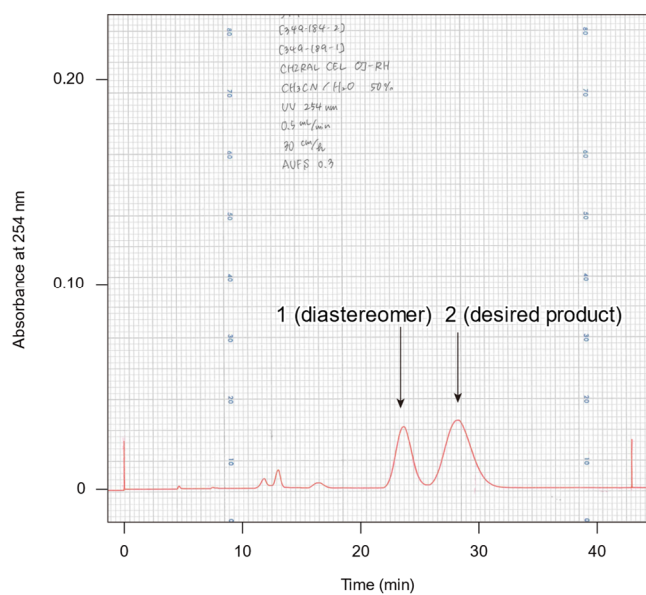


Peak No.	ret. time (min)	wight of paper (mg)	wight of paper (%)
1	16.7	87.9	98.8
2	19.6	1.1	1.2

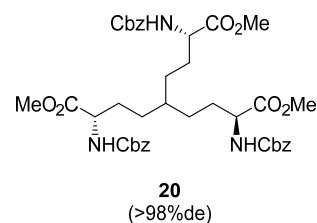
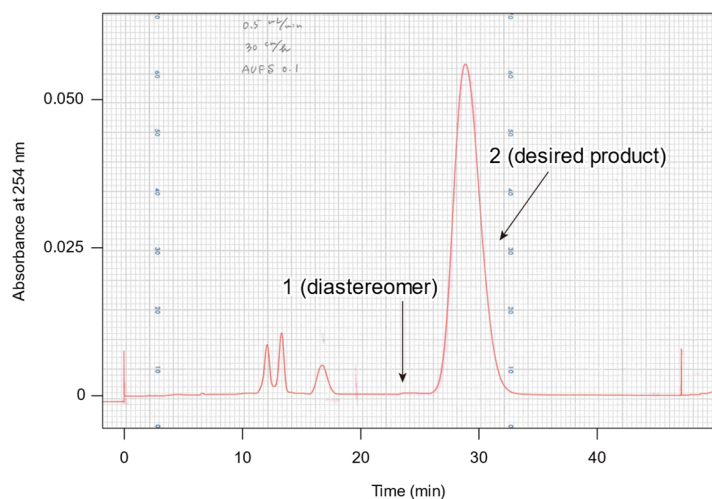
A diastereomer (peak 3 in the above chart) and enantiomer were not detected.



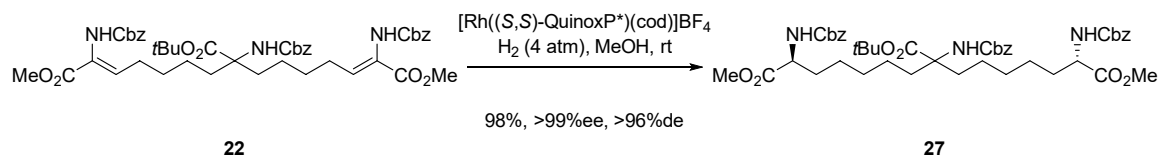
De was calculated from the peak area of each stereoisomer in HPLC (Daicel CHIRAL CEL OJ-RH, $\lambda = 254$ nm, $\text{CH}_3\text{CN}/\text{H}_2\text{O} = 1/1$, 0.5 mL/minutes) by weighing each peak.



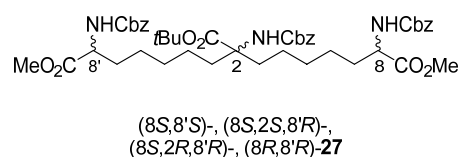
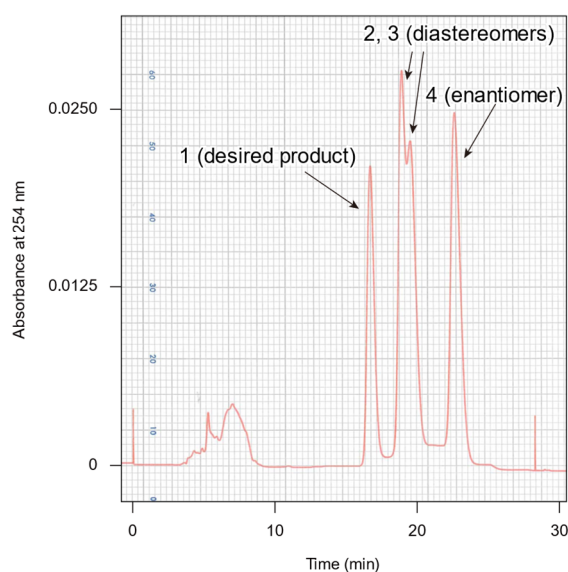
peak No.	ret. time (min)	wight of paper (mg)	wight of paper (%)
1	23.6	13.2	35.8
2	28.2	23.7	64.2



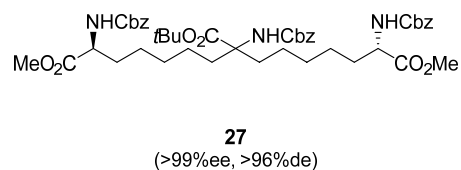
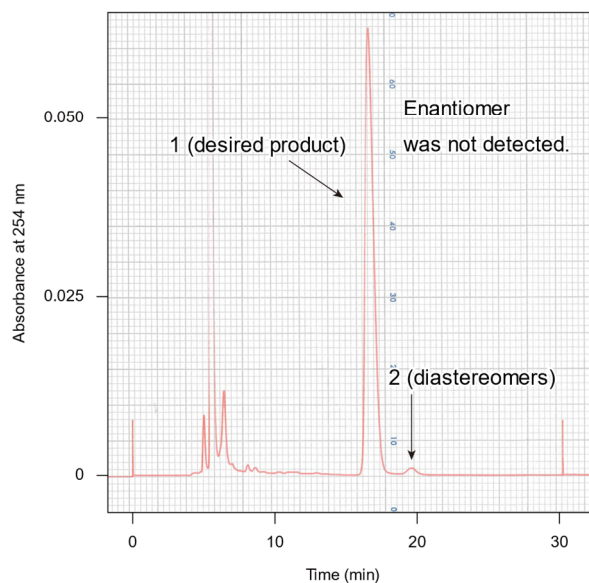
peak No.	ret. time (min)	wight of paper (mg)	wight of paper (%)
1	24.2	0.7	0.6
2	29.0	124.3	99.4



Ee and de were calculated from the peak area of each stereoisomer in HPLC (Daicel CHIRAL CEL OX-RH, $\lambda = 254 \text{ nm}$, $\text{CH}_3\text{CN}/\text{H}_2\text{O} = 7/3$, 0.5 mL/minutes) by weighing each peak.



peak No.	ret. time (min)	wight of paper (mg)	wight of paper (%)
1	16.7	21.3	18.6
2, 3	18.9, 19.6	56.8	49.7
4	22.6	36.2	31.7



peak No.	ret. time (min)	wight of paper (mg)	wight of paper (%)
1	16.6	75.4	98.2
2	19.6	1.4	1.8

Enantiomer was not detected.