Electronic Supplementary Material (ESI) for Organic & Biomolecular Chemistry.

Supporting Information

Asymmetric Synthesis of Vinylogous β-Amino Acids and Their Incorporation Into Mixed Backbone Oligomers

Hao Wu[†], Hongchan An[†], Shuting (Cynthia) Mo, and Thomas Kodadek*

Department of Chemistry, The Scripps Research Institute, 130 Scripps Way, Jupiter, FL 33458.

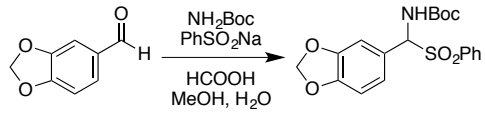
*Corresponding author (Kodadek@scripps.edu)

[†]These authors contributed equally to the study

General Information

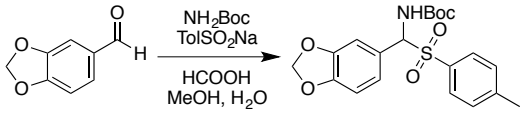
Fmoc-protected amino acids were purchased from AnaSpec (Fremont, CA). Synthetic resins were purchased from Rapp Polymere GmbH (Germany) or AnaSpec (Fremont, CA). All other reagents were purchased from Sigma-Aldrich or Alfa Aesar, unless otherwise specified. All the chemical reagents and solvents from commercial sources were used without further purification. 5 mL disposable reaction column was used as reaction vessels for solid phase synthesis. HPLC and LC-MS analysis was carried out by Agilent 1100 Series equipped with ZORBAX SB-C18 Rapid Res, 4.6 × 100mm × 3.5μm column, PDA detector and a linear gradient of 5% acetonitrile, 0.05% formic acid/aqueous solution to 95% acetonitrile, 0.05% formic acid/aqueous solution in 1.0 mL/min flow rate, 15 min gradient. MS and MS/MS (MALDI-TOF) were performed on a 4800 Proteomics Analyzer (Applied Biosystems) with α-cyano-4-hydroxycinnamic acid (CHCA) as a matrix. NMR spectra were recorded on a Bruker AM 400 spectrometer (operating at 400 and 101 MHz respectively) in $CDCl_3$ or DMSO-*d6* with 0.03% TMS as an internal standard, unless otherwise specified. Chemical shifts are reported in parts per million (ppm) downfield from TMS. High resolution mass spectra (HRMS) were recorded on a Quadrupole-Orbitrap mass spectrometer with electrospray ionization (Thermo Q Exactive). Melting points (m.p.) were measured on a Stuart SMP40 automatic melting point apparatus.

Synthetic Procedures



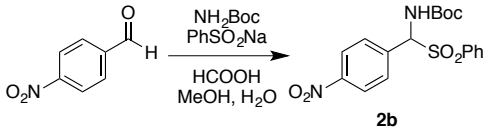
2a

***tert*-butyl (benzo[*d*][1,3]dioxol-5-yl(phenylsulfonyl)methyl)carbamate (2a)**[1]: To a solution of piperonal (1.0 equiv) and *tert*-butyl carbamate (1.0 equiv) in MeOH were added water, benzenesulfinic acid sodium salt (1.0 equiv) and formic acid (5.0 equiv). The reaction temperature was raised to 35 °C and the mixture was stirred overnight. The reaction mixture was filtered in vacuum and washed with hexane to afford powder **2a** as white solid in 64% yield. The powder **2a** was used for the next reaction without further purification: ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.61 (d, *J* = 10.7 Hz, 1H), 7.89 – 7.82 (m, 2H), 7.75 – 7.68 (m, 1H), 7.63 (dd, *J* = 8.4, 6.9 Hz, 2H), 7.31 (d, *J* = 1.7 Hz, 1H), 7.09 (dd, *J* = 8.1, 1.7 Hz, 1H), 6.93 (d, *J* = 8.0 Hz, 1H), 6.06 (s, 2H), 5.95 (d, *J* = 10.7 Hz, 1H), 1.18 (s, 9H).



2a'

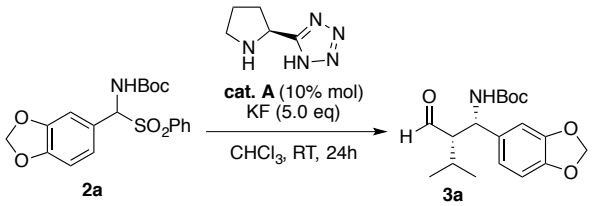
***tert*-butyl (benzo[*d*][1,3]dioxol-5-yl(tosyl)methyl)carbamate (2a').** To a solution of *tert*-butyl carbamate (1.0 equiv) in MeOH were added piperonal (2.0 equiv), water, *p*-toluenesulfinic acid sodium salt (2.5 equiv) and formic acid (2.0 equiv). The reaction mixture was stirred overnight. The reaction mixture was filtered in vacuum and the solid was suspended with diethyl ether and filtered again to afford 59% yield of powder **2a'** as white solid. The powder **2a**' was used for the next reaction without further purification: ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.57 (d, *J* = 10.7 Hz, 1H), 7.72 (d, *J* = 8.2 Hz, 2H), 7.43 (d, *J* = 8.0 Hz, 2H), 7.29 (d, *J* = 1.7 Hz, 1H), 7.07 (dd, *J* = 8.2, 1.7 Hz, 1H), 6.92 (d, *J* = 8.0 Hz, 1H), 6.06 (s, 2H), 5.88 (d, *J* = 10.7 Hz, 1H), 2.38 (s, 3H), 1.18 (s, 9H).



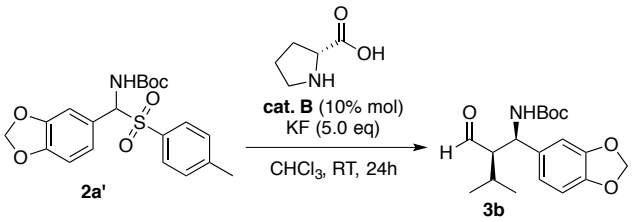
2b

***tert*-butyl ((4-nitrophenyl)(phenylsulfonyl)methyl)carbamate (2b)**[2]: A mixture of *p*-nitrobenzaldehyde (2.0 equiv), *tert*-butyl carbamate (1.0 equiv), and benzenesulfinic acid sodium salt (2.5 equiv) in methanol and water (1:1) heated, until all of the solids were dissolved. Subsequently, formic acid (5.0 equiv) was added into the mixture, stirred at room temperature for 72 h. The resulting precipitate was filtered and washed well with hexane. After drying under vacuum, the product **2b** was obtained as a white solid in 50% yield. ^{1}H-NMR (400 MHz; $CDCl_3$): δ 8.29-8.26 (m, 2H), 7.94 (d, *J* = 7.2 Hz,

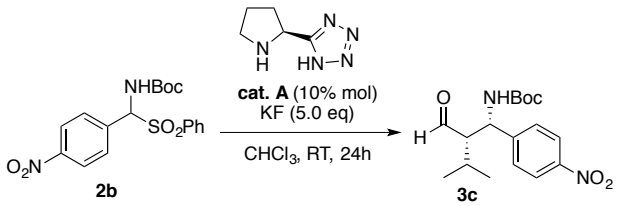
2H), 7.72-7.64 (m, 3H), 7.58 (t, *J* = 7.7 Hz, 2H), 6.04 (d, *J* = 10.7 Hz, 1H), 5.79 (d, *J* = 10.7 Hz, 1H), 1.26 (s, 9H).



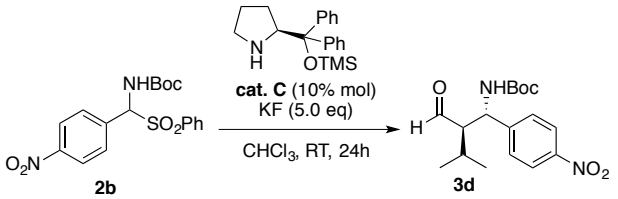
***tert*-butyl ((1*S*,2*S*)-1-(benzo[*d*][1,3]dioxol-5-yl)-2-formyl-3-methylbutyl)carbamate (3a)**: Isovaleraldehyde (2.0 equiv) was added to a solution of proline-derived tetrazole **catalyst A** (0.1 equiv) in chloroform. The reaction mixture was stirred for 5 min and amidosulfone **2a** (1.0 equiv) and potassium fluoride (5.0 equiv) were added successively. The reaction mixture was stirred for 48 h and diluted with dichloromethane. The diluted mixture was flushed through silica pad with 1:1 mixture of diethyl ether and dichloromethane. The solvent was removed *in vacuo* and filtration of the crude mixture triturated with cooled hexane gave 88% yield of the *syn*-Mannich adduct **3a** as white solid, which was used for the next reaction without further purification: ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.43 (d, *J* = 4.2 Hz, 1H), 6.68 – 6.61 (m, 3H), 5.87 (q, *J* = 1.5 Hz, 2H), 4.94 (s, 2H), 2.36 (s, 1H), 2.04 (dd, *J* = 14.1, 7.1 Hz, 1H), 1.34 (s, 9H), 1.05 (d, *J* = 6.9 Hz, 3H), 0.95 (d, *J* = 6.9 Hz, 3H).



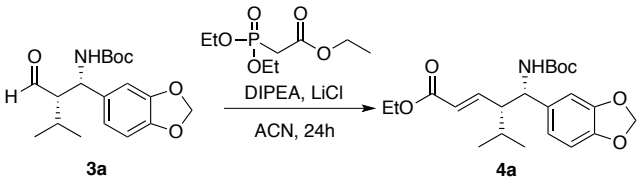
***tert*-butyl ((1*R*,2*R*)-1-(benzo[*d*][1,3]dioxol-5-yl)-2-formyl-3-methylbutyl)carbamate (3b)**: To a solution of amidosulfone **2a'** (1.0 equiv) in chloroform were added isovaleraldehyde (2.0 equiv), potassium fluoride (5.0 equiv) and D-proline (**catalyst B**, 0.1 equiv), successively. The reaction mixture was stirred overnight. The reaction was quenched with water and the mixture was extracted with EtOAc. The organic layer was washed with brine, dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (EtOAc/*n*-hexane) to afford 37% yield of *syn*-Mannich adduct **3b** as white solid: ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.42 (d, *J* = 4.2 Hz, 1H), 6.73 – 6.59 (m, 3H), 5.87 (q, *J* = 1.5 Hz, 2H), 4.93 (s, 2H), 2.35 (s, 1H), 2.03 (s, 1H), 1.33 (s, 9H), 1.04 (d, *J* = 6.9 Hz, 3H), 0.95 (d, *J* = 6.8 Hz, 3H).



***tert*-butyl ((1*S*,2*S*)-2-formyl-3-methyl-1-(4-nitrophenyl)butyl)carbamate (3c)**[3]: To a solution of the **catalyst A** (0.1 equiv) in $CHCl_3$ isovaleraldehyde (2 equiv) was added at room temperature. After 5 min stirring, α-amido sulfone **2b** (1.0 equiv) and KF (5 equiv.) were successively added. The reaction mixture was stirred at room temperature for 24 h. Then the crude reaction mixture was diluted with CH_2Cl_2 and flushed through a plug of silica, using CH_2Cl_2/Et_2O 1/1 as the eluent and extracted with H_2O/Et_2O and the combined organic layers were dried over Na_2SO_4 and concentrated. The residue was purified by flash column chromatography (hexane/Et_2O = 2/1). The compound was isolated as a pale yellow solid with 30% yield. (dr = 250:1, determined by integration of one set of ^{1}H NMR signal (δ_{major} 9.54 ppm - d, δ_{minor} 9.74 ppm - d)). ^{1}H-NMR (400 MHz; CDCl3): δ 9.54 (d, *J* = 3.4 Hz, 1H), 8.18 (d, *J* = 8.9 Hz, 2H), 7.44 (d, *J* = 8.7 Hz, 2H), 5.25 (td, *J* = 40.6, 8.1 Hz, 2H), 2.62 (s, 1H), 1.39 (s, 9H), 1.17 (d, *J* = 6.9 Hz, 3H), 1.02 (d, *J* = 6.9 Hz, 3H).

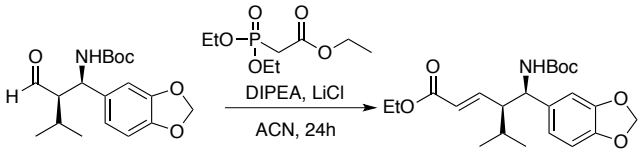


***tert*-butyl ((1*S*,2*R*)-2-formyl-3-methyl-1-(4-nitrophenyl)butyl)carbamate (3d)**[3]: The reaction was carried out following the pervious procedure of **3c**, but using catalyst **C** and ran over 24h at room temperature to furnish the crude product. The titled compound was isolated as a pale yellow solid by column chromatography (hexane/Et_2O = 2/1) in 33% yield. ^{1}H-NMR (400 MHz; $CDCl_3$): δ 9.72 (dd, *J* = 2.6, 0.9 Hz, 1H), 8.20-8.16 (m, 2H), 7.47-7.43 (m, 2H), 5.79-5.76 (m, 1H), 5.19-5.16 (m, 1H), 2.05-1.96 (m, 1H), 1.40 (s, 9H), 1.12 (d, *J* = 6.8 Hz, 3H), 1.09 (d, *J* = 6.8 Hz, 3H).

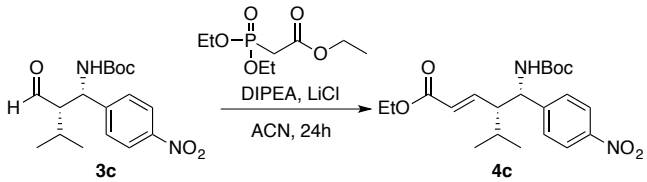


ethyl (*R*,*E*)-4-((*S*)-benzo[*d*][1,3]dioxol-5-yl((*tert*-butoxycarbonyl)amino)methyl)-5-methylhex-2-enoate (4a): Lithium chloride (2.0 equiv) was weighed and charged in round-bottom flask inside the glovebox and dry acetonitrile was added. Triethyl phosphonoacetate (2.0 equiv) and *N*,*N*-diisopropylethylamine (1.8 equiv) were added

successively. Mannich adduct **3a** (1.0 equiv) dissolved in dry acetonitrile and dry dichloromethane was added to the reaction mixture for solubility issue and the mixture was stirred for 48 h. The reaction was quenched with saturated ammonium chloride aqueous solution and the mixture was extracted with EtOAc. The organic layer was washed with brine, dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (EtOAc/*n*-hexane) to afford 91% of HWE-adduct **4a** as white solid with a small amount of remained Mannich-adduct which could be removed after hydrolysis of the HWE-adduct: ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.78 – 6.53 (m, 4H), 5.94 (s, 2H), 5.70 (d, *J* = 15.5 Hz, 1H), 4.80 (s, 2H), 4.21 – 4.14 (m, 2H), 2.28 (d, *J* = 15.4 Hz, 1H), 1.88 (s, 1H), 1.41 (s, 9H), 1.27 (q, *J* = 7.3 Hz, 3H), 1.03 (dd, *J* = 6.7, 3.7 Hz, 3H), 0.83 (d, *J* = 6.5 Hz, 3H).

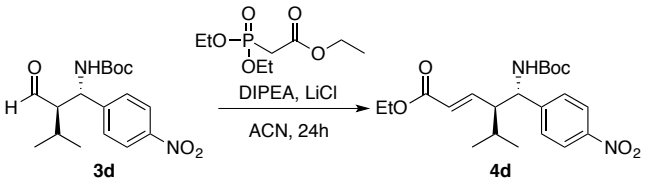


ethyl (*S*,*E*)-4-((*R*)-benzo[*d*][1,3]dioxol-5-yl((*tert*-butoxycarbonyl)amino)methyl)-5-methylhex-2-enoate (4b): Lithium chloride (2.0 equiv) was weighed and charged in round-bottom flask inside the glovebox and dry acetonitrile was added. Triethyl phosphonoacetate (2.0 equiv) and *N*,*N*-diisopropylethylamine (1.8 equiv) were added successively. Mannich adduct **3b** (1.0 equiv) dissolved in dry acetonitrile and dry dichloromethane was added to the reaction mixture and the mixture was stirred for 72 h. The reaction was quenched with saturated ammonium chloride aqueous solution and the mixture was extracted with EtOAc. The organic layer was washed with brine, dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (EtOAc/*n*-hexane) to afford 85% of HWE-adduct **4b** as white solid with a small amount of remained Mannich-adduct which could be removed after hydrolysis of the HWE-adduct: ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.77 – 6.55 (m, 4H), 5.94 (s, 2H), 5.70 (d, *J* = 15.5 Hz, 1H), 4.80 (s, 2H), 4.22 – 4.14 (m, 2H), 2.28 (d, *J* = 15.2 Hz, 1H), 1.88 (s, 1H), 1.41 (s, 9H), 1.27 (q, *J* = 7.3 Hz, 3H), 1.05 – 1.02 (m, 3H), 0.83 (d, *J* = 6.8 Hz, 3H).

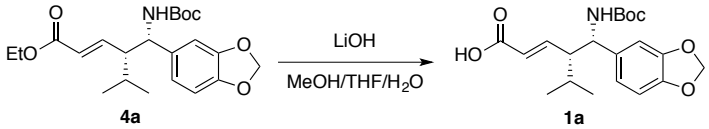


ethyl (*R*,*E*)-4-((*S*)-((*tert*-butoxycarbonyl)amino)(4-nitrophenyl)methyl)-5-methylhex-2-enoate (4c): The reactions were carried out under air and moisture free condition. Basic procedure was adopted from previous literature[4]. To a stirred suspension of LiCl

(2.0 equiv) in dry acetonitrile at room temperature, was added phosphonate (2.0 equiv), and DIPEA (1.8 equiv). After 30 min, compound **3c** (1.0 equiv) was added. The progress of the reaction was monitored by TLC. The flash chromatography (hexane/Et_2O = 2.5/1) was performed to obtain pure product **4c** in 80% yield. ^{1}H-NMR (400 MHz; $CDCl_3$): δ 8.19-8.15 (m, 2H), 7.35 (d, *J* = 8.6 Hz, 2H), 6.51 (dd, *J* = 15.6, 10.8 Hz, 1H), 5.67 (d, *J* = 15.6 Hz, 1H), 4.18-4.10 (m, 2H), 1.45 (s, 6H), 1.39 (s, 7H), 1.26 (t, *J* = 7.1 Hz, 4H), 1.04 (d, *J* = 7.2 Hz, 3H), 0.87 (d, *J* = 6.7 Hz, 3H).



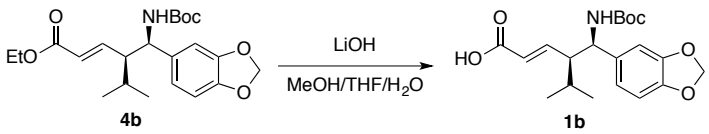
ethyl (*S*,*E*)-4-((*S*)-((*tert*-butoxycarbonyl)amino)(4-nitrophenyl)methyl)-5-methylhex-2-enoate (4d): The reactions were carried out under the same condition as **4c**, but aldehyde **3c** was used as starting material. The flash chromatography (hexane/Et_2O = 2.5/1) was performed to obtain pure product **4d** in 75% yield. ^{1}H-NMR (400 MHz; $CDCl_3$): δ 8.20-8.18 (m, 2H), 7.40-7.38 (m, 2H), 6.76 (dd, *J* = 15.6, 10.3 Hz, 1H), 5.68 (d, *J* = 15.5 Hz, 1H), 4.91 (d, *J* = 7.5 Hz, 2H), 4.19 (q, *J* = 7.2 Hz, 2H), 1.37 (s, 9H), 1.28 (t, *J* = 7.1 Hz, 4H), 0.89 (t, *J* = 6.0 Hz, 4H).



(*R*,*E*)-4-((*S*)-benzo[*d*][1,3]dioxol-5-yl((*tert*-butoxycarbonyl)amino)methyl)-5-methylhex-2-enoic acid (1a): To a solution of HWE-adduct **4a** (1.0 equiv) in tetrahydrofuran, methanol and water (2:2:1) was added lithium hydroxide monohydrate (2.0 equiv). The reaction mixture was stirred for 48 h. The reaction was quenched with saturated ammonium chloride aqueous solution and the mixture was extracted with EtOAc. The organic layer was washed with brine, dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (EtOAc/*n*-hexane) to afford 60% of vinylogous beta amino acid **1a** as white solid: ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.77 – 6.61 (m, 4H), 5.94 (s, 2H), 5.70 (d, *J* = 15.6 Hz, 1H), 4. 93 – 4.54 (m, 2H), 2.31 (q, *J* = 7.9 Hz, 1H), 1.88 – 1.75 (m, 1H), 1.41 (s, 9H), 1.02 (d, *J* = 6.6 Hz, 3H), 0.84 (d, *J* = 6.8 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 170.4, 154.9, 149.4, 147.8, 146.8, 133.9, 123.8, 120.8, 108.2, 107.5, 101.0, 79.8, 55.2, 54.9, 28.4, 21.5, 19.0

Retention time 10.324 min, 97.8% purity, detected at 254 nm. HRMS (ESI+) m/z: $[2M+H]^+$ Calcd for 755.3749; Found 755.3752. (ESI-) m/z: $[M-H]^-$ Calcd for 376.1765; Found 376.1766. $[2M-H]^-$ Calcd for 753.3603; Found 753.3613. m.p. = 81.0 – 83.0 °C.

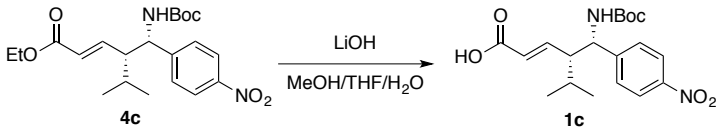


4b **1b**

(*S*,*E*)-4-((*R*)-benzo[*d*][1,3]dioxol-5-yl((*tert*-butoxycarbonyl)amino)methyl)-5-methylhex-2-enoic acid (1b): To a solution of HWE-adduct **4b** (1.0 equiv) in tetrahydrofuran, methanol and water (2:2:1) was added lithium hydroxide monohydrate (2.0 equiv). The reaction mixture was stirred for 48 h. The reaction was quenched with saturated ammonium chloride aqueous solution and the mixture was extracted with EtOAc. The organic layer was washed with brine, dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (EtOAc/*n*-hexane) to afford 63% of vinylogous beta amino acid **1b** as white solid: ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.77 – 6.58 (m, 4H), 5.93 (s, 2H), 5.69 (d, *J* = 15.6 Hz, 1H), 4.93 – 4.54 (m, 2H), 2.38 – 2.25 (m, 1H), 1.91 – 1.72 (m, 1H), 1.40 (s, 9H), 1.05 – 0.98 (m, 3H), 0.83 (d, *J* = 6.8 Hz, 3H).

^{13}C NMR (101 MHz; $CDCl_3$): δ 170.4, 154.9, 149.4, 147.8, 146.8, 134.0, 123.8, 120.8, 108.2, 107.5, 101.0, 79.8, 55.2, 54.9, 28.4, 21.5, 19.0

Retention time 10.327 min, 98.4% purity, detected at 254 nm.HRMS (ESI+) m/z: $[2M+H]^+$ Calcd for 755.3749; Found 755.3749. (ESI-) m/z: $[M-H]^-$ Calcd for 376.1765; Found 376.1767. $[2M-H]^-$ Calcd for 753.3603; Found 753.3613. m.p. = 86.0 – 88.0 °C



4c **1c**

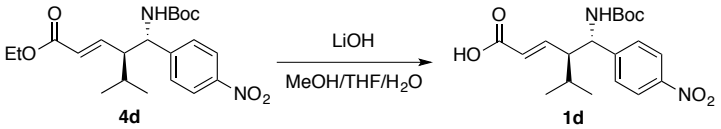
(*R*,*E*)-4-((*S*)-((*tert*-butoxycarbonyl)amino)(4-nitrophenyl)methyl)-5-methylhex-2-enoic acid (1c): Same procedure as above mentioned with LiOH mediated hydrolysis. 90% yield of crude material was used without further purification. ^{1}H-NMR (400 MHz; $CDCl_3$): δ 8.19-8.15 (m, 2H), 7.35 (d, *J* = 8.7 Hz, 2H), 6.51 (dd, *J* = 15.6, 10.8 Hz, 1H), 5.68 (d, *J* = 15.6 Hz, 1H), 2.33-2.30 (m, 1H), 1.86-1.81 (m, 1H), 1.39 (s, 9H), 1.05 (d, *J* = 6.7 Hz, 3H), 0.87 (d, *J* = 6.8 Hz, 3H).

For detailed characterization, the compound was purified by flash column chromatography on silica gel (EtOAc/*n*-hexane) to afford 85% of vinylogous beta amino acid **1c** as light yellow solid. Retention time 10.432 min, 97.8% purity, detected at 254 nm.

^{1}H NMR (400 MHz; DMSO-*d6*): δ 12.10 (br, 1H), 8.14 (d, *J* = 8.6, 2H), 7.69 (d, *J* = 9.1, 1H), 7.54 (d, *J* = 8.7, 2H), 6.46 (dd, *J* = 15.5, 10.8, 1H), 5.31 (d, *J* = 15.5, 1H), 4.75 (t, *J* = 10.0, 1H), 3.37 (br, 1H), 2.15 (dtt, *J* = 13.6, 6.8, 3.4, 1H), 1.34 (s, 9H), 0.85 (dd, *J* = 10.3, 7.0, 6H).

^{13}C NMR (101 MHz; 25 °C, DMSO-*d6*): δ 166.2, 155.0, 150.9, 146.4, 145.0, 128.6, 125.3, 123.3, 78.2, 54.9, 52.5, 28.2, 27.5, 21.4, 15.9.

HRMS (ESI+) m/z: $[2M+H]^+$ Calcd for 757.3655; Found 757.3652. (ESI-) m/z: $[M-H]^-$ Calcd for 377.1718; Found 376.1718. $[2M-H]^-$ Calcd for 755.3509; Found 755.3516. m.p. = 120.6 – 122.6 °C.



(S,E)-4-((S)-((tert-butoxycarbonyl)amino)(4-nitrophenyl)methyl)-5-methylhex-2-enoic acid (1d): Same procedure as above mentioned with LiOH mediated hydrolysis. 90% yield of crude material was used without further purification. ^{1}H-NMR (400 MHz; $CDCl_3$): δ 8.20 (d, *J* = 8.4 Hz, 2H), 7.40 (d, *J* = 8.4 Hz, 2H), 6.92 (dd, *J* = 26.9, 15.7 Hz, 1H), 5.69 (d, *J* = 15.5 Hz, 1H), 2.28 (s, 1H), 1.59 (dq, *J* = 13.0, 6.5 Hz, 1H), 1.28 (s, 9H), 0.93 (d, *J* = 6.5 Hz, 3H), 0.90 (d, *J* = 6.8 Hz, 3H).

For detailed characterization, the compound was purified by flash column chromatography on silica gel (EtOAc/*n*-hexane) to afford 80% of vinylogous beta amino acid **1d** as light yellow solid. Retention time 10.623 min, 95.7% purity, detected at 254 nm.
^{1}H NMR (400 MHz; DMSO-*d6*): δ 8.19 (d, *J* = 8.4, 2H), 7.61-7.53 (m, 3H), 6.74 (dd, *J* = 15.5, 10.3, 1H), 5.64 (d, *J* = 15.5, 1H), 4.81 (t, *J* = 8.9, 1H), 2.46 (tt, *J* = 9.3, 4.5, 1H), 1.34 (d, *J* = 15.3, 9H), 1.23 (d, *J* = 4.6, 1H), 0.80 (d, *J* = 6.7, 6H)
13-C NMR (101 MHz; rt, DMSO-*d6*): δ 166.6, 155.5, 155.1, 150.2, 146.5, 145.6, 128.3, 125.8, 123.5, 113.9, 97.2, 78.2, 77.0, 65.7, 55.1, 53.6, 33.2, 28.20, 28.13, 27.7, 23.3, 21.3, 17.3, 3.4

^{13}C NMR (101 MHz; rt, $CDCl_3$): δ 169.9 (minor), 169.5, 158.0 (minor), 157.4, 155.1, 147.3, 127.8, 123.87 (minor), 123.76, 108.0, 82.0, 80.55 (minor), 80.42, 67.8, 57.2, 55.10 (minor), 54.97, 29.2, 28.30 (minor), 28.23, 24.0, 21.5, 18.2

^{13}C NMR (101 MHz; rt, DMSO-*d6*): δ 166.6, 155.5, 155.1, 150.2, 146.5, 145.6, 128.3, 125.8, 123.5, 113.9, 97.2, 78.2, 77.0, 65.7, 55.1, 53.6, 33.2, 28.20, 28.13, 27.7, 23.3, 21.3, 17.3, 3.4

^{13}C NMR (101 MHz; 100 °C, DMSO-*d6*): δ 165.8, 154.5, 149.8, 146.4, 144.6, 127.9, 125.3, 122.7, 77.9, 55.2, 53.1, 27.76, 27.70, 27.3, 20.7, 17.1

HRMS (ESI+) m/z: $[2M+H]^+$ Calcd for 757.3655; Found 757.3654. (ESI-) m/z: $[M-H]^-$ Calcd for 377.1718; Found 376.1718. $[2M-H]^-$ Calcd for 755.3509; Found 755.3516. m.p. = 121.7 – 123.9 °C.

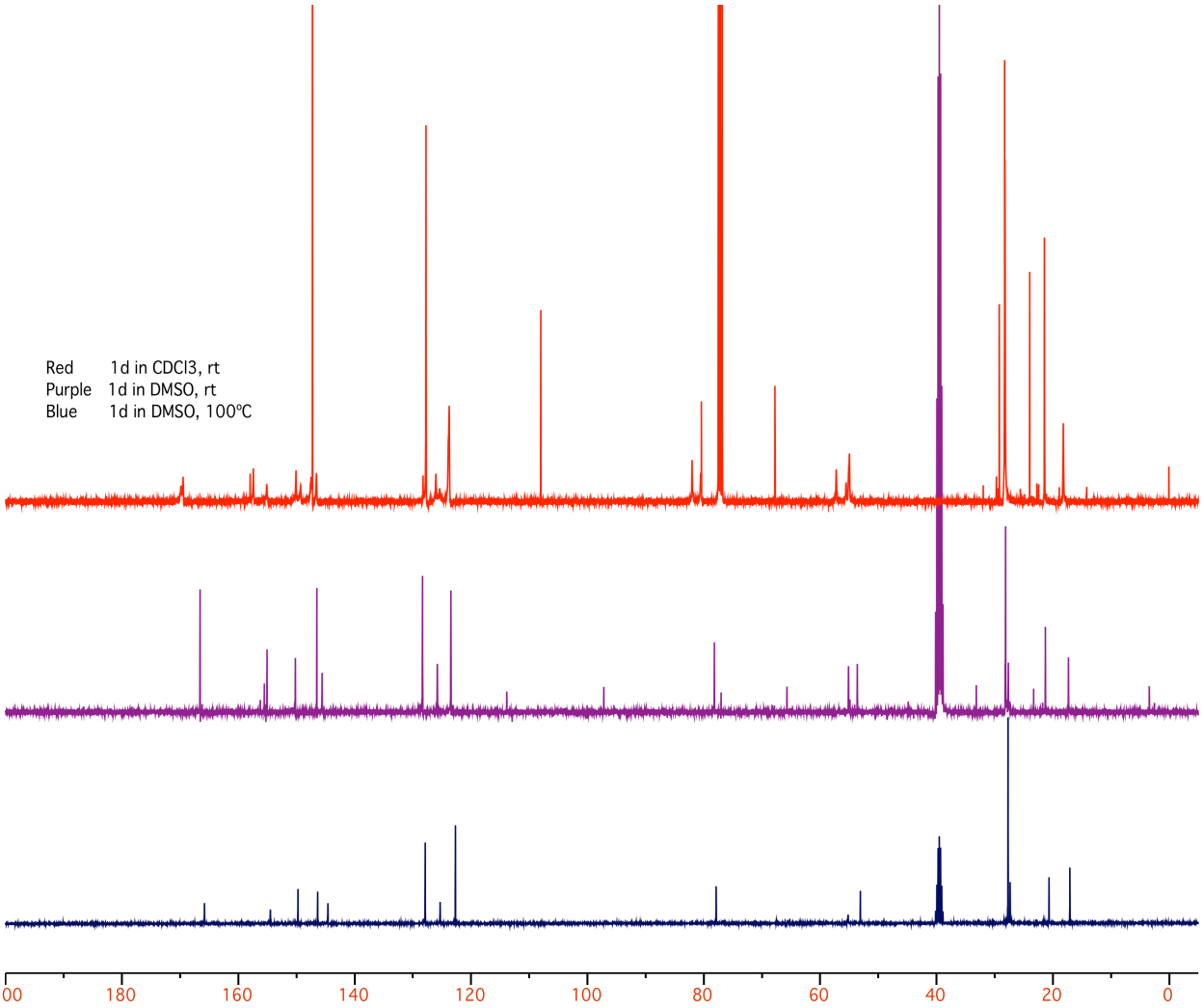
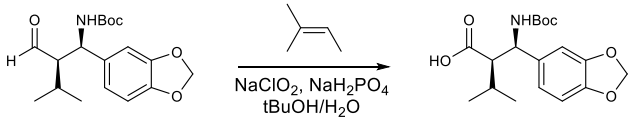


Fig. S1 *Overlaid 13C spectrum for 1d in $CDCl_3$ (rt, shown in red), DMSO-d6 (rt, shown in purple) and DMSO-d6 (100 °C, shown in blue)*



3b **5b**

(*R*)-2-((*R*)-benzo[*d*][1,3]dioxol-5-yl((tert-butoxycarbonyl)amino)methyl)-3-methylbutanoic acid (5b): To a solution of *syn*-Mannich adduct **3b** (204 mg, 0.61 mmol) in *tert*-butanol (5 mL) and water (1.0 mL) were added sodium chlorite (234 mg, 2.01 mmol) and sodium phosphate monobasic (125 mg, 1.03 mmol). To the reaction mixture was added 2-methyl-2-butene (2.10 mL of 2.0 M solution in THF, 4.20 mmol) and the mixture was stirred for 4 h. The reaction mixture was extracted with EtOAc. The organic layer was washed with brine, dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (EtOAc/*n*-hexane) to afford 177 mg (83%) of beta amino acid **5** as white solid: ^{1}H