Hetero-Diels-Alder Synthesis of 3-Hydroxypyridines: Access to the Nosiheptide Core

Jin-Yong Lu[†] and Hans-Dieter Arndt^{*, †, ‡}

[†]*Max-Planck-Institut für molekulare Physiologie, Otto-Hahn-Str. 11, D-44227 Dortmund, Germany, and* [‡]*Universität Dortmund, Fachbereich Chemie, Otto-Hahn-Str. 6, D-44221 Dortmund, Germany*

hans-dieter.arndt@mpi-dortmund.mg.de

Supporting Information

Table of contents

Table of contents	S1
General methods	S2
Preparation and characterization of 5g , 6c , 6d , 11 , 21 , 22	S3-S9
Enantiomeric excess determination of building block 23 and 25a	S9-S14
References	S14
¹ H NMR spectra for compounds 5-25	S16-S29

General methods

All solvents, when not purchased in suitable purity or dryness, were distilled using standard methods.¹ Deionized water was used for all experiments. Thin Layer Chromatography(TLC) was carried out on Merck precoated silica gel plates (60F-254) using ultraviolet light irradiation at 254 nm or the KMnO₄ solution (KMnO₄ 1 g, K₂CO₃ 6.6 g, 5% NaOH solution 1.7 mL, H₂O 100 mL) as staining reagent. Silica gel chromatography was performed using silica gel from J. T. Baker or Merck (particle size 40-60µm) under approximately 0.5 bar pressure. ¹H- and ¹³C-NMR spectra were recorded using a Varian Mercury 400 spectrometer (400 MHz (¹H) and 100.6 (¹³C)). Chemical shifts are expressed in parts per million (ppm) and the spectra are calibrated to residual solvent signals of CDCl₃ (7.26 ppm and 77.0 ppm), CD₃CN (1.94 ppm and 1.24 ppm), DMSO (2.50 ppm and 39.43 ppm). Coupling constants are given in Hertz (Hz) and the following notations indicate the multiplicity of the signals: s (singlet), d (doublet), t (triplet), q (quartet), m (multiple), br (broad signal).

Matrix assisted laser desorption ionization time-of-flight (MALDI-TOF) measurements were carried out with Voyager-DE Pro Biospectrometry. Workstation from PerSeptive Biosystems using 2,5-dihydrobenzoic acid as matrix (unless stated otherwise). High resolution mass spectra (HRMS, 70 ev) were measured on a Jeol SX 102 spectrometer by using electron impact (EI), fast atom bombardment (FAB) techniques with *m*-nitrobenzylalcohol as a matrix. Calculated masses were obtained by using the software ChemDraw Ultra (CambridgeSoft Corporation).

Gas chromatography – mass spectrometry (GC-MS) Spectra were obtained from a Hewlett Packard 6890 GC system coupled to a Hewlett Packard 5973 mass selective Detector. A HP 5TA capillary column (0.33 µm x 25 m x 0.2 mm) and helium flow rate of 2 mL/min were used. *Method A*: temperature gradient: 0 min (100°C) → 1 min (100°C) → 6 min (300°C) → 12 min (300°C). *Method B*: temperature gradient: 0 min (50°C) → 2 min (50°C) → 8 min (300°C) → 14 min (300°C).

Fourier transform infrared spectroscopy (FT-IR) spectra were obtained with a Bruker vector 22 spectrometer with a diffuse reflectance head A527 from Spectra Tech (KBr as matrix). The following notations indicate the intensity of the absorption bands: s = strong, m = middle, w = weak, b = broad.

Optical rotations were measured in a Schmidt + Haensch Polartronic HH8 polarimeter at 589 nm. Concentrations are given in g/100mL solvent.

Melting points were determined in a Büchi melting point B-540 apparatus in open capillaries (uncorrected).

All starting material and reagents were from commercial suppliers (Acros, Aldrich, Novabiochem, Fluka) and used without purification, with the following exceptions, which were prepared according to published procedures: oxime **30**, 1-aza-1,3-butadienes **6a** and **6b**, all halogenated alkynes, and bromothiazole **16**.^{2, 3, 4, 5}

1-Phenylprop-2-yn-1-one (**5n**)

To a cooled solution (0°C) of 1-phenyl-2-propyn-1-ol **29** (0.5 g, 3.8 mmol) in dry THF (10 mL) under argon was added dropwise a mixture of IBX (1.27 g, 4.5 mmol) in dry DMSO (10 mL). The solution was allowed warm to room temperature after 2 h and stirred for 1h (TLC control). The mixture was diluted with water (60 mL) and extracted with diethyl ether (4 x 50 mL). The combined extracts were dried over sodium sulfate and evaporated to dryness. Purification by column chromatography on silica gel (EtOAc/cyclohexane = 1 : 10) gave 0.47 g (3.6 mmol, 96%) ketone **5n** as a colorless solid. M. p. = 53-55°C. TLC: R_f = 0.53 (EtOAc/cyclohexane = 1 : 2). GC-MS (method

B): $T_R = 5.12$ min, 130 (M^+). $^1\text{H-NMR}$ (400 MHz, CD_3CN) $\delta = 3.92$ (1H, s, CH), 7.54-7.58 (2H, m, Ar), 7.69-7.72 (1H, m, Ar), 8.13-8.15 (2H, m, Ar). $^{13}\text{C-NMR}$ (100.6 MHz, CD_3CN) $\delta = 80.68$ (CCH), 82.96 (CH), 129.85 (Ar), 130.24 (Ar), 135.63 (Ar), 137.10 (Ar), 178.24 (C(O)Ar). IR (KBr) : $\nu = 3238$ s, 2095 s, 1662 m, 697 s cm^{-1} .

2-Methoxycarbonyl-1,3-bis(triethylsiloxy)-1-aza-1,3-butadiene (6c)

Triethylsilyl triflate (5.68 mL, 25 mmol) was added dropwise to a stirred solution of methyl oximino-acetoacetate **30** (1.81 g, 12.5 mmol) and 2,6-lutidine (5.80 mL, 50 mmol) in dry dichloromethane (15 mL) at 0°C under an argon. The mixture was allowed to warm to room temperature after 1 h and stirred for 12 h. Saturated NaCl solution (40 mL) was added and the mixture was extracted with dichloromethane (3 x 60 mL). The combined organic extracts were dried with Na_2SO_4 , concentrated to dryness and purified by column chromatography on silica gel (EtOAc/cyclohexane = 1 : 12) to give 4.39 g (11.8 mmol, 92%) 1-azadiene **6c** as a colorless oil. TLC: $R_f = 0.84$ (EtOAc/cyclohexane = 1 : 2). GC-MS (method A): $T_R = 7.45$ min, 373 (M^+) (95%), $T_R = 7.39$ min, 373 (M^+) (5%). $^1\text{H-NMR}$ (400 MHz, CDCl_3) $\delta = 0.71$ -0.97 (30H, m, TES), 3.83 (3H, s, COOMe), 4.64 (1H, d, $J = 2.0$, $\text{C}=\text{CH}_2$), 4.67 (1H, d, $J = 2.0$, $\text{C}=\text{CH}_2$). $^{13}\text{C-NMR}$ (100.6 MHz, CDCl_3) $\delta = 4.42$ (C-OSiCH_2), 4.98 (N-OSiCH_2), 6.60 ($\text{C-OSiCH}_2\text{CH}_3$), 6.68 ($\text{N-OSiCH}_2\text{CH}_3$), 52.11 (COOCH_3), 99.63 ($\text{C}=\text{CH}_2$), 148.92 ($\text{C}=\text{CH}_2$), 154.92 (C-COOMe), 164.09 (COOMe). IR (KBr) : $\nu = 2960$ s, 2736 s, 1757 s, 1600 s, 942 s cm^{-1} .

2-(4-Ethoxycarbonyl-thiazole-)-1,3-bis(triethylsiloxy)-1-aza-1,3-butadiene (6d)

A mixture of aminocrotonic thioamide **31** (1.16g, 10 mmol), ethyl bromopyruvate (1.4 mL, 13 mmol), triethylamine (2.07 mL, 15 mmol) and ethanol (5 mL) was heated to reflux for exactly 20 min (TLC control) and cooled quickly to room temperature. Water (100 mL) was added, the solid precipitate was filtered off and recrystallized from isopropanol (5 mL) to give 1.6 g (7.5 mmol, 76%) of thiazole **32** as a yellow solid.

M. p. = 109-110°C (isopropanol). TLC: R_f = 0.17 (EtOAc/cyclohexane = 1 : 2). GC-MS (method B): T_R = 7.21 min, 212 (M^+). NMR: ^1H -NMR (400 MHz, CDCl_3) δ = 1.36-1.39 (3H, t, J = 7.0, $-\text{CH}_2\text{CH}_3$), 1.99 (3H, s, CH_3), 4.33-4.49 (2H, q, J = 7.2, $-\text{CH}_2\text{CH}_3$), 5.18 (1H, s, $\text{CH}=\text{C}$), 6.46 (2H, s, NH_2), 7.70 (1H, s, CH). ^{13}C -NMR (100.6 MHz, CDCl_3) δ = 14.35 (CH_2CH_3), 22.19 (CH_3), 61.0 (CH_2CH_3), 88.33 ($\text{CH}=\text{C}$), 121.16 (CH), 145.97 ($\text{C}-\text{COOEt}$), 149.57 ($\text{C}-\text{NH}_2$), 161.61 ($\text{C}(\text{N})\text{S}$), 168.80 ($\text{COOCH}_2\text{CH}_3$). IR (KBr) : ν = 3410 s, 3100 s, 2980 s, 2903 m, 1715 s, 1633 w, 1219 s, 800 s cm^{-1} . HRMS (FAB), [M^+], Calc: 212.0619, found: 212.0607. Anal. Calcd for $\text{C}_9\text{H}_{12}\text{N}_2\text{O}_2\text{S}$: C, 50.92; H, 5.70; N, 13.20; found: C, 50.4; H, 5.6; N, 12.6.

Sodium nitrite (0.16g, 2.3 mmol) in water (5 mL) was added dropwise to a cooled thiazole **32** (0.48g, 2.3 mmol) in glacial acetic acid (5 mL) and water (5 mL). The mixture was stirred for 30 min and 2 h at room temperature. The mixture was diluted

with water (100 mL) and extracted with diethyl ether (3 x 50 mL). The ethereal layers were combined, washed with water (100 mL), saturated sodium bicarbonate (4 x 50 mL) and brine (50 mL). The ether layer was dried with sodium sulfate and concentrated to dryness. Purification by column chromatography on silica gel (EtOAc/cyclohexane = 1 : 6) delivered 0.34 g (1.4 mmol, 60%) of oxime **33** as a yellow solid. M. p. = 120-121°C. TLC: R_f = 0.33 (EtOAc/cyclohexane = 1 : 2). GC-MS (method B): T_R = 7.28 min, 242 (M^+). NMR: ^1H -NMR (400 MHz, CDCl_3) δ = 1.39-1.42 (3H, t, J = 7.2, CH_2CH_3), 2.61 (3H, s, CH_3), 4.39-4.45 (2H, q, J = 7.0, CH_2CH_3), 8.36 (1H, s, CH). ^{13}C -NMR (100.6 MHz, CDCl_3) δ = 14.22 (CH_2CH_3), 24.74 (CH_3), 61.89 (CH_2CH_3), 130.61 (CH), 143.67 (C-COOEt), 144.45 (C(N)OH), 155.07 (C(N)S), 159.85 ($\text{COOCH}_2\text{CH}_3$), 196.52 (C(O)CH_3). IR (KBr) : ν = 3100 s, 2983 s, 2956 m, 2529 b, 1727 s, 1692 m, 1227 s, 857 s cm^{-1} . HRMS (FAB), [M^+], Calc: 242.0361, found: 242.0371.

Oxime **33** (0.12 g, 0.5 mmol) gave 0.233 g (0.49 mmol, 99%) of 1-azadiene **6d** as a yellow oil following the procedure given for **6c**.

TLC: R_f = 0.65 (EtOAc/cyclohexane = 1 : 2). GC-MS (method B): T_R = 9.14 min, 470 (M^+). NMR: ^1H -NMR (400 MHz, CDCl_3) δ = 0.51-1.0 (30H, m, TES), 1.35-1.39 (3H, t, J = 7.2, CH_2CH_3), 4.36-4.41 (2H, q, J = 7.0, CH_2CH_3), 4.67 (1H, s, C=CH_2), 4.92 (1H, s, C=CH_2), 8.31 (1H, s, CH). ^{13}C -NMR (100.6 MHz, CDCl_3) δ = 4.24 (C-OSiCH_2), 4.69 (N-OSiCH_2), 6.43 ($\text{C-OSiCH}_2\text{CH}_3$), 6.50 ($\text{N-OSiCH}_2\text{CH}_3$), 14.17 (CH_2CH_3), 61.10 (CH_2CH_3), 98.10 (C=CH_2), 129.66 (CH), 146.18 (C=CH_2), 151.13 (C-COOEt), 152.58 (C(N)OTES), 154.12 (C(N)S), 161.51 ($\text{COOCH}_2\text{CH}_3$). IR (KBr) : ν = 2955 s, 2910 s, 2877 s, 1746 m, 1730 s, 1715 m, 1238 s, 857 s cm^{-1} .

Azadiene homodimer **11**.

1-azadiene **6a** (0.6 mL, 2.08 mmol) was heated to 150°C for 13 h in a sealed tube. The resulting mixture was purified by column chromatography on silica gel (EtOAc/cyclohexane = 1 : 6) to give 41 mg (0.16 mmol, 15.5%) of 3-hydroxypyridine **11** as a colorless solid. M. p. = 157-158°C. TLC: R_f = 0.29 (EtOAc/cyclohexane = 1 : 2). GC-MS (method B): T_R = 7.74 min, 254 (M^+). $^1\text{H-NMR}$ (400 MHz, CDCl_3) δ = 3.99 (3H, s, COOMe), 4.0 (3H, s, COOMe), 7.38, 7.40 (1H, d, J = 8.8, CH), 7.90, 7.93 (1H, d, J = 9.0, CH), 8.62 (1H, br, N-OH), 10.90 (1H, s, OH). $^{13}\text{C-NMR}$ (100.6 MHz, CDCl_3) δ = 52.60 (COOCH₃), 53.11 (COOCH₃), 127.0 (CH), 127.06 (CH), 129.36 (C-COOMe), 141.82 (C-C(N)OH), 151.13 (C-OH), 159.42 (C(N)OH), 163.40 (COOMe), 169.57 (COOMe). IR (KBr) : ν = 3480 s, 3457 s, 3159 b, 2963 s, 2922 s, 1745 s, 1673 s, 1469 s, 1234 s, 849 s, 804 s cm^{-1} . HRMS (ESI), $[M+H]^+$, calc: 255.0612, found: 255.0612.

(R)-2-Allyloxycarbonylamino-3-tritylthio-propionic acid (21).

A vigorously stirred solution of trityl L-cysteine **34** (1.0 g, 2.8 mmol) in 2 M NaOH (1.4 mL, 2.8 mmol) was cooled to 0°C. Allyl chloroformate (0.35 mL, 3.3 mmol) and 2 M NaOH (1.65 mL, 3.3 mmol) were added in portions over a period of 10 min. After being stirred at 0°C for 1 h, the reaction mixture was acidified to pH = 2 with 2 M HCl, and extracted with ethyl acetate (3 x 20 mL). The combined organic layers were dried with Na_2SO_4 and concentrated. Purification by column chromatography on silica gel ($\text{CH}_2\text{Cl}_2/\text{MeOH}$ = 20 : 1) gave 1.24 g (2.77 mmol, 99%) of acid **21** as a colorless solid. M. p. = 119-120°C. TLC: R_f = 0.25 ($\text{CH}_2\text{Cl}_2/\text{MeOH}$ = 10 : 1). $^1\text{H-NMR}$ (400 MHz, DMSO) δ = 2.38-2.58 (2H, m, CH₂), 3.81-3.86 (1H, d, J = 9.0, CH₂CH), 4.46, 4.47 (2H, d, J = 4.7, COOCH₂), 5.16, 5.19 (1H, d, J = 10.4, CH=CH₂), 5.28, 5.32 (1H, d, J = 17.3, CH=CH₂), 5.85-5.93 (1H, m, CH=CH₂), 7.23-7.35 (15H, m, trityl), 7.49, 7.51 (1H, d, J = 7.6, NHCOO). $^{13}\text{C-NMR}$ (100.6 MHz, DMSO) δ = 33.09 (CH₂CH), 53.37

(COOCH₂), 64.37 (CPh₃), 66.0 (CH₂CH), 116.88 (CH=CH₂), 126.66 (Ar), 127.93 (Ar), 128.98 (Ar), 133.38 (Ar), 144.19 (CH=CH₂), 155.45 (COOCH₂), 171.80 (COOH). IR (KBr): ν = 3417 b, 3061 s, 2917 w, 1730 s, 1714 s, 1504 s, 1445 s, 798 s, 701 s cm⁻¹. $[\alpha]^{20}_{\text{D}} = + 30.4$ (c = 1.0, CHCl₃). HRMS (ESI), [M+ Na⁺], Calc: 470.1397, found: 470.1397. Anal. calcd for C₂₆H₂₅NO₄S: C, 69.78; H, 5.63; N, 3.13; found C, 69.7; H, 6.0; N, 3.0.

(R)-2-Allyloxycarbonylamino-3-tritylthio-propionic thioamide (22).

To a stirred solution of acid **21** (1.0 g, 2.2 mmol) in THF (10 mL) was added HOSu (0.28 g, 2.4 mmol) and DCC (0.51 g, 2.4 mmol) at 0°C. The reaction mixture was stirred for 1 h at 0°C and then 5 h at room temperature. The mixture was filtered and concentrated to dryness. The residue was taken up in ethyl acetate (20 mL) and cooled to 0°C, then aqueous 25% NH₄OH solution (0.6 mL) was added dropwise and stirred for 1 h. The mixture was diluted with ethyl acetate (20 mL), washed with saturated aqueous NaHCO₃ solution (2 x 10 mL) and brine (20 mL), dried over Na₂SO₄ and concentrated. The resulting residue was purified on silica gel (EtOAc/light petroleum = 1 : 2) to give 0.99 g (2.2 mmol, 99%) of the primary amide **35** as a colorless solid. M. p. = 96-98°C. TLC: R_f = 0.21 (EtOAc/cyclohexane = 1 : 2). ¹H-NMR (400 MHz, DMSO) δ = 4.10-4.15 (2H, m, J = 6.8, CH₂), 4.57-4.58 (2H, t, J = 3.7, COOCH₂), 5.25, 5.28 (1H, d, J = 10.6, CH=CH₂), 5.38, 5.42 (1H, d, J = 17.2, CH=CH₂), 5.97-6.04 (1H, m, J = 5.3, CH=CH₂), 7.22 (1H, s, CH₂CH), 7.33, 7.34 (2H, d, J = 4.1, NH₂), 7.41-7.42 (15H, m, trityl), 7.47, 7.49 (1H, d, J = 8.4, NH). ¹³C-NMR (100.6 MHz, DMSO) δ = 33.96 (CH₂CH), 53.55 (COOCH₂), 59.64 (CH₂CH), 64.47 (CPh₃), 116.82 (CH=CH₂), 126.63 (Ar), 127.91 (Ar), 129.0 (Ar), 130.35 (Ar), 144.23 (CH=CH₂), 155.32 (COOCH₂), 171.75 (C(O)NH₂). IR (KBr): ν = 3317 b, 3030 s, 2926 s, 1682 s, 1232 s, 743 s, 701 s cm⁻¹. $[\alpha]^{20}_{\text{D}} = + 23.8$ (c = 1.0, CHCl₃). HRMS (ESI): [M+ Na⁺], Calc: 469.1556, found: 469.1554.

To a stirred solution of the primary amide **35** (2.74 g, 6.1 mmol) in dichloromethane (20 mL) at 0°C was added Lawesson's reagent (1.49 g, 3.7 mmol), and the reaction mixture was stirred at 0°C for 1 h and at room temperature for 12 h (TLC control). The reaction mixture was concentrated and purified by column chromatography (silica gel, EtOAc/cyclohexane = 1 : 2) to give 2.08 g (4.5 mmol, 74%) of thioamide **22** as a colorless solid. M. p. = 124-125°C. TLC: R_f = 0.28 (EtOAc/cyclohexane = 1 : 2). $^1\text{H-NMR}$ (400 MHz, CD_3CN) δ = 2.57-2.69 (2H, m, CH_2), 4.16, 4.17 (1H, d, J = 5.3, CH_2CH), 4.49, 4.499, 4.50 (2H, t, J = 1.8, COOCH_2), 5.18, 5.20 (1H, d, J = 17.2, $\text{CH}=\text{CH}_2$), 5.28, 5.32 (1H, d, J = 17.2, $\text{CH}=\text{CH}_2$), 5.81 (1H, br, NHCOO), 5.87-5.96 (1H, m, $\text{CH}=\text{CH}_2$), 7.23-7.41 (15H, m, trityl), 7.76, 8.05 (2H, d, J = 116.5, NH_2). $^{13}\text{C-NMR}$ (100.6 MHz, CD_3CN) δ = 37.26 (CH_2CH), 60.49 (COOCH_2), 66.24 (CPh_3), 67.72 (CH_2CH), 117.63 ($\text{CH}=\text{CH}_2$), 118.20 (Ar), 127.86 (Ar), 129.0 (Ar), 130.32 (Ar), 134.05 ($\text{CH}=\text{CH}_2$), 145.48 (COOCH_2), 207.56 ($\text{C}(\text{S})\text{NH}_2$). IR (KBr): ν = 3299 b, 3196 b, 2921 w, 1697 s, 1651 s, 1505 s, 891 b, 799 s cm^{-1} . $[\alpha]_D^{20}$ = +17.3 (c = 1.0, CHCl_3). HRMS (ESI), $[\text{M} + \text{Na}^+]$, Calc: 485.1328, found: 485.1325. Anal. calcd for $\text{C}_{26}\text{H}_{26}\text{N}_2\text{O}_2\text{S}_2$: C, 67.50; H, 5.66; N, 6.06; found: C, 66.8; H, 5.9; N, 5.8.

Enantiomeric excess (e.e.) determination of building block **23**.

Trifluoroacetic acid (10 μL) was added dropwise to a stirred solution of trityl thioether **23** (9.7 mg, 0.01 mmol) in dry dichloromethane (2 mL) at room temperature, then triethylsilane (6 μL) was added to the reaction mixture. The reaction mixture was stirred for 30 min (TLC control) and concentrated to dryness.

(*R*)-phenylethyl isocyanate (1.8 μL , 0.012 mmol) and pyridine (1 μL) were added to the above residue in dichloromethane (1 mL) at room temperature. The reaction mixture was

stirred for 10 h (TLC control), quenched by water (1 mL) and diluted by brine (10 mL), extracted with dichloromethane (3 x 10 mL), dried with Na₂SO₄ and concentrated to dryness. Purification by column chromatography (silica gel, EtOAc/cyclohexane = 1 : 3) to give 4.2 mg (0.005 mmol, 48%) of urea **23a** as a colorless solid. TLC: *R_f* = 0.21 (EtOAc/cyclohexane = 1 : 2); d.e. > 85%.

¹H-NMR of **23a**.

23b was obtained likewise from (*S*)-phenylethyl isocyanate (54% yield): colorless solid; d.e. > 60%.

¹H-NMR of **23b**.

Enantiomeric excess (e.e.) determination of building block **25a**.

Trifluoroacetic acid (0.6 mL) was added dropwise to a stirred solution of thioaminal **25a** (24 mg, 0.03 mmol) in dry dichloromethane (3 mL) at room temperature, then triethylsilane (0.6 mL) was added to the reaction mixture. The reaction mixture was stirred for 1 h (TLC control) and concentrated to dryness. (MALDI_TOF), [M + H⁺], calc: 599.0, found: 599.7.

Trityl chloride (13.6 mg, 0.05 mmol) was added to the above residue in DMF (2 mL) at room temperature and the reaction mixture was stirred for 2 days. The reaction mixture was diluted by dichloromethane (60 mL), washed by 10% sodium acetate solution (2 x 20 mL) and brine (2 x 20 mL), the organic layer was dried with Na₂SO₄ and concentrated to dryness. Purification by column chromatography (silica gel, EtOAc/light petroleum = 1 : 1) to give 18 mg (0.02 mmol, 67%) of the *S*-trityl aminothiols. TLC: *R_f* = 0.28 (EtOAc/light petroleum = 1 : 1), (MALDI_TOF), [M + H⁺], calc: 841.1, found: 842.0.

(*R*)-phenylethyl isocyanate (5 μ L, 0.033 mmol) and pyridine (2.7 μ L) were added to the *S*-trityl aminothiols (9 mg, 0.01 mmol) in dichloromethane (1 mL) at room temperature. The reaction mixture was stirred for 3 h, quenched with water (1 mL), diluted by brine (10 mL) and extracted with dichloromethane (3 x 10 mL). The organic extracts were dried with Na₂SO₄ and concentrated. Purification by column chromatography (silica gel, EtOAc/light petroleum = 1 : 4) to give 4.0 mg (0.004 mmol, 40%) of the urea **25b** as a colorless solid. TLC: *R_f* = 0.37 (EtOAc/light petroleum = 1 : 1). (MALDI_TOF), [M + Na⁺], calc: 1010.2, found: 1010.9; d.e. > 99%.

¹H-NMR of **25b**.

¹H-NMR of **25b** and **25c** after mixing:

References:

- ¹ Armarego, W. L. F.; Chai, C. L. L. *Purification of Laboratory Chemicals*, 5th Ed, Elsevier, 2002.
- ² Igarashi, J. -E.; Kawakami, Y.; Kinoshita, T.; Furukawa, S. *Chem. Pharm. Bull.* **1990**, *38*, 1832.
- ³ Li, L.-S.; Wu, Y.-L. *Tetrahedron Lett.* **2002**, *43*, 2427.
- ⁴ Barluenga, J.; Rodríguez, M. A.; Campos, P. J. *Tetrahedron Lett.* **1990**, *31*, 2751.
- ⁵ Kelly, T. R.; Lang, F. J. *Org. Chem.* **1996**, *61*, 4623.

¹H-spectra of compounds 6-25.