Synthesis of Cyclic Peptidomimetics from Aldol

Building Blocks

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Experimental Section

General. ^1H and ^{13}C NMR: Bruker Avance 400, Bruker AMX 600, spectra were recorded in CDCl_3 , except for the ROESY spectra of **12aa_ab** which were measured in DMSO-d_6 ; chemical shifts are calibrated to the residual proton and carbon resonance in CDCl_3 (7.25 ppm, 77.00 ppm). EI-MS; Finnigan Triple-Stage-Quadrupol (TSQ-70). HR-MS (EI): modified AMD Intectra MAT 711 A. HRMS (FT-ICR): BRUKER Daltonic APEX 2 with electrospray-ionization (ESI). Optical rotation: JASCO Polarimeter P-1020. IR: Jasco FT/IR-430 spectrometer. ATR-FT-IR: Bruker Vector 22. GC-MS: HP 6890 Series GC system with 5973 mass selective detector and 7683 Series injector. Flash chromatography: J. T. Baker silica gel 43-60 μm . Thin-layer chromatography Machery-Nagel Polygram Sil G/UV₂₅₄. Solvents were distilled prior to use; petroleum ether with a boiling range of 40-60 °C was used. Merrifield resin HL (100-200 mesh), loading 1.6 mmol g^{-1} from Novabiochem was used.

General procedures for solution phase reactions

General procedure for aldol reaction

To a solution of the oxazolidinone derivative **3a** (16.7 mmol) in dichloromethane (60 mL) at 0 °C was added dropwise dibutylboron triflate (20 mmol, 1 M in CH_2Cl_2) followed by the dropwise addition of Hünig's base (21.7 mmol). The reaction mixture was stirred for 1 h at 0 °C and then cooled to -78 °C. Thereafter, freshly distilled aldehyde **4a** (25.1 mmol) was added dropwise and the reaction mixture stirred at -78 °C for 1 h. The reaction mixture was warmed up to room temperature over a period of 1 h and stirred at the same temperature for 2 h. Then it was cooled to 0 °C and a mixture of pH 7 phosphate buffer (20 mL) and methanol (60 mL) was added. The resulting cloudy solution was then treated with a mixture of methanol and 30% H_2O_2 (2:1, 60 mL) via syringe at such a rate so as to keep the temperature below 10 °C. The solution was stirred for 1 h and the volatile materials were removed with a rotary evaporator. The resulting mixture was diluted with ethyl acetate and the organic layer was washed with 5% aqueous HCl solution, aqueous NaHCO_3 solution, brine, dried (Na_2SO_4), filtered,

and concentrated to give the crude product which was purified by flash column chromatography using 30% ethyl acetate in petroleum ether as an eluent to provide the aldol adduct **5aa** in 82% yield.

General procedure for allylation

To a solution of the aldol product **5aa** (2.7 mmol) in dichloromethane (3 mL) was added the trichloroacetimidate **6** (5.4 mmol), dissolved in cyclohexane (6 mL). The reaction mixture was cooled to 0 °C and triflic acid (100 µl) was added to it dropwise. The reaction mixture was allowed to stir at room temperature overnight. The solid was filtered off and the filtrate washed with saturated NaHCO₃ solution, water, brine, dried (Na₂SO₄), filtered and concentrated in vacuo. The crude product was purified by flash column chromatography using 12% ethyl acetate in petroleum ether as eluent to afford the O-allyl derivative **7aa** (68% yield).

General procedure for the preparation of the acids **8**

A solution of the O-allyl compound **7aa** (1.7 mmol), dissolved in a mixture of THF and H₂O (3:1, 20 mL) was treated dropwise at 0 °C with 30% H₂O₂ (9.2 mmol) and a solution of lithium hydroxide (6.7 mmol) in water (3 mL). The reaction mixture was allowed to stir at 0 °C for 1 h and at room temperature for 2.5 h. The excess of H₂O₂ was quenched by the addition of sodium sulfite (1 g in 5 mL of water). Most of the THF was removed with a rotavapor (water bath at 25-30 °C) and the water layer was extracted with dichloromethane to remove the oxazolidinone. The aqueous layer was acidified with 1 M aqueous HCl solution and extracted with ethyl acetate. The ethyl acetate layer was dried (Na₂SO₄), filtered and concentrated to give the crude product which was purified by flash column chromatography using 30% ethyl acetate in petroleum ether as an eluent to provide the acid **8aa** in 74% yield.

General procedure for the preparation of the amines **9**

To a solution of the acid **8aa** (0.5 mmol) in dry acetonitrile (3 mL), triethylamine (0.5 mmol) and diphenylphosphoryl azide (0.5 mmol) was added and the reaction mixture was heated at 50 °C for 1.5 h. After cooling to room temperature, 1N aqueous HCl solution (3 mL) was added and the reaction

mixture refluxed overnight. The acetonitrile was evaporated and the aqueous layer neutralized with solid NaHCO_3 and extracted with chloroform. The chloroform layer was dried (Na_2SO_4), filtered, and concentrated to give the crude product which was purified by flash column chromatography (on triethylamine impregnated silica gel) using 5 % methanol in chloroform as an eluent to give the required amine **9aa** in 78% yield. The silica gel was impregnated by making a slurry of the silica gel (100 g) in petroleum ether containing 5 mL of triethylamine. After cooling, the solvents are evaporated on the rotavapor.

General procedure for amide coupling

Ethyl-diisopropylamine (DIPEA) (0.72 mmol) was added to the mixture of amine **9aa** (0.24 mmol), the acid **8aa** (0.24 mmol) and BOP (0.29 mmol) in anhydrous acetonitrile (3 mL) at room temperature. After stirring at the same temperature for 1 h (monitored by TLC), brine was added, and the reaction mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with 10% citric acid solution, water, brine, dried (Na_2SO_4), filtered, and concentrated to give the crude product which was purified by flash column chromatography using 30% ethyl acetate in petroleum ether as an eluent to provide the amide **10aa_aa** in 95% yield.

General procedure for ring closing metathesis

To a solution of Grubb's catalyst **11** (0.0045 mmol) in dry dichloromethane (20 mL) (degassed for ½ h by argon bubbling), the amide derivative **10aa_aa** (0.09 mmol) in dry dichloromethane (3 mL) was added at room temperature. After stirring the reaction mixture for 5 h, water was added. The organic layer was separated, washed with brine, dried (Na_2SO_4), filtered, and concentrated to give the crude product which was purified by flash column chromatography to give the pure products **12aa_aa_E** and **12aa_aa_Z** in a 3:1 ratio as colorless solids; combined yield 73%.

General procedures for solid phase reactions

Washings of resin after the reaction was carried out using 5 mL of each solvent, agitating the resin suspension for 2 min. The yield was calculated on the basis of the change in weight after each reaction. In most of the cases the reaction was monitored by ATR-FT-IR technique.

General procedure for anchoring alcohol with Merrifield resin

To a suspension of sodium hydride (6.4 mmol) in dry DMF (3 mL) the alcohol **16** (5.3 mmol), dissolved in DMF (10 mL), was added at room temperature and agitating was continued for 3 h at the same temperature. Then Merrifield resin (1.11 g, 1.77 mmol) was added to the reaction mixture and it was agitated for 3 days. The resin was filtered and washed thoroughly with water, DMF, THF, DCM and dried overnight under vacuum to provide the loaded resin (95% loading, measured by chlorine content).

General procedure for removal of THP protecting group

A suspension of the resin **18** in a mixture of dichloromethane and methanol (1:1, 6 mL), containing dioxane (0.1 mL) and *p*-TsOH (8.86 mmol), was agitated for 3 h. After filtration, the resin was washed with DCM, MeOH, DCM and dried overnight under vacuum to provide the deprotected alcohol **19** in 82% yield. The deprotection progress was monitored by removing aliquots (20 μ L) from the reaction solution after every hour, diluting the aliquots with 80 μ L of DCM and injecting a sample (5 μ L) into the GC at 50 °C. Deprotection was judged complete when the ratio of the peak areas of methoxytetrahydropyran and dioxane was constant.¹

General procedure for preparation of imidate **20**

The loaded resin **19** was suspended in dry DCM (6 mL) and trichloroacetonitrile (35.5 mmol) was added to it under argon atmosphere followed by agitation for 5 minutes. DBU (1.6 mmol) was added

¹ (a) Kuisle, O.; Quiñoá, E.; Riguera, R. *J. Org. Chem.* **1999**, *64*, 8063-8075. (b) Hermann, C.; Giammasi, C.; Geyer, A.; Maier, M. E. *Tetrahedron* **2001**, *57*, 8999-9010.

dropwise to the suspension and the mixture was agitated for 3 h. Then the resin was washed with DCM, DMSO, THF and DCM, dried overnight under vacuum to provide the imidate **20** in 78% yield.

General procedure for the allylation of 20 with the aldol product 5

The loaded resin **20** was washed with anhydrous THF (2 times) under nitrogen atmosphere to remove moisture, then it was suspended in anhydrous cyclohexane. Now the alcohol **5bc** (3.6 mmol), dissolved in dry DCM (so that cyclohexane : dichloromethane = 1:1) was added to it followed by 5 minutes of shaking. Thereafter, $\text{BF}_3 \cdot \text{OEt}_2$ (5 μl per 100 mg of resin) was added and agitation was continued for 3 h. The resin was washed with DCM, DMF, THF and DCM and dried overnight in vacuum to give the oxazolidinone derivative **21** in 65% yield.

General procedure for hydrolysis

The resin was suspended in a mixture of water and THF (1:3, 6 mL) followed by the addition of LiOH (21.3 mmol) and agitated for 24 h. Then the solution was filtered off and the resin washed with water, DMF, THF, DCM and dried. Then the resin was suspended in 1N aqueous HCl in THF and agitated at room temperature for 24 h. Afterwards, the solution was filtered off and the resin washed with water, THF, DCM and dried overnight under vacuum to provide the acid **22** in 62% yield.

General procedure for amide coupling

The loaded resin **22** was suspended in DCM and amine **9aa** (4.43 mmol), PyBroP (5.32 mmol) and DIEA (10.64 mmol) were added at room temperature. The resulting mixture was shaken at room temperature for 12 h. Then the solution was filtered off and the resin washed with DMF, MeOH, DCM and dried overnight under vacuum to provide the amide **23** in 75% yield.

General procedure for ring closing metathesis

The loaded resin **23** was suspended in dry DCM and a solution of Grubb's catalyst **11** (0.088 mmol) in DCM was added to it under nitrogen atmosphere and it was agitated for 36 h at room temperature. Then the solution was filtered and the filtrate concentrated and subjected to flash column chromatography yielding the product **12bc_aa** (*cis* and *trans* isomer in 1:3 ratio) in 30% yield.

(4R)-4-Benzyl-3-[(2R,3S)-3-hydroxy-2-methyl-5-phenylpentanoyl]-1,3-oxazolidin-2-one (5bb).

$[\alpha]_D^{27} +55.9^\circ$ (c 1.73, CH_2Cl_2); ^1H NMR (400 MHz, CDCl_3): δ 7.19-7.36 (m, 10H), 4.68 (dddd, $J = 3.3, 7.1, 9.6, 10.6$ Hz, 1H), 4.19 (m, 2H), 3.97 (ddd, $J = 3.4, 3.5, 6.3$ Hz, 1H), 3.75 (dq, $J = 2.8, 7.1$ Hz, 1H), 3.24 (dd, $J = 3.3, 13.4$ Hz, 1H), 2.79 (m, 4H), 1.90 (m, 1H), 1.71 (m, 1H), 1.28 (d, $J = 7.1$ Hz, 3H); ^{13}C NMR (100 MHz, CDCl_3): δ 177.5, 152.9, 141.7, 134.9, 125.8-129.4 (6 lines), 70.5, 66, 54.9, 42.2, 37.7, 35.4, 32.1, 10.5; IR (neat): 3513 (br), 2940, 1779, 1694, 1386, 1211 cm^{-1} ; EI-MS (m/z): 367 $[\text{M}^+]$, 244, 234, 178, 117, 91.

(4R)-3-[(2R,3S)-3-(Allyloxy)-2-methyl-5-phenylpentanoyl]-4-benzyl-1,3-oxazolidin-2-one (7bb).

$[\alpha]_D^{27} +72.5^\circ$ (c 0.52, CH_2Cl_2); ^1H NMR (400 MHz, CDCl_3): δ 7.16-7.36 (m, 10H), 5.88-5.95 (m, 1H), 5.15-5.30 (m, 2H), 4.61 (m, 1H), 4.01-4.16 (m, 5H), 3.61 (ddd, $J = 4.1, 5.6, 7.8$ Hz, 1H), 3.29 (dd, $J = 3.3, 13.4$ Hz, 1H), 2.74-2.86 (m, 2H), 2.63 (m, 1H), 1.81-1.96 (m, 2H), 1.26 (d, $J = 6.8$ Hz, 3H); ^{13}C NMR (100 MHz, CDCl_3): δ 175.1, 153.1, 142.0, 135.3, 134.9, 125.7-129.4 (6 lines), 116.9, 79.9, 71.5, 65.9, 55.7, 41, 37.7, 33.7, 31.9, 12.9; IR (neat): 2929, 1779, 1694, 1383, 1209 cm^{-1} ; EI-MS (m/z): 408 $[\text{M} + 1]^+$, 349, 244, 172, 91.

(2R, 3S)-3-(Allyloxy)-2-methyl-5-phenylpentanoic acid (8bb). $[\alpha]_D^{24} +35.1^\circ$ (c 0.26, CH_2Cl_2); ^1H NMR (400 MHz, CDCl_3): δ 7.11-7.31 (m, 5H), 5.92 (m, 1H), 5.23 (m, 2H), 4.06 (tdq, $J = 1.5, 5.8, 12.4$ Hz, 2H), 3.66 (dt, $J = 4.8, 9.6$ Hz, 1H), 2.6-2.84 (m, 3H), 1.86 (m, 2H), 1.20 (d, $J = 7.1$ Hz, 3H); ^{13}C NMR (100 MHz, CDCl_3): δ 179.4, 141.6, 134.4, 128.4, 128.3, 125.9, 117.4, 79.5, 71.4, 42.7, 33.5, 31.8, 11.7; IR (neat): 3300, 2944, 1704, 1455 cm^{-1} ; EI MS (m/z): 248 $[\text{M}^+]$, 230, 190, 117, 91.

(4R)-4-Benzyl-3-[(2S,3R)-2-benzyl-3-hydroxy-5-phenylpentanoyl]-1,3-oxazolidin-2-one (5ab).

$[\alpha]_D^{22} +42.5^\circ$ (c 1.35, CH_2Cl_2); ^1H NMR (400 MHz, CDCl_3): δ 7.18-7.31 (m, 13H), 6.94-6.96 (m, 2H), 4.57-4.63 (m, 2H), 4.08 (t, $J = 8.33$ Hz, 1H), 3.97-4.00 (m, 2H), 3.14 (dd, $J = 10.6, 13.6$ Hz, 1H), 3.02 (dd, $J = 5.3, 13.4$ Hz, 1H), 2.92 (ddd, $J = 5.5, 9.3, 14.4$ Hz, 1H), 2.87 (dd, $J = 3.8, 13.9$ Hz, 1H), 2.7 (ddd, $J = 7.3, 9.4, 13.9$ Hz, 1H), 2.16 (dd, $J = 9.6, 13.6$ Hz, 1H), 1.85-2.00 (m, 2H); ^{13}C NMR (100 MHz, CDCl_3): δ 175, 153.4, 141.7, 138.6, 135.1, 125.9-129.4 (8 lines), 71.7, 65.7, 54.9, 49.2, 37.2,

35.4, 33.3, 32.3; IR (neat): 3499, 3026, 2924, 1779, 1694, 1390, 1211 cm^{-1} ; EI-MS (m/z): 444 $[\text{M} + 1]^+$, 426, 399, 310, 105, 91.

(4R)-3-[(2S,3R)-3-(Allyloxy)-2-benzyl-5-phenylpentanoyl]-4-benzyl-1,3-oxazolidin-2-one (7ab).

$[\alpha]_{\text{D}}^{27} +60.9^\circ$ (c 2.09, CH_2Cl_2); ^1H NMR (400 MHz, CDCl_3): δ 7.17-7.31 (m, 13H), 6.97 (m, 2H), 5.92 (dddd, $J = 5.6, 5.6, 10.6, 17.1$ Hz, 1H), 5.15-5.28 (m, 2H), 4.8 (ddd, $J = 5.3, 5.3, 10.6$ Hz, 1H), 4.58 (dddd, $J = 2.9, 7.6, 9.8, 11.9$ Hz, 1H), 3.95-4.17 (m, 4H), 3.60 (ddd, $J = 3.3, 5.3, 8.6$ Hz, 1H), 3.09 (dd, $J = 10.1, 13.4$ Hz, 1H), 2.87-2.99 (m, 3H), 2.62 (ddd, $J = 6.8, 9.9, 16.7$ Hz, 1H), 2.32 (dd, $J = 9.3, 13.6$ Hz, 1H), 1.88-2.04 (m, 2H); ^{13}C NMR (100 MHz, CDCl_3): δ 173.7, 153, 141.9, 138.7, 135.2, 134.7, 125.8-129.3 (8 lines), 117.2, 79.7, 71.4, 65.5, 55.5, 47.1, 37.3, 34.9, 33.6, 32.1; IR (neat): 3026, 1779, 1694, 1385, 1100 cm^{-1} ; EI-MS (m/z): 484 $[\text{M} + 1]^+$, 426, 399, 310, 105, 91.

(2S,3R)-3-(Allyloxy)-2-benzyl-5-phenylpentanoic acid (8ab).

$[\alpha]_{\text{D}}^{23} +37.7^\circ$ (c 1.58, CH_2Cl_2); ^1H NMR (400 MHz, CDCl_3): δ 7.11-7.29 (m, 2H), 5.91 (dddd, $J = 5.8, 5.8, 10.3, 16.2$ Hz, 1H), 5.17-5.28 (m, 2H), 3.98-4.07 (dtABq, $J = 1.3, 5.8, 12.4$ Hz, 2H), 3.57 (ddd, $J = 5.1, 5.1, 6.8$ Hz, 1H), 2.99-3.04 (m, 2H), 2.65 (ddd, $J = 8.6, 13.9, 16.2$ Hz, 1H), 1.93 (m, 2H); ^{13}C NMR (100 MHz, CDCl_3): δ 178.2, 141.5, 138.9, 134.2, 125.9-128.7 (5 lines), 117.6, 78.4, 70.9, 50.6, 33.8, 33.2, 31.5; IR (neat): 3300, 3026, 1707, 862 cm^{-1} ; EI-MS (m/z): 324 $[\text{M}^+]$, 306, 266, 175, 131, 117, 91.

(2S,3R)-3-(Allyloxy)-1,5-diphenyl-2-pentanamine (9ab).

$[\alpha]_{\text{D}}^{24} +10.7^\circ$ (c 0.47, CH_2Cl_2); ^1H NMR (400 MHz, CDCl_3): δ 7.10-7.29 (m, 10 H), 5.87-5.97 (m, 1H), 5.13-5.26 (m, 2H), 3.92-4.06 (dddt, $J = 5.5, 12.6, 18.3, 1.3$, 2H), 3.20-3.30 (m, 2H), 2.5-2.86 (m, 4H), 1.78-2.00 (m, 2H); ^{13}C NMR (100 MHz, CDCl_3): δ 142.1, 139.0, 135.0, 129.1, 128.5, 128.4, 126.3, 125.8, 116.8, 81.2, 70.9, 54.3, 39.1, 31.4, 31.0; IR (neat): 3371, 3025, 1495, 1453, 1075 cm^{-1} ; EI-MS (m/z): 296 $[\text{M} + 1]^+$, 204, 120, 91.

(2S,3R)-3-(Allyloxy)-N-[(1R,2S)-2-(allyloxy)-1-benzyl-4-phenylbutyl]-2-methyl-5-

phenylpentanamide (10bb_ab). $[\alpha]_{\text{D}}^{23} +0.9537^\circ$ (c 0.51, CH_2Cl_2); ^1H NMR (400 MHz, CDCl_3): δ 7.14-7.30 (m, 15H), 6.44-6.46(d, $J = 9$ Hz, 1H), 5.82-5.90(m, 2H), 5.09-5.30 (m, 4H), 4.52 (m, 1H), 3.93-4.05 (m, 4H), 3.40-3.44 (ddd, $J = 3.6, 5.3, 7.3$ Hz, 1H), 3.34 (m, 1H), 2.57-2.92 (m, 6H), 2.42-

2.48 (ddd, $J = 4.4, 7, 11.4$, 1H), 1.78-1.89 (m, 4H), 1.02 (d, $J = 6.8$ Hz, 1H); ^{13}C NMR (100 MHz, CDCl_3): δ 173.3, 141.9, 141.7, 138.3, 134.9, 134.5, 128.9, 128.2-128.3 (5 lines), 126.2, 125.8, 125.7, 116.7, 116.5, 80.6, 79.9, 77.3, 77, 76.68, 70.85, 70.65, 51.1, 42.8, 35.6, 32.4, 32.3, 31.9, 31.8, 12.9; IR (neat): cm^{-1} ; EI-MS (m/z): 526 $[\text{M} + 1]^+$, 434, 350, 131, 120, 91.

(2S,3R,6S,7R)-3-Benzyl-6-methyl-2,7-bis(2-phenylethyl)-1,8-dioxo-4-azacyclododec-10-en-5-one

(12bb_ab). *Z-isomer*: $[\alpha]_{\text{D}}^{23} +12.3^\circ$ (c 0.79, CH_2Cl_2); ^1H NMR (400 MHz, CDCl_3): δ 7.16-7.30 (m, 15H), 6.11-6.13 (d, $J = 9.4$ Hz, 1H), 5.82-5.88 (m, 1H), 5.68-5.73 (m, 1H), 4.44 (t, $J = 10.1$ Hz, 1H), 4.37 (m, 1H), 4.27-4.32 (dd, $J = 5.1, 14.6$ Hz, 1H), 4.17-4.21 (dd, $J = 5.6, 10.7$ Hz, 1H), 4.03-4.08 (dd, $J = 4.5, 14.1$ Hz, 1H), 3.56 (m, 1H), 3.31 (m, 1H), 2.90-2.95 (dd, $J = 4.5, 15.1$ Hz, 1H), 2.57-2.86 (m, 6H), 2.46 (m, 1H), 1.79-1.94 (m, 4H), 0.96 (d, $J = 7.2$ Hz, 3H); ^{13}C NMR (100 MHz, CDCl_3): δ 172.5, 141.7, 141.6, 138.6, 130.0, 125.9-129.4 (9 lines), 83.6, 80.6, 68.9, 66.9, 52, 42.6, 34.5, 33.9, 32.8, 32.5, 31.6, 11.6.

E-isomer: $[\alpha]_{\text{D}}^{25} -74.9^\circ$ (c 1.44, CH_2Cl_2); ^1H NMR (400 MHz, CDCl_3): δ 7.13-7.36 (m, 15 H), 5.60-5.67 (m, 1H), 5.42-5.49 (m, 1H), 5.09-5.11 (d, $J = 7.8$ Hz, 1H), 4.09-4.20 (m, 3H), 3.72-3.76 (dt, $J = 2.1, 7$ Hz, 1H), 3.52-3.58 (dd, $J = 8.9$ Hz, 12.4 Hz, 1H), 3.42-3.47 (dd, $J = 9.2, 12.7$ Hz, 1H), 3.33-3.37 (m, 1H), 2.99-3.03 (dd, $J = 3.8, 14.8$ Hz, 1H), 2.67-2.86 (m, 3H), 2.52-2.61 (m, 2H), 2.20-2.26 (dq, $J = 2.4, 7.3$ Hz, 1H), 2.02-2.11 (m, 1H), 1.80-1.92 (m, 3H), 0.97-0.98 (d, $J = 6.7$ Hz, 3H); ^{13}C NMR (100 MHz, CDCl_3): lines), 78.4, 77.4, 69.8, 67.7, 52.6, 41.8, 34.7, 33.1, 32.6, 32.2, 31.9, 8.9; IR (neat): 3340, 2925, 1650, 1532, 1456, 1096 cm^{-1} ; EI-MS (m/z): 498 $[\text{M} + 1]^+$, 406, 218, 91; HRMS: Calcd. for $\text{C}_{33}\text{H}_{39}\text{NO}_3$ 497.2929, found 497.2911.

Signal assignment for the *trans*-Isomer **12aa_ab_E** (DMSO, 600 MHz, 300 K). Geminal methylene groups (cf. 16) are labeled as lowfield (cf. 16^l) and highfield signal (16^h), respectively. The corresponding carbon atom appears two times in the table and is enclosed in brackets. m = multiplett, no coupling can be extracted.

	δ ¹ H ppm	<i>Integral</i>	J	δ ¹³ C ppm
2	3.62	1	7.1 Hz, 1.9 Hz	76.84
3	3.82	1	8.7 Hz	52.78
5	-	-	-	171.26
6	2.58	1	10.3 Hz	47.78
7	3.70	1	7.5 Hz, 2.1 Hz	78.23
9^l	3.98	1	12.2 Hz, 4.9 Hz	67.00
9^h	3.52	1	12.4 Hz, 9.5 Hz	(67.00)
10	5.56	1	15.2 Hz, 9.7 Hz, 5.1 Hz	131.93
11	5.83	1	15.4 Hz, 9.8 Hz, 5.8 Hz	131.93
12^l	4.09	1	11.9 Hz, 5.4 Hz	67.94
12^h	3.48	1	12.2 Hz, 9.6 Hz	(67.94)
13	1.80	2	m	33.66
14	2.66	2	m	31.94
15^l	2.84	1	14.9 Hz, 2.9 Hz	31.80
15^h	2.62	1	m	31.80
16^l	2.99	1	14.6 Hz, 9.9 Hz	28.55
16^h	2.50	1	m	(28.55)
17	1.49, 1.78	2	m	24.20
18	0.88	3	7.4 Hz	10.53

Ar-C: 125.2 – 142.03 ppm, 12 signals

Ar-H: 6.95 – 7.30 ppm, multiplett

N-H: 7.72 ppm, *J* = 7.2 Hz

Signal assignment for the *cis*-Isomer **12aa_ab_Z** (DMSO, 600 MHz, 300 K). Geminal methylene groups (cf. 16) are labeled as lowfield (cf. 16^l) and highfield signal (16^h), respectively. The corresponding carbon atom appears two times in the table and is enclosed in brackets. m = multiplett, no coupling can be extracted.

	δ ¹ H ppm	<i>Integral</i>	J	δ ¹³ C ppm
2	3.50	1	8.7 Hz, 3.5 Hz, 1.2 Hz	78.06
3	4.18	1	m	52.58
5	-	-	-	172.04
6	3.02	1	10.8 Hz, 3.3 Hz	48.79
7	3.44	1	10.7 Hz, 2.6 Hz	80.35
9^l	4.30	1	m	63.32
9^h	4.08	1	11.0 Hz, 6.4 Hz	(63.32)
10	5.68	1	m	129.39
11	5.73	1	m	130.61
12^l	4.30	1	m	63.12
12^h	3.86	1	11.1 Hz, 5.8 Hz	(63.12)
13	1.68, 1.78	2	m	33.95
14	2.51, 2.70	2	m	32.03
15	2.55, 2.70	2	m	33.64
16^l	2.88	1	13.8 Hz, 10.5 Hz	32.14
16^h	2.42	1	14.0 Hz, 3.2 Hz	(32.14)
17	1.52, 1.68	2	m	23.85
18	0.88	3	7.3 Hz	11.10

Ar-C: 125.2 – 142.03 ppm, 12 signals

Ar-H: 6.95 – 7.30 ppm, multiplett

N-H: 7.72 ppm, *J* = 7.2 Hz