Supplementary Material

Ring-Closing Metathesis of Chiral Allyl Amines. Enantioselective Synthesis of (2*S*,3*R*,4*S*)-3,4-Dihydroxyproline.

Rubén Martín, Montserrat Alcón, Miquel A. Pericàs, Antoni Riera*.

Unitat de Recerca en Síntesi Asimètrica (URSA-PCB), Parc Científic de Barcelona and Departament de Química Orgànica, Universitat de Barcelona, c/ Josep Samitier, 1-5. 08028-Barcelona, Spain.

ariera@pcb.ub.es

Contents:

Preparation and characterization of compounds: **3b**, **4b**, **3c**, **4c**, **5c**, **10a** and **11a**.

¹H NMR and ¹³C NMR of compounds **4a**, **4b**, **4c**, **5b**, **5c**, **7a**, **10a**, **11a**, **8**, **10b**, **11b**, **12b** and **13b**.

(4*S*,1'*S*)-*N*-(*tert*-Butoxycarbonyl)-*N*-(4-methoxybenzyl)-4-(1'-aminopent-4'enyl)[1,3]-dioxolane-2-thione (3b**).** The procedure described for the preparation of **3a** was followed. Starting from **2b** (17.6 g, 48.2 mmol), 16.08 g of **3b** (82% yield) were obtained as an oil. $[\alpha]_D^{+34.6}$ (*c* 1.9, CHCl₃). IR (film): $\nu = 2977, 1690, 1613, 1515, 1403 \text{ cm}^{-1}$. ¹H NMR (200 MHz, CDCl₃) δ 7.2 (broad d,

2H), 6.87 (d, $J = 8.4$ Hz, 2H), 5.8 (m, 1H), 5.1-5 (m, 2H), 4.4-3.9 (m, 6H), 3.8 (s, 3H), 2.2-1.8 (m, 4H), 1.5 (s, 9H). ^{13}C NMR (50 MHz, CDCl_3) δ 192 (C), 159.3 (C), 155.4 (C), 136.9 (CH), 129.1 (CH), 115.8 (CH_2), 114.3 (CH), 83.1 (CH), 81.6-81.2* (C), 71.8 (CH_2), 57.9 (CH), 55.2 (CH_3), 49 (CH_2), 29.6 (2 CH_2), 28.3 (3 CH_3) (signals marked with an asterisk correspond to a rotamer). MS (CI- NH_3) m/e 425 ($M + 18$, 66%), 408 ($M+1$, 18%), 309 (100%).

(3*S*)-*N*-(*tert*-butoxycarbonyl)-*N*-(4-methoxybenzyl)-(1-vinyl-pent-4-enyl)amine (4b). The procedure described for the preparation of **4a** was followed. Starting from **3b** (16.08 g, 39.5 mmol), 11.74 g of **4b** (90% yield) were obtained as an oil. $[\alpha]_{\text{D}} -31.0$ (c 1.6, CHCl_3). IR (film) ν 2977, 1690, 1642, 1613, 1515, 1457, 1403, 1366, 1302, 1248, 1167, 1038, 917, 772 cm^{-1} . ^1H NMR (200 MHz, CDCl_3) δ 7.18 (d, $J = 8.5$ Hz, 2H), 6.82 (d, $J = 8.5$ Hz, 2H), 5.9-5.6 (m, 2H), 5.1-4.9 (m, 4H), 4.3 (m, 3H), 3.78 (s, 3H), 1.95 (m, 2H), 1.65 (m, 2H), 1.44 (s, 9H). ^{13}C NMR (50 MHz, CDCl_3) δ 158.4 (C), 155.8 (C), 137.9 (CH), 137.5 (CH), 131.7 (C), 128.6 (2CH), 116.2 (CH_2), 114.7 (CH_2), 113.4 (2CH), 79.6 (C), 58.3 (CH), 55.1 (CH_3), 47.5 (CH_2), 31.4 (CH_2), 30.4 (CH_2), 28.3 (3 CH_3). MS (CI- NH_3) m/e 249 ($M+18$, 39%), 332 ($M + 1$, 100%), 293 (22%). HRMS calcd for $\text{C}_{20}\text{H}_{29}\text{NO}_3$ 331.2162, found 331.2147.

(4*S*,1'*S*)-*N*-(*tert*-Butoxycarbonyl)-*N*-(4-methoxybenzyl)-4-(1'-aminohept-5-enyl)[1,3]-dioxolane-2-thione (3c). The procedure described for the preparation of **3a** was followed. Starting from **2c** (310 mg, 0.82 mmol), 277 mg of **3c** (81% yield) were obtained. $[\alpha]_{\text{D}} +28.7$ (c 1.0, CHCl_3). IR (film) ν 2977, 1810, 1750, 1692, 1613, 1515, 1403 cm^{-1} . ^1H NMR (200 MHz, CDCl_3) δ 7.18 (broad d, 2H), 6.87 (d, $J = 8.4$ Hz, 2H), 5.76 (m, 1H), 5.0 (m, 2H), 4.8 (m, 1H), 4.5-3.8 (m, 5H), 3.81 (s, 3H), 2.2-1.7 (m, 4H), 1.5 (s, 9H), 1.4 (m, 2H). ^{13}C NMR (50 MHz, CDCl_3) δ 192 (C), 159.2 (C), 158 (C), 137.8 (CH), 130.0 (C), 129.0 (CH), 115.3 (CH_2), 114.3 (CH), 83.3 (CH), 81.6-81.2* (C), 71.9 (CH_2),

58.3 (CH), 55.3 (CH₃), 48.7 (CH₂), 33.3 (2 CH₂), 28.4 (3 CH₃), 24.9 (CH₂) (signals marked with an asterisk correspond to a rotamer). HRMS calcd for C₁₈H₂₃NO₅S (M-C₄H₈) 365.1297, found 365.1302.

(3S)-N-(*tert*-Butoxycarbonyl)-N-(4-methoxybenzyl)-(1-vinyl-hex-5-enyl)amine (4c). The procedure described for the preparation of **4a** was followed. Starting from **3c** (448 mg, 1.06 mmol), 196 mg of **4c** (69% yield) were obtained. $[\alpha]_D -25.7$ (*c* 1.8, CHCl₃). IR (film): $\nu = 2935, 1690, 1642, 1613, 1515, 1457 \text{ cm}^{-1}$. ¹H NMR (200 MHz, CDCl₃) δ 7.18 (d, *J* = 8.5 Hz, 2H), 6.82 (d, ³*J*(H,H) = 8.5 Hz, 2H), 5.9-5.6 (m, 2H), 5.15-4.85 (m, 4H), 4.4-4.1 (m, 3H), 3.78 (s, 3H), 2.0-1.9 (m, 2H), 1.7-1.2 (m, 4H), 1.43 (s broad, 9H). ¹³C NMR (50 MHz, CDCl₃) δ 158.3 (C), 155.8 (C), 138.4 (CH), 137.7 (CH), 131.7 (C), 128.5 (2CH), 116.0 (CH₂), 114.4 (CH₂), 113.4 (2CH), 79.6 (C), 58.5 (CH), 55.2 (CH₃), 47.4 (CH₂), 33.4 (CH₂), 31.5 (CH₂), 28.4 (3 CH₃), 25.6 (CH₂). HRMS calcd for C₂₁H₃₁NO₃ 345.2304, found 345.2312.

(1S)-N-(*tert*-Butoxycarbonyl)-N-(*p*-methoxybenzyl)-cyclohex-2-enylamine (5c). The procedure described for the preparation of **5b** was followed. Starting from **4c** (92 mg, 0.267 mmol), 80 mg of **5c** (95% yield) were obtained. $[\alpha]_D -61.0$ (*c* 1.5, CHCl₃). IR (film) ν 2933, 1690, 1615, 1613, 1455 cm⁻¹. ¹H NMR (200 MHz, CDCl₃) δ 7.15 (d broad, *J* = 8 Hz, 2H), 6.83 (d, *J* = 8 Hz, 2H), 5.79 (broad, 1H), 5.48 (m, 1H), 4.9-4.1 (m, 3H), 3.79 (s, 3H), 2.0-1.2 (m, 15H). ¹³C NMR (50 MHz, CDCl₃) δ 158.0 (C), 155.8 (C), 132.5 (C), 130.9 (CH), 129.6 (CH), 128.8 (CH), 128.1 (CH), 127.4 (CH), 113.4 (CH), 79.5 (C), 55.2 (CH₃), 54.1-52.9* (CH), 46.5 (CH₂), 28.4 (3CH₃), 28.1 (CH₂), 24.6 (CH₂), 21.6 (CH₂) (signals marked with an asterisk correspond to a rotamer). HRMS calcd for C₁₉H₂₈NO₃ (M+1) 318.2069, found 318.2054.

(1S)-N-Allyl-N-(4-methoxy-benzyl)-1-phenyl-allylamine (10a). To a ice-cooled solution of **7a** (2.9 g, 8.87 mmol) and 4-dimethylaminopyridine (2.60 g, 21.28 mmol) in anhydrous dichloromethane (50 mL), thiophosgene (0.97 mL, 10.64 mmol) was added dropwise under nitrogen.

The mixture was stirred 2 hours, being monitored by TLC. Evaporation of the solvent (using a KOH trap) afforded a crude thiocarbonate **9a** which was used in the next step without further purification.

In a 100 mL round bottomed flask, the crude thiocarbonate (2.9 g, 7.85 mmol) and freshly distilled 1,3-dimethyl-2-phenyl-[1,3,2]-diazaphospholidine (4.3 mL, 23.55 mmol) were placed under nitrogen. The reaction mixture was stirred at 65 °C for 24 h. The residual crude was directly purified by column chromatography eluting with hexanes/ethyl acetate mixtures to yield **10a** (2.0 g, 77 % overall yield from **7a**) as a colorless oil. $[\alpha]_D^{23} +25.04$ (c 1.35, CHCl_3). IR (NaCl) ν 3064, 1613, 1510, 1451 cm^{-1} . ^1H NMR (300 MHz, CDCl_3) δ 7.36-7.17 (m, 7H), 6.86 (d, $J=8.8$ Hz, 2H), 5.97 (m, 2H), 5.22 (m, 4H), 4.25 (d, $J=8.16$, 1H), 3.78 (s, 3H), 3.67 (d, $J=15.5$ Hz, 1H), 3.46 (d, $J=15.5$, 1H), 3.17 (d, $J=8.16$ Hz, 2H). ^{13}C NMR (75 MHz, CDCl_3) δ 158.5 (C), 142.0 (C), 136.8 (CH), 136.2 (CH), 132.2 (C), 129.7 (CH), 128.2 (CH), 128.0 (CH), 126.9 (CH), 118.2 (CH_2), 117.1 (CH_2), 113.6 (CH), 66.6 (CH), 55.2 (CH_3), 53.0 (CH_2), 52.10 (CH_2). MS (CI- NH_3) m/z (%): 294 (100) $[\text{M}+1]^+$, 311 (33) $[\text{M}+18]^+$. HRMS calcd for $\text{C}_{20}\text{H}_{23}\text{NO}$ 293.1780, found 293.1773.

(2S)-1-(4-Methoxy-benzyl)-2-phenyl-2,5-dihydro-1H-pyrrole (11a). To a solution of **10a** (1.5 g, 5.12 mmol) in anhydrous dichloromethane, Grubbs's catalyst (0.21 g, 10% mol) was added dropwise under nitrogen. The resulting mixture was stirred at room temperature. When the reaction was complete by TLC, the reaction mixture was concentrated, and the resulting black residue was purified by column chromatography eluting with hexanes/ethyl acetate mixtures which yielded **11a** (1.14g, 84% yield) as a white solid. $[\alpha]_D^{23} +221.05$ (c 1.1, CHCl_3). IR (NaCl) ν 3064, 1613, 1512, 1454 cm^{-1} . ^1H NMR (300 MHz, CDCl_3 , 55°C) δ 7.39-7.16 (m, 7H), 6.79 (d, 8.8 Hz, 2H), 5.78 (m, 1H), 5.64 (m, 1H), 4.46 (brs, 1H), 3.77 (d, $J=15.4$ Hz, 1H), 3.72 (m, 4H), 3.47 (d, $J=15.4$ Hz, 1H), 3.19 (m, 1H). ^{13}C NMR (75 MHz, CDCl_3) δ 158.4 (C), 143.2 (C), 132.8 (CH), 131.9 (C), 129.6 (CH), 128.3 (CH), 127.9 (CH), 127.3 (CH), 127.1 (CH), 113.6 (CH), 74.2 (CH), 59.2 (CH_2), 56.8 (CH), 55.3 (CH_3). MS (CI- NH_3) m/z

(%): 266 (100) $[M+1]^+$, 283 (9) $[M+18]^+$. Purity by DSC: 99.7 % (mp 60.85°C). Anal. Calcd. For $C_{18}H_{19}NO$: C, 81.47; H, 7.22; N, 5.28. Found: C, 81.64; H, 7.42; N, 5.31.

PMB-N-Boc

5c

^{13}C NMR (50 MHz, CDCl_3), $T=25^\circ\text{C}$

7a

^{13}C NMR (75 MHz, CDCl_3), $T=25^\circ\text{C}$

10b

^1H NMR (300 MHz, CDCl_3), $T=25^\circ\text{C}$

10b

 ^{13}C NMR (75 MHz, CDCl_3), $T=25^\circ\text{C}$

11b

 ^{13}C NMR (75 MHz, CDCl_3), $T=55^\circ\text{C}$