

Supplementary Information

Stereocontrol of palladium(II)-catalysed aza-Claisen rearrangements using a combination of 1,3-allylic strain and a solvent mediated directing effect

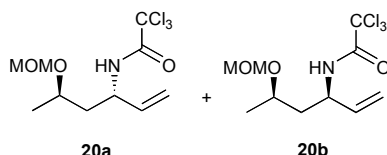
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General Experimental

All reactions were performed under a nitrogen atmosphere unless otherwise noted. Reagents and starting materials were obtained from commercial sources and used as received. THF was distilled from sodium and benzophenone. Flash column chromatography was carried out using Fisher Matrex silica 60. Macherey-Nagel aluminium backed plates pre-coated with silica gel 60 (UV₂₅₄) were used for thin layer chromatography and were visualised by staining with KMnO₄. ¹H NMR and ¹³C NMR spectra were recorded on a Bruker DPX 400 spectrometer with chemical shift values in ppm relative to residual chloroform (δ_{H} 7.28 & δ_{C} 77.2) as standard. Infrared spectra were recorded using Golden Gate apparatus on a JASCO FTIR 410 spectrometer and mass spectra were obtained using a JEOL JMS-700 spectrometer. Optical rotations were determined as solutions irradiating with the sodium D line ($\lambda = 589$ nm) using a AA series Automatic polarimeter. $[\alpha]_{\text{D}}$ values are given in units $10^{-1} \text{deg cm}^2 \text{g}^{-1}$.

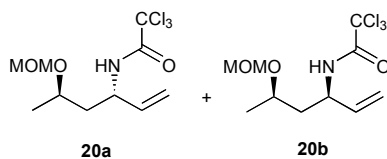
(3*S*,5*R*)-3-(Trichloromethylcarbonylamino)-5-methoxymethoxyhex-1-ene 20a and (3*R*,5*R*)-3-(Trichloromethylcarbonylamino)-5-methoxymethoxyhex-1-ene 20b (Table 1, entry 1).



(2*E*,5*R*)-5-Methoxymethoxyhex-2-en-1-ol **13** (0.18 g, 1.1 mmol) was dissolved in dichloromethane (25 mL) and cooled to 0 °C. 1,8-Diazabicyclo[5.4.0]undec-7-ene (0.2 mL, 1.3 mmol) was then added to the solution followed by trichloroacetonitrile (0.17 mL, 1.7 mmol). The reaction mixture was warmed to room temperature and stirred for 2 h. The reaction mixture was then filtered through a short pad of silica gel and washed with diethyl ether (100 mL). The resulting filtrate was then concentrated to give allylic acetimidate **16** which was used without further purification. Allylic acetimidate **16** was then dissolved in THF (10 mL) under a nitrogen atmosphere. Bis(acetonitrile)palladium(II) chloride (0.03 g, 0.1 mmol) was added to the solution and the mixture was stirred at room temperature overnight. The mixture was then filtered through a short pad of Celite[®] and washed with diethyl ether (100 mL). Concentration of the filtrate followed by flash column chromatography (elution with petroleum ether: diethyl ether 17:3) allowed separation of the title compounds giving these as light brown oils (combined weight and

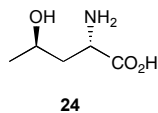
yield: 0.17 g, 50% over two steps). (3*S*,5*R*)-3-(Trichloromethylcarbonylamino)-5-methoxymethoxyhex-1-ene **20a**: $\nu_{\max}/\text{cm}^{-1}$ (neat) 3336 (NH), 2931 (CH), 1709 (CO), 1647 (C=C), 1516; $[\alpha]_{\text{D}}^{22} +9.9$ (*c* 1.0, CHCl₃); δ_{H} (400 MHz, CDCl₃) 1.26 (3H, d, *J* 6.1 Hz, 6-H₃), 1.81 (1H, ddd *J* 15.0, 6.2, 3.0 Hz, 4-*HH*), 1.95 (1H, ddd *J* 15.0, 10.1, 4.0 Hz, 4-*HH*), 3.39 (3H, s, OCH₃), 4.05 (1H, m, 5-H), 4.63 (2H, m, OCHHO and 3-H), 4.76 (1H, d, *J* 7.1 Hz, OCHHO), 5.23-5.29 (2H, m, 1-H₂), 5.85 (1H, ddd, *J* 17.3, 10.1, 5.0 Hz, 2-H), 8.12 (1H, br s, NH); δ_{C} (100 MHz, CDCl₃) 20.3 (CH₃), 40.2 (CH₂), 51.5 (CH₃), 56.0 (CH), 71.0 (CH), 93.0 (C), 95.1 (CH₂), 115.8 (CH₂), 135.7 (CH), 161.2 (C); *m/z* (CI) 304.0270 (MH⁺. C₁₀H₁₇NO₃³⁵Cl₃ requires 304.0274), 272 (100%) and 114 (26). (3*R*,5*R*)-3-(Trichloromethylcarbonylamino)-5-methoxymethoxyhex-1-ene **20b**: $\nu_{\max}/\text{cm}^{-1}$ (neat) 3330 (NH), 2932 (CH), 1698 (CO), 1645 (C=C), 1519; $[\alpha]_{\text{D}}^{22} -9.1$ (*c* 1.0, CHCl₃); δ_{H} (400 MHz, CDCl₃) 1.27 (3H, d, *J* 6.1 Hz, 6-H₃), 1.80 (1H, ddd, *J* 14.3, 6.0, 4.1 Hz, 4-*HH*), 1.90 (1H, dt, *J* 14.3, 8.1 Hz, 4-*HH*), 3.39 (3H, s, OCH₃), 3.84 (1H, m, 5-H), 4.34 (1H, m, 3-H), 4.63 (1H, d, *J* 7.1 Hz, OCHHO), 4.73 (1H, d, *J* 7.1 Hz, OCHHO), 5.22 (1H, dt, *J* 10.4, 1.1, 1-*HH*), 5.28 (1H, dt, *J* 17.5, 1.1 Hz, 1-*HH*), 5.85 (1H, ddd, *J* 17.5, 10.4, 6.0 Hz, 2-H), 7.15 (1H, br s, NH); δ_{C} (100 MHz, CDCl₃) 20.9 (CH₃), 41.5 (CH₂), 52.3 (CH₃), 55.6 (CH), 71.9 (CH), 93.0 (C), 95.4 (CH₂), 116.1 (CH₂), 136.6 (CH), 161.2 (C); *m/z* (CI) 304.0271 (MH⁺. C₁₀H₁₇NO₃³⁵Cl₃ requires 304.0274), 272 (100), 242 (51) and 224 (66).

(3*S*,5*R*)-3-(Trichloromethylcarbonylamino)-5-methoxymethoxyhex-1-ene 20a and (3*R*,5*R*)-3-(Trichloromethylcarbonylamino)-5-methoxymethoxyhex-1-ene 20b using toluene (Table 1, entry 4).



The rearrangement procedure described above was carried out with allylic trichloroacetimidate **16** (0.085 g, 0.3 mmol) except using toluene (10 mL) as the solvent. The above work-up and purification allowed separation of the title compounds as light brown oils (combined weight and yield: 0.06 g, 71%). Spectroscopic data as described above.

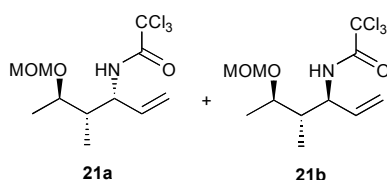
(2*S*,4*R*)-2-Amino-4-hydroxypentanoic acid 24.¹



(2*S*,4*R*)-2-(Trichloromethylcarbonylamino)-4-methoxymethoxypentanoic acid (0.085 g, 0.26 mmol) was dissolved in 6 M hydrochloric acid (10 mL) and heated under reflux overnight. The reaction mixture was cooled to room temperature and then extracted with diethyl ether (2 x 10 mL). The aqueous phase was then concentrated *in vacuo* to give the product in the lactone form. Purification by ion exchange chromatography (elution with 0.5 M NH₄OH solution) yielded (2*S*,4*R*)-2-amino-4-hydroxypentanoic acid **24** as a white solid (0.026 g, 74%). $[\alpha]_{\text{D}}^{25} -32.6$ (*c* 1.5, H₂O), lit.¹ $[\alpha]_{\text{D}} -30.5$ (*c* 0.75, H₂O); δ_{H} (400 MHz, D₂O) 1.10 (3H, d, *J* 7.1, Hz, 5-H₃), 1.78-1.92

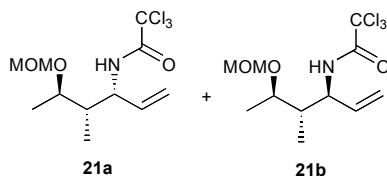
(2H, m, 3-H₂), 3.77 (1H, dd, *J* 6.0, 4.3 Hz, 2-H), 3.85 (1H, m, 4-H); *m/z* (CI) 134 (MH⁺, 82%) and 116 (100).

(3*S*,4*S*,5*R*)-3-(Trichloromethylcarbonylamino)-4-methyl-5-methoxymethoxyhex-1-ene 21a and (3*R*,4*S*,5*R*)-3-(trichloromethylcarbonylamino)-4-methyl-5-methoxymethoxyhex-1-ene 21b (Table 1, entry 2).



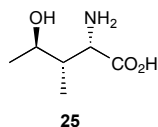
(2*E*,4*S*,5*R*)-4-Methyl-5-methoxymethoxyhex-2-en-1-ol **14** (0.15 g, 0.9 mmol) was dissolved in dichloromethane (25 mL) and cooled to 0 °C. 1,8-Diazabicyclo[5.4.0]undec-7-ene (0.15 mL, 1.0 mmol) was then added to the solution followed by trichloroacetonitrile (0.13 mL, 1.3 mmol). The reaction mixture was warmed to room temperature and stirred for 2 h. The reaction mixture was then filtered through a short pad of silica gel and washed with diethyl ether (100 ml). The resulting filtrate was then concentrated to give allylic acetimidate **17** which was used without further purification. Allylic acetimidate **17** was then dissolved in THF (10 mL) under a nitrogen atmosphere. Bis(acetonitrile)palladium(II) chloride (0.023 g, 0.09 mmol) was added to the solution and the mixture was stirred at room temperature overnight. The mixture was then filtered through a short pad of Celite[®] and washed with diethyl ether (100 mL). Concentration of the filtrate followed by flash column chromatography (elution with petroleum ether: diethyl ether 17:3) allowed separation of the title compounds giving these as light brown oils (combined weight and yield: 0.13 g, 49% over two steps). (3*S*,4*S*,5*R*)-3-(Trichloromethylcarbonylamino)-4-methyl-5-methoxymethoxyhex-1-ene **21a**: $\nu_{\max}/\text{cm}^{-1}$ (neat) 3341 (NH), 2930 (CH), 1716 (CO), 1643 (C=C), 1510; $[\alpha]_{\text{D}}^{22} +18.1$ (*c* 1.0, CHCl₃); δ_{H} (400 MHz, CDCl₃) 0.91 (3H, d, *J* 7.0 Hz, 4-CH₃), 1.17 (3H, d, *J* 6.1 Hz, 6-H₃), 1.85 (1H, m, 4-H), 3.31 (3H, s, OCH₃), 3.57 (1H, dq, *J* 9.3, 6.1 Hz, 5-H), 4.39 (1H, m, 3-H), 4.55 (1H, d, *J* 7.1 Hz, OCHHO), 4.69 (1H, d *J* 7.1 Hz, OCHHO), 5.16-5.23 (2H, m, 1-H₂), 5.76 (1H, m, 2-H), 8.22 (1H, br d, *J* 6.0 Hz, NH); δ_{C} (100 MHz, CDCl₃) 14.4 (CH₃), 18.3 (CH₃), 42.4 (CH), 55.8 (CH₃), 56.4 (CH), 76.2 (CH), 93.1 (C), 95.3 (CH₂), 115.9 (CH₂), 136.1 (CH), 161.4 (C); *m/z* (CI) 318.0426 (MH⁺. C₁₁H₁₉NO₃³⁵Cl₃ requires 318.0428), 288 (90), 286 (95), 258 (57), 238 (64), 188 (100) and 116 (40). (3*R*,4*S*,5*R*)-3-(Trichlorocarbonylamino)-4-methyl-5-methoxymethoxyhex-1-ene **21b**: $\nu_{\max}/\text{cm}^{-1}$ (neat) 3342 (NH), 2932 (CH), 1715 (CO), 1644 (C=C), 1509; $[\alpha]_{\text{D}}^{22} -16.3$ (*c* 0.8, CHCl₃); δ_{H} (400 MHz, CDCl₃) 0.95 (3H, d, *J* 7.0 Hz, 4-CH₃), 1.18 (3H, d, *J* 6.2 Hz, 6-H₃), 1.92 (1H, m, 4-H), 3.30 (3H, s, OCH₃), 3.64 (1H, quin, *J* 6.2 Hz, 5-H), 4.47-4.56 (2H, m, 3-H and OCHHO), 4.64 (1H, d *J* 7.1 Hz, OCHHO), 5.10-5.19 (2H, m, 1-H₂), 5.86 (1H, ddd, *J* 17.2, 10.5, 5.6 Hz, 2-H), 7.46 (1H, br d, *J* 6.0 Hz, NH); δ_{C} (100 MHz, CDCl₃) 14.5 (CH₃), 18.3 (CH₃), 42.5 (CH), 55.8 (CH₃), 56.4 (CH), 76.3 (CH), 93.1 (C), 95.3 (CH₂), 115.9 (CH₂), 136.1 (CH) 161.5 (C); *m/z* (CI) 318.0426 (MH⁺. C₁₁H₁₉NO₃³⁵Cl₃ requires 318.0428), 288 (90), 286 (95), 258 (77), 238 (84), 188 (100).

(3*S*,4*S*,5*R*)-3-(Trichloromethylcarbonylamino)-4-methyl-5-methoxymethoxyhex-1-ene 21a and (3*R*,4*S*,5*R*)-3-(trichloromethylcarbonylamino)-4-methyl-5-methoxymethoxyhex-1-ene 21b using toluene (Table 1, entry 5).



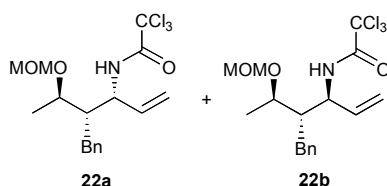
The rearrangement procedure described above was carried out with allylic trichloroacetimidate **17** (0.1 g, 0.3 mmol) except using toluene (10 mL) as the solvent. The above work-up and purification allowed separation of the title compounds as light brown oils (combined weight and yield: 0.066 g, 66%). Spectroscopic data as described above.

(2*S*,3*S*,4*R*)-2-Amino-3-methyl-4-hydroxypentanoic acid 25.²



(2*S*,3*S*,4*R*)-2-(Trichloromethylcarbonylamino)-3-methyl-4-methoxymethoxypentanoic acid (0.1g, 0.29 mmol) was dissolved in 6 M hydrochloric acid (10 mL) and heated under reflux overnight. The reaction mixture was cooled to room temperature and then extracted with diethyl ether (2 x 10 mL). The aqueous phase was then concentrated *in vacuo* to give the product in the lactone form. Purification by ion exchange chromatography (elution with 0.5 M NH₄OH solution) yielded (2*S*,3*S*,4*R*)-2-amino-3-methyl-4-hydroxypentanoic acid **25** as a white solid (0.023 g, 55%). [α]_D²⁷ +2.6 (*c* 1.0, H₂O); lit.² [α]_D^{27.5} +2.9 (*c* 1.0, H₂O); δ _H (400 MHz, D₂O) 0.89 (3H, d, *J* 7.2 Hz, 3-CH₃), 1.19 (3H, d, *J* 6.3 Hz, 5-H₃), 2.04 (1H, quin d, *J* 7.2, 2.7 Hz, 3-H), 3.72 (1H, quin, *J* 6.3 Hz, 4-H), 3.93 (1H, d, *J* 2.7 Hz, 2-H); *m/z* (CI) 148 (MH⁺, 25%), 130 (100) and 85 (15).

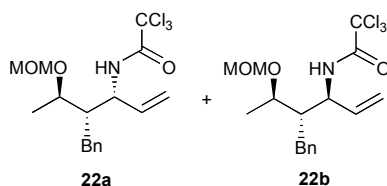
(3*S*,4*S*,5*R*)-3-(Trichloromethylcarbonylamino)-4-benzyl-5-methoxymethoxyhex-1-ene 22a and (3*R*,4*S*,5*R*)-3-(Trichloromethylcarbonylamino)-4-benzyl-5-methoxymethoxyhex-1-ene 22b (Table 1, entry 3).



(2*E*,4*S*,5*R*)-4-Benzyl-5-methoxymethoxyhex-2-en-1-ol **15** (0.2 g, 0.8 mmol) was dissolved in dichloromethane (25 mL) and cooled to 0 °C. 1,8-Diazabicyclo[5.4.0]undec-7-ene (0.13 mL, 0.96 mmol) was then added to the solution followed by trichloroacetonitrile (0.12 mL, 1.2 mmol). The reaction mixture was warmed to room temperature and stirred for 2 h. The reaction

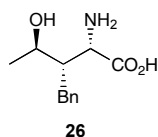
mixture was then filtered through a short pad of silica gel and washed with diethyl ether (100 ml). The resulting filtrate was then concentrated to give allylic acetimidate **18** which was used without further purification. Allylic acetimidate **18** was then dissolved in THF (10 mL) under a nitrogen atmosphere. Bis(acetonitrile)palladium(II) chloride (0.021 g, 0.08 mmol) was added to the solution and the mixture was stirred at room temperature overnight. The mixture was then filtered through a short pad of Celite[®] and washed with diethyl ether (100 mL). Concentration of the filtrate followed by flash column chromatography (elution with petroleum ether: diethyl ether 20:1) allowed separation of the title compounds giving these as light brown oils (combined weight and yield: 0.36 g, 72% over two steps). (3*S*,4*S*,5*R*)-3-(Trichloromethylcarbonylamino)-4-benzyl-5-methoxymethoxyhex-1-ene **22a**: $\nu_{\max}/\text{cm}^{-1}$ (neat) 3368 (NH), 2925 (CH), 1718 (CO), 1497, 1455; $[\alpha]_{\text{D}}^{25} +52.5$ (*c* 1.0, CHCl₃); δ_{H} (400 MHz, CDCl₃) 1.35 (3H, d, *J* 6.1 Hz, 6-H₃), 2.12 (1H, m, 4-H), 2.54 (1H, dd, *J* 14.2, 8.9 Hz, CHHPH), 2.79 (1H, dd, *J* 14.2, 5.6 Hz, CHHPH), 3.41 (3H, s, OCH₃), 3.80 (1H, dq, *J* 8.3, 6.1 Hz, 5-H), 4.45 (1H, m, 3-H), 4.62 (1H, d, *J* 6.9 Hz, OCHHO), 4.77 (1H, d, *J* 6.9 Hz, OCHHO), 5.26-5.35 (2H, m, 1-H₂), 5.89 (1H, ddd, *J* 16.9, 10.5, 6.3 Hz, 2-H), 7.16-7.34 (5H, m, Ph), 8.21 (1H, br d, *J* 6.8 Hz, NH); δ_{C} (100 MHz, CDCl₃) 19.0 (CH₃), 34.1 (CH₂), 49.5 (CH), 54.4 (CH₃), 56.4 (CH), 76.0 (CH), 93.2 (C), 96.0 (CH₂), 118.2 (CH₂), 126.7 (CH), 128.8 (CH), 128.9 (CH), 133.2 (CH), 139.1 (C), 160.7 (C); *m/z* (CI) 394.0747 (MH⁺. C₁₇H₂₃NO₃³⁵Cl₃ requires 394.0744, 15%), 362 (100%), 314 (24), 280 (10) and 171 (21). (3*R*,4*S*,5*R*)-3-(Trichloromethylcarbonylamino)-4-benzyl-5-methoxymethoxyhex-1-ene **22b**: $\nu_{\max}/\text{cm}^{-1}$ (neat) 3357 (NH), 2925 (CH), 1718 (CO), 1498 and 1454; $[\alpha]_{\text{D}}^{25} -19.4$ (*c* 0.5, CHCl₃); δ_{H} (400 MHz, CDCl₃) 1.28 (3H, d, *J* 6.0 Hz, 6-H₃), 2.04 (1H, m, 4-H), 2.67 (1H, dd, *J* 13.9, 8.7 Hz, CHHPH), 2.74 (1H, dd, *J* 13.9, 6.1 Hz, CHHPH), 3.38 (3H, s, OCH₃), 3.86 (1H, m, 5-H), 4.50 (1H, d, *J* 6.8 Hz, OCHHO), 4.63 (1H, m, 3-H), 4.71 (1H, d, *J* 6.8 Hz, OCHHO), 5.03-5.11 (2H, m, 1-H₂), 5.89 (1H, ddd, *J* 17.2, 10.6, 4.4 Hz, 2-H), 7.10-7.34 (5H, m, Ph), 7.92 (1H, br d, *J* 8.1 Hz, NH); δ_{C} (100 MHz, CDCl₃) 20.1 (CH₃), 37.1 (CH₂), 50.0 (CH), 54.6 (CH₃), 56.0 (CH), 76.5 (CH), 93.1 (C), 95.5 (CH₂), 114.6 (CH₂), 126.6 (CH), 128.9 (CH), 129.2 (CH), 137.1 (CH), 139.6 (C), 161.6 (C); *m/z* (CI) 394.0741 (MH⁺. C₁₇H₂₃NO₃³⁵Cl₃ requires 394.0744), 362 (100%), 328 (40), 314 (15) and 171 (20).

(3*S*,4*S*,5*R*)-3-(Trichloromethylcarbonylamino)-4-benzyl-5-methoxymethoxyhex-1-ene 22a and (3*R*,4*S*,5*R*)-3-(Trichloromethylcarbonylamino)-4-benzyl-5-methoxymethoxyhex-1-ene 22b using toluene (Table 1, entry 6).



The rearrangement procedure described above was carried out with allylic trichloroacetimidate **18** (0.105 g, 0.27 mmol) except using toluene (10 mL) as the solvent. The above work-up and purification allowed separation of the title compounds as light brown oils (combined weight and yield: 0.086 g, 82%). Spectroscopic data as described above.

(2*S*,3*S*,4*R*)-2-Amino-3-benzyl-4-hydroxypentanoic acid **26**



(2*S*,3*S*,4*R*)-2-(Trichloromethylcarbonylamino)-3-benzyl-4-methoxymethoxypentanoic acid (0.11 g, 0.27 mmol) was dissolved in 6 M hydrochloric acid (10 mL) and heated under reflux overnight. The reaction mixture was cooled to room temperature and then extracted with diethyl ether (2 x 10 mL). The aqueous phase was then concentrated *in vacuo* to give the product in the lactone form. Purification by ion exchange chromatography (elution with 0.5 M NH₄OH solution) yielded (2*S*,3*S*,4*R*)-2-amino-3-benzyl-4-hydroxypentanoic acid **26** as a white solid (0.033 g, 55%). $\nu_{\max}/\text{cm}^{-1}$ (KBr) 3400 (H-Bond), 3225 (OH), 2970 (CH), 1630 (CO), 1477; $[\alpha]_{\text{D}}^{25} +23.0$ (*c* 0.2, H₂O); δ_{H} (400 MHz, D₂O) 1.08 (3H, d, *J* 6.5, Hz, 5-H₃), 2.13 (1H, m, 3-H), 2.56 (1H, dd, *J* 13.6, 5.1 Hz, CHHPH), 2.62 (1H, dd, *J* 13.6, 10.0 Hz, CHHPH), 3.78 (1H, qd, *J* 6.5, 3.8 Hz, 4-H), 3.92 (1H, d, *J* 2.1 Hz, 2-H); δ_{C} (100 MHz, D₂O) 20.8 (CH₃), 32.1 (CH₂), 46.3 (CH), 54.6 (CH), 66.7 (CH), 126.6 (CH), 128.7 (CH), 129.3 (CH), 139.3 (C), 173.9 (C); *m/z* (EI) 205.1101 (M⁺-H₂O, C₁₂H₁₅NO₂ requires 205.1103), 131 (80), 114 (33), 91 (70) and 70 (100).

References

1. J. Ariza, J. Font and R. M. Ortuno, *Tetrahedron*, 1990, **46**, 1931.
2. R. F. Raffauf, T. M. Zennie, K. D. Onan and P. W. Le Quesne, *J. Org. Chem.*, 1984, **49**, 2714.