Supporting Information

for

Modular synthesis of the pyrimidine core of the manzacidins by divergent Tsuji–Trost coupling

Sebastian Bretzke¹, Stephan Scheeff², Felicitas Vollmeyer², Friederike Eberhagen², Frank Rominger¹ and Dirk Menche^{*2}

Address: ¹Institut für Organische Chemie, Ruprecht-Karls Universität Heidelberg, Im Neuenheimer Feld 270, 69120 Heidelberg, Germany and ²Kekulé-Institut für Organische Chemie und Biochemie, Universität Bonn, Gerhard-Domagk-Strasse 1, 53121 Bonn, Germany

Email: Dirk Menche* - dirk.menche@uni-bonn.de

* Corresponding author

This article is dedicated to the memory of Peter Hofmann. With deep gratitude I remember the joint time at the University of Heidelberg. He has been a role model in many ways.

Full experimental details, characterization data of all products, copies of ¹H and ¹³C NMR spectra and X-ray crystallographic data for

28, 32 and 39

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1. GENERAL INFORMATION

Reaction handling: All reactions were performed under argon atmosphere in flame-dried glassware which had been cooled under argon unless stated otherwise. All flasks were equipped with rubber septa and reactants were handled using standard Schlenk techniques. Temperatures above rt (23 °C) refer to oil bath temperatures which were controlled by a temperature modulator. For cooling, the following baths were used: ethanol/liquid nitrogen (-98 °C), acetone/dry ice (-78 °C), water/ice (0 °C). Reactions were magnetically stirred and monitored by (TLC) unless otherwise noted.

Solvents and reagents: Unless stated otherwise, solvents were purchased from the central chemical store of the Chemistry Department of the University of Heidelberg and were distilled. Dry solvents (dichloromethane, THF, toluene, acetonitrile and diethyl ether) were taken out of the solvent purification system MB SPS-800 with drying columns of the University of Heidelberg or purchased over molecular sieves from the following companies: Sigma-Aldrich, Acros-Organics, Fluka, Merck. Unless stated otherwise all of these chemicals were used without further purification.

TLC-analyses: Analytical thin layer chromatography (TLC) was carried out with "Polygram[®] Sil G/UV254" plastic sheets from Machery-Nagel GmbH & Co. KG. Detection was carried out using short wave UV light (254 nm and 366 nm), cerium (1% Ce(SO₄)₂, 2.5% (MoO₃)₁₂(H₃PO₄), 8 mL conc. H₂SO₄ in 100 mL H₂O), permanganate (0.6% KMnO₄ in water, with 1% K₂CO₃), vanillin (1–2 g of vanillin in 100 mL of EtOH, containing 1 mL of conc. H₂SO₄) or phosphomolybdic acid (PMA, 200 mL water, 4.84 g (NH₃)₃PMo₁₂O₄₀, 3 mL H₃PO₄).

Column chromatography: Flash column chromatography was accomplished using silica gel S (pore size 60 Å, 40–63 μ m) purchased from Sigma-Aldrich Chemie GmbH & Co. KG. The yields given refer to the purified products.

Optical Rotations were measured with a Perkin Elmer 241 polarimeter in a 1 dm cuvette, using a sodium lamp. The optical rotation at the sodium D-line ($[\alpha]_D$ value) was calculated according to the Drude equation:

$$[\alpha]_{D}^{T} = \frac{\alpha \cdot 100}{c \cdot d} \qquad A = \frac{\alpha_{578}}{\alpha_{546} - \alpha_{578}} \qquad [\alpha]_{D}^{T} = \frac{A \cdot \alpha_{546}}{A + 1.3727}$$

T = temperature [°C], d = path length [dm], α = measured rotation [°], c = concentration [g/100 mL], λ = wavelength [nm].

Melting points were measured on a Büchi B-540 melting point apparatus using open glass capillaries.

¹**H NMR spectroscopy:** ¹**H** NMR spectra were recorded at room temperature using the following spectrometers: 200 MHz: Bruker DRX-200; 250 MHz: Bruker ARX-250; 300 MHz: Bruker AC-300 or Bruker DRX-300; 500 MHz: Bruker DRX-500. Unless stated otherwise all spectra were recorded at room temperature in deuterochloroform which was purchased by Sigma Aldrich and all chemical shifts are given in δ units relative to CHCl₃ (singlet: $\delta^{H} = 7.27$). Data for ¹H NMR spectra are reported as follows: chemical

shift (multiplicity, coupling constants in hertz, number of hydrogens), for ¹³C NMR: chemical shift. Analyses followed first order and the following abbreviations were used throughout: s = singlet, bs = broad singlet, d = doublet, t = triplet, q = quartet, quin = quintet, sxt = sextet, sept = spt, dd = doublet of doublet, dt = doublet of triplet, m = multiplet, m_c= centered multiplet.

¹³C NMR spectroscopy: ¹³C NMR spectra were recorded at room temperature using the following spectrometers: 75 MHz: Bruker AC-300 or Bruker DRX-300; 125 MHz: Bruker DRX-500. Unless stated otherwise all spectra were recorded at room temperature in deuterochloroform which was purchased by Sigma Aldrich and all chemical shifts are given in δ units relative to CDCl₃ (central line of triplet: $\delta^{C} = 77.00$).

Mass spectra: Mass spectra (MS) and high resolution mass spectra (HRMS) were recorded at the Department of Organic Chemistry of the University of Heidelberg by Dr. Gross and his members of staff using the following mass spectrometers: Bruker ICR APEX-QE, Vacuum Generators ZAB-2F, Finnigan MAT TSQ 700 and JEOL JMS-700. Ionization processes and calculated exact mass were given.

X-ray diffraction: X-ray diffraction experiments have been carried out by Dr. F. Rominger at the Department of Organic Chemistry at the University of Heidelberg.

Synthesis and characterization data for compounds 12, 17, 18, 19, 23 and 24: Synthesis and characterization data for compounds 12, 17, 18, 19, 23 and 24 have already been reported in a preliminary publication.^[1] These data and copies of NMR spectra for these compounds can be found in the Supporting Information file of this publication.

^[1] Morgen, M.; Bretzke, S.; Li, P.; Menche, D. *Org. Lett.* **2010**, *12*, 4494-4497.

2. EXPERIMENTAL SECTION

(E)-Benzyl 5-hydroxy-1-phenylpent-3-enylcarbamate (14)



Chemical Formula: C₁₉H₂₁NO₃ Exact Mass: 311.15214 Molecular Weight: 311.37494

In a flame-dried and light-protected Schlenk flask, benzyl 1-phenylbut-3-enylcarbamate (**12**, 1.41 g, 5.00 mmol, 1.00 equiv) and Grubbs catalyst 2nd generation (**21**, 212 mg, 0.05 equiv) was diluted in 100 mL of dry dichloromethane at rt under an atmosphere of argon. To this solution was added *cis*-but-2-ene-1,4-diol (**13**, 2.20 g, 2.06 mL, 25.0 mmol, 5.00 equiv) dropwise. The reaction mixture was stirred at rt over night. The solvent was evaporated under vacuum and the residue was purified by column chromatography on silica gel using hexane/ethyl acetate 1:1 as eluent, to afford the desired product as a white solid in a yield of 23% (353 mg, 1.13 mmol). R_f: 0.37 (hexane/ethyl acetate 1:1); ¹H-NMR (300.13 MHz, CDCl₃): $\delta = 2.56$ (t, J = 6.22 Hz, 2H), 4.05 (t, J = 4.80 Hz, 2H), 4.75 – 4.86 (m, 1H), 5.02 – 5.15 (m, 3H), 5.57 (dt, J = 15.26, 6.78 Hz, 1H), 5.72 (dt, J = 15.45, 5.46 Hz, 1H), 7.22 – 7.43 (m, 10H); ¹³C-NMR (75.47 MHz, CDCl₃): $\delta = 39.45$, 54.74, 63.25, 66.83, 126.23, 127.43, 128.17, 128.50, 128.63, 132.89, 136.35, 155.67; HR-MS (ESI): calculated for C₁₉H₂₁NO₃Na⁺ [M+Na]⁺: m/z = 334.14191, found: m/z = 334.14181.

Benzyl (1-phenylbut-3-en-1-yl)(tosylcarbamoyl)carbamate (16)



Chemical Formula: C₂₆H₂₆N₂O₅S Exact Mass: 478.1562 Molecular Weight: 478.5600

To a cooled (- 78 °C) solution of benzyl (1-phenylbut-3-en-1-yl)carbamate (**12**, 380 mg, 1.35 mmol, 1.0 equiv) in dry diethyl ether (30 mL) was added a solution of *n*-BuLi (2.5 M in hexane, 600 μ L, 1.49 mmol, 1.1 equiv) over 5 min using a syringe pump. After 10 min a solution of tosyl isocyanate (200 μ L, 1.42 mmol, 1.1 equiv) in dry diethyl ether was added slowly over a period of 5 min. The reaction mixture was stirred at -78 °C for 1 h and quenched with aqueous saturated ammonium chloride (20 mL). The whole mixture was extracted with diethyl ether (3 x 20 mL). The combined organic phases were dried over MgSO₄ and concentrated under reduced pressure. The crude product was purified by column

chromatography on silica gel (100 mg) with ethyl acetate/hexane 1:9 as the eluent to afford the homoallylic amine (64.1 mg, 0.23 mmol, 17%) and the desired product as colorless solid (233 mg, 0.49 mmol, 36%, 43% brsm); R_f: 0.22 (ethyl acetate/hexane = 1:9); ¹H-NMR (300.13 MHz, CDCl₃): δ = 2.49 (s, 3H), 2.84 (t, *J* = 8.0 Hz, 2H), 4.86 (d, *J* = 17.0 Hz, 1H), 4.91 (d, *J* = 9.7 Hz, 1H), 5.00 (d, *J* = 11.9 Hz, 1H), 5.12 (d, *J* = 11.9 Hz, 1H), 5.60 (ddt, *J* = 7.3 Hz, 10.1 Hz, 17.4 Hz, 1H), 5.96 (t, *J* = 8.1 Hz, 1H), 7.08 (m, 4H), 7.24 (m, 3H), 7.36 (m, 5H), 8.01 (d, *J* = 8.2 Hz, 2H), 11.54 (bs, 1H); ¹³C-NMR (75.47 MHz, CDCl₃): δ = 22.1, 35.5, 55.8, 70.0, 118.6, 127.4, 127.7, 128.6, 128.9, 129.1, 129.2, 129.4, 129.8, 134.1, 134.3, 136.2, 139.4, 145.2, 150.8, 156.2; HR-MS (ESI⁺): calculated for C₂₆H₂₆N₂O₅SNa⁺ [M+Na]⁺: *m/z* = 501.2455, found: *m/z* = 501.2400.

1-((tert-Butyldimethylsilyl)oxy)propan-2-one (26)

OTBS

Chemical Formula: C₉H₂₀O₂Si Exact Mass: 188.1233 Molecular Weight: 188.3394

tert-Butyldimethylsilyl chloride (2.48 g, 16.5 mmol, 1.1 equiv) was added to a stirred solution of 1hydroxypropan-2-one (**25**, 1.11 g, 15.0 mmol, 1.0 equiv) and imidazole (1.43 g, 21.0 mmol, 1.4 equiv) in 20 mL dry dichloromethane at 0 °C. The mixture was stirred for 5 h at the same temperature, the solvent was evaporated under reduced pressure and the residue was extracted three times with diethyl ether and finally washed with water. The combined organic layer was dried over MgSO₄, filtered, concentrated and purified by column chromatography on silica gel (50 g) with ethyl acetate/hexane 1:40 as the eluent, which yielded the desired TBS-protected ketone as colorless liquid (2.48 g, 13.2 mmol, 88%). R_f: 0.18 (ethyl acetate/hexane = 1:40); ¹H-NMR (500.13 MHz, CDCl₃): δ = 0.09 (s, 6H), 0.93 (s, 9H), 2.17 (s, 3H), 4.15 (s, 2H); ¹³C-NMR (125.77 MHz, CDCl₃): δ = -5.5, 18.3, 25.7, 69.6, 209.2; HR-MS (EI⁺): calculated for C₉H₂₀O₂Si⁺ [M]⁺: *m/z* = 188.1227, found: *m/z* = 188.1242.

(S_s)-N-(1-((tert-Butyldimethylsilyl)oxy)propan-2-ylidene)-2-methylpropane-2-sulfinamide (29)

O J^{W^W</sub>S_NOTBS}

Chemical Formula: C₁₃H₂₉NO₂SSi Exact Mass: 291.1688 Molecular Weight: 291.5254 1-((*tert*-Butyldimethylsilyl)oxy)propan-2-one (**26**, 1.88 g, 10.0 mmol, 1.0 equiv) was dissolved in 20 mL of dry THF. To this solution titanium(IV) isopropoxide (4.85 mL, 25.0 mmol, 2.6 equiv) and (*S*)-2-methyl-2-propanesulfinamide (**27**, 1.18 g, 9.70 mmol, 1.0 equiv) were added and the mixture was stirred at 70 °C for 19 h. After cooling to rt, the solution was poured into an equal volume of brine with vigorous stirring. The resulting suspension was filtered and washed with ethyl acetate. The aqueous layer was extracted three times with ethyl acetate, the combined organic layer was washed with brine, dried over MgSO₄, concentrated. Purification by column chromatography on silica gel (100 g) with ethyl acetate/hexane 1:9 as the eluent, yielded the desired *N*-sulfinyl ketimine as light yellow oil (1.87 g, 6.43 mmol, 66%); R_f: 0.25 (ethyl acetate/hexane = 1:9); $[\alpha]^{20}_{D}$ = +174.1 (c = 1.00, CHCl₃); ¹H-NMR (500.13 MHz, CDCl₃): δ = 0.09 (s, 6H), 0.91 (s, 9H), 1.24 (s, 9H), 2.33 (s, 3H), 4.23 (s, 2H); ¹³C-NMR (125.77 MHz, CDCl₃): δ = -5.4, 18.2, 18.9, 22.2, 25.7, 56.6, 69.3, 184.2; HR-MS (FAB⁺): calculated for C₁₃H₃₀NO₂SSi⁺ [M+H]⁺: *m/z* = 292.1716, found: *m/z* = 292.1783.

(R_s)-N-(1-((tert-butyldimethylsilyl)oxy)propan-2-ylidene)-2-methylpropane-2-sulfinamide (30)

Chemical Formula: C₁₃H₂₉NO₂SSi Exact Mass: 291.1688 Molecular Weight: 291.5254

1-((*tert*-Butyldimethylsilyl)oxy)propan-2-one (**26**, 1.51 g, 8.02 mmol, 1.0 equiv) was dissolved in 15 mL of dry THF. To this solution titanium(IV) isopropoxide (3.88 mL, 20.0 mmol, 2.5 equiv) and (*R*)-2-methyl-2-propanesulfinamide (**28**) (970 mg, 8.02 mmol, 1.0 equiv) were added and the mixture was stirred at 70 °C for 14 h. After cooling to rt, the solution was poured into an equal volume of brine with vigorous stirring. The resulting suspension was filtered and washed with ethyl acetate. The aqueous layer was extracted three times with ethyl acetate, the combined organic layer was washed with brine, dried over MgSO₄, concentrated. Purification by column chromatography on silica gel (100 g) with ethyl acetate/hexane 1:9 as eluent, yielded the desired imine as light yellow oil (1.28 g, 4.41 mmol, 55%); R_f: 0.1 (ethyl acetate/hexane = 1:9); $[\alpha]^{20}_{D}$ = -126.4 (c = 1.00, CHCl₃); ¹H NMR (300.13 MHz, CDCl₃): δ = 0.09 (s, 6H), 0.92 (s, 9H), 1.24 (s, 9H), 2.34 (s, 3H), 4.24 (s, 2H); ¹³C NMR (75.47 MHz, CDCl₃): δ = -5.4, 18.2, 18.9, 22.2, 25.7, 56.6, 69.3, 184.2; HR-MS (FAB⁺): calculated for C₁₃H₃₀NO₂SSi⁺ [M+H]⁺: *m/z* = 292.1716, found: *m/z* = 292.1772.

 (R_{s}) -N-((S)-1-((tert-Butyldimethylsilyl)oxy)-2-methylpent-4-en-2-yl)-2-methylpropane-2-sulfinamide (33) and (R_{s}) -N-((R)-1-((tert-butyldimethylsilyl)oxy)-2-methylpent-4-en-2-yl)-2-methylpropane-2sulfinamide (34)



Chemical Formula: C₁₆H₃₅NO₂SSi Exact Mass: 333.2158 Molecular Weight: 333.6051

a flame-dried flask (R_s)-N-(1-((tert-butyldimethylsilyl)oxy)propan-2-ylidene)-2-methyl-propane-2-In sulfinamide (30, 620 mg, 2.13 mmol, 1.0 equiv) was dissolved in 6.0 mL toluene and the solution was cooled to -78 °C. To this mixture allylmagnesium bromide (1.0 M in Et₂O, 3.2 mL, 3.20 mmol, 1.5 equiv) was slowly added and the reaction was stirred for 2 h at -78 °C. The reaction was guenched with a solution of saturated Na₂SO₄, warmed to rt, filtered, washed with ethyl acetate and finally purified by column chromatography on silica gel (50 g) with ethyl acetate/hexane 1:9 as eluent, which yielded the desired diasteromers (major diastereomer 33, minor diastereomer 34) as colorless oils (64%, dr = 1:1.4). Major diastereomer $R_{\rm S}S$ (264 mg, 0.79 mmol, 37%): R_f: 0.13 (ethyl acetate/ hexane = 1:9); $[\alpha]^{20}_{\rm D}$ = -53.3 $(c = 1.00, CHCl_3)$; ¹H-NMR (300.13 MHz, CDCl_3): $\delta = 0.06$ (s, 6H), 0.91 (s, 9H), 1.19 (s, 12H), 2.48 (dd, J = 4.7 Hz, 7.4 Hz, 2H), 3.32 (d, J = 9.3 Hz, 1H), 3.49 (d, J = 9.3 Hz, 1H), 3.72 (bs, 1H), 5.11 (d, J = 10.4 Hz, 1H), 5.12 (d, J = 17.3 Hz, 1H), 5.80 (ddt, J = 7.7 Hz, 10.4 Hz, 17.8 Hz, 1H); ¹³C-NMR $(75.47 \text{ MHz}, \text{CDCl}_3)$: $\delta = -5.5$, 18.2, 22.1, 22.6, 25.8, 43.0, 55.5, 58.1, 69.2, 118.8, 133.8; HR-MS (FAB⁺): calculated for $C_{16}H_{36}NO_2SSi^+$ [M+H]⁺: m/z = 334.2231, found: m/z = 334.2226; minor diastereomer R_sR (192 mg, 0.58 mmol, 27%): R_{f} : 0.2 (ethyl acetate/hexane = 1:9); $[\alpha]_{D}^{20} = -40.7$ (c = 1.00, CHCl₃); ¹H-NMR $(300.13 \text{ MHz}, \text{CDCl}_3)$: $\delta = 0.06$ (s, 3H), 0.08 (s, 3H), 0.91 (s, 9H), 1.20 (s, 9H), 1.28 (s, 3H), 2.22 (dd, 3H)) J = 8.0 Hz, 13.7 Hz, 1H), 2.37 (dd, J = 6.9 Hz, 13.7 Hz, 1H), 3.48 (d, J = 9.3 Hz, 1H), 3.52 (d, J = 9.6 Hz, 1H), 3.77 (bs, 1H), 5.09 (d, J = 17.8 Hz, 1H), 5.10 (d, J = 9.9 Hz, 1H), 5.78 (ddt, J = 7.7 Hz, 10.7 Hz, 17.3 Hz, 1H); ¹³C-NMR (75.47 MHz, CDCl₃): δ = -5.5, 18.2, 22.3, 22.7, 25.8, 43.1, 55.6, 58.1, 69.9, 118.5, 133.6; HR-MS (FAB⁺): calculated for C₁₆H₃₆NO₂SSi⁺ [M+H]⁺: m/z = 334.2231, found: m/z = 334.2223.

(R)-1-Hydroxy-2-methylpent-4-en-2-aminium chloride (35a)



Chemical Formula: C₆H₁₄CINO Exact Mass: 151.0764 Molecular Weight: 151.6345

(S_s)-*N*-((*R*)-1-((*tert*-Butyldimethylsilyl)oxy)-2-methylpent-4-en-2-yl)-2-methylpropane-2-sulfinamide (**31**, 845 mg, 2.53 mmol, 1.0 equiv) was dissolved in 5.0 mL MeOH. Hydrogen chloride (4.0 M in dioxane, 6.5 mL, 6.50 mmol, 10 equiv) was added, the solution was stirred for 30 min at rt and concentrated in vacuo. To the residue was added diethylether (10 mL) and the mixture was stirred for 15 min at rt untill complete precipitation of the hydrochloride. The organic layer was removed and the hydrochloride was washed twice with diethylether. Finally, the solid was dried under high vacuum to afford the desired hydrochloride as colorless powder in quantitative yield (378 mg, 2.50 mmol, quant.). $[\alpha]^{20}_{D} = +2.1$ (c = 1.00, MeOH); ¹H-NMR (300.13 MHz, MeOH- d^4): $\delta = 1.26$ (s, 3H), 2.37 (dd, J = 7.5 Hz, 13.5 Hz, 1H), 2.44 (d, J = 11.5 Hz, 1H), 3.49 (d, J = 11.5 Hz, 1H), 3.56 (d, J = 11.5 Hz, 1H), 5.26 (dd, J = 1.9 Hz, 9.7 Hz, 1H), 5.84 (ddt, J = 7.5 Hz, 9.7 Hz, 17.4 Hz, 1H); ¹³C-NMR (75.47 MHz, MeOH- d^4): $\delta = 20.2$, 40.8, 58.3, 66.2, 121.4, 131.9; HR-MS (EI⁺): calculated for C₆H₁₄NO⁺ [M-CI]⁺: m/z = 116.1069, found: m/z = 116.1063.

(R)-2-Amino-2-methylpent-4-en-1-ol (35)

Chemical Formula: C₆H₁₃NO Exact Mass: 115.0997 Molecular Weight: 115.1735

(*R*)-1-Hydroxy-2-methylpent-4-en-2-aminium chloride (**35a**, 360 mg, 2.38 mmol, 1.0 equiv) was dissolved in water (8.0 mL). To this solution, potassium hydroxide (2.85 g, 50.3 mmol, 20.0 equiv) was added and the mixture was stirred at rt for 1 h. The solution was extracted three times with dichloromethane, the combined organic layers were dried over MgSO₄ and the solvent was removed in vacuo to afford the desired amino alcohol as yellow oil (273 mg, 2.37 mmol, 99%). [α]²⁰_D = +0.20 (c = 1.00, CHCl₃); ¹H-NMR (300.13 MHz, CDCl₃): δ = 1.05 (s, 3H), 1.94 (bs, 3H), 2.14 (d, *J* = 7.4 Hz, 2H), 3.29 (d, *J* = 10.4 Hz, 1H), 3.34 (d, *J* = 10.7 Hz, 1H), 5.11 (d, *J* = 16.7 Hz, 1H), 5.12 (d, *J* = 10.2 Hz, 1H), 5.83 (ddt, *J* = 7.4 Hz, 10.4 Hz, 17.8 Hz, 1H); ¹³C-NMR (75.47 MHz, CDCl₃): δ = 24.6, 44.4, 52.7, 70.1, 118.6, 133.8; HR-MS (El⁺): calculated for C₆H₁₄NO⁺ [M+H]⁺: *m/z* = 116.1069, found: *m/z* = 116.1048.

(R)-1-((tert-Butyldimethylsilyl)oxy)-2-methylpent-4-en-2-amine (36)

 NH_2 TBSO

Chemical Formula: C₁₂H₂₇NOSi Exact Mass: 229.1862 Molecular Weight: 229.4344

To an ice-cooled (0 °C) solution of (*R*)-2-amino-2-methylpent-4-en-1-ol (**35**, 225 mg, 2.22 mmol, 1.0 equiv), triethylamine (0.4 mL, 2.66 mmol, 1.2 equiv) and 4-(dimethylamino)pyridine (13.4 mg, 0.11 mmol, 5 mol %) in dichloromethane (2.5 mL) was added *tert*-butyldimethylsilyl chloride (368 mg, 2.44 mmol, 1.1 equiv). The mixture was allowed to warm to rt and was stirred overnight. The solution was washed with water and saturated NH₄Cl solution. The organic layer was dried over MgSO₄ and concentrated. The residue was purified by flash column chromatography on silica gel (30 g) using 5% MeOH in dichloromethane as eluent to afford pure (*R*)-1-((*tert*-butyldimethylsilyl)oxy)-2-methylpent-4-en-2-amine as pale yellow oil (503 mg, 2.20 mmol, 99%). R_f: 0.63 (MeOH/dichloromethane = 1:9); $[\alpha]^{20}_{D}$ = +2.90 (c = 1.00, CHCl₃); ¹H-NMR (300.13 MHz, CDCl₃): δ = 0.05 (s, 3H), 0.91 (s, 9H), 1.02 (s, 3H), 1.17 (bs, 2H), 2.15 (d, *J* = 7.4 Hz, 2H), 3.31 (d, *J* = 9.6 Hz, 1H), 3.36 (d, *J* = 9.3 Hz, 1H), 5.08 (d, *J* = 17.6 Hz, 1H), 5.09 (d, *J* = 17.6 Hz, 1H), 5.83 (ddt, *J* = 7.7 Hz, 11.3 Hz, 15.4 Hz, 1H); ¹³C-NMR (75.47 MHz, CDCl₃): δ = -5.5, 18.2, 24.3, 25.9, 43.9, 52.9, 71.1, 118.1, 134.3; HR-MS (ESI⁺): calculated for C₁₂H₂₈NOSi⁺ [M+H]⁺: *m/z* = 230.1935, found: *m/z* = 230.1935; [M+Na]⁺ calculated: *m/z* = 252.1754, found: *m/z* = 252.1754.

Mosher amide analysis of (R)-1-((tert-butyldimethylsilyl)oxy)-2-methyl-pent-4-en-2-amine (36)

(*R*)-*N*-((*R*)-1-((*tert*-Butyldimethylsilyl)oxy)-2-methylpent-4-en-2-yl)-3,3,3-trifluoro-2-methoxy-2-phenylpropanamide (36a)

Chemical Formula: C₂₂H₃₄F₃NO₃Si Exact Mass: 445.2260 Molecular Weight: 445.5910

(*R*)-1-((*tert*-Butyldimethylsilyl)oxy)-2-methylpent-4-en-2-amine (**36**, 22.1 mg, 96.4 μ mol, 1.2 equiv) was dissolved in 0.5 mL dichloromethane in a micro-reaction vial. (*S*)- α -Methoxy- α -(trifluoromethyl) phenylacetyl chloride (15.0 μ L, 80.4 μ mol, 1.0 equiv) and *N*,*N*-diisopropylethylamine (16.8 μ L, 96.4 μ mol, 1.2 equiv) were added. The mixture was stirred at rt for 15 min and diluted in 10 mL

dichloromethane. The solution was extracted with 3 x 15 mL of 5% HCl, washed with deionized water and dried over MgSO₄. A micro-flash column was prepared by packing a Pasteur pipette with glass wool and SiO₂. The residue was eluted using a mixture of hexane/ethyl acetate 3:1 to afford the desired Mosher amide (42.5 mg, 95.5 µmol, 99%) in quantitative yield for ¹H NMR analysis. R_f: 0.85 (ethyl acetate/ hexane = 1:3); $[\alpha]^{20}_{D}$ = -5.30 (c = 1.00, CHCl₃); ¹H-NMR (300.13 MHz, CDCl₃): $\overline{\delta}$ = 0.06 (s, 6H), 0.90 (s, 9H), 1.36 (s, 3H), 2.53 (ddt, *J* = 7.6 Hz, 13.8 Hz, 21.6 Hz, 2H), 3.41 (s, 3H), 3.48 (d, *J* = 9.8 Hz, 1H), 3.64 (d, *J* = 9.8 Hz. 1H), 5.07 (d, *J* = 13.2 Hz, 2H), 5.72 (ddt, *J* = 7.6 Hz, 8.8 Hz, 16.4 Hz, 1H), 7.01 (bs, 1H), 7.39 (m, 3H), 7.56 (m, 2H); HR-MS (ESI⁺): calculated for C₂₂H₃₅F₃NO₃Si⁺ [M+H]⁺: *m/z* = 446.2334, found: *m/z* = 446.2332; C₂₂H₃₄F₃NO₃SiNa⁺ [M+Na]⁺: *m/z* = 468.2153, found: *m/z* = 468.2152.

(*S*)-*N*-((*R*)-1-((*tert*-Butyldimethylsilyl)oxy)-2-methylpent-4-en-2-yl)-3,3,3-trifluoro-2-methoxy-2-phenylpropanamide (36b)

Chemical Formula: C₂₂H₃₄F₃NO₃Si Exact Mass: 445.2260 Molecular Weight: 445.5910

(*R*)-1-((*tert*-Butyldimethylsilyl)oxy)-2-methylpent-4-en-2-amine (**36**, 22.1 mg, 96.4 μmol, 1.2 equiv) was dissolved in 0.5 mL dichloromethane in a micro-reaction vial. (*R*)-α-Methoxy-α-(trifluoromethyl) phenylacetyl chloride (15.0 μL, 80.4 μmol, 1.0 equiv) and *N*,*N*-diisopropylethylamine (16.8 μL, 96.4 μmol, 1.2 equiv) were added. The mixture was stirred at rt for 15 min and diluted in 10 mL dichloromethane. The solution was extracted with 3 x 15 mL of 5% HCl, washed with deionized water and dried over MgSO₄. A micro-flash column was prepared by packing a Pasteur pipette with glass wool and SiO₂. The residue was eluted using a mixture of hexane/ethyl acetate 3:1 to afford the desired Mosher amide (42.5 mg, 95.5 μmol, 99%) for ¹H NMR analysis. R_f: 0.81 (ethyl acetate/ hexane = 1:3); $[\alpha]^{20}_{D}$ = +1.00 (c = 1.00, CHCl₃); ¹H-NMR (300.13 MHz, CDCl₃): δ = 0.06 (s, 6H), 0.89 (s, 9H), 1.33 (s, 3H), 2.57 (d, *J* = 7.3 Hz, 2H), 3.42 (s, 3H), 3.43 (d, *J* = 9.6 Hz, 1H), 3.66 (d, *J* = 9.6 Hz, 1H), 5.09 (d, *J* = 11.3 Hz, 1H), 5.10 (d, *J* = 15.7 Hz, 1H), 5.76 (ddt, *J* = 7.6 Hz, 8.8 Hz, 16.4 Hz, 1H), 7.01 (bs, 1H), 7.39 (m, 3H), 7.55 (m, 2H); HR-MS(ESI⁺): calculated for C₂₂H₃₅F₃NO₃Si⁺ [M+H]⁺: *m/z* = 446.2332, found: *m/z* = 446.2334; C₂₂H₃₄F₃NO₃SiNa⁺ [M+Na]⁺: *m/z* = 468.2152, found: *m/z* = 468.2154.

$F_{3}C$ $MeO Ph$ H $MeO Ph$ H					
$MTPA \underbrace{N}_{H} \underbrace{L_{1}}_{\Delta\delta^{SR} < 0} MTPA \underbrace{Me}_{H} \underbrace{Me}_{OTBS}$					
proton	δ (<i>S</i>)-Mosher amide (36b) [ppm]	δ (<i>R</i>)-Mosher amide (36a) [ppm]	$\Delta \delta^{SR}$		
1 2 3 4	5.10 5.76 2.57 3.55	5.07 5.72 2.53 3.56	+0.03 +0.04 +0.04 -0.01		

(R)-Benzyl (1-((tert-butyldimethylsilyl)oxy)-2-methylpent-4-en-2-yl)carbamate (37)

NHCbz TBSO

Chemical Formula: C₂₀H₃₃NO₃Si Exact Mass: 363.2230 Molecular Weight: 363.5664

To a stirred solution of (*R*)-1-((*tert*-butyldimethylsilyl)oxy)-2-methylpent-4-en-2-amine (**36**, 217 mg, 0.95 mmol, 1.0 equiv) in dichloromethane was added potassium carbonate (98.1 mg, 0.71 mmol, 75 mol %) and 0.5 mL of water. The mixture was warmed to 32 °C, and benzyl chloroformate (0.18 mL, 1.24 mmol, 1.5 equiv) was added dropwise while maintaining the temperature at 30–35 °C. The reaction mixture was stirred at 33 °C for 4 h, then aqueous NH₄Cl (0.5 mL) was added and stirring continued for further 15 min. After cooling to rt the phases were separated and the aqueous layer was washed with dichloromethane. Finally the combined organic phases were dried over MgSO₄, concentrated in vacuo and purified by flash column chromatography on silica gel (30 g) using ethyl acetate/hexane 1:40 as the eluent to afford pure carbamate in quantitative yield (344 mg, 0.95 mmol, quant.). [α]²⁰_D = +3.50 (c = 1.00, CHCl₃); R_f: 0.23 (ethyl acetate/hexane = 1:40); ¹H-NMR (300.13 MHz,

CDCl₃): $\delta = 0.05$ (s, 6H), 0.09 (s, 9H), 1.29 (s, 3H), 2.39 (dd, J = 7.4 Hz, 13.7 Hz, 1H), 2.52 (dd, J = 7.1 Hz, 13.5 Hz, 1H), 3.53 (d, J = 9.9 Hz, 1H), 3.61 (d, J = 9.6 Hz, 1H), 4.92 (bs, 1H), 5.09 (m, 4H), 5.79 (ddt, J = 7.4 Hz, 12.6 Hz, 14.8 Hz, 1H), 7.36 (m, 5H); ¹³C-NMR (75.47 MHz, CDCl₃): $\delta = -5.5$, 18.2, 21.3, 25.8, 40.5, 55.9, 66.1, 67.3, 118.5, 127.9, 128.0, 128.5, 133.6, 136.8, 155.0 ; HR-MS (ESI⁺): calculated for C₂₀H₃₄NO₃Si⁺ [M+H]⁺: m/z = 364.2302, found: m/z = 364.2303; C₂₀H₃₃NO₃SiNa⁺ [M+Na]⁺: m/z = 386.2121, found: m/z = 386.2123.

(*R*,*E*)-Benzyl (9,12,12,13,13-pentamethyl-3-oxo-2,4,11-trioxa-12-silatetradec-6-en-9-yl)-carbamate (38)

NHCbz TBSO OCO₂Me

Chemical Formula: C₂₃H₃₇NO₆Si Exact Mass: 451.2390 Molecular Weight: 451.6285

To a stirred solution of (R)-benzyl (1-((tert-butyldimethylsilyl))) a stirred solution of (R)-benzyl (1-(tert-butyldimethylsilyl)) a stirred solution of (R)-benzyl (1-((tert-butyldimethylsilyl))) a stirred solution of (R)-benzyl (1-(tert-butyldimethylsilyl)) a stirred solution of (R)-benzyl (1-(tert-butyl 665 mg, 1.83 mmol, 1.0 equiv) and (Z)-(but-2-ene-1,4-diyl)dimethyl dicarbonate (17, 934 mg, 4.58 mmol, 2.5 equiv) in dry toluene (5 mL) was added Grubbs catalyst 2nd generation (21, 155 mg, 0.18 mmol, 10 mol %). The reaction mixture was stirred for 15 h at 80 °C under an argon atmosphere and concentrated in vacuo. Purification by column chromatography on silica gel (100 g) with ethyl acetate/hexane 1:20 as the eluent yielded the desired isomers (major isomer trans-38, minor isomer cis-38b) as brown oils (71%, cis:trans = 1:5.3). Major isomer trans-38 (489 mg, 1.08 mmol, 59%): Rf: 0.11 (ethyl acetate/ hexane = 1:20); ¹H-NMR (300.13 MHz, CDCl₃): δ = 0.04 (s, 6H), 0.89 (s, 9H), 1.27 (s, 3H), 2.42 (dd, J = 7.1 Hz, 13.7 Hz, 1H), 2.54 (dd, J = 7.1 Hz, 13.7 Hz, 1H), 3.50 (d, J = 9.6 Hz, 1H), 3.58 (d, J = 9.9 Hz, 1H), 3.77 (s, 3H), 4.56 (d, J = 6.0 Hz, 2H), 4.89 (s, 1H), 5.05 (s, 2H), 5.64 (dt, J = 6.3 Hz, 15.4 Hz, 1H), 5.78 (dt, J = 7.7 Hz, 15.4 Hz, 1H), 7.36 (m, 5H); ¹³C-NMR (75.47 MHz, CDCl₃): $\delta = -5.6$, 18.2, 21.5, 25.8, 38.6, 54.7, 56.0, 66.1, 67.4, 68.3, 127.0, 128.0, 128.1, 128.5, 131.6, 136.7, 155.6; HR-MS (ESI⁺): calculated for $C_{23}H_{38}NO_6Si^+$ [M+H]⁺: m/z = 452.2462, found: m/z = 452.2466; $C_{23}H_{37}NO_6SiNa^+$ $[M+Na]^+$: m/z = 474.2282, found: m/z = 474.2285; $C_{23}H_{37}NO_6SiK^+$ $[M+K]^+$: m/z = 490.2021, found: m/z = 490.2024; minor isomer *cis*-360 (93.0 mg, 0.21 mmol, 12%): R_f: 0.12 (ethyl acetate/ hexane = 1:20); ¹H-NMR (300.13 MHz, CDCl₃): $\delta = 0.05$ (s, 6H), 0.09 (s, 9H), 1.30 (s, 3H), 2.47 (dd, J = 5.8 Hz, 14.6 Hz, 1H), 2.62 (dd, J = 6.0 Hz, 14.6 Hz, 1H), 3.53 (d, J = 9.6 Hz, 1H), 3.63 (d, J = 9.6 Hz, 1H), 3.74 (s, 3H), 4.68 (m, 2H), 5.01 (s, 1H), 5.05 (s, 2H), 5.70 (dt, J = 5.5 Hz, 11.8 Hz, 2H), 7.35 (m, 5H); ¹³C-NMR (75.47 MHz, CDCl₃): δ = -5.5, 18.2, 21.5, 25.8, 33.7, 54.7, 56.2, 63.5, 66.1, 67.4, 125.9, 128.0, 128.1, 128.5, 130.3, 136.7, 155.0, 155.7; HR-MS (ESI⁺): calculated for C₂₃H₃₈NO₆Si⁺ [M+H]⁺: *m/z* = 452.2462, found: *m*/*z* = 452.2465.

(4R,6S)-4-((tert- Butyldimethylsilyloxy)methyl)-4-methyl-6-vinyltetrahydropyrimidin-2(1H)-one (44)



Chemical Formula: C₁₄H₂₈N₂O₂Si Exact Mass: 284.1920 Molecular Weight: 284.4698

Sml₂ (0.1 M in THF, 7.5 mL, 754 µmol, 6 equiv) was added to a solution of (4R,6S)-4-((tertbutyldimethylsilyloxy)methyl)-4-methyl-1-tosyl-6-vinyltetrahydropyrimidin-2(1H)-one (42, 55.1 mg, 126 µmol) in dry THF (3.4 mL) at 0 °C and the reaction mixture was stirred at rt for 5 h. The reaction was quenched by the addition of a saturated NaHCO₃ solution (15 mL) and the mixture extracted with ethyl acetate until the color of the aqueous layer turned white. Afterwards, the combined organic extracts were washed with brine and dried over MgSO₄. The solvent was removed under reduced pressure and the residue purified by column chromatography on silica gel (5% MeOH in CH₂Cl₂) to yield the pyrimidine (36.1 mg, 127 μ mol, quant.) as a red solid. $R_{\rm f}$: 0.32 (5% MeOH in dichloromethane); $[\alpha]_{\rm D}^{20} = +10.9$ $(c = 0.5, CHCl_3)$; ¹H-NMR (400.13 MHz, CDCl_3): δ [ppm] = 0.06 (s, 6H), 0.90 (s, 9H), 1.26 (s, 3H), 1.44 (dd, J = 12.8, 11.6 Hz, 1H), 1.65 (dd, J = 12.8, 3.9 Hz, 1H), 3.40 (d, J = 9.4 Hz, 1H), 3.45 (d, J = 9.4 Hz, 1H), 3.45 (d, J = 9.4 Hz, 1H)H), 4.05 (ddd, J = 11.6, 7.1, 3.9 Hz, 1H), 4.94 (br. s, 1H), 5.11 (br. s, 1H), 5.17 (d, J = 10.2 Hz, 1 H), 5.30 (d, J = 17.1 Hz, 1H), 5.77 (ddd, J = 17.1, 10.2, 7.1 Hz, 1 H); ¹³C-NMR (100.62 MHz, CDCl₃): δ [ppm] = -5.4, -5.4, 18.4, 24.5, 26.0, 36.7, 50.8, 53.9, 71.3, 116.9, 138.2, 156.1; HR-MS (ESI⁺): calculated for $C_{14}H_{29}N_2O_2Si^+$ [M+H]⁺: m/z = 285.1993, found: m/z = 285.1989; Mp: 105 °C.

(4*R*,6*S*)-4-((*tert*-Butyldimethylsilyloxy)methyl)-6-(hydroxymethyl)-4-methyltetrahydropyrimidin-2(1*H*)-one (3)

TBSO

Chemical Formula: C₁₃H₂₈N₂O₃Si Exact Mass: 288.1869 Molecular Weight: 288.4585

A solution of (4R,6S)-4-((tert-butyldimethylsilyloxy)methyl)-4-methyl-6-vinyltetrahydropyrimidin-2(1H)-one (44, 49.3 mg, 173 μmol), 2,6-lutidine (40 μl, 347 μmol, 2 equiv) and OsO₄ (2.5 wt % in *tert*-butanol, 43 μL, 3.47 µmol, 2 mol %) in dioxane/water (1.7 mL, 3:1) was stirred at rt for 15 min. NaIO₄ (148 mg, 693 µmol, 4 equiv) was added and stirring was continued for 5 h. Afterwards, the organic layer was separated and the aqueous layer was extracted three times with dichloromethane. The combined organic extracts were washed with brine (1 x), dried over MgSO₄ and concentrated. The residue was dissolved in methanol (2 mL) and NaBH₄ (50.0 mg, 1.32 mmol, 7.6 equiv) was added in portions to the stirred solution at 0 °C. The reaction mixture was stirred at 0 °C for additional 2 h. Then the solution was allowed to warm to rt and stirring was continued for 18 h. The reaction was quenched by addition of a saturated NaHCO₃ solution (10 mL). The aqueous layer was extracted four times with dichloromethane and the combined organic extracts were dried over MgSO₄. The solvent was removed under reduced pressure and purification by column chromatography on silica gel (ethyl acetate/cyclohexane, 95:5 + 3% iPrNH₂) yielded the alcohol (32.6 mg, 113 µmol, 65%) as a colorless solid. $R_{\rm f}$: 0.20 (5% MeOH in dichloromethane) $[\alpha]_{\rm D}^{20} = +21.2$ $(c = 0.5, CHCl_3);$ Mp: 134 C. ¹H-NMR (400.13 MHz, CDCl_3): δ [ppm] = 0.06 (s, 6H), 0.90 (s, 9H), 1.25 (s, 3H), 1.34 (dd, J = 12.6, 12.2 Hz, 1H), 1.50 (dd, J = 12.6, 3.2 Hz, 1H), 3.14 (br. s, 1H), 3.49-3.39 (m, 3H), 3.73-3.64 (m, 2H), 5.09 (br. s, 1H), 6.49 (br. s, 1H); ¹³C-NMR (75.47 MHz, CDCl₃): δ [ppm] = -5.4, -5.4, 18.4, 24.3, 26.0, 32.1, 49.7, 53.6, 66.0, 71.4, 157.1; HR-MS (ESI⁺): calculated for C₁₃H₂₈N₂NaO₃Si⁺ $[M+Na]^+$: m/z = 311.1761, found: m/z = 311.1753.

(4R,6R)-4-((tert-Butyldimethylsilyloxy)methyl)-4-methyl-6-vinyltetrahydropyrimidin-2(1H)-one (45)



Chemical Formula: C₁₄H₂₈N₂O₂Si Exact Mass: 284.1920 Molecular Weight: 284.4698

А stirred solution of (4R,6R)-4-((tert-butyldimethylsilyloxy)methyl)-4-methyl-1-tosyl-6-vinyltetrahydropyrimidin-2(1H)-one (43, 615 mg, 1.40 mmol) in dry THF (18 mL) was cooled to 0 °C and SmI₂ (0.1 M solution in THF, 84 mL, 8.41 mmol, 6.0 equiv) was added. The blue reaction mixture was stirred for 10 min at 0 °C and for another 15 h at rt. After guenching the reaction with saturated sodium bicarbonate solution the aqueous phase was extracted four times with ethyl acetate. The combined organic layers were washed with brine, dried over MgSO₄, filtered and the volatiles were removed under reduced pressure. The crude product was purified by column chromatography (silica gel, dichloromethane/methanol 95:5) to yield the desired compound as a red oil (398 mg, 1.40 mmol, quant.). R_f: 0.34 (dichloromethane/methanol, 95:5); Mp: 104 °C; $[\alpha]_D^{20} = -49.6$ (c = 0.5, CHCl₃); ¹H NMR (300.13) MHz, CDCl₃): δ [ppm] = 0.05 (s, 6H), 0.89 (s, 9H), 1.21 (s, 3H), 1.38 (dd, J = 13.4, 11.5 Hz, 1H), 2.03 (dd, J = 13.4, 4.1 Hz, 1H), 3.36 (d, J = 9.7 Hz, 1H), 3.51 (d, J = 9.7 Hz, 1H), 3.95 (ddd, J = 11.5, 7.0, 4.1 Hz, 1H), 5.03 (br. s., 1H), 5.29-5.07 (m, 3H), 5.74 (ddd, J = 17.1, 10.1, 7.0 Hz, 1H); ¹³C NMR (75.47 MHz, CDCl₃): δ [ppm] = -5.4, -5.3, 18.3, 25.9, 25.9, 36.1, 51.2, 53.8, 69.1, 116.6, 138.4, 156.5; HR-MS (ESI+): calculated for $C_{14}H_{28}N_2O_2SiNa^+$ [M+Na]⁺: m/z = 307.1812, found: m/z = 307.1800.

(4*R*,6*R*)-4-((*tert*-Butyldimethylsilyloxy)methyl)-6-(hydroxymethyl)-4-methyltetrahydropyrimidin-2(1*H*)-one (4)



Chemical Formula: C13H28N2O3SiC₁₃H₂₈N₂O₃Si Exact Mass: 288.1869288,18692 Molecular Weight: 288.4585288,45852

To a solution of (4R,6R)-4-((*tert*-butyldimethylsilyloxy)methyl)-4-methyl-6-vinyltetrahydropyrimidin-2(1*H*)one (**45**, 372 mg, 1.31 mmol) in dioxane/water (13 mL, 3:1), 2,6-lutidine (0.3 mL, 2.61 mmol, 2.0 equiv) and OsO₄ (2.5 wt % in *tert*-butanol, 0.3 mL, 26.1 µmol, 2 mol %) were added. The reaction mixture was stirred for 10 min at rt before NalO₄ (1.12 g, 5.26 mmol, 4.0 equiv) was added. After 15 h of stirring the aqueous layer was extracted four times with dichloromethane. The combined organic layers were washed with brine, dried over MgSO₄, filtered and concentrated in vacuo. The residue was dissolved in methanol (17 mL), cooled to 0 °C and NaBH₄ (595 mg, 15.7 mmol, 12 equiv) was added. The resulting mixture was slowly warmed to rt, stirred at this temperature for 16 h and quenched by addition of saturated NaHCO₃ solution. The aqueous layer was extracted four times with dichloromethane and the combined organic layers were dried over MgSO₄, filtered and the solvent was removed under reduced pressure. Purification by column chromatography (silica gel, cyclohexane/ethyl acetate 1:9 and 10% isopropylamine) yielded the alcohol as a white solid (243 mg, 812 µmol, 62%). R_{*f*} 0.23 (dichlormethane/methanol, 95:5). Mp: 137 °C; $[\alpha]_D^{20} = -47.1$ (c = 0.5, CHCl₃); ¹H NMR (400.13 MHz, CDCl₃): δ [ppm] = 0.04 (s, 3H), 0.04 (s, 3H), 0.88 (s, 9H), 1.20 (s, 3H), 1.27 (dd, J = 13.1, 12.5 Hz, 1H), 1.89 (dd, J = 13.1, 3.6 Hz, 1H), 3.33 (d, J = 9.8 Hz, 1H), 3.43 (dd, J = 11.2, 7.8 Hz, 1H), 3.50 (d, J = 9.8 Hz, 1H), 3.59-3.52 (m, 1H), 3.66 (dd, J = 11.2, 2.8 Hz, 1H), 4.97 (brs, 1H), 6.54 (brs, 1H); ¹³C NMR (100.62 MHz, CDCl₃): δ [ppm] = -5.4, -5.4, 18.3, 25.9, 26.0, 31.4, 50.0, 53.6, 66.1, 68.8, 157.2; HR-MS (ESI+): calculated for C₁₃H₂₈N₂O₃SiNa⁺ [M+Na]⁺: m/z = 311.1761, found: m/z = 311.1755.

3. NMR Spectra





























































































4. X-RAY DATA ANALYSIS

CCDC 1461907 (**28**), 1461908 (**32**), and 1461909 (**39**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via <u>www.ccdc.cam.ac.uk/data_request/cif</u>.