Stereoselective synthesis of the bicyclic guanidine alkaloid (+)-monanchorin†

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A new approach for the stereoselective synthesis of the bicyclic guanidine alkaloid (+)-monanchorin has been developed using a palladium(II)-catalysed MOM-ether directed Overman rearrangement to establish the second stereogenic centre and a cross metathesis reaction to generate the carbon backbone. In the final stage, a one-pot acid mediated deprotection of aldehyde, guanidine and hydroxyl groups gave an intermediate that underwent facile cyclisation to (+)-monanchorin.

Introduction

(+)-Monanchorin, a guanidine alkaloid with an unusual bicyclic skeleton was isolated by McKee and co-workers from the sponge *Monanchora ungiculata* collected in the Maldives islands.[1] Using 2D NMR experiments, the carbon skeleton was assigned leading to two possible aminal structures **1** and **2** (Fig. 1). Calculated ^{13}C NMR shifts for **1** and **2**, and comparison of data from known bicyclic aminal natural products[2] suggested that **1** was the likely structure for monanchorin. The connectivity of the guanidine unit to the carbon chain and the absolute stereochemistry of the natural product was established by Yu and Snider who carried out the first and only synthesis to date of (+)- and (–)-monanchorin.[3] The key steps in their synthesis involved the ring opening of an optically pure epoxide with sodium azide that led to a guanidino alcohol, which was cyclised onto a pendant aldehyde side-chain under acidic conditions to give the bicyclic aminal structure. By synthesising both enantiomers, the absolute configuration of the natural product (+)-monanchorin was established as shown for structure **3**.

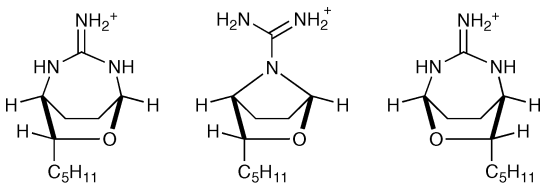
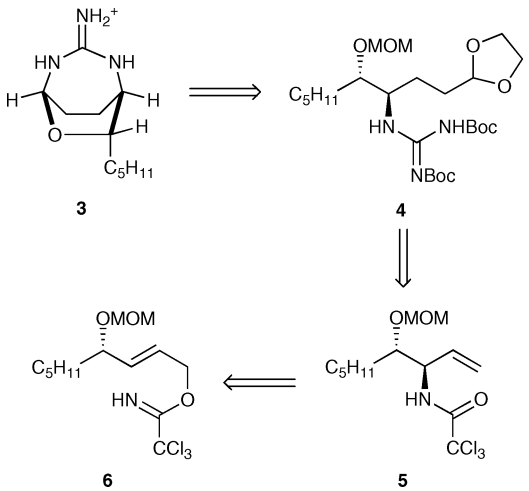


Fig. 1 Originally proposed (**1**) and actual structure (**3**) for (+)-monanchorin.

In recent years, we have studied the palladium(II)-catalysed Overman rearrangement of allylic trichloroacetimidates[4] containing adjacent stereogenic centres within the compound. This work led to the development of a MOM-ether directed rearrangement that allows the formation of *erythro*-products in diastereomeric ratios of up to 16 : 1.[5] This process has been utilised for the stereoselective synthesis of β- and γ-hydroxy-α-amino acids[5b,d,g,h] as well as for the preparation of the piperidine alkaloid (+)-α-conhydrine.[5f] As shown in Scheme 1, we believed that our MOM-ether directed Overman rearrangement could be used for a stereoselective synthesis of (+)-monanchorin (**3**). The proposed route involved preparation of allylic amide **5** using the ether-directed Overman rearrangement of allylic trichloroacetimidate **6**. Cross metathesis of **5** with 2-vinyl-1,3-dioxolane would generate the required carbon skeleton that would easily be converted to the guanidine **4**. A one-pot acid-mediated deprotection of the aldehyde, guanidine and hydroxyl groups would give an intermediate that could cyclise to give (+)-monanchorin (**3**). In this paper, we now report a new stereoselective synthesis of (+)-monanchorin from (*R*)-glycidol using the highly efficient MOM-ether directed Overman rearrangement to establish the second key stereogenic centre.



Scheme 1 Proposed synthesis of (+)-monanchorin (**3**) using a MOM-ether directed Overman rearrangement.

Results and discussion

The first stage of the synthesis involved the preparation of allylic alcohol **12** required for the MOM-ether directed Overman rearrangement (Scheme 2). Commercially available (*R*)-glycidol (**7**) was protected as the *tert*-butyldimethylsilyl ether and then subjected to a regioselective ring-opening reaction using *n*-butyllithium and copper iodide. This gave **8** in 90% yield. The secondary hydroxyl group of **8** was protected as the MOM-ether using bromomethyl methyl ether and Hünig's base. Removal

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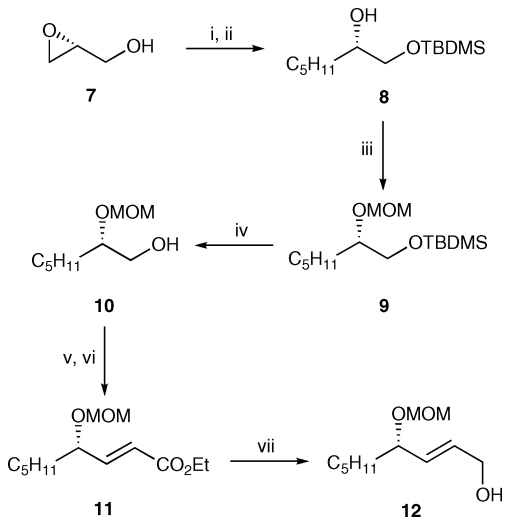
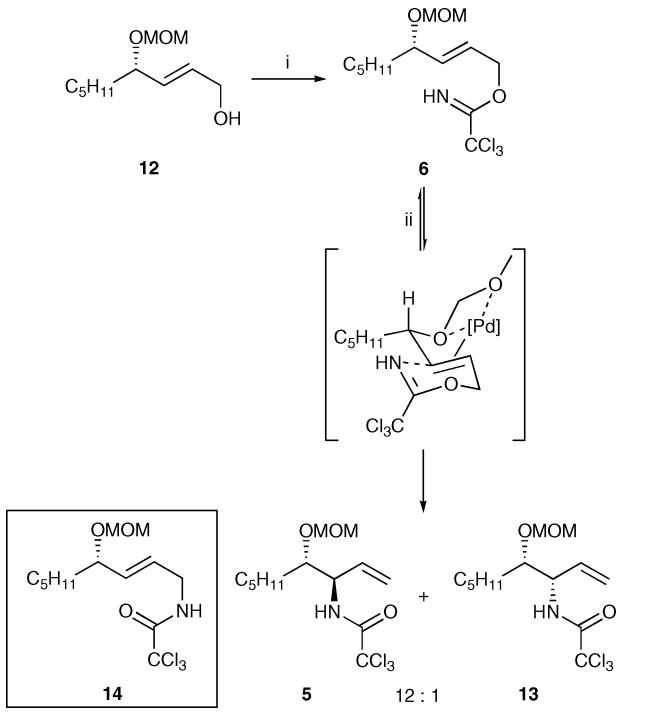


Scheme 2 *Reagents and conditions*: i. TBDMSCl, imidazole, THF, rt, 88%; ii. *n*-BuLi, CuI, THF, –78 °C, 90%; iii. MOMBr, EtN(*i*-Pr)$_2$, CH_2Cl_2, Δ, 96%; iv. TBAF, THF, 0 °C, 100%; v. $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, –78 °C; vi. $(EtO)_2POCH_2CO_2Et$, DBU, LiCl, MeCN, rt, 86% over two steps; vii. DIBAL-H, Et_2O, –78 °C, 92%.

of the silyl ether was then effected using TBAF to give the corresponding primary alcohol **10** in quantitative yield. A one-pot Swern oxidation and Horner–Wadsworth–Emmons reaction under Masamune–Roush conditions was used for the preparation of *E*-α,β-unsaturated ester **11**.[6,7] Reduction of ester **11** using DIBAL-H gave desired allylic alcohol **12** in 92% yield. While the synthesis of allylic alcohol **12** requires seven steps, the reactions involved are straightforward and generate **12** in good overall yield (60%).

Allylic trichloroacetimidate **6** was prepared by reaction of allylic alcohol **12** with trichloroacetonitrile and a catalytic amount of DBU (Scheme 3).[8] Allylic trichloroacetimidate **6** was initially treated with bis(acetonitrile)palladium(II) chloride (10 mol%) in the non-coordinating solvent, toluene.[5c] This gave the *erythro*- and *threo*-allylic trichloroacetamides **5** and **13** in 55% yield over the two steps and in a 12 : 1 ratio, respectively. Also isolated in trace amounts was allylic trichloroacetamide **14**. It is well-known that the use of Pd(II) during Claisen-type rearrangements gives exclusively the product of [3,3]-rearrangement (**5** and **13**) while Pd(0), *via* a non-concerted ionisation pathway produces predominantly the product of [1,3]-rearrangement (**14**).[9,10] During our studies on optimisation of the MOM-ether directed Overman rearrangement, we found that allylic trichloroacetimidates with bulky side-chains undergo slow rearrangement generating Pd(0) *in situ* by a competing β-elimination.[5b] The Pd(0) formed then catalyses the [1,3]-rearrangement, lowering the yield of the desired product of the [3,3]-rearrangement. It was discovered however, during our previous optimisation studies that the addition of *p*-benzoquinone to the MOM-ether directed rearrangement of bulky substrates results in the *in situ* oxidation of Pd(0) back to Pd(II) and the isolation of the products of [3,3]-rearrangement more cleanly and in higher yields.[5b] Thus, the rearrangement of allylic trichloroacetimidate **6** was repeated in the presence of *p*-benzoquinone and this again gave allylic trichloroacetamides **5** and **13** in a 12 : 1 ratio but in a substantially improved 84% yield over the two steps (Scheme 3). Furthermore, the desired major



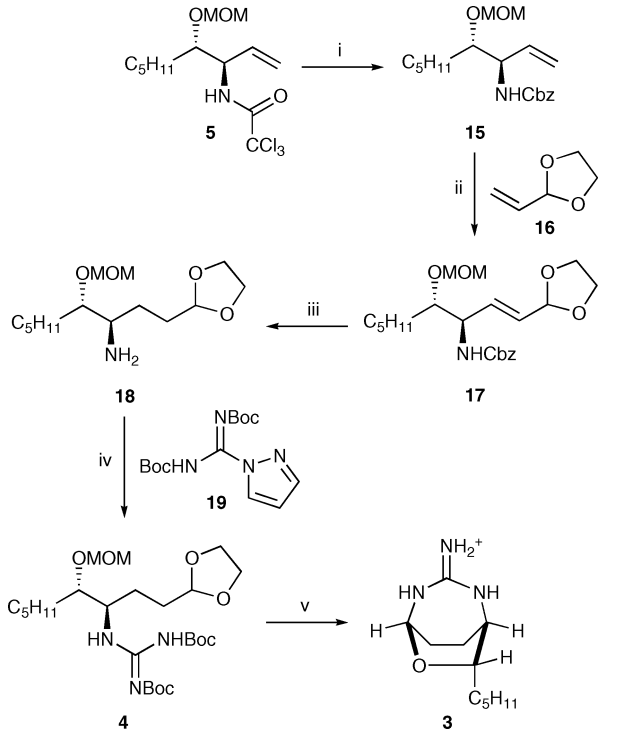
Scheme 3 *Reagents and conditions*: i. Cl_3CCN, DBU, CH_2Cl_2, rt; ii. $PdCl_2(MeCN)_2$, *p*-benzoquinone, toluene, 45 °C, 84% over two steps.

diastereomer **5** was easily isolated in 75% yield by flash column chromatography.

Having generated allylic trichloroacetamide **5**, initial attempts at forming the required carbon backbone of (+)-monanchorin (**3**) were achieved by direct cross coupling of **5** with metathesis partners such as crotonaldehyde, acrolein and acrolein diethyl acetal. While these gave the cross coupled products in varying yields, subsequent transformations in the presence of the trichloroacetyl protecting grouping proved incompatible. Instead, the trichloroacetyl group was replaced with the Cbz-protecting group in a one-pot reaction involving hydrolysis of the amide using sodium hydroxide followed by the addition of benzyl chloroformate (Scheme 4). This gave carbamate **15** in 81% yield. Cross metathesis of **15** was then investigated with 2-vinyl-1,3-dioxolane **16**[11] in the presence of Grubbs' 2nd generation catalyst (10 mol%).[12] On optimisation, this gave *E*-alkene **17** in 87% yield. Treatment of **17** with palladium on carbon under an atmosphere of hydrogen led to hydrogenation of the alkene and removal of the Cbz-protecting group. The resulting amine **18** was then coupled with commercially available *N*,*N*′-bis(*tert*-butoxycarbonyl)-1*H*-pyrazole-1-carboxamidine (**19**) in the presence of Hünig's base which gave guanidine **4** in 87% yield.[13,14] The synthesis of (+)-monanchorin (**3**) was then completed by reaction of **4** with TFA which led to the isolation of the natural product in 75% yield. Spectroscopic data and optical activity was entirely consistent with that previously published by the McKee and Snider groups.[1,3,15]

Conclusions

In summary, a fourteen-step synthesis of the bicyclic guanidine alkaloid (+)-monanchorin (**3**) has been developed in an overall yield of 15%. The key stages involved a highly efficient MOM-ether



Scheme 4 *Reagents and conditions*: i. 2 M NaOH, BnOCOCl, 45 °C, 81%; ii. **16**, Grubbs 2nd generation catalyst, CH_2Cl_2, Δ, 87%; iii. H_2, Pd/C, MeOH, rt, 71%; iv. **19**, EtN(*i*-Pr)$_2$, MeOH, rt, 87%; v. TFA, CH_2Cl_2, Δ, 75%.

directed Overman rearrangement that generated the second key stereogenic centre. This was followed by a cross metathesis reaction with 2-vinyl-1,3-dioxolane that allowed formation of the carbon backbone of the natural product. Acid mediated deprotection of the aldehyde, guanidine and hydroxyl groups gave an intermediate that underwent facile cyclisation to give the natural product. Investigation of new applications of the MOM-ether directed Overman rearrangement for natural product synthesis is currently under way.

Experimental

All reagents and starting materials were obtained from commercial sources and used as received. All dry solvents were purified using a PureSolv 500 MD solvent purification system. All reactions were performed under an atmosphere of argon unless otherwise mentioned. Brine refers to a saturated solution of sodium chloride. Flash column chromatography was carried out using Fisher matrix silica 60. Macherey-Nagel aluminium-backed plates pre-coated with silica gel 60 (UV_{254}) were used for thin layer chromatography and were visualised by staining with potassium permanganate. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker DPX 400 spectrometer with chemical shift values in ppm relative to tetramethylsilane as the standard. Assignment of ^{1}H and ^{13}C NMR signals are based on two-dimensional COSY and DEPT experiments, respectively. 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. Melting points were determined on a Reichert platform melting point apparatus. Optical rotations were determined as solutions irradiating with the sodium D line ($\lambda = 589$ nm) using an Autopol V polarimeter. $[\alpha]_D$ values are given in units 10^{-1} deg cm^2 g^{-1}.

(2*S*)-1-(*tert*-Butyldimethylsilyloxy)-2,3-epoxypropane[16]

A mixture of (*R*)-(+)-glycidol (**7**) (4.61 g, 0.05 mmol), *tert*-butyldimethylsilyl chloride (9.15 g, 60.7 mmol) and imidazole (4.13 g, 60.7 mmol) were dissolved in tetrahydrofuran (300 mL) and stirred overnight at room temperature. A white precipitate was removed by filtration and washed with diethyl ether (200 mL). The combined filtrate was concentrated and purified by flash column chromatography using (diethyl ether/petroleum ether, 1 : 10) which gave (2*S*)-1-(*tert*-butyldimethylsilyloxy)-2,3-epoxypropane (11.5 g, 88%) as a colourless oil. Spectroscopic data consistent with literature.[16] $[\alpha]_D^{23}$ −6.1 (*c* 1.3, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 0.09 (3H, s, $SiCH_3$), 0.10 (3H, s, $SiCH_3$), 0.81 (9H, s, $SiC(CH_3)_3$), 2.56 (1H, dd, *J* 5.1, 2.6 Hz, 1-*H*H), 2.70 (1H, dd, *J* 5.1, 4.1 Hz, 1-H*H*), 2.98–3.02 (1H, m, 2-H), 3.60 (1H, dd, *J* 11.9, 4.8 Hz, 3-*H*H), 3.80 (1H, dd, *J* 11.9, 3.1 Hz, 3-H*H*); δ_C (100 MHz, $CDCl_3$) −5.3 (CH_3), −5.2 (CH_3), 18.4 (C), 26.0 (3 × CH_3), 44.5 (CH_2), 52.4 (CH), 63.7 (CH_2); *m*/*z* (CI) 189.1309 (MH^+. $C_9H_{21}O_2Si$ requires 189.1311), 145 (35%), 131 (50), 89 (62), 73 (12).

(2*S*)-1-(*tert*-Butyldimethylsilyloxy)heptan-2-ol (8)[17]

A solution of *n*-butyllithium (2.5 M in hexane) (0.53 mL, 1.33 mmol) was added dropwise to a solution of copper iodide (0.11 g, 0.58 mmol) in THF (15 mL) at −78 °C and the white suspension was stirred for 1 h. (2*S*)-1-(*tert*-butyldimethylsilyloxy)-2,3-epoxypropane (0.10 g, 0.53 mmol) in THF (10 mL) was then added and the reaction mixture was warmed to 0 °C and stirred for 3 h. The reaction was quenched by the addition of a saturated solution of ammonium chloride (10 mL) and extracted with ethyl acetate (3 × 20 mL). The organic layers were combined, dried ($MgSO_4$) and concentrated *in vacuo*. Purification by flash column chromatography (petroleum ether/diethyl ether, 20 : 1) gave (2*S*)-1-(*tert*-butyldimethylsilyloxy)heptan-2-ol (**8**) (0.12 g, 90%) as a colourless oil. Spectroscopic data consistent with literature.[17] ν_{max}/cm^{-1} (NaCl) 3434 (OH), 2929 (CH), 1464, 1255, 1106, 837, 778; $[\alpha]_D^{23}$ +7.3 (*c* 1.0, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 0.09 (6H, s, 2 × $SiCH_3$), 0.79–0.84 (12H, m, 7-H_3 and $SiC(CH_3)_3$), 1.19–1.42 (8H, m, 3-H_2, 4-H_2, 5-H_2 and 6-H_2), 2.37 (1H, br s, OH), 3.31 (1H, dd, *J* 10.4, 8.3 Hz, 1-*H*H), 3.51–3.60 (2H, m, 1-H*H* and 2-H); δ_C (100 MHz, $CDCl_3$) −5.4 (CH_3), −5.3 (CH_3), 14.1 (CH_3), 18.3 (C), 22.6 (CH_2), 25.3 (CH_2), 25.9 (3 × CH_3), 32.0 (CH_2), 32.8 (CH_2), 67.3 (CH_2), 71.9 (CH); *m*/*z* (CI) 247 (MH^+, 11%), 206, (3), 150 (4), 88 (3), 52 (100).

(2*S*)-1-(*tert*-Butyldimethylsilyloxy)-2-(methoxymethoxy)heptane (9)

A solution of (2*S*)-1-(*tert*-butyldimethylsilyloxy)heptan-2-ol (**8**) (5.00 g, 20.3 mmol) was dissolved in dichloromethane (200 mL) and cooled to 0 °C. Diisopropylethylamine (10.6 mL, 61.0 mmol) was then added followed by bromomethyl methyl ether (3.40 mL, 41.7 mmol). The solution was stirred for 0.5 h at 0 °C then heated under reflux overnight. The reaction mixture was cooled to room temperature, acidified with 1.0 M hydrochloric acid (15 mL) and extracted with dichloromethane (3 × 100 mL). After removal of the solvent under reduced pressure, the

resulting material was purified by flash column chromatography (petroleum ether/diethyl ether, 20 : 1) to give (2*S*)-1-(*tert*-butyldimethylsilyloxy)-2-(methoxymethoxy)heptane (**9**) as a pale yellow oil (5.70 g, 96%). ν_{max}/cm^{-1} (NaCl) 2930 (CH), 1464, 1256, 1111, 1039, 838, 776; $[\alpha]_D^{23}$ −32.7 (*c* 1.0, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 0.01 (6H, s, $Si(CH_3)_2$), 0.80–0.86 (12H, m, 7-H_3 and $Si(CH_3)_3$), 1.24–1.43 (8H, m, 3-H_2, 4-H_2, 5-H_2 and 6-H_2), 3.33 (3H, s, OCH_3), 3.51–3.58 (3H, m, 1-H_2 and 2-H), 4.60 (1H, d, *J* 6.7 Hz, OC*H*HO), 4.73 (1H, d, *J* 6.7 Hz, OCH*H*O); δ_C (100 MHz, $CDCl_3$) −6.5 (CH_3), −6.4 (CH_3), 13.0 (CH_3), 17.3 (C), 21.6 (CH_2), 24.0 (CH_2), 24.9 (3 × CH_3), 30.7 (CH_2), 31.0 (CH_2), 54.4 (CH_3), 64.9 (CH_2), 77.2 (CH) 95.2 (CH_2); *m*/*z* (CI) 291.2354 (MH^+. $C_{15}H_{35}O_3Si$ requires 291.2355), 259 (100), 229 (12), 203 (6), 133 (3), 85 (8).

(2*S*)-2-(Methoxymethoxy)heptan-1-ol (10)

A solution of tetrabutylammonium fluoride (1.0 M in THF) (24.7 mL, 24.8 mmol) was added to a solution of (2*S*)-1-(*tert*-butyldimethylsilyloxy)-2-(methoxymethoxy)heptane (**9**) (6.00 g, 20.7 mmol) in THF (300 mL) at 0 °C. The reaction mixture was warmed to room temperature and stirred overnight. The reaction mixture was then concentrated and the resulting residue was re-suspended in diethyl ether (200 mL). The solution was washed with water (100 mL) and the aqueous layer was then extracted with diethyl ether (3 × 100 mL). The combined organic extracts were dried ($MgSO_4$), concentrated and purified by flash column chromatography (petroleum ether/diethyl ether, 5 : 2) to give (2*S*)-2-(methoxymethoxy)heptan-1-ol (**10**) as a colourless oil (3.65 g, 100%). ν_{max}/cm^{-1} (NaCl) 3450 (OH), 2931 (CH), 1466, 1103, 1041; $[\alpha]_D^{23}$ +57.1 (*c* 1.0, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 0.90 (3H, t, *J* 7.0 Hz, 7-H_3), 1.23–1.54 (8H, m, 3-H_2, 4-H_2, 5-H_2 and 6-H_2), 3.11 (1H, dd, *J* 8.7, 3.3 Hz, OH), 3.43 (3H, s, OCH_3), 3.48–3.62 (3H, m, 1-H_2 and 2-H), 4.70 (1H, d, *J* 6.9 Hz, OC*H*HO), 4.75 (1H, d, *J* 6.9 Hz, OCH*H*O); δ_C (100 MHz, $CDCl_3$) 14.1 (CH_3), 22.6 (CH_2), 25.2 (CH_2), 31.7 (CH_2), 31.8 (CH_2), 55.7 (CH_3), 65.8 (CH_2), 82.5 (CH), 97.0 (CH_2); *m*/*z* (CI) 177.1491 (MH^+. $C_9H_{21}O_3$ requires 177.1491), 145 (100), 143 (8), 115 (42), 97 (18).

Ethyl (2*E*,4*S*)-4-(methoxymethoxy)nona-2-enoate (11)

Dimethyl sulfoxide (3.35 mL, 47.4 mmol) was added to a stirred solution of oxalyl chloride (2.32 mL, 26.5 mmol) in dichloromethane (100 mL) at −78 °C. The reaction mixture was stirred for 0.3 h before (2*S*)-2-(methoxymethoxy)heptan-1-ol (**10**) (3.33 g, 19.0 mmol) in dichloromethane (50 mL) was slowly added. The mixture was stirred for a further 0.3 h before triethylamine (13.2 mL, 94.7 mmol) was added. This reaction mixture was stirred for 0.5 h at −78 °C and then allowed to warm to room temperature and stirred for a further 2 h. Meanwhile, a solution of lithium chloride (1.45 g, 34.1 mmol), triethyl phosphonoacetate (5.63 mL, 28.4 mmol) and 1,8-diazabicyclo[5,4,0]undec-7-ene (4.28 mL, 28.4 mmol) in acetonitrile (100 mL) was prepared and stirred for 1.0 h. The Swern solution was concentrated *in vacuo* and the Horner–Wadsworth–Emmons solution was added. The reaction mixture was stirred at room temperature overnight. The reaction was quenched by the addition of a saturated solution of ammonium chloride (50 mL) and concentrated to give an orange residue, which was then extracted with diethyl ether (4 × 100 mL). The organic layers were combined, dried ($MgSO_4$) and concentrated to give an orange oil. Purification by flash column chromatography using (diethyl ether/petroleum ether, 2 : 5) yielded ethyl (2*E*,4*S*)-4-(methoxymethoxy)nona-2-enoate (**11**) (4.62 g, 86%) as a colourless oil. ν_{max}/cm^{-1} (NaCl) 2934 (CH), 1723 (CO), 1658 (C=C), 1467, 1368, 1273, 1156, 1038; $[\alpha]_D^{23}$ −67.7 (*c* 1.0, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 0.89 (3H, t, *J* 6.7 Hz, 9-H_3), 1.28–1.43 (9H, m, 6-H_2, 7-H_2, 8-H_2 and OCH_2CH_3), 1.51–1.66 (2H, m, 5-H_2), 3.38 (3H, s, OCH_3), 4.16–4.24 (3H, m, 4-H and OCH_2CH_3), 4.57 (1H, d, *J* 6.8 Hz, OC*H*HO), 4.63 (1H, d, *J* 6.8 Hz, OCH*H*O), 5.92 (1H, d, *J* 15.7 Hz, 2-H), 6.82 (1H, dd, *J* 15.7, 6.4 Hz, 3-H); δ_C (100 MHz, $CDCl_3$) 14.0 (CH_3), 14.2 (CH_3), 22.6 (CH_2), 24.8 (CH_2), 31.7 (CH_2), 34.9 (CH_2), 55.6 (CH_3), 60.5 (CH_2), 75.2 (CH), 94.6 (CH_2), 121.8 (CH), 148.0 (CH), 166.3 (C); *m*/*z* (CI) 245.1752 (MH^+. $C_{13}H_{25}O_4$ requires 245.1753), 215 (22), 183 (100), 173 (10), 137 (4), 109 (4).

(2*E*,4*S*)-4-(Methoxymethoxy)nona-2-ene-1-ol (12)

Ethyl (2*E*,4*S*)-4-(Methoxymethoxy)nona-2-enoate (**11**) (4.56 g, 18.7 mmol) was dissolved in diethyl ether (350 mL) and cooled to −78 °C. DIBAL-H (1.0 M in hexane) (46.1 mL, 46.1 mmol) was added dropwise and the reaction mixture was stirred at −78 °C for 3 h, before warming to room temperature. The solution was cooled to 0 °C and quenched by the addition of a saturated solution of ammonium chloride (50 mL) and warmed to room temperature with vigorous stirring over 1 h. The reaction mixture was filtered through a pad of Celite® and washed with diethyl ether (400 mL). The filtrate was then dried ($MgSO_4$) and concentrated *in vacuo*. Flash column chromatography (diethyl ether/petroleum ether, 2 : 5) gave (2*E*,4*S*)-4-(methoxymethoxy)nona-2-ene-1-ol (**12**) (3.50 g, 92%) as a colourless oil. (Found: C, 65.18; H, 11.09. $C_{11}H_{22}O_3$ requires C, 65.34; H, 10.89); ν_{max}/cm^{-1} (NaCl) 3407 (OH), 2932 (CH), 1673 (C=C), 1467, 1378, 1213, 1115, 1096, 1039, 920; $[\alpha]_D^{23}$ −69.8 (*c* 1.0, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 0.89 (3H, t, *J* 6.7 Hz, 9-H_3), 1.27–1.55 (7H, m, 6-H_2, 7-H_2, 8-H_2 and OH), 1.58–1.64 (2H, m, 5-H_2), 3.37 (3H, s, OCH_3), 3.99–4.06 (1H, m, 4-H), 4.16 (2H, td, *J* 5.6, 1.4 Hz, 1-H_2), 4.53 (1H, d, *J* 6.7 Hz, OC*H*HO), 4.70 (1H, d, *J* 6.7 Hz, OCH*H*O), 5.56 (1H, ddt, *J* 15.5, 7.4, 1.4 Hz, 3-H), 5.82 (1H, dtd, *J* 15.5, 5.6, 0.6 Hz, 2-H); δ_C (100 MHz, $CDCl_3$) 14.1 (CH_3), 22.6 (CH_2), 25.1 (CH_2), 31.7 (CH_2), 35.5 (CH_2), 55.4 (CH_3), 62.8 (CH_2), 76.4 (CH), 93.6 (CH_2), 131.5 (CH), 132.1 (CH); *m*/*z* (CI) 203 (MH^+, 10%), 185 (19), 142 (83), 138 (37), 124 (100), 100 (19), 83 (49).

(3*R*,4*S*)-3-(Trichloromethylcarbonylamino)-4-(methoxymethoxy)nona-1-ene (5)

(2*E*,4*S*)-4-(Methoxymethoxy)nona-2-ene-1-ol (**12**) (0.74 g, 3.66 mmol) was dissolved in dichloromethane (30 mL) and cooled to 0 °C. 1,8-Diazabicyclo[5.4.0]undec-7-ene (0.12 mL, 0.91 mmol) was then added to the solution followed by trichloroacetonitrile (0.55 mL, 5.50 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 trichloroacetimidate **6**, which was used without further purification. The resulting allylic trichloroacetimidate **6** was dissolved in toluene (30 mL) and bis(acetonitrile)palladium(II)

chloride (0.10 g, 0.36 mmol) and *p*-benzoquinone (0.21 g, 2.00 mmol) were added. The reaction mixture was stirred at 45 °C for 24 h. The reaction mixture was concentrated and purification by flash column chromatography (diethyl ether/petroleum ether, 1 : 20) and gave (3*R*,4*S*)-3-(trichloromethylcarbonylamino)-4-(methoxymethoxy)nona-1-ene (**5**) as a colourless oil (0.90 g, 75% over 2 steps). ν_{max}/cm^{-1} (NaCl) 3284 (NH), 2933 (CH), 1715 (CO), 1644 (C═C), 1517, 1236, 1100, 1037, 822; $[\alpha]_D^{23}$ +59.0 (*c* 1.0, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 0.89 (3H, t, *J* 6.8 Hz, 9-H_3), 1.24–1.53 (6H, m, 6-H_2, 7-H_2 and 8-H_2), 1.58–1.68 (2H, m, 5-H_2), 3.43 (3H, s, OCH_3), 3.54–3.59 (1H, m, 4-H), 4.36–4.42 (1H, m, 3-H), 4.74 (1H, d, *J* 6.8 Hz, OC*H*HO), 4.66 (1H, d, *J* 6.8 Hz, OCH*H*O), 5.30–5.37 (2H, m, 1-H_2), 5.85 (1H, ddd, *J* 16.8, 10.4, 6.7 Hz, 2-H), 8.27 (1H, br d, *J* 7.6 Hz, NH); δ_C (100 MHz, $CDCl_3$) 14.0 (CH_3), 22.4 (CH_2), 25.4 (CH_2), 31.7 (CH_2), 33.0 (CH_2), 56.0 (CH), 56.7 (CH_3), 83.9 (CH), 93.0 (C), 98.2 (CH_2), 119.0 (CH_2), 131.6 (CH), 161.5 (C); *m*/*z* (FAB) 346.0747 (MH^+. $C_{13}H_{23}{}^{35}Cl_3NO_3$ requires 346.0744), 314 (57%), 284 (28), 213 (100), 201 (11), 179 (14), 123 (34).

(3*R*,4*S*)-3-(Benzyloxycarbonylamino)-4-(methoxymethoxy)nona-1-ene (15)

A solution of (3*R*,4*S*)-3-(trichloromethylcarbonylamino)-4-(methoxymethoxy)nona-1-ene (**5**) (2.00 g, 5.77 mmol) was dissolved in 2.0 M sodium hydroxide solution (70 mL) and heated at 45 °C overnight. The reaction mixture was cooled to room temperature and benzyl chloroformate (3.25 mL, 23.1 mmol) was added and stirred overnight at room temperature. The reaction mixture was extracted with ethyl acetate (4 × 100 mL) and the combined organic layers dried ($MgSO_4$) and concentrated in *vacuo*. Purification by flash column chromatography (diethyl ether/petroleum ether, 3 : 7) gave (3*R*,4*S*)-3-(benzyloxycarbonylamino)-4-(methoxymethoxy)nona-1-ene (**15**) (1.55 g, 81%) as a colourless oil. ν_{max}/cm^{-1} (NaCl) 3339 (NH), 2933 (CH), 1722 (CO), 1519, 1234, 1099, 1038; $[\alpha]_D^{23}$ +48.7 (*c* 1.0, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 0.88 (3H, t, *J* 6.9 Hz, 9-H_3), 1.27–1.60 (8H, m, 5-H_2, 6-H_2, 7-H_2 and 8-H_2), 3.39 (3H, s, OCH_3), 3.54–3.57 (1H, m, 4-H), 4.24 (1H, t, *J* 7.0 Hz, 3-H), 4.63 (1H, d, *J* 7.0 Hz, OC*H*HO), 4.68 (2H, m, OCH*H*O and NH), 5.11 (2H, s, PhCH_2), 5.20–5.28 (2H, m, 1-H_2), 5.76–5.89 (1H, m, 2-H), 7.28–7.38 (5H, m, Ph); δ_C (100 MHz, $CDCl_3$) 14.0 (CH_3), 22.3 (CH_2), 25.3 (CH_2), 31.5 (CH_2), 32.1 (CH_2), 55.8 (CH_3), 56.0 (CH), 66.5 (CH_2), 82.7 (CH), 97.3 (CH_2), 117.4 (CH_2), 128.0 (2 × CH), 128.5 (3 × CH), 133.8 (CH), 136.7 (C), 156.0 (C); *m*/*z* (CI) 336.2177 (MH^+. $C_{19}H_{30}NO_4$ requires 336.2175), 304 (45%), 260 (10), 228 (9), 181 (7), 147 (9), 91 (23).

2-[(1*E*,3*R*,4*S*)-3-(Benzyloxycarbonylamino)-4-(methoxymethoxy)nona-2-enyl]-1,3-dioxolane (17)

A solution of (3*R*,4*S*)-3-(benzyloxycarbonylamino)-4-(methoxymethoxy)nona-1-ene (**15**) (0.10 g, 0.30 mmol) was dissolved in dichloromethane (10 mL) and degassed with argon. 2-Vinyl-1,3-dioxolane (**16**) (0.09 g, 0.90 mmol) and Grubbs 2nd generation catalyst (0.03 g, 0.03 mmol) were added. The reaction mixture was heated under reflux overnight. The mixture was concentrated under vacuum. Purification by flash column chromatography (petroleum ether/ethyl acetate, 1 : 1) gave 2-[(1*E*,3*R*,4*S*)-3-(benzyloxycarbonylamino)-4-(methoxymethoxy)nona-2-enyl]-1,3-dioxolane (**17**) (0.11 g, 87%) as a yellow oil. ν_{max}/cm^{-1} (NaCl) 3338 (NH), 2953 (CH), 1722 (CO), 1522, 1235, 1149, 1037, 699; $[\alpha]_D^{23}$ +2.9 (*c* 1.5, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 0.88 (3H, t, *J* 6.5 Hz, 9-H_3), 1.27–1.58 (8H, m, 5-H_2, 6-H_2, 7-H_2 and 8-H_2), 3.38 (3H, s, OCH_3), 3.52–3.59 (1H, m, 4-H), 3.85–4.00 (4H, m, OCH_2CH_2O), 4.29–4.36 (1H, m, 3-H), 4.62 (1H, d, *J* 7.0 Hz, OC*H*HO), 4.70 (1H, d, *J* 7.0 Hz, OCH*H*O), 5.07 (1H, d, *J* 12.0 Hz, OC*H*HPh), 5.12 (1H, d, *J* 12.0 Hz, OCH*H*Ph), 5.29 (1H, d, *J* 5.9 Hz, OCHO), 5.70 (1H, dd, *J* 15.9, 5.6 Hz, 2-H), 5.84 (1H, d, *J* 8.8 Hz, NH), 5.90 (1H, dd, *J* 15.9, 5.9 Hz, 1-H), 7.28–7.35 (5H, m, Ph); δ_C (100 MHz, $CDCl_3$) 14.0 (CH_3), 22.3 (CH_2), 25.4 (CH_2), 31.7 (CH_2), 32.1 (CH_2), 54.6 (CH), 55.9 (CH_3), 64.8 (CH_2), 65.0 (CH_2), 66.6 (CH_2), 82.7 (CH), 97.3 (CH_2), 103.1 (CH), 128.1 (2 × CH), 128.5 (3 × CH), 129.4 (CH), 131.6 (CH), 136.6 (C), 155.8 (C); *m*/*z* (CI) 408.2381 (MH^+. $C_{22}H_{34}NO_6$ requires 408.2386), 377 (21%), 300 (12), 284 (31), 246 (100), 214 (32), 145 (21), 91 (92).

2-[(3*R*,4*S*)-3-(*N*,*N*′-Bis(*tert*-butoxycarbonyl)guanidino)-4-(methoxymethoxy)nonyl]-1,3-dioxolane (4)

To a solution of 2-[(1*E*,3*R*,4*S*)-3-(benzyloxycarbonylamino)-4-(methoxymethoxy)nona-2-enyl]-1,3-dioxolane (**17**) (0.02 g, 0.06 mmol) in methanol (5 mL) was added 10% palladium on carbon (0.03 g). The reaction mixture was allowed to stir under an atmosphere of hydrogen at room temperature for 18 h. The reaction mixture was filtered through a short pad of Celite® which was washed with methanol (50 mL). The resulting solution was concentrated *in vacuo* to give 2-[(3*R*,4*S*)-3-amino-4-(methoxymethoxy)nonyl]-1,3-dioxolane (**18**) (0.01 g, 71%) as a colourless oil which was used without further purification. 2-[(3*R*,4*S*)-3-Amino-4-(methoxymethoxy)nonyl]-1,3-dioxolane (**18**) (0.01 g, 0.04 mmol) was dissolved in methanol (7 mL). Diisopropylethylamine (0.06 mL, 0.33 mmol) and *N*,*N*′-bis(*tert*-butoxycarbonyl)-1*H*-pyrazole-1-carboxamidine (**19**) (0.02 g, 0.06 mmol) were then added. The reaction mixture was stirred for 20 h at room temperature. The methanol was removed *in vacuo*. The resulting residue was dissolved in ethyl acetate (10 mL) and acidified with 0.2 M hydrochloric acid. The organic layer was washed with brine (10 mL), extracted with ethyl acetate (2 × 10 mL), dried ($MgSO_4$) and concentrated *in vacuo*. Purification by flash column chromatography (petroleum ether/ethyl acetate, 10 : 1) gave 2-[(3*R*,4*S*)-3-(*N*,*N*′-bis(*tert*-butoxycarbonyl)guanidino)-4-(methoxymethoxy)nonyl]-1,3-dioxolane (**4**) (0.02 g, 87%) as a colourless oil. ν_{max}/cm^{-1} (NaCl) 3325 (NH), 2933 (CH), 1795, 1720 (CO), 1638 (C═N), 1332, 1155, 1034, 757; $[\alpha]_D^{23}$ −8.1 (*c* 1.5, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 0.89 (3H, t, *J* 6.7 Hz, 9-H_3), 1.25–1.35 (6H, m, 6-H_2, 7-H_2 and 8-H_2), 1.47 (9H, s, O^{t}Bu), 1.48 (9H, s, O^{t}Bu), 1.50–1.82 (6H, m, 1-H_2, 2-H_2 and 5-H_2), 3.38 (3H, s, OCH_3), 3.61–3.66 (1H, m, 4-H), 3.82–3.89 (2H, m, OC*H*HC*H*O), 3.94–3.99 (2H, m, OCH*H*CH*H*O), 4.34–4.42 (1H, m, 3-H), 4.62 (1H, d, *J* 6.9 Hz, OC*H*HO), 4.69 (1H, d, *J* 6.9 Hz, OCH*H*O), 4.88 (1H, t, *J* 4.4 Hz, OCHO), 8.44 (1H, d, *J* 9.2 Hz, NH), 11.53 (1H, br s, NH); δ_C (100 MHz, $CDCl_3$) 14.1 (CH_3), 22.6 (CH_2), 23.2 (CH_2), 25.5 (CH_2), 28.1 (3 × CH_3), 28.3 (3 × CH_3), 30.3 (CH_2), 31.1 (CH_2), 31.8 (CH_2), 52.0 (CH), 55.8 (CH_3), 64.8 (CH_2), 64.9 (CH_2), 78.8 (C), 79.7 (C), 82.8 (CH), 96.4 (CH_2), 104.3 (CH), 153.1 (C), 156.1 (C), 163.8 (C); *m*/*z* (FAB)

518.3443 (MH^+. $C_{25}H_{48}N_3O_8$ requires 518.3441), 462 (9%), 406 (55), 362 (22), 311 (14), 260 (7), 199 (6), 111 (12).

(+)-Monanchorin (3)[1,3]

To a solution of 2-[(3*R*,4*S*)-3-(*N*,*N*'-bis(*tert*-butoxycarbonyl)-guanidino)-4-(methoxymethoxy)nonyl]-1,3-dioxolane (**4**) (0.04 g, 0.07 mmol) in dichloromethane (5 mL) was added trifluoroacetic acid (0.35 mL, 4.64 mmol). The reaction mixture was heated under reflux for 12 h. The reaction was quenched with potassium carbonate (0.10 g, 0.77 mmol), filtered and concentrated under vacuum. Flash column chromatography (dichloromethane–methanol, 2 : 1) gave the TFA salt of (+)-monanchorin (**3**) (0.01 g, 75%) as a colourless oil. Spectroscopic data consistent with literature.[1,3] $[\alpha]_D^{22}$ +33.7 (*c* 0.8, MeOH), lit[1] $[\alpha]_D^{25}$ +39.0 (*c* 3.9, MeOH); δ_H (400 MHz, $CDCl_3$) 0.91 (3H, t, *J* 6.7 Hz, 3H, 15-H_3), 1.22–1.35 (5H, m, 12-*H*H, 13-H_2 and 14-H_2), 1.42–1.49 (2H, m, 2H, 11-*H*H, 12-H*H*), 1.60–1.66 (1H, m, 11-H*H*), 2.00–2.11 (2H, m, 8-*H*H and 9-*H*H), 2.19–2.23 (1H, m, 8-H*H*), 2.28–2.37 (1H, m, 9-H*H*), 3.23–3.27 (1H, m, 5-H), 4.29–4.35 (1H, m, 6-H), 4.84 (1H, t, *J* 6.2 Hz, 1-H), 8.56 (1H, br s, NH), 8.96 (1H, br s, NH); δ_C (100 MHz, $CDCl_3$) 14.0 (CH_3), 22.5 (CH_2), 23.8 (CH_2), 25.1 (CH_2), 28.9 (CH_2), 31.6 (CH_2), 33.6 (CH_2), 51.3 (CH), 76.7 (CH), 79.5 (CH), 159.1 (C); *m*/*z* (CI) 212 (MH^+, 85%), 170 (15), 129 (19), 113 (31), 81 (67).

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