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C-(4-Methoxybenzyloxymethyl)-*N*-methylnitrone Cycloaddition to Highly Functionalized Pyrrolinone: A Regio- and Stereoselective Approach to New Omuralide–Salinosporamide A Hybrids

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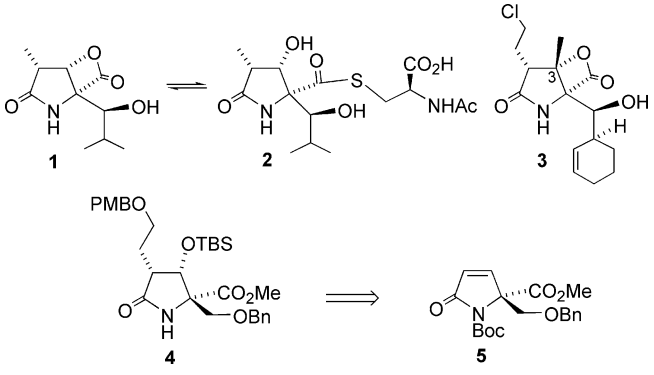
An advanced intermediate in the synthesis of new omuralide–salinosporamide A hybrids as potential proteasome 20S inhibitors was prepared in a few steps from methyl pyroglutamate. For this purpose, an *O*-protected hydroxyethyl chain has been successfully introduced to a highly functionalized pyrrolinone by a regio- and stereoselective *C*-(4-methoxybenzyloxymethyl)-*N*-methylnitrone 1,3-dipolar cycloaddition.

Introduction

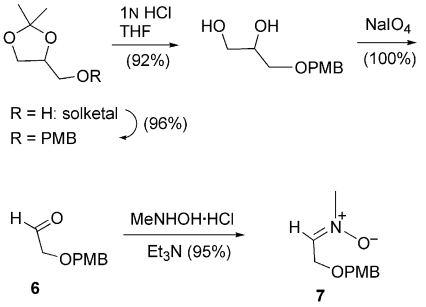
The remarkable biological activity of omuralide (**1**), a β-lactone derived from lactacystin (**2**),[1] has generated great interest in the synthesis of proteasome 20S inhibitors, particularly in the synthesis of the more potent salinosporamide A (**3**).[2–4]



Salinosporamides[5] and other closely related natural cinnabaramides, which have been recently isolated from terrestrial *Streptomyces* strain JS360,[6] are distinguished by the substitution pattern on the bicyclic γ-lactam-β-lactone core. In these compounds, the isopropyl moiety present in **1** is replaced by a cyclohexenyl group, and various substituents can also be present α to the lactam carbonyl such as ethyl, chloro- or bromoethyl, hexyl, or hydroxyhexyl. In addition, these compounds are substituted at C-3 by a methyl or an ethyl group which is not present in omuralide (**1**). However, structure–activity relationship studies have shown that this C-3 methyl group in salinosporamide A and its analogues weakly interacts with the target protein and that a hydrogen is also convenient in this position.[7] Therefore, we designed compound **4** as the synthetic goal suitable for potential further syntheses of new omuralide–salinosporamide hybrids.

Results and Discussion

Taking account of our previous work in this field,[8] we investigated the simultaneous introduction of a C-3 hydroxy and vicinal, protected, hydroxyethyl chain involving a suitable regio- and stereoselective *C*-alkoxymethylnitrone cycloaddition to pyrrolinone (±)-**5**, which was obtained in a few steps from methyl pyroglutamate. For this purpose, *C*-(4-methoxybenzyloxymethyl)-*N*-methylnitrone **7** (which has not been reported before, to the best of our knowledge) appeared to suit our needs and was particularly attractive for subsequent selective hydroxy deprotection. Thus, nitrone **7** was efficiently prepared (95%), according to Scheme 1, from the corresponding aldehyde **6**, derived from solketal.[9]



Scheme 1.

The protection of the solketal free hydroxy group with PMBBr (NaH, THF, 96%) was followed, as described, by the carefully controlled hydrolysis of the acetonide moiety

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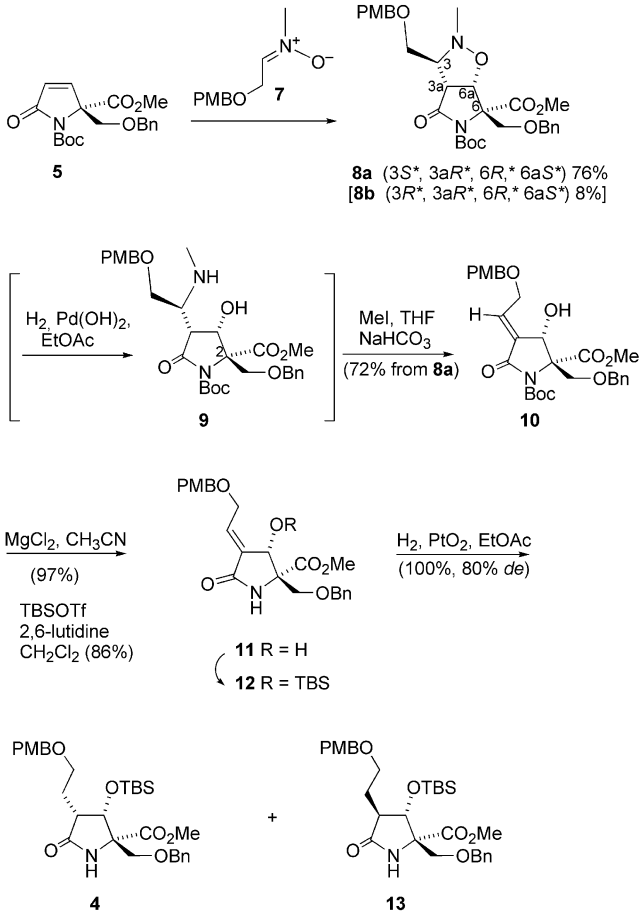
and subsequent oxidation of the vicinal diol with sodium periodate to give aldehyde **6** (92% over 2 steps).[9b] In the presence of triethylamine, *N*-methylhydroxylamine hydrochloride and aldehyde **6** in toluene were converted at room temp. to nitrone **7** as a single isomer, isolated in high yield. The (*Z*) configuration of **7** was postulated by analogy with other *C*-alkoxy- and *C*-(silyloxymethyl)nitrones,[10] and this attribution was confirmed by a NOESY experiment, which showed a correlation between the *N*-methyl and azomethine protons.

The cycloaddition of **7** to unsaturated γ-lactam **5** was carried out in toluene at 60 °C to give cycloadduct **8a** in 76% yield (Scheme 2), together with isomer **8b** (≈ 8%). It is important to note that using a higher temperature led to some dimeric by-products of nitrone **7**.[11]

The configurational assignments at the 3a and 6a positions were established by NMR spectroscopy. These data show that the regioselectivity is the same for both compounds and that the additions occurred on the same face of the dipolarophile. The close chemical shifts of H-6a (**8a**: 4.54 and **8b**: 4.63 ppm), and the nOe observed between these protons and the methylene 6-CH_2O agree with structures **8**. In addition to these high regio- and diastereofacial selectivities, a further indication of the relative configuration at C-3 in major diastereomer **8a** was given by the steric course of the subsequent elimination step leading to **10**. After reductive cleavage of the isoxazolidine N–O bond and *N*-dimethylation of the resulting crude product **9** with excess iodomethane, treatment with $NaHCO_3$ gave rise mainly to unsaturated compound **10**. The (*E*) configuration of **10** was confirmed by the high chemical shift of the ethylenic proton (δ = 6.85 ppm).[12] The formation of **10** by an *anti* elimination (72% yield for the three-step procedure) is compatible with the relative configurations indicated for **8a** in Scheme 2. The structure of cycloadduct **8a** was ascertained by X-ray analysis (Figure 1).[13] The postulated transition state leading to this highly *endo*-selective cycloaddition is depicted in Figure 2.



Scheme 2.

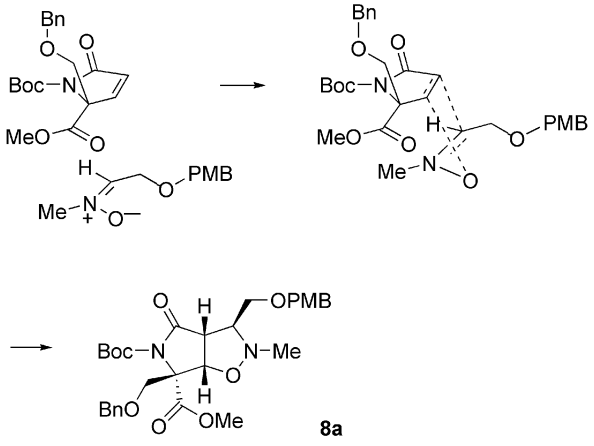


Figure 2. Postulated transition state in the formation of **8a**.

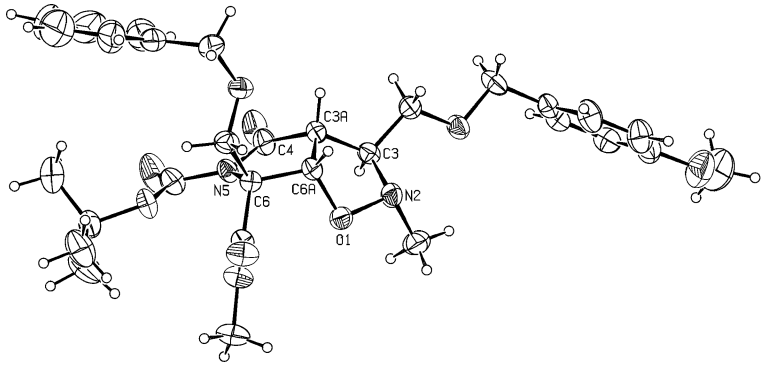


Figure 1. ORTEP diagram from the X-ray crystallographic analysis of cycloadduct **8a**.

A deprotection of the lactam nitrogen in **10** was first attempted with $ZnBr_2$ in dichloromethane,[14] but the *O*-protecting *p*-methoxybenzyl group was also partially removed with this mild reagent. A more chemoselective result was obtained with $MgCl_2$ in acetonitrile,[15,16] as **11** was readily formed in good yield (97%). The corresponding TBS ether (TBSOTf, 2,6-lutidine, room temp., 86%) was slowly hydrogenated over PtO_2 (100% yield, 80% *de*) leading to **4** by simple recrystallisation (79% yield, >95% pure according to ^1H NMR). Thus, these results match those obtained in the unsubstituted *N*-methylnitrone series,[8b] affording the required diastereomer in an efficient manner.

Conclusions

In conclusion, this short synthetic route to polysubstituted pyrrolidinone **4** was conducted by two diastereoselective steps, namely the regio-, facial-, and *endo*-selective 1,3-dipolar cycloaddition of *C*-(4-methoxybenzyloxymethyl)-*N*-methylnitrone **7** to unsaturated γ-lactam (±)-**5** and the hydrogenation of its derivative **12**. Thus, this work demonstrated that our previously developed synthetic scheme to omuralide (**1**) could be extended to the cycloaddition of more complex nitrones and could offer access to advanced precursors of new omuralide–salinosporamide A hybrids as well as several natural cinnabaramides.

Experimental Section

General: Melting points were uncorrected. NMR spectra were recorded with a Bruker spectrometer at 500 or 300 MHz for ^1H NMR and 125 or 75 MHz for ^{13}C NMR; chemical shifts are given in ppm relative to residual $CHCl_3$ (δ = 7.27 ppm for ^1H NMR and 77.14 ppm for the middle line in ^{13}C NMR); s, d, t, dd and m indicate singlet, doublet, triplet, doublet of doublets, and multiplet, respectively. Mass spectra and high-resolution mass spectra (*m*/*z*) were measured with ESI. All moisture-sensitive reactions were performed under argon. THF was freshly distilled from the sodium complex of benzophenone before use. Dichloromethane was freshly distilled from CaH_2. Toluene was distilled from sodium. Column chromatography was performed with silica gel (SDS 230–400 mesh), and preparative thin-layer chromatography (TLC) was performed with silica gel (Merck HF 254 + 366).

4-(4-Methoxybenzyloxymethyl)-2,2-dimethyl-1,3-dioxolane: Solketal (500 μL, 4.02 mmol) was added dropwise under Ar to a stirred suspension of NaH (60%, 206 mg, 5.37 mmol) in dry THF (8.0 mL) at 0 °C. The mixture was stirred for 10 min at 0 °C and then at room temp. for 1.5 h and cooled again to 0 °C. PMBBr (596 μL, 4.07 mmol) was then added, and the solution was stirred for 10 min at room temp. and then at reflux for 22 h. The solvent was evaporated, and heptane was added. The insoluble salts were filtered, and the solution was washed with water and dried with $MgSO_4$. After the usual workup, the product was purified by chromatography on silica gel (eluent: heptane/Et_2O, 1:1), giving rise to *O*-PMB solketal as a colourless liquid (975 mg, 96%). ^1H NMR (500 MHz, $CDCl_3$): δ = 7.27 (d, *J* = 8.5 Hz, 2 H, MeOAr-*H*), 6.88 (d, *J* = 8.5 Hz, 2 H, MeOAr-*H*), 4.54 (d, *J* = 11.3 Hz, 1 H, MeOArC*H*aO), 4.49 (d, *J* = 11.3 Hz, 1 H, MeOArC*H*bO), 4.29 (m, 1 H, H-4), 4.05 (dd, *J* = 8.2, *J′* = 6.4 Hz, 1 H, Ha-5), 3.73 (dd, *J* = 8.2, *J′* = 6.4 Hz, 1 H, Hb-5), 3.81 (s, 3 H, OMe), 3.54 (dd, *J* = 9.8, *J′* = 5.6 Hz, 1 H, PMBOC*H*a), 3.44 (dd, *J* = 9.8, *J′* = 5.6 Hz, 1 H, PMBOC*H*b), 1.43 (s, 3 H, Me), 1.37 (s, 3 H, Me) ppm (in full agreement with literature data).[9c]

3-(4-Methoxybenzyloxy)propane-1,2-diol: To a solution of *O*-PMB solketal (969.1 mg, 3.84 mmol) in THF (8.4 mL) was added 1 N HCl (8.3 mL). The mixture was stirred at room temp. until conversion was complete (6 h). $NaHCO_3$ was then added at 0 °C until the pH reached 8 and, after concentration of the mixture under reduced pressure, the resulting mixture was extracted with EtOAc. The organic layers were dried with $MgSO_4$, and the solvents were evaporated. Purification of the residue by silica gel chromatography (eluent: Et_2O) afforded the diol (749.9 mg, 92%) as a colourless oil. ^1H NMR (300 MHz, $CDCl_3$): δ = 7.26 (d, *J* = 8.5 Hz, 2 H, MeOAr-*H*), 6.88 (d, *J* = 8.5 Hz, 2 H, MeOAr-*H*), 4.49 (s, 2 H, Ar-CH_2O), 3.88 (m, 1 H, H-2), 3.82 (s, 3 H, OMe), 3.69 (dd, *J* = 11.4, *J′* = 3.9 Hz, 1 H, OCHa), 3.62 (dd, *J* = 11.4, *J′* = 5.5 Hz, 1 H, OCHb), 3.54 (m, 2 H, OCH_2), 2.55 (br., OH) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 159.51, 129.87, 129.57, 114.02, 73.36, 71.61, 70.73, 64.20, 55.40 ppm.[9b,9c]

2-(4-Methoxybenzyloxy)ethanal (6): To a solution of 3-(4-methoxybenzyloxy)propane-1,2-diol (636 mg, 3.0 mmol) in CH_2Cl_2 (6.4 mL) were added H_2O (0.35 mL) and $NaIO_4$ (770 mg, 3.6 mmol), and the biphasic mixture was stirred at room temp. for 22 h. After the addition of CH_2Cl_2 (35 mL), the mixture was dried over $MgSO_4$, the solvent was removed by evaporation, and the aldehyde (542 mg, 100%) obtained was pure enough for the next step. ^1H NMR (500 MHz, $CDCl_3$): δ = 9.71 (s, 1 H, CHO), 7.29 (d, *J* = 8.7 Hz, 2 H, MeOAr-*H*), 6.90 (d, *J* = 8.7 Hz, 2 H, MeOAr-*H*), 4.57 (s, 2 H, ArCH_2O), 4.07 (s, 2 H, PMBOCH_2), 3.82 (s, 3 H, OMe) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 200.76, 159.76, 129.88, 128.98, 114.11, 75.12, 73.45, 55.40 ppm.

[2-(4-Methoxybenzyloxy)ethylidene]methanamine Oxide (7): To a solution of aldehyde **6** (540 mg, 3.0 mmol) in dry toluene (15.6 mL), were added at room temp. MeNHOH hydrochloride (524 mg, 6.27 mmol) and NEt_3 (1.57 mL, 11.3 mmol). The mixture was stirred for 1.5 h. The insoluble salts were then filtered and washed with toluene. The solution was evaporated at 22 °C. The crude residue was purified by chromatography on silica gel (eluent: CH_2Cl_2/MeOH, 97:3) to give the pure nitrone (595 mg, 95%) as colourless crystals; m.p. 56 °C. ^1H NMR (500 MHz, $CDCl_3$): δ = 7.27 (d, *J* = 8.6 Hz, 2 H, MeOAr-*H*), 6.90 (d, *J* = 8.6 Hz, 2 H, MeOAr-*H*), 6.86 (m, 1 H, NCH), 4.51 (s, 2 H, MeOArCH_2O), 4.44 (m, 2 H, PMBOCH_2), 3.82 (s, 3 H, OMe), 3.68 (br. s, 3 H, NMe) ppm. ^{13}C (125 MHz, $CDCl_3$): δ = 159.63, 138.44, 129.72, 129.46, 114.04, 73.50, 65.57, 55.39, 52.25 ppm. HRMS (ESI, CH_2Cl_2/MeOH): calcd. for $C_{11}H_{15}NNaO_3$ $[M + Na]^+$ 232.0950; found 232.0946.

(3a*R,6*R**,6a*S**)-5-*tert*-Butyl 6-Methyl 6-(Benzyloxymethyl)-3-[(4-methoxybenzyloxy)methyl]-2-methyl-4-oxotetrahydro-2*H*-pyrrolo-[3,4-*d*]isoxazole-5,6(3*H*)-dicarboxylates (8):** A solution of (±)-**5** (330 mg, 0.91 mmol) in toluene (6.0 mL) was added to nitrone **7** (260 mg, 1.24 mmol), and the mixture was stirred at 60 °C for 27 h. The crude product obtained after evaporation of the solvent was purified by chromatography on silica gel (eluent: CH_2Cl_2/MeOH, 99:1) to give (3*S**,3a*R**,6*R**,6a*S**)-**8a** (398.0 mg, 76%) as a colourless oil and a mixture of starting material and **8b**. Diastereomer **8b** was formed in about 8% yield (established by NMR) and purified by preparative TLC (slow elution with CH_2Cl_2) to give (3*R**,3a*R**,6*R**,6a*S**)-**8b** (38 mg, 7%) as a colourless gum. Major cycloadduct (3*S**,3a*R**,6*R**,6a*S**)-**8a**: ^1H NMR (300 MHz, $CDCl_3$): δ = 7.36–7.20 (m, 5 H, Ph-*H*), 7.24 (masked d, *J* = 8.7 Hz,

2 H, MeOAr-*H*), 6.86 (d, *J* = 8.7, 2 H, MeOAr-*H*), 4.60–4.42 (m, 5 H, 2×ArCH_2O, H-6a), 4.13 (d, *J* = 9.6 Hz, 1 H, BnOC*H*a), 3.98 (d, *J* = 9.6 Hz, 1 H, BnOC*H*b), 3.80 (s, 3 H, OMe), 3.74 (s, 3 H, OMe), 3.58 (m, 2 H, PMBOCH_2), 3.47 (dd, *J* = 6.9, *J*′ = 4.5 Hz, 1 H, H-3a), 3.32 (br. m, 1 H, NCH), 2.71 (br. s, 3 H, NMe), 1.44 (s, 9 H, *t*Bu) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 173.60, 167.08, 159.35, 149.16, 137.32, 129.99, 129.38, 128.69, 128.08, 127.71, 113.93, 83.92, 79.51, 73.65, 73.05, 72.09, 70.30, 70.0 (br.), 55.37, 52.42, 45.4 (br.), 27.93 ppm. HRMS (ESI, CH_2Cl_2/MeOH): calcd. for $C_{30}H_{38}N_2NaO_9$ [M + Na]$^+$ 593.2475; found 593.2478. For X-ray analysis, **8a** was crystallised from EtOAc/pentane; m.p. 87–89 °C. Minor cycloadduct **8b**: ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.36–7.23 (m, 7 H, 5 Ph-*H*, 2×MeOAr-*H*), 6.87 (d, *J* = 8.7 Hz, 2 H, MeOAr-*H*), 4.63 (d, *J* = 7.4 Hz, 1 H, H-6a), 4.49 (2 H, ArCH_2O), 4.47 (2 H, ArCH_2O), 4.19 (dd, *J* = 10.7, *J*′ = 2.5 Hz, 1 H, PMBOC*H*a), 4.10 (d, *J* = 9.6 Hz, 1 H, BnOC*H*a), 4.01 (d, *J* = 9.6 Hz, 1 H, BnOC*H*b), 3.81 (s, 3 H, OMe), 3.76 (s, 3 H, OMe), 3.64 (dd, *J* = 10.7, *J*′ = 8.0 Hz, 1 H, PMBOC*H*b), 3.50 (1 H, H-3a), 2.93 (m, 1 H, H-3), 2.69 (s, 3 H, NMe), 1.42 (s, 9 H, *t*Bu) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 171.55, 167.46, 159.34, 148.67, 137.39, 130.32, 129.53, 128.72, 128.11, 127.76, 113.94, 83.73, 77.87, 73.71, 73.20, 70.86, 69.76, 67.48, 55.41, 53.97, 52.39, 44.84, 28.00 ppm. HRMS (ESI, CH_2Cl_2/MeOH): calcd. for $C_{30}H_{38}N_2NaO_9$ [M + Na]$^+$ 593.2475; found 593.2448.

(2*R,3*S**,4*R**)-1-*tert*-Butyl 2-Methyl 2-(Benzyloxymethyl)-3-hydroxy-4-[2-(4-methoxybenzyloxy)-1-(methylamino)ethyl]-5-oxopyrrolidine-1,2-dicarboxylate (9):** A solution of cycloadduct **8a** (199.5 mg, 0.35 mmol) in EtOAc (3.4 mL) was stirred under H_2 in the presence of $Pd(OH)_2$ (38 mg) at room temp. for 16 h. The catalyst was filtered through celite and washed with EtOAc. Evaporation of the solvent under reduced pressure afforded the crude hydrogenolysis product as a colourless gum (198 mg, 99%). ^{1}H NMR (500 MHz, $CDCl_3$/D_2O): δ = 7.36–7.18 (7 H, Ph-*H*, MeOAr-*H*), 6.87 (d, *J* = 8.5 Hz, 2 H, MeOAr-*H*), 4.59 (d, *J* = 6.8 Hz, 1 H, H-3), 4.50–4.46 (4 d, *J* ≈ 11.7 Hz, 4 H, 2×ArCH_2O), 4.13 (d, *J* = 9.8 Hz, 1 H, BnOC*H*a), 4.03 (d, *J* = 9.8 Hz, 1 H, BnOC*H*b), 3.80 (s, 3 H, OMe), 3.73 (s, 3 H, OMe), 3.73 (masked m, 1 H, PMBOC*H*a), 3.63 (masked m, 1 H, PMBOC*H*b), 3.60 (1 H, CH-4), 2.97 (dd, *J* = 6.8, *J*′ = 3.5 Hz, 1 H, H-4), 2.36 (s, 3 H, NMe), 1.44 (s, 9 H, *t*Bu) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 174.33, 168.43, 159.48, 149.62, 137.55, 129.94, 129.78, 129.48, 128.64, 128.00, 127.70, 114.03, 83.58, 74.87, 73.69, 73.06, 70.64, 69.17, 57.92, 55.39, 52.23, 45.41, 34.07, 27.98 ppm. HRMS (ESI, CH_2Cl_2/MeOH): calcd. for $C_{30}H_{41}N_2O_9$ [M + H]$^+$ 573.2812; found 573.2803.

(2*R,3*S**,*E*)-1-*tert*-Butyl 2-Methyl 2-(Benzyloxymethyl)-3-hydroxy-4-[2-(4-methoxybenzyloxy)ethylidene]-5-oxopyrrolidine-1,2-dicarboxylate (10):** Iodomethane (0.41 mL, 6.6 mmol) was added under argon to a solution of **9** (126.2 mg, 0.22 mmol) in dry THF (1.6 mL), and the mixture was stirred at room temp. for 24 h. MeI (0.41 mL, 6.6 mmol) and $NaHCO_3$ (25 mg, 0.3 mmol) were then added, and stirring was maintained for an additional 40 h before the solvent and reagent in excess were evaporated. The residue was filtered through silica gel (eluent: Et_2O) to give the crude product, which was purified by preparative TLC (eluent: CH_2Cl_2/MeOH, 98:2) affording **10** as a colourless gum (87.3 mg, 73% over 2 steps). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.35–7.15 (m, 7 H, Ph-*H*, MeOAr-*H*), 6.89 (d, *J* = 8.7 Hz, 2 H, MeOAr-*H*), 6.85 (m, 1 H, CH-4), 5.03 (m, 1 H, H-3), 4.57–4.48 (4 d, *J* = 11.5 Hz, 4 H, 2×ArCH_2O), 4.37 (centre of m, 2 H, PMBOCH_2), 4.17 (d, *J* = 9.8 Hz, 1 H, BnOC*H*a), 4.03 (d, *J* = 9.8 Hz, 1 H, BnOC*H*b), 3.99 (d, 1 H exchanged, OH), 3.82 (s, 3 H, OMe), 3.73 (s, 3 H, OMe), 1.46 (s, 9 H, *t*Bu) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 168.84, 165.72, 159.86, 149.73, 137.74, 136.47, 134.00, 129.87, 128.56, 128.34, 127.89, 127.68, 114.25, 83.83, 73.57, 73.52, 70.97, 69.32, 68.92, 68.07, 55.41, 52.40, 28.03 ppm. HRMS (ESI, CH_2Cl_2/MeOH): calcd. for $C_{29}H_{35}NNaO_9$ [M + Na]$^+$ 564.2210; found 564.2211.

(2*R,3*S**,*E*)-Methyl 2-(Benzyloxymethyl)-3-hydroxy-4-[2-(4-methoxybenzyloxy)ethylidene]-5-oxopyrrolidine-2-carboxylate (11):** Dried $MgCl_2$ (13.1 mg, 0.137 mmol) was added to a solution of **10** (82.0 mg, 0.151 mmol) in MeCN (1.1 mL), and the mixture was stirred at 40 °C for 2.5 h. After dilution with CH_2Cl_2 and filtration of the resulting mixture, the salt was washed with CH_2Cl_2. The solution was evaporated to dryness giving rise to deprotected **11** as colourless crystals (64.7 mg, 97%); m.p. 104 °C. ^{1}H NMR (500 MHz, $CDCl_3$/D_2O): δ = 7.37–7.25 (5 H, Ph-*H*), 7.23 (d, *J* = 8.5 Hz, 2 H, MeOAr-*H*), 6.89 (d, *J* = 8.5 Hz, 2 H, MeOAr-*H*), 6.69 (m, 1 H, CH-4), 4.70 (m, 1 H, H-3), 4.54 (apparent s, 2 H, ArCH_2O), 4.52 (masked 2 d, 2 H, ArCH_2O), 4.31 (m, 2 H, PMBOCH_2), 4.08 (d, *J* = 8.8 Hz, 1 H, BnOC*H*a), 3.82 (s, 3 H, OMe), 3.79 (s, 3 H, OMe), 3.35 (d, *J* = 8.8 Hz, 1 H, BnOC*H*b) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 170.09, 168.13, 159.85, 137.36, 134.37, 134.17, 129.84, 128.62, 128.08, 127.80, 114.26, 73.79, 73.69, 73.42, 69.87, 69.04, 67.74, 55.42, 52.90 ppm. HRMS (ESI, CH_2Cl_2/MeOH): calcd. for $C_{24}H_{27}NNaO_7$ [M + Na]$^+$ 464.1685; found 464.1675.

(2*R,3*S**,*E*)-Methyl 2-(Benzyloxymethyl)-3-(*tert*-butyldimethylsilyloxy)-4-[2-(4-methoxybenzyloxy)ethylidene]-5-oxopyrrolidine-2-carboxylate (12):** To a solution of **11** (63.1 mg, 0.143 mmol) in dry CH_2Cl_2 (0.86 mL) at 15 °C were successively added, under argon, 2,6 lutidine (117 μL, 1.0 mmol) and TBSOTf (117 μL, 0.51 mmol). The mixture was stirred for 6 h at the same temperature and then cooled to 0 °C before the addition of CH_2Cl_2 and $NaHCO_3$ (5% w/v). After extraction of the aqueous phase with CH_2Cl_2 and the usual workup, the product was purified by preparative TLC (eluent: heptane/Et_2O, 1:9) to afford **12** (68.3 mg, 86%) as colourless crystals; m.p. 115–116 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.4–7.2 (m, 5 H, Ph-*H*), 7.22 (masked d, *J* = 8.7 Hz, 2 H, MeOAr-*H*), 6.88 (d, *J* = 8.7 Hz, 2 H, MeOAr-*H*), 6.65 (ddd, *J* ≈ *J*′ ≈ 5.6, *J*′′ = 1 Hz, 1 H, CH-4), 6.32 (br. s, 1 H, NH), 4.84 (m, apparent br. s, 1 H, H-3), 4.56–4.40 (4 d, 4 H, PhCH_2O, MeOArCH_2O), 4.20–4.19 (m, 2 H, PMBOCH_2), 3.90 (d, *J* = 8.8 Hz, 1 H, BnOC*H*a), 3.82 (s, 3 H, OMe), 3.76 (s, 3 H, OMe), 3.23 (d, *J* = 8.8 Hz, 1 H, BnOC*H*b), 0.79 (s, 9 H, Si*t*Bu), 0.00 (s, 3 H, SiMe), –0.01 (s, 3 H, SiMe) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 169.30, 168.26, 159.59, 137.39, 134.54, 133.56, 129.57, 128.61, 128.05, 127.67, 114.06, 73.73, 73.26, 72.70, 71.25, 70.95, 66.83, 55.44, 52.67, 25.72, 18.01, –4.16, –4.46 ppm. HRMS (ESI, CH_2Cl_2/MeOH): calcd. for $C_{30}H_{41}NNaO_7Si$ [M + Na]$^+$ 578.2550; found 578.2535.

(2*R,3*S**,4*R**)-Methyl 2-(Benzyloxymethyl)-3-(*tert*-butyldimethylsilyloxy)-4-[2-(4-methoxybenzyloxy)ethyl]-5-oxopyrrolidine-2-carboxylate (4):** Compound **12** (55.0 mg, 1.0 mmol), dissolved in EtOAc (2.6 mL), was stirred under H_2 in the presence of PtO_2 (9 mg) for 60 h. The catalyst was filtered through celite and washed with EtOAc, and the solvent was evaporated under reduced pressure. The crude product (55.2 mg, *de* = 80%, as deduced from ^{1}H NMR) was recrystallized from Et_2O/pentane to afford **4** (43.5 mg, 79%, >95% pure according to ^{1}H NMR); m.p. 72–73 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.40–7.20 (m, 5 H, Ph-*H*), 7.26 (masked d, *J* = 8.7 Hz, MeOAr-*H*), 6.86 (d, *J* = 8.7 Hz, 2 H, MeOAr-*H*), 6.04 (br. s, 1 H, NH), 4.52 (apparent s, 2 H, PhCH_2O), 4.47 (d, *J* = 11.7 Hz, 1 H, MeOArC*H*aO), 4.42 (d, *J* = 11.7 Hz, 1 H, MeOArC*H*bO), 4.31 (d, *J* = 6.7 Hz, 1 H, H-3), 3.96 (d, *J* = 8.8 Hz, 1 H, BnOC*H*a), 3.80 (s, 3 H, OMe), 3.73 (s, 3 H, OMe), 3.70 (m, 1 H, PMBOC*H*a), 3.65 (m, 1 H, PMBOC*H*b), 3.43 (d, *J* = 8.8 Hz,

1 H, BnOC*H*b), 2.64 (m, 1 H, H-4), 1.91 (m, 2 H, CH_2-4), 0.86 (s, 9 H, Si*t*Bu), 0.05 (s, 3 H, SiMe), 0.03 (s, 3 H, SiMe) ppm. ^{13}C (125 MHz, $CDCl_3$): δ = 176.81, 170.17, 159.22, 137.39, 130.92, 129.39, 128.62, 128.06, 127.78, 113.85, 73.83 (CH and CH_2), 73.29, 72.65, 71.06, 67.96, 55.39, 52.58, 43.25, 25.87, 25.24, 18.13, –3.96, –4.74 ppm. HRMS (ESI, CH_2Cl_2/MeOH): calcd. for $C_{30}H_{43}NNaO_7Si$ $[M + Na]^+$, 100%): 580.2707; found 580.2700. A small amount of minor diastereomer **13** (ca 2.4 mg, 4%) was obtained from the mother liquor after preparative TLC (eluent: heptane/Et_2O/MeOH, 4:2:0.1). **13**: ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.40–7.25 (m, 5 H, Ph-*H*), 7.22 (d, *J* = 8.6 Hz, 2 H, MeOAr-*H*), 6.85 (d, *J* = 8.6 Hz, 2 H, MeOAr-*H*), 5.98 (br. s, NH), 4.52 (d, *J* = 12.0 Hz, 1 H, PhC*H*aO or MeOArC*H*aO), 4.49 (d, *J* = 12.0 Hz, 1 H, PhC*H*bO or MeOArC*H*bO), 4.38 (apparent s, 2 H, PhCH_2O or MeOArCH_2O), 4.21 (d, *J* = 6.9 Hz, 1 H, H-3), 4.03 (d, *J* = 8.8 Hz, BnOC*H*a), 3.80 (s, 3 H, OMe), 3.72 (s, 3 H, OMe), 3.66 (m, 1 H, PMBOC*H*a), 3.62 (m, 1 H, PMBOC*H*b), 3.31 (d, *J* = 8.8 Hz, 1 H, BnOC*H*b), 2.63 (m, 1 H, H-4), 1.93 (m, 2 H, CH_2-4), 0.84 (s, 9 H, Si*t*Bu), 0.04 (s, 3 H, SiMe), –0.01 (s, 3 H, SiMe) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 176.20, 170.24, 159.26, 137.49, 130.69, 129.40, 128.60, 128.05, 127.83, 113.84, 76.48, 73.76, 72.81, 72.67, 69.53, 67.67, 55.39, 52.51, 47.00, 27.95, 25.66, 17.84, –4.24, –4.66 ppm. HRMS (ESI, CH_2Cl_2/MeOH): calcd. for $C_{30}H_{43}NNaO_7Si$ $[M + Na]^+$ 580.2707; found 580.2707.

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