Tetrahedron 64 (2008) 7896–7901

Contents lists available at ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

Formal synthesis of salinosporamide A using a nickel-catalyzed reductive aldol cyclization–lactonization as a key step

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ARTICLE INFO

Article history:
Received 5 April 2008
Received in revised form 28 May 2008
Accepted 12 June 2008
Available online 14 June 2008

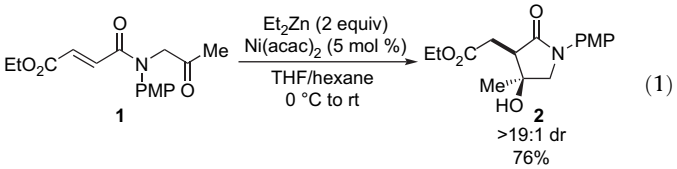
ABSTRACT

Application of a sequential nickel-catalyzed reductive aldol cyclization–lactonization reaction in a short formal synthesis of salinsporamide A, a potent 20S proteasome inhibitor and anti-cancer compound, is described.

1. Introduction

Advances in transition-metal-catalyzed cyclization reactions provide the means to access increasingly diverse carbocyclic and heterocyclic compounds from relatively simple starting materials, with often impressive levels of diastereo- and enantioselectivity.[1,2,3] Reductive cyclizations, where reaction is promoted by stoichiometric reductants such as molecular hydrogen, silanes, formic acid, stannanes, borohydrides or main-group organometallic reagents, represent an important class of these transformations.[2,3] Many of these reactions have been developed to a level of utility that enable their application in natural product synthesis.[4]

Our research in this area has led to the development of a series of metal-catalyzed reductive aldol cyclization reactions that form β-hydroxylactones and β-hydroxylactams in highly diastereoselective fashion.[5] A notable result is the cyclization of **1** using $Ni(acac)_2$ as the precatalyst and Et_2Zn as the stoichiometric reductant, which provided β-hydroxy-γ-lactam **2** as a single diastereomer (Eq. 1).[5d,6] This outcome was of interest because examination of the structure of **2** revealed similarities with the core of salinosporamide A (**3**) (Fig. 1), a secondary metabolite isolated by Fenical and co-workers from marine actinomycete bacteria of *Salinospora* strain CNB-392.[7] This compound has attracted significant attention because of its impressive biological activity.[7] Not only is **3** a highly potent inhibitor of the 20S proteasome, an abundant complex within cells that plays an important role in the degradation and removal of misfolded proteins,[8] it also exhibits promising potential as an anti-cancer therapeutic agent. Indeed, **3** is currently in clinical trials for this purpose.[9]



(1)

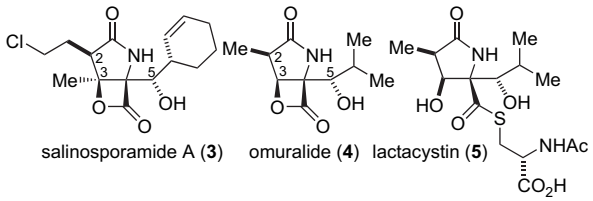


Figure 1.

Structurally, salinosporamide A (**3**) shares its fused γ-lactam-β-lactone bicyclic core with omuralide (**4**), a product derived from the terrestrial microbial metabolite lactacystin (**5**).[10,11] Although omuralide (**4**) is also an effective 20S proteasome inhibitor, differences between **3** and **4** at C2, C3 and C5 render **3** approximately 35 times more potent than **4**.[7] Salinosporamide A (**3**) has also elicited significant interest from a synthetic perspective, with a number of total and partial syntheses having been reported.[11c,12]

Given the huge interest in salinosporamide A (**3**), and the resemblance of β-hydroxy-γ-lactam **2** to the core of **3**, we became interested in the possibility of applying our nickel-catalyzed reductive aldol methodology[5d] in a synthetic route towards this natural product. Strategically, construction of the γ-lactam of **3** by formation of the C2–C3 bond has already been accomplished by Corey and co-workers (Scheme 1).[12a,b] In their original

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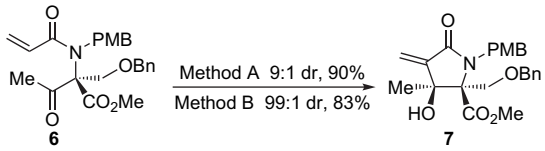
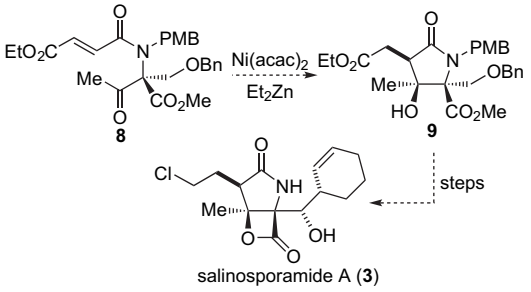
0040-4020/$ – see front matter © 2008 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2008.06.038

total synthesis of salinosporamide A (**3**), acrylamide **6** was cyclized in a Baylis–Hillman reaction[13] (method A) to provide γ-lactam **7** as a 9:1 mixture of diastereomers after 1 week.[12a] The same group subsequently developed improved conditions for this cyclization, involving the Kulinkovich reagent[14] formed from Ti(O*i*-Pr)$_4$ and cyclopentylmagnesium chloride (method B).[12b] A sequence of several steps including a tin hydride-mediated radical cyclization was then required to transform the exomethylene group of **7** into the chloroethyl functionality of salinosporamide A (**3**).[12a]



Scheme 1. Construction of γ-lactam **7** by Corey and co-workers.[12a,b]

Since the ethyl ester-containing side-chain in **2** can be converted into the chloroethyl group of salinosporamide A (**3**) without further carbon–carbon bond formation, we envisaged that a suitably more functionalized variant of Eq. 1 might prove advantageous in a synthetic route towards **3**. Accordingly, α,β-unsaturated amide **8** became a target for our investigations (Scheme 2).

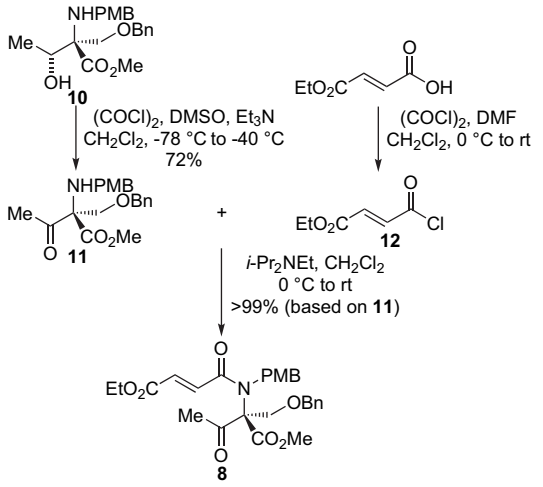


Scheme 2. Reductive aldol cyclization strategy towards **3**.

Compared with **1**, substrate **8** possesses a more densely functionalized, more sterically congested structure containing several Lewis basic groups that could potentially bind the catalyst and organometallic reductant and divert the course of the proposed cyclization towards deleterious side reactions. Furthermore, we would be reliant upon the single stereocenter present in **8** to control the absolute configurations of the two new stereocenters formed in the cyclization to provide **9** preferentially, and prediction of the sense of diastereoselectivity (if any) was by no means straightforward. Therefore, substrate **8** would provide a challenging test for our methodology. In this article, we describe the successful utilization of **8** in a formal synthesis of salinosporamide A (**3**).

2. Results and discussion

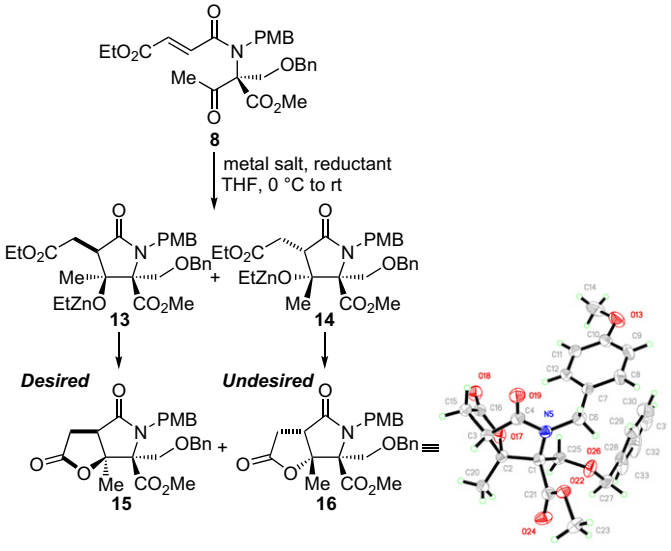
Cyclization precursor **8** was prepared in straightforward fashion as illustrated in Scheme 3. Swern oxidation[15] of the previously described amino alcohol **10**[12a] provided aminoketone **11**, which was then acylated with the acid chloride **12** derived from mono-ethyl fumarate[16] to afford α,β-unsaturated amide **8** in high yield.



Scheme 3. Preparation of substrate **8** for reductive aldol cyclization.

With **8** in hand, the crucial reductive aldol cyclization was attempted (Table 1). Unfortunately, exposure of **8** to Ni(acac)$_2$ and Et$_2$Zn (as in Eq. 1)[5d] provided only an intractable mixture of products (entry 1). The situation was not improved upon replacing Et$_2$Zn with Et$_3$Al[5c] (entry 2), or by replacing Ni(acac)$_2$ with Co(acac)$_2\cdot 2H_2O$[5c] (entries 3 and 4). The effect of phosphine ligands on the reaction was then examined. Although the combination of $CoCl_2$ and DPPF offered no improvement (entry 5), it was found that commercially available nickel–phosphine complexes were effective precatalysts. Using $(Ph_3P)_2NiBr_2$ (entry 6), none of the initially desired product **9** was isolated. Instead, fused γ-lactone-γ-lactam **15** containing the

Table 1
Reductive aldol cyclization of **8**



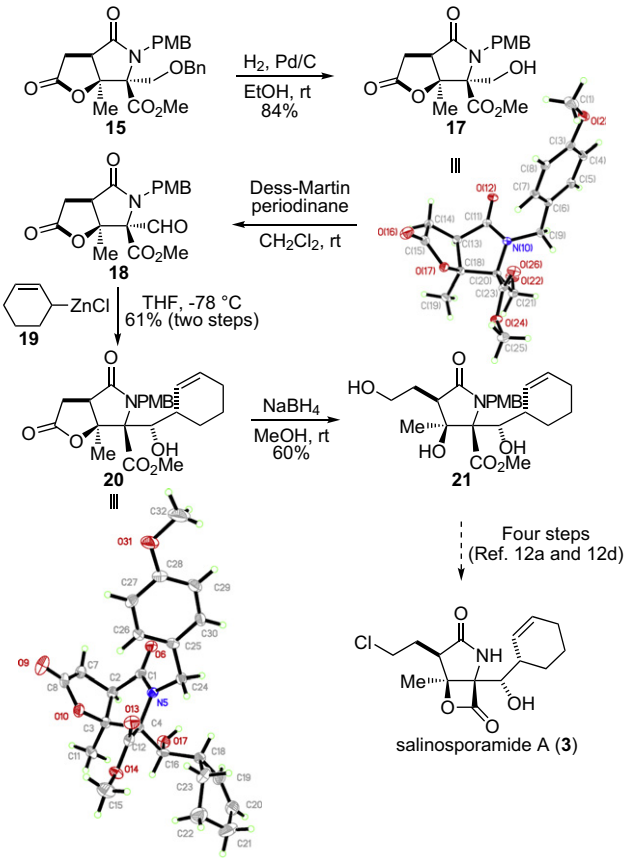
Entry	Precatalyst (10 mol %)	Reductant (2 equiv)	Result/yields
1	Ni(acac)$_2$	Et$_2$Zn	Intractable mixture
2	Ni(acac)$_2$	Et$_3$Al	Intractable mixture
3	Co(acac)$_2$	Et$_2$Zn	<10% Conversion
4	Co(acac)$_2$	Et$_3$Al	Intractable mixture
5	$CoCl_2$/DPPF	Et$_2$Zn	Intractable mixture
6	$(Ph_3P)_2NiBr_2$	Et$_2$Zn	35% of **15**,[a] 30% of **16**[a]
7[b]	$(Me_3P)_2NiCl_2$	Et$_2$Zn	42% of **15**,[a] 30% of **16**[a]

[a] Isolated yield.
[b] Initial reaction temperature of −15 °C. DPPF=1,1′-bis(diphenylphosphino)-ferrocene.

desired stereochemistry was isolated in 35% yield, along with a comparable amount of the alternative diastereomer **16**, the stereochemistry of which was established by X-ray crystallography.[17] Marginally superior results were obtained using $(Me_3P)_2NiCl_2$ at an initial temperature of −15 °C (entry 7). Attempts to increase the diastereoselectivity of the reaction in favor of **15** by further modification of the conditions have so far been unsuccessful.

The lactones **15** and **16** are produced presumably as a result of the zinc alkoxides **13** and **14**, formed upon reductive aldol reaction, cyclizing onto the pendant ethyl esters. Although lactonization was unexpected in light of the reaction shown in Eq. 1, it turned out to be a useful bonus, since it conveniently protected the tertiary alcohol towards subsequent transformations.[18]

The desired diastereomer **15** was subjected to palladium-catalyzed debenzylation to provide alcohol **17** (84% yield) (Scheme 4). X-ray crystallography of this compound allowed confirmation of its stereochemistry, and hence that of its immediate precursor **15**.[17] Oxidation of **17** to aldehyde **18** in readiness for installation of the cyclohexenyl group was accomplished using the Dess–Martin periodinane.[19] Aldehyde **18** proved to be somewhat unstable, and was immediately reacted with 2-cyclohexenylzinc chloride (**19**) as described by Corey and co-workers[12a] to give homoallylic alcohol **20** in highly selective fashion (one observable diastereomer by ^1H NMR analysis). X-ray crystallography of **20** showed that the desired stereochemistry had been obtained in the allylation.[17] Finally, reductive ring-opening of the lactone in **20** was accomplished using $NaBH_4$ to give triol **21**, the conversion of which into salinosporamide A (**1**) has already been described by the groups of Corey[12a] and Pattenden.[12d]



Scheme 4. Completion of the formal synthesis of **3**.

3. Conclusion

Largely following the strategy of Corey and co-workers,[12a] a concise formal synthesis of salinosporamide A (**3**) has been achieved. The distinguishing feature of the work described herein is the use of a sequential nickel-catalyzed reductive aldol cyclization–lactonization reaction of **8** to construct the γ-lactam of **3**. Although the diastereoselectivity of this transformation remains to be improved, this approach represents an attractive method to install the C2 side-chain with simultaneous protection of the C5 oxygen, and further demonstrates the utility of nickel catalysis in complex molecule synthesis.[1b,4a–c,f] Further applications of our reductive aldol cyclization methodology will be reported in due course.

4. Experimental section

4.1. General

All non-aqueous reactions were carried out under a nitrogen atmosphere in oven-dried apparatus. CH_2Cl_2 and THF were dried and purified by passage through activated alumina columns using a solvent purification system from www.glasscontoursolventsystems.com. 'Petrol' refers to that fraction of light petroleum ether boiling in the range 40–60 °C. Commercially available $CoCl_2$ was dried by heating under vacuum until it turned from purple to blue. All other commercially available reagents were used as received. Thin layer chromatography (TLC) was performed on Merck DF-Alufoilien $60F_{254}$ 0.2 mm precoated plates. Product spots were visualized by UV light at 254 nm, and subsequently developed using potassium permanganate or ceric ammonium molybdate solution as appropriate. Flash column chromatography was carried out using silica gel (Fisher Scientific 60 Å particle size 35–70 μm). Melting points were recorded on a Gallenkamp melting point apparatus and are uncorrected. Infra-red spectra were recorded on a Jasco FT/IR-460 Plus instrument as a thin film on sodium chloride plates or as a dilute solution in $CHCl_3$. ^1H NMR spectra were recorded on a Bruker DPX360 (360 MHz) spectrometer or a Bruker ARX250 (250 MHz) spectrometer. Chemical shifts (δ) are quoted in parts per million (ppm) downfield of tetramethylsilane, using residual protonated solvent as internal standard ($CDCl_3$ at 7.27 ppm). Abbreviations used in the description of resonances are: s (singlet), d (doublet), t (triplet), q (quartet), app (apparent) and br (broad). Coupling constants (J) are quoted to the nearest 0.1 Hz. Proton-decoupled ^{13}C NMR spectra were recorded on a Bruker ARX250 (62.9 MHz) spectrometer. Chemical shifts (δ) are quoted in parts per million (ppm) downfield of tetramethylsilane, using deuterated solvent as internal standard ($CDCl_3$ at 77.0 ppm). Assignments were made using the DEPT sequence with secondary pulses at 90° and 135°. High resolution mass spectra were recorded on a Finnigan MAT 900 XLT spectrometer using the electrospray (ES) positive ion mode at the EPSRC National Mass Spectrometry Service Centre, University of Wales, Swansea, or on a Finnigan MAT 900 XLT spectrometer or a Kratos MS50TC spectrometer at the School of Chemistry, University of Edinburgh. Optical rotations were performed on an Optical Activity POLAAR 20 polarimeter.

*4.1.1. (R)-Methyl 2-benzyloxymethyl-2-(4-methoxybenzylamino)-3-oxobutanoate (**11**)*

To a stirred solution of $(COCl)_2$ (1.67 mL, 18.8 mmol) in CH_2Cl_2 (40 mL) at −78 °C was added DMSO (2.70 mL, 37.6 mmol) dropwise over 3 min. After stirring for 15 min, a solution of the alcohol **10**[12a] (3.34 g, 8.94 mmol) in CH_2Cl_2 (30 mL) was added via cannula over 5 min. The reaction mixture was stirred at −78 °C for 1 h and Et_3N (5.23 mL, 37.6 mmol) was then added over 1 min. The reaction mixture was stirred at −78 °C for 1 h, allowed to warm to −40 °C over 2 h, and then quenched with saturated aqueous NH_4Cl

solution (40 mL). The aqueous layer was separated and extracted with CH_2Cl_2 (3×20 mL) and the combined organic layers were dried ($MgSO_4$) and concentrated in vacuo. Purification of the residue by column chromatography (10% EtOAc/petrol→20% EtOAc/petrol) gave the ketone **11** (2.39 g, 72%) as a pale yellow solid. R_f=0.55 (30% EtOAc/hexane); mp 60–62 °C; $[\alpha]_D^{25}$ −12.7 (*c* 1.02, $CHCl_3$); IR ($CHCl_3$) 3347 (NH), 2952, 2836, 1741 (C=O), 1718 (C=O), 1511, 1245, 1178, 1033, 700 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 7.39–7.28 (5H, m, Ar*H*), 7.25 (2H, dm, *J*=8.7 Hz, Ar*H*), 6.85 (2H, dm, *J*=8.7 Hz, Ar*H*), 4.59 (1H, d, *J*=12.4 Hz, CH_2Ar), 4.53 (1H, d, *J*=12.4 Hz, CH_2Ar), 4.02 (1H, d, *J*=10.1 Hz, CH_2Ar), 3.90 (1H, d, *J*=10.1 Hz, CH_2Ar), 3.80 (3H, s, OCH_3), 3.74 (3H, s, OCH_3), 3.59 (1H, d, *J*=12.3 Hz, CH_2OBn), 3.46 (1H, d, *J*=12.3 Hz, CH_2OBn), 2.53 (1H, br s, N*H*), 2.21 (3H, s, COCH_3); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 203.3 (C), 169.8 (C), 158.7 (C), 137.6 (C), 131.7 (C), 129.4 (2×CH), 128.4 (2×CH), 127.8 (3×CH), 113.7 (2×CH), 74.9 (C), 73.5 (CH_2), 68.1 (CH_2), 55.3 (CH_3), 52.7 (CH_3), 46.7 (CH_2), 25.7 (CH_3); HRMS (ES) exact mass calcd for $C_{21}H_{26}NO_5$ $[M+H]^+$: 372.1805, found: 372.1804.

4.1.2. (R)-Ethyl (E)-3-[N-(1-benzyloxymethyl-1-carbomethoxy-2-oxopropyl)-N-(4-methoxybenzyl)carbamoyl]acrylate (**8**)

To a stirred solution of mono-ethyl fumarate[16] (858 mg, 5.65 mmol) in CH_2Cl_2 (10 mL) at 0 °C was added $(COCl)_2$ (0.56 mL, 6.40 mmol) followed by DMF (one drop). The resulting mixture was stirred for 1 h at room temperature, and then transferred via cannula to a solution of the amine **11** (1.33 g, 3.60 mmol) and *i*-Pr_2NEt (1.10 mL, 6.40 mmol) in CH_2Cl_2 (10 mL) at 0 °C. The reaction mixture was stirred at 0 °C for 10 min and then at room temperature for 18 h, when it was quenched with saturated aqueous NH_4Cl solution (20 mL). The aqueous layer was separated and extracted with CH_2Cl_2 (3×20 mL), and the combined organic layers were dried ($MgSO_4$), filtered and concentrated in vacuo. Purification of the residue by column chromatography (20% EtOAc/petrol) gave the *amide* **8** (1.79 g, >99%) as a pale yellow oil. R_f=0.45 (30% EtOAc/hexane); $[\alpha]_D^{25}$ −18.2 (*c* 1.18, $CHCl_3$); IR (film) 2953, 2837, 1722 (C=O), 1658 (C=O), 1513, 1408, 1294, 1248, 1175, 1032, 974, 822 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 7.35–7.27 (5H, m, Ar*H*), 7.21 (1H, d, *J*=15.3 Hz, =C*H*), 7.14–7.11 (2H, m, Ar*H*), 6.91 (2H, dm, *J*=8.8 Hz, Ar*H*), 6.82 (1H, d, *J*=15.3 Hz, =C*H*), 4.94 (1H, d, *J*=18.3 Hz, CH_2Ar), 4.79 (1H, d, *J*=18.3 Hz, CH_2Ar), 4.31 (1H, d, *J*=11.9 Hz, CH_2Ar), 4.27 (1H, d, *J*=11.9 Hz, CH_2Ar), 4.18 (2H, q, *J*=7.1 Hz, OCH_2CH$_3$), 3.82 (3H, s, OCH_3), 3.80 (3H, s, OCH_3), 3.76 (2H, br s, CH_2OBn), 2.43 (3H, s, CH_3C=O), 1.25 (3H, t, *J*=7.1 Hz, OCH$_2$CH_3); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 197.6 (C), 168.0 (C), 167.5 (C), 165.2 (C), 158.9 (C), 136.5 (C), 133.3 (CH), 133.1 (CH), 129.7 (C), 128.4 (2×CH), 127.9 (CH), 127.5 (2×CH), 127.1 (2×CH), 114.1 (2×CH), 77.5 (C), 73.7 (CH_2), 70.1 (CH_2), 61.1 (CH_2), 55.2 (CH_3), 52.9 (CH_3), 48.9 (CH_2), 27.9 (CH_3), 14.0 (CH_3); HRMS (ES) exact mass calcd for $C_{27}H_{32}NO_8$ $[M+H]^+$: 498.2122, found: 498.2123.

4.1.3. (3aR,6R,6aS)-6-Benzyloxymethyl-5-(4-methoxybenzyl)-6a-methyl-2,4-dioxohexahydrofuro[2,3-c]pyrrole-6-carboxylic acid methyl ester (**15**) and (3aS,6R,6aR)-6-benzyloxymethyl-5-(4-methoxybenzyl)-6a-methyl-2,4-dioxohexahydrofuro[2,3-c]pyrrole-6-carboxylic acid methyl ester (**16**)

A solution of α,β-unsaturated amide **8** (875 mg, 1.76 mmol) and $(Me_3P)_2NiCl_2$ (115 mg, 0.175 mmol) in THF (75 mL) was stirred at room temperature for 30 min and then cooled to −15 °C (ice/salt bath). Et_2Zn (3.52 mL, 1 M solution in THF, 3.52 mmol) was then added over 0.5 min. The reaction mixture was allowed to warm slowly to room temperature over 18 h, and then quenched carefully with saturated aqueous NH_4Cl solution (50 mL) and extracted with EtOAc (3×30 mL). The combined organic layers were dried ($MgSO_4$) and concentrated in vacuo. Purification of the residue by column chromatography (20% EtOAc/petrol→35% EtOAc/petrol) gave the *double cyclization product* **15** (354 mg, 42%) as a pale yellow oil, followed by the *double cyclization product* **16** (253 mg, 30%) as a white solid. Recrystallization of **16** from EtOAc/petrol gave colorless blocks that were suitable for X-ray crystallography.

Data for ***15***: R_f=0.19 (30% EtOAc/$CHCl_3$); $[\alpha]_D^{25}$ −33.3 (*c* 1.02, $CHCl_3$); IR (film) 2955, 1789 (C=O), 1733 (C=O), 1699 (C=O), 1612, 1513, 1439, 1404, 1248, 1178, 1129, 736 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 7.35–7.25 (5H, m, Ar*H*), 7.12–7.08 (2H, m, Ar*H*), 6.60 (2H, dm, *J*=8.7 Hz, Ar*H*), 5.05 (1H, d, *J*=15.2 Hz, CH_2Ar), 4.28 (1H, d, *J*=15.2 Hz, CH_2Ar), 3.91 (1H, d, *J*=11.5 Hz, CH_2O), 3.83 (1H, d, *J*=10.4 Hz, CH_2O), 3.81 (1H, d, *J*=11.5 Hz, CH_2O), 3.81 (3H, s, OCH_3), 3.74 (3H, s, OCH_3), 3.21 (1H, d, *J*=10.4 Hz, CH_2O), 3.05 (1H, dd, *J*=9.3, 1.5 Hz, CH$_2$C*H*), 2.96 (1H, dd, *J*=18.3, 1.5 Hz, CH_2CH), 2.79 (1H, dd, *J*=18.3, 9.3 Hz, CH_2CH), 1.61 (3H, s, CH_3CO); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 173.5 (C), 172.9 (C), 166.9 (C), 158.9 (C), 136.7 (C), 130.0 (2×CH), 129.4 (C), 128.5 (2×CH), 127.9 (CH), 127.3 (2×CH), 113.6 (2×CH), 88.5 (C), 75.8 (C), 72.8 (CH_2), 67.7 (CH_2), 55.2 (CH_3), 52.8 (CH_3), 47.5 (CH), 45.1 (CH_2), 30.7 (CH_2), 19.4 (CH_3); HRMS (ES) exact mass calcd for $C_{25}H_{28}NO_7$ $[M+H]^+$: 454.1860, found: 454.1856.

Data for ***16***: R_f=0.08 (30% EtOAc/$CHCl_3$); mp 105–106 °C; $[\alpha]_D^{25}$ −17.9 (*c* 1.01, $CHCl_3$); IR (film) 2952, 2870, 1789 (C=O), 1743 (C=O), 1703 (C=O), 1613, 1512, 1434, 1246, 1128, 739 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 7.34–7.28 (3H, m, Ar*H*), 7.22–7.19 (2H, m, Ar*H*), 7.09 (2H, dm, *J*=8.8 Hz, Ar*H*), 6.78 (2H, d, *J*=8.8 Hz, Ar*H*), 4.68 (1H, d, *J*=15.2 Hz, CH_2Ar), 4.37 (1H, d, *J*=15.2 Hz, CH_2Ar), 4.30 (1H, d, *J*=11.7 Hz, CH_2Ar), 4.23 (1H, d, *J*=11.7 Hz, CH_2Ar), 3.90 (1H, d, *J*=10.2 Hz, CH_2OBn), 3.78 (3H, s, OCH_3), 3.71 (1H, d, *J*=10.2 Hz, CH_2OBn), 3.64 (3H, s, OCH_3), 3.03 (1H, dd, *J*=9.7, 1.9 Hz, CH$_2$C*H*), 3.00 (1H, dd, *J*=18.3, 1.9 Hz, CH_2CH), 2.84 (1H, dd, *J*=18.3, 9.7 Hz, CH_2CH), 1.47 (3H, s, CH_3CO); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 173.4 (C), 173.2 (C), 169.2 (C), 158.7 (C), 137.1 (C), 129.2 (2×CH), 129.0 (C), 128.3 (2×CH), 127.7 (3×CH), 113.6 (2×CH), 86.6 (C), 75.3 (C), 73.6 (CH_2), 68.7 (CH_2), 55.2 (CH_3), 52.8 (CH_3), 46.9 (CH), 45.1 (CH_2), 30.9 (CH_2), 21.8 (CH_3); HRMS (ES) exact mass calcd for $C_{25}H_{28}NO_7$ $[M+H]^+$: 454.1860, found: 454.1858.

4.1.4. (3aR,6R,6aS)-6-Hydroxymethyl-5-(4-methoxybenzyl)-6a-methyl-2,4-dioxohexahydrofuro[2,3-c]pyrrole-6-carboxylic acid methyl ester (**17**)

A mixture of benzyl ether **15** (354 mg, 0.78 mmol) and 10% Pd/C (99 mg, 0.093 mmol) in EtOH (5 mL) at room temperature was evacuated and flushed with H_2 (three times) and then stirred vigorously under an atmosphere of H_2 (1 atm, H_2 balloon) at room temperature for 18 h. The reaction mixture was filtered through Celite and concentrated in vacuo. Purification of the residue by column chromatography (50% EtOAc/petrol) gave the *alcohol* **17** (240 mg, 84%) as a white powder. Recrystallization of **17** from CH_2Cl_2/Et_2O gave colorless blocks that were suitable for X-ray crystallography. R_f=0.52 (100% EtOAc); mp 144–146 °C; $[\alpha]_D^{25}$ −30.1 (*c* 0.95, $CHCl_3$); IR ($CHCl_3$) 3437 (OH), 2955, 2837, 2253, 1787 (C=O), 1757 (C=O), 1692 (C=O), 1613, 1513, 1247, 1035, 951, 914, 731 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 7.37 (2H, dm, *J*=8.6 Hz, Ar*H*), 6.87 (2H, dm, *J*=8.6 Hz, Ar*H*), 5.22 (1H, d, *J*=15.2 Hz, NCH_2), 4.24 (1H, d, *J*=15.2 Hz, NCH_2), 3.95 (1H, dd, *J*=13.0, 8.9 Hz, CH_2OH), 3.83 (3H, s, OCH_3), 3.80 (3H, s, OCH_3), 3.43 (1H, dd, *J*=13.0, 5.5 Hz, CH_2OH), 3.04 (1H, dd, *J*=9.1, 1.7 Hz, CH$_2$C*H*), 2.96 (1H, dd, *J*=18.1, 1.7 Hz, CH_2CH), 2.85 (1H, dd, *J*=18.1, 9.1 Hz, CH_2CH), 1.69 (3H, s, CH_3CO); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 173.7 (C), 172.7 (C), 167.1 (C), 159.5 (C), 129.6 (2×CH and C), 114.6 (2×CH), 88.3 (C), 77.3 (C), 60.9 (CH_2), 55.3 (CH_3), 52.8 (CH_3), 47.6 (CH), 44.9 (CH_2), 30.5 (CH_2), 19.8 (CH_3); HRMS (ES) exact mass calcd for $C_{18}H_{25}N_2O_7$ $[M+NH_4]^+$: 381.1656, found: 381.1660.

4.1.5. (3aR,6R,6aS)-6-Formyl-5-(4-methoxybenzyl)-6a-methyl-2,4-dioxohexahydrofuro[2,3-c]pyrrole-6-carboxylic acid methyl ester (**18**)

To a solution of the alcohol **17** (30 mg, 0.082 mmol) in CH_2Cl_2 (0.8 mL) at room temperature was added Dess–Martin periodinane

(43 mg, 0.099 mmol). The reaction mixture was stirred for 1.5 h, quenched with H_2O (5 mL) and extracted with EtOAc (3×10 mL). The combined organic layers were dried (Na_2SO_4) and concentrated in vacuo to leave the *aldehyde* **18** as a pale yellow oil. This aldehyde was not very stable and was generally used immediately in the next step without purification. On one occasion, purification of a small amount of crude product by column chromatography (50% EtOAc/petrol) was performed for characterization purposes. R_f=0.34 (100% EtOAc); IR ($CHCl_3$) 2956, 1788 (C=O), 1760 (C=O), 1728 (C=O), 1687 (C=O), 1513, 1438, 1246, 1176, 949 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 9.47 (1H, s, C*H*O), 7.05 (2H, dm, *J*=8.7 Hz, Ar*H*), 6.81 (2H, dm, *J*=8.7 Hz, Ar*H*), 4.86 (1H, d, *J*=14.4 Hz, NCH_2), 4.39 (1H, d, *J*=14.4 Hz, NCH_2), 3.90 (3H, s, OCH_3), 3.78 (3H, s, OCH_3), 3.08 (1H, dd, *J*=9.7, 1.8 Hz, CH_2C*H*), 2.99 (1H, dd, *J*=18.4, 1.8 Hz, CH_2CH), 2.85 (1H, dd, *J*=18.4, 9.7 Hz, CH_2CH), 1.52 (3H, s, CH_3CO); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 195.5 (CH), 172.7 (C), 172.0 (C), 165.7 (C), 159.6 (C), 131.1 (2×CH), 126.8 (C), 114.2 (2×CH), 87.3 (C), 79.0 (C), 55.2 (CH_3), 53.4 (CH_3), 46.8 (CH), 45.6 (CH_2), 30.7 (CH_2), 20.5 (CH_3); LRMS (ES) 384 $[M+Na]^+$.

4.1.6. (3aR,6R,6aS)-6-[(S)-{(S)-Cyclohex-2-eny}hydroxymethyl]-5-(4-methoxybenzyl)-6a-methyl-2,4-dioxohexahydrofuro [2,3-c]pyrrole-6-carboxylic acid methyl ester (**20**)

To a solution of cyclohexenyltributyltin (**19**)[20] (ca. 85% pure by ^1H NMR analysis, 90 mg, 0.21 mmol) in THF (0.6 mL) at −78 °C was added *n*-BuLi (130 μL, 1.6 M solution in hexanes, 0.21 mmol). After stirring at −78 °C for 1 h, $ZnCl_2$ (420 μL, 0.5 M solution in THF, 0.21 mmol) was added and stirring was continued at this temperature for another 1 h. A solution of the unpurified aldehyde **18** from the above experiment (theoretically 0.082 mmol) in THF (0.4 mL) was then added via cannula, and after stirring for 3 h at −78 °C, the reaction was quenched with H_2O (5 mL) and extracted with EtOAc (3×5 mL). The combined organic layers were dried ($MgSO_4$) and concentrated in vacuo, and purification of the residue by column chromatography (50% EtOAc/petrol) gave the *homoallylic alcohol* **20** (22.4 mg, 61% over two steps) as a white solid. Recrystallization from **20** from a mixture of EtOAc/hexane and acetone (a few drops) gave colorless needles that were suitable for X-ray diffraction. R_f=0.61 (100% EtOAc); mp 114–116 °C; $[\alpha]_D^{25}$ +3.0 (*c* 1.47, $CHCl_3$); IR ($CHCl_3$) 3438 (OH), 2931, 2359, 1790 (C=O), 1755 (C=O), 1687 (C=O), 1512, 1440, 1246, 1175, 807 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 7.19 (2H, dm, *J*=8.7 Hz, Ar*H*), 6.84 (2H, dm, *J*=8.7 Hz, Ar*H*), 5.92 (1H, dm, *J*=10.3 Hz, =C*H*), 5.68 (1H, dm, *J*=10.3 Hz, =C*H*), 4.80 (1H, d, *J*=14.9 Hz, NCH_2), 4.54 (1H, d, *J*=14.9 Hz, NCH_2), 4.13 (1H, t, *J*=7.1 Hz, C*H*OH), 3.78 (6H, s, 2×OCH_3), 3.13 (1H, dd, *J*=6.8, 3.3 Hz, CH_2C*H*C=O), 2.92 (1H, br s, O*H*), 2.82–2.80 (2H, m, CH_2CHC=O), 2.32 (1H, br s, C*H*CHOH), 2.02 (2H, br s, (CH_2)$_3$), 1.81 (3H, s, CH_3CO), 1.76–1.66 (2H, m, (CH_2)$_3$), 1.57–1.46 (1H, m, (CH_2)$_3$), 1.44–1.33 (1H, m, (CH_2)$_3$); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 174.8 (C), 173.0 (C), 167.8 (C), 158.3 (C), 131.8 (CH), 129.3 (C), 127.6 (2×CH), 125.2 (CH), 113.7 (2×CH), 91.1 (C), 79.0 (C), 76.9 (CH), 55.2 (CH_3), 52.4 (CH_3), 47.9 (CH_2), 47.8 (CH), 38.3 (CH), 30.9 (CH_2), 27.0 (CH_2), 24.9 (CH_2), 20.6 (CH_2), 19.6 (CH_3); HRMS (ES) exact mass calcd for $C_{24}H_{33}N_2O_7$ $[M+NH_4]^+$: 461.2282, found: 461.2283.

4.1.7. (2R,3S,4R)-2-[(S)-{(S)-Cyclohex-2-enyl}hydroxymethyl]-3-hydroxy-4-(2-hydroxyethyl)-1-(4-methoxybenzyl)-3-methyl-5-oxopyrrolidine-2-carboxylic acid methyl ester (**21**)[12a]

To a solution of the lactone **20** (19.3 mg, 0.043 mmol) in MeOH (0.6 mL) at room temperature was added $NaBH_4$ (75 mg, 2.0 mmol) portionwise over 2 min. The solution was stirred for 18 h, quenched with H_2O (4 mL) and extracted with EtOAc (3×4 mL). The combined organic layers were dried (Na_2SO_4) and concentrated in vacuo. Purification of the residue by column chromatography (70% EtOAc/petrol) gave the triol **21** (11.7 mg, 60%) as a white foam. R_f=0.12 (70% EtOAc/$CHCl_3$); mp 83–84 °C; $[\alpha]_D^{25}$ +3.5 (*c* 0.565, $CHCl_3$); IR ($CHCl_3$) 3331 (OH), 2925, 2853, 1752 (C=O), 1670 (C=O), 1512, 1441, 1245, 1175, 1034, 801 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 7.30 (2H, dm, *J*=8.8 Hz, Ar*H*), 6.85 (2H, dm, *J*=8.8 Hz, Ar*H*), 5.97–5.91 (1H, m, =C*H*), 5.65–5.60 (1H, m, =C*H*), 4.77 (1H, d, *J*=15.2 Hz, NCH_2), 4.58 (1H, d, *J*=15.2 Hz, NCH_2), 4.15 (1H, app t, *J*=6.3 Hz, C*H*OH), 3.87–3.81 (1H, m, CH_2OH), 3.80–3.75 (1H, m, CH_2OH), 3.79 (3H, s, OCH_3), 3.71 (3H, s, OCH_3), 3.02 (1H, dd, *J*=8.1, 4.8 Hz, C*H*C=O), 2.20 (1H, br s, C*H*CHOH), 2.01 (2H, br s, (CH_2)$_3$ and/or CH_2CH$_2$OH), 1.93–1.78 (2H, m, (CH_2)$_3$ and/or CH_2CH$_2$OH), 1.76–1.65 (4H, m, (CH_2)$_3$ and/or CH_2CH$_2$OH), 1.64 (3H, s, CH_3CO), 1.54–1.41 (2H, m, (CH_2)$_3$ and/or CH_2CH$_2$OH); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 178.5 (C), 169.7 (C), 158.2 (C), 132.9 (CH), 130.2 (C), 128.0 (2×CH), 124.8 (CH), 113.7 (2×CH), 81.8 (C), 80.6 (C), 77.2 (CH), 61.7 (CH_2), 55.2 (CH_3), 51.9 (CH), 51.3 (CH_3), 47.8 (CH_2), 38.6 (CH), 28.2 (CH_2), 26.8 (CH_2), 25.0 (CH_2), 21.2 (CH_3), 20.6 (CH_2); HRMS (ES) exact mass calcd for $C_{24}H_{33}NO_7Na$ $[M+Na]^+$: 470.2149, found: 470.2150.

Interestingly, the NMR data we obtained for triol **21** (recorded above) displayed subtle but appreciable differences to those reported by Corey and co-workers for the same compound,[12a] most notably in the ^{13}C NMR chemical shifts. However, we have also obtained from Pattenden and co-workers copies of the NMR spectra for the same compound that was prepared in their total synthesis of salinosporamide A,[12d] and our ^{13}C NMR data are a good match for theirs (^{13}C NMR spectrum supplied by Pattenden in Supplementary data). The most likely explanation for this observation is that the values of the ^{13}C NMR chemical shifts for triol **21** are concentration-dependent; both our and the Pattenden group's ^{13}C NMR spectra were run at relatively low concentration, whereas the Corey group's ^{13}C NMR spectrum was run at relatively high concentration. Due to limited quantities of triol **21**, we were unable to verify this hypothesis.

Acknowledgements

This work was supported by the EPSRC (GR/T07466/01) and the European Commission (Project No. MEST-CT-2005-020744). We thank Professor Gerald Pattenden at the University of Nottingham and Professor Elias J. Corey at Harvard University for helpful discussions. In addition, we thank Professor Pattenden and Dr. Leleti Rajender Reddy (Corey group) for providing copies of ^1H NMR and ^{13}C NMR spectra of triol **21**. We are grateful to Professor Simon Parsons, Dr. Anna Collins and Laura E. Budd at the School of Chemistry, University of Edinburgh for assistance with X-ray crystallography. The EPSRC National Mass Spectrometry Service Centre at the University of Wales, Swansea is thanked for providing high resolution mass spectra.

Supplementary data

Copies of ^1H and ^{13}C NMR spectra for new compounds, and ^{13}C NMR spectrum of triol **21** supplied by Pattenden and co-workers. Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2008.06.038.

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