A concise total synthesis of salinosporamide A

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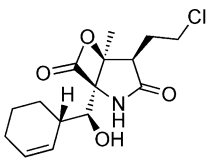
A concise and straightforward 14-step total synthesis of (±)-salinosporamide A, based on a diastereoselective acid-catalysed intramolecular cyclisation of 6 to the pyrrolidinone 7, and a regioselective reduction of the malonate derivative 8b to the aldehyde 9, is described.

Salinosporamide A (**1**) is a potent proteasome 20S inhibitor recently isolated from a marine bacterium of the new genus *Salinospora*, by Fenical *et al.*[1] The metabolite is unique, but is related to the β-lactone pyrrolidinone-based terrestrial natural product omuralide (also know as *clasto*-lactacystin β-lactone) **2**,[2] which is formed by lactonisation of the more familiar proteasome 20S inhibitor lactacystin **3**.[3] Salinosporamide A is reported to be approximately thirty five times more effective at proteosome inhibition than omuralide. The special proteasome inhibitory properties of the natural pyrrolidinones **1**, **2** and **3** have heightened interest in their potential in therapy for various types of cancer, also Alzheimer's disease, arthritis and asthma. It is not surprising therefore that these compounds have been attractive targets for total synthesis.[4]



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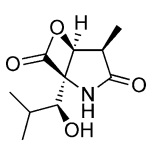

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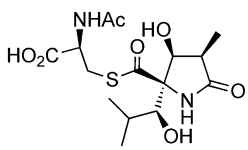

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The first total synthesis of salinosporamide A (**1**) was described by Corey *et al.*,[5] using a route starting from *S*-threonine. A year later Corey *et al.*[6] published a modified route to salinosporamide A from *S*-threonine and, simultaneously, Danishefsky *et al.*[7] presented an alternative synthesis of the natural product starting from a known chiral pool pyroglutamate derivative.[8] In earlier investigations we described a synthetic route to (+)-lactacystin **3**, which was based on a novel radical cyclisation of an α-ethynyl substituted serine as the key step.[9] We now present a concise and straightforward 14-step total synthesis of (±)-salinosporamide A, which is outlined in Scheme 1. Our synthesis of **1** hinges on: i) a stereocontrolled acid catalysed intramolecular cyclisation of the substituted amide **6** leading to the pyrrolidinone **7**, ii) a regioselective reduction of the malonate derivative **8b** producing the key aldehyde intermediate **9**, and iii) installation of the cyclohexenyl side chain, from **9**. Although no biosynthesis studies have been published, our synthetic approach has features in common with the most likely origin of the pyrrolidinone ring in salinosporamide A *in vivo*, *i.e.* an intramolecular aldolisation from a substituted β-keto amide intermediate derived from a β-keto acid and an α-amino acid.[10,11]

Thus, protection of the α-substituted β-keto ester **4**[12] as its dioxolan **5a**, followed by hydrolysis to the corresponding carboxylic acid **5b** and treatment with dimethyl 2-aminomalonate first gave the substituted amide **6**. When a solution of **6** in 4 : 1 acetic acid–water[13] was heated at 65 °C for 4 days, it underwent deprotection of the dioxolan and *in situ* intramolecular cyclisation leading to a single diastereomer of the (±)-pyrrolidinone **7**, which was obtained as colourless crystals, mp 82–83 °C. X-Ray crystallographic analysis showed that the pyrrolidinone had the expected *anti* arrangement between the C3–C4 alkyl chains shown in structure **7**.[14] Treatment of the tertiary alcohol **7** with excess TMSOTf in CH_2Cl_2 containing 2,6-lutidine at −78 °C to 0 °C, followed by 1 M HCl, gave the corresponding TMS ether **8a** in 91% yield.[15] The nitrogen centre in the pyrrolidinone **8a** was next protected as its PMB derivative **8b** which, to our satisfaction, underwent regioselective reduction using Super-hydride in CH_2Cl_2 at −78 °C producing the aldehyde **9** in 78% yield.[16]

The stage was now set to carry out the difficult operation of attaching the 2-cyclohexenyl side-chain to the aldehyde group in **9**, at the same time installing the correct stereochemistry for the newly introduced stereogenic centres. Fortunately, an elegant solution to this problem had already been worked out by Corey *et al.*,[5] and this protocol was also followed by Danishefsky *et al.*, in their synthesis of salinosporamide A. Thus, the aldehyde **9**, was treated with 2-cyclohexenylzinc bromide in THF at −78 °C, according to the protocol of Corey *et al.*, and we were delighted to find that the addition was essentially diastereoselective producing the adduct **10** in 87% yield.[17] Sequential deprotection of the TMS and benzyl ether groups in **10**, followed by the PMB group, then gave the triol ester **11**, which is the same intermediate in the synthesis of salinosporamide A presented by Corey *et al.*,[5] Hydrolysis of the methyl ester in **11**, followed by treatment of the resulting β-hydroxy acid, *in situ*, with BOP–Cl to give the corresponding β-lactone, and then chlorination with Ph_3PCl_2 finally gave (±)-salinosporamide A (**1**), as a colourless solid, mp 169–172 °C. The synthetic salinosporamide A showed ^1H and ^{13}C NMR spectroscopic data and mass spectrometric data which were identical to those presented for the natural product.

We have therefore developed a conceptually straightforward synthetic route to (±)-salinosporamide A (**1**), which uses 14 steps

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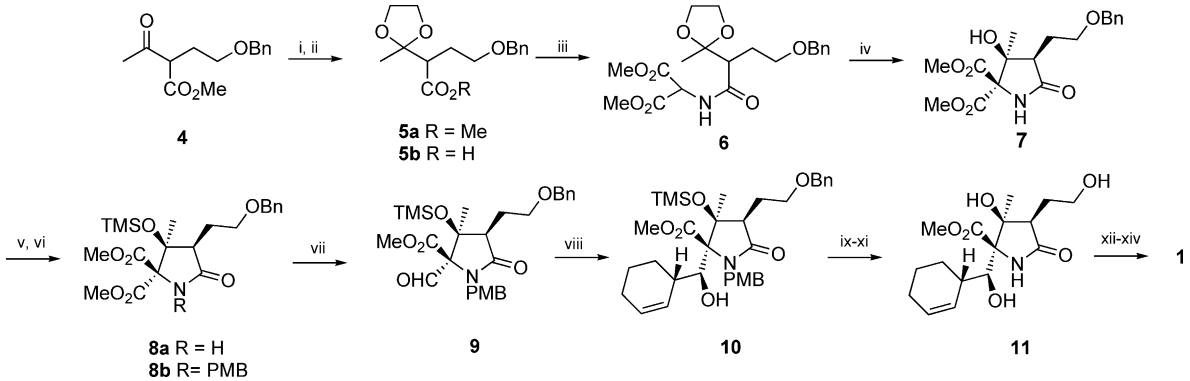

Scheme 1 *Reagents and conditions*: (i) ethylene glycol, *p*-TSA, PhH, 110 °C, 14 h; (ii) 2 M NaOH, EtOH, 70 °C, 3 h; (iii) dimethyl aminomalonate.HCl, HOBt, EDC.HCl, CH_2Cl_2, NMM, 0 °C to RT (82% over 3 steps); (iv) 4 : 1 AcOH–H_2O, 65 °C, 4 days (71%); (v) excess TMSOTf, 2,6-lutidine, CH_2Cl_2, −78 °C to 0 °C, then 1 M HCl (91%); (vi) PMB–Br, NaH, DMF, 0 °C to RT, 14 h (82%); (vii) Super-hydride (1.0 M in THF), CH_2Cl_2, −78 °C, 3 h (78%); (viii) 2-cyclohexenylzinc bromide, THF, −78 °C (87%); (ix) BCl_3.DMS, CH_2Cl_2, 24 h, 0 °C to RT; (x) 48% HF in H_2O–MeCN (1 : 9), RT, 22 h; (xi) CAN, MeCN, H_2O (3 : 1), 0 °C, 1 h (87% over 3 steps); (xii) $[MeTeAlMe_2]_2$, PhMe, RT, 24 h; (xiii) BOP–Cl, CH_2Cl_2, pyridine, RT, 3 h; (xiv) PPh_3Cl_2, MeCN, pyridine, RT, 4 h (45% over 3 steps).

from the substituted β-ketoester **4**. The key features of the synthetic route are the diastereoselective acid-catalysed cyclisation of **6** to **7**, and the facile regioselective reduction of the malonate **8b** to the aldehyde **9**, using Super-hydride at −78 °C. There are a range of options available to develop the route into an enantioselective synthesis of (+)-salinosporamide A, and some of those options are now being pursued.

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14 Crystal data for **7**: $C_{18}H_{23}NO_7$, $M = 365.37$, monoclinic, $a = 14.292(6)$, $b = 11.057(4)$, $c = 11.287(5)$ Å, $\beta = 92.090(7)°$, $U = 1782.5(13)$ Å^3, $T = 150(2)$ K, space group $P2_1/c$, $Z = 4$, μ(Mo–$K\alpha$) = 0.105 mm^{-1}, 15038 reflections measured, 4068 unique ($R_{int} = 0.124$). Final R_1 [3308 $F \geq 4\sigma(F)$] = 0.0421, wR_2 (all data) = 0.123. CCDC reference number 608046. For crystallographic data in CIF or other electronic format see DOI: 10.1039/b607109k.

15 A small amount (<10%) of the corresponding *O*-TMS epimer was produced concurrently, resulting from a retro-aldolisation process. The epimer was cleanly removed by chromatography.

16 The regioselective reduction of **8b**, leading to **9**, can be rationalised on steric grounds, with the bulky *O*-TMS group inhibiting hydride delivery to the adjacent *syn*-orientated CO_2Me group. It is also possible that the same *O*-TMS group exercises an inductive effect and activates the corresponding *anti*-orientated CO_2Me in **8b** to reduction, as a consequence of their antiplanar relationship.

17 Data for compound **10**: colourless solid, mp 157–160 °C; ν_{max} ($CHCl_3$)/cm^{-1} 3564, 2953, 1755, 1721, 1688, 1514; δ_H (360 MHz, $CDCl_3$) 7.34–7.26 (5H, m, C_6H_5), 7.23 (2H, d, *J* 8.7, Ar*H*), 6.80 (2H, d, *J* 8.7, Ar*H*), 6.05 (1H, app. d, *J* 10.2, CH_2CH=), 5.63 (1H, app. d, *J* 10.2, CH_2CH=C*H*), 4.80 (1H, d, *J* 15.3, OC*H*HPMB), 4.52 (2H, s, OCH_2Ph), 4.42 (1H, d, *J* 15.3 OCH*H*PMB), 4.20 (1H, dd, *J* 3.3, 7.9, C*H*(OH)), 3.89 − 3.80 (2H, m, CH_2OBn), 3.79 (3H, s, CO_2Me), 3.62 (3H, s, ArOMe), 3.03 (1H, dd, *J* 3.8, 9.4, C(=O)C*H*), 2.26 (1H, br s, CH_2CH=CHC*H*), 2.04 (2H, br s, CH_2), 1.91–1.89 (2H, m, CH_2), 1.76 (3H, s, CCH_3), 1.59–1.51 (2H, m, CH_2), 0.16 (9H, s, TMS); δ_C (90 MHz, $CDCl_3$) 177.7 (s), 169.5 (s), 157.8 (s), 138.7 (s), 134.7 (d), 130.6 (s), 128.2 (d), 127.7 (d), 127.3 (d), 127.1 (d), 123.8 (d), 113.2 (d), 86.2 (s), 82.4 (s), 76.8 (d), 72.9 (t), 68.8 (t), 55.2 (q), 51.7 (q), 48.3 (d), 47.7 (t), 38.2 (d), 29.4 (t), 26.1 (t), 25.0 (t), 20.8 (q), 20.5 (t), 2.7 (q); *m*/*z* (ES) Found 632.3041 (M + H$^+$, $C_{34}H_{47}NO_7SiNa$ requires 632.3014).

