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Stereoselective formal synthesis of the potent proteasome inhibitor: salinosporamide A☆

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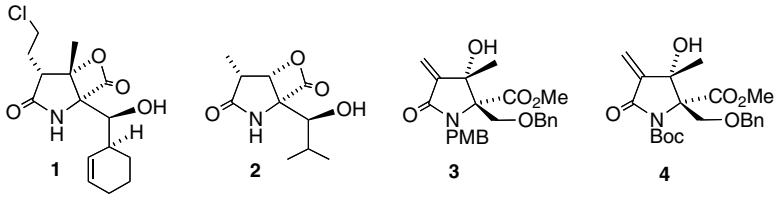
Dedicated to the memory of Guy Ourisson, deceased November 3 2006

Abstract—(2*R*,3*S*)-α-Methylenelactam **3**, the key intermediate in Corey's syntheses of salinosporamide A, has been synthesized from (*S*)-methyl 2-hydroxymethylpyroglutamate through chemoselective O-protection, regio- and stereoselective *N*-methylnitrone cycloaddition and quaternarization–elimination reactions as the main steps.

The microbial secondary metabolite salinosporamide A (**1**) was isolated in 2003 by Fenical and co-workers from *Salinispora tropica*, a unique marine microorganism belonging to the MAR 1 phylotype of these actinomycetes.[2] Produced by the CNB-392 strain, salinosporamide A is of considerable interest owing to its remarkable biological properties and potentialities. It indeed inhibits the three proteolytic sites of the proteasome 20S subunit in a particularly effective and selective way,[3] being even more potent than the structurally related β-lactone-γ-lactam omuralide (**2**) itself. Moreover, **1** was found to display high cytotoxicity towards many tumour cell lines, namely HCT-116 human colon carcinoma and thalomid- and bortezomib-resistant multiple myeloma cells,[4,5] and the molecule (as NPI-0052) is currently in clinical development for treatment of cancer.



These properties initiated several synthetic studies which, so far, led to the publication of four total syntheses by the groups of Corey, Danishefsky and Pattenden.[6–9] Both syntheses developed by Corey et al. involved the highly functionalized α-methylene-lactam **3** as a key intermediate.[6,7]

Recent efforts in our laboratory focused on the highly diastereoselective synthesis of **4**, as a closely related scaffold that contains the required functionalities and can provide access to the racemic target molecule. Our synthetic strategy relied on the practical preparation of pyrrolinone **5** as a suitable electron-deficient dipolarophile and was based on the regio- and stereo-selective 1,3-dipolar cycloaddition of *N*-methylnitrone leading to **6** (Scheme 1). Thus, **4** was obtained in two steps from the cycloadduct **6**, through hydrogenolysis with Pearlman's catalyst and subsequent quaternarization–elimination step.[10,11]

As an extension of this work, we next turned our attention towards an asymmetric route to **4** and to Corey's key intermediate **3** itself, and we report here our results in both directions.[1] To obtain the corresponding

Keywords: Proteasome inhibitor; Salinosporamide A; Pyroglutamate; 1,3-Dipolar cycloadditions; *N*-Methylnitrone; Selective O-benzylation.
☆ See Ref. 1.
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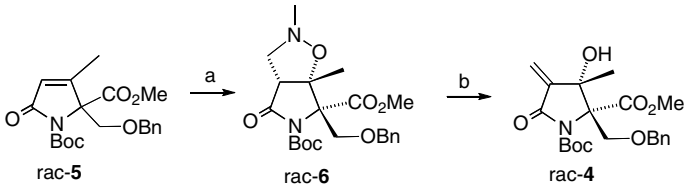


Scheme 1. Reagents and conditions: (a) *N*-methylnitrone, toluene, Δ, 57% and (b) (i) H_2, $Pd(OH)_2$, EtOAc–MeOH, 72%; (ii) MeI, THF, Et_3N, 65%.

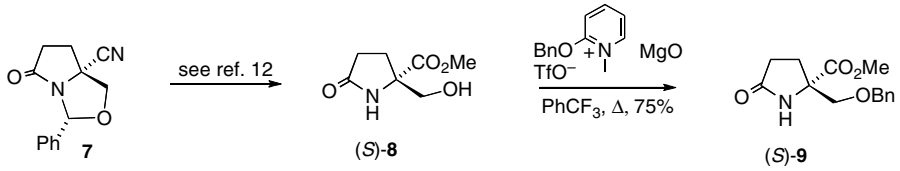
enantiopure **3** and **4** with 'natural' 2*R*,3*S* configurations, it was assumed that (*S*)-methyl 2-hydroxymethylpyroglutamate **8** could be the precursor of choice. This compound has been prepared for the first time from bicyclic nitrile **7** as an intermediate in the synthesis of deoxydysibetaine.[12]

Therefore, selective O-benzylation of (*S*)-**8** into (*S*)-**9** was investigated under varied conditions and shown to be rather difficult, due to the sensitivity of the methoxycarbonyl group towards hydrolysis or transesterification, giving rise to the corresponding carboxylic acid and benzyl ester.[13] N,O-Dibenzylation could not be avoided with benzylbromide and Cs_2CO_3 as the base, and experiments using benzyl 2,2,2-trichloroimidate failed.[14] The best results were reached with 2-benzyloxy-1-methylpyridinium triflate as a selective, mild and nearly neutral benzylating agent in the presence of MgO,[15] leading to (*S*)-**9** in 75% yield (Scheme 2).[16]

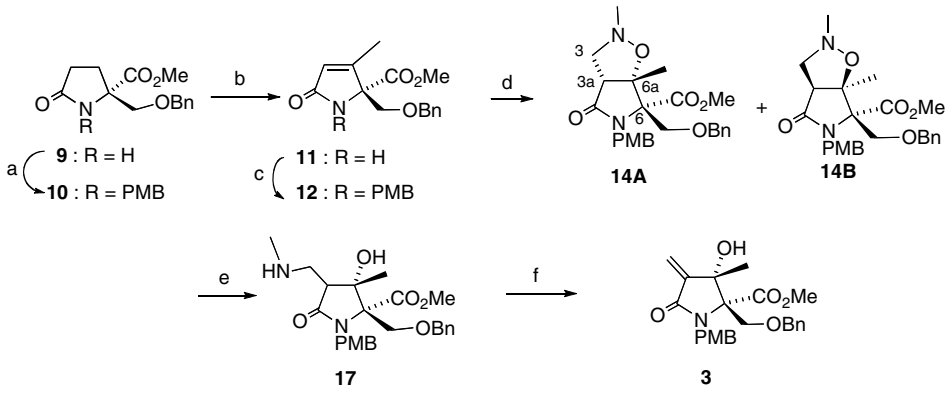
This result constitutes an access to enantiopure (2*R*,3*S*)-**4**, since the later steps to **4**, according to Scheme 1,[10] cannot lead to racemization. (*S*)-Methyl 2-benzyloxymethylpyroglutamate (*S*)-**9** could also lead to (2*R*,3*S*)-**3** following the route depicted below, and the validity of this pathway was demonstrated from racemic **9** (Scheme 3, relative configurations shown).

Accordingly, 2-benzyloxymethylpyroglutamate **9** was treated with KHMDS and 4-methoxybenzylbromide to give the *N*-PMB derivative **10** in high yield (93%). However, starting from **10**, the conjugate double bond could only be introduced in poor yield (17%) under classical conditions of phenylselenylation, using LDA as the base, followed by selenoxide elimination. This could be explained, in part, by lower reactivity of **10** compared to its *N*-Boc analogue, due to electronic factors. Consequently, the PMB group was introduced at a later stage of the synthesis. Pyrrolinone **11** was quantitatively obtained from **5** by removal of the *N*-Boc group and subsequent *N*-4-methoxybenzylation furnished the protected derivative **12** (57%).

N-Methylnitrone cycloaddition to pyrrolinone **12** was performed by heating in toluene and gave essentially a major product **14A** (54%; 79% based on recovered starting material) and small amounts of another cycloadduct **14B** (14%). The structures of these adducts were deduced from spectroscopic and particularly NMR data and comparison with related cycloadducts such as **6**,

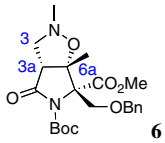
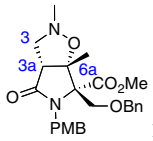
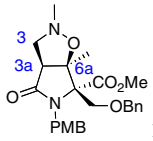
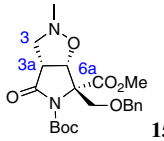
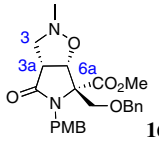


Scheme 2.



Scheme 3. Reagents and conditions: (a) KHMDS, PMBBr, THF, 93%; (b) (i) to **5**, see Ref.10; (ii) CF_3CO_2H, CH_2Cl_2, 100%; (c) Cs_2CO_3, PMBBr, DMF, 57%; (d) *N*-methylnitrone, toluene, Δ, 68%; (e) H_2, $Pd(OH)_2$, EtOAc–MeOH, 64% and (f) (i) MeI, MeOH; (ii) Na_2CO_3, CH_2Cl_2, 90%.

Table 1. Chemical shifts for characteristic protons and carbons of cycloadducts **6**, **14**–**16** (300 MHz, $CDCl_3$)

	H-6a	H-3	H-3a	C-6a	C-3	C-3a
 **6**	—	3.64 2.60	3.14	83.60	60.67	58.01
 **14A**	—	3.71 2.59	3.07	84.61	59.94	56.80
 **14B**	—	3.69 2.64	3.04	83.58	61.03	56.71
 **15**	4.66	3.64 2.62	3.59	78.66	60.63	53.20
 **16**	4.65	3.64 2.57	3.55	77.34	60.11	51.82

15 and **16**, previously prepared in our group. The informative chemical shifts of isoxazolidine protons and carbons are collected in Table 1. Similar values were observed for **14A** and **14B**, indicating that these two compounds result from the same regioselectivity in the 1,3-dipolar cycloaddition. Indeed, the protons at the ring junction (H-3a) give rise to signals at 3.07 and 3.04 ppm, whereas the corresponding methine carbons generate signals at 56.80 and 56.71 ppm, respectively. These chemical shifts are close to those of structural analogue **6**, in agreement with a position α to the *N*-methylene. A NOESY experiment performed on **14A** showed a correlation between 6a-CH_3 and one of the 6-CH_2 protons, consistent with these two groups being on the same side of the pyrrolidinone ring. This, consequently, allowed the assignment of the relative configurations of the stereoisomer **14B**. A X-ray analysis carried on **14B** confirmed these conclusions (Fig. 1).[17]

Therefore, the *N*-methylnitrone cycloaddition to **12** occurred with expected regioselectivity. As generally agreed, 1,3-dipolar cycloadditions are concerted and the regiochemistry appears to be controlled by frontier orbital interactions. The stereoselectivity (ratio 4:1) however was somewhat lower than those observed in the case of **5** when only one diastereoisomer was detected. This selectivity depends on a subtle interplay of several steric and electronic factors, and the nature of the protecting group at the lactam nitrogen seemed, indeed, to have a sensitive impact on the transition state, and therefore on the outcome of the reaction.[18–20]

With compound **14A** in hand, the synthesis was pursued towards intermediate **3**. The isoxazolidine ring was hydrogenolyzed in the presence of $Pd(OH)_2$ (Scheme 3). Fortunately, these conditions did not affect the *O*-benzyl protecting group and compound **17** was obtained in 64% yield. N-Methylation with iodomethane in methanol led to the corresponding trimethyl ammonium salt, which was treated straight away by a biphasic mixture of aqueous sodium carbonate and dichloromethane. This elimination step required a long reaction time to afford, after stirring for 4 days at room temperature, the target α-methylenelactam **3** in high yield

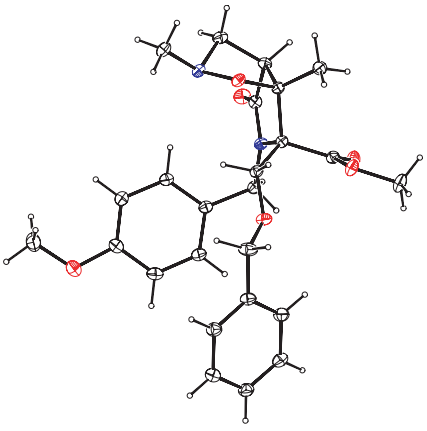


Figure 1. ORTEP diagram from the X-ray crystallographic analysis of cycloadduct **14B**.

(90%).[10,11] The whole analytical data of **3** are in full agreement with those described,[6,7] and these results complete the formal synthesis of salinosporamide A.

In conclusion, *N*-methylnitrone cycloaddition to a conveniently polysubstituted pyrrolinone derived from (*S*)-pyroglutaminol provides a valuable pathway to the key intermediate **3**, which has been converted to salinosporamide A by Corey and co-workers. The cycloaddition reaction occurred with good regio- and stereoselectivities. Extension of this methodology to the synthesis of various analogues, which could be designed by the binding mode of salinosporamide A,[21] is currently under investigation.

Acknowledgement

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16. Spectral data of (*S*)-**9**: Mp = 79–80 °C. $[\alpha]_D^{25}$ +25.7 (*c* 1.72, $CHCl_3$). IR: 3194, 3079, 2956, 1731, 1692, 1432, 1351. MS (ESI, MeOH) *m*/*z*: 287, 286 [$(MNa)^+$ 100%], 264. ^1H (300 MHz, $CDCl_3$): 7.36–7.26 (m, 5H, Ph), 6.18 (br s, 1H, NH), 4.53 (apparent s, 2H, OCH_2Ph), 3.83 (d, 1H, $J = 9.0$ Hz) and 3.45 (d, 1H, $J = 9.0$ Hz): OCH_2-2; 3.77 (s, 3H, OCH_3), 2.40–2.35 (m, 2H), 2.31 (m, 1H), 2.05 (m, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): 176.6, 172.9 (2CO), 137.2 (qC, Ph), 128.4, 127.8, 127.6 (CH, Ph), 74.9 (OCH_2-2), 73.4 (OCH_2Ph), 65.7 (C-2), 52.7 (OCH_3), 29.1, 27.7 (C-3, C-4).
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