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Studies toward the synthesis of salinosporamide A, a potent proteasome inhibitor

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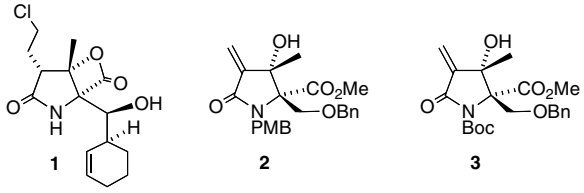
Dedicated to the memory of Pierre Potier, a friend, deceased February 3 2006

Abstract—An α-methylenepyrrolidinone bearing all the functionalities and relative configurations of an advanced intermediate in the synthesis of salinosporamide A and analogues has been synthesized from methyl pyroglutamate through regio- and stereoselective *N*-methylnitrone cycloaddition.

The examination of numerous *Salinispora* strains from a marine actinomycete *Salinispora tropica* showed that most of these organisms produce culture extracts displaying potent biological activity, and, particularly, growth inhibition of tumor cells such as human colon carcinoma HCT-116. *S. tropica* strain CNB-392 culture broth produces salinosporamide A (NPI 0052) **1**, which is structurally related to omuralide, a β-lactone derived from lactacystin.[1,2] Omuralide is known to specifically inhibit the proteolytic activity of the proteasome 20S subunit without affecting other proteasome activities.[3] Salinosporamide A (**1**) is a more effective proteasome inhibitor than omuralide, and exhibits cytotoxicity against many tumor cell lines,[4] and particularly, against Velcade® resistant multiple myeloma cells.[2,5] Two of the synthetic routes to salinosporamide A developed so far[4,6,7] involve the multifunctionalized α-methylene-lactam **2** as a key intermediate. This intermediate **2** was synthesized by Corey et al., through a cyclization step performed under Baylis–Hillman conditions,[4] or better, by treatment with Kulinkovich reagent,[6] and structural analogues have also been prepared in a similar way.[8,9]



1 **2** **3**

We describe here a novel diastereoselective route to a closely related α-methylene-lactam **3**, which possesses all the required functionalities, starting from inexpensive methyl pyroglutamate **4**. This diastereocontrolled synthesis, as outlined in Scheme 1, was based on a selective 1,3-dipolar cycloaddition of *N*-methylnitrone to introduce, in one step, the C-3 hydroxyl group and the precursor of C-4 exo-methylene group.

Our initial efforts were devoted to the preparation of an unsaturated 3-methylated intermediate **8**. The benzyloxymethyl group was directly introduced at C-2 of methyl pyroglutamate **4**. Regioselective deprotonation of **4** with LiHMDS (2.2 equiv),[10] and α-alkylation with chloromethylbenzylether gave rise to **5** (53%). Then, N-protection as *tert*-butyl carbamate **6** (100%), improving the reactivity of lactam carbonyl, allowed efficient classical introduction of the Δ^3 double bond to give **7** (89%, Scheme 1).

At this stage, two ways were investigated to convert pyrrolidinone **7** into its 3-methylated counterpart **8** (Scheme 2). The first one involved a 1,3-dipolar diazomethane cycloaddition followed by thermolysis. Literature surveys indicated that thermolysis of the adducts between diazomethane and α,β-unsaturated lactam derivatives received little attention for the preparation

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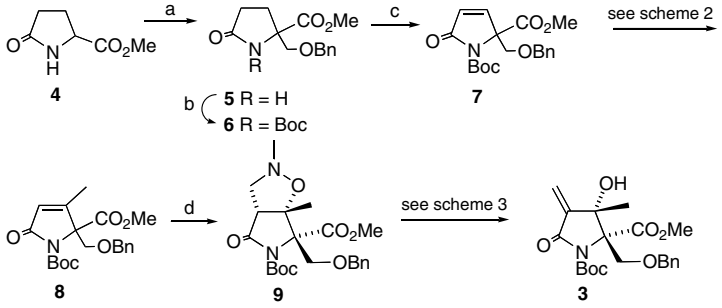
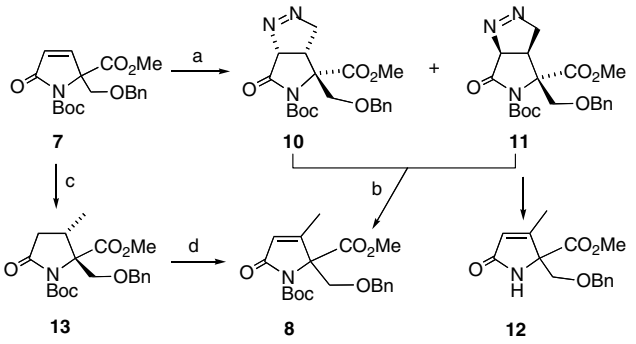


Scheme 1. Reagents: (a) LiHMDS, THF, $BnOCH_2Cl$ (53%); (b) $(Boc)_2O$, DMAP, CH_3CN (100%); (c) (i) LiHMDS, THF, PhSeCl; (ii) H_2O_2, CH_2Cl_2, py (89%); (d) *N*-methylnitrone, tol, Δ (57%).



Scheme 2. Reagents: (a) CH_2N_2, Et_2O (**11** + **12**: 50%); (b) toluene, Δ (70%); (c) Me_2CuLi, THF, TMSCl (83%); (d) (i) LiHMDS, THF, PhSeCl; (ii) H_2O_2, CH_2Cl_2, py (75%).

of methylated derivatives. The few examples using these dipolarophiles occurred however with high regioselectivity,[11–13] and we recently applied this methodology to a very short synthesis of pulchellalactam.[14] In order to prepare **8**, compound **7** was treated with an excess of diazomethane in Et_2O at rt to give pyrazolines **10** and **11**, isolated together in 50% yield (76% based on recovered **7**) and separated in a ratio of ca 3:1. The structures of these adducts, principally based on the chemical shifts in ^1H and ^{13}C NMR, indicated the formation of the expected regioisomers and the relative configurations were deduced from steric factors and NOESY (Scheme 2).

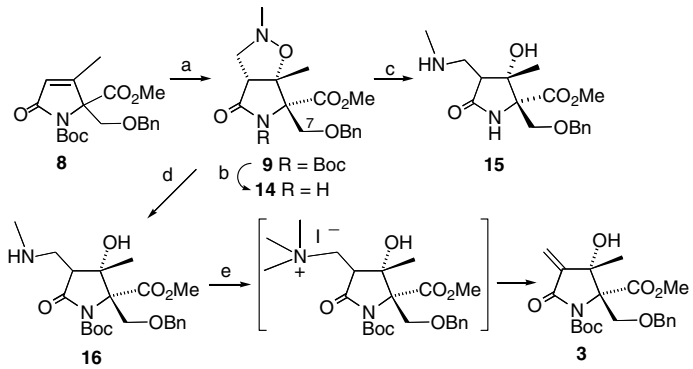
The thermolysis of Δ^1-pyrazolines **10** and **11** led to the same expected β-methyl unsaturated lactam **8** as the major product. However, under the same conditions (toluene, reflux), the results obtained from **10** and **11** were rather different: whereas **10** cleanly led to **8** (>85% determined by ^1H NMR), the rearrangement of **11** proceeded more slowly and also gave rise to the loss of *N*-*tert*-butoxycarbonyl protecting group with the formation of **12** (25%), as already observed in the thermolysis of *N*-Boc indoles, pyrroles, and pyrrolidinones.[15] It is also interesting to note the absence of cyclopropane formation during these thermolyses. Using a mixture of **10** and **11**, the β-methyl unsaturated lactam **8** was obtained in 70% yield.

According to the second, more classical route investigated to prepare **8**, the methylcuprate stereoselective addition to the unsaturated pyrrolidinone **7** gave rise to **13** in high yield (83%) as a sole detected diastereomer, the relative configuration of which was deduced from steric factors only. The introduction of Δ^3 double bond, as described for **7**, afforded **8** in 75% yield (Scheme 2). These nucleophilic and electrophilic additions of methyl and phenylselenyl groups, respectively, could be realized in one step, but the yield of **8** was dramatically lowered by the use of this procedure. Nevertheless, the comparison of the results in terms of efficiency is in favor of this second route (overall yield from **7**: 63% vs 35%).

With compound **8** in hand, we next investigated the 1,3-dipolar cycloaddition of *N*-methylnitrone to its trisubstituted double bond. We have shown that *N*-methylnitrone cycloadditions to more simple *N*-alkoxycarbonyl pyrrolinones proceed with good regio- and stereoselectivities.[16] Still higher selectivities were observed with **8**, although this compound is less reactive. It gave rise to **9** in 57% yield (96% based on recovered **8**) after being heated for 19 h at 110 °C. The structure of **9** was attributed by NMR spectral analysis, a NOESY experiment indicating a weak correlation between the *C*-methyl group and one of the two protons H-7. These attributions were confirmed by X-ray analysis of its hydrochloride, crystallized in a mixture of MeOH–Et_2O–pentane.[17]

To cleanly cleave isoxazoline N–O bonds, samarium diiodide is known to be efficient at rt,[18] and we used this reagent to keep intact the benzyloxymethyl group. However, the N-protecting group of **9** was first removed under these conditions. This result could be explained by chelation between samarium and the two carbonyl oxygens of lactam and carbamate functions, as observed with magnesium salts such as magnesium dichloride.[16a,19] Starting with previously N-deprotected compound **14** (100%), treatment with SmI_2 led to the 3-hydroxy-4-*N*-methylaminomethyl derivative **15** in 45% not optimized yield. Fortunately, the cleavage of **9** by hydrogenolysis under H_2 using Pearlman's catalyst proceeded chemoselectively, and did not affect the *O*-benzyl group, affording **16** in 72% yield. Methylation of **16** with excess iodomethane, followed by treatment with triethylamine, provided the target molecule **3** (65%, Scheme 3).[20]

In conclusion, pyrrolidinone **3** bearing all the functionalities and relative configurations of an advanced intermediate in the synthesis of salinosporamide A and



Scheme 3. Reagents: (a) *N*-methylnitrone, tol, Δ (57%); (b) CF_3CO_2H, CH_2Cl_2 (100%); (c) SmI_2, THF (45%); (d) H_2, $Pd(OH)_2$, EtOAc–MeOH, (72%); (e) MeI, THF, Et_3N (65%).

analogues has been elaborated from methyl pyroglutamate through regio- and stereoselective *N*-methylnitrone cycloaddition to a suitable substituted α,β-unsaturated lactam. An asymmetric version of this route is currently under investigation.

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20. Spectral data of **3**: IR: 3448, 2929, 1777, 1726, 1454, 1368, 1299, 1253 cm^{-1}. MS (ESI, MeOH) *m*/*z*: 428 $(MNa)^+$, 328 $[(MNa-Boc)^+$, 100%]. ^1H NMR (500 MHz, $CDCl_3$: 7.27 ppm): 7.29, 7.18 (5H, H–Ar), 6.27 and 5.68 (2s, 2H, $H_2C{=}C$), 4.45 (apparent s, 2H, CH_2Ph), 4.15 (d, 1H, $J = 10.4$ Hz, Ha-7), 4.03 (d, 1H, $J = 10.4$ Hz, Hb-7), 3.77 (s, 3H, OCH_3), 1.59 (s, 3H, CH_3-3), 1.49 (s, 9H, *t*-Bu). ^{13}C (125 MHz, $CDCl_3$: 77.14 ppm): 168.30 (CO, ester), 165.20 (NCO), 150.41 (NCO_2), 145.61 (qC, C-4), 137.52 (qC, Ar), 128.60, 127.96, 127.66 (CH, Ar), 120.38 ($CH_2{=}$), 84.07 (qC, *t*-Bu), 74.51, 74.04 (C-2, C-3), 73.62 (OCH_2Ph), 67.87 (C-7), 52.68 (OCH_3), 28.11 (CH_3, *t*-Bu), 21.06 (CH_3-3). HRMS: calcd for $C_{21}H_{27}NO_7Na$: 428.1685, found: 428.1682.