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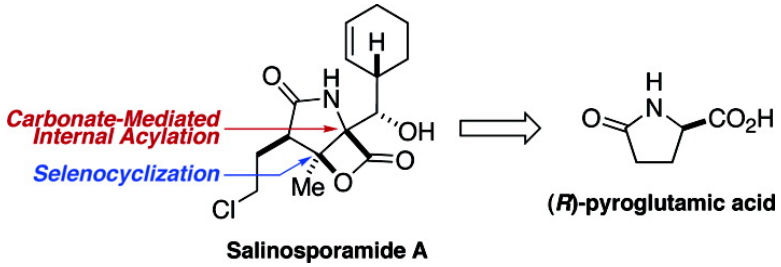

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Total Synthesis of Salinosporamide A

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Recently, Fenical and associates at the Scripps Institute of Oceanography reported on the cultivation and phylogenetic characterization of a new group of actinomycete bacteria, widely distributed in oceanic sediments.[1] The term *Salinospora* was advanced to correlate the strains. Following preliminary screening, a highly active metabolite, termed salinosporamide A (**1**, Figure 1), was identified and isolated from these sediments. Salinosporamide A displays remarkable in vitro cytotoxicity (IC_{50} of approximately 10 nM), and its activity appears to be directed to the inhibition of the 20S proteasome. Thus, salinosporamide A is approximately 35 times more potent than is omuralide (**2**), which is directed to the same molecular target. Our fascination with this target was first provoked by still another natural product, TMC-95A, which we synthesized in a manner that allowed us to conduct some telling SAR experiments.[2] Thus, when salinosporamide A came along, it seemed to us an appropriate target to broaden the involvement of our laboratory in the exciting field of naturally occurring 20S proteasome inhibitors.

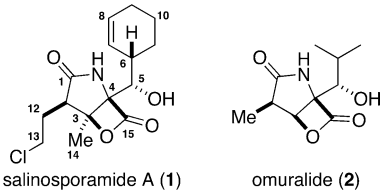


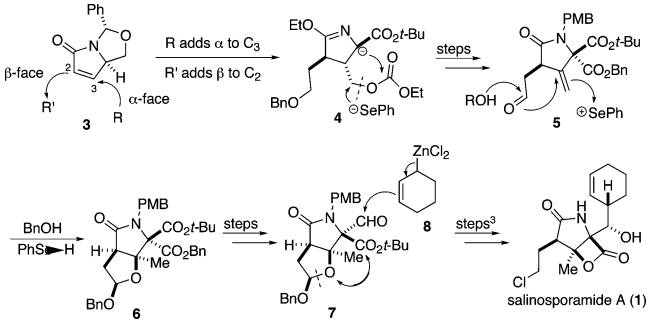
Figure 1. Structures of Salinosporamide A (**1**) and Omuralide (**2**).

At this writing, there is a single reported total synthesis of salinosporamide A (i.e., that of E. J. Corey and associates).[3] A remarkably enabling feature of that synthesis was the solution it offered to what might otherwise have been a most difficult problem, that is, that of providing stereochemical control at carbons 6 and 5. The coordinated Corey solution to both of these stereogenic centers involves the action of a cyclohexenyl zinc agent with an appropriately presented aldehyde function corresponding to C_5 of salinosporamide.

Indeed, the route described herein exploits use of the cyclohexenyl zinc methodology to solve the stereochemical issues at both C_5 and C_6. However, we first focused on solving the internal stereochemical issues associated with the building of the cis-fused pyrrolidone-β-lactone ensemble.

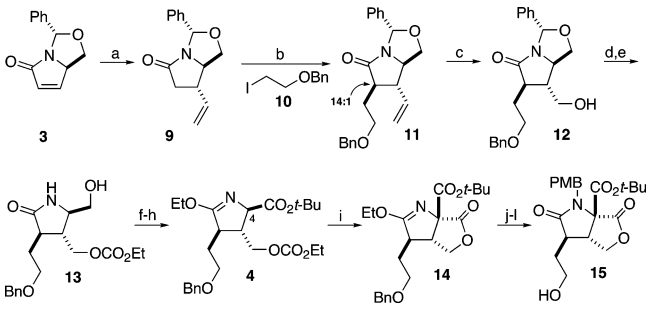
In Scheme 1, the overall stereochemical gestalt of our program is described. The strong facial bias of the pyroglutamate derivative, **3**, served to direct attack at C_3 (originally conducted by 1,4-addition of a vinyl cuprate nucleophile) from its α-face. Correspondingly, alkylation at C_2 proceeds with high selectivity from its β-face. The α-substituent, introduced at C_3, in time is presented as a carbonate ester. To enable the strategic C-acylation, a novel imidate ensemble (see formal structure **4**) was devised to direct lithiation to C_4. Following intramolecular acylation by the carbonate ester, as practiced in our recent synthesis of jiadifenin,[4] a structurally differentiated malonate moiety is created with complete stereochemical definition. In time, the substituent at C_3 is presented as an *exo*-methylene group (cf. **4** → **5**). An acetaldehyde residue, derivable at C_2, is used to differentiate the faces of this *exo*-methylene group (cf. **5** → **6**), thereby ensuring the properly configured β-lactone moiety. Adaptation of the Corey concept in the context of addition of the allylic zinc reagent **8**[3] to constrained aldehyde **7** provides remarkable stereoselection at both C_6 and C_5.

Scheme 1. Global Strategy toward Salinosporamide A



We now describe the orchestration of these general concepts en route to salinosporamide A. The bicyclic enamide **3**[5] was treated with divinyl cuprate under mediation by TMSCl,[6] affording **9** as a single product (Scheme 2). In a subsequent step, alkylation of **9**, as shown, furnished the lactam **11** in 77% yield as a 14:1 mixture of diastereomers.[7] We next turned to the conversion of the vinyl group to a carbonate ester acylating agent. Ozonolysis followed by reductive treatment with sodium borohydride afforded **12**. The derived ethyl carbonate was subjected to cleavage of the *N*,*O*-acetal

Scheme 2. Synthesis of Intermediate **15**[a]



[a] Key: (a) vinylmagnesium bromide, TMSCl, CuI, THF, −78 °C (75%); (b) **10**,[10] LDA, THF, room temperature (rt) (77%, *dr* = 14:1); (c) O_3, CH_2Cl_2−MeOH (3:1), −78 °C then $NaBH_4$, 0 °C (86%); (d) $ClCO_2Et$, pyridine, rt (96%); (e) TfOH, THF−H_2O (9:1), rt (quant); (f) Jones reagent, acetone, rt; (g) $Me_2NCH(Ot\text{-}Bu)_2$, toluene, reflux (72% in two steps); (h) Et_3OBF_4, K_2CO_3, CH_2Cl_2, rt (88%); (i) LHMDS, THF, −20 °C (82%); (j) 1 M HCl aq, THF, 0 °C (90%); (k) PMBCl, NaH, DMF, rt (61%); (l) $Pd(OH)_2$−C, H_2, EtOH, rt (quant).

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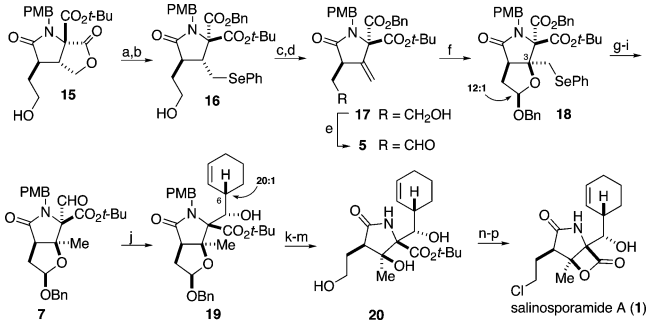
protecting arrangement to afford **13**. The hydroxymethyl lactam was converted to the imidate ester **4** as shown by a sequence consisting of Jones' oxidation, esterification, and treatment with Meerwein reagent (Et_3OBF_4). With the lactam functionality thus masked, treatment of **4** with LHMDS led to exclusive anion formation at C_4. Internal acylation with the pendant ethyl carbonate proceeded smoothly to afford lactone **14**.[4] Acidic treatment of **14** led to the restoration of the lactam moiety, which was subsequently protected with PMBCl. Removal of the benzyl protecting group afforded **15**.

The lactone of **15** was subjected to nucleophilic ring opening with phenylselenium anion,[8] and the resultant carboxylic acid was benzylated to afford the differentially esterified **16** (Scheme 3).

Scheme 3. Synthesis of Salinosporamide A[a]



[a] Key: (a) PhSeSePh, $NaBH_4$, EtOH, 60 °C; (b) BnBr, K_2CO_3, DMF, rt (65% in 2 steps); (c) 30% H_2O_2 aq, THF, rt; (d) toluene, 100 °C (94% in two steps, 72% **17** + 22% **5**); (e) Dess−Martin periodinane, CH_2Cl_2, rt (92%, 89% in three steps from **16**); (f) PhSeBr, $AgBF_4$, BnOH, CH_2Cl_2, −20 to 0 °C (74% as an anomeric mixture, 12:1); (g) AIBN, *n*-Bu_3SnH, toluene, 100 °C (98%); (h) $NaBH_4$, THF−EtOH (3:1), rt (85%); (i) Dess−Martin periodinane, CH_2Cl_2, rt (95%); (j) **8**, THF, −78 °C (88% for **19**, *dr* = 20:1); (k) ceric ammonium nitrate (CAN), CH_3CN-H_2O, 0 °C (90%); (l) Na, liq NH_3, −78 °C; (m) $NaBH_4$, THF−H_2O (2:1), rt (97% in two steps); (n) BCl_3, CH_2Cl_2, 0 °C; (o) BOPCl, TEA, CH_2Cl_2, rt; (p) Ph_3PCl_2, pyridine, CH_3CN, rt (51% in three steps).

Surprisingly, the subsequent selenide oxidation elimination sequence gave rise to a mixture of the expected alcohol **17** (72%), along with aldehyde **5** (22%), which was in fact a one-step advancement in our planned synthetic route. Upon purification, we converted the bulk unoxidized material, **17**, to aldehyde **5** through exposure to Dess−Martin periodinane.[9]

With intermediate **5** in hand, the stage was now set for a key acetal-mediated cationic cyclization.[11] We note that electrophilically induced cyclization at the aldehyde (or hemiacetal) oxidation level was central to the success of the project. Presumably, a tetrahydrofuran derived from haloetherification could not have been readily opened to expose the required functionalities at C_2 and C_3. Conversely, selenolactonization using an acetic acid residue at C_2 would have produced a lactone that would not be readily differentiable from the bis-acyl functionality already present at C_4. Thus, recourse to the benzyl glycoside modality for storing and unveiling the C_2-C_3 functionality was a unique solution to a difficult problem. Upon treatment with phenylselenenyl bromide and $AgBF_4$ in the presence of benzyl alcohol, an intermediate hemiacetal was generated, which presumably assisted in the phenylselenenylation of the exocyclic methylene to afford **18**. *Importantly, this reaction allowed for the introduction of the quaternary center at C_3 with complete stereoselectivity.* Radical deselenenylation provided the desired methyl functionality at C_3. Upon conversion of the benzyl ester to an aldehyde, intermediate **7** was in hand.

Treatment of **7** with the cyclohexenyl zinc reagent, **8**, under the Corey protocol[3] proceeded with excellent diastereocontrol to afford **19** in 88% yield (*dr* = 20:1 at C_6). By sharp contrast, the use of the corresponding imidate aldehyde derived from **14**[12] instead of **7** resulted in poor diastereoselectivity (78% yield, 4:3, configuration not determined). Obviously, the PMB group plays a critical role in diastereoselection in the novel Corey reaction.[3]

Removal of the PMB group from **19**, followed by reductive opening of the benzyl glycoside, gave rise to triol **20**. Acidic cleavage of the *tert*-butyl ester was effected through treatment with BCl_3, and the crude trihydroxy acid was then subjected to lactonization−chlorination[3] to provide **1**, whose spectroscopic properties were in complete accord with the natural material.[1] In addition, the structure of fully synthetic **1** was corroborated crystallographically.

In summary, an efficient and highly stereocontrolled enantioselective synthesis of salinosporamide A has been achieved. Several key features of our synthesis include the temporary masking of a lactam functionality to accomplish selective anion formation at C_4 (see **4**), the use of a nucleophilic selenium species to open a lactone in a regiocontrolled fashion (see **15**), and the use of an unusual cationic hemiacetal selenocyclization to install the quaternary center at C_3 in manageable form with complete stereocontrol.

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Supporting Information Available: Experimental procedures and characterization, including polarimetric data, for new compounds. In addition, confirmatory crystallographic data for **1** and **19** are included. This material is available free of charge via the Internet at http://pubs.acs.org.

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