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Total Synthesis of Salinosporamide A

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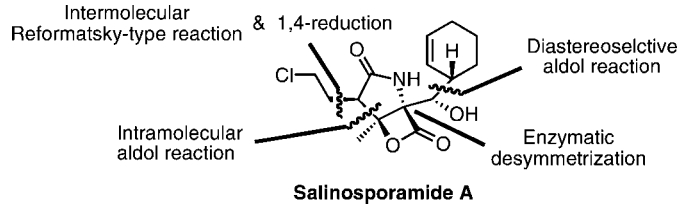
ABSTRACT



The total synthesis of salinosporamide A has been achieved through enzymatic desymmetrization, diastereoselective aldol reaction, intramolecular aldol reaction, and intermolecular Reformatsky-type reaction followed by 1,4-reduction as key reactions.

Salinosporamide A (**1**),[1] a potent 20S proteasome inhibitor, was discovered from marine actinomycete *Salinospora tropicana* by Fenical and co-workers in 2003 (Figure 1). The

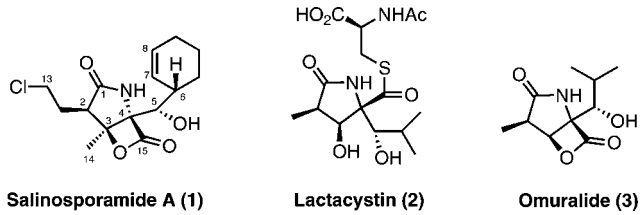


Figure 1. Structures of salinosporamide A (**1**), lactacystin (**2**), and omuralide (**3**).

β-lactone-γ-lactam bicycle structure is very similar to omuralide (**2**),[2] which is a well-known potent 20S proteasome inhibitor derived from lactacystin (**3**) first discovered by us in 1991 as a result of microbial screening for nerve growth factor-like activity.[3] The proteasome inhibitory activity of **1** is approximately 35 times greater than **2**, thus suggesting it as a strong candidate for development of new anticancer drugs, and related compounds are currently under investigation in clinical trials for the treatment of cancer.[1,4] The unique biological profile of salinosporamide A (**1**) in combination with its structural complexity has led to intensive research efforts by synthetic chemists. To date, several total syntheses of **1** have been reported,[5] most of which employ Corey's approach[5a] in the later stage of the total synthesis where there is stereoselective installation of the cyclohexene ring of **1**. We report herein the total synthesis of salinosporamide A (**1**) via the stereoselective construction of a cyclohexene ring by a new approach as a key reaction in an early stage of the total synthesis.

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(1) Feling, R. H.; Buchanan, G. O.; Mincer, T. J.; Kauffman, C. A.; Jensen, P. R.; Fenical, W. *Angew. Chem., Int. Ed.* **2003**, *42*, 355–357.
(2) Corey, E. J.; Li, W.-D. Z. *Chem. Pharm. Bull.* **1999**, *47*, 1–10.
(3) (a) Ômura, S.; Fujimoto, T.; Otoguro, K.; Matsuzaki, K.; Moriguchi, R.; Tanaka, H.; Sasaki, Y. *J. Antibiot.* **1991**, *44*, 113–116. (b) Ômura, S.; Matsuzaki, K.; Fujimoto, T.; Kosuge, K.; Furuya, T.; Fujita, S.; Nakagawa, A. *J. Antibiot.* **1991**, *44*, 117–118.
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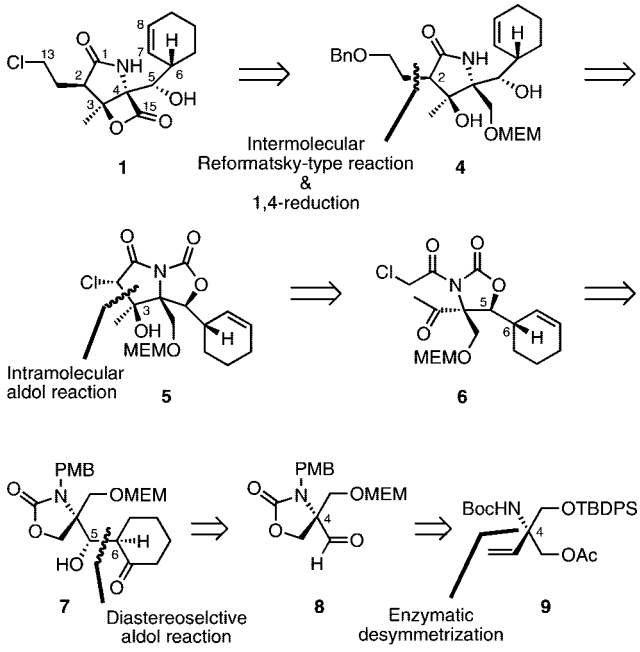
The retrosynthetic analysis of **1** is shown in Scheme 1. Stereoselective construction of the C2-side chain would be achieved by intermolecular Reformatsky-type reaction of

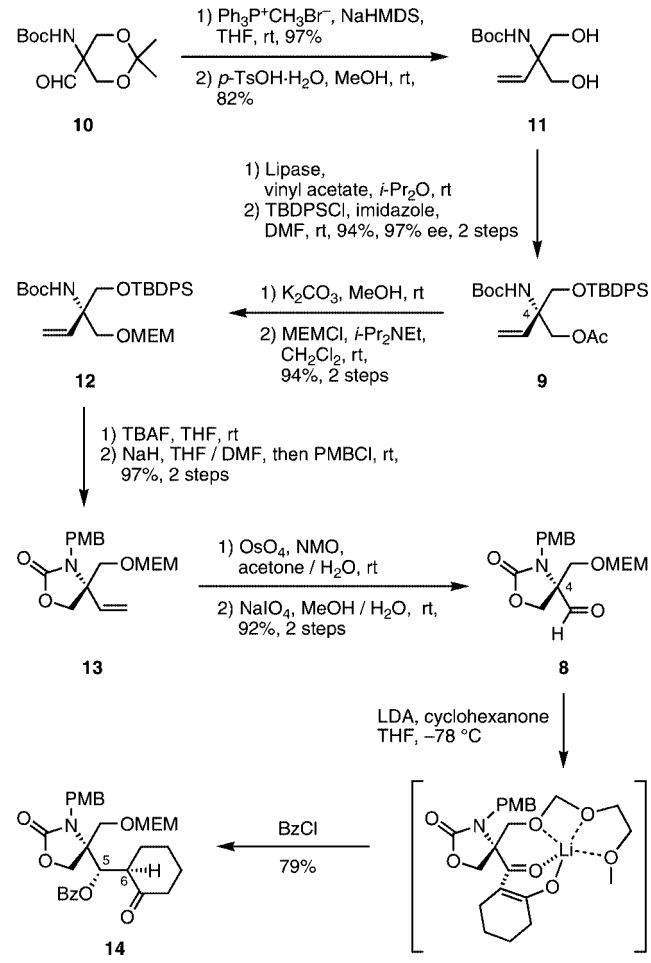
Scheme 1



α-chloro-γ-lactam **5** with benzyloxyacetaldehyde followed by dehydration and 1,4-reduction. Synthesis of the γ-lactam **5**, which exhibits C3-stereochemistry, could be accomplished by intramolecular chelation-controlled aldol reaction of *N*-acyloxazolidinone **6**, which itself would be delivered from ketone **7** via conversion of cyclohexanone into cyclohexene and subsequent transcarbamation. Diastereoselective aldol reaction of **8** with cyclohexanone was expected to afford ketone **7** with the construction of C5 and C6 stereogenic centers. The stereochemistry at C4 in intermediate **8** was to be controlled by enzymatic desymmetrization of the diol.

The total synthesis was commenced with Wittig olefination of the readily accessible aldehyde **10**,[6] which was converted to diol **11** by hydrolysis as shown in Scheme 2. Desymmetrization of the diol **11** with Lipase from *Pseudomonas* sp. in *i*-Pr_2O-vinyl acetate furnished the optically active acetate, and the remaining primary hydroxyl group was then im-

Scheme 2



mediately protected as a TBDPS ether to provide **9** (97% ee).[7] Removal of the acetyl group of **9** and protection of the alcohol afforded the MEM ether **12**. Deprotection of the TBDPS group of **12** followed by intramolecular cyclic carbamation with NaH and *N*-PMB protection afforded **13**. The carbamate **13** was subjected to osmium-catalyzed dihydroxylation followed by oxidative cleavage of the corresponding diol with $NaIO_4$ to give aldehyde **8**.

With the requisite aldehyde **8** in hand, aldol reaction of **8** with cyclohexanone was attempted in order to install both of the desired C5 and C6 stereogenic centers. The chelation-controlled aldol reaction smoothly proceeded, after quenching with BzCl, and the corresponding benzoate **14**[8] was furnished in 79% isolated yield (dr = 20:1[9]). Attachment of the cyclohexene ring with 2-cyclohexenylzinc chloride (Corey's

(5) Total synthesis: (a) Reddy, L. R.; Saravanan, P.; Corey, E. J. *Am. Chem. Soc.* **2004**, *126*, 6230–6231. (b) Reddy, L. R.; Fournier, J.-F.; Reddy, B. V. S.; Corey, E. J. *Org. Lett.* **2005**, *7*, 2699–2701. (c) Endo, A.; Danishefsky, S. J. *J. Am. Chem. Soc.* **2005**, *127*, 8298. (d) Ling, T.; Macherla, V. R.; Manam, R. R.; McArthur, K. A.; Potts, B. C. M. *Org. Lett.* **2007**, *9*, 2289–2292. (e) Takahashi, K.; Midori, M.; Kawano, K.; Ishihara, J.; Hatakeyama, S. *Angew. Chem., Int. Ed.* **2008**, *47*, 6244–6246. Racemic synthesis: (f) Mulholland, N. P.; Pattenden, G.; Walters, I. A. S. *Org. Biomol. Chem* **2006**, *4*, 2845–2846. (g) Ma, G.; Nguyen, H.; Romo, D. *Org. Lett.* **2007**, *9*, 2143–2146. Formal synthesis: (h) Caubert, V.; Masse, J.; Retailleau, P.; Langlois, N. *Tetrahedron Lett.* **2007**, *48*, 381–384. (i) Margalef, I. V.; Rupnicki, L.; Lam, H. W. *Tetrahedron* **2008**, *64*, 7896–7901. For a recent review, see: (j) Shibasaki, M.; Kanai, M.; Fukuda, N. *Chem. Asian J.* **2007**, *2*, 20–38.

(6) Ooi, H.; Ishibashi, N.; Iwabuchi, Y.; Ishihara, J.; Hatakeyama, S. *J. Org. Chem.* **2004**, *69*, 7765–7768.

(7) For determination of the ee and absolute configuration, see the Supporting Information.

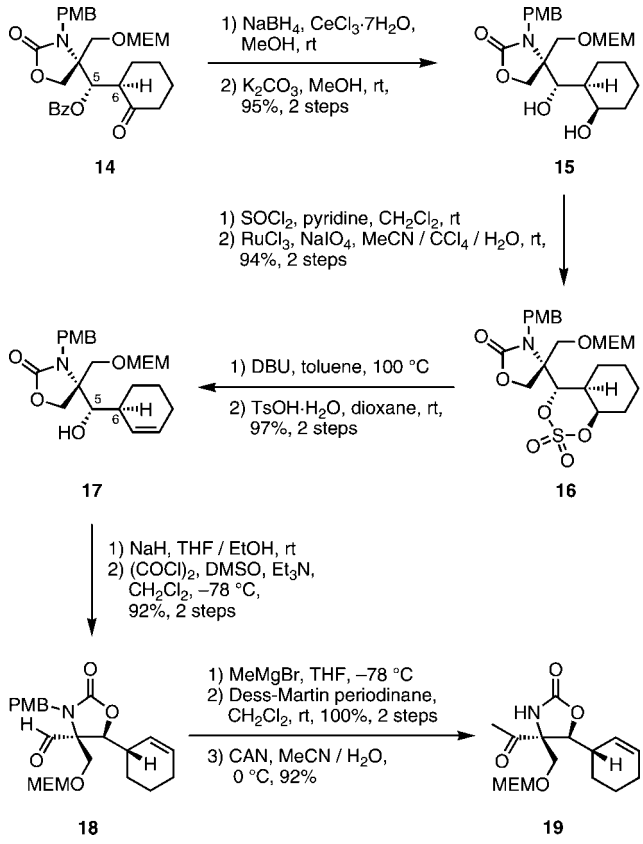
(8) Stereochemistries of C5 and C6 were confirmed by NOE experiment of an acetonide compound derived from diol **15**; also see the Supporting Information.

(9) The aldol reaction would proceed via a chelation-controlled six-membered transition state as shown in Scheme 2. The *re* face of the formyl group is considered to be sufficiently screened by the PMB group to favor highly selective formation of the desired aldol product; see: Corey, E. J.; Li, W.; Nagamitsu, T. *Angew. Chem., Int. Ed.* **1998**, *37*, 1676–1679.

procedure) or other 2-cyclohexenylmetal reagents produced **7** but with low stereoselectivity.[10]

We next turned to elaboration of the cyclohexene from cyclohexenone (Scheme 3). However, the conversion of

Scheme 3



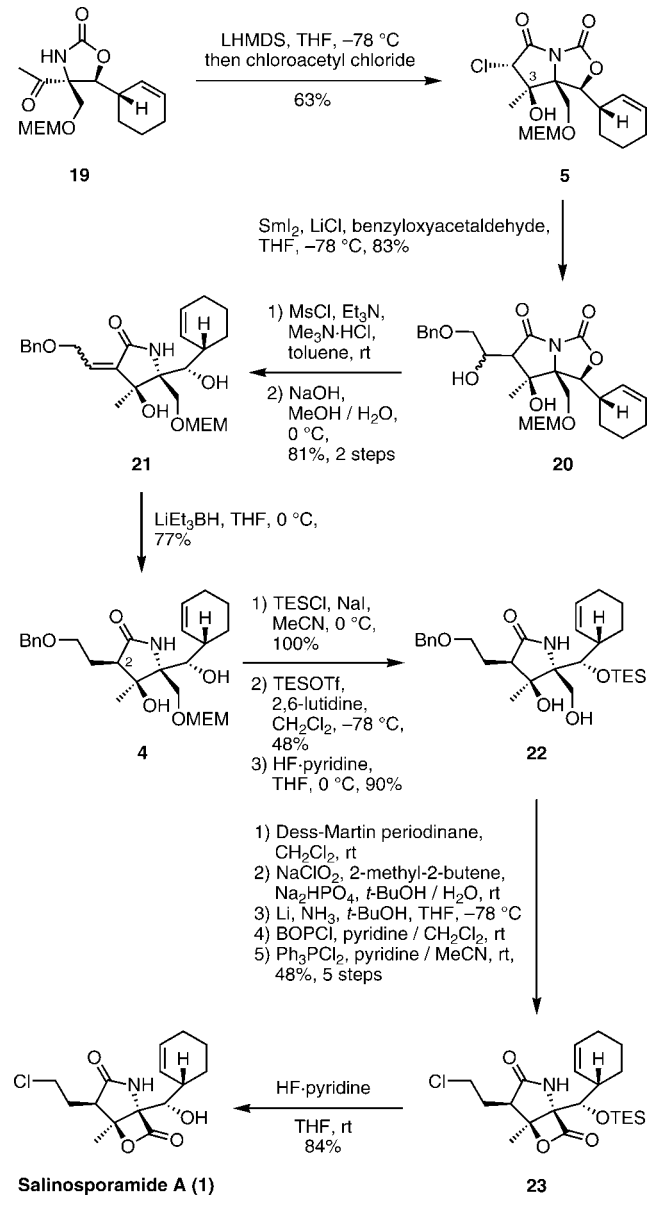
cyclohexanone to cyclohexene proved quite challenging. Shapiro reaction, reduction of the enol triflate using palladium chemistry, and reduction−dehydration procedures were all ultimately unsuccessful. After further investigation, the problem was solved by elimination of the cyclic sulfate derived from the diol.[11] The benzoate **14** was subjected to Luche reduction followed by solvolysis to afford the *anti*-1,3-diol **15** stereoselectively. Reaction of **15** with thionyl chloride gave the corresponding cyclic sulfite, which was oxidized with $NaIO_4$ and a catalytic amount of $RuCl_3$ to produce the cyclic sulfate **16**. Exposure of **16** to DBU at 100 °C followed by treatment of the resulting *O*-sulfonic acid with TsOH•H_2O gave the desired cyclohexene **17** in high overall yield from the benzoate **14** (82% in six steps).

Treatment of **17** with NaH triggered intramolecular transcarbamation, and the corresponding primary alcohol was converted to aldehyde **18** by Swern oxidation. Subsequent 1,2-addition of methylmagnesium bromide, followed by Dess−Martin oxidation and *N*-PMB deprotection gave ketone **19**.

Construction of the γ-lactam and C3 stereogenic center was established by *N*-acylation of **19** followed by intramolecular aldol reaction using LHMDS (2.4 equiv) and chloroacetyl chloride in one pot, in which the desired γ-lactam **5** was obtained as a single isomer.[12]

Next, we directed our efforts toward the installation of the C2 side chain using **5** or the dechlorinated γ-lactam, derived from **5** by reduction (Scheme 4).[13] After extensive

Scheme 4



investigation, only the aldehyde proved to be effective in intermolecular coupling. SmI_2-mediated intermolecular Reformatsky-type reaction of **5** with benzyloxy acetaldehyde afforded **20**. In this stage, attempts at deoxygenation reactions

(10) Cyclohexene ring construction of **8** with 2-cyclohexenylzinc chloride (Corey's procedure) gave the maximum yield and stereoselectivity (**17**; 40% yield, **17**: other stereoisomers = 1:1.1).

(11) Winkler, J. D.; Rouse, M. B.; Greaney, M. F.; Harrison, S. J.; Jeon, Y. T. *J. Am. Chem. Soc.* **2002**, *124*, 9726–9728.

were unsuccessful. Therefore, the β-hydroxy-γ-lactam **20** was converted to the α,β-unsaturated lactam **21** by mesylation-elimination followed by alkaline hydrolysis. Subsequent screening of reductants for the stereoselective 1,4-reduction of **21** led to the use of $LiEt_3BH$ to afford **4** (dr = 4.2:1). Deprotection of the MEM ether, TES protection of the primary and secondary alcohols, and selective deprotection of the primary TES ether with HF·pyridine afforded **22**. A tandem approach involving oxidation of the primary alcohol, Birch reduction to deprotect the benzyl group, β-lactonization with BOPCl, and chlorination with Ph_3PCl_2[5a] gave the desired β-lactone **23**. Finally, deprotection of the TES ether afforded salinosporamide A (**1**). Synthetic salinosporamide A (**1**) was identical to reported spectra in all respects[1] (mp, $[\alpha]_D$, ^1H and ^{13}C NMR, IR, FAB-MS).

In summary, we have achieved the total synthesis of salinosporamide A (**1**). The best feature of our synthetic route is the stereoselective construction of the cyclohexene ring with control of the C5 and C6 stereogenic centers through a chelation-controlled aldol reaction as a key reaction in an early stage of the total synthesis. This strategy differs from those of other previously reported total syntheses. Other key features of our total synthesis include enzymatic desymmetrization, intramolecular aldol reaction, and intermolecular Reformatsky-type reaction followed by 1,4-reduction. Further improvements to the total synthesis and development of salinosporamide A analogues are currently in progress in our laboratory.

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Note Added after ASAP Publication. In Scheme 4, the structure of compound **23** was corrected on September 10, 2008.

Supporting Information Available: Characterization data and experimental procedures. This material is available free of charge via the Internet at http://pubs.acs.org.

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(12) C3 stereochemistry was confirmed by NOE experiment of **5**; also see the Supporting Information.

(13) See the Supporting Information.