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A Simple Stereocontrolled Synthesis of Salinosporamide A

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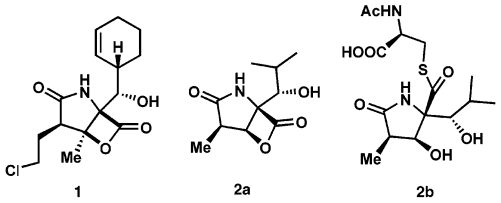
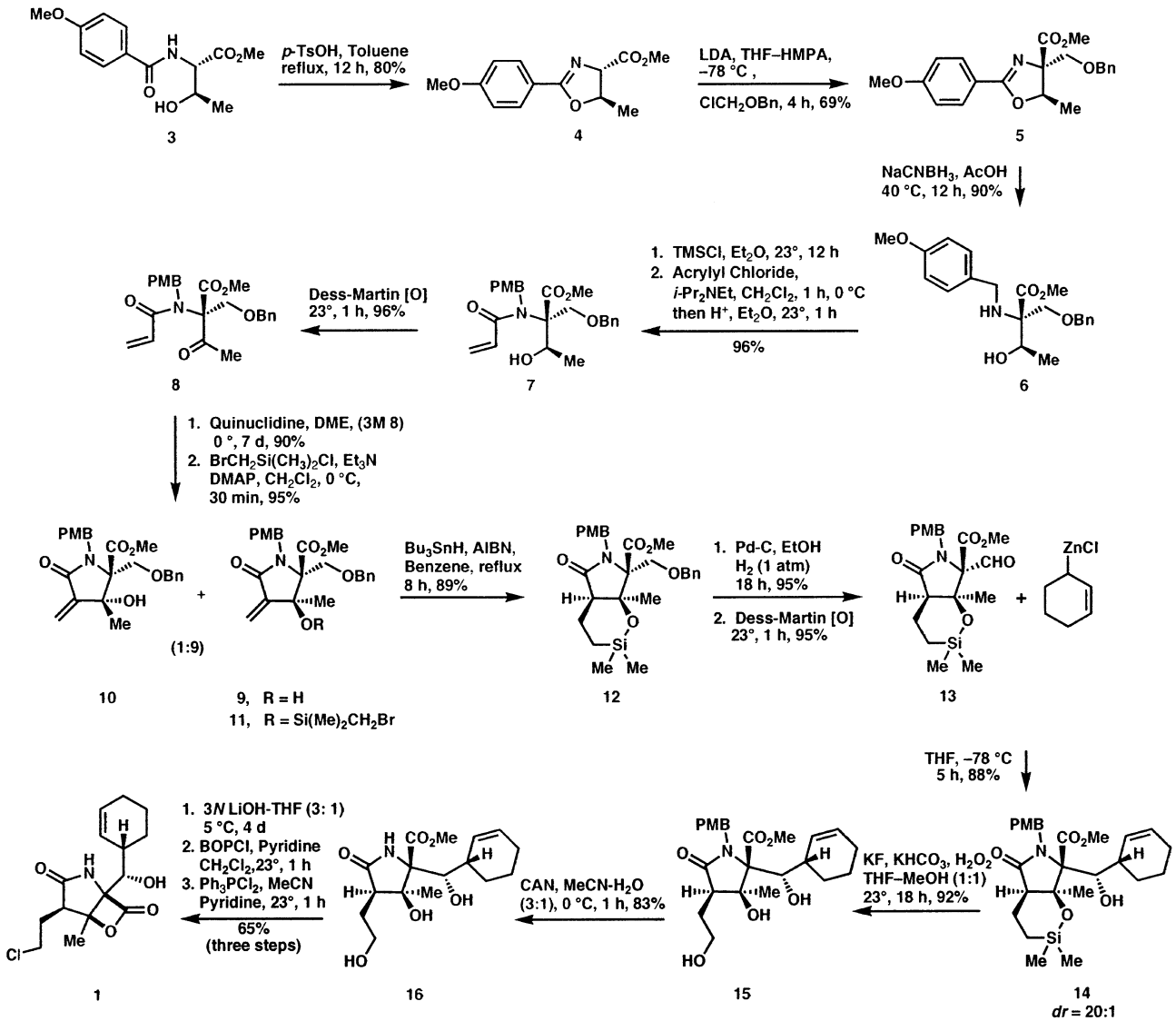
Salinosporamide A (**1**) was recently discovered by Fenical and his group as a bioactive product of a marine microorganism that is widely distributed in ocean sediments.[1] Structurally it closely resembles the terrestrial microbial product omuralide[2a] (**2a**) that we synthesized several years ago and demonstrated to be a potent inhibitor of proteasome function.[2] Omuralide is generated by β-lactonization of the *N*-acetylcysteine thiolester lactacystin (**2b**) that was first isolated by the Omura group as a result of microbial screening for nerve growth factor-like activity.[3] Salinosporamide A is an even more effective proteasome inhibitor than omuralide, and, in addition, it displays surprisingly high in vitro cytotoxic activity against many tumor cell lines (IC_{50} values of 10 nM or less). We report herein the first enantiospecific total synthesis of **1**.



The pathway of the synthesis of salinosporamide A is outlined in Scheme 1. (*S*)-Threonine methyl ester was *N*-acylated with

Scheme 1



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4-methoxybenzoyl chloride in CH_2Cl_2 at 23 °C to form the amide **3** (71%) which was then cyclized to oxazoline **4** (80%) by heating at reflux in toluene with *p*-toluenesulfonic acid. Deprotonation of **4** with lithium diisopropylamide in THF and alkylation of the resulting enolate with chloromethyl benzyl ether afforded the required tertiary stereocenter of **5** selectively in 69% yield. Reduction of **5** with $NaBH_3CN-HOAc$ gave the *N*-4-methoxybenzylamine **6** (90%) which was then transformed in 96% yield to the *N*-acrylyl-*N*-PMB derivative (PMB = 4-methoxybenzyl) by the one-flask sequence: (1) reaction with Me_3SiCl and Et_3N to form the TMS ether, (2) acylation with acrylyl chloride at 0 °C, and (3) acidic work up with aqueous HCl. Dess−Martin periodinane oxidation of **7** produced the keto amide ester **8** in 96% yield. Cyclization of **8** to the γ-lactam **9** was accomplished by means of an internal Baylis−Hillman-aldol reaction[4] using quinuclidine as the catalytic base in dimethoxyethane at 0 °C for 7 d. The cyclization product, obtained in 90% yield, consisted of **9** and the C(β) diastereomer (**10**) in a ratio of 9:1. The *N*-benzyl analogue of **10** was obtained in crystalline form, mp = 136−7 °C, and was demonstrated to possess the stereochemistry shown for **10** by single-crystal X-ray diffraction analysis. When the internal aldol reaction of **8** was conducted at 20 °C for 9 h, **9** and **10** were obtained in 90% yield and a ratio of 4:1. Silylation of **9** with bromomethyldimethylsilyl chloride afforded **11** in 95% yield. Silyl ether **11** and the diastereomeric silyl ether were easily and conveniently separated at this stage by silica gel column chromatography on a preparative scale.

The required stereochemical relationship about C(α) and C(β) of the γ-lactam core was established by tri-*n*-butyltin hydride-mediated radical-chain cyclization which transformed **11** cleanly into the *cis*-fused γ-lactam **12**.[5] Cleavage of the benzyl ether of **12** (H_2, Pd−C) and Dess−Martin periodinane oxidation provided the aldehyde **13** in ca. 90% yield from **12**. The next step, the attachment of the 2-cyclohexenyl group to the formyl carbon and the establishment of the remaining two stereocenters, was accomplished in a remarkably simple way. 2-Cyclohexenyl-tri-*n*-butyltin (from Pd(0)-catalyzed 1,4-addition of tributyltin hydride to 1,3-cyclohexadiene)[6] was sequentially transmetalated by treatment with 1 equiv of *n*-butyllithium and 1 equiv of zinc chloride to form 2-cyclohexenylzinc chloride in THF solution. Reaction of this reagent with the aldehyde **13** furnished the desired formyl adduct stereoselectively (20:1) in 88% yield.[7] Tamao−Fleming oxidation[8] of **14** gave the triol **15** in 92% yield. Ce(IV)-induced oxidative cleavage of the PMB group of **15** afforded the triol ester **16** which was hydrolyzed to the corresponding γ-lactam-carboxylic acid using 3 N lithium hydroxide in aqueous THF at 4 °C. This acid was converted to salinosporamide A (**1**) (65% overall yield) by successive reaction with 1.1 equiv of bis-(2-oxo-3-oxazolidinyl) phosphinic chloride (BOPCl) and pyridine at 23 °C for 1 h (to form the β-lactone) and then 2 equiv of triphenylphosphine dichloride in CH_3CN−pyridine at 23 °C for 1 h. The identity of synthetic **1** and natural salinosporamide A was established by comparison measurements of ^1H and ^{13}C NMR spectra, mp and mixed mp (168−170 °C), optical rotation, IR and mass spectra, and chromatographic mobilities in three different solvent systems.

There are a number of steps in the synthesis of **1** that require comment. The direct conversion of **6** to **7** with acrylyl chloride under a wide variety of conditions gave considerably lower yields than the process shown in Scheme 1 mainly because of competing O-acylation and subsequent further transformations. So far, quinuclidine has proved superior to other catalytic bases, for example, 1,4-diaza[2.2.2] bicyclooctane, for the cyclization of **8** to **9**. As indicated just above, the attachment of the 2-cyclohexenyl group to aldehyde **13** to form **14** worked best with the reagent 2-cyclohexenylzinc chloride.[7] Attempts to form **14** from **13** using Lewis acid-catalyzed reaction with tri-*n*-butyl-2-cyclohexenyltin were totally unsuccessful. The saponification of methyl ester **16** at temperatures above +5 °C led to lowered yields of the required carboxylic acid. Finally, the one-flask β-lactonization and chlorination reactions leading to **1** were remarkably clean and probably proceed in >90% yield per step.

In summary, this paper describes an efficient and short total synthesis of salinosporamide A that is capable of providing substantial quantities of this currently rare substance for further biological study, especially to determine its potential as an anticancer agent.

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Supporting Information Available: Experimental procedures for the synthetic sequences described herein, together with characterization data for reaction products. X-ray diffraction data (CIF) are provided for the *N*-benzyl analogue of **10**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(7) The stereochemistry of the conversion **13** → **14**, established by the identity of totally synthetic **1** with naturally formed salinosporamide A, is that predicted from a cyclic, chair-formed, six-membered transition state involving addition of the organozinc reagent to the sterically more accessible face of the formyl group. The use of 2-cyclohexenylzinc chloride is critical to successful formation of **14** because none of this product is obtained with 2-cyclohexenyllithium (probably because the initial carbonyl adduct undergoes retroaldol cleavage and decomposition; see: Corey, E. J.; Li, W.; Nagamitsu, T. *Angew. Chem., Int. Ed.* **1998**, *37*, 1676−1679).

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