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Total Synthesis of (−)-Salinosporamide A

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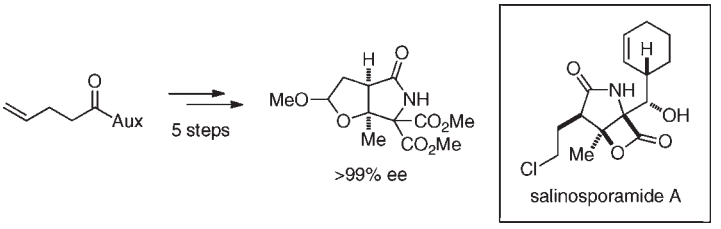
ABSTRACT



A concise and stereoselective total synthesis of (−)-salinosporamide A (1), a potent inhibitor of the 20S proteasome that is in clinical development as an anticancer drug candidate, has been accomplished in 14 steps with 19% overall yield from 4-pentenoic acid. Our synthesis features a stereoselective alkylation utilizing a chiral auxiliary, formation of a pyrrolidine unit, and oxidation of the pyrrolidine to a γ-lactam. To demonstrate the scalability of our synthesis, (−)-salinosporamide A has been synthesized on a gram scale.

(−)-Salinosporamide A (**1**, NPI-0052, marizomib) was isolated by Fenical and co-workers from a marine actinomycete *Salinospora tropica* that is distributed in ocean sediments around the Bahamas.[1] Salinosporamide A is a potent inhibitor of the 20S proteasome and is currently being tested as an anticancer drug candidate to treat patients with multiple myeloma.[2] In addition to its potent bioactivity, the highly functionalized structure of **1**, possessing a β-lactone, α,α-disubstituted amino acid moiety, cyclohexene ring, and five contiguous stereogenic centers, has attracted the attention of a number of synthetic chemists. Intensive efforts have therefore been made to establish efficient synthetic routes to **1**.[2e,3−6] In this communication, we report a concise and enantioselective synthesis of this natural product.

As illustrated in Scheme 1, salinosporamide A would be derived from **2** by differentiation of the diester and cleavage of the lactol. We envisioned that **2** could in turn be derived from acyclic amino ketone **3** in a stereoselective manner upon sequential cyclization. In the event,

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(2) (a) Chauhan, D.; Catley, L.; Li, G.; Podar, K.; Hideshima, T.; Velankar, M.; Mitsiades, C.; Mitsiades, N.; Yasui, H.; Letai, A.; Ovaa, H.; Berkers, C.; Nicholson, B.; Chao, T.-H.; Neuteboom, S. T. C.; Richardson, P.; Palladino, M. A.; Anderson, K. C. *Cancer Cell* **2005**, *8*, 407. (b) Macherla, V. R.; Mitchell, S. S.; Manam, R. R.; Reed, K. A.; Chao, T.-H.; Nicholson, B.; Deyanat-Yazdi, G.; Mai, B.; Jensen, P. R.; Fenical, W.; Neuteboom, S. T. C.; Lam, K. S.; Palladino, M. A.; Potts, B. C. M. *J. Med. Chem.* **2005**, *48*, 3684. (c) Fenical, W.; Jensen, P. R.; Palladino, M. A.; Lam, K. S.; Lloyd, G. K.; Potts, B. C. *Bioorg. Med. Chem.* **2009**, *17*, 2175. (d) Singh, A. V.; Palladino, M. A.; Lloyd, G. K.; Potts, B. C.; Chauhan, D.; Anderson, K. C. *Br. J. Hamaetol.* **2010**, *140*, 550. For a review, see: (e) Gulder, T. A. M.; Moore, B. S. *Angew. Chem., Int. Ed.* **2010**, *49*, 9346.

(3) For enantioselective syntheses, see: (a) Reddy, L. R.; Saravanan, P.; Corey, E. J. *J. Am. Chem. Soc.* **2004**, *126*, 6230. (b) Endo, A.; Danishefsky, S. J. *J. Am. Chem. Soc.* **2005**, *127*, 8298. (c) Ling, T.; Macherla, V. R.; Manam, R. R.; McArthur, K. A.; Potts, B. C. M. *Org. Lett.* **2007**, *9*, 2289. (d) Takahashi, K.; Midori, M.; Kawano, K.; Ishihara, J.; Hatakeyama, S. *Angew. Chem., Int. Ed.* **2008**, *47*, 6244. (e) Fukuda, T.; Sugiyama, K.; Arima, S.; Harigaya, Y.; Nagamitsu, T.; Omura, S. *Org. Lett.* **2008**, *10*, 4239. (f) Nguyen, H.; Ma, G.; Romo, D. *Chem. Commun.* **2010**, *46*, 4803. (g) Sato, Y.; Fukuda, H.; Tomizawa, M.; Masaki, T.; Shibuya, M.; Kanoh, N.; Iwabuchi, Y. *Heterocycles* **2010**, *81*, 2239. (h) Nguyen, H.; Ma, G.; Gladysheva, T.; Fremgen, T.; Romo, D. *J. Org. Chem.* **2011**, *76*, 2. (i) Kaiya, Y.; Hasegawa, J.; Momose, T.; Sato, T.; Chida, N. *Chem.—Asian J.* **2011**, *6*, 209.

(4) For racemic syntheses, see: (a) Mulholland, N. P.; Pattenden, G.; Walters, I. A. S. *Org. Biomol. Chem.* **2006**, *4*, 2845. (b) Ma, G.; Nguyen, H.; Romo, D. *Org. Lett.* **2007**, *9*, 2143.

(5) For formal syntheses, see: (a) Caubert, V.; Massé, J.; Retailleau, P.; Langlois, N. *Tetrahedron Lett.* **2007**, *48*, 381. (b) Margalef, I. V.; Rupnicki, L.; Lam, H. W. *Tetrahedron* **2008**, *64*, 7896. (c) Momose, T.; Kaiya, Y.; Hama, N.; Hasegawa, J.; Sato, T.; Chida, N. *Synthesis* **2009**, 2983. (d) Mosey, R. A.; Tepe, J. J. *Tetrahedron Lett.* **2009**, *50*, 295. (e) Struble, J. R.; Bode, J. W. *Tetrahedron* **2009**, *65*, 4957. (f) Ling, T.; Potts, B. C.; Macherla, V. R. *J. Org. Chem.* **2010**, *75*, 3882.

(6) For reviews of the syntheses, see: Shibasaki, M.; Kanai, M.; Fukuda, N. *Chem.—Asian J.* **2007**, *2*, 20 and ref 2f.

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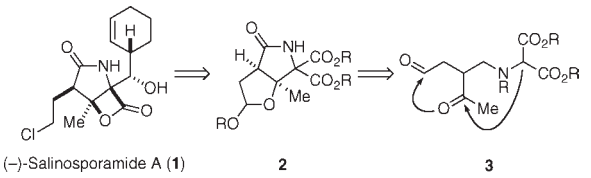
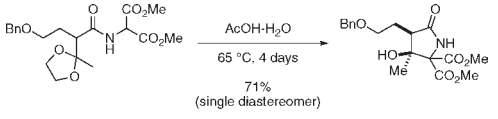
Scheme 1. Retrosynthesis



nucleophilic attack of the malonate on the ketone would produce an alcohol that would subsequently react with the aldehyde to generate the requisite *cis*-fused bicyclo[3.3.0] core. The carbonyl group of the lactam moiety was to be introduced after construction of the bicyclic skeleton to avoid racemization.[7]

Our synthesis commenced with a condensation reaction of commercially available 4-pentenoic acid (**4**) with a known chiral oxazolidinethione (Scheme 2).[8,9] Diastereoselective alkylation using a cyclic orthoester[10] afforded the product as a single isomer. After reductive removal of the chiral auxiliary, the resulting aldehyde was treated with dimethyl aminomalonate and $NaBH_3CN$ in a one-pot operation to provide enantiomerically pure amine **6** (> 99% ee). Upon formylation of the amine and subsequent deprotection of the ketone, spontaneous cyclization proceeded in part to give a diastereomeric mixture of pyrrolidines **7a** and **7b** along with the acyclic compound **8**. When the mixture of **7a**, **7b**, and **8** was subjected to ozonolysis followed by acidic treatment, significant erosion of enantiopurity of the bicyclic product **9** (*ca.* 90% ee) was observed (Scheme 3). Fortuitously, upon crystallization from Et_2O, the mixture of **7a**, **7b**, and **8** converged to crystalline **7a**,[11,12] which has a *cis* relationship between the allyl group and the hydroxy group. Ozonolysis of pure pyrrolidine **7a** and ensuing acidic treatment gave the product without racemization.

(7) In ref 4 the diastereoselective formation of a γ-lactam was reported as shown below. However, we could not apply this strategy to asymmetric synthesis because the reaction resulted in a complete racemization.



(8) (a) Delaunay, D.; Toupet, L.; Le Corre, M. *J. Org. Chem.* **1995**, *60*, 6604. (b) Wu, Y.; Yang, Y.-Q.; Hu, Q. *J. Org. Chem.* **2004**, *69*, 3990. (c) Palomo, C.; Oiarbide, M.; López, R.; González, P. B.; Gómez-Bengoa, E.; Saá, J. M.; Linden, A. *J. Am. Chem. Soc.* **2006**, *128*, 15236.

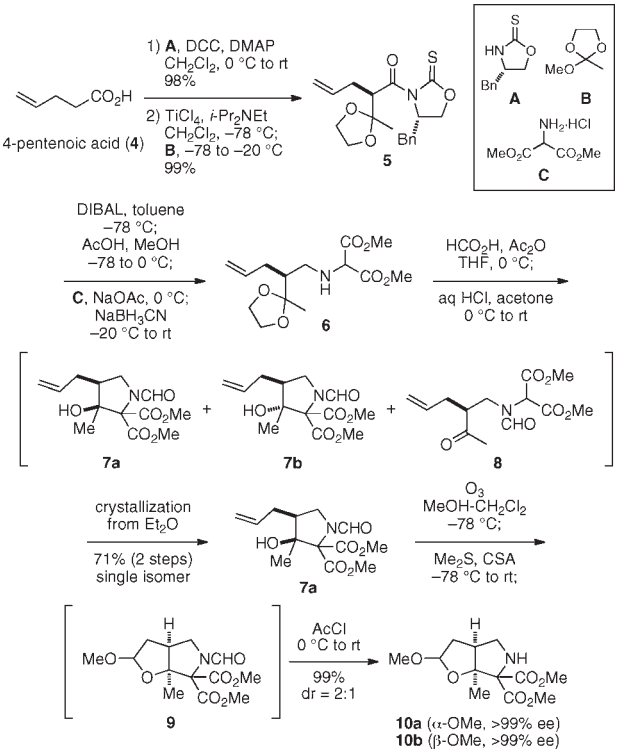
(9) Andrade, C. K. Z.; Rocha, A. R.; Vercillo, O. E.; Silva, W. A.; Matos, R. A. F. *Synlett* **2003**, 2351.

(10) Evans, D. A.; Urpi, F.; Somers, T. C.; Clark, J. S.; Bilodear, M. T. *J. Am. Chem. Soc.* **1990**, *112*, 8215.

(11) The structure of **7a** was determined by an X-ray crystallographic study.

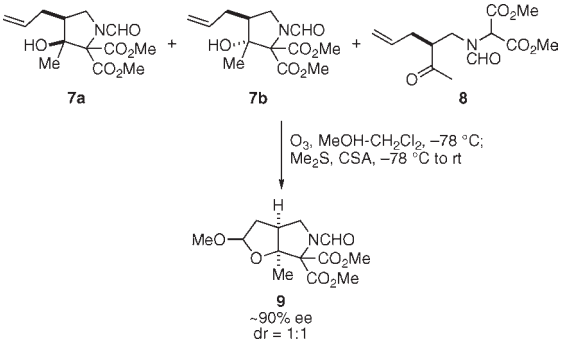
(12) Slow epimerization of **7a** was observed when taken up in $CDCl_3$. Thus we assumed that dynamic preferential crystallization of **7a** occurred in an aprotic solvent. On the other hand, **7a** was conformationally stable in CD_3OD and in $CDCl_3$–CD_3OD (1:1).

Scheme 2. Formation of Pyrrolidine



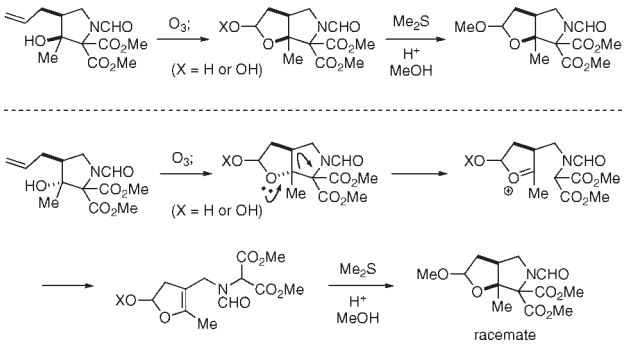
Subsequent removal of the formyl group in a one-pot operation provided the diastereomeric mixture of amines **10a** and **10b**.

Scheme 3. Erosion of Enantiopurity of the Bicyclic Product **9**



A proposed mechanism for the racemization is shown in Scheme 4. After ozonolysis, the resulting aldehyde or carbonyl oxide would be trapped by the neighboring hydroxy group. When the allyl and hydroxy groups are in the *cis* configuration, the intermediate would be transformed into the product without racemization. On the other hand, when the allyl and hydroxy groups are in the *trans* configuration, the strain of the resulting bicyclic skeleton might induce cleavage of the pyrrolidine ring by

Scheme 4. Mechanism of Racemization



electron donation of the ether. Deprotonation of the oxocarbenium ion would then lead to racemization.

With a route to enantiopure bicyclic amine **10** secured, we next focused on manipulation of the pyrrolidine ring. Initially, we attempted to oxidize the *N*-formyl derivative **9**. Upon treatment of **9** with 10 mol % ruthenium catalyst and excess sodium metaperiodate at room temperature, oxidation and concomitant removal of the formyl group occurred to provide the lactam **11**. However, the yield was variable and moderate (*ca.* 60%) due to the competing oxidation of the cyclic acetal. We then tried to oxidize the corresponding free amine **10** (Scheme 5). Oxidation of **10** with 2 mol % ruthenium catalyst proceeded at a faster rate even at 0 °C, affording lactam **11** in good yield (85% combined yield) with no appreciable oxidation of the cyclic acetal moiety. Since oxidation of secondary amines, such as piperidine or diethylamine, by ruthenium tetroxide has been reported to give "intractable products,"[13] we surmised that the steric hindrance or the electron-withdrawing nature

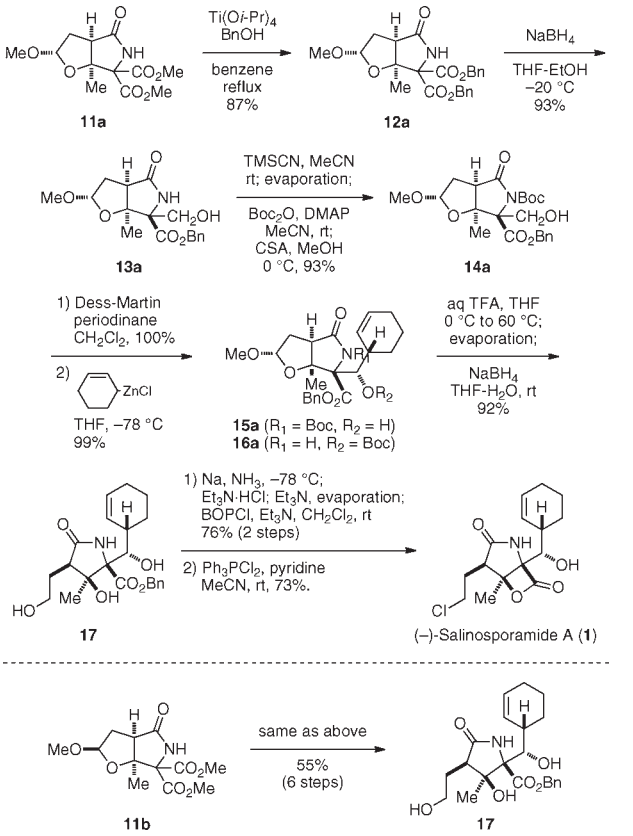
Scheme 5. Ru Oxidation of Secondary Amine

of the diester moiety played a crucial role in the oxidation.

The diastereomeric lactams **11a** and **11b** were separated by silica gel column chromatography at this stage, and each diastereomer was subjected to further transformations separately. The synthetic scheme from the α-OMe isomer **11a** is provided in Scheme 6. The *β*-OMe isomer **11b** could be converted into **17** under almost the same conditions in 55% overall yield (See Supporting Information). After transesterification of **11a** into a dibenzyl ester **12a**,[14] the less hindered α-ester in **12a** was reduced selectively with $NaBH_4$ to yield alcohol **13a**.

Having established a synthetic route to **13a**, the next task was to introduce the cyclohexenyl moiety. When the lactam moiety was not protected, the reaction of an aldehyde with cyclohexenylzinc chloride gave quite unsatisfactory results (< 20% yield, dr ~4:3[15]). We therefore realized that protection of the lactam moiety was needed prior to the introduction of the cyclohexene ring.

Scheme 6. Total Synthesis of Salinosporamide A

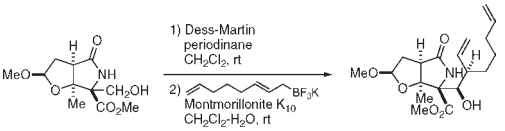


In situ protection of the primary alcohol with a TMS group followed by introduction of a Boc group to the lactam moiety afforded, after acidic treatment, **14a** in good yield. After oxidation of the alcohol, the resulting aldehyde was treated with cyclohexenylzinc chloride according to the reported procedure.[3a] While introduction

(13) Berkowitz, L. M.; Rylander, P. N. *J. Am. Chem. Soc.* **1958**, *80*, 6682.

(14) Shapiro, G.; Marzi, M. *J. Org. Chem.* **1997**, *62*, 7096.

(15) According to ref 3b, addition of the cyclohexenylzinc reagent gave poor selectivity when the lactam moiety was protected as its ethyl imidate. Thus protection of the nitrogen atom was essential to obtain the desired stereochemistry. We also tried introducing the cyclohexenyl moiety to the unprotected lactam by diastereoselective allylation followed by ring closing metathesis. In this case, the product turned out to be exclusively the undesired isomer.



of the cyclohexenyl moiety was accompanied by partial transposition of the Boc group to afford a mixture of **15a** and **16a**, the addition itself proceeded with complete diastereoselectivity.

Both removal of the Boc group and conversion of the methyl acetal into a lactol were performed under acidic conditions, and subsequent reduction of the lactol with $NaBH_4$ gave triol **17**. Finally, deprotection of the carboxylic acid and β-lactonization followed by chlorination of the primary alcohol[3a] furnished (−)-salinosporamide A.

In conclusion, a concise and enantioselective synthesis of (−)-salinosporamide A has been achieved in 14 steps and 19% overall yield from commercially available 4-pentenoic acid **4**. The synthesis features a stereoselective alkylation utilizing a chiral auxiliary, a pyrrolidine formation, and a ruthenium-catalyzed oxidation to a lactam. The present route is amenable to scale-up, and we have indeed succeeded in synthesizing 1.5 g of salinosporamide as described in the Supporting Information.

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