ORGANIC LETTERS

2005
Vol. 7, No. 13
2699−2701

New Synthetic Route for the Enantioselective Total Synthesis of Salinosporamide A and Biologically Active Analogues

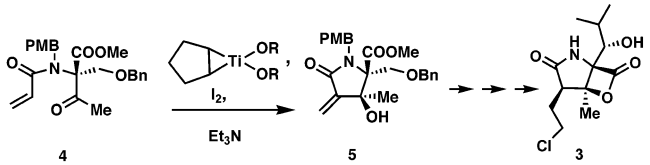
Leleti Rajender Reddy, Jean-François Fournier, B. V. Subba Reddy, and E. J. Corey*

Department of Chemistry and Chemical Biology, Harvard University, 12 Oxford Street, Cambridge, Massachusetts 02138

corey@chemistry.harvard.edu

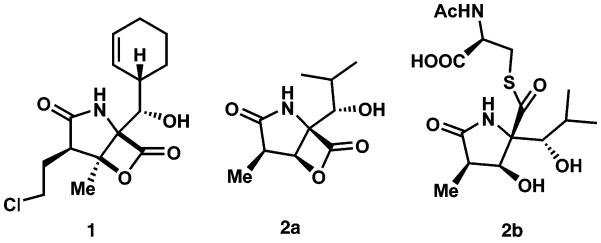
Received April 20, 2005

ABSTRACT



A total synthesis of the salinosporamide analogue 3 is described that starts with the novel cyclization 4 → 5.

One of the most fascinating biologically active natural products to have been isolated recently is the marine microbial metabolite salinosporamide A (**1**) first described by the Fenical group at the Scripps Oceanographic Institute.[1] Salinosporamide A is structurally related to omuralide (**2a**)[2] and lactacystin (**2b**),[3] natural products from a terrestrial



organism which are potent and useful covalent inhibitors of proteasome function and consequent protein degradation. Salinosporamide is a somewhat more potent inhibitor of the proteasome than omuralide. Even more interesting is the report that **1** is much more potent than **2a** in terms of in vitro cytotoxic activity against many tumor cell lines (IC_{50} values of 10 nM or less).[1,4] In continuation of our program on the study of proteasome inhibitors, we recently developed the first total synthesis of salinosporamide[5] by a route that started with *S*-threonine, which was converted in a few highly efficient steps to the keto acrylamide **4** (Scheme 1). A key early step in this synthesis was the Baylis−Hillman cycliza-

(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) (a) Reviewed in: Corey, E. J.; Li, W.-D. Z. *Chem. Pharm. Bull.* **1999**, *47*, 1−10. (b) Corey, E. J.; Reichard, G. A.; Kania, R. *Tetrahedron Lett.* **1993**, *34*, 6977−6980. (c) Corey, E. J.; Reichard, G. A. *J. Am. Chem. Soc.* **1992**, *114*, 10677−10678. (d) Fenteany, G.; Standaert, R. F.; Reichard, G. A.; Corey, E. J.; Schreiber, S. L. *Proc. Natl. Acad. Sci. U.S.A.* **1994**, *91*, 3358−3362.

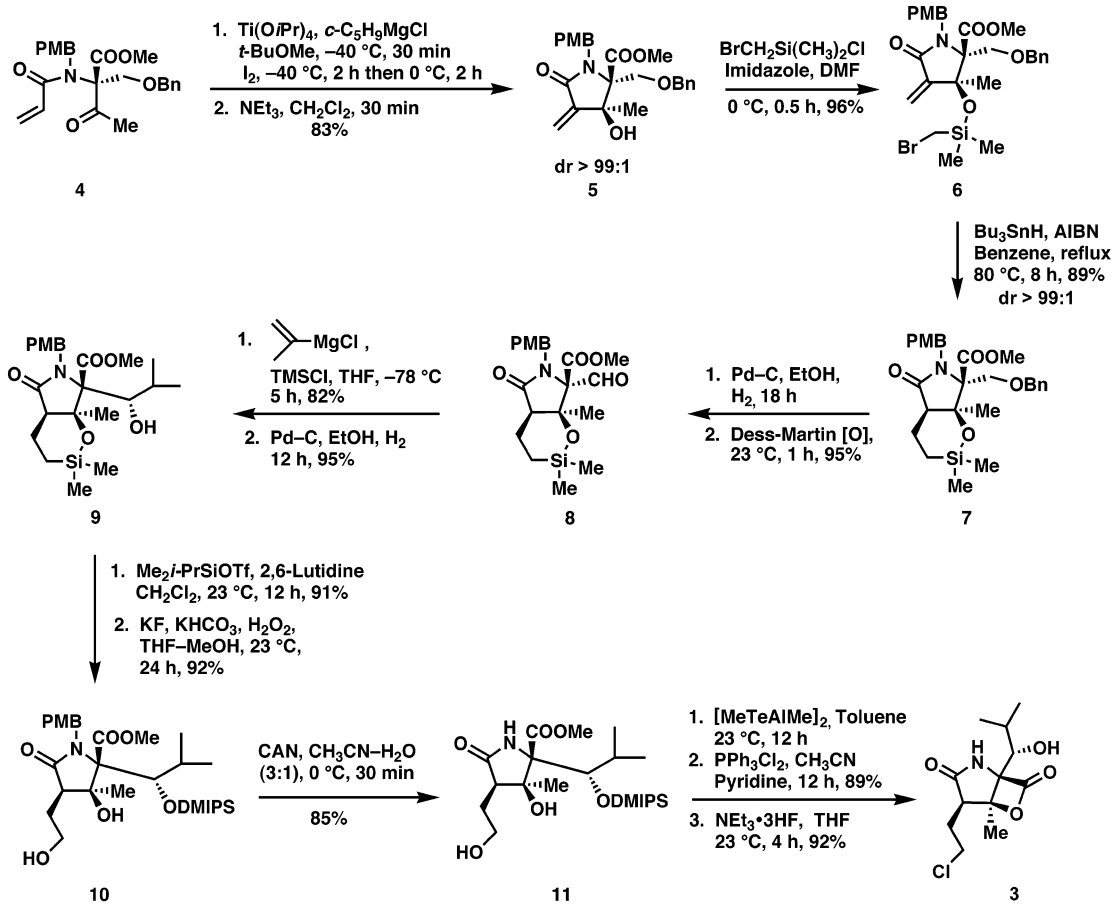
(3) (a) Omura, S.; Fujimoto, T.; Otoguro, K.; Matsuzaki, K.; Moriguchi, R.; Tanaka, H.; Sasaki, Y. *J. Antibiot.* **1991**, *44*, 113−116. (b) Omura, S.; Matsuzaki, K.; Fujimoto, T.; Kosuge, K.; Furuya, T.; Fujita, S.; Nakagawa, A. *J. Antibiot.* **1991**, *44*, 117−118.

(4) Bortezomib (Velcade), a peptidyl boronic acid which is a reversible (0.6 nM Ki) proteasome inhibitor, is currently in use and approved for the treatment of multiple myeloma. In addition, there are numerous ongoing clinical trials on the use of this agent for treatment of other malignant diseases. See: (a) Richardson, P. G.; Barlogie, B.; Berenson, J.; Singhal, S.; Jagannath, S.; Irwin, D.; Rajkumar, S. V.; Srkalovic, G.; Alsina, M.; Alexanian, R.; Siegel, D.; Orlowski, R. Z.; Kuter, D.; Limentani, S. A.; Lee, S.; Hideshima, T.; Esseltine, D.-L.; Kauffman, M.; Adams, J.; Schenkein, D. P.; Anderson, K. C. *N. Engl. J. Med.* **2003**, *348*, 2609−2617. (b) Richardson, P. G.; Hideshima, T.; Anderson, K. C. *Cancer Control* **2003**, *10*, 361−369. (c) Steinberg, D. *The Scientist* **2003**, *17* (S2), S18−S22. (d) Adams, J. *Proteasome Inhibitors in Cancer Therapy*; Humana Press: New York, 2004.

(5) Reddy, L. R.; Saravanan, P.; Corey, E. J. *J. Am. Chem. Soc.* **2004**, *126*, 6230−6231.

10.1021/ol0508734 CCC: $30.25
Published on Web 05/26/2005

Scheme 1



tion of **4** to the γ-lactam **5** with 9:1 diastereoselectivity and in good yield. We now report an unusual alternative cyclization which is completely diastereoselective, less time-consuming, and very efficient. The intermediate γ-lactam **5**, which can readily be converted to salinosporamide A (**1**), also serves to provide access to a variety of interesting salinosporamide/omuralide analogues by the new route that is outlined in Scheme 1.

The keto acrylamide **4** was allowed to react with the dark brown Kulinkovich reagent (3.5 equiv)[6,7] formed by reaction of 4 equiv of Ti(*i*-PrO)$_4$ with 7 equiv of cyclopentylmagnesium chloride in *t*-BuOMe at −40 °C for 30 min, and the mixture was maintained at −40 °C for an additional 30 min to effect cyclization. Iodine (5 equiv) was added to the resulting reaction mixture containing the α-titanamethyl-γ-lactam intermediate to generate, after 2 h at −40 °C and 2 h at 23 °C, the corresponding α-iodomethyl-γ-lactam which, without isolation, was exposed to Et_3N for 30 min at 23 °C. After extractive isolation and flash chromatography on silica gel, a single diastereomerically pure product, **5**, was obtained in 83% overall yield from **4**. As indicated in Scheme 1, the unsaturated γ-lactam **5** could be silylated to **6** (96% yield) which underwent radical-mediated stereoselective cyclization to the previously obtained bicyclic γ-lactam **7** (89%).[5] Debenzylation of **7** and Dess−Martin periodinane oxidation gave the aldehyde **8** which upon reaction with 2-propenylmagnesium chloride and trimethylsilyl chloride[8] in THF at −78 °C for 5 h was transformed into the corresponding secondary alcohol TMS ether. Treatment of this product with 1 atm of H_2 and Pd−C catalyst in ethanol produced pure **9** in good yield. The secondary hydroxyl group of **9** was protected as the dimethyl-*i*-propylsilyl (DMIPS) ether and the silicon bridge was excised[5] to form the dihydroxy γ-lactam **10** in 84% overall yield from **9**. Cleavage of the *N*-*p*-methoxybenzyl group in **10** by ceric ammonium nitrate produced **11**. The conversion of **11** to the required salinosporin-like target **3** was accomplished by a novel sequence of three reactions, the first of which involved the cleavage

(6) For reviews on the application of titanacyclopropane reagents, see (a) Kulinkovich, O. G. *Chem. Rev.* **2003**, *103*, 2597−2632. (b) Sato, F.; Okamoto, S. *Adv. Synth. Catal.* **2001**, *343*, 759−784.

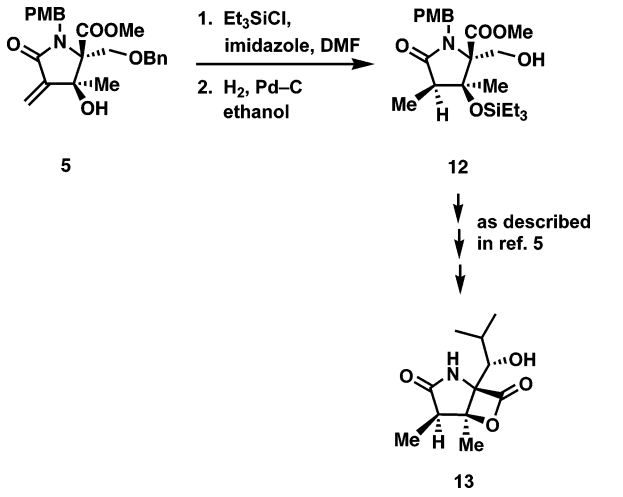
(7) For the closest precedent to this cyclization involving δ,ϵ-enones, see: (a) Kablaoui, N. M.; Buchwald, S. L. *J. Am. Chem. Soc.* **1996**, *118*, 3182−3191. (b) Mandal, S. K.; Amin, S. R.; Crowe, W. E. *J. Am. Chem. Soc.* **2001**, *123*, 6457−6458. (c) Crowe, W. E.; Vu, A. T. *J. Am. Chem. Soc.* **1996**, *118*, 1557−1558. (d) Quan, L. G.; Cha, J. K. *Tetrahedron Lett.* **2001**, *42*, 8567−8569.

(8) At −78 °C, the rate of reaction of 2-propenylmagnesium chloride with Me_3SiCl is slow relative to that with the aldehyde **8**. The inclusion of TMSCl in the reaction mixture allows rapid silylation of the alkoxide intermediate formed by attack of the Grignard reagent on **8**, thereby preventing retroaldol cleavage of this adduct. See: Corey, E. J.; Li. W.; Nagamitsu, T. *Angew. Chem., Int. Ed.* **1998**, *37*, 1676−1679.

of the methyl ester to generate the corresponding carboxylic acid. This turned out to be an unusually difficult and challenging step since none of the known general procedures for the conversion of RCOOMe to RCOOH[9] worked at all due to the strong steric shielding of the COOMe carbonyl in **11** and the propensity of **11** to undergo retroaldol cleavage and other decomposition reactions. Cleavage of the methyl ester function of **11** was accomplished cleanly using a new reagent, $Me_2AlTeMe$, that is generated by heating tellurium powder (1.2 equiv) and trimethylaluminum (1 equiv) in toluene at reflux for 6 h and cooling the product to ambient temperature to give a 0.8 M solution of $[Me_2AlTeMe]_2$ in toluene. Treatment of the dihydroxy ester **11** with a freshly prepared solution of $[Me_2AlTeMe]_2$ (0.8 M in toluene) at 23 °C for 12 h under nitrogen followed by quenching of the reaction mixture with 1 N hydrochloric acid and extractive isolation with ethyl acetate afforded the dihydroxy acid corresponding to **11** cleanly. **CAUTION**: Organotellurium reagents should be used only in a well-ventilated hood; treatment with 1 N hydrochloric acid (or bleach) effects their destruction and deodorization. When the crude acid was subjected to reaction with 4 equiv of Ph_3PCl_2 in dry 1:1 CH_3CN−pyridine at 23 °C for 12 h, it was transformed directly into the DMIPS ether of **3**, which was obtained as a colorless oil in 89% yield after extractive isolation with ethyl acetate and flash chromatography on silica gel. This very efficient operation combines side-chain chlorination with a novel method of β-lactone formation in a single step. Finally, desilylation afforded the target omuralide−salinosporamide hybrid **3** as a colorless solid in 92% yield after extractive isolation (EtOAc) and flash chromatography on silica gel.[10]

As mentioned above, the synthetic route outlined in Scheme 1 provides access to a host of interesting members of the salinosporamide/omuralide series. We have previously reported the conversion of intermediate **8** to salinosporamide A.[5] In addition, the γ-lactam **5** has been transformed efficiently into β-methyl omuralide (**13**) via **12** using reactions strictly analogous to those previously described for the synthesis of salinosporamide A.[5]

Scheme 2



In our experience, the synthetic methodology shown in Schemes 1 and 2 provide an efficient and practical pathway for the synthesis of omuralide analogues, such as **13**, and also salinosporamide A (**1**) and its analogues, such as **3**.

Acknowledgment. J.-F. Fournier is grateful to NSERC of Canada for a postdoctoral fellowship. We thank Millennium Pharmaceuticals, Inc. for a general research grant.

Supporting Information Available: Experimental procedures and spectral data for reaction products **3** and **5**−**13**. This material is available free of charge via the Internet at http://pubs.acs.org.

OL0508734

(9) For reviews, see: (a) Greene, T. W.; Wuts, P. G. M. *Protective Groups in Organic Synthesis*, 3rd ed.; John Wiley and Sons: New York, 1999. (b) Kocienski, P. J. *Protecting Groups*, 3rd ed.; Georg Thieme: Stuttgart, New York, 2004. (c) Salomon, C. J.; Mata, E. G.; Mascaretti, O. A. *Tetrahedron* **1993**, *49*, 3691−3734. (d) Nicolaou, K. C.; Estrada, A. A.; Zak, M.; Lee, S. H.; Safina, B. S. *Angew. Chem., Int. Ed.* **2005**, *44*, 1378−1382. (e) Olah, G. A.; Narang, S. C.; Salem, G. F.; Gupta, B. G. B. *Synthesis* **1981**, 142−143. (f) Marchand, P. S. *J. Chem. Soc., Chem. Commun.* **1971**, 667−668. (g) Bartlett, P. A.; Johnson, W. S. *Tetrahedron Lett.* **1970**, 4459−4462.

(10) Found for pure **3**: $R_f = 0.45$ (silica gel plate, EtOAc−hexane 1:1); mp = 144−145 °C; $[\alpha]_D^{23} = -22.5$ (*c* 0.5, $CHCl_3$); FTIR (film) ν_{max}: 3222, 2960, 2944, 2867, 1833, 1710, 1254, 1090, 1059, 852, 825, 777 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 6.43 (1H, s (br)), 3.97 (1H, m), 3. 84 (1H, t, $J = 6.5$ Hz), 3.77 (1H, m), 2.82 (1H, t, $J = 7.5$ Hz), 2.27 (1H, m), 2.12 (1H, m), 1.93 (1H, m), 1.82 (3H, s), 1.12 (3H, d, $J = 7.0$ Hz), 1.08 (3H, d, $J = 7.0$ Hz); ^{13}C NMR ($CDCl_3$, 125 mHz) δ 177.72, 167.47, 85.89, 79.04, 71.94, 44.92, 42.49, 31.53, 28.24, 19.92, 19.74, 18.76. HRMS (ESI) calcd for $C_{12}H_{19}ClNO_4$ $[M + H]^+$: 276.1002; found: 276.1006. The β-lactone **3** prepared by the route shown in Scheme 1 was identical with a sample of **3** that had been synthesized in these laboratories by a different route (submitted for publication).