ORGANIC LETTERS

2008
Vol. 10, No. 7
1461−1463

Total Synthesis of (±)-Dysibetaine

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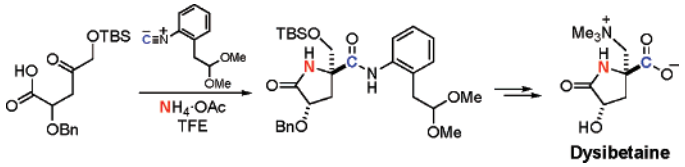
Received February 2, 2008

ABSTRACT



The marine natural product dysibetaine was synthesized in racemic form from a levulinic acid derivative using a convertible isocyanide and an ammonium acetate in the Ugi 4-center-3-component condensation reaction.

(−)-Dysibetaine (**1**) is a member of a group of natural products that were isolated by Sakai and co-workers in the late 1990s from the Micronesian sponge *Dysidea herbacea*.[1] It was first synthesized by Snider and Gu,[2] who also established the absolute stereochemistry of the natural product, and has been totally synthesized or studied synthetically by three other groups.[3] We were drawn to dysibetaine by its potential biological activity and because of our desire to employ the Ugi four-center three-component reaction, which, along with a recently developed convertible isocyanide **2**, would allow us to quickly assemble the cyclic pyroglutamic acid core from a linear precursor (Figure 1).

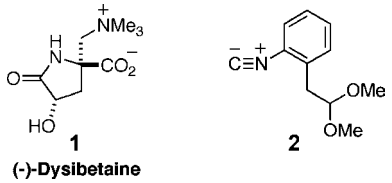


Figure 1. Structures of (−)-dysibetaine (**1**) and convertible isocyanide **2**.

The Ugi four-center three-component reaction (U4C-3CR)[4] has long been established as a useful method to create pyroglutamic acid amides from an amine, isocyanide and γ-ketoacid.[5] Until recently, however, it was not possible to elaborate the products to their corresponding carboxylic acid derivatives.[6] Using this technology, our laboratory reported a stereocontrolled formal total synthesis of omuralide that employed **2** as a convertible isocyanide in a U4C-3CR.[7] We now wish to report the application of this technology to the racemic total synthesis of dysibetaine.

Following the U4C-3CR, the amide derived from isocyanide **2** is readily converted to the corresponding *N*-acylindole, which is then easily hydrolyzed.[8] Indole formation dramatically alters the character of the amide by decreasing the double-bond character of the C−N amide bond and greatly weakens the bond. This, in turn, makes it possible to selectively cleave this amide bond to the corresponding ester under very mild conditions.

(1) (a) Sakai, R.; Oiwa, C.; Takaishi, K.; Kamiya, H.; Tagawa, M. *Tetrahedron Lett.* **1999**, *40*, 6941−6944. (b) Sakai, R.; Suzuki, K.; Shimamoto, K.; Kamiya, H. *J. Org. Chem.* **2004**, *69*, 1180−1185.

(2) Snider, B. B.; Gu, Y. *Org. Lett.* **2001**, *3*, 1761−1763.

(3) (a) Wardrop, D. J.; Burge, M. S. *Chem. Commun.* **2004**, 1230−1231. (b) Langlois, N.; Le Nguyen, B. K. *J. Org. Chem.* **2004**, *69*, 7558−7564. (c) Katoh, M.; Hisa, C.; Honda, T. *Tetrahedron Lett.* **2007**, *48*, 4691−4694.

(4) (a) Ugi, I.; Dömling, A. *Angew. Chem., Int. Ed.* **2000**, *39*, 3168−3210. (b) Dömling, A. *Chem. Rev.* **2006**, *106*, 17−89.

(5) (a) Short, K. M.; Mjalli, A. M. M. *Tetrahedron Lett.* **1997**, *38*, 359−362. (b) Harriman, G. C. B. *Tetrahedron Lett.* **1997**, *38*, 5591−5594. (c) Hanusch-Kompa, C.; Ugi, I. *Tetrahedron Lett.* **1998**, *39*, 2725−2728.

(6) (a) Isaacson, J.; Gilley, C. B.; Kobayshi, Y. *J.* Org. *Chem.* **2007**, *72*, 3913−3916. (b) Vamos, M.; Ozboya, K.; Kobayashi, Y. *Synlett* **2007**, 1595−1599. (c) Kreye, O.; Westermann, B.; Wessjohann, L. A. *Synlett* **2007**, 3188−3192.

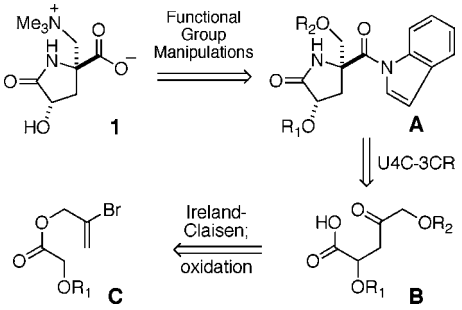
(7) Gilley, C. B.; Buller, M. J.; Kobayashi, Y. *Org. Lett.* **2007**, *9*, 3631−3634.

(8) Arai, E.; Tokuyama, H.; Linsell, M. S.; Fukuyama, T. *Tetrahedron Lett.* **1998**, *39*, 71−74.

10.1021/ol800245m CCC: $40.75
Published on Web 03/05/2008

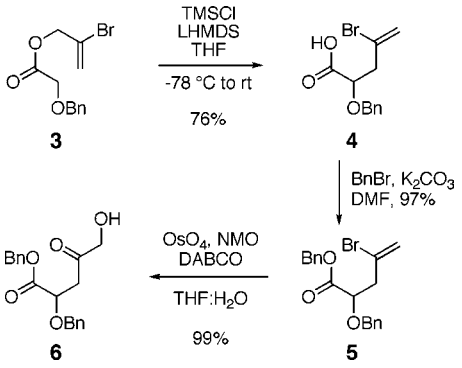
The plan for our synthesis of dysibetaine is shown in Scheme 1. From the natural product, a few functional group

Scheme 1. Retrosynthetic Analysis of Dysibetaine (**1**)



modifications lead retrosynthetically to the *N*-acylindole **A**. This activated intermediate, which is readily transformed to the corresponding ester, would be derived from a linear γ-ketoacid precursor **B** using the U4C-3CR and **2**. **B**, in turn, could be synthesized from 2-bromoallyl ester **C** via a sequence of Ireland−Claisen rearrangement followed by oxidation of the resulting *exo*-bromoolefin.

Scheme 2. Preparation of a Functionalized Levulinic Acid by Ireland−Claisen Rearrangement



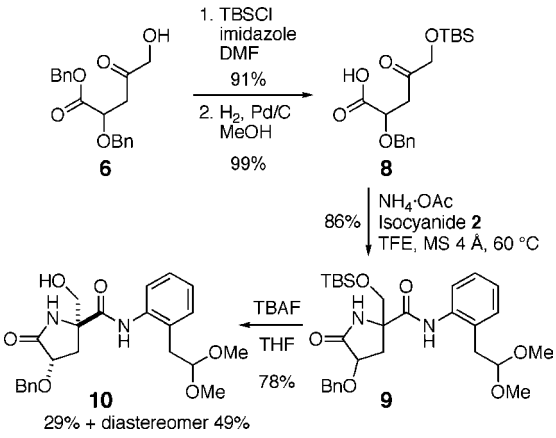
Scheme 2 shows the plan in action as we commenced by constructing the necessary γ-ketoacid precursor. Coupling commercially available 2,3-dibromopropene and benzyloxyacetic acid (not shown) using potassium carbonate in DMF provided ester **3** in 86% yield. Treating **3** with LHMDS in the presence of TMSCl affected the Ireland−Claisen rearrangement to yield acid **4** as a racemic mixture.[9] Benzyl protection of the carboxylic acid afforded **5**, which was then oxidized using the Upjohn method.[10] Dihydroxylation of the bromo-olefin allowed regiocontrolled installation of the ketone and alcohol functionalities in a single step, affording **6** in excellent yield.

(9) (a) Ireland, R. E.; Mueller, R. H.; Willard, A. K. *J. Am. Chem. Soc.* **1976**, *98*, 2868−2877. (b) Koch, G.; Janser, P.; Kottirsch, G.; Romero-Giron, E. *Tetrahedron Lett.* **2002**, *43*, 4837−4840.

(10) VanRheenen, V.; Kelly, R. C.; Cha, D. Y. *Tetrahedron Lett.* **1976**, *17*, 1973−1976.

Preparation of the γ-ketoacid **8** was completed by TBS-protection of the primary alcohol to give **7** (not shown). This was followed by selective hydrogenolysis of the benzyl ester, cleanly yielding the free acid (Scheme 3).

Scheme 3. Ugi Reaction of Levulinic Acid Derivative **8** to Afford Pyroglutamic Acid Amide **10**



The stage was now set for the U4C-3CR. The amine and isocyanide components were carefully chosen to ensure success later in the synthesis. We necessarily chose **2** as the isocyanide because the Ugi product amide derived from **2** is readily cleaved (vide infra). Although primary amines are most commonly used in the U4C-3CR, we have found that ammonium acetate works well in this reaction as an ammonia equivalent.[6] This eliminates the need for a later deprotection step that would likely require harsh conditions.[11] We believe that the intramolecular relationship between the ketone and acid in the γ-ketoacid prevents acetic acid from being incorporated as the acid component in the Ugi reaction, and no such product is ever observed. The U4C-3CR also proceeds smoothly using methanol as solvent, but our experience has shown that TFE gives better yields.

When the U4C-3CR was tried with the primary alcohol unprotected (obtained by hydrogenation of **6**), the yield was greatly diminished (26%). When the reaction was tried with the secondary alcohol unprotected (obtained by thorough hydrogenation of **7**), a similar decrease in yield was seen. We therefore decided on the fully protected γ-ketoacid **8** and were satisfied to obtain the Ugi product **9** in 86% yield as a mixture of diastereomers.

Moving forward, the TBS group of the Ugi product **9** was removed using TBAF in THF and at this stage the diastereomers were readily separated by silica gel chromatography to give **10** as a single racemic diastereomer. X−ray analysis revealed that the minor isomer, **10**, which is less polar by TLC, was the isomer needed to reach dysibetaine. The results of the X−ray analysis of **10** are included in Figure 2.[12]

(11) Corey, E. J.; Li, W.; Nagamitsu, T. *Angew. Chem., Int. Ed.* **1998**, *37*, 1676−1679.

(12) Please see Supporting Information for complete X-ray crystal data.

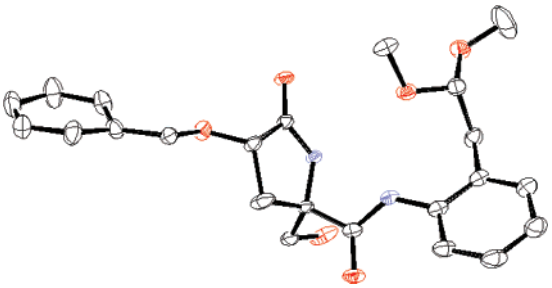
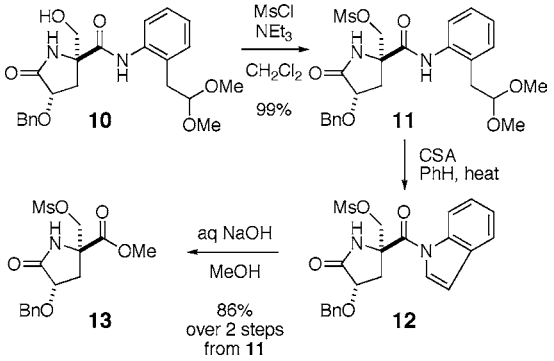


Figure 2. ORTEP projection of X-ray crystal structure of **10**.

With **10** in hand, we were ready for the final functional group manipulations needed to reach (±)-dysibetaine (**1**). The primary alcohol in **10** (Scheme 4) was protected as the

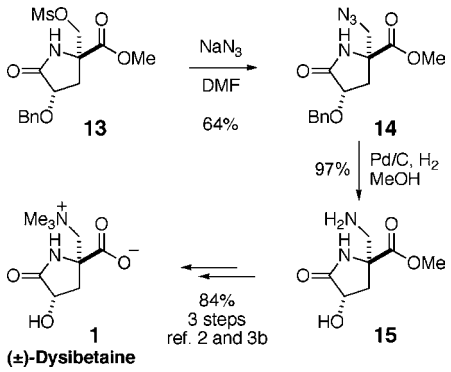
Scheme 4. Methanolysis of the Anilide **10** via *N*-Acylindole **12**



mesylate using MsCl and Et_3N in dichloromethane to give **11**. Hydrolysis of the external amide of **11** is a formidable task due to the presence of another amide in the molecule. It is further complicated by the presence of an adjacent, fully substituted carbon center. Fortunately, the inclusion of **2** as the isocyanide in the U4C-3CR provides a facile solution to the problem. Heating **11** with CSA in benzene for less than an hour affords the *N*-acylindole **12**. Methanolysis to **13** was achieved using only a catalytic amount of aqueous sodium hydroxide. The amide hydrolysis is notable for the mild, selective conditions, compared to the very strong acid or base/refluxing conditions that would normally be used.

Scheme 5 illustrates the final steps toward the synthesis of (±)-dysibetaine (**1**). Mesylate **13** was heated in DMF with sodium azide to afford azide **14** in 64% yield (plus 21% recovered starting material). Palladium−charcoal hydrogenation of **14** allowed concomitant deprotection of the benzyl

Scheme 5. Completion of Total Synthesis of (±)-Dysibetaine (**1**)



ether and reduction of the azide to the corresponding amine **15**, which matched the corresponding synthetic intermediate reported by the Langlois group.[3b] **15** was elaborated to the final product using the three step procedure devised for the corresponding ethyl ester by Snider,[2] consisting of Clarke−Eschweiler dimethylation of the amine followed by quaternization with iodomethane and cleaveage of the methyl ester using basic resin.[3b] We thus arrived at (±)-dysibetaine (**1**) in 16 steps and 9% overall yield from commercially available materials. The ^1H and ^{13}C NMR spectra of the synthetic material corresponded closely to those reported for the natural product.[1]

We have completed a total synthesis of the biologically interesting molecule (±)-dysibetaine (**1**) using the Ugi four-center three-component reaction and a recently developed cleavable isocyanide **2**. The present synthesis also revealed that a more efficient synthesis could be achieved by incorporating the amine into the γ-ketoacid before the Ugi reaction and by finding a more efficient synthesis of the necessary γ-ketoacid precursor. Using these lessons, an asymmetric synthesis of dysibetaine is underway and will be reported in due course.

Acknowledgment. We acknowledge Dr. Yongxuan Su of the UCSD Mass Spectrometry Facility as well as Dr. Antonio DiPasquale and Professor Arnold Rheingold of the UCSD Small Molecule X−Ray Facility. We also thank Cynthia Gilley (UCSD) for her experimental help at the preliminary stage.

Supporting Information Available: Detailed experimental prodcedure, copies of ^1H and ^{13}C NMR spectra, and CIF file for compound **10**. This material is available free of charge via the Internet at http://pubs.acs.org.

OL800245M