Natural Product Synthesis

DOI: 10.1002/anie.200805709

An Ugi Reaction in the Total Synthesis of (−)-Dysibetaine**

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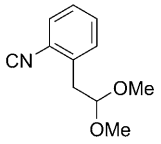
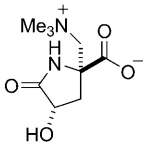
The Ugi reaction has been extensively used by chemists because of its unique ability to generate complex products from diverse starting materials in a single step. The four-component condensation brings together an amine, a carboxylic acid, a ketone or aldehyde, and an isocyanide functionality to yield an α-acylaminoamide.[1] The wide variability of the components makes the Ugi reaction an attractive tool for both diversity-oriented and target-oriented synthesis.[2] When two of the components, for example a ketone and a carboxylic acid functionality, are incorporated into a single molecule, cyclic products are formed.[3,1a] We previously showed that incorporation of convertible isocyanide **1** into this type of Ugi 4-center-3-component cyclization reaction (U4C-3CR) is an efficient method for the synthesis of pyroglutamic acid analogues[4] and therefore sought to apply this reaction to the stereocontrolled total synthesis of the marine natural product (−)-dysibetaine (**2**). In the course of synthesizing **2** we discovered a unique and unusual Ugi reaction in which an ester functions as the carboxylic acid component in the reaction.



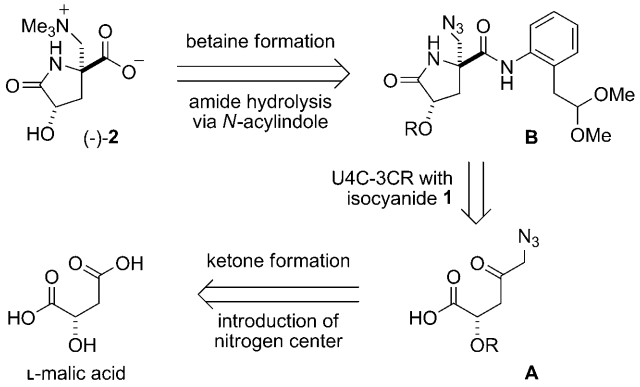
convertible isocyanide **1**



(−)-dysibetaine (**2**)

(−)-Dysibetaine (**2**) is a member of a group of natural products that were isolated by Sakai et al. in the late 1990s from the Micronesian sponge *Dysidea herbacea*.[5] We were initially drawn to **2** by its potential neuroexcitotoxin activity and because it is an attractive target for taking full advantage of the U4C-3CR. We recently reported a racemic synthesis of the molecule,[6] and it has been synthesized or studied synthetically by various other research groups,[7] notably by Snider and Gu,[8] who completed the first total synthesis and established the absolute stereochemistry of the molecule.

Scheme 1 outlines the retrosynthetic plan that we initially envisioned for the synthesis of **2**. The synthesis can be broken down into three distinct phases, the first of which is the enantioselective synthesis of the necessary γ-ketoacid **A**, with the masked amine already installed. L-Malic acid is the natural choice for the starting material because it contains the necessary stereocenter and the carbon framework is sufficiently oxidized. The second phase is the stereocontrolled formation of **B** through a multiple functional group condensation/cyclization reaction, specifically the U4C-3CR. The final challenges in our synthesis will be selective cleavage of the amide bond and the unveiling of the betaine moiety.



Scheme 1. Retrosynthetic analysis of (−)-dysibetaine (**2**).

In complex syntheses, a key factor underlying the utility of the Ugi reaction is the ability to make further, successful modifications to the products derived from the reaction. To reach **2** it is necessary to selectively cleave one of the two amide groups in intermediate **B**, both formed during the U4C-3CR (Scheme 1). Compound **1** was therefore chosen as the isocyanide because after the Ugi reaction the amide group resulting from **1** is readily converted into *N*-acylindole, which is hydrolyzed with mild reaction conditions.[9]

The first problem to overcome in this synthesis was the elaboration of L-malic acid to the necessary γ-ketoacid **A**. In the past, we have had success on similar molecules using (trimethylsily)diazomethane to elaborate a succinic acid derivative to the corresponding ketone moiety.[4a] However, attempts to apply the same chemistry to various protected L-malic acid monoester derivatives failed, possibly as a result of the intramolecular participation of the alcohol (protected or unprotected) with the intermediate diazoketone[10]—although no such products were recovered. Fortunately, we found that this problem had been solved by using the strongly electron-

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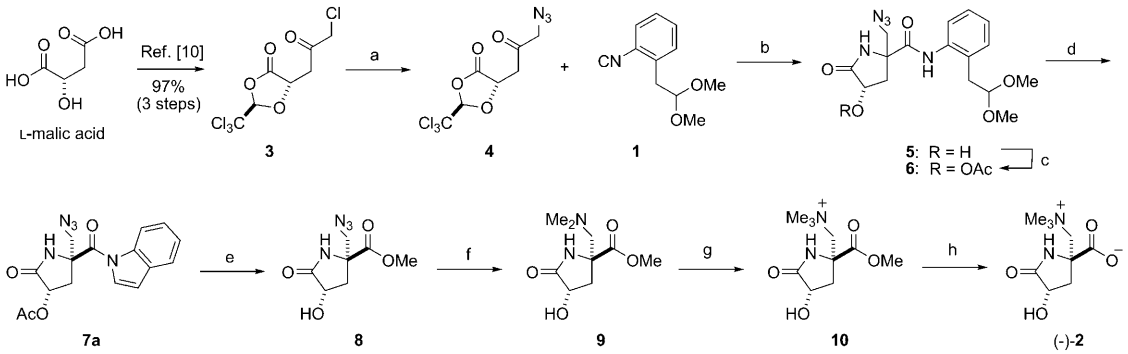
[**] We thank the University of California for financial support as well as the UCSD Mass Spectrometry Facility and UCSD Small Molecule X-Ray Facility.

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/anie.200805709.



Scheme 2. Synthesis of (−)-dysibetaine (**2**). a) NaN_3 (2 equiv), NaI (1 equiv), acetonitrile, RT, 1.5 h (99%); b) **1** (1 equiv), **4** (1.5 equiv) HMDS (6 equiv), HFIP, RT, 18 h (85%); c) Ac_2O (12 equiv), pyridine (10 equiv), CH_2Cl_2, RT, 24 h (92%); d) CSA (0.2 equiv), benzene, 60°C, 1.5 h (**7a**: 29% and diastereomer **7b**: 50%); e) 1 M aq NaOH (0.03 equiv), MeOH, RT, 36 h (62%); f) 37% aq CH_2O (10 equiv), H_2, Pd/C, 1 M aq HCl (1 equiv), MeOH, RT, 18 h; then $NaHCO_3$(s) (99%); g) MeI (40 equiv), THF, RT, 24 h (84%); h) Dowex 550A, MeOH (100%). CSA = (±)-camphorsulfonic acid, THF = tetrahydrofuran.

withdrawing chloral-derived protecting group.[11] The resulting α-chloroketone **3** was transformed into **4** in good yield using the reaction conditions shown in Scheme 2.

With **4** in hand the task before us now was to successfully elaborate that molecule into a suitable γ-ketoacid, such as **A** (Scheme 1). However, various problems presented themselves which made it difficult to incorporate **4** into a successful synthesis of **2** when beginning with the removal of the chloral group. Although the chloral group is a common protecting group for diols,[12] there is little precedent for using it to protect an β-hydroxy acid such as in **4**. The common method for removal of a chloral protecting group involves reduction with zinc to remove chlorine before deprotection occurs[12]—reaction conditions that are incompatible with both **3** and **4**. We could convert **4** into the corresponding free-alcohol/methyl ester (not shown) by treating it with a variety of bases in methanol, but yields varied widely and were not reproducible.

A key to the success of our overall strategy is the ability to reach the Ugi reaction in a reasonable number of steps. Numerous other problems were encountered while trying to elaborate **4** into a suitable γ-ketoacid, they include an excessive number of steps and low yields. Finally, we decided to submit **4** directly to the conditions of the Ugi 4-center-3-component cyclization reaction. Pleasingly, **5** did form, revealing that the Ugi reaction can take place directly from the ester **4**. Reaction conditions were eventually developed to make this a synthetically viable step. This unique Ugi reaction is discussed in more detail below.

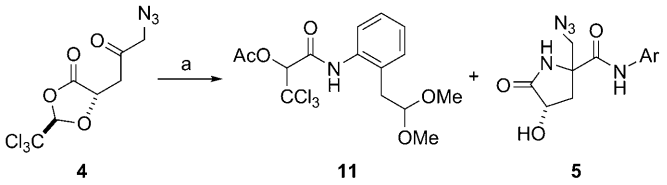
With a straightforward pathway to the Ugi product available, we could now focus on the elaboration of **5** into the natural product. The free alcohol in **5** was acetylated in high yield to afford **6** (Scheme 2). Upon treatment with catalytic acid, **6** cleanly converted into the corresponding *N*-acylindole. At this point the two diastereomers could be separated to give **7a** and **7b** (not shown).[13] X-Ray analysis of the major diastereomer (**7b**) revealed that the minor diastereomer (**7a**) is the one required to reach **2**.[14] It was possible to form the indole directly from **7**; however acetylation of the free alcohol was necessary to separate the diastereomers.

Indole formation provided the activation needed for the selective cleavage of the amide bond, and treatment of **7a** with a catalytic amount of NaOH (aq) in methanol afforded methyl ester **8** with concomitant removal of the acetate ester. As a testament to the ease of amide cleavage, TLC analysis indicated that cleavage of the amide bond was very fast (taking only a few minutes), meanwhile the acetate ester group was removed much more slowly.

We were now ready to take **8** through the final steps needed to reach **2**. Previous syntheses suggested a stepwise reduction of the azide in **8** and subsequent Clarke–Eschweiller methylation of the resulting amine group under high pressure.[7b,8] We found that these steps were easily completed in one pot under H_2 at atmospheric pressure to give **9** in good yield. The final steps followed existing procedures.[7b,8] Quaternization of the amine group using methyl iodide gave **10**, and subsequent hydrolysis with basic resin gave the natural product (−)-dysibetaine (**2**), the spectral properties of which matched with the natural product and our own previous work.[5a,6] The synthesis was completed in 12 steps in the longest linear sequence and in just 11 steps from L-malic acid.

The key to the success of this synthesis was the unique Ugi reaction in which an ester functions as the carboxylic acid component. This is particularly surprising because the acid component is believed to act as a Brønsted acid by activating the Schiff base to react with the isocyanide.[1a] This result is not completely without precedence, however, as amides have been known to participate in similar intramolecular multicomponent reactions (MCRs).[15] We initially chose ammonium acetate as the amine source and **1** as the isocyanide, with 2,2,2-trifluoroethanol (TFE) as the solvent. The desired Ugi product did form, albeit in very low yield. The major product recovered from the reaction was the Passerini adduct of chloral **11**, acetic acid, and **1** (Scheme 3). To eliminate the possibility of **11** forming we chose to use 1,1,1,3,3,3-hexamethyldisilazane (HMDS), which has been used previously as an ammonia equivalent in MCRs.[4a,16] Compound **4** was then converted into the desired Ugi product **5** as a mixture of diastereomers, although with unsatisfactory yield.

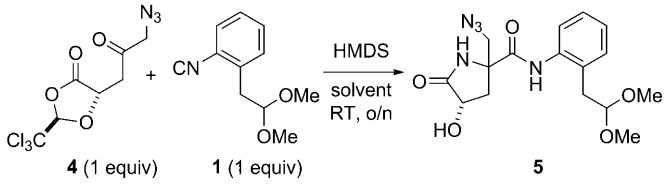
A screen of typical organic solvents as well as a range of alcohols, acetic acid, and water revealed that the only other



Scheme 3. Reagents and conditions: a) **1** (1 equiv), NH_4OAc (2 equiv), TFE, RT, 16 h (**11**: 80% and **5**: 18%). Ar = 2-(2,2-dimethoxyethyl)-phenyl.

solvent conducive to this reaction was 1,1,1,3,3,3-hexafluoroisopropanol (HFIP), which was found to be the best choice. While attempting to improve the yield through modified reaction conditions, we noticed that additional equivalents of HMDS lowered the yield when TFE was the solvent, but improved the yield when HFIP was used. The results of these experiments are summarized in Table 1.

Table 1: Effect of changing the amount of the amine component (HMDS) with varying the solvent between TFE and HFIP.



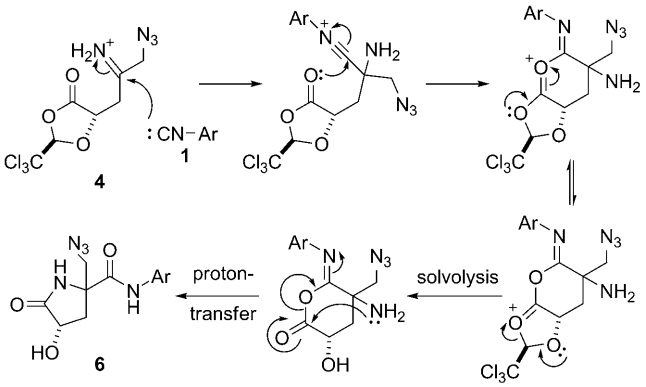
4 (1 equiv) **1** (1 equiv) **5**

Solvent	HMDS [equiv]	Yield of **5** [%]
F_3C OH	1	33
	2	29
	3	21
	4	17
OH F_3C CF_3	1	25
	2	40
	3	52
	4	59

This difference between solvents gives us insight into the mechanism. In the case of TFE, **4** is decomposed by the solvent and this effect is increased when more HMDS is added. HFIP, however, is a non-nucleophilic solvent.[17] As the solvent cannot react with the chloral-protected ester in **4**, we can rule out any mechanism involving such interactions.

We therefore propose a mechanism in which the newly formed keto imine reacts with isocyanide **1** to give an activated intermediate that can then react directly with the activated ester group. Mumm rearrangement[1a] and subsequent solvolysis of the chloral protecting group then leads directly to **6** (Scheme 4). The chloral protecting group was originally chosen to inhibit intramolecular participation of the thusly protected alcohol with a diazoketone intermediate. It is therefore remarkable that the same protecting group allows the intramolecular participation of the ester in the Ugi reaction.

After screening a variety of reaction conditions, it was determined that the best yield of **6** was obtained by using the following conditions: **1** (1 equiv), **4** (1.5 equiv), and HMDS (6 equiv) in HFIP. Unfortunately, none of the reaction



Scheme 4. Proposed mechanism of the U4C-3CR between **4** and **1**.

conditions screened yielded **6** with better than 3:2 diastereoselectivity. While a diastereoselective Ugi reaction continues to be an underlying goal for us, a general solution to this problem remains elusive.

Our research group has previously reported a racemic, 16-step synthesis of (−)-dysibetaine by using the U4C-3CR.[6] The current stereoselective synthesis allowed us to access the natural product in just 11 steps and in 11% overall yield from L-malic acid. Employing **1** as the isocyanide and HMDS as the amine in the cyclization reaction allowed the Ugi product to be elaborated to (−)-dysibetaine using mild reaction conditions. A key to the success of this synthesis was the discovery that the activated ester **4**, containing the necessary carbon and heteroatom framework, could successfully participate in the Ugi 4-center-3-component cyclization reaction.

Received: November 21, 2008
Published online: January 27, 2009

Keywords: betaines · isocyanides · natural products · total synthesis · Ugi reaction

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[13] See the Supporting Information for full data and experimental details.
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