Cascade Cyclization, Dipolar Cycloaddition to Bridged Tricyclic Amines Related to the *Daphniphyllum* Alkaloids
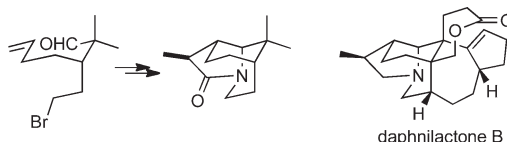
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ABSTRACT

daphnilactone B

A tandem one-pot reaction of an aldehyde with a primary amine involving condensation and then cyclization (*N*-alkylation), followed by intramolecular dipolar cycloaddition of the resulting nitrone or azomethine ylide, provides a synthesis of bridged tricyclic amines. The reaction was most successful using hydroxylamine, and when the dipolarophile was an unsaturated ester, subsequent reduction of the N–O bond and cyclization to the lactam provided the core ring system of the yuzurimine, daphnilactone B, and bukittinggine type *Daphniphyllum* alkaloids.

The *Daphniphyllum* alkaloids are a large and growing group of complex natural products. There are several structural types of these alkaloids, including the daphniphylline, secodaphniphylline, yuzurimine, yuzurine, daphnilactone A, daphnilactone B, bukittinggine, daphnezomine, daphnicyclidin, daphmanidin, daphniglaucin, calyciphyllin, and paxdaphnine alkaloids.[1] Other than an inspired biomimetic synthesis of some of the members of these alkaloids,[2] there are only a few approaches to the core ring systems of these structurally complex alkaloids.[3]

We have recently reported an efficient entry to tricyclic products by a cascade of condensation, cyclization, and then cycloaddition.[4] This chemistry has allowed access to fused tricyclic products, and we wondered if a similar approach would be successful for the synthesis of bridged tricyclic compounds, as found in many *Daphniphyllum* alkaloids. For example, yuzurimine B, daphnilactone B, and bukittinggine have a bridged core ring system, of which compound **1** is representative (Scheme 1). Denmark and co-workers have reported some elegant cascade cycloaddition–cycloaddition chemistry for the preparation of the core of daphnilactone B.[3a] Disconnection of the core ring system **1** to the aldehyde **2** would allow us to probe whether our cascade cyclization–cycloaddition chemistry would be amenable to the synthesis of the core bridged ring system of these alkaloids. In this paper we report our successful preliminary results using such chemistry.

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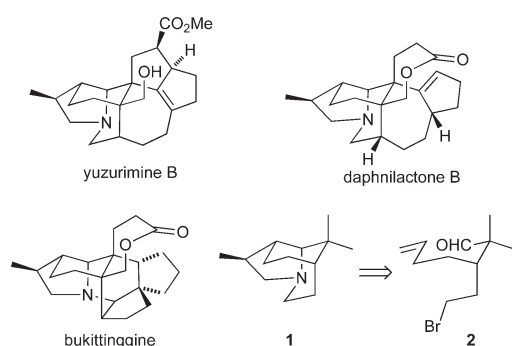[‡] Eli Lilly and Company.

(1) (a) Kobayashi, J.; Kubota, T. *Nat. Prod. Rep.* **2009**, *26*, 936. (b) Dong, M.; Zhang, M. L.; Shi, Q. W.; Gu, Y. C.; Kiyota, H. *Curr. Org. Chem.* **2009**, *13*, 646. (c) Kobayashi, J.; Morita, H. In *The Alkaloids*; Cordell, G. A., Ed.; Academic Press: San Diego, 2003; Vol. 60, pp 165–205.

(2) (a) Heathcock, C. H.; Hansen, M. M.; Ruggeri, R. B.; Kath, J. C. *J. Org. Chem.* **1992**, *57*, 2544. (b) Heathcock, C. H.; Stafford, J. A. *J. Org. Chem.* **1992**, *57*, 2566. (c) Heathcock, C. H.; Stafford, J. A.; Clark, D. L. *J. Org. Chem.* **1992**, *57*, 2575. (d) Heathcock, C. H.; Ruggeri, R. B.; McClure, K. F. *J. Org. Chem.* **1992**, *57*, 2585. (e) Heathcock, C. H.; Kath, J. C.; Ruggeri, R. B. *J. Org. Chem.* **1995**, *60*, 1120.

(3) (a) Denmark, S. E.; Baiazitov, R. Y.; Nguyen, S. T. *Tetrahedron* **2009**, *65*, 6535. (b) Denmark, S. E.; Nguyen, S. T.; Baiazitov, R. Y. *Heterocycles* **2008**, *76*, 143. (c) Denmark, S. E.; Baiazitov, R. Y. *J. Org. Chem.* **2006**, *71*, 593. (d) Ueda, M.; Walczak, M. A. A.; Wipf, P. *Tetrahedron Lett.* **2008**, *49*, 5986. (e) Solé, D.; Urbaneja, X.; Bonjoch, J. *Org. Lett.* **2005**, *7*, 5461. (f) Cordero-Vargas, A.; Urbaneja, X.; Bonjoch, J. *Synlett* **2007**, 2379. (g) Ikeda, S.; Shibuya, M.; Kanoh, N.; Iwabuchi, Y. *Org. Lett.* **2009**, *11*, 1833. (h) Tanabe, K.; Fujie, A.; Ohmori, N.; Hiraga, Y.; Kojima, S.; Ohkata, K. *Bull. Chem. Soc. Jpn.* **2007**, *80*, 1597.

(4) (a) Coldham, I.; Burrell, A. J. M.; White, L. E.; Adams, H.; Oram, N. *Angew. Chem., Int. Ed.* **2007**, *46*, 6159. (b) Burrell, A. J. M.; Coldham, I.; Watson, L.; Oram, N.; Pilgram, C. D.; Martin, N. G. *J. Org. Chem.* **2009**, *74*, 2290. (c) Burrell, A. J. M.; Coldham, I.; Oram, N. *Org. Lett.* **2009**, *11*, 1515. (d) Burrell, A. J. M.; Watson, L.; Martin, N. G.; Oram, N.; Coldham, I. *Org. Biomol. Chem.* **2010**, *8*, 4530.

Scheme 1. Some *Daphniphyllum* Alkaloids and Disconnection of the Core Bridged Tricyclic Amine

yuzurimine B

daphnilactone B

bukittinggine

Scheme 2. Synthesis of Aldehyde **2**

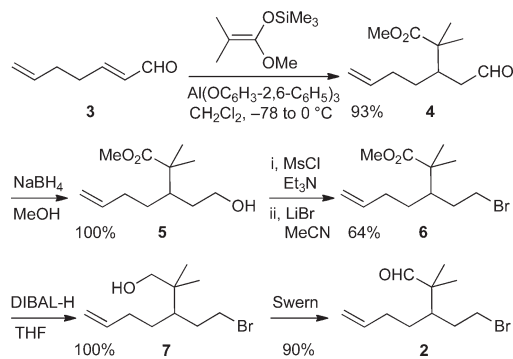**Scheme 3.** Treatment of Aldehyde **2** with Amines

Our cascade strategy relies on the ability to form a 1,3-dipole from an aldehyde using a condensation with a primary amine and in situ cyclization (*N*-alkylation) of the imine.[5] This is followed by dipolar cycloaddition with an alkene. For the core of these *Daphniphyllum* alkaloids, we needed access to the aldehyde **2** to test this chemistry. This has a one-carbon bridging atom between the aldehyde and the branch-point for the alkyl halide and the dipolarophile, and we chose this bridging atom to have a *gem*-dimethyl group to mimic the natural products and to avoid problems of diastereomers of the substrate and potential enolization or enamine formation on reaction of the aldehyde and amine.
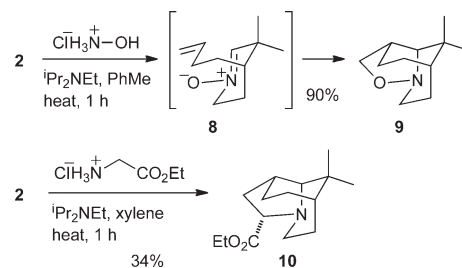
The aldehyde **2** was prepared as shown in Scheme 2. Our strategy involved conjugate addition to the known unsaturated aldehyde **3**,[6] using the method of Yamamoto and co-workers with a silyl ketene acetal in the presence of a bulky Lewis acid catalyst.[7] This gave the aldehyde **4** selectively by 1,4- rather than 1,2-addition. The aldehyde **4** was reduced (in the presence of the ester) to the alcohol **5** with NaBH₄.[8] Care must be taken to avoid heat or traces of the aluminum catalyst from the previous step, as otherwise cyclization to the lactone occurs readily. Conversion of the alcohol **5** to the bromide **6** was achieved via the intermediate mesylate. Finally, reduction of the ester to the alcohol **7** and then Swern oxidation gave the aldehyde **2**.

We were pleased to find that heating aldehyde **2** with hydroxylamine hydrochloride and ^{i}Pr₂NEt in toluene gave the desired bridged tricyclic product **9** as a single isomer in

high yield (Scheme 3). This product must arise from condensation to give the oxime, cyclization with formation of the nitrone **8**, and then intramolecular cycloaddition. However, heating the aldehyde **2** with glycine in toluene or xylene failed to give any of the desired pyrrolidine product resulting from the expected azomethine ylide intermediate. Heating with glycine ethyl ester gave a mixture of products containing some of the desired cycloadduct **10**, formed as a single stereoisomer (stereochemistry determined by ^{1}H NOESY experiments) resulting from cycloaddition through the expected S-shaped ylide.[9]

The low yields for the reactions of the azomethine ylides are probably due to their slow reaction with an unactivated alkene combined with the requirement for the alkenyl tether to be located in a pseudoaxial position for successful cycloaddition. Therefore, we anticipated that direct formation of the desired product **1** (by cycloaddition of the azomethine ylide generated using glycine and a *Z*-methyl-substituted alkene) would be unsuccessful. To increase the rate of cycloaddition, an electron-withdrawing group could be located on the alkene. To test this, the aldehydes **11** and **12** were prepared by cross metathesis of **2** with phenyl vinyl sulfone or methyl acrylate, catalyzed by Grubbs' second generation catalyst (Scheme 4). The activated substrate **11** did undergo the in situ condensation, cyclization, and cycloaddition using glycine to give the tricyclic product **13**; however the yield was very poor. An

(5) For related chemistry, see: (a) Pearson, W. H.; Stoy, P.; Mi, Y. *J. Org. Chem.* **2004**, *69*, 1919. (b) Pearson, W. H.; Kropf, J. E.; Choy, A. L.; Lee, I. Y.; Kampf, J. W. *J. Org. Chem.* **2007**, *72*, 4135. (c) Dondas, H. A.; Grigg, R.; Hadjisoteriou, M.; Markandu, J.; Thomas, W. A.; Kennewell, P. *Tetrahedron* **2000**, *56*, 10087. (d) Coldham, I.; Jana, S.; Watson, L.; Pilgram, C. D. *Tetrahedron Lett.* **2008**, *49*, 5408. (e) Yeom, H.-S.; Lee, J.-E.; Shin, S. *Angew. Chem., Int. Ed.* **2008**, *47*, 7040. (f) Lévesque, F.; Bélanger, G. *Org. Lett.* **2008**, *10*, 4939. (g) Coldham, I.; Jana, S.; Watson, L.; Martin, N. G. *Org. Biomol. Chem.* **2009**, *7*, 1674.
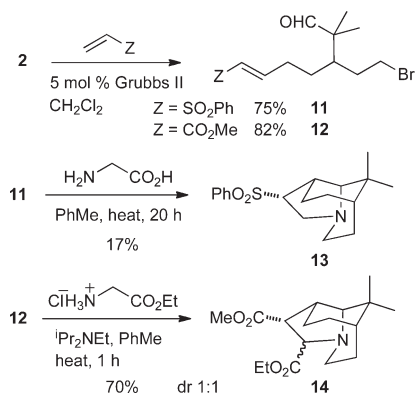
(6) (a) Bestmann, H. J.; Koschatzky, K. H.; Platz, H.; Suess, J.; Vostrowsky, O.; Knauf, W.; Burghardt, G.; Schneider, I. *Liebigs Ann.* **1982**, 1359. (b) Whittaker, M.; McArthur, C. R.; Leznoff, C. C. *Can. J. Chem.* **1985**, *63*, 2844.

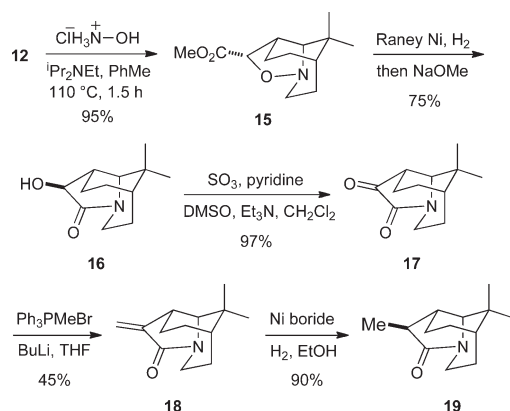(7) Maruoka, K.; Imoto, H.; Saito, S.; Yamamoto, H. *J. Am. Chem. Soc.* **1994**, *116*, 4131.

(8) For a related sequence of reactions starting with an aldehyde-ester, see: Cheney, D. L.; Paquette, L. A. *J. Org. Chem.* **1989**, *54*, 3334.

(9) (a) Coldham, I.; Hufton, R. *Chem. Rev.* **2005**, *105*, 2765. (b) Burrell, A. J. M.; Coldham, I. *Curr. Org. Synth.* **2010**, *7*, 312.

Scheme 4. Cross Metathesis and Cyclization/Cycloaddition

Scheme 5. Cyclization/Cycloaddition Using Hydroxylamine

Figure 1. X-ray structures of the products **16** and **19**.

was not verified at this stage. This product was treated with Raney nickel and then sodium methoxide in methanol (to complete the partial cyclization) to give the lactam **16**. The stereochemistry of this compound was confirmed by single crystal X-ray structure analysis (Figure 1). This was the expected stereoisomer based on the anticipated concerted cycloaddition across the *E*-alkene **12** (to give isomer **15**). Oxidation of the alcohol **16** gave the ketone **17**, and Wittig reaction gave the alkene **18**.[10] Finally, reduction of the alkene with $Ni(OAc)_2 \cdot 4H_2O/NaBH_4$ under an atmosphere of hydrogen gave the desired ring system **19**, as a single stereoisomer. An X-ray single crystal structure of product **19** (Figure 1) confirmed the configuration of the methyl group, which matches that of the *Daphniphyllum* alkaloids.

In summary, cascade chemistry involving condensation, cyclization, and then intramolecular dipolar cycloaddition has been extended successfully to bridged tricyclic products. This has allowed the synthesis of the core bridged ring system of the yuzurimine, daphnilactone B, and bukittinggine type alkaloids.

Supporting Information Available. Experimental procedures, spectroscopic data, and copies of NMR spectra for the products **2−7**, **9−19**, and X-ray structures for **16** (CCDC 802281) and **19** (CCDC 802282). This material is available free of charge via the Internet at http://pubs.acs.org.

(10) For a related sequence of reactions, see ref 3c.

attempted reaction of the activated substrate **12** with glycine was unsuccessful (decomposition). However, with glycine ethyl ester, the tricyclic products **14** were obtained in good yield. These were formed as a mixture of stereoisomers at the carbon center bearing the ethyl ester group. Cycloaddition through the S-shaped ylide may be less favored in this case due to a steric clash with the methyl ester in the transition state.

Heating the aldehyde **12** with hydroxylamine in toluene gave the cycloadduct **15** in excellent yield (Scheme 5). A si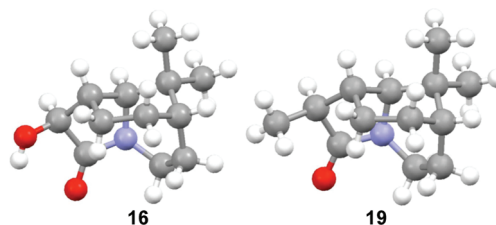ngle isomer was formed, although the stereochemistry