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Enantioselective Total Synthesis of (−)-Dehydrobatzelladine C

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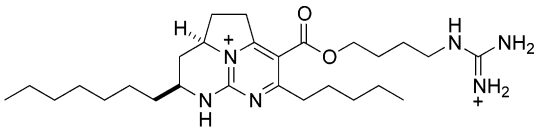
ABSTRACT



(−)-dehydrobatzelladine C

The oxidation of two tethered Biginelli adducts was examined as a potential key step in total syntheses of highly oxidized batzelladine and crambescidin alkaloids. Although angular hydroxyl substitution could not be introduced, dehydrogenation was readily accomplished. This latter conversion is a key step in the first total synthesis of dehydrobatzelladine C.

A variety of structurally intricate guanidine alkaloids are present in marine sources.[1] Among the most notable of these are the crambescidin[2] and batzelladine[3] alkaloids, which have been isolated primarily from sponges belonging to the orders Poecilosclerida and Axinellida.[1] Diverse biological activities have been reported for these secondary metabolites, including cytotoxicity toward several cancer cell lines, antifungal and antiviral activities, and inhibition of HIV-1 fusion.[1,4] The novel structures of these marine alkaloids have inspired the development of many strategies for assembling polycyclic guanidines that contain the octahydro-5,6,6a-triazaacenaphthalene (**1**) and hexahydro-5,6,6a-triazaacenaphthalene (**2**) moieties common to the crambescidin and batzelladine alkaloids.[1,5,6]

Intramolecular variants of the Biginelli condensation[7] have been developed in our laboratories for the synthesis of crambescidin[6] and batzelladine[8] alkaloids as well as simplified congeners.[9] In this communication, we report our preliminary efforts to access rare members of the crambescidin family that possess either angular hydroxyl substitution on the central tricyclic octahydro-5,6,6a-triazaacenaphthalene fragment such as crambescidin 816 (**4**) or a tetrahy-

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dro-5,6,6a-triazaacenaphthalene moiety (**3**) such as that found in crambidine (**5**)[10] and dehydrobatzelladine C (**6**).[11] The total synthesis of (−)-dehydrobatzelladine C (**6**) achieved during these investigations constitutes the first total synthesis of a member of the crambescidin or batzelladine families that contains the tetrahydro-5,6,6a-triazaacenaphthalene fragment.

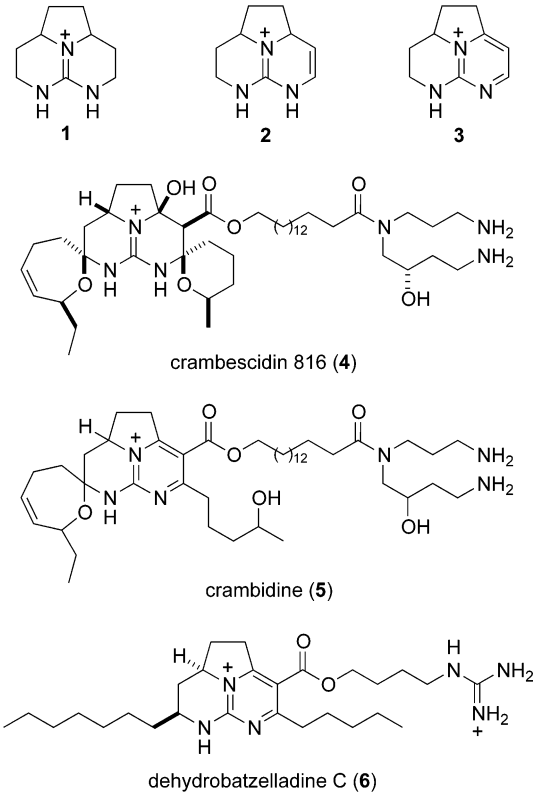
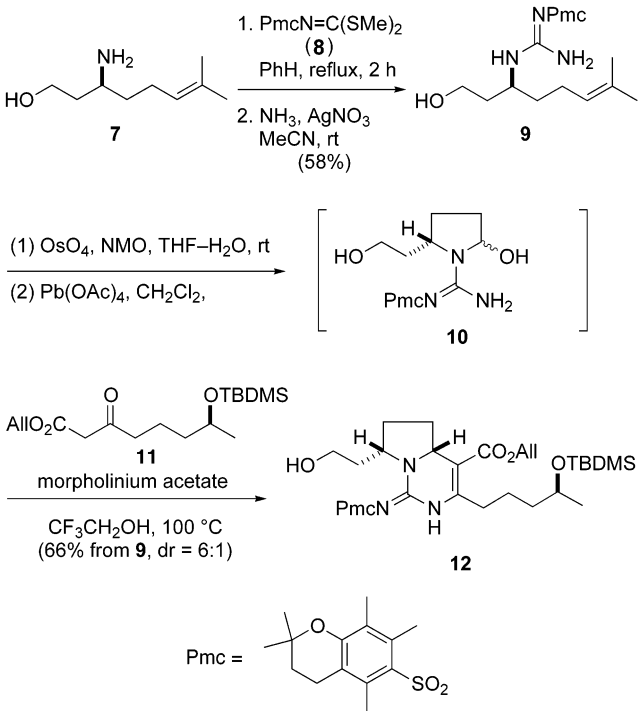


Figure 1. Representative polycyclic guanidine alkaloids containing hydro-5,6,6a-triazaacenaphthalene fragments.

1-Oxo- or 1-iminohexahydropyrrolo[1,2-*c*]pyrimidine carboxylic esters were key intermediates in our earlier total syntheses of crambescidin alkaloids.[6,7] In this investigation, we first prepared an *N*-sulfonyl-protected version of the latter intermediate, **12**,[12] which we hoped could be selectively hydroxylated at the angular carbon β to the ester substituent (Scheme 1). The 2,2,5,7,8-pentamethylchroman-6-sulfonyl (Pmc) guanidine fragment was introduced in two steps by sequential reaction of amino alcohol **7**[6c] with carboimidodithioate **8** and ammonia.[13] Oxidative cleavage of the double bond of **9**, followed by tethered Biginelli condensation of the resulting crude product **10** with β-ketoester **11**, provided sulfonyliminopyrrolopyrimidine **12** in 66% yield from **9**.[14]

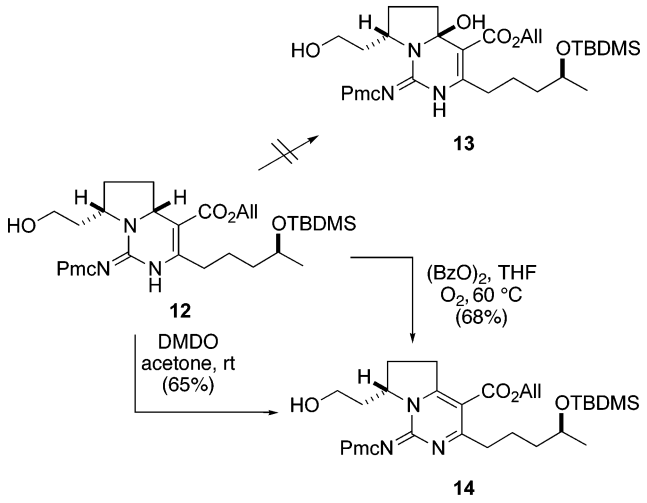
We explored oxidation of **12** with a variety of agents. Unfortunately, all attempts to convert **12** to **13** by reaction

Scheme 1. Synthesis of Pmc-Protected 1-Imino-hexahydropyrrolo[1,2-*c*]pyrimidine Carboxylic Ester **12**



of the former with reagents such as $Pb(OAc)_4$, H_2O_2, *t*-BuO_2H, SeO_2, RuO_2, or DDQ, under a variety of reaction conditions, were unsuccessful (Scheme 2).[15] Only the reaction

Scheme 2. Oxidation of **12**



of **12** with dimethyldioxirane or benzoyl peroxide delivered a clean product, in these cases the didehydro derivative **14**. This dehydrogenation of **12** suggested a straightforward way to synthesize alkaloids such as **5** or **6** that contain a 2-aminopyrimidinium unit.[16]

Dehydrobatzelladine C (**6**) was chosen as our initial target (Scheme 3). The total synthesis of **6** began by DMAP-

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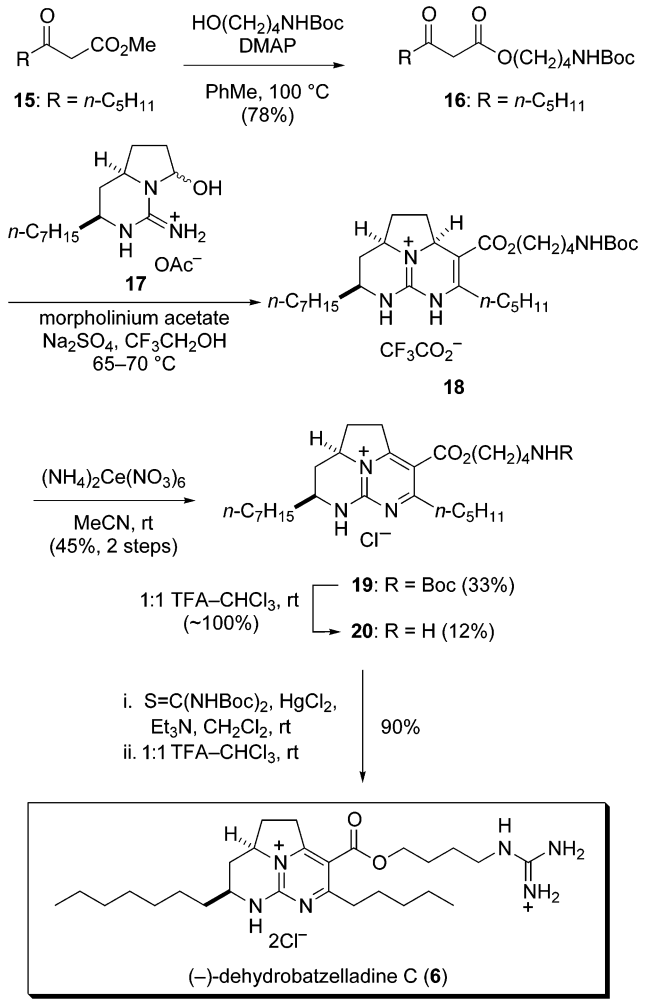
Scheme 3. Synthesis of (−)-Dehydrobatzelladine C



catalyzed transesterification[17] of methyl 3-oxooctanoate (**15**) with *N*-Boc-protected 4-aminobutanol to provide β-keto ester **16** in 78% yield. Biginelli condensation of 2.7 equiv of **16** with enantiopure guanidine aminal **17**, which is available in 10 steps from commercial materials,[18] took place in CF_3CH_2OH at 65−70 °C with high stereoselectivity (>10:1) to form hexahydro-5,6,6a-triazaacenaphthalene **18**. As this product was difficult to separate from residual β-ketoester,[19] a mixture of these compounds was oxidized directly with 1 equiv of cerric ammonium nitrate at room temperature in acetonitrile.[20] Purification of this product by reverse-phase preparative HPLC then provided **19** as the hydrochloride salt in 33% overall yield and 12% of the corresponding primary amine **20**. This latter product is readily generated from Boc derivative **19** by reaction with a 1:1 mixture of TFA/$CHCl_3$. Following extensive experimentation, it was found that primary amine **20** was best elaborated to the corresponding guanidine by first condensing the crude amine with *N*,*N*′-di(*tert*-butoxycarbonyl)thiourea followed by removal of the Boc groups with acid. Purification of this product by reverse-phase preparative HPLC provided pure (−)-dehydrobatzelladine C (**6**) as its dihydrochloride salt in 90% yield. The synthetic product, $[\alpha]_D$ −88 (*c* 0.23, MeOH), showed ^{1}H NMR spectra consistent with that of the natural product.[21] Moreover, ^{13}C NMR spectra of the diacetate salt of **6** matched perfectly (±0.1 ppm for all signals) with those reported for the natural alkaloid.[11] The optical rotation of the marine isolate was not reported,[11] precluding comparison of this property.

In summary, a wide variety of 1-iminohexahydropyrrolo-[1,2-*c*]pyrimidine carboxylic esters can be prepared by tethered Biginelli condensations.[6,7] These products can be selectively dehydrogenated to generate congeners containing a 2-aminopyrimidinium moiety. This oxidation is a key step in the first total synthesis of dehydrobatzelladine C (**6**).

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Supporting Information Available: Experimental procedures and characterization data for 2,2,5,7,8-pentamethylchroman-6-sulfonamide, *S*,*S*-dimethyl *N*-(2,2,5,7,8-pentamethyl-chroman-6-sulfonyl)carbonimidodithioate (**8**), and new compounds reported in Schemes 1−3, as well as ^{1}H and ^{13}C NMR spectra of synthetic (−)-dehydrobatzelladine C (**6**). This material is available free of charge via the Internet at http://pubs.acs.org.

OL0498141

(14) The trans epimer of **12** was isolated in 8% yield. The relative configuration of these epimers was assigned by analogy to closely related Biginelli products whose configuration had been established rigorously by chemical correlation.[12]

(15) These reactions either returned **12** or resulted in the formation of intractable mixtures.

(16) There are several examples of the conversion of simple Biginelli adducts to pyrimidines; see: (a) Kappe, O. C. *Acc. Chem. Res.* **2000**, *33*, 879. (b) Kappe, O. C. *Org. React.* **2004**, *63*, in press.

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(18) For the preparation of the enantiomer of **17**, see ref 8a.

(19) Tethered Biginelli adduct **18** could be isolated in pure form (48% yield) by preparative reverse-phase HPLC.

(20) This oxidation can also be accomplished in similar yield with benzoyl peroxide; however, purification of the product is more cumbersome.

(21) We thank Professor Braekman for a copy of the 600 MHz ^{1}H NMR spectrum of authentic dehydrobatzelladine C.