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A convergent approach to batzelladine alkaloids. Total syntheses of (+)-batzelladine E, (−)-dehydrobatzelladine C, and (+)-batzelladine K

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ABSTRACT

We recently reported a convergent strategy to access the polycyclic guanidinium alkaloid (+)-batzelladine B via an aldol addition–retro-aldol–aza-Michael addition cascade. Here we describe the application of this approach toward the total syntheses of (+)-batzelladine E, (−)-dehydrobatzelladine C, and (+)-batzelladine K. The identification of suitable methods to functionalize a common tropane core by electrophilic alkynylation and nucleophilic 1,2-addition were essential to generalizing this approach. We provide evidence for the intermediacy of an acylallene species in the cascade reaction.

1. Introduction

The batezlladines are a family of marine alkaloids that possess a tricyclic guanidinium core (Fig. 1).[1–5] Two linear hydrocarbon side chains of varying length extend from this system. The guanidinium residue is embedded in an *anti*- or *syn*-2,5-disubstituted pyrrolidine ring, as exemplified by (+)-batzelladine A (**1**) and (+)-batzelladine B (**3**), respectively.[1]

The challenges presented by this ring system have attracted considerable attention from synthetic chemists over the preceding decades.[6–26] We recently disclosed the first total synthesis of the *syn*-pyrrolidine alkaloid (+)-batzelladine B (**3**) by a convergent approach.[27] As shown in Scheme 1A, diastereoselective electrophilic alkynylation of the enoxysilane **7** using Waser's reagent (TMS-EBX)[28] provided the alkynylation product **8** (>80%). A key step then involved the conversion of the tropane intermediate **8** to the bicyclic guanidine **12** by an aldol addition–retro-aldol–aza-Michael addition cascade, using lithium benzyl octanoate (**9**) as nucleophile. Hydrogenolysis and decarboxylation then afforded the ketone **13** (48% from **8**).

As outlined in Scheme 1B, this convergent approach could conceivably enable access to additional targets by modulating the

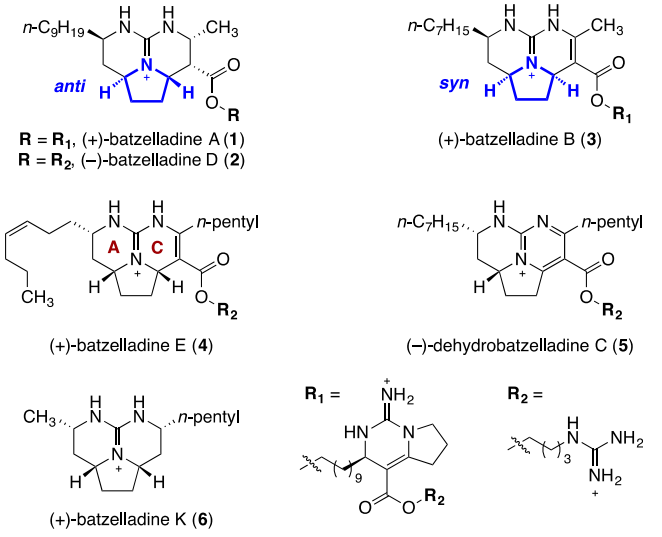

Fig. 1. Structures of (+)-batzelladine A (**1**), (−)-batzelladine D (**2**), (+)-batzelladine B (**3**), (+)-batzelladine E (**4**), (−)-dehydrobatzelladine C (**5**), and (+)-batzelladine K (**6**).

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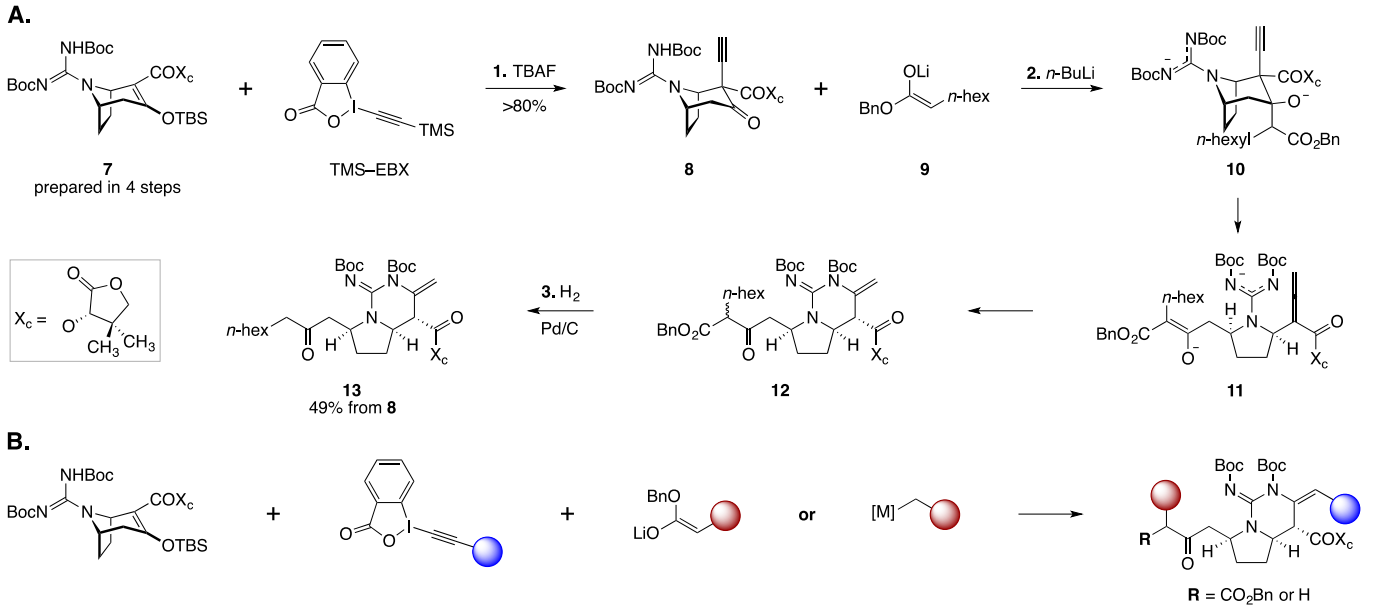
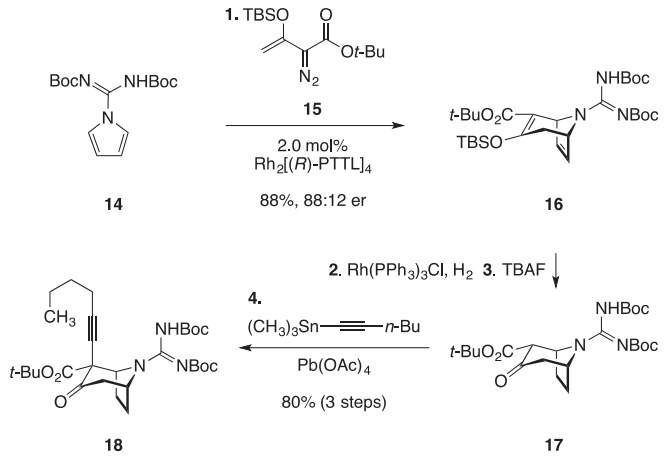


Scheme 1. A. Synthesis of the bicyclic guanidine **13**, a precursor to (+)-batzelladine B (**3**), via an aldol addition–retro-aldol–aza-Michael addition cascade. **B.** Outline of a general synthetic strategy toward *syn*-pyrrolidine guanidinium natural products.

alkynylation and nucleophilic reagents. In particular we sought to investigate the suitability of unstabilized nucleophiles in the addition, as this would eliminate the extraneous decarboxylation required in the original synthesis (**12** → **13**, Scheme 1A). Here we describe the realization of this goal and the syntheses of (+)-batzelladine E (**4**),[1] (−)-dehydrobatzelladine C (**5**),[3] and (+)-batzelladine K (**6**).[4]

2. Results and discussion

Our synthetic route began with the *N*-amidinylpyrrole **14**, which is accessible in two steps and 75% yield from 3-pyrroline (Scheme 2).[27] In our original work, we prepared the dehydrotropane intermediate **7** by a double stereo-differentiating, formal [4 + 3] cycloaddition using a chiral α-diazoester and a chiral dirhodium catalyst. In the present work, we employed a chiral catalyst and the achiral α-diazoester **15** instead, as this combination provided acceptable levels of stereoselectivity. Moreover, the use of a bulky *tert*-butyl ester was necessary in the subsequent organometallic addition (vide infra). Because (+)-batzelladine E (**4**), (−)-dehydrobatzelladine C (**5**), and (+)-batzelladine K (**6**) are pseudoenantiomeric with respect to the positionally-equivalent sites within (+)-batzelladine B (**3**), the pseudoenantiomeric dehydrotropane **16** was prepared. In the event, heating **14** and **15** with dirhodium(II) tetrakis[*N*-phthaloyl-(*R*)-*tert*-leucinate] (Rh_2[(*R*)-pttl]$_4$) as catalyst provided the dehydrotropane **16** in 88% yield and 88:12 er.[27,29] The β-ketoester **17** was obtained by selective hydrogenation of the less-hindered olefin with chlorotris(triphenylphosphine)rhodium(I) as catalyst, followed by cleavage of the enoxysilane (tetra-*n*-butylammonium fluoride, TBAF). Treatment of the unpurified product **17** with lead(IV) acetate in the presence of trimethylstannyl(butyl)acetylene then furnished the α-alkynyl-β-ketoester **18** as a single diastereomer (^{1}H NMR analysis; 80% from **16**).[30,31] The relative stereochemistry of **18** was assigned by analogy to **8**. The use of trimethylstannyl(butyl)acetylene in the alkynylation allows for introduction of the requisite C-ring extension and a handle for construction of the C-ring in a single operation (see Fig. 1).



Scheme 2. Synthesis of the α-alkynyl-β-ketoester **18**.

The addition of unstabilized nucleophiles to the tropane **18** proved to be challenging. In our original synthesis using ester enolates as nucleophiles, the initial product formed following the retro-aldol possesses an acidic β-ketoester function, which can neutralize the ester enolate leaving group (see **10** → **11**, Scheme 1). When unstabilized nucleophiles are employed, this acidic proton is not present, and products derived from elimination of the guanidine substituent were frequently observed. After extensive experimentation, we found that pre-complexation of the alkyne **18** with lanthanum(III) chloride bis(lithium chloride) complex[32] (1 equiv) for 1 h at −40 °C, followed by treatment with an excess of an organomagnesium reagent at the same temperature resulted in clean and efficient conversion to the corresponding 1,2-addition products **19a**–**d** (71–89%, Scheme 3). In each instance, a single diastereomer was formed, and the relative stereochemistry was established by 2D NOESY analysis. This analysis revealed the nucleophile added to the *endo*-face of the ketone. While isolation of **19a**–**d** decreases the efficiency of the synthesis, this was mitigated