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Synthesis of Batzelladine E and its *E* Isomer

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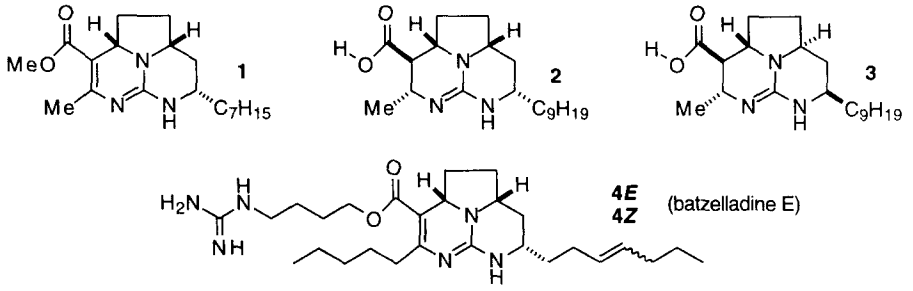
Abstract: The synthesis of **4E** established that batzelladine E (**4Z**) has the *Z*- rather than the *E*-stereochemistry previously depicted. Batzelladine E (**4Z**) has been synthesized by an efficient 9-step route in 3% overall yield.

Keywords: guanidines; Biginelli reaction.

In 1995, Patil and Faulkner reported the isolation of five cytotoxic guanidine alkaloids, batzelladines A-E, from the Caribbean sponge *Batzella* sp, two of which, batzelladines A and B, inhibit the binding of HIV gp-120 to CD4.[1] The structures were elucidated by interpretation of spectral data and chemical degradation. Batzelladines F-I were reported by the same group in 1997.[2] We were intrigued by these structures since the tricyclic portion of batzelladine B differs from a ptilomycalin A model that we synthesized in 1993[3] by a shorter side chain and the absence of a methoxy group. Using the strategy developed for our synthesis of the pentacyclic portion of ptilomycalin A,[4a] we prepared **1**, the methanolysis product of batzelladine B, **2**, the proposed hydrolysis product of batzelladine A whose stereochemistry had been incorrectly assigned, and **3**, the actual hydrolysis product of batzelladine A.[5] Rama Rao developed a 24-step enantiospecific synthesis of the alcohol corresponding to acid **2** starting from an optically active azetidinone.[6] Overman has reported another synthesis of **1**,[7] and Murphy has developed a short route to the analogue of **2** lacking the carboxylic acid.[8]



We report here the synthesis of batzelladine E (**4**), the first batzelladine to be synthesized, using the procedure developed for the synthesis of **1**.[5] We chose to prepare **4E** since a trans double bond was indicated in the structure in the isolation paper. The guanidino butyl ester was introduced prior to formation of the polycyclic guanidine since our synthetic studies of the related crambines (crambescins)[9] indicated that esters could not be prepared after the polycyclic framework had been constructed. We established that the CBZ groups could be cleaved from protected guanidino alcohol **5a**[9] on brief treatment with 30% HBr in AcOH and that **1** was stable to these conditions. DMAP-catalyzed condensation[10] of **5a** with methyl 3-oxooctanoate[11] afforded 65% of the desired trans-esterification product **6a**. Reduction of ethyl 4*E*-octenoate with LAH in THF afforded 94% of 4*E*-octen-1-ol, which was oxidized with PCC/Al_2O_3 in THF to give 82% of 4*E*-octenal (**7**). Aldehyde **7** was converted to **8** as previously reported for the saturated analogue;[5] addition of

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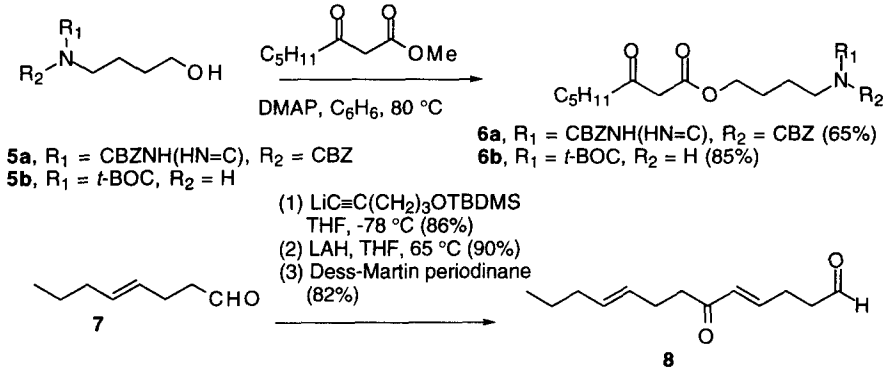
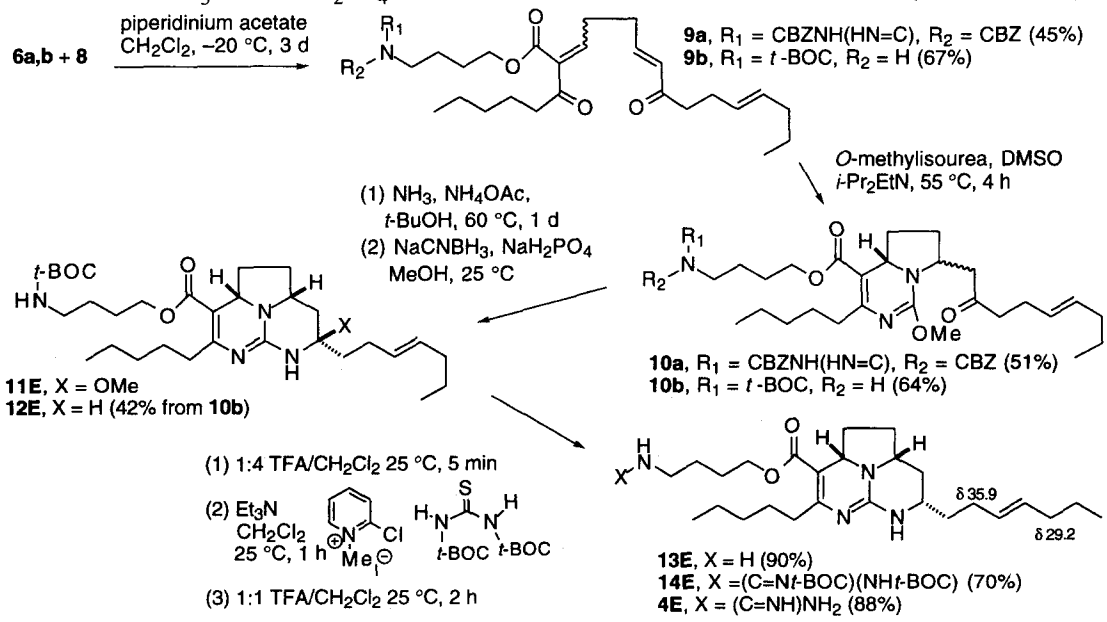
$LiC{\equiv}C(CH_2)_3OTBDMS$ (86%), reduction of the propargylic alcohol and deprotection of the silyl ether with LAH in THF at reflux (90%), and Dess-Martin oxidation (82%).

Knoevenagel condensation of β-keto ester **6a** with aldehyde **8** (CH_2Cl_2, 0.3 equiv piperidinium acetate, 3 d, -20 °C) gave 45% (85% based on recovered **6a** and **8**) of bis enone **9a** as a 1:1 mixture of stereoisomers.[12] Heating **6a** with *O*-methylisourea hydrogensulfate[13] (1.5 equiv) and *i*-Pr_2EtN (1.8 equiv) in DMSO at 75 °C for 5 h afforded 67% of **10a** as a ≈ 6:1 trans/cis mixture. Unfortunately, heating a solution of this mixture with excess NH_4OAc in *t*-BuOH saturated with anhydrous NH_3 for 2 d at 60 °C gave an intractable mixture. One of the two CBZ groups was cleaved in the ammonolysis step[9] giving a mixture of monoprotected side-chain guanidines that further complicates a complex reaction mixture. We therefore prepared the tricyclic framework with a protected aminobutyl ester and elaborated the amino group to the guanidine to complete the synthesis.



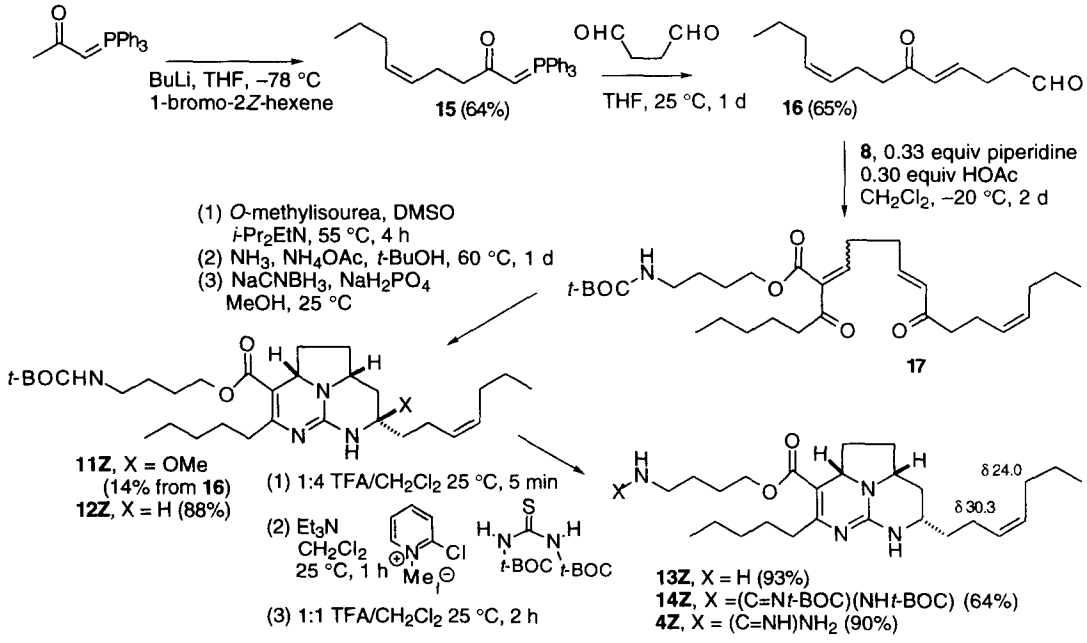
4-Amino-1-butanol was treated with di-*t*-butyl dicarbonate and Et_3N to give 96% of **5b**. DMAP-catalyzed condensation of **5b** with methyl 3-oxooctanoate provided 85% of **6b**, which underwent Knoevenagel condensation with **8** to give 67% of **9b**. Addition of *O*-methylisourea gave 64% of **10b** as a ≈ 6:1 mixture of trans and cis isomers. Ammonolysis with excess NH_4OAc in *t*-BuOH saturated with anhydrous NH_3 for 1 d at 60 °C now proceeded uneventfully providing **11E**. Careful reduction of **11E** with $NaBH_3CN$ in NaH_2PO_4-buffered MeOH at 25 °C for 40 h afforded **12E** (42% from **10b**).



The *t*-BOC group of **12E** was easily removed by brief dissolution in 1:4 TFA/CH_2Cl_2 which gave 90% of **13E**. We were unable to attach the guanidine to **13E** by treatment with *S*-methylthioisourea sulfate in methanol,[14] or with *N,N'*-di-(*t*-butoxycarbonyl)thiourea, $HgCl_2$, and Et_3N in methanol.[15] Fortunately, treatment of **13E** with *N,N'*-di-(*t*-butoxycarbonyl)thiourea, 2-chloro-*N*-methylpyridinium iodide and Et_3N in CH_2Cl_2 by Lipton's procedure[16] afforded 70% of the desired protected guanidine **14E.** Deprotection by dissolution in 1:1 TFA/CH_2Cl_2 for 2 h provided 88% of **4E** as the bis trifluoroacetate salt.[17]

The ^1H and ^{13}C NMR data of synthetic **4E** are different from those reported for batzelladine E, most notably in the region of the side chain double bond. The alkene hydrogens of **4E** absorb at δ 5.52 and δ 5.44 , each as dt, J = 15.5, 6.0, while the alkene hydrogens of batzelladine E overlap and coupling constants were not assigned in the literature. The allylic methylene groups of **4E** absorb at δ 2.12-2.2 and 1.99 while those of batzelladine E absorb at δ 2.13-2.28 and 2.06. Most significantly, the allylic carbons of **4E** absorb at δ 29.2 and δ 35.9, while those of batzelladine E absorb at δ 24.0 and δ 30.3. Since allylic carbons of cis alkenes absorb 5-6 ppm upfield of those of trans alkenes because of the γ-effect, these data suggest that batzelladine E has a *Z*, rather than an *E*, double bond in the side chain. The double bond stereochemistry of batzelladine E was not discussed in the isolation paper.[1] Although it was drawn as the E isomer, the text did state that it is Z isomer.

We therefore modified our synthesis to prepare **4Z**. Deprotonation of acetylmethylenetriphenylphosphorane with *n*-BuLi and alkylation with 1-bromo-2*Z*-hexene afforded 64% of **15** as described by Murphy for the saturated analogue.[8] Condensation with succinaldehyde[18] afforded 65% of **16**. The Knoevenagel condensation leading to **17** was problematic since the isolated double bond isomerized partially to the *E* isomer when piperidinium acetate was used as the catalyst. This isomerization could be suppressed by using 0.33 equiv of piperidine and 0.30 equiv of acetic acid so that the reaction medium was basic. Treatment of crude **17** with *O*-methylisourea and ammonolysis was uneventful giving 14% of **11Z** from **16**. The last four steps proceeded analogously to the preparation of **4E**, giving batzelladine E (**4Z**) as the bis trifluoroacetate salt in 9 steps and 3% overall yield.



The ^1H and ^{13}C NMR spectra of **4Z** are very similar to, but not identical to, those reported for batzelladine E, which were obtained in CD_3OD containing formic acid. Both the ^1H and ^{13}C chemical shifts of guanidines are pH dependent. The spectra are slightly different since synthetic batzelladine E is obtained as a bis trifluoroacetate salt in the deprotection step and is fully protonated while natural batzelladine E is not fully protonated in CD_3OD containing formic acid. The chemical shifts of the synthetic material do not change when formic acid is added to the solution of the bis trifluoroacetate salt in CD_3OD, which indicates that the guanidines are fully protonated. On the other hand, the chemical shifts change greatly when NH_3 is bubbled through the solution for 2 min. For instance, the ^1H NMR signal for the ring hydrogen at δ 2.2 moves to δ 2.0, as compared to the intermediate reported value of δ 2.10.[1] Similarly, the ^{13}C NMR signals at δ 65.1 and δ 166.5 move to δ 63.8 and δ 169.0, as compared to the intermediate reported values of δ 64.5 and δ 167.5.[1] The NMR absorptions shift back upon partial evaporation of the NH_3, and are restored to their original positions after evaporation of all the NH_3.

In conclusion, we have completed the first synthesis of a batzelladine, which gave batzelladine E (**4Z**) in 3% overall yield in only nine steps.

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17. (**4E**) ^1H NMR (CD_3OD) 5.52 (dt, 1, J = 15.5, 6.0), 5.44 (dt, 1, J = 15.5, 6.0), 4.55 (dd, 1, J = 9.5, 6.0). 4.20 (t, 2, J = 5.8), 3.79 (m, 1), 3.53 (m, 1), 3.22 (t, 2, J = 6.5), 2.76 (ddd, 1, J = 13.5, 9.5, 7.0), 2.63 (ddd, 1, J = 13.5, 9.5, 6.0), 2.53 (m, 1), 2.43 (ddd, 1, J = 13.5, 5.5, 3.0), 2.12-2.20 (m, 3), 1.99 (dt, 2, J = 6.5, 7.0), 1.53-1.80 (m, 10). 1.30-1.45 (m, 7), 0.93 (t, 3, J = 7.0), 0.91 (t, 3, J = 6.9); ^{13}C NMR (CD_3OD) 166.3, 158.7, 148.5, 147.6, 133.1, 129.9, 102.9, 65.2, 58.3, 57.3, 51.0, 42.1, 35.9, 34.9, 34.1, 33.9, 32.8, 31.8, 29.4, 29.2, 27.6, 27.1, 26.8, 23.8, 23.6, 14.4, 14.1; (**4Z**) ^1H NMR (CD_3OD) 5.47 (dt, 1, J = 11.2, 6.8), 5.41 (dt, 1, J = 11.2, 6.8), 4.55 (dd, 1, J = 9.6, 6.4), 4.21 (t, 2, J = 6.0), 3.76-3.85 (m, 1), 3.50-3.58 (m, 1), 3.22 (t, 2, J = 7.0), 2.77 (ddd, 1, J = 12.8, 9.6, 6.8), 2.64 (ddd, 1, J = 12.8, 9.6, 6.8), 2.54 (dddd, 1, J = 12.4, 9.2, 5.8, 3.4), 2.43 (ddd, 1, J = 13.2, 4.8, 2.8), 2.13-2.28 (m, 3), 2.06 (dt, 2, J = 6.8, 7.0), 1.55-1.82 (m, 10), 1.36-1.46 (m, 7), 0.92 (t, 6, J = 7.4); ^{13}C NMR (CD_3OD) 166.5, 158.8, 148.8, 147.8, 132.5, 129.2, 102.9, 65.1, 58.4, 57.3, 51.2, 42.2, 34.9, 34.2, 34.0, 32.8, 31.8, 30.4, 29.3, 27.7, 27.2, 26.9, 24.0, 24.0, 23.6, 14.5, 14.3.
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