A Concise Diastereoselective Approach to the Left-Hand Side of Batzelladine A

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Abstract: A highly diastereoselective three-component coupling reaction has been used in a concise approach to the left-hand side of batzelladine A. The stereoselectivity of this reaction, along with related observations described herein, provides insight into the mechanism of this reaction.

Key words: multicomponent reactions, alkaloids, imines, stereoselectivity, isothiocyanates

The batzelladine alkaloids form part of a structurally and biologically fascinating group of natural products obtained from marine sources.[1] Fifteen members of this group have now been isolated,[2] with representative structures shown in Figure 1. Batzelladines A (**1**) and B (**2**) inhibit the binding of HIV glycoprotein gp120 to the CD4 receptor, and so are of therapeutic interest for the treatment of HIV. Batzelladines C–E, of which batzelladine D (**3**) is structurally representative, are cytotoxic. Various analogues of the batzelladine alkaloids have also been shown to disrupt the gp120-CD4 interaction.[3]

These compounds have been the subject of a number of synthetic studies, leading to the development of a wealth of new methodology. In particular, batzelladines A,[4] D,[5] E,[6] F,[7] and dehydrobatzelladine C[8] have been synthesized.[9]

Our own work in this area[10] has focused on the use of the Kishi three-component coupling[11] of an alkylidenepyrrolidine with a silyl isothiocyanate and an aldehyde to give the key pyrrolo[1,2-*c*]pyrimidine core. However, with a stereochemical directing-group at the 5-position of the pyrrolidine, as shown in Scheme 1, the stereoselectivity is typically 2:1, which falls far short of the total stereocontrol which we observed during the formation of similar compounds by annulation of alkenylazolines with isocyanates.[12]

In order to improve the stereoselectivity of this reaction, we sought an understanding of the reaction mechanism. The mechanism originally proposed required initial N-acylation of the alkylidenepyrrolidine by the isothiocyanate, followed by condensation with the aldehyde and cyclisation. However, isothiocyanates only react with alkylidenepyrrolidines under relatively forcing conditions,[13] giving only the product of acylation of the enamine carbon. On this basis, we would tentatively exclude this mechanism.

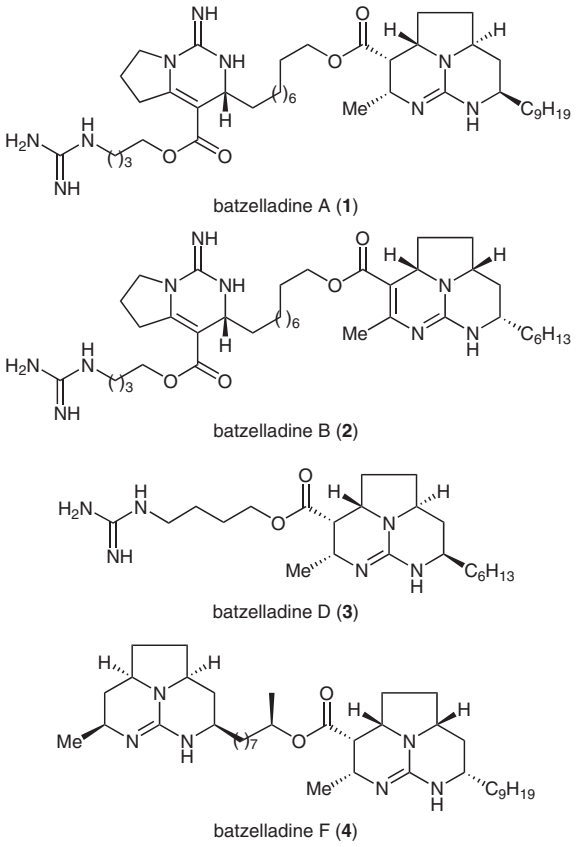

Figure 1

The reaction of trimethylsilyl isothiocyanate with aldehydes under Lewis acidic conditions is known to give compounds of general structure **8**.[14] This provides precedent for the nucleophilic addition of trimethylsilyl isothiocyanate onto aldehydes, so that generation of an intermediate of structure **9** or **10** is not unreasonable. Such species would presumably be capable of reacting with the enamine carbon of alkylidenepyrrolidine **11** to give a compound **12**, which would undergo rapid tautomerism to compound (*Z*)-**13**. Double-bond isomerisation could then provide the *E*-isomer, which would cyclise to give the final product **14** (Scheme 2).

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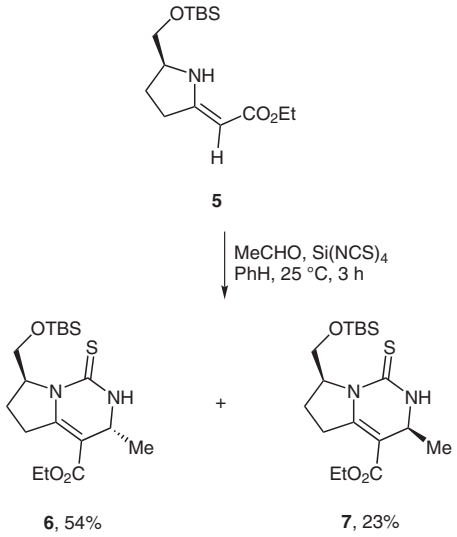
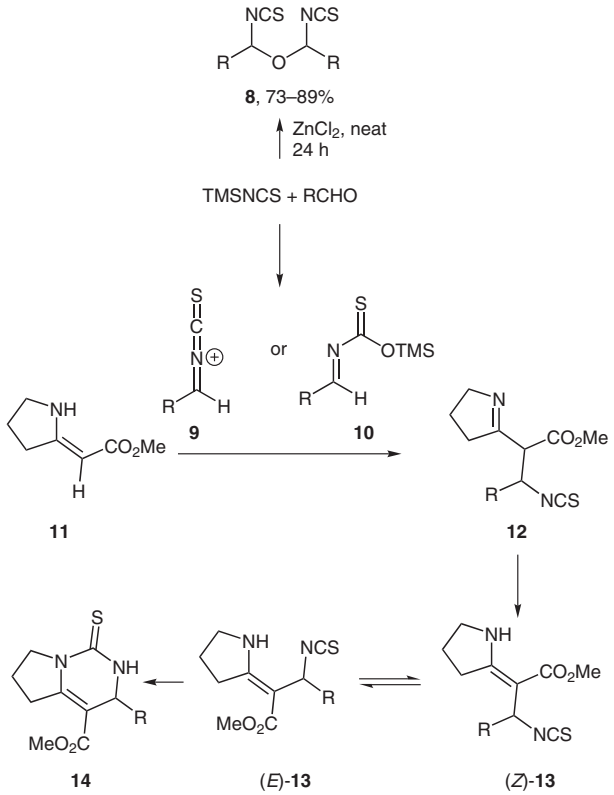
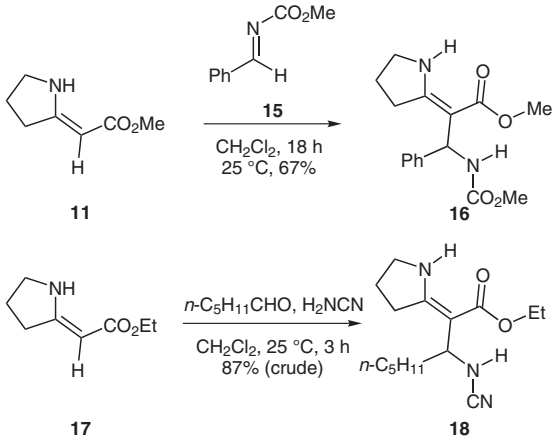


Scheme 1



Scheme 2

We felt that intermediates such as **13** could be stabilised by additional hydrogen bonding, and therefore investigated the reaction of alkylidenepyrrolidine **11** with known imine **15**, and the corresponding ethyl ester **17** with the *N*-cyanoimine formed in situ from hexanal and cyanamide. These gave compounds **16**[15] and **18**,[16] respectively (Scheme 3), thus lending support to our mechanistic hypothesis. While compound **16** was stable, compound **18** reverted to the alkylidenepyrrolidine **17** over approximately three days.

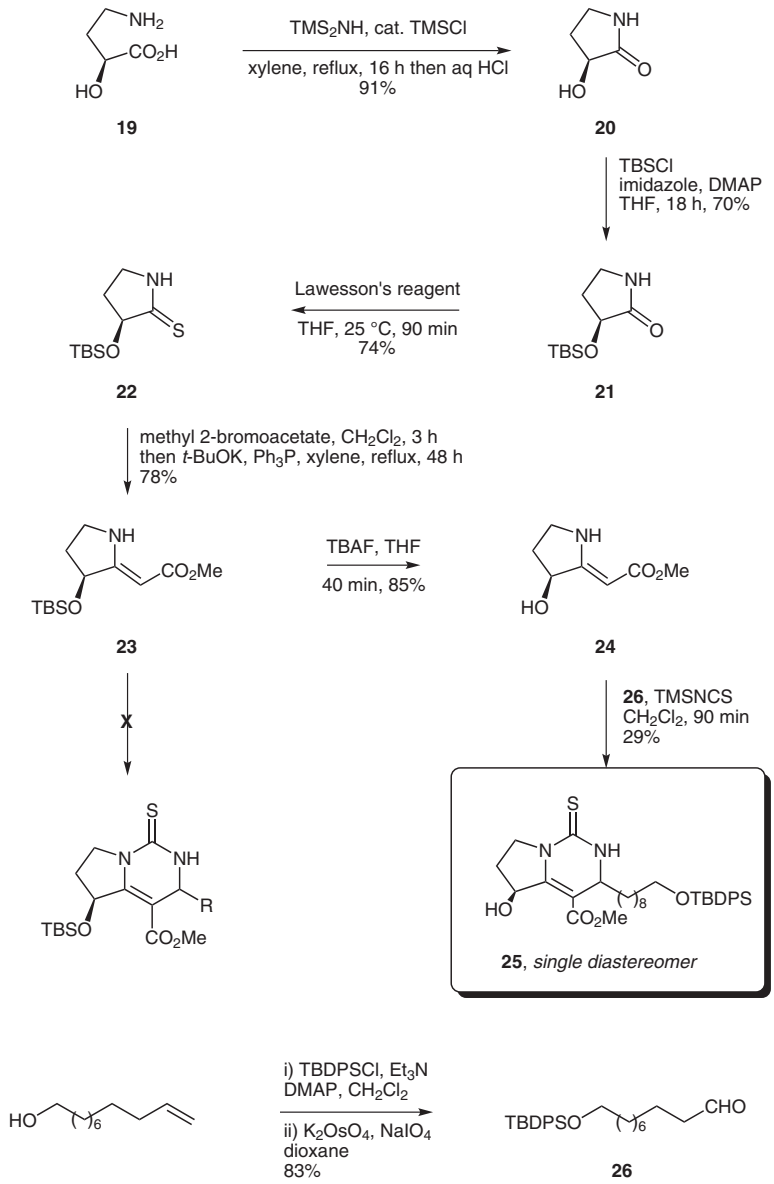


Scheme 3

If this stereogenic centre in the Kishi three-component coupling reaction is formed by attack of an electrophile at the alkene carbon adjacent to the ester, the closest site for a stereochemical directing group would be the 3-position of the pyrrolidine ring. A protected hydroxy directing group was chosen, with the eventual goal of removal by deoxygenation. Therefore, commercially available amino acid **19** was readily converted into lactam **20** (Scheme 4). The primary alcohol in this compound was silylated efficiently under the conditions shown, whereas use of TBSCl in CH_2Cl_2 with Et_3N and DMAP gave mixtures of the desired product and the silyl iminoether. Thionation of lactam **21** was followed by Eschenmoser sulfide contraction to give the alkylidenepyrrolidine **23**. This compound was smoothly deprotected to give compound **24**. To our surprise, alkylidenepyrrolidine **23** is unreactive under the conditions of the three-component coupling. However, compound **24** underwent a completely diastereoselective three-component coupling reaction with aldehyde **26** to give pyrrolo[1,2-*c*]pyrimidine **25** corresponding to the left-hand side of batzelladine A.[17]

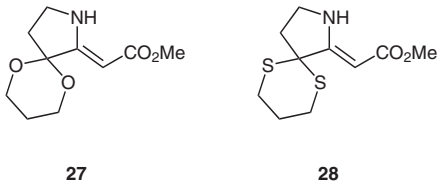
This short and efficient sequence (6 steps, 9% overall yield) compares extremely favourably with the three previously reported routes to this part of the natural product.[4,18] Compound **25** exhibited no diagnostic NOE enhancements which would permit direct assignment of the stereochemistry. However, the required stereoisomer for the natural product could be formed by appropriate choice of starting-material enantiomer followed by deoxygenation and guanidine formation from compound **25**.[19]

While we had expected the bulky silyl ether in compound **23** to block one face of the alkylidenepyrrolidine, it actually prevents reaction completely. This is particularly perplexing, since Kishi has reported successful and high yielding three-component coupling reactions with a dioxane **27** or a dithiane **28** at this position (Figure 2).[11] Although improved diastereoselectivity was anticipated in the reaction of compound **24** compared to that of compound **5**, we were particularly delighted to see the formation of only one isomer of product **25**. While the details are presently unclear, we would attribute this high level of



Scheme 4

stereocontrol to a direct interaction between the reacting electrophile and the hydroxy group.



27 **28**

Figure 2

In conclusion, we have completed a short synthesis of the bicyclic guanidine core present in batzelladine A, and in doing so gained insight into the mechanism of the Kishi three-component coupling reaction. Further studies are under way to delineate the mechanism of this fascinating reaction.

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(15) **(*Z*)-Methyl [3-Methoxycarbonylamino)-3-phenyl-2-pyrrolidin-2-ylidene]propionate (16)**

Methyl *N*-phenylmethylenecarbamate (**15**, 62 mg, 0.38 mmol) was added to a solution of (*Z*)-pyrrolidin-2-ylidene-acetic acid methyl ester (**11**, 54 mg, 0.38 mmol) in CH_2Cl_2 (5 mL). The resulting solution was stirred at r.t. overnight, concentrated in vacuo, and purified by flash column chromatography (eluent: hexane–EtOAc, 2:1; R_f = 0.4) to give the title compound (78 mg, 67%) as a colourless oil. HRMS: *m/z* calcd for $C_{16}H_{21}N_2O_4$ [M]: 305.1501. Found: 305.1515 [MH^+]. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.27 (1 H, br s, NH), 7.21–7.18 (4 H, m, *J* = 4.2 Hz, arom. CH), 7.14–7.08 (1 H, m, arom. CH), 5.91 (1 H, app. br d, *J* = 9.4 Hz, NH), 5.11 (1 H, d, *J* = 10.0 Hz, C*H*Ph), 3.65 (3 H, s, Me), 3.54–3.50 (2 H, m, CH_2N), 3.42 (3 H, s, Me), 3.05 (1 H, ddd, *J* = 16.8, 8.6, 6.9 Hz, one of CH_2), 2.70 (1 H, ddd, *J* = 16.8, 8.8, 7.1 Hz, one of CH_2C=C) and 2.00–1.94 (2 H, m, CH_2). ^{13}C NMR (62.5 MHz, $CDCl_3$): δ = 169.7 (C=O), 166.2 (C=O), 157.1 (*C*=CCO_2Me), 143.2 (arom. C), 128.0 (arom. CH), 126.3 (arom. CH), 125.8 (arom. CH), 90.1 (C=*C*CO_2Me), 53.6 (CH), 52.0 (CH_3), 50.1 (CH_3), 47.5 (CH_2), 31.5 (CH_2), 21.7 (CH_2). MS (TOF AP$^+$): *m/z* (%) = 305 (22) [MH^+], 230 (100), 195 (43).

(16) **(*Z*)-Ethyl 3-(Cyanoamino)-2-(pyrrolidin-2-ylidene)octanoate (18)**

Cyanamide (16 mg, 0.4 mmol) was added to a solution of hexanal (48 μL, 0.4 mmol) in dry CH_2Cl_2 (4 mL) under N_2, and the resulting suspension was stirred at 25 °C for 30 min. A solution of (*Z*)-pyrrolidin-2-ylidene-acetic acid ethyl ester (**17**, 60 mg, 0.4 mmol) in CH_2Cl_2 (2 mL) was added, and the resulting mixture was stirred at 25 °C for 3 h. The solvent was then removed in vacuo to afford the title compound as a pale yellow gum (94 mg, 87% crude yield). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.26 (1 H, br s, NH), 4.37 (1 H, br s, NHCN), 4.00–4.18 (2 H, m, CO_2CH_2), 3.75 (1 H, app. q, *J* = 7.4 Hz, C*H*NHCN), 3.50 (2 H, app. t, *J* = 7.0 Hz, CH_2NH), 2.78 (1 H, ddd, *J* = 16.1, 9.1, 7.0 Hz, one of CH_2C=C), 2.58 (1 H, ddd, *J* = 16.1, 9.2, 6.9 Hz, one of CH_2C=C), 1.89–2.03 (2 H, m, pyrrolidine CH_2CH_2NH), 1.64–1.85 (2 H, m, CH_2CHNHCN), 1.14–1.26 [9 H, m, $(CH_2)_3$ and $CO_2CH_2CH_3$], 0.81 (3 H, t, *J* = 6.9 Hz, CH_3CH_2-alkyl). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 169.0 (ester *C*=O), 166.0 (*C*=CCO_2Et), 117.3 (NHC≡N), 88.3 (C=*C*CO_2Et), 59.0 (CO_2CH_2), 47.3 (*C*HNHCN), 35.2 (CH_2NH), 31.6 (CH_2C=C), 31.5 (CH_2CHNHCN), 26.6 (CH_2CH_2NH), 22.5 (CH_2) 22.4 (CH_2), 21.6 (CH_3CH_2-alkyl), 14.6 ($CO_2CH_2CH_3$), 13.9 (CH_3CH_2-alkyl).

(17) **Methyl (5*S*)-1,2,3,5,6,7-Hexahydro-3-(9-*tert*-butyldiphenylsilyloxynonyl)-5-hydroxy-1-thioxopyrrolo[1,2-*c*]pyrimidine-4-carboxylate (25)**

Trimethylsilyl isothiocyanate (62 μL, 0.45 mmol) was added to a solution of aldehyde **26** (183 mg, 0.45 mmol) in dry CH_2Cl_2 (3 mL) under N_2, and the resulting brown solution was stirred for 30 min at 25 °C. A solution of alkylidene-pyrrolidine **24** (70 mg, 0.45 mmol) in CH_2Cl_2 (2 mL) was then added, and the reaction was stirred for 3 h. The reaction was quenched with ca. 0.1 M aq NaOH solution (20 ml) and the layers separated. The aqueous layer was washed with CH_2Cl_2 (3 × 25 mL), the combined organic layers dried with Na_2SO_4, and the solvent removed in vacuo. The resulting orange gum was purified by column chromatography (eluent: hexane–EtOAc, 2.5:1; R_f = 0.55) to give the title compound (79 mg, 29%) as a yellow gum. HRMS: *m/z* calcd for $C_{34}H_{49}N_2O_4SiS$ [M]: 609.3182. Found: 609.3196 [MH^+]. IR (CH_2Cl_2): ν_{max} = 3401, 3205, 2883, 1675, 1629, 1531, 1462, 1416, 1324 and 1255 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.70–7.55 (4 H, m, arom. CH), 7.41–7.28 (6 H, m, arom. CH), 6.99 (1 H, br s, NH), 5.20 (1 H, br s, OH), 5.10 (1 H, app. t, *J* = 8.0 Hz, C*H*OH), 4.24 (1 H, app. dt, *J* = 7.8, 3.8 Hz, C*H*NH), 4.06 (1 H, ddd, *J* = 11.6, 8.8, 3.3 Hz, one of CH_2NCS), 3.89 (1 H, ddd, *J* = 11.6, 9.0, 8.0 Hz, one of CH_2NCS), 3.65 (3 H, s, CO_2CH_3), 3.58 (2 H, t, *J* = 6.5 Hz, CH_2OTBDPS), 2.40–2.33 (1 H, m, one of CH_2CHOH), 2.00–1.95 (1 H, m, one of CH_2CHOH), 1.54–1.40 (6 H, m, 3 × CH_2) and 1.36–1.10 [19 H, m, 5 × CH_2 and ((CH_3)$_3$C]. ^{13}C NMR (125 MHz, $CDCl_3$): d = 175.3 (C=S), 166.2 (C=O), 153.2 (*C*=CCO_2Me), 139.8 (arom. C), 134.6 (arom. CH), 128.5 (arom. CH), 126.6 (arom. CH), 99.6 (C=*C*CO_2Me), 71.2 (CHOH), 63.0 (CH_2OTBDPS), 51.2 (CO_2CH_3), 50.9 (*C*H-alkyl), 48.7 (CH_2NC=S), 36.1 (pyrrolidine *C*H_2CHOH), 31.6 (CH_2CH-NH), 28.8 (CH_2),

28.6 (CH_2), 28.4 (CH_2), 28.2 (CH_2), 28.1 (CH_2), 25.9 [(CH_3)$_3$C], 24.8 (CH_2), 23.0 (CH_2), 18.2 [(CH_3)$_3$*C*]. MS (ES^+): *m/z* (%) = 609 (25) [MH^+], 577 (32), 279 (100). $[a]_D$ –30 (*c* 1, CH_2Cl_2).

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