An Enantiospecific Synthesis of the Tricyclic Guanidine Segment of the Anti-HIV Marine Alkaloid Batzelladine A

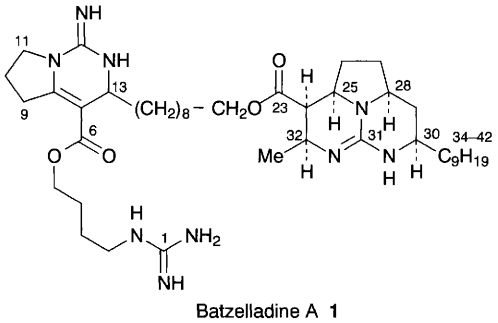
A. V. Rama Rao,* Mukund K. Gurjar and Jayasree Vasudevan
Indian Institute of Chemical Technology, Hyderabad 500 007, India

An enantiospecific synthesis of the tricyclic guanidine segment **19** of the new anti-HIV alkaloid batzelladine A, isolated from a marine sponge of genus *batzella*, starting from [3*R*(1′*R*,4*R*)]-4-acetoxy-3-[1-(*tert*-butyldimethylsilyloxy)ethyl]-2-azetidinone **3** is described.

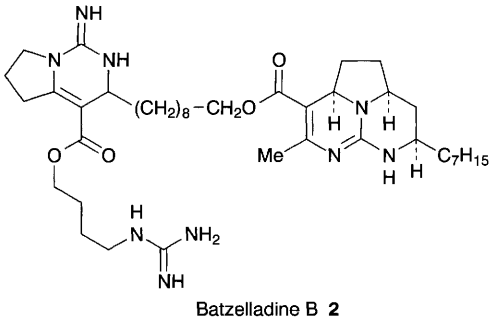
A recent report[1] from Smith-Kline Beecham describes novel structures in polycyclic guanidine alkaloids batzelladines A **1** and B **2** isolated from the methanol extract of a bright red Caribbean sponge of genus *batzella*. These alkaloids possess potent anti-HIV activity which is attributed to their ability to inhibit CD4–gp120 interaction.

These fascinating heterocyclic substances are basically the combination of a crambine derivative and the novel and unknown tricyclic guanidine segments joined together *via* an ester linkage. This communication describes the first stereocontrolled synthesis of the tricyclic guanidine moiety of **1** starting from the commercially available and optically active azetidinone precursor **3** (Scheme 1). The azetidinone derivative **3** was selected as the starting material primarily because of the inherent stereochemical correlation between the three contiguous centres at C-3, C-4 and C-1′ of **3** with those at C-25, C-24 and C-32 of **1**.

The coupling reaction[2] of **3** with the Grignard reagent in THF at 0 °C occurred with a high degree of stereospecificity providing the *trans* product whose free NH group was protected using $(Boc)_2O$ to give **4**.† The characteristic coupling constant, ($J_{2,3}$ 3.0 Hz) observed in the ^1H NMR spectrum of the coupled product substantiated the stereochemical assignment. In order to open the azetidinone ring, **4** was treated with 1 mol dm^{-3} LiOH in methanol to afford **5**† which was desilylated to provide the alcohol **6**. Conversion of **6** into the diacetate derivative **7** was conveniently achieved by successive reduction with DIBAL-H in dichloromethane at −20 °C and acetylation with acetic anhydride and DMAP.



Batzelladine A **1**



Batzelladine B **2**

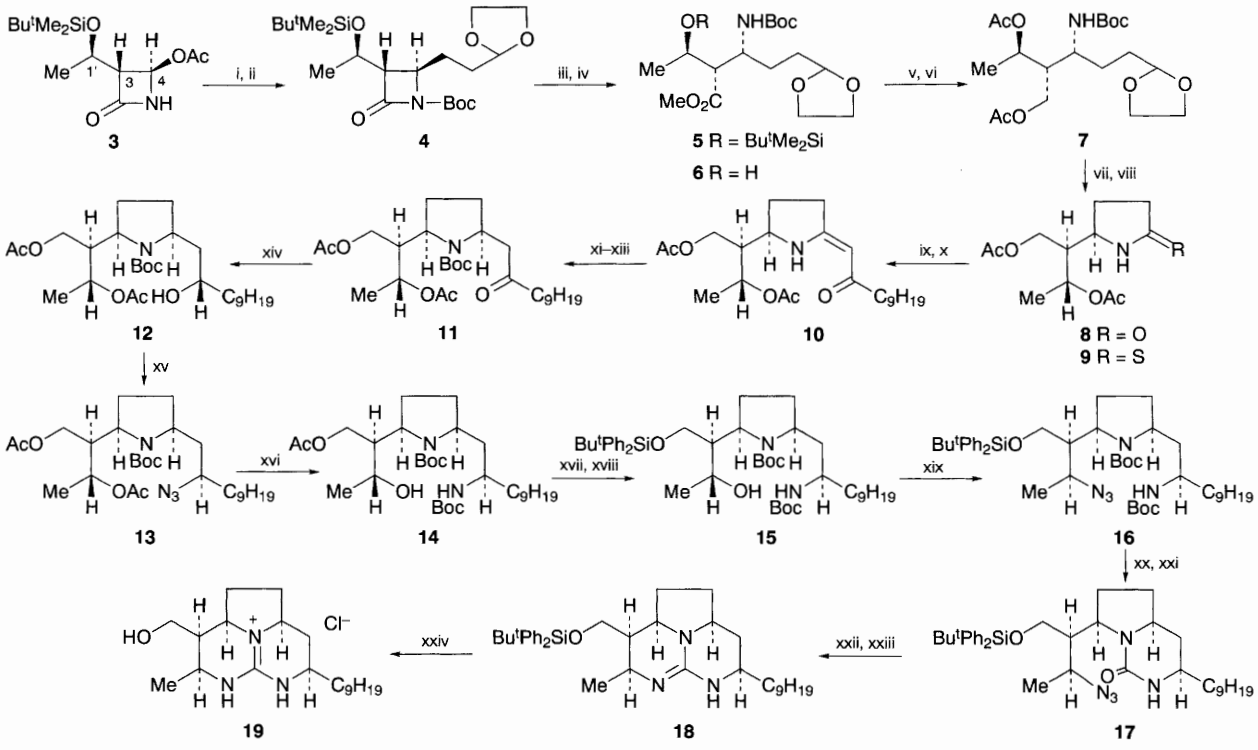
The next critical reaction involved the transformation of **7** into the 2-pyrrolidone derivative **8**. It was gratifying to note that this transformation was accomplished very efficiently by a one step oxidation with Jones reagent in refluxing acetone. In principle, compound **6** underwent successive deacetalization, oxidation of the intermediary hemi-aminal derivative, coupled with concomitant *N*-Boc deprotection.

In order to elaborate the right-hand side chain, Eschenmoser's sulfide contraction methodology was invoked.[3] For example, on treatment with Lawesson's reagent, **8** afforded the thiolactam **9**† which on typical sulfide contraction reaction with $BrCH_2COC_9H_{19}$ yielded the α,β-unsaturated ketone **10**.† In the ^1H NMR spectrum of **10** the characteristic singlet due to the =CH proton was located at δ 5.00, whilst the chemical shift of the NH proton observed at δ 10.00 suggested the *Z* configuration.[3] Reduction of **10** over PtO_2 in acetic acid followed by *N*-Boc protection and Jones oxidation gave rise to **11** as the sole product.[4]

Stereoselective reductions of 1,3-acylamino ketones has been a topic of interest.[5] Based on literature examples[5] compound **11** was reduced with K-Selectride at −78 °C to provide a 4:1 mixture of the *anti*:*syn* 1,3-acylamino alcohols from which the required isomer **12** was conveniently isolated by column chromatography. The absolute stereochemical assignment of **12** was determined by NOE studies.[6] The nucleophilic displacement reaction of **9** with HN_3 under Mitsunobu conditions[7] occurred smoothly to give the azido derivative **13**† which was hydrogenated in the presence of Pd–C and $(Boc)_2O$ in ethyl acetate to afford compound **14**. Saponification of **14** with LiOH followed by selective silylation of the primary hydroxy group with *tert*-butyldiphenylsilylchloride and imidazole gave **15** which on consequent Mitsunobu reaction with HN_3 gave the azido derivative **16**. Conversion of **16** into the cyclic urea derivative **17**† was effected by first removing both the *N*-Boc groups and then tethering the amino groups with 1,1′-carbonyldiimidazole. Treatment of **14** with freshly distilled dimethyl sulfate produced the corresponding methyl lactim ether which was immediately subjected[8] to hydrogenation over Pd–$BaSO_4$ at normal temperature and pressure to obtain the guanidine derivative **18**. The structure of **18** was confirmed by the ^1H NMR and MS, the latter indicating the highest mass peak at *m/z* 573 corresponding to M^+. Furthermore the fragmentation pattern of the MS of **18** was compatible with the assigned structure.[9] The removal of the silyl protection in **18** with 1 mol dm^{-3} HCl in methanol gave the guanidine segment **19**.† The structure of **19** was assigned by the ^1H NMR spectral analysis including COSY, NOESY and proton decoupling experiments. In addition, the long range NOEs (greater than three bonds) as shown in Fig. 1 unequivocally proved the stereochemical assignments

We are grateful to Drs A. D. Patil and J. W. Westley, SB, USA, for drawing our attention to the isolation of these alkaloids. We also thank Dr A. C. Kunwar for NMR studies on compound **19**. J. V. is grateful to CSIR for financial assistance in the form of a SRF.

Received, 13th December 1994; Revised manuscript received, 18th April 1995; Com. 4/07600A



Scheme 1 *Reagents and conditions*: i, $[O(CH_2)_2O]CH(CH_2)_2MgBr$, THF, 0 °C, 10 min; ii, $(Boc)_2O$, DMAP, THF, room temp., 0.5 h, 81%; iii, 1 mol dm^{-3} LiOH, MeOH, THF, room temp., 0.5 h; iv, Bu_4NF, THF, room temp., 1 h, 70%; v, DIBAL-H, CH_2Cl_2, −20 °C, 0.5 h; vi, Ac_2O, DMAP, CH_2Cl_2, room temp., 1 h, 75%; vii, Jones' reagent, MeCOMe, 56 °C, 10 min; viii, Lawesson's reagent, C_6H_6, heat, 0.5 h, 62%; ix, $C_9H_{19}COCH_2Br$, CH_2Cl_2, room temp., 0.5 h, $KHCO_3$; x, PPh_3, $KOBu^t$ (0.2 equiv), Bu^tOH, C_6H_6, heat, 65%; xi, H_2, PtO_2, AcOH, 45 psi (1 psi = 6.894 kPa), 6 h; xii, $(Boc)_2O$, $KHCO_3$, H_2O–EtOAc; xiii, Jones' reagent, MeCOMe, 0 °C, 0.5 h, 91%; xiv, K-Selectride, THF, −78 °C, 0.5 h, 80%; xv, diethyl azodicarboxylate (DEAD), HN_3, PPh_3, THF, room temp., 12 h, 90%; xvi, H_2, Pd–C, EtOAc, $(Boc)_2O$; xvii, 1 mol dm^{-3} LiOH, MeOH, room temp., 0.5 h; xviii, Bu^tPh_2SiCl (1 equiv.), CH_2Cl_2, imidazole, room temp., 12 h, 81%; xix, DEAD, HN_3, PPh_3, THF, room temp., 6 h; xx, TFA, CH_2Cl_2, 0 °C, room temp., 0.5 h; xxi, 1,1′-carbonyldiimidazole, THF, 0 °C, room temp., 65%; xxii, Me_2SO_4, C_6H_6, heat, 16 h; xxiii, H_2, Pd–$BaSO_4$, MeOH, 12 h, 65%; xxiv, 1 mol dm^{-3} HCl, MeOH, 50 °C, 2 h, 90%

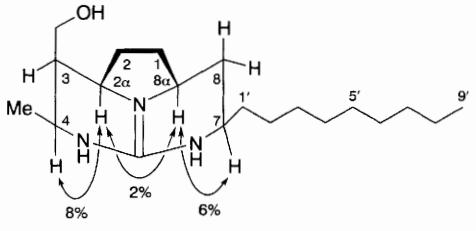


Fig. 1 Long range NOEs for **19**

Footnote

† Selected ^1H NMR data for **4**: (200 MHz, $CDCl_3$) δ 0.02 (s, 6H), 0.78 (s, 9H), 1.15 (d, 3H, *J* 6.1 Hz), 1.46 (s, 9H), 1.64 (m, 3H), 2.11 (m, 1H), 2.67 (t, 1H, *J* 3.0 Hz), 3.75–4.10 (m, 5H), 4.18 (m, 1H), 4.82 (t, 1H, *J* 4.0 Hz).

For **5**: δ (200 MHz, $CDCl_3$) 0.02 (s, 6H), 0.81, (s, 9H), 1.08 (d, 3H, *J* 6.0 Hz), 1.35 (s, 9H), 1.40 (m, 4H), 2.48 (dd, 1H, *J* 3.7, 8.3 Hz), 3.60 (s, 3H), 3.65–4.15 (m, 6H), 4.73 (t, 1H, *J* 4.1 Hz), 5.42 (d, 1H, *J* 10.4 Hz).

For **9**: δ (200 MHz, $CDCl_3$) 1.27 (d, 3H, *J* 6.8 Hz), 1.95 (m, 1H), 2.09, 2.10 (2s, 6H), 2.14 (m, 1H), 2.38 (m, 1H), 2.86 (m, 2H), 4.05–4.30 (m, 3H), 5.11 (m, 1H), 7.86 (bs, 1H).

For **10**: δ (200 MHz, $CDCl_3$) 0.88 (t, 3H, *J* 5.7 Hz), 1.22 (bs, 17H), 1.55 (m, 2H), 1.88 (m, 2H), 2.06, 2.18 (2s, 6H), 2.15 (m, 1H), 2.61 (m, 2H), 4.06 (m, 1H), 4.13 (d, 2H, *J* 5.5 Hz), 5.00 (s, 1H), 5.15 (m, 1H), 10.0 (bs, 1H).

For **13**: δ (200 MHz, $CDCl_3$) 0.89 (t, 3H, *J* 6.0 Hz), 1.27 (bs, 19H), 1.30–2.20 (m, 7H), 1.57 (s, 9H), 2.00, 2.02 (2s, 6H), 3.16 (bs, 1H), 3.90 (bs, 1H), 4.18 (dd, 1H, *J* 7.7, 11.3 Hz), 4.25 (dd, 1H, *J* 6.5, 11.3 Hz), 4.93 (m, 1H).

For **17**: δ (200 MHz, $CDCl_3$) 0.88 (t, 3H, *J* 6.3 Hz), 1.04 (s, 9H), 1.27 (s, 16H), 1.29 (d, 3H, *J* 6.0 Hz), 1.40–2.25 (m, 7H), 2.75 (m, 1H), 3.38 (m, 1H), 3.59 (dd, 1H, *J* 9.0, 11.3 Hz), 3.68 (m, 1H), 3.81 (dd, 1H, *J* 4.5, 11.3 Hz), 4.11 (m, 1H), 4.31 (s, 1H), 7.38 (m, 6H), 7.68 (m, 4H).

For **19**: δ (400 NHz, $CDCl_3$) δ 0.81 (t, 3H, *J* 6.9 Hz, 9′-Me), 1.12 (brs, 14H, 7 CH_2), 1.16 (m, 1H, H-8β), 1.32 (d, 3H, *J* 6.9 Hz, 4-Me), 1.38 (m, 1H, H-1′a), 1.56 (m, 1H, H-1′b), 1.66 (m, 1H, H-1β), 1.80 (p, 1H, *J* 3.5 Hz, H-3), 2.06 (m, 1H, H-2α), 2.10 (m, 1H, H-8α), 2.12 (m, 1H, H-1α), 2.20 (m, 1H, H-2β), 3.26 (m, 1H, H-7), 3.56 (m, 1H, H-8a), 3.65 (dq, 1H, *J* 3.5, 6.9 Hz, H-4), 3.67 (dd, 1H, *J* 4.1, 12.1 Hz, CH_2OH), 3.72 (dd, 1H, *J* 3.7, 12.1 Hz, CH_2OH), 3.88 (ddd, 1H, *J* 2.0, 3.9, 5.2 Hz, H-2a), 7.71 (s, 1H, NH), 8.05 (s, 1H, NH).

References

1 S. H. Mai, V. K. Nagulapalli, A. D. Patil, A. Truneh and J. W. Westley, *P.C.T. Int. Appl.* W09301, 193 (CA: 1993, 118: 225662x); A. D. Patil, N. V. Kumar, W. C. Kokke, M. F. Bean, A. J. Freyer, C. De Brosse, S. Mai, A. Truneh, B. Carte, A. L. Breen, R. P. Hertzberg, R. K. Johnson, J. W. Westley, B. C. M. Potts and D. J. Fankner, *J. Org. Chem.*, 1995, **60**, 1182.

2 D. H. Hua and A. Verma, *Tetrahedron Lett.*, 1985, **26**, 547.

3 M. Roth, P. Dubs, E. Gotschi and A. Eschenmoser, *Helv. Chim. Acta*, 1971, **54**, 710.

4 D. J. Hart and Y. Tsai, *J. Org. Chem.*, 1982, **47**, 4403.

5 K. T. Warner and G. Hofner, *Tetrahedron*, 1991, **47**, 1895; J. Barluenga, E. Aguilar, S. Fustero, B. Olano and A. L. Viado, *J. Org. Chem.*, 1992, **57**, 1219 and references cited therein.

6 A. V. Rama Rao, M. K. Gurjar and J. Vasudevan, unpublished results.

7 O. Mitsunobu, *Synthesis*, 1981, 1.

8 R. E. Benson and T. L. Cairus, *J. Am. Chem. Soc.*, 1948, **70**, 2115; M. Brugger and F. Karte, *Liebigs. Ann. Chem.*, 1972, **764**, 112.