Pergamon

Tetrahedron Letters, Vol. 37, No. 39, pp. 6977-6980, 1996

0040-4039/96 $15.00 + 0.00

PII: S0040-4039(96)01575-4

Synthesis of the Tricyclic Portions of Batzelladines A, B and D. Revision of the Stereochemistry of Batzelladines A and D

Barry B. Snider* and Jinsheng Chen

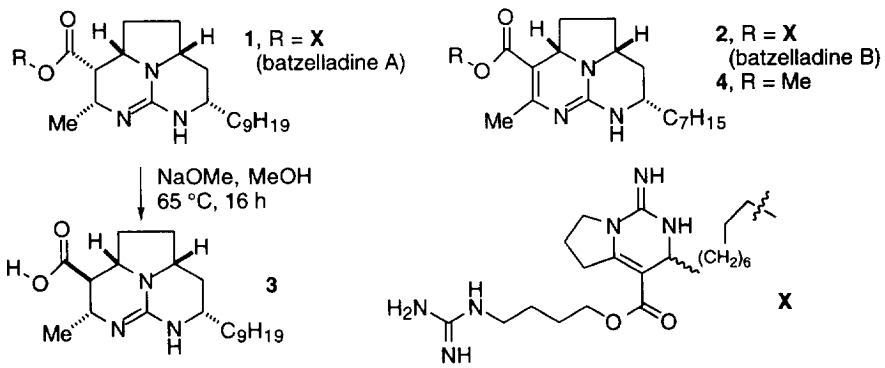
Department of Chemistry, Brandeis University, Waltham, MA 02254-9110

Ashok D. Patil and Alan J. Freyer

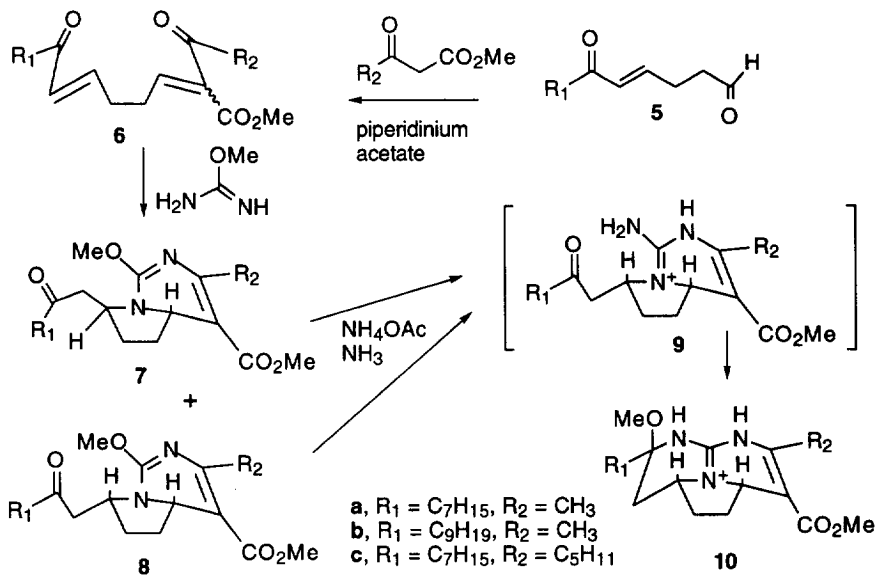
Depts of Biomolecular Discovery, Analytical Sciences, SmithKline Beecham Pharmaceuticals, King of Prussia, PA 19406-0939

Abstract: The tricyclic portion **4** of batzelladine B (**2**) is obtained from **10a**, which differs in one side chain from the ptilomycalin A model **10c** that we prepared several years ago, by reduction with $NaBH_3CN$ in buffered MeOH. Hydrogenation of **11b** over Rh/Al_2O_3 at 50 PSI H_2 affords the proposed tricyclic portion **12b** of batzelladine A (**1**). Epimerization of **12b** and hydrolysis affords acid **3**, which is similar to, but different from, the acid obtained from hydrolysis of **1**. A five step sequence converts **7b** to the anti tricyclic acid **15**, which is identical to the hydrolysis product of **1**. The stereochemistry of the hydrolysis product **15** was confirmed by NOE experiments.

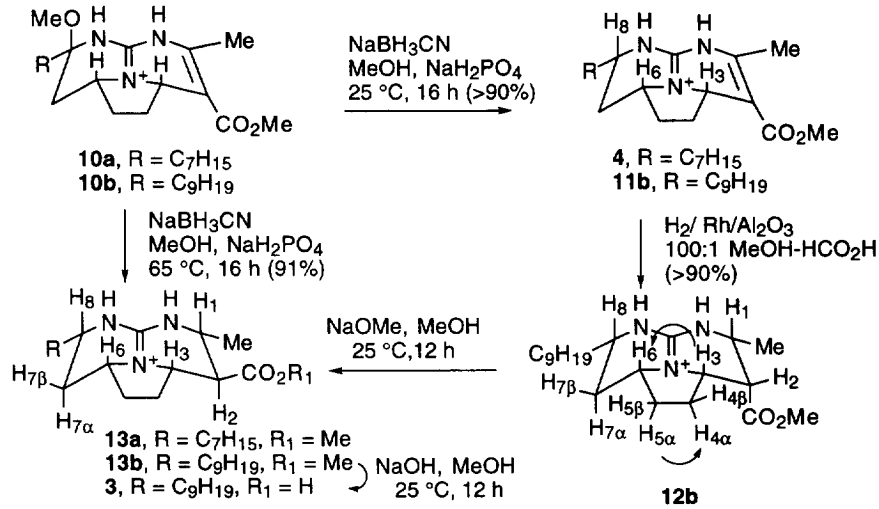
In 1995, Patil and Faulkner reported the isolation of five guanidine alkaloids, batzelladines A-E, from the Caribbean sponge *Batzella* sp, two of which, batzelladines A (**1**) and B (**2**), inhibit the binding of HIV gp-120 to CD4.[1] The structures were elucidated by interpretation of spectral data and chemical degradation. Hydrolysis of batzelladine A (**1**) gives acid **3** resulting from epimerization of the axial carboxylate of **1**; methanolysis of batzelladine B (**2**) provides methyl ester **4**. We were intrigued by these structures since the bicyclic portion **X** is very similar to crambescin A (crambine A),[2] which we synthesized in 1992,[3] and the tricyclic portion **4** differs from the ptilomycalin A model **10c**, which we synthesized in 1993,[4] by a shorter side chain and the absence of a methoxy group. We therefore set out to adapt the strategy developed for our synthesis of the pentacyclic portion of ptilomycalin A[5] to the preparation of the tricyclic portions of the batzelladines. Rama Rao has reported a 24 step enantiospecific synthesis of an alcohol corresponding to the proposed tricyclic portion of **1** starting from an optically active azetidinone.[6]



We prepared **10a**, the precursor to **4**, by the procedure we developed for the preparation of the ptilomycalin A model **10c**[4,5a] condensing aldehyde **5a**[4,5a] with methyl acetoacetate rather than methyl 3-oxooctanoate. Knoevenagel condensation[7] of **5a** with methyl acetoacetate (CH_2Cl_2, 0.2 equiv piperidinium acetate, 2 d, -20 °C) gives bis enone **6a** as a 1:1 mixture of stereoisomers.[8] Heating bis enone **6a** with *O*-methylisourea hydrogen sulfate[9] (1.5 equiv) and *i*-Pr_2EtN (1.8 equiv) in DMSO at 75 °C for 5 h affords a ≈6:1 mixture of the *trans*-isomer **7a** and the *cis*-isomer **8a** in 35% yield from **5a**. Heating a solution of this mixture with excess NH_4OAc in MeOH saturated with anhydrous NH_3 for 2 d at 60 °C in a sealed tube provides 56% of **10a** as the only isolable product.



Careful reduction of **10a** with $NaBH_3CN$ in NaH_2PO_4-buffered MeOH at 25 °C for 16 h provides >90% of **4**,[10] the tricyclic portion of batzelladine B (**2**) and <5% of over reduction product **13a**. The ^1H NMR data of synthetic **4** are identical to those of **4** obtained by methanolysis of batzelladine B (**2**) and the ^{13}C NMR data correspond to those of the tricyclic portion of batzelladine B. Reduction of **10a** thus provides an efficient, stereospecific route, with the expected axial delivery of hydride, to the tricyclic portion of batzelladine B.

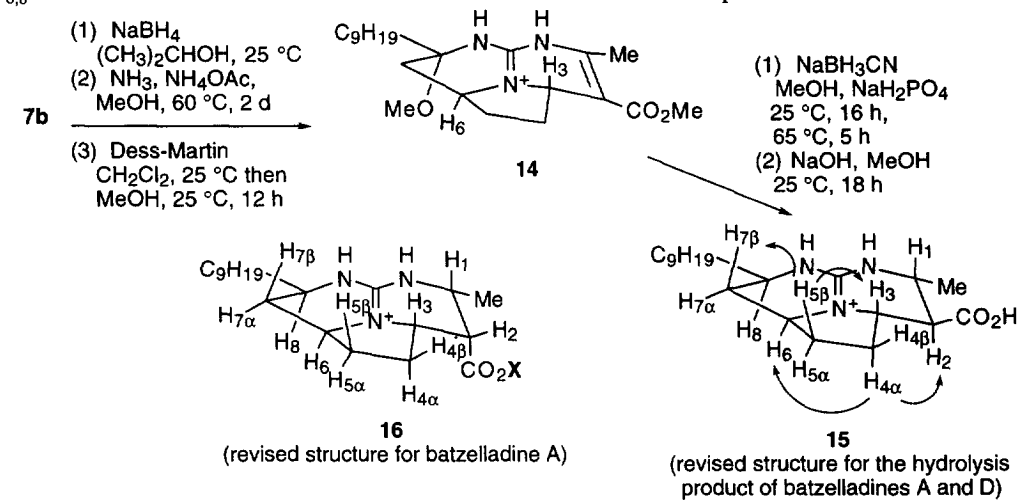


Batzelladine A (**1**) has a two carbon longer side chain than batzelladine B (**2**). Tricyclic guanidine **11b** was therefore prepared by an analogous series of reactions using decanal, rather than octanal, to prepare **5b**. Hydrogenation of **11b** over 5% Rh/Al_2O_3 at 50 psi H_2 in 100:1 MeOH–formic acid for 12 h provides **12b** in >90% yield. The structure of **12b** follows from the NMR signal of H_2 at δ 3.11 (dd, 1, J = 4, 4 Hz) which corresponds closely to that of batzelladine A. The ^1H and ^{13}C NMR spectra of **12b**[10] are similar to, but sufficiently different from, those of the tricyclic portion of batzelladine A (**1**), to suggest that the tricyclic portions are not the same. We therefore converted **12b** to **3**, the hydrolysis product of **1**. Epimerization of **12b** with 0.5 M

NaOMe in MeOH at 25 °C for 12 h gives >90% of methyl ester **13b**.[10] Axial hydrogen H_2 absorbs at δ 2.37 (dd, 1, J = 10.5, 10.5 Hz) indicating that **13b** has the correct stereochemistry with H_1, H_2, and H_3 axial as in **3**. Ester **13b** can also be obtained in 91% yield in one step from **10b** by reduction with $NaBH_3CN$ in NaH_2PO_4-buffered MeOH at reflux for 16 h. Both H_1 and H_2 are delivered axially in this reduction. Hydrolysis of **13b** with 0.25 M NaOH in MeOH at 25 °C for 12 h gives 85% of acid **3**.[10]

The ^1H and ^{13}C NMR spectra of synthetic **3** are clearly different from those of natural **3**[10] indicating that one of the structures is wrong.[11] The FABMS of natural and synthetic **3** show the same peaks with slight variation in peak height consistent with stereoisomerism. H_2 absorbs as a doublet of doublets, J = 10.2, 10.2 Hz, in both natural and synthetic **3**, indicating that H_1, H_2 and H_3 are axial in both compounds. The upfield H_7 absorbs as a ddd, J = 12, 11, 11 Hz, in both compounds indicating that H_6 and H_8 are axial in both compounds.

Therefore the difference must be in the syn/anti relationship of the two six-membered rings. The syn relationship was quite reasonably assumed in the isolation work since this relationship was present in all natural and synthetic compounds known at that time. However, isocrambescidin 800 with an anti relationship between the two six-membered rings was recently isolated.[12] In fact, molecular mechanics calculations suggest that anti saturated tricyclic guanidine **15** is 0.2 kcal/mol more stable than the syn isomer **3**.[13] The opposite is true for unsaturated tricyclic guanidines; **4** is calculated to be 4.2 kcal/mol more stable than the anti isomer. $H_{1\text{-}3}$ and $H_{6,8}$ are axial in both **3** and **15** so that both structures are consistent with the spectral data.



The two independent syntheses of **3** from **10b** suggested that the stereochemistry of synthetic **3** is correct. The stereochemistry of **4** was unambiguously determined by NOESY experiments. NOESY spectra of synthetic **3** show a small cross peak between H_3 (δ 4.05) and H_6 (δ 3.76) and a strong cross peak between $H_{4\alpha}$ (δ 1.80) and $H_{5\alpha}$ (δ 1.55).

We therefore prepared **15** from the *trans*-isomer **7b**. Reduction with $NaBH_4$ in isopropanol, followed by ammonolysis as in the formation of **10** and Dess-Martin oxidation of the alcohol affords anti isomer **14**. Equilibration of the stereochemistry by retro Michael and Michael reactions cannot occur with an alcohol in the side chain and does not occur under the mild conditions of the Dess-Martin oxidation. Reduction of **14** with $NaBH_3CN$ in buffered methanol at 25 °C and then at reflux, followed by hydrolysis affords the anti tricyclic acid **15**, whose spectral data are identical to those of the batzelladine A hydrolysis product. The stereochemistry of the natural hydrolysis product was confirmed as **15** by a series of NOE experiments in CD_3OD/pyr which showed NOEs between $H_{4\alpha}$ (δ 1.72) and both H_2 (δ 2.01) and H_6 (δ 3.58), and between $H_{5\beta}$ (δ 1.57) and both H_3 (δ 3.60) and $H_{7\beta}$ (δ 1.35). Therefore **16** is the structure of batzelladine A and **15** is the structure of the hydrolysis product of batzelladines A and D.

In conclusion, we have developed a short route to **4**, the tricyclic portion of batzelladine B, **3**, the proposed syn tricyclic portion of batzelladines A and D, and **15**, the actual anti tricyclic portion of batzelladines A and D. These constitute the first syntheses of the tricyclic portions of the batzelladines since Rama Rao[6] prepared only

the alcohol corresponding to **12b** with syn stereochemistry.[14] We are currently applying this chemistry to the syntheses of batzelladines D and E.

Acknowledgment. We are grateful to the National Institutes of Health for financial support. We thank Professor Thomas Pochapsky, Dr. Anping Wang, Mr. Huaping Mo, and Ms. Chaoyu Xie for 2D NMR experiments and Dr. Mark F. Bean for FABMS data of synthetic **3**.

References and Notes

1. Patil, A. D.; Kumar, N. V.; Kokke, W. C.; Bean, M. F.; Freyer, A. F.; De Brosse, C.; Mai, S.; Truneh, A.; Faulkner, D. J.; Carte, B.; Breen, A. L.; Hertzberg, R. P.; Johnson, R. K.; Westley, J. W.; Potts, B. C. M. *J. Org. Chem.* **1995**, *60*, 1182.
2. (a) Berlinck, R. G. S.; Braekman, J. C.; Daloze, D.; Hallenga, K.; Ottinger, R.; Bruno, I.; Riccio, R. *Tetrahedron Lett.* **1990**, *31*, 6531. (b) Berlinck, R. G. S.; Braekman, J. C.; Daloze, D.; Bruno, I.; Riccio, R.; Rogeau, R.; Amade, P. *J. Nat. Prod.* **1992**, *55*, 528. (c) Jares-Erijman, E. A.; Ingrum, A. A.; Sun, F.; Rinehart, K. *J. Nat. Prod.* **1993**, *56*, 2186.
3. (a) Snider, B. B.; Shi, Z. *J. Org. Chem.* **1992**, *57*, 2526. (b) Snider, B. B.; Shi, Z. *J. Org. Chem.* **1993**, *58*, 3828.
4. Snider, B. B.; Shi, Z. *Tetrahedron Lett.* **1993**, *34*, 2099.
5. (a) Synthesis of the pentacyclic portion of ptilomycalin A: Snider, B. B.; Shi, Z. *J. Am. Chem. Soc.* **1994**, *116*, 549. (b) Synthesis of ptilomycalin A: Overman, L. E.; Rabinowitz, M. H.; Renhowe, P. E. *J. Am. Chem. Soc.* **1995**, *117*, 2657. (c) Other studies: Murphy, P. J.; Williams, H. L.; Hurthouse, M. B.; Malik, K. M. A. *J. Chem. Soc., Chem Commun.* **1994**, 119. Murphy, P. J.; Williams, H. L. *J. Chem. Soc., Chem Commun.* **1994**, 819. Grillot, A. L.; Hart, D. J. *Heterocycles* **1994**, *39*, 435. Louwrier, S.; Ostendorf, M.; Tuynman, A.; Hiemstra, H. *Tetrahedron Lett.* **1996**, *37*, 905.
6. Rama Rao, A. V.; Gurjar, M. K.; Vasudevan, J. *J. Chem. Soc., Chem. Commun.* **1995**, 1369.
7. Jones, G. *Organic Reactions* **1967**, *15*, 204.
8. Bogdanov, V. S.; Ugrak, B. I.; Krasnaya, Zh. A.; Stytsenko, T. S. *Izv. Akad. Nauk SSSR, Ser. Khim.* **1990**, 356; *Bull. Acad. Sci. USSR, Chem. Ser.* **1990**, 298.
9. (a) O'Reilly, B. C.; Atwal, K. S. *Heterocycles* **1987**, *26*, 1185 and 1189. (b) Atwal, K. S.; Rovnyak, G. C.; O'Reilly, B. C.; Schwartz, J. *J. Org. Chem.* **1989**, *54*, 5898.
10. Synthetic **3** (400 MHz, CD_3OD) ^1H NMR 3.71-3.82 (m, 2), 3.55 (dq, 1, J = 10.2, 6.4), 3.38-3.45 (m, 1), 2.29-2.14 (m, 3), 1.87 (dd, 1, J = 10.2, 10.2), 1.78-1.85 (m, 1), 1.6-1.7 (m, 1), 1.5-1.6 (m, 2), 1.25-1.45 (m, 14), 1.27 (d, 3, J = 6.4),1.23 (ddd, 1, $J \approx$ 12, 11, 11) 0.89 (t, 3, J = 6.8); ^{13}C NMR 177.3, 150.8, 60.5, 58.1, 56.2, 51.7, 50.5, 36.0, 34.9, 33.2, 31.2, 30.8 (3 C), 30.6, 29.9, 26.4, 23.9, 19.3, 14.6; Natural **15** (natural **3**) (400 MHz, CD_3OD) ^1H NMR 3.55-3.68 (m, 3), 3.45-3.52 (m, 1), 2.31 (ddd, 1, J = 12.6, 5.2, 2.3), 2.13-2.24 (m, 2), 1.99 (dd, 1, J = 10.2, 10.2), 1.67-1.74 (m, 1), 1.5-1.64 (m, 3), 1.36 (ddd, 1, J ≈ 12, 11, 11), 1.25-1.38 (m, 14), 1.27 (d, 3, J = 6.3), 0.89 (t, 3, J = 6.8); ^{13}C NMR 177.0, 151.0, 59.2, 58.7, 55.0, 53.0, 52.1, 36.1, 34.2, 33.0, 31.7, 30.8 (3 C), 30.4, 30.3, 26.2, 23.7, 20.3, 14.4; Synthetic **4** (300 MHz, CD_3OD) 4.52 (dd, 1, J = 9, 6), 3.75-3.85 (m, 1), 3.74 (s, 3), 3.48-3.57 (m, 1), 2.53 (dddd, 1, J = 12.1, 9.1, 5.5, 2.7), 2.42 (ddd, 1, J = 13.4, 5.1, 2.7), 2.30 (s, 3), 2.10-2.28 (m, 1), 1.55-1.8 (m, 4), 1.25-1.48 (m, 13), 0.90 (t, 3, J = 6.8) (the ^1H NMR spectral data are superimposable with those of the batzelladine B hydrolysis product); 167.1, 147.4, 144.0, 103.4, 58.5, 57.3, 52.0, 51.7, 35.2, 34.1, 33.9, 33.1, 30.6, 30.4, 27.6, 26.4, 23.8, 18.0, 14.6; **12b** (300, 500 MHz, CD_3OD) ^1H NMR 4.0-4.1 (m, 1), 3.80-3.88 (m, 1), 3.73-3.80 (m, 1), 3. 75 (s, 3), 3.40-3.50 (m, 1), 3.11 (dd, 1, J = 4, 4), 2.15-2.32 (m, 3), 1.7-1.85 (m, 1), 1.5-1.7 (m, 3), 1.2-1.5 (m, 15), 1.27 (d, 3, J = 6.3), 0.89 (t, 3, J = 6.8); ^{13}C NMR 171.4, 152.0, 59.0, 58.1, 52.4, 51.8, 45.5, 36.1, 34.5, 33.2, 31.2, 30.79 (2 C), 30.75, 30.6, 28.2, 26.3, 23.9, 18.0, 14.6 (one carbon is obscured by CD_3OD at 49-50); **13b** (300 MHz, CD_3OD) ^1H NMR 3.7-3.9 (m, 2), 3.78 (s, 3), 3.66 (dq, 1, J = 10.2, 6.4); 3.38-3.50 (m, 1), 2.37 (dd, 1, J = 10.5, 10.5), 2.1-2.3 (m, 3), 1.65-1.85 (m, 2), 1.5-1.65 (m, 2), 1.2-1.4 (m, 15), 1.27 (d, 3, J = 6.4), 0.91 (d, 3, J = 6.8); ^{13}C NMR 172.1, 150.7, 59.5, 58.0, 53.2, 52.0, 51.8, 49.8, 35.9, 34.5, 33.2, 30.9, 30.7 (2 C), 30.7, 30.6, 29.8, 26.4, 23.8, 18.9, 14.6.
11. The ^1H NMR spectrum of synthetic **3** indicates the presence of <5% of **15**, which may be derived from **7b** that formed tricyclic material without equilibration.
12. Jares-Erijman, E. A.; Ingrum, A. L.; Carney, J. R.; Rinehart, K. L.; Sakai, R. *J. Org. Chem.* **1993**, *58*, 4805. Berlinck, R. G. S.; Braekman, J. C.; Daloze, D.; Bruno, I.; Riccio, R.; Ferri, S.; Spampinato, S.; Speroni, E. *J. Nat. Prod.* **1993**, *56*, 1007.
13. Molecular mechanics calculation were carried out using MODEL version KS 2.99 obtained from Prof. Kosta Steliou, Boston University.
14. For another synthesis of **4** see: Franklin, A. S.; Overman, L. E. Presented at the 212th National Meeting of the American Chemical Society, Orlando, FL, August 1996.

(*Received in USA* 28 *June* 1996; *revised* 5 *August* 1996; *accepted* 8 *August* 1996)