Pergamon

Tetrahedron Letters 42 (2001) 6637–6640

TETRAHEDRON LETTERS

Stereoselective construction of the azabicyclic core applicable to the biologically important polyguanidinium alkaloids batzelladine A and D using a free radical cyclization

P. Andrew Evans* and Thara Manangan

Department of Chemistry, Indiana University, Bloomington, IN 47405, USA

Received 22 June 2001; revised 20 July 2001; accepted 23 July 2001

Abstract—The intramolecular addition of the free radical derived from the alkyl bromide **13** provides an expeditious and stereoselective approach to the azabicyclic core **14**, which is applicable to the biologically important polyguanidinium alkaloids batzelladine A (**1**) and D (**2**). © 2001 Published by Elsevier Science Ltd.

The batzelladines are a growing family of novel and highly complex polyguanidinium alkaloids that were isolated from the Caribbean sponge *Batzella* sp. by Patil and Faulkner.[1,2] Batzelladine A (**1**, Fig. 1) is particularly pertinent because it competitively inhibits the binding of the HIV envelope protein gp-120 to the human CD4 receptor with micromolar affinity. Since acquired immunodeficiency syndrome (AIDS) is associated with the progressive decline in the number of $CD4^+$ cells, which in turn leads to the failure of the immune system and ultimately death through susceptibility to infection, this relationship is clearly important and mechanistically intriguing. Hence, the therapeutic significance of the batzelladines coupled with their unique and complex skeletal composition has stimulated significant synthetic attention.[3–5] The stereochemical revision of batzelladine A and D by Snider and co-workers to an *anti*-relationship of the angular hydrogens flanking the pyrrolidine nitrogen, allowed Overman and co-workers to accomplish the first asymmetric total synthesis of batzelladine D.[6,7]

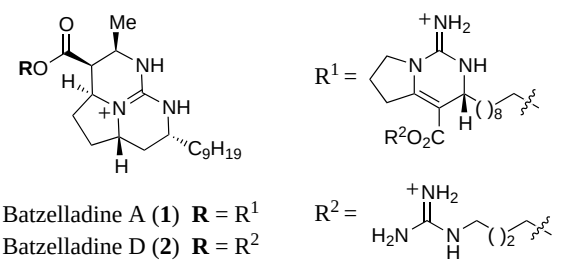


Figure 1.

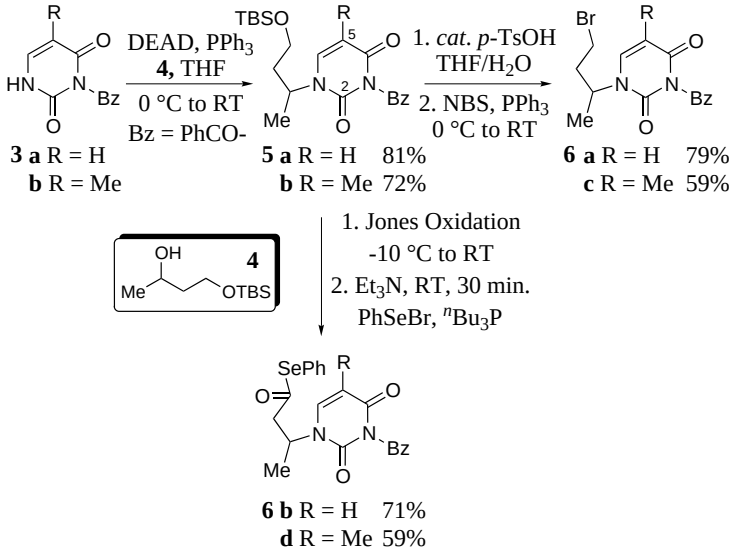
We have recently demonstrated that oxauracil and oxathymine provide excellent free radical acceptors for a variety of radical cyclization reactions.[8] This type of approach, with 5-(hydroxymethyl)uracil, was expected to provide a diastereoselective route to an intermediate, which would be applicable to the guanidinium core of batzelladine A and D. Furthermore, this strategy would circumvent the problem associated with controlling the C-5 carboxylate stereochemistry (thymine numbering). Herein, we now describe an adaptation to our previous studies, which provides both an expeditious and diastereoselective route to the azabicyclic core of these important natural products.

Scheme 1 summarizes the synthetic routes utilized for the preparation of the prerequisite alkyl bromides **6a**/**c** and acyl selenides **6b**/**d** for our initial study. Treatment of the secondary alcohol **4** with 3-*N*-benzoyl protected uracil and thymine **3a**/**b** under Mitsunobu conditions furnished **5a** and **5b** in 81% and 72% yield, respectively.[9,10] The alkyl halides **6a**/**c** were then prepared via the acid-catalyzed hydrolysis of the *tert*-butyldimethylsilyl group **5a**/**b**, and treatment of the resulting primary alcohol with *N*-bromosuccinimide and triphenylphosphine.[11] The acyl radical cyclization reactions were examined for comparative purposes, in which additional functionality was expected to be useful for analog studies. Oxidation of the primary *tert*-butyldimethylsilyl ethers **5a**/**b** with Jones reagent

Keywords: radical cyclization; natural products; batzelladine A and D; anti-HIV.

* Corresponding author. E-mail: paevans@indiana.edu

0040-4039/01/$ - see front matter © 2001 Published by Elsevier Science Ltd.
PII: S0040-4039(01)01340-5



3 a R = H
b R = Me

5 a R = H 81%
b R = Me 72%

6 a R = H 79%
c R = Me 59%

6 b R = H 71%
d R = Me 59%

Scheme 1.

furnished the corresponding carboxylic acids, which were converted using the Crich protocol to the acyl selenides **6b**/**d** in good yield.[12,13]

Table 1 summarizes the results for the alkyl and acyl radical cyclization reactions. Treatment of **6a**/**b** with tris(trimethylsilyl)silane and triethylborane, in the presence of air, furnished the corresponding azacycles **7a**/**b** with $\geq$19:1 diastereoselectivity (entries 1–2).[15,16] The origin of the *trans*-diastereoselectivity was attributed to non-bonding interactions between the C-2 carbonyl of uracil and the incipient α-amino stereogenic center.[8,17] The synthesis of the batzelladines using this strategy requires the introduction of an additional stereogenic center at C-5.

We envisioned that thymine would serve as a useful model to examine the stereoselectivity of a radical reduction at C-5. Treatment of **6c**/**d** under analogous reaction conditions furnished the azabicycles **7c**/**d** with $\geq$19:1 diastereoselectivity at C-5/6 (entries 3–4). The origin of diastereocontrol at C-5 is presumably a consequence of the conformational bias of the azabicyclic core derived after the cyclization, which results in reduction from the more accessible convex face of the molecule, as illustrated in Fig. 2.[18]

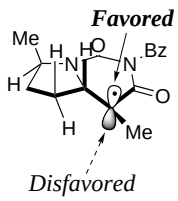
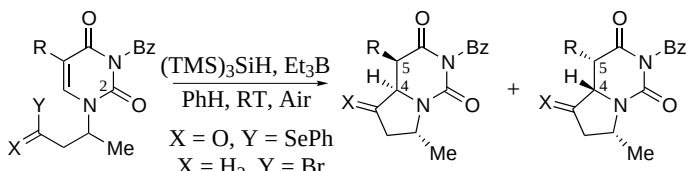


Figure 2.

Table 1. Intramolecular alkyl and acyl radical additions with uracil and thymine derivatives[14]



6 Bz = PhCO

7 + **8**

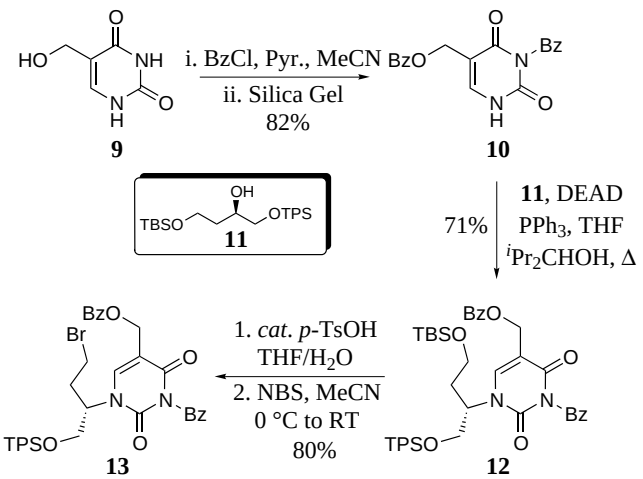
Entry		Radical precursor **6**[a]			Conc. (M)	Ratio of **7**/**8**[b]	Yield (%)[c]
		R =	X =	Y =			
1	**a**	H	H_2	Br	0.02	$\geq$19:1	78
2	**b**	H	O	SePh	0.02	$\geq$19:1	70
3	**c**	Me	H_2	Br	0.02	$\geq$19:1	72
4	**d**	Me	O	SePh	0.02	$\geq$19:1	81

[a] All reactions were carried out on a 0.5 mmol reaction scale.
[b] Ratios of diastereoisomers were determined by 400 MHz ^{1}H NMR integration.
[c] Isolated yields.

Scheme 2 outlines the preparation of alkyl bromide **13** required for the batzelladine polycyclic guanidinium core.[14] Selective protection of 5-(hydroxymethyl)uracil **9** with benzoyl chloride and pyridine followed by purification on a silica gel, furnished bis-*N*,*O*-benzoyl-5-(hydroxymethyl)uracil **10** in 82% overall yield. The alkyl bromide **13** was then prepared in an analogous fashion to **6a**, albeit with an enantiomerically enriched secondary alcohol **11** derived from (*R*)-malic acid.[19]

Treatment of **13** under the standard free radical cyclization conditions furnished the azabicycle **14** as the major *diastereoisomer* (Scheme 3).[14] The stereochemistry of **14** was confirmed with the aid of an NOE NMR experiment, which established the *syn*-relationship of the protons at C-5/6 (thymine numbering).

In conclusion, we have demonstrated that *intramolecular* addition of alkyl and acyl radicals to uracil, thymine and 5-(hydroxymethyl)uracil derivatives provides a diastereoselective route to 5,6-azabicycles, in which the latter is applicable to the polycyclic guanidinium core of batzelladine A and D. Furthermore, the azabicyclic cores represent unnatural nucleoside analogs that may serve as useful mechanistic probes.



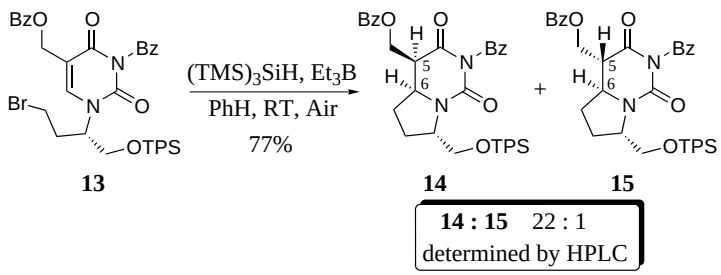
Scheme 2.

Acknowledgements

We sincerely thank the National Institutes of Health (GM58877) for generous financial support. We also thank Eli Lilly for a *Young Faculty Grantee Award* GlaxoWellcome for a *Chemistry Scholar Award* and Novartis Pharmaceuticals for an *Academic Achievement Award*. The Camille and Henry Dreyfus Foundation is thanked for a *Camille Dreyfus Teacher-Scholar Award* (P.A.E.), and the Development and Promotion of Science and Technology Talents Project (DPST)-Thailand for a Graduate Fellowship (T.M.).

References

1. For the isolation and biological evaluation of batzelladines A–E, see: Patil, A. D.; Kumar, N. V.; Kokke, W. C.; Bean, M. F.; Freyer, A. J.; DeBrosse, C.; Mai, S.; Truneh, A.; Faulkner, D. J.; Carté, B.; Breen, A. L.; Hertzberg, R. P.; Johnson, R. K.; Westley, J. W.; Potts, B. C. M. *J. Org. Chem.* **1995**, *60*, 1182.
2. For the isolation and biological evaluation of batzelladines F–I, see: Patil, A. D.; Freyer, A. J.; Taylor, P. B.; Carté, B.; Zuber, G.; Johnson, R. K.; Faulkner, D. J. *J. Org. Chem.* **1997**, *62*, 1814.
3. For a short review on the batzelladines, see: Berlinck, R. G. S. *Nat. Prod. Rep.* **1999**, 339.
4. For synthetic approaches to the batzelladines, see: (a) Rao, A. V. R.; Gurjar, M. K.; Vasudevan, J. *J. Chem. Soc., Chem. Commun.* **1995**, 1369; (b) Louwrier, S.; Ostendorf, M.; Tuynman, A.; Hiemstra, H. *Tetrahedron Lett.* **1996**, *37*, 905; (c) Snider, B. B.; Chen, J. *Tetrahedron Lett.* **1998**, *39*, 5697; (d) Franklin, A. S.; Ly, S. K.; Mackin, G. H.; Overman, L. E.; Shaka, A. J. *J. Org. Chem.* **1999**, *64*, 1512; (e) Black, G. P.; Murphy, P. J.; Thornhill, A. J.; Walshe, N. D. A.; Zanetti, C. *Tetrahedron* **1999**, *55*, 6547; (f) Nagasawa, K.; Koshino, H.; Nakata, T. *Tetrahedron Lett.* **2001**, *42*, 4155 and pertinent references cited therein.
5. For the synthesis and determination of the absolute configuration of the batzelladine A (**1**) side chain, see: Duron, S. G.; Gin, D. Y. *Org. Lett.* **2001**, *3*, 1551.
6. For the revision of the stereochemistry of batzelladines A and D, see: Snider, B. B.; Chen, J.; Patil, A. D.; Freyer, A. J. *Tetrahedron Lett.* **1996**, *39*, 6977.
7. For the first enantioselective total synthesis of batzelladine D, see: Cohen, F.; Overman, L. E.; Ly Sakata, S. K. *Org. Lett.* **1999**, *1*, 2169.



Scheme 3.

8. Evans, P. A.; Manangan, T.; Rheingold, A. L. *J. Am. Chem. Soc.* **2000**, *122*, 11009.
9. For the preparation of 3-*N*-benzoyluracil and thymine, see: Cruickshank, K. A.; Jiricny, J.; Reese, C. B. *Tetrahedron Lett.* **1984**, *25*, 681.
10. For a recent review on the Mitsunobu reaction, see: Hughes, D. L. *Org. React.* **1992**, *42*, 335. For a related example using maleimide, see: Walker, M. A. *J. Org. Chem.* **1995**, *60*, 5352.
11. Yuasa, Y.; Kano, S.; Shibuya, S. *Heterocycles* **1991**, *32*, 2311.
12. Evans, P. A.; Roseman, J. D.; Garber, L. T. *Synth. Commun.* **1996**, *26*, 4685.
13. Batty, D.; Crich, D. *Synthesis* **1990**, 273.
14. All new compounds exhibited spectroscopic (IR, ^{1}H and ^{13}C NMR) and analytical (HRMS) data in accord with the assigned structure. Representative data given for compound **14**: $[\alpha]_D^{19}$ +1.52 ($c=1.1$, $CHCl_3$); IR ($CDCl_3$) 3018 (m), 2957 (m), 2930 (m), 2858 (m), 1752 (s), 1706 (s), 1662 (s) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.99–7.20 (m, 4H), 7.59–7.51 (m, 6H), 7.41–7.29 (m, 8H), 7.24–7.20 (m, 2H), 4.82 (dd, $J=3.5$, 11.8, 1H), 4.77 (dd, $J=4.2$, 11.8, 1H), 4.30 (dd, $J=3.6$, 10.4, 1H), 4.19–4.07 (m, 2H), 3.57 (dd, $J=1.6$, 10.4 Hz, 1H), 2.94 (dt, $J=3.8$, 12.2 Hz, 1H), 2.58–2.51 (m, 1H), 2.25–2.13 (m, 2H), 1.84–1.73 (m, 1H), 0.97 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.45 (e), 168.28 (e), 166.10 (e), 148.85 (e), 135.52 (o), 135.44 (o), 134.55 (o), 133.38 (e), 132.86 (e), 132.64 (e), 132.51 (e), 130.19 (o), 129.84 (o), 129.71 (o), 129.30 (e), 129.01 (o), 128.50 (o), 127.78 (o), 127.74 (o), 62.95 (e), 59.94 (e), 59.52 (o), 56.29 (o), 46.97 (o), 32.01 (e), 26.75 (o), 25.78 (e), 19.17 (e); HRMS (CI, M^+) calcd for $C_{39}H_{40}N_2O_6Si$ 660.2656, found 660.2662.
15. For a recent reviews on this reagent, see: (a) Chatgilialoglu, C. *Acc. Chem. Res.* **1992**, *25*, 188; (b) Chatgilialoglu, C.; Ferreri, C.; Gimisis, T. In *The Chemistry of Organic Silicon Compounds*; Rappoport, S.; Apeloig, Y., Eds.; Wiley: London, 1998; Vol. 2, Chapter 25, p. 1539.
16. For related examples of the intramolecular addition of aryl and alkyl radicals to uracil derivatives, see: (a) Yoshimura, Y.; Otter, B. A.; Ueda, T.; Matsuda, A. *Chem. Pharm. Bull.* **1992**, *40*, 1761; (b) Zhang, W.; Pugh, G. *Tetrahedron Lett.* **1999**, *40*, 7591 and pertinent references cited therein.
17. For a related example of a stereoselective free radical cyclization where a similar nonbonding interaction is invoked to rationalize the *trans*-diastereoselectivity, see: (a) Hart, D. J.; Kanai, K. *J. Am. Chem. Soc.* **1983**, *105*, 1255; (b) Beckwith, A. L. J.; Joseph, S. P.; Mayadunne, R. T. A. *J. Org. Chem.* **1993**, *58*, 4198.
18. For recent reviews on alkyl and acyl radicals in synthesis, see: (a) Curran, D. P. In *Comprehensive Organic Synthesis*; Trost, B. M.; Fleming, I., Eds.; Pergamon: Oxford, 1992; Vol. 4; (b) Chatgilialoglu, C.; Crich, D.; Komatsu, M.; Ryu, I. *Chem. Rev.* **1999**, *99*, 1991 and pertinent references cited therein.
19. McCauley, J. A.; Nagasawa, K.; Lander, P. A.; Mischke, S. G.; Semones, M. A.; Kishi, Y. *J. Am. Chem. Soc.* **1998**, *120*, 7647.