Available online at www.sciencedirect.com
ScienceDirect
Tetrahedron Letters
Tetrahedron Letters 47 (2006) 9187–9189

An efficient Mitsunobu coupling to adenine-derived carbocyclic nucleosides

Xue-qiang Yin, Wei-kuan Li and Stewart W. Schneller*

Department of Chemistry and Biochemistry, Auburn University, Auburn, AL 36849-5312, United States

Received 21 August 2006; revised 23 October 2006; accepted 24 October 2006

Abstract—Adenine is a poor substrate for the Mitsunobu process to carbocyclic nucleosides. However, *N*-6 amino bis-Boc-protected adenine is reported herein to undergo an efficient coupling under these conditions as a result of its increased solubility and the reduced competing nucleophilicity of the free adenine amino substituent. Products from this reaction are readily converted to aristeromycin, neplanocin, and analogs there from, including 5′-homoaristeromycin, a promising antiviral agent.

Taken together, aristeromycin (**1**) and neplanocin A (**2**) provide the centerpiece for a wide range of biologically relevant adenine derived carbocyclic nucleoside derivatives.[1] It was within this context that we found 5′-homoaristeromycin (**3**) to possess an important antiviral (orthopox) activity.[2] To facilitate an exploration of this latter observation a more efficient route to **3** was desired (Fig. 1).

In that direction, the commonly used Mitsunobu reaction[3] for achieving carbocyclic nucleosides[4] from substituted cyclopentan(en)ols and heterocyclic bases has found a limited application when used with adenine.[5]

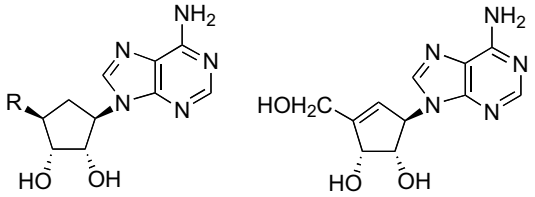


Figure 1.

This result may reside in one or both of the following: (1) the low solubility of adenine in THF, the solvent of choice for the Mitsunobu process, and (2) complicating nucleophilic based side reactions involving the free C-6 adenine amino group. To circumvent these obstacles, 6-chloropurine has been employed as the heterocyclic unit.[6,7] However, such an approach requires an additional high temperature/pressure amination step to achieve the requisite amino center, which affects the overall yield.[6,7]

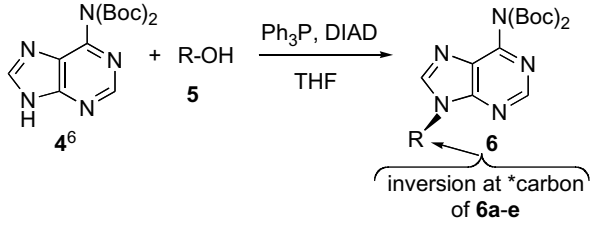
A thorough scrutiny of the literature suggested the *t*-butoxycarbonyl protected adenine derivative **4**[8] (Table 1) as a worthy candidate to subject to the Mitsunobu reaction with **5a** as the start of a convergent pathway leading to **3**. To our delight **6a**[9] was achieved within 5 h at room temperature. The desired **3** was then conveniently obtained from the hydroboration of **6a** followed by acid deprotection.[4,10a,b]

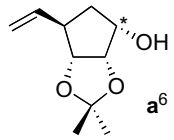
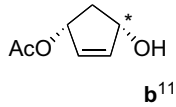
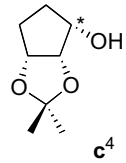
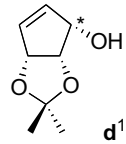
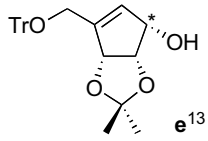
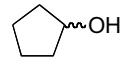
To evaluate the versatility of **4** as the favored adenine Mitsunobu substrate for other adenine derived carbanucleosides, the equally favorable results[9] presented in Table 1 were found. For allylic alcohols **5b**,[11] **5d**,[12] and **5e**[13] the coupling occurred within 30 min at 0 °C in yields near 90%. On the other hand, for the non-allylic cyclopentanols **5a** and **5c** a longer reaction time (2–5 h) at room temperature was required for the yields of 85%. Compound **5f**[14] proceeded under the least restrictive conditions and resulted in the highest yield (96%). This may be due to the presence of the sterically unencumbered hydroxyl of **5f**.

Keywords: Aristeromycin and neplanocin analogs; Boc protected adenine; Mitsunobu.
* Corresponding author. Tel.: +1 334 844 5737; fax: +1 334 844 5748; e-mail: schnest@auburn.edu

0040-4039/$ - see front matter © 2006 Published by Elsevier Ltd.
doi:10.1016/j.tetlet.2006.10.126

Table 1. Mitsunubo reaction of bis-Boc-adenine **4** with substituted cyclopentan(en)ols



Entry	R-OH	Reaction conditions	Yield[a] (%)
1	 **a**[6]	rt, 5 h	85
2	 **b**[11]	0 °C, 30 min	88
3	 **c**[4]	rt, 2 h	85
4	 **d**[12]	0 °C, 30 min	93
5	 **e**[13]	0 °C, 30 min	92
6	 **f**[14]	0 °C, 10 min	96

[a] Based on ^{1}H NMR analysis for **6a**, **6c**–**6f** (using the purine H-2, ca. δ 8.0 ppm, the H-8, ca. δ 8.8 ppm, or the isopropyl CH, ca. δ 5.0 ppm, for the integrative determinations).

Structural confirmation for the adenine coupled products (**6b**–**6f** in Table 1) was accomplished by conversion[10b,c] to their unprotected carbocyclic nucleoside derivative: **8**[7] (for **6b**), **9**[15,16] (for **6c**), **10**[17] (for **6d**), **2**[18] (for **6e**) and **11**[19] (for **6f**) (Fig. 2).

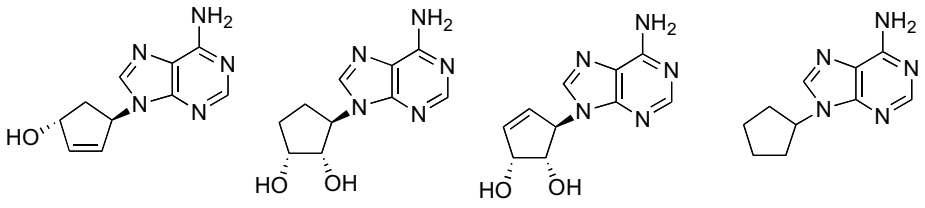


Figure 2.

Acknowledgements

This research was supported by funds from the NIH (AI 56540).

References and notes

1. (a) Wolfe, M. S.; Borchardt, R. T. *J. Med. Chem.* **1991**, *34*, 1521–1530; (b) Schneller, S. W. *Curr. Top. Med. Chem.* **2002**, *2*, 1087–1092; (c) Rodriguez, J. B.; Comin, M. J. *Mini-Rev. Med. Chem.* **2003**, *3*, 95–114.
2. Yang, M.; Schneller, S. W. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 149–151.
3. (a) Mitsunobu, O. *Synthesis* **1981**, 1–28; (b) Martin, S. F.; Dodge, J. A. *Tetrahedron Lett.* **1991**, *32*, 3017–3020; (c) Hughes, D. L. *Org. Prep. Proced. Int.* **1996**, *28*, 127–164.
4. Yang, M.; Zhou, J.; Schneller, S. W. *Tetrahedron* **2006**, *62*, 1295–1300.
5. See, for example: (a) Kitade, Y.; Ando, T.; Yamaguchi, T.; Hori, A.; Nakanishi, M.; Ueno, Y. *Bioorg. Med. Chem.* **2006**, *14*, 5578–5583; (b) Yang, M.; Schneller, S. W.; Korba, B. B. *J. Med. Chem.* **2005**, *48*, 5043–5046.
6. Yang, M.; Ye, W.; Schneller, S. W. *J. Org. Chem.* **2004**, *69*, 3993–3996.
7. Dyatkina, N. B.; Theil, F.; von Janta-Lipinski, M. *Tetrahedron* **1995**, *51*, 761–772.
8. Dey, S.; Garner, P. *J. Org. Chem.* **2000**, *65*, 7697–7699.
9. A typical procedure: To a solution of alcohol (**5a**–**f**) (1 mmol), triphenyphosphine (1.2 mmol) and **4**[8] in dry THF (10 mL) at 0 °C were added dropwise, di*iso*propyl azodicarboxylate (DIAD) (1.2 mmol). In most cases a pale orange or colorless clear solution was observed immediately following the addition of DIAD. Upon completion of the reaction (by TLC), the mixture was evaporated in vacuo to dryness and the resultant residue purified by flash chromatography. (Chromatography solvents were the mixtures of hexanes and EtOAc.) The reaction conditions and yields are presented in Table 1.
10. (a) Hydroboration/hydrogen peroxide treatment[4] of **6a** followed by deprotection[10b] produced **3**. (b) Deprotection could be accomplished in a good yield by dissolving the requisite precursor in 3 N HCl in MeOH followed by heating at 50 °C overnight. Removal of the solvent was followed by neutralization with IRA-67 resin in MeOH. Evaporation of the reaction mixture yielded a residue that was purified by flash chromatography (EtOAc/MeOH). (c) To fully deprotect **6b**, deacetylation was carried out using K_2CO_3 in MeOH for 1 h after the removal of the Boc groups.[10b]
11. Siddiqi, S. M.; Chen, X.; Schneller, S. W. *Nucleosides Nucleotides* **1993**, *12*, 267–278.
12. Seley, K. L.; Schneller, S. W.; Rattendi, D.; Lane, S.; Bacchi, C. J. *J. Med. Chem.* **1997**, *40*, 625–629.
13. Schneller, S. W.; Yang, M. In *Antiviral Drug Discovery for Emerging Diseases and Bioterrorism Threats*; Torrence, P. F., Ed.; Wiley-Interscience, 2005; pp 139–152.

14. Commercially available.
15. Wolfe, M. S.; Lee, Y.; Bartlett, W. J.; Borcherding, D. R.; Borchardt, R. T. *J. Med. Chem.* **1992**, *35*, 1782–1791.
16. Seley, K. L.; Schneller, S. W.; Korba, B. *J. Med. Chem.* **1998**, *41*, 2168–2170.
17. Borcherding, D. R.; Scholtz, S. A.; Borchardt, R. T. *J. Org. Chem.* **1987**, *52*, 5457–5461.
18. Wolfe, M. S.; Anderson, B. L.; Borcherding, D. R.; Borchardt, R. T. *J. Org. Chem.* **1990**, *55*, 4712–4717.
19. NMR data for **11**: white solid, mp 149–151 °C; δ_H (400 MHz; $CDCl_3$; Me_4Si) 8.37 (s, 1H), 7.86 (s, 1H), 5.76 (br s, 2H), 4.93 (p, $J = 7.2$ Hz, 1H), 2.29 (m, 2H), 1.96–2.01 (m, 4H), 1.82 (m, 2H); δ_C (100 MHz; $CDCl_3$; Me_4Si) 155.4, 152.7, 150.2, 138.7, 120.0, 56.0, 32.8, 23.8.