Available online at www.sciencedirect.com
SCIENCE DIRECT®
Tetrahedron Letters 46 (2005) 1927–1929
Tetrahedron Letters

Isomers of neplanocin A and 2′-deoxyneplanocin A possessing a C-1′/C-6′ double bond

Xue-qiang Yin and Stewart W. Schneller*

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

Received 16 December 2004; revised 12 January 2005; accepted 13 January 2005

Abstract—Missing among the unsaturated carbocyclic nucleosides is the 1′,6′-double bond isomer of neplanocin A. A practical synthesis of this compound and its 2′-deoxy derivative is reported from readily accessible cyclopentenols.

Considerable evidence has shown that the introduction of a rigid structural element into the cyclopentyl moiety of carbocyclic nucleosides can lead to compounds with interesting biological properties.[1] The most studied examples in this class are neplanocin A (**1**),[2] fused cyclopropyl derivatives (as represented by **2**[3]), and 2′,3′-didehydro-2′,3′-dideoxy derivatives of carbaguanosine.[4] These results prompted our interest in the neplanocin C-1′/C-6′[5a] alkenic isomer **3**, which presents a planar arrangement at the C-1′ center. Such derivatives[6,7] lend themselves to interesting biological studies by presenting, for example, an unexplored structural dimension for mono-, oligo-, and polymeric nucleosidic compositions.[1,5b,8]

Our initial goal in investigating this class of nucleosides was to develop a general synthetic procedure that would be adaptable to a variety of heterocyclic base derivatives. In this direction, because adenine is the base component of neplanocin A, **3** and the 2′-deoxy **4** were selected to serve as the platform from which to develop this series. A preliminary account of the preparation of **3** and **4** is reported here (Fig. 1).

The key feature of our plan to **3** and **4** was to place a leaving group at C-6′[5a] of a requisite adenine derivative and conduct a 1,2-elimination procedure between C-1′ and C-6′. Epoxides were envisioned as offering stereochemically and functionally versatile synthetic frameworks for this purpose.

The preparation of **3** began with allylic alcohol **5**,[9] which was converted to the β-alcohol **6** by, first, a Mitsunobu reaction followed by ammonolysis (Scheme 1). The crucial precursor for this investigation, **7**, was then prepared from **6** following a literature procedure[10] and protected as its *p*-methoxybenzyl derivative **8**. Direct epoxidation of **8** gave exclusively β-epoxide rather than

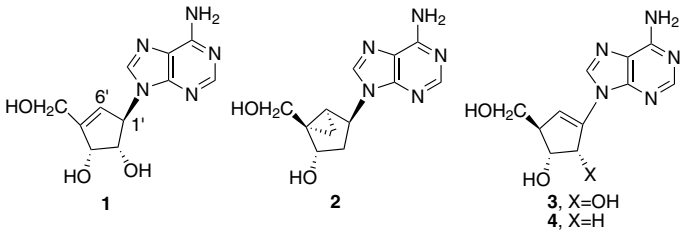
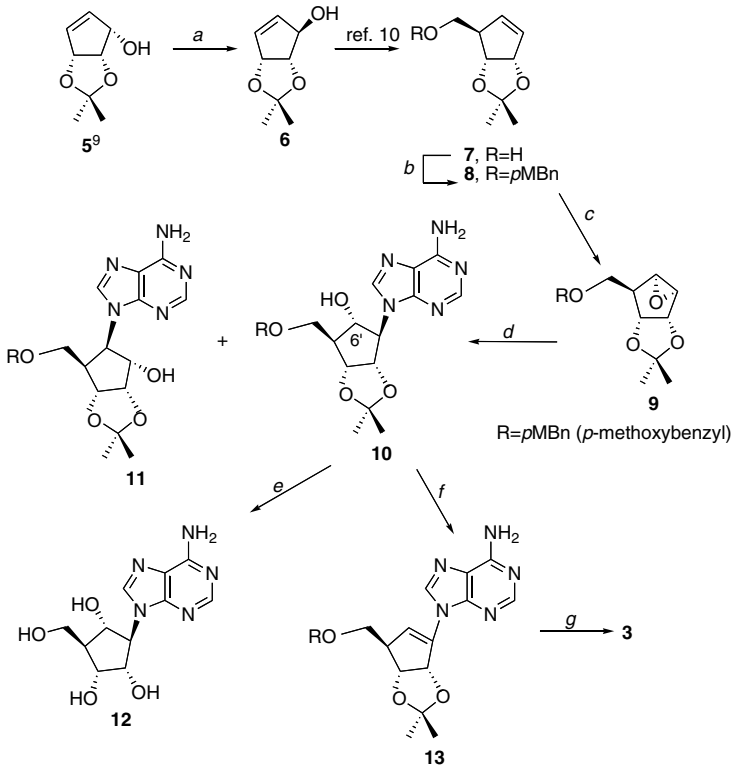


Figure 1.

Keywords: Carbocyclic nucleosides; Neplanocin analogs; Epoxide ring opening; Antiviral.
* Corresponding author. Tel.: +1 334 844 5737; fax: +1 334 844 5748; e-mail: schnest@auburn.edu

0040-4039/$ - see front matter
doi:10.1016/j.tetlet.2005.01.061



Scheme 1. Reagents and conditions: (a) (i) *p*-nitrobenzoic acid, DIAD, Ph_3P, THF; (ii) NH_3, MeOH (81% for two steps); (b) *p*MBnCl, NaH, DMF (86%); (c) (i) HCl, MeOH; (ii) *m*CPBA, CH_2Cl_2; (iii) $Me_2C(OMe)_2$, acetone, *p*TSA (80% for three steps); (d) adenine, NaH, 15-crown-6, DMF (**10**, 43%; **11**, 39%); (e) (i) TFA; (ii) 1 N HCl (83%); (f) (i) $HC(OMe)_2NMe_2$, DMF; (ii) MsCl, DMAP, CH_2Cl_2; (iii) NaOMe, THF/MeOH, reflux; (iv) MeOH, reflux (60% for four steps); (g) (i) 10% TFA, CH_2Cl_2; (ii) 1 N HCl (51% for two steps).

the α-isomer **9**, which was desired for purine nucleophilic ring opening.[11] Since formation of the β-isomer could be rationalized by invoking *iso*-propylidene steric control embodied within the Henbest rule,[11,12] the following sequence to **9** as the only product was employed: deprotection of the *iso*-propylidene of **8** (to the 2,3-diol), epoxidation with *m*CPBA, and re-introduction of the *iso*-propylidene (step c, Scheme 1). Nucleophilic opening of **9** with adenine gave, after careful silica gel column chromatographic separation (MeOH/EtOAc, 1:30), **10** (43%) and **11** (39%). A similar result was achieved with sodium azide as nucleophilic source on a substrate analogous to **9**.[11,13]

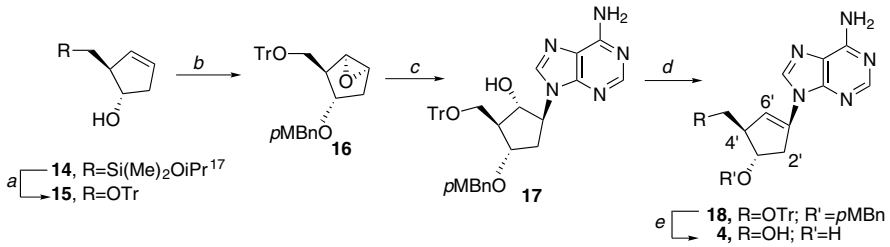
The structure of **10** was established by comparing NMR spectra: (i) compound **10** with a similarly C-5′ protected aristeromycin[11] and (ii) compound **12**, from deprotection of **10**, with a racemic analog.[11] Compound **11** was confirmed by using a proton–proton COSY NMR analysis, which will be detailed in the full paper on this research.

Introduction of a mesylate to C-6′ of **10** was sought to provide the desired leaving group at this center. However, direct mesylation of **10** using methylsulfonyl chloride failed. In view of this, blocking the C-6 purine amine of **10** with *N*,*N*-dimethylformamide dimethyl acetal then allowed smooth mesylate formation. Refluxing this amino protected compound (not shown) with sodium methoxide in tetrahydrofuran followed by methanol provided **13** (4 steps, 65% yield from **10**). Debenzylation of **13** with trifluoroacetic acid and, subsequent acidic deketalization completed the synthesis of **3**[14] (Scheme 1). Structural confirmation for **3** came from a proton NMR analysis[15]: (i) appearance of a peak at δ 6.60 is in the expected region[16] for H-6′; (ii) H-6′ of isomeric neplanocin A has been reported to appear at δ 5.69[15b]; and (iii) presence of an H-4′ peak for **3** (δ 2.79) while there was, of course, no corresponding peak for neplanocin A.[15b]

The synthesis of **4** began with a Tamao oxidation of **14**[17] (Scheme 2) followed by selective trityl protection of the resultant primary alcohol to give **15** in 65% yield. Epoxidation[11] of **15** followed by methoxybenzylation afforded **16**. Nucleophilic opening[18] of **16** with adenine resulted in the desired, single product **17**.[18] Following the same steps for converting **10**–**3** (steps f and g of Scheme 1), target **4**[14b,19a] was obtained from **17** (via **18**).

The regiochemistry of **4** was confirmed by analyzing its ^1H NMR spectrum,[19] which was substantially different from the isomeric 2′-deoxyneplanocin.[19,20] Particularly diagnostic was its H-6′ absorption (δ 6.48), which is very similar to **3**, while the H-6′ for 2′-deoxyneplanocin exists further upfield (δ 5.75).

The biological analysis of **3** and **4** is underway and will be presented in the full paper on this new class of nucleoside derivatives.



Scheme 2. Reagents and conditions: (a) (i) KF, $KHCO_3$, H_2O_2, MeOH/THF (v/v, 50%), 75%; (ii) TrCl, pyridine, DMAP, 86%; (b) (i) *m*CPBA, CH_2Cl_2, 75%; (ii) *p*MBnCl, NaH, DMF, 94%; (c) adenine, NaH,15-crown-6, DMF, 91%; (d) (i) $HC(OMe)_2NMe_2$, DMF; (ii) MsCl, DMAP, CH_2Cl_2; (iii) NaOMe, THF/MeOH, reflux; (iv) MeOH, reflux (65% for four steps); (e) (i) 10% TFA, CH_2Cl_2; (ii) 1 N HCl (55% for two steps).

Acknowledgements

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

References and notes

1. (a) Marquez, V. E. *Adv. Antivir. Drug Des.* **1996**, *2*, 89–146; (b) Ferrero, M.; Gotor, V. *Chem. Rev.* **2000**, *100*, 4319–4347.
2. (a) De Clercq, E. *Antimicrob. Agents Chemother.* **1985**, *28*, 84–89; (b) Bray, M.; Raymond, J. L.; Geisbert, T.; Baker, R. O. *Antivir. Res.* **2002**, *55*, 151–159.
3. Marquez, V. E.; Russ, P.; Alonso, R.; Siddiqui, M. A.; Hernandez, S.; George, C.; Nicklaus, M. C.; Dai, F.; Ford, H., Jr. *Helv. Chim. Acta* **1999**, *82*, 2119–2129.
4. Crimmins, M. T.; King, B. W.; Zuercher, W. J.; Choy, A. L. *J. Org. Chem.* **2000**, *65*, 8499–8509.
5. (a) Ref. 5b establishes precedence for this atom numbering; (b) Xu, Y.; Kino, K.; Sugiyama, H *J. Biomol. Struct. Dyn.* **2002**, *20*, 437–446.
6. Madhavan, G. V. B.; McGee, D. P. C.; Rydzewski, R. M.; Boehme, R.; Martin, J. C.; Prisbe, E. J. *J. Med. Chem.* **1988**, *31*, 1798–1804, reported a small amount (3%) of a racemic C-1′/C-6′ alkenic compound accompanying the synthesis of an α-fluoroaristeromycin derivative.
7. Biggadike, K.; Borthwick, A. D.; Exall, A. M. *J. Chem. Soc., Chem. Commun.* **1990**, 458–459, mentioned the low yield of a protected carbathymidine arising during their preparation of the pyrimidine analog of 2′-deoxyneplanocin A.
8. Altmann, K.-H.; Bévierre, M.-O.; De Mesmaeker, A.; Moser, H. E. *Bioorg. Med. Chem. Lett.* **1995**, *5*, 431–436.
9. Seley, K. L.; Schneller, S. W.; Rattendi, D.; Lane, S.; Bacchi, C. J. *J. Med. Chem.* **1997**, *40*, 625–629.
10. Ovaa, H.; Lastdrager, B.; Codée, J. D. C.; van der Marel, G. A.; Overkleeft, H. S.; van Boom, J. H. *J. Chem. Soc., Perkin Trans. 1* **2002**, 2370–2377.
11. Cheikh, A. B.; Craine, L. E.; Recher, S. G.; Zemlicka, J. *J. Org. Chem.* **1988**, *53*, 929–936.
12. Henbest, H. B.; Wilson, R. A. L. *J. Chem. Soc.* **1957**, 1958–1965.
13. Yin, X.; Schneller, S.W., unpublished results.
14. (a) HRMS for compound **3**, 263.1014 (calcd 263.1018); (b) satisfactory microanalytical data was obtained for compounds **3** and **4**.
15. (a) *NMR data for compound* **3**: ^{1}H (DMSO-d_6) δ 8.31 (s, 1H), 8.20 (s, 1H), 7.35 (br s, 2H), 6.60 (d, J = 1.75 Hz, 1H, H-6′), 5.30 (d, J = 4.25 Hz, 1H), 4.95 (t, J = 6.50 Hz, 1H), 4.83 (d, J = 7.0 Hz, 1H), 4.14 (m, 1H), 3.85 (m, 1H), 3.67 (m, 1H), 3.42 (m, 1H), 2.79 (m, 1H, H-4′). ^{13}C (DMSO-d_6) δ 161.6, 158.4, 154.7, 143.9, 143.3, 125.0, 124.5, 77.9, 76.4, 67.3, 57.8; (b) *NMR data for neplanocin*[21]: ^{1}H (DMSO-d_6) δ 8.11 (s, 1H), 8.05 (s, 1H), 7.20 (br s, 2H), 5.69 (s, 1H, H-6′), 5.33 (br d, J = 2.5 H, 1H), 5.16–4.92 (br s, 3H), 4.42 (d, J = 5.4 Hz, 1H), 4.30 (t, J = 5.4 Hz, 1H), 4.11 (m, 2H). ^{13}C (DMSO-d_6) δ 156.0, 152.3, 150.1, 149.7, 139.5, 123.4, 119.2, 76.6, 72.2, 64.2, 58.6.
16. Yin, X.; Schneller, S. W. *Tetrahedron* **2004**, *60*, 3451–3455.
17. Matsuumi, M.; Ito, M.; Kobayashi, Y. *Synlett* **2002**, 1508–1510.
18. Biggadike, K.; Borthwick, A. D.; Exall, A. M.; Kirk, B. E.; Roberts, S. M.; Youds, P. *J. Chem. Soc., Chem. Commun.* **1987**, 1083–1084.
19. (a) *NMR data for compound* **4**: ^{1}H (DMSO-d_6) δ 8.27 (s, 1H), 8.20 (s, 1H), 7.33 (br s, 2H), 6.48 (s instead of expected d, 1H, H-6′), 5.04 (d, J = 4.75 Hz, 1H), 4.70 (t, J = 5.50 Hz, 1H), 4.17 (m, 1H), 3.48–3.20 (m, 3H), 2.78–2.72 (m, 2H). ^{13}C (DMSO-d_6) δ 156.2, 153.1, 148.2, 148.1, 138.9, 133.1, 119.3, 116.7, 70.6, 62.5, 56.3, 41.1. Satisfactory microanalytical data was obtained for compound **4**; (b) *NMR data for 2′-deoxyneplanocin*[20]: ^{1}H (DMSO-d_6) δ 8.13 (s, 1H), 7.97 (s, 1H), 7.17 (br, 2H), 5.75 (d, 1H, H-6′), 5.64 (m, 1H), 5.06 (d, 1H), 4.85–5.0 (m, 2H), 4.15 (br, 2H), 2.2–2.4 (m, 2H).
20. Fukukawa, K.; Ueda, T.; Hirano, T. *Chem. Pharm. Bull.* **1983**, *31*, 1842–1847.
21. Trost, B. M.; Madsen, R.; Guile, S. D.; Brown, B. *J. Am. Chem. Soc.* **2000**, *122*, 5947–5956.