Available online at www.sciencedirect.com
SCIENCE DIRECT
Tetrahedron Letters 47 (2006) 4057–4059
Tetrahedron Letters

A practical synthetic route to 4′-alkylaristeromycin derivatives: 4′-methylaristeromycin

Xue-qiang Yin and Stewart W. Schneller*

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

Received 17 March 2006; accepted 29 March 2006
Available online 2 May 2006

Abstract—(−)-(1*S*,4*R*)-4-Hydroxy-2-cyclopenten-1-yl acetate provided a convenient entry point for a 16-step chiral preparation of 4′-methylaristeromycin. This procedure is adaptable to a number of carbocyclic nucleosides with a diversity of substitution at C-4′ and C-5′ and a variety of heterocyclic bases.

Nucleosides substituted at the C-4′ center have attracted moderate attention[1,2] because of (1) the synthetic challenges they pose[1,2] and (2) the biological properties of, for example, nucleocidin[3] and 4′-cyano, -azido, and -methoxy and related derivatives.[1,2] While carbocyclic nucleosides have had some representation among this class of compounds, 4′-alkyl derivatives have received little attention.[2c,g,h] Research underway in our laboratories demanded that we develop a facile and stereospecific pathway with flexibility for analog development for this latter series. For that purpose, 4′-methylaristeromycin (**1**, see Scheme 1) was chosen as the initial target to develop the prototypical procedure.

Our investigations into carbocyclic nucleosides have been guided by the desire to use a common starting point for as many of the synthetic targets as possible. This role has been played by (−)-(1*S*,4*R*)-4-hydroxy-2-cyclopenten-1-yl acetate (**2**),[4] which, for this project, was silylated[5] to **3**. Glycolization of **3**, followed by acetonide formation, provided **4**, which was then subjected to ammonolysis to give **5**.[6] Oxidation of the secondary alcohol of **5** under Dess–Martin periodinane conditions (to **6**)[6] and a subsequent 1,2-addition of methylmagnesium bromide furnished **7**.[7] Our plan to obtain the target compound next required enone **8**. Conversion of **7** through diol **9**, following the literature method[8] failed to give **8** in consistent yields. However, enone **8** was achieved efficiently by a three-step reaction sequence (step h of Scheme 1): (i) dehydration of **7** using a Mitsunobu-type[5] elimination; (ii) desilylation to give a mixture of exocyclic and endocyclic alkenes (1:1, vinylic NMR analysis); and (iii) subsequent oxidation with PCC and Celite.

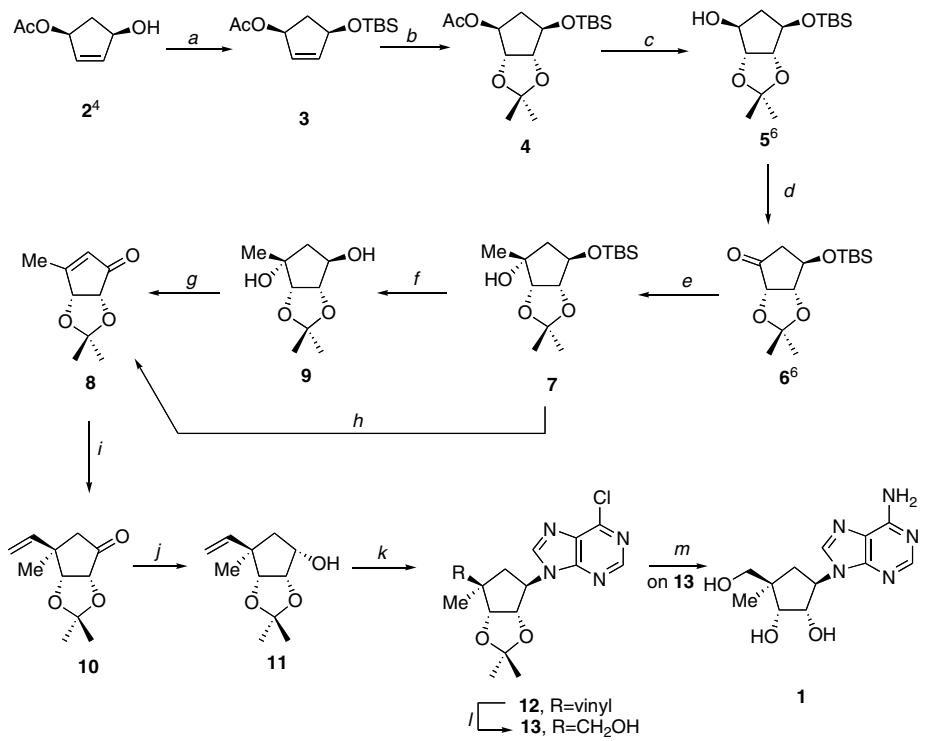
Attempts to treat **8** with a protected primary alcohol C-5′ synthon, such as the lithium salt of *t*-butyl methyl ether, via a Michael addition[9] failed, possibly, because of the *t*-butyl steric demands. With this outcome, the less bulky vinyl magnesium bromide was employed to give exclusively the convex-face selective product **10**[8] in yields as high as 76% if the reaction mixture was allowed to rise to room temperature after initial addition of enone at −78 °C.[10] After reduction of **10** with lithium aluminum hydride, a Mitsunobu coupling of the resultant **11** with 6-chloropurine yielded a mixture of the desired product **12** and the inseparable by-product arising from azadicarboxylate. This mixture was used in the next step without further purification.

Transformation of the C-4′ ethylene of **12** to the hydroxymethyl group of **13** was accomplished in a two-step sequence:[10] (i) oxidative cleavage of the double bond with osmium tetroxide/sodium periodate, followed by (ii) sodium borohydride reduction. Ammonolysis of **13** with subsequent hydrolytic deprotection proceeded smoothly to furnish 4′-methylaristeromycin (**1**).[11]

In conclusion, the synthetic route disclosed herein allows for a number of C-4′ and C-5′ substituted carbocyclic nucleosides possessing a variety of bases by

Keywords: Carbocyclic nucleosides; Mitsunobu coupling; Cyclopentanones.
* Corresponding author. Tel.: +1 334 844 5737; fax: +1 334 844 5748; e-mail: schnest@auburn.edu

0040-4039/$ - see front matter © 2006 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2006.03.188



Scheme 1. Reagents and conditions: (a) TBSCl, imidazole, CH_2Cl_2, 90%; (b) (i) NMO, OsO_4, THF/H_2O; (ii) *p*-TSA, 2,2-dimethoxypropane, acetone, 88% for two steps; (c) NH_3, MeOH, 85%; (d) Dess–Martin periodinane,[6,8] CH_2Cl_2, 95%; (e) MeMgBr, THF, 94%; (f) TBAF, THF, 94%; (g) (i) PCC, NaOAc; (ii) HOAc;[8] (h) (i) TPP, DIAD, toluene; (ii) TBAF, THF, 86% for two steps; (iii) PCC, Celite, CH_2Cl_2, 91%; (i) CH_2=CHMgBr, HMPA, TMSCl, CuBr·Me_2S, THF, 76%; (j) DIBAL, THF, 95%; (k) TPP, DIAD, 6-chloropurine, THF; (l) (i) OsO_4, $NaIO_4$, MeOH; (ii) $NaBH_4$, MeOH, 33% from **11**; (m) (i) NH_3, MeOH; (ii) 0.5 N HCl, MeOH, 73% for two steps.

choosing different Grignard reagents (step e, Scheme 1), manipulating the transformation-rich vinyl moiety (of **12**), and changing the heterocyclic substrate employed in the Mitsunobu transformation (step k).

Acknowledgements

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

References and notes

1. (a) Maag, H.; Rydzewski, R. M.; McRoberts, M. J.; Crawford-Ruth, D.; Verheyden, J. P. H.; Prisbe, E. J. *J. Med. Chem.* **1992**, *35*, 1440–1451; (b) Reed, A. D.; Hegedus, L. S. *Organometallics* **1997**, *16*, 2313–2317; (c) Crich, D.; Hao, X. *J. Org. Chem.* **1998**, *63*, 3796–3797; (d) Crich, D.; Hao, X. *J. Org. Chem.* **1999**, *64*, 4016–4024; (e) Jung, M. E.; Toyota, A. *J. Org. Chem.* **2001**, *66*, 2624–2635; (f) Hegedus, L. S.; Hervert, K. L.; Matsui, S. *J. Org. Chem.* **2002**, *67*, 4076–4080; (g) Hegedus, L. S.; Geisler, L.; Riches, A. G.; Salman, S. S.; Umbricht, G. *J. Org. Chem.* **2002**, *67*, 7649–7655; (h) Haraguchi, K.; Takeda, S.; Tanaka, H. T. *Org. Lett.* **2003**, *5*, 1399–1402.
2. (a) Biggadike, K.; Borthwick, A. D. *J. Chem. Soc., Chem. Commun.* **1990**, 1380–1382; (b) Borthwick, A. D.; Biggadike, K.; Paternoster, I. L.; Coates, J. A. V.; Knight, D. J. *Bioorg. Med. Chem. Lett.* **1993**, *3*, 2577–2580; (c) Kitano, K.; Miura, S.; Ohrui, H.; Meguro, H. *Tetrahedron* **1997**, *53*, 13315–13322; (d) Kato, K.; Suzuki, H.; Tanaka, H.; Miyasaka, T. *Tetrahedron: Asymmetry* **1998**, *9*, 911–914; (e) Wachtmeister, J.; Mühlman, A.; Classon, B.; Samuelsson, B. *Tetrahedron* **1999**, *55*, 10761–10770; (f) Nieto, M. I.; Blanco, J. M.; Caamaño, O.; Fernández, F.; Garcia-Mera, X.; López, C.; Balzarini, J.; De Clercq, E. *Nucleosides Nucleotides Nucleic Acids* **1999**, *18*, 2253–2263; (g) Gumina, G.; Chong, Y.; Choi, Y.; Chu, C. K. *Org. Lett.* **2000**, *2*, 1229–1231; (h) Roy, A.; Schneller, S. W. *J. Org. Chem.* **2003**, *68*, 9269–9273; (i) Hegedus, L. S.; Cross, J. *J. Org. Chem.* **2004**, *69*, 8492–8495; (j) Kumamoto, H.; Haraguchi, K.; Tanaka, H.; Nitanda, T.; Baba, M.; Dutschman, G. E.; Cheng, Y.-C.; Kato, K. *Nucleosides Nucleotides Nucleic Acids* **2005**, *24*, 73–83; (k) Kim, A.; Hong, J. H. *Nucleosides Nucleotides Nucleic Acids* **2005**, *24*, 63–72.
3. Jenkins, I. D.; Verheyden, J. P. H.; Moffatt, J. G. *J. Am. Chem. Soc.* **1971**, *93*, 4323–4324.
4. (a) Deardorff, D. R.; Myles, D. C. *Org. Synth.* **1989**, *67*, 114–120; (b) Siddiqi, S. M.; Chen, X.; Schneller, S. W. *Nucleosides Nucleotides* **1993**, *12*, 267–278.
5. Yin, X.-q.; Schneller, S. W. *Tetrahedron Lett.* **2005**, *46*, 7535–7538.
6. Nakashima, H.; Sato, M.; Taniguchi, T.; Ogasawara, K. *Synthesis* **2000**, *6*, 817–823.
7. The stereochemical assignment for the 1,2-addition product **7** was based on the literature precedence.[8]
8. Nakashima, H.; Sato, M.; Taniguchi, T.; Ogasawara, K. *Tetrahedron Lett.* **2000**, *41*, 2639–2642.
9. Wolfe, M. S.; Anderson, B. L.; Borcherding, D. R.; Borchardt, R. T. *J. Org. Chem.* **1990**, *55*, 4712–4717.
10. Yang, M. M.; Ye, W.; Schneller, S. W. *J. Org. Chem.* **2004**, *69*, 3993–3996.

11. Selected data for **1**: white solid, mp > 216 °C (dec.); $[\alpha]_D^{22.9}$ −4.17 (*c*, 0.048 in MeOH); (Found: C, 49.58; H, 6.06; N, 23.75. $C_{12}H_{17}N_5O_3 \cdot 0.7H_2O$ requires C, 49.33; H, 6.30; N, 23.98.) δ_H (250 MHz; DMSO-d_6; Me_4Si) 8.18 (s, 1H), 8.10 (s, 1H), 7.17 (br s, 2H), 4.93 (m, 2H), 4.63 (d, $J = 4.5$ Hz, 1H), 4.57 (m, 1H), 4.37 (m, 1H), 3.77 (t, $J = 4.5$ Hz, 1H), 3.43 (m, 1H), 3.27 (m, 1H), 1.88–1.77 (m, 2H), 0.98 (s, 3H); δ_C (100 MHz; DMSO-d_6; Me_4Si) 156.3, 152.4, 150.0, 140.4, 119.6, 75.2, 73.4, 69.2, 58.6, 44.8, 37.7, 20.1.