

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

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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.

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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, nucleocidin³ 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 silylated⁵ 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 method⁸ 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-type⁵ 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.

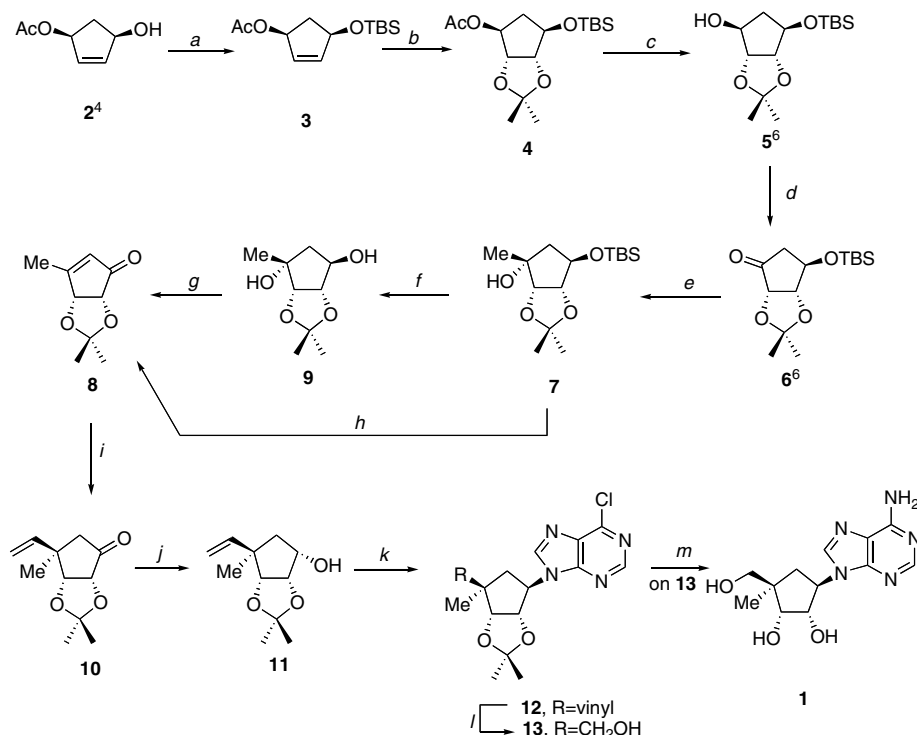
Attempts to treat **8** with a protected primary alcohol C-5' synthon, such as the lithium salt of *t*-butyl methyl ether, via a Michael addition⁹ failed, possibly, because of the *t*-butyl steric demands. With this outcome, the less bulky vinyl magnesium bromide was employed to give exclusively the 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.

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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) $\text{CH}_2=\text{CHMgBr}$, HMPA, TMSCl, $\text{CuBr}\cdot\text{Me}_2\text{S}$, 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).

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11. Selected data for **1**: white solid, mp > 216 °C (dec.); $[\alpha]_{\text{D}}^{22.9} -4.17$ (*c*, 0.048 in MeOH); (Found: C, 49.58; H, 6.06; N, 23.75. $\text{C}_{12}\text{H}_{17}\text{N}_3\text{O}_3 \cdot 0.7\text{H}_2\text{O}$ requires C, 49.33; H, 6.30; N, 23.98.) δ_{H} (250 MHz; DMSO- d_6 ; Me₄Si) 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 ; Me₄Si) 156.3, 152.4, 150.0, 140.4, 119.6, 75.2, 73.4, 69.2, 58.6, 44.8, 37.7, 20.1.