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

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Abstract—(−)-(1S,4R)-4-Hydroxy-2-cyclopeten-1-yl acetate provided a convenient entry point for a 16-step chiral preparation of 4'-methyalaristeromycin. This procedure is adaptable to a number of carboxyclic 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 attention1,2 because of (1) the synthetic challenges they pose1,2 and (2) the biological properties of, for example, nucleosidin3 and 4'-cyano, -azido, and -methoxy and related derivatives.1,2 While carboxyclic nucleosides have had some representation among this class of compounds, 4'-alkyl derivatives have received little attention.2e,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'-methyalaristeromycin (1, see Scheme 1) was chosen as the initial target to develop the prototypical procedure.

Our investigations into carboxyclic 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 (−)-(1S,4R)-4-hydroxy-2-cyclopeten-1-yl acetate (2),4 which, for this project, was silylated5 to 3. Glycologism of 3, followed by acetamide 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-butylic steric demands. With this outcome, the less bulky vinyl magnesium bromide was employed to give exclusively the convex-face selective product 10 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 azadecarboxylate. 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'-methyalaristeromycin (1).11

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

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References and notes


7. The stereochemical assignment for the 1,2-addition product 7 was based on the literature precedence.8


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. $C_{12}H_{17}N_{2}O_{3} \cdot 0.7H_{2}O$ requires C, 49.33; H, 6.30; N, 23.98.) $\delta_{H}$ (250 MHz; DMSO-$d_{6}$, Me$_{4}$Si) 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); $\delta_{C}$ (100 MHz; DMSO-$d_{6}$, Me$_{4}$Si) 156.3, 152.4, 150.0, 140.4, 119.6, 75.2, 73.4, 69.2, 58.6, 44.8, 37.7, 20.1.