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A 9-STEP ENANTIOSPECIFIC SYNTHESIS OF (-)-ARISTEROMYCIN FROM D-RIBONIC ACID γ-LACTONE

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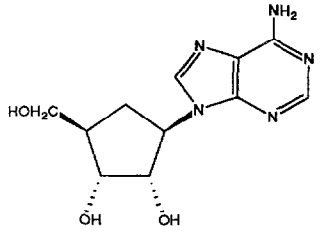
Abstract: A short, efficient, enantiospecific total synthesis of (-)-aristeromycin, which can be modified for making analogues of this carbocyclic nucleoside, is reported.

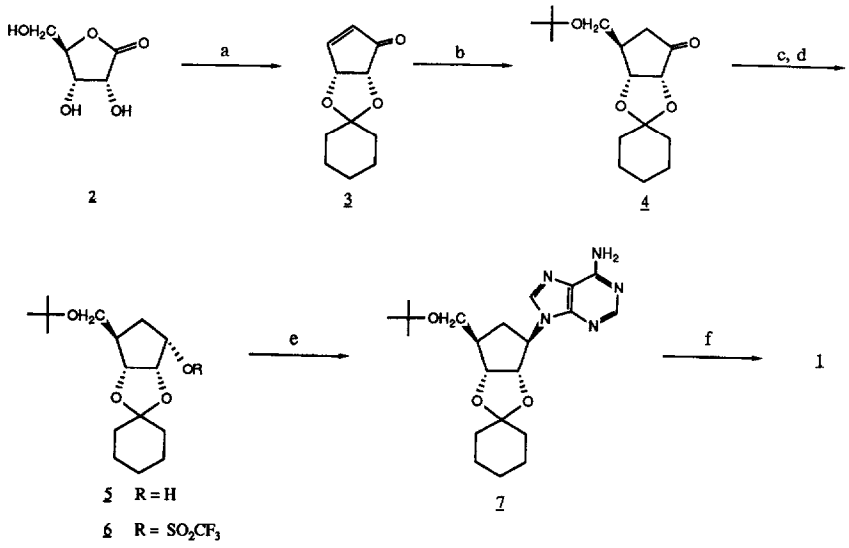
The adenosine analogue (-)-aristeromycin (1), isolated from *S. citricolor*,[1] is among several carbocyclic nucleoside analogues with antiviral and cytotoxic activities.[2] The interesting biochemical characteristics of 1, as well as the challenge it presents to organic chemists, have prompted racemic,[3] enantioselective[4] and enantiospecific[5] syntheses. In this communication, we report an enantiospecific total synthesis of 1, which has the advantages, over previously reported enantiospecific syntheses, of fewer steps (9 vs. the shortest, 12) and more versatility for the synthesis of potentially bioactive analogues of 1.



1

The synthesis (scheme I) begins with D-ribonic acid γ-lactone (2), a useful chiral building block extolled by Bhat, et. al.[6] Compound 2 was converted to cyclopentenone 3 in four steps as previously reported from this laboratory.[7] This enone was treated with lithium di-(t-butoxymethylene)cuprate[8] to afford the conjugate-addition product 4 in 81% purified yield.[9] The compound was diastereomerically pure by ^{1}H- and ^{13}C-NMR. Decoupling experiments revealed $J(H_3H_4)$ = 1 Hz, corresponding to a dihedral angle of either 65° or 105° according to the Karplus equation. Molecular models illustrate that the former angle is not attainable with H_3 and H_4 in either a *cis* or *trans* relationship. The latter angle is easily attainable with these protons *trans* to

Scheme I



a) 4 steps. See ref. 7 b) $[(CH_3)_3COCH_2]_2CuLi$, -78° to -30°C c) DIBAH, CH_2Cl_2, 0°C, 3 h. d) $(CF_3SO_2)_2O$, pyridine, CH_2Cl_2, 0°C, 30 min. e) adenine, NaH, 18-crown-6 (3 eq. each), DMF, 0°C, 18 h.[10] f) CF_3COOH/H_2O (2:1), 50°C, 3 h.[13,14]

each other, but not when they are *cis*, providing evidence that the alkyl portion of the cuprate added to the least hindered face of the enone as expected.

Cyclopentanone 4 was then reduced with diisobutylaluminum hydride (DIBAH) to give alcohol 5 in 96% crude yield.[10] Spectroscopic analyses indicated the compound was 92% diastereomerically pure; the two diastereomers were readily separated by silica gel chromatography (Et_2O: hexane, 1:1). Deuterium exchange of the hydroxyl proton and irradiation of $H_{5\alpha}$ and $H_{5\beta}$ revealed that $J(H_1H_2)$ = 5 Hz for the major isomer and $J(H_1H_2)$ = 0 Hz for the minor isomer. Again, using models and the Karplus equation, the major isomer has H_1 and H_2 in a *cis* relationship (i.e., DIBAH approached selectively from the least hindered face).

The alcohol was then converted to the triflate 6 with triflic anhydride in 95% yield.[11,12] Displacement with sodium adenide in DMF at 0°C gave 7 in 30% yield.[13] The chemical shift values for the purine carbons in the ^{13}C-NMR spectrum were consistent with N-9 substitution.[14] No N-7 substituted isomer was detected. Mesylation[15] of alcohol 5 proceeded in a quantitative crude yield, but the subsequent adenide displacement was sluggish even at 90°C. Compound 7 was deprotected by heating to 50°C in trifluoroacetic acid/water (2:1, 3h) resulting in 1 in 79% yield.[16,17] The final compound was one diastereomer by HPLC and coeluted with an authentic sample of 1. Spectroscopic data, optical rotation and melting point matched literature values for 1, or, where not provided in the literature, were consistent with its structure.

Modification of the preceding sequence to provide analogues of 1 is in progress in this laboratory. Other substituents can replace the hydroxymethylene group by reacting 3 with different organocuprates. This is important in the design of more selective chemotherapeutic agents based on 1 since the hydroxymethylene group has been implicated with cytotoxic effects of carbocyclic nucleoside analogues.[18]

ACKNOWLEDGEMENTS

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9) IR (KBr, cm^{-1}): 2960, 2930, 2915, 2860, 1750, 1450, 1365, 1205, 1165, 1110, 1075, 1000. ^{1}H-NMR ($CDCl_3$, ppm): 1.10 (s, 9H), 1.30-1.70 (m, 10H), 2.04 (d, J = 17 Hz, 1H), 2.55 (dt, J_1 = 9 Hz, J_2 = 2 Hz, 1H), 2.73 (dd, J_1 = 17 Hz, J_2 = 9 Hz, 1H), 3.36 (dd, J_1 = 9 Hz, J_2 = 2 Hz, 1H), 3.55 (dd, J_1 = 9 Hz, J_2 = 2 Hz, 1H), 4.23 (d, J = 5 Hz, 1H), 4.62 (d, J = 5 Hz, 1H). ^{13}C-NMR ($CDCl_3$, ppm): 23.6, 23.9, 25.0, 27.1, 34.0, 36.4, 37.4, 37.6, 63.1, 73.3, 78.7, 81.6, 111.5, 213.1. MS (EI, 70 eV, m/e): 282 (M^+), 226, 197, 183, 140, 98, 69, 57. M.p. = 81-83° C. $[\alpha]_D$= -154° (c = 0.184, $CHCl_3$).

10) IR (neat, cm^{-1}): 3515, 2965, 2930, 2855, 1450, 1395, 1365, 1285, 1250, 1235, 1200, 1165, 1150, 1110, 1090, 1040, 1015, 955, 915, 890, 855. ^{1}H-NMR ($CDCl_3$, ppm): 1.15 (s, 9H), 1.35-1.75 (m, 10H), 1.85 (m, 2H), 2.20 (m, 1H), 2.55 (d, J = 10 Hz, 1H, exchanged with D_2O), 3.20 (dd, J_1 = 4 Hz, J_2 = 9 Hz, 1H), 3.30 (dd, J_1 = 4 Hz, J_2 = 9 Hz, 1H), 4.20 (m, 1H), 4.45 (m, 2H). ^{13}C-NMR ($CDCl_3$, ppm): 23.6, 24.0, 25.2, 27.4, 33.8, 36.0, 36.1, 42.2, 63.1, 72.1, 72.5, 79.2, 83.1, 111.3. MS (EI, 70 eV, m/e): 284 (M^+), 255, 241, 229, 185, 167, 113, 99, 95, 57. $[\alpha]_D$ = -13° (c = 0.726, $CHCl_3$).

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12) ^{1}H-NMR ($CDCl_3$, ppm): 1.10 (s, 9H), 1.25-1.75 (m, 10H), 1.95 (m, 1H), 2.25 (m, 2H), 3.20 (dd, J_1 = 2 Hz, J_2 = 8 Hz, 1H), 3.35 (dd, J_1 = 4 Hz, J_2 = 8 Hz, 1H), 4.35 (d, J = 5 Hz, 1H),

4.50 (dd, J_1 = 5 Hz, J_2 = 5 Hz, 1H), 5.25 (m, 1H). ^{13}C-NMR ($CDCl_3$, ppm): 23.7, 23.9, 25.1, 27.2, 33.0, 34.0, 35.8, 41.4, 63.0, 73.0, 78.2, 83.2, 87.1, 112.3, 119.0 (q, CF_3).

13) Work up involved suction filtration, distillation of solvent, extraction between CH_2Cl_2 and water, followed by silica gel chromatography with CH_2Cl_2: EtOH (17:3). IR (KBr, cm^{-1}): 3320, 3160, 2960, 2930, 2855, 1640, 1595, 1575, 1470, 1365, 1100, 650. ^{1}H-NMR ($CDCl_3$, ppm): 1.25 (s,9H), 1.35-1.90 (m, 10H), 2.25-2.65 (m, 3H), 3.50 (dd, J_1 = 6 Hz, J_2 = 9 Hz, 1H), 3.60 (dd, J_1 = 4 Hz, J_2 = 9 Hz, 1H), 4.65 (dd, J_1 = 4 Hz, J_2= 6 Hz, 1H), 4.85 (m, 1H), 5.05 (dd, J_1 = 5 Hz, J_2 = 6 Hz, 1H), 6.40 (br.s., 2H), 7.95 (s, 1H), 8.35 (s, 1H). ^{13}C-NMR ($CDCl_3$, ppm): 23.4, 23.9, 25.0, 27.4, 34.3, 34.6, 37.4, 44.0, 61.8, 62.3, 72.8, 81.2, 83.5, 113.9, 120.1, 139.4, 150.0, 152.6, 155.7. MS (EI, 70 eV, m/e): 402(M+1), 358, 344, 246, 216, 136, 57, 41. $[\alpha]_D$ = -32° (c = 0.630, $CHCl_3$).

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