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An efficient synthesis of (−)-3-deazaaristeromycin

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Abstract—The coupling reaction of 4-chloro-1*H*-imidazo[4,5-*c*]pyridine (6-chloro-3-deazapurine) and (3a*S*,4*S*,6*R*,6a*R*)-tetrahydro-2,2-dimethyl-6-vinyl-3a*H*-cyclopenta-[*d*][1,3]dioxo-4-ol under Mitsunobu reaction conditions provides, after three subsequent straightforward reactions, ready access to the highly biologically active (−)-3-deazaaristeromycin. The versatility of this procedure opens access to a diverse pool of 3-deazapurine carbocyclic nucleosides.

Medicinal chemists and biochemists have long used structural modification of naturally occurring nucleosides as a source for new agents that fit their research objectives.[1] Replacing the N-3 of purine nucleosides with a methine unit (hence, a 3-deazapurine) has been particularly rewarding.[2,3] Particularly noteworthy within the 3-deazapurine collection are the carbocyclic nucleosides 3-deazaaristeromycin (**1**)[4] and 3-deazaneplanocin (**2**),[5] both of which display potent biological activity. A limiting feature for an extensive study of **1** and analogs derived therefrom has been the lack of a versatile, high yielding synthetic pathway (Fig. 1).

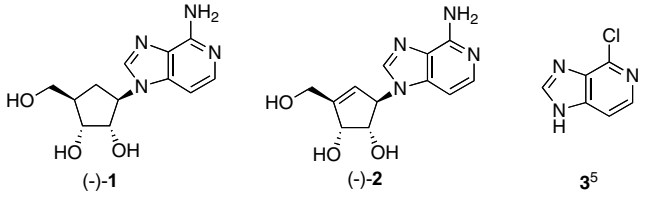
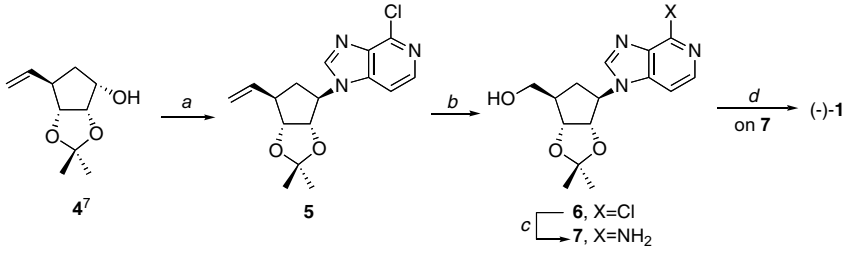


Figure 1.

To address this situation our attention turned to the Mitsunobu reaction,[6] which has been widely used for preparing carbocyclic nucleosides from 6-chloropurine and various cyclopentanols in generally good yields. It was surprising to find that the Mitsunobu reaction with 4-chloro-1*H*-imidazo[4,5-*c*]pyridine (6-chloro-3-deazapurine, **3**)[5] and cyclopentanols had not been reported. Thus, this reaction was investigated as the beginning point to a practical synthesis of 3-deazaaristeromycin.

In that direction, reaction of **3**[5] with the vinyl substituted cyclopentanol **4**[7] under standard Mitsunobu conditions (diisopropyl azodicarboxylate and



Scheme 1. Reagents: (a) DIAD, Ph_3P, THF, 70%; (b) i. OsO_4, $NaIO_4$, MeOH; ii. $NaBH_4$, MeOH, 81% for two steps; (c) i. NH_2NH_2, THF; ii. Ra-Ni, MeOH/H_2O, 75% for two steps; (d) HCl/MeOH, 89%.

Keywords: Carbocyclic nucleosides; Aristeromycin; 3-Deazapurine; Mitsunobu reaction.
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triphenylphosphine) gave a 70% yield of the adduct **5**.[8] Manipulation of the vinyl group of **5** to the requisite hydroxymethyl side chain (**6**)[9] was accomplished in two steps in the same reaction vessel: (i) osmium tetroxide/sodium periodate oxidative (to the aldehyde) followed by (ii) sodium borohydride reduction.[7] Evoking a standard procedure for introducing the C-6 amino group to 6-chloro-3-deazapurine (i.e., hydrazinolysis followed by Raney nickel reduction) yielded **7**.[10] Acidic deprotection of **7** completed the pathway to **1**[11] (Scheme 1).

Acknowledgements

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8. Selected data for **5**: colorless oil (70%); δ_H (250 MHz, $CDCl_3$) 8.23 (d, $J = 5.7$ Hz, 1H), 8.04 (s, 1H), 7.60 (d, $J = 5.7$ Hz, 1H), 5.94 (m, 1H), 5.22 (m, 2H), 4.67 (m, 2H), 4.58 (m, 1H), 2.92 (m, 1H), 2.68 (m, 1H), 2.33 (m, 1H), 1.64 (s, 3H), 1.33 (s, 3H); δ_C (62.9 MHz, $CDCl_3$) 143.2, 142.0, 141.8, 140.2, 138.3, 137.0, 117.0, 114.8, 106.6, 84.9, 83.9, 62.3, 47.7, 35.7, 27.5, 25.1. Anal. Calcd for $C_{16}H_{18}ClN_3O_2$: C, 60.09; H, 5.67; N, 13.14. Found: C, 60.06; H, 5.60; N, 12.79.
9. Selected data for **6**: white foam (81%); δ_H (400 MHz, $CDCl_3$) 8.63 (s, 1H), 8.20 (d, $J = 5.6$ Hz, 1H), 7.81 (d, $J = 5.6$ Hz, 1H), 4.86 (m, 2H), 4.80 (t, $J = 6.5$ Hz, 1H), 4.57 (dd, $J = 4.5$, 7.0 Hz, 1H), 3.55 (t, $J = 5.5$ Hz, 2H), 2.46 (m, 1H), 2.21 (m, 1H), 2.19 (m, 1H), 1.58 (s, 3H), 1.26 (s, 3H); δ_C (100 MHz, $CDCl_3$) 145.3, 142.0, 141.7, 140.9, 138.2, 113.7, 108.2, 84.9, 81.8, 62.9, 62.8, 46.1, 33.7, 28.2, 26.0. Anal. Calcd for $C_{15}H_{18}ClN_3O_3$: C, 55.64; H, 5.60; N, 12.98. Found: C, 55.87; H, 5.67; N, 12.79.
10. Selected data for **7**: white solid (75%), mp 203–205 °C; δ_H (250 MHz, DMSO-d_6) 8.22 (s, 1H), 7.66 (d, $J = 5.8$ Hz, 1H), 6.87 (d, $J = 5.8$ Hz, 1H), 6.38 (br, 2H), 4.74 (q, $J = 6.8$ Hz, 1H), 4.69 (m, 1H), 4.55 (m, 1H), 3.51 (d, $J = 4.8$ Hz, 2H), 2.39–2.17 (m, 3H), 1.50 (s, 3H), 1.23 (s, 3H); δ_C (62.9 MHz, DMSO-d_6) 152.38, 139.97, 139.89, 138.07, 126.90, 112.57, 97.25, 84.00, 80.93, 61.81, 61.59, 45.24, 32.93, 27.42, 25.14. The proton NMR data compares favorably with that reported for (±)-**7** (Secrist, J. A.; Comber, R. N.; Gray, R. J.; Gilroy, R. B.; Montgomery, J. A. *J. Med. Chem.* **1993**, *36*, 2102–2106).
11. Montgomery, J. A.; Secrist, J. A. III World Patent, 9418971, Sept 1, 1994 presents a chemical and enzymatic synthesis of (−)-**1** by routes less practical and versatile than the one described here. Similarly, Houston, D. M.; Dolence, E. K.; Keller, B. T.; Patel-Thombre, U.; Borchardt, R. T. *J. Med. Chem.* **1985**, *28*, 471–477, reported the preparation of (±)-**1**. Selected data for **1**·HCl: white solid (89%), mp > 231 °C (dec); δ_H (250 MHz, DMSO-d_6) 8.63 (s, 1H), 8.50 (br, 2H), 7.74 (d, $J = 7.0$ Hz, 1H), 7.30 (d, $J = 7.0$ Hz, 1H), 4.72 (q, $J = 9.5$ Hz, 1H), 4.14 (dd, $J = 9.3$, 5.4 Hz, 1H), 3.82 (dd, $J = 5.4$, 2.8 Hz, 1H), 3.46 (d, $J = 5.3$ Hz, 2H), 2.31 (dt, $J = 12.7$, 8.8 Hz, 1H), 2.09 (m, 1H), 1.75 (m, 1H); δ_C (62.9 MHz, DMSO-d_6) 148.9, 143.5, 140.1, 129.0, 126.1, 99.3, 76.1, 72.0, 62.7, 61.0, 45.4, 28.9.