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(+)-Neplanocin F, 2′-fluoroneplanocin, and a 6′-*iso*neplanocin via a common versatile cyclopentenol precursor

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ABSTRACT

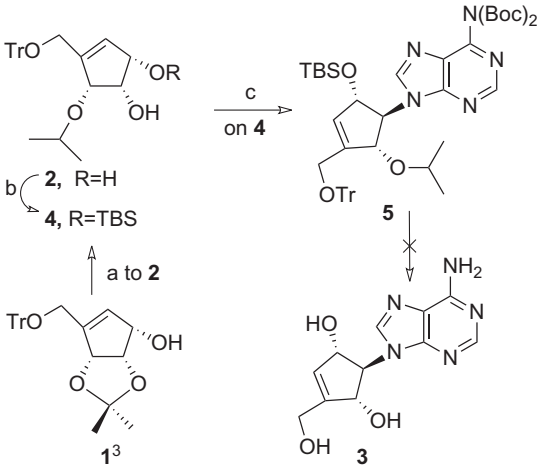
Reductive (di*iso*butylaluminum hydride) ring opening of an acetal protected cyclopentenol has provided a precursor adaptable to uniquely substituted carbocyclic nucleosides. To illustrate the broad implication of this process the preparation of unnatural (+)-neplanocin F, an *ara*-like 2′-fluoroneplanocin, and a 6′- isomeric L-like neplanocin analog is described.

For a number of years our laboratories at Auburn have been engaged in embellishing known adenine derived carbocyclic nucleosides as biological entities.[1] In that effort, there continues to be a need for access to uniquely substituted cyclopentyl representatives. We recognized that, perhaps, the frequently used 2′O/3′O acetal/ketal protecting partner in carbocyclic nucleoside syntheses could be partially opened in such a way that a fragment of the protector would be retained as a removable ether substituent availing versatile carbocyclic nucleoside precursors. Our investigations led us to the reaction of di*iso*butylaluminum hydride[2] with acetals.

To assess this idea we began with the protected cyclopentenol **1**[3] (Scheme 1[9]) and found that 5 equiv of DIBAH yielded **2**[4] (64%) as a possible precursor to neplanocin cohorts that require a free 2′-hydroxyl for development. To build on this achievement for the stated goals, the known,[5a] but structurally unique, (+)-neplanocin F (**3**) was sought. Thus, the treatment of **2** with *t*-butyldimethylsilyl chloride (TBSCl) (to **4**) followed by Mitsunobu coupling with N^6(bisBoc) protected adenine[6] provided **5**. However, complete deprotection of **5** (to **3**) could not be accomplished with the *iso*propoxyl substituent remaining after a number of conditions were attempted.

This result led to the consideration of using the benzylidene protected 2,3-diol **6** (prepared via Scheme 2[10]) for our stated purposes with the hope that debenzylation would be more productive. In that direction, treatment of **6** with DIBAH as before (5 equiv) led to the requisite **16**. Structural confirmation for **16** was accomplished by relating its COSY analysis to that previously described for **2**.[4]

As presented in the detailed synthetic steps of Scheme 3,[11] it was possible to move **16** forward to (+)-neplanocin F (**3**).[5a] To further explore **16** as a versatile precursor to other carbocyclic nucleosides, its conversion to the *ara*-like 2-fluoroneplanocin (**17**)[7] and the L-like 6′-*iso*neplanocin (**18**)[8] are likewise specifically shown in Scheme 3.



Scheme 1. Reagents and conditions: (a) 5 equiv DIBAH, CH_2Cl_2, 64%; (b) TBSCl, imidazole, CH_2Cl_2, 82%; (c) PPh_3, DIAD, Ad(Boc)$_2$, THF, 77%. (TBSCl = *t*BuMe_2SiCl).

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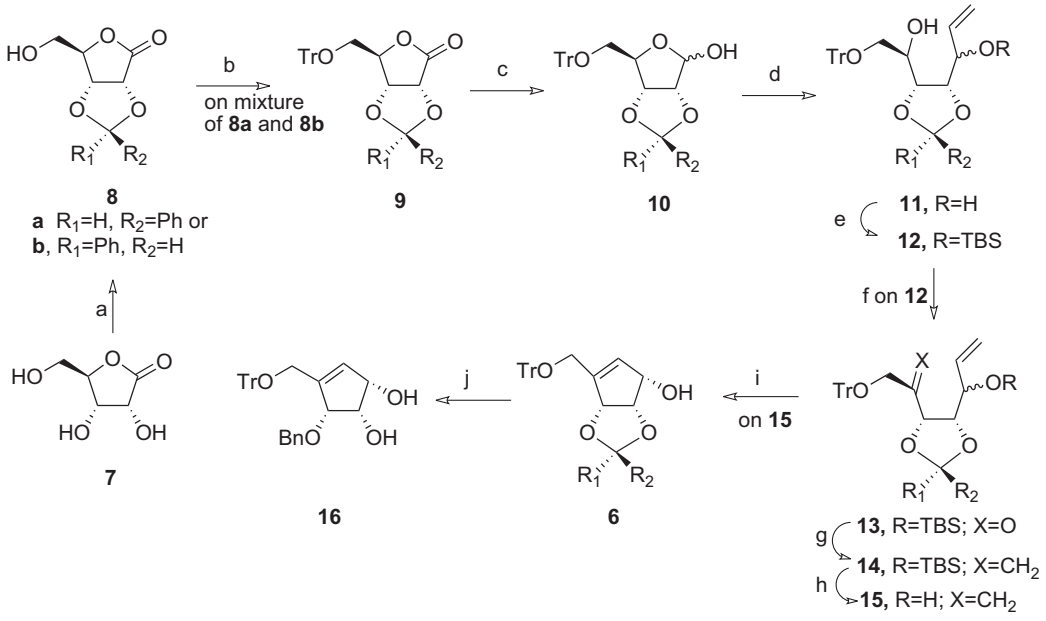
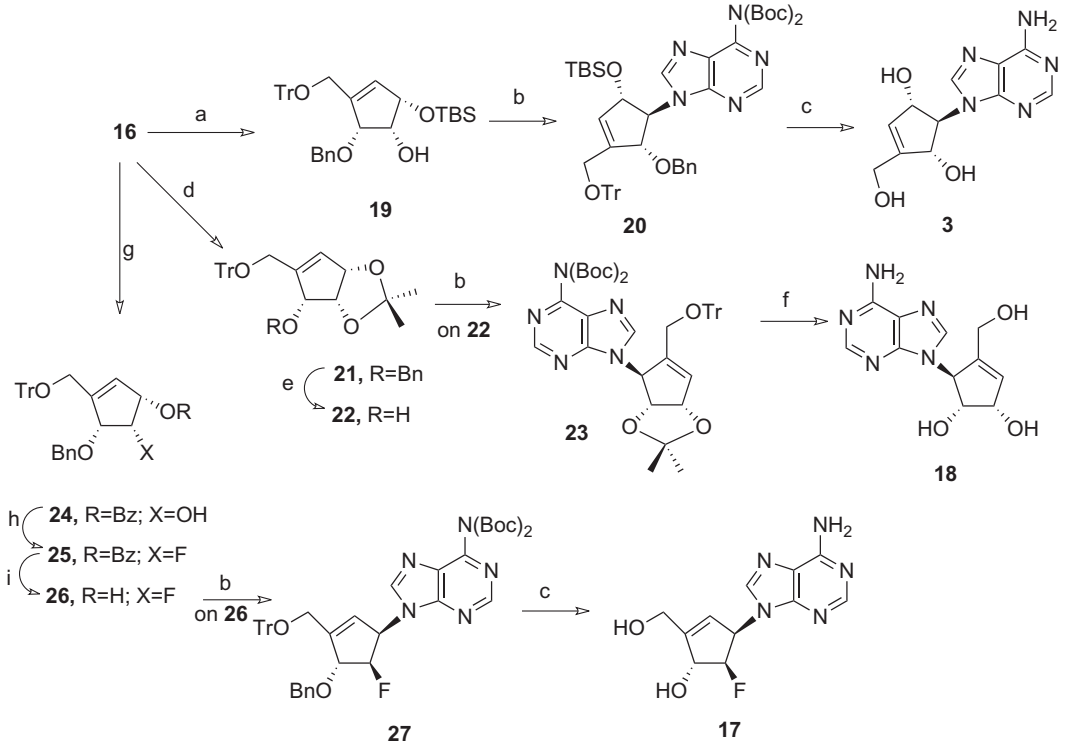


Scheme 2. Reagents and conditions: (a) $ZnCl_2$, PhCHO, 67% for mixture; (b) DMF, trityl chloride, DMAP, NEt_3, 91%; (c) DIBAH, THF, −78 °C, 67%; (d) vinylmagnesium bromide, THF, −78 °C, 95%; (e) TBSCl, imidazole, CH_2Cl_2, 78%; (f) oxalyl chloride, DMSO, CH_2Cl_2, NEt_3, 94%; (g) *n*-BuLi, Ph_3PCH_3Br, THF; (h) TBAF, THF, 90%; (i) 2nd generation Grubbs cat., CH_2Cl_2, 83%; (j) 5 equiv DIBAH, CH_2Cl_2, 61%. (TBSCl = *t*$BuMe_2SiCl$).



Scheme 3. Reagents and conditions: (a) TBSCl, CH_2Cl_2–DMF, imidazole, 85%; (b) PPh_3, DIAD, $Ad(Boc)_2$, THF, 77% for **20**, 87% for **23**, 88% for **27**; (c) (i) BCl_3, CH_2Cl_2, (ii) HCl/MeOH, 81% for **3**, 77% for **17**; (d) TsOH, 2,2-dimethoxypropane, acetone, 94%; (e) $BF_3{\cdot}Et_2O$, CH_2Cl_2, 76%; (f) HCl/MeOH, 83%; (g) BzCl, pyridine, 78%; (h) DAST, CH_2Cl_2, 74%; (i) NaOH, MeOH, 77%. (TBSCl = *t*$BuMe_2SiCl$).

Further investigations are underway to expand this method to other neplanocin derivatives (e.g., 2′-deoxy), aristeromycin analogs, free 3′-hydroxy frameworks resembling **16**, and 5′-homo products.

Acknowledgment

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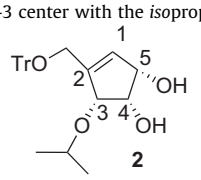
References and notes

1. For recent references see: (a) Yin, X.-q.; Li, W.-k.; Yang, M.; Schneller, S. W. *Bioorg. Med. Chem.* **2009**, *17*, 3126–3129; (b) Ye, W.; He, M.; Schneller, S. W. *Tetrahedron Lett.* **2009**, *50*, 7156–7158.
2. (a) Ishihara, K.; Mori, A.; Arai, I.; Yamamoto, H. *Tetrahedron Lett.* **1986**, *26*, 983–986; (b) Mori, A.; Ishihara, K.; Yamamoto, H. *Tetrahedron Lett.* **1986**, *27*, 987–990; (c) Mori, A.; Fujiwara, J.; Maruoka, K.; Yamamoto, H. *J. Organomet. Chem.* **1985**, *285*, 83–94.
3. Cho, J. H.; Bernard, D. L.; Sidwell, R. W.; Kern, E. R.; Chu, C. K. *J. Med. Chem.* **2006**, *49*, 1140–1148.
4. The structural assignment for **2** was accomplished by a ^{1}H COSY experiment in the following way: the H-1 vinyl proton at δ 6.00 ppm correlated with the H-5 proton, which, in turn, correlated with its hydroxyl proton. With this data, H-3 and H-4 could be identified and only H-4 showed correlation with a hydroxyl hydrogen, rendering the C-3 center with the *iso*propoxyl substituent.



2

5. (+)-Neplanocin F: (a) Comin, M. J.; Leitofuter, J.; Rodriguez, J. B. *Tetrahedron* **2002**, *58*, 3129–3136 (b) Selected data for **3**: white solid; ^{1}H NMR (400 MHz, MeOH), δ 8.20 (s, 1H), 8.12 (s, 1H), 5.91 (td, *J* = 1.6, 2.0 Hz, 1H), 5.50 (m, 1H), 4.62 (d, *J* = 6.0 Hz, 1H), 4.39 (t, *J* = 6.0 Hz, 1H), 4.32 (m, 2H); ^{13}C NMR (100 MHz, MeOH) δ 155.7, 151.9, 150.0, 149.9, 140.0, 124.0, 119.1, 77.3, 72.7, 65.1, 58.9; HRMS calcd for $C_{11}H_{13}N_5O_3$ $[M+H]^+$ 264.1097, found 264.1093.
6. Dey, S.; Garner, P. *J. Org. Chem.* **2000**, *65*, 7697–7699.
7. Chu, C. K.; Cho, J. H.; Kim, H. J. U.S. Patent 0,270,431, 2009. Selected data for **17**: white solid; ^{1}H NMR (400 MHz, MeOH), δ 8.22 (s, 1H), 8.00 (s, 1H), 5.97 (m, 1H), 5.87 (m, 1H), 5.12 (ddd, *J* = 2.8, 5.6, 48 Hz, 1H), 4.97 (m, 1H), 4.35 (m, 2H); ^{13}C NMR (100 MHz, MeOH) δ 157.5,153.4 (d, *J* = 6 Hz), 153.3, 151.1, 141.7,122.4, 120.2, 97.8 (d, *J* = 194 Hz), 79.3 (d, *J* = 26 Hz), 59.8, 59.1 (d, *J* = 17 Hz); HRMS calcd for $C_{11}H_{12}FN_5O_2$ $[M+H]^+$ 266.1053, found 266.1044.
8. Selected data for **18**: white solid; ^{1}H NMR (400 MHz, MeOH), δ 8.17 (s, 1H), 8.11 (s, 1H), 6.11 (s, 1H), 5.51 (d, *J* = 5.6 Hz, 1H), 4.69 (m, 1H), 4.60 (t, *J* = 5.6 Hz, 1H), 3.02–3.14 (m, 2H); ^{13}C NMR (100 MHz, MeOH) δ 155.9, 152.2, 149.6, 144.6, 140.9, 129.6, 119.2, 76.4, 71.9, 65.4, 58.2; HRMS calcd for $C_{11}H_{13}N_5O_3$ $[M+H]^+$ 264.1097, found 264.1094.
9. For leading references for the less customary procedures see Ref. 1b.
10. For leading references for the less customary procedures see Refs. 1, 2 and (a) Yin, X.-q.; Schneller, S. W. *Tetrahedron Lett.* **2005**, *46*, 1927–1929; (b) Yang, M.; Ye, W.; Schneller, S. W. *J. Org. Chem.* **2004**, *69*, 3993–3996.
11. For leading references for the less customary procedures see Ref. 1 and (a) Yin, X.-q.; Schneller, S. W. *Tetrahedron* **2005**, *61*, 1839–1843; (b) Zhou, J.; Yang, M.; Akdag, A.; Wang, H.; Schneller, S. W. *Tetrahedron* **2008**, *64*, 433–438.