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Tetrahedron Letters
Tetrahedron Letters 46 (2005) 8913–8915

Enantiospecific synthesis of 5′,5′,5′-trifluoro-5′-deoxyneplanocin A

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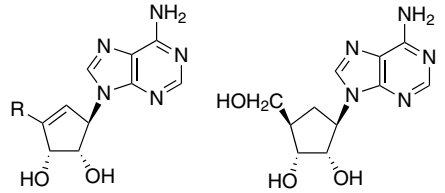
Received 24 September 2005; accepted 17 October 2005
Available online 4 November 2005

Abstract—(−)-(1*S*,4*R*)-4-Hydroxy-2-cyclopenten-1-yl acetate provided a convenient entry point for a 12-step chiral preparation of 5′,5′,5′-trifluoro-5′-deoxyneplanocin A.

Inhibition of *S*-adenosyl-L-homocysteine (AdoHcy) hydrolase, an enzyme with major responsibilities in modulating biological methylations dependent on *S*-adenosylmethionine (AdoMet), has served as a point of convergence for antiviral drug design.[1] From these efforts, two structural features have arisen as meaningful: nucleosides with (i) a carbocyclic framework[2] and (ii) C-5′ fluorination.[3] Neplanocin A (**1**) represents a prominent entity in this area.[4] Of particular relevance to our program based on **1** (Fig. 1), and its saturated derivative aristeromycin (**2**), for antiviral therapy research was the report from De Clercq's laboratory that 5′-fluoro-5′-deoxyneplanocin A has broad spectrum potential.[3a] From this, and the fact that a C-5′ polyflourinated adenosine has displayed mechanism-based inhibition of AdoHcy hydrolase,[3b] we sought access to the 5′,5′,5′-trifluoro-5′-deoxyneplanocin analogue (**3**). This route is communicated herein.



1, R = CH_2OH
3, R = CF_3
2

Figure 1.

The synthesis of **3** began with (−)-(1*S*,4*R*)-4-hydroxy-2-cyclopenten-1-yl acetate (**4**)[5] and its conversion to **5** in high yield through a sequence of reactions (Scheme 1): (i) hydroxyl protection, (ii) glycolization, (iii) isopropylidenation, (iv) deacetylation, and (v) pyrdinium chlorochromate oxidation. Compound **5** was then transformed to the trifluoromethyl derivative **6** by, first, reaction with Ruppert's reagent[6,7] (CF_3SiMe_3) in the presence of a catalytic amount of tetrabutylammonium fluoride (0 °C) followed by desilylation with tetrabutylammonium fluoride (room temperature). While the ultimate stereochemical outcome of the 1,2-addition reaction (Scheme 1, step b (i)) is not relevant to the goal of obtaining **3**, the configuration shown is likely because of the hindered bottom face of **5** that blocks the α-addition of the trifluoromethyl group.

Based on the success of the Mitsunobu coupling reaction for preparing carbocyclic nucleosides,[8] the allylic alcohol **9** was sought. This required the precursor ketone **8** that, in turn, was expected to be accessible by subjecting **6** to an oxidation followed by elimination procedure.[9] In that direction, oxidation of **6** with pyridinium chlorochromate was found to produce **7** in 78% yield (reaction conditions not specified in the scheme). A similar result was also obtained when **6** was oxidized with Dess–Martin periodinane reagent. The trifluoromethyl enone **8** was then obtained in 50% yield from **7** by reaction with methanesulfonyl chloride and triethylamine (Scheme 1). In order to improve the yield of **8** from diol **6**, a literature precedent was followed.[10] In this regard, a modified Pfitzner–Moffatt oxidation[11] of **6** afforded a mixture of **7** in 40% yield and **8** in 36% yield. However, when this reaction was left for 6 days in the presence of excess oxidizing agent (8 equiv), compound **8** was obtained as the only product in high yield (80%).

Keywords: Carbocylic nucleosides; Oxidation and elimination; Mitsunobu coupling.
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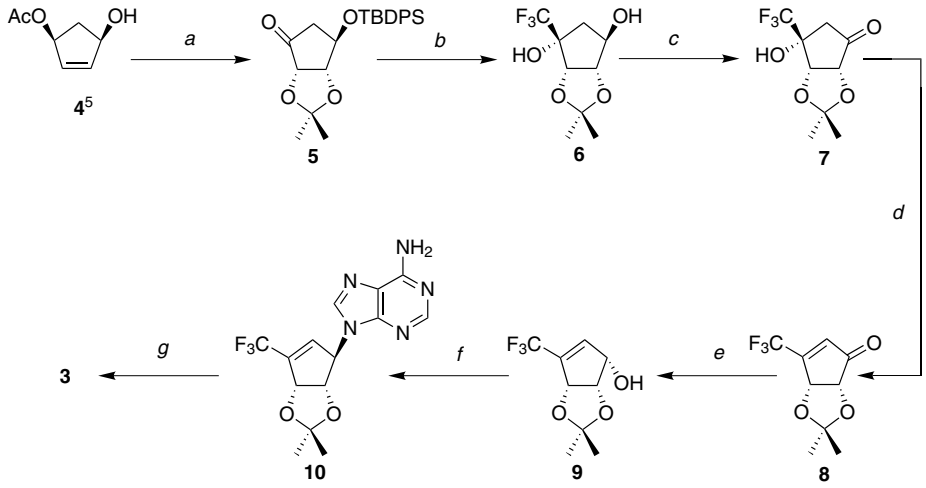
doi:10.1016/j.tetlet.2005.10.064

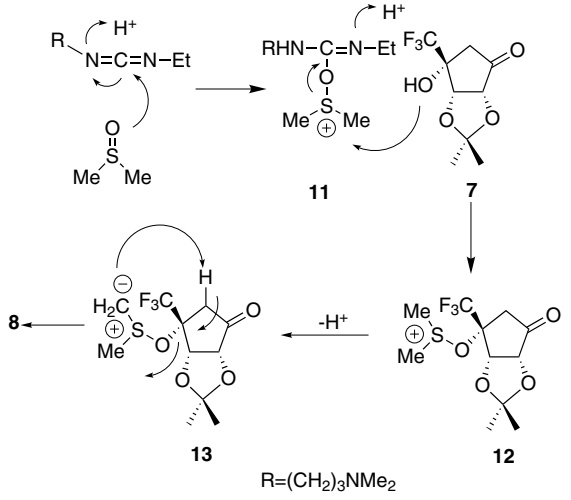


Scheme 1. Reagents and conditions: (a) (i) TBDPSCl, imidazole, DMF, rt, 95%; (ii) OsO_4, NMO, THF–H_2O, acetone (8:1:1), rt, 90%; (iii) $Me_2C(OMe)_2$, acetone, H^+, rt, 94%; (iv) satd NH_3 in MeOH, 100 °C, 92%; (v) PCC, CH_2Cl_2, rt, 90%; (b) (i) CF_3SiMe_3, TBAF (cat), THF, 0 °C; (ii) TBAF, rt, 81% for two steps; (c) DMSO, CH_2Cl_2, EDC, HCl, pyridinium trifluoroacetate, 10 °C then rt for 36 h: 40% for **7**, 36% for **8**; for 6 days with 8 equiv of oxidizing agent, only **8** (80%); (d) MsCl, Et_3N, CH_2Cl_2, rt, 50%; (e) $NaBH_4$, $CeCl_3{\cdot}7H_2O$, MeOH, 0 °C, 78%; (f) (i) PPh_3, DIAD, 6-chloropurine; (ii) satd NH_3 in MeOH, 68% for two steps; (g) Dowex H^+, MeOH, H_2O (19:1), 90 °C, 80%. EDC = *N*-(3-dimethylaminopropyl)-*N*′-ethylcarbodiimide.

Reduction of the trifluoromethyl enone **8** with sodium borohydride in methanol (using the Luche method) yielded the alcohol **9**. Mitsunobu reaction of **9** with 6-chloropurine followed by ammonolysis provided **10**. Acidic deprotection of **10** furnished the target **3**.[12]

A proposed pathway to **8** from **6** is presented in Scheme 2 and follows from the initial oxidation to the key intermediate **7** and calls upon the work of Moffatt and his collaborators[13] to evoke the *N*-(3-dimethylaminopropyl)-*N*′-ethylcarbodiimide hydrochloride (EDC)-DMSO adduct (**11**). The transformation of **13** into **8** would be favored by a six-membered transition state.

In conclusion, a highly efficient synthetic route to 5′-deoxy-5′,5′,5′-trifluoro neplanocin A **3** has been described via a key intermediate **8**. The biological analysis of **3** is underway and will be presented in a full paper on this nucleoside derivative.



Scheme 2.

Acknowledgments

This research was supported by funds from the NIH (AI 56540).

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12. Selected data for **3**: Crystalline solid, mp 235.1–236.3 °C; $[\alpha]_D^{24.3}$ 8.05 (*c* 0.22, DMSO); (Found: C, 43.5; H, 3.4; N, 22.8. $C_{11}H_{10}F_3N_5O_2{\cdot}0.17H_2O$ requires C, 43.4; H, 3.4; N, 23.0); δ_H (400 MHz; DMSO-d_6; Me_4Si) 3.56–3.66 (1H, m, 1′-H), 4.28 (1H, q, *J* 7.30, 2′-H), 5.11 (1H, t, *J* 6.7, 3′-H), 5.47 (1H, d, *J* 7.6, 2′-OH), 5.70 (1H, d, *J* 7.2, 3′-OH), 6.57 (1H, d, *J* 2.1, 6′-H), 7.46 (2H, br s, 6-NH_2), 8.25 (1H, s, 8-H), 8.35 (1H, s, 2-H); δ_C (100 MHz; DMSO-d_6; Me_4Si) 53.2 (q, $^4J_{C,F}$ 26.6), 69.0, 72.1, 109.7 (q, $^3J_{C,F}$ 3.3) 119.1, 127.2 (q, $^1J_{C,F}$ 277.1), 138.4, 139.8, 149.4, 153.5, 156.2; δ_F(250 MHz; DMSO-d_6; $CF_3C_6H_5$) −71.1 (d, *J* 8.5).
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