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Chemoenzymatic Synthesis of 1,3-Dideoxynojirimycin

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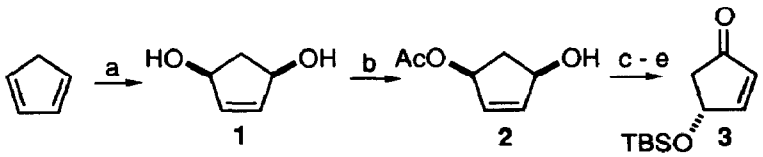
Abstract: Enone **3**, readily available from cyclopentadiene, was transformed *via* Pd(0)-mediated carbon monoxide coupling, ozonolysis and reductive amination to enantiopure 1,3-dideoxynojirimycin (**7**) in high diastereoselectivity.

Polyhydroxylated piperidines have been shown to be potent inhibitors of glycosidases.[1] This has led to widespread interest in these compounds as possible therapeutic agents for the treatment of metabolic diseases,[2] the inhibition of tumor metastasis[3] and the control of infections of viruses, notably the human immunodefiency virus (HIV).[4] Numerous papers describing new methods for the synthesis of polyhydroxylated piperidines have appeared.[5] While most syntheses rely on transformations of the natural D-pentoses and D-hexoses, many structural analogues can be more effectively achieved by a total synthesis approach.

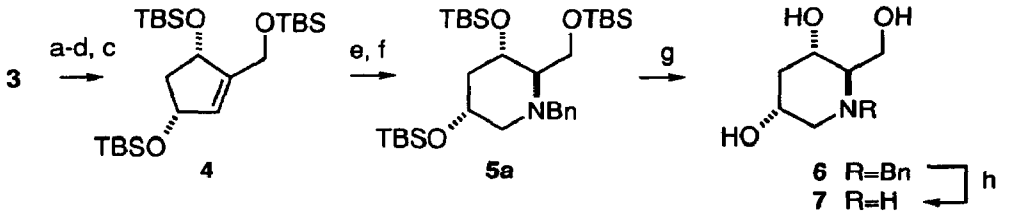
Scheme 1[a]



[a]Reagents and conditions: (a) $^1O_2$, *hv*, rose bengal, thiourea; (b) *Candida antarctica* lipase B (Novo Nordisk SP 435), isopropenyl acetate, 50 °C[6]; (c) TBSCl, imidazole, DMF, 20 °C; (d) KOH, MeOH; e) PDC, CH_2Cl_2.

Recently we reported the enzymatic asymmetrization of meso diol **1** obtained in two steps from cyclopentadiene (Scheme 1).[6] The optically pure monoacetate **2** can then be transformed into enone **3** following the known procedure.[7] Functionalization of enone **3** was accomplished by α-iodination,[8] Luche reduction, and Pd(0)-mediated carbon monoxide coupling,[9] leading to cyclopentene derivative **4** (Scheme 2).

Scheme 2[a]



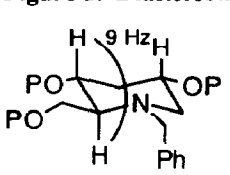
[a]Reagents and conditions: (a) I_2, (1.8 eq.), pyridine/CCl_4 (93%); (b) $NaBH_4$, $CeCl_3$, MeOH, -78 °C (96%); (c) TBS-Cl, imidazole, DMF (98%); (d) CO (1 atm.), Bu_3SnH, $Pd(PPh_3)_4$ 5 mol%, THF; then $NaBH_4$, $CeCl_3 \cdot 7H_2O$, MeOH, -78 °C (86%); (e) O_3, MeOH, -78 °C then DMS, 20 °C (100%, crude); (f) 1.5 eq. $BnNH_3Cl$, 1.5 eq. $NaCNBH_3$, MeOH, 25 °C (62%); (g) 1N HCl-MeOH (83%); (h) H_2, 30 psi, Pd/C, MeOH (80%).

Ozonolysis of **4**, followed by reductive work-up gave the corresponding keto aldehyde which was then transformed into trisilylated 1,3-dideoxy-*N*-benzyl-nojirimycin (**5a**) *via* reductive amination with benzylamine and sodium cyanoborohydride in methanol. This protocol was recently applied to the synthesis of polyhydroxylated piperidines from dicarbonyl sugars.[10] Indeed, we found this method not only to be

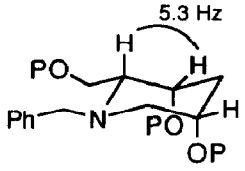
facile, but also highly diastereoselective (*syn* : *anti* - **5a** : **5b**; >20:1,) in our system. Acidic hydrolysis, followed by hydrogenation yield the title compound **7** as a white solid.[11] Ozonolysis and reductive amination starting from diol **8** (Scheme 3) resulted in poor diastereoselectivity (syn : anti - 1 : 2) allowing separation and conformational analysis of both products.

The diastereomeric assignments for the two nojirimycins were made by ^{1}H NMR spectroscopy. The coupling constant (J = 9.0 Hz) between H4 and H5 protons indicates axial : axial interactions, leading to the conclusive 4,5-*anti* stereochemistry (Figure 1, **5a**). The same coupling constant for the minor isomer is substantially smaller ($J_{4,5}$ = 5.3 Hz) leading to the *syn*-diastereoisomer assignment (Figure 1, **5b**).

Figure 1. Diastereomers of **5**.

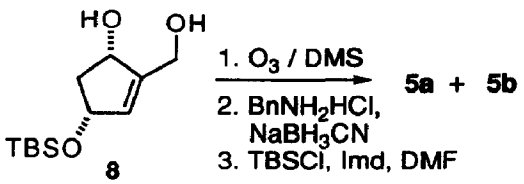


5a



P=TBS **5b**

Scheme 3



In conclusion, the synthesis of 1,3-dideoxynojirimycin (**6**) has been achieved starting from cyclopentadiene using enzymatic asymmetrization and subsequent diastereoselective transformations. Further utilization of this methodology in the synthesis of polyhydroxylated piperidines and related systems as well as relevant biological data will be reported in due course.

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11. Physical Data: **6:** mp 88-89 °C. $[\alpha]^{22}_D$ −35.3 (*c* 1.0, H_2O) ^{1}H NMR (D_2O) δ 7.35-7.33 (m, 5H); 4.11-4.07 (m, 2H); 3.96-3.92 (m, 1H); 3.67-3.57 (m, 2H); 3.45-3.41 (d, 1H, J = 13.2 Hz); 2.86 (bd, J = 10.8 Hz, 1H); 2.32-2.30 (m, 1H); 2.05 (bd, J = 9.6 Hz, 1H); 1.85 (dd, J = 10.8, 10.8 Hz, 1H); 1.23 (ddd, J = 11.0, 11.0, 11.0 Hz, 1H); ^{13}C NMR (D_2O) δ 136.2, 130.3, 128.4, 127.7, 67.4, 65.2, 63.8, 57.9, 57.0, 56.5, 41.0.

    7: mp 192-193 °C (decomp.). $[\alpha]^{20}_D$ +24.9 (*c* 0.5, H_2O) ^{1}H NMR (D_2O) δ 3.84 (dd, J = 11.5, 3.0 Hz, 1H); 3.69 (m, 1H); 3.59 (dd, J = 11.6, 6.1 Hz, 1H); 3.45 (ddd, J = 10.7, 10.7, 4.9 Hz, 1H); 3.11 (dd, J = 12.0, 3.8 Hz, 1H); 2.37 (m, 3H); 1.45 (bs, 1H); 1.35 (ddd, J = 10.5, 10.5, 10.5 Hz, 1H); ^{13}C NMR (D_2O) δ 73.7, 73.1, 68.6, 64.6, 57.7, 48.4.

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