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Enantiopure 2,3-dihydro-4-pyridones as synthetic intermediates: asymmetric synthesis of 1-deoxynojirimycin

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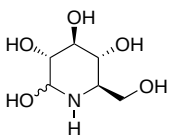
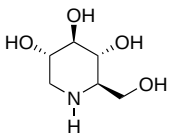
Abstract—An asymmetric synthesis of 1-deoxynojirimycin (**2**) mediated by a chiral auxiliary is reported. The dihydropyridone **4** was converted to diol **11** in three steps by acetoxylation, hydrolysis, and stereoselective reduction. Dihydroxylation of **11** followed by catalytic reduction afforded **2**.

Considerable synthetic effort has been devoted to the preparation of azasugars such as nojirimycin (**1**) and 1-deoxynojirimycin (**2**). These natural products and related monosaccharide analogs have shown promise as potential chemotherapeutic agents for treating diabetes, cancer, and viral infections.[1,2] Derivatives of 1-deoxynojirimycin have been shown to inhibit the development of HIV in vitro.[3]



nojirimycin

1



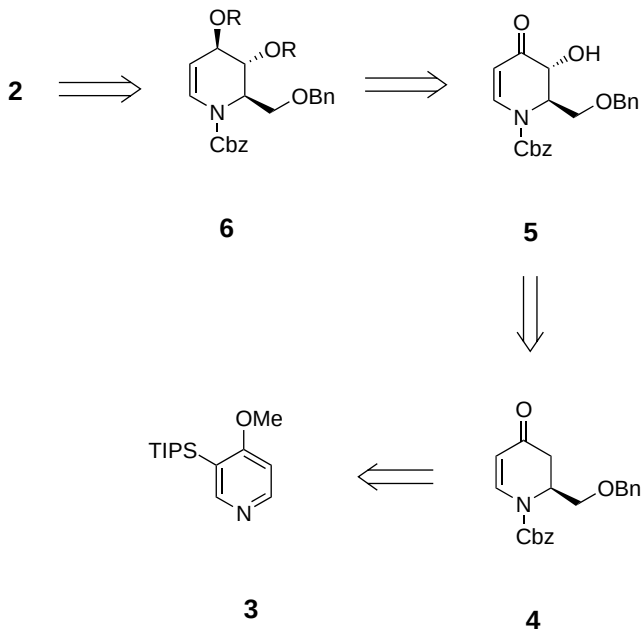
1-deoxynojirimycin

2

As part of the program directed at exploring the utility of *N*-acyl-2,3-dihydro-4-pyridones as chiral building blocks, we examined a strategy (Scheme 1) for an asymmetric synthesis of 1-deoxynojirimycin (**2**).

It was anticipated that the target molecule (**2**) could be prepared from tetrahydropyridine **6**, which would arise via hydroxydihydropyridone **5**. The precursor **4** would be synthesized in an asymmetric fashion from pyridine **3** using our 1-acylpyridinium salt chemistry.[4]

The required *N*-acyldihydropyridone **4** was prepared in three steps. The addition of (benzyloxy)methylcuprate **7**[5] to a 1-acylpyridinium salt, formed in situ from 4-methoxy-3-(triisopropylsilyl)pyridine[6] (**3**) and (1*R*,2*S*)-2-(1-methyl-1-phenylethyl)cyclohexanol ((–)-TCC),[7] gave dihydropyridone **8** in 64% yield (Scheme 2). HPLC analysis of the crude product showed that the reaction proceeded in 90% de. One-pot removal of the chiral auxiliary (>95% recovery) and the C-5 TIPS group provided enantiopure **9** in 74% yield as a white solid, mp 107–107.5°C. Deprotonation with *n*-BuLi and addition of benzyl chloroformate gave a 99% yield of carbamate **4**; $[\alpha]_D^{27}$ –40.2 (*c* 1.31, $CHCl_3$). Acetoxylation of **4** with $Pb(OAc)_4$ in refluxing toluene (22 h)



Scheme 1.

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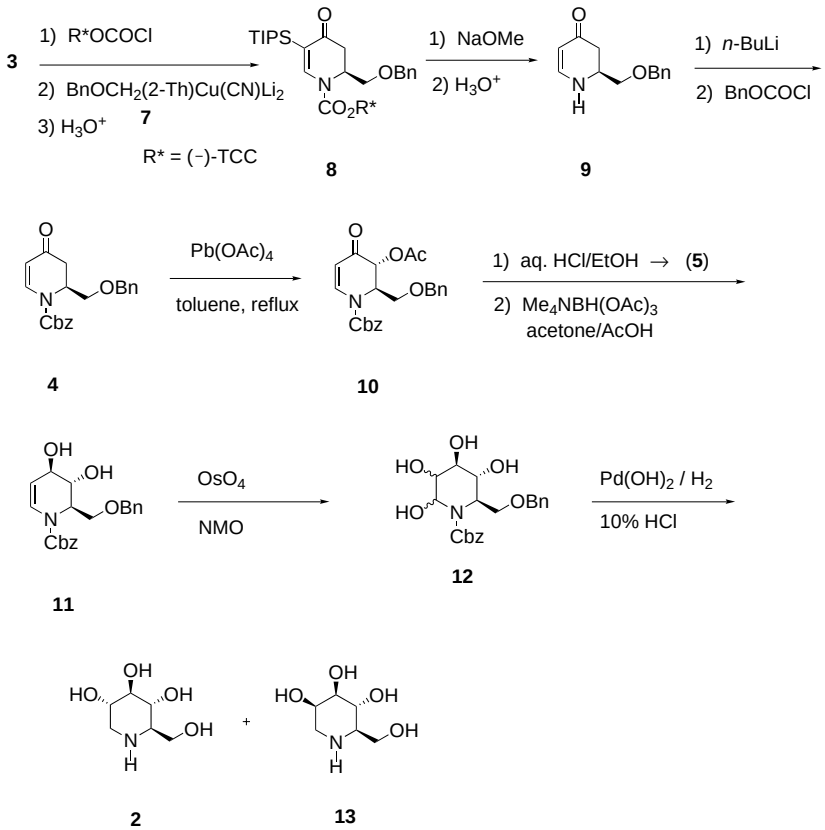

Scheme 2.

afforded the desired dihydropyridone **10** in 78% yield. The *trans* stereochemistry was obtained by acetate delivery from the axial direction via a chair-like transition state.[8] The acetate group of **10** was hydrolyzed with aqueous 10% HCl in ethanol to provide alcohol **5** (75%; $[\alpha]_D^{22}$+50.1 (*c* 0.67, $CHCl_3$)). Reduction of **5** with tetramethylammonium triacetoxyborohydride afforded diol **11** (83%) with complete stereoselectivity.[9]

The next step in our plan called for a stereoselective hydroxylation of **11** at C-5. Several attempts using various hydroboration conditions proved nonselective and/or low yielding.[10] Dihydroxylation of **11** was studied next with the hope that the C-4 hydroxyl group would direct the oxidation to the opposite face of the olefin (the Kishi rule).[11] Treatment of **11** with osmium tetroxide and 4-methylmorpholine *N*-oxide afforded the tetrahydroxypiperidines **12**, which proved unstable to silica gel chromatography. When the crude mixture was hydrogenated with $Pd(OH)_2$ and 10% HCl, a 2.7:1 ratio of **2**:**13** resulted (^{13}C NMR analysis of the crude product). Neutralization and chromatographic purification (silica gel, 75% $MeOH/CH_2Cl_2$;1% TEA) provided 1-deoxynojirimycin (**2**) in 55% yield and 1-deoxymannojirimycin (**13**) in 21% yield. The spectral properties of our (−)-**2** and **13** are in agreement with reported data.[12]

In summary, 1-deoxynojirimycin was prepared enantioselectively in eight steps from readily available pyridine **3** in 13% overall yield. This strategy should be amenable to the asymmetric synthesis of various nojirimycin analogs and other azasugars.

Acknowledgements

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12. The structure assigned to each new compound is in accord with its IR and ^{1}H and ^{13}C NMR spectra and elemental analysis or high-resolution mass spectra. Selected characterization data: Compound **10**: colorless oil; $[\alpha]_D^{26} = +82.9$ (*c* 1.37, $CHCl_3$); IR (neat) 3032, 2867, 1733, 1678, 1605, 1386, 1318, 1266, 1210, 1117, 1030 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.90 (d, 1H, $J = 8.4$ Hz), 7.5–7.1 (m, 10H), 5.38 (d, 1H, $J = 8.4$ Hz), 5.25 (s, 3H), 4.78 (t, 1H, $J = 5.1$ Hz), 4.46 (s, 2H), 3.7–3.6 (m, 2H), 2.08 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 186.7, 169.6, 152.7, 143.0, 137.4, 134.8, 129.1, 128.9, 128.6, 128.0, 127.9, 127.8, 127.6, 105.6, 73.5, 70.1, 69.5, 67.5, 57.6, 21.1. Anal. calcd for $C_{23}H_{23}NO_6$: C, 67.47; H, 5.66; N, 3.42. Found: C, 67.51; H, 5.71; N, 3.46.
Compound **11**: colorless oil; $[\alpha]_D^{22} = -91.6$ (*c* 1.62, $CHCl_3$); IR (neat) 3416, 3031, 2871, 1708, 1652, 1397, 1341, 1027 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.5–6.9 (m, 11H), 5.3–4.9, (m, 3H), 4.6–4.2 (m, 3H), 4.2–3.6 (m, 4H), 2.1 (bs, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 137.0, 135.8, 128.8, 128.7, 128.6, 128.32, 128.26, 127.9, 126.9, 126.8, 126.7, 126.4, 105.1, 73.8, 71.4, 69.2, 68.5, 68.3, 64.6, 56.1, 41.6. Anal. calcd for $C_{21}H_{23}NO_5$; C, 68.28; H, 6.28; N, 3.79. Found: C, 68.32; H, 6.23; N, 3.77.
Compound **2·HCl**: white solid, mp 204–205°C; $[\alpha]_D^{27} = +39.8$ (*c* 0.465, H_2O); IR (Nujol) 3380, 3175, 1664 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.82 (dd, 1H, $J = 2.5$, 11.5 Hz), 3.62 (dd, 1H, $J = 6.2$, 11.6 Hz), 3.52–3.44 (m, 1H), 3.35–3.18 (m, 2H), 3.11 (dd, 1H, $J = 4.9$, 12.3 Hz), 2.56–2.40 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 79.4, 71.0, 70.1, 63.2, 60.9, 49.1.