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Asymmetric synthesis of novel isoindolines: azasaccharide mimics as potential enzyme inhibitors

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Abstract

2′,3′-Dideoxy-2′,3′-didehydronucleosides and azasaccharides are known to possess antiviral activity. The synthesized 1-methoxyisoindoline system (**10**), which is related to the above nucleosides, is potentially stable in-vivo. The 1-methoxyisoindoline was synthesized from the achiral phthalaldehyde in 10 steps via an enantiomerically pure diol obtained by Sharpless asymmetric dihydroxylation. The new heterocyclic compound is an azosaccharide mimic which provides an access to a new series of nucleoside analogues with potential as antiretroviral agents (anti-HIV) and as glycosidase inhibitors.

Introduction

Aminosugars, in which the pyranose or furanose ring oxygen is replaced by a nitrogen, can have a variety of biological activities; examples include the glucosidase inhibitor, castanospermine (**II**; Figure 1) (Look et al 1993) and the antiviral compound, 1-deoxynojirimycin (**I**) (Van den Broek 1997). Azasugars also inhibit HIV replication by altering the glycosylation of the HIV-1 envelope glycoprotein gp120 and gp41 (Van den Broek 1997). This may be due to the disrupting effect that aminosugars have on the biosynthesis of oligosaccharides in the cell membrane. Recently, the nucleoside analogue **III**, based on 1,3-dihydrobenzo[*c*]furan, has been synthesized (Ewing et al 1999, 2000) as an analogue of 2′,3′-didehydro-2′,3′-dideoxythymine IV (d4T, stavudine, a commercial anti-HIV nucleoside approved by the US FDA) (Balzarini et al 1987). This novel d4T analogue has the 2′,3′ double bond incorporated into a benzene ring. This modification retains a phosphorylation site, has enhanced lipophilicity compared with d4T, but the substrate is likely to be more resistant to the hydrolytic process that contributes to the short half-life of d4T in-vivo. Furthermore, this system is clearly very rigid. It has been speculated (Harte et al 1991) that the conformational restriction imposed by the double bond in d4T is an important factor in its interaction with viral enzymes. Nucleoside analogues with conformational rigidity imposed by cyclopropanation of a furanose or carbocyclic ring have been reported recently (Marquez et al 1996; Chun et al 2000).

Initial biological test results for pyrimidine nucleoside analogues based on 1,3-dihydrobenzo[*c*]furan (unpublished data) have shown no anti-HIV activity. Changing the glycone ring heteroatom from oxygen to nitrogen is one obvious way to expand the chemotherapeutic potential of this system. Thus the isoindoline system **V** with a nitrogen atom in the ring will have different ring dimensions, a different charge distribution around the 'glycosidic' bond and different hydrogen

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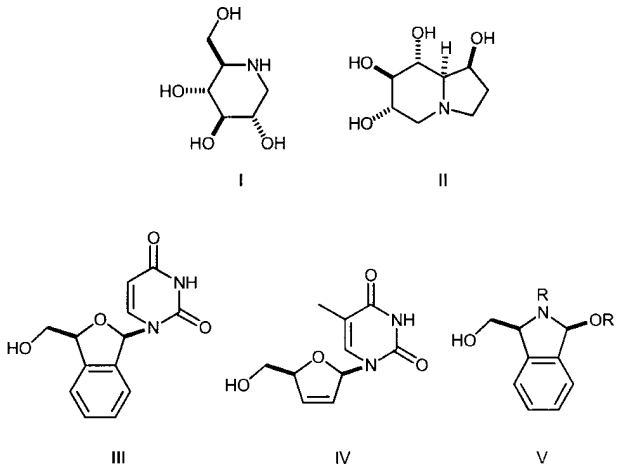

Figure 1 Structures of aminosugars I, II, IV and 2′-3′-dideoxynucleosides III, IV.

bonding possibilities. These factors are likely to have significant effect on the nature of an enzyme–substrate interaction of the isoindoline system when incorporated as a saccharide mimic in a nucleoside analogue.

We report here the first synthesis of the isoindoline system with 1,3 disposed hydroxy and hydroxymethyl substituents. This arrangement of substituents parallels that found in the 1,3-dihydrobenzo[*c*]furan glycone incorporated in **III** and mimics the crucial features of all saccharide glycones. Our strategy involves ring closure of a suitably protected amino aldehyde. Although azasaccharides have been obtained by a similar route (Huang et al 1993), the only example where the isoindoline system has been obtained in this way involves formylation of a protected benzylamine (Simig 1990), a methodology which is of limited application since the 1-hydroxyindoline products are unstable and easily revert back to the amino aldehyde. Furthermore our novel approach to the isoindoline system is based on an asymmetric synthesis which leads to an enantiomerically pure product, (3*S*)-2-acetyl-3-acetoxymethyl-1-methoxyisoindoline, starting from the convenient, inexpensive, achiral substrate, phthalaldehyde.

Materials and Methods

Chemistry

NMR spectra were recorded with a Lambda 400 spectrometer using standard conditions with a data point resolution of ca. 0.1 Hz. ^{1}H Chemical shifts were measured relative to Me_4Si and ^{13}C chemical shifts relative to $CDCl_3$ (77.0 ppm) or $(CD_3)_2SO$ (39.5 ppm). All coupling constants are given in Hz. Assignments of the ^{1}H spectra were made by detailed analysis using decoupling or correlation techniques where appropriate. Diastereoisomer ratios were determined from the integration of suitable peaks. Column chromatography was performed on silica gel (230–400 mesh; Prolabo) and TLC on silica gel 60, F_{254} (Merck) with detection by UV absorbance or phosphomolybdic acid. MeOH–NH_3 is methanol saturated with ammonia gas at room temperature.

*(1S)-1-Azido-2-benzoyloxy-1-[2-(1,3-dioxan-2-yl)phenyl]ethane (**4**)*

Mesyl chloride (6.40 g, 56 mmol) was added drop-wise to a stirred solution of (1*R*)-2-benzoyloxy-1-[2-(1,3-dioxan-2-yl)phenyl]ethanol (**2**; Figure 2) (9.2 g, 28 mmol) in pyridine (60 mL) at 0°C. After 12 h, volatile matter was evaporated under reduced pressure and then lithium azide (2.25 g, 46 mmol) in dimethylformamide (DMF; 100 mL) was added and the solution heated at 100°C for 3 h. After the addition of saturated aqueous NH_4Cl (100 mL) the mixture was extracted with CH_2Cl_2, the extract worked up and the crude product purified by column chromatography (hexane–EtOAc, 90:10) to give **4** (76%) as a white solid, mp 68–72°C; δ_H ($CDCl_3$) 1.46, 2.27, 4.02, 4.29 (6 H, m, dioxanyl), 4.42 (1 H, dd, $J = 9.1$, 11.4, CH_2O), 4.73 (1 H, dd, $J = 3.8$, 11.4, CH_2O), 5.72 (1 H, s, dioxanyl), 5.78 (1 H, dd, $J = 3.8$, 9.1, CHN_3), 7.53 (9 H, m, aromatic H); δ_C ($CDCl_3$) 26.1, 67.9, 101.9 (dioxanyl), 60.8 (CN_3), 68.3 (C-2), 128.9, 130.2, 133.6 (Ph), 128.0, 128.1, 129.0, 129.9, 134.8, 136.8 (aromatic C). Calculated for $C_{19}H_{19}O_4N_3$: C, 64.58; H, 5.42; N, 11.89. Found: C, 64.71; H, 5.50; N, 11.73.

*(2S)-2-Azido-2-[2-(1,3-dioxan-2-yl)phenyl]ethanol (**7**)*

A mixture of **4** (6.50 g, 18.4 mmol) was stirred in MeOH–NH_3 (300 mL) for 16 h at room temperature. Volatile matter was evaporated under reduced pressure and the residue purified by column chromatography (hexane–EtOAc, 60:40) to give **7** as an oil (95%); δ_H ($CDCl_3$) 1.36, 2.19, 3.91, 4.21 (6 H, m, dioxanyl), 3.68 (2 H, m, CH_2O), 5.39 (1 H, dd, $J = 4.8$, 8.0, CHN_3), 5.61 (1 H, s, dioxanyl), 7.35–7.51 (4 H, m, aromatic H); δ_C ($CDCl_3$) 26.1, 68.0, 101.8 (dioxanyl), 63.8 (CN_3), 66.6 (C-2,), 127.8, 128.1, 128.6, 129.9, 135.7, 136.7 (aromatic C). Calculated for $C_{12}H_{15}O_3N_3$: C, 57.82; H, 6.06; N,16.86. Found: C, 57.93; H, 6.33; N, 16.62.

*(2S)-2-Amino-2-[2-(1,3-dioxan-2-yl)phenyl]ethanol (**8**)*

A mixture of **7** (3.80 g, 15.2 mmol) and PPh_3 (4.40 g, 16.8 mmol) in THF (tetrahydrofuran; 100 mL) was

stirred at room temperature for 24 h. Volatile matter was evaporated under reduced pressure and the residue taken up in MeOH–NH_3. After 24 h at room temperature, the volatile matter was evaporated under reduced pressure and the residue was purified by column chromatography ($CHCl_3$–MeOH, 70:30) to give **8** as an oil (54%); δ_H ($CDCl_3$) 1.44, 2.23, 3.98, 4.25 (6 H, m, dioxanyl), 3.65 (1 H, dd, $J = 4.9$, 10.7, CH_2O), 3.73 (1 H, dd, $J = 8.2$, 10.7, CH_2O), 4.53 (1 H, dd, $J = 4.9$, 8.1, $CHNH_2$), 5.68 (1 H, s, dioxanyl), 7.57–7.31 (4 H, m, aromatic H); δ_C ($CDCl_3$) 26.0, 67.9, 68.0, 101.0 (dioxanyl), 52.5 ($CHNH_2$), 67.6 (C-2′), 126.4, 127.2, 127.7, 129.8, 136.3, 141.4 (aromatic C).

*(1S)-1-Acetylamino-2-acetoxy-1-[2-(1,3-dioxan-2-yl)phenyl]ethane (**9**)*

A mixture of **8** (504 mg, 2.26 mmol) and anhydride acetic acid (1.27 mL) in pyridine (10 mL) was stirred at room temperature for 12 h. Volatile matter was evaporated under reduced pressure and the residue was purified by silica gel column chromatography ($CHCl_3$–MeOH, 90:10) to give **9** as an oil (91%); δ_H ($CDCl_3$): 1.38, 2.17, 4.0, 4.18 (6 H, m, dioxanyl), 1.88, 1.99 (6H, s, $COCH_3$), 4.28 (2 H, m, CH_2O), 5.61 (1 H, m, CHNHAc), 5.80 (1 H, s, dioxanyl), 7.26–7.61 (4 H, m, aromatic H); δ_C ($CDCl_3$) 21.3, 23.5 (CH_3), 26.0, 67.7, 99.6 (dioxanyl), 48.8 (CHNHAc), 66.3 (C-2), 126.8, 127.0, 128.3, 129.4, 136.8, 136.9 (aromatic C), 170.2, 171.7 (CO).

*(3S)-3-Acetoxymethyl-2-acetyl-1,3-dihydro-1-methoxyisoindole (**10**)*

Compound **9** was dissolved in methanolic HCl (1%, 10 mL) and the mixture stirred for 2 h at room temperature. Water was added and the mixture extracted with diethyl ether. The extract was worked up and the crude product purified by column chromatography ($CHCl_3$–MeOH, 99:1) to give **10** (34%) (*cis* and *trans* 1:1) as an oil; *cis* isomer, δ_H ($CDCl_3$) 1.92, 2.25 (6H, two s, COMe), 3.1 (3H, s, OMe), 4.39 (1 H, dd, $J = 6.1$, 11.0, CH_2O), 4.67 (1 H, dd, $J = 4.0$, 11.0, CH_2O), 5.28 (1 H, dd, $J = 4.1$, 6.0, CHNHAc), 6.29 (1 H, s, $CHOCH_3$), 7.35 (4 H, m, aromatic H); δ_C($CDCl_3$) 21.2, 22.7 (COMe), 50.5 (OMe), 60.6 (CHNHAc), 65.1 (C-2), 91.2 (CHOMe), 123.8, 124.5, 129.0, 130.4, 135.8, 139.2 (aromatic C), 170.9, 172.6 (CO); *trans* isomer, δ_H ($CDCl_3$) 1.79, 2.27 (6H, s, COMe), 2.77 (3H, s, OMe), 4.53 (1 H, dd, $J = 6.1$, 11.0, CH_2O), 4.67 (1 H, dd, $J = 4.0$, 11.0, CH_2O), 5.4 (1 H, dd, $J = 4.1$, 6.0, CHNHAc), 6.41 (1 H, s, CHOMe), 7.35 (4 H, m, aromatic H); δ_C ($CDCl_3$) 21.0, 23.0 (2C, COMe), 48.6 (OCH_3), 62.2 (CHNHAc), 63.7 (C-2), 90.4 (CHOMe), 123.4, 129.1, 129.7, 130.3, 135.7, 139.0 (aromatic C), 170.9, 172.6 (CO).

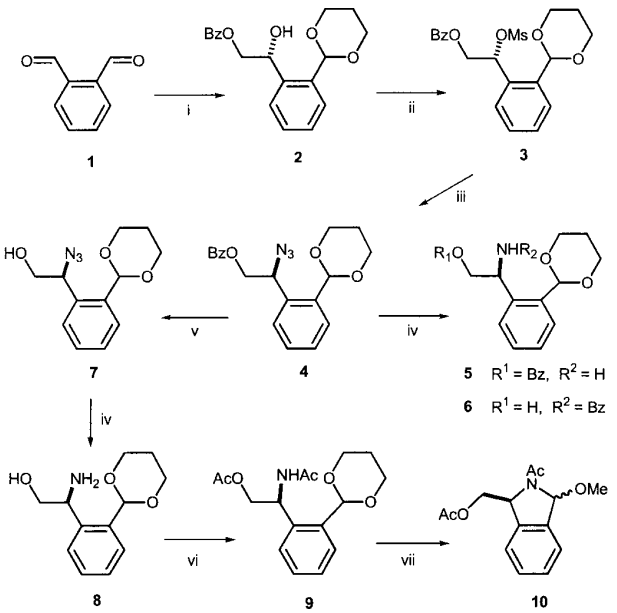

Figure 2 Synthesis of (3*S*)-3-acetoxymethyl-2-acetyl-1,3-dihydro-1-methoxyisoindole (**10**). Reagents and conditions: i, Ewing et al (2000); ii, MsCl, pyridine; iii, LiN_3, DMF; iv, PPh_3, NH_3, THF; v, NH_3, MeOH; vi, Ac_2O, pyridine; vii, HCl 1%, MeOH.

Results and Discussion

The protected dihydroxyaldehyde **2** was easily prepared (Figure 2) from phthalaldehyde (**1**) (Ewing 1999, 2000) in four steps including asymmetric dihydroxylation with Admix β. The dihydroxylation step is completely stereoselective, which is important in generating the *R* configuration at the chiral centre (which will become part of the new ring). The essential strategy to get an appropriate nitrogen functionality in place requires the insertion, with inversion, of an azido group at the chiral site, and this was achieved by *O*-mesylation followed by treatment with lithium azide in dimethylformamide to give intermediate **4** in 76% yield. Reduction of the azido group in **4** was best accomplished with the Staudinger procedure using PPh_3–NH_3 in methanol. Under these conditions, an O-to-N migration of the benzoyl group occurred to some extent and a mixture of the ester **5** and the amide **6** was obtained. This mixture was not amenable to separation by column chromatography. However, this problem could be avoided by removing the protecting benzoyl group before reduction. Thus, the azido alcohol **7** was reduced (54% yield), and the primary hydroxy group reprotected, by acetylation.

Removal of the aldehyde protection led to spontaneous cyclization to give (3*S*)-3-acetoxymethyl-2-acetyl-1,3-dihydro-1-methoxyisoindole **10** as a pair of diastereoisomers. The presence of a 1-methoxy group prevents both reversion to the corresponding amidoaldehyde and 1,3 dehydration to an isoindole.

Compound **10** has the potential to behave as an azasaccharide and hence couple with a silylated nucleobase using trimethylsilyl triflate as a catalyst (the Vorbruggen procedure) to provide access to novel nucleoside analogues. The bioassay of compound **10** and related nucleoside analogues will be reported elsewhere.

In conclusion, the 1-methoxyisoindoline derivatives (**10**) possessing two asymmetric carbon atoms were conveniently prepared in good overall yield starting from achiral phthalaldehyde. A stereoselective method employing asymmetric dihydroxylation gave stable enantiomerically pure azasaccharides. These compounds have potential biological activity and could be used to form novel glycone moieties in nucleoside chemistry.

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