Pergamon

Tetrahedron: *Asymmetry* 11 (2000) 4995–5002

TETRAHEDRON: *ASYMMETRY*

Facile separation of chiral 1,3-dihydrobenzo[*c*]furan derivatives using a D-xylose moiety as a protecting group

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Received 24 November 2000; accepted 4 December 2000

Abstract

1,2-*O*-Isopropylidene-α-D-xylofuranose has been used to protect one aldehyde group of *o*-phthalaldehyde. This chiral protecting group acts as a resolving agent and this leads to separable diastereoisomers when a new stereogenic centre is created by the conversion of the second aldehyde group to a benzyloxyhydroxyethyl chain. These separated diastereoisomers were cyclised to 1,3-dihydrobenzo[*c*]furans with retention of chiral integrity at the C3 site thus allowing further elaboration to enantiomerically pure nucleoside analogues. © 2001 Published by Elsevier Science Ltd.

1. Introduction

Nucleoside analogues are among the most effective of an increasing number of anti-HIV drugs which have been developed for clinical use and 2′,3′-deoxynucleosides and 2′,3′-didehydro-2′,3′-dideoxynucleosides such as AZT, ddC, ddA, d4T, with the β-D-configuration, have been approved for the treatment of AIDS.[1–3] The importance of a 2′,3′ double bond in the furanose ring has been widely appreciated since Balzirini et al.[4] demonstrated that d4T [1-(2,3-dideoxy-β-D-*glycero*-pent-2-enofuranosyl)thymine, **1**] had potent activity against HIV and much effort has been devoted to the synthesis of this and related unsaturated compounds.[5] Notably d4T is less toxic and less inhibitory to mitochondrial DNA replication than AZT.[6] The lipophilicity of any anti-viral compound is an important property and this is well illustrated by the enhanced activity against cell lines of HIV and other retroviruses which is observed[7] when d4T is converted to the much more lipophilic alaninylmonophosphate derivative **2**.

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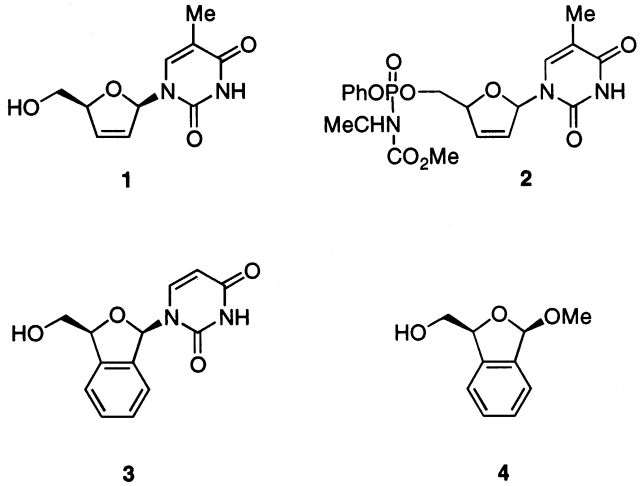
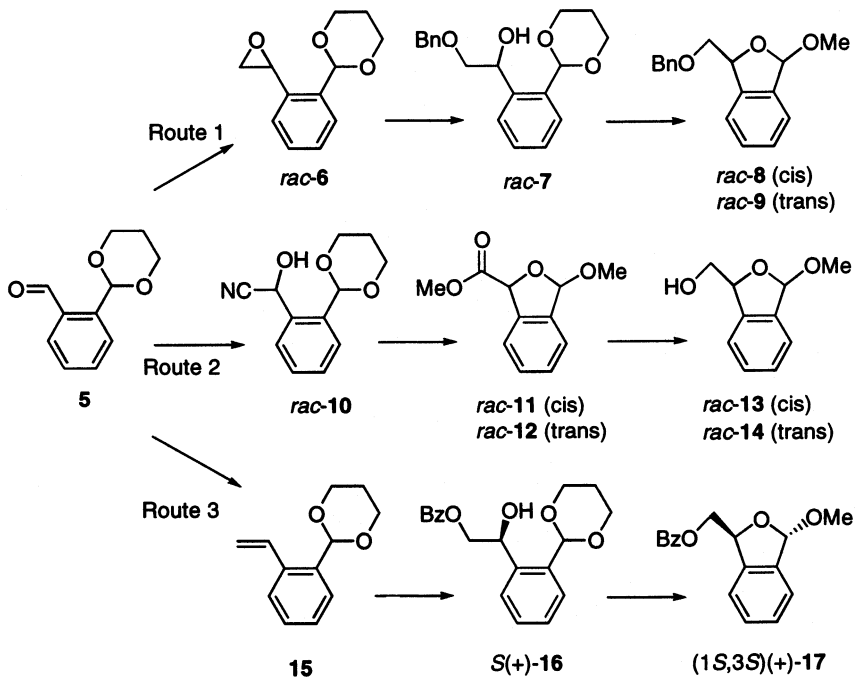
PII: S0957-4166(00)00488-2



We have shown recently[8,9] that nucleoside analogues based on a 1,3-dihydrobenzo[*c*]furan glycone as shown in compound **3** can be obtained readily. The thymine analogue of **3** corresponds to d4T with the double bond in the sugar ring incorporated into a benzene ring and this bicyclic system will have increased lipophilicity. The synthesis of **3** and related pyrimidine and purine nucleoside analogues requires access to the glycone, 1,3-dihydro-3-hydroxymethyl-1-methoxybenzo[*c*]furan **4**.

Various routes to the glycone **4** have been investigated[8,9] starting in all cases from phthalaldehyde half-protected as the acetal with propan-1,3-diol and these routes are summarised in Scheme 1. Since two new stereogenic centres are created in the formation of the dihydroben-



Scheme 1. Routes to 1,3-dihydrobenzo[*c*]furan glycone. Details of reagents are available elsewhere[8b,9]

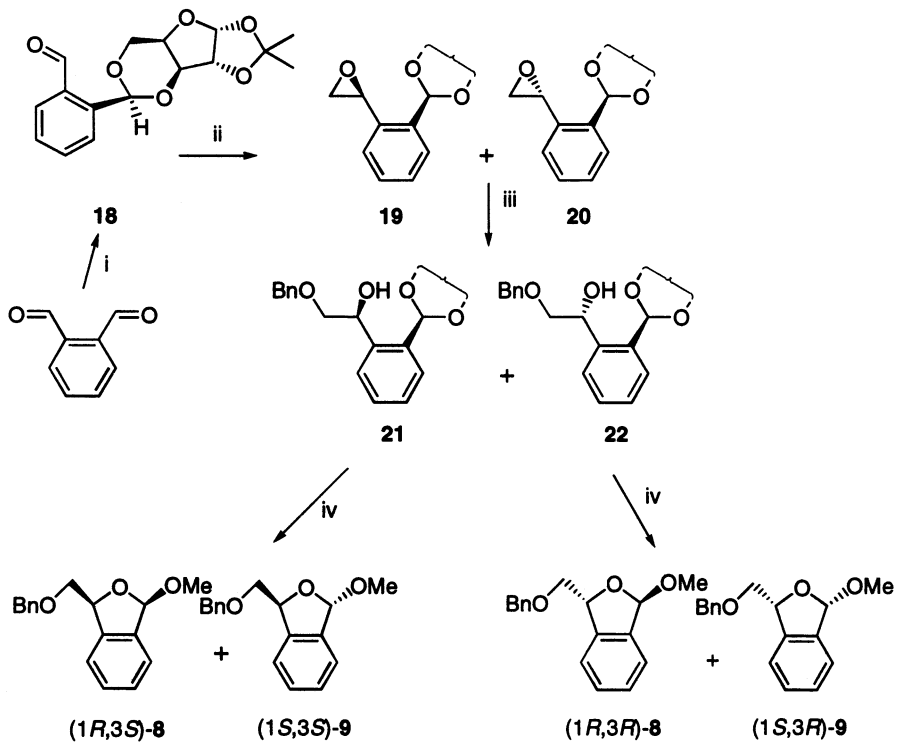
zo[*c*]furan system by any of these routes, the extent to which the stereochemistry can be controlled is an important aspect of this chemistry. In route 1 the epoxidation step gave the racemic compound **6**, and hence no stereocontrol was possible over the cyclisation step. Thus a mixture of racemic diastereoisomers **8** and **9** was obtained (*cis–trans* ratio = 1.5:1). This mixture is difficult to separate and only the *trans*-isomer **9** was obtained stereochemically pure. Route 2 is similarly non-selective, giving a racemic cyanohydrin **10** which led to a mixture of racemic diastereoisomers **13** and **14** (*cis–trans* ratio = 1:1.25). Again only the *trans*-isomer could be obtained in pure form.

Route 3 employed the Sharpless asymmetric dihydroxylation methodology[10] which was completely stereoselective in this case and the protected diol **16** was obtained in 100% ee [either (*S*)-(+) or (*R*)-(−) depending on which of the two Sharpless reagents was used]. Cyclisation of compounds (*S*)-(+)-**16** and (*R*)-(−)**16** was also stereospecific and thus both enantiomers of the *trans*-form of the benzoylated glycone (1*S*,3*S*)-(+)-**17** and (1*R*,3*R*)-(−) **17**, respectively, were obtained. Diastereoselectivity at the 1-position is always lost during attachment of a nucleoside base but separation of the diastereoismers is relatively easy at the nucleoside stage and thus all four pure enantiomers of nucleoside analogue **3** were obtained[9] by route 3. This permits independent evaluation of the influence of the stereochemistry of the C1 site (analogous to α/β configurations in carbohydrates) and the C3 site (analogous to D/L-configurations in carbohydrates). The potential of nucleosides with the unnatural L-configuration as antiviral agents has only recently been appreciated[11] and hence further exploration of stereocontrol of the C3 site in **4** is worthwhile.

2. Results and discussion

As is evident from Scheme 1 access to the benzo[*c*]furan system starts conveniently from phthalaldehyde with one aldehyde group protected. Previously propan-1,3-diol has been used to form an acetal but, reasoning that a chiral protecting group might provide greater stereocontrol in the generation a stereogenic centre from the second aldehyde group, we have sought to protect phthalaldehyde with a sugar derivative. The formation of benzaldehyde acetals with methyl hexopyranosides is a well established protocol for the protection of sugars[12] but we have found that although the reaction of *o*-phthalaldehyde with methyl β-D-glucopyranoside gives only one acetal stereoisomer, the yield is poor (15%). In contrast we have found that 1,2-*O*-isopropylidene-α-D-xylofuranose[13] reacts with *o*-phthalaldehyde to form a benzylidene derivative **18**, in 50% yield (Scheme 2). Although a new stereogenic centre is generated in the 1,3-dioxane ring only the diastereoisomer with the (*S*)-configuration (Fig. 1) at this new centre is formed, presumably since the condensation is preferentially directed by the chiral furanose ring.

MM2 modelling of **18** indicates that the dioxan ring adopts a chair conformation with an equatorial phenyl group, as confirmed by a strong NOE interaction between the three axial protons in this ring. Starting from the MM2 geometry the energy of each of the conformations of **18** was evaluated by semi-empirical calculations at the PM3 level. The most stable form (Fig. 1) has the plane of the phenyl group exactly bisecting the dioxolan ring. The formyl group is oriented *exo* with respect to the bicyclic system formed by the furanose and dioxolan rings and the carbonyl bond is *anti* to the benzylidene group. Both the phenyl and formyl groups would be expected to exhibit a twofold rotational potential and the other conformations were also



Scheme 2. *Reagents and conditions*: (i) 1,2-*O*-isopropylidene-α-D-xylofuranose, *p*TSA, THF, reflux; (ii) $Me_3SO^+I^-$, NaH, DMSO, rt; (iii) NaH, BnOH, DMF, 100°C; (iv) HOAc (80%), 60°C then MeOH/HCl (1%), rt

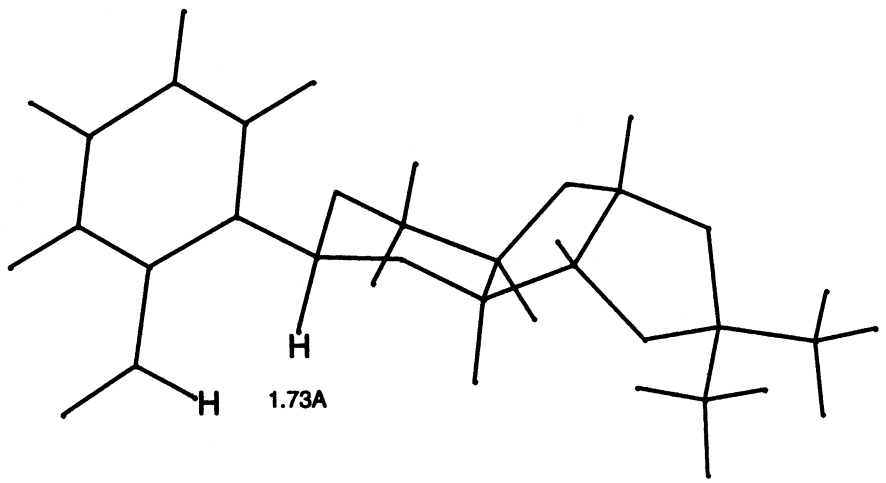


Figure 1. Lowest energy conformation of compound **18** (PM3 energy)

investigated. The conformer with the corresponding *syn* orientation of the carbonyl bond is 3.8 kJ mol^{-1} higher in energy. Rotation of the benzene ring in **18** by 180° gives a notional *endo–anti* conformation. In fact the symmetry of this form is lower since the formyl group is twisted about 35° to point the formyl hydrogen to one or other of the dioxolan oxygen atoms (H···O separation ca. 2.5 Å). These forms are about 5 kcal mol^{-1} above the stable form in Fig. 2.

A stable conformation of the *endo–syn* type does not exist but a twisted configuration with the phenyl group axial is over 5 kcal mol^{-1} higher in energy.

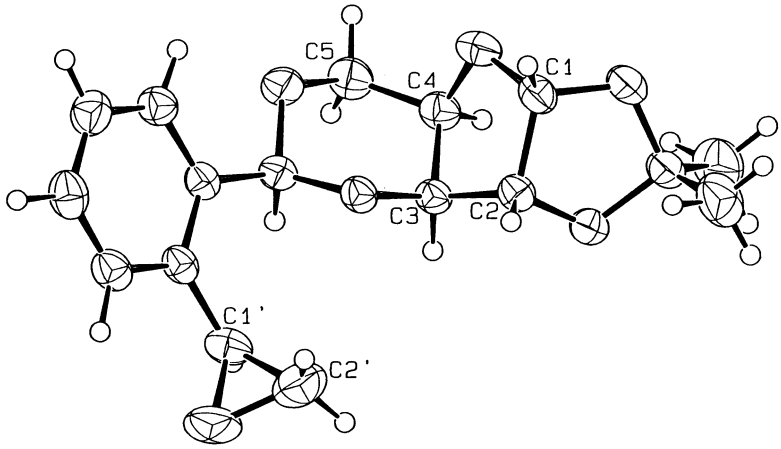


Figure 2. Configuration and conformation of epoxide **19** as determined by X-ray crystallography

With the chiral protecting group attached the sequence of reactions shown in Scheme 2 was carried through. The epoxidation step[8b] afforded a mixture of stereoisomers **19** and **20** (arising from the (*S*) and (*R*) configurations of the new stereogenic centre, respectively) in the ratio 1:1. It is notable that the presence of a chiral protecting group has not produced any selectivity in the formation of these epoxides. It is likely that the chiral influence of the xylose group is too remote to exercise any stereocontrol. Separation of these epoxides was difficult but a pure sample of **19** could be isolated in 14% yield by crystallisation. The configuration of this pure diastereoisomer was established unequivocally by X-ray crystallography (Fig. 1). This structure also confirms the configuration at the benzylidene carbon.

Compound **19** was easily converted to the benzylated diol **21** (by treatment with the sodium salt of benzyl alcohol). However it was more efficient to convert the mixture of epoxides **19** and **20** to the mixture of the benzylated diols **21** and **22** since these diastereoisomers could be separated cleanly by column chromatography. Thus the presence of a stereogenic protecting group has achieved the desired objective by allowing the effective resolution of the stereogenic centre which becomes C3 in the glycone. Removal of the chiral protecting group from compound **21** by treatment with 80% acetic acid was followed by spontaneous cyclisation. Conversion to the pseudo-glycosides with methanolic HCl gave a mixture of the diastereoisomers (1*R*,3*S*)-**8** and (1*S*,3*S*)-**9**. Since the C1 centre is always epimerised under these conditions it is evident that cyclisation has occurred without any loss in the chiral integrity of the (*S*)-configuration at the C3 centre. Similarly compound **22** gave the corresponding diastereoisomer mix with the (*R*)-configuration at C3. We have already established that the analogues of **8** or **9** with a benzoyl protecting group, prepared as pure C3 epimers by asymmetric induction, can be converted to pyrimidine nucleosides by standard procedures.[9] Although the C1 site is always epimerised the *cis*-and *trans*-diastereoisomers of these nucleoside analogues are easily separated by chromatography to give access to the four enantiomers arising from the two stereogenic centres in uracil derivatives of type **3**. Thus the use of 1,2-*O*-isopropylidene-α-D-xylofuranose as a chiral protecting group achieves the same result, in one set of reactions, as the use of the Sharpless catalytic dihydroxylation reagents which of course requires two parallel reaction sequences.

3. Experimental

3.1. General

Melting points were determined on a digital melting-point apparatus (Electrothermal) and are uncorrected. Optical rotations were recorded at 22°C in $CHCl_3$ or MeOH solutions with a digital polarimeter DIP-370 (Jasco) using a 1 dm cell and rotations are given in 10^{-1} deg cm^2 g^{-1}. ^{1}H NMR and ^{13}C NMR spectra were recorded in $CDCl_3$ or Me_2SO-d_6 (internal Me_4Si), respectively, at 300.13 MHz and at 75.47 MHz (Bruker AM WB-300). Coupling constants (J) are given in Hz. TLC was performed on Silica F_{254} (Merck) with detection by UV light at 254 nm or by charring with phosphomolybdic–H_2SO_4 reagent. Column chromatography was effected on Silica Gel 60 (Merck, 230 mesh). Commercial reagents were supplied by Lancaster or Across. Molecular modelling and molecular orbital calculations were performed by the MM2 and PM3 methods, respectively, using the MOPAC package as provided in the Chem3D suite from ChemOffice. In all cases the reliability of a conformational minimum was rigorously established by repeated minimisation from different points in the energy surface.

3.2. Syntheses

3.2.1. 3,5-O-(2-Formylbenzylidene)-1,2-O-isopropylidene-α-D-xylofuranose **18**

A stirred mixture of *o*-phthalaldehyde (5.0 g, 37.73 mmol), 1,2-*O*-isopropylidene-α-D-xylofuranose[13] (7.1 g, 37.73 mmol), toluene-4-sulfonic acid (0.1 g) and tetrahydrofuran (50 mL) was refluxed for 5 h. Triethylamine (2 mL) was added and the reaction mixture was cooled and extracted with diethyl ether (20 mL). The extract was worked up and the crude product purified by column chromatography (hexane–diethyl ether, 70:30) to afford **18** (5.6 g, 49%) as a solid, mp 86.0–86.3°C; [α] +13 (*c* 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$): δ 7.82, 7.59 (2H, m, H-3, H-6), 7.43, 7.50 (2H, m, H-4, H-5), 5.98 (1H, d, $J_{1',2'}$ 3.6, H-1′), 5.92 (1H, s, CH), 4.51 (1H, d, $J_{2',3'}$ 0, H-2′), 4.41 (1H, bs, H-4′), 4.37 (1H, d, H-5′a), 4.12 (1H, dd, $J_{4',5'b}$ 1.6, $J_{5'a,5'b}$ 13.1, H-5′b), 4.08 (1H, bs, H-3′), 1.44 (3H, s, Me), 1.24 (3H, s, Me). ^{13}C NMR ($CDCl_3$): δ 192.4 (CHO), 138.2 (C-1), 133.9 (C-2), 133.4, 130.5, 129.5, 127.3 (C-3, C-4, C-5, C-6), 111.8 (C_{iso}), 105.5 (C-1′), 97.8 (CH), 83.6 (C-2′), 79.1 (C-4′), 72.0 (C-3′), 66.8 (C-5′), 26.6, 26.0 (Me). Anal. calcd for $C_{16}H_{18}O_6$ (306.31): C 62.74; H 5.92; found: C 62.60, H 6.08.

3.2.2. 3,5-O-[2-((S)-Oxiranyl)benzylidene]-1,2-O-isopropylidene-α-D-xylofuranose **19** and 3,5-O-[2-((R)-oxiranyl)benzylidene]-1,2-O-isopropylidene-α-D-xylofuranose **20**

A mixture of trimethylsulfoxonium iodide (7.8 g, 35.3 mmol) and sodium hydride (1.1 g, 35.3 mmol) in dry dimethyl sulfoxide (100 mL) was stirred for 30 min at 10°C. A solution of compound **18** (8.0 g, 26.1 mmol) in dimethyl sulfoxide (100 mL) was added dropwise to the above mixture at 10°C and then the mixture stirred for 30 min at rt. Saturated aqueous NH_4Cl (200 mL) was added and the mixture extracted with diethyl ether. The extract was worked up and the crude product purified by column chromatography (hexane–diethyl ether, 70:30) to give a mixture of compounds **19** and **20** (4.2 g, 50%). A pure sample of **19** was obtained by careful crystallisation from ethanol.

Compound **19**. Mp 143.4–143.9°C, [α] +50.6 (*c* 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$): δ 7.45 (2H, m, H-3 and H-6), 7.27 (2H, m, H-4 and H-5), 6.01 (1H, d, $J_{1',2'}$ 3.6, H-1′), 5.62 (1H, s, CH), 4.57

(1H, d, $J_{2',3'}$ 0, H-2′), 4.44 (1H, d, H-5′a), 4.40 (1H, bs, H-4′), 4.27 (1H, dd, *J* 2.6, oxiranyl), 4.11 (1H, dd, $J_{4',5'b}$ 1.7, $J_{5'a,5'b}$ 13.5, H-5′b), 4.11 (1H, bs, H-3′), 3.13 (1H, dd, *J* 5.6, oxiranyl), 2.67 (1H, dd, *J* 3.9, oxiranyl), 1.49 (3H, s, Me), 1.30 (3H, s, Me). ^{13}C NMR ($CDCl_3$): δ 136.2 (C-1), 135.4 (C-2), 129.5, 127.6, 126.6, 124.6 (4C, C-3, C-4, C-5, C-6), 111.8 (C_{iso}), 105.6 (C-1′), 99.1 (CH), 83.7 (C-2′), 78.9 (C-4′), 72.0 (C-3′), 66.7 (C-5′), 50.9, 49.8 (oxiranyl), 26.6, 26.1 (Me). Anal. calcd for $C_{17}H_{20}O_6$ (320.34): C 63.74; H 6.29; found: C 63.67; H 6.40.

Compound **20**. ^{1}H NMR ($CDCl_3$): δ 7.49 (2H, m, H-6, H-3), 7.27 (2H, m, H-4, H-5), 5.99 (1H, d, $J_{1',2'}$ 3.6, H-1′), 5.61 (1H, s, CH), 4.56 (1H, d, $J_{2',3'}$ 0, H-2′), 4.42 (1H, d, H-5′a), 4.39 (1H, bs, H-4′), 4.26 (1H, m, oxiranyl), 4.11 (1H, dd, $J_{4',5'b}$ 1.7, $J_{5'a,5'b}$ 13.5, H-5′b), 4.10 (1H, bs, H-3′), 3.06 (1H, dd, oxiranyl), 2.62 (1H, dd, oxiranyl), 1.48 (3H, s, CH_3), 1.29 (3H, s, Me). ^{13}C NMR ($CDCl_3$): δ 136.1 (C-1), 135.3 (C-2), 129.5, 127.5, 126.4, 124.5 (4C, C-3, C-4, C-5, C-6), 111.9 (C_{iso}), 105.6 (C-1′), 98.8 (CH), 83.8 (C-2′), 78.9 (C-4′), 72.0 (C-3′), 66.6 (C-5′), 50.8, 49.7 (oxiranyl), 26.7, 26.1 (Me).

*3.2.3. 3,5-*O*-[2-((*S*)-2-Benzyloxy-1-hydroxyethyl)benzylidene]-1,2-*O*-isopropylidene-α-D-xylofuranose **21** and 3,5-*O*-[2-((*R*)-2-benzyloxy-1-hydroxyethyl)benzylidene]-1,2-*O*-isopropylidene-α-D-xylofuranose **22***

Benzyl alcohol (1.2 g, 11.24 mmol) was added to a suspension of sodium hydride (337 mg, 11.24 mmol) in dry DMF (60 mL) and the mixture stirred at room temperature under nitrogen for 30 min. A mixture of oxiranes **19** and **20** (4.0 g, 12.49 mmol) in DMF (20 mL) was added dropwise and the mixture was stirred for a further 3 h at 100°C. The solution was poured into ice-water and extracted with diethyl ether. The extract was worked up and the crude product purified by column chromatography (hexane–acetone, 80:20) to afford a first component **21** (1.8 g, 34%) and a second component **22** (1.9 g, 36%).

This synthetic step was also applied to the pure diastereoisomer **19** to give compound **21,** identical in all respect to the sample obtained by chromatography.

Compound **21**. [α] +23.6 (*c* 0.8, $CHCl_3$); ^{1}H NMR ($CDCl_3$): δ 7.56, 7.50 (2H, m, H-3, H-6), 7.36, 7.23 (2H, m, H-4, H-5), 6.02 (1H, d, $J_{1',2'}$ 3.6, H-1′), 5.56 (1H, s, CH), 5.30 (1H, dd, *J* 2.9, *J* 8.7, CHOH), 4.61 (2H, q, *J* 7.5, *J* 12.2, CH_2Ph), 4.45 (1H, d, $J_{2',3'}$ 0, H-2′), 4.35 (1H, d, H-5′a), 4.31 (1H, bs, H-4′), 4.07 (1H, bs, H-3′), 4.02 (1H, d, $J_{5a',5'b}$ 13.1, H-5′b), 3.67 (1H, dd, *J* 3.1, CH_2OBn), 3.49 (1H, dd, *J* 10.0, *J* 8.9, CH_2OBn), 3.10 (1H, s, OH), 1.51 (3H, s, Me), 1.30 (3H, s, Me). ^{13}C NMR ($CDCl_3$): δ 138.5 (Bn), 138.1 (C-1), 134.4 (C-2), 129.4, 127.6, 127.0, 126.7 (C-3, C-4, C-5, C-6), 128.4 (Bn), 127.6 (Bn), 111.8 (C_{iso}), 105.6 (C-1′), 98.4 (CH), 83.7 (C-2′), 78.8 (C-4′), 75.1 (CH_2OBn), 72.9 (OCH_2Ph), 72.0 (C-3′), 68.7 (CHOH), 66.7 (C-5′), 26.7, 26.2 (Me). Anal. calcd for $C_{24}H_{28}O_7$ (428.48): C 67.28, H 6.59; found: C 67.17, H 6.85.

Compound **22**. [α] −27.3 (*c* 0.6, $CHCl_3$); ^{1}H NMR ($CDCl_3$): δ 7.56, 7.45 (2H, m, H-3 and H-6), 7.29 (2H, m, H-4 and H-5), 6.06 (1H, d, $J_{1',2'}$ 3.4, H-1′), 5.52 (1H, s, CH), 5.32 (1H, dd, *J* 2.9, *J* 8.7, CHOH), 4.56 (2H, q, *J* 7.5, *J* 12.2, CH_2Ph), 4.50 (1H, d, $J_{2',3'}$ 0, H-2′), 4.28 (1H, d, H-5′a), 4.31 (1H, bs, H-4′), 4.04 (1H, bs, H-3′), 3.97 (1H, d, $J_{5a',5'b}$ 13.1, H-5′b), 3.64 (1H, dd, *J* 3.1, CH_2OBn), 3.45 (1H, dd, *J* 10.0, *J* 8.9, CH_2OBn), 3.10 (1H, s, OH), 1.49 (3H, s, Me), 1.28 (3H, s, Me). ^{13}C NMR ($CDCl_3$): δ 138.9 (Bn), 138.0 (C-1), 134.3 (C-2), 129.4, 127.7, 127.0, 126.6 (C-3, C-4, C-5, C-6), 128.4 (Bn), 127.8 (Bn), 111.8 (C_{iso}), 105.6 (C-1′), 98.6 (CH), 83.8 (C-2′), 78.8 (C-4′), 75.5 (CH_2OBn), 73.4 (OCH_2Ph), 72.0 (C-3′), 69.2 (CHOH), 66.5 (C-5′), 26.7, 26.1 (Me). Anal. calcd for $C_{24}H_{28}O_7$ (428.48): C 67.28, H 6.59; found: C 67.17, H 7.06.

*3.2.4. Cyclisation to stereoisomers of 3-benzyloxymethyl-1,3-dihydro-1-methoxybenzo[c]furan **8** and **9***

Compound **21** (100 mg, 0.23 mmol) was taken up in 5.8 mL of 80% acetic acid and heated at 60°C for 2 h. After evaporation and co-evaporation with toluene, the residue was dissolved in methanolic HCl (1%, 2 mL) and the mixture stirred for 2 h at 20°C. Water (5 mL) was added and the mixture extracted with diethyl ether. The extract was worked up and the crude product purified by column chromatography (hexane–acetone, 95:05) to afford a 1:1 diastereoisomeric mixture of (1*R*,3*S*)-**8** and (1*S*,3*S*)-**9** (37 mg, 58%). Similarly, compound **22** gave a mixture of (1*S*,3*R*)-**8** and (1*R*,3*R*)-**9** (39 mg, 60%). In all cases the ^{1}H and ^{13}C NMR data were identical to those for the racemic compounds.[8b]

Acknowledgements

We thank Professor G. Nowogrocki for the X-ray studies.

References

1. De Clercq, E. *J. Med.Chem.* **1995**, *38*, 2491–2517.
2. Huryn, D.; Okabe, M. *Chem. Rev.* **1992**, *92*, 1745–1768.
3. Nasr, M.; Litterst, C.; McGowan, J. *Antiviral Res.* **1990**, *14*, 125–148.
4. Balzarini, J.; Kang, G.-J.; Dalal, M.; Herdewijn, P.; De Clercq, E.; Broder, S.; Johns, D. G. *Mol. Pharmacol.* **1987**, *32*, 162–167.
5. (a) Diaz, Y.; El-Laghdach, A.; Matheu, M. I.; Castillon., S. *J.Org. Chem.* **1997**, *62*, 1501–1505; (b) Clive, D. L. J.; Wickens, P. L.; Sgarbi, P. W. M. *J.Org. Chem.* **1996**, *61*, 7426–7437; (c) McDonald, F. E.; Gleason, M. M. *J. Am. Chem. Soc.* **1996**, *118*, 6648–6659; (d) Larsen, E; Kofoed, T.; Pedersen, E. B. *Synthesis*, **1995**, 1121–1125; (e) Lipshutz, B. H.; Stevens, K. L; Lowe, R. F. *Tetrahedron Lett.* **1995**, *36*, 2711–2712; (f) Luzzio, F. A.; Menes, M. E. *J. Org. Chem.* **1994**, *59*, 7267–7272 and references cited therein.
6. Simpson, M. V.; Chin, C. D.; Keilbaugh, S. A.; Lin, T. S.; Prusoff, W. H. *Biochem. Pharmacol.* **1989**, *38*, 1033–1036.
7. Balzarini, J.; Egberink, H.; Hartmann, K.; Cahard, D.; Vahlenkamp, T.; Thormar, H.; De Clercq, E.; McGuigan, C. *Mol. Pharmacol.* **1986**, *50*, 1207–1213.
8. (a) Ewing, D. F.; Fahmi, N.; Len, C.; Mackenzie, G.; Ronco, G.; Villa, P.; Shaw, G. *Collect. Czech. Chem. Commun.* **1996**, *61*, S145–S147; (b) Ewing, D. F.; Fahmi, N.-E.; Len, C.; Mackenzie, G.; Ronco, G.; Villa, P.; Shaw, G. *Nucleosides Nucleotides* **1999**, *18*, 2613–2630.
9. Ewing, D. F.; Fahmi, N.-E.; Len, C.; Mackenzie, G; Pranzo, A. *J. Chem. Soc., Perkin Trans. 1* **2000**, 3561–3565.
10. Kolb, H. C.; VanNieuwenhze, M. S.; Sharpless, K. B. *Chem. Rev.* **1994**, *94*, 2483–2547.
11. (a) Lin, T.-S.; Luo, M.-Z.; Liu, M.-C.; Pai, S. B.; Dutschman, G. E.; Cheng, Y.-C. *J. Med. Chem.* **1994**, *37*, 798–803; (b) Ma, T. W.; Lin, J.-S.; Newton, M. G.; Cheng, Y.-C.; Chu, C. K. *J. Med. Chem.* **1997**, *40*, 2750–2754 and references cited therein; (c) Wang, J. H.; Choudhury, D.; Chattopadhyaya, J.; Eriksson, S. *Biochemistry* **1999**, *38*, 16993–16999.
12. Svaan, M.; Anthonsen, T. *Acta Chem. Scand.* **1986**, *40*, 112–122.
13. Moravcova, J.; Capkova, J.; Stanek, J. *Carbohydr. Res.* **1994**, *263*, 61–66.