Pergamon

Tetrahedron Letters 40 (1999) 3259–3262

TETRAHEDRON LETTERS

Components for a Combinatorial Library of Rigid Azabicyclic α-L-Fucose Mimics: First X-Ray Crystal Structure of a Stable Monoalkylated Triazene formed by Hydrogenation of an Azide

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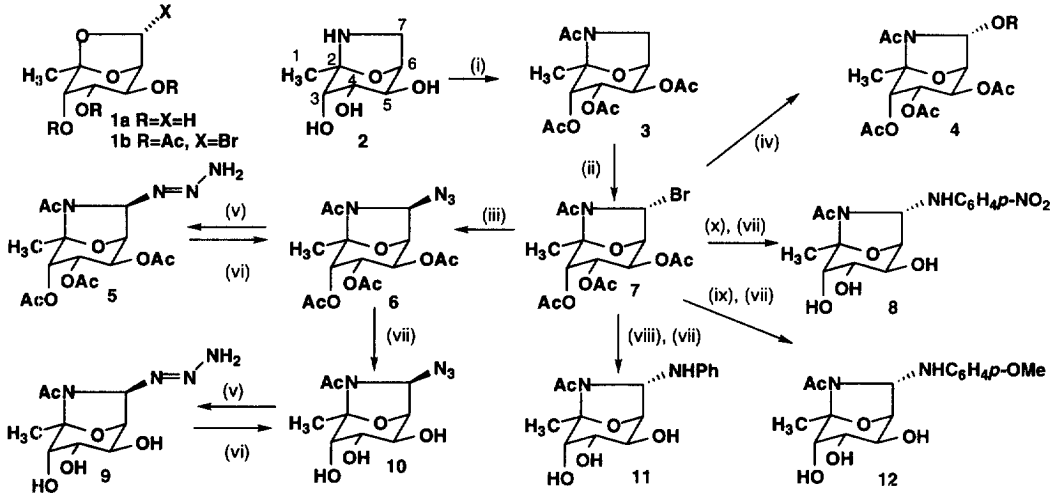
Received 15 January 1999; accepted 17 February 1999

Abstract: Photobromination of the rigid aza-bicyclic fucose mimic **3** gave a reactive glycosyl type bromide **7** as a divergent intermediate for the synthesis of both 7-*O* and 7-*N* linked bicyclic L-fucose derivatives by direct displacement with alcohols or amines. Displacement of the bromide **7** with sodium azide gave an azide **6** which on hydrogenation gave a stable monoalkyl triazene **5**, the structure of which was established by X-ray crystallographic analysis. Hydrolysis of **7** allowed access to a monocyclic L-fucose mimic with a nitrogen substituent at C-5. © 1999 Elsevier Science Ltd. All rights reserved.

The preceding paper describes the photobromination[1] of the peracetate of a rigid bicyclic analogue **1a** of L-fucose to give the bromide **1b** with the objective of generating a series of fucose mimics by nucleophilic displacement of the bromide with oxygen and nitrogen nucleophiles.[2] The azabicyclic derivative **2** and some of its *N*-substituted derivatives are potent fucosidase and weak fucosyl transferase inhibitors.[3]



Scheme 1: (i) Ac_2O, C_5H_5N, 70%; (ii) Br_2, $MeCCl_3$, hυ, 70%; (iii) NaN_3, DMF, 56%; (iv) ROH -see text (v) H_2, Pd; (vi) MeOH, Br_2; (vii) MeOH, MeONa; (viii) $PhNH_2$, $MeCCl_3$, 93%; (ix) *p*-$MeOC_6H_4NH_2$, $MeCCl_3$, 67%; (x) *p*-$NO_2C_6H_4NH_2$, $MeCCl_3$, 29%.

This paper describes a radical bromination of the bicyclic peracetate **3** to generate a reactive bromide **7** which may be a divergent intermediate for the formation of azafucose mimics with the required conformational environment of the secondary hydroxyl groups in the fucose ring.[4] Displacement of the bromide **7** with amines and with oxygen nucleophiles [ROH to give **4**] proceeds with overall retention of configuration at C-7; oxidation of the hydrolysis product **13** allows access to monocyclic fucose analogues, such as **21**, with nitrogen substituents at C-5. Reaction of **7** with sodium azide in DMF gives **6** with inversion of configuration at C-7; hydrogenation of the azide **6** gives a stable monoalkyl triazene **5**, the structure of which was firmly established by X-ray crystallographic analysis [Figure 1].[5]

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PII: S0040-4039(99)00378-0

The bicyclic fucose analogue **2** was protected as the known tetraacetate **3** by treatment with pyridine and acetic anhydride [Scheme 1]. Irradiation of the amide **3** with a 400W tungsten filament bulb in 1,1,1-trichloroethane in the presence of bromine afforded a single monobromide **7** in 70% yield.[6] The α-bromoamide **7** was considerably less stable than the oxygen analogue **1b** – presumably because fragmentations of **7** to a cation stabilised by a nitrogen lone pair occurs more readily than to a carbocation from **1b** stabilised by an oxygen lone pair. The appearance of H-7 as a singlet strongly suggests the H-7 proton is an *endo* substituent, and hence indicated formation of the *exo* bromide; the four crystal structures in this and the preceding paper, together with earlier literature precedents,[1] indicate that the coupling between H-6 and an *endo*-H-7 is zero [that is, for *exo*- substituents at C-7] whereas the coupling between H-6 and an *exo*-H-6 is approximately 4-5 Hz [indicating an *endo* substituent at C-7].

Nucleophilic displacement of the bromide in **7** with azide afforded the more sterically hindered *endo* azide **6**, m.p. 169-171°C (diethyl ether); $[\alpha]_D^{20}$ -26.8 (*c*, 1.01 in $CHCl_3$); a coupling constant $J_{7,6}$ 5.3 Hz indicated an S_N2 reaction had occurred [55% overall yield from **3**] with the proton in an *exo*-environment. It was expected that hydrogenation of azide **6** would form the corresponding amine [or possibly a mixture of anomeric amines] which would be a useful intermediate for the synthesis of *N*-linked fucose analogues, as described for the oxygen analogue in the preceding paper.[2] However, hydrogenation of the azide **6** afforded a single product **5** which was only slightly more polar than the azide itself and was shown to be a stable, crystalline monosubstituted triazene; the structure of **5**[7] was confirmed by X-ray crystallography[5] [Figure 1]. It was not possible to transform the triazene into the corresponding amine, nor indeed to form any well-defined derivatives; for example, all attempts at acylation of **5** with acid chlorides gave complex mixtures of products. However, the triazene **5** may be efficiently oxidised by bromine back to the azide **6** in 60% isolated yield. Removal of the *O*-acetate protecting groups in the azide **6** gave the triol **10**[8] in 87% yield. Hydrogenation of the unprotected azide **10** again resulted in isolation of a triazene **9** as the major product; the absence of any azide stretch in the i.r. spectrum of **9** indicated all the starting material had been reduced. In this case, however, the triazene **9** was unstable and decomposed quickly to an unidentifiable mixture; **9** was characterised on the basis of its similarity to **5** and its re-oxidation by bromine to the azido triol **10**. No products resembling anomeric amines or their derivatives was isolated from any of these reactions.

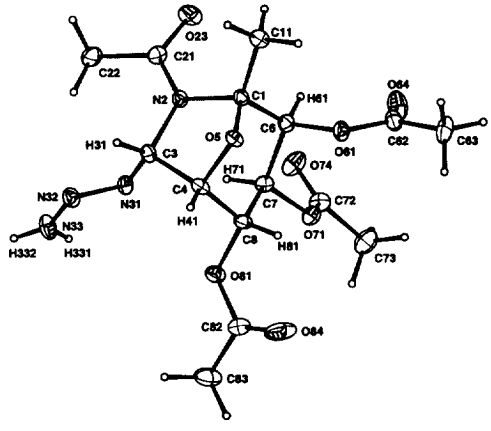


Figure 1 X-Ray structure of the monoalkyltriazine **5**

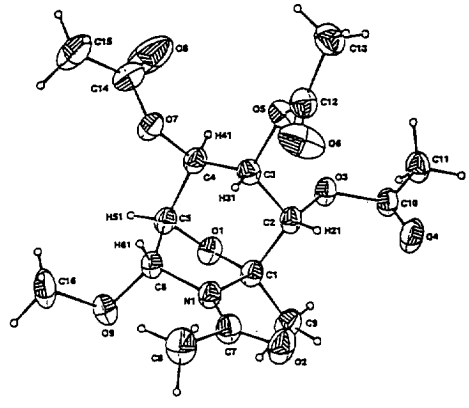
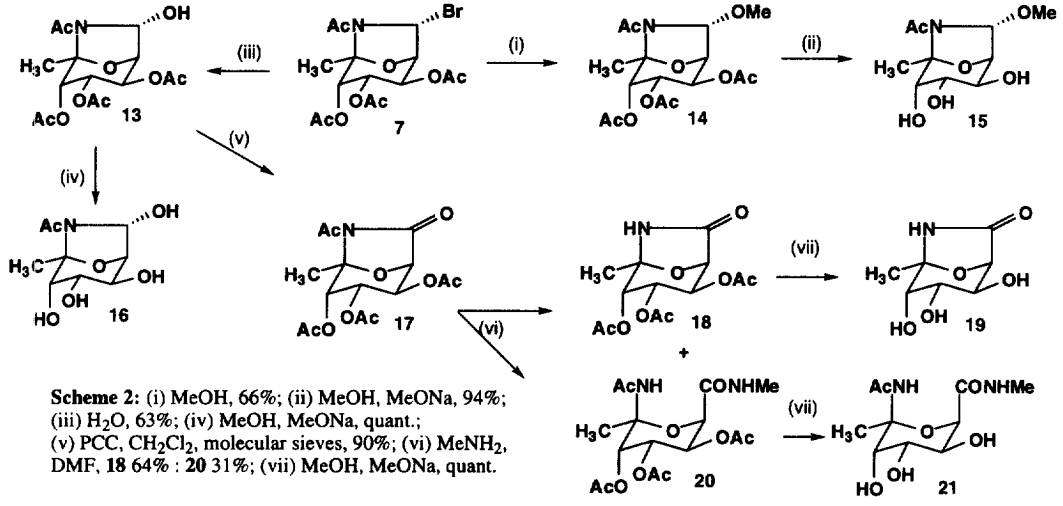


Figure 2 X-Ray structure of methyl glycoside **14**

Although monosubstituted triazenes have been known for a long time,[9] they are usually unstable and decompose to the corresponding amines; triazenes are commonly accepted as intermediates in many of the reductions of azides to amines. There are other rare examples of stable monosubstituted triazenes,[10] but this paper reports the first example of a crystal structure which firmly establishes the *trans*-nature of the substituents on N=N. It is possible that the relative stability of some triazenes in the reduction of some sugar anomeric azides accounts for the poor yields of the corresponding amines.

A different approach was therefore required for development of the *N*-linked analogues of **2**; direct displacement of the bromide in **7** by amines give the corresponding triacetates from which acetate protecting groups can be efficiently removed allowing access to substituted anomeric amines. Treatment of the crude bromide **7** with aniline resulted in direct displacement to afford, after removal of the acetate protecting groups with sodium methoxide in methanol, the *N*-phenyl linked L-fucose analogue, **11**, as an oil, $[\alpha]_D^{25}$ -151.5 (*c*, 0.68 in CH_3OH) in 88% yield. Similar reactions with *p*-anisidine and *p*-nitroaniline gave access to the *p*-methoxyphenyl substituted compound, **12**, m.p. 103-104°C; $[\alpha]_D^{25}$ -112.0 (*c*, 1.12 in CH_3OH), in 29% overall yield from **3**, and the *p*-nitrophenyl substituted derivative, **8**, m.p. 210°C, dec; $[\alpha]_D^{20}$ -165.2 (*c*, 0.52 in MeOH), in 47% overall yield from **3**. In all cases, the appearance of H-7 as a singlet provides strong evidence that the isolated amines are *exo*-substituents, showing that the nucleophilic displacement has proceeded with overall retention of configuration at the anomeric position, in contrast to the inversion reaction found for the azide displacement above. There are several rationalisations for this outcome, the simplest of which is that the reactions proceed by S_N1 pathways with capture of the intermediate cation from the least hindered side. Alternatively, it might be that the initially formed more hindered *endo*-amines anomerise subsequently to the more stable less hindered *exo*-amines; no evidence was found to support this hypothesis. If the reactions were to proceed with neighbouring group participation by the neighbouring acetate group, it might be expected that other products would arise from trapping the intermediate acylium ion. However, regardless of the mechanism of the displacement it is clear that displacement of the bromide **7** by nitrogen nucleophiles leads to an efficient synthesis of N-linked derivatives of the bicyclic fucose mimic **2**.

In contrast to the complications caused by acetate neighbouring group participation in the displacement of the bromide **1b** by oxygen nucleophiles,[2] displacement of the *exo*-bromide **7** by water and by methanol proceeded in high yield to give *exo*-products, in all of which H-7 appears as a singlet [Scheme 2].



Scheme 2: (i) MeOH, 66%; (ii) MeOH, MeONa, 94%; (iii) H_2O, 63%; (iv) MeOH, MeONa, quant.; (v) PCC, CH_2Cl_2, molecular sieves, 90%; (vi) $MeNH_2$, DMF, **18** 64% : **20** 31%; (vii) MeOH, MeONa, quant.

Treatment of the crude bromide **7** with anhydrous methanol afforded the pseudo glycoside **14** in 66% overall yield from **3**; the stereochemistry of this glycoside was confirmed by X-ray crystallography [Figure 2]. The methyl glycoside was quantitatively deprotected in basic methanol to give the methoxytriol **15**. The

efficiency of this nucleophilic displacement augurs well for the use of the bromide **7** for the incorporation of the bicyclic azafucose **2** unit into oligosaccharides. When the crude bromide reaction mixture was treated with water, the single lactol **13** was obtained in 63% overall yield from **3**; removal of the acetate protecting groups afforded a quantitative yield of the homofucose analogue **16**, m.p. 207-209°C (ethyl acetate); $[\alpha]_D^{22}$ -101.7 (*c*, 1.08 in MeOH), Oxidation of the protected alcohol **13** by pyridinium chlorochromate gave the lactam **17**, m.p. 128°C, $[\alpha]_D^{25}$ –33.3 (*c*, 0.98 in $CHCl_3$. Reaction of **17** with methylamine gave a mixture of the monocyclic secondary amide **20**, m.p. 187-188°C, $[\alpha]_D^{25}$ +5.0 (*c*, 0.26 in $CHCl_3$), and the partially deacylated lactam **18**, m.p. >230°C, $[\alpha]_D^{25}$ -39.4 (*c*, 0.72 in $CHCl_3$). Deprotection of **20** with methoxide in methanol gave **21**, as a hygroscopic white foam, $[\alpha]_D^{23}$ +26.0 (*c*, 0.30 in H_2O); energy minimisation calculations, consistent with the ^1H NMR of **21** suggest it adopts a twist boat conformation. The lactam **18** was also deprotected by treatment with methoxide in methanol to give **19**, m.p. 190-192°C, $[\alpha]_D^{23}$ -74.0 (*c*, 0.30 in H_2O). The methodology described in this and the preceding paper provides for efficient incorporation of rigid bicyclic analogues of fucose **1** and **2** into a wide range of novel structures; such procedures might also be used to incorporate other rigid pyranoses into a number of combinatorial libraries.[12]

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4. Jeffries, I; Bowen, BR *Bioorg. Med. Chem. Lett.*, 1997, **7**, 1171 and references cited therein.
5. The atomic coordinates for the triazene **5** and the methyl glycoside **15** are available on request from the Cambridge Crystallographic Data Centre, University Chemical Laboratory, Lensfield Road, Cambridge CB2 1EW; the crystallographic numbering system differs from that used elsewhere in the text. Any request should be accompanied by the full literature citation for this paper.
6. Selected data for bromide, **7**: δ_H (200 MHz; $CDCl_3$): 1.75 (3H, s, CH_3), 1.96, 2.11, 2.17, 2.40 (4 x 3H, 4 x s, 4 x $COCH_3$), 4.79 (1H, d, H-6, $J_{6,5}$ 4.8 Hz), 4.97 (1H, dd, H-4, $J_{4,5}$ 9.7 Hz, $J_{4,3}$ 4.8 Hz), 5.24 (1H, dd, H-5, $J_{5,6}$ 4.8 Hz, $J_{5,4}$ 9.7 Hz), 5.62 (1H, d, H-3, $J_{3,4}$ 4.8 Hz), 5.98 (1H, s, H-7).
7. Data for triazene triacetate **5**: M.p. 129-130°C (ethyl acetate); $[\alpha]_D^{20}$ -148.1 (*c*, 0.58 in $CHCl_3$); υ_{max} (KBr): 3403 (NH), 1747 (C=O, ester), 1635 (C=O, amide) cm^{-1}; δ_H (200 MHz; $CDCl_3$): 1.60 (3H, s, CH_3), 1.81, 1.92, 2.13, 2.19 (4 x 3H, 4 x s, 4 x $COCH_3$), 4.59 (1H, dd, H-6, $J_{6,7}$ 5.6 Hz, $J_{6,5}$ 4.0 Hz), 5.07 (1H, dd, H-5, $J_{5,6}$ 4.0 Hz, $J_{5,4}$ 10.3 Hz), 5.52 (1H, d, H-7, $J_{7,6}$ 5.6 Hz), 5.59 (1H, d, H-3, $J_{3,4}$ 4.8 Hz), 5.76 (1H, dd, H-4, $J_{4,5}$ 10.3 Hz, $J_{4,3}$ 4.8 Hz), 8.23 (2H, brs, 2 x NH, D_2O exchanges); δ_C (125 MHz; $CDCl_3$): 19.9, 20.5, 20.5, 24.1, 29.6 (C-1, 4 x $COCH_3$), 67.8, 69.5, 70.5, 74.4, 81.4 (C-3,4,5,6,7), 95.5 (C-2), 168.6, 169.3, 169.7, 170.1 (4 x C=O); *m/z* (LC/MS, ES+): 387 ($M+H^+$, 100%).
8. Data for azide triol **10**: white foam. $[\alpha]_D^{20}$ -100.1 (*c*, 1.71 in MeOH); υ_{max} (Film): 3369 (OH), 2122 (N_3), 1652 (C=O) cm^{-1}; δ_H (500 MHz, 90°C; DMSO): 1.56 (3H, s, CH_3), 2.08 (3H, s, $COCH_3$), 3.72 (1H, dd, H-5, $J_{5,6}$ 4.0 Hz, $J_{5,4}$ 9.7 Hz), 3.77 (1H, d, H-3, $J_{3,4}$ 5.0 Hz), 3.89 (1H, dd, H-4, $J_{4,5}$ 9.7 Hz, $J_{4,3}$ 5.0 Hz), 4.38 (1H, dd, H-6, $J_{6,7}$ 5.5 Hz, $J_{6,5}$ 4.0 Hz), 5.75 (1H, d, H-7, $J_{7,6}$ 5.5 Hz); δ_C (50 MHz; CD_3OD): 19.2, 22.1 (C-1, $COCH_3$), 69.1, 70.3, 71.0, 73.1, 75.4 (C-3,4,5,6,7), 96.8 (C-2), 170.5 (C=O).
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10. Gaoni, Y *J. Org. Chem.*, **1994**, *59*, 6853.
11. Data for methoxy triol, **15**: m.p. 166-167°C (ethyl acetate); $[\alpha]_D^{22}$ -140.7 (*c*, 0.90 in MeOH); δ_H (500 MHz, CD_3OD): 1.76 (3H, s, CH_3), 2.17 (3H, s, $COCH_3$), 3.37 (1H, dd, H-4, $J_{4,5}$ 9.2 Hz, $J_{4,3}$ 4.7 Hz), 3.38 (1H, s, OCH_3), 3.76 (1H, dd, H-5, $J_{5,6}$ 4.9 Hz, $J_{5,4}$ 9.2 Hz), 4.07 (1H, d, H-3, $J_{3,4}$ 4.7 Hz), 4.25 (1H, d, H-6, $J_{6,5}$ 4.9 Hz), 5.12 (1H, s, H-7).

12. This work was supported by a GlaxoWellcome studentship to KHS. All new compounds in this paper have microanalytical and/or spectroscopic data consistent with the structures proposed.