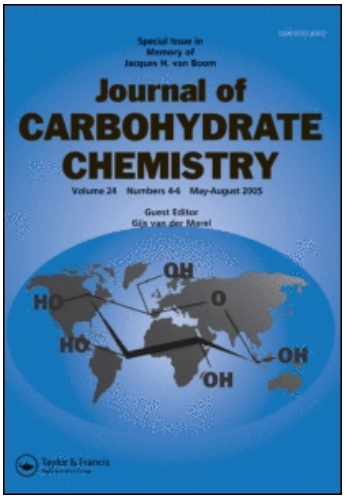


Journal of Carbohydrate Chemistry
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713617200

Synthesis of An Unusual Tetrahydrofuro[3,4-*D*] Oxazole Ring System

José Molina; Claire Simons

To cite this Article Molina, José and Simons, Claire(2000) 'Synthesis of An Unusual Tetrahydrofuro[3,4-*D*] Oxazole Ring System', Journal of Carbohydrate Chemistry, 19: 8, 991 — 996
To link to this Article: DOI: 10.1080/07328300008544130
URL: http://dx.doi.org/10.1080/07328300008544130

J. CARBOHYDRATE CHEMISTRY, 19(8), 991–996 (2000)

SYNTHESIS OF AN UNUSUAL TETRAHYDROFURO[3,4-*d*] OXAZOLE RING SYSTEM

José Molina and Claire Simons*

Medicinal Chemistry Division, Welsh School of Pharmacy, Cardiff University, King Edward VII Avenue, Cardiff CF10 3XF, U.K.

Received May 19, 2000 - Final Form July 25, 2000

ABSTRACT

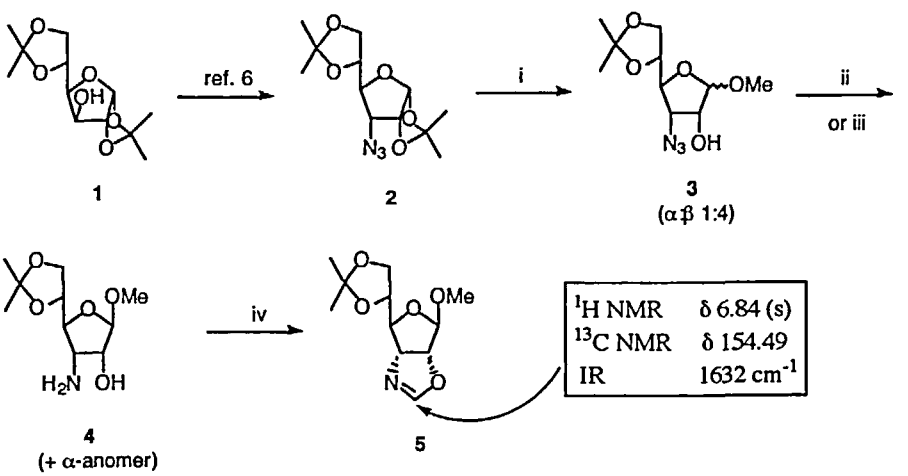
Treatment of methyl 3-amino-3-deoxy-5,6-*O*-isopropylidene-β-D-allofuranoside, prepared in four steps from diacetone-D-glucose, with *N*,*N*-dimethylformamide dimethyl acetal resulted in the formation of a novel bicyclic tetrahydrofuro[3,4-*d*]oxazole ring system.

INTRODUCTION

Nitrogen-containing bicyclic carbohydrate systems, such as castanospermine,[1] swainsonine[2] and kifunensine,[3] have shown good activity as glycosidase inhibitors and resulted in an interest in the synthesis of novel nitrogen-containing compounds.[4] This report describes an efficient route for the synthesis of a novel bicyclic nitrogen-containing carbohydrate structure, a tetrahydrofuro[3,4-*d*]oxazole bicyclic system (**5**), which to the best of our knowledge, has not been described in the literature. Such compounds may have potential as glycosidase inhibitors and the methodology described may be applicable to the synthesis of other synthetic and naturally occurring oxazoles.

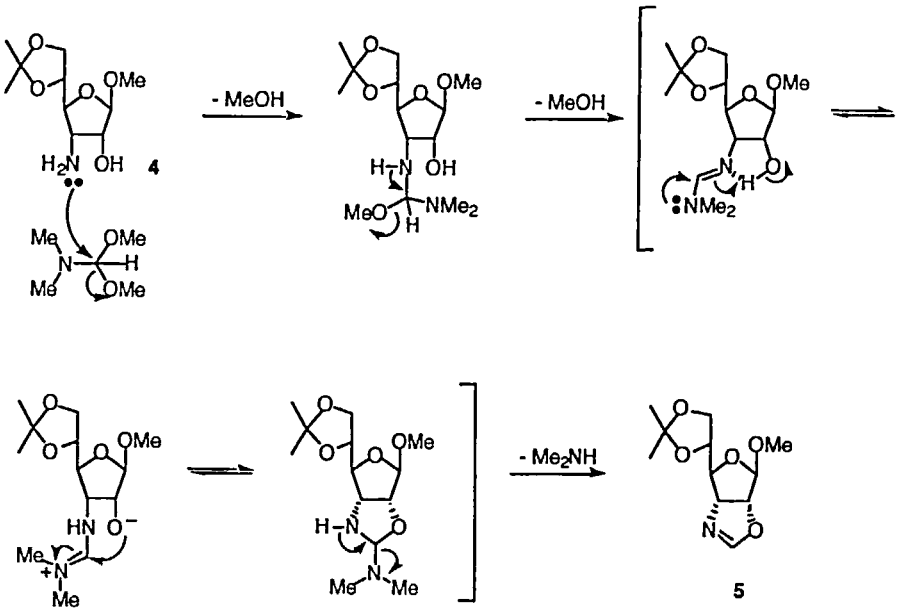
RESULTS AND DISCUSSION

Using our previously described methodology,[5] the preparation of methyl 3-azido-3-deoxy-5,6-*O*-isopropylidene-α,β-D-allofuranoside (**3**) was effectively accomplished in a one-pot procedure, from the readily available 3-azido-3-deoxy-1,2:5,6-di-*O*-isopropylidene-α-D-allofuranose (**2**),[6] on treatment with 0.5% iodine/methanol (w/v). Conversion to the 3-aminoallofuranoside (**4**), with the β-anomer being the major product, was achieved by either triphenylphosphine/water reduction or $LiAlH_4$ reduction. A better yield was obtained with the triphenylphosphine/water reduction, however the $LiAlH_4$ reduction did not require column chromatography purification.



Scheme 1. Reagents and conditions: (i) I_2, MeOH (0.5% w/v), rt, 4 h then acetone, 40 °C, 18 h, 64% (ii) PPh_3, THF, H_2O, 60 °C, 2 h, 80% (iii) $LiAlH_4$, THF, rt, 2 h, 55% (iv) DMFDMA, DMF, rt, 18 h, 51%.

Compound **4** was then reacted with *N,N*-dimethylformamide dimethyl acetal (DMFDMA) to give the bicyclic tetrahydrofuro[3,4-*d*]oxazole (**5**), with only the β-anomer isolated. The mechanism of formation of **5** is described in Scheme 2. Initially the DMF protected amino compound is formed, then the hydroxyl group at C-2, after a prototropic equilibrium, attacks the imine resulting in ring closure and consecutive elimination of dimethylamine.



Scheme 2

The structure of compound **5** was confirmed by NMR which indicated the imine proton at 6.84 ppm in the ^{1}H NMR and the imine carbon at 154 ppm in the ^{13}C NMR. Furthermore, the IR of **5** showed a typical imine double bond stretching at 1632 cm^{-1} and the absence of any hydroxyl stretching within the region 3200-3700 cm^{-1}.

CONCLUSION

In this paper, we have described a short and efficient synthesis of a novel bicyclic oxazole ring system *via* an addition-elimination reaction of the 3-aminoallofuranoside (**4**) and *N,N*-dimethylformamide dimethyl acetal.

EXPERIMENTAL

General methods. ^{1}H and ^{13}C NMR spectra were recorded with a Brucker Avance DPX300 spectrometer operating at 300 and 75 MHz respectively, in $CDCl_3$ unless stated otherwise, with Me_4Si as internal standard. Chemical shifts are expressed in parts per million downfield from TMS. Microanalyses were determined by Medac Ltd., Surrey. HRMS were recorded at the EPSRC National Mass Spectrometry Service Centre,

University of Swansea. Infrared spectra were recorded with a Perkin Elmer 1600 FT-IR spectrometer. Flash column chromatography was performed with silica gel 60 (230-400 mesh) (Merck) and TLC were carried out on precoated silica plates (kiesel gel 60 F_{254}, BDH). Melting points were measured with a Gallenkamp Melting Point Apparatus and are reported uncorrected. All the reactions were carried out under nitrogen using anhydrous solvents from Aldrich except for acetone, which was obtained from Fisher and dried over 4 Å molecular sieves.

Methyl 3-azido-3-deoxy-5,6-*O*-isopropylidene-α,β-D-allofuranoside (3). Compound **2** (7.54 g, 26.43 mmol) was refluxed in 0.5% (w/v) iodine / methanol (162 mL) for 4 h. The reaction mixture was allowed to cool to room temperature and acetone (120 mL) added. The mixture was then stirred at 70 °C for 2 h and overnight at 40 °C. Aqueous saturated $Na_2S_2O_3$ was added to the cooled mixture until it became colourless and the resulting salts were removed by filtration. The filtrate was concentrated and the residue dissolved in ethyl acetate (250 mL) and washed with water (2 x 100 mL). The aqueous layer was back-extracted with ethyl acetate (5 x 100 mL) and all the organic extracts were combined, dried ($MgSO_4$) and solvent evaporation furnished the crude product as a yellow syrup that was purified by column chromatography (chloroform - methanol 9:1 v/v) to give 4.36 g (64%) of the title compound, α: β ratio = 1:4. Both anomers were isolated on a small scale for characterisation. Compound **3**, *α-anomer*, amorphous solid. ^{1}H NMR δ 4.79 (d, $J_{1,2}$ = 4.5, 1, H-1), 4.18 (m, 1, H-2), 4.04 (m, 2, H-6), 3.90 (dd, J = 3.3, J = 7.6, 1, H-5), 3.83 (dd, J = 3.5, J = 5.4, 1, H-4), 3.78 (m, 1, H-3), 3.39 (s, 3, OCH_3), 2.82 (bs, 1, OH), 1.40 (s, 3, CH_3), 1.29 (s, 3, CH_3); ^{13}C NMR δ 110.38 (C, CMe_2), 102.47 (CH, C-1), 83.17 (CH, C-3), 76.02 (CH, C-5), 72.95 (CH, C-2), 66.88 (CH_2, C-6), 61.46 (CH, C-4), 55.94 (CH_3, OCH_3), 26.83 (CH_3) and 25.16 (CH_3). IR (cm^{-1}): 3396, 2993, 2936, 2111. Compound **3**, *β-anomer*, waxy solid, mp 43-45 °C. ^{1}H NMR δ 4.84 (s, 1, H-1), 4.19 (m, 3, H-2 and H-6), 4.04 (m, 3, H-3, H-4 and H-5), 3.36 (s, 3, OCH_3), 2.62 (bs, 1, OH), 1.51 (s, 3, CH_3), 1.41 (s, 3, CH_3); ^{13}C NMR δ 110.34 (C, CMe_2), 108.30 (CH, C-1), 82.79 (CH, C-3), 78.11 (CH, C-2), 76.01 (CH, C-5), 68.33 (CH_2, C-6), 66.05 (CH, C-4), 55.43 (CH_3, OCH_3), 26.92 (CH_3) and 25.61 (CH_3); IR (cm^{-1}): 3347, 2990, 2933, 2111.

Anal. Calcd for anomeric mixture $C_{10}H_{17}O_5N_3$ (259.264): C, 46.33; H, 6.61; N, 16.20. Found: C, 46.18; H, 6.45, N, 16.15.

Methyl 3-amino-3-deoxy-5,6-*O*-isopropylidene-α,β-D-allofuranoside (4). **Method A.** Triphenylphosphine (402 mg, 1.53 mmol) was added to a solution of compound **3** (331 mg, 1.28 mmol) in tetrahydrofuran (7 mL). The mixture was stirred at room temperature until all the nitrogen had been expelled (1.5 h), then water (253 μL, 253

mg, 14.04 mmol) was added and the reaction mixture was stirred at 60 °C for 2 h. The cooled mixture was absorbed over silica gel 60 (230-400 mesh) and purified by column chromatography (chloroform - methanol 40:1 v/v) to give 240 mg (80%) of the title compound (α: β ratio = 1:4) as a pale yellow oil. Only the ^{13}C NMR data of the β-anomer (major) is given. Compound **4**, anomeric mixture: ^{1}H NMR δ 4.96 (d, $J_{1,2}$ = 4.1, H-1α), 4.92 (s, H-1β), 4.24 (m, 1, H-2), 4.06 (m, 3, H-6 and H-5), 3.70 (m, 2, H-4 and H-3), 3.54 (s, $OCH_3\alpha$), 3.42 (s, $OCH_3\beta$), 2.56 (bs, ex., 3, OH and NH_2), 1.52 (CH_3), 1.46 (CH_3); ^{13}C NMR, *β-anomer*, δ 109.92 (CH, C-1), 109.33 (C, CMe_2), 79.43 (CH, C-3), 77.04 (CH, C-2), 75.89 (CH, C-5), 68.49 (CH_2, C-6), 57.08 (CH, C-4), 55.32 (CH_3, OCH_3), 27.28 (CH_3) and 25.69 (CH_3). HRMS Calcd for $C_{10}H_{20}O_5N$ $[M+H]^+$: 234.1341. Found: 234.1340.

Method B. To a cooled (0 °C) solution of **3** (0.585 g, 2.26 mmol) in tetrahydrofuran (18 mL) was added lithium aluminium hydride (1M in THF, 4.5 mL, 4.51 mmol), then the reaction was stirred at room temperature for 30 min. The reaction was cooled in ice and quenched by the addition of ethyl acetate (50 mL). This solution was washed with water (50 mL), dried (MgSO4) and concentrated under reduced pressure to give 290 mg (55%) of the product **4** as a pale yellow oil. NMR data as for Method A.

4-(2,2-Dimethyl-[1,3]dioxolan-4-yl)-6-methoxy-3a,4,6,6a-tetrahydrofuro[3,4-*d*] oxazole (5). Dimethylformamide dimethyl acetal (50 μL, 42 mg, 0.35 mmol) was added dropwise to a solution of the 3-amino sugar **4** (75 mg, 0.32 mmol) in *N,N*-dimethylformamide (1.6 mL) at room temperature. The mixture was stirred overnight and then concentrated under reduced pressure. The residue was absorbed over silica gel 60 (230-400 mesh) and purified by column chromatography (petroleum ether - ethyl acetate 1:1 v/v) to give 40 mg (51%) of the β-imine **5** as a white solid, mp 89-91 °C. Compound **5**: ^{1}H NMR δ 6.84 (s, 1, CH=N), 5.02 (s, 1, H-1), 4.84 (m, 2, H-6), 4.13 (m, 2), 4.05 (m, 2), 3.36 (s, 3, OCH_3), 1.50 (s, 3, CH_3), 1.40 (s, 3, CH_3); ^{13}C NMR δ 154.49 (CH, CH=N), 110.27 (C, CMe_2), 109.96 (CH, C-1), 88.56 (CH, C-3), 86.08 (CH, C-2), 76.62 (CH, C-5), 72.90 (CH, C-4), 67.96 (CH_2, C-6), 55.46 (CH_3, OCH_3), 27.50 (CH_3) and 25.83 (CH_3); IR (cm^{-1}): 2991, 1632.

Anal. Calcd for $C_{11}H_{17}O_5N$ (243.262): C, 54.31; H, 7.04; N, 5.76. Found: C, 54.30; H, 7.17, N, 5.57.

ACKNOWLEDGMENTS

We would like to thank the EPSRC National Mass Spectrometry Service Centre, University of Swansea for HRMS data.

REFERENCES AND NOTES

1. R. Saul, R.J. Molyneux and A.D. Elbein, *Arch. Biochem. Biophys.*, **230**, 668 (1984).
2. P.G. Dorling, C.R. Huxtable and S.M. Colegate, *Biochem. J.*, **191**, 649 (1980).
3. M. Iwami, O. Nakayama, H. Terano, M. Kohaka, H. Aoki and H. Imanaka, *J. Antibiot.*, **40**, 612 (1987).
4. G.C. Look, C.H. Fotsch and C-H. Wong, *Acc. Chem. Res.*, **26**, 182 (1993).
5. J. Molina-Arévalo and C. Simons, *J. Carbohydr. Chem.*, **18**, 535 (1999).
6. L. Daley, P. Roger and C. Monneret, *J. Carbohydr. Chem.*, **16**, 25 (1997).