ELSEVIER

Carbohydrate Research 282 (1996) 181–187

CARBOHYDRATE RESEARCH

Note

Decarboxylation of a sialic acid derivative

Jeffrey J. Potter, Mark von Itzstein *

Department of Medicinal Chemistry, Victorian College of Pharmacy, Monash University, 381 Royal Parade, Parkville, Victoria, 3052 Australia

Received 8 June 1995; accepted 15 September 1995

Keywords: Sialic acid; Decarboxylation

The importance of sialic acids in a wide range of biological processes has led to a great deal of interest in the chemistry of this class of carbohydrate in recent times [1–4]. Their role in many biological processes, ranging from immunological events to cell recognition, has been extensively reviewed [5,6].

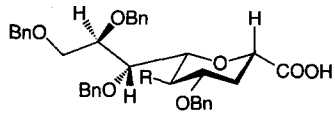
We have been interested in the biological activity of compounds that can be considered as sialic acids with modifications at C-1 and C-2. To this end we have investigated methods of decarboxylating sialic acid derivatives to produce protected octoses suitable for subsequent refunctionalisation.

Decarboxylations of sialic acid derivatives to provide 2-deoxyaldo-octoses have been previously described [7–9]. Vasella and co-workers have used lead(IV) acetate to convert the carboxyl groups of 4,7,8,9-tetra-*O*-benzyl-2-deoxysialic acid (**1**) and 3-benzyloxy-2-deoxy-4,7,8,9-tetra-*O*-benzylsialic acid (**2**) to acetate groups [7,8], while Wong and co-workers have reductively decarboxylated 2,4,7,8,9-penta-*O*-acetylsialic acid (**3**) to give **6**α using Barton's radical-mediated conditions [9]. Both of these methods have been previously applied to the decarboxylation of other carbohydrate acids [10,11].

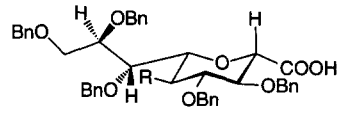
The use of either of these two methods provides a C-8 carbohydrate that can be readily refunctionalised by the attack of a suitable nucleophile at the anomeric carbon. The resultant product would then require an oxidative step to restore the anomeric carbon to the oxidation level of sialic acid. We wished to avoid this reoxidation and so sought a route to the lactone **4**.

* Corresponding author.

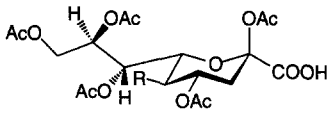
SSDI 0008-6215(95)00374-6



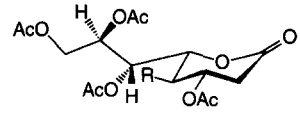
1



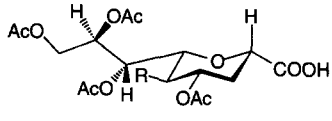
2



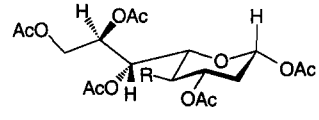
3



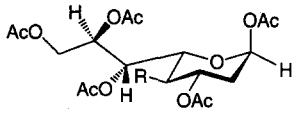
4



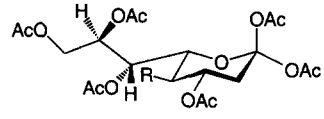
5



6α



6β

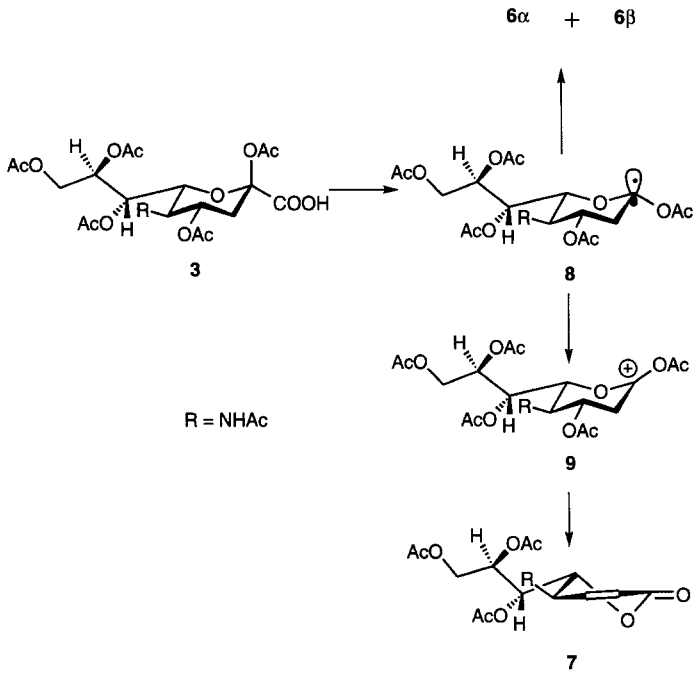


10

R = NHAc

Earlier work in our laboratory had shown that the 2,6-anhydronononic acid tetra-acetate **5** could be converted smoothly to the two peracetylated octoses **6**α and **6**β in a ratio of ca. 1:6 by lead(IV) acetate using conditions similar to those reported by Vasella and co-workers for the decarboxylation of the corresponding tetra-*O*-benzyl-2-deoxy-sialic acid (**1**) [7,8]. We had observed that the reaction of **5** proceeded rather more efficiently when toluene was used as a co-solvent [8], although the α:β ratio of products was not changed. We sought to employ these conditions to decarboxylate sialic acid pentaacetate **3**, which we expected to afford, after workup, the octonolactone **4**.

Thus treatment of 2,4,7,8,9-penta-*O*-acetylsialic acid with lead(IV) acetate in a mixture of toluene and pyridine at 70–90 °C for 2 h gave a mixture of products that could be separated by preparative TLC. The expected product **4** had undergone a β-elimination (Scheme 1) to give the α,β-unsaturated lactone **7** in a disappointing 13% isolated yield. Surprisingly a mixture of the two peracetylated octoses, **6**α and **6**β, was

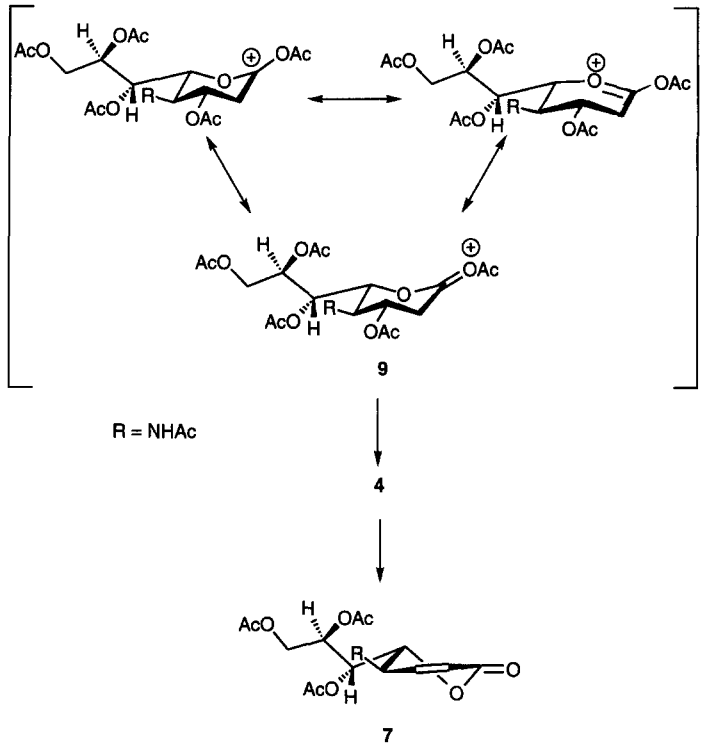


Scheme 1.

also formed (Scheme 1) in 13% isolated yield, with the β-acetate predominating. Interestingly, the use of neat pyridine as solvent produced the lactone **7** in better yield (23%), but again traces of the octoses **6**α and **6**β were detectable in the crude reaction mixture; the ratio of **7**:**6** being ca. 10:1 as estimated by ^{1}H NMR spectroscopy.

The unexpected formation of the acetates **6** presumably arises from the abstraction of a hydrogen atom from toluene by the radical intermediate **8** (Scheme 1). The stability afforded to the intermediate radical **8** by the two α-oxygen substituents may be sufficient to extend its life time to such an extent that hydrogen abstraction would compete with the single-electron oxidation of the radical to the glycosyl cation **9** by the lead species. There is some precedent for the replacement of a carboxylic acid by a hydrogen atom as a result of lead(IV) acetate decarboxylation. Photolytic decomposition of primary lead(IV) carboxylates in chloroform has been reported to give good yields of the corresponding alkane [12]. Furthermore, ESR studies of the photolytic decomposition of lead(IV) carboxylates in a solid benzene matrix at −196 °C show the initial formation of alkyl radicals, followed by the appearance of α-carboxyalkyl radicals, whose formation was attributed to hydrogen abstraction by the less stable alkyl radicals [13].

A not unreasonable mechanism for the formation of the α,β-unsaturated lactone **7** is via a β-elimination of acetic acid from the lactone **4** (Scheme 2). This lactone can be formed either by hydrolysis of the 1,1-diacetyl orthoester **10** during workup, or by loss of the acetyl group from the C-1 oxygen of the glycosyl cation **9**. Compound **10** can be



Scheme 2.

formed by the trapping of **9** by acetate and would be prone to hydrolysis under basic conditions [14], such as those encountered during the aqueous workup prior to acidification. Such conditions would also be conducive to a base-catalysed β-elimination. More likely, however, is the direct loss of the acetyl group from the C-1 oxygen of **9**, followed by β-elimination. Both of these processes seem feasible in hot pyridine, which can act as nucleophile for the deacetylation and base for the elimination. The formation of traces of **6** in the absence of toluene was surprising, and its mechanism of formation under these conditions is not clear.

The reported outcome of the Barton decarboxylation [9], together with other literature precedents (see, inter alia, ref. [15]), suggests that hydrogen abstraction by this glycosyl radical should favour the formation of the α-acetate **6**α. The fact that the ratio of the two anomeric acetates obtained from the lead(IV)-mediated decarboxylation is similar to that obtained from the corresponding reactions of 2,6-anhydronononic acid (2-deoxy-sialic acid) derivatives suggests that these products arise by way of a similar attack of acetate on an intermediate glycosyl cation. This is consistent with the initial formation of the α-acetate, which is then able to equilibrate under the reaction conditions to afford the thermodynamically favoured mixture of anomeric acetates, in which the β-anomer again predominates [16]. We have observed that other anomeric acetates will equilibrate

under the reaction conditions, and that the ratios of α:β-acetates, which we obtain from reactions of short reaction times (20 min rather than 2 h), are closer to 1:2 than to the 1:10 ratio obtained when the longer reaction times are used.

Thus we suggest that the initial radical-mediated hydrogen abstraction from toluene leads to the formation of an α-acetate that can equilibrate under the reaction conditions to give the thermodynamically preferred mixture of products in which the β-acetate predominates. This provides a route from 2,4,7,8,9-penta-*O*-acetylsialic acid (**3**) [17] to the 1,3,6,7,8-penta-*O*-acetyloctoses **6**α and **6**β in which **6**β predominates to complement that of Wong and co-workers [9], which provides the anomer **6**α.

1. Experimental

Decarboxylation of 5-acetamido-4,7,8,9-tetra-O-*acetyl-2,6-anhydro-3,5-dideoxy-β*-D-erythro-L-*gluco-nononic acid* (**5**).—A solution of **5** (100 mg, 0.21 mmol) in dry toluene (20 mL) and pyridine (2 mL) was treated with lead(IV) acetate (200 mg, 0.4 mmol) and heated at 80–100 °C for 2 h. The reaction mixture was then cooled and filtered. The precipitate was washed with chloroform, and the washings and filtrate were combined, washed with 2 M hydrochloric acid, dried over calcium chloride and concentrated under reduced pressure. Chromatography (silica gel–ethyl acetate) afforded 4-acetamido-1,3,6,7,8-penta-*O*-acetyl-2,4-dideoxy-D-*glycero*-α- and β-D-*galacto*-octopyranose (**6**) (83 mg, 81%). NMR showed the α:β ratio to be ca. 1:6. (FABMS) 498 (M + Na, 36%), ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.90, 1.91 (α and β NAc, 3 H), 2.03, 2.04, 2.07, 2.11, 2.14 (5 s, 15 H, 5 Ac β-anomer), 2.05, 2.06, 2.09, 2.10, 2.13 (5 s, 5 Ac α-anomer), 3.76 (dd, $J_{5,6}$ 2.4, $J_{5,4}$ 10.4 Hz, 0.15 H H-5α), 3.9–4.1 (m, 3 H), 4.22 (dd, J 4.8, 4.9 Hz, 0.85 H), 4.35 (dd, $J_{8,7}$ 2.6, $J_{8,8'}$ 12.4 Hz, 0.85 H, H-8β), 5.0–5.5 (m, 3 H), 5.64 (dd, $J_{1,2\,eq}$ 2.1, $J_{1,2\,ax}$ 10.4 Hz, 0.15 H, H-1α), 6.29 (d, $J_{1,2}$ 3.2 Hz, 0.85 H, H-1β).

Decarboxylation of 2,4,7,8,9-penta-O-*acetylsialic acid* (**3**).—*Method A.* 2,4,7,8,9-Penta-*O*-acetylsialic acid (**3**) [17] (130 mg, 0.24 mmol) in dry toluene (8 mL) and pyridine (2 mL) was treated with lead(IV) acetate (400 mg, 0.9 mmol) and heated under dry nitrogen at 70–90 °C for 2 h. The reaction mixture was then cooled to room temperature, partitioned between ice–water (50 mL) and ethyl acetate (25 mL) and acidified with 4 M hydrochloric acid and filtered. The organic layer was separated and washed with 2 M hydrochloric acid, the combined aqueous layers were extracted with ethyl acetate (2 × 25 mL), and the combined organic layers were dried over magnesium sulfate and concentrated under reduced pressure to give a red oil. Crude NMR analysis showed ca. 1:1 lactone–acetate.

Preparative thin-layer chromatography (eluting twice with ethyl acetate) afforded 4-acetamido-1,3,6,7,8-penta-*O*-acetyl-2,4-dideoxy-D-*glycero*-α- and β-D-*galacto*-octopyranose (**6**) as an oil (15 mg, 13%) and 4-acetamido-6,7,8-tri-*O*-acetyl-2,3,4-trideoxy-D-*glycero*-oct-2-enono-1,5-lactone (**7**) as an oil (12 mg, 13%). Compound **6** was identical by ^{1}H NMR spectroscopy and FABMS to that obtained by decarboxylation of compound **5** as described above.

Compound **7**. R_f 0.31 (19:1 ethyl acetate–acetic acid); (FABMS) 480 (100%, M + thioglycerol + 1), 372 (M + 1, 56%), 330 (M − CH_3CO + 1, 27%); ν_{max} (liq film)

3460 (NH), 1755, 1737, 1659 (C=O); ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.04, 2.06, 2.09, 2.12 (4 s, 12 H, 4 Ac), 4.26 (dd, 1 H, $J_{8',8}$ 10.6, $J_{8,7}$ 4.5 Hz, H-8), 4.42 (dd, 1 H, $J_{8',8}$ 10.6, $J_{8',7}$ 2.3 Hz, H-8'), 4.46–4.55 (m, 1 H, H-4), 4.76 (dd, 1 H, $J_{5,4}$ 7.8, $J_{5,6}$ 1.7 Hz, H-5), 5.29 (dd, 1 H, $J_{6,7}$ 7.5, $J_{6,5}$ 1.7 Hz, H-6), 5.34 (ddd $J_{7,6}$ 7.5, $J_{7,8}$ 4.5, $J_{7,8'}$ 2.3 Hz, H-7), 6.04 (dd, 2 H, $J_{2,3}$ 9.8, $J_{2,4}$ 2.0 Hz, NH, H-2) 6.79 (dd, 1 H, $J_{3,2}$ 9.8, $J_{3,4}$ 3.3 Hz, H-3); ^{13}C NMR (75.45 MHz, $CDCl_3$): δ 20.7, 20.9 ($CH_3COO \times 3$), 23.1 (CH_3CONH), 29.69 (C-5), 44.5 (C-4), 61.6 (C-8), 68.9, 69.5 (C-6, C-7), 120.9 (C-2), 145.9 (C-3), 161.4 (C-1), 169.7, 170.0, 170.4, 170.5 (CH_3COO and CH_3CONH). Anal. Calcd for $C_{16}H_{21}NO_9 \cdot 0.5\ H_2O$: C, 50.5; H, 5.85; N, 3.7%. Found: C, 50.4; H, 5.8; N, 3.6%.

Method B. 2,4,7,8,9-Penta-*O*-acetylsialic acid (**3**) (200 mg, 0.38 mmol) in dry pyridine (6 mL) was treated with lead(IV) acetate (400 mg, 0.9 mmol) and heated under dry nitrogen at 80–100 °C for 20 min. The reaction mixture was then cooled to room temperature, partitioned between ice–water (50 mL) and ethyl acetate (25 mL) and acidified with 4 M hydrochloric acid and filtered. The organic layer was separated and washed with 2 M hydrochloric acid, the combined aqueous layers were extracted with ethyl acetate (2 × 25 mL), and the combined organic layers were dried over magnesium sulfate and concentrated under reduced pressure. The residue (71 mg) was examined by 300 MHz NMR spectroscopy, revealing traces of **6**. Comparison of the integrals of H-1α and H-1β of **6** to those of H_2 and H_3 of **7** suggested that the ratio of **6**:**7** was < 1:10 in the crude product. The crude product was purified by preparative-layer chromatography, eluting with 19:1 ethyl acetate–acetic acid to afford 4-acetamido-6,7,8-tri-*O*-acetyl-2,3,4-trideoxy-D-*glycero*-oct-2-enono-1,5-lactone **7** (32 mg, 23%) as an oil. The product was identical with that from Method A by ^{1}H NMR spectroscopy.

Acknowledgements

We thank Glaxo, Australia for financial support of this work.

References

[1] M.P. DeNinno, *Synthesis*, (1991) 583–593.
[2] A.P. Corfield and R. Schauer, in R. Schauer (Ed.), *Sialic Acids, Chemistry, Metabolism and Function*, Cell Biology Monographs, Vol. 10, Springer, Vienna, 1982, pp 5–39.
[3] A. Lubineau and J. Le Gallic, *J. Carbohydr. Chem.*, 10 (1991) 263–268.
[4] G. Estenne, A. Saroli, and A. Doutheau, *J. Carbohydr. Chem.*, 10 (1991) 181–195.
[5] J. Roth, C. Zuber, P. Wagner, I. Blaha, D. Bitter-Suermann, and P.U. Heitz, *Lab. Invest.*, 62 (1988) 55–60.
[6] W. Reutter, E. Köttgen, C. Bauer, and W. Gerok, in R. Schauer (Ed), *Sialic Acids: Chemistry, Metabolism and Function*, Cell Biology Monographs, Vol. 10, Springer, Vienna, 1982, pp 263–305.
[7] K. Wallimann and A. Vasella, *Helv. Chim. Acta*, 73 (1990) 1359–1372.
[8] A. Vasella and R. Wyler, *Helv. Chim. Acta*, 74 (1991) 451–463.
[9] T. Sugai, G.-J. Shen, Y. Ichikawa, and C.-H. Wong, *J. Am. Chem. Soc.*, 115 (1993) 413–421.
[10] D. Crich and T.J. Richie, *J. Chem. Soc., Chem. Commun.*, (1988) 1461–1463.

[11] D.D. Dhavale, E. Tagliavini, C. Trombini, and A. Umani-Ronchi, *Tetrahedron Lett.*, 29 (1988) 6163–6166.
[12] J.K. Kochi and J.D. Bacha, *J. Org. Chem.*, 33 (1968) 2746–2754.
[13] R.A. Sheldon and J.K. Kochi, *Org. React.*, 19 (1972) 279–422.
[14] J.D. Bacha and J.K. Kochi, *J. Org. Chem.*, 33 (1968) 83–93.
[15] D. Kahne, D. Yang, J.J. Lim, R. Miller, and E. Paguaga, *J. Am. Chem. Soc.*, 110 (1988) 8716–8717.
[16] P. Deslongchamps, *Stereoelectronic Effects in Organic Chemistry*, Pergamon Press, Oxford, 1983.
[17] A. Marra and P. Sinaÿ, *Carbohydr. Res.*, 190 (1989) 317–322.