ELSEVIER

Carbohydrate Research 281 (1996) 179–182

CARBOHYDRATE RESEARCH

Note

An improved synthesis of 1,6-anhydro-2,3-di-*O*-benzyl-β-D-*xylo*-hexopyranos-4-ulose

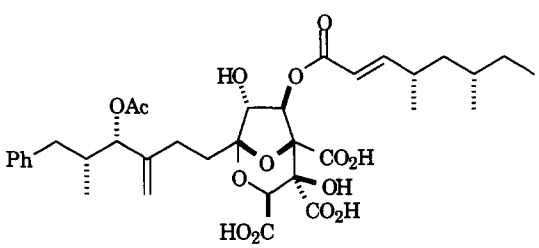
Stéphane Caron, Andrew I. McDonald, Clayton H. Heathcock *

Department of Chemistry, University of California, Berkeley, CA 94720, USA

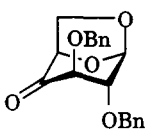
Received 31 August 1995; accepted 15 September 1995

Keywords: Zaragozic acid; Anhydrohexos-4-ulose

In our effort towards the preparation of squalene synthase inhibitor zaragozic acid A (squalestatin S1, **1**) [1–3], we have employed ketone **2**, a 1,6-anhydropyranose [4]. As our need for larger quantities of ketone **2** increased, we realized that we needed an improved synthesis of this compound. Although the overall yield from β-D-galactose pentaacetate (**4**) was acceptable (30%), the number of steps was large and the synthesis required the use of air-sensitive reagents such as sodium hydride, $LiAlH_4$ and $AlCl_3$ on rather large scale. We report herein an improved procedure for the preparation of ketone **2**.



1

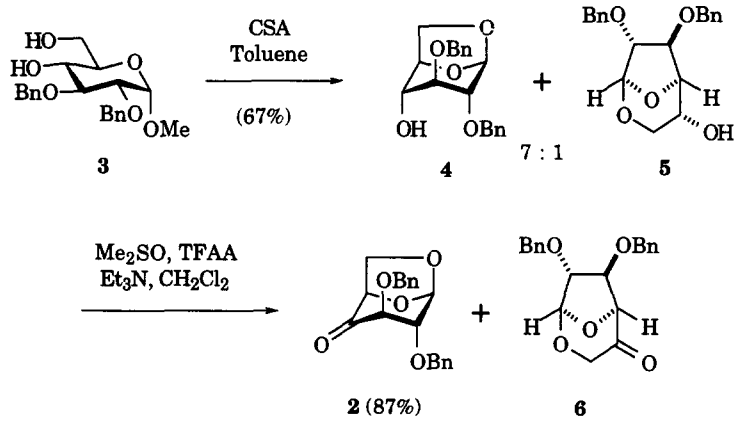


2

In his study of the dehydration of the hexoses, Angyal showed that the 1,6-anhydrofuranoses were formed as the major product [5]. Since the 1,6-anhydropyranose

* Corresponding author.

0008-6215/96/$15.00 © 1996 Elsevier Science Ltd. All rights reserved
SSDI 0008-6215(95)00335-5



3 4 5

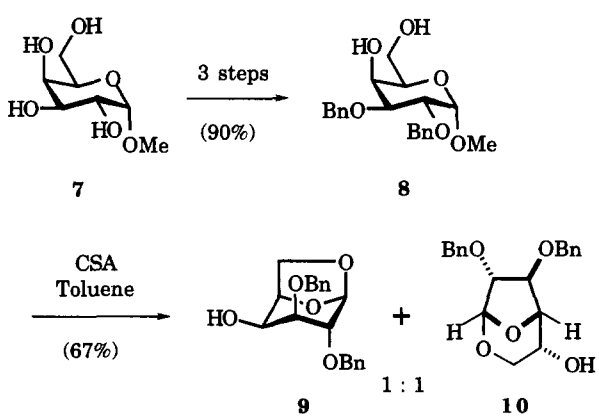
2 (87%) 6

Scheme 1.

skeleton is usually accessed by increasing the quality of the leaving group at the anomeric position [6], we hoped that a methoxyl group at C-1 would allow for the generation of the cyclic oxonium ion preferentially and provide the desired 1,6-anhydropyranose in only a few steps.

As shown in Scheme 1, our synthesis began with the well-known 4,6-diol **3** [7], available in three steps and 82% overall yield from methyl α-D-glucopyranoside. Although cyclization to the anhydro form did not proceed in benzene with *p*-TsOH or camphorsulfonic acid using a Dean–Stark apparatus, a 7:1 mixture of the 1,6-anhydropyranose **4** and 1,6-anhydrofuranose **5** could be obtained in toluene with camphorsulfonic acid. Because the mixture of 1,6-anhydro sugars could not be separated at this stage, it was oxidized to provide ketone **2** in 87% yield after recrystallization. On a smaller scale, a mixture of ketone **2** (78%) and **6** (6%) could be separated by chromatography on Silica Gel (Scheme 1).

As shown in Scheme 2, a similar reaction sequence was repeated starting from methyl α-D-galactopyranoside (**7**). The known diol **8** [8] could be prepared in 90% yield,



7 8

9 10

Scheme 2.

but we were disappointed to find that equal amounts of the two 1,6-anhydro sugars (**9** and **10**) were obtained upon dehydration.

In conclusion, a rapid, safe, and high yielding synthesis of 1,6-anhydro-2,3-di-*O*-benzyl-β-D-*xylo*-hexopyranos-4-ulose (**2**), a key intermediate in the total synthesis of zaragozic acid A (**1**), was developed from methyl α-D-glucopyranoside.

1. Experimental section

General.—Unless otherwise noted, starting materials were obtained from commercial suppliers and used without further purification. Benzene, toluene, CH_2Cl_2, and Et_3N were distilled from CaH_2. Organic extracts were dried with $MgSO_4$ and concentrated with a rotary evaporator under reduced pressure (aspirator). Silica gel chromatography was carried out with ICI SiliTech 32-63 D A Silica Gel according to Still's procedure [9]. Thin-layer chromatography (TLC) was performed with Merck F-254 TLC plates. Melting points are uncorrected and were measured in open capillary tubes. ^1H and ^{13}C NMR spectra were measured in $CDCl_3$. ^1H NMR are tabulated in the order: multiplicity (s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broad), number of protons, coupling constants (J) in Hertz (Hz). Chemical shifts are expressed in ppm of the δ scale relative to Me_4Si (0.00 ppm). IR spectra were measured as thin films on NaCl plates unless otherwise indicated. Optical rotations were measured at room temperature. Elemental analyses were performed by the Microanalytical Laboratory operated by the UCB College of Chemistry.

*1,6-Anhydro-2,3-di-*O*-benzyl-β-D-xylo-hexopyranos-4-ulose* (**2**) *and 1,6-anhydro-2,3-di-*O*-benzyl-β-D-xylo-hexofuranos-4-ulose* (**6**).—To a solution of camphorsulfonic acid (6.00 g, 25.8 mmol) in toluene (400 mL) heated in a Dean–Stark apparatus was added by small portions diol **3** (10.0 g, 26.7 mmol). After addition, the solution was heated for an additional hour, cooled to RT, and $NaHCO_3$ was slowly added until no evolution of CO_2 was noticed. The mixture was filtered through a plug of silica gel and washed thoroughly with ether (700 mL). The filtrate was concentrated to provide a 83% yield of a 7:1 mixture of 1,6-anhydropyranose **4** and 1,6-anhydrofuranose **5** respectively, as determined from analysis of the ^1H NMR spectrum.

To a solution of Me_2SO (6.00 mL, 84.6 mmol) in CH_2Cl_2 (100 mL) at −78 °C was added trifluoroacetic anhydride (6.00 mL, 42.3 mmol), and the solution was stirred for 20 min. A mixture of alcohols **4** and **5** (7.55 g, 22.5 mmol) in CH_2Cl_2 (20 mL, 2 × 5 mL rinse) was added at −78 °C, and the solution was stirred for 45 min, followed by addition of Et_3N (13.0 mL, 97.3 mmol). The mixture was allowed to warm to −10 °C over 90 min, poured into H_2O (100 mL), and extracted with CH_2Cl_2 (2 × 225 mL). The organic extracts were washed with H_2O (3 × 150 mL) and brine (100 mL), dried, filtered, and concentrated. The crude solid was recrystallized from EtOAc–hexane to provide ketone **2**, mp 69–70 °C (6.56 g, 87%). The spectral properties of this compound were identical to those of a sample prepared by another route and previously reported [4].

The oxidation of **4** and **5** was also performed on 652 mg and the crude product

purified by chromatography on silica gel to afford ketone **6** (38 mg, 6%) and ketone **2**, mp 90–91 °C (0.506 g, 78%).

*1,6-Anhydro-2,3-di-*O*-benzyl-β-*D*-xylo-hexofuranos-4-ulose* (**13**).—TLC: R_f 0.43 (EtOAc–hexanes 30:70). $[\alpha]_D$: +13.4 (*c* 0.19, $CHCl_3$). IR (KBr): 2889, 1740, 1497, 1454, 1398, 1116, 1023, 922, 738, 694 cm^{-1}. ^1H NMR (500 MHz): δ 4.13 (d, 1 H, *J* 1.7 Hz), 4.27 (d, 1 H, *J* 17.7 Hz), 4.31–4.34 (m, 1 H), 4.34 (dd, 1 H, *J* 17.7 Hz, 0.6), 4.41 (d, 1 H, *J* 11.6 Hz), 4.52 (d, 1 H, *J* 11.8 Hz), 4.56 (d, 1 H, *J* 11.4 Hz), 4.57 (d, 1 H, *J* 11.8 Hz), 4.79 (d, 1 H, *J* 7.3 Hz), 5.46 (s, 1 H), 7.26–7.38 (m, 10 H); ^{13}C NMR (100 MHz): δ 69.09, 72.11, 72.90, 83.42, 84.12, 86.53, 100.99, 127.92, 127.98, 128.15, 128.19, 128.53, 128.57, 136.55, 136.94, 201.71. Anal. Calcd for $C_{20}H_{20}O_5$: C, 70.58; H, 5.92. Found: C, 70.30; H, 5.82.

References

[1] J.D. Bergstrom, M.M. Kurtz, D.J. Rew, A.M. Amend, J.D. Karkas, R.G. Bostedor, V.S. Bansal, C. Dufresne, F.L. VanMiddlesworth, O.D. Hensens, J.M. Liesch, D.L. Zink, R.G. Jenkins, L. Huang, M.S. Meinz, L. Quinn, R.W. Burg, Y.L. Kong, S. Mochales, M. Mojena, I. Martin, F. Pelaez, M.T. Diez, and A.W. Alberts, *Proc. Natl. Acad. Sci. USA*, 90 (1993) 80–84.

[2] M.J. Dawson, J.E. Farthing, P.S. Marshall, R.F. Middleton, M.J. O'Neill, A. Shuttleworth, C. Stylli, R.M. Tait, P.M. Taylor, H.G. Wilman, A.D. Buss, D. Langley, and M. Hayew, *J. Antibiot.*, 45 (1992) 639–647.

[3] P.J. Sidebottom, R.M. Highcock, S.J. Lane, P.A. Procopiou, and N.S. Watson, *J. Antibiot.*, 45 (1992) 648–658.

[4] S. Caron, A.I. McDonald, and C.H. Heathcock, *J. Org. Chem.*, 60 (1995) 2780–2785.

[5] S.J. Angyal and R.J. Beveridge, *Aust. J. Chem.*, 31 (1978) 1151–1155.

[6] M. Kloosterman, M.J. Dees, G.A. van der Marel, and J.H. van Boom, *Recl. Trav. Chim. Pays-Bas*, 104 (1985) 116–119.

[7] D.J. Bell and J. Lorber, *J. Chem. Soc.*, (1940) 453–455.

[8] J. Kiss and F. Burkhardt, *Helv. Chim. Acta*, 53 (1970) 1000–1011.

[9] W.C. Still, M. Kahn, and A. Mitra, *J. Org. Chem.*, 43 (1978) 2923–2925.