A Polyhydroxylated Cyclopentene: A Useful Synthon toward the Synthesis of Carbocyclic D-Fructofuranoid

Mohindra Seepersaud, Richard Bucala, Yousef Al-Abed*

The Picower Institute for Medical Research, 350 Community Drive, Manhasset, N.Y. 11030

Z. Naturforsch. 54b, 565–568 (1999); received March 3, 1999

D-Arabinofuranosyl- and D-Fructofuranosyl, Polyhydroxylated Cyclopentene, Grubb’s and Schrock’s Catalyst

A polyhydroxylated cyclopentene has been synthesized in five steps with an overall yield of 61%, starting from 2,3,5-tri-O-benzyl-D-arabinofuranose.

Introduction

Fructose 2,6-bisphosphate (1) is formed by phosphorylation of fructose-6-phosphate, a key substrate in the glycolysis pathway, in a reaction catalyzed by phosphofructokinase-2 (PFK-2) [1]. Fructose-2,6-bisphosphate is a powerful allosteric regulator of glycolysis via its potent stimulatory effect on phosphofructokinase-1 activity and its inhibitory effect on fructose-1,6-bisphosphatase. The recent identification of an inducible isoform of PFK-2 that is specifically induced by inflammation stimuli or oncogenic transformation has suggested that fructose analogs might serve as useful pharmacophores for inhibiting cell activation and cancer cell growth [2, 3]. Unlike phosphorylated fructose, carbocyclic D-fructofuranoside (2) (Fig. 1) cannot be metabolized and therefore can be shuttled repeatedly through cycles of kinase and phosphatase activity.

Wilcox and Guadino [4] have shown the first and only synthetic approach to carbocyclic D-fructofuranoside (3) (Scheme 1). The overall synthesis involved 12 steps. Cyclopentane ring closure was accomplished utilizing a free-radical mediated cyclization. The present report examines the cyclopentane annulation via an olefin metathesis.

Results and Discussion

Ring closing metathesis (RCM) is a powerful tool for the synthesis of medium (5–8) to large (10–13 and higher) carbocyclic or heterocycles [5]. Recently, there have been two reports concerning RCM on functionalized substrates. The first is the synthesis of the six-membered polysubstituted cyclohexene valiolamine employing the Schrock’s catalyst [6] and the second is the synthesis of the seven-membered heterocyclic oxepine skeleton [7] utilizing Grubb’s catalyst. Herein we describe the synthesis of a polyhydroxylated cyclopentene, carbafructofuranose precursor (4a) (Scheme 1) using the RCM methodology. In this synthetic approach, 4 can arise via an RCM of a diene precursor 5 which could be readily assembled from a carbohydrate derivative.

Treatment of the commercially available 2,3,5-tri-O-benzyl-D-arabinofuranose [8] (6) under Wittig and Swern conditions furnished 8 in 78% yield. Addition of vinylmagnesiumbromide afforded the single diene alcohol precursor 9. The origin of the stereochemistry at this centre cannot be readily predicted and is probably a result of the stereo-directing effect of the chiral α-benzyloxy group. The alcohol was subsequently protected as the benzyl ether and then subjected to RCM conditions. Treatment of 5a with 20 mol% of the Schrock’s catalyst [9] in anhydrous CH2Cl2 furnished the cyclopentene (4a) exclusively in 87% yield. Of note, treatment of 5a with the ruthenium alkylidene metal complex [9] gave the desired...
The stereochemistry of the cyclic product was established using NOE analysis. NOE analysis previously has been used in the structural assignment of similar five and six-membered cyclic compounds [6, 10]. The 1H NMR signals of 4a were first identified by COSY. The NOE analysis allowed for structural assignment (Fig. 2). An NOE of 1.5% between H3 and one of the benzyl protons H1 and also a 1.0% NOE between H2 and the other benzyl proton H3 was observed. These data provide strong support for a syn relationship between C-2/C-3 benzyl oxy groups and assigns the framework of 4a with the correct stereochemistry at C-2, 3 and C-4 of 1, since the stereochemistry at C-3 and C-4 was conserved from 6.

The diene 5b (Scheme 2) is readily prepared from the commercially available 1,2:3,5-di-O-isopropylidene-α-D-apiose [11] or 2,3,5-tri-O-benzyl-D-arabinofuranose and studies presently are underway for the synthesis and metathesis of these intermediates. Further elaboration of 4a to carbafucoturanose and other polyhydroxylated derivatives, and the investigation of the derivatives as inhibitors of PFK2 are also being actively pursued.

In summary, we have demonstrated a concise and efficient synthesis of the carbafucoturanose precursor 4a, utilizing a potentially general pathway in 5 steps with an overall yield of 61%.

**Experimental**

**General part**
TLC was carried out on aluminum sheets precoated with silica gel 60 (HF-254, E. Merck) to a thickness of 0.25 mm. Flash column chromatography (FCC) was performed using Kieselgel 60 (230–400 mesh, E. Merck) and usually employed a stepwise solvent polarity gradient, correlated with TLC mobility. 1H and 13C NMR spectra were obtained on JEOL 270 instrument. Unless otherwise noted, spectra were recorded at 270 and 67.5 MHz respectively. Mass spectral analysis were performed by Hunter college and University of Illinois mass spectrometral facilities. Dry THF was obtained by distillation, under nitrogen from potassium-benzophenon ketyl. Dichloromethane was distilled from P2O5. Other solvents were purified and dried by using standard procedures.

**Compound 7:** nBuLi (11.0 mmol, 1.6 M in hexane) is added to a suspension of methyl triphenylphosphonium bromide (4.28 g, 12.0 mmol) in dry
THF (25 ml) at 0 °C under N₂. The suspension was allowed to stir for 30 min at 0 °C then warmed up to rt (1 h). 2,3,5-tri-O-benzyl-D-arabinofuranose (6) (2.0 g, 5 mmol) was dissolved in THF (5 ml) and transferred by cannula dropwise over 10 min. The reaction mixture was allowed to warm to rt, followed by addition of Et₂O (100 ml). The suspension was filtered through celite and the excess solvent evaporated. FCC (10-30% EtOAc:PE) furnished a clear oil 7 (1.8 g, 87%). Rf 0.6 (20% EtOAc:PE); 1H NMR (270 MHz, CDCl₃) δ 7.34 (m, 15H), 5.95 (m, 1H), 5.34 (m, 2H), 4.62 (ABq, δ = 0.09 ppm, 2H, J = 11.9 Hz), 4.52 (m, 2H), 4.50 (ABq, δ = 0.23 ppm, 2H, J = 11.2 Hz), 4.1 (m, 1H), 4.04 (m, 1H), 3.64 (m, 3H). 13C NMR (67.5 MHz, CDCl₃) δ 138.3, 138.2, 138.0, 135.2, 128.5-127.8 (8 signals), 119.2, 80.6, 74.2, 73.5, 71.0, 70.8, 70.5. - MS (ES) m/z 467 [M+N⁺], 181 (base peak).

**Compound 8:** To a solution of oxalyl chloride (549 mg, 4.3 mmol) in anhydrous CH₂Cl₂ (5 ml) at -78 °C under N₂ was added DMSO (375 mg, 4.8 mmol) and the mixture allowed to stir for 20 min. The alcohol 7 (200 mg, 0.48 mmol, dissolved in CH₂Cl₂ (4 ml)) then was added and the reaction allowed to stir for 25 min. Et₃N (847 mg, 0.036 mmol) followed by BnBr (156 mg, 0.9 mmol) then was added and the reaction mixture allowed to stir for 30 min. The reaction was quenched by dropwise addition of MeOH (2 ml), then water (15 ml) and the aqueous mixture was extracted with Et₂O (3×15 ml). The combined Et₂O extract was washed with saturated aqueous NaHCO₃ (30 ml) and then was added and the reaction mixture allowed to stir for 25 min. Et₃N (847 mg, 0.088 mmol) was added. Bu₄NI (13 mg, 0.036 mmol) followed by BnBr (156 mg, 0.9 mmol) then was added and the reaction mixture allowed to stir for 30 min. The reaction was quenched by dropwise addition of MeOH (2 ml), then water (15 ml) and the aqueous mixture was extracted with Et₂O (3×15 ml). The combined Et₂O extract was washed with saturated aqueous NaHCO₃ (10 ml), brine (10 ml) and excess solvent evaporated to give tetrabenzylated product 5a (94 mg, 98%). Rf 0.7 (10% EtOAc:PE); 1H NMR (270 MHz, CDCl₃) δ 7.33 (m, 20H), 6.08 (dd, 1H, J = 10.6, 18.0 Hz), 6.01 (m, 1H), 5.34 (d, 1H, J = 1.7 Hz), 5.28 (m, 1H), 5.22 (m, 1H), 4.74 (ABq, δ = 0.08 ppm, 2H, J = 11.1 Hz), 4.53 (ABq, δ = 0.11 ppm, 2H, J = 11.6 Hz), 4.4 (ABq, δ = 0.36 ppm, 2H, J = 11.9 Hz), 4.34 (m, 2H), 4.11 (dd, 1H, J = 3.0, 7.7 Hz), 3.82 (d, 1H, J = 10.9 Hz), 3.76 (d, 1H, J = 3.2 Hz), 3.52 (d, 1H, J = 10.9 Hz). 13C NMR (67.5 MHz, CDCl₃) δ 139.8, 138.9, 138.2, 138.1, 137.3, 137.2, 128.5-127.0 (9 signals), 117.7, 116.1, 86.7, 82.8, 79.8, 76.3, 73.3, 70.2, 70.1, 65.1. - MS (ES) m/z 557 [(M+N⁺), (base peak)], 535 (M+H⁺).

**Compound 4a:** The diene 5a (70 mg, 0.131 mmol) dissolved in anhydrous CH₂Cl₂ (1.0 ml) was added to a homogeneous orange-red solution of Schrock’s catalyst 2,6-Diisopropylphenylimido neophylenemolybdenum (IV) bis(hexafluoro-r-butoxide) (20 mg, 0.026 mmol) in anhydrous CH₂Cl₂ (4 ml) under N₂. The reaction mixture was stirred at 20 °C for 18 h, at which time TLC showed formation of new material. The reaction mixture was quenched by exposure to air for 2 h then excess solvent evaporated in vacuo. The black residue was purified by FCC (5-10% EtOAc:PE) to give the diene 4a (57.6 mg, 87%). Rf 0.5 (10% EtOAc : PE); 1H NMR (270 MHz, CDCl₃) δ 7.25 (m, 20H), 6.05 (d, 1H, J = 6.0 Hz, H-5), 5.77 (d, 1H, J = 6.0 Hz, H-6), 4.78 (m, 1H), 4.70 (m, 1H, H-4), 4.56-4.46 (m, 6H), 4.34 (m, 1H), 4.05 (d, 1H, J = 4.0 Hz, H-3), 3.57 (ABq, δ = 8.4 Hz), 3.18 (d, 1H, J = 11.9 Hz), 3.07 (m, 1H), 2.87 (m, 1H), 2.67 (m, 1H), 2.57 (m, 1H), 2.06 (s, 3H), 1.95 (s, 3H), 1.4 (s, 21H). - MS (ES) m/z 947 [(M+N⁺), (base peak)], 925 (M+H⁺).
$0.07 \text{ ppm}, 2H, J = 9.5 \text{ Hz}, H-1)$. $^{13}$C NMR (67.5 MHz, CDC$_3$) $\delta$ 139.5, 138.7, 138.4, 138.3, 135.5, 134.0, 128.5–126.2 (8 signals), 89.1, 87.5, 84.7, 75.0, 73.6, 72.8, 71.6, 67.2. HRMS (FABMS) calculated for C$_{34}$H$_{34}$O$_4$ (M$+H^+$) 507.253535, found 507.253500.

**Acknowledgements**

The authors wish to thank Mrs. Shu Ya Chen for her advice on the Grubb’s catalyst, Dr. Clifford Soll for the mass spectral analysis, Dr. Kirk Manogue for his help in preparation of this manuscript and Dr. Angeles Dios for her assistance.

[1] a) C. A. Hasemann, E. S. Istvan, K. Uyeda, J. Deisenhofer, Structure 4, 1017 (1996);
   c) G. G. Rousseau, L. Hue, Prog. Nucl. Acid Res. Mol. Biol. 45, 99 (1993);
   b) M. Nishimura, S. Federov, K. Uyeda, J. Biol. Chem. 269, 26100 (1994).
cala, R. Proc. Natl. Acad. Sci. USA 6, 3047 (1999);
   b) J. M. Argiles, B. Azcon-Biet, J. Mol and Cell. Bioch. 81, 3 (1988);
   b) A. Furstner, K. Langemann, Synthesis 1997, 792.
   b) M. Nishimura, S. Federov, K. Uyeda, J. Biol. Chem. 269, 26100 (1994).
[9] This compound is available from Strem Chemicals.