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

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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) can not 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.

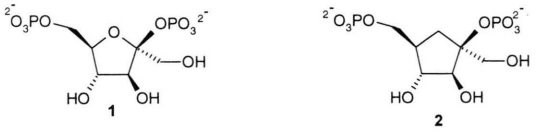

Fig. 1. Structure of fructose-2,6-bisphosphate (**1**) and carbocyclic D-fructofuranoside (**2**).

Results and Discussion

Ring closing metathesis (RCM) is a powerful tool for the synthesis of medium (5–8) to large (10–13 and higher) carbo or heterocycles [5]. Recently, there have been two reports concerning RCM on functionalized substrates. The first is the synthesis of the six-membered poylsubstituted 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 desribe 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 stereodirecting effect of the chiral α-benzyloxy group. The alcohol was subsequentially 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 CH_2Cl_2 furnished the cyclopentene (**4a**) exclusively in 87% yield. Of note, treatment of **5a** with the ruthenium alkylidene metal complex [9] gave the desired

* Reprint requests to Dr. Yousef Al-Abed.

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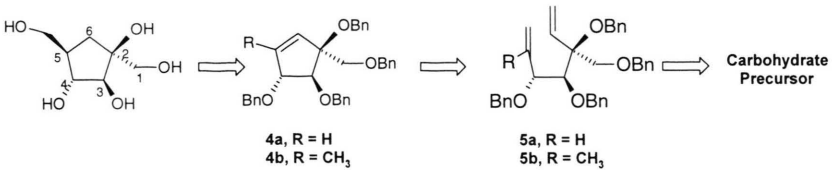


Scheme 1.

compound in 35% and the starting material **5a** in 49% yield (Scheme 2).

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 ^{1}H NMR signals of **4a** were first identified by COSY. The NOE analysis allowed for structural assignment (Fig. 2). An NOE of 1.5% between H_3 and one of the benzylic protons H_1 and also a 1.0% NOE between H_6 and the other benzylic proton H_1 was observed. These data provide strong support for a *syn* relationship between C-2/C-3 benzyloxy 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 carbafructofuranose 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 carbafructofuranose precursor **4a**, utilizing a potentially general pathway in 5 steps with an overall yield of 61%.

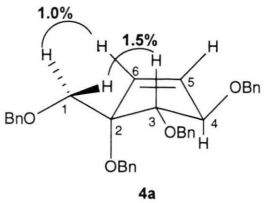


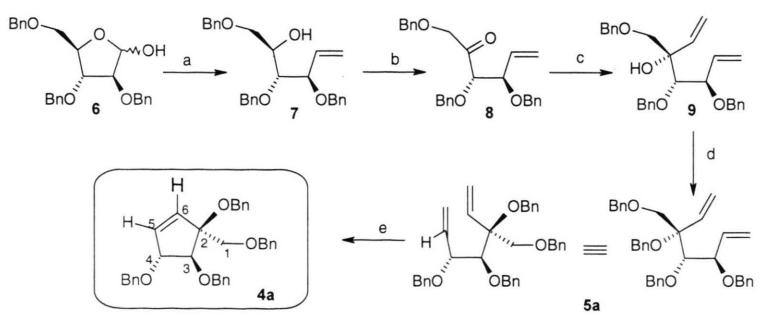
Fig. 2. The NOE analysis of **4a**.

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. ^{1}H and ^{13}C 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 P_2O_5. Other solvents were purified and dried by using standard procedures.

Compound **7**: *n*BuLi (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



Scheme 2. (a) BuLi (2.1 eq.), $CH_3PPh_3^+$ (2.3 eq.), THF, 0 °C to rt, 87%; (b) DMSO (5 eq.), Et_3N (10 eq.), $(COCl)_2$ (4.8 eq.), CH_2Cl_2, −78 °C to rt, 90%; (c) CH_2=CH_2MgBr (1 M in THF, 3 eq.), THF, −78 °C to 0 °C, 92%; (d) BNBR (3 eq.), NaH (2.9 eq.), Bu_4Nl (0.1 eq.), DMF 98%; (e) i. Schrock's catalyst (20 mmol-%), CH_2Cl_2, rt, 18 h, 87% (**4a**), ii. Grubb's catalyst (10 mol-%), CH_2Cl_2, rt, 3 d, 35% (**4a**), 49% (**5a**).

THF (25 ml) at 0 °C under N_2. 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 Et_2O (100 ml). The suspension was filtered through celite and the excess solvent evaporated. FCC (10–30% EtOAc:PE) furnished a clear oil **7** (1.81 g, 87%). Rf 0.6 (20% EtOAc:PE); ^{1}H NMR (270 MHz, $CDCl_3$) δ 7.34 (m, 15H), 5.95 (m, 1H), 5.34 (m, 2H), 4.62 (ABq, $\Delta\delta$ = 0.09 ppm, 2H, J = 11.9 Hz), 4.52 (m, 2H), 4.50 (ABq, $\Delta\delta$ = 0.23 ppm, 2H, J = 11.2 Hz), 4.1 (m, 1H), 4.04 (m, 1H), 3.64 (m, 3H). ^{13}C NMR (67.5 MHz, $CDCl_3$) 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.

Compound **8**: To a solution of oxalyl chloride (549 mg, 4.3 mmol) in anhydrous CH_2Cl_2 (5 ml) at −78 °C under N_2 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 CH_2Cl_2 (4 ml)] then was added and the reaction allowed to stir for 25 min. Et_3N (847 mg, 8.6 mmol) then was added and the solution warmed to 0 °C. Et_2O (50 ml) was added and the combined organic washed with saturated aqueous $NaHCO_3$ (30 ml), brine (30 ml) and dried ($MgSO_4$). The Et_2O extract was concentrated *in vacuo* and purified by FCC (10–40% EtOAc:PE), to give the ketone **8** (179 mg, 90%). Rf 0.75 (25% EtOAc:PE); ^{1}H NMR (270 MHz, $CDCl_3$) δ 7.30 (m, 15H), 5.91 (m, 1H), 5.33 (m, 1H), 4.48–4.60 (m, 4H), 4.35 (m, 2H), 4.28 (m, 2H), 4.19 (m, 1H), 4.00 (d, 1H, J = 3.5 Hz). ^{13}C NMR (67.5 MHz, $CDCl_3$) δ 207.7, 137.6, 137.5, 136.9, 134.2, 128.6–127.8 (6 signals), 119.9, 85.9, 81.0, 74.7, 74.4, 73.4, 71.0. – MS (ES) m/z 439 ($M+Na^+$), 434.2 ($M+NH4^+$), 181 (base peak).

Compound **9**: The azeotropically dried ketone **8** (190 mg, 0.5 mmol) intermediate was dissolved in THF (5 ml), and cooled to −78 °C. A 1M solution of vinylmagnesiumbromide (1.40 mmol, 1.4 ml) then was added dropwise and the solution was allowed to warm up to 0 °C. The reaction was quenched by addition to cold saturated NH_4Cl (15 ml). The mixture was extracted with Et_2O (3×20 ml), washed with saturated aqueous $NaHCO_3$ (30 ml), brine (30 ml) and dried ($MgSO_4$). The Et_2O extract was concentrated *in vacuo* and purified by FCC (20–60% EtOAc:PE), to give the alcohol **9** (204 mg, 92%) Rf 0.4 (10% EtOAc:PE); ^{1}H NMR (270 MHz, $CDCl_3$) δ 7.32 (m, 15H), 6.17 (dd, 1H, J = 1.7, 17.3 Hz), 5.99 (m, 1H), 5.45 (dd, 1H, J = 1.7, 17.3 Hz), 5.3 (m, 2H), 5.17 (dd, 1H, J = 1.7, 10.6 Hz), 4.67 (ABq, $\Delta\delta$ = 0.07 ppm, 2H, J = 11.1 Hz), 4.42 (ABq, $\Delta\delta$ = 0.34 ppm, 2H, J = 11.4 Hz), 4.45 (m, 2H), 4.18 (dd, 1H, J = 2.2, 8.2 Hz), 3.72 (d, 1H, J = 2.2 Hz), 3.79 (d, 1H, J = 8.4 Hz), 3.25 (d, 1H, J = 8.4 Hz). ^{13}C NMR (67.5 MHz, $CDCl_3$) δ 140.3, 138.2, 138.1, 137.3, 136.1, 128.7–127.7 (7 signals), 118.9, 114.5, 82.0, 81.6, 78.3, 76.0, 74.4, 73.5, 70.6. – MS (ES) m/z 467 ($M+Na^+$), 181 (base peak).

Compound **5a**: Alcohol **9** (80 mg, 0.18 mmol) was disolved in DMF (3 ml, anhydrous) and the solution was cooled to 0 °C and NaH (35 mg, 0.88 mmol) was added. Bu_4NI (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 Et_2O (3×15 ml). The combined Et_2O extract was washed with saturated aqueous $NaHCO_3$ (10 ml), brine (10 ml) and excess solvent evaporated to give tetrabenzylated product **5a** (94 mg, 98%). Rf 0.7 (10% EtOAc:PE); ^{1}H NMR (270 MHz, $CDCl_3$) 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, 2H), 5.22 (m, 1H), 4.74 (ABq, $\Delta\delta$ = 0.08 ppm, 2H, J = 11.1 Hz), 4.53 (ABq, $\Delta\delta$ = 0.11 ppm, 2H, J = 11.6 Hz), 4.4 (ABq, $\Delta\delta$ = 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). ^{13}C NMR (67.5 MHz, $CDCl_3$) 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 [($M+Na^+$), (base peak)], 535 ($M+H^+$).

Compound **4a**: The diene **5a** (70 mg, 0.131 mmol) dissolved in anhydrous CH_2Cl_2 (1.0 ml) was added to a homogeneous orange-red solution of Schrock's catalyst 2,6-Diisopropylphenylimido neophylidenemolybdenum (IV) bis-(hexafluoro-*t*-butoxide) (20 mg, 0.026 mmol) in anhydrous CH_2Cl_2 (4 ml) under N_2. The resulting 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); ^{1}H NMR (270 MHz, $CDCl_3$) 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, $\Delta\delta$ =

0.07 ppm, 2H, J = 9.5 Hz, H-1).^{13}C NMR (67.5 MHz, $CDCl_3$) δ 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.

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[1] a) C. A. Hasemann, E. S. Istvan, K. Uyeda, J. Deisenhofer, Structure **4,** 1017 (1996);
b) S. J. Pilkis, T. H . Claus, I. J. Kurland, A. J. Lange, Ann. Rev. Biochem. **64,** 799 (1995);
c) G. G. Rousseau, L. Hue, Prog. Nucl. Acid Res. Mol. Biol. **45,** 99 (1993);
d) K. Uyeda, In Study of Enzymes II. (Kuby S. A., ed.) 445 (1991).

[2] a) D. M. Nathan, Ann. Int. Med. **124,** 86 (1996);
b) M. Nishimura, S. Federov, K. Uyeda, J. Biol. Chem. **269,** 26100 (1994).

[3] a) J. Chesney, R. Mitchell, F. Benigni, M. Bacher, L. Spiegel, Y. Al-Abed, J. Hee Han, C. Metz, R. Bucala, R. Proc. Natl. Acad. Sci. USA **6,** 3047 (1999);
b) J. M. Argiles, B. Azcon-Biet, J. Mol and Cell. Biochem. **81,** 3 (1988);
c) L. Hue, G. G. Rousseau, Adv. Enzyme Regul. **33,** 97 (1993).

[4] C. S. Wilcox, J. J. Guadino, J. Am. Chem. Soc. **108,** 3102 (1986).

[5] a) R. H. Grubbs, S. J. Miller, Acc. Chem. Res. **28,** 446 (1995);
b) A. Furstner, K. Langemann, Synthesis **1997,** 792;
c) K. C. Nicaloau, Y. He, D. Vouloumis, H. Vallberg, F. Roschangar, F. Sarabia, S. Ninkovic, Z. Yang, J. I. Trujillo, J. Am. Chem. Soc. **119,** 10073 (1997);
d) M. T. Crimmins, A. L. Choy, J. Org. Chem. **62,** 7548 (1997);
e) H. G. Schmalz, Angew. Chem., Int. Ed. Engl. **34,** 1833 (1995);
f) M. Arisawa, E. Takezawa, A. Nishida, M. Miwako, M. Nakagawa, Synlett. 1179 (1997).

[6] O. Sellier, P. Van de Weighe, L. D. Nouen, C. Strehler, J. Eustache, Tetrahedron Lett. **40,** 853 (1999).

[7] H. Ovaa, M. A. Leeeuwenburgh, H. S. Overkleeft, G. A. van der Marel, J. H. van Boom, Tetrahedron Lett. **39,** 3025 (1998).

[8] F. Freeman, R. D. Robarge, Carbohydr. Res. **154,** 270 (1986).

[9] This compound is available from Strem Chemicals.

[10] M. Seepersaud, D. R. Mootoo, M. Blumenstein, Tetrahedron **53,** 5711 (1997).

[11] R. J. Nachman, M. Honel, T. M. Williams, R. C. Halaska, H. S. Mosher, J. Org. Chem. **51,** 4802 (1986). This compound is available from Pfanstiehl Laboraties, Inc., cat. no. D-115.