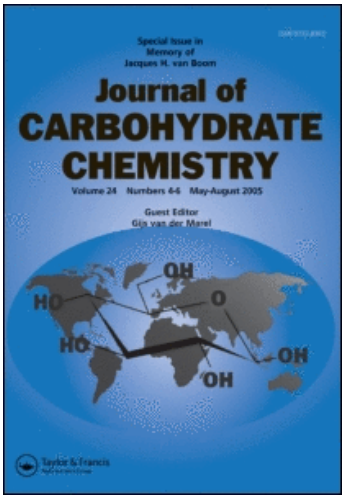

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Total Synthesis of Sphydrofuran

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TOTAL SYNTHESIS OF SPHYDROFURAN[1]

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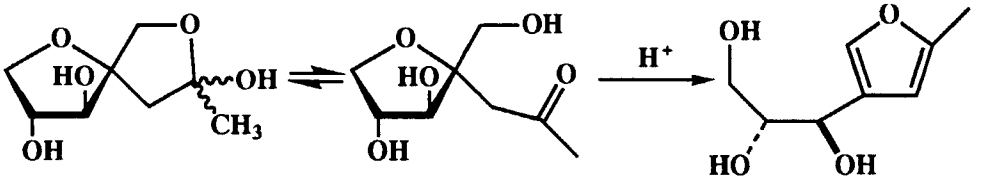
ABSTRACT

Sphydrofuran (**1**) has been synthesized via a short chemoenzymatic approach starting from achiral precursors. Rabbit muscle aldolase (RAMA)-promoted aldol condensation between dihydroxyacetone phosphate (DHAP) and chloroacetaldehyde yielded the **D**-*threo*-pentulose derivative **3**. After suitable protection of the hydroxyl functions of **3**, sphydrofuran could be obtained via a highly diastereoselective Grignard addition of allylmagnesium bromide followed by a Wacker reaction.

INTRODUCTION

Chemical screening methods using *Ehrlich's reagent* led to the detection and isolation[2] of sphydrofuran (**1**)(Fig 1). This metabolite is a component in culture filtrates of a variety of streptomycetes strains. During the isolation procedure the amount of **1** decreased due to conversion to the furan derivative **2** under the mild acidic conditions used.[3] This furan derivative exhibited some growth promotion for different bacteria and viruses. Recently the relative and absolute configuration of sphydrofuran have been assigned.[3] We focused our efforts on developing an efficient synthesis of



1 2

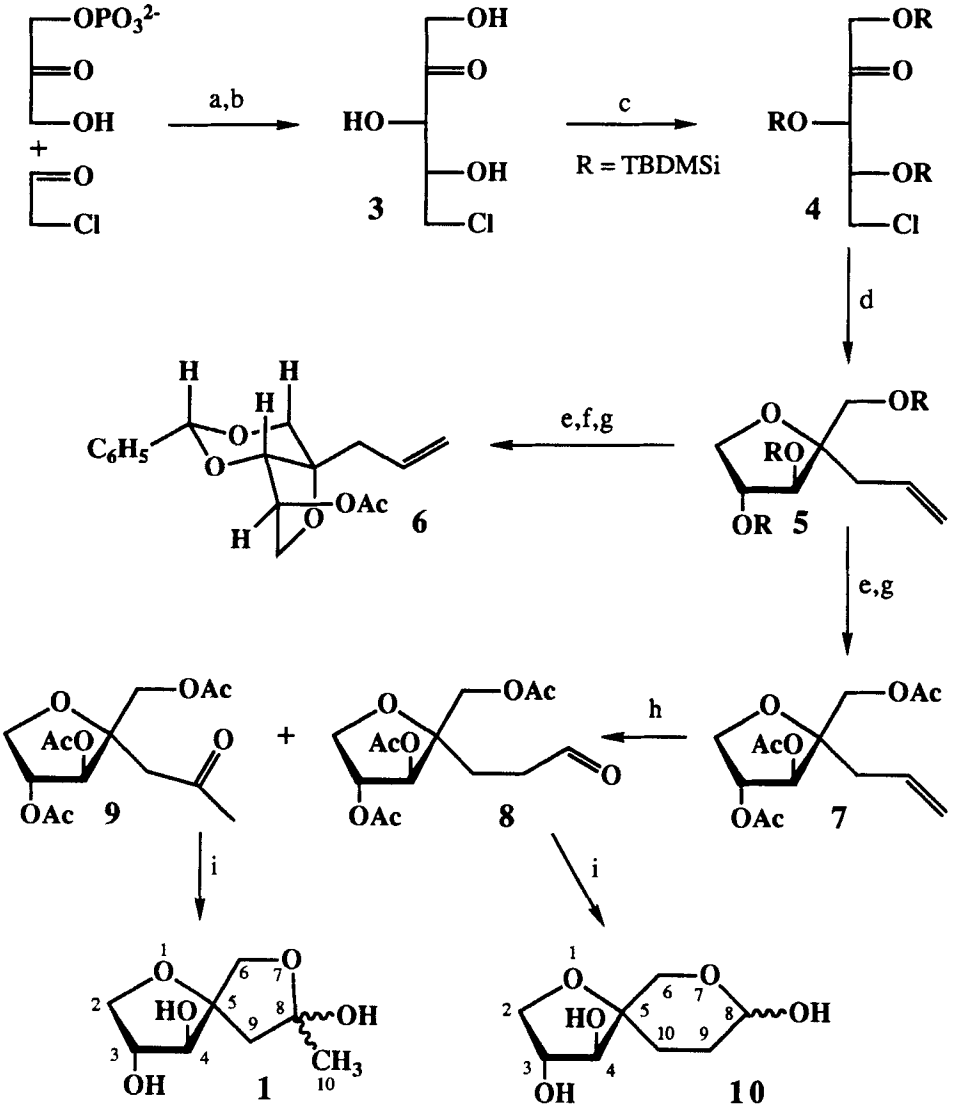
Figure 1

sphydrofuran since to our knowledge no synthetic approach leading to this metabolite has been reported until recently.[4]

RESULTS AND DISCUSSION

We started our reaction sequence with the rabbit muscle aldolase (RAMA; E.C.4.1.2.13)-catalyzed aldol condensation between chloroacetaldehyde and dihydroxyacetone phosphate (DHAP; Scheme 1). RAMA-catalyzed aldol condensation between DHAP and a variety of aldehydes is well established[5] and generates a vicinal diol having the **D**-*threo* (3*S*,4*R*) configuration.[6] Dihydroxyacetone phosphate necessary for our condensation was generated *in situ* from fructose-1,6-bisphosphate (FDP) by using RAMA and triosephosphate isomerase (TIM; E.C.5.3.1.1), following protocols reported.[5,6] The phosphate group present in the intermediary addition product was cleaved by acid phosphatase (APase; E.C.3.1.3.2). 5-Deoxy-5-chloro-**D**-*threo*-pentulose (**3**) obtained by this procedure already contained two of the three chiral centers of the target molecule sphydrofuran.

Treatment of **3** with 3.3 equivalents of *t*-butyldimethylsilyl triflate in dry dichloromethane at -40 °C in the presence of 6.6 equivalents of triethylamine gave the silylated derivative **4**. Addition of allylmagnesium bromide to **4** in dry ether at -70 °C yielded exclusively the **D**-*threo*-pentulose-*C*-allyl-glycoside derivative **5**. For a first assignment of the



Scheme 1: (a) RAMA; FDP; TIM (b) APase (c) TBDMSiOTf/Et_3N (d) AllylMgBr/THF (e) TBAF (f) $C_6H_5CH(OCH_3)_2$/TsOH (g) Ac_2O/pyr/DMAP (h) $PdCl_2/H_2O$/THF (i) $NaOCH_3$

stereochemistry of the quarternary center generated by the Grignard reaction, **5** was transformed into the bicyclic derivative **6** in three steps.[7,8] NOE studies performed on derivative **6** indicated a *syn* relationship between the hydrogen at C-3 of the furanose derivative and the allyl moiety at

the "anomeric" center. The conformation shown in Scheme 1 is also in agreement with the coupling constant between H-3 and H-4 of ~ 0 Hz.

Attempts to introduce the carbonyl functionality present in sphydrofuran via a Wacker reaction[9] by treatment of derivative **5** with $PdCl_2$ in H_2O/THF failed and led only to decomposition products. Thus we were forced to change the protective groups. Cleavage of the silyl ethers present in **5** with tetrabutylammonium fluoride (TBAF) followed by acetylation of the hydroxyl groups under standard conditions afforded **7** in nearly quantitative yield. The addition of 1.1 equivalents of $PdCl_2$ into a solution of **7** in H_2O/THF (10/1) led to a 2.7 : 1 mixture of the desired sphydrofuran precursor **9** and the corresponding aldehyde analogue **8** in high yields. After saponification with sodium methoxide in dry methanol sphydrofuran (**1**) and its aldehyde analogue **10** were obtained in quantitative yield and were easily separated by column chromatography.

The chemo-enzymatic approach reported demonstrates a short and efficient route for the synthesis of sphydrofuran. Furthermore, problems reported from acidic work-up procedures during the isolation of this metabolite out of natural sources can be avoided. Since the sequence also allows the use of labelled starting materials and reagents, specifically labelled sphydrofuran could be synthesized which may be of interest for biosynthetic studies.

EXPERIMENTAL

General Procedures. Chemicals were purchased from Aldrich and were reagent grade. Solvents were dried and distilled before use. Enzymes were purchased from Sigma. Analytical thin layer chromatography was performed on Merck plates (silica gel F_{254}, 0.25 mm thick). Compounds that were not visualized by UV were detected by spraying with a solution of 3 % $Ce(SO_4)_2$ in 1 N H_2SO_4 followed by heating. Flash chromatography was performed using Merck silica gel 60 (0.04

- 0.063 mm). ^{1}H and ^{13}C NMR were recorded with a BRUKER AM 400 spectrometer. Specific rotations were determined with a Perkin Elmer 241 polarimeter.

5-Deoxy-5-chloro-D-*threo*-pentulose (3). A solution of 2.269 g of fructose-1,6-bisphosphate (FDP Ca-salt; 6 mmol) in 300 mL of distilled water was stirred with Amberlyst 15 H^+ for 2 h. The resin was filtered off and the pH of the solution was adjusted to 7.0 by the addition of 1 N NaOH. After the addition of 1.6 mL of chloroacetaldehyde (45 % w/w in water; 11.5 mmol), 200 U of RAMA and 500 U of triose phosphate isomerase were added. The reaction mixture was slowly stirred for 48 h. The pH was adjusted to 5.0 and 200 U of acid phosphatase were added. Stirring was continued for 24 h followed by readjustment of the pH to 7.0 and evaporation of the solvent in vacuum, keeping the temperature below 40 °C. The residue was suspended in 10 mL of methanol and purified by chromatography over 100 g of silica gel (CH_2Cl_2/CH_3OH = 4/1). Yield: 1.126 g (58%) colorless oil. ^{1}H NMR (D_2O; HDO set to 4.8) δ 3.61(dd,1H,H_{5a}), 3.69(dd,1H,H_{5b}), 4.22(dd,1H, J=6.2 Hz,J=7.1 Hz,H_4), 4.51(d,1H,J=19.5 Hz,H_{1a}), 4.53(bs,1H, H_3), 4.61(d,1H,H_{1b}); ^{13}C NMR(D_2O; external standard 1,4-dioxane δ=67.6) δ 213.62; 76.34; 72.84; 67.09; 45.21.

5-Deoxy-5-chloro-1,3,4-tri-*O*-*t*-butyldimethylsilyl-D-*threo*-pentulose (4). After cooling a solution of 588 mg of **3** (3.5 mmol) in 60 mL of CH_2Cl_2 to -40 °C, 3.3 mL of triethylamine (24 mmol) were added. The reaction mixture was stirred for 10 min followed by treatment with 2.76 mL of *t*-butyldimethylsilyl trifluoromethanesulfonate (TBDMSiOTf; 12 mmol). The reaction mixture was allowed to warm to room temperature within 4 h and stirring was continued for 16 h followed by treatment with 50 mL of saturated $NaHCO_3$ solution. The organic layer was separated and the water layer was extracted five times with 40 mL portions of ether. The combined organic phases were dried over $MgSO_4$, filtered and the solvent removed in vacuum. Chromatography over 50 g silica gel (hexanes/ethyl acetate = 9/1) yielded 1.161 g of **4** (65%). ^{1}H NMR ($CDCl_3$) δ 0.01; 0.05; 0.06; 0.07(4s,18H,CH_3); 0.84;

0.87; 0.92(3s,27H,*t*-butyl); 3.28(dd,1H,J=10.8 Hz,H_{5a}); 3.58 (dd,1H,H_{5b}); 4.09(ddd,1H,J=8.0 Hz,J=5.3 Hz,H_4); 4.42(d,1H, J=2.4 Hz,H_3); 4.49(ABm,2H,$H_{1a,b}$); ^{13}C NMR($CDCl_3$) δ 209.09; 76.55; 75.01; 69.07; 43.25; 25.83; 25.71; 25.68; 18.43; 18.16; 17.95; -4.63; -4.71; -4.90; -5.02;-5.26; -5.50; Mass spectrum (FAB; M^++Na; $C_{23}H_{51}ClO_4Si_3$) Calcd m/e 533.2681. Found 533.2668;

Anal. Calcd: C, 54.08; H, 10.08. Found: C, 53.85; H, 10.10.

2-*C*-Allyl-1,3,4-tri-*O*-*t*-butyldimethylsilyl-D-*threo*-pentulofuranose (5). A solution of 220 mg (0.43 mmol) of **4** in 10 mL of dry tetrahydrofuran was cooled under argon to -70 °C and treated with 0.6 mmol (600 μL of a freshly prepared 1 M solution in ether) of allylmagnesium bromide. The temperature was kept at -70 °C for 2 h and allowed to warm to 10 °C over an additional 2 h followed by treatment with 20 mL of a saturated solution of NH_4Cl in water. The organic phase was separated and the water phase extracted four times with 40 mL portions of ether. The combined organic phases were dried over $MgSO_4$, filtered and the solvent evaporated. The residue was purified by chromatography over 20 g of silica gel (CH_2Cl_2/hexanes = 2/3) yielding 210 mg of **5** (90%). ^1H NMR ($CDCl_3$) δ 0.00; 0.02; 0.03; 0.04; 0.07(5s, 18H,CH_3); 0.86; 0.87; 0.89(3s,27H,*t*-butyl); 2.33(dd, 1H,-CH_2-allyl); 2.42(dd,1H,J=5.7 Hz,J=11.1 Hz,-CH_2-allyl); 3.45(d,1H, J=8.5 Hz,H_{1a}); 3.56(dd,1H,J=7.1 Hz,H_{5a}); 3.63(d,1H,H_{1b}); 3.96 (d,1H,H_3); 4.01(dd,1H,H_{5b}); 4.22 (ddd,1H,J=2.9 Hz,J=3.2 Hz, J=4.3 Hz,H_4); 5.04-5.09(m,2H,=CH_2); 5.82(m,1H,-CH=); ^{13}C NMR($CDCl_3$) δ 134.56; 117.77; 85.82; 81.40; 78.97; 72.62; 64.61; 38.27; 25.89; 25.79; 25.76; 18.29; 17.91; 17.82;-4.53; -4.79; -5.48; Mass spectrum (FAB; M^++Na; $C_{26}H_{56}O_4Si_3$) Calcd m/e 539.3384. Found 539.3403;

Anal. Calcd: C, 60.46; H, 10.85. Found: C, 60.10; H, 11.09.

2-*C*-Allyl-4-*O*-acetyl-1,3-benzyliden-D-*threo*-pentulofuranose (6). To a solution of 145 mg (0.28 mmol) of **5** in 10 mL of dry THF, 0.9 mmol TBAF was added while keep-

ing the solution at 0 °C. After 4 h the solvent was evaporated and the crude product was passed over a column filled with 7 g of silica gel (methanol/CH_2Cl_2 = 1/8). The product (45 mg) was redissolved in 2.5 mL of dimethylformamide and 200 µL of benzaldehyde dimethylacetal and 5 mg of *p*-toluenesulfonic acid were added. The reaction mixture was heated to 60 °C for 90 min, followed by removing the solvent in vacuum. The crude product was dissolved in 2 mL of dry pyridine and 1.5 mL of acetic anhydride as well as 4 mg of 4-*N*,*N*-Dimethylaminopyridine (DMAP) were added. After stirring for 18 h the solvents were removed and the residue chromatographed over 4 g of silica gel (ethyl acetate/hexanes = 1/9). The yield was 6 mg (8%) of **6** which was only used for further NMR studies. ^1H NMR ($CDCl_3$) δ 2.09(s,3H,OAc); 2.27(dd,1H,-CH_2-allyl); 2.47 (dd,1H,J=6.2 Hz,J=14.3 Hz,-CH_2-allyl); 3.89(dd,1H,J=10.7 Hz, H_{5a}); 3.93(d, 1H,J=12.8 Hz,H_{1a}); 4.14(d,1H,H_{1b}); 4.25(s,1H, H_3); 4.52(dd,1H, H_{5b}); 5.10-5.15(m,2H,=CH_2); 5.24(dd,1H,J=5.6 Hz,J=1.8 Hz,H_4); 5.40(s,1H,$C_6H_5C\underline{H}$); 5.82(m,1H,-CH=); 7.32; 7.45(2m,5H,C_6H_5); ^{13}C NMR($CDCl_3$) δ 169.72; 137.55; 132.23; 129.05; 128.25; 128.12; 119.07; 99.01; 81.69; 79.24; 78.69; 72.05; 69.96; 38.49; 20.96.

2-*C*-Allyl-1,3,4-tri-*O*-acetyl-D-*threo*-pentulofuranose (7). A solution of 110 mg (0.2 mmol) of **5** in 4 mL of dry tetrahydrofuran was treated with 3.5 eq of tetrabutylammonium fluoride and stirring was continued for 18 h. The solvent was evaporated and the residue filtered through a short column filled with 3 g of silica gel. The crude product obtained was redissolved in 2 mL of dry pyridine and 1 mL of acetic anhydride as well as 5 mg of DMAP were added. After 12 h the solvent was removed by coevaporation with toluene and the residue purified by chromatography over 10 g of silica gel (hexanes/acetone = 1/1). Yield: 58 mg (95%). ^1H NMR ($CDCl_3$) δ 2.07; 2.10(2s,9H,3xOAc); 2.47(m,2H,-CH_2-allyl); 3.79(dd,1H,J=3.5 Hz,J=10.3 Hz,H_{5a}); 3.99(d,1H,J=11.8 Hz,H_{1a}); 4.23(d,1H,H_{1b}); 4.30(dd,1H,J=6.2 Hz,H_{5b}); 5.10-5.25(m,3H,H_4, =CH_2); 5.35(d,1H,J=3.4 Hz,H_3); 5.80(m,1H,-CH=); ^{13}C NMR ($CDCl_3$) δ 170.38; 170.19; 169.53; 137.70; 119.70; 83.69; 79.27; 78.38; 70.30; 63.96; 39.06; 20.88; 20.82; 20.71.

Anal. Calcd for $C_{14}H_{20}O_7$: C, 55.99; H, 6.71. Found: C, 56.12; H, 6.83.

2-*C*-(2'-oxo-prop-1'-yl)-1,3,4-tri-*O*-acetyl-D-*threo*-pentulofuranose (8) and 2-*C*-(3'-oxo-prop-1'-yl)-1,3,4-tri-*O*-acetyl-D-*threo*-pentulofuranose (9). To a solution of 50 mg (0.16 mmol) of **7** in a mixture of 5 mL of THF and 0.5 mL of water, 43 mg (0.24 mmol) of $PdCl_2$ were added at room temperature. After 3 h TLC (hexanes/acetone = 1/1) showed completion of the reaction. The reaction mixture was filtered through a bed of celite, the solvent was evaporated and the residue purified by chromatography over 5 g of silica gel. Yield (**8**+**9**): 47 mg (92%; ratio **8** : **9** = 2.7 : 1). ^1H NMR for **8** ($CDCl_3$) δ 2.01; 2.03(2s,9H,3xOAc); 2.13 (s,3H,CH_3); 2.75(d,1H,J=16,2 Hz,$H_{1'a}$); 2.94(d,1H,$H_{1'b}$); 3.76 (dd, 1H,J=3.4 Hz,J=10.3 Hz, H_{5a}); 4.02(d,1H,J=11.8 Hz,H_{1a}); 4.18(dd,1H,H_{5b}); 4.29(d,1H,H_{1b}); 5.12(m,1H,H_4); 5.44(d,1H, J=3.5 Hz,H_3); ^{13}C NMR for **8** ($CDCl_3$) δ 205.33; 170.19; 170.01; 169.56; 82.37; 79.52; 78.04; 70.15; 63.77; 47.24; 31.52; 20.83; 20.82; 20.66;

Anal. Calcd for $C_{14}H_{20}O_8$: C, 53.16; H, 6.37. Found: C, 52.98; H, 6.14.

^1H NMR for **9** ($CDCl_3$) δ 2.01; 2.03(2s,9H,3xOAc); 2.51(m, 2H, $H_{2'a,b}$); 3.67(dd,1H,H5a); 3.90(d,1H,J=11.3 Hz,H1a); 4.18 (m, 2H,H1b,H5b); 5.12(m,1H,H4); 5.20(d,1H,J=3.0 Hz,H3); 9.71 (t, 1H,J=1.5 Hz,H3'); ^{13}C NMR for **9** ($CDCl_3$) δ 200.91; 170.20; 170.10; 169.46; 83.40; 79.40; 78.31; 70.36; 63.20; 37.79; 20.83; 20.64; 20.54;

Anal. Calcd for $C_{14}H_{20}O_8$: C, 53.16; H, 6.37. Found: C, 52.84; H, 6.01.

(3*R*,4*S*,5*S*)-1,7-Dioxaspiro[4,5]decane-3,4,8-triol (10). Compound **10** was obtained in quantitative yield by treating **8** (50 mg) with 20 mg $NaOCH_3$ in 5 mL of dry methanol for 2 h, followed by evaporation of the solvent and chromatograpy over 3 g of silica gel (methanol/CH_2Cl_2 = 1/4). ^1H NMR (D_2O; HDO set to 4.8; complex mixture of the α and β anomers) δ 1.80-2.20(complex m,4H,$H_{9a,b}$,$H_{10a,b}$); 3.50-4.30 (complex m,$H_{2a,b,3,4,6a,b}$,α+β); 4.89(dd,1H,J=10.4 Hz,J=2.5

Hz,$H_{8\beta}$); 5.18(t,1H,J=3.4 Hz,$H_{8\alpha}$); ^{13}C NMR(D_2O; external standard 1,4-dioxane δ=67.6; complex mixture of the α and β anomers) δ 98.92; 96.01; 85.89; 85.85; 85.34; 84.69; 81.79; 81.60; 75.13; 74.92; 70.69; 66.66; 34.65; 32.83; 31.69; 31.49; $[\alpha]_D$ = -18.5° (c = 0.2; H_2O).

(3*R*,4*S*,5*S*)-8-Methyl-1,7-dioxaspiro[4,4]nonane-3,4,8-triol (1). Compound **1** was obtained in quantitative yield by deacetylation of **9**. ^1H NMR (D_2O; HDO set to 4.8; complex mixture of the α and β anomers as well as the open chain compound) δ 1.64; 1.69(2s,2xCH_3,α+β anomer); 2.34 (ABq, $H_{9a,b}$,α+β anomer); 2.37(s,3H,CH_3-open chain); 3.12(ABq, 2H, J=16.7 Hz,$H_{9a,b}$-open chain); 3.65-4.40(complex m,6H, $H_{2a,b,3,4,6a,b}$); ^{13}C NMR(D_2O; external standard 1,4-dioxane δ=67.6; complex mixture of the α and β anomers as well as the open chain compound; C-8 of the open chain compound not detected) δ 110.64; 110.47; 97.28; 96.15; 85.34; 84.76; 84.62; 81.09; 81.02; 80.75; 76.35; 76.25; 76.10; 75.84; 74.76; 66.56; 53.05; 51.24; 51.19; 35.51; 30.93; 29.99; ^{252}Cf-plasma desorption flight time MS: M^++Na = 213.4; $[\alpha]_D$ = +14.9° (*c* = 0.2; H_2O); ref.3: $[\alpha]_D$ = +16.0° (*c* = 0.5; H_2O).

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