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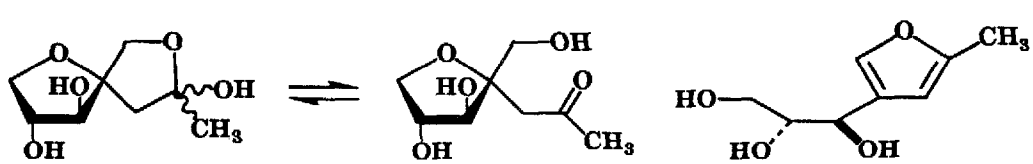
CHEMO-ENZYMATIC SYNTHESIS OF NATURAL PRODUCTS: SYNTHESIS OF SPHYDROFURAN

Balu P. Maliakel and Walther Schmid*

Institut für Organische Chemie der Universität Wien, Währingerstraße 38, A-1090 Vienna, AUSTRIA

Abstract: A novel synthesis for sphydrofuran **1** has been developed. Starting with achiral materials the chiral centers of the target molecule were introduced via enzymatic methods as well as via a diastereoselective Grignard reaction. Rabbit muscle aldolase (RAMA)- catalyzed aldol condensation of chloroacetaldehyde **3** with dihydroxyacetone phosphate (DHAP) **4** affords the C-5 skeleton of **5** which was transformed to sphydrofuran **1** and its analogue **10** via a Grignard addition of allylmagnesium bromide followed by a Wacker reaction.

The application of enzymes for the synthesis of polyol systems represents still a challenging field.[1] The synthetic use of aldolases, especially rabbit muscle aldolase (RAMA; E.C.4.1.2.13) is well established.[2] This enzyme catalyzes the aldol condensation between dihydroxyacetone phosphate (DHAP) and a broad variety of aldehydes as an electrophilic component. The vicinal diol generated has the D-*threo* (3S,4R) configuration. Numerous syntheses utilizing this enzyme specificity are reported.[1-4] To further demonstrate the broad applicability of RAMA we report the synthesis of sphydrofuran **1** (Fig.1).



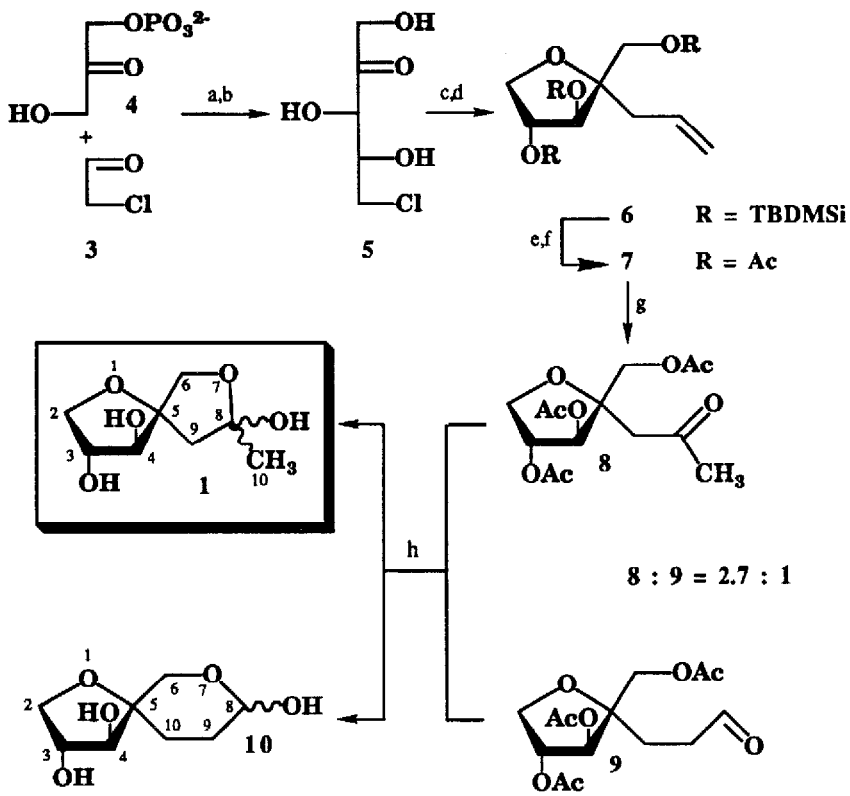
1 **2**

Fig.1

Sphydrofuran is a structurally unique secondary metabolite produced by Actinomycetes.[5] It can be isolated from culture filtrates of various strains of Streptomycetes.[5,6] Under the mild acidic conditions used

during work-up, the amount of **1** decreases by dehydration to the benefit of the furan derivative **2**.[5] The furan derivative **2** exhibits growth promotion for some bacteria and viruses[5] which stimulated biosynthetic studies on this type of compound. The relative[7] and absolute[5] configuration of sphydrofuran was assigned recently. We focused our efforts on an efficient synthesis of sphydrofuran, starting from achiral precursors and introducing the chiral centers of the target molecule via enzymatic as well as chemical reaction steps.

We started our reaction sequence (Scheme 1) with the RAMA catalyzed aldol condensation of chloroacetaldehyde **3** with DHAP **4**, which was generated *in situ* from fructose-1,6-bisphosphate with RAMA and triosephosphate isomerase (TIM; E.C.5.3.1.1).[1-4] The phosphate group present in the addition product



Scheme 1: (a) RAMA, TIM, FDP (b) APase (c) TBDMSiOTf, CH_2Cl_2, Et_3N, -40°C (d) AllylMgBr, THF, -70°C (e) TBAF, THF (f) Ac_2O, pyr, DMAP (g) $PdCl_2$, THF, H_2O (h) NaOMe, MeOH

was cleaved using acid phosphatase (APase; E.C.3.1.3.2) to obtain **5** in 58% yield. After suitable protection of the hydroxyl functions with t-butyldimethylsilyl triflate, allylmagnesium bromide in dry THF was added to generate the cyclic derivative **6** in 60% yield, following a procedure reported.[4] All the stereocenters in **6** have

been assigned unambiguously.[4] However, attempts to introduce the carbonyl functionality present in sphydrofuran **1** via a Wacker reaction[8] starting from **6** by treatment with $PdCl_2$ in THF/H_2O failed and led only to decomposition products, which forced us to change the protecting groups. Thus, the silyl ethers were cleaved with 3.3 equiv. tetrabutylammonium fluoride (TBAF) in THF followed by acetylation of the hydroxyl functions under standard conditions to afford the peracetylated derivative **7** in quantitative yield. The addition of 1.1 equiv. $PdCl_2$ into a solution of **7** in THF/H_2O (10/1) led to a 2.7 : 1 mixture of the desired sphydrofuran precursor **8** and the corresponding aldehyde derivative **9** in 90% yield.[9] Both derivatives were deprotected using sodium methoxide in dry methanol to yield sphydrofuran **1**[10] and its analogue **10**,[11] which could be separated easily on a silica gel column using dichloromethane/methanol (8:1) as eluent. The analytical and spectroscopical data of **1** are in full agreement with those obtained for the product isolated from natural sources.[5,7]

Since the final deprotection step in our reaction sequence was performed under mild basic conditions, we were able to circumwent problems described for an acidic work-up procedure.[5] The synthetic route presented in Scheme 1 demonstrates a short and efficient approach to sphydrofuran and is to our knowledge the first total synthesis of this metabolite. Since this sequence also allows labelling of this metabolite on certain positions by using labelled reagents within the route, it is of interest for biosynthetic studies. Further investigations are under way.

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9. Characteristics for **8**:
^{1}H-NMR (400 MHz; $CDCl_3$): δ = 5.44 (d, 1H, J = 3.5 Hz, H-C(4)); 5.12 (m, 1H, H-C(3)); 4.29 (d, 1H, J = 11.8 Hz, H_a-C(6)); 4.18 (dd, 1H, J = 10.3 Hz, H_a-C(2)); 4.02 (d, 1H, H_b-C(6)); 3.76 (dd, 1H, J = 3.4 Hz, H_b-C(2)); 2.94 (d, 1H, J 0 16.2 Hz, H_a-C-(9)); 2.75 (d, 1H, H_b-C(9)); 2.13 (s, 3H, H-C(10)); 2.03; 2.01 (2s, 9H, 3xAc). ^{13}C-NMR (100 MHz; $CDCl_3$): 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.
Characteristics for **9**:
^{1}H-NMR (400 MHz; $CDCl_3$): δ = 9.71 (t, 1H, J = 1.5 Hz, H-C(8)); 5.20 (d, 1H, J = 3.0 Hz, H-C(4)); 5.12 (m, 1H, H-C(3)); 4.18 (m, 2H, H_a-C(2); H_a-C(6)); 3.90 (d, 1H, J = 11.3 Hz, H_b-C(6)); 3.67 (dd, 1H, H_b-C(3)); 2.51 (m, 2H, $H_{a,b}$-C(9)); 2.03; 2.01 (2s, 9H, 3xAc); 2.01 (m, 2H, $H_{a,b}$-C(10). ^{13}C-NMR (100 MHz; $CDCl_3$): 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.
10. Characteristics for **1**:
$[\alpha]_D$ = +14.9° (c = 0.2; H_2O); ref.5: $[\alpha]_D$ = +16.0° (c = 0.5; H_2O); ^{252}Cf - plasmadesorption flight time MS: M^++Na = 213.4; ^{1}H-NMR (400 MHz; D_2O; complex mixture of the α and β anomers as well as the open chain compound): δ = 4.40 - 3.65 (m, 6H, $H_{2a,b,3,4,6a,b}$); 3.12 (AB-quartett, J = 16.7 Hz; $H_{a,b}$-C(9) open chain); 2.37 (s, 3H, H-C(10) open chain); 2.34 (AB-quartett, $H_{a,b}$-C(9)-α+β anomers); 1.69; 1.64 (2s, H-C(10) α+β anomers). ^{13}C-NMR (100 MHz; D_2O; 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.
11. Characteristics for **10**:
$[\alpha]_D$ = -18.5° (c = 0.2; H_2O); ^{1}H-NMR (400 MHz; D_2O; complex mixture of the α and β anomers): δ = 5.18 (t, J = 3.4 Hz, H_α-C(8)); 4.89 (dd, J 0 18.4 Hz, J = 2.5 Hz, $H\beta$-C(8)); 4.40 - 3.50 (complex m, H-C($2_{a,b}$,3,4,$6_{a,b}$),α+β); 2.20 - 1.80 (complex m, H-C($9_{a,b}$,$10_{a,b}$)). ^{13}C-NMR (100 MHz; D_2O; 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.

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