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A Short Route to Chiral Synthons: Preparation of Ketoeicosanoids with Hydropyrane Fragments

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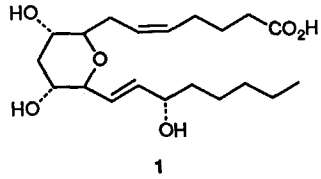
To prepare ketoeicosanoids with hydropyrane fragments, new synthons were obtained from the $BF_3 \cdot OEt_2$ catalysed reaction of tri-*O*-acetyl-D-glucal with methyl 5-trimethylsilyloxyhex-5-enoate, methyl 10-trimethylsilyloxyundec-10-enoate and the bis(trimethylsilyl)ether of *o*-hydroxyacetophenone.

The hydropyrane fragment is part of the molecular structure of many natural compounds. Examples include such bioactive species as the antibiotics pseudomonic acid,[1] lasalocid[2] and monensin,[3] the fungicide ambruticin[4] and the toxin okadaic acid.[5] The tetrahydroyrane metabolite of arachidonic acid **1**[6] is very attractive in this respect.

Proceeding from the interest displayed in 6-ketoprostanoids,[7,8] we started to develop a common approach to chiral ketoacids with dihydropyrane fragments that would further serve as a basis for the synthetic preparation of structural analogues of 6-ketoeicosanoids **2**.

Lewis acid catalysed reactions of glycals with enolsilyl ethers



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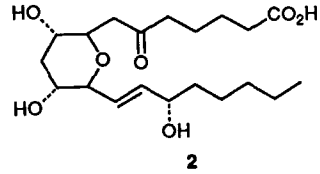

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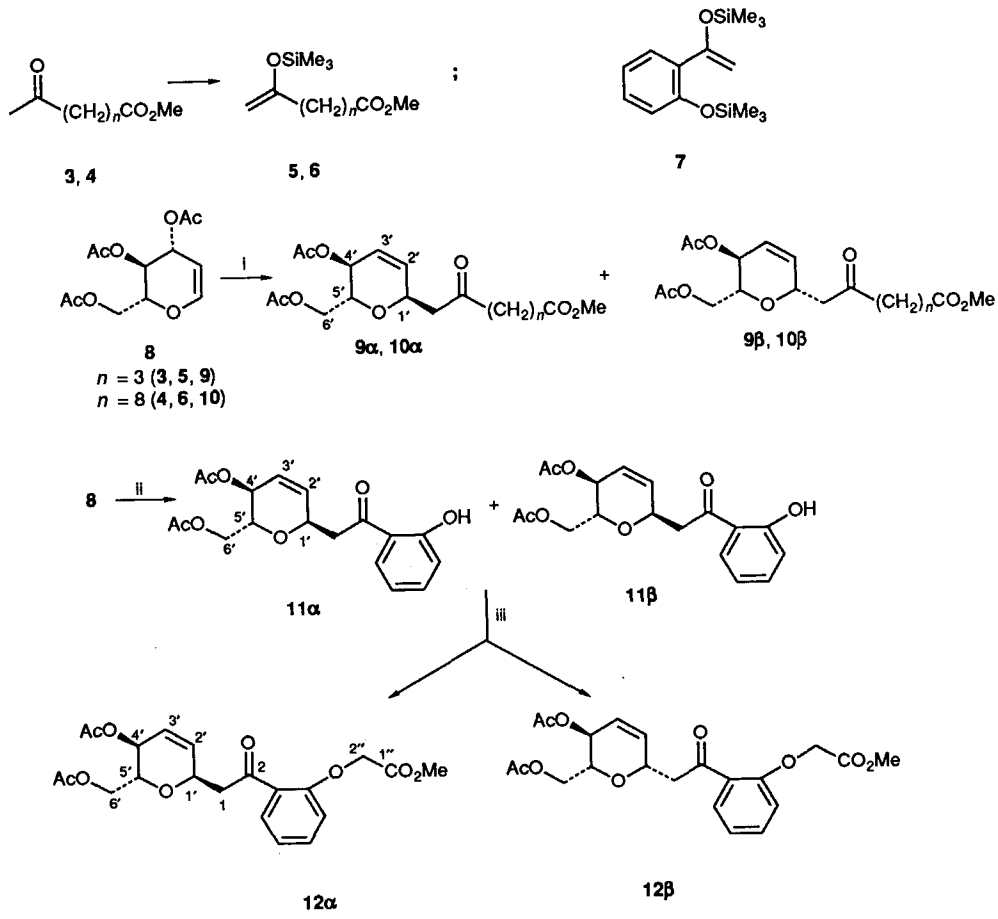
were the best choice for our key transformation. The stereochemical aspects of the reaction have been reported in detail and are illustrated by experiments with 1-trimethylsilyloxystyrene.[9] Available tri-*O*-acetyl-D-glucal **8**, methyl



Scheme 1 *Reagents and conditions:* i, **5** or **6**, $BF_3 \cdot OEt_2$, MeCN, −30°C, 0.5 h; ii, **7**, $BF_3 \cdot OEt_2$, CH_2Cl_2, −45°C, 0.5 h; iii, $BrCH_2CO_2Me$, K_2CO_3, MeC(O)Et, 60°C, 4 h

5-trimethylsilyloxyhex-5-enoate **5**, methyl 10-trimethylsilyloxyundec-10-enoate **6** and the bis(trimethylsilyl)ether of *o*-hydroxyacetophenone **7**[10] were used as starting compounds in our experimental work. The silyl ethers **5** and **6** were prepared according to the reported technique[11] from the esters of ketoacids **3** and **4**. The latter were obtained *via* oxidation of the related esters of ω-unsaturated acids with O_2 in the presence of catalyst $PdCl_2$–CuCl.[12,13]

The reaction of tri-*O*-acetyl-D-glucal **8** with the enolsilyl ether **5**, catalysed by $BF_3 \cdot OEt_2$ in a solution of CH_3CN was found to give a 65% yield of a mixture of C-1′ anomeric ketoesters (**9α**:**9β** = 4:1).† The coupling of **8** with the silyl ether **6** under otherwise equal conditions led to a mixture of ketoesters **10α** and **10β** (3:1). The mixtures of the α- and β-anomeric products (**9** and **10**) were separated by HPLC. According to our expectations, the reaction of **8** with the bis(silyl)ether **7** in the presence of $BF_3 \cdot OEt_2$ in a solution of CH_2Cl_2 was a stereoselective process that resulted in a 90% yield of a mixture of anomers **11α** and **11β** (4:1). The mixture could be easily separated by chromatography on silica gel. Related esters of ketoacids **12α** and **12β**‡ yielded 91% after alkylation of the isomers **11α** and **11β** with the methyl ester of bromoacetic acid in a solution of methyl ethyl ketone in the presence of K_2CO_3.

The stereochemistry of the individual anomers **9–12** was assigned to the α- and β-series, arising from a comparison of the coupling constant data for detectable protons at C-4′ and C-5′ with those reported in the literature[10]: $J_{4',5'} < 6.5$ Hz for the α-anomers and $J_{4',5'} > 8$ Hz for the β-anomers.

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† *Spectral data for* **9α**: $[\alpha]_D^{24}$ +61° (*c* 0.71, $CHCl_3$). ^1H NMR ($CDCl_3$) δ 1.89 (m, 2H, 3-H), 2.06, 2.09 (2s, 6H, 2Ac), 2.33 (t, 2H, 2-H, *J* 7.2 Hz), 2.54 (t, 2H, 4-H *J* 7.0 Hz), 2.56 (dd, 1H, 6-H_a, $J_{6,1}$, 6.4, J_{gem} 14.5 Hz), 2.83 (dd, 1H, 6-H_b, J_{gem} 15.8, $J_{6b,1'}$ 8.2 Hz), 3.67 (s, 3H, OMe), 3.92 (ddd, 1H, 5′-H, $J_{5',6'a}$ 3.57, $J_{5',6'b}$ 6.40, $J_{5',4'}$ 6.50 Hz), 4.11 (dd, 1H, 6′-H_a, $J_{6'a,5'}$ 3.52, J_{gem} 11.79 Hz), 4.20 (dd, 1H, 6′-H_b, $J_{6'b,5'}$ 6.73, J_{gem} 11.91 Hz), 4.71 (m, 1H, 1′-H), 5.12 (m, 1H, 4′-H), 5.84 (ddd, 1H, 3′-H, $J_{3',4'}$ 2.6, $J_{3',1'}$ 2.2, $J_{3',2'}$ 10.4 Hz) and 5.93 (ddd, 1H, 2′-H, $J_{2',1'}$ 2.5, $J_{2',4'}$ 1.4, $J_{2',3'}$ 10.4 Hz). For **9β**: $[\alpha]_D^{24}$ +77° (*c* 0.85, $CHCl_3$). ^1H NMR ($CDCl_3$) δ 2.27 (t, 2H, 2-H, *J* 7.12 Hz), 2.43 (dd, 1H, 6-H_a, $J_{1',6a}$, 6.0, J_{gem} 16.0 Hz), 2.47 (t, 2H, 4-H, *J* 7.0 Hz), 2.68 (dd, 1H, 6-H_b, $J_{1',6b}$ 7.4, J_{gem} 16.0 Hz), 3.70 (ddd, 1H, 5′-H, $J_{5',6'b}$ 3.1 $J_{5',6'a}$ 5.21, $J_{5',4'}$ 9.8 Hz), 4.05 (dd, 1H, 6′-H_a, $J_{6'a,5'}$ 5.20 Hz), 4.1 (dd, 1H, 6′-H_b, $J_{6'b,5'}$ 3.1, J_{gem} 12.0 Hz) and 5.21 (ddd, 1H, 4′-H, $J_{4',5'}$ 8.8, $J_{4',3'}$ 1.9, $J_{4',2'}$ 1.7 Hz).

‡ *Spectral data for* **12α**: $[\alpha]_D^{24}$ +36.9° (*c* 1.94, $CHCl_3$). ^1H NMR ($CDCl_3$) δ 2.03, 2.06 (2s, 6H, 2Ac); 3.46 (m, 1H, 1-H_a), 3.78 (m, 1H, 1-H_b), 3.84 (s, 3H, OMe), 3.95 (ddd, 1H, 5′-H, $J_{5',6'a}$ 3.0, $J_{5',6'b} = J_{5',4'}$ 6.43 Hz), 4.10 (dd, 1H, 6′-H_a, $J_{6'a,5'}$ 3.5, J_{gem} 11.8 Hz), 4.21 (dd, 1H, 6-H_b, $J_{6'b,5'}$ 6.30, J_{gem} 11.9 Hz), 4.72 (s, 2H, 2″-H), 4.87 (m, 1H, 1′-H), 5.15 (m, 1H, 4′-H), 5.78 (ddd, 1H, 3′-H, $J_{3',1'}$ 1.6, $J_{3',2'}$ 10.4, $J_{3',4'}$ 2.17 Hz), 6.06 (ddd, 1H, 2′-H, $J_{2',1'}$ 2.6, $J_{2',3'}$ 10.35, $J_{2',4'}$ 1.6 Hz) and 6.82–7.75 (m, 4H, Ph). For **12β**: $[\alpha]_D^{24}$ +90.6° (*c* 0.61, $CHCl_3$). ^1H NMR ($CDCl_3$) δ 3.32 (dd, 1H, 1-H_a, $J_{1a,1'}$ 6.9, J_{gem} 17.4 Hz), 3.43 (dd, 1H, 1-H_b, $J_{1b,1'}$ 6.6 Hz), 3.75 (ddd, 1H, 5′-H, $J_{5',6'a}$ 5.13 $J_{5',6'b}$ 3.38, $J_{5',4'}$ 8.85 Hz), 4.13 (dd, 1H, 6′-H_a, J_{gem} 12.03, $J_{6'a,5'}$ 5.21 Hz), 4.18 (dd, 1H, 6′-H_b, J_{gem} 12.1, $J_{6'b,5'}$ 3.38 Hz), 4.74 (s, 2H, 2″-H) and 4.83 (m, 1H, 1′-H), 5.25 (ddd, 1H, 4′-H, $J_{4',3'}$ 3.0, $J_{4',2'}$ 1.9, $J_{4',5'}$ 9.0 Hz).

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