

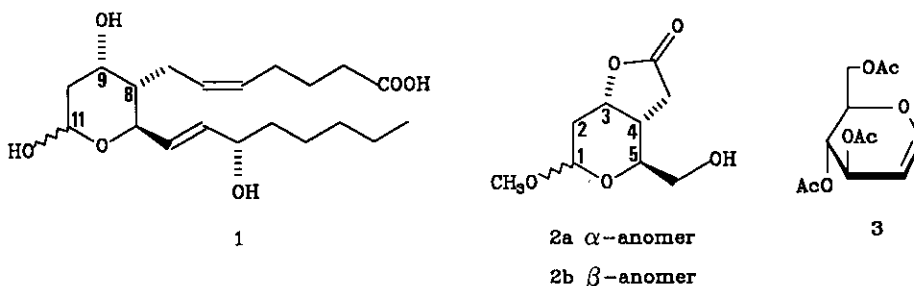
PALLADIUM ASSISTED SYNTHESIS OF A THROMBOXANE B₂ PRECURSOR

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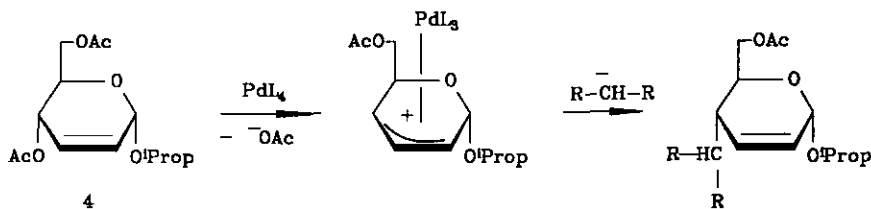
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Abstract—The stereospecific synthesis of a bicyclic precursor for thromboxane B₂, using palladium mediated transformations of tri-*O*-acetyl-*D*-glucal, is described.

An important intermediate in the synthesis of the natural product thromboxane B₂ (**1**) from carbohydrates, is the bicyclic lactone (**2a**) which is prepared *via* the introduction of a two carbon moiety at the C-4 position of the sugar. The α -side chain and the C-9 hydroxyl group of the target molecule can be established by simple chemical manipulations of the lactone ring. Various procedures have been utilized for the introduction of the crucial C-4 substituent of the synthon (**2a**) in syntheses starting from *D*-glucose such as a Wittig-Horner condensation with a sugar ketone,¹ Claisen condensation of an appropriate entity with an unsaturated sugar² and allylation of a sugar 3,4-oxirane with a Grignard reagent.³ Our interest in the palladium mediated transformations of unsaturated sugars⁴ resulted in the development of a short, facile synthetic route towards the thromboxane B₂ intermediate (**2b**), the β -anomer of **2a**, starting from tri-*O*-acetyl-*D*-glucal (**3**).

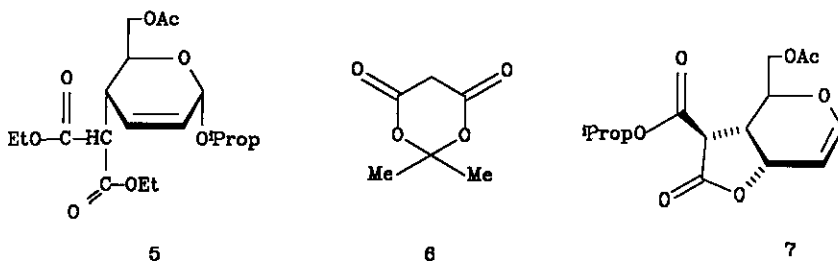


2,3-Unsaturated sugars such as (**4**) form η^3 -complexes with palladium(0) species which react readily with stabilized carbanions⁵ to afford the C-4 substituted sugars (scheme 1). Ferrier⁶ reported an efficient method for the conversion of **3** into various pseudo-glycals, using BF_3 as a catalyst. In our hands, this



Scheme 1

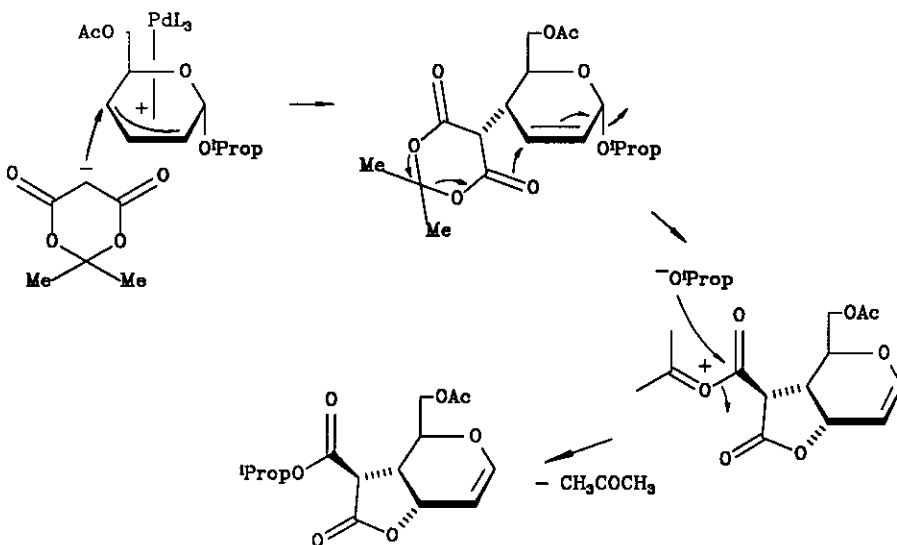
method required special care to avoid polymerization and unwanted side reactions. However, this conversion could be performed using Pd(II) as a catalyst. The reaction involves treatment of **3** with 0.1 molar equivalent of $\text{Pd}(\text{CH}_3\text{CN})\text{Cl}_2$ and two molar equivalents of cupric ditriflate in the appropriate alcohol under anhydrous conditions at 40°C . This conversion probably involves alkoxy-palladation followed by the elimination of $\text{Pd}(\text{OAc})\text{Cl}$. In the absence of the Cu(II) reagent the reaction does not go to completion due to the reduction of the Pd(II) catalyst to Pd(0). In this way **3** was converted into (**4**)[†] in a quantitative yield.



It was envisaged that the introduction of a malonate moiety at the C-4 α -position of **4** would render the carboxymethyl entity required for conversion into the lactone (**2b**). This requires the use of a malonate nucleophile with a protecting group for the diacid functionality which could be removed selectively in the presence of an acetate group. However, di-*t*-butyl malonate failed to react with **4** under the same conditions in which **4** was treated with the sodium salt of diethyl malonate and 0.1 molar equivalent of $\text{Pd}(\text{PPh}_3)_4$ in THF at 80°C to afford **5** in a quantitative yield. An alternative approach envisaged that the isopropylidene protecting group of Meldrum's acid (**6**) could be removed by mild acidic conditions without hydrolysis of the acetate ester. Initial experiments involving the attempted condensation of the sodium salt of **6** with **4**, using $\text{Pd}(\text{PPh}_3)_4$ as a catalyst in THF at 80°C , failed to give any product possibly due to the low solubility of the sodium salt of **6** in the reaction medium. The use of other solvents such as HMPA and

[†]All products were fully characterized with ir, ¹H and ¹³C-nmr and mass spectrometry.

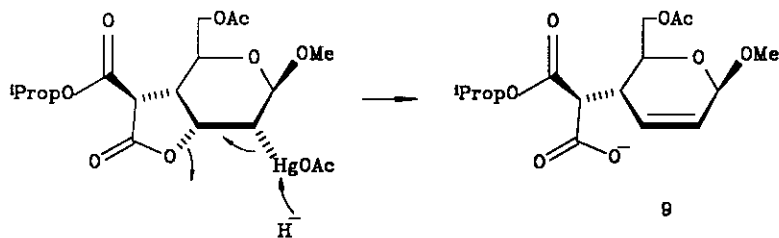
acetonitrile failed to alleviate the solubility problem. Since Meldrums' acid is soluble in THF, it was decided to perform the reaction in the absence of a base. This procedure (5 molar equivalents of **6** and 0.1 molar equivalent $\text{Pd}(\text{PPh}_3)_4$) furnished a single product which was identified as the bicyclic lactone (**7**) [mp $68 - 70^\circ$, $[\alpha]_D^{22} +62.9^\circ$ ($c = 1$, CHCl_3), $^1\text{H-nmr}$ (CDCl_3) δ 1.29 (d, 6H, $J = 6.2$ Hz, $\text{CH}(\text{CH}_3)_2$), 2.99 (ddd, 1H, $J_{3,4} = 6.2$, $J_{4,4'} = 4.2$ and $J_{4,5} = 9.0$ Hz, H-4), 3.48 (d, 1H, $J_{4,4'} = 4.2$ Hz, H-4'), 5.03 (dd, 1H, $J_{1,2} = 6.4$ and $J_{2,3} = 1.5$ Hz, H-2), 5.10 (dd, 1H, $J_{2,3} = 1.5$ and $J_{3,4} = 6.2$ Hz, H-3), 6.62 (d, $J_{1,2} = 6.4$ Hz, H-1), m/z 298 (M^+ , 10)]. The acetate ion liberated during the formation of the η^3 -palladium complex, probably serves as the base required for the deprotonation of **6**. Nucleophilic attack of the resultant carbanion on the α -face of the substrate molecule introduces Meldrums' acid at C-4. This is followed immediately by Pd(0) or acid catalysed lactonization with concomitant shifting of the double bond to the 1,2-position and liberation of isopropoxide. Nucleophilic attack of isopropoxide on the resultant oxonium ion, followed by liberation of acetone affords the bicyclic lactone (**7**) (scheme 2). This cascade of reactions unexpectedly provided a very short route for the conversion of **4** into **7** in a yield of 76%.



Scheme 2

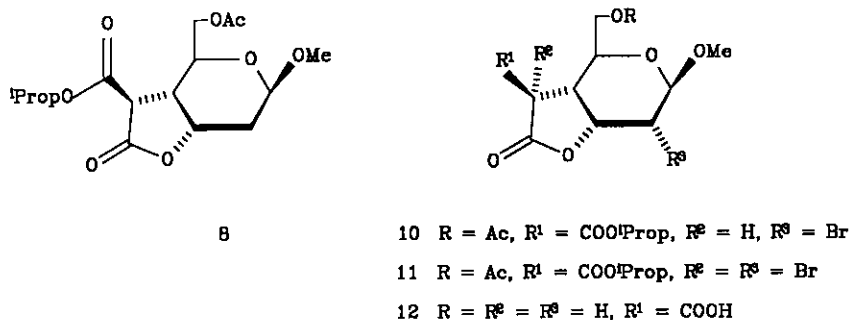
The next step in the synthesis involved the introduction of a methoxy group at the C-1 position of (**7**). The use of BF_3/MeOH or $\text{MeCOOH}/\text{MeOH}$ as reagents for this reaction gave complex mixtures of products. Reaction of **7** with mercuric acetate in methanol followed by attempted demercuration of the intermediate with sodium borohydride, did not give the expected 2-deoxysugar (**8**), but afforded a product of high polarity. It was suspected that this product may be the carboxylate (**9**), resulting from a reductive elimination reaction⁷ (Scheme 3). This suspicion was confirmed when the bicyclic lactone (**7**) was formed

upon acidification with CF_3COOH . In the hope of overcoming the problem of reductive elimination, the organomercury intermediate was treated with tributylstannane, a hydrogen radical donor. This reaction gave only 31% of the desired 2-deoxy compound (**8**) [mp $92 - 93^\circ$, $[\alpha]_{\text{D}}^{22} -52^\circ$ ($c = 2.2$, CHCl_3), $^1\text{H-nmr}$ (CDCl_3) δ 1.86 (ddd, 1H, $J_{1,2b} = 8.8$, $J_{2a,2b} = 15.0$ and $J_{2b,3} = 4.6$ Hz, H-2b), 2.29 (ddd, 1H, $J_{1,2a} = J_{2a,3} = 2.4$ and $J_{2a,2b} = 15.0$, H-2a), 3.48 (s, 3H, OCH_3), 4.57 (dd, 1H, $J_{1,2a} = 2.4$ and $J_{1,2b} = 8.8$ Hz, H-1), m/z 329 ($\text{M}^+ - \text{H}$, 3)]. The first step of an alternative method for the preparation of **8** involved the slow addition of bromine (1.5 equivalent) to a solution of **7** in methanol at low temperature to afford a mixture of the monobrominated and dibrominated compounds (**10**) [$[\alpha]_{\text{D}}^{19} -59.6^\circ$ ($c = 1$, CHCl_3), $^1\text{H-nmr}$ δ 3.95 (dd, 1H, $J_{1,2} = 8.5$ and $J_{2,3} = 3.9$ Hz, H-2), 4.61 (d, 1H, $J_{1,2} = 8.5$ Hz, H-1), m/z 409 (M^+ , 1)] and (**11**) [m/z 488 (M^+ , 4)] in a combined yield of 83%. Reductive debromination of the mixture of **10** and **11** was accomplished using tributylstannane and α, α' -azobisisobutyronitrile in toluene under reflux to give the deoxygenated product (**8**) in an essentially quantitative yield.



Scheme 3

Selective removal of the two ester groups in the presence of the lactone function of **8**, using 2 equivalents of aqueous sodium hydroxide in THF, proceeded without any difficulty and gave the desired product (**12**) after acidification in a yield of 81% which was used directly in the subsequent reaction. The final step in the preparation of **2** involved decarboxylation of the C-4' carboxylic acid side chain. This was achieved by inserting the reaction vessel into a preheated oil bath at 170°C . Decarboxylation of **12** was completed



within 3 minutes. The synthon (2) [mp 118 – 120^o, $[\alpha]_D^{23}$ –121^o (c = 1.5, CHCl₃), ¹H-nmr δ 1.22 (bs, 1H, OH), 1.75 (ddd, 1H, J_{1,2b} = 9.3, J_{2a,2b} = 14.7 and J_{2b,3} = 4.2 Hz, H-2b), 2.23 (d, 1H, J_{4'a,4'b} = 17.5 Hz, H-4'b), 2.31 (d, 1H, J_{2a,2b} = 14.7 Hz, H-2a), 2.51 (ddd, 1H, J_{3,4} = 4.8, J_{4,4'a} = 7.2 and J_{4,5} = 10.7 Hz, H-4), 2.68 (dd, 1H, J_{4,4'a} = 7.2 and J_{4'a,4'b} = 17.5 Hz, H-4'a), 3.41 (ddd, J_{4,5} = 10.7, J_{5,6a} = 2.8 and J_{5,6b} = 4.7 Hz, H-5), 3.49 (s, 3H, OCH₃), 3.58 (dd, 1H, J_{5,6b} = 4.7 and J_{6a,6b} = 12.1 Hz, H-6b), 3.79 (dd, 1H, J_{5,6a} = 2.7 and J_{6a,6b} = 12.1 Hz, H-6a), 4.59 (dd, 1H, J_{1,2a} = 2.2 and J_{1,2b} = 9.3 Hz, H-1), 4.77 (m, 1H, H-3), m/z 201 (M⁺, 3), 171 (M⁺–OCH₃, 100)] was obtained in an overall yield of 48% from 3. It is envisaged that the completion of the thromboxane B₂ synthesis via intermediate 2b would follow the same route as that reported for syntheses via the α-anomer (2a).¹⁻³

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