PALLADIUM ASSISTED SYNTHESIS OF A THROMBOXANE B_2 PRECURSOR

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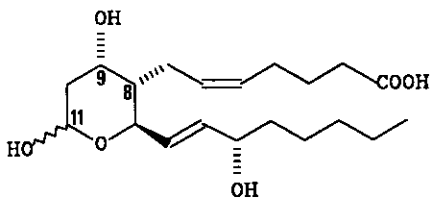
Abstract–The stereospecific synthesis of a bicyclic precursor for thromboxane B_2, using palladium mediated transformations of tri–O–acetyl–D–glucal, is described.

An important intermediate in the synthesis of the natural product thromboxane B_2 (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 sugar[2] and allylation of a sugar 3,4–oxirane with a Grignard reagent.[3] Our interest in the palladium mediated transformations of unsaturated sugars[4] resulted in the development of a short, facile synthetic route towards the thromboxane B_2 intermediate (2b), the β–anomer of 2a, starting from tri–O–acetyl–D–glucal (3).



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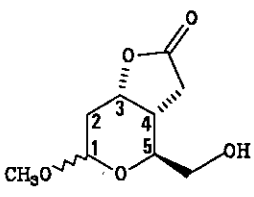
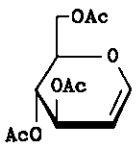


2a α–anomer

2b β–anomer



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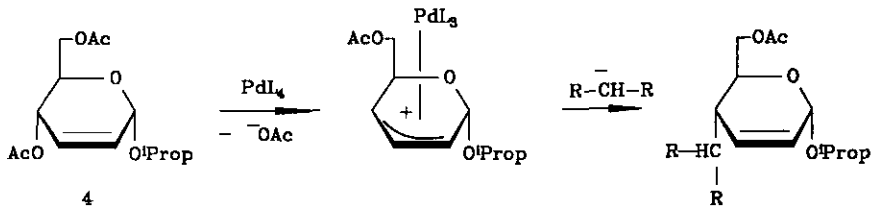
2,3–Unsaturated sugars such as (4) form η^3–complexes with palladium(0) species which react readily with stabilized carbanions[5] to afford the C–4 substituted sugars (scheme 1). Ferrier[6] reported an efficient method for the conversion of 3 into various pseudo–glycals, using BF_3 as a catalyst. In our hands, this



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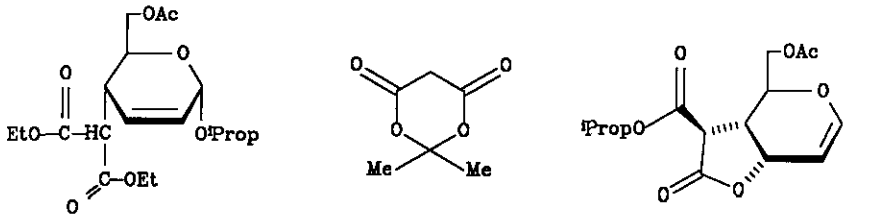
Scheme 1

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 $Pd(CH_3CN)Cl_2$ and two molar equivalents of cupric ditriflate in the appropriate alcohol under anhydrous conditions at 40^o C. This conversion probably involves alkoxypalladation followed by the elimination of Pd(OAc)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.

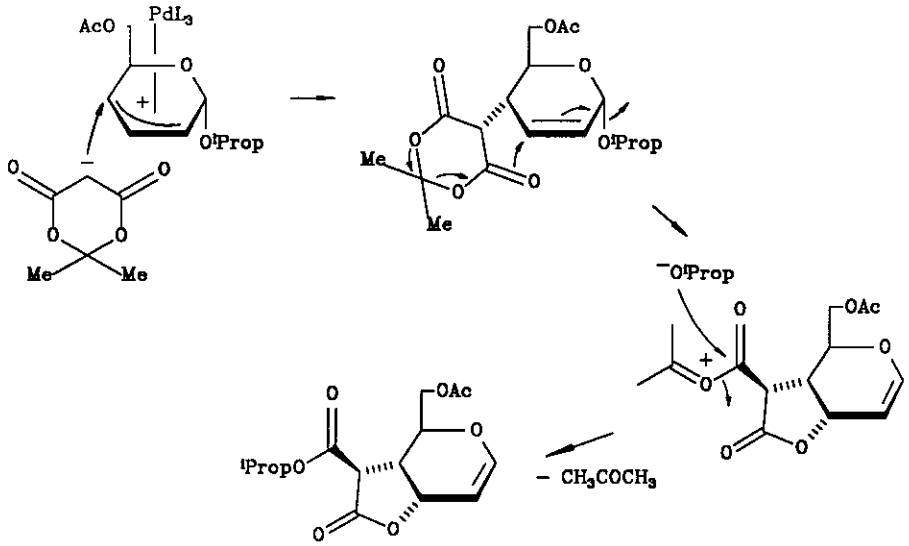


5 6 7

It was envisaged that the introduction of a malonate moiety at the C–4α–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 $Pd(PPh_3)_4$ in THF at 80^o C to afford 5 in a quantitative yield. An alternative approach envisaged that the isopropylidene protecting group of Meldrums' 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 $Pd(PPh_3)_4$ as a catalyst in THF at 80^o 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, ^{1}H and ^{13}C–nmr and mass spectrometry.

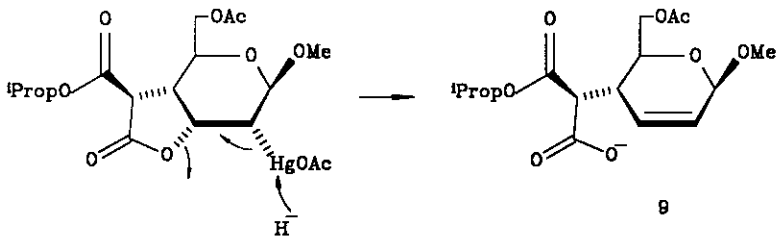
acetonitrile failed to alleviate the solubility problem. Since Meldrums' acid is soluble in THF, it was decided to perform the reaction in the absence of a base. This procedure (5 molar equivalents of 6 and 0.1 molar equivalent $Pd(PPh_3)_4$) furnished a single product which was identified as the bicyclic lactone (7) [mp 68 – 70°, $[\alpha]_D^{22}$ +62.9° (c = 1, $CHCl_3$), ^{1}H–nmr ($CDCl_3$) δ 1.29 (d, 6H, J = 6.2 Hz, $CH(C\underline{H}_3)_2$), 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

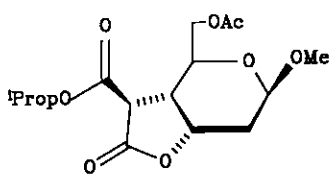
The next step in the synthesis involved the introduction of a methoxy group at the C–1 position of (7). The use of BF_3/MeOH or MeCOOH/MeOH as reagents for this reaction gave complex mixtures of products. Reaction of 7 with mercuric acetate in methanol followed by attempted demercuration of the intermediate 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 reaction[7] (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°, $[\alpha]_D^{22}$ –52° (c = 2.2, $CHCl_3$), ^{1}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, $OC\underline{H}_3$), 4.57 (dd, 1H, $J_{1,2a}$ = 2.4 and $J_{1,2b}$ = 8.8 Hz, H–1), m/z 329 (M^+–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) [$[\alpha]_D^{19}$ –59.6° (c = 1, $CHCl_3$), ^{1}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



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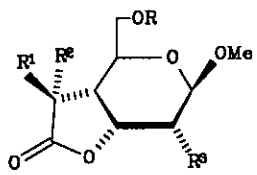

10 R = Ac, R^1 = COO^{i}Prop, R^2 = H, R^3 = Br

11 R = Ac, R^1 = COO^{i}Prop, R^2 = R^3 = Br

12 R = R^2 = R^3 = H, R^1 = COOH

within 3 minutes. The synthon (2) [mp 118 – 120°, $[\alpha]_D^{23}$ –121° (c = 1.5, $CHCl_3$), ^{1}H–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, $OC\underline{H}_3$), 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^+–OCH_3, 100)] was obtained in an overall yield of 48% from 3. It is envisaged that the completion of the thromboxane B_2 synthesis via intermediate 2b would follow the same route as that reported for syntheses via the α–anomer (2a).[1–3]

ACKNOWLEDGEMENT

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