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# PROSTANOIDS FROM D-GLUCOSE. PALLADIUM-CATALYZED ALKYLATION OF 1,2-O-ISOPROPYLIDENE-3-DEOXY-5-ACETOXY-α-D-ERYTHRO-PENT-5-EN-FURANOSE

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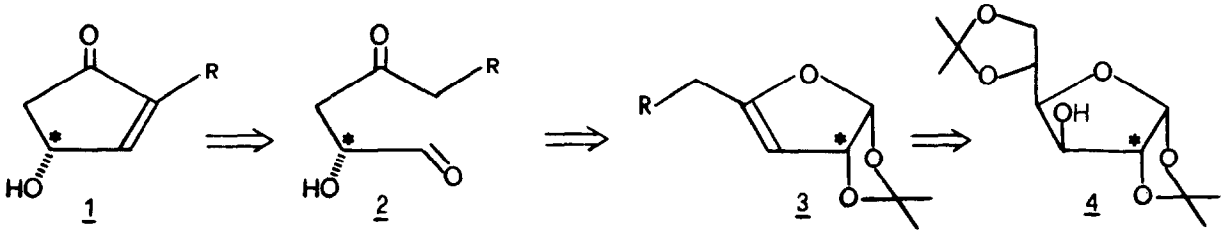
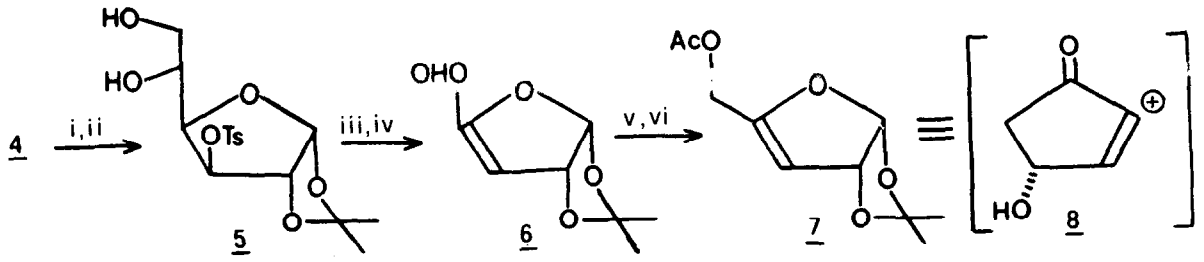
Abstract- Pd-Catalyzed C-C bond forming reactions on an allylic acetate derived from D-glucose are performed to prepare potentially useful precursors of (R)-4-hydroxycyclopent-2-en-1-ones.

One of the most useful strategies to the synthesis of optically pure organic molecules makes use of starting materials already containing the proper chirality which will be carried over the whole synthetic sequence up to the target molecule. Easily available natural substances constitute the "chiral pool"[1] for this purpose. Among them carbohydrates have found extensive use[2]. However concerning prostaglandins only a few syntheses have been reported in which the chiral C-11 carbon comes from D-glucose[3-5]. For example (R)-4-hydroxycyclopent-2-en-1-one derivatives 1 (R = 1,3-dithian-2-yl[4] and benzyloxy[5]) have been prepared from the D-glucose derivative 1,2,5,6-bis-O-isopropylidene-α-D-glucofuranose (4). In these synthetic sequences the immediate precursor of the target compound 1 is an unstable hydroxyketoaldehyde 2 coming from the acidic hydrolysis of the cyclic vinyl-ether 3. The carbon which preserves its chirality is marked in the formulae.



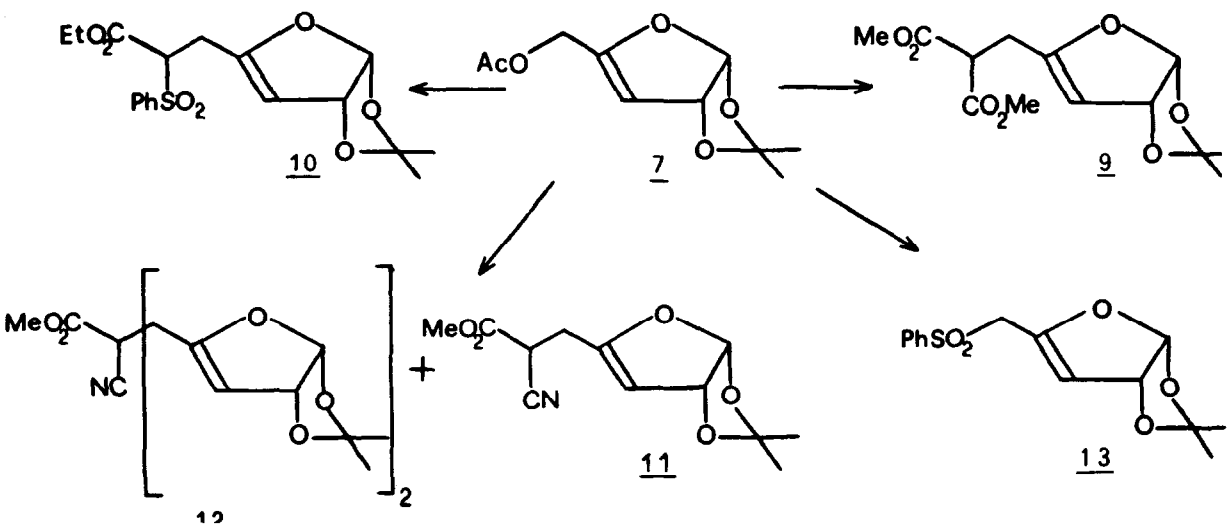

We wish to report here the results of our preliminary efforts aimed at preparing chiral synthons of general structure 3, exploiting as key intermediate the allylic acetate 7, which is obtained in 57% overall yield from 4 by routine experimental procedures.

The acetate 7 smoothly undergoes substitution reactions with several soft nucleophiles under the catalytic action of zerovalent palladium species[6], so behaving as a synthetic equivalent of (R)-4-hydroxycyclopent-2-en-1-one-2-yl methyl cation 8.




i: TsCl, Py (90%); ii: Amberlyst $H^+$, MeOH, 60°C (70% conv., 97% yield); iii: $NaIO_4$, $H_2O$, acetone; iv: $Et_3N$, $C_6H_6$ (82% from 5); v: $NaBH_4$, MeOH, 0°C; vi: $Ac_2O$, $Et_3N$, DMAP (80% from 6).

We obtained the best result using the preformed anion of dimethyl malonate (5 equiv., from dimethyl malonate and sodium hydride in THF) in the presence of tetrakis(triphenylphosphine)palladium (0.05 equiv.) and triphenylphosphine (0.5 equiv.), by heating the reaction mixture in THF at reflux for 2 h[7]. Noteworthy the nucleophilic attack takes place exclusively at the unsubstituted terminus of the allylic moiety to produce in 87% yield the product 9 having the "endo" double bond, in agreement with previous findings on the reaction of sodium malonates with 1-(1'-acetoxyethyl)cyclopentene[7]. No trace of the regioisomeric alkylation product was detected by $^{13}C$-NMR, TLC and capillary GC analyses. When diethyl malonate was employed, the corresponding compound was obtained in slightly lower yield. The use of highly dispersed palladium on graphite (Pd-Gr)[8] or 10% Pd/C (0.1 equiv.) and potassium carbonate as the heterogeneous base[9] allows the use of only two equivalents of malonate, and avoids the necessity of preliminary preparation of the anion, but the product 9 was obtained in only 67% yield (83% yield with respect to reacted 7) after refluxing for 40 h. However the same yield was obtained after 6 h in refluxing THF by combining the use of homogeneous catalyst $Pd(Ph_3P)_4$ and heterogeneous base, with the relative ratios 7 : malonate : Pd : $K_2CO_3$ = 1 : 2 : 0.1 : 3 and without additional ligand. In every case the diallylated malonate was produced in less than 5% yield and in some cases in only trace amounts.



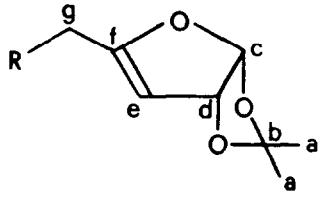
Adopting the last conditions we carried out reactions of 7 with other nucleophiles. Ethyl benzenesulphonylacetate and methyl cyanoacetate display the same regioselective attack in reaction with 7. The monoalkylated products 10 and 11 were obtained in 58% and 18% yield respectively. The dialkylated nitrile 12 was formed in 53% yield from the cyanoacetate reaction, its formation probably being due to the relatively minor steric hindrance of the cyano group compared to the carboxymethyl and benzenesulphonyl groups. When sodium benzenesulphinate was employed as nucleophile on 7 the sulphone 13 was obtained in 47% yield using our previously published conditions[8], and in 36% yield following the alternative procedure with $Pd(Ph_3P)_4$[10]. In both experiments tarry materials, apparently from the decomposition of 7, were produced.

$^{13}C$-NMR spectra (Table), $^{1}H$-NMR, IR, m.p. and optical activity for all new compounds have been determined[11].

The compounds 9-11 and 13 represent extremely versatile and useful intermediates for the synthesis of target molecules having structure 1. By submitting 9-11 to decarboxylation[12] cyclic vinyl ethers 3 (R = $CO_2Me$[13], CN, $SO_2Ph$) are easily available; they are suitable substrates for further manipulations, such as functional group interconversion, chain elongation exploiting stabilized anions, etc., leading to a variety of substituted chiral hydroxycyclopentenones.

We are now examining new nucleophilic reactions on acetate 7[14] as well as on other allylic acetates derived from sugars.

TABLE: $^{13}C$-NMR DATA*




7: R = $MeCO_2$ ; 9: R = $CH(CO_2Me)_2$

10: R = $PhSO_2CHCO_2Et$ ; 11: R = $NCCHCO_2Me$

12: R = $NCCCO_2Me$ ; 13: R = $PhSO_2$

| COMPOUND | CARBONS | | | | | | | OTHER CARBONS IN R |
|---|---|---|---|---|---|---|---|---|
| | a | b | c | d | e | f | g | |
| 7 | 28.1<br>27.9 | 112.3 | 106.6 | 83.5 | 100.8 | 156.6 | 58.7 | 170.0($MeCO_2$), 20.5($MeCO_2$) |
| 9 | 28.0 | 112.1 | 106.1 | 83.8 | 99.2 | 158.6 | 28.0 | 48.6($MeO_2CCHCO_2Me$),<br>168.7($MeCO_2$), 52.7($MeCO_2$) |
| 10 | 28.1<br>27.8 | 112.2 | 106.1 | 83.6 | 100.3<br>99.9 | 154.4 | 25.8<br>26.0 | 67.5($PhSO_2CHCO_2Et$),<br>164.8($EtCO_2$),134.5,129.2(Ph)<br>62.4($CH_2CH_3$), 13.7($CH_2CH_3$) |
| 11 | 28.1<br>27.8 | 112.4 | 106.3 | 83.6 | 101.2<br>101.1 | 155.9 | 28.7<br>28.2 | 34.5($NCCHCO_2Me$),115.3(CN),<br>165.5($MeCO_2$), 53.8($MeCO_2$) |
| 12 | 28.1<br>27.9 | 112.4 | 106.3 | 83.4 | 102.4 | 155.2 | 35.8 | 46.1($NCCCO_2Me$), 117.1(CN),<br>167.6($MeCO_2$), 53.8($MeCO_2$) |
| 13 | 27.9<br>27.7 | 112.5 | 106.2 | 83.2 | 105.1 | 140.2 | 55.8 | 138.0,134.1,129.1,128.4(Ph) |

*Spectra were recorded at 20 MHz in $CDCl_3$ solutions containing tetramethylsilane as internal standard, chemical shifts are reported in ppm.

## References and Notes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11. $^1$H-NMR spectra were recorded at 90MHz in $CDCl_3$ solutions containing tetramethylsilane as internal standard, chemical shifts are given in ppm. IR absorptions are given in $cm^{-1}$.
7: $[\alpha]_D^{25}$ = +4.6 (1.51, MeOH); IR: 1745(C=O), 1665(C=C); $^1$H-NMR: 6.01(d, J=4Hz, 1H, OCHO), 5.35-5.2(m, 2H, CH= + CH-O), 4.6(s, 2H, $CH_2O$), 2.05(s, 3H, $CH_3C$=O), 1.4(s, 6H, $Me_2CH$).
9: $[\alpha]_D^{25}$ = -21.2 (1.34, MeOH); IR: 1740(C=O), 1665(C=C); $^1$H-NMR: 6.0(d, J= 5Hz, 1H, OCHO), 5.3(m, 1H, CH=), 5.0(m, 1H, CH-O), 3.7(s, 6H, $CH_3O$), 3.65(t, 1H, $CH_2$-CH), 2.8(d, 2H, $CH_2$-CH), 1.4(s, 6H, $Me_2CH$).
10: m.p. 81°C; IR: 1735(C=O), 1660(C=C); $^1$H-NMR: 8.0-7.4(m, 5H, Ph), 5.95(d, J=4Hz, 1H, OCHO), 5.2(m, 1H, CH-O), 5.05(br s, 1H, CH=), 4.4-3.9(m, 3H, $CH_2$-O + $CH_2$-CH), 3.9(d, 2H, $CH_2$-CH), 1.4(br s, 6H, $Me_2CH$), 1.1(t, 3H, O-$CH_2$-$CH_3$).
11: IR: 2260(CN), 1755(C=O), 1665(C=C); $^1$H-NMR: 6.1(d, J=4Hz, 1H, OCHO), 5.4-5.1(m, 2H,CH= + CH-O), 3.85(s, 3H, $CH_3O$), 3.85(t, 1H, $CH_2$-CH), 2.8(d, 2H, $CH_2$-CH), 1.45(br s, 6H, $Me_2CH$).
12: m.p. 93°C; IR: 2250(CN), 1750(C=O), 1665(C=C); $^1$H-NMR: 6.0(d, J=4Hz, 2H, OCHO), 5.35-5.15(m, 4H, CH= + CH-O), 3.8(s, 3H, $CH_3O$), 2.8(s, 4H, $CH_2$-C), 1.4(br s, 12H, $Me_2CH$).
13: m.p. 107-109°C; $[\alpha]_D^{25}$ = -16.9 (1.06, MeOH); IR: 1650(C=C); $^1$H-NMR: 8.1-7.4(m, 5H, Ph), 5.9(d, J=4Hz, 1H, OCHO), 5.35-5.1(m, 2H, CH= + CH-O), 4.0(s, 2H, $CH_2SO_2$), 1.4(br s, 6H, $Me_2CH$).

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13. Partial saponification of 9 with stoichiometric amounts of KOH and 18-crown-6 ether in a benzene-methanol solution, followed by methanol distillation and refluxing for 1 h, afforded the corresponding monoester in 80% yield: $[\alpha]_D^{25}$ = +3.96 (1.54, MeOH); IR: 1745(C=O), 1660(C=C); $^1$H-NMR: 6.1(d, J=4Hz, 1H, OCHO), 5.4-4.9(m, 2H, CH= + CH-O), 4.2(s, 3H, $CH_3O$), 2.5(br s, 4H, $CH_2$-$CH_2$), 1.45(s, 6H, $Me_2CH$). See D. M. Hunter and R. A. Perry, Synthesis, 37 (1977).

14. Attempts to use 6 in coupling reactions with the copper (I) reagents $(n\text{-}C_6H_{13})_2Cu\cdot MgBr$ and $n\text{-}C_6H_{13}CuCN\cdot MgBr$ did not give satisfactory results.



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