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OLEFIN ADDITION TO ACETYLATED GLYCALS. A NEW ROUTE TO C-GLYCOSIDES.

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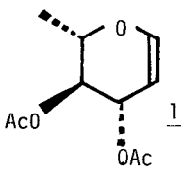
Abstract : Olefins react with glycals in the presence of Lewis acids providing a new route to C-glycosides.

Much attention has been paid to the stereocontrolled formation of a C-C bond at the anomeric center of a carbohydrate[1], in connection with the synthesis of chiral building blocks and naturally occurring products[2]. Despite the availability of many methods for the synthesis of C-glycosides, there still exists a need for new convenient and selective procedures allowing the direct introduction of polyfunctional aglycons.

It was recently reported that peracetylated glycals reacted with silyl enol ethers[3,4], allyltrimethylsilane[5] and ß dicarbonyl compounds[6] to give the corresponding 2',3'-unsaturated C-glycosides[7]. These molecules are versatile intermediates with an high synthetic potential for the preparation of functionalized C-glycosides[8].

As a part of a program directed toward the total synthesis of antitumoral compounds we needed to develop an olefin-based[9] approach to hexenopyranosyl C1'-branched derivatives. We now demonstrate that the condensation of peracetylated glycals with alkenes in the presence of Lewis acids leads to the stereoselective formation of a C-glycosidic bond. In addition this facile entry to C-glycosides provides a simple method for the direct introduction of polyfunctional aglycons.

3,4-di-O-acetyl-L-rhamnal 1 and 3,4,6-tri-O-acetyl-D-glycal 2 reacted very smoothly with olefins in the presence of $EtAlCl_2$, $SnCl_4$, $BF_3.Et_2O$ or trimethylsilyl triflate (TMSOTf). The condensation was carried out in dichloromethane at -15°C and afforded a stereoisomeric mixture of C-glycosides in good to excellent yields. Purification by flash chromatography furnished the α and ß anomers in the indicated ratios (see Table).



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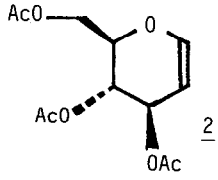
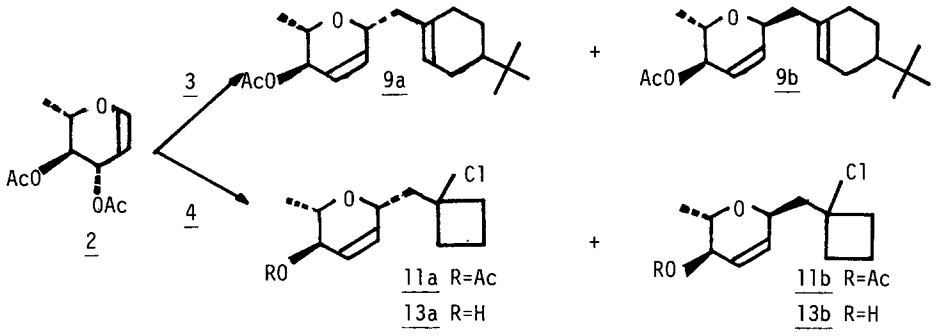


2

Examination of the NMR spectra revealed that the condensation led to two different products. Thus reaction of rhamnal 1 with methylene 4-tert-butyl-cyclohexane 3 gave rise to the cyclohexene derivatives 9a and 9b[10]. When the same procedure was conducted with methylene cyclobutane 4, C-glycosides 11a and 11b with a chloro aglycon were produced.[11]



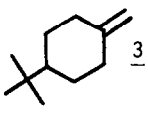
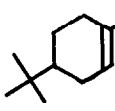
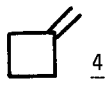
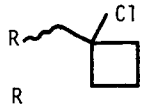
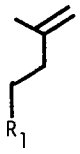
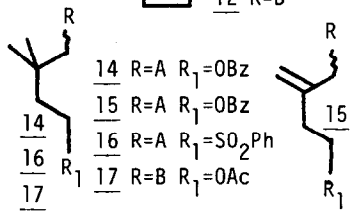
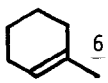
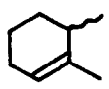
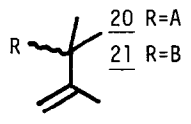
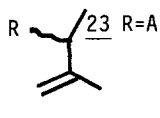
The configuration at C1' for the C-glycosides 9 and 11 was established from the finding of Achmanowitz and al.[12]. The fast moving isomers 9a and 11a displayed a $J_{4',5'}$ = 9.5Hz coupling constant and were assigned as the ß anomers. This large value was in accordance with the preferred equatorial orientation of all the substituants. In the other hand some configurational mobility could be expected for the α epimers. Accordingly the observed data were respectively 5Hz and 6Hz for the more polar isomers 9b and 11b.

In order to ascertain the above assignments in an unambigous manner alcohols 13a and 13b[13] were treated with MCPBA[14]. On epoxidation the minor isomer 13a gave a 2',3'-anhydro glycoside with a $J_{1',2'}$ value of 0Hz in its ^1H NMR spectrum, while the major anomer 13b afforded an epoxy derivative with $J_{1',2'}$ = 4 Hz. Therefore the major product has the configuration and the minor product the ß configuration in complete accordance with initial assignations.

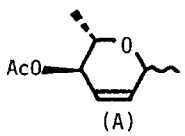
Other examples were studied and results were summarized in the Table. For each reaction the configuration at the anomeric center was assigned from the $J_{4',5'}$ coupling constants. It is well established from previous reports[15] that the only regioisomer observed was the one arising from entry of the olefin at C1' with transposition of the double bond at C2'-C3'. Furthermore the α anomer dominated widely over the ß anomer. Our results are consistent with these findings. However when D-glucal was reacted with 2,3-dimethyl butene 7 the ß anomer was predominant. In an attemps to modify the chemoselectivity of the reaction, the use of several Lewis acids was investigated but no significative improvement was recorded. Finally it must be pointed out that both 3-R and 3-S α anomers were isolated when glycals 1 and 2 were treated with 2-methyl 2-butene 8. In addition spectroscopic evidences suggested that C-glycosides 14,16 and 17 were obtained as a mixture of diastereoisomers.

The reactions described here provided a new and simple entry to C-glycosides by the condensation of peracetylated glycals with readily available olefins. Application of this method to the synthesis of chiral synthons starting from polyfunctional alkenes are now under investigation.

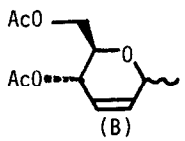
Table

Olefin	Product[a]	catalyst	Yield[b]%(α/β)
 3	 9 R=A, 10 R=B	$EtAlCl_2$	9 92(15/1)
		BF_3Et_2O	9 92(15/1)
		$EtAlCl_2$	10 70(9/1)
 4	 11 R=A, 12 R=B	$EtAlCl_2$	11 83(8/1)
		$SnCl_4$	11 83(8/1)
		$EtAlCl_2$	12 72(12/1)
 5a R_1=OBz, 5b R_1=SO_2Ph, 5c R_1=OAc	 14 R=A R_1=OBz, 15 R=A R_1=OBz, 16 R=A R_1=SO_2Ph, 17 R=B R_1=OAc	$EtAlCl_2$	14 60(12/1), 15 5(1/-)
		$EtAlCl_2$	16 60(12/1)
		$EtAlCl_2$	17 60(12/1)
 6	 18 R=A, 19 R=B	$EtAlCl_2$	18 72(15/1)[16]
		TMSOTf	19 57(20/1)[16]
 7	 20 R=A, 21 R=B, 22 R=B	TMSOTf	20 40(3/2)
		$SnCl_4$	21 70(1/2), 22 15(1/2)
 8	 23 R=A, 24 R=A, 25 R=B	$EtAlCl_2$	23 34(19/1), 24 30(9/1)
		$EtAlCl_2$	25 52(6/5)

a) A 0.2M solution of glycal in CH_2Cl_2 was treated with alkene (1.1eq) and catalyst (1.5-2 eq) at -15°C. The mixture was stirred for 5 mn and quenched with pH 4 phosphate buffer.
b) yields refer to isolated and purified materials.



(A)



(B)

References and notes

1. For some recent examples see :a) M.D Lewis, J.K. Cha, Y. Kishi. J.Am.Chem.Soc. 104, 4976 (1982). b) T.L. Cupps, D.S. Wise, L.B. Townsend. J.Org.Chem. 47, 5115 (1982). c) A.P. Kozikowski, K.L. Sorgi, B.C. Wang, X. Zu. Tetrahedron Lett. 24, 1563 (1983). d) R.M. Williams, A.O. Stewart. Tetrahedron Lett. 24, 2715 (1983). e) J.M. Lancelin, P.H. Amvam Zollo, P. Sinay. Tetrahedron Lett. 24 4833 (1983). f) A. Hosomi, Y. Sakata, H. Sakurai. Tetrahedron Lett. 25, 2383 (1984).
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5. S. Danishefsky, J.F. Kerwin. J. Org. Chem. 47. 3803 (1982).
6. S.Yougai, T. Miwa. J. Chem. Soc.Chem. Commun, 68, (1983).
7. Nomenclature rules for complex carbohydrates were applied (see ref.4).
8. For some utilisations of C-glycosides in organic synthesis see : S. Hanessian. Total synthesis of natural products : The 'Chiron' approach. Pergamon Press. Oxford (1983).
9. a) T. Ogawa, A.G.Pernet, S. Hanessian. Tetrahedron Lett. 3543 (1973).
b) T.L. Cupps, D.S. Wise, L.B. Townsend. Carbohyd.Res. 115, 59 (1983)
These publications reported the preparation of a furanosyl C-glycoside by the reaction of tetra-O-acyl D-ribose with 1-hexene.
10. Possibly 9a and 9b are a mixture of two diastereoisomers (4-R,4-S). The following NMR data ascertain the stereochemistry at C1' and prove the presence of a double bond at C1-C2. 9a ^{1}H NMR (60MHz, $CDCl_3$)δ5.83(m, 2H), 5.6(m, 1H), 5.13(ddd, J=9.5 3 , 1 Hz, 1H), 4.3(br t, J=7Hz, 1H), 3.6 (dd, J=9.5, 6 Hz, 1H), 2.33-1.66(m, 9H) 2.13(s , 3H), 1.25(d, J=6 Hz, 3H), 0.86 (s, 9H). 9b ^{1}H NMR (60MHz, $CDCl_3$)δ5.86 (m, 2H) 5.55(m, 1H), 4.96(ddd, J=5, 2.5, 2.5 Hz, 1H), 4.25(br t, J=7 Hz, 1H), 3.95 (dd, J=6.5, 5 Hz, 1H), 2.41-2.16(m, 9H), 2.11(s, 3H),1.23(d, J= 6.5 Hz, 3H), 0.88 (s, 9H).
11. 11a ^{1}H NMR (60MHz, $CDCl_3$)δ5.75(m, 2H), 5.06(ddd, J=9.5, 3, 1 Hz, 1H), 4.5(m, 1H) 3.6(dd, J=9.5, 6.5 Hz), 2.9-1.6(m, 8H), 2.1(s, 3H), 1.23(d, J=6.5 Hz, 3H). ^{13}C NMR (20MHz $CDCl_3$) 168.9(s), 131.6(d), 123.9(d), 71.3(s), 70.6(d), 69.5(d), 69.3(d) 45.7(t), 38.5(t), 36.9(t), 19.5(q), 16.9(q), 14.14(t). 11b ^{1}H NMR (60MHz $CDCl_3$)δ5.8(m, 2H), 4.93(ddd, J=6, 2, 2 Hz, 1H), 4.58(m,1H), 3.8(dd, J=6.5, 6 HZ 1H), 2.73-1.66(m, 8H), 2.08(s, 3H), 1.23(d, J=6.5 Hz, 3H). ^{13}C NMR (20MHz $CDCl_3$) 168.9(s), 132.1(d), 123(d), 69.8(s), 68.7(d), 68.2(d), 66.2(d), 48.5(t), 38.6(t) 37.3(t), 19.9(q),16.3(q), 14.7(t).
12. O. Achmanowitz, P.Bukowski. Rocz. Chem. 47, 99 (1973) and reference 4.
13. The alcohols 13a and 13b were readily prepared from the acetates 11a and 11b (MeONa,MeOH,RT).
14. D.H.Buss, L. Hough, L.D. Hall, J.F. Manville. Tetrahedron. 21. 69 (1965).
In the case of 2,3-anhydro sugars the $J_{1,2}$ and $J_{3,4}$ values are 2-4 Hz for cis protons and 0 Hz for trans protons. The oxidation of 2-cyclohexen-1-ol gave the cis-epoxide stereoselectively, (H.B. Henbest, R.A.L. Wilson. J.Chem.Soc. 1958 (1957). Therefore the configuration at C1' could be assigned from the caracteristic $J_{1',2'}$ coupling constants.
15. R.J.Ferrier, N. Prasad. J.Chem.Soc. C, 570, (1969) and reference 3-6.
16. With 1-methyl cyclohexene 6 the 1-methyl 6-(hex-2'-enopyranosyl) cyclohexenes 19 and 20 were isolated instead of the expected methylene cyclohexane derivatives. This result was previously reported for ene reactions of aldehydes and explained by the aprotic reaction conditions. B.B. Snider, D.J. Rodini. Tetrahedron Lett.21 1815 (1980).

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