Tetrahedron Letters,Vol.28,No.17,pp 1933-1936,1987 0040-4039/87 $3.00 + .00
Printed in Great Britain Pergamon Journals Ltd.

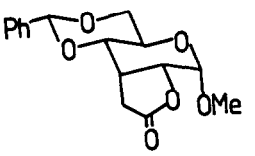
THE "OFF-TEMPLATE" PROBLEM: SYNTHESIS AND ALKYLATION OF A FUSED-BUTYROLACTONE FROM D-GLUCOSE

William W.Wood* and Abdul Rashid

Department of Chemistry, University of Sheffield, Sheffield S3 7HF. U.K.

The synthesis of a fused-butyrolactone from D-glucose and its stereospecific alkylation in an off-template position is described, together with an unusual silyl protecting group migration.

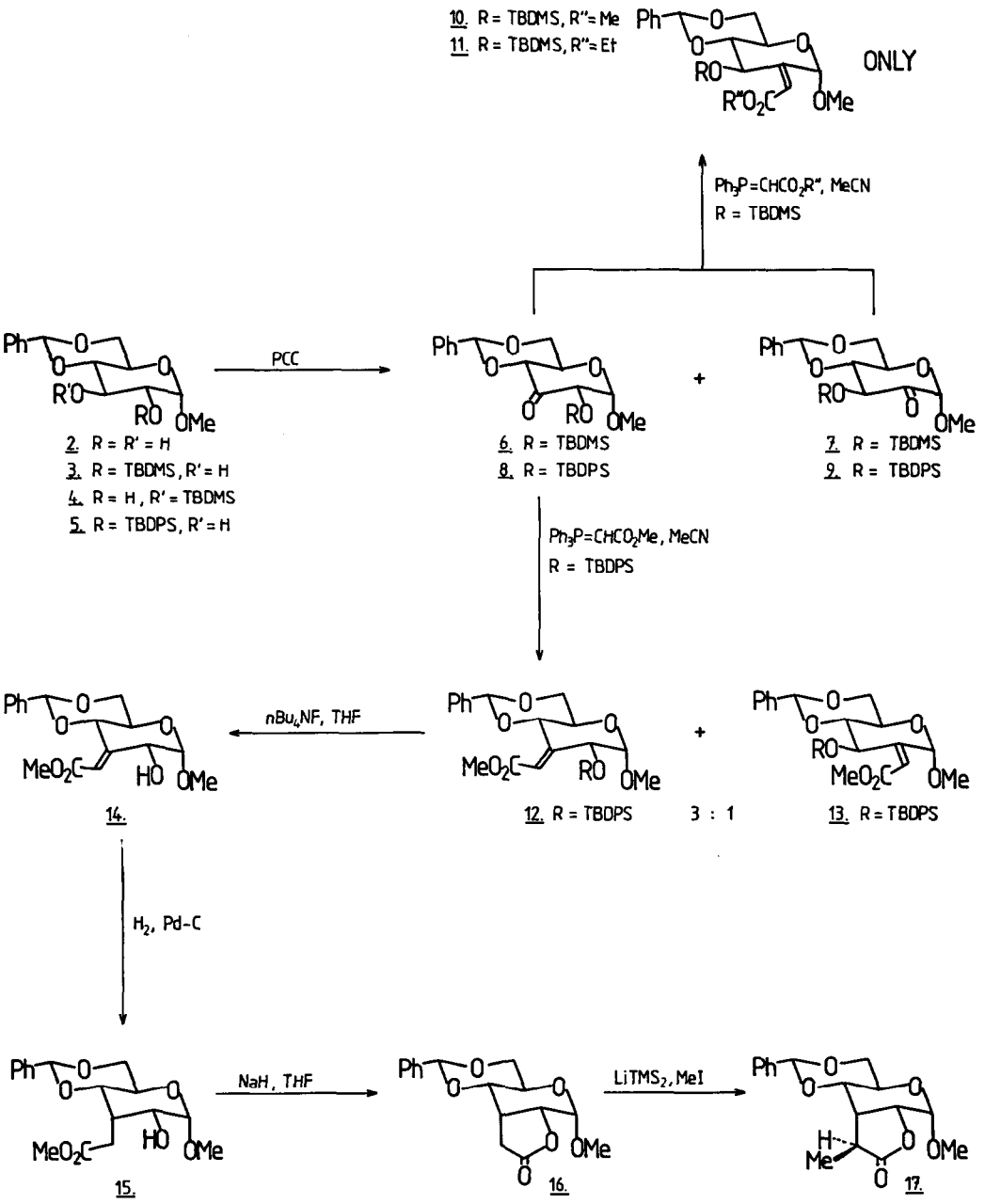
One of the major problems associated with the synthesis of natural products from carbohydrates is the creation of new chiral centres at carbon atoms which were not part of the original carbohydrate template. In work directed towards the solution of this problem, Fraser-Reid has prepared a series of carbohydrate derivatives with a cyclohexane ring fused to the original pyranoside and has made use of the conformational preferences of such compounds to direct the stereochemistry at new chiral centres [1].



1

We reasoned that, where only a single new chiral centre was required, a fused-butyrolactone of type 1 would provide a useful solution to the problem, since the methylene group of the butyrolactone ring would possess distinct exo- and endo- faces and alkylation would occur from the exo-face. We describe herein the successful realization of this goal in the synthesis and stereospecific alkylation of 16. Preparation of the ethyl ester 11 and its C-3 regioisomer from 6 and 7 respectively has been reported previously by Fraser-Reid and co-workers, following the route shown in the Scheme. We therefore started our synthesis by repeating this preparation [2].

In our hands, treatment of the diol 2 with TBDMSCl (TBDMSCl, pyr.) gave a 3:1 mixture of 3 and 4 respectively. These two ethers were separated chromatographically and oxidized (PCC, CH_2Cl_2) to give the ketones 6 and 7, which were clearly distinguishable by high field n.m.r. spectroscopy. To our surprise, however, separate treatment of 6 and 7 with a Wittig reagent according to the published conditions ($Ph_3P{=}CHCO_2Me$, MeCN, reflux), led to the exclusive formation of the C-2 olefin 10 [3]. Repeating the literature experiments exactly ($Ph_3P{=}CHCO_2Et$, MeCN, reflux) gave the same unexpected result, leading to the formation of the C-2 olefin 11 from both 6 and 7.


10. R = TBDMS, R'' = Me
11. R = TBDMS, R'' = Et
ONLY
Ph3P=CHCO2R'', MeCN
R = TBDMS
PCC
2. R = R' = H
3. R = TBDMS, R' = H
4. R = H, R' = TBDMS
5. R = TBDPS, R' = H
6. R = TBDMS
8. R = TBDPS
7. R = TBDMS
9. R = TBDPS
Ph3P=CHCO2Me, MeCN
R = TBDPS
nBu4NF, THF
14.
12. R = TBDPS
3 : 1
13. R = TBDPS
H2, Pd-C
NaH, THF
15.
16.
LiTMS2, MeI
17.

Scheme

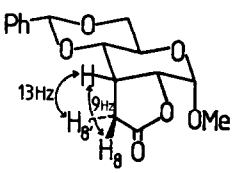
Our first explanation of these observations was that the ketones 6 and 7 equilibrated under the basic conditions of the Wittig reaction, and that the C-2 ketone 7 was the major component of the mixture. However, when this was checked by treating 6 with triethylamine (Et_3N, MeCN, reflux, 6h), 6 itself was found to be the major component of the mixture, being present in 4:1 ratio with 7. Further exposure to triethylamine did not change the ratio of 6 to 7.

It would therefore appear that the effect which caused the exclusive formation of a C-2 olefin was kinetic in nature. Thus, under the conditions of the Wittig reaction, an equilibrium between 6 and 7 is established with 6 as the major component. However 7 reacts with the Wittig reagent at a faster rate than 6 as the ketone of 7 is in a less hindered position. The result of this is that 10 is the only observed product.

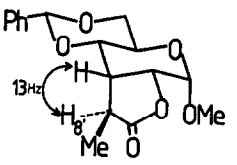
In order to overcome this problem and to find a route that would allow us to prepare a C-3 olefin, we reasoned that a more bulky protecting group might be less prone to migration into the hindered C-3 position. Thus the t-butyldiphenylsilyl group (TBDPS) was chosen. Treatment of 2 with TBDPSCl (TBDPSCl, pyr., cat. imidazole, 94%) led to the exclusive formation of 5. Oxidation of 5 (PCC, CH_2Cl_2, 80%) gave 8 which underwent a slow Wittig reaction to give a mixture of the desired C-3 olefin 12 (60%) and the rearranged product 13 (20%). Hydrogenation of 12 was not possible, and so the silyl group was removed (nBu_4NF, THF, 76%). Hydrogenation (Pd-C, H_2, quant.) then gave 15 as the sole product and treatment with base (NaH, THF, 89%) gave the target fused-butyrolactone 16.

The crucial alkylation step was next addressed. Treatment of 16 with base and methyl iodide ($LiNTMS_2$, Et_2O, MeI, 90%) resulted in the exclusive formation of a new product which was assigned the structure 17. The structural assignment was based on n.m.r. data. The methylene group of the parent lactone 16 appeared as an ABX system with coupling constants of 17 (AB), 13 and 9Hz. Examination of molecular models indicated that H-3 and H-8′ were trans-diaxially orientated, implying that coupling between these protons would account for the larger coupling constant of 13 Hz. On methylation, the coupling pattern of the remaining proton at the acidic centre appeared as a doublet of quartets with a 13 Hz coupling between H-8′ and H-3. This result clearly demonstrated that the methyl group was on the exo-face of the molecule in accord with prediction.

The route described above to the lactone 16 allows the preparation of the target in good yield and by a short route. Protection of C-2 of 2 with the TBDPS group provides a valuable new method for the differentiation of the hydroxyl groups of 2, leading to a similar degree of differentiation to the stannylene method of Munavu and Szmant [4]. Two complimentary routes are now available for the preparation of olefins from 2 - one involving an unusual silyl migration giving a C-2 olefin exclusively, the other giving the C-3 olefin preferentially.



16



17

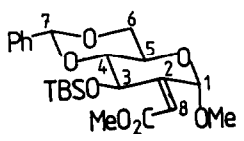
The authors thank Professor B.Fraser-Reid for helpful discussion and the University of Sheffield for a Postdoctoral Fellowship (to A.R.).

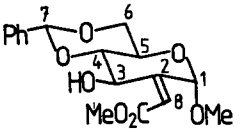
REFERENCES

[1] R.Tsang and B.Fraser-Reid, J.Am.Chem.Soc., 1986,108,8102.

[2] D.B.Tulshian, R.Tsang and B.Fraser-Reid, J.Org.Chem., 1984,49,2347.

[3] The structural assignment of the product from Wittig reaction of 6 and 7 is based on the high field n.m.r. of the product. The table below lists the n.m.r. data for compounds 10 and its desilylated derivative 18. The position of the double-bond at C-2 can be unequivocally assigned by the appearance of the coupling between H-3 and the OH group in compound 18, while the stereochemical assignment at C-3 is based on $J_{3,4}$ which indicates a trans-diaxial coupling between H-3 and H-4.





10					18				
δ	Mult.	Int.	J	Assign.	δ	Mult.	Int.	J	Assign.
7.50	m	2	-	aromatic	7.47	m	2	-	aromatic
7.35	m	3	-	aromatic	7.37	m	3	-	aromatic
6.38	s	1	-	H-7	6.11	t	1	2.0	H-8
6.20	d	1	2.0	H-8	5.55	s	1	-	H-7
5.51	s	1	-	H-1	4.85	d	1	4.0	H-1
4.69	dd	1	2.0,10.0	H-3	4.31	dd	1	4.0,9.0	H-6′
4.28	dd	1	5.0,10.0	H-6′	4.23	ddd	1	1.0,2.0,4.0	H-2
4.01	td	1	5.0,10.0	H-5	4.15	dd	1	2.0,9.0	H-4
3.73	s	3	-	COOMe	3.86	td	1	4.0,9.0	H-5
3.72	t	1	10.0,10.0	H-6	3.76	t	1	9.0	H-6
3.48	s	3	-	OMe	3.72	d	1	1.0	OH
3.45	t	1	10.0,10.0	H-4	3.47	s	3	-	COOMe
0.88	s	9	-	t-Bu	3.31	s	3	-	OMe
0.07	s	6	-	2 x MeSi					

[4] R.M.Munavu and H.H.Szmant, J.Org.Chem., 1976,41,1832.

(Received in UK 23 January 1987)