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STEREOSPECIFIC SYNTHESIS OF 5,6-DIHYDRO-2H-PYRAN SYSTEM. HIGH-PRESSURE CYCLOADDITION OF 1:2,3:4-DI-O-ISOPROPYLIDENE-α-D-GALACTOPYRANOSE-6-ULOSE TO 1-METHOXYBUTA-1,3-DIENE

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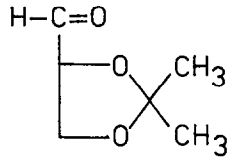
Summary: The high-pressure cycloaddition of 1:2,3:4-di-O-isopropylidene-α-D-galactopyranos-6-ulose (3) to 1-methoxybuta-1,3-diene (1) afforded diastereoisomerically pure cycloadduct 4 whose absolute configuration was determined.

A few years ago we described the high-pressure cycloaddition of some simple carbonyl compounds (e.g. acetaldehyde, benzaldehyde, methyl pyruvate, ω-trifluoroacetophenone) to 1-methoxybuta-1,3-diene (1).[1] This process gives an easy access to 6-substituted 2-methoxy--5,6-dihydro-2H-pyrans which are versatile synthons for the syntheses of sugars,[2] antibiotics,[3] and pheromones.[4] Very recently we have shown that application of 2,3-O-isopropylidene-D-glyceraldehyde (2), bearing a chiral centre located in the α-position with respect to the formyl group, in a high-pressure reaction with diene 1, afforded a diastereoisomeric mixture of the expected Diels-Alder adducts, with high asymmetric induction (40-74% diastereoisomeric excess).[5]



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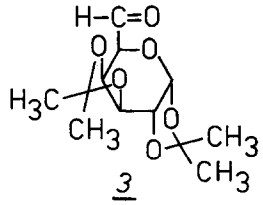

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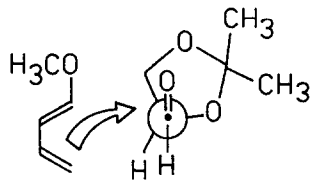
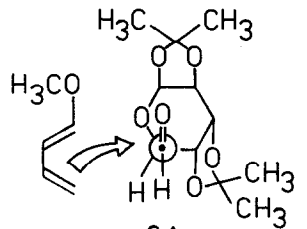


2A

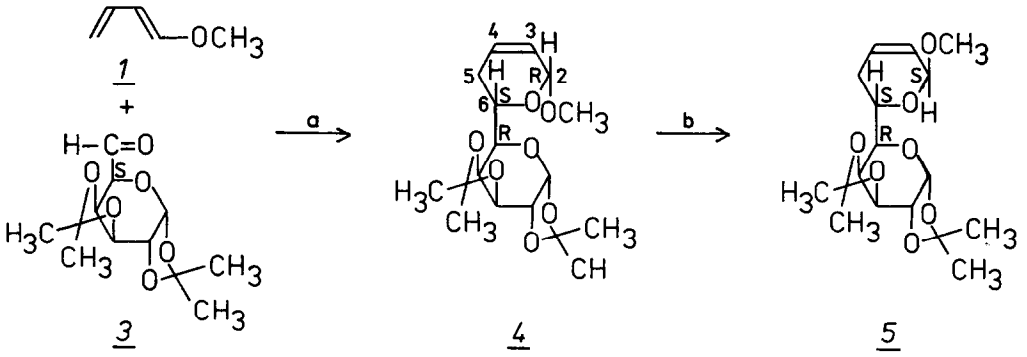


3A

Scheme 1. Comparison of the approaches of diene 1 to the less hindered faces of dienophiles 2A and 3A.

We expected that the use of an aldehyde with a steric hindrance exceeding that of 2, should lead in the high-pressure reaction with 1 to a better diastereoselectivity. For verification of this hypothesis we directed our attention to the easily accessible 1:2,3:4-di-O-isopropylidene-α-D-galactopyranos-6-ulose (3).[6] Analysis of Felkin's stereochemical models[7] of the reactions of 1 with 2 and 3, respectively, suggested that diastereoface differentation is much higher for the molecule of 3 than for 2 (Scheme I).

In practice, under high-pressure conditions[8] diene 1 reacted with aldehyde 3 to afford cycloadduct 4[9] with complete stereoselectivity, as shown in Scheme II.

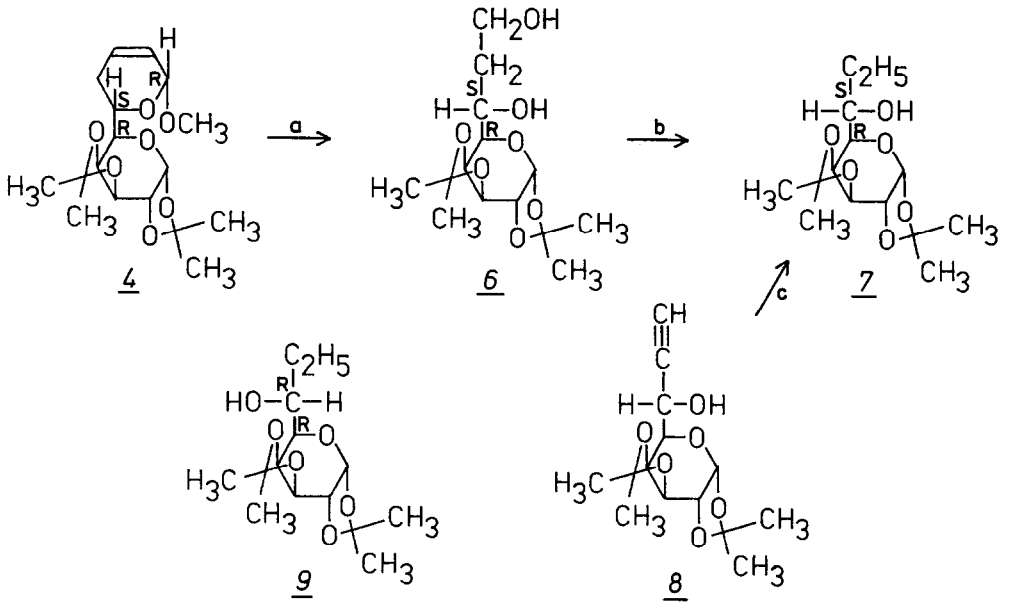


Scheme II. The high-pressure cycloaddition of 3 to 1:(a) 20kbar, 53°C, CH_2Cl_2, 20h, as well as isomerization of the resulting cis-adduct 4 to trans-5:(b) PPTS, acetone, RT, 24h

Analysis of ^{1}H NMR spectrum[10] shows that cycloadduct 4 exhibits the cis arrangement of the methoxy group with respect to the sugar moiety, as a result of endo-addition.[5] Isomerization of 4 to 5 with pyridinum p-toluenesulphonate (PPTS) in acetone, and comparison the ^{1}H NMR spectra[10] of the diastereoisomers, proved the stereochemical purity of the original adduct 4.[11] This fact was confirmed independently by ^{1}H NMR experiments with Eu(fod)$_3$;[12] no additional signals derived from other diastereoisomers were observed in the europium-shifted spectra of 4 and 5.

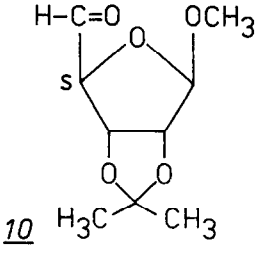
The absolute configuration of the chiral centre created at C-6 was established by the chemical correlation of 4 with compound 7 whose absolute configuration is known, since it has been obtained from D-galactose.[13] This correlation is represented in Scheme III.

Ozonolysis of 4, followed by ozonide degradation with dimethylsulphide, afforded the corresponding aldehyde which was reduced with lithiumaluminium hydride, whereupon the product was hydrolyzed to diol 6. Compound 6 was treated with p-toluenesulphonyl chloride, affording a mono-tosylate which was purified by chromatography, and then reduced with sodium borohydride in dimethylsulphoxide,[14] yielding compound 7. The specific rotation[15] of 7 was almost identical with that found for 7 obtained by hydrogenation of compound 8.[13]



Scheme III. Determination of absolute configuration of the chiral centre at C-5 of cycloadduct 4. Reagents and reaction conditions: (a) (i) O_3 (CH_2Cl_2), -78°C, 0.5h; (ii) Me_2S (CH_2Cl_2), -78°C→RT; (iii) $LiAlH_4$ (abs. ether), RT, 1h; (iv) PTSA (acetone-H_2O, 95:5v/v), reflux, 6h; (b) (i) TsCl, pyridine (CH_2Cl_2) RT, 20h; (ii) $NaBH_4$ (DMSO), 80°C, 6h; (c) H_2, 10% Pd-C (EtOH), 5h.

The high-pressure cycloadditions of two other sterically hindered sugar aldehydes, 10[6] and 11[16] to diene 1 afforded similar results; 100% asymmetric induction on the chiral centre was created at C-6 of the dihydropyran moiety.



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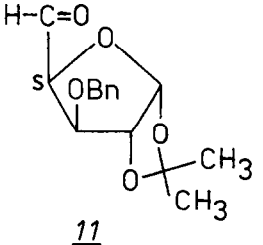

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The present results illustrate the usefulness of high-pressure techniques for solving stereochemical problems in organic synthesis. High-pressure conditions enable the title cycloaddition, which could not be performed under atmospheric pressure, to be carried out in high yield (70%). Moreover, this 100% asymmetric induction has never been achieved before in a non-catalyzed Diels-Alder reaction.

References and Notes

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8. For the high-pressure experiments we used the piston-cylinder type apparatus described earlier.[1]
9. Satisfactory analyses and spectral data were obtained for all new compounds.
10. ^{1}H NMR (360 MHz, $CDCl_3$):4, δ, 6.00(1H,m,H-4), 5.66(1H,m,H-3), 5.50(1H,d), 5.04 (1H,m,H-2), 4.60(1H,m), 4.49(1H,m), 4.04(1H,m,H-6), 3.84(1H,m), 4.29(1H,m),3.49 (3H,s,OCH_3), 2.30-2.14(m,2H,H-5,H-5'), 1.51,1.46,1.39,1.32ppm(12H,4s); 5, δ,6.04 (1H,m,H-4), 5.74(1H,m,H-3), 5.52(1H,d), 4.85(1H,m,H-2), 4.60(1H,m), 4.48(1H,m), 4.29(1H,m), 4.16(1H,m,H-6), 3.69(1H,m), 3.44(3H,s,OCH_3), 2.28(1H,m,H-5), 2.01 (1H,m,H-5') 1.53.1.44.1.34,1.33ppm(12H,4s).
11. The ^{1}H NMR spectra of diastereoisomers cis-4 and trans-5 exhibited differences in chemical shifts for all proton signals derived from the dihydropyran moiety. These differences are in good agreement with those observed for other pairs of cis- and trans-2,6-disubstituted-5,6-dihydro-2H-pyran derivatives; O.Achmatowicz, J.Jurczak, A.Konował and A. Zamojski, Org.Magn.Resonance, 2, 55 (1970); M.Chmielewski, J.Jurczak, A.Zamojski, and H.Achmatowicz, Ibid., 20, 249 (1982).
12. $CDCl_3$-solutions with complex/C substance values up to 0.4 were measured.
13. A.Gonzales, A.Llamas, and R.Mestres, Carbohydr.Res., 59, 598 (1977).
14. J.Thiem and B.Meyer, Chem.Ber., 113, 3067 (1980).
15. The specific rotation of 7 obtained in these studies was $[\alpha]_D$-53°(c1, $CHCl_3$), whereas that found by Gonzales et al.[13] was $[\alpha]_D$-50° (c1,$CHCl_3$). It is noteworthy that the specific rotation of diastereoisomer 9 with opposite configuration at C-6 was $[\alpha]_D$-81°(c1,$CHCl_3$).[13]
16. M.L.Wolfrom and S.Hanessian, J.Org.Chem., 27, 1800 (1962).

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