Straightforward Route to 2- and 3-Formyl Hex-1- and -2-enopyranosides and Their highly Stereoselective Hetero Diels–Alder Reaction with Ethyl Vinyl Ether

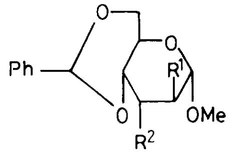
J. Cristobal Lopez,* Eric Lameignere, and Gabor Lukacs*

Institut de Chimie des Substances Naturelles du C.N.R.S., Avenue de la Terrase, B.P. No 1, 91190 Gif sur Yvette, France

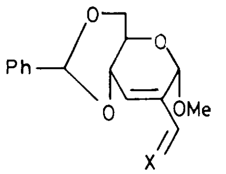
A straightforward route from D-glucose to conjugated enal and diene pyranoses through a dithiane-based methodology is disclosed; hetero Diels–Alder reaction of the enals with ethyl vinyl ether occurs with high stereoselectivity.

The use of carbohydrates as chiral building blocks is well recognized.[1,2] The incorporation of α,β-unsaturated carbonyl systems into carbohydrates has greatly extended the versatility of the sugar nuclei as stereochemical templates allowing cyclic transfer of chirality.[1] Alkyl hex-2-enopyranose-4-uloses, first described by Fraser-Reid[3] and exploited by his group,[4] provide examples in pyranoid units. Introduction of such a system in furanoid derivatives, the carbonyl unit being an aldehyde[5] or a lactone,[6] has also been described.

In this context, and in connection with an ongoing programme directed towards the synthesis of natural products from carbohydrates, we report here the preparation, *via* a

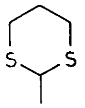


(**1**) R^1 = DT, R^2 = OH
(**2**) R^1 = DT, R^2 = OAc
(**3**) R^1 = OH, R^2 = DT
(**4**) R^1 = OMs, R^2 = DT

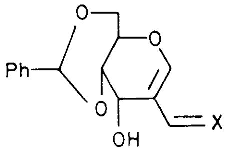


(**5**) X = O
(**8**) X = CH_2

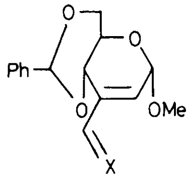
DT =



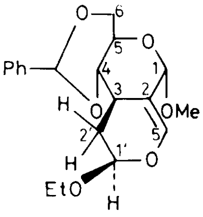
Ms = SO_2Me



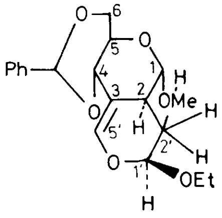
(**6**) X = O
(**9**) X = CH_2



(**7**) X = O
(**10**) X = CH_2



(**11**)



(**12**)

dithiane-based methodology, of pyranoid conjugated enal systems and their hetero Diels–Alder reaction with an enol ether. The potential of these conjugated enals for the construction of chiral bicyclic systems is also obvious from their straightforward transformation into the corresponding diene homologues, ready for Diels–Alder reaction with various dienophiles.†

When subjected to alkylative hydrolytic conditions [MeI, $CaCO_3$, $MeCN–H_2O$ (4:1)], methyl 4,6-*O*-benzylidene-2-deoxy-2-(1,3-dithian-2-yl)-α-D-altropyranoside (**1**),‡ readily available from D-glucose, afforded by a β-elimination process a mixture of unsaturated aldehydes (**5**) and (**6**) in 16 and 57% yield, respectively. In order to reverse the regioselectivity of the elimination, enhancement of the leaving group properties of the C-3 hydroxy group of (**1**) seemed advisable. When hydrolytic conditions [$HgO–HgCl_2$ (1:2), 1.2 equiv., $MeCN–H_2O$ (4:1), 80 °C for 2 h then 120 °C], were applied to the acetyl derivative (**2**),[7] aldehydes (**5**) and (**6**) were obtained in 66 and 11% yield, respectively. On the other hand, oxidative removal of the dithiane unit from (**1**) (cerium ammonium nitrate, 2 min, room temperature) furnished exclusively (**6**) (84%).§

Extension of the methodology to the mesylate (**4**), derived from (**3**), gave the unsaturated aldehyde (**7**) in 73% yield.

In the presence of methyltriphenylphosphonium bromide, transformation of the unsaturated aldehydes (**5**)—(**7**) into their diene homologues (**8**)—(**10**), respectively, proceeded smoothly in high yields.

The heterodienic system of unsaturated aldehydes (**5**) and (**7**) was expected to exhibit high Diels–Alder reactivity towards enol ethers. Using ethyl vinyl ether as the dienophile and $Eu(fod)_3$ (fod = 1,1,1,2,2,3,3-heptafluoro-7,7-dimethyloctane-4,6-dionato) as the catalyst,[8] (**5**) and (**7**) furnished (**11**) (77%) and (**12**) (71%), respectively, as almost exclusive isomers. The anomeric substituent in the newly formed dihydropyran ring of (**11**) and (**12**) adopts a pseudo-equatorial orientation as shown by the large coupling constants [(**11**) ^3J $H_{1',2'ax}$ 9 and (**12**) ^3J $H_{1',2'ax}$ 9 Hz]. Attack of the enol ether takes place in both cases from the β side, the products resulting from an *endo* approach. The stereostructure of the hetero Diels–Alder adduct (**11**) is based on the large triplet ^1H n.m.r. signal (^3J $H_{3,4}$ = $H_{4,5}$ 10 Hz) of *H*-4. The stereochemistry at C-2 of adduct (**12**) was determined from the sharp singlet anomeric proton signal of its acid-catalysed monocyclic degradation product; this will be reported in our full paper.

A recent elegant paper by Chapleur and Euvrard[9] reported a new strategy for the synthesis of multichiral arrays from α,β-unsaturated carbohydrate derived ketones. The unsaturated aldehydes reported in this communication represent another alternative for the construction of chiral bicyclic systems. Further study of these conjugated enal and diene systems including their Diels–Alder reactivity and the stereochemical course of the reaction is continuing.

J.C.L. thanks the Ministerio de Educacion y Ciencia, Spain, for a post-doctoral MEC-MRT fellowship.

Received, 2nd November 1987; Com. 1590

References

1 B. Fraser-Reid and R. C. Anderson, *Fortschr. Chem. Org. Naturst.*, 1980, **39**, 1.
2 S. Hannessian, 'Total Synthesis of Naturals Products. The Chiron Approach,' Pergamon Press, Oxford, 1983.
3 B. Fraser-Reid, A. McLean, and E. W. Usherwood, *J. Am. Chem. Soc.*, 1969, **91**, 5392.
4 B. Fraser-Reid, *Acc. Chem. Res.*, 1982, **104**, 367.
5 K. Mo Sun and B. Fraser-Reid, *Synthesis*, 1982, 29; *J. Am. Chem. Soc.*, 1982, **104**, 367; K. Mo Sun, R. M. Guiliano, and B. Fraser-Reid, *J. Org. Chem.*, 1985, **50**, 4774; A. Sundin, T. Frejt, and G. Magnusson, *Tetrahedron Lett.*, 1985, **26**, 5605; *J. Org. Chem.*, 1986, **51**, 3927.
6 K. L. Bhat, S. Y. Chen, and M. M. Jouillie, *Heterocycles*, 1985, **23**, 691.
7 A. M. Sepulchre, G. Lukacs, G. Vass, and S. D. Gero, *Angew. Chem., Int. Ed. Engl.*, 1972, **11**, 148.
8 M. Bednarski and S. Danishefsky, *J. Am. Chem. Soc.*, 1983, **105**, 3716.
9 Y. Chapleur and M. N. Euvrard, *J. Chem. Soc., Chem. Commun.*, 1987, 884.

---

† Access to dienes (**8**) and (**10**) *via* vinyl homologation of appropriate uloses and subsequent thionyl chloride mediated hydroxy elimination is complicated by the formation of mixtures of regioisomers and chlorinated products as will be reported elsewhere.

‡ Compound (**1**) was not previously described although its acetate was known;[7] nevertheless modification of the published procedure allows us to increase the yield of (**1**) and (**2**) up to 75% compared with the 30% yield previously reported.

Methyl 2,3-anhydro-4,6-*O*-benzylidene-α-D-allopyranoside was added as a solid to the stirred solution of the lithium salt of 1,3-dithiane (3 equiv.) in tetrahydrofuran at −48 °C (MeCN, dry ice). After 1 h the temperature was raised to −15 °C and maintained for two days with occasional shaking of the solution, followed by standard work-up and chromatography.

§ All new compounds gave satisfactory spectroscopic and analytical data.