Stereochemical Versatility in Synthesis of Substituted Cycloalkanes from Acyclic Unsaturated Sugars

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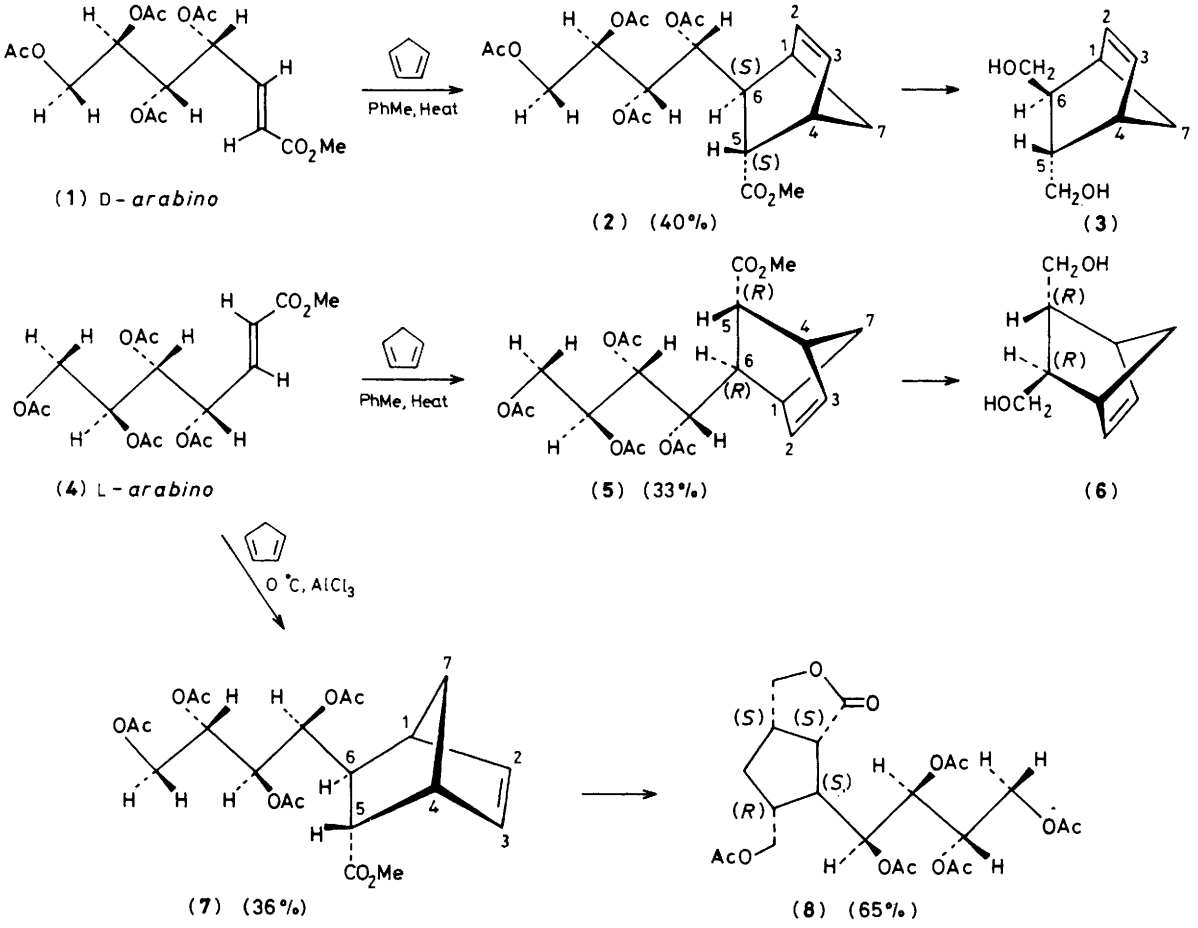
Acyclic unsaturated sugars obtained by Wittig extension of *aldehydo* arabinose precursors undergo stereoselective Diels–Alder addition of cyclopentadiene, permitting isolation of a single, crystalline, optically pure norbornene adduct whose stereochemistry may be controlled by the enantiomeric form of the sugar used and the conditions of the cycloaddition reaction.

This report consolidates and extends the scope of the reaction[1] between unsaturated acyclic sugar derivatives and cyclopentadiene to give crystalline, optically pure norbornene adducts that serve as precursors to chiral, tetra-*C*-substituted cyclopentanes of potential synthetic interest, especially for prostaglandin analogues.

Wittig addition of Ph_3PCHCO_2Me to *aldehydo*-D-arabinose tetra-acetate[2] gives an 87% yield of crystalline methyl (*E*)-4,5,6,7-tetra-*O*-acetyl-2,3-dideoxy-D-*arabino*-hept-2-enonate[3] (**1**), m.p. 116—117 °C, $[\alpha]_D$ +35° ($CHCl_3$), which reacted in boiling toluene with an excess of cyclopentadiene to give a mixture of adducts from which methyl (5*S*,6*S*)-6-*endo*-(1,2,3,4-tetra-*O*-acetyl-D-*arabino*-tetritol-1-yl)bicyclo[2.2.1]hept-2-ene-5-*exo*-carboxylate (**2**) was isolated crystalline in 40% yield, m.p. 103.5—104.5 °C, $[\alpha]_D$ +73° ($CHCl_3$). The n.m.r. spectrum of (**2**) established the ester group to be *exo*



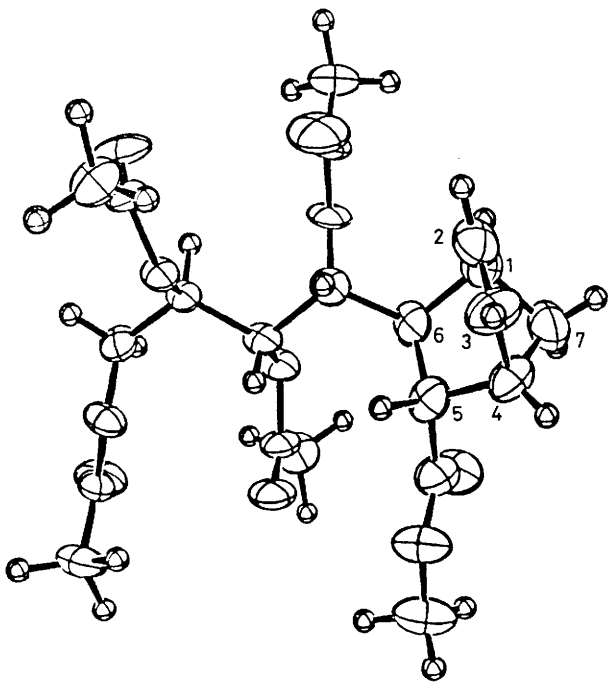


Figure 1. ORTEP view of the *X*-ray structure of adduct (**2**).

and the sugar chain *endo*, and the sequence *O*-deacetylation–periodate oxidation–$LiAlH_4$ reduction gave optically pure (5*S*,6*S*)-5,6-bis(hydroxymethyl)bicyclo[2.2.1]hept-2-ene (**3**), m.p. 39—40 °C, $[\alpha]_D$ −23° ($CHCl_3$). Reduction of (**3**) with H_2–Pt followed by toluene-*p*-sulphonylation gave the known,[4] optically pure (2*S*,3*S*)-2,3-bis(*p*-tolylsulphonyloxymethyl)-bicyclo[2.2.1]heptane, m.p. 99.5—100.5 °C, $[\alpha]_D$ +32.2° (Me_2CO) (lit.[4] m.p. 100—101 °C, $[\alpha]_D$ +32.5°). Independent verification of the relative stereochemistry was provided by *X*-ray structure analysis† of crystals of (**2**) obtained from ethanol. The absolute stereochemistry of (**2**) is thereby established as that in Figure 1 from the known D-*arabino* configuration of the sugar chain.

The foregoing sequence of reactions (**1**) → (**2**) → (**3**), performed with L-arabinose as the starting material, furnished the optically pure, crystalline enantiomers of (**1**)—(**3**), namely the L-*arabino* dienophile (**4**) (m.p. 116—117 °C, $[\alpha]_D$ −36°), the L-*arabino*-(5*R*,6*R*)-norbornene adduct (**5**) (m.p. 102—103.5 °C, $[\alpha]_D$ −72°), and the (5*R*,6*R*)-norbornenedimethanol

† The crystals were orthorhombic, space group $P2_12_12_1$, with a = 8.243(2), b = 9.896(6), c = 27.052(8) Å, at −57.2 °C. Data (5335 reflections) were collected at −81.1 °C with a Syntex *P*1 autodiffractometer in the ω–2θ mode with Mo-$K\alpha$ radiation. The structure was solved by direct methods (MULTAN 74) using a full data set with 3622 unique reflections. Final refinement by the CRYM program with anisotropic temperature factors for all non-hydrogen atoms yielded an *R* factor of 0.0725. The atomic co-ordinates for this work are available on request from the Director of the Cambridge Crystallographic Data Centre, University Chemical Laboratory, Lensfield Road, Cambridge CB2 1EW. Any request should be accompanied by the full literature citation for this communication.

(**6**) (m.p. 36—38 °C, $[\alpha]_D$ +23°).‡ Careful chromatography of the remaining products from the thermal Diels–Alder reaction with the dienophile (**4**) gave in smaller amounts the other three possible, isomeric adducts, including the (6*S*)-*exo*-sugar chain (5*S*)-*endo*-ester isomer (**7**), but not in preparatively useful yields. However, when the addition of cyclopentadiene to (**4**) was performed at 0 °C in the presence of $AlCl_3$ as catalyst, the ratio of the products was markedly altered and isomer (**7**) was isolated crystalline in 36% yield, m.p. 77—78 °C, $[\alpha]_D$ +55° ($CHCl_3$).

The foregoing results demonstrate that any one of the four possible stereoisomeric norbornene derivatives may be obtained, both crystalline and optically pure, as desired. Control is exercised by appropriate choice of the chirality of the starting sugar (both of the arabinoses are readily available at low cost) and conditions of the reaction (thermal without catalyst, or at low temperature with added Lewis acid). This reaction therefore offers potential scope, through selection of the accessible D or L, (*E*) or (*Z*) sugar dienophile and the appropriate cyclic diene, for useful general syntheses of carbocycles having four functional carbon side-chains of defined and controllable absolute stereochemistry.

Oxidative double-bond cleavage of the adduct (**7**) formed under Lewis acid catalysis, with osmium tetraoxide–sodium metaperiodate, followed by borohydride reduction and subsequent acetylation, gave 65% of the chiral, tetra-*C*-substituted cyclopentane derivative (**8**), m.p. 92—94 °C, $[\alpha]_D$ −14° ($CHCl_3$). This product has the same absolute stereochemistry as that in the carbocycle and side-chain of prostaglandin $F_{1\alpha}$ and may be considered a precursor to 9,11-bishomoprostaglandins.

‡ In the earlier report,[1] the names and structures given as L-*arabino* should be corrected to read D-*arabino*. The commercial L-arabinose used in that work was subsequently found to be the D-enantiomer. All stereochemical attributions for the carbocyclic products remain valid and the present independent correlations reaffirm the optical purity of the crystalline products.

It is unlikely that, even under the conditions of the uncatalysed Diels–Alder addition reported here, the reaction proceeds to equilibrium through repeated dissociation and recombination of addends. Adduct (**7**), obtained from the low-temperature, Lewis acid-catalysed reaction, was recovered unchanged after boiling for 36 h in toluene in the presence of a large excess of cyclopentadiene.

While these examples of cycloaddition to acyclic, unsaturated sugars, and parallel studies with fused-ring unsaturated sugars,[5] demonstrate evident practical utility and versatility, interpretation of the sense of asymmetric induction must still be approached with caution[6] until more is known about the conformation of the dienophile during the reaction, and the relative influence of the various functional groups in the vicinity of the reaction site.

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