Application of Ultrasound in Carbohydrate Chemistry. Synthesis of Optically Pure Functionalised Hexahydro-anthracenes and -naphthacenes

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Reactions of the carbohydrate enone (**5**) with the *o*-xylylenes derived from 1,2-bis(bromomethyl)benzene and 2,3-bis(bromomethyl)naphthalene by treatment with zinc powder under ultrasound irradiation gave the tri- and tetra-cyclic products (**6**) and (**7**), which were converted into the hexahydro-anthracene and -naphthacene derivatives (**18**) and (**19**) which are related to several important natural products; in particular, the latter compound has the carbon framework, A-ring functionality, and stereochemistry similar to those of some anthracyclinones.

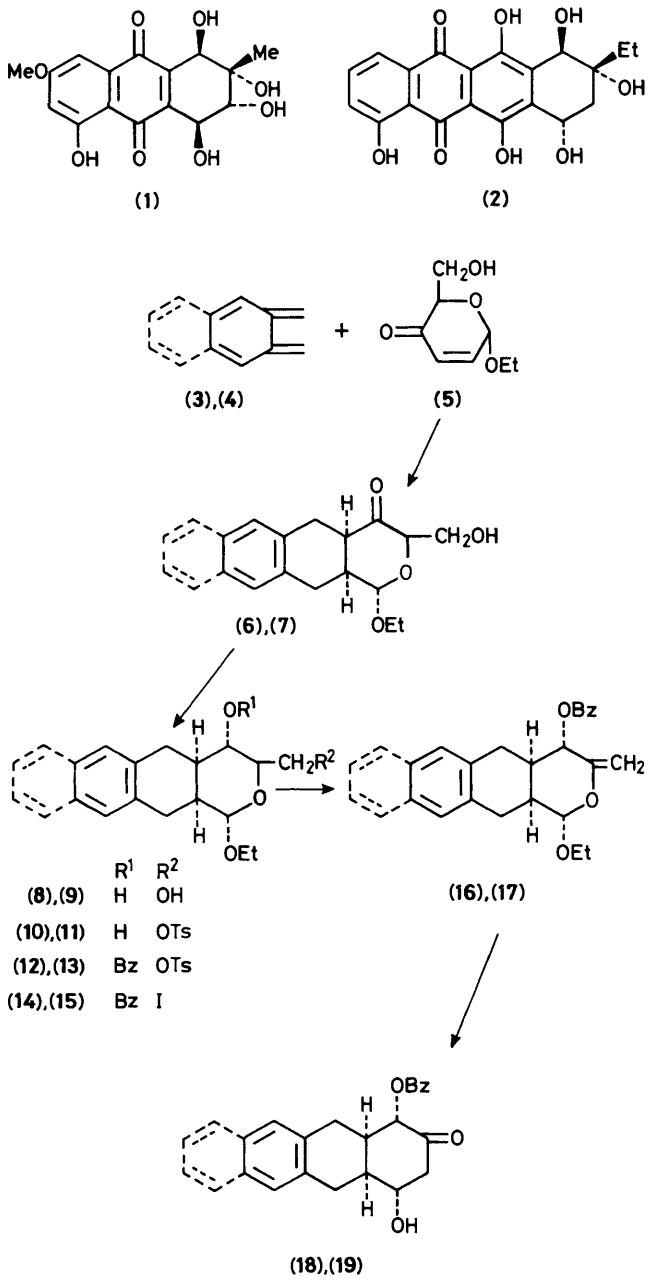
Recent interest in the annelation of sugar derivatives[1] and ours in the use of 6-deoxyhex-5-enopyranosyl compounds in the preparation of functionalised cyclohexanones[2] have led us to develop syntheses of compounds (**18**) and (**19**) which have carbon frameworks related to those of several polyketide-derived natural products. For example compound (**1**), altersolanol A, is a fungal metabolite,[3] and β-rhodomycinone, an anthracyclinone, has structure (**2**).[4] Our methods, being dependent on the initial use of D-glucose, afford the products in optically pure form. Previously, sugars have been used to afford functionalised, saturated A rings of anthracyclinone-like compounds by treating *leuco*-quinazarin with an *aldehydo*-carbohydrate derivative to introduce a chiral side chain which was ring closed.[5]

There are few reported examples of the application of the Diels–Alder reaction involving carbohydrate dienophiles which have electronically isolated or vinyl ether double bonds, an example being the thermal addition of cyanobenzocyclobutene to a glycal derivative.[6] Several examples, however, have utilised compounds in which the carbohydrate double bond is rendered electron-deficient by conjugation with electron-withdrawing groups; *e.g.* the addition of cyclopentadiene to a 5,6-dideoxy-6-nitrohex-5-enofuranose derivative[7] and to 2,3-dideoxyhept-2-enonate esters to give fused-ring products containing usefully functionalised cyclopentane systems.[8]

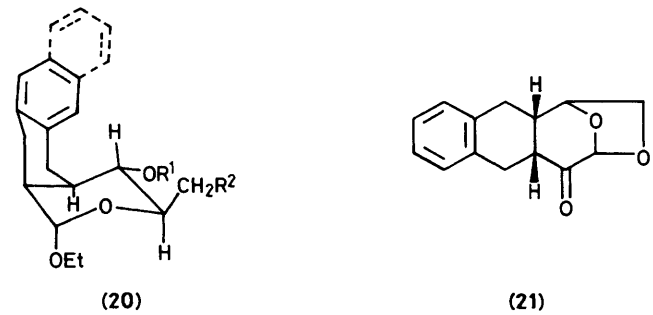
Cyclic carbohydrate enones are suitable dienophiles as is illustrated by the thermal cycloaddition of cyclopentadiene and 1,2,3,4-tetrachloro-5,5-dimethoxycyclopentadiene to 1,6-anhydro-3,4-dideoxy-β-D-*glycero*-hex-3-enopyranos-2-ulose (levoglucosenone),[9] and the reaction of butadiene with ethyl 6-*O*-acetyl-2,3-dideoxyhex-2-enopyranosid-4-ulose at low temperatures in the presence of aluminium chloride.[10] A closely related study reported the successful use of 1-(trimethylsilyloxy)butadiene and very similar hex-2-enopyranosid-4-uloses and the consequent production of 2,3-benzannelated hexopyranoside derivatives.[11]

With the objective of extending these methods to give products with three and four rings we have used the *o*-xylylenes (**3**) and (**4**), derived from 1,2-bis(bromomethyl)benzene and 2,3-bis(bromomethyl)naphthalene, together with the D-glucose-based enone (**5**)[10] to obtain the adducts (**6**) and (**7**) and have converted these into the anthracene and naphthacene derivatives (**18**) and (**19**) (Scheme 1).

o-Xylylene annelation of unsaturated carbohydrate compounds has been reported before,[6,12] but the reactive intermediates were produced from substituted benzocyclobutenes which necessarily restricts their use. In the present work the unsubstituted intermediates (**3**) and (**4**) were generated from the corresponding dibromides by treatment with zinc dust in an ultrasound bath[13] (50 kHz), and in the presence of the enone (**5**), gave the crystalline adducts (**6**) and (**7**) in 70 and 20—30% yield, respectively. Reductions of the carbonyl groups were effected with sodium borohydride in ethanol to give the diols (**8**) and (**9**) (62 and 65% yield) together with



Scheme 1. The dotted rings imply that the lower-numbered compounds did not have these rings whereas the higher-numbered compounds did have them.



their epimers. The main products were selectively tosylated at the primary positions to give compounds (**10**) and (**11**), were then benzoylated at the secondary centres to give the diesters (**12**) and (**13**), and the tosyloxy groups were displaced by treatment with sodium iodide in refluxing butanone. The iodides (**14**) and (**15**) gave the alkenes (**16**) and (**17**) on treatment with either 1,5-diazabicyclo[5.4.0]undec-5-ene in *N,N*-dimethylformamide or with silver fluoride in pyridine, and the alkenes were converted into the cyclohexanones (**18**) and (**19**) by heating with mercury(II) acetate in aqueous acetone as previously reported.[2] Compound (**18**) had m.p. 194 °C, $[\alpha]_D$ −143° ($CHCl_3$); compound (**19**) had m.p. 215 °C, $[\alpha]_D$ −152° (Me_2CO).

The ring protons at the new secondary positions of compounds (**8**)—(**15**) all resonated as broad triplets (*J ca.* 10 Hz), indicating their *trans*-axial relationship with the protons on the neighbouring carbon atoms, which permits the conclusions that the initial cycloaddition reactions occurred from the β-face of the dienophile as expected from previously reported results,[10,11] and that reduction of the carbonyl groups also took place by preferential borohydride attack from this face. Card[11] reported analogous reduction of related bicyclic ketones, but Primeau *et al.*[10] concluded that preferential attack occurred from the α-side of their ketone on the basis of narrow ^1H resonances for the new ring proton. Compounds (**8**)—(**15**) are therefore assumed to adopt the conformation (**20**) and, in keeping with this, the acetal ring protons resonated as broadened singlets ($w_{\frac{1}{2}}$ 4 Hz). On the basis of the broad doublets (*J* 11 Hz) observed for the ester ring protons of the cyclohexanones (**18**) and (**19**), these compounds are taken to assume analogous conformations, and the width of the alcohol ring proton signals ($w_{\frac{1}{2}}$ 9 Hz) of these compounds leads to the conclusion that the stereochemistry at the new asymmetric centres is *S* as illustrated.

Treatment of levoglucosenone with *o*-xylylene as described above gave the crystalline adduct (**21**) in 53% yield.

All compounds gave correct analytical data and appropriate ^1H and ^{13}C n.m.r. spectra.

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