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Preliminary communication

Regiospecific and asymmetric introduction of functionalized branching in carbohydrates*

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Because of their polyfunctional nature, carbohydrates may be considered as versatile substrates for the development of new synthetic routes that would be of general applicability in organic chemistry. Whereas the introduction of groups containing hetero-atoms (such as OR, NR, and SR groups) into carbohydrate derivatives has been an area of continued interest over the years, considerably less work has been done in developing practical and innovative routes to branched-chain sugars in which functionalized C–C linkages are involved. In this Communication, we describe two routes for the regiospecific formation of such linkages, and demonstrate the possibility of chiral control in some of these reactions.

Reaction of methyl 2,3-anhydro-β-D-ribofuranoside[2] (1) (see Scheme 1) with four equivalents of diethyl sodiomalonate in boiling benzene for 24 h under reflux, followed by conventional processing and distillation of the excess of diethyl malonate, gave a syrup that crystallized from ether–isopropyl ether to give the lactone 2, m.p. 57–59° (39%). Chromatography of the mother liquors on silica gel afforded additional material; total yield 65%. Recrystallization from the same solvent mixture gave an analytical sample** of 2, m.p. 62–63°; $[\alpha]_D^{25}$ -64.3° (*c* 2.9, chloroform).

Three treatments of a solution of 2 in tetrahydrofuran with triethylamine and deuterium oxide resulted in almost complete exchange of the one-proton doublet at 3.83 p.p.m. (H_m, $J_{m,3}$ 6.25 Hz)*** and the two-proton, broad singlet at 3.41 p.p.m. ($-COCH_2CO$) corresponding to the malonic ester protons of the lactone and mixed ester

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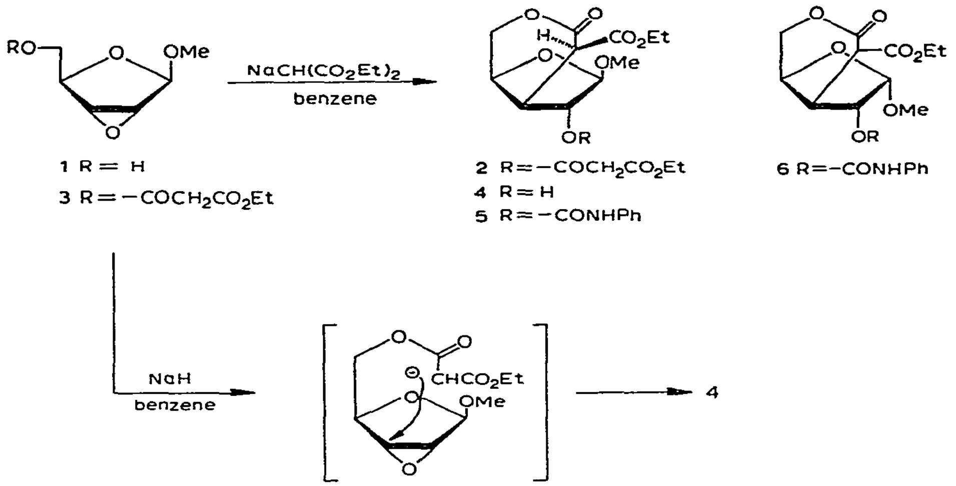
*Part of a series on preparative and exploratory carbohydrate chemistry. For related reactions, see ref. 1.

**Melting points are uncorrected. Crystalline compounds gave correct microanalyses and spectral data that were in accord with their structures. N.m.r. spectra were recorded with a Jeol 100-MHz spectrometer, and mass spectra with an MS-902 high-resolution spectrometer. Optical rotations were measured with a Model 141 Perkin–Elmer, photoelectric polarimeter.

***The subscript m refers to the malonic ester proton(s), $-COCH_2CO$.



Scheme 1

group, respectively. In addition, the quartet due to H-3 at 3.20 p.p.m. ($J_{m,3}$ 6.25 Hz; $J_{3,4}$ 7.8 Hz) was now simplified to a doublet centered at 3.20 p.p.m. ($J_{3,4}$ 7.8 Hz). Treatment of the deuterated product with triethylamine in water–tetrahydrofuran regenerated 2. Thus, the initial condensation and cyclization to give 2, and subsequent carbanion formation and reprotonation, occur with chiral control, to give, presumably, the thermodynamically more stable isomer.

A noteworthy innovation in this area of regiospecific, C–C bond formation is the demonstration of an intramolecular attack of the carbanion (formed from a malonic half-ester situated at a suitable site in the molecule) upon a leaving group, such as an epoxide grouping in the same molecule. Treatment of the mixed ester derivative 3 (from 1 and the ethyl ester of malonyl monochloride) in benzene with 6 equivalents of sodium hydride under reflux for 20 h in a nitrogen atmosphere, followed by chromatographic purification of the product on silica gel, gave the lactone ester derivative 4 as a syrup in 60% yield; ν 1731 (C=O) and 3460 cm^{-1} (OH); n.m.r. data: 3.03 p.p.m. (H-3, $J_{m,3}$ 7.07 Hz, $J_{3,4}$ 7.8 Hz); $M^{\ddagger}$ 260.0836. Compound 4 could be obtained from 2 by treatment with sodium ethoxide, thus establishing the configurational and structural relationship between 2 and 4. A crystalline phenylurethan derivative (5) was obtained in the usual way; m.p. 136.5–137°, $[\alpha]_D^{25}$ +37.27° (*c* 2.62, chloroform). These reactions were also applicable to the α anomer of 1, and a crystalline phenylurethan derivative (6), m.p. 144–146° (corresponding to 5 in the β series) was obtained.

In our second approach to chain-branching, we demonstrated the utility of episulfonium ions in conformationally rigid molecules* as immediate precursors to branched-chain sugars. The formation of C–C bonds by a nucleophilic attack of carbanions on episulfonium ions has not, to the best of our knowledge, been reported in the literature. The following are pertinent examples. Treatment of the readily available, thio sugar

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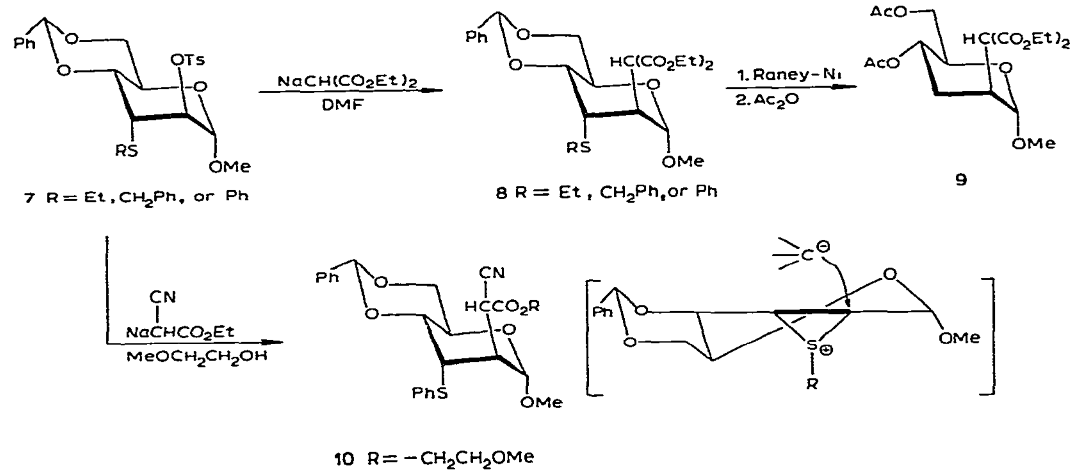
*Evidence accumulated indicated similar application to nonrigid systems, resulting in the formation of isomeric, branched-chain, thioether derivatives.

derivative 7 (R = Et) with diethyl sodiomalonate in *N*,*N*-dimethylformamide under reflux for 1.5 h afforded a 60% yield of the crystalline 2-*C*-ethyl malonyl derivative 8 (R = Et), m.p. 129.5–130.5°; $[\alpha]_D^{25}$ +24.6° (*c* 1.70, chloroform); ν 1740 and 1735 cm^{-1} (C=O).



Scheme 2

Reductive desulfurization and simultaneous removal of the benzylidene group with Raney nickel in boiling ethanol under reflux for 2.5 h, followed by acetylation and chromatographic purification, gave the 2,3-dideoxy-2-*C*-ethyl malonyl derivative 9 as a syrup in 52% overall yield; $[\alpha]_D^{25}$ +82.4° (*c* 9.5, chloroform); n.m.r. data: 3.58 p.p.m. (H_m, d, $J_{m,2}$ 11 Hz), 2.58 p.p.m. (H_2, m)*; *m/e* 373 (M–OMe); 359 (M–OEt). The overall process leads to a regiospecific branching, according to the established rules of analogous, ring-opening reactions as depicted in Scheme 2, and extends the synthetic application of the reaction with the option of reductive desulfurization. Application of the reaction to the *S*-benzyl (7, R = CH_2Ph) and *S*-phenyl (7, R = Ph)[3] derivatives in *N*,*N*-dimethylformamide under reflux gave the branched-chain sugars 8 (R = CH_2Ph), m.p. 151–152° (70%); $[\alpha]_D^{25}$ -87.6° (*c* 3.75, chloroform) and 8 (R = Ph), m.p. 153–154° (30%); $[\alpha]_D^{25}$ +7.5° (*c* 2.25, chloroform), respectively. The possibility of using other carbanions of functional utility was demonstrated in the case of the phenylthio derivative 7 (R = Ph). Treatment with ethyl sodiocyanoacetate in methylCellosolve under reflux for 1 h gave the crystalline derivative **10**, m.p. 131–133°; $[\alpha]_D^{25}$ +6.7° (*c* 2.20, chloroform), in which the ethyl group was interchanged with the solvent**.

These reactions illustrate numerous possibilities for the systematic and regiospecific introduction of *C*-substituents in polyfunctional compounds. The wealth of chemistry reported for malonic esters (and related derivatives containing active hydrogen atoms) broadens the scope of these reactions in the carbohydrate series. Branched-chain

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* Assignments were confirmed by decoupling experiments.

This interchange is of no synthetic consequence, as the R portion in **10 can be varied at will.

sugars of the types illustrated in this work could be used, after appropriate transformations, as models for establishing configurational identity of chiral *C*-branch points in other, more-complex organic molecules*.

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* For an interesting illustration of this type of application in the determination of absolute configuration in the antimycin series, see ref. 4.