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NEIGHBORING-GROUP PARTICIPATION IN CARBOHYDRATES: THE (METHYLTHIO)CARBONYL NEIGHBORING GROUP

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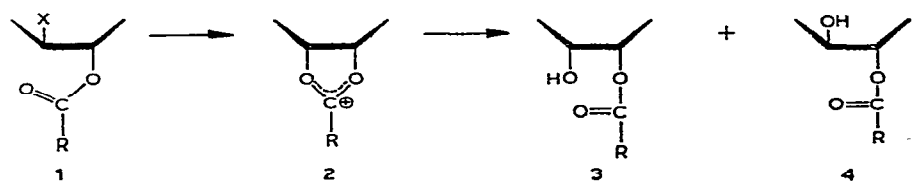
ABSTRACT

The use is described of the (methylthio)carbonyl group as a means of preparing carbohydrates having *cis*-oriented functional groups, by way of stable, intermediate, cyclic carbonates. By this route, methyl 2-*O*-*p*-tolylsulfonyl-α-D-arabinopyranoside was prepared from methyl α-D-lyxopyranoside. Methyl α-D-lyxofuranoside was prepared from methyl 5-*O*-acetyl-3-bromo-3-deoxy-α-D-arabinofuranoside.

RESULTS AND DISCUSSION

The use of neighboring-group participation for effecting a controlled inversion at specific asymmetric centers has been of great utility for the preparation of new sugars. A recent review[1] by Goodman gives a comprehensive survey of the role of participation reactions in sugars. The majority of these reactions proceed *via* a transitory, orthoester ion, such as **2**, which is opened to give either *cis* (**3**) or *trans* (**4**) bifunctional products as the end product.

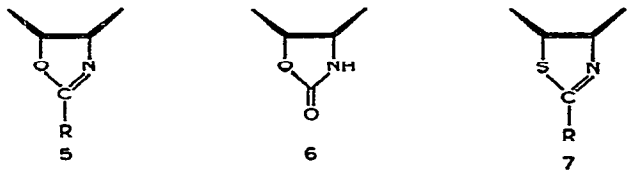


1 2 3 4

The relative proportions of *cis* and *trans* products are dependent on the reaction conditions[2]. A recent report[3] on the synthesis of 9-β-D-lyxofuranosyladenine, corresponding to **3** from a derivative of 9-β-D-xylofuranosyladenine, corresponding to **1**, described the conditions necessary for obtaining the maximum ratio of *cis* to *trans* products. In this example, as in the majority of others involving *O*-acyl participation through an orthoester ion, the ultimate product consisted of a mixture of *cis* and *trans* compounds, their ratio depending on the reagents and starting materials employed. The separation of the pure product can be a tedious operation[3].

More specific are neighboring-group reactions in amino sugar chemistry; they

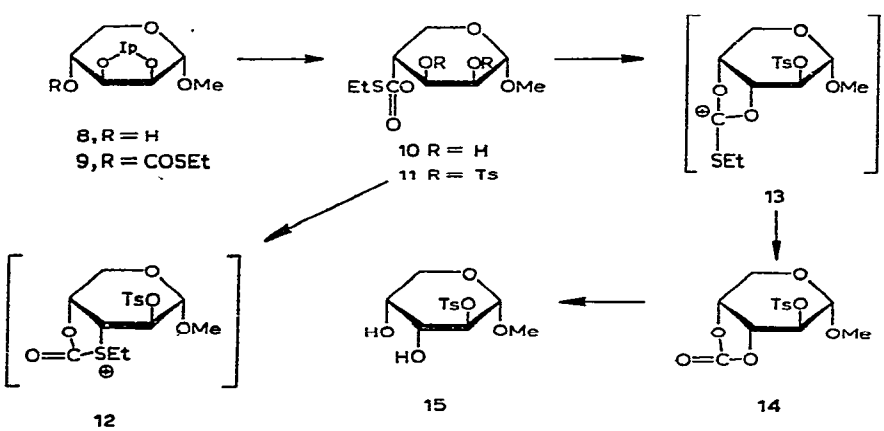
give relatively stable, *uncharged*, cyclic intermediates (such as 5–7), that may[4] or may not[5] be hydrolyzed under the conditions of the reaction.



5 6 7

As far as nitrogen-free carbohydrates are concerned, apparently no example has been reported of the use of a carbonate participating group, although the latter should react in a similar way, to give a cyclic carbonate. Saponification would result in a *cis* product. The use of an *S*-alkyl thiocarbonate, such as **10**, would give the added possibility that participation could occur through sulfur, and thus serve as a convenient method for the introduction of sulfur into the sugar molecule. An investigation of the use of the *S*-ethylthiocarbonate in this reaction is described in this paper.

Treatment of methyl 2,3-*O*-isopropylidene-α-D-lyxopyranoside[6] (**8**) with *S*-ethyl chlorothioformate gave methyl 4-*O*-(ethylthio)carbonyl-2,3-*O*-isopropylidene-α-D-lyxopyranoside (**9**) as a distillable oil. Deacetonation of **9** with aqueous acetic acid gave crystalline methyl 4-*O*-(ethylthio)carbonyl-α-D-lyxopyranoside (**10**). Esterification of **10** with *p*-toluenesulfonyl chloride gave a good yield of crystalline methyl 4-*O*-(ethylthio)carbonyl-2,3-di-*O*-*p*-tolylsulfonyl-α-D-lyxopyranoside (**11**), the starting material desired for the participation reaction.



8, R = H
9, R = COSEt

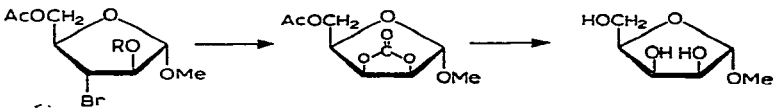
10 R = H
11 R = Ts

12 13 14 15

Treatment of **11** with sodium fluoride in anhydrous *N*,*N*-dimethylformamide for 3 days at 140° gave a semicrystalline solid, from which crystalline methyl 2-*O*-*p*-tolylsulfonyl-α-D-arabinopyranoside 3,4-cyclic carbonate (**14**) was readily isolated. There was no evidence for any products that might have arisen from participation by sulfur; however, the yield of crude product was quite low, so the possibility that participation by sulfur occurred, by way of **12**, to give water-soluble products has not yet been eliminated.

Deacetylation of **14** gave crystalline methyl 2-*O*-*p*-tolylsulfonyl-α-D-arabinopyranoside (**15**), having identical properties (except for the optical rotation, which was equal but opposite) with those reported for methyl 2-*O*-*p*-tolylsulfonyl-α-L-arabinopyranoside[7].

A similar participation-reaction was demonstrated in the furanose series, although the reaction appeared to be slower. Methyl 5-*O*-acetyl-3-bromo-3-deoxy-α-D-arabinofuranoside[8] (**16**) was acylated with *S*-ethyl chlorothioformate in pyridine, to give methyl 5-*O*-acetyl-3-bromo-3-deoxy-2-*O*-(ethylthio)carbonyl-α-D-arabinofuranoside (**17**) as an analytically pure oil. Treatment of **17** with sodium fluoride in dry *N*,*N*-dimethylformamide for 7 days at 150° gave an oil that contained approximately equal amounts of starting material (**17**) and product (**18**), as estimated by the relative intensities of the carbonyl absorption in the i.r. spectrum. The separation of unreacted **17** from methyl 5-*O*-acetyl-α-D-lyxofuranoside 2,3-cyclic carbonate (**18**)



16 , R = H
17 , R = COSEt

18

19

was accomplished by means of thick-layer chromatography on silica gel. Deacylation of **18** with methanolic sodium methoxide gave methyl α-D-lyxofuranoside (**19**), having physical properties in good agreement with those reported[9]. As in the case of the pyranoside **11**, no products that could have arisen by participation of sulfur were isolated.

The use of the acyclic carbonic ester as a source of anchimeric assistance for the preparation of *cis* derivatives of sugars should be useful, especially in such syntheses as that of lyxofuranosyladenine, where the normal, orthoester-ion intermediate gives mixtures of *cis* and *trans* products that are difficult to separate.

EXPERIMENTAL

General methods. — Melting points are corrected. Thin-layer chromatograms were performed on Silica Gel HF (E. Merck AG, Darmstadt). The solvents used were: *A*, 9:1 benzene–ethyl acetate; *B*, 1:3 cyclohexane–ethyl ether. Spots were detected with iodine vapor. Solutions in organic solvents were dried with anhydrous magnesium sulfate.

Methyl 4-O-(ethylthio)carbonyl-2,3-O-isopropylidene-α-D-lyxopyranoside (**9**). — A solution of 5.0 g (23.3 mmoles) of methyl 2,3-*O*-isopropylidene-α-D-lyxopyranoside[6] (**8**) in 100 ml of dry pyridine was cooled to 0° under nitrogen, and 10.0 ml (105 mmoles) of *S*-ethyl chlorothioformate was added dropwise, with stirring and continued cooling. After the addition was complete, the mixture was stirred for 18 h at room temperature.

The solution was cooled in an ice bath, and the excess of reagent was decom-

posed by the addition of 10 drops of water. The mixture was partitioned between ether (50 ml) and saturated aqueous sodium hydrogen carbonate (50 ml). The ether layer was washed with water, dried, and evaporated to dryness to give 7.38 g of crude product as an oil. Purification by distillation gave 4.7 g (65%) of **9**, b.p. 140°/0.08 torr; λ_{max}^{film} 5.78 (C=O), 8.70 μm (C–O–C).

Anal. Calc. for $C_{12}H_{20}O_6S$: C, 49.4; H, 6.85; S, 11.0. Found: C, 49.7; H, 6.90; S, 11.3.

Methyl 4-O-(ethylthio)carbonyl-α-D-lyxopyranoside (**10**). — A suspension of 4.5 g (15.4 mmoles) of **9** in 70 ml of 60% aqueous acetic acid was heated with stirring for 3 h at 70–75°, by which time, dissolution was complete. The solution was evaporated to dryness *in vacuo*, and the last traces of acetic acid were removed by the addition and evaporation of toluene (10 ml), to leave 3.59 g of crude **10** as a colorless solid, m.p. 112–123°, which was satisfactory for the next step.

An analytical sample of **10**, prepared by recrystallization from benzene, had m.p. 128.5–129.0°; $[\alpha]_D^{22}$ +17° (*c* 1, methanol); λ_{max}^{Nujol} 2.90 (OH) 5.78 (C=O), 8.60 μm (C–O–C).

Anal. Calc. for $C_9H_{16}O_6S$: C, 42.9; H, 6.40; S, 12.7. Found: C, 43.2; H, 6.35; S, 13.0.

Methyl 4-O-(ethylthio)carbonyl-2,3-di-O-p-tolylsulfonyl-α-D-lyxopyranoside (**11**). — A solution of 2.88 g (11.4 mmoles) of **10** in 50 ml of dry pyridine was cooled to 0° under nitrogen, and 10.9 g (57.2 mmoles) of *p*-toluenesulfonyl chloride was added, with stirring and continued cooling. After ~0.5 h at 0°, the mixture was stirred for 18 h at room temperature. The excess of *p*-toluenesulfonyl chloride was decomposed by the addition of a small amount of ice, and the mixture was partitioned between chloroform (30 ml) and water (30 ml). The chloroform layer was washed successively with saturated aqueous sodium hydrogen carbonate, and water, dried, and evaporated to dryness *in vacuo*, to give 6.55 g of crude product as an oil. Trituration of the oil with methanol gave 5.15 g (81%) of crystals, m.p. 91–94°.

An analytical sample was obtained by recrystallization from methanol, and had m.p. 93.5–95.5°; λ_{max}^{Nujol} 5.75 (C=O); 8.31, 8.45 (SO_2), and 8.75 μm (C–O–C).

Anal. Calc. for $C_{23}H_{28}O_{10}S_3$: C, 49.4; H, 5.04; S, 17.2. Found: C, 49.5; H, 5.02; S, 17.3.

Methyl 2-O-p-tolylsulfonyl-α-D-arabinopyranoside 3,4-cyclic carbonate (**14**). — A suspension of 1.9 g of dry sodium fluoride and 2.0 g (3.6 mmoles) of **11** in 120 ml of dry *N,N*-dimethylformamide was heated for 72 h at 145°, with stirring under nitrogen. The mixture was cooled, water (1 ml) was added, and the mixture was stirred for 2–3 h and evaporated to dryness *in vacuo*. The residue was partitioned between ether (30 ml) and water (30 ml). The ether layer was successively washed with saturated aqueous sodium hydrogen carbonate and water, and dried. The solution was evaporated to dryness *in vacuo*, to give 0.77 g (62%) of crude product as a semicrystalline solid which, on trituration with methanol gave 0.25 g of crystals, m.p. 109.5–111.5°. T.l.c. of the mother liquors with solvent *A* showed them mainly to contain **14** (R_F 0.3), together with several trace components.

An analytical sample was obtained by recrystallization from methanol, and had m.p. 113.5–115.0°; λ_{max}^{Nujol} 5.45 (cyclic carbonate C=O) and 8.45 μm (SO_2^-).

Anal. Calc. for $C_{14}H_{16}O_8S$: C, 48.9; H, 4.66; S, 9.30. Found: C, 49.3; H, 4.59; S, 9.58.

Methyl 2-O-p-tolylsulfonyl-α-D-arabinopyranoside (**15**). — A solution of 100 mg (0.29 mmoles) of **14** in 2 ml of 10 mM methanolic sodium methoxide was stirred for 2 h at room temperature and then the base was neutralized with Dowex-50 (H^+) ion-exchange resin. The resin was filtered off, and the filtrate was evaporated to dryness *in vacuo*, to give 80 mg of product as a colorless solid which was partitioned between chloroform and water. The chloroform layer was dried, and evaporated to dryness in *vacuo* to give 75 mg of an oil that crystallized when triturated with ether; it had m.p. 131.5–132.5°; $[\alpha]_D^{24}$ +17° (*c* 1.0, chloroform); λ_{max}^{Nujol} 2.90, 2.98 (OH) 7.30–7.45 μm (OSO_2^-).

Mukherjee and Todd[7] reported m.p. 129–130°, $[\alpha]_D$ −15° (*c* 4.88, chloroform) for methyl 2-*O*-*p*-tolylsulfonyl-α-L-arabinopyranoside.

Methyl 5-O-acetyl-3-bromo-3-deoxy-2-O-(ethylthio)carbonyl-α-D-arabinofuranoside (**17**). — A solution of 2.0 g (7.4 mmoles) of methyl 5-*O*-acetyl-3-bromo-3-deoxy-α-D-arabinofuranoside[8] (**16**) in 25 ml of dry pyridine was cooled to 0° under nitrogen, and 2.4 ml (25 mmoles) of *S*-ethyl chlorothioformate was added dropwise, with stirring. After the addition was complete, the reaction was kept overnight at room temperature.

The excess of acid chloride was decomposed by adding ~1 g of ice and stirring for 1 h. The mixture was partitioned between ether (25 ml) and water (25 ml). The ether layer was successively washed with saturated, aqueous sodium hydrogen carbonate and water, dried, and evaporated to dryness *in vacuo*, to give 2.9 g of product as an oil. A small amount of inorganic material was removed by treating the product with methanol, and filtering to remove an insoluble precipitate. The filtrate was evaporated to dryness *in vacuo*, and dried at 0.1 torr for 24 h, to give 2.85 g of material having $[\alpha]_D^{21}$ +44° (*c* 1.0, chloroform); λ_{max}^{film} 5.75, 5.88 (C=O); 8.15 (acetate C–O–C), and 8.85 μm (thiocarbonate C–O–C).

Anal. Calc. for $C_{11}H_{17}BrO_6S$: C, 37.0; H, 4.80; S, 8.98; Br, 22.4. Found: C, 37.3; H, 4.80; S, 8.79; Br, 22.3.

Methyl 5-O-acetyl-α-D-lyxofuranoside 2,3-cyclic carbonate (**18**). — A mixture of 2.0 g (5.6 mmoles) of **17** and 2.4 g of sodium fluoride in 200 ml of dry *N*,*N*-dimethylformamide was heated for 7 days at 150°, with stirring under nitrogen. The mixture was cooled to room temperature, 1 ml of water was added, and the mixture was stirred for 4 h and then evaporated to dryness *in vacuo*.

The residue was partitioned between ether and water. The ether layer was successively washed with saturated, aqueous sodium hydrogen carbonate and water, dried, and evaporated to dryness *in vacuo*, to give 1.24 g of an oily residue. T.l.c. (solvent *B*) showed major spots at R_F 0.22 (assigned to the product, **24**) and R_F 0.82 assigned to **17**, together with trace components having R_F values of 0.65 and 0.10.

The pure product was isolated by thick-layer chromatography with solvent *B*,

to give 0.3 g of **18** as an oil, λ_{max}^{film} 5.50, 5.71 (C=O) 8.10 (acetate C–O–C), and 8.60 μm (cyclic carbonate C–O–C).

Anal. Calc. for $C_9H_{12}O_7$: C, 46.6; H, 5.21. Found: C, 46.9; H, 5.43.

Methyl α-D-lyxofuranoside (**19**). — A solution of 100 mg of **18** in 4 ml of 10 mM methanolic sodium methoxide was stirred under nitrogen for 18 h at room temperature neutralized to pH 7 with Dowex-50 (H^+) ion-exchange resin, and filtered through a Celite pad. The filtrate was evaporated to dryness *in vacuo*, to give 71 mg of product as an oil. Crystallization was effected by trituration with ether. Recrystallization from ethyl acetate gave methyl α-D-lyxofuranoside (**19**) as colorless crystals, m.p. 97.5–98.5°; $[\alpha]_D^{22}$ +128° (*c* 1, methanol); lit.[9] m.p. 96.5–97°; $[\alpha]_D$ +128° (water).

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