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An alternative synthesis of methyl 2,3-anhydro-4,6-*O*-benzylidene-α-D-allopyranoside using carbonate esters

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ABSTRACT

New simple routes to the title epoxide, using carbonate esters of methyl 4,6-*O*-benzylidene-α-D-glucopyranoside, are described. Some mechanistic aspects of the reactions are discussed.

INTRODUCTION

Sugar epoxides (oxiranes) are of considerable practical importance[1–4]. They are usually prepared from sulfonic esters, with unsubstituted or esterified vicinal hydroxyl groups, by treatment with alkali. Methanesulfonic or toluene-*p*-sulfonic esters are commonly employed. Nitric esters behave similarly but are preparatively unattractive. The mechanism and stereochemistry of this process has been discussed comprehensively[3,4].

Alternative syntheses of limited application include treatment of deoxyhalo sugars with alkali[3,4], nitrous acid deamination of amino sugars[3,4], the treatment of certain diols with triphenylphosphine/diethyl azodicarboxylate (DEAD)[5], the reaction of unsaturated derivatives with peroxy acids or hydrogen peroxide[3,4], and the treatment of some *cis*-diols with Viehe's salt[6].

The chemistry of sugar oxiranes has been reviewed[1,2,4].

An efficient alternative synthesis of the anhydro-alloside derivative **1** resulted during recent attempts to prepare the cyclic carbonate **2** from the glucoside **3**, by base-catalysed ester-exchange with diethyl carbonate. Details of this study and some associated aspects are reported.

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RESULTS AND DISCUSSION

Several examples of the formation of cyclic carbonate esters from carbohydrate derivatives by transesterification with simple carbonate esters[7–11] have been described. A trace of alkaline catalyst is necessary in most cases. The exchange probably proceeds[9] in two stages involving a mono-ester intermediate.

Treatment of the glucoside **3** in boiling diethyl carbonate containing a catalytic amount of potassium carbonate yielded only the di-ester **4** (99%). When a solution of **4** in bis(2-methoxyethyl) ether containing potassium carbonate (10 mol%) was heated at 140°C for 48 h in the presence of a trace of tetrabutylammonium bromide, analysis (GLC) demonstrated the presence of the desired **2**, together with another component, in the proportion 2:1. The other material did not correspond to either of the known[12] mono-esters **5** or **6**. It was isolated from the crude reaction product by selective crystallisation from ethanol and was identified[13] by ^{1}H and ^{13}C NMR spectroscopy as methyl 2,3-anhydro-4,6-*O*-benzylidene-α-D-allopyranoside (**1**). It was characterised by treatment with a solution of sodium methoxide in methanol to give the known[14] 2-methyl ether **7**.

No reaction was observed when similar mixtures were maintained at room temperature for 48 h, or at 85°C for 22 h; component **4** was then recovered unchanged.

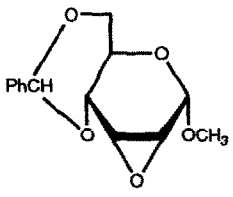
When **4** in *N,N*-dimethylformamide was treated with potassium carbonate at 135°C the epoxide **1** became the major product (63%). A shorter modification of this procedure was then investigated. Treatment of the glucoside **3** with a mixture of diethyl carbonate and potassium carbonate in *N,N*-dimethylformamide for 6 h at 135°C gave **1** (72%).

The foregoing crude product mixtures contained (GLC) only traces (0.5–1.0%) of the alternative epoxide **8** and small amounts (5–7%) of the glucoside **3**, which demonstrated the high regioselectivity of the reaction.

The formation of anhydro derivatives by base-catalysed thermal decomposition of carbonate esters has been reported[15–18], and these studies indicated that the cyclic carbonate group was probably necessary. It has earlier[18] been claimed that formation of the 3,6-anhydro derivative **9** from the cyclic ester **10** occurred on simple thermolysis. Attempts to repeat this reaction were unsuccessful unless a weakly basic catalyst was included[17].

Analysis (GLC) of samples taken at random intervals during the course of the reactions revealed the presence of the cyclic carbonate **2**, the diester **4**, and the two mono-esters **5** and **6**, in various amounts, in addition to the epoxide **1**. Accordingly, the reactions of the individual compounds **2**, **5**, and **6** were investigated under similar conditions.

The formation of the *trans*-fused cyclic ester **2** from **3** in excellent yields has been described[12,19]. Treatment of **2** with ethanol in the presence of a catalytic amount of triethylamine yielded[12,19] compounds **5** and **6** in the proportion 1:1, after column chromatography.



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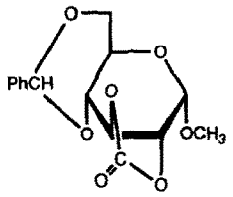

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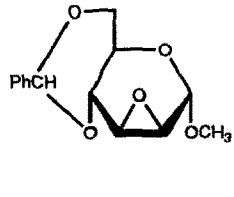

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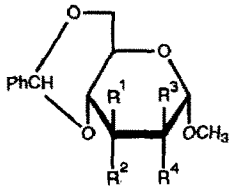
3 $R^1 = R^4 = OH$, $R^2 = R^3 = H$

4 $R^1 = R^4 =$ O-C(O)-OEt, $R^2 = R^3 = H$

5 $R^1 =$ O-C(O)-OEt, $R^4 = OH$, $R^2 = R^3 = H$

6 $R^1 = OH$, $R^4 =$ O-C(O)-OEt, $R^2 = R^3 = H$



7 $R^1 = R^4 = H$, $R^2 = OH$ $R^3 = OCH_3$

13 $R^1 = R^4 = H$, $R^2 = R^3 = OH$

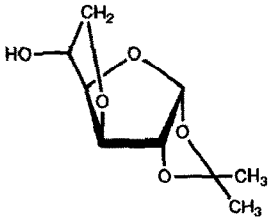
14 $R^1 = R^4 = H$, $R^2 = OH$, $R^3 =$ OTs

15 $R^1 = R^3 = OH$, $R^2 = R^4 = H$

17 $R^1 = R^3 = H$, $R^2 = R^4 = OH$

19 $R^1 = R^3 = H$, $R^2 = OH$, $R^4 =$ OTs

20 $R^1 = R^3 = H$, $R^2 =$ OTs, $R^4 = OH$



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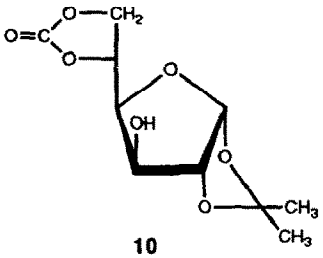

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Treatment of a solution of **2** in *N,N*-dimethylformamide with potassium carbonate yielded **1** (81%). Thermolysis of **2** at 235°C in vacuo failed to yield **1**, thereby confirming the base-catalysed nature of the reaction.

When compound **5** was treated in a similar manner, **1** (14%) was obtained; the remainder of the material was identified as the glucoside **3**. Compound **6** in the same way yielded only **3**.

The formation of oxirane rings on pyranoid derivatives requires that the interacting groups are *trans* and essentially diaxial towards each other. The glucoside **3** is locked in the $^4C_1$ conformation by the benzylidene substituent, which prevents it from adopting the alternative $^1C_4$ form. The pyranose ring must adopt

a skew[4] or $B_{2,5}$ boat conformation[3,5] in order to attain the antiperiplanar geometry required for epoxide formation.

The substanstial yields of **1** obtained directly from the diester **4** or from **3** on treatment with diethyl carbonate contrasted the reactivity of the two mono-esters **5** and **6**. With compound **4**, preferred reaction at the C-2 ester group, followed by intramolecular attack at the C-3 position by the O-2 oxyanion thus generated must account for the formation of **1**. The absence of significant amounts of epoxide **8** in the products from these reactions demonstrated that the alternative formation of an anion at O-3 was not preferred. There would be an unfavourable polar interaction between the C-1 methoxyl group and the ester group on C-2 in this intermediate. This would be emphasised in the corresponding transition state as C-1 and C-4 moved towards coplanarity, eventually leading to eclipsing of the two groups. It is for this reason that compound **6** yielded only the glucoside **3**. The absence of substantial amounts of **3** in the product obtained from **4** demonstrated the specificity of the reaction and suggests that it may be a rapid and synchronous process.

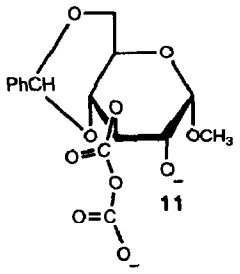
Although the formation of **1** from **2** was efficient, it cannot be an essential intermediate. The cyclic ester group on **2** must be opened to achieve the required molecular geometry for epoxide formation. The high specificity of the subsequent reactions show that nucleophilic attack by carbonate ions on the carbonyl carbon of **2** probably yields[15] an intermediate pyrocarbonate ester-alkoxide ion **11**, which undergoes intramolecular displacement to yield **1**. The alternative opening of **2** at O-3, leading to the intermediate **12**, would again produce an unfavourable polar interaction between the aglycon group and the ester group.

Evidence has been presented[21,22] that the base-catalysed hydrolysis of simple aliphatic cyclic carbonates is a two-stage process leading to alkyl hydrogen carbonate intermediates. Isotopic labelling experiments demonstrated that cleavage occurs with carbonyl–oxygen fission at both stages, with retention of configuration.

Our attention was then directed towards the reaction of the other *trans*-fused diastereoisomers of the glucoside **3** under similar conditions for comparative purposes. The altroside **13** already posseses the required antiperiplanar geometry of the diol group at C-2 and C-3 in its favoured conformation and, on reaction in the same way, yielded a mixture of **1** (55%) and **8** (15%) after column chromatography. The intermediacy of a cyclic carbonate is excluded completely in this reaction, and the relative proportions of the two products suggest that generation of an anion at the more hindered O-3 position with subsequent attack of an ester group at C-2 is the preferred pathway. The formation of **1** from the tosylate **14** is known[23] to be an extremely facile reaction.

The mannoside **15** yielded only the cyclic ester **16** (82%) when treated in the same manner. Compound **16** is known to be formed readily under similar conditions[9] and *cis*-fused carbonate rings undergo ring opening much less readily[24]. Previous attempts[17] to form an epoxide from **16** were unsuccessful.

Treatment of the alloside **17** with the reagent mixture yielded (GLC) 36% of **1**,



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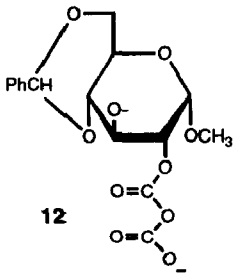

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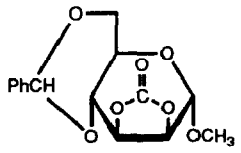

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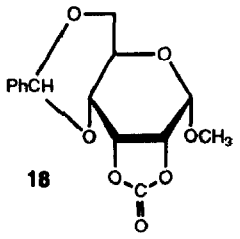

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which was isolated in 21% yield after column chromatography. This result was unexpected and is difficult to explain, since compound **17** cannot achieve the required *trans*-diaxial relationship at C-2 and C-3 whatever conformation it adopts, and would have been expected to yield only the known[25] stable *cis*-fused cyclic carbonate **18**. The formation of **1**, albeit in modest yield, suggests that **17** must have undergone some configurational inversion at C-2. Previous studies[26] have shown that neither of the sulfonic esters **19** and **20** yields an epoxide on treatment with alkali.

Supportive evidence for these mechanistic proposals may be difficult to obtain in view of the known[8] instability of hydrogen carbonate esters and related derivatives.

The simple procedures described here represent new and convenient routes to **1** from **3**, which compare favourably with the traditional routes[4]. Application of the method to other suitable derivatives is currently in progress.

EXPERIMENTAL

General.—Optical rotations were determined with a Perkin–Elmer Model 241 automatic polarimeter on 1% solutions in $CHCl_3$ at 20°C. Column chromatography was performed on Silica Gel 60 with the solvent mixtures indicated. GLC was conducted with a Hewlett–Packard HP 5890 gas chromatograph, using a capillary column (25 m) of HP-1, a temperature program from 100 to 250°C at 15°C/min, followed by 10 min at 250°C (isothermal), and N_2 as the carrier gas at 2 mL/min

(0.5 atm). *N,N*-Dimethylformamide was redistilled from CaH_2 and stored over 4A molecular sieves. NMR spectra were recorded with a Bruker AM 400 spectrometer operating at 400 MHz for ^1H and 100.6 MHz for ^{13}C spectroscopy, on solutions in $CDCl_3$ (internal standard Me_4Si).

Methyl 4,6-O-benzylidene-2,3-di-O-(ethoxycarbonyl)-α-D-glucopyranoside (**4**).—A stirred mixture of methyl 4,6-*O*-benzylidene-α-D-glucopyranoside (**3**; 10.0 g, 35.5 mmol), diethyl carbonate (150 mL), and potassium carbonate (0.5 g, 3.6 mmol) was heated under reflux for 16 h, with continuous removal of the EtOH that was formed, using a Dean–Stark assembly. The cooled product mixture was poured into a mixture of toluene (200 mL) and 2 M HCl (100 mL), and the separated organic layer was washed with water (3 × 100 mL), dried (Na_2SO_4), and concentrated in vacuo, to yield **4** (15.05 g, 99.5%) as a colourless syrup; $[\alpha]_D$ +65°; lit.[12] $[\alpha]_D$ +67°. ^1H NMR data: δ 7.32–7.44 (m, 5 H, aromatic H), 5.50 (s, 1 H, PhC*H*), 5.40 (t, 1 H, $J_{2,3}$ 9.98, $J_{3,4}$ 9.68 Hz, H-3), 5.04 (d, 1 H, $J_{1,2}$ 3.66 Hz, H-1), 4.76 (dd, 1 H, H-2), 4.31 (dd, 1 H, $J_{5,6eq}$ 4.70, $J_{6ax,6eq}$ −10.27 Hz, H-6*eq*), 4.18–4.21 (m, 4 H, OCH_2CH_3), 3.93 (ddd, 1 H, $J_{4,5}$ 9.68, $J_{5,6ax}$ 10.27 Hz, H-5), 3.68 (dd, 1 H, H-4), 3.41 (s, 3 H, OCH_3), and 1.24–1.31 (2 t, 6 H, OCH_2CH_3).

Reaction of potassium carbonate.—(a) With compound **4** *in bis(2-methoxyethyl) ether.* A stirred mixture of **4** (2.68 g, 6 mmol), anhyd potassium carbonate (0.1 g, 0.7 mmol), and tetrabutylammonium bromide (10 mg) in bis(2-methoxyethyl) ether (50 mL), maintained under N_2, was heated at 135–140°C for 48 h, with continuous removal of the EtOH that was produced during the reaction. The cooled mixture was treated with toluene (100 mL) and 2 M HCl (50 mL), and the separated organic layer was washed with water (3 × 50 mL), dried (Na_2SO_4), and concentrated in vacuo. Recrystallisation of the residue from EtOH gave methyl 2,3-anhydro-4,6-*O*-benzylidene-α-D-alloside (**1**; 0.51 g, 32%); mp 204–205°C, $[\alpha]_D$ +138°; lit.[14] mp 199–200°C; $[\alpha]_D$ +140°. ^1H NMR data: δ 7.25–7.50 (m, 5 H, aromatic H), 5.56 (s, 1 H, PhC*H*), 4.88 (d, 1 H, $J_{1,2}$ 2.8 Hz, H-1), 4.23 (dd, 1 H, $J_{6ax,6eq}$ −10.1, $J_{5,6eq}$ 5.1 Hz, H-6*eq*), 4.08 (ddd, 1 H, $J_{4,5}$ 9.1, $J_{5,6ax}$ 10.5 Hz, H-5), 3.95 (dd, 1 H, H-4), 3.68 (t, 1 H, H-6*ax*), 3.46 (s, 3 H, OCH_3), and 3.45–3.51 (m, 2 H, H-2,3). ^{13}C NMR data: δ 137.1 (s), 129.2 (s), 128.3 (d, 2 C), 126.3 (d, 2 C), 102.7 (s), 95.3 (s), 77.8 (s), 68.8 (s), 60.0 (s), 55.8 (s), 53.1 (s), and 50.7 (s).

Treatment[14] of a sample of **1** with M methanolic NaOMe yielded **7** (78%); mp 96–100°C (from isopropyl ether); $[\alpha]_D$ +103.5°; lit.[14] mp 98°C; $[\alpha]_D$ +102.7°.

(b) With compound **4** *in* N,N-*dimethylformamide.* A stirred solution of **4** (3.0 g, 7 mmol) in dry *N,N*-dimethylformamide (100 mL) containing anhyd potassium carbonate (0.4 g, 2.9 mmol) and tetrabutylammonium bromide (10 mg), maintained under N_2, was heated at 115–120°C for 5 h, with continuous removal of the EtOH that was produced. The cooled mixture was set aside to stir at room temperature for 16 h and then poured into ice-cold satd aq NaCl (150 mL). The precipitated material was collected by filtration, washed with ice–water, dried in vacuo (P_2O_5), and recrystallised from CH_2Cl_2–isopropyl ether, to give **1** (1.17 g, 63%), mp 198–201°C; $[\alpha]_D$ +138°.

(c) With methyl 4,6-O-benzylidene-2,3-O-carbonyl-α-D-glucoside (**2**). A stirred mixture of **2**[12] (3.08 g, 10 mmol) in *N,N*-dimethylformamide (30 mL) containing anhyd potassium carbonate (0.3 g, 2.17 mmol) and tetrabutylammonium bromide (15 mg) was heated at 125–130°C for 6 h and then processed as in (*b*), to yield **1** (2.14 g, 81%); mp 201–203°C; $[\alpha]_D$ +138°.

Reaction of diethyl carbonate–potassium carbonate.—(a) With compound **3**. A stirred mixture of **3** (3.0 g, 10.65 mmol), diethyl carbonate (12 mL), anhyd potassium carbonate (0.3 g, 2.17 mmol), and tetrabutylammonium bromide (10 mg) in *N,N*-dimethylformamide (20 mL), maintained under N_2, was heated at 130–135°C for 6 h, with continuous removal of the EtOH that was produced. The cooled mixture was poured into ice-cold satd aq NaCl (250 mL) and then stored at 0°C for 18 h. The precipitated material was collected by filtration, washed with ice water, dried in vacuo (P_4O_{10}), and recrystallised (CH_2Cl_2–isopropyl ether), to give **1** (2.02 g, 72%); mp 199–203°C; $[\alpha]_D$ +137.5°.

(b) With methyl 4,6-O-benzylidene-α-D-altropyranoside (**13**). A solution of **13**[27] (1.0 g, 3.55 mmol) in *N,N*-dimethylformamide (10 mL) was treated with diethyl carbonate (6 mL), anhyd potassium carbonate (0.12 g, 0.88 mmol), and tetrabutylammonium bromide (5 mg) at 130°C for 7 h, and processed as in (*a*). Column chromatography (3:2 1,2-dimethoxyethane–cyclohexane) of the resulting material gave **8** (143 mg, 15%); mp 143–145°C; $[\alpha]_D$ +105°.

Further elution (3:1 EtOAc–light petroleum) gave **1** (514 mg, 55%); mp 198–203°C; $[\alpha]_D$ +139.5°.

(c) With methyl 4,6-O-benzylidene-α-D-mannopyranoside (**15**). Treatment of **15**[28] (2.0 g, 3.55 mmol) in the manner described in (*a*), followed by recrystallisation of the resultant crude product (1.966 g) from toluene–hexane, gave **16** (1.79 g, 82%); mp 123–125°C; $[\alpha]_D$ −18.5°; lit.[9] mp 125.5–126°C; $[\alpha]_D$ −20.9°.

(d) With methyl 4,6-O-benzylidene-α-D-allopyranoside (**17**). A solution of **17**[26] (150 mg) in *N,N*-dimethylformamide (5 mL) was treated with diethyl carbonate (3 mL), anhyd potassium carbonate (15 mg), and tetrabutylammonium bromide (1 mg) at 135°C for 6.5 h as in (*a*). The cooled mixture was poured into a mixture of ice–water (20 mL) and CH_2Cl_2 (50 mL). The separated CH_2Cl_2 layer was washed with water (4 × 10 mL), dried (Na_2SO_4), and concentrated in vacuo. Column chromatography (3:1 EtOAc–light petroleum) of the residue gave **1** (29.5 mg, 21%); mp 199–203°C; $[\alpha]_D$ +137°.

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