The Synthesis of Several Octose Derivatives Related to Octosyl Acids A and B

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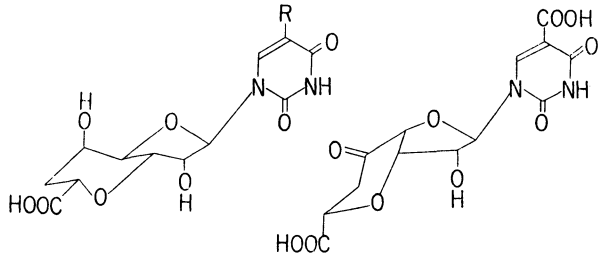
Starting from 1,2: 5,6-di-*O*-isopropylidene-α-D-allofuranose (**3a**), the sugar portion of octosyl acids **A** and **B** (**1a** and **1b**) was synthesised, though with some protecting groups. Compound **7a**, thus obtained, was found to be acid-liable, and treatment of **7a** in a dilute hydrochloric acid in methanol resulted in furanose-ring opening, affording an isopropylidene compound **8**.

Octosyl acids **A**, **B**, and **C**, which have been isolated from the fermentation broth of a polyoxin-producing microorganism *Streptomyces cacaoi* var. asoensis,[1] have been reported to have the structures **1a**, **1b**, and **2** by Isono, Crain, and McClosky.[2]



1a R=COOH
1b R=CH_2OH

2

These compounds are considered to be carbo-analogues of cyclic AMP,[2] and exploitation of a synthetic route to them may also contribute to the synthesis of other cyclic AMP analogues. We wish to report here the synthesis of the sugar portion of octosyl acids **A** and **B** with some protecting groups.

1,2: 5,6-Di-*O*-isopropylidene-α-D-allofuranose(**3a**)[3] was chosen as the starting material. Reaction of **3a** with methyl bromoacetate in the presence of sodium hydride in tetrahydrofuran afforded the methyl ester **3b**. Similarly, the ethyl ester **3c** was prepared.

To construct the bicyclic skeleton of octosyl acids, bond formation between the carbon at 3-O and C_6 in **3c** is necessary; for this purpose, an attempt was made to convert **3c** to a malonic acid derivative **3d** in order to activate the carbon atom at 3-O in **3c**.

Reaction of the ester **3c** with diethyl carbonate in the presence of one equivalent of sodium hydride in refluxing tetrahydrofuran afforded two products, which were separated by silica gel chromatography. The less polar compound, which was indistinguishable from the starting material on TLC, was actually found to be the required malonic acid derivative **3d**, showing two carbonyl bands at 1770 and 1740 cm^{-1} in the IR spectrum, a mass fragment ion at *m/e* 403 corresponding to M^+-CH_3, and a singlet a δ 4.78 in the NMR spectrum corresponding to one methine proton at 3-O–C. The more polar compound was found to be a Claisen condensation product **4**, showing a mass fragment ion at *m/e* 631 corresponding to M^+-CH_3. Though **4** was homogeneous on TLC, and the NMR spectrum showed a methine proton singlet at δ 4.78, the anomeric proton signal appeared as a multiplet (δ 5.68—5.88), suggesting that **4** was a mixture of the stereoisomers at the carbon atom flanked by two carbonyl groups. The yield ratio of **3d** to **4** varied markedly in several experiments, though the latter was predominant in every case. However, if the reaction was carried out in refluxing diethyl carbonate (bp 127 °C) instead of refluxing tetrahydrofuran (bp 66 °C), the formation of **3d** was predominant and the ratio of **3d** to **4** was found constantly to be 9: 1. On the contrary, **4** was formed exclusively when the reaction was carried out at 0 °C.

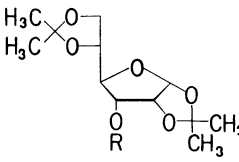
Treatment of **3d** in 70% acetic acid at 37 °C for 3 h was effective in obtaining the monoacetonated compound **5a** in a good yield. Reaction of **5a** with an equimolar amount of tosyl chloride afforded the 6-*O*-tosylate **5b** almost exclusively; a small amount of the ditosylate **5d** as well as the starting material were also isolated from the reaction mixture. With excess tosyl chloride, the ditosylate **5d** was formed exclusively. Reaction of **5b** with acetic anhydride in pyridine afforded the acetyl tosyl compound **5c**, whose proton signal at C-5 appeared in a lower field (δ 5.31) than that of **5b** (δ 3.8), showing the correctness of the assignment of **5b** as the 5-hydroxy compound.

The monotosylate **5b** was treated with an equimolar amount of sodium hydride in tetrahydrofuran at room temperature to give two products, which were separated by silica gel chromatography. The less polar one was the epoxy compound **6a**, the NMR spectrum of which still showed a singlet at δ 4.68, corresponding to one methine proton of the malonic acid moiety. The shifts of the proton signals at C_5 and C_6 in **6a** to higher fields showed the formation of an epoxide ring. The mass spectrum of **6a** showed intense peaks at *m/e* 345, 302, and 169 corresponding to M^+-CH_3, $M^+-CH_3-CH_2CH(-O-)$, and $M^+-CH_3-(C_2H_5OOC)_2CHO-H$.

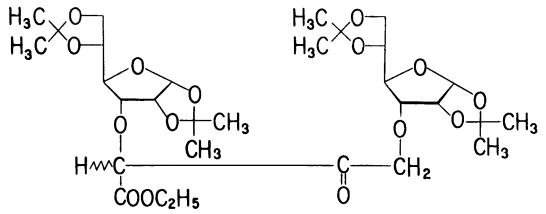
The more polar one was found to have the same molecular formula as **6a** (M^+-CH_3 *m/e* 345) and was identified as the required **7a**, which showed an IR absorption at 3500 cm^{-1} corresponding to a hydroxyl group. The methine proton signal at δ 4.68 in the NMR spectrum in **5b** was lost **7a**, showing the bond formation between 3-O–C and C_6. The yield ratio of **6a** to **7a** was 1/2 to 1/3 throughout several experiments. Attempts at the conversion of **6a** to **7a** in the presence of varying amounts of sodium hydride (0.1 to 1.0 equivalent) failed, suggesting that the reaction to **6a** and **7a** from **5b** proceeded independently.

Similarly, the ditosylate **5d** and the acetyl tosylate **5c** were converted into two ring-formation compounds, **7c** and **7b**. In the latter case, the reaction conditions were

more vigorous (under reflux in tetrahydrofuran for 2 days) than in the former case (at room temperature in tetrahydrofuran for 20 h).



3a R=H
3b R=CH_3OOCH_2
3c R=$C_2H_5OOCH_2$
3d R=$(C_2H_5OOC)_2CH$
3e R=$NCCH_2$



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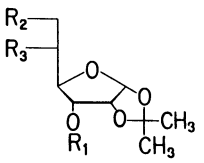
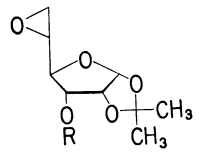


5a R_1=$(C_2H_5OOC)_2CH$, R_2, R_3=OH
5b R_1=$(C_2H_5OOC)_2CH$, R_2=*p*-$CH_3C_6H_4SO_3$, R_3=OH
5c R_1=$(C_2H_5OOC)_2CH$, R_2=*p*-$CH_3C_6H_4SO_3$, R_3=CH_3CO_2
5d R_1=$(C_2H_5OOC)_2CH$, R_2, R_3=*p*-$CH_3C_6H_4SO_3$
5e R_1=$C_2H_5OOCCH_2$, R_2, R_3=OH
5f R_1=$C_2H_5OOCCH_2$, R_2=*p*-$CH_3C_6H_4SO_3$, R_3=OH
5g R_1=$C_2H_5OOCCH_2$, R_2=*p*-$CH_3C_6H_4SO_3$, R_3=$C_6H_5CO_2$
5h R_1=$C_2H_5OOCCH_2$, R_2, R_3=*p*-$CH_3C_6H_4SO_3$
5i R_1=$C_2H_5OOCCH_2$, R_2=I, R_3=$C_6H_5C_3O_2$
5j R_1=$NCCH_2$, R_2, R_3=OH
5k R_1=$NCCH_2$, R_2=*p*-$CH_3C_6H_4SO_3$, R_3=OH
5l R_1=$NCCH_2$, R_2, R_3=*p*-$CH_3C_6H_4SO_3$



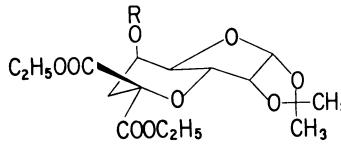
6a R=$(C_2H_5OOC)_2CH$
6b R=$C_2H_5OOCCH_2$
6c R=$NCCH_2$

Attempts were made to construct the bicyclic system of octosyl acids by intramolecular cyclization of the monocarboxylic acid ethyl ester **5f** and its cyanomethyl analogue **5k**. As in the case of the tosylate **5b**, the tosylate **5f** was prepared from the partially deacetonated product **5e** of **3c**; **5e** was also converted into the ditosylate **5h** with excess tosyl chloride.

The cyanomethyl derivative **3e** was obtained in a moderate yield on treatment of **3a** with chloroacetonitrile or bromoacetonitrile in the presence of sodium hydride. Partial deacetonation of **3e** in 70% acetic acid afforded **5j**, which was then converted to the mono- and ditosylate, **5k** and **5l**.

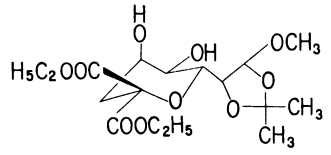
The ester **5f** and the nitrile **5k** gave exclusively the epoxy compounds **6b** and **6c**; the required products were not obtained.

The benzoyl tosylate **5g**, the ditosylate **5h** and the iodo compound **5i**, which had been prepared from **5h** by treatment with sodium iodide in ethyl methyl ketone, were found to be inert to sodium hydride or lithium bis(trimethylsil)amide at room temperature or under reflux. These results were somewhat surprising, because, as has been mentioned previously, the diacetonated compound **3c** was converted into **4** even at 0 °C by treatment with sodium hydride.

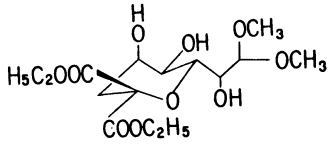


7a R=H
7b R=CH_3CO
7c R=*p*-$CH_3C_6H_4SO_2$

Attempts at acetolysis of **7a**, followed by reaction with bis(trimethylsilyl)uracil using a $SnCl_4$ catalyst[4] to obtain a nucleoside related to octosyl acids, failed. The failure may be attributable to the susceptibility of the 3,7-anhydrooctose skeleton of **7a** to acids, which was also shown by the following results: in a dilute methanolic solution of hydrochloric acid (0.01 M) **7a** was converted into the ring-opened acetonate **8**, and under more vigorous conditions (0.5 M) the deacetonated product **9** was obtained. We feel now that the binding of the aglycon should be prior to the formation of the bicyclic system of the sugar portion in the synthesis of octosyl acids.



8



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Experimental

1,2:5,6-Di-O-isopropylidene-3-O-ethoxycarbonylmethyl-α-D-allofuranose (3c). Sodium hydride (550 mg, 23 mmol), freshly prepared from a commercially available oil-coated product (NaH content, 50%) by washing with hexane, was added to a solution of **3a** (5.2 g, 20 mmol) in dry tetrahydrofuran (20 mmol). After the evolution of hydrogen had ceased, the mixture was cooled to 0 °C and ethyl bromoacetate (5 g, 30 mmol) was added dropwise. The mixture was stirred overnight at room temperature. The remaining sodium hydride was quenched by adding ethanol at 0 °C, and a few drops of acetic acid were added to keep the mixture acidic during processing. After the mixture had been concentrated, it was distributed between ethyl acetate and water. The organic layer was washed with water and then concentrated to dryness to give a crude product, which was crystallized from hexane; yield, 5.8 g (84%); mp 89—90 °C; ν_{CO}^{KBr} 1750 cm^{-1}; M^+-CH_3 *m/e* 331; NMR (100 MHz, $CDCl_3$) δ: 1.30 (t, 3H, ethyl ester J=7 Hz), 1.38 and 1.46 (2s, 6H, two

methyls of one isopropylidene group), 1.38 and 1.58 (2s, 6H, two methyls of one isopylropyidene group), 4.78 (t, 1H, H-2, $J_{1,2}$=4 Hz, $J_{2,3}$=4 Hz), 5.76 (s, 1H, H-1, $J_{1,2}$=4 Hz).

Found: C, 55.87; H, 7.69%. Calcd for $C_{16}H_{26}O_8$: C, 55.48; H, 7.57%.

1,2:5,6-Di-O-isopropylidene-3-O-methoxycarbonylmethyl-α-D-allofuranose (3b). Compound **3a** (5.2 g, 20 mmol) was treated with methyl bromoacetate (4.6 g, 30 mmol) and sodium hydride (550 mg, 23 mmol) in dry tetrahydrofuran (50 ml) as has been described in the preceding section. The product was crystallized from hexane; yield, 4.7 g (70%). Silica gel chromatography, developed with a mixture of benzene and ethyl acetate (2: 1), gave an analytically pure sample; mp 80—81 °C; ν_{CO}^{KBr} 1760 cm^{-1}; M$^+$−CH$_3$ *m/e* 317; NMR (100 MHz, $CDCl_3$) δ: 1.36 and 1.46 (2s, 6H, two methyls of one isopropylidene group), 1.36 and 1.58 (2s, 6H, two methyls of one isopropyridene group), 3.75 (s, 3H, methyl ester), 4.76 (t, 1H, H-2, $J_{1,2}$=4 Hz, $J_{2,3}$=4 Hz), 5.76 (d, 1H, H-1, $J_{1,2}$=4 Hz).

Found: C, 54.06; H, 7.16%. Calcd for $C_{15}H_{24}O_8$: C, 54.21; H, 7.28%.

3-O-Bis(ethoxycarbonyl)methyl-1,2:5,6-di-O-isopropylidene-α-D-allofuranose (3d). A suspension of sodium hydride (500 mg, 20 mmol) in diethyl carbonate (150 ml) previously dried over sodium was heated to reflux, and then the reaction vessel was taken off from the heater. Immediately, the ester **3c** (6.92 g, 20 mmol) was added portionwise. The mixture was further heated under reflux for 2 h and cooled to −15 °C. Ethanol (10 ml) and then acetic acid (2 ml) were added and the mixture was concentrated below 35 °C.

Silica gel chromatography of the ethyl acetate extracts, developed with mixtures of benzene and ethyl acetate (2—1: 1), afforded 6.6 g (80%) of the main product as a syrup, which was subsequently crystallized from ether and hexane; yield, 5.50 g; mp 50—51 °C; 1770 and 1740 cm^{-1}; M$^+$−CH$_3$ *m/e* 403; NMR (100 MHz, $CDCl_3$) δ: 4.70 (t, 1H, H-2, $J_{1,2}$=4 Hz, $J_{2,3}$=4 Hz), 4.80 (s, 1H, $H_5C_2OOCC\underline{H}COOC_2H_5$), 5.80 (d, 1H, H-1, $J_{1,2}$=4 Hz).

Found: C, 54.71; H, 7.19%. Calcd for $C_{19}H_{30}O_{10}$: C, 54.53; H, 7.23%.

From the reaction mixture was also isolated the Claisen condensation product **4**, which was more polar than **3d**; yield, 0.70 g.

The Claisen Condensation Product 4. The ester **3c** (500 mg, 1.45 mmol) was treated with sodium hydride (40 mg, 1.65 mmol) in tetrahydrofuran (30 ml) first at 0 °C for 8 h and at room temperature for 16 h. The mixture was cooled again at 0 °C. After ethanol (1 ml) and a few drops of acetic acid had been added, it was concentrated and the product was extracted with ethyl acetate. Silica gel chromatography developed with a mixture of benzene and ethyl acetate (1: 1) afforded 310 mg (70%) of a syrup, which was fractionally precipitated from ethyl acetate and hexane for analysis; ν_{CO}^{KBr} 1740 cm^{-1}; M$^+$−CH$_3$ *m/e* 631; NMR (100 MHz, $CDCl_3$) δ: 4.72 (s, 1H, $OC\underline{H}COOC_2H_5$), 5.68—5.88 (m, 2H, two anomeric protons).

Found: C, 55.72; H, 7.17%. Calcd for $C_{30}H_{46}O_{15}$: C, 55.73; H, 6.98%.

The same reaction was carried out in a mixture of tetrahydrofuran and diethyl carbonate (9: 1) at room temperature. However, no trace of **3d** could be detected as was shown by IR. Note that the separation of **3d** from **3c** on TLC was unsucessful by any combination of solvents.

3-O-Bis(ethoxycarbonyl)methyl-1,2-O-isopropylidene-α-D-allofuranose (5a). A solution of **3d** (1.9 g) in 70% acetic acid (100 ml) was allowed to stand at 37 °C for 3 h and was evaporated to dryness keeping the temperature below 37 °C. To the residue was added an ice-cooled solution of sodium hydrogencarbonate, and the products were extracted with chloroform. TLC showed the presence of trace amounts of the starting material as well as one major and one minor product, the latter presumably being the di-deacetonated product, 3-*O*-bis(ethoxycarbonyl)methyl-D-allose.

The major one was isolated by silica gel chromatography, developed first with a mixture of benzene and ethyl acetate (1: 1) and then with ethyl acetate; yield, 1.4 g (82%). For further purification it was fractionally precipitated from benzene and hexane to give a syrup, which, on standing, was gradually converted into a solid melting at 53 °C; ν_{CO}^{KBr} 1773 and 1738 cm^{-1}; M$^+$−CH$_3$ *m/e* 363; NMR (100 MHz, $CDCl_3$) δ: 1.32 (t, 6H, ethyl ester, J=7 Hz), 1.35 and 1.56 (two s, 6H, two isopropylidene methyls), 4.64 (t, 1H, H-2, $J_{1,2}$=4 Hz, $J_{2,3}$=4 Hz), 4.74 (s, 1H, $H_5C_2OOCC\underline{H}COOC_2H_5$), 5.80 (d, 1H, H-1, $J_{1,2}$=4 Hz).

Found: C, 51.07; H, 6.58%. Calcd for $C_{16}H_{26}O_{10}$: C, 50.79; H, 6.93%.

3-O-Bis(ethoxycarbonyl)methyl-1,2-O-isopropylidene-6-O-tosyl-α-D-allofuranose (5b). Tosyl chloride (0.8 g, 4.2 mmol) was added all at once to a solution of **5a** (1.4 g, 3.7 mmol) in pyridine (50 ml) cooled at −15 °C, after which the mixture was allowed to stand at room temperature overnight. An ice-cooled solution of sodium hydrogencarbonate was added and the products were extracted with ethyl acetate. The main product was isolated by silica gel chromatography, developed with a mixture of benzene and ethyl acetate (2: 1); yield, 1.35 g (70%); M−CH$_3$ *m/e* 517; NMR (100 MHz, $CDCl_3$) δ: 1.30 (t, 6H, ethyl ester, J=7 Hz), 1.32 and 1.52 (two s, 6H, two isopropylidene methyls), 2.44 (s, 3H, one methyl of the tosyl group), 4.67 (s, 1H, $H_5C_2OOCC\underline{H}COOC_2H_5$), 5.72 (d, 1H, H-1, $J_{1,2}$=4 Hz), 7.33 and 7.82 (two d, 4H, four aromatic protons of the tosyl group, J_{ortho}=9 Hz).

Found: C, 51.93; H, 6.00; S, 5.97%. Cacld for $C_{23}H_{32}O_{12}S$: C, 51.87; H, 6.06; S, 6.02%.

3-O-Bis(ethoxycarbonyl)methyl-5,6-di-O-tosyl-1,2-O-isopropylidene-α-D-allofuranose (5d). Treatment of **5a** (500 mg) with tosyl chloride (1 g) in pyridine (20 ml) at 37 °C for 2 days afforded a single product. The pyridine was removed by evaporation, and an ice-cooled solution of sodium hydrogencarbonate was added. Extraction with ethyl acetate and silica gel chromatography, developed with a mixture of benzene and ethyl acetate (4: 1), gave a syrup; yield, 700 mg; NMR (100 MHz, $CDCl_3$) δ: 1.23 and 1.28 (two t, 6H, ethyl ester), 1.27 and 1.43 (two s, 6H, two isopropylidene methyls), 2.41 (s, 6H, two methyls of the tosyl group), 4.51 (t, 1H, H-2), 4.59 (s, 1H, $H_5C_2OOCC\underline{H}COOC_2H_5$), 5.11 (m, 1H, H-5), 5.46 (d, 1H, H-1, $J_{1,2}$=4 Hz).

Found: C, 53.05; H, 5.49; S, 9.01%. Calcd for $C_{30}H_{38}O_{14}S_2$: C, 52.47; H, 5.58; S, 9.34%.

5-O-Acetyl-3-O-bis(ethoxycarbonyl)methyl-1,2-O-isopropylidene-6-O-tosyl-α-D-allofuranose (5c). A solution of **5b** (700 mg) in a mixture of acetic anhydride (5 ml) and pyridine (2 ml) was allowed to stand at 37 °C for 3 h; after it was evaporated to dryness, the product was precipitated from ether and hexane to give a syrup; yield, 650 mg; NMR (100 MHz, $CDCl_3$) δ: 1.30 (t, 6H, ethyl ester, J=7 Hz), 1.32 and 1.52 (two s, 6H, two isopropylidene methyls), 2.03 (s, 3H, acetyl), 2.44 (s, 3H, one methyl of the tosyl group), 4.62 (t, 1H, H-2, $J_{1,2}$=4 Hz, $J_{2,3}$=4 Hz), 4.64 (s, 1H, $H_5C_2OOCC\underline{H}COOC_2H_5$), 5.31 (q, 1H, H-5), 5.70 (d, 1H, H-1, $J_{1,2}$=4 Hz), 7.35 and 7.82 (two d, 4H, four aromatic protons of the tosyl group, J_{ortho}=9 Hz).

Found: C, 52.36; H, 6.11; S, 5.56%. Calcd for $C_{25}H_{34}O_{13}S$: C, 52.25; H, 5.96; S, 5.58%.

5,6-Anhydro-3-O-bis(ethoxycarbonyl)methyl-1,2-O-isopropylidene-

α-D-allofuranose (6a) and 3,7-Anhydro-7-bis(C-ethoxycarbonyl)-6-deoxy-1,2-O-isopropylidene-α-D-allo-heptose (7a). To a solution of **5b** (700 mg, 1.3 mmol) in dry tetrahydrofuran (20 ml), cooled at −15 °C, has been added sodium hydride (34 mg, 1.4 mmol). After the mixture had been stirred for 20 h at room temperature, it was cooled again to −15 °C. Ethanol (1 ml) was added to quench the remaining sodium hydride, and acetic acid (1 ml) was added to keep the reaction mixture acidic during processing. Concentration, extraction with ethyl acetate, and developing on a silica gel column with mixtures of benzene and ethyl acetate (4—1: 1) afforded two products.

The less polar compound (132 mg) was identified as the epoxide **6a** and was obtained as a syrup by precipitation from benzene and hexane; MS (75 eV) *m/e*: 345 (M^+-CH_3), 302 ($M^+-CH_3-CH_2CH(-O-)$), 169 ($M^+-CH_3-H_5C_2OOCCH(O)COOC_2H_5-H$), 127 ($M^+-CH_3-H_5C_2OOCCH(O)COOC_2H_5-CH_2CH(-O-)$); NMR (100 MHz, $CDCl_3$) δ 1.31 and 1.38 (two t, 6H, ethyl ester, J=7 Hz), 1.36 and 1.56 (two s, 6H, two isopropylidene methyls), 2.82 (t, 1H, H_a-6, J_{gem}=4.5 Hz, $J_{5,6a}$=4.5 Hz), 3.10 (q, 1H, H_b-6, J_{gem}=4.5 Hz, $J_{5,6b}$=3 Hz), 3.32 (m, 1H, H-5), 3.81 (q, 1H, H-3, $J_{3,4}$=8 Hz, $J_{2,3}$=4 Hz), 4.28 and 4.29 (two q, 4H, two methylenes of the ester groups, J=7 Hz), 4.41 (q, 1H, H-4, $J_{3,4}$=8 Hz, $J_{4,5}$=2 Hz), 4.63 (t, 1H, H-2, $J_{1,2}$=4 Hz, $J_{2,3}$=4 Hz), 4.68 (s, 1H, $H_5C_2OOCC\underline{H}COOC_2H_5$), 5.80 (d, 1H, H-1, $J_{1,2}$=4 Hz).

Found: C, 53.10; H, 6.48%. Calcd for $C_{16}H_{24}O_9$: C, 53.33; H, 6.71%.

The more polar compound (387 mg) was obtained as a syrup by precipitation from benzene and hexane and was identified as **7a**: IR (KBr) cm^{-1}: 3500 (OH), 1770, sh and 1743 (CO); M^+-CH_3 *m/e* 345 (intense); NMR (100 MHz, $CDCl_3$) δ: 1.27 and 1.29 (two t, 6H, ethyl ester), 1.37 and 1.59 (two s, 6H, two isopropylidene methyls), 2.15 (broad, 1H, OH), 2.31 and 2.77 (two dd, 2H, H_a-6 and H_b-6, $J_{5,6a}$=3 Hz, $J_{5,6b}$=4 Hz, J_{gem}=15 Hz), 3.92 (dd, 1H, H-4, $J_{3,4}$=12 Hz, $J_{4,5}$=3 Hz), 4.29 (q, 4H, two methylenes of the ester groups, J=7 Hz), 4.35 (dd, 1H, H-3, $J_{2,3}$=4 Hz, $J_{3,4}$=12 Hz), 4.49 (broad, 1H, H-5), (4.79 (t, 1H, H-2, $J_{1,2}$=4 Hz, $J_{2,3}$=4 Hz), 5.77(d, 1H, H-1, $J_{1,2}$=4 Hz).

Found: C, 53.64; H, 6.67%. Calcd for $C_{16}H_{24}O_9$: C, 53.33; H, 6.71%.

5-O-Acetyl-3,7-anhydro-7-bis(C-ethoxycarbonyl)-6-deoxy-1,2-O-isopropylidene-α-D-allo-heptose (7b). A mixture of **5c** (535 mg, 0.93 mmol) and sodium hydride (30 mg, 1.3 mmol) in dry tetrahydrofuran (10 ml) was refluxed for 2 days and cooled to −15 °C. Ethanol (0.5 ml) and a few drops of acetic acid were added, and the mixture was concentrated. The product was extracted with ethyl acetate and purified by silica gel chromatography, developed with a mixture of benzene and ethyl acetate (2: 1); yield, 255 mg. For analysis it was fractionally precipitated from ethyl acetate and hexane to give a syrup; M^+-CH_3 *m/e* 387 (intense): NMR (100 MHz, $CDCl_3$) δ: 1.26 and 1.30 (two t, 6H, ethyl ester, J=7 Hz), 1.35 and 1.58 (two s, 6H, two isopropylidene methyls), 2.00 (s, 3H, acetyl), 2.39 and 2.90 (two dd, 2H, H_a-6 and H_b-6, $J_{5,6a}$=3 Hz, $J_{5,6b}$=4 Hz, J_{gem}=15 Hz), 3.95 (dd, 1H, H-4, $J_{3,4}$=10 Hz, $J_{4,5}$=3 Hz), 4.1—4.5 (m, 5H, H-3 and four methylene protons of the ester groups), 4.80 (t, 1H, H-2, $J_{1,2}$=4 Hz, $J_{2,3}$=4 Hz), 5.52 (m, 1H, H-5), 5.78 (d, 1H, H-1, $J_{1,2}$=4 Hz).

Found: C, 53.91; H, 6.55%. Calcd for $C_{18}H_{26}O_{10}$; C, 53.72; H, 6.51%.

3,7-Anhydro-7-bis(C-ethoxycarbonyl)-6-deoxy-1,2-O-isopropylidene-6-O-tosyl-α-D-allo-heptose (7c). A mixture of **5d** (710 mg, 1.03 mmol) and sodium hydride (38 mg, 1.5 mmol) in dry tetrahydrofuran (20 ml) was stirred at room temperature overnight and was treated as has been described in the preceding section. Silica gel chromatography, developed with a mixture of benzene and ethyl acetate (4: 1) followed by crystallization from ethyl acetate and hexane, afforded 318 mg of **7c**; mp 146—147 °C; MS (75 eV) *m/e*: 499 (M^+-CH_3), 427 ($M^+-CH_3-COOC_2H_5+H$), 342 ($M^+-CH_3C_6H_4SO_3H$); NMR (100 MHz, $CDCl_3$) δ: 1.26 and 1.31 (two t, 6H, ethyl ester), 1.33 and 1.52 (two s, 6H, two isopropylidene methyls), 2.42, (s, 3H, tosyl), 2.46 and 3.06 (two dd, 2H, H_a-6 and H_b-6, $J_{5,6a}$=3 Hz, $J_{5,6b}$=4 Hz, J_{gem}=15 Hz), 3.82 (dd, 1H, H-4, $J_{3,4}$=10 Hz, $J_{4,5}$=3 Hz), 4.1—4.5 (m, 5H, H-3 and four methylene protons of the ester groups), 4.72 (t, 1H, H-2, $J_{1,2}$=4 Hz, $J_{2,3}$=4 Hz), 5.09 (broad, 1H, H-5), 5.54 (d, 1H, H-1, $J_{1,2}$=4 Hz).

Found: C, 53.61; H, 5.83; S, 6.33%. Calcd for $C_{23}H_{30}O_{11}S$: C, 53.68, H, 5.88; S, 6.23%.

3-O-Ethoxycarbonylmethyl-1,2-O-isopropylidene-α-D-allofuranose (5e). A solution of **3c** (5 g, 14.5 mmol) in 70% acetic acid (100 ml) was allowed to stand at 37 °C for 3 h and was evaporated to dryness. An ice-cooled solution of sodium hydrogencarbonate was added, and the product was extracted with chloroform. TLC showed the presence of one major product as well as a small amount of the starting material and a by-product, the latter being presumably the di-deacetonated product, 3-*O*-ethoxycarbonylmethyl-D-allose.

Silica gel chromatography, developed with a mixture of ethyl acetate and methanol (9: 1), afforded 2.51 g (8.2 mmol, 57%) of **5e**, which was fractionally precipitated from benzene and hexane for analysis; M^+-CH_3 *m/e* 291; NMR (100 MHz, $CDCl_3$) δ: 1.30 (t, 3H, ethyl ester, J=7 Hz), 1.36 and 1.58 (2s, 6H, two isopropylidene methyls), 4.68 (t, 1H, H-2, $J_{1,2}$=4 Hz, $J_{2,3}$=4 Hz), 5.77 (d, 1H, H-1, $J_{1,2}$=4 Hz).

Found: C, 50.99; H, 7.18%. Calcd for $C_{13}H_{22}O_8$: C, 50.97; H, 7.24%.

3-O-Ethoxycarbonylmethyl-1,2-O-isopropylidene-6-O-tosyl-α-D-allofuranose (5f). Compound **5e** (828 mg, 2.7 mmol) was treated with tosyl chloride (420 mg, 2.7 mmol) much as in the preparation of **5b**. The main product was isolated by silica gel chromatography, developed with mixtures of benzene and ethyl acetate (2—1: 1); it was obtained as a syrup from ethyl acetate and hexane; yield, 810 mg; IR (KBr) cm^{-1}: 3470 (OH), 1735 (ester); M^+-CH_3 *m/e* 445; NMR (100 MHz, $CDCl_3$) δ: 1.26 (t, 3H, ethyl ester, J=7 Hz), 1.33 and 1.52 (2s, 6H, two isopropylidene methyls), 2.42 (1s, 3H, methyl of the tosyl group), 5.71 (d, 1H, H-1, $J_{1,2}$=4 Hz), 7.32 and 7.80 (two d, 4H, four aromatic protons of the tosyl group).

Found: C, 52.23; H, 5.95; S, 6.95%. Calcd for $C_{20}H_{28}O_{10}S$: C, 52.16; H, 6.13; S, 6.96%.

5,6-Di-O-tosyl-3-O-ethoxycarbonylmethyl-1,2-O-isopropylidene-α-D-allofuranose (5h). Compound **5e** (306 mg, 1 mmol) was treated with tosyl chloride (760 mg, 4 mmol) much as in the preparation of **5d**. Silica gel chromatography, developed with mixtures of benzene and ethyl acetate (4—1: 1), afforded 450 mg of the product, which was crystallized from ethyl acetate and hexane; mp 115—116 °C; NMR (100 MHz, $CDCl_3$) δ: 1.26 (t, 3H, ethyl ester, J=7 Hz), 1.31 and 1.48 (2s, 6H, two isopropylidene methyls), 2.44 (s, 6H, two methyls of the tosyl group), 4.58 (t, 1H, H-2, $J_{1,2}$=4 Hz, $J_{2,3}$=4 Hz), 5.07 (m, 1H, H-5), 5.47 (d, 1H, H-1, $J_{1,2}$=4 Hz), 7.33 and 7.72 (two d, 4H, four aromatic protons of one tosyl group, J_{ortho}=8 Hz), 7.33 and 7.76 (two d, 4H, four aromatic protons of one tosyl group, J_{ortho}=8 Hz).

Found: C, 52.79; H, 5.56; S, 10.42%. Calcd for $C_{27}H_{34}O_{12}S_2$: C, 52.75: H, 5.58; S, 10.43%.

5-O-Benzoyl-3-O-ethoxycarbonylmethyl-1,2-O-isopropylidene-6-O-tosyl-α-D-allofuranose (5g). To a solution of **5f** (3 g,

6.6 mmol) in pyridine (50 ml), cooled at −15 °C, was added benzoyl chloride (3 g, 21 mmol), after which the solution was stirred for 1 h at room temperature. An ice-cooled solution of sodium hydrogencarbonate was added, and the product was extracted with ethyl acetate. Precipitation from ether and hexane afforded 3.10 g of a syrup (83%); M^+-CH_3 *m/e* 549; NMR (100 MHz, $CDCl_3$) δ: 1.20 (t, 3H, ethyl ester, J=7 Hz), 1.32 and 1.55 (2s, 6H, two isopropylidene methyls), 2.34 (s, 3H, methyl of the tosyl group), 4.68 (t, 3H, H-2, $J_{1,2}$=4 Hz, $J_{2,3}$=4 Hz), 5.5—5.7 (m, 2H, H-1 and H-5), 7.18 and 7.72 (2d, 4H aromatic protons of the tosyl group, J_{ortho}=8 Hz), 7.3—7.6 (m, 3H, *meta* and *para* protons of the benzoyl group), 7.94 (dd, 2H, *ortho* protons of the benzoyl group, J_{ortho}=8 Hz, J_{meta}=1.5 Hz).

Found: C, 57.51; H, 5.73; S, 5.48%. Calcd for $C_{27}H_{32}O_{11}S$: C, 57.43; H, 5.71; S, 5.68%.

5-O-Benoyl-z6-deoxy-3-O-ethoxycarbonylmethyl-6-iodo-1,2-O-isopropylidene-α-D-allofuranose (5i). A solution of **5g** (2.46 g, 4.6 mmol) and sodium iodide (3 g, 20 mmol) in ethyl methyl ketone (50 ml) was refluxed for 17 h. After the solvent had been evaporated to dryness, the residue was distributed between water and ethyl acetate. The organic layer was washed with an aqueous solution of sodium hydrogensulfite. TLC showed the formation of a sigle product, which was isolated by silica gel chromatograpy developed with mixtures of benzene and ethyl acetate (9—4: 1) yield, 1.65 g. For analysis it was fractionally precipitated from ether and hexane. It gradually decomposed at 56 °C *in vacuo*; MS (75 eV) *m/e*: 505 (M^+-CH_3), 393 (M^+-1); NMR (100 MHz, $CDCl_3$) δ: 1.20 (t, 3H, ethyl ester, J=7 Hz), 1.34 and 1.59 (two s, 6H, two isopropylidene methyls), 4.71 (t, 1H, H-2, $J_{1,2}$=4 Hz, $J_{2,3}$=4 Hz), 5.35 (q, 1H, H-5, $J_{4,5}$=6 Hz, $J_{5,6}$=6 Hz), 5.71 (d, 1H, H-1, $J_{1,2}$=4 Hz), 7.3—7.7 (m, 3H, *meta* and *para* protons of the benzoyl group), 8.08 (dd, 2H, *ortho* protons of the benzoyl group, J_{ortho}=8 Hz, J_{meta}=1.5 Hz).

Found: C, 46.98; H, 4.95; I, 23.76%. Calcd for $C_{20}H_{25}O_8I$: C, 47.20; H, 5.09; I, 32.75%.

5,6-Anhydro-3-O-ethoxycarbonylmethyl-1,2-O-isopropylidene-α-D-allofuranose (6b). A mixture of **5f** (689 mg, 1.5 mmol) and sodium hydride (36 mg, 1.5 mmol) in dry terahydrofuran (10 ml) was refluxed for 2 h and then cooled to −15 °C. Ethanol (1 ml) and a few drops of acetic acid were added, and the mixture was concentrated to dryness. The product was extracted with chloroform, and crystallized from ether and hexane; yield, 227 mg; mp 55—57 °C; ν_{CO}^{KBr} 1755 cm^{-1}; MS (75 eV) *m/e*: 273 (M^+-CH_3), 169 ($M^+-CH_3-C_2H_5OOCCH_2O-H$), 127 ($M^+-CH_3-C_2H_5OOCCH_2O-CH_2CH(-O-)$); NMR (100 MHz, $CDCl_3$) δ: 1.32 (t, 3H, ethyl ester, J=7 Hz), 1.39 and 1.60 (2s, 6H two isopropylidene methyls), 2.84 (t, 1H, H_a-6, $J_{5,6a}$=5 Hz, J_{gem}=5 Hz), 3.01 (q, 1H, H_b-6, $J_{5,6b}$=3 Hz, J_{gem}=5 Hz), 3.26 (m, 1H, H-5), 3.82 (q, 1H, H-4, $J_{3,4}$=9 Hz, $J_{4,5}$=5 Hz), 4.71 (t, 1H, H-2, $J_{1,2}$=4 Hz, $J_{2,3}$=4 Hz), 5.79 (d, 1H, H-1, $J_{1,2}$=4 Hz).

Found: C, 54.28; H, 6.81%. Calcd for $C_{13}H_{20}O_7$; C, 54.16; H, 6.99%.

3-O-Cyanomethyl-1,2:5,6-di-O-isopropylidene-α-D-allofuranose (3e). To a stirred mixture of **3a** (19.5 g, 7.5 mmol) and sodium hydride (1.8 g, 7.5 mmol) in dry tetrahydrofuran (200 ml), cooled at −15 °C, was added bromoacetonitrile (10 g, 8.3 mmol) dropwise. The mixture gradually became dark and was stirred at room temperature for 3 h. Ethanol (10 ml) was added at 0 °C to quench any remaining sodium hydride. After concentration of the mixture, the products were extracted with ethyl actate. TLC showed the presence of one major product as well as a few minor ones. Silica gel chromatography, developed with mixtures of benzene and ethyl actate (4—2: 1), and crystallization from ethyl actate and hexane, afforded 7.5 g (33%) of **3e**: mp 109 °C. Similarly, from 13 g of **3a** and 10 g of chloroacetonitrile, 5.1 g of **3e** was obtained; M^+-CH_3 *m/e* 284 (base peak); NMR (100 MHz, $CDCl_3$) δ: 1.36 and 1.49 (2s, 6H,two methyls of one isopropylidne group), 1.36 and 1.57 (2s, 6H two methyls of one isopropylidene group), 4.41 and 4.54 (two d, 2H, OCH_2CN, J_{gem}=16 Hz), 5.81 (d, 1H, H-1, $J_{1,2}$=4 Hz).

Found: C, 55.78; H, 6.96; N, 4.56%. Calcd for $C_{14}H_{21}O_6N$: C, 56.17; H, 7.07; N, 4.68%.

3-O-Cyanomethyl-1,2-O-isopropylidene-α-D-allofuranose (5j). A solution of **3e** (1 g) in 70% acetic acid (50 ml) was allowed to stand at room temperature overnight and was concentrated below 37 °C to dryness. The residue was well dried over phosphorous pentoxide and sodium hydroxide; it was subsequently chromatographed on silica gel developed with ethyl acetate and with a mixture of ethyl acetate and methanol (9: 1) to give a syrup; yield, 730 mg (76%); MS (75 eV) *m/e*: 244 (M^+-CH_3), 198 (M^+-HOCH_2CHOH); NMR (100 MHz, $CDCl_3$) δ: 1.36 and 1.55 (two s, 6H, two isopropylidene methyls), 5.84 (d, 1H, H-1, $J_{1,2}$=4 Hz).

Found: C, 50.68; H, 6.52; N, 5.21%. Calcd for $C_{11}H_{17}NO_6$: C, 50.96; H, 6.61; N, 5.40%.

3-O-Cyanomethyl-1,2-O-isopropylidene-6-O-tosyl-α-D-allofuranose (5k) and 3-O-Cyanomethyl-5,6-di-O-tosyl-1,2-O-isopropylidene-α-D-allofuranose (5l). A mixture of **5j** (1.84 g, 7.1 mmol) and tosyl chloride (2.6 g, 13.6 mmol) in pyridine (30 ml) was allowed to stand at room temperature overnight, and ice water was added. TLC of the chloroform extract showed the formation of two products, which were separated by silica gel chromatography developed with mixtures of benzene and ethyl acetate (4—1: 1).

The less polar compound, identified as the ditosylate **5l**, was obtained as a syrup (1.3 g) by precipitation from benzene and hexane; M^+-CH_3 *m/e* 552; NMR (100 MHz, $CDCl_3$) δ: 1.32 and 1.49 (2s, 6H, two isopropylidene methyls), 2.43 (s, 6H, methyls of two tosyl groups), 4.35 (s, 2H, OCH_2CN), 4.69 (t, 1H, H-2, $J_{1,2}$=4 Hz, $J_{2,3}$=4 Hz), 4.90 (m, 1H, H-5), 5.55 (d, 1H, H-1, $J_{1,2}$=4 Hz).

Found: C, 52.72; H, 5.15; N, 2.48; S, 11.11%. Calcd for $C_{25}H_{29}O_{10}NS_2$: C, 52.90; H, 5.15; N, 2.47; S, 11.30%.

The more polar compound, identified as the monotosylate **5k**, was obtained as a syrup by precipitation from benzene and hexane; M^+-CH_3 *m/e* 398; NMR (100 MHz, $CDCl_3$) δ: 1.34 and 1.52 (two s, 6H, two isopropylidene methyls), 2.44 (s, 3H, methyl of the tosyl group), 4.35 and 4.43 (two d, 2H, OCH_2CN, J=16 Hz), 4.72 (t, 1H, H-2, $J_{1,2}$=4 Hz, $J_{2,3}$=4 Hz), 5.77 (d, 1H, H-1, $J_{1,2}$=4 Hz), 7.34 and 7.80 (2d, 4H four aromatic protons of the tosyl group, J_{ortho}=8 Hz).

Found: C, 52.26; H, 5.63; N, 3.23; S, 7.53%. Calcd for $C_{18}H_{23}O_8NS$: C, 52.29; H, 5.61; N, 3.39; S, 7.76%.

5,6-Anhydro-3-O-cyanomethyl-1,2-O-isopropylidene-α-D-allofuranose (6c). A mixture of **5k** (306 mg, 0.74 mmol) and sodium hydride (21 mg, 0.87 mmol) in dry tetrahydrofuran (10 ml) was stirred at room temperature for 20 h. TLC showed the formation of a single product. Ethanol (1 ml) and a few drops of acetic acid were added, and, after the mixture had been concentrated, the product was extracted with ethyl acetate. Precipitation from ether and hexane afforded 152 mg of a syrup; MS (75 eV) *m/e*: 226 (M^+-CH_3), 169 ($M^+-CH_3-CNCH_2O-H$), 127 ($M^+-CH_3-CNCH_2O-CH_2CH(-O-)$), NMR (100 MHz, $CDCl_3$ δ: 1.35 and 1.54 (2s, 6H two isopropylidene methyls), 2.73 (q, 1H, H_a-6, $J_{5,6a}$=3 Hz, J_{gem}=5 Hz), 2.88 (t, 1H, H_b-6, $J_{5,6b}$=5 Hz, J_{gem}=5 Hz), 3.20 (q, 1H, H-5), 3.88 (q, 1H, H-3, $J_{2,3}$=4 Hz, $J_{3,4}$=8 Hz), 4.08 (q, 1H, H-4, $J_{3,4}$=8 Hz, $J_{4,5}$=3.5 Hz), 4.38

and 4.47 (two d, 2H, OCH_2CN, $J_{gem}=16$ Hz), 4.72 (t, 1H, H-2, $J_{1,2}=4$ Hz, $J_{2,3}=4$ Hz), 5.82 (d, 1H, H-1, $J_{1,2}=4$ Hz).

Found: C, 54.65; H, 6.25; N, 5.71%. Calcd for $C_{11}H_{15}NO_5$: C, 54.76; H, 6.27; N, 5.81%.

Methyl 3,7-Anhydro-7-bis(C-ethoxycarbonyl)-6-deoxy-1,2-O-isopropylidene-D-allo-heptoside (8). A solution of **7a** (270 mg) in methanol containing dry HCl (0.01 M, 10 ml) was allowed to stand at room temperature for 7 h and concentrated while keeping the temperature below 40 °C. An ice-cooled solution of sodium hydrogencarbonate was added, and the product was extracted with ethyl acetate. Silica gel chromatography, developed with a mixture of benzene and ethyl acetate (1: 1), and crystallization from benzene and hexane afforded 177 mg of **8**; mp 90 °C; MS (75 eV) *m/e*: 377 (M^+-CH_3), 361 (M^+-OCH_3); NMR (100 MHz, $CDCl_3$) δ: 1.23 and 1.29 (two t, 6H, ethyl ester $J=7$ Hz), 1.47 and 1.49 (two s, 6H, two isopropylidene methyls), 2.23 and 2.76 (two dd, 2H, H_a-6 and H_b-6, $J_{5,6a}=3$ Hz, $J_{5,6b}=4$ Hz, $J_{gem}=15$ Hz), 3.41 (s, 3H, OCH_3), 5.33 (d, 1H, H-1, $J_{1,2}=1$ Hz).

Found: C, 50.61; H, 7.08%. Calcd for $C_{17}H_{28}O_{10}$: C, 50.29; H, 6.63%.

3,7-Anhydro-7-bis(C-ethoxycarbonyl)-6-deoxy-D-allo-heptose Dimethyl Acetal (9). A solution of **7a** (193 mg) in methanol containing dry HCl (0.5 M, 10 ml) was allowed to stand at room temperature overnight; subsequently it was concentrated while keeping the temperature below 40 °C. An ice-cooled solution of sodium hydrogencarbonate was added, and the product was extracted with ethyl acetate. Silica gel chromatography, developed with ethyl acetate followed by a mixture of ethyl acetate and methanol (9: 1), afforded 60 mg of an amorphous solid. For analysis it was fractionally precipitated from ethyl acetate and hexane. It showed no definite mp; NMR (100 MHz, $CDCl_3$) δ: 1.25 and 1.29 (two t, 6H, ethyl ester, $J=7$ Hz), 2.21 and 2.77 (two dd, 2H, H_a-6 and H_b-6, $J_{5,6a}=3$ Hz, $J_{5,6b}=4$ Hz, $J_{gem}=15$ Hz), 3.44 and 3.76 (two s, 6H, $2OCH_3$).

Found: C, 49.11; H, 6.90%. Calcd for $C_{15}H_{26}O_{10}$: C, 49.17; H, 7.15%.

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