# Selective Formation of 2 Esters of Some Methyl α-D-Hexopyranosides via Dibutylstannylene Derivatives

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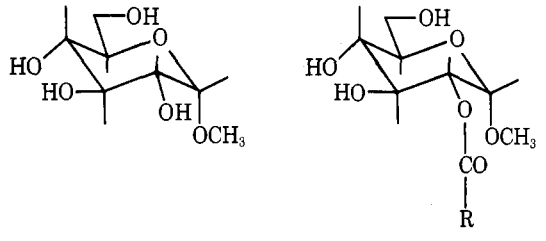
Selective esterification of several methyl D-hexopyranosides by means of base-catalyzed transesterification, *N*-acylimidazoles, and dibutylstannylene derivatives of the carbohydrates revealed the last mentioned method to be most effective when dealing with the α-pyranosides. The NMR spectra and differences in reactivity suggest that the selective formation of C2 esters is associated with a coordination of tin with the α-methoxy group. The selective formation of C2 esters of methyl α-D-gluco-, α-D-allo-, and α-D-galactopyranosides is described even in the presence of the unblocked C6-hydroxyl group.

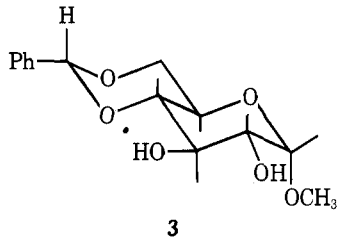
The primary hydroxyl groups of carbohydrates are considered to be more reactive toward esterification and alkylation than the secondary hydroxyl groups.[1] Consequently, the synthesis of carbohydrates substituted at a secondary hydroxyl group and containing a free primary hydroxyl usually requires the application of blocking–deblocking techniques[2] as well as tedious separation procedures that lower the yields of the desired product. The conversion of methyl α-D-glucopyranoside (1) to methyl 2-*O*-benzoyl-α-D-glucopyranoside (**2a**),[3] for example, or of the corresponding 2-*O*-mesyl and 2-*O*-tosyl esters,[4] required a three-step procedure and the separation from relatively large amounts of the 3 isomers.



1



2



3

a, R = Ph
b, R = $CH_3(CH_2)_{10}$
c, R = $CH_3(CH_2)_{12}$

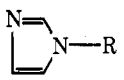
Our interest in isomerically pure monoesters of sugars prompted a search for a more efficient route to 2 esters (e.g., **2**). This paper describes the results of base-catalyzed transesterifications as well as a selective, high-yield process for accomplishing the desired transformation in essentially one step by using the dibutylstannylene intermediates of the carbohydrates.

## Results and Discussion

The direct esterification of 4,6-*O*-benzylidene D-hexopyranosides leads to a mixture of 2 and 3 esters depending on the nature of the esterifying reagent (see Table I). When the corresponding benzal derivative of 1 (**3**) was allowed to react with ethyl myristrate under base-catalyzed transesterification conditions there was obtained a mixture of the two monoesters, the diester, and unreacted starting material even though the esterification was limited to only two hydroxyl sites. The analogous transesterification in the presence of potassium methoxide and 18-crown-6 did not affect the ratio of the 2 and 3 esters.

Selective esterification by means of base-catalyzed transesterification is complicated also by the possibility of intramolecular migration of the acyl group. Thus, when the 2-myristate of **3** (**4**) was heated for ca. 40 h in DMF in the presence of a catalytic amount of solid $K_2CO_3$, the starting material and the corresponding 3 ester (**5**) were isolated in equal amounts.

In view of the considerable success of acylimidazoles[6] in selective esterification reactions,[7] we allowed **2** to react with **6** in refluxing chloroform for a period of 16 h. It was found that

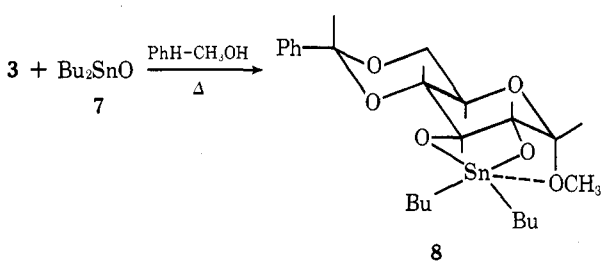


6

a, R = PhCO
b, R = $CH_3(CH_2)_{12}CO$
c, R = *p*-$CH_3PhSO_2$
d, R = $CH_3(CH_2)_{10}CO$

the initially formed 2 esters were subect to imidazole-catalyzed isomerization and longer reaction times (30–40 h) led to varying amounts of the 2 and 3 esters. Methyl 4,6-*O*-benzylidene-β-D-glucopyranoside and methyl 4,6-*O*-benzylidene-α-D-mannopyranoside could not be selectively esterified by means of this procedure.[7f,9]

Di-*n*-butyltin oxide (**7**) was recently used for the selective introduction of a tosyl group at the 2′-OH group of nucleosides.[8] We have found that an equimolar mixture of **3** and **7** upon heating in methanol–benzene (1:10) for 45 min gave a crystalline material (**8**) which was isolated upon the removal of the solvents in vacuo. The elemental analysis and NMR



7 8

spectrum were consistent with the structure of methyl 4,6-*O*-benzylidene-2,3-*O*-dibutylstannylene-α-D-glucopyranoside (**8**). The chemical shifts of representative protons in **3** and **8** are given in Table II. The chemical shift differences between **3** and **8** are attributed to (a) the deshielding of the anomeric hydrogen and of the C1 methoxy group because of a coordination between the C1 methoxy group and tin as suggested in **8**; and (b) a conformational change in the dioxane ring induced by the tendency of the five-membered stannylene ring to approach coplanarity.

When **8** was treated at room temperature with a dioxane solution of benzoyl chloride in the presence of triethylamine the 2-benzoate was isolated in 85% yield. Similarly it was possible to prepare the 2-myristate (**4**), the 2-laurate, and the 2-*O*-tosylate in good yields (70–90%). In the case of the car-

Table I. Selective Esterification of 4,6-*O*-Benzylidene D-Hexopyranosides

| Compd | Conditions[e] | 2 ester, % | 3 ester, % | 2,3 diester, % | Ref |
|---|---|---|---|---|---|
| α-D-Glucoside | A | 24 | 6 | 35 | *a* |
| | B | 13 | 25 | 9 | *a* |
| | C | 25 | 20 | 10 | *b* |
| | D | 82 | 0 | 0 | *b* |
| | D′ | 93 | 7 | 0 | *b* |
| | E | 92 | 1 | 0 | *b* |
| | E | 94 | 1 | 0 | *b* |
| | F | 62 | 0 | 0 | *d* |
| β-D-Glucoside | C | 26 | 34 | 0 | *b* |
| | D | 30 | 35 | 0 | *b* |
| | E′ | 30 | 20 | 0 | *b* |
| α-D-Mannoside | A | 19 | 20 | 33 | *c* |
| | C | 37 | 32 | 3 | *b* |
| | D | 50 | 50 | | *d* |
| | F | 57 | 25 | | *d* |
| | E′ | 25 | 35 | | *b* |
| α-D-Galactoside | E″ | 64 | 0 | 0 | *b* |
| α-D-Alloside | E′ | 91 | 0 | 0 | *b* |

[a] R. W. Jeanloz and D. A. Jeanloz, *J. Am. Chem. Soc.*, 79, 2579 (1957). [b] This work. [c] R. W. Jeanloz and D. A. Jeanloz, *J. Am. Chem. Soc.*, 80, 5692 (1958); [d] S. A. Abbas and A. H. Haines, *Carbohydr. Res.*, 39, 358 (1975). [e] A, PhCOCl, $C_5H_5N$; B, $(PhCO)_2O$, $C_5H_5N$; C, $CH_3(CH_2)_{12}CO_2Et$, $K_2CO_3$; D, PhCO–imidazole, $CHCl_3$; D′, $CH_3(CH_2)_{12}CO$–imidazole, $CHCl_3$; E, $Bu_2SnO$, $CH_3(CH_2)_{12}COCl$, $Et_3N$; E′, $Bu_2SnO$, PhCOCl, $Et_3N$; E″, $Bu_2SnO$, *p*-TsCl, $Et_3N$; F, PhCOCN, $Et_3N$.

Table II. NMR Parameters for Some Protons in 3 and 8 in $CDCl_3$[a]

| Compd | δ PhC(=O)–H | MeO–C(=O)–H | –C–OCH₃ |
|---|---|---|---|
| 3 | 5.52 (s) | 4.75 (d) ($J_{1,2}$ = 3.5 Hz) | 3.38 (s) |
| 8 | 5.45 (s) | 4.85 (d) ($J_{1,2}$ = 3.0 Hz) | 3.45 (s) |

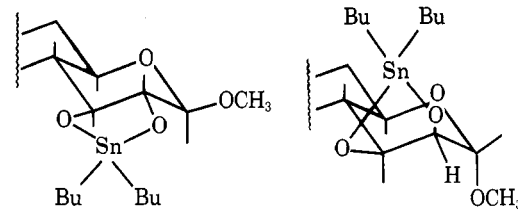
[a] δ($Me_4Si$) 0.

boxylic acid esters, the reaction was complete in 5–15 min, while the formation of the tosylate turned out to be much slower (3–5 h). During the formation of the 2-laurate there was isolated 3% of the 3-laurate.

Acylation of the analogous tin derivatives of methyl β-D-glucopyranoside and methyl α-D-mannopyranoside failed to be selective. In each case there were obtained approximately equal amounts of the 2 and 3 esters in addition to a rather high recovery of the starting sugars. The explanation for this difference in behavior may be in the inability of the respective tin compounds **9** and **10** to give coordination between the metal and the α-methoxy group as suggested in the case of **8**. This explanation is consistent with the fact that the tin compound of methyl 4,6-*O*-benzylidene-α-D-galactopyranoside (**11**) again give the 2-tosylate selectively when it was treated with *p*-toluenesulfonyl chloride and triethylamine. Likewise the methyl 2-*O*-benzoyl-α-D-allopyranoside was prepared in 90% yield when methyl 4,6-*O*-benzylidene-2,3-*O*-dibutylstannylene-α-D-allopyranoside was treated with benzoyl chloride in the presence of triethylamine.

Selective esterification brought about by means of dibutylstannylene derivatives was next investigated using the free, unprotected sugars.

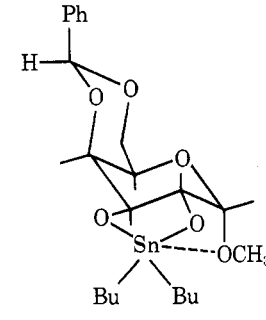
The reaction of equimolar amounts of dibutyltin oxide and methyl α-D-glucopyranoside (**1**) in methanol gave a quantitative yield of **12** and the latter was then converted to the



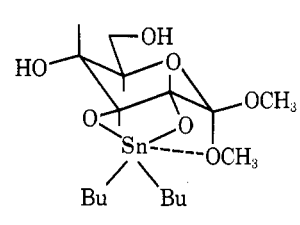
**9**



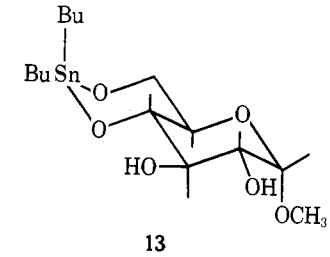
**10**



**11**

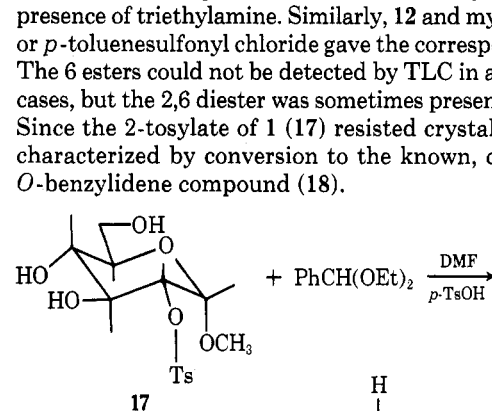


**12**

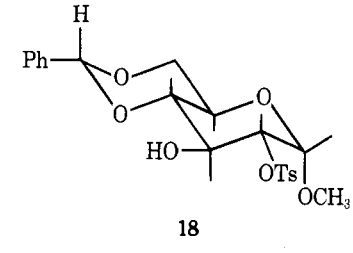


**13**

methyl 2-*O*-benzoyl-α-D-glucopyranoside in 80–90% yield by means of a subsequent reaction with benzoyl chloride in the presence of triethylamine. Similarly, **12** and myristoyl chloride or *p*-toluenesulfonyl chloride gave the corresponding 2 esters. The 6 esters could not be detected by TLC in any of the above cases, but the 2,6 diester was sometimes present in 1–2% yield. Since the 2-tosylate of **1** (**17**) resisted crystallization, it was characterized by conversion to the known, crystalline, 4,6-*O*-benzylidene compound (**18**).



**17**

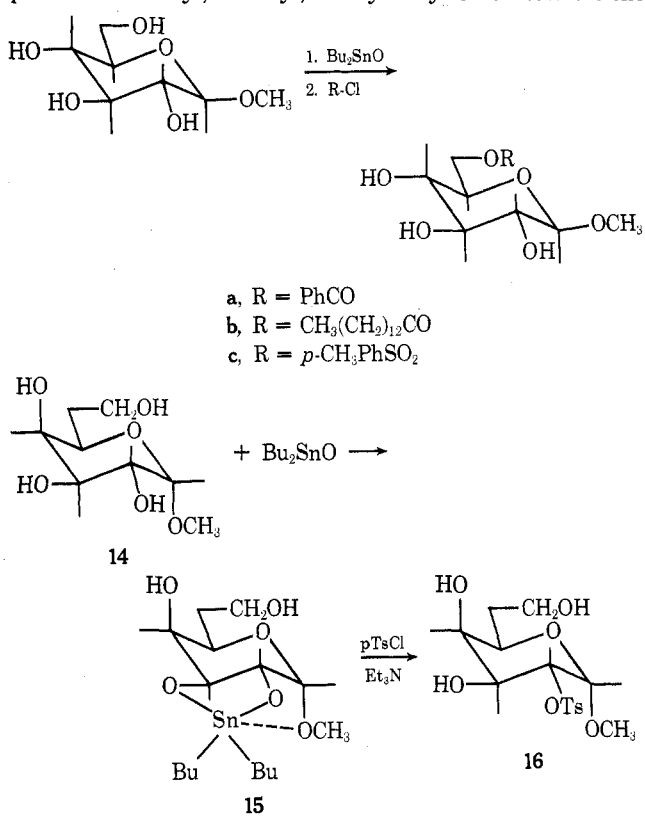


**18**

The fact that the 2 esters were formed in the presence of the "more reactive" primary C6-OH suggests that the dibutylstannylene of **1** has the structure **12** rather than **13**. The presumed preference for the formation of the five-membered stannylene ring could be due to the favorable semiequatorial conformation of the *gem*-di-*n*-butyl groups, whereas one of these bulky groups would be forced into an unfavorable axial conformation in the case of the six-membered compound **13**. A similar rationale is sometimes offered[10] to explain the great tendency of acetone to form the five-membered dioxolanes with glucose, while benzaldehyde favors the six-membered dioxanes. Unfortunately this hypothesis could not be tested, so far, owing to the hydrolytic instability of the tin compounds.

Structure **12** may also be favored over **13** because of the additional coordination of tin with the C1 methoxy group.

By contrast, methyl β-D-glucopyranoside could not be selectively esterified at position 2 under the conditions successful with its α anomer **1**. In fact, only the 6 esters were obtained (~80% yield) when the material obtained by treatment of methyl β-D-glucopyranoside with **7** was treated with either *p*-toluenesulfonyl, benzoyl, or myristoyl chlorides. On the other hand, methyl α-D-galactopyranoside (**14**) was easily converted to 2-tosylate **16** via the tin compound presumed to have the structure **15**. The syrupy **16** was characterized by its conversion to the known crystalline methyl 2-*O*-tosyl-4,6-*O*-benzylidene-α-D-galactopyranoside using a DMF solution of benzaldehyde diethyl acetal in the presence of *p*-TsOH catalyst.




14 15 16

In conclusion, the method described here for the selective preparation of 2 esters of methyl α-D-gluco-, α-D-galacto-, and α-D-allopyranosides illustrates an extremely useful application of organotin alkoxides in organic synthesis.[11] Its success appears to depend on the selective reactivity at the C2-O when the 2,3-stannylene intermediate is capable of coordination between the α-methoxy group and tin. Work is in progress to extend this selective esterification method to disaccharides such as sucrose.

## Experimental Section

Melting points were determined by means of a Mel-Temp apparatus and are uncorrected. TLC was carried out on silica gel G coated plates and detection was effected by charring with 50% $H_2SO_4$. NMR spectra were recorded at 60 MHz with a Varian A-60A spectrometer using $Me_4Si$ as an internal standard. Ir spectra were recorded as KBr pellets with a Perkin-Elmer Model 475 spectrometer. Elemental analyses were carried out by M-H-W Laboratories, Garden City, Mich.

**Methyl 2,3-*O*-Dibutylstannylene-α-D-glucopyranoside (12).** Dibutyltin oxide (12.50 g, 50 mmol) was added to a solution of methyl α-D-glucopyranoside (**1**, 9.7 g, 50 mmol) in methanol (200 ml) and the resulting milky solution was refluxed until it became homogeneous and clear (45 min). After refluxing for an additional 0.5 h, the solvents were evaporated in vacuo to leave a white solid, mp range 105–115 °C. Anal. Calcd for $C_{15}H_{30}O_6Sn$: C, 42.12; H, 7.06. Found: C, 41.63; H, 7.18.

**Methyl 2-*O*-Myristoyl-α-D-glucopyranoside (2c). A.** Methyl 2,3-*O*-dibutylstannylene-α-D-glucopyranoside (**12**, 4.25 g, 10 mmol) in dioxane (75 ml) was treated with triethylamine (1.54 ml, 11 mmol) followed by a slow addition (5 min) of myristoyl chloride (2.71 g, 11 mmol) in dioxane (10 ml). After 1 h at room temperature, TLC (ethyl acetate, silica gel G) indicated the absence of starting material and the presence of a major spot at $R_f$ 0.55 and of a minor spot at $R_f$ 0.78. After stirring for an additional 1 h, the salts were filtered and washed with dioxane (15 ml). Evaporation of the combined filtrates in vacuo gave a syrup which was passed through a column of silica gel G (200 g) using ethyl acetate as the eluent. The fractions containing the 2-*O*-myristoyl derivative were combined and crystallized from ethyl acetate–petroleum ether (bp 30–60 °C) at 5 °C to give a white solid (2.95 g, 73%) mp 94–96 °C, mmp (with product prepared as in B below) 94–97 °C. Anal. Calcd for $C_{21}H_{40}O_7$: C, 62.38; H, 9.90. Found: C, 62.31; H, 9.82.

**B.** Methyl 2-*O*-myristoyl-4,6-*O*-benzylidene-α-D-glucopyranoside (**4**, 1 g) was hydrolyzed using 75% aqueous acetic acid to give the methyl 2-*O*-myristoyl-α-D-glucopyranoside (**2c**) in 80% yield, mp 95–96 °C, mmp 94–97 °C.

**Methyl 2-*O*-Benzoyl-α-D-glucopyranoside (2a). A.** To a magnetically stirred, slightly cloudy solution of methyl 2,3-*O*-dibutylstannylene-α-D-glucopyranoside (**12**, 4.25 g, 10 mmol) in dioxane (75 ml) there was added triethylamine (1.54 ml, 11 mmol) followed by slow addition of benzoyl chloride (1.32 ml, 11 mmol). The solution became clear upon addition of the benzoyl chloride but a white precipitate started forming ~2 min later. TLC examination of the solution (ethyl acetate, silica gel G) after 1 h showed the presence of a major spot at $R_f$ 0.50 and a minor spot at $R_f$ 0.70. The salts were filtered and washed with dioxane (20 ml) and the combined filtrates were evaporated in vacuo to leave a syrup which was fractionated on a column of silica gel G (120 g) using ethyl acetate as eluent. The first compound eluted from the column was methyl 2,6-di-*O*-benzoyl-α-D-glucopyranoside (0.08 g, ~2%), mp 139–140 °C (lit.[3] 141–142 °C). Anal. Calcd for $C_{21}H_{22}O_8$: C, 62.67; H, 5.51. Found: C, 62.55; H, 5.77.

The second compound eluted from the column was the desired material **2a** (2.05 g, 70%). Crystallization from EtOAc–petroleum ether gave white crystals, mp 179–180 °C, mmp 177.5–178.5 °C (lit.[3] mp 174–175 °C). Anal. Calcd for $C_{14}H_{18}O_7$: C, 56.37; H, 6.04. Found: C, 56.38; H, 6.09.

**B.** Methyl 2-*O*-benzoyl-4,6-*O*-benzylidene-α-D-glucopyranoside (1.5 g) was heated at 75–80 °C for 1 h in 75% aqueous acetic acid. The solvents were then removed in vacuo and the white residue was dissolved in hot ethyl acetate to which light petroleum ether (bp 30–60 °C) was added until crystallization started. The white crystals which were collected (1.10 g, 98%) had mp 177–178.5 °C and mmp 177.5–179 °C.

**Methyl 4,6-*O*-Benzylidene-2,3-*O*-dibutylstannylene-α-D-glucopyranoside (8).** A mixture of **3** (8.50 g, 30 mmol) and dibutyltin oxide (7.70 g, 30 mmol) was refluxed in benzene–methanol (150–15 ml) until the solution became clear (~45 min). It was then left at 50–55 °C for 14 h and then the solvents were removed in vacuo to leave a white solid (14.5 g, 91%), mp 194–195 °C. Anal. Calcd for $C_{22}H_{34}O_6Sn$: C, 51.50; H, 6.60. Found: C, 51.35; H, 6.69.

**Methyl 4,6-*O*-Benzylidene-2-*O*-tosyl-α-D-glucopyranoside.** Triethylamine (1.44 ml) was added to the tin compound **8** (5.14 g) in dioxane (100 ml) followed by *p*-TsCl (1.90 g) in dioxane (20 ml). The solution was stirred overnight and then the undissolved salts were filtered and washed with dioxane. The syrup obtained on evaporation of the solvent in vacuo was dissolved in hot ethyl acetate and light petroleum ether was added to initiate crystallization. The product was collected as white needles (3.05 g, 70%), mp 153–154 °C (lit.[12] mp 153–154 °C).

**Methyl 2-*O*-Benzoyl-4,6-*O*-benzylidene-α-D-glucopyranoside. A.** Triethylamine (1.44 ml) was added to the tin compound **8** (5.14 g, 10 mmol) dissolved in dioxane (100 ml). Benzoyl chloride (1.20 ml, 10 mmol) in dioxane (20 ml) was then slowly added to the cooled (~5 °C) mixture. The solution was stirred for 6 h at ambient temperature and the solids filtered. The solvent was evaporated to leave a syrup which was dissolved in hot ethyl ether to which was slowly added petroleum ether (bp 30–60 °C) until milky. Crystals of the title compound were collected after 16 h at 5 °C, mp 168–170 °C (3.35 g, 86%).

**B.** The tin compound **8** was prepared in situ by refluxing a solution of **3** (1.41 g, 5 mmol) and dibutyltin oxide (1.25 g, 5 mmol) in dry methanol (50 ml) for 45 min. After the solution was cooled to 5 °C, triethylamine (3.5 ml, 25.0 mmol) was added at once followed by slow addition of benzoyl chloride (3.0 ml, 25 mmol). TLC examination of the reaction mixture after 5 min indicated the presence of a single spot at $R_f$ 0.70 (ethyl ether–petroleum ether, 2:1 v/v). After 2 h at ambient

temperature, the solvents were removed in vacuo, the resulting residue was dissolved in acetone, and the triethylamine hydrochloride was filtered. Evaporation of the acetone extract left a syrupy material which was placed on a silica gel G column (120 g) and eluted with ethyl ether–petroleum ether (2:1 v/v). The first fractions collected contained methyl benzoate. The second compound eluted from the column was the desired material (1.32 g), mp 165 °C. Crystallization from ethyl ether–petroleum ether gave the pure compound as needles, mp 173.5–175 °C (lit.[13] mp 169–170 °C). Anal. Calcd for $C_{21}H_{22}O_7$: C, 65.28; H, 5.70. Found: C, 65.20; H, 5.89.

Lastly, the unreacted starting sugar **3** was eluted from the column (0.27 g). The reaction occurred with 81% conversion and the yield was 85%.

**Methyl 4,6-*O*-Benzylidene-2-*O*-tosyl-α-D-galactopyranoside.** Methyl α-D-galactopyranoside (**14**, 9.7 g) was refluxed with $Bu_2SnO$ (12.5 g) in MeOH (170 ml) for 1.5 h. Evaporation of the MeOH in vacuo at 50 °C left a glassy solid (**15**), mp 75–85 °C. Anal. Calcd for $C_{15}H_{30}O_6 \cdot H_2O$: C, 40.83; M, 7.04. Found: C, 40.63; H, 7.22. Methyl 2,3-*O*-dibutylstannylene-α-D-galactopyranoside (**15**, 3.20 g) in dioxane (50 ml) was treated successively with $Et_3N$ (1.2 ml) and *p*-TsCl in dioxane (10 ml). After 1 h at ambient temperature TLC indicated the presence of a major spot at $R_f$ 0.20 (EtOAc) and a minor spot at the origin. The reaction was complete after 6 h at 25 °C. The salts were filtered and washed, and the filtrates were evaporated under diminished pressure to leave a syrup which resisted crystallization. Treatment of the syrup (1.20 g) with benzaldehyde diethyl acetal (5 ml) in DMF (10 ml) and a catalytic amount of *p*-toluenesulfonic acid monohydrate for 16 h followed by neutralization of the acid (solid $K_2CO_3$) and evaporation of the solvents left a syrup which was crystallized from ethyl acetate to give needles, mp 176–178 °C (lit.[14] mp 179–180 °C). Anal. Calcd for $C_{21}H_{24}O_8S$: C, 57.80; H, 5.51; S, 7.34. Found: C, 58.00; H, 5.60; S, 7.50.

**Methyl 4,6-*O*-Benzylidene-2-*O*-lauroyl-α-D-glucopyranoside. A.** Triethylamine (0.7 ml) was added to a stirred solution of **8** (2.57 g) in dioxane (50 ml) and this was followed by slow addition of 1.0 g (10 ml) of lauroyl chloride. After 40 min at ambient temperature the solid salts were filtered and washed with dioxane (10 ml). The combined solvents were evaporated to leave a white residue which was placed on a column of silica gel and eluted with ether–petroleum ether (1:1 v/v). The 2-*O*-lauroyl derivative of **3** was eluted first (1.26 g, 81%), mp 87–89 °C. Anal. Calcd for $C_{26}H_{40}O_7$: C, 67.46; H, 8.62. Found: C, 67.92; H, 9.07. The second fraction from the column was the 3-laurate (0.06 g, 3%), mp 115–117 °C. Anal. Calcd for $C_{26}H_{40}O_7$: C, 67.46; H, 8.62. Found: C, 67.80; H, 8.97. A portion of unreacted **3** (0.50 g) was recovered.

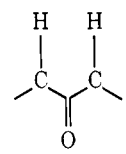
**B.** Lauroylimidazole [**6d**, R = $CH_3(CH_2)_{10}CO$] was prepared from imidazole (0.68 g, 0.01 mol), dissolved in reagent grade $CHCl_3$ (10 ml), and lauroyl chloride (1.1 g, 0.005 mol) added dropwise to the magnetically stirred solution kept at 10 °C. The resulting white suspension was filtered and the filtrate (containing *N*-lauroylimidazole) was added to **3** (1.41 g, 0.005 mol) in $CHCl_3$ (20 ml). After the mixture was refluxed for 20 h the solution was cooled and extracted successively with 5% bicarbonate (20 ml) and saturated NaCl (2 × 10 ml). After drying over $Na_2SO_4$ the $CHCl_3$ solution was evaporated to leave 2.2 g of product and this was separated on a column of silica gel using ether–petroleum ether to give the 2-laurate (83%) and the 3-laurate (6.3%).

**Methyl 4,6-*O*-Benzylidene-2-*O*-myristoyl-β-D-glucopyranoside by Transesterification.** Methyl 4,6-*O*-benzylidene-β-D-glucopyranoside (3.0 g, 11 mmol) was placed in a 100-ml three-neck round-bottom flask containing dry $Me_2SO$ (60 ml), fitted with a magnetic stirring bar, a nitrogen inlet tube, and a rubber septum and connected to a regulated water aspirator. The mixture was heated to 80 °C and then ethyl myristate (2.56 g, 10 mmol) was added, followed by 0.05 g of solid, finely ground $K_2CO_3$. After 90 h at 80 °C and 60 Torr, the solvent was taken off in vacuo to leave a solid which was extracted with ether. The ethereal extract was washed with 5% NaCl solution, dried ($Na_2SO_4$), and evaporated to leave 4.5 g of material. This was placed on a column of silica gel (200 g) and eluted using ether–petroleum ether (1:1 v/v). Ethyl myristate was eluted first (1.6 g). Next was eluted the methyl 4,6-*O*-benzylidene-2-*O*-myristoyl-β-D-glycopyranoside. It was crystallized from hexane to give white needles (200 mg), mp 113–115 °C. Anal. Calcd for $C_{28}H_{44}O_7$: C, 68.30; H, 8.94. Found: C, 68.50; H, 8.92.

The corresponding 3-myristate was eluted next and it was similarly crystallized from hexane to give white flakes (270 mg), mp 89–90 °C. Anal. Calcd for $C_{28}H_{44}O_7$: C, 68.30; H, 8.94. Found: C, 68.50; H, 8.77. The methyl 4,6-*O*-benzylidene-β-D-glucopyranoside was eluted last (2.5 g).

**Methyl 4,6-*O*-Benzylidene-2-*O*-myristoyl-α-D-glucopyranoside by Transesterification. Methyl 4,6-*O*-benzylidene-α-D-glucopyranoside** (**3**, 6.5 g, 23 mmol) was placed in a 250-ml three-neck flask fitted with a magnetic stirring bar, a nitrogen inlet tube, and a rubber septum and connected to a regulated water aspirator. Dry $Me_2SO$ (120 ml) was added and the mixture was stirred and brought up to 80 °C. After 10 min, ethyl myristate (2.56 g, 10 mmol) was added followed by solid, finely ground potassium carbonate (0.05 g). The water aspirator was regulated to give 60 Torr during the duration of the reaction. After 50 h, the solvent was taken off in vacuo to leave a solid which was equilibrated between ether and water. The ether layer was washed with concentrated NaCl solution, dried ($Na_2SO_4$), and evaporated to leave a solid which was shown (TLC) to contain **3**, the 2-myristoyl, 3-myristoyl, and 2,3-dimyristoyl derivatives. Separation of the material on column chromatography using petroleum ether–ether (4:1 v/v) as eluent gave ethyl myristate (1.4 g); the 2,3-dimyristate (41 mg), mp 80–82 °C, crystallized from hexane; the 2-myristate (**4**, 615 mg), mp 94–96 °C, crystallized from hexane; and 3-myristate (**5**, 915 mg), mp 121–123 °C, also crystallized from hexane. Compound **3** was eluted last (4.5 g).

The structures of the two monoesters **4** and **5** were deduced from their NMR and ir spectra and by conversion to the corresponding glucopyranosid-3- and -2-uloses using the Pfitzer–Moffatt[5] reagent. Thus the NMR spectrum of the 3-ulose revealed the expected anomeric doublet at δ 5.35 ($J_{1,2}$ = 4.6, $J_{2,4}$ = 1.5 Hz) corresponding to C2 H. The long-range coupling of δ 1.5 Hz is to be expected because the two hydrogen atoms form a symmetrical U relationship around the C3 carbonyl.




On the other hand, the NMR spectrum of the 2-ulose revealed an anomeric singlet at δ 5.28 in agreement with an oxidation at C2.

**Base-Catalyzed Equilibration of 4 and 5.** Methyl 3-*O*-myristoyl-4,6-*O*-benzylidene-α-D-glucopyranoside (30 mg) in DMF (5 ml) was kept at 85 °C in the presence of solid $K_2CO_3$ (10 mg). After 16 h, TLC (ethyl ether–petroleum ether, 1:1) indicated the presence of **4**, **5**, **3**, and some 2,3 diester. Separation was accomplished by preparative TLC: **4** (24%); **5** (24%); **3** (34%); and the diester (18%).

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**Registry No.**—**1**, 93-30-3; **2a**, 21056-53-1; **2c**, 58463-68-6; **3**, 3162-96-7; **4**, 58463-69-7; **5**, 58463-70-0; **6d**, 3867-67-2; **8**, 58463-75-5; **12**, 58525-83-0; **14**, 3396-99-4; **15**, 58463-76-6; dibutyltin oxide, 818-08-6; methyl 2,6-di-*O*-benzoyl-α-D-glucopyranoside, 26927-44-6; methyl 2-*O*-benzoyl-4,6-*O*-benzylidene-α-D-glucopyranoside, 28642-64-0; methyl 4,6-*O*-benzylidene-2-*O*-tosyl-α-D-galactopyranoside, 58463-71-1; methyl 4,6-*O*-benzylidene-2-*O*-lauroyl-α-D-glucopyranoside, 33650-78-1; methyl 4,6-*O*-benzylidene-3-*O*-lauroyl-α-D-glucopyranoside, 58463-72-2; methyl 4,6-*O*-benzylidene-2-*O*-myristoyl-β-D-glucopyranoside, 58463-73-3; methyl 4,6-*O*-benzylidene-β-D-glucopyranoside, 14155-23-8; ethyl myristate, 124-06-1; methyl 4,6-*O*-benzylidene-3-*O*-myristoyl-β-D-glucopyranoside, 58463-74-4; lauroyl chloride, 112-16-3.

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# Halo Sugar Nucleosides. 5.[1] Synthesis of Angustmycin A and Some Base Analogues

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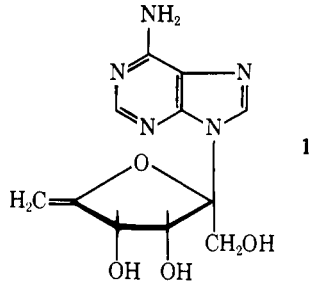
An efficient synthesis of 9-(5-deoxy-β-D-*erythro*-pent-4-enofuranosyl)adenine (**3**) is described via dehydrohalogenation of 5′-deoxy-5′-iodo-$N^6$,$N^6$,$O^{2'}$,$O^{3'}$-tetrabenzoyladenosine (**2c**) with either silver fluoride in pyridine or with DBN in DMF. The synthesis of 1,3,4-tri-*O*-benzoyl-6-deoxy-6-iodo-D-psicofuranosyl bromide (**9**) was achieved starting with D-fructose via oxidation of the 1,2:4,5-di-*O*-isopropylidene derivative followed by borohydride reduction, acid-catalyzed isomerization to the psicofuranose derivative, and iodination by several different routes. Condensation of **9** with several derivatives of adenine provides the 9-(1,3,4-tri-*O*-benzoyl-6-deoxy-6-iodo-β-D-psicofuranosyl) nucleosides (**11**) together with lesser amounts of the α anomers **12**. Dehydrohalogenation of **11** followed by deblocking provides a total synthesis of the nucleoside antibiotic angustmycin A (**1**). Related sequences starting with condensations of **9** with cytosine or 3-methoxycarbonyl-1,2,4-triazole lead to the corresponding base analogues of angustmycin A, **16** and **21**. By appropriate manipulation of the intermediates in the above routes, syntheses of the β-D-psicofuranosyl derivatives of cytosine (**25a**) and of 1,2,4-triazole-3-carboxamide (**22**) are also described.

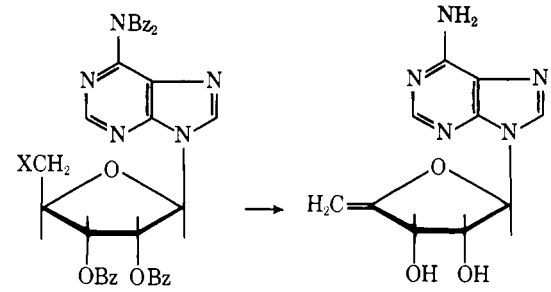
The nucleoside antibiotic angustmycin A,[3] which shows modest antimicrobial[4,6] and antitumor[5] activity, was originally isolated from *S. hygroscopicus* by Yüntsen et al.[6] and an incorrect structure was assigned.[7] Subsequently the antibiotic decoyinine was shown to be identical with angustmycin A, and, based upon spectroscopic evidence, the correct structure was shown to be 9-(6-deoxy-β-D-*erythro*-hex-5-enofuran-2-ulosyl)adenine (**1**).[8]



**1**

The structure of **1** is interesting since it is the only naturally occurring enofuranosyl nucleoside and at the same time is, together with the closely related antibiotic psicofuranine,[8] one of the few examples of nucleosides derived from ketose sugars. Considerable work has already appeared concerning the synthesis of ketohexose nucleosides derived from psicose,[9] fructose,[10] and sorbose,[11] and the structure of angustmycin A stimulated our own interest in the synthesis of 4′,5′-unsaturated ribonucleosides.[12] During the course of our work the conversion of psicofuranine to angustmycin A was described by McCarthy et al.[13] The key to this synthesis was the ingenious use of an orthoformate ester for the simultaneous and selective blocking of the 1′-, 3′-, and 4′-hydroxyl groups in the intact psicofuranine molecule. In the present paper we describe a totally different approach to the synthesis of angustmycin A in which the problem of selective protection is resolved in a key carbohydrate intermediate that can be efficiently condensed with a variety of heterocyclic bases, thus allowing the synthesis of analogues of **1**.

As a prelude to the synthesis of **1** itself we have first examined the synthesis of the somewhat simpler 9-(5-deoxy-β-D-*erythro*-pent-4-enofuranosyl)adenine (**3**). The lability of pent-4-enofuranosides toward acids precluded the use of the 2′,3′-*O*-isopropylidene group for protection of the adenosine sugar moiety. Subsequently, however, it was shown that the 2′,3′-*O*-ethoxymethylidene group could be removed without extensive hydrolysis of the vinyl ether.[13] We preferred to use base labile protecting groups for this purpose, and accordingly fully benzoylated 5′-*O*-trityladenosine giving the $N^6$,$N^6$,$O^{2'}$,$O^{3'}$-tetrabenzoate (**2a**)[14] in essentially quantitative yield. This compound was originally considered to be the $N^1$,$N^6$,$O^{2'}$,$O^{3'}$-tetrabenzoyl derivative but recent work has shown that fully benzoylated adenosine derivatives have both *N*-benzoyl groups at $N^6$.[15] Subsequent detritylation of **2a** with hydrogen chloride in chloroform then gave crystalline $N^6$,$N^6$,$O^{2'}$,$O^3$-tetrabenzoyladenosine (**2b**) in 86% yield without need for chromatography (cf. ref 14). Iodination of **2b** was readily achieved using methyltriphenoxyphosphonium iodide[16] which gave the crystalline 5′-iodo derivative **2c** in 87% yield after only a 10-min reaction at room temperature. It should be noted that attempted iodination of 2′,3′-*O*-isopropylideneadenosine with this reagent gave only an $N^3$,5′-cyclonucleoside.[16] Acylation of the adenine ring, however, is known to substantially reduce the tendency of adenosine derivatives to form such cyclonucleosides.[17] Treatment of **2c** with silver fluoride in pyridine, a reaction used extensively in the pyrimidine series,[12] was only modestly successful in effecting dehydrohalogenation. Following debenzoylation with methanolic ammonium hydroxide and ion exchange chromatography on a basic resin[18] crystalline **3** was obtained, but only in 15% overall yield. Much better results were obtained



**2a**, X = Tr
**b**, X = OH
**c**, X = I

**3**