Neighboring-Group Participation in Carbohydrate Chemistry. V.[1] Direct Evidence for the Participation of the β-Trans-Axial Benzoyloxy Group in the Nucleophilic Displacement of Methylsulfonate of Methyl 4,6-Di-*O*-benzoyl-3-*O*-methyl-2-*O*-methylsulfonyl-β-D-galactopyranoside and Methyl 2,6-Di-*O*-benzoyl-3-*O*-methyl-4-*O*-methylsulfonyl-β-D-mannopyranoside[2]

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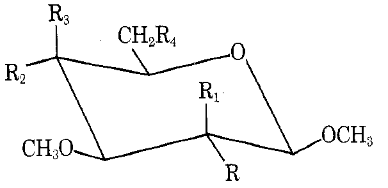
Refluxing of an *N,N*-dimethylformamide solution of methyl 4,6-di-*O*-benzoyl-3-*O*-methyl-2-*O*-methylsulfonyl-β-D-galactopyranoside (7) (120 hr) or methyl 2,6-di-*O*-benzoyl-3-*O*-methyl-4-*O*-methylsulfonyl-β-D-mannopyranoside (11) (10 hr) with potassium benzoate gave methyl 2,4,6-tri-*O*-benzoyl-3-*O*-methyl-β-D-galactopyranoside (4) and methyl 2,4,6-tri-*O*-benzoyl-3-*O*-methyl-β-D-mannopyranoside (6) as the only isolable products, the **6**:**4** ratio being the same in both cases (~3:1). The greater reactivity of **11** vs. **7**, as well as the predominant formation of **6** vs. **4** was rationalized in terms of the electron-withdrawing effect of the anomeric carbon atom.

It is known that the reactivity of the sulfonyloxy group of a hexopyranoside toward direct nucleophilic displacement strongly depends upon its position in the carbohydrate molecule,[4] and upon the energy of the SN2 transition state,[3-5] i.e., upon the torsional strain, steric nonbonded and electrostatic interactions between the approaching nucleophile or leaving sulfonate, and other substituents of the pyranoside ring.

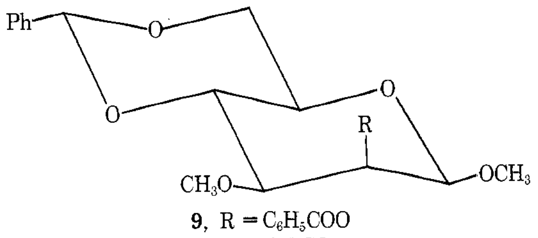
Except for the 6-sulfonate of galactopyranoside derivatives, direct nucleophilic displacement of the sulfonyloxy group attached to the primary (C-6) carbon atom is considerably faster than direct nucleophilic displacement of sulfonates attached to a secondary carbon atom of the pyranoid ring, permitting thus the selective displacement of the former.[4,7]

In the absence of a β-trans-axial substituent, the C-4 sulfonyloxy group of a β-D-hexopyranoside is much more reactive toward the direct nucleophilic displacement than the C-2 sulfonate. Thus, whereas the direct nucleophilic displacement with benzoate of an equatorially oriented C-4 sulfonyloxy group in refluxing *N,N*-dimethylformamide is complete in 16 hr (D-galacto isomer reacts ca. five times faster than the D-gluco isomer[6]), the direct nucleophilic displacement of an equatorially oriented C-2 sulfonyloxy group requires ca. 120 hr for completion.[3]

In connection with some other work we have attempted the nucleophilic displacement of methylsulfonyloxy groups of methyl 3-*O*-methyl-2,4,6-tri-*O*-methylsulfonyl-β-D-glucopyranoside (2) with potassium benzoate in refluxing *N,N*-dimethylformamide. By monitoring the reaction with thin layer chromatography (using 7:1 benzene–ethyl acetate) the following observations have been made. After 15 min the starting material **2** was completely consumed and the reaction mixture consisted of methyl 6-*O*-benzoyl-3-*O*-methyl-2,4-di-*O*-methylsulfonyl-β-D-glucopyranoside (**3**, 68%) (identified by its ir and NMR spectra and by microanalysis) and, in trace amount, of methyl 4,6-di-*O*-benzoyl-3-*O*-methyl-2-*O*-methylsulfonyl-β-D-galactopyranoside (**7**) (identified by chromatographic comparison with the authentic material). After 6 hr the reaction mixture contained significantly increased amounts of **7**, whereas the amount of **3** was proportionately decreased. Furthermore, the formation of two additional, less polar products **4** and **6** has been observed. After 16 hr the galactopyranoside dibenzoate **7** was the predominant product of the reaction (72%), and the amounts of the two less polar products **4** and **6** were markedly increased, whereas the glucopyranoside monobenzoate **3** was not present in the reaction mixture anymore.



1, R = R$_2$ = R$_4$ = OH; R$_1$ = R$_3$ = H
2, R = R$_2$ = R$_4$ = CH_3SO_3; R$_1$ = R$_3$ = H
3, R = R$_2$ = CH_3SO_3; R$_1$ = R$_3$ = H; R$_4$ = C_6H_5COO
4, R = R$_3$ = R$_4$ = C_6H_5COO; R$_1$ = R$_2$ = H
5, R = R$_3$ = R$_4$ = OH; R$_1$ = R$_2$ = H
6, R = R$_3$ = H; R$_1$ = R$_2$ = R$_4$ = C_6H_5COO
7, R = CH_3SO_3; R$_1$ = R$_2$ = H; R$_3$ = R$_4$ = C_6H_5COO
8, R = R$_3$ = H; R$_1$ = C_6H_5COO; R$_2$ = R$_4$ = OH
10, R = R$_3$ = H; R$_1$ = C_6H_5COO; R$_2$ = R$_4$ = CH_3SO_3
11, R = R$_3$ = H; R$_1$ = R$_4$ = C_6H_5COO; R$_2$ = CH_3SO_3
12, R = CH_3SO_3; R$_1$ = R$_2$ = H; R$_3$ = R$_4$ = OH
13, R = CH_3SO_3; R$_1$ = R$_2$ = H; R$_3$ = R$_4$ = CH_3O
15, R = R$_4$ = CH_3O; R$_1$ = R$_2$ = H; R$_3$ = CH_3SO_3



9, R = C_6H_5COO
16, R = CH_3SO_3

When an *N,N*-dimethylformamide solution of methyl 4,6-di-*O*-benzoyl-3-*O*-methyl-2-*O*-methylsulfonyl-β-D-galactopyranoside (**7**) was heated at reflux with potassium benzoate for 120 hr, the galactodibenzoate **7** was completely consumed and products **4** and **6** were obtained in a good yield (18 and 54%, respectively).

The NMR spectra of **4** and **6** indicated that each product contains three benzoyl and two methoxy groups, thus excluding the elimination as the possible pathway for their formation. The possibility that either **4** or **6** has been formed by direct displacement of the equatorially oriented C-2 methylsulfonyloxy group with benzoate was ruled out on the basis of previous findings that direct displacement of an equatorially oriented sulfonyloxy group of a pyranoside is strongly impeded in the presence of a trans-axial substituent at the β carbon atom[5,9–11] and it was unambiguously excluded on the basis of the following chemical evidence. Refluxing of an *N,N*-dimethylformamide solution of methyl 3,4,6-tri-*O*-methyl-2-*O*-methylsulfonyl-β-D-galactopyranoside (**13**) with potassium benzoate for 120 hr gave as the only isolable product the starting material. The unreactivity of **13** under the described experimental conditions also suggested that neither **4** nor **6** could be the product of ring contraction of **7**, as it has been previously observed in cases where direct substitution of an equatorially oriented sulfonyloxy group was not possible owing to the presence of a β-trans-axial substituent [e.g., methyl 6-deoxy-2,3-*O*-isopropylidene-4-*O*-methylsulfonyl-α-D- (or L-) mannopyranosides[12,13]].

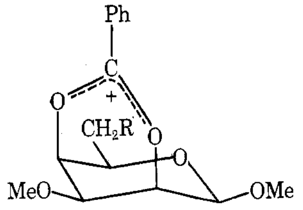
It has been therefore concluded that products **4** and **6** have been formed by intramolecular displacement of the C-2 methylsulfonyloxy group of **7** with the axially oriented C-4 benzoyl group, resulting in the formation of the six-membered benzoyloxonium intermediate **14** and followed by a nucleophilic attack with benzoate at either the C-2 or the C-4 carbon atom. Consequently, methyl 2,4,6-tri-*O*-benzoyl-3-*O*-methyl-β-D-galactopyranoside should be formed in the former, and methyl 2,4,6-tri-*O*-benzoyl-3-*O*-methyl-β-D-mannopyranoside in the latter case. That these were indeed the structures of **4** and **6** was proven by benzoylation of methyl 3-*O*-methyl-β-D-galactopyranoside (**5**)[14] and methyl 2-*O*-benzoyl-3-*O* methyl-β-D-mannopyranoside (**8**) with benzoyl chloride in pyridine. The product obtained by benzoylation of **5** (an amorphous solid) was identical (ir and NMR spectra) with **4**, whereas the product obtained by benzoylation of **8** (an amorphous solid) was identical (ir and NMR spectra) with **6**.

Since the same cyclic six-membered benzoyloxonium intermediate **14** could be expected to be formed by nucleophilic displacement of the equatorially oriented C-4 methylsulfonyl group in the presence of the C-2 trans-axial acyloxy group, the reaction of methyl 2-*O*-benzoyl-3-*O*-methyl-4,6-di-*O*-methylsulfonyl-β-D-mannopyranoside (**10**) with potassium benzoate in refluxing *N,N*-dimethylformamide was investigated. The reaction was monitored by thin layer chromatography using 7:1 benzene–ethyl acetate as eluent.

After 10 min the reaction mixture did not contain starting material **10** anymore, and in addition to trace amount of two less polar products, chromatographically identical with **4** and **6**, methyl 2,6-di-*O*-benzoyl-3-*O*-methyl-4-*O*-methylsulfonyl-β-D-mannopyranoside (**11**, 87%) (identified by ir and NMR spectra, and by microanalysis) was the predominant product of the reaction. After refluxing an *N,N*-dimethylformamide solution of **10** with potassium benzoate for 10 hr, the only products isolated from the reaction mixture were **4** (20%) and **6** (65%). The **6**:**4** ratio (3.2:1) was practically the same as has been found by using **2** under the same experimental conditions (3:1).

Although the participation by a β-trans-acyloxy group with formation of a cyclic six-membered acyloxonium intermediate was already postulated in the acid-catalyzed conversion of methyl 6-*O*-acetyl-3,4-anhydro-2-*O*-benzyl-α-D-altropyranoside[15] into methyl 6-*O*-acetyl-2-*O*-benzyl-α-D-idopyranoside and in the isomerization of 3,4,6-tri-*O*-acetyl-α-D-glucopyranose-1,2-*O*-acetoxonium hexachloroantimonate into 1,2,3,4-tetra-*O*-acetyl-α-D-idopyranose,[16] the formation of galactotribenzoate **4** and mannotribenzoate **6** is, to the best of our knowledge, the first example for the participation of a β-trans-acyloxy group with the formation of a cyclic six-membered acyloxonium intermediate in the nucleophilic displacement of a sulfonyloxy group attached to a pyranoside ring.[17]

The finding that the mannotribenzoate **6** was the predominant product in nucleophilic displacement with benzoate of the C-2 methylsulfonate of **7** as well as the C-4 methylsulfonate of **11** (the manno:galacto ratio was 3.1:1 in the former and 3.2:1 in the latter case) indicated that the C-4 carbon of the cyclic six-membered benzoyloxonium intermediate **14** is considerably more susceptible to the nucleophilic attack than the C-2 carbon atom. This is in a good agreement with our observation[6] that the direct nucleophilic displacement of the C-4 methylsulfonate of methyl 2,3,6-tri-*O*-methyl-4-*O*-methylsulfonyl-β-D-galactopyranoside (**15**) is ca. 2.7 times faster than direct nucleophilic displacement of the C-2 methylsulfonyloxy group of methyl 4,6-*O*-benzylidene-3-*O*-methyl-2-*O*-methylsulfonyl-β-D-mannopyranoside (**16**). The observed difference in reactivities of the C-2 and the C-4 carbon atoms of the cyclic six-membered benzoyloxonium intermediate **14** toward the nucleophilic attack, as well as the observed large difference in reactivity of the C-2 carbon atom of **7** and the C-4 carbon atom of **11** (120 vs. 10 hr), is compatible with the postulated rationalization[18] that the electropositive character of the α carbon to the reacting carbon atom should decrease the rate of the nucleophilic displacement if the amount of positive charge on the reacting carbon atom in the transition state is greater than in the ground state. Furthermore, the observation that both the intramolecular displacement of the C-2 methylsulfonate of **7** with the participation of the β-trans-axial benzoyloxy group and the direct displacement with benzoate of the C-2 methylsulfonate of **16** require ca. 120 hr for completion, in spite of the fact that in the former case the attacking nucleophile is the uncharged C-4 benzoyloxy group whereas in the latter case the attacking nucleophile is negatively charged benzoate anion, suggests that the dipolar interactions between the axially approaching nucleophile and the C_1–O_1 and C_1–O_5 dipoles, proposed recently[3] as the possible explanation for the observed low reactivity of the C-2 methylsulfonate of **16** toward the direct displacement, seem to be, under the given experimental conditions (refluxing *N,N*-dimethylformamide), relatively unimportant.



14, R = C_6H_5COO

Experimental Section

General. The silica gel used for column chromatography was E. Merck (Darmstadt, Germany) silica gel, particle size <0.08 mm and M. Woelm (Eschwege, Germany) silica gel, particle size <0.063 mm. The melting points are uncorrected. Optical rotations were determined with a Cary 60 spectropolarimeter in a 1.0-cm cell. The ir spectra were recorded with a Perkin-Elmer infrared spectrophotometer, Model 267. The proton NMR spectra were recorded with a Varian T-60 spectrometer using tetramethylsilane as an internal standard. Chemical shifts (δ) are expressed in parts per million (ppm).

Methyl 3-*O*-methyl-2,4,6-tri-*O*-methylsulfonyl-β-D-glucopyranoside (2). To a pyridine solution (100 ml) of **1** (1.300 g, 6.24 mmol), methanesulfonyl chloride (7.00 ml, 41.27 mmol) was added dropwise and the reaction mixture was kept at room temperature for 6 hr. The excess of methanesulfonyl chloride was destroyed with methanol and the solvents were evaporated in vacuo. The residue (3.800 g) was chromatographed on silica gel (170 g). Elution with 5:1 benzene–ethyl acetate gave impure **2** (2.800 g), which was rechromatographed on silica gel (140 g). Elution with 5:1 benzene–ether afforded pure **2** (2.260 g, 88%) as an amorphous solid: $[\alpha]^{27}\text{D}$ −25° (*c* 0.57, $CHCl_3$); ir ($CHCl_3$) 1362 and 1175 cm^{-1} (asymmetric and symmetric SO_2 stretch); NMR ($CDCl_3$) δ 4.8–4.1 (m, 5, H-1, H-2, H-4, H-6, and H-6′), 4.0–3.4 (m, 2, H-3 and H-5), 3.72 and 3.57 (two s, 6, C-1 and C-3 methoxy groups), 3.17, 3.12, and 3.07 (three s, 9, methyl from C-2, C-4, and C-6 methylsulfonyl groups).

Anal. Calcd for $C_{11}H_{22}O_{12}S_3$: C, 29.86; H, 5.01; S, 21.74. Found: C, 30.06; H, 5.04; S, 22.01.

Reaction of Methyl 3-*O*-Methyl-2,4,6-tri-*O*-methylsulfonyl-β-D-glucopyranoside (2) with Potassium Benzoate in Refluxing *N,N*-Dimethylformamide (15 min). An *N,N*-dimethylformamide solution (5 ml) containing **2** (117 mg, 0.26 mmol) and potassium benzoate (212 mg, 1.32 mmol) was heated at reflux for 15 min. After the reaction mixture was cooled to room temperature, it was diluted with chloroform, the precipitate was filtered off, and the filtrate was evaporated in vacuo. The crude product (134 mg) was chromatographed on silica gel (15 g). Elution with 3:1 benzene–ethyl acetate gave pure **3** (84 mg, 68%): $[\alpha]^{27}\text{D}$ −27° (*c* 1.17, $CHCl_3$); ir ($CHCl_3$) 1720 and 1270 (C=O and C–O stretch, benzoate), 1360, and 1175 cm^{-1} (asymmetric and symmetric SO_2 stretch); NMR ($CDCl_3$) δ 8.2–7.3 (m, 5, phenyl), 5.0–4.4 (m, 2, H-1 and H-2), 4.47 (t, $J_{3,4} \approx J_{4,5}$ = 8.0 Hz, 1, H-4), 4.47 (d, $J_{5,6}$ = 6.4 Hz, 2, H-6 and H-6′), 4.0–3.4 (m, 2, H-3 and H-5), 3.67 and 3.50 (two s, 6, C-1 and C-3 methoxy groups), 3.11 and 3.10 (two s, 6, methyl from C-2 and C-4 methylsulfonyl groups).

Anal. Calcd for $C_{17}H_{24}O_{11}S_2$: C, 43.58; H, 5.16; S, 13.69. Found: C, 43.79; H, 5.12; S, 13.45.

Reaction of Methyl 3-*O*-Methyl-2,4,6-tri-*O*-methylsulfonyl-β-D-glucopyranoside (2) with Potassium Benzoate in Refluxing *N,N*-Dimethylformamide (16 hr). An *N,N*-dimethylformamide solution (20 ml) containing **2** (260 mg, 0.63 mmol) and potassium benzoate (470 mg, 2.93 mmol) was heated at reflux for 16 hr. The solvent was then evaporated in vacuo, water was added to the residue, and the suspension obtained was extracted with chloroform. After the combined chloroform extract was dried over anhydrous $MgSO_4$, the chloroform was removed in vacuo and the residue (485 mg) was chromatographed on silica gel (50 g). Elution with 7:1 benzene–ethyl acetate gave three fractions. The first fraction (26 mg, 8.5%) was methyl 2,4,6-tri-*O*-benzoyl-β-D-galactopyranoside (**4**), whose structure was deduced from comparison (ir and NMR spectra) with an authentic sample synthesized by benzoylation of methyl 3-*O*-methyl-β-D-galactopyranoside (**5**) (vide infra). The second fraction (79 mg, 25.8%) was pure methyl 2,4,6-tri-*O*-benzoyl-3-*O*-methyl-β-D-mannopyranoside (**6**), whose structure was proved by comparison (ir and NMR spectra) with an authentic sample synthesized by benzoylation of methyl 3-*O*-methyl-β-D-mannopyranoside (**8**) with benzoyl chloride in pyridine (vide infra). The third fraction (134 mg, 46.1%) was pure crystalline methyl 4,6-di-*O*-benzoyl-3-*O*-methyl-2-*O*-methylsulfonyl-β-D-galactopyranoside (**7**). An analytical sample of **7** was obtained by recrystallization from acetone–isopropyl ether: mp 152–152.5°; $[\alpha]^{27}\text{D}$ −24° (*c* 1.3, $CHCl_3$); ir ($CHCl_3$) 1720 and 1265 (C=O and C–O stretch, benzoate), 1362, and 1175 cm^{-1} (asymmetric and symmetric SO_2 stretch); NMR ($CDCl_3$) δ 8.2–7.3 (m, 5, phenyl), 5.87 (two d, $J_{3,4}$ <1.6 and $J_{4,5}$ = 3.4 Hz, 1, H-4), 4.9–3.6 (m, 6, H-1, H-2, H-3, H-5, H-6, and H-6′), 3.59 and 3.46 (two s, 6, C-1 and C-3 methoxy groups), 3.07 (s, 3, methyl from C-2 methylsulfonyl group).

Anal. Calcd for $C_{23}H_{26}O_{10}S$: C, 55.87; H, 5.30; S, 6.48. Found: C, 56.07; H, 5.30; S, 6.21.

Reaction of Methyl 4,6-Di-*O*-benzoyl-3-*O*-methyl-2-*O*-methylsulfonyl-β-D-galactopyranoside (7) with Potassium Benzoate in Refluxing *N,N*-Dimethylformamide (120 hr). An *N,N*-dimethylformamide solution (40 ml) of **7** (260 mg, 0.53 mmol) was heated with potassium benzoate (421 mg, 2.63 mmol) at reflux for 120 hr. The solvent was removed in vacuo and the residue (245 mg) was chromatographed on silica gel (12 g). Elution with 5:1 benzene–ethyl acetate gave two fractions. The first fraction (51 mg, 17.6%) was pure **4**, whereas the second fraction (156 mg, 54.0%) was pure **6**, the **6**:**4** ratio being thus 3.1:1.

Methyl 2,4,6-Tri-*O*-benzoyl-3-*O*-methyl-β-D-galactopyranoside (4). A pyridine solution (1 ml) containing **5** (48 mg, 0.23 mmol) and benzoyl chloride (0.4 ml, 2.36 mmol) was kept at room temperature for 1 hr; the reaction mixture was then poured into saturated aqueous $NaHCO_3$ solution and extracted with chloroform. The combined chloroform extract was dried over anhydrous $MgSO_4$, and the solvent was evaporated in vacuo. The residue (390 mg) was chromatographed on silica gel (15 g). Elution with 7:1 benzene–ethyl acetate gave pure **4** (106 mg, 88%) as an amorphous solid: $[\alpha]^{27}\text{D}$ +34° (*c* 1.0, $CHCl_3$); ir ($CHCl_3$) 1720 and 1265 cm^{-1} (C=O and C–O stretch, benzoate); NMR ($CDCl_3$) δ 8.2–7.2 (m, 15, three phenyl groups), 5.93 (two d, $J_{3,4}$ = 3.4 and $J_{4,5}$ <1 Hz, 1, H-4), 5.53 (two d, $J_{1,2}$ = 1.8 and $J_{2,3}$ = 9.8 Hz, 1, H-2), 4.72 (d, $J_{1,2}$ = 1.8 Hz, 1, H-1), 4.8–3.9 (m, 3, H-5, H-6, and H-6′), 3.70 (two d, $J_{2,3}$ = 9.8 and $J_{3,4}$ = 3.4 Hz, 1, H-3), 3.52 and 3.37 (two s, 6, C-1 and C-3 methoxy groups).

Anal. Calcd for $C_{29}H_{28}O_9$: C, 66.91; H, 5.42. Found: C, 67.16; H, 5.61.

Methyl 2,4,6-Tri-*O*-benzoyl-3-*O*-methyl-β-D-mannopyranoside (6). To a pyridine solution (4 ml) of **8** (49 mg, 0.16 mmol), benzoyl chloride (0.08 ml, 0.47 mmol) was added and the reaction mixture was kept at room temperature for 3 hr. The pyridine was then removed in vacuo and the residue was chromatographed on silica gel (15 g). Elution with 7:1 benzene–ethyl acetate gave pure **6** (74 mg, 90%) as an amorphous solid: $[\alpha]^{27}\text{D}$ −95° (*c* 2.19, $CHCl_3$); ir ($CHCl_3$) 1720 and 1265 cm^{-1} (C=O and C–O stretch, benzoate); NMR ($CDCl_3$) δ 8.2–7.2 (m, 15, three phenyl groups), 5.90 (broad d, $J_{1,2}$ <1 and $J_{2,3}$ = 3.4 Hz, 1, H-2), 5.77 (t, $J_{3,4} \approx J_{4,5}$ = 9.4 Hz, 1, H-4), 4.9–4.3 (m, 3, H-1, H-6, and H-6′), 4.2–3.8 (m, 1, H-5), 3.74 (two d, $J_{2,3}$ = 3.4 and $J_{3,4}$ = 9.4 Hz, 1, H-3), 3.52 and 3.39 (two s, 6, C-1 and C-3 methoxy groups).

Anal. Calcd for $C_{29}H_{28}O_9$: C, 66.91; H, 5.42. Found: C, 67.08; H, 5.55.

Methyl 2-*O*-Benzoyl-3-*O*-methyl-β-D-mannopyranoside (8). A 50% aqueous acetic acid solution (5 ml) of **9** (188 mg, 0.47 mmol) was heated at 100° for 30 min. The solvent was removed in vacuo and the residue (160 mg) was chromatographed on silica gel (20 g). Elution with 6:1 benzene–methanol afforded pure **8** (137 mg, 93%) as an amorphous solid: $[\alpha]^{27}\text{D}$ −94° (*c*, 1.23, CH_3OH); ir ($CHCl_3$) 3420 (broad peak, OH), 1715, and 1270 cm^{-1} (C=O and C–O stretch, benzoate); NMR ($CDCl_3$) δ 8.1–7.2 (m, 5, phenyl), 5.68 (broad d, $J_{1,2}$ <1 and $J_{2,3}$ = 3.0 Hz, 1, H-2), 4.48 (broad s, $J_{1,2}$ <1 Hz, 1, H-1), 4.1–3.7 (m, 3, H-4, H-6, and H-6′), 3.5–3.10 (m, 2, H-3 and H-5), 3.41 and 3.35 (two s, 6, C-1 and C-3 methoxy groups), 2.99 and 2.94 (two broad d, 2, C-4 and C-6 hydroxyl groups).

Anal. Calcd for $C_{15}H_{20}O_7$: C, 57.68; H, 6.46. Found: C, 57.58; H, 6.54.

Methyl 2-*O*-Benzoyl-3-*O*-methyl-4,6-di-*O*-methylsulfonyl-β-D-mannopyranoside (10). To a pyridine solution (5 ml) of **8** (137 mg, 0.44 mmol), methanesulfonyl chloride (0.27 ml, 1.62 mmol) was added and the reaction mixture was kept at room temperature for 2 hr. The pyridine was then removed in vacuo and the residue was chromatographed on silica gel (20 g). Elution with 9:1 benzene–methanol afforded slightly impure **10** (212 mg), which was rechromatographed on silica gel (20 g). Elution with 95:5 benzene–2-propanol gave pure crystalline **10** (192 mg, 93%). An analytical sample was obtained by recrystallization from acetone–isopropyl ether: mp 165–166° dec; $[\alpha]^{27}\text{D}$ −65° (*c* 1.11, $CHCl_3$); ir ($CHCl_3$) 1720 and 1262 (C=O and C–O stretch, benzoate), 1362 and 1175 cm^{-1} (asymmetric and symmetric SO_2 stretch); NMR ($CDCl_3$) δ 8.2–7.3 (m, 5, phenyl), 5.87 (broad d, $J_{1,2}$ ≤1 and $J_{2,3}$ = 3.4 Hz, 1, H-2), 4.80 (t, $J_{3,4} \approx J_{4,5}$ = 10.0 Hz, 1, H-4), 4.7–4.4 (m, 3, H-1, H-6, and H-6′), 4.0–3.7 (m, 1, H-5), 3.64 (q, $J_{2,3}$ = 3.4 and $J_{3,4}$ = 10.0 Hz, 1, H-3), 3.52 and 3.47 (two s, 6, C-1 and C-3 methoxy groups), 3.10 (s, 6, methyl from C-4 and C-6 methylsulfonyl groups).

Anal. Calcd for $C_{17}H_{24}O_{11}S_2$: C, 43.58; H, 5.16; S, 13.69. Found: C, 43.61; H, 5.26; S, 13.43.

Reaction of Methyl 2-*O*-Benzoyl-3-*O*-methyl-4,6-di-*O*-methylsulfonyl-β-D-mannopyranoside (10) with Potassium Benzoate in Refluxing *N,N*-Dimethylformamide (10 min). An *N,N*-dimethylformamide solution (20 ml) containing **10** (176 mg, 0.38 mmol) and potassium benzoate (399 mg, 2.49 mmol) was heated at reflux for 10 min. The solvent was removed in vacuo and the residue was chromatographed on silica gel (30 g). Elution with 4:1 benzene–ethyl acetate afforded pure methyl 2,6-di-*O*-benzoyl-3-*O*-methyl-4-*O*-methylsulfonyl-β-D-mannopyranoside (**11**) as white needles (161 mg, 87%). An analytical sample was obtained by recrystallization from acetone–isopropyl ether: mp 177.5–178°; $[\alpha]^{27}\text{D}$ −95° (*c* 0.77, $CHCl_3$); ir ($CHCl_3$) 1720 and 1270 (C=O and C–O stretch, benzoate), 1362, and 1175 cm^{-1} (asymmetric and symmetric SO_2 stretch); NMR ($CDCl_3$) δ 8.2–7.1 (m, 10, two phenyl groups), 5.85 (q, $J_{1,2}$ = 2.2 and $J_{2,3}$ = 3.0 Hz, 1, H-2), 5.03 (t, $J_{3,4} \approx J_{4,5}$ = 9.0 Hz, 1, H-4), 4.82 (d, $J_{1,2}$ = 2.2 Hz, 1, H-1), 4.7–4.3 (m, 2, H-6 and H-6′), 4.2–3.5 (m, 2, H-3 and H-5), 3.45 (s, 6, C-1 and C-3 methoxy groups), 3.08 (s, 3, methyl from C-4 methylsulfonyl group).

Anal. Calcd for $C_{23}H_{26}O_{10}S$: C, 55.87; H, 5.30; S, 6.49. Found: C, 56.03; H, 5.38; S, 6.33.

Reaction of Methyl 2-*O*-Benzoyl-3-*O*-methyl-4,6-di-*O*-methylsulfonyl-β-D-mannopyranoside (10) with Potassium Benzoate in Refluxing *N,N*-Dimethylformamide (10 hr). An *N,N*-dimethylformamide solution (10 ml) containing **10** (105 mg, 0.22 mmol) and potassium benzoate (250 mg, 1.56 mmol) was heated at reflux for 10 hr. The precipitate was filtered off and the filtrate was evaporated in vacuo. The residue was chromatographed on silica gel (30 g). Elution with 7:1 benzene–ethyl acetate gave two fractions. The first fraction (23 mg, 20%) was pure **4**, whereas the second fraction (75 mg, 65%) was pure **6**, the **6**:**4** ratio being 3.2:1.

Methyl 3-*O*-Methyl-2-*O*-methylsulfonyl-β-D-galactopyranoside (12). To a methanolic solution (10 ml) of **7** (220 mg, 0.44 mmol), metallic sodium (55 mg, 2.30 mmol) was added and the reaction mixture was heated at 60° for 30 min. The solution was neutralized with acetic acid and the solvents were evaporated in vacuo. The residue was chromatographed on Al_2O_3 (12 g). Elution with benzene (20 ml), ethyl acetate (20 ml), and 1:1 ethyl acetate–methanol (40 ml) gave pure **12** (125 mg, 98%): mp 164–165°; $[\alpha]^{27}\mathrm{D}$ +3° (*c* 1.12, CH_3OH); ir ($CHCl_3$) 3500 cm^{-1} (broad peak, OH); NMR ($CDCl_3$) δ 3.37 and 3.28 (two s, 6, C-1 and C-3 methoxy groups), 3.07 (s, 3, methyl from C-2 methylsulfonyl group).

Anal. Calcd for $C_9H_{18}O_8S$: C, 37.76; H, 6.34; S, 11.20. Found: C, 37.82; H, 6.27; S, 10.98.

Methyl 3,4,6-Tri-*O*-methyl-2-*O*-methylsulfonyl-β-D-galactopyranoside (13). To a benzene solution (20 ml) of **12** (117 mg, 0.41 mmol), Ag_2CO_3 (300 mg, 1.1 mmol) and methyl iodide (1 ml, 15.96 mmol) were added and the reaction mixture was heated at reflux for 6 hr. [after 2 hr additional amounts of silver carbonate (300 mg) and methyl iodide (1 ml) were added]. The precipitate was filtered off and the filtrate was evaporated in vacuo. The crystalline residue (132 mg) was chromatographed on silica gel (10 g). Elution with 95:5 benzene–2-propanol gave pure crystalline **13** (119 mg, 92%). An analytical sample was obtained by recrystallization from acetone–isopropyl ether: mp 138°; $[\alpha]^{27}\mathrm{D}$ −22° (*c* 0.50, $CHCl_3$); ir ($CHCl_3$) 1360 and 1175 cm^{-1} (asymmetric and symmetric SO_2 stretch); NMR ($CDCl_3$) δ 4.69 (two d, $J_{1,2} = 7.8$ and $J_{2,3} = 9.8$ Hz, 1, H-2), 4.31 (d, $J_{1,2} = 7.8$ Hz, 1, H-1), 3.77 (two d, $J_{3,4} \leq 1$ and $J_{4,5} = 3.0$ Hz, 1, H-4), 3.56, 3.51 and 3.40 (three s, 12, C-1, C-3, C-4, and C-6 methoxy groups), 3.07 (s, 3, methyl from C-2 methylsulfonyl group).

Anal. Calcd for $C_{11}H_{22}O_8S$: C, 42.03; H, 7.06; S, 10.20. Found: C, 42.36; H, 7.06; S, 9.96.

Reaction of Methyl 3,4,6-Tri-*O*-methyl-2-*O*-methylsulfonyl-β-D-galactopyranoside (13) with Potassium Benzoate in Refluxing *N,N*-Dimethylformamide (120 hr). An *N,N*-dimethylformamide solution (15 ml) containing **13** (81 mg, 0.26 mmol) and potassium benzoate (206 mg, 1.29 mmol) was heated at reflux for 120 hr. The solvent was evaporated in vacuo and the residue (168 mg) was chromatographed on silica gel (15 g). Elution with 95:5 benzene–2-propanol gave the pure crystalline starting material (44 mg, 54%) as the only isolable product.

Registry No.—**1**, 14982-01-5; **2**, 54307-86-7; **3**, 54307-87-8; **4**, 34939-95-2; **5**, 34698-07-2; **6**, 54307-88-9; **7**, 54307-89-0; **8**, 54307-90-3; **9**, 52260-50-1; **10**, 54307-91-4; **11**, 54307-92-5; **12**, 51385-26-3; **13**, 54307-93-6; methanesulfonyl chloride, 124-63-0; potassium benzoate, 582-25-2; benzoyl chloride, 98-88-4.

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Structural Relationships and Interconversions of Isomeric Astilbins[1a]

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Several isomers of astilbin [2(*R*):3(*R*)-3,3′,4′,5,7-pentahydroxyflavanone-3-α-L-rhamnoside] (**1**) are assigned absolute configurations on the basis of NMR and chiroptical properties. Neoastilbin (**2**), isoastilbin (**3**), and neoisoastilbin (**4**) are assigned 2(*S*):3(*S*), 2(*R*):3(*S*), and 2(*S*):3(*R*) configurations respectively. Similar configurational assignments are made in the engeletin series. Studies of the isomerization of **1** have shown that heating **1** with D_2O–pyridine at 75° results in chalcone formation, while isomerization of **1** in ethanolic NaOAc at room temperature yields selective epimerization at C-2 and C-3.

Astilbin (**1**) and engeletin (**5**) from wood bark are members of a rare group of natural products,[2] 3-*O*-glycosyl derivatives of 3-hydroxyflavanones. In 1960, Tominaga described isomeric compounds of **1**[3] and **5**[4] and suggested the existence of cis,trans isomers[5,6] involving C-2 and C-3 of the heterocyclic ring. The preparation of cis-3-substituted flavanones is difficult since acid epimerization readily gives a mixture of cis and trans isomers. cis-3-Hydroxyflavanones are unknown, although *cis*-3-methoxy,[7] *cis*-3-bromo,[8] and *cis*-3-methylflavanones[9] have been prepared[7a,8,9] or isolated.[7b] The structures of the isomeric astilbins and engeletins are established herein and their mecha-