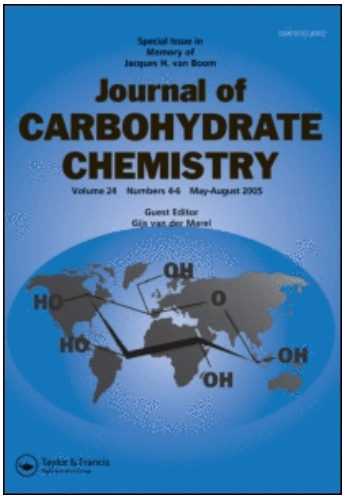

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ONE-POT *p*-TOLUENESULFONYLATION OF ADENOSINE AND METHYL GLYCOSIDES WITH A SUBSTOICHIOMETRIC AMOUNT OF ORGANOTIN MEDIATORS

Masajiro Kawana,* Masafumi Tsujimoto, and Shunya Takahashi*

RIKEN (The Institute of Physical and Chemical Research),
Wako-shi, Saitama 351-0198, Japan

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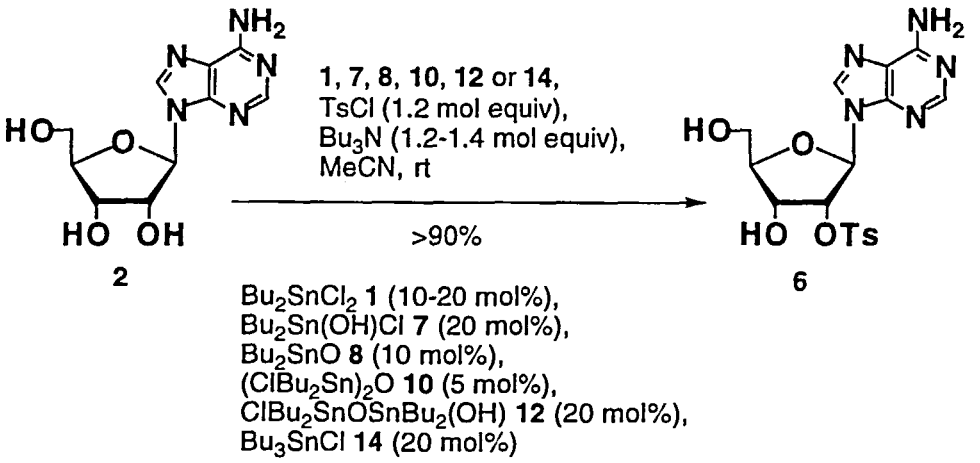
ABSTRACT

A substoichiometric amount (10-20 mol%) of dibutyltin dichloride **1** was found to be effective for promoting the regioselective 2'-*O*-tosylation of adenosine **2** with TsCl in a one-pot manner, wherein a turnover step for tin dichloride **1** was involved. Dibutylchlorotin hydroxide **7**, dibutyltin oxide **8**, bis(dibutylchlorotin) oxide **10**, its hydroxy congener **12**, and tributyltin chloride **14** were also effective in a substoichiometric amount for the 2'-*O*-tosylation of the nucleoside **2**. The method was applicable to some methyl glycopyranosides. The tosylation with tin dichloride **1** was not sensitive to the presence of water in the reaction mixture. Possible reaction pathways are discussed.

INTRODUCTION

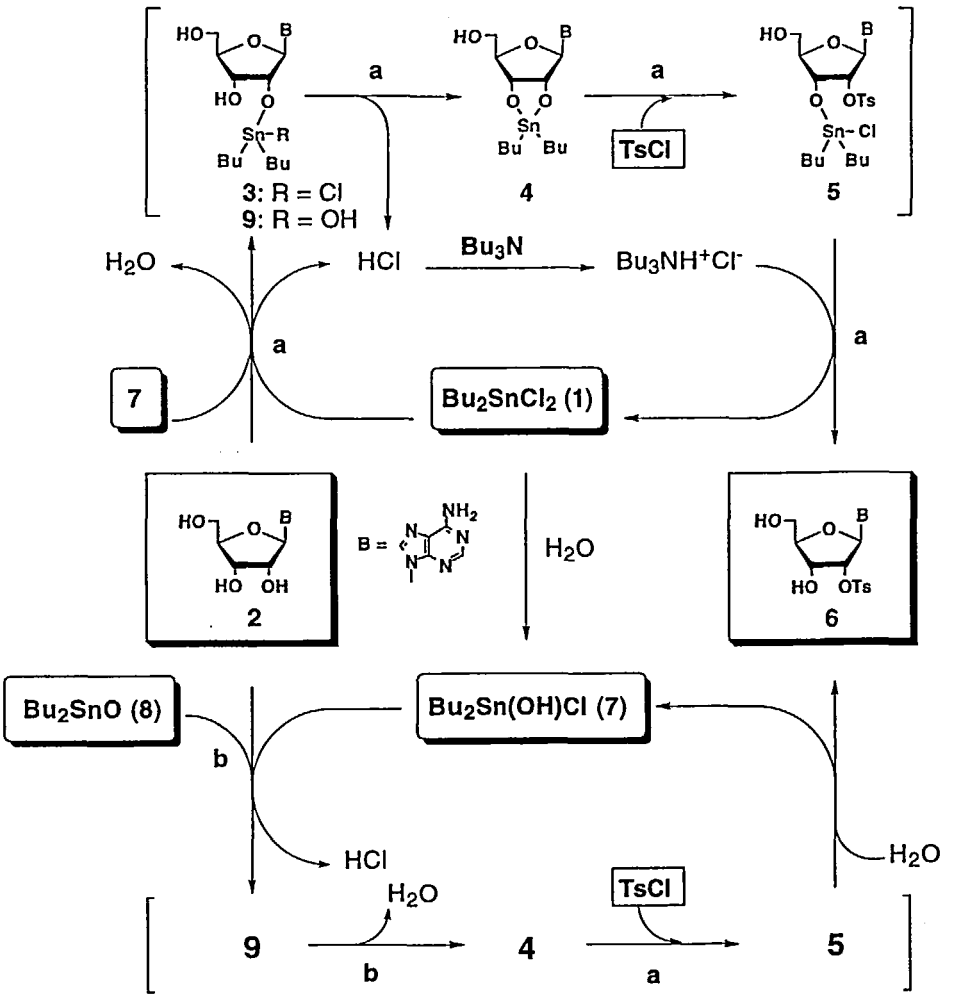
In the 1970's, Moffatt et al.[1] and David[2] introduced the efficient, regioselective organotin-mediated activation of hydroxyl groups of carbohydrates using bis(tributyltin) oxide [$(Bu_3Sn)_2O$][1a] or dibutyltin oxide (Bu_2SnO) **8**.[3] Since then the method has played an important role for the modification of di- and polyols, because it allows for the easy functionalization and manipulation of hydroxyl groups without laborious hydroxyl



Scheme 1

protection.[4,5] The traditional activation method is usually carried out by refluxing a mixture of stoichiometric amounts of a substrate and the organotin mediator in benzene or toluene with azeotropic removal of water. Subsequently, the respective stannyl derivative formed is submitted to regioselective acylation, alkylation, sulfonation, etc.[6] In the original method,[1b] for instance, a mixture of equimolar amounts of adenosine **2** and tin oxide **8** in MeOH was refluxed to provide 2',3'-*O*-(dibutylstannylene)adenosine **4** (Schemes 1 and 2), which was used for further modifications such as tosylation with a large excess of *p*-toluenesulfonyl chloride (TsCl) in the presence of triethylamine (Et_3N), yielding 2'-*O*-tosyladenosine (**6**) in 70% yield.

However, the toxicological data of organotin compounds including tin oxide **8** and bis(tributyltin) oxide call for judicious and careful handling of these chemicals.[4a] There is, therefore, still need of more efficient methods, which require only substoichiometric to catalytic amounts of the tin compounds or less hazardous surrogates in the hydroxyl activation. In this respect, recently Valverde et al.[7] reported a one-pot benzoylation of alcohols with a substoichiometric amount (20 mol%) of tin oxide **8** under microwave irradiation and proposed a mechanism for the reaction.[8] We wish to report here an improved method for organotin-mediated tosylation, wherein a substoichiometric amount of organotin compound was employed without microwave irradiation. The possible reaction pathways are also discussed.



Scheme 2

RESULTS AND DISCUSSION

To evaluate the activity of organotin mediators, we chose the well-established tosylation of nucleoside 2.[1b,9] Our diagnostic reaction conditions consisted of a stirred mixture of nucleoside 2 and TsCl (1.2 mol equiv) in dry acetonitrile (MeCN) at room temperature (rt) for 24 h in the presence of tributylamine (Bu3N, 1.2-1.4 mol equiv) as a proton scavenger. Without any effective mediators as additives, only a small amount of tosylate was formed within this reaction time. The use of triethylamine instead of

tributylamine was found to promote the 2'-*O*-tosylation to a considerable extent as judged by TLC analysis, product formation being due to the intrinsic difference in steric bulkiness between the two bases[10] as well as the differences in acidity[11] of the hydroxyl groups in nucleoside **2**. The mechanistic consideration for the organotin-mediated tosylation led us to employ dibutyltin dichloride (Bu_2SnCl_2) **1** as an activator of the hydroxyl group. When a substoichiometric amount (0.2 mol equiv) of tin dichloride **1** was added to our diagnostic reaction mixture, the tosylation was found to proceed in the desired regiocontrolled fashion and was complete within 24 h to give crystalline tosylate **6**, which was isolated in 90% yield by just filtering the reaction mixture. In this reaction an initial suspension of nucleoside **2** in MeCN was gradually changed, not through a stage of a homogeneous solution, into another suspension consisting of the insoluble product **6**.

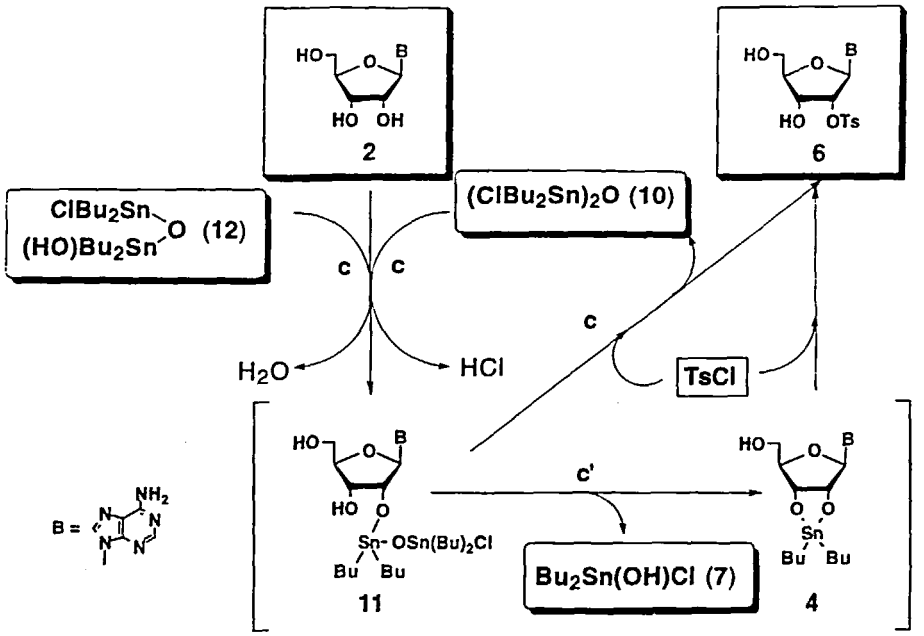
Prior to this tosylation we had already confirmed that reaction of nucleoside **2** with tin dichloride **1**[12] in stoichiometric amounts under the diagnostic reaction conditions excluding TsCl gave an approximately 8:2 mixture of nucleoside **2** and stannolane **4** (data not shown). Therefore, at the beginning of this work we considered that our variant of tosylation with tin dichloride **1** proceeded most probably through route a (**3** → **4** → **5**) outlined in Scheme 2.[13] *In situ* generated tributylamine hydrochloride (Bu_3N-HCl) would readily quench the tosylated intermediate **5** to give the tosylate **6** along with the starting tin dichloride **1**. Thus our reaction system also involved a turnover step[7] for tin dichloride **1**.

It is particularly worthy to take water molecules into consideration in the present tosylation. The water molecule was thought, if present in the reaction mixture, to be an alternative species[7] to attack the tin of intermediate **5**. Thus tosylate **6** and the known dibutylchlorotin hydroxide [$Bu_2Sn(OH)Cl$] **7**[14a] would be liberated therefrom. It has been known that tin dichloride **1** reacts with the water to give tin hydroxide **7**, which is converted, in turn, into 1,1,3,3-tetrabutyl-1,3-dichlorodistannoxane [$(ClBu_2Sn)_2O$] **10**,[14] its monohydroxy and dihydroxy congeners ([$ClBu_2SnOSnBu_2(OH)$] **12** and [$(Bu_2HOSn)_2O$] **13**), and ultimately tin oxide **8**.[4b] A bromo analogue of stannoxane **12**, 1-bromo-1,1,3,3-tetrabutyl-3-hydroxydistannoxane [$BrBu_2SnOSnBu_2(OH)$],[15] has been found to be generated in the traditional Bu_2SnO-mediated allylation with allyl bromide. In the present reaction, several reaction pathways were envisioned for the further transformation of the tin hydroxide **7**; for example, to (i) tin oxide **8**[7]; (ii or iii) intermediate

3 or **9** with nucleoside **2**; (iv) distannoxane **10**[14] with tin dichloride **1** or with another species of **7**. In practice, each of these pathways in our tosylation using tin dichloride **1** could not be demonstrated, but we found some independent routes to tosylate **6** using a substoichiometric amount of the organotin compounds derived from tin dichloride **1**.[4b]

When 0.1 mol equiv of tin oxide **8**, only slightly soluble in MeCN, was added to the diagnostic reaction mixture, the tosylation begun after about 1.5 h of a time lag and was complete within 24 h, furnishing tosylate **6** (route b) in a comparable yield to that for the use of tin dichloride **1**. No microwave irradiation was necessary in this case. Attempts to detect the formation of the expected intermediate **4** under the diagnostic reaction conditions with tin oxide **8** (10 mol%) in the absence of TsCl were unsuccessful, but when stoichiometric amounts of both components (**2** and **8**) were used, formation of a very small amount of stannolane **4** (3 mol%, by ^{1}H NMR) could be observed. Therefore, the route b *via* stannolane **4** might be the initial course of this reaction. After the time lag, species such as tin dichloride **1** and tin hydroxide **7** generated from intermediate **5** would promote the tosylation. It has been reported that tin dichloride **1** and its bromo counterpart were generated in the traditional Bu_2SnO-mediated benzoylation[16] and benzylation,[17] respectively. The diagnostic reaction with 0.2 mol equiv of tin hydroxide **7**, prepared according to the literature method,[14b] gave tosylate **6** in 90% yield. However, only a trace amount of the intermediate **4** was formed in the stoichiometric reaction of nucleoside **2** with tin hydroxide **7**. Furthermore, contrary to the mechnism of the Bu_2SnO-mediated benzoylation under microwave irradiation,[7] recycling of tin hydroxide **7** to tin oxide **8** in our case seems unlikely, because the former was not converted into the latter in the presence of tributylamine. At the present time, the reaction pathway using tin oxide **7** as well as **8** remained to be unresolved.

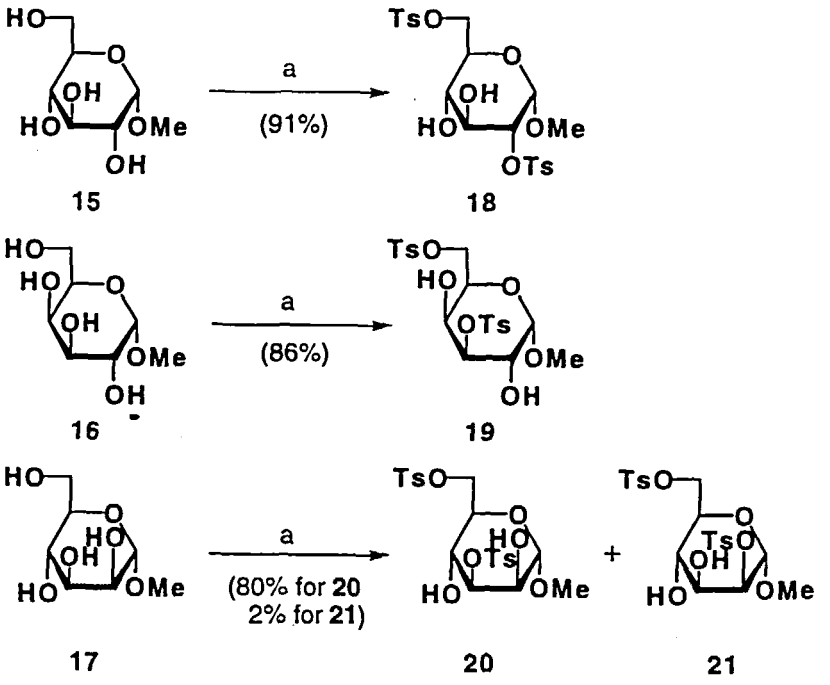
Similarly, the use of 0.05 mol equiv of distannoxane **10** or **12**[14b] resulted in formation of tosylate **6** in more than 90%,[18] probably regenerating distannoxane **10** from a postulated intermediate, an acyclic tin ketal **11** (Scheme 3, route c).[19] Recently, while this work was in progress, Otera et al.[20] reported the $(ClBu_2Sn)_2O$-catalysed regioselective acylation of diols. Treatment of a 1:1 mixture of **2** and distannoxane **10** or **12** under the diagnostic reaction conditions without TsCl gave an approximately 8:2 mixture of nucleoside **2** and stannolane **4**. Therefore in the distannoxane-mediated tosylation we were unable to eliminate the existence of by-path c' (**11** → **4** → **6**).



Scheme 3

On the basis of the present findings coupled with mechanistic considerations, we deduced that the diagnostic reaction with the tin dichloride **1** would be able to accommodate water molecule to some extent, assuming that it did not decompose TsCl, thus generating organotin species useful for promoting the tosylation. It was then determined that even when 50 mol% of water was added to the diagnostic reaction mixture containing tin dichloride **1** (0.1 mol equiv), the desired tosylate **6** was obtained in more than 90% yield (data not shown), the value of which was almost the same as for the corresponding anhydrous reaction conditions.

We thought that the initial intermediate **3** or **9** (in route a or b in Scheme 2, respectively), bearing a resemblance to acyclic tin ketal **11**, might be an alternative candidate active enough for undergoing direct 2'-*O*-tosylation. This assumption encouraged us to test monovalent tributyltin chloride (Bu3SnCl) **14** for its activity to promote the tosylation. As expected, the formation of tosylate **6** in 92% was achieved when 0.2 mol equiv of tin chloride **14** was used.



Scheme 4. a) Bu_2SnCl_2 **1** (40 mol%), TsCl (2.4 mol equiv), Et_3N (2.8 mol equiv), MeCN, rt.

From a preparative point of view, triethylamine instead of tributylamine was the base of choice in the present tosylation, because the former has a lower boiling point and is cheaper in price than the latter. Furthermore, treatment of nucleoside **2** with tin dichloride **1** (0.1 mol equiv) in the presence of triethylamine gave tosylate **6** in 90% yield. Additionally, our method proved to be applicable to methyl glycosides (Scheme 4). Methyl α-D-glucopyranoside **15** was easily tosylated under the conditions similar to those for nucleoside **2** to give a 91% yield of methyl 2,6-di-*O*-tosyl-α-D-glucopyranoside **18**,[21] which had been prepared from **15** by stoichiometric $(Bu_3Sn)_2O$-mediated tosylation.[21b] Similarly, tosylation of the D-*galacto*- or D-*manno*-isomer (**16** or **17**) proceeded nicely to give 3,6-di-*O*-tosylate **19**[22] or the corresponding mannoside **20**,[23] in yields of 86 and 80%, respectively. It has been reported that both compounds were obtained in a low yield under standard conditions (2.0-3.0 mol equiv of *p*-TsCl in pyridine).[22,23] According to a

literture report,[23] the tosylate **21** was isolated as a mixture with the corresponding 4,6-isomer.

In summary, we have developed a simple, one-pot tin-mediated tosylation, in which a substoichiometric amount (5-40 mol%) of the tin compounds, **1**, **7**, **8**, **10**, **12**, and **14** was employed. Among them, **1**, **8**, **10** and **14** are commercially available. Our method differs from that of the precedent, which requires the stannylation by azeotropic dehydration or microwave irradiation. A notable practical advantage of the method with tin dichloride **1** is that anhydrous reaction conditions were unnecessary. The insolubility of a starting material and/or a final product in MeCN used as a solvent brought about no serious problems for the tosylation. We anticipate that our method will be able to be applied to other hydroxyl modifications.

EXPERIMENTAL

General Procedures. Melting points were determined with a Yamato micro melting-point apparatus and are uncorrected. Optical rotations were determined with a JASCO DIP-370 polarimeter. NMR spectra were recorded on JEOL α- 400 (400 MHz) spectrometer. Reactions were monitored by TLC on a HPTLC plate (silica gel 60 F_{254}, Merck). TLC detection was done using UV (254 nm) or spraying the plates with a solution of MeOH - sulfuric acid - *p*-anisaldehyde (85:15:5, v/v/v), or 3% ethanolic phosphomolybdic acid followed by heating them on a hot plate. Column chromatography was performed using silica gel 60 (70-230 mesh, Merck). Solvents were reagent grade and used without purification. Dry solvents were prepared over molecular sieves 4A. Reagents were purchased from Aldrich or Tokyo Kasei (Tokyo).

2'-*O*-Tosyladenosine (6). Typical procedure; with tributylamine. To a stirred solution of Bu_3N (139 mg, 0.75 mmol) in dry MeCN (12 mL) was added nucleoside **2** (134 mg, 0.5 mmol) and Bu_2SnCl_2 (30 mg, 0.1 mmol, 20 mol %) [or the organotin compound described in Scheme 2] at room temperature. After being stirred for 3 min, TsCl (115 mg, 0.6 mmol) was added, and the suspension was stirred at this temperature for 24 h. The undissolved materials were collected by filtration, washed successively with dry MeCN (3 mL) and dichloromethane (3 mL) to give nucleoside **6** (189 mg, 90%), which was >98% pure as judged by ^1H NMR spectroscopy.

With triethylamine. To a stirred solution of Et_3N (707 mg, 7 mmol) in MeCN (120 mL) was added nucleoside **2** (1.34 g, 5 mmol) and Bu_2SnCl_2 (152 mg, 0.5 mmol, 10 mol %) at room temperature. After being stirred for 5 min, TsCl (1.15 g, 6 mmol) was added, and the suspension was stirred at this temperature for 24 h. The undissolved materials were collected by filtration, washed successively with MeCN (25 mL) and dichloromethane (25 mL), and then air-dried. The crude product was suspended in a 9 : 1 mixture of 1,4-dioxane and concd ammonium hydroxide (80 mL). After the suspension had been stirred at rt for 10 min, a trace amount of the undissolved material was removed by filtration through a filter paper and washed with the same solvent (4 mL). The combined filtrate and washings were concentrated and the resulting syrup containing crystals was triturated with hot methanol (25 mL) to give crystalline nucleoside **6** (1.92 g, 91%): mp 222-223 °C (dec.) [lit.[24] mp 222-223 °C]; ^{1}H NMR (DMSO-d_6) δ 2.27 (3H, s, Me-Ph), 3.54 (1H, m, H-5'a), 3.64 (1H, dt, $J_{5'a,5'b}$ = 12 Hz, $J_{5'b,OH}$ = 3.4 Hz, H-5'b), 4.06 (1H, brm, H-4'), 4.34 (1H, brt, J = 4.9 Hz, H-3'), 5.44 (1H, dd, $J_{1',2'}$ = 7.3 Hz, $J_{2',3'}$ = 4.9 Hz, H-2'), 5.79 (1H, dd, $J_{5',OH}$ = 8.5 and 3.4 Hz, 5'-OH), 6.03 (1H, d, $J_{3',OH}$ = 4.9 Hz, 3'-OH), 6.08 (1H, d, $J_{1',2'}$ = 7.3 Hz, 1'-H), 6.98 (2H, d, J = 8.3 Hz, H-Ph), 7.35 (2H, d, J = 8.3 Hz, H-Ph), 7.37 (2H, brs, NH_2), 7.96 (1H, s, H-2) and 8.14 (1H, s, H-8). The ^{1}H NMR signals were identical with those of an authentic sample prepared by the literature method.[1b]

Methyl 2,6-Di-*O*-tosyl-α-D-glucopyranoside (18). To a stirred solution of dry Et_3N (141 mg, 1.4 mmol) in dry MeCN (12 mL) was added successively glucoside **15** (97 mg, 0.5 mmol), Bu_2SnCl_2 (61 mg, 0.2 mmol, 0.4 mol equiv), and TsCl (229 mg, 1.2 mmol) at room temperature, and the suspension was stirred at this temperature for 24 h. The mixture was quenched with water and extracted with Et_2O (50 mL). The extract was washed successively with water, aqueous sodium hydrogencarbonate, and water, dried ($MgSO_4$), and concentrated to dryness. Chromatography on silica gel with hexane-ethyl acetate (1 : 1) as the eluent yielded the di-*O*-tosylate **18** (228 mg, 91%): $[\alpha]_D^{22}$ +56.9° (*c* 1.21, $CHCl_3$) {lit[21b] $[\alpha]_D^{22}$ +55.7° ($CHCl_3$)}; ^{1}H NMR ($CDCl_3$) δ 2.43 (6H, s, Me-Ph), 3.21 (3H, s, OMe), 3.35-3.48 (3H, m, 3-, 4-H and 4-OH), 3.71 (1H, ddd, $J_{4,5}$ = 7.3 Hz, $J_{5,6}$ = 4.4 Hz, $J_{5,6'}$ = 1.6 Hz, 5-H), 3.88 (1H, brt, $J_{2,3}$ = 9.5 Hz, $J_{3,4}$ = 9.1 Hz, H-3), 4.18 (1H, dd, $J_{1,2}$ = 3.7 Hz, $J_{2,3}$ = 9.5 Hz, H-2), 4.22 (1H, dd, $J_{6,6'}$ = 11 Hz, $J_{5,6}$ = 1.6 Hz, H-6'), 4.27 (1H, dd, $J_{6,6'}$ = 11 Hz, $J_{5,6'}$ = 4.4 Hz, H-

6'), 4.58 (1H, d, $J_{1,2}$ = 3.7 Hz, H-1), 7.32 (2H, d, J = 8.1 Hz, H-Ph), 7.34 (2H, d, J = 8.1 Hz, H-Ph) and 7.77 (2H, d, J = 8.6 Hz, H-Ph), 7.80 (2H, d, J = 8.6 Hz, H-Ph).

Methyl 3,6-Di-*O*-tosyl-α-D-galactopyranoside (19). Treatment of methyl galactoside **16** (388 mg, 2.0 mmol) as described for preparation of **18** yielded the 3,6-di-*O*-tosylate **19** (867 mg, 86%): mp 63-64 °C {lit[22a] mp 89-90 °C}; $[\alpha]_D^{24}$ +128° (*c* 1.34, $CHCl_3$) {lit[22a] $[\alpha]_D^{18}$ +82.2° (*c* 1.1, $CHCl_3$)}; ^1H NMR ($CDCl_3$) δ 1.83 (1H, d, J = 10 Hz, 2-OH), 2.41 (1H, d, $J_{4,OH}$ = 3.9 Hz, 4-OH), 2.45 (6H, s, Me-Ph), 3.37 (3H, s, OMe), 3.92 (1H, ddd, $J_{1,2}$ = 3.9 Hz, $J_{2,3}$ = $J_{2,OH}$ = 10 Hz, 2-H), 3.99 (1H, t, $J_{5,6}$ = $J_{5,6'}$ = 5.8 Hz, H-5), 4.14 (1H, ddd, $J_{3,4}$ = 3.0 Hz, $J_{4,5}$ = 1.2 Hz, $J_{4,OH}$ = 3.9 Hz, H-4), 4.15 (1H, dd, $J_{5,6}$ = 5.8 Hz, $J_{6,6'}$ = 11 Hz, H-6), 4.20 (1H, dd, $J_{5,6'}$ = 5.8 Hz, $J_{6,6'}$ = 11 Hz, H-6'), 4.57 (1H, dd, $J_{2,3}$ = 10 Hz, $J_{3,4}$ = 3.0 Hz, H-3), 4.74 (1H, d, $J_{1,2}$ = 3.9 Hz, H-1), 7.34 (4H, d, J = 8.1 Hz, H-Ph), 7.79 (2H, d, J = 8.3 Hz, H-Ph) and 7.83 (2H, d, J = 8.3 Hz, H-Ph).

Methyl 3,6-Di-*O*-tosyl-α-D-mannopyranoside (20) and Methyl 2,6-Di-*O*-tosyl-α-D-mannopyranoside (21). Treatment of methyl mannoside **17** (388 mg, 2.0 mmol) as described for preparation of **18** yielded the 3,6-di-*O*-tosylate **20** (804 mg, 80%) and its 2,6-isomer **21** (20 mg, 2%). **20**: $[\alpha]_D^{24}$ +41.4° (*c* 1.1, $CHCl_3$) {lit[23] $[\alpha]_D^{21}$ +37.0° (*c* 0.7, $CHCl_3$)}; ^1H NMR ($CDCl_3$) δ 2.42, 2.43 (total 6H, each s, Me-Ph), 2.73 (1H, brs, OH), 2.86 (1H, d, $J_{4,OH}$ = 4.4 Hz, OH), 3.27 (3H, s, OMe), 3.70 (1H, ddd, $J_{4,5}$ = 9.7 Hz, $J_{5,6}$ = 4.8 Hz, $J_{5,6'}$ = 2.4 Hz, 5-H), 3.97 (1H, brs, 2-H), 4.01 (1H, dd, $J_{3,4}$ = 9.5 Hz, $J_{4,5}$ = 9.7 Hz, $J_{4,OH}$ = 4.4 Hz, 4-H), 4.25 (1H, dd, $J_{5,6}$ = 2.4 Hz, $J_{6,6'}$ = 11 Hz, H-6), 4.32 (1H, dd, $J_{5,6}$ = 4.8 Hz, $J_{6,6'}$ = 11 Hz, H-6'), 4.59 (1H, dd, $J_{2,3}$ = 3.1 Hz, $J_{3,4}$ = 9.5 Hz, 3-H), 4.62 (1H, d, $J_{1,2}$ = 1.8 Hz, 1-H), 7.32 (2H, d, J = 8.1 Hz, H-Ph), 7.35 (2H, d, J = 8.1 Hz, H-Ph), 7.79 (2H, d, J = 8.2 Hz, H-Ph) and 7.83 (2H, d, J = 8.2 Hz, H-Ph).

21: $[\alpha]_D^{24}$ +14.7° (*c* 0.92, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 1.50-1.78 (2H, brs, OH), 2.45, 2.46 (total 6H, each s, Me-Ph), 3.27 (3H, s, OMe), 3.62 (1H, dd, $J_{3,4}$ = 9.8 Hz, $J_{4,5}$ = 9.2 Hz, H-4), 3.69 (1H, ddd, $J_{4,5}$ = 9.2 Hz, $J_{5,6}$ = 4.4 Hz, $J_{5,6'}$ = 1.0 Hz, H-5), 3.86 (1H, dd, $J_{2,3}$ = 3.0 Hz, $J_{3,4}$ = 9.8 Hz, H-3), 4.26 (1H, dd, $J_{5,6}$ = 4.4 Hz, $J_{6.6''}$ = 11 Hz, H-6), 4.29 (1H, dd, $J_{5,6}$ = 1.0 Hz, $J_{6.6''}$ = 11 Hz, H-6'), 4.64 (1H, d, $J_{1,2}$ = 1.5 Hz, H-1), 4.67 (1H, dd, $J_{1,2}$ = 1.5 Hz, $J_{2,3}$ = 3.0 Hz, H-2), 7.35 (2H, d, J = 7.8 Hz, H-Ph), 7.36 (2H, d, J = 7.8 Hz, H-Ph), 7.79 (2H, d, J = 8.2 Hz, H-Ph) and 7.81 (2H, d, J = 8.2 Hz, H-Ph); HR-FABMS Calcd for $C_{21}H_{27}O_{10}S_2$: 503.1046. Found: 503.1035.

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