Bis *C*-Glycosylated Diphenylmethanes for Stable Glycoepitope Mimetics

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Received 19 March 1999

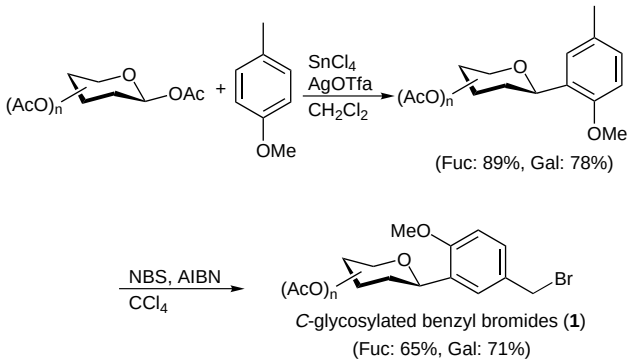
Abstract: Bis *C*-glycosylated diphenylmethanes, in which two sugar units protrude from a diphenylmethane scaffold by *C*-glycosylated bonds, were synthesized as versatile glycoepitope mimetics using *C*-glycosylated aryl tins and *C*-glycosylated benzyl bromides. The synthetic method was applied to the synthesis of a sLe^X mimetic. Besides, triphenylphosphine oxide was found to be a crucial additive in the Stille coupling reaction.

Key words: Stille coupling reaction, additive, aryl *C*-glycoside, sialyl Lewis X, mimetic

Glycoconjugates expressed on cell surfaces or extracellular matrices have been recognized to be deeply involved in numerous cellular processes.[1] Although glycoconjugates are huge and complex biomolecules, some small specific epitopes on them are thought to be responsible for some specific activity. Identification and extraction of pharmacophore of those glycoepitopes and effective presentation of the extracts on a small scaffold will permit the reproduction of some properties of huge glycoconjugates by simple glycoepitope mimetics. Many groups have reported the successful production of glycoepitope mimetics by linking several monosaccharides on various scaffolds with *O*-linkage or by replacing a sialic acid with a carboxylic acid;[2] few groups, however, have reported on the examination of *C*-glycosides for glycoepitope mimetics[2,3] in spite of several advantages of *C*-glycoside glycomimetics over natural oligosaccharides, such as increased physiological stability, in vivo half-time, and bioavailability.

We report here the facile preparation of bis *C*-glycosylated diphenylmethanes, wherein each sugar unit component is intentionally changed, and two sugar units are arranged on a diphenylmethane scaffold in such a way as to protrude from the scaffold. The synthesis was carried out by the Stille coupling[4] of *C*-glycosylated aryl tins,[5] including *C*-sialylated aryl tin, with *C*-glycosylated benzyl bromides (**1**) that are newly designed as benzyl electrophiles bearing *C*-glycoside. Besides, in searching for good coupling conditions, triphenylphosphine oxide was found to be a crucial additive for excellent coupling yields.

Having previously investigated the coupling of *C*-glycosylated aryl tins with various benzyl bromides under the Stille reaction condition,[6] we designed *C*-glycosylated benzyl bromides (**1**) as counterparts for the palladium mediated cross-coupling. The *C*-glycosylated benzyl bromides (**1**) were synthesized as follows (Scheme 1). Peracetylated sugars were coupled with 4-methoxytoluene using tin (IV) chloride-silver trifluoroacetate combination to afford the β-*C*-glycosylated toluenes.[7] Subsequent brominations at the benzyl position of the *C*-glycosylated toluenes using *N*-bromosuccinimide and azobisisobutyronitrile afforded the *C*-glycosylated benzyl bromides (**1**).

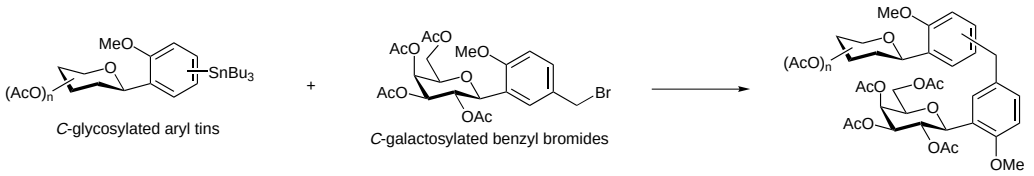


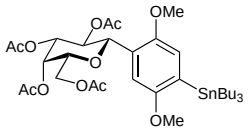
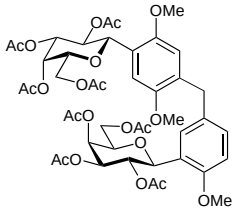
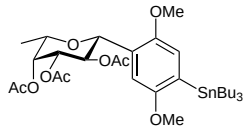
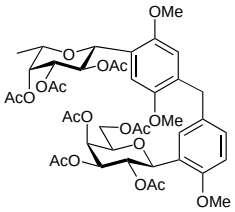
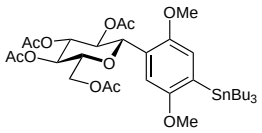
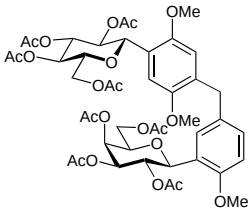
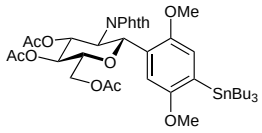
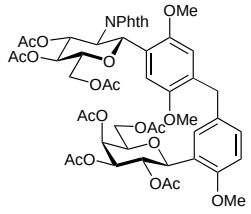
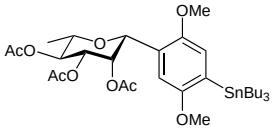
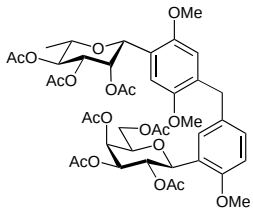
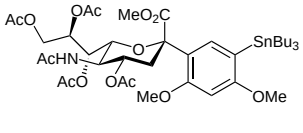
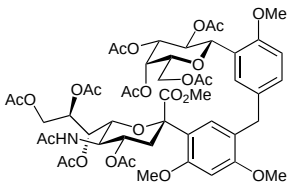
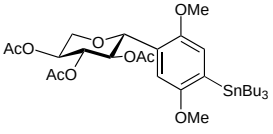
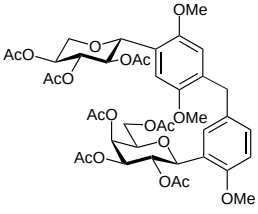
Scheme 1 Synthesis of *C*-Glycosylated Benzyl Bromides

Of several trials searching for good coupling conditions for *C*-galactosylated aryl tin, 3 equivalent *C*-galactosylated benzyl bromide, tetrakis(triphenylphosphine)palladium (0), and potassium carbonate in refluxing 1,4-dioxane were found to afford the bis *C*-glycosylated diphenylmethane in good yield (Condition A). 1 Equivalent *C*-galactosylated benzyl bromide decreased the coupling yield from 80% to 33%. The coupling of a number of *C*-glycosylated aryl tins with *C*-galactosylated benzyl bromide was examined using Condition A. The results are summarized in the Table.

Likewise, a *C*-fucosylated aryl tin and a *C*-glucosylated aryl tin reacted with the *C*-galactosylated benzyl bromide and afforded the bis *C*-glycosylated diphenylmethanes in yields of 97% and 64%, respectively (entries 2, and 3). The sugar part of *C*-glycosylated aryl tins, however, was found to be quite sensitive for the coupling yield. In the case of *N*-phthaloyl-D-glucosamine- and L-rhamnose-derived aryl tins, Condition A afforded the bis *C*-glycosylated diphenylmethanes in low yields (22% and 28%, respectively) (entries 4, and 5). Moreover, the *C*-sialylated aryl tin did not afford the bis *C*-glycosylated diphenylmethane at all. It only afforded a destannylated product[8] of the *C*-sialylated aryl tin in 79% yield.

Table Synthesis of Bis *C*-Glycosylated Diphenylmethanes



Entry	*C*-glycosylated aryl tins	bis *C*-glycosylated diphenylmethanes	Condition A[a]	Condition B[b]
1			80%	
2			97%	
3			64%	
4			22%	82%
5			28%	76%
6			<1%	63%
7				76%

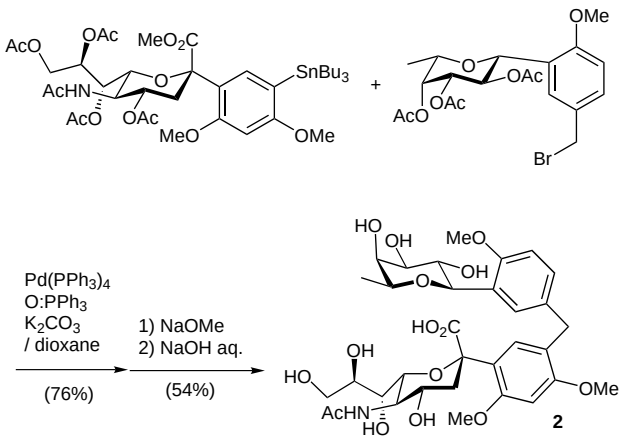
[a] Condition A: all reaction were carried out in refluxing 1,4-dioxane using *C*-glycosylated aryl tin, *C*-glycosylated benzyl bromide, $Pd(PPh_3)_4$ and K_2CO_3 under the following equivalency (1: 3 : 0.1 : 2). [b] Condition B: 1 eq. of $O:PPh_3$ was added to Condition A.

After a number of trials using various additives under Condition A for the coupling of *C*-sialylated aryl tin and *C*-galactosylated benzyl bromide, augmenting the process with 1 equivalent triphenylphosphine oxide (Condition B) was found to increase the coupling yield dramatically from <1% to 63%; no reduction in the product of *C*-sialylated aryl tin was observed by TLC analysis (entry 6).

In the case of the *N*-phthaloyl-D-glucosamine- and the L-rhamnose-derived aryl tins, triphenylphosphine oxide as a further additive was found to improve the coupling yield. Condition B increased the coupling yield of the *N*-phthaloyl-D-glucosamine-derived aryl tin and the *C*-galactosylated benzyl bromide from 22% to 82% (entry 4). L-Rhamnose- and D-xylose-derived aryl tins also afforded the corresponding bis *C*-glycosylated diphenylmethanes, both in yields of 76% (entries 5, and 7). This result shows that the addition of triphenylphosphine oxide is quite indispensable in the synthesis of these particular bis *C*-glycosylated diphenylmethanes. A study on this effect of triphenylphosphine oxide is now under way in our laboratory.

As sialylated oligosaccharides are involved in a large variety of biological events, a facile synthesis of sialylated glycomimetics may offer the possibility for the discovery of lead compounds having novel biological activities and pharmaceutical value.

As one example, we tried to synthesize sialyl Lewis X (sLe^X) [NeuAcα2-3Galβ1-3(Fucα1-4)GlcNAc] mimetics. Since the structure-activity studies[9] and the molecular modeling studies[10] on sLe^X have revealed that sialic acid and fucose residue are critical for the binding with selectins, we decided to couple a sialic acid and a fucose on a diphenylmethane scaffold with *C*-linkage using our method (Scheme 2).



Scheme 2 The Coupling of *C*-Sialylated Aryl Tin and *C*-Fucosylated Benzyl Bromide

The reaction afforded the bis *C*-glycosylated diphenylmethane in 76% yield under Condition B. Deprotection of the product according to the conventional method[11] afforded compound (**2**). We believe this is one of the shortest synthesis of physiologically stable *C*-linked sLe^X mimetics.

The sLe^X mimetic (**2**) and a sLe^X derivative [NeuAcα2-3Galβ1-3(Fucα1-4)GlcNAcβ1-(O(CH_2)$_8$$CO_2$Me)], which showed selectin antagonistic activities of 0.75, 0.033 and 0.015 mM for E-, L- and P-selectins, respectively (IC_{50}, Foxall's ELISA assay[12]), inhibited binding of sLe^X (conjugated with [^{3}H]-polyacrylamide) to guinea pig eosinophils by 56% at 7.2 mM and IC_{50} of 15 mM, respectively. This assay established by us uses [^{3}H]-polyacrylamide as a determinant; therefore, IC_{50} value in this assay is comparatively higher than that in the ELISA assay.

In conclusion, we established the synthetic method of the novel class of *C*-glycosides. Their potential utility for glycoepitope mimetics was demonstrated in the synthesis of sLe^X mimetic (**2**) which showed good selectin antagonistic activity. Further application of this method in various glycoepitopes is currently under investigation.

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Article Identifier:
1437-2096,E;1999,0,06,0737,0740,ftx,en;Y06099ST.pdf