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Friedel–Crafts and modified Vorbrüggen ribosylation. A short synthesis of aryl and heteroaryl-C-nucleosides

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Abstract

A direct coupling of aryl donor and tetra-*O*-acetylribose in the presence of Lewis acid led to β-C-nucleosides in good yields. In contrast, for deactivated electron-poor aromatics, a modified Vorbrüggen ribosylation reaction was investigated and successfully applied in the case of 2-trimethylsilyl-thiazole.

Keywords: Friedel–Crafts ribosylation; Modified Vorbrüggen reaction; C-Nucleosides

C-Nucleosides are important targets in organic synthesis due to their high potential value as therapeutic agents and biochemical probes. They have been found in a lot of naturally occurring and synthetic products with potent antiviral or antitumour activities. Among them, tiazofurin has recently been approved as an orphan drug for the treatment of chronic myelogenous leukemia in accelerated phase or blast crisis.[1] The benzamide riboside is another tiazofurin analogue with improved biological properties.[1] Recently, several synthetic C-nucleosides have been studied not only as chemotherapeutic agents, but also as building blocks in DNA and RNA containing artificial bases and in a number of other biochemical applications.[2] Another attractive feature of C-nucleosides arises from the presence of *C–C* glycosidic bond which confers to these analogues a greater resistance towards chemical and enzymatic hydrolysis than to the classical N-nucleosides. Therefore, efficient and short synthetic methods which allow access to suitable precursors are of great importance.

Various routes have been recently developed for the synthesis of *C*-aryl-nucleosides, among them, the addition of aryl-metallated species to an appropriate activated sugar. However, this methodology led in many cases to the undesired α-anomer as the major product.[3] The coupling between lithiated aryls and the ribonolactone followed by Lewis acid-mediated hemiacetal 1′-deoxygenation is also a well known procedure developed in the synthesis of aryl and heteroaryl series. Unfortunately, the 1′-deoxygenation led, in many cases, to poor yields and diastereoselectivity.[4] Other stereocontrolled procedures have been successfully developed to overcome these drawbacks.[5] The palladium-catalyzed coupling of halogenated aryls with glycals is another well-utilized procedure but this approach is only applicable in 2′-deoxy series.[6] Otherwise, most of the available procedures have some limitations in terms of yield and the number of steps required to assess the suitable C-nucleosides (Fig. 1).

On the other hand, the Friedel–Crafts reaction is an efficient and attractive procedure which has been particularly developed in pyranose series with aryl donors and glycosyl acceptors.[7] Surprisingly, only limited examples were reported in ribofuranose series for the elaboration of C-nucleosides.[8] Moreover, in our knowledge, the analogous

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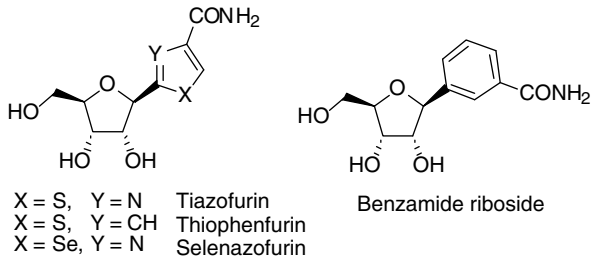


Fig. 1. Structure of tiazofurin and analogues.

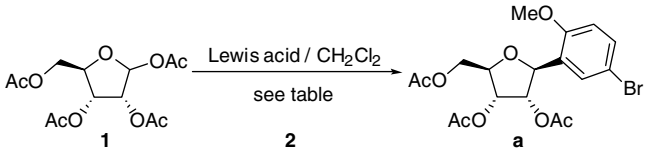
Friedel–Crafts reaction with electron-deficient aryls and ribosyl acceptors was not reported in the literature.

In continuation of our studies aimed at the development of efficient synthetic routes of aryl and heteroaryl-C-nucleosides for their incorporation into oligonucleotides and to assess their biological activities,[9] we report herein a direct ribosylation based on Friedel–Crafts and modified Vorbrügguen reactions. These methodologies provide a direct two-step access to aryl and heteroaryl C-nucleosides.

First, we examined the survey of the Friedel–Crafts reaction conditions by using the commercially available tetra-*O*-acetylribose **1** and *p*-bromoanisole to avoid *ortho*/*para* selectivity. Different conditions were studied for the optimization of Lewis acid-mediated ribosylation reaction. The results are listed in Table 1.

We started our study with BF_3–Et_2O, a classically used Lewis acid. In this case, no reaction was observed between *p*-bromoanisole and ribose **1** (entries 1–3) even under forced conditions (large excess of Lewis acid, elevated temperatures and a longer reaction time). Moreover, the use of other Lewis acids such as $SnBr_4$, $AlCl_3$ and metal triflates did not efficiently afford the desired ribosylated product (entries 4–9). The use of $TiCl_4$ and a couple of TMSCl/$AgClO_4$ only afforded low yields (entries 10–12). The best results were obtained with $SnCl_4$ at low temperature (entries 14 and 15). Under these conditions, the protected C-nucleosides **2a** was obtained in 70% yield together with a small amount of the α-anomer (⩽5%).[10] Concerning the stereo- and regio-chemistry of **2a**β, this was unambiguously attested by NOESY and HMBC experiments. Indeed, the ^{1}H 2D NOESY spectrum shows correlations between $H_{1'}$–$H_{4'}$, and the HMBC experiment shows $H_{5'}$–C_1 (C–OMe) and $H_{5'}$–C_3 cross coupling, in accordance with the proposed structure for **2a**β (Fig. 2).

Table 1
Survey of the ribosylation conditions



1 2 a

Entries	Lewis acid[a]	*T* (°C)	Yield[b] (%)
1	BF_3·Et_2O	rt	0
2	BF_3·Et_2O	0	0
3	BF_3·Et_2O	−78	0
4	$AlCl_3$	—	0
5	$SnBr_4$	0 or rt	<5
6	$Sn(OTf)_2$	—	0
7	$Zn(OTf)_2$	—	0
8	$Cu(OTf)_2$	—	0
9	TMSOTf	—	<10
10	$TiCl_4$	0	20
11	$TiCl_4$	−78	15
12	TMSCl/$AgClO_4$	0 or rt	28
13	$SnCl_4$	rt	60
14	$SnCl_4$	0 to rt	70
15	$SnCl_4$	−78 to rt	68

[a] Conditions: **1** (1 mmol), Lewis acid (1.1 equiv), aryl (2.1 equiv), 16 h.
[b] Yield of isolated product.

To get further information on the scope of this procedure, other aryl and heteroaryl donors were subjected to the same reaction conditions (Scheme 1). Both methoxyaryl derivatives and pyrene underwent clean conversion giving the desired products in 45–72% yields (**2b**, **2c** and **2g**). The five-membered ring heterocycles (thiophene, bromothiophene and furan) also gave the requisite compounds in satisfactory yields (**2d**–**f**, 55–70%).[10] However, in the case of electron-rich aryls such as methoxynaphthalene and furan, when the reaction time was prolonged, a concomitant double arylation was observed leading to the bis-arylated products, which decreased the overall yield. As proposed in Scheme 2 for the methoxynaphthalene, this double arylation reaction probably resulted from Lewis acid-promoted ring opening of **2c**, favoured by aryl assistance, followed by a second aryl addition on intermediate **I** to afford **3c** (Scheme 2).[11]

Interestingly, this concomitant double alkylation was overcome by using a catalytic amount of the promoter (20% molar of $SnCl_4$) and 1.2 equiv of 1-methoxynaphthalene. Under these conditions, compound **2c** as well as the ortho isomer was obtained in 69% yield (*ortho*/*para* = 40:60).

While this process appears to be efficient in terms of cost and time, for example, one step and rapid access to C-nucleosides in the case of aryl donors, the use of electron-deficient aryls resulted in no glycosylation reaction. For example, no reaction occurred between free thiazole and ribose **1** in the presence of $SnCl_4$. Therefore, to overcome the lower reactivity of the thiazole in the C-glycosylation process, we investigated a modified Vorbrüggen reaction. The Vorbrüggen method is a well-known N-glycosylation procedure that involved the coupling between silylated forms of nitrogen- or amide-containing heterocycles and activated sugars, in the presence of Lewis acid

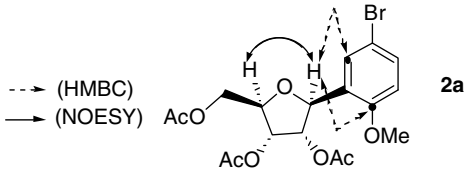
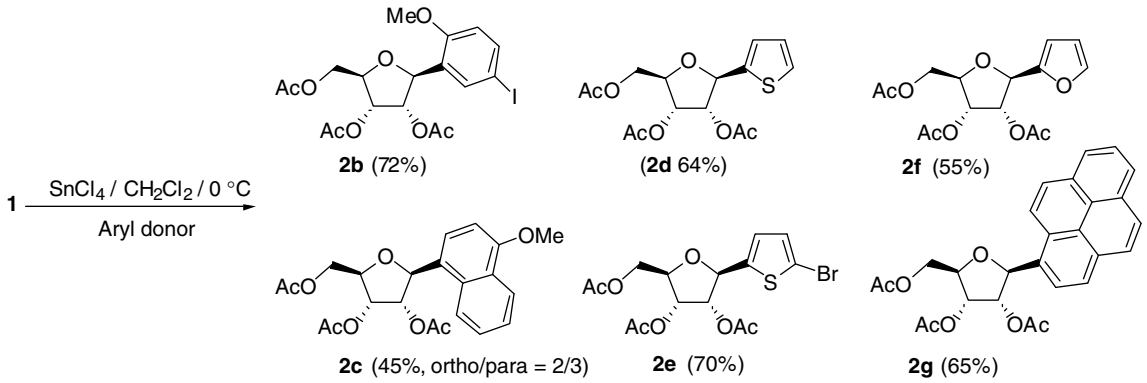
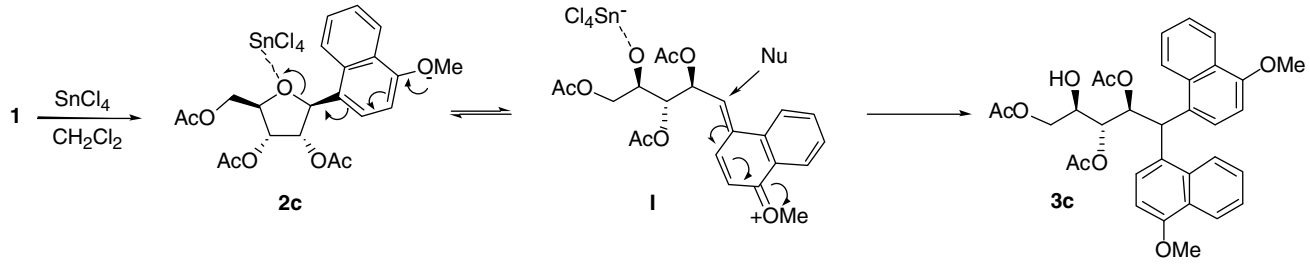


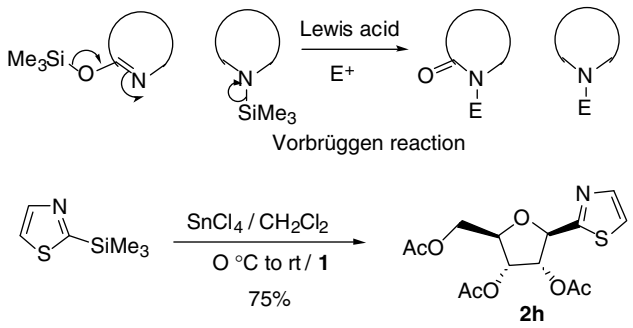
Fig. 2. Significant NOESY and HMBC (J_3) correlations (**2a**β).



Scheme 1. Reagents and conditions: **1** (1 mmol), Lewis acid (1.1 equiv), aryl (2.1 equiv), 0 °C to rt.



Scheme 2. Plausible mechanism for the double arylation with methoxynaphthalene.

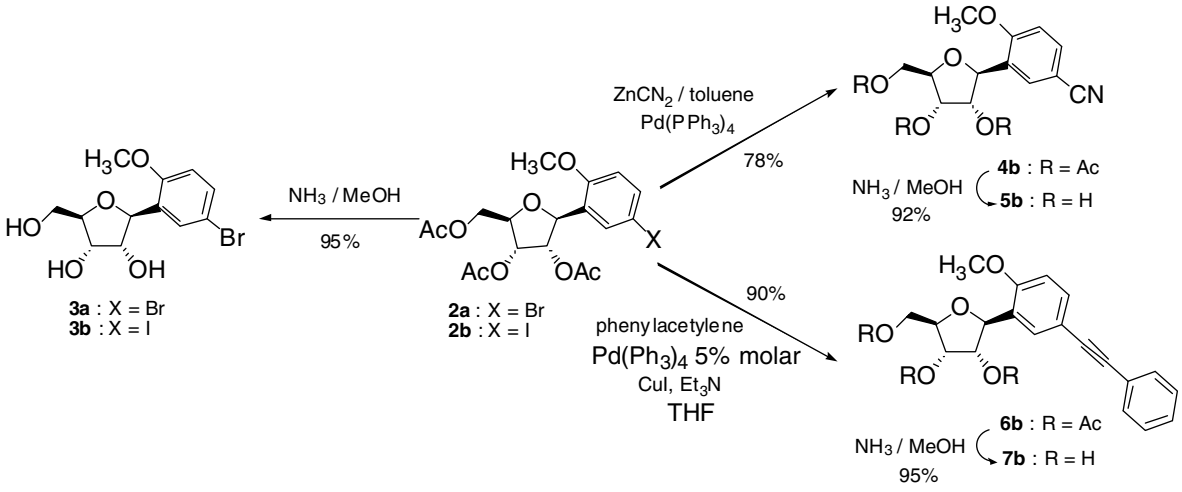


Scheme 3. Example of modified Vorbrüggen reaction.

(Scheme 3). It has been extensively explored with a large number of N-heterocycles including the natural nucleobases.[12]

In the modified version, we used 2-TMS-thiazole instead of thiazole to activate the C2 position. Interestingly, the treatment of 2-TMS-thiazole and ribose **1** with $SnCl_4$ in CH_2Cl_2 led to 75% of the ribosylated product **2h** (Scheme 3).[13,14] This result clearly shows the potential application of this modified reaction for the ribosylation of deactivated heteroaryl systems.

In summary, we developed an efficient one-step synthesis of new C-nucleosides featuring aryl and heteroaryl rings



Scheme 4. Example of post-synthetic transformations of compounds **2a** and **2b**.

as aglycone moiety. We found that the Friedel–Crafts reaction could be directly applied to assess C-nucleosides with electron-rich aromatics, whereas deactivated aryls required Si-metallation to undergo clean ribosylation. Generally good, although not optimized, yields were obtained. Moreover, the process is compatible with functional groups such as halogens and offers several possibilities for further post-synthetic transformations. For example, bromo- and iodo-derivatives **2a** and **2b** were subjected to different conditions to assess their reactivities (Scheme 4). Thus, the treatment of **2a** and **2b** with NH_3 in MeOH gave the corresponding free nucleosides **3a** and **3b**, respectively (95%). On the other hand, cyanation of **2b** was also efficiently achieved using Pd-coupling ($ZnCN_2$, $Pd(PPh_3)_4$) to give **4b** (78%), which upon NH_3 treatment led to the free nucleoside **5b** (95%). Finally, the new C-nucleoside **7b** was prepared following Sonogashira coupling between **2b** and phenylacetylene to give **6b** and subsequent protecting group cleavage (85% in two steps, Scheme 4).[15] Taken together, our results illustrate the efficiency of the given synthetic methodology for the supply of a variety of C-nucleosides for further biophysical and biological applications. The development of the modified *C–C* Friedel–Crafts/Vorbrüggen reactions is underway.

Acknowledgements

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10. Typical procedure: To a stirred solution of tetra-*O*-acetylribose (3 mmol) in CH_2Cl_2 (15 ml) and aryl (2.1 equiv) was added dropwise, at 0 °C, $SnCl_4$ (1.1 equiv). The mixture was stirred and warmed to room temperature and monitored by TLC (in general, the colour of the reaction mixture changes as the reaction progresses). The mixture was quenched with saturated aqueous $NaHCO_3$ solution and extracted with methylene chloride (3 × 50 ml). The combined organic layers were dried ($MgSO_4$), concentrated and subjected to silica gel chromatography (cyclohexane/AcOEt: 80:20 to 50:50). Selected spectral data: **2a**: ^{1}H NMR (200 MHz, $CDCl_3$) δ ppm 1.77 (s, 3H, Ac), 2.02 (s, 3H, Ac), 2.09 (s, 3H, Ac), 3.74 (s, 3H, OMe), 4.15 (dd, 1H, $J = 12.8$ and 5.5 Hz, H-5′), 4.40 (m, 2H, H-5′ and H-4′), 5.37 (dd, 1H, $J = 8.2$ and 4.4 Hz, H-3′), 5.44 (d, 1H, $J = 3.2$, H-1′), 5.77 (dd, 1H, $J = 4.4$ and 3.2 Hz, H-2′), 6.64 (d, 1H, $J = 8.7$ Hz, H-6 Ar), 7.31 (dd, 1H, $J = 8.7$ and 2.6 Hz, H-5 Ar), 7.63 (d, 1H, $J = 2.6$, H-3 Ar). ^{13}C NMR (50 MHz, $CDCl_3$) δ ppm 20.38, 20.56, 20.91, 26.95, 55.62, 63.64, 71.92, 72.55, 111.46, 112.64, 126.58, 130.38, 131.41, 155.01, 169.41, 169.88, 170.81. MS (ES^+) *m/z*: 467–469 $(MNa)^+$, 484–486 $(MK)^+$. HRMS (ES^+) calcd for $C_{18}H_{22}O_8Br$ $[M+H]^+$, 447.04779 (^{81}Br); found, 447.04721. Compound **2b**: ^{1}H NMR (200 MHz, $CDCl_3$) δ ppm 1.81 (s, 3H, Ac), 2.05 (s, 3H, Ac), 2.12 (s, 3H, Ac), 3.76 (s, 3H, OMe), 4.19 (dd, 1H, $J = 12.8$ and 5.3 Hz, H-5′), 4.42 (m, 2H, H-5′ and H-4′), 5.40 (dd, 1H, $J = 8.0$ and 4.5 Hz, H-3′), 5.46 (d, 1H, $J = 3.2$, H-1′), 5.78 (dd, 1H, $J = 4.3$ and 3.2 Hz, H-2′), 6.56 (d, 1H, $J = 8.6$ Hz, H-6 Ar), 7.53 (dd, 1H, $J = 8.6$ and 2.3 Hz, H-5 Ar), 7.77 (d, 1H, $J = 2.3$ Hz, H-3 Ar). ^{13}C NMR (50 MHz, $CDCl_3$) δ ppm 20.47, 20.65, 21.00, 53.56, 55.60, 63.74, 72.02, 72.66, 76.95, 82.51, 112.14, 126.91, 136.29, 137.61, 155.93, 169.49, 169.95, 170.90. MS (ES^+) *m/z*: 514.9 $(MNa)^+$. HRMS (ES^+) calcd for $C_{18}H_{22}O_8I$ $[M+H]^+$, 493.03534; found, 493.03539. Compound **2d**: ^{1}H NMR (200 MHz, $CDCl_3$) δ ppm 1.99 (s, 3H, Ac), 2.03 (s, 3H, Ac), 2.04 (s, 3H, Ac), 4.13 (dd, 1H, $J = 11.7$ and 3.8 Hz, H-5′), 4.23 (m, 1H, H-4′), 4.36 (dd, 1H,$J = 11.7$ and 3.0 Hz, H-5′), 5.15 (m, 2H, H-1′ and H-2′), 5.26 (t, 1H, $J = 4.8$ Hz, H-3′), 6.90 (dd, 1H, $J = 5.0$ and 3.5 Hz, H-4), 7.01 (m, 1H, H-3), 7.21 (dd, 1H, $J = 5.0$ and 1.3 Hz, H-5). ^{13}C NMR (50 MHz, $CDCl_3$) δ ppm 20.46, 20.55, 20.77, 63.44, 71.78, 76.51, 78.54, 79.94, 125.37, 125.73, 126.86, 141.22, 169.56, 169.68, 170.50. MS (ES^+) *m/z*: 365 $(MNa)^+$, 382 $(MK)^+$. **2e**: ^{1}H NMR (200 MHz, $CDCl_3$) δ ppm 2.00 (s, 3H, Ac), 2.03 (s, 3H, Ac), 2.05 (s, 3H, Ac), 4.13 (dd, 1H, $J = 11.7$ and 3.6 Hz, H-5′), 4.24 (m, 1H, H-4′), 4.34 (dd, 1H, $J = 11.7$ and 2.9 Hz, H-5′), 5.07 (br d, 2H, $J = 2.6$ Hz, H-1′ and H-2′), 5.22 (dd, 1H, $J = 4.4$ and 2.6 Hz, H-3′), 6.76 (d, 1H, $J = 3.7$ Hz, H-4), 6.86 (d, 1H, $J = 3.8$ Hz, H-3). ^{13}C NMR (50 MHz, $CDCl_3$) δ ppm 20.62, 20.70, 20.96, 63.45, 71.77, 76.43, 78.83, 80.17, 112.83, 125.71, 129.82, 143.03, 158.17, 169.71, 169.83, 170.67. MS (ES+) *m/z*: 443-445 $(MNa)^+$, 459-461 $(MK)^+$. Small amount of the α-anomer was also observed in these reactions (⩽8%).
11. Compound **3c**: ^{1}H NMR (200 MHz, $CDCl_3$) δ ppm 1.20 (s, 3H, Ac), 1.86 (s, 3H, Ac), 1.91 (s, 3H, Ac), 2.34 (br d, 1H, $J = 6.7$ Hz, OH-4′), 3.80 (s, 3H, OMe), 3.95 (s, 3H, OMe), 4.03 (dd, 1H, $J = 12.0$ and 6.7 Hz, H-5′), 4.20 (m, 2H, H-5′ and H-4′), 5.28 (dd, 1H, $J = 7.2$ and 2.7 Hz, H-3′), 6.07 (dd, 1H, $J = 10.6$ and 2.7 Hz, H-2′), 6.18 (d, 1H, $J = 10.6$, H-1′), 6.53 (d, 1H, $J = 7.1$ Hz, H-Ar), 6.87 (d, 1H, $J = 8.1$ Hz, H-Ar), 7.31 (m, 3H, H-Ar), 7.41 (m, 1H, H-Ar), 7.57 (ddd, 1H, $J = 8.5$, 7.0 and 1.5 Hz, H-Ar), 7.83 (d, 2H, $J = 8.1$ Hz, H-Ar), 8.20 (m, 2H, H-Ar), 8.48 (d, 1H, $J = 8.5$ Hz, H-Ar). ^{13}C NMR (50 MHz, $CDCl_3$) δ ppm 20.11, 20.84, 39.80, 55.40, 55.60, 65.88,

68.66, 73.19, 76.00, 103.17, 103.65, 122.61, 122.72, 123.19, 123.78, 124.68, 125.02, 125.66, 125.96, 126.38, 126.64, 127.08, 128.06, 129.35, 132.77, 133.48, 154.35, 154.81, 169.76, 170.40, 171.33. MS (ES^+) *m/z*: 597.4 $(MNa)^+$, 613.3 $(MK)^+$. HRMS (ES^+) calcd for $C_{33}H_{34}O_9Na$ $[M+Na]^+$, 597.21002; found, 597.20950.

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13. Compound **2h**: ^1H NMR (200 MHz, acetone) δ ppm 2.05 (br s, 9H, Ac), 4.47 (dd, 2H, $J = 12.8$ Hz, 2H-5′), 4.76 (m, 1H, H-4′), 5.46 (t, 1H, $J = 5.4$ Hz, H-3′), 5.68 (dd, 1H, $J = 5.7$ and 4.0 Hz, H-2′), 6.69 (d, $J = 4.0$ Hz, 1H, H-1′), 8.60 (br s, 1H, H-thiazole), 8.73 (br s, 1H, H-thiazole). ^{13}C NMR (50 MHz, acetone) δ ppm 20.49, 20.62, 20.86, 63.18, 70.29, 76.10, 83.38, 95.52, 128.80, 134.87, 158.69, 169.96, 170.37, 170.56. ^{13}C DEPT sequence only shows two CH signals. MS (ES^+) *m/z*: 344.5 $(MH)^+$.
14. For reviews of arylsilanes in electrophilic aromatic substitutions, see: (a) Eaborn, C. *J. Organomet. Chem.* **1975**, *100*, 43; (b) Fleming, I.. In *Comprehensive Organic Chemistry*; Barton, D. H. R., Ollis, W. D., Eds.; Pergamon: Oxford, 1979; Vol. 3, Chapter 13, p 613.
15. Selected spectral data: **5b**: ^1H NMR (200 MHz, CD_3OD) δ ppm 3.57 (dd, 1H, $J = 12.1$ and 4.6 Hz, H-5′), 3.92 (s, 3H, OMe), 3.75–4.02 (m, 2H, H-5′ and H-4′), 4.13–4.30 (m, 2H, H-3′ and H-2′), 5.16 (d, 1H, $J = 2.7$ Hz, H-1′), 6.96 (d, 1H, $J = 8.6$ Hz, H-6 Ar), 7.52 (dd, 1H, $J = 8.6$ and 2.0 Hz, H-5 Ar), 7.69 (d, 1H, $J = 1.9$ Hz, H-3 Ar). ^{13}C NMR (50 MHz, $CDCl_3$) δ ppm 56.40, 63.14, 73.27, 73.82, 79.09, 83.01, 104.10, 111.73, 120.56, 130.04, 132.81, 134.02, 160.85. MS (ES^+) *m/z*: 288 $(MNa)^+$, 553 $(2MNa)^+$. Compound **7b**: ^1H NMR (200 MHz, MeOD) δ ppm 3.17 (dd, 1H, $J = 12.1$ and 4.6 Hz, H-5′), 3.31 (s, 3H, OMe), 3.39 (m, 1H, H-5′), 3.52 (m, 1H, H-4′), 3.79 (m, 2H, H-3′ and H-2′), 4.77 (d, 1H, $J = 1.6$ Hz, H-1′), 6.39 (d, 1H, $J = 8.6$ Hz, H-6 Ar), 6.88 (m, 6H, H-Ar), 7.18 (d, 1H, $J = 1.6$ Hz, H-3 Ar). ^{13}C NMR (50 MHz, MeOD) δ ppm 55.97, 63.21, 73.42, 73.89, 79.36, 82.93, 88.51, 90.79, 110.94, 116.01, 125.04, 128.31, 128.93, 129.03, 129.45, 132.25, 132.39, 132.58, 157.56. MS (ES^+) *m/z*: 363.3 $(MNa)^+$. HRMS (ES^+) calcd for $C_{20}H_{21}O_5$ $[M+H]^+$ 341.13843; found, 341.13835.