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Tetrahedron Letters
Tetrahedron Letters 47 (2006) 4807–4811

A highly efficient microwave-assisted solvent-free synthesis of α- and β-2′-deoxy-1,2,3-triazolyl-nucleosides

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Received 7 April 2006; revised 9 May 2006; accepted 10 May 2006

Abstract—Microwave activation coupled with Cu(I) catalysis, under solvent-free conditions, was found to dramatically enhance the 1,3-dipolar cycloaddition between azido-2′-deoxyribose and terminal alkynes. The process is highly efficient and quantitatively affords, in few minutes, the corresponding 4-substituted 1,2,3-triazolyl-nucleosides.

Apart from being the genomic building blocks, nucleosides interact with nucleic acids, enzymes, and proteins. Naturally occuring and synthetic analogs of nucleosides have been the cornerstone of antiviral therapy over the last decades. The growing interest in such analogs also rises from their high potential value as therapeutic agents, biochemical probes and as building blocks in artificial nucleic acid syntheses.[1] Among them, nucleosides with five membered ring nucleobase are of great interest. Thus, Bredinin (**1**) is an imidazole nucleoside clinically used as immunosuppressant and Ribavirin (**2**), a triazolyl nucleoside, is the unique small molecule drug currently used for the treatment against hepatitis C virus, in combination with interferon-α-peg (Fig. 1).

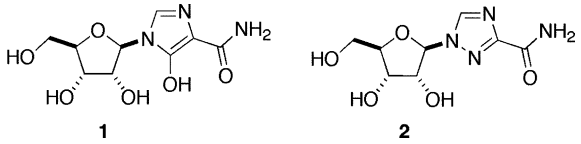

Figure 1. Structure of five membered ring nucleosides, Bredinin (**1**) and Ribavirin (**2**).

Huisgen azide–alkyne 1,3-dipolar cycloaddition is a versatile route to 1,2,3-triazoles, and the progress in this area has been extensively studied.[2] In general, 1,2,3-triazole formation requires harsh conditions, that is, high temperature and longer reaction times. Recently, several examples of Cu(I)-catalyzed alkyne–azide 1,3-dipolar cycloaddition under milder conditions have been described.[3] The first mechanistic proposal of the Cu(I)-catalyzed alkyne–azide 1,3-dipolar cycloaddition was recently reported and was found to involve polar transition states, favorable for a microwave activation.[4]

Microwave heating has emerged as a powerful technique to enhance reaction rates of a variety of chemical transformations.[5] Moreover, microwave reactions under solvent-free conditions are attractive in the growing field of green chemistry.[5c] Some of us have reported for the first time on the microwave-assisted azide–alkyne cycloaddition.[6] Recently, an example of microwave-assisted azide–alkyne cycloaddition was reported by Katritzky et al.[7] However, these reactions involved only primary azides and acetylenic amide. Moreover, drastic conditions, that is, sealed tube and high reaction temperature and pressure, were necessary for the reaction to proceed. Furthermore, it has been shown that cycloaddition between primary azide and terminal alkynes gave a mixture of regioisomers.[8] Microwave- and Cu(I)-assisted 'click-chemistry' has been recently reported. However, this method was restricted to primary azides and terminal alkynes using drastic conditions, sealed-vessel under high pressure and super-heated solvents.[9]

Keywords: 1,3-Dipolar cycloaddition; Microwave activation; Cu(I)/SiO_2; Regiocontrolled process; Nucleoside analogs.
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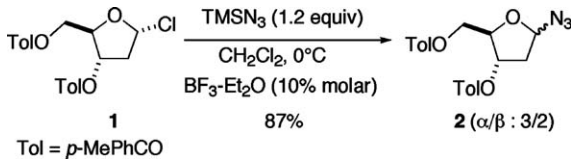
doi:10.1016/j.tetlet.2006.05.050



Scheme 1.

As an effort in the development of original nucleoside chemistry, we report herein on the first example of Cu(I) promoted regioselective synthesis of functionalized α- or β-1,2,3-triazolyl nucleosides through a 1,3-dipolar cycloaddition between α- or β-azido-2-deoxyribose and different terminal alkynes, by using microwave activation under atmospheric pressure and solvent-free conditions. The obtained nucleosides were further deprotected on their 3′- and 5′-positions to give the corresponding free analogs.

The starting material, azido-2-deoxyribose **2**, was synthesized from protected α-chloro-2-deoxyribose[10] under mild conditions ($TMSN_3$, BF_3–Et_2O, 0 °C). Compound **2** was obtained in 87% yield as a mixture of separable α/β anomers (ratio 3/2, Scheme 1).[11]

First, we examined the survey of the 1,3-dipolar cycloaddition reaction conditions by using azide **2**β and phenylacetylene as models. These conditions, which are collected in Table 1, included nature of the solvent, copper(I) source, temperature, and additives (ligand, co-solvent, etc.).

We found that the reaction performed in toluene in the presence of diisopropylethylamine (DIEA, entry 5)[12] provided the desired cycloadduct **3a**β as a single regioisomer in 87% yield and without any epimerization of the C1′ stereocenter.[13] Reaction without copper(I) and/or ligand did not work even at higher temperature and longer reaction time (entries 1 and 2), and even under microwave activation (entries 8 and 9). The recently reported conditions for primary azide–alkyne cyclocondensation in water also failed to give any product.[14] It is noteworthy that the Sharpless conditions using Cu(II) and sodium ascorbate as a reducing agent led to moderate yields (40%, entry 6)[4a] and, stoichiometric amount of the catalyst was required to achieve the reaction after 24 h (entry 7).

Concerning the stereo- and regio-chemistry of **3a**β (β-configuration and phenyl in position 4), this was unambiguously attested by NOESY and HMBC experiments. Indeed, the ^1H 2D NOESY spectrum shows correlations between $H_{1'}$–$H_{4'}$ and H_5–H_{Ph}, and the ^1H–^{13}C HMBC experiment shows $C_{1'}$–H_5 and H_5–C_{Ph} cross coupling, in accordance with the proposed structure for **3a**β (Fig. 2).

The promissing results obtained with CuI/DIEA in toluene at 110 °C (Table 1, entry 5) prompted us to further optimize the cycloaddition process by using microwave activation under solvent-free conditions. Thus, by using silica gel as a solid support for the bimolecular reaction, we found that the same reagents and substrates (**2**β, phenylacetylene and CuI/DIEA) when adsorbed on SiO_2

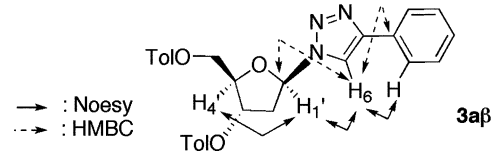
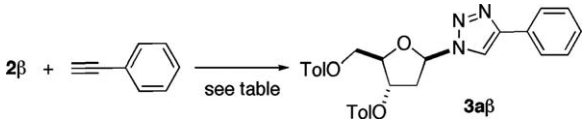


Figure 2. Significant NOESY and HMBC correlations.

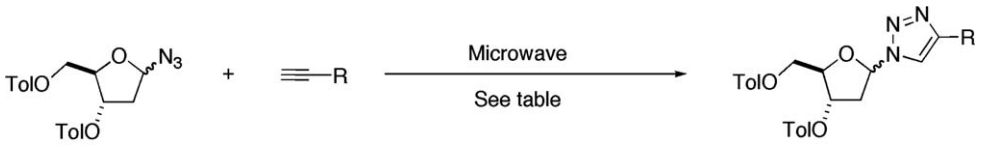
Table 1. Survey of the cycloaddition conditions



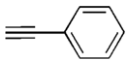
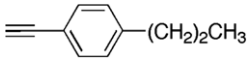
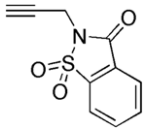
Entry[a]	Catalyst	Ligand/conditions	Solvent/time	*T* (°C)	Yield[e] (%)
Conventional heating					
1	No	No	Toluene/24 h	110	0
2	CuI	No	Toluene/24 h	110	<5
3[b]	CuI	DIEA	Toluene/72 h	rt	10
4[b]	CuI	Et_3N	Toluene/24 h	110	68
5[b]	CuI	DIEA	Toluene/24 h	110	87
6[c]	$CuSO_4$	Sodium ascorbate	H_2O/*t*BuOH/24 h	rt	40
7[d]	$CuSO_4$	Sodium ascorbate	H_2O/*t*BuOH/24 h	rt	86
Microwave irradiation					
8	No	MW	Toluene, 5 min	90	0
9	No	MW	Toluene/DMF (1/1), 5 min	140	<5
10	CuI[a]	DIEA, MW	Adsorbed on SiO_2, 3 min	115	95

[a] Azide (1 mmol), alkyne (1.2 equiv).
[b] CuI (2 equiv), amine (5 equiv).
[c] Under catalytic conditions (see Ref. 3a).
[d] Under stoichiometric conditions.
[e] Yield of the isolated product.

Table 2. 1,3-Dipolar cycloaddition under Cu(I) and microwave activation



2α or 2β **3a-jα or 3a-jβ**

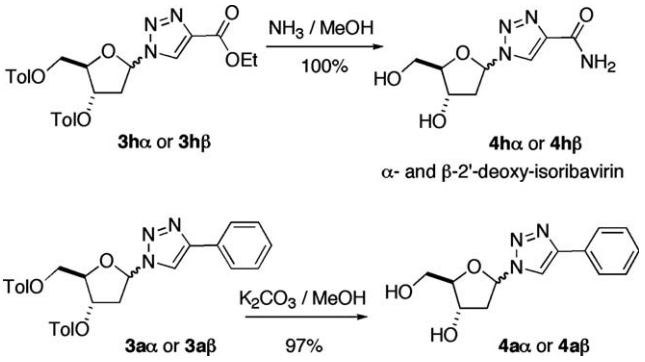
Entry[a]	Alkyne: ≡—R	Azide	Irradiation time (min)	Product	Yield[b] (%)
1		**2**α	3	**3a**α	97
2		**2**β	3	**3a**β	95
3	≡—$(CH_2)_5CH_3$	**2**α	3	**3b**α	94
4		**2**β	3	**3b**β	96
5	≡—$(CH_2)_7CH_3$	**2**α	3	**3c**α	98
6		**2**β	3	**3c**β	93
7	≡—CH_2OH	**2**α	1.5	**3d**α	96
8		**2**β	1.5	**3d**β	95
9	≡—$CH(OH)CH_3$	**2**α	1.5	**3e**α	91
10		**2**β	1.5	**3e**β	95
11	≡—$CH(OH)(CH_2)_4CH_3$	**2**α	1.5	**3f**α	96
12		**2**β	1.5	**3f**β	97
13	≡—CO_2H	**2**α	3	**3g**α	0
14		**2**β	3	**3g**β	0
15	≡—CO_2Et	**2**α	2	**3h**α	98
16		**2**β	2	**3h**β	95
17		**2**α	3	**3i**α	94
18		**2**β	3	**3i**β	96
19		**2**α	2	**3j**α	93
20		**2**β	2	**3j**β	91

[a] Conditions: azide (1 mmol), alkyne (2 equiv), CuI (2 equiv) and DIEA (5 equiv) were adsorbed on silica gel (1 g/mmol of azide) and irradiated ($95\ °C < T < 115\ °C$, reaction temperature was digitaly measured).
[b] Yields based on ^1H NMR of the crude products.

(1 g/mmol) and irradiated for 3 min in a simple microwave oven in open vessel afforded 95% of **3a**β as the sole product of the reaction (Table 1, entry 10). The cooperative effect between a microwave heating and Cu(I) catalysis allowed the dipolar cycloaddition to proceed cleanly, and the formed cycloadduct was isolated by simple elution from the silica gel support.

With this efficient procedure in hand, we investigated its scope and generalization. Thus, the Cu(I)-assisted solvent-free cycloaddition reaction between a range of functionalized terminal alkynes and azido-2′-deoxyribose **2**α or **2**β was examined under microwave activation. The potential and general applicability of this novel procedure is illustrated by the examples collected in Table 2.[15]

Indeed, the α- and β-1,2,3-triazolyl-nucleosides were isolated in high yields under a short period of microwave irradiation from their corresponding azide **2**α or **2**β and alkynes, excepting in the case of propargylic acid (entries 13 and 14). It is worth noting that only a single regioisomer was obtained in each of these reactions. This regioselectivity is most likely due to the expected steric factors in the azide–alkyne transition state. Disappointingly, the reaction between propargylic acid and azido-sugar **2**α or **2**β did not proceed even with a large excess of catalyst and increased reaction time. This is probably due to a strong chelation of Cu(I) with the acid function, as supported by the formation of a green gum thus inactivating the catalyst and, consequently, preventing the reaction to occur. This is further supported by the formation in high yields of the expected



Scheme 2. Cleavage of 3′- and 5′-tolouyl protective group.

cycloadducts **3h**α,β from **2**α,β and propargylic ethylester, respectively (entries 15 and 16). In the same way, with saccharin-substituted alkyne anchoring a sulfonamide function, the corresponding triazolyl-nucleosides **3j**α and **3i**β were obtained in 93% and 90% yield, respectively (entries 19 and 20).

Finally, the obtained α- and β-nucleosides **3a**–**j** were further deprotected at their 3′- and 5′-positions. Typical examples are shown in Scheme 2. Thus, by simple treatment of **3h**α and **3h**β with aq NH_3 solution, we quantitatively isolated the free nucleosides **4h**α and **4h**β, respectively, as close analogs of the potent ribavirin drug **2**. In the same way, methanolysis of **3a**α and **3a**β afforded nucleosides **4a**α and **4a**β in 95% yield (Scheme 2).[16]

In summary, we efficiently synthesized new 2′-deoxynucleosides featuring a functionalized 1,2,3-triazolyl ring as aglycone moiety. Reactions were achieved in high yields by using a cooperative effect of Cu(I) and microwave activation in the 1,3-dipolar cycloaddition. The procedure is highly convenient since reactions were carried out in open vessels, without solvent and by using silica gel as a solid support. Moreover, all reactions were achieved in fast and clean fashion since, few minutes are necessary under microwave irradiation and the cycloadducts **3a**–**j** were easily isolated. The scope and limitations of this process together with its generalization to the ribo series and disubstituted alkynes are underway.

Acknowledgements

We gratefully acknowledge the CNRS (convention d'échange France-Maroc), Région Provence Alpes Côtes d'Azur and Université de Nice-Sophia Antipolis for financial support (Med-Accueil Graint to K. El Akri).

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12. The best combination was found to be azide/CuI/DIEA = 1/2/5.
13. Compound **3a**β: ^{1}H NMR (200 MHz, $CDCl_3$) δ 2.37 (s, 3H, CH_3), 2.44 (s, 3H, CH_3), 2.90 (m, 1H, H-2′), 3.15 (m, 1H, H-2′), 4.45–4.80 (m, 3H, H-5′ and H-4′), 5.80 (m, 1H, H-3′), 6.57 (t, 1H, $J = 6.4$ Hz, H-1′), 7.18 (d, 2H, $J = 8.0$ Hz, H-Tol), 7.25–7.45 (m, 5H, 2 × H-Tol and 3 × H-Ph), 7.62 (dd, 2H, $J = 7.5$ and 1.3 Hz, 2 × H-Ph), 7.87 (d, 2H, J = 8.2 Hz, H-Tol), 7.75 (d, 2H, $J = 8.2$ Hz, H-Tol), 7.92 (s, 1H, H-5), 7.95 (d, 2H, $J = 8.2$ Hz, H-Tol). ^{13}C NMR ($CDCl_3$): δ 21.8, 21.9, 31.1, 38.8, 63.9, 74.9, 83.8, 89.2, 118.0, 125.8, 126.5, 126.7, 128.3, 128.8, 129.4, 129.5, 129.8, 129.9, 130.3, 144.4, 144.7, 148.3, 162.8, 166.0, 166.3. MS (ES^+): $m/z = 520$ $(M+Na)^+$.
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15. General procedure for triazolyl-nucleosides synthesis under microwave irradiation (for general safety and cautions relating to the use of microwave apparatus see,

for example, Refs. 5a,c). Microwave experiments were carried out in a non-modified domestic oven (BlueSky 900 W). After a careful determination of the higher density electric spot using an aqueous solution of cobalt chloride,[17] reactions were performed in this point at the maximum continuous power output of 900 W. To a solution of azido-sugar **2** (1 mmol) in methylene chloride or toluene (10 mL) was added: alkyne (1.05–1.5 equiv), CuI (2 equiv), DIEA (5 equiv) and 1 g of silica gel. The mixture was stirred for 5 min and the solvent was evaporated at room temperature. The resulting yellow powder was placed into a microwave oven and irradiated for the desired amount of time (the final temperature was evaluated at the end of the irradiation by digital thermometric probe). The mixture was eluted twice with ethyl acetate and the solvent evaporated under reduced pressure to give a crude product with, in general, good purity. The crude product could be subjected to a simple filtration on silica gel (cyclohexane/ethyl acetate: 80/20).

Selected spectral data: Compound **3a**α: ^{1}H NMR (200 MHz, $CDCl_3$): δ 2.27 (s, 3H, CH_3), 2.36 (s, 3H, CH_3), 2.80–3.20 (m, 2H, H-2′), 4.56 (m, 2H, H-5′), 4.77 (m, 1H, H-4′), 5.61 (td, 1H, $J = 6.3$ and 1.9 Hz, H-3′), 6.51 (dd, 1H, $J = 6.4$ and 1.5 Hz, H-1′), 7.07 (d, 2H, $J = 7.9$ Hz, H-Tol), 7.20 (d, 2H, $J = 7.9$ Hz, H-Tol), 7.31 (m, 3H, H-Ph), 7.59 (d, 2H, $J = 8.2$ Hz, H-Tol), 7.70 (dd, 2H, $J = 7.9$ and 1.4 Hz, H-Ph), 7.75 (d, 2H, $J = 8.2$ Hz, H-Tol), 8.05 (s, 1H, H-5). ^{13}C NMR ($CDCl_3$): δ 21.7, 21.8, 38.9, 64.1, 74.7, 85.1, 90.2, 118.0, 125.8, 126.2, 126.8, 128.3, 128.8, 128.9, 129.3, 129.4, 129.7, 129.9, 129.9, 130.6, 144.4, 144.5, 147.9, 165.9, 166.2. MS (ES+): $m/z = 520$ $(M+Na)^+$.

Compound **3b**α: ^{1}H NMR (200 MHz, $CDCl_3$): δ 0.82 (t, 3H, $J = 6.4$ Hz, CH_3), 1.20–1.60 (m, 8H, $(CH_2)_4$), 2.32 (s, 3H, CH_3), 2.35 (s, 3H, CH_3), 2.63 (t, 2H, $J = 7.9$ Hz, CH_2), 2.80–3.20 (m, 2H, H-2′), 4.65 (m, 2H, H-5′), 4.70 (m, 1H, H-4′), 5.55 (td, 1H, $J = 4.5$ and 2.0 Hz, H-3′), 6.41 (dd, 1H, $J = 6.3$ and 1.5 Hz, H-1′), 7.12 (d, 2H, $J = 8.0$ Hz, H-Tol), 7.19 (d, 2H, $J = 8.0$ Hz, H-Tol), 7.52 (br s, 1H, H-5), 7.61 (d, 2H, $J = 8.2$ Hz, H-Tol), 7.87 (d, 2H, $J = 8.2$ Hz, H-Tol). ^{13}C NMR ($CDCl_3$): δ 14.2, 21.8, 22.7, 25.9, 29.1, 29.6, 31.7, 38.8, 64.1, 74.8, 84.8, 89.9, 118.8, 126.4, 126.9, 129.3, 129.4, 129.8, 144.4, 144.5, 148.8, 166.1, 166.3. MS (ES^+): $m/z = 528$ $(M+Na)^+$.

Compound **3b**β: ^{1}H NMR (200 MHz, $CDCl_3$): δ 0.80 (t, 3H, $J = 6.8$ Hz, CH_3), 1.20–1.60 (m, 8H, $(CH_2)_4$), 2.34 (s, 3H, CH_3), 2.36 (s, 3H, CH_3), 2.55 (t, 2H, $J = 8.0$ Hz, CH_2), 2.70 (m, 1H, H-2′), 2.70 (m, 1H, H-2′), 3.01 (m, 1H, H-2′), 4.40–4.60 (m, 3H, H-5′ and H-3′), 5.68 (m, 1H, H-3′), 6.41 (t, 1H, $J = 6.4$ Hz, H-1′), 7.16 (d, 2H, $J = 8.0$ Hz, H-Tol), 7.20 (d, 2H, $J = 8.0$ Hz, H-Tol), 7.37 (s, 1H, H-5), 7.61 (d, 2H, $J = 8.2$ Hz, H-Tol), 7.87 (d, 2H, $J = 8.2$ Hz, H-Tol). ^{13}C NMR ($CDCl_3$): δ 14.2, 21.8, 21.9, 22.7, 25. 8, 29.1, 29.3, 31.7, 38.5, 64.1, 75.0, 83.6, 88.9, 119.1, 125.8,129.4,129.8, 129.9,144.3, 144.6, 149.2,166.3. MS (ES^+): $m/z = 528$ $(M+Na)^+$. Compound **3c**α: ^{1}H NMR (200 MHz, $CDCl_3$): δ 0.79 (t, 3H, $J = 6.7$ Hz, CH_3), 1.20–1.40 (m, 10H, $(CH_2)_5$), 1.61 (m, 2H, CH_2), 2.32 (s, 3H, CH_3), 2.35 (s, 3H, CH_3), 2.63 (t, 2H, $J = 7.8$ Hz, CH_2), 2.8–3.1(m, 2H, H-2′), 4.55 (m, 2H, H-5′), 4.70 (m, 1H, H-4′), 5.61 (td, 1H, J = 6.5 and 2.0 Hz, H-3′); 6.46 (dd, 1H, $J = 5.5$ and 1.5 Hz, H-1′), 7.12 (d, 2H, $J = 8.0$ Hz, H-Tol), 7.20 (d, 2H, $J = 8.0$ Hz, H-Tol), 7.52 (s, 1H, H-5), 7.56 (d, 2H, $J = 8.1$ Hz, H-Tol), 7.87 (d, 2H, $J = 8.1$ Hz, H-Tol). ^{13}C NMR ($CDCl_3$): δ 14.2 , 21.8, 22.8, 25.9, 29.3, 29.5, 29.6, 32.0, 38.8, 64.1, 74.8, 84.8, 89.9, 126.4, 126.8, 129.3, 129.4, 129.8, 144.4, 144.5, 166.1, 166.3. MS (ES^+): $m/z = 534$ $(M+H)^+$, 556 $(M+Na)^+$.

Compound **3c**β: ^{1}H NMR (200 MHz, $CDCl_3$): δ 0.80 (t, 3H, $J = 6.7$ Hz, CH_3), 1.2–1.4 (m, 10H, $(CH_2)_5$), 1.6 (m, 2H, CH_2), 2.41 (2s, 6H, 2Me), 2.62 (t, 2H, $J = 7.8$ Hz, CH_2), 2.8–3.1(m, 2H, H-2′), 4.5 (m, 2H, H-5′), 4.6 (m, 1H, H-4′), 5.7 (m, 1H, H-3′), 6.44 (t, 1H, $J = 6.4$ Hz,H-1′), 7.16 (d, 2H,$J = 8.0$ Hz, H-Tol), 7.20 (d, 2H, $J = 8.0$ Hz, H-Tol), 7.37 (s, 1H, H-5), 7.80 (d, 2H, $J = 8.2$ Hz, H-Tol), 7.87 (d, 2H, $J = 8.2$ Hz, H-Tol). ^{13}C NMR ($CDCl_3$): δ 14.0, 21.8, 21.9, 22.8, 25.8, 29.3, 29.4, 32.0, 38.5, 43.4, 51.9, 64.1, 75.0, 83.6, 88.9, 126.5, 126.8, 129.4, 129.8, 129.9, 144.3, 144.6,166.0, 166.3. MS (ES^+): $m/z = 556$ $(M+Na)^+$.

16. Selected spectral data:
Compound **4a**α: ^{1}H NMR (200 MHz, CD_3OD) δ 2.52–2.60 (m, 1H, H-2′), 2.87–2.93 (m, 1H, H-2′), 3.62 (dd, 1H, $J = 12.0$ and 5.0 Hz, H-5′), 3.74 (dd, 1H, $J = 12.0$ and 4.0 Hz, H-5′), 4.31 (q, 1H, $J = 4.0$ Hz, H-4′), 4.49 (m, 1H, H-3′); 6.50 (dd, 1H, $J = 7.6$ and 2.3 Hz, H-1′), 7.37 (t, 1H, $J = 7.4$ Hz, H-Ph), 7.46 (t, 2H, $J = 7.4$ Hz, H-Ph), 7.84 (m, 2H, H-Ph), 8.62 (s, 1H, H-5). ^{13}C NMR (CD_3OD): δ 41.6 (C-2′), 62.8 (C-5′), 72.1 (C-3′), 90.2 (C-4′), 90.9 (C-1′), 120.4 (C-5), 126.4 (C-Ph), 129.1 (C-Ph), 129.6 (C-Ph), 131.0 (C-Ph), 148.9 (C-4). MS (ES^+): $m/z = 284$ $(M+Na)^+$.
Compound **4a**β: ^{1}H NMR (200 MHz, CD_3OD) δ 2.31–2.47 (m, 1H, H-2′), 2.69–2.75 (m, 1H, H-2′), 3.56 (dd, 1H, $J = 11.9$ and 5.0 Hz, H-5′), 3.66 (dd, 1H, $J = 12.0$ and 4.1 Hz, H-5′), 3.95 (q, 1H, $J = 4.1$ Hz, H-4′), 4.45 (m, 1H, H-3′); 6.35 (dd, 1H, $J = 5.7$ and 5.6 Hz, H-1′), 7.24 (tt, 1H, $J = 7.5$ and 1.2 Hz, H-Ph), 7.33 (tt, 2H, $J = 7.9$ and 1.2 Hz, H-Ph), 7.72 (m, 2H, H-Ph), 8.41 (s, 1H, H-5). ^{13}C NMR (CD_3OD): δ 41.7 (C-2′), 63.2 (C-5′), 72.2 (C-3′), 89.7 (C-4′), 90.3 (C-1′), 120.8 (C-5), 126.7 (C-Ph), 129.4 (C-Ph), 129.9 (C-Ph), 131.6 (C-Ph), 148.9 (C-4). MS (ES^+): $m/z = 262$ $(M+H)^+$, 284 $(M+Na)^+$.

17. Villemin, D.; Thibault-Starzyk, F. *J. Chem. Educ.* **1991**, 346.