Efficient Synthesis of α- and β-2′-Deoxy-heteroaryl-*C*-nucleosides

Marie Spadafora, Alain Burger,* Rachid Benhida*

Laboratoire de Chimie des Molécules Bioactives et des Arômes, UMR 6001 CNRS, Institut de Chimie de Nice, Université de Nice-Sophia Antipolis, 28 Avenue de Valrose, 06108 Nice Cedex 2, France
Fax +33(4)92076151; E-mail: benhida@unice.fr

Received 22 January 2008

Abstract: A short and efficient method for the synthesis of a series of 2′-deoxy-heteroaryl-*C*-nucleosides has been developed by the application of aryl–aldol condensation followed by *p*-toluenesulfonic acid (PTSA)-mediated isopropylidene cleavage and subsequent cycloetherification.

Key words: *C*-nucleosides, aryl–aldol condensation, cycloetherification

C-Nucleosides are well-known nucleoside analogues that contain a carbon–carbon linkage between the furanose ring and the heterocyclic base, instead of the carbon–nitrogen bond in the classical *N*-nucleosides. The presence of such a C–C bond confers to these analogues higher stability towards chemical and enzymatic hydrolysis than the *N*-nucleoside derivatives. Another attractive feature of *C*-nucleosides arises from their high-potential value as therapeutic agents and biochemical probes.[1] They have been found in a number of natural and synthetic products such as tiazofurin, pyrazofurin, formycin, showdomycin, and pseudouridine reported as potent antitumor or antibiotic compounds.[2] Therefore a large number of synthetic approaches to *C*-ribofuranosyl nucleosides have recently been explored.[1,3] However, less attention has been focused on their 2′-deoxy analogues which are promising targets in medicinal chemistry and especially in the growing nucleic acid chemistry by their incorporation into artificial DNA and RNA oligonucleotides.[4]

One of the most well-known strategies is the conversion of ribo-*C*-nucleosides into their 2′-deoxy analogues using the radical Barton–McCombie 2′-deoxygenation methodology which requires additional steps and, thus, decreases the overall yield.[5] The standard S_N2 process of an activated sugar or base construction have also been largely used but were in some cases low yielding.[6] The Heck reaction between halogenated aryls and protected glycals is also a known strategy to construct *C*-nucleosides. However, this approach requires protection–deprotection steps to avoid functional group interconversion and yields are generally very low particularly with electron-rich aromatics.[7]

In connection with our ongoing project aimed at using α- and β-2′-deoxy-heteroaryl-*C*-nucleosides of type **A** (Figure 1) as probe-like *C*-nucleosides by their incorporation into oligonucleotides,[8,9] we envisioned the preparation of 2′-deoxy-*C*-nucleosides **4a**–**f** as advanced precursors. A sensitive and functionalized fluorophore would be introduced at a late stage making the methodology more attractive for post-functionalization.

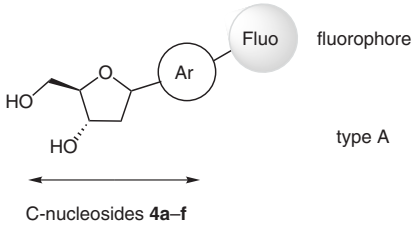


Figure 1 Structure of targeted *C*-nucleosides

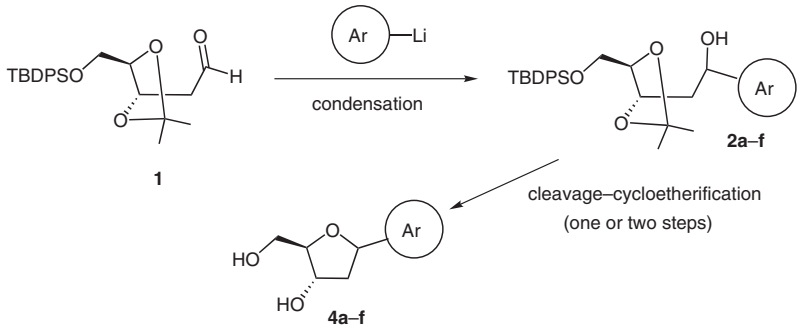
Therefore, we set out to develop an efficient synthetic methodology which would allow the access of 2′-deoxy-heterocyclic *C*-nucleosides **4a**–**f** precursors of both α- and β-anomeric configuration.

We report herein a short synthesis (two, three steps) of 2′-deoxy-*C*-nucleosides **4a**–**f** starting from the masked deoxyribose aldehyde **1**.[10] The two key steps consist into (i) aryl–aldol-like condensation and (ii) tandem 3′,4′-isopropylidene cleavage–C′4–C1′ cycloetherification (Scheme 1).

First, the aryl condensation on aldehyde **1** was studied by varying the nature of the aryl and the base, the reaction temperature and the stoichiometry. Then, the alcohols **2a**–**f** were obtained by slow addition of electrophile **1** to the freshly lithiated aryl species. The results of this study are summarized in Table 1. For exemple, the regiocontrolled *ortho* lithiation of benzofuran using LDA in THF at –78 °C or 0 °C followed by addition of the protected aldehyde **1** afforded the alcohol product **2a** in low yield (Table 1, entries 1 and 2). Interestingly and as expected, the use of a strong *n*-BuLi base at 0 °C increase the yield to 83% by increassing the lithiation efficiency. The alcohol **2a** was obtained as a mixture of *R* and *S* diastereomers in a 2:3 ratio (Table 1, entry 3).[11]

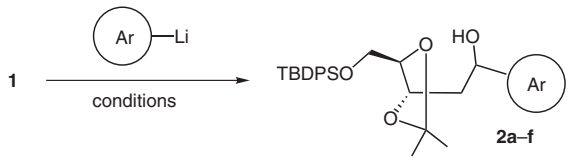
The *R*/*S* ratio was determined based on ^{1}H NMR of the crude product, and the stereochemistry of each diol was assigned based on the anomeric stereochemistry of their respective cyclized products **3a**–**f** (vide infra). All the other heterocycles were subjected to the same reaction conditions. Furan and benzothiophene also react cleanly with aldehyde **1** giving the desired products **2b** (65%) and **2c**

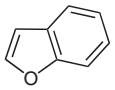
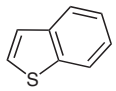
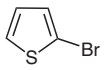
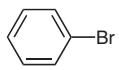
SYNLETT 2008, No. 8, pp 1225–1229
Advanced online publication: 16.04.2008
DOI: 10.1055/s-2008-1072589; Art ID: G04008ST



Scheme 1 Synthetic strategy (i) aryl–aldol condensation and (ii) isopropylidene cleavage–cycloetherification

Table 1 Addition of Electrophile **1** to Lithiated Aryl Species



Entry[a]	Aryl	Base	Temp (°C)	Time (h)	Yield of **2a–f** (%)[b]	*R*/*S* Ratio[c]
1		LDA	–78	4	**2a** 30	40:60
2		LDA	0	1.5	**2a** 35	40:60
3		*n*-BuLi	0	1.5	**2a** 83	35:65
4		LDA	0	1	**2b** 10	50:50
5		*n*-BuLi	0	1	**2b** 65	50:50
6		LDA	–78	1	**2c** 81	45:55
7		LDA	–78	1	**2d** 89	40:60
8		*n*-BuLi	–78 to 0	1	**2e** 82	40:60
9		*n*-BuLi	0	0.5	**2f** 40	50:50
10		*n*-BuLi	–78	4	**2f** 75	40:60

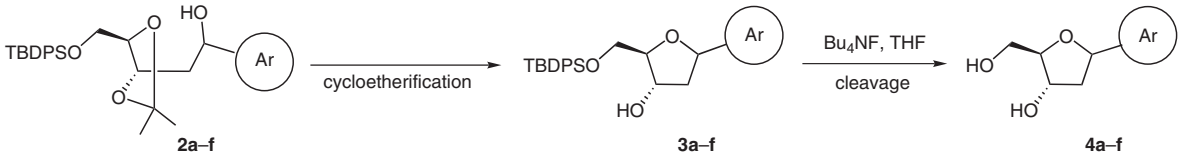
[a] Aryl (2 equiv), base (2.1 equiv), THF.
[b] Yield of pure isolated products.
[c] *S*/*R* Ratio based on ^{1}H NMR.

(81%), respectively. However, the LDA was found to be more effective with benzothiophene than furan and benzofuran (Table 1, entries 1, 2, 4, and 6) due in part to the sulfur stabilization of the lithiated intermediate in the case of the benzothiophene derivative. In the case of 2-bromothiophene, halogen–metal exchange followed by addition of **1** afforded the 2-thiophenyl alcohol **2e** in 82% yield (Table 1, entry 8) while the use of LDA under the same reaction conditions gave the 2-bromothiophenyl-substituted product at the 5-position in 89% yield (metalation at position 5, Table 1, entry 7).[12] Interestingly, the bromine atom remained intact and should allow post-synthetic transformation. In the same way, treatment of bromobenzene with *n*-BuLi at –78 °C, using the same protocol, led to the desired compound **2f** in 75% yield (Table 1, entry 10).

With alcohols **2a–f** in hand, the synthesis of *C*-nucleosides was next studied, following isopropylidene cleavage and subsequent C4′–C1′ cyclization. The conditions used in this study are depicted in Table 2.

For the survey of the cycloetherification reaction conditions, we started with benzofuran alcohol **2a** for which the diastereomeric diols were easily separated (Table 2). We first try the in situ mesylation followed by isopropylidene cleavage using $SnCl_2$ to perform the direct cyclization starting from **2a** (*R*/*S* = 40:60). Unfortunately, under these conditions only a poor yield of the cyclized product **3a** was obtained (Table 2, entry 1). Treatment of **2a** (*R*/*S* = 40:60) with TFA (Table 2, entry 2) afforded the free nucleoside **4a** (25% yield) as a mixture of α/β anomers in a 30:70 ratio, with a partial anomerization in favor of the β anomer. Related α-to-β epimerization has been reported recently using TFA and benzenesulfonic acid.[13] Interestingly, conversion of **2a** into **3a** was best achieved using PTSA in refluxing toluene and gave a good yield of **3a** (70%, entry 3) with an unchanged α/β ratio (α/β = 40:60).

Table 2 Synthesis of C-Nucleosides, Isopropylidene Cleavage, and C4′–C1′ Cyclization



Entry	*R*/*S* Ratio of alcohols **2a–f**	Conditions	α/β Ratio[a] of products **3a–f**, (yield, %)[b]	Nucleosides **4a–f** (yield, %)[b]
1	**2a** (40:60)	MsCl then $SnCl_2$	**3a** (<10)	
2	**2a** (40:60)	TFA, dioxane, H_2O	–	α,β-**4a** (25)[c]
3	**2a** (40:60)	PTSA, toluene	α,β-**3a** 40:60 (70)	α,β-**4a** (83)
4	**2a** (100:0)	PTSA, toluene	α-**3a** >95:5 (72)	α-**4a** (85)
5	**2a** (0:100)	PTSA, toluene	β-**3a** >5:95 (75)	β-**4a** (95)
6	**2b** (40:60)	PTSA, toluene	α,β-**3b** 40:60 (72)	α,β-**4b** (89)
7	**2d** (40:60)	PTSA, toluene	α,β-**3d** 40:60 (86)	α,β-**4d** (86)
8	**2e** (40:60)	PTSA, toluene	α,β-**3e** 40:60 (95)	α,β-**4e** (90)
9	**2f** (40:60)	PTSA, toluene	α,β-**3f** 40:60 (70)	α,β-**4f** (85)

[a] The *S*/*R* and α/β ratios based on ^{1}H NMR of the crude products.
[b] Yield of pure isolated products.
[c] With TFA only **4a** was obtained in 30:70 α/β ratio.

In view of this observation, it appears that alcohols **2a** cyclize, under PTSA treatment, according to an S_N2 process. This result was attested by treatment of separated pure (*R*)-**2a** and (*S*)-**2a** under the same reaction conditions (Table 2, entries 4 and 5), which afforded the cyclized products α-**3a** and β-**3a**, respectively without any epimerization. This novel procedure was then applied to the other alcohols **2b–f**. In all cases, these mild conditions gave satisfactory yields of the cyclized products **3b–f** (Table 2, entries 6–9).[14]

The α/β-anomeric configuration of each *C*-nucleoside **3a–f** was established by 2D COSY–NOESY experiments. The most significant NOE correlations are represented in Figure 2 for the benzofuryl nucleosides α-**3a** and β-**3a**. Indeed, the β configuration was clearly evidenced by the observed NOE correlation between H1′ and H4′. In the same way, we observed for the other anomer clear NOE correlations between H1′–H3′ and H1′–H5′ in accordance with an α configuration.

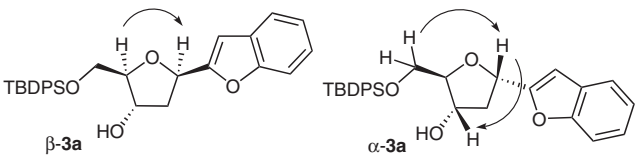


Figure 2 α/β-Configuration assignment (NOESY correlations)

The last step is the cleavage of the TBDPS protecting group. Thus, treatment of protected precursors **3a–f** with Bu_4NF in THF afforded good yields (83–95%) of the corresponding free nucleosides **3a–f**, respectively (Table 2).[15]

In conclusion, we have developed a short and straightforward synthesis of 2′-deoxy-*C*-nucleosides featuring aryl and heteroaryl nucleobases. The methodology involves sequential aryl–aldol condensation and tandem isopropylidene cleavage–cycloetherification. The process is also compatible with sensitive groups and allows access to halogenated heterocyclic nucleosides. Moreover, the presence of bromine would provide useful post-synthetic transformations for the preparation of 2′-deoxythiophenyl-*C*-nucleosides functionalized with fluorophores for their incorporation into oligonucleotides. This work is under way.

Acknowledgment

The authors thank ANR (Agence Nationale de la Recherche), CNRS and Ministère de l'Education Nationale et de la Recherche for financial support and for a doctoral fellowship (MENRT) to M. Spadafora.

References and Notes

(1) For recent reviews on the chemistry of *C*-glycoside analogues, see: (a) Wu, Q.; Simons, C. *Synthesis* **2004**, 1533. (b) Bililign, T.; Griffith, B. R.; Thorson, J. S. *Nat. Prod. Rep.* **2005**, *22*, 742. (c) Lee, D. Y. W.; He, M. S. *Curr. Top. Med. Chem.* **2005**, *5*, 1333.

(2) For a brief overview of the biological and clinical impact of tiazofurin, see: (a) For pyrazofurin and formycin, see: Grifantini, M. *Curr. Opin. Investig. Drugs* **2000**, *1*, 257. (b) Shaban, M. A. E.; Nasr, A. Z. In *Advances in Heterocyclic Chemistry*, Vol. 68; Katritzky, A. R., Ed.; Academic Press: San Diego, **1997**, 259. (c) For showdomycin, see: Shaban, M. A. E.; Nasr, A. Z. In

Advances in Heterocyclic Chemistry, Vol. 70; Katritzky, A. R., Ed.; Academic Press: San Diego, **1998**, 230. (d) Nishimura, H.; Mayama, M.; Komatsu, Y.; Kato, H.; Shimsoka, N.; Tanaka, Y. *J. Antibiot., Ser. A* **1964**, *17*, 148. (e) Rabinovitz, M.; Uehara, Y.; Vistica, D. T. *Science* **1979**, *206*, 1085. (f) Barett, A. G. M.; Broughton, H. B. *J. Org. Chem.* **1986**, *51*, 495.

(3) (a) Adamo, M. F. A.; Adlington, R. M.; Baldwin, J. E.; Day, A. L. *Tetrahedron* **2004**, *60*, 841. (b) Hashmi, I. A.; Ali, F. I.; Feist, H.; Michalik, M.; Reinke, H.; Peseke, K. *Synthesis* **2007**, 2819. (c) Oda, H.; Hanami, T.; Iwashita, T.; Kojima, M.; Itoh, M.; Hayashizaki, Y. *Tetrahedron* **2007**, *63*, 11021. (d) Hainke, S.; Singh, I.; Hemmings, J.; Seitz, O. *J. Org. Chem.* **2007**, *72*, 8811.

(4) (a) Kool, E. T. *Acc. Chem. Res.* **2002**, *35*, 936. (b) Sismour, A. M.; Benner, S. A. *Nucleic Acids Res.* **2005**, *33*, 5640. (c) Leconte, A. M.; Matsuda, S.; Hwang, G. T.; Romesberg, F. E. *Angew. Chem. Int. Ed.* **2006**, *45*, 4326.

(5) See, for example: (a) Tanaka, K.; Shinoya, M. *J. Org. Chem.* **1999**, *64*, 5002. (b) Seela, F.; Debelak, H. *J. Org. Chem.* **2001**, *66*, 3303.

(6) See, for example: (a) Chen, D.-W.; Beuscher, A. E.; Stevens, R. C.; Wirsching, P.; Lerner, R. A.; Janada, K. D. *J. Org. Chem.* **2001**, *66*, 1725. (b) Griesang, N.; Richert, C. *Tetrahedron Lett.* **2002**, *43*, 8755. (c) Aketani, S.; Tanaka, K.; Yamamoto, K.; Ishihama, A.; Cao, H.; Tengeiji, A.; Hiraoka, S.; Shiro, M.; Shionoya, M. *J. Med. Chem.* **2002**, *45*, 5594.

(7) (a) For the synthesis of aryl *C*-glycosides via the Heck reaction, see: Wellington, K. W.; Benner, S. A. *Nucleosides, Nucleotides Nucleic Acids* **2005**, 1309; (review). (b) Oda, H.; Hanami, T.; Iwashita, T.; Kojima, M.; Itoh, M.; Hayashizaki, Y. *Tetrahedron* **2007**, *63*, 12747.

(8) (a) Guianvarc'h, D.; Benhida, R.; Fourrey, J.-L.; Maurisse, R.; Sun, J.-S. *Chem. Commun.* **2001**, 1814. (b) Guianvarc'h, D.; Fourrey, J.-L.; Sun, J.-S.; Maurisse, R.; Benhida, R. *Bioorg. Med. Chem.* **2003**, *11*, 2751. (c) Guianvarc'h, D.; Fourrey, J.-L.; Tran Huu Dau, M.-E.; Guérineau, V.; Benhida, R. *J. Org. Chem.* **2002**, *67*, 3724. (d) Guianvarc'h, D.; Fourrey, J.-L.; Maurisse, R.; Sun, J.-S.; Benhida, R. *Org. Lett.* **2002**, *4*, 4209.

(9) Ratiometric fluorescent probes will be used (unpublished results). For classical fluorescent nucleosides, see: Wilson, J. N.; Kool, E. T. *Org. Biomol. Chem.* **2006**, *4*, 4265.

(10) (a) Joos, P. E.; Esmans, E. L.; Domise, R. A.; De Bruyn, A.; Balzarini, J. M.; De Clercq, E. D. *Helv. Chim. Acta* **1992**, *75*, 613. (b) Aldehyde **1** was obatined from 2′-deoxyribose in four steps and 62% overall yield.

(11) **Typical Procedure**
To a solution of benzofuran (2 mmol) in anhyd THF (6 mL) was added dropwise *n*-BuLi (1.6 M in hexane, 2 mmol) at 0 °C. The mixture was stirred for 30 min and aldehyde **1** (412 mg, 1 equiv) in anhyd THF (2 mL) was slowly added. The reaction was stirred during 90 min and warmed slowly to r.t., then quenched with a cold solution of NH_4Cl and extracted with CH_2Cl_2 (3 × 40 mL). The combined organic layers were dried ($MgSO_4$) and evaporated under reduced pressure to give a crude oil. Silica gel column chromatography purification using gradient elution [cyclohexane (100%) to EtOAc–cyclohexane (8:92)] afforded (*S*)-**2a** and (*R*)-**2a** as yellow oils (440 mg, 83%, *R*/*S* = 35:65).
Compound (*S*)-**2a**: TLC (cyclohexane–EtOAc, 7:3). R_f = 0.49. ^{1}H NMR (200 MHz, $CDCl_3$): δ = 0.95 (s, 9 H, *t*-Bu), 1.28 (s, 3 H, CH_3), 1.37 (s, 3 H, CH_3), 2.06–2.27 (m, 1 H, H-2′), 2.37–2.47 (m, 1 H, H-2′), 3.72 (d, 2 H, *J* = 6.3 Hz, 2 × H-5′), 4.30 (q, 1 H, *J* = 6.2 Hz, H-4′), 4.42–4.52 (m, 1 H, H-3′), 5.12 (dd, 1 H, *J* = 3.8, 8.7 Hz, H-1′), 6.67 (s, 1 H, H-furan), 7.26 (m, 2 H, 2 × H-Ar), 7.36 (m, 7 H, 6 × H-Ph and 1 × H-Ar), 7.55 (m, 1 H, H-Ar), 7.64 (m, 4 H, 4 × H-Ph) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 19.10 (Me_3C), 25.44 (Me_2C), 26.75 (Me_3C), 27.91 (Me_2C), 35.36 (C-2′), 62.19 (C-5′), 68.14 (C-1′), 76.85 (C-3′), 77.51 (C-4′), 102.49 (C-3), 108.78 (Me_2C), 111.15 (C-7), 120.96 (C-4), 122.63 (C-5), 123.92 (C-6), 127.70 (C-Ph), 127.72 (C-Ar), 129.77, 132.90, and 135.51 (C-Ph), 154.75 (C-Ar), 158.64 (C-2) ppm. MS (ESI$^+$): *m*/*z* = 568.5 [MK^+], 552.6 [MNa^+].
Compound (*R*)-**2a**: TLC (cyclohexane–EtOAc, 7:3). R_f = 0.40. ^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.00 (s, 9 H, *t*-Bu), 1.26 (s, 3 H, CH_3), 1.38 (s, 3 H, CH_3), 2.22–2.45 (m, 2 H, 2 × H-2′), 3.69–3.74 (m, 2 H, 2 × H-5′), 4.20–4.29 (m, 1 H, H-4′), 4.42–4.52 (m, 1 H, H-3′), 5.08–5.16 (m, 1 H, H-1′), 6.65 (s, 1 H, H-furan), 7.26 (m, 2 H, 2 × H-Ar), 7.36 (m, 7 H, 6 × H-Ph and 1 × H-Ar), 7.55 (m, 1 H, H-Ar), 7.64 (m, 4 H, 4 × H-Ph) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 19.19 (Me_3C), 25.54 (Me_2C), 26.86 (Me_3C), 28.08 (Me_2C), 34.12 (C-2′), 62.36 (C-5′), 66.52 (C-1′), 74.52 (C-3′), 77.48 (C-4′), 102.69 (C-3), 108.35 (Me_2C), 111.21 (C-7), 120.99 (C-4), 122.75 (C-5), 123.97 (C-6), 127.79 (C-Ph), 128.30 (C-Ar), 129.87, 133.04, and 135.62 (C-Ph), 154.90 (C-Ar), 159.56 (C-2) ppm. MS (ESI$^+$): *m*/*z* = 552.6 [MNa^+], 450.7.

(12) All products gave satisfactory spectral data. Data for selected products are given here.
Compound (*R*,*S*)-**2b**: TLC (cyclohexane–EtOAc, 7:3): R_f = 0.70–0.75. ^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.04 (s, 9 H, *t*-Bu), 1.34 (s, 3 H, CH_3), 1.41 (s, 3 H, CH_3), 1.50–2.2 (m, 2 H, H-2′), 3.68–3.71 (m, 2 H, 2 × H-5′), 4.21–4.42 (m, 2 H, H-4′, H-3′), 4.88–4.95 (m, 1 H, H-1′), 6.25–6.26 (m, 2 H, 2 × H-Ar), 7.38–7.41 (m, 7 H, 6 × H-Ph, 1 × H-Ar), 7.62–7.66 (m, 4 H, 4 × H-Ph) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 19.29 (Me_3C), 25.66 (Me_2C), 26.93 (Me_3C), 28.14 (Me_2C), 35.40 (C-2′), 62.43 (C-5′), 67.64–65.66 (C-1′), 76.54–74.36 (C-3′), 77.18 (C-4′), 106.01–108.69 (C-Ar), 108.83 (Me_2C), 110.26–111.95 (C-Ar), 127.91, 129.96, 133.17, 135.70, 142.03 (C-Ph and C-Ar) ppm. MS (ESI$^+$): *m*/*z* = 503.2 [MNa^+].
Compound (*R*,*S*)-**2e**: TLC (cyclohexane–EtOAc, 7:3). R_f = 0.50–0.53. ^{1}H NMR (200 MHz, $CDCl_3$): δ = 0.96 (s, 9 H, *t*-Bu), 1.27 (s, 3 H, CH_3), 1.31 (s, 3 H, CH_3), 1.50–2.11 (m, 2 H, H-2′), 3.59–3.65 (m, 2 H, 2 × H-5′), 4.12–4.22 (m, 1 H, H-4′), 4.30–4.37 (m, 1 H, H-3′), 5.00–5.10 (m, 0.4 H, H-1′), 5.11–5.20 (m, 0.6 H, H-1′), 6.80–6.89 (m, 2 H, 2 × H-Ar), 7.20–7.26 (m, 1 H, H-Ar), 7.30–7.40 (m, 6 H, 6 × H-Ph), 7.52–7.58 (m, 4 H, 4 × H-Ph) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 19.29 (Me_3C), 25.63 (Me_2C), 26.98 (Me_3C), 28.17 (Me_2C), 37.91 (C-2′), 62.54 (C-5′), 68.01 (C-1′), 77.37 (C-3′), 77.62 (C-4′), 108.42 (Me_2C), 123.27, 124.43, 126.85, 127.88, 129.96, 133.10, 135.69, 149.07 (C-Ph and C-Ar) ppm. MS (ESI$^+$): *m*/*z* = 534.6 [MK^+], 518.7 [MNa^+], 497.6 [MH^+].

(13) Jiang, Y. L.; Stivers, J. T. *Tetrahedron Lett.* **2003**, *44*, 4051.

(14) **General Procedure**
To a solution of **2a** (*R* or *S*, 1 mmol) in toluene (25 mL) was added PTSA (0.2 mmol, 0.2 equiv). The mixture was stirred at 50 °C for 4 h then quenched with a sat. soln of $NaHCO_3$ and extracted with CH_2Cl_2 (3 × 30 mL). The combined organic layers were dried over $MgSO_4$ and evaporated under reduced pressure to give a crude oil. Silica gel column chromatography purification using gradient elution [cyclohexane (100%) to EtOAc–cyclohexane (20:80)] afforded **3a** as a yellow oil.
Compound α-**3a**: TLC (cyclohexane–EtOAc, 7:3). R_f = 0.43. ^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.08 (s, 9 H, *t*-Bu), 2.27–2.39 (m, 1 H, H-2′), 2.66–2.80 (m, 1 H, H-2′), 3.69–3.88 (m, 2 H, 2 × H-5′), 4.16–4.20 (m, 1 H, H-4′), 4.52–

4.59 (m, 1 H, H-3′), 5.24–5.31 (dd, 1 H, *J* = 8.0, 5.3 Hz, H-1′), 6.69 (s, 1 H, H-furan), 7.39–7.66 (m, 10 H, 6 × H-Ph and 4 × H-Ar), 7.67–7.71 (m, 4 H, 4 × H-Ph) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 19.40 (Me_3C), 27.05 (Me_3C), 39.40 (C-2′), 64.98 (C-5′), 74.04 and 74.78 (C3′, C-1′), 86.53 (C-4′), 103.95, 111.48, 121.31, 123.03, 124.54, 127.97, 129.99, 135.75, 156.72 (C-Ph and C-Ar) ppm. MS (ESI^+): *m/z* = 510.8 [MK^+], 495.1 [MNa^+].

Compound β-**3a**: TLC (cyclohexane–EtOAc, 7:3): R_f = 0.26. ^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.07 (s, 9 H, *t*-Bu), 2.20–2.42 (m, 1 H, H-2′), 2.47–2.56 (m, 1 H, H-2′), 3.68–4.01 (m, 2 H, 2 × H-5′), 4.02–4.07 (m, 1 H, H-4′), 4.62–4.67 (m, 1 H, H-3′), 5.30 (dd, 1 H, *J* = 9.3, 6.2 Hz, H-1′), 6.63 (s, 1 H, H-furan), 7.31–7.60 (m, 10 H, 6 × H-Ph and 4 × H-Ar), 7.62–7.79 (m, 4 H, 4 × H-Ph) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 19.40 (Me_3C), 27.05 (Me_3C), 39.56 (C-2′), 64.77 (C-5′), 73.82 (C-1′), 74.40 (C-3′), 87.22 (C-4′), 104.08, 111.43, 121.16, 122.81, 124.34, 127.90, 129.96, 135.74, 156.72 (C-Ph and C-Ar) ppm. MS (ESI^+): *m/z* = 510.8 [MK^+], 495.1 [MNa^+].

(15) Compound α-**4a**: TLC (CH_2Cl_2–MeOH, 98:2). R_f = 0.3. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 2.33–2.37 (m, 1 H, H-2′), 2.61–2.64 (m, 1 H, H-2′), 3.73–3.76 (m, 2 H, 2 × H-5′), 4.01–4.04 (q, 1 H, *J* = 4.7 Hz, H-4′), 4.43–4.45 (q, 1 H, *J* = 5.7 Hz, H-3′), 5.21 (t, 1 H, *J* = 6.9 Hz, H-1′), 6.67 (s, 1 H, H-furan), 7.16–7.20 (t, 1 H, *J* = 7.2 Hz, H-Ar), 7.22–7.25 (m, 1 H, H-Ar), 7.42 (d, 1 H, *J* = 8.2 Hz, H-Ar), 7.50 (d, 1 H, *J* = 7.6 Hz, H-Ar) ppm. ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 39.23 (C-2′), 58.74 (C-5′), 62.74 (C-3′), 73.23 (C-1′), 85.69 (C-4′), 103.95 (C-3), 111.35 (C-7), 121.85 (C-4), 122.87 (C-5), 124. (C-6), 128.15 (C-Ar), 154.75 (C-Ar), 157.30 (C-2) ppm. MS (ESI^+): *m/z* = 256.7 [MNa^+], 241.9 [MLi^+], 214.7 [$M^+ - H_2O$].

Compound β-**4a**: TLC (CH_2Cl_2–MeOH, 98:2). R_f = 0.28. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 2.17–2.30 (m, 1 H, H-2′), 2.45–2.51 (m, 1 H, H-2′), 3.75 (d, 2 H, *J* = 4.4 Hz, 2 × H-5′), 4.05 (m, 1 H, H-4′), 4.56 (m, 1 H, H-3′), 5.30 (dd, 1 H, *J* = 6.6, 8.8 Hz, H-1′), 6.67 (s, 1 H, H-furan), 7.18–7.21 (m, 1 H, H-Ar), 7.22–7.25 (m, 1 H, H-Ar), 7.45 (d, 1 H, *J* = 8.3 Hz, H-Ar), 7.52 (d, 1 H, *J* = 7.8 Hz, H-Ar) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 39.91 (C-2′), 58.82 (C-5′), 63.54 (C-3′), 73.78 (C-1′), 87.73 (C-4′), 104.23 (C-3), 111.45 (C-7), 121.12 (C-4), 122.89 (C-5), 124.46 (C-6), 128.15 (C-Ar), 155.18 (C-Ar), 156.81 (C-2) ppm. MS (ESI^+): *m/z* = 256.7 [MNa^+], 241.9 [MLi^+], 214.7 [$M^+ - H_2O$].