Concise synthesis of aryl-*C*-nucleosides by Friedel–Crafts alkylation

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A fast and simplified synthesis of 1′,2′-dideoxy-1′-pyrenyl-riboside and several other *C*-nucleosides is shown. Shelf-stable 1-*O*-methyl-3,5-di-*O*-toluoyl-2-deoxyribose is demonstrated to serve as a versatile glycosyl donor in Lewis acid promoted Friedel–Crafts alkylations of unsubstituted pyrene and other inexpensive arenes such as fluorene and methylnaphthalene. The reaction conditions favour the formation of β-configurated *C*-nucleosides which renders additional epimerisation steps unnecessary. As a result, protected β-aryl-*C*-nucleosides are available directly from non-substituted arenes in three steps overall.

Introduction

The introduction of non-natural nucleobases into DNA provides a powerful tool to study DNA–DNA and DNA–protein interactions.[1] Amongst the numerous base analogues investigated, polycyclic aryl groups are of particular interest due to their supreme base stacking abilities.[2] Accordingly, aryl-*C*-nucleosides have found an increasing number of applications. After their incorporation into DNA-oligomers *via* phosphoramidite chemistry, the aryl-*C*-nucleosides have been used to assess base stacking in DNA–DNA duplexes[2] or to explore the reaction mechanisms of DNA-polymerases[3] or DNA repair enzymes.[4] Recently, Kool *et al.*[5] used different *C*-nucleosides as building blocks for the synthesis of oligomeric lightsensitive fluorophores in a combinatorial approach. We synthesized aryl-*C*-nucleosides with an aim to probe the mechanism of base flipping DNA-methyltransferases such as *MTaq*I.[6] In these and other studies[4] the pyrene *C*-nucleotide proved particularly valuable due to its ability to fill the abasic site formed upon enzyme mediated flipping of the target base out of the DNA helix.

In the synthesis of aryl-*C*-nucleosides such as **3**, the β-selective formation of the *C*-glycosidic bond is a critical step. Various routes to gain access to 1′-*C*-aryl-2′-deoxyribosides have been developed.[7] For example, the establishment of a *C*-glycosidic bond in phenyl, naphthyl and bipyridyl nucleosides was achieved by using the reaction of protected ribonolactones with aryllithium reagents and subsequent removal of the anomeric hydroxyl group by triethylsilane reduction.[8,9] *C*-nucleosides have also been obtained by palladium-catalysed coupling of aryl iodides with glycals and stannyl glycals.[10] One of the most widely used synthetic methods is based on the coupling of organocadmium compounds[11] (Ar₂Cd) or, preferably, Normant-cuprates[6] (Ar₂CuMgX) with Hoffer's chlorosugar[12] (2-deoxy-3,5-di-*O*-toluoyl-D-ribofuranosyl chloride) **2** (Scheme 1). This method yields the α-anomers **3α** as major products which have to be subjected to acid-mediated epimerisation[11,13] in order to obtain the often desired, naturally configured β-anomers **3β**.

Most of the currently available procedures give relatively low overall yields and require cumbersome and costly reaction sequences to access suitable *C*-glycoside donors and glycosyl acceptors. In comparison to organometal-mediated coupling reactions of aryl halides with sophisticated glycosyl donors, the direct alkylation of aryl compounds by glycosyl cations is expected to provide significant advantages.[14] In such Friedel–Crafts alkylations, relatively simple glycosyl donors such as chloro sugar **2** or methoxy sugar **1** may be employed (Scheme 1).[15] Moreover, the Lewis-acid conditions in Friedel–Crafts alkylation favour the formation of β-configurated *C*-nucleosides,[16] rendering additional epimerisation steps un-
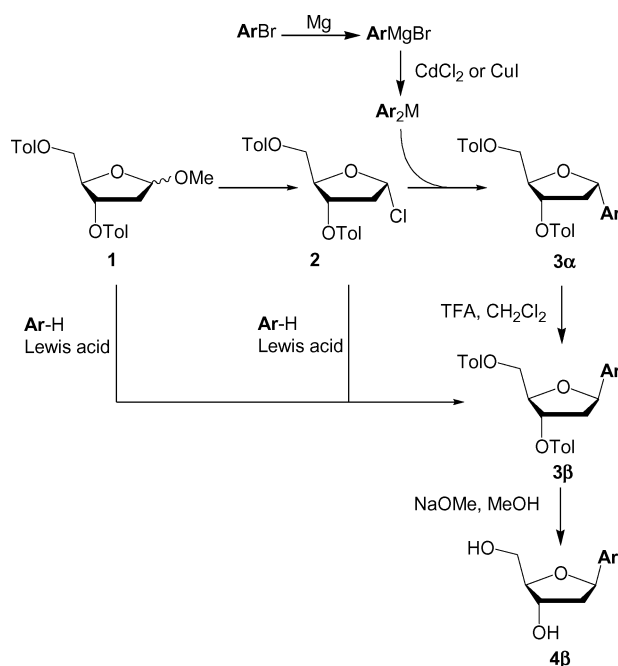
Scheme 1 Comparison of aryl *C*-nucleoside synthesis by organometal reagents with Friedel–Crafts alkylation. (M = Cd or CuMgX, Tol = toluoyl, X = halide).

necessary. It is also an advantage that unsubstituted arenes can be employed instead of more expensive bromo- or iodoarenes. Though simplicity, cost and conciseness argue for the Friedel–Crafts glycosylation route, applications to the synthesis of 2′-deoxy-aryl-*C*-nucleosides are scarce,[16] presumably due to envisaged limitations as far as the generality of the method is concerned. In the following we present a systematic study of 2′-deoxy-*C*-nucleoside synthesis by Friedel–Crafts alkylation. It is shown that variation of the electronic properties of the aryl aglycons demands careful optimisation of Lewis acid promotors and glycosyl donors. Friedel–Crafts alkylation is demonstrated to provide unparalleled rapid and cost-efficient access to interesting β-aryl-*C*-nucleosides including pyrenyl, fluorenyl and methylnaphthyl 2′-deoxy-*C*-ribosides.

Results

In the previous syntheses of pyrenyl nucleoside **4aβ**(Ar = 1-pyrenyl), 1-α-chloro-3,5-di-*O*-toluoyl-2-deoxyribose **2** was used as glycosyl donor in coupling reactions with cadmium organyls

Table 1 Results of the Friedel–Crafts alkylation of Hoffer's chlorosugar **2** with pyrene

Entry	Promoter (eq.)	Time/min	Solvent	Yield of **3a** (%)	Ratio **3aβ** : **3aα**[a]
1	BF₃·OEt₂ (1.3)	20	CH_2Cl_2	54	70 : 30
2	BF₃·OEt₂ (1.7)	20	$ClCH_2CH_2Cl$	52	70 : 30
3	AgBF₄ (1.1)	120	CH_2Cl_2	57	75 : 25
4	AgBF₄ (1.1)	60	$ClCH_2CH_2Cl$	9	76 : 24

[a] Selectivity determined by ¹H-NMR-spectroscopy *via* comparison of the signal intensity of the anomeric protons.
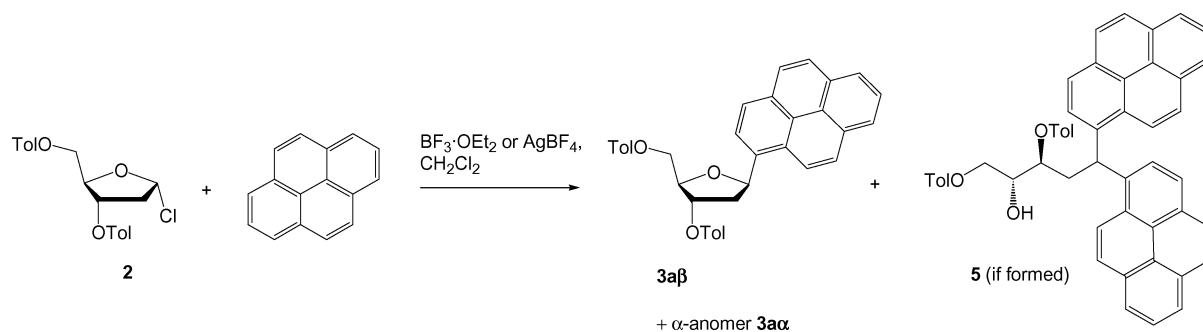
Scheme 2 Coupling reaction of chlorosugar **2** with pyrene.

and Normant cuprates prepared from bromopyrene.[6,11] We thought that the same donor could be employed in a Lewis-acid promoted Friedel–Crafts reaction with non-substituted pyrene (Scheme 2). Indeed, it was found that the mild Lewis acid boron trifluoride etherate in dichloromethane was able to induce the formation of toluoyl protected *C*-nucleoside **3aα/β** which was isolated in 54% yield (Table 1, entry 1). The α/β-selectivity of the *C*-glycosylation was assessed by ¹H-NMR and analytical HPLC analysis. Under the Lewis acid conditions, product **3a** was formed as a mixture of anomers **3aβ** : **3aα** of 7 : 3. The anomeric mixture was separated by flash chromatography to afford the pure β-anomer **3aβ** in 33% yield. Friedel–Crafts alkylations in dichoroethane often proceed with higher yields than in dichloromethane. However, the BF₃-promoted *C*-glycosylation furnished almost identical yields in both solvents (Table 1, entry 2). The milder Lewis acid silver tetrafluoroborate required extension of the reaction time to 2 h in dichloromethane (Table 1, entry 3). In this case, *C*-glycosylation occurred in almost identical 57% yield with a slightly more favourable selectivity of **3aβ** : **3aα** of 75 : 25. The reaction with silver tetrafluoroborate in dichloroethane instead of dichloromethane under otherwise unchanged conditions led to the formation of a new product (2*R*,3*S*)-2-hydroxy-5,5-dipyrenylpentyl 1,3-di-toluoate **5** in 22% yield, while the desired compounds **3aα/β** were obtained in only 9% yield. NMR-analysis (¹H-; ¹³C-, ¹H-¹H-COSY) and mass spectroscopy of the isolated new product suggested the bispyrenyl structure **5** as product of a second

Friedel–Crafts-alkylation with the desired (α,β)-1′,2′-dideoxy-1′-(1-pyrenyl)-3′,5′-di-*O*-toluoyl-ribose **3aα/β**.

The 33% yield of pure β-pyrenyl *C*-nucleoside obtained by Friedel–Crafts alkylation was considered as practically useful, particularly when taking the cost and conciseness of the synthesis into account. For that reason, we tested the scope of the reaction by allowing chloro sugar **2** to react with anthracene and fluorene as glycosyl acceptors. However, under the mildly Lewis-acid conditions the reactivity of these arenes was too low and the desired anthracenyl- and fluorenyl-*C*-nucleosides were only formed in trace amounts. The use of stronger Lewis acids such as SnCl₄ led to rapid decomposition of chloro sugar **2**. Recently, methoxy sugars were demonstrated to serve as suitable glycosyl donors in SnCl₄-promoted *C*-glycosylation reactions.[16] In light of its ease of synthesis and long shelf life, the application of 1-*O*-methyl-3,5-di-*O*-toluoyl-2-deoxyribose **1** appeared attractive (Scheme 3). Accordingly, the reaction of methoxy sugar **1** with pyrene induced by addition of SnCl₄ was studied. The desired pyrenyl-*C*-nucleoside **3aα/β** was obtained in yields and selectivities which compared well with the BF₃-promoted reactions. The pure β-anomer **3aβ** was isolated in 39% yield (Table 2). For the reaction of the less reactive arenes fluorene, 1-methylnaphthalene, phenanthrene, benzothiophene and thioanisole, it was deemed important to further increase the Lewis acidity by adding silver trifluoroacetate (AgOTfa).[17] The reaction of fluorene with methoxysugar **1** in dichloroethane proceeded smoothly under catalysis of tin tetrachloride/silver

Table 2 Results of the Friedel–Crafts alkylation of different arenes with methoxysugar **1** in dichloroethane

Arene	Promoter (eq.)	Temperature/°C	Product	Yield (%)	β : α ratio
Pyrene	SnCl₄ (0.51)	0	**3a**	61	75 : 25
Pyrene[a]	SnCl₄ (2.3)	−15	**3a**	56	70 : 30
Fluorene	SnCl₄ (1.0), AgOTfa(1.5)	−15	**3b**	49	85 : 15
Benzothiophene	SnCl₄ (1.0), AgOTfa(1.5)	−15	**3c**	45	76 : 24
1-Methylnaphthalene	SnCl₄ (1.0), AgOTfa(1.5)	−15	**3d**	51	73 : 27
Thioanisole	SnCl₄ (2.0), AgOTfa(1.5)	20 °C	**3e**	33	63 : 37
Phenanthrene	SnCl₄ (2.0), AgOTfa(1.5)	0 °C	No reaction	—	—

[a] Reaction in dichloromethane as solvent.
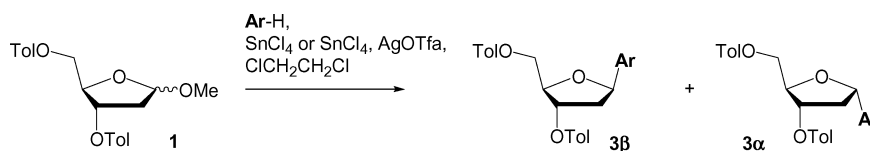
Scheme 3 Friedel–Crafts glycosylation with methoxysugar **1**.

trifluoroacetate (SnCl$_4$/AgOTfa) to yield 41% of β-1',2'-dideoxy-1'-(2-fluorenyl)-3',5'-di-*O*-toluoyl-ribose **3bβ** and 9% of α-1',2'-dideoxy-1'-(2-fluorenyl)-3',5'-di-*O*-toluoyl-ribose **3bα** (Table 2). Changing the reaction conditions by using only SnCl$_4$ as promoter or dichloromethane as solvent lead to significantly decreased yields. Structures were verified by ^{1}H- and ^{1}H-^{1}H-NOESY-NMR-spectroscopy (Fig. 1). The NOESY-spectrum of the β-anomer showed characteristic interactions between H1' and H2'α and also H3' and H2'β which proved the anomeric configuration. The configuration at the fluorene was validated by the cross peaks between the H9 protons of the fluorene and the H1 proton which formed a singlet (Fig. 1).

The methoxy sugar **1** was allowed to react with benzothiophene and 1-methylnaphthalene. Promotion of *C*-glycosylation by addition of the SnCl$_4$/AgOTfa promotor combination resulted in the formation of bis-toluoyl aryl-*C*-nucleosides **3cα/β** and **3dα/β** in 45% and 51% yield (Table 2). NMR-spectroscopy (^{1}H-^{13}C-HMBC, HMQC and ^{1}H-^{1}H-NOESY) confirmed the supposed structures. In the case of the benzothiophene nucleoside **3cβ**, the H2-proton shows no correlation with other benzothiophene ring protons in the NOESY-NMR spectrum. Electrophilic attack at the aromatic ring systems occurred at the expected 3- and 4-positions of benzothiophene and 1-methylnaphthalene, respectively.

Next, the *C*-glycosylation of thioanisole was examined as the only monocyclic arene in this study. This reaction proceeded sluggishly when performed with stoichiometric amounts of SnCl$_4$ at −15 °C, which indicated that thioanisole is a less powerful substrate than polycyclic arenes. However, through increases of the SnCl$_4$-promoter load (2 eq.) and reaction temperature (20 °C) *C*-nucleoside **3eβ** was afforded in a moderate 21% yield. Furthermore, the Friedel–Crafts glycosylation of phenanthrene and unsubstituted naphthalene was attempted. The desired reaction products could not be detected.

Deprotection of the β-anomeric toluoylated 2'-desoxyribose-*C*-nucleosides **3bβ**–**3eβ** was carried out following standard procedures by treatment with sodium methoxide in dry methanol. After column chromatography the corresponding unprotected *C*-nucleosides **4β** were obtained in good to excellent yields (72%–95%).

Discussion

The reaction yields obtained in a given aryl-*C*-nucleoside synthesis can be correlated with the reactivities of the arenes used. The reactivity of an arene in Friedel–Crafts alkylations is commonly characterised by means of its σ^+_{arene} parameters from the Hammett–Brown relationship.[18] Phenanthrene and naphthalene, which proved unreactive in SnCl$_4$/AgOTfa-promoted reactions with methoxy sugar **1**, have the lowest reactivity,

given by parameters of $\sigma^+ = -0.39$ and -0.35, respectively. Fluorene ($\sigma^+ = -0.48$), benzothiophene ($\sigma^+ = -0.54$) and 1-methylnaphthalene ($\sigma^+ = -0.57$) are more reactive arenes and reacted successfully under promotion of SnCl$_4$/AgOTfa. It is conceivable that the thioether structure of benzothiophene offers a coordination site to soft metal electrophiles which might explain the need for over-stoichiometric loads of Lewis acid. A further increase of arene reactivity requires the use of milder reaction conditions. Therefore pyrene ($\sigma^+ = -0.68$), the most reactive arene examined in this study, was coupled by using catalytic amounts of SnCl$_4$ to avoid side reactions and decomposition of the desired products. Even milder Lewis acids like BF$_3$ or AgBF$_4$ can be employed when increasing the reactivity of the glycosyl donor such as in Friedel–Crafts glycosylations with chloro sugar **2**.

Aryl-*C*-nucleosides such as pyrenyl nucleoside **4aβ** have emerged as powerful designer nucleotides to probe DNA–DNA and DNA–protein interactions. We presumed that research in the field would benefit if synthetic access to the required *C*-glycosides was facilitated. To the best of our knowledge, the Friedel–Crafts glycosylation route shown in Scheme 1 and Scheme 3 provides the shortest route to aryl-*C*-nucleotide building blocks suitable for automated DNA-synthesis. Starting from 2-deoxyribose only two steps are needed for the synthesis of key glycosyl donor **1**.[19] As a result of the β-selective Friedel–Crafts glycosylation reaction, β-aryl-*C*-nucleosides **4β** are available directly from non-substituted arenes ($\sigma^+ < −0.4$) in four steps overall.

Conclusion

In summary, we have developed a fast and simplified synthesis of the known pyrene-*C*-nucleoside **4a** and several other new *C*-nucleosides *via* Friedel–Crafts alkylation using the SnCl$_4$/AgOTfa-promoter system or SnCl$_4$ and shelf-stable methoxysugar **1** as glycosyl donor. Importantly, the Friedel–Crafts glycosylation is in favour of the formation of β-anomers. According to this convenient protocol and in contrast to most other methods of aryl-*C*-nucleoside synthesis, additional steps such as arene metallation or acid catalysed anomerisation reactions are not required.

Experimental

General

Reagents and chemicals were obtained from Acros and Lancaster and were used without further purification. Hoffer's chlorosugar **2** was synthesised according to literature procedures.[19] Dichloromethane was freshly distilled from CaH$_2$,
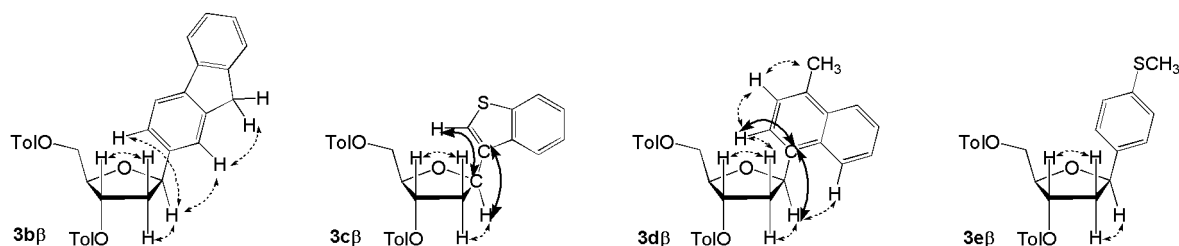

Fig. 1 Aryl-*C*-nucleosides and important correlations in 1H-1H-NOESY (dashed) and 1H-13C-HMBC (bold) NMR-spectra.

dichloroethane was dried over molecular sieve MS 4 Å. All NMR spectra were recorded on a Bruker DPX-300 or a Bruker AV 400 spectrometer. The signal of the residual protonated solvent was used as a reference signal. Coupling constants J are reported in Hz. Flash chromatography was performed using Merck silica gel 60 (particle size 0.040–0.063 mm). TLC was performed with aluminium-baked silica gel 60 F254 plates (Merck). Analytical reversed phase HPLC was performed with an Agilent 1100 series system. A Macherey & Nagel RP-C18 CC 125/4 Nucleosil C18 gravity column was used. As the mobile phase a binary mixture of A (98.9% H_2O/1% acetonitrile/0.1% TFA) and B (98.9% acetonitrile/1% H_2O/0.1% TFA) was used. Products were eluted with the following gradient: 0–6 min (20% B); 6–7 min (20–75% B); 7–27 min (75%B) and detected by UV absorbance at 254 nm, where the relationship between the extinction coefficients of **3aβ** : **3aα** is 1.14 as calibrated by a mixture of known decomposition of **3aα/β**.

Friedel–Crafts-alkylation with Hoffer's chlorosugar 2; typical procedure

To a solution of 81 mg of chlorosugar **2** (0.21 mmol) and 93 mg of pyrene (0.47 mmol; 2 eq.) in dry dichloromethane (3 ml) was added 45 mg silver tetrafluoroborate (0.23 mmol; 1.1 eq.) at 0 °C. After stirring at that temperature for 2 h the reaction mixture was treated with 10 ml saturated aquous sodium bicarbonate and extracted with 10 ml dichloromethane(×3). The combined organic layer was washed with saturated NaHCO₃ solution (×3) and brine (×1), dried over anhydrous MgSO₄ and concentrated *in vacuo*. Flash chromatography (cyclohexane–ethyl acetate 19:1) yielded 65 mg (0.12 mmol; 57%) of the desired (α,β)-1′,2′-dideoxy-1′-(1-pyrenyl)-3′,5′-di-O-toluoyl-ribose **3aα/β**.

β-1′,2′-Dideoxy-1′-(1-pyrenyl)-3′,5′-di-O-toluoyl-ribose 3aβ[11]. R_f: 0.25 (cyclohexane–ethyl acetate 6 : 1); δ_H (300 MHz, CDCl₃) 8.31–7.95 (13H, m, Ar–H), 7.32 (2H, d, J 8.0, Ar–H), 7.17 (2H, d, J 8.3, Ar–H), 6.29 (1H, dd, $J_{H1',H2'\alpha}$ 10.7, $J_{H1',H2'\beta}$ 4.9, H1′), 5.74 (1H, dd, J 5.1, $J_{H3',H4'}$ 1.9, H3′), 4.84–4.80 (2H, m, H5′), 4.75–4.71 (1H, td, $J_{H4',H5'}$ 3.5, $J_{H3',H4'}$ 2.3, H4′), 2.89 (1H, ddd, $J_{H2'\alpha,H2'\beta}$ 13.9, $J_{H1',H2'\alpha}$ 5.1, $J_{H3',H2'\alpha}$ 0.8, H2′α), 2.43–2.36 (1H, m, H2′β), 2.45 (s, 3H, Ar–Me), 2.36 (s, 3H, Ar–Me); δ_c (75 MHz, CDCl₃) 166.5 (C_q, -COOR), 166.3 (C_q, -COOR),144.3 (C_q, Ar), 143.9 (C_q, Ar), 134.1–122.3(Ar–C), 83.4, 78.2, 77.4, 64.8, 41.6, 21.8 (Ar–Me), 21.7 (Ar–Me); HPLC: R_t: 26.3 min; HRMS(EI): m/z C₃₇H₃₀O₅⁺ calcd. 554.2093(M), found 554.2093.

α-1′,2′-Dideoxy-1′-(1-pyrenyl)-3′,5′-di-O-toluoyl-ribose 3aα[11]. R_f: 0.17 (cyclohexane–ethyl acetate 6 : 1); δ_H (300 MHz, CDCl₃) 8.34 (1H, d, $J = 7.8$, Ar–H), 8.22–7.86 (10H, m, Ar–H), 7.60 (2H, d, J 8.2, Ar–H), 7.27 (2H, d, J 8.1, Ar–H), 7.08 (2H, d, J 7.9, Ar–H); 6.39 (1H, dd, $J_{H1',H2'\beta}$ 7.6, $J_{H1',H2'\alpha}$ 5.8, H1′), 5.77–5.71 (1H, ddd, $J_{H3',H2'\beta}$ 7.0, $J_{H3',H2'\alpha}$ 3.7, $J_{H3',H4'}$ 2.8, H3′), 4.97 (1H, td, $J_{H4',H5'}$ 4.7, $J_{H3',H4'}$ 2.8, H4′), 4.73 (2H, m, H5′), 3.31 (1H, ddd, $J_{H2'\alpha,H2'\beta}$ 13.5, $J_{H1',H2'\beta}$ 7.6, $J_{H3',H2'\beta}$ 7.0, H2′β), 2.50 (1H, ddd, $J_{H2'\alpha,H2'\beta}$ 13.5, $J_{H1',H2'\alpha}$ 5.8, $J_{H3',H2'\alpha}$ 3.7, H2′α), 2.43 (3H, s, Ar–Me), 2.34 (3H, s, Ar–Me); δ_c (75 MHz, CDCl₃) 166.5 (C_q, -COOR), 166.1 (C_q, -COOR), 144.0 (C_q, Ar), 136.0 (C_q, Ar), 131.4–122.4 ((Ar–C)), 82.6, 78.4, 76.5, 64.8, 40.6, 21.8 (Ar–Me), 21.7 (Ar–Me); HPLC: R_t: 25.0 min; HRMS(ESI): m/z C₃₇H₃₀O₅Na⁺ calcd. 577.1985(M + Na⁺), found 577.1999.

(2R,3S)-2-Hydroxy-5,5-dipyrenylpentyl 1,3-ditoluoate 5. R_f: 0.10 (cyclohexane–ethyl acetate 4.5 : 1); δ_H (300 MHz, CDCl₃) 8.57 (1H, d, J 9.3, Ar–H), 8.34 (1H, d, J 9.3, Ar–H), 8.32–7.93 (15H, m, Ar–H), 7.85 (1H, d, J 9.3, Ar–H), 7.74 (4H, m, Ar–H), 7.03 (4H, m, Ar–H), 6.44 (1H, t, $J_{H5,H4}$ 7.2, H5), 5.56 (1H, m, H3), 4.53 (1H, dd, $J_{vic.}$ 11.4, $J_{H1,H2}$ 4.2, H1), 4.45–4.33 (2H, m, H1, H2), 3.16 (2H, t, J 6.6, H4), 3.03 (1H, br, -OH), 2.35 (s, 3H, Ar–Me), 2.30 (s, 3H, Ar–Me); δ_c (75 MHz, CDCl₃) 166.8, 166.5 (C_q, -COOR), 166.1 (C_q, -COOR), 144.0 (C_q, Ar), 143.8 (C_q, Ar), 138.7 (Cq, Ar), 137.0 (C_q, Ar), 131.4–122.4, 74.9, 72.2,

65.5, 38.7, 37.2, 21.7 (Ar–Me); HRMS(ESI): m/z C₅₃H₄₀O₅Na⁺ calcd. 779.2768(M + Na⁺), found 779.2768.

Friedel–Crafts-alkylation with the methoxysugar 1; Typical procedure. To a solution of 200 mg of 1-O-methyl-3,5-di-O-toluoyl-2-deoxyribose **1** (0.52 mmol), 172.3 mg silver trifluoroacetate (0.78 mmol) and 218 μl of 1-methylnaphthalene (1.56 mmol; 3 eq.) in dry dichloroethane (3 ml) was added 61 μl SnCl₄ (0.52 mmol; 1.0 eq.) at −15 °C. After stirring for 10 min the reaction mixture was treated with 10 ml saturated aqueous sodium bicarbonate and extracted with 20 ml dichloromethane(×3). The combined organic layer was washed with saturated NaHCO₃ solution (×3) and brine (×1), dried over anhydrous MgSO₄ and concentrated. Flash chromatography (cyclohexane–ethyl acetate 19:1) yielded 96 mg (0.19 mmol; 37%) of β-1′,2′-dideoxy-1′-(1-(4-methyl)naphthyl)-3′,5′-di-O-toluoyl-ribose **3dβ** and 35 mg (0.07 mmol; 14%) of α-1′,2′-dideoxy-1′-(1-(4-methyl)naphthyl)-3′,5′-di-O-toluoyl-ribose **3dα**.

β-1′,2′-Dideoxy-1′-(1-(4-methyl)naphthyl)-3′,5′-di-O-toluoyl-ribose 3dβ. R_f: 0.40 (cyclohexane–ethyl acetate 4.5 : 1); δ_H (300 MHz, CDCl₃) 8.06–8.02 (4H, m, Ar–H), 7.93 (2H, d, J 8.2, Ar–H), 7.66 (1H, d, J 7.3, Ar–H), 7.56–7.46 (2H, m, Ar–H), 7.32–7.27 (3H, m, Ar–H), 7.19 (2H, d, J 8.0, Ar–H), 5.96 (1H, dd, $J_{H1',H2'\alpha}$ 10.7, $J_{H1',H2'\beta}$ 5.0, H1′), 5.67 (1H, d, J 6.3, H3′), 4.72 (2H, d, J 3.9, H5′), 4.67–4.62 (1H, m, H4′), 2.78 (1H, ddd, $J_{H2'\alpha,H2'\beta}$ 13.8, $J_{H1',H2'\alpha}$ 5.1, $J_{H3',H2'\alpha}$ 1.1, H2′α), 2.68 (s, 3H, Ar–Me), 2.45 (s, 3H, Ar–Me), 2.39 (s, 3H, Ar–Me), 2.32 (1H, ddd, $J_{H2'\alpha,H2'\beta}$ 13.8, $J_{H1',H2'\beta}$ 10.8, $J_{H3',H2'\beta}$ 6.2, H2′β); δ_c (75 MHz, CDCl₃) 166.5 (C_q, -COOR), 166.2 (C_q, -COOR),144.2 (C_q, Ar), 143.8 (C_q, Ar), 134.6–122.1(Ar–C), 82.6, 78.0, 77.5, 64.7, 40.9, 21.8 (Ar–Me), 21.7 (Ar–Me), 19.6 (Ar–Me); MS(EI): m/z 494(M⁺, 10%), 358(M⁺–C₇H₇COOH, 8), 222(M⁺–2C₇H₇COOH, 35), 169(1-(4-methyl)-naphthyl-(CO)⁺,100); HRMS(EI): m/z C₃₂H₃₀O₅⁺ calcd. 494.2093(M), found 494.2094.

α-1′,2′-Dideoxy-1′-(1-(4-methyl)naphthyl)-3′,5′-di-O-toluoyl-ribose 3dα. R_f: 0.34 (cyclohexane–ethyl acetate 4.5 : 1); δ_H (300 MHz, CDCl₃) 8.06–7.13 (14H, m, Ar–H), 6.05 (1H, t, J 6.7, H1′), 5.67 (1H, ddd, $J_{H3',H2'\beta}$ 6.6, $J_{H3',H2'\alpha}$ 3.4, $J_{H3',H4'}$ 3.4, H3′), 4.83 (1H, td, $J_{H4',H5'}$ 4.7, $J_{H3',H4'}$ 2.9, H4′), 4.66 (2H, m, H5′), 3.17 (1H, ddd, $J_{H2'\alpha,H2'\beta}$ 14.2, $J_{H1',H2'\beta}$ 7.3, $J_{H3',H2'\beta}$ 7.3, H2′β), 2.70 (3H, s, Ar–Me), 2.56 (1H, ddd, $J_{H2'\alpha,H2'\beta}$ 13.9, $J_{H1',H2'\alpha}$ 7.1, $J_{H3',H2'\alpha}$ 2.0, H2′α), 2.41 (3H, s, Ar–Me); 2.37 (3H, s, Ar–Me); δ_c (75 MHz, CDCl₃) 166.5 (C_q, -COOR), 166.1 (C_q, -COOR),144.1 (C_q, Ar), 143.9 (C_q, Ar), 136.1–122.1(Ar–C), 82.3, 78.1, 76.5, 65.2, 39.8, 21.8 (Ar–Me), 21.7 (Ar–Me), 19.6 (Ar–Me); HRMS(EI): m/z C₃₂H₃₀O₅⁺ calcd. 494.2093(M), found 494.2093.

β-1′,2′-Dideoxy-1′-(2-fluorenyl)-3′,5′-di-O-toluoyl-ribose 3bβ. R_f: 0.42 (cyclohexane–ethyl acetate 4.5 : 1); δ_H (400 MHz, CDCl₃) 8.06–8.02 (4H, m, Ar–H), 7.93 (2H, d, J 8.2, Ar–H), 7.66 (1H, d, J 7.3, Ar–H), 7.56–7.46 (2H, m, Ar–H), 7.32–7.27 (3H, m, Ar–H), 7.19 (2H, d, J 8.0, Ar–H), 5.64 (1H, dd, J 5.1, $J_{H3',H4'}$ 1.2, H3′), 5.33 (1H, dd, $J_{H1',H2'\alpha}$ 10.9, $J_{H1',H2'\beta}$ 5.0, H1′), 4.74–4.64 (2H, m, H5′), 4.67–4.62 (1H, td, $J_{H4',H5'}$ 3.9, $J_{H3',H4'}$ 2.0, H4′), 3.79 (d, 2H, CH₂), 2.56 (1H, ddd, $J_{H2'\alpha,H2'\beta}$ 13.7, $J_{H1',H2'\alpha}$ 5.0, $J_{H3',H2'\alpha}$ 0.7, H2′α), 2.43 (s, 3H, Ar–Me), 2.38 (s, 3H, Ar–Me), 2.29 (1H, ddd, $J_{H2'\alpha,H2'\beta}$ 13.8, $J_{H1',H2'\beta}$ 11.0, $J_{H3',H2'\beta}$ 6.0, H2′β); δ_c (75 MHz, CDCl₃) 166.4 (C_q, -COOR), 166.2 (C_q, -COOR), 144.2, 143.9, 143.7, 143.4, 141.6, 141.4, 139.3, 129.8, 129.7, 129.2, 127.1, 127.0,126.7, 125.0, 124.8, 122.5, 119.9, 119.8, 83.0, 81.2, 77.4, 64.9, 42.1, 36.8, 21.8 (Ar–Me), 21.7 (Ar–Me); MS(EI): m/z 518(M⁺, 14%), 382(M⁺–C₇H₇COOH, 4), 246(M⁺–2C₇H₇COOH, 18), 169 (fluorenyl-(CO)⁺,100); HRMS(EI): m/z C₃₄H₃₀O₅⁺ calcd. 518.2093(M), found 518.2092.

α-1′,2′-Dideoxy-1′-(2-fluorenyl)-3′,5′-di-O-toluoyl-ribose 3bα. R_f: 0.37 (cyclohexane–ethyl acetate 4.5 : 1); δ_H (300 MHz, CDCl₃) 8.97–7.06 (15H, m, Ar–H), 5.61 (1H, ddd, $J_{H3',H2'\beta}$ 6.8, $J_{H3',H2'\alpha}$

3.8, $J_{H3',H4'}$ 3.0, H3'), 5.43 (1H, t, J 6.7, H1'), 4.73 (1H, td, $J_{H4',H5'}$ 4.8, $J_{H3',H4'}$ 3.0, H4'), 4.58 (2H, m, H5'), 3.84 (s, 2H, CH$_2$), 2.96 (1H, ddd, $J_{H2'\alpha,H2'\beta}$ 14.0, $J_{H1',H2'\beta}$ 7.1, $J_{H3',H2'\beta}$ 7.1, H2'β), 2.40 (3H, s, Ar–Me), 2.32 (3H, s, Ar–Me); HRMS(EI): m/z C$_{34}$H$_{30}$O$_5$$^+$ calcd. 518.2093(M), found 518.2093.

β-1′,2′-Dideoxy-1′-(3-benzothiophenyl)-3′,5′-di-O-toluoyl-ribose 3cβ.

R_f: 0.38 (cyclohexane–ethyl acetate 4.5 : 1); δ_H (400 MHz, CDCl$_3$) 8.00 (2H, d, J 8.2, Ar–H), 7.93 (2H, d, J 8.2, Ar–H), 7.86 (2H, m, Ar–H), 7.46 (1H, s, Ar–H), 7.35–7.19 (6H, m, Ar–H), 5.67 (1H, d, J 5.7, H3'), 5.59 (1H, dd, $J_{H1',H2'\alpha}$ 10.6, $J_{H1',H2'\beta}$ 5.2, H1'), 4.74–4.64 (2H, m, H5'), 4.58 (1H, td, $J_{H4',H5'}$ 3.8, $J_{H3',H4'}$ 2.3, H4'), 2.68 (1H, ddd, $J_{H2'\alpha,H2'\beta}$ 13.6, $J_{H1',H2'\alpha}$ 5.2, $J_{H3',H2'\alpha}$ 0.9, H2'α), 2.44 (s, 3H, Ar–Me), 2.39 (s, 3H, Ar–Me), 2.50–2.40 (1H, m, H2'β); δ_c (75 MHz, CDCl$_3$) 166.4 (C$_q$, -COOR), 166.2 (C$_q$, -COOR), 144.2, 143.9, 141.0, 137.1, 135.6, 129.8, 129.7, 129.3, 129.2, 127.1, 127.0, 124.5, 124.1, 123.0, 122.6, 122.2, 82.8, 77.0, 76.9, 64.6, 39.7, 21.8 (Ar–Me), 21.7 (Ar–Me); HRMS(ESI): m/z C$_{34}$H$_{30}$O$_5$Na$^+$ calcd. 509.1393(M + Na$^+$), found 509.1392.

α-1′,2′-Dideoxy-1′-(3-benzothiophenyl)-3′,5′-di-O-toluoyl-ribose 3cα.

R_f: 0.33 (cyclohexane–ethyl acetate 4.5 : 1); δ_H (300 MHz, CDCl$_3$) 7.91 (2H, d, J 8.2, Ar–H), 7.85–7.77 (2H, m, Ar–H), 7.70 (2H, d, J 8.3, Ar–H), 7.39 (1H, d, J 1.0, Ar–H), 7.31–7.27 (2H, m, Ar–H), 7.19–7.10 (4H, m, Ar–H), 5.64–5.57 (2H, m, H1',H3'), 4.64 (1H, td, $J_{H4',H5'}$ 4.6, $J_{H3',H4'}$ 3.0, H4'), 4.61–4.50 (2H, m, H5'), 2.97 (1H, ddd, $J_{H2'\alpha,H2'\beta}$ 13.8, $J_{H1',H2'\beta}$ 7.1, $J_{H3',H2'\beta}$ 7.1, H2'β), 2.43 (1H, ddd, $J_{H2'\alpha,H2'\beta}$ 13.8, $J_{H1',H2'\alpha}$ 5.9, $J_{H3',H2'\alpha}$ 3.7, H2'α), 2.34 (s, 3H, Ar–Me), 2.32 (s, 3H, Ar–Me); δ_c (75 MHz, CDCl$_3$) 166.4 (C$_q$, -COOR), 166.2 (C$_q$, -COOR), 144.1, 143.9, 141.0, 137.2, 136.9, 129.8, 129.7, 129.2, 129.1, 127.1, 126.8, 124.5, 124.2, 123.0, 122.3, 122.2, 82.0, 77.3, 76.4, 64.6, 38.3, 21.7 (Ar–Me); HRMS(EI): m/z C$_{34}$H$_{30}$O$_5$$^+$ calcd. 486.1501(M), found 486.1501.

β-1′,2′-Dideoxy-1′-(4-(methylthio)phenyl)-3′,5′-di-O-toluoyl-ribose 3eβ.

R_f: 0.41 (cyclohexane–ethyl acetate 4.5 : 1); δ_H (400 MHz, CDCl$_3$) 7.98 (2H, d, J 8.2, Ar–H), 7.94 (2H, d, J 8.2, Ar–H), 7.33–7.19 (6H, m, Ar–H), 5.60 (1H, dd, J 5.2, $J_{H3',H4'}$ 1.1, H3'), 5.21 (1H, dd, $J_{H1',H2'\alpha}$ 10.9, $J_{H1',H2'\beta}$ 5.1, H1'), 4.69–4.59 (2H, m, H5'), 4.55–4.50 (1H, m, H4'), 2.51 (1H, dd, $J_{H2'\alpha,H2'\beta}$ 14.0, $J_{H1',H2'\alpha}$ 5.0, H2'α), 2.46 (s, 3H, -SMe), 2.43 (s, 3H, Ar–Me), 2.40 (s, 3H, Ar–Me), 2.21 (1H, ddd, $J_{H2'\alpha,H2'\beta}$ 13.8, $J_{H1',H2'\beta}$ 11.0, $J_{H3',H2'\beta}$ 6.1, H2'β); δ_c (75 MHz, CDCl$_3$) 166.4 (C$_q$, -COOR), 166.1 (C$_q$, -COOR), 144.2, 143.9, 138.0, 137.6, 129.7, 129.7, 129.2, 129.2, 126.7, 126.5, 83.0; 80.5, 77.3, 64.8, 41.7, 21.8 (Ar–Me), 21.7 (Ar–Me), 15.9 (-SMe); HRMS(ESI): m/z C$_{34}$H$_{30}$O$_5$Na$^+$ calcd. 499.1550(M + Na$^+$), found 499.1550.

α-1′,2′-Dideoxy-1′-(4-(methylthio)phenyl)-3′,5′-di-O-toluoyl-ribose 3eα.

R_f: 0.35 (cyclohexane–ethyl acetate 4.5 : 1); δ_H (300 MHz, CDCl$_3$) 8.06–7.13 (12H, m, Ar–H), 5.59 (1H, m, H3'), 5.33 (1H, t, J 6.6, H1'), 4.67 (1H, m, H4'), 2.91 (1H, ddd, $J_{H2'\alpha,H2'\beta}$ 14.0, $J_{H1',H2'\beta}$ 7.1, $J_{H3',H2'\beta}$ 7.1, H2'β), 2.48 (3H, s, -SMe), 2.43 (3H, s, Ar–Me), 2.39 (3H, s, Ar–Me); δ_c (75 MHz, CDCl$_3$) 166.1 (C$_q$, -COOR), 166.1 (C$_q$, -COOR), 144.0 (C$_q$, Ar), 143.7 (C$_q$, Ar), 139.4, 137.5, 129.7, 129.7, 129.2, 129.1, 126.8, 126.2, 82.1, 79.9, 76.4, 64.6, 40.4, 21.7 (Ar–Me), 21.7 (Ar–Me), 16.1 (Ar–Me)); HRMS(EI): m/z C$_{34}$H$_{30}$O$_5$$^+$ calcd. 476.1657(M), found 476.1658.

Deprotection of toluoylated C-nucleosides; typical procedure

Sodium methoxide (107 mg, 3 eq.) was added to a solution of 330 mg of compund **3d**β (0.66 mmol) in 5 ml of dry methanol. After 6 h of stirring the solution was neutralised with solid NH$_4$Cl until a pH of 8 is reached and water was added. The aqueous layer was extracted three times with 30 ml of ethyl acetate. The combined organic layers were dried over anhydrous MgSO$_4$ and evaporated to dryness. Flash chromatography

CH$_2$Cl$_2$–CH$_3$OH 100:3) yielded 164 mg (0.63 mmol; 95%) of β-1′,2′-dideoxy-1′-(1-(4-methyl)naphthyl)-ribose **3d**β.

β-1′,2′-Dideoxy-1′-(1-(4-methyl)naphthyl)-ribose 4dβ.

R_f: 0.37 (ethyl acetate); δ_H (300 MHz, CDCl$_3$) 8.08–8.02 (2H, m, Ar–H), 7.56–7.51 (3H, m, Ar–H), 7.30 (1H, d, J 7.2, Ar–H), 5.88 (1H, dd, $J_{H1',H2'\alpha}$ 10.1, $J_{H1',H2'\beta}$ 5.6, H1'), 4.88 (1H, m, H3'), 4.11 (1H, td, $J_{H4',H5'}$ = 3.8, $J_{H3',H4'}$ = 4.1, H4'), 3.85 (2H, m, H5'), 2.68 (s, 3H, Ar–Me), 2.47 (1H, ddd, $J_{H2'\alpha,H2'\beta}$ 13.2, $J_{H1',H2'\alpha}$ 5.7, $J_{H3',H2'\alpha}$ 2.2, H2'α), 2.32 (1H, ddd, $J_{H2'\alpha,H2'\beta}$ 13.2, $J_{H1',H2'\beta}$ 9.8, $J_{H3',H2'\beta}$ 6.5, H2'β), 2.00 (br, 2H, OH); δ_c (75 MHz, CDCl$_3$) 135.0, 134.3, 132.8, 130.8, 126.2, 125.8, 125.5, 124.9, 123.9, 121.7, 86.9, 77.2, 73.8, 63.4, 43.0(C-2'), 19.6 (Ar–Me); MS(EI): m/z C$_{16}$H$_{18}$O$_3$$^+$ calcd. 258.1(M), found 258.1.

β-1′,2′-Dideoxy-1′-(1-pyrenyl)-ribose 4aβ.

185 mg (85%), NMR- and MS-analysis confirmed the identity with previously synthesized material.

β-1′,2′-Dideoxy-1′-(2-fluorenyl)-ribose 4bβ.

141 mg (72%); R_f: 0.37 (ethyl acetate); δ_H (300 MHz, methanol-d$_4$) 7.77–7.72 (2H, m, Ar–H), 7.59 (1H, s, H1), 7.52 (1H, d, J 7.5, Ar–H), 7.39–7.23 (3H, m, Ar–H), 5.19 (1H, dd, $J_{H1',H2'\alpha}$ 10.5, $J_{H1',H2'\beta}$ 5.6, H1'), 4.34 (1H, m, H3'), 3.97 (1H, td, $J_{H4',H5'}$ = 5.2, $J_{H3',H4'}$ = 2.4, H4'), 3.86 (s, 2H, CH$_2$), 3.70 (2H, m, H5'), 2.23 (1H, ddd, $J_{H2'\alpha,H2'\beta}$ 13.2, $J_{H1',H2'\alpha}$ 5.4, $J_{H3',H2'\alpha}$ 1.7, H2'α), 2.00 (1H, ddd, $J_{H2'\alpha,H2'\beta}$ 13.2, $J_{H1',H2'\beta}$ 10.5, $J_{H3',H2'\beta}$ 6.1, H2'β); δ_c (75 MHz, methanol-d$_4$) 144.6, 144.6, 142.5, 141.6, 127.7, 127.7, 126.0, 126.0, 123.8, 120.7, 120.5, 89.1, 81.9, 74.4, 64.1, 45.1, 37.6; MS(EI): m/z C$_{18}$H$_{18}$O$_3$$^+$ calcd. 282.1(M), found 282.1.

β-1′,2′-Dideoxy-1′-(3-benzothiophenyl)-ribose 4cβ.

112 mg (82%); R_f: 0.35 (ethyl acetate); δ_H (300 MHz, CDCl$_3$-methanol-d$_4$ 6 : 1) 7.87–7.80 (2H, m, Ar–H), 7.41 (1H, s, Ar–H), 7.39–7.32 (2H, m, Ar–H), 5.52 (1H, dd, $J_{H1',H2'\alpha}$ 9.6, $J_{H1',H2'\beta}$ 5.7, H1'), 4.42 (1H, m, H3'), 4.02 (1H, td, $J_{H4',H5'}$ = 4.9, $J_{H3',H4'}$ = 3.4, H4'), 3.75 (2H, d, $J_{H4',H5'}$ = 5.0, H5'), 2.39 (1H, ddd, $J_{H2'\alpha,H2'\beta}$ 13.3, $J_{H1',H2'\alpha}$ 5.9, $J_{H3',H2'\alpha}$ 2.4, H2'α), 2.22 (1H, ddd, $J_{H2'\alpha,H2'\beta}$ 13.3, $J_{H1',H2'\beta}$ 9.9, $J_{H3',H2'\beta}$ 6.5, H2'β); δ_c (75 MHz, CDCl$_3$-methanol-d$_4$ 6:1) 140.9, 137.5, 136.5, 124.6, 124.2, 123.0, 122.3, 122.1, 87.3; 76.7, 75.7; 73.0, 63.0, 41.4; MS(EI): m/z C$_{13}$H$_{14}$O$_3$S$^+$ calcd. 250.1(M), found 250.1.

β-1′,2′-Dideoxy-1′-(4-(methylthio)phenyl)-ribose 4eβ.

17 mg (quant.); R_f: 0.42 (ethyl acetate); δ_H (300 MHz, CDCl$_3$-methanol-d$_4$ 6 : 1) 7.27–7.15 (4H, m, Ar–H), 5.04 (1H, dd, $J_{H1',H2'\alpha}$ 10.3, $J_{H1',H2'\beta}$ 5.6, H1'), 4.26 (1H, m, H3'), 3.88 (1H, td, $J_{H4',H5'}$ = 5.1, $J_{H3',H4'}$ = 2.8, H4'), 3.63 (2H, m, H5'), 2.41 (s, 3H, SMe), 2.15 (1H, ddd, $J_{H2'\alpha,H2'\beta}$ 13.2, $J_{H1',H2'\alpha}$ 5.6, $J_{H3',H2'\alpha}$ 1.9, H2'α), 1.90 (1H, ddd, $J_{H2'\alpha,H2'\beta}$ 13.2, $J_{H1',H2'\beta}$ 10.3, $J_{H3',H2'\beta}$ 6.3, H2'β); δ_c (75 MHz, CDCl$_3$-methanol-d$_4$ 6:1) 138.1, 137.8, 126.6, 87.5, 79.8, 73.0, 63.0, 43.3, 15.8; MS(ESI): m/z C$_{13}$H$_{14}$O$_3$SNa$^+$ calcd. 263.1(M + Na$^+$), found 263.2.

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