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Synthesis of 1',2'- Dideoxy-aryl-C-riboside (Nucleosides Analogues) by Friedel-Crafts Alkylation Reaction

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□ ABSTRACT □

A fast and simplified synthesis of 1',2'-dideoxy-1'-Pyrenyl-riboside and several other *C*-glycosides (nucleosides analogues) is shown. Shelf-stable 1-*O*-methyl-3,5-di-*O*-tolyl-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. Variation of the electronic properties of the aryl aglycons demands careful optimisation of Lewis acid promotors and glycosyl donors. The reaction conditions favour the formation of β-configurated *C*-glycosides which renders additional epimerisation steps unnecessary. As a result, protected β-aryl-*C*-glycosides (nucleosides analogues) are available directly from non-substituted arenes in three steps :

1. Fridel – Grafts alkylation using the $Sncl_4$ / AgOTfa-promoter system or $Sncl_4$ and 1-methoxysugar as glycosyl donor.
2. Deprotection of the β-anomeric by treatment with sodium methoxide in dry methanol.
3. Assesment of the α/β selectivity of the C-glycosylation by ^1H NMR spectroscopy and HPLC analysis.

Key words: 1-Methoxysugar, alkylation, Lewis acid, Pyrene and other arenes, aryl-c-glycosides, synthesis.

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اصطناع أريل - C - ريبوزيد منقوص الأوكسجين (مشابهات النوكليوزيدات) باستخدام تفاعل الألكلة بوسائط فريدل كرافت

الدكتورة نجوى حداد*

(قبل للنشر في 2006/6/19)

□ الملخّص □

نعرض اصطناعاً بسيطاً وسريعاً لـ 1',2' dideoxy-1'- pyrenyl- riboside وغيره من -C- غليكوزيدات (مشابهات النوكليوزيدات).

أظهر المركب 1-O-methyl- 3,5-di-O-tolyl-2- deoxyribose ثبوتية أثناء التخزين وأمكن استخدامه كمانح جيد لزمر الغليكوزيل في تفاعلات فريدل – كرافت أثناء ألكلة البيرين غير المستبدل وغيره من الأرينات الرخيصة مثل الفلورين والمتيل نفتالين. وقد لوحظ أن تغيير الخواص الإلكترونية للأغليكون الأريلي يتطلب تعديلاً في حموض لويس ومانحات الـ gylcosyl.

يتشكل في شروط التفاعل المطبقة التشكيل β-C– غليكوزيدات، مما يسمح بالتخلي عن خطوة التحول إلى الإيبيمير. فقد أمكن الحصول على β – أريل C – غليكوزيدات (مشابهات النوكليوزيدات) مباشرة من الأرينات غير المستبدلة في ثلاث خطوات هي:

1- يؤلكل ميتوكسي السكاريد باستخدام أرينات مختلفة وبحضور نظام التحريض $SnCl_4$/AgOTfa أو $SnCl_4$.

2- نزع الحماية لـ الأنومير – β بالمعالجة بميتوكسيد الصوديوم في الميتانول الجاف.

3- استخدمت مطيافية ^1H NMR و HPLC لتحديد الانتقائية α / β.

كلمـــات مفتاحيـــة: ميتوكســي السكاريـد، ألكلـة، حمـوض لـويس، البيـرين وأرينـات أخـرى، اريـل – C –غليكوزيـدات، اصطناع.

أُجري البحث في ألمانيا خلال مدة الإيفاد بمهمة بحث علمي.

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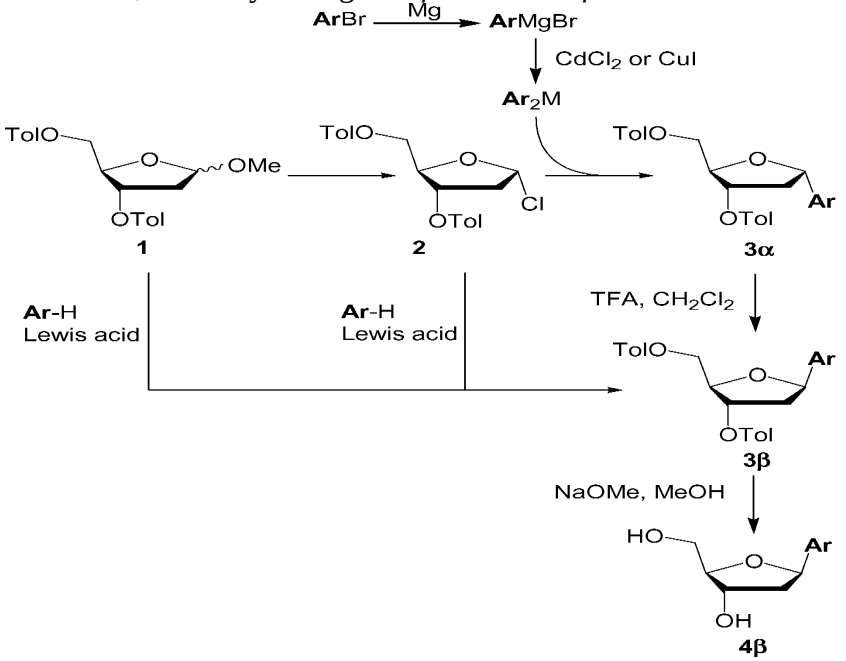
INTRODUCTION:

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

In the synthesis of aryl-*C*-glycosides 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 glycosides 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*-glycosides have also been obtained by palladium-catalysed coupling of aryl iodides with glycals (as Glycosyl Donors) and stannyl glycals [10]. One of the most widely used synthetic methods is based on the coupling of organocadmium compounds (Ar_2Cd) [11] or, preferably, Normant cuprates (Ar_2CuMgX) [6] with Hoffer's chlorosugar (2-deoxy-3,5-di-*O*-tolyl-D-ribofuranosyl chloride) **2** [12] (Scheme 1). This method yields the α-anomers **3**α as major products which have to be subjected to acid-catalyzed epimerization [11-13] in order to obtain the often desired, naturally configured β-anomers **3**β.



Scheme 1 Comparison of aryl *C*-glycosides synthesis by organometal reagents with Friedel–Crafts alkylation. (M = Cd or CuMgX, Tol = tolyl, X = halide).

Most of the currently available procedures give relatively low overall yields and require expensive and very complicated reaction sequences to access suitable *C*-glycoside donors and glycosyl acceptors. In comparison to organometal-catalyzed coupling reactions of aryl halides with suitable 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 unnecessary. It is also an advantage that unsubstituted arenes can be employed instead of more expensive bromo- or iodoarenes. 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 low cost method for synthesis of β-aryl-*C*-nucleosides analogues including pyrenyl, fluorenyl and methylnaphthyl 2'-deoxy-*C*-ribosides.

TARGET:

Synthesis of β-aryl-*C*-glycosides for using as powerful designer nucleotides to probe DNA-DNA and DNA-Protein interactions, or to study the reaction mechanisms of DNA-Polymerases or DNA repair enzymes.

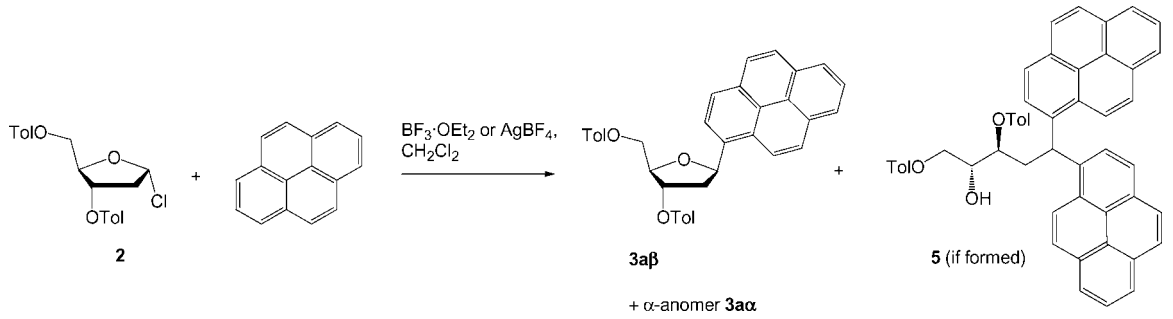
RESULTS:

In the previous syntheses of pyrenyl nucleoside **4a**β(Ar = 1-pyrenyl), 1-α-chloro-3,5-di-*O*-tolyl-2-deoxyribose **2 (**scheme 1) was used as glycosyl donor in coupling reactions with organometallic reagents (Ar_2Gd and Ar_2CuMgX) 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

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

Entry	Promoter (eq.)	Time/min	Solvent	Yield of 3α (%)	Ratio 3aβ: 3aα[a]
1	BF3·OEt2 (1.3)	20	CH2Cl2	54	70 : 30
2	BF3·OEt2 (1.7)	20	ClCH2CH2Cl	52	70 : 30
3	AgBF4 (1.1)	120	CH2Cl2	57	75 : 25
4	AgBF4 (1.1)	60	ClCH2CH2Cl	9	76 : 24

[a] Selectivity determined by 1H-NMR-spectroscopy *via* comparison of the signal intensity of the anomeric protons.



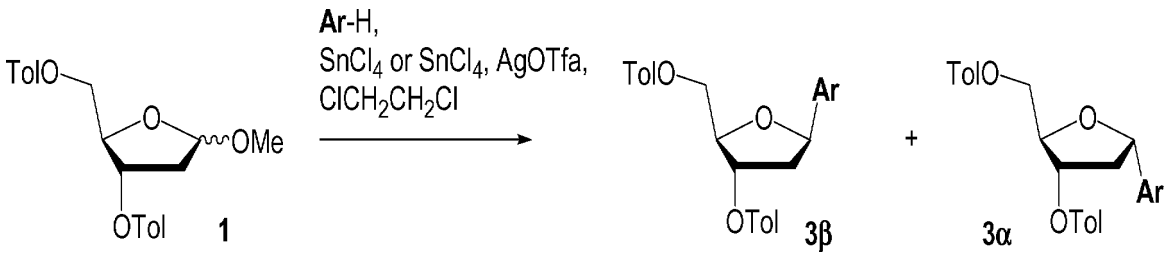
Scheme 2 Coupling reaction of chlorosugar 2 with pyrene.

induce the formation of toluoyl protected *C*-nucleoside **3a**α/β which was isolated in 54% yield (Table 1, entry 1). The α/β-selectivity of the *C*-glycosylation was assessed by ^{1}H-NMR and analytical HPLC analysis. Under the Lewis acid conditions, product **3a** was formed as a mixture of anomers **3a**β : **3a**α of 7 : 3. The anomeric mixture was separated by flash chromatography to afford the pure β-anomer **3a**β in 33% yield. Friedel–Crafts alkylations in dichloroethane often proceed with higher yields than in dichloromethane. However, the BF_3-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 **3a**β : **3a**α 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-1,3-ditolyl- 5,5-dipyrenyl pentane **5** in 22% yield, while the desired compounds **3a**α/β were obtained in only 9% yield. NMR-analysis (^{1}H-; ^{13}C-, ^{1}H, ^{1}H-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*-tolyl-ribose **3a**α/β.

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

Arene	Promoter (eq.)	Temp./◦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.

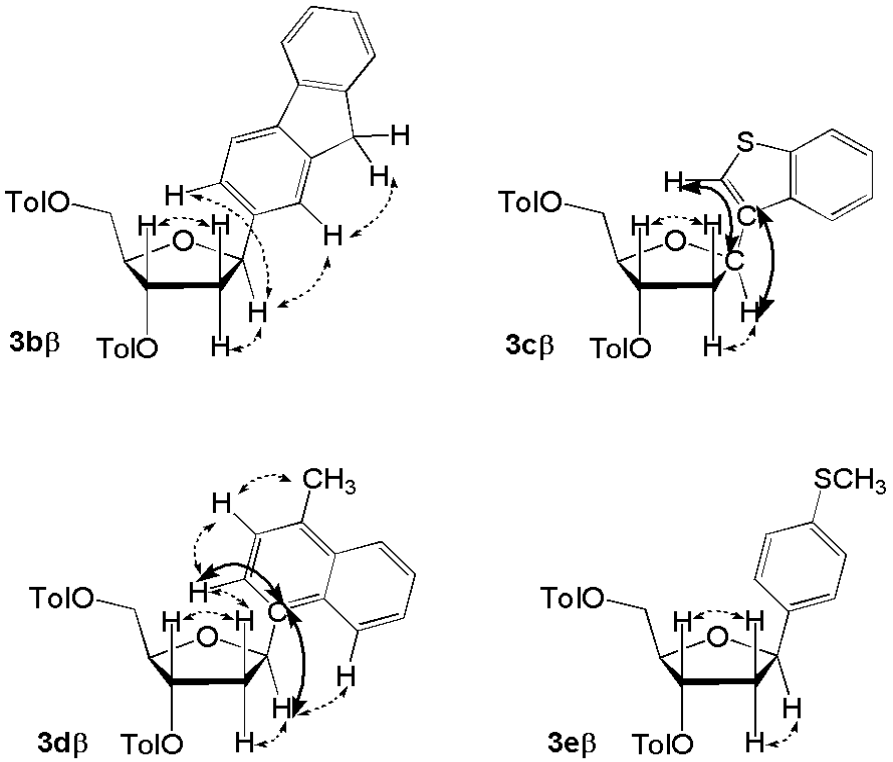


Fig. 1 Aryl-*C*-nucleosides and important correlations in 1H-1H-NOESY (dashed) and 1H-13C-HMBC (bold) NMR-spectra.

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 $SnCl_4$ led to rapid decomposition of chloro sugar **2**. Recently, methoxy sugars were demonstrated to serve as suitable glycosyl donors in $SnCl_4$-promoted

C-glycosylation reactions [16]**.** Due to easy of synthesis and long shelf life, the application of 1-*O*-methyl-3,5-di-*O*-tolyl-2-deoxyribose **1** appeared attractive (Scheme 3). Accordingly, the reaction of methoxy sugar **1** with pyrene induced by addition of $SnCl_4$ was studied. The desired pyrenyl-*C*-nucleoside **3a**α/β was obtained in yields and selectivities which compared well with the BF_3- promoted reactions. The pure β-anomer **3a**β was isolated in 39% yield (Table 2). For the reaction of the less reactive arenas fluorene, 1-methylnaphthalene, phenanthrene, benzothiophene and thioanisole, it was considered 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 trifluoroacetate ($SnCl_4$/AgOTfa) to yield 41% of β-1',2'-dideoxy-1'-(2-fluorenyl)-3',5'-di-*O*-tolyl-ribose **3b**β and 9% of α-1',2'-dideoxy-1'-(2-fluorenyl)-3',5'-di-*O*-tolyl-ribose **3b**α (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-tolyl aryl-*C*-nucleosides **3c**α/β and **3d**α/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 **3c**β, 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 equivalent.) and reaction temperature (20 ◦C) *C*-nucleoside **3e**β 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 tolylated 2'-desoxyribose- *C*-nucleosides **3b**β–**3e**β was carried out following standard procedures by treatment with sodium methoxide in dry methanol. After column chromatography the corresponding unprotected *C*-nucleosides **4**β 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 arenas used. The reactivity of an arene in Friedel–Crafts alkylations is commonly characterised by means of its σ^+_{arene} (nucleophilic reactivities) 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 **4a**β 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 **4**β 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.

ACKNOWLEDGEMENTS:

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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, 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.AMacherey&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 **3a**β : **3a**α is 1.14 as calibrated by a mixture of known decomposition of **3a**α/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 $NaHCO_3$ solution (×3) and brine (×1), dried over anhydrous $MgSO_4$ 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 **3a**α/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, $CDCl_3$) 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, $CDCl_3$) 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* $C_{37}H_{30}O_5$ + 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, $CDCl_3$) 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, $J_{H2'a,H2'\beta}$ 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, $CDCl_3$) 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* $C_{37}H_{30}O_5Na^+$ calcd. 577.1985(M + Na^+), found 577.1999.

(2*R*,3*S*)-2-Hydroxy-5,5-dipyrenylpentyl 1,3-ditoluoate 5. R_f: 0.10

(cyclohexane–ethyl acetate 4.5 : 1); δ_H (300 MHz, $CDCl_3$) 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); δc (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 (C_q, 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* $C_{53}H_{40}O_5Na^+$ 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 $SnCl_4$ (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 $NaHCO_3$ solution (×3) and brine (×1), dried over anhydrous $MgSO_4$ and concentrated. Flash chromatography (cyclohexane–ethyl acetate 19:1) yielded 96mg (0.19 mmol; 37%) of β-1',2'-dideoxy-1'-(1-(4-methyl)naphthyl)-3',5'-di-*O*-toluoylribose **3d**β and 35 mg (0.07 mmol; 14%) of α-1',2'-dideoxy-1'- (1-(4-methyl)naphthyl)-3',5'-di-*O*-toluoyl-ribose **3d**α.

β-1',2'-Dideoxy-1' -(1-(4-methyl)naphthyl)-3',5'-di-*O*-toluoylribose 3dβ.

R_f: 0.40 (cyclohexane–ethyl acetate 4.5 : 1); δH (300 MHz, $CDCl_3$) 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, $CDCl_3$) 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^+–C_7H_7COOH, 8), 222(M^+–$2C_7H_7COOH$, 35), 169(1-(4-methyl)-naphthyl- $(CO)^+$,100); HRMS(EI): *m/z* $C_{32}H_{30}O_5$ $^+$ calcd. 494.2093(M), found 494.2094.

α-1',2'-Dideoxy-1' -(1-(4-methyl)naphthyl)-3',5'-di-*O*-toluoylribose 3dα.

R_f: 0.34 (cyclohexane–ethyl acetate 4.5 : 1); δ_H (300 MHz, $CDCl_3$) 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, $CDCl_3$) 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* $C_{32}H_{30}O_5$ + 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 (400MHz,$CDCl_3$) 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, CH_2), 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, $CDCl_3$) 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^+–C_7H_7COOH, 4), 246(M^+– $2C_7H_7COOH$, 18), 169 (fluorenyl-$(CO)^+$,100); HRMS(EI): *m/z* $C_{34}H_{30}O_5^+$ 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 (300MHz,$CDCl_3$) 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*-toluoylribose 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); *d*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* $C_{34}H_{30}O_5N\alpha^+$ calcd. 509.1393(M + Na^+), found 509.1392.

α-1',2'-Dideoxy-1' -(3-benzothiophenyl)-3',5' -di-*O*-toluoylribose 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); *d*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* $C_{34}H_{30}O_5Na^+$ 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* $C_{34}H_{30}O5^+$ 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_4Cl 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_2Cl_2–CH_3OH 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); δc (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, CH2), 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); δc (75MHz,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* $C_{13}H_{14}O_3S^+$ 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, $J_{H2'a,H2'b}$ 13.2, $J_{H1',H2'b}$ 10.3, $J_{H3',H2'b}$ 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* $C_{13}H_{14}O_3SNa^+$ calcd. 263.1(M + Na^+), found 263.2.

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