Ribbonucleotide reductases (RNRs) catalyze the 2'-reduction of ribonucleotides, thus producing 2'-deoxyribonucleotides, the monomers for DNA biosynthesis. The current mechanistic hypothesis for the catalysis effected by this class of enzymes involves a sequence of radical reactions. A reversible 3'-hydrogen abstraction, effected by a radical at the enzyme's active site, is believed to initiate the catalytic cycle. For the study of this substrate–enzyme interaction, a series of 4'-benzophenone-substituted model compounds was designed and synthesized. In these models, the benzophenone carbonyl group is oriented such that irradiation is expected to result in an enzyme-like, reversible 3'-hydrogen abstraction. The key step of our synthetic approach is the highly diastereoselective (dr > 95:5) Grignard-addition of carbonyl-protected o-benzophenone magnesium bromide to 2,3-O-isopropylidene-β-L-erythrofuranose. The configuration of the newly established chiral center was unambiguously proven by X-ray crystallography. The erythritol derivative thus obtained was dehydrated to a base-free, 4'-benzophenone-substituted nucleoside analog. This first model system was further modified by transforming the free 2',3'-hydroxy groups into the mono- and bis-methyl ethers, into the cyclic carbonate, and into the mono- and bis-mesylates. Alternatively, the primary hydroxyl group of the erythritol intermediate was selectively oxidized to the aldehyde. In the furanose thus obtained, the stage is set for the additional introduction of a nucleobase at the 1'-position.

**Introduction**

In all known organisms, 2'-deoxyribonucleotides are synthesized by 2'-reduction of ribonucleotides. This deoxygenation (eq 1) is effected by ribonucleotide reductases (RNRs). Therefore, RNRs play a central role in DNA biosynthesis and in cell division, and they are potential drug targets for tumor and viral diseases. A mechanism involving the radicals A–C has been proposed for the action of ribonucleotide reductases (Scheme 1). In this proposal, the catalytic cycle is initiated by the regioselective attack of a radical species X' in the enzyme's active site on the 3'-position of the substrate nucleotide. As a result, the hydrogen atom Hα is homolytically removed and the so-called “3'-radical” A (I → II, Scheme 1) is generated. Protonation of the 2'-hydroxyl group and elimination of water gives rise to the radical cation B (II → III → IV, Scheme 1). The formal transfer of a hydride anion from the cysteinylcysteinyl ensemble present in the active site leads to the radical species C (IV → V, Scheme 1). The radical C is again a “3'-radical”. However, it is now the precursor to the 2'-deoxygenated product. The reduction of the ribonucleotide is completed by the back-transfer of the hydrogen atom Hα to the 3'-position of the ribose moiety (V → VI, Scheme 1). After reduction of the cystine disulfide bond in the active site to two cysteinyl thiol groups, the enzyme is ready for the next turnover. This proposed mechanism of catalysis is based on studies with isotopically labeled substrates and substrate analogs, as well as on the investigation of enzymes modified by site-directed mutagenesis. Most importantly, at least one of the three classes of RNRs is known to harbor a stable tyrosyl radical. In fact, the so-called “aerobic” RNR from E. coli was the first radical enzyme found. Finally, the X-ray
crystal structures of the two protein subunits (R1 and R2) of this enzyme, which have become available only recently, support the idea of a radical deoxygenation sequence involving three cysteine residues: Two cysteines act as the formal hydride donor/redox shuttle, while the third one most likely represents the radical X• in the enzyme's active site. The oxidation of the third cysteine to the catalytically competent thiyl radical is believed to take place by electron transfer to the remote tyrosyl radical.

As plausible as this mechanism may seem, it is so far not supported by direct observation of the intermediate substrate-derived radicals A–C (Scheme 1). Furthermore, there is no close analogy in the radical chemistry of carbohydrates. With this in mind, we found it worthwhile to design and synthesize model compounds that would allow for the selective generation of the 3'-radical A (Scheme 1) proposed for the catalytic cycle of RNRs. Of special interest are model compounds that are able to imitate the proposed reversible hydrogen abstraction from the 3'-carbon atom of the nucleotide by the protein radical X•. In the long run, our mechanistic studies are hoped to lead to new selective, mechanism-based inhibitors of ribonucleotide reductases and to biomimetic catalysts for RNR-type regioselective deoxygcnations of polyols/carbohydrates.

Carbonyl compounds, and in particular benzophenones, are able to initiate reversible homolytic hydrogen abstractions upon photochemical excitation into their triplet states. Therefore, nucleoside derivatives were designed that incorporate a benzophenone substituent into the sugar moiety (Scheme 2). With the carbonyl oxygen atom of the benzophenone moiety being fixed near the 3'-hydrogen atom, these model compounds are expected to reversibly generate "3'-radicals" upon irradiation. Molecular models suggest the attachment of the benzophenone substructure to the 4'-position of the ribose ring (for the sake of clarity, the conventional numbering of the ribose unit in nucleosides is maintained throughout the text). In this arrangement, the carbonyl oxygen atom should be at a favorable distance to the 3'-hydrogen atom. In this paper, the synthesis of nine 4'-benzophenone-substituted model compounds is described. Eight are simplified nucleoside analogs in that the nucleobase is replaced by a hydrogen atom. The ninth one possesses (9) Breslow, R. Chem. Soc. Rev. 1972, 1, 553.
(11) A 4'-hydrogen abstraction might occur as well. However, the photoenol formed by 4'-hydrogen abstraction can rapidly tautomerize back to the starting material, thus making this reversible abstraction process unproductive.
the intact anomeric hemiacetal center and may thus serve as a precursor for the construction of nucleotide analogs carrying both a nucleobase and the benzophenone chromophore. The mechanistic investigation of the photochemical reactivity of these models will be described in a subsequent paper.  

Results

Our synthetic sequence is summarized in Scheme 3. The ethylene glycol-protected o-bromobenzophenone 1 and the enantiomerically pure 2,3-O-isopropylidene-β-L-erythrofuranose (2) served as starting materials. They were synthesized by modified literature procedures in three steps each from 2-bromobenzoic acid (65%) and from L-(+)-rhamnose (67%), respectively.

In the first step of our sequence, the Grignard compound was prepared by treatment of the benzophenone derivative 1 with Rieke magnesium. The protected erythrofuranose 2 was treated with 3 equiv of the organomagnesium reagent in THF. The addition proceeded with excellent anti-like-selectivity; only one diastereomer was detected by NMR analysis of the crude product (i.e., diastereomeric ratio > 95:5). The best results (57% chemical yield) were obtained at room temperature. At −78 °C, no reaction occurred. Warming of the reaction mixture to ambient temperature before quenching gave the diol 3 in 13% yield. Running the coupling reaction in refluxing THF gave a 52% yield of the addition product 3. According to NMR analyses, the diastereoselectivity of the reaction did not change with temperature. The configuration of the newly formed stereogenic center (R) was unambiguously established by the X-ray crystal structure of the silylated derivative 8 (Scheme 3, inset). Of course, the vicinal H–C–C–H coupling constants measured for the bicycle 4 (Scheme 3) also supported this configurational assignment (vide infra).

For the synthesis of the model compounds lacking the nucleobase, the diol 3 was treated with tosyl chloride in pyridine at −30 °C. After the mixture was warmed to room temperature and stirred for several days, tetrahydrofuran derivative 4 was obtained in quantitative yield. The primary tosylate that should be formed as an intermediate could not be isolated. Nevertheless, the intramolecular cyclization 3 → 4 is most reasonably

interacted by nucleophilic displacement of the primary tosylate by the secondary (benzyl) hydroxyl group. Consequently, the configuration at the benzyl position should remain unchanged. In fact, only one diastereomer was formed. As mentioned above, the (R)-configuration of the benzyl stereogenic center could clearly be deduced from the vicinal H–C–H–C coupling constant \( \gamma_{\text{H-3H}} = 2.2 \text{ Hz} \) measured for the bicycle \( \text{B} \). \( \text{J} \) values below 3 Hz strongly indicate a trans-relationship for the corresponding protons, whereas a cis-configuration should result in \( \text{J} \) values larger than 3.5 Hz. \( \gamma \) The model compound \( \text{5} \) was finally obtained in 76% yield by deprotection of the bis-dioxolane \( \text{4} \). Thus, the final product \( \text{5} \) was synthesized in a stereospecific manner, starting from commercially available \( \text{L} \)-(−)-rhamnose in 29% overall yield.

The proposed mechanism of RNR action involves the acid-catalyzed elimination of the 2'-hydroxyl group from the 3'-radical (Scheme 1, 11 → 111 → IV). For the successful modeling of this reaction step, it may well be necessary to “tune” the nucleofugal properties of the 2'-hydroxyl group by derivatization. For example, treatment of the diol \( \text{5} \) with 1,1'-carbonyldiimidazole/DMAP gave the bicyclic carbonate \( \text{11} \) in 99% yield (Scheme 4). The dimethyl ether \( \text{12} \) was obtained from \( \text{5} \) by alkylation using the methyl Meerwein salt in the presence of the proton sponge 1,8-bis(dimethylamino)naphthalene \( \text{20} \) (55%). Finally, the bismesityl \( \text{13} \) was synthesized from \( \text{5} \) and mesyl chloride/triethylamine in 95% yield.

Numerous attempts were made to selectively prepare the 2'- or 3'-monomethylated or monomesylylated derivatives of \( \text{5} \). Under a variety of reaction conditions, mixtures of both monoderivatized products and the dimethyl ether \( \text{12} \) or the bismesityl \( \text{13} \), respectively, were obtained. Although their separation—even by preparative HPLC—proved difficult, we were able to isolate the compounds \( \text{14–17} \) in pure form, albeit in small (mg) quantities. Nevertheless, the structural assignment, i.e., the distinction of 2'- vs 3'-derivatization, could be unambiguously done on the basis of \( \text{J} \) OH–CH–OH couplings in the \( \text{H}-\text{NMR spectra} \).

In order to provide access to model compounds carrying a nucleobase in the 1'-position, the primary hydroxyl group of the diol \( \text{3} \) must be selectively oxidized to an aldehyde. Due to the higher inherent reactivity of the secondary, benzylic hydroxyl group, common oxidizing agents like PCC or activated derivatives of DMSO afforded the corresponding ketone instead of the desired aldehyde. Nevertheless, the selective oxidation of the primary alcohol was achieved either by using the protecting group strategy outlined in Scheme 3 or by using PCC adsorbed on neutral alumina. In the former approach, the furanose \( \text{9} \) was synthesized from the diol \( \text{3} \) in five steps and 52% overall yield. In the first step, the primary hydroxyl group of \( \text{3} \) was selectively benzylation, and the ester \( \text{6} \) was obtained quantitatively. Treatment with TBDMSOTf \( \text{20} \) afforded the doubly protected compound \( \text{7} \) in 92% yield. Basic hydrolysis yielded the primary alcohol \( \text{8} \). This material readily crystallized from diethyl ether, thus affording single crystals suitable for X-ray structural analysis (Scheme 3, inset). The crystal structure of the silyl ether \( \text{8} \), together with the known absolute configuration of the two stereogenic centers derived from 2,3-O-isopropylidene-β-L-erythroranose \( \text{2} \), allowed for the unambiguous assignment of the (R)-configuration to the newly formed benzylic stereocenter. The oxidation of \( \text{8} \) with PCC and the removal of the silyl group with \( \text{Bu}_3\text{NF} \) afforded the benzophenone-substituted furanose \( \text{9} \) in 57% yield. The latter approach (one-step oxidation of the diol \( \text{3} \)) gave the desired furanose \( \text{9} \) in 34% yield.

The furanose \( \text{9} \) is in the oxidation state required for the nucleophilic introduction of a nucleobase by the Vorbrüggen method. \( \text{21} \) It may thus serve as a precursor for the model system of type \( \text{10} \) (Scheme 3), carrying both a benzophenone moiety and a nucleobase.

Discussion

The key step of our synthetic sequence is the highly diastereoselective addition of the Grignard reagent derived from the bromoarene \( \text{1} \) to the erythrose \( \text{2} \). The mechanism accounting for the observed extreme selectivity merits further consideration. The presence of Lewis-acidic magnesium salts suggests a chelate-controlled mechanism accounting for the observed extreme selectivity merits further consideration. The presence of Lewis-acidic magnesium salts suggests a chelate-controlled method of addition to the ring-opened form of the erythrose \( \text{2} \). Besides the carbonyl oxygen atom, the molecule contains three further oxygen atoms that may participate in chelating a magnesium ion (formulas \( \text{1} \)–\( \text{111} \)). Since the re-face of the aldehyde is attacked, a

(19) Procedure according to Dier, M. J.; Burow, D. F.; Fry, J. L. J. Org. Chem. 1977, 42, 1801. The attempted methylation of \( \text{5} \) using methyl iodide failed under a variety of reaction conditions.

(20) TBDMSOTf failed to react with the sterically hindered secondary hydroxyl group.


(23) (a) Mekki, Singh, G., Wightman, R. H. Tetrahedron Lett. 1991, 32, 5143. (b) There is a single report of syn-diastereoselectivity in the addition of methyl magnesium chloride to the erythrofuranose \( \text{2} \) (see ref 24). However, the authors of ref 24 do not state how the configurational assignment was done.

Conclusions

A convenient, convergent, and stereospecific synthetic access to 4′-benzophenone-substituted nucleoside analogs has been developed. Starting from commercially available L- (+)-rhamnose, nine model systems were synthesized. With the exception of the monomethylated and monomesyalted compounds 14–17, quite reasonable overall yields were achieved (16–29%). In our approach, 2,3-O-isopropylidene- β- L-erythofuranose 2 served as a central intermediate. It was shown that Grignard reagents can be added to this furanose with extremely high anti-/like-selectivity. Most likely, efficient chelate control accounts for the selectivity of this process. It is expected that the model systems described in this paper will for the first time allow for the selective, photochemical generation and study of the radicals postulated as intermediates in the catalytic cycle of the ribonucleotide reductases (RNRs). Furthermore, the modular character of our synthetic sequence [Grignard addition to the erythofuranose 2, elaboration to furanoses of the type 9/10 or simpler, “base-free” structures of the type 5 (Scheme 3)] may provide a wide variety of other nucleoside analogs—potentially even by combinatorial methods.

Experimental Section

General Methods. Unless otherwise noted, all reagents were purchased from commercial suppliers and were used as received. L- (+)-Rhamnose monohydrate (high purity grade) was purchased from E. Merck. Pyridinium chlorochromate (PCC) and PCC/Al2O3 were prepared according to Corey et al. [26] and Tietze et al. [27] respectively. All solvents were distilled. Methylecne chloride was stirred for 2 °C with concd sulfuric acid, decanted, washed with water and aqueous NaHCO3, dried over MgSO4, distilled from P2O5, and stored over 4 Å molecular sieves. THF was distilled from sodium benzophenone ketyl prior to use. Triethylamine and pyridine were distilled from CaH2 and stored over 3.3 Å molecular sieves. Methanol was purchased from E. Merck. Pyridinium chlorochromate was purchased from commercial suppliers and were used as received. Radial chromatography was performed on a Harrison Research Chromatotron Model 8924 with E. Merck silica gel 60 PF254 (with gypsum). Preparative HPLC was performed on an E. Merck-Septech NovaPrep 5000 System using an E. Merck LiChrosorb 100 RP-18, 10 µm, 250 × 50 mm column at a flow rate of 78 mL/min. Analytical HPLC was performed on an E. Merck-Hitachi L-6200 A/L-4500 DAD system using a Hewlett-Packard Lichrospher 100 Achromatograph. Purification of the products was achieved by preparative HPLC (MeOH/H2O 6:4, 1 mL/min) as a colorless, solid foam: 1H-NMR (300 MHz, DMSO-d6) δ 7.4-7.7 (m, 7H), 7.59 (d, J = 7.7 Hz, 1H), 7.65 (d, J = 7.4 Hz, 1H); 13C-NMR (75 MHz, DMSO-d6) δ 65.1 (t), 109.5 (s), 121.9 (s), 126.6 (d), 126.7 (d), 127.8 (d), 128.2 (d), 129.8 (d), 135.0 (d), 140.3 (s), 140.4 (s); IR (KBr, pellet) 3058, 2887, 1585, 1447, 1206, 1092, 1074, 1026, 753 cm−1; TLC (EtOAc/hexane 1:1) Rf 0.56; mp 137 °C (lit. [14] mp 137 °C). Anal. Calcd for C21H21O2 Br: C, 49.04; H, 4.29. Found: C, 49.14; H, 4.38.

[35α-(3α,4α,6α)]-Tetrahydro-2,2-dimethyl-furo[3,4-d,1,3-dioxol-4-ol]=Tetrahydro-2,2-dimethyl-furo[3,4-d,1,3-dioxol-4-ol]=Tetrahydro-2,2-dimethyl-furo[3,4-d,1,3-dioxol-4-ol]=Tetrahydro-2,2-dimethyl-furo[3,4-d,1,3-dioxol-4-ol]=Tetrahydro-2,2-dimethyl-furo[3,4-d,1,3-dioxol-4-ol](3). A mixture of 1.78 g (18.7 mmol) of anhydrous MgCl2, 1.57 g (9.45 mmol) of KI, and 1.32 g (33.7 mmol) of potassium in 35 mL of anhydrous THF was refluxed under argon for 2 h with vigorous stirring. The oil bath was removed, and stirring was continued for another 1.5 h. A solution of 2.86 g (9.37 mmol) of 1 in 30 mL of anhydrous THF was added in a dropwise manner to the resulting back suspension with stirring at room temperature. Stirring at ambient temperature was continued for another 3 h, and a solution of 0.50 g (3.12 mmol) of 2 in 15 mL of anhydrous THF was added. The reaction mixture was stirred at room temperature for another 18 h, and 100 mL of 10% aqueous NH4Cl was added (CAUTION: In some cases, especially during scale-up (20–30 g K), traces of unreacted potassium remained. In this case, 2-propanol was added dropwise prior to quenching with aqueous NH4Cl.) The layers were separated, and the aqueous layer was extracted with 2 × 100 mL of EtOAc and 100 mL of Et2O. The combined organic phases were washed with 4 × 50 mL of water and dried over MgSO4. Evaporation afforded 2.54 g of the crude product as a clear, pale yellow oil. Flash chromatography (EtOAc/hexane 1:1) of 2.16 g of the crude product afforded 0.58 g (57%) of 3 as a colorless, solid foam. An analytically pure sample was prepared by preparative HPLC (MeOH/H2O 6:4, 1.5 mm) as a colorless, solid foam: 1H-NMR (300 MHz, DMSO-d6) δ 1.00 (s, 3H), 1.10 (s, 3H), 3.27–3.37 (m, 1H), 3.65 (dd, J = 10.7, 8.2, 5.5 Hz, 1H), 3.81–4.19 (m, 5H), 4.38 (dd, J = 9.2, 6.3 Hz, 1H), 4.76 (d, J = 4.8 Hz, 1H, exchangeable with D2O), 4.78 (d, J = 5.5 Hz, 1H, exchangeable with D2O), 5.23 (dd, J = 9.2, 4.8 Hz, 1H), 7.23–7.42 (m, 7H), 7.59 (d, J = 7.3 Hz, 1H), 7.65 (d, J = 7.4 Hz, 1H); 13C-NMR (75 MHz, DMSO-d6) δ 25.0 (q), 27.6 (q), 60.6 (t), 64.2 (t), 64.7 (t), 65.0 (d), 78.0 (d), 79.1 (d), 107.1 (s), 109.1 (s), 126.4 (d), 126.7 (d), 127.7 (d), 127.9 (d), 128.1 (d), 128.4 (s), 139.3 (s), 140.9 (s), 142.1 (s); IR (Nal, film) 3412, 3063, 2036, 1473, 1371, 1217, 1271, 1048, 757, 700 cm−1; MS (CI) m/z 387 [M + H]+, 386 [M]+, 371, 368, 353, 352, 308, 295; TLC (EtOAc/hexane 1:1) Rf 0.28; mp 42–47 °C; [α]D25 +74.7° (c 1.35, MeOH). Anal.

1,4-chelation involving the primary alcohohate anion appears most likely (I). In fact, a similar re-selectivity has also been observed in the additions of other organo-magnesium compounds to the 1-erythrofuranose 2. The central intermediate. It was shown that Grignard reagents can be added to this furanose with extremely high anti-/like-selectivity. Most likely, efficient chelate control accounts for the selectivity of this process. It is expected that the model systems described in this paper will for the first time allow for the selective, photochemical generation and study of the radicals postulated as intermediates in the catalytic cycle of the ribonucleotide reductases (RNRs). Furthermore, the modular character of our synthetic sequence [Grignard addition to the erythofuranose 2, elaboration to furanoses of the type 9/10 or simpler, “base-free” structures of the type 5 (Scheme 3)] may provide a wide variety of other nucleoside analogs—potentially even by combinatorial methods.
Calcd for C$_{22}$H$_{24}$O$_{5}$: C, 71.82; H, 5.67. Anal. Calcd for C$_{17}$H$_{16}$O$_{4}$: C, 71.82; H, 5.67. Found: C, 71.81; H, 5.63.

A suspension of 128 mg (0.34 mmol) of 8 in 40 mL of anhydrous MeOH was added to a solution of 771 mg (1.27 mmol) of powdered NaOH. The suspension was stirred at room temperature for 23 h. The reaction mixture was then partitioned between 50 mL of water and 50 mL of Et$_2$O. The layers were separated, and the aqueous layer was extracted with 2 × 50 mL of CH$_2$Cl$_2$. The combined organic phases were washed with 2 × 50 mL of water, dried over MgSO$_4$, and rota-evaporated. Purification of the crude product by flash chromatography (EtOAc/hexane 1:1) afforded 978 mg (92%) of 9 as a colorless foam. 1H-NMR (300 MHz, DMSO-d$_6$) δ 7.75 (m, 1H), 7.70 (d, J = 6.6 Hz, 1H), 7.40 (d, J = 6.3 Hz, 1H), 7.30 (d, J = 4.3 Hz, 1H), 7.15 (d, J = 6.3 Hz, 1H), 5.21 (s, 2H), 4.63 (d, J = 6.3 Hz, 1H), 4.25 (t, J = 6.6 Hz, 1H), 3.80 (d, J = 6.6 Hz, 1H), 3.75 (q, J = 6.6 Hz, 1H), 2.90 (s, 3H), 1.95 (s, 3H), 0.90 (s, 3H).

**X-ray Structural Analysis of 8.** Single crystals suitable for X-ray structural analysis were obtained by slow evaporation of a solution of 8 in Et$_2$O at room temperature. X-ray crystal dimensions: 0.40 × 0.30 × 0.40 mm. Crystal data: monoclinic P2$_1$; a = 1143 (1) pm, b = 1016.5 (6) pm, c = 1250 (1) pm, β = 106.00 (8)°, V = 1395.50 × 10$^3$ pm$^3$; Z = 2; D$_c$ = 1.192 g cm$^{-3}$ (200 K), number of reflections used for unit cell parameter refinement 24. Data were collected at 200 K on a Siemens SMART R3M V diffractometer using a graphite monochromator and Mo Kα radiation; scan range: 2$\theta$ < 45.1°, $2\theta$-scan with $\Delta \omega$ = 0.75°, scan rate 6.0–29.3°/min, number of reflections collected: 2035, independent reflections: 1929, number of unique data with I > 2σ(I): 1843. Applied corrections: Lorentz and polarization correction; exp. absorption

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**Table 1:** Selected 1H and 13C NMR Data for Compound 8 (DMSO-d$_6$).
correction, Ψ-scan (ΔΨ = 10°). The structure was solved by direct methods using SHELXTL and SHELX93 and refined by least squares procedures.29

Refined parameters: 326, maximum residual electron density: 0.29 × 10⁻⁶ eÅ⁻³, R₁ = 0.0311, R_w = 0.082 (F² refinement).30

[3AR-[3α,4β,6α,9α])-Tetrahydro-2,2-dimethyl-6-(2-(phenyl-1,3-dioxolan-2-yl)phenyl)furo[3,4-d]-1,3-dioxol-4(9)]. (a) From 8. International Tables for X-ray Crystallography


8.5 mg (104 µmol) of 8. Anhydrous CH₂Cl₂ was added to a suspension of 4.6 mg (56 µmol) of NaOAc and 67.1 mg (311 µmol) of PCC in 0.5 mL of anhydrous CH₂Cl₂ in a dropwise manner at room temperature. After the mixture was stirred for 2.5 h, another 68.2 mg (316 µmol) of PCC was added and stirring was continued for 16 h. The reaction mixture was filtered through Celite. The filtrate was washed with 2 × 5 mL of anhydrous Et₂O, 7.28 × 10⁻³ Hz, 1H), 5.50 (s, 1H), 6.93 (d, J = 7.7, 1.1 Hz, 1H), 7.28–7.42 (m, 7H), 7.57 (dd, J = 7.4, 4.0, 3.3 Hz, 1H); 13C-NMR (75 MHz, DMSO-d₆) δ 128.2 (d), 128.4 (d), 128.7 (d), 129.3 (d), 138.3 (s), 139.6 (s), 153.9 (s), 153.9 (s), 153.9 (s), 197.9 (s); IR (NaCl, film) ν 2975, 1742, 1601, 1573, 1371, 1253, 1079, 1057, 767, 735, 705 cm⁻¹; TLC (EtOAc/hexane 8:2) Rₗ 0.28; mp 48–55 °C; [α]D₉² –2.9°, [α]D₉² +4.6°, [α]D₉² +10.9° –120.2° (c 1.10, CH₂Cl₂); HRMS m/z 310.0853 (M⁺, 310.0841 calcd for C₁₈H₁₄O₇S₂). Anal. Calcd for C₁₈H₁₄O₇S₂: C, 52.00; H, 4.57; S, 14.47.

[2R-2α,3′/4′/4′)-Phenyl[2-(tetrahydro-3,4-dimethoxy-2-furanyl)phenyl]methanone (12). Under argon, a solution of 500 mg (1.76 mmol) of 4 in 5 mL of anhydrous CH₂Cl₂ was added to a suspension of 1.35 g (9.13 mmol) of trimethylxionium difluoroborate and 823 g (3.88 mmol) of 1,8-bis(dimethylamino)naphthalene in 60 mL of anhydrous CH₂Cl₂ at room temperature. The mixture was stirred for 3 d, and another 530 mg (3.58 mmol) of trimethylxionium difluoroborate and 823 g (3.88 mmol) of 1,8-bis(dimethylamino)naphthalene were added. Stirring was continued for 1 d, and 50 mL of CH₂Cl₂ and 50 mL of water were added. The layers were separated, and the aqueous layer was extracted with 2 × 50 mL of CH₂Cl₂. The combined organic phases were washed with 5% K₂CO₃ and 2 × 50 mL of water, dried over MgSO₄, and evaporated. Purification of the crude product by column chromatography (EtOAc/hexane 2:8, two runs) and preparative HPLC (MeOH/H₂O 65:35, tₐ 14.7 min) afforded 301 mg (55%) of 12 as colorless crystals: 1H-NMR (300 MHz, CDCl₃) δ 3.37 (s, 3H), 3.38 (s, 3H), 3.76 (dd, δ = 9.8, 4.1 Hz, 1H), 3.81 (dd, δ = 9.9, 2.6 Hz, 1H), 3.92–3.98 (m, 2H), 4.99 (d, δ = 6.6, 1.5 Hz, 1H), 7.21 (d, δ = 7.4 Hz, 1H), 7.34 (dd, δ = 7.5, 6.3, 1.2 Hz, 1H), 7.38–7.47 (m, 4H), 7.51–7.57 (m, 1H), 7.76–7.79 (m, 2H); 13C-NMR (75 MHz, CDCl₃) δ 57.4 (q), 58.2 (q), 69.5 (t), 78.9 (t), 81.4 (d), 86.5 (d), 126.9 (d), 127.4 (d), 128.3 (d), 129.2 (d), 129.8 (d), 132.9 (d), 137.5 (s), 137.6 (s), 139.7 (s), 197.9 (s); IR (KBr, pellet) 3056, 2894, 1657, 1595, 1450, 1135, 1074, 935, 720, 703 cm⁻¹; TLC (EtOAc/hexane 8:2) Rₗ 0.34; mp 58–61 °C; [α]D₉² –13.8° (c 1.53, CHCl₃); HRMS m/z 312.1346 (M⁺, 312.1362 calcd for C₁₉H₁₈O₈S₂). Anal. Calcd for C₁₉H₁₈O₈S₂: C, 52.00; H, 4.57; S, 14.47.

[2R-2α,3′/4′/4′)-Phenyl[2-(tetrahydro-3,4-bis(methylsulfonyl)oxy)-2-furanyl]phenyl]methanone (13). To a solution of 417 mg (1.47 mmol) of 5 in 15 mL of anhydrous CH₂Cl₂ were added 1.22 mL (8.80 mmol) of Et₃N and 0.57 mL (5.73 mmol) of K₂CO₃ at room temperature under argon. After the mixture was stirred for 17 h, 10 mL of saturated aqueous NaHCO₃ was added. The layers were separated, and the aqueous layer was extracted with 2 × 10 mL of CH₂Cl₂. The combined organic phases were dried over MgSO₄, and evaporated. Purification of the crude product by radial chromatography (EtOAc/hexane 2:8, 2:8, two runs) and preparative HPLC (MeOH/H₂O 64:16, tₐ 16.0 min) afforded 612 mg (93%) of 13 as a colorless solid: 1H-NMR (300 MHz, CDCl₃) δ 2.90 (s, 3H), 3.13 (s, 3H), 4.02 (dd, δ = 10.7, 3.3 Hz, 1H), 4.13 (dd, δ = 10.7, 4.7 Hz, 1H), 5.12 (d, δ = 7.0 Hz, 1H), 5.27 (pseudo dd, δ ≈ 8, 5 Hz, 1H), 5.36 (dd, δ = 4.8, 1.0 Hz, 1H), 7.31 (d, δ = 7.7 Hz, 1H), 7.39–7.67 (m, 2H), 7.74–7.77 (m, 1H); 13C-NMR (75 MHz, CDCl₃) δ 38.1 (q), 38.6 (q), 71.2 (t), 76.8 (d), 80.7 (d), 82.0 (d), 128.1 (d), 128.2 (d), 128.5 (d), 128.8 (d), 130.1 (d), 133.2 (d), 133.6 (s), 137.1 (s), 137.6 (s), 198.0 (s); IR (KBr, pellet) 2983, 2800, 1596, 1449, 1363, 1178, 935, 766, 704 cm⁻¹; MS (Cl) m/z 441 (M + H⁺), 345, 249; TLC (EtOAc/hexane 2:1) Rₗ 0.15; mp 55–62 °C; [α]D₉² +1.5°, [α]D₉₂ +0.7°, [α]D₉₂ –2.6°, [α]D₉₂ –58.3° (c 1.22, CHCl₃). Anal. Calcd for C₁₉H₁₈O₂S₂: C, 51.81; H, 4.58, S, 14.56. Found: C, 52.00; H, 4.57; S, 14.47.
Synthesis of Substituted Nucleoside Derivatives


naphthalene and 26 mg (176 μmol) of trimethylxonium tetrafluoroborate in 0.2 mL of anhydrous CH2Cl2 at room temperature. The mixture was stirred for 7 d at room temperature, and 1.5 mL of CH2Cl2 and 1.5 mL of water were added. The layers were separated, and the aqueous layer was extracted with 2 × 0.7 mL of CH2Cl2. The combined organic phases were washed with 2 × 1.0 mL of 5% K2CO3 and 1.0 mL of water, dried over MgSO4, filtered through silica gel, and rota-evaporated. Purification of the crude product (74 mg) by radial chromatography (gradient: EtOAc/hexane 1:9, 2:8, 3:7, 6:4) afforded a mixture of the two isomers: 5.2 mg (10%) 14 and 9.7 mg (19%) 15 (determined by NMR). The isomers 14 and 15 were separated by preparative HPLC (MeCN/H2O 4:6).

14: 1H-NMR (300 MHz, DMso-d6) δ 3.30 (s, 3H), 3.57 (dd, J = 9.6, 2.3 Hz, 1H), 3.63 (dd, J = 9.6, 3.7 Hz, 1H), 3.69 (dd, J = 4.4, 3.7, 2.3 Hz, 1H), 4.05 (dd, J = 7.9, 7.4, 4.4 Hz, 1H), 4.67 (d, J = 7.9 Hz, 1H), 5.08 (d, J = 7.4 Hz, 1H, exchangeable with D2O), 7.21 (d, J = 7.4 Hz, 1H), 7.35–7.40 (m, 1H), 7.46–7.52 (m, 4H), 7.60–7.67 (m, 3H); TLC (EtOAc/hexane 8:2) Rf 0.53; preparative HPLC tR 19.4 min.

15: 1H-NMR (300 MHz, DMso-d6) δ 3.15 (s, 3H), 3.52 (dd, J = 9.6, 2.2 Hz, 1H), 3.61 (dd, J = 7.9, 4.3 Hz, 1H), 3.77 (dd, J = 9.6, 4.1 Hz, 1H), 4.22 (dddd, J = 4.4, 4.3, 4.1, 2.2 Hz, 1H), 4.81 (d, J = 7.9 Hz, 1H), 4.90 (d, J = 4.4 Hz, 1H, exchangeable with D2O), 7.20–7.23 (m, 1H), 7.36–7.42 (m, 1H), 7.47–7.54 (m, 4H), 7.60–7.69 (m, 3H); TLC (EtOAc/hexane 8:2) Rf 0.53; preparative HPLC tR 17.3 min.


To a solution of 100 mg (352 μmol) of 5 and 73 μL (528 μmol) of Et3N in 2 mL of anhydrous CH2Cl2 were added 30 μL (387 μmol) of Me3Cl at −40 °C under argon. After the solution was stirred for 2 h at −40 °C and 45 h at room temperature, 10 mL of CH2Cl2 and 20 mL of saturated aqueous NaHCO3 were added. The layers were separated, and the aqueous layer was extracted with 2 × 10 mL of CH2Cl2. The combined organic phases were dried over MgSO4 and rota-evaporated. Purification of the crude product by flash chromatography (Et2O/hexane 2:1) afforded (1) 30 mg pure 13 as a colorless, viscous oil; (2) 51 mg of a mixture of 13, 16, and 17 (13 16:17 1.0:6:1, determined by NMR) as a colorless, viscous oil, and (3) 16 mg of a mixture of 16 and 17 (16:17 1.0:1.2, determined by NMR) as a colorless oil (yields: 13, 24%, 16, 33%, 17, 14%). The isomers 16 and 17 were separated by preparative HPLC (MeCN/H2O 4:6).

16: 1H-NMR (300 MHz, CDC13) δ 3.31 (s, 3H), 4.13 (ddd, J = 8.5, 4.4, 3.7 Hz, 1H), 4.16 (dd, J = 11.0, 1.8 Hz, 1H), 4.43 (dd, J = 11.0, 4.1 Hz, 1H), 4.99 (d, J = 8.5 Hz, 1H), 5.19 (d, J = 3.7, 1H, exchangeable with D2O), 5.26 (ddd, J = 4.4, 4.1, 1.8 Hz, 1H), 7.33–7.41 (m, 2H), 7.44–7.49 (m, 2H), 7.57–7.65 (m, 2H), 7.71–7.80 (m, 3H); 13C-NMR (75 MHz, CDC13) δ 39.1 (q), 71.7 (t), 76.9 (d), 80.1 (d), 81.1 (d), 126.8 (d), 127.1 (d), 128.5 (d), 130.0 (d), 131.0 (d), 132.0 (d), 133.8 (d), 137.0 (s), 137.2 (s), 140.4 (s), 198.8 (s); TLC (Et2O/hexane 2:1) Rf 0.10; analytical HPLC (MeCN/H2O 4:6) tR 17.7 min.

17: 1H-NMR (300 MHz, CDC13) δ 2.97 (s, 3H), 3.79 (dd, J = 9.6, 4.4 Hz, 1H), 4.10 (dd, J = 9.6, 5.1 Hz, 1H), 4.55 (pseudo dd, J = 4.8, 4.4 Hz, 1H), 5.08 (dd, J = 6.2, 4.8 Hz, 1H), 5.16 (d, J = 6.2 Hz, 1H), 7.29–7.60 (m, 7H), 7.74–7.77 (m, 2H); 13C-NMR (75 MHz, CDC13) δ 38.1 (q), 70.2 (t), 72.5 (d), 80.2 (d), 85.4 (d), 127.6 (d), 127.8 (d), 128.5 (d), 128.7 (d), 130.1 (d), 130.3 (d), 133.3 (d), 137.3 (s), 137.6 (s), 137.8 (s), 197.7 (s); TLC (Et2O/hexane 2:1) Rf 0.10; analytical HPLC (MeCN/H2O 4:6) tR 15.7 min.

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