Stereoselective Synthesis of 4′-Benzophenone-Substituted Nucleoside Analogs: Photoactive Models for Ribonucleotide Reductases†

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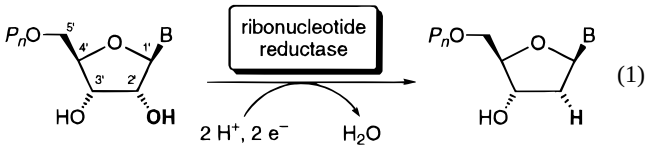
Ribonucleotide reductases (RNRs) catalyze the 2′-reduction of ribonucleotides, thus providing 2′-deoxyribonucleotides, the monomers for DNA biosynthesis. The current mechanistic hypothesis for the catalysis effected by this class of enzymes involves a sequence of radical reactions. A reversible 3′-hydrogen 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′-hydroxyl 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).[1] Therefore, RNRs play a central role in



(1)

DNA biosynthesis and in cell division, and they are potential drug targets for tumor and viral diseases.[2] A mechanism involving the radicals **A**−**C** has been proposed for the action of ribonucleotide reductases (Scheme 1).[3] 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 H_a 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 cysteine/cysteinate 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 H_a 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 cysteine thiol groups, the enzyme is ready for the next turnover. This proposed mechanism of catalysis is based on studies with isotopically labeled substrates[4] and substrate analogs,[5] as well as on the investigation of enzymes modified by site-directed mutagenesis.[6] Most importantly, at least one of the three classes of RNRs is known to harbor a stable tyrosyl radical.[7] In fact, the so-called "aerobic" RNR from *E. coli* was the first radical enzyme found.[1] Finally, the X-ray

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† Dedicated to Professor Waldemar Adam on the occasion of his 60th birthday.

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(7) See refs 1a and 6a.

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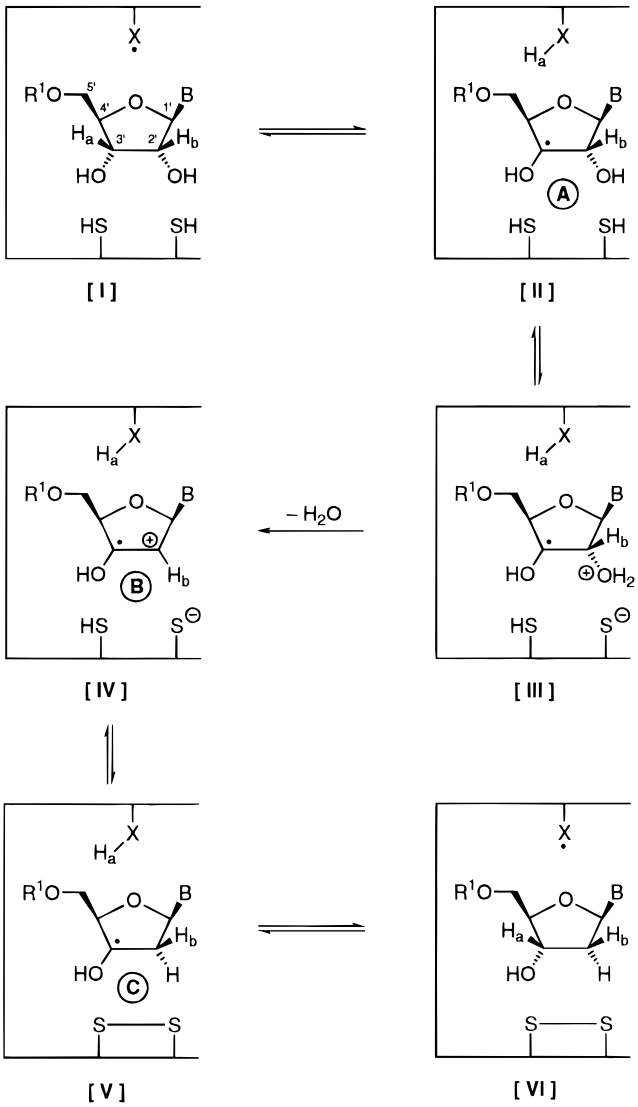
Scheme 1. Postulated Mechanism of Ribonucleotide Reductases

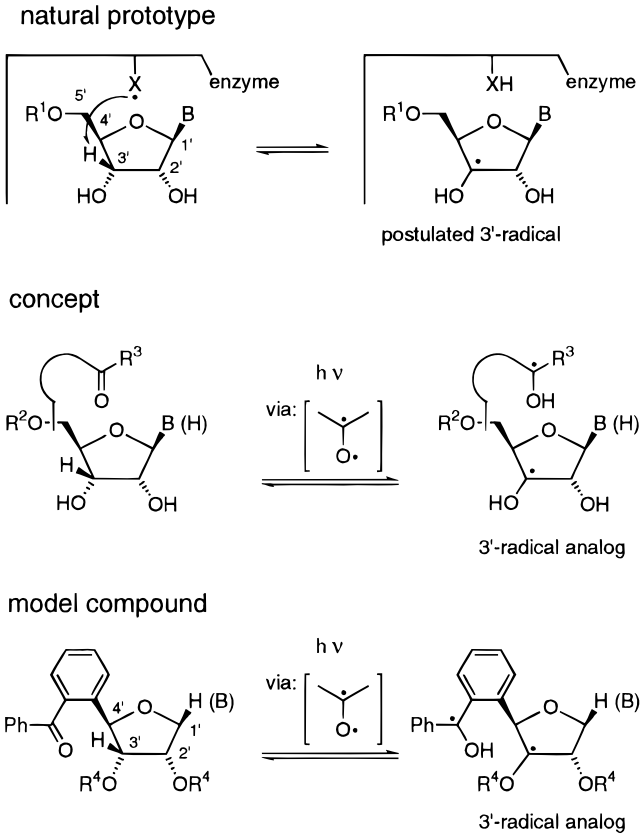


X•: protein radical; B: nucleobase; R^1: *PP* or *PPP*

crystal structures of the two protein subunits (R1 and R2) of this enzyme, which have become available only recently,[8] 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.[8]

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

Scheme 2. Design of Model Compounds



X•: protein radical; B: nucleobase; R^1: *PP* or *PPP*; R^2: *PP* or *PPP* or H; R^3: Alkyl, Aryl; R^4: H, Me, Ms or R^4,R^4 = CO

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[9] for RNR-type regioselective deoxygenations of polyols/carbohydrates.

Carbonyl compounds, and in particular benzophenones, are able to initiate reversible homolytic hydrogen abstractions upon photochemical excitation into their triplet states.[10] 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[11] (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.[12] Eight are simplified nucleoside analogs in that the nucleobase is replaced by a hydrogen atom. The ninth one possesses

(8) (a) Uhlin, U.; Eklund, H. *Nature* **1994**, *370*, 533. (b) Nordlund, P.; Sjöberg, B.-M.; Eklund, H. *Nature* **1990**, *345*, 593.

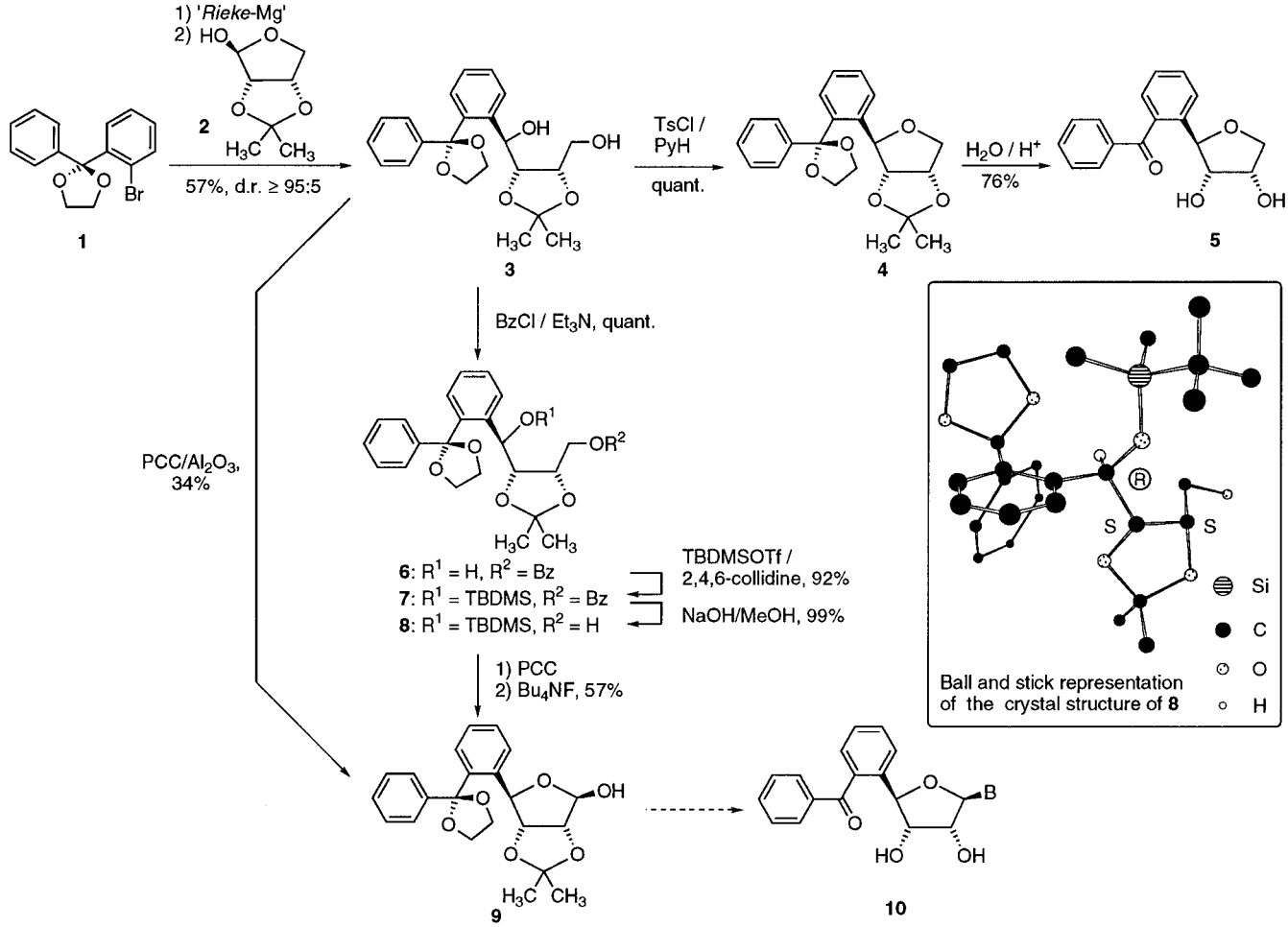
(9) Breslow, R. *Chem. Soc. Rev.* **1972**, *1*, 553.

(10) (a) Wagner, P.; Park, B.-S. In *Organic Photochemistry;* Pawda, A., Ed.; Dekker: New York, 1991; Vol. 11; p 227. (b) Wagner, P. J. *Top. Curr. Chem.* **1976**, *66*, 1. (c) Wagner, P. J. *Acc. Chem. Res.* **1971**, *4*, 168.

(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.

(12) Lehmann, T. E. Dissertation, Universität Heidelberg, 1995.

Scheme 3. Synthesis of 4′-Benzophenone-Substituted Nucleoside Derivatives



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.[13]

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.[14,15] They were synthesized by modified literature procedures[14,15] 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.[16] The protected erythrofuranose **2** was treated with 3 equiv of the organomagnesium reagent in THF. The addition proceeded with excellent *anti*-(*like*-)selectivity;[17] 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[18] 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

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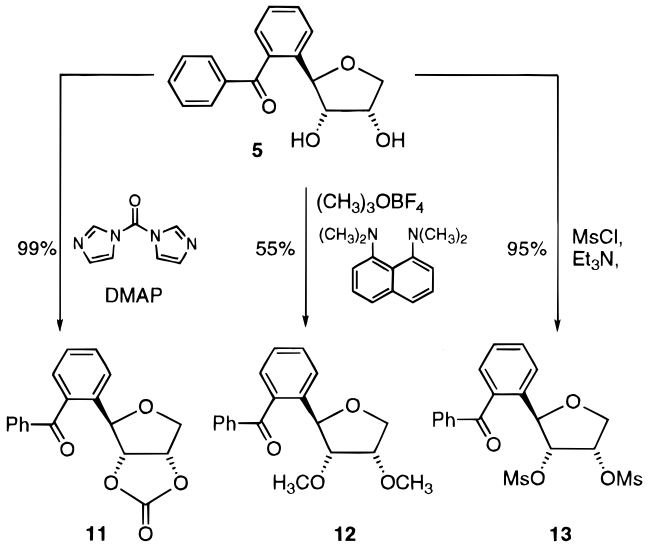
(14) Lohner, W.; Praefcke, K. *J. Organomet. Chem.* **1981**, *205*, 167.
(15) Baxter, J. N.; Perlin, A. S. *Can. J. Chem.* **1960**, *38*, 2217.
(16) (a) Rieke, R. D. *Acc. Chem. Res.* **1977**, *10*, 301. (b) Rieke, R. D.; Bales, S. E. *J. Am. Chem. Soc.* **1974**, *96*, 1175. Nonactivated magnesium failed to react with **1**. Activating agents such as I_2 or CCl_4 had no effect.
(17) For definitions see: (a) Masamune, S.; Kaiho, T.; Garvey, D. S. *J. Am. Chem. Soc.* **1982**, *104*, 5521. (b) Seebach, D.; Prelog, V. *Angew. Chem.* **1982**, *94*, 696; *Angew. Chem., Int. Ed. Engl.* **1982**, *21*, 654. For a recent review see: Helmchen, G. In *Stereoselective Synthesis, Methods of Organic Chemistry (Houben-Weyl)*; Helmchen, G., Hoffmann, R. W., Mulzer, J., Schaumann, E., Eds.; Thieme: Stuttgart, 1995; Vol. E 21a; p 1.
(18) (a) Saenger, W. *Principles of Nucleic Acid Structure*, 2nd ed.; Springer: Heidelberg, 1988; p 48. (b) Davies, D. B., *Prog. NMR Spectrosc.* **1978**, *12*, 135.

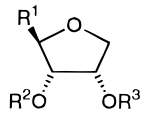
Scheme 4. Synthesis of Di-O-substituted Derivatives of 5



interpreted by nucleophilic displacement of the primary tosylate by the secondary (benzylic) hydroxyl group. Consequently, the configuration at the benzylic position should remain unchanged. In fact, only one diastereomer was formed. As mentioned above, the (*R*)-configuration of the benzylic stereogenic center could clearly be deduced from the vicinal H−C−C−H coupling constant[18] $^3J_{4'H-3'H}$ = 2.2 Hz measured for the bicycle **4**. ^3J values below 3 Hz strongly indicate a *trans*-relationship for the corresponding protons, whereas a *cis*-configuration should result in ^3J values larger than 3.5 Hz.[18] The model compound **5** was finally obtained in 76% yield by deprotection of the bis-dioxolane **4**. Thus, the final product **5** was synthesized in a stereospecific manner, starting from commercially available L-(+)-rhamnose in 29% overall yield.

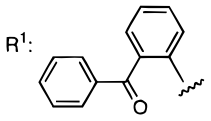
The proposed mechanism of RNR action involves the acid-catalyzed elimination of the 2′-hydroxyl group from the 3′-radical (Scheme 1, II → III → IV). For the successful modeling of this reaction step, it may well be necessary to "tune" the nucleofugal properties of the 2′-hydroxyl group by derivatization. For example, treatment of the diol **5** with 1,1′-carbonyldiimidazole/DMAP gave the bicyclic carbonate **11** in 99% yield (Scheme 4). The dimethyl ether **12** was obtained from **5** by alkylation using the methyl Meerwein salt in the presence of the proton sponge 1,8-bis(dimethylamino)naphthalene[19] (55%). Finally, the bismesylate **13** was synthesized from **5** and mesyl chloride/triethyl amine in 95% yield.

Numerous attempts were made to selectively prepare the 2′- or 3′-monomethylated or monomesylated derivatives of **5**. Under a variety of reaction conditions, mixtures of both monoderivatized products and the dimethyl ether **12** or the bismesylate **13**, respectively, were obtained. Although their separation—even by preparative HPLC—proved difficult, we were able to isolate the compounds **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 $^3J_{OH-CH}$-couplings in the ^{1}H-NMR spectra.



14–17

14: R^2 = H, R^3 = CH_3
15: R^2 = CH_3, R^3 = H
16: R^2 = H, R^3 = Ms
17: R^2 = Ms, R^3 = H



In order to provide access to model compounds carrying a nucleobase in the 1′-position, the primary hydroxyl group of the diol **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 **9** was synthesized from the diol **3** in five steps and 52% overall yield. In the first step, the primary hydroxyl group of **3** was selectively benzoylated, and the ester **6** was obtained quantitatively. Treatment with TBDMSOTf[20] afforded the doubly protected compound **7** in 92% yield. Basic hydrolysis yielded the primary alcohol **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 **8**, together with the known absolute configuration of the two stereogenic centers derived from 2,3-*O*-isopropylidene-*β*-L-erythrofuranose (**2**), allowed for the unambiguous assignment of the (*R*)-configuration to the newly formed benzylic stereocenter. The oxidation of **8** with PCC and the removal of the silyl group with Bu_4NF afforded the benzophenone-substituted furanose **9** in 57% yield. The latter approach (one-step oxidation of the diol **3**) gave the desired furanose **9** in 34% yield. The furanose **9** is in the oxidation state required for the nucleophilic introduction of a nucleobase by the Vorbrüggen method.[21] It may thus serve as a precursor for the model system of type **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 **1** to the erythrose **2**. The mechanism accounting for the observed extreme selectivity merits further consideration. The presence of Lewis-acidic magnesium salts suggests a chelate-controlled[22] addition of the nucleophile to the ring-opened form of the erythrose **2**. Besides the carbonyl oxygen atom, the molecule contains three further oxygen atoms that may participate in chelating a magnesium ion (formulas **I**−**III**). Since the *re*-face of the aldehyde is attacked, a

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

(20) TBDMSCl failed to react with the sterically hindered secondary hydroxyl goup.

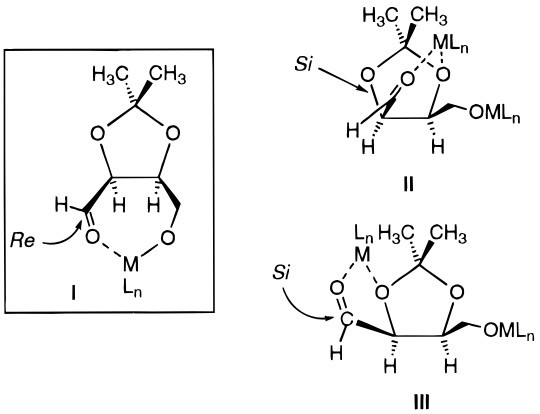
(21) Vorbrüggen, H.; Bennua, B. *Chem. Ber.* **1981**, *114*, 1279.

(22) (a) Reetz, M. T. *Angew. Chem.* **1984**, *96*, 542; *Angew. Chem., Int. Ed. Engl.* **1984**, *23*, 556. (b) Devant, R. M.; Radunz, H.-E. Formation of C−C Bonds by Addition To Carbonyl Groups, Addition of s-Type Organometallic Compounds. In *Stereoselective Synthesis, Methods of Organic Chemistry (Houben-Weyl)*; Helmchen, G., Hoffmann, R. W., Mulzer, J., Schaumann, E., Eds.; Thieme: Stuttgart, 1995; Vol. E 21 b; p 1151.

(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 **2** (see ref 24). However, the authors of ref 24 do not state how the configurational assignment was done.

(24) Williams, D. R.; Klingler, F. D. *J. Org. Chem.* **1988**, *53*, 2134.

1,4-chelation involving the primary alcoholate anion appears most likely (**I**). In fact, a similar *re*-selectivity has also been observed in the additions of other organomagnesium compounds to the L-erythrosefuranose **2**.[23,24]



Conclusion

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 monomesylated compounds **14**−**17**, quite reasonable overall yields were achieved (16−29%). In our approach, 2,3-*O*-isopropylidene-*β*-L-erythrofuranose **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).[13] Furthermore, the modular character of our synthetic sequence [Grignard addition to the erythrofuranose **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.[25]

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/Al_2O_3 were prepared according to Corey et al.[26] and Tietze et al.[27] respectively. All solvents were distilled. Methylene chloride was stirred for 2 d with concd sulfuric acid, decanted, washed with water and aqueous $NaHCO_3$, dried over $MgSO_4$, distilled from P_4O_{10}, and stored over 4 Å molecular sieves. THF was distilled from sodium benzophenone ketyl prior to use. Triethylamine and pyridine were distilled from CaH_2 and stored over 3.3 Å molecular sieves. Methanol was distilled from magnesium. Flash chromatography was carried out on E. Merck or Macherey-Nagel silica gel 60 (230−400 mesh). Radial chromatography was performed on a Harrison Research Chromatotron Model 8924 with E. Merck silica gel 60 PF_{254} (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 RP-18, 5 μm, 250 × 4 mm column at a flow rate of 0.7 mL/min. For the other analytical instrumentation used, see ref 28.

2-(2-Bromophenyl)-2-phenyl-1,3-dioxolane (1) was prepared in 3 steps from 2-bromobenzoic acid by the method of Praefcke et al.[14] in 65% yield as a colorless, crystalline solid: ^{1}H-NMR (300 MHz, $CDCl_3$) δ 3.99−4.06 (m, 2H), 4.10−4.24 (m, 2H), 7.19 (ddd, J = 7.7, 7.7, 1.8 Hz, 1H), 7.30−7.34 (m, 3H), 7.37 (ddd, J = 7.7, 7.7, 1.1 Hz, 1H), 7.42−7.47 (m, 2H), 7.58 (dd, J = 7.7, 1.1 Hz, 1H), 7.86 (dd, J = 7.7, 1.8 Hz, 1H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 65.1 (t), 109.5 (s), 121.9 (s), 126.6 (d), 126.7 (d), 127.8 (d), 128.2 (d), 128.7 (d), 129.8 (d), 135.0 (d), 140.1 (s), 140.4 (s); IR (KBr, pellet) 3058, 2887, 1585, 1447, 1206, 1092, 1074, 1026, 765, 703 cm^{-1}; TLC (EtOAc/hexane 1:1) R_f 0.56; mp 137 °C (lit.[14] mp 137 °C). Anal. Calcd for $C_{15}H_{13}BrO_2$: C, 59.04; H, 4.29. Found: C, 59.14; H, 4.38.

[3a*S*-(3aα,4α,6aα)]-Tetrahydro-2,2-dimethyl-furo[3,4-*d*]-1,3-dioxol-4-ol (2,3-*O*-isopropylidene-*β*-L-erythrofuranose) (2) was prepared in three steps from L-(+)-rhamnose by the method of Perlin et al.[15] in 67% yield as a colorless, crystalline solid: ^{1}H-NMR (300 MHz, DMSO-d_6) δ 1.22 (s, 3 H), 1.33 (s, 3 H), 3.76 (d, J = 10.3 Hz, 1 H), 3.84 (dd, J = 10.3, 3.5 Hz, 1 H), 4.38 (d, J = 5.9 Hz, 1 H), 4.77 (dd, J = 5.9, 3.5 Hz, 1 H), 5.14 (d, J = 4.1 Hz, 1 H), 6.23 (d, J = 4.1 Hz, 1 H, exchangeable with D_2O); ^{13}C-NMR (75 MHz, DMSO-d_6) δ 24.8 (q), 26.3 (q), 70.9 (t), 79.9 (d), 85.4 (d), 101.1 (d), 111.3 (s); IR (NaCl, film) 3428, 2987, 1459, 1375, 1101, 1069 cm^{-1}; TLC (EtOAc/hexane 1:1) R_f 0.29; mp 29.5−30 °C (lit.[15] mp 29−31 °C); $[\alpha]^{20}_D$ +74.8° (*c* 2.51, MeOH) [lit.[15] $[\alpha]^{20}_D$ +72° (*c* 2.4, MeOH)]. Anal. Calcd for $C_7H_{12}O_4$: C, 52.49; H, 7.55. Found: C, 52.72; H, 7.63.

[4*R*-[4α{*R},5α]]-2,2-Dimethyl-α^4-[2-(2-phenyl-1,3-dioxolan-2-yl)phenyl]-1,3-dioxolane-4,5-dimethanol (3).** A mixture of 1.78 g (18.7 mmol) of anhydrous $MgCl_2$, 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 black 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 NH_4Cl 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 NH_4Cl.) The layers were separated, and the aqueous layer was extracted with 2 × 100 mL of EtOAc and 100 mL of Et_2O. The combined organic phases were washed with 4 × 50 mL of water and dried over $MgSO_4$. 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 obtained by preparative HPLC (MeOH/H_2O 6:4, t_R 15.5 min) as a colorless, solid foam: ^{1}H-NMR (300 MHz, DMSO-d_6) δ 1.00 (s, 3H), 1.10 (s, 3H), 3.27−3.37 (m, 1H), 3.65 (ddd, 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 D_2O), 4.78 (d, J = 5.5 Hz, 1H, exchangeable with D_2O), 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); ^{13}C-NMR (75 MHz, DMSO-d_6) δ 25.0 (q), 27.6 (q), 60.6 (t), 64.2 (t), 64.7 (t), 65.0 (d), 78.0 (d), 79.2 (d), 107.1 (s), 109.1 (s), 126.1 (d), 126.4 (d), 126.7 (d), 127.7 (d), 127.9 (d), 128.1 (d), 128.4 (d), 139.3 (s), 140.9 (s), 142.1 (s); IR (NaCl, film) 3442, 3063, 2036, 1473, 1371, 1217, 1071, 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) R_f 0.28; mp 42−47 °C; $[\alpha]^{22}_D$ −74.7° (*c* 1.35, MeOH). Anal.

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Calcd for $C_{22}H_{26}O_6$: C, 68.38; H, 6.78. Found: C, 68.20; H, 6.86.

[3a*R*-(3aα,4α,6aα)]-Tetrahydro-2,2-dimethyl-4-[2-(2-phenyl-1,3-dioxolan-2-yl)phenyl]furo[3,4-*d*]-1,3-dioxole (4). Tosyl chloride [0.74 g (3.88 mmol)] was added to a solution of 1.50 g (3.88 mmol) of the diol **3** in 30 mL of anhydrous pyridine at −30 °C in small portions. The solution was allowed to warm to room temperature. After the solution was stirred for 2 d, an additional equivalent of TsCl was added with cooling as described above. After being stirred for 4 d at room temperature, the reaction mixture was taken up in a mixture of 50 mL of Et_2O and 50 mL of water. The organic layer was separated and washed with 50 mL of water. The combined aqueous layers were extracted with 2 × 25 mL of Et_2O. The combined organic phases were dried over $MgSO_4$ and rota-evaporated. Purification by flash chromatography (EtOAc/hexane 3:7) afforded 1.44 g (quantitative) of **4** as a clear, colorless oil. An analytically pure sample was obtained by radial chromatography (EtOAc/hexane 3:7): ^{1}H-NMR (300 MHz, DMSO-d_6) δ 1.20 (s, 3H), 1.40 (s, 3H), 3.72 (dd, J = 10.3, 2.9 Hz, 1H), 3.86−4.08 (m, 4 H), 4.13 (dd, J = 10.3, 5.5 Hz, 1H), 4.53 (dd, J = 6.3, 2.2 Hz, 1H), 4.88 (ddd, J = 6.3, 5.5, 2.9 Hz, 1H), 5.41 (d, J = 2.2 Hz, 1H), 7.27−7.38 (m, 8H), 7.58−7.62 (m, 1H); ^{13}C-NMR (75 MHz, DMSO-d_6) δ 25.1 (q), 27.0 (q), 64.5 (t), 64.6 (t), 73.4 (t), 80.3 (d), 82.3 (d), 86.9 (d), 109.3 (s), 111.8 (s), 126.4 (d), 127.3 (d), 127.5 (d), 128.1 (d), 128.3 (d), 128.7 (d), 138.6 (s), 138.7 (s), 141.7 (s); IR (NaCl, film) 3062, 2937, 1601, 1474, 1380, 1207, 1088, 1070, 759, 700 cm^{-1}; MS (EI) m/z 368 (M^+), 353, 323, 222, 177, 149, 105; TLC (EtOAc/hexane 1:1) R_f 0.76; $[\alpha]^{20}_D$ +18.4° (*c* 1.01, MeOH). Anal. Calcd for $C_{22}H_{24}O_5$: C, 71.72; H, 6.57. Found: C, 71.81; H, 6.63.

[2*R*-(2α,3*β*,4*β*)]-Phenyl[2-(tetrahydro-3,4-dihydroxy-2-furanyl)phenyl]methanone (5). A suspension of 128 mg (348 μmol) of **4** in 0.6 mL of AcOH/H_2O 4:1 was stirred under argon at room temperature for 7 d. It was then neutralized by the addition of 0.79 g of K_2CO_3 and 5 mL of water. The mixture was extracted with 3 × 5 mL of CH_2Cl_2. The combined organic phases were dried over $MgSO_4$ and rota-evaporated. Purification by flash chromatography (Et_2O/hexane 8:2) afforded 75 mg (76%) of **5** as colorless crystals. ^{1}H-NMR (200 MHz, DMSO-d_6) δ 3.43 (dd, J = 9.3, 1.7 Hz, 1H), 3.66 (dd, J = 9.3, 3.7 Hz, 1H), 3.87−4.00 (m, 2H), 4.65 (d, J = 7.3 Hz, 1H), 4.89 (d, J = 3.4 Hz, 1H, exchangeable with D_2O), 5.00 (d, J = 6.6 Hz, 1H, exchangeable with D_2O), 7.20 (d, J = 7.3 Hz, 1H), 7.34−7.53 (m, 5H), 7.58−7.69 (m, 3H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 71.6 (d), 73.7 (t), 79.6 (d), 80.5 (d), 126.6 (d), 126.8 (d), 128.5 (d), 129.8 (d), 131.0 (d), 132.0 (d), 133.8 (d), 136.6 (s), 137.1 (s), 141.7 (s), 199.0 (s); IR (NaCl, film) 3397, 3062, 2945, 1664, 1597, 1449, 1316, 1059, 936, 758, 703 cm^{-1}; MS (EI) m/z 284 (M^+), 266, 222, 211, 194, 133, 105; TLC (Et_2O/hexane 8:2) R_f 0.22; mp 90.5−91.5 °C; $[\alpha]^{20}_D$ −23.7° (*c* 0.38, EtOH). Anal. Calcd for $C_{17}H_{16}O_4$: C, 71.82; H, 5.67. Found: C, 71.54; H, 5.68.

[4*S*-[4α,5α(*S)]]-4-[(Benzoyloxy)methyl]-2,2-dimethyl-5-[[2-(2-phenyl-1,3-dioxolan-2-yl)phenyl]hydroxymethyl]-1,3-dioxolane (6).** To a solution of 1.00 g (2.59 mmol) of **3** in 40 mL of anhydrous CH_2Cl_2 were added 2.16 mL (15.5 mmol) of Et_3N and 0.90 mL (7.76 mmol) of benzoyl chloride at −45 °C. After being stirred for 7 h at ca. −40 °C, the reaction mixture was poured into 40 mL of cold water. The layers were separated, and the organic layer was washed with 40 mL of water. The combined aqueous layers were extracted with 3 × 20 mL of Et_2O. The combined organic phases were washed with 20 mL of water, dried over $MgSO_4$, and rota-evaporated. Purification by flash chromatography (EtOAc/hexane 3:7) afforded 1.28 g (quantitative) of **6** as a colorless foam: ^{1}H-NMR (300 MHz, DMSO-d_6) δ 1.05 (s, 3 H), 1.13 (s, 3 H), 3.85−4.08 (m, 4H), 4.25 (dd, J = 11.0, 7.0 Hz, 1H), 4.40−4.49 (m, 3 H), 4.94 (d, J = 5.2 Hz, 1 H, exchangeable with D_2O), 5.30 (dd, J = 8.5, 5.2 Hz, 1 H), 7.23−7.43 (m, 7 H), 7.50−7.55 (m, 2 H), 7.62−7.69 (m, 3 H), 7.99−8.02 (m, 2 H); ^{13}C-NMR (75 MHz, DMSO-d_6) δ 25.1 (q), 27.5 (q), 63.9 (t), 64.2 (t), 64.7 (t), 64.9 (d), 74.6 (d), 79.2 (d), 107.8 (s), 109.1 (s), 126.1 (d), 126.3 (d), 126.8 (d), 127.7 (d), 127.9 (d), 128.0 (d), 128.4 (d), 128.6 (d), 129.3 (d), 129.7 (s), 133.2 (d), 139.3 (s), 141.1 (s), 142.0 (s), 165.7 (s); IR (NaCl, film) 3516, 3063, 2936, 1720, 1602, 1451, 1381, 1275, 1217, 1098, 1070, 1027, 756, 713, 702 cm^{-1}; MS (EI) m/z 490 (M^+), 475, 428, 255, 235, 211, 177, 149, 105; TLC (EtOAc/hexane 3:7) R_f 0.33; mp 50−62 °C; $[\alpha]^{20}_D$ −40.5° (*c* 2.00, MeOH). Anal. Calcd for $C_{29}H_{30}O_7$: C, 71.01; H, 6.16. Found: C, 71.17; H, 6.33.

[4*S*-[4α,5α(*S)]]-4-[(Benzoyloxy)methyl]-5-[[[(1,1-dimethylethyl)dimethylsilyl]oxy][2-(2-phenyl-1,3-dioxolan-2-yl)phenyl]methyl]-2,2-dimethyl-1,3-dioxolane (7).** To a solution of 861 mg (1.76 mmol) of **6** in 1.8 mL of anhydrous CH_2Cl_2 were added at room temperature 0.51 mL (3.86 mmol) of 2,4,6-trimethylpyridine and 0.61 mL (2.64 mmol) of TBDMSOTf. After being stirred for 19 h at room temperature, the reaction mixture was poured into 10 mL of water. The layers were separated, and the aqueous layer was extracted with 3 × 20 mL of CH_2Cl_2. The combined organic layers were washed with 3 × 20 mL of water, dried over $MgSO_4$, and rota-evaporated. Purification of the crude product by flash chromatography (EtOAc/hexane 1:9) afforded 978 mg (92%) of **7** as a colorless foam: ^{1}H-NMR (300 MHz, DMSO-d_6) δ −0.64 (s, 3 H), −0.21 (s, 3 H), 0.77 (s, 9 H), 1.11 (s, 3 H), 1.25 (s, 3 H), 3.91−4.08 (m, 4 H), 4.18−4.24 (m, 2 H), 4.38−4.45 (m, 1H), 4.60−4.65 (m, 1H), 5.57 (d, J = 4.0 Hz, 1H), 7.28−7.75 (m, 12 H), 7.98−8.02 (m, 2H); ^{13}C-NMR (75 MHz, DMSO-d_6) δ −5.3 (q), −5.2 (q), 17.8 (s), 25.5 (q), 25.6 (q), 27.9 (q), 64.7 (t), 65.1 (t), 68.2 (d), 74.6 (d), 80.7 (d), 107.5 (s), 109.1 (s), 126.1 (d), 126.8 (d), 127.4 (d), 127.9 (d), 128.3 (d), 128.4 (d), 128.6 (d), 128.8 (d), 129.4 (d), 129.8 (s), 133.4 (d), 138.6 (s), 139.8 (s), 141.8 (s), 161.9 (s); IR (KBr, pellet) 3964, 2931, 1721, 1602, 1472, 1380, 1273, 1253, 1085, 1069, 838, 779, 712 cm^{-1}; TLC (EtOAc/hexane 1:9) R_f 0.26; mp 43−51 °C; $[\alpha]^{20}_D$ −90.2° (*c* 1.55, $CHCl_3$); HRMS m/z 604.2909 (M^+, 604.2856 calcd for $C_{35}H_{44}O_7Si$). Anal. Calcd for $C_{35}H_{44}O_7Si$: C, 69.51; H, 7.33. Found: C, 69.48; H, 7.39.

[4*S*-[4α,5α(*S)]]-5-[[[(1,1-Dimethylethyl)dimethylsilyl]oxy][2-(2-phenyl-1,3-dioxolan-2-yl)phenyl]methyl]-2,2-dimethyl-4-(hydroxymethyl)-1,3-dioxolane (8).** To a solution of 771 mg (1.27 mmol) of **7** in 40 mL of anhydrous MeOH was added 254 mg (6.35 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_2O. The layers were separated, and the aqueous layer was extracted with 2 × 50 mL of Et_2O. The combined organic phases were washed with 2 × 40 mL of water, dried over $MgSO_4$, and rota-evaporated. The crude product was purified by flash chromatography (EtOAc/hexane 3:7), affording 626 mg (99%) of **8** as colorless, crystals. ^{1}H-NMR (300 MHz, DMSO-d_6) δ −0.74 (s, 3H), −0.29 (s, 3H), 0.74 (s, 9H), 1.07 (s, 3H), 1.17 (s, 3H), 3.46 (ddd, J = 11.0, 9.2, 4.8 Hz, 1H), 3.67 (ddd, J = 11.0, 6.3, 2.9 Hz, 1H), 3.88−4.05 (m, 5H), 4.10 (dd, J = 6.6, 5.9 Hz, 1H), 4.39 (dd, J = 6.3, 4.8 Hz, 1H, exchangeable with D_2O), 5.41 (d, J = 6.6 Hz, 1H), 7.26−7.43 (m, 7H), 7.57 (dd, J = 7.6, 1.3 Hz, 1H), 7.70 (dd, J = 7.6, 1.6 Hz, 1H); ^{13}C-NMR (75 MHz, DMSO-d_6) δ −5.3 (q), −5.1 (q), 17.8 (s), 25.6 (q), 25.7 (q), 28.2 (q), 61.3 (t), 64.6 (t), 64.7 (t), 67.7 (d), 78.5 (d), 80.9 (d), 106.9 (s), 109.1 (s), 126.2 (d), 126.7 (d), 127.2 (d), 128.1 (d), 128.2 (d), 128.3 (d), 128.4 (d), 138.7 (s), 140.5 (s), 141.9 (s); IR (KBr, pellet) 3562, 1089, 1029, 840, 778 cm^{-1}; MS (CI) m/z 500 (M^+), 499 [($M - H$)$^+$], 485, 443, 439, 368, 325, 293, 249, 207, 149, 133, 115, 101; TLC (EtOAc/hexane 3:7) R_f 0.48; mp 144.5−145.5 °C; $[\alpha]^{20}_D$ −66.7° (*c* 0.68, MeOH). Anal. Calcd for $C_{28}H_{40}O_6Si$: C, 67.17; H, 8.05. Found: C, 67.21; H, 8.05.

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_2O at room temperature. 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 × 10^6 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 Nicolet Syntex R3m/V diffractometer using a graphite monochromator and Mo Kα radiation; scan range 3.4° < 2θ < 45.1°; ω-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 $I > 2\sigma$: 1843. Applied corrections: Lorentz and polarization correction; exp. absorption

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} e/pm^3, R_1 = 0.0311, R_w = 0.082 (F^2 refinement).[30]

[3a*R*-(3aα,4α,6α,6aα)]-Tetrahydro-2,2-dimethyl-6-[2-(2-phenyl-1,3-dioxolan-2-yl)phenyl]furo[3,4-*d*]-1,3-dioxol-4-ol (9). (a) From 8. A solution of 100 mg (200 μmol) of **8** in 0.4 mL of anhydrous CH_2Cl_2 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 CH_2Cl_2 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 × 1 mL of water, and the aqueous phase was extracted with 1 mL of CH_2Cl_2. The combined organic phases were dried over $MgSO_4$, filtered through Celite and silica gel, and evaporated. The resulting clear, colorless oil (83 mg) was dissolved in 0.9 mL of anhydrous THF and 157 mg (498 μmol) of $Bu_4NF{\cdot}3\ H_2O$ were added at 0 °C. After stirring for 10 min at 0 °C and 50 min at room temperature, the reaction mixture was partitioned between 10 mL of 10% aqueous NH_4Cl and 10 mL of Et_2O. The layers were separated, and the aqueous layer was extracted with 2 × 10 mL of Et_2O. The combined organic phases were washed with 2 × 5 mL of water, dried over $MgSO_4$, and concentrated. Purification by flash chromatography (EtOAc/hexane 3:7) afforded 44 mg (57%) of **9** as a clear, colorless oil.

(b) From 3. A solution of 200 mg (518 μmol) of **3** in 0.5 mL of anhydrous CH_2Cl_2 was added to a stirred suspension of 8.5 mg (104 μmol) of NaOAc and 520 mg (520 μmol) of PCC/Al_2O_3 (1 mmol PCC/g) in 0.5 mL of anhydrous CH_2Cl_2 at room temperature. After the mixture was stirred for 20 h, 10 mL of Et_2O was added. The suspension was filtered, and the filtrate was washed with 2 × 5 mL of water. The combined aqueous layers were extracted with 10 mL of Et_2O. The combined organic phases were dried over $MgSO_4$ and rota-evaporated. The resulting crude mixture of **3** and **9** was separated by flash chromatography (EtOAc/hexane 3:7), affording 68 mg (34%) of **9** and 80 mg (40%) of **3** as clear, pale yellow oils.

9: ^{1}H-NMR (300 MHz, DMSO-d_6) δ 1.18 (s, 3H), 1.40 (s, 3H), 3.87−4.09 (m, 4H), 3.39−4.44 (m, 2H), 5.24 (dd, *J* = 4.8, 1.5 Hz, 1H), 5.50 (s, 1H), 6.93 (d, *J* = 4.8 Hz, 1H, exchangeable with D_2O), 7.28−7.42 (m, 7H), 7.57 (dd, *J* = 7.4, 1.5 Hz, 1H), 7.86 (dd, *J* = 7.7, 1.1 Hz, 1H); ^{13}C-NMR (75 MHz, DMSO-d_6) δ 25.4 (q), 27.2 (q), 64.6 (t), 64.7 (t), 83.0 (d), 85.8 (d), 86.4 (d), 103.6 (d), 109.2 (s), 111.7 (s), 126.4 (d), 126.6 (d), 127.2 (d), 128.2 (d), 128.4 (d), 128.7 (d), 129.3 (d), 138.3 (s), 139.6 (s), 141.7 (s); IR (NaCl, film) 3426, 3058, 2891, 1481, 1375, 1208, 1077, 982, 875, 762, 702 cm^{-1}; MS (EI) *m*/*z* 384 (M^+), 369, 322, 307, 255, 211, 149, 133; HRMS *m*/*z* 384.1605 (M^+, 384.1573 calcd for $C_{22}H_{24}O_6$); TLC (EtOAc/hexane 3:7) R_f 0.22.

[3a*R*-(3aα,4α,6aα)]-4-(2-Benzoylphenyl)tetrahydrofuro-[3,4-*d*]-1,3-dioxol-2-one (11). A solution of 500 mg (1.76 mmol) of **5** in 6 mL of anhydrous CH_2Cl_2 was added to a suspension of 898 mg (5.54 mmol) of 1,1′-carbonyldiimidazole and 43 mg (0.35 mmol) of DMAP in 3 mL of anhydrous CH_2Cl_2 at room temperature under argon. The mixture was stirred for 7 d in the dark, and 10 mL of CH_2Cl_2 and 5 mL of water were added. The layers were separated, and the aqueous layer was extracted with 5 mL of CH_2Cl_2. The combined organic phases were dried over $MgSO_4$, filtered through silica gel and rota-evaporated. Purification of the crude product by radial chromatography (EtOAc/hexane 2:8, 4:6) afforded 543 mg (99%) of **11** as a clear, colorless oil. An analytically pure sample was obtained by preparative HPLC (MeOH/H_2O 6:4, t_R 16.3 min) as a colorless, solid foam: ^{1}H-NMR (300 MHz, $CDCl_3$) δ 4.02−4.04 (m, 2H), 5.22 (ddd, *J* = 7.4, 4.0, 3.3 Hz, 1H), 5.28 (dd, *J* = 7.4, 2.6 Hz, 1H), 5.38 (d, *J* = 2.6 Hz, 1H), 7.35−7.61 (m, 7H), 7.73−7.77 (m, 2H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 72.7 (t), 79.8 (d), 85.3 (d), 85.4 (d), 127.1 (d), 128.0 (d), 128.5 (d), 129.7 (d), 130.0 (d), 130.6 (d), 133.4 (d), 136.4 (s), 137.0 (s), 137.1 (s), 153.9 (s), 197.9 (s); IR (NaCl, film) 3062, 2928, 1819, 1659, 1597, 1473, 1290, 1270, 1159, 1079, 1057, 769, 735, 705 cm^{-1}; TLC (Et_2O/hexane 8:2) R_f 0.28; mp 48−55 °C; $[\alpha]^{22}_D$ −2.9°, $[\alpha]^{22}_{578}$ −4.6°, $[\alpha]^{22}_{546}$ −10.9°, $[\alpha]^{22}_{436}$ −120.2° (*c* 1.10, CH_2Cl_2); HRMS *m*/*z* 310.0853 (M^+, 310.0841 calcd for $C_{18}H_{14}O_5$). Anal. Calcd for $C_{18}H_{14}O_5$: C, 69.67; H, 4.55. Found: C, 69.40; H, 4.60.

[2*R*-(2α,3*β*,4*β*)]-Phenyl[2-[tetrahydro-3,4-dimethoxy-2-furanyl]phenyl]methanone (12). Under argon, a solution of 500 mg (1.76 mmol) of **5** in 15 mL of anhydrous CH_2Cl_2 was added to a suspension of 1.35 g (9.13 mmol) of trimethyloxonium tetrafluoroborate and 2.33 g (10.8 mmol) of 1,8-bis-(dimethylamino)naphthalene in 60 mL of anhydrous CH_2Cl_2 at room temperature. The mixture was stirred for 3 d, and another 530 mg (3.58 mmol) of trimethyloxonium tetrafluoroborate and 823 g (3.88 mmol) of 1,8-bis(dimethylamino)-naphthalene were added. Stirring was continued for 1 d, and 50 mL of CH_2Cl_2 and 50 mL of water were added. The layers were separated, and the aqueous layer was extracted with 2 × 50 mL of CH_2Cl_2. The combined organic phases were washed with 2 × 50 mL of 5% K_2CO_3 and 10 mL of water, dried over $MgSO_4$, filtered through silica gel, and rota-evaporated. Purification of the crude product by radial chromatography (Et_2O/hexane 2:8, two runs) and preparative HPLC (MeOH/H_2O 65:35, t_R 14.7 min) afforded 301 mg (55%) of **12** as colorless crystals: ^{1}H-NMR (300 MHz, $CDCl_3$) δ 3.37 (s, 3H), 3.38 (s, 3H), 3.76 (dd, *J* = 9.9, 4.1 Hz, 1H), 3.81 (dd, *J* = 9.9, 2.6 Hz, 1H), 3.92−3.98 (m, 2H), 4.99 (d, *J* = 6.6 Hz, 1H), 7.21 (d, *J* = 7.4 Hz, 1H), 7.34 (ddd, *J* = 7.5, 6.3, 2.2 Hz, 1H), 7.38−7.47 (m, 4H), 7.51−7.57 (m, 1H), 7.76−7.79 (m, 2H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 57.4 (q), 58.2 (q), 69.5 (t), 78.9 (d), 81.4 (d), 86.5 (d), 126.9 (d), 127.4 (d), 127.6 (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 (Et_2O/hexane 8:2) R_f 0.34; mp 58−61 °C; $[\alpha]^{20}_D$ −13.8° (*c* 1.53, $CHCl_3$); HRMS *m*/*z* 312.1346 (M^+, 312.1362 calcd for $C_{19}H_{20}O_4$). Anal. Calcd for $C_{19}H_{20}O_4$: C, 73.06; H, 6.45. Found: C, 72.88; H, 6.34.

[2*R*-(2α,3*β*,4*β*)]-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 CH_2Cl_2 were added 1.22 mL (8.80 mmol) of Et_3N and 0.57 mL (7.33 mmol) of MsCl at room temperature under argon. After the mixture was stirred for 17 h, 10 mL of saturated aqueous $NaHCO_3$ was added. The layers were separated, and the aqueous layer was extracted with 2 × 10 mL of CH_2Cl_2. The combined organic phases were dried over $MgSO_4$, filtered through silica gel, and rota-evaporated. Purification of the crude product by radial chromatography (EtOAc/hexane 1:9, 2:8, two runs) and preparative HPLC (MeOH/H_2O 6:4, t_R 16.0 min) afforded 612 mg (95%) of **13** as a colorless, solid foam: ^{1}H-NMR (300 MHz, $CDCl_3$) δ 2.90 (s, 3H), 3.13 (s, 3H), 4.02 (dd, *J* = 10.7, 3.3 Hz, 1H), 4.13 (dd, *J* = 10.7, 4.7 Hz, 1H), 5.12 (d, *J* = 7.0 Hz, 1H), 5.27 (pseudo dd, J ≈ 8, 5 Hz, 1H), 5.36 (dd, *J* = 7.4, 4.8 Hz, 1H), 7.31 (d, *J* = 7.7 Hz, 1H), 7.38−7.61 (m, 6H), 7.74−7.77 (m, 2H); ^{13}C-NMR (75 MHz, $CDCl_3$) 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), 130.2 (d), 133.5 (d), 136.6 (s), 137.1 (s), 137.6 (s), 198.0 (s); IR (KBr, pellet) 3059, 2983, 1663, 1596, 1449, 1363, 1178, 935, 766, 704 cm^{-1}; MS (CI) *m*/*z* 441 (($M + H)^+$), 345, 249; TLC (Et_2O/hexane 2:1) R_f 0.15; mp 55−62 °C; $[\alpha]^{20}_D$ +1.5°, $[\alpha]^{20}_{578}$ +0.7°, $[\alpha]^{20}_{546}$ −2.6°, $[\alpha]^{20}_{436}$ −58.3° (*c* 1.22, $CHCl_3$). Anal. Calcd for $C_{19}H_{20}O_8S_2$: C, 51.81; H, 4.58; S, 14.56. Found: C, 52.00; H, 4.57; S, 14.47.

[2*R*-(2α,3*β*,4*β*)]-Phenyl[2-(tetrahydro-3-hydroxy-4-methoxy-2-furanyl)phenyl]methanone (14) and [2*R*-(2α,3*β*,4*β*)]-Phenyl[2-(tetrahydro-4-hydroxy-3-methoxy-2-furanyl)-phenyl]methanone (15). Under argon, a solution of 50 mg (176 μmol) of **5** in 0.35 mL of anhydrous CH_2Cl_2 was added to a suspension of 45 mg (211 μmol) of 1,8-bis(dimethylamino)-

(29) (a) Sheldrick, G. M. SHELX93, Universität Göttingen, 1993. (b) Sheldrick, G. M. SHELXTL PLUS, Universität Göttingen, 1988. (c) *International Tables for X-ray Crystallography*; Kynoch-Press: Birmingham, 1974; Vol. 4.

(30) The author has deposited atomic coordinates for **8** with the Cambridge Crystallographic Data Centre. The coordinates can be obtained, on request, from the Director, Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, CB2 1EZ, UK.

naphthalene and 26 mg (176 μmol) of trimethyloxonium tetrafluoroborate in 0.2 mL of anhydrous CH_2Cl_2 at room temperature. The mixture was stirred for 7 d at room temperature, and 1.5 mL of CH_2Cl_2 and 1.5 mL of water were added. The layers were separated, and the aqueous layer was extracted with 2 × 0.7 mL of CH_2Cl_2. The combined organic phases were washed with 2 × 1.0 mL of 5% K_2CO_3 and 1.0 mL of water, dried over $MgSO_4$, 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/H_2O 4:6).

14: ^{1}H-NMR (300 MHz, DMSO-d_6) 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 (ddd, J = 4.4, 3.7, 2.3 Hz, 1H), 4.05 (ddd, 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 D_2O), 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) R_f 0.53; preparative HPLC t_R 19.4 min.

15: ^{1}H-NMR (300 MHz, DMSO-d_6) 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 D_2O), 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) R_f 0.53; preparative HPLC t_R 17.3 min.

[2*R*-(2α,3*β*,4*β*)]-Phenyl[2-[tetrahydro-3-hydroxy-4-[(methylsulfonyl)oxy]-2-furanyl]phenyl]methanone (16) and [2*R*-(2α,3*β*,4*β*)]-Phenyl[2-[tetrahydro-4-hydroxy-3-[(methylsulfonyl)oxy]-2-furanyl]phenyl]methanone (17). To a solution of 100 mg (352 μmol) of **5** and 73 μL (528 μmol) of Et_3N in 2 mL of anhydrous CH_2Cl_2 were added 30 μL (387 μmol) of MsCl 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 CH_2Cl_2 and 20 mL of saturated aqueous $NaHCO_3$ were added. The layers were separated, and the aqueous layer was extracted with 2 × 10 mL of CH_2Cl_2. The combined organic phases were dried over $MgSO_4$ and rota-evaporated. Purification of the crude product by flash chromatography (Et_2O/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** 1.0:6.1:1.6, 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/H_2O 4:6).

16: ^{1}H-NMR (300 MHz, $CDCl_3$) δ 3.21 (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 D_2O), 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); ^{13}C-NMR (75 MHz, $CDCl_3$) 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 (Et_2O/hexane 2:1) R_f 0.10; analytical HPLC (MeCN/H_2O 4:6) t_R 17.7 min.

17: ^{1}H-NMR (300 MHz, $CDCl_3$) 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); ^{13}C-NMR (75 MHz, $CDCl_3$) 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 (Et_2O/hexane 2:1) R_f 0.10; analytical HPLC (MeCN/H_2O 4:6) t_R 15.7 min.

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