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Synthesis of Benzophenone Nucleosides and Their Photocatalytic Evaluation for [2+2] Cycloaddition in Aqueous Media

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Four benzophenone nucleosides that are *para*-substituted (–NH_2, –NMe_2, –OMe, and –Me) in relation to the carbonyl group were synthesized and characterized by their optical properties. The electron-donating character of the substituents influenced the optical properties of these nucleosides, especially the bathochromic shift of the charge-transfer band in their UV/Vis absorption spectra. The solubility of the synthetic nucleosides in aqueous solution allowed for a photocatalytic intramolecular [2+2] cycloaddition of a quinolone substrate to take place in H_2O/MeCN by irradiating the mixture with 365 nm light-emitting diode (LED) lamps. The MeO- and Me-substituted benzophenone nucleosides were subjected to these reaction conditions in substoichiometric amounts. After prolonged irradiation times, substrate conversions competed with product decomposition. On the basis of our results, we determined that the Me-substituted benzophenone nucleoside has potential applications in the development of photocatalytically active DNAzymes for both in vivo applications in chemical biology and enantioselective photocatalysis in aqueous solutions.

Introduction

For decades, benzophenones (BP) have played a substantial and central role in photochemistry.[1–3] The major advantages of benzophenones are: (i) their chemical and photochemical stability, (ii) their nearly quantitative yield of intersystem crossing and formation of the triplet state, (iii) the relatively long-lived nature of the triplet state, and (iv) their UV-A absorption properties, which allow for the use of 365 nm light-emitting diodes (LEDs) for excitation. Benzophenones are also important chromophores for enantioselective photocatalysis.[2,3]

Both template-assisted triplet-triplet energy transfer[4] and photoinduced triplet electron transfer[5] have been used for enantioselective [2+2] cycloadditions and cyclizations, which are synthetically valuable C–C bond forming reactions.[2,3] To bring this photocatalysis to aqueous media and thereby to potential biological applications, it seemed reasonable to design new *C*-nucleosides that have a benzophenone moiety as an artificial DNA base. A backbone that consists of sugar and phosphodiester units can enhance the solubility of benzophenone in water and might serve as a template. Because benzophenone is known to sensitize DNA damage,[6] there are few published examples of benzophenone-modified nucleoside analogues as models for ribonucleotide reductases,[7] as photoreactive dyads,[8] and as initiators for interstrand crosslinks.[9] We recently synthesized a *C*-nucleoside that contains a conventional unmodified benzophenone, and the dinucleotides thereof have one of the natural nucleotides (A, C, T and G).[10] These dinucleotides represent both interesting biologically relevant systems with respect to DNA damage and the starting point for future applications in chemical biology and photocatalysis.

The exploration of the benzophenone dinucleotides by time-resolved transient absorption spectroscopy and theoretical methods, including molecular dynamics, revealed charge-transfer processes predominantly with guanosine as the second component.[11] It became clear that the solvent, H_2O or MeOH, controls the conformational distribution and thereby actually gates the charge-transfer process as a result of differences in the distance and degree of stacking between benzophenone and the second component of the dinucleotide. Our results gave a full understanding of the photophysical properties of the singlet and triplet state of the BP chromophore in the context of each of the four different DNA bases.[11] Moreover, these studies clearly revealed that nucleotides that contain conventional benzophenone as the artificial DNA base are not suited to serve as a photochemically inert architecture for benzophenone-mediated photocatalysis. However, dinucleotides and oligonucleotides with less reactive but still photocatalytically active benzophenone might be considered for the design of stable DNA photocatalysts. On the basis of substituted quinolone **2** as the substrate for a photocatalyzed reaction (see below), a triplet energy of at least E_T = 2.86 eV[12] is required to provide the triplet-triplet energy transfer as sensitization. Conventional benzophenone has a triplet energy of E_T = 2.98 eV, which clearly fulfills this requirement.[13]

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Moreover, modified benzophenones with slightly lower singlet and triplet states would also allow the driving force ΔG to be tuned for electron transfer to more positive values and thereby energetically inhibit a reductive excited state quenching, as observed with conventional benzophenones.[11] An electron-donating group bonded to one of the phenyl groups and *para* to the carbonyl group should render singlet and triplet energy states of benzophenones into the desired direction. For instance, 4-aminobenzophenone **1a** provides a singlet state of E_S = 3.03 eV,[13] which corresponds to 410 nm, and thereby allows a selective excitation outside the absorption range of substrate **2**. The triplet state of 4-aminobenzophenone **1a** is E_T = 2.91 eV in benzene,[14] which is still sufficient to sensitize substrate **2**. The major drawback, however, for the substitution of 4-aminobenzophenone **1a** is that the quantum yield of intersystem crossing is reduced to Φ_T = 0.82 in nonpolar solvents.[15] Herein, we follow this approach and present the synthesis of *C*-nucleosides that contain 4-aminobenzophenone (i.e., **1a**), 4-(dimethylamino)benzophenone (i.e., **1b**), 4-methoxybenzophenone (i.e., **1c**), and 4-methylbenzophenone (i.e., **1d**) as aglycons. The optical and electrochemical properties of **1a**–**1d** and an evaluation of them as photosensitizers for substrate **2**, especially in aqueous media, are also presented.

Results and Discussion

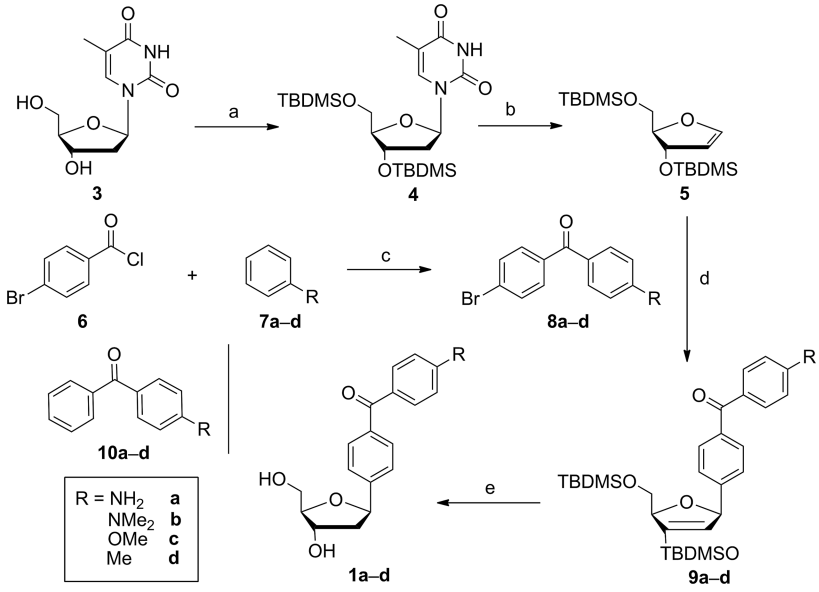
C-Nucleosides **1a**–**1d** that contain 4-aminobenzophenone, 4-(dimethylamino)benzophenone, 4-methoxybenzophenone, and 4-methylbenzophenone moieties, respectively, were synthesized in four steps by using a Heck-type coupling reaction as the central step (Scheme 1).[16] Aminosubstituted benzophenone **8a** was synthesized in 59% yield by the acylation of bromobenzene with 4-nitrobenzoyl chloride followed by reduction of the nitro group with concentrated hydrochloric acid in the presence of iron. The other functionalized benzophenones **8b**–**8d** that were used as precursors to the glycosidic coupling were synthesized by Friedel–Crafts-type acylations between 4-bromobenzoyl chloride and the corresponding aryl components. The yields varied as reported in Table 1. Glycal **5** was obtained in a yield of 57% by *tert*-butyldimethylsilyl (TBDMS) protection of thymidine **3** at the 3′- and 5′-positions and subsequent elimination of thymine as described by Hammer et al. and Engels et al.[17,18] For the central Heck-type coupling between the brominated benzophenones **8a**–**8d** and the glycal **5**, several palladium catalysts were screened and $Pd(dppf)Cl_2$ [dppf = 1,1′-bis(diphenylphosphino)ferrocene] was determined to be the catalyst of choice. After deprotection of the glycosides **9a**–**9d** at their 3′- and 5′-positions and reduction of the intermediate 3′-keto derivatives by treatment with $NaBH(OAc)_3$ as described by Hocek et al.,[19] *C*-nucleosides **1a**–**1d** were obtained.

Table 1. Benzophenone nucleosides yields.

	Friedel–Crafts acylation [% yield]	Heck-type coupling [% yield]	Deprotection and reduction [% yield]
1a	27[a]	52	65
1b	38	28	75
1c	96	46	65
1d	76	55	66

[a] Friedel–Crafts reaction with 4-bromo-4′-nitrobenzophenone was then followed by reduction of the nitro group.

It is important to point out that both steps: (i) the palladium-catalyzed coupling reaction and (ii) the final reduction are highly stereoselective. The stereoselectivity re-



Scheme 1. Synthesis of benzophenone nucleosides **1a**–**1d** and structure of the benzophenones **10a**–**10d**. Reagents and conditions: (a) imidazole, TBDMS-Cl, *N*,*N*-dimethylformamide (DMF), room temp., 16 h, 99%; (b) hexamethyldisilazane (HMDS), $(NH_4)SO_4$, 120 °C, 4 h, 58%; (c) $AlCl_3$, reflux, 16 h; (d) **5**, $Pd(dppf)Cl_2$, Et_3N, MeCN, 75 °C, 48 h; (e) (1) $Et_3N{\cdot}3HF$, tetrahydrofuran (THF), 0 °C, 12 h; (2) $NaBH(OAc)_3$, MeCN/AcOH, 1:1, 0 °C, 8 h.

sults are a consequence of substrate control because: (i) the lower face of glycal **5** is effectively shielded by the sterically demanding TBDMS group in the 3′-position to give only the desired β-anomers[16] and (ii) the free 5′-hydroxy group binds to the boron atom of $NaBH(OAc)_3$ thereby leading to a hydride attack of the C=O bond from the top to recover the 2′-deoxyribofuranoside configuration.[20]

The influence of substituent R on the optical properties of the nucleosides is tremendous as shown by the UV/Vis absorption spectra of benzophenone-*C*-nucleosides **1a**–**1d** (Figure 1) and also compared to those of non-nucleosidic chromophores **10a**–**10d** (see Supporting Information). All optical measurements were performed in H_2O/MeCN (4:1), which is the aqueous solvent of the later photocatalytic experiments (in which all ingredients are soluble). The typical absorption of an unsubstituted benzophenone can be attributed to the π–π* and n–π* transitions of the carbonyl group. With an electron-donating substituent, the absorption of the benzophenone is extended because of an additional charge-transfer (CT) state.[21] This is clearly seen in the absorptions of synthesized nucleosides **1a**–**1d**. 4-(Dimethylamino)benzophenone-*C*-nucleoside **1b** displays an absorption maximum at 370 nm, whereas the maxima of **1a** and **1c** are found at 335 and 293 nm, respectively. Nucleoside **1d** with the methyl substituent has an absorption maximum at 270 nm, which is very similar to that of unsubstituted benzophenone (260 nm). The unsymmetric shape of that absorption band and the broad shoulder at approximately 290 nm indicates the occurrence of a CT band in this nucleoside. As the electron-donating ability of the substituent increases, the bathochromic shift of the CT band of the corresponding nucleoside also increases. This tracks well with the oxidation potentials of the benzophenones, which are 1.15 V for **10b**, which has a dimethylamino substituent, 1.26 V for **10a**, 2.20 V for **10c**, and 2.60 V for methyl-substituted **10d** (vs. Ag/AgCl).[22] Unsubstituted benzophenone has the highest oxidation potential of 2.85 V.[22]

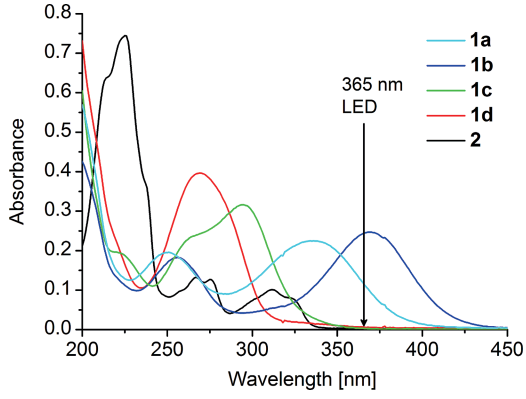


Figure 1. UV/Vis absorption spectra of **1a**–**1d** and substrate **2** in H_2O/MeCN (4:1, 20 μM).

Suppan et al. showed that the energy of the CT band of benzophenone **10a** in polar solvents, such as isopropyl alcohol, is located energetically below the nπ* band, whereas in nonpolar solvents, such as cyclohexane, the CT band is above it.[21] Hence, we can assume that the triplet-triplet energy transfer that is required for the photocatalytic conversion of substrate **2** in aqueous solution primarily originates from the CT states of nucleosides **1a**–**1d** as photocatalysts.[23] Hence, the observed CT state as the lowest triplet state probably plays a major role in the later photocatalytic experiments that take place in aqueous solutions. Typically, in different polar solvent mixtures, the absorption of the nucleoside with the strongest electron-donating group (i.e., **1b**) demonstrates solvatochromic behavior that supports the assignment of the CT state (Figure 2), as the bathochromic shift tracks well with the polarity of the solvents according to the $E_T(30)$ values of Reichardt.[24] The strongest bathochromic shift is observed in H_2O and has a maximum at 370 nm. This corresponds to an excited state with an energy of 3.3 V that – despite the fact that the triplet state might by slightly lower than this value – should be sufficiently high for photocatalysis to occur with substrate **2**.

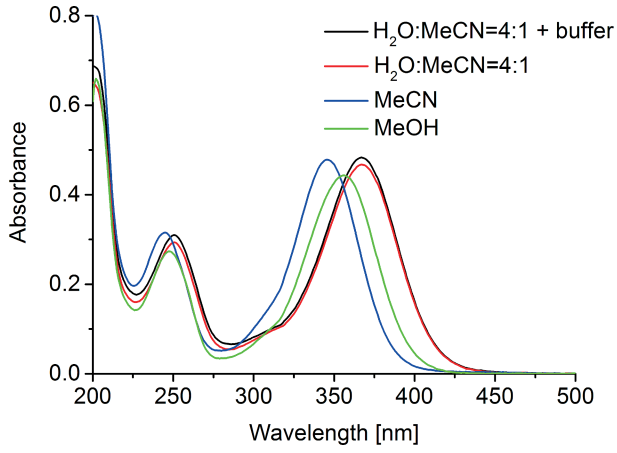


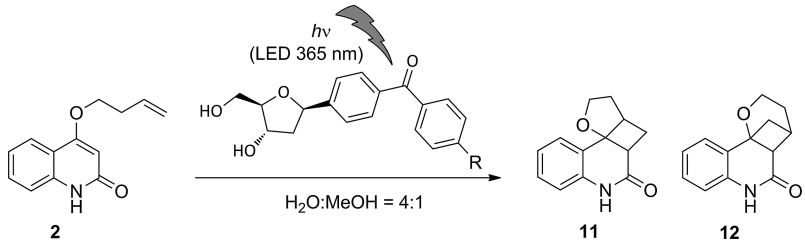
Figure 2. UV/Vis absorption spectra of **1b** in different solvent mixtures (buffer: 10 mM Na_2HPO_4/NaH_2PO_4, pH = 8.55).

For the photocatalytic experiments, we investigated the commonly used substrate **2** that can undergo an intramolecular [2+2] cycloaddition reaction to afford the two products **11** and **12**.[25] In principle, enantiomeric pairs of both products resulted, but a templated photocatalytic process by Bach et al. achieved this conversion enantioselectivity.[26] Two 365 nm LED lamps were used as a light source, and although the corresponding extinction coefficients of nucleosides **1a**–**1d** are rather low (Table 2), this excitation wavelength is required to avoid direct excitation of substrate

Table 2. Optical and electrochemical parameters of nucleosides **1a**–**1d**.

Nucleoside	λ_{max} [nm][a]	λ_{max} [nm][b]	$\varepsilon^{\lambda max}$ [$mM^{-1} cm^{-1}$][b]	$\varepsilon^{365\ nm}$ [$mM^{-1} cm^{-1}$][b]
1a	335	321	13.0	1.5
1b	370	345	14.3	9.1
1c	293	285	15.4	0.7
1d	270	262	22.4	0.3

[a] Solvent: H_2O. [b] Solvent: MeCN.



Scheme 2. Intramolecular [2+2] cycloaddition of substrate **2**.

2. A 20% solution of MeCN in water was required to guarantee sufficient solubility of substrate **2** along with the photocatalysts nucleosides **1a**–**1d**. The conversions of **2** and the yields of **11** and **12** were determined by HPLC analysis.

Among the four nucleosides **1a**–**1d**, the amino-substituted nucleosides, especially **1b**, have the best match to the 365 nm LED, as their extinction coefficients are highest at this excitation wavelength. However, all experimental attempts to employ nucleosides **1a** and **1b** as photocatalysts failed, although the CT states of these nucleosides should provide sufficient energy for an efficient triplet-triplet energy transfer to substrate **2**, as reported[14,21,23] and indicated by the UV/Vis absorption spectra described above. Control experiments in pure (i.e., nonaqueous) MeCN revealed the successful conversion of substrate **2** in the presence of nucleosides **1a** and **1b**. Hence, the excited state proton transfer by the protic solvent interferes with the energy transfer in the corresponding photocatalytic experiments. We assume that this proton transfer occurs to the carbonyl group, which is conjugated to the *para*-amino group of **1a** and **1b**, respectively.

In contrast, the photocatalytic experiments with nucleosides **1c** and **1d** clearly show conversion of substrate **2** in H_2O/MeCN (4:1; Scheme 2, Table 3). According to their absorption properties described above, the CT states of both nucleosides provide enough energy to be transferred to the substrate. Additionally, the absence of a nitrogen atom in the substituents of these two benzophenone derivatives lowers the basicity significantly, which reduces the interference from a proton transfer. All of these experiments afforded the regioisomeric mixture **11**/**12** in a 2.2:1 ratio.

Table 3. Photocatalytic reactions with **1c** and **1d** [25 μM (substoichiometric) or 100 μM (stoichiometric)] and substrate **2** (100 μM).

Entry	Photocatalyst	Time [min][a]	Conv. [%]	Yield [%]	Time [min]	Conv. [%]	Yield [%][b]
1	**1c**[c]	25	79	48	30	85	47
2	**1d**[c]	15	88	77	30	89	64
3	**1c**[d]	120	85	51	30	33	14
4	**1d**[d]	60	88	53	30	66	46

[a] Irradiation time for maximum yield. [b] All experiments gave the regioisomeric mixture **11**/**12** (2.2:1). No enantioselectivity was observed. [c] Reagents and conditions: **1c** or **1d** (100 μM), **2** (100 μM), H_2O/MeCN (4:1), Na_2HPO_4/NaH_2PO_4 (10 mM), pH = 8.55, 365 nm, 10 °C. Reaction was monitored by HPLC analysis. [d] Reagents and conditions: **1c** or **1d** (25 μM), **2** (100 μM), H_2O/MeCN (4:1), Na_2HPO_4/NaH_2PO_4 (10 mM), pH = 8.55, 365 nm, 10 °C. Reaction was monitored by HPLC analysis.

Careful HPLC analysis, however, revealed that the yield of the products **11** and **12** did not track with conversion at irradiation times longer than 15–25 min. The loss of yield was especially observed between 15 and 30 min of irradiation time with nucleoside **1d**, as indicated by decomposition of the products **11** and **12** upon their formation. When nucleoside **1c** was used as the photocatalyst in a stoichiometric amount (100 μM), the optimum results of 79% conversion and 48% yield were reached within 25 min of irradiation time (Table 3, Entry 1). However, a substoichiometric approach (25 μM) resulted in 85% conversion and 51% yield after 120 min of irradiation time (Table 3, Entry 3). Nucleoside **1d** was more efficient, and 88% conversion along with 77% yield of the product was obtained after 15 min of irradiation time by using a stoichiometric amount of the photocatalyst (Table 3, Entry 2). A substoichiometric amount of catalyst **1d** gave 88% conversion and 53% yield after 60 min of irradiation time. The photochemical decomposition of products **11** and **12** was faster in the presence of nucleoside **1c** than in experiments with nucleoside **1d** (Figure 3).

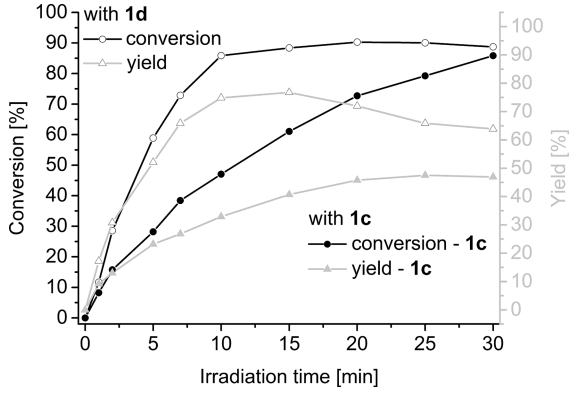


Figure 3. Time-dependent conversion of **2** and yield of **11** and **12** during irradiation in the presence of **1c** and **1d**. Reagents and conditions: **1d** or **1c** (100 μM), **2** (100 μM), H_2O/MeCN (4:1), Na_2HPO_4/NaH_2PO_4 (10 mM), pH = 8.55, 365 nm (LED), 10 °C.

Conclusions

In summary, we have presented the synthesis of four *C*-nucleosides that contain several benzophenones with electron-donating substituents as aglycons to develop photocatalysts for [2+2] cycloaddition reactions in aqueous media. The optical properties of nucleosides **1a**–**1d** reveal CT states with triplet energies that depend on the electron-donating

character of the benzophenone chromophore and solvent polarity. Quinolone **2** was employed as typical substrate to evaluate the benzophenone nucleosides as photosensitizers in aqueous media. Although the CT bands of the amino-substituted benzophenone nucleosides **1a** and **1b** had the best match to the 365 nm LED as a light source, the conversion of **2** was not detectable in aqueous solvents. Overall, benzophenone nucleoside **1d** was the most powerful catalyst for this type of [2+2] cycloaddition in aqueous media, as the conversion of substrate **2** tracked well with the yield within 15 min of irradiation time. Nucleoside **1d** can be employed in the development of photocatalytically active DNAzymes for both in vivo applications in chemical biology and enantioselective photocatalysis in aqueous solutions.

Experimental Section

General Methods: All reagents were purchased from Aldrich, Alfa Aesar, ABCR, Fluka, and TCI and used without further purification. The NMR spectroscopic data were recorded with a 75, 101, and 300 MHz instrument. The chemical shifts in the ^{1}H and ^{13}C NMR spectra are reported in parts per million (ppm) relative to tetramethylsilane as an internal standard. Coupling constants (*J*) are given in Hertz (Hz), and the multiplicity of signals are reported as follows: s (singlet), d (doublet), t (triplet), q (quadruplet), quint (quintet), sext (sextet), m (multiplet), br. s (broad singlet), dt (doublet of triplets), and td (triplet of doublets). Mass spectrometry was performed on a Finnigan Modell MAT 95 with FAB and EI as ionization methods. Thin layer chromatography was performed on Fluka silica gel 60 F254 coated aluminium foil. Flash chromatography was carried out on silica gel 60 from Aldrich (43–60 μm). Chiral HPLC analyses were recorded on a Varian ProStar apparatus with a Chiralpak IB column (250 mm × 4.6 mm, 5 μm). The UV/Vis absorption measurements were recorded on a Perkin–Elmer Lambda 750 spectrometer. Irradiation experiments were performed with two Nichia UV-LEDs (NCSU033B) at 365 nm.

Photocatalytic Reactions: Catalyst **1a**–**1d** (25 or 100 μM) and substrate **2** (100 μM) in H_2O/MeCN (4:1, 4 mL) that contained Na_2HPO_4/NaH_2PO_4 buffer (10 mM, pH = 8.55) were degassed in a 4 mL cuvette by bubbling argon through the solution for 10 min. The reaction mixture was irradiated with two LEDs (365 nm) at 10 °C. During the irradiation, samples (250 μL) were taken for HPLC analysis. The samples were concentrated under vacuum and dissolved in the HPLC eluent (50 μL). HPLC analyses were recorded at 242 nm by using heptane/isopropyl alcohol (9:1) as an isocratic eluent.

4-(ω-Butenyloxy)quinolin-2(1*H*)-one (2): By starting with commercially available 4-nitroquinoline-*N*-oxide, substrate **2** was synthesized as described in the literature.[27,28]

3′,5′-Bis-*O*-(*tert*-butyldimethylsilyl)thymidine (4): A mixture of 2′-deoxythymidine (10.0 g, 41.3 mmol) and imidazole (11.8 g, 173 mmol) in anhydrous DMF was stirred at room temperature for 5 min. Then *tert*-butyldimethylsilyl chloride (13.1 g, 86.7 mmol) was added, and the mixture was stirred for another 12 h. After adding water (100 mL), the reaction mixture was extracted with hexane, dried with Na_2SO_4 and concentrated under vacuum to give **4** (19.3 g, 99%) as a white solid; R_f = 0.81 (CH_2Cl_2/MeOH, 19:1). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.30 (s, 1 H), 7.47 (d, *J* = 1.3 Hz, 1 H), 6.33 (dd, *J* = 7.9, 5.8 Hz, 1 H), 4.40 (dt, *J* = 5.5, 2.6 Hz, 1 H), 3.97–3.82 (m, 1 H, 2′-H), 3.76 (dd, *J* = 11.4, 2.4 Hz, 1 H), 2.25 (ddd, *J* = 13.1, 5.8, 2.6 Hz, 1 H), 2.00 (ddd, *J* = 13.1, 8.0, 6.0 Hz, 1 H), 1.92 (d, *J* = 1.2 Hz, 3 H), 0.93 (s, 9 H), 0.89 (s, 9 H), 0.11 (d, *J* = 0.8 Hz, 6 H), 0.08 (d, *J* = 2.1 Hz, 6 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = –5.3, –5.2, –4.7, –4.5, 12.7, 18.1, 18.5, 25.9, 26.0, 41.5, 63.1, 72.4, 85.0, 88.2, 111.0, 135.6, 150.5, 164.1 ppm. MS (FAB): calcd. for $C_{22}H_{43}N_2O_5Si_2$ $[M + H]^+$ 471.3; found 471.4.

3,5-Bis-*O*-(*tert*-butyldimethylsilyl)-1,2-dideoxy-2,2-didehydro-D-ribofuranose (5): A mixture of **4** (3.00 g, 6.40 mmol) and ammonium sulfate (337 mg, 2.55 mmol) was dissolved in hexamethyldisilazane (11.7 g, 72.5 mmol) in a dry flask, and the resulting mixture was heated at reflux for 4 h. After the solvents were removed under vacuum, the residue was dissolved in CH_2Cl_2. The solution was washed with saturated $NaHCO_3$ solution, water, and brine, dried with Na_2SO_4, and concentrated under vacuum. The crude product was purified by silica gel column chromatography (hexane/Et_2O, 19:1) to give **4** (1.27 g, 58%) as a yellow oil; R_f = 0.70 (hexane/Et_2O, 19:1). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 6.4 (dd, *J* = 2.7, 1.0 Hz, 1 H), 5.01 (t, *J* = 2.6 Hz, 1 H), 4.86 (td, *J* = 2.7, 1.1 Hz, 1 H), 4.29 (td, *J* = 6.0, 2.7 Hz, 1 H), 3.69 (dd, *J* = 10.7, 5.7 Hz, 1 H), 3.51 (dd, *J* = 10.7, 6.4 Hz, 1 H), 0.89 (d, *J* = 2.0 Hz, 18 H), 0.07 (d, *J* = 2.8 Hz, 12 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = –5.2, –5.1, –4.3, –4.1, 18.3, 18.4, 26.0, 26.0, 63.0, 76.1, 89.1, 103.6, 149.1 ppm.

(4-Aminophenyl)(4-bromophenyl)methanone (8a): A solution of 4-nitrobenzoyl chloride (2.00 g, 10.7 mmol) and bromobenzene (1.69 g, 10.7 mmol) in anhydrous CH_2Cl_2 (60 mL) was cooled to 0 °C. $AlCl_3$ (2.85 g, 21.4 mmol) was added, and the reaction was stirred for 1 h. After the mixture was stirred for 14 h at room temperature, it was poured into ice water (300 mL). The aqueous solution was extracted with EtOAc, and the combined organic layers were dried with Na_2SO_4 and concentrated under vacuum. The crude product was purified by silica gel column chromatography (hexane/EtOAc, 40:1) to give (4-bromophenyl)(4-nitrophenyl)methanone (0.873 g, 27%) as a yellow solid; R_f = 0.41 (hexane/EtOAc, 40:1). ^{1}H NMR (300 MHz, [D$_6$]DMSO): δ = 8.40–8.34 (m, 2 H), 7.99–7.93 (m, 2 H), 7.84–7.78 (m, 2 H), 7.74–7.68 (m, 2 H) ppm. ^{13}C NMR (75 MHz, [D$_6$]DMSO): δ = 193.7, 149.5, 142.1, 135.0, 131.9, 130.8, 127.7, 123.7 ppm. MS (EI): calcd. for $C_{13}H_9BrNO_3$ $[M + H]^+$ 307.1; found 307.1. A mixture that contained (4-bromophenyl)(4-nitrophenyl)methanone (0.203 g, 0.660 mmol), iron powder (0.174 g, 3.12 mmol), concentrated HCl (0.0700 g, 1.92 mmol), and EtOH (80% in water) was placed in an ultrasonic bath at 85 °C for 14 h. The remaining iron was removed by filtration, and the solvents were removed under vacuum. The residue was dissolved in EtOAc, and the resulting solution was washed with Na_2CO_3 solution (10% in water), dried with Na_2SO_4, and concentrated under vacuum. The crude product was purified by silica gel column chromatography (hexane/EtOAc, 5:1) to give **8a** (0.106 g, 59%) as an orange solid; R_f = 0.20 (hexane/EtOAc, 5:1). ^{1}H NMR (300 MHz, [D$_6$]DMSO): δ = 7.73–7.68 (m, 2 H), 7.57–7.48 (m, 4 H), 6.63–6.56 (m, 2 H), 6.23 (s, 2 H) ppm. ^{13}C NMR (75 MHz, [D$_6$]DMSO): δ = 192.2, 154.0, 138.1, 132.7, 131.1, 130.8, 124.7, 123.2, 112.5 ppm. MS (EI): calcd. for $C_{13}H_{11}BrNO$ $[M + H]^+$ 276.0; found 276.0.

(4-Bromophenyl)[4-(dimethylamino)phenyl]methanone (8b): After cooling 4-bromobenzoyl chloride (5.00 g, 22.8 mmol) and *N*,*N*-dimethylaniline (4.31 g, 34.2 mmol) in anhydrous Et_2O (100 mL) to 0 °C, $AlCl_3$ (8.81 g, 66.1 mmol) was added. The mixture was stirred at 0 °C for 1 h and then heated at reflux for 12 h. The reaction was poured into a mixture of ice water (500 mL) and concentrated HCl (45 mL). The aqueous layer was extracted with $CHCl_3$. The com-

bined organic layers were washed with 1 N HCl, water, and brine, dried with Na_2SO_4, and concentrated under vacuum. The crude product was purified by silica gel column chromatography (hexane/EtOAc, 10:1) to give **8b** (2.62 g, 38%) as a yellow solid; R_f = 0.24 (hexane/EtOAc, 10:1). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.71 (s, 2 H), 7.57 (d, J = 8.0 Hz, 2 H), 7.46 (d, J = 7.5 Hz, 1 H), 7.28 (s, 1 H), 3.07 (s, 1 H), 3.01–2.84 (m, 4 H), 2.28 (quint, J = 8.0 Hz, 2 H), 2.02 (s, 6 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 146.8, 139.2, 137.2, 136.9, 126.9, 126.4, 125.1, 123.3, 122.0, 118.1, 117.6, 76.5, 37.8, 29.9, 24.1, 15.2 ppm. MS (EI): calcd. for $C_{15}H_{14}BrNO$ $[M]^+$ 303.0; found 303.0.

(4-Bromophenyl)(4-methoxyphenyl)methanone (8c): After cooling 4-bromobenzoyl chloride (5.00 g, 22.8 mmol) in anhydrous nitrobenzene (25 mL) to 0 °C, $AlCl_3$ (3.34 g, 25.1 mmol) was added. The mixture was stirred for 10 min, and anisole (7.50 g, 34.2 mmol) was added slowly through a dropping funnel. The mixture was stirred at 0 °C for 30 min and then at room temperature for 12 h. The reaction mixture was then poured into ice water (200 mL). The aqueous layer was extracted with CH_2Cl_2. The combined organic layers were washed with 1 N HCl, dried with Na_2SO_4, and concentrated under vacuum. The crude product was purified by silica gel column chromatography (hexane/EtOAc, 20:1) to give **8c** (6.39 g, 96%) as a white solid; R_f = 0.22 (hexane/EtOAc, 20:1). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.79 (dd, J = 8.9, 1.2 Hz, 2 H), 7.62 (t, J = 1.0 Hz, 4 H), 7.03–6.89 (m, 2 H), 3.89 (s, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 194.5, 163.6, 137.2, 132.6, 131.6, 131.4, 129.9, 127.0, 113.8, 55.7 ppm. MS (EI): calcd. for $C_{14}H_{12}BrO_2$ $[M + H]^+$ 291.0; found 291.0.

(4-Bromophenyl)(4-tolyl)methanone (8d): A mixture of 4-bromobenzoyl chloride (3.00 g, 13.7 mmol) and $AlCl_3$ (2.73 g, 20.5 mmol) in anhydrous toluene (30 mL) was heated at reflux for 2 h. The reaction was then poured into a mixture of ice water (100 mL) and concentrated HCl (9 mL). The aqueous layer was extracted with EtOAc. The combined organic layers were washed with 1 N HCl, water, and brine, dried with $MgSO_4$, and concentrated under vacuum. The crude product was purified by recrystallization (hexane) to give **8d** (2.84 g, 76%) as a light pink solid; R_f = 0.46 (hexane/EtOAc, 20:1). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.67–7.53 (m, 6 H), 7.26–7.19 (m, 2 H), 2.39 (s, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 195.5, 143.7, 136.8, 134.6, 131.6, 130.3, 129.2, 127.3, 21.8 ppm. MS (EI): calcd. for $C_{14}H_{11}BrO$ $[M]^+$ 274.0; found 274.0.

1β-{[4-(Amino)phenyl](phenyl)methanone}-3,5-bis-*O*-(*tert*-butyldimethylsilyl)-1,2-dideoxy-2,3-didehydro-D-ribofuranose (9a): A mixture of **8a** (0.321 g, 0.917 mmol), **5** (0.252 g, 0.917 mmol), and triethylamine (0.197 g, 1.95 mmol) was dissolved in acetonitrile (20 mL) in a dry vial, and the resulting mixture was degassed by a pump–freeze–thaw method. [1,1′-Bis(diphenylphosphino)ferrocene]dichloropalladium(II) (0.111 g, 0.154 mmol) was added, and the mixture was heated at 60 °C for 20 h. The reaction was concentrated under vacuum, and the crude product was purified by silica gel column chromatography (hexane/EtOAc, 5:1 + 0.1% Et_3N) to give **9a** (0.251 g, 52%) as a yellow oil; R_f = 0.54 (hexane/EtOAc, 5:1). ^{1}H NMR (300 MHz, [D$_6$]DMSO): δ = 7.61–7.44 (m, 6 H), 6.77 (d, J = 8.3 Hz, 1 H), 6.60 (d, J = 8.3 Hz, 1 H), 6.16 (d, J = 5.2 Hz, 2 H), 5.11 (dd, J = 10.8, 5.3 Hz, 1 H), 4.34 (d, J = 5.0 Hz, 1 H), 3.85 (d, J = 5.3 Hz, 1 H), 3.68 (dd, J = 10.7, 4.5 Hz, 1 H), 3.54 (dd, J = 10.7, 6.8 Hz, 1 H), 0.14, 0.11 (d, J = 0.8 Hz, J = 0.9 Hz, 18 H), 0.06, 0.01 (d, J = 0.8 Hz, J = 0.8 Hz, 12 H) ppm. ^{13}C NMR (101 MHz, [D$_6$]DMSO): δ = 193.1, 153.7, 145.5, 138.0, 132.6, 128.8, 125.7, 123.8, 112.5, 88.1, 79.1, 73.9, 43.5, 1.8, 0.2, –0.5 ppm.

1β-{[4-(*N*,*N*-Dimethylamino)phenyl](phenyl)methanone}-3,5-bis-*O*-(*tert*-butyldimethylsilyl)-1,2-dideoxy-2,3-didehydro-D-ribofuranose (9b): A mixture of **8b** (0.250 g, 0.821 mmol), **5** (0.283 g, 0.821 mmol), and Et_3N (0.178 g, 1.77 mmol) was dissolved in MeCN (20 mL) in a dry vial, and the resulting mixture was degassed by a pump–freeze–thaw method. [1,1′-Bis(diphenylphosphino)ferrocene]dichloropalladium(II) (0.101 g, 0.123 mmol) was added, and the mixture was heated at 60 °C for 20 h. The reaction was concentrated under vacuum, and the crude product was purified by silica gel column chromatography (hexane/EtOAc, 40:1 + 0.1% Et_3N) to give **9b** (0.335 g, 28%) as a yellow oil; R_f = 0.14 (hexane/EtOAc, 20:1). ^{1}H NMR (300 MHz, [D$_6$]DMSO): δ = 7.71–7.52 (m, 6 H), 6.76 (d, J = 8.7 Hz, 2 H), 5.73 (d, J = 2.7 Hz, 1 H), 5.03 (s, 1 H), 4.54 (s, 1 H), 3.86–3.61 (m, 2 H), 3.03 (s, 6 H), 0.92 (s, 9 H), 0.85 (s, 9 H), 0.23 (s, 3 H), 0.20 (s, 3 H), 0.01 (s, 6 H) ppm. ^{13}C NMR (101 MHz, [D$_6$]DMSO): δ = 193.3, 153.2, 150.2, 146.5, 138.1, 132.1, 128.7, 126.8, 123.6, 110.7, 102.1, 83.4, 63.5, 59.8, 39.6, 25.8, 18.2, 17.7, –5.2, –5.4 ppm. MS (FAB): calcd. for $C_{32}H_{50}NO_4Si_2$ $[M + H]^+$ 568.3; found 568.4.

1β-{[4-(Methoxy)phenyl](phenyl)methanone}-3,5-bis-*O*-(*tert*-butyldimethylsilyl)-1,2-dideoxy-2,3-didehydro-D-ribofuranose (9c): A mixture of **8c** (0.500 g, 1.71 mmol), **5** (0.591 g, 1.171 mmol), and Et_3N (0.373 g, 3.69 mmol) was dissolved in MeCN (15 mL) in a dry vial, and the resulting mixture was degassed by a pump–freeze–thaw method. [1,1′-Bis(diphenylphosphino)ferrocene]dichloropalladium(II) (0.210 g, 0.258 mmol) was added, and the mixture was heated at 75 °C for 60 h. The reaction was concentrated under vacuum, and the crude product was purified by silica gel column chromatography (hexane/EtOAc, 20:1 + 0.1% Et_3N) to give **9c** (0.435 g, 46%) as a yellow oil; R_f = 0.20 (hexane/EtOAc, 20:1). ^{1}H NMR (300 MHz, [D$_6$]DMSO): δ = 7.77–7.68 (m, 2 H), 7.62 (s, 4 H), 7.08 (d, J = 8.8 Hz, 2 H), 5.78–5.69 (m, 1 H), 5.02 (d, J = 1.9 Hz, 1 H), 4.57–4.48 (m, 1 H), 3.80 (d, J = 2.0 Hz, 1 H), 3.72 (dd, J = 11.4, 3.6 Hz, 1 H), 0.92 (s, 9 H), 0.84 (s, 9 H), 0.21 (d, J = 10.1 Hz, 6 H), 0.01 (s, 6 H) ppm. ^{13}C NMR (101 MHz, [D$_6$]-DMSO): δ = 162.9, 150.2, 147.4, 136.9, 132.1, 129.4, 129.1, 126.9, 113.9, 83.3, 63.5, 55.6, 25.7, 25.4, 22.1, 18.1, 17.7, –5.4 ppm. MS (FAB): calcd. for $C_{31}H_{47}O_5Si_2$ $[M + H]^+$ 555.3; found 555.3.

1β-{[4-(Methyl)phenyl](phenyl)methanone}-3,5-bis-*O*-(*tert*-butyldimethylsilyl)-1,2-dideoxy-2,3-didehydro-D-ribofuranose (9d): A mixture of **8d** (0.500 g, 1.80 mmol), **5** (0.626 g, 1.180 mmol), and Et_3N (0.395 g, 3.90 mmol) was dissolved in MeCN (15 mL) in a dry vial, and the resulting mixture was degassed by bubbling argon through the solution as it was placed in an ultrasonic bath for 5 min. [1,1′-Bis(diphenylphosphino)ferrocene]dichloropalladium(II) (0.233 g, 0.300 mmol) was added, and the mixture was heated at 75 °C for 48 h. The reaction was concentrated under vacuum, and the crude product was purified by silica gel column chromatography (hexane/EtOAc, 20:1 + 0.1% Et_3N) to give **9d** (0.538 g, 55%) as a yellow oil; R_f = 0.17 (hexane/EtOAc, 20:1). ^{1}H NMR (300 MHz, [D$_6$]-DMSO): δ = 7.71–7.60 (m, 6 H), 7.39–7.31 (m, 3 H), 5.76–5.71 (m, 1 H), 4.55–4.50 (m, 1 H), 3.85–3.78 (m, 1 H), 3.74–3.70 (m, 1 H), 2.41 (s, 3 H), 0.92 (s, 9 H), 0.84 (s, 9 H), 0.20 (d, J = 7.4 Hz, 6 H), –0.01 (d, J = 5.1 Hz, 6 H) ppm. ^{13}C NMR (75 MHz, [D$_6$]DMSO): δ = 195.1, 150.2, 147.7, 143.1, 136.5, 134.4, 129.8, 129.2, 128.5, 126.9, 101.9, 83.2, 25.8, 25.4, 21.2, 18.1, 17.7, –5.2, –5.5 ppm. MS (FAB): calcd. for $C_{31}H_{46}O_4Si_2$ $[M]^+$ 538.3; found 538.3.

(4-Aminophenyl){4-[(4*S*,5*R*)-4-hydroxy-5-(hydroxymethyl)-tetrahydrofuran-2-yl]phenyl}methanone (1a): Under argon, **9a** (0.123 g, 0.230 mmol) was dissolved in anhydrous THF (6 mL), and the solution was cooled to 0 °C. $NEt_3{\cdot}3HF$ (0.309 g, 1.92 mmol) was added, and the reaction mixture was stirred at 0 °C for 15 min and then at 30 °C for 12 h. The reaction mixture was eluted with acetone through a short silica gel column (1 cm), and the eluate was

concentrated under vacuum. Without further purification, the residue was dissolved in AcOH/MeCN (1:1, 8 mL), and the solution was cooled to 0 °C. $NaBH(OAc)_3$ (0.109 g, 0.510 mmol) was added, and the reaction mixture was stirred at room temperature for 2 h and then neutralized with EtOH/water (1:1, 5 mL). The resulting mixture was concentrated under vacuum, and the crude product was purified by silica gel chromatography (CH_2Cl_2/MeOH, 20:1 + 0.1% Et_3N) to give **1a** (46.1 mg, 65%) as an orange solid; R_f = 0.13 (CH_2Cl_2/MeOH, 20:1). ^1H NMR (300 MHz, [D$_6$]DMSO): δ = 7.70–7.39 (m, 6 H), 6.60 (d, J = 8.40 Hz, 2 H), 6.15 (s, 2 H), 5.09 (dd, J = 10.3, 5.4 Hz, 1 H), 4.22 (d, J = 5.3 Hz, 1 H), 3.83 (s, 1 H), 3.48 (dd, J = 11.9, 5.2 Hz, 1 H), 3.48 (dd, J = 11.9, 5.2 Hz, 1 H), 2.14 (dd, J = 12.1, 5.4 Hz, 1 H), 1.90–1.76 (m, 2 H) ppm. ^{13}C NMR (75 MHz, [D$_6$]DMSO): δ = 193.2, 153.7, 146.0, 137.9, 132.6, 128.9, 125.7, 123.8, 112.5, 90.0, 78.9, 72.5, 62.5, 43.6 ppm. HRMS (FAB): calcd. for $C_{18}H_{20}NO_4$ [M + H]$^+$ 314.1387; found 314.1386.

(4-*N*,*N*-Dimethylaminophenyl){4-[(4*S*,5*R*)-4-hydroxy-5-(hydroxymethyl)-tetrahydrofuran-2-yl]phenyl}methanone (1b): Under argon, **9b** (0.740 g, 0.130 mmol) was dissolved in anhydrous THF (5 mL), and the solution was cooled to 0 °C. NEt_3·3HF (59.0 mg, 0.360 mmol) was added, and the reaction mixture was stirred at 0 °C for 15 min and then at room temperature for 12 h. The mixture was eluted with acetone through a short silica gel column (1 cm), and the eluate was concentrated under vacuum. Without further purification, the residue was dissolved in AcOH/MeCN (1:1, 8 mL), and the resulting solution was cooled to 0 °C. $NaBH(OAc)_3$ (42.0 mg, 0.200 mmol) was added, and the reaction mixture was stirred at room temperature for 20 min and then neutralized with EtOH/water (1:1, 2 mL). The reaction mixture was concentrated under vacuum, and the crude product was purified by silica gel column chromatography (CH_2Cl_2/MeOH, 40:1 + 0.1% Et_3N) to give **1b** (33.0 mg, 75%) as a yellow oil; R_f = 0.12 (CH_2Cl_2/MeOH, 20:1). ^1H NMR (300 MHz, [D$_6$]DMSO): δ = 7.70–7.54 (m, 4 H), 7.50 (d, J = 7.9 Hz, 2 H), 6.76 (d, J = 8.8 Hz, 2 H), 5.10 (dd, J = 10.3, 5.4 Hz, 1 H), 4.82 (br. s, 1 H), 4.22 (d, J = 5.2 Hz, 1 H), 3.88–3.76 (m, 1 H), 3.58–3.26 (m, 3 H), 3.03 (s, 6 H), 2.21–2.09 (m, 1 H), 1.88–1.72 (m, 1 H) ppm. ^{13}C NMR (101 MHz, [D$_6$]DMSO): δ = 193.3, 153.2, 146.2, 137.7, 132.1, 128.9, 125.7, 123.7, 110.7, 87.8, 78.8, 72.4, 64.4, 43.6, 39.6 ppm. HRMS (FAB): calcd. for $C_{20}H_{24}NO_4$ [M + H]$^+$ 342.1700; found 342.1703.

(4-Methoxyphenyl){4-[(4*S*,5*R*)-4-hydroxy-5-(hydroxymethyl)-tetrahydrofuran-2-yl]phenyl}methanone (1c): Under argon, **9c** (0.435 g, 0.780 mmol) was dissolved in anhydrous THF (15 mL), and the solution was cooled to 0 °C. NEt_3·3HF (59.0 mg, 0.360 mmol) was added, and the reaction mixture was stirred at 0 °C for 15 min and at 30 °C for 12 h. The mixture was then eluted with acetone through a short silica gel column (1 cm), and the eluate was concentrated under vacuum. Without further purification, the residue was dissolved in AcOH/MeCN (1:1, 8 mL) and cooled to 0 °C. $NaBH(OAc)_3$ (533 mg, 2.51 mmol) was added, and the reaction mixture was stirred at room temperature for 20 min and then neutralized with EtOH/water (1:1, 20 mL). The mixture was concentrated under vacuum, and the crude product was purified by silica gel chromatography (CH_2Cl_2/MeOH, 40:1) to give **1c** (166.0 mg, 65%) as a yellow oil; R_f = 0.38 (CH_2Cl_2/MeOH, 20:1). ^1H NMR (300 MHz, [D$_6$]DMSO): δ = 7.74 (d, J = 8.8 Hz, 2 H), 7.65 (d, J = 8.2 Hz, 2 H), 7.53 (d, J = 8.2 Hz, 2 H), 7.09 (d, J = 8.8 Hz, 2 H), 5.11 (q, J = 5.8 Hz, 2 H), 4.79 (t, J = 5.3 Hz, 1 H), 4.22 (s, 1 H), 3.86 (d, J = 1.8 Hz, 3 H), 3.83 (dd, J = 5.5, 2.2 Hz, 1 H), 3.56–3.39 (m, 2 H), 2.16 (ddd, J = 12.6, 5.5, 1.6 Hz, 1 H), 1.80 (ddd, J = 12.8, 10.5, 5.5 Hz, 1 H) ppm. ^{13}C NMR (101 MHz, [D$_6$]DMSO): δ = 162.88, 147.20, 132.13, 129.43, 125.85, 113.88, 88.00, 78.81, 72.43, 62.41, 55.57 ppm. HRMS (FAB): calcd. for $C_{19}H_{21}O_5$ [M + H]$^+$ 329.1384; found 329.1382.

(4-Methylphenyl){4-[(4*S*,5*R*)-4-hydroxy-5-(hydroxymethyl)-tetrahydrofuran-2-yl]phenyl}methanone (1d): Under argon, **9d** (1.06 g, 1.97 mmol) was dissolved in anhydrous THF (30 mL), and the solution was cooled to 0 °C. NEt_3·3HF (0.890 g, 5.50 mmol) was added, and the reaction mixture was stirred at 0 °C for 15 min and at 30 °C for 12 h. The reaction mixture was then eluted with acetone through a short silica gel column (1 cm), and the eluate was concentrated under vacuum. Without further purification, the residue was dissolved in AcOH/MeCN (1:1, 40 mL), and the resulting mixture was cooled to 0 °C. $NaBH(OAc)_3$ (1.01 g, 4.81 mmol) was added, and the reaction mixture was stirred at room temperature for 40 min and then neutralized with EtOH/water (1:1, 40 mL). The reaction mixture was concentrated under vacuum, and the crude product was purified by silica gel chromatography (CH_2Cl_2/MeOH, 20:1) to give **1d** (406 mg, 66%) as a yellow oil; R_f = 0.15 (CH_2Cl_2/MeOH, 20:1). ^1H NMR (300 MHz, [D$_6$]DMSO): δ = 7.65 (t, J = 8.7 Hz, 4 H), 7.52 (d, J = 8.0 Hz, 2 H), 7.35 (d, J = 7.8 Hz, 2 H), 5.11 (t, J = 5.5 Hz, 2 H), 4.79 (t, J = 5.5 Hz, 1 H), 4.20 (d, J = 4.9 Hz, 1 H), 3.87–3.76 (m, 1 H), 3.46 (m, J = 17.2, 6.0 Hz, 2 H), 2.39 (s, 3 H), 2.15 (dd, J = 12.8, 5.5 Hz, 1 H), 1.79 (td, J = 12.1, 5.4 Hz, 1 H) ppm. ^{13}C NMR (75 MHz, [D$_6$]DMSO): δ = 195.1, 147.6, 143.0, 136.2, 134.4, 129.8, 129.6, 129.1, 125.9, 88.0, 78.8, 72.5, 62.4, 43.6, 21.1 ppm. HRMS (FAB): calcd. for $C_{19}H_{21}O_4$ [M + H]$^+$ 313.1434; found 313.1436.

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