Total Synthesis of a *Cis*-Syn 2-Carbomethoxypsoralen Furan-Side Thymidine Monoadduct

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Abstract: The first total chemical synthesis of a *cis*-syn furan-side photoproduct between a psoralen derivative and thymidine is described. The key step in the synthesis was an intramolecular [2 + 2] photocycloaddition, which directed the stereochemical course of the reaction to afford a product equivalent to that formed when a psoralen molecule is allowed to react at a 5′-TpA-3′ site in DNA. A model system consisting of a simple benzofuranyl acid tethered to the 5′ hydroxyl of thymidine showed that it was possible to bias the stereochemical outcome of the photochemical reaction in favor of the desired *cis*-syn product. Further refinement of the model system allowed for the elaboration of a benzofuran−thymidine photoproduct into a *cis*-syn 2-carbomethoxypsoralen furan-side thymidine monoadduct. The stereochemistry of all photoproducts as established by NMR and CD spectroscopy indicated that the cycloadditions occurred on the 3′ face of thymine, the equivalent of a psoralen monoadduct in a 5′-TpA-3′ site in DNA. Previously, the inability to program the sequence context of psoralen−DNA adducts has constrained certain biological studies, such as experiments aimed at deciphering the transcriptional effects of adducts at TATA sites. This method is a key step toward overcoming that problem.

Introduction

Psoralens are linear furocoumarins used medicinally for the treatment of skin disorders[1] and cutaneous T-cell lymphoma.[2] The double stranded nucleic acids of cells treated with psoralen react by a [2 + 2] photocycloaddition with pyrimidines. These bulky psoralen−pyrimidine adducts lead to mutations and have been shown to be genotoxic.[3] Psoralen−DNA adducts have been used as tools for studying DNA repair,[4] for probing protein−DNA interactions,[5] and for arresting transcription.[6] Because of the usefulness of psoralens as molecular probes, many synthetic derivatives such as 2-carbomethoxypsoralen, 3-aminomethyltrioxsalen (AMT), and 3-hydroxymethyltrioxsalen (HMT) have been made with the aim of enhancing water solubility and photoreactivity.[7]

Immediately before the photochemical reaction of psoralen with DNA, psoralen intercalates between the bases of a helical nucleic acid. Upon exposure to long-wave UV light (320−410 nm), either the pyrone or furan double bonds of psoralen can react with the 5,6-double bond of a pyrimidine to form an initial monoadduct. A furan-side adduct can absorb a second photon and react with an adjacent pyrimidine on the opposite strand forming an interstrand cross-link. By contrast, pyrone-side monoadducts cannot absorb long wave UV light and therefore do not form cross-links. When irradiated in the presence of model oligonucleotides, psoralens show sequence selectively as evidenced by the 100-fold preference for reaction at 5′-TpA-3′ as compared to 5′-ApT-3′ sites.[8] All psoralen photoadducts can be reversed by 254 nm light;[9] cross-links and furan-side adducts can also be reversed by treatment with base.[10]

Hearst and co-workers have isolated and characterized the three major psoralen−DNA monoadducts.[9b,11] The structure of

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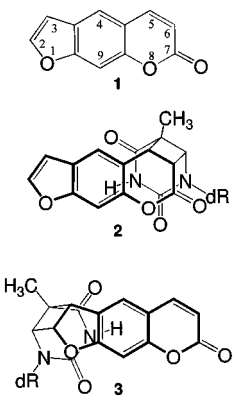
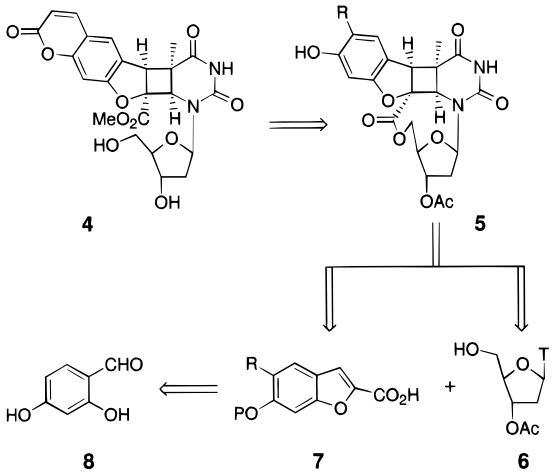


Figure 1. Structure of psoralen **1** and the structures of the major monoadducts between psoralen and thymidine: *cis*-syn pyrone-side photoproduct **2** and *cis*-syn furan-side photoproduct **3**. dR = deoxyribose.

psoralen **1** and the structures and stereochemistries of the isolated adducts are shown in Figure 1.[12] The adducts consist of a psoralen−thymidine *cis*-syn pyrone-side adduct **2** and both diastereomers of a *cis*-syn furan-side adduct **3**. The two furan-side adducts arise from reaction of the psoralen on either the 5′ or the 3′ face of thymidine. The stereoselectivity of the photoreaction is exceptional given that 64 monoadducts are theoretically possible between thymidine and psoralen; 48 of these adducts however, do not form apparently because they would contain a highly strained and sterically hindered *trans* fusion about the pyrimidine or psoralen rings. Elimination of these strained isomers still leaves eight possible isomers for each monoadduct. Attempts to synthesize these adducts in the absence of DNA have met with modest success. DNA helps to control the stereochemistry of the photochemical reaction because the hydrophobic psoralen molecule intercalates between the nucleobases resulting in primarily *cis* photoproducts; in addition, DNA also inhibits psoralen photodimerization.[13] Two similar approaches to mimic the intercalation step involve irradiation of frozen aqueous solutions or evaporated thin films containing psoralen and thymidine.[14] Unfortunately, numerous photoproducts were isolated and in very poor yields. A more promising strategy by Lhomme and co-workers utilized succinic acid to attach a hydroxy psoralen derivative to the 5′-hydroxyl of thymidine to control stereochemistry and eliminate psoralen photodimerization.[15] Unfortunately, this method provides only the pyrone *cis*-anti isomer and not the desired *cis*-syn isomer. In addition, the removal of the succinyl linker was not reported.

As a continuation of our biochemical and genetic studies on damaged nucleosides caused by carcinogens, ionizing radiation, or chemotherapeutic agents we desired to synthesize a psoralen furan-side monoadduct. Our strategy involved linking a psoralen retron to thymidine in order to control the stereochemistry of the photoreaction. Based on some earlier results with tethered thymidine-psoralen derivatives, we determined that attachment at the 2 position of psoralen could afford the *cis*-syn stereoisomer. Because psoralen dimerization is a severe problem in the absence of double stranded DNA, we chose benzofuran as a psoralen synthon. Benzofuran is missing the photochemically

Scheme 1



more reactive pyrone ring of psoralen, thereby minimizing dimerization.[15] Interestingly, the furan double bond has been shown to be the more reactive double bond when intercalated in DNA owing to its juxtaposition to the 5,6 thymidine double bond in a 5′-TpA-3′ site.[16] After setting the stereochemistry with the photochemical step, the benzofuran−thymidine adduct could be elaborated into the desired 2-carbomethoxypsoralen−thymidine adduct. In this paper we describe the details of our model study using benzofuran as a psoralen synthon and report its successful application to the first total synthesis of a *cis*-syn furan-side monoadduct between a psoralen derivative and thymidine.

Results and Discussion

The retrosynthetic route to *cis*-syn 2-carbomethoxypsoralen−thymidine furan-side adduct **4** is shown in Scheme 1. Removal of the pyrone ring would provide benzofuran photoproduct **5**. Photoproduct **5** could be formed in a stereospecific manner from a benzofuranyl acid **7** linked to the 5′-hydroxyl of thymidine **6**.[15] Benzofuranyl acid **7** is readily obtained from salicylaldehyde **8**. The key step in the total synthesis would be the photochemical reaction with benzofuran. The photochemistry of benzofuranyl esters was not known, and we believed it was necessary to test our strategy in a model system. The primary goal of the model system was to direct the stereochemical outcome of the photochemical reaction to obtain the desired *cis*-syn stereochemistry. The successful application of this model is shown in Scheme 2.

Commercially available salicylaldehyde **9** was allowed to react with diethyl bromomalonate to give a benzofuran ester, which was saponified to afford benzofuranyl acid **10**. Esterification of **10** with a 3′-protected thymidine, **6**, provided photoprecursor **11** in 75% yield. Irradiation of an acetone sensitized, argon degassed, dilute (<0.002 M) solution of **11** in acetonitrile afforded two diastereomers with a 4:1 ratio in 71% overall yield. To our surprise, attempts to purify photoproducts **12a** and **12b** by using standard silica gel chromatography with methylene chloride and methanol as an eluent, transesterified the nine-membered lactone of the major isomer **12a** to give ring opened photoproduct **13** containing a methyl ester. The minor isomer **12b** did not transesterify with methanol and silica gel and could be purified as the lactone using methanol as the eluent. We have tested a few alcohols in an attempt to transesterify the major isomer **12a**, and so far only methanol

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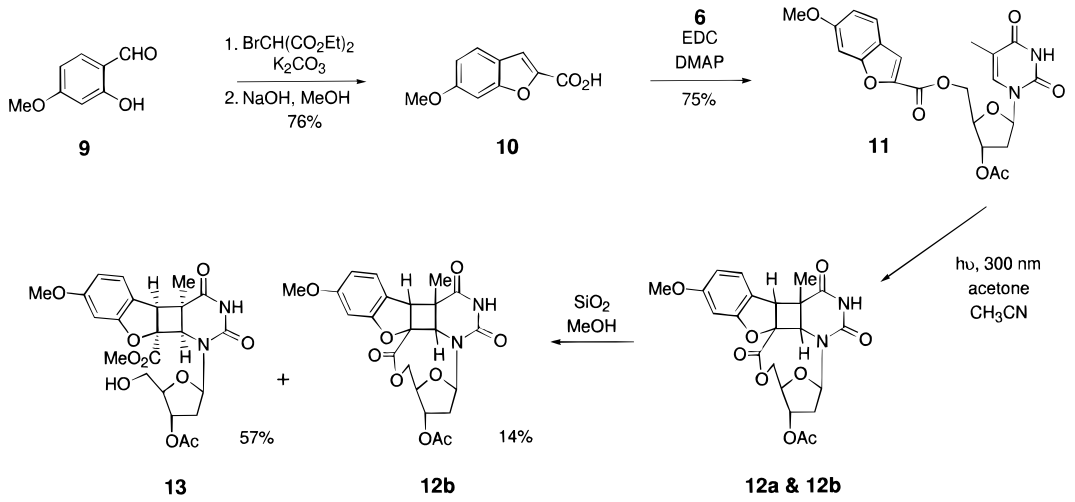
Scheme 2



and water effect this transformation. In fact, a 50:50 solution of methanol and ethanol led only to methyl ester photoproduct **13**. It is possible that ethanol is too sterically hindered to transesterify the major isomer because the nucleophilicity between methanol and ethanol are minimal.

We used NMR to determine both the regio- and stereochemistry of the isolated photoproducts **12b** and **13**. The regiochemistry of both photoproducts was determined by observing the coupling constant between the H6 proton of thymidine and the H3 proton of benzofuran. Only long range coupling (2 Hz) was observed for both photoproducts, which is indicative of syn stereochemistry.[17] To determine if the thymidine methyl group were on the same side of the four-membered ring as the H3 and H6 protons as desired, an NOE difference experiment was performed (Figure 2). Irradiation of the thymidine methyl group of major isomer **13** gave a positive NOE for both ring protons, which confirmed that the major photoproduct possessed the desired *cis*-stereochemistry. Irradiation of the thymidine methyl group of minor isomer **12b** gave only one positive NOE for the H6 proton of thymidine (Figure 2c). Hence, the minor isomer is the *trans*-syn isomer. Attempts to crystallize the major photoproduct, to assign on which face of the thymidine ring the [2 + 2] cycloaddition occurred, have yet to yield a crystal of X-ray diffraction quality. However, Hearst et al. have shown that the CD spectrum of a 5′-TpA-3′ psoralen adduct has a negative ellipticity from 270 to 360 nm, whereas the 5′-ApT-3′ adduct has a positive ellipticity in the same range.[8a] It appears that the contribution of the deoxyribose ring affects the CD spectrum minimally, and the two diastereomers behave as enantiomers in the presence of polarized light. Although the model compound did not contain the full coumarin ring, we believed that the facial selectivity could be ascertained from a CD spectrum. The CD spectrum of the major isomer **13**, shown in Figure 2, has a negative ellipticity from 260 to 290 nm suggesting the cycloaddition had occurred on the 3′ face of thymidine.

Having firmly established a methodology to construct a *cis*-syn photoproduct by using benzofuran as a psoralen guise, we were confident that a 2-carbomethoxypsoralen−thymidine adduct was achievable by total synthesis. Two minor modifications of the model system were necessary. First, a simple change of a protecting group on the phenol would allow for a mild deprotection when coupled to the nucleoside. The second

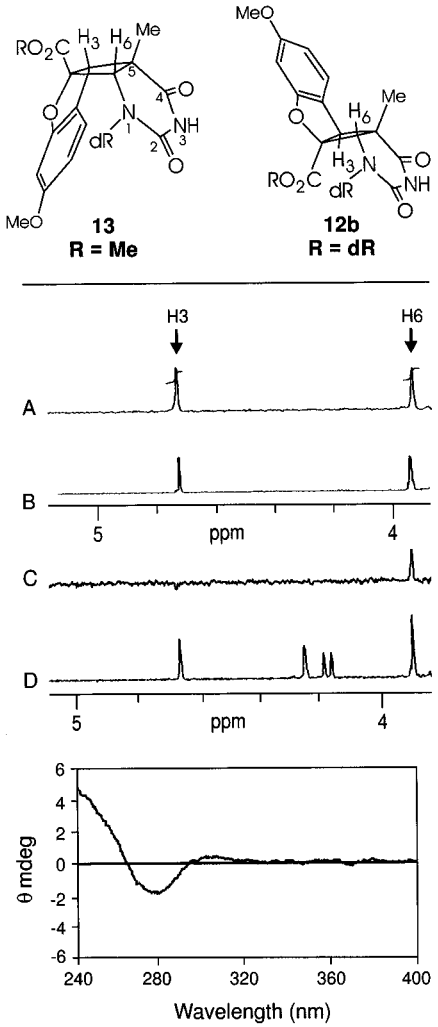


Figure 2. (Above) Structures of the benzofuran-thymidine photoproducts **13** and **12b**, where dR = 2′-deoxy-3′-*O*-acetylribose. (Middle) Nuclear Overhauser enhancements for photoproducts **13** and **12b**. (A) difference spectrum between the major isomer **13** irradiated at the thymidine methyl resonance (1.78 ppm) and (B); (B) proton NMR spectrum of the major isomer **13** (4.0−5.0 ppm). (C) difference spectrum between the minor isomer **12b** irradiated at the thymidine methyl resonance (1.28 ppm) and (D); (D) proton NMR spectrum of the minor isomer **12b** (4.0−5.0 ppm). (Below) Circular dichroism spectrum of the benzofuran−thymidine major photoproduct **13**.

modification was to incorporate an aldehyde *ortho* to the methoxymethyl (MOM) protected phenol. Addition of a formyl

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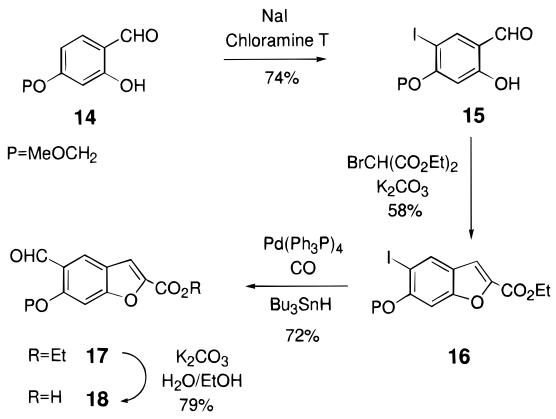
Scheme 3



group at this position would allow for a mild conversion of the benzofuran photoproduct into the desired psoralen−thymidine adduct.[18] Earlier formylations of 6-alkoxybenzofurans utilized DMF-$POCl_3$ to formylate directly the benzofuran. However, these conditions resulted in primarily 7-formylbenzofurans and afforded little 5-formyl product.[7e] Scheme 3 depicts a two step approach utilizing halogenation followed by a palladium(0) catalyzed formylation[19] to attain a 5-formylbenzofuran. Treatment of selectively protected **14**[20] with sodium iodide and chloramine T gave primarily *para* iodinated **15**.[21] Cyclization of **15** to benzofuran **16** was accomplished with diethyl bromomalonate and potassium carbonate. The desired aldehyde was synthesized using a Stille coupling.[19] Palladium(0) coupling with **16**, carbon monoxide, and slow addition of tributyltin hydride gave 5-formylbenzofuran **17**. The overall two step yield for incorporation of the 5-aldehyde was 53%. Saponification of **17** yielded benzofuranyl acid **18**.[22]

With the benzofuran portion of the molecule in hand, the next task was to couple it to thymidine and produce a photoprecursor. The synthesis began with carbodiimide coupling of **18** with 3′-*O*-actetylthymidine **6** to give esterified **19**, as shown in Scheme 4. Removal of the protecting group using trityl cation afforded phenol **20** in 90% yield.[23] Efforts to use HCl/methanol to remove the MOM group led to side products and lower yields. All attempts at photochemistry with aldehyde **20** resulted in no reaction presumably owing to fluorescence quenching by the benzaldehyde moiety. To circumvent this problem, aldehyde **20** was protected by reduction $NaBH_4$ to the readily oxidizable benzylic alcohol **21**. A dilute solution of photoprecursor **21** in 20:1 acetonitrile/acetone was irradiated with 300 nm light and afforded only one diastereomer, which was transesterified with silica gel and methanol to afford the ring opened photoproduct **22** in 58% yield. Selective oxidation of **22** with oxygen in the presence of CuCl and TEMPO afforded aldehyde **23**.[24] Typically harsh, basic conditions are needed to construct the pyrone ring from *ortho* formyl phenols.[25] Barton and others have used enediamines or commercially available acetamide acetals to effect this transformation under relatively mild conditions.[18] Treatment of aldehyde **23** with *N*′,*N*′-dimethylacetamide dimethylacetal in the presence of 4 Å sieves at room temperature gave coumarin **24** in 38% yield. Although the yield for this step is moderate, the chemoselectivity of the reagent to form a carbon−carbon double bond in the presence of a free primary hydroxyl and imide is noteworthy. The protected 2-carbomethoxypsoralen−thymidine adduct was converted into the desired photoproduct **4** using DBU in methanol.

Determination of the stereochemistry of photoproduct **4** was identical to the model system. The coupling constant between the H6 thymidine proton and the H3 benzofuran proton of psoralen was small, 1.7 Hz, confirming the syn regioisomer. Figure 3a shows the difference NOE experiment where irradiation of the thymidine methyl shows an enhancement of both H6 and H3 protons confirming the stereochemistry as *cis*. The final stereochemical determination was whether the 2-carbomethoxypsoralen was situated on the 5′ or 3′ face of thymidine. The CD spectrum of the synthesized adduct **4**, was nearly identical with the CD spectra of an isolated psoralen−thymidine adduct even though the psoralen moieties are slightly different (Figure 3).[8a,11f] The synthesized 2-carbomethoxypsoralen−thymidine adduct is the adduct equivalent to the reaction occurring at a 5′-TpA-3′ site in DNA; this is the 100-fold most prevalent adduct under normal conditions of DNA damage.

Summary

We have described the first total synthesis of a *cis*-syn furanside monoadduct between thymidine and a psoralen derivative. Linking a benzofuranyl acid derivative to the 5′ hydroxyl of thymidine was crucial in the control of the regio- and stereochemistry to give a *cis*-syn adduct. The key [2 + 2] cycloaddition occurs with high facial selectivity giving primarily or only the *cis*-syn 3′ face adduct, which is the most prominent adduct found upon DNA−psoralen irradiation or a medicinal treatment. The benefit of this total synthetic approach is that it affords the opportunity to place psoralen adducts into DNA sequence contexts containing multiple sites of adduction. Efforts to incorporate these adducts into DNA for biological studies are underway.

Experimental Section

General Procedures. Unless otherwise specified, materials were obtained from commercial suppliers and were used without further purification. Tetrahydrofuran (THF) was distilled from potassium/benzophenone ketyl. Methanol (MeOH) was distilled from sodium metal and used immediately after distillation. Anhydrous solvents were otherwise obtained from Aldrich. Column chromatography was performed on Merck silica gel (230−400 mesh). ^{1}H NMR spectra were recorded at 500 or 300 MHz on superconducting FT spectrometers. ^{13}C NMR spectra were proton decoupled and were recorded at 125 or 75 MHz. Coupling constants are measured in hertz. Melting points (pyrex capillary) are uncorrected.

6-Methoxy-2-benzofuran Carboxylic Acid (10). To a solution of 5.74 g (37.7 mmol) of 4-methoxysalicylaldehyde **9** in 400 mL of dry 2-butanone were added 9.70 mL (56.6 mmol) of diethyl bromomalonate and 15.6 g (113 mmol) of oven dried K_2CO_3. The solution was stirred vigorously and heated to reflux for 7 h, cooled, and filtered. The solvents were removed and the solids were diluted in 100 mL of methanol and 200 mL of 1 N NaOH solution. The solution was then heated to reflux for 1 h. After cooling to room temperature, the reaction mixture was extracted once with ethyl acetate and then acidified to pH 1. The tan precipitate that formed was collected, rinsed with 1 N HCl, and dried to afford 5.53 g (76%) for two steps: ^{1}H NMR (500 MHz, DMSO-d_6) δ 3.82 (s, 3 H), 6.96 (dd, 1 H, J = 2.0, 8.3), 7.28 (d, 1 H, J = 1.5), 7.58 (s, 1 H), 7.63 (d, 1 H, J = 8.3); ^{13}C NMR δ 55.62, 95.81, 101.70, 113.60, 119.89, 123.18, 145.24, 156.37, 159.86, 159.95; HRMS (EI) calcd for $C_{10}H_8O_4$ $(M)^+$ 192.0423, found 192.0424.

5′-*O*-(6-Methoxy-2-benzofuranyl)-3′-*O*-acetylthymidine (11). To a solution of 0.38 g (1.52 mmol) of compound **10** in 5 mL of dry

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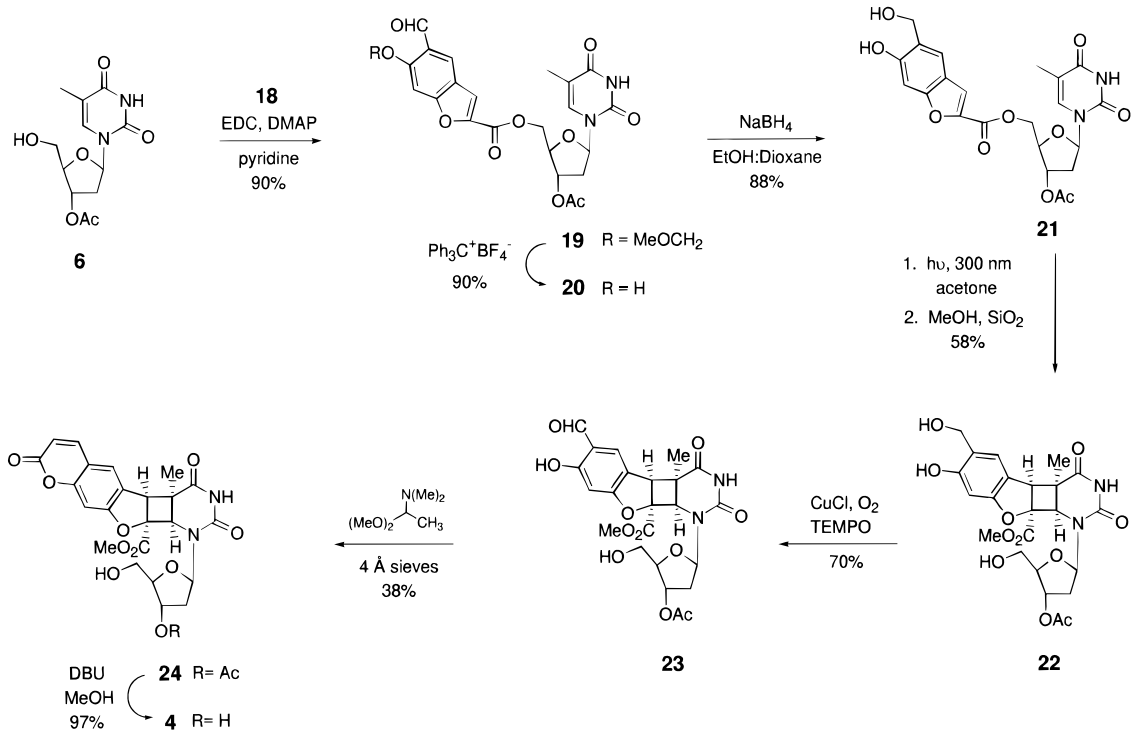
Scheme 4



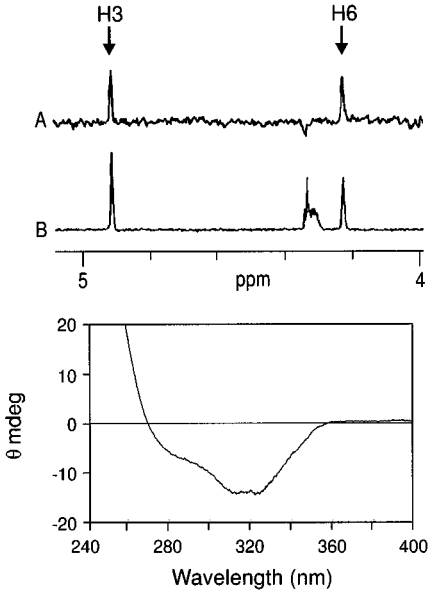


Figure 3. (Above) Nuclear Overhauser enhancements for the 2-carbomethoxypsoralen-thymidine furan-side mono-adduct **4**. (A) difference spectrum between sample irradiated at the thymidine methyl resonance (1.80 ppm) and (B); (B) 4.0−5.0 ppm region of the proton NMR spectrum. (Below) Circular dichroism spectrum of the 2-carbomethoxypsoralen-thymidine furan-side mono-adduct **4**.

pyridine were added 0.46 g (1.60 mmol) of 3′-*O*-acetylthymidine **6**, 0.35 g (1.82 mmol) of 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDC), and 20 mg (0.15 mmol) of DMAP. The solution was stirred at room temperature under an argon atmosphere for 16 h. The reaction mixture was concentrated, dissolved in CH_2Cl_2, washed with 1 N HCl and saturated $NaHCO_3$, and then dried over Na_2SO_4. The crude product was purified by silica gel chromatography eluting with 100:1 dichloromethane/methanol to afford 0.54 g (75%) of a white foam: ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.63 (app s, 3 H), 2.12 (s, 3 H), 2.38 (ddd, 1 H, J = 6.2, 8.8, 14), 2.50 (app dd, 1 H, J = 5.6, 14), 3.84 (s, 3 H), 4.36 (app d, 1 H, J = 1.6), 4.59 (dd, 1 H, J = 2.5, 12), 4.66 (dd, 1 H, J = 2.9, 12), 5.35 (app d, 1 H, J = 6.2), 6.44 (dd, 1 H, J = 5.6, 8.8), 6.92−6.96 (m, 2 H), 7.26−7.54 (m, 3 H), 9.54 (br s, 1 H); ^{13}C NMR δ 12.18, 20.78, 37.52, 55.71, 64.55, 74.89, 82.35, 84.89, 95.48, 111.52, 114.52, 115.44, 119.98, 123.21, 134.76, 143.80, 150.49, 157.21, 158.61, 161.11, 163.53, 170.35; UV_{max} (CH_3CN) 312, 268, 246 nm; HRMS (FAB$^+$, 3-NBA) calcd for $C_{22}H_{22}O_{19}N_2$ $(M + H)^+$ 459.1404, found 459.1404.

5′-*O*-(6-Methoxy-2-benzofuranyl)-3′-*O*-acetylthymidine Photoproduct. A solution of 75 mg (0.16 mmol) of photoprecursor **11** in 85 mL of dry CH_3CN was deaerated with argon bubbling for 30 min. Acetone (4.25 mL) was added and the solution was irradiated with 300 nm light in a 16 bulb Rayonet photoreactor for 5 h at room temperature. The solvent was removed *in vacuo*, and the crude material was dissolved in 25 mL of methanol with 150 mg of silica gel and stirred at room temperature for 30 min to effect transesterification. The methanol was removed, and the absorbed material was directly added to the top of a silica gel column. Elution with a gradient of 100:1 to 50:1 dichloromethane/methanol afforded 45 mg (57%) of a major isomer **13** and 10 mg (14%) of a minor isomer **12b**.

Major isomer *cis*-syn (13): ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.78 (s, 3 H), 2.07−2.12 (m, 1 H), 2.08 (s, 3 H), 2.37 (ddd, 1 H, J = 2.0, 5.4, 14), 3.76 (s, 3 H), 3.79−3.83 (m, 2 H), 3.86−3.88 (m, 1 H), 3.87 (s, 3 H), 3.95 (d, 1 H, J = 2.0), 4.73 (d, 1 H, J = 2.0), 5.19−5.22 (m, 1 H), 5.95 (dd, 1 H, J = 5.4, 9.3), 6.46−6.48 (m, 2 H), 6.99 (d, 1 H, J = 7.8), 7.06 (br s, 1 H); ^{13}C NMR δ 21.00, 22.71, 36.12, 46.34, 53.44, 55.52, 56.05, 57.85, 62.58, 74.48, 84.25, 85.42, 86.72, 96.49, 108.75, 115.30, 126.81, 150.69, 161.70, 162.33, 169.67, 170.65, 170.69; UV_{max} (CH_3CN) 284 nm; HRMS (FAB$^+$, 3-NBA) calcd for $C_{23}H_{26}O_{10}N_2$ $(M + H)^+$ 491.1666, found 491.1664.

Minor isomer *trans*-syn (12b): ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.28 (s, 3 H), 2.10 (s, 3 H), 2.24 (app dd, 1 H, J = 7.3, 15), 2.84 (ddd, 1 H, J = 5.9, 8.8, 15), 3.80 (s, 3 H), 3.89 (s, 1 H), 4.18 (app d, 1 H, J = 12), 4.25 (app d, 1 H, J = 2.0), 4.66 (s, 1 H), 5.19 (dd, 1 H, J = 2.0, 12), 5.48 (app d, 1 H, J = 5.9), 6.35 (app t, 1 H, J = 8.8), 6.55−6.58 (m, 2H), 7.15 (d, 1 H, J = 8.3), 7.50 (br s, 1 H); ^{13}C NMR δ 20.98, 22.49, 32.25, 48.00, 55.61, 65.59, 67.57, 77.20, 77.85, 82.60, 87.86, 91.55, 97.13, 108.35, 114.93, 126.97, 151.24, 161.12, 161.73, 165.55, 170.58, 171.77; HRMS (FAB$^+$, 3-NBA) calcd for $C_{22}H_{22}O_9N_2$ $(M + H)^+$ 459.1404 found 459.1398.

2-Hydroxy-5-iodo-4-(methoxymethyl)benzaldehyde (15). Chloramine T (4.54 g, 20.6 mmol) in 15 mL of DMF was added over a 10 min period to a solution of 3.13 g (17.2 mmol) of **14** and 3.09 g (20.6 mmol) of sodium iodide in 50 mL of DMF. The solution was stirred for an additional 30 min, diluted with ethyl acetate, and washed with 1 N HCl and 5% sodium thiosulfate. The organic layer was then extracted twice with 1 N NaOH, and the aqueous extractions were

separated. The aqueous layers were acidified with 1 N HCl in the presence of ethyl acetate. The organic layer was dried over $MgSO_4$. Purification of the crude product by silica gel chromatography eluting with 15:1 hexanes/ethyl acetate afforded 3.92 g (74%) of a white flaky solid: ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.34 (s, 3 H), 5.12 (s, 2 H), 6.48 (s, 1 H), 7.72 (s, 1H), 9.52 (s, 1 H), 11.13 (s, 1 H); ^{13}C NMR δ 56.74, 74.47, 94.81, 102.55, 117.70, 143.81, 162.15, 164.08, 193.61; HRMS (EI) calcd for $C_9H_9O_4I$ $(M)^+$ 307.9546, found 307.9545. Anal. Calcd for $C_9H_9O_4I$: C, 35.09; H, 2.94; I, 41.19. Found: C, 35.24; H, 3.04; I, 41.52; mp 77−79 °C.

2-Carboethoxy-5-iodo-6-(methoxymethyl)benzofuran (16). To a solution of 3.89 g (12.6 mmol) of compound **15** in 200 mL of dry 2-butanone were added 3.25 mL (18.9 mmol) of diethyl bromomalonate and 5.25 g (37.8 mmol) of oven dried K_2CO_3. The solution was stirred vigorously and heated to reflux for 24 h, cooled, and filtered. Removal of the solvents *in vacuo* and purification by silica gel chromatography eluting with 10:1 hexanes/ethyl acetate afforded 2.76 g (58%) of a fluffy white solid: ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.39 (t, 3 H, J = 7.1), 3.49 (s, 3 H), 4.39 (q, 2 H, J = 7.1), 5.26 (s, 2 H), 7.31 (s, 1 H), 7.36 (s, 1 H), 8.05 (s, 1 H); ^{13}C NMR δ 14.23, 56.39, 61.39, 82.87, 95.30, 98.59, 112.47, 123.26, 132.27, 145.81, 155.31, 156.51, 159.09; HRMS (EI) calcd for $C_{13}H_{13}O_5I$ $(M)^+$ 375.9808, found 375.9807. Anal. Calcd for $C_{13}H_{13}O_5I$: C, 41.51; H, 3.48; I, 33.74. Found: C, 41.42; H, 3.48; I, 33.93; mp 90−91 °C.

2-Carboethoxy-5-formyl-6-(methoxymethyl)benzofuran (17). A solution of 1.00 g (2.66 mmol) of compound **16** and 231 mg (0.20 mmol) of $Pd(Ph_3P)_4$ in 10 mL of dry THF was heated to 50 °C under an CO atmosphere (1 atm). A solution of 0.79 mL (2.93 mmol) of tributyltin hydride in 20 mL of dry THF was added to the solution over a 6 h period. The solution was cooled to room temperature and the solvents were removed *in vacuo*. The crude material was purified by a short silica gel column eluting with chloroform to separate the tin impurities from the product. Purification of the tin free product eluting with a gradient of 10:1 hexanes/ethyl acetate to 5:1 hexanes/ethyl acetate afforded 0.53 g (72%) of yellow-white solid: ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.35 (t, 3 H, J = 7.2), 3.48 (s, 3 H), 4.36 (q, 2 H, J = 7.2), 5.30 (s, 2 H), 7.33 (s, 1 H), 7.42 (s, 1 H), 8.09 (s, 1 H), 10.43 (s, 1 H); ^{13}C NMR δ 14.10, 56.39, 61.43, 95.04, 98.36, 113.99, 121.14, 123.38, 123.42, 146.62, 158.73, 159.47, 159.49, 188.76; HRMS (EI) calcd for $C_{14}H_{14}O_6$ $(M)^+$ 278.0790, found 278.0792. Anal. Calcd for $C_{14}H_{14}O_6$: C, 60.43; H, 5.07. Found: C, 60.34; H, 5.07; mp 70−71 °C.

5-Formyl-6-(methoxymethyl)-2-benzofuran Carboxylic Acid (18). A solution of 0.49 g (1.77 mmol) of compound **17** and 7.5 mL of saturated aqueous K_2CO_3 in 30 mL of ethanol was heated to reflux for 30 min. The solvents were removed, the crude product was dissolved in water, and the aqueous layer was washed twice with ethyl acetate. The aqueous layer was acidified to pH 3 with 0.1 M H_2SO_4. The resulting precipitate was filtered, washed with cold pH 3 water, and dried overnight to afford 0.35 g (79%) of a white solid: ^{1}H NMR (300 MHz, DMSO-d_6) δ 3.46 (s, 3 H), 5.43 (s, 2H), 7.52 (s, 1 H), 7.67 (s, 1 H), 8.13 (s, 1 H), 10.39 (s, 1 H); ^{13}C NMR δ 56.31, 94.91, 98.64, 114.11, 121.14, 123.17, 123.44, 147.23, 158.84, 159.02, 159.62, 188.74; HRMS (FAB^+, glycerol) calcd for $C_{12}H_{10}O_6$ $(M + H)^+$ 251.0556, found 251.0552.

5′-*O*-[5-Formyl-6-(methoxymethyl)-2-benzofuranyl]-3′-*O*-acetylthymidine (19). To a solution of 0.30 g (1.18 mmol) of compound **18** in 4 mL of dry pyridine were added 0.36 g (1.25 mmol) of 3′-*O*-acetylthymidine **6**, 0.29 g (1.50 mmol) of 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDC), and a catalytic amount of DMAP. The solution was stirred at room temperature under an argon atmosphere for 24 h. The solvent was concentrated, dissolved in CH_2Cl_2, washed with 1 N HCl and saturated $NaHCO_3$, and then dried over $MgSO_4$. The crude product was purified by silica gel chromatography eluting with 100:1 dichloromethane/methanol to afford 0.50 g (90%) of a white foam: ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.67 (d, 3 H, J = 1.2), 2.12 (s, 3 H), 2.37 (ddd, 1 H, J = 6.4, 9.0, 14), 2.51 (ddd, 1 H, J = 1.3, 5.5, 14), 3.52 (s, 3 H), 4.34−4.37 (m, 1 H), 4.59 (dd, 1 H, J = 2.7, 12), 4.67 (dd, J = 3.1, 12), 5.32−5.37 (m, 1 H), 5.34 (s, 2 H), 6.42 (dd, 1 H, J = 5.5, 9.0), 7.32 (s, 1 H), 7.44 (d, 1 H, J = 1.2), 7.62 (s, 1 H), 8.19 (s, 1 H), 9.46 (br s, 1 H), 10.48 (s, 1 H); ^{13}C NMR δ 12.31, 20.83, 37.43, 56.58, 64.91, 74.70, 82.13, 84.87, 95.14, 98.31, 111.51, 115.75, 120.98, 123.85, 123.94, 134.71, 145.64, 150.45, 158.13, 159.59, 160.00, 163.52, 170.43, 188.76; HRMS (FAB^+, 3-NBA) calcd for $C_{24}H_{24}O_{11}N_2$ $(M + H)^+$ 517.1458, found 517.1458.

5′-*O*-(5-Formyl-6-hydroxy-2-benzofuranyl)-3′-*O*-acetylthymidine (20). To a solution of 0.44 g (0.86 mmol) of compound **19** in 20 mL of dry CH_2Cl_2 was added 0.32 g (0.95 mmol) of trityl tetrafluoroborate. The solution was stirred at room temperature under an argon atmosphere for 30 min. Completion of the reaction was monitored by the product's green fluorescence under long wave UV light (366 nm). The solution was diluted with CH_2Cl_2, washed with water, and dried over Na_2SO_4. Purification of the crude product by silica gel chromatography eluting with a gradient of 100:1 to 50:1 dichloromethane/methanol afforded 0.50 g (90%) of a white foam: ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.68 (d, 3 H, J = 1.0), 2.12 (s, 3 H), 2.37 (ddd, 1 H, J = 6.4, 8.8, 14), 2.53 (ddd, 1 H, J = 1.3, 5.5, 14), 4.35−4.38 (m, 1 H), 4.60 (dd, 1 H, J = 3.0, 12), 4.67 (dd, 1 H, J = 3.4, 12), 5.34 (app d, 1 H, J = 6.4), 6.39 (dd, 1 H, J = 5.5, 8.8), 7.02 (s, 1 H), 7.39 (d, 1 H, J = 1.0), 7.61 (s, 1 H), 7.93 (s, 1 H), 9.58 (br s, 1 H), 9.95 (s, 1 H), 11.23 (s, 1 H); ^{13}C NMR δ 12.33, 20.83, 37.39, 64.93, 74.63, 82.16, 85.04, 99.88, 111.45, 115.20, 119.51, 120.08, 130.23, 134.66, 145.80, 150.45, 158.08, 160.13, 162.20, 163.60, 170.45, 195.79; HRMS (FAB^+, 3-NBA) calcd for $C_{22}H_{20}O_{10}N_2$ $(M + H)^+$ 473.1196, found 473.1202.

5′-*O*-[6-Hydroxy-5-(hydroxymethyl)-2-benzofuranyl]-3′-*O*-acetylthymidine (21). To a solution of 0.32 g (0.69 mmol) of compound **20** in 8 mL of a 1:1 mixture of ethanol/dioxane was added 10 mg (0.26 mmol) of $NaBH_4$. The solution was stirred at room temperature for 15 min, neutralized with saturated NH_4Cl, diluted with CH_2Cl_2, washed with water, and dried over $MgSO_4$. The crude product was purified by silica gel chromatography eluting with a gradient of 20:1 to 10:1 dichloromethane/methanol to afford 0.29 g (88%) of a white solid: ^{1}H NMR (300 MHz, acetone-d_6) δ 1.63 (d, 3 H, J = 1.8), 2.10 (s, 3 H), 2.47 (ddd, 1 H, J = 6.4, 8.7, 14), 2.55 (ddd, 1 H, J = 2.0, 5.9, 14), 2.87 (br s, 1 H), 4.40−4.42 (m, 1 H), 4.59 (dd, 1 H, J = 3.7, 12), 4.67 (dd, 1 H, J = 4.0, 12), 4.79 (d, 2 H, J = 2.0), 5.42−5.45 (m, 1 H), 6.38 (dd, 1 H, J = 5.9, 8.7), 7.03 (s, 1 H), 7.63 (d, 1 H, J = 2.6), 7.71 (app s, 2 H); ^{13}C NMR (DMSO-d_6) δ 11.97, 20.74, 35.88, 58.37, 64.33, 74.15, 81.14, 84.03, 96.62, 109.97, 115.65, 118.32, 120.62, 128.04, 135.50, 142.75, 150.39, 155.53, 155.91, 158.36, 163.55, 170.02; UV_{max} (CH_3CN) 314, 270, 249 nm; HRMS (FAB^+, glycerol) calcd for $C_{22}H_{22}O_{10}N_2$ $(M + H)^+$ 475.1353, found 475.1355. Anal. Calcd for $C_{22}H_{22}O_{10}N_2$: C, 55.70; H, 4.67; N, 5.91. Found: C, 55.48; H, 4.76; N, 5.63.

[2-Carbomethoxy-6-hydroxy-(5-methylalcohol)benzofuran]-3′-*O*-acetylthymidine *Cis*-Syn Photoproduct (22). A solution of 0.25 g (0.52 mmol) of compound **21** in 350 mL of dry CH_3CN was deaerated with argon bubbling for 60 min. Acetone (17.5 mL) was added, and the solution was irradiated with 300 nm light in a 16 bulb Rayonet photoreactor for 3 h at room temperature. Removal of the solvents and absorption of the crude material onto silica gel using methanol as the solvent effected the ring opening. The absorbed compound was loaded on top of a silica gel column and purified by eluting with a gradient of 30:1 to 15:1 dichloromethane/methanol to afford 0.15 g (58%) of a clear foam: ^{1}H NMR (300 MHz, acetone-d_6) δ 1.70 (s, 3 H), 2.00−2.11 (m, 2 H), 2.06 (s, 3 H), 3.69−3.71 (m, 2 H), 3.85 (s, 3 H), 3.88−3.90 (m, 1 H), 4.00 (d, 1 H, J = 1.0), 4.04 (t, 1 H, J = 5.4, (-OH)), 4.55 (d, 1 H, J = 13), 4.63 (d, 1 H, J = 13), 4.84 (d, 1 H, J = 2.0), 5.17−5.19 (m, 1 H), 6.18 (dd, 1 H, J = 5.4, 9.3), 6.37 (s, 1 H), 6.94 (s, 1 H), 8.71 (br s, 1 H), 8.93 (br s, 1 H); ^{13}C NMR δ 21.07, 22.95, 35.80, 47.35, 53.43, 56.76, 57.56, 61.68, 63.06, 75.56, 84.42, 84.84, 88.11, 98.32, 116.04, 122.28, 126.57, 152.55, 157.85, 162.83, 170.87, 170.93; UV_{max} (CH_3CN) 287 nm; HRMS (FAB^+, 3-NBA) calcd for $C_{23}H_{26}O_{11}N_2$ $(M + H)^+$ 507.1615, found 507.1611.

(2-Carbomethoxy-5-formyl-6-hydroxybenzofuran)-3′-*O*-acetylthymidine *Cis*-Syn Photoproduct (23). To a solution of 0.16 g (0.31 mmol) of compound **22** in 2 mL of DMF were added 13 mg (0.08 mmol) of TEMPO and 8 mg (0.08 mmol) of CuCl. Oxygen was bubbled through the solution for 2 h after which another 13 mg of TEMPO and 8 mg of CuCl were added. After stirring under an oxygen atmosphere for 6 h, the reaction was diluted with ethyl acetate and washed with 1 N HCl, saturated $NaHCO_3$, and brine, and then dried over $MgSO_4$. Purification of the crude product by silica gel chromatography eluting with 50:1 dichloromethane/methanol afforded 0.11 g (70%) of a white foam: ^{1}H NMR (300 MHz, acetone-d_6) δ 1.75 (s, 3

H), 1.96−2.11 (m, 2 H), 2.06 (s, 3 H), 3.70−3.73 (m, 2 H), 3.88 (s, 3 H), 3.89−3.91 (m, 1 H), 4.16 (app s, 1 H), 4.95 (d, 1 H, J = 1.8), 5.18−5.21 (m, 1 H), 6.19 (dd, 1 H, J = 5.6, 9.3), 6.49 (s, 1 H), 7.47 (d, 1 H, J = 0.7), 9.80 (d, 1 H, J = 0.7); ^{13}C NMR δ 21.07, 22.78, 35.84, 47.50, 53.70, 55.04, 57.55, 63.04, 75.59, 84.53, 84.77, 89.53, 98.98, 117.57, 119.14, 133.49, 152.30, 166.11, 169.34, 169.73, 170.59, 170.87, 196.10; HRMS (FAB$^+$, 3-NBA) calcd for $C_{23}H_{24}O_{11}N_2$ (M + H)$^+$ 505.1458, found 505.1455.

(2-Carbomethoxypsoralen)-3′-*O*-acetylthymidine *Cis*-Syn Photoproduct (24). To a solution of 43 mg (0.09 mmol) of compound **23** in 0.4 mL of dry THF were added 4 Å sieves and 125 mL (0.85 mmol) of *N*,*N*-dimethylacetamide dimethylacetal. The solution stirred for 2 h at room temperature under an argon atmosphere. The reaction was diluted with ethyl acetate, washed with saturated NH_4Cl, saturated $NaHCO_3$, and brine, and then dried over $MgSO_4$. The crude product was purified by silica gel chromatography eluting with a gradient of 50:1 to 33:1 dichloromethane/methanol to afford 17 mg (38%) of a white foam: ^{1}H NMR (300 MHz, acetone-d_6) δ 1.76 (s, 3 H), 2.01−2.05 (m, 1 H), 2.07 (s, 3 H), 2.13 (ddd, 1 H, J = 2.0, 5.9, 14), 3.71−3.73 (m, 2 H), 3.88 (s, 3 H), 3.90−3.92 (m, 1 H), 4.11 (t, 1 H, J = 5.4, (-OH)), 4.24 (s, 1 H), 4.97 (d, 1 H, J = 2.0), 5.20−5.22 (m, 1 H), 6.20 (dd, 1 H, J = 5.9, 9.8), 6.24 (d, 1 H, J = 9.3), 6.90 (s, 1 H), 7.39 (s, 1 H), 7.90 (d, 1 H, J = 9.3); ^{13}C NMR ($CDCl_3$) δ 21.00, 22.85, 35.80, 46.60, 53.68, 54.97, 57.28, 62.53, 74.27, 84.10, 84.94, 87.77, 99.35, 113.81, 114.41, 121.48, 125.81, 143.23, 150.43, 156.32, 160.47, 163.98, 169.20, 169.70, 170.69; UV (MeOH) 324, 293; HRMS (FAB$^+$, 3-NBA) calcd for $C_{25}H_{24}O_{11}N_2$ (M + H)$^+$ 529.1458, found 529.1456.

2-Carbomethoxypsoralen Thymidine *Cis*-Syn Photoproduct (4). To a solution of 9 mg (17 mmol) of compound **24** in 0.5 mL of freshly distilled methanol was added 50 mL of DBU. After stirring for 10 min at room temperature the reaction was diluted with ethyl acetate, washed with saturated NH_4Cl, saturated $NaHCO_3$, and brine, and then dried over Na_2SO_4. The crude product was purified by silica gel chromatography eluting with 25:1 dichloromethane/methanol to afford 8 mg (97%) of a white foam: ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.80 (s, 3 H), 1.87 (br s, 2 H), 2.02−2.11 (m, 1 H), 2.27 (ddd, 1 H, J = 3.1, 5.9, 14), 3.70 (dd, 1 H, J = 3.8, 12), 3.80−3.89 (m, 5 H), 3.89 (s, 3 H), 4.02 (s, 1 H), 4.39−4.43 (m, 1 H), 4.77 (d, 1 H, J = 1.7), 5.96 (dd, 1 H, J = 5.9, 8.1), 6.27 (d, 1 H, J = 9.5), 6.91 (s, 1 H), 7.24 (s, 1 H), 7.40 (br s, 1 H), 7.60 (d, 1 H, J = 9.5); ^{13}C NMR (methanol-d_4) δ 22.92, 38.64, 48.44, 54.01, 56.16, 57.97, 63.36, 72.41, 85.16, 87.35, 89.97, 99.67, 113.97, 115.85, 124.40, 127.84, 145.90, 153.72, 157.68, 162.91, 166.21, 170.73, 172.26; UV (1:1 methanol:water) 332, 294; HRMS (FAB$^+$, 3-NBA) calcd for $C_{23}H_{22}O_{10}N_2$ (M + H)$^+$ 487.1353, found 487.1349.

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