Synthesis of an Optically Active Template for 4′-Substituted Nucleoside Analogs via Chromium Carbene Complex Photochemistry

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Procedures for the efficient synthesis and handling of [ethoxy((benzyloxy)methyl)carbene]pentacarbonylchromium(0) have been developed. Photolysis in the presence of the optically active ene carbamate **12** followed by Baeyer-Villiger oxidation and oxazolidinone elimination gave (*R*)-(+)-5-ethoxy-5-((benzyloxy)methyl)-2(5*H*)-furanone in good yield and with high enantiomeric purity. This compound provides a potential template for the synthesis of 4′-substituted nucleoside analogs.

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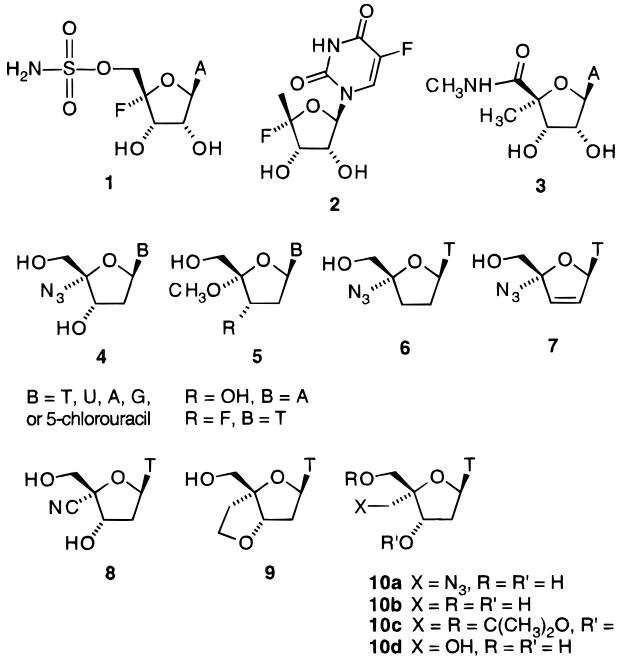
Introduction

Nucleosides bearing substituents at the 4′-position are relatively uncommon, but several have unusual biological activity. For example, nucleodin (**1**)[1] exhibits antibiotic activity, 5′-deoxy-4′,5-difluorouridine (**2**) has anticancer activity,[2] and nucleoside **3** displays agonistic activity for adenosine receptors.[3] In addition, a number of synthetic 4′-substituted nucleosides (**4**−**10**)[4] are active against HIV. Interestingly, the axiomatic notion that nucleosides must be devoid of the 3′-hydroxy group to inhibit HIV[5] was not true in this instance, since the 3′-hydroxy group was necessary for the activity of compound **4**.

Most 4′-substituted nucleosides have been synthesized from existing nucleosides,[6−11] and the syntheses are often long and relatively nonstereoselective. Further, only the enantiomer corresponding to the *natural* nucleoside precursor is available by these procedures, a limitation in light of recent evidence suggesting that *unnatural* enantiomers of nucleoside antiviral compounds may retain their biological activity but not their toxicity.[12] Nucleosides substituted at the 4′-position have also been synthesized from carbohydrates,[13,14] as well as *de novo* approaches from methallyl alcohol[15] and 1,4-diacetoxycyclopent-2-ene.[16] However, these latter approaches were limited in the range of functionality available at the 4′-position.

Nucleoside analogs lacking additional functionality at the 4′-position have been synthesized from an optically



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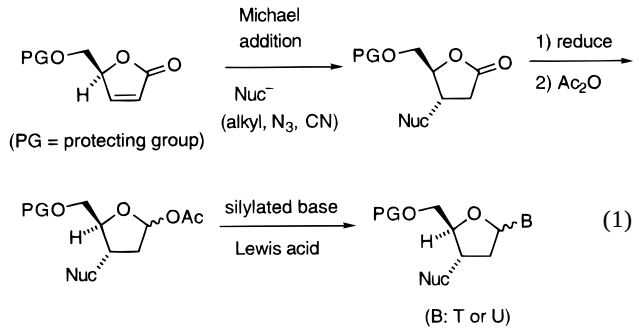
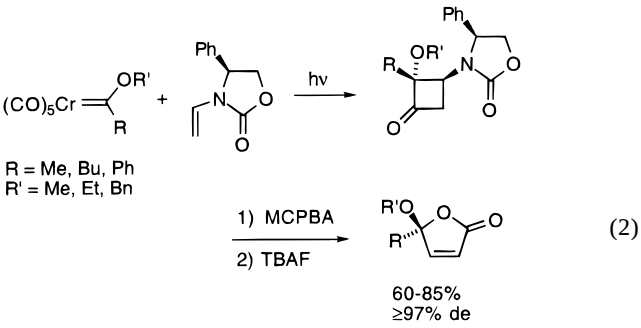
active butenolide template (eq 1),[17] suggesting that 4,4-disubstituted butenolides might be appropriate precursors to 4′-substituted nucleoside analogs. An efficient



(1)

asymmetric synthesis[18] and functionalization[19] of 4,4-disubstituted butenolides has recently been reported from these laboratories (eq 2). The absolute configura-

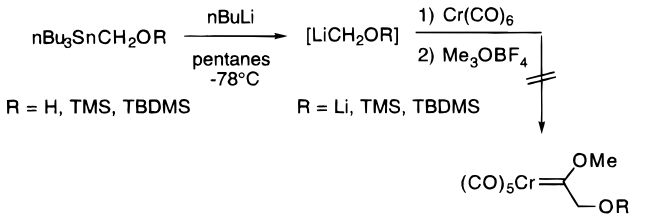


(2)

tion of the chiral center in these butenolides is determined by the absolute configuration of the phenyl glycine derived oxazolidinone, and both enantiomers are available with equal facility, giving access to both the natural and the unnatural series of nucleoside analogs. The application of this methodology to the synthesis of a butenolide template for 4′-substituted nucleoside analogs is reported below.

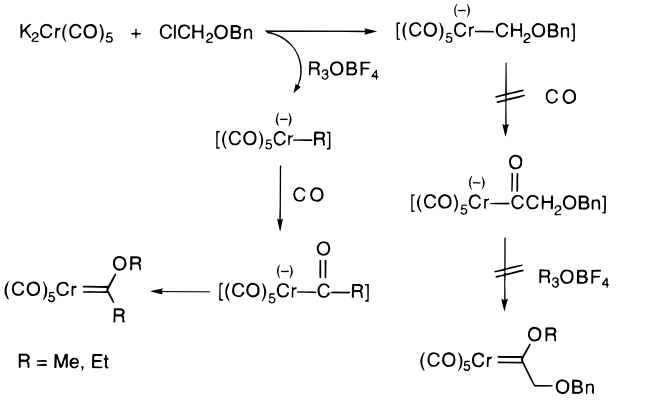
Results and Discussion

The critical element for nucleoside analog biological activity is the presence of the 4′-hydroxymethyl group, which translates, in the context of eq 2, into the requirement for R to be a protected hydroxymethyl group ($PGOCH_2$) in the starting chromium carbene complex. The most commonly used synthesis of chromium alkoxycarbene complexes involves the reaction of organolithium reagents with chromium hexacarbonyl followed by O-alkylation with a hard alkylating agent.[20] Dilithiation of tri-*n*-butyl(hydroxymethyl)stannane or monolithiation of its silylated derivatives produced the requisite organolithium reagents.[21] Unfortunately these were unreactive toward chromium hexacarbonyl at low temperatures and decomposed upon warming, making the desired chromium carbene complex unavailable by this route (eq 3).



(3)

A second approach to chromium carbene complexes is via carbonylation of anionic (σ-alkyl)chromium carbonyl complexes.[22] However, treatment of chloromethyl benzyl ether with the chromium pentacarbonyl dianion[23] failed to produce the desired carbene complex. In the absence of carbon monoxide pressure, no anionic acyl complex could be isolated. In the presence of 40 psi of carbon monoxide, only chromium hexacarbonyl was recovered. Attempts to alkylate the presumed anionic acyl complex intermediate with Meerwein's reagent instead led to the low-yield production of carbene complexes from the alkylating agent (eq 4).



(4)

Either chloromethyl benzyl ether was not attacked by chromium pentacarbonyl dianion or, more likely, the resulting anionic alkyl complex failed to undergo carbon monoxide insertion. Electron-withdrawing groups such as alkoxy groups dramatically decrease the migratory aptitude of such substituted alkyl groups.[24] The production of small amounts of carbene complex from the Meerwein alkylating agent confirms that carbene complexes are available by this approach if both alkylation and CO insertion are favorable.

A third approach to chromium carbene complexes is the reaction of chromium pentacarbonyl dianion with acid chlorides, followed by alkylation of the resulting anionic acyl complex with Meerwein's reagent.[25] The reported yields were only modest for aroyl halides (40−65%), which were the best substrates, and were substantially lower (14−37%) for other classes of acid chlorides. Since the ((benzyloxy)methyl)carbene complex was to be required in large amounts, a high-yield synthesis was important, and the acid chloride approach appeared to be too inefficient. Indeed, when the approach was tried with α-(benzyloxy)acetyl chloride

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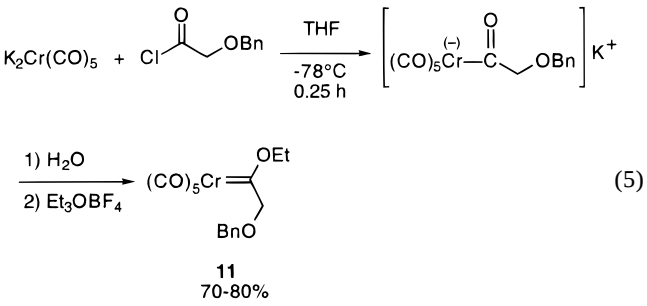
under standard conditions,[25] yields varying from 20 to 40% were obtained. Careful observation indicated that decomposition was occurring on prolonged contact with the acid chloride and upon warming of the initial reaction mixture to room temperature. By adding the acid chloride[26] to the dianion slowly at −78 °C, pouring this cold slurry over ice after only 0.25 h, and adding Et_3OBF_4 to this slurry, reproducible 70−80% yields of the desired carbene complex **11** were obtained on a 5 g scale (eq 5). (The ethoxycarbene complex was more stable than the methoxy complex and was used for the further studies.)

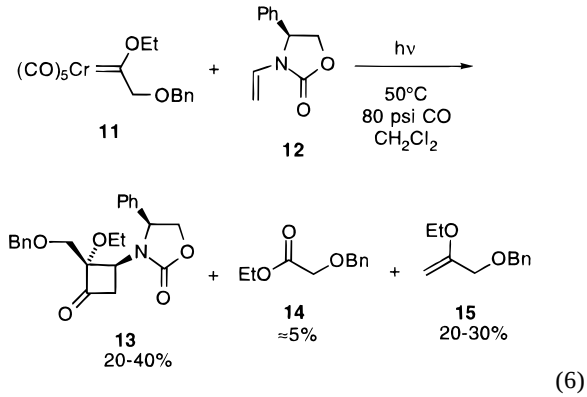


(5)

With a ready source of carbene complex **11** at hand, photocycloaddition studies commenced. Photolysis of chromium carbene complex **11** in the presence of ene carbamate **12** under standard reaction conditions (CH_2Cl_2, 50 °C, 80 psi of CO, 18−30 h, 450 W Hanovia lamp, Pyrex) resulted in poor yields of the desired cyclobutanone, along with a number of identified and unidentified byproducts (eq 6). The relative instability of chromium carbene complex **11** had already been noted in its preparation and was a suspected source of the inefficiency of the photoreactions. Indeed, simply stirring complex **11** with substrate **12** at 50 °C without irradiation produced substantial amounts of 2-ethoxy-3-(benzyloxy)propene (**15**), probably by a thermal metathesis reaction (eq 7). Electron-rich olefins are known[27] to undergo metathesis with chromium carbene complexes under thermal conditions, and the presence of the electron-withdrawing benzyloxy group apparently facilitates this process.

Carrying the photolysis out at 0 °C increased the yield of the desired cyclobutanone **13** by about 10% and markedly decreased the production of thermal decomposition product **15**. However, the yields remained unacceptably low and the desired product was still accompanied by substantial amounts of unidentified decomposition products.

Most simple chromium alkoxycarbene complexes are stable to irradiation at wavelengths above 300 nm (through Pyrex) and can be recovered unchanged even after prolonged (days) exposure to light of the above wavelength.[28] In contrast, irradiation of complex **11** in the absence of substrate, even at −35 °C, resulted in complete decomposition to unidentified products within 18 h. An examination of the UV−visible spectrum of complex **11** showed substantial absorption between the



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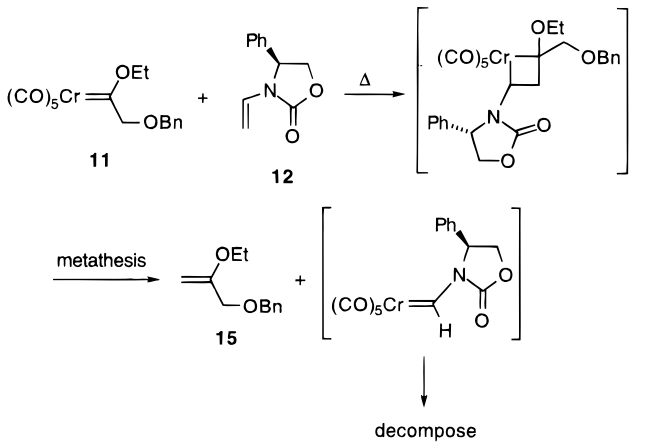

(7)

300 nm cutoff of Pyrex and the metal-to-ligand charge transfer band (MLCT) responsible for CO insertion at 380 nm. This absorption is likely due to low-lying ligand field (LF) transitions, excitation of which weakens both metal−carbonyl and metal-carbene carbon bonds, resulting in photolytic decomposition of the carbene complex.[29]

The photochemical reaction in eq 6 was carried out at −35 °C through a series of filter solutions[30] with absorption cutoffs between 300 and 350 nm. The results are summarized in Table 1. Of the filters studied, a solution of carbazole in DMF, with an absorption at 348 nm, was by far the most efficient, and reproducibly high yields of the desired cyclobutanone **13** could be obtained on a 1 g scale. Baeyer-Villiger oxidation followed by elimination of the oxazolidinone by treatment with TBAF completed an efficient approach to the desired 4′-substituted nucleoside template **17** (eq 8). The results of studies to convert this compound to a series of 4′-substituted nucleoside analogs as in eq 1 will be reported in due course.

Experimental Section

General Procedures. The NMR spectra (300 MHz for ^1H NMR and 75 MHz for ^{13}C NMR) were recorded in $CDCl_3$, and chemical shifts are given in δ relative to $CDCl_3$ (δ 7.24 for ^1H and δ 77.0 for ^{13}C) unless otherwise indicated. Optical rotations were obtained using a Perkin-Elmer 24 polarimeter at a wavelength of 589 nm (sodium D line) in a 1.0 dm cell with a total volume of 1 mL. Specific rotation is reported in

(26) The corresponding acid anhydride or mixed *tert*-butyl anhydride could also be used, but the yields were lower and the isolation more difficult.

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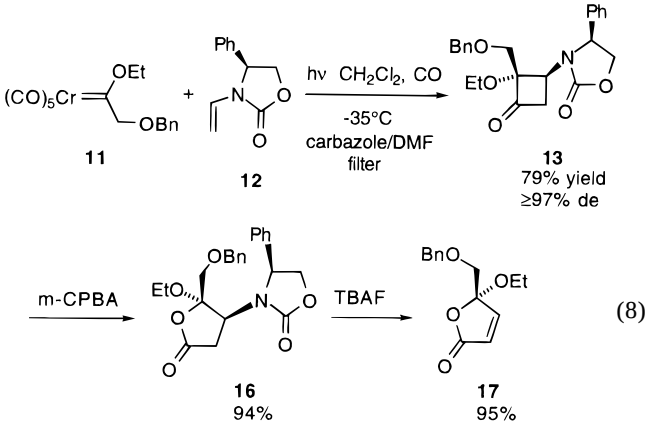

(8)

degrees per decimeter at the specified temperature and the concentration (*c*) given in grams per 100 mL in the specified solvent. Chromatography was performed using silica gel 60 PF_{254} (with gypsum, E. Merck Science), and flash chromatography was performed with ICN 32−63 μm, 60 A silica gel. Elemental analyses were performed by M-H-W Laboratories, Phoenix, AZ. Photolysis reactions were performed in Ace pressure tubes with size #15 Ace-Thread, placed at a distance of 10 cm from a Conrad-Hanovia 7825 medium-pressure mercury lamp operating at 450 W, which was placed in a water-cooled immersion well (Pyrex). A Conrad-Hanovia 7830-C power supply was used for the mercury lamp. Reactions run under CO pressure were saturated with CO (3 cycles, 80 psi) and were photolyzed under 70−90 psi of CO.

[Ethoxy((benzyloxy)methyl)carbene]pentacarbonylchromium(0) (11). Potassium metal (1.17 g, 30.0 mmol) was added to flame-dried graphite (2.95 g, 245 mmol), and the mixture was heated at 120 °C under vacuum until a bronze laminate formed (1 h). The flask was cooled to room temperature and filled with argon, and argon-saturated THF (40 mL) was added. After the mixture was cooled to −78 °C, chromium hexacarbonyl (3.00 g, 13.6 mmol) was then added. The reaction mixture was stirred at this temperature for 1.5 h and then warmed to 25 °C. After it was recooled to −78 °C, α-(benzyloxy)acetyl chloride[31] (2.64 g, 14.3 mmol) in 5 mL of THF was slowly added to the $K_2Cr(CO)_5$ solution. The reaction mixture was stirred at −78 °C for 20 min, after which it was poured into a beaker. Ice (50 mL) and water (50 mL) were added, and Et_3OBF_4 was added to the aqueous solution until a pH of ∼2 was obtained. The mixture was filtered through Celite and washed several times with ether. The filtrate was separated, and the aqueous layer was extracted with ether. The organic layers were combined and dried over $MgSO_4$. Purification by flash column chromatography (6:1 hexanes/ether) gave an orange solid (3.82 g, 76%). Note: the workup procedure and purification were performed in the dark, and argon was used for the flash column chromatography. ^{1}H NMR: δ 1.63 (t, 3H, J = 7.1 Hz), 4.41 (s, 2H), 4.59 (s, 2H), 5.12 (q, 2H, J = 7.1 Hz), 7.29−7.36 (m, 5H). ^{13}C NMR: δ 353.3, 223.4, 216.3, 137.2, 128.5, 128.0, 87.7, 73.6, 30.9, 15.5. IR (thin film): ν 2063, 1922 cm^{-1}. The complex lacked sufficient stability to permit elemental analysis.

Cyclobutanone 13. The carbene complex **11** (1.17 g, 3.17 mmol) and ene carbamate **12** (600 mg, 3.17 mmol) were combined in a pressure tube. Degassed CH_2Cl_2 was added to the tube via a cannula. The pressure tube was flushed with CO (3 × 80 psi) and filled with 80 psi of CO. The pressure tube was placed in a larger tube containing a saturated solution (2 g/L) of carbazole in DMF, and this entire unit was placed in an unsilvered Dewar containing 1:1 ethylene glycol/water and cooled to −35 °C by a Cryocool unit. The reaction mixture was irradiated through the unsilvered Dewar by an adjacent Hanovia lamp at this temperature for 1 day. The pressure tube was removed from the solution, and the CO was released. More carbene complex **11** (977 mg, 2.64 mmol) was added to the reaction mixture, and the pressure tube was flushed and filled with CO as before. This mixture was irradiated in the carbazole/DMF solution at −35 °C for 1 day. The CO was released from the tube, and the solvent was removed. Chromium hexacarbonyl was sublimed under vacuum at 50 °C. Purification by column chromatography (10:2:1 hexanes/ethyl acetate/CH_2Cl_2) gave 988 mg (79%) of the product. ^{1}H NMR: δ 1.14 (t, 3H, J = 7.0 Hz), 2.43 (dd, 1H, J = 10.6, 18.0 Hz), 2.87 (dd, 1H, J = 10.0, 18.0 Hz), 3.55−3.67 (m, 2H), 3.78 (d, 1H, J = 9.5 Hz), 3.92 (d, 1H, J = 9.5 Hz), 3.97 (dd, 1H, J = 3.6, 8.5 Hz), 4.38 (t, 1H, J = 8.5 Hz), 4.49 (d, 1H, J = 11.3 Hz), 4.55 (d, J = 11.3 Hz), 4.59 (t, 1H, J = 10.3 Hz), 4.89 (dd, 1H, J = 3.6, 8.5 Hz), 6.95 (m, 2H), 7.25−7.39 (m, 8H). ^{13}C NMR: δ 206.3, 158.3, 140.0, 137.0, 129.3, 128.7, 128.6, 128.2, 128.1, 125.8, 97.7, 74.3, 70.3, 68.7, 61.5, 59.7, 47.7, 45.2, 15.6. Anal. Calcd for $C_{22}H_{25}NO_5$: C, 69.85; H, 6.36; N, 3.54. Found: C, 69.65; H, 6.46; N, 3.53. $[\alpha]_D^{25}$ = +59.9° (c = 0.715 in ether).

Table 1. Effect of Filters on Photochemical Cycloaddition (eq 8)

filter	cutoff, nm	yield of **3**, %
aq $Zn(NO_3)_2$	335	29
aq Cu_2SO_4	∼310	34
aq $K_4Fe(CN)_6$	∼400	16
DMF/carbazole	348	79

Lactone 16. *m*-CPBA (986 mg, 3.37 mmol, 60% mixture) was added to a CH_2Cl_2 solution of the cyclobutanone **13** (740 mg, 1.87 mmol) and Na_2HPO_4 (2.12 g, 14.9 mmol). The reaction was stirred at room temperature for 15 h. An aqueous solution of $Na_2S_2O_3$ was added, and the mixture was stirred vigorously for 1 h. The layers were separated, and the water layer was extracted with CH_2Cl_2. The organics were combined and washed with a saturated aqueous solution of $NaHCO_3$. The organics were dried over $MgSO_4$ and filtered, and the solvents were removed. Purification by column chromatography (1:3 ethyl acetate/hexanes) gave the product (724 mg, 94%) as a white foam. ^{1}H NMR: δ 1.14 (t, 3H, J = 7.0 Hz), 2.32 (m, 2H), 3.61 (m, 1H), 3.72 (d, 1H, J = 11.1 Hz), 3.81 (m, 1H), 3.89 (dd, 1H, J = 3.1, 7.9 Hz), 4.18 (t, 1H, J = 8.4 Hz), 4.54 (d, 1H, J = 1.1 Hz), 4.62 (d, 1H, J = 11.1 Hz), 4.75 (dd, 1H, J = 3.1, 8.4 Hz), 4.78 (t, 1H, J = 7.9 Hz), 6.97 (dd, 2H, J = 1.5, 7.5 Hz), 7.21−7.37 (m, 8H). ^{13}C NMR: δ 172.1, 158.3, 140.2, 136.6, 129.3, 129.0, 128.6, 128.3, 125.8, 109.1, 75.5, 70.7, 68.9, 58.8, 58.3, 54.8, 32.4, 15.1. Anal. Calcd for $C_{22}H_{25}NO_6$: C, 67.24; H, 6.12; N, 3.41. Found: C, 67.13; H, 6.17; N, 3.41. $[\alpha]_D^{25}$ = +74.7° (c = 0.825 in ether).

Butenolide 17. Tetrabutylammonium fluoride (1.0 M, 2.28 mmol) was added to a THF solution of the lactone **16** (522 mg, 1.27 mmol). The solution was stirred at room temperature for 1 h. It was then poured into water and extracted with ether. The ether layers were dried over $MgSO_4$, and the solvent was removed. Purification by column chromatography (1:4 ethyl acetate/hexanes) gave the product (300 mg, 95%) as an oil. ^{1}H NMR: δ 1.18 (t, 3H, J = 7.0 Hz), 3.42 (m, 1H), 3.53 (m, 1H), 3.61 (d, 1H, J = 10.8 Hz), 3.81 (d, 1H, J = 11.1 Hz), 4.56 (s, 2H), 6.22 (d, 1H, J = 5.7 Hz), 7.22 (d, 1H, J = 5.7 Hz), 7.25−7.35 (m, 5H). ^{13}C NMR: δ 169.6, 152.6, 137.2, 128.4, 127.8, 127.7, 125.3, 109.2, 73.9, 71.5, 59.7, 15.1. Anal. Calcd for $C_{14}H_{16}O_4$: C, 67.73; H, 6.50. Found: C, 67.76; H, 6.30. $[\alpha]_D^{25}$ = +64.2° (c = 0.600 in ether).

2-Ethoxy-3-(benzyloxy)propene (15). This is the main byproduct of the photochemical reaction described above. ^{1}H NMR: δ 1.27 (t, 3H, J = 7.2 Hz), 4.07 (s, 2H), 4.21 (q, 2H, J = 7.2 Hz), 4.62 (s, 2H), 7.30−7.35 (m, 7H). ^{13}C NMR: δ 170.3, 137.1, 128.5, 128.0, 73.3, 67.2, 60.8, 14.2. HRMS: *m/e* calcd 192.1150, found 192.1147.

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(Benzyloxy)acetone. This product was often isolated from the photochemical reaction. Its source is the hydrolysis of enol ether **15**. ^{1}H NMR: δ 2.14 (s, 3H), 4.04 (s, 2H), 4.58 (s, 2H), 7.34 (m, 5H). ^{13}C NMR: δ 206.7, 137.1, 128.5, 128.0, 127.9, 75.2, 73.3, 26.4.

Ethyl α-(benzyloxy)acetate (14). This was the main oxidation product of **1** in the presence of light. ^{1}H NMR: δ 1.27 (t, 3H, J = 7.2 Hz), 4.07 (s, 2H), 4.21 (q, 2H, J = 7.2 Hz), 4.62 (s, 2H), 7.30−7.35 (m, 5H). ^{13}C NMR δ 170.3, 137.1, 128.5, 128.0, 73.3, 67.2, 60.8, 14.2. MS (CI): *m*/*e* 195 (M + 1), 181 (37), 91 (100). HRMS: *m*/*e* calcd 195.1021, found 195.1011.

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