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(5H)-furanone in good yield and with high enantiomeric purity. This compound provides a potential template for the synthesis of 4'-substituted nucleoside analogs.

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 HIV⁵ 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

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toxicity.¹² Nucleosides substituted at the 4'-position have also been synthesized from carbohydrates,^{13,14} as well as *de novo* approaches from methallyl alcohol¹⁵ 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 4,4disubstituted butenolides might be appropriate precursors to 4'-substituted nucleoside analogs. An efficient





asymmetric synthesis¹⁸ and functionalization¹⁹ of 4,4disubstituted butenolides has recently been reported from these laboratories (eq 2). The absolute configura-



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 (PGOCH₂) 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 silvlated 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).



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 dianion²³ 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).



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 chloride²⁶ to the dianion slowly at -78 °C, pouring this cold slurry over ice after only 0.25 h, and adding Et₃OBF₄ 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.)

$$\kappa_{2}Cr(CO)_{5} + CI \xrightarrow{O}OBn \xrightarrow{THF} \left[\begin{array}{c} O\\ (CO)_{5}Cr - C & OBn \end{array} \right] K^{+}$$

$$\xrightarrow{1) H_{2}O} (CO)_{5}Cr \xrightarrow{OEt} BnO$$

$$\xrightarrow{11} 70-80\% \qquad (5)$$

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 (CH₂Cl₂, 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 known²⁷ 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



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 solutions³⁰ 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. Baever-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 ¹³C NMR) were recorded in CDCl₃, and chemical shifts are given in δ relative to CDCl₃ (δ 7.24 for ¹H and δ 77.0 for ¹³C) 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

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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 PF₂₅₄ (with gypsum, E. Merck Science), and flash chromatography was performed with ICN 32–63 μ m, 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 chloride³¹ (2.64 g, 14.3 mmol) in 5 mL of THF was slowly added to the K₂Cr(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 Et₃OBF₄ was added to the aqueous solution until a pH of \sim 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 MgSO₄. 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. ¹H 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). ¹³C 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): v 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

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 ₂ SO ₄	${\sim}310$	34
aq K ₄ Fe(CN) ₆	${\sim}400$	16
DMF/carbazole	348	79

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/CH2Cl2) gave 988 mg (79%) of the product. ¹H 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, J = 0.5 Hz)1H, J = 11.3 Hz), 4.55 (d, J = 11.3 Hz), 4.59 (t, 1H, J = 10.3Hz), 4.89 (dd, 1H, J = 3.6, 8.5 Hz), 6.95 (m, 2H), 7.25–7.39 (m, 8H). ¹³C 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 C₂₂H₂₅NO₅: C, 69.85; H, 6.36; N, 3.54. Found: C, 69.65; H, 6.46; N, 3.53. $[\alpha]_D^{25} = +59.9^\circ$ (c = 0.715 in ether).

Lactone 16. m-CPBA (986 mg, 3.37 mmol, 60% mixture) was added to a CH₂Cl₂ solution of the cyclobutanone 13 (740 mg, 1.87 mmol) and Na₂HPO₄ (2.12 g, 14.9 mmol). The reaction was stirred at room temperature for 15 h. An aqueous solution of Na₂S₂O₃ was added, and the mixture was stirred vigorously for 1 h. The layers were separated, and the water layer was extracted with CH₂Cl₂. The organics were combined and washed with a saturated aqueous solution of NaHCO₃. The organics were dried over MgSO₄ 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. ¹H 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). ¹³C 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 C₂₂H₂₅NO₆: C, 67.24; H, 6.12; N, 3.41. Found: C, 67.13; H, 6.17; N, 3.41. $[\alpha]_D^{25} = +74.7^\circ$ (*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 MgSO₄, and the solvent was removed. Purification by column chromatography (1:4 ethyl acetate/hexanes) gave the product (300 mg, 95%) as an oil. ¹H 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). ¹³C 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 C₁₄H₁₆O₄: C, 67.73; H, 6.50. Found: C, 67.76; H, 6.30. [α]_D²⁵ = +64.2° (*c* = 0.600 in ether).

2-Ethoxy-3-(benzyloxy)propene (15). This is the main byproduct of the photochemical reaction described above. ¹H 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). ¹³C 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.** ¹H NMR: δ 2.14 (s, 3H), 4.04 (s, 2H), 4.58 (s, 2H), 7.34 (m, 5H). ¹³C 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. ¹H 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). ¹³C 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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