Photochemical Ring Expansion of α-Alkoxycyclobutanones to 2-Acetoxy-5-alkoxytetrahydrofurans: Nucleophilic Reactions at the 2-Position

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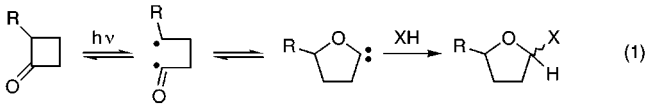
Photolysis of cyclobutanones in the presence of acetic acid produced 2-acetoxy-5-alkoxytetrahydrofurans regiospecifically and with retention of configuration at the migrating α-position. The acetoxy group was replaced by nucleophiles such as allylsilane, trimethylsilyl azide, diethylaluminum cyanide, and silylated thymine in the presence of Lewis acids.

Introduction

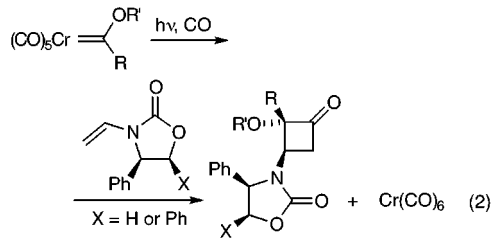
The photochemical ring expansion of strained ketones to oxacarbenes with subsequent trapping by protic nucleophiles of the type X−H was originally reported with the cyclocamphone ring system[1] but was soon extended to cyclobutanones and cyclopentanones.[2] The mechanism (eq 1)[3] is thought to involve photochemical α-cleavage of the cyclobutanone to the diradical with subsequent expansion to the oxacarbene and irreversible trapping by protic nucleophiles. α-Substitution favors ring expansion over decarbonylation and cleavage pathways. Ring expansion toward the more substituted α-position is also favored. With radical-stabilizing α-substituents, formation of the oxacarbene is thought to be reversible. Notwithstanding the intermediacy of a diradical, stereogenic centers in the α-position retain stereochemistry on forming the oxacarbene-derived product, while the oxacarbene center is trapped with little or no stereoselectivity.



(1)

In addition to its mechanistic interest, the photochemical ring expansion of cyclobutanones has been used to synthesize dioxabicyclic [*n*.3.0] ring systems by intramolecular[3] and intermolecular[4] trapping of the oxacarbene by alcohols. Trapping with imides and imidazoles produced cyclic α-amino acetals,[5] while use of purine and pyrimidine bases led to dideoxynucleosides.[6] (In these latter two cases, mixtures of diastereoisomers at the anomeric position were obtained.)

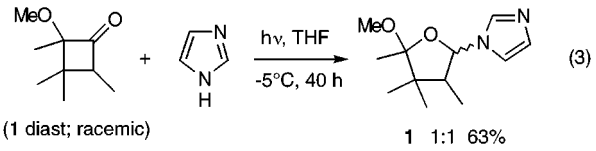
Research in these laboratories has centered on the development of photochemical reactions of chromium carbene complexes for use in organic synthesis.[7] Among the processes developed was the efficient synthesis of optically active cyclobutanones (eq 2),[8] potential substrates for the photochemical ring expansion discussed above. Below are reported the results of studies of the process, as well as reactions of the resulting cyclic ketals.



(2)

Results and Discussion

To assess the feasibility of utilizing the photolytic ring expansion of cyclobutanones with α-alkoxycyclobutanones, the model reaction in eq 3 was carried out. As expected, insertion into the α-position bearing the alkoxy group was observed exclusively, while a 1:1 mixture of diastereoisomers at the anomeric carbon was obtained.



(3)

The reactivity of optically active cyclobutanone **2** was next addressed (eq 4). Photolysis of **2** in the presence of methanol and carboxylic acids resulted in fair to good yields of functionalized tetrahydrofurans as mixtures of epimers at the ketal (anomeric) carbon, while the use of dimethyl malonate led to decomposition. Photolysis of **2** in the presence of phenylacetylene resulted in no reaction after 24 h, with recovery of starting material without racemization of the α-position. In contrast, photolysis of **2** in the presence of water led to an excellent yield of ketoaldehyde **4** from ring opening of the lactol

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(7) For a recent review, see: Hegedus, L. S. *Tetrahedron* **1997**, *53*, 4105.
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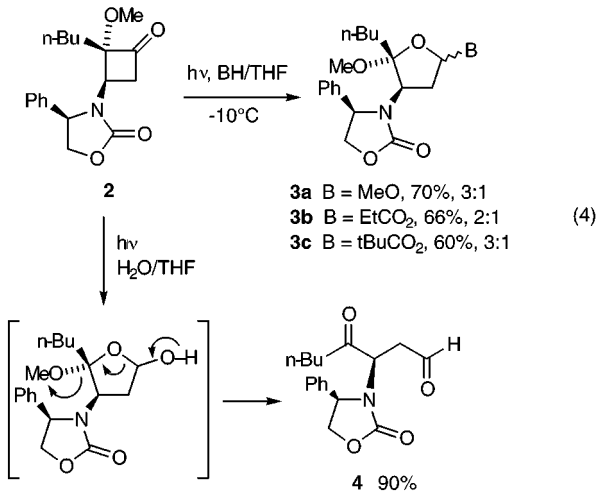
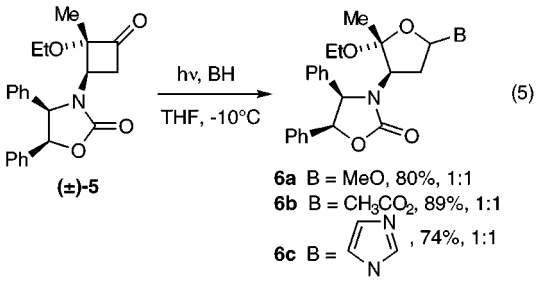
within 20 h. (This same compound was obtained from the DIBALH reduction of the Baeyer−Villiger lactone of **2** via the same lactol.) These last two examples confirm that the cyclobutanone-to-oxacarbene conversion is reversible and stereospecific in this system. Attempts to trap the oxacarbene with adenine or *N*-benzyladenine resulted in very low yields of the desired product, primarily because of the low solubility of these nucleophiles.



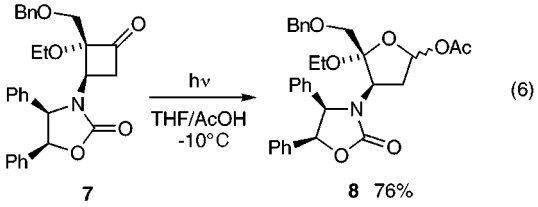
(4)

Chiral racemic cyclobutanone **5**, having the more easily-deprotected diphenyloxazolidinone moiety, was next examined. It showed similar reactivity to cyclobutanone **2**, although the ratios of isomers at the anomeric carbon were uniformly 1:1 with this substrate (eq 5).



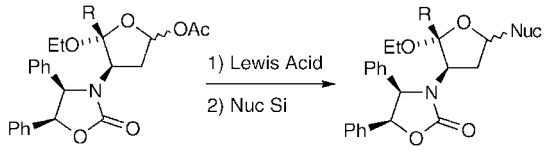
(5)

Again, the use of diethyl malonate led to decomposition, phenylacetylene failed to react, the use of 9-benzyladenine resulted in low (<20%) yields, and water almost quantitatively cleaved the product to give the ketoaldehyde corresponding to **4**. Finally, ring expansion of chiral, optically active cyclobutanone **7** (a potential precursor to 4′-disubstituted nucleoside analogs) with acetic acid trapping was also efficient (eq 6).

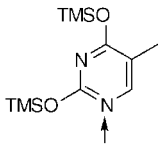
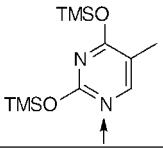


(6)

Tetrahydrofurans **6b** and **8** are interesting substrates for Vorbrüggen-type[9] couplings at the positions α to the ring oxygen in that both the 2 and 4 positions are potentially reactive. The α-acetoxy group was expected to be more reactive than the α′-alkoxy group, and this proved to be the case. Treatment of **6b** with a number of nucleophiles in the presence of Lewis acids resulted in clean replacement of the α-acetoxy group without competitive reaction at the α-ethoxy position (eq 7). Unfortunately, the two resident chiral centers had no influence on the stereochemistry of this process, and all products, with the exception of that from thymine (**9d**), were obtained as a 1:1 mixture of diastereoisomers. Thus, allylsilane, trimethylsilyl azide, and diethylaluminum cyanide all coupled in good yield, while vinylsilanes and silylenol ethers of ketones failed to react at all. The formation of a low yield of a single epimer of thymine product **9d** suggests that only one epimer of **6b** underwent coupling and the other decomposed during workup.



(7)

R	Lewis Acid	Nuc Si	Yield, %
Me (**6b**)	TMSOTf		**9a**, 95, 1:1
	Me_2AlCl	$TMSN_3$	**9b**, 81, 1:1
	Et_2AlCN	---	**9c**, (Nuc = CN) 78, 1:1
	Me_2AlCl		**9d**, 45 (1 epimer)
$BnOCH_2$ (**8**)	Me_2AlCl	$TMSN_3$	**10a**, 51, (one epimer)
	Et_2AlCN	---	**10b**, (Nuc = CN) 22 (one epimer)
	Me_2AlCl		**10c**, 57, (1:1)

The two epimers of **9b** as well as those of **9c** were separable, and the stereochemistry of those of **9b** was assigned on the basis of HETCOR and NOE NMR studies. In contrast, the stereochemistry of the epimers of **9c** could *not* be assigned on the basis of the same measurements, nor could they be assigned by comparison to those of **9b**. Similarly, the stereochemistry of **9d** (a single epimer on the basis of the ^{1}H NMR spectrum of the crude reaction mixture after quenching with water and filtration to remove aluminum salts) could not be confidently assigned on the basis of comparison of ^{1}H and ^{13}C NMR spectra with those of the epimers of **9b**.

In contrast to **6b**, compound **8** underwent acetate replacement reactions in lower yields, and the resulting products **10a**−**c** were considerably less stable, decomposing on standing over the course of hours or days. In addition, they proved very difficult to purify, and assignment of structures was based primarily on comparison of spectra with **9a**−**d**. The reason for this difference in stability is unknown.

In summary, photolysis of chiral cyclobutanones in the presence of nucleophiles resulted in efficient ring expan-

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sion to tetrahydrofurans, with retention of configuration of all resident stereocenters, but with no stereoselectivity at the newly formed stereogenic center. Acetic acid was the most efficient nucleophile, and the resulting 2-acetoxytetrahydrofurans underwent efficient but nonstereoselective Lewis acid-catalyzed replacement of the acetate by a variety of nucleophiles. Since the oxazolidinone moiety in all of the new compounds can readily be removed by catalytic hydrogenolysis, to give the free NH_2 group,[10] this chemistry offers routes to amino-substituted tetrahydrofurans and nucleoside analogs.

Experimental Section

General Procedures. Photoreactions to produce cyclobutanones were carried out using a 450 W Hanovia 7825 medium-pressure mercury vapor lamp immersed in a Pyrex well and Pyrex tubes or Ace pressure tubes equipped with a pressure head capable of withstanding 150 psi. All NMR data were obtained in $CDCl_3$ filtered through basic alumina immediately before use. Unless otherwise noted, the spectra were obtained at 300 MHz for protons and 75 MHz for carbon. The following compounds were prepared according to literature methods: [(ethoxy)(methyl)carbene]pentacarbonylchromium-(0),[11] [(benzyloxymethyl)(ethoxy)carbene]pentacarbonylchromium-(0),[12] and *syn*-4,5-diphenyl-3-vinyl-2-oxazolidinone.[13]

General Procedure for Ring-Expansion Reactions. The cyclobutanone and the nucleophile were placed in a 12 × 100 mm oven-dried Pyrex test tube. The test tube was flushed with argon and capped with a rubber septum. Degassed dichloromethane or tetrahydrofuran was added with a syringe. The tube was then irradiated at 0 °C until TLC showed no cyclobutanone remaining, typically 3−4 days. The contents of the test tube were then poured into a separatory funnel, and the test tube was rinsed with additional dichloromethane. The combined organic layers were washed with water, dried over $MgSO_4$, and concentrated by rotary evaporation. The residue was separated by column chromatography. In some cases, radial chromatography was used to separate epimers. The anomeric ratio was determined by integration of the appropriate anomeric proton NMR signals of the crude product.

Photolysis of 2-Methoxy-2,3,3,4-tetramethylcyclobutanone in the Presence of Imidazole To Produce Tetrahydrofuran 1 (eq 3). Photolysis (40 h) of the cyclobutanone (49 mg, 0.31 mmol) and imidazole (22 mg, 0.32 mmol) in 2 mL of THF at −5 °C (degassed) gave 44 mg (63%) of a clear oil after chromatography on silica gel (diethyl ether with increasing amount of methanol to 8%). The product consisted of a 1:1 mixture of two epimers at C-1′, determined by integration of the corresponding acetal protons and methoxy protons: ^{1}H NMR δ 0.58 (d, 3H, J = 7.5 Hz), 0.87 (s, 3H), 0.89 (s, 3H), 0.91 (d, 3H, J = 7.2 Hz), 0.98 (s, 3H), 1.00 (s, 3H), 1.26 (s, 3H), 1.36 (s, 3H), 2.66 (quintet, 1H, J = 7.8 Hz), 2.76 (dq, 1H, J = 9, 7.2 Hz), 3.20 (s, 3H), 3.29 (s, 3H), 5.32 (d, 1H, J = 8.7 Hz), 5.77 (d, 1H, J = 8.4 Hz), 6.92−7.01 (m, 4H), 7.54−7.57 (m, 2H); ^{13}C NMR δ 8.5, 9.8, 14.8, 14.9, 18.7, 20.1, 21.8, 44.9, 46.2, 46.8, 47.9, 48.6, 48.9, 53.3, 87.9, 91.1, 110.2, 111.2, 117.3, 128.9, 129.7, 135.7 136.8; IR (film) ν 2966, 1491, 1459, 1379 cm^{-1}; HRMS ((*m* + 1)/*z*) calcd for $C_{12}H_{21}N_2O_2$ 225.1603, found 225.1614.

Photolysis of Cyclobutanone 2. (a) With Methanol To Give 3a. Photolysis (22 h) of **2** (51 mg, 0.16 mmol) and methanol (distilled over sodium, 2 mL) in 8 mL of THF (degassed) gave 20 mg (36%) of epimer A and 22 mg (39%) of epimer B as clear oils after chromatography on silica gel (hexane/ethyl acetate 4:1). The product consisted of a 3:1 mixture of two epimers at C-1′, as determined by integration of the corresponding acetal proton signals and methoxy proton signals in the crude ^{1}H NMR. **Epimer A:** ^{1}H NMR (C_6D_6) δ 0.97 (t, 3H, J = 7.2 Hz), 1.32−1.80 (m, 6H), 2.00−2.09 (m, 1H), 2.21 (ddd, 1H, J = 5.1, 7.8, 13.0 Hz), 3.14 (s, 3H), 3.16 (s, 3H), 3.41 (dd, 1H, J = 2.5, 8.5 Hz), 3.83 (t, 1H, J = 8.4 Hz), 4.31 (dd, 1H, J = 2.5, 8.3 Hz), 4.64 (t, 1H, J = 5.6 Hz), 4.98 (d, 1H, J = 6.5 Hz), 6.88−6.98 (m, 5H); ^{13}C NMR (C_6D_6) δ 14.0, 23.4, 25.5, 30.4, 34.8, 48.2, 55.9, 58.2, 59.8, 70.3, 106.0, 111.9, 126.1, 128.7, 129.2, 141.9, 158.0; IR (film) ν 2959 m, 1755s, 1721s, 1459m, 1412m, 1383w, 1211m, 1121m, 1069m cm^{-1}; TLC (hexane/ethyl acetate 1:1) R_f = 0.55; HRMS ((*m* + 1)/*z*) calcd for $C_{19}H_{28}NO_5$ 350.1967, found: 350.1976.

Epimer B: ^{1}H NMR δ 0.93 (t, 3H, J = 7.0 Hz), 1.22−1.67 (m, 5H), 1.81−1.89 (m, 2H), 2.27 (ddd, 1H, J = 6.6, 9.1, 15 Hz) 3.21 (s, 3H), 3.29 (s, 3H), 4.00 (dd, 1H, J = 1.2, 8.3 Hz), 4.48−4.54 (m, 2H), 4.86 (dd, 1H, J = 2.3, 6.6 Hz), 5.02 (d, 1H, J = 6.8 Hz), 7.18−7.38 (m, 5H); ^{13}C NMR (acetone D_6) δ 14.2, 23.6, 25.8, 32.1, 33.5, 48.5, 55.9, 57.0, 58.9, 72.0, 104.7, 111.9, 126.8, 128.7, 129.6, 143.4, 158.0; TLC (hexane/ethyl acetate 1:1) R_f = 0.58.

(b) Reaction with Propionic Acid To Give 3b. Photolysis (2.5 days) of **2** (37 mg, 0.12 mmol) and propionic acid (distilled, 0.1 mL, 1.3 mmol) in 5 mL of THF (degassed) gave 31 mg (66%) of a 2:1 mixture of epimers as a clear oil after chromatography on silica gel (hexane/ethyl acetate 4:1) (mixture of two diastereomers, minor indicated with superscript M): ^{1}H NMR δ 0.88−0.92 (m, 3H), 1.02−1.08 (m, 3H), 1.20−1.45 (m, 6H), 1.68−1.76 (m, 1H), 1.99−2.09 (m, 1H), 2.15−2.27 (m, 3H + 0.5H), 2.49−2.51 (m, 0.5H), 3.13 (s, 3H), 3.20 (s, 3H), 4.02 (dd, 1H, J = 1.2, 8.4 Hz), 4.08 (dd, 1H, J = 2.4, 8.6 Hz), 4.51 (t, 1H, J = 8.5 Hz), 4.57 (dd, 1H, J = 2.2, 9.1 Hz), 4.70 (d, 1H, J = 7.7 Hz), 4.75 (dd, 1H, J = 2.2, 8.4 Hz), 4.96 (d, 1H, J = 7.1 Hz), 5.87 (dd, 1H, J = 5.0, 6.5 Hz), 6.01 (dd, 1H, J = 2.5, 7.1 Hz), 7.19−7.41 (m, 5H); ^{13}C NMR δ 8.6, 13.6, 13.7^M, 22.8, 24.6, 24.9, 27.5, 29.1, 30.0, 32.3, 33.8, 48.4, 48.6^M, 56.6, 57.9, 58.0, 59.2, 70.9, 71.4^M, 96.0^M, 96.8, 112.1^M, 112.5, 125.6, 126.0, 129.1, 129.3, 129.5, 140.7, 141.1, 158.1, 158.4^M, 172.9^M, 173.7; IR (film) ν 2944m, 2878, 1747s, 1455w, 1411m, 1378w, 1318w, 1208m, 1170m, 1071m, 1054m, 972m, 890w, 758w, 714w cm^{-1}; TLC (hexane/ethyl acetate 2:1) R_f = 0.33, HRMS ((*m* + 1)/*z*) calcd for $C_{21}H_{30}NO_6$ 392.2073, found 392.2053.

(c) Reaction with Pivalic Acid To Give 3c. Photolysis (3.5 days) of **2** (40 mg, 0.13 mmol) and pivalic acid (distilled, 0.15 mL, 1.3 mmol) in 5 mL of THF (degassed) gave 15 mg of epimer A, 9 mg of a mixture of both epimers, and 5 mg of not completely clean epimer B (overall yield 55%) (~3:1 mixture of epimers) as clear oils after chromatography on silica gel (hexane/ethyl acetate 4:1).

Epimer A: ^{1}H NMR δ 0.85−0.93 (m, 3H), 1.11 (s, 9H), 1.22−1.42 (m, 6H), 1.74 (dd, 1H, J = 6.6, 14.9 Hz), 2.02−2.06 (m, 1H), 2.22 (ddd, 1H, J = 5.0, 8.0, 14.8 Hz), 3.16 (s, 3H), 4.07 (dd, 1H, J = 2.3, 8.6 Hz), 4.51 (t, 1H, J = 8.5 Hz), 4.69 (d, 1H, J = 7.9 Hz), 4.75 (dd, 1H, J = 2.2, 8.4 Hz), 5.84 (dd, 1H, J = 5.1, 6.4 Hz), 7.28−7.42 (m, 5H); ^{13}C NMR δ 13.7, 22.9, 25.0, 27.0, 29.1, 34.1, 38.6, 48.6, 58.0, 59.3, 71.0, 97.3, 112.6, 126.0, 129.3, 129.6, 140.7, 158.1, 177.7; IR (film) ν 2960m, 2873w, 1745s, 1459m, 1414m, 1210m, 1148m, 1056m, 975m, 893w, 826w, 760w, 716w, 702w cm^{-1}; TLC (hexane/ethyl acetate 2:1) R_f = 0.40; $[\alpha]_D$ = −68.5° (*c* = 0.93, CH_2Cl_2); mp 135−137 °C.

Epimer B: ^{1}H NMR δ 0.89−0.93 (m, 3H), 1.12 (s, 9H), 1.23−1.63 (m, 6H), 1.75−1.83 (m, 1H), 1.88−1.98 (m, 1H), 2.36−2.46 (m, 1H), 3.22 (s, 3H), 4.06 (dd, 1H, J = 1.7, 8.3 Hz), 4.55 (t, 1H, J = 7.7 Hz), 4.93 (d, 1H, J = 6.2 Hz), 6.01 (dd, 1H, J = 3.7, 6.9 Hz), 7.21−7.40 (m, 5H); TLC (hexane/ethyl acetate 2:1) R_f = 0.36.

Reaction with Water To Give 4. Photolysis (2 days) of **2** (51 mg, 0.16 mmol) and water (2 mL) in 17 mL of THF (degassed) gave 48 mg (>90%) of a clear oil after chromatography on silica gel (hexane/ethyl acetate 1:1): ^{1}H NMR δ 0.82 (t, 3H, J = 7.5 Hz), 1.16−1.26 (m, 2H), 1.37−1.50 (m, 2H), 2.20−2.31 (m, 1H) 2.44−2.55 (m, 1H), 2.74 (dd, 1H, J = 6.6,

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18.6 Hz), 3.10 (dd, 1H, J = 6.3, 18.6 Hz), 4.27 (t, 1H, J = 6.3 Hz), 4.34 (dd, 1H, J = 7.2, 8.9 Hz), 4.65 (t, 1H, J = 8.9 Hz), 4.83 (dd, 1H, J = 7.2, 8.9 Hz), 7.39−7.46 (m, 5H), 9.64 (s, 1H); ^{13}C NMR δ 13.7, 22.0, 25.4, 38.7, 41.8, 56.4, 60.2, 70.3, 128.0, 129.4, 129.7, 137.4, 157.1, 199.1, 205.3; IR (film) ν 2958m, 1754s, 1721s, 1411s, 1361m, 1224m, 1171m, 1115m, 1086m, 1034m, 766m cm^{-1}; TLC (hexane/ethyl acetate 1:1) R_f = 0.33; $[\alpha]_D$ = +23.8 (c = 0.011, CH_2Cl_2); HRMS ((m + 1)/z) calcd for $C_{17}H_{21}NO_4$ 303.1471, found 303.1480.

(±)-Cyclobutanone 5. [(Ethoxy)(methyl)carbene]pentacarbonylchromium(0) (1.00 g, 3.80 mmol) and racemic *syn*-4,5-diphenyl-3-vinyl-2-oxazolidinone (0.50 g, 1.90 mmol) were placed in an Ace pressure tube. Dichloromethane (25 mL) was added, and the tube was sealed with a pressure head. The contents were degassed with three freeze−pump−thaw cycles. The pressure tube was flushed three times with 65 psi of CO, charged with 65 psi CO, and irradiated overnight at room temperature. The solvent was removed by rotary evaporation, and the $Cr(CO)_6$ was recovered by sublimation at reduced pressure. The remaining solid was purified by flash chromatography (3:1:1 hexanes/EtOAc/CH_2Cl_2, SiO_2) to give a single diastereomer (0.49 g, 72%) of cyclobutanone as a white solid: mp 179−181 °C; ^{1}H NMR δ 1.14 (t, 3H, J = 6.9 Hz), 1.51 (s, 3H), 2.55 (dd, 1H, J = 10.3, 18.1 Hz), 2.92 (dd, 1H, J = 9.2, 18.0 Hz), 3.54 (m, 2H), 4.53 (t, 1H, J = 9.6 Hz), 5.06 (d, 1H, J = 7.5 Hz), 5.88 (d, 1H, J = 7.5 Hz), 6.81−7.08 (m, 10H); ^{13}C NMR δ 15.6, 43.3, 48.8, 60.7, 66.0, 80.2, 95.5, 126.1, 127.2, 128.0, 128.2, 128.6, 128.7, 133.6, 158.2, 206.4. Anal. Calcd for $C_{22}H_{23}NO_4$: C, 72.31; H, 6.34; N, 3.83. Found: C, 72.14; H, 6.39; N, 3.83.

(±)-Methanol Adduct 6a. (±)-Cyclobutanone (118 mg, 0.32 mmol) and methanol (1.5 mL) were used. The crude reaction mixture was concentrated without washing, and the residue was further dried under reduced pressure before chromatography. A proton NMR spectrum of the crude product showed both epimers present in a 1:1 ratio, but flash chromatography (SiO_2; 1:1 hexanes/EtOAc) followed by radial chromatography (10:1 hexanes/EtOAc) resulted in isolation of only one epimer (59 mg, 46%) as a white solid: ^{1}H NMR δ 1.13 (t, 3H, J = 7.0 Hz), 1.54 (s, 3H), 2.32 (ddd, 1H, J = 6.6, 8.6, 15.1 Hz), 3.31 (s, 3H), 3.51−3.61 (m, 2H), 4.48 (dd, 1H, J = 2.0, 9.0 Hz), 4.86 (dd, 1H, J = 2.1, 6.6 Hz), 5.24 (d, 1H, J = 7.2 Hz), 5.81 (d, 1H, J = 7.2 Hz), 6.90−7.10 (m, 11H); ^{13}C NMR δ 15.6, 18.6, 32.5, 56.1, 57.0, 58.5, 63.7, 81.2, 105.0, 110.2, 126.0, 126.2, 127.7, 127.8, 128.1, 128.4, 133.7, 136.5, 158.8. Anal. Calcd for $C_{23}H_{27}NO_5$: C, 69.50; H, 6.85; N, 3.52. Found: C, 69.56; H, 6.92; N, 3.63.

(±)-Acetic Acid Adduct 6b. (±)-Cyclobutanone (300 mg, 0.82 mmol) and acetic acid (0.2 mL, 3.4 mmol) were used, equally divided between two test tubes. The reaction mixture was washed with $NaHCO_3$ (saturated aqueous) and dried over Na_2SO_4, and after concentration the product was further dried under reduced pressure to yield a white foam (310 mg, 89%). The crude product, a 1.1:1 mixture of anomers, was not further purified as it was not stable to chromatography on SiO_2: ^{1}H NMR δ 1.13 (t, 3 × 0.5H, J = 7.1 Hz), 1.14 (t, 3 × 0.5H, J = 7.1Hz), 1.56 (s, 3 × 0.5H), 1.58 (s, 3 × 0.5H), 1.97 (s, 3 × 0.5H), 1.98 (s, 3 × 0.5H), 2.25−2.35 (m, 2 × 0.5H), 2.53−2.63 (m, 2 × 0.5H), 3.48−3.64 (m, 2H), 4.59 (dd, 1 × 0.5H, J = 1.1, 9.1 Hz), 4.72 (dd, 1 × 0.5H, J = 1.1, 8.2 Hz), 4.91 (d, 1 × 0.5H, J = 7.6 Hz), 5.14 (d, 1 × 0.5H, J = 7.2 Hz), 5.81 (m, 1H), 5.96 (dd, 1 × 0.5H, J = 5.1, 6.5 Hz), 6.05 (dd, 1 × 0.5H, J = 2.0, 6.8 Hz), 6.85−7.23 (m, 10H); ^{13}C NMR δ 15.2, 15.4, 17.3, 17.8, 21.0, 21.1, 32.2, 33.1, 57.0, 57.2, 58.6, 61.0, 63.0, 63.4, 80.8, 81.3, 96.9, 97.0, 110.7, 110.9, 125.8, 125.9, 126.1, 126.3, 126.4, 126.5, 126.6, 126.7, 128.0, 128.1, 128.2, 128.3, 128.4, 128.5, 128.8, 133.3, 133.4, 136.0, 136.1, 158.2, 158.6, 169.1, 170.1; IR ν 1752 cm^{-1}. The product was not sufficiently stable for elemental analysis and was used without further purification.

(±)-Imidazole Adduct 6c. (±)-Cyclobutanone (115 mg, 0.31 mmol) and imidazole (63 mg, 0.93 mmol) were used. The crude reaction mixture was concentrated without washing. Chromatography (SiO_2; 1:1 hexanes/EtOAc to remove any less polar materials, followed by 19:1 CH_2Cl_2/MeOH to elute the product) gave the pure imidazole adduct (yellow solid, 101 mg, 74%) as a 1.1:1 mixture of anomers: ^{1}H NMR δ 1.05 (t, 3 × 0.5H, J = 6.9 Hz), 1.14 (t, 3 × 0.5H, J = 6.9 Hz), 1.60 (s, 3 × 0.5H), 1.68 (s, 3 × 0.5H), 2.04−2.09 (m, 2H), 2.51 (ddd, 1 × 0.5H, J = 6.1, 9.0, 15.7 Hz), 2.81 (ddd, 1 × 0.5H, J = 7.8, 8.0, 14.9 Hz), 3.20−3.31 (m, 1 × 0.5H), 3.46−3.72 (m, 2H + 1 × 0.5H), 4.64 (dd, 1 × 0.5H, J = 7.8, 9.0 Hz), 4.75 (dd, 1 × 0.5H, J = 1.2, 8.0 Hz), 5.34 (d, 1 × 0.5H, J = 7.5 Hz), 5.44 (d, 1 × 0.5H, J = 7.5 Hz), 5.91−5.98 (m, 1H), 6.07−6.14 (m, 1H), 6.90−7.18 (m, 10H), 7.61 (s, 1 × 0.5H), 7.68 (s, 1 × 0.5H); ^{13}C NMR δ 15.0, 15.5, 17.3, 18.1, 33.2, 34.3, 57.2, 57.4, 60.4, 61.8, 63.4, 64.4, 80.7, 80.8, 84.1, 85.8, 109.8, 110.7, 116.4, 117.1, 126.0, 126.9, 127.1, 127.8, 127.9, 128.1, 128.4, 128.5, 128.6, 128.9, 129.8, 130.0, 133.2, 135.1, 135.3, 135.9, 136.5, 158.1, 158.3. Anal. Calcd for $C_{25}H_{27}N_3O_4$: C, 69.27; H, 6.28; N, 9.69. Found: C, 69.23; H, 6.53; N, 9.43.

(±)-Ketoaldehyde Derived from Cyclobutanone 5. (±)-Cyclobutanone (115 mg, 0.31 mmol) and distilled water (1 mL) were dissolved in THF in a test tube. Argon was bubbled through the reaction for 20 min. The test tube was then irradiated as above. $MgSO_4$ was added to the solution, which was then filtered through Celite. The tube was rinsed three times with CH_2Cl_2, and the combined organic layers were concentrated by rotary evaporation. Flash chromatography (SiO_2; 2:1:1 hexanes/CH_2Cl_2/EtOAc) gave the white solid product in nearly quantitative yield (105 mg): ^{1}H NMR δ 2.25 (s, 3H), 2.76 (dd, 1H, J = 6.0, 18.6 Hz), 3.00 (ddd, 1H, J = 0.7, 6.3, 18.6 Hz), 4.52 (t, 1H, J = 6.3 Hz), 5.09 (d, 1H, J = 8.4 Hz), 5.90 (d, 1H, J = 8.4 Hz), 6.80−7.15 (m, 10H), 9.49 (s, 1H); ^{13}C NMR δ 27.1, 42.1, 57.3, 64.4, 80.3, 125.8, 127.8, 127.9, 128.2, 128.3, 128.4, 128.8, 128.9, 134.1, 134.3, 157.8, 198.5, 203.1.

Cyclobutanone 7. [(Benzyloxymethyl)(ethoxy)carbene]-pentacarbonylchromium(0) (1 equiv) and *syn*-4,5-diphenyl-3-vinyl-2-oxazolidinone (2 equiv) were combined in a pressure tube under argon. Degassed dichloromethane (enough to dissolve all solids) was added via cannula, and the tube was sealed with a pressure head. The apparatus was flushed three times with 65 psi of CO, charged with 65 psi of CO, and irradiated at −35 °C until clear, typically 4−7 days. The solvent was removed by rotary evaporation, and the $Cr(CO)_6$ was recovered by sublimation at reduced pressure. The remaining solid was purified by flash chromatography (SiO_2, 9:1 hexanes/EtOAc to remove excess ene−carbamate followed by 3:1 hexanes/EtOAc) to give the product. If racemic ene−carbamate was used, the resulting racemic cyclobutanone could be recrystallized (hexanes/EtOAc) to give a white solid, mp 156−158 °C, and yields were typically 50−60%. If enantiomerically pure ene−carbamate was used, the cyclobutanone was a clear oil and yields were typically 30−40%: ^{1}H NMR δ 1.35 (t, 3H, J = 7.3 Hz), 2.42 (dd, 1H, J = 10.6, 18.2 Hz), 2.68 (dd, 1H, J = 9.8, 18.2 Hz), 3.66−3.80 (m, 2H), 3.84 (d, 1H, J = 9.2 Hz), 4.05 (d, 1H, J = 9.2 Hz), 4.53 (d, 1H, J = 11.2 Hz), 4.67 (d, 1H, J = 11.2 Hz), 4.78 (t, 1H, J = 10.2 Hz), 5.02 (d, 1H, J = 7.7 Hz), 5.58 (d, 1H, J = 7.7 Hz), 6.45−7.46 (m, 15H); ^{13}C NMR δ 15.7, 46.1, 48.0, 61.7, 64.8, 69.1, 74.4, 80.4, 97.7, 125.9, 126.8, 127.7, 127.8, 127.9, 128.0, 128.1, 128.3, 128.4, 128.8, 133.6, 135.5, 137.2, 158.5, 206.4; $[\alpha]_D$ for product derived from (+)-ene−carbamate = 42.4° (c = 1, CH_2Cl_2).

Ring Expansion of Cyclobutanone 7. The ring-expansion procedure for the model system was used. Cyclobutanone **7** (154 mg, 0.33 mmol) and acetic acid (0.06 mL, 1.0 mmol) were converted to 132 mg (76%) of tetrahydrofuran **8** as a 1.2:1 mixture of anomers. This clear oil was used without further purification: ^{1}H NMR δ 1.10−1.21 (m, 3H), 1.68−1.90 (m, 1H + 1H × 0.5), 1.92 (s, 3H × 0.5), 1.94 (s, 3H × 0.5), 2.22−2.43 (m, 1H × 0.5), 3.45−4.05 (m, 2H), 4.45−5.02 (m, 5H + 1H × 0.5), 5.26 (dd, 1H × 0.5, J = 7.3, 12.8 Hz), 6.02 (dd, 1H × 0.5, J = 2.9, 5.6 Hz), 6.13 (dd, 1H × 0.5, J = 2.9, 5.6 Hz), 6.46−6.51 (m, 1H × 0.5), 6.85−7.46 (m, 15H); ^{13}C NMR δ 15.3, 15.5, 32.1, 34.0, 56.9, 57.3, 63.3, 63.4, 68.4, 69.2, 74.5, 74.6, 80.4, 80.8, 96.2, 96.8, 109.9, 110.1, 125.9, 126.1, 127.5, 127.6, 127.7, 127.8, 127.9, 128.0, 128.1, 128.2, 128.3, 128.4, 128.5, 128.6, 128.7, 128.8, 133.6, 133.7, 136.2, 136.5, 137.4, 137.7, 158.3,

158.6, 169.2, 170.0. The product was not sufficiently stable for elemental analysis and was used without further purification.

Representative Substitution Reaction Procedure: Azide Substitution Products 9b. A 25 mL round-bottomed flask was charged with (±)-acetate **6b** (120 mg, 0.28 mmol), $TMSN_3$ (0.12 mL, 0.90 mmol), 15 mL of dichloromethane, and a stir bar. The reaction vessel was chilled in an ice bath for 10 minutes, and Me_2AlCl (1.0 M in hexanes; 0.90 mL, 0.90 mmol) was added. The reaction was allowed to stir and slowly warm to room temperature overnight. After 15 h, the reaction was quenched by adding saturated $NaHCO_3$ solution. The reaction mixture was filtered through Celite to remove the aluminum salts, and the layers were separated. The aqueous layer was extracted with dichloromethane (2 × 15 mL). The combined organic layers were washed with distilled water (1 × 15 mL) and brine (1 × 15 mL), dried over $MgSO_4$, and concentrated by rotary evaporation. Flash chromatography (SiO_2, 3:1 hexanes/EtOAc) removed any polar impurities and gave 105 mg of a clear oil, a 1:1 mixture of anomers. The anomers were separated by radial chromatography (12:1 hexanes/EtOAc) to give 45 mg of epimer A, 43 mg of epimer B, and an additional 5 mg of mixed epimers, for a total of 93 mg (0.22 mmol, 81%). Assignments were made by HETCOR measurements, and the epimers were subsequently identified by NOE difference experiments. Anal. Calcd for $C_{22}H_{24}N_4O_4$: C, 64.69; H, 5.92; N, 13.72. Found: C, 64.83; H, 6.00; N, 13.89.

Epimer A (N_3 and oxazolidinone *trans*): ^{1}H NMR δ 1.24 (t, 3H, J = 7.0 Hz), 1.40 (dd, 1H, J = 7.3, 12.7 Hz), 1.61 (s, 3H), 1.90 (dt, 1H, J = 6.5, 12.6 Hz), 3.59−3.68 (m, 2H), 4.58 (dd, 1H, J = 7.2, 12.4 Hz), 5.18 (d, 1H, J = 6.4 Hz), 5.32 (d, 1H, J = 7.6 Hz), 5.81 (d, 1H, J = 7.5 Hz), 6.92-7.23 (m, 10H); ^{13}C NMR δ 15.9, 20.7, 33.9, 56.9, 57.8, 63.8, 80.8, 88.6, 107.7, 126.1, 127.8, 128.1, 128.3, 133.8, 136.3, 158.4; IR ν 2114, 1745 cm^{-1}.

Epimer B (N_3 and oxazolidinone *cis*): ^{1}H NMR δ 1.31 (t, 3H, J = 7.0 Hz), 1.55 (s, 3H), 1.57−1.67 (m, 1H), 1.79−1.88 (m, 1H), 3.58−3.78 (m, 2H), 4.40 (dd, 1H, J = 8.2, 12.1 Hz), 5.19 (t, 1H, J = 6.6 Hz), 5.40 (d, 1H, J = 7.4 Hz), 5.83 (d, 1H, J = 7.4 Hz), 6.93−7.06 (m, 10H); ^{13}C NMR δ 15.6, 19.8, 32.6, 57.0, 59.2, 63.7, 81.0, 89.2, 106.8, 126.1, 127.8, 127.9, 128.3, 128.4, 128.5, 128.7, 128.8, 133.8, 136.3, 158.4; IR ν 2108, 1761 cm^{-1}.

(±)-Allyl Substitution Product 9a. (±)-Acetate **6b** (112 mg, 0.26 mmol) and allyltrimethylsilane (0.13 mL, 0.79 mmol) were dissolved in acetonitrile and chilled in an ice bath; TMSOTf (one drop) was added and the reaction allowed to proceed as above. No filtration was required. Flash chromatography (SiO_2; 5:1−3:1 hexanes/EtOAc) gave 102 mg (95%) of a clear oil. This 1:1 mixture of epimers proved inseparable: ^{1}H NMR δ 0.93 (t, 3H × 0.5, J = 7.0 Hz), 1.18 (t, 3H × 0.5, J = 7.0 Hz), 1.44−1.56 (m, 1H), 1.65−1.82 (m, 1H), 1.95−2.16 (m, 1H), 2.22 (s, 3H × 0.5), 2.26 (s, 3H × 0.5), 2.92−3.14 (m, 2H), 3.27−3.77 (m, 2H), 4.29 (dd, 1H × 0.5, J = 5.1, 7.8 Hz), 4.64 (dd, 1H × 0.5, J = 3.3, 9.9 Hz), 4.74−4.81 (m, 2H × 0.5), 4.91−4.96 (m, 1H × 0.5), 5.12−5.26 (m, 2H), 5.48−5.62 (m, 1H × 0.5), 5.92 (d, 1H × 0.5, J = 8.4 Hz), 6.04 (d, 1H × 0.5, J = 8.4 Hz), 6.87−7.11 (m, 10H); ^{13}C NMR δ 15.1, 15.5, 27.4, 28.4, 33.0, 33.4, 37.7, 38.1, 59.5, 61.1, 63.6, 64.0, 65.0, 75.0, 75.3, 80.7, 80.8, 117.3, 117.7, 125.9, 126.0, 127.7, 127.8, 127.9, 128.1, 128.2, 128.3, 133.5, 134.4, 135.5, 136.6, 158.4, 158.7, 205.4, 206.0. Anal. Calcd for $C_{25}H_{29}NO_4$: C, 73.69; H, 7.17; N, 3.44. Found: C, 73.75; H, 7.03; N, 3.59.

(±)-Cyanide Substitution Product 9c. (±)-Acetate **6b** (243 mg, 0.57 mmol) was dissolved in CH_2Cl_2 and chilled in an ice bath. Et_2AlCN (1.0 M in toluene; 1.71 mL, 1.71 mmol) was added and the reaction allowed to proceed as above. The crude product was separated by flash chromatography (SiO_2; 1:1 hexanes/EtOAc) to obtain a white foam as a 1:1 mixture of epimers (175 mg, 78%). The epimers were partially separable by radial chromatography (12:1 hexanes/EtOAc). Although NOE experiments were carried out, it was still not possible to assign the stereochemistry of these epimers: IR ν 2237, 1751 cm^{-1}. Anal. Calcd for $C_{23}H_{24}N_2O_4$: C, 70.39; H, 6.16; N, 7.14. Found: C, 70.28; H, 6.41; N, 7.00.

Epimer A: ^{1}H NMR δ 1.23 (t, 3H, J = 7.0 Hz), 1.59 (s, 3H), 1.81−1.89 (m, 1H), 2.01−2.14 (m, 1H), 3.59 (q, 2H, J = 7.0 Hz), 4.47 (dd, 1H, J = 2.4, 9.4 Hz), 4.62 (dd, 1H, J = 8.1, 12.1 Hz), 5.31 (d, 1H, J = 7.4 Hz), 5.82 (d, 1H, J = 7.6 Hz), 6.92−7.09 (m, 10H); ^{13}C NMR δ 15.8, 19.6, 31.6, 57.0, 58.8, 62.7, 63.7, 80.9, 107.5, 118.2, 126.1, 127.0, 127.9, 128.0, 128.4, 128.5, 133.6, 136.1, 158.3.

Epimer B: ^{1}H NMR δ 1.20 (t, 3H, J = 7.0 Hz), 1.58 (s, 3H), 1.92 (dd, 1H, J = 8.5, 14.4 Hz), 2.60 (ddd, 1H, J = 7.1, 8.0, 14.1 Hz), 3.55−3.70 (m, 2H), 4.25 (dd, 1H, J = 7.2, 8.5 Hz), 4.72 (d, 1H, J = 8.1 Hz), 4.83 (d, 1H, J = 7.8 Hz), 5.78 (d, 1H, J = 7.8 Hz), 6.92−7.12 (m, 10H); ^{13}C NMR δ 14.8, 16.4, 32.8, 57.6, 60.6, 63.0, 63.8, 80.6, 110.8, 119.2, 125.9, 128.0, 128.1, 128.7, 129.0, 133.3, 135.8, 158.0.

(±)-Thymine Substitution Product 9d. Thymine (283 mg, 2.24 mmol) and *N*,*O*-bis(trimethylsilyl)acetamide (1.22 mL, 4.93 mmol) were heated to reflux for 8 h in 1,2-dichloroethane. This mixture was cooled to room temperature and then placed in an ice bath. (±)-Acetate **6b** (318 mg, 0.75 mmol) was added, the reaction was allowed to stir for 5 min at 0 °C, and Me_2AlCl (1.0 M in hexanes, 5.68 mL, 5.68 mmol) was added. The reaction was allowed to proceed as above. Only one epimer was detected by proton NMR of the crude product. Recrystallization (MeOH/H_2O or DMSO/H_2O) gave off-white needles of product (165 mg, 45%) as a single epimer: ^{1}H NMR (DMSO-d_6) δ 1.24 (t, 3H, J = 7.0 Hz), 1.64 (s, 3H), 1.86 (s, 3H), 1.93 (m, 1H), 2.50 (m, 1H), 3.51 (m, 1H), 3.71 (m, 1H), 4.67 (dd, 1H, J = 0.7, 7.6 Hz), 5.44 (d, 1H, J = 8.5 Hz), 6.19 (d, 1H, J = 7.7 Hz), 6.34 (t, 1H, J = 7.3 Hz), 7.18 (m, 10H), 7.54 (s, 1H), 11.38 (bs, 1H); ^{13}C NMR (DMSO-d_6) δ 12.1, 15.0, 17.6, 30.4, 57.1, 60.8, 61.9, 79.7, 83.8, 109.5, 110.5, 126.1, 127.6, 128.1, 128.3, 134.2, 135.9, 136.7, 150.7, 157.5, 163.5; IR ν 3178, 1736 cm^{-1}. Anal. Calcd for $C_{27}H_{29}N_3O_6$: C, 65.98; H, 5.95; N, 8.55. Anal. Calcd for $C_{27}H_{29}N_3O_6 \cdot 0.5H_2O$: C, 64.79; H, 6.04; N, 8.40. Found: C, 64.90; H, 6.39; N, 8.03.

Azide Replacement Product 10a. As in the representative procedure, acetate **8** (170 mg, 0.32 mmol), $TMSN_3$ (0.13 mL, 0.96 mmol), and Me_2AlCl (1.0 M in hexanes, 0.96 mL) were allowed to react. Flash chromatography (SiO_2, 3:1 hexanes/EtOAc) followed by radial chromatography gave 84 mg of one epimer of product (51%) as a clear oil that quickly degraded to a yellow glasslike solid upon standing neat overnight or in solution for 2 h. Because of its instability, assignment of structure is based primarily on the similarity of its ^{13}C spectrum to that of **9b**: ^{1}H NMR δ 1.16−1.26 (m, 3H), 1.68−1.77 (m, 1H), 1.81−1.90 (m, 1H), 3.59−4.11 (m, 4H), 4.65 (d, 1H, J = 3.6 Hz), 4.83−4.92 (m, 2H), 5.22−5.29 (m, 2H), 6.64−6.68 (m, 1H), 6.93−7.46 (m, 15H); ^{13}C NMR δ 15.3, 34.0, 57.6, 63.4, 68.7, 74.5, 80.3, 90.9, 109.8, 125.9, 126.2, 127.0, 127.7, 128.3, 128.7, 133.5, 136.1, 137.3, 158.1; IR ν 2111, 1755 cm^{-1}.

Cyanide Replacement Product 10b. As in the model system reaction, 132 mg (0.25 mmol) of acetate **8** was treated with 0.74 mL of Et_2AlCN (1.0 M in toluene). The crude product (79 mg) was obtained as a white foam consisting of a 2:1:1 mixture of a single epimer of product and each epimer of starting material. This mixture was partially separated by radial chromatography to give 15 mg of product (22% based on recovered starting material) as well as an additional 50 mg (38%) of pure starting material and 10 mg of a mixture of product and starting material: ^{1}H NMR δ 1.21−1.27 (m, 3H), 1.93 (ddd, 1H, J = 2.3, 8.5, 14.0 Hz), 2.47 (ddd, 1H, J = 7.1, 8.0, 14.0 Hz), 3.60−3.81 (m, 3H), 3.88 (d, 1H, J = 11.2 Hz), 4.36 (dd, 1H, J = 7.1, 8.0 Hz), 4.55 (d, 1H, J = 11.4 Hz), 4.66−4.76 (m, 1H), 4.91 (dd, 1H, J = 2.3, 8.0 Hz), 5.00 (d, 1H, J = 7.7 Hz), 6.60−6.64 (m, 1H), 6.92−7.47 (m, 15H); ^{13}C NMR δ 14.9, 32.6, 57.1, 59.1, 63.1, 64.4, 66.3, 74.5, 80.2, 110.0, 118.8, 125.9, 127.7, 127.8, 128.0, 128.3, 128.4, 128.6, 128.8, 128.9, 133.4, 136.1, 137.0, 158.0. Anal. Calcd for $C_{30}H_{30}N_2O_5$: C, 72.27; H, 6.06; N, 5.62. Found: C, 72.08; H, 6.14; N, 5.44.

Thymine Substitution Product 10c. Thymine (27 mg, 0.21 mmol) and *N*,*O*-bis(trimethylsilyl)acetamide (0.11 mL, 0.44 mmol) were stirred in 10 mL of acetonitrile for 1 h. Acetate **8** (75 mg, 0.14 mmol) was dissolved in a minimum amount of acetonitrile and added to the silylated thymine

mixture. The reaction was cooled in an ice bath for 15 min, and 0.85 mL of Me_2AlCl (1.0 M in hexanes) was added. The reaction was allowed to stir and warm to rt overnight. Rochelle's salt (15 mL of a saturated aqueous solution) was slowly added to quench the reaction and the biphasic mixture stirred for 1 h. The quenched reaction was transferred to a separatory funnel, 10 mL each of ethyl acetate and distilled water were added, and the layers were separated. The aqueous layer was extracted with EtOAc (3 × 10 mL). The combined organic layers were washed with distilled H_2O (2 × 10 mL) and brine (1 × 10 mL), dried over $MgSO_4$, and evaporated to give 100 mg of a gummy yellow solid. Flash chromatography (SiO_2, 2% MeOH in CH_2Cl_2) yielded 48 mg of a gummy white solid (57%). A ^{1}H NMR spectrum of this material showed the product to be present as a 1:1 mixture of epimers, but further attempts at purification by chromatography and crystallization failed: ^{1}H NMR (DMSO-d_6) δ 0.85−1.27 (m, 3H), 1.70−2.22 (m, 3H), 3.37−4.14 (m, obscured by water), 4.47−4.85 (m, 3H), 4.99 (dd, 1 × 0.5H, J = 8.4, 12.0 Hz), 5.11 (d, 1 × 0.5H, J = 7.5 Hz), 5.18 (d, 1 × 0.5H, J = 7.5 Hz), 5.50 (d, 1 × 0.5H, J = 7.8 Hz), 5.64 (d, 1 × 0.5H, J = 7.5 Hz), 5.86 (d, 1 × 0.5H, J = 6.6 Hz), 5.91 (d, 1 × 0.5H, J = 7.5 Hz), 5.96−6.23 (m, 3H), 6.46 (dd, 1 × 0.5H, J = 3.0, 9.5 Hz), 6.82−7.69 (m, 15H), 11.21−11.34 (bm, 1H); ^{13}C NMR (DMSO-d_6) after 15.5 h, the following peaks could be seen: δ 11.5, 15.7, 54.9, 62.5, 67.4, 73.0, 106.7, 126.0, 127.6, 128.1, 128.3, 150.0; HRMS ((*m* + 1)/*z*) calcd for $C_{34}H_{35}N_3O_7Na$ 620.2373, found 620.2362.

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Supporting Information Available: ^{1}H NMR and ^{13}C NMR spectra for compounds **1**, **3a**−**c**, **4**, **6b**, **8**, **9b**−**d**, **10a**−**c** and HRMS for compound **10c** (42 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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