Cross Coupling of Alkyl Cobaloximes with Maleic Anhydrides. Basic Studies and Applications to the Synthesis of Chaetomellic Acid A Anhydride and C-Glycosyl Maleic Anhydrides

Rachel M. Slade and Bruce P. Branchaud*

Department of Chemistry, University of Oregon, Eugene, Oregon 97403-1253

Received October 7, 1997

Abstract: Photochemical cross coupling of alkyl cobaloximes with maleic anhydrides and PhSSPh led to addition of an alkyl moiety and an SPh moiety across the alkene. Oxidation of the sulfide to a sulfoxide followed by elimination of phenyl sulfenic acid provided substituted maleic anhydrides. Alkyl cobaloximes could also be coupled with maleic anhydrides in the absence of PhSSPh to provide substituted maleic anhydrides directly. These methods are applied to a short and efficient synthesis of the anhydride of the Ras farnesyl protein transferase inhibitor chaetomellic acid A and in preparations of C-glycosyl maleic anhydrides, in which the carbohydrate anomeric carbon is directly attached to a maleic anhydride alkene carbon, in modest yields (19−46%).

Substituted maleic anhydrides, maleimides, γ-hydroxybutenolides, and butenolides are widespread in Nature and are in biologically active molecules such as the anticancer antibiotic showdomycin (**1**),[1] the cardiotonic drug digitoxin (**2**),[2] the antiinflammatory phospholipase A_2 inhibitor manoalide (**3**),[3] the Ras farnesyl protein transferase inhibitor chaetomellic acid A (**4**),[4] and the serine/threonine phosphatase inhibitor tautomycin (**5**).[5] Previous communications from our group have reported the development of methods for radical cross coupling of alkyl cobaloximes with maleic anhydrides[6] and an application of that method to the synthesis of chaetomellic acid A anhydride.[7] In this paper, experimental details are reported on that work. Applications of the method to the preparation of C-glycosyl maleic anhydrides of glucose and mannose in which the carbohydrate anomeric carbon is directly attached to a maleic anhydride alkene carbon are reported. Finally, a new and direct method for cross coupling alkyl cobaloximes with maleic anyhydrides is reported.

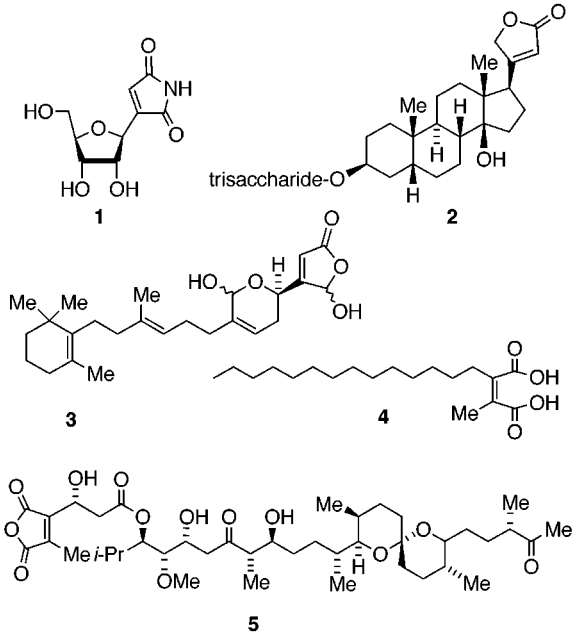


Figure 1.

Results and Discussion

Alkyl Cobaloxime Synthesis, Radical Trapping, and Oxidation/Elimination Studies. Primary and secondary alkyl cobaloximes can be prepared by oxidative addition (alkylation) of py(dmgH)$_2$Co$^-$Na$^+$ with alkyl bromides, iodides, or sulfonate esters. The py(dmgH)$_2$Co$^-$Na$^+$ can be formed by $NaBH_4$ reduction of ClCo(dmgH)$_2$py[8] or in situ from $CoCl_2$, dimethylglyoxime, NaOH, pyridine, and $NaBH_4$.[9] The reaction of py(dmgH)$_2$Co$^-$Na$^+$ (formed in situ) with *n*-decyl bromide under anaerobic conditions at 0 °C to room temp in CH_3OH produced decyl cobaloxime **6** in 81% isolated yield (eq 1). The α-acetoxy cobaloxime **7** was prepared from 1-bromo-1-acetoxy-3-methylbutane[10] in 37% isolated yield using py(dmgH)$_2$Co$^-$Na$^+$ formed from ClCo(dmgH)$_2$py and $NaBH_4$ under anaerobic conditions at 0 °C to room temp in CH_3CN (eq 2). The preparation of 2,3,4,6-tetra-*O*-benzoyl-D-mannopyranosyl cobaloxime **8** from 2,3,4,6-

* Corresponding author. Email = bbranch@oregon.uoregon.edu, phone = (541)346-4627, FAX = (541)346-4645.

(1)) *The Merck Index*, 12th ed.; Budavari, S., Ed.; Merck and Co.: New Jersey, 1996, entry 8627 and references therein.

(2) *The Merck Index*, 12th ed.; Budavari, S., Ed.; Merck and Co.: New Jersey, 1996, entry 3206 and references therein.

(3) De Rosa, S.; Crispino, A.; De Guilio, A.; Iodice, C.; Tommonaro, G. *J. Nat. Prod.* **1997**, *60*, 844 and references therein.

(4) (a) Desai, S. B.; Argade, N. P. *J. Org. Chem.* **1997** *62*, 4862 and references therein. (b) Poigny, S.; Guyot, M.; Samadi, M. *J. Chem. Soc., Perkin Trans. 1* **1997**, 2175. (c) Ratemi, E. S., Dolence, J. M., Poulter, C. D.; Vederas, J. C. *J. Org. Chem.* **1996**, *61*, 6296. (c) Gibbs, J. B.; Pompliano, D. L.; Mosser, S. D.; Rands, E.; Lingham, R. B.; Singh, S. B.; Scolnick, E. M.; Kohl, N. E.; Oliff, A. *J. Biol. Chem.* **1993**, *268*, 7617.

(5) Sheppeck, J. E., II; Liu, W.; Chamberlin, A. R. *J. Org. Chem.* **1997**, *62*, 387 and references therein.

(6) Branchaud, B. P.; Slade, R. M.; Janisse, S. K. *Tetrahedron Lett.* **1993**, *34*, 7885.

(7) Branchaud, B. P.; Slade, R. M. *Tetrahedron Lett.* **1994**, *35*, 4071.

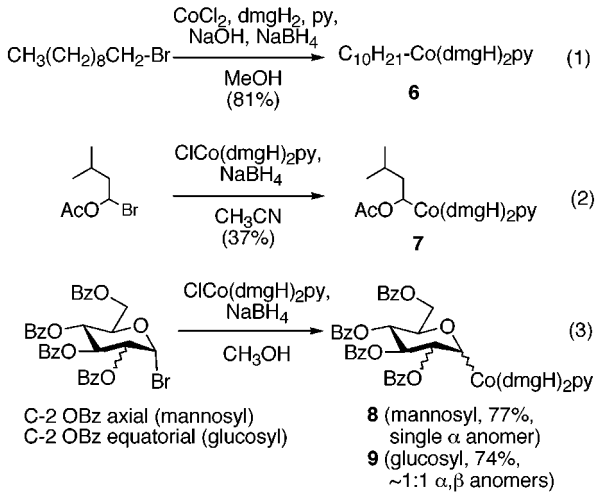
(8) Schrauzer, G. N. *Inorg. Synth.* **1968**, *11*, 61.

(9) (a) Schrauzer, G. N.; Windgassen, R. J. *J. Am. Chem. Soc.* **1967**, *89*, 1999. (b) Branchaud, B. P.; Meier, M. S.; Malekzadeh, M. N. *J. Org. Chem.* **1987**, *52*, 212.

(10) Bigler, P.; Muhle, H.; Neuenschwander, M. *Synthesis* **1978**, 593.

S0022-3263(97)01852-5 CCC: $15.00
Published on Web 05/13/1998

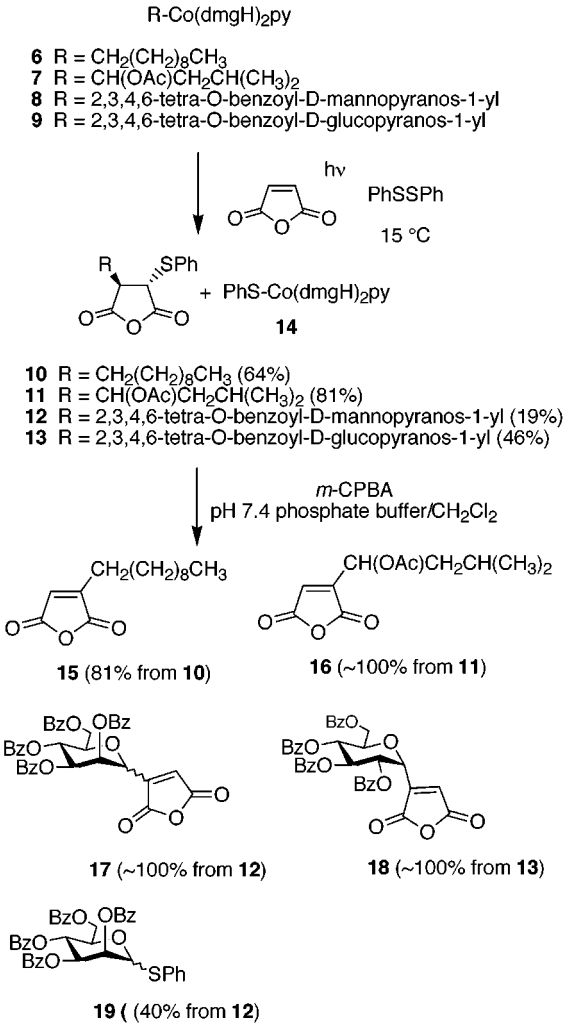
tetra-*O*-benzoyl-α-D-mannopyranosyl bromide was accomplished in 77% isolated yield using py(dmgH)$_2$Co$^-$Na$^+$ formed from ClCo(dmgH)$_2$py and NaBH$_4$ under anaerobic conditions in CH$_3$OH (eq 3). Cobaloxime **8** was obtained as a single diastereomer at the anomeric center, presumed to be the α anomer. Analogously, 2,3,4,6-tetra-*O*-benzoyl-D-glucopyranosyl cobaloxime **9** was prepared as a 1:1 mixture of α,β anomers in 74% isolated yield from 2,3,4,6-tetra-*O*-benzoyl-α-D-glucopyranosyl bromide (eq 3).



Initial attempts to directly cross couple **6** with maleic anhydride were unsuccessful. Cobaloxime **6** was slowly consumed under anaerobic photolysis in EtOH with 10−20 equiv of maleic anhydride, but none of the desired cross coupling product **15** (Scheme 1) was detected. The decyl radical formed from photolysis of **6** should have added to maleic anhydride since the rate constants for addition of nucleophilic alkyl radicals to maleic anhydride are approximately 10^7 M^{-1} s^{-1},[11] about 100 times faster than for other activated alkenes which have successfully undergone cobaloxime-mediated cross couplings. It was postulated that the decyl radical did add to maleic anhydride but β-H elimination was unfavorable due to ring strain in the maleic anhydride moiety, allowing oligomerization and other side reactions to become dominant.

Assuming that the decyl radical formed from photolysis of **6** did add to maleic anhydride, conditions were devised to trap the intermediate substituted succinic anhydride radical with PhSSPh (Scheme 1). The reaction solvent was changed to CH$_3$CN for better solubility. An initial set of studies was done with **6** (20 mM), maleic anhydride (200 mM, 10 equiv), and PhSSPh (21 mM, 1.05 equiv) in 10 mL CH$_3$CN using one 300 W light bulb for photolysis (instead of two as described in the Experimental Section). The yields versus reaction time were determined in multiple runs of the reaction which were stopped and worked up at various times with the following results: time in h (yield of **10**, as determined by ^{1}H NMR using Ph$_3$CH as an internal standard), 1 (14%), 2 (27%), 3 (33%), 4 (37%), 7 (46%), 10 (56%), 20 (60%), 24 (64%), 30 (78%), 41 (77%). The thiophenyl cobaloxime **14**[9b] was also obtained as a major product (yields not determined). Only the trans diastereomer of **10** could be detected by ^{1}H NMR. More efficient coupling was achieved using two light bulbs as described in the Experimental Section: photolysis of **6** (20 mM), maleic anhydride (400 mM, 20 equiv), and PhSSPh (21 mM, 1.05 equiv) for only 10 h at 15 °C led to the production of **10** in 87% yield (determined by ^{1}H NMR using Ph$_3$CH as an internal standard) and in 64% isolated yield after purification. Reaction of **7** under the same conditions with maleic anhydride provided **11** in 81% yield as a 6:4 mixture of diastereomers at the *C*H(OAc)CH$_2$CH(CH$_3$)$_2$ center, with trans stereochemistry on the anhydride.

Scheme 1



Oxidation of **10** with *m*-chloroperoxybenzoic acid in a biphasic buffered solvent system,[12] followed by syn elimination at 0 °C (or during workup at ambient temperature), produced **15** in 81% yield.[13] Performing the same procedure on **11** produced **16** in quantitative yield. The high yields of these syn β-H eliminations confirm that radical addition and subsequent trapping by PhSSPh is a trans addition.

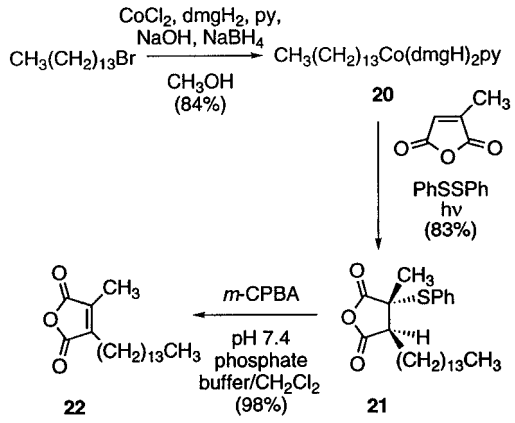
Visible light photolyses of **8** and **9** under the conditions optimized for the decylcobaloxime cross-couplings pro-

(11) Lorand, H. Carbon-Centered Radicals: Radical-Molecule Addition Reactions. In *Landolt-Bornstein Numerical Data and Functional Relationships in Science and Technology*; Hellwege, K.-H., Madelung, O., Eds. in Chief, *Radical Reaction Rates in Liquids, Vol. 13, Subvolume a*, Fischer, H., Ed.; Springer-Verlag: New York, 1984; pp 135−251.

(12) Imuta, M.; Ziffer, H. *J. Org. Chem.* **1979**, *44*, 1351.

(13) Sulfoxide elimination played a central role in a radical synthesis of showdomycin utilizing aryl tellurium glycosides and Barton ester chemistry: Barton, D. H. R.; Ramesh, M. *J. Am. Chem. Soc.* **1990**, *112*, 891.

Scheme 2



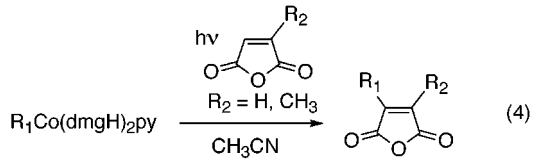
vided the trapped products in yields of 19% for **12** (along with 40% of **19**) and 46% for **13**. Subsequent oxidation of each sulfide and syn elimination of the sulfoxide led to quantitative yields (based on **12** and **13**) of mannopyranosyl- or glucopyranosyl-substituted maleic anhydrides **17** and **18**. Compound **17** was obtained as a mixture of anomers, with one anomer predominating, according to ^{1}H NMR, but it was not possible to determine which anomer was the major one. Compound **18** was obtained as single anomer, according to ^{1}H NMR, presumed to be α.

Studies directed toward a synthesis of showdomycin **1** were undertaken. Significant difficulties in the generation of the desired ribofuranosyl cobaloxime were encountered and are fully discussed elsewhere.[14]

Synthesis of Chaetomellic Acid A Anhydride. Chaetomellic acid A (**4**) is a potent and selective inhibitor of ras farnesyl protein transferase (Ras FPTase). Inhibition of farnesylation prevents Ras membrane localization and blocks Ras-induced cell transformation. Ras FTPase inhibitors have the potential to be effective in anticancer therapy.[15] Chaetomellic acid A is unstable in the acid form and readily converts to the stable anhydride **22** which is the form in which it is typically isolated.[16] Aqueous base hydrolysis (pH 7.5) of **22** readily forms the biologically active dianion. Several syntheses of **4** have been reported.[4] Our previously communicated synthesis,[7] described in detail here, utilizes alkyl cobaloxime-mediated radical chemistry to provide a simple and efficient synthetic route.

Preparation of myristyl cobaloxime **20** from commercially available myristyl bromide proceeded in 84% isolated yield (Scheme 2). Anaerobic photolysis of cobaloxime **20** (20 mM), methylmaleic anhydride (20 equiv, 400 mM), and PhSSPh (1.05 equiv, 21 mM) in CH_3CN provided 3-methyl-3-(phenylthio)-4-myristylsuccinic anhydride (**21**) in 83% yield. Note that the regioselectivity and stereoselectivity of this reaction are the same as in organomercury/$NaBH_4$ radical addition reactions to methylmaleic anhydride.[17] Oxidation to the sulfoxide was followed by immediate syn elimination under the reaction conditions, producing chaetomellic acid A anhydride **22** in 98% yield.

Direct Cross-Coupling Studies. After much of the preceding work was completed, it was discovered that direct cross couplings could be performed using CH_3CN as the solvent rather than EtOH (eq 4). Direct cross



6 $R_1 = (CH_2)_9CH_3$
20 $R_1 = (CH_2)_{13}CH_3$

15 $R_1 = (CH_2)_9CH_3$, $R_2 = H$
22 $R_1 = (CH_2)_{13}CH_3$, $R_2 = CH_3$
23 $R_1 = (CH_2)_{13}CH_3$, $R_2 = H$

coupling of **6** with maleic anhydride in CH_3CN (10 h photolysis, 20 equiv of maleic anhydride) produced **15** in 66% yield (determined by ^{1}H NMR using Ph_3CH as an internal standard). As noted earlier, no cross coupling was seen under similar conditions in EtOH. In benzene only 32% of **15** was formed. Anaerobic photolysis of myristylcobaloxime **20** (20 mM) and methylmaleic anhydride (20 equiv, 400 mM) in CH_3CN provided **22** in 89% yield. Direct cross coupling of **20** with maleic anhydride in CH_3CN provide **23** in 48% yield when 10 equiv of maleic anhydride was used and in 66% yield when 20 equiv of maleic anhydride was used. On the basis of these results, it is clear that solvent effects are very important for successful cross couplings, but the exact reason direct cross couplings do not work in EtOH is still unknown.

Conclusion

The methods described here provide a facile way to attach the maleic anhydride moiety to functionalized molecules under mild conditions. These reactions could be useful in bioorganic and medicinal chemistry. The chaetomellic acid A synthesis could be adapted to the synthesis of chaetomellic acid A analogues. C-Glycosyl maleic anhydrides may be useful in glycoconjugate chemistry. Maleic anhydride has been used to label free amino groups of peptides and proteins rapidly and specifically,[18] and such reactions of C-glycosyl maleic anhydrides could be used to attach mono- or oligosaccharides onto protein or cell surfaces.

Experimental Section

General. All solvents were reagent grade unless otherwise noted and were used as received with the exception of CH_3CN (fractionally distilled over CaH_2 under nitrogen for cobaloxime preparations or purchased as spectroscopic grade and kept under nitrogen for photolysis experiments), THF (distilled over benzophenone/Na under nitrogen), and pyridine (fractionally distilled over KOH under nitrogen then stored over 4 Å molecular sieves). A standard procedure was used to prepare $ClCo(dmgH)_2py$.[8] Maleic anhydride was recrystallized from CCl_4 and Ph_3CH was recrystallized from EtOH.

Silica gel chromatography was performed using 60−200 mesh, grade 62 silica gel. Analytical TLC was performed on aluminum-backed silica gel plates with UV-indicator.

All ^{1}H NMR spectra were recorded at 300 MHz in $CDCl_3$. For quantitative ^{1}H integration to determine reaction yields, the delay time was extended to at least 5 s. ^{13}C NMR spectra were measured at 75.48 MHz. Low resolution mass spectra

(14) Slade, R. M.; Branchaud, B. P. *Organometallics* **1996**, *15*, 2585.
(15) (a) Tamanoi, F. *Trends Biochem. Sci.* **1993**, *18*, 349. (b) Gibbs, J. B. *Cell* **1991**, *65*, 1.
(16) Singh, S. B.; Zink, D. L.; liesch, J. M.; Goetz, M. A.; Jenkins, R. G.; Nallin-Omstead, M.; Silverman, K. C.; Bills, G. F.; Mosley, R. T.; Gibbs, J. B.; Albers-Schonberg, G.; Lingham, R. B. *Tetrahedron* **1993**, *49*, 5917.
(17) Giese, B.; Kretzschmar, G. *Chem. Ber.* **1984**, *117*, 3175.
(18) Butler, P. J. G.; Harris, J. I.; Hartley, B. S.; Leberman, R. *Biochem. J.* **1969**, *112*, 679.

were generated using electron impact at 70 eV. FAB MS was used in some cases with Xe bombardment at 8 kV from a 3-nitrobenzyl alcohol or magic bullet matrix. High-resolution mass spectra (HRMS) were performed using the peak match method. Melting points are uncorrected.

General Procedures for the Synthesis of Alkyl Cobaloximes. Reactions were conducted under anaerobic nitrogen. Solvents were deoxygenated by saturation with nitrogen bubbling for approximately 1 min/mL unless noted otherwise. Reactions for formation of light-sensitive alkyl cobaloximes (especially **7**) were performed with fume hood lights turned off and flasks wrapped in aluminum foil. Column chromatography was performed anaerobically, using deoxygenated solvents, foil-wrapped columns, and bubbling of column fractions with nitrogen as they were being collected.

Bis(dimethylglyoximato)(pyridine)(1-*n*-decyl)cobalt (6). A 500 mL round-bottom flask containing $CoCl_2$ hexahydrate (2.408 g, 10.1 mmol), dimethylglyoxime (2.344 g, 20.2 mmol), and MeOH (200 mL) was deoxygenated with nitrogen and then cooled to 0 °C. Pyridine (2.5 mL, 30.9 mmol) and NaOH (1.62 g, 20.2 mmol of 50% aq solution) were added. After 10 min $NaBH_4$ (0.785 g, 20.6 mmol) was added in portions, producing the deep green/black $Co(dmgH)_2py$ anion. A solution of decyl bromide (1.05 mL, 5.06 mmol) in freshly distilled THF (10 mL) was deoxygenated and then added to the $Co(dmgH)_2py$ anion solution by cannula. The solution was monitored by TLC for disappearance of decyl bromide. After stirring for 3 h at 0 °C, the solution was warmed to room temperature and the reaction was stirred for an additional 30 min. Excess $NaBH_4$ was quenched by the addition of 2 mL of deoxygenated acetone. The reaction solution was transferred by cannula into a nitrogen-purged 500 mL round-bottom flask containing 3 g of silica gel. The solvent was evaporated (rotary evaporator) leaving a dry powder which was loaded onto a column packed with 20 g of silica gel and deoxygenated EtOAc. The orange band was eluted with deoxygenated EtOAc and was collected in a nitrogen-purged round-bottom flask. The solvent was evaporated (rotary evaporator), and then the residue was placed on a vacuum line for complete removal of residual solvent. Decyl cobaloxime **6** was obtained as an orange solid in 81% yield. ^{1}H NMR: δ 0.85 (m, 5H), 1.20 (br m, 14H), 1.61 (t, 2H; J = 8.3 Hz), 2.10 (s, 12H), 7.29 (t, 2H), 7.69 (t, 1H), 8.57 (d, 2H), 18.10 (br s). ^{13}C NMR: δ (contains some overlapping peaks) 11.92, 14.06, 22.63, 29.30, 29.41, 29.54, 29.65, 30.64, 30.70, 31.87, 32.37 (br, v. short), 125.05, 137.26, 148.96, 149.97. LRMS: (FAB) *m*/*z* (rel intensity); 509 (10%, M), 430, 290 (100%), 205, 155, 117. HRMS: calcd for $C_{23}H_{40}N_5O_4Co$ 509.2412, obsd 509.2422.

Bis(dimethylglyoximato)(pyridine)(1-acetoxy-3-methylbutyl)cobalt (7). A solution of $ClCo(dmgH)_2py$ (5.789 g, 14.3 mmol) in freshly distilled CH_3CN (70.0 mL) was deoxygenated by bubbling with nitrogen for 25 min while cooling to 0 °C. In portions, $NaBH_4$ (0.713 g, 18.8 mmol) was added; the solution turned dark green-black. A deoxygenated solution of 1-bromo-1-acetoxy-3-methylbutane[10] (1.003 g, 4.80 mmol) in CH_3CN (10 mL) was added via cannula to the cold green solution, the cannula was rinsed through with approximately 3 mL more of dry CH_3CN, and then the solution was stirred at 0 °C for another 2.5 h. The reaction solution was warmed to room temp over 50 min and then was cannula-transferred into a nitrogen-purged 250 mL round-bottom flask equipped with a stir bar, and the alkyl cobaloxime was extracted with deoxygenated EtOAc and H_2O until the H_2O layer was only faintly yellow in color. The residue from evaporation of the organic layer was adsorbed onto 5 g of silica gel as described for **6**. Chromatography on 25 g of silica gel using deoxygenated EtOAc was performed as described for **6**, providing solid orange-red α-acetoxycobaloxime **7** in 37% yield (0.89 g, 1.79 mmol). ^{1}H NMR: δ 0.77 (t, 6H; J = 5.5 Hz), 1.25 (br t, 2H; J = 6.4 Hz), 1.44 (m, 1H), 1.98 (s, 3H), 2.10 (s, 6H), 2.18 (s, 6H), 5.36 (t, 1H; J = 6.6 Hz), 7.28 (t, 2H), 7.69 (t, 1H), 8.52 (d, 2H), 17.96 (br s). ^{13}C NMR: δ (contains some overlapping peaks) 11.86, 12.09, 21.08, 21.51, 23.93, 25.15, 45.16, 63.27, 125.04, 137.33, 149.93, 149.96, 150.39, 169.90. LRMS: (FAB) *m*/*z* (rel intensity); 498 (5%, M + 1), 419, 290 (100%), 234, 218, 205, 155, 117, 43. HRMS: calcd for $C_{20}H_{33}N_5O_6Co$ (M + 1) 498.1763, obsd 498.1741.

2,3,4,6-Tetra-*O*-benzoyl-α-D-mannopyranosyl Bromide. This known compound[19] was synthesized from 1,2,3,4,6-penta-*O*-benzoyl-D-mannopyranose following a literature procedure for the preparation of 2,3,4,6-tetra-*O*-benzoyl-α-D-glucopyranosyl bromide from 1,2,3,4,6-penta-*O*-benzoyl-D-glucopyranose.[20] The crude product was used immediately for the next step.

Bis(dimethylglyoximato)(pyridine)(2,3,4,6-tetra-*O*-benzoyl-D-mannopyranosyl)(cobalt) (8). Following the general procedure for the synthesis and purification of **6** but using $ClCo(dmgH)_2py$ as the source of $py(dmgH)_2Co^-$ Na^+, **8** was synthesized from 2,3,4,6-tetra-*O*-benzoyl-α-D-mannopyranosyl bromide (2.711 g, 2.86 mmol), $ClCo(dmgH)_2py$ (1.730 g, 4.29 mmol), dry MeOH (150 mL), dry THF (10.0 mL), and $NaBH_4$ (approximately 0.52 g, 13.6 mmol) to provide **8** as an orange foam in 77% yield after silica gel chromatography with anaerobic EtOAc. Characterization data are for the single anomer obtained, believed to be the α anomer. ^{1}H NMR: δ 2.21 (s, 6H), 2.30 (s, 6H), 3.97 (br d, 1H; J = 9.9 Hz), 4.25 (br dd, 1H; J = 1.5, 12.0 Hz), 4.42 (br dd, 1H; J = 2.1, 12.0 Hz), 5.36 (d, 1H; J = 3.0 Hz), 5.55 (s, 1H), 5.69 (dd, 1H; J = 3.0, 10.2 Hz), 6.21 (t, 1H; J = 10.0 Hz), 7.18−7.56 (m, 13H), 7.77 (m, 4H), 7.96 (d, 4H; J = 7.5 Hz), 8.12 (d, 2H; J = 7.5 Hz), 8.62 (d, 2H: J = 5.1 Hz), 18.55 (br s). ^{13}C NMR: δ (contains some overlapping peaks) 12.45, 12.81, 62.75, 66.95, 71.64, 72.35, 73.10, 125.19, 127.99, 128.19, 128.21, 128.26, 129.50, 129.57, 129.63, 129.74, 129.80, 129.83, 130.24, 132.61, 132.71, 132.98, 137.61, 149.60, 151.15, 152.52, 162.22, 165.38, 165.45, 166.20. LRMS: (FAB) *m*/*z* (rel intensity); 948 (5%, M + 1), 868, 579, 289 (100%), 231, 154, 136, 77. HRMS: calcd for $C_{42}H_{42}N_4O_{13}Co$ (M − Pyr + H) 869.2080, obsd 869.2097.

Bis(dimethylglyoximato)(pyridine)(2,3,4,6-tetra-*O*-benzoyl-D-glucopyranosyl)(cobalt) (9). Following the procedure for the synthesis and purification of **8**, **9** was synthesized from commercially available 2,3,4,6-tetra-*O*-benzoyl-α-D-glucopyranosyl bromide (0.796 g, 1.21 mmol), $ClCo(dmgH)_2py$ (0.733 g, 1.82 mmol), dry MeOH (90 mL), dry THF (15 mL), and $NaBH_4$ (approximately 0.164 g, 4.32 mmol) to produce **9** as an orange foam in 74% yield after silica gel chromatography with anaerobic EtOAc. The anomeric ratio is α:β ∼ 1:1. ^{1}H NMR ($CDCl_3$) δ 2.05−2.15 (singlets, 24H; 12H for each anomer), 3.78 (m, 1H), 3.95 (m, 1H), 4.30 (m, 3H), 4.55 (m, 2H), 5.01−5.22 (m, 3H), 5.45−5.69 (m, 4H), 7.10−8.90 (m, 50H; 25H for each anomer), 18.20 (ss, 4H, O−H−O protons); ^{13}C NMR ($CDCl_3$) δ 12.09, 12.18, 12.24, 63.26, 63.84, 70.11, 70.17, 70.51, 72.63, 73.70, 73.83, 75.39, 77.72, 125.00, 125.07, 127.98, 128.21, 128.33, 128.49, 129.72, 129.92 129.98, 130.51, 132.26, 132.62, 132.73, 132.84, 133.01, 133.25, 137.56, 137.61, 149.67, 149.74, 150.21, 150.29, 151.11, 164.82, 164.95, 165.27, 165.36, 165.60, 166.08, 166.21, 166.27 (some carbon peaks were superimposed). LRMS: (FAB) *m*/*z* (rel intensity); 948 (15%, M + 1), 870, 757, 579, 290 (100%), 231, 205, 155, 137, 117, 105, 77. HRMS: calcd for $C_{47}H_{47}N_5O_{13}Co$ (M + 1) 948.2502, obsd 948.2479.

General Procedure for Photolyses. Anaerobic nitrogen was further deoxygenated by passage through warm BASF R3-11 catalyst. Reaction solutions were made anaerobic by bubbling nitrogen through solutions for at least 1 min/mL. Reactions were performed in magnetically stirred septum-sealed Pyrex test tubes under positive nitrogen pressure. Tubes were placed in a 1000 mL beaker containing a stir bar and a copper coil through which a 15 °C H_2O/ethylene glycol cooling solution was pumped. Two 300 W light bulbs were clamped on each side of the beaker, roughly 4 in. away from the beaker sides. The test tubes were allowed to come to thermal equilibrium while stirring (∼5 min) before the lights were turned on. It is important to monitor the rate of stirring

(19) Ness, R. K.; Fletcher, H. G., Jr.; Hudson, C. S. *J. Am. Chem. Soc.* **1950**, *72*, 2200.

(20) Furniss, B. S.; Hannaford, A. J.; Smith, P. W. G.; Tatchell, A. R. *Vogel's Textbook of Practical Organic Chemistry*, 5th ed.; Longman Scientific: Essex, 1989; p 648.

to ensure that solid $PhSCo(dmgH)_2py$, which forms as a product of the reaction, stays near the bottom of each tube as a lightly stirred precipitate rather than as a vigorously stirred cloudy suspension which will slow the rate of reaction.

2-Decyl-3-(thiophenyl)succinic Anhydride (10). Following the general procedure for photolyses, a solution of decyl cobaloxime **6** (0.1054 g, 0.207 mmol), PhSSPh (0.0476 g, 0.218 mmol), and maleic anhydride (0.4069 g, 4.15 mmol) in dry CH_3CN (10.0 mL) in an 18 mL Pyrex test tube was photolyzed for 10 h. Removal of the volatiles (rotary evaporation) and silica gel chromatography provided **10** as a yellowish waxy solid. Further purification by sublimation of excess maleic anhydride and PhSSPh in a coldfinger sublimation apparatus at room temp under vacuum, providing pure **10** in 64% isolated yield. ^{1}H NMR: δ 0.88 (m, 3H), 1.27 (br s, 14H), 1.45 (m, 2H), 1.69−1.95 (m, 2H), 2.92−2.99 (m, 1H), 3.83 (d, 1H; J = 6.0 Hz), 7.39 (m, 3H), 7.55 (m, 2H). ^{13}C NMR: δ (contains some overlapping peaks) 13.85, 14.24, 22.63, 25.84, 26.31, 29.06, 29.22, 29.48, 29.92, 30.20, 47.09, 50.22, 121.20, 129.40, 129.71, 130.02, 134.68, 135.32, 169.36, 170.97. HRMS: calcd for $C_{20}H_{28}O_3S$ 348.1759, obsd 348.1764.

2-(1-Acetoxy-3-methylbutyl)-3-(thiophenyl)succinic Anhydride (11). This compound was synthesized and purified as described for **10**; α-acetoxycobaloxime **7** (0.1053 g, 0.212 mmol), PhSSPh (0.0486 g, 0.226 mmol), and maleic anhydride (0.4179 g, 4.26 mmol) in CH_3CN (10.0 mL) were photolyzed for 10 h at 15 °C to give **11** in 81% yield. After purification, **11** was obtained as a clear yellow liquid as a 6:4 mixture of diastereomers. ^{1}H NMR: δ (containing both isomers) 0.91−0.99 (m, 6H), 1.46 (m, 1H), 1.61 (m, 2H), 2.00 and 2.05 (2s, 3H), 3.15 and 3.22 (2m, 1H), 3.97 and 4.18 (2d, 1H; J = 4.5 and 5.1 Hz), 5.30 and 5.48 (2m, 1H), 7.43 (m, 3H), 7.55 (m, 2H). ^{13}C NMR: δ (for both isomers; contains some overlapping peaks) 20.57, 20.68, 21.98, 22.32, 22.41, 22.54, 24.64, 24.74, 29.66, 40.03, 41.08, 45.84, 47.91, 51.15, 70.47, 70.84, 129.23, 129.84, 129.88, 130.30, 135.05, 135.16, 167.48, 168.55, 168.94, 169.05, 169.14, 170.28. LRMS: (EI) *m*/*z* (rel intensity); 336 (15%, M), 294 (100%), 276, 249, 165, 95, 43. HRMS: calcd for $C_{17}H_{20}O_5S$ 336.1031, obsd 336.1035.

Decylmaleic Anhydride (15). A two-phase system of **10** (0.0850 g, 0.244 mmol) and *m*-CPBA (0.0509 g, 0.295 mmol) in 5.0 mL of CH_2Cl_2 and 5.0 mL of 0.2 M pH 7.4 phosphate buffer was stirred under nitrogen at 0 °C for 2.5 h. The reaction was poured into a 100 mL separatory funnel, 5.0 mL of cold phosphate buffer was added, and the product was extracted with cold CH_2Cl_2 (3 × 10 mL). The organic layers were combined, washed successively with dilute cold $Na_2S_2O_3$ and cold phosphate buffer (1 × 25 mL each), dried over Na_2SO_4, filtered, and evaporated (rotary evaporator). After removal of residual solvent on a vacuum line, clear liquid product **15** was obtained in 81% yield. ^{1}H NMR: δ 0.88 (t, 3H), 1.26 (br m, 14H), 1.63 (m, 2H), 2.51 (t, 2H; J = 7.2 Hz), 6.58 (s, 1H). ^{13}C NMR: δ (contains some overlapping peaks) 14.04, 22.62, 25.91, 26.90, 29.04, 29.09, 29.22, 29.35, 29.46, 31.82, 128.39, 153.80, 163.98, 165.84. LRMS: (FAB) *m*/*z* (rel intensity); 239 (M, 45%), 186, 151, 141, 137, 125 (100%), 112, 109. HRMS: calcd for $C_{14}H_{23}O_3$ (M + 1) 239.1647, obsd 239.1652.

(1-Acetoxy-3-methylbutyl)maleic Anhydride (16). Following the procedure for the synthesis of **15**, **16** was synthesized from **11** (0.1416 g, 0.421 mmol) and *m*-CPBA (0.0890 g, 0.516 mmol) in CH_2Cl_2 (10.0 mL) and 0.2 M pH 7.4 phosphate buffer (10.0 mL) in quantitative yield. ^{1}H NMR: δ 0.96 (s, 3H), 0.98 (s, 3H), 1.68−1.80 (m, 3H), 2.15 (s, 3H), 5.72−5.77 (m, 1H), 6.68 (s, 1H). ^{13}C NMR: δ 20.58, 21.52, 22.97, 24.76, 41.91, 66.71, 135.33, 152.07, 162.77, 163.36, 169.64. LRMS: (FAB, magic bullet) *m*/*z* (rel intensity); 227 (M, 20%), 185, 167, 149, 134, 124, 118, 84, 72, 54, 42 (100%). HRMS: calcd for $C_{11}H_{15}O_5$ (M + 1) 227.0919, obsd 227.0930.

(2,3,4,6-Tetra-*O*-benzoyl-D-mannopyranosyl)maleic Anhydride (17). Following the procedure for the synthesis and purification of **10**, **12** was synthesized from **8** (0.1439 g, 0.152 mmol), PhSSPh (0.0348 g, 0.159 mmol), maleic anhydride (0.2973 g, 3.03 mmol), and 7.6 mL of dry CH_3CN to produce **12** in 19% yield (determined by ^{1}H NMR using Ph_3CH as an internal standard). Without further isolation, crude **12** was used directly for the next step. Following the procedure for the synthesis and purification of **15**, crude **12** (0.0510 g, 0.0648 mmol), *m*-CPBA (0.0139 g, 0.0805 mmol), dry CH_2Cl_2 (5.0 mL), and 0.2 M pH 7.4 phosphate buffer (5.0 mL) provided **17** in quantitative yield. ^{1}H NMR: δ 4.47−4.72 (m, 4H), 5.91 (br s, 1H), 6.06 (dd, 1H, J = 3.0, 10.1 Hz), 6.29 (t, 1H; J = 10.1 Hz), 6.63 (s, 1H), 7.29−8.22 (20H). ^{13}C NMR: δ (contains some overlapping peaks) 29.67, 62.40, 66.28, 69.47, 69.99, 71.21, 91.40, 128.37, 128.43, 128.47, 128.62, 128.69, 128.77, 129.75, 129.88, 129.93, 130.11, 132.97, 133.33, 133.47, 133.60, 133.79, 133.99, 163.77, 165.10, 165.27, 165.34, 165.99. LRMS: (EI) *m*/*z* (rel intensity); 677 (5%, M + 1), 579, 307, 289, 219, 154 (100%), 137, 105, 77. HRMS: calcd for $C_{38}H_{29}O_{12}$ (M + 1) 677.1659, obsd 677.1640.

1-(Thiophenyl)-2,3,4,6-tetra-*O*-benzoyl-D-mannopyranose (19). The product mixture from a reaction to convert **8** to **12** (see preceding paragraph) was purified by silica gel column chromatography using 1:1 hexanes:EtOAc to provide **19** in 40% isolated yield. ^{1}H NMR: δ 4.53−4.69 (m, 2H), 4.99−5.03 (br m, 1H), 5.79 (s, 1H), 5.87 (dd, 2H; J = 3.1, 10.1 Hz), 5.98 (s, 1H), 6.15 (t, 1H; J = 10.2 Hz), 7.11−7.58 (m, 16H), 7.86 (d, 2H; J = 7.5 Hz), 8.01−8.06 (m, 6H). ^{13}C NMR: δ (contains some overlapping peaks) 63.08, 67.14, 69.92, 70.44, 71.95, 85.98, 126.27, 128.07, 128.33, 128.38, 128.60, 128.90, 129.23, 129.43, 129.76, 129.82, 129.84, 132.08, 132.71, 133.03, 133.27, 133.51, 165.30, 165.43, 165.48, 166.09. LRMS: (magic bullet + NaI) *m*/*z* (rel intensity); 711 (80%, M + Na), 579, 481, 323, 177, 105 (100%). HRMS: calcd for $C_{40}H_{32}O_9SNa$ 711.1665, obsd 711.1610.

(2,3,4,6-Tetra-*O*-benzoyl-D-glucopyranosyl)maleic Anhydride (18). Following the procedure for the synthesis of **10**, **13** was synthesized from **9** (0.1945 g, 0.205 mmol), PhSSPh (0.0506 g, 0.232 mmol), maleic anhydride (0.4023 g, 4.10 mmol), and 10.0 mL of dry CH_3CN to produce **13** in 46% yield (determined by ^{1}H NMR using Ph_3CH as an internal standard). Following the procedure for the synthesis and purification of **15**, crude **13** (0.1133 g, 0.144 mmol), *m*-CPBA (0.0299 g, 0.173 mmol), dry CH_2Cl_2 (5.0 mL), and 0.2 M pH 7.4 phosphate buffer (5.0 mL) provided **18** in quantitative yield. Characterization data is given for the major isomer, presumed to be the α isomer. ^{1}H NMR: δ 4.46 (dd, 1H; J = 3.8, 12.2 Hz), 4.63−4.69 (m, 1H), 5.15 (d quart, 1H; J = 3.3, 9.0, 12.2 Hz), 5.42 (t, 1H; J = 3.8 Hz), 5.68 (m, 2H), 5.88 (t, 1H; J = 4.2 Hz), 7.01 (d, 1H; J = 1.5 Hz), 7.2−8.3 (m, 20H). ^{13}C NMR: δ (contains some overlapping peaks) 60.94, 66.07, 66.92, 67.52, 67.86, 124.32, 128.39, 128.52, 128.69, 128.80, 129.26, 129.70, 129.92wd1, 133.42, 133.60, 133.94, 134.01, 135.36, 148.41, 162.71, 163.16, 164.52, 164.99, 165.25, 166.20. LRMS: (EI) *m*/*z* (rel intensity); 676 (5%, M), 579, 335, 310, 231, 122, 105 (100%), 77, 51. HRMS: calcd for $C_{38}H_{28}O_{12}$ 676.1581, obsd 676.1602.

Bis(dimethylglyoximato)(pyridine)(1-myristyl)cobalt (20). Following the procedure for the synthesis of **6**, **20** was synthesized from bromotetradecane (myristyl bromide; 1.73 mL, 5.8 mmol), $CoCl_2$ hexahydrate (2.757 g, 11.6 mmol), dimethylglyoxime (2.714 g, 23.4 mmol), pyridine (2.8 mL, 34.6 mmol), NaOH (50% aq solution; 1.63 g, 20.4 mmol), $NaBH_4$ (0.519 g, 13.7 mmol), CH_3OH (175 mL), and THF (5 mL). After addition of the alkyl bromide, the reaction was stirred for 1 h at 0 °C and at room temp for 7.5 h, monitoring the disappearance of the alkyl bromide by TLC. Following the general procedure for the isolation and purification of **6** provided **20** as an orange solid in 84% isolated yield after chromatography. ^{1}H NMR: δ 0.894 (m, 5H), 1.17−1.24 (m, 22H), 1.62 (t, 2H; J = 8.7 Hz), 2.17 (s, 12H), 7.30 (t, 2H), 7.70 (t, 1H), 8.58 (d, 2H), 18.24 (br. s, dmgH−O−H). ^{13}C NMR: δ (contains some overlapping peaks) 11.92, 14.06, 22.66, 29.32, 29.44, 29.63, 29.67, 30.66, 30.72, 31.89, 125.04, 137.23, 148.93, 149.98. LRMS: (FAB) *m*/*z* (rel intensity); 565 (10%, M), 487, 463, 290 (100%), 205, 155, 117, 43. HRMS: calcd for $C_{27}H_{48}N_5O_4Co$ 565.3037, obsd 565.3017.

2-Methyl-2-(thiophenyl)-3-myristylsuccinic Anhydride (21). Following the procedure for the synthesis and purification of **10**, **21** was synthesized from myristyl cobaloxime (**20**;

0.1139 g, 0.201 mmol), PhSSPh (0.0469 g, 0.215 mmol), and methylmaleic anhydride (citraconic anhydride; 0.35 mL, 3.89 mmol) in 10 mL of dry CH_3CN to produce **21** in 83% yield (determined by ^{1}H NMR using Ph_3CH as an internal standard). ^{1}H NMR: δ 0.878 (m, 3H), 1.26 (br s, 24H), 1.59 (m, 2H), 2.16 (s, 3H), 2.89 (quart, 1H; J = 2.7, 5.8 Hz), 7.30 (t, 2H; J = 6.9 Hz), 7.38−7.53 (m, 3H). ^{13}C NMR: δ (contains some overlapping peaks) 14.04, 18.21, 21.48, 22.64, 24.73, 26.87, 27.48, 29.62, 31.88, 50.08, 51.94, 55.46, 56.07, 128.50, 129.10, 129.42, 130.71, 130.80, 137.16, 170.67, 171.91. LRMS: (EI) *m*/*z* (rel intensity); 418 (20%, M), 346, 290, 280, 263, 207, 150, 126 (100%), 110. HRMS: calcd for $C_{25}H_{38}O_3S$ 418.2541, obsd 418.2549.

Chaetomellic Acid A Anhydride (22). Following the procedure for the synthesis and purification of **15**, **22** was synthesized from **21** (0.1172 g, 0.280 mmol), *m*-CPBA (0.0578 g, 0.335 mmol), dry CH_2Cl_2 (5.0 mL), and 0.2 M pH 7.4 phosphate buffer (5.0 mL) to provide **22** (0.0846 g, 0.274 mmol) in 98% yield. ^{1}H NMR: δ 0.877 (t, 3H; J = 6.5 Hz), 1.25 (br s, 22H), 1.59 (m, 2H), 2.07 (s, 3H), 2.45 (t, 2H; J = 7.7 Hz). ^{13}C NMR: δ (contains some overlapping peaks) 9.45, 14.07, 22.65, 24.42, 27.56, 29.16, 29.32, 29.40, 29.53, 29.59, 29.61, 29.64, 31.89, 140.37, 144.75, 165.82, 166.22. LRMS: (EI) *m*/*z* (rel intensity); 308 (15%, M), 280, 263, 207, 150, 126 (100%), 110. HRMS: calcd for $C_{19}H_{32}O_3$ 308.2351, obsd 308.2354.

Acknowledgment. This research was supported by NSF CHE 8806805, NSF CHE 9423782, and a fellowship from the U.S. Department of Education GAANN program (R.M.S.).

Supporting Information Available: ^{1}H NMR spectra for compounds **6**, **7**, **8**, **9**, **15**, **16**, **17**, **18**, **19**, **20**, and **22** (11 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.

JO971852T