# A Cobaloxime-Mediated Radical Route to Butenolides

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Abstract: Photolysis of alkyl cobaloximes with maleic anhydride and PhSSPh proceeds via radical alkene addition and subsequent PhSSPh trapping. The product *trans* 3-phenylthio 4-alkyl succinic anhydrides can be converted by oxidation and thermal syn elimination into 3-substituted maleic anhydrides, which are known to be regioselectively and chemoselectively reduced to produce γ-hydroxybutenolides or butenolides

Cobalt-mediated radical alkyl-alkenyl cross couplings have been shown to be synthetically useful reactions.[2] These reactions are non-reductive. Regeneration of the alkene functionality in the products can be exploited for further synthetic elaboration or can be used to form an alkene in a target molecule. An attractive application of this chemistry, shown in the scheme on the next page, is a cobalt-mediated approach to the synthesis of substituted maleic anhydrides, which can then be converted to maleimides, γ-hydroxybutenolides, or butenolides[3] These moieties are widespread in Nature and are included in biologically active molecules such as the anticancer antibiotic showdomycin (1),[4] the anti-inflammatory phospholipase A_2 inhibitor manoalide (2),[5] and the cardiotonic drug digitoxin (3).[6]
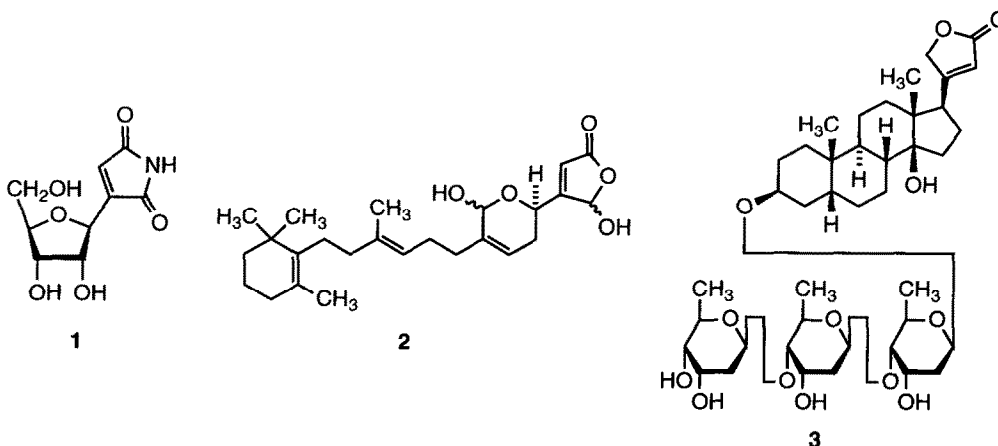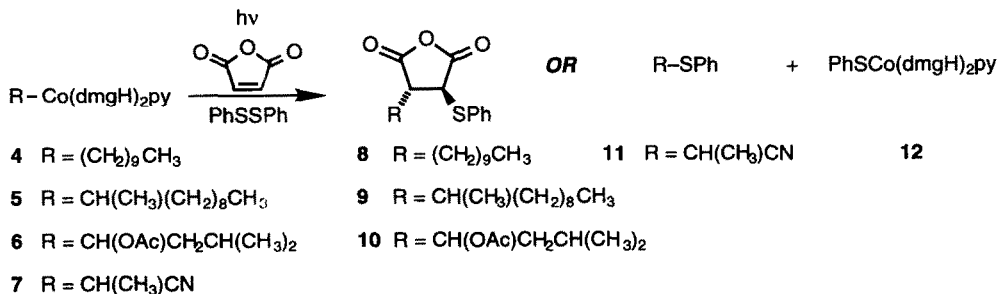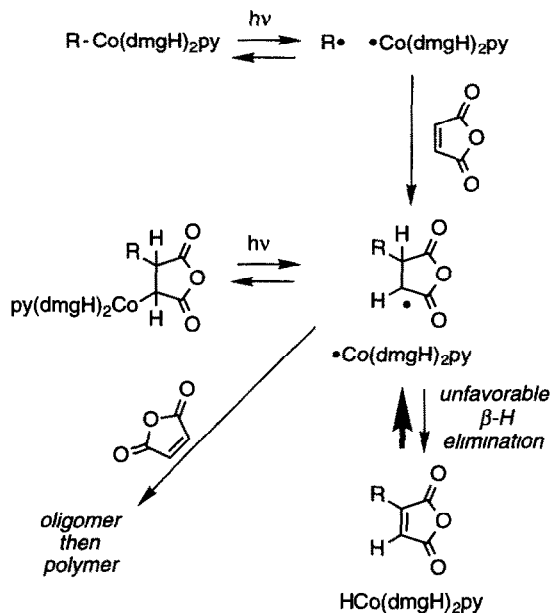

The results of a model study using decyl cobaloxime 4[7] and maleic anhydride were disappointing; 4 was slowly consumed but none of the desired cross coupling product could be detected. *This was an unusual result.* Rate constants for the addition of nucleophilic alkyl radicals to maleic anhydride are approximately 10^7 M^{-1} s^{-1},[8] which are 10^2 times faster than for other activated alkenes which smoothly undergo cobalt-mediated radical cross coupling under similar conditions. The decyl radical must be adding to the maleic anhydride but β-H elimination may be unfavorable due to ring strain in the maleic anhydride moiety, allowing oligomerization and other side reactions to become dominant.
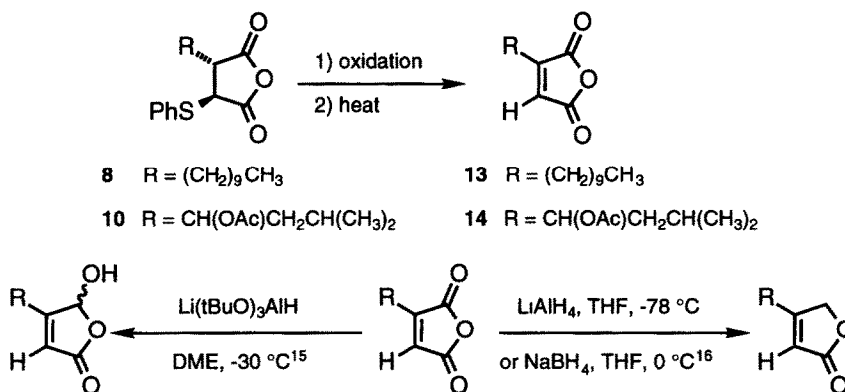
Since the rate of addition of nucleophilic alkyl radicals to maleic anhydride is so fast and radical polymerization of maleic anhydride is so slow,[9] conditions were devised to trap the alkyl radical with a maleic anhydride moiety followed by capture of the resulting radical with PhSSPh. Anaerobic visible light photolysis[10] of a CH_3CN solution of **4** (20 mM), maleic anhydride (200 mM, 10 equiv), and PhSSPh (20 mM, 1 equiv) for 24 hr at 15-20 °C led to **12** (yield not determined)[11] and a 64% yield of **8**. Only a single diastereomer of **8**, which proved to be the trans isomer shown, could be detected by ^{1}H NMR. Examination of the production of **8** vs time of photolysis using the concentrations of reactants indicated above provided the following results: reaction time in hours (% yield ±5%): 1 (14%), 2 (27%), 3 (33%), 4 (37%), 5 (37%), 7 (46%), 10 (56%), 20 (60%), 30 (78%), 41 (77%). Several variables were tested in an attempt to raise the yield of **8** and/or reduce the reaction time. Using two 300 W light bulbs instead of one for 11 hours of photolysis at 20 °C raised the yield of **8** to 68%. Changing from acetonitrile to benzene as the solvent and lowering the concentration of **4** from 20 mM to 10 mM each resulted in a lower yield of **8** (11 h of photolysis, two 300 W bulbs, 20 °C, 56% and 58% yields, respectively). Addition of 20 equiv (400 mM) of maleic anhydride, in the presence of 1.05 equiv of PhSSPh, increased the yield of **8** to 80-85% after only 10 hrs of photolysis (20 °C, two 300 W bulbs). These optimized conditions were used for the remainder of the study.

Reaction of **5** under the same conditions provided **12** and a 78% yield of **9**.[12] A 1:1 mixture of diastereomers of **9** at the $-CH(CH_3)(CH_2)_8CH_3$ center was observed but only the trans isomer on the succinic anhydride ring could be detected by ^{1}H NMR. Reaction of **6** under the same conditions provided an 81% yield of **10**. A 6:4 mixture of diastereomers of **10** at the $-CH(OAc)CH_2CH(CH_3)_2$ center was observed but only the trans isomer on the succinic anhydride ring could be detected by ^{1}H NMR. Reaction of **7** under the same conditions provided **12** and a 41% isolated yield of **11**. No reaction of the $•CH(CH_3)CN$ radical with maleic anhydride could be detected. This result can be explained by considering that the reaction of maleic anhydride, a very electrophilic alkene, with an electrophilic radical such as $•CH(CH_3)CN$ will be much slower than with nucleophilic alkyl radicals formed from **4, 5** and **6**.

4 R = $(CH_2)_9CH_3$

5 R = $CH(CH_3)(CH_2)_8CH_3$

6 R = $CH(OAc)CH_2CH(CH_3)_2$

7 R = $CH(CH_3)CN$

8 R = $(CH_2)_9CH_3$

9 R = $CH(CH_3)(CH_2)_8CH_3$

10 R = $CH(OAc)CH_2CH(CH_3)_2$

11 R = $CH(CH_3)CN$

12

Treatment of **8** with *meta*-chloroperoxybenzoic acid followed by *syn* elimination at 0 °C (or during work-up at ambient temperature) produced **13** in 81% yield.[13,14] Treatment of **10** with *meta*-chloroperoxybenzoic acid followed by thermal *syn* elimination at 0 °C produced **14** in essentially quantitative yield Conditions are known for the regioselective reduction of 3-substituted maleic anhydrides to the corresponding γ-hydroxybutenolides[15] or to the corresponding butenolides.[16]

8 R = $(CH_2)_9CH_3$	**13** R = $(CH_2)_9CH_3$
10 R = $CH(OAc)CH_2CH(CH_3)_2$	**14** R = $CH(OAc)CH_2CH(CH_3)_2$

Radical reactions can be performed under mild conditions and are compatible with a wide range of functional groups Primary and secondary cobaloximes can be readily prepared from the corresponding alkyl bromides, iodides or alcohol sulfonate esters. The method described here should be very useful for the introduction of the maleic anhydride, butenolide and γ-hydroxybutenolide moieties into natural products and their synthetic analogs. For example, the sequence of reactions **6** to **10** to **14** is a model for an approach to the synthesis of manoalide and analogs.[17]

References and Notes

1. Undergraduate research participant.
2. Some recent references: (a) Baldwin, J E.; Moloney, M. G.; Parsons, A. F. *Tetrahedron Lett.* **1992**, *48*, 9373. (b) Thomas, G.; Giese, B. *Helv Chim. Acta* **1992**, *75*, 1123. (c) Giese, B.; Erdmann, P.; Gobel, T.; Springer, R. *Tetrahedron Lett.* **1992**, *33*, 4545. (d) Giese, B.; Carboni, B.; Goebel, T.; Muhn, R.; Wetterich, F. *Tetrahedron Lett.* **1992**, *33*, 2673. (e) Ali, A.; Harrowven, D. C.; Pattenden, G. *Tetrahedron Lett.* **1992**, *33*, 2851. (f) Giese, B.; Carboni, B.; Göbel, T.; Muhn, R.; Wetterich, F. *Tetrahedron Lett.* **1992**, *33*, 2673. (g) Hu, C. M.; Qiu, Y. L *J. Org. Chem.* **1992**, *57*, 3339. (h) Cooper, J.; Knight, D. W.; Gallagher, P. T. *J. Chem. Soc. Perkin Trans. I* **1992**, 553. (i) Branchaud, B. P.; Detlefsen, W. D. *Tetrahedron Lett.* **1991**, *32*, 6273. (j) Branchaud, B. P.; Yu, G.-X. *Tetrahedron Lett.* **1991**, *32*, 3639. (k) Branchaud, B. P ; Yu, G.-X. *Organometallics* **1991**, *10*, 3795. (l) Harrowven, D. C.; Pattenden, G. *Tetrahedron Lett.* **1991**, *32*, 243. (m) Pattenden, G.; Reynolds, S. J. *Tetrahedron Lett.* **1991**, *32*, 259. (n) Giese, B.; Zehnder, M.; Neuburger, M.; Trach, F. *J. Organomet. Chem.* **1991**, *412*, 415. (o) Hartung, J.; Giese, B. *Chem. Ber.* **1991**, *124*, 387. (p) Baldwin, J. E.; Adlington, R. M.; Kang, T. W. *Tetrahedron Lett.* **1991**, *32*, 7093. (q) Baldwin, J. E.; Moloney, M. G.; Parsons, A. F., *Tetrahedron* **1991**, *47*, 155. (r) Essig, S.; Scheffold, R., *Chimia*, **1991**, *45*, 30. (s) Yamamoto, K., Abrecht, S.; Scheffold, R. *Chimia* **1991**, *45*, 86. (t) Lee, E. R.; Lakomy, I.; Bigler, P.; Scheffold, R. *Helv. Chim. Acta* **1991**, *74*, 146. (u) Giese, B.; Thoma, G. *Helv. Chim. Acta* **1991**, *74*, 1135 and 1143. (v) Baldwin, J. E.; Moloney, M. G.; Parsons, A. F. *Tetrahedron* **1990**, *46*, 7263. (w) Veit, A.; Giese, B. *Synlett* **1990**, 166. (x) Busato, S.; Tinembart, O.;

Zhang, Z. D ; Scheffold, R. *Tetrahedron* **1990**, *46*, 3155   (y) Clark, A. J., Jones, K. *Tetrahedron Lett.* **1989**, *30*, 5485.

3   Other preparative methods for γ-hydroxybutenolides: (a) Lee, G. C. M.; Syage, E. T.; Harcourt, D. A.; Holmes, J. M., Garst, M. E. *J Org. Chem* **1991**, *56*, 7007. (b) Bourguignon, J J.; Wermuth, C G. *J. Org Chem.* **1987**, *52*, 4788. (c) Feringa, B. L *Recl. Trav. Chim. Pays-Bas* **1987**, *106*, 469. (d) Larcheveque, M., Lequent, C.; Debal, A., Lallemand, J. Y *Tetrahedron Lett* **1981**, *22*, 1595. (e) Cooper, G K., Dolby, L. J. *J. Org. Chem.* **1979**, *44*, 3414

4.   Showdomycin syntheses· (a) Pino Gonzalez, M. S., Dominguez Aciego, R. M.; Lopez Herrera, F. J *Tetrahedron* **1988**, *44*, 3715   (b) ref. 13   A good review of syntheses through 1986 can be found in *Synform*, **1989**, *7*, 253.

5.   (a) Potts, B. C. M ; Faulkner, D. J.; de Carvalho, M. S., Jacobs, R. S. *J. Am. Chem. Soc.* **1992**, *114*, 5093. (b) Potts, B. C. M ; Faulkner, D. J ; Jacobs, R. S. *J. Nat. Prod.* **1992**, *55(12)*, 1701. (c) Reynolds, L. J.; Morgan, B. P ; Hite, G A., Mihelich, E D.; Dennis, E. A. *J. Am. Chem. Soc.* **1988**, *110*, 5172. (d) ref 3(a).

6.   (a) *Comprehensive Medicinal Chemistry,* Hansch, C.; Sammes, P G.; Taylor, J. B., Eds ; Pergammon Press. New York, 1990, Vol. 2, p. 206. (b) *The Merck Index, 11th Edition,* Budavari, S., Ed.; Merck and Co.. New Jersey, 1989, p 3144, and references therein

7.   Cobaloxime **4** is a known compound, synthesized from decyl bromide in 80% yield as described in ref 11, and characterized in this work by ^{1}H NMR, ^{13}C NMR, IR, MS, & high resolution MS. Cobaloxime **5** is a known compound, synthesized from 2-undecyl bromide in 17% yield as described in ref 11, and characterized in this work by ^{1}H NMR & IR. Cobaloxime **6** was synthesized from 1-bromo-1-acetoxy-3-methylpropane (prepared as described in ref 2(b)) in 32% yield following the general procedure for cobaloxime synthesis described in ref 11, modified by using CH3CN as solvent and an anaerobic extraction technique. Cobaloxime **6** was characterized by ^{1}H NMR, ^{13}C NMR, IR, MS, & high resolution MS. Cobaloxime **7** is a known compound, synthesized in 66% yield as described by Schrauzer, G. N., Windgassen, R J. *J. Am. Chem. Soc* **1967**, *89*, 1999, and characterized in this work by ^{1}H NMR & ^{13}C NMR   All yields are for isolated, chromatographically purified (silica gel) materials.

8   *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, Carbon-Centered Radicals: Radical-Molecule Addition Reactions*, Lorand, L.P , Ed.; Springer-Verlag. New York, 1984, pp 135-251

9   Initial rate of maleic anhydride polymerization is 6.2×10^4 M^{-1} sec^{-1} at 74.5 °C· Joshi, R. M. *Makromol Chem.* **1962**, *53*, 33.

10. All reactions were run in Pyrex test tubes in CH3CN under Ar or N$_2$. Visible light photolysis was provided by either one or two 300 W incandescent light bulbs held several inches from the tube. Reactions were maintained near room temperature with a circulating constant temperature cooling bath.

11   Branchaud, B. P.; Meier. M. S.; Malekzadeh, M. N. *J. Org. Chem.* **1987**, *52*, 212

12   Compound **8** was characterized by ^{1}H NMR, ^{13}C NMR, IR, MS & high resolution MS. Compound **9** was characterized by ^{1}H NMR & IR. Compound **10** was characterized by ^{1}H NMR, ^{13}C NMR, MS & high resolution MS. Compound **11** is a known compound (Makosza, M.; Bialecka, E.; Ludwikow, M *Tetrahedron Lett.* **1972**, *23*, 2391) and was characterized in this work by ^{1}H NMR & MS

13   Sulfoxide elimination played a central role in a recently reported 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

14. Compound **13** was characterized by ^{1}H NMR, ^{13}C NMR, MS, & high resolution MS. Compound **14** was characterized by ^{1}H NMR, ^{13}C NMR, IR, MS, & high resolution MS.

15   (a) Knight, D W ; Pattenden, G. *J Chem. Soc , Perkin Trans. 1* **1979**, 62. (b) Begley, M J.; Knight, D W ; Pattenden, G *Tetrahedron Lett.* **1975**, *48*, 4279.

16   For reductions to the butenolide, see (a) Morand, P., Salvator, J , Kayser, M M. *J Chem Soc., Chem Commun.* **1982**, 458. (b) Kayser, M. M ; Morand, P *Can. J. Chem.* **1980**, *58*, 2484. (c) Kayser, M. M., Morand, P *Can. J Chem.* **1978**, *56*, 1524.

17   For a discussion of, and leading references on, synthetic approaches to manoalide see Potts, B. C M , Faulkner, D. J ; de Carvalho, M. S ; Jacobs, R S. *J. Am. Chem. Soc.* **1992**, *114*, 5093