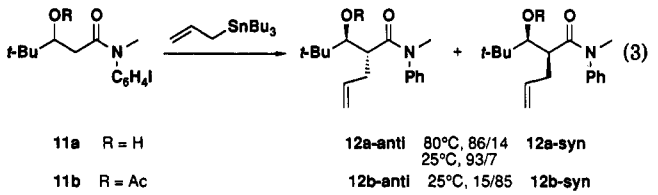
pected product **9j**, a side product **10j** resulting from further addition of the cyclic radical to the anilide ring formed.[10] Fortunately, the poor yields of desired products seem limited to the simplest of substrates; as the complexity of the precursors increased, so did the yields. Generally, the reduced, cyclized products **9** were isolated in high yields, although in two cases (entries e and h) significant amounts of the products of simple reductive deiodination (not shown) formed. Assuming that these simple reduction products form because cyclization is not rapid enough, their yields could be decreased by lowering the tin hydride concentration. The cis/trans ratios of product **9** are uniformly low, as is typical for simple carbonyl-substituted radicals.[2] In contrast, a side-chain substituent apparently provides a good level of asymmetric induction (entry g). Only two of the four possible products are formed from the cyclization of **8g**, and their configurations are assigned from Beckwith's guidelines.[11] *o*-Iodoanilides are also good precursors for tandem radical cyclizations (entries k–n). Cyclization of **8n** provides of striking example of conducting a new type of tandem cyclization through a cyclopentadiene, which we hope will be useful for a synthesis of the crinipellin family of tetraquinanes.[12]

o-Iodoanilides also offer interesting possibilities for conducting radical addition reactions. We have conducted a variety of bimolecular radical allylations with allyltributylstannane, and we illustrate this type of reaction by the two intriguing examples in eq 3. Radical allylation



of β-hydroxy anilide **11a** under Keck's standard thermal conditions (80 °C)[13] provided an inseparable mixture of isomers **12a**-anti/syn in a ratio 86/14.[14] By using Keck's standard photolytic conditions[14] (25 °C), the **12a**-anti/syn ratio increased to 93/7 (64% isolated yield). In sharp contrast, allylation of the β-acetoxy anilide **11b** under the photolytic conditions provided **12b**-anti/syn in a reversed ratio of 15/85 (41% isolated yield). Similar trends were observed in deuterium trapping experiments with tributyltin deuteride.[15] These preliminary results hold forth the promise that radical addition reactions are suitable for dictating 1,2-asymmetric induction in acyclic systems[16] and that the stereochemical outcome can be reversed by simple adjustments of substituents. Indeed, recent studies from our lab[17a] and Giese's[17b] have already led to the formulation of a transition state model that will be detailed in a forthcoming joint paper.

In summary, *o*-iodoanilides are easily introduced, stable precursors that permit the use of C–H bonds as precursors for radical formation adjacent to carbonyl groups in functionalized molecules. The intramolecular hydrogen-transfer reactions of these precursors are exceedingly rapid, and the resulting radicals can be used for standard radical addition and cyclization reactions. Finally, although removal is clearly a matter of concern, we have not yet extensively investigated the excision of the anilide auxiliary from the product. In two cases (Table I, entries d and n), we successfully hydrolyzed the products to carboxylic acids under standard conditions (NaOH, THF/water, 100 °C, 12 h). In the long run, we believe that the design of modified *o*-iodoanilides will result in groups that are even easier to remove.

Acknowledgment. We thank the National Institutes of Health and ICI Pharmaceuticals for funding of this work. We are grateful to Dr. C. Eric Schwartz for conducting the cyclization of **8n** and to Dr. Philip Yeske for conducting the hydrolysis of **9n**.

Supplementary Material Available: Representative experimental procedures and copies of ^{13}C and ^{1}H NMR spectra and mass spectra of all new products (71 pages). Ordering information is given on any current masthead page.

(10) Consistent with the proposed pathway, the ratio **9j**/**10j** increased as a function of increasing tin hydride concentration. We speculate that the cyclohexadienyl radicals formed by additions to the aromatic ring might not react rapidly with tin hydride at low concentrations, but might instead react by other pathways. This could explain both the difficulties in maintaining chains for entries a and i, and also the lack of clean formation of reduced products.

(11) Beckwith, A. L. J.; Schiesser, C. H. *Tetrahedron* **1985**, *41*, 3925.

(12) Schwartz, C. E.; Curran, D. P. *J. Am. Chem. Soc.* **1990**, *112*, 9272.

(13) Keck, G. E.; Enholm, E. J.; Yates, J. B.; Wiley, M. R. *Tetrahedron* **1985**, *41*, 4079.

(14) Samples **12a**/**12b** were correlated by the following reactions:

$$\textbf{12a}\text{-syn/anti} \xrightleftharpoons[\text{L-Selectride}]{\text{acetyl chloride}} \textbf{12b}\text{-syn/anti}$$

Stereostructures were assigned by standard ^{1}H and ^{13}C NMR trends for β-hydroxy carbonyls. See: Heathcock, C. H. In *Asymmetric Synthesis*; Morrison, J. D., Ed.; Academic Press: Orlando, 1984: Vol. 3, Chapter 2.

(15) Reduction of **11a** with Bu_3SnD (25 °C) gave an 88/12 ratio of anti/syn deuteration, while reduction of **11b** gave a 23/77 ratio. Deuteration ratios were determined by ^{2}H NMR, and proton assignments were made by the standard trends $J_{anti} > J_{syn}$ (see ref 14).

(16) (a) Related allylations of β-alkoxy esters have just recently appeared. Guindon, Y.; Lavallée, J.-F.; Boisvert, L.; Chabot, C.; Delorme, D.; Yoakim, C.; Hall, D.; Lemieux, R.; Simoneau, B. *Tetrahedron Lett.* **1991**, *32*, 27. All five examples reported gave syn selectivity. (b) For recent observations of related group (thiopyridyl) and atom (H) transfer reactions, see: Giese, B.; Zehnder, M.; Roth, M.; Zeitz, H.-G. *J. Am. Chem. Soc.* **1990**, *112*, 6741. Guindon, Y.; Yoakim, C.; Lemieux, R.; Boisvert, L.; Delorme, D.; Lavallée, J.-F. *Tetrahedron Lett.* **1990**, *31*, 2845.

(17) (a) Ramamoorthy, P. S., unpublished results. (b) Giese, B.; Bulliard, M.; Zeitz, H.-G. *Synlett*, in press.

A New Vinylsilane Substitution Reaction with Glyoxylate: Asymmetric Synthesis of α-Hydroxy β,γ-Unsaturated Esters

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Summary: The vinylsilane substitution reaction with glyoxylate and the asymmetric version thereof are described. These new reactions provide α-hydroxy β,γ-unsaturated esters of biological and synthetic importance in high enantiomeric and geometric purity.

The development of efficient methods for the regio- and stereocontrolled formation of carbon–carbon bonds, especially in the asymmetric cases, is the subject of intense current study. Vinylsilanes are well-known to undergo substitution reactions with a wide range of electrophiles

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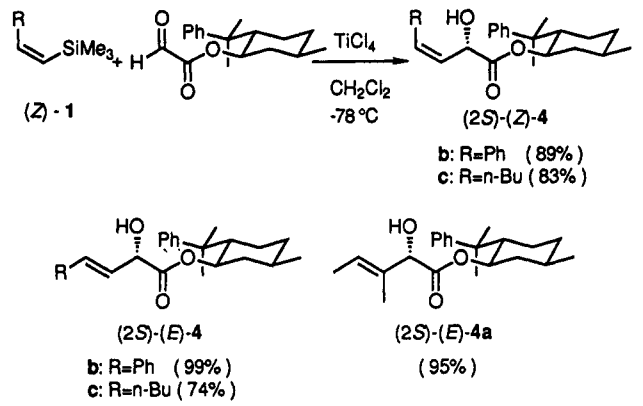
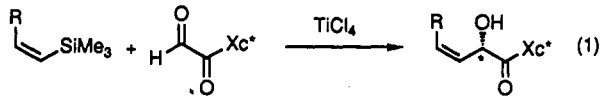
Scheme I

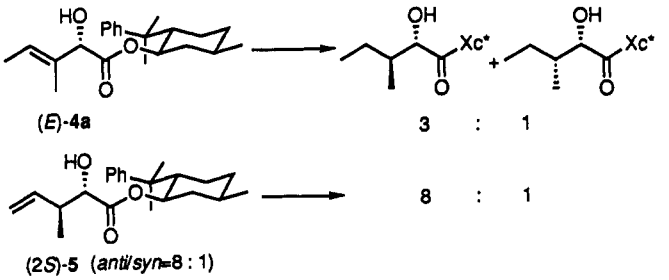


to give substitution products in regio- and stereospecific manners through the so-called β-silyl effect.[1] However, the number of carbon electrophiles presently available for the vinylsilane substitution reaction is severely limited[1,2] and thus the asymmetric version of this reaction has never been developed. Reported herein are the first examples of the vinylsilane substitution reaction with glyoxylate and the asymmetric version thereof, which provide α-hydroxy β,γ-unsaturated esters of biological and synthetic importance[3] with a high degree of stereocontrol (eq 1).

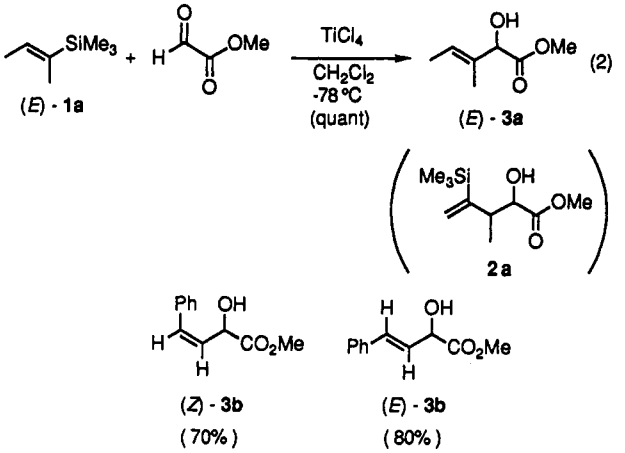


In the course of our research concerning Lewis acid promoted carbonyl–ene reactions with vinylsilanes,[4] we made the surprising observation that the reaction of (*E*)-vinylsilane **1a** with methyl glyoxylate, when promoted by $TiCl_4$ instead of $SnCl_4$,[5] did not provide any of the expected ene product **2a** but gave instead the substitution (S_E) product **3a** as a single isomer[6] (eq 2). This new type

Scheme II



of vinylsilane substitution reaction is quite general and highly stereospecific, affording the α-hydroxy β,γ-unsaturated esters with complete retention of configuration. Thus, stereochemically defined (*E*)- and (*Z*)-β-(trimethylsilyl)styrenes[7] provide the (*E*)- and (*Z*)-α-hydroxy esters **3b**, respectively.[8]



More importantly, the asymmetric version of this substitution reaction using 8-phenylmenthol[9]-derived glyoxylate[10] was found to proceed with an extremely high level of asymmetric induction (>99% de, 2*S*) (Scheme I). Particularly notable is the reaction with (*E*)-α,β-disubstituted vinylsilane (**1a**),[7] which provides the (*E*)-trisubstituted product (**4a**), exclusively.[11] The 2*S* configuration of the substitution product was determined after hydrogenation of **4a** through correlation (HPLC) to the ene product **5** with (*Z*)-2-butene[10] (Scheme II).[12] Thus, the asymmetric substitution reaction provides a new route to optically active α-hydroxy β,γ-unsaturated esters of bio-

(1) Reviews: (a) Colvin, E. W. *Silicon in Organic Synthesis*; Butterworths: London, 1983. (b) Fleming, I.; Dunogues, J.; Smithers, R. *Org. React.* **1989**, *37*, 57. Fleming, I. In *Comprehensive Organic Chemistry*; Barton, D. H. R., Ollis, W. D., Eds.; Pergamon: Oxford, 1979; Vol. 3, p 539. (c) Weber, W. P. *Silicon Reagents for Organic Synthesis*; Springer-Verlage: Berlin, 1983. (d) Magnus, P. D.; Sarker, T.; Djuric, S. In *Comprehensive Organometallic Chemistry*; Wilkinson, G. W., Stone, F. G. A., Abel, F. W., Eds.; Pergamon: Oxford, 1982; Vol. 7, p 515. (e) Hudrlik, P. F. In *Journal Organometallic Chemistry Library*; Seyferth, D., Ed.; Elsevior: Amsterdam, 1976; Vol. 1, p 127. (f) Overview of the α-, β-, γ-, and δ-silyl effects: Lambert, J. B. *Tetrahedron* **1990**, *46*, 2677. (g) For a recent theoretical study on the β-effect and many leading references, see: Wierschke, S. G.; Chandrasekhar, J.; Jorgensen, W. L. *J. Am. Chem. Soc.* **1985**, *107*, 1496.

(2) (a) Acid halide: Pillot, J.-P.; Dunogues, J.; Calas, R. *Bull. Soc. Chim. Fr.* **1975**, 2143. Fleming, I.; Pearce, A. *J. Chem. Soc., Chem. Commun.* **1975**, 633. (b) Acetal: Shikhmamedbekova, A. Z.; Sultanov, R. A. *J. Gen. Chem., U.S.S.R.* **1970**, *40*, 72. Pillot, J.-P.; Dunogues, J.; Calas, R. *Bull. Soc. Chim. Fr.* **1975**, 2143. (c) Chloral: Deleris, G.; Dunogues, J.; Calas, R. *J. Organomet. Chem.* **1975**, *93*, 43. (d) Chlorosulfonyl isocyanate: Barton, T. J.; Rogido, R. J. *J. Org. Chem.* **1975**, *40*, 582.

(3) (a) Reviews: Omura, S. *J. Synth. Org. Chem. Jpn.* **1986**, *44*, 127. Hanessian, S. *The Chiron Approach*; Pergamon: Oxford, 1983. Mori, K. In *The Total Synthesis of Natural Products*; Apsimon, J., Ed.; Wiley: New York, 1981; Vol. 4, Chapter 1. Seebach, D.; Hungerbuhler, E. In *Modern Synthetic Methods*; Schefford, R., Ed.; Verlag: Frankfurt, 1980; Vol. 2. (b) Reviews on α-amino β,γ-unsaturated acids: Williams, R. M. *Synthesis of Optically Active α-Amino Acids*; Pergamon: Oxford, 1989. Also see: Fowden, L.; Smith, A.; Millington, D. S.; Sheppard, A. R. *Phytochemistry* **1969**, *8*, 437.

(4) Mikami, K.; Loh, T.-P.; Nakai, T. *J. Am. Chem. Soc.* **1990**, *112*, 6737.

(5) The Lewis acidities have been reported to follow the order: $TiCl_4 > BF_3 > SnCl_4$: Satchell, D. P. N.; Satchell, R. S. *Chem. Rev.* **1969**, *69*, 25. Susz, B. P. *Bull. Soc. Chim. Fr.* **1965**, 2671.

(6) ^1H NMR 1.58 (s, 3 H), 1.65 (d, J = 4 Hz, 3 H), 3.30 (br s, 1 H), 3.80 (s, 3 H), 4.58 (s, 1 H), 5.76 (q, J = 4 Hz, 1 H) ppm.

(7) Vinylsilanes are prepared following the literature procedure: Colvin, E. W. *Silicon Reagents in Organic Synthesis*; Academic Press: New York, 1988; Chapter 3, and references therein.

(8) (*Z*)-**3b**: ^1H NMR 5.65 (dd, J = 9.6 and 11.4 Hz, 1 H), 6.81 (d, J = 11.4 Hz, 1 H) ppm; IR (neat) 770 cm^{-1}. (*E*)-**3b**: ^1H NMR 6.26 (dd, J = 5.7 and 15.9 Hz, 1 H), 6.81 (dd, J = 1.6 and 15.9 Hz, 1 H) ppm; IR (neat) 970 cm^{-1}.

(9) 8-Phenylmenthol auxiliary: (a) Diels–Alder reaction: Corey, E. J.; Ensley, H. E. *J. Am. Chem. Soc.* **1975**, *97*, 6908. Ensley, H. E.; Parnell, C. A.; Corey, E. J. *J. Org. Chem.* **1978**, *43*, 1610. (b) Intramolecular ene reaction and 1,4-additions: Oppolzer, W. In *Current Trends in Organic Synthesis*; Nozaki, H., Ed.; Pergamon: Oxford, 1983.

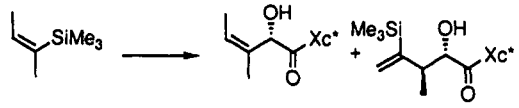
(10) Review on the use of 8-phenylmenthyl glyoxylate in ene reactions: Whitesell, J. K. *Acc. Chem. Res.* **1985**, *18*, 280.

(11) ^{13}C NMR δ_{COH}: (2*S*)-(*Z*)-**4b**, 66.8 ppm; (2*S*)-(*E*)-**4b**, 70.7 ppm; (2*S*)-(*Z*)-**4c**, 67.2 ppm; (2*S*)-(*E*)-**4c**, 69.7 ppm; (2*S*)-(*Z*)-**4a**, 73.3 ppm; (2*S*)-(*E*)-**4a**, 76.2 ppm.

(12) Anti selectivity observed in the cationic rhodium-catalyzed hydrogenation of (*E*)-**4a** is rather surprising in view of the high syn selectivity reported for a similar hydrogenation of an allylic alcohol system: Brown, J. M. *Angew. Chem., Int. Ed. Engl.* **1987**, *26*, 190. Evans, D. A.; Morrissey, M. M. *J. Am. Chem. Soc.* **1984**, *106*, 3866. We could suggest that the proximal ester group rather than the hydroxy group directs the stereochemical course of the present hydrogenation. Further studies are underway in our laboratory.

logical and synthetic importance.[3]

From a mechanistic point of view, the reaction with vinylsilane provides valuable insight into the continuum of mechanisms ranging from cationic substitution to the pericyclic ene pathway, depending critically on both the particular Lewis acid[5] used and the vinylsilane geometry (eq 3). In sharp contrast to the exclusive formation of



(3)

(Z)-1a $TiCl_4$ (quant) 1 : 1
$SnCl_4$ (quant) 0 : 100 (>99% *anti*)

substitution product with (*E*)-vinylsilane, (*Z*)-vinylsilane provides not only the substitution product[11] but also the ene product.[13] More significantly, the use of $SnCl_4$ provides only the ene product.[13,14] Thus, vinylsilane may represent a novel mechanistic probe for Lewis acid promoted ene reactions.[15]

Supplementary Material Available: Experimental details of the substitution reactions and physical data of the products (7 pages). Ordering information is given on any current masthead page.

(13) ^1H NMR 0.00 (s, 9 H), 5.30 (d, J = 2.2 Hz, 1 H), 5.55 (d, J = 2.2 Hz, 1 H) ppm.

(14) The $SnCl_4$-promoted ene reaction provides a high enantiomeric purity (>99% de) along with enhanced anti diastereoselectivity[4] (>99%) as compared with (*E*)-2-butene without the silyl group (94% anti).[10]

(15) For a mechanistic probe based on primary kinetic isotope effect: Snider, B. B.; Ron, E. *J. Am. Chem. Soc.* **1985**, *107*, 8160. Song, Z.; Beak, P. *Ibid.* **1990**, *112*, 8126 and references.

Stereocontrolled Synthesis of a Trihydroxylated A Ring as an Immediate Precursor to 1α,2α,25-Trihydroxyvitamin D_3

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Summary: 3-Bromo-2-pyrone (1) was coaxed into inverse-electron-demand Diels–Alder cycloaddition with dioxole 2 under sufficiently mild thermal conditions to allow isolation of functionally and stereochemically rich bicycloadduct *endo*-3 that was transformed into trihydroxylated A-ring allylic phosphine oxide as an immediate precursor to 1α,2α,25-trihydroxyvitamin D_3.

Metabolic hydroxylation of vitamin D_3 produces 1α,25-dihydroxyvitamin D_3 (calcitriol)[1] that is a potent regulator of cell differentiation and proliferation[2] as well as intestinal calcium and phosphorus absorption and bone calcium mobilization. Calcitriol is used currently for clinical treatment of osteoporosis and for chemotherapy of certain metabolism disorders such as neonatal hypocalcemia, chronic renal failure, and hypoparathyroidism.[3] Various calcitriol analogues having modified D-ring side chains are being developed internationally for chemotherapy of psoriasis, a disease characterized by hyperproliferation of skin cells.[4] In comparison, relatively little effort, however, has been devoted to preparing ring-A modified vitamin D_3 derivatives.[5] Herein we report an efficient, practical, and stereocontrolled synthesis of a trihydroxylated A ring as an immediate precursor to 1α,2α,25-trihydroxyvitamin D_3, a new vitamin D_3 analogue.

We have recently shown that electron-deficient 3-sulfinyl- and 3-sulfonyl-2-pyrones undergo inverse-electron-demand Diels–Alder cycloadditions with various electron-rich dienophiles under sufficiently mild conditions to allow isolation of the initial rigid, bridged, bicyclic adducts without loss of CO_2 by cycloreversion and without subsequent aromatization.[6] We have now discovered that even 3-bromo-2-pyrone (1), readily prepared on multigram scale from 5,6-dihydro-2-pyrone[7a] and at least 20 times *less* reactive than 3-(*p*-tolylsulfonyl)-2-pyrone (as determined by a competition experiment), also cycloadds as an electron-deficient diene under carefully controlled thermal conditions.[8] For example, heating 3-bromo-2-pyrone (1) and 2,2-dimethyl-1,3-dioxole (2)[6b,9] along with a small

(1) (a) *Vitamin D. Chemical, Biochemical, and Clinical Update*; Proceedings of the Sixth Workshop on Vitamin D, Merano, Italy, March 1985; Norman, A. W., Schaefer, K., Grigoleit, H. G., Herrath, D. V. Eds.; W. de Gruyter: New York, 1985. (b) Brommage, R.; DeLucca, H. F. *Endocrine Rev.* **1985**, *6*, 491. (c) Dickson, I. *Nature* **1987**, *325*, 18. (d) Cancela, L.; Theofon, G.; Norman, A. W. In *Hormones and Their Actions, Part I*; Cooke, B. A.; King, R. J. B.; Van der Molen, H. J., Eds.; Elsevier: Holland, 1988.

(2) (a) Tsoukas, C. D.; Provvedini, D. M.; Manolagas, S. C. *Science (Washington, D.C.)* **1984**, *224*, 1438. (b) Provvedini, D. M.; Tsoukas, C. D.; Deftos, L. J.; Manolagas, S. C. *Science (Washington, D.C.)* **1983**, *221*, 1181.

(3) *Vitamin D. Chemical, Biochemical, and Clinical Endocrinology of Calcium Metabolism*; Proceedings of the Fifth Workshop on Vitamin D, Williamsburg, VA, Feb. 1982, Norman, A. W., Schaefer, K., Herrath, D. V., Grigoleit, H. G., Eds.; W. de Gruyter: New York, 1982; pp 901–940.

(4) For example, see: Calverley, M. J. In *Vitamin D: Molecular, Cellular, and Clinical Endocrinology*; Norman, A. W., Ed.; de Gruyter: Berlin, 1988; p. 51. Calverley, M. J. *Tetrahedron* **1987**, *43*, 4609.

(5) For some exceptions, see: (a) Okano, T.; Tsugawa, N.; Masuda, S.; Takeuchi, A.; Kobayashi, T.; Takita, Y.; Nishii, Y. *Biochem. Biophys. Res. Commun.* **1989**, *163*, 1444. (b) Kobayashi, Y.; Nakazawa, M.; Kumadaki, I.; Taguchi, T.; Ohshima, E.; Ikekawa, N.; Tanaka, Y.; DeLucca, H. F. *Chem. Pharm. Bull.* **1986**, *34*, 1568. (c) Miyamoto, K.; Kubodera, N.; Ochi, K.; Matsunaga, I.; Murayama, E. Eur. Pat. Appl. EP 184,206; *Chem. Abstr.* **1986**, *105*, 115290y. (d) Ishikawa, M.; Kaneko, C.; Sasaki, S.; Suda, T.; Yamada, S.; Sugimoto, A. German Patent 2535308 (1976); *Chem. Abstr.* **1976**, *85*, 46962y.

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(7) (a) Posner, G. H.; Harrison, W.; Wettlaufer, D. G. *J. Org. Chem.* **1985**, *50*, 5041. (b) Posner, G. H.; Wettlaufer, D. G. *J. Am. Chem. Soc.* **1986**, *108*, 7373.

(8) For normal-electron-demand cycloaddition using 3-bromo-2-pyrone involving as the major reaction pathway thermal extrusion of CO_2 from the initial bicycloadducts, see: Nesterova, T. L.; Shusherina, N. P.; Shulishov, E. V. *Zh. Org. Khim.* **1985**, *21*, 427 (*J. Org. Chem. U.S.S.R.* **1985**, *21*, 387) and references therein. For an extensive listing of cycloadditions with other pyrones, see: *Dienes in the Diels-Alder Reaction*; Fringuelli, F., Taticchi, A., Eds.; John Wiley, Inc.: New York, 1990.

(9) Mattay, J.; Thünker, W.; Scharf, H.-D. *Synthesis* **1983**, 208.

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