stitution–spiroannulation, when El = a leaving group, nucleophilic-promoted fragmentation can be achieved to constitute an alkylative elimination or secoalkylation sequence[14] from a saturated ketone.

Acknowledgment. We thank the National Science Foundation for their generous support of our programs.

Registry No. 1b, 37609-29-3; **2** (isomer 1), 86971-86-0; **2** (isomer 2), 86971-87-1; **3** (isomer **1**), 86971-88-2; **3** (isomer2), 86971-89-3; **4**, 86971-90-6; **5**, 86971-91-7; **6**, 86971-92-8; **7**, 86971-93-9; **8**, 86971-94-0; **9**, 86971-95-1; **10**, 87037-57-8; **11**, 82517-58-6; **12**, 86971-96-2; **13**, 82517-59-7; **14**, 86971-97-3; **15**, 86971-98-4; **16**, 87037-58-9.

(14) Trost, B. M.; Bogdanowicz, M. J. *J. Am. Chem. Soc.* **1972**, *94*, 4777. Trost, B. M.; Bogdanowicz, M. J.; Frazee, W. J.; Salzmann, T. N. *Ibid.* **1978**, *100*, 5512.

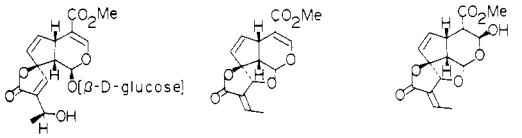
Biomimetic Approach to Plumericin

Barry M. Trost,* James M. Balkovec, and Michael K.-T. Mao

Samuel M. McElvain Laboratories of Organic Chemistry
Department of Chemistry, University of Wisconsin
Madison, Wisconsin 53706

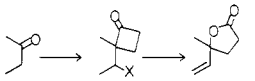
Received June 6, 1983

In 1951, Little and Johnstone isolated a compound that exhibited antifungal, antibacterial, and subsequently antitumor activity.[1] The compound, called plumericin, has been shown to possess the structure **2** by Albers-Schonberg and Schmid.[2] Closely related to plumericin is a hydrated analogue **3** known as allamandin,[3] a compound also possessing high antitumor activity. These densely functionalized molecules represent substantial synthetic challenges. A strategy emerges from the possibility that plumeride (**1**)[4,5] may be a biosynthetic precursor of plumericin.



1 2 3

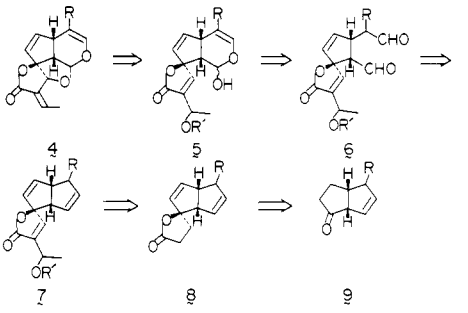
This suggestion led us to consider a conjugate addition–elimination approach for the formation of the tetrahydrofuran unit which simplifies the problem to **5** (see Scheme I). The dihydropyran ring of **5** represents a cyclized form of a dialdehyde such as **6**, which in turn, may derive from an oxidative cleavage of an olefin as in **7**. Anticipating that the butenolide substitution of **7** can evolve from the reactivity of the enolate of a saturated lactone as in **8**, a major structural simplification to the saturated ketone **9** is permitted by use of the concept of substitutive spiroannulation as embodied in eq 1. The establishment of the stereochemistry



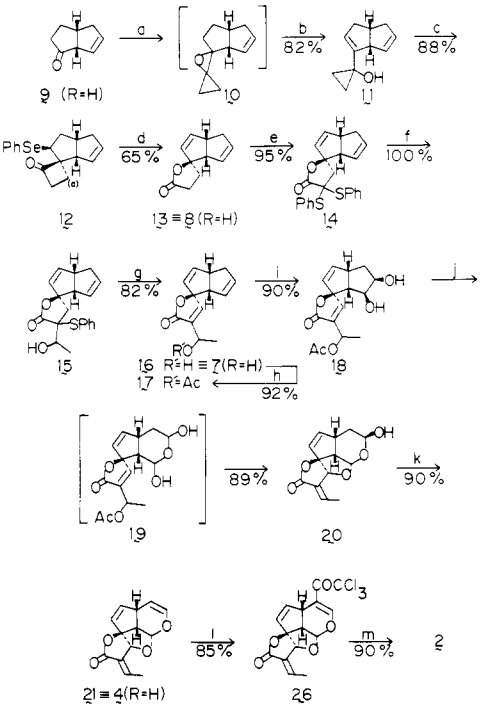
(1)

of the five chiral centers of **4** factors to the stereochemistry of the conversion of **9** to **8** since only the α-anomer of **5** can geometrically reach to form **4**. While, at first glance, the need for the carbomethoxy group at C(4) of **2** tempts us to incorporate that carbon from the start, the fact that **9** (R = H) is a well-known

Scheme I



Scheme II[a]



[a] (a) $\triangleright$—$S^+Ph_2BF_4^-$, KOH, Me_2SO, room temperature; (b) LiN$(C_2H_5)_2$, pentane, room temperature; (c) PhSeBr (1.5 equiv), $(C_2H_5)_3N$ (2.0 equiv), CH_2Cl_2, −40 °C; (d) MCPBA, CH_2Cl_2, −78 → 0 °C then add $CH_2{=}CHOC_2H_5$, room temperature; (e) LDA, THF, then $PhSSO_2Ph$, THF, −78 °C → room temperature; (f) C_2H_5MgBr, ether, THF, 0 °C, then CH_3CHO; (g) MCPBA, CH_2Cl_2, −78 °C → room temperature, then CCl_4, $CaCO_3$, reflux; (h) Ac_2O, C_5H_5N, DMAP, 0 °C; (i) cat OsO_4,  $\cdot H_2O$ THF, H_2O, 0 °C; (j) $NaIO_4$ (3 equiv), ether, H_2O, room temperature, then add NaOAc; (k) Ac_2O, DMAP, $(i\text{-}C_3H_7)_2NC_2H_5$, CH_2Cl_2, room temperature, and distill crude through quartz tube at 500 °C; (l) CCl_3COCl (50 equiv), 2,6-$(t\text{-}C_4H_9)_2C_5H_3N$ (5 equiv), CH_2Cl_2, room temperature; $Mg(OCH_3)_2$, CH_3OH, THF, −45 °C; (n) All new compounds have been fully characterized by spectral means, and elemental composition was determined by combustion analysis and/or high-resolution mass spectroscopy.

compound both in the racemic[6] and optically active[7] form led us to gamble that, even though methodology did not exist for the carbomethoxylation of an enol ether at the start of this program, a method could be found to carbomethoxylate descarbometh-

(1) Little, J. E.; Johnstone, D. B. *Arch. Biochem.* **1951**, *30*, 445.
(2) Albers-Schonberg, G.; Schmid, G. *Helv. Chim. Acta* **1961**, *44*, 1447.
(3) Kupchan, S. M.; Dessertine, A. L.; Blaylock, B. T.; Bryan, R. F. *J. Org. Chem.* **1974**, *39*, 2477.
(4) Schmid, H.; Bickel, H.; Meijer, T. M. *Helv. Chim. Acta*, **1952**, *35*, 415. Halpern, O.; Schmid, H. *Ibid.* **1958**, *41*, 1105.
(5) Also see: Inoue, K.; Takeda, Y.; Nishimura, H.; Inouye, H. *Chem. Pharm. Bull.* **1979**, *27*, 3115.

(6) Available in 80% yield in 3 steps from 1,3-cyclooctadiene. Apparu, M.; Barrelle, M. *Tetrahedron* **1978**, *34*, 1541. Whitesell, J. K.; Matthews, R. S.; Wang, P. K. S. *Synth. Commun.* **1977**, *7*, 355. Crandall, J. K.; Banks, D. B.; Colyer, R. A.; Watkins, R. J.; Arrington, J. P. *J. Org. Chem.* **1968**, *33*, 423. LeBel, N. A.; Spurlock, L. A. *Tetrahedron* **1964**, *20*, 215.
(7) Kuritani, H.; Takaoka, Y.; Shingu, K. *J. Org. Chem.* **1979**, *44*, 452.
Note Added in Proof: An additional method for resolution of the alcohol precursor has been reported: Whitesell, J. K.; Minton, M. A.; Felman, S. W. *J. Org. Chem.* **1983**, *48*, 2193.

0002-7863/83/1505-6755$01.50/0

oxyplumericin (**4**, R = H). We wish to record the first synthesis of plumericin that totally avoids the need for any protecting groups. In addition, we developed new methodology for carbomethoxylation of enol ethers. The key features of this synthesis are (1) a substitution–spiroannulation using diphenylsulfonium cyclopropylide, (2) a γ-butyrolactone elaboration via sulfenylated intermediates, (3) a facile biomimetic cyclization of a lactol hydroxyl group onto a butenolide in a conjugate addition–elimination reaction, and (4) a chemoselective procedure for carbomethoxylation of an enol ether.

Scheme II outlines the synthesis. A Me_2SO solution of **9** (R = H) condenses with cyclopropyldiphenylsulfonium fluoroborate in the presence of powdered potassium hydroxide.[8] The Me_2SO solution of the reaction mixture is directly extracted with pentane. A solution of lithium diethylamide in a hexane–pentane mixture is added directly to the concentrated pentane extracts of the oxaspiropentane **10** to give the vinylcyclopropanol **11**. The critical stereochemistry of plumericin is put into place by temperature-controlled, chemoselective electrophilically initiated ring expansion of **11**[9] with the complex derived from mixing triethyl amine and benzeneselenenyl bromide at −40 °C to give **12** in >100:1 diastereomeric purity. ^{13}C NMR spectroscopy permits assignment of the indicated sterochemistry since C(a) of **12** shows a signal at δ 18.2; whereas, the cyclobutanone epimer shows this signal at δ 21.8.[10] The successful completion of the synthesis verifies this assignment.

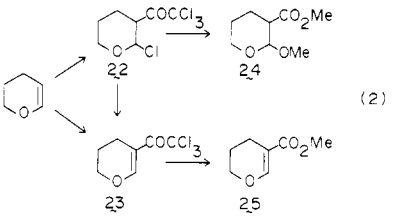
The conversion of **12** to **13** requires a double oxidation, a Baeyer–Villiger reaction of the cyclobutanone[11,12] and conversion to the selenoxide and elimination.[13] Chemoselective bis oxidation with 2 equiv of MCPBA at −78–0 °C produces the selenoxide and γ-butyrolactone. Adding of ethyl vinyl ether at this point and allowing the temperature to rise to room temperature completes the elimination to **13**—a sequence that accomplishes both oxidative changes in a single step.

For elaboration of the butenolide,[14] generation of a clean solution of the magnesium enolate of the sulfenylated lactone by reaction of the bis(sulfide) **14** with ethylmagnesium bromide and quenching it with acetaldehyde to give **15** proved vastly superior to use of amide bases on the monosulfenylated lactone.[15] Oxidation to the sulfoxide allowed elimination to the butenolide **16**, which proceeds smoothly at 76 °C.[16] To prime the hydroxyl group of **16** for its role as a leaving group in the biomimetic cyclization, it was acetylated to give **17**.

Of the three double bonds of **17**, we require a reagent that discriminates on the basis of steric hindrance and the nucleophilicity of the double bond since, on both counts, the double bond we wish to cleave should be the most reactive. Cis hydroxylation with a catalytic amount of osmium tetraoxide proved to be the preferred reagent for initiating the olefin cleavage sequence.[17] Exposing the resultant diol **18** to sodium metaperiodate for 5 min apparently forms **19**. Addition of sodium acetate to buffer the acidic solution of the periodate cleavage reaction suffices to equilibrate **19** and cyclizes the requisite diastereomer to descarbomethoxyallamandin **20**, mp 195–200 °C (dec). The facility of the cyclization reaction under such extraordinarily mild conditions reinforces the suggestion that it may represent the biosynthetic pathway and may not require enzyme catalysis. In this cyclization, a small amount of the geometric isomer of the exocyclic double bond is detected in the NMR spectrum [δ 2.08 for **20** and 2.28 for isodecarbomethoxyallamandin].

Acetylation of the lactol hydroxyl group of **20** and distillation of the crude acetate in vacuo through a hot tube as a workup effects net dehydration to (±)-descarbomethoxyplumericin **21**, mp 105–7 °C.

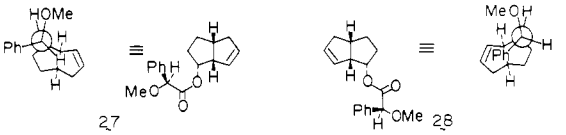
From model work with dihydropyran, carbomethoxylation[18] of an enol ether was best initiated by formation of the 1:1 adduct **22** (eq 2) with neat trichloroacetyl chloride (room temperature)[19]



(2)

which either upon heating in vacuo (60 °C, 15 mm Hg) or subjecting to Hunig's base at 0 °C in CH_2Cl_2 gives **23** in 84% yield. The latter forms directly from dihydropyran by carrying out the condensation of dihydropyran and trichloroacetyl chloride in the presence of 2,6-di-*tert*-butylpyridine. Methanolysis of **22** (anhydrous CH_3OH, Na_2CO_3) followed by haloform cleavage [$(C_2H_5)_3N$, CH_3OH, room temperature] gives the lactol ether **24**. Haloform cleavage of **23** [$Mg(OCH_3)_2$, CH_3OH, room temperature] gives the carbomethoxylated enol ether **25** in 97% yield. The ability of a substrate such as **21**, which possesses a great deal of functionality including several double bonds, to participate in such a sequence appeared to be a formidable obstacle.[20] Gratifyingly, application of the direct sequence from dihydropyran to **23** to descarbomethoxyplumericin chemoselectively produces the trichloro ketone **26**, mp 180–181 °C. Dissolving **26** in methanol and adding a solution of magnesium methoxide in methanol at −45 °C (temperature critical) completes the carbomethoxylation sequence and simultaneously the synthesis of (±)-plumericin, mp 176–178 °C. All spectral properties agreed with those recorded for the natural product.[2,21]

The question of an asymmetric synthesis was briefly addressed. While a resolution method for the alcohol precursor of **9** (R = H) has been reported using camphanyl chloride,[7] we examined the HPLC behavior of the *O*-methylmandelate esters **27** and **28**.[22,23] Indeed, two nearly base-line separated peaks using 9:1



hexane–ethyl acetate on a 10 μ Porasil column can be observed. The shorter retention time isomer showed absorptions for the vinyl protons at δ 5.38 and 5.68; whereas, these absorptions appeared at δ 4.86 and 5.40 for the longer retention time isomer. Using Mosher's model and viewing **27** and **28** in an extended Newman projection, we assign the stereochemistry depicted in **27** to the shorter retention time diastereomer. This assignment is confirmed by cleavage to the alcohol which showed a positive rotation, in agreement with the literature. The easy availability of either enantiomer by this simple method should allow the synthesis of either enantiomer of the iridoids.

(8) Trost, B. M.; Bogdanowicz, M. J. *J. Am. Chem. Soc.* **1973**, *95*, 5311.
(9) Trost, B. M.; Mao, M. K. *J. Am. Chem. Soc.*, preceding communication in this issue.
(10) Trost, B. M.; Scudder, P. H. *J. Am. Chem. Soc.* **1977**, *99*, 7601.
(11) Trost, B. M.; Bogdanowicz, M. J. *J. Am. Chem. Soc.* **1973**, *95*, 5321.
(12) Use of neutral hydrogen peroxide leads to an alternative regioisomeric γ-butyrolactone in which the selenium serves as a regiochemical control element. See: Trost, B. M.; Buhlmayer, P.; Mao, M. *Tetrahedron Lett.* **1982**, *23*, 1443.
(13) For a review see: Reich, H. J. *Acc. Chem. Res.* **1979**, *12*, 22.
(14) Trost, B. M.; Mao, M. K. *Tetrahedron Lett.* **1980**, *21*, 3523.
(15) For an independent study of the use of amide bases see: Hoye, T.; Kurth, M. J. *J. Org. Chem.* **1980**, *45*, 3549.
(16) Trost, B. M.; Salzmann, T. N.; Hiroi, K. *J. Am. Chem. Soc.* **1976**, *98*, 4887. Trost, B. M.; Leung, K. K. *Tetrahedron Lett.* **1975**, 4197. For a review, see: Trost, B. M. *Acc. Chem. Res.* **1978**, *11*, 453; *Chem. Rev.* **1978**, *78*, 363.
(17) Van Rheenan, V.; Kelly, R. C.; Cha, D. Y. *Tetrahedron Lett.* **1976**, 1973.
(18) Cf. carbomethoxylation of electron-rich aromatic rings: Bailey, D. H.; Johnson, R. E.; Albertson, N. F. *Org. Synth.* **1971**, *51*, 100 and references therein.
(19) Effenberger, F.; Maier, R.; Schonwalder, K.-H.; Ziegler, T. *Chem. Ber.* **1982**, 2766.
(20) Compounds **20**, **21**, and **26** proved to be extremely sensitive to bases of all types. On the other hand, they appear to tolerate acids somewhat better.
(21) Pai, B. R.; Subramanian, P. S.; Rao, V. R. *Indian J. Chem.* **1970**, *8*, 851.
(22) Trost, B. M. *ACS Symp. Ser.* **1982**, *185*, 1.
(23) Dale, J. A.; Mosher, H. S. *J. Am. Chem. Soc.* **1973**, *95*, 512.

Acknowledgment. We thank the National Cancer Institute of the National Institutes of Health for their generous support of our programs. Dr. P. Buhlmayer performed some of the model studies associated with this route.

Registry No. (±)-**2**, 87037-55-6; (±)-**9**, 65861-37-2; **10**, 86971-73-5; (±)-**11**, 86971-74-6; (±)-**12**, 82517-60-0; (±)-**13**, 87037-56-7; (±)-**14**, 86993-52-4; **15**, 86971-75-7; **16**, 86971-76-8; **17**, 86971-77-9; **18**, 86971-78-0; (±)-**20**, 86971-79-1; (±)-**20** acetate, 86971-80-4; (±)-**21**, 83124-70-3; **23**, 83124-87-2; **24**, 86971-82-6; **25**, 86971-83-7; (±)-**26**, 86993-53-5; **27**, 86971-84-8; **28**, 86971-85-9; CH_3CHO, 75-07-0; CCl_3COCl, 76-02-8; cyclopropyldiphenylsulfonium fluoroborate, 33462-81-6; dihydropyran, 110-87-2.

Supplementary Material Available: Structures and experimental data for **13**, **17**, **20**, **21**, **26**, and **2** (2 pages). Ordering information is given on any current masthead page.

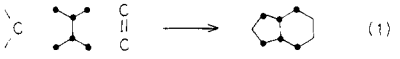
An Umpolung of Allyl Bis(silanes). Tandem [6.5] Annulations via a Biallyl Equivalent

Barry M. Trost* and Makoto Shimizu

Samuel M. McElvain Laboratories of Organic Chemistry
Department of Chemistry, University of Wisconsin
Madison, Wisconsin 53706

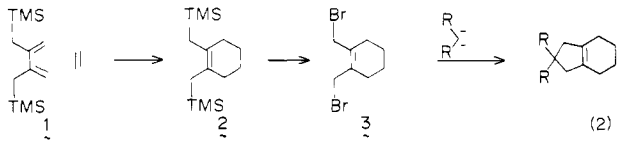
Received July 31, 1983

The widespread occurrence of [6.5] ring systems in natural products stimulates the development of new strategies.[1] A potentially very flexible approach envisions a two-stage "cycloaddition" methodology of a two and subsequently a one carbon fragment to a biallyl skeleton as outlined in eq 1. The convenience



(1)

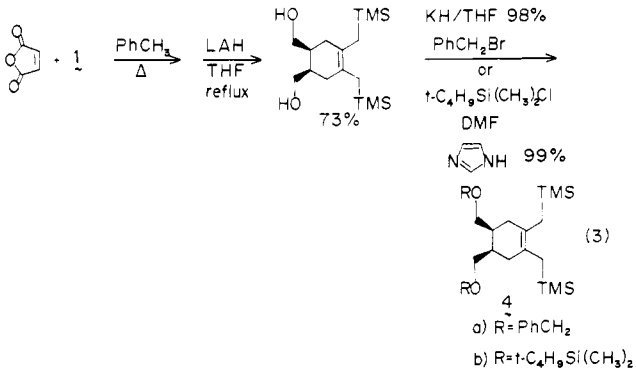
and ease of handling of 2,3-bis[(trimethylsilyl)methyl]-1,3-butadiene (**1**)[2] and the ability to manipulate the intermediate **2** prior to creation of the reactive dibromide **3**[3] suggested the sequence outlined in eq. 2. The key to this sequence was to devise a method



(2)

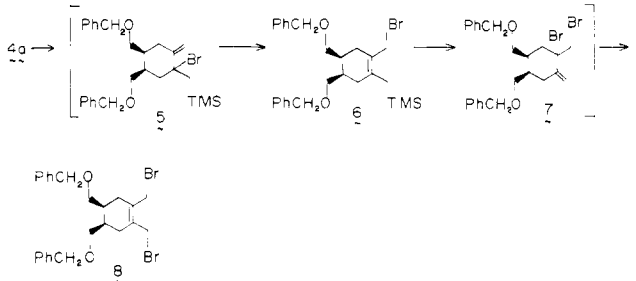
to effect an umpolung of the allylbis(silane) **2** *without allyl inversion.* We wish to record a simple solution to this problem and its utility in forming [6.5] ring systems especially with respect to the use of bis(phenylsulfonyl)methane in cycloalkylations.

We chose the dibenzyl ether **4**, which derives from the adduct of **1** and maleic anhydride according to eq 3, as a model in which the key was envisioned to be the rearrangement of allyl bromides



(3)

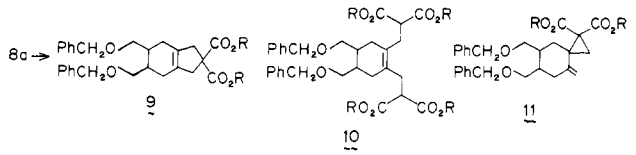
5 and **7** to the thermodynamically more stable isomers **6** and **8**.



Reacting 2 equiv of freshly recrystallized NBS with **4** in THF in the presence of propylene oxide at -78 to 0 °C indeed gave a 47% yield of **8**. Believing the presence of trimethylsilyl bromide may improve the rearrangement of **5** to **6** and/or **7** to **8** led us to use bromine with the result of a slight improvement in yield to 57%. The ability of cupric bromide to serve as a brominating agent[4] led us to explore the possibility that allylsilanes might also be brominated by this reagent. If an allylcopper species is involved, the regioselectivity of the bromination might be independent of the structure of the allysilane. Indeed, addition of a catalytic amount of cupric bromide to the bromination reaction dramatically improved the yield of **8** to 82%.

Experimentally, 1 equiv of bromine in carbon tetrachloride is added to a solution of 1 equiv of the bis(silane), 10 equiv of propylene oxide, and 1 mol % cupric bromide in THF at -78 °C (15 min). After warming to 0 °C (15 min) and recooling to -78 °C, an additional 1 equiv of bromine in carbon tetrachloride is added (15 min) and the mixture warmed to 0 °C (15 min). The reaction is quenched with sodium sulfite and worked up in standard fashion. Table I summarizes the results. The chemoselectivity is noteworthy in that ester, ketone, amide, and *tert*-butyldimethylsilyl ether groupings all are compatible. Most remarkably, the dihydro aromatic ring of entry 7 does not aromatize under the reaction conditions.

The use of such dibromides in cycloalkylation with malonic esters[5] showed a surprising dependence on the choice of the ester of the malonate. In all cases, to minimize or avoid the dialkylation product **10**, the malonate was added dropwise to a mixture of NaH and the dibromide **8a** in DMF. With dimethyl malonate, a



mixture of the cyclopentene **9** and the cyclopropanes **11** was

(1) Outside the obvious natural products such as steroids, which provided much of the stimulus in this field, a few recent cases of terpenes illustrate the widespread occurrence of such structural fragments and the need for new methodology. Stearylvelutinal: Favre-Bonvin, J.; Gluchoff-Fiasson, K.; Bernillon, J. *Tetrahedron Lett.* **1982**, *23*, 1907. Melleolide: Midland, S. L.; Izac, R. R.; Wing, R. M.; Zaki, A. I.; Mannecke, D. E.; Sims, J. *Ibid.* **1982**, *23*, 2515. Sterpuric acid: Ayer, W. A.; Saeedi-Ghomi, M. H.; van Engen, D.; Tagle, B.; Clardy, J. *Tetrahedron Suppl.* **1981**, *No. 9*, 379. Alliacolide and dihydrobotrydial: Hanson, J. R. *Pure Appl. Chem.* **1981**, *53*, 1155. Broderol: Ayer, W. A.; McCaskill, R. H. *Can. J. Chem.* **1981**, *59*, 2150. Merulidial: Quack, W.; Anke, T.; Oberwinkler, F.; Giannetti, B. M.; Steglich, W. *J. Antibiot.* **1978**, *31*, 737. Calomelanolactone: Bardouille, V.; Mootoo, B. S.; Hirotsu, K.; Clardy, J. *Phytochem.* **1978**, *17*, 275. Isolactarorufin: Daniewski, W. M.; Kocor, M.; Thoren, S. *Pol. J. Chem.* **1978**, *52*, 561.

(2) Trost, B. M.; Shimizu, M. *J. Am. Chem. Soc.* **1982**, *104*, 4299.

(3) Cf: Gaoni, Y.; Sadeh, S. *J. Org. Chem.* **1980**, *45*, 870. Hamon, D. P. G.; Spurr, P. R. *Synthesis* **1981**, 878. Bellus, D.; von Bredaw, K.; Sauter, M.; Weiss, C. D. *Helv. Chim. Acta* **1973**, *56*, 3004. Zahierezhy, V.-I.; Musso, H. *Justus Liebigs Ann. Chem.* **1973**, 1777. Butler, G. B.: Ottenbride, R. M. *Tetrahedron Lett.* **1967**, 4873.

(4) For example, see: Haruta, A. M.; Satoh, J. Y. *Chem. Lett.* **1980**, 473. Kojima, Y.; Usui, K.; Kawaguchi, S. *Bull. Chem. Soc. Jpn.* **1972**, *45*, 3127. Kosower, E. M.; Cole, W. J.; Wu, G.-S.; Cardy, D. E.; Meisters, G. *J. Org. Chem.* **1963**, *28*, 630. Nonhebel, D. C.; Russell, J. A. *Tetrahedron* **1970**, *26*, 2781.

(5) For a recent study of this type of reaction and its problems see: Oediger, H.; Moller, F. *Justis Liebigs Ann. Chem.* **1976**, 348.

0002-7863/83/1505-6757$01.50/0