Calcd for $C_6H_{13}BrO_2$: C, 36.57; H, 6.65. Found: C, 36.21; H, 6.48.

Cleavage of the 2-substituted tetrahydrofurans **29**, **35**, **38**, **41**, and **44** was similarly performed, and yields are reported in Table III. Similarly, yields of the opening of the 2-substituted tetrahydrofurans **47**, **50**, **53**, **56**, **59**, and **62** are reported in Table IV whereas for the disubstituted tetrahydrofuran **65** the yield is reported in Table V. For the cleavage of the other monosubstituted tetrahydrofurans **73**, **75**, and **79** yields are reported in Table VI.

Cleavage of Disubstituted Tetrahydrofuran 67. To a cold (0 °C) solution of the disubstituted tetrahydrofuran **67**[5] (100 mg, 0.24 mmol) in 1.6 mL of dry methylene chloride and triethylamine (0.003 mL, 0.025 mmol) was added dropwise a solution of dimethylboron bromide (1.56 M, 0.41 mL). The ice bath was removed and the solution stirred at room temperature for 18 h. The reaction mixture was poured over a stirred solution of saturated sodium bicarbonate and extracted with ether. The organic layer was washed with brine (2×), dried with sodium sulfate, filtered, and evaporated to dryness. The two compounds were separated by flash chromatography using 10% ethyl acetate/hexane, affording 38 mg (33%) of the bromo alcohol **68** as an oil [^{1}H NMR ($CDCl_3$) δ 1.08 (s, 9 H, *t*-Bu), 1.28 (t, 3 H, CH_3), 1.77 (m, 2 H, CH_2), 2.40 (d, 2 H, CH_2COOEt), 2.79 (d, 1 H, OH, D_2O exchangeable), 3.20 (dd, 2 H, CH_2Br), 3.36 (dd, 1 H, CH_2Br), 4.16 (q, 2 H, OCH_2CH_3), 4.10–4.40 (m, 2 H, CHOH, CHOSi), 7.38–7.74 (m, 10 H, Ar)] and 15 mg (13%) of the more polar bromo alcohol **69** as an oil of which the diastereoisomers are distinguishable by ^{1}H NMR [($CDCl_3$) δ 1.10 (s, 9 H, *t*-Bu), 1.27 (t, 3 H, CH_3), 1.86 (br t, 1 H, OH, D_2O exchangeable), 1.90–2.00 (m, 2 H, CH_2), 2.71 and 2.86 (2 m, 2 H, CH_2COOEt), 3.44–3.58 (m, 2 H, CH_2OH, which appears as 2 ddd on D_2O exchange), 4.02 (m, 1 H, CH), 4.17 (q, 2 H, OCH_2CH_3), 4.24 and 4.58 (m, 1 H, CH), 7.36–7.80 (m, 10 H, Ar)].

Cleavage of Disubstituted Tetrahydrofuran 70. To a cold (0 °C) solution of the disubstituted tetrahydrofuran **70** (71 mg, 0.41 mmol) in dry methylene chloride (1.6 mL) and triethylamine (0.066 mL, 0.48 mmol) was added, dropwise, a solution of dimethylboron bromide (1.56 M, 0.79 mL) in methylene chloride. After being stirred 3 h at 0 °C, the reaction mixture was poured over a stirred solution of saturated sodium bicarbonate and extracted with ether. The organic layer was washed with brine (2×), dried with Na_2SO_4, filtered, and evaporated to dryness, giving 94 mg (90%) of the crude bromo alcohol **71**: IR (neat), 3420 (OH), 1725 cm^{-1} (C=O); ^{1}H NMR ($CDCl_3$) δ 1.30 (t, 3 H, CH_3), 1.74 (t, 2 H, CH_2), 2.51 (d, 2 H, CH_2COOEt), 3.48 (d, 2 H, CH_2Br), 3.08–3.70 (m, 2 H, 20 H), 4.17 (q, 2 H, OCH_2CH_3), 3.95–4.51 (m, 2 H, 2 CHOH).

Cleavage of 2-(Benzamidomethyl)tetrahydrofuran (77). To a cold (0 °C) stirred solution of 2-(benzamidomethyl)tetrahydrofuran (**77**) (205 mg, 1 mmol) in dry methylene chloride (4 mL) and triethylamine (0.16 mL, 1.15 mmol) was added dropwise a solution of dimethylboron bromide (1.56 M, 1.92 mL) in methylene chloride. The ice bath was then removed and the solution stirred 18 h at 25 °C. The solution was poured over a stirred solution of sodium bicarbonate and extracted with ether. The organic layer was washed with brine (2×), dried over sodium sulfate, filtered, and evaporated to dryness. The white solid residue was triturated in ether, filtered, and air-dried, giving 250 mg (87%) of the pure bromo alcohol **78**: mp 77–79 °C; IR (KBr) 3340 (OH, NH), 1640 cm^{-1} (C=O); ^{1}H NMR ($CDCl_3$) δ 1.57–1.79 (m, 2 H, CH_2), 1.92–2.18 (m, 2 H, CH_2), 3.00 (d, 1 H, OH), 3.38–3.46 (m, 1 H, CHNH), 3.49 (t, 2 H, CH_2Br), 3.64–3.74 (m, 1 H, CHNH), 3.83–3.95 (m, 1 H, CHOH), 6.66 (s, 1 H, NH), 7.42–7.82 (m, 5 H, Ar). Anal. Calcd for $C_{12}H_{16}BrNO_2$: C, 50.36; H, 5.64; Br, 27.92; N, 4.89. Found: C, 50.10; H, 5.69; Br, 28.07; N, 4.84.

Acknowledgment. We extend our appreciation for helpful discussions in the preparation of this manuscript with Dr. H. E. Morton and Dr. J. G. Atkinson and to Dr. M. A. Bernstein for his collaboration in the obtention of NMR data.

Supplementary Material Available: Spectral data of final products obtained by cleavage of unsymmetrical tetrahydrofuran derivatives (5 pages). Ordering information is given on any current masthead page.

Quassinoid Synthesis. 2. Preparation of a Tetracyclic Intermediate Having the Bruceantin Tetrahydrofuran Ring

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Received August 6, 1986

A synthetic approach to the quassinoid compound bruceantin is described. Tricyclic acid **5**, prepared from 2-(methoxycarbonyl)cyclohexanone in one step by the method of Fuchs, is converted into ketal lactone **6** and thence into diol **7**. The primary hydroxyl may be selectively protected to give any of several derivatives, including the tetrahydropyranyl derivative **10**. Allylic oxidation of this substance provides enone **13**, which is dehydrated by treatment with 4-(dimethylamino)pyridine in refluxing acetic anhydride to obtain **16**. Lithium/ammonia reduction of **16** yields saturated ketone **23**, which is carboxylated by the Stiles procedure to obtain the enolic β-keto ester **26**. This material is dehydrogenated to **28** by a novel procedure wherein the enol is heated with thionyl chloride and collidine in refluxing carbon tetrachloride. It is proposed that the dehydrogenation occurs by sulfenylation on carbon, followed by pyrolytic elimination of the resulting sulfenyl chloride (Scheme III). The elements of the eventual tetrahydropyranone ring are introduced at this stage by reaction of **28** with silyl ketene acetal **29** at high pressure. The product, enol silane **31**, is deprotected by treatment with pyridinium *p*-toluenesulfonate in warm ethanol to obtain **39**. Bromocyclization of this material upon treatment with *N*-bromosuccinimide in tetrahydrofuran affords bromo ether **40**, which rearranges to tetrahydrofuran **41** upon being heated at reflux in *N*,*N*-dimethylformamide solution. Deprotection of the latter material provides the β-keto ester **42**, a viable intermediate for a bruceantin synthesis.

The quassinoids, a group of related diterpenoids found in plants of the family *Simaroubacea*, possess a wide spectrum of biological activity.[1] One quassinoid that has elicited considerable medicinal[1] and synthetic[2] interest is

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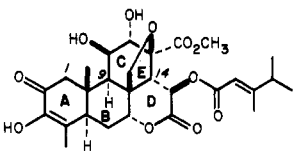
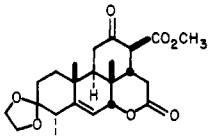
bruceantin (1).

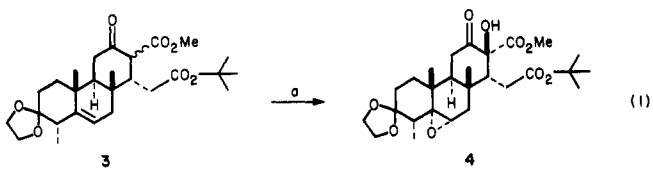


1



2

Our previously published approach to the synthesis of bruceantin was successful in producing the tetracyclic quassinoid precursor **2**, containing the ABCD ring skeleton of 1.[1n] This approach was not successful in forming the tetrahydrofuran E ring. When **4**, obtained from the *m*-chloroperoxybenzoic acid oxidation of β-keto ester **3** (eq 1), is subjected to Barton–Kalvoda reaction conditions,[3] only products resulting from the cleavage of the α-hydroxy carbonyl moiety of **3** are observed.



(1)

a. m-$ClC_6H_4CO_3H$, CH_2Cl_2

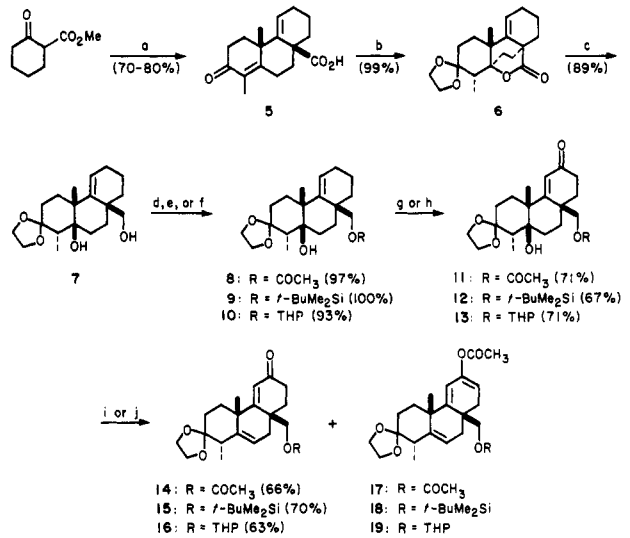
In this paper we report a new approach to **1** that culminates in the synthesis of the tetracyclic ABCE ring intermediate **42**. The choice of a starting material already bearing functionality at what will become the C-8 substituent circumvents difficulties we encountered in our previous attempted remote functionalization. An appropriate protecting group for the functionality at this position is critical to the success of this approach.

The synthesis begins with the known acid **5** (Scheme I), previously prepared by Watt in two steps from 2-carbethoxycyclohexanone.[4] Following the report of a one-step bis-annulation by Fuchs,[1e] we found that **5** is more conveniently prepared by treating 2-carbomethoxycyclohexanone with 2.5 equiv of 1-chloro-2-pentanone in a refluxing solution of sodium methoxide in methanol. This modification allows the production of **5** in one step from commercially available starting materials in 70–80% yield. The known ketal lactone **6** is obtained in nearly quantitative yield by treating acid **5** under standard ketalization conditions. The structure of **6** has been unequivocally established by Watt. Lithium aluminum hydride reduction of **6** affords the crystalline diol **7** in 85% yield.

We initially chose to protect the C-8 hydroxymethyl group of diol **7** as the corresponding acetate. Treatment of **7** with acetic anhydride in pyridine at room temperature affords the monoacetate **8** in nearly quantitative yield. Allylic oxidation of the acetate **8** with Collin's reagent[5] affords the enone **11** (71%).

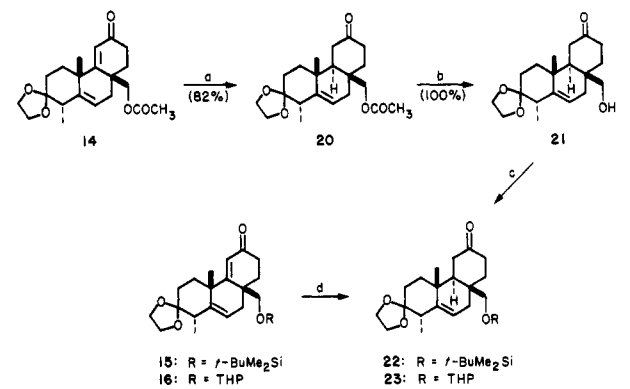
In analogy with our previous approach, our synthetic strategy required introduction of a double bond between positions 5 and 6 of the B ring for the eventual elaboration of the lactone D ring. This requires a formal anti elimination of water from tertiary alcohol **11** to give dienone **14**. The discovery of reaction conditions that would accomplish this transformation followed the observation of

Scheme I[a]



[a] (a) $ClCH_2CH_2COCH_2CH_3$, NaOMe, MeOH, reflux; (b) $(CH_2OH)_2$, p-TsOH, benzene, reflux; (c) $LiAlH_4$, THF, reflux; (d) Ac_2O, C_5H_5N; (e) t-$BuMe_2Si$-Im, CH_2Cl_2; (f) DHP, PPTS, CH_2Cl_2; (g) $CrO_3{\cdot}(C_5H_5N)_2$, CH_2Cl_2; (h) CrO_3·DMP, CH_2Cl_2, 0 °C; (i) DMAP, Ac_2O, reflux; (j) DMAP, C_5H_5N, Ac_2O, reflux.

Scheme II[a]



[a] (a) H_2, Pd/C, EtOH; (b) $Ba(OH)_2$, MeOH; (c) t-$BuMe_2Si$-Im, CH_2Cl_2 (**22**, 80%); (d) Li, NH_3, t-BuOH (**22**, 90%; **23**, 89%).

(1) Polonsky, J. In *Progress in the Chemistry of Organic Natural Products*; Herz, W., Grisbach, H., Kirby, G. W., Eds.; Springer-Verlag: Berlin, 1973; Vol. 30, p 102.

(2) (a) Kupchan, S. M.; Britton, W. R.; Lacadie, J. A.; Ziegler, M. F. *J. Org. Chem.* **1975**, *40*, 648. (b) Kupchan, S. M.; Britton, W. R.; Ziegler, M. F.; Sigel, C. W. *J. Org. Chem.* **1973**, *38*, 178. (c) Suryawanshi, S. N.; Fuchs, P. L. *J. Org. Chem.* **1986**, *51*, 902. (d) Suryawanshi, S. N.; Fuchs, P. L. *Tetrahedron Lett.* **1984**, *25*, 27. (e) Pariza, R. J.; Fuchs, P. L. *J. Org. Chem.* **1983**, *48*, 2306. (f) Dailey; O. D.; Fuchs, P. L. *J. Org. Chem.* **1980**, *45*, 216. (g) Batt, D. G.; Takamura, N.; Ganem, B. *J. Am. Chem. Soc.* **1984**, *106*, 3353. (h) Voyle, M.; Dunlap, N. K.; Watt, D. S. *J. Org. Chem.* **1983**, *48*, 3242. (i) Voyle, M.; Kyler, K. S.; Arseniyadas, S.; Dunlap, N. K.; Watt, D. S. *J. Org. Chem.* **1983**, *48*, 470. (j) Shishido, K.; Saitoh, T.; Fukumoto, K.; Kametani, T. *J. Chem. Soc., Perkin Trans. 1* **1985**, 2139. (k) Ziegler, F. E.; Klein, S. I.; Pati, U. K.; Wang, T.-F. *J. Am. Chem. Soc.* **1985**, *107*, 2730. (l) Kraus, G. A.; Taschner, M.; Shimagaki, M. *J. Org. Chem.* **1982**, *47*, 4271. (m) Kraus, G. A.; Taschner, M. *J. Org. Chem.* **1980**, *45*, 1175. (n) Heathcock, C. H.; Mahaim, C.; Schlecht, M. F.; Utawanit, T. *J. Org. Chem.* **1984**, *49*, 3264.

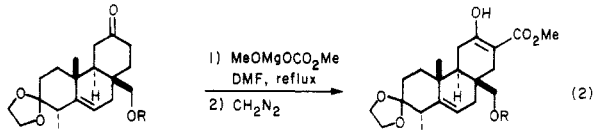
(3) Kalvoda, J.; Heusler, K. *Synthesis* **1971**, 501.

(4) (a) Snitman, D. L.; Watt, D. S. *Synth. Commun.* **1978**, *8*, 187. (b) Snitman, D. L.; Himmelsbach, R. J.; Watt, D. S. *J. Org. Chem.* **1978**, *43*, 4758.

(5) (a) Collins, J. C.; Hess, W. W.; Frank, F. J. *Tetrahedron Lett.* **1968**, 3363. (b) Dauben, W. G.; Lorber, M.; Fullerton, D. S. *J. Org. Chem.* **1969**, *34*, 3587.

a small amount of 5,6-dehydro side product in the acylation of diol **7** under more vigorous conditions than those reported above. When **11** is treated with 1.2 equiv of 4-(dimethylamino)pyridine (DMAP) in refluxing acetic anhydride, dienone **14** is obtained in 66% yield after chromatography. The only observed side product in this reaction is the C-ring enol acetate **17**.

Catalytic hydrogenation of enone **14** affords the saturated ketone **20** in 82% yield (Scheme II). The trans geometry of the BC ring juncture of **20** was tentatively assigned on the basis of ^{1}H NMR decoupling and nuclear Overhauser enhancement (NOE) experiments. The validity of this assignment is confirmed by correlation to a material of known relative stereochemistry (vide infra). As the acetate group later proved to be unacceptable (see eq 2, vide infra), it was removed at this point. Hydrolysis of



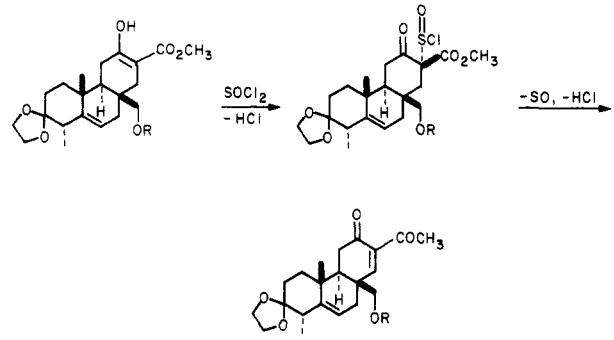
20: R = $COCH_3$
22: R = *t*-$BuMe_2Si$
23: R = THP

24: R = $COCH_3$ (0%)
25: R = *t*-$BuMe_2Si$ (95%)
26: R = THP (85%)

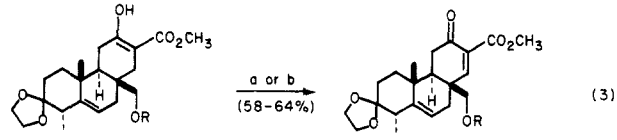
acetate **20** with barium hydroxide in methanol gives alcohol **21** in quantitative yield. The hydroxyl group of **21** is reprotected as the *tert*-butyldimethylsilyl (TBDMS) ether by treatment with *N*-(*tert*-butyldimethylsilyl)imidazole to afford silyl ether **22** in 80% yield. This awkward interconversion of acetate to silyl protecting group is avoided by installing the TBDMS protecting group at the stage of diol **7**. Treatment of **7** with *N*-(*tert*-butyldimethylsilyl)-imidazole affords ether **9** in quantitative yield (Scheme I). Allylic oxidation of **9** with Collin's reagent proceeds in 67% yield to give enone **12**, which undergoes elimination under the same conditions reported for acetate **11** to afford dienone **15** in 70% yield. In the latter case, the variable (5–10%) amount of enol acetate **18** produced can be converted to dienone **15** by hydrolysis (potassium carbonate/methanol). Reduction of silyl dienone **15** with lithium in ammonia affords saturated ketone **22**, identical in all respects with material obtained from acetate **20** (Scheme II). Reaction of diol **7** with dihydropyran and catalytic pyridinium *p*-toluenesulfonate affords the THP ether **10** in 93% yield (Scheme I). Allylic oxidation of **10** is carried out with a 3,5-dimethylpyrazole complex of chromium trioxide, generated in situ,[6] to give enone **13** in 71% yield. Elimination of the tertiary hydroxyl group of **13** is accomplished by treatment with DMAP and pyridine in refluxing acetic anhydride to give dienone **16** in 63% yield, along with 6% of enol acetate **19**. Dienone **16** undergoes lithium in ammonia reduction in 89% yield to afford ketone **23**.

We next required introduction of a carbomethoxy group at C-13. Treatment of acetate **20** with Stiles' reagent (methoxymagnesium methyl carbonate)[7] followed by treatment with diazomethane produces none of the desired β-keto ester **24**. Apparently, the acetate group of **20** is not stable to the basic reaction conditions of the Stiles' reaction and the free hydroxy group on the C-8 substituent interferes with the carboxylation. However, when silyl ether protected ketone **22** or THF protected ketone **23** is treated with Stiles' reagent followed by diazomethane the β-keto esters **25** and **26** are obtained in 95% and 85% yield, respectively, after chromatography (eq 2). The ratio of keto to enol forms of β-keto ester **25** produced is variable; equilibration between the tautomers on silica gel results in a predominance of the enol form.

Scheme III



With **25** and **26** in hand, we readied the C ring for eventual introduction at C-14 of the elements of the D ring. Treatment of **25** by the method of Reich for the dehydrogenation of ketones[8] affords the enone **27** in 58% yield (eq 3). The modest yield and difficulties we encountered



25: R = *t*-$BuMe_2Si$
26: R = THP

27: R = *t*-$BuMe_2Si$
28: R = THP

a. i. NaH, PhSeCl; ii. H_2O_2.
b. $SOCl_2$, *s*-collidine, CCl_4, reflux.

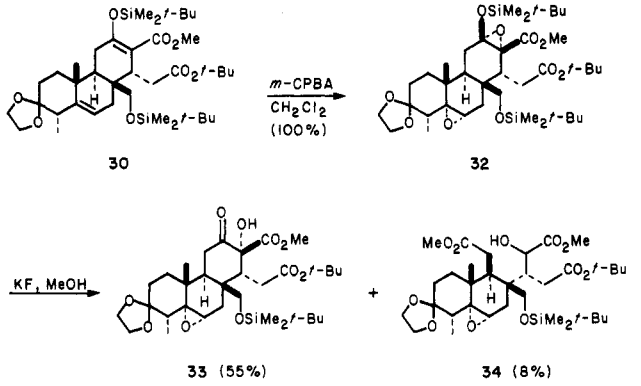
when scaling up this reaction led us to search for another method for accomplishing this transformation. Previous experience in our laboratories has shown that β-keto esters undergo dehydrogenation when treated with thionyl chloride. Thus, when **25** is treated with thionyl chloride and pyridine in refluxing carbon tetrachloride, enone **27** is obtained in 52% yield after chromatography. Optimization of this reaction with β-keto ester **26** indicates that *syn*-collidine serves better as a base than pyridine. Treatment of **26** under these modified conditions affords enone **28** in 64% yield.

This thionyl chloride induced dehydrogenation has precedence in the previously reported "anomalous" thionyl chloride oxidation of carboxylic acids[9] and the phenylsulfinyl chloride dehydrogenation of thiolactams and thio esters.[10] We propose that this reaction proceeds by enolization, sulfinylation at carbon, and elimination of HCl and sulfur monoxide (Scheme III).

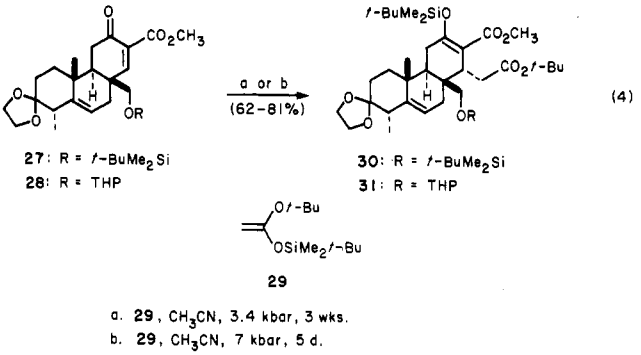
With enone **27** in hand we were ready to introduce at C-14 the acetic acid residue necessary for future elaboration of the D-ring lactone. We had found previously on a similar system that this goal could be accomplished in a stereoselective manner by the high pressure Michael addition of ketene acetal **29**.[11] When enone **27** and ketene acetal **29** in acetonitrile are pressurized to 3.2 kbar for 3 weeks, the Michael adduct **30** is isolated in 62% yield along with 16% of recovered **27** (eq 4).[12] Only one adduct is

(6) (a) Corey, E. J.; Fleet, G. W. J. *Tetrahedron Lett.* **1973**, 4499. (b) Salmond, W. G.; Barta, M. A.; Havens, J. L. *J. Org. Chem.* **1978**, *43*, 2057.
(7) Finkbeiner, H. L.; Stiles, M. *J. Am. Chem. Soc.* **1963**, *85*, 616.
(8) Reich, H. J.; Renga, J. M.; Reich, I. L. *J. Am. Chem. Soc.* **1975**, *97*, 5434.
(9) (a) Krubsack, A. J.; Higa, A. *Tetrahedron Lett.* **1968**, 5149. (b) Cushman, M.; Cheng, L. *J. Org. Chem.* **1978**, *43*, 3781.
(10) Magnus, P.; Pappalardo, P. A. *J. Am. Chem. Soc.* **1986**, *108*, 212.
(11) Bunce, R. A.; Schlecht, M. F.; Dauben, W. G.; Heathcock, C. H. *Tetrahedron Lett.* **1983**, *24*, 4943.

Scheme IV



obtained; the C-14 α stereochemistry is assigned on the basis of steric and stereoelectronic arguments and analogy to our previous work.



(4)

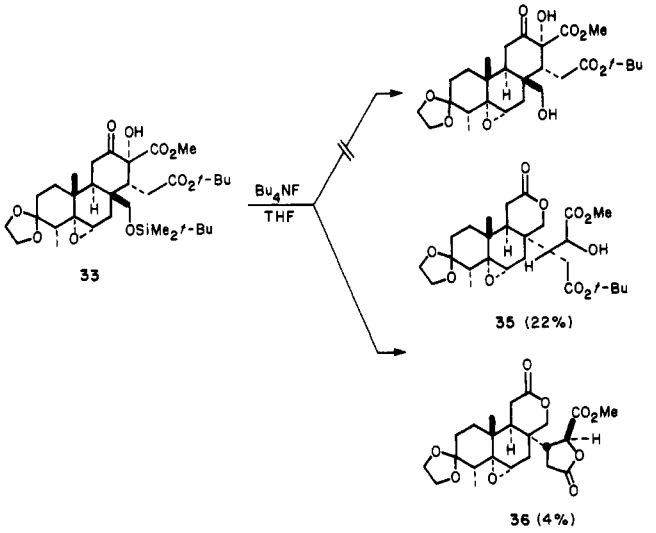
Michael adduct **30** is epoxidized with 2 equiv of *meta*-chloroperoxybenzoic acid to afford diepoxide **32** in quantitative yield (Scheme IV). Attack of the peracid reagent at the two double bonds in **30** occurs at about the same rate; use of only 1 equiv of peracid results in a mixture of starting adduct **30**, two different monoepoxides, and the diepoxide **32**. The stereochemistry of the C ring epoxide of **32** was determined to be α as shown (vide infra), while the B-ring epoxide was assigned the α stereochemistry based on the ^{1}H NMR chemical shift of the C-4 methyl group, which resonates at 0.7 ppm.

Treatment of the diepoxide **32** with potassium fluoride in methanol results in a mixture of products from which the α-hydroxy ketone **33** is isolated in 55% yield. The bis(methyl ester) **34**, isolated in 8% yield, is a side product in this reaction. Compound **34** presumably arises from deprotonation of the methanol solvent followed by attack at the C-12 carbonyl.

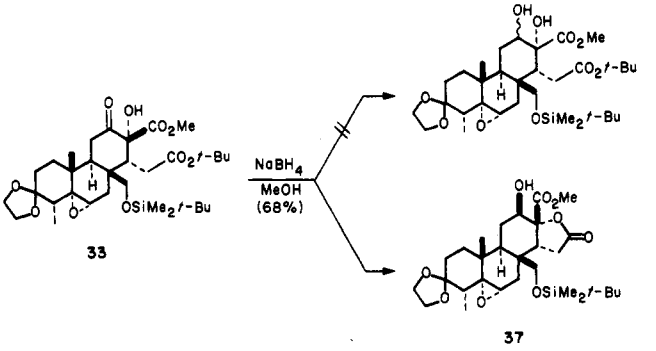
The facility with which the C ring carbonyl in **33** undergoes nucleophilic attack followed by C ring cleavage became more evident as we attempted to cleave the TBDMS ether of **33**. Treatment of **33** with tetrabutylammonium fluoride results in a complex mixture of products. The δ-lactones **35** and **36** are isolated after chromatography in 22% and 4% yields, respectively (Scheme V). A variety of other conditions (potassium fluoride in methanol, hydrofluoric acid in acetonitrile, acetic acid in THF/water) also give complex product mixtures from which none of the desired alcohol can be isolated. Attempts to deprotect the C-8 hydroxymethyl TBDMS ether at the stage of Michael adduct **30**, enone **27**, and β-keto ester **25** also met with failure.

In order to avoid the C-ring cleavage, we attempted to reduce the offending C-12 carbonyl. Treatment of hydroxy

Scheme V

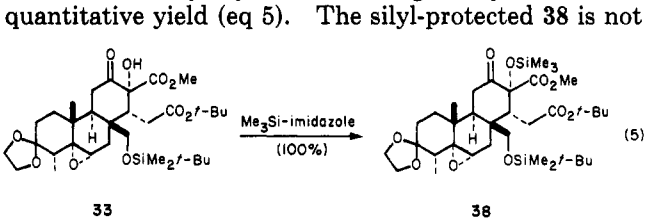


Scheme VI



ketone **33** with a variety of reducing agents gives mixtures of three or more products; however, when **33** is treated with sodium borohydride in methanol one major product **37** is formed in 68% yield (Scheme VI). The equatorial orientation of the C-12 hydroxyl group in **37** is assigned on the basis of ^{1}H NMR coupling constants. The ease of formation on the δ-lactone ring in **37** leads us to assign the α stereochemistry to the C-13 oxygen substituent. Thus the hydroxyl group in α-hydroxyl ketone **33** and the C ring epoxide in diepoxide **32** must also both have α stereochemistry.

In an attempt to circumvent δ-lactone formation of α-hydroxy ketone **33** during reduction, the hydroxyl group was protected as the trimethylsilyl ether by treating **33** with *N*-(trimethylsilyl)imidazole to give silyl ether **38** in quantitative yield (eq 5). The silyl-protected **38** is not

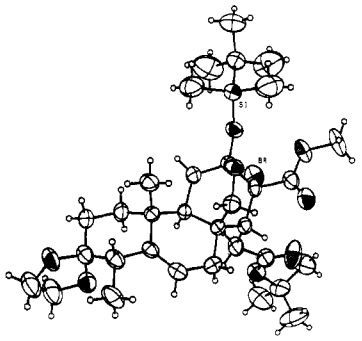


(5)

reduced as readily as **33**; the use of more vigorous conditions only results in complex mixtures of products.

Because of the difficulty in removing the TBDMS protecting group we turned our attention toward the THP-protected enone **28** (vide supra). Michael addition of ketene acetal **29** to enone **28** at 7 kbar gives adduct **31** in 81% yield after 5 days (eq 4). As in the case of TBDMS-protected enone **27** only one diastereomer is produced in the Michael addition and this isomer is assigned the α stereochemistry.

(12) We thank Prof. W. Pirkle, University of Illinois, for carrying out this reaction for us in his apparatus.



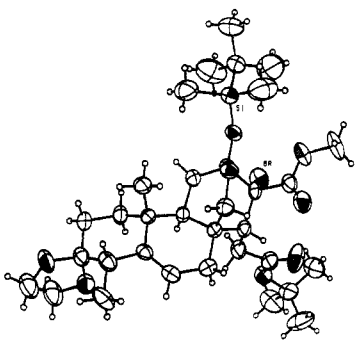
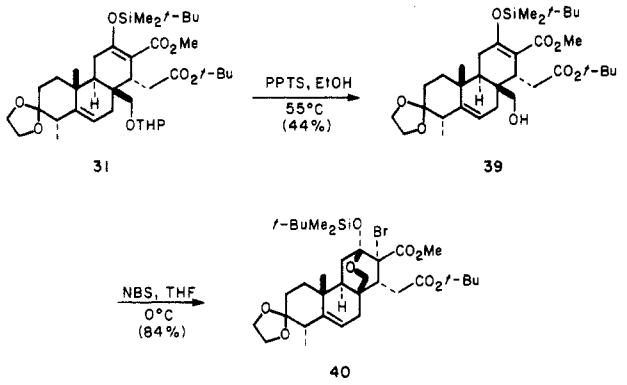
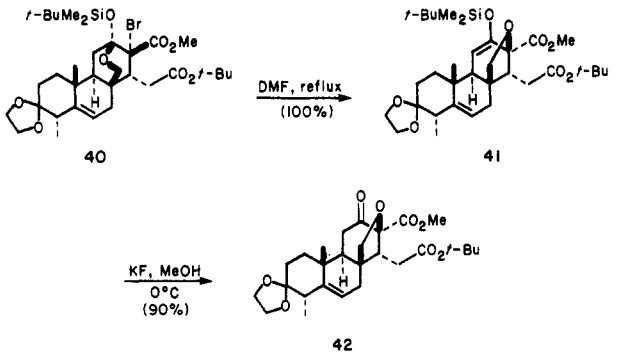


Figure 1. ORTEP stereoscopic projection of compound **40**.

Scheme VII



Scheme VIII



Removal of the THP acetal of **31** is accomplished, albeit in only modest yield, by treatment with pyridinium *p*-toluenesulfonate in ethanol at 55 °C for 3.5 h. The desired alcohol **39** is isolated from the product mixture in 44% yield along with 11% of recovered Michael adduct **31** and smaller amounts of material resulting from A-ring ketal hydrolysis (Scheme VII). Having discovered that electrophilic epoxidation of the C-ring silyl enol ether double bond of Michael adduct **30** occurs from the α face, we attempted to form the tetrahydrofuran E ring by displacement of a suitable leaving group at C-14.[13] Bromination of deprotected Michael adduct **39** with *N*-bromosuccinimide results in the formation of the tetrahydropyranyl ketal bromide **40** in 84% yield. No products resulting from B-ring double-bond bromination are observed. The stereostructure of bromide **40** was determined by single-crystal X-ray analysis, which revealed that the bromine is on the α face of the C-ring. The dihedral angle between the bromine and the C-13 bridging oxygen is 165°. Additionally, the trans B–C ring juncture and the α stereochemistry of the C-14 side chain and the C-4 methyl group are confirmed by this structure (Figure 1).[14]

Although initial attempts to force the ring contraction of bromide **40** under silver ion assisted ionization conditions failed, thermal ring contraction occurs when **40** is heated in refluxing DMF to give silyl enol ether **41** in quantitative yield (Scheme VIII). Compound **41** is not further purified due to its instability to silica gel but is desilylated by treatment with potassium fluoride in methanol to afford the ketone **42** in 90% yield.

Thus the tetracyclic ketone **42** is available in 3.6% overall yield from 2-carbomethoxycyclohexanone by the sequence: **5** → **6** → **7** → **10** → **13** → **16** → **23** → **26** → **28** → **31** → **39** → **40** → **41** → **42**.

We are in the process of continuing the synthesis of bruceantin from an intermediate such as **42** utilizing the methodology of our previous work for the elaboration of the lactone D ring.

Experimental Section

General. Unless otherwise noted, materials were obtained from commercial suppliers and used without further purification. Ether and tetrahydrofuran were distilled from sodium/benzophenone immediately prior to use. Methylene chloride, carbon tetrachloride, pyridine, and *N*,*N*-dimethylformamide were distilled from calcium hydride. Absolute ethanol was distilled from magnesium. Benzene was stored over 3-Å molecular sieves. Chromium trioxide was dried overnight at reduced pressure and stored over P_2O_5. Melting points are uncorrected. The high-pressure reactions were performed by sealing the reaction mixture in a length of Teflon tubing with metal pinch-caps and placing the tube within the piston cavity of a hydraulic oil press, at either 7 or 3.4 kbar, for varying lengths of time. Large-scale high-pressure reactions at 3.4 kbar were carried out by Professor William Pirkle at the University of Illinois. ^1H and ^{13}C NMR spectra were determined with superconducting FT spectrometers operating at 200, 250, 300, and 500 MHz. All NMR spectra were determined with $CDCl_3$ as the solvent. Chemical shifts are expressed in ppm downfield from internal tetramethylsilane. Significant ^1H NMR data are tabulated in order: multiplicity (s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet), number of protons, coupling constants in hertz. Flash chromatography refers to the method of Still, Kahn, and Mitra.[15] Preparative radial chromatography was performed with a Harrison Research Model 7924 chromatotron.

Keto Acid 5. A 2-L three-necked flask was flame-dried and equipped with a mechanical stirrer and a condenser. While the system was kept under dry nitrogen, methanol (1 L, dried by distillation from magnesium methoxide) was added and stirring was begun. Freshly cut sodium metal (46 g, 2 mol) was added slowly. After the sodium had completely reacted, 2-carbomethoxycyclohexanone (78 g, 0.5 mol) was added and the solution was

(13) Grieco, P. A.; Shaw, H. L.; Inanaga, J.; Kim, H.; Tuthill, P. A. *J. Chem. Soc., Chem. Commun.* **1984**, 1345.

(14) The atomic coordinates for this structure are available upon request from the Director of the Cambridge Crystallographic Data Centre, University Chemical Laboratory, Lensfield Road, Cambridge CB2 1EW, England. Any request should be accompanied by the full literature citation for this paper.

(15) Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923.

heated to gentle reflux. 1-Chloro-3-pentanone (134 g, 1.12 mol) was added dropwise over 14 h (syringe pump). Heating at reflux was continued for 2 h. The solvent was then removed under vacuum, and the residue was neutralized by the addition of 5% HCl. The organic layer was extracted into chloroform (3 × 500 mL). The combined organic solution was dried over $MgSO_4$, and the solvent was removed under reduced pressure to give a yellow oil (136 g, 100%). This oil was used without further purification for the next step. A sample of the oil was crystallized to give the tricyclic acid 1 as a white solid, mp 161 °C, which displays IR and ^1H NMR spectra identical with those reported by Watt.

Tricyclic Lactone 6. To a stirring solution of acid **5** (136 g, crude from the foregoing step) and *p*-toluenesulfonic acid (4 g) in benzene (1800 mL) was added ethylene glycol (150 mL). The mixture was heated at reflux under a Dean–Stark trap for 20 h. The benzene layer was washed with 2 N NaOH (80 mL), saturated $NaHCO_3$ (100 mL), and brine (2 × 100 mL). The benzene layer was dried ($MgSO_4$) and treated with activated charcoal (1 g). The organic mixture was filtered, and the filtrate was concentrated under reduced pressure to give a semisolid that was dried at 60 °C (0.5 torr) for 2 h. The solid was then recrystallized from ether to give the lactone **2** as white crystals (90 g, 70%), mp 166–167 °C, (lit. mp 146–150 °C): ^{13}C NMR δ 6.60, 18.19, 21.70, 22.42, 24.33, 27.35, 30.45, 30.77, 31.18, 40.76, 42.46, 42.83, 64.54, 65.46, 86.80, 110.02, 120.13, 144.06, 177.03.

Diol 7. A solution of 52.0 g (0.16 mmol) of lactone **12** in THF was added dropwise to a cooled (ice bath) slurry of 13.5 g (0.35 mol) of lithium aluminum hydride in 300 mL of THF. After the addition was complete, the ice bath was removed, and the mixture was heated at reflux for 5 h. The reaction was quenched by dropwise addition of freshly prepared saturated Na_2SO_4 solution. The precipitate was filtered and the solvent evaporated. Recrystallization of the residue from ether gave 44.9 g (89%) of diol **7** as white crystals, mp 140 °C: IR ($CHCl_3$) 3200–3650 cm^{-1}; ^1H NMR δ 0.99 (d, 3 H, J = 7), 1.17 (s, 3 H), 1.20–2.20 (m, 17 H), 3.56 (d, 1 H, J = 11), 3.70 (s, 1 H), 3.80–4.00 (m, 4 H), 5.71 (s, 1 H); mass spectrum (70 eV), m/z 322 (M^+), 304, 291. Anal. Calcd for $C_{19}H_{30}O_4$: C, 70.77; H, 9.38. Found: C, 70.81; H, 9.42.

Acetate 8. To a solution of 15 g (46.6 mmol) of diol **7** in 15 mL of pyridine was added 7 mL (0.1 mol) of acetic anhydride. The mixture was stirred for 75 min at room temperature, and the excess reagent and solvent were removed in vacuo at 50 °C. The solid residue was taken up in CH_2Cl_2 and the resulting solution was washed once each with 2 N HCl, 2 N NaOH, saturated $NaHCO_3$ solution, and brine. Drying ($MgSO_4$) and evaporation of the solvent furnished 16.5 g (97%) of acetate **8** pure enough for further use. An analytical sample, mp 111 °C, was obtained by recrystallization from ether: IR ($CHCl_3$) 3400–3600, 1720 cm^{-1}; ^1H NMR δ 1.00 (br d, 3 H, J = 7), 1.16 (br s, 3 H), 2.06 (s, 3 H), 1.2–2.2 (m, 16 H), 3.8–4.0 (m, 4 H), 4.00 (d, 1 H, J = 11), 4.80 (br s, 1 H), 5.65 (t, 1 H, J = 4). Anal. Calcd for $C_{21}H_{32}O_5$: C, 69.20; H, 8.85. Found: C, 69.08; H, 8.76.

Silyl Ether 9. To a suspension 18.44 g (57.3 mmol) of diol **7** in 30 mL of CH_2Cl_2 was added 30 mL of a 0.9 M solution of *N*-(*tert*-butyldimethylsilyl)imidazole (TBDMSI) in CH_2Cl_2. The mixture was stirred for 2 h. As TLC monitoring showed that the conversion was not complete, another 20 mL (18 mmol) of TBDMSI solution was added. After another 30 min, the mixture was taken up in more CH_2Cl_2 and washed twice with 2 N HCl, saturated $NaHCO_3$, and brine. Drying ($MgSO_4$) and evaporation of the solvent gave 26 g of crude silyl ether **9** (quantitative), which was pure enough to be used in the following oxidation step. An analytical sample was obtained by chromatography (SiO_2, 0% to 15% ether in hexane) as a colorless viscous oil: IR ($CHCl_3$) 3300–3600 cm^{-1}; ^1H NMR δ 0.03 (s, 3 H), 0.05 (s, 3 H), 0.88 (s, 9 H), 1.02 (br s, 3 H), 1.13 (br s, 3 H), 0.95–2.2 (m, 16 H), 3.37 (br d, 1 H, J = 9), 3.85–4.0 (m, 5 H), 5.59 (t, 1 H, J = 3.5). Anal. Calcd for $C_{25}H_{44}O_4Si$: C, 68.76; H, 10.16. Found: C, 68.49; H, 10.19.

The TBDMSI solution used in the foregoing procedure was prepared by dissolving 16.5 g (109 mmol) of *tert*-butyldimethylsilyl chloride in 55 mL of CH_2Cl_2 and adding a solution of 15.4 g (226 mmol) of imidazole in 55 mL of CH_2Cl_2. The mixture was stirred for 1 h at room temperature and then filtered to remove the precipitate that was washed with 11 mL of CH_2Cl_2 to give a 0.9 M solution of the reagent.

Acetal 10. To a slurry of 20 g (62 mmol) of diol **7** in 250 mL of CH_2Cl_2 was added 27.5 g (0.33 mol) of dihydropyran and 376 mg of pyridinium *p*-toluenesulfonate. The mixture was stirred under nitrogen at room temperature for 2.5 h. An additional 300 mL of CH_2Cl_2 was added, and the solution was washed with saturated $NaHCO_3$ (2 × 100 mL) and brine (1 × 100 mL) and dried over $MgSO_4$. The solvent was evaporated, and the resulting semisolid mass was recrystallized from ether to give 11.30 g (45%) of the desired acetal, predominantly one diastereomer, as a white powder, mp 124–125 °C. Flash chromatography of the mother liquor afforded 12.15 g (48%) of acetal enriched in the other diastereomer. The two fractions (93% overall yield) were combined for the following step: IR ($CHCl_3$) 3450 cm^{-1}; ^1H NMR (approximately a 1:1 mixture of diastereomers due to the THP acetal) δ 0.95 (d, 3 H, J = 7), 1.15 (m, 3 H), 1.30–2.20 (m, 21 H), 3.07 (d, $^1/_2$ H, J = 9), 3.40–3.60 (m, 2 H), 3.70–3.98 (m, 5 H), 4.03 (d, $^1/_2$ H, J = 9), 4.57 (m, 1 H), 5.59 (m, 1 H); mass spectrum (70 eV), m/z 406 (M^+), 388, 358. Anal. Calcd for $C_{24}H_{38}O_5$: C, 70.90; H, 9.42. Found: C, 70.79; H, 9.44.

Enone 11. A solution of 10.9 g (30 mmol) of acetate **8** in 110 mL of CH_2Cl_2 was added to a well-stirred solution of 38 g (0.15 mol) of CrO_3·2Py complex dissolved in 500 mL of CH_2Cl_2. After 1 h an additional batch of 19 g (74 mmol) of the complex dissolved in 250 mL of CH_2Cl_2 was added. After 2 h a final batch of 8 g of the complex in 125 mL of CH_2Cl_2 was added. After 3 h (TLC monitoring advisable) the reaction mixture was decanted from the precipitate. The tarry solid in the flask was rinsed twice with CH_2Cl_2, and the combined organic solution was washed twice with 10% $KHCO_3$, 2 N HCl, and once with brine. After drying ($MgSO_4$), the solvent was evaporated and the crude product purified by flash chromatography (50 g SiO_2, 30% ethyl acetate in hexane) to yield 8.0 g (71%) of **11**, which was judged to be pure by ^1H NMR spectroscopy. An analytical sample, mp 119–120 °C, was obtained by recrystallization from ether: IR ($CHCl_3$) 3300–3600, 1725, 1660 cm^{-1}; ^1H NMR δ 0.98 (d, 3 H, J = 7), 1.27 (br s, 3 H), 2.05 (s, 3 H), 1.40–2.25 (m, 12 H), 2.35 (br dd, 1 H, J = 19, 6), 2.60 (ddd, 1 H, J = 19, 14, 5), 3.80–4.00 (m, 4 H), 4.21 (d, 1 H, J = 12), 4.74 (d, 1 H, J = 12), 6.13 (s, 1 H). Anal. Calcd for $C_{21}H_{30}O_6$: C, 66.65; H, 7.99. Found: C, 66.70; H, 8.04.

The CrO_3·2Py complex was prepared according to the procedure of Dauben[5b] and dried overnight at 0.2 torr. It could be stored in a tightly capped flask at room temperature for several months without loss of activity.

Enone 12 was prepared in the same way as enone **11** in 67% yield (purification by flash chromatography, 0% to 40% ethyl acetate in hexane). Crystallization from ether/hexane furnished white crystals, mp 145–146 °C: IR ($CHCl_3$) 3300–3600, 1655 cm^{-1}; ^1H NMR δ −0.02 (s, 3 H), 0.02 (s, 3 H), 0.88 (s, 9 H), 1.00 (d, 3 H, J = 7), 1.24 (br s, 3 H), 1.6–2.2 (m, 12 H), 2.33 (br dd, 1 H, J = 13, 6), 2.55 (ddd, 1 H, J = 19, 13, 5), 3.54 (d, 1 H, J = 9), 3.80–4.05 (m, 5 H), 6.09 (s, 1 H). Anal. Calcd for $C_{25}H_{42}O_5Si$: C, 66.62; H, 9.39. Found: C, 66.59; H, 9.46.

Enone 13. Into a three-necked, 1-L round-bottomed flask fitted with an inlet for nitrogen, a mechanical stirrer and a stopper were placed 22 g (0.22 mol) of CrO_3 and 230 mL of CH_2Cl_2. The mixture was cooled for 30 min in a dry ice/acetone bath and 3,5-dimethylpyrazole (21 g, 0.22 mol) was added in one portion with stirring. The resulting deep red solution was stirred for an additional 30 min, and a solution of acetal **10** in 50 mL of CH_2Cl_2 was added. The reaction mixture was stirred for 35 min, and 90 mL of ice-cold 5 N NaOH was added. After being stirred at 0 °C for 30 min, the reaction mixture was mixed with Celite and filtered through a glass wool plug. The resulting mixture was carefully washed with water (100 mL), brine (100 mL), water (50 mL), 2 N HCl (2 × 100 mL), and brine (100 mL). The organics were passed through a plug of silica gel (100 g), which was eluted with 1:4 ethyl acetate/hexanes to give 6.57 g (71%) of enone **13** as a slightly yellow foam: IR ($CHCl_3$) 3450, 1660 cm^{-1}; ^1H NMR (approximately a 1:1 mixture of diastereomers due to THP acetal) δ 0.97 (d, 3 H, J = 7), 1.24 (m, 3 H), 1.20–2.20 (m, 18 H), 2.34 (m, 1 H), 2.54 (m, 1 H), 3.41 (d, $^1/_2$ H, J = 9), 3.40–3.60 (m, 2 H), 3.66 (d, $^1/_2$ H, J = 9), 3.65–4.09 (m, 5 H), 4.59 (m, 1 H), 6.06 (s, 1 H). Anal. Calcd for $C_{24}H_{36}O_6$: C, 68.54; H, 8.63. Found: C, 68.29; H, 8.64.

Dienone 14 and Enol Acetate 17. To a solution of 5.9 g (15.6 mmol) of enone **11** in 74 mL of acetic anhydride was added 2.09

g (17.1 mmol) of DMAP. The mixture was heated at reflux for 90 min. The acetic anhydride and acetic acid were removed by distillation in vacuo. The dark brown residue was taken up in CH_2Cl_2. This solution was washed twice with saturated aqueous $NaHCO_3$ and 2 N HCl, once again with saturated aqueous $NaHCO_3$, and finally with brine. After drying ($MgSO_4$) and evaporation of the solvent, the crude mixture was filtered through a plug of silica gel. Subsequent flash chromatography (110 g of SiO_2, 20% to 50% ether in hexane) gave 0.64 g (10%) of enol acetate **17** as the first fraction (oil) and 3.7 g of dienone acetate **14** (66%) as the second fraction. An analytical sample of compound **14**, mp 144–145 °C, was obtained by crystallization from ether/hexane.

Dienone 14: IR ($CHCl_3$) 1745, 1675 cm^{-1}; ^1H NMR δ 1.03 (d, 3 H, J = 7), 1.27 (s, 3 H), 2.07 (s, 3 H), 1.5–2.7 (m, 10 H), 2.73 (m, 1 H), 3.85–4.05 (m, 4 H), 4.13 (d, 1 H, J = 11), 4.21 (d, 1 H, J = 11), 5.47 (br d, 1 H, J = 6), 6.19 (s, 1 H). Anal. Calcd for $C_{21}H_{28}O_5$: C, 69.98; H, 7.83. Found: C, 70.03; H, 7.73.

Enol acetate 17: IR ($CHCl_3$) 1740 cm^{-1}; ^1H NMR δ 0.96 (d, 3 H, J = 7), 1.28 (s, 3 H), 2.03 (s, 3 H), 2.10 (s, 3 H), 1.5–2.5 (m, 8 H), 2.70 (m, 1 H), 3.8–4.0 (m, 4 H), 3.93 (d, 1 H, J = 10), 4.02 (d, 1 H, J = 10), 5.20 (ddd, 1 H, J = 6, 2, 1.5), 5.33 (dm, 1 H, J = 5), 5.73 (d, 1 H, J = 2).

Dienone 15 and Enol Acetate 18. To a solution of 20 g (44.4 mmol) of silyl ether **12** in 200 mL of acetic anhydride (freshly distilled over anhydrous NaOAc) was added 5.97 g (48.8 mmol) of DMAP. The mixture was heated at reflux for 80 min. The acetic acid/acetic anhydride was distilled off in vacuo (0.2 torr). The dark brown residue was taken up in CH_2Cl_2 and filtered over 100 g of flash silica and eluted with 20% ethyl acetate in hexanes. The filtrate was concentrated with a rotary evaporator to a thick oil which was freed of remaining acetic anhydride in vacuo with the help of a heat gun to obtain 20.4 g of yellow oil. Crystallization in several batches from hexanes yielded 11.4 g (59%) of pure dienone **15**, mp 89 °C. Chromatography of the mother liquor on 140 g of flash silica (0%, 10%, and 20% ethyl acetate in petroleum ether) gave 1.09 g (5%) of enol acetate **18** as first fraction. The second fraction yielded another 1.92 g of **15** after crystallization from hexanes (total yield of **15**, 70%).

Dienone 15: IR ($CHCl_3$) 1660 cm^{-1}; ^1H NMR δ −0.02 (s, 3 H), 0.00 (s, 3 H), 0.84 (s, 9 H), 0.99 (d, 3 H, J = 7), 1.22 (s, 3 H), 1.4–2.6 (m, 10), 2.70 (m, 1 H), 3.52 (d, 1 H, J = 10), 3.61 (d, 1 H, J = 10), 3.8–4.0 (m, 4 H), 5.43 (dm, 1 H, J = 6), 6.10 (s, 1 H). Anal. Calcd for $C_{25}H_{40}O_4Si$: C, 69.40; H, 9.32. Found: C, 69.11; H, 9.50.

Enol acetate 18: IR (film) 1760 cm^{-1}; ^1H NMR δ −0.01 (s, 3 H), 0.00 (s, 3 H), 0.88 (s, 3 H), 1.00 (d, 3 H, J = 7), 1.25 (s, 3 H), 1.55–1.85 (m, 5 H), 1.99 (dd, 1 H, J = 17, 2), 2.13 (s, 3 H), 2.50–2.77 (m, 2 H), 2.64 (dd, 1 H, J = 17, 7), 3.38 (d, 1 H, J = 10), 3.47 (d, 1 H, J = 10), 3.8–4.0 (m, 4 H), 5.16 (ddd, 1 H, J = 7, 2, 1.5), 5.38 (dm, 1 H, J = 6), 5.66 (d, 1 H, J = 1.5). Anal. Calcd for $C_{27}H_{42}O_5Si$: C, 68.31; H, 8.92. Found: C, 68.54; H, 9.18.

Dienone 16 and Enol Acetate 19. Into a 250-mL, round-bottomed flask were placed 23 mL of pyridine, 23 mL of acetic anhydride, 6.43 g (15.3 mmol) of enone **13**, and 765 mg (7 mmol) of DMAP. The mixture was heated at reflux for 2.5 h and the resulting dark-colored mixture was allowed to cool, diluted with 250 mL of ether, and washed with water (3 × 75 mL). The organic layer was passed through a plug of silica gel (10 g) and eluted with 200 mL of ether. The organics were washed with 10% HCl (3 × 50 mL) and brine (70 mL) and dried over $MgSO_4$. Evaporation of solvent gave a thick brown oil that was further purified by flash chromatography (180 g of silica gel; 0% to 30% ethyl acetate in hexanes) to afford 3.85 g (63%) of dienone **16** as a slightly yellow oil and 0.42 g (6%) of enol acetate **19**.

Dienone 16: IR ($CHCl_3$) 1690 cm^{-1}; ^1H NMR (approximately a 1:1 mixture of diastereomers due to THP acetal) δ 1.01 (m, 3 H), 1.26 (s, $^3/_2$ H), 1.29 (s, $^3/_2$ H), 1.45–2.20 (m, 14 H), 2.25–2.45 (m, 2 H), 2.65–2.80 (m, 1 H), 3.39 (d, $^1/_2$ H, J = 9), 3.43 (d, $^1/_2$ H, J = 9), 3.45–3.56 (m, 2 H), 3.70–4.05 (m, 5 H), 4.55 (m, 1 H), 5.47 (br d, 1 H, J = 6), 6.15 (s, $^1/_2$ H), 6.16 (s, $^1/_2$ H). Anal. Calcd for $C_{24}H_{34}O_5$: C, 71.61; H, 8.51. Found: C, 71.82; H, 8.77.

Enol acetate 19: IR (film) 1765, 1660 cm^{-1}; ^1H NMR (approximately a 1:1 mixture of diastereomers due to THP acetal) δ 0.90 (m, 3 H), 1.26 (s, 3 H), 1.44–1.91 (m, 11 H), 2.12 (s, 3 H), 2.00–2.20 (m, 1 H), 2.53–2.77 (m, 2 H), 3.16 (d, $^1/_2$ H, J = 9), 3.23 (d, $^1/_2$ H, J = 9), 3.46 (m, 1 H), 3.61 (d, $^1/_2$ H, J = 9), 3.65 (d, $^1/_2$ H, J = 9), 3.70–4.00 (m, 6 H), 4.52 (m, 1 H), 5.22 (m, 1 H), 5.37 (m, 1 H), 5.68 (m, 1 H).

Keto Acetate 20. A solution of 239 mg (0.66 mmol) of dienone acetate **14** in 15 mL of ethanol was charged with 24 mg of palladium on carbon. The mixture was stirred vigorously under an atmosphere of hydrogen for 50 min. The catalyst was removed by filtration and rinsed with ethanol, and the filtrate was evaporated. The crude product was purified by chromatography (12 g of SiO_2, 20% to 40% ether in hexane) to yield 195 mg (82%) of keto acetate **20**. Recrystallization from ether gave colorless crystals, mp 144 °C: IR ($CHCl_3$) 1740, 1720 cm^{-1}; ^1H NMR δ 1.00 (d, 3 H, J = 7), 1.03 (s, 3 H), 1.97 (s, 3 H), 1.55–2.45 (m, 13 H), 2.60 (m, 1 H), 3.8–4.0 (m, 4 H), 4.36 (d, 1 H, J = 10), 4.44 (dd, 1 H, J = 10, 1.5), 5.38 (ddd, 1 H, J = 6, 1.5, 1.5); ^{13}C NMR 9.88, 18.46, 20.94, 30.99, 34.82, 35.50, 35.67, 37.33, 37.57, 37.83, 39.02, 40.70, 52.33, 62.94, 65.00, 111.04, 116.76, 142.11, 171.14, 211.53. Anal. Calcd for $C_{21}H_{30}O_5$: C, 69.59; H, 8.34. Found: C, 69.33; H, 8.52.

Keto Alcohol 21. A solution of 2.63 g (7.26 mmol) of keto acetate **20** in 20 mL of methanol was mixed with a solution of 680 mg of barium hydroxide (4 mmol) in 20 mL of methanol. The mixture was stirred at room temperature for 12 min and quenched by addition of saturated NH_4Cl solution. The aqueous layer was extracted four times with CH_2Cl_2. The combined organic extracts were washed once with brine and dried over $MgSO_4$. Evaporation of the solvent gave 2.99 (100 %) of crude keto alcohol **21** pure enough for further use. An analytical sample of **21**, mp 144 °C, was obtained by crystallization from ether/hexane: IR ($CHCl_3$) 1710 cm^{-1}; ^1H NMR δ 1.00 (d, 3 H, J = 7), 1.01 (s, 3 H), 1.15–1.30 (m, 2 H), 1.55–1.90 (m, 6 H), 2.20–2.60 (m, 5 H), 2.70 (m, 1 H), 3.80 (dd, 1 H, J = 10, 3), 3.85–4.05 (m, 5 H), 5.39 (ddd, 1 H, J = 6, 1.5, 1.5). Anal. Calcd for $C_{19}H_{28}O_4$: C, 71.22; H, 8.81. Found: C, 71.20; H, 8.82.

Keto Ether 22. A. From Keto Alcohol 21. To 2.99 g (7.26 mmol) of keto alcohol **21** was added 14 mL of a 0.9 M *N*-(*tert*-butyldimethylsilyl)imidazole solution in CH_2Cl_2. The mixture was stirred for 12 h at room temperature and then taken up in more CH_2Cl_2. The organic layer was washed twice with 2 N HCl, once with saturated aqueous $NaHCO_3$, and once with brine and dried ($MgSO_4$). Flash chromatography, after removal of the solvent (60 g of SiO_2, 0% to 25% ether in petroleum ether), gave 2.51 g of keto ether **22** (80%).

B. From Dienone 15. To 500 mL of liquid ammonia, distilled from sodium, was added 0.161 g (23 mmol) of lithium, followed by a solution of 0.75 (8 mmol) of *t*-butyl alcohol in 10 mL of THF (dropwise). A solution of 3.1 g (7.17 mmol) of dienone **15** in 100 mL of THF was added dropwise over 10 min. As the blue color was discharged a further 45 mg (6.4 mmol) of lithium was added. After a total of 30 min, the reaction was quenched by the addition first of some methanol and then of saturated aqueous NH_4Cl. The ammonia was allowed to evaporate overnight. Water was added to the residue, and this mixture was extracted four times with CH_2Cl_2. The combined organics were washed with saturated aqueous NH_4Cl (2 × 50 mL), water (2 × 50 mL), and brine. Drying over $MgSO_4$ and evaporation of solvent gave a yellow oil, which was filtered through a plug of silica to yield 2.81 g (90%) of keto ether **22** as a slightly yellow oil which crystallized upon standing to give a solid, mp 92 °C: IR ($CHCl_3$) 1705 cm^{-1}; ^1H NMR δ 0.03 (s, 6 H), 0.88 (s, 9 H), 1.01 (s, 3 H), 1.01 (d, 3 H, J = 7), 1.10–1.60 (m, 5 H), 1.84 (dd, 1 H, J = 14, 4), 2.20–2.40 (m, 5 H), 2.55 (m, 1 H), 2.58 (dd, 1 H, J = 14, 14), 2.70 (m, 1 H), 3.63 (d, 1 H, J = 10), 3.86 (d, 1 H, J = 11), 3.8–4.0 (m, 4 H), 5.38 (d, 1 H, J = 6); ^{13}C NMR δ −5.64, −5.59, 10.00, 18.13, 18.51, 25.83 (3 C), 31.07, 35.59, 36.37, 36.46, 37.38, 37.61, 38.29, 39.31, 40.69, 52.14, 62.40, 64.99, 65.35, 111.18, 117.51, 141.94, 213.10. Anal. Calcd for $C_{25}H_{42}O_4Si$: C, 69.08; H, 9.74. Found: C, 68.76; H, 9.67.

Keto Acetal 23. To 500 mL of ammonia, distilled from sodium, was added 0.184 g (26.5 mmol) of lithium, followed by a solution of 0.590 g (5.7 mmol) of *t*-butyl alcohol in 5 mL of THF. A solution of 2.30 g (5.7 mmol) of dienone **16** in 60 mL of THF was added dropwise over 10 min. After 1 h the reaction was quenched, first with methanol and then with saturated aqueous NH_4Cl. The ammonia was allowed to evaporate overnight. The residue was taken up in water and extracted into CH_2Cl_2 (4 × 75 mL). The combined organics were washed with saturated NH_4Cl (2 × 75 mL) and brine (1 × 75 mL) and dried over $MgSO_4$. Evaporation

of solvent and filtration of solvent through a plug a silica gel afforded 2.05 g (89%) of ketone **23** as a clear oil: IR ($CHCl_3$) 1710 cm^{-1}; ^1H NMR (approximately a 1:1 mixture of diastereomers due to THP ether) δ 1.00 (m, 6 H), 1.20 (m, 2 H), 1.45–1.85 (m, 11 H), 2.00 (m, 1 H), 2.20–2.45 (m, 4 H), 2.45–2.75 (m, 3 H), 3.42 (d, $^1/_2$ H, J = 10), 3.53 (m, 1 H), 3.58 (d, $^1/_2$ H, J = 10), 3.75–4.0 (m, 5 $^1/_2$ H), 4.19 (d, $^1/_2$ H, J = 10), 5.38 (br d, 1 H, J = 6); ^{13}C NMR δ 9.88, 18.12, 18.50, 19.24, 25.28, 25.35, 30.58, 30.96, 35.13, 35.44, 35.59, 36.23, 36.48, 37.28, 37.35, 37.44, 37.52, 37.53, 38.14, 38.51, 39.17, 39.41, 40.61, 52.19, 52.41, 61.93, 62.43, 65.28, 66.89, 68.54, 98.82, 111.09, 111.12, 117.30, 117.38, 141.87, 212.74, 213.15. Anal. Calcd for $C_{24}H_{36}O_5$: C, 71.26; H, 8.97. Found: C, 71.39; H, 9.04.

Compound 25. A solution of 7.96 g (18.3 mmol) of keto ether **22** in 44 mL of 2 M Stiles reagent in DMF was heated to 100 °C for 12 h while a slow stream of nitrogen was bubbled through the mixture. The ice-cooled mixture was digested with 120 mL of 1 N HCl and extracted three times with ethyl acetate. The combined organic extracts were dried ($MgSO_4$) and concentrated to ca. a 100 mL volume. This solution was charged with 100 mL of a 0.27 M solution of diazomethane in ether. After 15 min, acetic acid was added to destroy the excess diazomethane and the solvent was removed in vacuo. Flash chromatography of the crude product (50 g SiO_2, 20% ethyl acetate in petroleum ether) gave 8.6 g (95%) of compound **25** as a slightly yellow oil: IR ($CHCl_3$) 1735, 1710, 1660, 1620 cm^{-1}; ^1H NMR δ −0.08 (s, 3 H), −0.05 (s, 3 H), 0.84 (s, 9 H), 1.02 (d, 3 H, J = 7), 1.06 (s, 3 H), 1.2–2.6 (m, 11 H), 2.74 (m, 1 H), 2.84 (d, 1 H, J = 16), 3.41 (br s, 2 H), 3.73 (s, 3 H), 3.85–4.05 (m, 4 H), 5.40 (dm, 1 H, J = 6); ^{13}C NMR δ −5.86, −5.65, 9.89, 18.10, 19.87, 25.70 (3 C), 27.26, 31.14, 33.27, 34.98, 36.02, 36.31, 38.38, 40.70, 46.84, 51.22, 62.14, 64.95, 65.38, 95.68, 111.26, 117.82, 141.48, 171.13, 172.78. All of the NMR data presented is for the enol form of **25**. Anal. Calcd for $C_{27}H_{44}O_6Si$: C, 65.82; H, 9.00. Found: C, 65.80; H, 9.12.

Compound 26 was prepared in the same manner as **25**. Flash chromatography (3 g, SiO_2, 7% ethyl acetate in petroleum ether) gave 0.121 g (85%) of a white foam: IR ($CHCl_3$) 1740, 1725, 1665, 1625 cm^{-1}; ^1H NMR (approximately a 1:1 mixture of diastereomers due to the THP ether) δ 1.02 (m, 3 H), 1.08 (s, 3 H), 1.32 (m, 2 H), 1.4–1.95 (m, 11 H), 2.20–2.60 (m, 3 H), 2.74 (m, 1 H), 2.85 (d, $^1/_2$ H, J = 16), 2.97 (d, $^1/_2$ H, J = 16), 3.19 (d, $^1/_2$ H, J = 6), 3.21 (d, $^1/_2$ H, J = 6), 3.45 (m, 1 H), 3.5–3.8 (m, 2 H), 3.75 (m, 3 H), 3.85–4.05 (m, 5 H), 4.42 (br t, $^1/_2$ H, J = 1), 4.55 (m, $^1/_2$ H), 5.4 (m, 1 H). Anal. Calcd for $C_{25}H_{38}O_7$: C, 66.64; H, 8.50. Found: C, 66.66; H, 8.55.

Enone 27. To a suspension of 527 mg of 50% NaH (11 mmol, washed twice with hexane) in 15 mL of THF was added a solution of 4.15 g (8.45 mmol) of compound **25** in 15 mL of THF. The mixture was stirred for 80 min at room temperature. A solution of 1.78 g (9.3 mmol) of phenylselenyl chloride in 13 mL of THF was added at 0 °C. The mixture was stirred for another 30 min at 0 °C and then for 30 min at room temperature. The THF was removed in vacuo and the residue taken up in 130 mL of CH_2Cl_2. This solution was washed once with saturated aqueous NH_4Cl and twice with brine. It was chilled to 0 °C and mixed with 50 mL of pH 7 phosphate buffer, 1 mL of pyridine, and 3.5 mL of hydrogen peroxide (30%). After 30 min the vigorously stirred mixture was allowed to warm to room temperature and was stirred overnight. The layers were separated, the aqueous layer was extracted three times with CH_2Cl_2, and the combined organic layers were washed once with saturated $NaHCO_3$, twice with 2 N NaOH, once with 2 N HCl, and twice with brine. Drying ($MgSO_4$) and removal of the solvent gave the crude product which was purified by flash chromatography (80 g of SiO_2, 0% to 25% ethyl acetate/hexane) to yield 2.45 g (58%) of enone **27**. White crystals, mp 135–137 °C, were obtained from ether/hexane: IR ($CHCl_3$) 1740, 1680 cm^{-1}; ^1H NMR δ −0.04 (s, 3 H), −0.02 (s, 3 H), 0.82 (s, 9 H), 1.02 (d, 3 H, J = 7), 1.15 (s, 3 H), 1.00–1.40 (m, 3 H), 1.70–1.85 (m, 2 H), 2.10–2.20 (m, 2 H), 2.44 (dd, 1 H, J = 4.5, 17), 2.72 (m, 1 H), 3.02 (dd, 1 H, J = 15, 17), 3.56 (d, 1 H, J = 10), 3.80 (s, 3 H), 3.85 (m, 4 H), 4.08 (d, 1 H, J = 10), 5.37 (m, 1 H), 7.20 (s, 1 H); ^{13}C NMR δ −5.81, −5.72, 9.82, 17.60, 17.99, 25.63 (3 C), 30.85, 33.74, 36.59, 36.95, 37.66, 40.33, 40.65, 48.19, 52.15, 64.99, 65.32 (2 C), 111.08, 116.01, 131.39, 143.06, 162.13, 165.20, 196.04. Anal. Calcd for $C_{27}H_{42}O_6Si$: C, 66.09; H, 8.62. Found: C, 66.03; H, 8.89.

Enone 28. A solution of 0.83 g of compound **26**, 4.7 mL of *sym*-collidine, and 15 mL of CCl_4 was heated to reflux in a three-necked, round-bottomed flask fitted with a reflux condenser and an addition funnel. A solution of 1.2 mL of thionyl chloride in 5 mL of CCl_4 was added dropwise over a period of 4 h. After an additional 1.5 h, the mixture was partitioned between CH_2Cl_2 (70 mL) and water (20 mL). The organic layer was washed with 2 N HCl (2 × 15 mL), saturated $NaHCO_3$ (1 × 20 mL), and brine. The solution was dried over $MgSO_4$ and evaporated to give a light brown oil which was purified by flash chromatography (15 g of SiO_2, 5–25% ethyl acetate in hexanes) to give 0.532 g (64%) of enone **28** as a light yellow oil: IR ($CHCl_3$) 1750, 1690 cm^{-1}; ^1H NMR (approximately a 1:1 mixture of diastereomers due to the THP acetal) δ 1.0 (d, 3 H, J = 7), 1.11 (s, $^3/_2$ H), 1.17 (s, $^3/_2$ H), 1.22 (m, 1 H), 1.4–1.8 (m, 10 H), 2.05–2.35 (m, 2 H), 2.48 (dd, 1 H, J = 17, 5), 2.72 (m, 1 H), 2.91 (dd, $^1/_2$ H, J = 17, 15), 2.97 (dd, $^1/_2$ H, J = 17, 15 Hz), 3.40 (m, 2 H), 3.60–3.80 (m, 2 H), 3.81 (s, 3 H), 3.90–4.20 (m, 5 H), 4.48 (m, $^1/_2$ H), 4.53 (m, $^1/_2$ H), 5.41 (m, 1 H), 7.4 (s, $^1/_2$ H), 7.45 (s, $^1/_2$ H). Anal. Calcd for $C_{26}H_{36}O_7$: C, 67.78; H, 7.88. Found: C, 67.57; H, 7.93.

Compound 30. To a solution of 4.5 g (9.18 mmol) of enone **27** in 70 mL of acetonitrile was added 6.2 g (27 mmol) of ketene acetal **29**. The mixture was compressed at 3.4 kbar for 3 weeks. Concentration in vacuo gave a yellow oil which was purified by flash chromatography (160 g of SiO_2, 0% to 20% ethyl acetate in petroleum ether). The first fraction contained adduct **30** as a colorless oil (4.12 g, 62% or 74% based on recovered enone **27**), the second fraction was starting material **27** (0.73 g): IR (film) 1720, 1640 cm^{-1}; ^1H NMR δ −0.05 (s, 3 H), −0.04 (s, 3 H), 0.18 (s, 6 H), 0.85 (s, 9 H), 0.94 (s, 9 H), 1.01 (d, 3 H, J = 7), 1.06 (s, 3 H), 1.43 (s, 9 H), 1.20–2.35 (m, 11 H), 2.73 (m, 1 H), 3.39 (br d, 1 H, J = 9), 3.52 (d, 1 H, J = 9), 3.58 (dd, 1 H, J = 7, 3), 3.63 (s, 3 H), 3.85–4.05 (m, 4 H), 5.39 (dm, 1 H, J = 5); ^{13}C NMR δ −5.65 (2 C), −3.83, −3.70, 9.90, 18.16, 18.39, 19.97, 25.81 (3 C), 25.83 (3 C), 28.07 (3 C), 29.35, 30.13, 31.18, 35.89, 36.48, 38.69, 39.37, 40.73, 42.22, 50.73, 62.95, 64.95, 65.35, 79.25, 111.21, 112.10, 118.51, 140.46, 157.51, 167.32, 172.03. Anal. Calcd for $C_{39}H_{68}O_8Si_2$: C, 64.96; H, 9.50. Found: C, 65.16; H, 9.71.

Michael Adduct 31. To a solution of 550 mg (1.2 mmol) of enone **28** in 6 mL of acetonitrile was added 763 mg of ketene acetal **29**. The mixture was pressurized at 7 kbar for 5 days. Evaporation of solvent in vacuo gave a yellow oil, which was purified by preparative radial chromatography (10% to 30% ethyl acetate in hexanes) to give 630 mg (81%) of adduct **31** as a clear oil: IR ($CHCl_3$) 1715, 1640 cm^{-1}; ^1H NMR (approximately a 1:1 mixture of diastereomers due to THP acetal) δ 0.19 (m, 6 H), 0.94 (m, 9 H), 1.00 (dd, 3 H, J = 7, 3), 1.70 (br s, 3 H), 1.20–2.40 (m, 3 H), 1.42 (m, 9 H), 2.72 (m, 1 H), 3.20 (m, 1 H), 3.40 (m, 1 H), 3.65 (br d, 3 H, J = 4), 3.50–4.10 (m, 7 H), 4.43 (m, $^1/_2$ H), 4.60 (m, $^1/_2$ H), 5.40 (m, 1 H). Anal. Calcd for $C_{38}H_{62}O_9Si$: C, 66.05; H, 9.04. Found: C, 65.94; H, 9.14.

Diepoxide 32. A solution of 100 mg (0.14 mmol) of adduct **30** in 3 mL of CH_2Cl_2 was treated with 70 mg (0.41 mmol) of *m*-chloroperoxybenzoic acid and stirred 3 h at room temperature. More CH_2Cl_2 was added, and the solution was washed twice with 2% aqueous Na_2CO_3. The aqueous layers were re-extracted once with CH_2Cl_2, and the combined organic extracts were washed with brine and dried ($MgSO_4$). Evaporation of the solvent yielded 104 mg (100%) of crude diepoxide **32**, which was judged to be pure by ^1H NMR spectroscopy. An analytical sample, mp 90–93 °C, was obtained by flash chromatography (10% to 20% ether in hexane): IR (film) 1730 cm^{-1}; ^1H NMR δ 0.08 (s, 3 H), 0.11 (s, 3 H), 0.13 (s, 3 H), 0.16 (s, 3 H), 0.70 (d, 3 H, J = 7), 0.83 (s, 9 H), 0.92 (s, 9 H), 1.08 (s, 3 H), 1.39 (s, 9 H), 1.4–2.0 (m, 8 H), 2.08 (br d, 1 H, J = 18), 2.38 (q, 1 H, J = 7), 2.39 (dd, 1 H, J = 18, 2), 2.64 (dd, 1 H, J = 18, 10), 2.93 (dd, 1 H, J = 10, 2), 3.04 (d, 1 H, J = 2), 3.61 (d, 1 H, J = 10), 3.68 (d, 1 H, J = 10), 3.68 (s, 3 H), 3.8–4.1 (m, 4 H); ^{13}C NMR δ −5.78, −5.42, −3.75, −3.37, 5.42, 17.63, 18.09, 18.44, 25.35 (3 C), 25.96 (3 C), 27.42, 27.55, 28.04 (3 C), 30.49, 31.91, 32.05, 35.91 (2 C), 36.78, 38.08, 38.77, 51.82, 53.47, 63.28, 64.74, 65.49, 66.24, 66.88, 79.88, 85.81, 110.04, 169.03, 172.02. Anal. Calcd for $C_{39}H_{68}O_{10}Si_2$: C, 62.20; H, 9.10. Found: C, 62.51; H, 9.42.

Compounds 33 and 34. A solution of 90 mg (1.34 mmol) of KF (dried in vacuo) in 2.2 mL of methanol was added to 462 mg (0.614 mmol) of diepoxide **32** dissolved in 1 mL of methanol. The mixture was stirred for 5 min at room temperature. Brine was added, and the aqueous phase was extracted three times with CH_2Cl_2. The combined organic extracts were washed once with water and brine and dried ($MgSO_4$). Evaporation of the solvent and chromatography of the crude product (15 g SiO_2, 20% to 50% ethyl acetate in hexane) gave 211 mg (55%) of compound **33** and 33 mg (8%) of compound **34**.

Compound 33. White crystals, mp 182 °C, were obtained from CH_2Cl_2/hexane: IR (film) 3400–3600, 1710 cm^{-1}; ^1H NMR δ 0.04 (s, 3 H), 0.05 (s, 3 H), 0.72 (d, 3 H, J = 7), 0.89 (s, 9 H), 1.13 (s, 3 H), 1.39 (s, 9 H), 1.4–1.8 (m, 4 H), 1.99 (br s, 2 H), 2.30 (dd, 1 H, J = 18, 14), 2.32 (dd, 1 H, J = 17, 3), 2.43 (q, 1 H, J = 7), 2.49 (dd, 1 H, J = 18, 6), 2.61 (dd, 1 H, J = 14, 6), 2.84 (dd, 1 H, J = 17, 11), 3.08 (dd, 1 H, J = 1.5, 1.5), 3.21 (dd, 1 H, J = 11, 3), 3.37 (d, 1 H, J = 10.5), 3.59 (d, 1 H, J = 10.5), 3.84 (s, 3 H), 3.97 (s, 1 H), 3.8–4.1 (m, 4 H); ^{13}C NMR δ –5.71, –5.52, 5.57, 16.88, 18.29, 25.83 (3 C), 28.03 (3 C), 28.60, 30.49, 32.03, 32.50, 34.08, 36.38, 36.88, 37.73, 39.71, 44.20, 53.32, 53.48, 63.47, 64.71, 65.47, 67.20, 79.92, 80.05, 110.14, 172.86, 173.13, 205.77. Anal. Calcd for $C_{33}H_{54}O_{10}Si$: C, 62.04; H, 8.52. Found: C, 62.28; H, 8.61.

Compound 34: IR (film) 1730 cm^{-1}; ^1H NMR δ 0.03 (s, 3 H), 0.04 (s, 3 H), 0.70 (d, 3 H, J = 7), 0.88 (s, 9 H), 1.14 (s, 3 H), 1.38 (s, 9 H), 1.60 (br d, 1 H, J = 17), 1.63–1.72 (m, 4 H), 2.19 (dd, 1 H, J = 17, 2), 2.39 (q, 1 H, J = 7), 2.41 (dd, 1 H, J = 17, 2), 2.47 (dd, 1 H, J = 17, 3), 2.55 (dd, 1 H, J = 17, 8.5), 2.61 (dd, 1 H, J = 8.5, 3), 2.63 (br d, 1 H, J = 9), 2.84 (br d, 1 H, J = 17), 2.99 (d, 1 H, J = 4.5), 3.06 (br d, 1 H, J = 2), 3.37 (d, 1 H, J = 11), 3.57 (d, 1 H, J = 11), 3.63 (s, 3 H), 3.71 (s, 3 H), 3.80–4.05 (m, 4 H), 5.02 (d, 1 H, J = 4.5). Anal. Calcd for $C_{34}H_{58}O_{11}Si$: C, 60.87; H, 8.71. Found: C, 61.20; H, 8.94.

Compounds 35 and 36. To 50 mg (0.078 mmol) of compound **33** was added 0.203 mL of a 0.5 M solution of tetrabutylammonium fluoride trihydrate (TBAF) in THF. The mixture was stirred for 20 min at room temperature and then diluted with CH_2Cl_2. This solution was directly chromatographed on 3 g of flash silica (30% to 50% ethyl acetate in petroleum ether) to give three fractions. The first fraction consisted of two compounds which were not further identified. Fraction two (9 mg, 22%) was identified as δ-lactone **35**. The third fraction (1.5 mg, 4%) was dilactone **36**.

Compound 35: IR (film) 3600–3200, 1740 cm^{-1}; ^1H NMR δ 0.73 (d, 3 H, J = 7), 1.22 (s, 3 H), 1.42 (s, 9 H), 1.55–1.85 (m, 4 H), 2.14 (m, 2 H), 2.35–2.50 (m, 4 H), 2.58 (dd, 1 H, J = 16, 4), 2.64 (dd, 1 H, J = 18, 9), 2.96 (d, 1 H, J = 4), 3.11 (br d, 1 H, J = 4), 3.78 (s, 3 H), 3.8–4.1 (m, 6 H), 5.07 (br d, 1 H, J = 4); ^{13}C NMR δ 5.28, 16.93, 23.98, 25.79 (may be due to an impurity), 27.89 (3 C), 28.26, 30.12, 31.39, 32.45, 37.20, 37.80, 38.39, 41.04, 42.54, 52.10, 52.96, 63.02, 64.79, 65.60, 68.60, 70.92, 80.84, 109.63, 171.26, 171.97, 175.85; HRMS (FABMS, M + 1 + diethanolamine) calcd for $C_{31}H_{52}NO_{12}$ 630.3489, found 630.3492.

Compound 36: IR (film) 1790, 1750 cm^{-1}; ^1H NMR δ 0.73 (d, 3 H, J = 7), 1.21 (s, 3 H), 1.60–1.85 (m, 5 H), 2.03 (dd, 1 H, J = 16, 4), 2.10 (br dd, 1 H, J = 9, 8), 2.28 (dd, 1 H, J = 18, 3), 2.48 (q, 1 H, J = 7), 2.48 (dd, 1 H, J = 16, 8), 2.61 (dd, 1 H, J = 16, 9), 2.74 (dd, 1 H, J = 18, 11), 2.88 (ddd, 1 H, J = 11, 3, 2.5), 3.15 (d, 1 H, J = 4), 3.80 (s, 3 H), 3.8–4.1 (m, 6 H), 5.58 (d, 1 H, J = 2.5); CI-MS, m/z 451 (M + 1).

Compound 37. To a solution of 15 mg (0.024 mmol) of compound **33** in 1 mL of methanol was added 3.5 mg (0.092 mmol) of sodium borohydride. The mixture was stirred for 4 h at room temperature. Saturated NH_4Cl solution was added, and the aqueous phase was extracted three times with CH_2Cl_2. The combined organic extracts were washed once with brine and dried ($MgSO_4$). Evaporation of the solvent gave the crude product which was purified by recrystallization from CH_2Cl_2/hexanes to give 9 mg (68%) of lactone **37**: IR (film) 3650–3200, 1795, 1750 cm^{-1}; ^1H NMR δ 0.04 (s, 3 H), 0.06 (s, 3 H), 0.71 (d, 3 H, J = 7), 0.89 (s, 9 H), 1.09 (s, 3 H), 1.52–1.86 (m, 5 H), 1.57 (br d, 1 H, J = 16.5), 1.92 (dd, 1 H, J = 12.5, 1), 1.99 (dd, 1 H, J = 12.5, 12), 2.06 (dd, 1 H, J = 16.5, 4), 2.45 (q, 1 H, J = 7), 2.50 (dd, 1 H, J = 18, 10), 2.56 (dd, 1 H, J = 18, 13.5), 2.69 (d, 1 H, J = 9.5), 3.01 (d, 1 H, J = 4), 3.44 (d, 1 H, J = 10), 3.47 (dd, 1 H, J = 13.5, 10), 3.71 (ddd, 1 H, J = 12, 9.5, 5), 3.74 (d, 1 H, J = 10), 3.76 (s, 3 H), 3.80–4.05 (m, 4 H); ^{13}C NMR δ –3.84, –3.29, 6.30, 17.88, 18.27, 25.87 (3 C), 27.83, 30.96, 31.33, 31.59, 32.90, 35.72, 37.91, 38.73, 39.17, 43.42, 52.83, 53.23, 63.71, 64.66, 65.32, 65.97, 74.97, 87.18, 110.40, 170.36, 173.30.

Compound 38. A solution of 84 mg (0.132 mmol) of compound **33** in 0.5 mL of *N*-(trimethylsilyl)imidazole was heated at 100 °C for 90 min. The mixture was taken up in hexanes, and the resulting solution was washed twice with water, once with brine, and dried ($MgSO_4$). Evaporation of the solvent gave 96 mg (100%) of crude **38**. An analytical sample (white foam) was prepared by flash chromatography (2.5 g of SiO_2, 0% to 7% ethyl acetate in petroleum ether): IR (film) 1750, 1730 cm^{-1}; ^1H NMR δ 0.03 (s, 3 H), 0.05 (s, 3 H), 0.11 (s, 9 H), 0.69 (d, 3 H, J = 7), 0.88 (s, 9 H), 1.16 (s, 3 H), 1.39 (s, 9 H), 1.6–1.8 (m, 4 H), 1.82 (dd, 1 H, J = 18, 2), 1.98 (dd, 1 H, J = 18, 1.5), 2.30 (dd, 1 H, J = 18, 3), 2.31 (dd, 1 H, J = 16, 4), 2.45 (q, 1 H, J = 7), 2.47 (dd, 1 H, J = 14, 4), 2.60 (dd, 1 H, J = 16, 14), 2.61 (dd, 1 H, J = 18, 9), 3.05 (dd, 1 H, J = 9, 3), 3.08 (br s, 1 H), 3.44 (d, 1 H, J = 12), 3.50 (d, 1 H, J = 12), 3.70 (s, 3 H), 3.8–4.05 (m, 4 H). Anal. Calcd for $C_{36}H_{62}O_{10}Si_2$: C, 60.81; H, 8.79. Found: C, 60.47; H, 8.92.

Compound 39. To a solution of 34 mg of adduct **31** in 40 mL of rigorously dried ethanol was added 12 mg of pyridinium *p*-toluenesulfonate. The mixture was stirred at 55 °C for 3.5 h, the solvent was evaporated, and the residue was purified by radial chromatography to give 13 mg (44%) of alcohol as a white solid. Recrystallization from ether gave an analytically pure sample, mp 135 °C: IR ($CHCl_3$) 3400–3600, 1725, 1680 (sh), 1640 (sh) cm^{-1}; ^1H NMR δ 0.19 (s, 3 H), 0.20 (s, 3 H), 0.95 (s, 9 H), 1.01 (br d, 3 H, J = 7), 1.08 (br s, 3 H), 1.43 (s, 9 H), 1.60–1.75 (m, 6 H), 1.87 (br t, 1 H, J = 10), 1.94 (dm, 1 H, J = 17), 2.18 (dd, 1 H, J = 17, 7), 2.24 (d, 2 H, J = 10), 2.27 (dm, 1 H, J = 16), 2.43 (dd, 1 H, J = 16, 6), 2.73 (m, 1 H), 3.40 (br t, 1 H, J = 5), 3.54 (br s, 1 H), 3.71 (s, 3 H), 3.85–4.05 (m, 4 H), 5.40 (m, 1 H). Anal. Calcd for $C_{33}H_{54}O_8Si$: C, 65.32; H, 8.97. Found: C, 65.33; H, 9.11.

Compound 40. A solution of 31 mg of alcohol **39** in 1 mL of THF was chilled in an ice/water bath under an atmosphere of nitrogen. *N*-Bromosuccinimide (8 mg) was added and the solution was stirred at 0 °C for 4 h. The reaction mixture was poured into a separatory funnel containing 15 mL of ether. The mixture was washed with saturated aqueous $NaHCO_3$ (2 × 10 mL) and brine (10 mL) and dried over $MgSO_4$. The solvent was evaporated and the residue purified by flash chromatography (1 g of SiO_2; 0%, 5% ethyl acetate in hexanes) to give 29 mg (84%) of faintly yellow solid. Recrystallization from hexanes gave white prisms, mp 152–153 °C: IR ($CHCl_3$) 1730 (br) cm^{-1}; ^1H NMR δ 0.04 (s, 3 H), 0.16 (s, 3 H), 0.90 (s, 9 H), 1.00 (d, 3 H, J = 7), 1.20 (s, 3 H), 1.41 (s, 9 H), 1.48–1.88 (m, 6 H), 2.10 (dm, 1 H, J = 17), 2.24 (br t, 1 H, J = 7), 2.50 (dd, 1 H, J = 16, 3), 2.62 (m, 1 H), 2.71 (dd, 1 H, J = 16, 11), 3.38 (dd, 1 H, J = 12, 3), 3.73 (br d, 1 H, J = 9), 3.80 (s, 3 H), 3.81–4.00 (m, 4 H), 4.04 (d, 1 H, J = 9), 5.36 (m, 1 H); ^{13}C NMR δ –2.92, –2.77, 9.64, 17.86, 19.44, 25.48 (3 C), 27.91 (3 C), 28.91, 30.74, 31.90, 33.23, 36.64 (2 C), 38.14, 40.20, 40.83, 46.41, 53.31, 64.71, 65.33, 71.97, 74.72, 80.40, 99.52, 110.83, 166.67, 114.23, 170.28, 171.51. Anal. Calcd for $C_{33}H_{53}O_8BrSi$: C, 57.80; H, 7.79. Found: C, 57.57; H, 7.72. The structure of compound **40** was elucidated by single-crystal X-ray analysis; an ORTEP representation is shown in Figure 1.[14]

Compound 41. A solution of 45 mg (0.066 mmol) of bromide **40**, 0.01 mL of *sym*-collidine (1.1 equiv), and 5.3 mL of DMF was heated at reflux under an atmosphere of nitrogen for 7 h. The solvent was removed in vacuo, and the residue was dissolved in 60 mL of ethyl acetate and washed with water (10 mL), brine (10 mL), and dried over $MgSO_4$. Evaporation of solvent gave 39 mg (100%) of crude silyl enol ether **41** as a yellow oil: IR ($CHCl_3$) 1740 (br), 1660 cm^{-1}; ^1H NMR δ 0.18 (s, 3 H), 0.19 (s, 3 H), 0.88 (s, 9 H), 0.97 (d, 3 H, J = 7), 1.12 (s, 3 H), 1.45 (s, 9 H), 1.60–1.95 (m, 5 H), 2.20–2.35 (m, 2 H), 2.39 (dd, 1 H, J = 18, 2), 2.61 (m, 1 H), 2.69 (dd, 1 H, J = 8, 2), 2.79 (dd, 1 H, J = 18, 8), 3.61 (dd, 1 H, J = 9, 2), 3.71 (s, 3 H), 3.85–4.05 (m, 4 H), 4.49 (d, 1 H, J = 9), 4.73 (d, 1 H, J = 2), 5.39 (m, 1 H).

Compound 42. A solution of 39 mg (0.066 mmol) of enol silane **41** in 3 mL of methanol was cooled to 0 °C. To the solution was added 3 mL of a saturated solution of KF in methanol. The mixture was stirred for 1 h and was then dissolved in ethyl acetate and washed with water (5 mL) and brine (5 mL) and dried over $MgSO_4$. The residue upon evaporation of solvent was dissolved in 1:1 ethyl acetate/ether and passed through a plug of silica gel.

Removal of the solvent in vacuo gave 29 mg (90%) of ketone **42** as a pale yellow solid, mp 206–209 °C. Recrystallization from ethyl acetate/hexanes afforded analytically pure material as white needles, mp 217–219 °C: IR ($CHCl_3$) 1760, 1740 cm^{-1}; ^1H NMR δ 1.01 (d, 3 H, J = 7), 1.27 (s, 3 H), 1.46 (s, 9 H), 1.50–1.85 (m, 6 H), 2.04 (dm, 1 H, J = 16), 2.22 (dd, 1 H, J = 18, 5), 2.28 (br d, 1 H, J = 20), 2.31 (dd, 1 H, J = 20, 6), 2.69 (m, 1 H), 3.02 (dd, 1 H, J = 16, 13), 3.09 (br t, 1 H, J = 4), 3.78 (s, 3 H), 3.79 (dd, 1 H, J = 9, 1), 3.87–4.03 (m, 4 H), 4.68 (d, 1 H, J = 9), 5.42 (m, 1 H); ^{13}C NMR δ 9.82, 18.32, 28.45 (3C), 29.23, 29.31, 30.73, 36.31, 37.64, 40.84, 43.94, 44.80, 44.94, 49.98, 52.44, 64.97, 65.36, 81.12, 88.95, 110.77, 117.22, 142.14, 167.92, 170.57, 205.58; mass spectrum (70 eV), m/z 490 (M^+), 434, 419, 389, 327, 345. Anal. Calcd for $C_{27}H_{38}O_8$: C, 66.10; H, 7.81. Found: C, 65.92; H, 7.76.

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Palladium-Complex-Catalyzed Reactions of Ketenes with Allylic Carbonates or Acetates. Novel Syntheses of α-Allylated Carboxylic Esters and 1,3-Dienes

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Diphenylketene and ethylphenylketene react with allylic carbonates or acetates in the presence of a catalytic amount of tetrakis(triphenylphosphine)palladium to give α-allylated esters or 1,3-dienes, respectively. For example, the reaction of diphenylketene with allyl methyl carbonate in DMF at 0 °C gave methyl 2,2-diphenyl-4-pentenoate in 67% yield. The reaction of diphenylketene with allyl acetate in benzene at 25 °C gave 1,1-diphenyl-1,3-butadiene in 72% yield. Marked solvent effects were observed.

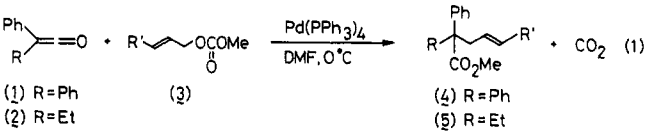
In organic syntheses catalyzed by palladium, π- or σ-allyl palladium complexes have often been recognized as important intermediates.[1] For example, nucleophilic attack of a carbonucleophile on a π-allyl ligand on a palladium complex has been revealed to be a key step in several important carbon–carbon bond-formation reactions.[1]

On the other hand, ketenes are known to undergo a variety of characteristic reactions due to their high reactivity. However, catalytic processes using a transition-metal complex are rare.[2] In the course of our study on the development of catalytic reactions utilizing ketenes, we have found palladium-catalyzed reactions of ketenes with terminal acetylenes[3] or acid halides[4] to give disubstituted acetylenes or α,β-unsaturated ketones, respectively.

In this paper, along with the concept to build up a catalytic cycle involving the reaction of ketene with a π- or σ-allyl palladium complex as a key step, reactions of ketenes with allylic carbonates or acetates have been investigated; products were expected α-allylated carboxylic esters or unexpected 1,3-dienes, respectively. Preliminary results appear in a previous paper.[5]

Results and Discussion

Reaction of Ketenes with Allylic Carbonates. The reaction of ketene **1** or **2** with allylic carbonate **3** in the presence of a catalytic amount of tetrakis(triphenylphosphine)palladium gives α-allylated carboxylic ester **4** or **5** in high yields by alkoxy allylation of the ketene accompanied by decarboxylation (eq 1). The reaction

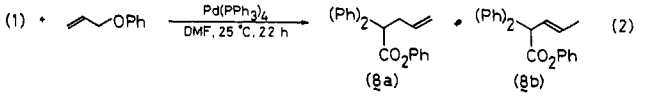


(1) R=Ph (2) R=Et (3) (4) R=Ph (5) R=Et

proceeds rapidly under mild conditions (0 °C, 0.5 h, in DMF). Results using various carbonates are summarized in Table I.

A usual allyl rearrangement was observed in the ester formation reaction. Both crotyl (**3c**) and 1-methylallyl carbonate (**3d**) gave products **4c** and **4d** in ratios of 94:6 and 80:20, respectively (Table I, runs 3 and 4). 2-Hexenyl (**3e**) or cinnamyl carbonate (**3f**), having a large substituent, gave **4e** or **4f** selectively (Table I, runs 5 and 6). The ester from geranyl carbonate (**3i**) kept the E configuration during the reaction; however, that from neryl carbonate (**3j**) was a mixture of isomers (Z:E = 8:2). Myrtenyl (**3k**) and perillyl carbonate (**3l**), which have terpene skeletones, also gave esters in high yields. The reaction using ethylphenylketene **2** proceeded similarly, affording the corresponding esters in moderate yields (runs 13 and 14).

The reaction using allyl phenyl ether as an allyl moiety instead of the carbonate also gave allylated phenyl ester **8a** and its isomer **8b** in 66% yield (**8a**:**8b** = 1:1) (eq 2).



(8a) (8b)

However, use of allyl phenyl ether required a longer reaction time than that for the carbonate. Allyl alkyl ether did not react at all. When N,N-dimethylallylamine was allowed to react with diphenylketene in DMF or THF, allylated amide was not obtained but N,N-dimethyl-2,2-

(1) For a recent review, see: Heck, R. F. *Palladium Reagents in Organic Syntheses*; Academic: New York, 1985; Chapter 5. Tsuji, J. In *The Chemistry of the Metal–Carbon Bond*; Patai, S., Ed.; Wiley: New York, 1985; Vol. 3, p 163.

(2) (a) Hong, P.; Sonogashira, K.; Hagihara, N. *Tetrahedron Lett.* **1971**, 1105. (b) Hong, P.; Yamazaki, H.; Sonogashira, K.; Hagihara, N. *Chem. Lett.* **1978**, 535.

(3) Mitsudo, T.; Kadokura, M.; Watanabe, Y. *Tetrahedron Lett.* **1985**, *26*, 3697.

(4) (a) Mitsudo, T.; Kadokura, M.; Watanabe, Y. *Tetrahedron Lett.* **1985**, *26*, 5143. (b) Kadokura, M.; Mitsudo, T.; Watanabe, Y. *J. Chem. Soc., Chem. Commun.* **1986**, 252.

(5) Mitsudo, T.; Kadokura, M.; Watanabe, Y. *J. Chem. Soc., Chem. Commun.* **1986**, 1539.

0022-3263/87/1952-1695$01.50/0