persion, 3.17 mmol) in 5 mL of DME in a resealable tube were added allyl alcohol in DME (0.50 mL, 1.0 M, 0.05 mmol) and keto ester **22** (614 mg, 3.37 mmol) in 5 mL of DME.[21] After H_2 evolution ceased (15 min), iodide **10** (670 mg, 2.00 mmol) in 5 mL of DME was added and the tube was immersed in an oil bath at 120 °C for 22 h. The mixture was cooled, diluted with water, neutralized with 10% HCl, and extracted with ether. The combined organic layers were washed with water, dried ($MgSO_4$), and concentrated in vacuo. Flash chromatography (40:1 hexane–EtOAc) afforded 484 mg (62%) of **33** as a 1:1 mixture of diastereomers: ^{1}H NMR 5.93 (tdd, 1, J = 6, 10, 17), 5.79 (tdd, 1, J = 6, 10, 17), 5.33 (tdd, 1, J = 1.5, 1.5, 17), 5.26 (tdd, 1, J = 1.5, 1.5, 10), 5.03 (tdd, 1, J = 1.5, 1.5, 17), 4.93 (tdd, 1, J = 1.5, 1.5, 10), 4.62 (ddd, 2, J = 1.5, 1.5, 6), 3.48 (dd, 0.5 × 1, J = 4.3, 6.2), 3.46 (dd, 0.5 × 1, J = 4.3, 6.2), 2.74–2.58 (m, 2), 2.55–2.44 (m, 1), 2.38–2.24 (m, 2), 2.18–2.00 (m, 2), 1.96 (s, 0.5 × 3), 1.95 (s, 0.5 × 3), 1.94–1.79 (m, 1), 1.68–1.17 (m, 8), 1.46 (s, 3), 0.95 (s, 3), 0.81 (s, 3); ^{13}C NMR 204.2 (C), (170.2, 170.1) (C), 169.4 (C), 136.7 (CH), 131.5 (CH), 119.0 (CH_2), 115.5 (CH_2), 87.3 (C), 65.8 (CH_2), 59.7 (CH), (53.7, 53.5) (CH), (40.9, 40.8) (CH_2), 40.5 (CH_2), 37.4 (CH_2), (35.5, 35.4) (C), 32.5 (CH_3), (30.5, 30.3) (CH_2), 27.4 (CH_2), 24.7 (CH_2), 22.9 (CH_3), 22.0 (CH_3), 20.7 (CH_3), 19.7 (CH_2); IR (neat) 1730, 990, 910.

4-[(*trans*-2-Acetoxy-2,6,6-trimethylcyclohexyl)ethyl]-4-iodo-1,8-nonadien-5-one (7). To keto ester **33** (106 mg, 0.27 mmol) in 1 mL of pentane were added Et_3N (33 mg, 0.32 mmol), TMSCl (35 mg, 0.32 mmol), and NaI in CH_3CN (1.18 mL, 1.0 M, 1.18 mmol).[13f] The solution was stirred for 20 min and worked up as described above for the preparation of **24** to afford 101 mg (89%) of silyl enol ether that was added directly to a burgundy colored mixture of $Pd_2(dba)_3$ (11 mg, 0.01 mmol) and dppe (10 mg, 0.02 mmol) in 2 mL of THF.[14] The solution was stirred for 45 min, NIS (135 mg, 0.60 mmol) in 4 mL of THF was added to the resultant olive-green mixture, and the flask was wrapped in foil. The solution was stirred for 1 h and worked up as described above for the preparation of **26** to afford crude light-sensitive **7**. Flash chromatograph (40:1 hexane–EtOAc) afforded 47 mg (41%) of pure α-iodo ketone **7** as a 1:1 mixture of diastereomers: ^{1}H NMR 5.86 (tdd, 1, J = 6, 10, 17), 5.72 (tdd, 1, J = 6, 10, 17), 5.20 (br d, 1, J = 10), 5.18 (br d, 1, J = 17), 5.09 (tdd, 1, J = 1.5, 1.5, 17), 5.02 (tdd, 1, J = 1.5, 1.5, 10), 3.14–2.82 (m, 4), 2.60–2.51 (m, 1), 2.42 (app q, 2, J = 7), 2.18 (ddd, 1, J = 3, 10, 15), 2.16 (ddd, 1, J = 3, 10, 15), 1.99 (s, 0.5 × 3), 1.95 (s, 0.5 × 3), 1.71–1.18 (m, 8), 1.52 (s, 0.5 × 3), 1.48 (s, 0.5 × 3), 0.99 (s, 0.5 × 3), 0.94 (s, 0.5 × 3), 0.86 (s, 0.5 × 3), 0.84 (s, 0.5 × 3); ^{13}C NMR 204.3, 136.9, 134.0, 119.1, (115.6, 115.5), (87.5, 87.6), (60.3, 60.2), 53.9, 43.6, 41.4, 40.7, 37.6, (36.4, 36.3), 35.9, 35.7, 32.7, 28.9, 24.2, 23.2, 21.9, 20.2, 19.7; IR (neat) 1740, 1705, 990, 910.

Velloziolone Acetate (34) and (1*S,5*R**)-1-[((1*R**,2*R**)-2-Acetoxy-2,6,6-trimethylcyclohexyl)ethyl]-6-methylenebicyclo[3.2.1]octan-2-one (35).** A benzene solution (1.2 mL, 0.3 M) of α-iodo ketone **7** (38 mg, 0.08 mmol) and Bu_6Sn_2 (5 mg, 0.01 mmol) was irradiated at 150 °C as described above for the preparation of **26**. Benzene (1.2 mL) and DBU (37 mg, 0.24 mmol) were added, and the tube was immersed in an oil bath at 135 °C for 3 h.[7] Workup as described above for the preparation of **28** afforded a 1:1 mixture of **34** and **35**. Flash chromatography (40:1 petroleum ether/EtOAc) afforded 3 mg (11%) of **34**, followed by 3 mg (11%) of a 1:1 mixture of **34** and **35**, followed by 4 mg (15%) of a 4:1 mixture of **35** and **34**.

The data for **34**: ^{1}H NMR 5.06 (br s, 1), 4.98 (br s, 1), 2.87 (m, 1), 2.53–2.21 (m, 8), 1.97 (s, 3), 1.92–1.16 (m, 11), 1.47 (s, 3), 1.01 (s, 3), 0.84 (s, 3); ^{13}C NMR 213.4, 170.4, 152.8, 106.6, 87.7, 57.1, 54.3, 43.8, 42.4, 41.8, 40.3, 37.5, 37.3, 36.1, 35.6, 33.8, 32.4, 23.0, 22.5 (2 C), 20.5, 19.8.

The data for **35** (determined from the mixture): ^{1}H NMR 5.06 (br s, 1), 4.97 (br s, 1), 2.87 (m, 1), 2.52–2.23 (m, 8), 1.98 (s, 3), 1.92–1.16 (m, 11), 1.47 (s, 3), 0.99 (s, 3), 0.84 (s, 3); ^{13}C NMR 213.3, 170.4, 152.8, 106.6, 87.6, 57.1, 54.1, 43.3, 42.3, 42.0, 40.3, 37.3, 37.1, 36.1, 35.6, 33.7, 32.5, 23.0, 22.4 (2C), 20.5, 19.8.

(±)-Velloziolone (3). The less polar acetate **34** (2 mg, 0.006 mmol) in 0.5 mL of 10% KOH in MeOH was heated reflux for 2 h. The mixture was cooled, concentrated in vacuo to one quarter of its volume, neutralized with 10% HCl, and extracted with ether. The combined organic layers were dried ($MgSO_4$) and concentrated in vacuo. Flash chromatography (10:1 hexane–EtOAc) afforded 1.3 mg (72%) of pure **3**: ^{1}H NMR 5.06 (br s, 1), 4.96 (br s, 1), 2.87 (m, 1), 2.49–2.24 (m, 8), 1.92–1.15 (m, 11), 1.19 (s, 3), 0.95 (s, 3), 0.77 (s, 3); ^{13}C NMR 213.7 (C-9), 152.5 (C-16), 106.6 (C-17), 73.6 (C-10), 58.1 (C-5), 57.5 (C-8), 43.0 (C-14), 42.6 (C-1), 42.3 (C-13), 42.2 (C-3), 41.4 (C-15), 38.2 (C-7), 35.9 (C-11), 35.3 (C-4), 33.7 (C-12), 32.6 (C-19), 23.6 (C-20), 22.0 (C-6), 21.2 (C-18), 20.4 (C-2); IR (neat) 3490, 2920, 1710, 880; MS (EI) m/e (rel intensity) 304.2 (M^+, 34), 286.2 (29), 268.2 (28), 253.2 (15), 225.2 (15), 177.1 (20), 163.1 (20), 135.1 (100), 109.1 (35). The spectral data are identical to those reported for the natural product.[2]

(1*S,5*R**)-1-[((1*R**,2*R**)-2-Hydroxy-2,6,6-trimethylcyclohexyl)ethyl]-6-methylenebicyclo[3.2.1]octan-2-one (36).** The 4:1 mixture of **35** and **34** (2 mg, 0.006 mmol) was treated as described above for **34**. Flash chromatography (10:1 hexane–EtOAc) afforded 1.6 mg (89%) of a 4:1 mixture of **36** and **3**.

The data for **36** were determined from the mixture: ^{1}H NMR 5.07 (br s, 1), 4.99 (br s, 1), 2.87 (m, 1), 2.49–2.24 (m, 8), 2.04–1.10 (m, 11), 1.19 (s, 3), 0.93 (s, 3), 0.76 (s, 3); ^{13}C NMR 213.7 (C-9), 152.7 (C-16), 106.7 (C-17), 74.4 (C-10), 58.0 (C-5), 57.5 (C-8), 44.7 (C-14), 42.3 (C-13), 41.8 (C-1), 41.4 (C-15), 41.0 (C-3), 38.3 (C-7), 36.2 (C-11), 35.3 (C-4), 34.1 (C-12), 32.6 (C-19), 23.7 (C-20), 22.1 (C-6), 21.1 (C-18), 20.3 (C-2).

Acknowledgment. We are grateful to the National Institutes of Health for generous financial support. We thank Prof. Dennis Curran, University of Pittsburgh, for helpful discussions regarding the temperature effect on the yield of the cyclization.

Supplementary Material Available: ^{1}H and ^{13}C NMR spectra of **3**, **7**, **16**, **20**, **25**, **26**, **28**, and **33–36** (22 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

Synthetic Studies on Wortmannin and 11-Desacetoxywortmannin

Chris A. Broka* and Beatrice Ruhland

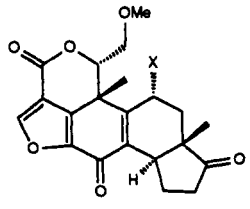
Syntex Research, Institute of Bio-Organic Chemistry, 3401 Hillview Avenue, Palo Alto, California 94304

Received April 3, 1992

This report describes the first synthesis of the highly reactive furanocyclohexadienone lactone subunit of the natural products wortmannin (**1**) and 11-desacetoxywortmannin (**2**). The simplified wortmannin analogue **6** was prepared by acid treatment of aminomethylene lactone **22** in analogy to the known conversion of lactone **3** into wortmannin. Compound **22** was, in turn, prepared from the readily accessible lactone **18** through sequential oxidations and introduction of the aminomethylene unit using tris(dimethylamino)methane.

Wortmannin (**1**)[1] and its desacetoxy derivative **2**[2] are antifungal antibiotics isolated from the culture filtrates of several *Penicillium* and *Myrothecium* species. Both **1** and **2** are potent antiinflammatory agents, a fact first

0022-3263/92/1957-4888$03.00/0

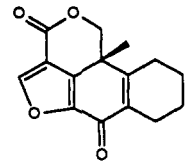


1 X = OAc
2 X = H

recognized by Hauser and his colleagues at Sandoz who showed them to compare favorably with indomethacin in several in vivo assays.[3] Unfortunately, their toxicity rendered them unsuitable for clinical development. Wortmannin has been shown to inhibit fMet-Leu-Phe-stimulated superoxide production and phospholipase D activation in human neutrophils, perhaps by disrupting the function of a GTP-binding protein involved in transduction of the fMet-Leu-Phe signal.[4]

In spite of their interesting biological activities and challenging structures, 1 and 2 have received little synthetic attention. This fact may be due, in part, to their chemical instability which promises to complicate any effort directed toward their synthesis. This report describes the first successful approach to the chemically reactive furanocyclohexadienone lactone subunit of 1 and 2. The present route circumvents many of the difficulties associated with the instability of 1 and 2 and should, moreover, prove sufficiently versatile to allow for the preparation of both the natural substances and a variety of unnatural analogues. Our retrosynthetic analysis of 1 is outlined below (Scheme I).

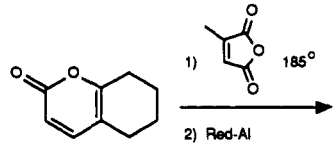
That 3 should serve as the immediate precursor of 1 follows from the chemical investigations of the Sandoz group. Haefliger and Hauser demonstrated that 1 and 2 are both active alkylating agents, reacting with ammonia, aniline, and diethylamine to give derivatives exactly analogous to 3.[5] In contrast to 1 and 2, these aminomethylene lactones are stable to a range of nucleophilic conditions. Furthermore, treatment of these materials with acid regenerates 1. Thus, 3 and similar compounds may be thought of as protected forms of 1 and were, in fact, employed in this capacity by the Sandoz group to prepare semisynthetic analogues of 1 and 2. (Note also that acid treatment should serve to deprotect the cyclopentanone moiety of 3). The preparation of 3 can therefore be considered equivalent to the preparation of 1 itself. It seemed reasonable to hope that 3 could be obtained from the diol lactone 4 and that this compound could, in turn, be obtained from the Diels–Alder derived intermediate 5. However, we did not wish to undertake anything so ambitious as the total synthesis of 1 without the prior assurance that our key transformations (i.e., 5 → 4 → 3) could be made to take place. Accordingly, the simplified wortmannin analogue 6, which still contains the reactive functionality present in the natural systems, was selected as an initial target. Its synthesis is detailed below.



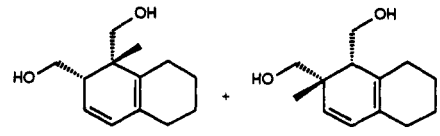
6

Results and Discussion

The diol 8a, our surrogate for 5, was prepared in a straightforward manner. Diels–Alder reaction of citraconic anhydride with the known[6] 4,5,6,7-tetrahydrocoumarin (7) gave a mixture of anhydrides which, without isolation, were treated with excess Red-Al giving 8a,b.



7



8a (13%) 8b (26%)

Several unsuccessful attempts, one involving the use of high pressure,[7] were made to improve the poor regioselectivity and meager yield of the cycloaddition. However, since the starting materials were easy to obtain and also because the *intermolecular* Diels–Alder reaction used to prepare 8a was irrelevant from the standpoint of our contemplated wortmannin synthesis (Scheme I), it was decided to carry out the preparation of this starting material once, on a multigram scale, thereby ensuring an adequate supply of the compound.

Taking advantage of the steric encumbrance of the neopentyl hydroxy group of 8a, this compound was differentially protected to afford 9. Early efforts to construct the lactone ring of 6 while the diene unit was still intact were unsuccessful, and we thus proceeded to osmylate the more accessible of its two double bonds and to protect the resulting diol 10 as its acetonide 11. Removal of the pivaloate moiety with MeLi (which proved far superior to the use of DIBAL or other methods) gave 12 in good overall yield from 9 (Scheme II).

Conversion of the alcohol 12 into its mesylate and treatment of this compound with NaCN afforded the expected nitrile 14. This compound was deprotected, mesylated, and treated with alkaline H_2O_2[8] in the hope of achieving its conversion into lactone 17. Unfortunately, the mesylate failed to react under these conditions. We found, however, that treatment of 14 with DIBAL cleanly produced aldehyde 15 and that this compound could be

(1) (a) MacMillan, J.; Vanstone, A. E.; Yeboah, S. K.; *J. Chem. Soc., Chem. Commun.* **1968**, 613. (b) MacMillan, J.; Vanstone, A. E.; Yeboah, S. K. *J. Chem. Soc., Perkin Trans. 1* **1972**, 2898. (c) Petcher, T. J.; Weber, H.-P.; Kis, Z. *J. Chem. Soc., Chem. Commun.* **1972**, 1061. (d) MacMillan, J.; Simpson, T. J.; Yeboah, S. K. *J. Chem. Soc., Chem. Commun.* **1972**, 1063.

(2) Haefliger, W.; Hauser, D. *Helv. Chim. Acta* **1973**, *56*, 2901.

(3) Wiesinger, D.; Gubler, H. U.; Haefliger, W.; Hauser, D. *Experientia* **1974**, 135.

(4) (a) Baggiolini, M.; Dewald, B.; Schnyder, J.; Ruch, W.; Cooper, P. H.; Payne, T. G. *Exp. Cell Res.* **1987**, *169*, 408. (b) Dewald, B.; Thelen, M.; Baggiolini, M. *J. Biol. Chem.* **1988**, *263*, 16179. (c) Bonser, R. W.; Thompson, N. T.; Randall, R. W.; Garland, L. G. *Biochem. J.* **1989**, *264*, 617. (d) Reinhold, S. L.; Prescott, S. M.; Zimmerman, G. A.; McIntyre, T. M. *FASEB* **1990**, *210*, 208. (e) Bonser, R. W.; Thompson, N. T.; Randall, R. W.; Tateson, J. E.; Spacey, G. D.; Hodson, H. F.; Garland, L. G. *Br. J. Pharmacol.* **1991**, *103*, 1237.

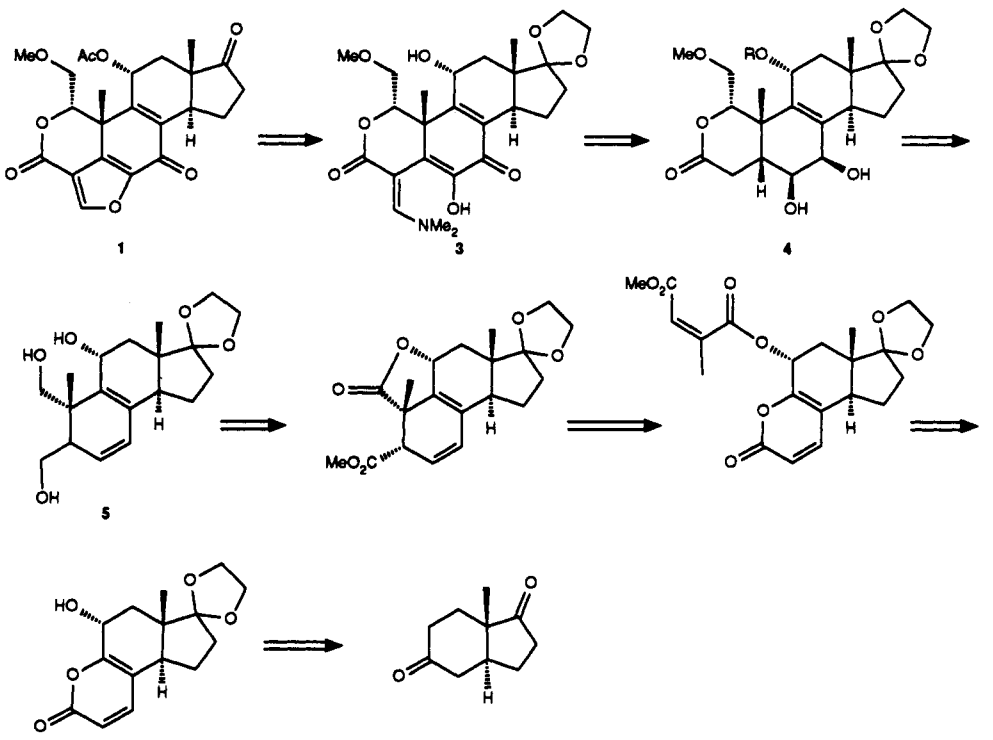
(5) (a) Haefliger, W.; Kis, Z.; Hauser, D. *Helv. Chim. Acta* **1975**, *58*, 1620. (b) Haefliger, W.; Hauser, D. *Helv. Chim. Acta* **1975**, *58*, 1629. (c) Haefliger, W.; Hauser, D. *Synthesis* **1980**, 236.

(6) Dionne, G.; Engel, C. R. *Can. J. Chem.* **1978**, *56*, 419.

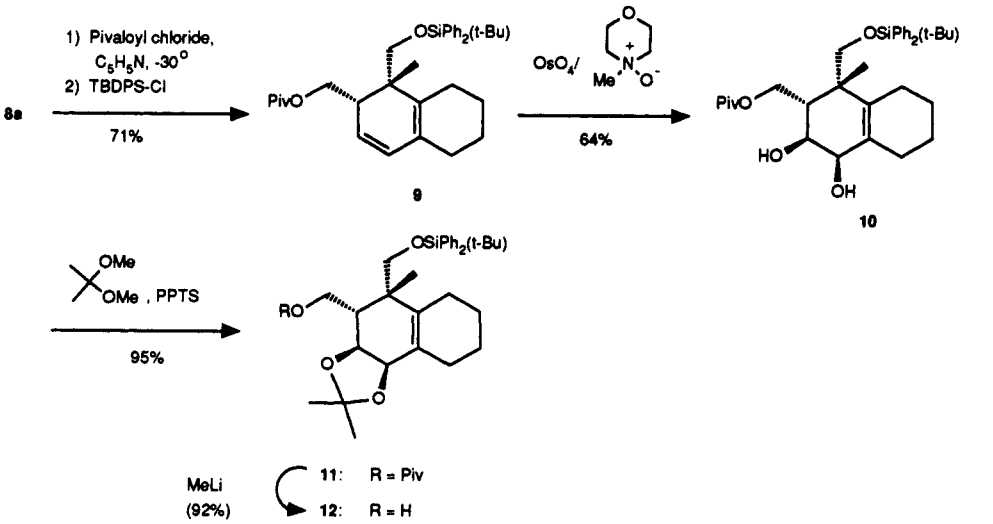
(7) We are grateful to Professor W. Dauben (UC Berkeley) for the use of his high-pressure equipment. Replacement of citraconic anhydride with chloromethylmaleic anhydride (see Schreiber, J.; Leimgruber, W.; Pesaro, M.; Schudel, P.; Threlfall, T.; Eschenmoser, A. *Helv. Chim. Acta* **1961**, *44*, 540) also failed to improve the outcome of the cycloaddition.

(8) Corey, E. J.; Kamiyama, K. *Tetrahedron Lett.* **1990**, *31*, 3995.

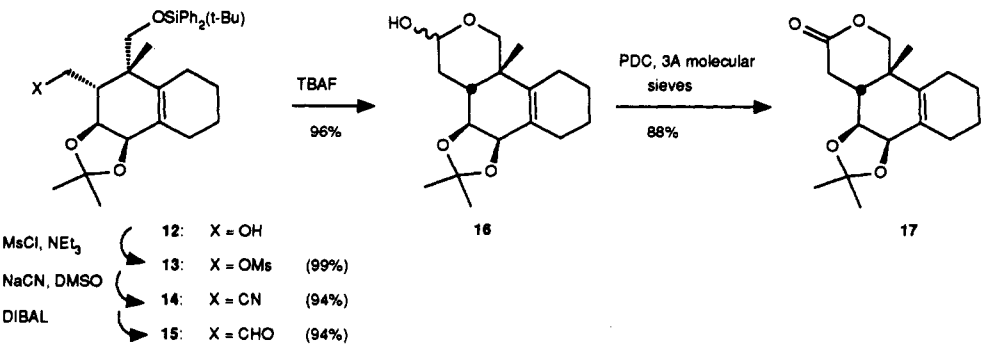
Scheme I



Scheme II



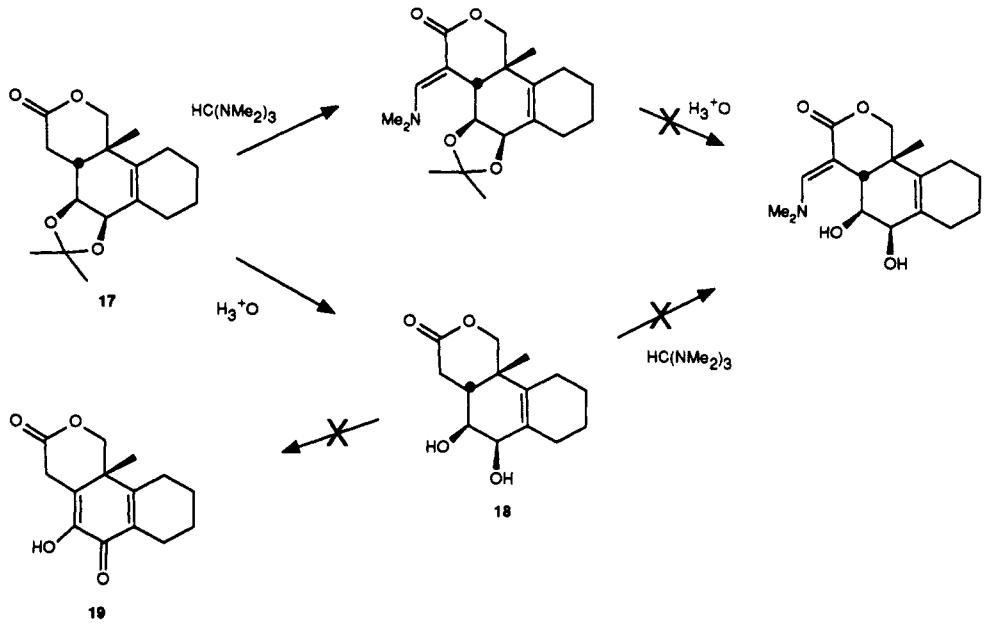
Scheme III



converted into the hemiacetal **16** and thence into **17** in excellent overall yield by sequential deprotection and oxidation (Scheme III).

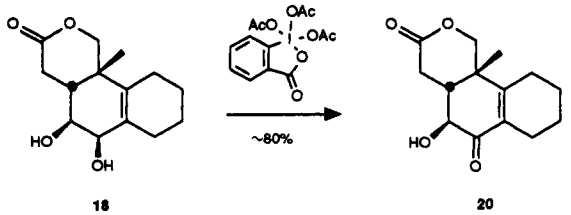
With **17** now in hand it only remained to introduce the aminomethylene unit and to convert the protected diol into the required diosphenol. At the outset, though, it was far from clear in which order (or even how) these transformations were to be brought about. We quickly discovered that treatment of **17** with excess tris(dimethylamino)-methane[9,10] (neat, 73 °C, 12 h) produced the expected

Scheme IV

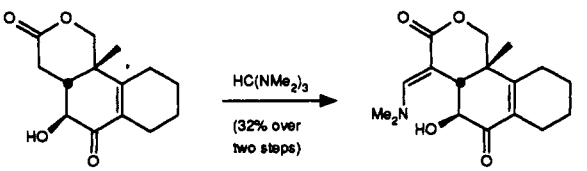


aminomethylene lactone in 68% yield (Scheme IV). However, attempts to remove the acetonide protecting group from this compound without destroying the aminomethylene unit failed. Accordingly, **17** was first deprotected giving the diol **18**, and then this compound was reacted with tris(dimethylamino)methane. Unfortunately, we were not able to convert **18** into the desired aminomethylene diol either. It may well be that the free diol unit of **18** reacts with tris(dimethylamino)methane generating an unstable dimethylformamide acetal. In any case, no characterizable products could be isolated from reaction of **18** with tris(dimethylamino)methane or similar reagents. At the same time, efforts were under way to convert **18** into the diosphenol **19** in hopes that this compound would react productively with tris(dimethylamino)methane. Treatment of **18** with a variety of oxidizing agents (including PCC, PDC, oxygen under basic conditions, and $(COCl)_2$–DMSO) led to no isolable products. In some reactions the formation of a yellowish, UV-active, product was noted but the material invariably decomposed on attempted purification.

Faced with these disappointments, we arrived at the idea of oxidizing **18** to the diosphenol in separate stages. In analogy with literature precedent,[11] **18** could be oxidized with freshly prepared Fetizon's reagent to the α-hydroxyenone **20**. (We were not able to achieve this transformation using MnO_2). In due course it was found that **20** could be obtained still more efficiently from **18** using the Dess–Martin reagent[12] and carefully monitoring the reaction to prevent overoxidation.



The α-hydroxyenone **20** proved to be rather unstable and, although it could be purified for NMR characterization, it was usually carried forward as such to avoid extensive loss of material.[13] Efforts were made to oxidize **20** to **19** using several reagents of which $Cu(OAc)_2$[14] showed the most promise. However, this exploratory work was brought to a halt by the discovery that **20** *could* be made to react with tris(dimethylamino)methane giving **21**, albeit in modest yield! While it was neither sufficiently stable nor available in quantities large enough for full characterization, the ^1H NMR spectrum of **21**, which showed the aminomethylene unit to be present and the protons adjacent to the lactone carbonyl to be absent, clearly confirmed its structure. (We have no evidence regarding the stereochemistry of the aminomethylene double bond although we have presented **21** as the *E* isomer in accordance with literature precedent.)



Building upon our earlier findings, we subjected **21** to $Cu(OAc)_2$ oxidation (MeOH, 0 °C, 90 min). The starting material disappeared cleanly, generating a less polar and less stable product, presumed to be the diosphenol **22**. Following extractive workup to remove the copper salts, the crude product was quickly taken up in dioxane and treated with HCl under the conditions employed by Haefliger and Hauser.[5a] We were pleased to find that the intermediate diosphenol was consumed, giving rise to a new product which answered to the description of **6** (42% yield over two steps) (Scheme V).

The spectra of our product were fully consistent with its assigned structure and agreed well with the corresponding data reported[1] for wortmannin itself. The furan

(9) (a) Bredereck, H.; Effenberger, F.; Brendle, T.; Muffler, H. *Chem. Ber.* **1968**, *101*, 1885. (b) Weingarten, H.; Edelman, N. K. *J. Org. Chem.* **1967**, *32*, 3293.

(10) Abdulla, R. F.; Brinkmeyer, R. S. *Tetrahedron* **1979**, *35*, 1675.

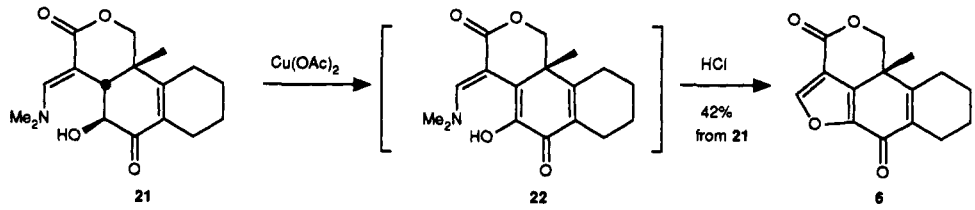
(11) Tronchet, J. M. J.; Tronchet, J.; Birkhauser, A. *Helv. Chim. Acta* **1970**, *53*, 1489.

(12) Dess, D. B.; Martin, J. C. *J. Org. Chem.* **1983**, *48*, 4155.

(13) In practice it is desirable to carry out the last four steps of the synthesis over a period of no more than a few days. Both **20** and **22** deteriorate upon prolonged storage.

(14) Wendler, N. L.; Taub, D.; Graber, R. P. *Tetrahedron* **1959**, *7*, 173.

Scheme V



proton appears as a singlet at δ 8.19 while in wortmannin it appears at δ 8.22. The methyl group of **6** is observed at δ 1.62 and that of wortmannin at δ 1.71. The lactone methylene appears as a geminally coupled doublet of doublets centered at δ 4.35. Infrared absorptions for the carbonyls of **6**, at 1732 and 1674 cm^{-1}, corresponded with those of wortmannin at 1732 and 1684 cm^{-1}. A strong molecular ion (m/z = 258.0892) was present in the high-resolution mass spectrum of **6**, indicating an empirical formula of $C_{15}H_{14}O_4$ for the compound. Strong peaks were observed at m/z = 243 and m/z = 228 which correspond to the loss of the methyl group and formaldehyde, respectively, from **6**. The mass spectrum of wortmannin also exhibits a molecular ion peak as well as peaks corresponding to the loss of one methyl group and the loss of $MeOCH_2CHO$. The UV spectrum of **6** coincided almost exactly with that of wortmannin with λ_{max} = 257 nm (ϵ 13 800) and 293 nm (ϵ 8100). (For wortmannin itself λ_{max} = 257 nm (ϵ 11 770) and 292 nm (ϵ 7700).[1b])

Conclusions

We have been successful in preparing the furanocyclohexadienone lactone **6**, a simplified analogue of wortmannin (**1**), by a route which takes advantage of Hauser's discovery that this reactive system may be reversibly protected as a dialkylaminomethylene lactone. It has been found that the order in which the three key transformations leading from **18** to **22** (two oxidations and introduction of the aminomethylene unit) are performed is crucial for success. To our surprise, most of the difficulties which were encountered in the transformation of **18** into **6** resulted from the instability of the three intermediates **20**, **21**, and **22**. Nevertheless, a judicious choice of reaction conditions did make possible the conversion of **18** into **6** in 13.5% overall yield and it seems likely that further refinements will succeed in increasing this figure to something more acceptable. It also seems likely that the methods developed for the synthesis of **6** will, without major modification, prove usable for the synthesis of the natural products **1** and **2**.

The wortmannin analogue **6** was tested for its ability to block fMet-Leu-Phe-stimulated generation of superoxide by neutrophils and was found to be inactive under conditions where wortmannin itself possessed an IC_{50} of 0.1 μM.

Experimental Section

General Procedures. THF and ether were distilled from sodium benzophenone. CH_2Cl_2 was distilled from calcium hydride, and benzene and toluene were distilled from sodium. Other reagents and solvents were purified as needed. Column chromatography was performed using Scientific Products silica gel (230–240 mesh). Analtech plates measuring 20 cm × 10 cm with a layer of silica gel 1-mm thick were used for preparative TLC. Analytical TLC was performed using Analtech glass-blocked (0.25-mm) silica gel plates. TLC plates were visualized by fluorescence quenching and developed with phosphomolybdic acid or anisaldehyde reagent. Anisaldehyde reagent was prepared from 90% aqueous EtOH (300 mL), AcOH (3.7 mL), H_2SO_4 (12.3 mL), and *p*-anisaldehyde (9.1 mL). All reactions, unless indicated otherwise, were performed in oven-dried (135 °C) glassware under nitrogen.

1,2-Bis(hydroxymethyl)-1-methyl-1,2,5,6,7,8-hexahydronaphthalene (8a) and Its Regioisomer 8b. A mixture of 4,5,6,7-tetrahydrocoumarin (6.6 g, 0.044 mol) and citraconic anhydride (7.39 g, 0.066 mol) was heated at 185 °C, under argon, in a sealed tube for 11 h. After the mixture was cooled, the crude product was dissolved in a 700 mL of a THF–toluene mixture (1:1) and treated with Red-Al (38 mL of a 3.4 M solution in toluene, 0.13 mol) for 15 h at reflux. After the mixture was cooled, water was added (80 mL) and the two layers were separated. The aqueous layer was extracted with dichloromethane (3 × 300 mL), and the combined organic layers were dried ($MgSO_4$) and evaporated in vacuo. The residue was purified by flash chromatography (silica gel, 10% ethyl acetate in hexane) to give the diol **8a** (1.2 g, 13%) and the diol **8b** (2.4 g, 26%).

Diol **8a**: *colorless gum*; R_f = 0.47 (*hexane/ethyl acetate* (1:1)); IR (neat) ν_{max} 3271, 2961, 1464, 1260, 1090, 1018 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.72 (dd, J = 9.5, 1.9 Hz, 1 H), 5.61 (dd, J = 9.5, 4.2 Hz, 1 H), 3.74 (2 dd tbs, J = 11.4, 2.7, 11.5, 6 Hz, 3 H), 3.31 (d tbs, J = 11.3 Hz, 3 H), 2.28 (m, 1 H), 2.05–1.95 (m, 4 H), 1.65–1.55 (m, 4 H), 1.58 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$), δ 133.8, 128.9, 127.8, 64.1, 61.7, 46.4, 41.6, 29.24, 23.2, 22.4, 19.7; MS m/e 208 (M^+), 190, 178, 147, 105; HRMS calcd for $C_{13}H_{20}O_2$ m/z 208.1463, found 208.1463.

Diol **8b**: colorless gum; R_f = 0.53 (hexane/ethyl acetate (1:1)); IR (neat) ν_{max} 3377, 3020, 2925, 1456, 1418, 1052, 1036 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.63 (d, J = 9.5 Hz, 1 H), 5.21 (d, J = 9.5 Hz, 1 H), 3.78–3.66 (m, 2 H), 3.45–3.39 (m, 2 H), 3.22–2.84 (bs 2 H), 2.18–2.02 (m, 1 H), 2.01–1.87 (m, 4 H), 1.71–1.56 (m, 4 H), 1.00 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 129.53, 128.65, 127.36, 127.20, 68.87, 60.08, 49.92, 40.12, 29.39, 27.96, 23.04, 22.99, 21.93; MS m/z 208 (M^+), 190, 178, 147, 105; HRMS calcd for $C_{13}H_{20}O_2$ m/z 208.1463, found 208.1465.

1-[[(Diphenyl-*tert*-butylsilyl)oxy]methyl]-1-methyl-2-[(pivaloyloxy)methyl]-1,2,5,6,7,8-hexahydronaphthalene (9). A solution of the diol **8a** (0.930 g, 4.47 mmol) in dichloromethane (10 mL) and dry pyridine (542 μL, 6.7 mmol) was stirred for 10 min at −30 °C. Then trimethylacetyl chloride (605 μL, 4.91 mmol) was added, and the remaining solution was stirred for 1 h at −30 °C. The reaction mixture was poured into saturated sodium bicarbonate (3 mL) and extracted with dichloromethane. The combined organic layers were dried ($MgSO_4$) and evaporated in vacuo. The residue was purified by flash chromatography (silica gel, 5% ethyl acetate in hexane) to give the ester (0.956 g, 74%): colorless gum; R_f = 0.44 (hexane/ethyl acetate (8:2)); ^1H NMR (300 MHz, $CDCl_3$) δ 5.69 (dd, J = 9.5, 1.5 Hz, 1 H), 5.61 (dd, J = 9.5, 4 Hz, 1 H), 4.37 (dd, J = 11, 5.2 Hz, 1 H), 4.06 (dd, J = 11, 7.6 Hz, 1 H), 2.46–2.51 (m, 1 H), 2.05–1.85 (m, 5 H), 1.61–1.54 (m, 4 H), 1.19 (s, 9 H), 1.08 (s, 3 H).

A solution of the ester (0.940 g, 3.21 mmol) in DMF (30 mL) was cooled at 0 °C. Imidazole (0.437 g, 6.42 mmol) was added, and after 5 min of stirring at 0 °C *tert*-butyldiphenylsilyl chloride (1.25 mL, 4.81 mmol) was added. After being stirred for 15 min at 0 °C, the solution was heated at 70 °C and stirred for 15 h. After being cooled, the reaction mixture was poured into saturated sodium bicarbonate solution and extracted with dichloromethane. The combined organic layers were dried ($MgSO_4$) and evaporated in vacuo. The residue was purified by flash chromatography (silica gel, 10% ethyl acetate in hexane) to give the protected diol **9** (1.55 g, 96%): colorless gum; R_f = 0.72 (hexane/ethyl acetate (9:1)); IR (neat) ν_{max} 2962, 2921, 2852, 1733, 1456, 1260, 1093, 1020 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.67–7.63 (m, 4 H), 7.45–7.35 (m, 6 H), 5.70–5.61 (m, 2 H), 4.41 (dd, J = 10.6, 4 Hz, 1 H), 4.16 (dd, J = 10.2, 10.2, Hz, 1 H), 3.57 (d, J = 10 Hz, 1 H), 3.43 (d, J = 10 Hz, 1 H), 2.56–2.53 (m, 1 H), 2.05–1.94 (m, 3 H), 1.82 (m, 1

H), 1.56–1.46 (m, 4 H), 1.16 (s, 12 H), 1.06 (s, 9 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 178.63, 135.79, 135.72, 135.64, 134.30, 133.43, 129.62, 129.59, 128.45, 127.67, 127.60, 125.10, 65.22, 64.88, 43.09, 40.93, 38.76, 28.96, 27.20, 26.90, 24.69, 23.12, 22.33, 19.96, 19.26; MS *m/e* 503 (M + 1), 371, 311, 283, 159.

1-[[(Diphenyl-*tert*-butylsilyl)oxy]methyl]-1-methyl-2-[(pivaloyloxy)methyl]-3,4-dihydroxy-1,2,3,4,5,6,7,8-octahydronaphthalene (10). A small crystal of osmium tetraoxide was added to a solution of the diene **9** (1.36 g, 2.70 mmol) in 55 mL of an acetone–water mixture (9:1) containing 4-methylmorpholine *N*-oxide (0.348 g, 2.97 mmol). This resulting mixture was stirred for 2 days at 25 °C and then poured into saturated sodium bicarbonate and extracted with dichloromethane (2 × 50 mL) and with ethyl acetate (2 × 50 mL). The combined organic layers were dried ($MgSO_4$) and evaporated in vacuo. The residue was purified by flash chromatography (silica gel, 20% ethyl acetate in hexane) to give the diol **10** (0.970 g, 64%): colorless gum; R_f = 0.2 (hexane/ethyl acetate 8:2); IR (neat) ν_{max} 3450, 2930, 1726, 1420, 1280, 1161, 1027 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.63–7.57 (m, 4 H), 7.47–7.34 (m, 6 H), 4.61 (dd, *J* = 11.6, 4.4 Hz, 1 H), 4.46 (dd, *J* = 11.6, 6.4 Hz, 1 H), 4.39 (dd, *J* = 11.8, 4.2 Hz, 1 H), 3.86 (d, *J* = 4.2 Hz, 1 H), 3.48 (d, *J* = 11.1 Hz, 1 H), 3.43 (d, *J* = 11.1 Hz, 1 H), 2.51–2.44 (m, 1 H), 2.03–1.91 (m, 2 H), 1.83–1.63 (m, 4 H), 1.53–1.32 (m, 2 H), 1.18 (s, 9 H), 1.03 (s, 9 H), 0.97 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 178.26, 136.20, 135.75, 135.67, 132.97, 132.90, 130.36, 129.83, 127.79, 127.68, 70.17, 69.88, 66.16, 64.80, 44.91, 44.46, 38.66, 29.07, 27.15, 26.92, 24.28, 22.99, 22.64, 21.65, 19.14, 14.21; MS *m/e* 564 (M$^+$), 507, 462, 387, 309, 283, 193; HRMS calcd for $C_{34}H_{48}O_5Si$ *m/z* 564.3271, found 564.3278.

Acetonide 11. A solution of the diol **10** (0.967 g, 1.71 mmol) in dichloromethane (30 mL) was treated with 2,2-dimethoxypropane (632 μL, 5.13 mmol) in the presence of a catalytic amount of pyridinium *p*-toluenesulfonate (5 mg, 20 μmol) at 25 °C for 20 h. The mixture was then poured into a saturated sodium bicarbonate solution and extracted with dichloromethane. The combined organic layers were dried ($MgSO_4$) and evaporated in vacuo. The residue was purified by flash chromatography (silica gel, 2.5% ethyl acetate in hexane) to give the acetonide **11** (0.982 g, 95%): colorless gum; R_f = 0.7 (hexane/ethyl acetate (8:2)); IR (neat) ν_{max} 2960, 1729, 1157, 1062 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.63–7.57 (m, 4 H), 7.46–7.34 (m, 6 H), 4.50 (dd, *J* = 10.7, 6.4 Hz, 1 H), 4.44–4.27 (m, 3 H), 3.46 (d, *J* = 10.8 Hz, 1 H), 3.36 (d, *J* = 10.7 Hz, 1 H), 2.49–2.39 (m, 1 H), 2.2–1.52 (m, 8 H), 1.47 (s, 3 H), 1.36 (s, 3 H), 1.13 (s, 9 H), 1.01 (s, 9 H), 0.97 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 178.51, 136.73, 135.68, 135.60, 132.94, 129.79, 127.93, 127.79, 127.69, 107.81, 75.29, 74.33, 66.51, 63.95, 46.64, 44.37, 38.56, 29.70, 28.41, 28.34, 27.15, 26.81, 25.74, 25.04, 22.96, 22.22, 20.52, 19.04; MS *m/e* 604 (M$^+$), 547, 502, 387, 283, 233; HRMS calcd for $C_{37}H_{52}O_5Si$ *m/z* 604.3584, found 604.3581.

Alcohol Acetonide 12. A solution of the ester **11** (0.698 g, 1.15 mmol) in dichloromethane (50 mL) was treated with a large excess of methyllithium (10 mL of a 1.4 M solution in ether, 14 mmol) at −78 °C for 90 min. The reaction mixture was poured into saturated sodium bicarbonate solution (15 mL) and extracted. The aqueous layer was extracted with dichloromethane (3 × 20 mL), and the combined organic layers were dried ($MgSO_4$) and evaporated in vacuo. The residue was purified by flash chromatography (silica gel, 10% ethyl acetate in hexane) to give the alcohol **12** (0.553 g, 92%): colorless gum; R_f = 0.48 (hexane/ethyl acetate (8:2)); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.64–7.56 (m, 4 H), 7.48–7.35 (m, 6 H), 4.82 (dd, *J* = 10.8, 6.3 Hz, 1 H), 4.30 (d, *J* = 6.3 Hz, 1 H), 4.05–3.94 (m, 3 H), 3.63–3.54 (bs, 1 H), 3.29 (d, *J* = 10.7 Hz, 1 H), 3.20 (d, *J* = 10.7 Hz, 1 H), 2.44–2.38 (m, 1 H), 2.17–1.53 (m, 8 H), 1.51 (s, 3 H), 1.39 (s, 3 H), 1.03 (s, 9 H), 0.91 (s, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 136.89, 135.69, 135.65, 132.76, 132.65, 129.89, 127.87, 127.78, 127.71, 108.37, 76.76, 75.15, 65.71, 63.97, 48.01, 44.36, 28.63, 28.37, 26.83, 25.85, 24.62, 22.86, 22.15, 19.97, 19.05.

Mesylate 13. A solution of the alcohol **12** (0.553 g, 1.06 mmol) in dichloromethane (10 mL) was treated with NEt_3 (590 μL, 4.2 mmol) and mesyl chloride (164 μL, 2.1 mmol) and stirred for 1 h at 25 °C. The solution was then poured into a saturated sodium bicarbonate solution and extracted with dichloromethane. The combined organic layers were dried ($MgSO_4$) and evaporated in vacuo. The residue was purified by flash chromatography (silica gel, 10% ethyl acetate in hexane) to give the mesylate **13** (0.630 g, 99%): colorless gum; R_f = 0.39 (hexane/ethyl acetate (8:2)); IR (neat) ν_{max} 2962, 1360, 1260, 1086, 1021 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.64–7.55 (m, 4 H), 7.44–7.34 (m, 6 H), 4.67–4.52 (m, 3 H), 4.37 (d, *J* = 6.4 Hz, 1 H), 3.56 (d, *J* = 10.9 Hz, 1 H), 3.55 (d, *J* = 10.9 Hz, 1 H), 2.94 (s, 3 H), 2.48–2.38 (m, 1 H), 2.09–1.52 (m, 8 H), 1.46 (s, 3 H), 1.37 (s, 3 H), 1.03 (s, 9 H), 0.94 (s, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 135.77, 135.70, 129.86, 128.09, 127.84, 127.69, 108.09, 75.28, 72.51, 68.67, 67.09, 66.42, 47.57, 44.52, 36.98, 28.44, 26.83, 25.73, 24.78, 22.82, 22.15, 20.20; MS *m/e* 598 (M$^+$), 483, 387, 277, 199; HRMS calcd for $C_{33}H_{46}O_6SSi$ *m/z* 598.2784, found 598.2777.

Nitrile 14. A solution of the mesylate **13** (255 mg, 0.43 mmol) in DMSO (10 mL) was treated with potassium cyanide (85 mg, 1.31 mmol) at 65 °C for 15 h. After being cooled, the reaction mixture was poured into a saturated sodium bicarbonate solution and extracted with dichloromethane. The organic layer was dried ($MgSO_4$) and evaporated in vacuo. The residue was purified by flash chromatography (silica gel, 10% ethyl acetate in hexane) to give the nitrile **14** (215 mg, 94%): white crystalline solid; mp 117–121 °C; R_f = 0.52 (hexane/ethyl acetate (8:2)); IR (neat) ν_{max} 2932, 2220, 1590, 1428, 1215, 1082 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.62–7.56 (m, 4 H), 7.47–7.37 (m, 6 H), 4.46 (dd, *J* = 10.9, 6.2 Hz, 1 H), 4.29 (d, *J* = 6.2 Hz, 1 H), 3.39 (d, *J* = 11.6 Hz, 1 H), 3.36 (d, *J* = 11.6 Hz, 1 H), 2.63 (d, *J* = 6 Hz, 2 H), 2.48–2.37 (m, 1 H), 2.04–1.62 (m, 8 H), 1.50 (s, 3 H), 1.38 (s, 3 H), 1.03 (s, 9 H), 0.98 (s, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 136.15, 135.68, 135.65, 132.64, 132.58, 129.99, 129.95, 128.27, 127.84, 127.77, 120.41, 108.53, 75.67, 74.99, 65.29, 45.21, 44.94, 28.53, 28.51, 26.86, 25.85, 24.95, 22.81, 22.07, 20.14, 19.02, 15.50; MS *m/e* 529 (M$^+$), 472, 414, 199; HRMS calcd for $C_{33}H_{43}NO_3Si$ *m/z* 529.3012, found 529.3014.

Aldehyde 15. A solution of the nitrile **14** (537.5 mg, 1.01 mmol) in toluene (25 mL) was cooled at −78 °C and treated with diisobutylaluminium hydride (1.12 mL of a 1 M solution in hexane). After the solution was stirred for 3 h at −78 °C, the reaction was quenched with methanol (7 mL) and the solution was allowed to warm to room temperature. The solution was diluted with dichloromethane, poured into water, and extracted. The aqueous layer was extracted with dichloromethane and with chloroform. The combined organic layers were dried ($MgSO_4$) and evaporated in vacuo. The residue was purified by flash chromatography (silica gel, 10% ethyl acetate in hexane) to give the aldehyde **15** (507 mg, 94%): white crystalline solid; mp 90–93 °C; R_f = 0.33 (hexane/ethyl acetate (8:2)); IR (neat) ν_{max} 2932, 1725, 1173, 1082 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.80 (t, *J* = 2.5 Hz, 1 H), 7.63–7.56 (m, 4 H), 7.48–7.35 (m, 6 H), 4.58 (dd, *J* = 10.8, 6.2 Hz, 1 H), 4.33 (d, *J* = 6.2 Hz, 1 H), 3.30 (s, 2 H), 2.54 (dd, *J* = 5.9, 2.3 Hz, 2 H), 2.51–2.43 (m, 1 H), 2.19–1.51 (m, 8 H), 1.44 (s, 3 H), 1.35 (s, 3 H), 1.01 (s, 9 H), 0.81 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 202.74, 136.39, 135.54, 135.40, 132.74, 132.54, 129.72, 127.93, 127.66, 127.56, 108.09, 76.87, 75.05, 65.56, 44.73, 43.52, 43.37, 28.54, 28.11, 26.65, 25.67, 24.99, 22.76, 22.07, 19.87, 18.87; MS *m/e* 532 (M$^+$), 474, 418, 417, 339, 295, 276, 199, 135; HRMS calcd for $C_{33}H_{44}O_4Si$ *m/z* 532.3008, found 532.3009.

Hemiacetal 16. A solution of the aldehyde **15** (498 mg, 0.935 mmol) in THF (30 mL) was cooled at 0 °C and treated with tetrabutylammonium fluoride (1.03 mL of a 1 M solution in THF, 1.03 mmol). The solution was stirred for 2 h at 0 °C, diluted with water, and then extracted with dichloromethane. The combined organic layers were dried ($MgSO_4$) and evaporated in vacuo. The residue was purified by flash chromatography (silica gel, 20% of ethyl acetate in hexane) to give **16** (264 mg, 96%): colorless gum (ca. 1:1 mixture of isomers as judged by NMR); R_f = 0.55 (hexane/ethyl acetate (1:1)); IR (neat) ν_{max} 3210, 2983, 1387, 1216, 1071 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.08 (t, *J* = 3.7 Hz) and 4.80 (dd, *J* = 7.4, 2.9 Hz, 1 H), 4.24 and 4.02 (m, 2 H), 3.82 and 3.53 (2d, *J* = 12 Hz, 1 H), 3.38 and 2.99 (2d, *J* = 12 Hz, 1 H), 2.32–2.18 (m, 1 H), 1.90–1.41 (m, 8 H), 1.57 and 1.56 (2s, 3 H), 1.55 and 1.54 (2s, 3 H), 1.07 and 1.03 (2s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 135.42, 135.16, 127.32, 127.17, 108.35, 95.16, 91.77, 76.62, 76.10, 75.44, 75.25, 69.87, 66.09, 40.57, 37.94, 37.53, 37.06, 31.72, 30.14, 28.51, 28.12, 27.85, 27.80, 27.74, 25.51, 24.67, 24.40, 23.14, 22.98, 22.31, 22.27, 20.72; HRMS calcd for $C_{17}H_{26}O_4$ *m/z* 294.1831, found 294.1833.

Lactone 17. A solution of the hemiacetal **16** (264 mg, 0.897 mmol) in dichloromethane (30 mL), containing Celite (100 mg) and molecular sieves (3 Å), was treated with pyridinium dichromate (505 mg, 1.34 mmol) at 25 °C for 17 h. The reaction mixture was filtered through Florisil and concentrated in vacuo. The residue was purified by flash chromatography (silica gel, 10% ethyl acetate in hexane) to give the lactone **12** (230 mg, 88%): colorless gum; R_f = 0.35 (hexane/ethyl acetate (7:3)); IR (neat) ν_{max} 2859, 1733, 1378, 1234, 1160, 1026 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 4.31 (d, J = 5.5 Hz, 1 H), 4.12 (d, J = 11.7 Hz, 1 H), 4.07 (d, J = 5.7 Hz, 1 H), 3.92 (d, J = 11.6 Hz, 1 H), 2.79 (d, J = 9.3 Hz, 1 H), 2.73 (d, J = 9.3 Hz, 1 H), 2.42–2.25 (m, 3 H), 2.11–1.89 (m, 2 H), 1.64–1.61 (m, 4 H), 1.42 (s, 3 H), 1.37 (s, 3 H), 1.24 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.97, 132.53, 130.32, 108.97, 76.21, 74.30, 73.85, 38.96, 37.01, 30.44, 27.86, 27.55, 26.01, 24.62, 22.86, 22.07, 21.42; HRMS calcd for $C_{17}H_{24}O_4$ m/z 292.1675, found 292.1675.

Diol Lactone 18. A solution of acetonide **17** (250 mg, 0.85 mmol) in 10 mL of a H_2O–MeOH mixture (1:1) was treated with pyridinium p-toluenesulfonate (10 mg, 0.04 mmol) at 60 °C for 3 days. After being cooled, the reaction mixture was poured into saturated sodium bicarbonate and extracted with ethyl acetate. The combined organic layers were dried ($MgSO_4$) and evaporated in vacuo. The residue was purified by flash chromatography (silica gel, 50% ethyl acetate in hexane) to give the diol **18** (200 mg, 93%): white crystalline solid; mp 135–138 °C; R_f = 0.33 (hexane/ethyl acetate (2:8)); IR (neat) ν_{max} 3406, 2927, 1735, 1399, 1260, 1027 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 4.05 (d, J = 11.5 Hz, 1 H), 3.97 (d, J = 11.7 Hz, 1 H), 3.87 (d, J = 3.7 Hz, 1 H), 3.59 (dd, J = 10.7, 3.8 Hz, 1 H), 2.78 (m, 2 H), 2.42–2.36 (m, 1 H), 2.13–1.48 (m, 8 H), 1.23 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.33, 134.37, 131.48, 72.64, 70.74, 69.91, 39.02, 38.64, 30.06, 28.67, 24.72, 23.26, 22.75, 22.23; MS m/e 252 (M^+), 234, 175, 162, 150, 140; HRMS calcd for $C_{14}H_{20}O_4$ m/z 252.1362, found 252.1365.

α-Hydroxy Ketone 20. A solution of the diol **18** (31 mg, 0.124 mmol) in dichloromethane (7 mL) was added to a solution of the Dess–Martin periodinane (Aldrich) (79 mg, 0.186 mmol) in dichloromethane (3 mL). After 2 h of stirring at 25 °C, the reaction mixture was diluted with ethyl acetate and poured into saturated sodium bicarbonate containing an excess of sodium thiosulfate. The mixture was stirred for 10 min at 25 °C, and the layers were separated. The organic layer was washed with saturated sodium bicarbonate, dried (Na_2SO_4), and evaporated in vacuo to give 43 mg of crude product. This compound was very sensitive and was used immediately for the next step without purification. A sample purified by flash chromatography (silica gel, 30% ethyl acetate in hexane) gave the following data: R_f = 0.31 (hexane/ethyl acetate (1:1)); ^1H NMR (300 MHz, $CDCl_3$) δ 4.34 (d, J = 11.7 Hz, 1 H), 4.13 (dd, J = 11.7, 1.7 Hz, 1 H), 4.02 (d, J = 12.8 Hz, 1 H), 3.58 (d, J = 1.6 Hz, 1 H), 2.97 (dd, J = 19, 2.7 Hz, 1 H), 2.82 (dd, J = 19.2, 7.7 Hz, 1 H), 2.46–2.58 (m, 1 H), 2.32–2.23 (m, 1 H), 2.12–1.99 (m, 3 H), 1.79–1.72 (m, 2 H), 1.50–1.34 (m, 2 H), 1.29 (s, 3 H).

Aminomethylene Lactone 21. Tris(dimethylamino)methane (2.8 mL, 16.2 mmol) was added dropwise to a solution of crude α-hydroxy ketone [28 mg, 0.08 mmol (theory)] in dry 1,4-dioxane (1.4 mL). The resulting solution was allowed to stir for 24 h at 25 °C. Then the solution was concentrated in vacuo and the residue was dissolved in 1,4-dioxane (1.4 mL) and treated again with fresh tris(dimethylamino)methane (2.8 mL) at 25 °C for 48 h. Then the mixture was concentrated in vacuo and the residue was purified by preparative thin-layer chromatography (5% methanol in dichloromethane) to give the enamine **15** (7.7 mg, 32% over the two last steps). This compound was very sensitive and was used immediately for the next step: R_f = 0.28 (dichloromethane/methanol (95:5)); ^1H NMR (300 MHz, $CDCl_3$) δ 7.93 (s, 1 H), 4.38 (d, J = 11.5 Hz, 1 H), 4.11 (dd (apparent t), J = 12.7 Hz, 2 H), 3.7 (s, 1 H), 3.11 (s, 6 H), 2.63–2.52 (m, 1 H), 2.42–2.25 (m, 1 H), 2.18–2.02 (m, 3 H), 1.88–1.75 (m, 2 H), 1.51–1.42 (m, 2 H), 1.39 (s, 3 H).

Wortmannin Analogue 6. A solution of **21** (7.7 mg, 25.2 μmol) in methanol (2.5 mL) was cooled at 0 °C and treated with a solution of copper(II) acetate monohydrate (6 mg, 30.2 μmol) in methanol (500 μL) at 0 °C. After the solution was stirred for 90 min at 0 °C, water (500 μL) was added and the mixture was stirred for 15 min at 0 °C and then extracted with dichloromethane. The combined organic layers were dried (Na_2SO_4) and evaporated in vacuo to give the crude diosphenol **22** (7.7 mg). This compound was used directly for the next step.

A solution of the diosphenol (7.7 mg, 25.2 μmol (theory)) in 1,4-dioxane (1.23 mL) was treated with HCl (250 μL of a 1 M solution in water, 250 μmol) for 18 h at 25 °C. The solution was concentrated in vacuo, and the residue was dissolved in water and extracted quickly with ethyl acetate. The combined organic layers were dried (Na_2SO_4), and the residue was purified by flash chromatography (silica gel, 15% ethyl acetate in hexane) to give compound **6** (2.7 mg, 42% over the two last steps): pale yellow solid; R_f = 0.6 (hexane/ethyl acetate (1:1)); IR ($CHCl_3$) ν_{max} 3019, 2987, 2961, 1732, 1674, 1375, 1220; λ_{max} ($CHCl_3$) 257 nm (ϵ 13800) and 293 nm (ϵ 8100); ^1H NMR (300 MHz, $CDCl_3$) δ 8.19 (s, 1 H), 4.55 (d, J = 10.5 Hz, 1 H), 4.14 (d, J = 10.5 Hz, 1 H), 2.59–2.40 (m, 2 H), 2.15–2.04 (m, 1 H), 1.79–1.69 (m, 5 H), 1.62 (s, 3 H); MS m/e 258 (M^+), 243, 228, 200, 185; HRMS calcd for $C_{15}H_{14}O_4$ m/z 258.0892, found 258.0899.

Acknowledgment. We thank the National Institutes of Health for their support of this work. We also thank Dan Gamache and Chuck Ramesha for their determination of the biological activity of **6**.

Supplementary Material Available: NMR (^{13}C and/or ^1H) spectra of most compounds described in the Experimental Section (23 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.