VOLUME 69, NUMBER 17 JOC Articles AUGUST 20, 2004

Syntheses of (−)-TAN-2483A, (−)-Massarilactone B, and the Fusidilactone B Ring System. Revision of the Structures of and Syntheses of (±)-Waol A (FD-211) and (±)-Waol B (FD-212)

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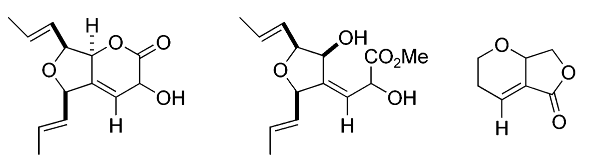
Received December 22, 2003

The structure of waol A has been revised from **1** to **6**, the vinylogue of TAN-2483A (**5**). Aldol reaction of hydroxybutanolides **13b**,**c** with 2,4-hexadienal affords **12b**,**c**, which are subjected to iodoetherification with bis(*sym*-collidine)IPF_6 to provide **11b(c)**. Treatment with Et_3N in CH_2Cl_2 completes the three-step syntheses of TAN-2483A (**5**) and waol A (**6**). Aldol reaction of hydroxybutanolide **31** with 2,4-hexadienal affords **32**, which is subjected to iodoetherification to provide **34**, which in turn is treated with Bu_3SnCl, $NaBH_3CN$, and oxygen to provide diol **60**. Further elaboration completes the first syntheses of massarilactone B (**7**) and the fusidilactone B (**9**) ring system.

Introduction

Mizoue and co-workers reported the isolation of waol A (FD-211, **1**), which has a broad spectrum of activity against cultured tumor cell lines, including adriamycin-resistant HL-60 cells, from the fermentation broth of *Myceliophthora lutea* TF-0409 (Figure 1).[1] More recently, they reported the isolation of waol B (FD-212, **2**), which has similar biological activity from the same source.[2] Tadano has reported an approach to the synthesis of **1**.[3]

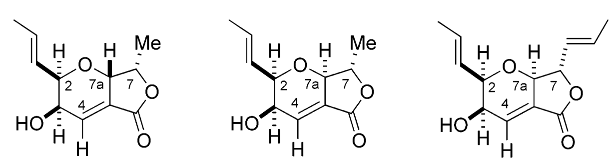


proposed structure of waol A (FD-211, **1**) proposed structure of waol B (FD-212, **2**) likely ring system of waol A (**3**)

FIGURE 1. Proposed structures of waols A (**1**) and B (**2**).

However, the carbonyl group of waol A absorbs at 1767 cm^{-1},[1] which is characteristic of a γ-lactone, rather than the δ-lactone of **1**. The alkene ring hydrogen of waol A absorbs at δ 6.90,[1] while that of **1** would be expected to absorb between δ 5 and 6. An absorbance at δ 6.90 is characteristic of CH=C−C=O. Taken together, these discrepancies suggest that waol A might be a substituted 2,3,7,7a-tetrahydro-5*H*-furo[3,4-*b*]pyran-5-one (**3**).

A literature search uncovered a 1999 patent reporting two closely related compounds with this ring system, TAN-2483B (**4**) and TAN-2483A (**5**) (Figure 2), that show strong c-src kinase inhibitory action and inhibit PTH-induced bone resorption of a mouse femur.[4] The structure of **5** was assigned crystallographically, the absolute stereochemistry was assigned by the Mosher ester method, and the relative stereochemistry of **4** was determined by NOE experiments.[5] The carbonyl groups of **4** and **5** absorb at 1760 cm^{-1} and the alkene ring hydrogens absorb at δ 7.12 and 6.90, respectively. H_2 and H_3 of TAN-2483B (**4**) absorb at δ 4.35 and 4.45, while H_2 and H_3 of both TAN-2483A (**5**) and waol A absorb at δ 4.05 and 4.10, respectively. This suggests that waol A might be the vinylogue of TAN-2483A (**5**) with structure **6**.



TAN-2483B (**4**) TAN-2483A (**5**) revised structure of waol A (FD-211, **6**)

FIGURE 2. Structures of TAN-2483A (**5**) and TAN-2483B (**4**), and the revised structure of waol A (**6**).

Other related compounds have since been isolated. These include the antibacterial massarilactone B (**7**), isolated by Gloer from the freshwater aquatic fungus

(1) Nozawa, O.; Okazaki, T.; Sakai, N.; Komurasaki, T.; Hanada, K.; Morimoto, S.; Chen, Z.-X.; He, B.-M.; Mizoue, K. *J. Antibiot.* **1995**, *48*, 113−118.
(2) Nazawa, O.; Okazaki, T.; Morimoto, S.; Chen, Z.-X.; He, B.-M.; Mizoue, K. *J. Antibiot.* **2000**, *53*, 1296−1300.
(3) Suzuki, E.; Takao, K.-i.; Tadano, K.-i. *Heterocycles* **2000**, *52*, 519−523.
(4) Hayashi, K.; Takizawa, M.; Noguchi, K. Japanese Patent 10287679, 1998; *Chem. Abstr.* **1999**, *130*, 3122e.
(5) Hayashi, K. Takeda Chemical Industries. Unpublished results.

10.1021/jo0358628 CCC: $27.50 © 2004 American Chemical Society
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Massarina tunicata in 2001,[6] and fusidilactones A (**8**) and B (**9**), isolated by Krohn from an endophytic *Fusidium sp.* in 2002 (Figure 3).[7,8]

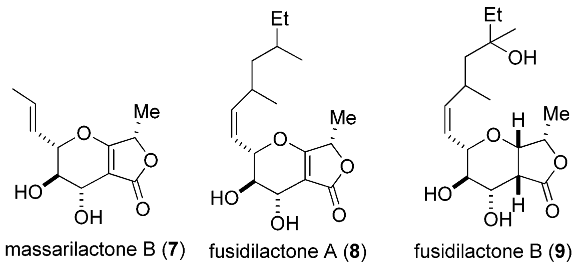
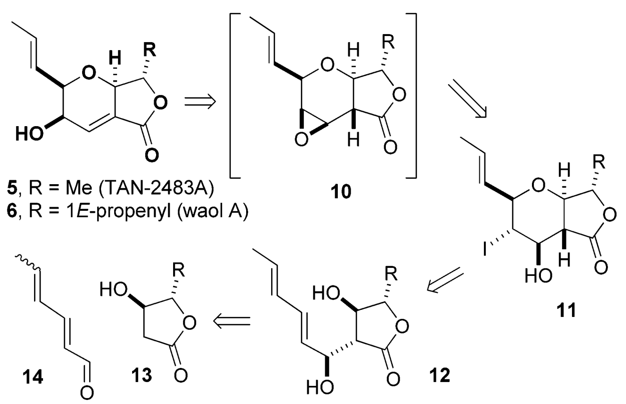


FIGURE 3. Structures of massarilactone B (**7**) and fusidilactones A (**8**) and B (**9**).

Retrosynthetic analysis (Scheme 1) suggested that TAN-2483A (**5**) and waol A (**6**) should be available from epoxy lactone **10**, which should be easily formed from iodohydrin **11**. Iodohydrin **11** should be accessible stereospecifically by iodoetherification of diene diol **12**, which can be prepared by an aldol reaction of the dianion of hydroxyfuranone **13** with 2,4-hexadienal (**14**). Aldol reactions of **13** occur stereospecifically from the face opposite the hydroxy group, but give mixtures of isomers at the hydroxy group on the side chain.[9,10]

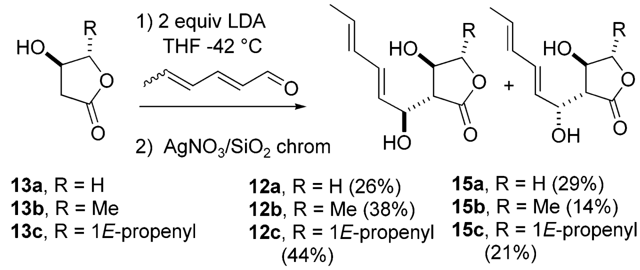
SCHEME 1



Results and Discussion

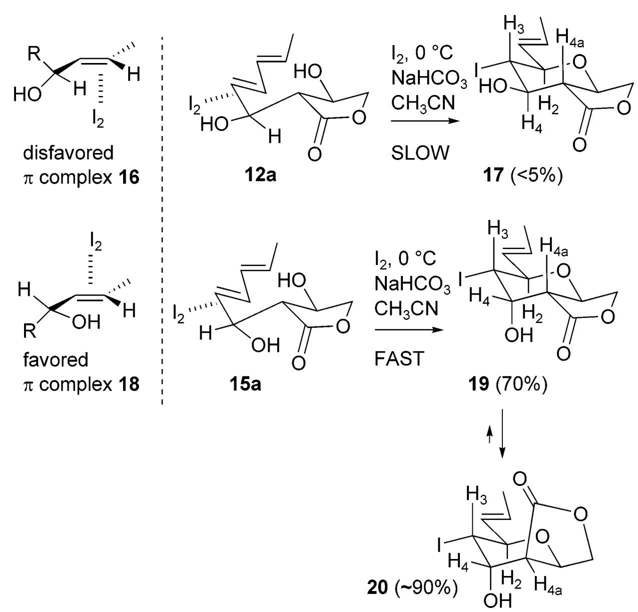
Model Studies. A model study was carried out with commercially available (*S*)-dihydro-4-hydroxyfuranone (**13a**) and 2,4-hexadienal (**14**), which is a 4:1 mixture of (2*E*,4*E*)- and (2*E*,4*Z*)-isomers (Scheme 2). *Note that structures **13a**, **12a**, **15a**, **17**, and **19**−**24** are drawn for clarity with the same absolute stereochemistry as TAN-2483A, although they are the enantiomers.* Treatment of **13a** with 2 equiv of LDA in THF and addition of dienal **14** at −42 °C as described by Prestwich[9a] affords a readily separable mixture of **12a** and **15a**, both as a 4:1 mixture of (2*E*,4*E*)- and (2*E*,4*Z*)-isomers. The stereochemistry of the side chain alcohol could not be determined by spectral analysis and was established from the spectra of iodohydrins **17** and **19** (see below). Flash chromatography on 20% $AgNO_3$ on silica gel removes the undesired *Z*-isomer giving pure **12a** (26%) and **15a** (29%). Low-temperature crystallization has been reported as a means of preparing pure (2*E*,4*E*)-hexadienal.[11] This procedure was not very successful in our hands and equilibration to give a mixture of (2*E*,4*E*)- and (2*E*,4*Z*)-2,4-hexadienal occurs readily.

SCHEME 2



Iodoetherification of the desired isomer **12a** under a wide variety of conditions provides <5% iodo alcohol **17**, while iodoetherification of the undesired isomer **15a** with I_2 and solid $NaHCO_3$ in CH_3CN affords 70% of iodo alcohol **19** (Scheme 3).[12] In **17**, $J_{2,3} = 10.4$ Hz, $J_{3,4} = 9.8$ Hz, $J_{4,4a} = 10.4$ Hz, and $J_{4a,7a} = 11.6$ Hz indicating that all the hydrogens on the tetrahydropyran ring are axial and all the substituents are equatorial. In **19**, $J_{2,3} = 10.4$ Hz, $J_{3,4} < 1$ Hz, $J_{4,4a} < 1$ Hz, and $J_{4a,7a} = 11.6$ Hz indicating that the H_4 is equatorial and the hydroxy group is axial. Isomerization of **19** to the cis-fused isomer **20** occurs easily on heating in the presence of $NaHCO_3$ or on silica gel.

SCHEME 3



We were initially puzzled as to why **15a** undergoes facile iodoetherification to give **19**, while **12a** fails to give

(6) Oh, H.; Swenson, D. C.; Gloer, J. B.; Shearer, C. A. *Tetrahedron Lett.* **2001**, *42*, 975−977.

(7) Krohn, K.; Biele, C.; Drogies, K.-H.; Steingröver, K.; Aust, H.-J.; Draeger, S.; Schulz, B. *Eur. J. Org. Chem.* **2002**, 2331−2336.

(8) Reference 7 provides different structures for fusidilactone B: **9** on p 2331 and **68** on p 2332. Our synthetic studies suggest that structure **9** on page 2331 is correct.

(9) (a) Shieh, H.-M.; Prestwich, G. D. *J. Org. Chem.* **1981**, *46*, 4319−4321. (b) Chen, S. Y.; Joullie, M. *J. Org. Chem.* **1984**, *49*, 2168−2174.

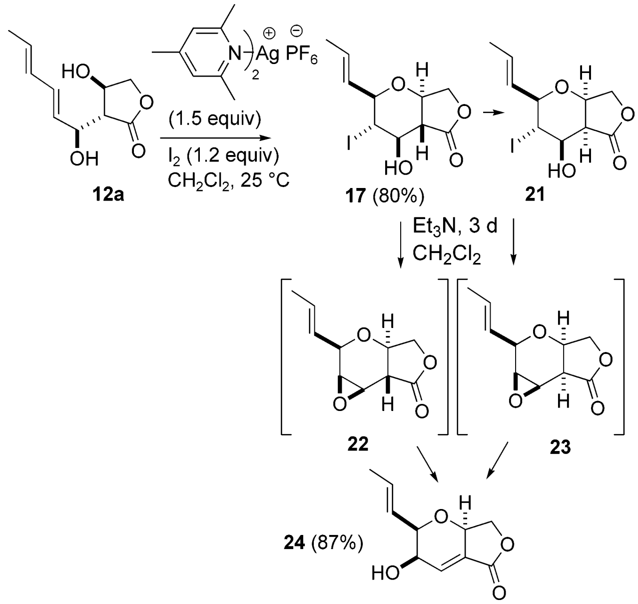
(10) For a preliminary communication on a portion of this work see: Gao, X.; Nakadai, M.; Snider, B. B. *Org. Lett.* **2003**, *5*, 451−454.

(11) Albriktsen, P.; Harris, R. K. *Acta Chem. Scand.* **1973**, *27*, 3993−4000.

the more stable isomer **17** with an equatorial hydroxy group. Closer examination of the literature revealed that Chamberlin and Yoshida had made related observations[12] and that Chamberlin and Hehre had explained the origins of these effects.[13] Cyclizations in which the nucleophile is in the R group proceed slowly through the disfavored π complex **16** with the hydrogen eclipsed with the double bond and rapidly through the favored π complex **18** with the hydroxy group eclipsed with the double bond. The π complex formed from **12a** has the hydrogen eclipsed with the double bond and therefore cyclizes slowly to give **17**. The π complex formed from **15a** has the hydroxy group eclipsed with the double bond and therefore cyclizes rapidly to give **19**.

A more reactive iodinating agent is needed to convert **12a** to **17** in high yield. Bis(*sym*-collidine)IPF_6 is a very reactive, but moisture-sensitive, iodinating reagent that can easily be prepared in situ from bis(*sym*-collidine)-$AgPF_6$ and iodine.[14] We were delighted to find that reaction of nonhygroscopic bis(*sym*-collidine)$AgPF_6$ (1.5 equiv) and iodine (1.2 equiv) in CH_2Cl_2, addition of **12a**, and stirring for 1.5 h affords 80% of **17**, which can be purified by flash chromatography on water-deactivated silica gel (Scheme 4). Partial isomerization to the more stable cis-fused isomer **21** occurs otherwise. Much lower yields of **17** were obtained with commercially available bis(*sym*-collidine)IPF_6.

SCHEME 4

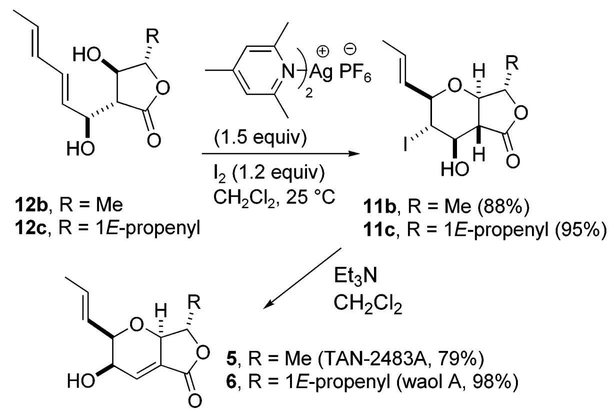


Treatment of either **17** or **21** with Et_3N in CH_2Cl_2 for 3 d at 25 °C affords epoxides **22** or **23**, which react further to give 87% of **24**, with spectral data similar to those of TAN-2483A (**5**) and waol A (**6**). The iodide and hydroxy groups of **17** are in diequatorial arrangement. Formation of the epoxide requires either that the pyran ring of **17** adopts a boat conformation with these groups antiperiplanar or that the flexible cis-fused isomer **21** adopts the chair conformation with the iodide and hydroxy groups antiperiplanar.

Synthesis of TAN-2483A. TAN-2483A precursor (−)-*trans*-dihydro-4-hydroxy-5-methyl-2(3*H*)-furanone (**13b**) was prepared by Hatakeyama's procedure in >90% ee.[15] Dihydroxylation of methyl 3*Z*-pentenoate[16] with OsO_4 and NMO and treatment of the resulting diol with acid gives (±)-**13b**. Treatment with Novozyme lipase, vinyl acetate, and 1,4,8,11-tetrathiacyclotetradecane in diisopropyl ether affords (−)-**13b** and the readily separable enantiomeric acetate.

We were pleased to find that the selectivity for **12** in the aldol reaction improves with an alkyl substituent on furanone **13**. Treatment of the dianion of **13b** with **14** affords 38% of the desired adduct **12b** and only 14% of **15b** after $AgNO_3$ chromatography (Scheme 2). Iodoetherification of **12b** with bis(*sym*-collidine)$AgPF_6$ and iodine provides 88% of iodo alcohol **11b**, which gives 79% of TAN-2483A (**5**) on treatment with Et_3N in CH_2Cl_2 at 25 °C for 3 d (Scheme 5). The ^1H and ^{13}C NMR spectra of **5** are identical with those of the natural product. The optical rotation, $[\alpha]_D$ −236, has the same sign, but is somewhat smaller than that reported, $[\alpha]_D$ −292,[4] confirming the assignment of the absolute stereochemistry.

SCHEME 5



Syntheses of Waols A and B. Waol A precursor propenyl lactone **13c** was made by modification of Griengl's procedure (Scheme 6).[17] Reaction of 2*E*-butenal with NaCN and HCl[18] and silylation[19] gives 34% (unoptimized) of **25**. Reaction of **25** with Zn, TMSCl, and $BrCH_2CO_2Me$[20] affords 86% of keto ester **26** as a mixture of keto and enol tautomers. Reduction of **26** with $NaBH_4$ in MeOH at −15 °C gives 97% of **27** as a 5:1 mixture of isomers. Reduction of **26** with $NaBH_4$ in 49:1 THF/MeOH

(12) (a) Chamberlin, A. R.; Dezube, M.; Dussault, P.; McMills, M. C. *J. Am. Chem. Soc.* **1983**, *105*, 5819−5825. (b) Tamaru, Y.; Hojo, M.; Kawamura, S.-i.; Sawada, S.; Yoshida, Z.-i. *J. Org. Chem.* **1987**, *52*, 4062−4072.

(13) Chamberlin, A. R.; Mulholland, R. L., Jr.; Kahn, S. D.; Hehre, W. J. *J. Am. Chem. Soc.* **1987**, *109*, 672−677.

(14) (a) Homsi, F.; Robin, S.; Rousseau, G. *Org. Synth.* **1999**, *77*, 206−211. (b) Brunel, Y.; Rousseau, G. *J. Org. Chem.* **1996**, *61*, 5793−5800. (c) Evans, R. D.; Magee, J. W.; Schauble, J. H. *Synthesis* **1988**, 862−868.

(15) Nishiyama, T.; Nishioka, T.; Esumi, T.; Iwabuchi, Y.; Hatakeyama, S. *Heterocycles* **2001**, *54*, 69−72.

(16) Krebs, E.-P. *Helv. Chim. Acta* **1981**, *64*, 1023−1026.

(17) Johnson, D. V.; Fischer, R.; Griengl, H. *Tetrahedron* **2000**, *56*, 9289−9295.

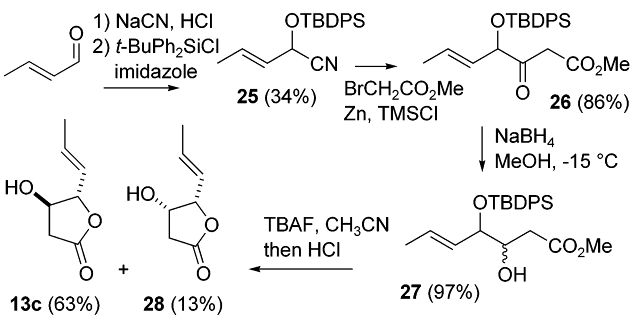
(18) Anderson, J. R.; Edwards, R. L.; Whalley, A. J. S. *J. Chem. Soc., Perkin Trans. 1* **1982**, 215−221.

(19) (a) Brussee, J.; Loos, W. T.; Kruse, C. G.; Van Der Gen, A. *Tetrahedron* **1990**, *46*, 979−986. (b) Warmerdam, E. G. J. C.; van den Nieuwendijk, A. M. C. H.; Kruse, C. G.; Brussee, J.; van der Gen, A. *Recl. Trav. Chim. Pays-Bas* **1996**, *115*, 20−24.

(20) Hannick, S. M.; Kishi, Y. *J. Org. Chem.* **1983**, *48*, 3833−3835.

or THF provides **27** as a 1.5:1 and 1.2:1 mixture of isomers, respectively. Deprotection of the 5:1 mixture of isomers of **27** with TBAF in CH_3CN and acid-catalyzed lactonization provides 63% of (±)-**13c** and 13% of (±)-**28**.[21]

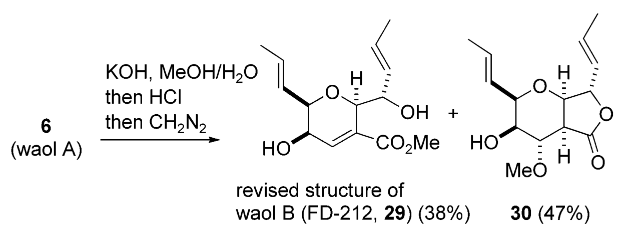
SCHEME 6



Treatment of the dianion of **13c** with 2,4-hexadienal (**14**) affords 44% of the desired adduct **12c** and 21% of **15c** after $AgNO_3$ chromatography (Scheme 2). Iodoetherification of **12c** with bis(*sym*-collidine)$AgPF_6$ and iodine provides 95% of iodo alcohol **11c**, which gives 98% of **6** on treatment with Et_3N in CH_2Cl_2 at reflux overnight (Scheme 5). The ^{1}H and ^{13}C NMR spectra of **6** are identical with those of waol A (FD-211) indicating that the revised structure we proposed is correct.

Hydrolysis of **6** with KOH in MeOH/H_2O, followed by acidification and immediate reaction with CH_2N_2 affords 38% of **29** with ^{1}H and ^{13}C NMR spectral data identical with those of waol B (FD-212) and 47% of MeOH adduct **30** resulting from conjugate addition of methoxide and protonation to give the cis-fused ring system (Scheme 7).

SCHEME 7

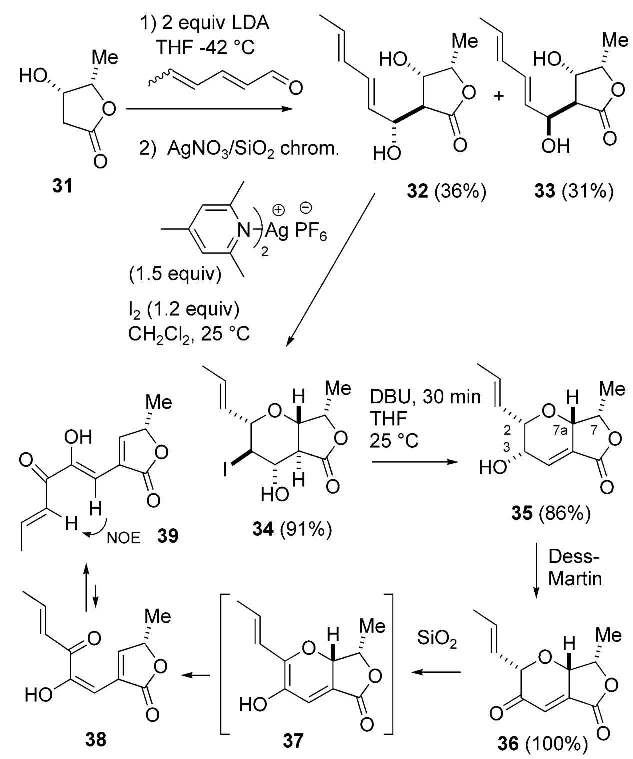


The conversion of aldol adducts **12b**,**c** to TAN-2483A (**5**) and waol A (**6**) requires only two steps and proceeds in excellent yield as indicated in Scheme 5. Although the aldol reaction of the substituted lactones **13b**,**c** is much more selective for **12b**,**c** than that of the unsubstituted model lactone **13a**, there is still room for improvement in the selectivity of the aldol reaction. However, initial attempts at improving the stereoselectivity of the aldol reaction, e.g., addition of $ZnCl_2$ to make the zinc enolate,[22] were not promising.

Biological Studies. Since waol A was reported to have a broad spectrum of antitumor activity,[1] we submitted synthetic (−)-TAN-2483A (**5**), (±)-waol A (**6**), and (+)-**24** (the enantiomer of the structure shown) to the NCI human disease-oriented 60-cell line, in vitro antitumor screening protocol. All three compounds showed similar activity, with GI_{50} activity values ranging from 10^{-5} to 10^{-6} M. Since **5** and **24** have the opposite absolute stereochemistry and **6** is racemic, the similar activity observed with all three compounds suggests that the antitumor activity may result from the ability of these compounds to act as Michael acceptors, as in the formation of **30** from **6**, rather than from more specific binding.

Approaches to TAN-2483B. We prepared lactone **31** as a potential precursor to TAN-2483B from methyl 3*E*-pentenoate by addition of OsO_4 and NMO to form (±)-**31** or AD-mix-α to form (−)-**31**.[23] Addition of 2,4-hexadienal (**14**) to the dianion of **31** provides 36% of **32** and 31% of **33**. The selectivity for **32** is much lower with *cis*-lactone **31** than the selectivity for **12b**,**c** with *trans*-lactones **13b**,**c**. Iodoetherification of **32** affords 92% of **34** (Scheme 8). Treatment of **34** with Et_3N in CH_2Cl_2 at reflux for 3 d provides only 32% of **35** and 61% of recovered **34**. As expected, the spectral data for **35** are different than those for TAN-2483B (**4**), which is epimeric to TAN-2483A (**5**) at C_{7a} while **35** is epimeric to the enantiomer of **5** at C_7.

SCHEME 8



The formation of **35** from **34** is much slower than the formation of **5** and **6** from iodohydrins **11b**,**c**. This suggests that conformations with the iodide and hydroxy groups antiperiplanar are more strained with the methyl group cis to the pyran oxygen as in **34** and the epimeric cis-fused lactone than with the methyl group trans to the pyran oxygen as in **11b**,**c** and the epimeric cis-fused lactone. Treatment of **34** with 5 equiv of the stronger base DBN in CH_2Cl_2 for 1 h at 0 °C gives 89% of **35**, while

(21) Attempted enzymatic resolution of **13c**, as successfully carried out for **13b**, gives the opposite enantiomer, (+)-**13c**, in 18% ee. Reduction of **26** with $NaBH_4$ and (D)-tartaric acid[17] and further elaboration yields 30% of (+)-**13c** (38% ee) and 45% of **28**.

(22) House, H. O.; Crumrine, D. S.; Teranishi, A. Y.; Olmstead, H. D. *J. Am. Chem. Soc.* **1973**, *95*, 3310−3324.

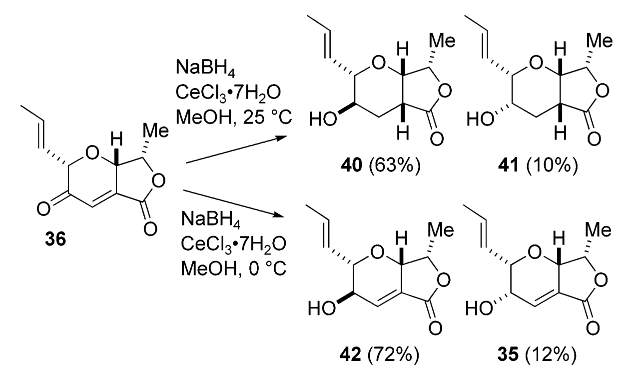
(23) (a) Harcken, C.; Brückner, R.; Rank, E. *Chem. Eur. J.* **1998**, *4*, 2342−2352. (b) Harcken, C.; Brückner, R. *New J. Chem.* **2001**, *25*, 40−54.

treatment of **34** with 5 equiv of DBU in THF for 30 min at 25 °C affords 86% of **35**.

Pyranofuranone **35** has the same relative stereochemistry as TAN-2483B (**4**) at C_7 and C_{7a} and the opposite stereochemistry at C_2 and C_3. It might be possible to convert **35** to **4** by oxidation to give enone **36**, epimerization to give the β-propenyl group at C_2, and reduction of the enone from the α-face to give the β-alcohol at C_3. Dess–Martin oxidation of **35** provides enone **36** quantitatively. Surprisingly, enone **36** is unstable on silica gel chromatography, affording only 40–50% of **36** and 40–50% of butenolide **39**. The stereochemistry of the enol of **39** was established by the NOE shown. Presumably, enone **36** tautomerizes to give dienol **37**, which undergoes electrocyclic ring opening to give **38**, which isomerizes to give the more stable enol **39**.

The facile isomerization of **36** to **39** precluded the epimerization of the propenyl side chain. Nevertheless, we chose to investigate the stereochemistry of the enone reduction. Reduction of crude **36** with $NaBH_4$ (1.2 equiv) and $CeCl_3{\cdot}7H_2O$ at 25 °C affords saturated alcohols **40** (63%) and **41** (10%) (Scheme 9). Preventing reduction of the double bond in this case is particularly challenging because 1,4-hydride addition can occur to enone **36** or to allylic alcohols **42** and **35**, which still contain an unsaturated lactone that is very susceptible to conjugate addition as shown by the formation of **30** during the hydrolysis of waol A (**6**) (Scheme 7). Conjugate reduction was avoided by reducing **39** with only 0.5 equiv of $NaBH_4$ and $CeCl_3{\cdot}7H_2O$ at 0 °C to give **42** (72%) and **35** (12%). Pyranofuranone **42** is epimeric to TAN-2483B (**4**) at C_2.

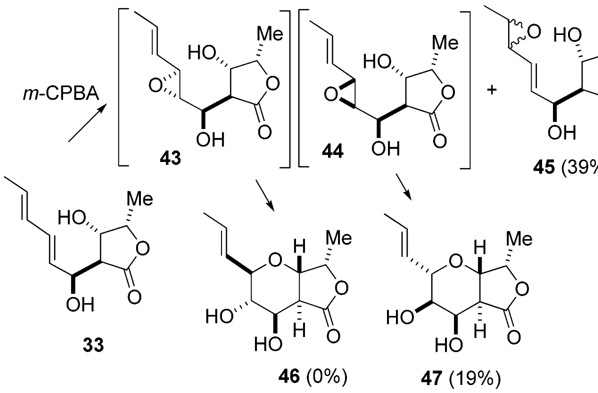
SCHEME 9



We then considered a final route to TAN-2483B (**4**) in which the pyran ring would be formed by cyclization of an epoxy alcohol. Directed epoxidation of dienol **33** with *m*-CPBA was expected to give mainly *threo* alcohol **43** (Scheme 10).[24] Cyclization of **43** should give pyranofuranone **46**. Conversion of the diol to the β-epoxide and treatment with base would complete the synthesis of TAN-2483B (**4**). However, epoxidation of **33** with *m*-CPBA affords 19% of **47**, resulting from cyclization of the *erythro* epoxide **44**, and 39% of a mixture of terminal epoxides **45**. It is conceivable that the lactone alcohol helps direct epoxidation to the terminal double bond.

All of the sequences involving iodoetherification or cyclization of an epoxide provide a pyran with an equatorial propenyl group as required for TAN-2483A (**5**), but not TAN-2483B (**4**). Comparison of the two structures suggested that they might be biosynthesized by reduction of a common intermediate **50**, which might be formed by condensation of an aldehyde such as **48**, with the common natural product γ-methyltetronic acid (**49**)[25] as shown in Figure 4. Initial model studies aimed at developing such a biomimetic route by condensing tetronic acid with 2,4-hexadienal (**14**) and other aldehydes were unsuccessful.

SCHEME 10



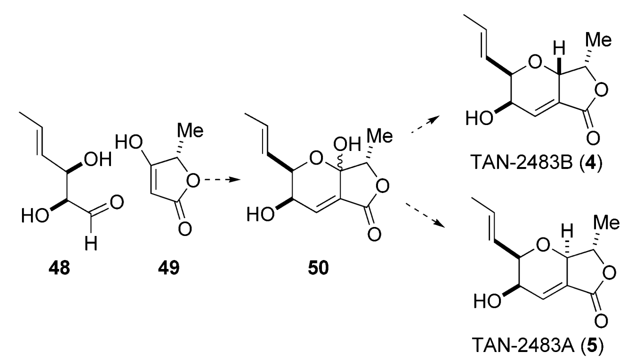
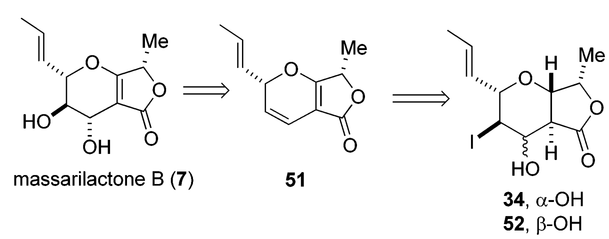


FIGURE 4. Possible biosynthesis of TAN-2483A (**5**) and TAN-2483B (**4**).

Synthesis of Massarilactone B (7). We now turned our attention to the synthesis of massarilactone B (**7**). We planned to construct the diol by epoxidation of diene **51**, which might be available by a double elimination reaction of either iodohydrin **34** or **52** (Scheme 11). Hsung has reported the epoxidation of analogous pyranopyranones.[26]

SCHEME 11



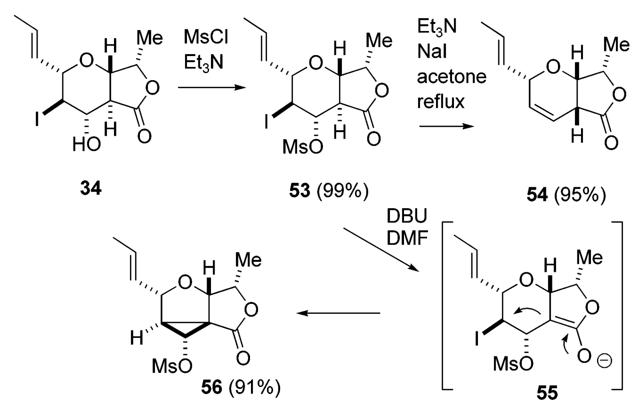
Reaction of **34** with MsCl and Et_3N affords mesylate **53** in 99% yield (Scheme 12). Initial attempts at double

(24) Adam, W.; Alsters, P. L.; Neumann, R.; Saha-Möller, C. R.; Sloboda-Rozner, D.; Zhang, R. *J. Org. Chem.* **2003**, *68*, 1721–1728 and references therein.

(25) (a) Boll, P. M.; Sørensen, E.; Balieu, E. *Acta Chem. Scand.* **1968**, *22*, 3251–3255. (b) Bloomer, J. L.; Kappler, F. E. *J. Chem. Soc., Perkin Trans. 1* **1976**, 1485–1491.

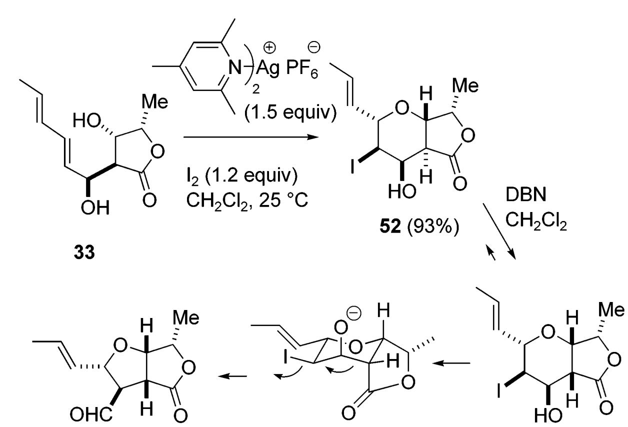
elimination gave complex mixtures. Eventually we concluded that the iodide liberated in the elimination is reducing iodo mesylate **53** to form alkene **54**. Addition of sodium iodide makes this the major process; treatment of **53** with NaI and Et_3N in acetone at reflux provides alkene **54** in 95% yield. The reduction can be suppressed by use of DBU in DMF. However, these conditions result in enolization to give **55** and elimination of the iodide to give cyclopropane **56** in 91% yield. Both the iodide and mesylate in **53** are equatorial so that the mesylate is not aligned properly with the enolate to undergo elimination to give the conjugated lactone, while the iodide is aligned perfectly with the enolate to give the cyclopropane.[27]

SCHEME 12



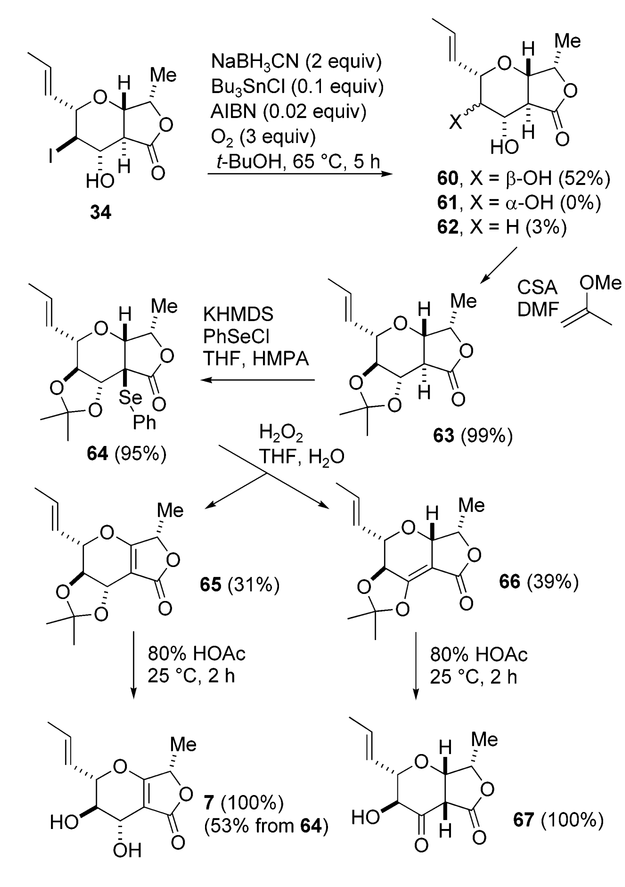
Iodoetherification of minor aldol adduct **33** affords iodohydrin **52** in 93% yield (Scheme 13). Treatment of **52** with DBN in THF results in equilibration to give **57** with the more stable cis ring fusion. Deprotonation of the alcohol of **57** forms alkoxide **58**, which rearranges to provide aldehyde **59** in 87% yield.[28] These studies indicated that double elimination from **34** or **52** is not straightforward, so we investigated other approaches to massarilactone B (**7**).

SCHEME 13



It should be possible to prepare massarilactone B (**7**) by dehydration of dihydromassarilactone B (**60**), which will be formed by replacing the iodide of **34** with a hydroxy group with retention of configuration. Since the newly introduced hydroxy group of **60** is equatorial, it should be possible to achieve this transformation by reducing the iodide of **34** and trapping the resulting radical with oxygen from the less hindered β-face to give the more stable equatorial alcohol.[29] Treatment of **34** (prepared from (−)-**31**) with 2 equiv of $NaBH_3CN$, 0.1 equiv of Bu_3SnCl, and 0.02 equiv of AIBN in *t*-BuOH at 65 °C for 5 h under 3 equiv of oxygen affords the desired diol **60** in 52% yield, none of the axial alcohol isomer **61**, and reduction product **62** in only 3% yield (Scheme 14). The yield of **60** is quite sensitive to the reaction conditions. Use of excess oxygen leads to recovered starting material and a low yield of **60**, probably due to the formation of $(Bu_3Sn)_2O$.[29] A similar reaction in toluene with Bu_3SnH (3 equiv) and AIBN (1 equiv) and with air bubbling through it, rather than under oxygen, gives 41% of a 10:1 mixture of **60** and **61** and 32% of reduction product **62**.

SCHEME 14



Protection of the diol of **60** with 2-methoxypropene and CSA in DMF provides acetonide **63** (99%). Phenylselenation[30] with KHMDS and PhSeCl in THF/HMPA affords cis-fused phenylselenide **64** (95%). Oxidation of **64** with

(26) Zehnder, L. R.; Wei, L.-L.; Hsung, R. P.; Cole, K. P.; McLaughlin, M. J.; Shen, H. C.; Sklenicka, H. M.; Wang, J.; Zificsak, C. A. *Org. Lett.* **2001**, *3*, 2141−2144.

(27) For a similar cyclopropane synthesis see: Arai, Y.; Takeda, K.; Masuda, K.; Koizumi, T. *Chem. Lett.* **1985**, 1531−1534.

(28) For a similar rearrangement see: Knapp, S.; Naughton, A. J.; Jaramillo, C.; Pipik, B. *J. Org. Chem.* **1992**, *57*, 7328−7334.

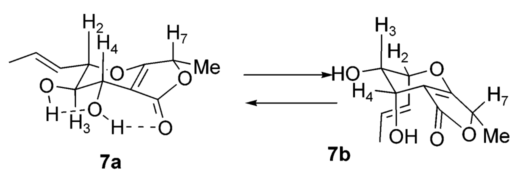
(29) (a) Mayer, S.; Prandi, J. *Tetrahedron Lett.* **1996**, *37*, 3117−3120. (b) Sawamura, M.; Kawaguchi, Y.; Nakamura, E. *Synlett* **1997**, 801−802.

(30) For a similar phenylselenation and oxidative elimination see: Paquette, L. A.; Sivik, M. R. *Synth. Commun.* **1991**, *21*, 467−479.

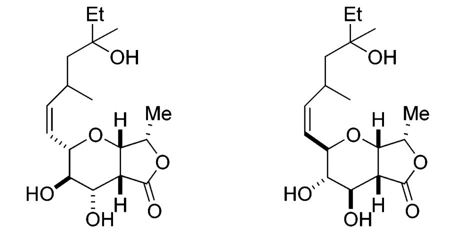
hydrogen peroxide in aqueous THF for 8 h affords the desired unsaturated acetonide **65** (31%), the undesired unsaturated acetonide **66** (39%), and massarilactone B (**7**, 24%) resulting from cleavage of the acetonide of **65** under the oxidation conditions. Hydrolysis of **65** in 80% HOAc for 2 h provides **7** quantitatively, while a similar hydrolysis of **66** yields hydroxy ketone **67**. The preparation of **7** was most conveniently carried out by oxidation of phenylselenide **64** with hydrogen peroxide in aqueous THF for 2.5 d to give 53% of **7** as the sole isolable product. The acetonides of both **65** and **66** hydrolyze during the longer reaction time. Hydroxy ketone **66** is oxidized further by hydrogen peroxide to form a complex mixture of polar products.

To our surprise, the ^{1}H and ^{13}C NMR spectra of synthetic massarilactone B (**7**) do not match those reported by Gloer.[6] We suspected that these differences result from a concentration dependence of the NMR spectrum as we have previously noted in erinacine A.[31] In dilute solution (1 mg/mL), intramolecular hydrogen bonding is more important, favoring structure **7a** with all equatorial substituents (Scheme 15). At higher concentrations, structure **7b** may be more important. Molecular mechanics calculations suggest that **7a** is only 1 kcal/mol more stable than **7b**. The NMR spectra of dilute solutions of synthetic and natural massarilactone B[32] are identical and the ^{1}H and ^{13}C NMR spectra of a mixture of the two show that only one compound is present, thereby establishing that the structures of the natural and synthetic materials are identical. NMR spectra of a more concentrated solution of **7** (10 mg/mL) display spectral data intermediate between that of the dilute solution and the reported values. For instance, the coupling pattern of H_3 changes from dd, $J = 8.5$, 6.1 Hz in dilute solution, to dd, $J = 7.9$, 6.1 Hz in more concentrated solution, to dd, $J = 6.6$, 5.1 Hz in the reported spectrum.[4] A full tabulation of the differences is provided in the Supporting Information. The optical rotation of synthetic massarilactone B (**7**) ($[\alpha]^{22}_D$ −96) is similar to that reported for the natural material ($[\alpha]^{28}_D$ −109) confirming Gloer's assignment of the absolute stereochemistry.

SCHEME 15



Synthesis of the Fusidilactone B Ring System. There is some question as to whether fusidilactone B has structure **9** or **68** (Figure 5).[7,8] The side chain of fusidilactone B is much longer than the propenyl group of TAN-2483, massarilactone B, and waol A, with two unassigned stereocenters and a cis double bond. We thought that structure **9** was more likely and decided to prepare **72** with a cis double bond as a model for it. Comparison of the NMR spectra of the natural product and **72** should



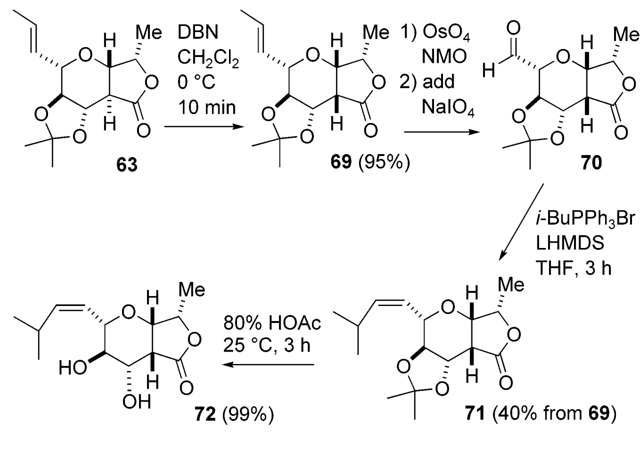
fusidilactone B (**9**) alternative structure for fusidilactone B (**68**)

FIGURE 5. Possible structures for fusidilactone B.

allow us to unambiguously establish whether fusidilactone B has structure **9** or **68**.

The trans-fused lactone of **63** is sensitive to hydrolytic ring opening. It is therefore best to epimerize **63** to the more stable cis-fused lactone **69** prior to oxidative cleavage of the alkene and Wittig reaction. Treatment of **63** with DBN in CH_2Cl_2 for 10 min at 0 °C provides **69** (95%). Oxidative cleavage with OsO_4 and NMO followed by addition of $NaIO_4$ affords the unstable aldehyde **70**. Wittig reaction with isobutyltriphenylphosphonium bromide and LHMDS in THF affords the desired cis alkene **71** (40% from **69**). Hydrolysis of the acetonide in 80% AcOH for 3 h provides 99% of the desired model **72**. The ^{1}H and ^{13}C NMR spectra of **72** tabulated in the Supporting Information correspond very closely to those of fusidilactone B, except for the expected differences due to the shorter side chain, thereby establishing that the natural product has structure **9**, not **68**. In conclusion, we have reassigned the structures of waols A and B as **6** and **29**, and completed the first syntheses of these molecules and (−)-TAN-2483A (**5**) in three steps from lactones **12** by aldol reaction, iodoetherification, and elimination. A longer sequence starting from lactone **31** using an aldol reaction, iodoetherification, radical substitution of the iodide by a hydroxy group, and oxidation completes the first synthesis of massarilactone B (**7**). Finally, we have prepared **72** and shown that it has the same ring system as fusidilactone B, thereby establishing that the natural product has structure **9**.

SCHEME 16



Experimental Section

General Procedures. NMR spectra were recorded at 400 MHz in $CDCl_3$ unless otherwise indicated. Chemical shifts are reported in δ, coupling constants in Hz, and IR spectra in cm^{-1}.

(31) Snider, B. B.; Vo, N. H.; O'Neil, S. V. *J. Org. Chem.* **1998**, *63*, 4732−4740.
(32) We thank Prof. Gloer for copies of the spectra and a sample of massarilactone B.

The 20% $AgNO_3$ on silica gel was prepared by suspending 50 g of silica gel in a solution of $AgNO_3$ (10 g) in CH_3CN (200 mL). The solvent was removed under reduced pressure and the 20% $AgNO_3$ on silica gel was stored in a foil-covered flask in the dark.

2,5-Dideoxy-2-[(1*S*,2*E*,4*E*)-1-hydroxy-2,4-hexadienyl]-L-arabinonic Acid, γ-Lactone (12b) and 2,5-Dideoxy-2-[(1*R*,2*E*,4*E*)-1-hydroxy-2,4-hexadienyl]-L-arabinonic Acid, γ-Lactone (15b). Lithium diisopropylamide was prepared from diisopropylamine (292 μL, 2.08 mmol) and *n*-BuLi (745 μL, 2.79 M in hexanes, 2.08 mmol) in THF (4 mL) at 0 °C. The solution was cooled to −23 °C and treated with **13b** (116 mg, 1 mmol) in THF (1 mL). The mixture was stirred for 15 min, cooled to −42 °C, and treated with a 4:1 mixture of (2*E*,4*E*)- and (2*E*,4*Z*)-2,4-hexadienal (**14**) (110 μL, 1 mmol). The mixture was stirred at −42 °C for 1 h and saturated aqueous NH_4Cl solution (1 mL) was added to quench the reaction. The resulting mixture was diluted with ether (80 mL), washed with brine, dried (Na_2SO_4), and concentrated to give a yellow oil. Flash chromatography on silica gel (2:1 hexanes/EtOAc) gave **15b** (42 mg, 20%) as a colorless oil, followed by **12b** (103 mg, 49%) as a white solid. Both of these compounds are a 4:1 mixture of (2*E*,4*E*) and (2*E*,4*Z*) isomers. Flash chromatography of the mixture of **12b** isomers on 20% $AgNO_3$ on silica gel (2:1 hexanes/EtOAc) gave (2*E*,4*E*)-**12b** (80 mg, 38%). Similar chromatography of the mixture of **15b** isomers gave (2*E*,4*E*)-**15b** (30 mg, 14%).

Data for **12b**: ^{1}H NMR 6.32 (dd, 1, *J* = 15.3, 10.4), 6.07 (ddq, 1, *J* = 15.3, 10.4, 1.2), 5.79 (dq, 1, *J* = 15.3, 6.7), 5.67 (dd, 1, *J* = 15.3, 7.3), 4.53 (ddd, 1, *J* = 7.3, 6.7, 3.1), 4.26 (dq, 1, *J* = 7.9, 6.1), 3.98 (ddd, 1, *J* = 8.5, 7.9, 4.3), 3.18 (d, 1, *J* = 3.1, OH), 2.85 (dd, 1, *J* = 8.5, 6.7), 2.46 (d, 1, *J* = 4.3, OH), 1.77 (dd, 3, *J* = 6.7, 1.2), 1.46 (d, 3, *J* = 6.1); ^{13}C NMR 174.6, 133.7, 132.0, 130.1, 127.7, 80.1, 75.2, 71.3, 54.3, 18.1, 18.0; IR (KBr) 3401, 1761, 1662; HRMS (CI/NH_3) calcd for $C_{11}H_{20}NO_4$ (MNH_4^+) 230.1392, found 230.1395.

Data for **15b**: ^{1}H NMR 6.37 (dd, 1, *J* = 15.3, 10.4), 6.07 (dd, 1, *J* = 15.3, 10.4), 5.78 (dq, 1, *J* = 15.3, 6.1), 5.69 (dd, 1, *J* = 15.3, 6.1), 4.73 (ddd, 1, *J* = 6.1, 4.3, 3.7), 4.27 (dq, 1, *J* = 8.5, 6.1), 4.20 (ddd, 1, *J* = 8.5, 7.9, 4.3), 2.79 (dd, 1, *J* = 7.9, 3.7), 2.74 (d, 1, *J* = 4.3, OH), 2.64 (d, 1, *J* = 4.3, OH), 1.77 (d, 3, *J* = 6.1), 1.46 (d, 3, *J* = 6.1); ^{13}C NMR 174.4, 132.1, 131.4, 130.3, 128.8, 80.1, 74.3, 69.1, 55.0, 18.11, 18.07; IR (KBr) 3430, 1759, 1661.

(2*R*,3*S*,4*R*,4a*R*,7*S*,7a*R*)-Hexahydro-4-hydroxy-3-iodo-7-methyl-2-(1*E*)-1-propenyl-5*H*-furo[3,4-*b*]pyran-5-one (11b). Dry bis(*sym*-collidine)silver(I) hexafluorophosphate (238 mg, 0.48 mmol) was slurried in dry CH_2Cl_2 (3 mL) with vigorous stirring, iodine (97 mg, 0.38 mmol) was added in one portion, and the solution was stirred for 5 min. A yellow precipitate was produced instantly. Diene diol **12b** (68 mg, 0.32 mmol) in dry CH_2Cl_2 (1 mL) was added and the resulting mixture was stirred at room temperature for 1.5 h and filtered through Celite. The filtrate was washed with 10% aqueous $Na_2S_2O_3$ solution and saturated aqueous $NaHCO_3$ solution, dried (Na_2SO_4), and concentrated to give a yellow oil. Flash chromatography on silica gel (6:1 hexanes/EtOAc) gave **11b** (95 mg, 88%) as a pale yellow solid: ^{1}H NMR 5.92 (dq, 1, *J* = 15.3, 6.7), 5.45 (ddq, 1, *J* = 15.3, 7.9, 1.2), 4.45 (dq, 1, *J* = 8.6, 6.1, H_7), 4.25 (dd, 1, *J* = 11.0, 7.9, H_2), 4.13 (ddd, 1, *J* = 10.4, 9.8, 2.4, H_4), 3.59 (dd, 1, *J* = 11.0, 9.8, H_3), 3.48 (dd, 1, *J* = 11.6, 8.6, H_{7a}), 3.07 (d, 1, *J* = 2.4, OH), 2.47 (dd, 1, *J* = 11.6, 10.4, H_{4a}), 1.80 (dd, 3, *J* = 6.7, 1.2), 1.51 (d, 3, *J* = 6.1); ^{13}C NMR 169.9, 134.2, 127.6, 84.9, 80.6, 78.3, 73.2, 51.6, 38.6, 17.74, 17.71; IR (KBr) 3469, 1784.

(2*R*,3*R*,7*S*,7a*R*)-2,3,7,7a-Tetrahydro-3-hydroxy-7-methyl-2-(1*E*)-1-propenyl-5*H*-furo[3,4-*b*]pyran-5-one [(−)-TAN-2483A, 5]. To a solution of **11b** (95 mg, 0.28 mmol) in dry CH_2Cl_2 (3 mL) was added Et_3N (2 mL). The resulting mixture was stirred at room temperature for 3 days and diluted with CH_2Cl_2 (80 mL), washed with 10% aqueous HCl, saturated aqueous $NaHCO_3$ solution, and brine, dried (Na_2SO_4), and concentrated to give a yellow oil. Flash chromatography on silica gel (4:1 hexanes/EtOAc) gave **5** (47 mg, 79%) as a colorless oil: $[\alpha]^{22}_D$ −236 (*c* 1.20, $CHCl_3$) {lit.[4] $[\alpha]^{23}_D$ −293 (*c* 0.59, $CHCl_3$)}; ^{1}H NMR 6.88 (dd, 1, *J* = 3.7, 2.4, H_4), 5.94 (dq, 1, *J* = 15.3, 7.0), 5.70 (ddq, 1, *J* = 15.3, 6.1, 1.8), 4.34 (dq, 1, *J* = 7.3, 6.1, H_7), 4.25 (ddd, 1, *J* = 7.3, 2.4, 2.4, H_{7a}), 4.04−4.11 (m, 2, $H_{2,3}$), 1.78 (br d, 3, *J* = 7.0), 1.56 (d, 3, *J* = 6.1); ^{13}C NMR 166.6, 133.4 (2 C), 131.3, 125.6, 79.9, 79.7, 79.0, 64.1, 18.8, 18.1; IR (neat) 3436, 1773, 1642; HRMS (CI/NH_3) calcd for $C_{11}H_{18}NO_4$ (MNH_4^+) 228.1236, found 228.1233. The spectral data are identical with those of the natural product.[4]

2-(*tert*-Butyldiphenylsilyloxy)-3*E*-pentenenitrile (25). To a stirred solution of *trans*-2-butenal (2.8 g, 40 mmol) in ether (6 mL) at −10 °C was added a precooled (−10 °C) solution of NaCN (1.96 g, 40 mmol) in H_2O (5 mL) over 3 min. A solution of HCl [36% HCl (2 mL) + H_2O (2 mL)] was added dropwise over 2 h at −10 °C. The mixture was stirred at room temperature for 3 h, and the ether layer was separated, washed with water, dried (Na_2SO_4), and concentrated to give a yellow oil. Without further purification, the crude cyanohydrin was added to a solution of imidazole (3.78 g, 56 mmol) and *tert*-butyldiphenylsilyl chloride (7.2 mL, 28 mmol) in dry DMF (75 mL) at 0 °C. The resulting mixture was stirred overnight from 0 °C to room temperature and poured into 80 mL of H_2O, which was extracted with ether, which was washed with brine and concentrated to give a yellow oil. Flash chromatography on silica gel (40:1 hexanes/ether) gave **25**[19] (4.69 g, 34%) as a colorless oil.

Methyl 4-(*tert*-Butyldiphenylsilyloxy)-3-oxo-5*E*-heptenoate (26). Powdered zinc was activated by washing sequentially with 3 M HCl, water, EtOH, and ether and drying under reduced pressure.[20] To a solution of activated zinc dust (1.06 g, 16.22 mmol) in dry THF (15 mL) was added TMSCl (189 μL, 1.49 mmol). The solution was stirred for 20 min and treated with **25** (1.93 g, 5.76 mmol), and the mixture was heated to reflux. Methyl bromoacetate (1.69 mL, 17.90 mmol) was added dropwise over 50 min and heating was continued for 70 min. The mixture was cooled to 5 °C, 3 M HCl (9 mL) was added, and the resulting solution was stirred at room temperature for 2 h. The mixture was poured into saturated aqueous $NaHCO_3$ solution (50 mL) forming an emulsion that was broken by the addition of water (50 mL). The aqueous phase was extracted with EtOAc (5 × 80 mL), and the combined organic layers were dried (Na_2SO_4) and concentrated to give a yellow oil. Flash chromatography on silica gel (20:1 hexanes/ether) gave **26** (2.03 g, 86%) as an 87:13 keto/enol mixture: ^{1}H NMR (keto) 7.59−7.62 (m, 4), 7.36−7.44 (m, 6), 5.62 (ddq, 1, *J* = 15.3, 6.7, 1.2), 5.35 (ddq, 1, *J* = 15.3, 6.4, 1.8), 4.58 (br d, 1, *J* = 6.4), 3.67 (s, 3), 3.57 (s, 2), 1.59 (ddd, 3, *J* = 6.7, 1.8, 1.2), 1.10 (s, 9); ^{1}H NMR (enol) 11.8 (s, 1, OH), 5.44 (s, 1); ^{13}C NMR (keto) 202.6, 167.7, 135.8 (2 C), 135.7 (2 C), 132.9, 132.6, 130.9, 130.1, 129.9, 127.8 (2C), 127.6 (2C), 126.9, 80.5, 52.2, 43.9, 26.9 (3 C), 19.3, 17.8; IR (neat) 2955, 1755, 1725; HRMS (DCI/NH_3) calcd for $C_{24}H_{34}NO_4Si$ (MNH_4^+) 428.2257, found 428.2265.

Methyl 4-(*tert*-Butyldiphenylsilyloxy)-3-hydroxy-5*E*-heptenoate (27). To a stirred solution of **26** (1 g, 2.43 mmol) in MeOH (10 mL) at −15 °C was added $NaBH_4$ (111 mg, 2.92 mmol) in portions. The solution was stirred for 5 min and 10% aqueous HCl was added to quench the reaction. After concentration to remove the MeOH, the aqueous phase was extracted with EtOAc (3 × 80 mL), which was washed with saturated aqueous $NaHCO_3$ solution and brine, dried (Na_2SO_4), and concentrated to give a yellow oil. Flash chromatography on silica gel (4:1 hexanes/ether) gave 970 mg (97%) of an inseparable 5:1 mixture of **27a** and **27b**.

Partial data for **27a** were determined from the mixture: ^{1}H NMR 3.656 (s, 3), 2.65 (d, 1, *J* = 3.7, OH), 2.48 (dd, 1, *J* = 15.9, 4.3), 2.45 (dd, 1, *J* = 15.9, 7.9).

Partial data for **27b** were determined from the mixture: ^{1}H NMR 3.663 (s, 3), 2.78 (d, 1, *J* = 4.3, OH), 2.52 (dd, 1, *J* = 15.2, 3.7), 2.36 (dd, 1, *J* = 15.2, 8.5).

(4*R*,5*S*)-*rel*- and (4*R*,5*R*)-*rel*-Dihydro-4-hydroxy-5-(1*E*)-1-propenyl-2(3*H*)-furanone (13c and 28). To a cooled solution (5 °C) of the 5:1 mixture of **27a** and **27b** (890 mg, 2.16 mmol) in THF (20 mL) was added TBAF (6.8 mL, 0.7 M in CH_3CN, 4.76 mmol) dropwise. The reaction was stirred for 48 h at room temperature and treated with 10% aqueous HCl (2 mL). The solution was stirred for 1 h. Ethyl acetate and solid NaCl were added. The layers were separated and the organic layer was washed with saturated aqueous $NaHCO_3$ solution and brine, dried (Na_2SO_4), and concentrated to give a yellow oil. Flash chromatography on silica gel (1:1 hexanes/EtOAc) gave **13c** (193 mg, 63%) as a colorless oil, followed by **28** (40 mg, 13%) also as a colorless oil.

Data for **13c**: ^{1}H NMR 5.88 (dq, 1, J = 15.3, 6.7), 5.46 (dd, 1, J = 15.3, 6.7), 4.77 (dd, 1, J = 6.7, 1.8), 4.33 (m, 1), 2.89 (br, 1, OH), 2.81 (dd, 1, J = 17.7, 6.7), 2.51 (dd, 1, J = 17.7, 4.3), 1.75 (d, 3, J = 6.7); ^{13}C NMR 175.4, 131.2, 125.7, 87.7, 72.1, 37.0, 17.8; IR (neat) 3432, 1778, 1672; HRMS (CI/NH_3) calcd for $C_7H_{14}NO_3$ (MNH_4^+) 160.0974, found 160.0969.

Data for **28**: ^{1}H NMR 6.01 (dq, 1, J = 15.3, 6.7), 5.63 (ddq,1, J = 15.3, 6.7, 1.8), 4.86 (dd, 1, J = 6.7, 3.7), 4.48 (m, 1), 2.78 (dd, 1, J = 17.7, 5.7), 2.62 (dd, 1, J = 17.7, 1.8), 2.12 (d, 1, J = 3.1, OH), 1.82 (br d, 3, J = 6.7); ^{13}C NMR 175.7, 133.6, 122.8, 84.9, 69.7, 38.7, 18.0; IR (neat) 3432, 1765.

(3*S*,4*S*,5*R*)-*rel*-Dihydro-4-hydroxy-3-[(1*R*,2*E*,4*E*)-1-hydroxy-2,4-hexadienyl]-5-(1*E*)-1-propenyl-2(3*H*)-furanone (12c) and (3*R*,4*R*,5*S*)-*rel*-Dihydro-4-hydroxy-3-[(1*R*-2*E*,4*E*)-1-hydroxy-2,4-hexadienyl]-5-(1*E*)-1-propenyl-2(3*H*)-furanone (15c). Lithium diisopropylamide was prepared from diisopropylamine (493 μL, 3.52 mmol) and *n*-BuLi (1.41 mL, 2.5 M in hexanes, 3.52 mmol) in THF (10 mL) at 0 °C. This solution was cooled to −42 °C and treated with **13c** (200 mg, 1.41 mmol) in THF (1 mL). The solution was stirred for 15 min and a 4:1 mixture of (2*E*,4*E*)- and (2*E*,4*Z*)-2,4-hexadienal (**14**) (156 μL, 1.42 mmol) was added. The mixture was stirred at −42 °C for 1 h and saturated aqueous NH_4Cl solution (1 mL) was added to quench the reaction. The resulting mixture was diluted with ether (125 mL), washed with brine, dried (Na_2SO_4), and concentrated to give a yellow oil. Flash chromatography on silica gel (1:1 hexanes/ether) gave **15c** (90 mg, 27%) followed by **12c** (188 mg, 56%). Both of these compounds are a 4:1 mixture of (2*E*,4*E*) and (2*E*,4*Z*) isomers. Flash chromatography of the mixture of **12c** isomers on 20% $AgNO_3$ on silica gel (1:1 hexanes/EtOAc) gave (2*E*,4*E*)-**12c** (147 mg, 44%) as a white solid. Similar chromatography of the mixture of **15c** isomers gave (2*E*,4*E*)-**15c** as a white solid (71 mg, 21%).

Data for **12c**: mp 83−84 °C; ^{1}H NMR 6.32 (dd, 1, J = 15.3, 11.0), 6.07 (ddq, 1, J = 15.3, 11.0, 1.8), 5.97 (dq, 1, J = 15.3, 6.7), 5.79 (dq, 1, J = 15.3, 6.7), 5.67 (dd, 1, J = 15.3, 7.3), 5.49 (ddq, 1, J = 15.3, 6.9, 1.8), 4.49−4.53 (m, 2), 4.08 (ddd, 1, J = 11.6, 9.2, 3.7), 3.11 (d, 1, J = 3.1, OH), 2.84 (dd, 1, J = 9.2, 6.7), 2.34 (d, 1, J = 3.7, OH), 1.77 (dd, 6, J = 6.7, 1.8); ^{13}C NMR 174.2, 133.8, 133.6, 132.2, 130.1, 127.7, 125.9, 84.1, 74.1, 71.6, 53.6, 18.2, 17.9; IR (KBr) 3397, 1733, 1672; HRMS (CI/NH_3) calcd for $C_{13}H_{22}NO_4$ (MNH_4^+) 256.1549, found 256.1553.

Data for **15c**: mp 95−98 °C; ^{1}H NMR 6.36 (dd, 1, J = 15.3, 10.4), 6.08 (ddq, 1, J = 15.3, 10.4, 1.8), 5.96 (dq, 1, J = 15.3, 6.7), 5.77 (dq, 1, J = 15.3, 6.7), 5.71 (dd, 1, J = 15.3, 6.1), 5.52 (ddq, 1, J = 15.3, 7.9, 1.8), 4.74 (ddd, 1, J = 6.1, 4.3, 3.7), 4.49 (dd, 1, J = 7.9, 7.9), 4.31 (ddd, 1, J = 10.4, 7.9, 4.3), 2.82 (d, 1, J = 3.7, OH), 2.80 (d, 1, J = 4.3, OH), 2.46 (dd, 1, J = 10.4, 4.3), 1.77 (br d, 6, J = 6.7); ^{13}C NMR 173.9, 133.4, 132.2, 131.4, 130.2, 128.6, 126.2, 84.3, 73.1, 69.2, 54.2, 18.1, 17.9; IR (KBr) 3337, 1767, 1676.

(2*R*,3*S*,4*R*,4a*R*,7*S*,7a*R*)-*rel*-Hexahydro-4-hydroxy-3-iodo-2,7-di-(1*E*)-1-propenyl-5*H*-furo[3,4-*b*]pyran-5-one (11c). Dry bis(*sym*-collidine)silver(I) hexafluorophosphate (255 mg, 0.52 mmol) was slurried in dry CH_2Cl_2 (3 mL) with vigorous stirring and iodine (104 mg, 0.41 mmol) was added in one portion forming a yellow precipitate instantly. The solution was stirred for 5 min and diene diol **12c** (81 mg, 0.34 mmol) in dry CH_2Cl_2 (2 mL) was added. The resulting mixture was stirred at room temperature for 2 h and filtered through Celite. The filtrate was washed with 10% aqueous $Na_2S_2O_3$ solution and saturated aqueous $NaHCO_3$ solution, dried (Na_2SO_4), and concentrated to give a yellow oil. Flash chromatography on silica gel (3:1 hexanes/ether) gave **11c** (118 mg, 95%) as a pale yellow solid: mp 125−127 °C; ^{1}H NMR 6.01 (dq, 1, J = 15.3, 6.7), 5.90 (dq, 1, J = 15.3, 6.7), 5.49 (ddq, 1, J = 15.3, 7.9, 1.2), 5.43 (ddq, 1, J = 15.3, 7.9, 1.2), 4.71 (dd, 1, J = 8.6, 7.9, H_7), 4.24 (dd, 1, J = 10.4, 7.9, H_2), 4.14 (dd, 1, J = 10.4, 9.8, H_4), 3.61 (dd, 1, J = 11.6, 8.6, H_{7a}), 3.60 (dd, 1, J = 10.4, 9.8, H_3), 3.17 (br, 1, OH), 2.48 (dd, 1, J = 11.6, 10.4, H_{4a}), 1.79 (dd, 3, J = 6.7, 1.2), 1.78 (dd, 3, J = 6.7, 1.2); ^{13}C NMR 169.7, 135.0, 134.2, 127.5, 124.9, 84.9, 82.3, 79.2, 73.1, 51.3, 38.6 18.0, 17.7; IR (KBr) 3449, 1768, 1677.

(2*R*,3*R*,7*S*,7a*R*)-*rel*-2,3,7,7a-Tetrahydro-3-hydroxy-2,7-di-(1*E*)-1-propenyl-5*H*-furo[3,4-*b*]pyran-5-one [(±)-Waol A, 6]. To a solution of **11c** (90 mg, 0.25 mmol) in dry CH_2Cl_2 (10 mL) was added Et_3N (2 mL). The resulting mixture was stirred at reflux overnight, diluted with CH_2Cl_2 (125 mL), washed with 10% aqueous HCl, saturated aqueous $NaHCO_3$ solution, and brine, dried (Na_2SO_4), and concentrated to give a yellow oil. Flash chromatography on silica gel (1:1 hexanes/ether) gave **6** (57 mg, 98%) as a colorless oil: ^{1}H NMR 6.89 (dd, 1, J = 3.7, 2.4, H_4), 6.01 (dq, 1, J = 15.3, 6.7), 5.92 (dq, 1, J = 15.3, 6.7), 5.71 (ddq, 1, J = 15.3, 6.7, 1.2), 5.61 (ddq, 1, J = 15.3, 7.9, 1.2), 4.60 (dd, 1, J = 7.9, 7.9, H_7), 4.38 (ddd, 1, J = 7.9, 2.4, 1.8, H_{7a}), 4.04−4.08 (m, 2, $H_{2,3}$), 2.07 (br d, 1, J = 7.9, OH), 1.79 (dd, 6, J = 6.7, 1.2); ^{13}C NMR 166.4, 134.0, 133.6, 132.9, 131.3, 125.9, 125.7, 82.9, 79.8, 78.5, 64.1, 18.1, 17.9; IR (neat) 3440, 1762, 1674; HRMS (CI/NH_3) calcd for $C_{13}H_{20}NO_4$ (MNH_4^+) 254.1392, found 254.1381. The spectral data are identical with those of natural waol A.[1]

Methyl (2*S*,5*S*,6*S*)-*rel*-5,6-Dihydro-5-hydroxy-2-[(1*R*,2*E*)-1-hydroxy-2-butenyl]-6-(1*E*)-1-propenyl-2*H*-pyran-3-carboxylate [(±)-Waol B, 29] and (2*R*,3*R*,4*S*,4a*S*,7*S*,7a*R*)-*rel*-Hexahydro-3-hydroxy-4-methoxy-2,7-di-(1*E*)-1-propenyl-5*H*-furo[3,4-*b*]pyran-5-one (30). A solution of **6** (20 mg, 0.08 mmol) in 5 mL of 1:1 $MeOH/H_2O$ containing 142 mg of KOH was stirred for 1 h. The MeOH was removed by concentration and the resulting aqueous solution was acidified with 0.5 M HCl to pH 3 and extracted with Et_2O (3 × 15 mL). The combined extracts were washed with H_2O and dried (Na_2SO_4). A solution of diazomethane in ether was added dropwise to the Et_2O solution at 0 °C. Concentration afforded an oil that was purified by flash chromatography on silica gel (3:1 hexanes/EtOAc) to give **30** (10.6 mg, 47%) as a colorless oil, followed by **29** (8.6 mg, 38%) as a colorless oil.

Data for **29**: ^{1}H NMR 7.13 (dd, 1, J = 6.4, 2.0, H_4), 5.84 (dq, 1, J = 15.3, 6.7), 5.62−5.71 (m, 2), 5.44 (ddq, 1, 15.3, 6.7, 1.8), 4.76 (br s, 1), 4.59−4.63 (m, 1), 3.91−3.97 (m, 2), 3.76 (s, 3), 2.55 (d, 1, J = 8.5, OH), 1.90 (d, 1, J = 10.4, OH), 1.77 (d, 3, J = 6.7), 1.68 (dd, 3, J = 6.7, 1.2); ^{13}C NMR 165.7, 137.9, 132.7, 130.3, 128.9, 128.5, 126.7, 77.2, 76.8, 72.7, 64.3, 52.0, 18.1, 17.8; IR (neat) 3415, 1717; HRMS (CI/NH_3) calcd for $C_{14}H_{24}NO_5$ (MNH_4^+) 286.1654, found 286.1656. The spectral data are identical with those of natural waol B.[2]

Data for **30**: ^{1}H NMR 5.81−5.94 (m, 2), 5.54 (ddq, 1, J = 15.3, 6.7, 1.8), 5.42 (ddq, 1, J = 15.3, 5.5, 1.8), 4.98 (d, 1, J = 5.5, H_7), 4.28 (d, 1, J = 4.9, H_{7a}), 4.16 (dd, 1, J = 6.7, 1.2, H_2), 3.99 (dd, 1, J = 2.4, 1.8, H_4), 3.65 (dd, 1, J = 4.8, 2.4, H_3), 3.47 (s, 3), 2.74 (dd, 1, J = 4.9, 1.8, H_{4a}), 1.83 (d, 1, J = 4.8, OH), 1.72−1.76 (m, 6); ^{13}C NMR 174.4, 130.2, 130.0, 126.7, 124.4, 84.2, 76.0, 75.6, 72.8. 66.8, 57.9, 39.9, 18.0, 17.8; IR (neat) 3477, 1770; HRMS (CI/NH_3) calcd for $C_{14}H_{24}NO_5$ (MNH_4^+) 286.1654, found 286.1656.

2,5-Dideoxy-2-[(1*R*,2*E*,4*E*)-1-hydroxy-2,4-hexadienyl]-L-xylonic Acid, γ-Lactone (32) and 2,5-Dideoxy-2-[(1*S*,-2*E*,4*E*)-1-hydroxy-2,4-hexadienyl]-L-xylonic acid, γ-Lactone (33). Lithium diisopropylamide was prepared from diisopropylamine (1.43 mL, 10.18 mmol) and *n*-BuLi (6.37 mL, 1.6 M in hexanes, 10.18 mmol) in THF (12 mL) at 0 °C. The solution was cooled to −42 °C and treated with (−)-**31** (568 mg, 4.90 mmol) in THF (4 mL). The mixture was stirred for 15 min, and treated with a 4:1 mixture of (2*E*,4*E*)- and (2*E*,4*Z*)-2,4-hexadienal (**14**) (595 μL, 5.39 mmol). The mixture was stirred at −42 °C for 1.2 h and 10% HCl solution (7 mL) was added to quench the reaction. The organic layer was separated and the aqueous layer was extracted with ether (3 × 50 mL). The combined organic layers were washed with brine, dried (Na_2SO_4), and concentrated to give a yellow oil. Flash chromatography on silica gel (2:1 hexanes/EtOAc) gave **33** (405 mg, 39%) as a colorless oil, followed by **32** (467 mg, 45%) as a colorless oil. Both of these compounds are a 4:1 mixture of (2*E*,4*E*) and (2*E*,4*Z*) isomers. Flash chromatography of the mixture of **32** isomers on 20% $AgNO_3$ on silica gel (2:1 hexanes/EtOAc) gave (2*E*,4*E*)-**32** (374 mg, 36%). Similar chromatography of the mixture of **33** isomers gave (2*E*,4*E*)-**33** (324 mg, 31%).

Data for **32**: $[\alpha]^{22}_D$ −65 (*c* 1.2, MeOH); ^{1}H NMR 6.30 (dd, 1, *J* = 15.3, 10.4), 6.06 (ddq, 1, *J* = 15.3, 10.4, 1.3), 5.79 (dq, 1, *J* = 15.3, 6.7), 5.68 (dd, 1, *J* = 15.3, 7.3), 4.70 (dq, 1, *J* = 6.7, 6.7), 4.53 (ddd, 1, *J* = 7.3, 6.5, 3.1), 4.45 (br dd, 1, *J* = 6.7, 6.7), 3.03 (d, 1, *J* = 3.1, OH), 2.81 (dd, 1, *J* = 6.7, 6.5), 2.65 (d, 1, *J* = 4.9, OH), 1.77 (br d, 3, *J* = 6.7), 1.38 (d, 3, *J* = 6.7); ^{13}C NMR 175.5, 133.6, 132.1, 130.1, 127.7, 78.8, 71.5, 70.7, 53.6, 18.2, 14.2; IR (neat) 3374, 1736; HRMS (DCI/NH_3) calcd for $C_{11}H_{18}NO_3$ (M + NH_4^+ − H_2O) 212.1287, found 212.1291.

Data for **33**: ^{1}H NMR 6.32 (dd, 1, *J* = 15.3, 10.4), 6.07 (ddq, 1, *J* = 15.3, 10.4, 1.2), 5.77 (dq, 1, *J* = 15.3, 6.7), 5.65 (dd, 1, *J* = 15.3, 6.1), 4.65−4.73 (m, 2), 4.51 (br dd, 1, *J* = 9.8, 4.9), 3.02 (d, 1, *J* = 4.9, OH), 2.96 (d, 1, *J* = 4.9, OH), 2.72 (dd, 1, *J* = 4.3, 3.7), 1.77 (br d, 3, *J* = 6.7), 1.37 (d, 3, *J* = 6.7); ^{13}C NMR 176.8, 132.2, 131.3, 130.3, 128.9, 79.9, 70.2, 69.7, 55.0, 18.1, 14.1; IR (neat) 3416, 1744.

(2*S*,3*R*,4*S*,4a*S*,7*S*,7a*S*)-Hexahydro-4-hydroxy-3-iodo-7-methyl-2-(1*E*)-1-propenyl-5*H*-furo[3,4-*b*]pyran-5-one (34). Dry bis(*sym*-collidine)silver(I) hexafluorophosphate (294 mg, 0.59 mmol) was slurried in dry CH_2Cl_2 (10 mL) with vigorous stirring, iodine (121 mg, 0.48 mmol) was added in one portion, and the solution was stirred for 5 min. A yellow precipitate was produced instantly. Diene diol **32** (84 mg, 0.40 mmol) in dry CH_2Cl_2 (2 mL) was added. The resulting mixture was stirred at 25 °C for 2.5 h and filtered through Celite. The Celite was washed with CH_2Cl_2 (60 mL) and the combined filtrate was washed with 10% aqueous $Na_2S_2O_3$ solution, 10% HCl solution, and saturated aqueous $NaHCO_3$ solution, dried (Na_2SO_4), and concentrated to give a yellow oil. Flash chromatography on silica gel (6:1 hexanes/EtOAc) gave iodohydrin **34** (121 mg, 91%) as a pale yellow oil: $[\alpha]^{22}_D$ −9.3 (*c* 1.1, MeOH); ^{1}H NMR 5.91 (dq, 1, *J* = 15.3, 6.7), 5.47 (ddq, 1, *J* = 15.3, 7.9, 1.2), 4.81 (dq, 1, *J* = 7.3, 6.7, H_7), 4.27 (dd, 1, *J* = 10.4, 7.9, H_2), 4.14 (ddd, 1, *J* = 10.4, 10.4, 2.4, H_4), 4.00 (dd, 1, *J* = 12.2, 7.3, H_{7a}), 3.58 (dd, 1, *J* = 10.4, 10.4, H_3), 3.16 (d, 1, *J* = 2.4, OH), 2.53 (dd, 1, *J* = 12.2, 10.4, H_{4a}), 1.80 (dd, 3, *J* = 6.7, 1.2), 1.41 (d, 3, *J* = 6.7); ^{13}C NMR 170.3, 133.8, 127.7, 84.9, 76.2, 75.6, 73.6, 46.5, 38.7, 17.7, 13.5; IR (neat) 3474, 1781.

(2*S*,3*R*,4*S*,4a*S*,7*S*,7a*S*)-Hexahydro-3,4-dihydroxy-7-methyl-2-(1*E*)-1-propenyl-5*H*-furo[3,4-*b*]pyran-5-one (60). AIBN (5 mg, 0.03 mmol), $NaBH_3CN$ (192 mg, 2.96 mmol), Bu_3SnCl (20 μL, 0.07 mmol), and iodohydrin **34** (500 mg, 1.48 mmol) in *t*-BuOH (6 mL) were placed in a 100-mL round-bottomed flask that was connected to an empty thick-walled natural latex rubber balloon. After being degassed under reduced pressure, the flask was filled with O_2. The resulting mixture was stirred at 65 °C for 2.5 h and another portion of Bu_3SnCl (20 μL, 0.07 mmol) was added to the mixture. The reaction mixture was stirred for another 2.5 h and poured into water (6 mL), which was extracted with ether (3 × 50 mL) and CH_2Cl_2 (3 × 50 mL). The combined extracts were dried ($MgSO_4$) and concentrated to give a yellow oil. Flash chromatography on silica gel (1:1 hexanes/EtOAc) gave (2*R*,4*R*,4a*S*,7*S*,7a*S*)-hexahydro-4-hydroxy-7-methyl-2-(1*E*)-1-propenyl-5*H*-furo[3,4-*b*]pyran-5-one (**62**) (9 mg, 3%) as a colorless oil followed by diol **60** (175 mg, 52%) as a white solid.

A flask was charged with a solution of iodohydrin **34** (125 mg, 0.37 mmol) in toluene (2 mL) with air bubbling in it at 65 °C, to which a solution of Bu_3SnH (298 μL, 1.11 mmol) and AIBN (61 mg, 0.37 mmol) in toluene (3 mL) was added in 3 portions over 12 h. The solvent was evaporated and 10 mL of hexanes and 10 mL of CH_3CN were added to the residue. The resulting two-phased mixture was stirred vigorously for 5 min. The CH_3CN layer was separated and the hexanes layer was extracted with CH_3CN (3 × 30 mL). The combined CH_3CN layers were washed with hexanes (3 × 10 mL) and concentrated to give a yellow oil. Flash chromatography on silica gel (1:1 hexanes/EtOAc) gave alcohol **62** (25 mg, 32%) as a colorless oil followed by a 10:1 mixture of diols **60** and **61** (34 mg, 41%) as a white solid. Yields vary in the other runs. Diols **60** and **61** cannot be separated via flash chromatography on silica gel, but after the two hydroxyl groups were protected, the two acetonides can be separated easily via flash chromatography on silica gel.

Data for **60**: $[\alpha]^{22}_D$ −55 (*c* 1.30, MeOH); mp 149−151 °C; ^{1}H NMR 5.93 (dq, 1, *J* = 15.3, 6.7), 5.55 (ddq, 1, *J* = 15.3, 7.9, 1.2), 4.77 (dq, 1, *J* = 7.3, 6.7), 4.00 (dd, 1, *J* = 12.2, 7.3), 3.96 (dd, 1, *J* = 10.4, 8.6), 3.84 (dd, 1, *J* = 9.4, 7.9), 3.67 (br s, 1, OH), 3.30 (ddd, 1, *J* = 9.4, 8.6, 3.1), 2.88 (d, 1, *J* = 3.1, OH), 2.62 (dd, 1, *J* = 12.2, 10.4), 1.78 (dd, 3, *J* = 6.7, 1.2), 1.40 (d, 3, *J* = 6.7); ^{13}C NMR 171.9, 132.7, 127.4, 83.1, 76.1, 75.8, 75.4, 71.9, 44.7, 18.0, 13.5; IR (neat) 3428, 1782; HRMS (EI, 20 EV) calcd for $C_{11}H_{16}O_5$ (M^+) 228.0998, found 228.1006.

Data for **62**: ^{1}H NMR 5.80 (dq, 1, *J* = 15.3, 6.7), 5.53 (ddq, 1, *J* = 15.3, 7.3, 1.2), 4.79 (dq, 1, *J* = 7.3, 6.7), 4.02−4.13 (m, 2), 3.81 (dd, 1, *J* = 12.2, 7.3), 2.91 (d, 1, *J* = 2.4, OH), 2.40 (dd, 1, *J* = 12.2, 9.7), 2.09 (ddd, 1, *J* = 13.3, 4.9, 2.4), 1.74 (dd, 3, *J* = 6.7, 1.2), 1.41 (d, 3, *J* = 6.7), 1.40 (ddd, 1, *J* = 13.3, 11.6, 10.4); ^{13}C NMR 173.0, 129.5, 129.4, 79.5, 76.6, 75.5, 67.1, 46.4, 40.0, 17.8, 13.6; IR (neat) 3448, 1774; HRMS (EI, 20 EV) calcd for $C_{11}H_{16}O_4$ (M^+) 212.1049, found 212.1041.

Acetonide 63. A mixture of diol **60** (169 mg, 0.74 mmol) and D-(+)-camphor-10-sulfonic acid (26 mg, 0.11 mmol) in dry DMF (1 mL) was prepared and added to a solution of 2-methoxypropene (1.42 mL, 14.80 mmol) in dry DMF (3 mL) at 25 °C. The resulting mixture was stirred at 25 °C for 1.5 h, diluted with EtOAc (120 mL), washed with saturated aqueous $NaHCO_3$ solution, H_2O, and brine, dried ($MgSO_4$), and concentrated to give a yellow oil. Flash chromatography on silica gel (10:1 hexanes/EtOAc) gave acetonide **63** (197 mg, 99%) as a colorless oil: $[\alpha]^{22}_D$ −51 (*c* 1.20, MeOH); ^{1}H NMR 5.82 (dq, 1, *J* = 15.3, 6.7), 5.56 (ddq, 1, *J* = 15.3, 7.3, 1.8), 4.83 (dq, 1, *J* = 7.3, 6.7), 4.09 (dd, 1, *J* = 9.7, 7.3), 3.93 (dd, 1, *J* = 11.6, 7.3), 3.74 (dd, 1, *J* = 10.4, 8.5), 3.18 (dd, 1, *J* = 9.7, 8.5), 2.86 (dd, 1, *J* = 11.6, 10.4), 1.79 (dd, 3, *J* = 6.7, 1.8), 1.50 (s, 3), 1.49 (s, 3), 1.43 (d, 3, *J* = 6.7); ^{13}C NMR 169.9, 132.6, 126.6, 112.1, 81.5, 80.9, 76.7, 76.4, 76.3, 44.9, 26.6, 26.5, 18.1, 13.8; IR (neat) 1786; HRMS (EI, 20 EV) calcd for $C_{14}H_{20}O_5$ (M^+) 268.1311, found 268.1315.

The *cis* acetonide was obtained as a minor product of the protection of the 10:1 mixture of diols **60** and **61**: ^{1}H NMR 5.90 (dq, 1, *J* = 15.3, 7.1), 5.76 (ddq, 1, *J* = 15.3, 7.9, 1.2), 4.77 (dq, 1, *J* = 6.7, 6.1), 4.41 (dd, 1, *J* = 9.1, 4.9), 4.25 (dd, 1, *J* = 7.9, 2.4), 4.05 (dd, 1, *J* = 4.9, 2.4), 3.78 (dd, 1, *J* = 12.2, 6.7), 2.65 (dd, 1, *J* = 12.2, 9.1), 1.79 (br d, 3, *J* = 7.1), 1.56 (s, 3), 1.40 (d, 3, *J* = 6.1), 1.37 (s, 3); ^{13}C NMR 172.3, 131.5, 126.0, 110.0, 80.4, 75.8, 74.9, 74.5, 72.3, 42.5, 28.7, 26.1, 17.9, 13.7; IR (neat) 1786.

Phenylselenide 64. To a solution of potassium bis(trimethylsilyl)amide (840 μL, 0.42 mmol, 0.5 M in toluene) in dry THF (3 mL) was added a solution of acetonide **63** (94 mg, 0.35 mmol) in dry THF (2 mL) at −78 °C over 30 min. This mixture was stirred at −78 °C for 15 min and treated with a solution of phenylselenyl chloride (80 mg, 0.42 mmol) and HMPA (70 μL, 0.39 mmol) in dry THF (1 mL). The resulting mixture was stirred for 3 h from −78 to 25 °C, diluted with ether, washed with brine, dried ($MgSO_4$), and concentrated to give a yellow oil. Flash chromatography on silica gel (10:1 hexanes/ethyl ether) gave **64** (141 mg, 95%) as a colorless oil: $[\alpha]^{22}_D$ −53 (*c* 1.3, MeOH); ^1H NMR 7.77 (dd, 2, *J* = 8.0, 1.2), 7.47 (ddd, 1, *J* = 7.3, 7.3, 1.2), 7.37 (dd, 2, *J* = 8.0, 7.3), 5.82 (dq, 1, *J* = 15.3, 6.7), 5.44 (ddq, 1, *J* = 15.3, 6.7, 1.2), 5.01 (dq, 1, *J* = 2.4, 6.7), 3.91 (d, 1, *J* = 2.4), 3.71 (dd, 1, *J* = 9.2, 6.7), 3.50 (d, 1, *J* = 9.2), 3.38 (dd, 1, *J* = 9.2, 9.2), 1.72 (dd, 3, *J* = 6.7, 1.2), 1.52 (s, 3), 1.43 (s, 3), 1.41 (d, 3, *J* = 6.7); ^{13}C NMR 170.5, 138.6 (2 C), 130.9, 130.4, 129.4 (2 C), 126.8, 123.5, 110.8, 80.9, 78.7, 78.5, 76.8, 76.3, 52.3, 26.5, 26.3, 18.0, 13.7; IR (neat) 1767; HRMS (DCI/NH_3) calcd for $C_{20}H_{25}O_5Se$ (MH^+) 425.0867, found 425.0861.

(2*S*,3*R*,4*S*,7*S*)-2,3,4,7-Tetrahydro-3,4-dihydroxy-7-methyl-2-(1*E*)-1-propenyl-5*H*-furo[3,4-*b*]pyran-5-one (Massarilactone B, 7). To a stirred solution of **64** (50 mg, 0.12 mmol) in THF (2 mL) at 0 °C was added 30% H_2O_2 (300 μL) dropwise. The resulting mixture was stirred from 0 to 25 °C for 2.5 d, diluted with ether (100 mL), and washed with saturated aqueous Na_2CO_3 solution. The aqueous phase was extracted with ether (3 × 30 mL) and CH_2Cl_2 (3 × 30 mL). The combined organic layers were dried ($MgSO_4$) and concentrated to give a yellow oil. Flash chromatography on silica gel (1:2 hexanes/EtOAc) gave **7** (14 mg, 53%) as a colorless oil: $[\alpha]^{22}_D$ −96 (*c* 0.70, MeOH) {lit.[6] $[\alpha]^{28}_D$ −109 (*c* 2.2, MeOH)}; ^1H NMR 5.99 (dq, 1, *J* = 15.3, 6.7), 5.68 (ddq, 1, *J* = 15.3, 7.9, 1.2), 4.86 (dq, 1, *J* = 1.2, 6.7), 4.63 (dd, 1, *J* = 7.9, 7.9), 4.55 (br d, 1, *J* = 6.1), 3.81 (dd, 1, *J* = 7.9, 6.1), 3.65 (br s, 1, OH), 3.13 (br s, 1, OH), 1.81 (dd, 3, *J* = 6.7, 1.2), 1.48 (d, 3, *J* = 6.7); ^{13}C NMR 177.3, 171.4, 134.7, 124.8, 100.7, 84.1, 74.0, 71.9, 65.3, 18.0, 17.2; IR (neat) 3418, 1738, 1664; HRMS (DCI/NH_3) calcd for $C_{11}H_{15}O_5$ (MH^+) 227.0919, found 227.0916.

To a stirred solution of **64** (13 mg, 0.03 mmol) in THF (1 mL) at 0 °C was added 30% H_2O_2 (78 μL) dropwise. The resulting mixture was stirred from 0 to 25 °C for 8 h, diluted with ether (30 mL), and washed with saturated aqueous Na_2CO_3 solution. The aqueous phase was extracted with ether (3 × 15 mL) and CH_2Cl_2 (3 × 15 mL). The combined organic layers were dried ($MgSO_4$) and concentrated to give a yellow oil. Flash chromatography on silica gel (4:1 to 1:2 hexanes/EtOAc) gave acetonide **66** (3.2 mg, 39%), followed by acetonide **65** (2.5 mg, 31%) and **7** (1.7 mg, 24%).

Data for **65**: ^1H NMR 6.11 (dq, 1, *J* = 15.3, 6.7), 5.64 (ddq, 1, *J* = 15.3, 7.9, 1.2), 4.95 (dd, 1, *J* = 10.4, 7.9), 4.82 (dq, 1, *J* = 1.8, 6.7), 4.44 (dd, 1, *J* = 8.0, 1.8), 3.65 (dd, 1, *J* = 10.4, 8.0), 1.85 (dd, 3, *J* = 6.7, 1.2), 1.54 (s, 3), 1.53 (s, 3), 1.47 (d, 3, *J* = 6.7); IR (neat) 1760, 1638.

Data for **66**: ^1H NMR 5.98 (dq, 1, *J* = 15.3, 6.7), 5.62 (ddq, 1, *J* = 15.3, 6.7, 1.8), 4.91 (dd, 1, *J* = 6.7, 3.0), 4.78 (dq, 1, *J* = 6.7, 6.1), 4.41 (dd, 1, *J* = 9.2, 3.0), 4.22 (dd, 1, *J* = 9.2, 6.7), 1.81 (br d, 3, *J* = 6.7), 1.68 (s, 3), 1.60 (s, 3), 1.26 (d, 3, *J* = 6.1); ^{13}C NMR 164.0, 154.0, 132.4, 126.8, 118.4, 90.5, 79.2, 76.7, 76.2, 75.2, 26.8, 23.7, 18.0, 14.6; IR (neat) 1758, 1721.

Acetonide **65** (2.5 mg, 0.009 mmol) in 80% AcOH (0.5 mL) was stirred at 25 °C for 2 h. Removal of the solvent under reduced pressure with heating gave **7** (2.1 mg, 100%) as a pale yellow oil.

Cis-Fused Acetonide 69. To a stirred solution of acetonide **63** (120 mg, 0.45 mmol) in dry CH_2Cl_2 (6 mL) was added DBN (138 μL, 1.12 mmol) dropwise at 0 °C under N_2. The mixture was stirred at 0 °C for 10 min, diluted with CH_2Cl_2 (120 mL), washed with H_2O and brine, dried ($MgSO_4$), and concentrated to give a yellow oil. Flash chromatography on silica gel (4:1 hexanes/EtOAc) gave **69** (114 mg, 95%) as a white solid: ^1H NMR 5.89 (dq, 1, *J* = 15.3, 6.7), 5.53 (ddq, 1, *J* = 15.3, 6.7, 1.2), 4.57 (dq, 1, *J* = 3.0, 6.7), 4.22 (dd, 1, *J* = 3.7, 3.0), 3.92 (dd, 1, *J* = 9.2, 6.7), 3.84 (dd, 1, *J* = 9.8, 4.5), 3.40 (dd, 1, *J* = 4.5, 3.7), 3.36 (dd, 1, *J* = 9.8, 9.2), 1.76 (dd, 3, *J* = 6.7, 1.2), 1.52 (s, 3), 1.48 (s, 3), 1.45 (d, 3, *J* = 6.7); ^{13}C NMR 171.6, 130.6, 127.0, 110.9, 78.6, 78.2, 76.3, 75.9, 75.4, 46.6, 26.4, 26.3, 17.9, 13.6; IR (KBr) 1781.

Protected Fusidilactone B Ring System 71. To a stirred solution of acetonide **69** (25 mg, 0.09 mmol) in acetone (1 mL) and H_2O (1 mL) was added NMO (33 mg, 0.28 mmol) at 0 °C followed by 2.5 wt % of OsO_4 in *t*-BuOH (122 μL, 10 mmol %). The reaction mixture was warmed to 25 °C then stirred for 12 h and $NaIO_4$ (50 mg, 0.23 mmol) was added. The resulting mixture was stirred for another 4 h, diluted with CH_2Cl_2 (30 mL), and washed with saturated aqueous NH_4Cl solution. The aqueous phase was extracted with CH_2Cl_2 (3 × 20 mL) and the combined organic layers were dried ($MgSO_4$) and concentrated to give aldehyde **70** (25 mg) as a colorless residue, which was used in the next step without further purification.

To a suspension of isobutyltriphenylphosphonium bromide (56 mg, 0.14 mmol) in dry THF (1 mL) was added LHMDS (140 μL, 1.0 M in THF) at 0 °C. The mixture was stirred for 5 min and treated dropwise with aldehyde **70** (25 mg) in dry THF (1 mL). The resulting mixture was stirred from 0 to 25 °C for 3 h and poured into saturated aqueous NH_4Cl solution (2 mL). The aqueous phase was extracted with EtOAc (3 × 30 mL) and the organic layers were washed with brine, dried ($MgSO_4$), and concentrated to give a yellow oil. Flash chromatography on silica gel (4:1 hexanes/EtOAc) gave **71** (11 mg, 40% for two steps) as a colorless oil: ^1H NMR 5.55 (dd, 1, *J* = 11.0, 10.4), 5.29 (dd, 1, *J* = 11.0, 8.5), 4.55 (dq, 1, *J* = 3.0, 6.7), 4.27 (dd, 1, *J* = 9.2, 8.5), 4.22 (dd, 1, *J* = 3.6, 3.0), 3.85 (dd, 1, *J* = 9.2, 5.5), 3.39 (dd, 1, *J* = 5.5, 3.6), 3.36 (dd, 1, *J* = 9.2, 9.2), 2.56−2.66 (m, 1), 1.51 (s, 3), 1.46 (s, 3), 1.44 (d, 3, *J* = 6.7), 1.00 (d, 6, *J* = 6.7); ^{13}C NMR 171.6, 143.6, 122.9, 111.0, 78.2, 76.2, 76.0, 75.6, 74.7, 46.8, 27.8, 26.5, 26.4, 23.1, 23.0, 13.7; IR (neat) 1777, 1664; HRMS (DCI/NH_3) calcd for $C_{16}H_{25}O_5$ (MH^+) 297.1702, found 297.1708.

(2*R*,3*S*,4*R*,4a*S*,7*R*,7a*R*)-*rel*-Hexahydro-3,4-dihydroxy-2-[(1*Z*)-3-methyl-1-butenyl]-7-methyl-5*H*-furo[3,4-*b*]pyran-5-one (72). Acetonide **71** (5.4 mg, 0.02 mmol) in 80% AcOH (1 mL) was stirred at 25 °C for 3 h. Removal of the solvent under reduced pressure with heating gave **72** (4.6 mg, 99%) as a white solid: ^1H NMR (acetone-d_6) 5.42 (dd, 1, *J* = 11.0, 10.4), 5.26 (dd, 1, *J* = 11.0, 7.9), 4.67 (dq, 1, *J* = 3.0, 6.7), 4.37 (dd, 1, *J* = 3.0, 3.0), 4.21 (d, 1, *J* = 3.7, OH), 4.05 (d, 1, *J* = 9.8, OH), 3.97 (dd, 1, *J* = 9.2, 7.9), 3.86 (ddd, 1, *J* = 9.8, 9.2, 6.7), 3.37 (dd, 1, *J* = 6.7, 3.0), 3.15 (ddd, 1, *J* = 9.2, 9.2, 3.7), 2.65−2.75 (m, 1), 1.35 (d, 3, *J* = 6.7), 0.96 (d, 3, *J* = 6.7), 0.95 (d, 3, *J* = 6.7); ^{13}C NMR (acetone-d_6) 178.0, 143.1, 125.7, 79.8, 76.7, 75.4, 74.6, 72.5, 47.8, 28.4, 23.5, 23.3, 13.8; IR (neat) 3459, 1780; HRMS (DCI/NH_3) calcd for $C_{13}H_{21}O_5$ (MH^+) 257.1389, found 257.1387. The spectral data of **72** fit very well to those of natural fusidilactone B (**9**),[7] except for the expected differences due to the side chain.

Acknowledgment. We thank the National Institutes of Health (GM-50151) for financial support. We thank Dr. Kozo Hayashi (Takeda Chemical Industries) for information about the structures of and copies of the spectra of TAN-2483A and TAN-2483B, Dr. Kazutoshi Mizoue (Taisho Pharmaceutical Co.) for copies of the spectra of waols A and B, Prof. James Gloer (University of Iowa) for spectra and a sample of massarilactone B, and Prof. Krohn (Universität Padeborn) for helpful discussions regarding the stereochemistry of fusidilactone B. We thank Dr. Masakazu Nakadai for carrying out preliminary experiments. We thank Ms. Carol Palmer for preparing the cover art and Prof. Carol A. Shearer, University of Illinois, for a photograph of *Massarina tunicata*.

Supporting Information Available: Additional experimental procedures, analysis of the concentration dependence of the spectra of **7**, comparison of the spectra of **9** and **72**, and copies of ^1H and ^{13}C NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

JO0358628