Total Synthesis of the Actin-Depolymerizing Agent (−)-Mycalolide A: Application of Chiral Silane-Based Bond Construction Methodology

James S. Panek* and Ping Liu

Contribution from the Department of Chemistry and Center for Streamlined Synthesis, Metcalf Center for Science and Engineering, Boston University, 590 Commonwealth Avenue, Boston, Massachusetts 02215

Received June 30, 2000

Abstract: A highly convergent asymmetric synthesis of the actin-depolymerizing agent (−)-mycalolide A has been achieved through the assembly and union of the C1−C19 trisoxazole fragment **2** and the C20−C35 aliphatic fragment **3**, respectively. The C1−C19 fragment **2** was constructed via a Kishi−Nozaki coupling between the C1−C6 subunit **4** and the C7−C19 subunit **5**, which in turn was obtained from a highly stereoselective crotylation reaction of silane (*S*)-**7** with trisoxazole aldehyde **8**. The synthesis of the C20−C35 fragment **3** has been accomplished using chiral silane-based bond construction methodology for the introduction of the stereochemical relationships. Union of the advanced intermediates **2** and **3** through a Schlosser−Wittig protocol, macrocyclization utilizing Yamaguchi conditions, and subsequent functional group adjustments completed the total synthesis of (−)-mycalolide A. The synthesis confirms the relative and absolute stereochemistry of (−)-mycalolide A, as well as illustrates the application of chiral silane-based C−C bond construction methodology to the asymmetric synthesis of complex molecules.

Introduction

During the course of a search for bioactive metabolites from marine invertebrates, Fusetani and co-workers reported the isolation and planar structure of (−)-mycalolide A (1), a new secondary metabolite produced by a sponge of the genus *Mycale*.[1] This marine macrolide belongs to an emerging class of trisoxazole-containing natural products, which include ulapualides,[2] kabiramides,[3] halichondramides,[4] and jaspisamides.[5] These natural products display a wide range of biological activities, such as antifungal, antileukemic, and ichthyotoxic properties. Mycalolide A exhibits potent antifungal activity against a diverse array of pathogenic fungi and cytotoxicity toward B-16 melanoma cells with IC_{50} values of 0.5−1.0 ng/mL.[1] Interest in mycalolide A was further heightened by its reported ability to selectively inhibit the actomyosin Mg^{2+}−ATPase.[6] In that regard, it has been suggested that mycalolide A acts as an actin-depolymerizing agent which may find eventual applications in pharmacology as a probe of actin-mediated cell functions, such as muscle contraction, cell motility, and cell division.[7] This activity profile is similar to that of scytophycin B, a related natural product isolated from the cultures of a terrestial blue-green algae.[8] Other natural products exhibiting the same mechanism of action include latrunculins,[9] swinholides,[10] and aplyronins.[11]

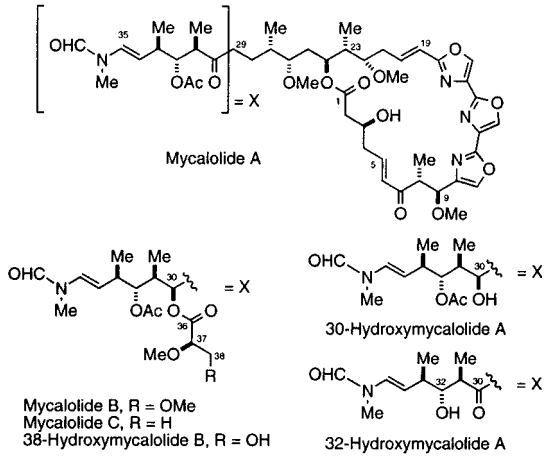


Figure 1. The mycalolide family.

Recently the relative and absolute stereochemistry of mycalolides (Figure 1) has been determined through a combination of chemical degradation, extensive ^1H and ^{13}C NMR analysis, and structural correlation experiments.[12] Mycalolide A, as well

(1) Fusetani, N.; Yasumuro, K.; Matsunaga, S.; Hashimoto, K. *Tetrahedron Lett.* **1989**, *30*, 2809−2812.

(2) Roesener, J. A.; Scheuer, P. J. *J. Am. Chem. Soc.* **1986**, *108*, 846−847.

(3) (a) Matsunaga, S.; Fusetani, N.; Hashimoto, K. *J. Am. Chem. Soc.* **1986**, *108*, 847−849. (b) Matsunaga, S.; Fusetani, N.; Hashimoto, K.; Koseki, K.; Noma, M.; Noguchi, H.; Sankawa, U. *J. Org. Chem.* **1989**, *54*, 1360−1363.

(4) Kernan, M. R.; Molinski, T. F.; Faulkner, J. D. *J. Org. Chem.* **1988**, *53*, 5014−5020.

(5) Kobayashi, J.; Murata, O.; Shigemori, H. *J. Nat. Prod.* **1993**, *56*, 787−791.

(6) Hori, M.; Saito, S.; Shin, Y.; Ozaki, H.; Fusetani, N.; Karaki, H. *FEBS Lett.* **1993**, *322*, 151−154.

(7) Saito, S.; Watabe, S.; Ozaki, H.; Fusetani, N.; Karaki, H. *J. Biol. Chem.* **1994**, *269*, 29710−29714.

(8) Smith, C. D.; Carmeli, S.; Moore, R. E.; Patterson, G. M. L. *Cancer Res.* **1993**, *53*, 1343−1347.

(9) Ayscough, K. R.; Stryker, J.; Pokala, N.; Sanders, M.; Crews, P.; Drubin, D. G. *J. Cell Biol.* **1997**, *137*, 399−416 and references therein.

(10) Bubb, M. R.; Spector, I.; Bershadsky, A. D.; Korn, E. D. *J. Biol. Chem.* **1995**, *270*, 3463−3466.

(11) Suenaga, K.; Kamei, N.; Okugawa, Y.; Takagi, M.; Akao, A.; Kigoshi, H.; Yamada, K. *Bioorg. Med. Chem. Lett.* **1997**, *7*, 269−274 and references therein.

(12) Matsunaga, S.; Liu, P.; Celatka, C. A.; Panek, J. S.; Fusetani, N. *J. Am. Chem. Soc.* **1999**, *121*, 5605−5606.

10.1021/ja002377a CCC: $19.00
Published on Web 11/01/2000

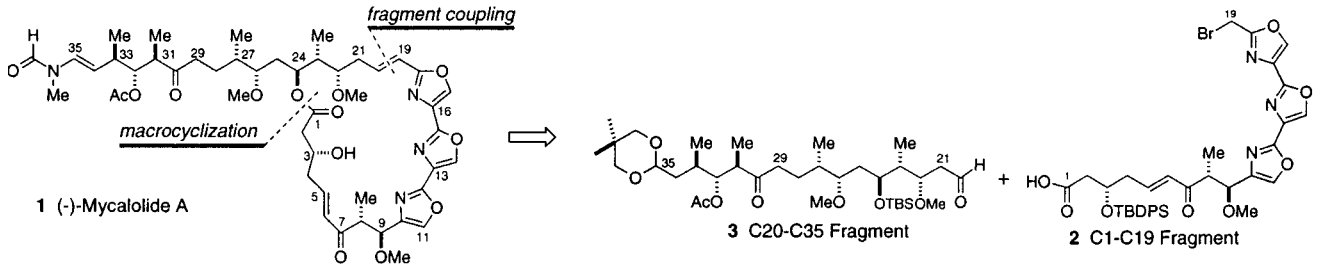


Figure 2. Retrosynthetic analysis of mycalolide A (**1**).

as other related marine macrolides, is constructed around a 28-membered lactone which incorporates a trisoxazole subunit linked by σ bonds, and an 11-carbon, polyketide side chain terminating with an *N*-methyl-*N*-alkenylformamide moiety. These unique structural features, together with their diverse biological activities, have motivated a number of research groups to develop synthetic strategies.[13] In that regard, we viewed mycalolide A as an ideal synthetic target for several reasons. First, since a total synthesis had not yet been reported for any member of the trisoxazole-containing natural products,[14] a synthesis would constitute a meaningful contribution. Second, mycalolide A was identified as a suitably complex target to expand the scope of our asymmetric crotylation methodology. Finally, in view of the ambiguity over the stereochemical assignment of mycalolides and other related trisoxazole-containing natural products (cf. ulapualides and kabiramides), a definitive assignment of stereochemistry could be made. Herein we report a detailed account of our efforts that culminated in the first total synthesis of mycalolide A.[15]

Synthetic Plan

The synthetic plans developed for mycalolide A were guided by the structural features of the molecule as well as our intention to extend the utility of chiral silane-based bond construction methodology. Through cleavage of the macrolide linkage and the C19−C20 olefin bond, mycalolide A (1) was divided into two primary fragments of comparable complexity (Figure 2). These disconnections revealed the C1−C19 trisoxazole fragment **2** and the C20−C35 aliphatic fragment **3**, union of which was envisaged via a Schlosser−Wittig olefination[16] followed by macrocyclization to form the 28-membered lactone.

Further disconnection of fragment **2** at the C6−C7 σ bond led to two smaller subunits, **4** and **5** (Figure 3). In the synthetic

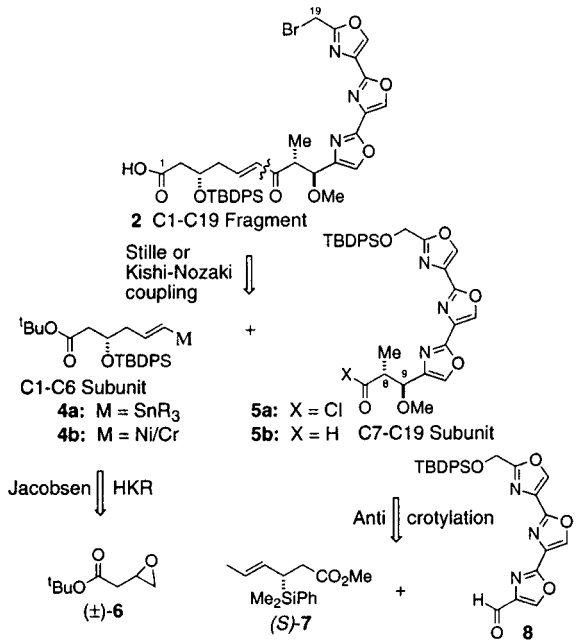


Figure 3. Retrosynthetic analysis of the C1−C19 fragment **2**.

direction, this bond construction corresponds to a Stille-type cross coupling[17] or a $CrCl_2/NiCl_2$-mediated Kishi−Nozaki-type coupling.[18] We had envisioned that the stereogenic center in subunit **4** could be accessed by a hydrolytic kinetic resolution (HKR) of terminal epoxide **6**,[19] and the anti stereochemical relationship at the C8 and C9 in subunit **5** would be established with a chelation-controlled anti crotylation using a chiral silane reagent.[20,21]

The retrosynthetic analysis of the C20−C35 aliphatic fragment **3** is outlined in Figure 4. After functional group adjustments, disconnection of **9** at C29−C30 was considered feasible, since this operation would divide the molecule into two similar segments, the C20−C29 subunit and the C30−C35 subunit. These two advanced intermediates were desirable since the stereochemical relationships could be installed by asymmetric crotylation reactions.[13f] In particular, the two pairs of syn stereogenic centers at C22/C23 and C26/C27 in subunit **10** would be established through two syn crotylation reactions, while the remaining oxygenated stereogenic center would be

(13) For earlier synthetic studies on related trisoxazoles, see (a) Knight, D. W.; Pattenden, G.; Rippon, D. E. *Synlett* **1990**, 36−37. (b) Kiefel, M. J.; Maddock, J.; Pattenden, G. *Tetrahedron Lett.* **1992**, *33*, 3227−3230. (c) Pattenden, G. *J. Heterocycl. Chem.* **1992**, *29*, 607−618. (d) Yoo, S.-K. *Tetrahedron Lett*. **1992**, *33*, 2159−2162. (e) Chattopadhyay, S. K.; Pattenden, G. *Tetrahedron Lett.* **1995**, *36*, 5271−5274. (f) Panek, J. S.; Beresis, R. T.; Celatka, C. A. *J. Org. Chem*. **1996**, *61*, 6494−6495. (g) Panek, J. S.; Beresis, R. T. *J. Org. Chem*. **1996**, *61*, 6496−6497. (h) Liu, P.; Celatka, C. A.; Panek, J. S. *Tetrahedron Lett.* **1997**, *38*, 5445−5448. (i) Celatka, C. A.; Liu, P.; Panek, J. S. *Tetrahedron Lett*. **1997**, *38*, 5449−5452. (j) Chattopadhyay, S. K.; Pattenden, G. *Synlett* **1997**, 1342−1344. (k) Chattopadhyay, S. K.; Pattenden, G. *Synlett* **1997**, 1345−1348. (l) Liu, P.; Panek, J. S. *Tetrahedron Lett.* **1998**, *39*, 6143−6146. (m) Liu, P.; Panek, J. S. *Tetrahedron Lett.* **1998**, *39*, 6147−6150. (n) Kempson, J.; Pattenden, G. *Synlett* **1999**, 533−536.

(14) A total synthesis of one diastereomer of ulapualide A has been reported; see: (a) Chattopadhyay, S. K.; Pattenden, G. *Tetrahedron Lett.* **1998**, *39*, 6095−6098. (b) Ulapualide: Chattopadhyay, S. K.; Pattenden, G. *J. Chem. Soc., Perkin Trans. 1*, **2000**, *15*, 2429−2454. (c) Trisoxazole: Rippon, D. E.; Waite, D. *J. Chem. Soc., Perkin Trans. 1* **2000**, *15*, 2415−2428.

(15) Preliminary communication: Liu, P.; Panek, J. S. *J. Am. Chem. Soc*. **2000**, *122*, 1235−1236.

(16) (a) Schlösser, M.; Schaub, B. *J. Am. Chem. Soc.* **1982**, *104*, 5821−5823. (b) For a review on Wittig reaction, see: Maryanoff, B. E.; Reitz, A. B. *Chem. Rev*. **1989**, *89*, 863−927.

(17) (a) For a review, see: Stille, J. K. *Angew. Chem., Int. Ed. Engl.* **1986**, *25*, 508−524. (b) For a monograph on Stille coupling, see: Farina, V.; Krishnamurthy, V.; Scott, W. J. *Org. React.* **1997**, *50*, 1−652.

(18) (a) Jin, H.; Uenishi, J.; Christ, W. J.; Kishi, Y. *J. Am. Chem. Soc.* **1986**, *108*, 5644−5646. (b) Takai, K.; Tagashira, M.; Kuroda, T.; Oshima, K.; Utimoto, K.; Nozaki, H. *J. Am. Chem. Soc.* **1986**, *108*, 6048−6050.

(19) Tokunaga, M.; Larrow, J. F.; Kakiuchi, F.; Jacobsen, E. N. *Science* **1997**, *277*, 936−938.

(20) For a review, see: Masse, C. E.; Panek, J. S. *Chem. Rev*. **1995**, *95*, 1293−1316.

(21) For literature precedent of anti crotylation, see: (a) Liu, P.; Panek, J. S. *Tetrahedron Lett.* **1998**, *39*, 6143−6146. (b) Masse, C. E.; Panek, J. S. *Angew. Chem., Int. Ed*. **1999**, *38*, 1093−1095.

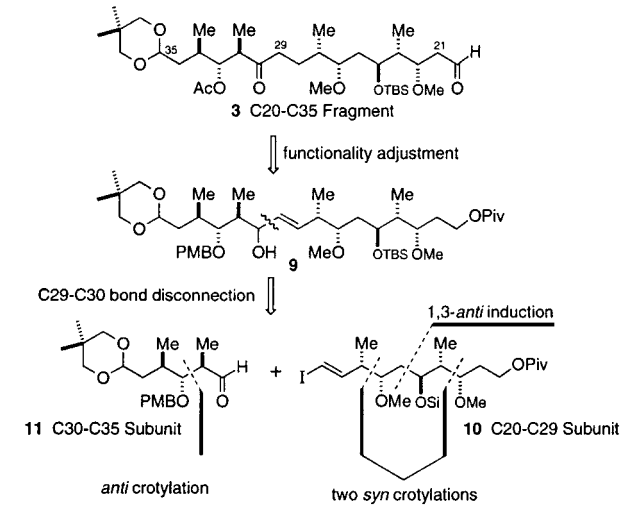
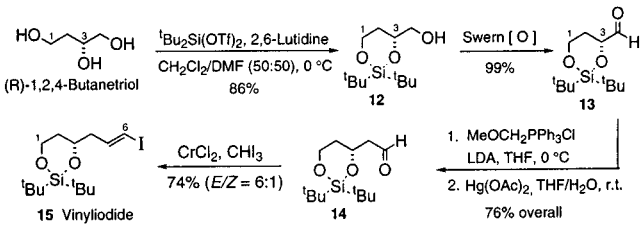


Figure 4. Retrosynthetic analysis of the C20−C35 fragment **3**.

Scheme 1



constructed by substrate-controlled 1,3-anti induction. Inspection of the C30−C35 subunit revealed an anti−anti stereochemical triad which, we anticipated, could be installed through a double stereodifferentiating anti crotylation reaction, a valuable extension of syn crotylation bond construction recently developed in our laboratories.[22] In the following discussion, the successful implementation of our synthetic plan is detailed.

Results and Discussion

Synthesis of the C1−C6 Subunit. Our initial approach to the C1−C6 subunit utilized commercially available (*R*)-1,2,4-butanetriol as the source of C3 chirality (Scheme 1). Selective protection of the 1,3-diol was cleanly achieved with ^{t}Bu$_2$Si(OTf)$_2$/2,6-lutidine in CH_2Cl_2/DMF (1:1 v/v) and afforded the primary alcohol **12** in 86% yield. This material was subjected to a Swern oxidation (oxalyl chloride, DMSO, Et_3N, −78 °C to room temperature)[23] to provide aldehyde **13**. This aldehyde was homologated to the five-carbon aldehyde **14** through a two-step process: one-carbon homologation with (methoxymethyl)-triphenylphosphonium ylide and hydrolysis of the resulting enol ether with $Hg(OAc)_2$.[24] The C1−C6 subunit was completed using Takai's $CrCl_2$-mediated olefination protocol,[25] furnishing (*E*)-vinyl iodide **15** (*E*:*Z* = 6:1) in 74% yield.

Although the described approach to **15** was acceptable in terms of overall yield, there were two drawbacks. First, the Takai olefination provided modest selectivity (*E*:*Z* = 6:1), and in our hands the *E*/*Z* olefin isomers could not be separated by SiO_2 chromatography. Second, the requirement of a carboxylate at C1 necessitated a late-stage oxidation.

Recently, an assortment of useful chiral synthons has been made available as a result of advances in the area of asymmetric catalysis.[26] We were interested in the possibility of incorporating the catalytic asymmetric strategies into our synthesis, and envisioned that the stereogenic center in the C1−C6 subunit could be established using Jacobsen's HKR of terminal epoxides.[19] Bearing in mind the protecting group strategy, *tert*-butyl 3,4-epoxybutanoate (**6**) was chosen as the starting point of the new synthetic sequence (Scheme 2). Thus, the synthesis of **4** was initiated by a HKR of the readily available racemic epoxide **6**,[27] providing (*R*)-**6** with 99% ee in 94% yield.[28] Nucleophilic opening of the resolved epoxide using higher order cuprate **16**[29] provided homoallylic alcohol **17** in 76% yield. Protection of the free hydroxyl as its TBDPS ether followed by stannane−iodine exchange completed the sequence to subunit **4** (four steps, 61% overall yield).

The advantage of this approach to **4** is that there are no undesired stereochemical products. The C1 oxidation state is set, since the product, after conversion of the *tert*-butyl ester to the carboxylic acid, would be ready for macrolide formation.

Synthesis of the C7−C19 Subunit. The synthesis of this subunit centers on the installation of the C8/C9 anti relationship through a stereoselective crotylation reaction of silane (*S*)-**7** and trisoxazole aldehyde **8**. Previous studies from our laboratory concerning the reaction of the (*E*)-crotylsilanes with unfunctionalized, achiral aldehydes have demonstrated universal syn selectivity in the formation of homoallylic alcohols[30] and ethers.[31] The stereochemical outcome of these crotylation reactions can be explained by an anti-S_E mechanism[32] in which the absolute stereochemistry of the newly formed methyl-bearing center is controlled by the chirality of the silane reagent. In the cases of double stereodifferentiating condensation reactions between (*E*)-crotylsilane reagents and chiral, heterosubstituted aldehydes, anti bond constructions could be achieved.[22] Once again, the chirality of the methyl-bearing center was determined by the orientation of the C−SiR_3 bond, while the configuration of the hydroxy-bearing center can be rationalized through Felkin induction[33] or through Cram chelation.[34]

Accordingly, the use of a bidentate Lewis acid (such as $TiCl_4$) and the condensation between trisoxazole aldehyde **8**[13h] and silane (*S*)-**7**,[35] in analogy with the reaction of monooxazole aldehyde and the (*S*)-silane reagent,[36] would provide a homoal-

(22) (a) Jain, N. F.; Takenaka, N.; Panek, J. S. *J. Am. Chem. Soc.* **1996**, *118*, 12475−12476. (b) Jain, N. F.; Cirillo, P. F.; Pelletier, R.; Panek, J. S. *Tetrahedron Lett.* **1995**, *36*, 8727−8730. (c) Panek, J. S.; Beresis, R. T. *J. Org. Chem.* **1993**, *58*, 809−811.

(23) Mancuso, A. J.; Swern, D. *Synthesis* **1981**, 165−185.

(24) Maercker, A. *Org. React.* **1965**, *14*, 270−490.

(25) Takai, K.; Nitta, K.; Utimoto, K. *J. Am. Chem. Soc.* **1986**, *108*, 7408−7410.

(26) (a) Jacobsen, E. N., Pfaltz, A., Yamamoto, H., Eds. *Comprehensive Asymmetric Catalysis*; Springer: New York, 1999; Vols. 1−3. (b) Ager, D. J., Ed. *Handbook of Chiral Chemicals*; Marcel Dekker: New York, 1999. (c) Ojima, I., Ed. *Catalytic Asymmetric Synthesis*; VCH Publishers: New York, 1993. (d) Noyori, R. *Asymmetric Catalysis in Organic Synthesis*; John Wiley & Sons: New York, 1989.

(27) Racemic **6** was prepared by epoxidation of *tert*-butyl vinylacetate with *m*-CPBA, which was in turn prepared according to the procedure described in Ozeki, T.; Kusaka, M. *Bull. Chem. Soc. Jpn.* **1966**, *39*, 1995−1998.

(28) The kinetic resolution yield is expressed as a percentage of the theoretical maximum yield of 50%; the ee was determined by HPLC analysis of the phenylthio derivatives of **6** with a Chiracel OD column.

(29) Behling, J. R.; Ng, J. S.; Babiak, K. A.; Campbell, A. L.; Elsworth, E.; Lipshutz, B. H. *Tetrahedron Lett.* **1989**, *30*, 27−30.

(30) Panek, J. S.; Cirillo, P. F. *J. Org. Chem.* **1993**, *58*, 294−296.

(31) Panek, J. S.; Beresis, R. T.; Xu, F.; Yang, M. *J. Org. Chem.* **1991**, *56*, 7341−7344.

(32) Hayashi, T.; Konishi, M.; Ito, H.; Kumada, M. *J. Am. Chem. Soc.* **1982**, *104*, 4962−4963.

(33) (a) Cherest, M.; Felkin, H.; Prudent, N. *Tetrahedron Lett.* **1968**, *9*, 2199−2204. (b) Anh, N. T.; Eisenstein, O. *Nouv. J. Chim.* **1977**, *1*, 61−70.

(34) Cram, D. J.; Kopecky, K. R. *J. Am. Chem. Soc.* **1959**, *81*, 2748−2755. (b) Reetz, M. T. *Acc. Chem. Res.* **1993**, *26*, 462−468.

(35) For preparation of (*S*)-**7**, see: Panek, J. S.; Yang, M. G.; Solomon, J. *J. Org. Chem.* **1993**, *58*, 1003−1010.

(36) Panek, J. S.; Liu, P. *Tetrahedron Lett.* **1998**, *39*, 6147−6150.

Scheme 2

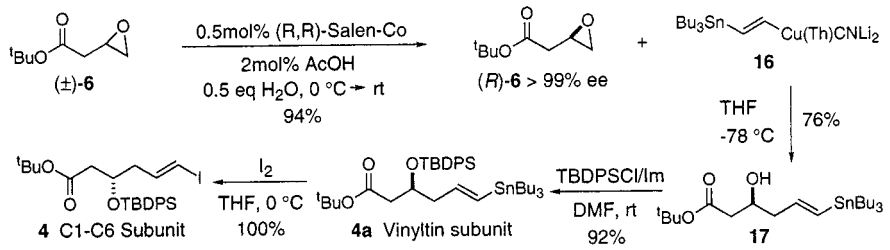
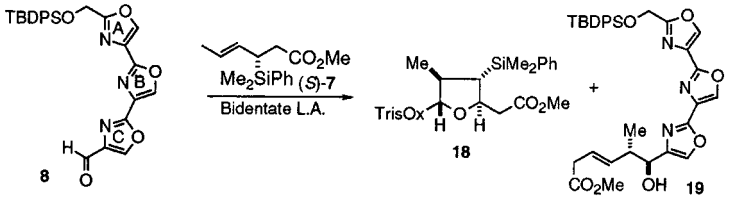


Table 1. Lewis Acid Promoted Addition of Silane **7** to Aldehyde **8**



entry	Lewis acid	conditions[a]	dr of **18** and **19**[b]	yield of **18**[c] (%)	yield of **19**[c] (%)
1	$TiCl_4$	−78 to −50 °C, 12 h	>30:1	99	0
2	$TiCl_4$	−78 °C to room temperature, 24 h	>30:1	0	65
3	$SbCl_5$	−78 to −50 °C, 12 h	>30:1	30	13
4	$SnCl_4$	−78 to −50 °C, 12 h	>30:1	50	0
5	$SnCl_4$	−78 °C to room temperature, 12 h	>30:1	30	10

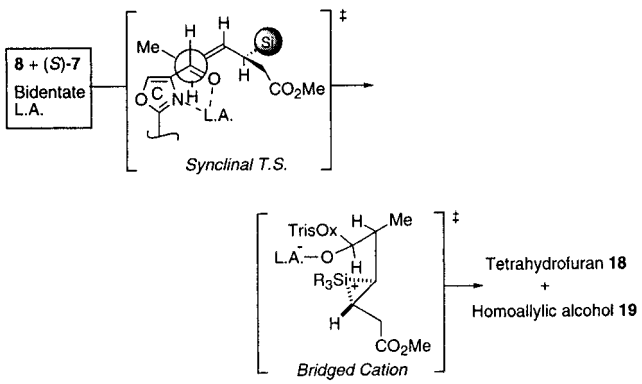
[a] All reactions were run in CH_2Cl_2. [b] Diastereoselection was determined by ^1H NMR analysis of the crude products. [c] Yields refer to pure materials isolated after chromatography on SiO_2.

lylic alcohol with an anti bond construction.[36] The results of these experiments are summarized in Table 1.[37] At low temperatures (<−50 °C), tetrahydrofuran **18** was the dominant product formed; upon warming, the tetrahydrofuran underwent ring opening to give anti homoallylic alcohol **19** (entries 1 and 2). Of the Lewis acids examined, freshly distilled $TiCl_4$ performed the best. These reaction conditions allowed quantitative formation of tetrahydrofuran at −50 °C and upon warming to room temperature promoted ring opening to **19** in 65% yield. Other less effective Lewis acids, such as $SbCl_5$ and $SnCl_4$, are shown in Table 1 (entries 3−5).

Earlier reports from these laboratories have documented the formation of tetrahydrofurans in reactions of chiral silane reagents to aldehydes.[38] For this process, we have postulated that the initial asymmetric C−C bond construction occurs by an anti-$S_{E'}$ mode of addition and the emerging β-silyl carbocation is stabilized through the $\sigma \rightarrow \pi$ conjugation of the adjacent C−Si bond. A 1,2-cationic silyl group migration then proceeds via a bridged cation, followed by heterocyclization, producing tetrahydrofuran **18** (Scheme 3). The relative stereochemical outcome of this condensation reaction could be accounted for through a synclinal transition state, where a bidentate Lewis acid coordinates to the aldehyde carbonyl and the oxazole nitrogen to form a five-membered chelate, which results in a turnover of the aldehyde π-facial selectivity to deliver an anti stereochemical relationship.

Although tetrahydrofuran **18** was produced in nearly quantitative yield in the presence of $TiCl_4$, direct formation of the desired homoallylic alcohol **19** could only be achieved in modest yield.

Scheme 3



Consequently, reaction conditions for the conversion of tetrahydrofuran **18** to homoallylic alcohol **19** were evaluated. For the Lewis acids surveyed, $BF_3{\cdot}OEt_2$ was most effective, affording clean furan opening. All other Lewis acids surveyed, including $TiCl_4$, $SnCl_4$, and $SbCl_5$, gave complex reaction mixtures. Accordingly, $BF_3{\cdot}OEt_2$ was used to effect the conversion of tetrahydrofuran **18** to homoallylic alcohol **19**; however, to obtain complete coversion to **19**, the starting furan was recycled three times. In this way, homoallylic alcohol **19** could be obtained in a combined 90% yield.

With the C8/C9 anti stereochemical relationship established, the synthesis of the C7−C19 subunit **5** was completed. A straightforward three-step sequence was used: methylation of alcohol **19** with Ag_2O/MeI,[39] dihydroxylation of olefin **20** with OsO_4/TMANO,[40] and cleavage of the resulting diol with $Pb(OAc)_4$ provided aldehyde **5** (Scheme 4).

Construction of the C6−C7 Bond. The carbon backbone of the C1−C19 fragment was assembled by joining the C1−

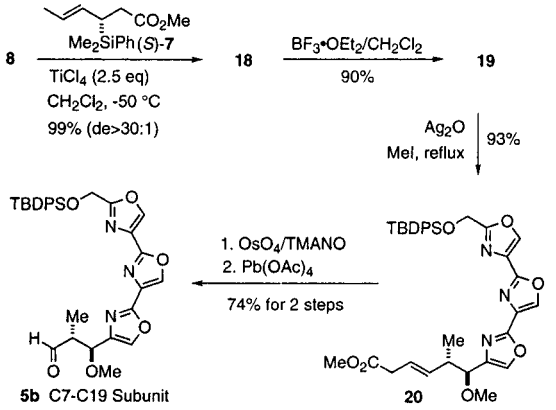
(37) The absolute stereochemistry of **18** and **19** was based on an anti-$S_{E'}$ addition mode. The relative stereochemistry of **18** was assigned in correlation with **19**, whose anti stereochemical relationship was secured by measuring the $^3J_{Ha,Hb}$ value (10.8 Hz) of the derived acetonide; see the Supporting Information for experimental details.

(38) (a) Panek, J. S.; Yang, M. *J. Am. Chem. Soc.* **1991**, *26*, 9868−9870. (b) Beresis, R. T.; Panek, J. S. *Bioorg. Med. Chem. Lett.* **1993**, *3*, 1609−1613.

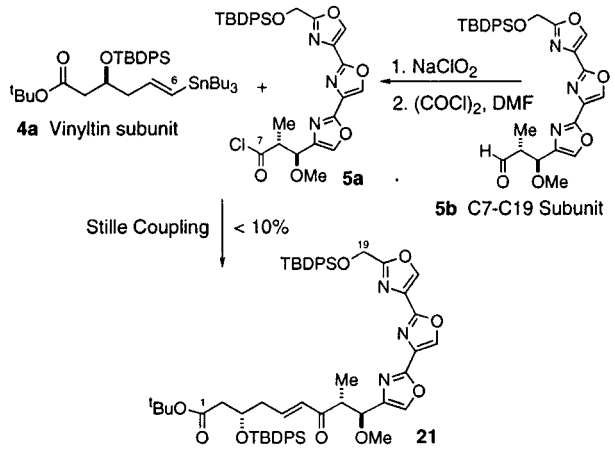
(39) Greene, A. E.; Drian, C. L.; Grabbe, P. *J. Am. Chem. Soc.* **1980**, *102*, 7583−7584.

(40) VanRheenen, V.; Kelley, R. C.; Cha, D. *J. Org. Chem.* **1978**, *43*, 2480−2482.

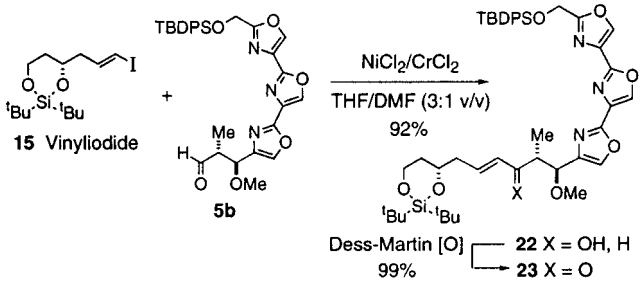
Scheme 4



Scheme 5



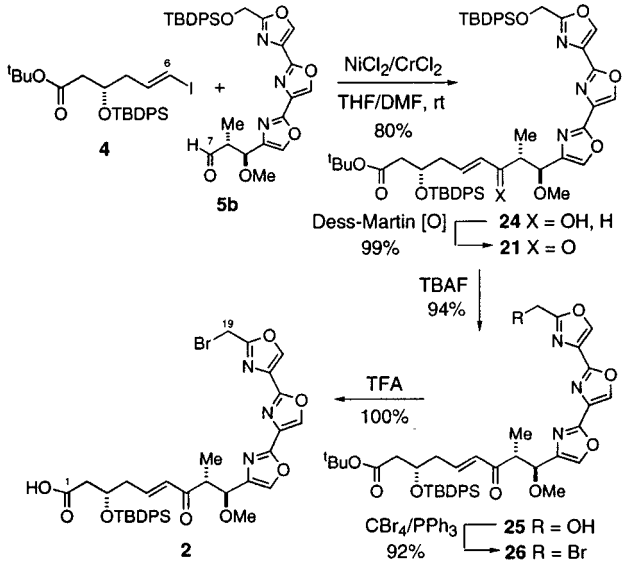
Scheme 6



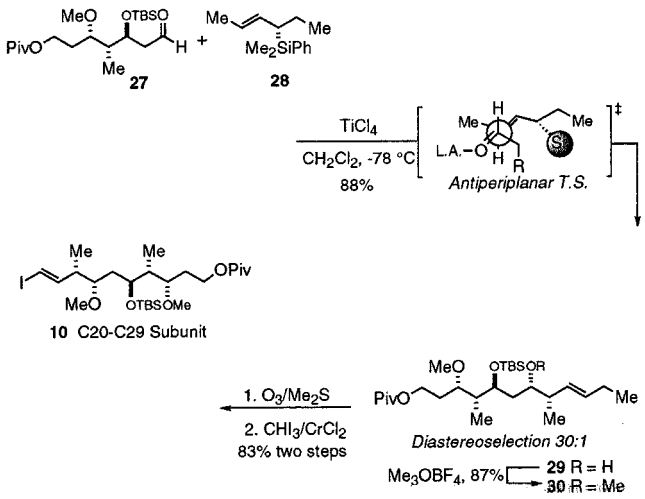
C6 and C7−C19 subunits (Scheme 5). In this reaction sequence, however, the Pd-mediated cross coupling reaction of organotin **4a** and acid chloride **5a** turned out to be quite problematic. After numerous experiments with different Pd sources, including Pd(PPh$_3$)$_4$, (PPh$_3$)$_2$PdCl$_2$, Pd$_2$(dba)$_3$, and PhCH$_2$Pd(Cl)(PPh$_3$)$_2$, it was found only Pd$_2$(dba)$_3$ (toluene, Et$_3$N, 35 °C) could deliver the desired product **21**, and in less than 10% yield. We then turned our attention to a NiCl$_2$/CrCl$_2$-mediated coupling of aldehydes and iodoolefins developed by Kishi and Nozaki.[18] The nickel−chromium-mediated coupling between vinyl iodide **15** and aldehyde **5b** was examined first to determine the precise conditions for this transformation. As illustrated in Scheme 6, the optimal procedure developed for this model system entailed treatment of **15** and **5b** in THF/DMF (3:1 v/v) with NiCl$_2$/CrCl$_2$ at room temperature, affording the coupling product **22** in 92% yield, as roughly a 1:1 mixture of the allylic alcohol isomers. Dess−Martin oxidation of alcohol **22** provided enone **23** in nearly quantitative yield.[41]

Under reaction conditions established for the model system, the coupling of the actual intermediates, the C1−C6 subunit **4** and the C7−C19 subunit **5b**, provided the desired allylic alcohol **24** in 80% yield, as a 1:1 mixture of the stereoisomers (Scheme 7). This material was oxidized to enone **29** using Dess−Martin periodinane (Scheme 7).[41] Selective deprotection of the primary TBDPS ether with ^{n}Bu$_4$NF (1 equiv), followed by conversion of the resulting alcohol **25** to bromide **26** (CBr$_4$/PPh$_3$) and hydrolysis of the *tert*-butyl ester with TFA, completed the synthesis of the C1−C19 fragment **2**.

Scheme 7



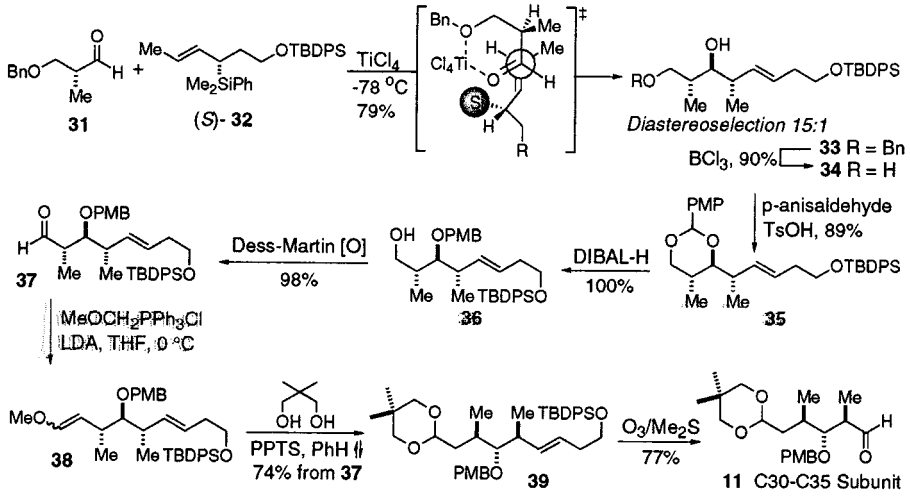
Scheme 8



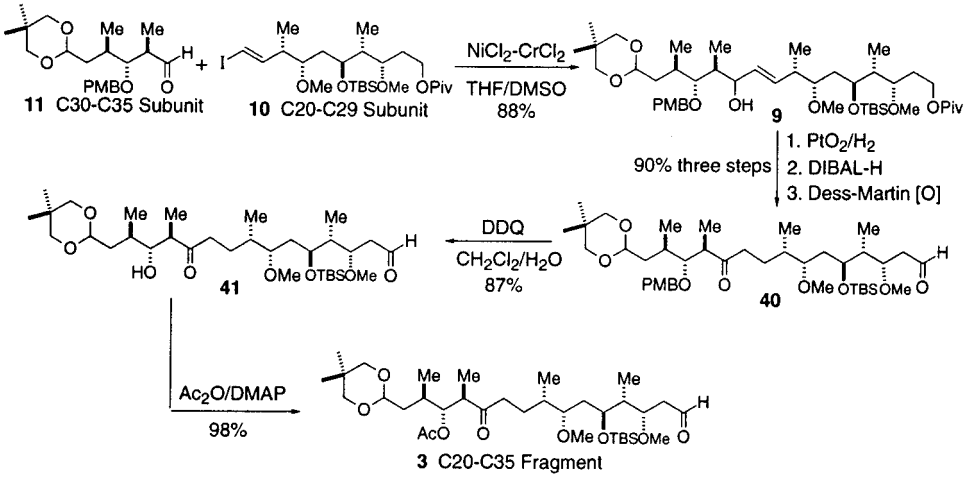
Synthesis of the C20−C29 Subunit. In accord with a previous report from this laboratory,[13f] the synthesis of the C20−C29 subunit was initiated by a condensation reaction between aldehyde **27** and (*S*)-silane **28** (2.0 equiv) in the presence of TiCl$_4$ (1.2 equiv, −78 °C, 8 h), affording homoallylic alcohol **29** in 88% yield (Scheme 8). *O*-Methylation of **29** with Me$_3$OBF$_4$ (6.0 equiv) and Proton Sponge (6.0 equiv) gave homoallylic ether **30** in 87% yield. Oxidative cleavage of the olefin under standard ozonolysis conditions gave the expected aldehyde, which was immediately subjected to a Takai olefination[25] to provide subunit **10** in 83% yield (two steps).

(41) (a) Dess, D. B.; Martin, J. C. *J. Org. Chem.* **1983**, *48*, 4155−4156. (b) Dess, D. B.; Martin, J. C. *J. Am. Chem. Soc.* **1991**, *113*, 7277−7287. For two improved procedures for the preparation of DMP, see: (c) Ireland, R. E.; Liu, J. *J. Org. Chem.* **1993**, *58*, 2899. (d) Meyers, S. D.; Schreiber, S. L. *J. Org. Chem.* **1994**, *59*, 7459−7552.

Scheme 9



Scheme 10



Synthesis of the C30−C35 Subunit. The synthesis of the C30−C35 subunit **11** centers on the installation of the anti−anti stereochemical triad. This stereochemical relationship was constructed with a double stereodifferentiating crotylation reaction of (*R*)-3-(benzyloxy)-2-methylpropional (**31**) with silane (*S*)-**32** (Scheme 9).[13f,22] In the presence of $TiCl_4$ (1.2 equiv) this anti-selective crotylation proceeded through a chelate-controlled transition state to give homoallylic alcohol **33** (anti:syn = 15:1) in 79% yield, thus introducing the required stereochemical relationship for subunit **11**. Removal of the benzyl group was effected by BCl_3 (2 equiv), providing the 1,3-diol **34** in 90% yield.[42] Protection of the derived 1,3-diol (PMBCHO, 1.3 equiv; catalytic *p*-TsOH) afforded the *p*-methoxybenzylidine acetal **35** (89%), which was subjected to nucleophilic opening (DIBAL-H, 5.0 equiv; CH_2Cl_2; −50 °C; 14 h) to give primary alcohol **36** in quantitative yield as a single diastereomer. Oxidation of the alcohol using Dess−Martin periodinane provided aldehyde **37** in 98% yield.[41] A one-carbon homologation with (methoxymethyl)triphenylphosphonium ylide resulted in the formation of enol ether **38** (*E*:*Z* = 1:1), which was directly converted to the C35 acetal by 2,2-dimethyl-1,3-propanediol and a catalytic amount of PPTS (74% from **37**). Cleavage of the *trans*-olefin under standard ozonolysis conditions afforded aldehyde **11** in 77% yield, thus completing the synthesis of the C30−C35 subunit.

Synthesis of the C20−C35 Fragment. After the C20−C29 and C30−C35 subunits were synthesized, their union would assemble the backbone of fragment **3** (Scheme 10). This bond construction was achieved through a NiI_2-$CrCl_2$-mediated coupling reaction.[18] We had learned that a successful outcome of this coupling reaction was highly dependent on solvent combination. During the course of these coupling experiments, we learned that the combination THF/DMSO (3:1 v/v) gave the best results. When subunits **10** and **11** were treated with $NiCl_2$-$CrCl_2$ in THF/DMSO (3:1 v/v), coupling product **9** was obtained in 88% yield as a 1:1 mixture of the alcohol diastereomers. This mixture of alcohols was converted to ketoaldehyde **40** by a three-step process: catalytic hydrogenation of the olefin with PtO_2/H_2,[43] removal of the pivaloate with DIBAL-H,[44] and oxidation of the resulting diol with Dess−Martin periodinane.[41] This three-step sequence provided **40** as a single diastereomer in 90% yield. Completion of the synthesis of fragment **3** was accomplished by deprotection of the PMB group using DDQ[45] and installation of an acetyl group at the C32 hydroxyl.

(42) Williams, D. R.; Brown, D. L.; Benbow, J. W. *J. Am. Chem. Soc.* **1989**, *111*, 1923−1925.

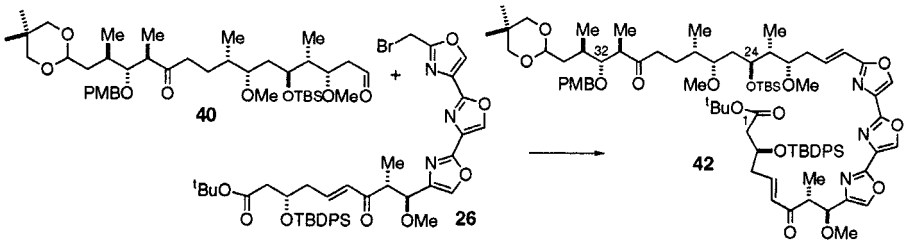
(43) Rylander, P. N. *Hydrogenation Methods*; Academic Press: New York, 1985; pp 41−44.

(44) Nicolaou, K. C.; Webber, S. E. *Synthesis* **1986**, 453−461.

(45) Oikawa, Y.; Yoshioka, T.; Yonemitsu, O. *Tetrahedron Lett.* **1982**, *23*, 885−888.

(46) (a) Zhao, Z.; Scarlato, G. R.; Armstrong, R. W. *Tetrahedron Lett.* **1991**, *32*, 1609−1612. (b) Ogawa, A. K.; DeMattei, J. A.; Scarlato, G. R.; Tellew, J. E.; Chong, L. S.; Armstrong, R. W. *J. Org. Chem.* **1996**, *61*, 6153−6161.

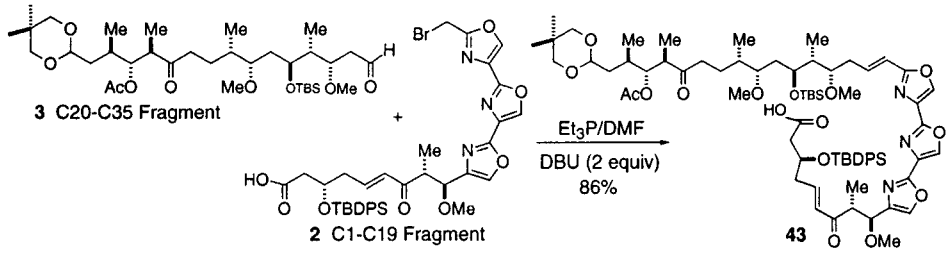
Table 2. Results of the Olefination Reaction between **26** and **40**



entry	conditions[a]	result
1	$^{n}Bu_3P$/DMF; LDA (1.0 equiv)	<10%
2	$^{n}Bu_3P$/DMF; KHMDS (1.0 equiv)	<10%
3	$^{Et}{}_3P$/DMF; KO^{t}Bu (1.0 equiv)	decomposition
4	$(EtO)_3P$, reflux; KHMDS (1.0 equiv)[b]	decomposition
5	$(EtO)_3P$, reflux; LiCl (1.2 equiv); DBU (1.2 equiv)[c]	no desired product
6	Et_3P/DMF; DBU (1.0 equiv)	93%

[a] All the reactions were run under an argon atmosphere. [b] Distilled THF was the reaction solvent. [c] The reaction was run in acetonitrile.

Scheme 11



Fragment Coupling. Having established viable routes to the advanced intermediates **2** and **3**, the critical fragment coupling via a Schlösser−Wittig[16] protocol was investigated. During the planning stages of this synthesis, the task of achieving a union between **2** and **3** with a phosphorus-based olefination was not regarded as a difficult one. We were optimistic however, given the precedents set by Armstrong[46] and Evans,[47] who successfully constructed an (*E*)-olefinated monooxazole in their calyculin syntheses. We had also established precedence in model studies of the construction of the trisoxazole (*E*)-olefin by a similar protocol.[13i] However, this Wittig reaction proved to be extremely challenging, and our results concerning the olefination reaction between intermediates **26** and **40** are summarized in Table 2.

Conventional bases such as LDA, KHMDS, and KO^{t}Bu with different solvent systems including DMF, THF, and their combinations (not shown) failed to deliver a synthetically useful yield of the desired product. Then recourse was made to a Horner−Emmons olefination protocol[48] (entries 4 and 5).

It has been well documented that mild organic bases such as Et_3N, Hünig's base, and DBU are effective for the formation of carbonyl-stabilized ylides.[49] In our case, the electron-deficient heteroaromatic systems provided sufficient stabilization for an ylide as effectively as a carbonyl. Therefore, tertiary amines should be sufficiently basic to effect oxazole-stabilized ylide formation, and the ylide thus formed would react with aldehydes to form *trans*-olefins. Gratifyingly, when aldehyde **40** and the in situ generated Wittig salt derived from **26** were treated with DBU at 0 °C, the desired product **42** was formed as a single olefin isomer in 93% yield (entry 6).

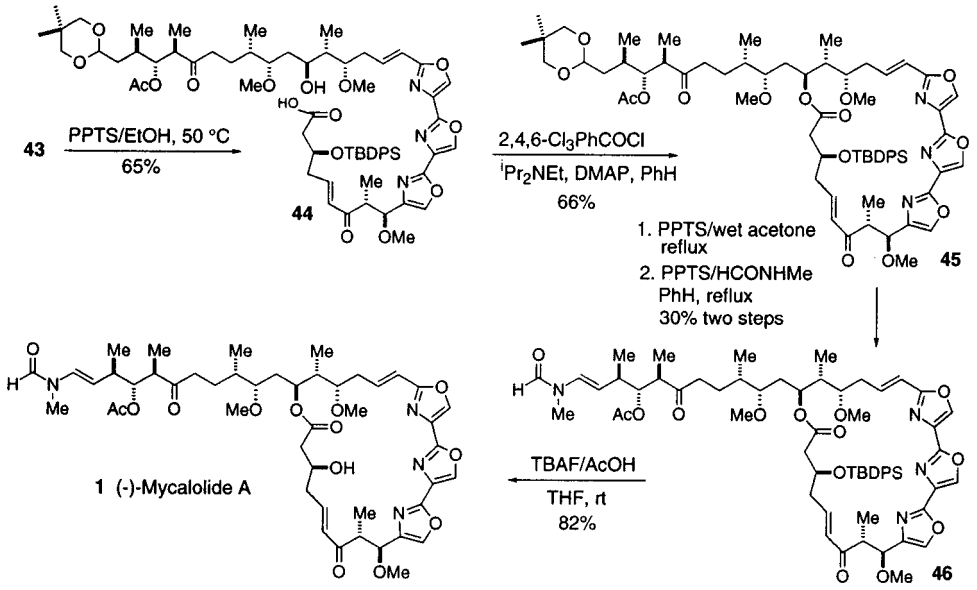
At this crucial conjuncture, we needed to calibrate the reactivity of advanced intermediate **42** to pursue the final stage of the synthesis. The immediate subgoal was to prepare the seco acid by defining appropriate conditions to remove the C1 carboxyl and C24 hydroxyl protecting groups. However, attempts to reach the free carboxylic acid were met with considerable problems. For instance, the use of catalytic TsOH in refluxing benzene[50] and TFA/CH_2Cl_2 at 0 °C[51] decomposed the starting material. In addition, the C24 TBS group was stable toward HF/pyridine and TBAF/silica.[52] However, PPTS (EtOH, 50 °C)[53] was effective in this case. Finally, removal of the PMB group using DDQ[45] gave a low yield (<10%) of the desired product as well as many byproducts which could not be identified.

From the above experiments, we concluded that the C1 carboxyl protecting group and the PMB group needed to be removed before fragment coupling. Therefore, the Schlosser−Wittig olefination[16] between carboxylic acid **2** and aldehyde **3** was carried out. Complete conversion to the ylide required 2.0 equiv of DBU, which delivered coupling product **43** as a single isomer in 86% yield (Scheme 11).

Macrocyclization and Completion of the (−)-Mycalolide A Synthesis. In preparation for macrocyclization, cleavage of the C24 TBS protecting group was required to afford seco acid **44** (Scheme 12). Since PPTS (EtOH, 50 °C) could remove the TBS group of intermediate **42**, the same reaction conditions were applied to coupling product **43**, which provided **44** in 65% yield. Macrolactonization of seco acid **44** was effected by modified Yamaguchi conditions first reported by Yonemitsu (DMAP,

(47) Evans, D. A.; Gage, J. R.; Leighton J. L. *J. Am. Chem. Soc*. **1992**, *114*, 9434−9453.
(48) Wadsworth, W. S., Jr.; Emmons, W. D. *J. Am. Chem. Soc*. **1961**, *83*, 1733−1738.
(49) For a literature precedent of using Et_3N (PhH, reflux) to generate a carbonyl-stabilized ylide, see: Trippett, S.; Walker, D. M. *J. Chem. Soc.* **1961**, 1266−1268.
(50) Hermann, J. L.; Berger, M. H.; Schlessinger, R. H. *J. Am. Chem. Soc*. **1973**, *95*, 7923.
(51) Wender, P. A.; Schaus, J. M.; White, A. W. *J. Am. Chem. Soc.* **1980**, *102*, 6157−6159.
(52) Clark, J. *J. Chem. Soc., Chem. Commun*. **1978**, 789−791.
(53) White, J. D.; Kawasaki, M. *J. Am. Chem. Soc*. **1990**, *112*, 4991−4993.

Scheme 12



Hünig's base, 2,4,6-Cl_3PhCOCl, and the seco acid in PhH at room temperature),[54] which afforded the desired macrolactone in 66% yield.

Having successfully arrived at macrocycle **45**, completion of the synthesis of mycalolide A required installation of the terminal *N*-methylformamide and removal of the TBDPS hydroxyl protecting group at C3. This was accomplished by hydrolysis of the acetal (PPTS/wet acetone, reflux),[55] followed by vinylformamide formation with PPTS/HCONHMe.[13b] The final deprotection step proceeded cleanly with TBAF/AcOH,[56] affording mycalolide A. The synthetic material was identical with a natural sample,[57] including 400 MHz ^{1}H NMR, 75 MHz ^{13}C NMR, IR, $[\alpha]_D$, and TLC R_f values in three different solvent systems.[58]

Conclusion

The first total synthesis of the actin-depolymerizing agent (−)-mycalolide A has been achieved by employing a highly convergent and stereocontrolled strategy. The synthesis is noteworthy in that nine of the eleven stereogenic centers within the target molecule were established through asymmetric crotylation reactions. Synthetic highlights featured in this work include the use of DBU to effect the Schlosser−Wittig olefination, the Kishi−Nosaki coupling to construct the C6−C7 and C29−C30 bonds, and the Jacobsen HKR to install the C3 stereogenic center. The completion of the total synthesis serves to confirm the relative and absolute stereochemistry of (−)-mycalolide A, as well as to illustrate the application of our chiral silane-based C−C bond construction methodology to the assembly of complex molecules. The synthetic plan presented here offers a general approach to access the remaining members of this class of natural products as well as other potentially bioactive analogues.

Acknowledgment. We are grateful to Dr. Richard T. Beresis (Merck & Co., Inc.), Prof. Eric N. Jacobsen, Dr. Scott E. Schaus (Harvard University), Prof. John A. Porco, Jr., and Ms. Cassandra A. Celatka (Boston University) for helpful discussions. Financial support was obtained from the NIH/NCI (Grant R01CA56304).

Supporting Information Available: Complete experimental procedures and physical and spectral data for all intermediates and final products (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

JA002377A

(54) (a) Hikota, M.; Sakurai, Y.; Horita, K.; Yonemitsu, O. *Tetrahedron Lett.* **1990**, *31*, 6367−6370. (b) Hikota, M.; Tone, H.; Horita, K.; Yonemitsu, O. *J. Org. Chem.* **1990**, *55*, 7−9.

(55) Sterzycki, R. *Synthesis* **1979**, 724−725.

(56) (a) All other reagents surveyed including HF/pyridine, TBAF, HF, and $LiBF_4$ led to decomposition of the starting material. (b) For a recent example of using TBAF/AcOH to remove TBS, see: Smith, A. B., III; Ott, G. R. *J. Am. Chem. Soc.* **1998**, *120*, 3935−3948.

(57) We are indebted to Professors S. Matsunaga and N. Fusetani of the University of Tokyo for providing a reference sample of natural (−)-mycalolide A.

(58) HCl-free $CDCl_3$ (K_2CO_3-treated commercial $CDCl_3$) was used for measuring the NMR spectra of mycalolide A due to the acid-labile *N*-methyl-*N*-alkenylformamide group in the natural product.