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An Enantioselective Synthesis of FR182877 Provides a Chemical Rationalization of Its Structure and Affords Multigram Quantities of Its Direct Precursor

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Abstract: The evolution of a strategy culminating in an efficient, enantioselective synthesis of the potent microtubule-stabilizing agent FR182877 is described. Guided by a proposed biogenesis of this complex natural product, a solution emerged that involved the first reported example of a double transannular Diels−Alder reaction to fashion the key elements of its hexacyclic structure. This pivotal transformation creates a complex pentacycle from a 19-membered macrocyclic pentaene, forming seven new stereogenic centers in a fully diastereocontrolled fashion. The efficiency of the approach ultimately enabled the preparation of multigram quantities of the direct precursor of FR182877 for conversion to the relatively unstable natural product when required. The reactivity of the strained, bridgehead olefin of this secondary metabolite with biologically relevant nucleophiles is also described.

Introduction

Instances of self-organization are pervasive in nature and in science. Molecular self-assembly implies the formation of higher-ordered structures or aggregates by the spontaneous union of two or more components through either covalent or noncovalent bonding.[1] The self-organization of the ribosome from its protein and RNA components and the formation of Buckminsterfullerene via the condensation of vaporized carbon are grand examples of noncovalent and covalent self-assemblies in nature, respectively.

Architectural complexity can be encoded in the structures of relatively simple molecules. For example, the folding of linear polypeptides and nucleic acids into the complicated three-dimensional structures of proteins and RNA molecules, and the cascade cyclizations of squalene oxide en route to the polycyclic triterpenoids accomplish substantial increases in structural complexity and are excellent examples of noncovalent and covalent architectural self-constructions, respectively. Powerful approaches for syntheses of architecturally complex natural products can result when the concept of architectural self-construction is an integral part of planning, and oftentimes these approaches parallel the biogenesis of the target. The spectacular biomimetic syntheses of polycyclic terpenoids by Johnson[2] and van Tamelen,[3] the endiandric acids by Nicolaou,[4] and the *Daphniphyllum* alkaloids by Heathcock[5] are representative achievements that exploited the intrinsic capacity of complex polycyclic molecules to self-construct from appropriately functionalized polyunsaturated precursors. Our approach to the chemical problem posed by the complex structure of FR182877 was predicated on the following question: Does a straightforward pathway for an architectural self-construction of this natural product exist, and if so, could we demonstrate its feasibility in the laboratory?

The unprecedented architecture of FR182877 (**1**) was recently described by scientists at Fujisawa when this cytotoxic fungal metabolite was discovered in the course of a broad screen for novel cell cycle inhibitors.[6] Designated WS9885B in the original report,[6a] this hexacyclic natural product contains 12 contiguous stereocenters and a strained bridgehead olefin that exists as part of a vinylogous carbonate moiety. It has been demonstrated that FR182877 stabilizes microtubules in vitro[6c] and shows efficacy comparable to that of Taxol against several human cancer cell

(1) For reviews and discussions on self-assembly, see: (a) Lindsey, J. S. *New J. Chem.* **1991**, *15*, 153−180. (b) Klug, A. *Angew. Chem., Int. Ed.* **1983**, *22*, 565−636. (c) Michl, J. In *Chemical Synthesis*: *Gnosis to Prognosis*; Chatgilialoglu, C., Snieckus, V., Eds.; Kluwer Academic Publishers: Boston, 1996; pp. 429−452. (d) Eschenmoser, A.; Loewenthal, E. *Chem. Soc. Rev.* **1992**, 1−16. (e) An entire Special Feature issue of *Proc. Natl. Acad. Sci. U.S.A.* was devoted to Supramolecular Chemistry and Self-Assembly. See *Proc. Natl. Acad. Sci. U.S.A.* **2002**, *99*, Issue 8. (f) Whitesides, G. M.; Grzybowski, B. *Science* **2002**, *295*, 2418−2421.

(2) For reviews, see: (a) Johnson, W. S. *Angew. Chem., Int. Ed. Engl.* **1976**, *15*, 9−17. (b) Johnson, W. S. *Bioorg. Chem.* **1976**, *5*, 51−98.

(3) For discussions, see: van Tamelen, E. E. *Acc. Chem. Res.* **1975**, *8*, 152−158.

(4) On the basis of the striking hypothesis about the origin of the endiandric acids by Black and co-workers (see Bandaranayake, W. M.; Banfield, J. E.; Black. D. St. C. *J. Chem. Soc., Chem. Commun.* **1980**, 902−903), Nicolaou and co-workers accomplished total syntheses of this family of natural products, see: (a) Nicolaou, K. C.; Petasis, N. A.; Zipkin, R. E.; Uenishi, J. *J. Am. Chem. Soc.* **1982**, *104*, 5555−5557. (b) Nicolaou, K. C.; Petasis, N. A.; Uenishi, J.; Zipkin, R. E. *J. Am. Chem. Soc.* **1982**, *104*, 5557−5558. (c) Nicolaou, K. C.; Zipkin, R. E.; Petasis, N. A. *J. Am. Chem. Soc.* **1982**, *104*, 5558−5560. (d) Nicolaou, K. C.; Petasis, N. A.; Zipkin, R. E. *J. Am. Chem. Soc.* **1982**, *104*, 5560−5562.

(5) For a discussion, see: Heathcock, C. H. *Proc. Natl. Acad. Sci. U.S.A.* **1996**, *93*, 14323−14327.

(6) (a) Muramatsu, H.; Miyauchi, M.; Sato, B.; Yoshimura, S. *40th Symposium on The Chemistry of Natural Products*; Fukuoka, Japan, 1998; Paper #83, pp 487−492. (b) Sato, B.; Muramatsu, H.; Miyauchi, M.; Hori, Y.; Takase, S.; Hino, M.; Hashimoto, S.; Terano, H. *J. Antibiot.* **2000**, *53*, 123−130. (c) Sato, B.; Nakajima, H.; Hori, Y.; Hino, M.; Hashimoto, S.; Terano, H. *J. Antibiot.* **2000**, *53*, 204−206. (d) Yoshimura, S.; Sato, B.; Kinoshita, T.; Takase, S.; Terano, H. *J. Antibiot.* **2000**, *53*, 615−622.

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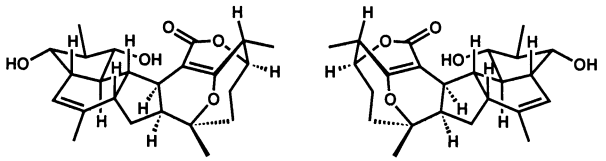

(+)-1: (+)-FR182877 (−)-1: (−)-FR182877

Figure 1. Initially reported structure for FR182877 [(+)-**1**] and the natural enantiomer [(−)-**1**].

lines.[6b] Promising preliminary in vivo results in mouse models[6b] indicate that this natural product has potential as a chemotherapeutic agent or as a lead compound.

Taken together, these attributes have led to considerable interest in FR182877 as an objective for research in organic synthesis. Studies toward this target have been reported by our laboratory,[7] Armstrong,[8] Clarke[9] and Nakada.[10] Our recent preliminary communication[11] describing the first synthesis of (+)-FR182877 was followed shortly after by a report from Evans and Starr describing a synthesis of the natural enantiomer through a closely related approach.[12]

FR182877 was isolated from the fermentation broth of *Streptomyces* sp. No9885. Its constitution and relative stereochemistry were elucidated via a combination of NMR and X-ray crystallographic methods, and its absolute stereochemistry was proposed to be as shown for (+)-**1** (Figure 1) based upon advanced Mosher ester analysis.[6d] A recent revision of its absolute stereochemistry by the Fujisawa scientists corroborated our discovery that the initial assignment was incorrect.[11−14]

The strained bridgehead olefin, which is implicated in FR182877's biological activity (see below), is particularly reactive. This moiety undergoes smooth conjugate additions with primary or secondary amines under neutral conditions, and with alcohols under basic conditions.[15] The olefin of this vinylogous carbonate is also highly susceptible to oxidation by molecular oxygen.[6d] Interestingly, the resulting epoxide lacks microtubule-stabilizing activity, suggesting that the strained olefin of FR182877 could be a site of reactivity if covalent processes are involved in its mechanism of action.

FR182877 is a member of a growing family of secondary metabolites that bind and stabilize cellular microtubules. Other members of this important family of natural products include Taxol, the epothilones, discodermolide, the sarcodictyins and eleutherobin, and laulimalide.[16] That this novel compound shows microtubule-stabilizing activity on the same order of magnitude as Taxol suggests that it may prove clinically useful, or could serve as a lead for the development of new anticancer therapeutics.

The fascinating structure and biological activity of FR182877, as well as the intriguing reactivity of its strained olefin, would generally prove sufficient to motivate synthetic studies toward this natural product. However, we were further inspired to undertake chemical studies on FR182877 when we pondered its structural origin. We sought to answer the following question: Can the unique architecture of FR182877 arise spontaneously from a polyunsaturated precursor by a cascade of cyclizations?

Results and Discussion

1. A Synthetic Approach Based upon Biosynthetic Considerations. Our consideration of the structural origin of FR182877 led to a general hypothesis in which the complex hexacycle might derive from a linear, polyunsaturated compound via a macrocyclization event and two cycloaddition reactions in either of two possible orders. As depicted in Scheme 1, tetraenal **2** could undergo a sequence of type I intramolecular Diels−Alder reaction[17,18] to afford **3**, a Knoevenagel[19] macrocyclization to afford the 12-membered ring of **4**, and subsequent transannular hetero Diels−Alder[20,21] cycloaddition of the electron-poor enone 4-π system with the trisubstituted olefin to afford FR182877 after lactonization.[22] An alternative ordering of events would entail an intramolecular condensation of **2** to afford the polyunsaturated 19-membered ring **6**, followed by two transannular Diels−Alder reactions:[23,24] the first a carbocyclic cycloaddition, succeeded by the same hetero Diels−Alder reaction shown in the first sequence.

(7) (a) Vanderwal, C. D.; Vosburg, D. A.; Weiler, S.; Sorensen, E. J. *Org. Lett.* **1999**, *1*, 645−648. (b) Vanderwal, C. D.; Vosburg, D. A.; Sorensen, E. J. *Org. Lett.* **2001**, *3*, 4307−4310.
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(9) Clarke, P. A.; Davie, R. L.; Peace, S. *Tetrahedron Lett.* **2002**, *43*, 2753−2756.
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(13) Yoshimura, S.; Sato, B.; Kinoshita, T.; Takase, S.; Terano, H. *J. Antibiot.* **2002**, *55*, C1.
(14) Our synthetic work was initially directed toward the originally disclosed stereostructure (+)-**1**, and as such, most depictions of the natural product and synthetic intermediates in this work are of this enantiomeric series.
(15) Dr. Seiji Yoshimura, Fujisawa Pharmaceutical Company, personal communication.
(16) (a) For a recent proposal of a common pharmacophore that unites paclitaxel, the epothilones, eleutherobin, discodermolide, and a paclitaxel analogue, see: Ojima, I.; Chakravarty, S.; Inoue, T.; Lin, S.; He, L.; Horwitz, S. B.; Kuduk, S. D.; Danishefsky, S. J. *Proc. Natl. Acad. Sci. U.S.A.* **1999**, *96*, 4256−4261. (b) For a recent review focusing on solution and tubulin-bound conformations of small-molecule microtubule-stabilizing compounds, see: Jiménez-Barbero, J.; Amat-Guerri, F.; Snyder, J. P. *Curr. Med. Chem.: Anti-Cancer Agents*, **2002**, *2*, 91−122.
(17) For reviews of the intramolecular Diels−Alder reaction, see: (a) Oppolzer, W. *Angew. Chem., Int. Ed. Engl.* **1977**, *16*, 10−23. (b) Brieger, G.; Bennett, J. N. *Chem. Rev.* **1980**, *80*, 63−97. (c) Fallis, A. G. *Can. J. Chem.* **1984**, *62*, 183−234. (d) Ciganek, E. *Org. React.* **1984**, *32*, 1−374. (e) Taber, D. F. *Intramolecular Diels-Alder and Alder Ene Reactions*; Springer-Verlag: Berlin, 1984. (f) Craig, D. *Chem. Soc. Rev.* **1987**, *16*, 187−238. (g) Roush, W. R. In *Advances in Cycloaddition*; Curran, D. P. Ed.; JAI Press: Greenwich, Connecticut, 1990; Vol. 2, pp 91−146. (h) Roush, W. R. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon Press: New York, 1991; Vol. 5, pp 513−550.
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(19) For reviews of the Knoevenagel reaction, see: (a) Jones, G. *Org. React.* **1967**, *15*, 204−599. (b) Tietze, L. F.; Beifuss, U. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon Press: New York, 1991; Vol. 2, pp 341−394.
(20) For excellent discussions of inverse electron demand and hetero Diels−Alder reactions, see: (a) Boger, D. L. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon Press: New York, 1991; Vol. 5, pp 451−512. (b) Boger, D. L.; Weinreb, S. M. *Hetero Diels−Alder Methodology In Organic Synthesis*; Academic Press: San Diego, 1987. (c) Tietze, L. F.; Kettschau, G. *Top. Curr. Chem.* **1997**, *189*, 1−120. (d) Tietze, L. F.; Kettschau, G.; Gewert, J. A.; Schuffenhauer, A. *Curr. Org. Chem.* **1998**, *2*, 19−62.
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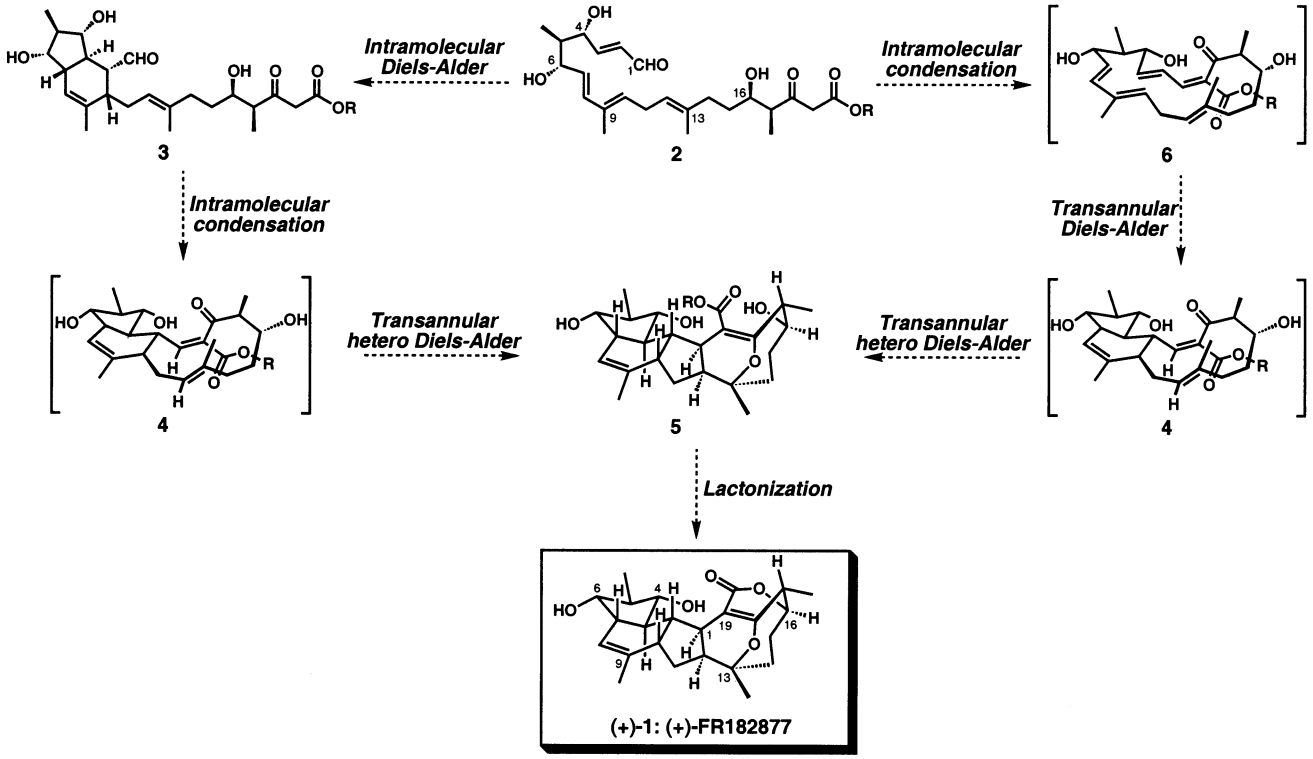
(22) Although in Scheme 1 we suggest that lactonization might be the final step in the proposed biogenetic sequences, there is no reason that the lactone could not be in place before the series of cyclizations (**2** could be in the β-keto-δ-lactone form prior to the condensation and cycloaddition steps).

Scheme 1. Is FR182877 the Product of an Architectural Self-Construction?



This biogenetic model rationalizes the complex, hexacyclic architecture of FR182877, and simplifies the question of its biogenesis to that of a much simpler, linear structure that could have a polyketide origin. A laboratory synthesis of compound **2** or a suitably protected surrogate would permit an evaluation of its propensity for undergoing the cascade of cyclizations shown in Scheme 1. By testing the chemical basis of this hypothesis, we hoped to uncover a highly efficient synthetic route to this natural product.

Our biogenetic postulate was firmly supported by a report from Zeeck and co-workers describing the isolation, structure determination, and biosynthetic origin of hexacyclinic acid (**7**, Figure 2).[25] FR182877 and hexacyclinic acid have identical carbon skeletons and differ only with respect to relative stereochemical relationships at two stereogenic centers, the oxidation state at the C9 allylic methyl group, and hydration of the bridgehead olefin. Both secondary metabolites also derive from *Streptomyces* organisms. Feeding experiments by the Zeeck group with ^{13}C-labeled acetic and propionic acids led to the conclusion that hexacyclinic acid is a polyketide. The observation that FR182877 can be reduced to the same alternating sequence of six acetate and four propionate units suggests that it too has a polyketide origin (see structure **8**). The different diastereorelationships of these two secondary metabolites appear to be manifestations of initial Diels−Alder cycloaddition (**2**→**3**, or **6**→**4**, Scheme 1) through an *endo* (FR182877) or *exo* (hexacyclinic acid) mode.

In light of our structure-driven hypothesis concerning the origin of FR182877, we were also intrigued by the structures

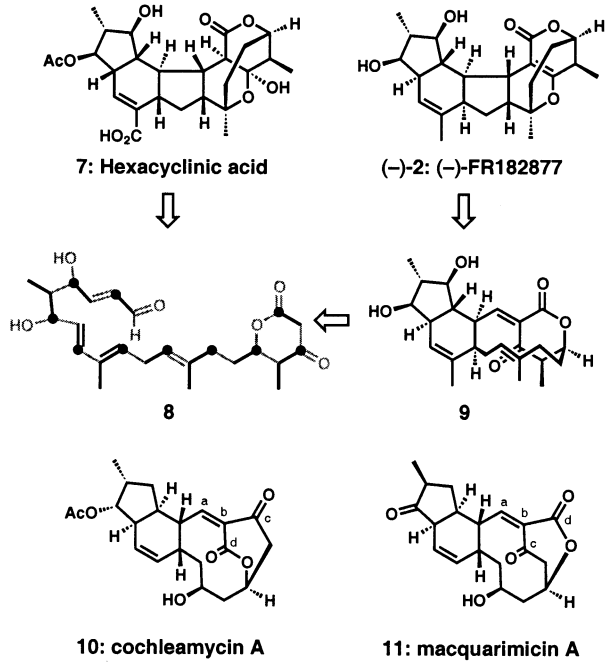


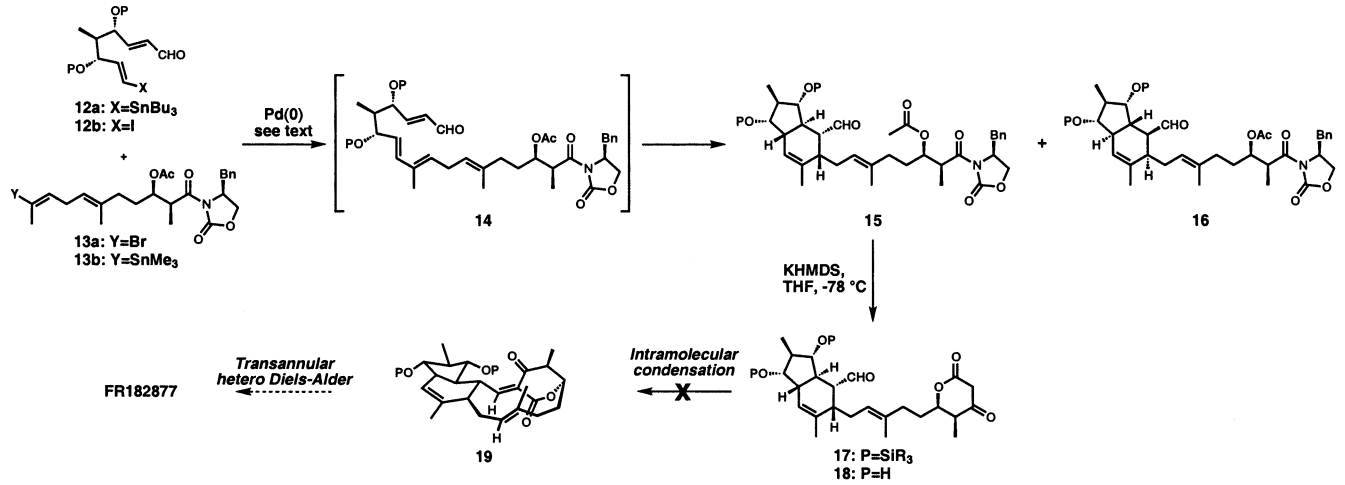
Figure 2. Potential biogenetic relationships among FR182877, hexacyclinic acid, cochleamycin A, and macquarimicin A.

(23) (a) For an excellent review by the pioneer in the development of the transannular Diels−Alder strategy in organic synthesis, see: Marsault, E.; Toró, A.; Nowak, P.; Deslongchamps, P. *Tetrahedron* **2001**, *57*, 4243−4260. (b) For a recent and elegant biomimetic natural product synthesis featuring intermolecular and transannular Diels−Alder reactions, see: Layton, M. E.; Morales, C. A.; Shair, M. D. *J. Am. Chem. Soc.* **2002**, *124*, 773−775. (c) For an example of a proposed biosynthetic transannular hetero Diels−Alder reaction, see: Cartagena, E.; Bardón, A.; Catalán, C. A. N.; de Hernández, Z. N. J.; Hernández, L. R.; Joseph-Nathan, P. *J. Nat. Prod.* **2000**, *63*, 1323−1328.

(24) For reviews of the Diels−Alder reaction in natural product biosynthesis, see: (a) Ichihara, A.; Oikawa, H. In *Comprehensive Natural Products Chemistry*; Barton, D. H. R., Nakanishi, K., Meth-Cohn, O., Eds.; Elsevier: New York, 1999; Vol. 5, pp 367−408. (b) Ichihara, A.; Oikawa, H. *Curr. Org. Chem.* **1998**, *2*, 365−394. (c) Laschat, S. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 289−291. (d) Stipanovic, R. D. *Environ. Sci. Res.* **1992**, *44*, 319−328. (d) Stockings, E. M.; Williams, R. M. *Angew. Chem., Int. Ed.* **2003**, in press.

(25) Höfs, R.; Walker, M.; Zeeck, A. *Angew. Chem., Int. Ed.* **2000**, *39*, 3258−3261.

Scheme 2. Efficient Route to Knoevenagel Substrates **17** and **18** Featuring a Tandem Stille Coupling/Intramolecular Diels−Alder Process



of two related families of natural products. Cochleamycin A (**10**) and its relatives were discovered at Kirin and reported to have antitumor activity.[26] The macquarimicins, of which macquarimicin A (**11**) is representative, were found to have weak antibacterial activity by researchers at Abbott.[27] Despite their isolation from disparate organisms, these two metabolites are structurally homologous. In the context of the structural relationships shown in Scheme 1, we were drawn to the salient α-alkylidene-β-keto-δ-lactone moiety found in both compounds **10** and **11**. This structural motif comprises the hetero-diene component in our proposed transannular hetero Diels−Alder substrate **4**; the transannular cycloaddition that could convert **4** to pentacycle **5** obscures a biogenetic relationship that may well exist between the cochleamycins, the macquarimicins, FR182877, and hexacyclinic acid. It is plausible that both the macquarimicins and the cochleamycins derive from biogenetic Diels−Alder and ring-forming condensation reactions.[28] This proposal has been put forth in the case of the cochleamycins, and biosynthetic studies have shown this family to be of polyketide origin.[26d] Synthetic studies toward cochleamycin A by Chang and Paquette,[29] and toward the macquarimicins by Tadano and co-workers,[30] have been reported recently.

In this disclosure, we report the evolution of our synthetic studies, which were always guided by thoughts on the structural origin of FR182877. These efforts culminated in an efficient and scalable enantioselective route to this fascinating natural product.

2. A Strategy Featuring a Diels−Alder/Knoevenagel/Diels−Alder Sequence. Initially, we addressed the variant of the biogenetic model that involved first a type I intramolecular Diels−Alder cycloaddition, followed sequentially by cyclocondensation and transannular hetero-Diels−Alder reaction (**2**→**3**→**4**→**5**→**1**, Scheme 1). At the outset, we had no reason to suspect that this sequence of reactions was a closer counterpart to a genuine biosynthetic process than the alternative pathway shown in Scheme 1, but this approach for synthesis did seem more conservative.

In a preliminary communication, we described a synthesis of a close relative of the long-chain, polyunsaturated compound **2** to evaluate its reactivity and suitability as an intermediate in a synthesis of FR182877.[7a] As depicted in Scheme 2, convergent union of xylose-derived fragment **12** with geraniol-derived compound **13** afforded **14**. We reported the case wherein stannane **12a**, bearing a cyclic silylene ketal as the 1,3-diol protecting group, coupled smoothly with bromide **13a** under Stille[31] conditions to deliver **14**. This polyenic intermediate could not be induced to undergo intramolecular Diels−Alder reaction, presumably due to conformational constraints as a result of the cyclic protecting group that kept the dienophilic enal moiety separated from the diene. Subsequent studies led to the discovery that the desired type I intramolecular Diels−Alder reaction was exceedingly facile when acyclic silicon protecting groups were used to mask the diol moiety. Thus, when **12a** bearing TBS ether protection was reacted with **13a**, isolation of **14** was not possible, as it underwent cycloaddition under the reaction conditions to yield a mixture of desired *endo* cycloadduct **15** and undesired *endo* product **16**.[32] This coupling was typically performed by using catalytic Pd_2dba_3 with triphenylarsine as ligand in THF at reflux over approximately 24 h; under these conditions, it was not surprising that cycloaddition might occur. However, it was also observed that a Stille coupling of the corresponding iodide **12b** and trimethylstannane **13b**, with a catalytic amount of $Cl_2Pd(MeCN)_2$ in DMF at ambient temperature, was also attended by a spontaneous [4 + 2] cycloaddition to compounds **15** and **16**. Tetraene **14** was never observed even under these mild conditions.[33]

The facility with which tetraenals of type **14** undergo type I intramolecular Diels−Alder reactions complicated efforts to induce this key transformation to be diastereoface-selective. Fortunately, however, it was possible to obtain *endo* cycloadduct

(26) (a) Shindo, K.; Kawai, H. *J. Antibiot.* **1992**, *45*, 292−295. (b) Shindo, K.; Matsuoka, M.; Kawai, H. *J. Antibiot.* **1996**, *49*, 241−243. (c) Shindo, K.; Iijima, H.; Kawai, H. *J. Antibiot.* **1996**, *49*, 244−248. (d) Shindo, K.; Sakakibara, M.; Kawai, H. *J. Antibiot.* **1996**, *49*, 249−252.

(27) (a) Jackson, M.; Karwowski, J. P.; Theriault, R. J.; Rasmussen, R. R.; Hensey, D. M.; Humphrey, P. E.; Swanson, S. J.; Barlow, G. J.; Premachandran, U.; McAlpine, J. B. *J. Antibiot.* **1995**, *48*, 462−466. (b) Hochlowski, J. E.; Mullally, M. M.; Henry, R.; Whittern, D. M.; McAlpine, J. B. *J. Antibiot.* **1995**, *48*, 467−470.

(28) For a brief discussion concerning the differing reported olefin geometries of **10** and **11**, please refer to the Supporting Information.

(29) Chang, J.; Paquette, L. A. *Org. Lett.* **2002**, *4*, 253−256.

(30) Munakata, R.; Ueki, T.; Katakai, H.; Takao, K.; Tadano, K. *Org. Lett.* **2001**, *3*, 3029−3032.

(31) Farina, V.; Krishnamurthy, V.; Scott, W. J. *Org. React.* **1997**, *50*, 1−652.

(32) For another example of a tandem Stille coupling−intramolecular Diels−Alder reaction, see: Humphrey, J. M.; Liao, Y.; Ali, A.; Rein, T.; Wong, Y.-L.; Chen, H.-J.; Courtney, A. K.; Martin, S. F. *J. Am. Chem. Soc.* **2002**, *124*, 8584−8592.

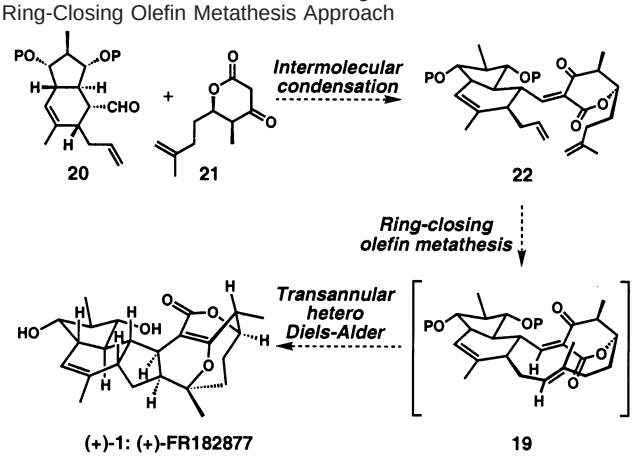
(33) For a brief discussion concerning the facility of these type I intramolecular Diels−Alder reactions, please refer to the Supporting Information.

15 in pure form via silica gel chromatography, and this compound could be advanced to β-keto-δ-lactone **17** in the course of a base-mediated Claisen-like condensation.[7a,34] This ring-forming process, which afforded compound **17** cleanly without epimerization of the aldehyde-bearing stereocenter, is best effected with potassium hexamethyldisilazide and provides efficient access to β-keto-γ-alkyl-δ-lactones. Our goal was to transform **17** or its deprotected relative **18** into tetracycle **19** via a ring-forming Knoevenagel condensation.[35] There are few literature precedents for this type of ring closure, and all efforts to accomplish this transformation were unsuccessful. Compounds **17** and **18** decomposed under most of the conditions that were screened. Substrates containing acyclic β-keto esters in place of the keto lactone moiety appeared to be more stable; however, attempts to transform these compounds to complex α-alkylidene-β-keto-esters of type **4** (Scheme 1) were also unsuccessful.

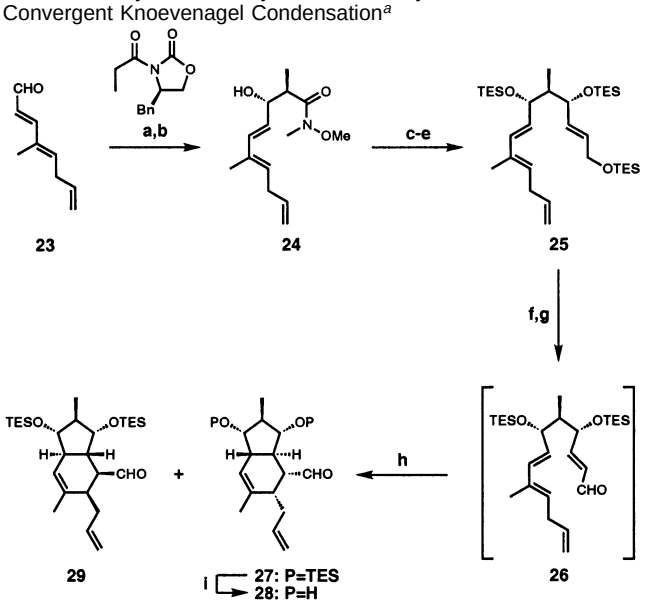
It is important to note here that the Stille product **14** bearing the cyclic silylene ketal protecting group, which did not undergo [4 + 2] cycloaddition, seemed to be an ideal substrate for a preliminary study of the alternative approach featuring a large-ring-forming condensation and 2-fold transannular Diels−Alder reactions (**2**→**6**→**4**→**5**→**1**, Scheme 1). Thus, many attempts were made to induce the nucleophilic ketolactone or ketoester derived from **14** to undergo intramolecular reaction with the unsaturated aldehyde. Unfortunately, no products consistent with a Knoevenagel-type cyclization were observed. The lack of productive reactivity in this context was not unexpected, as literature examples of both macrocyclizing Knoevenagel reactions and condensations with unsaturated aldehydes are scarce.[35,36]

3. An Intermolecular Knoevenagel/Ring-Closing Olefin Metathesis Approach. With the lack of success of the intramolecular Knoevenagel condensation, we considered an alternative, highly convergent approach involving a much more precedented intermolecular condensation, followed by a ring-closing olefin metathesis[37] reaction to form our penultimate intermediate, the substrate for the transannular hetero Diels−Alder reaction (Scheme 3). In this case, a truncated hydrindene aldehyde such as **20** would be condensed with a simple β-keto-δ-lactone **21**. The desired *E* isomer **22**, which we hoped to obtain selectively, would then be employed as a substrate for a ring-closing metathesis reaction to establish the 12-membered ring in **19**.

Scheme 3. Intermolecular Knoevenagel Condensation/ Ring-Closing Olefin Metathesis Approach



Scheme 4. Synthesis of Hydrindene Aldehydes **27** and **28** for Convergent Knoevenagel Condensation[a]



[a] (a) *n*-Bu_2BOTf, Et_3N, CH_2Cl_2, 0 °C, then **23**, −78 → 0 °C. (b) Me_3Al, MeONHMe·HCl, THF, −20 → 23 °C, 78% over two steps. (c) (*E*)-1-Iodo-3-triethylsilyloxypropene, *t*-BuLi, Et_2O, −78 °C, then $MgBr{\cdot}OEt_2$, −78 °C, then **24**, −78 → 0 °C. (d) Et_2BOMe, $NaBH_4$, THF/MeOH, −78 → 0 °C. (e) TESCl, imidazole, DMF, 69% over three steps. (f) TBAF, THF, −20 °C, 84% (g) Dess−Martin periodinane, $NaHCO_3$, CH_2Cl_2. (h) NMP, 23 °C, 36 h, 42% of **27**, 21% of **29**. (i) $Et_3N{\cdot}3HF$, CH_2Cl_2, 23 °C, 91%.

The transannular proximity between 4π- and 2π-electron systems in **19** was expected to favor a cycloaddition to the full framework of FR182877.

Initial work on this approach focused on gaining efficient access to hydrindene aldehydes such as **20**. This goal was met by the sequence depicted in Scheme 4. The *syn* stereochemical relationship in compound **24** was established in the course of an Evans asymmetric aldol addition reaction between trienal **23**[38] and the chiral propionyl oxazolidinone[39] shown in Scheme 4. The subsequent conversion of the imide to the Weinreb amide[40] of **24** was also efficient. From compound **24**, tetraene **25** was constructed by the following sequence of reactions: (1)

(34) Brandänge, S.; Leijonmarck, H. *Tetrahedron Lett.* **1992**, *33*, 3025−3028. For related Claisen-type cyclizations of acetate enolates, see: (a) Brandänge, S.; Flodman, L.; Norberg, Å. *J. Org. Chem.* **1984**, *49*, 927−928. (b) Brandänge, S.; Leijonmarck H. *J. Chem. Soc., Chem. Commun.* **1985**, 1097−1098. (c) Leijonmarck, H. K. E. *Chem. Commun.* (Stockholm University) **1992**, *3*, 1−33.

(35) To the best of our knowledge, reports of macrocyclizing Knoevenagel reactions are limited to the formation of cyclic oligomers of heterocyclic systems. For one such example, see: Zhang, Y.; Wada, T.; Sasabe, H. *J. Chem. Soc., Chem. Commun.* **1996**, 621−622.

(36) Knoevenagel condensations of α,β-unsaturated aldehydes are known to be plagued by competing 1,4-addition reaction pathways. For some examples of successful condensations of 4-hydroxy-2-pyrones with cyclic enals, see: (a) Hua, D. H.; Chen, Y.; Sin, H.-S.; Maroto, M. J.; Robinson, P. D.; Newell, S. W.; Perchellet, E. M.; Ladesich, J. B.; Freeman, J. A.; Perchellet, J.-P.; Chiang, P. K. *J. Org. Chem.* **1997**, *62*, 2, 6888−6896. (b) Hsung, R. P.; Shen, H. C.; Douglas, C. J.; Morgan, C. D.; Degen, S. J.; Yao, L. J. *J. Org. Chem.* **1999**, *64*, 4, 690−691. (c) Zehnder, L. R.; Hsung, R. P.; Wang, J.; Golding, G. M. *Angew. Chem., Int. Ed.* **2000**, *39*, 3876−3879. (d) Sunazuka, T.; Handa, M.; Nagai, K.; Shirahata, T.; Harigaya, Y.; Otoguro, K.; Kuwajima, I.; Omura, S. *Org. Lett.* **2002**, *4*, 367−369.

(37) For recent reviews of olefin metathesis, see: (a) Grubbs, R. H.; Chang, S. *Tetrahedron* **1998**, *54*, 4413−4450. (b) Schrock, R. R. *Tetrahedron* **1999**, *55*, 8141−8153. (c) Fürstner, A. *Angew. Chem., Int. Ed.* **2000**, *39*, 3012−3043.

(38) For two straightforward syntheses of trienal **23**, see the Supporting Information.

(39) (a) Gage, J. R.; Evans, D. A. *Organic Syntheses*; Wiley & Sons: New York, 1993; Collect. Vol. VIII, pp 339−343. (b) Evans, D. A. *Aldrichimica Acta* **1982**, *15*, 23−32.

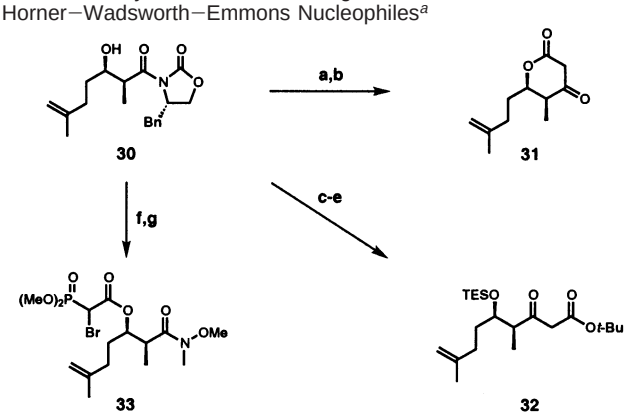
reaction of **24** with the Grignard reagent derived from (*E*)-1-iodo-3-triethylsilyloxypropene;[41] (2) diastereoselective reduction of the resulting ketone with Et_2BOMe and $NaBH_4$;[42] and (3) triethylsilylation of both hydroxyl groups. A selective deprotection[43] of the primary silyl ether with 1 equiv of tetra-*n*-butylammonium fluoride afforded an allylic alcohol that could be smoothly oxidized to intramolecular Diels−Alder precursor **26** with activated barium manganate or Dess−Martin periodinane[44] buffered with solid sodium bicarbonate.

On the basis of our previous experiences with tandem Stille−intramolecular Diels−Alder reactions, we anticipated a facile cycloaddition of **26**. This was in fact the case. When the crude tetraenal **26** was allowed to stand in solution at ambient temperatures for 24 to 48 h, it was converted to a mixture of diastereoisomeric *endo* cycloadducts. Initial reactions in dichloromethane afforded mixtures enriched in the undesired product **29** by a nearly 2:1 ratio. The stereochemistry of the adducts was elucidated by 2D-ROESY experiments on desired isomer **27**, deprotected **28**, and undesired **29**.

Attempts to alter this ratio to favor **27** through the use of Lewis acid catalysis led only to an increased production of the undesired cycloadduct **29**. We then attempted to use reagent control to overcome the intrinsic facial bias of this system. Unfortunately, treatment of **26** with Yamamoto's CAB catalyst[45] had no positive effect on the diastereochemical outcome of the cycloaddition. This was not so surprising since this, and most other chiral Lewis acids, generally show poor results with unsaturated aldehydes lacking substituents in the α position. Attempts to use Yamamoto's BLA catalyst,[46] specifically designed to function on unsubstituted enals, did not prove satisfactory in our hands. Finally, MacMillan's organocatalyst[47] was also examined, and though a moderate increase in diastereoselectivity in the desired direction was observed, an unidentified byproduct proved to be the major product in all cases.[48]

In the face of a Diels−Alder process in which half of our material was lost to the undesired cycloaddition pathway, we opted to study the dependence of reaction diastereoselectivity on the nature of the solvent.[49] We had noted a solvent-dependent change in diastereoisomeric ratio during our tandem Stille-Diels−Alder reactions; those reactions performed in THF led to equimolar quantities of the two cycloadducts, whereas reactions in DMF favored the desired isomer by a modest ratio of 1.5:1. The results of the solvent study on compound **26** indicated that the desired *endo* cycloadduct **27** could be preferentially formed at ambient temperature in dipolar aprotic solvents such as NMP (**27**:**29** = 1.9:1), DMF (1.8:1), DMPU (1.8:1), and DMSO (1.7:1). Chlorinated solvents, hydrocarbons, and tertiary amine solvents afforded the opposite ratio of products, whereas ethereal and hydroxylic solvents delivered equimolar ratios. At this point, efforts to improve upon the selectivity of this cycloaddition were terminated, and two-step yields of nearly 50% for the oxidative formation of **26** and Diels−Alder reaction to afford **27** were accepted.

Scheme 5. Synthesis of Knoevenagel and Horner−Wadsworth−Emmons Nucleophiles[a]



[a] (a) Ac_2O, Et_3N, CH_2Cl_2, 23 °C. (b) KHMDS, THF, −78 °C, 78% over two steps. (c) TESCl, Et_3N, DMAP, CH_2Cl_2, 23 °C. (d) EtSLi, THF, −78 → 23 °C. (e) LDA, *t*-BuOAc, THF, −78 → 0 °C, 71% over three steps. (f) Me_3Al, MeONHMe·HCl, THF, −20 → 23 °C. (g) DCC, $(MeO)_2P(O)CHBrCO_2H$, DMAP, CH_2Cl_2, 0 → 23 °C, 84% over two steps.

To test the intermolecular Knoevenagel reaction, we required appropriate nucleophiles to combine with the electrophilic aldehyde in **27**. Beginning with Evans aldol adduct **30** (Scheme 5), the enantiomer of which is known in the literature,[50] we first synthesized enantiopure ketolactone **31** using the acetate enolate Claisen cyclization[7a,34] that had served us well previously. We also desired an acyclic β-ketoester with which to test the condensation reaction, and thus compound **32** was made through the intermediacy of the TES-protected thioester[51] derived from **30**. Unfortunately, no Knoevenagel adducts (cf. **34**) were ever observed in reactions of **31** or **32** with aldehyde **27** (Scheme 6) under a vast array of reaction conditions. Fearing that the bulk of the proximal triethylsilyl protecting group in aldehyde **27** may be hindering the approach of the nucleophile, we also tested deprotected hydrindene aldehyde **28** as a Knoevenagel substrate. As matters transpired, we could achieve intermolecular condensations between aldehyde **28** and compounds **31** and **32**; however, these unions were uniformly

(40) (a) Basha, A.; Lipton, M.; Weinreb, S. M. *Tetrahedron Lett.* **1977**, 4171−4174. (b) Nahm, S.; Weinreb, S. M. *Tetrahedron Lett.* **1981**, *22*, 3815−3818. (c) Levin, J. I.; Turos, E.; Weinreb, S. M. *Synth. Commun.* **1982**, *12*, 989−993. (d) Evans, D. A.; Bender, S. L. *Tetrahedron Lett.* **1986**, *27*, 799−802. For a review of the chemistry of Weinreb amides, see: Sibi, M. P. *Org. Prep. Proced. Int.* **1993**, *25*, 15−40.

(41) (*E*)-1-Iodo-3-triethylsilyloxypropene was prepared in two steps from propargyl alcohol by triethylsilylation of the hydroxyl group, followed by a hydrozirconation−iodination sequence. See Supporting Information for details.

(42) (a) Chen, K.-M.; Hardtmann, G. E.; Prasad, K.; Repic, O.; Shapiro, M. J. *Tetrahedron Lett.* **1987**, *28*, 155−158. (b) Evans, D. A.; Kaldor, S. W.; Jones, T. K.; Clardy, J.; Stout, T. J. *J. Am. Chem. Soc.* **1990**, *112*, 7001−7031.

(43) For a review concerning the selective deprotection of silyl ethers, see: Nelson, T. D.; Crouch, R. D. *Synthesis* **1996**, 1031−1069.

(44) Dess, D. B.; Martin, J. C. *J. Org. Chem.* **1983**, *48*, 4155−4156.

(45) Yamamoto and co-workers reported that achiral decatrienals were converted to *trans*-fused hydrindenes in an enantioselective fashion in the presence of a chiral acyloxyborane (CAB) complex. Furuta, K.; Kanematsu, A.; Yamamoto, H.; Takaoka, S. *Tetrahedron Lett.* **1989**, *30*, 7231−7232. See also: Furuta, K.; Shimizu, S.; Miwa, Y.; Yamamoto, H. *J. Org. Chem.* **1989**, *54*, 1481−1483.

(46) Yamamoto and co-workers recently reported a catalyst system for the catalytic asymmetric Diels−Alder reaction of α-unsubstituted enals, including achiral decatrienals. Ishihara, K.; Kurihara, H.; Matsumoto, M.; Yamamoto, H. *J. Am. Chem. Soc.* **1998**, *120*, 6920−6930.

(47) Ahrendt, K. A.; Borths, C. J.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2000**, *122*, 4243−4244. We thank Professor MacMillan for a generous gift of his catalyst.

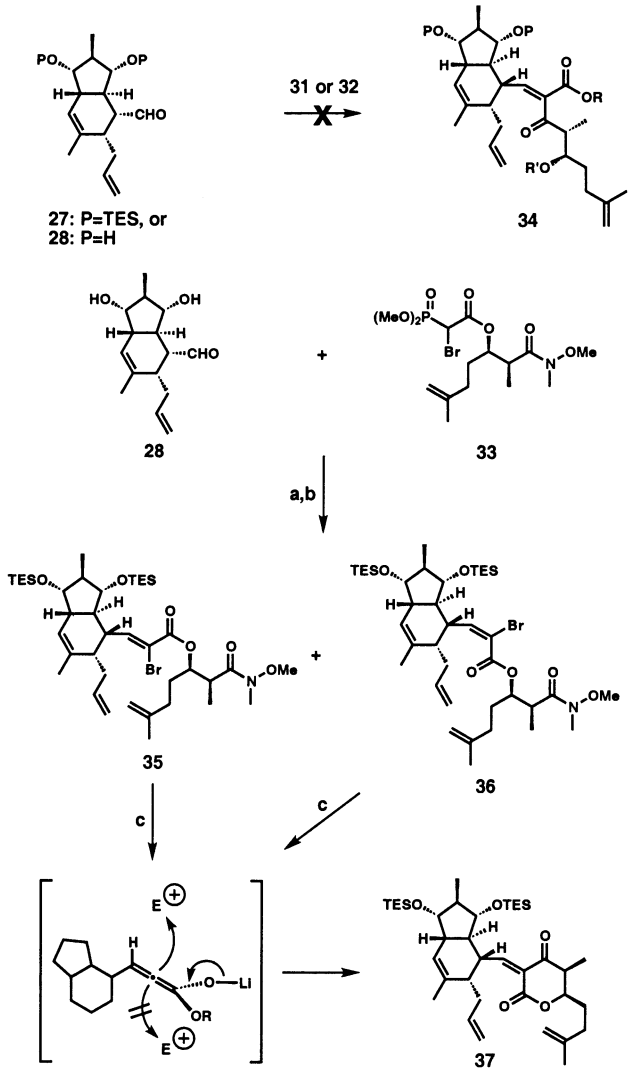
(48) For a brief summary of our attempts to exploit the structural elements inherent in the [4 + 2] cycloaddition substrates to improve upon the facial selecivity of this Diels−Alder reaction, please refer to the Supporting Information.

(49) For some examples of solvent-dependent changes in diastereoface-selectivity in intramolecular Diels−Alder reactions, see: (a) Parker, K. A.; Iqbal, T. *Tetrahedron Lett.* **1986**, *27*, 6291−6294. (b) Handa, S.; Jones, K.; Newton, C. G. *J. Chem. Soc., Chem. Commun.* **1986**, 1797−1799. (c) Melekhov, A.; Forgione, P.; Legoupy, S.; Fallis, A. G. *Org. Lett.* **2000**, *2*, 2793−2796.

(50) Irie, O.; Fujiwara, Y.; Nemoto, H.; Shishido, K. *Tetrahedron Lett.* **1996**, *37*, 9229−9232.

(51) For the conversion of Evans acyl oxazolidinones into thioesters, see: Damon, R. E.; Coppola, G. M. *Tetrahedron Lett.* **1990**, *31*, 2849−2852.

Scheme 6. Attempted Knoevenagel and Successful Horner−Wadsworth−Emmons Condensations[a]



[a] (a) **33**, $Ba(OH)_2$, THF, then **28**, THF/H_2O, 0 °C. (b) TESCl, Et_3N, DMAP, CH_2Cl_2, 71% over two steps for 6.5:1 *Z*/*E* mixture (**35**:**36**). (c) *t*-BuLi, THF, −78 °C, 90−100%.

inefficient (≤10% yield), and they afforded a nearly equimolar mixture of four compounds: the alkene geometrical isomers derived from both **28** and the undesired C2 epimer of **28**.

At this point, we were convinced that typical Knoevenagel condensations were not going to efficiently afford the required alkylidene dicarbonyl moiety. Clearly, it became necessary to bring a new method to bear on the problem of constructing this grouping in a stereocontrolled fashion. The method we favored was founded on the idea that a reactive organometallic species derived by a reduction of an α-bromoenoate such as **35** (Scheme 6) would attack the proximal Weinreb amide carbonyl and result in the formation of an α-alkylidene-*β*-keto-*δ*-lactone of the desired type. To this end, bromophosphonoacetate **33**[52] was elaborated from compound **30** by the reactions shown in Scheme 5[53] and subsequently joined with aldehyde **28** via a Horner−Wadsworth−Emmons condensation[54] (Scheme 6). This union was best effected in the presence of activated $Ba(OH)_2$[55] in wet THF and afforded a 6.5:1 mixture of the geometrically isomeric α-bromoenoates enriched in the desired *Z* isomer. After resolution of this mixture by silica gel chromatography, the 1,3-diols were protected as triethylsilyl ethers **35** and **36**.

We then hoped to transform *Z*-α-bromoenoate **35** into an α-alkylidene-*β*-keto-*δ*-lactone through a reductive carbon−carbon bond-forming process.[56] To test the feasibility of this plan, we treated **35** with *tert*-butyllithium in THF at −78 °C, and observed a rapid and quantitative cyclization. Initial excitement about this outcome, which clearly showed that the desired alkylidene ketolactone functionality was formed, gave way to disappointment upon further spectroscopic analysis. It turned out that this efficient reaction was highly stereoselective but not stereospecific, thus yielding the *Z*-alkylidene dicarbonyl **37** rather than the desired geometrical isomer. A ^{1}H-coupled ^{13}C NMR experiment[57] supported the geometry shown for alkylidene dicarbonyl **37**. We reasoned that the exclusive formation of **37** occurred through the intermediacy of a transient lithium allenolate[7b,58] (see Scheme 6); support for this hypothesis and our geometrical assignment of product **37** followed from one simple experiment. When the minor olefination product **36** was exposed to the reducing action of *tert*-butyllithium under the same conditions, the same *Z*-alkylidene dicarbonyl **37** was produced in excellent yield. Presumably, upon reductive lithiation of either bromoenoate, rapid equilibration to the same lithium allenolate occurs, and the ensuing reaction with the tethered Weinreb amide electrophile proceeds with high stereocontrol due to the preferential shielding of one face of the allene by the bulky hydrindene. The carbonyl electrophile engages the allenolate on the side of the small hydrogen atom.

Having established an efficient route to the desired functionality with incorrect geometry, we expended a strong effort to isomerize the activated olefin of **37** to the desired *E* geometry.[59] Unfortunately, the instability of the alkylidene dicarbonyl functionality precluded most manipulations, as it decomposed readily even upon attempted silica gel chromatography.

4. Application of a Stereoselective Chemical Equivalent of the Knoevenagel Condensation. Although the reductive *C*-acylations of α-bromoenoates **35** and **36** afforded a single alkylidene dicarbonyl with the undesired geometry, we wondered how this type of chemistry would perform in a more sophisticated molecular context and turned to the problem of

(52) The use of bromophosphonoacetates as bromoolefinating reagents was first reported by Wadsworth and Emmons: Wadsworth, W. S., Jr.; Emmons, W. D. *J. Am. Chem. Soc.* **1961**, *83*, 1733−1738. For examples of their use in natural product total synthesis, see: (a) Semmelhack, M. F.; Brickner, S. J. *J. Am. Chem. Soc.* **1981**, *103*, 3945−3947. (b) Danishefsky, S.; Chackalamannil, S.; Harrison, P.; Silvestri, M.; Cole, P. *J. Am. Chem. Soc.* **1985**, *107*, 2474−2484.

(53) For a general synthesis of α-bromophosphonoacetates, see: McKenna, C. E.; Khawli, L. A. *J. Org. Chem.* **1986**, *51*, 5467−5471.

(54) For a comprehensive review on the Wittig reaction that includes a significant treatise of the Horner−Wadsworth−Emmons olefination, see: Maryanoff, B. E.; Reitz, A. B. *Chem. Rev.* **1989**, *89*, 863−927.

(55) Paterson, I.; Yeung, K.-S.; Smaill, J. B. *Synlett* **1993**, 774−776.

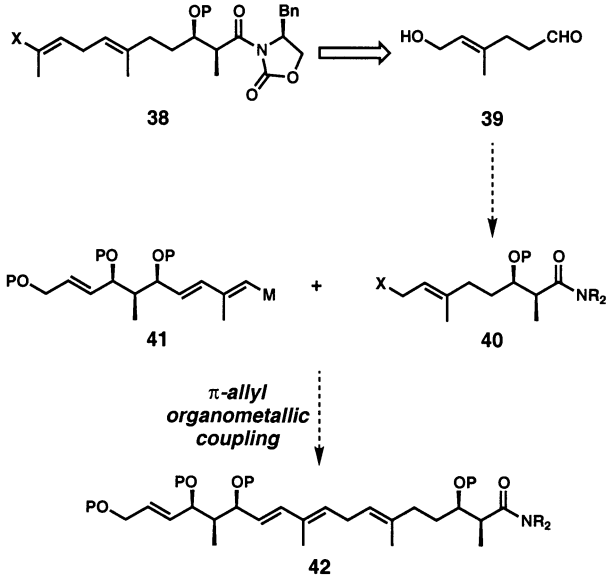
(56) For selected examples of intramolecular acylations of organolithium intermediates, see: (a) Flann, C. J.; Overman, L. E. *J. Am. Chem. Soc.* **1987**, *109*, 6115−6118. (b) Parham, W. E.; Bradsher, C. K. *Acc. Chem. Res.* **1982**, *15*, 300−305.

(57) The determination of olefin bond geometry for Knoevenagel products of aldehydes by ^{1}H-coupled ^{13}C NMR spectroscopy is well precedented: (a) Reference 19b. (b) Kingsbury, C. A.; Draney, D.; Sopchik, A.; Rissler, W.; Durham, D. *J. Org. Chem.* **1976**, *41*, 3863−3868.

(58) For selected studies of allenolates, see: (a) Marino, J. P.; Linderman, R. J. *J. Org. Chem.* **1981**, *46*, 3696−3702. (b) Marino, J. P.; Linderman, R. J. *J. Org. Chem.* **1983**, *48*, 4621−4628. (c) Matsumoto, K.; Oshima, K.; Utimoto, K. *Chem. Lett.* **1994**, 1211−1214. (d) Nilsson, K.; Andersson, T.; Ullenius, C.; Gerold, A.; Krause, N. *Chem. Eur. J.* **1998**, 4, 2051−2058. (e) Trost, B. M.; Oi, S. *J. Am. Chem. Soc.* **2001**, *123*, 1230−1231. (f) Ma, D.; Zhu, W. *Org. Lett.* **2001**, *3*, 3927−3929.

(59) We attempted to isomerize the olefin using iodine, light, and tertiary amine catalysts. Under no circumstances did we see evidence that any of the desired *E* geometrical isomer had been formed.

Scheme 7. π-Allyl Organometallic-Based Coupling Strategy



synthesizing compound **52** (Scheme 8). Could the configuration at C16 in **52** override the steric preferences of a transient allenolate ion or even preclude allenolate formation altogether, thereby favoring the formation of the desired *E* alkylidene β-keto-δ-lactone (see **19** in Scheme 3)? The transannular proximity between 2π- and 4π-electron systems in the latter structure would then be expected to facilitate a cycloisomerization to a compound having the full architecture of FR182877.

Although we had already defined a relatively concise route to polyenic intramolecular Diels−Alder substrates through the use of a Stille bond construction between sp^2-hybridized carbons (as in Scheme 2),[7a] examination of our synthesis of the dienyl halide moiety in **38** (Scheme 7) led us to consider a different bond construction. Our original approach entailed the preparation of cross-coupling partners of general type **38** from geraniol-derived aldehyde **39** in six or seven steps.[7a] Thus, the allylic alcohol function of **39** was homologated using modified Shapiro chemistry,[7a] and the aldehyde was utilized in an Evans asymmetric aldol reaction to afford coupling partner **38**. The key to greater efficiency in our synthetic route lay in the realization that geraniol-derived starting materials such as **39** were well suited to rapid elaboration via organometallic π-allyl-based cross-coupling technology.[60] The facile generation of aldol products bearing allylic leaving groups (**40**) and subsequent palladium-mediated coupling with trienylmetal reagents **41** should form the basis for a much improved synthesis of polyunsaturated key intermediates of type **42**.

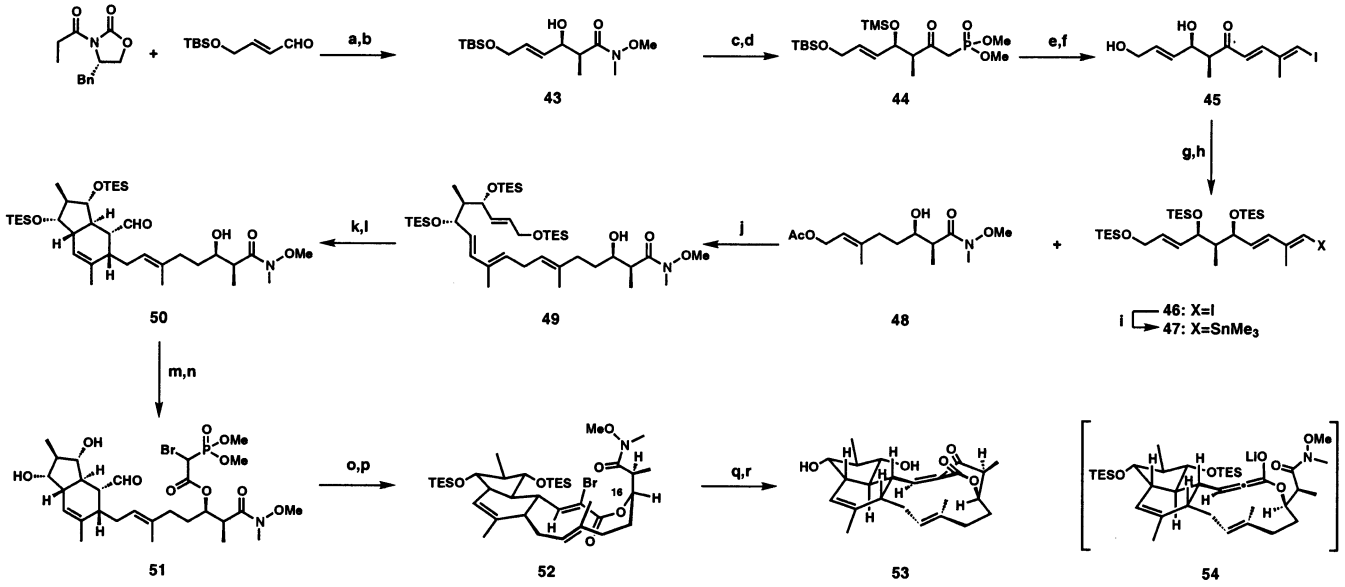
To examine the suitability of this new convergent approach, we needed to prepare an intermediate of type **41**. An improved route to the stereotriad present in such an intermediate was established by the replacement of our earlier xylose-based procedure[7a] with a sequence closely related to that disclosed by Evans and co-workers in their elegant synthesis of cytovaricin[42b] which we had already adapted to our synthesis of **25** in Scheme 4. Asymmetric aldol reaction with the known (*E*)-4-*tert*-butyldimethylsilyloxy-but-2-enal[61] (see Scheme 8) provided a hydroxyimide that was readily converted to the corresponding Weinreb amide **43**. Protection of the free hydroxyl group as its trimethylsilyl ether prevented cyclic phosphonate formation when the amide was treated with an excess of dimethyl lithiomethylphosphonate.[62] The resulting β-ketophosphonate **44** was then used in a Horner−Wadsworth−Emmons reaction with β-iodomethacrolein.[63] This particular olefination proceeded most smoothly when mediated by activated $Ba(OH)_2$,[55] and following mild hydrolysis of the silyl ethers, iododienone **45** was obtained in high yield. Chelation-controlled 1,3-reduction of the β-hydroxy ketone[42] once again afforded a *syn*-diol with high efficiency, and the crude product was globally protected with chlorotriethylsilane. Palladium-catalyzed stannylation[64] of the resulting dienyl iodide **46** with a slight excess of hexamethylditin afforded dienylstannane **47** in high yield. Such 2-substituted-1-stannyl-1,3-dienes are known to be extremely labile to traces of acid, affording the protodestannylated diene with ease.[65] As such, silica gel chromatography was not an option for purification, thus an aqueous workup was performed to remove the trimethyltin halide byproduct, followed by rapid filtration through basic alumina to separate the stannane from residual palladium. Finally, excess hexamethylditin was removed in vacuo at 1 mmHg at 45 °C for 48 h. The resulting orange oil consisted of essentially pure dienylstannane **47**, contaminated only by traces of triphenylphosphine derived from the palladium catalyst. With **47** in hand, preparation of the requisite allylic electrophile was addressed. The more electron-rich olefin of inexpensive geranyl acetate was dihydroxylated according to a literature procedure,[66] and the resulting glycol was cleaved with silica gel-supported sodium periodate.[67] The known aldehyde,[68] the acetate ester of **39** (Scheme 7), was converted into **48** by the straightforward sequence of Evans asymmetric *syn*-aldol reaction and Weinreb amidification.

The union of stannane **47** with allylic acetate **48** afforded low yields of **49** and its geometrical isomer when initially attempted with catalytic tris(dibenzylideneacetone) dipalladium (0) and lithium chloride in DMF or NMP at 60 °C. Yields were improved by the addition of Hünig's base to prevent protodestannylative destruction of **47**, and the geometrical integrity of the allylic acetate olefin could be maintained by simply decreasing the reaction temperature to 40 °C. As a result, a truly efficient convergent reaction[69] emerged, forging the required C10−C11 bond in a reproducible yield of 85%. Due to the residual triphenylphosphine from the stannylation reaction, a minimum precatalyst loading of 10% Pd_2dba_3 (20 mol % Pd)

(60) We were inspired by Negishi's exceptional one-pot synthesis of α-farnesene, a 1,3,7-triene with a substitution pattern identical to that in **42**. The sequence of enyne carboalumination and palladium-mediated cross-coupling with an allylic electrophile, or some equivalent, seemed well suited to our needs. See: Matsushita, H.; Negishi, E. *J. Am. Chem. Soc.* **1981**, *103*, 2882−2884.

(61) (a) Roush, W. R.; Koyama, K. *Tetrahedron Lett.* **1992**, *32*, 6227−6230. (b) Marshall, J. A.; Garofalo, A. W. *J. Org. Chem.* **1996**, *61*, 8732−8738.
(62) Theisen, P. D.; Heathcock, C. H. *J. Org. Chem.* **1988**, *53*, 2374−2378.
(63) Baker, R.; Castro, J. L. *J. Chem. Soc., Perkin Trans. 1* **1990**, 47−65.
(64) (a) Wulff, W. D.; Peterson, G. A.; Bauta, W. E.; Chan, K.-S.; Faron, K. L.; Gilbertson, S. R.; Kaesler, R. W.; Yang, D. C.; Murray, C. K. *J. Org. Chem.* **1986**, *51*, 277−279. (b) Scott, W. J.; Stille, J. K. *J. Am. Chem. Soc.* **1986**, *108*, 3033−3040.
(65) The instability of 2-substituted-1-stannyl-1,3-dienes has been documented. For an example, see: Uenishi, J.; Kawahama, R.; Tanio, A.; Wakabayashi, S. *J. Chem. Soc., Chem. Commun.* **1993**, 1438−1439.
(66) Xu, D.; Park, C. Y.; Sharpless, K. B. *Tetrahedron Lett.* **1994**, *35*, 2495−2498.
(67) Zhong, Y.-L.; Shing, T. K. M. *J. Org. Chem.* **1997**, *62*, 2622−2624.
(68) Canonica, L.; Rindone, B.; Santaniello, E.; Scolastico, C. *Tetrahedron* **1972**, *28*, 4395−4404.
(69) The π-allyl Stille coupling reaction is a general and reliable method for generating 1,4-dienes. See ref 31. For another example from our group of its use in a complex context, see: Shipe, W. D.; Sorensen, E. J. *Org. Lett.* **2002**, *4*, 2063−2066.

Scheme 8. Synthesis of Macrocyclic *Z*-Alkylidene Dicarbonyl **53** via Allenolate **54**[a]



[a] (a) *n*-Bu_2BOTf, Et_3N, CH_2Cl_2, 0 °C, −78 → −20 °C. (b) Me_3Al, MeONHMe·HCl, THF, 0 °C, 75% over two steps. (c) TMSCl, imidazole, DMAP, CH_2Cl_2, 23 °C. (d) $LiCH_2P(O)(OMe)_2$, THF, −78 °C. (e) $Ba(OH)_2$, THF, then (*E*)-β-iodomethacrolein, THF/H_2O, 0 °C. (f) PPTS, MeOH, 23 °C, 79% over four steps. (g) Et_2BOMe, $NaBH_4$, THF/MeOH, −78 → 0 °C. (h) TESCl, imidazole, DMAP, CH_2Cl_2, 23 °C, 86% over two steps. (i) $Me_3SnSnMe_3$, $Pd(Ph_3P)_4$, *i*-Pr_2NEt, PhH, 80 °C, 97%. (j) Pd_2dba_3, LiCl, *i*-Pr_2NEt, NMP, 40 °C, 86%. (k) TBAF, THF, 0 °C. (l) MnO_2, DMF, 23 °C, 65% over two steps, 1.6:1 dr favoring **50**. (m) $(MeO)_2P(O)CHBrCO_2H$, DCC, $NaHCO_3$, CH_2Cl_2, 0 °C, 90%. (n) $Et_3N·3HF$, CH_2Cl_2, 23 °C, 85%, separation yields 50% desired *endo* diastereoisomer **51**, 35% of undesired. (o) $Ba(OH)_2$, THF/H_2O, 0 °C, 74%. (p) TESCl, imidazole, DMAP, CH_2Cl_2, 23 °C. (q) *t*-BuLi, THF, −78 °C, 86% over two steps. (r) PPTS, MeOH, 23 °C, 100%. Yields reported in this scheme for steps (a−i) may vary slightly from those reported in the Supporting Information, which describes the large-scale synthesis of the enantiomeric series of these intermediates.

was required to overcome the ligand-derived inhibition and obtain consistently high yields in reasonable reaction times.

The primary allylic TES ether was then selectively cleaved[43] with 1 equiv of tetra-*n*-butylammonium fluoride, and the resulting crude diol was selectively oxidized at the allylic alcohol with activated MnO_2. Consistent with observations made during our previous studies, the resulting enal underwent spontaneous intramolecular Diels−Alder reaction during the course of the oxidation reaction. Rather than attempt to isolate the oxidation product, a solvent screen was conducted to optimize a tandem allylic oxidation−intramolecular Diels−Alder sequence. As we had noted before, polar aprotic solvents led to optimal facial bias in the cycloaddition process; however, manganese dioxide oxidations are known to be markedly less effective in polar solvents,[70] as the solvent molecules compete for the reactive surface area of the heterogeneous reagent. We were therefore pleasantly surprised when DMF emerged as an ideal solvent environment for both a highly selective oxidation and smooth intramolecular Diels−Alder reaction to afford **50**. The desired hydrindene isomer and the other *endo* diastereoisomer were isolated as an inseparable 1.6:1 mixture in a combined 65% yield over the three-step, two-pot process.

Acylation of the free hydroxyl groups of **50** and its admixed isomer with α-bromodimethylphosphonoacetic acid mediated by DCC was followed by cleavage of the triethylsilyl ethers with triethylamine trihydrofluoride. This sequence yielded a mixture of four diastereomeric compounds, as both *endo* cycloadducts now carried diastereoisomeric bromophosphonoacetate groups. Fortunately, the mixture could be separated at this stage by simple chromatography to deliver the key Horner−Wadsworth−Emmons precursor **51** as a single isomer about the hydrindene and as an equimolar mixture about the bromophosphonate. Removal of the silicon protecting groups facilitated separation at this stage, and it was also deemed necessary as Horner−Wadsworth−Emmons reactions of the aldehyde moiety of a hydrindene bearing diol protecting groups were inefficient. This mixture of deprotected bromophosphonates was treated with activated $Ba(OH)_2$[71] in wet THF. A very rapid reaction ensued and afforded the desired tricyclic α-bromo-α,β-unsaturated lactone as a single geometrical isomer in good yield. Initial experiments were performed at high dilution (5 mM), but ultimately it was found that nearly identical efficiency could be attained at concentrations as high as 0.1 M. This suggests that this substrate is predisposed toward macrocyclization in the face of competing oligomerization. The rigid structural elements in **51** and the short reaction times observed are in agreement with this scenario.

In preparation for the key reductive lithiation step, the diol moiety was reprotected with triethylsilyl groups. Exposure of the resulting macrocyclic bromoenoate **52** to 2.3 equiv of *tert*-butyllithium in THF at −78 °C resulted in an efficient reductive cyclization to afford an alkylidene dicarbonyl, once again as the undesired *Z* isomer about the alkylidene dicarbonyl double bond. The assignment was again made on the basis of observed $^1H-^{13}C$ coupling constants[57] of the reaction product (bis-TES protected **53**). Clearly the configuration at C16 in combination with the geometrical constraints of the 12-membered ring were insufficient to prevent the formation of putative allenolate ion

(70) For several preparations of activated MnO_2, and a brief discussion of solvent effects on the oxidation reaction, see: Cahiez, G.; Alami, M. In *Encyclopedia of Reagents for Organic Synthesis*; Paquette, L. A., Ed.; John Wiley & Sons: Ltd: Chichester, 1995; Vol. 5, pp 3229−3235.

(71) For examples of $Ba(OH)_2$-mediated macrocyclizations, see: (a) Lafontaine, J. A.; Provencal, D. P.; Gardelli, C.; Leahy, J. W. *Tetrahedron Lett.* **1999**, *40*, 4145−4148. (b) Williams, D. R.; Cortez, G. S.; Bogen, S. L.; Rojas, C. M. *Angew. Chem., Int. Ed.* **2000**, *39*, 4612−4615.

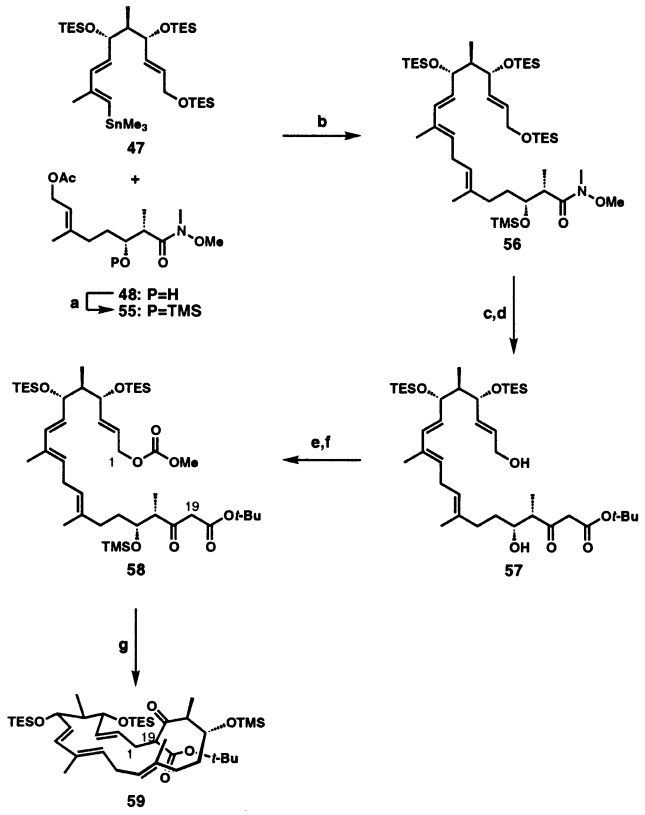
54; the subsequent formation of the more strained *Z* isomer was highly favored, proceeding in 86% yield. No trace of the desired *E* isomer could be detected. Considerable efforts involving a systematic variation of solvent, temperature, and reducing agent did not afford any positive results. Even a sequence involving selective reduction of the Weinreb amide of **52** to the corresponding aldehyde followed by a Nozaki−Hiyama−Kishi reaction[72] ultimately afforded the undesired geometrical isomer. Interestingly, whereas the analogous product in our olefin metathesis-based approach (**37** in Scheme 6) proved unstable to chromatography, the macrocyclic alkylidene dicarbonyl was found to be stable to silica gel. Acidic methanolysis of the triethylsilyl ethers then afforded compound **53**. It is possible that the strain-derived lack of conjugation in the alkylidene dicarbonyl system may actually impose greater stability to this typically reactive functionality, resulting in the improved ease of handling of **53** with respect to **37**. Our structural assignment of **53**, based initially upon 2D-ROESY experiments, was confirmed by an X-ray crystallographic analysis of this crystalline diol.[73]

Despite the fact that preliminary experiments have indicated a lack of generality of this allenolate method for the construction of simpler alkylidene dicarbonyls, it should be noted that in the related contexts of cochleamycin A and macquarimicin A, this sequence may indeed prove useful.

5. An Approach Based on Tandem Transannular Diels−Alder Reactions Yields Success. At this juncture, it seemed that we had exhausted the possibilities for a synthesis of FR182877 via approaches based upon our first biogenetically inspired route. Having gained the ability to efficiently create polyunsaturated compounds approximating **2** (Scheme 1), we sought to examine the feasibility of synthesizing the natural product via some version of a macrocyclizing condensation to afford a 19-membered ring, followed by sequential transannular Diels−Alder reactions (**2→6→4→5→1**, Scheme 1). We had performed some preliminary studies of the ring-closing Knoevenagel reaction on protected versions of **2** early on in our efforts to create FR182877, with only discouraging results. Since that time, however, we had gained an appreciation for the practical utility of palladium π-allyl intermediates for carbon−carbon bond formation in rather complex settings. Indeed, our highly efficient π-allyl Stille reaction, along with ample literature precedent,[74] suggested to us that perhaps a large ring might be formed by palladium-mediated allylic alkylation of a β-keto-ester or β-keto-δ-lactone. Toward this end, we required an appropriately functionalized, linear, polyunsaturated intermediate similar to **2**, and we approached this goal as depicted in Scheme 9.

In the same manner as before, a π-allyl Stille reaction of **47** with **55**, the trimethylsilyl protected version of allylic acetate **48**, proceeded in 85% yield. To examine the key macrocyclization event, we required the appendage of two carbons onto the Weinreb amide function of Stille product **56**. This was accomplished by reacting **56** with an excess of the lithium enolate of *tert*-butyl acetate,[75] affording ketoester **57** after selective cleavage of the secondary TMS and primary TES ethers with 2 equiv of tetra-*n*-butylammonium fluoride. Selective methoxycarbonylation of the primary alcohol was efficient, and resilylation[76] of the secondary hydroxyl group afforded **58**, the substrate for a Trost−Tsuji[74,77] ring closure. To our delight, the critical C1−C19 ring closure was smoothly achieved in 80% yield by treatment of **58** with catalytic Pd_2dba_3 (10 mol %) in dilute THF solution at 40 °C. The 19-membered macrocycle **59** was obtained as a single diastereoisomer, although the configuration at C19 was not determined.

Scheme 9. Synthesis of 19-Membered Macrocycle via a Trost−Tsuji Reaction[a]



[a] (a) TMSCl, imidazole, CH_2Cl_2, 23 °C, 96%. (b) Pd_2dba_3, LiCl, *i*-Pr_2NEt, NMP, 40 °C, 85%. (c) LDA, *t*-BuOAc, THF, −78 → 0 °C, 81%. (d) TBAF, THF, −30 → −10 °C, 86%. (e) MeOCOCl, pyridine, CH_2Cl_2, 23 °C, 93%. (f) TMSCl, imidazole, CH_2Cl_2, 23 °C, 95%. (g) Pd_2dba_3, THF (0.005 M), 40 °C, 80%. Yields reported in this scheme may vary slightly from those reported in the Supporting Information, which describes the large-scale synthesis of the enantiomeric series of these intermediates.

With macrocycle **59** in hand, introduction of unsaturation between carbons 1 and 19 was required prior to attempting the key sequential transannular Diels−Alder reactions.[78] Traditional selenium-based methods[79] were investigated for the introduction of the needed olefin. Formation of the stabilized potassium enolate of **59** with KHMDS in THF at −10 °C followed by quenching with phenylselenenyl bromide afforded a 3:1 mixture

(72) For recent reviews of chromium-mediated carbon−carbon bond constructions, see: (a) Wessjohann, L. A.; Scheid, G. *Synthesis* **1999**, 1−36. (b) Fürstner, A. *Chem. Rev.* **1999**, *99*, 991−1045.

(73) For an ORTEP representation of the X-ray crystallographic structure, as well as a discussion of the strained nature of **53**, please see the Supporting Information.

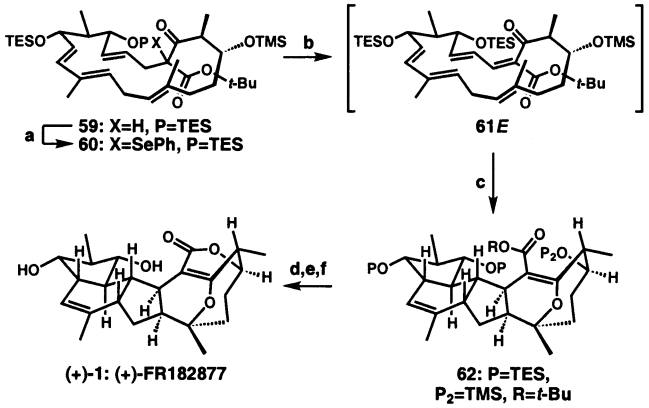
(74) (a) For an impressive, early example of a palladium-mediated macrocyclization, see: Trost, B. M.; Brickner, S. J. *J. Am. Chem. Soc.* **1983**, *105*, 568−575. (b) For a review, see: Trost, B. M. *Angew. Chem., Int. Ed.* **1989**, *28*, 1173−1192.

(75) Turner, J. A.; Jacks, W. S. *J. Org. Chem.* **1989**, *54*, 4229−4231.

(76) For a brief discussion concerning our decision to desilylate and resilylate the C16 hydroxyl group, please refer to the Supporting Information.

(77) (a) For pioneering work on the use of allylic carbonates for allylic alkylations under neutral conditions, see: Tsuji, J.; Shimizu, I.; Minami, I.; Ohashi, Y. *Tetrahedron Lett.* **1982**, *23*, 4809−4812. (b) For a review, see: Tsuji, J. *Tetrahedron* **1986**, *42*, 4361−4401. (c) For an example of a macrocyclization of an allylic carbonate/β-keto ester, see: Jones, P.; Pattenden, G. *Synlett* **1997**, 398−400.

Scheme 10. Completion of the Synthesis of (+)-FR182877 via a Double Transannular Diels–Alder Reaction[a]



[a] (a) KHMDS, PhSeBr, THF, −10 °C, 91%, 3:1 dr. (b) *m*CPBA, CH_2Cl_2, −78 °C. (c) $NaHCO_3$, $CHCl_3$, 40 °C, 4 h, 40% over two steps. (d) PPTS, MeOH, 23 °C. (e) TFA/CH_2Cl_2 (1:9), 0 → 23 °C. (f) EDC, DMAP, CH_2Cl_2, 23 °C, 62% over three steps. Yields reported in this scheme may vary slightly from those reported in the Supporting Information, which describes the large-scale synthesis of the enantiomeric series of these intermediates.

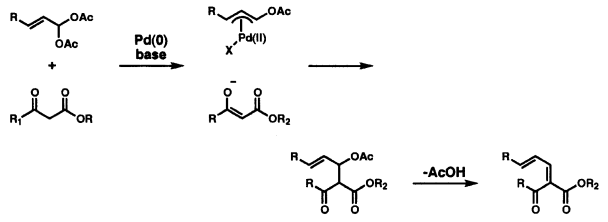
of diastereoisomeric selenides **60** in high yield (Scheme 10). Initial small-scale oxidative deselenenylations with biphasic aqueous H_2O_2 and dichloromethane at 0 °C successfully afforded an approximately equimolar crude mixture of olefin geometrical isomers, **61*E*** and **61*Z*** (not shown); however, the reproducibility of this transformation suffered greatly on scales above a few milligrams. The use of 1 equiv of *m*CPBA in dichloromethane at −78 °C proved much more reliable upon scale-up, and the same equimolar and inseparable olefin mixture was obtained in this fashion.[80] Attempts to isolate the individual geometrical isomers were precluded by the high reactivity of these macrocyclic pentaenes. Transannular cycloaddition reactivity was observed at ambient temperature, and these processes were accelerated upon contact with silica gel. On standing in a chloroform solution buffered with solid sodium bicarbonate at ambient temperature, complete conversion of the isomeric pentaenes to three major products was observed over the course of 24 h. More conveniently, the mixture could be warmed to 40 °C for 4 h to achieve the same result. The major product of this two-step oxidative deselenenylation-cycloaddition process was pentacycle **62**, a compound bearing the same diastereorelationships as the natural product FR182877. This stereochemically complex structure is formed in 40% yield over the two steps and is the product of a facile double transannular Diels–Alder process, in which seven new stereogenic centers are formed with high control. The two byproducts, which make up the majority of the mass balance, are presumably formed from the *Z* isomer of the pentaene (see below).

To complete the synthesis, the three silyl ethers in **62** were methanolyzed under mild acidic conditions and the *tert*-butyl ester was cleaved with trifluoroacetic acid in dichloromethane. Cleavage of all four protecting groups in one operation with TFA was possible, but led to penultimate triol carboxylic acid of lower purity. Finally, an EDCI-mediated lactonization delivered (+)-FR182877 [(+)-**1**] in 62% yield over the last three steps. The white solid thus produced exhibited spectral characteristics that were identical to those reported for the natural product, with the exception of its specific rotation. The sign was opposite and magnitude slightly higher[81] than that reported by the Fujisawa researchers, indicating that the originally disclosed stereostructure of FR182877[6] was incorrect, a finding that was later corroborated by a revision of absolute stereochemistry[13] published just after the completion of our synthesis. This finding is of biosynthetic interest as it demonstrates that FR182877 and hexacyclinic acid are closely related with respect not only to constitution, but also to absolute stereochemistry.

6. Optimization of the Sequence for a Large-Scale Synthesis of Natural FR182877. With a successful synthesis of the enantiomer of the natural product completed and a desire to enter into collaborative endeavors regarding the mechanism of action of this fascinating natural product, we chose to optimize our synthesis to produce significant quantities of natural (−)-FR182877. The major limitations of our approach were a loss of at least half of our material to the undesired *Z* isomer in the selenium-based desaturation process, and a somewhat capricious final lactonization step. Even with these exceptions, we felt that our route still had excellent potential to afford large quantities of FR182877.

By chemistry completely analogous to that depicted in Scheme 8, the enantiomer of stannane **47** was produced on large scale. This route was found to be highly efficient and reproducible (Scheme 11), as 60 g of dienyl stannane *ent*-**47** were synthesized in one run over nine steps and in 45–50% overall yield. Its Stille coupling partner, allylic acetate *ent*-**55**, was also conveniently available in three steps and 87% overall yield from the known geranyl acetate-derived aldehyde, and 47 g of this substrate were accessed in one run. The convergent Stille coupling[82] also proved robust; indeed, a single reaction afforded 65 g of the desired tetraene *ent*-**56**. The previously established

(78) We were mindful that the use of an allylic carboxylate or carbonate at a higher oxidation state (for example, a geminal bis-acetate at C1), might lead to a macrocycle with a β-leaving group that could be easily eliminated to afford directly the Knoevenagel-type product. See: Trost, B. M.; Vercauteren, J. *Tetrahedron Lett*. **1985**, *63*, 131–134.



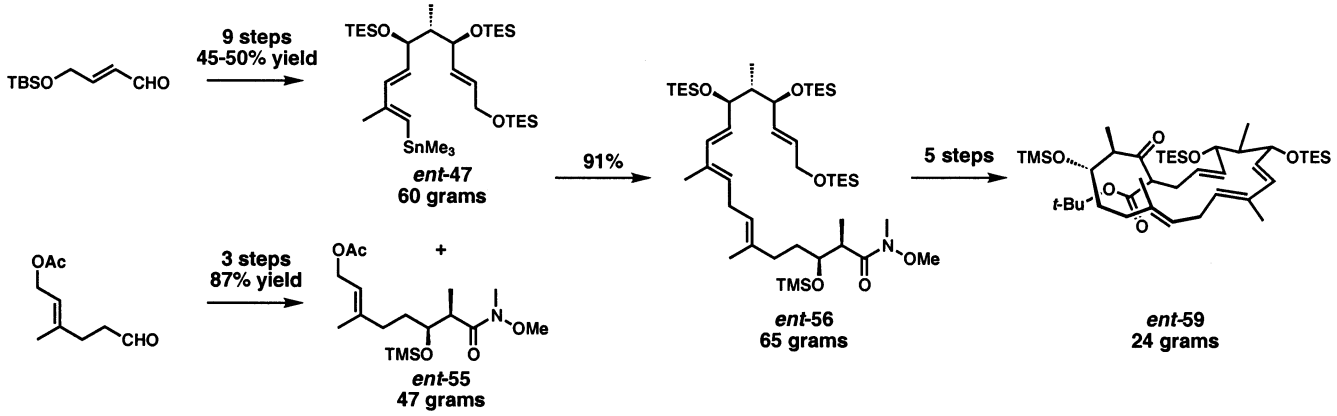
However, the conditions recommended for aldehyde to bis-acetate conversion were too harsh for our substrate. A very recent report of palladium π-allyl generation from dimethyl acetals of unsaturated aldehydes and their reaction with malonate derivatives to generate formal Knoevenagel products may warrant further investigation of this strategy using acetals of our enal. See: Mikami, K.; Ohmura, H. *Org. Lett.* **2002**, *4*, 3355–3357.

(79) (a) Sharpless, K. B.; Lauer, R. F. *J. Am. Chem. Soc*. **1973**, *95*, 2697–2699. (b) Reich, H. J.; Reich, I. L.; Renga, J. M. *J. Am. Chem. Soc*. **1973**, *95*, 5813–5815. (c) Nicolaou, K. C.; Petasis, N. A. *Selenium in Natural Products Synthesis*; CIS, Inc.: Philadelphia, 1984.

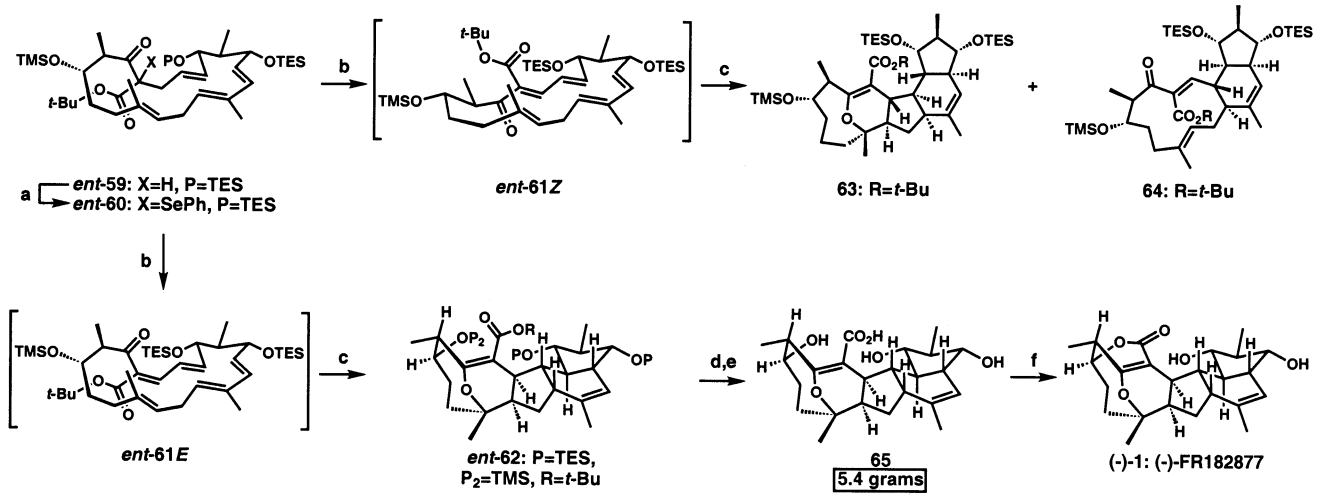
(80) Attempts to directly introduce a phenylseleninyl group (with subsequent elimination) using benzeneseleninyl chloride was never successful. For examples, see: (a) Reich, H. J.; Renga, J. M.; Reich, I. L. *J. Am. Chem. Soc*. **1975**, *97*, 5434–5447. (b) Smith, A. B.; Sestelo, J. P.; Dormer, P. G. *Heterocycles* **2000**, *52*, 1315–1328. The use of benzeneseleninic anhydride did lead to productive reactivity, but the conditions required for desaturation led to partial deprotection of the substrate/products, making isolation very difficult. For the use of benzeneseleninic anhydride to introduce unsaturation, see: Ouellet, L.; Langlois, P.; Deslongchamps, P. *Synlett* **1997**, 689–690 and references therein. The Evans synthesis of FR182877 made use of phenylseleninic anhydride on a much less acid-labile substrate. See ref 12.

(81) We observed a specific rotation of $[\alpha]^{23}_D = +5.7$ ($c = 0.67$, MeOH) for our synthetic (+)-FR182877. The specific rotation reported by the Fujisawa group in ref 6b was $[\alpha]^{23}_D = -3.5$ ($c = 1.0$, MeOH). Evans and Starr reported $[\alpha]^{23}_D = -5$ ($c = 0.15$, MeOH) for their synthetic (−)-FR182877 in ref 12.

Scheme 11. Large-Scale Synthesis of 19-Membered Macrocycle *ent*-**59**



Scheme 12. Completion of the Large-Scale Synthesis of (−)-FR182877[a]



[a] (a) NaHMDS, PhSeBr, <1 min, 23 °C, 89%, 10:1 dr. (b) *m*CPBA, CH_2Cl_2, −78 °C. (c) $NaHCO_3$, $CHCl_3$, 45 °C, 4 h, 61−66% of *ent*-**62** over two steps (8−15% each of **63** and **64** also isolated). (d) PPTS, MeOH, 0 → 23 °C, 100%. (e) TFA/CH_2Cl_2 (1:9), 0 → 23 °C, 96%. (f) *N*-methyl-2-chloropyridinium iodide, Et_3N, CH_2Cl_2/MeCN (9:1), 23 °C, 60% + 21% recovered starting material.

procedures for converting the Stille product to the macrocyclization precursor were easily adapted to large scales, and even the Trost−Tsuji ring closure proceeded smoothly in a good yield. Interestingly, our initial concerns about performing such a macrocyclization on large scale under high dilution conditions were unwarranted, as this reaction cleanly afforded the desired 19-membered ring in 60% yield at the relatively high concentration of 0.05 M, allowing for the production of 24 g of tetraene *ent*-**59** in only 1 L of solvent.

We were next faced with the task of improving the overall sequence of desaturation and double transannular Diels−Alder reactions. The first hint that this process may be made more efficient came with the observation that the separated phenylselenide diastereoisomers afforded, to no great surprise, a different ratio of geometrically isomeric olefin products on exposure to *m*CPBA. In fact, the major component of the 3:1 mixture of selenides afforded an olefin mixture enriched in the undesired *Z* isomer *ent*-**61*Z*** (Scheme 12). The minor diastereoisomer delivered *ent*-**61*E*** preferentially in a 2.3:1 ratio. Clearly there is a nonlinear correlation between selenide diastereomeric ratio and olefin geometric composition, but this is not so surprising given that the oxidation process is likely to afford phenylselenoxides that are diastereoisomeric at selenium. The elimination step then allows for the abstraction of either of two β hydrogens, the choice of which likely depends on a complex interplay between phenylselenoxide diastereoisomerism and subtle macrocyclic conformational dynamics. What we had learned, however, was that if phenylselenenylation conditions could be devised in which the currently minor diastereoisomer could be produced preferentially, we might be able to obtain at least two-thirds of the olefin mass balance as the desired *E* olefin. It is important to mention at this point that no effort was made to elucidate the structure of the isomeric selenides, since it was apparent that with all of the variables involved in the oxidative elimination step, and the inability to characterize the intermediate selenoxides (elimination occurs well below 0 °C), little useful information would result. Rather, we searched for an empirical solution to the problem.

One of our early experiments involved conducting the selenenylation at −78 °C. We observed an 8:1 ratio of diastereoisomers, further favoring the isomer that would lead preferentially to the undesired olefin geometry. Interestingly, a significant alteration of product composition could be achieved simply by decreasing the temperature from −10 to −78 °C (Table 1). We next examined the reaction at ambient temper-

(82) For a discussion of alternative organometallic coupling methods that were explored to obviate the use of large quantities of trimethyltin derivatives, please see the Supporting Information.

Table 1. Some Representative Selenenylation Diastereoisomer Ratios, and the Resulting Olefin Geometric Ratios

selenenylation conditions	selenide dr	*ent*-61 *E*:*Z*
KHMDS, THF, −78 °C	8:1	1:2
KHMDS, THF, −10 °C	3:1	
KHMDS, THF, 23 °C	1:3	
NaHMDS, Et_2O, 23 °C	1:10	2.2:1

ature, and to our delight, the other organoselenide diastereoisomer became the major component of a 3:1 mixture. Further optimization of base and solvent (Table 1) led to a reproducible reaction in which the ratio was further increased to 10:1, and the mixture could be isolated in 89% yield, even on large scale. The crucial observation that this selenenylation reaction appears to be reversible at ambient temperature led to an optimized procedure in which an ethereal solution of phenylselenenyl bromide is added rapidly (over less than 1 min) to a solution of the stabilized enolate in ether at ambient temperature, and the reaction is quenched after a further 30 s to afford the favorable ratio of products. Prolonged reaction times led to a rapid deterioration in ratio, such that after 15 min at ambient temperature, the initial 10:1 ratio had reversed to 1:3, which appeared to be the steady state or thermodynamic ratio under these conditions, as it did not change significantly if left longer. Conceivably, the reaction product could be reduced to the stabilized enolate by bromide ion in the reverse reaction, although it is also possible that excess hexamethyldisilazide causes the reductive deselenenylation.[83,84]

With the availability of this 10:1 mixture of selenide epimers, the subsequent oxidative deselenenylation−cycloaddition chemistry could be examined. The 2.2:1 *E*:*Z* ratio of olefins obtained on treatment of the selenides with *m*CPBA smoothly converted to a mixture of three cycloadducts (Scheme 12). The major component was the desired pentacycle *ent*-**62**. In this case, the key cycloadduct was isolated in 66% yield, suggesting that *ent*-**61*E*** is transformed with high fidelity to the pentacycle required for a synthesis of (−)-FR182877. Indeed, if it is assumed that the *E* isomer composes 69% of the crude olefin mixture, then *ent*-**61*E*** must yield *ent*-**62** with high diastereocontrol in nearly quantitative yield. Scale-up of this process afforded a 61% yield of *ent*-**62**, delivering nearly 10 g of this complex pentacycle in a single reaction sequence. The two other cycloadducts **63** and **64**, each isolated in 8−15% yield, account for the bulk of the mass balance. As expected, they both derive from the *Z* olefin isomer *ent*-**61*Z***, and their structures were elucidated by 2D-ROESY experiments on the desilylated compounds. Pentacycle **63** is the product of carbocyclic transannular cycloaddition in the *endo* mode opposite from that which is operative in the reaction of the *E* isomer, followed by a transannular hetero Diels−Alder reaction of the enone 4-π system. Of more interest, the tricyclic product **64** derives from a carbocyclic transannular Diels−Alder reaction through an *exo* transition state, and contains a hydrindene bearing identical diastereorelationships to those found in hexacyclinic acid.

(83) We have found instances in which monobrominated phosphonoacetates such as **33** (Schemes 5 and 6) and **51** (Scheme 8) can be reductively debrominated by sodium hexamethyldisilazide, presumably with the formation of the resulting *N*-brominated species. It might be possible that a similar reductive deselenenylation to form the stabilized anion is operative in this case.

(84) For a discussion of a TLC-based screen for diastereoselectivity in the introduction of the phenylselenyl group, please see the Supporting Information.

The production of natural FR182877 was completed as before by methanolysis of the three silyl ethers and acid-induced cleavage of the *tert*-butyl ester group to afford **65**, followed by a final lactonization. The EDCI-mediated lactonization procedure that was utilized to fashion (+)-FR182877 proved to be unreliable on scales above 10 mg. Mukaiyama's reagent[85] with triethylamine provided the most reproducible conditions for this final bond formation after a screening of several commonly used esterification processes. The methods tested included the Yamaguchi protocol,[86] Keck's DMAP·HCl/DCC conditions,[87] pyridyl thioester technology,[88] and BOP-Cl-mediated[89] lactonization. Subjection of the triol carboxylic acid **65** to 10 equiv each of *N*-methyl-2-chloropyridinium iodide and triethylamine in 9:1 dichloromethane/acetonitrile (0.05 M) afforded (−)-FR182877 [(−)-**1**] in 60% yield, along with 21% recovered starting material. Yields were lower and variable when the acetonitrile cosolvent was omitted, presumably due to the limited solubility of both the reagent and the triol carboxylic acid in dichloromethane. The natural enantiomer thus produced exhibited a specific rotation of the same sign, but of slightly higher magnitude than that originally reported by the Fujisawa researchers.

At this stage, ca. 100 mg of the natural FR182877 has been synthesized, as we have found, consistent with reports by the Fujisawa group,[6d] that the natural product is not stable to long-term storage. Our practice has been to store our material in the form of the stable triol carboxylic acid, ready for conversion to the natural product when required for collaborative investigation. In the manner just described, 5.4 g of the triol carboxylic acid has been produced.

The high diastereoselectivity and efficiency of the key tandem transannular Diels−Alder sequence described above and the mildness of the conditions required to induce it have led us to believe that we may have uncovered a biogenetically relevant process leading to the synthesis of FR182877. *Perhaps the most striking aspect of this process is that polyunsaturated macrocycles such as **6** (Scheme 1) and ent-**61E** (Scheme 12) contain essentially all of the molecular information needed to produce the architecturally and stereochemically complex structure of FR182877.* We remain curious as to what biosynthetic steps may be used to convert an acyclic polyketide precursor related to **2** into a macrocarbocyclic cycloaddition precursor such as **6** (or their enantiomers, see Scheme 1). As far as we are aware, polyketide synthases, while adept at forming macrolactone

(85) Mukaiyama, T.; Usui, M.; Saigo, K. *Chem. Lett.* **1976**, 49−50. Evans and Starr also made use of Mukaiyama's reagent for the final lactonization step. See ref 12.

(86) Inanaga, J.; Hirata, K.; Saeki, H.; Katsuki, T.; Yamaguchi, M. *Bull. Chem. Soc. Jpn.* **1979**, *52*, 1989−1993. For a recent application of this method for the formation of a δ-lactone, see: Kadota, I.; Kadowaki, C.; Takamura, H.; Yamamoto, Y. *Tetrahedron Lett.* **2001**, *42*, 6199−6202.

(87) Boden, E. P.; Keck, G. E. *J. Org. Chem.* **1985**, *50*, 2394−2395. Carbodiimide-mediated lactonizations of the triol carboxylic acid were plagued by the formation of variable amounts of the corresponding *N*-acylurea. We had hoped that Keck's solution to this problem in a macrocyclization context might transfer well to this situation.

(88) Corey, E. J.; Nicolaou, K. C. *J. Am. Chem. Soc.* **1974**, *96*, 5614−5616. For selected applications of this method for the formation of δ-lactones, see: (a) Pougny, J.-R.; Rollin, P.; Sinay, P. *Tetrahedron Lett.* **1982**, *23*, 4929−4932. (b) Ho, P.-T.; Wong, S. *Can. J. Chem.* **1985**, *63*, 2221−2224.

(89) Diago-Meseguer, J.; Palomo-Coll, A. L.; Fernández-Lizarbe, J. R.; Zugaza-Bilbao, A. *Synthesis* **1980**, 547−551. For a context in which BOP-Cl outperformed other lactonization methods for the formation of strained *trans*-fused γ-lactones, see: Strekowski, L.; Visnick, M.; Battiste, M. A. *Synthesis* **1983**, 493−494. For an application to δ-lactone synthesis, see: Miyaoki, H.; Isaji, Y.; Kajiwara, Y.; Kunimune, I.; Yamada, Y. *Tetrahedron Lett.* **1998**, *39*, 6503−6506.

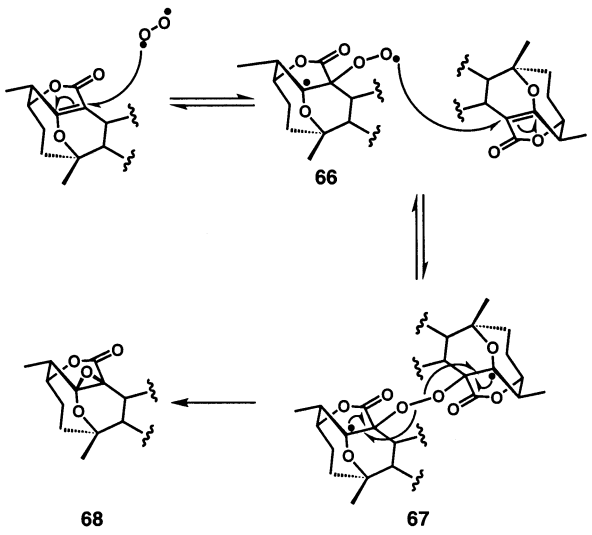


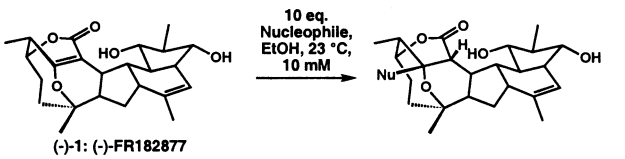
Figure 3. Proposed mechanism for the oxidation of FR182877.

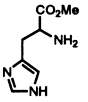
structures,[90] are not known to mediate large-ring condensation reactions to form new carbon−carbon bonds. As a result of our success with this transannular cycloaddition approach to FR182877, we also surmise that a variant of this approach may ultimately prove most effective in the synthesis of the related cochleamycins[26] and macquarimicins.[27]

7. A Study of the Reactivity of the Strained Olefin of FR182877. In their initial publication,[6d] the Fujisawa scientists described that FR182877 is epoxidized in a concentration-dependent manner when stored in solution. Aside from the concentration dependence, they also observed that this oxidation was likely caused by molecular oxygen, as degassed solutions of the natural product were significantly more stable. These observations imply a mechanism analogous to that disclosed by Lease and Shea,[91] who discovered that strained bridgehead olefins that they had produced in the course of studies on the intramolecular type II Diels−Alder reaction underwent similar concentration dependent oxidations. A plausible mechanism, corresponding to that described by Shea, is depicted in Figure 3. Molecular oxygen could add reversibly to the strained olefin with relief of strain to form the tertiary, oxygen-stabilized radical **66**. In concentrated solution, the resulting peroxyradical could add, in a similar manner, to a second molecule of FR182877. Irreversible collapse of diradical **67** then would afford two molecules of FR182877 epoxide **68**. Interestingly, the oxidized natural product is much less active in tubulin-binding assays and is not significantly cytotoxic.[6d] It is thus possible that the strained olefin of FR182877 could be the site of reactivity if covalent processes are involved.

It was also observed that simple amines were taken up by the reactive alkene under neutral conditions, as were alcohols (presumably alkoxides) under basic conditions.[15] With a large supply of FR182877 in hand, we elected to study the reaction of its strained bridgehead double bond with a variety of nucleophiles.[92] Table 2 shows the results of our reactivity study,

Table 2. Reaction of FR182877 with representative nucleophiles[a]



Nucleophile	Reaction time	Product notes
	<1 hour	clean, isolated pure
	3 hours	clean, isolated pure
	3 hours	clean, isolated pure
	<1 hour	clean, inseparable from excess nucleophile
	<1 hour	mix of regioisomeric adducts on imidazole ring, inseparable from excess nucleophile
	<1 hour	clean thiol adduct, isolated pure
	<1 hour	clean, inseparable from excess nucleophile
	3 hours 48 hours	20% conversion incomplete reaction, >3 products
	>48 hours	no reaction
NaOEt	<1 hour	2 products, consistent with ethanol addition product and lactone ethanolysis product

[a] Unless otherwise indicated, all reactions proceeded cleanly and in essentially quantitative yield as judged by ^{1}H NMR analysis of the crude reaction mixtures.

which clearly indicate that this strained and reactive site cleanly reacts with amines, thiols, and even imidazole. It appears that the reaction is a process of simple addition driven by strain release; under the conditions of our study, no products of addition−elimination to regenerate an enoate and a nine-membered ring were observed. These experiments were performed by adding 10 equiv of nucleophile to a 10 mM solution of FR182877 in absolute ethanol. In the case of amino acid methyl ester hydrochlorides, an equimolar amount of triethylamine was added to neutralize the salt.

As the results in Table 2 demonstrate, alkylamines add cleanly and rapidly to the strained olefin, with propylamine reacting at a faster rate than that of the bulkier morpholine and the less nucleophilic glycine methyl ester. Imidazole proved to be an effective nucleophile, with rapid and quantitative reaction of both the parent heterocycle and histidine methyl ester, which afforded a mixture of regioisomeric adducts on its unsym-

(90) For a review on aliphatic polyketide biosynthesis that focuses on macrolactone antibiotics, see: Staunton, J.; Wilkinson, B. *Top. Curr. Chem.* **1998**, *195*, 49−92.

(91) (a) Lease, T. G.; Shea, K. J. *J. Am. Chem. Soc.* **1993**, *115*, 2248−2260. For reviews concerning the synthesis, structure, and reactivity of bridgehead alkenes, see: (b) Shea, K. J. *Tetrahedron* **1980**, *36*, 1683−1715. (c) Warner, P. M. *Chem. Rev.* **1989**, *89*, 1067−1093.

(92) For a recent study of the reaction of an electrophilic natural product pharmacophore with biologically relevant nucleophiles, see: Sakakura, A.; Takayanagi, Y.; Kigoshi, H. *Tetrahedron Lett.* **2002**, *43*, 6055−6058.

metrical imidazole ring. As anticipated, thiols also proved to be effective, as cysteine methyl ester and 2-mercaptopyridine cleanly and rapidly afforded the products of sulfur addition. Benzyl mercaptan, however, proved to be quite sluggish, with a mixture of products formed in an incomplete reaction after long reaction times. Aniline did not react at all with FR182877 after 48 h. Finally, sodium ethoxide was observed to react quickly with FR182877, affording two products whose spectral data are consistent with an ethanol addition product and a lactone ethanolysis product. Complex mixtures of products arose from the reaction of FR182877 with sodium phenoxide, benzenethiol, sodium azide, sodium cyanide, and adenosine. Reaction of the natural product with reduced glutathione did not occur, likely due to its insolubility in our standard reaction solvent.

Conclusions and Future Studies

In summary, an efficient and scalable synthesis of both enantiomeric forms of the cytotoxic natural product FR182877 has been developed. Our synthesis proceeds by way of two key organometallic π-allyl-mediated carbon−carbon bond constructions that set the stage for the first reported example of a double transannular Diels−Alder reaction. This tandem process produces a complex pentacycle from a single 19-membered macrocyclic pentaene, forming in one step four new bonds and seven stereocenters with high control. We believe that this successful, potentially biomimetic route provides a chemical rationalization of the complex molecular structure of FR182877. This route has made available large quantities of the natural enantiomer, and we have begun explorations into the reactivity of its strained alkene. This study demonstrated the high reactivity of FR182877 with biologically relevant nucleophiles. We are currently pursuing other studies on the reactivity of FR182877 in biological systems, with the ultimate goal of understanding in greater detail its mechanism of cytotoxicity. The studies described herein indicate that FR182877 is the type of molecular structure that has an intrinsic capacity to form itself from a much less complex polyunsaturated precursor. The architectural self-construction process uncovered in the course of this synthesis is the foundation of current efforts to develop a chemical approach to the problem of creating polyketide diversity.[93,94]

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Supporting Information Available: Experimental procedures and compound characterization, as well as certain experimental details, observations, and conclusions (PDF). X-ray crystallographic file (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

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(93) For representative reports of chemical approaches to polyketide diversity, see: (a) Reggelin, M.; Brenig, V. *Tetrahedron Lett.* **1996**, *37*, 6851−6852. (b) Paterson, I.; Scott, J. P. *Tetrahedron Lett.* **1997**, *38*, 7441−7444. (c) Paterson, I.; Scott, J. P. *Tetrahedron Lett.* **1997**, *38*, 7445−7448. (d) Gennari, C.; Ceccarelli, S.; Piarulli, U.; Aboutayab, K.; Donghi, M.; Paterson, I. *Tetrahedron* **1998**, *54*, 14999-15016. (e) Reggelin, M.; Brenig, V.; Welcker, R. *Tetrahedron Lett.* **1998**, *39*, 4801−4804. (f) Paterson, I.; Scott, J. P. *J. Chem. Soc., Perkin Trans. 1* **1999**, 1003−1014. (g) Paterson, I.; Donghi, M.; Gerlach, K. *Angew. Chem., Int. Ed.* **2000**, *39*, 3315−3319. (h) Harrison, B.; Verdine, G. *Org. Lett.* **2001**, *3*, 2157−2159. (i) Paterson, I.; Temal-Laieb, T. *Org. Lett.* **2002**, *4*, 2473−2476.

(94) For recent reviews of biosynthetic engineering approaches to polyketide diversity, see: (a) Khosla, C. *Chem. Rev.* **1997**, *97*, 2577−2590. (b) Khosla, C. *Chemtracts* **1998**, *11*, 1−15. (c) Khosla, C. In *Combinatorial Chemistry and Molecular Diversity in Drug Discovery*; Gordon, E. M., Kerwin, J. F., Jr., Eds.; Wiley-Liss: New York, 1998, pp 401−417. (d) Cane, D. E.; Walsh, C. T.; Khosla, C. *Science* **1998**, *282*, 63−68. (e) Khosla, C. *Bioprocess Technology* **1999**, *24*, 203−225.