Synthesis and Absolute Stereochemical Assignment of (+)-Miyakolide

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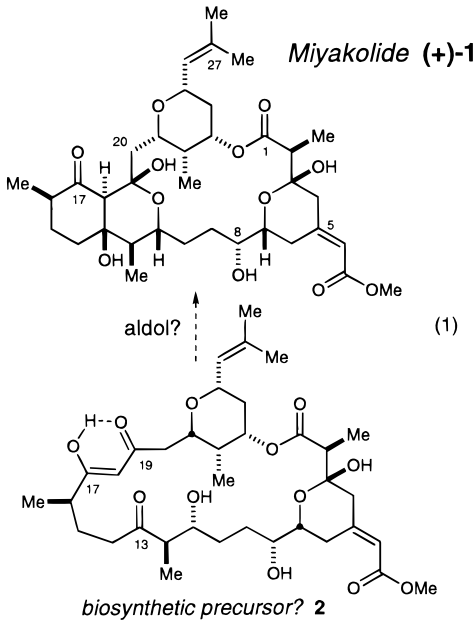
Abstract: The first total synthesis of the marine macrolide miyakolide has been achieved, and its absolute stereochemistry has been determined. The carbon skeleton is assembled in a convergent fashion from three fragments via esterification, [3 + 2] dipolar cycloaddition, and aldol addition. The utility of β-ketoimide aldol reactions in fragment coupling was demonstrated on fully elaborated intermediates. The coupled material was transformed into a 1,3,7-triketone-containing macrocycle that underwent a facile transannular aldol reaction followed by hemiketalization to form the oxydecalin ring system of the natural product. Deprotection afforded *ent*-miyakolide, which was produced in 6.8% overall yield and 29 linear steps.

The architecture of natural products has long provided the stimulus for the development of new reactions.[1] Similarly, postulated biosynthetic pathways to natural products have focused attention on the laboratory simulation of these pivotal events.[2,3] We viewed miyakolide (**1**) as an ideal synthetic target for these reasons (vide infra). Miyakolide was isolated in 1992 from a sponge of the genus *Polyfibrospongia* by Higa and coworkers.[4] Its relative stereochemistry was assigned by X-ray crystallography and supported by detailed NMR spectroscopic studies. Structurally, miyakolide displays a number of features seen in several bioactive marine macrolides. The C_1-C_3 β-hemiketal ester/acid functionality is shared by natural products such as aplasmomycin,[5] aplysiatoxin,[6] callipeltoside A,[7] and lonomycin A,[8] while the C_5 exocyclic unsaturated ester is a structural element also found in the bryostatin class of natural products.[9]

Synthesis Plan.[10] The premise underlying the synthesis plan rested on the presumption that the $C_{11}-C_{19}$ oxydecalin subunit in miyakolide might be assembled spontaneously through an intramolecular aldol reaction (eq 1). If miyakolide is biosynthesized according to the standard polyketide model, an iterative linear chain of subunits would be assembled, followed by macrolactonization, cyclizations, and rearrangements.[11] If mac-



(1) (a) Seebach, D. *Angew. Chem., Int. Ed. Engl.* **1990**, *29*, 1320−1367. (b) Ireland, R. E. *Aldrichim. Acta* **1988**, *21*, 59−69. (c) Norcross, R. D.; Paterson, I. *Chem. Rev.* **1995**, *95*, 2041−2114.

(2) Synthesis has been used as a tool to produce isotopically labeled putative biosynthetic intermediates that are fed to the producing plant or animal in order to study their incorporation into the biosynthetic pathway. Some recent examples in the field of polyketide biosynthesis include: (a) Cane, D. E.; Luo, G. *J. Am. Chem. Soc.* **1995**, *117*, 6633−6634. (b) Yue, S.; Duncan, J. S.; Yamamoto, Y.; Hutchinson, C. R. *J. Am. Chem. Soc.* **1987**, *109*, 1253−1254.

(3) Proposed biosynthetic transformations have been reproduced in laboratory syntheses of natural products in order to test their practicality outside of the biological system and take advantage of the powerful transformations. Some examples include: (a) Johnson, W. S.; Gravestock, M. B.; McCarry, B. E. *J. Am. Chem. Soc.* **1971**, *93*, 4332−4334. (b) Gravestock, M. B.; Johnson, W. S.; McCarry, B. E.; Parry, R. J.; Ratcliffe, B. E. *J. Am. Chem. Soc.* **1978**, *100*, 4274−4282. (c) Chapman, O. L.; Engel, M. R.; Springer, J. P.; Clardy, J. C. *J. Am. Chem. Soc.* **1971**, *93*, 6696−6698. (d) Nicolaou, K. C.; Petasis, N. A.; Zipkin, R. E. *J. Am. Chem. Soc.* **1982**, *104*, 5560−5562. (e) Evans, D. A.; Ratz, A. M.; Huff, B. E.; Sheppard, G. S. *J. Am. Chem. Soc.* **1995**, *117*, 3448−3467. (f) Williams, D. R.; Coleman, P. J.; Henry, S. S. *J. Am. Chem. Soc.* **1993**, *115*, 11654−11655.

(4) Higa, T.; Tanaka, J.; Komesu, M.; Gravalos, D. C.; Puentes, J. L. F.; Bernardinelli, G.; Jefford, C. W. *J. Am. Chem. Soc.* **1992**, *114*, 7587−7588.

(5) Okazaki, T.; Kitahara, T.; Okami, Y. *J. Antibiot.* **1976**, *29*, 1019−1025.

(6) Mynderse, J. S.; Moore, R. E. *J. Org. Chem.* **1978**, *43*, 2301−2303.

(7) Zampella, A.; D'Auria, M. D.; Minale L.; Debitus, C.; Roussakis, C. *J. Am. Chem. Soc.* **1996**, *118*, 11085−11088.

(8) (a) Otake, N.; Koenuma, M.; Miyamae, H.; Sato, S.; Saito, Y. *Tetrahedron Lett.* **1975**, 4147−4150. (b) Omura, S.; Shibata, M.; Machida, S.; Sawada, J.; Otake, N. *J. Antibiot.* **1976**, *29*, 15−20. (c) Riche, C.; Pascard-Billy, C. *J. Chem. Soc., Chem. Commun.* **1975**, 951−952.

(9) Petit, G. R.; Gao, F.; Sengupta, D.; Coll, J. C.; Herald, C. L.; Doubek, D. L.; Schmidt, J. M.; Van Camp, J. R.; Rudloe, J. J.; Nieman, R. A. *Tetrahedron* **1991**, *47*, 3601−3610.

(10) Progress toward the total synthesis of miyakolide has been reported: Yoshimitsu, T.; Song, J. J.; Wang, G.-Q.; Masamune, S. *J. Org. Chem.* **1997**, *62*, 8978−8979.

10.1021/ja990789h CCC: $18.00
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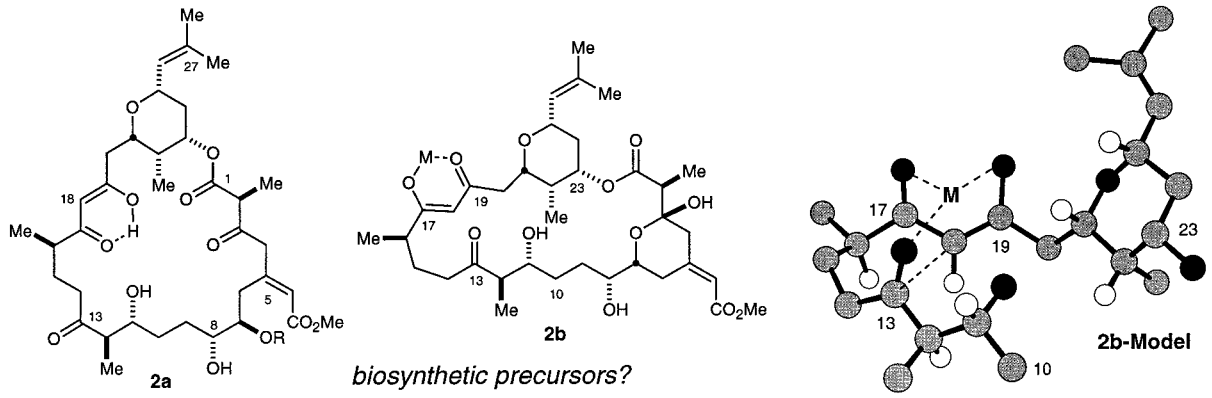


Figure 1. Proposed miyakolide biosynthetic precursors **2a** and **2b**. The **2b-Model** structure, less the metal ion M, minimized using the AMBER forcefield.[13] C1−C9 and C_{21}−C_{27} not shown.

rolactonization indeed precedes the indicated intramolecular aldol construction, macrocyclic precursors such as **2** (Figure 1) could well be found along the biosynthetic pathway. If this reaction is to be integrated into a synthesis plan, the desired aldol adduct constitutes one of four possible product diastereomers, and while this process might be enzymatically mediated, it could also be simply controlled by the conformation of the macrocycle.[3ef,12,13] In implementing this strategy, it was felt that macrocycle **2b** might provide more conformational ordering in the aldol step than its ring-chain tautomer **2a**. To assess the probability that the desired aldol macrocyclic stereocontrol might be possible in **2b**, a multiconformational search of the crucial enol ketone intermediate was undertaken using the AMBER force field, restricting the C_{18}−C_{13} atom distance to a maximum of 4.5 Å.[14] Figure 1 depicts the lowest energy structure generated by this search, wherein the C_{18} and C_{13} diastereofaces are disposed to deliver the desired stereochemistry following an intramolecular aldol reaction. While a generic metal ion, M, has been incorporated into the **2b-Model** illustration, this does not imply that the metal ion was part of the calculation. In this conformation, the chair transition state for the aldol addition is accessible. The other low-energy conformation of **2b**, differing by only 0.1 kcal/mol, presents the C_{17}−C_{19} (*si*) enol diastereoface opposite to that of the C_{13} carbonyl moiety; however, the resulting aldol reaction must proceed via a boat transition state.

Since a spontaneous transannular aldol addition was anticipated when the three carbonyl groups at C_{13}, C_{17}, and C_{19} were revealed, we felt it was important to also have the C_{11} alcohol in its unprotected state prior to this bond construction. The aldol adduct would thus undergo immediate hemiketalization, masking the C_{17}−C_{19} diketone moiety and suppressing elimination of the C_{13} hydroxyl moiety. We then elected to mask the C_{17}−C_{19} diketone as its derived isoxazole,[15] which might undergo spontaneous ring closure upon reduction of the N−O bond.[16] While two possible isoxazole structures were entertained, we chose to employ isoxazole **3** bearing nitrogen at C_{19} since the reduction product of **3** might be easily hydrolyzed with assistance of the C_{11} alcohol following the aldol reaction (Scheme 1).[17] In the event that the enaminone failed to participate in oxydecalin formation, this functionality might be hydrolyzed under conditions likely to effect the transannular aldol step.[18,19]

(11) For recent reviews on the biosynthesis of polyketides, see: (a) Cortes, J.; Haydock, S. F.; Roberts, G. A.; Bevitt, D. J.; Leadlay, P. F. *Nature* **1990**, *348*, 176−178. (b) Donadio, S.; Staver, M. J.; McAlpine, J. B.; Swanson, S. J.; Katz, L. *Science* **1991**, *252*, 675−679. (c) Malpartida, F.; Hopwood, D. A. *Nature* **1984**, *309*, 462−464. (d) O'Hagan, D. *Nat. Prod. Rep.* **1995**, 1−33.

(12) Transannular reactions have been postulated in a number of biosynthetic pathways. The dolabellanes are postulated to be biosynthetically converted to the clavularanes and dolastanes via transannular ring-contracting reactions: (a) Look, S. A.; Fenical, W. *J. Org. Chem.* **1982**, *47*, 4129−4134. Dactylol is postulated to be biosynthesized from humulene, via a ring-contracting cationic olefin cyclization followed by cyclopropyl cation rearrangement and solvolysis: (b) Schmitz, F. J.; Hollenbeak, K. H.; Vanderah, D. J. *Tetrahedron* **1978**, *34*, 2719−2722. (c) Hayasaka, K.; Ohtsuka, T.; Shirahama, H. *Tetrahedron Lett.* **1985**, *26*, 873−876. The endiandric acids are postulated to be biosynthesized via a cascade of electrocyclic reactions, including a ring-contracting cyclization: (d) Bandaranayake, W. M.; Banfield, J. E.; Black, D. St. C. *J. Chem. Soc., Chem. Commun.* **1980**, 902−903.

(13) Macrocyclic conformation has been employed as a control element in synthesis in several instances: (a) Still, W. C.; Romero, A. G. *J. Am. Chem. Soc.* **1986**, *108*, 2105−2106. (b) Schreiber, S. L.; Sammakia, T.; Hulin, B.; Schulte, G. *J. Am. Chem. Soc.* **1986**, *108*, 2106−2108. (c) Vedejs, E.; Gapinski, D. M. *J. Am. Chem. Soc.* **1983**, *105*, 5058−5061. Macrocyclic ring contractions have been used with success to control diastereoselectivity of the contracted ring-forming reaction. (d) Myers, A. G.; Condroski, K. R. *J. Am. Chem. Soc.* **1993**, *115*, 7926−7927.

(14) All calculations were performed using the AMBER force field on structures generated by a Monte Carlo multiconformer search using MacroModel (Version 5.0) provided by Professor W. Clark Still, Columbia University. The dielectric coefficient (ELE) in the force field was set at 60 to simulate a polar solvent. Only structures with a C_{18} to C_{13} atom distance of 4.5 Å or less that were generated three or more times during the search (out of 150, 000 structures generated) were considered. The AMBER force field was selected because it generated a minimized structure of miyakolide that more closely fit the X-ray crystal structure than structures generated using the MM2 and MM3 force fields.

(15) For a review on the use of isoxazoles in synthesis, see: (a) Baraldi, P. G.; Barco, A.; Benetti, S.; Pollini, G. P.; Simoni, D. *Synthesis* **1987**, 857−869. (b) Little, R. D. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon Press: New York, 1991; Vol. 5 pp 239−270. (c) Torssell, K. B. G. *Nitrile Oxides, Nitrones, and Nitronates in Organic Synthesis*; VCH Publishers: New York, 1988. (d) Caramella, P.; Grunanger, P. In *1,3-Dipolar Cycloaddition Chemistry*; Padwa, A., Ed.; John Wiley & Sons: New York, 1984; Vol. 1, pp 291−392.

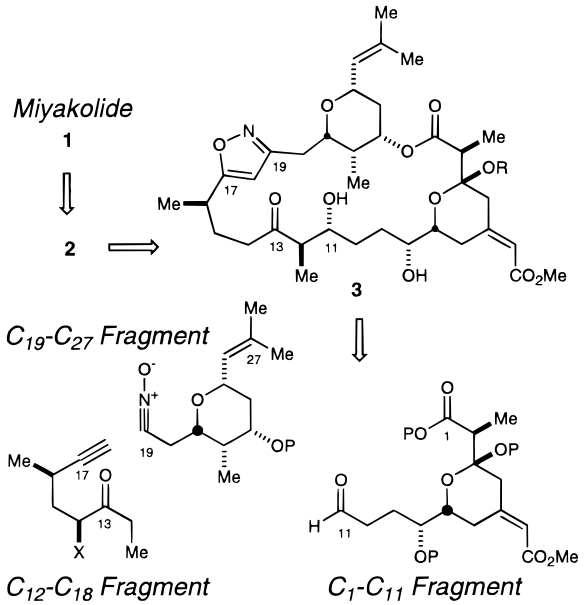
(16) Although deprotonation of an enaminone (NaOH) was required to promote an aldol reaction (Yuste, F.; Sanchez-Obregon, R. *J. Org. Chem.* **1982**, *47*, 3665−3668), we hoped that the intramolecularity of our transformation would force the reacting partners together and facilitate a reaction under milder conditions.

(17) The regioisomeric isoxazole containing nitrogen at C_{17} was deemed an inferior intermediate, as the aldol adduct would contain a C_{17} imine that could tautomerize, epimerizing the C_{16} stereocenter.

(18) (a) Kato, N.; Hamada, Y.; Shioiri, T. *Chem. Pharm. Bull.* **1984**, *32*, 1679−1682. (b) Eiden, F.; Patzelt, G. *Arch. Pharm. (Weinheim, Ger.)* **1986**, *319*, 242−251. (c) Auricchio, S.; Ricca, A.; DePava, O. V. *Gazz. Chim. Ital.* **1980**, *110*, 567−570. (d) Kobuke, Y.; Kokubo, K.; Munakata, M. *J. Am. Chem. Soc.* **1995**, *117*, 12751−12758. (e) Kashima, C.; Mukai, N.; Tsuda, Y. *Chem. Lett.* **1973**, 539−540.

(19) Mineral acids are most commonly employed to achieve this transformation (see ref 18), but model studies on 3-amino-5-oxo-1-phenyloct-3-ene demonstrated that this hydrolysis could be achieved under milder conditions such as 4:4:1 AcOH/THF/water; PPTS in THF/water; or CuX_2 (X = Cl, OTf, BF_4) and water in a variety of organic solvents.

Scheme 1

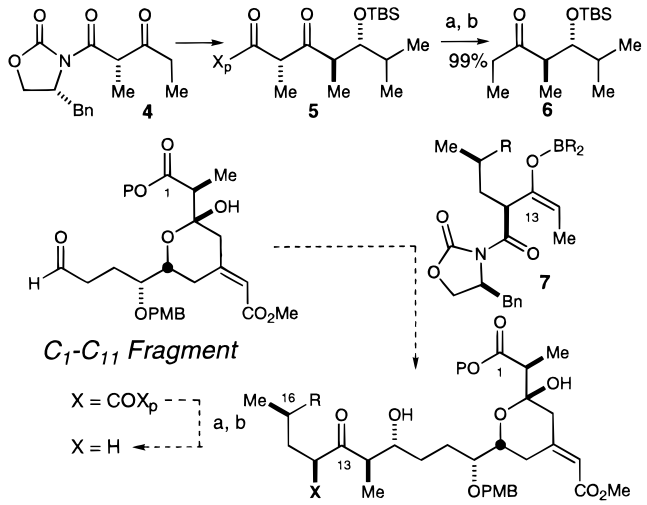


Isoxazole **3** was conveniently disconnected into three fragments via [3 + 2] dipolar cycloaddition, $C_{11}-C_{12}$ aldol addition, and esterification/lactonization transforms (Scheme 1). Of the three fragment coupling processes, the $C_{11}-C_{12}$ aldol addition was the most speculative. Neither the $C_{12}-C_{18}$ ketone fragment nor the C_1-C_{11} aldehyde bears a stereocenter sufficiently near the reacting centers to provide reasonable diastereocontrol during bond formation. Furthermore, regioselective enolization of the C_{13} ketone was problematic. Both of these issues were addressed through the incorporation of a removable substituent, X, at C_{14} that would serve both to direct enolization and to provide a stereochemical control element for the aldol reaction. The principal constraint on the selection of X was that it must be removed under mild conditions on a multifunctional intermediate. The solution to this stereochemical issue is summarized in Scheme 2.[20] Using methodology developed in conjunction with this project, syn and anti aldol adducts such as **5** are available in high yield and diastereoselectivity from β-ketoimide **4**.[21] Conditions were developed to effect the illustrated hydrolysis and decarboxylation of the (oxazolidinyl)carbonyl moiety (see **5** → **6**). The mild reaction conditions (thiolate transesterification of the imide followed by silver(I)-promoted hydrolysis of the thioester) provide rapid access to aldol adducts such as **6**. Accordingly, the C_{14} (oxazolidinyl)carbonyl auxiliary was employed as the chiral controller X.

Results and Discussion

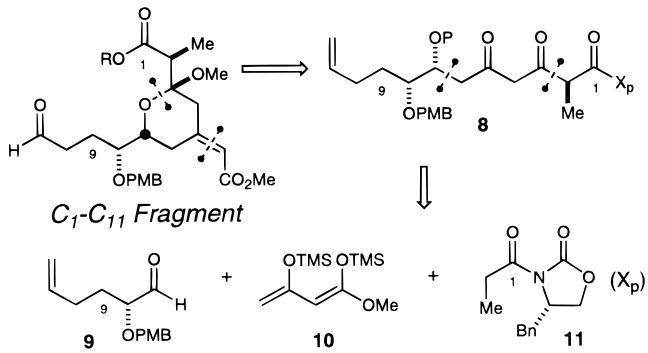
Synthesis of the C_1-C_{11} Subunit. The synthesis plan for the C_1-C_{11} fragment is illustrated below (Scheme 3). We chose to employ a fully elaborated synthon, despite the anticipated sensitivity of the β,γ-unsaturated lactol moiety, rather than risk late-stage manipulations on a complex, multifunctional system. This approach confers the advantage of reducing the number of orthogonal protecting groups required for masking the reactive functionalities. We envisioned installing the C_5 enoate using a Horner−Wadsworth−Emmons[22] or Peterson[23] reaction

Scheme 2



on the pyranone precursor, relying on the steric and electronic biases of the substrate for establishing the desired olefin geometry. Unraveling the ketal to the open-chain tautomer reveals keto alcohol **8**. Although the methyl-bearing stereocenter at C_2 is prone to epimerization, the kinetic lability of this functionality can be attenuated through the use of an oxazolidinone auxiliary at the carboxyl terminus.[21b,24] The 1,2-*syn*-diol relationship at C_7-C_8 suggests a chelate-controlled aldol addition of Chan's diene[25] (**10**) to aldehyde **9**.

Scheme 3



Addition of allylmagnesium bromide to (*S*)-*O*-trityl glycidol[26] (THF, 0 °C) cleanly afforded the expected alcohol, which was protected as the *p*-methoxybenzyl (PMB) ether **13** (Scheme 4). Deprotection of the primary trityl ether (HCl, 93%) followed by Swern oxidation[27] under controlled conditions (DMSO, $(COCl)_2$, −78 °C; *i*-Pr_2NEt, −30 °C)[28] afforded aldehyde **9** of sufficient purity for the subsequent aldol reaction. Complexation of this aldehyde with $TiCl_2(O\text{-}i\text{-}Pr)_2$ (−78 °C),[29] followed by

(20) Evans, D. A.; Ripin D. H. B.; Johnson, J. S.; Shaughnessy, E. A. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 2119−2121.

(21) (a) Evans, D. A.; Clark, J. S.; Metternich, R.; Novack, V. J.; Sheppard, G. S. *J. Am. Chem. Soc.* **1990**, *112*, 866−868. (b) Evans, D. A.; Ng, H. P.; Clark, J. S.; Rieger, D. L. *Tetrahedron* **1992**, 2127−2142.

(22) For a review, see: Boutagy, J.; Thomas, R. *Chem. Rev.* **1974**, *74*, 87−99.

(23) (a) Peterson, D. J. *J. Org. Chem.* **1968**, *33*, 780−784. (b) Shimoji, K.; Taguchi, H.; Oshima, K.; Yamamoto, H.; Nozaki, H. *J. Am. Chem. Soc.* **1974**, *96*, 1620−1621.

(24) A β-ketoimide has been employed in an analogous intramolecular ketalization without epimerization of the α-stereocenter in a synthesis of lonomycin (ref 3e).

(25) Brownbridge, P.; Chan, T. H.; Brook, M. A.; Kang, G. J. *Can. J. Chem.* **1983**, *61*, 688−693.

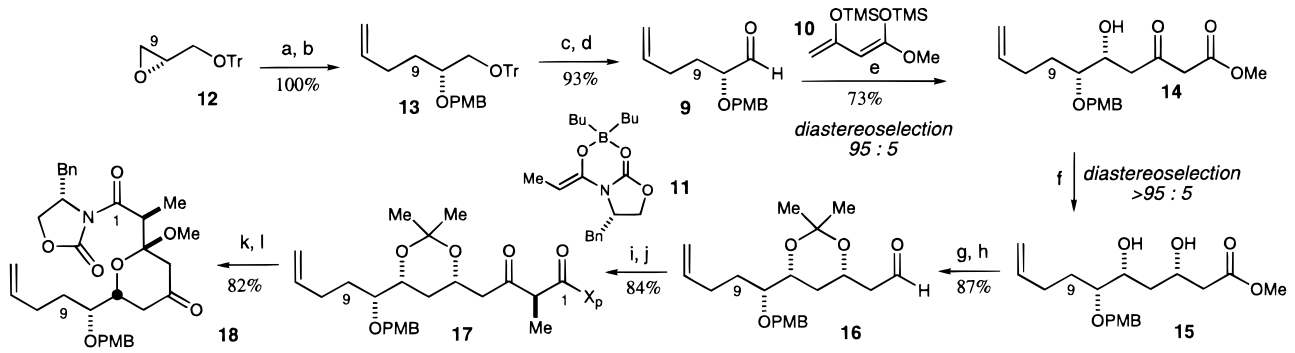
(26) Hendrickson, H. S.; Hendrickson, E. K. *Chem. Phys. Lipids* **1990**, *53*, 115−120.

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

(28) Evans, D. A.; Gage, J. R.; Leighton, J. L. *J. Am. Chem. Soc.* **1992**, *114*, 9434−9453.

(29) (a) Izawa, T.; Mukaiyama, T. *Chem. Lett.* **1978**, 409−412. (b) Hagiwara, H.; Kimura, K.; Uda, H. *J. Chem. Soc., Perkins Trans. 1* **1992**, 693−700.

Scheme 4[a]



[a] Key: (a) CH_2CHCH_2MgBr, THF, 0 °C; (b) NaH, PMBBr, DMF/THF; (c) HCl, MeOH/Et_2O, 0 °C; (d) $(COCl)_2$, DMSO, *i*-Pr_2NEt, −78 to −30 °C; (e) $TiCl_2(O\text{-}i\text{-}Pr)_2$, **10**, CH_2Cl_2, −78 to 0 °C; (f) Et_2BOMe, $NaBH_4$, THF/MeOH, −78 °C; (g) $Me_2C(OMe)_2$, HCl ; (h) DIBAL-H, CH_2Cl_2, −78 °C, then MeOH, −78 °C; (i) **11**, Bu_2BOTf, *i*-Pr_2NEt, CH_2Cl_2, 0 °C, then **16**, −78 °C; (j) $(COCl)_2$, DMSO, *i*-Pr_2NEt, −78 → 0 °C; (k) TsOH, MeCN/MeOH, −22 °C; (l) $(COCl)_2$, DMSO, Et_3N, −78→0 °C.

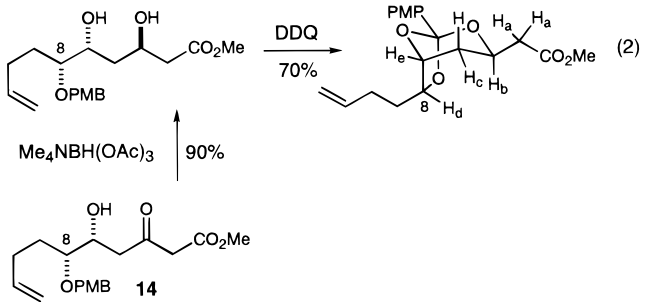
addition of Chan's diene **10** (−78→0 °C), with presumed chelate control, afforded ketoester **14** in 73% yield as an inseparable 20:1 mixture of isomers whose stereochemical proof will be described below (eq 2). Syn reduction of keto alcohol **14** (Et_2BOMe, $NaBH_4$)[30] cleanly produced *syn*-diol **15** as a >20:1 diastereomeric mixture in 99% yield.[31] The unpurified diol, protected as it derived acetonide, was treated with DIBAL-H (CH_2Cl_2, −78 °C)[32] to provide aldehyde **16** in 87% yield. Dibutylboron triflate-mediated aldol addition of (4*S*)-3-propionyl-4-benzyloxazolidinone (**11**) to aldehyde **16** proceeded in 84% yield to furnish the aldol adduct as a single diastereomer as determined by ^1H NMR spectroscopy.[33] Swern oxidation gave *β*-ketoimide **17** quantitatively. Cyclization of *β*-ketoimide **17** to the lactol methyl ether (TsOH, MeOH/MeCN, −22 °C) proceeded in 71% yield (82% after re-submission of recovered starting material).[24] Finally, oxidation of the C_5 alcohol to ketone **18** was accomplished quantitatively by the Swern procedure.[27]

The syn stereochemistry of the aldol addition step (**9** → **14**) was confirmed by conversion to the illustrated bicyclic ortho ester derivative (eq 2). Anti reduction of keto alcohol **14** with $Me_4NBH(OAc)_3$[34] (10:1 diastereoselectivity, 90%) followed by DDQ oxidation (70%)[35] afforded the illustrated ortho ester. NMR spectroscopic analysis of this ortho ester confirmed that the desired stereochemical relationships had been established (Table 1) and the addition process had indeed been chelate controlled.

A number of strategies were investigated to stereoselectively incorporate the C_5 enoate (**18** → **19-E**) (eq 3, Table 2). Conversion of **18** to exocyclic olefin **19-E** (eq 3) under Horner−Wadsworth−Emmons conditions[22] (trimethyl phosphonoacetate, NaHMDS, 0 °C, 2.5 h) afforded an 83% yield of a separable 1:1.8 mixture of isomers favoring the undesired *Z* isomer. Alternatively, Peterson−Yamamoto[23b] olefination (LDA, methyl (trimethylsilyl)acetate, −78 °C, 1 h) afforded a favorable 3:1 mixture of isomers (Table 2, entry 1), while the sodium enolate (NaHMDS, methyl (trimethylsilyl)acetate, −78 °C, 1 h) was found to reverse the selectivity (Table 2, entry 2).[36] Use of ether or toluene as solvent attenuated the selectivity (Table 2, entries 3 and 4). On a large scale, it was optimal to run the olefination at −110 °C, providing 73:27 selectivity in 99% yield. The relative stereochemistry of the C_5 enoate was assigned by chemical shift analysis of **19-E** (H_{4e} δ 2.73, H_{6e} δ 3.83).

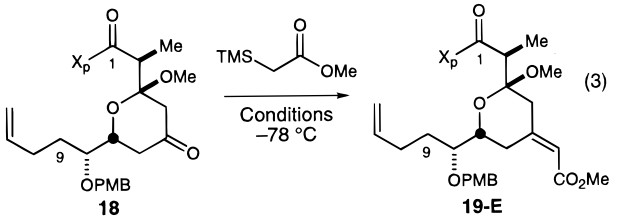
Imide **19-E** was hydrolyzed (LiO_2H, DMF/THF/H_2O)[37] to the derived carboxylic acid, which was transformed to its benzyl ester **20** in 99% yield for the two steps (Scheme 5). Successive osmium-catalyzed dihydroxylation and periodate cleavage afforded aldehyde **21** in 85% yield with no detectable cleavage

Table 1. Relevant NOEs



^1H	NOE (%)
H_b	H_d (11)
H_c	H_a (4), H_e (3), H_d (4)
H_d	H_b (13)

Table 2. Selective Peterson Olefination of ketone 18



entry	base	solvent	*E*:*Z*
1	**LDA**	**THS**	**73:27**
2	NaHMDS	THF	18:82
3	LDA	Et_2O	66:33
4	LDA	PhMe	66:33

(30) Chen, K.-M.; Hardtmann, G. E.; Prasad, K.; Repic, O.; Shapiro, M. J. *Tetrahedron Lett.* **1987**, *28*, 155−158.

(31) This reaction provided a higher yield and selectivity than the reaction with $Me_4NBH(OAc)_3$, leading us to temporarily employ this configuration at C_5 to mask the exocyclic enoate.

(32) Zakharkin, L. I.; Khorlina, I. M. *Tetrahedron Lett.* **1962**, 619−620.

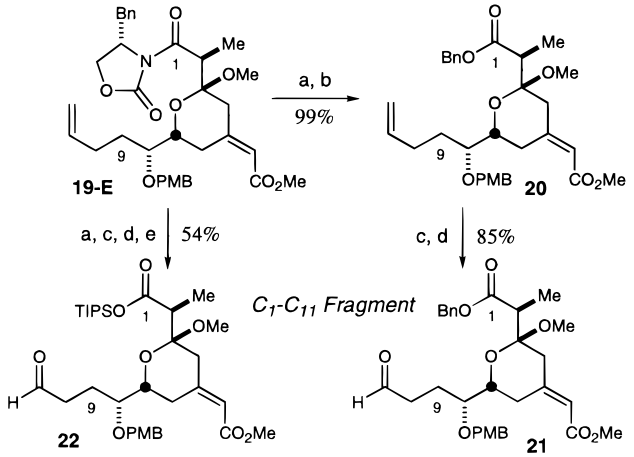
(33) (a) Evans, D. A.; Bartroli, J.; Shih, T. L. *J. Am. Chem. Soc.* **1981**, *103*, 2127−2129. (b) Gage, J. R.; Evans, D. A. *Org. Synth.* **1989**, *68*, 77−82.

(34) Evans, D. A.; Chapman, K. T.; Carreira, E. M. *J. Am. Chem. Soc.* **1988**, *110*, 3560−3578.

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

(36) Trapping of the lithium and sodium enolates used for the olefinations with TBSOTf gave identical silyl ketene acetals.

Scheme 5[a]



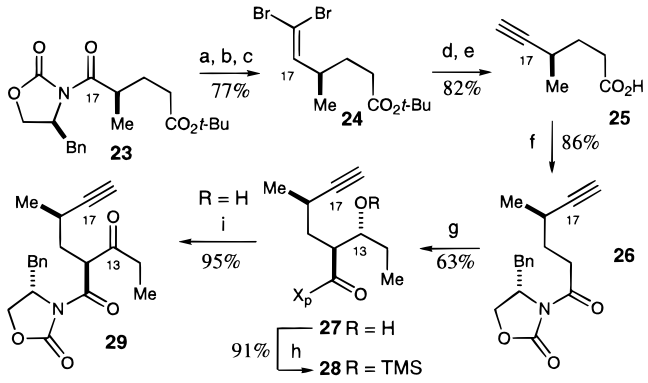
[a] Key: (a) LiOOH, THF/DMF/H_2O, 0 → 23 °C; (b) BnBr, Cs_2CO_3, DMF/CH_2Cl_2; (c) OsO_4, NMO, THF/*t*-BuOH/H_2O; (d) $NaIO_4$, $NaHCO_3$, THF/*t*-BuOH/H_2O; (e) TIPSCl, Et_3N, then Et_3NHOAc.

of the enoate. This fragment was thus prepared in 17 steps in an overall yield of 24%. The analogous TIPS-protected ester **22**, required for an alternate fragment assembly strategy (vide infra), was prepared in four steps from **19-E** (imide hydrolysis, osmylation, periodate cleavage, and TIPS protection) without purification of intermediates in 54% yield. This fragment is available in 17 steps with an overall yield of 15%.

Synthesis of the $C_{12}-C_{18}$ Subunit. The synthesis of the $C_{12}-C_{18}$ fragment began with intermediate **23**, available in 88% yield and >95:5 selectivity via Michael addition of the titanium enolate of the propionyl oxazolidinone to *tert*-butyl acrylate (Scheme 6).[28,38] The imide was selectively reduced in the presence of the *tert*-butyl ester using $LiBH_4$,[39] the primary alcohol was oxidized,[27] and the aldehyde was immediately olefinated (Ph_3P, CBr_4)[40] to afford dibromoolefin **24** (77%, three steps). Cleavage of the *tert*-butyl ester (TFA/CH_2Cl_2, 99%) followed by treatment with 4 equiv of *n*-butyllithium (THF, −78 °C) to effect elimination of the dibromoolefin delivered alkyne **25** in 83% yield. Acid chloride formation followed by imide acylation with lithiated (4*S*)-4-benzyloxazolidinone formed imide **26** in 86% yield. Following another boron aldol reaction (**26** → **27**) and subsequent protection, **28**, one of the two $C_{12}-C_{18}$ fragments was constructed. The other $C_{12}-C_{18}$ synthon used in an alternative assemblage sequence, **29**, was prepared by oxidiation of **27** (SO_3·pyridine, DMSO, *i*-Pr_2NEt, −15 °C)[41] in 95% yield. This sequence provided the two $C_{12}-C_{18}$ fragments in nine steps and 31% and 32% overall yield, respectively, for **28** and **29** from Michael adduct **23**.

Synthesis of the $C_{19}-C_{27}$ Subunit. The plan for the synthesis of the $C_{19}-C_{27}$ fragment is illustrated in Scheme 7. The origin for the chirality in this subunit is the known methyl ketone **32** and its associated aldol reactions precedented in the work of

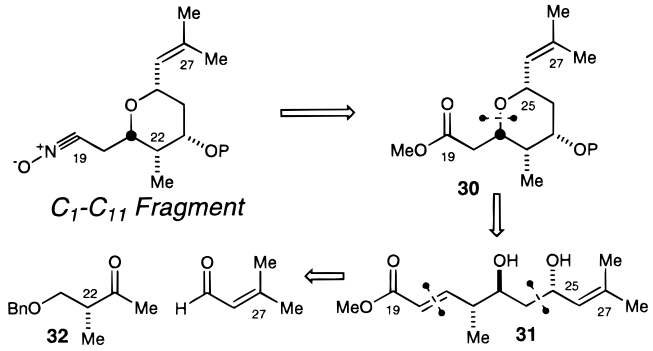
Scheme 6[a]



[a] Key: (a) $LiBH_4$, MeOH, THF, 0 °C; (b) $(COCl)_2$, DMSO, Et_3N, −78 to 0 °C; (c) Ph_3P, CBr_4, CH_2Cl_2, 0 °C; (d) TFA/CH_2Cl_2; (e) *n*-BuLi, THF, −78 °C; (f) $(COCl)_2$, C_6H_6; ii) XpH (Xp = (4*S*)-4-benzyloxazolidinone), *n*-BuLi, THF, 0 °C; (g) Bu_2BOTf, Et_3N, CH_2Cl_2, 0 °C, then EtCHO, −78 °C; (h) TMSCl, imidazole, CH_2Cl_2; (i) SO_3·pyr, *i*-Pr_2NEt, DMSO/CH_2Cl_2, −15 °C.

Paterson.[42] The use of a heteroconjugate addition (**31** → **30**) of the C_{25} alkoxide under conditions that allowed for equilibration of the product diastereomers was the plan selected for the construction of the pyran ring.

Scheme 7



The synthesis of this fragment began with the aldol addition of ketone **32** to senecialdehyde (*c*-hex_2BCl, Et_3N, Et_2O, −78 °C), which proceeded in 7.5:1 (98%) diastereoselectivity favoring 1,4-syn product **33** (Scheme 8).[42] While the two C_{25} diastereomers could not be separated at this point, after anti reduction ($Me_4NBH(OAc)_3$, AcOH/CH_3CN, −35 °C),[34] the desired diol **34a** was purified by crystallization in 76% yield. Successive protection of the diol as the bis-TES ether, benzyl ether removal[43] (LDBB, 96%), and oxidation[41] of the derived primary alcohol afforded aldehyde **35** in 85% overall yield. Horner−Wadsworth−Emmons homologation (LiCl, Et_3N, $(MeO)_2P(O)CH_2CO_2Me$, MeCN)[44] afforded the *E* enoate (92%), which was successively transformed to diol **36** and cyclized under basic conditions (KO*t*-Bu, THF, −10 °C)[45] to give an apparent kinetic 1.5:1 mixture of tetrahydropyrans **37** and **38** in 96% yield. While it had been anticipated that this heteroconjugate addition would be reversible under these conditions, this proved not to be the case; however, silyl protection of the

(37) (a) Jacobi, P. A.; Murphree, S.; Rupprecht, F.; Zheng, W. *J. Org. Chem.* **1996**, *61*, 2413−2427. Attempted oxazolidinone cleavage under standard conditions (LiOOH, THF/H_2O, 0 °C) was sluggish; a large excess of LiOOH at rt was required to achieve completion and competitive hydrolysis of the unsaturated ester was observed. (b) Evans, D. A.; Britton, T. C.; Ellman, J. A. *Tetrahedron Lett.* **1987**, *28*, 6141−6144.

(38) Evans, D. A.; Bilodeau, M. T.; Somers, T. C.; Clardy, J.; Cherry, D.; Kato, Y. *J. Org. Chem.* **1991**, *56*, 5750−5752.

(39) (a) Penning, T. D.; Djuric, S. W.; Haack, R. A.; Kalish, V. J.; Miyashiro, J. M.; Rowell, B. W.; Yu, S. S. *Synth. Commun.* **1990**, 307−312. (b) Kim, A. S. Ph.D. Thesis, Harvard University, 1996.

(40) Corey, E. J.; Fuchs, P. L. *Tetrahedron Lett.* **1972**, 3769−3972.

(41) Parikh, J. R.; Doering, W. v. E. *J. Am. Chem. Soc.* **1967**, *89*, 5505−5507.

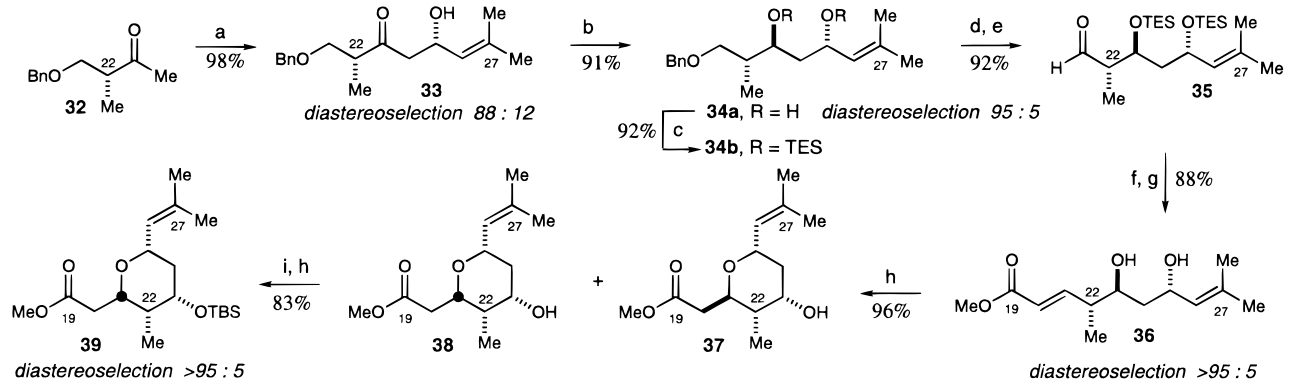
(42) Paterson, I.; Goodman, J. M.; Isaka, M. *Tetrahedron Lett.* **1989**, *30*, 7121−7124.

(43) (a) Freeman, P. K.; Hutchinson, L. L. *J. Org. Chem.* **1980**, *45*, 1924−1930. (b) Ireland, R. E.; Smith, M. G. *J. Am. Chem. Soc.* **1988**, *110*, 854−860.

(44) Blanchette, M. A.; Choy, W.; Davis, J. T.; Essenfield, A. P.; Masamune, S.; Roush, W. R.; Sakai, T. *Tetrahedron Lett.* **1984**, *25*, 2183-2186.

(45) Evans, D. A.; Carreira, E. M. *Tetrahedron Lett.* **1990**, *31*, 4703−4706.

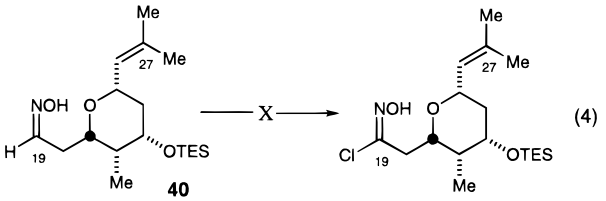
Scheme 8



[a] Key: (a) c-hex$_2$BCl, Et$_3$N, Et$_2$O, Me$_2$CCHCHO, −78 °C; (b) Me$_4$NBH(OAc)$_3$, MeCN/AcOH, −35 °C; (c) TESCl, imidazole, CH$_2$Cl$_2$; (d) LDBB, THF, −78 °C; (e) SO$_3$·pyridine, *i*-Pr$_2$NEt, DMSO/CH$_2$Cl$_2$, −15 °C; (f) LiCl, Et$_3$N, (MeO)$_2$P(O)CH$_2$CO$_2$Me, MeCN, 0 → 23 °C; (g) TBAF, H$_2$O/THF; (h) KO-*t*-Bu, THF, −10 °C; (i) TBSOTf, 2,6-lutidine, CH$_2$Cl$_2$, −78 °C.

mixture (TBSOTf, 2,6-lutidine, 97%) followed by re-submission of the mixture of silyl ethers to the basic cyclization conditions afforded *cis*-tetrahydropyran **39** in >95:5 selectivity and 86% yield. The structure of **39** was confirmed by NOE analysis and subsequently an X-ray structure of tetrahydropyran **38**.[46]

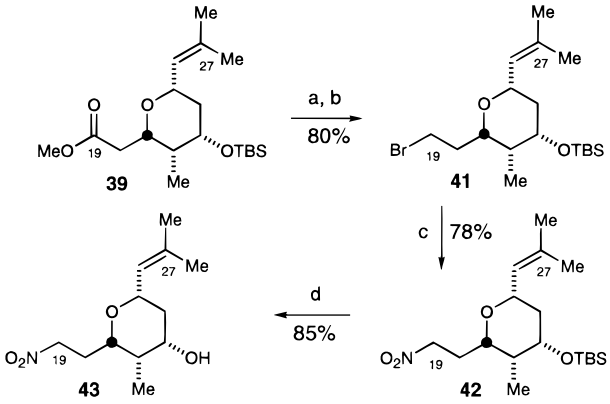
Two different approaches were explored for the conversion of esters **38** or **39** to a functional nitrile oxide precursor. In the first approach, the TES ether of methyl ester **38** was transformed into oxime **40**. Unfortunately, oxidation of **40** under a variety of conditions to the desired chlorooxime (eq 4)[47,48] failed due



to unanticipated competitive chlorination of the trisubstituted olefin. In an alternative approach, methyl ester **39** was transformed in a conventional series of steps to the derived nitro pyran **43** (Scheme 9). In the noteworthy step, bromide **41** was converted to nitro pyran **42** with silver nitrite[49] in 78% yield along with the corresponding nitrate ester in 17% yield. This route provided access to the C$_{19}$−C$_{27}$ nitrile oxide precursors **42** and **43** in 13 and 14 steps, respectively, and 31% overall yield from methyl ketone **32** (Scheme 8).

Fragment Coupling Strategies. The principal fragments of the miyakolide skeleton were designed so that they might be assembled in several different sequences (Scheme 10). The assemblage strategy deemed most conservative is depicted as

Scheme 9[a]



[a] Key: (a) DIBAL-H, THF, −78 → 23 °C; (b) Ph$_3$P, Br$_2$, imidazole, CH$_2$Cl$_2$/2-methyl-2-butene; (c) AgNO$_2$, Et$_2$O; (d) HF·pyridine, pyr, THF.

path A. Aldol fragment coupling of the C$_{12}$−C$_{18}$ *β*-ketoimide and the C$_1$−C$_{11}$ aldehyde should afford adduct **44**. The subsequent [3 + 2] dipolar cycloaddition to append the C$_{19}$−C$_{27}$ nitrile oxide would then provide intermediate **45** containing all of the carbon atoms present in miyakolide. Decarboxylation, deprotection, and macrolactonization would provide the key isoxazole-containing macrocycle **48**. Alternatively, the [3 + 2] coupling between the C$_{12}$−C$_{18}$ fragment and the C$_{19}$−C$_{27}$ nitrile oxide cycloaddition to give adduct **46** (path B) could be followed by a more complex *β*-ketoimide aldol coupling with the C$_1$−C$_{11}$ aldehyde to return to the common intermediate **45**. A third variation (path C) would involve the same C$_1$−C$_{18}$ aldol-coupled intermediate **44** as in path A. After deprotection of the C$_1$ ester, the C$_{19}$−C$_{27}$ fragment would be incorporated via an esterification reaction affording **47**. Macrocyclization via [3 + 2] cycloaddition followed by decarboxylation and deprotection would again afford macrocycle **48**. During the course of this synthesis, all three assemblage strategies were evaluated (vide infra).

Path A: Aldol → Cycloaddition → Esterification. While *β*-ketoimide **4** has been utilized as a dipropionyl synthon for the assemblage of a number of polypropionate targets,[3e,28,39b,50] this methodology has not been previously used for the coupling of complex fragments such as **29** or **46** (Scheme 10). In the

(46) Crystallographic data for **38**: C$_{13}$H$_{22}$O$_4$ M_w = 242.3, orthorhombic, colorless, $P2_12_12_1$°, a = 6.0062 (2) Å, b = 11.4838 (5) Å, c = 19.5391 (8) Å, v = 1347.69 (9) Å^3, Z = 4, D_c = 1.194 g cm^{-3}, F(000) = 528, μ(Mo Kα) = 0.087 mm^{-1}; R = 0.0569, R_w = 0.1340, GOF on F^2 = 1.124 for 5207 observed reflections. $R = \sum||F_o| - |F_c||/\sum|F_o|$. $R_w = (\sum[w(F_o^2 - F_c^2)^2]/\sum[wF_o^4])^{1/2}$, where $w = q/\sigma^2(F_o^2) + (aP)^2 + bP$. See the Experimental Section for details.

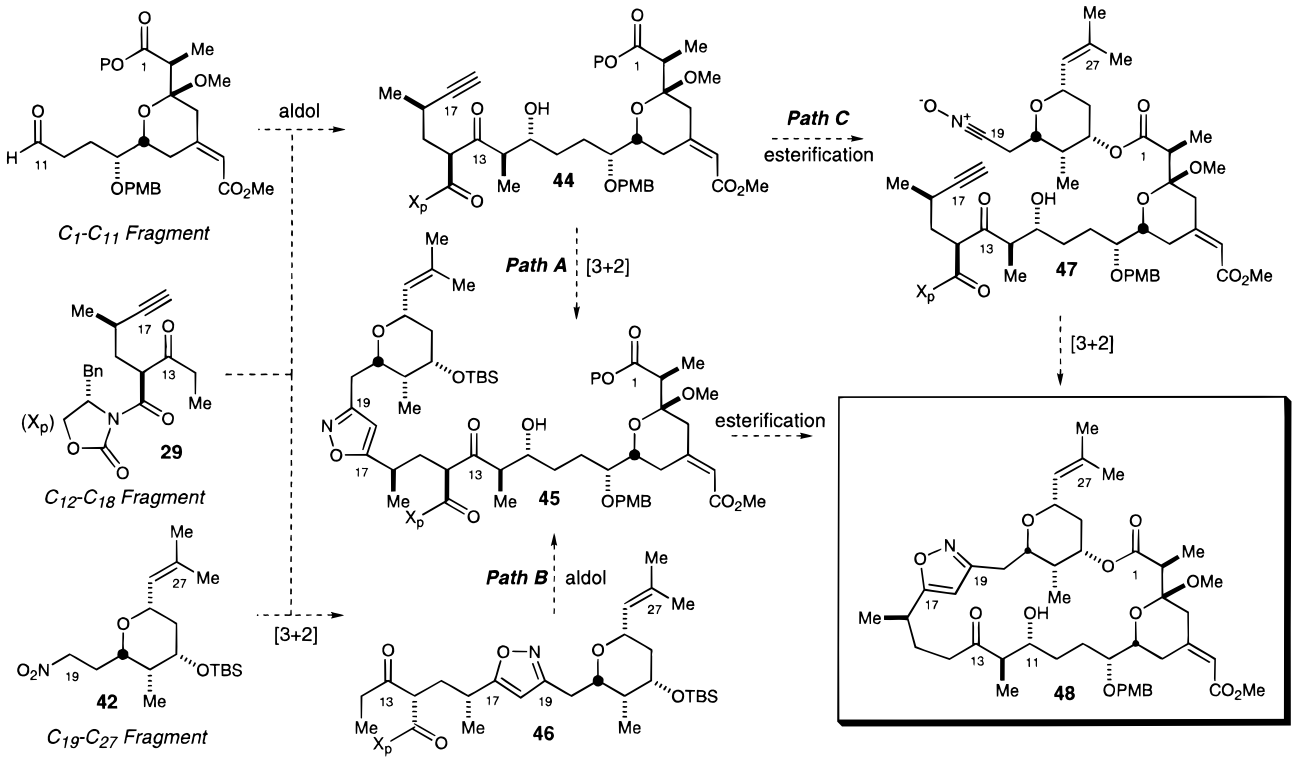
(47) Chlorinating agents tried included isocyanuric chloride, *tert*-butyl hypochlorite at −78 °C (ref 48a), NCS (ref 48b, c), and NaOCl in a biphasic system (ref 48d, e).

(48) (a) Stevens, R. V.; Beaulieu, N.; Chan, W. H.; Daniewski, A. R.; Takeda, T.; Waldner, A.; Williard, P. G.; Zutter, U. *J. Am. Chem. Soc.* **1986**, *108*, 1039−1049. (b) Stevens, R. V. *Tetrahedron* **1976**, *32*, 1599−1612. (c) Liu, K.-C.; Shelton, B. R.; Howe, R. K. *J. Org. Chem.* **1980**, *45*, 3916−3918. (d) Ponzio, G.; Busti, G. *Gazz. Chim. Ital. II* **1906**, *36*, 338. (e) Grundmann, C.; Datta, S. K. *J. Org. Chem.* **1969**, *34*, 2016−2018.

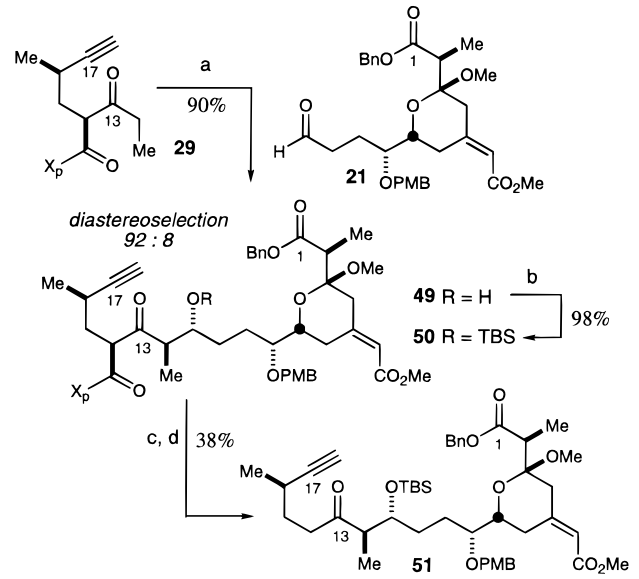
(49) (a) Kornblum, N.; Taub, B.; Ungnade, H. E. *J. Am. Chem. Soc.* **1954**, *76*, 3209−3211. (b) Kornblum, N.; Ungnade, H. E. *Organic Syntheses*; Wiley: New York, 1963; Collect. Vol. IV, pp 724−727.

(50) For examples, see: (a) Evans, D. A.; DiMare, M. *J. Am. Chem. Soc.* **1986**, *108*, 2476−2478. (b) Evans, D. A.; Ng, H. P.; Rieger, D. L. *J. Am. Chem. Soc.* **1993**, *115*, 11446−11459. (c) Evans, D. A.; Kim, A. S. *J. Am. Chem. Soc.* **1996**, *118*, 11323−11324.

Scheme 10



Scheme 11[a]



[a] Key: (a) c-hex$_2$BCl, Me$_2$NEt, Et$_2$O, 0 °C, then **21**, −78 → 0 °C; (b) TBSOTf, 2,6-lutidine, CH_2Cl_2, −78 °C; (c) EtSH, KH, THF; (d) $AgNO_3$, 2,6-lutidine, THF/H_2O.

event, β-ketoimide **29** was transformed into its derived (*E*)-boron enolate (1.3 equiv of c-hex$_2$BCl, Me$_2$NEt, ether, 0 °C)[21b] to which was added 0.5 equiv of aldehyde **21** at −78 °C (Scheme 11). The aldol adduct **49** was isolated in 90% yield (based on aldehyde) in 92:8 diastereoselectivity along with good recovery of the starting materials. It is noteworthy that the standard isolation used for this reaction (NH_4Cl quench followed by IRA-743 resin, CH_2Cl_2) often resulted in product decomposition. Alternatively, if the reaction was quenched with 5% $NaHCO_3$ followed by immediate flash chromatography of the partially concentrated organic layer, reproducible yields of the aldol adduct could be obtained. The stereochemistry at C_{12} and C_{11} was assigned on the basis of analogy to previous studies[21b] and confirmed by NOE analysis of a later intermediate (vide infra).

Theoretically, aldol adducts **49** or **50** could be decarboxylated either preceding or following [3 + 2] cycloaddition. As the conditions required to dehydrate the primary nitroalkane moiety to its derived nitrile oxide[51] (ArNCO, R_3N, 90 °C) would likely epimerize the α-center of a β-ketoimide, we initially chose to examine a route that placed the decarboxylation step prior to coupling. Treatment of aldol adduct **50** with potassium ethanethiolate (THF, 25 °C, 3 h) followed by purification provided a mixture of C_{14}-epimeric β-ketothioesters in quantitative yield (Scheme 11).[52,20] It was encouraging that the resident functionality in **50** emerged from these conditions unscathed. Unfortunately, treatment of the resulting thioesters with silver nitrate and 2,6-lutidine (5:1 THF/H_2O, 48 h)[53,20] failed to produce more than a 38% yield of desired decarboxylated material **51**. The remainder of the isolated products lacked the alkyne functionality, which was clearly interfering with the desired transformation.

The incompatibility of the alkyne functionality in **50** with the Ag(I)-promoted hydrolysis/decarboxylation was easily overcome by delaying the hydrolysis until after the nitrile oxide cycloaddition step (Scheme 12). Alkyne **50** was premixed with 3-ClPhNCO and *i*-Pr$_2$NEt in toluene at 90 °C[51] followed by addition of 2 equiv of nitroalkane **42** over 24 h.[54] This procedure afforded coupled isoxazole **52** in 96% yield. Surprisingly, almost no epimerization (<5%) of the C_{14} stereocenter was observed, presumably due to the steric congestion of the silyl-protected

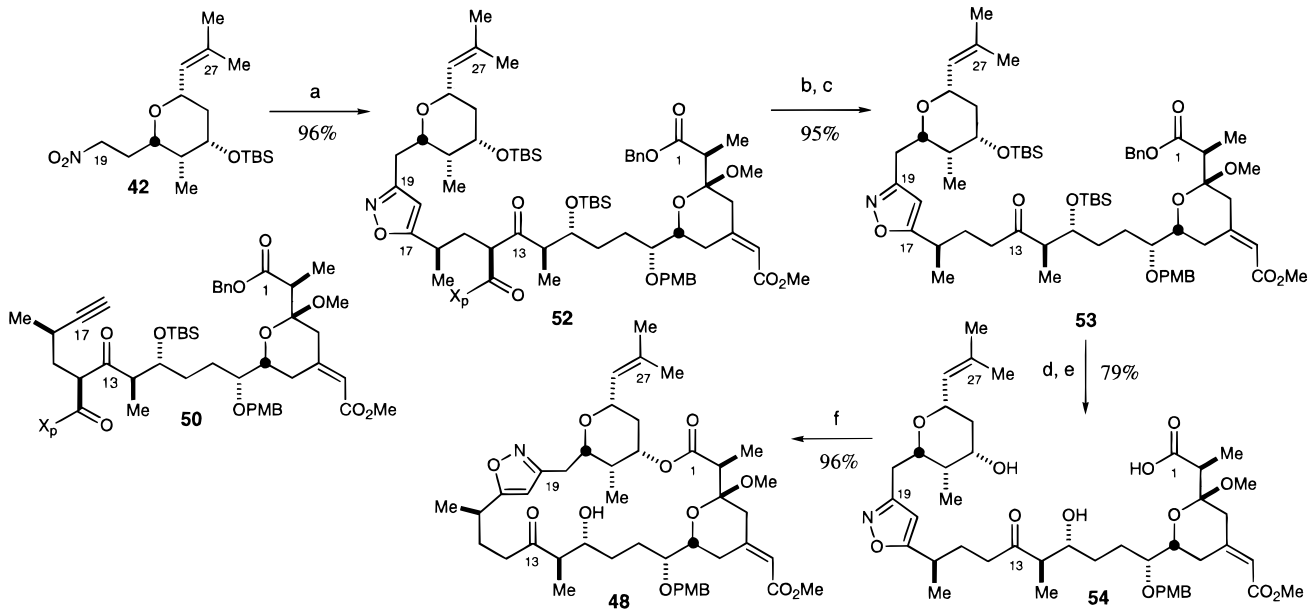
(51) Mukiyama, T.; Hoshino, T. *J. Am. Chem. Soc.* **1960**, *82*, 5339−5342.

(52) Damon, R. E.; Coppola, G. M. *Tetrahedron Lett.* **1990**, *31*, 2849−2852.

(53) (a) Corey, E. J.; Bock, M. C. *Tetrahedron Lett.* **1975**, 3269−3270. (b) Schwyzer, R.; Hurlimann, C. *Helv. Chim. Acta* **1954**, *18*, 155−166.

(54) Since nitrile oxides readily dimerize to furoxans (ref 15c), they must be generated at low concentration in the presence of the efficient dipolarophile.

Scheme 12[a]



[a] Key: (a) 3-ClPhNCO, *i*-Pr_2NEt, PhMe, 24 h addition of **42**, 90 °C; (b) EtSH, KH, THF; (c) $AgNO_3$, 2,6-lutidine, THF/H_2O; (d) HF·pyr, 2,6-lutidine; (e) 10% Pd/C, 1,4-cyclohexadiene, EtOH; (f) 2,4,6-Cl_3PhCOCl, *i*-Pr_2NEt, DMAP.

aldol adduct. The regiochemistry of the [3 + 2] cycloaddition was confirmed by the characteristic ^{1}H NMR chemical shift of the C_{18} trigonal proton (δ = 5.95) on the isoxazole nucleus.[55] At this juncture, the hydrolysis/decarboxylation proceeded uneventfully to afford a 95% yield of ketone **53**.[20] The subsequent desilylation of the C_{11} and C_{23} TBS ethers in **53** (HF·pyridine, 2,6-lutidine) proceeded in good yield;[39b] however, cleavage of the terminal benzyl ester in the presence of the trisubstituted olefin, enoate, and isoxazole proved challenging. While transfer hydrosilylation[56] afforded good yields (75−79%) of the diol acid on a small (<10 mg) scale, this result was irreproducible on scale-up.[57] In the end, transfer hydrogenation proved to be the more reliable method for removing the benzyl ester (10% Pd/C, 1,4-cyclohexadiene, 100%),[58] requiring only filtration through Celite to deliver diol acid **54** in high purity. No evidence of over-reduction was observed in this reaction. Macrolactonization via the Yamaguchi procedure[59] (2,4,6-Cl_3PhCOCl, *i*-Pr_2NEt, DMAP, benzene) afforded **48** in 97% yield, with no observable participation of the C_{11} alcohol. This completed the synthesis of the macrocyclic precursor to the miyakolide carbon skeleton.

Path B: Cycloaddition → Aldol → Esterification. In principle, path B (Scheme 10) provides the shortest possible linear route to miyakolide. Because of the conditions required to generate the nitrile oxide for the [3 + 2] cycloaddition (vide supra), we presented the β-ketoimide fragment as the C_{13}-protected secondary alcohol **28** as a precaution against epimerization of the C_{14} stereocenter. To a premixed solution of 1.4 equiv of **28**, 3-ClPhNCO, and *i*-Pr_2NEt in toluene at 90 °C[51] was added nitroalkane **42** over 24 h, affording isoxazole **55** in 66% (Scheme 13). Deprotection of the C_{13} TMS ether and Parikh−Doering oxidation[41] delivered desired β-ketoimide **57** in 94% yield. Enolization of ketone **57** (1.4 equiv) followed by addition of a solution of aldehyde **21** (1.0 equiv) provided a 50% yield of desired aldol adduct **58** in 90:10 selectivity. The remainder of both the aldehyde and ketone starting materials could be recovered in good yield (80% of unreacted **57**, 48% of **21**). On the basis of the recovery of aldehyde component **21**, this coupling process is quite viable. Nevertheless, despite extensive reaction optimization, we were never able to raise the yield of this reaction above the 50% level. Aldol adduct **58** was then converged with path A through the four-step sequence outlined in Schemes 12 and 13 in 72% overall yield. One of the attributes of the path A−path B strategy is the excellent yield (96%) of the intramolecular macrolactonization step to form **48** (Scheme 13).

Path C: Aldol → Esterification → Cycloaddition. The third assemblage strategy includes a penultimate macrocyclization via [3 + 2] cycloaddition[60] (path C, Scheme 10). This fragment coupling requires that the C_1 ester be deprotected in the presence of the C_{17}−C_{18} alkyne; accordingly, the TIPS-protected C_1−C_{11} aldehyde fragment **22** was utilized. Aldol fragment coupling between β-ketoimide **29** and aldehyde **22** (*c*-hex_2BCl, Me_2NEt) furnished the desired adduct **59** in 79% yield (Scheme 14). Protection of the aldol adduct as its TES ether proceeded with loss of the TIPS ester on workup (TESCl, imidazole; Et_3NHOAc), producing acid **60**. Submission of this acid to modified Yamaguchi conditions[59] with alcohol **43** ((2,4,6-Cl_3PhCO)$_2$O, *i*-Pr_2NEt, DMAP, benzene) afforded ester **61** in 45% yield from alcohol **59**.[61,62] Slow addition of nitroalkylalkyne **61** to 3-ClPhNCO and *i*-Pr_2NEt in refluxing benzene furnished

(55) A regioisomeric isoxazole bearing substituents at the 3 and 4 positions, with a proton at the 5 position would have a singlet resonance around δ 8.40. 3,5-Dimethylisoxazole has a C_4 singlet resonance at δ 5.85, and 3-methylisoxazole has a C_4 resonance at δ 6.25 and a C_5 resonance at δ 8.40. *The Aldrich Library of NMR Spectra, Edition II*; Pouchert, C. J., Ed.; Aldrich Chemical Co.: Milwaukee, WI, 1983; Vol. 2, p 503.

(56) Sakaitani, M.; Kurokawa, N.; Ohfune, Y. *Tetrahedron Lett.* **1986**, *27*, 3753−3754.

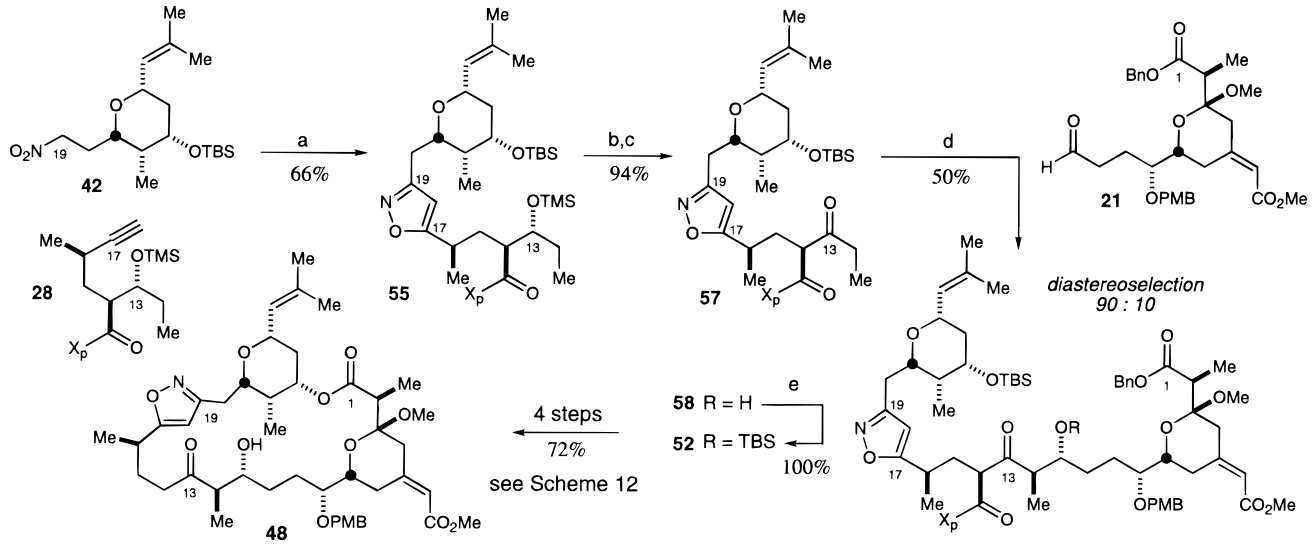
(57) The breakdown of the intermediate triethylsilyl ester required exposure to silica gel (chromatography) to reveal the highly polar diol acid. Recovering the acid from silica gel was difficult, and the silyl ester hydrolysis efficiency decreased as loading on silica gel increased. The desired diol acid proved extremely acid sensitive, and an efficient alternative cleavage of the TES ester was not found.

(58) Felix, A. M.; Heimer, E. P.; Lambros, T. J.; Tzougraki, C.; Meienhofer, J. *J. Org. Chem.* **1978**, *43*, 4194−4196.

(59) Inanaga, J.; Hirata, K.; Saeki, H.; Katsuki, T.; Yamaguchi, M. *Bull. Chem. Soc. Jpn.* **1979**, *52*, 1989−1993.

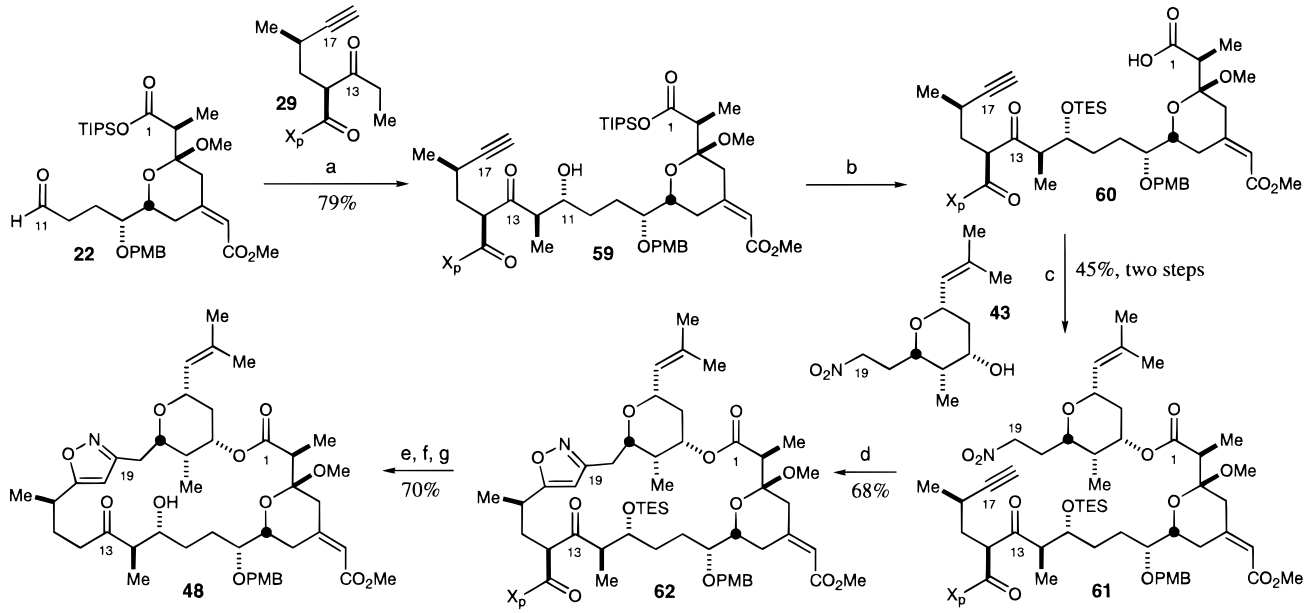
(60) Macrolactonization via intramolecular [3 + 2] cycloaddition has been demonstrated to be highly selective and efficient. Ko, S. S.; Confalone, P. N. *Tetrahedron* **1985**, *41*, 3511−3518.

Scheme 13[a]



[a] Key: (a) 3-ClPhNCO, *i*-Pr_2NEt, PhMe, 24 h addition of **42**, 90 °C; (b) PPTS, MeOH, 0 °C; (c) SO_3·pyr, *i*-Pr_2NEt, DMSO/CH_2Cl_2, −15 °C; (d) c-hex_2BCl, Me_2NEt, Et_2O, 0 °C, then **21**, −78 °C → 0 °C; (e) TBSOTf, 2,6-lutidine, CH_2Cl_2, −78 °C.

Scheme 14[a]



[a] Key: (a) *c*-hex_2BCl, Me_2NEt, Et_2O, 0 °C; **22**, −78→0 °C; (b) TESCl, imidazole, CH_2Cl_2, then Et_3NHOAc; (c) (2,4,6-Cl_3PhCO)$_2$O, *i*-Pr_2NEt, DMAP, C_6H_6, **43**; (d) 3-ClPhNCO, *i*-Pr_2NEt, C_6H_6, 90 °C, 20 h addition of **61**; (e) EtSH, NaHMDS, THF; (f) $AgNO_3$, 2,6-lutidine, THF/H_2O; (g) HF·pyr,THF.

macrocyclic isoxazole **62** in 68% yield. No regioisomeric isoxazole was observed, and epimerization of the C_{14} stereocenter was again minimal. Decarboxylation was effected via sodium ethanethiolate transesterification of the imide followed by hydrolysis with $AgNO_3$ and 2,6-lutidine in 4:1 THF/water.[20] Desilylation using HF·pyridine buffered by excess pyridine delivered macrocycle **48** in 70% yield from **62**. The selectivity of the hydrolysis procedure[20] implemented on the advanced intermediate **62** is noteworthy.

The Miyakolide Precursor. The high-risk portion of the synthesis plan was contained in the final intramolecular aldol step to construct the C_{11}−C_{19} oxydecalin Miyakolide subunit. To ensure the success of the terminal transformations, a number of experiments were carried out on the isoxazole-containing macrocycle **48** and its N−O reduction product **64** (Scheme 15). Prior to isoxazole reduction, macrocycle **48** was used to model the propensity of the C_3 lactol methyl ether toward hydrolysis and potential ring-chain tautomerism (**65** → **66**). If keto ester **66** is readily accessed under hydrolysis conditions, the integrity of the C_5 unsaturated ester would be placed in jeopardy as would the stereochemistry of the C_2 methyl group. In the event, treatment of macrolactone **48** with TsOH (MeCN/water 5:1)

(61) Excess alcohol **43** was converted to its 2,4,6-trichlorobenzoate ester. All other esterification conditions investigated (EDC (ref 62a−c), diisopropylcarbodiimide (ref 62a−c), PyBrOP (ref 62d), and BOP−Cl (ref 62e)) failed to deliver any esterified product.

(62) (a) Sheehan, J. C.; Hess, G. P. *J. Am. Chem. Soc.* **1955**, *77*, 1067−1068. (b) Cruickshank, P. A.; Sheehan, J. C. *J. Org. Chem.* **1961**, *26*, 2525−2528. (c) Hegarty, A. F.; Bruice, T. C. *J. Am. Chem. Soc.* **1970**, *92*, 6568−6574. (d) Castro, B.; Coste, J. Fr. Patent 89-02-361. (e) Diago-Meseguer, J.; Palomo-Coll, A. L.; Fernandez-Lizarbe, J. R.; Zugaza-Bilbao, A. *Synthesis* **1980**, 547−551.

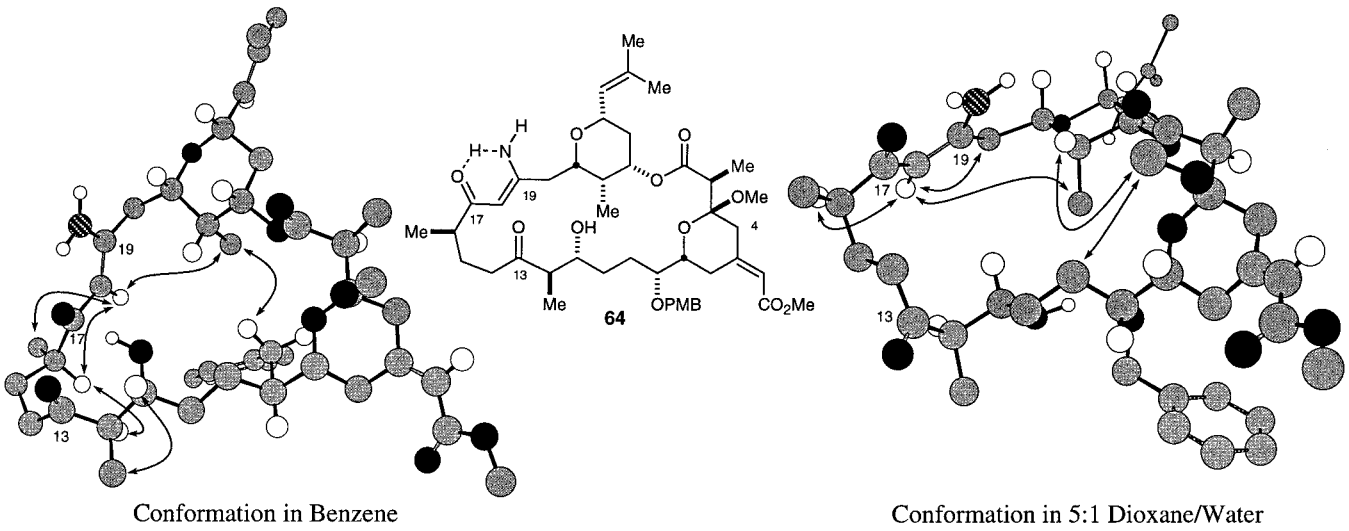
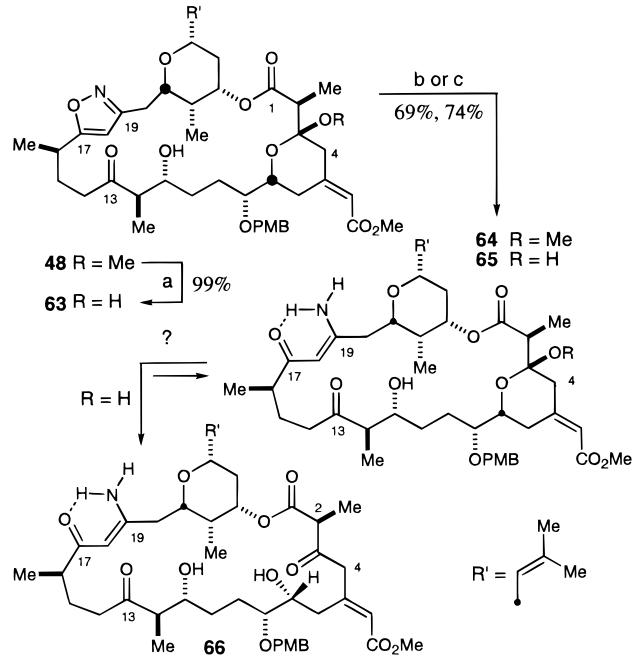


Figure 2. Conformations of macrocycle **64** in benzene and in 5:1 dioxane/water. (arrows indicate observed NOEs).

Scheme 15[a]



[a] Key: (a) TsOH, MeCN/H_2O; (b) **48** → **64**: $Mo(CO)_6$, H_2O, MeCN, reflux; (c) **63** → **65**: W-2 Raney Ni, 1 atm H_2, EtOH/AcOH.

delivered a 99% yield of hemiketal **63**, which is stable for several days at room temperature without significant isomerization. Selective reduction of the N−O bond in isoxazoles **48** and **63** could be achieved using W-2 Raney nickel under 1 atm of hydrogen (20:1 EtOH/AcOH) to afford lactol methyl ether **64** in 59% yield from **48** and hemiketal **65** in 74% yield from **63**.[63] A small amount of over-reduction of the C_{26} olefin was also observed in this reaction. The $Mo(CO)_6$ reduction procedure of Nitta,[64] ($Mo(CO)_6$, MeCN−H_2O, 70 °C) proved to be a better reducing agent affording a 69% yield of enaminone **64**, which proved to be surprisingly stable. In contrast to expectation, enaminone **64** failed to undergo the desired transannular aldol reaction with the C_{13} ketone.

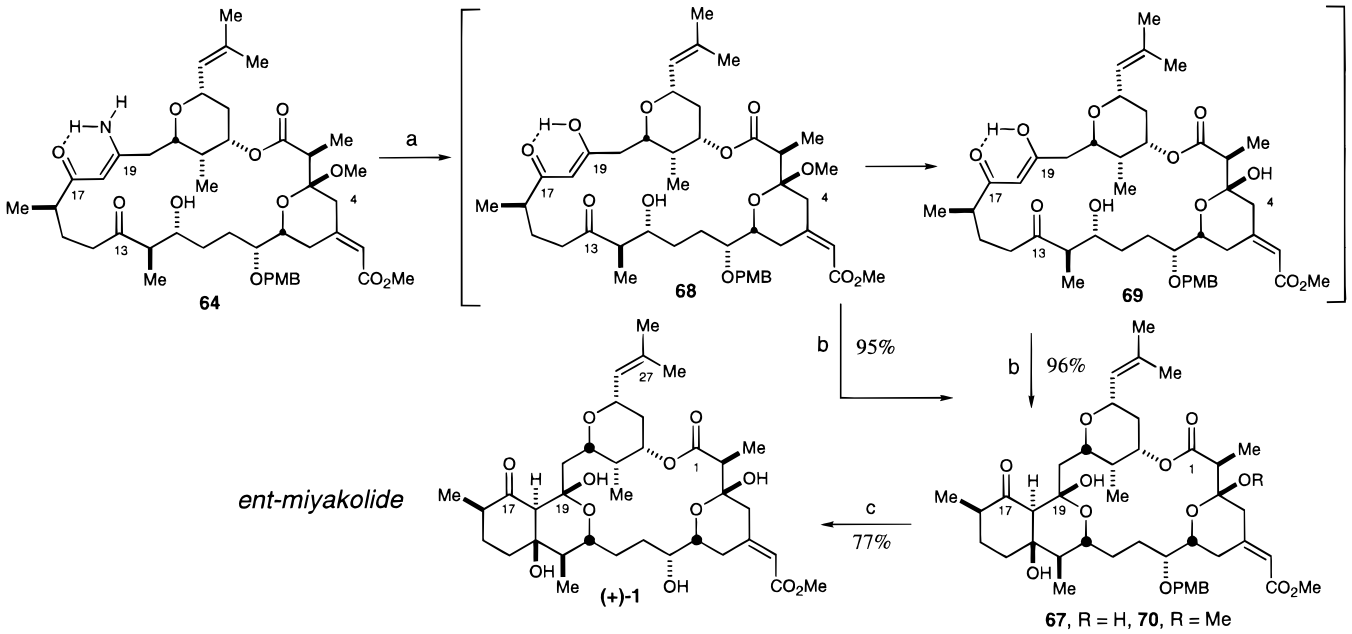
The conformations of intermediate **64** in both benzene and 5:1 dioxane/water were examined through the use of NOESY experiments (Figure 2). Several conclusions were drawn from this study. First, the correct diastereofaces of the C_{17}−C_{19} enaminone and C_{13} carbonyl are properly oriented in both solvents. Second, there seems to be a noticeable solvent effect on the conformation. In benzene, the macrocycle appears to be significantly compressed, as evidenced by transannular NOE enhancements between protons on C_{12} and C_{16} and between the PMB methylene and the C_{22} methyl group. In dioxane/water the macrocycle appears to be in a more open conformation as evidenced by NOE enhancements between the C_3 methyl ketal and the C_{22} methine and both C_9 hydrogens. The C_{13} ketone is pointing toward the exterior of the macrocycle.

Completion of the Synthesis. Treatment of enaminone **64** with Lewis acids such as Ti(O-*i*-Pr)$_4$ or Et_2BOMe in CH_2Cl_2 failed to effect any reaction from −78 °C to room temperature (Scheme 16). The intent of these reactions was to activate the C_{13} ketone with the assistance of the C_{11} alcohol. Although no reaction was observed, starting material was recovered unchanged, allaying concern that the C_3 mixed methyl ketal would eliminate under Lewis acidic conditions. No reaction was observed until the molecule was heated to 90 °C in dioxane/pH 7 buffer. After 2 weeks, starting material had disappeared, and a number of products were isolated, including an analogue of the transannular aldol adduct **70** (Scheme 16) along with aldol elimination products and a small amount of the transannular aldol product still bearing nitrogen at C_{19}. Although there are only a few examples of enaminones participating in aldol reactions,[16] we had hoped that the forced proximity of the reacting centers would facilitate such a reaction in this case. As this did not seem to be the situation, we expected hydrolysis of the enaminone to the corresponding 1,3-diketone would provide a more reactive system. Given the success of the hydrolysis of mixed methyl ketal **48**, we decided to attempt the simultaneous hydrolyses of the enaminone and mixed methyl ketal. *When enaminone **64** was treated with 1.5 equiv of TsOH in 5:1 MeCN/water for 18 h, followed by addition of pH 10 buffer and stirring for an additional 15 min at room temperature, PMB-protected miyakolide **67** was obtained in 96% yield for the one-pot, three-transformation process (Scheme 16).*

A closer examination of the details of the acid hydrolysis step revealed that enaminone **64** could be selectively hydrolyzed in the presence of the lactol methyl ether (AcOH/THF/water 4:4:1; or 0.95 equiv TsOH, MeCN/water 5:1),[19] providing 1,3-diketone **68** (enol/keto tautomer ratio 5:1). This triketone, which

(63) Stagno D'Alcontres, G. *Gazz. Chim. Ital.* **1950**, *80*, 441.
(64) Nitta, M.; Kobayashi, T. *J. Chem. Soc., Chem. Commun.* **1982**, 877−878.

Scheme 16[a]



[a] Key: (a) 1.5 equiv of TsOH, MeCN/H_2O; (b) then pH 10 buffer; (c) DDQ, H_2O, CH_2Cl_2.

does not cyclize under acidic conditions, could be isolated in high purity. On treatment with pH 10 buffer ($NaHCO_3$, Na_2CO_3) in dioxane (15 min, 25 °C), the desired 3-methyl-8-OPMB-miyakolide **70** was obtained in 95% yield for the two steps as a single diastereomer. On the basis of these results, it appears that in the one-pot, three-step process described earlier, enaminone **64** is hydrolyzed to **68** first, followed by hydrolysis of the mixed methyl ketal to **69**, and finally cyclization to **67**. Subjecting enaminone **64** itself to pH 10 buffer in dioxane resulted in no reaction; stronger bases such as NaH are generally employed to deprotonate enaminones[65] but would be incompatible with this intermediate.

Final deprotection of the PMB group in **67** (DDQ, water, CH_2Cl_2)[35] produced (+)-miyakolide in 77% yield (Scheme 16). The synthetic material displayed spectral characteristics identical to those of the natural product (^{1}H NMR, ^{13}C NMR, IR, HRMS, TLC) and an equal but opposite specific rotation (natural $[\alpha]^{23}_D$ −24° (c = 1.05, $CHCl_3$),[4] synthetic $[\alpha]^{23}_D$ +23° (c = 0.4, $CHCl_3$)). To further confirm that (+)-miyakolide had been produced, crystals were grown from a mixture of CCl_4, ethyl acetate, and hexanes; (+)-miyakolide cocrystallized with CCl_4, allowing both the structure and absolute configuration to be determined (Figure 3).[66] This conclusively demonstrated that the absolute configuration of natural miyakolide is enantiomeric to that depicted in eq 1.

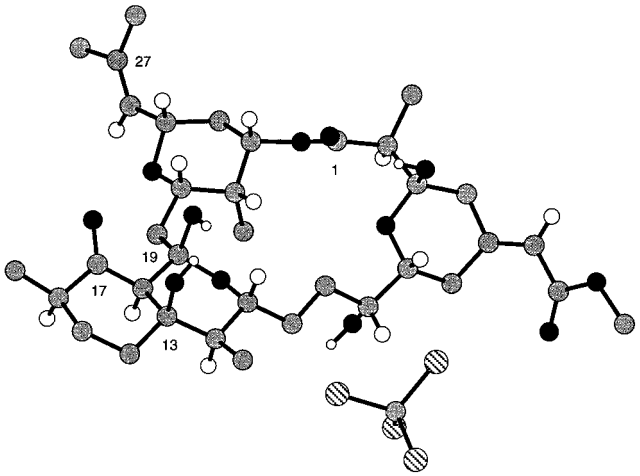


Figure 3. X-ray structure of (+)-miyakolide with CCl4.

Conclusions

A total synthesis of the marine natural product miyakolide has been achieved in a highly convergent manner from three fragments in 29 linear steps and 6.8% overall yield, establishing the absolute stereochemistry of the natural product. This synthesis provided the impetus for the development of *N*-acylimides as α-keto chiral auxiliaries via the development of the *β*-ketoimide decarboxylation reaction. In addition, the utility and limitations of *β*-ketoimide aldol reactions as large fragment coupling processes have been demonstrated. The large array of functionality tolerated in the decarboxylation process validates this as a viable two-step fragment coupling procedure. Finally, the synthesis of a proposed biosynthetic intermediate and its facile transformation into miyakolide demonstrate the validity of this intermediate as a possible precursor to miyakolide.

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Supporting Information Available: Full experimental details and complete analytical data for all compounds reported in this and X-ray crystallographic data. This material is available free of charge via the Internet at http://pubs.acs.org.

JA990789H

(65) Kashima, C.; Katoh, A.; Yokota, Y.; Omote, Y. *Synthesis* **1983**, 151−153.

(66) Crystallographic data for (+)-**1**: $C_{36}H_{54}O_{12}$ (CCl_4) M_w = 678.9/153.8, orthorhombic, colorless, $P2_12_12_1$°, a = 12.821(3) Å, b = 14.992(3) Å, c = 21.088(4) Å, ν = 4053.3(14) Å^3, Z = 4, D_c = 1.364 g cm^{-3}, F(000) = 1760, μ(Mo Kα) = 0.087 mm^{-1}; R = 0.0694, R_w = 0.1348, GOF on F^2 = 1.141 for 18549 observed reflections. $\mathbf{R} = \sum||F_o| - |F_c||/\sum|F_o|$. $\mathbf{R}_w = (\sum[w(F_o^2 - F_c^2)^2]/\sum[wF_o^4])^{1/2}$, where $w = q/\sigma^2(F_o^2) + (aP)^2 + bP$. See the Experimental Section (Supporting Information) for details.