Application of Complex Aldol Reactions to the Total Synthesis of Phorboxazole B

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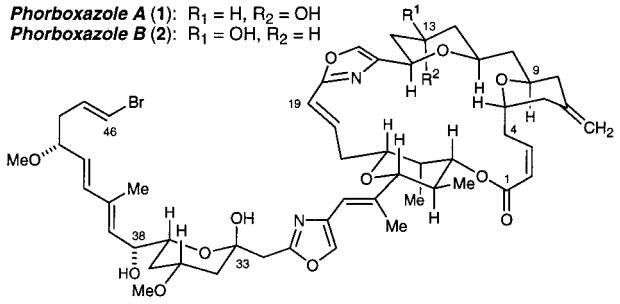
Abstract: The synthesis of phorboxazole B has been accomplished in 27 linear steps and an overall yield of 12.6%. The absolute stereochemistry of the C_4-C_{12}, $C_{33}-C_{38}$, and $C_{13}-C_{19}$ fragments was established utilizing catalytic asymmetric aldol methodology, while the absolute stereochemistry of the $C_{20}-C_{32}$ fragment was derived from an auxiliary-based asymmetric aldol reaction. All remaining chirality was incorporated through internal asymmetric induction, with the exception of the C_{43} stereocenter which was derived from (*R*)-trityl glycidol. Key fragment couplings include a stereoselective double stereodifferentiating aldol reaction, a metalated oxazole alkylation, an oxazole-stabilized Wittig olefination, and a chelation-controlled addition of the fully elaborated alkenyl metal side chain.

Introduction

Phorboxazoles A (**1**) and B (**2**) are marine natural products isolated from a recently discovered species of Indian Ocean sponge (genus *Phorbas sp.*) near Muiron Island, Western Australia.[2] These substances are representative of a new class of macrolides differing only in their C_{13} hydroxyl-bearing stereocenters. The relative stereochemistry within the macrolactone (C_1-C_{24}) and lactol ($C_{33}-C_{37}$) ring systems was assigned by extensive two-dimensional NMR spectroscopy.[2a] The absolute configuration of these ring systems and the C_{38} and C_{43} stereocenters were determined using a combination of Mosher's ester analysis, degradation, and chemical correlation.[2b,c]



The phorboxazoles are among the most cytostatic natural products known, inhibiting the growth of tumor cells at nanomolar concentrations.[2] The mean GI_{50} reported for phorboxazole A against the National Cancer Institute's (NCI) panel of 60 tumor cell lines was 1.58×10^{-9} M.[3] The most recently reported in vitro studies showed that **1** selectively inhibited the growth of colon tumor cells HCT-116 (GI_{50} 4.36×10^{-10} M) and HT29 (3.31×10^{-10} M), as well as leukemia CCRF−CBM (2.45×10^{-10} M), prostate cancer PC-3 (3.54×10^{-10} M), and breast cancer MCF7 cell lines (5.62×10^{-10} M).[2b] In addition to this impressive anticancer activity, phorboxazoles A and B also exhibit potent in vitro antifungal activity against *Candida albicans* and *Saccharomyces carlsbergensis* at 0.1 μg/disk in the agar disk diffusion assay.[2a]

Both the inhibition and promotion of tubulin polymerization have been shown to be important in the mechanism of action of several known antineoplastic natural products that arrest the cell cycle during the M phase, the period in which mitotic division of the cell takes place.[4] Although the precise mechanism of action of the phorboxazoles is unknown, it has been shown that they do not inhibit tubulin polymerization or interfere with the integrity of microtubules. Additionally, Burkitt lymphoma

(1) This work is taken in part from the Ph.D. Thesis of D. M. Fitch, Harvard University, 2000.

(2) (a) Searle, P. A.; Molinski, T. F. *J. Am. Chem. Soc.* **1995**, *117*, 8126−8131. (b) Searle, P. A.; Molinski, T. F.; Brzezinski, L. J.; Leahy, J. W. *J. Am. Chem. Soc*. **1996**, *118*, 9422−9423. (c) Molinski, T. F. *Tetrahedron Lett.* **1996**, *37*, 7879−7880.

(3) GI_{50} is defined as the concentration at which cell growth is inhibited by 50%. Phorboxazoles A and B were reported to display comparable biological activities; see ref 2b.

(4) Hardman, J. G.; Gilman, A. G.; Limbird, L. E. *The Pharmacological Basis of Therapeutics*, 9th ed.; McGraw-Hill: New York, 1996.

(5) Initial communications of this work: (a) Evans, D. A.; Cee, V. J.; Smith, T. E.; Fitch, D. M.; Cho, P. S. *Angew. Chem., Int. Ed. Engl.* **2000**, *39*, 2533−2536. (b) Evans, D. A.; Fitch, D. M. *Angew. Chem., Int. Ed. Engl.* **2000**, *39*, 2536−2540.

(6) Phorboxazole synthetic studies: (a) Rychnovsky, S. D.; Thomas, C. R. *Org. Lett.* **2000**, *2*, 1217−1219. (b) Pattenden, G.; Plowright, A. T. *Tetrahedron Lett.* **2000**, *41*, 983−986. (c) Schaus, J. V.; Panek, J. S. *Org. Lett*. **2000**, *2*, 469−471. (d) Wolbers, P.; Hoffmann, H. M. R.; Sasse, F. *Synlett* **1999**, *11*, 1808−1810. (e) Smith, A. B., III; Verhoest, P. R.; Minbiole, K. P.; Lim, J. J. *Org. Lett.* **1999**, *1*, 909−912. (f) Smith, A. B., III.; Minbiole, K. P.; Verhoest, P. R.; Beauchamp, T. J. *Org. Lett.* **1999**, *1*, 913−916. (g) Wolbers, P.; Misske, A. M.; Hoffmann, H. M. R. *Tetrahedron Lett.* **1999**, *40*, 4527−4530. (h) Evans, D. A.; Cee, V. J.; Smith, T. E.; Santiago, K. J. *Org. Lett*. **1999**, *1*, 87−90. (i) Wolbers, P.; Hoffmann, H. M. R. *Synthesis* **1999**, *5*, 797−802. (j) Misske, A. M.; Hoffmann, H. M. R. *Tetrahedron* **1999**, *55*, 4315−5324. (k) Williams, D. R.; Clark, M. P. *Tetrahedron Lett.* **1999**, *40*, 2291−2294. (l) Williams, D. R.; Clark, M. P.; Berliner, M. A. *Tetrahedron Lett.* **1999**, *40*, 2287−2290. (m) Wolbers, P.; Hoffmann, H. M. R. *Tetrahedron* **1999**, *55*, 1905−1914. (n) Rychnovsky, S. D.; Hu, Y.; Ellsworth, B. *Tetrahedron Lett.* **1998**, *39*, 7271−7274. (o) Paterson, I.; Arnott, E. A. *Tetrahedron Lett*. **1998**, *39*, 7185−7188. (p) Pattenden, G.; Plowright, A. T.; Tornos, J. A.; Ye, T. *Tetrahedron Lett*. **1998**, *39*, 6099−6102. (q) Ye, T.; Pattenden, G. *Tetrahedron Lett.* **1998**, *39*, 319−322. (r) Ahmed, F.; Forsyth, C. J. *Tetrahedron Lett.* **1998**, *39*, 183−186. (s) Cink, R. D.; Forsyth, C. J. *J. Org. Chem.* **1997**, *62*, 5672−5673. (t) Lee, C. S.; Forsyth, C. J. *Tetrahedron Lett.* **1996**, *37*, 6449−6452. (u) Greer, P. B.; Donaldson, W. A. *Tetrahedron Lett.* **2000**, *41*, 3801−3803.

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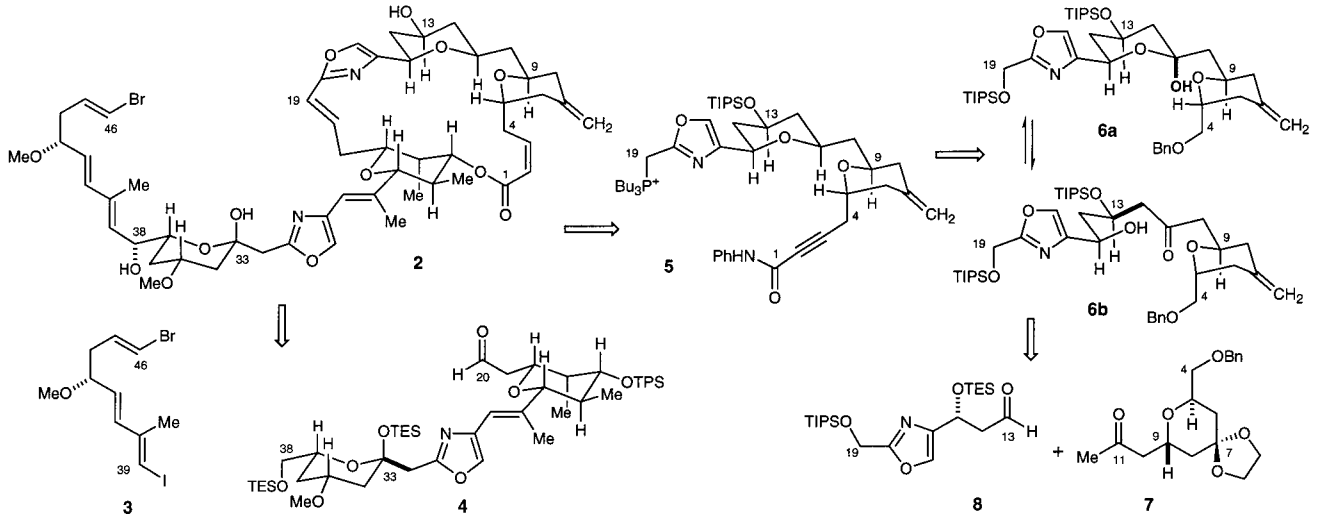
Scheme 1



CA46 cells treated with phorboxazole A showed cell cycle arrest in the S phase, the period in which DNA is replicated.[2c] These results suggest that the phorboxazoles may interact with a unique intracellular target. Identification of this target may aid in the discovery of new antineoplastic agents.

Results and Discussion

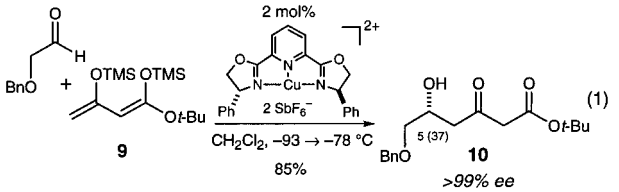
Synthesis Plan. The unique structure and impressive biological activity of the phorboxazoles have led to extensive efforts directed toward the synthesis of these compounds.[5,6] The total synthesis of phorboxazole A was recently reported by Forsyth and co-workers.[7] This synthesis featured fragment assemblage through an oxazole assemblage process involving amide bond formation followed by cyclodehydration.[8] The present approach, directed at the synthesis of phorboxazole B, has relied on exploitation of the inherent reactivity of the intact oxazole moieties, which might actively participate in the fragment coupling exercise.

The illustrated synthesis plan (Scheme 1) calls for disconnection of the $C_{38}-C_{39}$ bond to provide the triene side chain **3**, allowing the remainder of the molecule to be truncated into fragments of comparable complexity. Disconnection through the $C_{19}-C_{20}$ (*E*) olefin and macrolactone moieties provides the $C_{20}-C_{38}$ core fragment **4** and the C_1-C_{19} bis(pyran) fragment **5**. The retrosynthesis of the C_1-C_{19} subunit **5** begins with the disconnection of the peripheral functionality at C_4 and C_{19}, and the masking of leaving groups at these positions as differentially protected primary hydroxyls. The C_7 exocyclic olefin is masked as a protected ketone, and the C_{11} stereocenter is envisioned to arise via reduction of hemiketal **6a**. Ring-chain tautomerization (**6a** → **6b**) and $C_{12}-C_{13}$ aldol disconnection leads to methyl ketone and the oxazole aldehyde fragments **7** and **8**.

In principle, stereochemical control in the proposed aldol union of ketone **7** and aldehyde **8** might arise from either the C_{15} stereocenter on the aldehyde fragment (1,3-induction) or from the C_9 stereocenter on the methyl ketone fragment (1,5-induction). In the Lewis acid-catalyzed aldol reaction of β-alkoxy aldehydes, the inherent facial bias of the aldehyde component, rationalized by a preferred dipole orientation, while affording the potential for 1,3-anti asymmetric induction, carries the restriction that sterically demanding silyl protecting groups on the β-oxygen cannot be employed.[9] Since the C_{15} hydroxyl must carry a readily removable protecting group for subsequent transformations, the synthesis plan relied on an aldol coupling that would exploit stereoinduction from the C_9 stereocenter in methyl ketone **7** (1,5-induction) for which precedent had been established.[10]

During the course of our synthesis of altohyrtin C (spongistatin 2),[11] it was discovered that boron enolates of β-alkoxy methyl ketones add to aldehydes with high levels of 1,5-anti asymmetric induction.[10a] In the original study, methyl ketones containing either *p*-methoxybenzyl-protected β-hydroxy groups or β-benzylidene acetals were found to provide excellent levels of diastereoselectivity when the aldol reaction was carried out in ethereal solvents at low temperature. Furthermore, identical levels of 1,5-anti stereochemical induction were obtained upon addition to enantiomeric chiral aldehydes, which suggests that the stereochemical outcome is controlled entirely by the facial bias of the enolate. The following discussion describes the application of this methodology to the construction of the C_1-C_{19} fragment of phorboxazole B.

C_1-C_{19} Subunit. The development of catalytic enantioselective aldol reactions has been an objective of numerous research groups.[12] The adducts obtained from some of these reactions are attractive synthons for the construction of polyketide-derived natural products (eq 1). In the illustrated reaction,[13] it



(1)

was discovered that the addition of bis(trimethylsilyl)dienol ether

(7) Forsyth, C. J.; Ahmed, F.; Cink, R. D.; Lee, C. S. *J. Am. Chem. Soc.* **1998**, *120*, 5597−5598.

(8) For the cyclodehydration of amide aldehydes to form 2,4-disubstituted oxazoles, see: (a) Wipf, P.; Lim, S. *J. Am. Chem. Soc.* **1995**, *117*, 558−559. (b) Wipf, P.; Miller, C. P. *J. Org. Chem.* **1993**, *58*, 3604−3603.

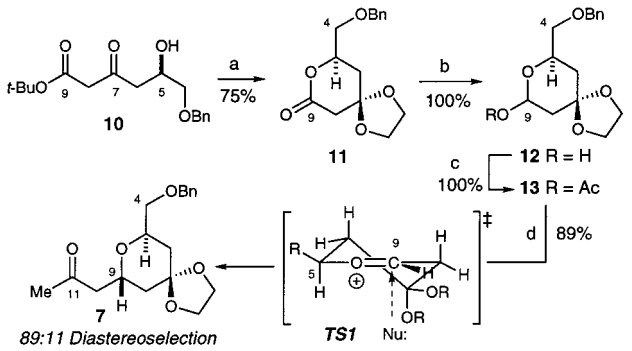
(9) (a) Evans, D. A.; Duffy, J. L.; Dart, M. J. *Tetrahedron Lett.* **1994**, *35*, 8537−8540. (b) Evans, D. A.; Dart, M. J.; Duffy, J. L.; Yang, M. G. *J. Am. Chem. Soc.* **1996**, *118*, 4322−4343.

(10) (a) Evans, D. A.; Coleman, P. J.; Côté, B. *J. Org. Chem.* **1997**, *62*, 788−789. See also: (b) Paterson, I.; Gibson, K. R.; Oballa, R. M. *Tetrahedron Lett.* **1996**, *37*, 8585−8588.

(11) Evans, D. A.; Trotter, B. W.; Coleman, P. J.; Côté, B.; Dias, L. C.; Rajapakse, H. A.; Tyler, A. N. *Tetrahedron* **1999**, *55*, 8671−8726.

(12) Reviews: (a) Nelson, S. G. *Tetrahedron: Asymmetry* **1998**, *9*, 357−389. (b) Gröger, H.; Vogl, E. M.; Shibasaki, M. *Chem. Eur. J.* **1998**, *4*, 1137−1141. (c) Mahrwald, R. *Chem. Rev.* **1999**, *99*, 1095−1120.

Scheme 2[a]



[a] Key: (a) $HO(CH_2)_2OH$, TMSCl, CH_2Cl_2, rt. (b) DIBALH, tol, −78 °C. (c) Ac_2O, pyr, cat DMAP, CH_2Cl_2, rt. (d) TMSOTf, 2-(trimethylsilyloxy)propene, cat. pyr, CH_2Cl_2, −78 °C.

9 to (benzyloxy)acetaldehyde catalyzed by a bis(oxazolinyl)-pyridine Cu(II) complex provided the desired aldol adduct **10** in excellent yield and enantioselectivity (eq 1).[13a] The δ-hydroxy-β-ketoester **10** was viewed as an ideal starting material for the synthesis of both the C_4-C_9 and $C_{33}-C_{38}$ subunits of phorboxazole B. Given the identical absolute configuration of the C_5 and C_{37} stereocenters, a single reaction provided material for the construction of both fragments.

The synthesis of methyl ketone **7** began with the merged cyclization−ketal protection of aldol adduct **10** upon treatment with ethylene glycol and trimethylsilyl chloride to deliver lactone **11** in 75% yield (Scheme 2).[14] Reduction of lactone **11** (DIBAlH, toluene, −78 °C) followed by acetylation (Ac_2O, pyridine, cat. DMAP, CH_2Cl_2) afforded **13** in quantitative yield as a 92:8 mixture of β/α anomers.[15,16] Treatment of the anomeric acetates with trimethylsilyl trifluoromethanesulfonate (TMSOTf)[17] and 2-(trimethylsilyloxy)propene resulted in an 89:11 mixture of diastereomeric tetrahydropyrans,[18] favoring the desired trans isomer **7**.[19] The relative stereochemistry of the major product was inferred from precedent and later established by X-ray crystallographic analysis of aldol adduct **14** (vide infra). Axial attack of the nucleophile from the bottom face of the oxocarbenium ion derived from **13** (as depicted in **TS1**) via a chairlike transition structure provides a rationalization for the formation of the major product.[20] This diastereoface is partially hindered by the axial oxygen substituent associated with the C_7 ketal, which may explain the formation of a minor amount of the undesired cis isomer. The desired C_4-C_{12} trans tetrahydropyran fragment **7** was obtained in five steps and 50% overall yield from (benzyloxy)acetaldehyde.

In the synthesis plan outlined in Scheme 1, it was necessary to establish whether 1,5-anti induction from the C_9 oxygen-bearing stereocenter in methyl ketone **7** in the aldol union with aldehyde **8** was possible during the $C_{12}-C_{13}$ bond construction. In our original study on related aldol reactions, the methyl ketones employed contained either *p*-methoxybenzyl-protected β-hydroxy groups or β-benzylidene acetals.[10a] As a consequence, it was unclear whether the β-tetrahydropyranyl moiety, as in **7,** would afford an analogous directing effect. This point was tested in a simple model study (eq 2). Addition of the dibutylboron enolate derived from ketone **7** to dihydrocinnamaldehyde provided the desired adduct **14** as a single isomer in good yield (eq 2). The relative stereochemistry of the product, established by X-ray crystallographic analysis, was found to possess the desired 1,5-anti relationship (Figure 1) as predicted from related aldol reactions.[21]

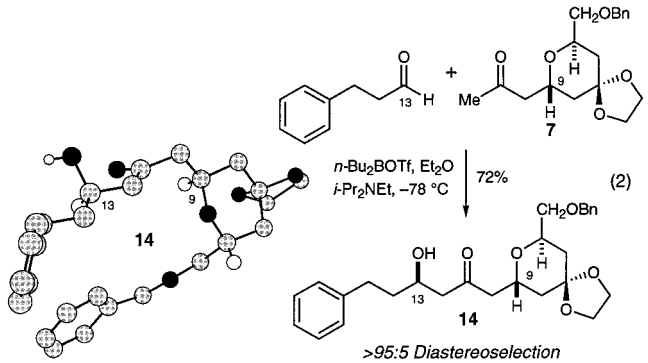


Figure 1. X-ray crystal structure of model aldol adduct **14**.

With the requisite methyl ketone fragment in hand and precedent for the 1,5-induction aldol reaction established, the synthesis of the $C_{13}-C_{19}$ aldehyde **8** was investigated (Scheme 3). The use of auxiliary-based aldol additions of haloacetyloxazolidinones as masked chiral acetate enolate equivalents has proven reliable in this laboratory.[22] To explore the viability of subsequent fragment couplings, an approach to aldehyde **8** was undertaken utilizing this methodology. The requisite aldehyde **17** was constructed from the known oxazole ester **15**[23] via silylation of the primary hydroxyl (TIPSOTf, 2,6-lutidine, CH_2Cl_2, 0 °C; 100%) followed by partial reduction of the ester (DIBAlH, CH_2Cl_2, −94 °C; 97%). An aldol reaction between the dibutylboron enolate derived from chloroacetyloxazolidinone **18**[22] and aldehyde **17** provided the desired adduct **19** in excellent yield (90%) and diastereoselectivity (>95:5).[15] Dechlorination of **19** was accomplished in 91% yield upon treatment with zinc dust and glacial acetic acid at room temperature. Silylation of the free hydroxyl (TESCl, imidazole, cat. DMAP, DMF, rt; 100%) was followed by reductive cleavage of the auxiliary ($LiBH_4$, Et_2O, H_2O, rt; 85%)[24] and Swern oxidation (oxalyl chloride, DMSO, CH_2Cl_2; Et_3N, −78 °C; 99%) to afford aldehyde **8** in seven steps and 67% overall yield from ester **15**.

As is often the case, the synthesis of complex natural products provides the impetus for extending the scope of known reactions.

(13) (a) Evans, D. A.; Kozlowski, M. C.; Murry, J. A.; Burgey, C. S.; Campos, K. R.; Connell, B. T.; Staples, R. J. *J. Am. Chem. Soc.* **1999**, *121*, 669−685. (b) Evans, D. A.; Burgey, C. S.; Kozlowski, M. C.; Tregay, S. W. *J. Am. Chem. Soc.* **1999**, *121*, 686−699. (c) Evans, D. A.; MacMillan, D. W. C.; Campos, K. R. *J. Am. Chem. Soc.* **1997**, *119*, 10859−10860.

(14) Chan, T. H.; Brook, M. A.; Chaly, T. *Synthesis* **1983**, 203−205.

(15) Product ratio determined by ^{1}H NMR spectral analysis (500 MHz) of the unpurified reaction mixture.

(16) Although the anomers were separable by silica gel chromatography, the mixture was generally taken on without purification.

(17) Use of stronger Lewis acids such as $BF_3{\cdot}OEt_2$ or $TiCl_4$ led to high levels of decomposition.

(18) For an early example of nucleophilic addition to oxocarbenium ions in the synthesis of *C*-glycosides, see: Lewis, M. D.; Cha, J. K.; Kishi, Y. *J. Am. Chem. Soc.* **1982**, *104*, 4976−4978.

(19) Optimal results were obtained when buffering the reaction with 20 μol % pyridine. Diastereoselectivity was determined by ^{1}H NMR and HPLC analysis (Zorbax silica gel, 20% EtOAc/hexanes, 1.0 μL/min, $\lambda = 254$ nm, T_r major = 11 min, T_r minor = 13 min).

(20) Eliel, E. L.; Wilen, S. H.; Mander, L. N. *Stereochemistry of Organic Compounds*; Wiley: New York, 1994; Chapter 11.

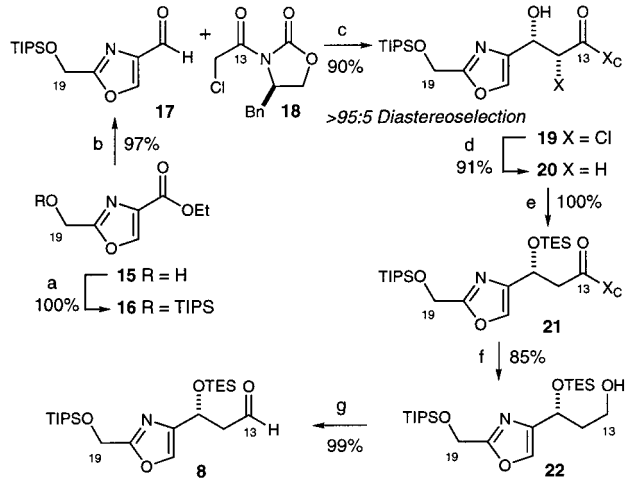
(21) The diastereoselectivity of this reaction was previously misreported as 89:11 (see ref 10a). The X-ray crystal structure of **14** was determined by Mr. Kevin Campos. See Supporting Information for the coordinates.

(22) (a) Evans, D. A.; Sjogren, E. B.; Weber, A. E.; Conn, R. E. *Tetrahedron Lett.* **1987**, *28*, 39−42. For an application of this methodology toward the synthesis of bryostatin 2, see: (b) Evans, D. A.; Carter, P. H.; Carreira, E. M.; Charette, A. B.; Prunet, J. A.; Lautens, M. *J. Am. Chem. Soc.* **1999**, *121*, 7540−7552.

(23) Ester 15 is available in five steps from cinnamamide and ethyl bromopyruvate; see: Panek, J. S.; Beresis, R. T. *J. Org. Chem.* **1996**, *61*, 6496−6497.

(24) Penning, T. D.; Djuric, S. W.; Haack, R. A.; Kalish, V. J.; Miyashiro, J. M.; Rowell, B. W.; Yu, S. S. *Synth. Commun.* **1990**, *20*, 307−312.

Scheme 3[a]



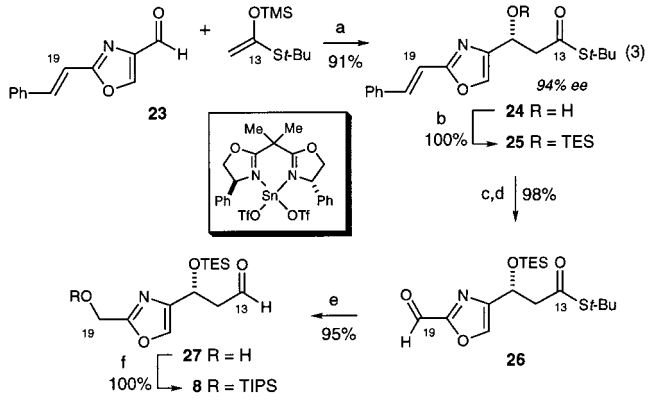
[a] Key: (a) 2,6-lutidine, CH_2Cl_2, 0 °C. (b) DIBALH, CH_2Cl_2, −94 °C. (c) *n*-Bu_2BOTf, Et_3N, CH_2Cl_2, −78 °C to rt; then **17**, −78 °C. (d) Zn, AcOH, THF, rt. (e) TESCl, imidazole, cat DMAP, DMF, rt. (f) $LiBH_4$, Et_2O, H_2O, rt. (g) oxalyl chloride, DMSO, CH_2Cl_2, Et_3N, −78 °C.

A family of catalyst systems, developed in this laboratory, offers excellent levels of enantioselectivity in the addition of silylketene acetals to chelating electrophiles.[13] Since α-oxazole aldehyde **23** could be viewed as a potential bidentate electrophile, experiments were initiated to expand the scope of these catalytic processes. Indeed, bidentate coordination of an α-oxazole aldehyde to a chelating Lewis acid has been reported in the literature.[25] In direct analogy to our previously reported Sn(II)-catalyzed enantioselective aldol addition of silylketene acetals to ethyl glyoxylate,[13c] addition of the *tert*-butyl thioacetate-derived silylketene acetal to aldehyde **23**[26] catalyzed by 10 mol % [Sn((*S*,*S*)-Ph-box)](OTf)$_2$) afforded adduct **24** in excellent yield (91%) and enantioselectivity (94% ee) (Scheme 4, eq 3).[27] The absolute configuration of **24** was assigned following its conversion to aldehyde **8** (vide infra), which had been prepared by the previously described auxiliary-based route (Scheme 3). The high level of asymmetric induction obtained in this transformation provides circumstantial evidence that aldehyde **23** is binding in a two-point fashion to the Sn(II) catalyst.

Silylation of aldol adduct **24** (TESCl, imidazole, cat. DMAP, DMF; 100%) was followed by osmium-mediated dihydroxylation[28] and oxidative cleavage of the derived diol ($Pb(OAc)_4$, K_2CO_3, CH_2Cl_2, 0 °C; 98%, two steps) to provide aldehyde **26** in excellent overall yield (Scheme 4). Simultaneous reduction of both the C_{19} aldehyde and the C_{13} *tert*-butyl thioester functionalities was accomplished in a single step upon treatment with DIBAlH. Subsequent silylation (TIPSOTf, 2,6-lutidine, CH_2Cl_2, 0 °C; 100%) completed the improved synthesis of the $C_{13}-C_{19}$ oxazole aldehyde **8** in six steps and 85% overall yield from **23**.

In the crucial $C_{12}-C_{13}$ aldol fragment coupling, treatment of the dibutylboron enolate derived from diastereomerically pure

Scheme 4[a]



[a] Key: (a) 10 mol % [Sn(*S*,*S*)-Ph-box)](OTf)$_2$ catalyst, CH_2Cl_2, −78 °C. (b) TESCl, imidazole, cat DMAP, DMF. (c) cat $K_2OsO_4(H_2O)_2$, cat quinoline, $K_3Fe(CN)_6$, K_2CO_3, methanesulfonamide, 1:1 *t*-BuOH/H_2O. (d) $Pb(OAc)_4$, K_2CO_3, CH_2Cl_2, 0 °C. (e) DIBALH, CH_2Cl_2, −78 °C. (f) 2,6-lutidine, TIPSOTf, CH_2Cl_2, 0 °C.

ketone **7** with aldehyde **8** in ether at −105 °C afforded adduct **28** in good yield as a single diastereomer,[15] with the remaining mass balance composed of recovered starting materials (Scheme 5). Interestingly, when the reaction was carried out using the 8:1 mixture of diastereomers (trans/cis) of ketone 7 originally obtained in the oxocarbenium alkylation reaction, the aldol adduct was isolated as a 12:1 mixture of separable isomers (82%) along with a 4:1 (trans/cis) mixture of recovered ketone **7** (17%). The partial kinetic resolution is believed to be a consequence of a kinetically matched reaction. While the β-stereocenter of the enolate controls the absolute configuration of the newly formed stereocenter, it is kinetically matched with respect to the aldehyde β-stereocenter.[9,29] Silylation (TIPSOTf, 2,6-lutidine, CH_2Cl_2, 0 °C; 99%) of the C_{13} free hydroxyl of aldol adduct **28**, followed by selective deprotection of the C_{15} triethylsilyl ether (HF·pyridine, pyridine, THF, H_2O, 0 °C; 99%) provided hemiketal **6**.[30] Axial hydride reduction of the C_{11} hemiketal ($BF_3{\cdot}OEt_2$, Et_3SiH, CH_2Cl_2, −78 → −50 °C)[18] afforded (bis)tetrahydropyran **30** in excellent yield (96%) and diastereoselectivity (>95:5).[15] Axial attack of the hydride nucleophile from the bottom face of the oxocarbenium ion derived from hemiketal **6** (as depicted in **TS2**) via a chairlike transition structure rationalizes the formation of the observed product **30**.[20] Unlike the alkylation of the oxocarbenium ion derived from **13** (Scheme 2), all of the ring substituents in the present case are pseudo-equatorial. This may be responsible for the higher level of diastereoselectivity observed in the hydride reduction reaction relative to the previously described alkylation.

The relative stereochemistry of both aldol adduct **28** and reduction product **30** was inferred from precedent and verified by ROESY NMR analysis of intermediate **33** (vide infra), which showed NOE enhancements between the C_{11} axial methine proton and the axial methine protons of C_{13} and C_{15}.

With the requisite stereochemistry incorporated into **30**, some refunctionalization was required to complete the synthesis of the C_4-C_{19} fragment. While the use of more harshly acidic conditions led to the competitive cleavage of the C_{19} primary

(25) Liu, P.; Panek, J. S. *Tetrahedron Lett.* **1998**, *39*, 6143−6146.

(26) Aldehyde **23** was obtained from reduction (see Supporting Information for details) of the known ethyl ester. See ref 23.

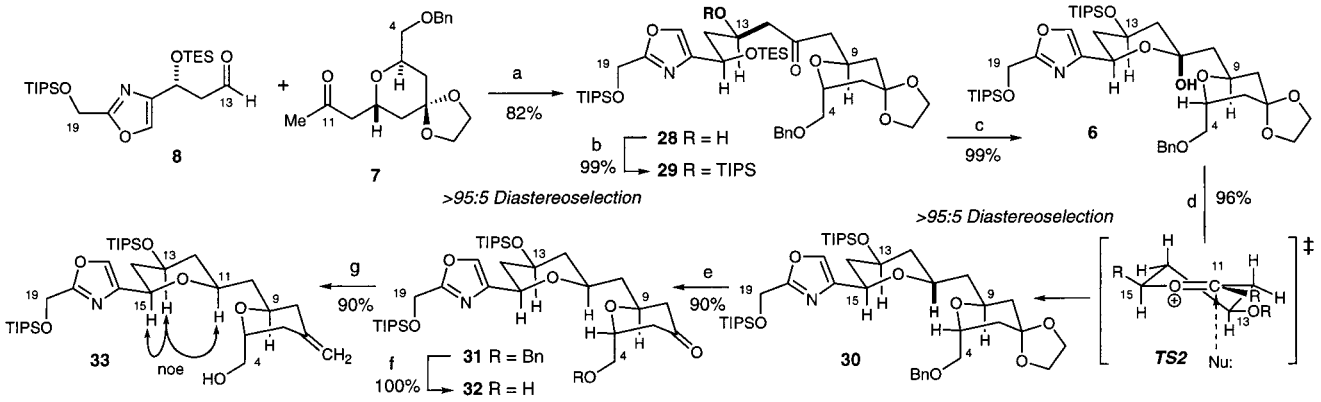
(27) Dr. David MacMillan is gratefully acknowledged for the development of this reaction. Enantiomeric excess was determined by chiral HPLC analysis (Chiralcel OD-H column, 4% EtOH/hexanes, 1.0 mL/min, λ = 254 nm, (*R*) enantiomer T_r = 34.2 min, (*S*) enantiomer T_r = 36.8 min).

(28) The dihydroxylation was performed using the achiral ligand, quinuclidine. For a review of asymmetric dihydroxylation under these conditions, see: Kolb, H. C.; VanNieuwenhze, M. S.; Sharpless, K. B. *Chem. Rev.* **1994**, *94*, 2483−2547.

(29) A more dramatic kinetic resolution was observed in this laboratory during the synthesis of roxaticin, in which a 1,5-induction aldol reaction involving a 7:1 mixture of aldehyde diastereomers result in a >95:5 ratio of product isomers along with a 1:1 mixture of diastereomers of the recovered aldehyde. Evans, D. A.; Connell, B. T. Manuscript in preparation.

(30) Hemiketal **6** existed as a 92:8 mixture of the closed hemiketal to open hydroxy ketone. This mixture was taken on together in the subsequent reduction.

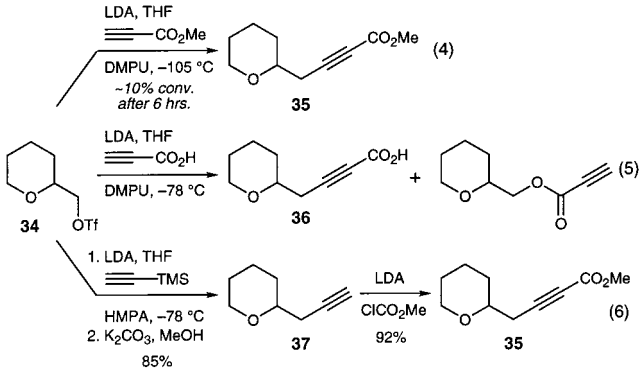
Scheme 5[a]



[a] Key: (a) *n*-Bu_2BOTf, *i*-Pr_2NEt, CH_2Cl_2, −105 °C. (b) TIPSOTf, CH_2Cl_2, 0 °C. (c) HF·pyr, pyr, THF, H_2O, 0 °C. (d) BF_3·OEt_2, Et_3SiH, CH_2Cl_2, −78 to −50 °C. (e) $FeCl_3$·SiO_2, $CHCl_3$, acetone, rt. (f) 1 atm H_2, Pd/C, *i*-PrOH. (g) Ph_3PCH_3Br, PhLi, THF, 0 °C.

triisopropylsilyl ether, ketal hydrolysis with $FeCl_3$·SiO_2 in 10:1 CH_3Cl/acetone provided ketone **31** in 90% yield.[31] Debenzylation of **31** (1 atm H_2, Pd/C, *i*-PrOH; 100%) was followed by a Wittig reaction with methylene−triphenylphosphorane to incorporate the C_7 exocyclic olefin in 90% yield.

At this point, the synthesis plan called for the displacement of a leaving group at C_4 with an appropriately functionalized three-carbon fragment. Exploratory experiments performed on trifluoromethanesulfonate **34**, derived from the commercially available tetrahydropyran-2-methanol, were informative. The lithium anions of methyl and ethyl propiolate proved too weakly nucleophilic at low temperature to alkylate the model trifluoromethanesulfonate (eq 4) while at higher temperatures, de-



composition was observed.[32] Although the propiolic acid dianion was sufficiently nucleophilic to displace the primary trifluoromethanesulfonate, a mixture of C- and O-alkylated products was obtained under a variety of conditions (eq 5). Ultimately, a stepwise approach was investigated. Alkylation of trifluoromethanesulfonate **34** with the lithium (trimethylsilyl)acetylide[33] followed by desilylation (K_2CO_3, MeOH) provided alkyne **37** in 85% yield. Deprotonation of the terminal alkyne with 1 equiv of lithium diisopropylamide (LDA) followed by acylation with methyl chloroformate afforded the desired ester **35** in 92% yield (eq 6).

Scheme 6

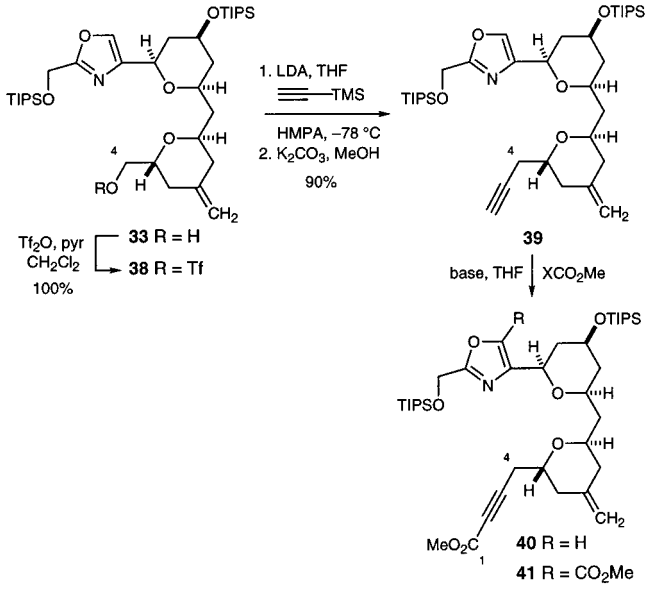


Table 1. Alkyne Carboalkoxylation

base	equiv	temp (°C)	X	yield (**40**, %)	yield (**41**, %)
LDA	1	−78	Cl	50	
LDA	2	−78	Cl	50	30
EtMgBr	10	reflux	CN	80	

Treatment of alcohol **33** with trifluoromethanesulfonic anhydride and pyridine afforded the chromatographically stable primary trifluoromethanesulfonate **38** in quantitative yield (Scheme 6). Utilizing conditions employed on the model compound 34, displacement of the primary trifluoromethanesulfonate with lithium (trimethylsilyl)acetylide followed by desilylation provided alkyne **39** in 90% overall yield. As before, deprotonation of the terminal alkyne with 1 equiv of LDA followed by the addition of methyl chloroformate provided the desired alkynoate ester **40**. However, under these conditions the reaction did not proceed beyond 50% conversion (Table 1). The use of multiple equivalents of base or higher reaction temperatures resulted in the formation of byproduct **41**, in which a second carbomethoxy group was incorporated at the 5-position of the oxazole ring. After some experimentation, it was

(31) Kim, K. S.; Song, Y. H.; Lee, B. H.; Hahn, C. S. *J. Org. Chem.* **1986**, *51*, 404−407.

(32) In addition to aldehydes and ketones, the lithium anion of methyl propiolate was found to decompose at temperatures above −100 °C, while the ethyl ester variant was found to be stable up to −78 °C. See: Midland, M. M.; Tramontano, A.; Cable, J. R. *J. Org. Chem.* **1980**, *45*, 28−29.

(33) For the displacement of sugar-derived primary trifluoromethanesulfonates with the lithium anion of (trimethylsilyl)acetylene, see: Shen, Q.; Sloss, D. G.; Berkowitz, D. B. *Synth. Commun.* **1994**, *24*, 1519−1530.

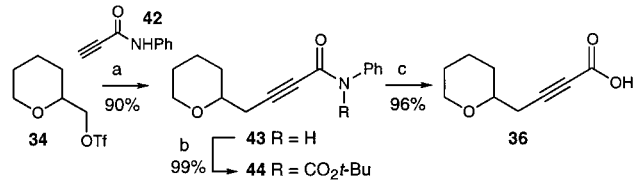
(34) For the synthesis of *β*-keto esters by the addition of lithium enolates to methyl cyanoformate, see: Mander, L. N.; Sethi, S. P. *Tetrahedron Lett.* **1983**, *24*, 5425−5428.

discovered that an 80% yield of the desired compound **40** could be obtained upon deprotonation of **39** with ethylmagnesium bromide in refluxing THF followed by the addition of methyl cyanoformate.[34]

While the preceding reaction sequence accomplished the three-carbon homologation, the overall efficiency of this process was lacking. Accordingly, the alkylation sequence outlined in Scheme 7 was investigated. Prior work from this laboratory on the synthesis of bryostatin 2[22b] showed that an *N*-phenyl amide could act as a carboxyl surrogate with attenuated nucleophilicity. With this in mind, trifluoromethanesulfonate 34 was treated with the *N*-phenyl propynamide derived dianion[35] to provide the desired amide **43** in 90% yield with no accompanying N-alkylation byproducts. Subsequent amide hydrolysis[36] through *N*-Boc imide **44** with LiOH afforded acid **36** in excellent overall yield.

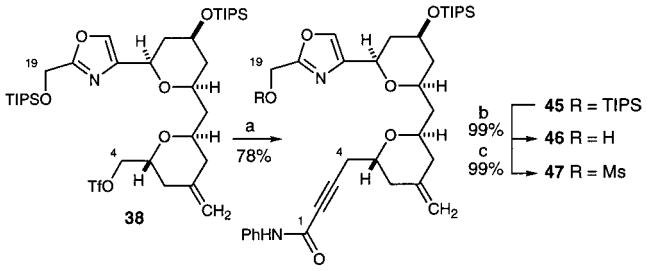
In the actual application to the synthesis, displacement of the required primary trifluoromethanesulfonate **38** with the dianion derived from **42** afforded the desired amide **45** in 78% yield (Scheme 8). In this case, the reaction was considerably slower than in the alkylation of the model compound **34**, perhaps owing to the conformational effects present in a more hindered trifluoromethanesulfonate. As a consequence, minor byproducts resulting from carboxyl and double alkylation were isolated. Selective deprotection (TBAF, THF, −50 °C; 99%) of the C_{19} triisopropylsilyl ether of **45** followed by formation of the primary methanesulfonate (MsCl, *i*-Pr_2NEt, CH_2Cl_2, −5 °C; 99%) completed the synthesis of the C_1-C_{19} subunit **47** in 17 steps (longest linear sequence from aldehyde **23**) and 40% overall yield.

Scheme 7[a]



[a] Key: (a) **42**, *n*-BuLi, THF, −78 to −10 °C; then **34**. (b) Boc_2O, DMAP, MeCN. (c) LiOH, THF, H_2O, rt.

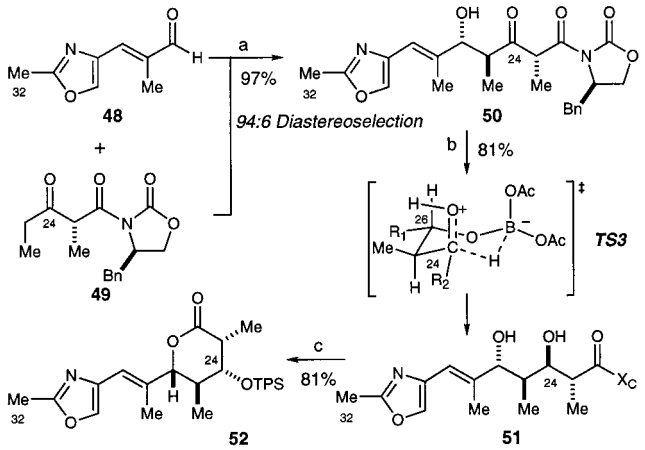
Scheme 8[a]



[a] Key: (a) **42**, *n*-BuLi, THF, −78 to −20 °C; then **38**. (b) TBAF, THF, −50 °C. (c) MsCl, *i*-Pr_2NEt, CH_2Cl_2, −5 °C.

C_{20}-C_{38} Subunit. The synthesis of the polypropionate region of the central polyketide fragment **4** began with the addition of the (*E*) boron enolate derived from *β*-ketoimide **49**[37] to the known aldehyde **48**,[38] which delivered the desired anti aldol adduct **50** in 97% yield (94:6 dr,[39] (Scheme 9).[40] Subsequent hydroxyl-directed reduction (**TS3**)[41] of the C_{24} ketone provided the 1,3-anti diol **51,** which was isolated in 81% yield as a single diastereomer after crystallization.[15] Cyclization of **51** under basic conditions (cat. DBU, CH_2Cl_2, rt) followed by in situ protection of the C_{24} hydroxyl as its triphenylsilyl ether (TPSCl, imidazole) yielded lactone **52**. X-ray crystallographic analysis of **52** confirmed the relative stereochemical assignment.[42]

Scheme 9[a]



[a] Key: (a) c-(hex)$_2$BCl, $EtNMe_2$, Et_2O, 0 °C; then **48**, −78 to 0 °C. (b) $Me_4NBH(OAc)_3$, AcOH, 0 °C to rt. (c) cat DBU, CH_2Cl_2, rt; then imidazole, TPSCl, rt.

Alkylation of lactone **52** with the lithium enolate derived from *tert*-butyl acetate provided hemiketal **53** (Scheme 10). Reduction of the unpurified hemiketal (BF_3·OEt_2, Et_3SiH, CH_2Cl_2, −78 → −30 °C)[18] afforded the desired cis tetrahydropyran 54 (>95:5 dr) in 91% yield for the two steps.[15] The stereochemical assignment of **54** was supported by ^1H NMR coupling constants, which were consistent with a tetrahydropyran ring containing the desired substitution in a chair conformation. As expected, oxocarbenium ion reduction was again (Scheme 5) in accord with precedent.[18] Reduction of the ester ($LiAlH_4$, Et_2O/THF, −20 °C; 96%) and silylation of the resulting primary hydroxyl (TMSCl, imidazole, cat. DMAP, DMF, rt; 99%) completed the $C_{20}-C_{32}$ tetrahydropyran fragment **56** in 55% overall yield for the eight-step sequence from aldehyde **48**.

The $C_{33}-C_{38}$ hydroxy pyran subunit was employed as a focal point for the union of the bromotrienyl terminus ($C_{38}-C_{39}$ bond construction) and the central oxazole-containing subunit ($C_{32}-C_{33}$ bond construction) (Scheme 11). One possible chiral precursor to this building block was the aldol adduct 10 (eq 1) while the other was the hetero-Diels−Alder adduct **57** (eq 7). During the course of this synthesis, this Cu(II)-catalyzed heterocycloaddition was also evaluated for its potential applica-

(35) For the synthesis of **42**, see: (a) Coppola, G. M.; Damon, R. E. *Synth. Commun.* **1993**, *23*, 2003−2010. For the alkylation of carbonyl compounds with the dianion of *N*-benzyl propynamide, see: (b) Coppola, G. M.; Damon, R. E. *J. Heterocycl. Chem.* **1995**, *32*, 1133−1139.

(36) Flynn, D. L.; Zelle, R. E.; Grieco, P. A. *J. Org. Chem.* **1983**, *48*, 2424−2426.

(37) Evans, D. A.; Ennis, M. D.; Le, T.; Mandel, N.; Mandel, G. *J. Am. Chem. Soc.* **1984**, *106*, 1154−1156.

(38) Aldehyde **48** is available in four steps from serine methyl ester hydrochloride and ethyl acetimidate hydrochloride; see: (a) Boger, D. L.; Curran, T. T. *J. Org. Chem.* **1992**, *57*, 2235−2244. (b) Provencal, D. P.; Gardelli, C.; Lafontaine, J. A.; Leahy, J. W. *Tetrahedron Lett.* **1995**, *36*, 6033−6036. (c) Barrish, J. C.; Singh, J.; Spergel, S. H.; Han, W.-C.; Kissick, T. P.; Kronenthal, D. R.; Mueller, R. H. *J. Org. Chem.* **1993**, *58*, 4494−4496.

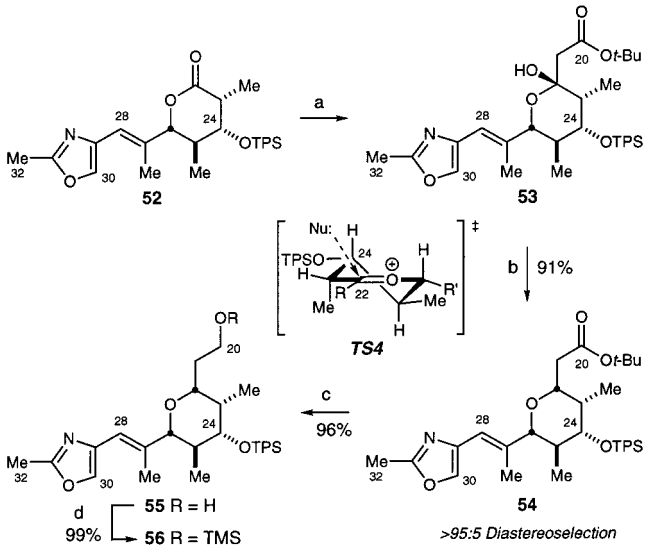
(39) Product ratio determined by HPLC analysis of the unpurified reaction mixture (Zorbax, 4.6 mm × 150 mm, 5 μm silica gel; 3% *i*-PrOH/CH_2Cl_2, flow rate = 1 mL/min; T_r minor = 12.5 min; T_r major = 14.9 min).

(40) Evans, D. A.; Ng, H. P.; Clark, J. S.; Rieger, D. L. *Tetrahedron* **1992**, *48*, 2127−2142.

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

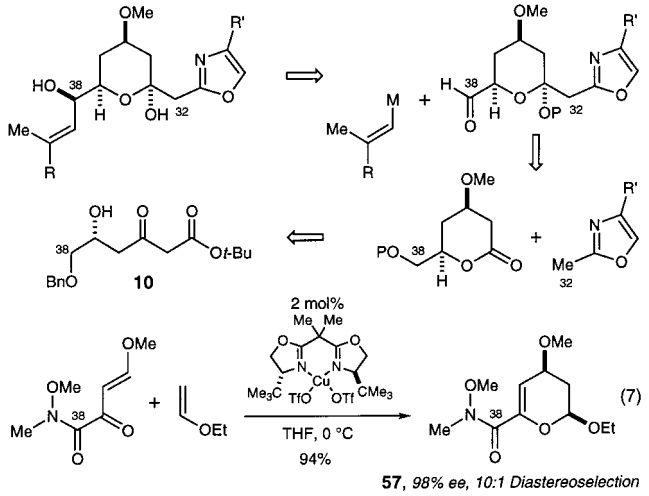
(42) The X-ray crystal structure of **52** was determined by Mr. Jason Tedrow. See Supporting Information for the coordinates.

Scheme 10[a]



[a] Key: (a) *tert*-butyl acetate, LDA, THF, −78 °C; then **52**. (b) $BF_3{\cdot}OEt_2$, Et_3SiH, CH_2Cl_2, −78 to −30 °C. (c) $LiAlH_4$, Et_2O/THF, −20 °C. (d) TMSCl, imidazole, cat DMAP, DMF, rt.

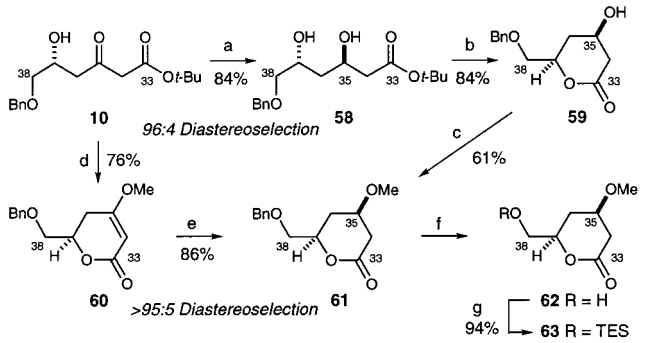
Scheme 11



tion to this project.[43,44] However, the chronology of the reaction discoveries and the advantage of using a common starting material for both the C_4-C_9 and $C_{33}-C_{38}$ pyran rings biased the selection of the pathway illustrated in Scheme 11.

The initial route to the $C_{33}-C_{38}$ lactone began with the hydroxyl-directed reduction of **10**, which provided the desired anti diol in 84% yield as a 96:4 mixture of isomers (Scheme 12). Cyclization under acidic conditions (CF_3CO_2H, CH_2Cl_2, rt) afforded lactone 59 in 84% yield.[45] What had initially appeared to be an uneventful methylation of the C_{35} hydroxyl became an obstacle. Several mild hydroxyl methylation methods were unsuccessfully explored,[46] including methyl trifluo-

Scheme 12[a]



[a] Key: (a) $Me_4NBH(OAc)_3$, AcOH/MeCN, −33 °C. (b) CF_3CO_2H, CH_2Cl_2, rt. (c) Me_3OBF_4, Proton Sponge, CH_2Cl_2, 0 °C. (d) TMSCl, MeOH, CH_2Cl_2, 0 °C. (e) 1 atm H_2, Raney-Ni, *i*-PrOH, rt. (f) 1 atm H_2, 10% Pd/C, EtOAc, rt. (g) TESCl, imidazole, cat. DMAP, rt.

romethanesulfonate with 2,6-di-*tert*-butyl-4-methylpyridine[47] and various catalyzed diazomethane procedures.[48] The use of freshly prepared Ag_2O and iodomethane[49] was found to provide the desired ether **61** in moderate and highly variable yields (50−80%). Treatment with Meerwein's salt (Me_3OBF_4)[50] and 1,8-bis(dimethylamino)naphthalene (Proton Sponge) proved more reliable on a large scale and afforded the desired compound in a reproducible 61% yield.

The problematic methylation of the C_{35} hydroxyl led to an alternative sequence from the *δ*-hydroxy-*β*-ketoester **10** (Scheme 12). Cyclization of **10** to the unsaturated lactone **60** was accomplished in 76% yield under similar conditions (TMSCl, MeOH, CH_2Cl_2, 0 °C)[14] to those employed in the synthesis of lactone **11** (Scheme 2). Diastereoselective hydrogenation of **60** was accomplished with Raney-nickel[51] to afford methyl ether **61** with the desired (*R*) configuration of the ring-containing methoxyl residue (86%; >95:5 dr).[15] In two subsequent steps, the benzyl group was replaced with a triethylsilyl group, providing the requisite $C_{33}-C_{38}$ lactone **63** in five steps and 52% overall yield from (benzyloxy)acetaldehyde.

Oxazole Metalation. The plan for coupling of lactone **63** with fragment **56** involved oxazole metalation at the C_{32} methyl group followed by alkylation with the lactone to form the $C_{32}-C_{33}$ bond (Scheme 11).[52] Initial studies performed on 2-methyloxazole **64** were discouraging. Deprotonation of **64** with lithium diisopropylamide (LDA) (−78 °C) followed by the addition of

(43) Reviews: (a) Evans, D. A.; Rovis, T.; Johnson, J. S. *Pure Appl. Chem.* **1999**, *71*, 1407−1415. (b) Johnson, J. S.; Evans, D. A. *Acc. Chem. Res.* **2000**, *33*, 325−335. (c) Rovis, T.; Evans, D. A. *Prog. Inorg. Chem.*, in press. (d) Jørgensen, K. A.; Johannsen, M.; Yao, S.; Audrain, H.; Thorhauge, J. *Acc. Chem. Res.* **1999**, *32*, 605−613.

(44) (a) Evans, D. A.; Johnson, J. S.; Olhava, E. J. *J. Am. Chem. Soc.* **2000**, *122*, 1635−1649. See also: (b) Thorhauge, J.; Johannsen, M.; Jørgensen, K. A. *Angew. Chem., Int. Ed. Engl.* **1998**, *37*, 2404−2406.

(45) The preparation of lactone **59** following the identical sequence has been previously reported; see ref 22b.

(46) The major decomposition pathways are believed to involve either elimination or retro-aldol reactions.

(47) (a) Walba, D. M.; Thurmes, W. N.; Haltiwanger, R. C. *J. Org. Chem.* **1988**, *53*, 1046−1056. (b) Evans, D. A.; Ratz, A. M.; Huff, B. E.; Sheppard, G. S. *Tetrahedron Lett.* **1994**, *35*, 7171−7172.

(48) (a) Ohno, K.; Nishiyama, H.; Nagase, H. *Tetrahedron Lett.* **1979**, *20*, 4405−4406. (b) Neeman, M.; Hashimoto, Y. *J. Am. Chem. Soc.* **1962**, *84*, 2972−2978.

(49) Finch, N.; Fitt, J. J.; Hsu, I. H. S. *J. Org. Chem.* **1975**, *40*, 206−215.

(50) (a) Curphey, T. J. *Org. Synth.* **1971**, *51*, 142−147. (b) Meerwein, H.; Hinz, G.; Hofmann, P.; Kronig, E.; Pfeil, E. *J. Prakt. Chem.* **1937**, *147*, 257. See also ref 47b

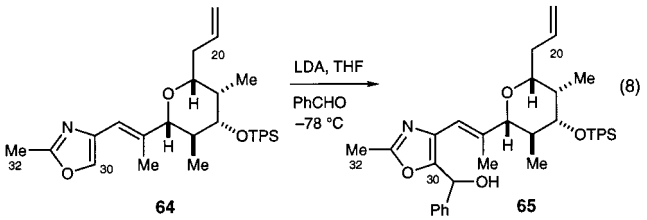
(51) For a related reduction with Raney-Ni, see: Bacardit, R.; Moreno-Mañas, M. *Tetrahedron Lett.* **1980**, *21*, 551−554.

(52) For a study on the metalation and alkylation of trisubstituted 2-methyloxazoles, see: Lipshutz, B. H.; Hungate, R. W. *J. Org. Chem.* **1981**, *46*, 1410−1413.

(53) For other examples of alkylation of the 5-position of 2-methyloxazoles and creative solutions to the problem, see: (a) Hamana, H.; Sugasawa, T. *Chem. Lett.* **1983**, 333−336. (b) Meyers, A. I.; Lawson, J. P. *Tetrahedron Lett.* **1981**, *22*, 3163−3166. (c) Gangloff, A. R.; Akermark, B.; Helquist, P. *J. Org. Chem.* **1992**, *57*, 4797−4799. (d) Wood, R. D.; Ganem, B. *Tetrahedron Lett.* **1983**, *24*, 4391−4392. (f) Nagao, Y.; Yamada, S.; Fujita, E. *Tetrahedron Lett.* **1983**, *24*, 2287−2290. For related examples, see: (g) Williams, D. R.; Brooks, D. A.; Meyer, K. G.; Pagel, M. *Tetrahedron Lett.* **1998**, *39*, 8023−8026. For a review of oxazole metalation, see: (g) Iddon, B. *Heterocycles* **1994**, *37*, 1321−1346.

(54) Knaus, G.; Meyers, A. I. *J. Org. Chem.* **1974**, *39*, 1192−1195.

benzaldehyde provided predominantly **65** as a 1:1 mixture of diastereomers (eq 8). Unfortunately, the competitive kinetic



acidity of the C_{30} ring proton led to alkylation of the undesired 5-position of the oxazole.[53]

In a study on the metalation and alkylation of 4-substituted 2-methylthiazoles, Meyers and Knaus discovered that the regioselectivity of the reaction was highly dependent on the steric bulk of the base employed as well as the temperature at which the reaction was carried out.[54] While elevated temperatures were shown to lead to the thermodynamically favored 2-lithiomethylthiazole, the complex functionality that would be present in the desired oxazole anion coupling would require milder conditions. This prompted a model study on 2-methyloxazole **66**[6h] where the effect of base structure on metalation regioselectivity was examined (eq 9). While lithium diisopropylamide (LDA) afforded moderate selectivity for alkylation at the 5-position of the oxazole (C_{30}), use of a sterically more demanding base, lithium tetramethylpiperidide (LiTMP), resulted in a slight preference for alkylation at the 2-methyl position (C_{32}) (Table 2), in agreement with the Meyers observations on the thiazole systems.[54] *Quite surprisingly, deprotonation with the sterically less demanding base, lithium diethylamide, resulted in the exclusive formation of 67 as the alkylation product.*

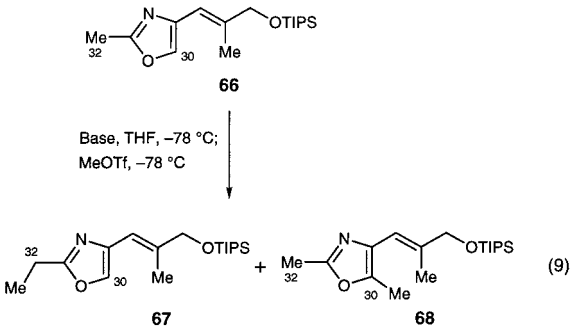


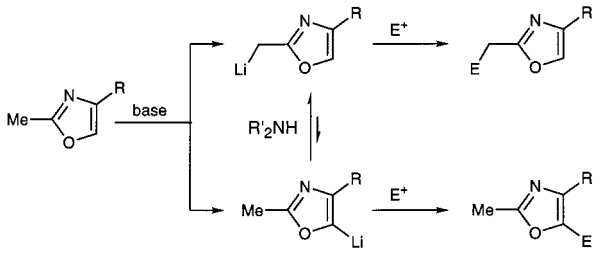
Table 2. Oxazole Alkylation (Eq 9)

base	ratio (**67**:**68**)[a]
n-BuLi	61:39
LDA	34:66
LiTMP	58:42
$LiNEt_2$	>95:<5

[a] Ratio determined by ^{1}H NMR analysis.

The striking result obtained upon deprotonation with lithium diethylamide prompted a full investigation of the scope and mechanism of the metalation process.[6h] Reaction selectivity was found to be general for oxazoles containing a variety of substituents at the 4-position. Additionally, similar selectivities were observed for similarly substituted thiazoles. We conclude that deprotonation of the 2-methyloxazole at low temperature with *n*-butyllithium provides a kinetic mixture of noninterconverting 2-lithiomethyloxazole and 5-lithiooxazole species, which upon addition of the electrophile gives rise to the respective regioisomeric products. In the presence of an amine, a pathway

Scheme 13



for the equilibration of the lithiated regioisomers is available, facilitating the conversion of the 5-lithiooxazole to the thermodynamically more stable 2-lithiomethyloxazole isomer. The rate of equilibration is strongly dependent on the steric encumbrance of the amine, with diethylamine effecting rapid equilibration at −78 °C. In contrast, anion equilibration in the presence of hindered bases such as tetramethylpiperidine is quite slow at this temperature.[55] In conclusion, the remarkable selectivity observed in metalations with lithium diethylamide is due to an intervening equilibration process mediated by the diethylamine.

In the required fragment coupling, deprotonation of **56** with lithium diethylamide followed by addition of lactone **63** afforded the desired hemiketal **69** as a single regio- and stereoisomer (Scheme 14).[15] Although stable to silica gel chromatography, this material was carried forward without purification through the subsequent two transformations for operational simplicity. While reported methods for lactol silylation[56] led to high levels of decomposition when applied to substrate **69**, the use of triethylsilyl trifluoromethanesulfonate and pyridine in an ether/acetonitrile mixture proved successful, providing the desired mixed-silyl ketal **70** as a single anomer.[57] Selective cleavage of the C_{20} primary trimethylsilyl ether under basic conditions ($NaHCO_3$, MeOH, rt) afforded the intermediate alcohol **71** (80% yield from **56**), which upon subsequent oxidation with the Dess−Martin periodinane[58] provided the C_{20}−C_{38} core fragment **4** in 44% overall yield with a longest linear sequence of 12 steps from aldehyde **48**.

Stabilized Wittig Reaction. At the inception of this project, significant precedent existed for highly (*E*)-selective oxazole-stabilized Wittig olefination reactions. In studies toward the total synthesis of the calyculins, Armstrong and co-workers discovered that the anion of a phosphonium salt, generated in situ from the treatment of a 4-halomethyloxazole with tributylphosphine, added to aldehydes to provide the (*E*) olefin in excellent

(55) This conclusion is supported by the results of Fraser et al., who have reported that the rate of proton exchange between amines and lithiated amides decreases with increasing steric bulk. Fraser, R. R.; Baignee, A.; Bresse, M.; Hata, K. *Tetrahedron Lett.* **1982**, *23*, 4195−4198.

(56) (a) Smith, A. B., III; Condon, S. M.; McCauley, J. A.; Leazer, J. L., Jr.; Leahy, J. W.; Maleczka, R. E., Jr. *J. Am. Chem. Soc.* **1997**, *119*, 962−973. (b) Smith, A. B., III.; Condon, S. M.; McCauley, J. A.; Leazer, J. L., Jr.; Leahy, J. W.; Maleczka, R. E., Jr. *J. Am. Chem. Soc.* **1995**, *117*, 5407−5408.

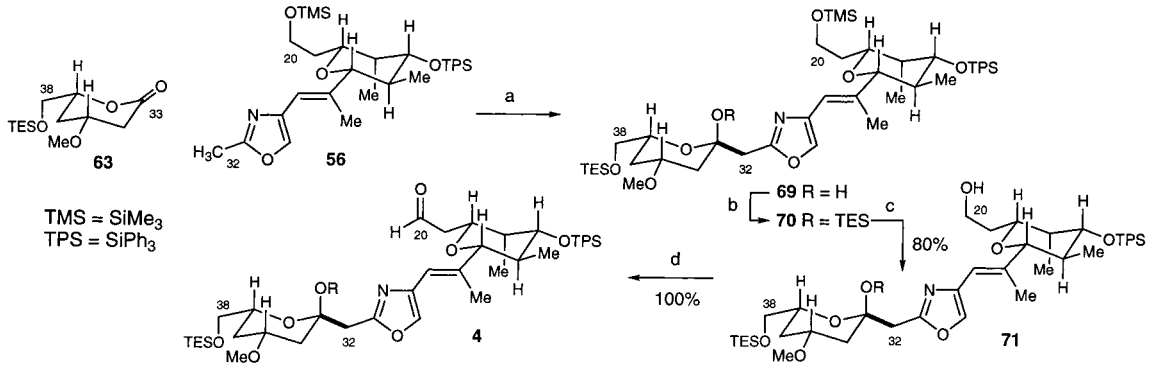
(57) Conditions adapted from: Heathcock, C. H.; Young, S. D.; Hagen, J. P.; Pilli, R.; Badertscher, U. *J. Org. Chem.* **1985**, *50*, 2095−2105.

(58) Dess, D. B.; Martin, J. C. *J. Am. Chem. Soc.* **1991**, *113*, 7277−7287.

(59) (a) Zhao, Z.; Scarlato, G. R.; Armstrong, R. W. *Tetrahedron Lett.* **1991**, *32*, 1609−1612. For an early example of (*E*)-selective Wittig olefinations utilizing trialkylphosphines, see: (b) Schlosser, M.; Schaub, B. *J. Am. Chem. Soc.* **1982**, *104*, 5821−5823.

(60) (a) Evans, D. A.; Gage, J. R.; Leighton, J. L. *J. Am. Chem. Soc.* **1992**, *114*, 9434−9453. For other examples of the utilization of this methodology in the synthesis of the calyculins, see: (b) Ogawa, A. K.; Armstrong, R. W. *J. Am. Chem. Soc.* **1998**, *120*, 12435−12442. (c) Smith, A. B., III; Friestad, G. K.; Barbosa, J.; Bertounesque, E.; Duan, J. J.-W., Hull, K. G., Iwashima, M., Qui, Y.; Spoors, P. G.; Salvatore, B. A. *J. Am. Chem. Soc.* **1999**, *121*, 10478−10486. (d) Yokokawa, F.; Hamada, Y.; Shioiri, T. *J. Chem. Soc., Chem. Commun.* **1996**, 871−872.

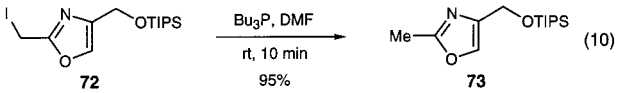
Scheme 14[a]



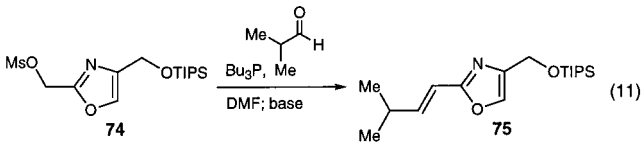
[a] Key: (a) **56**, $LiNEt_2$, THF, −78 °C; then **63**. (b) TESOTf, pyr, 10:1 Et_2O/MeCN, −50 °C. (c) $NaHCO_3$, MeOH, rt. (d) Dess−Martin periodinane, pyr, CH_2Cl_2, rt.

selectivity.[59] This methodology proved highly effective for the final fragment coupling in the total synthesis of (+)-calyculin A carried out by this laboratory.[60] During studies directed toward the synthesis of the tris(oxazole) macrolide ulapualide A, which contains a 4-substituted *trans*-2-alkenyloxazole reminiscent of the one found in the phorboxazole macrocycle, Panek and co-workers found that conditions similar to those reported by Armstrong offered high levels of (*E*) selectivity in the Wittig coupling of 2-iodomethyloxazoles.[61]

In the Panek investigation, oxazole systems containing an electron-withdrawing substituent at the 4-position, such as an ester or another oxazole, were exclusively studied.[61a] In the case of the phorboxazoles, however, there is an alkyl substituent at the 4-position of the oxazole contained within macrocyclic (C_{16}). To examine the reactivity of these species, experiments were carried out on the model 2-iodomethyloxazole **72**.[62] Upon treatment of iodide **72** with tributylphosphine, 2-methyloxazole **73**, resulting from reductive dehalogenation, was isolated in 95% yield (eq 10). While the source of the difference in reactivity



(10)



(11)

Table 3. Model Wittig Olefination Conditions (Eq 11)

base	equiv	temp (°C)	time	yield (%)	(*E*/*Z*) ratio[a]
LDA	1	0	15 min	88	27:1
DBU	1	25	45 min	94	21:1
Et_3N	5	25	48 h	92	21:1

[a] Ratio determined by ^1H NMR analysis.

between this oxazole system and those employed by Panek is unclear, the formation of **73** is presumably due to attack of the soft phosphorus nucleophile on the soft iodine atom to form a 2-methyloxazole anion that is quenched upon workup.

In an attempt to exploit the hard/soft differences between different leaving groups, Wittig olefination experiments were initiated on 2-methanesulfonylmethyloxazole **74** (eq 11).[63] With this leaving group, in situ formation of the tributylphosphonium ylide proceeded smoothly. Introduction of isobutyraldehyde and LDA at 0 °C afforded the desired olefin **75** in 88% yield as a 27:1 mixture of (*E*/*Z*) isomers (Table 3).[15] Bearing in mind the sensitive functionality that would be present in the constituents of the Wittig coupling required for the phorboxazole synthesis, milder conditions were investigated. Indeed, trialkylamines were found to be effective in providing the desired trans olefin in excellent yield and selectivity (Table 3). Optimal conditions involved the use of 1 equiv of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) at room temperature, which obviated the need for an aqueous workup, allowing for an operationally simplified procedure.[64]

Phorboxazole B Macrocycle. In situ formation of the tributylphosphonium salt of methanesulfonate **47** followed by addition of aldehyde **4** and DBU resulted in the exclusive formation of the desired (*E*) olefin **76** in 81% yield (Scheme 15).[15] Pursuant to revealing the terminal carboxylic acid residue, *N*-phenylamide 76 was activated through its *N*-Boc imide **77** and hydrolyzed with LiOH.[36] Use of excess LiOH resulted in the concomitant cleavage of the C_{38} triethylsilyl and C_{24} triphenylsilyl ethers, which could not be differentiated under a variety of conditions. At this point, an effort was made to execute a selective macrolactonization of diol acid **78** in the hope that conformational and entropic effects might favor cyclization onto the desired C_{24} hydroxyl moiety. Unfortunately, under standard Yamaguchi conditions (2,4,6-trichlorobenzoyl chloride, Et_3N, THF; then DMAP, benzene, rt),[65] cyclization occurred exclusively at the less hindered C_{38} primary hydroxyl to provide the undesired 31-membered macrocycle **79** in 85% yield.[66]

Attempts to selectively silylate the C_{38} primary hydroxyl under standard conditions (TESCl, imidazole, CH_2Cl_2) were complicated by competitive silylation of both the C_1 carboxyl and the C_{24} secondary hydroxyl moieties. Ultimately, a change in the base from imidazole to 2,6-lutidine led to exclusive silylation of the desired C_{38} primary hydroxyl (Scheme 15).[67] With the C_{38} hydroxyl now protected, macrolactonization of

(61) (a) Celatka, C. A.; Liu, P.; Panek, J. S. *Tetrahedron Lett.* **1997**, *38*, 5449−5452. For other examples of stabilized Wittig reactions of 2-halomethyloxazoles, see: (b) Chattopadhyay, S. K.; Pattenden, G. *Synlett* **1997**, 1345−1348 and ref 6o.

(62) Iodide **72** was prepared from methanesulfonate **74** upon treatment with sodium iodide. See Supporting Information for details.

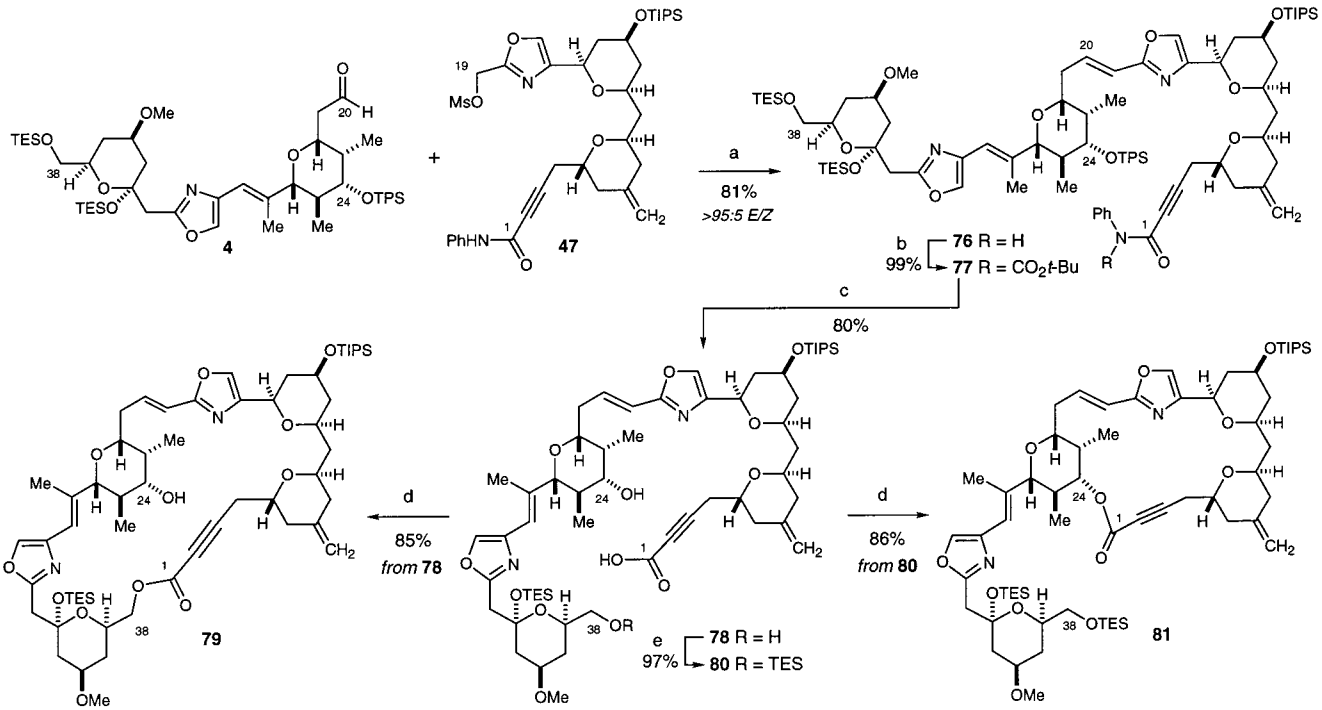
(63) Methanesulfonate **74** was prepared in six steps from the known ethyl (2-((*E*)-2-phenyl-1-ethenyl)-1,3-oxazol-4-yl)formate (see ref 23). See Supporting Information for details.

(64) Similar conditions have recently appeared in the literature for an oxazole-stabilized Wittig coupling; see: Liu, P.; Panek, J. S. *J. Am. Chem. Soc.* **2000**, *122*, 1235−1236.

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

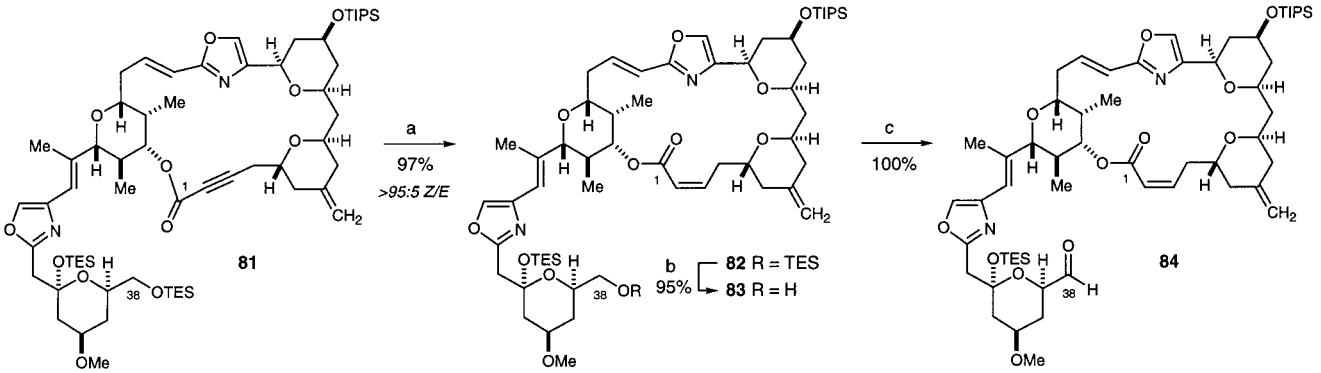
(66) The regioselectivity of the cyclization was determined by one-dimensional ^1H and two-dimensional COSY NMR experiments. See Supporting Information for characterization data.

Scheme 15[a]



[a] Key: (a) PBu_3, DMF, DBU, rt. (b) Boc_2O, DMAP, MeCN. (c) LiOH, THF, H_2O, rt. (d) 2,4,6-trichlorobenzoyl chloride, Et_3N, THF; then DMAP, benzene. (e) 2,6-lutidine, TESCl, CH_2Cl_2, −78 °C.

Scheme 16[a]



[a] Key: (a) 1 atm H_2, Lindlar cat, quinoline, 1-hexene, acetone. (b) HF·pyr, pyr, THF, 0 °C. (c) SO_3·pyr, Et_3N, DMSO, CH_2Cl_2.

hydroxy acid **80** under the previous conditions[65] proceeded smoothly to provide the desired 21-membered macrocycle **81** in excellent yield.

Concerns over the isomerization of an activated cis enoate during the macrolactonization step prompted cyclization to the macrocyclic alkynoate **81** prior to alkyne reduction.[68] At this stage, Lindlar reduction provided the complete C_1-C_{38} macrocyclic region of phorboxazole B in 97% yield and >95:5 *Z*/*E* selectivity (Scheme 16).[15,69] Selective deprotection of the C_{38} primary triethylsilyl ether (HF·pyridine, pyridine, THF, 0 °C; 95%) was followed by Parikh−Doering oxidation (SO_3·pyridine, Et_3N, DMSO, CH_2Cl_2)[70] to afford the requisite α-alkoxyaldehyde **84** in quantitative yield.

$C_{39}-C_{46}$ Triene Side Chain. The synthesis plan (Scheme 1) calls for the late-stage construction of the $C_{38}-C_{39}$ bond by addition of a $C_{39}-C_{46}$ alkenyl metal fragment to the C_1-C_{38} aldehyde **84** to deliver protected phorboxazole B. Two strategies

(67) The difference in reactivity between the two bases is perhaps due to formation of a more active silylating agent derived from the reaction of imidazole with the silyl chloride. Presumably, there is no reaction between the silyl chloride and 2,6-lutidine, which simply acts as a base. A comparison study of the reaction of seven different trimethylsilyl donors with silica gel showed trimethylsilylimidazole to be, by far, the most active, with silica gel coverage after ≤1 h at 60 °C equivalent to that provided by chlorotrimethylsilane and pyridine in refluxing toluene for 67 h. See: McMurtrey, K. D. *J. Liq. Chromatogr.* **1988**, *11*, 3375−3384.

(68) For an example of the isomerization of a cis α,β-unsaturated thioester in the presence of DMAP, see: Keck, G. E.; Boden, E. P.; Mabury, S. A. *J. Org. Chem.* **1985**, *50*, 709−710. See also: Carter, P. H. Ph.D. Thesis, Harvard University, 1998.

(69) The use of 1-hexene as a cosolvent was found to effectively suppress any overreduction. For related conditions, see: Ho, T.-L.; Liu, S.-H. *Synth. Commun.* **1987**, *17*, 969−973.

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

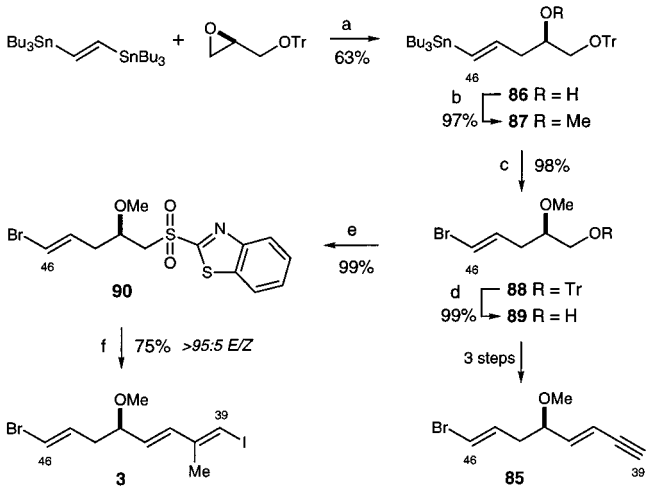
(71) Negishi, E.-i. *Acc. Chem. Res.* **1987**, *20*, 65−72.

(72) Wakefield, B. J. In *Lithium*; Bach, R. O., Ed.; Wiley: New York, 1985.

(73) (*E*)-Bis(tributylstannyl)ethylene was prepared by the following method: (a) Corey, E. J.; Wollenberg, R. H. *J. Am. Chem. Soc.* **1974**, *96*, 5581−5583. See also: (b) Nesmeyanov, A. N.; Borisov, A. E. *Dokl. Akad. Nauk SSSR* **1967**, *174*, 96.

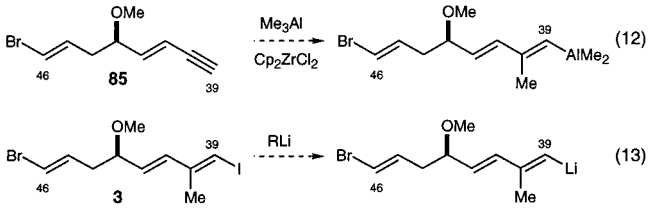
(74) For BF_3·OEt_2 promoted organolithium additions to epoxides, see: Eis, M. J.; Wrobel, J. E.; Ganem, B. *J. Am. Chem. Soc.* **1984**, *106*, 3693−3694.

Scheme 17[a]



[a] Key: (a) *n*-BuLi, THF, −78 °C; then $BF_3{\cdot}OEt_2$ and (*R*)-trityl glycidol, −78 °C. (b) NaH, DMF, 0 °C; then MeI, rt. (c) NBS, MeCN, 0 °C. (d) TsOH, 1:1 Et_2O/MeOH, rt. (e) 2-mercaptobenzthiazole, Ph_3P, DIAD, THF, rt; then $(NH_4)_6Mo_5O_{24}{\cdot}(H_2O)_4$, H_2O_2, MeOH, 0 °C. (f) (*E*)-3-iodo-2-methylprop-2-enal, THF, −78 °C; then NaHMDS, −78 °C to rt.

for the generation of the $C_{39}-C_{46}$ alkenyl metal were recognized. One approach involves the carboalumination[71] of an alkyne precursor to generate the alkenylalane (eq 12), while another

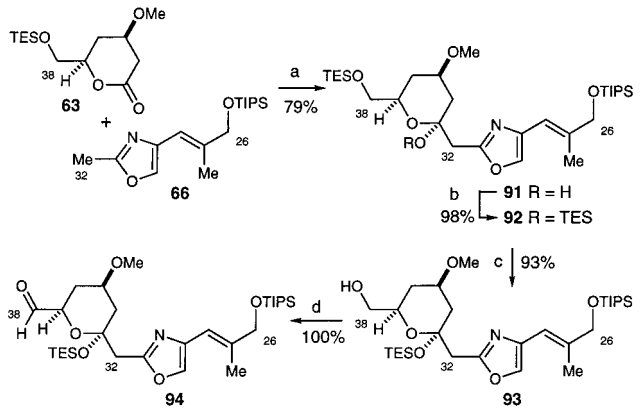


approach involves the selective lithium−halogen exchange[72] of a bis-halogenated substrate to provide the alkenyl lithium (eq 13).

The syntheses of the $C_{39}-C_{46}$ alkenyl metal precursors are illustrated in Scheme 17. Transmetalation of bis-tributylstannyl ethylene[73] (*n*-BuLi, THF, −78 °C) followed by addition of $BF_3{\cdot}OEt_2$ and (*R*)-trityl glycidol provided alcohol **86** in 63% yield.[74] Methylation of the free hydroxyl (NaH, DMF, 0 °C; MeI, rt; 97%) was followed by tin−bromine exchange (NBS, CH_3CN, 0 °C; 98%) and trityl deprotection (TsOH, 1:1 Et_2O/MeOH, rt; 99%) to afford the versatile primary alcohol **89,** which could be converted in three steps[75] to the $C_{39}-C_{46}$ terminal alkyne **85**. Alternatively, alcohol **89** could be transformed into the benzthiazole sulfone **90** by a two-step, one-pot procedure (Ph_3P, DIAD, 2-mercaptobenzthiazole, THF; then MeOH, $(NH_4)_6Mo_5O_{24}{\cdot}(H_2O)_4$, H_2O_2; 99%).[76] A subsequent Julia olefination was accomplished by the addition of sodium hexamethyldisilyl azide to a premixed solution of sulfone **90** and (*E*)-3-iodo-2-methylprop-2-enal,[77] which delivered the $C_{39}-C_{46}$ bis-halide **3** in 75% yield with >95:5 *E*:*Z* selectivity for the newly formed olefin.[15,78]

With the desired $C_{39}-C_{46}$ precursors in hand, a model $C_{26}-C_{38}$ aldehyde was constructed to investigate the projected fragment coupling (Scheme 18). In analogy to the parent system **70**, reaction of the lithiated methyloxazole **66**[6h] with lactone **63** provided lactol **91,** which was subsequently protected as its triethylsilyl ether. Selective removal of the primary triethylsilyl group (HF·pyridine, pyridine, THF, 0 °C; 93%) followed by Parikh−Doering oxidation (SO_3·pyridine, Et_3N, DMSO, CH_2Cl_2; 100%)[70] delivered model aldehyde **94** in 72% overall yield for the four-step sequence.

Scheme 18[a]



[a] Key: (a) $LiNEt_2$, THF, −78 °C; then **63**. (b) TESOTf, pyr, 3:2 Et_2O/MeCN, −50 °C. (c) HF·pyr, pyr, THF, 0 °C. (d) SO_3·pyr, Et_3N, DMSO, CH_2Cl_2, −5 °C.

At this stage, the carboalumination strategy for the $C_{38}-C_{39}$ bond construction was investigated. While alkenylalanes derived from the zirconocene dichloride catalyzed carboalumination of terminal alkynes are typically unreactive toward aldehydes, they may be converted into the more reactive aluminate species by the introduction of an alkyl lithium.[79] The following study was undertaken to determine if a model alkenyl aluminate could engage in the required chelation-controlled[80] addition to aldehyde **94** to provide the desired (*R*) configuration at the C_{38} stereocenter (eq 14).[81] After carboalumination of model alkyne

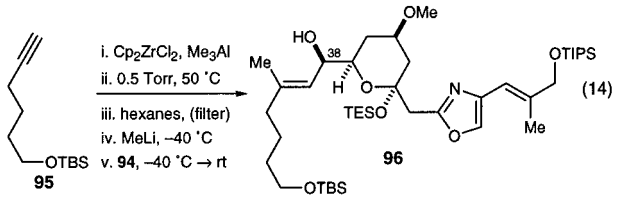


Table 4. Model Carboalumination/Alkylation (Eq 14)

entry	Cp_2ZrCl_2	yield (%)	C_{38} diastereoselectivity (*R*/*S*)
1	removed[a]	90	98:02[b]
2	present	89	30:70[c]

[a] Removal of zironocene dichloride was accomplished by filtration at step iii. [b] Diastereoselectivity determined by HPLC analysis. [c] Diastereoselectivity determined by ^1H NMR analysis (400 MHz).

95[82] under standard conditions,[83] all solvent and excess trimethylaluminum were removed in vacuo. The solid material was taken up in hexanes and filtered to give a zirconocene-free

(75) See Supporting Information for details.

(76) Conditions adapted from: Bellingham, R.; Jarowicki, K.; Kocienski, P.; Martin, V. *Synthesis* **1996**, 285−296.

(77) (*E*)-3-Iodo-2-methylprop-2-enal is available in four steps from diethyl methylmalonate: Baker, R.; Castro, J. L. *J. Chem. Soc., Perkin Trans. 1* **1990**, 47−65.

(78) Conditions adapted from ref 6p.

(79) Okukado, N.; Negishi, E.-i. *Tetrahedron Lett.* **1978**, 2357−2360.

(80) Reetz, M. T. *Angew. Chem., Int. Ed. Engl.* **1984**, *23*, 556−569.

(81) The chelating ability of alkenyl aluminates has been reported: Imogai, H.; Petit, Y.; Larcheveque, M. *Tetrahedron Lett.* **1996**, *37*, 2573.

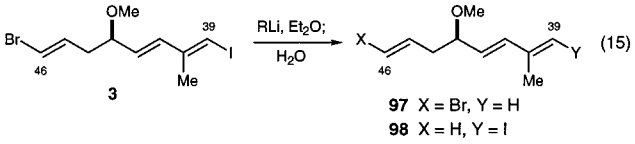
(82) Alkyne **95** is available in one step from 5-hexyn-1-ol; see: Kalivretenos, A.; Stille, J. K.; Hegedus, L. S. *J. Org. Chem.* **1991**, *56*, 2883−2894.

(83) Van Horn, D. E.; Negishi, E.-i. *J. Am. Chem. Soc.* **1978**, *100*, 2252−2254.

solution of the alkenylalane (Table 4, entry 1). The aluminate was generated by addition of methyllithium, and after the introduction of aldehyde **94**, the desired diastereomer **96** was obtained in excellent yield (90%) and selectivity (98:02). It is important to appreciate the influence of the zirconocene salts on the outcome of the reaction. Prior to this work, Leahy and co-workers reported poor selectivity for this type of reaction carried out in the presence of the zirconocene salts from the carboalumination step.[2b] Failure to remove the zirconocene salts in this study (entry 2) resulted in a moderate preference for the undesired diastereomer, consistent with the Leahy result.

With the conditions for the projected stereoselective coupling reaction in hand, the carboalumination of alkyne **85** was undertaken. Unfortunately, all attempts to carboaluminate this substrate under standard conditions[83] were met with decomposition of the starting material.[84] It is believed that the Lewis-acidic conditions of the reaction facilitate starting material decomposition by elimination of the C_{43} methoxy group. Difficulty in the carboalumination of propargylic ethers has been documented,[85] although in the case of this vinylogous propargylic ether, the highly unsaturated nature of the substrate may have been the most detrimental factor.

Given the harsh conditions required for carboalumination, the alternative lithium−halogen exchange approach was investigated (eq 15). It is generally accepted that the rate of vinylic lithium−



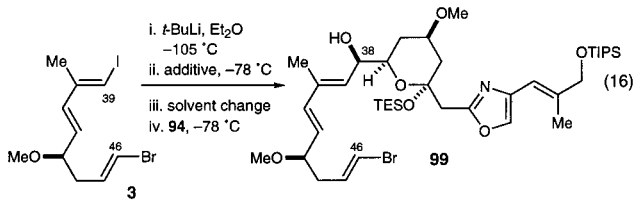
(15)

Table 5. Lithium−Halogen Exchange Conditions (Eq 15)

entry	RLi	equiv	temp (°C)	time (min)	selectivity (**97**:**98**)[a]
1	*n*-BuLi	1	−78	60	>20:1
2	*t*-BuLi	2	−78	5	10:1
3	*t*-BuLi	2	−105	5	20:1

[a] Regioselectivity determined by ^{1}H NMR analysis (500 MHz).

halogen exchange follows the trend Cl < Br < I;[86] however, few examples of the selective exchange in a bis(halogenated) system have been reported.[87] In the case of bis-vinyl halide **3**, it was found that treatment with *n*-BuLi in Et_2O at −78 °C results in >20:1 regioselectivity for the desired exchange to afford **97** upon quenching with water (Table 5, entry 1). A selective exchange reaction is also possible with 2 equiv of *t*-BuLi, which provided the desired product in 10:1 selectivity at −78 °C (entry 2). This could be improved to 20:1 by cooling both substrate and *t*-BuLi to −105 °C prior to mixing (entry 3). Ultimately, the *t*-BuLi conditions were selected for the formation of the alkenyl lithium owing to concern over potential side reactions with the equivalent of *n*-butyl iodide that accompanies the exchange with *n*-BuLi.



(16)

Table 6. Chelation-Controlled Alkenyl Metal Addition (Eq 16)

entry	additive	solvent	yield (%)	C_{38} diastereoselectivity[a] (*R*/*S*)
1		Et_2O	54	1:2
2	Me_2Zn	Et_2O	80	9:1
3	Me_2Zn	CH_2Cl_2	60	20:1
4	$MgBr_2$	Et_2O	77	5:1
5	$MgBr_2$	CH_2Cl_2	79	>20:1
6	Me_3Al	CH_2Cl_2	71	>20:1
7	$CeCl_3$	Et_2O/THF	35	1:7

[a] Ratio determined by ^{1}H NMR analysis (500 MHz).

With conditions for the generation of the $C_{39}-C_{46}$ alkenyl lithium species in hand, model studies were undertaken with aldehyde **94** to identify the ideal conditions for the stereoselective construction of the $C_{38}-C_{39}$ bond (eq 16). Because the alkenyl lithium favored the undesired C_{38} diastereomer (Table 6, entry 1), it was necessary to transmetalate to a more chelate-prone alkenyl metal. The derived alkenyl zincate,[88] Grignard, and aluminate[81] each provided modest levels of diastereoselectivity in ethereal solvents (entries 2 and 4). It was found that chelate-controlled selectivity could be substantially improved by execution of the addition in methylene chloride (entries 3, 5, and 6).[89] Ultimately, the higher yielding and more diastereoselective Grignard reagent (entry 5), derived from freshly prepared $MgBr_2$,[90] was chosen for the final fragment coupling.

Synthesis of Phorboxazole B. In accord with the conditions developed for the coupling to model aldehyde **94**, site-selective lithium−halogen exchange of vinyl iodide **3**, transmetalation to the alkenyl Grignard, and solvent exchange ($Et_2O \rightarrow CH_2Cl_2$), followed by the addition of α-alkoxyaldehyde **84** to the alkenyl magnesium intermediate, provided the protected natural product **100** in 72% yield as a single isomer (Scheme 19).[15] It is noteworthy that no addition or isomerization of the (*Z*) lactone functionality takes place during the addition process. The final deprotection of 100 with tetrabutylammonium fluoride (0 °C, THF) afforded phorboxazole B (**2**) in 88% yield. The synthetic phorboxazole B was identical to the natural material as judged by ^{1}H NMR spectroscopy (600 MHz, $CDCl_3$), HPLC (two solvent systems), TLC R_f, electrospray mass spectrometry, ultraviolet spectroscopy, infrared spectroscopy, and optical rotation. The overall yield of 12.6% through 27 linear steps attests to the efficiency of the synthesis plan.

Conclusions

The importance of the enol(enolate)−carbonyl bond constructions in the assemblage of polyketide-derived natural products cannot be underestimated, and the preceding phorboxazole synthesis provides a good forum for highlighting the advances that have been made in the development of stereoselective variants of these processes (Scheme 20). As illustrated, Cu(II)-

(84) An attempt to carboaluminate alkyne **85** under conditions developed by Wipf resulted in no reaction with clean recovery of starting material; see: Wipf, P.; Lim, S. *Angew. Chem., Int. Ed. Engl.* **1993**, *32*, 1068−1071.

(85) (a) Marshall, J. A.; Johns, B. A. *J. Org. Chem.* **2000**, *65*, 1501−1510. (b) Barrett, A. G. M.; Bennett, A. J.; Menzer, S.; Smith, M. L.; White, A. J. P.; Williams, D. J. *J. Org. Chem.* **1999**, *64*, 162−171.

(86) Bailey, W. F.; Patricia, J. J. *J. Organomet. Chem.* **1988**, *352*, 1−46.

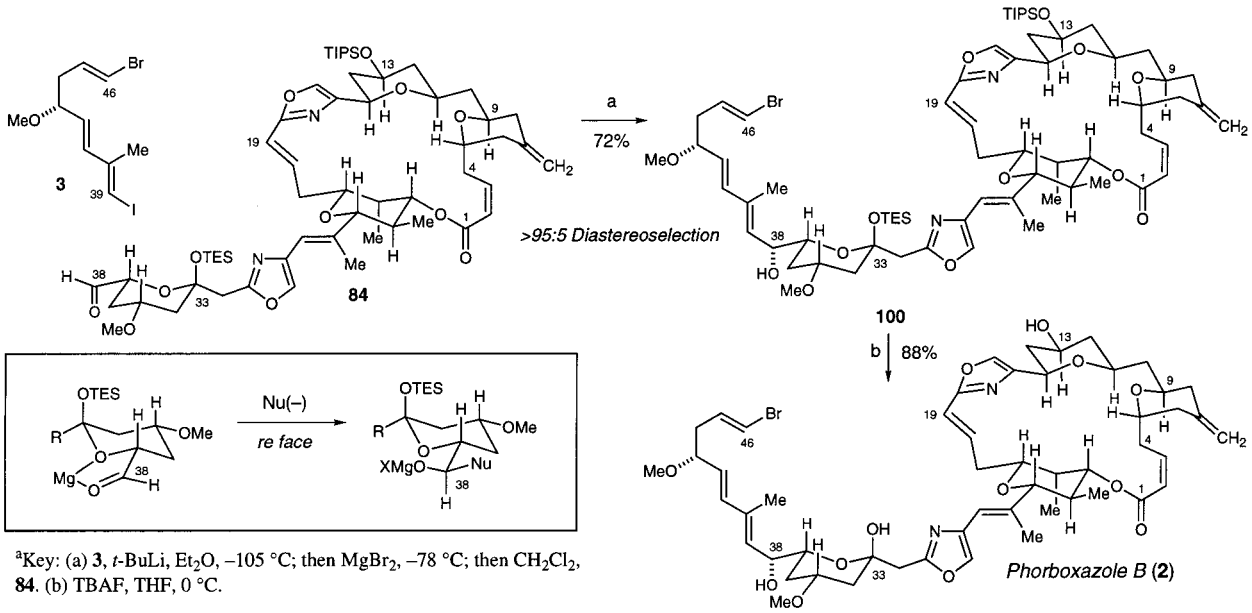
(87) For a report involving bis-halogenated arenes, see: Kihara, M.; Kashimoto, M.; Kobayashi, Y. *Tetrahedron* **1992**, *48*, 67−78.

(88) For an example of a chelation-controlled alkenyl zincate addition, see: Williams, D. R.; Kissel, W. S. *J. Am. Chem. Soc.* **1998**, *120*, 11198−11199.

(89) This solvent effect has been previously reported for additions of alkenyl Grignards to α-alkoxyaldehydes: Keck, G. E.; Andrus, M. B.; Romer, D. R. *J. Org. Chem.* **1991**, *56*, 417−420.

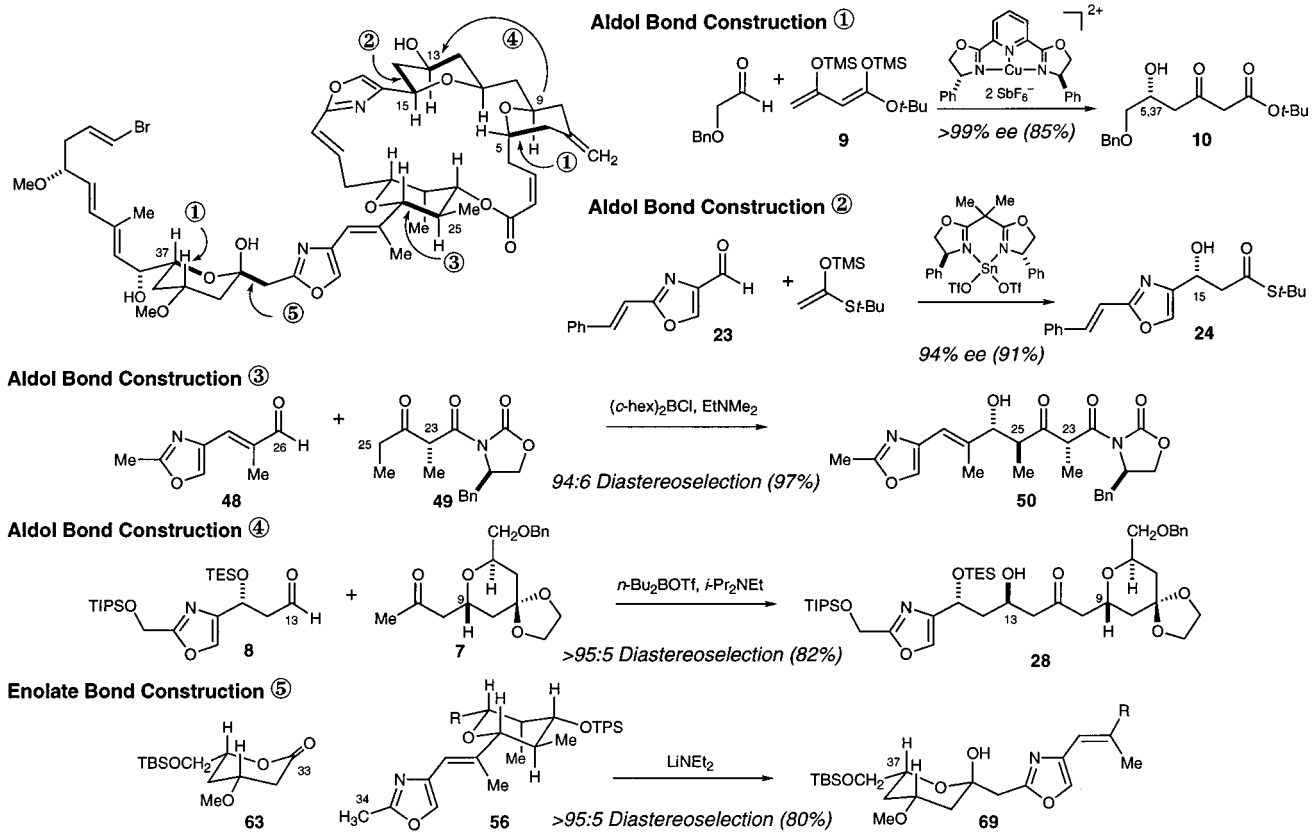
(90) For the preparation of $MgBr_2$ as a solution in Et_2O/benzene, see: Nakatsuka, M.; Ragan, J. A.; Sammakia, T.; Smith, D. B.; Uehling, D. E.; Schreiber, S. L. *J. Am. Chem. Soc.* **1990**, *112*, 5583−5601.

Scheme 19[a]



[a] Key: (a) **3**, *t*-BuLi, Et_2O, −105 °C; then $MgBr_2$, −78 °C; then CH_2Cl_2, **84**. (b) TBAF, THF, 0 °C.

Scheme 20



[13a] and Sn(II)-catalyzed enantioselective aldol reactions[13c] were employed to provide the C_5, C_{15}, and C_{37} stereocenters in high enantiomeric purity (bond constructions 1 and 2). Alternatively, auxiliary-based asymmetric aldol methodology,[40] coupled with hydroxyl-directed triacetoxyborohydride reduction,[41] was employed to introduce the polypropionate segment containing the C_{23}, C_{25}, and C_{26} stereocenters (bond construction 3). In some instances, complex synthesis projects yield the unexpected. Such an instance is found in the $C_{12}-C_{13}$ aldol-based bond construction that was based on a precedent discovered during the course of our altohyrtin C synthesis (bond construction 4).[10a,11] Finally, the C_{33} stereocenter was obtained through diastereoselective metalated oxazole addition process (bond construction 5), and during the course of developing this process, new insights into oxazole metalation were uncovered.[6h]

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Supporting Information Available: Experimental details and analytical data for all new compounds and comparison data for natural and synthetic phorboxazole B (2). This material is available free of charge via the Internet at http://pubs.acs.org. See any current masthead page for ordering information and Web access instructions.

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