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# Evolution of the Petasis–Ferrier Union/Rearrangement Tactic: Construction of Architecturally Complex Natural Products Possessing the Ubiquitous *cis*-2,6-Substituted Tetrahydropyran Structural Element

AMOS B. SMITH III,* RICHARD J. FOX, AND THOMAS M. RAZLER

*Department of Chemistry, Monell Chemical Senses Center, and Laboratory for Research on the Structure of Matter, University of Pennsylvania, Philadelphia, Pennsylvania 19104*

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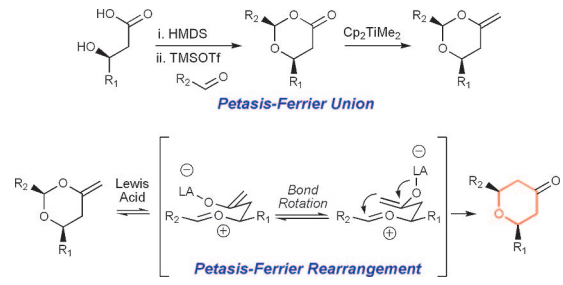
## CONSPECTUS




The frequent low abundance of architecturally complex natural products possessing significant bioregulatory properties mandates the development of rapid, efficient, and stereocontrolled synthetic tactics, not only to provide access to the biologically rare target but also to enable elaboration of analogues for the development of new therapeutic agents with improved activities and/or pharmacokinetic properties. In this Account, the genesis and evolution of the Petasis–Ferrier union/rearrangement tactic, in the context of natural product total syntheses, is described. The reaction sequence comprises a powerful tactic for the construction of the 2,6-*cis*-substituted tetrahydropyran ring system, a ubiquitous structural element often found in complex natural products possessing significant bioactivities. The three-step sequence, developed in our laboratory, extends two independent methods introduced by Ferrier and Petasis and now comprises: condensation between a chiral, nonracemic $\beta$-hydroxy acid and an aldehyde to furnish a dioxanone; carbonyl olefination; and Lewis-acid-induced rearrangement of the resultant enol acetal to generate the 2,6-*cis*-substituted tetrahydropyranone system in a highly stereocontrolled fashion. To demonstrate the envisioned versatility and robustness of the Petasis–Ferrier union/rearrangement tactic in complex molecule synthesis, we exploited the method as the cornerstone in our now successful total syntheses of (+)-phorboxazole A, (+)-zampanolide, (+)-dactylolide, (+)-spongistatins 1 and 2, (−)-kendomycin, (−)-clavosolide A, and most recently, (−)-okilactomycin. Although each target comprises a number of synthetic challenges, this Account focuses on the motivation, excitement, and frustrations associated with the evolution and implementation of the Petasis–Ferrier union/rearrangement tactic. For example, during our (+)-phorboxazole A endeavor, we recognized and exploited the inherent pseudo symmetry of the 2,6-*cis*-substituted tetrahydropyranone product to overcome the inherent chelation bias of an adjacent oxazolidine ring during the Lewis-acid-promoted rearrangement. In addition, we discovered that a more concentrated solution of $Cp_2TiMe_2$ (0.7 versus 0.5 M in THF) with the addition of ethyl pivalate dramatically improves the yield in the Petasis–Tebbe olefination. During the (+)-zampanolide and (+)-dactylolide programs, we observed that the addition of trifluoromethanesulfonic acid (TfOH), especially on a preparative scale, was crucial to the efficiency of the initial condensation/union reaction, while our efforts toward (−)-kendomycin led to the improved implementation of a modified Kurihara condensation of the $\beta$-hydroxy acid and aldehyde involving *i*-PrOTMS and TMSOTf. Finally, the successful deployment of the Petasis–Ferrier tactic in our synthesis of (−)-clavosolide A validated the viability of this tactic with a system possessing the highly acid-labile cyclopropylcarbinyl moiety, while the challenges en route to (−)-okilactomycin demonstrated that a neighboring alkene functionality can participate in an intramolecular Prins cyclization during the TMSOTf-promoted union process, unless suitably protected.

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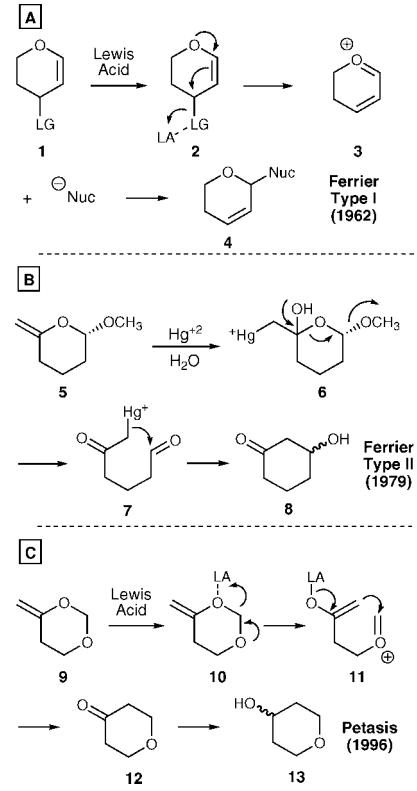
## Introduction

Genesis of the Petasis–Ferrier union/rearrangement tactic for construction of the ubiquitous 2,6-*cis*-tetrahydropyran moiety often found in architecturally complex natural products derives from the pioneering work of Robin Ferrier, who in 1962, introduced a powerful tactic for the construction of 2,3-unsaturated glycosides, via Lewis-acid-promoted rearrangement of 1,2-glycals in the presence of O-, S-, and N-linked nucleophiles.[1] This process, now termed the type I Ferrier reaction (Scheme 1A), involves coordination of the Lewis acid to the leaving group in **1** to induce the formation of allyloxocarbenium ion **3**, which is subsequently trapped by a nucleophile to furnish the 2,3-unsaturated glycosyl product **4**. In 1979, this synthetic tactic was extended to the type II Ferrier reaction for the preparation of $\beta$-hydroxy cyclohexanones via a mercury(II)-induced rearrangement of cyclic enol acetals (Scheme 1B).[2] In a similar fashion to the type I reaction, this process proceeds via initial coordination of mercury(II) to the *exo*-olefin of **5**, with the capture of the resulting carbocation by water to furnish **6**. After fragmentation of the hemiacetal (**6**) to form ketone **7**, an intramolecular aldol leads to $\beta$-hydroxy cyclohexanone **8**.

After 2 decades, the Petasis group reported an innovative synthesis of tetrahydropyranols involving a similar rearrangement cascade exploiting Al(*i*-Bu)$_3$ as the promoter (i.e., **9** → **13**; Scheme 1C). In essence, Petasis et al. migrated the oxygen atom in the Ferrier substrate (**9**) into the ring.[3] However, because of the presence of $\beta$-hydrogens on the Lewis acid promoter [Al(*i*-Bu)$_3$], a nonstereoselective Meerwein–Ponndorf–Verley reduction[4] of ketone **12** ensues to furnish tetrahydropyranol **13**.

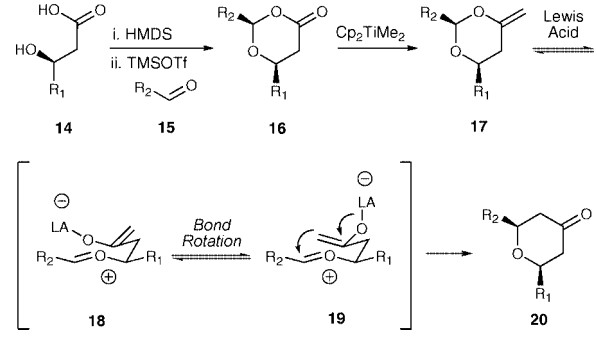
Recognizing the considerable promise that the Petasis and Ferrier rearrangements could play in the contexts of complex molecule synthesis, we began a program in the late 1990s to develop a three-step union/rearrangement tactic involving: (A) condensation[5] between a chiral nonracemic bis-silyated $\beta$-hydroxy acid and an aldehyde to afford a dioxanone (i.e., **14** + **15** → **16**; Scheme 2), (B) olefination via either the Tebbe[6] or Petasis[7] protocol, and (C) rearrangement via zwitterionic intermediates **18** and **19** of the derived enol ether (i.e., **17**), promoted by a Lewis acid to furnish the 2,6-*cis*-substituted tetrahydropyranone (i.e., **20**). At the outset of this program, the importance of the diastereoselectivity in the initial condensation between the $\beta$-hydroxy acid and aldehyde was not clear. History now shows that this stereochemical question is not relevant to the overall outcome of what we now term the Petasis–Ferrier union/rearrangement tactic. In this Account, we

**SCHEME 1**




will describe the evolution of this reaction sequence beginning with our phorboxazole synthetic venture, followed in turn with applications to the total syntheses of (+)-zampanolide, (+)-dactylolide, (+)-spongistatins **1** and **2**, (−)-kendomycin, (−)-clavosolide A, and most recently, (−)-okilactomycin.

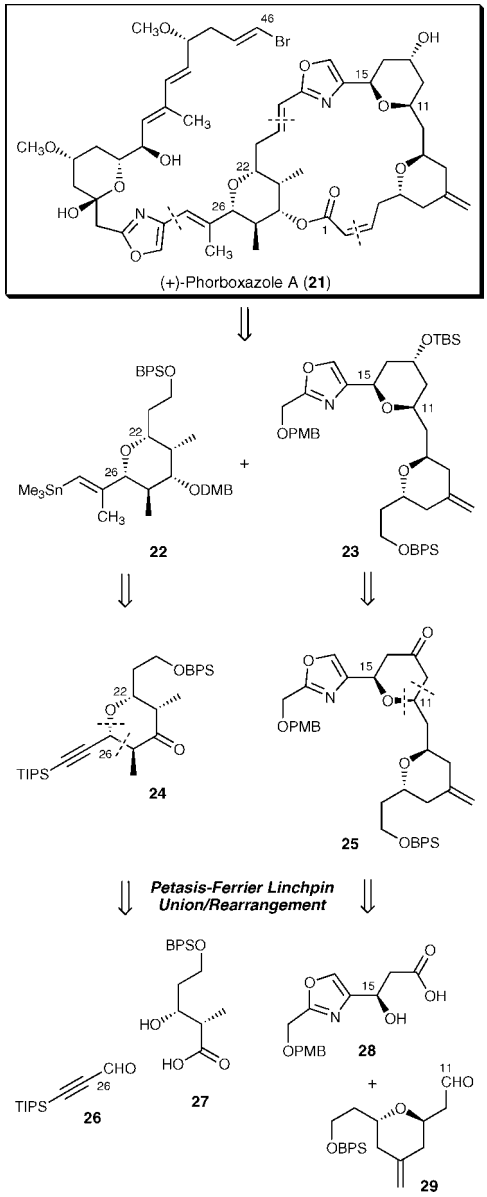
**SCHEME 2**




## (+)-Phorboxazole A

Our initial interest in the utility of the Petasis–Ferrier union/rearrangement tactic involved the architecturally complex marine natural product (+)-phorboxazole A (Scheme 3).[8,9] Central to this venture was the need to access the two densely functionalized 2,6-*cis*-tetrahydropyrans inscribed at C(11–15) and C(22–26) in the phorboxazole macrocycle. Although what we now term the Petasis–Ferrier union/rearrangement appeared ideal, the utility and practicality of such a tactic in

**SCHEME 3**



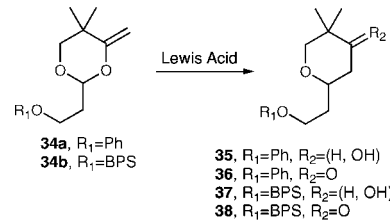

the context of complex molecule total synthesis had not been demonstrated.

With this scenario in mind, disconnection of the C(1)–C(26) macrocycle of (+)-phorboxazole A (**21**) at the C(2,3) and C(19,20) olefins (Scheme 3), followed by further simplification of tetrahydropyranones **24** and **25** via the Petasis–Ferrier union/rearrangement transform led respectively to $\beta$-hydroxy acids **27** and **28** and aldehydes **26** and **29**.

We began with construction of the C(11–15) tetrahydropyranone **25** (Scheme 4). After bis-silylation of $\beta$-hydroxy acid (+)-**28**,[10] condensation with aldehyde (–)-**29** promoted by TMSOTf furnished dioxanone (–)-**30** in 78% yield with modest diastereoselectivity [i.e., 3:1 diastereomeric ratio (dr)]. Treatment of the latter with the Petasis–Tebbe reagent[7] (i.e., $Cp_2TiMe_2$) at 65 °C for 48 h led to a moderately stable enol-acetal (–)-**31** in 82% yield. Exposure of the latter to Al(*i*-Bu)$_3$, the promoter prescribed by the Petasis group, however, failed to produce tetrahydropyran **32**.[10]

We therefore undertook a model study with the simplified enol acetals **34a** and **34b** to devise viable reaction conditions (Table 1)). This study revealed that $Me_2AlCl$ was the optimal Lewis acid promoter. Of importance, from the perspective of complex molecule synthesis, the indiscriminate reduction of the resultant ketone, as occurs with *i*-Bu$_3$Al, was not observed.

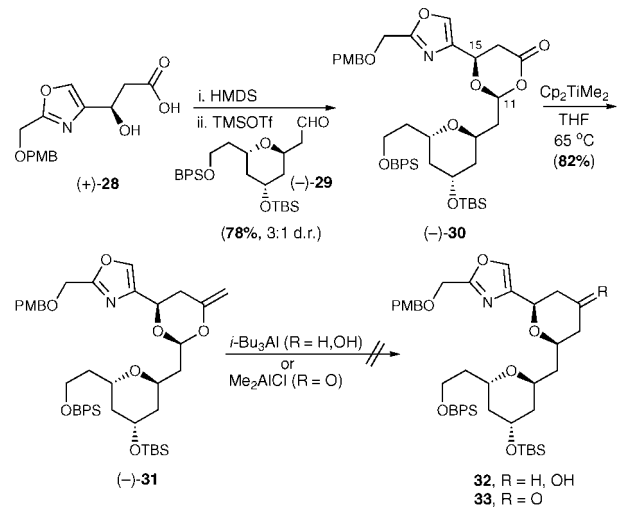
**TABLE 1**




| Lewis Acid | $R_1$=Ph | $R_1$=BPS |
|---|---|---|
| *i*-Bu$_3$Al | 87% (**35**) | 85% (**37**) |
| $ZnCl_2$ | 25% (**36**) | 0% |
| **$Me_2AlCl$** | **95% (36)** | **92% (38)** |
| $MeAlCl_2$ | 60% (**36**) | -- |
| $BF_3{\bullet}OEt_2$ | 0% | -- |
| $TiCl_4$ | 0% | -- |
| $TiCl_2(O\text{-}iPr)_2$ | 0% | -- |
| $SnCl_4$ | 0% | -- |

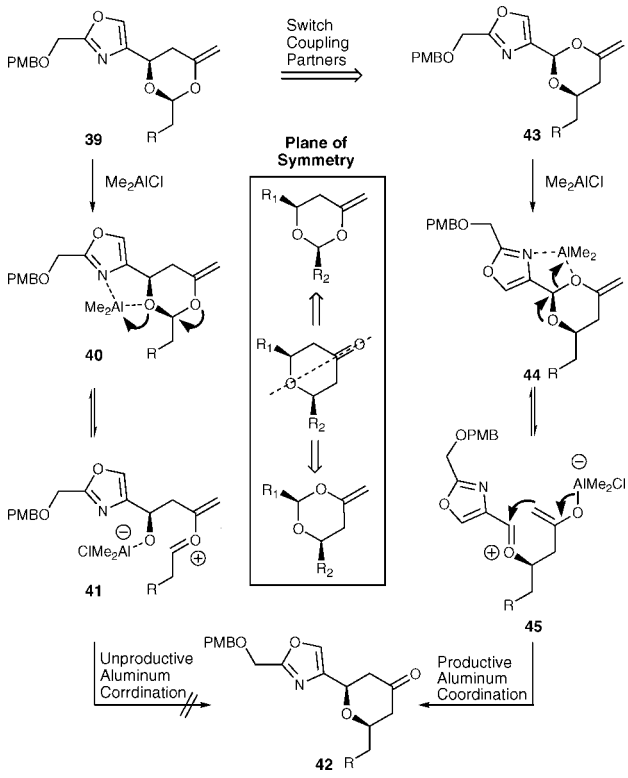
Returning to the synthesis of (+)-phorboxazole A, we were surprised to find that treatment of enol-acetal (–)-**31** with $Me_2AlCl$ again failed to deliver tetrahydropyranone **33** (Scheme 4). We reasoned that an unproductive chelation event, involving the more Lewis basic acetal oxygen and the

**SCHEME 4**



oxazole nitrogen, might preclude the rearrangement (Scheme 5).[10] Forced to reconsider the strategy, we recognized the

**SCHEME 5**

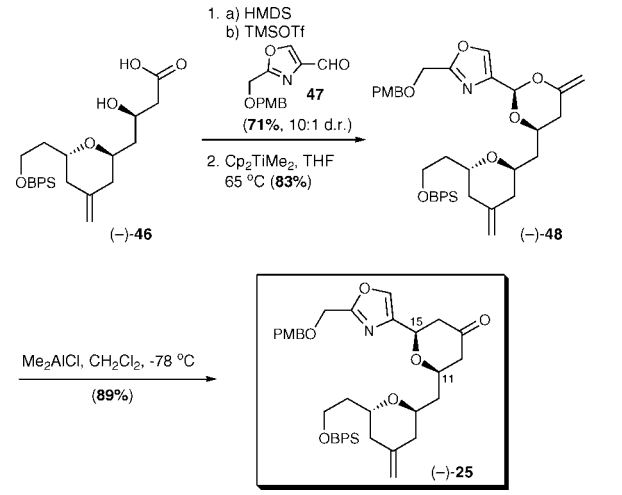



inherent pseudo symmetry of the Petasis–Ferrier union/rearrangement tactic. That is, by simply switching the $\beta$-hydroxy acid and aldehyde coupling partners, we could arrive at a new substrate, wherein the oxazole nitrogen, by rotation about the enol acetal-oxazole $\sigma$ bond as in **44**, might aid in directing the Lewis acid to the requisite site to permit rearrangement to the C(11–15) *cis*-substituted tetrahydropyranone (**42**).

We therefore prepared a second-generation Petasis–Ferrier substrate via TMSOTf-promoted condensation between $\beta$-hydroxy acid (−)-**46** and oxazole aldehyde **47**, followed by Petasis–Tebbe olefination (Scheme 6). Enol acetal (−)-**48** was obtained in 59% yield over the two steps. Pleasingly, exposure of (−)-**48** to $Me_2AlCl$ furnished tetrahydropyranone (−)-**25** in excellent yield (89%).[10]

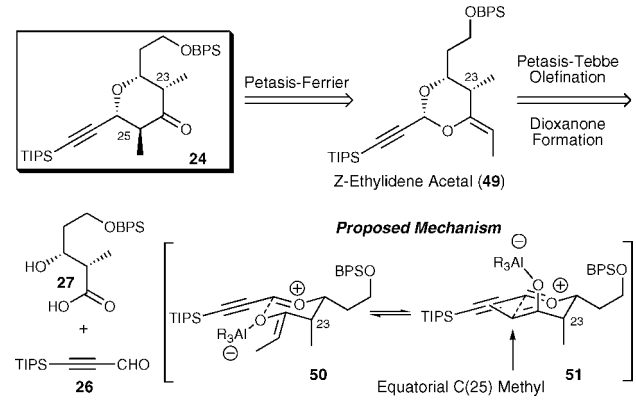
Encouraged by these results, we turned to construction of the C(22–26) *cis*-substituted tetrahydropyran **24** (Scheme 7). From the outset, we envisioned using asymmetric aldol technology to install the C(23) methyl stereocenter in **24** via the requisite $\beta$-hydroxy acid **27**.[11] However, to introduce the C(25) equatorial methyl, extension of the Petasis–Ferrier rearrangement would be required.[12] Here, we envisioned that rearrangement of the cyclic *Z*-ethylidene enol acetal **49** would proceed via a least motion pathway, involving a chair-like

**SCHEME 6**



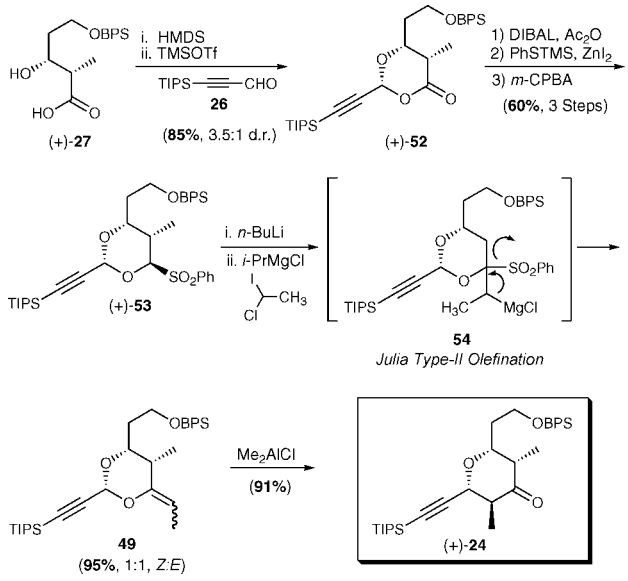

transition state (cf. **51**), to install the desired C(25) equatorial methyl. The caveat of this approach however would be access to the required *Z*-ethylidene acetal in a stereocontrolled fashion.

**SCHEME 7**




The requisite dioxanone (+)-**52** was prepared in 85% yield as a mixture of diastereomers (i.e., 3.5:1 dr) via bis-silylation of $\beta$-hydroxy acid (+)-**27**, followed by condensation with propargylic aldehyde **26** (Scheme 8). Not surprisingly, controlled construction of the *Z*-ethylidene enol acetal proved challenging (Scheme 8). After surveying a variety of conditions, the elegant Julia type-II olefination protocol,[13] used to great advantage in our first-generation spongistatin 1 synthesis,[14] permitted access to **49**. Specifically, DIBAL reduction of dioxanone (+)-**52**, followed in turn by exposure to acetic anhydride, treatment with $ZnI_2$ and PhSTMS, and oxidation furnished sulfone (+)-**53** in 60% yield for the three steps. Julia type-II olefination was then achieved via sulfone deprotonation (*n*-BuLi), followed by treatment with 1,1-chloroiodoethane and *iso*-propylmagnesium chloride. Elimination of the resultant Grignard intermediate (**54**) furnished ethylidene acetal **49**

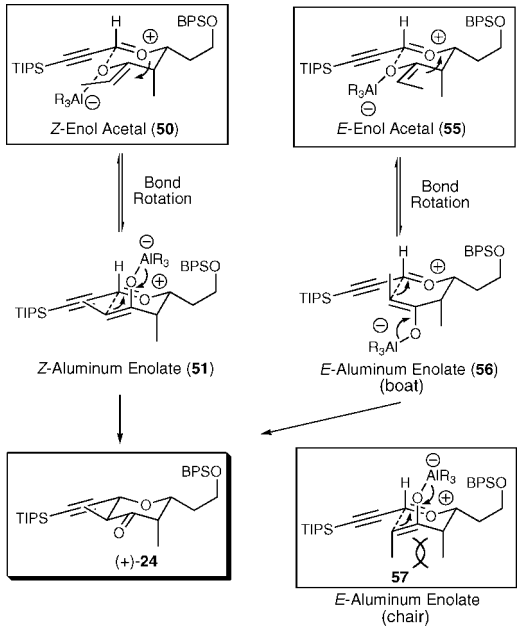
**SCHEME 8**




in 95% yield, as a mixture of *Z* and *E* isomers (1:1). Unable to effect separation, we exposed **49** as a mixture to $Me_2AlCl$ to trigger the Petasis–Ferrier rearrangement. To our delight, albeit also surprise, tetrahydropyranone (+)-**24** was isolated as a single diastereomer in 91% yield possessing the requisite 2,6-*cis*-disubstitution![12]

Recall that we had postulated that the *Z*-ethylidene acetal would undergo the Petasis–Ferrier rearrangement via a least-motion chair-like transition state (Scheme 9). In doing so, the

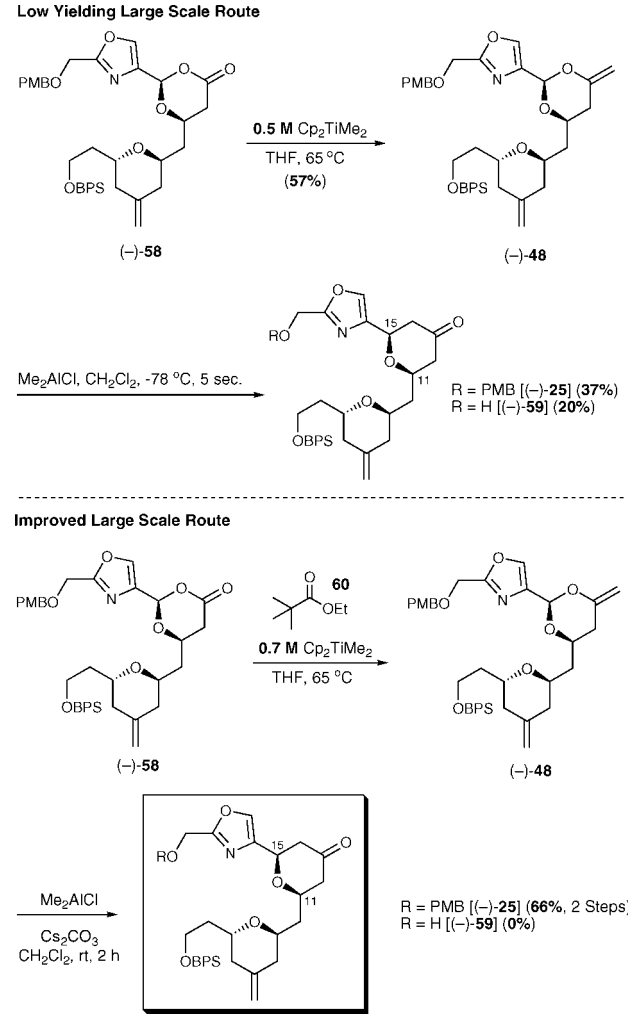
**SCHEME 9**




methyl group of the *Z*-aluminum enolate would adopt a pseudo-equatorial orientation to deliver the C(25) equatorial methyl group. If the *E*-ethylidene acetal were to undergo a similar rearrangement via a chair-like transition state (i.e., **57**), the acetal methyl group would adopt a pseudo-axial orientation and thereby likely encounter a significant 1,3-diaxial interaction with the C(23) methyl group. To circumvent this destabilizing interaction, we suggest that the *E*-ethylidene acetal adopts a boat-type conformation to deliver, upon rearrangement, the desired C(25) equatorial methyl congener (+)-**24**.[12] We view this reaction sequence as a divergent–convergent event.

During the development of an improved second-generation total synthesis of (+)-phorboxazole A, a more efficient three-step protocol for the Petasis–Ferrier union/rearrangement was divised for the construction of (−)-**25**, thus improving the efficiency for multigram-scale advancement of material.[15] The improved protocol (Scheme 10) calls for a more concentrated solution of $Cp_2TiMe_2$ (0.7 versus 0.5 M in THF) in the Petasis–Tebbe olefination to decrease the reaction time from 48 to 24 h. The rate increase minimizes the decomposition products that occur because of prolonged

**SCHEME 10**



exposure of the enol acetal to the Petasis–Tebbe reagent. Employing ethyl pivalate (i.e., **60**) as an additive in the olefination also greatly increases the reaction yield of enol acetal, presumably by acting as a $Cp_2TiMe_2$ scavenger to prevent unwanted [2 + 2] reactions between the product enol acetal and the excess $Cp_2TiMe_2$.[16]

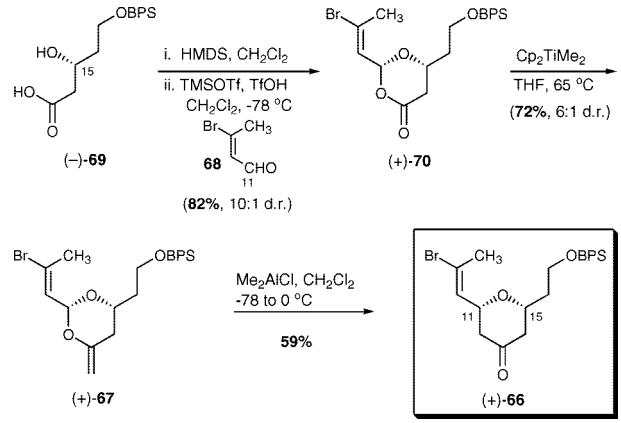
During our second-generation total synthesis of (+)-phorboxazole A, we also discovered during the large-scale preparation of (−)-**25** that the Petasis–Ferrier rearrangement of enol acetal (−)-**48** led to a significant loss of the C(19) PMB group to furnish alcohol (−)-**59** (Scheme 10). Presumably, the $Me_2AlCl$ promotes this process. A careful screen of a variety of reaction conditions revealed that addition of $Cs_2CO_3$ completely suppressed the loss of the PMB group. This observation, in conjunction with both the longer reaction times (i.e., 2 h versus 5 s) required to complete the rearrangement and literature precedent,[17] suggests the formation of an aluminum–carbonate complex, which renders the rearrangement easier to control.

## (+)-Zampanolide and (+)-Dactylolide

Our second encounter with the Petasis–Ferrier union/rearrangement tactic arose in conjunction with our synthetic interest in (+)-zampanolide (**61**) and (+)-dactylolide (**62**), two extremely scarce, architecturally complex sponge metabolites[18] of unknown absolute configuration possessing impressive cytotoxicity (Scheme 11). Central to their structures is incorporation of a 2,6-*cis*-substituted tetrahydropyran in an unsaturated 20-membered macrolactone and an unusual *N*-acyl hemiaminal side chain. Construction of the tetrahydropyran provided another opportunity to explore the three-step Petasis–Ferrier union/rearrangement. Success here would represent the first example employing an α,β-unsaturated coupling partner (i.e., aldehyde **68**).[19–21]

In this case, the Petasis–Ferrier rearrangement called for construction of enol acetal **67**. Toward this end, treatment of β-hydroxy acid (−)-**69**[12] with HMDS to furnish the bis-silylated derivative (Scheme 12), followed by TMSOTf-promoted

**SCHEME 12**

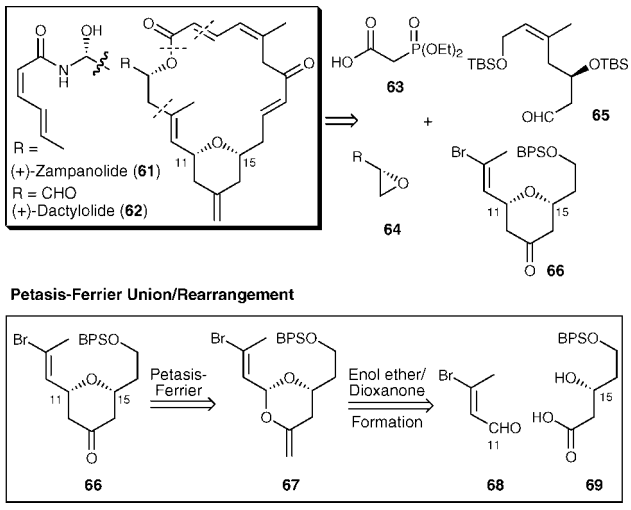



condensation with aldehyde **68** led to (+)-**70** in 82% yield with excellent diastereoselectivity (i.e., 10:1 dr). The addition of a catalytic amount of trifluoromethanesulfonic acid (TfOH, 5–15 mol%) proved essential when this transformation was carried out on a large scale (ca. 5 g). Presumably, adventitious water, more pronounced on a small scale, generates TfOH in situ from TMSOTf, greatly accelerating dioxanone formation. With dioxanone (+)-**70** in hand, olefination provided a mixture (i.e., 6:1 dr) of enol acetals, which upon exposure to one equivalent of $Me_2AlCl$ at −78 °C triggered the Petasis–Ferrier rearrangement to furnish C(11–15) 2,6-*cis*-substituted tetrahydropyranone (+)-**66** in 59% yield. A minor amount of the C(11) *trans* isomer (12%) was also observed. Presumably, the decreased steric demand of the C(11) $sp^2$-hybridized substituents reduces the destabilization of the 1,3-diaxial interaction with the C(15) substituent in the chair-like transition state, leading to the *trans* isomer of (+)-**66**.[21]

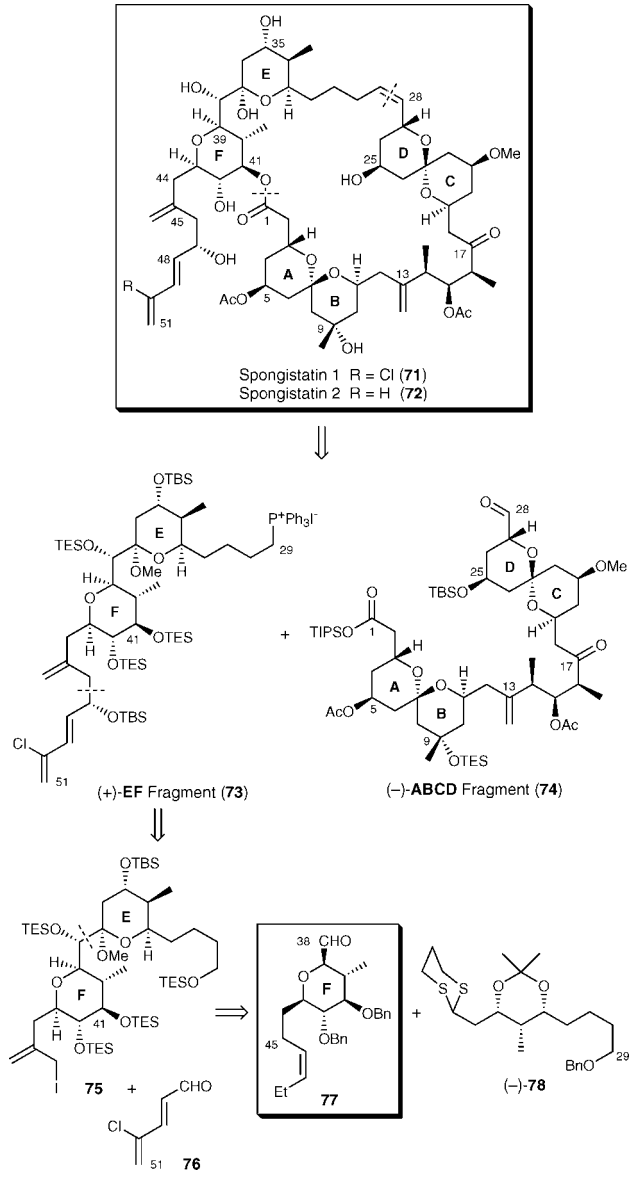
## (+)-Spongistatin 1

In 2003, we disclosed our first-generation total synthesis of (+)-spongistatin 1 (**71**; Scheme 13), a remarkably intriguing marine antitumor macrolide; the synthesis proceeded with a longest linear sequence of 29 steps and in 0.5% overall yield.[22] Although pleased with this synthetic achievement, comprising an endgame strategy involving the union of EF Wittig salt (+)-**73** with ABCD aldehyde (−)-**74**, we recognized that access to significant quantities of (+)-spongistatin 1 (ca. 1 g), as well as analogues for further biological evaluation, would require a more efficient, scalable synthesis of the EF fragment. On the basis of our initial

**SCHEME 11**



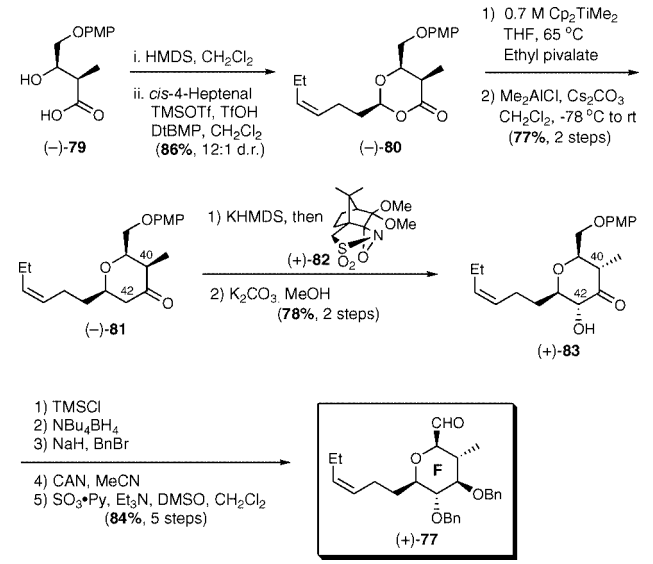
**SCHEME 13**




successes with the Petasis–Ferrier union/rearrangement tactic, in conjunction with recognition of the 2,6-*cis*-fused tetrahydropyranol inscribed in the spongistatin side chain, we redesigned our EF synthetic strategy to entail the construction and union of three fragments: aldehyde **76**, 2,6-*cis*-substituted tetrahydropyran **77**, and dithiane (–)-**78**, with the latter employed in our first-generation synthesis for the stereoselective elaboration of ring E.

Construction of aldehyde **77** proceeded smoothly both in high yield and diastereoselectivity via the TMSOTf-promoted condensation of the bis-TMS-protected $\beta$-hydroxy acid of (–)-**79** and *cis*-4-heptenal to furnish dioxanone (–)-**80** (Scheme 14). As observed in our (+)-zampanolide and (+)-dactylolide ventures, the addition of a catalytic amount of TfOH was critical for large-scale reactions. Subsequent methylenation and rearrangement under our now optimized Petasis–Ferrier rearrangement conditions [i.e., 0.7 M $Cp_2TiMe_2$/ethyl pivalate (10:1) in THF and then $Me_2AlCl$/$Cs_2CO_3$] furnished the 2,6-*cis*-substituted tetrahydropyranone [(–)-**81**] as a single isomer in good yield for the two steps. The stereochemical outcome was assigned by NOE analysis. Installation of the C(42) hydroxyl group was next achieved via treatment of the potassium enolate derived from (–)-**81** with oxaziridine (+)-**82** to furnish, after base-promoted epimerization of the C(40) methyl group, α-hydroxy ketone (+)-**83**. A five-step sequence comprising silylation, axial carbonyl reduction, bis-benzylation, oxidative removal of the *p*-methoxyphenyl group (PMP), and Parikh–Doering oxidation[23] completed construction of aldehyde (+)-**77** in a highly efficient manner (cf. 85%). Most importantly, the second-generation synthesis of the F ring exploiting the Petasis–Ferrier union/rearrangement provided large-scale access (>15 g) of (+)-**77** for our ongoing gram-scale synthesis of (+)-spongistatin 1.

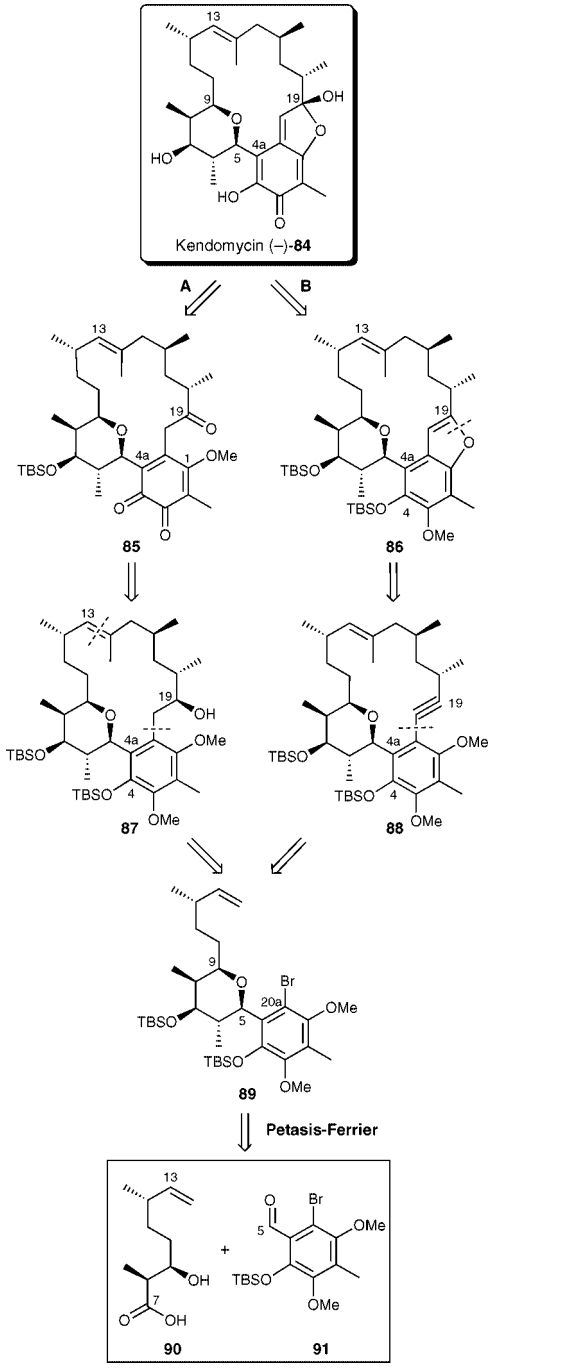
**SCHEME 14**




## (–)-Kendomycin

To demonstrate further the utility of the Petasis–Ferrier union/rearrangement tactic, we next took on the construction of (–)-kendomycin (**84**), an architecturally novel polyketide macrocycle derived from both *Streptomyces violaceoruber* and various strains of *Actinomycetes*, displaying a variety of bioactivities (Scheme 15). Particularly significant is the remarkable cytotoxicity toward a wide series of human tumor cell lines (HMO2, HEP G2, MCF7, and $GI_{50}$ < 0.1 $\mu$M).[24] From the outset, we envisioned two synthetic scenarios based on ring-closing olefin metathesis to construct the kendomycin macrocyclic ring. Endgame **A**, inspired by the biosynthetic

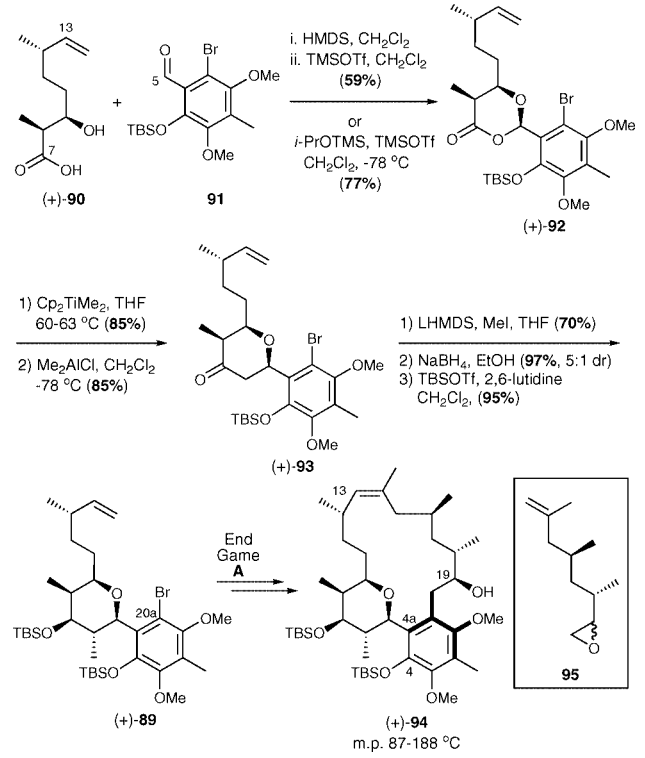
**SCHEME 15**




postulate proposed by Zeeck and co-workers,[24] would rely on the premise that hydrolysis of the C(1) methyl enol ether in **85** or a closely related congener would be followed by in situ cyclization involving the C(19) ketone to furnish the thermodynamically more stable C(19) lactol chromophore. Alternatively, in endgame **B**, this advanced C(4a–19) chromophore would arise from benzofuran **86** via an oxidation/hydration sequence. Further disconnection of both **85** and **86** quickly revealed *cis*-5,9-disubstituted tetrahydropyran **89**, a common intermediate for both endgames, to be an ideal target for the Petasis–Ferrier union/rearrangement. Required here, however, would be the construction of a sterically congested dioxanone, assumed to arise via condensation of aromatic aldehyde **91** with $\beta$-hydroxy acid **90**. Ethylidenation of the dioxanone carbonyl to introduce the requisite C(6) methyl group would then be followed by execution of the Petasis–Ferrier rearrangement as in our first-generation phorboxazole synthesis.

Having secured gram quantities of both aldehyde **91** and $\beta$-hydroxy acid (+)-**90**, we turned to the Petasis–Ferrier union/rearrangement to assemble tetrahydropyran **89** (Scheme 16).[25] Condensation of **91** with the bis-TMS derivative of (+)-

**SCHEME 16**




**90**, promoted by TMSOTf, led at best to a modest yield of dioxanone (+)-**92** (ca. 59%), presumably because of the steric congestion of the bis-ortho-substituted aldehyde **91**. Fortunately, a high yield (cf. 77%) of a single diastereomer [(+)-**85**] could be obtained by employing the Kurihara condensation protocol,[26] involving the use of *i*-PrOTMS and TMSOTf to effect in situ bis-silylation and in turn union of **91** with (+)-**90**. We now recommend the Kurihara protocol for all dioxanone constructions. Continuing with the Petasis–Ferrier tactic, initial attempts to execute a Takai *ethylidenation*[27] of the carbonyl in (+)-**92** [e.g., $CH_3CHBr_2$; $Zn/TiCl_4/PbCl_2$-(catalyst)], which upon rearrangement would directly install the C(6) methyl group, proved unsuccessful because of complica-

tions with the pendant terminal olefin, as well as proto-debromination of the aryl bromide. Undaunted, we turned to *methylidenation* of dioxanone (+)-**92**, which in turn would require installation of the C(6) methyl following tetrahydropyranone construction. Methylenation and exposure of the resulting enol ether to $Me_2AlCl$ led to tetrahydropyranone (+)-**93** as a single isomer in high yield. Diastereoselective C(6) methylation via the kinetically derived enolate, reduction with $NaBH_4$, and TBS protection of the resulting C(7) hydroxyl furnished tetrahydropyran (+)-**89**. Subsequent coupling with epoxide **95** and ring-closing metathesis (RCM), as proposed for endgame **A**, completed construction of macrocycle (+)-**94**, albeit solely as the undesired C(13,14) *cis*-olefin. The structure and relative configuration of (+)-**94** were confirmed by X-ray analysis.

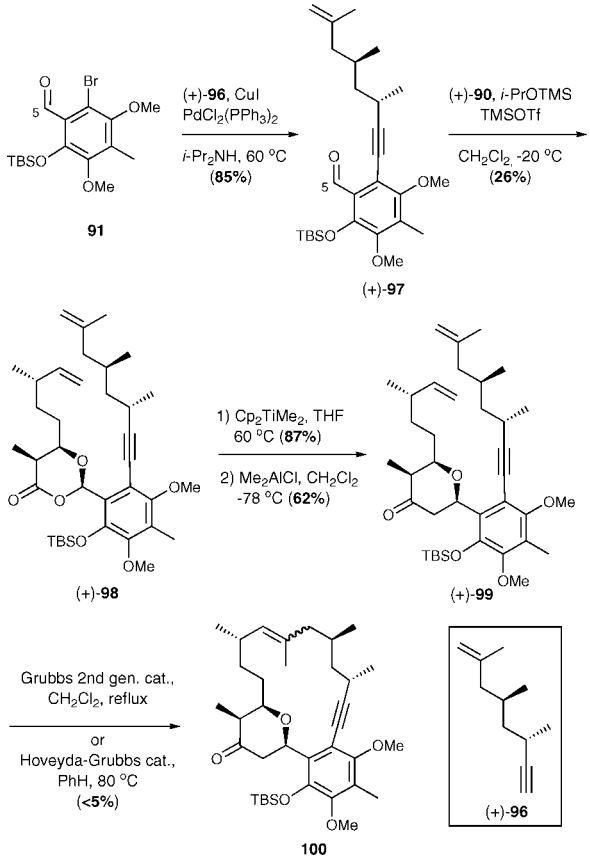
Having obtained the undesired *cis* C(13,14) olefin in endgame **A**, we turned to the alternative RCM substrate proposed for endgame **B** (Scheme 15). Despite extensive efforts, we were not able to couple advanced bromide (+)-**89** with alkyne (+)-**96** via the Sonogashira reaction. Success was however achieved upon the union of bromo aldehyde **91** with alkyne (+)-**96** to afford (+)-**97** (Scheme 17). Subsequent condensation between (+)-**90** and (+)-**97** employing the Kurihara protocol[26] led to dioxanone (+)-**98** in modest yield. Moving forward, Petasis–Tebbe methylenation and execution of the Petasis–Ferrier rearrangement with $Me_2AlCl$ furnished tetrahydropyranone (+)-**99** in good yield. However, neither the Grubbs nor the Hoveyda–Grubbs second-generation catalysts proved effective for ring closure; only trace amounts (<5%) of macrocycle **100** were observed by $^1H$ NMR.

Fortunately, returning to endgame **A**, isomerization of the trisubstituted olefin to the requisite *E* isomer proved possible via a three-step sequence: *cis*-dihydroxylation of olefin (+)-**94**, epoxide formation, and Sharpless stereospecific deoxygenation with $WCl_6$/*n*-BuLi.[28] Kendomycin [(−)-**84**] was then secured upon execution of the Zeeck biosynthetic hypothesis.[24] In retrospect, one of the highlights of the (−)-kendomycin synthetic venture was the application of the Petasis–Ferrier rearrangement to construct a sterically encumbered tetrahydropyran ring, thus further demonstrating the utility of this method in complex molecule synthesis.

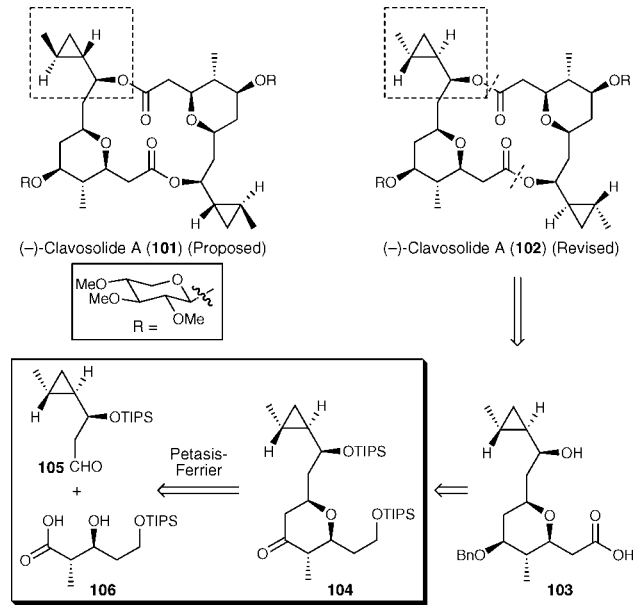
## (−)-Clavosolide A

Continuing with our goal to demonstrate the utility of the Petasis–Ferrier union/rearrangement tactic with increasingly complex and/or sensitive synthetic targets, we initiated a program directed at construction of the clavosolide family of marine natural products (Scheme 18). In this case, our objective was to test the viability of the Petasis–Ferrier rearrangement with a substrate possessing a highly acid-labile functionality, namely, rearrangement of the cyclopropylcarbinyl system.[29]

**SCHEME 17**




**SCHEME 18**

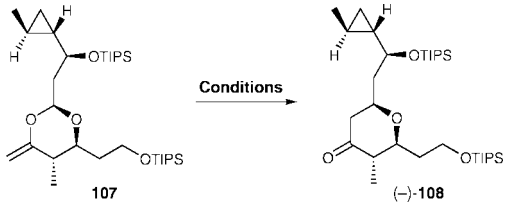


The original structure of clavosolide A (i.e., **101**), reported by Faulkner and co-workers in 2002,[30] is illustrated in Scheme 18. However, following the first total synthesis of the *reported* structure by Willis and co-workers,[31] as well as observations made by Chakraborty and Reddy,[32] the cyclopropyl carbinyl stereochemistry required reassignment. Lee and co-workers subsequently secured the revised relative configuration (i.e., **102**) via total synthesis, albeit misassigned the absolute stereochemistry.[33]

From the retrosynthetic perspective, we envisioned that removal of both glycosides and disconnection of the lactone linkages would afford monomer **103**. Further simplification of **103** would then involve the Petasis–Ferrier union/rearrangement retron, leading to aldehyde **105**, possessing the acid-labile cyclopropylcarbinyl moiety and the $\beta$-hydroxy acid **106**.

Prior to the reassignment of the relative configuration by Willis and Lee, the requisite Petasis–Ferrier rearrangement conditions were developed and optimized in our laboratory with enol ether **107** (Scheme 19).[34] Not surprisingly, because of the lability of the cyclopropylcarbinyl moiety to rearrangement under Lewis acid conditions,[29] the Petasis–Ferrier rearrangement of **107** proved highly dependent upon the reaction conditions. Careful experimentation revealed that an extremely rapid addition of $Me_2AlCl$ to the enol ether at ambient temperature followed by rapid reaction termination was required. Use of either slower and/or inverse addition protocols, in conjunction with lower reaction temperatures, alternative Lewis acids (i.e., $Me_3Al$), and/or additives (e.g., $Cs_2CO_3$ and DtBMP), led to either poor yields or no reaction!

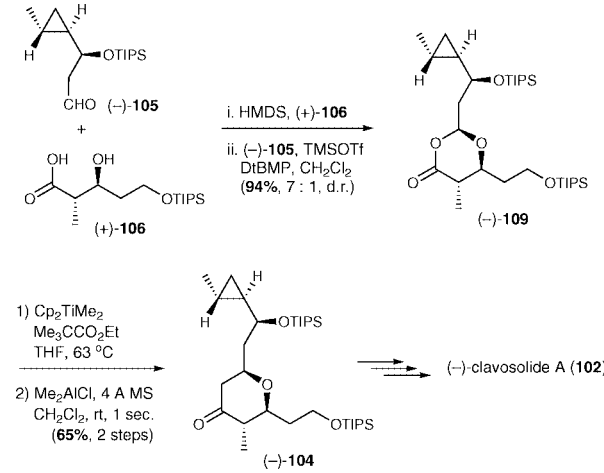
**SCHEME 19**




| $Me_2AlCl$ (equiv.) | $Cs_2CO_3$ (equiv.) | Conditions | Yield |
|---|---|---|---|
| 2.6 | 1.6 | -78 °C / 1 h | decomp. |
| 1.3 | 1.6 | -78 °C / 1 h | no reaction |
| 1.3 | 1.6 | 0 °C / 5 min. | 40% |
| 1.3 | 1.6 | rt / 15 min. | 30% |
| 1.1 | - | rt / 1 min. | 31% |
| 1.1 | - | rt / 1 sec. | 60% |

With the conditions optimized, we turned to the revised structure of (–)-clavosolide A. Condensation of aldehyde (–)-**105** and $\beta$-hydroxy acid (+)-**106** promoted by TMSOTf furnished dioxanone (–)-**109** in 94% yield as an inseparable mixture (i.e., 7:1 dr) of diastereomers (Scheme 20). Pleasingly, the Petasis–Tebbe methylenation[7] followed by exposure of the resulting enol ether to the optimized rearrangement conditions developed for **107** led to tetrahydropyranone (–)-**104** as a single diastereomer in 65% yield over the two steps, which was converted to (–)-clavosolide A (**102**), thereby confirming assignment of the relative configuration of Willis and Lee[31,33] and permitting reassignment of the absolute configuration.[34] The successful application of the Petasis–Ferrier union/rearrangement tactic to a substrate possessing a highly acid-labile functionality again demonstrates and further extends the utility of this tactic in complex molecule synthesis.

**SCHEME 20**

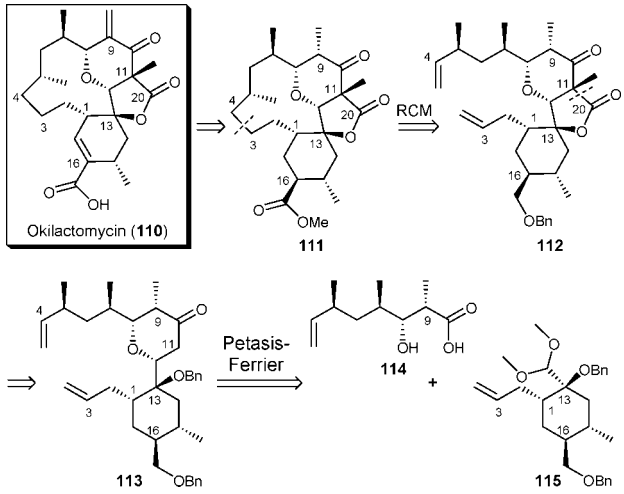



## (–)-Okilactomycin

Our most recent application of the Petasis–Ferrier union/rearrangement comprises construction of (+)-okilactomycin (**110**), a novel polyketide antitumor antibiotic isolated in 1987 by Imai and co-workers from a bioactive filtrate of *Streptomyces griseoflavus* (Scheme 21).[35] Although the connectivity and relative configuration of (+)-**110** had been confirmed by X-ray analysis, the absolute stereochemistry was unknown at the outset of this synthetic venture. Our initial interest in (+)-okilactomycin comprises a combination of the complex architecture, the significant in vitro cytotoxicity, and the unknown absolute configuration.

We initially envisioned (–)-okilactomycin (**110**) to arise via oxidative elimination of a bis-selenide derived from **111** (Scheme 21), which in turn would arise via RCM, followed by oxidation-state adjustment. Further simplification to tetrahydropyranone **113** would then permit application of the Petasis–Ferrier retron to reveal the two requisite coupling partners, $\beta$-hydroxy acid **114** and dimethyl acetal **115**. The

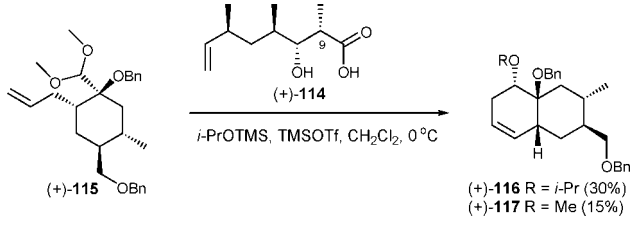
**SCHEME 21**




successful union of these two partners would represent the first use of an acetal in the Petasis–Ferrier union/rearrangement sequence, in conjunction with the presence of a sterically demanding α-quaternary center.

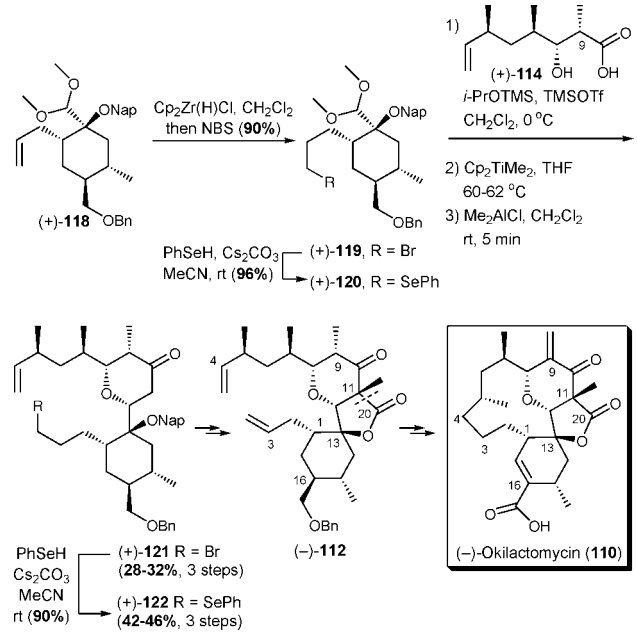
After the preparation of gram quantities of both β-hydroxy acid (+)-**114** and dimethyl acetal (+)-**115**, we turned to the Petasis–Ferrier union/rearrangement sequence. We quickly discovered that the terminal C(3,4) olefin in (+)-**115** preferentially undergoes an intramolecular Prins cyclization[36] with the dimethyl acetal moiety during the TMSOTf-promoted condensation with β-hydroxy acid (+)-**114** to furnish bicyclic products (+)-**116** and (+)-**117** (Scheme 22).

**SCHEME 22**




To combat the Prins process, we masked the terminal olefin as the corresponding alkyl bromide [i.e., (+)-**119**] via a hydrozirconation/bromination[37] sequence (Scheme 23). Pleasingly, the Petasis–Ferrier tactic now furnished the desired tetrahydropyranone (+)-**121**, albeit in modest yield (i.e., 28–32% over the three steps). Not withstanding the modest yield, this sequence represented the first example of the Petasis–Ferrier union involving both an acetal and a sterically demanding, fully substituted, α center. The requisite terminal olefin was then regenerated via conversion to selenide (+)-**122** followed by oxidative elimination. Because of the competitive elimination of the bromide during the Petasis olefination, resulting in several byproducts,

**SCHEME 23**




we investigated the use of selenide (+)-**120** in the Petasis–Ferrier sequence. To our delight, selenide (+)-**120** was converted to (+)-**122** in an improved 42–46% yield for the three-step union/rearrangement sequence. With tetrahydropyranone (+)-**122** in hand, conditions were subsequently developed for the conversion to RCM substate (–)-**112**, followed by eventual preparation of (–)-okilactomycin (**110**).[38]

## Summary

The Petasis–Ferrier union/rearrangement sequence comprises a powerful tactic for the construction of the 2,6-*cis*-substituted tetrahydropyran ring, a ubiquitous structural element often found in architecturally complex natural products possessing significant bioregulatory properties. The three-step sequence entails condensation between a chiral, nonracemic β-hydroxy acid and an aldehyde to furnish a dioxanone, followed in turn by carbonyl olefination, and Lewis-acid-induced rearrangement of the resultant enol acetal to generate the 2,6-*cis*-disubstituted tetrahydropyranone system. To demonstrate the versatility and robustness of the Petasis–Ferrier tactic in complex molecule synthesis, we have exploited this method as a cornerstone in our now complete total syntheses of (+)-phorboxazole A (**21**), (+)-zampanolide (**61**), (+)-dactylolide (**62**), (+)-spongistatins **1** and **2** (**71** and **72**), (–)-kendomycin (**84**), (–)-clavosolide A (**102**), and most recently, (–)-okilactomycin (**110**). Studies to extend and expand the utility of the Petasis–Ferrier union/rearrangement tactic, especially in the

context of library synthesis of natural product-like compounds, continues in our laboratory and will be reported in due course.

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## BIOGRAPHICAL INFORMATION

**Amos B. Smith, III**, born in Lewisburg, PA, in 1944, completed Bucknell University's inaugural B.S.–M.S. degree in chemistry in 1966. After a year in medical school at the University of Pennsylvania, he entered The Rockefeller University, completing his Ph.D. degree in 1972, followed by a year as a Postdoctoral Associate at Rockefeller. In 1973, he joined the Department of Chemistry at the University of Pennsylvania, where he is currently the Rhodes–Thompson Professor of Chemistry. From 1988 to 1996, he served as Chair of the Department. In addition, he is a Member of the Monell Chemical Senses Center, the Associate Director of the Penn Center for Molecular Discovery (PCMD), and an Honorary Member of the Kitasato Institute, Tokyo, Japan. Currently, Professor Smith also serves as the inaugural Editor-in-Chief of *Organic Letters*. Professor Smith has received numerous awards, including the Kitasato Institute Microbial Chemistry Award (1990), the ACS Cope Scholar Award (1991), the ACS Ernest Guenther Award in the Chemistry of Natural Products (1993), the ACS Award for Creative Work in Synthetic Organic Chemistry (1997), the Centenary Medal of the Royal Society of Chemistry (2002), the Yamada Prize, Tokyo, Japan (2003), the Order of the Rising Sun, Gold Rays with Neck Ribbon from the Government of Japan (2004), and the Simonsen Award of the Royal Society of Chemistry (2008). In 2006, he was elected to the American Academy of Arts and Sciences. His research interests include organic synthesis, particularly, the synthesis of architecturally complex bioactive natural products, bioorganic chemistry (in collaboration with Professor Ralph Hirschmann, University of Pennsylvania), and materials science.

**Richard J. Fox** received his B.S. degree (*summa cum laude*) in chemistry from Union College in 2000. In 2006, he obtained his Ph.D. degree in organic chemistry from the University of Pennsylvania under the guidance of Professor Amos B. Smith, III. After a postdoctoral opportunity with Professor Robert G. Bergman at the University of California, Berkeley, CA, he joined Bristol-Myers Squibb Process Research and Development in New Brunswick, NJ, where he is a Research Investigator II.

**Thomas M. Razler** received his B.S. degree in chemistry from the University of Delaware in 1998. From 1998–2001, he worked as a Research Assistant at the Johnson & Johnson Pharmaceutical Research Institute in Raritan, NJ. In 2006, he obtained his Ph.D. degree in organic chemistry from the University of Pennsylvania under the guidance of Professor Amos B. Smith, III. Currently, he is a Research Investigator II for Bristol–Myers Squibb Process Research and Development in New Brunswick, NJ.

## FOOTNOTES

*To whom correspondence should be addressed. Fax: 215-898-5129. E-mail: smithab@sas.upenn.edu.

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