Acc. Chem. Res. **1998,** *31,* 35−46

Total Synthesis of Immunosuppressants: Unified Strategies Exploiting Dithiane Couplings and σ-Bond Olefin Constructions†

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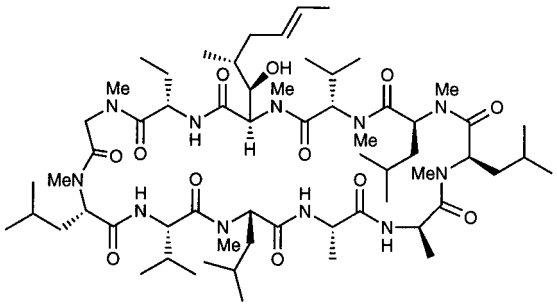
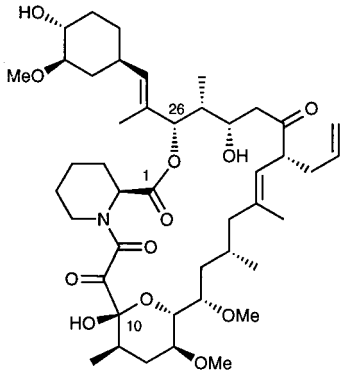
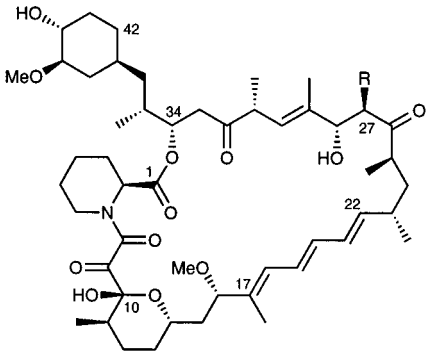
Received July 8, 1997



Cyclosporin A (CsA) (**1**)



(-)-FK506 (**2**)



(-)-Rapamycin (**3**, R = OMe)
(-)-Demethoxyrapamycin (**4**, R = H)

Although the immunomodulator cyclosporin A (CsA, **1**)[1] has engendered dramatic progress in organ transplantation, recurrent clinical complications have stimulated an ongoing search for more potent and less toxic agents. The discovery of FK506 (**2**)[2] and the reinvestigation of rapamycin (**3**)[3] and demethoxyrapamycin (**4**)[4] heralded major advances in immunosuppressant research; not only are these natural products more potent than CsA, but they also selectively inhibit two distinct steps in the immune response. CsA and FK506, bound to immunophilins cyclophilin A and FKBP, respectively, prevent cells from entering the G_1 phase of the cell cycle, whereas the rapamycin−FKBP complex blocks progression into the S phase. The molecular biology, immunology and pharmacology of CsA, FK506, and rapamycin have been recently reviewed.[5]

Discodermolide (**5**), first described in 1990,[6] displays immunomodulating activity intermediate between those of CsA and FK506.[7] In Burkitt lymphoma cells, discodermolide causes marked microtubule bundling, thereby arresting cellular development at the G_2/M transition.[8] This mode of action is similar to that of Taxol, albeit its binding affinity is much higher than Taxol. As such, (+)-discodermolide could prove to be an effective therapeutic agent for the treatment of cancer.[8]

The complex architecture and therapeutic importance of these nonpeptidal immunomodulators have attracted considerable interest among synthetic chemists, culmi-

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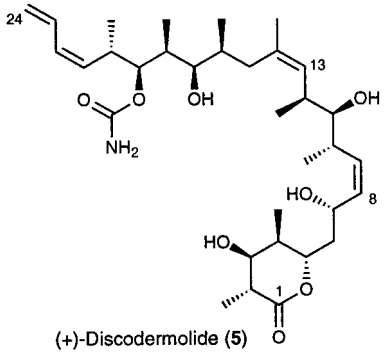
† This account is dedicated to Professors William C. Agosta, Harold W. Heine, and Ralph F. Hirschmann on the occasions of their 65th and 75th birthdays.

S0001-4842(96)00289-0 CCC: $15.00
Published on Web 01/20/1998



(+)-Discodermolide (**5**)

nating in two total syntheses[9,10] and three formal syntheses of FK506,[11−13] as well as four syntheses of rapamycin[14−17] and a single construction of its 27-demethoxy congener.[17] (+)-Discodermolide and its bioactive (−) antipode have also recently succumbed to total synthesis,[18−20] and a variety of fragment preparations have been reported.[21]

Common structural features of these targets include the substituted cyclohexane appendages and pipecolinate/tricarbonyl binding domains shared by FK506 and the rapamycins, in addition to an array of trisubstituted olefins, diene and triene units, and aldol linkages. At the outset of our efforts, the stereocontrolled generation of the requisite alkenes and the efficient union of advanced intermediates loomed as significant challenges. Accordingly, in designing our approaches to FK506,[13] rapamycin and demethoxyrapamycin,[17] and discodermolide,[20] we focused on two unifying strategic goals: (i) to exploit the stereochemical potential of σ-bond olefin formation and (ii) to employ dithiane anions for the coupling of complex fragments and installation of aldol moieties. As presented in this Account, we have successfully demonstrated the power of these strategies in the development of highly convergent synthetic routes to immunosuppressant natural products. In addition, we have uncovered striking effects of 2,2-disubstituted dithiane moieties on the reactivity of pendant functionalities.

Stereocontrolled σ-Bond Formation of Trisubstituted Olefins. Traditional π-bond methodologies, principally the Wittig reaction and its Horner−Emmons variant, serve as powerful tools for the stereoselective installation of *E* and *Z* disubstituted olefins.[22] Unfortunately, the application of these methods to unsymmetrical trisubstituted olefins is often problematic, as even sterically biased ketones and α,α-disubstituted ylides often yield unacceptable isomer mixtures. We therefore decided to explore a variety of σ-bond constructions, which we define as those whereby a vinylic carbon−carbon σ-bond is formed last. Application of this tactic for the stereocontrolled introduction of trisubstituted as well as disubstituted olefins proved highly effective.

Our analysis of FK506, the first target in our immunosuppressant program, is outlined retrosynthetically in Figure 1. The key disconnection of the C(22−24) aldol linkage generated the C(24−34) dithiane subtarget **6** and the highly functionalized C(10−23) iodo ether **7**. The dogma prevalent at the time offered little hope that **7** would prove to be a viable electrophile (vide infra). For installation of the C(19,20) trisubstituted olefin in FK506, other groups had employed several π-bond approaches with only modest success (ca. 2.5−1:1, *E*/*Z*).[9−12,23] Kociènski et al. recently described an alternative σ-bond strategy.[24]

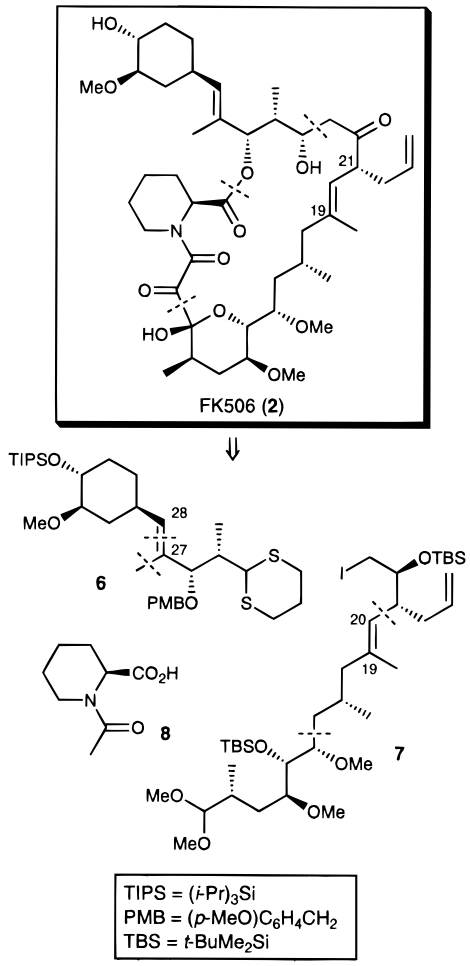
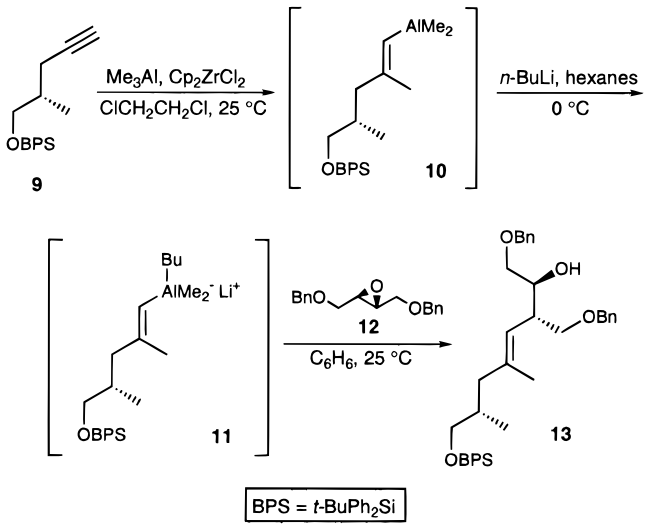


FIGURE 1. Retrosynthetic analysis of FK506 (**2**).

Our first example of stereocontrolled σ-bond construction of a trisubstituted olefin began with terminal acetylene **9** (Scheme 1). Carboalumination with trimethylalu-

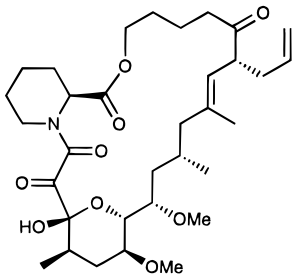
Scheme 1



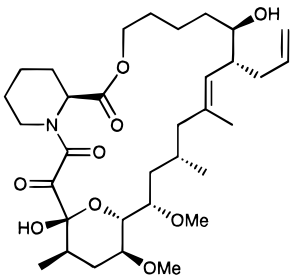
minum and zirconocene dichloride[25] provided (*E*)-vinyl alane **10**. Addition of *n*-BuLi afforded the ate complex (**11**),[25] which then smoothly coupled with the C_2 disubstituted epoxide **12** to furnish **13**. This three-step, one-pot sequence, conveniently performed on a decagram scale, apparently represented the first construction of a trisubstituted olefin via reaction of an alane ate complex with a disubstituted epoxide. Importantly, this tactic reduces the problem of stereoselective trisubstituted olefin synthesis to stereoselective carboalumination, a process known to proceed with excellent selectivity.[26]

Olefin **13** was also employed in our synthesis of two analogues designed to probe the binding and effector domains of FK506 [(−)-**14** and (−)-**15**, Table 1].[27] The bioassay data seem to indicate that the cyclohexyl moiety is crucial for tight binding to FKBP but does not greatly influence the ability of the resultant analogue−FKBP complex to inhibit calcineurin.

Table 1. Biological Activity of Designed FK506 Analogues



(-)-**14**



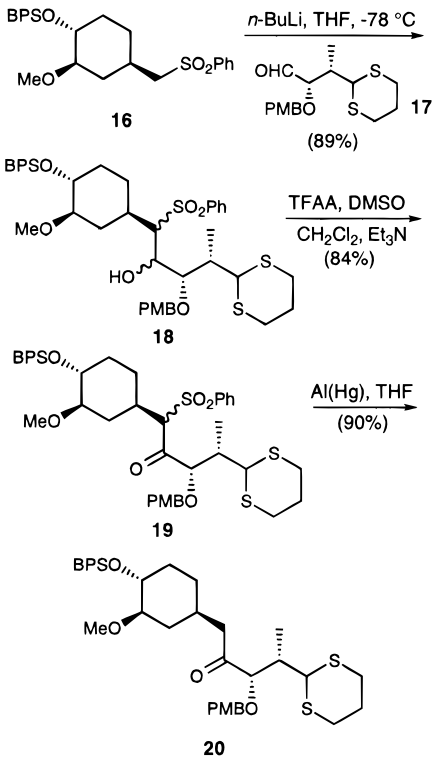
(-)-**15**

	FKBP Binding	Calcineurin Inhibition by FKBP Complex
FK506	8×10^{-10} M	2×10^{-8} M
(-)-**14**	2.5×10^{-5} M	3.5×10^{-7} M
(-)-**15**	2.2×10^{-5} M	$> 10^{-4}$ M

The C(27,28) linkage of FK506 presented a second opportunity to exploit the stereoselective σ-bond methodology. Other strategies employed for the construction of this bond have included Horner−Emmons[28] and α-lithio imine[29] olefinations of aldehydes, the Reformatsky reaction,[12] and alkyne hydrozirconation/halogenation.[23] In addition, Rao,[30] Schreiber,[10] and Danishefsky[11] treated a C(27) ketone with methylmagnesium bromide and dehydrated the resultant tertiary alcohol, obtaining predominately the desired isomer. We opted instead to install the π-system first, as a vinyl triflate, and then to introduce the methyl moiety via cuprate coupling. To this end, lithiation of sulfone **16**, addition to aldehyde **17**, Swern oxidation, and desulfonylation in the presence of the dithiane moiety furnished ketone **20** (Scheme 2).

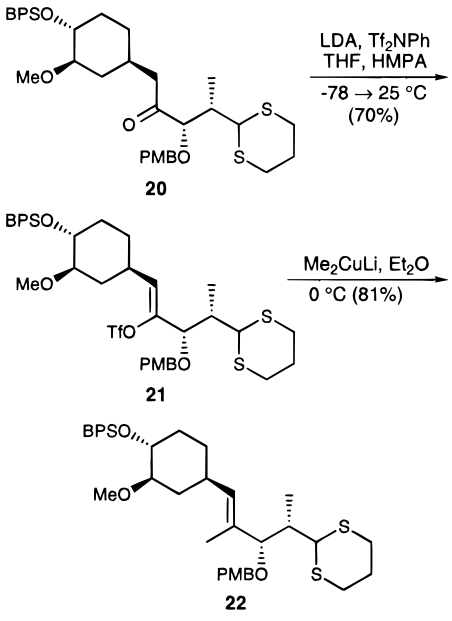
In 1980, McMurry and Scott first reported that vinyl triflates couple with organocopper(I) reagents with retention of olefin configuration.[31] Thus, regio- and stereoselective enolization of **20** and enolate trapping was expected to furnish triflate **21**; alkylation with lithium dimethylcopper(I) would then provide the alkene. In

Scheme 2



natural product synthesis, this tactic has been applied to a number of cyclic ketones;[32] however, its utility in acyclic cases has been limited by problems encountered in selective enolization of the precursor ketones,[33] manipulation of the intermediate vinyl triflates,[34] and formation of side products in the cuprate reactions.[35] Deprotonation of **20** and subsequent enolate trapping provided exclusively the desired (*Z*)-vinyl triflate **21**; treatment of the latter with lithium dimethylcopper(I) in ether[36] then gave the *E* trisubstituted olefin **22** in 81% overall yield (Scheme 3).

Scheme 3



Following the successful construction of the C(27,28) trisubstituted olefin in FK506, we sought to exploit and extend this methodology in the total synthesis of rapamycin.[37,38] Our rapamycin−demethoxyrapamycin strategy, outlined retrosynthetically in Figure 2, provided for

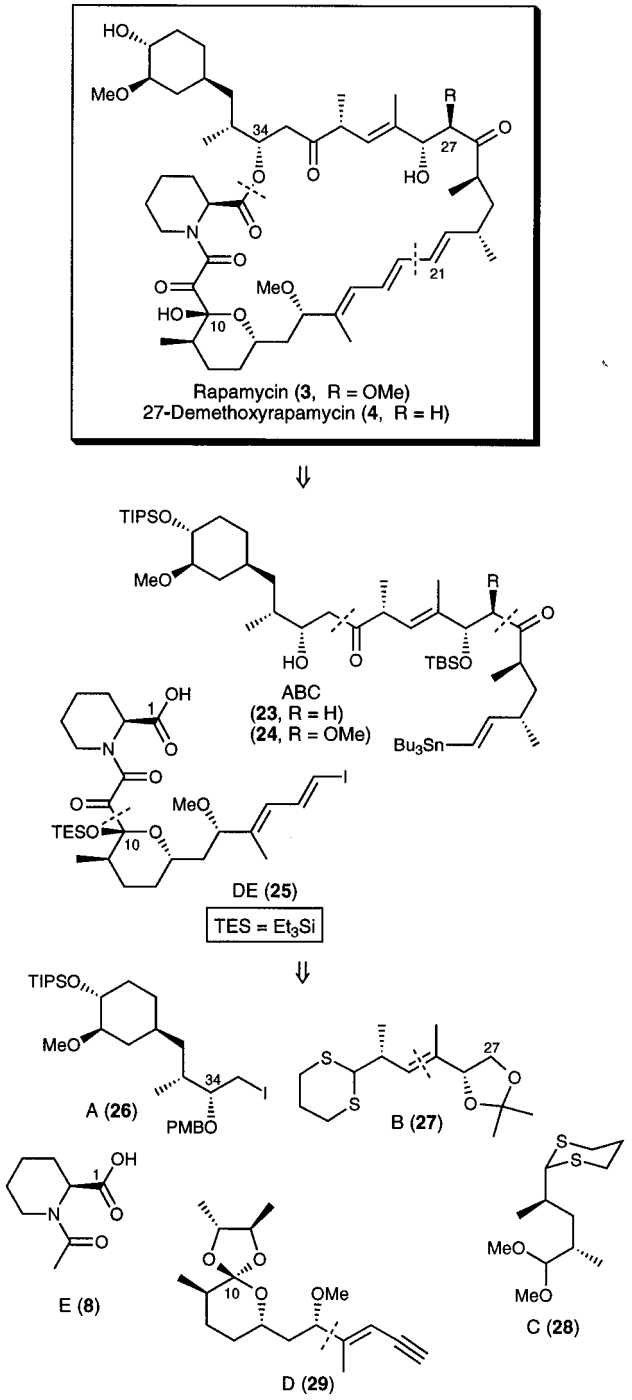
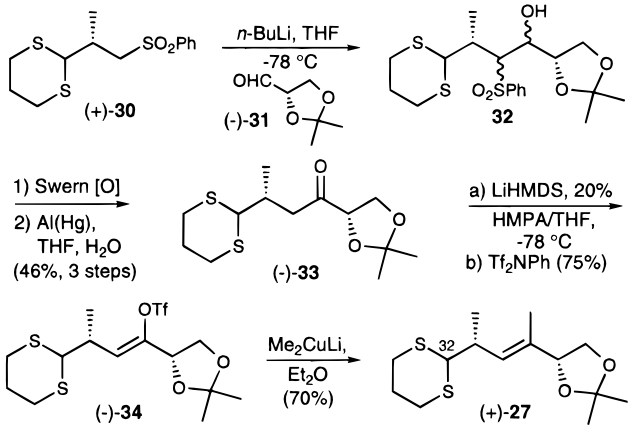


FIGURE 2. Retrosynthetic analysis of rapamycin (**3**) and 27-demethoxyrapamycin (**4**).

the highly convergent assembly of both targets from common precursors A−E (**8**, **26**−**29**). Importantly, we were able to apply the σ-bond construction tactics to access the C(17,18), C(19,20), C(21,22), and C(29,30) olefinic linkages with complete stereochemical control (vide infra).

For generation of the C(29,30) trisubstituted olefin of the rapamycins, sulfone (+)-**30** was added to aldehyde (−)-**31**; oxidation and desulfonylation then furnished ketone (−)-**33** (Scheme 4). The previously described

Scheme 4



conditions for vinyl triflate formation (e.g., LDA, THF, HMPA, Tf_2NPh) led only to the undesired regioisomer. Utilization of the sterically more bulky base, LiHMDS, followed by enolate trapping, and alkylation of the (*Z*)-vinyl triflate (−)-**34** with lithium dimethylcopper(I) in ether completed construction of the requisite *E* olefin (+)-**27**. The alternative *E* trisubstituted olefin could not be detected by either 500 MHz ^{1}H or 125 MHz ^{13}C NMR.

Our synthetic strategy for discodermolide (**5**; Figure 3) evolved from the recognition of three identical stereochemical triads, separated by the C(8,9) and C(13,14)

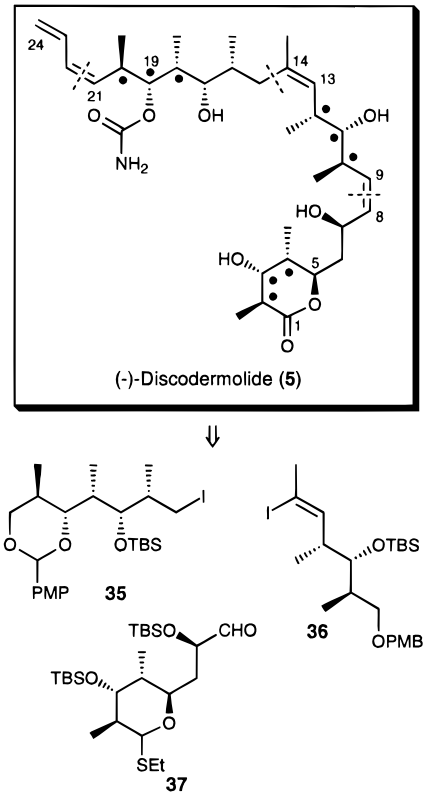
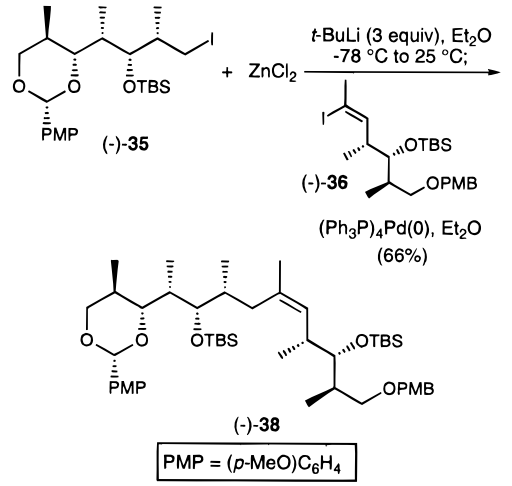


FIGURE 3. Retrosynthetic analysis of (−)-discodermolide (**5**).

olefinic linkages; initial disconnections divided the molecule into the major fragments **35**, **36**, and **37**.

Confident that the C(13,14) trisubstituted olefin would likewise be accessible via a σ-bond strategy, we focused on a modification of the Negishi alkyl zinc/vinyl iodide coupling procedure.[39] The requisite (*Z*)-vinyl iodide (−)-**36** was prepared in a stereocontrolled manner via the Zhao α-iodomethyl Wittig reagent.[40] Treatment of a mixture of iodide (−)-**35** and anhydrous $ZnCl_2$ with *t*-BuLi followed by warming and addition of vinyl iodide (−)-**36** and $(Ph_3P)_4Pd$ provided the coupling product (−)-**38** in 66% yield with greater than 20:1 selectivity (Scheme 5).

Scheme 5



The stereoselective σ-bond construction of trisubstituted olefins served us well en route to several key fragments of these immunosuppressant natural products. We next required an efficient method for union of the substargets.

Dithiane Couplings of Complex Building Blocks. A key objective in most of our synthetic planning is maximum convergency, ideally leaving only the linkage of fully functionalized subunits and deprotection for the final transformations. This goal requires coupling reactions that can be performed efficiently with structurally complex substrates. We have extensively exploited the couplings of dithiane anions with a variety of electrophiles, processes which generate fully or partially protected aldol linkages (Figure 4).[41,42] The advantages of this method vis-á-vis the classical aldol reaction include the following: (1) the product carbonyl group is masked, circumventing a separate protection step; (2) the aldol hydroxyl can be either protected or unprotected, via suitable choice of electrophile; (3) the configuration of the β-hydroxyl is defined prior to the coupling step; (4) the reaction is not reversible; and (5) carbonyl self-condensation is avoided. Each of the dithiane couplings illustrated in Figure 4 has been advantageously employed in our immunosuppressant program for the union of major fragments.

Although many investigators have utilized the 1,3-dithiane linchpin in total synthesis of natural products,[43−46] most applications have involved relatively simple reactant structures.[47] In contrast with the parent dithiane, which

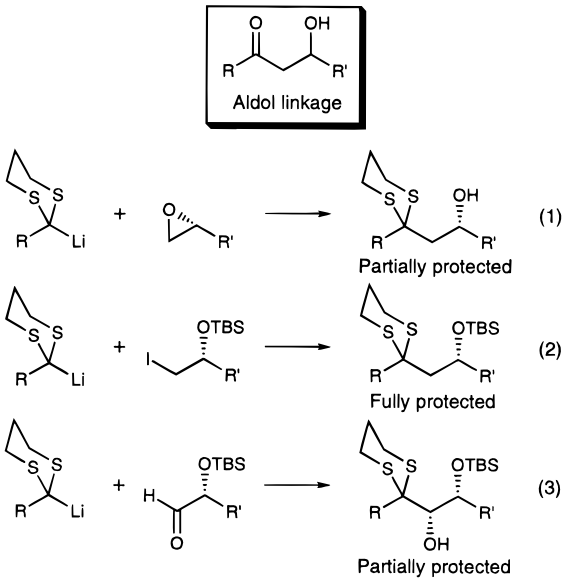


FIGURE 4. Construction of aldol linkages via dithiane couplings.

is readily deprotonated by *n*-BuLi, 2-substituted derivatives bearing oxygen substitutents often require stronger bases,[48] solvent additives, and a myriad of time and temperature regimes. Furthermore, capricious behavior of highly oxygenated dithiane anions has been reported[49,50] and attributed to the increased kinetic basicity of these species.[51] Finally, until the recent advent of the Stork−Zhao bis(trifluoroacetoxy)iodobenzene protocol,[52] unmasking of the ketone moiety often proved problematic. By assimilating and developing effective solutions to these problems, we have been able to exploit the considerable power of dithiane couplings for assembly of complex structures.

For the alkylation of dithiane (−)-**6** with iodo ether (−)-**7** in our FK506 program, we evaluated numerous metalation/addition protocols; ultimately we employed the metalation conditions introduced by Williams (*t*-BuLi, HMPA/THF, −78 °C).[53] In this fashion, we obtained in 79% yield the C(10−34) FK506 backbone (−)-**39**, which contained 12 stereogenic centers, three olefin moieties, and numerous protected hydroxyl and carbonyl groups (Scheme 6). Importantly, the coupling could be effected on a large scale (ca. 2 g).[54]

Notwithstanding this very gratifying result, it was the rapamycin venture which led to our current appreciation for the simplicity and generality of the dithiane coupling process. A highly convergent and flexible synthetic design (Figure 2) enabled us to explore alternative assembly strategies involving a variety of dithiane alkylations. A key finding emerged from the preliminary experiments in which we sought to couple dithiane (+)-**40** with epoxide (−)-**41** (Scheme 7). After considerable experimentation, we observed that the short-lived lithio dithiane could be generated almost instantaneously in the presence of (−)-**41** with *t*-BuLi in 10% HMPA/THF at −78 °C.[55] In practice, premixing of (+)-**40** and (−)-**41** followed by exposure to *t*-BuLi furnished the C(30−42) fragment (−)-**42** in 60% yield.

Scheme 6

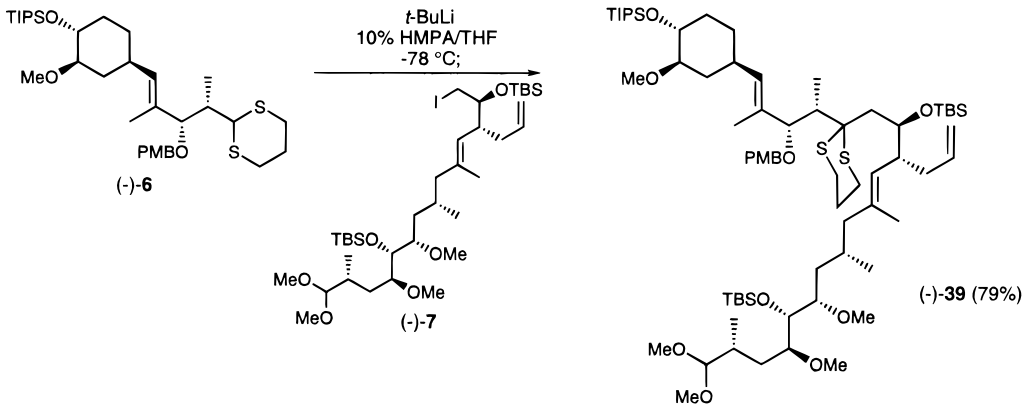
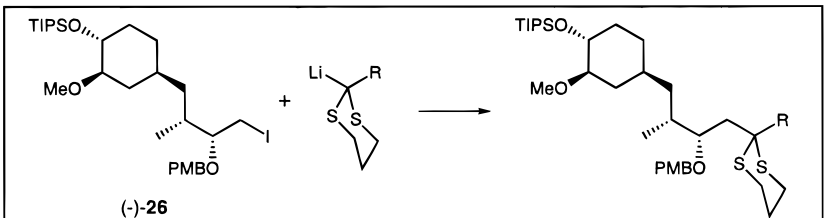
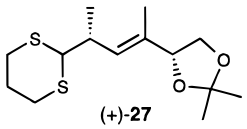
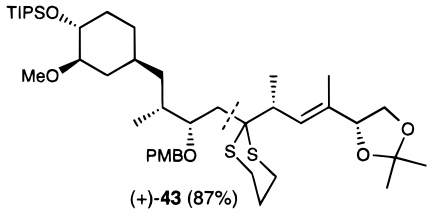
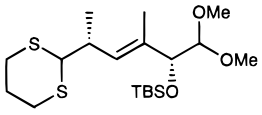
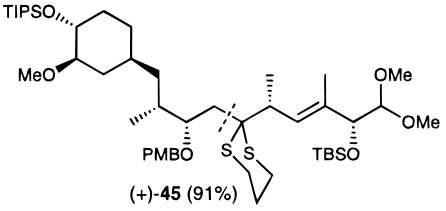
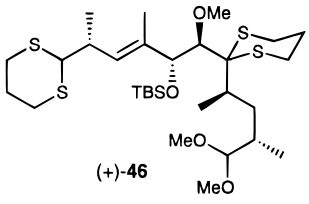
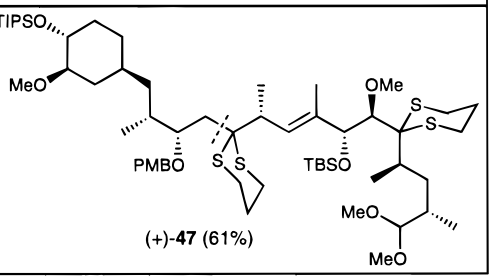


Table 2. Rapamycin Dithiane Alkylations with Iodo Ether 26

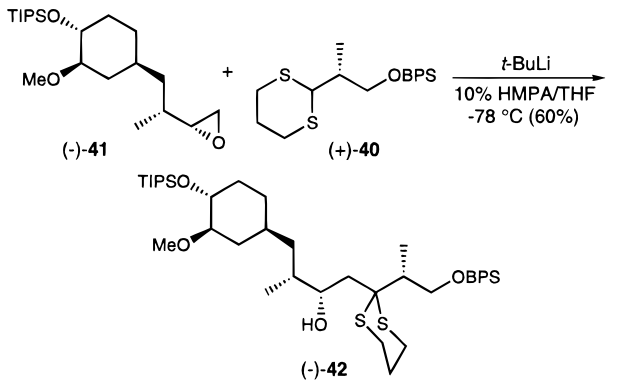


Dithiane	Product (yield)
 (+)-**27**	 (+)-**43** (87%)
 (+)-**44**	 (+)-**45** (91%)
 (+)-**46**	 (+)-**47** (61%)

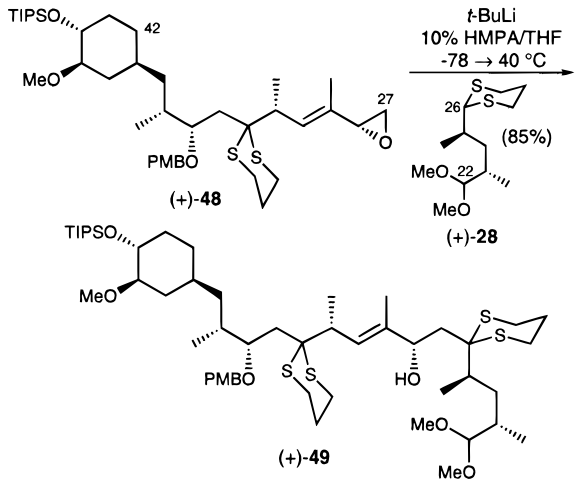
Upon recognizing that 2-alkyl-1,3-dithiane anions are formed very rapidly (within ca. 1 min) under these conditions but gradually lose their reactivity on standing, we began to introduce the precooled (−78 °C) electrophile immediately after the addition of *t*-BuLi; this practice invariably furnished the best yields of coupled products. This procedure was employed for coupling of iodo ether (−)-**26** with three dithianes of increasing complexity (Table 2). Acetonide (+)-**43** and dimethyl acetals (+)-**45** and (+)-**47** proved to be key advanced intermediates in our demethoxyrapamycin and rapamycin syntheses. For example, **47** could be transformed into rapamycin in 10 steps.

We also demonstrated the value of this protocol with more complex electrophiles. A key coupling reaction for demethoxyrapamycin involved the C(22−26) dithiane (+)-**28** and the C(27−42) epoxide (+)-**48** (Scheme 8). Metalation of (+)-**28** followed by rapid delivery of a cooled solution of (+)-**48** and warming to −40 °C gave alcohol (+)-**49** in 85% yield.[56]

Scheme 7

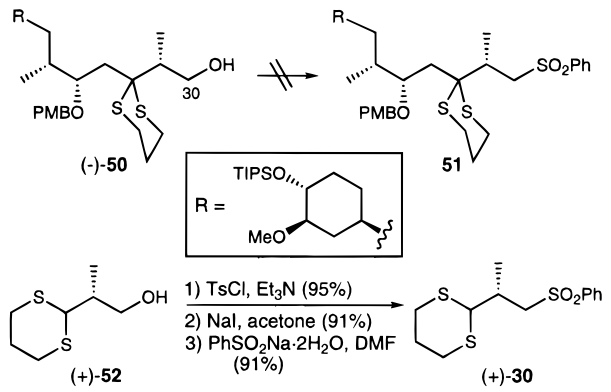


Scheme 8



Anomalous Reactivity of Pendant Functionalities in 2,2-Disubstituted Dithianes. Early in the rapamycin program, we attempted unsuccessfully to convert alcohol (−)-**50** to sulfone **51**, whereas the required transformations proceeded uneventfully with the simplified substrate (+)-**52** (Scheme 9). Efforts to displace the C(30) tosylate

Scheme 9



and mesylate derived from alcohol (−)-**50** under a variety of conditions led only to complex mixtures.

Although nucleophilic displacements proximal to 2,2-disubstituted-1,3-dithiane moieties are not without precedent,[57] the reaction is complicated by the Thorpe−Ingold effect[58] associated with the geminally disubstituted heterocycle.[59] We believe that intramolecular nucleophilic attack by sulfur is favored in highly congested systems such as mesylate (−)-**53** (Figure 5). Sulfonium ion **54**[60] then decomposes, for example via ring opening to **55**.[61]

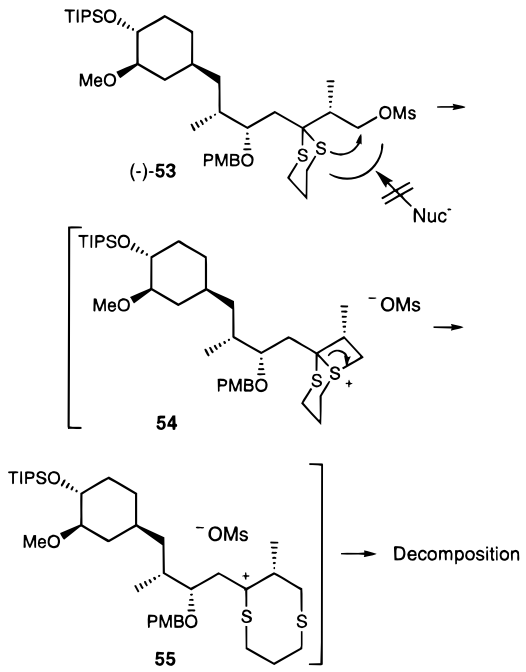
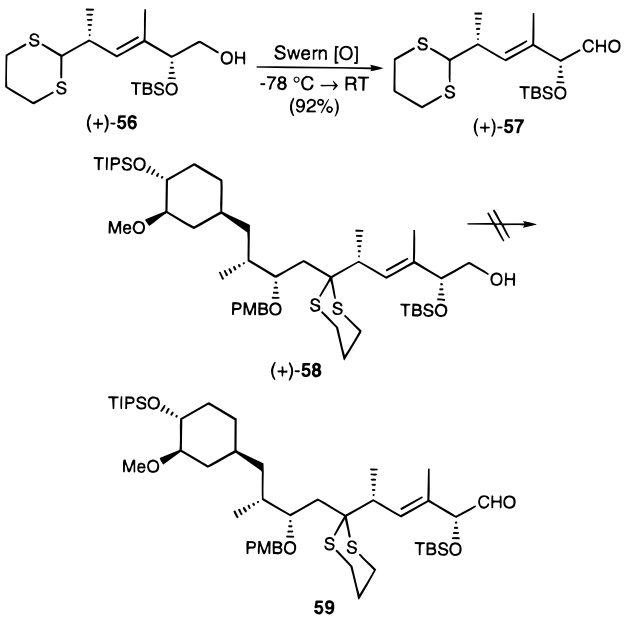


FIGURE 5. Proposed mechanism for decomposition of mesylate **53**.

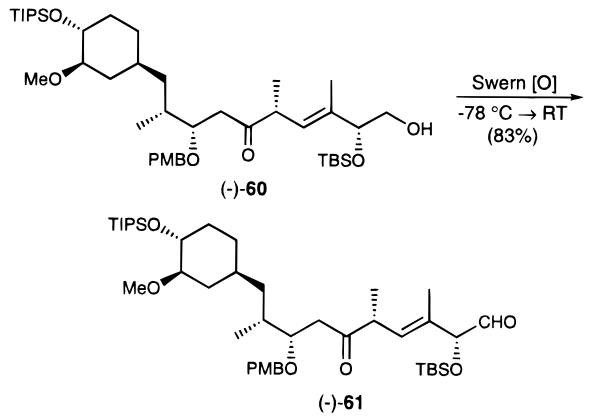
Additional reactivity differences were observed between other 2-monosubstituted dithianes and their 2,2-disubstituted counterparts. For example, Swern oxidation of C(27−32) alcohol (+)-**56** provided aldehyde (+)-**57** in 92% yield (Scheme 10), but a chain-extended disubstituted dithiane, the C(27−42) alcohol (+)-**58**, decomposed under

Scheme 10



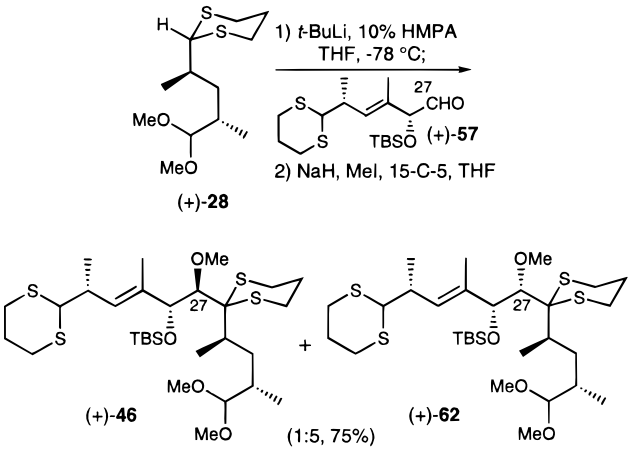
the Swern oxidation conditions. The behavior of **58** must be attributed uniquely to the *disubstituted* dithiane moiety,[62] as both monosubstituted dithiane (+)-**56** and ketone (−)-**60** (Scheme 11), the latter obtained by hydrolysis of the dithiane in (+)-**58**, reacted normally under Swern conditions.

Scheme 11



In one instance, we sought to turn the anomalous reactivity of 2,2-disubstituted dithianes to our advantage. Our rapamycin strategy called for installation of the C(27) stereocenter via coupling of aldehyde (+)-**57** with dithiane (+)-**28** (Scheme 12). Although this reaction proved to be relatively efficient, the undesired (*S*)-epimer (+)-**62** predominated in a 5:1 mixture.

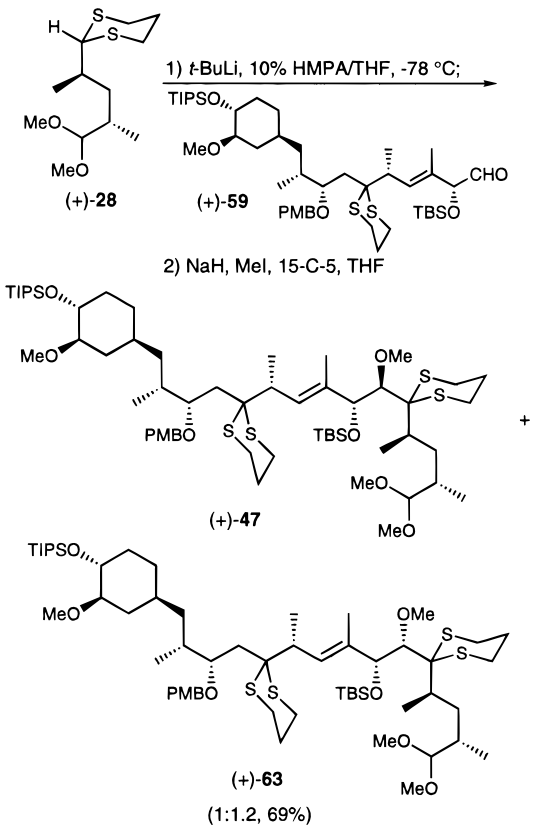
Scheme 12



At this juncture, we speculated that a disubstituted dithiane ring might induce a conformational change in the substrate aldehyde, perhaps leading to a more useful product ratio. We prepared the C(27−42) aldehyde (+)-**59** via a route that avoided the problematic oxidation step described above.[17] A nearly 1:1 mixture of C(27) alcohols was obtained in coupling with (+)-**28** (Scheme 13), affording significantly improved material throughout for the total synthesis of (−)-rapamycin.

Installation of the Rapamycin Triene via Organostannane *σ*-Bond Methodologies. For elaboration of the triene array in the rapamycin/demethoxyrapamycin endgame, we employed three different protocols for stereo-

Scheme 13



controlled alkyne stannylation: (i) the C(17,18) trisubstituted olefin was generated via stannylcupration of a silyl diyne followed by addition of the vinyllithium derivative to a C(16) aldehyde; (ii) the central C(19,20) vinyl group arose via free-radical enyne hydrostannylation; and (iii) the C(21,22) disubstituted olefin was installed via palladium-catalyzed hydrostannylation of an alkyne (Figure 6). An intramolecular Stille cross-coupling then established the C(20,21) vinyl *σ*-bond linkage, closing the macrocyclic ring.

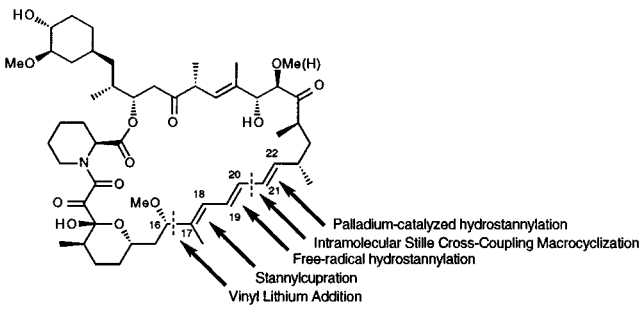
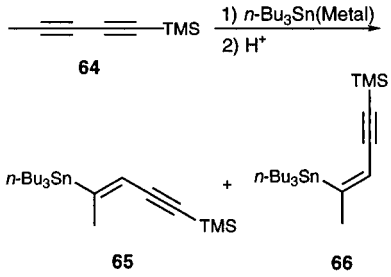


FIGURE 6. *σ*-Bond strategy for installation of the rapamycin/demethoxyrapamycin triene.

The enyne building block **65** was prepared stereoselectively via stannylcupration of diyne **64** (Table 3). Interestingly, the *Z* isomer (**66**) could also be accessed through careful control of the reaction conditions: treatment of **64** with *n*-$Bu_3Sn(Bu)Cu(CN)Li_2$[63] and protonation at −78 °C provided a 15:1 mixture of **65** and **66**, whereas substitution of *n*-$Bu_3Sn(Me)Cu(CN)Li_2$ and warming to

Table 3. Stannylcupration of Diyne 64



Reaction Conditions	Ratio **65**:**66**
1) *n*-$Bu_3Sn(Bu)Cu(CN)Li_2$, THF, -78 °C; 2) Aq NH_4Cl/MeOH (61%, 2 steps)	15 : 1
1) *n*-$Bu_3Sn(Me)Cu(CN)Li_2$, THF, -78 → -30 °C; 2) Aq NH_4Cl/MeOH (68%, 2 steps)	1 : 27

−30 °C led predominantly to **66** (1:27 ratio). We believe, based on similar results,[63b] that initial attack of the organometallic reagent affords the *syn*-bimetallic species **67** (Figure 7), which isomerizes upon warming to the thermodynamically favored *anti*-precursor **68**. Protonation of **67** and **68** then furnishes **65** or **66**, respectively.

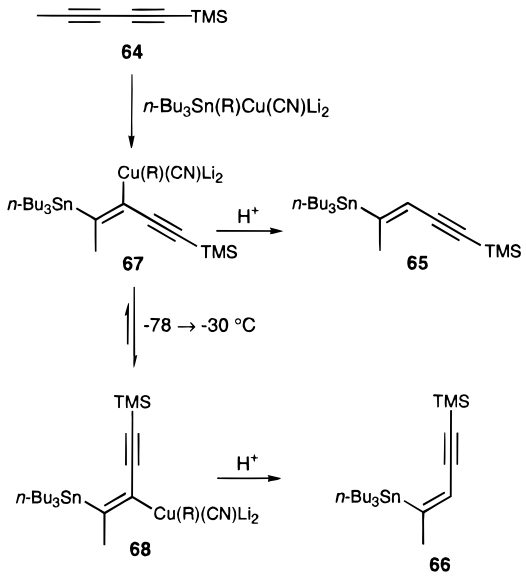
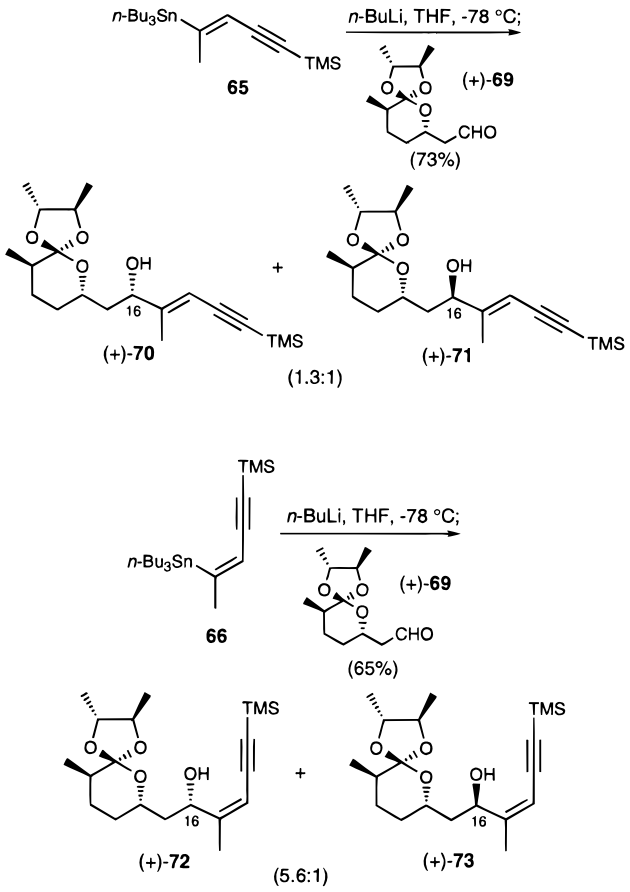


FIGURE 7. Proposed pathways for formation of vinyl stannanes **65** and **66**.

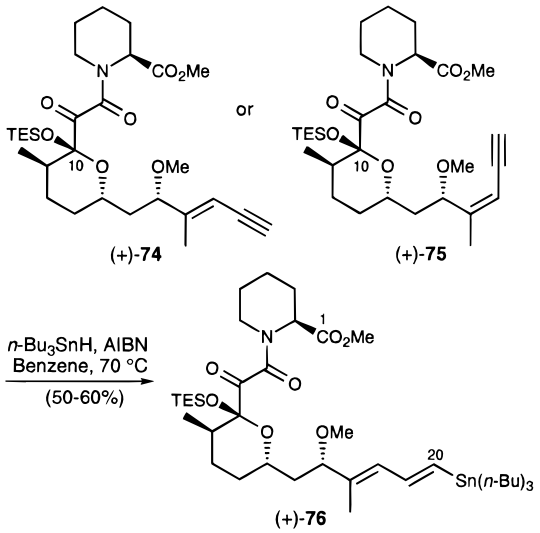
For incorporation of the C(17,18) trisubstituted olefin, we initially added the *E* organolithium derived from **65** to aldehyde (+)-**69** (Scheme 14), producing a 1.3:1 mixture of alcohols (+)-**70** and (+)-**71** in 73% yield. However, upon substitution of the *Z* stannane **66** for **65**, the stereoselectivity improved to 5.6−1. The major epimer (+)-**72** contained the requisite C(16) configuration; we thus anticipated that the correct olefin geometry could be secured via *Z*-to-*E* isomerization during the proposed hydrostannylation step. To test this possibility, the *E* and *Z* enynes (**70** and **72**) were transformed to the corresponding C(1−20) pipecolinates (+)-**74** and (+)-**75** (Scheme 15).[17] Indeed, exposure of either isomer to free-radical

Scheme 14



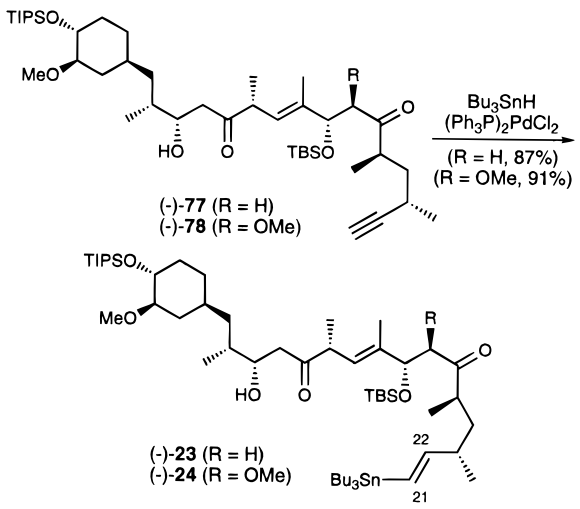
hydrostannylation provided the desired *E*,*E* dienyl stannane (+)-**76** via the intermediacy of a common allylic radical.[64]

Scheme 15



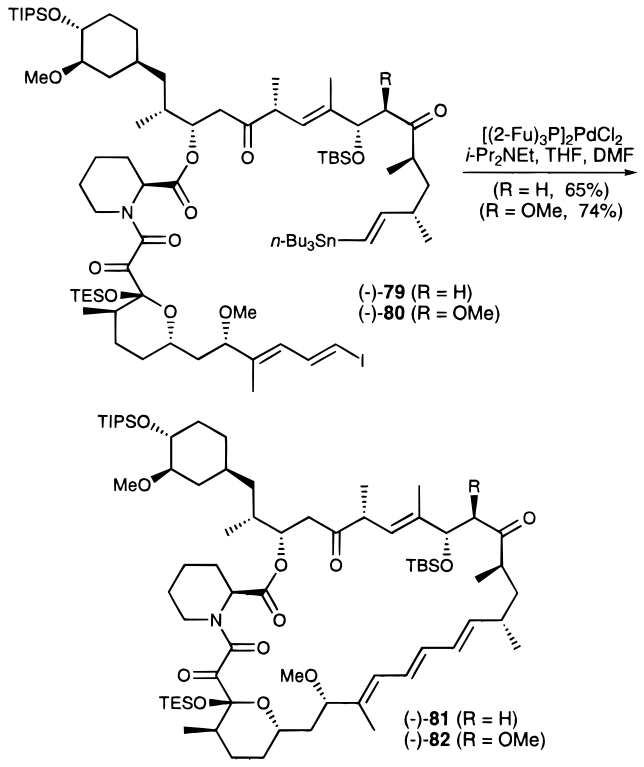
Guibé Pd(0)-catalyzed hydrostannylation of terminal alkynes (−)-**77** and (−)-**78** proved ideal for introduction of the C(21,22) vinyl stannane moiety (Scheme 16).[65] Thus, the three olefins comprising the rapamycin triene were successfully installed via organotin σ-bond methodologies: stannylcupration, free-radical hydrostannylation, and Pd(0)-mediated hydrostannylation.

Scheme 16



We were now poised for final assembly of the triene system. Based on model reactions involving various rapamycin and demethoxyrapamycin building blocks,[66] we selected an intramolecular Stille coupling[67] of a dienyl iodide and vinyl stannane for generation of the C(20,21) vinylic σ-bond and closure of the macrocyclic ring. Few research groups have employed this transformation for the synthesis of complex natural products,[68,69] although Nicolaou did exploit a two-component variant to install the central olefinic linkage and construct the macrocyclic ring of rapamycin.[14] In our laboratory, exposure of *seco* intermediates (−)-**79** and (−)-**80** to the Farina−Scott catalyst[70] provided macrocyclic trienes (−)-**81** and (−)-**82** in good yields (65 and 74%, respectively; Scheme 17).

Scheme 17



Desilylation then furnished the target molecules, completing the rapamycin synthetic venture.

Summary. During our investigation of immunosuppressant total synthesis, we have strived to develop effective unified strategies. A primary focus has been the stereocontrolled σ-bond construction of trisubstituted olefins. Among numerous successful applications, the use of copper-mediated alkylation of vinyl triflates in complex acyclic systems is particularly noteworthy.

For dithiane couplings of advanced subtargets, a second major thrust, our investigations have clearly established that treatment with *t*-BuLi in 10% HMPA/THF at −78 °C constitutes a superior protocol for *rapid* metalation. This process is then exploited via immediate addition of diverse electrophiles affording suitably protected aldol linkages. Whereas dithiane cleavage at the end of a synthesis has often proven to be challenging, we have found that the Stork procedure[52] offers important advantages including mildness and broad functional group compatibility. In addition, we have discovered striking effects of 2,2-disubstituted dithiane moieties on the reactivity of pendant functional groups.

Our efforts in these areas will continue as we seek to design and implement unified, highly convergent strategies for the synthesis of architecturally novel natural products.

Financial support for this research was provided by the National Institutes of Health (Institute of General Medical Sciences) through Grant GM-29028. S.M.C. and J.A.M. gratefully acknowledge a Carolyn Hoff Lynch Graduate Fellowship and a University of Pennsylvania School of Arts and Sciences Dissertation Fellowship, respectively.

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