Evolution of Dithiane-Based Strategies for the Construction of Architecturally Complex Natural Products

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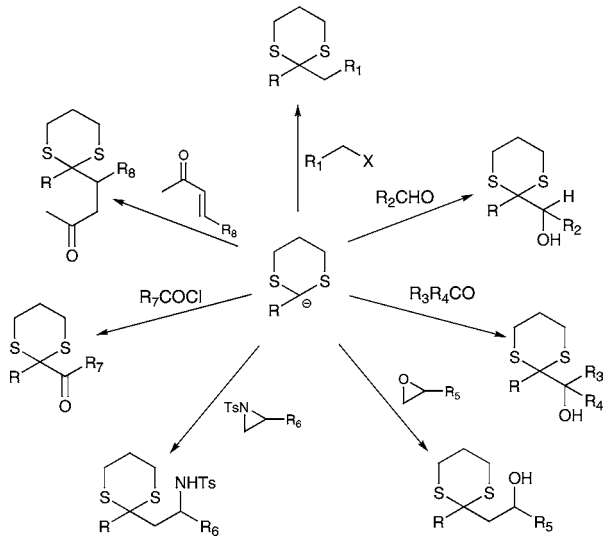
ABSTRACT
Umpolung-based strategies play a significant role in organic synthesis. Particularly important are 1,3-dithiane linchpins, which serve as convenient acyl anion equivalents. The general synthetic accessibility and impressive reactivity of 1,3-dithianes have thus led to widespread application. Since the late 1970s, dithianes have featured prominently in our program directed toward the synthesis of complex natural and unnatural products, both for effective union of advanced fragments and for multicomponent linchpin couplings. In this Account, we present the evolution of dithiane chemistry in our laboratory.

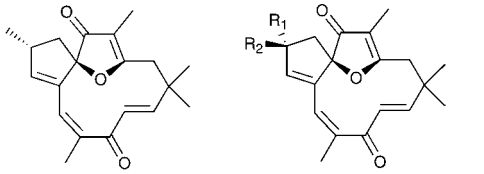
The concept of umpolung, first introduced by Wittig in 1921 to describe the inversion of charge,[1] was not generally accepted by the chemical community until Seebach reintroduced the term in 1974[2] to describe "dipole inversion" or inversion of reactivity.[3] The obvious need for the term grew out of the pioneering work of Corey and Seebach on the design and applications of 1,3-dithianes,[4,5] which are now well recognized as excellent strategic elements for the construction of complex natural and unnatural products[6] (Scheme 1). Importantly, improved protocols for the removal of the dithiane moiety to reinstate the carbonyl functionality have paralleled the development of dithiane reactions.[7]

Scheme 1



Enone Additions

Early in our synthetic program, we were attracted to the dithiane functionality for simple 1,2-addition to carbonyls, in conjunction with the construction of members of the jatrophone class[8,9] of diterpene cytotoxic agents (**1**−**3**, Figure 1). The jatrophones, isolated from the extracts of *Jatropha gossypiifolia* L (Euphorbiaceae) by the late Professor Kupchan,[10] possess an unusual macrocyclic spiroether skeleton.



(+)-Jatrophone (**1**)

(+)-Hydroxyjatrophone A (**2**): $R_1 = OH$, $R_2 = CH_3$
(+)-Hydroxyjatrophone B (**3**): $R_1 = CH_3$, $R_2 = OH$

FIGURE 1. The jatrophone family of natural products.

We envisioned that a unified approach to members of the jatrophone family could be developed by taking advantage of a dithiane-based strategy, involving union of anion **9** and cyclopentenone **8** (Scheme 2). Dithiane **9** was to serve both as an acyl ion equivalent and as a masked carbonyl for a future aldol reaction with aldehyde **7**.

When the scheme was put into practice, anion **9** added smoothly to racemic cyclopentenone **8** in high chemical yield (95%); removal of the dithiane[7b] led to ketone **10**. Not unexpectedly, the addition proceeded with poor facial selectivity (ca. 3:1 in favor of the undesired isomer) and required redress. In recognition of the allylic nature of the tertiary hydroxyl, a Mislow−Evans sulfenate−sulfoxide rearrangement[11] was enlisted to convert **10** to **11**, where the acidic nature of the hydrogen α to the sulfoxide would permit base-mediated equilibration of the isomers (Scheme 3).

Amos B. Smith, III, was born in Lewisburg, PA, in 1944, where in 1966, he completed Bucknell University's first combined B. S.−M. S. degree in chemistry. 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, was promoted to Professor of Chemistry in 1981, and 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 and the Laboratory for Research on the Structure of Matter and an Honorary Member of the Kitasato Institute, Tokyo, Japan. Currently, Professor Smith serves as the inaugural Editor-in-Chief of *Organic Letters*. In recognition of his accomplishments, 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 University of Oregon Creativity Award (1997), the Centenary Medal of the Royal Society of Chemistry (2002), and most recently the Yamada Prize, Tokyo, Japan (2003). 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.

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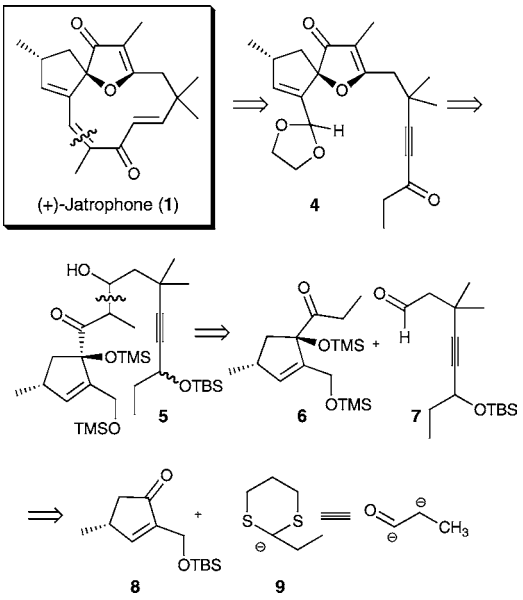
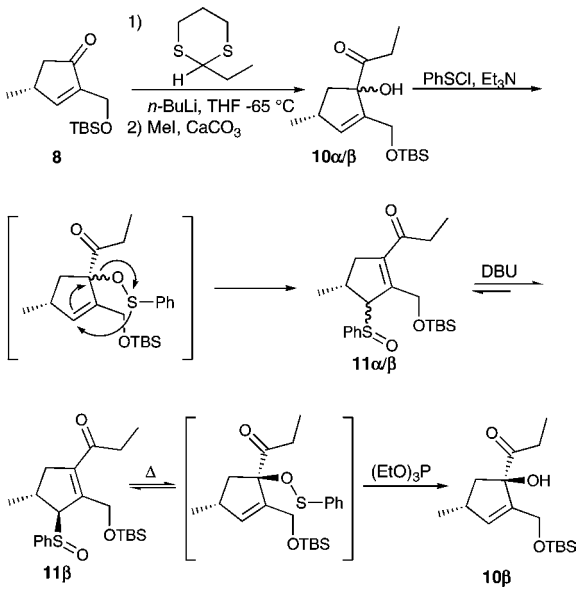
Scheme 2



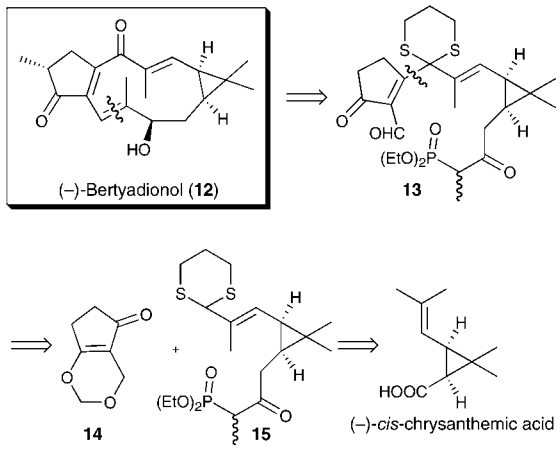
After epimerization with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU), **11*β*** undergoes a thermal Mislow−Evans sulfoxide−sulfenate rearrangement with the sulfenate intercepted with $(EtO)_3P$ to furnish **10*β*** as a single isomer. Spirofuranone ring generation, refunctionalization, and macrocyclization of **5** (Scheme 2), the latter an early example of an intramolecular Mukaiyama aldol reaction,[12] then led to the first total synthesis of jatrophone (**1**). A similar strategy provided access to the hydroxyjatrophones A and B (**2** and **3**).

Scheme 3



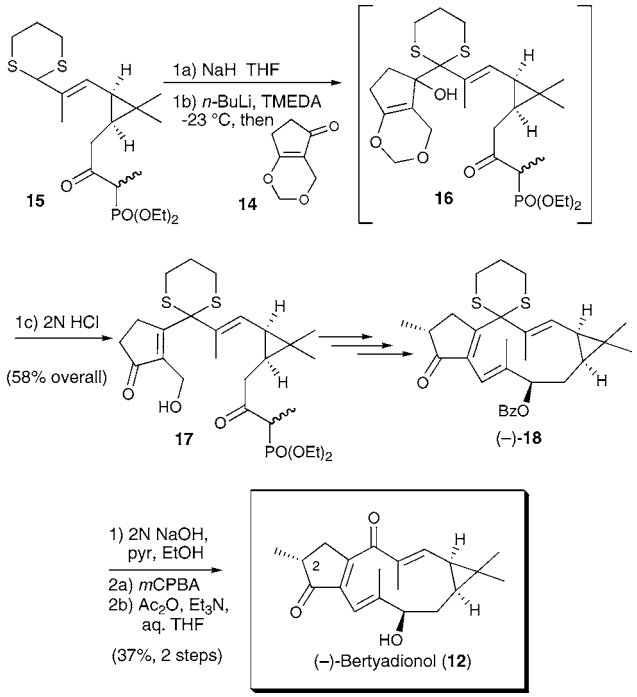
Having achieved success with the umpolung tactic, we turned to the total synthesis of (−)-bertyadionol (**12**),[13] a macrocyclic cytotoxic diterpene.[14] Again we envisioned 1,2-addition of a dithiane to an enone. In this case, a more complex dithiane (e.g., **15**) was employed to permit a highly convergent strategy (Scheme 4). The addition regioselectivity, with respect to both the unsaturated ketone and the vinylogous dithiane anion, was however a question of some concern.

Scheme 4



In the event, dithiane **15**, readily available from (−)-*cis*-chrysanthemic acid, was first treated with NaH in tetrahydrofuran (THF) (0 °C) to generate the keto phosphonate anion, followed by addition of *n*-BuLi and *N*,*N*,*N*,*N*-tetramethyl-1,2-ethylenediamine (TMEDA) at −23 °C to furnish the dianion (Scheme 5). Addition to enone **14** furnished the 1,2-adduct, which upon acidic hydrolysis led to alcohol **17**. Complete regiocontrol at both the dithiane carbon and the enone carbonyl was observed.

Scheme 5



Subsequent manipulations, including the use of the Stork−Nicolaou macrocyclization[15] and stereoselective methylation at C(2) furnished macrocycle (−)-**18**. At this juncture, all that remained was the seemingly simple task of removing the benzoate ester and dithiane moieties.

These transformations however proved challenging, particularly with respect to removal of the dithiane; indeed, all attempts exploiting most, if not all, of the known protocols[7] were unsuccessful, most likely due to the vinylogous α relationship of the dithiane and the cyclopropyl ring, which under the acidic conditions raised the specter of cyclopropyl−carbonyl rearrangements. Eventually, we developed a hydrolysis protocol, involving saponification of the benzoate, followed by oxidation of the dithiane with *m*-chloroperoxybenzoic acid (*m*-CPBA)[16] to furnish a mixture of monosulfoxides, which permitted use of a "Pummerer-like" hydrolysis process to furnish (−)-bertyadionol (**12**).

Dithiane Couplings with Epoxides, α-Siloxy Halides, and α-Siloxy Aldehydes

Encouraged by the robust reactivity of the dithiane anion, we next explored the reactions of dithiane anions with terminal epoxides, α-siloxy primary halides, and α-siloxy aldehydes as alternatives to the aldol reaction to gain access to the recurring 1,3-oxygenation pattern found in many polyketide natural products (Figure 2). Synthetic targets at the time included FK506,[17,18] rapamycin,[19,20] and discodermolide,[21,22] each reported to possess significant immunosuppressant activity. [23]

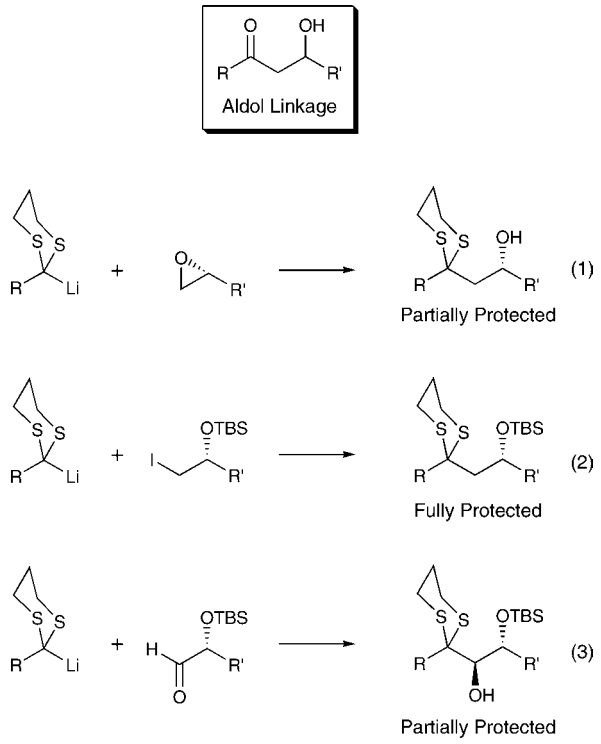


FIGURE 2. Construction of aldol linkages via dithiane couplings.

The advantages of this synthetic tactic in relation to the classical aldol reaction include the following: (1) the resultant carbonyl group is masked, circumventing a separate protection step; (2) the aldol hydroxyl can be either protected or unprotected via appropriate choice of electrophile; (3) the configuration of the β-hydroxyl is secured prior to the coupling event; (4) the reaction is not reversible; (5) carbonyl self-condensation is avoided.[24] Each of the dithiane couplings illustrated in Figure 2 have been employed with considerable success in our immunosuppressant synthetic venture for the union of advanced fragments (Figure 3).[24] Importantly, these unions can be carried out on multigram scale.

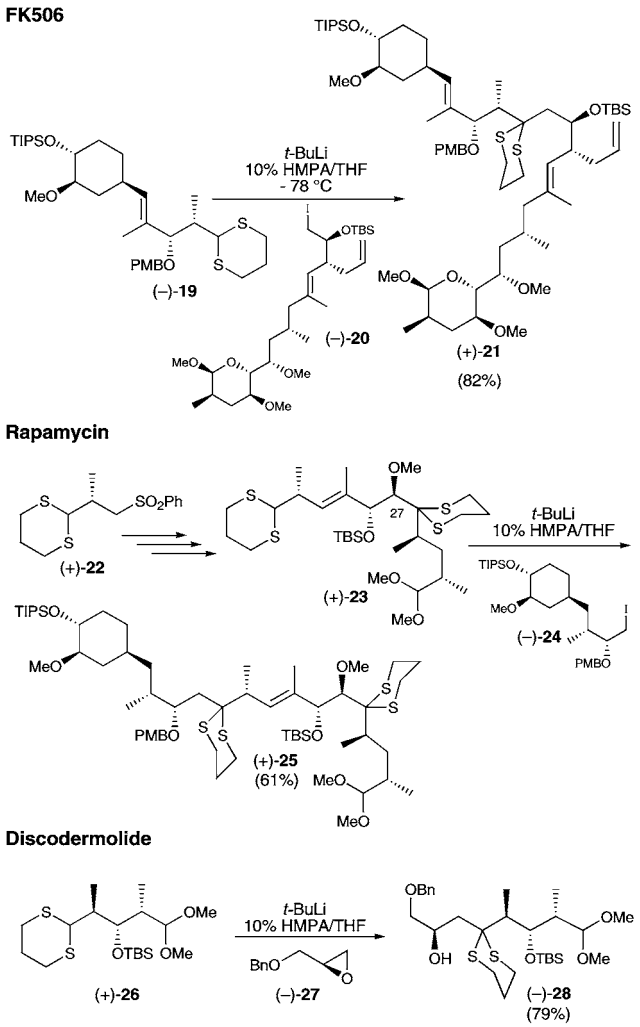
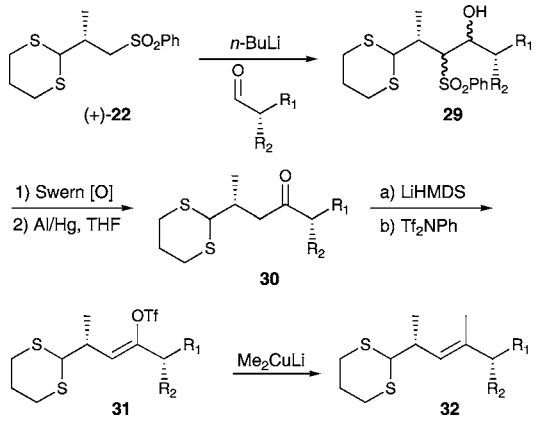


FIGURE 3. Notable dithiane couplings during our immunosuppressant program.

The combination of a dithiane with a phenyl sulfone [e.g., (+)-**22**], as employed in our rapamycin and 27-demethoxyrapamycin syntheses, provided us with our first insight on the potential of dithiane chemistry for bidirectional fragment coupling (vide infra). This linchpin not only served as a means to append two large fragments but in addition provided a facile, stereoselective entry to trisubstituted olefins via a combination of sulfone and enol-triflate chemistry (Scheme 6). The latter tactic, termed by us σ-bond construction of trisubstituted olefins,[24] involves chemoselective lithiation of the sulfone carbon followed by reaction with an aldehyde to produce a β-hydroxy sulfone. Oxidation to the corresponding ketone, followed by reductive removal of the sulfone, regio- and stereoselective enolate formation, triflation, and subsequent insertion of an alkyl cuprate into the C−O bond, affords the trisubstituted olefinic dithiane in a highly stereocontrolled manner.[25]

Scheme 6

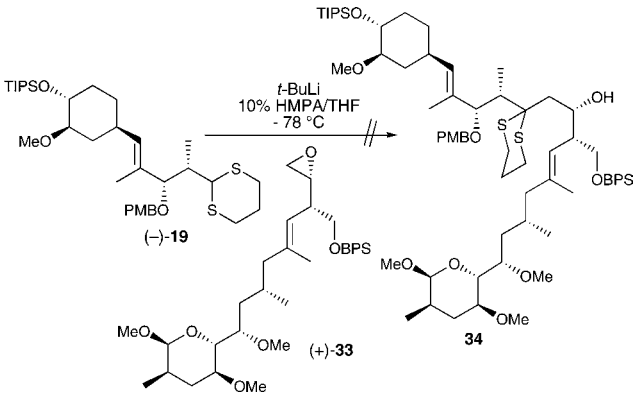


Difficulties Encountered with the Dithiane Tactic: First-Generation FK506 and Calyculin Synthetic Strategies

We have found that the best means to lithiate dithianes involves treatment with *t*-BuLi in 10% hexamethylphosphoramide (HMPA)/THF,[26] conditions first introduced by Williams.[27] DMPU [1,3-dimethyl-3,4,5,6-tetrahydro-2(1*H*)-pyrimidinone] can be employed as a replacement for HMPA; however, yields are often inferior. Although these conditions are our method of first choice, the lithiation and reactions of complex dithianes are substrate-specific. Three difficult examples will be presented.

The first arose during our FK506 formal synthesis.[28] Central to the initial plan was the proposed union of dithiane (−)-**19** with epoxide (+)-**33** (Scheme 7). Unfortunately, despite successful lithiation of (−)-**19** (*t*-BuLi, 10% HMPA/THF; 90% deuterium incorporation), epoxide (+)-**33** proved unreactive.[29] This event led us to explore the union of (−)-**19** with the corresponding α-alkoxy iodide (−)-**20** (Figure 3). Pleasingly, iodide (−)-**20** was a most effective coupling partner, furnishing the C(10)−C(34) fragment of FK506 in 82% yield and, in turn, a formal total synthesis of FK506.[28]

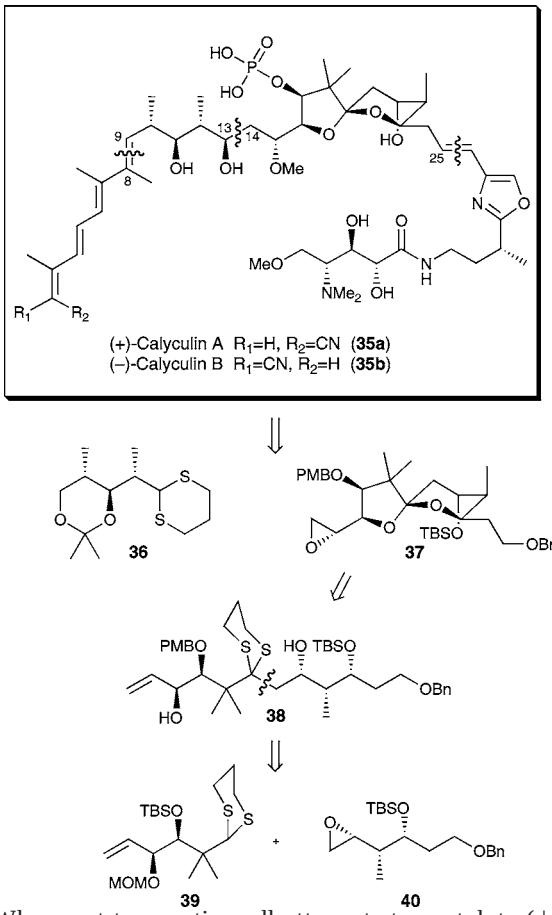
Scheme 7



Calyculins A and B: Development of a Viable Dithiane Alternative

The second difficult case arose with the calyculins, highly selective serine−threonine phosphatase inhibitors possessing a striking array of stereochemical and structural elements.[30] Two strategic dithiane−epoxide couplings were envisioned.[31] The first entailed union of dithiane **36** with epoxide **37** (Scheme 8). Second, construction of the C(13−25) spiroketal would rely on the alkylation of dithiane **39** with epoxide **40**.

Scheme 8



When put to practice, all attempts to metalate (+)-**39** employing the standard protocol (*t*-BuLi, 10% HMPA/THF), or for that matter, any of a variety of strong bases and additives, failed to furnish the desired anion (Scheme 9).

Scheme 9

Cognizant that protecting groups often play a role in metalation processes,[6c,32] we prepared three related dithianes. Again, metalation with a variety of strong bases and solvent systems proved modest at best. We reasoned that the lack of reactivity was most likely due to the interaction of the dithiane C−S σ^* orbital, known to play a critical stereoelectronic role in promoting dithiane acidity,[33] with the π system of the olefin. That is, the two interconverting chairlike conformations (**41** or **42**; Figure 4), induced by the geminal dimethyl Thorpe−Ingold effect[34] in (+)-**39**, would lead to close proximity of the C−S σ^* dithiane orbital and the olefin π system, an interaction that would reduce the acidity of the dithiane hydrogen.

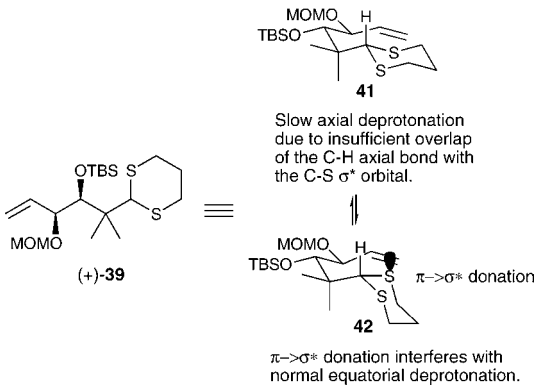
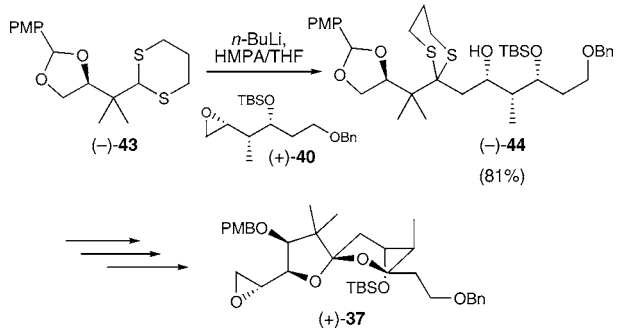


FIGURE 4. Conformation **41** disfavors metalation given the axial proton;[35] conformation **42** permits donation of electron density from the olefin π orbital to the C−S σ^* orbital, thereby reducing the role of the σ^* orbital in promoting acidity.

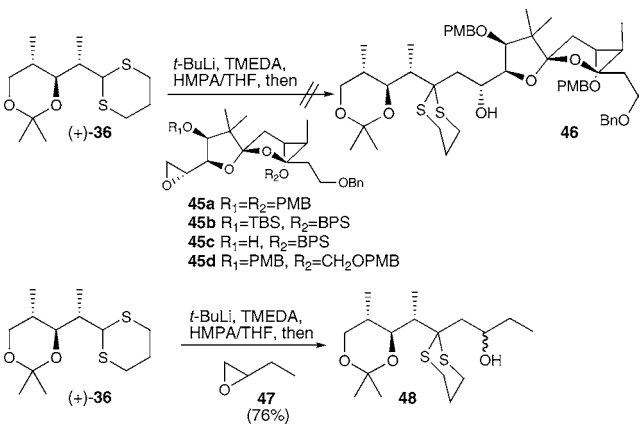
To circumvent this difficulty dithiane (−)-**43**, devoid of the suspect olefin, was successfully lithiated; addition of epoxide (+)-**40** yielded alcohol (−)-**44** in 81% yield (Scheme 10). Subsequent manipulations then led to the requisite calyculin spiroketal (+)-**37**.

Scheme 10



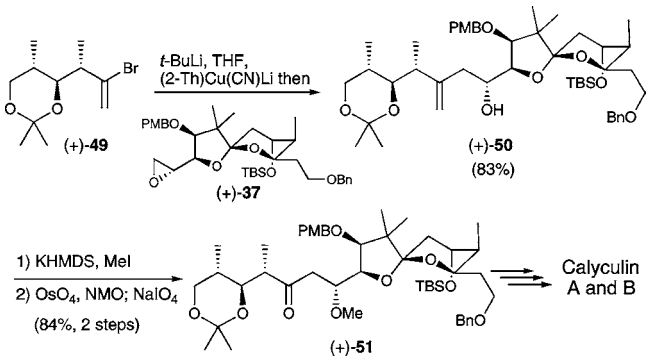
The second dithiane tactic proved even more difficult. The plan called for alkylation of (+)-**36** with an advanced epoxide (**45a**). Dithiane (+)-**36** could be efficiently lithiated and was shown to be a competent nucleophile by efficient reaction with a simple epoxide (**47**). However, alkylation with any of a series of advanced epoxides (**45a**−**d**) failed to occur (Scheme 11). The steric encumbrance around the epoxide again appeared to be the problem.

Scheme 11



We therefore turned to a vinyl anion synthetic equivalent of the dithiane, which we reasoned would be more reactive and possibly less sterically encumbered. Success was in hand upon the generation of the mixed cuprate[36] from vinyl bromide (+)-**49** followed by reaction with epoxide (+)-**37**; the yield of the coupled product was 83% (Scheme 12). Protection of the resultant hydroxyl and oxidative cleavage of the olefin then afforded ketone (+)-**51**, which permitted completion of the calyculin A and B total syntheses.[31] Thus, a viable equivalent to the dithiane linchpin tactic, in cases of severe steric encumbrance at the electrophile, is use of a vinyl anion equivalent.

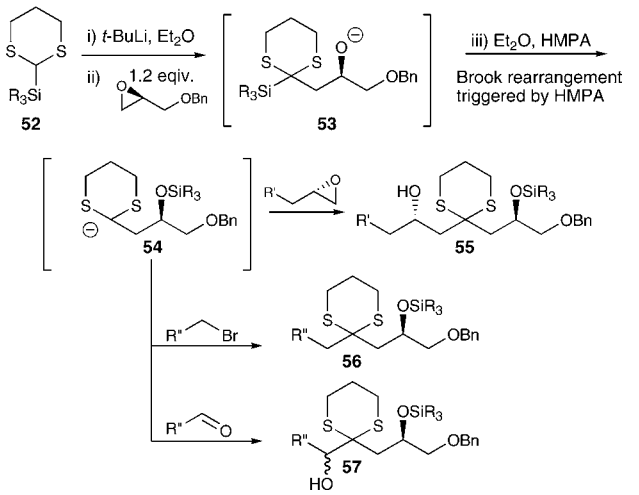
Scheme 12



The Spongistatins: Multicomponent Couplings with Silyl Dithianes

In 1994, Tietze and co-workers[37] reported the symmetrical bis-alkylation of trimethylsilyldithianes with simple epoxides. This innovative result suggested the possibility of effecting unsymmetrical alkylations as a new approach to the bidirectional construction of 1,3-polyols;[38] this indeed proved to be the case. In 1997, we reported that lithiation of silyl dithianes **52** with *t*-BuLi in diethyl ether (Scheme 13), followed by alkylation with a simple epoxide, results in an intermediate oxyanion. Treatment with HMPA triggers a 1,4-Brook rearrangement[39,40] and thereby the generation of a new reactive dithiane anion. Addition of a second, different epoxide furnishes a differentially silyl-protected 1,5-diol.[41,42] From a strategic sense, the location of the silyl protecting group can be orchestrated simply by the order of the epoxide additions.[43] Extension of this synthetic tactic to other "second" electrophiles such as

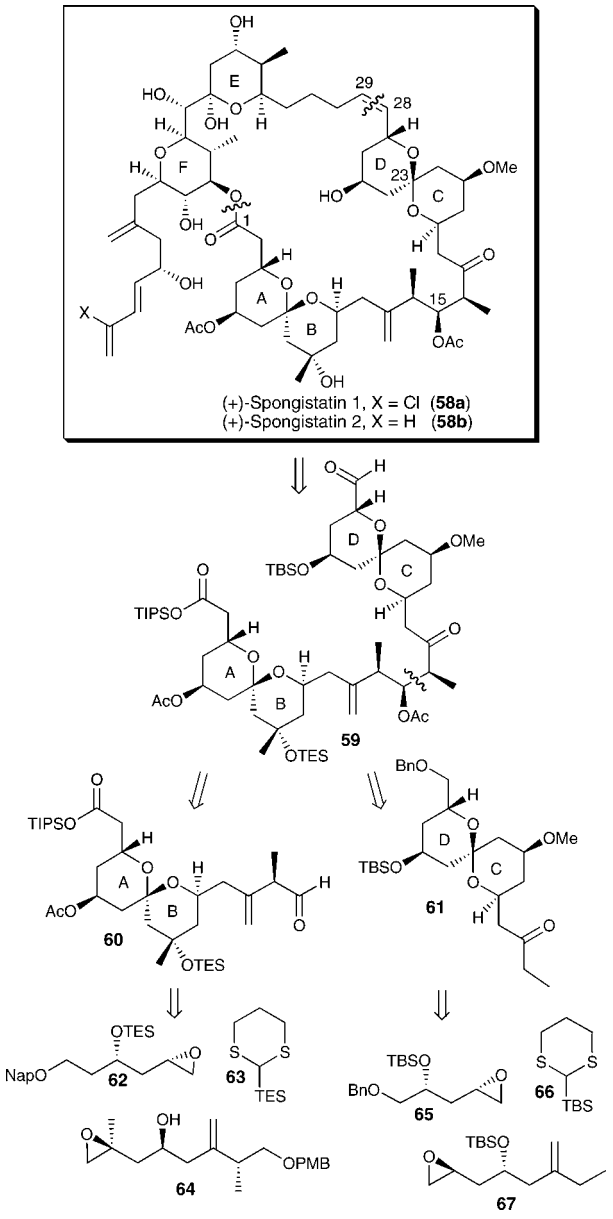
Scheme 13



alkyl bromides and aldehydes has been demonstrated in our laboratory.[41]

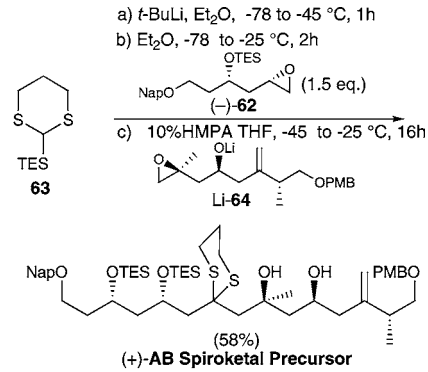
Concurrent with the development of the multiple component coupling tactic, we became intrigued with the spongistatins, extraordinarily potent, architecturally complex tumor cell growth inhibitory macrolides.[44] The extreme scarcity of the spongistatins, in conjunction with both their novel architecture and their potential benefit to cancer chemotherapy, led us to undertake their synthesis (Scheme 14).[45] A central feature of this venture entailed the multicomponent linchpin tactic for the construction of the acyclic fragments of the **AB** and **CD** spiroketals.

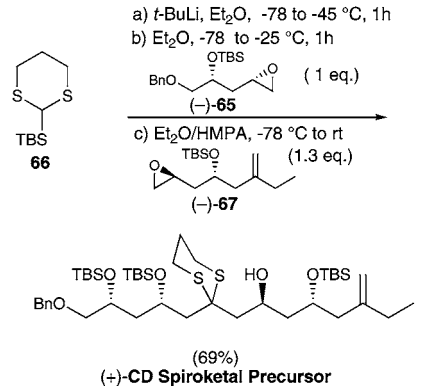
Scheme 14



As illustrated in Scheme 15, this tactic has proven to be highly effective in what is now a second-generation gram-scale approach to these important targets.[46] Notably, both multicomponent reactions can be run on a 10 g scale on way to the **ABCD** advanced fragment (Scheme 14).

Scheme 15

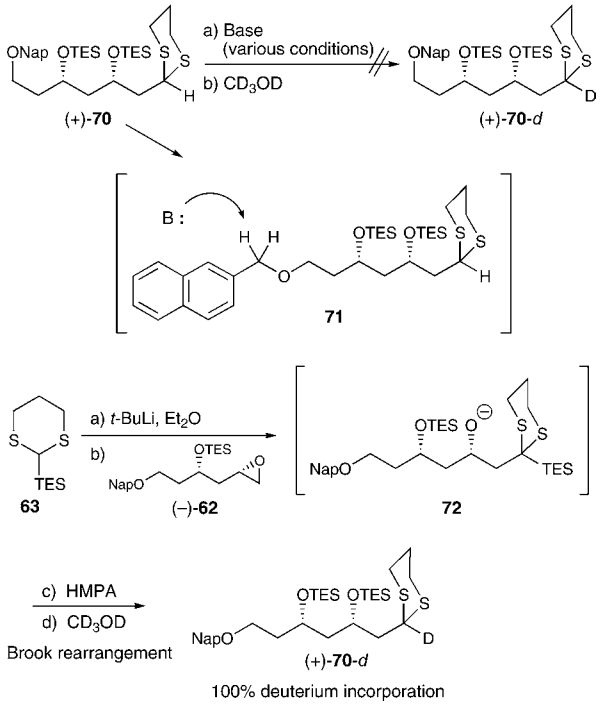




An Alternate Dithiane Lithiation Procedure

Dithianes resistant to metalation can be lithiated via the Brook rearrangement in appropriate cases. For example, although dithiane (+)-**70** could not be metalated due to competing deprotonation of the more acidic naphthyl protons (Scheme 16), alkylation of the requisite epoxide (−)-**62** with silyl dithiane **63**, followed by solvent-controlled

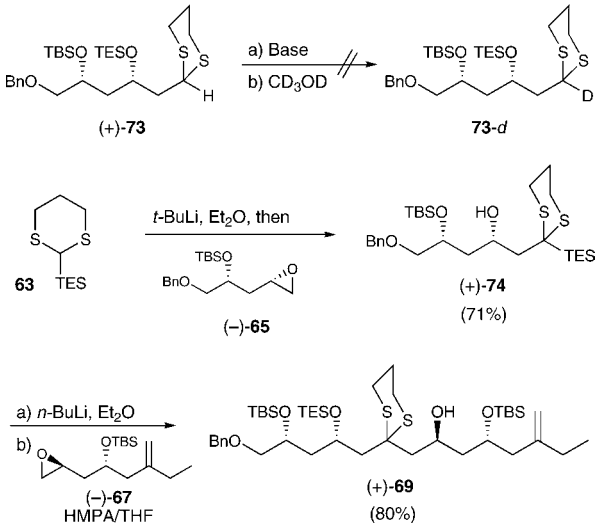
Scheme 16



Brook rearrangement effectively generated the desired lithiated dithiane as demonstrated by deuterium incorporation.[42]

In a second case, wherein dithiane (+)-**73** failed to undergo lithiation (Scheme 17), the lithium alkoxide of silyl dithiane (+)-**74**, prepared from **63** and (−)-**65**, was readily generated. Brook rearrangement triggered by HMPA then permitted alkylation with epoxide (−)-**67** to afford (+)-**69** in 80% yield.[42]

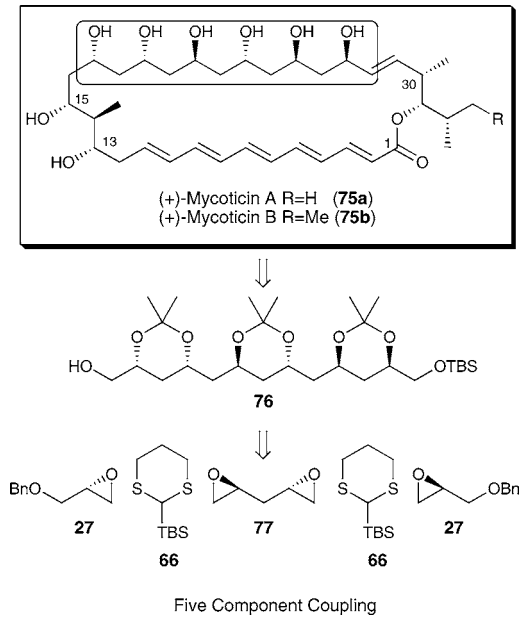
Scheme 17



The Mycoticins: A Remarkable One-Pot Five-Component Coupling

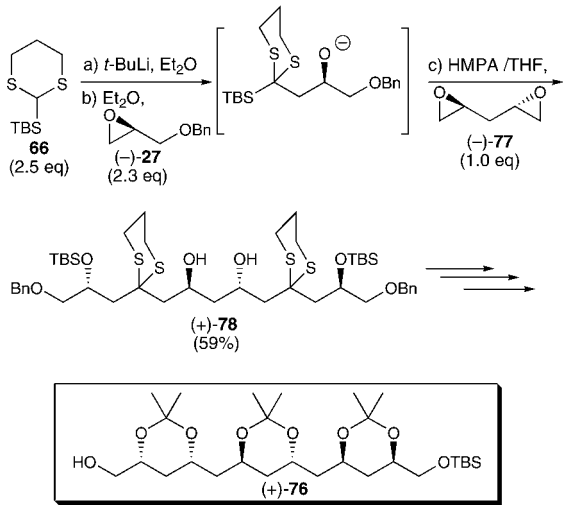
A more ambitious multicomponent union of silyl dithianes and epoxides was achieved in our formal total synthesis of the antifungal agent mycoticin A.[47,48] Here we envisioned construction of the C(16−28) polyol portion employing a "one-pot" five-component coupling tactic (Scheme 18).

Scheme 18



This transformation entailed generation of 2.5 equiv of lithiated *tert*-butyldimethylsilyl−dithiane **66**, which is reacted with 2.3 equiv of (−)-benzyl glycidyl ether **(**Scheme 19). After the initial alkylation is complete, addition of HMPA to promote the Brook rearrangement, followed by 1.0 equiv of bis-epoxide (−)-**77**, furnished (+)-**78** in 59% yield, wherein four new carbon−carbon σ bonds were established in one flask! Seven additional steps where then required to arrive at (+)-**76**, an intermediate in the Schreiber total synthesis of mycoticin A.[48,49] The overall sequence required eight steps, five fewer than the Schreiber route.

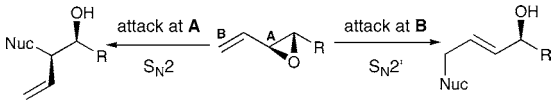
Scheme 19



The Reaction of Dithianes with Vinyl Epoxides

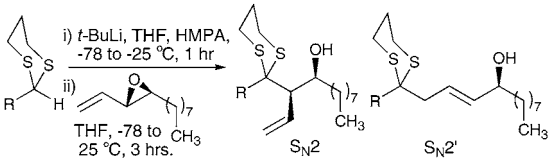
To expand the scope of the dithiane linchpin, we next examined vinyl epoxides as the electrophile, which offer both S_N2 and S_N2' reactivity (Scheme 20). Opportunely,

Scheme 20



simple adjustment of the steric bulk at the dithiane carbon permits selective reaction via either manifold (Scheme 21).[50] Less sterically encumbered dithiane anions afford

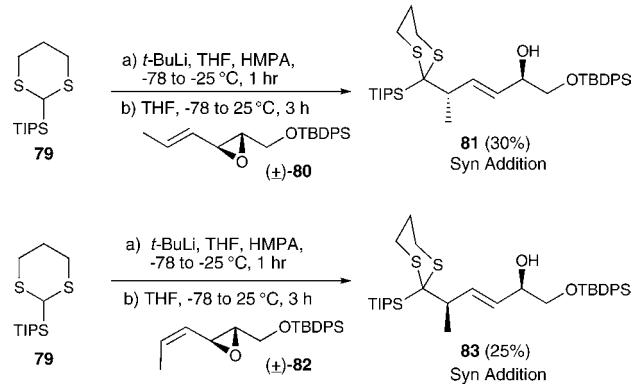
Scheme 21



Entry	R	Yield %	Ratio S_N2 : S_N2'
1	H	83	> 99 : 1
2	Ph	85	> 99 : 1
3	$SiMe_3$	83	> 95 : 5
4	Si^iPr_3	85	> 1 : 99
5	Et	81	> 1 : 99
6	^iPr	81	> 1 : 99

exclusively the product of S_N2 addition, whereas with large substituents, the S_N2' process predominates. Further investigation with 1-substitued vinyl epoxides (**80** and **82**) revealed that the S_N2' process occurs exclusively by syn addition, albeit with modest efficiency (Scheme 22).[50]

Scheme 22



Rimocidinolide: A Showcase for the S_N2/S_N2' Synthetic Tactic

The impressive control over the site of nucleophilic attack obtained with vinyl epoxides, coupled with the utility of silyl dithianes as linchpins, led us to rimocidinolide,[51] the aglycone of the potent antifungal agent rimocidin (Scheme 23).[52] To access the southern perimeter of this macrolide, we envisioned a series of S_N2 and S_N2' dithiane couplings beginning with the enantiomers of vinyl epoxide **93**.

For epoxide (−)-**87**, S_N2' addition of the anion of triisopropylsilyl (TIPS) dithiane (**79**) to epoxide (+)-**93**, followed in turn by concommitant removal of the TBS group and acetonide formation, fluoride-mediated TIPS removal, and olefin reduction afforded (+)-**95** in excellent yield. The resulting dithiane was then lithiated and treated with epoxide (+)-**89** to furnish (−)-**96**. Epoxide (+)-**89** was also prepared from vinyl epoxide (+)-**93** via S_N2 addition of phenyldithiane, removal of the TBS protecting group, and Fraser−Reid epoxide formation.[53] Subsequent manipulations generated epoxide (−)-**87** (Scheme 24). Importantly, both the S_N2 and S_N2' processes proceeded with excellent selectivity and good overall efficiency.

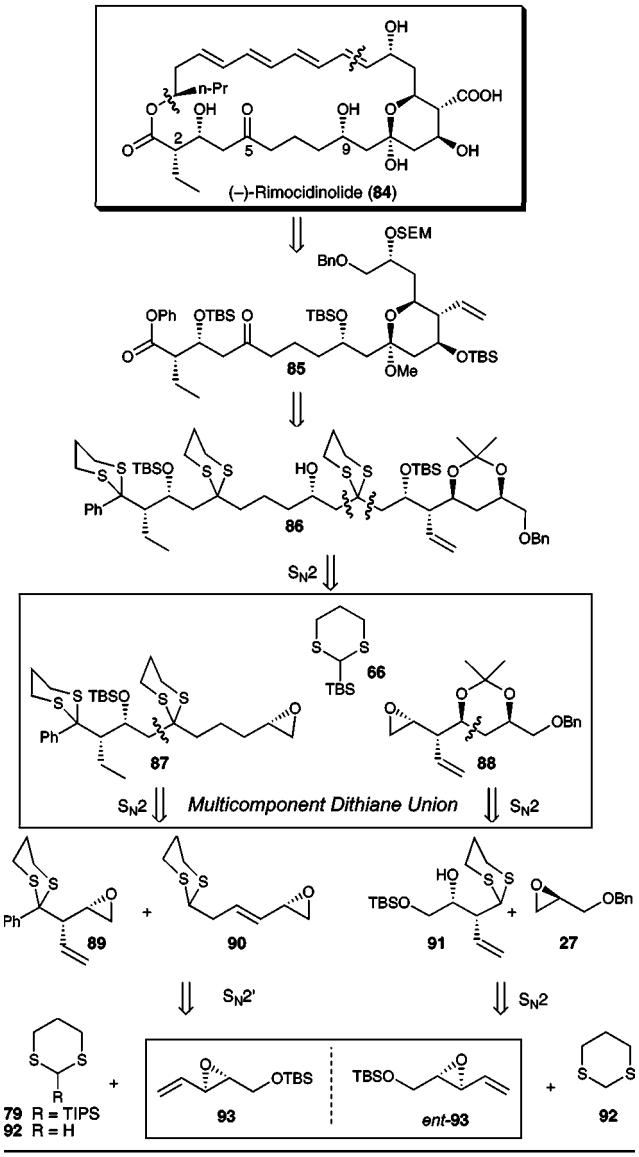
Construction of advanced epoxide (−)-**88** (Scheme 25) began with the enantiomer of vinyl epoxide (+)-**93**. Reaction with lithio-1,3-dithiane afforded alcohol (−)-**91**, which upon silylation and lithiation, coupled in an S_N2 fashion with benzyl glycidyl ether to provide alcohol (−)-**98**, the progenitor of epoxide (−)-**88**.

The strategic union of (−)-**87** and (−)-**88** was then achieved in 56% yield via our multicomponent coupling protocol and in turn completion of the C(1−18) fragment [(+)-**85**] for incorporation into rimocidinolide (Scheme 26).[54]

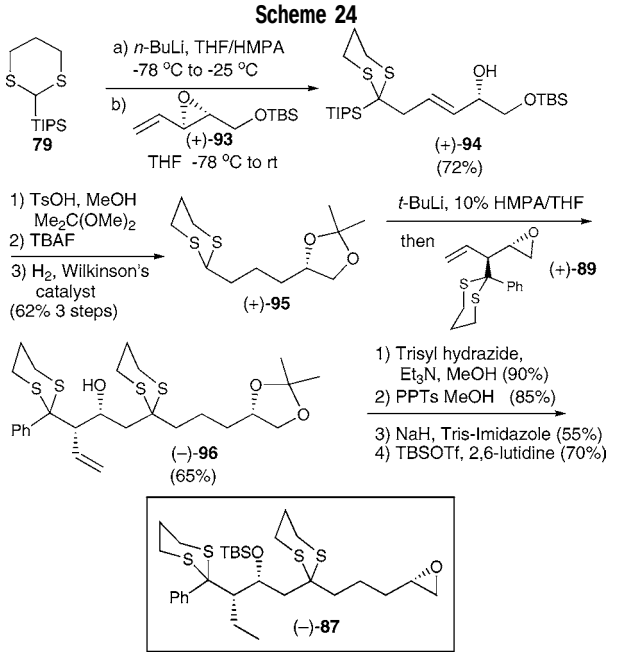
The Tedanolides: Development of a New Bidirectional Linchpin

To extend the concept of bidirectional dithiane linchpins with complementary nucleophilic functionalities, we se-

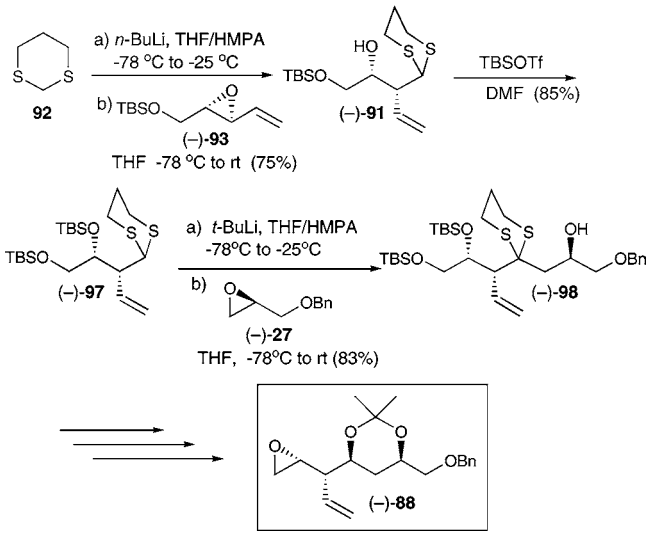
Scheme 23



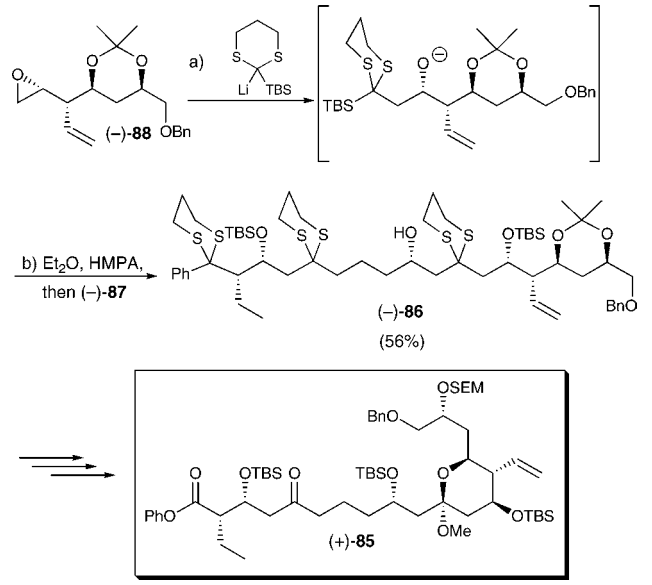
Scheme 24



Scheme 25



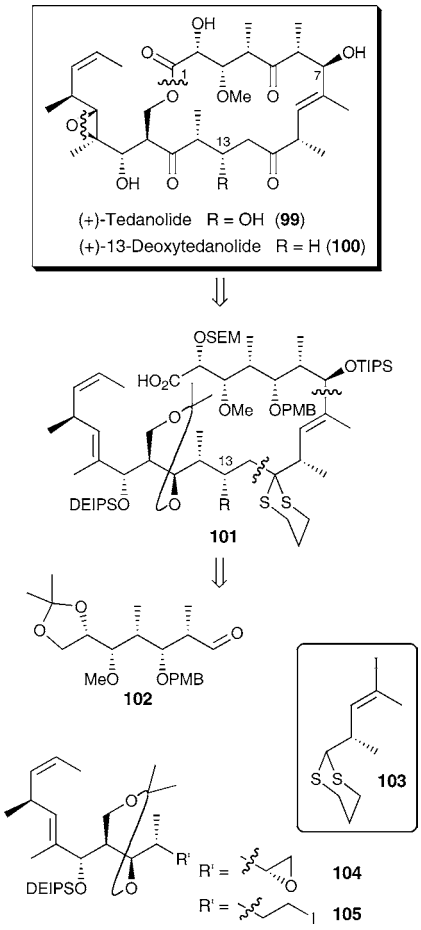
Scheme 26



lected as synthetic targets (+)-tedanolide (**99**) and (+)-13-deoxytedanolide (**100**), isolated respectively by Schmitz in 1984[55] and by Fusetani in 1991[56] (Scheme 27). Like rapamycin and 27-demethoxyrapamycin, these extremely potent antitumor agents possess a trisubstituted olefin, which appeared well suited for bidirectional construction, albeit now employing a dithiane and a vinyl anion equivalent (e.g., **103**) instead of the phenyl sulfone employed earlier. From the outset, we envisioned a strategy that would lead to both (+)-tedanolide and (+)-13-deoxytedanolide comprised of aldehyde **102**, linchpin **103**, and epoxide **104** or iodide **105**, respectively, for (+)-tedanolide (**99**) and (+)-13-deoxytedanolide (**100**).

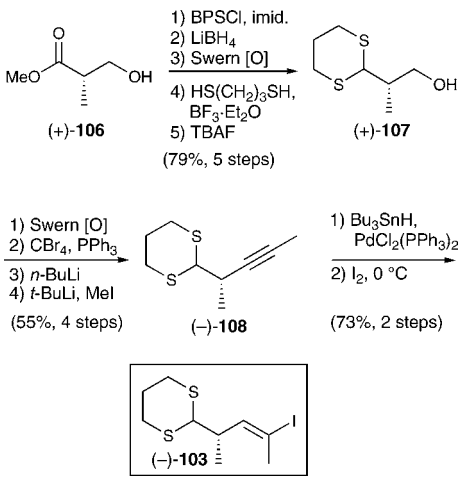
Linchpin (−)-**103** was prepared in a straightforward fashion from Roche's ester (+)-**106** as outlined in Scheme

Scheme 27



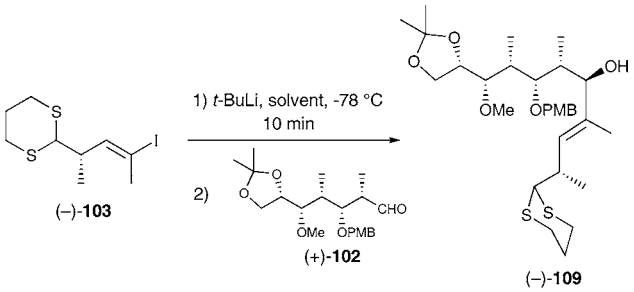
28. With the bidirectional linchpin (−)-**103** available, we employed first the vinyl iodide. Metal−halogen exchange, without interference from the dithiane, followed by

Scheme 28



addition to aldehyde (+)-**102** furnished allylic alcohol (−)-**109** in good yield (Scheme 29). Best selectivity was obtained with the mixed solvent system toluene/ether (ca. 12:1).

Scheme 29

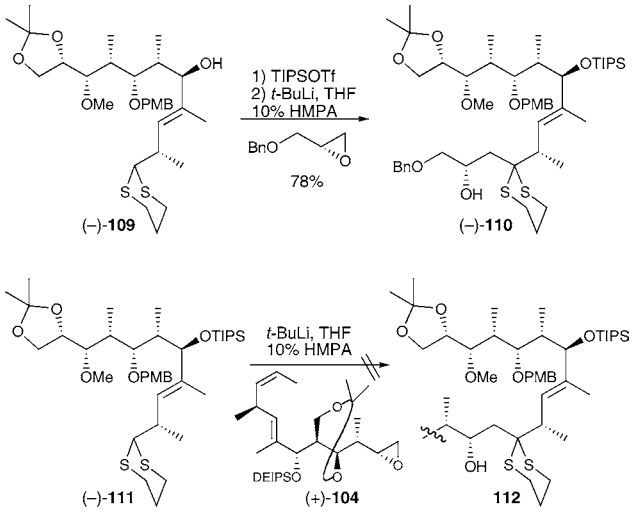


Solvent	Ratio (β:α)	Yield (%)
THF	2.7:1	58
Et_2O	3.5:1	65
t-BuOMe	3.5:1	43
Et_2O/pentane	4.0:1	85
Toluene/Et_2O	12:1	87

Total Synthesis of 13-Deoxytedanolide

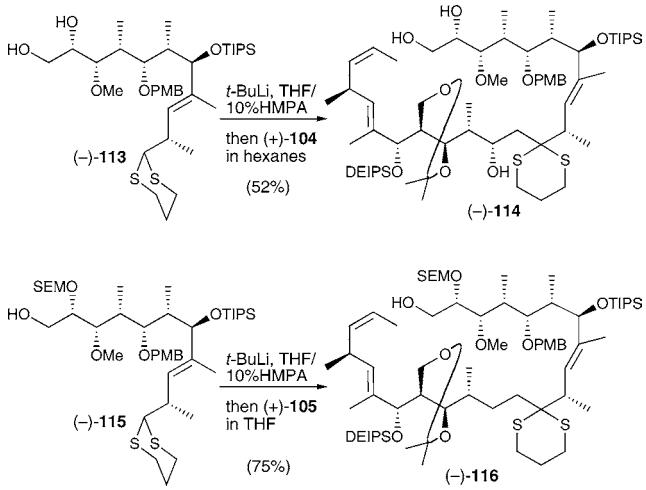
Our strategy for (+)-tedanolide (**99**) next called for union of dithiane (−)-**109** and epoxide (+)-**104**. Although the anion of dithiane (−)-**111**, obtained by TIPS protection of (−)-**109** and metalation, proved to be a competent nucleophile [e.g., reacted with (+)-benzyl glycidyl ether; 78% yield],[57] no reaction occurred with advanced epoxide (+)-**104**. Presumably the steric environment of the epoxide, as observed in our FK506 and calyculin programs, prevented addition (Scheme 30).

Scheme 30



We reasoned that changing the aggregation state of either the lithiated dithiane or a closely related congener might increase the reactivity and thereby negate a major strategy redesign. After considerable experimentation, generation of the trianion of (−)-**113** via removal of the acetonide protecting group and treatment with 3 equiv of *t*-BuLi, followed by addition of epoxide (+)-**104** in a low-polarity solvent system, led to (−)-**114**, possessing the complete carbon skeleton of the tedanolides (Scheme 31). Although the 52% yield might have proven acceptable for material advancement, the reaction required a large excess

Scheme 31



(7 equiv) of the valuable advanced epoxide (+)-**104**.[58] We therefore explored an alkyl iodide as the electrophilic partner, in a fashion similar to our FK506/rapamycin syntheses. The initial target would now be (+)-13-deoxytedanolide. Pleasingly, the dianion of (−)-**115**, possessing a SEM [2-(TMS)ethoxymethyl] moiety at the C(2)-hydroxyl, reacted with excellent efficiency (75% yield), requiring only 1.1 equiv of iodide (+)-**105**.

Having achieved the critical union, and thereby the complete carbon backbone of (+)-13-deoxytedanolide, we next addressed oxidation of the primary hydroxyl to the requisite seco-acid for macrocyclization. We were, of course, critically aware of the potential liability of the dithiane moiety to oxidation.[59] Indeed, all attempts to oxidize (−)-**116**, or the readily available aldehyde (Parikh–Doering oxidation), to the carboxylic acid employing a variety of conditions failed. A new oxidation method was thus required. We were drawn by our colleague, Professor Marisa Kozlowski, to the Evans–Tishchenko reaction,[60] at the time employed exclusively for directed reductions of β-hydroxy ketones. This reaction of course could also be viewed as a means to convert a sacrificial β-hydroxy ketone to the corresponding ester attached to the reduced carbonyl. That is, in addition to achieving reduction of the ketone to a hydroxyl in the Evans–Tishchenko reaction, the aldehyde is converted to an attached carboxylate (Figure 5).

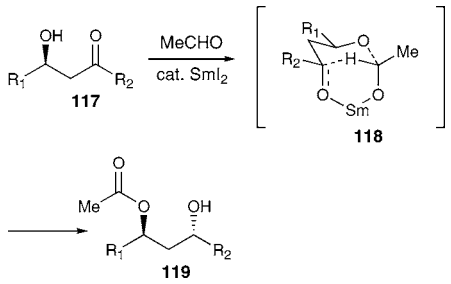
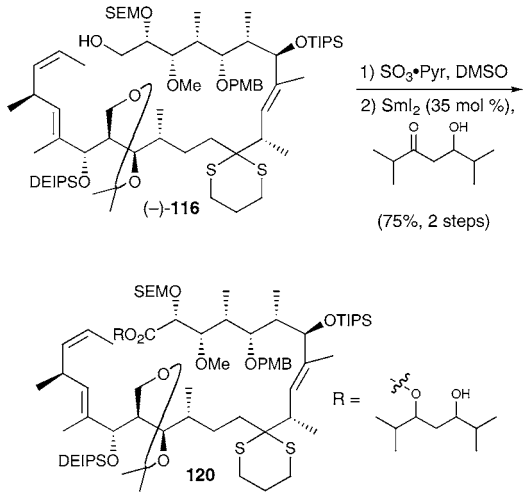


FIGURE 5. Transition state structure for the Evans–Tishchenko reaction proposed by Evans and Hoveyda.[60]

Pleasingly, when put into practice the SmI_2-promoted[61] oxidation of aldehydes to esters proceeded efficiently, not

only in the presence of sulfur but also in the presence of other electron-rich atoms, including P, N, Se, and Sn.[62] The successful oxidation of (−)-**116** exploiting this tactic led to seco-ester **120** in 75% yield (two steps) and ultimately to the first total synthesis of (+)-13-deoxytedanolide[63] (Scheme 32).

Scheme 32



Summary

Since the late 1970s, we have employed dithiane-based strategies for the union of advanced intermediates to achieve syntheses of architecturally complex natural products. The tactic both is efficient and leads to highly convergent synthetic strategies. More recently, we have demonstrated that dithianes are effective linchpins both for efficient union with vinyl epoxides and for multicomponent couplings involving three, four, and even five components, achievable in a single flask. Studies to extend and expand the utility of dithiane-based synthetic strategies continue in our laboratory and will be reported in due course.

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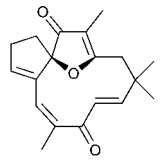

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