

Synthesis of Saturated Tetrahydropyrans

Matthew A. Perry, Scott D. Rychnovsky, and Nicholas Sizemore

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Abstract Tetrahydropyran (THP) rings are important motifs in biologically active molecules. This review presents common strategies for THP synthesis based on

M.A. Perry • S.D. Rychnovsky (✉) • N. Sizemore
Department of Chemistry, University of California, 1102 Natural Sciences II, Irvine,
CA 92697-2025, USA
e-mail: srychnov@uci.edu

Table 1 Comparison of the frequency and median yields for the disconnections discussed in this survey

Disconnection	Strategy	<i>n</i>	Median % yield
O1–C2	Conjugate addition	14	75
	Nucleophilic substitution cyclization	10	84
	Alkene-mediated cyclization	8	81
	Epoxide opening	2	82
C2–C3	Prins cyclization	13	68
	Petasis–Ferrier union/rearrangement	3	77
	Panek annulation	4	78
C3–C4	Class 1 ring-closing metathesis	5	94
	Class 2 ring-closing metathesis	3	73
Others	Hetero-Diels–Alder	8	69
	Lactol reduction	4	95
	Lactone reduction/reductive acetylation	13	84

typical retrosynthetic disconnections. General mechanistic and stereochemical considerations for each disconnection are included. The various strategies related to THP ring formation are discussed in the context of natural product synthesis.

Keywords Etherification • Hetero-Diels–Alder • Oxocarbenium ion • Reductive acetylation • Ring-closing metathesis • Tetrahydropyran

1 Introduction

Tetrahydropyran (THP) rings are important motifs in natural products and medicinal chemistry programs. As such, several reviews on the synthesis of THP rings have been reported [1–3]. The focus of this review is to present the strategies for THP synthesis in a systematic way. This chapter is divided into sections based on the retrosynthetic disconnections typically used to construct THP rings. Each section begins with a brief introduction of the different strategies for each disconnection and includes discussion of general mechanistic and stereochemical considerations. Finally, examples of each disconnection are given with respect to the synthesis of a select group of natural products.

The single-bond disconnections presented in this review are O1–C2, C2–C3, and C3–C4. A section on the synthesis of dihydropyran (DHP) rings using hetero-Diels–Alder reactions is included since these products are easily reduced to THP products. The functionalization of lactones and lactols is also included because these methods have found widespread use in THP synthesis. Table 1 shows a statistical snapshot of the disconnections and strategies in terms of yields presented in this review.

Given the wealth of THP-containing natural products and reports of THP syntheses, we decided that a small subset of natural products would be chosen to reduce the data set to a manageable size. The natural products shown in Fig. 1 were

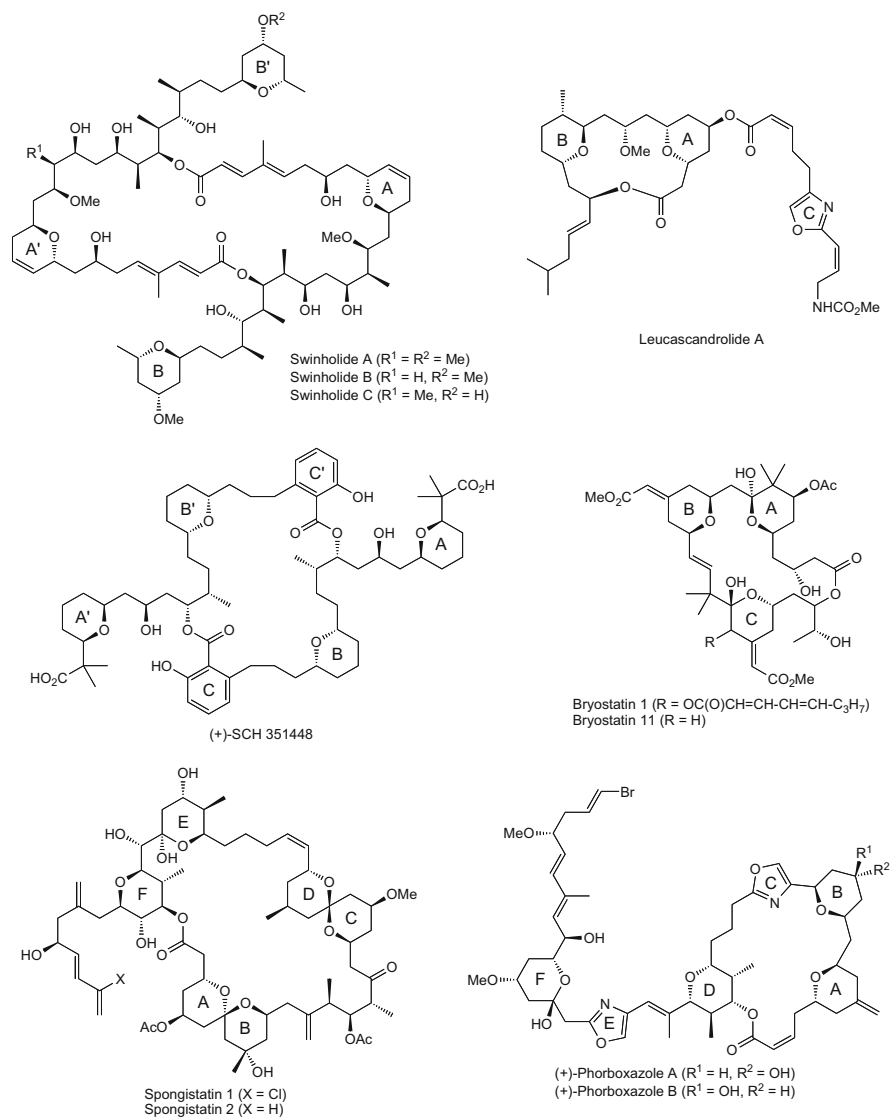


Fig. 1 The representative natural products selected for this survey

selected in order to give a broad range of substrate complexity and a variety of substitution patterns (including, but not limited to, 2,6-*cis* and 2,6-*trans* THP rings) [4–12]. These natural products have the added benefit of having been synthesized many times using various strategies, which allows for direct comparison across the different synthetic methods. This approach allowed for maximum utility within the chapter using a relatively small subset of THP-containing natural products.

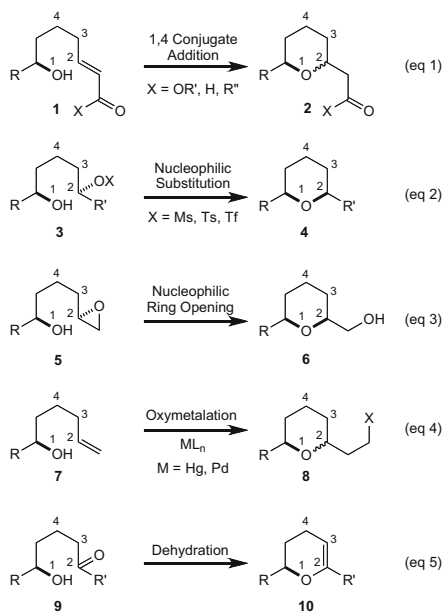
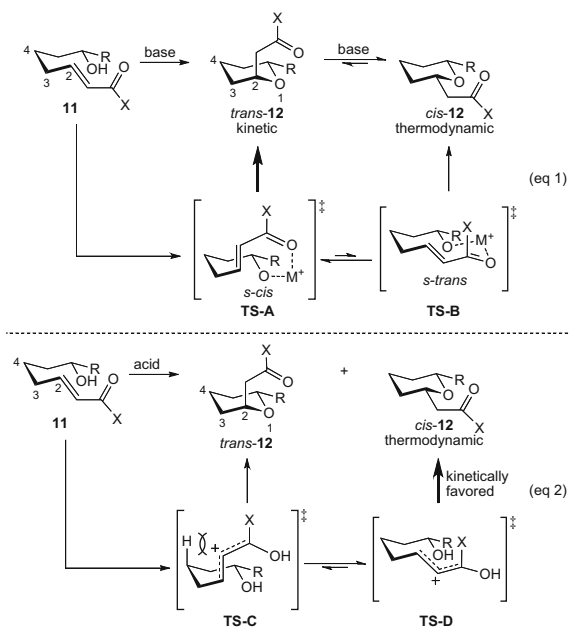
2 O1–C2 THP-Forming Processes

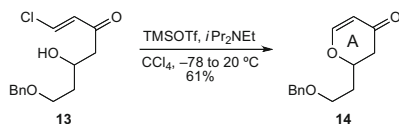
Of the numerous connections for the construction of THP rings, O1–C2 bond formation has proven to be an efficient, stereochemically predictable, and reliable approach. Such methods encompass S_N2 and S_N1 nucleophilic addition, conjugate addition, metal-promoted, and dehydrative cyclizations as represented in Scheme 1. This section will only cover those processes that produce tetrahydropyrans (Scheme 1, Eqs. 1–4). As such, the common O1–C2 closure by dehydration of δ -hydroxy ketones to give dihydropyrans will not be discussed (Scheme 1, Eq. 5). The goal of this section is to highlight methods used for the stereoselective construction of tetrahydropyrans in the context of complex natural product synthesis.

2.1 Conjugate Addition

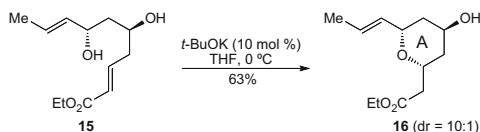
Conjugate addition has found widespread use in organic synthesis and, not surprisingly, in the construction of oxygen-containing heterocycles [13]. As shown in Scheme 2, intramolecular nucleophilic hydroxyl attack onto the electron-deficient β -carbon of an α,β -unsaturated carbonyl system proceeds through an *exo* (or *endo*) ring closure to provide the corresponding tetrahydropyran. The most common mode of ring closure involves 6-*exo-trig* cyclization of α,β -unsaturated hydroxy ketones or esters. Cyclization can be carried out under Brønsted basic or acidic conditions. Under basic conditions, 2,6-*trans* THPs are kinetically favored at low temperatures (-78°C) and short reaction times, whereas 2,6-*cis* THPs are thermodynamically favored at higher temperatures and longer reaction times. The stereoselectivity observed for base-mediated reactions has been described by the difference in energy and HOMO/LUMO orbital overlap between the *s-cis* (**TS-A**, lower energy, better orbital overlap) and *s-trans* (**TS-B**, higher energy, decreased orbital overlap) TS conformations (Scheme 2, Eq. 1) [14–18]. Under acidic conditions, the transition state (**TS-D**) leading to the thermodynamic 2,6-*cis* disubstituted pyran is now kinetically favored based on a frontier molecular orbital (FMO) theory argument (Scheme 2, Eq. 2). Inspection of the FMO coefficients of the allylic cationic species and the orbital overlap with the oxygen lone pair indicates greater stereoelectronic stabilization in **TS-D** than **TS-C** [13, 19]. These arguments validate the observed selectivity for simple 2,6-substituted tetrahydropyrans, but the stereochemical outcome of more complex THPs requires conformational analysis of the resultant heterocycle.

Paterson et al. reported perhaps the simplest intramolecular oxyanion conjugate addition in the synthesis of the C1–C15 fragment of swinholide A [20, 21]. This particular cyclization constitutes one of the first examples of the less common *endo* conjugate addition to a dihydropyran. Cyclization of **13** under Lewis acid/Brønsted basic conditions provided the racemic dihydropyrone **14** in good yield (61 %) (Scheme 3). Attempts at reaction optimization by changing solvent had little effect,

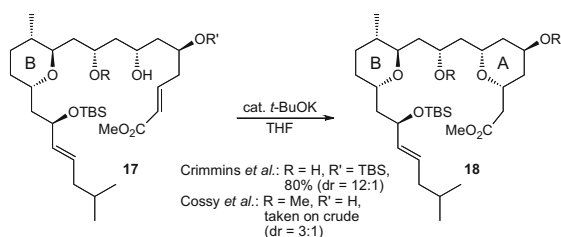

Scheme 1 General approaches to O1–C2 bond formation

Scheme 2 Stereochemical consequences of reaction conditions in conjugate additions



Scheme 3 *Endo* conjugate addition approach to the A ring of swinholide A [21]



Scheme 4 Early installation of A ring fragment of leucascandrolide A [22]



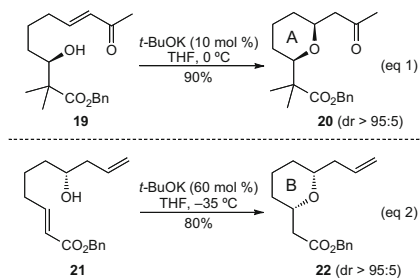
Scheme 5 Late-stage A ring assembly of leucascandrolide A [23, 24]

and alternative cyclization conditions gave only traces of the DHP (~20 %). This fragment was later used for a Ferrier-type rearrangement to give the 2,6-disubstituted DHP.

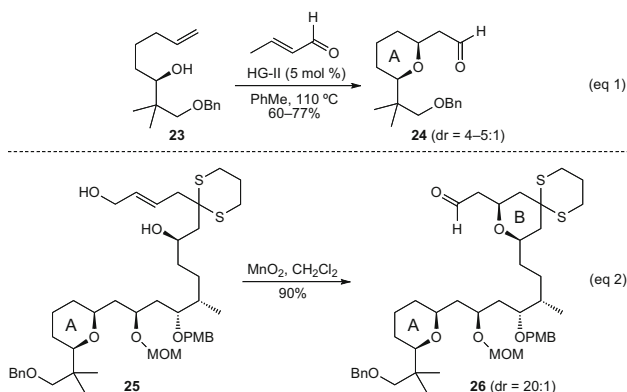
One of the many benefits of the conjugate addition approach stems from the ability of the product to self-catalyze the reaction. Carreira and Fettes reported on an oxa-conjugate addition in the synthesis of leucascandrolide A in 2002 [22]. Exposure of hydroxy enone **15** to a catalytic quantity potassium *tert*-butoxide under thermodynamic conditions provided the A ring pyran **16** in good yield (63 %) and with a dr of 10:1 favoring the 2,6-*cis* product (Scheme 4).

Both Crimmins and Siliphaivanh, as well as Cossy *et al.*, utilized the catalytic base-promoted conjugate addition in the total synthesis of leucascandrolide A. Crimmins first reported on the cyclization of alcohol **17** to provide the A ring THP **18** in very good yield (80 %) and a dr of 12:1 (Scheme 5) [23]. In 2007, Cossy described the same reaction using a very similar substrate to provide the 2,6-*cis* disubstituted THP with low diastereoselectivity (dr = 3:1) [24]. These examples clearly illustrate the subtle effects that remote functionality bears on stereoselectivity.

De Brabander *et al.* described a conjugate addition approach to both the A and B ring of (+)-SCH 351448 (Scheme 6) [25]. Treatment of neopentyl alcohol **19** with a catalytic amount of base under equilibrating conditions provided 2,6-*cis* THP **20** in high yield and high diastereoselectivity (90 %, dr > 95:5). Similarly, homoallylic



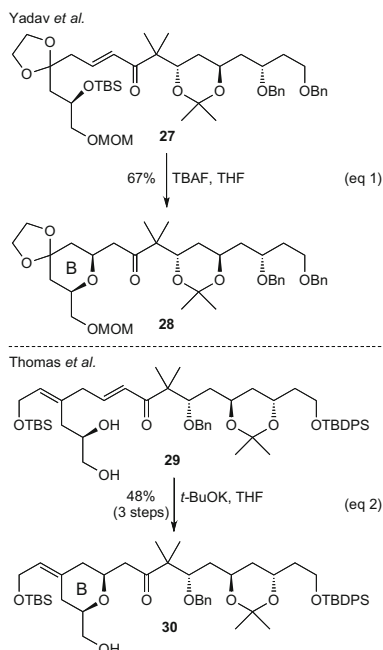
Scheme 6 Synthesis of key fragments for convergent synthesis of (+)-SCH 351448 [25]



Scheme 7 Cross-metathesis and oxidation/conjugation addition cascades leading to (+)-SCH 351448 [26]

alcohol **21** afforded *cis*-substituted B ring **22** in 80 % yield and a dr > 95:5. Interestingly, in both cyclizations, the diastereoselectivity was shown to be exquisitely controlled through reaction conditions (kinetic conditions led to a dr of 7:93 in both cases).

An appealing feature of oxa-Michael cyclizations is their ability to participate in cascade sequences. Hong et al. utilized a tandem cross-metathesis/conjugate addition sequence in a formal synthesis of SCH 351448 [26]. Use of Hoveyda–Grubbs second generation catalyst (HG-II) with methylacrolein and alkenyl alcohol **23** afforded 2,6-*cis* THP aldehyde **24** in good yield (60–77 %) with moderate diastereoselectivity (dr = 4–5:1) (Scheme 7, Eq. 1). In the same report, Hong et al. described an allylic oxidation/conjugate addition sequence to access the tetrahydropyranyl B ring. Oxidation of allylic alcohol **25** using manganese dioxide provided an intermediate enal that was subsequently trapped by the pendant alcohol to provide dithiane-protected 2,6-*cis* disubstituted pyrone **26** in 90 % yield and a dr of 20:1 (Scheme 7, Eq. 2).

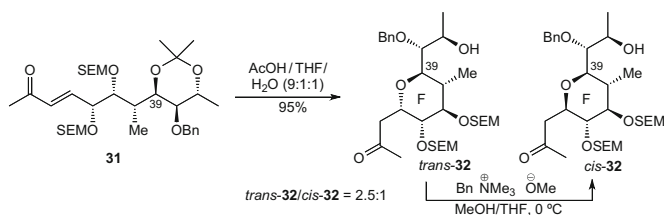


Scheme 8 Related approaches to the B ring of the bryostatins [27, 28]

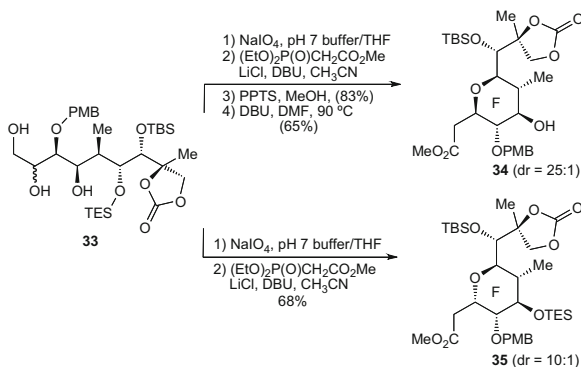
The THP rings contained within the bryostatin family of natural products have also succumbed to synthesis by Michael-type cyclization. Yadav *et al.* reported the tandem desilylation and conjugate addition to give the B ring of bryostatin 1 [27]. TBAF-mediated deprotection of silyl ether **27** resulted in 67 % isolated yield of 2,6-*cis* THP **28** (Scheme 8, Eq. 1). Thomas and coworkers described a similar approach on a related substrate to that of Yadav *et al.* (Scheme 8, Eq. 2) [28]. Cleavage of TES and TMS ethers with HF/pyridine resulted in diol **29**, and a subsequent cyclization with catalytic base proceeded stereoselectively to 2,6-*cis*-4-methylene THP **30** (48 % yield over three steps).

Brønsted acid-mediated THP synthesis provides an effective alternative to the more commonly used Brønsted base protocol. Paterson and Keown were able to effect cyclization under mildly acidic conditions en route to spongistatin 1 (Scheme 9) [29]. Acetonide deprotection with acetic acid followed by conjugate addition of the resultant diol provided 2,6-*trans* and 2,6-*cis* THPs (*trans*-**2.32** and *cis*-**32**, respectively) in a dr of 2.5:1 and 95 % yield. Fortunately, treatment of the mixture with Triton methoxide provided the required *cis*-isomer in 70 % overall yield.

A Horner–Wadsworth–Emmons (HWE) olefination/conjugate addition sequence was reported by Roush *et al.* for the synthesis of the bis-THP subunit of spongistatin 1 (Scheme 10) [30]. This example demonstrates how substitution affects product distribution of conjugate additions under thermodynamic control.



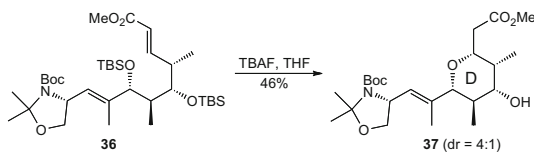
Scheme 9 Conjugate addition approach to the highly substituted F ring of spongistatin 1 [29]



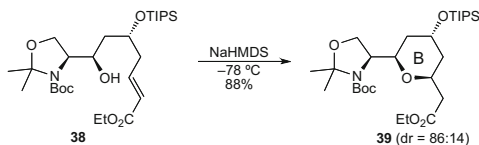
Scheme 10 Selective synthesis of the F ring subunit of spongistatin 1 [30]

The terminal diol of **33** was oxidatively cleaved, and the resulting crude aldehyde was subjected to an HWE reaction using excess LiCl at room temperature. Under these conditions, the TES group migrated from the C39 hydroxyl to the C41 hydroxyl, and the newly revealed alcohol underwent 1,4-addition to the enoate. This one-pot olefination/silyl migration/1,4-addition sequence furnished the undesired 2,6-*trans* THP **35** as the major diastereomer (dr = 10:1) in 68 % yield. Diastereoselectivity was reversed by employing a stepwise procedure involving HWE olefination, subsequent cleavage of the TES ether, followed by 1,4-addition under thermodynamic conditions to afford the 2,6-*cis* THP **34** as the major diastereomer (dr = 25:1) in 65 % yield.

Forsyth and coworkers provided one of the earliest examples of the desilylation/conjugate addition sequence en route to the total synthesis of phorboxazole A (Scheme 11) [31, 32]. Subjecting silyl ether **36** to fluoride-mediated deprotection furnished the alkoxide, which upon conjugate addition to the enoate gave the THP-containing ester **37** in moderate yield and diastereoselectivity (46 %, dr = 4:1) after 3 days. The use of shorter reaction times provided a mixture of mono- and dihydroxy acrylate and THP products. Attempts at improving conversion to the desired THP including increased temperature, longer reaction times, and stronger bases were unsuccessful.



Scheme 11 Desilylation/conjugate addition approach to the D ring of phorboxazole A [31]

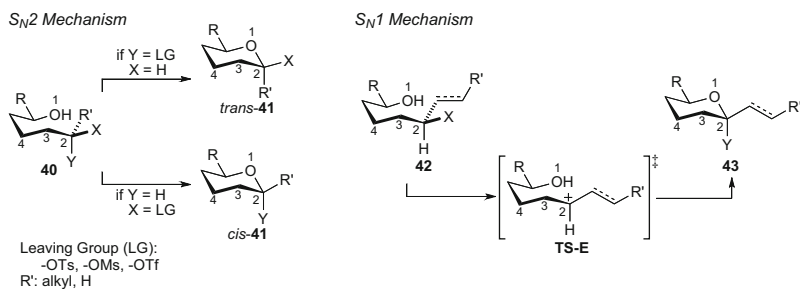


Scheme 12 Synthesis of B ring fragment of phorboxazole A [33]

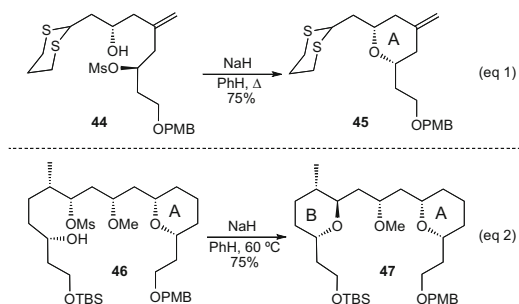
Pattenden and Plowright described the synthesis of the B ring of phorboxazole by a simple conjugate addition (Scheme 12) [33]. Treatment of alcohol **38** with NaHMDS under typical kinetic control conditions ($-78\text{ }^{\circ}\text{C}$) resulted in a selective intramolecular oxyanion conjugate addition to produce the thermodynamically favored 2,6-*cis* THP **39** in 88 % yield and a dr of 86:14. No attempt at equilibration under thermodynamic conditions to give a higher *cis/trans* ratio was reported. This example demonstrates the dramatic effects that subtle changes in substitution can have on stereochemical outcomes.

2.2 Nucleophilic Substitution Cyclizations

Cyclizations based on nucleophilic substitution represent the simplest strategy leading to tetrahydropyrans. The plethora of methods for the stereoselective installation of secondary alcohols allows efficient synthesis of the requisite hydroxy nucleophile as well as the leaving group (usually derived from a chiral alcohol). The 6-*exo-tet* cyclization proceeds with inversion at the electrophilic carbon center in accord with a Williamson reaction [34]. In this way, both the 2,6-*cis* and 2,6-*trans* THP are readily accessible based on the configuration of the reactive center (Scheme 13). Reactivity toward nucleophilic substitution follows the rate trend of primary > secondary > tertiary; most examples covered herein utilize secondary electrophiles with secondary alcohol nucleophiles. In contrast to $\text{S}_{\text{N}}2$ -like processes, $\text{S}_{\text{N}}1$ processes involve the generation of stabilized allylic or benzylic carbocations for nucleophilic trapping. In this method, the stereochemical outcome of the cyclization is dictated by the stereogenic composition of the substrate and the experimental conditions.



Scheme 13 Mechanistic considerations for nucleophilic substitution cyclizations

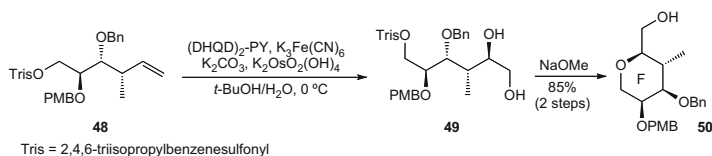


Scheme 14 Nucleophilic substitution approach to the bis-THP fragment of leucascandrolide A [35]

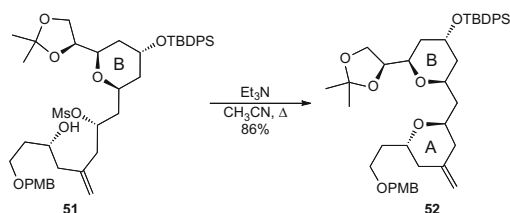
The ability of nucleophilic substitution to provide either 2,6-*cis* or 2,6-*trans* THP has been exploited in the synthesis of several natural products. Williams and coworkers reported the formation of both the A and B ring of leucascandrolide A by nucleophilic substitution (Scheme 14) [35]. Both examples relied on a methanesulfonate leaving group and secondary alcohol nucleophile. Subjecting mesylate **44** (or **46**) to sodium hydride deprotonation followed by heating resulted in THP product **45** (or **47**) in 75 % yield as a single diastereomer.

The relative ease of cyclization with primary electrophilic centers prompted Smith and coworkers to use this method in their scalable route to (+)-spongistatin 1 (Scheme 15) [36]. Sharpless asymmetric dihydroxylation of alkene **48** provided diol **49**, which underwent cyclization in the presence of sodium methoxide to afford THP **50** in 85 % yield over two steps as a single diastereomer.

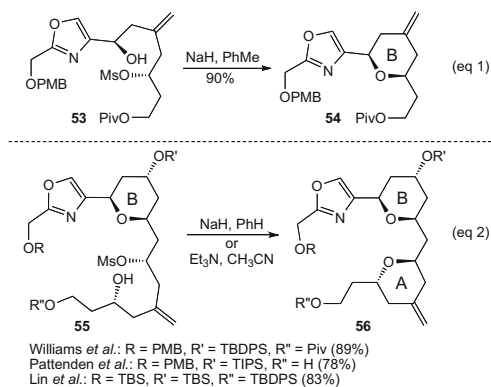
The utility of sequential displacement cyclization strategies has been demonstrated in the construction of the phorboxazole bis-THP subunit. Milder conditions can be used for effective cyclization in cases where existing functionality can result in undesired side product formation. Cink and Forsyth reported an elimination pathway that resulted in formation of a conjugated diene when alcohol **51** was treated with sodium hydride [37]. Use of a less basic hindered amine in refluxing



Scheme 15 Dihydroxylation/displacement strategy to the F ring of spongistatin 1 [36]



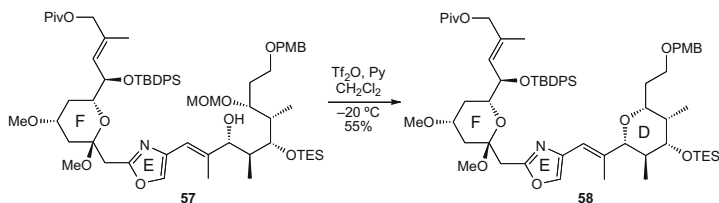
Scheme 16 Mild basic displacement to the A ring of phorboxazole A [37]



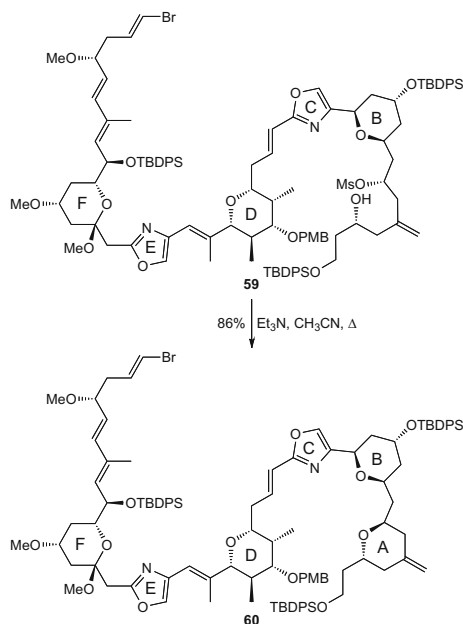
Scheme 17 Displacement strategies for the synthesis of the B ring in phorboxazoles [33, 38, 39]

acetonitrile proceeded smoothly to furnish bis-THP **52** in 86 % yield as a single diastereomer (Scheme 16).

Williams *et al.*'s synthesis of phorboxazole A utilized a direct displacement strategy to produce both THP rings in the bis-THP fragment of the natural product [38]. Sodium hydride deprotonation of alcohol **53** and displacement gave B ring intermediate **54** in high yield (90 %) as a single diastereomer (Scheme 17, Eq. 1). Following the same procedure, Williams *et al.* also effected cyclization of **55** to afford the A ring in 89 % yield (Scheme 17, Eq. 2). This method and substrate were subsequently used by both Pattenden and Plowright and Lin and coworkers to construct the bis-THP domain, with the only modification being the use of triethylamine as the base [33, 39]. Of note, substrate control can provide both 2,6-*cis* and 2,6-*trans* THPs by the same method.



Scheme 18 Carbocation-induced D ring closure en route to phorboxazole A [40]



Scheme 19 Late-stage displacement strategy to the A ring of phorboxazole A [42]

In addition to the A and B rings, Williams et al. also used an interesting cationic process to build the D ring contained in phorboxazole A (Scheme 18) [40]. The transformation involved formation of the triflate from **57** followed by expulsion of triflic acid to generate an allylic carbocation. Subsequent internal trapping of the transoid allylic cation intermediate by the C22 methoxymethyl ether and concomitant alkylation of the resultant oxonium species provided THP **58** in moderate yield (55 %) as the sole diastereomer.

White and coworkers reported perhaps the most noteworthy example of nucleophilic substitution in a complex setting. The late-stage closure of the A ring of phorboxazole A proceeded smoothly under mild conditions [41, 42]. Exposure of mesylate **59** to Et_3N afforded 2,6-*trans* THP **60** in high yield (86 %) as a single diastereomer (Scheme 19).

2.3 Alkene-Mediated Cyclizations

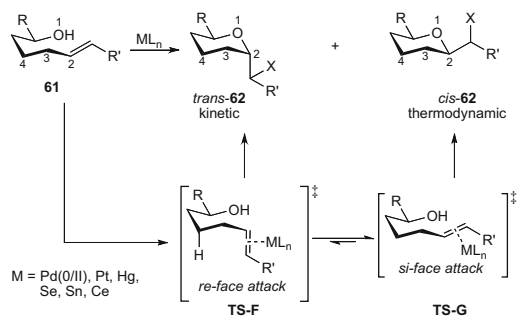
Electrophile-activated alkene additions are a common chemical transformation of carbon-carbon double bonds. This section will review some of the more common methods encountered in the context of macrolide natural product synthesis. Typically, THP formation occurs by a 6-*exo-trig* cyclization of δ -hydroxy alkenes in the presence of an appropriate metal salt. Activation of the π -system occurs through reversible formation of a π -complex or an onium intermediate that leads to the heterocycle by attack of the pendant oxygen nucleophile [43]. The stereochemical outcome of the cyclization is dictated by the nucleophilic attack occurring on the face opposite electrophilic π -complexation (Scheme 20). Facial discrimination of the alkene can therefore be achieved through either substrate control (chiral directing-group coordination) or chiral metal reagent/catalyst.

Metal-activated alkene additions can be classified as stoichiometric or catalytic processes. Stoichiometric processes for THP synthesis typically involve the use of mercury(II) salts and to a lesser extent iodo and seleno reagents. The progress of intramolecular oxymercuration is determined by the stability of the cationic intermediates. Product stereochemistry is under substrate control and usually leads to the thermodynamically more stable THP product. Catalytic variations generally involve palladium complexes [44], but other transition metals are becoming more common (e.g., Pt [45], Ag [46], Sn [47], Ce [48]). The oxidation state of Pd determines the catalyst reactivity. Palladium(0) complexes are nucleophilic and participate in tetrahydropyran synthesis through π -allyl cation intermediates, whereas Pd(II) complexes possess electrophilic character and progress through a reversible π -complex.

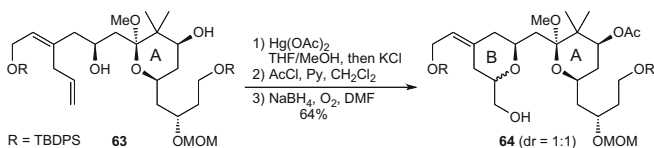
Masamune et al. reported on an oxymercuration approach to the synthesis of the B ring of bryostatin 1 (Scheme 21) [49]. Mercury acetate-mediated cyclization of **63** followed by acetylation of the C7 alcohol allowed for oxidative cleavage of the organomercurial intermediate to give a 1:1 diastereomeric mixture of 4-methylene THP **64** in good yield (64 % over three steps). The lack of diastereoselection can be attributed to the absence of a chelating directing group near the reacting alkene center.

Leighton et al. described an effective and mild palladium-catalyzed tandem alkene addition/carbonylation procedure in the synthesis of leucascandrolide A [50]. Intramolecular alkoxy-carbonylation of diol **65** under Semmelhack conditions proceeded efficiently to provide the desired 2,6-*cis*-tetrahydropyran **66** in 75 % yield with a dr of >10:1 (Scheme 22). Reaction optimization showed that use of benzonitrile as a cosolvent leads to cleaner and more efficient reactions. The functional group tolerance and chemoselectivity of the reaction simplified the protecting group strategy.

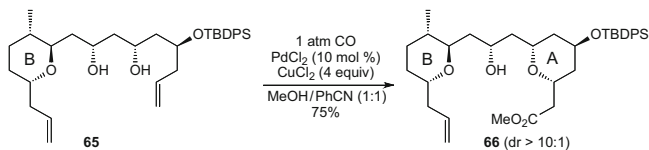
Fettes and Carreira were the first to describe the use of a selenium-based reagent to effect alkoxy-metallation of an alkene to give a 2,6-*trans* tetrahydropyran in the total synthesis of leucascandrolide A [22]. Various electrophiles (I_2 , IBr, and $Hg(OAc)_2$) gave disappointing levels of diastereoselectivity (1:1), whereas



Scheme 20 Stereochemical outcomes of metal-mediated alkene cyclizations



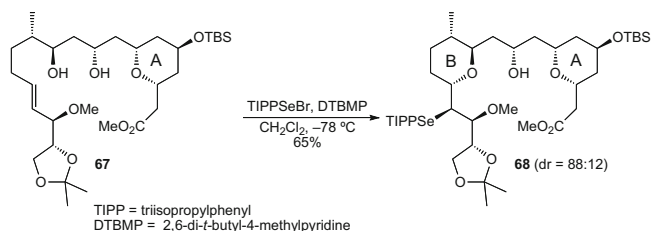
Scheme 21 Oxymercuration strategy to the B ring of the bryostatins [49]



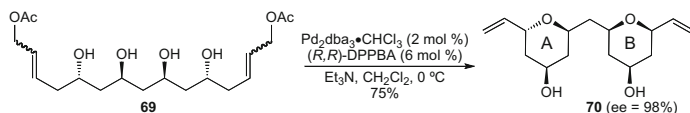
Scheme 22 Pd-catalyzed alkoxy carbonylation to the bis-THP fragment of leucascandrolide A [50]

phenylselenenyl chloride gave a diastereomeric ratio of 3:1 (*trans/cis*). That finding prompted the examination of bulkier, substituted phenylselenenyl halides in order to increase the diastereoselectivity. Treatment of hydroxy alkene **67** with 2,4,6-triisopropylphenylselenenyl bromide afforded the desired 2,6-*trans* tetrahydropyran **68** in 65 % yield with a dr of 88:12 (Scheme 23). The *trans* stereoselectivity can be rationalized by conformational analysis whereby the selenide complexes to the allylic strain minimized alkene from the less hindered *re* face (that of the methoxy group) forcing attack of the alcohol to occur from the *si* face.

Lucas and Burke reported on a Pd(0)-catalyzed asymmetric allylic etherification/desymmetrization of *meso* substrates by double cyclizations to the bis-THP subunit of phorbaxozoles A and B [51]. Based on Trost and Toste's transition state model for the diphenylphosphino benzoic acid (DPPBA) ligand system [52], Burke rationalized that cyclization of tetraol **69** with (*R,R*)-DPPBA ligand would effect the double cyclization to give the *trans*-A ring and *cis*-B ring in bis-THP **70** (Scheme 24). Under optimized conditions, tetraol **69** was converted to **70** in 75 %



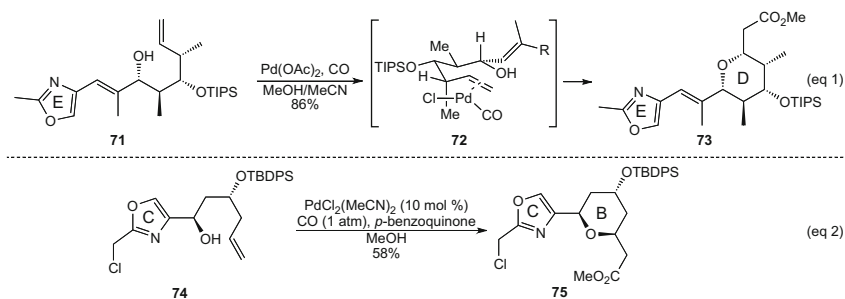
Scheme 23 Selenium-mediated alkene cyclization to construct the B ring of leucascandrolide A [22]



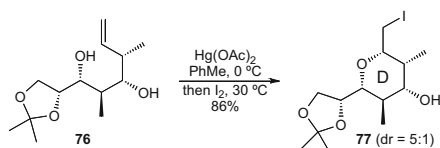
Scheme 24 Pd-catalyzed desymmetrization to the bis-THP fragment of the phorbaxozoles [51]

yield with an er of 99:1 and dr of 6.4:1 (*trans*–*cis*/*cis*–*cis*). Fast ligand-controlled cyclization installs the *cis*-substituted B ring, inhibits formation of the other enantiomer, and leads to the high levels of enantioselectivity observed. The moderate diastereoselectivity arises from a competitive ligand-controlled cyclization to the *trans*-substituted A ring with the substrate-controlled cyclization to the *cis*-substituted A ring. Specifically, as a result of a matched interaction between ligand control and steric bias, the B ring allylic stereogenic center has been set in the *R* configuration. However, the second cyclization event represents a mismatched case of ligand control and inherent steric bias. Cyclization of the A ring under ligand control provided the desired *R,R* (*cis*–*trans*)-isomer with one equatorial and one axial vinyl group. Cyclization under substrate control provided the more stable *S,R* (*cis*–*cis*)-isomer with two equatorial vinyl groups. This example highlights the utility of ligand-controlled Pd-catalyzed desymmetrization to expeditiously produce useful chiral bis-THP building blocks.

White et al. also reported on the palladium(II)-catalyzed 1,2-alkoxycarbonylation in the synthesis of both the B and D rings of phorbaxozole A (Scheme 25) [41]. The D ring THP **73** was prepared in high yield (86 %) from cyclization of hydroxy alkene **71**. The stereochemistry and efficiency of the reaction is best described by a minimization of steric interactions between the α -methyl substituent and the *exo* Pd substituent (e.g., Cl) of the complexed alkene intermediate **72** preceding cyclization. Unfortunately, an excess of palladium acetate was required to compensate for the reduction of Pd(II) to inactive Pd(0). For the synthesis of the B ring, use of a stoichiometric oxidant, *p*-benzoquinone, with catalytic palladium circumvented this issue. Under these improved conditions, trisubstituted B ring THP **75** was isolated as a single diastereomer in a moderate 58 % yield along with 15–20 % recovered starting material **74**.



Scheme 25 Pd-catalyzed alkoxyacylation to the D and B ring fragments of phorboxazole A [41]

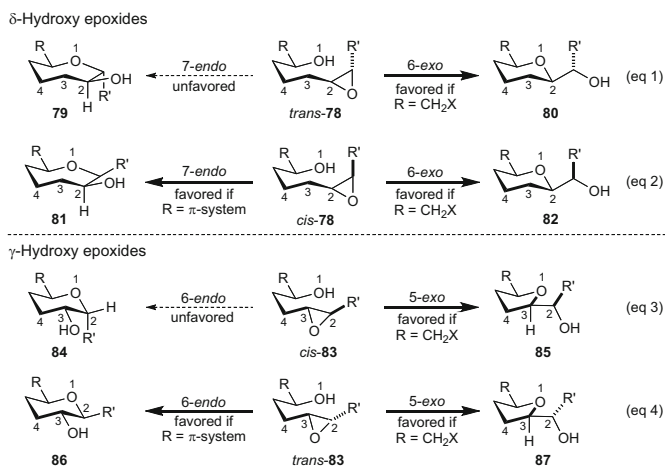


Scheme 26 Iodomercuration of the D ring of the phorboxazoles [39]

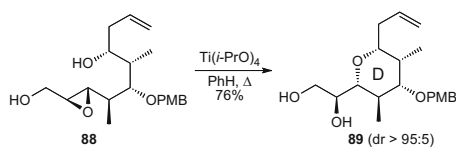
The ability of mercury salts to effect nucleophilic alkene addition is apparent in Lin and coworkers' synthesis of the phorboxazole D ring (Scheme 26) [39]. Initial attempts at cyclization proceeded by addition to a halo-activated alkene. The use of iodine under basic conditions afforded the desired THP in 46 % yield as a 2.6:1 ratio of *cis/trans* isomers. The use of bulkier NIS increased the diastereoselectivity to 7.7:1 with no increase in yield. A more efficient cyclization was realized by using mercury(II) acetate. Installation of the iodide was accomplished by the addition of iodine after cyclization was complete. These conditions gave 2,6-*cis* THP **77** in 86 % yield and moderate diastereoselectivity (5:1). This method also benefits from the displacement of the organomercurial intermediate in a single-pot procedure, thereby mitigating the isolation of potentially toxic mercury-containing substrates.

2.4 Nucleophilic Substitution Cyclizations by Epoxide Opening

Analogous to the nucleophilic substitution methods, nucleophilic epoxide opening provides access to substituted THP adducts in a stereospecific manner. Seminal studies by Nicolaou et al. established the structural requirements necessary for regio- and stereocontrolled synthesis of THP adducts [53, 54]. Regioselectivity is highly dependent on the configuration of the epoxide (Scheme 27); δ -hydroxy *trans*-epoxides show high selectivity for THP formation over oxepane formation



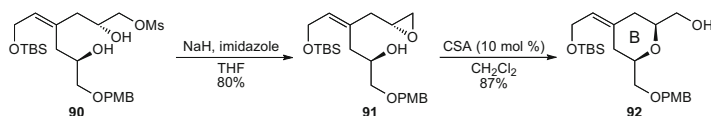
Scheme 27 Stereochemical consequences of intramolecular epoxide opening



Scheme 28 Lewis acid-mediated epoxide-opening cyclization to D ring of phorbosaxazole A [57]

irrespective of the R substituent (Eq. 1). For *cis*-epoxides, saturated R substituents prefer 6-*exo* cyclization, whereas unsaturated R substituents prefer 7-*endo* cyclizations (Eq. 2). In the case of γ -hydroxy *cis/trans*-epoxides, either can undergo 6-*endo-tet* or 5-*exo-tet* cyclization (Eqs. 3–4). *Cis*-epoxides give 5-*exo* products (THF), whereas *trans*-epoxides are dependent on the identity of the R substituent. If R = alkane, *trans*-epoxides give 5-*exo* products (THF), whereas if R = π -system, 6-*endo* products are preferred (THP). This method benefits from the availability of several stereoselective epoxidation methods, the introduction of useful functional groups for further elaboration, and the ability to form polycyclic frameworks by an iterative process. However, the constraints imposed by the pendent epoxide substituents require a high level of substrate design with regard to stereochemistry and substitution of the cyclization precursor. Blanc and Toste, as well as Morimoto and coworkers, have described similar methods that do not follow the general trend described above [55, 56].

Ye and Pattenden described an epoxide-opening/cyclization approach to the synthesis of the pentasubstituted C22–C26 THP of phorbosaxazole A (Scheme 28) [57]. The use of a *trans*-epoxide with a hydroxymethylene side chain allowed selective formation of a 2,6-*cis* THP by 6-*exo* cyclization. Subjecting hydroxy epoxide **88** to Lewis acid in refluxing benzene provided desired THP **89** in 76 % yield with high diastereoselectivity (dr > 95:5).



Scheme 29 Brønsted acid-catalyzed epoxide opening to the B ring of the bryostatins [58]

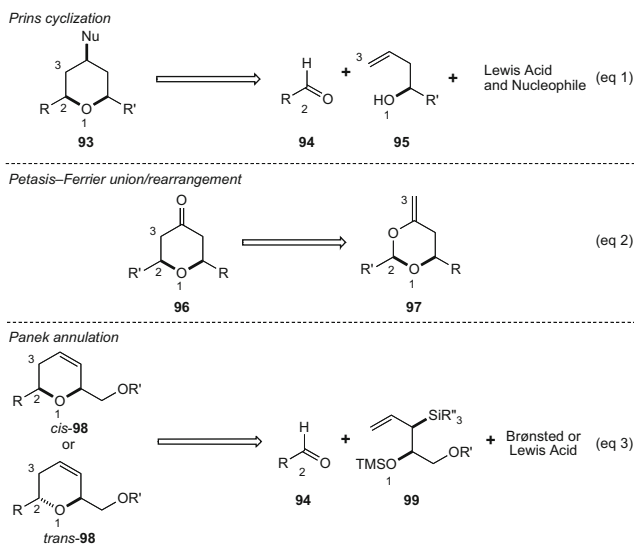
Hale et al. reported on the synthesis of the bryostatin B ring by acid-catalyzed nucleophilic epoxide opening (Scheme 29) [58]. Their goal was to convert *O*-mesylate epoxide precursor **90** directly into THP **92** by treatment with two equivalents of sodium hydride and imidazole. However, the only product isolated was epoxy alcohol **91** in 80 % yield. To effect the desired 6-*exo-tet* ring closure, epoxide **91** was treated with a catalytic amount of camphorsulfonic acid. Tetrahydropyran **92** was acquired as the sole product in 87 % yield as a single diastereomer.

2.5 Summary

The above examples represent some of the most efficient, reliable, and powerful methods for the construction of tetrahydropyrans by oxygen–carbon bond-forming processes. The conjugate addition approach can provide both 2,6-*cis* and 2,6-*trans* THPs by simple modification of the reaction conditions. Additionally, the precursors are amenable to the use of tandem processes that maximize step economy. Nucleophilic substitution methods benefit from the plethora of stereoselective alcohol-forming transformations but are limited chiefly to primary and secondary electrophiles. Epoxide-opening/cyclization processes are effective within a very specific context and thus lack generality. Electrophile-induced alkene addition reactions are efficient and can be stereoselective provided the substrate or catalyst contains the structural elements necessary for π -facial discrimination of the alkene. This method also benefits from the continued growth of palladium and other transition metal-mediated chemistry. While several approaches are available for the synthesis of tetrahydropyrans by O–C bond formation, the advantages and disadvantages of each approach must be evaluated when considering a 1,2 disconnection.

3 C2–C3 THP-Forming Processes

A common strategy for the synthesis of tetrahydropyran rings is C2–C3 disconnection (Scheme 30). The natural order of reactivity typically generates an oxocarbenium ion at C2 while C3 acts as the nucleophile. This strategy is manifested in three general classes of reactions: Prins cyclizations (Eq. 1), Petasis–Ferrier union/rearrangements (Eq. 2), and Panek annulation (Eq. 3).

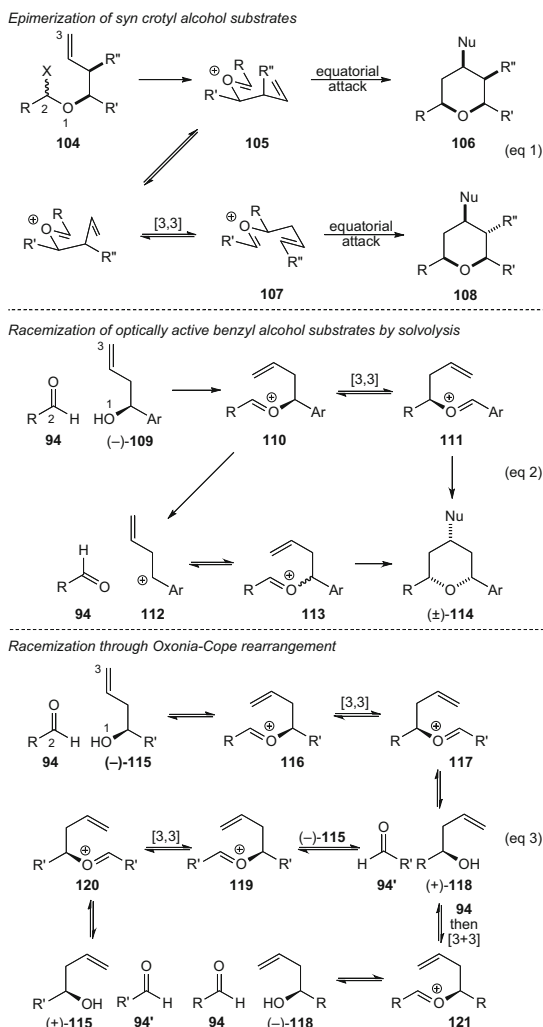


Scheme 30 Common retrosynthetic approaches that forge C2–C3 bonds

3.1 Prins Cyclization Strategies

Prins cyclization is a two-component coupling reaction between homoallylic alcohol **94** and aldehyde **95** that proceeds by Lewis acid-induced formation of oxocarbenium ion **101** (Scheme 31) [59–63]. Prins cyclizations proceed through chair-like transition state **TS-A**, where resulting secondary carbocation **102** is stabilized by orbital overlap [64]. The stereochemical outcome at C4 is dictated by the nature of the nucleophilic trapping agent, which is usually a Lewis acid counterion (Scheme 32) [65]. Dissociated ion pairs (e.g., SnBr_5^-) undergo equatorial nucleophilic attack to give the all *cis* arrangement (**93**), whereas tight ion pairs (e.g., Br^- from TMSBr) show a preference for axial attack, leading to the nucleophile at C4 being *trans* to the C2 and C6 groups (**103**).

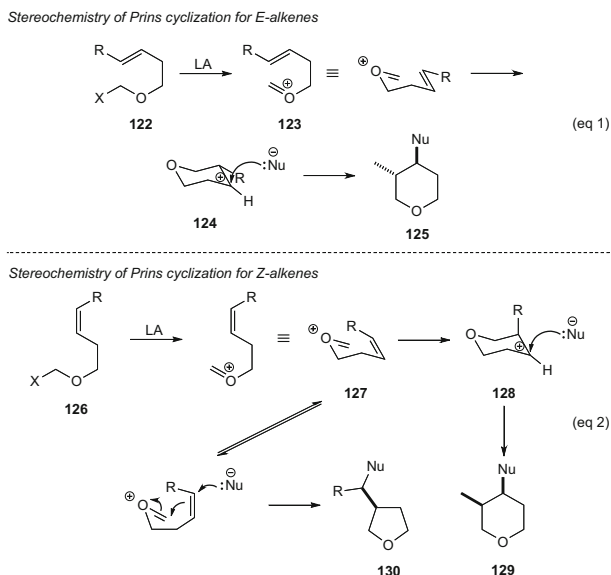
Prins cyclization can suffer from degradation of optical purity through a variety of pathways [66]. The primary mode of racemization/epimerization in Prins cyclizations is by oxonia-Cope rearrangement (Scheme 33) [67, 68]. There are three primary examples of problematic substrates: *syn*-crotyl alcohols (Eq. 1), aryl-substituted homoallylic alcohols (Eq. 2), and allyl-alkyl or allyl-aryl carbinols (Eq. 3). Prins cyclization transition states of *syn*-crotyl alcohols exhibit significant diaxial interactions between the C3 hydrogen and the C5 substituent (Scheme 33, Eq. 1). As a result, a [3,3]-sigmatropic rearrangement (oxonia-Cope) can occur through a boat conformation. Resulting oxocarbenium ion **107** can then undergo a Prins cyclization where the C5 substituent can adopt an equatorial conformation. The overall result is a net epimerization of the C5 substituent while maintaining a 2,4,6-*cis* relationship in the THP ring (**106** vs. **108**). Substrate racemization can also



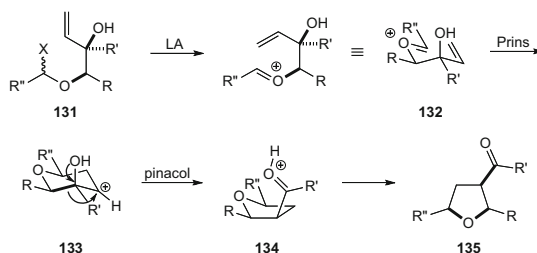
Scheme 33 Potential pathways for the degradation of stereochemistry in Prins cyclizations

The alkene geometry of the homoallylic alcohol dictates the C3 stereochemistry relative to the nucleophilic trap in Prins cyclizations (Scheme 34) [70]. For example, *E*-alkene **122** undergoes facile Prins cyclization through a chair-like transition state where the C3 substituent is in an equatorial position. Subsequent equatorial nucleophilic attack gives rise to 3,4-*trans* THP **125**. In contrast, *Z*-alkene **126** can undergo Prins cyclization leading to 3,4-*cis* product **129**; however, diaxial interactions from the axially disposed substituent often suppress this pathway in favor of an envelope transition state leading to THF **130** [71].

The reactive nature of carbocationic THP intermediates in Prins cyclizations is not limited to intermolecular nucleophilic trapping. The cyclic carbocation **133**



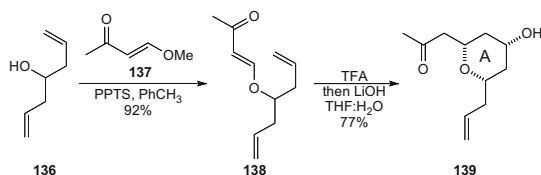
Scheme 34 Relative stereochemistry in the Prins cyclization is dictated by alkene geometry



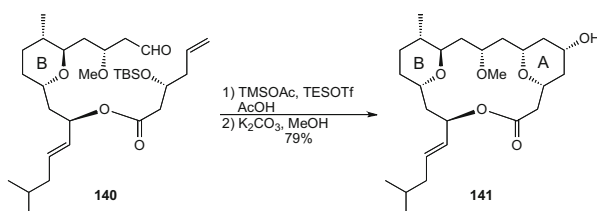
Scheme 35 Allylic 1,2-diols undergo Prins–pinacol reactions

formed when employing allylic 1,2-diols in Prins cyclization readily undergoes ring contraction through a pinacol rearrangement to give 3-acyl THF **135** (Scheme 35) [72–74]. The difficulties associated with attenuating the Prins–pinacol pathway must be considered when planning a synthetic strategy to access THP rings bearing an alcohol.

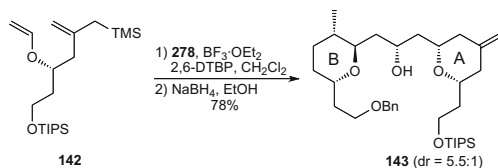
The 2,6-*cis* THP ring of leucascandrolide A has been approached by classical Prins methods as well as been a testing ground for novel extensions of this reaction. Kozmin and coworkers performed a vinylogous transesterification of alcohol **136** to afford Prins cyclization precursor **138** (Scheme 36) [75, 76]. Subsequent treatment of enol ether **138** with trifluoroacetic acid initiated a Prins cyclization, and basic ester hydrolysis provided the 2,4,6-*cis* THP alcohol **139** in 77 % as a single diastereomer.



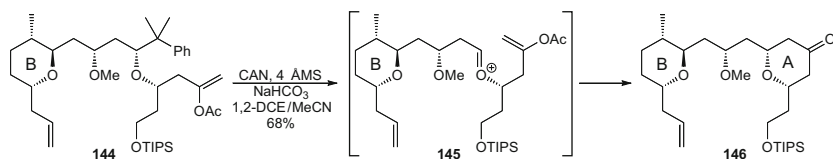
Scheme 36 Brønsted acid-mediated Prins cyclization to A ring of leucascandrolide A [75]



Scheme 37 Late-stage Prins macrocyclization toward leucascandrolide A [77]



Scheme 38 Convergent assembly of the bis-THP portion of leucascandrolide A by MAP method [78]



Scheme 39 A ring closure of leucascandrolide A by ETIC method [80]

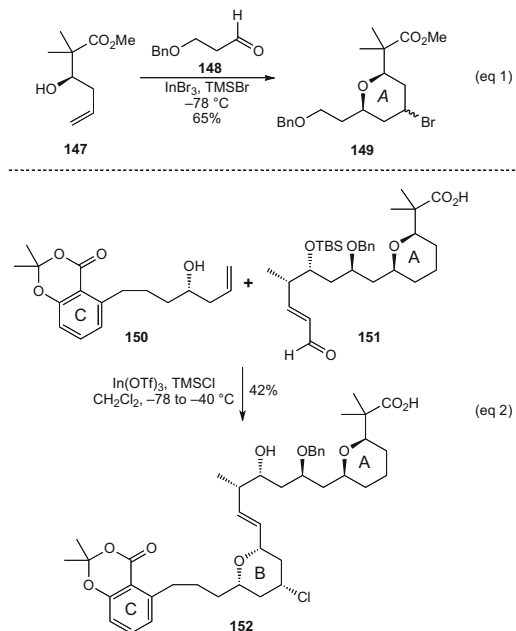
Yadav et al. utilized a Prins reaction in the context of a macrocyclization strategy toward leucascandrolide A (Scheme 37) [77]. Lewis acid activation of aldehyde **140** leads to oxocarbenium ion formation and Prins cyclization with nucleophilic acetate trapping. Direct base hydrolysis afforded macrocyclic fragment **141** as a single diastereomer in good yield (79 % over two steps).

Kopecky and Rychnovsky also targeted leucascandrolide A to demonstrate their Mukaiyama Aldol-Prins (MAP) method (Scheme 38) [78]. The MAP reaction generates an oxocarbenium intermediate from an enol ether and an aldehyde, which is capable of undergoing a Prins cyclization with the pendant allylsilane. Aldehyde **278** (from Scheme 73, Eq. 1) in the presence of enol ether **142** and boron trifluoride etherate underwent the MAP cascade without incident. The reaction mixture was treated with sodium borohydride to reduce any of the unreacted aldehyde and simplify purification. Desired alcohol **143** was then isolated in 78 % yield as a 5.5:1 mixture of diastereomers.

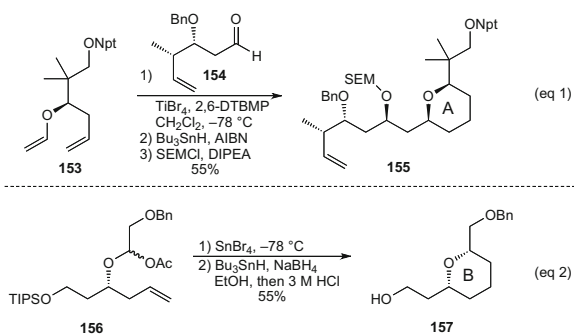
While use of Lewis or Brønsted acids is the most common way to generate the requisite oxocarbenium ion for a Prins cyclization, single electron pathways offer an attractive alternative. The mild, functional group tolerant conditions of electron transfer initiated cyclization (ETIC) method pioneered by Floreancig and coworkers were highlighted in their synthesis of leucascandrolide A [80]. Oxidative benzylic carbon–carbon bond cleavage of ether **144** was achieved by treatment with ceric ammonium nitrate to give oxocarbenium ion **145** (Scheme 39). Subsequent attack of the enol acetate through a chair-like transition state led to 2,6-tetrahydropyran-4-one **146** (68 % yield as a single diastereomer).

Indium Lewis acids have garnered attention due to their mild reactivity and air and water stability. Both Li et al. and Chan and Loh have shown that In(III) complexes are suitable Lewis acids for Prins cyclizations [81, 82]. These reports prompted Loh and coworkers to embark on a synthesis of (+)-SCH 351488 that utilized this strategy (Scheme 40) [83]. Condensation of homoallylic alcohol **147** and aldehyde **148** in the presence of indium tribromide and TMSBr gave 4-bromo THP **149** in 65 % overall yield as an inconsequential mixture of diastereomers (2,4-*cis*/2,4-*trans* = 75:25). Complete retention of the homoallylic alcohol stereochemistry is responsible for the key 2,6-*cis* relationship in the product. Initial attempts to apply these same conditions to the B ring resulted in acetonide deprotection and no THP formation. Subsequent optimization revealed that indium triflate and TMSCl were competent additives to effect cyclization. Careful temperature control was required to suppress an undesired Prins side reaction. The combination of homoallylic alcohol **150** and aldehyde **151** in the presence of the appropriate Lewis acids at $-78\text{ }^{\circ}\text{C}$, followed by warming to $-40\text{ }^{\circ}\text{C}$ for 4 h, led to the desired monomer precursor **152** in 42 % yield.

Rychnovsky et al. used their MAP strategy to construct the A ring of (+)-SCH 351488, while the B ring was constructed using a reductive acetylation/Prins cyclization protocol (Scheme 41) [84]. Use of enol ether **153** and aldehyde **154** in the presence of titanium tetrabromide afforded the ring-closed product with the appended side chain. The resulting bromide was reduced under radical conditions, and SEM protection of the alcohol gave advanced alkene **155** in 55 % yield over three steps. The B ring was constructed using α -acetoxy ether **156**, derived from reductive acetylation of the corresponding ester, as a Prins precursor. Treatment of **156** with tin tetrabromide led to THP formation. Reduction of the bromide and acidic removal of the silyl moiety afforded 2,6-*cis* THP alcohol **157** in 55 % yield over two steps. These examples demonstrate the utility of masked oxocarbenium ions (aldehyde equivalents) in expanding the scope of this method.

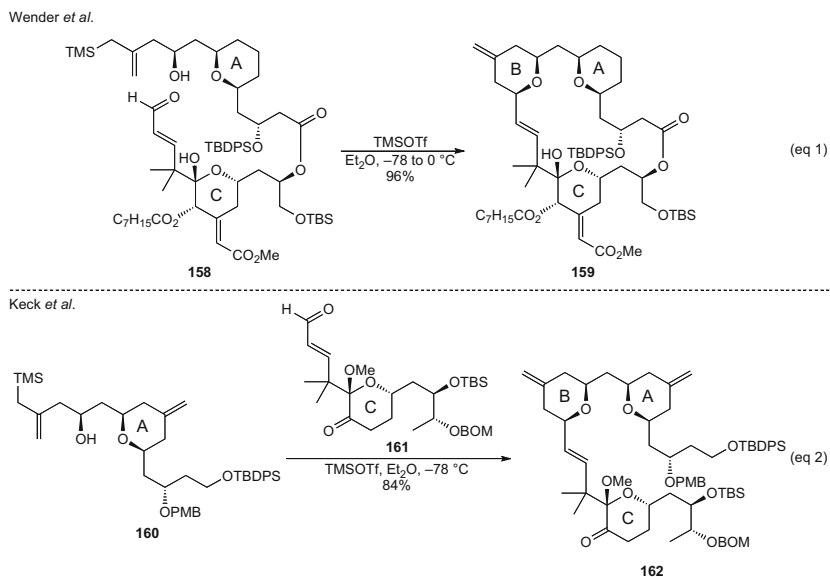


Scheme 40 Indium(III)-promoted Prins cyclization in the progress toward (+)-SCH 351488 [83]

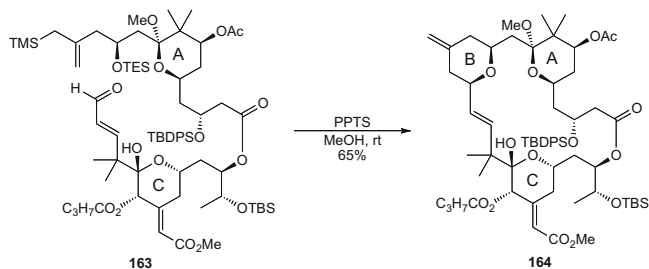


Scheme 41 MAP and Prins approaches to key intermediates for (+)-SCH 351488 [84]

The synthesis of bryostatins and related congeners contains some of the most complex examples of Prins cyclizations in natural products synthesis. Simultaneous reports by both Wender and coworkers and Keck et al. illustrate the power and tolerance of Prins cyclization on complex bryostatin analogs (Scheme 42)



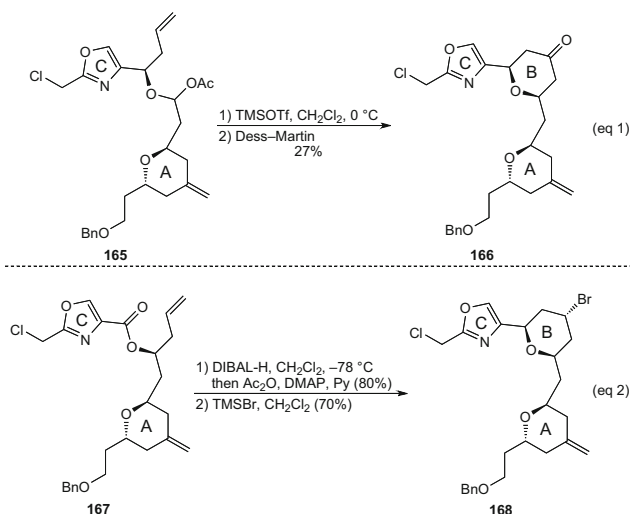
Scheme 42 B ring assembly of bryostatin analogs in intra- and intermolecular contexts [85, 86]



Scheme 43 Highly functionalized Prins macrocyclization en route to bryostatin 9 [87]

[85, 86]. Wender *et al.* implemented a Prins reaction in the context of a late-stage macrocyclization event. Treatment of allylsilane aldehyde **158** with TMSOTf gave excellent conversion to 20-membered macrocycle **159** (96 % yield). Keck *et al.* also disclosed a related intermolecular strategy incorporating an allylsilane and an enal. In the presence of TMSOTf, allylsilane **160** and enal **161** led to macrocyclic precursor **162** in an impressive 84 % yield. The highly functionalized substrates used in these examples underscore the mildness of the reaction conditions.

A subsequent report by Wender and Schrier implemented a similar late-stage macrocyclization in the synthesis of bryostatin 9 (Scheme 43) [87]. The Lewis acid, TMSOTf, was abandoned in favor of pyridinium *p*-toluenesulfonate (PPTS) in order to mitigate side reactions due to the ketal functionality in the A ring. As a result, treatment of allylsilane aldehyde **163** with PPTS in MeOH unveiled the



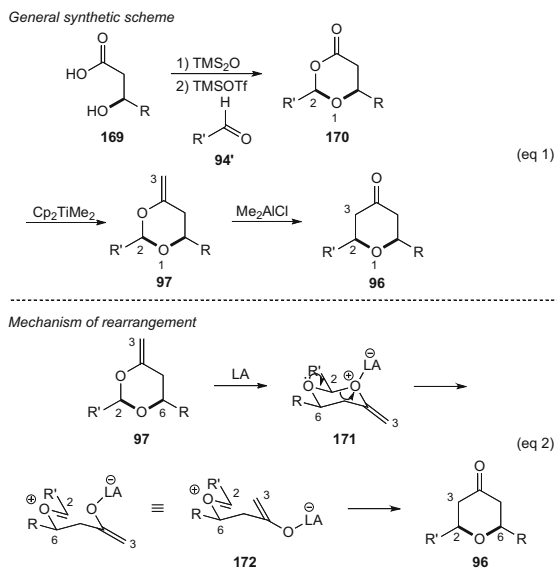
Scheme 44 Reductive acetylation approaches to the bis-THP fragment of phorboxazole B [88]

TES-protected alcohol, which underwent Prins cyclization to form the B ring in 20-membered macrocycle **164** in 65 % yield. This advanced intermediate was carried forward to bryostatin 9 in four synthetic steps. These convergent strategies represent concise approaches to the bryostatin family of natural products and highlight the utility of Prins cyclizations in complex settings.

The flexible nature of a reductive acetylation/Prins cyclization protocol was demonstrated by Rychnovsky et al. in the synthesis of the bis-THP fragment of phorboxazole B (Scheme 44) [88]. The initial strategy of using α -acetoxy ether **165** as a Prins precursor proved problematic due to unwanted reactivity from the oxazole moiety translating to a 27 % yield of 2,6-*cis*-4-one THP **166**. Switching the relative location of the α -acetoxy and homoallylic moieties attenuated the unwanted pathway, a strategy that required minimal functionalization of advanced intermediates. The second-generation Prins precursor **167** underwent facile cyclization to give 4-bromo THP **168** in 70 % yield.

3.2 Petasis–Ferrier Union/Rearrangement

Synthesis of Petasis–Ferrier union/rearrangement substrates usually involves the condensation of bis-silylated β -hydroxy acid **169** and aldehyde **94'** to afford dioxanone **170** (Scheme 45, Eq. 1) [89, 90]. Carbonyl olefination (typically using Cp₂TiMe₂) followed by treatment with a Lewis acid (often alkyl aluminum

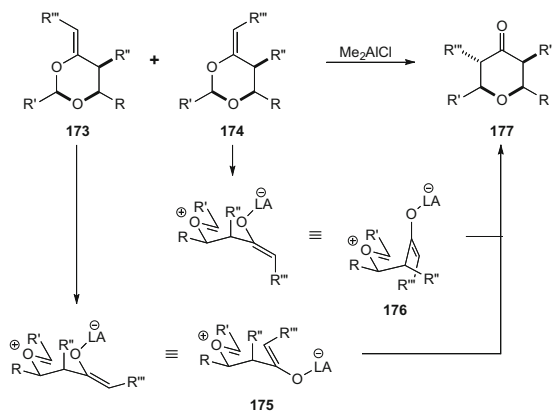


Scheme 45 Synthesis and mechanism of the Petasis–Ferrier union/rearrangement from β -hydroxy acids

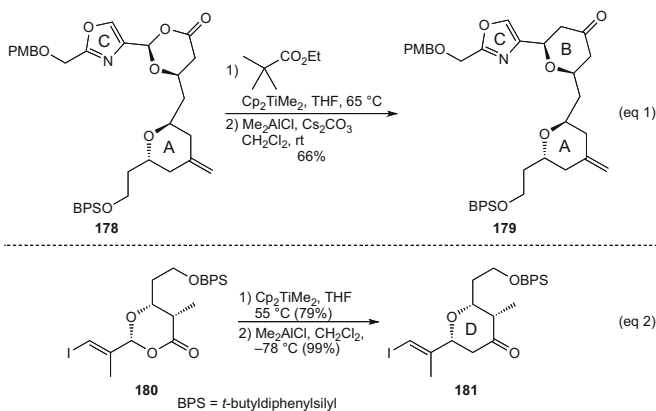
reagents) gives either 2,6-*cis*-tetrahydropyran-4-ones **96** or 2,6-*cis*-tetrahydropyran-4-ols depending on the Lewis acid used. As in both Prins cyclizations and Panek annulations, this 2,3 disconnection relies on Lewis acid-mediated oxocarbenium ion formation. In the Petasis–Ferrier reaction, the Lewis basic oxygen (attached to C4) coordinates to the Lewis acid to open the acetal, simultaneously revealing an oxocarbenium ion and an enolate (e.g., **172**). Upon bond rotation, enolate attack onto the oxocarbenium ion furnishes THP **96** (Scheme 45, Eq. 2). The use of *i*-Bu₃Al leads to reduction to the alcohol, whereas Me₂AlCl affords the ketone. One tactical advantage is that the Petasis–Ferrier strategy allows for the construction of highly substituted THPs (i.e., 2,3,5,6-tetrasubstituted) in a predictive manner.

When trisubstituted alkenes are present in the substrate, both *E*- and *Z*-alkenes converge to the same major diastereomer (Scheme 46). This observation is rationalized as follows; upon bond rotation, *Z*-enolate **175** proceeds through a chair-like transition state that places the alkene substituent in an equatorial position. (*E*)-Enolate **176** must adopt a boat-like transition state in order to reduce diaxial interactions. Both transition states lead to a *trans* relationship between the C2 and C3 substituents in product **177**.

The Petasis–Ferrier method to construct 2,6-*cis*-4-one THP rings has been extensively developed and implemented by Smith and coworkers en route to a number of natural products [90]. This strategy has proven especially useful in the preparation of highly substituted THP rings present in (+)-phorbaxazole B (the B



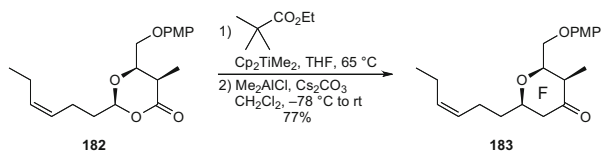
Scheme 46 Convergent Petasis–Ferrier reaction with trisubstituted alkenes



Scheme 47 Petasis–Ferrier approaches to the B and D rings of phorbaxazole A [91]

and D rings) and (+)-spongistatin 2 (the F ring). The resulting ketone moiety on the THP ring allows for subsequent functionalization by standard enolate chemistries.

Smith and coworkers envisaged both the B and D rings of (+)-phorbaxazole A arising from Petasis–Ferrier union/rearrangements (Scheme 47) [91]. The olefination of dioxanone **178** proceeds in the presence of dimethyltitanocene (Petasis reagent). Ethyl pivalate acts as a slow in situ scavenger to mitigate any side reactivity from Petasis reagent. The resulting enol acetal was then treated with dimethylaluminum chloride to afford rearranged 2,6-*cis* THP product **179**. The use of cesium carbonate was crucial for suppressing cleavage of the PMB group and allowed for construction of the B ring product in 66 % yield over two steps as a single diastereomer. A similar olefination union/rearrangement strategy was brought to bear on dioxanone **180**. Olefination proceeded in 79 % and the



Scheme 48 Petasis–Ferrier union/rearrangement to F ring fragment of spongistatin 1 [36, 92]

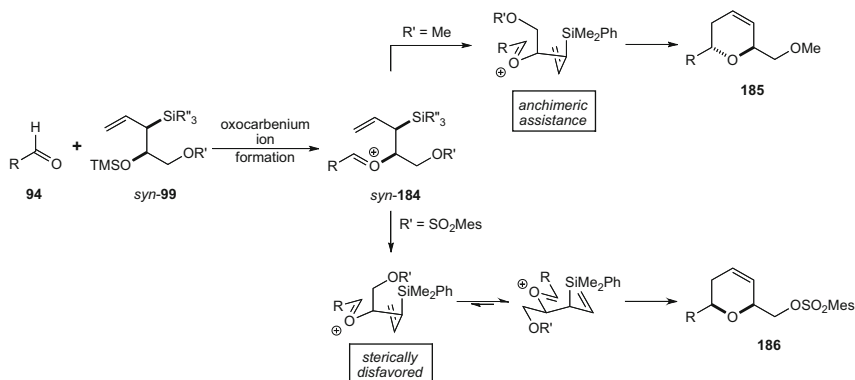
rearrangement occurred in excellent yield (99 %) to afford ketone **181**. This product was further elaborated to the 2,3,5,6-tetrasubstituted THP by substrate-controlled stereoselective lithium enolate alkylation with methyl iodide to set the 3,5-*trans* relationship.

The highly substituted F ring of (+)-spongistatin 1 was also constructed using a Petasis–Ferrier union/rearrangement strategy by Smith and coworkers (Scheme 48) [36, 92, 93]. Using the conditions developed for the B ring synthesis in (+)-phorboxazole B (ethyl pivalate and cesium carbonate as additives), dioxanone **182** underwent smooth conversion to desired ketone **183** in 77 % yield as a single diastereomer. In this case, the ketone was stereoselectively hydroxylated at the C5 position using Davis oxaziridine reagent.

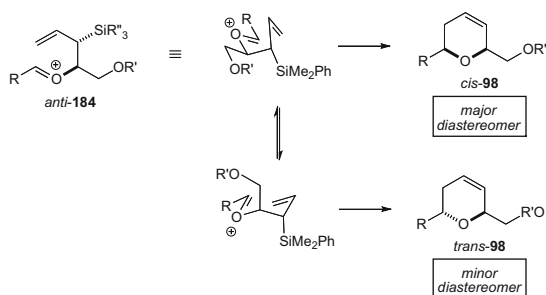
3.3 Panek [4+2]-Annulation Strategies

Panek annulation describes the Brønsted or Lewis acid-mediated formal [4+2]-cyclization of a *syn*-allylsilane and an aldehyde (e.g., *syn*-**99** and **94**) leading to a dihydropyran product (**185** or **186**) [94, 95]. The reaction is highly diastereoselective and the relative configuration (2,6-*cis* or 2,6-*trans*) depends on the R' substituent employed (Scheme 49). This method complements the Prins cyclization, RCM, and lactone/lactol functionalization strategies due the stereodivergent nature of the reaction. Panek and coworkers subsequently developed a stereoselective annulation method employing *anti*-allylsilanes to afford *cis*-DHP rings [96]. These protocols take advantage of the established methods for asymmetric synthesis of the allylsilane substrates.

The stereochemical outcome of Panek annulation when using *syn*-allylsilanes is rationalized as follows (Scheme 49). Trimethylsilyl ether *syn*-**99**, in the presence of a Brønsted or Lewis acid, condenses on aldehyde **94** to give oxocarbenium ion *syn*-**184**. When the substituent on the pendant oxygen (R') is small and electron-donating (i.e., Me), anchimeric-assisted stabilization of the methyl ether onto the oxocarbenium ion leads to a twist-boat conformation that places the silyl group pseudo-axial to provide 2,6-*trans* DHP **185**. In contrast, when R' is large and electron withdrawing (i.e., SO₂Me), destabilizing 1,2-diaxial interactions lead to a chair conformation and ultimately 2,6-*cis* DHP **186**.



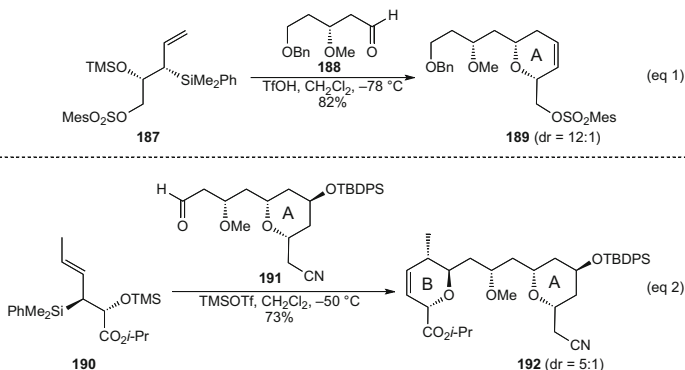
Scheme 49 Rationale for the observed stereoselectivities in Panek annulation of *syn*-allylsilanes



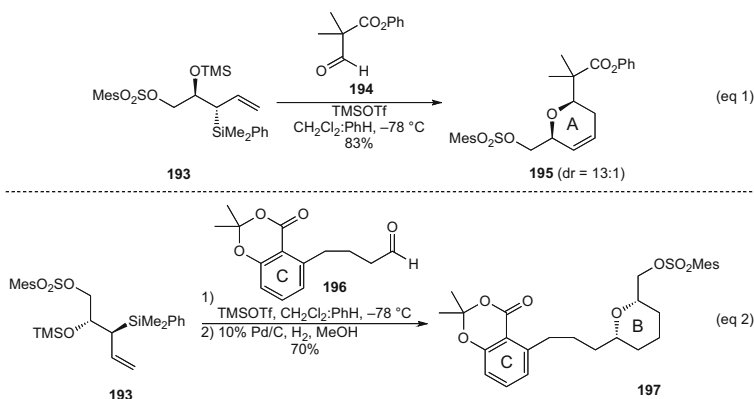
Scheme 50 Panek annulation with *anti*-allylsilanes leads to 2,6-*cis* DHPs

Sterically demanding aldehydes can give inconsistent results with *syn*-allylsilane annulation. Building upon the work of Roush and Dilley [97] concerning the annulation of *anti*- β -hydroxysilanes and aldehydes to form 2,6-*cis* DHP products, Panek developed an *anti*-allylsilane annulation protocol [96]. The rationale for selectivity, analogous to Roush's, is shown in Scheme 50. Upon formation of the oxocarbenium ion derived from an *anti*-allylsilane (e.g., *anti*-**184**), equilibrium is established between the boat and chair conformations. The favored boat conformation places only the silyl group pseudo-axial, whereas the chair conformation is destabilized by the axial disposition of both the silyl group and OR' side chain. As a result, Panek annulation with *anti*-allylsilanes affords 2,6-*cis* DHP **cis-98** as the major diastereomer, regardless of the electronic or steric effects of R'.

Su and Panek's synthesis of leucascandrolide A highlights the versatility of this annulation strategy (Scheme 51) [98]. Treatment of *syn*-allylsilane **187** with triflic acid in the presence of aldehyde **188** led to desired DHP **189** in high yield and diastereoselectivity (82 %, dr = 12:1). DHP **189** was subsequently oxymercured to install the required C4 oxygen without incident (76 % yield) and further elaborated to aldehyde **191**. The 2,6-*trans* B ring of the natural product was installed using the previously described *anti*-crotylsilane protocol [94]. Thus,



Scheme 51 [4+2]-annulation using both allyl- and crotylsilanes en route to leucascandrolide A [98]



Scheme 52 A common precursor provides the A and B rings of (+)-SCH 351448 [96]

treatment of *anti*-crotylsilane **190** with TMSOTf in the presence of aldehyde **191** afforded the desired 2,6-*trans* DHP **192** in good yield and moderate selectivity (73 %, dr = 5:1). Simple hydrogenation with Pd/C proceeded in high yield (89 %) to provide the B ring of leucascandrolide A.

Zhu and Panek utilized the *anti*-allylsilane annulation protocol to construct both the A and B rings of (+)-SCH 351448 (Scheme 52) [96]. The 2,6-*cis* configuration of both rings in the natural product dictated that sulfonate allylsilane **193** be employed as the nucleophile. Treatment of hindered aldehyde **194** and silane **193** with TMSOTf afforded 2,6-*cis* DHP **195** in 83 % yield with a dr of 13:1. This example is particularly remarkable given the steric demand of the neopentyl electrophile. Subsequent use of silane **193** with aliphatic aldehyde **196** under identical conditions, followed by reduction of the resultant 2,6-*cis* DHP, led to the desired 2,6-*cis* THP **197** in good yield (70 % over two steps) as a single diastereomer. The use of the same silane to construct both rings allowed for a highly convergent route to this macrodiolide.

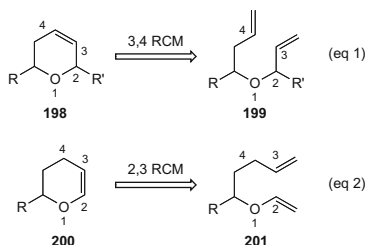
3.4 Summary

C2–C3 Disconnections remain attractive retrosynthetic strategies for the construction of THP rings. Prins cyclization protocols are the predominate method for such disconnections in the context of natural product synthesis. The wide utility and scope of this transformation must be balanced by careful selection of substrates, since a variety of side reactions or loss of stereochemical information is possible (*vide supra*). This method has proved extremely reliable for the installation of 2,6-*cis* THP rings. The related Petasis–Ferrier method also provides access to 2,6-*cis* THP rings, with the added advantages of increased THP substitution patterns and the C4 ketone as a functional handle. Panek annulation allows rapid access to either 2,6-*cis* or 2,6-*trans* DHP rings by judicious substrate selection (*R'* for allyl substrates and *syn/anti* for crotylsilanes). These DHP products can easily be converted to THP rings through simple reduction or be elaborated further by manipulation of the alkene moiety. Each of these methods has proven useful in complex natural product synthesis and will continue to remain useful for constructing THP motifs.

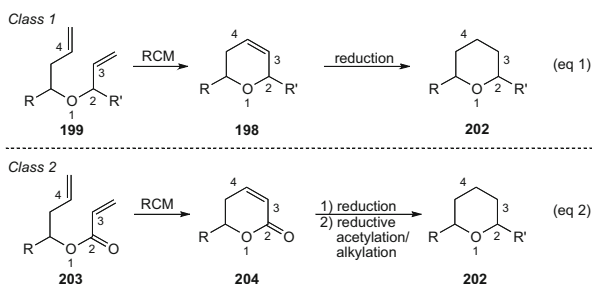
4 C3–C4 THP-Forming Processes

Ring-closing metathesis (RCM) is a powerful method for carbon–carbon bond formation that is often employed in the synthesis of complex natural products [99, 100]. Oxygen-containing heterocycles, such as tetrahydropyran (THP) rings, can be envisioned to arise from such transformations (Scheme 53) [101]. When considering such disconnections, the C3–C4 ring closure is preferable to the slower and more problematic C2–C3 metathesis [102]. RCM strategies for THP synthesis are useful due to the mild conditions, excellent functional group compatibility, retention of stereochemical information, and high yields. The main drawback is that stereochemistry must be installed prior to the reaction and further reduction is necessary to reach the THP oxidation state.

There are two main classes of RCM reactions that are important in the synthesis of THP rings (Scheme 54). Class 1 involves the ring closure of ether **199** bearing allylic and homoallylic functionalities to afford 3,4-dihydropyrans **198**, which upon simple reduction leads to THP **202**. Class 2 involves an RCM of homoallylic acrylate substrate **203** to provide unsaturated lactone **204**, which can be further functionalized to THP **202**. All of the RCM metathesis examples in this survey utilize either the first-generation Grubbs catalyst (**G-I**) or the second-generation Grubbs catalyst (**G-II**), shown in Fig. 2.



Scheme 53 Possible retrosynthetic disconnections for THP synthesis using ring-closing metathesis (RCM)



Scheme 54 RCM leading to DHPs (class 1) and RCM leading to α,β -unsaturated lactones (Class 2)

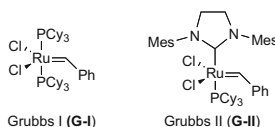
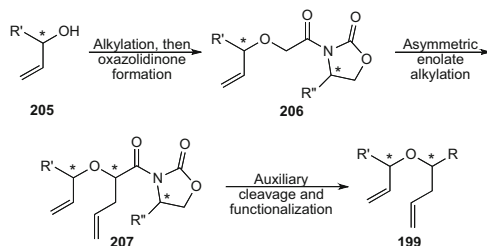


Fig. 2 Common ruthenium catalysts used for RCM

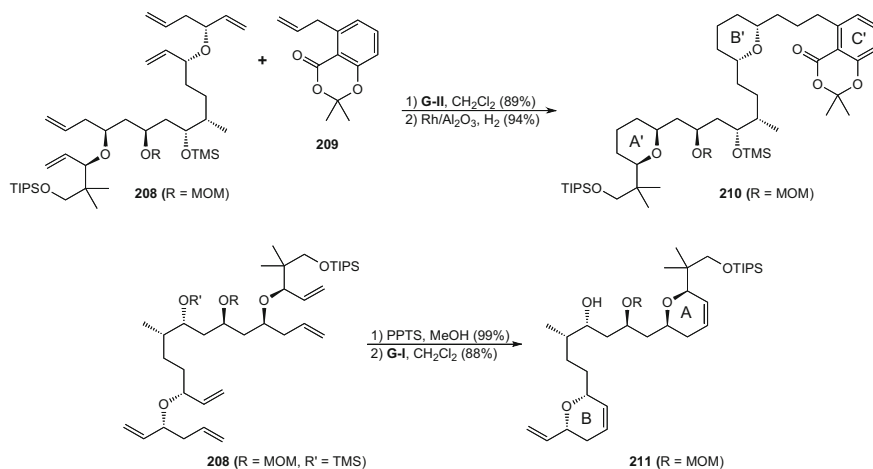
4.1 Class 1 Ring-Closing Metathesis

A general synthetic strategy for the synthesis of Class 1 RCM substrates is shown in Scheme 55. Easily accessible chiral allylic alcohols, such as **205**, can be alkylated with haloacetic acids and derivatized to the oxazolidinone **206**. The chiral auxiliary can undergo standard enolate alkylation to provide the homoallylic ether **207** in high diastereoselectivity. The major advantage to this approach is that either 2,6-*cis* or 2,6-*trans* stereochemistry can be accessed from the allylic alcohol [103]. Unfortunately, this approach requires extra synthetic operations to append and remove the stoichiometric chiral auxiliary, as well as further functionalization in order to access the RCM substrate **199**.

Perhaps the most striking example of the power of the Class 1 RCM reaction comes from Vanier and Crimmins in their enantioselective total synthesis of the



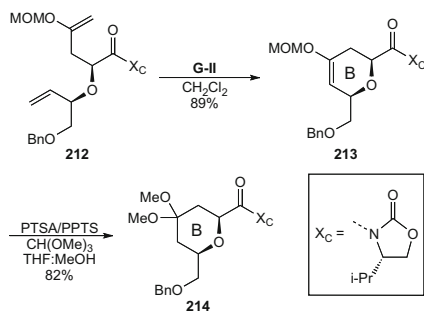
Scheme 55 General strategy for stereoselective synthesis of Class 1 RCM substrates



Scheme 56 Differentiated monomer units of (+)-SCH 351448 from tandem Class 1 RCM [104]

dimeric diolide (+)-SCH 351448 (Scheme 56) [104]. The acyclic polyene monomer precursor **208**, in the presence of catalyst **G-II** and dioxenone **209**, undergoes a tandem double ring-closing metathesis/cross-metathesis in 89 % yield. This reaction forms three carbon–carbon bonds by closing both rings and appending the required salicylic moiety. Rhodium-catalyzed hydrogenation proceeds smoothly to afford monomer **210** in 94 % yield. The same precursor **208** was also subjected to double ring-closing metathesis after acid-induced cleavage of the silyl ether. In this example, Vanier and Crimmins used catalyst **G-I** to close both dihydropyran rings, which provided alcohol **211** in 88 % yield. These differentiated monomer units **210** and **211** were then coupled in a stepwise fashion to give a remarkably convergent approach to this selective activator of LDL-R.

Another variation on the Class 1 RCM reaction employs allylic ethers bearing a pendent enol ether. Upon hydrolysis or deprotection, this strategy affords 4-tetrahydropyranones. This method is complementary to the Petasis–Ferrier rearrangement (Sect. 3.2), with the advantage that it also allows access to 2,6-*trans*-substituted tetrahydropyrans. Nakagawa and Crimmins employed this



Scheme 57 Enol ether Class 1 RCM to access the B ring of the bryostatins [105]

variation to form the B ring in their northern fragment synthesis of the bryostatins (Scheme 57) [105]. Enol ether **212** in the presence catalyst **G-II** affords the ring-closed product **213** in 89 % yield. Subsequent acid-catalyzed MOM cleavage and dimethyl acetal protection gave the 2,6-*cis* THP **214** in 82 % yield.

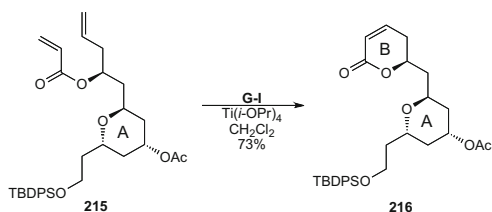
4.2 Class 2 Ring-Closing Metathesis

Class 2 RCM reactions, involving the use of homoallylic acrylate esters to form unsaturated lactones, have also found synthetic utility in the context of THP-containing natural products. These acrylate substrates are rapidly accessed from the straightforward esterification of a homoallylic alcohol. While the second class does not formally yield a THP, the lactone affords the appropriate handles for a reductive acetylation/alkylation protocol, which is a powerful method for THP functionalization (Sect. 6.2).

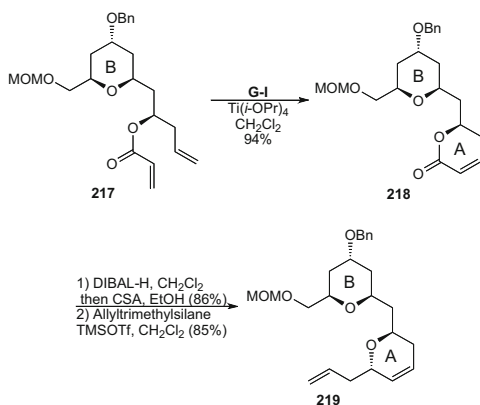
The bis-THP segment of the cytostatic phorboxazole natural products has been shown to be a portion suitable to a Class 2 RCM strategy. Greer and Donaldson demonstrated in 2000 that the B ring could be constructed from a Class 2 RCM reaction of the acrylate **215** by the action of catalyst **G-I** in the presence of titanium tetrakisopropoxide to give lactone **216** in 73 % yield (Scheme 58) [106].

Subsequent studies by Yadav and coworkers established that assembling the lower A ring of the bis-THP fragment by a Class 2 RCM reaction was also a viable strategy [107]. When the corresponding acrylate **217** was treated to the same conditions described by Greer and Donaldson, lactone **218** was formed in 94 % yield. Subsequent reduction and alkylation proceeded in good yield to provide bis-THP **219** with the required 2,6-*trans* relationship on the newly formed A ring (Scheme 59).

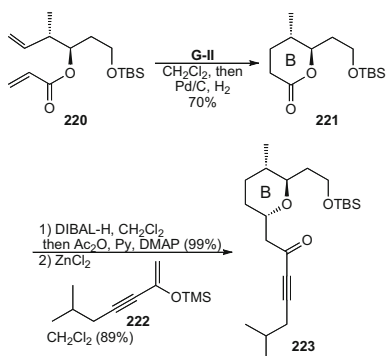
Cossy and coworkers also employed a Class 2 RCM to form the B ring in their formal total synthesis of the anticancer macrolide leucascandrolide A (Scheme 60) [108]. Using catalyst **G-II** followed by in situ reduction afforded the lactone **221**



Scheme 58 Class 2 RCM strategy to the A ring fragment of the phorbaxozoles [106]



Scheme 59 Class 2 RCM strategy to the B ring fragment of the phorbaxozoles [107]



Scheme 60 Class 2 RCM/reductive acetylation/alkylation sequence to B ring fragment of leucascandrolide A [108]

from acrylate **220** in 70 % yield. The resulting lactone **221** was then subjected to reductive acetylation and alkylated with silyl enol ether **222** in the presence of zinc chloride to afford the 2,6-*trans* THP intermediate **223**.

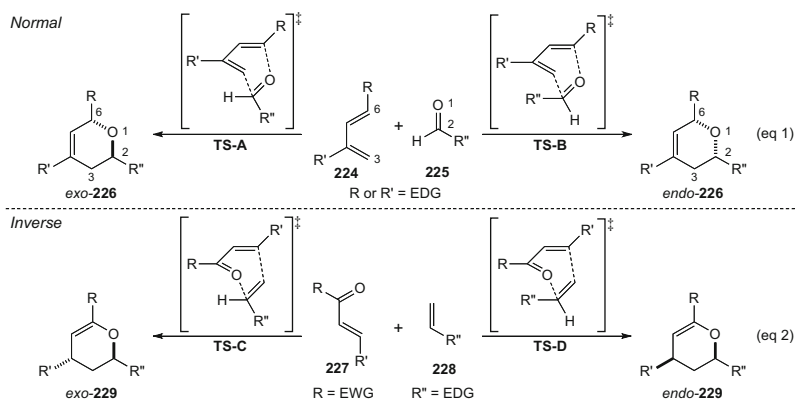
4.3 Summary

These representative examples demonstrate the versatility of RCM reactions for THP synthesis in the context of complex natural products. Both Class 1 and Class 2 substrates afford a reliable way to construct 6-membered oxygen-containing rings in high yields. The Class 1 RCM is versatile from the standpoint of having a number of ways to stereoselectively install the allylic and homoallylic moieties, whereas the strength of Class 2 RCM lies in the versatile synthetic handles afforded in the unsaturated lactone products. While neither of these reactions directly yield THP rings, the established functionalization methods certainly make RCM an attractive strategy. These methods will no doubt be a common strategy in the future.

5 O1–C6 and C2–C3 DHP-Forming Processes

The Diels–Alder (DA) reaction is a powerful method for the efficient and stereoselective formation of highly functionalized six-membered rings. The pivotal role of DA reactions in the construction of carbocyclic frameworks can be translated to the synthesis of moderately complex heterocycles [2]. The hetero-Diels–Alder (HDA) reaction generally proceeds with high regio- and diastereoselectivity (setting up to 4 contiguous stereogenic centers in a single step) and moderate to excellent yield [109]. From a retrosynthetic perspective, a THP is assembled by bond formation at O1–C6 and C2–C3 followed by reduction of the resultant alkene at C4–C5. For DHP synthesis, there are two modes of reactivity: the normal-electron demand (Scheme 61, Eq. 1) and inverse-electron demand systems (Scheme 61, Eq. 2). The normal-electron demand system uses a carbonyl compound dienophile with a conjugated diene, whereas inverse demand systems have an alkene dienophile and an α,β -unsaturated carbonyl as the diene. Cycloadduct stereochemistry is dependent on transition state geometries [110]. There are four different transition structures that arise from dienophile orientation (*endo* vs. *exo*) and diene geometry (*E*- vs. *Z*-isomers). The examples discussed herein concern only normal demand systems using a carbonyl and (*E*)-olefin dienes and can therefore be described by the transition states (i.e., **TS-A** and **TS-B**) leading to **226**.

There are two main HDA approaches to stereocontrolled THP synthesis. The first uses a chiral auxiliary to direct π -facial selectivity and generally proceeds through an *endo* transition state to give 2,6-*cis* cycloadducts. The second approach uses coordination of a chiral Lewis acid to activate the carbonyl while directing the approach of the diene to one face of the carbonyl dienophile. Several catalysts have been developed for the asymmetric HDA reaction with Jacobsen's Cr(III) complexes [111, 112] exhibiting good to excellent enantioselectivities with a variety of substrates [113].



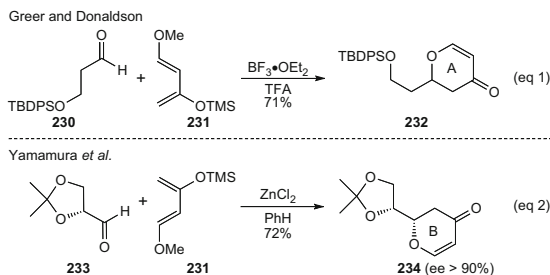
Scheme 61 Stereochemical consequences of hetero-Diels–Alder (HDA) approaches to THPs

5.1 Hetero-Diels–Alder (HDA) Reactions

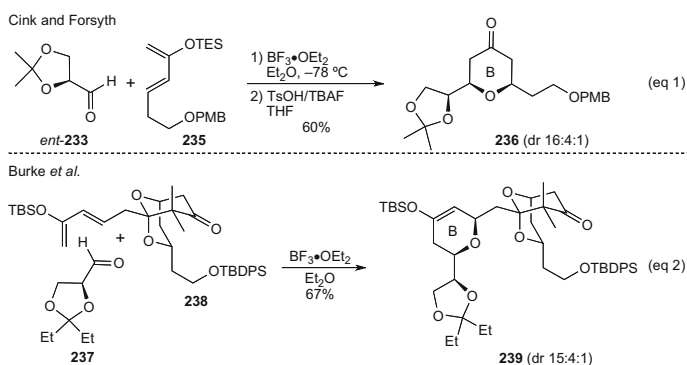
Danishefsky's diene [114] has found use in DHP synthesis but is limited by the loss of stereochemistry from formation of the enone double bond. In the absence of chirality, the Lewis acid-activated HDA reaction of **230** and **231** leads to (\pm)-dihydropyrone **232** as reported in Greer and Donaldson's synthesis of phorboxazole A (Scheme 62, Eq. 1) [106]. This particular method is useful for subsequent DHP elaboration (e.g., conjugate addition regioselective α -substitution of the enone) but fails to capitalize on the ability of the HDA reaction to install multiple stereogenic centers in a convergent, stereoselective fashion. Similarly, Yamamura et al. reported the use of enantioenriched aldehyde **233** and diene **231** provided the B ring of bryostatin 3 in good yield (72 %) and high enantioselectivity (ee > 90 %) (Scheme 62, Eq. 2) [115].

Chiral acetonides and siloxydienes allow for the synthesis of 2,6-*cis* THP rings. Cink and Forsyth reported a convergent HDA in the synthesis of phorboxazole A (Scheme 63, Eq. 1) [37]. Use of *ent*-**233** with diene **235** followed by cleavage of the resultant silyl enol ether provided the desired tetrahydropyrone **236** as the major diastereomer (dr = 16:4:1) in 60 % yield over two steps. Burke and coworkers later capitalized on this strategy in the synthesis of the bryostatin 1 B ring (Scheme 63, Eq. 2) [116]. Subjecting chiral acetonide **237** and the complex diene **238** to Lewis acidic conditions provided the 2,6-*cis* DHP **239** in 67 % yield with a dr of 15:4:1. The desired major product was easily separated and taken forward to the natural product. This complex example shows the utility and functional group compatibility of the HDA reaction.

Chiral Lewis acid-catalyzed HDA reactions have found application in the asymmetric synthesis of THP-containing natural products. Chiral chromium complexes, especially the adamantyl-Cr(III) complexes discovered by Jacobsen et al., have been applied to the use of unactivated aldehyde dienophiles with various diene partners [111]. Paterson and coworkers employed this variation in the synthesis of



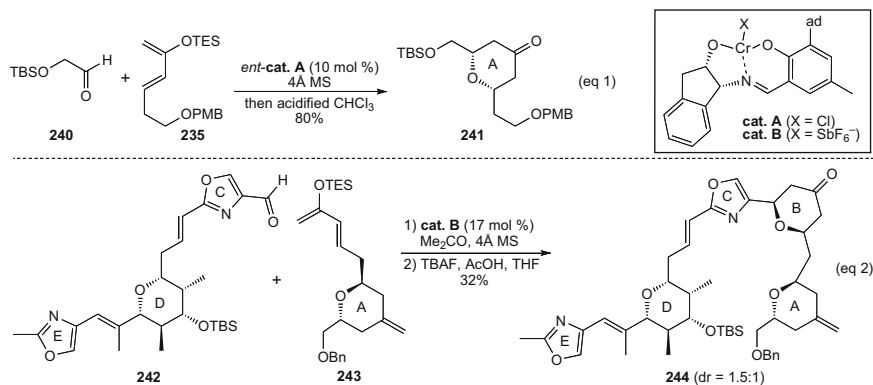
Scheme 62 Danishefsky's diene in HDA reactions toward phorbaxazole and bryostatin natural products [106, 115]



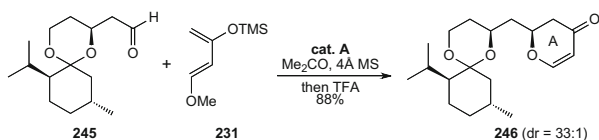
Scheme 63 Chiral acetonide dienophiles in HDA reactions toward phorbaxazole and bryostatin natural products [37, 116]

leucascandrolide A and phorbaxazole A as shown in Scheme 63. In a simple context, the use of aldehyde **240**, siloxydiene **235**, and catalytic Lewis acid *ent*-cat. **A** followed by acidic cleavage of the resultant silyl enol ether provided 2,6-*cis* THP **241** for leucascandrolide A (Scheme 64, Eq. 1) [117]. This example exhibited excellent enantio- and diastereoselectivity with concomitant high yield. One of the more challenging examples of the asymmetric catalytic HDA reactions was reported in Paterson's total synthesis of phorbaxazole A (Scheme 64, Eq. 2) [118]. In the context of a convergent route, the union of aldehyde **242** and siloxydiene **243** proceeded in moderate yield (44 %, 90 % brsm) and low diastereoselectivity (dr = 1.5:1 of *endo*-cycloadducts) to provide the B ring THP **244**.

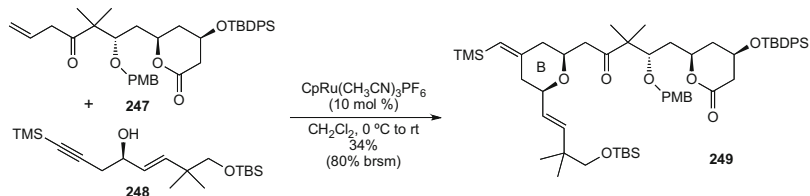
Wender *et al.* reported an interesting example that appears to exhibit a cooperative or matched-matched case for the chiral Lewis acid-catalyzed HDA of an aldehyde bearing a chiral auxiliary and Danishefsky's diene (Scheme 65) [119]. Subjecting chiral aldehyde **245** and siloxydiene **231** to Jacobsen's catalyst resulted in the formation of 2,3-DHP **246** in 88 % yield with excellent diastereoselectivity (dr = 33:1).



Scheme 64 Early- and late-stage applications of Cr(III)-catalyzed HDA reactions to leucascandrolide A and phorbaxazole A [117, 118]



Scheme 65 Highly diastereoselective Cr(III)-catalyzed HDA reaction with chiral dienophile to access A ring fragment of bryostatins [119]



Scheme 66 Ru-catalyzed tandem alkene–alkyne coupling/Michael addition en route to bryostatins [121]

While the asymmetric HDA has proven to be an effective method for the construction of DHP/THP motifs, additional methods based on a metal-mediated/metal-catalyzed coupling and cyclization strategy are burgeoning. The study of cationic ruthenium in ene-type addition of alkenes to acetylenes has been studied previously [120], and Trost et al. recently reported an alternative approach to HDA THP cycloadducts by a similar process [121]. The first step of the transformation involves addition of the Ru-alkene complex of **247** to acetylene **248** followed by reductive elimination to give an enone. The enone subsequently undergoes a conjugate addition with the pendant alcohol to afford the desired 2,6-*cis*-tetrahydropyran **249**.

The tandem Ru-catalyzed alkene–alkyne coupling/conjugate addition sequence occurred in modest yield (34 %) yet showed remarkable chemoselectivity and functional group tolerance (80 % brsm) (Scheme 66).

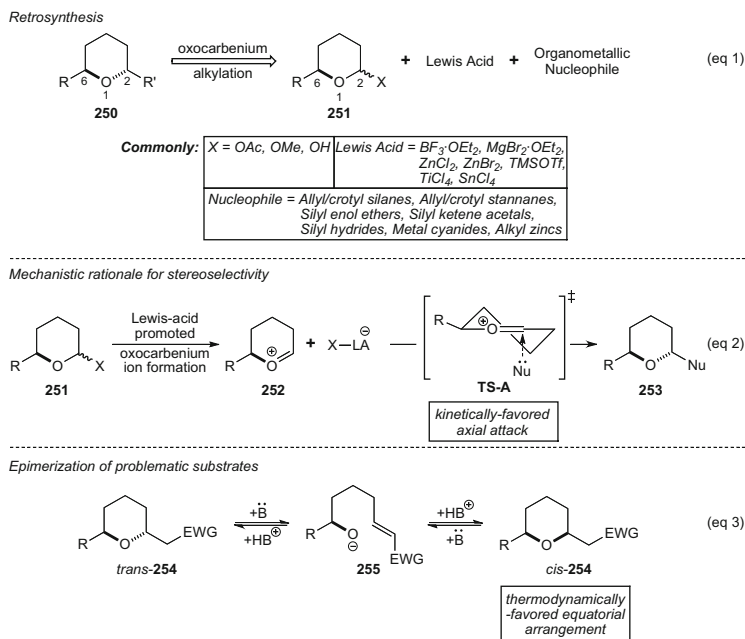
5.2 Summary

These representative examples demonstrate the usefulness of HDA reactions for THP synthesis in the context of complex natural products. Both chiral auxiliary and asymmetric catalysis methods offer a reliable way to construct 6-membered oxygen heterocycles in high yield and stereoselectivity. The chiral auxiliary approach benefits from the wide array of available chiral auxiliaries as well as a number of ways to stereoselectively install chiral moieties contained within the natural product. Removal of the auxiliary imposes additional synthetic considerations. The strength of the asymmetric catalysis tactic comes from the ability to generate chiral products from achiral substrates with high levels of stereocontrol. While these approaches produce DHP rings, there are several methods available for their transformation to highly substituted THP products making HDA an attractive method.

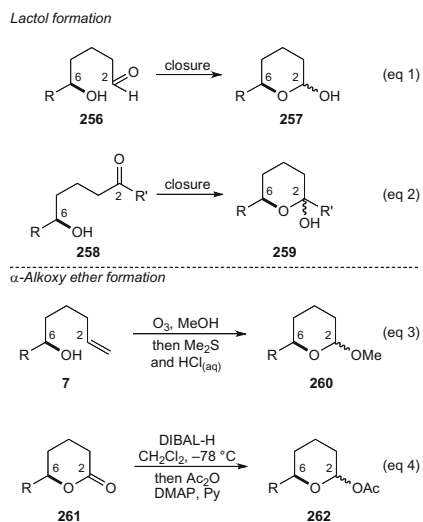
6 C2 Functionalization of Lactols and Lactones

Functionalization of lactols or lactones is a useful method for introducing substitution at the C2 position of tetrahydropyran rings [122]. Retrosynthetically, this transformation can be envisioned as arising from a Lewis acid-mediated alkylation of an oxocarbenium ion by an organometallic nucleophile (Scheme 67, Eq. 1). The stereochemical outcome of the reaction is predicted by axial attack of the nucleophile on the half-chair conformation of oxocarbenium ion **252**, to provide kinetically favored 2,6-*trans* THP **253** (Scheme 67, Eq. 2) [123]. The electronics of the newly formed side chain must be taken into account when considering such disconnections. For example, side chains bearing an electron-withdrawing group (EWG) can sufficiently lower the pK_a of the hydrogen on C2. As a result, C2 isomerization can occur through acid- or base-catalyzed mechanisms leading to the thermodynamically favored 2,6-*cis*-**254** (Scheme 67, Eq. 3) [124]. Another minor drawback is that substrate functionality must be tolerant of Lewis acids. Despite these small concerns, such lactone/lactol functionalization strategies for THP synthesis remain useful due to the number of methods to access lactols and lactones, the mild reaction conditions, predictive stereochemical outcomes, and high yields.

Lactol **257** (or **259**) is commonly accessed by the spontaneous closure of alcohol **256** (or **258**) on an aldehyde (or ketone) six atoms away (Scheme 68, Eq. 1–2) [125]. Note that lactols derived from ketones can lead to a 2,6-*cis* arrangement for R and R' using a hydride nucleophile in the presence of a Lewis acid. α -Alkoxy ether **260** is typically synthesized by ozonolysis of the 5-alken-1-ol **7** followed by treatment with dimethyl sulfide and aqueous acid (Scheme 68, Eq. 3). Lactone



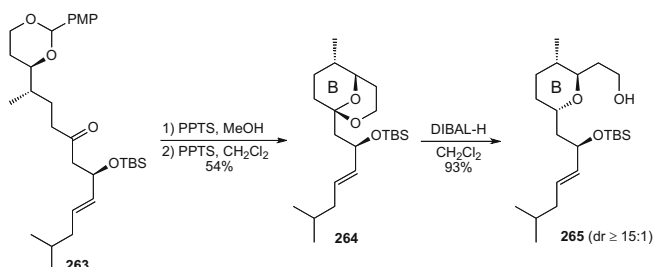
Scheme 67 Reductive C2 functionalization: mechanistic and structural implications



Scheme 68 Common methods for the synthesis of reductive C2 functionalization precursors

reduction with DIBAL-H at low temperatures and subsequent trapping with acetic anhydride leads to the synthetically useful α -acetoxy ether **262** (Scheme 68, Eq. 4) [126, 127]. Of the available methods, the relative stability of the α -acetoxy ether intermediate and the variety of available methods for lactone formation make the reductive acetylation strategy preferable.

6.1 Lactol Reduction

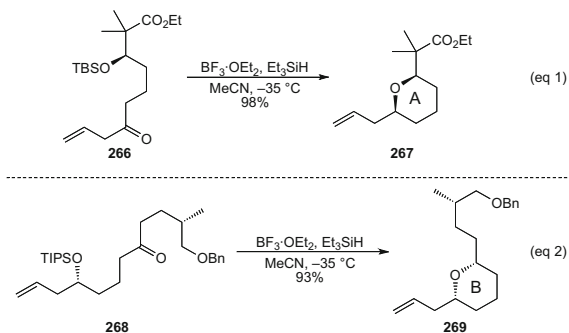


Scheme 69 Chelate-controlled reduction to the B ring fragment of leucascandrolide A [23]

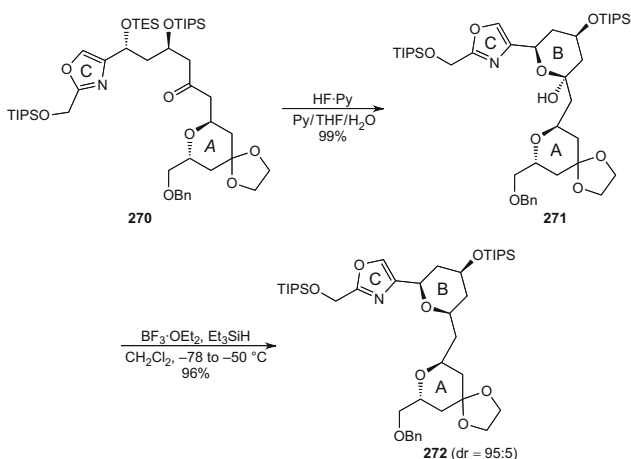
An interesting example of mixed ketal reduction can be found in Crimmins and Siliphaivanh's synthesis of leucascandrolide A (Scheme 69) [23]. The 1,3-protected diol **263** is deprotected in protic solvent in the presence of acid, followed by the acid-catalyzed formation of mixed ketal **264**. Bridged bicyclic ketals lead to either 2,6-*cis* or 2,6-*trans* arrangements depending on the reagents employed (Lewis acid and triethylsilane, or DIBAL-H, respectively). Chelate-controlled hydride delivery with DIBAL-H affords the desired 2,6-*trans* THP **265** in high yield and good diastereoselectivity (93 %, dr \geq 15:1).

The two 2,6-*cis* THP rings present in the monomeric unit of the dimeric diolide (+)-SCH 351448 offered Backes and Koert an opportunity to exploit stereoselective lactol reduction (Scheme 70) [128]. Lewis acid activation of ketones **266** and **268** with $\text{BF}_3 \cdot \text{OEt}_2$, followed by closure with the pendant silyl ether, provides lactol intermediates. Subsequent oxocarbenium ion formation and hydride delivery by triethylsilane afforded the 2,6-*cis* THP rings **267** and **269** in high yields (98 % and 93 %, respectively) as single diastereomers.

Evans' synthesis of (+)-phorboxazole B demonstrates the functional group tolerance of lactol reduction in a complex setting (Scheme 71) [129]. Selective deprotection of the triethylsilyl ether **270** provides the lactol **271**, as a 92:8 mixture of closed/open forms that was carried on directly. Subsequent reduction of lactol **271** using the standard conditions afforded the bis-THP fragment **272** in good yield and high selectivity (96 %, dr = 95:5).



Scheme 70 Condensation/hydride reduction sequence to key fragments of (+)-SCH 351448 [128]

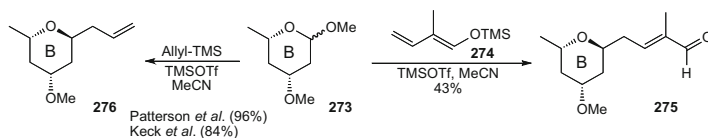


Scheme 71 Lactol formation/reduction protocol to access bis-THP fragment of phorbaxazole B [129]

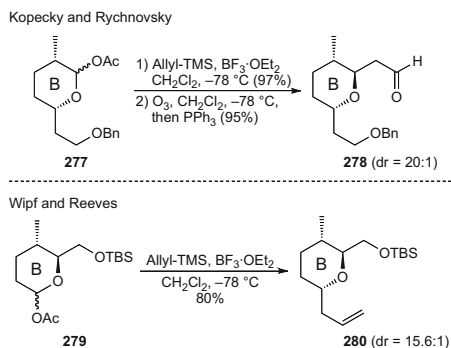
6.2 Lactone Reduction and Reductive Acetylation

Both Paterson et al. and Keck and Lundquist have used the α -methoxy ether **273** derived from ozonolysis of the requisite 5-alken-1-ol to functionalize the B ring of the swinholid family of natural products (Scheme 72) [20, 130]. Initial attempts by Paterson et al. to introduce a complex side chain using siloxydiene **274** were plagued by low yields. However, treatment of α -methoxy ether **273** with allyltrimethylsilane in the presence of a catalytic amount of trimethylsilyl triflate (10 mol %) afforded allyl THP **276** in good yields (96 % and 84 %, respectively) as a single diastereomer.

Perhaps no other natural product has highlighted the synthetic utility of a reductive acetylation/alkylation strategy for constructing 2,6-*trans* THP rings as



Scheme 72 Alkylation of α -methoxy ether to access the B ring of the swinholides [20, 130]

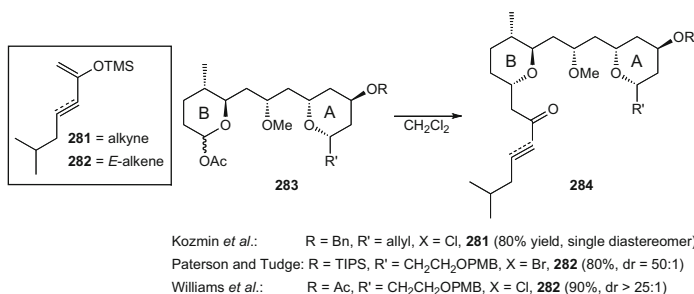


Scheme 73 Alkylation of α -acetoxy ethers to functionalize either side of the B ring fragment of leucascandrolide A [78, 79]

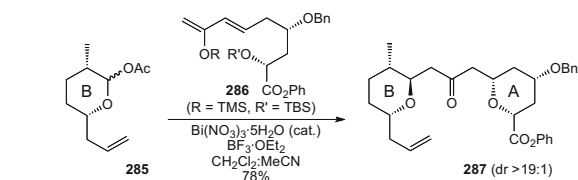
much as leucascandrolide A. The B ring of this cytotoxic macrolide has been assembled using variations of this method no less than seven times. Kopecky and Rychnovsky were the first to demonstrate the alkylation of α -acetoxy ether **277** with allyltrimethylsilane in the presence of boron trifluoride etherate in high yield and diastereoselectivity (97 %, dr \geq 20:1) [78]. The resulting alkene was cleaved by ozonolysis to furnish aldehyde **278**, which was necessary for coupling the two THP fragments together (Scheme 73, Eq. 1; for coupling, see Scheme 38). Wipf and Reeves later utilized this strategy for alkylating the opposite side of the B ring to provide allyl fragment **280** (80 %, dr = 15.6:1), as shown in Scheme 73, Eq. 2 [79].

Reductive acetylation/alkylation has also provided access to advanced bis-THP intermediates of the type **284** in several reported pursuits of leucascandrolide A (Scheme 74) [76, 117, 131]. These complex examples highlight the remarkable functional group tolerance of this reaction type. The elaborate α -acetoxy ethers **283** demonstrate that a number of protecting groups (benzyl, silyl derivatives, and esters) survive the reaction conditions. Unsaturated silyl enol ethers (i.e., **281** and **282**) are effective nucleophiles and provide advanced intermediates like **284** in excellent yields and diastereoselectivities (80–90 %, dr \geq 25:1 for all cases). A similar strategy, coupled with ring-closing metathesis, was also used by Cossy and coworkers for this natural product (Scheme 60) [108].

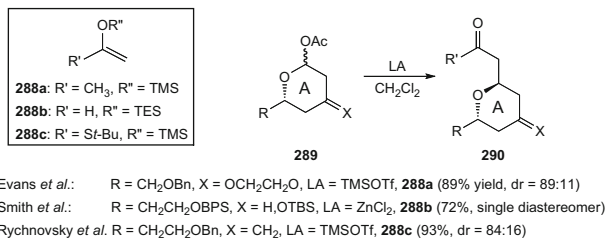
The rapid and highly convergent assembly of the bis-THP fragment **287** in Evans and Andrews' synthesis of leucascandrolide A relied on a reductive acetylation/alkylation strategy (Scheme 75) [132]. Treatment of α -acetoxy ether **285** with



Scheme 74 Complex alkylations of α -acetoxy ethers employing silyl enol ether nucleophiles in the context of leucascandrolide A [76, 117, 131]



Scheme 75 Convergent strategy to bis-THP fragment of leucascandrolide A through α -acetoxy ether alkylation/conjugate addition sequence [132]



Scheme 76 A ring fragment functionalization of phorbioxazoles [88, 91, 129]

boron trifluoride etherate in the presence of siloxydiene **286** at -40 °C leads to an enone intermediate, which upon warming to 0 °C with a catalytic amount of bismuth(III) nitrate pentahydrate closes in an oxa-Michael fashion to give bis-THP **287** in high yield and diastereoselectivity (78 %, dr \geq 19:1). The use of bismuth as a Brønsted acid was important not only for the promotion of the conjugate addition but also to reduce epimerization of the B ring to the thermodynamically favored 2,6-*cis* configuration (*vide supra*).

The A ring of the cytotoxic macrolide phorbioxazole family of natural products has also proven to be accessible through a number of reductive acetylation/alkylation protocols (Scheme 76) [88, 91, 129]. These examples employ silyl enol ethers and thioacetate nucleophiles **288a–288c** and α -acetoxy ether derivatives **289** to access

THP derivatives **290** that contain the pendant oxygen functionality required to construct the B ring contained in the natural products. In all cases, the products are obtained in high yields and good diastereoselectivities (72–93 %, dr = 84:16 to dr = 100:0).

6.3 Summary

Lactols and α -alkoxy ethers have proven to be useful intermediates for the synthesis of THP-containing natural products. These representative examples demonstrate that while most commonly used to access 2,6-*trans* motifs, careful substrate design and judicious choice of nucleophile also allows for the synthesis of 2,6-*cis* THP rings. The mild conditions for these functional group tolerant transformations allow for rapid construction of complex fragments in good yield and with high levels of predictable diastereoselectivity. In addition, the variety of methods for synthesizing lactols and lactones increases the overall utility of such approaches.

7 Conclusion

The examples described herein demonstrate the variety, efficiency, reliability, and stereofidelity of THP-forming processes in complex natural product synthesis over the last few decades. The seemingly straightforward construction of tetrahydropyrans through O1–C2 bond formation includes methods ranging from the long-standing S_N2/S_N1 and oxa-Michael-based cyclizations to the more recent transition metal-catalyzed reactions. The recent developments in epoxide-opening cyclizations allow for selective formation of THPs over the more favored THFs as well as the ability to construct fused tetrahydropyran units simultaneously by a cascade sequence. The less obvious C2–C3 bond-forming processes include the venerable Prins cyclization, Petasis–Ferrier rearrangement, and Panek annulation strategies. The reliability of the Prins in the formation of 2,6-*cis* THP rings and the ability to trap various nucleophiles at the C4 position have made this transformation a cornerstone in THP synthesis. Similarly, the Petasis–Ferrier method provides access to 2,6-*cis*-tetrahydropyran-4-ones, with the added advantages of increased THP substitution patterns and the C4 ketone for further functionalization. Panek annulation provides either 2,6-*cis* or 2,6-*trans* DHP rings that can be rapidly converted to highly functionalized THPs but require careful substrate selection. Only upon the advent of alkene metathesis was the C3–C4 disconnection made practical. The RCM strategy benefits from the variety of asymmetric methods to install allylic and homoallylic alcohols (Class 1) and/or the synthetic handles afforded in the unsaturated lactone products for further functionalization (Class 2). The improvement in asymmetric hetero-Diels–Alder reactions, due to the development of chiral organocatalytic and Lewis acid-catalyzed procedures, has provided

functionalized THP scaffolds with high regio-, diastereo-, and enantioselectivity (up to four contiguous chiral centers in a single step). The fabrication of THPs by lactone/lactol functionalization remains an attractive method due to the ease of access to lactols and lactones, mild reaction conditions, and the ability to construct 2,6-*trans* THPs. The scope of such ring-forming strategies has been established by the total synthesis of a large number of structurally complex natural products. Furthermore, emerging concepts and methods will continue to facilitate developments in this field.

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