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Phosphate Tethers in Natural Product Synthesis

Paul R. Hanson, Susanthi Jayasinghe, Soma Maitra, and Jana L. Markley

Abstract Recent advances in phosphate tether-mediated natural product synthesis are reviewed. Synthetic approaches toward dolabelide C, (−)-salicylihalimide A, (−)-tetrahydrolipstatin, and (+)-strictifolione are included. In addition, current efforts in method development are briefly reviewed, including a detailed study on the effect of stereochemical complexity on the phosphate-mediated, diastereoselective ring-closing metathesis reaction and recent advances in multi-reaction, one-pot sequential processes mediated by the phosphate tether. Overall, this review seeks to highlight the utility of phosphate triesters to serve as multifunctional tethers with protecting group and latent leaving group characteristics and the ability to orchestrate multiple, orthogonal reaction pathways to allow for the facile synthesis of complex, bioactive small molecules and their analogs.

Keywords Chemical methods · Chemoselective transformations · Cross metathesis (CM) · Natural product synthesis · One-pot · Phosphate · Phosphorus-based tether systems · Ring-closing metathesis (RCM) · Sequential processes · Tether methodologies

Contents

all co-authors have equal contribution

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Abbreviations

2,2-DMP	Dimethoxypropane
9-BBN	9-Borabicyclo(3.3.1)nonane
BOPCl	Bis(2-oxo-3-oxazolidinyl)phosphonic chloride
CH_2Cl_2	Dichloromethane
CM	Cross metathesis
DCE	1,2-Dichloroethane
DDQ	2,3-Dichloro-5,6-dicyano-1,4-benzoquinone
DIAD	Diisopropyl azodicarboxylate
DMAP	4-Dimethylaminopyridine
DMSO	Dimethyl sulfoxide
Et_3N	Triethylamine
G-I	Grubbs first generation catalyst $[(PCy_3)_2(Cl)_2Ru{=}CHPh]$
G-II	Grubbs second generation catalyst $[(IMesH_2)(PCy_3)(Cl)_2Ru{=}CHPh]$
HG-II	Hoveyda–Grubbs second generation catalyst
$LiAlH_4$	Lithium aluminum hydride
LiDBB	Lithium di-*tert*-butyl biphenylide
LLS	Longest linear sequence
Me_2SO_4	Dimethylsulfate
MeCN	Acetonitrile
MES	Mesityl
MOM	Methoxymethyl
NaHMDS	Sodium bis(trimethylsilyl)amide
NMO	*N*-Methylmorpholine-*N*-oxide
o-NBSH	*o*-Nitrobenzene sulfonyl hydrazine
PMB	*para*-Methoxybenzyl
PPTS	Pyridinium *p*-toluenesulfonate
RCM	Ring-closing metathesis
TBAF	Tetra-*n*-butylammonium fluoride
TBSCl	*tert*-Butyldimethylsilyl chloride
TES	Triethylsilyl
TIPS-	Triisopropylsilyl-
TMS-diazomethane	Trimethylsilyldiazomethane

1 Introduction

Streamlining of natural product syntheses through the development of new step-, atom-, and redox-economical methods stands at the forefront of modern-day synthesis and drug discovery [1–3]. In this regard, some of the most efficient synthetic methods are those which couple a wide array of simple, as well as complex, chemical fragments – preferably in an iterative and manipulatable fashion – to rapidly access key portions of a wide array of bioactive small molecules. While silicon-based tethers are the most prevalent systems reported in the literature [4–8], the vast majority of applications couple fragments occupying only two of the four available valencies on the silicon atom, leaving the remaining two vacancies to ancillary groups. The synthetic utility of multivalent phosphorus, in particular the ability of phosphate triesters to serve as protecting groups, functional handles for transition metal-mediated transformations, and latent leaving groups (Fig. 1) [9–13], provides a compelling argument in favor of the use of phosphate triesters as multifunctional tripodal tethers in the synthesis of bioactive small molecules.

Towards this goal, in 2005, Hanson and coworkers published the first use of phosphate triesters as tripodal tethers for the synthesis of 1,3-skipped polyol-containing bioactive small molecules (Scheme 1) [14]. Inspired by the work of Burke and coworkers with ketal tethers [15, 16], the authors envisioned that the tripodal coupling of a chiral, non-racemic 1,3-*anti*-dienediol [as shown (*S*,*S*)-**1.1**] with phosphorus oxychloride and allyl alkoxide could provide a phosphate triester [as shown (*S*,*S*)-**1.2**] in which three-dimensional conformation could bias the reactivity of each olefin in the once C_2-symmetric dienediol. Symmetry breaking ring-closing metathesis, promoted by $(IMesH_2)(PCy_3)(Cl)_2Ru{=}CHPh$ (Grubbs second generation catalyst, **G-II**) [17] or Hoveyda-Grubbs second generation catalyst (**HG-II**) [18–20], yields the corresponding bicyclo[4.3.1]phosphate (**1.3**) as a single diastereomer. The synthesis of **1.3** was later simplified to a three-step process, whereby dichlorodione **1.4** undergoes enantioselective hydrogenation under Noyori conditions [21] to provide dichlorodiol (*S*,*S*)-**1.2** [22]. Subsequent olefination using $Me_3S^+I^-$ ylide furnishes the desired dienediol [(*S*,*S*)-**1.1**], which, upon treatment with phosphorodiamidite **1.6**, oxidation with *t*BuOOH, and

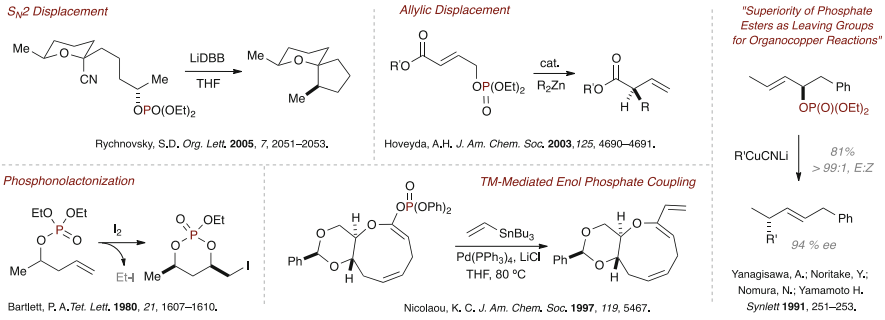
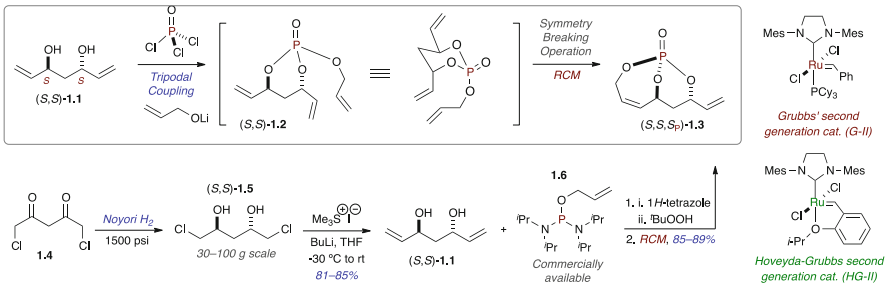


Fig. 1 Representative reactivity profile of phosphates in organic synthesis



Scheme 1 Synthesis of bicyclo[4.3.1]phosphate **1.3**

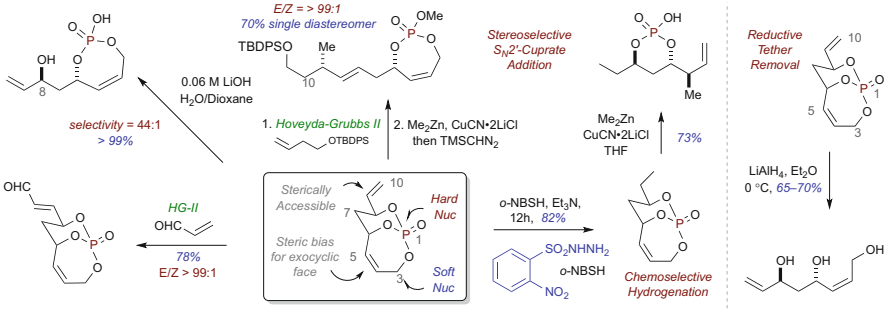


Fig. 2 Synthetic utility of bicyclo[4.3.1]phosphates

diastereoselective RCM with **G-II**, affords bicyclo[4.3.1]phosphate **1.3** in good overall yield.

Since this initial report, efforts have been focused on the establishment of a reactivity profile for this bicyclo[4.3.1]phosphate system so as to fully understand its behavior in a variety of conditions (Fig. 2) [23]. This profile includes a variety of nucleophilic additions, stability in acidic and basic media, reductive tether removal with lithium aluminum hydride ($LiAlH_4$), cross metathesis with a number of olefin cross-partners, chemoselective hydrogenation of the exocyclic olefin utilizing mild diimide reduction conditions [24], and stereoselective S_N2'-cuprate additions to both the original diene-containing bicyclic phosphate and the hydrogenated analog. Several significant features of phosphate tethers continue to emerge from these investigations, including: (1) orthogonal stability, (2) latent leaving group ability which orchestrates selective cleavage pathways within the phosphate tether, (3) inherent stereochemical restraints which dictate regioselective hydrogenation and facile cross metathesis (CM), and (4) stereo- and regioselective cuprate addition into the cyclic allylic phosphate.

The ongoing investigations involving the use of multivalent phosphate tethers have led to a series of publications and reviews [25, 26] on the application of this methodology to the total and formal syntheses of a number of biologically active

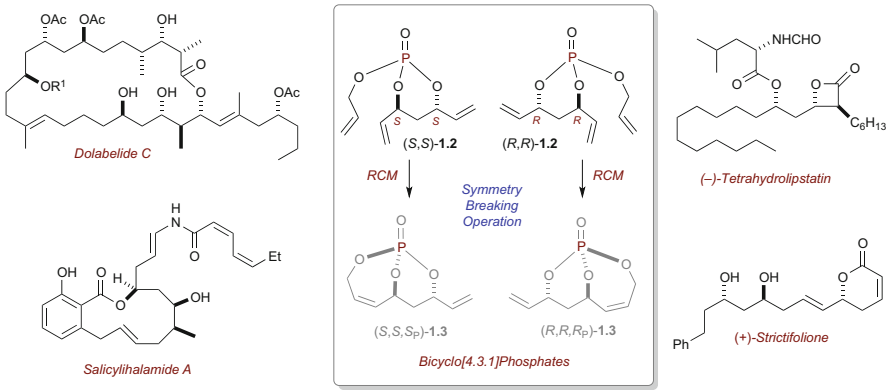
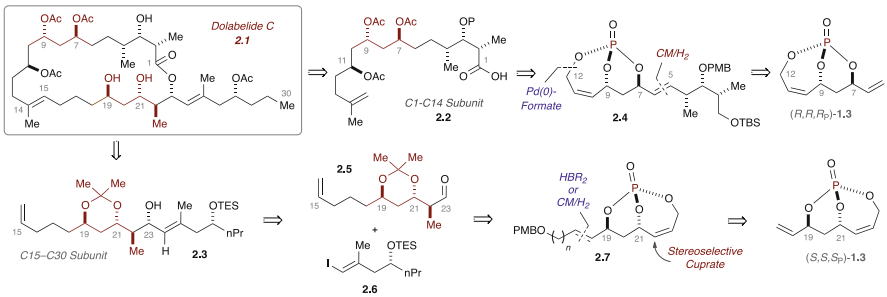


Fig. 3 Targeted natural products synthesized via the use of phosphate tether methodologies

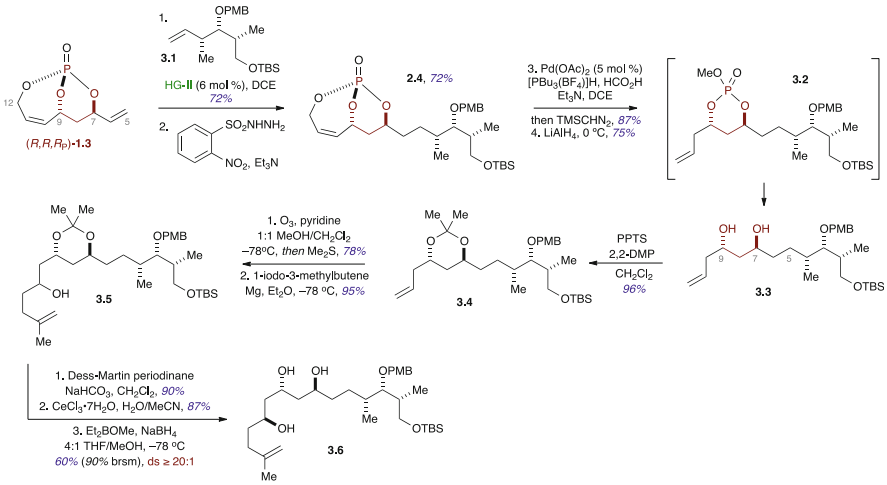
natural products and their analogs, including dolabelide C, salicylihalamide A, (−)-tetrahydrolipstatin, and (+)-strictifolione (Fig. 3). This review highlights these syntheses, as well as certain advances in the development of this methodology which have allowed for the stream-lined synthesis of stereochemically complex polyol-containing intermediates with minimal purification and multiple points of diversification to provide facile routes for library-amenable synthesis.

2 Total Synthesis of Dolabelide C

Dolabelide C (**2.1**) was isolated and characterized by Yamada and coworkers in 1995, from sea hare *Dolabella auricularia*, and was shown to possess potent cytotoxicity against HeLa S_3 cells ($IC_{50} = 1.0$ μg/mL) – a trait it shares with the other members of the dolabelide family (dolabelides A–D (Dolabelides A and B were isolated 2 years prior to the isolation of dolabelides C and D, [27]), Scheme 2) [28]. In 2008, the first two establishments of the northern and southern fragments toward the total synthesis of dolabelide C were published [29, 30], followed by the first complete total synthesis of the 24-membered macrolide in 2011 [31]. Retrosynthetic analysis showed that **2.1** could be obtained through the synthesis and coupling of two major fragments which could be generated from both enantiomers of [4.3.1]-bicyclic phosphate **1.3**: C1–C14 subunit **2.2** and C15–C30 subunit **2.3** (Scheme 2). The eastern portion of **2.2** could be installed via cross-metathesis/chemoselective hydrogenation of (R,R,R_P)-**1.3** with the suitable type II cross partner [32]. Subsequent Pd(0)-formate ring opening of the bicyclic phosphate **2.4** would provide a terminal olefin for further diversification. Subunit **2.3** could be produced via organolithium addition of vinyl iodide **2.6** to aldehyde **2.5**, which could be acquired from a series of transformations utilizing bicyclic phosphate intermediates **2.7** ($n = 0, 3$). In turn, intermediates **2.7** could be provided via a chemoselective hydroboration/oxidation pathway (through the intermediate where



Scheme 2 Retrosynthetic analysis in the total synthesis of dolabelide C



Scheme 3 Synthesis of C1–C14 fragment

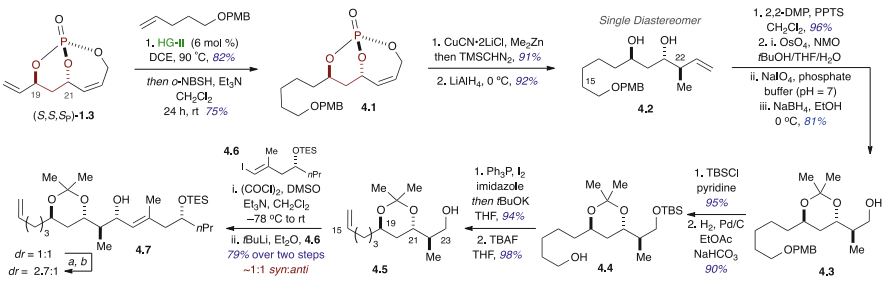
$n = 0$)[1] or a cross-metathesis/chemoselective hydrogenation pathway (through the intermediate where $n = 3$) from the simple [4.3.1]-bicyclic phosphate (S,S,S_P)-**1.3**.

The synthesis of the C1–C14 fragment of dolabelide C commenced with the cross-metathesis of (R,R,R_P)-**1.3** with olefin **3.1** – which was obtained in four steps from the corresponding TBS-protected Roche ester – in the presence of **HG-II** catalyst (6 mol%) in refluxing DCE (Scheme 3) (see footnote 1; [29, 31]). The resultant 1,2-disubstituted olefin was then hydrogenated selectively, in the presence of the internal olefin of the bicyclic phosphate, using mild diimide reduction, which is generated in situ from *o*-nitrobenzene sulfonyl hydrazine [24], affording the

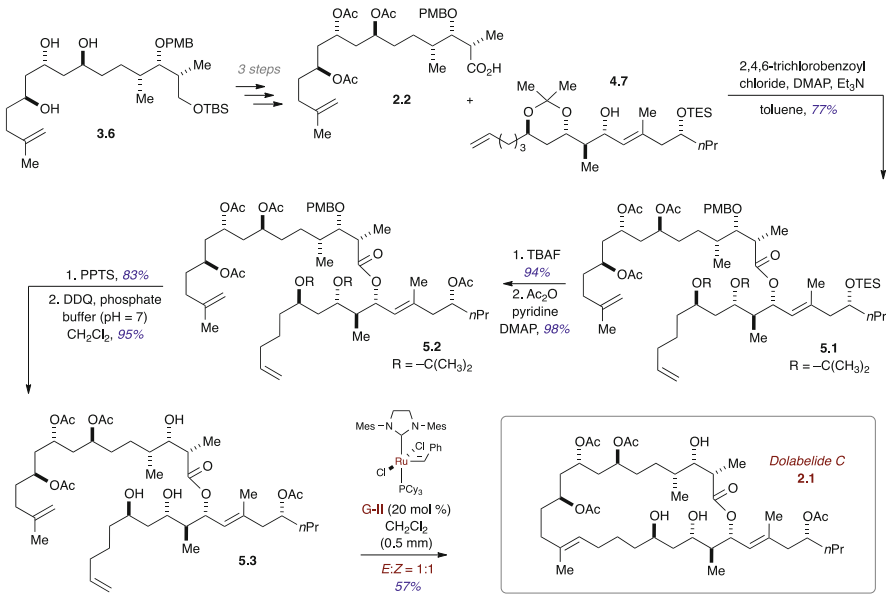
[1] This was the route involved in our first synthetic plans (see [30]); however, in light of the shorter second generation synthesis of this fragment which involves a one-pot, sequential cross-metathesis/hydrogenation, this first route is not addressed in this review.

desired [4.3.1]-bicyclic phosphate **2.4** in 72% yield. Subsequent transposition of the allylic phosphate olefin under Pd(0)-formate conditions, followed by methylation of the free phosphate with TMS-diazomethane, selectively provided intermediate **3.2** containing the desired western terminal olefin – with regioselectivity of the opening arising from orthogonal orbital alignment within the [4.3.1]-bicyclic phosphate precursor [14, 29]. Phosphate removal with $LiAlH_4$ generated diol **3.3**, which, upon treatment with 2,2-dimethoxypropane (2,2-DMP) and pyridinium *p*-toluenesulfonate (PPTS), provided acetal **3.4**, in 75% and 96% yields, respectively. Next, ozonolysis of the terminal olefin to form the terminal aldehyde and Grignard addition with 1-iodo-3-methylbutene yielded a 1:1 diastereomeric mixture of alcohol **3.5**, which was successfully converted to a single diastereomer **3.6** via a three-step sequence involving oxidation of the secondary alcohol, acetonide deprotection with cerium trichloride heptahydrate, and directed *anti*-reduction of the resultant ketone under Evans' conditions (60% yield, 90% based on recovered starting material, ds $\geq$ 20:1) [33].

The synthesis of the C15–C30 fragment of dolabelide C was initiated using a cross-metathesis/chemoselective hydrogenation pathway which coupled [4.3.1]-bicyclic phosphate (S,S,S_P)-**1.3** and PMB-protected 4-penten-1-ol to provide the corresponding bicyclic phosphate **4.1** in good overall yield (Scheme 4). Stereo- and regioselective S_N2' cuprate addition to the bicyclic phosphate (the regio- and stereoselective nature of this S_N2' cuprate addition can be attributed to both electronic and steric constraints inherent to the [4.3.1]-bicyclic phosphate system; see Scheme 4 in [14]), followed by tether removal with lithium aluminum hydride, afforded the corresponding diol (**4.2**) in 91% and 92% yields, for each respective transformation. Acetonide formation with 2,2-DMP and PPTS, followed by dihydroxylation/reductive cleavage to form a terminal aldehyde which was reduced to the alcohol with sodium borohydride without purification, furnished alcohol **4.3** in excellent overall yield. TBS-protection of the eastern alcohol and PMB-deprotection of the western alcohol generated **4.4**, which was successfully converted to the desired olefin via the formation and elimination of an intermediate iodide followed by TBS-deprotection. Oxidation of the primary alcohol under Swern conditions [34] to the corresponding aldehyde, followed by organolithium



Scheme 4 Synthesis of C15–C30 fragment. (**a**) Dess–Martin periodinane, CH_2Cl_2, 85%; (**b**) $NaBH_4$, MeOH, 0°C, 89%

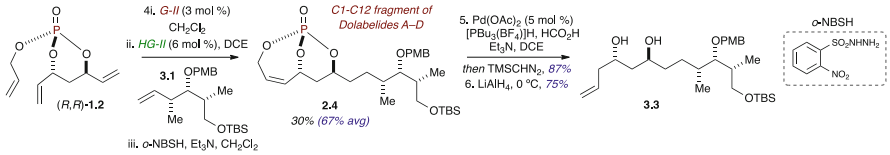


Scheme 5 Endgame of total synthesis of dolabelide C

addition of vinyl iodide **4.6** using *tert*-butyllithium, produced **4.7** in good yield, albeit a 1:1 diastereomeric mixture. This stereoselectivity was increased to nearly 3:1 *syn*:*anti* via oxidation and subsequent reduction with sodium borohydride, allowing for some recovery of material (Scheme 4).

With the syntheses of the C1–C14 and C15–C30 fragments complete, coupling of carboxylic acid **2.2** – obtained in three steps from **3.6** – with secondary alcohol **4.7** under Yamaguchi conditions [35] provided ester **5.1** in 77% yield (Scheme 5). Protecting group interconversion (TES to acetate), followed by acetonide and PMB-deprotection with PPTS and 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ), furnished the macrocyclization precursor **5.3** in 73% overall yield (over four reactions). Finally, ring-closing metathesis in the presence of the **G-II** catalyst (20 mol%) afforded dolabelide C (**1.1**), along with the undesired *Z*-stereoisomer (1:1 *E*:*Z*), in a 24-step longest linear sequence (LLS) from commercially available starting materials. While the authors were hoping to improve the stereoselectivity of the final macrocyclization by varying catalyst and conditions, efforts proved fruitless, although new and improved methods in reagent-controlled, stereoselective macrocyclic ring-closing metathesis could provide a means of averting loss of precious material in this final step (for recent examples of reagent-controlled *E*-selective metathesis processes, see [36, 37]).

One valuable aspect of tether methodologies, particularly those whose stereochemical influences impart orthogonal reactivity patterns within a functionality-rich system, is the potential to combine multiple steps into a one-pot, single

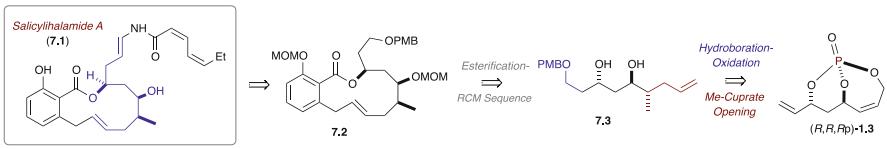


Scheme 6 One-pot, sequential RCM/CM/chemoselective hydrogenation route to C1–C12 of dolabelide C

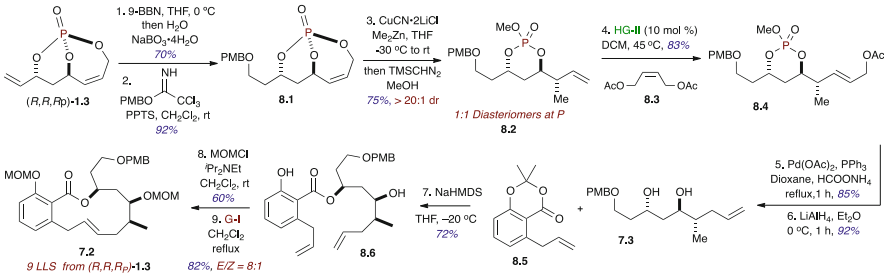
purification sequence which allows for more efficient and streamlined syntheses of complex intermediates. In 2012, Hanson and coworkers published a series of studies on the combination of ring-closing metathesis, cross-metathesis, and chemoselective hydrogenation into a single three-reaction, one-pot sequential sequential process [38]. Within this study, the application of this one-pot, sequential protocol to the C1–C14 fragment of dolabelide C was included (Scheme 6). Exposure of (*R*,*R*)-**1.2** to the **G-II** catalyst (3 mol%), followed by addition of the **HG-II** catalyst (6 mol%) and olefin cross partner, would provide the corresponding di-olefin-containing [4.3.1]-bicyclic phosphate product, which, upon treatment with *o*-NBSH and triethylamine (Et_3N), would afford **2.4** selectively in 30% yield (67% average per reaction). Subsequent allylic phosphate transposition with Pd(0)-formate, methylation of the free phosphate, and tether removal with $LiAlH_4$ would then generate the C1–C14 fragment (*trans* the carboxylic acid) **3.3** in five linear steps from the commercially available starting materials. This protocol would also reduce the LLS of the total synthesis of dolabelide C from 24 LLS to 22 LLS. Further investigations involving other one-pot sequential processes mediated by the phosphate tether could potentially streamline this synthesis – and other syntheses of complex small molecules – moving forward.

3 Formal Synthesis of (−)-Salicylihalamides A

Salicylihalamide A (**7.1**) was isolated from *Halicona sp*. by Boyd, Erickson, and coworkers in 1997 (Scheme 7) [39, 40]. This marine macrolide was found to exhibit potent cytotoxicity (an average 15 nM GI_{50}) against 60 NCI human tumor cell lines and selective inhibition of H^+-ATPase (V-ATPase), with an IC_{50} value <1.0 nM against bovine brain V-ATPase [41]. In 2011, Hanson and coworkers reported the formal syntheses of salicylihalamides A and B from (R,R,R_P)-bicyclo[4.3.1]phosphate **1.3** (Scheme 7) [42]. The synthetic route involves the construction of the core macrocycle via a late stage esterification of the diol fragment **7.3** followed by an *E*-selective RCM. Diol intermediate **7.3** could likewise be generated from bicyclic phosphate **1.3** via chemoselective hydroboration-oxidation of the exocyclic olefin, followed by a stereoselective S_N2'-methylcuprate addition to open the bicyclic structure.



Scheme 7 Retrosynthetic analysis for salicylihalamide A

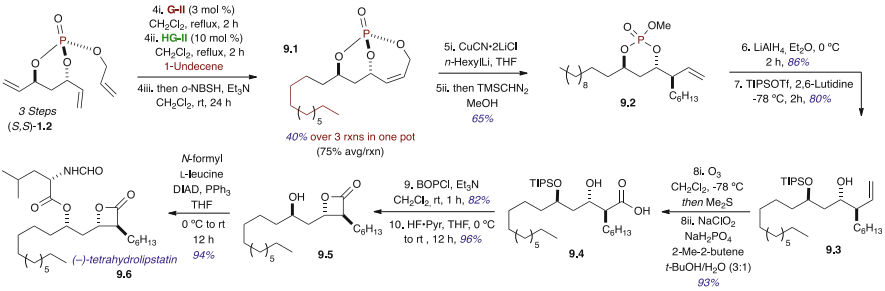


Scheme 8 Synthesis of advanced intermediate **7.2**

Bicyclo(4.3.1)-phosphate (R,R,R_P)-**1.3** was treated with 9-borabicyclo[3.3.1] nonane (9-BBN), followed by oxidation with sodium perborate tetrahydrate ($NaBO_3$•$4H_2O$), to provide the intermediate primary alcohol as the sole product; subsequent PMB-protection furnished the corresponding bicyclic phosphate intermediate **8.1** in good overall yield (Scheme 8). Next, regio- and diastereoselective methylcuprate addition to **8.1**, followed by methylation of the resultant free phosphate, afforded phosphate monocycle **8.2** (75% yield, dr > 20:1) with a terminal olefinic functional handle. Monophosphate **8.2** was then subjected to cross metathesis with (*Z*)-2-butene-1,4-diyl diacetate (**8.3**) to generate monophosphate **8.4** in 83% yield; subsequent regioselective, Pd-catalyzed reductive allylic transposition, followed by phosphate removal with $LiAlH_4$ produced diol **7.3** in excellent overall yield. The targeted diol **7.3** was esterified by treatment with sodium bis (trimethylsilyl)amide (NaHMDS) followed by exposure to **8.5**, affording ester **8.6** as a 3.6:1 (desired:undesired) mixture of regioisomers. Gratifyingly, the other regioisomer was successfully converted back to the starting material **7.3** for further recycling. Finally, MOM-protection of the remaining secondary alcohol, followed by RCM with $(PCy_3)_2(Cl)_2Ru{=}CHPh$ (Grubbs first generation catalyst, G-I), provided macrolactone core **7.2** in 9 longest linear steps (LLS).

4 Total Synthesis of (−)-Tetrahydrolipstatin

(−)-Tetrahydrolipstatin (THL, **9.6**), or, as it is more commonly known, Orlistat®, is a stable, saturated analog of lipstatin (for information on the isolation and biological activity of lipstatin and its analogs, see: [43–47] and references cited therein) which



Scheme 9 Total synthesis of (−)-tetrahydrolipstatin

has been used as an anti-obesity agent but has found renewed interest as a potential anti-cancer agent because of its selective inhibition of thioesterase activity of fatty acid synthase (FAS) in cancer cells (Scheme 9) [48, 49] (see also [50, 51] and references cited therein). In 2010, a concise total synthesis of THL was reported utilizing a phosphate tether-mediated, one-pot sequential, ring-closing metathesis/cross-metathesis/chemoselective hydrogenation protocol to afford the desired bioactive small molecule in nine steps from the readily accessible (*S*,*S*)-dienediol **1.1** [22].

Prepared in three steps from (*S*,*S*)-dienediol **1.1**, phosphate triene (*S*,*S*)-**1.2** was transformed into [4.3.1]-bicyclic phosphate **9.1** via the aforementioned RCM/CM/chemoselective hydrogenation protocol. Treatment with the **G-II** catalyst (3 mol%), followed by the addition of **HG-II** catalyst (10 mol%) and 1-undecene, provided the intermediate diene-containing bicyclic phosphate, which could be converted to **9.1** via selective olefin hydrogenation under mild diimide reduction conditions in 40% yield (75% average per reaction). Subsequent stereoselective S_N2' cuprate addition of *n*-hexyllithium, directed by the concave nature of the bicyclic phosphate **9.1**, followed by methylation of the free phosphate, furnished phosphate-containing **9.2** in 65% yield over two steps. Phosphate removal with $LiAlH_4$ and chemoselective protection of the more sterically accessible alcohol with TIPS-triflate generated olefinic alcohol **9.3** in good yield. Ozonolysis of the terminal C–C double bond to generate a terminal aldehyde, followed by oxidation under Pinnick conditions [52], produced carboxylic acid **9.4** in 93% yield over two steps. β-Lactonization using bis(2-oxo-3-oxazolidinyl)phosphonic chloride (BOPCl) and subsequent TIPS-deprotection with HF•pyridine yielded β-lactone **9.5**, which, under exposure to *N*-formyl leucine and Mitsunobu conditions developed by Schneider [53], afforded (−)-tetrahydrolipstatin (**9.6**) in 94% yield.

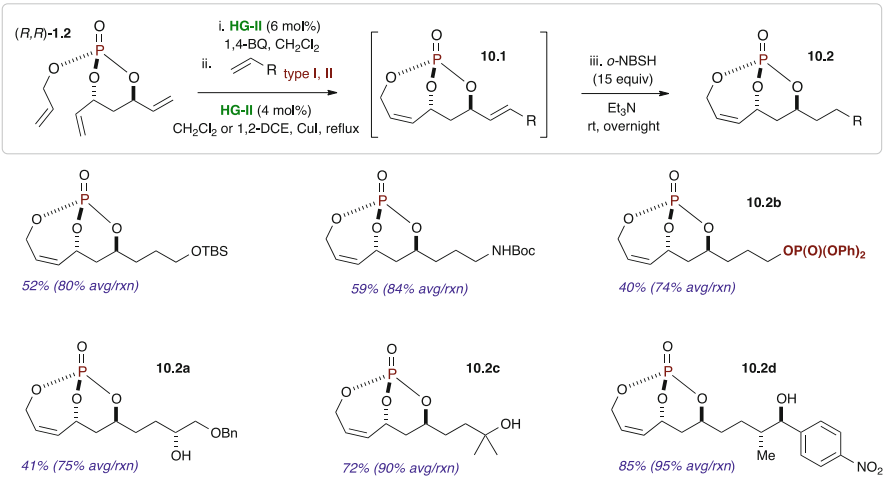
5 Phosphate Tether-Mediated One-Pot, Sequential Processes to Functionalized Polyols

In 2012, Hanson and coworkers developed a three-reaction, one-pot sequential methodology involving RCM, CM, and chemoselective hydrogenation, without intermediate isolation, to facilitate the efficient synthesis of complex and diverse polyol fragments [38]. In this protocol, phosphate triene [as shown (*R*,*R*)-**1.2**] would be treated with catalytic HG-II (6 mol%), in the presence of 1,4-benzoquinone additive, to facilitate a diastereotopic ring-closing metathesis reaction (Scheme 10). Upon completion of the RCM, the solvent (CH_2Cl_2) was evaporated, and CH_2Cl_2 or 1,2-dichloroethane, an olefin cross-partner, and additional catalyst were added to the crude reaction mixture to promote cross-metathesis with the terminal olefin of the resultant bicyclic phosphate and provide substituted intermediates **10.1**.[2] After the completion of CM, chemoselective diimide reduction (utilizing *o*-NBSH) was performed to generate hydrogenated CM bicyclic phosphates **10.2** in good to excellent overall yield (40%–85%, 74%–95% average per reaction). The observed chemoselectivity presumably arises from the deactivated nature of the endocyclic olefin, as well as steric constraints within the bicyclic structure – characteristics innate to the phosphate tether which allow for a certain amount of orthogonal reactivity between the two olefins. The terminal olefin of the initial intermediate bicyclic phosphate, which shows nearly type III [32] olefin behavior in CM reaction, readily undergoes cross-metathesis with a variety of type I and type II olefin cross partners, including those containing free alcohols (**10.2a**), electron-withdrawing groups (**10.2b**), and steric bulk (**10.2c**). In addition, stereochemically-rich cross-partners could allow for the facile synthesis of more complex bicyclic phosphate intermediates (**10.2d**, as well as the application to C1–C14 of dolabelide C), which could prove useful in the simple and efficient synthesis of polyol-containing bioactive small molecules.

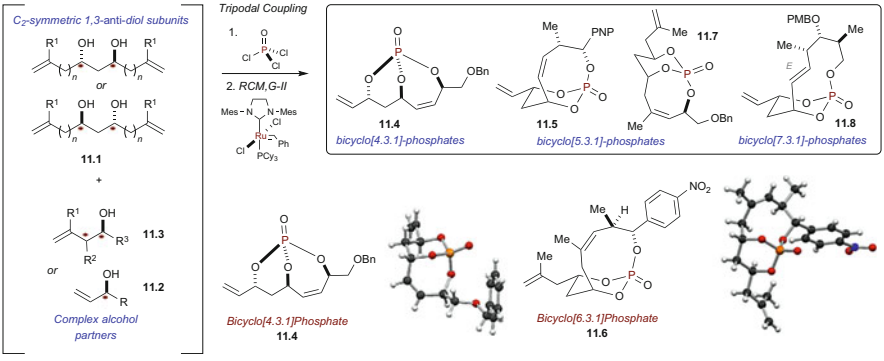
In 2013, Hanson and coworkers reported a detailed study to investigate the effect of ring-size, stereochemistry, and substitution in the context of RCM reactions to provide bicyclo[*n*.3.1]phosphate tether systems (Scheme 11) [54]. In this study, a series of phosphate tethered trienes were synthesized via the tripodal coupling of different 1,3-*anti* diene diols (**11.1**), allylic (**11.2**) and homoallylic alcohol partners (**11.3**) with phosphorus oxychloride ($P(O)Cl_3$). Various bicyclo[*n*.3.1]phosphates (**11.4**–**11.8**) were obtained in good to moderate yields, highlighting the potential of phosphate tethers to mediate the coupling of stereochemically rich alcohols. For seven- to nine-membered ring systems, exclusive *Z*-selectivity was observed (**11.4**–**11.7**), while the ten-membered ring formations were highly *E*-selective (**11.8**).

More importantly, with respect to the eight-membered ring formation, the allylic methyl substitution played a significant role in dictating which of the diastereomeric trienes **SM 5.9** would participate in RCM (Scheme 12). When treated with

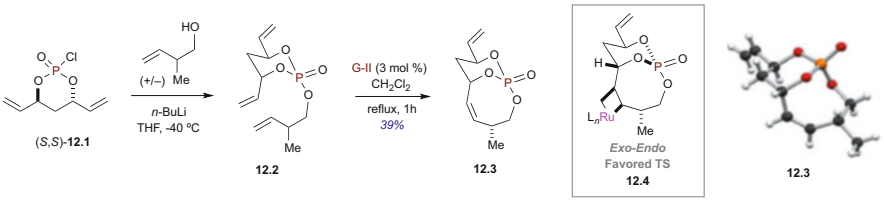
[2] It was observed that the inclusion of CuI, as well as freeze-degas-thawed solvents, increased the yield of cross-metathesis, as well as contributed to an overall cleaner reaction as observed by TLC.



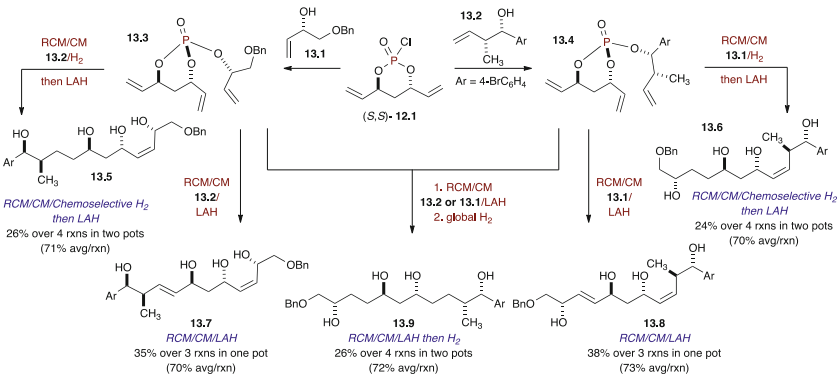
Scheme 10 RCM/CM/chemoselective hydrogenation protocols to functionalized bicyclic phosphates



Scheme 11 Detailed study of the effects of substitution, ring size, and stereochemical complexity on the formation of bicyclic phosphates



Scheme 12 Double diastereotopic differentiation via kinetic resolution by RCM



Scheme 13 General reaction conditions: RCM – HG-II (3 mol%), 1,2-DCE/CH_2Cl_2, 2 h; CM – HG-II (3 mol%), CH_2Cl_2, CM partner (3–5 equiv.); LAH reduction – $LiAlH_4$ (2–4 equiv.), THF, 0°C, 2 h; chemoselective H_2 – *o*-NBSH (12 equiv.), CH_2Cl_2, Et_3N, overnight; global H_2 – *o*-NBSH (20 equiv.), CH_2Cl_2, Et_3N, overnight

G-II, the 1:1 mixture of diastereomeric trienes **12.2** provided bicyclic phosphate **12.3** as a single diastereomer, along with diastereomerically enriched unreacted starting material. Product formation was rationalized according to the favored transition state **12.4**, in which the RuL_n-metallocyclobutane and adjacent methyl group were *trans* to each other, with the larger of the two (the metallocyclobutane) exocyclic with respect to the newly formed bicyclic phosphate. This double diastereotopic differentiation via kinetic resolution by RCM could prove useful in the selective synthesis of stereochemically rich polyol-containing intermediates but also currently presents a limitation and a challenge to the scope of molecules which can be acquired via this specific protocol. Taken collectively, the RCM study demonstrated the utility of phosphate tether in synthesizing complex systems with high diastereoselectivity and also facilitated our understanding of the underlying factors governing RCM for such complex systems.

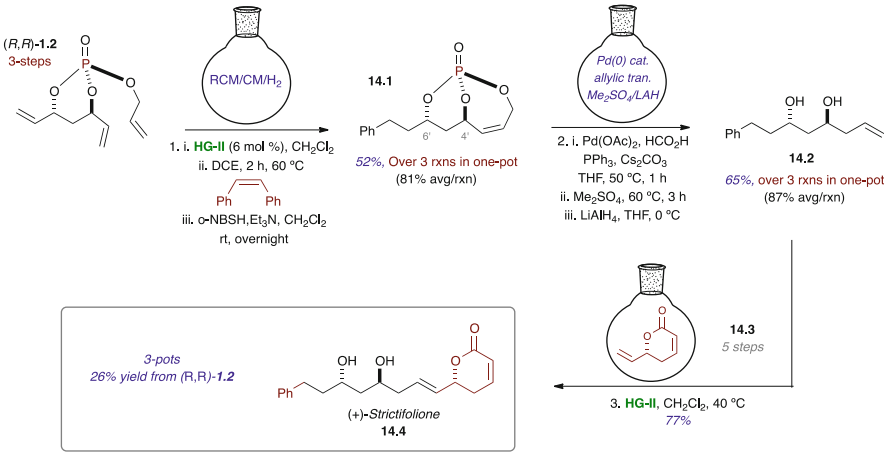
Building upon the previous two studies described above, in 2014, Hanson and coworkers united the idea of coupling stereochemically rich fragments with one-pot, sequential processes to synthesize a variety of polyol scaffolds by phosphate tether-mediated one/two-pot sequential methods (Scheme 13) [55]. The strategy relies on the order of addition of the alcohol partners for tripodal coupling and the cross metathesis steps, thereby generating scaffolds bearing differentiated olefinic ends. Thus, pseudo-C_2-symmetric monophosphate (*S*,*S*)-**12.1** was coupled separately with allylic alcohol **13.1** and homoallylic alcohol **13.2**, yielding two different trienes, **13.3** and **13.4**, respectively. Triene **13.3** was subjected to RCM and subsequent CM with homoallylic alcohol **13.2**, followed by chemoselective hydrogenation in the presence of *o*-NBSH (*ortho*-nitrobenzenesulfonylhydrazide), produced bicyclic phosphate intermediate (not shown in the scheme). Upon tether removal of the resulting bicyclic phosphate intermediate, polyol **13.5** was obtained in an overall yield of 26% over four reactions performed in a two-pot sequence (71% avg/rxn). Similarly, triene **13.4** was subjected to the same two-pot protocol to

furnish polyol **13.6** in an overall yield of 24% over four reactions performed in a two-pot sequence (70% avg/rxn).

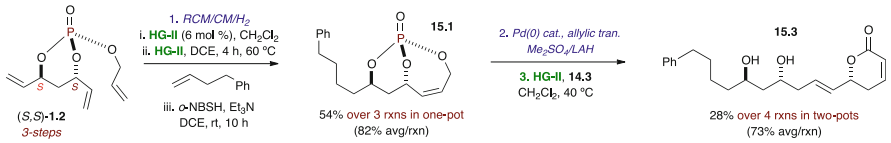
Next, triene **13.3** was subjected to RCM, CM with homoallylic alcohol **13.2**, and subsequent tether removal with LAH to produce polyol **13.7**, bearing both (*Z*)- and (*E*)-configured olefins, in an overall yield of 35% over three reactions (70% avg/rxn) in a one-pot sequence. Following a similar one-pot protocol, polyol **13.8** was generated from triene **13.4** in an overall yield of 35% over three reactions (70% avg/rxn). Starting from triene **13.4**, a one-pot sequential RCM/CM/LAH and global hydrogenation, in the presence of excess *o*-NBSH, furnished polyol **13.9** in an overall yield of 26% in two pots over four reactions (72% avg/rxn). The same polyol **13.9** was obtained from triene **13.3** following similar reaction sequences. Importantly, this study highlighted that stereochemically enriched polyol scaffolds bearing both (*Z*)- and (*E*)-olefinic geometries – which would otherwise be difficult to produce via (Z)- and (E)-selective CM of 1,3-*anti* diol subunits with olefinic partners – can be generated via phosphate tether-mediated one-/two-pot reaction protocols which minimize the time and effort spent on individual purification steps.

6 Total Synthesis of (+)-Strictifolione

In 2013, Hanson and co-workers reported a library-amenable, "pot-economical" synthetic approach utilizing two consecutive, phosphate tether-mediated, one-pot sequential processes and a cross metathesis reaction to afford two antifungal natural products, (+)-strictifolione (**14.4**, Scheme 14) and (6*R*)-6[(*E*,4*R*,6*R*)-4,6-dihydroxy-10-phenyl-1-decenyl]-5,6-dihydro-2*H*-2-pyrone (**15.3**, Scheme 15), in good yield



Scheme 14 Total synthesis of (+)-strictifolione via *P*-tether mediated, one-pot sequential protocols



Scheme 15 Total synthesis of **15.3** via *P*-tether mediated, one-pot sequential protocols

with minimal purification [56]. Exposure of phosphate triene (*R*,*R*)-**1.2** to one-pot, sequential RCM/CM/chemoselective hydrogenation conditions, similar to those described above [38], with olefin cross-partner *cis*-stilbene, provided bicyclic phosphate **14.1** in 52% overall yield (81% avg/rxn). Subsequent allylic transposition under Pd(0)-formate conditions, in situ methylation of the resultant free phosphate with dimethylsulfate [Me_2SO_4], and phosphate tether removal with $LiAlH_4$ furnished differentiated diol **14.2** in a single, high yielding purification step (65% overall yield, 87% avg/rxn). Finally, cross-metathesis of diol **14.3** with lactone **14.4**, prepared in five steps according to via the Jacobsen protocol [57–59], afforded (+)-strictifolione (**14.4**) in 77% yield and excellent *E*-selectivity. This three-pot concise route generated the desired natural product in 26% overall yield from (*R*,*R*)-**1.2** and provides an efficient, scalable, and library-amenable approach to strictifolione, as the protocol allows for easy diversification of the western and eastern portions of the molecule through simple modification of cross-metathesis cross partners.

Similarly, the total synthesis of (6*R*)-6[(*E*,4*R*,6*R*)-4,6-dihydroxy-10-phenyl-1-decenyl]-5,6-dihydro-2*H*-2-pyrone (**15.3**) was accomplished following the three-pot protocol utilized in the total synthesis of (+)-strictifolione. Exposure of phosphate triene (*S*,*S*)-**1.2** to RCM/CM/chemoselective hydrogenation conditions with olefin cross-partner phenyl-but-1-ene provided bicyclic phosphate **15.1** in 54% overall yield (82% avg/rxn). Next, one-pot Pd-catalyzed allylic transposition, in situ methylation of the resultant free phosphate, and reductive removal of the phosphate tether, followed by cross metathesis with **14.3**, afforded the desired natural product (**15.3**) and good overall yield. Notably, this streamlined modular approach takes full advantage of orthogonal protecting- and leaving-group properties innate to the phosphate tether to eliminate the protecting group manipulations which – though often unavoidable – decrease the atom economy and simplicity of a straightforward synthesis.

7 Conclusions

The use of multivalent phosphate tethers, which couple both simple and complex alcohol fragments, has proven to be a valuable tool in the synthesis of stereochemically rich, polyol-containing bioactive small molecules. Moreover, the ability of the phosphate tether to mediate multiple orthogonal reaction

sequences in a single purification step highlights its synthetic utility in the streamlining of routes toward both simple and complex intermediates, while providing facile means for the synthesis of analog libraries. Hopefully, as the understanding of these orthogonal reactivity patterns innate to the phosphate tether deepens, the potential of this method to simplify the synthesis of complex natural products and their analogs will incite other researchers to view these tethers as profitable complements to more established silicon counterparts.

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