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Divalent and Multivalent Activation in Phosphate Triesters: A Versatile Method for the Synthesis of Advanced Polyol Synthons

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The construction of mono- and bicyclic phosphate triesters possessing divalent and multivalent activation and their subsequent use in the production of advanced polyol synthons is presented. The method highlights efforts to employ phosphate tethers as removable, functionally active tethers capable of multipositional activation and their subsequent role as leaving groups in selective cleavage reactions. The development of phosphate tethers represents an integrated platform for a new and versatile tether for natural product synthesis and sheds light on new approaches to the facile construction of small molecules.

Introduction

The development of new synthetic strategies allowing for efficient asymmetric syntheses of complex biologically active targets, with minimal protecting group manipulations and chemical steps, is an enormous challenge in natural product synthesis. A powerful way of addressing this challenge is through the use of convergent methodologies employing the temporary tethering of two advanced intermediates. Historically, silicon has been the most widely used temporary tether due to its facile installation/cleavage attributes as well as its innate protecting group properties.[1] Moreover, the ability of silicon tethers to undergo myriad functional-group transformations positions them as ideal tethers in the realm of total synthesis.[2] In comparison, phos-

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phorus has the ability to mediate di- and tripodal couplings, provide orthogonal protection and has innate leaving group properties. Although the potential advantages of phosphate tethers are evident, their application in synthesis has until recently largely focused on monovalent activation of a single phosphate ester appendage. Such classical use of phosphates in complex synthesis has focused on nucleophilic displacement reactions of allylic phosphates,[3] cross-coupling/reduction reactions with enol-phosphates,[4] and direct displacements of phosphates in more recent cyclization protocols.[5] Additional uses of phosphate triesters in iodophosphonylation procedures[6] and their role in oligonucleotide synthesis[7] further highlight both nucleophilic properties and facile coupling characteristics innate to phosphates.

While the aforementioned attributes of phosphate triesters is impressive, their reactivity profile is overshadowed by the vast extent to which nature uses the anionic counterparts, organophosphate mono- and dianions, which play a dominant role in a number of key biological processes.[8] A seminal paper in 1987 by Westheimer[8] addresses the issue where he surmises, "while nature capitalizes on the unique features of phosphate monoanions, chemists cannot afford to use compounds as stable as the phosphate anion and with the poor leaving group capabilities of either phosphate anions or dianions." This concept can be summarized as the phosphate "brake" (Figure 1), which is predicated upon the longer 11-year half-life of the hydrolysis of dimethylsodium phosphate when compared with trimethyl phosphate.

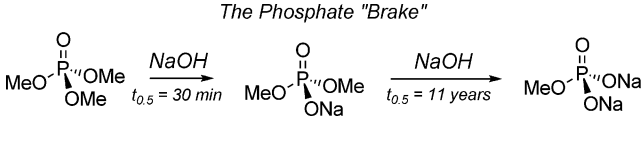


Figure 1. Hydrolysis half-life of trimethyl- and dimethylsodium phosphate.

The ubiquity of phosphates in nature points to their potential utility in the development of new synthetic methodology. In particular, several attractive features were uncovered in three recent studies illustrating the ability of phosphate triesters to serve as functionally active tethers.[9] These studies showed phosphate tethers capable of coupling two carbinol-containing subunits via ring-closing metathesis (RCM), serving as leaving groups with the ability to undergo selective cleavage reactions and imparting type-III properties in cross-metathesis (CM) reactions with the exocyclic appendant olefin. These studies capitalized on the unique features of the phosphate mono- and dianions as a means of expanding current phosphate methodology to the arena of total synthesis.[9] Reported herein is a summary of efforts to employ phosphate tethers as removable, functionally active tethers capable of multipositional activation and their subsequent role as latent leaving groups in selective cleavage reactions. The development of phosphate tethers (Figure 2) represents an integrated platform for a new and versatile tether for natural product synthesis and sheds light on new approaches to the facile construction of small molecules.

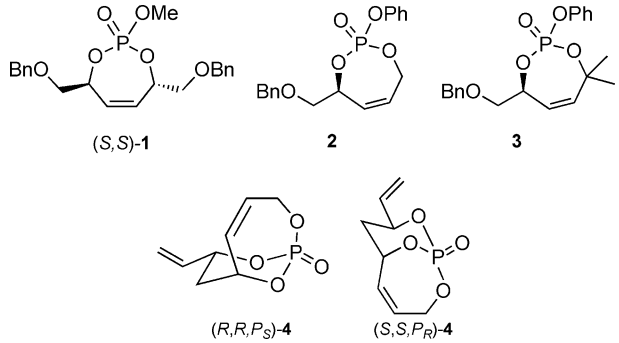


Figure 2. Monocyclic and bicyclic phosphates.

Divalent Activation in Phosphate Tethers

In 1991, Yamamoto and co-workers reported the superiority of phosphates as allylic leaving groups (Figure 3).[10] In this report, they subjected an allylic phosphate to a copper-mediated *anti*-S_N2' displacement to afford products with high *E*:*Z* selectivity and with excellent chirality transfer. These observations were also reported by Chong and Knochel.[11]

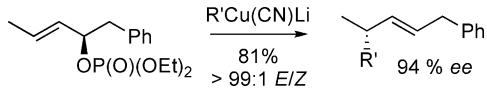
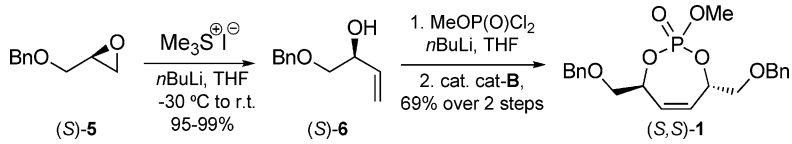


Figure 3. Seminal report of cuprate addition to allylic phosphates.

More recently, enantioselective allylic displacements via an *anti*-S_N2' pathway with chiral Schiff base equivalents have been shown to desymmetrize *meso*-1,3-*syn*-allylic phosphates [Figure 4, Equation (1)].[12a] Other reagent controlled asymmetric cuprate additions include additional applications of Schiff bases [Equation (2)], BINAP [Equation (3)] and N-heterocyclic carbene ligands [Equation (4)], all of which provide chiral nonracemic products in very good to excellent *ee* from allylic phosphates.[11b–13]

In 2004, a phosphate tether was used to construct the *pseudo*-C_2-symmetric monocyclic phosphate **1** en route to desymmetrization studies leading to advanced polyol synthons.[9b] Although the original intent to desymmetrize the C_2-symmetric monocyclic phosphate via cuprate additions was met, interesting conformational effects led to further investigations of unsymmetric phosphates, which provided experimental insight into the Corey mechanism of cuprate displacements.[3a]

In this method, a three-step protocol was used starting from glycidol ether (*S*)-**5** to generate (*S*,*S*)-monocyclic phosphate **1** (Scheme 1) in good yields.[9b] First, treatment of **5** with a sulfur ylide, generated in situ, gave allylic alcohol (*S*)-**6** in excellent yield on multigram scale.[14] After generation of the corresponding alkoxide, condensation with $(MeO)POCl_2$ yielded a phosphate triester, which underwent ring-closing metathesis (RCM) with Grubbs second-generation catalyst cat-**B** (Figure 5) to afford cyclic phosphate (*S*,*S*)-**1**.[15]



Scheme 1. Synthesis of monocyclic phosphate **1**.

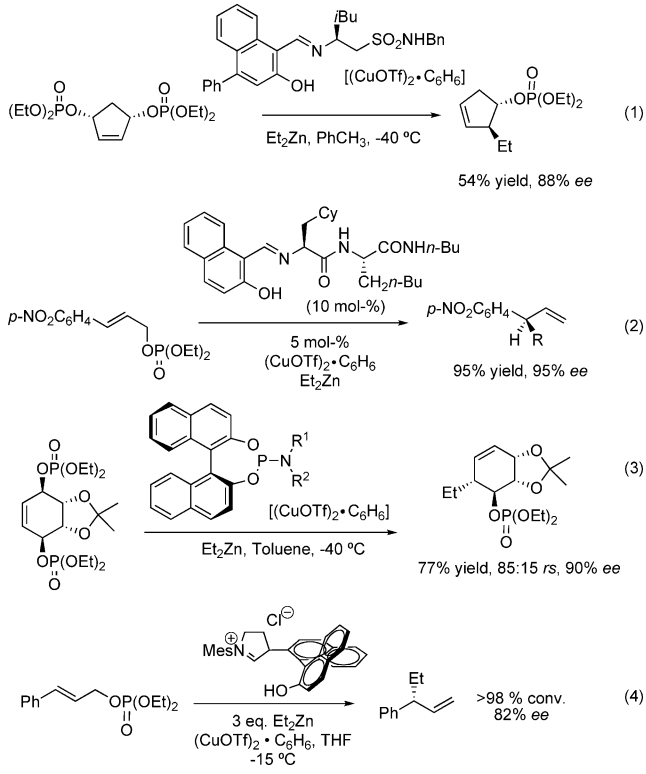


Figure 4. Examples of allylic phosphate displacements using cuprates.

Initial investigations of the reactivity profile of **1** revealed facile cleavage of the phosphate tether when subjected to an excess amount of $LiAlH_4$ (Scheme 2) to yield diol **7**.[9b] Removal of the endocyclic olefin was achieved providing cyclic phosphate **8**, followed by tether removal to afford diol **9**.

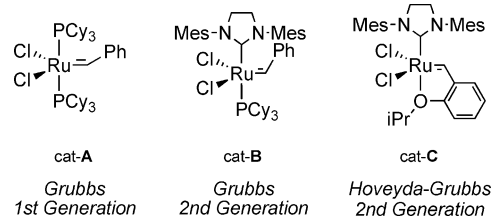
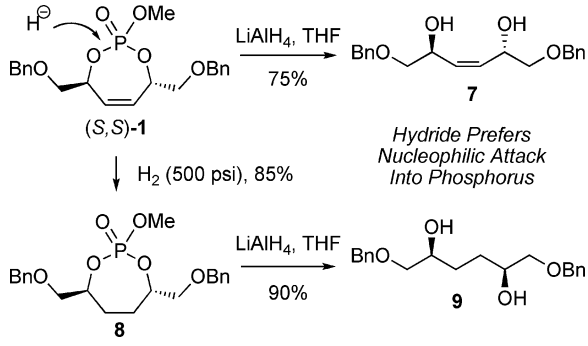
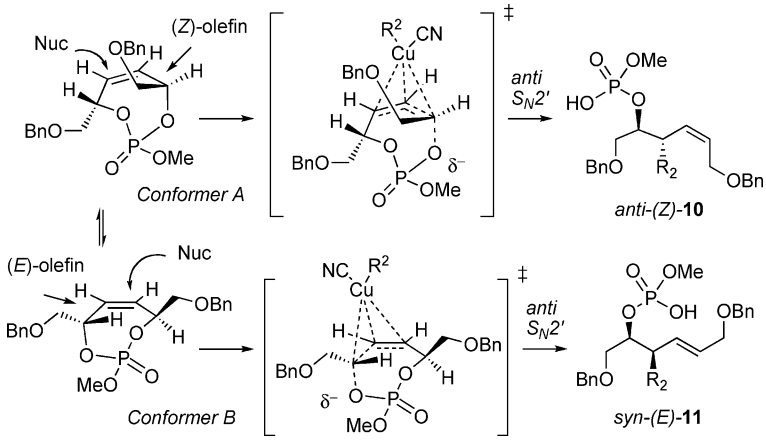


Figure 5. Olefin metathesis catalysts.



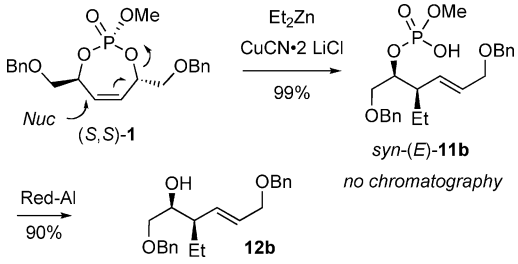
Scheme 2. Preparation of 1,4-diols via phosphate cleavage.

Studies toward desymmetrization of **1** by using a cuprate displacement reaction were investigated in accordance with the previously shown examples of allylic phosphate displacements operating through an *anti*-S_N2' pathway.[9b] The prerequisite for the aforementioned examples is that the leaving group be orthogonal to the approaching cuprate, requiring coplanar alignment of the σ* and π* orbitals. Thus, cyclic phosphate **1** possesses two possible productive conformations (Scheme 3).



Scheme 3. Possible modes for cuprate addition.

Although four diastereotopic olefin orbitals exist in **1**, pseudo-symmetry dictates only two possible products *anti*-(*Z*)-**10** and *syn*-(*E*)-**11**.[16] Treatment of (*S*,*S*)-**1** with Et_2Zn/CuCN·2LiCl resulted in formation of phosphate acid **11b** as a single diastereomer (>20:1), determined by ^{31}P NMR (after acidic workup, no chromatography required). Cleavage of the primary phosphate, in the presence of RedAl®, afforded chiral, nonracemic homoallylic alcohol **12b** in a two-step sequence from **1** (Scheme 4).



Scheme 4. Cuprate addition/phosphate acid cleavage sequence.

Rationalization of the excellent selectivity displayed by the cuprate addition can be explained by using Corey's proposed concerted, asynchronous mechanism (Figure 6).[3a] The transition state occurs through coordination of the σ* of the phosphate ester leaving group and the π* of the olefin. Since both σ* orbitals in conformers A and B (Scheme 3) are roughly equal in energy, diastereoselectivity is dictated by allylic $A^{1,3}$-strain from the CH_2OBn-side chain, which is more prominent in conformer A when attaining the proper coplanar σ* and π* alignment.[17]

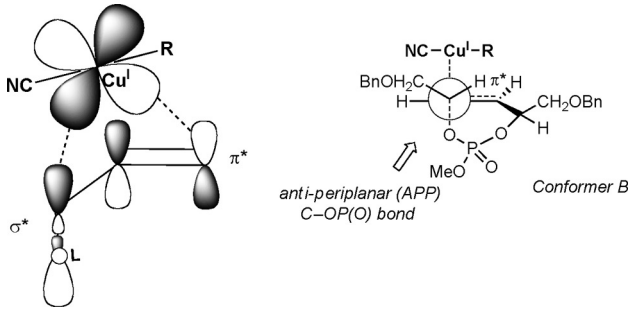


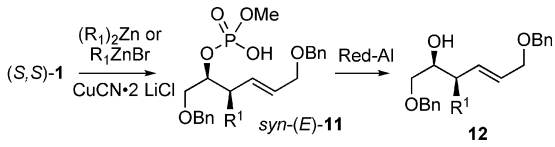
Figure 6. Corey model for rationalizing stereoselectivity.

The scope of this reaction was observed with an array of zinc-based organocuprates (Entries 1–3, Table 1).[9b] In all cases, the corresponding homoallylic alcohol **12** was afforded by phosphate cleavage in the presence of RedAl®.

In this study, it was shown that functionally sensitive R groups, e.g. Entries 6–7 in Table 1, gave lower yields after cleavage of the phosphate acid. However, by converting the phosphate acid to the corresponding phosphate ester by in situ methylation ($TMSCHN_2$), better yields of the desired homoallylic alcohol were obtained (Scheme 5).[9b]

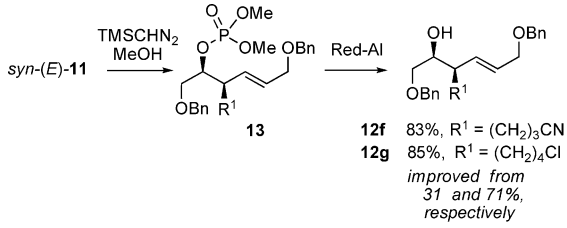
After investigating activation pathways of pseudo-symmetric **1** in cuprate additions, a number of unsymmetric P-tethered systems were constructed where the electronic energies of the σ* orbitals of the leaving phosphate ester are differentiated by substitution at the reacting carbinol. Cyclic phosphate **2** was synthesized bearing primary and secondary phosphate leaving groups (Scheme 6). From diol **6**,

Table 1. Cuprate addition/phosphate acid cleavage sequence.

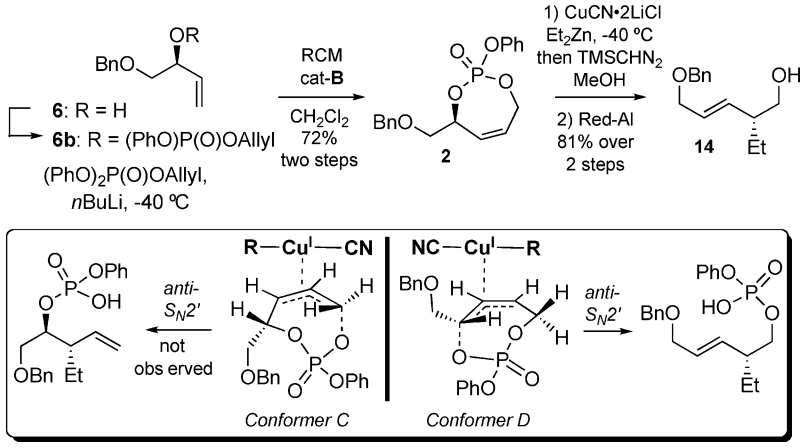


Entry	$(R^1)_2Zn$ or R^1ZnBr	Phosphate acid - **11** yield (*dr*)	Homoallylic alcohol - **12**	% Yield
1	Me_2Zn [a]	99% (20:1) **11a**	**12a**	83
2	Et_2Zn [a]	99% (>20:1) **11b**	**12b**	90
3	iPr_2Zn [a]	99% (>20:1) **11c**	**12c**	95
4	*c*HexZnI [b]	99% (>20:1) **11d**	**12d**	70
5	BnZnBr [b]	99% (>20:1) **11e**	**12e**	84
6	$CN(CH_2)_3ZnBr$ [b]	99% (>20:1) **11f**	**12f**	31
7	$Cl(CH_2)_4ZnBr$ [b]	99% (>20:1) **11g**	**12g**	71
8	$CH_2=CH(CH_2)_3ZnBr$ [b]	99% (>20:1) **11h**	**12h**	65

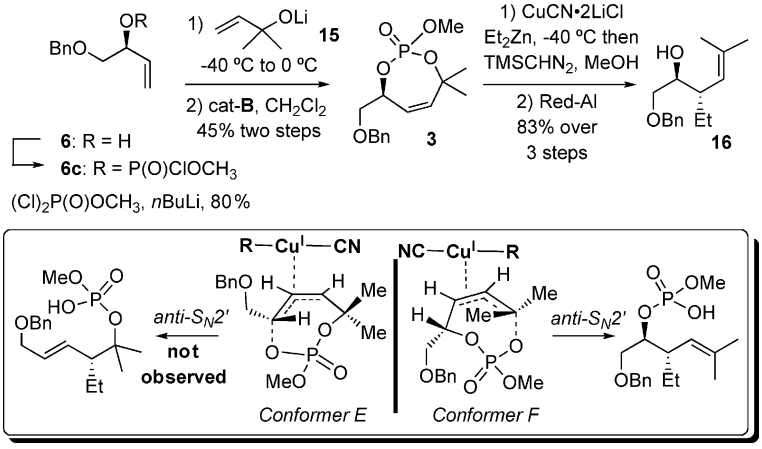
[a] Method required 4–5 equiv. of organocuprate. [b] Method required 8–9 equiv. of organocuprate.



Scheme 5. Methylation/phosphate cleavage.



Scheme 6. Unsymmetric monocyclic phosphates.



Scheme 7. Secondary vs. tertiary allylic phosphate leaving groups.

phosphorylation and RCM afforded **2** in good yield over the 2-step protocol. Subjecting the monocyclic phosphate **2** to 3.0 equiv. of a diethylzinc-derived organocuprate, followed by phosphate cleavage, furnished homoallylic alcohol **14** as a single stereoisomer. Whereas the stereoselectivity of **1** was based upon conformational preferences, **2** does not encounter the same type of governing $A^{1,3}$-strain. Instead, the electronic bias of the more labile secondary phosphate-leaving group explains the regioselectivity observed in the allylic displacement. Overall, this study contrasted the importance of steric vs. electronic effects in these systems.[9b]

To determine the extent to which allylic strain and electronic factors compete, investigations turned toward the unsymmetric phosphate **3** bearing secondary and tertiary allylic phosphate positions (Scheme 7). Subjection of **3** to a diethylzinc-derived organocuprate, followed by phosphate cleavage afforded homoallylic alcohol **16**, where displacement of the tertiary allylic phosphate occurred exclusively to provide a single stereoisomer.[9b]

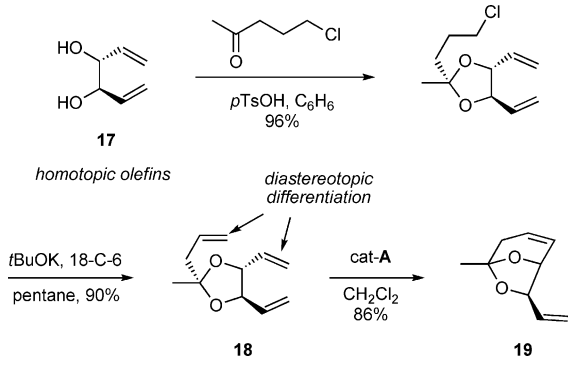
An interesting bias of electronic effects over steric effects arises from the observed formation of **16**. The preference of conformer F (Scheme 7) reveals severe $A^{1,3}$ allylic strain between the *gem*-dimethyl terminus and the olefin. The regioselectivity seen is consistent with the result from allylic displacement of phosphate **2**, where the more labile tertiary phosphate-leaving group is preferred. Looking back on the three examples shown, these results are consistent with the asynchronous concerted transition state proposed by Corey, where bond breakage of the lower-energy and more substituted σ* is preferred.[9b]

In summary, the aforementioned phosphate tethers show similar qualities to silicon[1,2] in terms of facile dipodal coupling, stability, and facile removal. Moreover, the leaving group ability and unique geometry of these heterocycles allow for stereoselective cuprate addition reactions affording a variety of chiral, nonracemic allylic alcohols.[9b]

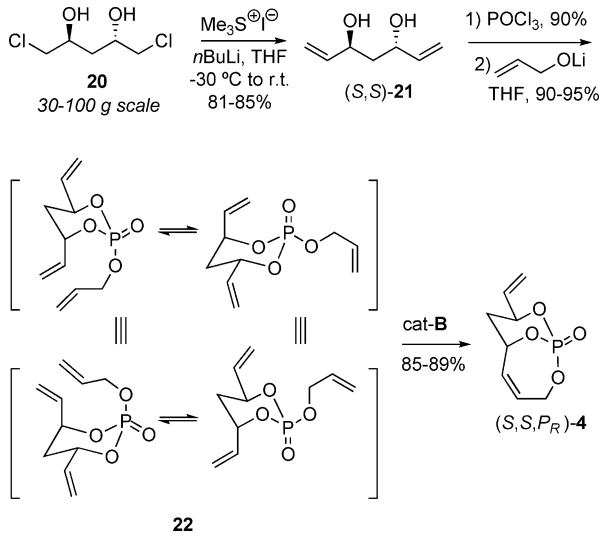
Multivalent Activation in Phosphate Tethers

The implementation of dipodal coupling to construct cyclic phosphates led further investigations employing tripodal coupling to construct more complex bicyclic phosphates such as (S,S,P_R)-**4** (Scheme 9). Seminal studies by Burke and co-workers had previously demonstrated utilization of a ketal tether desymmetrization method with C_2-symmetric diol **17** (Scheme 8). In this study, ketalization, elimination, and subsequent RCM occurred in the presence of cat-**A**

yielding a single product **19**.[18] Overall, the ketal tether allowed for facile differentiation of the homotopic vinyl groups of the starting diol **17** to produce the chiral, nonracemic bicyclic ketal **19**.



Scheme 8. Burke method of desymmetrization.



Scheme 9. Use of RCM in the construction of the *P*-chiral, bicyclo[4.3.1]phosphate (*S,S,P*$_R$)-**4**.

It was anticipated that a similar approach could be taken for the assembly of the bicyclic phosphate triester by using desymmetrization of the C_2-symmetric 1,3-*anti*-diol **21** (Scheme 9). Diol **21** was accessed from dichloro-1,3-*anti*-diol **20**,[19] by using a modified Mioskowski-Christie protocol.[14] Condensation with $POCl_3$, followed by coupling with a lithium alkoxide derived from allyl alcohol, gave triene **22** in good yields. Differentiation of the vinyl groups occurs through RCM (cat-**B**, CH_2Cl_2, 40 °C) where the chair conformer bearing the allyl ester *cis* to the vinyl group leads to formation of a single chiral, nonracemic bicyclic product (*S*,*S*,*P*$_R$)-**4**.[9a]

A key feature within **4** is that 7 of the 9 non-oxygen atoms possess electrophilic character, and thus nucleophilic attack can occur at phosphorus or any of the three carbinols [C3, C6, and C8] as well as at allylic phosphate carbons [C4, C5, and C12], respectively (Figure 7).[9a] It was these characteristics that prompted investigations yielding chemo-, regio-, and stereoselective processes.

The first of these observations was the notable stability of **4** toward a variety of acidic conditions. Exposure to 10% HCl (aq.)/dioxane and TMSCl afforded clean, unreacted starting material after prolonged reaction times. The enhanced stability appears to be a result of the lack of *anti*-periplanar (*app*) lone pairs on the adjacent oxygen atoms to the phosphoryl group, which impedes enhancement of the P=O basicity (Figure 8). This observation is consistent with decreased proton affinities of cyclic phosphites and the inordinate stability of bicyclic phosphates.[20]

As stated earlier, subjecting phosphates to basic hydrolysis conditions are known to stop at the monoanion salt (Figure 1).[8] Taking this fact into consideration, hydrolysis of **4** could likely give rise to three regioisomeric phosphate mono-acid salts (Figure 9).

Subjecting **4** to LiOH (aq.) in dioxane provided a quantitative and selective cleavage as determined by ^{31}P NMR spectroscopy.[9a] The appearance of a major singlet at –0.06 ppm showed the formation of a major regioisomer formed (*rs* = 44:1). ^{13}C NMR comparative analysis revealed a diagnostic upfield shift of the resonance corresponding to the C8 carbinol. This indicated regioisomer **23a** was formed as the major product (Figure 10). Further evidence of this selective hydrolysis was determined from the loss of C–P coupling at the C8 carbinol. This observation was surprising in the fact that selective phosphate hydrolysis[21] has been considered quite limited[22] in a number of extensive studies[23] done on acidic and basic hydrolysis of phosphate esters.

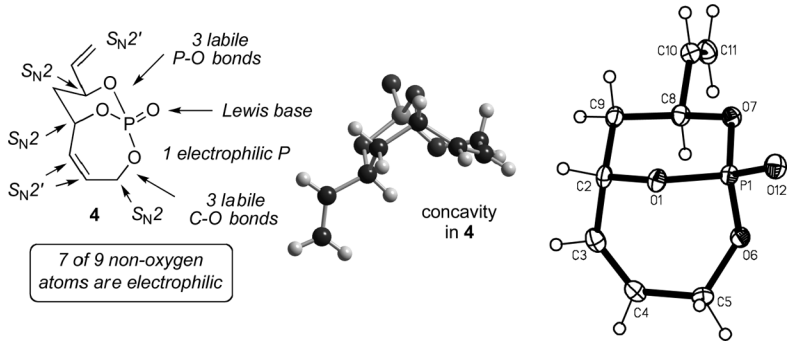


Figure 7. Features of *P*-chiral bicyclo[4.3.1]phosphate **4**.

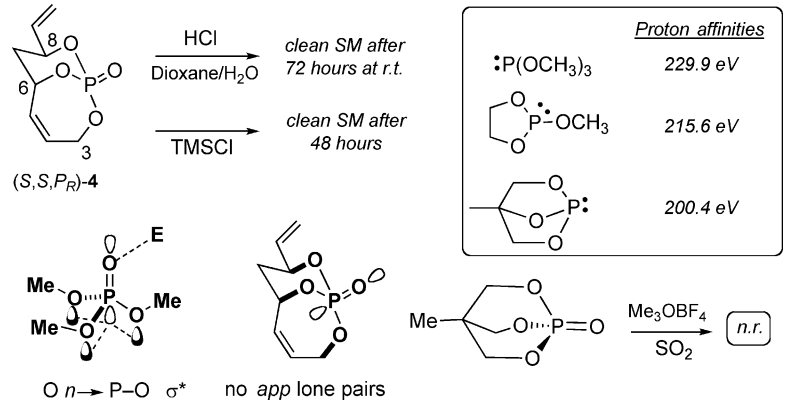


Figure 8. Stability of **4** toward acidic conditions.

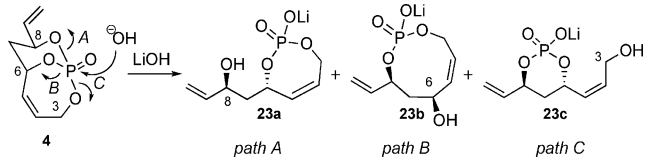


Figure 9. Possible hydrolysis products from **4**.

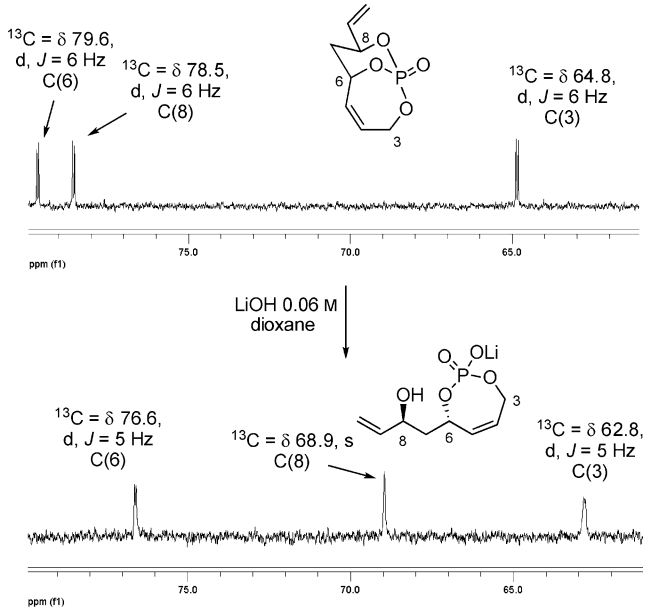
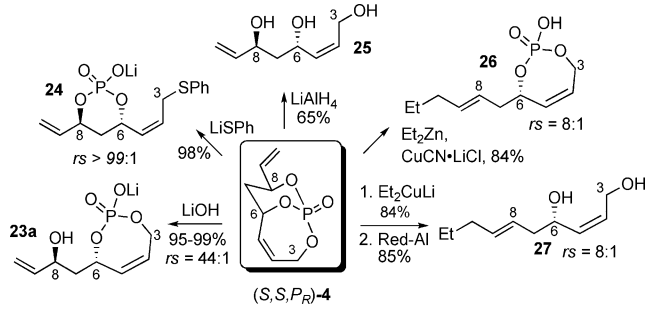


Figure 10. ^{13}C analysis of basic hydrolysis of **4**.

Other nucleophiles were probed showing good regio- and stereoselectivities (Scheme 10). In contrast to hydrolysis, addition of LiSPh gave preferential attack toward the C3 carbinol (*rs* > 99:1) in nearly quantitative yield to afford linear phosphate **24**. As shown earlier (Scheme 2), subjection to excess $LiAlH_4$ resulted in removal of the *P*-tether furnishing **25** in 65% yield. Consistent with the assembly of *syn*-(*E*)-homoallylic alcohols, addition of diethyl-zinc derived organocuprate yielded phosphate acid **26** followed by cleavage with RedAl® to afford diol **27** from allylic displacement at the more sterically accessible exocyclic olefin.[9a]

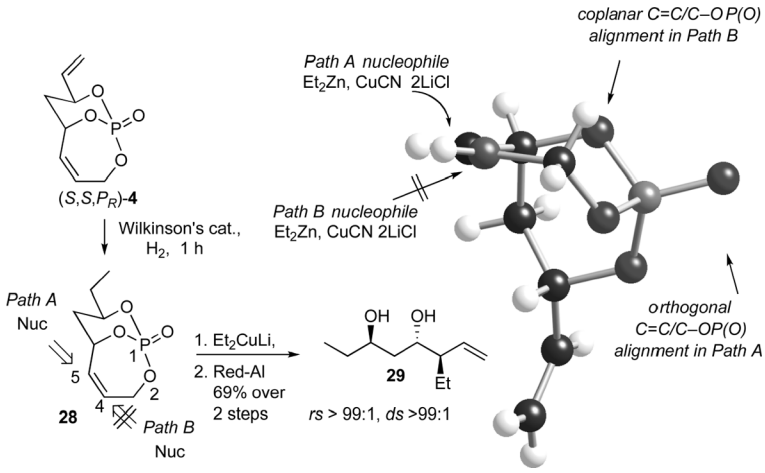


Scheme 10. Regio- and diastereoselective reactivity of **4**.

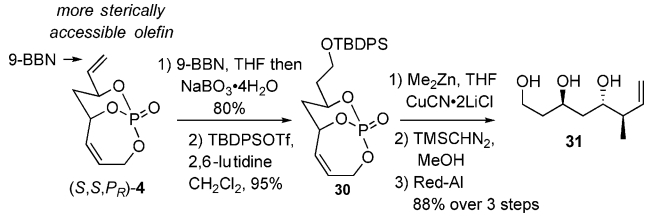
Having established the preference of the organocuprate to approach toward the more sterically accessible olefin, investigations were done to observe selectivity on allylic displacement of the endocyclic olefin. Reduction of the exocyclic double bond was carried out under an atmosphere of H_2 in presence of Wilkinson's catalyst to generate **28** (Scheme 11). Treatment with ethyl cuprate resulted in preferential addition to the C5 carbon. Subsequent phosphate cleavage produced 1,3-*anti* diol **29** as a single diastereomer. The regioselectivity is attributed to proper coplanar alignment of the π* orbital of the olefin and the σ* orbital of the C–OP(O) moiety (Path A, Scheme 11). Facial selectivity was rationalized by the geometry of the bicyclic skeleton, shielding approach of the organocuprate from the concave face. This result was quite exciting from a standpoint of natural product synthesis, since numerous targets bear the *anti*/*anti*-1,3,4-stereotriad within **29**.[24]

Another highlight of selective functionalization of **4** was seen in hydroboration (Scheme 12).[9a] Addition of 9-BBN across the exocyclic olefin, followed by mild oxidation of the corresponding borane ($NaBO_3 \cdot 4H_2O$)[25] furnished a primary alcohol,[26] which was protected with TBDPSOTf to give silyl ether **30** in good yield. Further conversion to triol **31**[27] was accomplished by using the same cuprate/methylation/cleavage sequence shown previously to afford triol **31** as the sole product (Scheme 5).

The utility of the phosphate tether for the rapid generation of advanced polyol subunits is highlighted in Scheme 13. After coupling cyclic phosphoryl chloride **21**

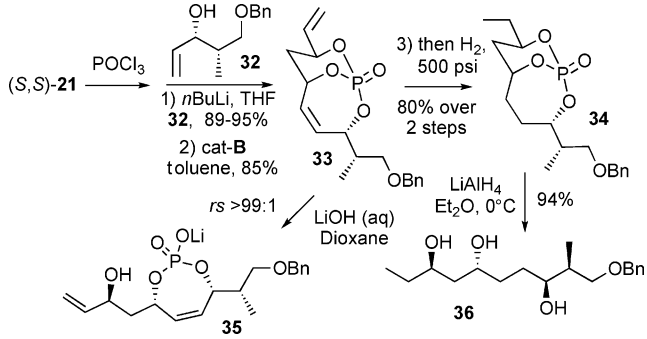


Scheme 11. Cuprate selectivity on endocyclic olefin of **4**.



Scheme 12. Hydroboration/cuprate/cleavage sequence of **4**.

with chiral allylic alcohol **32**, successful RCM gave the complex phosphate **33**. Hydrolysis of the phosphate yielded **35** as the phosphate lithio-salt in 3 steps from **21**. Exhaustive hydrogenation[28] of both olefins (H_2, 500 psi) and quantitative phosphate cleavage ($LiAlH_4$) afforded the polyol subunit **36** in an efficient 4-step protocol from **21**.[9a]



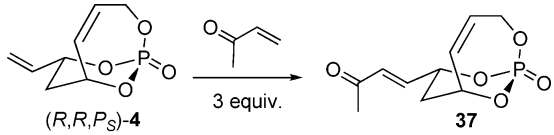
Scheme 13. Construction of complex differentiated polyol subunits from **4**.

Overall, a number of selective nucleophilic additions to **4** have been demonstrated. These observations highlight the ability of multivalent activation in phosphate triesters to rapidly access complex, differentiated polyol subunits, which are applicable to natural product synthesis.

Phosphate Tethers in Cross Metathesis

Interest in further manipulation of the bicyclic phosphate through olefin cross-metathesis (CM) led additional studies. Olefin CM has established itself as a powerful technique for accessing highly substituted olefins in a rapid, mild, and selective manner.[29] It was thought that the exocyclic olefin in **4** could be utilized as a cross partner to further functionalize the phosphate scaffold. Initially studies sought to acquire a compatible metathesis catalyst by using excess amounts of methyl vinyl ketone in refluxing CH_2Cl_2 (Table 2).[9c] Neither Grubbs first- or second-generation catalysts (cat-**A** and cat-**B**)[30] were efficient in obtaining CM adduct **37**. However, subjecting (*R*,*R*,P_S)-**4** to Hoveyda–Grubbs second-generation catalyst cat-**C**[31] gave improved yields. The conditions employed in Entries 4 and 5 were developed by Blechert and co-workers, which are compatible with electron-deficient systems.[32] Excellent olefin selectivity was observed (*E*:*Z* = 44:1 for Entry 4 and 15:1 for Entry 5), where more dilute conditions promoted a more efficient CM.

Table 2. Catalyst screening for CM of **4** and methyl vinyl ketone.

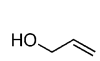
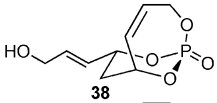
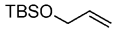
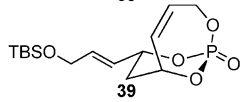
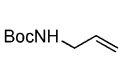
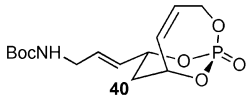
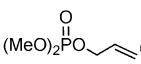
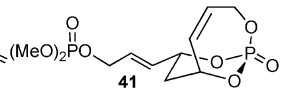
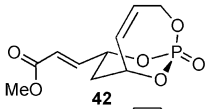
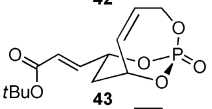
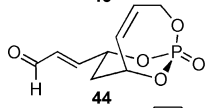
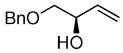
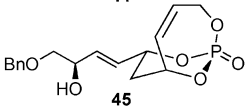
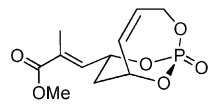
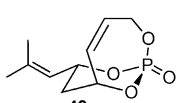
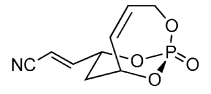


Entry	Catalyst (10 mol-%)	Conc./ solvent	% Yield
1	cat-**A**	0.05 M / CH_2Cl_2	<5 [a]
2	cat-**B**	0.05 M / CH_2Cl_2	25 [a]
3	cat-**B**	0.1 M / CH_2Cl_2	26 [a]
4	cat-**C**	0.05 M / CH_2Cl_2	75 [b]
5	cat-**C**	0.1 M / CH_2Cl_2	71 [b,c]

[a] Conversion determined by ^{31}P NMR spectroscopy. [b] Yields determined by isolated, purified products. [c] Used 4.0 equiv. of MVK.

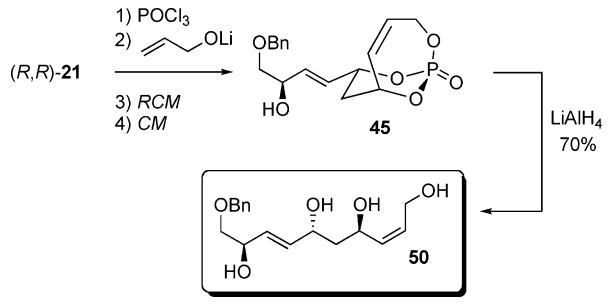
With this result in hand, a series of CM were carried out with various Type I (characterized by rapid homodimerization) and Type II (slow homodimerization) olefins.[33] Using 1.1 equiv. of allyl alcohol and TBS-protected alcohol gave excellent yields and selectivity in presence of 10 mol-% of cat-**C** (Entries 1–2 in Table 3). When switching to a Boc-protected allylamine (Entry 3), yield of the corresponding CM product decreased, however selectivity was maintained. Implementing allyloxy dimethoxyphosphate (Entry 4) afforded **37** in good yield, albeit in low *E*:*Z* selectivity.[9c]

Table 3. CM of **4** with type I, II, and III olefins. All entries reported used with cat-**C** catalyst.

Entry	CM partner	Product	% Yield	*E*/*Z*	Type
1		 **38**	86	>99:1	I
2		 **39**	87	>99:1	I
3		 **40**	69	>99:1	I
4		 **41**	80	2:1	I
5		 **42**	78	8:1	II
6		 **43**	60	5:1	II
7		 **44**	78	>99:1	II
8	 **46**	 **45**	72	>99:1	II
9		 **47**	<5 [a]	n/a	III
10		 **48**	<5 [a]	n/a	III
11			<5 [b]	n/a	III
12		 **49**	n.r. [b]	n/a	III

[a] Used 4.0 equiv. of CM partner. [b] Reaction attempted neat.

Screening electron-deficient Type II olefins revealed 4–5 equiv. of cross-partner, and 10–12 mol-% of cat-**C** were required for optimum results. Treatment with methyl acrylate and *tert*-butyl acrylate (Entries 5–6) gave good selectivity. When switching to acrolein, selectivity increased greatly. Entry 8 shows an attractive extension of this chemistry in which more elaborate cross partners can be exploited to achieve complex subunits. In this example, treatment of **4** with (*R*)-1-(benzyloxy)but-3-en-2-ol **46** provided smooth conversion to phosphate **45** in good yield and excellent selectivity. Subsequent facile removal of the phosphate-tether was achieved in the presence of $LiAlH_4$ (Scheme 14) to construct **50** in a concise five-step sequence.[9c]

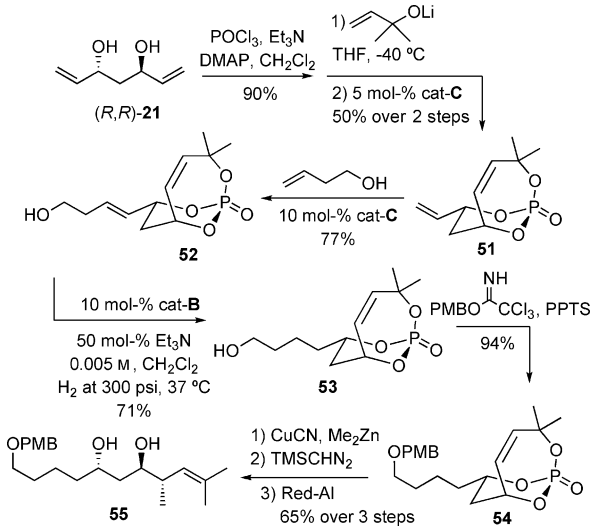


Scheme 14. Five-step protocol from (*R*,*R*)-**21** to polyol **50**.

When attempting CM with various Type-III olefins (no homodimerization),[33] poor reactivity was observed. Treatment with methyl methacrylate for 12 h resulted in clean recovery of the cross partner (Table 3, Entry 9). Trace amounts of product were seen when using varying equivalents of isobutylene (Table 3, Entries 10 and 11). Use of acrylonitrile also resulted in no reaction with the electron-deficient cross partner (Table 3, Entry 12).[34] Throughout these studies, no homodimerization was observed even when subjecting **4** to cat-**C** for 24 h, leading to the conclusion that the exocyclic olefin behaves as a Type-III partner. A simple sequence to the complex polyol **50** starting from (*R*,*R*)-**21** highlights the power of this method (Scheme 14).

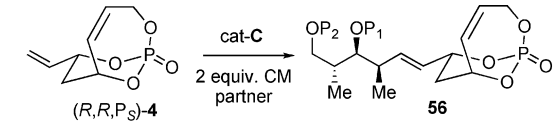
Overall, this method has been utilized for the synthesis of complex polyketide structures, namely **55**, which possesses a key stereotriad found in a number of natural products.[24] Compound **55** was accessed through incorporating a geminal dimethyl group to construct **51**, which underwent successful CM with homoallyl alcohol (Scheme 15). Regioselective hydrogenation of the exocyclic olefin was achieved,[35] followed by subsequent PMB-protection of the primary alcohol to afford **52**. Consistent with earlier results seen in cuprate additions to these cyclic phosphates, the same three-step protocol towards the *anti*/*anti* stereotriad, in compound **55** was achieved in 65% yield.[9c]

Investigations were carried out to find a cross partner bearing the *syn*/*anti* stereotriad contained within dolabelides A-D.[24a,24b] A noticeable steric effect was observed when changing the protecting group on the primary alcohol of the cross partner (Table 4).[36]



Scheme 15. CM/hydrogenation/cuprate sequence.

Table 4. Remote steric effects of cross partners in CM with **4**.

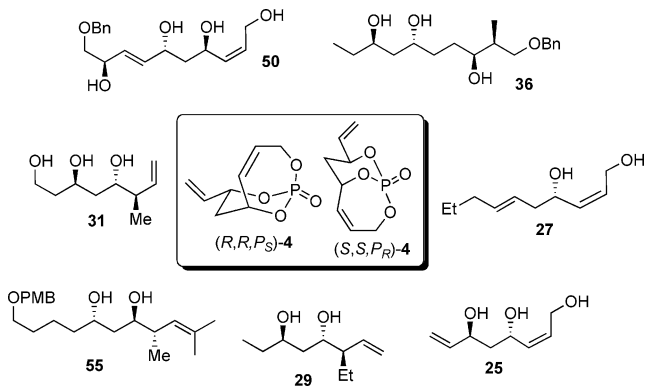


CM partner	cat-**C** loading	Solvent	Temp. (°C)	Yield (%)
PMBO OTBDPS Me Me **57**	6 mol-%	$PhCH_3$	60	N.A.
	6 mol-%	$PhCH_3$	90	28
	12 mol-%	$PhCH_3$	90	31
PMBO OTBS Me Me **58**	6 mol-%	CH_2Cl_2	50	42
	6 mol-%	$PhCH_3$	90	45
	12 mol-%	$PhCH_3$	90	60
	6 mol-%	DCE	90	72
PMP Me Me **59**	6 mol-%	CH_2Cl_2	50	32
	6 mol-%	$PhCH_3$	90	63
	6 mol-%	DCE	90	73

Using the bulky *tert*-butyldiphenylsilyl (TBDPS, **57** in Table 4) as a protecting group gave poor results, showing the poor reactivity of the cross partner. Switching to the less sterically demanding *tert*-butyldimethylsilyl (TBS, **58**) protecting group gave much better conversion. Optimal conditions were found to utilize 6 mol-% of Hoveyda–Grubbs second-generation catalyst cat-**C** at elevated temperatures (90 °C) in 1,2-dichloroethane (DCE). Alternatively, use of a PMP-acetal **59** gave similar results to that of **58**.[36]

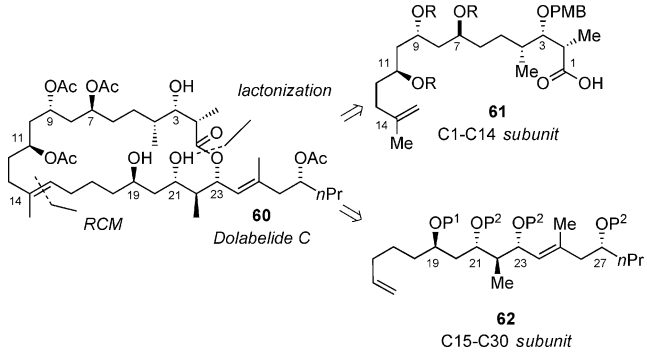
Phosphate Tethers in Natural Product Synthesis

Given the observations from the use of diastereo- and chemoselective cuprate additions, regioselective hydrogenation, cross-metathesis, and facile tether removal in presence of a hydride source, the next step was applying this method in natural product synthesis, namely aimed at the total synthesis of dolabelide C. Fragments **50** and **55** (Scheme 16) were attractive subunits in obtaining the requisite C1–C14 and C15–C30 subunits bearing the necessary stereochemistry required in the total synthesis of the macrolactone dolabelide C.



Scheme 16. Differentiated polyol subunits accessed from **4**.

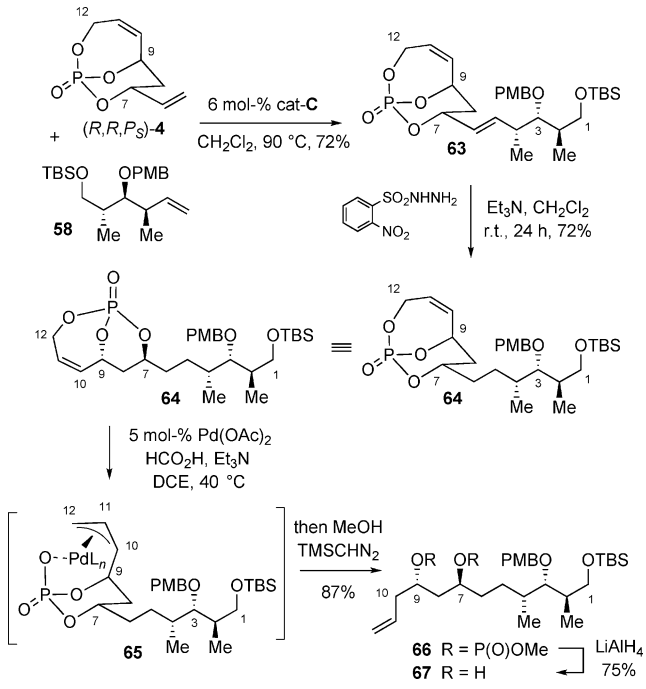
Dolabelides A–D were isolated from a sea hare, *Dolabella auricularia*.[24a,24b] To date, Leighton's total synthesis of Dolabelide D stands as the lone synthesis of any member in this family.[37] Retrosynthetic analysis revealed two subunits (**61** and **62**, Scheme 17) bearing stereochemistry, which can be accessed by using the developed *P*-tether technology. The C1–C14 subunit could be accessed by using chemistry similar to that of fragment **50**, and the C15–C30 subunit could be accessed by using chemistry similar to that of fragment **55** (Scheme 9).



Scheme 17. Retrosynthetic analysis of dolabelide C.

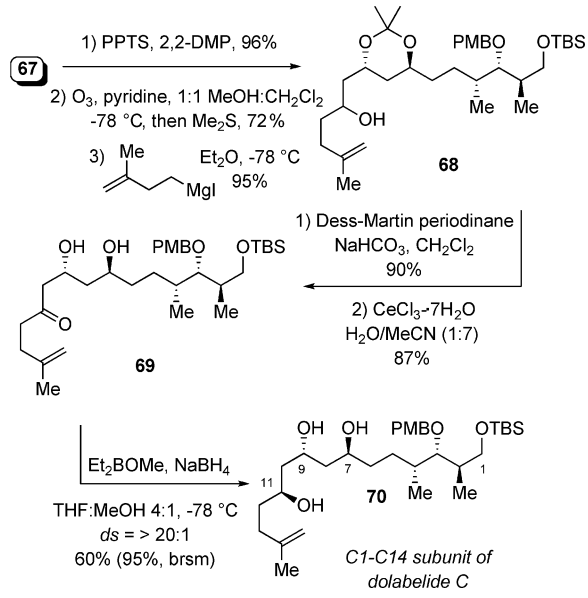
Employing the previously developed CM methodology for the union of bicyclic phosphate (*S*,*S*,P_R)-**4** and the readily prepared subunit **58** resulted in clean reaction to generate the advanced homoallylic PMB-ether **63** in 72% yield. Subsequent regioselective diimide hydrogenation[38] of the exocyclic olefin gave **64**. A Pd-formate reduction was next utilized to transpose the C10–C11 olefin to the C11–C12

position for necessary alkene oxidation to introduce the C13–C14 fragment as well as to obtain the C11 carbinol.[36] In this protocol, Pd-formate reduction[39] gave excellent regio-selectivity (preferred internal addition into π-allyl complex **65**) of allylic phosphate displacement to afford **66** after methylation of the phosphate acid. Removal of the phosphate ester in presence of $LiAlH_4$ completed a phosphate-mediated sequence constructing the C1–C11 subunit (Scheme 18).

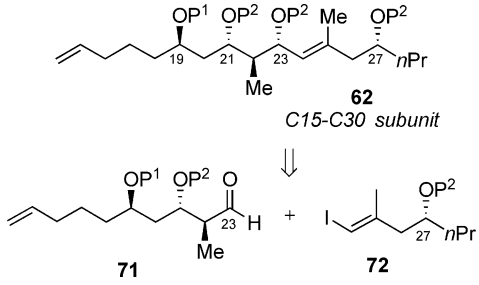


Scheme 18. Phosphate-mediated construction of C1–C11 subunit.

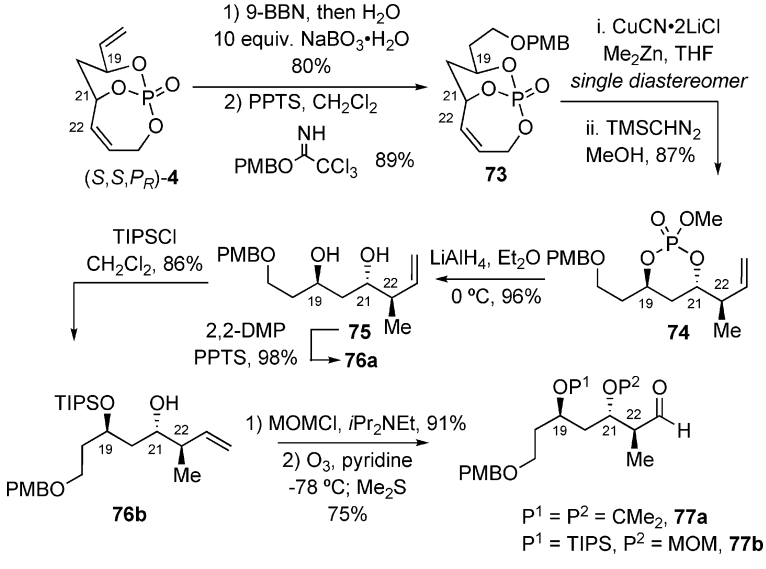
Final steps to completing the C1–C14 framework included acetonide protection, followed by ozonolysis of the terminal C11–C12 olefin and Grignard addition (derived from 1-iodo-3-methyl-3-butene) to produce **68** (Scheme 19). Oxidation of the C11 carbinol (Dess–Martin periodinane) and removal of the acetonide by using $CeCl_3 \cdot 7H_2O$ set the stage for a stereoselective reduction of **69** by using Evan's



Scheme 19. Final steps to C1–C14 subunit.



Scheme 20. Retrosynthetic analysis of the C15–C30 subunit.



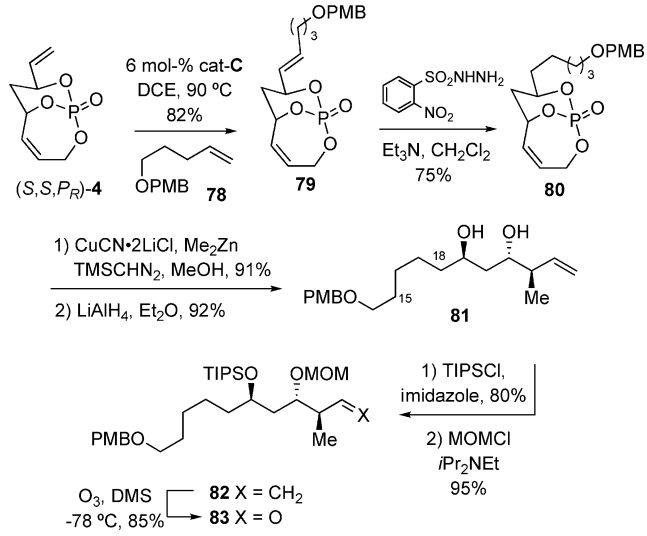
Scheme 21. Phosphate-mediated approach to aldehydes **76a** and **76b**.

syn-reduction[40] conditions (20:1 ds of desired C11 epimer), affording all of the necessary stereocenters (**70**) in 13 steps from phosphate (*S*,*S*,P_R)-**4**.[36]

The strategy toward the C15–C30 subunit employed phosphate-mediated synthesis of aldehyde **71** (Scheme 20), which was then to be subjected toward a coupling with vinyl iodide **72** to afford desired intermediate **62**.[41] Utilizing the aforementioned regioselective hydroboration, starting from (*R*,*R*,P_S)-**4**, the resultant primary alcohol was protected by using PMB-imidate. Intermediate **73** was subjected to cuprate conditions (Me_2Zn, CuCN·2LiCl), yielding a single diastereomer at C22 (Scheme 21). Subsequent methylation gave phosphate ester **74**, followed by tether removal, afforded diol **75**. Acetonide protection of the 1,3-diol or a two-step sequence to obtain orthogonal protection yielded intermediates **76a** and **76b**, respectively. Both species underwent successful oxidation of their terminal olefins under ozonolysis conditions to yield both aldehydes (**77a** and **77b**) by a phosphate-mediated approach.

Alternatively, a CM-selective hydrogenation approach (as previously shown in Scheme 15), was also employed to append the C15–C18 framework. The two-step protocol smoothly converted (*S*,*S*,P_R)-**4** to **79**, followed by cuprate addition and tether removal to afford diol **81**. Orthogonal protection and ozonolysis furnished aldehyde **83** over a three-step sequence (Scheme 22).[41]

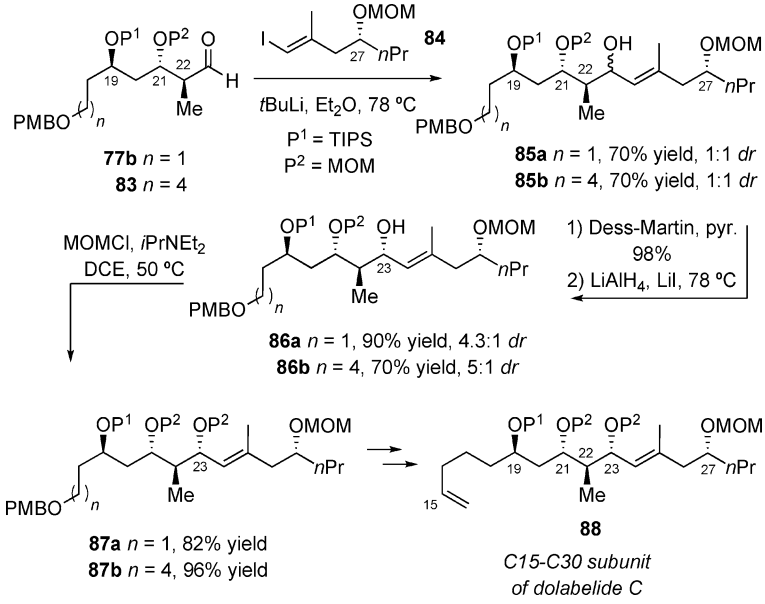
Aldehydes **77b** and **83** were coupled together with a vinyl-lithiate generated from treating vinyl iodide **84** with *tert*-butyllithium to give a 1:1 ratio of C23 epimers for both cases (Scheme 23). Protection of the C23 carbinol with MOMCl gave fully protected polyols **87a** and **87b**, which were converted to a C15–C30 subunit of dolabelide C **88**, via different pathways.



Scheme 22. Alternative approach to C15–C30 subunit.

Conclusions

Phosphate tethers are effective tools in constructing advanced polyol synthons rapidly from simple glycidyl ether **6** or C_2-symmetric diol **20**. Utilization of divalent activation from monocyclic tethers **1**–**3** to construct homoallylic alcohols by regio- and stereoselective cuprate additions further display the effectiveness of S_N2' displacements of allylic phosphates. In addition, multivalent activation from the bicyclo[4.3.1]phosphate **4** has been expanded by the aforementioned cuprate chemistry, along with other selective nucleophilic additions, including hydride, hydroxide, and sulfide. Furthermore, regioselective hydrogenation and



Scheme 23. Final steps to the C15–C30 subunit of dolabelide C.

hydroboration, in conjunction with Type-III behavior in cross-metathesis reactions position this method for use in advanced polyol synthesis. Overall, synthons accessed by this methodology have been applied to natural product synthesis. The potential for further application of *P*-tethers in total synthesis will be reported in due course.

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