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Discovery of a Phosphine-Mediated Cycloisomerization of Alkynyl Hemiketals: Access to Spiroketals and Dihydropyrazoles via Tandem Reactions

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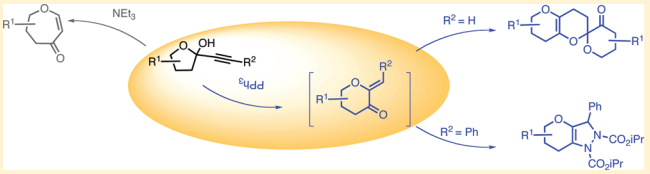
Supporting Information

ABSTRACT: Reported here are details on the discovery of a phosphine-catalyzed isomerization of hemiketals and subsequent reactions of the cyclic keto enol ether products. The new cycloisomerization complements a previously reported amine-catalyzed process that gave oxepinones from the same hemiketal starting materials. In the absence of functionality (R^2) on the cyclic keto enol ether, a rapid and facile dimerization occurs, giving spiroketal products. When the enone is substituted (i.e., R^2 = Ph), the cyclic keto enol ether is sufficiently stable so that it can be isolated; it can then be further reacted in the same pot to provide the corresponding dihydropyrazoles. Both the spiroketal and dihydropyrazole products arise by a tandem reaction that begins with the novel cycloisomerization. The method allows for the rapid introduction of complexity in the products from relatively simple starting materials. It should find application in the synthesis of natural product-like molecules.



INTRODUCTION

Tandem, or domino, reactions that serially organize multiple bond forming events in a single operation have emerged as a powerful tool for the construction of complex molecules starting from simple starting materials.[1−4] Tandem methods typically circumvent conventional multistep processes and have become a prevalent objective in organic reaction development. When such reactions use a catalyst, the transformations serve as candidates for the creation of diversity-oriented libraries of small, highly functionalized molecules for the discovery of medicinally important molecules in an economical and environmentally acceptable way. Here we report on the discovery of a reaction that isomerizes alkynyl hemiketals to their corresponding cyclic keto enol ethers via phosphine catalysis. In the absence of substitution on the enone moiety, the products undergo a spontaneous hetero-Diels−Alder cycloaddition, yielding novel dimeric spiroketals. When the enone is substituted, a subsequent reaction with an azodicarboxylate yields the corresponding dihydropyrazole.

A number of methods for the synthesis of spiroketals have been developed.[5−11] They were inspired by the challenge of natural product total synthesis, physical investigations into the fundamental principles governing spiroketal configuration, and the biological activities associated with spiroketal-containing natural products. Representative examples of natural product spiroketals are oligomycin B (**1**),[12−14] berkelic acid (**2**),[15−17] and reveromycin A (**3**) (Figure 1).[18−20] Among the structures in Figure 1, oligomycin B is noteworthy because it contains a ketone α to the spiroketal which parallels the organization of functionality that develops in the new tandem reaction reported here. Activities reported for **1**−**3** include cytotoxicity by inhibition of ATP or protein synthesis, inhibition of proteases such as MMP-3 and caspase-1, and antifungal activity. Following the lead of these and related natural products, spiroketals have been utilized as the core component of small molecule libraries.[21−26] The synthetic methods themselves follow a few main strategies: acid-mediated ketalization of keto-diols or hydroxy-hemiketals, cyclization of glycal epoxides, and hetero-Diels−Alder reactions of enones and enol ethers. Each of these approaches has been effective at generating natural product and natural product-like spiroketals. The new tandem sequence reported here involves a [4 + 2] hetero-Diels−Alder reaction as the spiroketal forming step; in fact, it is the facile access to and reactivity of the keto enol ether via a phosphine-catalyzed cycloisomerization that enable the cycloaddition reaction.

Phosphine-catalyzed annulation reactions are a powerful means for the synthesis of a variety of carbocycles and heterocycles.[27,28] Previous syntheses commonly used formal cycloaddition approaches, tethered bifunctional nucleophilic additions to activated ylides, or Morita−Baylis−Hillman (MBH)-type reactions.[27] There are only a few reports in the literature on phosphine-catalyzed oxacycle synthesis from linear precursors.[29−32] Pioneering work by Trost demonstrated a 1,3-bis(diphenylphosphino)propane (dppp)-catalyzed cyclization of hydroxy-2-alkynoates.[29] The ordinarily nucleophilic γ position of the internal alkynoate **4** (eq 1) was made electrophilic ("umpoled") through conjugate addition by the phosphine followed by sequential isomerization and proton transfer steps. Subsequent addition of the pendant hydroxyl group to the γ position and release of the phosphine resulted in the formation of the corresponding tetrahydrofuran **5**. Fu and co-workers

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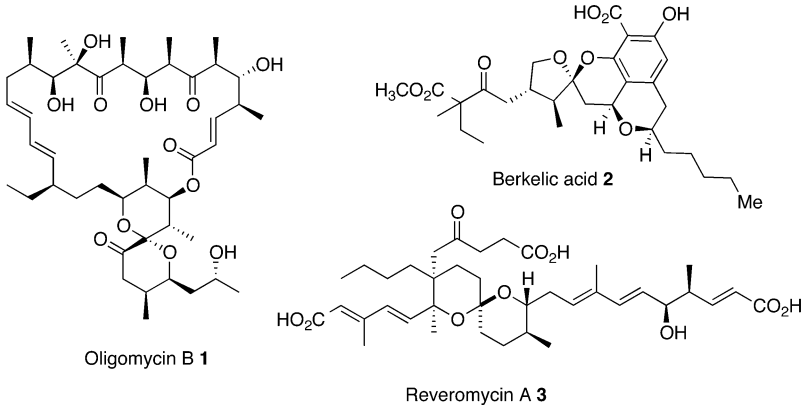
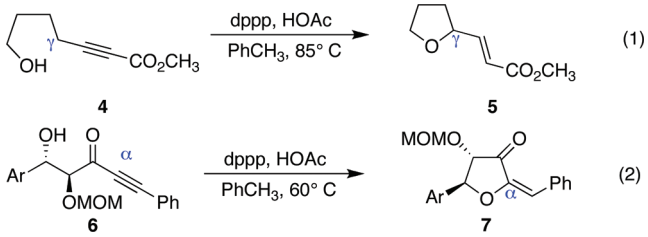


Figure 1. Representative natural products containing a spiroketal moiety.

have recently reported the asymmetric variant of this transformation using a chiral phosphine catalyst which has expanded the utility of the reaction.[30] Similar annulation reactions have been reported where an internal hydroxyl group attacks at the α position of an ynone (**6** in eq 2). Here the α carbon of the ynone was rendered electrophilic through conjugate addition by a phosphine and proton transfer. The cyclized products (i.e., **7**) are substituted keto enol ethers, a motif that occurs naturally in aurones.[33] In fact, several reports on the stepwise synthesis of aurones have appeared in the literature.[34,35] Keto enol ethers can serve as important intermediates for further elaboration through either the ketone or the exocyclic enol ether functionality.[31,32]

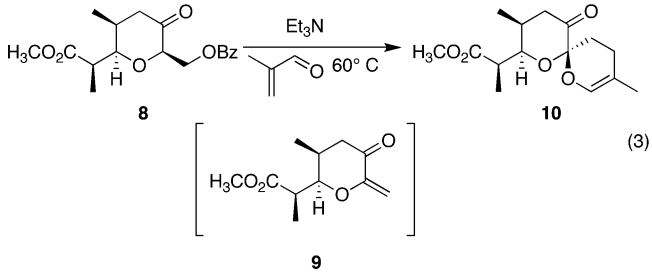
The keto enol ether unit also exhibits reactivity in inverse electron demand Diels–Alder reactions, particularly when



(1) (2)

substituents on the exocyclic olefin are absent; in the absence of a partner for the cycloaddition, a dimerization occurs. Here 1 equiv of the enone acts as an electron-deficient diene and the enol ether portion of another acts as the dienophile.[36] An early report by Ireland on the cycloaddition of unsubstituted keto enol ethers mentioned that dimerization was a side reaction,[37] while others simply noted the relative reactivity or instability of related unsubstituted keto enol ethers.[38−40] In the Ireland work, dimerization of the keto enol ether **9** (eq 3) was prevented by conducting the reaction in the presence of a large excess of methacrolein. A crossed cycloaddition to form **10** (as the major product isomer) by trapping the keto enol ether was affected in situ. While such transformations demonstrated the potential to be used for the synthesis of complex spiroketal scaffolded libraries,[37] a study on the precise reactivity of this class of enones has remained largely unexplored.

We recently developed a method to synthesize oxepinones such as **14** by triethylamine-mediated isomerization of hemiketals (**11** in eq 4).[41] The oxepinone products were to serve as intermediates in the preparation of ring-expanded glycals (oxepines) that have been synthetic targets in our group.[42,43]



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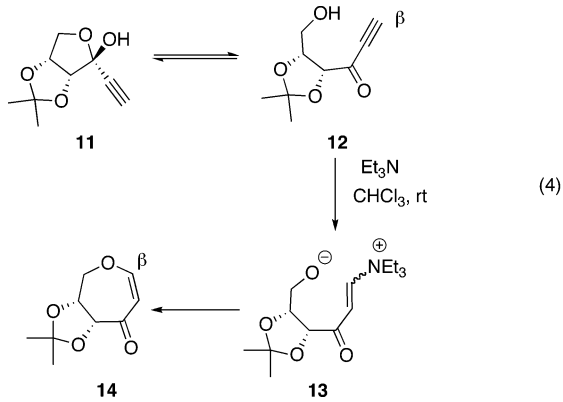
In the reaction, **14** was obtained by oxygen addition to the β position of activated enone **13** and release of triethylamine. Intermediate **13** was itself generated by the addition of triethylamine to starting hemiketal (masked alkynone **12**). Mindful of the complementary reactivity of phosphines in comparison to amines, we set about investigating the phoshine-mediated cyclization of **11**. Here we detail the discovery of a new cycloisomerization of hemiketals such as **11**, the scope and reactivity of the subsequent isomerization product, and mechanistic investigations for the transformation.



(4)

RESULTS AND DISCUSSION

Discovery, Optimization, and Scope. The investigation began by reacting hemiketal **11** with PMe_3 as catalyst (Table 1 and Figure 2). Analysis of the reaction mixture by thin layer chromatography (TLC) revealed a product that was less polar than the starting material. It was isolated in 33% yield and analyzed by ^1H and ^{13}C NMR spectroscopy. The data clearly indicated a product that was different from the previously observed oxepinone **14**. Duplicate signals in both ^1H and ^{13}C NMR suggested a dimeric structure, which was further

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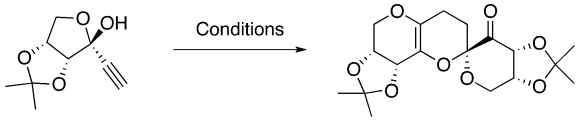
Table 1. Investigation of Initial Reaction Conditions for the Isomerization−Cycloaddition Dimerization



11 15

entry[a]	phosphine[b]	solvent	yield %
1	PMe_3	$CHCl_3$	33
2	PBu_3	$CHCl_3$	30
3	$PtBu_3$	$CHCl_3$	10
4	PPh_3	$CHCl_3$	96
5	PPh_3[c]	$CHCl_3$	85
6	PPh_3[e]	$CHCl_3$	77
7	dppe	$CHCl_3$	72
8	dppp	$CHCl_3$	84
9	PPh_2Me	$CHCl_3$	88
10	$P(pFPh)_3$	$CHCl_3$	35
11	PPh_3	toluene	70[d]
12	PPh_3	THF	0
13	PPh_3	CH_3OH	<2

[a]All reactions conducted at rt for 6 h. [b]Phosphine loading was 0.25 equiv except in entry 5. [c]Phosphine loading was 0.05 equiv in this case. Reaction took longer (~1 day) to complete and significantly low yielding for other substrates (e.g., with **13**, only 18% product was isolated). [d]Reaction in toluene was run overnight (~12 h). [e]Reaction performed at 0 °C.

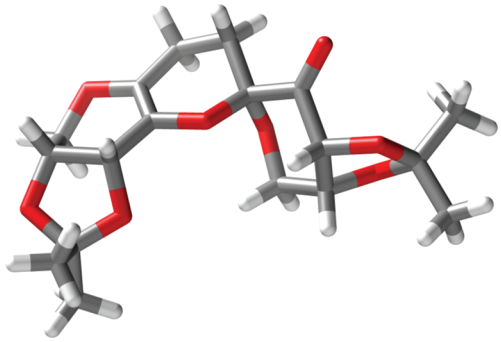


Figure 2. Structure of compound **15** from X-ray data.

supported by ESI-MS analysis. The connectivity of the dimeric structure was identified by diagnostic NMR signals and 2D NMR correlations (see Supporting Information for spectra). For example, a ^{13}C NMR signal at 198 ppm indicated a ketone, and signals at 127 and 138 ppm suggested an olefin and a signal at 98 ppm was diagnostic of a spiroketal. A crystal structure of the product, shown in Figure 2, unambiguously proved the connectivity of **15**. The structure shows that a ring expansion of the original hemiketal occurs along the course of the reaction. Additionally, a third ring forms as a result of the dimerization. Over the course of the tandem reaction, a bicyclic bis-enol ether is formed to which is attached an additional ring via a spiroketal linkage. Ascertaining the efficiency and scope of the reaction then became our priority.

We proceeded to optimize the reaction conditions. Use of PBu_3 failed to improve the yield, and a bulkier alkyl phosphine like $P(tBu)_3$ resulted in lower efficiency (entries 2 and 3). The difference in electronics between trialkyl and triaryl phosphines favors different pathways with respect to reaction of allenoates.[44−48] We therefore next investigated how aryl phosphines might fare in the reaction. Gratifyingly, the use of catalytic PPh_3 provided **15** in 96% yield (entry 4). Lowering the catalyst loading (entry 5) or temperature (entry 6) provided **15**, albeit in a slightly lower yield. In comparison to PPh_3, alkyl/aryl-substituted diphosphines showed a slight decrease in reaction efficiency (entries 7−9). This came as a surprise because we anticipated that the diphosphine catalysts would improve the yield based on the cyclization mechanism originally put forth by Trost.[29] The electron-deficient $P(pFPh)_3$ gave low conversion (35%, entry 10). The use of solvents other than chloroform also had a measurable effect on the reaction. Toluene resulted in a similar product yield but required a longer reaction time (entry 11). Notably, neither tetrahydrofuran (THF) nor methanol showed significant product formation (entries 12 and 13).

To gather information about the scope of the reaction, a number of different hemiketals (**16**−**20**) were prepared by addition of TMS-acetylide to the corresponding lactones and subsequent deprotection of the trimethylsilyl group (Figure 2).[41] It is noteworthy that the cyclic hemiketal structure is maintained for **16**−**18**, whereas **19** and **20** proved to be acyclic ynones. Under the optimized cyclization/dimerization conditions, acetonide-protected hemiketals **16** and **17** underwent conversion to tricyclic molecules **21** and **22** in 80 and 71% yields, respectively. Substrate **18**, lacking an acetonide on the C2−C3 diol, yielded **23** in moderate yield (55%), which suggested that rigidifying the starting material played a role in the efficiency of the transformation.[49] Efficiency similar to the other rigid substrates was achieved for cyclization of **19** and **20**, giving spiroketals **24** and **25** in 90 and 79% yields, respectively.

The structure of each product in Figure 3 was assigned based on comparison of its NMR spectra to that of **15**. Specifically, the appearance of a new signal (~96−99 ppm) in the ^{13}C NMR indicated the presence of the spiroketal moiety. Designating the configuration of the spiroketal for **21**−**25** was necessary because we did not have X-ray crystallographic data as we did in the case of **15**. Products **21**−**23** gave only one of two possible diastereomeric products; the spiroketal stereochemistry was tentatively assigned as shown (Figure 3) based on the structural (and reactive) similarity of the putative keto enol ether to one that has been reported previously.[36,50] Products **24** and **25** were isolated as a mixture of diastereomers. We speculate that the spiroketal stereochemistry is constant for **24** and **25**, and that the diastereomers are due to the relationship of the two methyl groups in the tricyclic structures (*syn*/*anti*).

Initial Mechanistic Considerations. Having established that the new reaction was relatively general, we sought insight into the pathway of the transformation. Ylide **28** (Scheme 1) presented itself as a key intermediate to the transformation. Attack at the carbon between the carbonyl and the phosphonium of **27** by the pendant oxygen gave rise to **28**. A study that reported on the intermolecular α addition of nitrogen nucleophiles giving dehydroamino acids served as a model for our thinking.[51] That intermolecular reaction required buffered conditions (for proton transfer) along with the phosphine catalyst. The intramolecular reaction reported here does not require buffered conditions; it does, however, favor the formation of α-functionalized products. Phosphine addition at the β position of the ynone likely facilitates attack at the α carbon on both electronic and steric grounds. The central question to us was the fate of ylide **28** in subsequent steps of the transformation. We wanted to know if formation of dimeric

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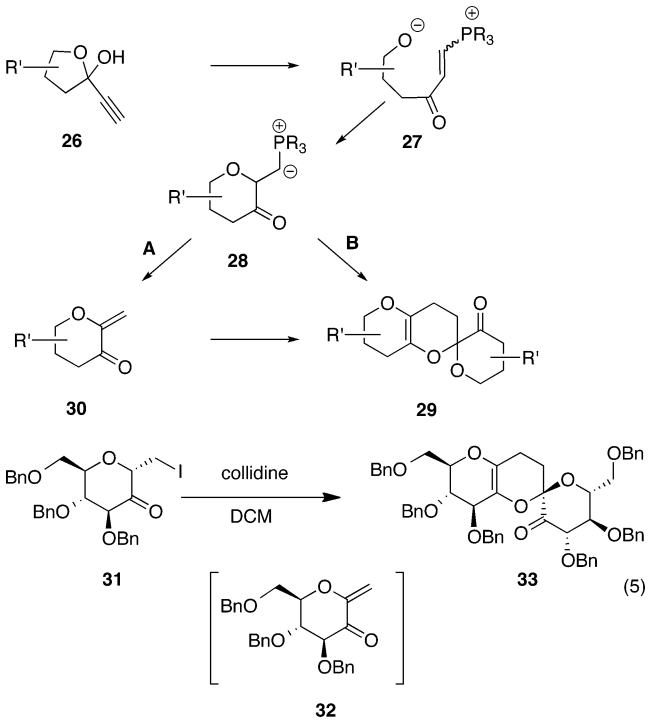
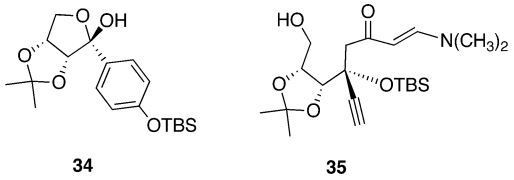
species **29** occurred by a concerted [4 + 2] pathway by way of cyclic keto enol ether **30** (path A) or by a phosphine-mediated stepwise process (path B). In the stepwise sequence, ylide **28** could add onto either hemiketal **26** or enone **30** in a secondary cycle.[52] Conversely, cyclic keto enol ether **30** could undergo a spontaneous homodimerization in a hetero-Diels–Alder reaction.

The sole precedent for dimerization of unsubstituted cyclic keto enol ethers was of the glucose derivative **31** being converted to **33** reported by Martin et al. (eq 5).[36] Dimerization was also mentioned in regard to **9** (eq 3),[37] although a dimeric product was not characterized. These observations suggested that a concerted pathway was likely in our system even though phosphine was present in the reaction. Because a cyclic keto enol ether had been trapped with excess methacrolein,[37] trapping seemed to be a logical place to begin our mechanistic investigations. Our strategy was to evaluate both dienophiles and dienes as capture agents. Reactions using 1 equiv of diphenyl acetylene and diethyl acetylene dicarboxylate as dienophiles or 2 equiv of Danishefsky's diene with hemiketal **11** as starting material under the established reaction conditions led to isolation of **15** as the only product. Using 2 equiv of Rawal's diene, however, led to other products besides **15**, which was isolated in 29% yield. Phenolic hemiketal **34** was a minor product (5%) and came about by Diels–Alder between the diene and the terminal alkyne of **11**.[53] Mukaiyama aldol product **35** was also isolated from the reaction in 61% yield; reactivity of this sort has been observed in another system.[54] We assigned the newly developed stereocenter based on the product of reduction of **42** (vide infra). Unfortunately, the trapping experiments did not provide solid support for either mechanism.

Scheme 1





In a different approach, we set out to synthesize compounds that were precursors of the cyclic keto enol ether by a route that did not utilize the phosphine-catalyzed isomerization (Scheme 2). The objective was to access a general precursor that could allow the generation of a series of cyclic keto enol ethers by a simple operation. We thought such an experiment would create more value in the current context of the phosphine-catalyzed cycloisomerization process and give more insight into the mechanistic aspects. An *exo*-glycal with a vinyl iodide unit was targeted as the synthetic handle in our strategy.

Diol **36**, prepared by known TMS-acetylide addition to the corresponding lactol followed by silyl deprotection,[55,56] was

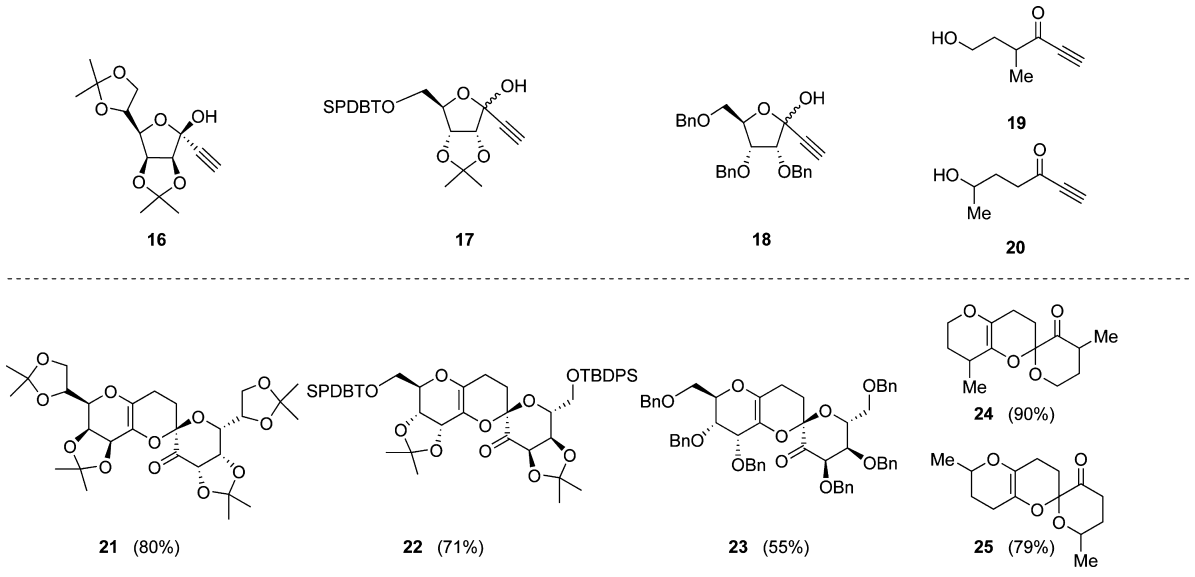


Figure 3. Hemiketals and ynones **16–20** (top) and the corresponding dimeric spiroketals **21–25** (bottom) prepared by the tandem cycloisomerization–cycloaddition reactions. Yields for the conversion are given in parentheses.

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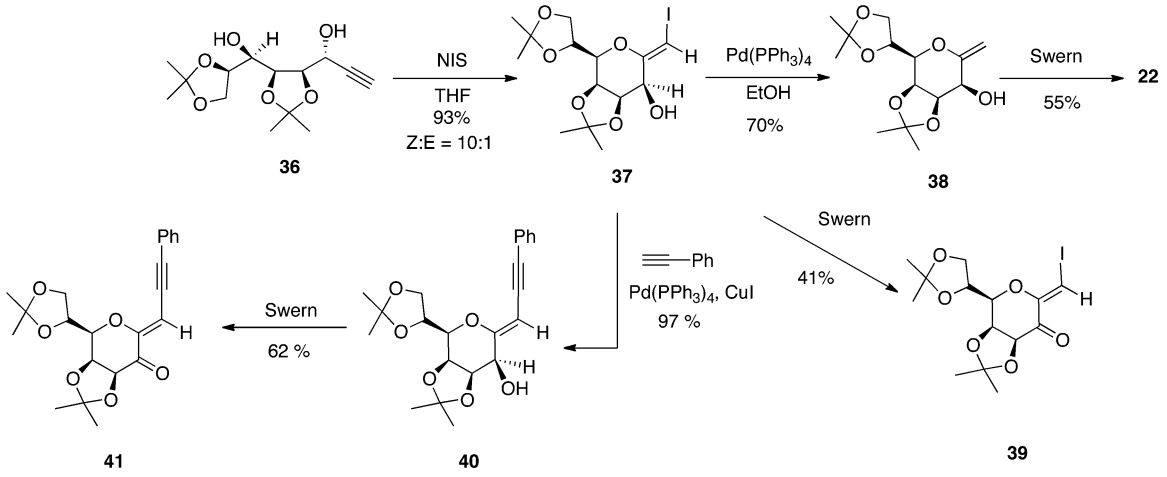
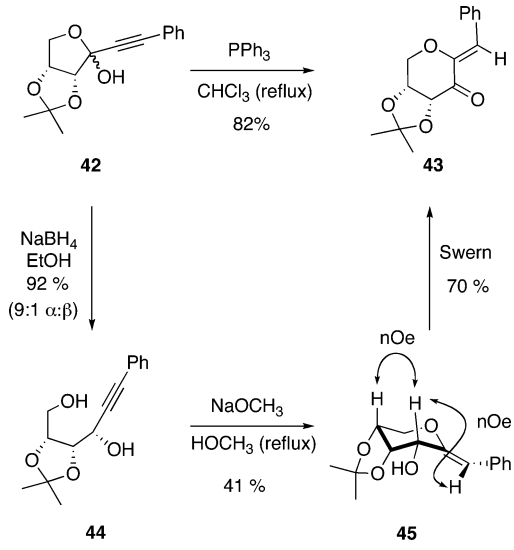
Scheme 2



readily transformed to *exo*-glycal **37** using NIS with a high preference for the *Z* isomer (*Z*/*E* 10:1). This cyclization could serve as a complementary process to other existing methods to obtain *exo*-glycals[57−62] and is novel in its own right; *exo*-glycal **37** contained free C2 hydroxyl and vinyl iodide groups, both of which were available for further functionalization. Upon Pd-catalyzed dehalogenation, *exo*-glycal **37** was transformed to **38**; Swern oxidation of this material resulted in isolation of dimer **22** in 55% yield. Isolation of the dimeric material was a clear indication that the hetero-Diels−Alder reaction was certainly viable in our tandem reaction. Notably, Swern oxidation of **37** provided iodo-substituted keto enol ether **39**, although decomposition was observed upon prolonged storage.[63] When **37** was converted to **40** and subjected to Swern conditions, cyclic keto enol ether **41** was the only isolated material. Compound **41** was found to be unreactive in terms of the dimerization under a number of reaction conditions. For example, when **41** was refluxed in chloroform or toluene in either the presence or the absence of PPh_3, no further reaction was noted. Even in reactions where **41** was subjected to higher temperature (180 °C) under microwave conditions, no evidence for dimerization was found. Considered collectively, the results suggested that the cyclic keto enol ethers readily formed from hemiketals with or without substitution on the alkyne; further, only when the alkyne was unsubstituted did the subsequent dimerization occur.

Phosphine-Catalyzed Cycloisomerization of Alkynyl-Substituted Hemiketals. On the basis of the control experiments conducted, we hypothesized that the phosphine-catalyzed reaction of substituted hemiketals such as **42** (Scheme 3) would stop at the keto enol ether product unless a secondary phosphine-catalyzed pathway to the dimer was operative.[64−68] When **42** was treated with PPh_3 under conditions used previously for similar substrates such as **11**, only unreacted starting material was recovered after 12 h. The appearance of a new product, however, was observed with higher catalyst loading (50 mol %) in refluxing chloroform. The new product was isolated in 96% yield as a single isomer and tentatively assigned as **43**. NMR analysis showed characteristic signals of a cyclic keto enol ether, but at this stage, it was difficult to determine the geometry of the *exo*-glycal as *E* or *Z*. A corroborative study was undertaken to determine if the *Z* geometry shown for **43** was correct. Sodium borohydride reduction of the hemiketal **42** provided a mixture of diols **44** in a 9:1

Scheme 3



diastereomeric ratio (92%, combined yield).[69] The major diastereomer of **44** was then subjected to known conditions for cyclization[61] that provided *Z* isomer **45** exclusively in 41% isolated yield. Olefin geometry was determined by observation of nOes (via NOESY spectra) between the olefin proton and H2 and H2−H4 of *exo*-glycal **45**. Swern oxidation on **45** provided a cyclic keto enol ether (70%) which after NMR analysis was found to be compound **43**. This result illuminated two important features of the our tandem process. First, formation of enone **43** provided additional evidence toward the conclusion that isomerization of the hemiketal to an intermediate cyclic keto enol ether followed by a hetero-Diels−Alder reacton is the most likely pathway to the tricyclic spiro compounds as described earlier. The inertness of **43** in the presence of PPh_3 even under conditions that included refluxing chloroform reflects a greater electron density of the double bond than in typical enone functionalities. We reasoned that this class of compounds was a better fit as electron-deficient diene and that substitution on the olefin (e.g., the terminal phenyl group) most likely prevented the hetero-Diels−Alder reaction under reflux or microwave heating due to sterics. Although

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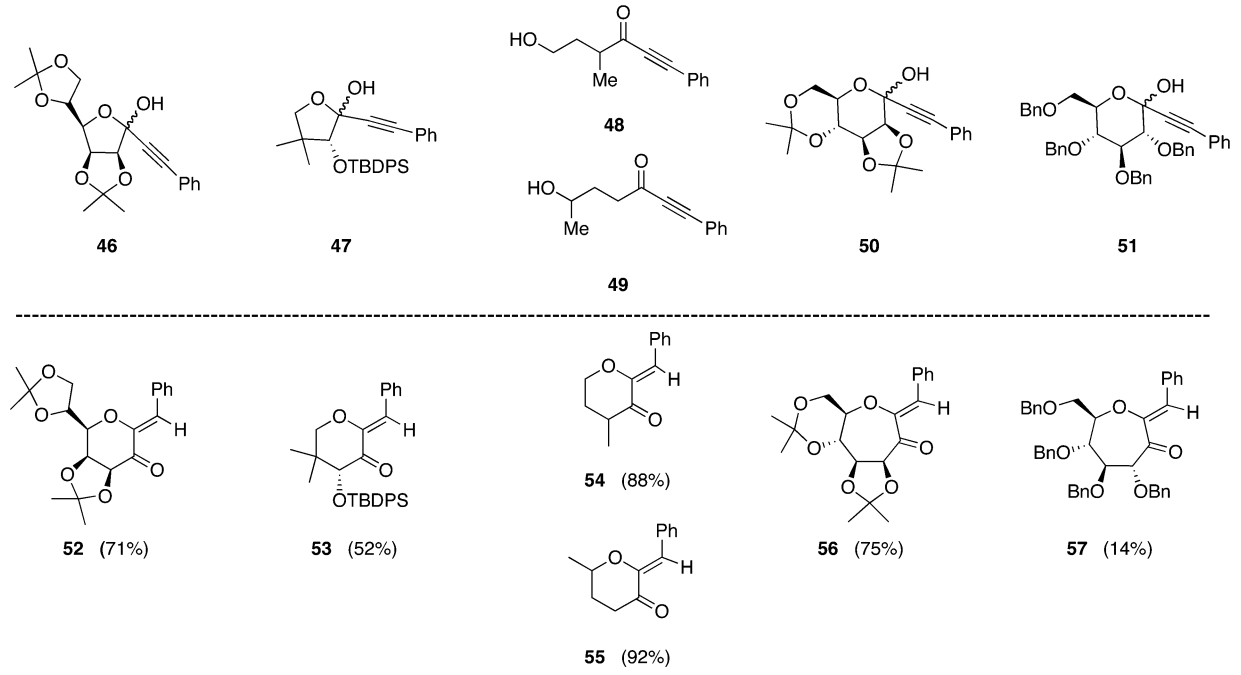


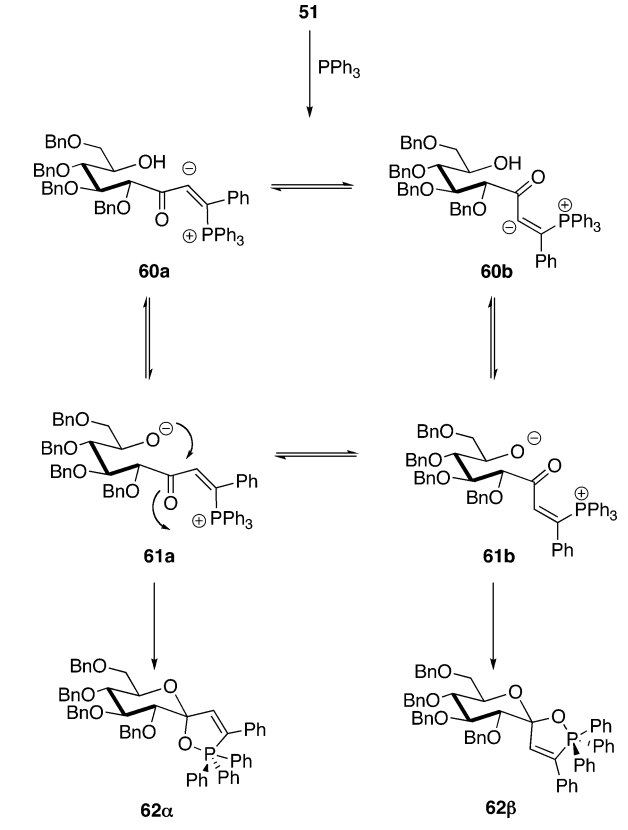
Figure 4. Hemiketals and ynones **46**–**51** (top) and the corresponding cyclic keto enol ethers **52**–**57** (bottom) prepared by the cycloisomerization reaction. Yields for the conversion are given in parentheses.

we have not investigated it here, we anticipate that alkyl groups at this position would demonstrate similar behavior.

The second key feature of the transformation was the exclusive formation of the *Z* isomer of **43**. Interestingly, Gouverneur et al.[32] studied a phosphine-catalyzed cycloisomerization analogous to ours and obtained five-membered keto enol ethers, but predominantly with the *E* olefin configuration. On the basis of the ease of preparation of the hemiketal starting materials and the high efficiency for their transformation to the *Z* keto enol ethers, we opted to examine the scope of our cycloisomerization with substrates **46**–**51** (Figure 4). The substrates were synthesized by addition of phenylacetylide onto the corresponding lactones. Among them, **46**–**50** were converted to substituted keto enol ethers **52**–**56** in 52–92% yield. Hemiketal **47** exhibited only moderate reactivity for the conversion to **53** (52%). Interestingly, the six-membered hemiketal **50** was transformed to the seven-membered keto enol ether **56** with good efficiency (75%), illustrating the versatility of the method.

To our surprise, however, hemiketal **51** provided only 14% of expected product **57**. The major product of the reaction, isolated in 78% yield, was found to be a 1:1 mixture of diastereomers of a previously unidentified material. After separation of the two components by column chromatography, we began a structural analysis on one of the isomers. ESI-MS analysis recorded a major peak at *m*/*z* 903 that immediately indicated it as a PPh_3 adduct [M + PPh_3] of the starting hemiketal **51**. Therefore, a ^{31}P NMR analysis was performed to confirm the incorporation of phosphorus in the isolated material. An upfield signal at −44 ppm[70] strongly suggested a pentacoordinated phosphorus species instead of tetravalent phosphines.[71] A ^{13}C NMR spectrum confirmed the presence of a spiro linkage with a signal at 98 ppm and a distinct downfield signal for vinyl carbon at 154 ppm, which was further confirmed with a DEPT-135 experiment. Further, this signal correlated to a downfield shifted vinyl proton at 7.5 ppm in ^1H NMR. $^3J_{P,H}$ and $^2J_{P,C}$ values for the vinyl proton were determined by HSQC and found to be 52.5 and 21 Hz, which were in a close agreement to those of reported compound **58**.[72] On the basis of the comparison the reported data for **58** to the data we collected for the isolated material, we proposed the structures to be a 1,2-λ^5 oxaphospholenes **62** (Scheme 4).

Scheme 4



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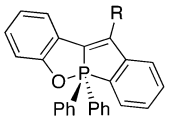

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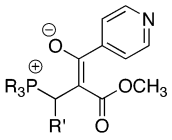

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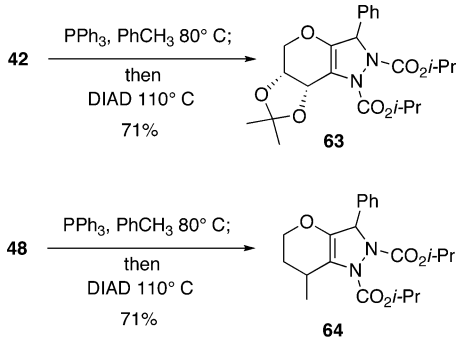
Intermediates along the pathway for the formation of **62** are presented in Scheme 4; the rationale behind the proposed mechanism was motivated by the reported molecules **58** and **59**. Kwon et al.[71] isolated a zwitterionic tetravalent phosphoium enolate species (i.e., **59**) which originated from a three-component reaction of an alkyl or aryl phosphine, an alkynoate, and an aldehyde. In that study, the addition of phosphine to the alkynoate generated a zwitterion akin to **60**, which then reacted with the aldehyde to form the tetravalent zwitterion. Formation of **62** from **51** follows a related pathway. Attack of PPh_3 onto the ynone results in the formation of **60**. In Scheme 4, the species on the left and right show how the diastereomers of **62** (α and β) arise by a bond rotation in the acyclic precursors **60** and **61**. Upon proton transfer, carbanion **60** generated alkoxide **61**. Instead of adding onto the carbon α to the carbonyl as in all of the other examples, attack occurred on the carbonyl carbon itself and resulted the formation of spirocycle **62**. This alternate pathway is probably due to a combination of two factors. First, the formation of a six-membered ring (attack at carbonyl) is kinetically favored relative to formation of the seven-membered ring (attack at α carbon), and second, the lack of rigidifying features on the substrate disfavors α attack. The consequence of the attack by oxygen at the carbonyl carbon is that the reaction course has been changed (trapped) to form oxaphospholene **62**. Following the rationale of Kwon, the relatively poor ability of the phenyl groups (compared to alkyl groups) to stabilize the phosphonium species contributes to the formation of the oxaphospholene instead of the corresponding zwitterionic species. The formation of compound **62** therefore constitutes another example of an isolable oxaphospholene.

Annulations with Substituted Cyclic Enol Ethers and a Unified Mechanism. Because substituted cyclic enol ethers **52**–**57** were largely refractory to concerted cycloaddition reactions, we sought to demonstrate their reactivity in a stepwise annulation. Dihydropyrazoles are medicinally important compounds[73] that presented themselves as viable targets. The strategy was to utilize the phosphine catalyst present in the cycloisomerization to react with diisopropylazodicarboxylate (DIAD) to initiate a second transformation in one pot. The reaction of azodicarboxylate compounds (DIAD in our case) with phosphines forms a Huisgen zwitterion;[74] these species have found application in different transformations ranging from Mitsunobu reactions[75] to reactions involving carbonyl compounds.[76−79] Among these examples, the recent demonstration of dihydropyrazole synthesis from the Huisgen zwitterion and enones inspired our strategy.[79] In the event, hemiketal **42** was treated with 1.5 equiv of PPh_3 in toluene and heated for 4 h to isomerize it to the corresponding cyclic keto enol ether **43**. When conversion to **43** was deemed complete by TLC, 1.5 equiv of DIAD was added to the mixture and then refluxed overnight. Dihydropyrazole **63** was obtained in 71% yield in this tandem, one-pot process (Scheme 5). The efficiency was only slightly less than that obtained (80%) in a stepwise process between keto enol ether and DIAD under similar conditions. Acyclic ynone **48**, treated in a similar manner, provided **64** in 58% yield as a mixture of diastereomers. In the dihydropyrazole formation,

Scheme 5



higher equivalents of PPh_3 were utilized to affect the dehydrative "second" transformation as it required stoichiometric PPh_3. A key point is that the cycloisomerization is, in fact, catalytic in phosphine and therefore available for subsequent steps in the same pot.

The cycloisomerization that converts alkynyl hemiketals such as **65** to their corresponding cyclic keto enol ethers **72** is common to both tandem processes described here. A mechanism for the reaction, emphasizing the catalytic role of the phosphine, is depicted in Scheme 6. Conjugate addition by the phosphine to ynone **66** gives allenoate **67**. Proton transfer[80] then gives keto phosphonium species **68** which proceeds, through intramolecular attack by oxygen on the carbon α to the carbonyl, to ylide **69**. The umpoled (electrophilic) behavior of this carbon is courtesy of the adjacent phosphonium. Another proton transfter gives zwitterionic phosphonium enolate **70**, which may be more accurately considered as its oxaphospholene resonance form **71**. Loss of the catalytic phosphine then delivers **72**. The identity of the alkynyl substituent R^2 determines the subsequent fate of the cyclic keto enol ether **72**. When R^2 is hydrogen (the unsubstituted series), a facile hetero-Diels–Alder reaction then gives spiroketal **73**; the phosphine-catalyzed cycloisomerization followed by the [4 + 2] cycloaddition is the tandem process. When R^2 is phenyl, **72** is a stable, isolable product that is resistant to cycloadditions under a variety of conditions. However, a stepwise annulation with DIAD gives rise to dihydropyrazoles **74**.

CONCLUSION

We have discovered a phosphine-catalyzed reaction that isomerizes hemiketals (masked ynones) to cyclic keto enol ethers. Most of the previously available methods utilized stepwise functionalization either by elimination from a keto substrate or by oxidation of allylic alcohols; a ring expansion of lactones has also been reported.[81] Substituted keto enol ethers can also be transformed to important building blocks upon manipulating either the enol ether or the keto group. For example, one served as a key intermediate in the synthesis of the natural product Herbicidin B.[82] The products of our phosphine-catalyzed cycloisomerization were complementary to those from an earlier amine-catalyzed isomerization. That is, the amine-catalyzed isomerization provided oxepinone products, and the phosphine reaction gave cyclic keto enol ethers. The divergence in reaction pathways and the umpoled reactivity under phosphine catalysis are consistent with reports of ynone and ynoate reactivity in other systems. Moreover, our observations indicate a dependence on the nature of the alkynyl substituent for the ultimate identity of the product. When the β

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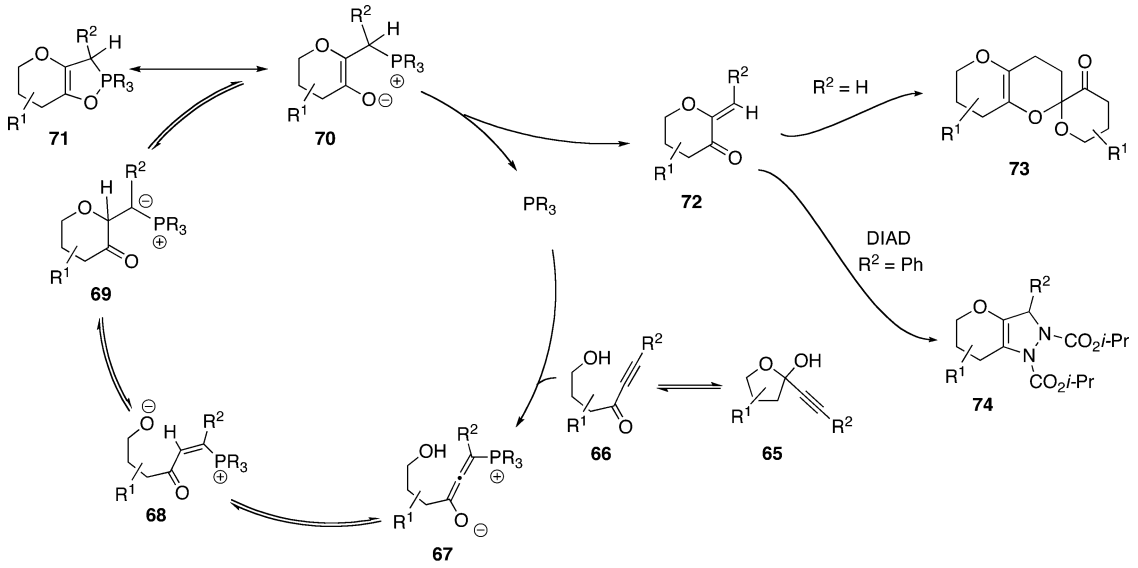
Scheme 6



carbon of the enone was unsubstituted, rapid dimerization gave spiroketal products. Data collected in this study suggest that the dimerization occurs via a concerted hetero-Diels–Alder process. In the cases where a phenyl group was on the β carbon, the cyclic keto enol product was stable and isolable. On the basis of the reaction conditions, this substituted cyclic keto enol ether could be further derivatized in the same pot to afford dihydropyrazoles. The one-pot transformation certainly offers more avenues for new reaction discovery to prepare diverse heterocyclic scaffolds. In total, the tandem method allows for the rapid introduction of complexity in the products from relatively simple starting materials.

EXPERIMENTAL SECTION

General Procedure for Cycloisomerization of 11 and 16–20. PPh_3 (0.25 equiv, 0.004–0.0125 mmol) was added to a solution of the hemiketals (**11**, **16**–**18**) or ynones (**19** and **20**) (0.15–0.5 mmol) in $CHCl_3$ (1.5–5.0 mL) and stirred at room temperature for 6–12 h. The progress of the reaction was monitored by thin layer chromatography (TLC). Upon completion of the reaction as deteremined by the disappearance of the starting material in TLC, the reaction solvent was removed in vacuo and the residue was purified by flash column chromatography to obtain dimeric spiroketals **15** and **21**–**25** in 55–96% yields.

Compound 15. Following the general procedure, **15** was obtained from cycloisomerization and dimerization of **11** (0.050 g, 0.27 mmol) in 96% yield as a white solid (0.048 g): mp 116–118 °C; R_f 0.47 (7:3 Hex/EtOAc); $[\alpha]_D$ −79.3 (*c* 1.4, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.87 (d, *J* = 5.6 Hz, 1H), 4.62 (ddd, *J* = 0.9, 2.3, 5.6 Hz, 1H), 4.52 (d, *J* = 6.0 Hz, 1H), 4.49 (dd, *J* = 2.3, 13.4 Hz, 1H), 4.31 (ddd, *J* = 3.5, 6.5 Hz, 1H), 4.00 (d, *J* = 13.4, 1H), 3.87 (dd, *J* = 3.4, 11.5 Hz, 1H), 3.75 (dd, *J* = 6.5, 11.5 Hz, 1H), 2.32 (ddd, *J* = 10, 15.2 Hz 1H), 2.05 (d, *J* = 16.0 Hz, 1H), 2.0 (m, 2H), 1.47 (s, 3H), 1.45, (s, 3H), 1.38 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 198.9, 138.4, 127.7, 110.4, 110.3, 97.0, 78.8, 75.9, 72.4, 69.3, 65.9, 59.5, 28.3, 27.4, 26.4, 26.3, 24.3, 19.5; HRMS *m*/*z* (M + H)$^+$ calcd for $C_{18}O_8H_{25}$ 369.1549, found 369.1549.

Compound 21. Following the general procedure, compound **21** was obtained from **16** (0.07 g, 0.25 mmol) in 80% yield (0.055 g): R_f 0.41 (7:3 Hex/EtOAc); $[\alpha]_D$ +69.4 (*c* 2.3, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.87 (d, *J* = 5.4 Hz, 1H), 4.68–4.59 (m, 2H), 4.58–4.52 (m, 1H), 4.40–4.27 (m, 3H), 4.08 (d, *J* = 5.2 Hz, 2H), 3.99 (dd, *J* = 8.7, 6.2 Hz, 1H), 3.88 (dd, *J* = 8.7, 4.8 Hz, 1H), 3.60 (dd, *J* = 1.3, 8.0 Hz, 1H), 3.37–2.21 (m, 1H), 2.01–1.19 (m, 3H), 1.49 (s, 3H), 1.43–1.36 (m, 15H), 1.34 (s, 3H), 1.31 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 199.0, 136.2, 130.7, 111.1, 110.6, 109.7, 109.6, 96.6, 78.4, 77.4, 75.7, 74.3, 74.0, 73.8, 69.7, 69.1, 66.8 (2), 27.9, 27.3, 27.1, 27.0, 26.4, 26.1, 25.4, 25.3, 24.3, 19.4; HRMS *m*/*z* (M)$^+$ calcd for $C_{28}O_{12}H_{40}$ 568.2520, found 568.2516.

Compound 22. Compound **22** was obtained in 71% yield (0.023 g) using hemiketal **17** as starting material (0.037 g, 0.071 mmol) under the general reaction conditions: R_f 0.68 (7:3 Hex/EtOAc); $[\alpha]_D$ +13.2 (*c* 1.1, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.72–7.63 (m, 8H), 7.43–7.34 (m, 12 H), 4.74–4.69 (m, 2H), 4.38 (d, *J* = 5.8 Hz, 1H), 4.18–4.11 (m, 1H), 4.08–4.02 (m, 1H), 4.00–3.80 (m, 4H), 3.31 (ddd, *J* = 1.9, 4.8, 9.8 Hz, 1H), 2.40–2.28 (m, 1H), 2.13–1.93 (m, 3H), 1.55 (s, 3H), 1.48 (s, 3H), 1.37 (s, 3H), 1.27 (s, 3H), 1.08–1.03 (m, 18H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 199.5, 137.9, 136.0, 135.8, 133.9, 133.7, 133.5, 130.0, 129.9, 129.8, 127.9, 127.8, 127.7 (2), 126.7, 110.6, 109.7, 97.1, 77.4, 75.7, 74.9, 70.7, 69.6, 64.6, 63.0, 28.4, 27.2, 27.1, 25.9, 25.8, 19.6, 19.4, 19.2; HRMS *m*/*z* (M)$^+$ calcd for $C_{52}O_{10}H_{64}Si_2$ 904.4038, found 904.4009.

Compound 23. Following the general procedure, compound **23** was obtained in 55% yield (0.027 g) from cycloisomerization and dimerization of **18** (0.047 g, 0.11 mmol): R_f 0.59 (7:3 Hex/EtOAc); $[\alpha]_D$ +51.1 (*c* 1.2, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.69–7.14 (m, 30H), 4.87–4.77 (m, 3H), 4.72–4.64 (m, 3H), 4.61–4.48 (m, 5H), 4.35 (dd, *J* = 2.7 Hz, 1H), 4.26–4.11 (m, 3H), 4.08–405 (m, 2H), 3.94–3.84 (m, 3H), 3.73–3.67 (m, 2H), 2.41–2.30 (m, 1H), 2.23–1.96 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 199.9, 139.0, 138.4, 138.3, 138.0, 137.9, 137.6, 136.5, 128.7, 128.6, 128.5, 128.4 (2), 128.3, 128.2, 128.1 (2), 128.0 (2), 127.8, 127.7, 127.6, 127.4, 127.2, 98.6, 79.7, 77.4, 76.0, 75.3, 73.9, 73.8, 73.5, 72.8, 72.6, 72.5, 72.3, 70.8, 70.3, 68.8, 25.1, 19.4; HRMS *m*/*z* (M + H)$^+$ calcd for $C_{56}O_{10}H_{56}$ 888.3874, found 888.3858.

Compound 24. Following the general procedure, compound **19** (0.049 g, 0.39 mmol) was converted to **24** as a mixture of diastereomers in 90% overall yield (0.044 g): R_f 0.62 (17:3 Hex/EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.21 (m, 1H), 3.89 (m, 2H), 3.71 (m, 1H), 3.13 (ddd, *J* = 6.3 Hz, 1H), 2.41 (m, 1H), 2.26 (m, 1H), 2.07 (m, 4H), 1.88 (m, 2H), 1.62 (m, 1H), 1.12–1.07 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 205.1, 205.0, 133.6, 133.4, 132.0, 131.8, 96.5, 96.4, 64.1, 63.0, 60.6, 39.5, 39.3, 38.2, 38.1, 31.9, 31.2, 28.2, 27.7, 25.7, 25.6, 20.2, 20.0, 19.8, 18.8, 14.2, 14.1; HRMS *m*/*z* (M + H)$^+$ calcd for $C_{14}H_{21}O_4$ 253.1440, found 253.1408.

Compound 25. Following general procedure, compound **25** (0.019 g, 0.15 mol) was obtained from **20** as mixture of diastereomers in overall 79% yield (0.015 g): R_f 0.53 (85:15 Hex/EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.36 (m, 1H), 3.87 (m, 1H), 2.97 (tdd, *J* = 13.9, 7.6, 6.4, 2.1 Hz, 1H), 2.38 (m, 1H), 2.32–2.22 (m, 2H), 2.15–1.99

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(m, 4H), 1.93−1.64 (m, 4H), 1.29−1.20 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 203.9, 203.7, 133.6, 133.4, 127.6, 96.3, 71.5, 71.3, 66.1, 66.0, 36.1, 35.4, 30.1, 29.6, 25.8, 25.6, 23.4, 23.0, 21.0, 20.9, 20.6, 20.2, 19.8; HRMS m/z (M + H)$^+$ calcd for $C_{14}H_{21}O_4$ 253.1440, found 253.1408.

Compound 19. Alkynone **19** was prepared following similar procedure as used to prepare **20** as described below and was isolated in 60% (2 steps) as a yellow oil (0.226 g) from 0.300 g of the lactone (3.0 mmol): R_f 0.24 (70:30 Hex/EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.67−3.57 (m, 2H), 3.32 (s, 1H), 2.79−2.70 (m, 1H), 2.08−2.0 (m, 1H), 1.67−1.60 (m, 1H), 1.18 (d, J = 7.2 Hz, 3H), 1.14 (t, J = 7.1 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 191.5, 80.6, 80.1, 71.1, 59.9, 45.4, 34.9; HRMS m/z (M + H)$^+$ calcd for $C_7H_{11}O_2$ 127.0759, found 127.0753.

Compound 20. TMS-acetylene (0.47 mL, 3.29 mmol) was dissolved in dry THF (2 mL) and cooled to −78 °C. To this solution was added *n*BuLi (2.0 mL, 1.6 M) dropwise into the resulting solution for 30 min while maintaining the temperature at −78 °C. To this homogeneous solution was added valerolactone (0.3 g, 3.0 mmol) as a solution in THF (2 mL) dropwise and stirred at −78 °C for 3 h. Progress of the reaction was monitored by TLC. Upon complete disappearance of the lactone, the mixture was diluted with additional 5 mL of THF and quenched with addition of saturated NH_4Cl (5 mL). The organic layer was extracted in EtOAc (2 × 15 mL) and washed with H_2O (20 mL) and brine (10 mL). The organic layers were dried over Na_2SO_4, and the solvent was removed under reduced pressure. This material was subjected to the next step without further purification. It was taken in a mixture of CH_3CN/H_2O (10:1), and CsF (0.65 g, 4.5 mmol) was added at 0 °C. The mixture was allowed to warmed to rt over 2 h. EtOAc(10 mL) was added to the mixture, and it was then washed with H_2O (10 mL). The organic layer was dried with Na_2SO_4 and concentrated under reduced pressure. The residue was purified by column chromatography using 4:1 Hex/EtOAc as eluent to give **20** as yellow oil (0.26 g, 68% over 2 steps): R_f 0.23 (70:30 Hex/EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.69−3.62 (m, 2H), 2.78−2.71 (m, 1H), 2.10−2.0 (m, 2H), 1.67−1.60 (m, 1H), 1.21 (d, J = 7.1 Hz, 3H), 0.23 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 191.7, 101.2, 99.4, 60.3, 45.3, 35.2, 16.2, 0.62; HRMS m/z (M + H)$^+$ calcd for $C_7H_{11}O_2$ 127.0759, found 127.0715.

Reaction of 11 with Rawal's Diene. PPh_3 (0.014 g, 0.05 mmol) was added to a solution of Rawal's diene (0.118 g, 0.52 mmol) and hemiketal **11** (0.048 g, 0.26 mmol) in $CHCl_3$ (12 mL) and stirred 5 h at rt. The reaction was monitored by TLC. Upon completion, the solvent was removed under reduced pressure and the crude product was purified by flash chromatography which afforded **15** (0.014 g, 29%), compound **34** (0.005 g, 5%), and the aldol product **35** (0.065 g, 61%) in a 3:1:12 ratio.

Compound 34: R_f 0.9 (1:1 Hex/EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.45 (d, J = 8.5 Hz, 2H), 6.82 (d, J = 8.5 Hz, 2H), 4.96 (dd, J = 4.0, 5.8 Hz, 1H), 4.59 (d, J = 5.7 Hz, 1H), 4.22−4.17 (m, 1H), 4.13−4.09 (m, 1H), 1.37 (s, 3H), 1.25 (s, 3H), 0.98 (s, 9H), 0.20 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 128.3, 127.9, 120.2, 119.5, 112.7, 107.2, 86.0, 81.0, 71.1, 26.4, 25.9, 24.9, −4.2; HRMS m/z (M + H)$^+$ calcd for $C_{19}H_{31}O_5Si$ 367.1941, found 367.1945.

Compound 35: R_f 0.17 (1:1 Hex/EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.53 (d, J = 12.5 Hz, 1H), 5.14 (d, J = 12.5 Hz, 1H), 4.55 (d, J = 6.2 Hz, 1H), 4.40−4.33 (m, 1H), 4.03−3.91 (m, 2H), 3.14−2.99 (m, 4H), 2.83 (br s, 3H), 2.75 (d, J = 13.9 Hz, 1H), 2.63 (s, 1H), 1.52 (s, 3H), 1.37 (s, 3H), 0.88 (s, 9H), 0.29 (s, 3H), 0.27 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 192.2, 153.1, 108.2, 97.6, 85.8, 80.5, 78.6, 75.8, 71.4, 61.7, 52.2, 45.0, 37.2, 27.7, 26.2, 25.6, −2.6, −2.2; HRMS m/z (M + H)$^+$ calcd for $C_{21}H_{37}NO_5Si$ calcd 412.2519, found 412.2528.

Compound 37. Diol **36** (0.087 g, 0.30 mmol) was taken in dry THF (6 mL), and NIS (0.1 g, 0.39 mmol) was added at rt. After stirring overnight, the mixture was diluted with an additional 10 mL of THF and to it was added a 10% (v/v) $Na_2S_2O_3$ solution(10 mL) and extracted with EtOAc (2 × 5 mL). The combined organic layers were dried over Na_2SO_4 and the solvent removed under reduced pressure. The residue was purified by column chromatography using 4:1 Hex/EtOAc as eluent to give **37** (Z/E 10:1) as a white solid (0.116 g, 93%): R_f 0.56 (70:30 Hex/EtOAc); $[\alpha]_D$ +103.2 (c 0.45, CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.47 (s, 1H), 4.90 (t, J = 5.0 Hz, 1H), 4.48−4.43 (m, 2H), 4.26 (m, 1H), 4.21 (dd, J = 8.1, 1.2 Hz, 1H), 4.08 (dd, J = 8.8, 6.0 Hz, 1H), 4.02 (dd, J = 8.6, 4.3 Hz, 1H), 1.96 (d, J = 2.8 Hz, 1H), 1.39 (s, 3H), 1.37 (s, 3H), 1.34 (s, 3H), 1.32 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 155.0, 110.3, 109.7, 74.5, 74.3, 73.9, 71.7, 67.6, 67.0, 55.2, 27.1, 26.4, 25.5, 24.8; HRMS m/z (M + H)$^+$ calcd for $C_{14}H_{22}IO_6$ 413.0461, found 413.0454.

Compound 38. Compound **37** (0.024 g, 0.058 mmol) was dissolved in EtOH (2 mL); solid $Pd(PPh_3)_4$ (3.3 mg, 0.0029 mmol) was added, and the resulting solution was refluxed for 4 h. After removal of solvent under reduced pressure, the crude residue was purified by column chromatography to afford compound **38** (0.011 g, 70%) as white solid: R_f 0.40 (70:30 Hex/EtOAc); $[\alpha]_D$ +59.4 (c 0.7, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.55 (d, J = 8.0 Hz, 1H), 4.46−4.42 (m, 2H), 4.35−4.26 (m, 2H), 4.22−4.21 (m, 2H), 4.14−4.09 (m, 2H), 1.95 (s, 1H), 1.46 (s, 6H), 1.40 (s, 3H), 1.38 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.2, 110.2, 109.6, 92.0, 74.1, 74.0, 72.8, 71.9, 69.6, 67.1, 27.1, 26.5, 25.5, 24.8; HRMS m/z (M + H)$^+$ calcd for $C_{14}H_{23}O_6$ 287.1495, found 287.1483.

Compound 39. Following the same procedure as for **43** below,[43] compound **37** (0.016 g, 0.039 mmol) was converted compound **39** (0.007 g, 41%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.82 (s, 1H), 4.79 (dd, J = 7.2, 1.6 Hz, 1H), 4.49−4.46 (m, 2H), 4.29−4.23 (m, 2H), 3.73 (dd, J = 8.4, 1.7 Hz, 1H), 1.51 (s, 3H), 1.47−1.40 (m, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 186.7, 155.4, 112.9, 112.6, 110.0, 74.7, 74.3, 73.1, 72.7, 66.8, 27.2, 26.3, 25.1, 25.0; HRMS m/z (M + H)$^+$ calcd for $C_{14}H_{20}IO_6$ 411.0305, found 411.0315.

Swern Oxidation of 38. Following the general procedure for Swern oxidation,[43] compound **38** (0.05 g, 0.17 mmol) yielded dimer **21** (0.027 g, 55%).

Compound 40.[58] Compound **37** (0.011 g, 0.03 mmol) was dissolved in diethylamine (0.5 mL), and the solution was thoroughly degassed by bubbling N_2 through the mixture. To this solution were added $Pd(PPh_3)_4$ (2.0 mg, 0.0013 mmol), CuI (1.0 mg, 0.0052 mmol), and phenyl acetylene (6 μL, 0.030 mmol) successively. The reaction was stirred at rt, and TLC was monitored until disappearance of the starting materials. The reaction was then diluted with EtOAc (2 × 5 mL) and washed with H_2O (5 mL). Solvents were removed under reduced pressure, and the residue was purified by column chromatography to afford compound **40** (0.011 g, 97%): R_f 0.48 (70:30 Hex/EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42−740 (m, 2H), 7.33−7.28 (m, 3H), 5.33 (s, 1H), 5.08 (t, J = 2.0, 1H), 4.60−4.54 (m, 2H), 4.37−4.30 (m, 2H), 4.17−4.09 (m, 2H), 2.21 (br s, 1H), 1.46 (s, 3H), 1.45 (s, 3H), 1.40 (s, 3H), 1.38 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.9, 131.3, 128.4, 127.9, 124.0, 110.3, 109.7, 92.8, 89.7, 84.9, 73.9, 73.8, 71.9, 67.0, 65.2, 27.1, 26.5, 25.5, 24.8; HRMS m/z (M + H)$^+$ calcd for $C_{22}H_{27}O_6$ 387.1808, found 387.1779.

Compound 41. Following the general procedure Swern oxidation, compound **40** (0.010 g, 0.026 mmol) afforded cyclic keto enol ether **41** (0.0062 g, 62%): R_f 0.56 (12:0.5 DCM/Et_2O); $[\alpha]_D$ 161.6 (c 0.5, CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.56−7.45 (m, 2H), 7.38−7.30 (m, 3H), 5.80 (s, 1H), 4.77 (d, J = 7.6 Hz, 1H), 4.52 (d, J = 7.2 Hz, 1H), 4.56−4.39 (m, 1H), 4.21−4.07 (m, 2H), 3.69 (d, J = 7.8 Hz, 1H), 1.54 (s, 3H), 1.47−1.43 (m, 6H), 1.40 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 188.4, 156.1, 132.1, 128.8, 128.4, 112.7, 110.0, 99.9, 98.8, 85.5, 77.4, 75.6, 75.1, 73.5, 66.8, 27.1, 26.4, 25.3, 25.2; HRMS m/z (M + H)$^+$ calcd for $C_{22}H_{25}O_6$ 385.1651, found 385.1625.

Compound 43. *Swern Oxidation Method.* To a solution of oxalyl chloride (6 μL, 0.07 mmol) in dry DCM (1 mL) was added DMSO (9 μL, 0.12 mmol), and the mixture was stirred for 30 min at −78 °C. A separate solution of compound **45** (0.015 g, 0.06 mmol) in DCM was prepared and added dropwise to the former solution and stirred for an additional 1 h while maintaining the temperature at −78 °C. TEA (80 μL, 0.6 mmol) was next added to the reaction mixture as a solution in DCM and slowly warmed to room temperature over a period of 4 h. Solvents were removed under reduced pressure, and the crude was subjected to flash column chromatography, which

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afforded cyclic keto enol ether **43** (0.01 g, 70%) as a colorless oil: $[\alpha]_D$ −63.4 (*c* 0.5, CH_2Cl_2); R_f 0.79 (12:0.5 CH_2Cl_2/Et_2O); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.79 (d, *J* = 8.0 Hz, 2H), 7.40−7.28 (m, 3H), 6.71 (s, 1H), 4.76 (m, 1H), 4.57 (d, *J* = 7.8 Hz, 1H), 4.24−4.14 (m, 2H), 1.54 (s, 3H), 1.45 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 191.4, 149.0, 133.5, 131.2, 129.2, 128.7, 115.8, 112.0, 75.2, 73.6, 67.6, 26.9, 25.2; HRMS *m*/*z* $(M + H)^+$ calcd for $C_{15}H_{17}O_4$ 261.1127, found 261.1125.

Compound 44. Hemiketal **42** (0.04 g, 0.15 mmol) was taken in absolute EtOH (3 mL) and cooled to 0 °C in an ice bath. $NaBH_4$ (0.009 g, 0.225 mmol) was then added to the solution. The solution was allowed to warm to rt and stirred overnight. The reaction mixture was then quenched with dropwise addition of AcOH, and pH was adjusted to neutral. The solution was then diluted with EtOAc (10 mL), and the organic layer was washed with H_2O (10 mL) and dried over Na_2SO_4. The crude residue was purified by column chromatography using 7:3 Hex/EtOAc as eluent, which gave diol **44** (0.037 g, 92%) in a 9:1 mixture of diastereomers. Data for the major isomer are as follows: white solid, mp 69−70 °C; R_f 0.21 (70:30 Hex/EtOAc); ^{1}H NMR (500 MHz, CD_3OD) δ 7.46−7.44 (m, 2H), 7.37−7.34 (m, 3H), 4.67 (d, *J* = 6.8 Hz, 1H), 4.39−4.34 (m, 1H), 4.32 (t, *J* = 6.7 Hz, 1H), 4.01 (dd, *J* = 11.7, 3.7 Hz, 1H), 3.87 (m, 1H), 1.54 (s, 3H), 1.41 (s, 3H); ^{13}C NMR (125 MHz, CD_3OD) δ 132.7, 129.8, 129.6, 129.5, 110.3, 88.8, 86.8, 81.1, 79.6, 62.5, 61.9, 27.9, 25.6; HRMS *m*/*z* $(M + H)^+$ calcd for $C_{15}H_{19}O_4$ 263.1283, found 263.1257.

Compound 45. Compound **44** (0.023 g, 0.088 mmol) was taken in CH_3OH (4 mL) and treated with NaOMe (0.02 g, 0.35 mmol). The solution was then heated under reflux conditions at 100 °C for 4 h. After, the reaction was cooled to rt, CH_3OH was removed in vacuo, and the crude material was taken in EtOAc (10 mL), washed with 0.1 N HCl (0.5 mL), and washed with H_2O (10 mL). The organic layer was concentrated and purified by flash chromatography, which afforded compound **45** in 41% yield (0.0094 g): R_f 0.62 (1:1 Hex/EtOAc); ^{1}H NMR (400 MHz, CD_3OD) δ 7.58 (d, *J* = 8.0 Hz, 2H), 7.24 (t, *J* = 7.6 Hz, 2H), 7.09 (t, *J* = 7.6 Hz, 1H), 5.41 (s, 1H), 4.53−4.49 (m, 2H), 4.40 (dd, *J* = 7.9, 2.8 Hz, 1H), 4.21 (dd, *J* = 12.1, 1.8 Hz, 1H), 4.16 (d, *J* = 2.9 Hz, 1H), 1.35 (s, 3H), 1.34 (s, 3H); ^{13}C NMR (100 MHz, CD_3OD) δ 151.9, 137.7, 129.5, 129.1, 126.6, 111.0, 107.6, 75.8, 73.8, 71.7, 26.9, 24.9; HRMS *m*/*z* $(M + H)^+$ calcd for $C_{15}H_{19}O_4$ 263.1283, found 263.1312.

Compound 42. Phenyl acetylene (0.46 mL, 4.16 mmol) was taken in dry THF (1 mL), and the solution was cooled to −78 °C in a dry ice/acetone bath. To this solution was added *n*BuLi (2.8 mL, 1.6 M), and the temperature was allowed to rise slowly to −65 °C until formation of a homogeneous solution was noted. D-Erythronolactone (0.33 g, 2.08 mmol) was dissolved in 4 mL of dry THF and slowly added to the mixture over a period of 10 min, and it was allowed to warm to −50 °C over a period of 4 h. Upon completion (as monitored by TLC), the reaction was quenched with saturated NH_4Cl solution (5 mL) and diluted with EtOAc (15 mL). The organic layer was washed with H_2O (20 mL) and brine (10 mL), dried over Na_2SO_4, and filtered. The filtrate was concentrated in vacuo, and the crude residue was purified by flash column chromatography using 4:1 Hex/EtOAc as eluent, which gave hemiketal **42** (0.45 g, 83%) as a diastereomeric mixture of hemiketals (10:1) (white solid): mp 62−64 °C; R_f 0.42 (70:30 Hex/EtOAc); ^{1}H NMR (400 MHz, CD_3OD) δ 7.49−7.47 (m, 2H), 7.39−7.33 (m, 3H), 4.92 (dd, *J* = 5.6, 3.7 Hz, 1H), 4.82 (s, 1H), 4.55 (d, *J* = 5.6 Hz, 1H), 4.04 (dd, *J* = 10.3, 3.7 Hz, 1H), 3.95 (d, *J* = 10.2 Hz, 1H), 1.52 (s, 3H), 1.36 (s, 3H); ^{13}C NMR (100 MHz, CD_3OD) δ 132.8, 130.0, 129.6, 114.1, 101.6, 88.2, 86.6, 86.3, 82.0, 72.1, 26.9, 25.6; HRMS *m*/*z* $(M + H)^+$ calcd for $C_{15}H_{17}O_4$ 261.1127, found 261.1121.

Compound 46. Hemiketal **46** was prepared following a similar procedure as used to prepare **42**. From the corresponding lactone (0.243 g, 0.940 mmol), **46** was isolated in 84% (0.284 g) as an anomeric mixture as white solid: R_f 0.6 (70:30 Hex/EtOAc); ^{1}H NMR (400 MHz, CD_3OD) δ 7.48−7.46 (m, 2H), 7.38−7.33 (m, 3H), 4.87 (dd, *J* = 5.5, 3.5 Hz, 1H), 4.79 (s, 1H), 4.61 (d, *J* = 5.6 Hz, 1H), 4.41 (m, 1H), 4.14−4.08 (m, 2H), 4.02 (m, 1H), 1.53 (s, 3H), 1.42 (s, 3H), 1.36 (s, 3H), 1.35 (s, 3H); ^{13}C NMR (100 MHz, CD_3OD) δ 132.8, 130.0, 129.6, 123.6, 114.4, 110.3, 101.2, 88.7, 86.5, 81.7, 80.8, 74.5, 67.9, 27.2, 26.7, 25.7, 25.6; HRMS calcld for $C_{20}H_{23}O_5$ $(M + H - H_2O)^+$ 343.1545, found 343.1523.

Compound 47. Hemiketal **47** was prepared following the procedure used for **42**. From the lactone (0.100 g, 0.271 mmol), **47** was isolated in 51% yield (0.065 g) as a mixture of diastereomers: R_f 0.45 (70:30 Hex/EtOAc); ^{1}H NMR (400 MHz, CD_3OD) δ 7.86−7.82 (m, 2H), 7.78−7.69 (m, 6H), 7.47−7.29 (m, 22H), 4.38 (s, 1H), 4.05 (s, 1H), 3.92 (s, 0.4 H), 3.74 (d, *J* = 8.4 Hz, 0.5H), 3.60−3.54 (m, 2H), 3.51−3.39 (m, 3H), 1.15−1.13 (m, 24H), 1.06 (s, 3H), 0.99 (s, 3H); ^{13}C NMR (100 MHz, CD_3OD) δ 190.7, 137.9, 137.8, 137.6, 137.5, 135.6, 134.8, 134.6, 134.3, 134.0, 132.7, 132.1, 131.3, 131.1, 131.0, 130.9, 129.9, 129.8, 129.6, 129.3, 128.8, 128.6, 128.5, 124.2, 121.3, 103.2, 98.4, 95.4, 89.8, 89.5, 87.1, 84.8, 78.5, 78.0, 69.1, 43.8, 42.2, 41.9, 27.9, 27.8, 23.7, 22.2, 21.6, 20.8, 20.7, 20.6; ; HRMS *m*/*z* $(M + H)^+$ calcd for $C_{30}H_{35}O_3Si$ 471.2355, found 471.2327.

Compound 48. **48** was prepared following the procedure used on **42**. Starting with 1.5 g of the lactone (14.5 mmol), **48** was isolated in 61% as acyclic ynone (1.8 g): R_f 0.52 (80:20 DCM/Et_2O); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.54−7.51 (m, 2H), 7.42−7.38 (m, 1H), 7.34−7.36 (m, 2H), 3.73−3.63 (m, 2H), 2.88−2.79 (m, 2H), 2.15−2.07 (m, 1H), 1.72−1.64 (m, 1H), 1.24 (d, *J* = 7.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 192.0, 133.0, 130.7, 128.6, 119.9, 92.1, 86.9, 60.0, 45.4, 35.3, 16.2; HRMS *m*/*z* $(M + H)^+$ calcd for $C_{13}H_{15}O_2$ 203.1072, found 203.1076.

Compound 49. **49** was prepared from γ-valerolactone following a similar procedure as was used to prepare **42**. Starting from 0.5 g of valerolactone (4.99 mmol), **49** was isolated in 57% yield (0.575 g) as the acyclic ynone: R_f 0.57 (80:20 DCM/Et_2O); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.54 (d, *J* = 7.8, 2H), 7.42 (t, *J* = 7.4 Hz, 1H), 7.35 (t, *J* = 7.6 Hz, 2H), 3.85 (m, 1H), 2.87−2.75 (m, 2H), 2.38 (d, *J* = 4.4 Hz, 1H), 1.92−1.78 (m, 2H), 1.22 (d, *J* = 6.3 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 188.2, 133.1, 130.8, 128.7, 119.9, 91.1, 87.9, 67.0, 42.0, 33.0, 23.6; HRMS *m*/*z* $(M + H)^+$ calcd for $C_{13}H_{15}O_2$ 203.1072, found 203.1076.

Compound 50. Hemiketal **50** was prepared following a similar procedure used to prepare **42**; from the lactone (0.059 g, 0.24 mmol), **50** was isolated in 57% yield (0.049 g): R_f 0.18 (7:3 Hex/EtOAc); ^{1}H NMR (400 MHz, MeOD) δ 7.64−7.58 (m, 2H), 7.54−7.44 (m, 3H), 4.91 (dd, *J* = 1.5, 8.5 Hz, 1H), 4.72 (d, *J* = 8.6 Hz, 1H), 3.84−3.79 (m, 2H), 3.77−3.72 (m, 1H), 3.64−3.54 (m, 1H), 1.67 (s, 3H), 1.45 (s, 3H), 1.36 (s, 3H), 1.27 (s, 3H); ^{13}C NMR (400 MHz, MeOD) δ 134.0, 132.2, 130.2, 121.6, 112.5, 100.2, 94.8, 88.7, 82.4, 79.6, 78.5, 72.3, 65.9, 63.5, 28.9, 27.1, 25.9, 18.6; HRMS *m*/*z* $(M + H)^+$ calcd for $C_{20}H_{24}O_6$ 361.1651, found 361.1666.

Compound 51. Six-membered hemiketal **51** was prepared following the procedure used for **42**. Starting with 0.094 g of the lactone (0.175 mmol), **51** was isolated in 92% yield (0.103 g) as a mixture of anomers: R_f 0.58 (70:30 Hex/EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.56−7.20 (m, 25H), 5.18 (d, *J* = 11.1 Hz, 1H), 5.06−4.97 (m, 2H), 4.93−4.89 (m, 2H), 4.72 (dd, *J* = 12.2, 5.1 Hz, 1H), 4.66−4.58 (m, 2H), 4.23−4.11 (m, 1H), 4.07 (t, *J* = 9.3 Hz, 1H), 3.99−3.90 (m, 2H), 3.87−3.70 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.9, 138.8, 138.7, 138.3, 138.2, 138.0(2), 132.3, 132.0, 129.2, 129.1, 128.5, 128.4(2), 128.3, 128.2, 128.1, 128.0, 127.9, 127.8, 127.7, 121.8, 121.6, 96.3, 92.3, 88.4, 88.2, 85.0, 84.6, 84.3, 84.0, 83.8, 82.7, 77.9, 77.6, 76.0, 75.9, 75.3, 75.1, 74.6, 74.3, 73.6, 73.5, 72.0, 68.7, 68.5; ; HRMS *m*/*z* $(M + H)^+$ calcd for $C_{42}H_{41}O_6$ 641.2903, found 641.2913.

General Procedure for Cycloisomerization of 42 and 46−51. To a solution of hemiketals/ynones (**42** and **46−51**) (0.15 mmol) in $CHCl_3$ (6 mL) was added PPh_3 (0.075 mmol). The mixture was heated to reflux at 70 °C overnight (progress of the reaction was monitored by TLC). The solvent was removed under reduced pressure, and the residue was purified by flash column chromatography, which afforded corresponding cyclic keto enol ethers **43** and **52−57** in 52−92% yields.

Compound 43. Following the general procedure, hemiketal **42** was transformed to compound **43** in 96% yield. Spectra for **43** were identical to those from its preparation via Swern oxidation as described above.

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Compound 52. Hemiketal **46** (0.035 g, 0.098 mmol) was transformed to compound **52** (0.025 g, 0.069 mmol) in 71% yield following the general procedure: $[\alpha]_D$ +145.4 (*c* 2.6, CH_2Cl_2); R_f 0.58 (12:0.5 CH_2Cl_2/Et_2O); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.75 (d, *J* = 7.4 Hz, 2H), 7.39−7.33 (m, 3H), 6.70 (s, 1H), 4.80 (d, *J* = 7.3 Hz, 1H), 4.57−4.53 (m, 2H), 4.28 (dd, *J* = 8.8, 6.3 Hz, 1H), 4.21 (dd, *J* = 8.8, 4.8 Hz, 1H), 3.87 (d, *J* = 7.3 Hz, 1H), 1.52 (s, 3H), 1.48 (s, 3H), 1.45 (s, 3H), 1.43 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 190.9, 148.4, 133.5, 131.1, 129.2, 128.4, 116.0, 112.6, 109.9, 77.0, 74.8, 74.7, 73.9, 67.0, 27.1, 26.6, 25.3; HRMS *m*/*z* (M + H)$^+$ calcd for $C_{20}H_{25}O_6$ 361.1651, found 361.1626.

Compound 53. Following the general procedure, hemiketal **47** (0.020 g, 0.041 mmol) was transformed to **53** in 52% yield (0.010 g, 0.021 mmol): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.79−7.76 (m, 2H), 7.72−7.68 (m, 4H), 7.44−7.31 (m, 9H), 6.52 (s, 1H), 4.10 (d, *J* = 11.2 Hz, 1H), 4.01 (s, 1H), 3.87 (d, *J* = 11.2 Hz, 1H), 1.18 (s, 3H), 1.13 (s, 12H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 192.8, 148.6, 136.3, 136.2, 130.6, 129.9, 129.7, 128.5, 128.3, 127.7, 127.4, 112.9, 80.8, 74.4, 38.5, 27.4, 27.3, 23.0, 20.3, 19.0; HRMS *m*/*z* (M + H)$^+$ calcd for $C_{30}H_{35}O_3Si$ 471.2355, found 471.2315.

Compound 54. Under the general reaction conditions, hemiketal **48** (0.068 g, 0.34 mmol) was converted to compound **54** (0.060 g, 0.30 mmol) in 88% yield: R_f 0.70 (70:30 Hex/EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.78 (d, *J* = 7.9 Hz, 2H), 7.36 (t, *J* = 7.6 Hz, 2H), 7.28 (m, 1H), 6.69 (s, 1H), 4.40 (dt, *J* = 11.0, 4.2 Hz, 1H), 4.24 (dt, *J* = 10.9, 3.0 Hz, 1H), 2.62 (m, 1H), 2.25 (m, 1H), 2.01 (m, 1H), 1.30 (d, *J* = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 197.2, 149.1, 134.5, 130.6, 128.5, 128.3, 113.0, 65.8, 40.5, 30.9, 16.2; HRMS *m*/*z* (M + H)$^+$ calcd for $C_{13}H_{15}O_2$ 203.1068, found 203.1047.

Compound 55. Hemiketal **49** (0.0780 g, 0.38 mmol) was converted to compound **55** in 92% yield using the general procedure (0.072 g, 0.35 mmol): R_f 0.57 (70:30 Hex/EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.81 (d, *J* = 8.3 Hz, 2H), 7.36 (t, *J* = 7.6 Hz, 2H), 7.28 (m, 1H), 6.67 (s, 1H), 4.33 (m, 1H), 2.69 (ddd, *J* = 18.3, 3.3, 2.6 Hz, 1H), 2.58 (m, 1H), 2.16−1.99 (m, 2H), 1.51 (d, *J* = 6.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 194.2, 149.3, 134.4, 130.7, 128.5, 128.3, 112.6, 73.2, 35.4, 29.6, 21.5; HRMS *m*/*z* (M + H)$^+$ calcd for $C_{13}H_{15}O_2$ 203.1072, found 203.1068.

Compound 56. Following the general procedure, hemiketal **50** (0.033 g, 0.085 mmol) was converted to compound **56** in 75% yield (0.023 g, 0.064 mmol): $[\alpha]_D$ +20.7 (*c* 1.0 $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.73−7.70 (m, 2H), 7.40−7.35 (m, 3H), 7.05 (s, 1H), 4.97 (d, *J* = 9.7 Hz, 1H), 4.24 (dd, *J* = 8.0 Hz, 1H), 4.13−4.08 (m, 2H), 3.93 (dd, *J* = 9.2 Hz, 1H), 3.48 (m, 1H), 1.63 (s, 3H), 1.56 (s, 3H), 1.53 (s, 3H), 1.45 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 191.8, 150.3, 132.4, 131.1, 130.3, 128.9, 122.6, 112.2, 99.7, 81.7, 78.7, 76.2, 74.3, 62.7, 28.9, 27.3, 26.7, 19.2; HRMS *m*/*z* (M + H)$^+$ calcd for $C_{20}H_{25}O_6$ 361.1651, found 361.1667.

Compound 57. Following the general procedure, hemiketal **51** (0.100 g, 0.16 mmol) gave the corresponding cyclic keto enol ether **57** in 14% yield (0.014 g, 0.022 mmol): $[\alpha]_D$ +65.6 (*c* 1.98, CH_2Cl_2); R_f 0.59 (70:30 Hex/EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.89 (d, *J* = 7.6 Hz, 2H), 7.46 (d, *J* = 7.9 Hz, 2H), 7.39−7.26 (m, 19H), 7.15−7.14 (m, 2H), 6.99 (s, 1H), 5.06 (d, *J* = 5.4 Hz, 1H), 4.89 (d, *J* = 11.6 Hz, 1H), 4.76 (d, *J* = 11.6 Hz, 1H), 4.64−4.60 (m, 2H), 4.56 (d, *J* = 5.3 Hz, 1H), 4.54 (d, *J* = 5.8 Hz, 1H), 4.48−4.39 (m, 3H), 4.11 (dd, *J* = 10.2, 7.5 Hz, 1H), 4.02 (t, *J* = 4.7 Hz, 1H), 3.90 (dd, *J* = 4.3, 1.8 Hz, 1H), 3.78 (dd, *J* = 10.2, 4.7 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 193.9, 150.0, 138.2, 138.1, 138.0, 137.3, 133.2, 131.1, 129.4, 128.9, 128.6, 128.4, 128.0, 127.9, 127.8, 119.8, 86.3, 82.5, 81.7, 73.6(2), 72.7, 72.2, 70.7; HRMS *m*/*z* (M + H)$^+$ calcd for $C_{42}H_{41}O_6$ 641.2903, found 641.2878.

Compound 62. Oxaphospholene **62** was obtained in 78% yield as a mixture of diastereomers during the reaction of hemiketal **51** with PPh_3. To a solution of **51** (0.100 g, 0.16 mmol) in $CHCl_3$ (4 mL) was added PPh_3 (0.082 g, 0.03 mmol), and the mixture was heated to reflux overnight. Formation of polar diastereomers was observed by TLC. These were partially separated by flash column chromatography using 7:3 Hex/EtOAc as eluent, which separated the first diastereomer (R_f 0.30) of **62** (0.020 g, 14%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.59−6.93 (m, 40H), 6.73 (d, *J* = 7.0 Hz, 1H), 4.88 (d, *J* = 12.4 Hz, 1H), 4.82−4.76 (m, 2H), 4.68 (d, *J* = 12.1 Hz, 1H), 4.63 (d, *J* = 12.4 Hz, 1H), 4.44 (d, *J* = 10.7 Hz, 1H), 4.10−3.99 (m, 2H), 3.92−3.81 (m, 4H), 3.53 (d, *J* = 8.4 Hz, 1H), 3.19 (br s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.4 (d, *J* = 21.3), 144.4, 143.1, 139.0, 138.8, 138.6, 131.7, 129.0, 128.5, 128.4, 128.2, 128.1, 127.9, 127.7, 127.6, 127.2, 127.1, 98.1, 83.0, 75.5, 75.4, 75.1, 73.5, 73.3, 72.9, 71.6, 70.1; ^{31}P NMR (300 MHz, $CDCl_3$) δ −44.3. Mixed fractions containing both diastereomers were obtained (0.065 g, 46%). The second diastereomer (R_f 0.17) was isolated using 1:1 Hex/EtOAc as eluent (0.0.25 g, 18%): $[\alpha]_D$ +44.3 (*c* 0.4, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.47−6.91 (m, 40H), 6.75 (d, *J* = 7.4 Hz, 1H), 4.88 (d, *J* = 11.6 Hz, 1H), 4.84−4.78 (m, 2H), 4.76−4.71 (m, 2H), 4.59 (d, *J* = 12.3 Hz, 1H), 4.45−4.41 (m, 1H), 3.93−3.86 (m, 1H), 3.74 (dd, *J* = 9.5 Hz, 1H), 3.67 (d, *J* = 9.5 Hz, 1H), 3.43 (dd, *J* = 10.6, 2.7 Hz, 1H), 3.21 (d, *J* = 10.2 Hz, 1H), 3.08 (d, *J* = 10.7 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 153.2 (d, *J* = 23.1 Hz), 144.1, 139.3, 139.2, 139.1, 139.0, 138.8, 138.6, 132.5, 129.4, 128.8, 128.5, 128.4, 128.2, 128.1, 127.9, 127.8, 127.7, 127.6, 127.2, 126.9, 126.8, 126.2, 98.2, 84.8, 83.9, 78.8, 75.7, 75.5, 74.9, 73.5, 71.7, 68.5; ^{31}P NMR (300 MHz, $CDCl_3$) δ −48.7; HRMS *m*/*z* (M + H)$^+$ calcd for $C_{60}H_{56}O_6P$ 903.3736, found 903.3771.

Compound 63. Hemiketal **42** (0.049 g, 0.19 mmol) was taken in dry toluene (3 mL) and treated with PPh_3 (0.075 g, 0.28 mmol). The resulting mixture was heated to 80 °C for 4 h. To that mixture was then added 60 μL of diisopropylazodicarboxylate (DIAD), and the mixture was refluxed at 110 °C for an additional 6 h. The solvent was removed under reduced pressure, and the crude residue was purified by flash column chromatography using 70:30 Hex/EtOAc as eluent, which afforded compound **63** as a single diastereomer (0.063 g) in 73% yield as a white solid: mp 86−88 °C; R_f 0.47 (70:30 Hex/EtOAc); $[\alpha]_D$ −99.2 (*c* 0.6, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40−7.28 (m, 5H), 5.72 (s, 1H), 5.34 (d, *J* = 5.8 Hz, 1H), 5.09−5.02 (m, 2H), 4.43−4.35 (m, 2H), 4.01 (dd, *J* = 12.6, 1.3 Hz, 1H), 1.45 (s, 3H), 1.43 (s, 3H), 1.31 (d, *J* = 2.3 Hz, 3H), 1.30 (d, *J* = 2.3 Hz, 3H), 1.27 (d, *J* = 4.3 Hz, 3H), 1.25 (d, *J* = 4.3 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.6, 157.2, 143.8, 137.4, 128.9, 128.3, 126.1, 114.8, 111.1, 72.2, 70.9, 70.7, 69.1, 67.5, 64.8, 28.4, 27.1, 22.2, 22.1 (3); HRMS *m*/*z* (M + H)$^+$ calcd for $C_{23}H_{31}N_2O_7$ 447.2131, found 447.2117.

Compound 64. **64** was obtained from ynone **48** (0.039 g, 0.19 mmol) following the same procedure as was used to prepare **63**. The product was isolated as mixture of diastereomers in 58% yield (0.043 g): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.63 (d, *J* = 7.9 Hz, 1H), 7.37−7.25 (m, 2H), 7.14 (m, 1H), 6.70−6.71 (m, 1H), 5.40 (s, 1H), 5.12−4.90 (m, 3H), 4.24−4.08 (m, 1H), 2.61−2.35 (m, 1H), 2.06 (s, 2H), 1.47−1.43 (m, 3H), 1.36−1.19 (m, 12H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.5, 155.8, 150.6, 150.3, 147.5, 136.2, 130.9, 129.0, 128.9, 128.5, 128.4, 128.3, 126.1, 102.9, 72.4, 71.0, 70.4, 70.1, 64.5, 64.0, 31.0, 22.3, 22.2(3), 22.1, 22.0, 21.9(2), 19.9, 19.6; HRMS *m*/*z* (M + H)$^+$ calcd for $C_{21}H_{29}N_2O_5$ 389.2076, found 389.2051.

■ ASSOCIATED CONTENT

Supporting Information

Crystallographic data for **15** are in the Cambridge Crystallographic Data Centre (CCDC), No. 864322. Copies of this information may be obtained free of charge from CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: +44−1223−336033; web: www.ccdc.cam.ac.uk/conts/retrieving/html; email: deposit@ccdc.cam.ac.uk). Experimental details and characterization data including ^{1}H and ^{13}C NMR spectra of all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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