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Stereoselective Synthesis of Cyclic Ethers via the Palladium-Catalyzed Intramolecular Addition of Alcohols to Phosphono Allylic Carbonates

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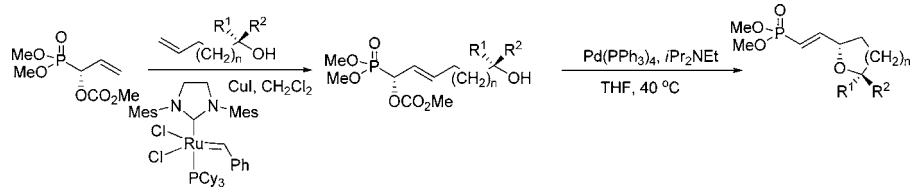
ABSTRACT



Cross metathesis of the acrolein-derived phosphono allylic carbonate and hydroxy alkenes using second generation Grubbs catalyst and copper(I) iodide gave the substituted phosphonates in good yield. Stereospecific palladium(0)-catalyzed cyclization gave tetrahydrofuran and tetrahydropyran vinyl phosphonates. Regioselective Wacker oxidation of the vinyl phosphonate gave the *β*-keto phosphonate, which underwent HWE reaction with benzaldehyde to yield the unsaturated ketone. The utility of the cross metathesis/cyclization protocol was further demonstrated by a formal synthesis of centrolobine.

Tetrahydrofurans (thf) and tetrahydropyrans (thp) are structures frequently found in several important classes of biologically active natural products, such as polyether antibiotics, acetogenins, and C-glycosides. Specific examples inlcude the cyctotoxic amphidinolides E and F, the acetogenin mucocin, and the brown algae lipids (Figure 1).[1] Not surprisingly, the importance of thf- and thp-containing molecules has caught the attention of synthetic chemists, and several approaches to their synthesis have been reported.[2]

Reactions most frequently used include oxidation of dienes and hydroxy alkenes, intramolecular addition of alcohols to epoxides and alkenes, cyclodehydration of diols and application of the chiral pool (carbohydrates) via reduction or

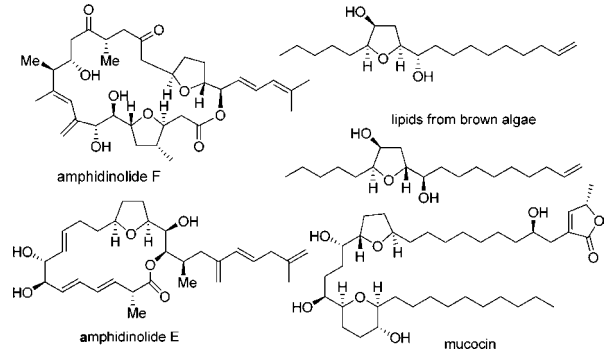


Figure 1. Some natural products containing thf and thp.

nucleophilic addition of carbon nucleophiles to oxacarbenium ions.[1] Each of these methods has its own advantages and disadvantages that tend to be specific to each substrate or target molecule. However, many of the methods leading to

(1) (a) Kobayashi, J.; Ishibashi, M.; Murayama, T.; Takamatsu, M.; Iwamura, M.; Ohizumi, Y.; Sasaki, T. *J. Org. Chem.* **1990**, *55*, 3421. (b) Tsuda, M.; Ishibashi, M.; Shigemori, H.; Yamasu, T.; Hirota, H.; Sasaki, T. *J. Antibiot.* **1991**, *44*, 1259. (c) Shi, G.; Alfonso, D.; Fatope, M. O.; Zeng, L.; Gu, Z.-M.; Zhao, G.-X.; He, K.; MacDougal, J. M.; McLaughlin, J. L. *J. Am. Chem. Soc.* **1995**, *117*, 10409. (d) Warren, R. G.; Wells, R. J.; Blount, J. F. *Aust. J. Chem.* **1980**, *33*, 891.

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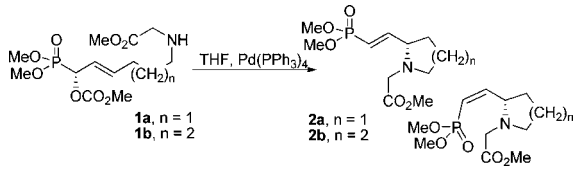
the formation of 2,5-disubstituted thf or 2,6-disubstituted thp rings are limited to the formation of either the *cis* or *trans* isomer, or the level of diastereoselectivity can be an issue.

We set out to design a method that allows selective access to both *cis*- and *trans*-2,5-disubstituted tetrahydrofurans and 2,6-tetrahydropyrans. A further goal was to include functionality in the molecule that would allow for additional C−C bond formations to aid in the coupling of fragments for complex molecule synthesis.

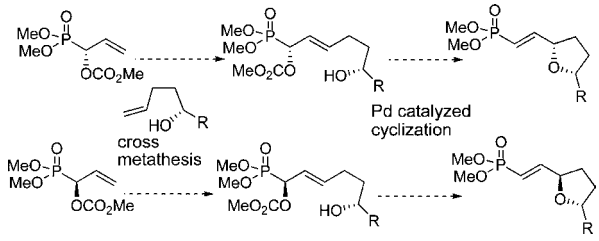
We have been investigating the application of allylic α-hydroxyphosphonates as building blocks for natural product synthesis.[3] We reported the palladium-catalyzed cyclization of phosphono allylic carbonates (**1a** and **1b**) with a pendant amine to give pyrollidine- and piperidine-subsitituted vinyl phosphonates (**2a** and **2b**) (Scheme 1).[3b] This cyclization reaction showed an unusual temperature dependence. The *Z* to *E* ratio in the vinyl phosphonates was dependent upon the reaction temperature, with the *Z* product being dominant at lower tempertaures.

Scheme 1. Cyclization of Amino Phosphono Allylic Carbonates



It was clear that the related cyclization of a pendant alcohol would lead to thf and thp ring systems (Scheme 2). Since the addition of the alcohol to the palladiun π-allyl complex is expected to be stereospecific, the stereochemistry of the cyclic ether should be predetermined by the stereochemistry of the coupling partners in the cross metathesis reaction. Furthermore, the vinyl phosphonate can be converted into β-keto phosphonate,[4] α-and β- hydroxy phosphonates,[5,6] saturated phosphonate,[7] and aldehyde.[8]

Scheme 2. Proposed Approach to Cyclic Ethers



The intermolecular addition of alcohol nucleophiles to palladium π-allyl complexes is more problematic than the well-known addition of amine nucleophiles.[9−11] However, the corresponding intramolecular additions appear to proceed more smoothly.[12−15] Stork first demonstrated chirality transfer in the intramolecular palladium(0)-catalyzed addition of alcohol to an allylic benzoate.[12] Trost later explored the regioselectivity for the cyclization of a series of racemic diols. The ring size preference is 5 > 6 > 7 and primary, secondary, and tertiary alcohols were all viable nucleophiles.[13] There are several examples of the cyclization of more complex substrates in natural product synthesis.[14] In particular, Burke demonstrated an elegant use of the Trost ligand in the cyclo desymmetrization of diols and tetraols.[15] The cyclization of a C_2 1,2-diol represents one of the most efficient bidirectional approaches to the bis-furan core found in some acetogenins.[15a]

The required phosphono allylic carbonates were prepared by the cross metathesis of alkenols (**4**) with the acrolein-derived phosphono carbonate (**3**) (Table 1).[16] Initial reactions with Grubbs second generation catalyst alone (5−7%, Method A) proved to be sluggish. A typical reaction usually required 3 days to achieve good conversion and gave modest ioslated yields. However, the addition of CuI as a cocatalyst[17] resulted in a remarkable acceleration in the reaction rate and improved isolated yields (e.g., entries 1 and 2). The reactions were typically run with either the alkenol (**4**) or the phosphonate (**3**) in a 2:1 excess. The choice of alkenol or phosphonate as the reagent in excess did not seem to affect the overall yield.

Reaction of the phosphono allylic carbonates in the presence of $Pd(PPh_3)_4$ or $Pd_2(dba)_3$/dppe in THF and Hunig's base at 40 °C gave the corresponding tetrahydrofuran and tetrahydropyran (*E*)-vinyl phosphonates (**6a** and **6b**), respectively (Scheme 3). The reactions proceeded equally well with

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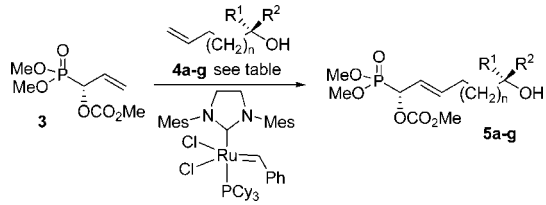
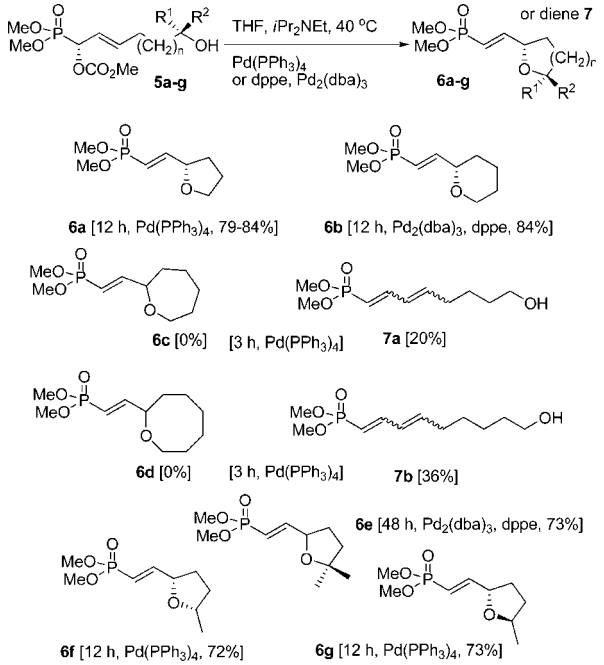
Table 1. Cross Metathesis



no.	compd **4/5**	R^1	R^2	n	conditions[a]	ratio **3**:**4**	yield (%)[b]
1	a	H	H	1	A	2:1	51
2	a	H	H	1	B	2:1	66
3	b	H	H	2	A	1:2	62
4	b	H	H	2	B	1:2	67
5	c	H	H	3	B	1:2	65
6	d	H	H	4	B	1:2	62
7	e	Me	Me	1	B	2:1	85
8	f	Me	H	1	A	1.5:1	53
9	f	Me	H	1	B	2:1	69
10	g	H	Me	1	A	2:1	56
11	g	H	Me	1	B	2:1	62

[a] (A) 5−7 mol % Grubbs II, CH_2Cl_2, reflux, 3 days. (B) 5−7 mol % Grubbs II, 10−15 mol % CuI, CH_2Cl_2,reflux, 3 h. [b] Yields are isolated.

Scheme 3. Cyclization of Hydroxy Phosphono Allylic Carbonates

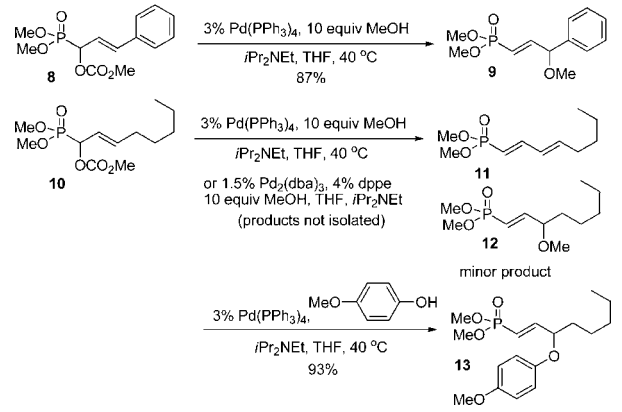


either Ph_3P or dppe as ligand, but chromatographic separation of the product from the ligand residues was more easily achieved with dppe. The cyclization reaction also proceeded at 25 °C; however, in contrast to the intramolecular addition of nitrogen nucleophiles,[3b] only the (*E*)-vinyl phopshonate was observed. Furthermore, a cyclization of nonracemic phosphonate (**5a**) resulted in formation of the thp vinyl phosphonate (**6a**) with complete chirality transfer (HPLC analysis). Tertiary alcohols were also viable nucleophiles for thf formation (**6e**). However, the cyclization to form the larger seven- and eight-membered cyclic ethers (**6c** and **6d**) was unsucessful, and diene formation (**7a** and **7b**) was the predominant reaction pathway.

To further examine the stereochemical features of the cyclization reaction, both the (*S*) and (*R*) enantiomers of 2-hydroxy-hex-5-ene were reacted with the (*R*) acrolein phosphonate (**3**) (70% ee, 5.5:1 er) to give the diastereoisomeric phosphono allylic carbonates (**5f** and **5g**) (Table 1). Palladium-catalyzed cyclization (Scheme 3) resulted in the formation of the diastereoisomeric thf vinyl phosphonates (*cis*-**6f** and *trans*-**6g**). The isomeric ratio, determined by ^{1}H NMR spectroscopy was 1:5.5 and 5.5:1, respectively, reflecting the ratio of the starting carbonates (**5f** and **5g**) and indicating that the cyclization reaction is stereospecific.

In contrast, the intermolecular additions of alcohols to phosphono allylic carbonates showed a marked substrate dependency (Scheme 4). Methanol added smoothly to the

Scheme 4. Intermolecular Reaction of Alcohols



cinnamyl carbonate (**8**) to give the γ-methoxy vinyl phosphonate (**9**) in good yield. However, the attempted addition of methanol to the alkyl substituted allylic carbonate (**10**) resulted in a crude mixture contianing the dienes (**11**) as the major products. Not suprisingly,[18] *p*-methoxyphenol reacted with the alkyl substituted allylic carbonate (**10**) without incident.

The transformation of the racemic vinyl phosphonate (**6a**) into functional groups appropriate for C−C bond formation was examined. Reduction of the alkene with hydrogen over palladium on carbon gave the saturated phosphonate (**14**). Wacker oxidation of thp vinyl phosphonate (**6a**) using the traditional method [$PdCl_2$/CuCl/O_2/H_2O/DMF] was unsuccessful and resulted in recovered starting material.[4b] However, application of conditions designed for electron-deficient alkenes (Na_2PdCl_4/*t*-BuOOH),[4a] gratifyingly yielded the β-ketophosphonate (**15**) as the only product, although extended reaction times (6 days) were required. In compari-

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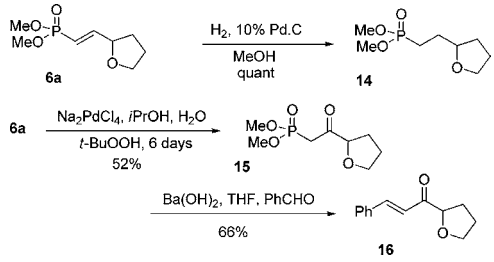
son, vinyl phosphonates with carbon substituents in the γ-position could be oxidized using the traditional Wacker oxidation conditions in 3 days in >80% yield.[3a] Presumably, the inductive effect of the oxygen substituent is responsible for the reduced the reactivity of the vinyl phosphonate. Wadsworth−Emmons reaction of the β-ketophosphonate with benzaldehyde using barium hydroxide as base[19] gave the unsaturated ketone (**16**) in good yield.

Scheme 5. Further Reactions of Vinyl Phosphonates

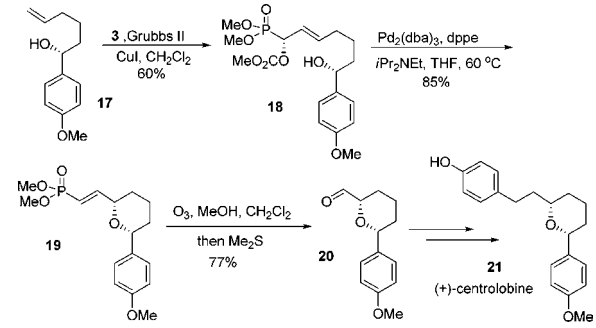


Finally, as an illustration of the utility of the cross metathesis/cyclization protocol for cyclic ether formation, a formal synthesis of (+)-centrolobine was undertaken (**21**). Both (+)- and (−)-centrolobline have been isolated from the heartwood of various *Centrolobium* species,[20] and it was recently shown that the (−)-centrolobine possesses anti-leishmananial activity.[21] The unique structure and biological activity has made centrolobine a popular demonstration target for new methods for the synthesis of 2,6-disubstituted tetrahydropyrans.[22]

Synthesis of the *cis* thp ring of centrolobine requires the (*R*)-phosphonate (**3**) and (*R*)-alkenol (**17**). A known alkenol[23] (**17**) was resolved via kinetic resolution using Birman's method.[24] A cross-metathesis reaction of the alkenol (**17**) (97% ee) and the (*R*)-phosphono carbonate (**3**) (97% ee) gave the substituted phosphono carbonate (**18**). The stereospecific palladium-catalyzed cyclization proceeded uneventfully to give the *cis*-thp-substituted vinyl phosphonate (**19**) in good yield. Ozonolysis of the vinyl phosphonate (**19**) yielded the aldehyde (+)-**20**. The (−)-enantiomer of **20** is a known intermediate[20] on route to (−)-centrolobine (**21**), and thus using published procudures from (+)-**20** would lead to the synthesis of (+)-centrolobine (**21**).

In summary, cross metathesis of alkenols and the acrolein-derived phosphonate gave phosphono allylic carbonates bearing pendant hydroxyl groups. The palladium-catalyzed cyclization leads to thf and thp cyclic ethers with predictable stereochemistry. The vinyl phosphonate can be further manipulated into additional useful functional groups.

Scheme 6. Formal Synthesis of (+)-Centrolobine



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Supporting Information Available: Typical experimental procedures and spectral data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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