ORGANIC LETTERS

2013
Vol. 15, No. 17
4470–4473

Stereoselective Synthesis of Dienyl Phosphonates via Extended Tethered Ring-Closing Metathesis

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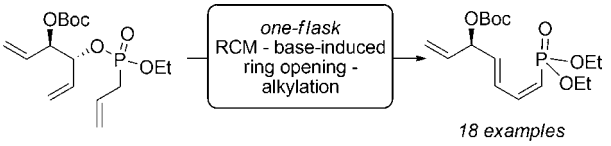
Received July 17, 2013

ABSTRACT



Allylphosphonates of allylic alcohols were converted to conjugated dienyl phosphonates in a one-flask reaction, comprising a ring-closing metathesis (RCM), a base-induced ring-opening, and an alkylation. The ring-opening proceeds with very high diastereoselectivity, giving exclusively the (1*Z*,3*E*)-configured dienes. Single diastereomers and mixtures of diastereomers can be used as starting materials without noticeable effect on the diastereoselectivity of the sequence.

Due to their high and specific binding affinities to several biological receptors, phosphonic acids are very common structural elements in drugs and drug candidates.[1,2] They are often administered as a prodrug to improve bioavailability, e.g., as the corresponding phosphonate or phosphonic acid diamide. An example of a phosphonate-containing prodrug is tenofovir disoproxil fumarate (**1**), which is a reverse transcriptase inhibitor used as an AIDS therapeutic. In contrast, the antibiotic fosfomycin (**2**) is administered as its disodium salt.[3] The furan-2-phosphonic acid **3** has been designed as a 5′-adenosinemonophosphate mimic and was evaluated for its potency as a fructose-1,6-bisphosphatase inhibitor, with a view toward the treatment of type-2 diabetes.[4] The cyclic enol phosphonate **4** and its three diastereomers were synthesized as hydrolytically more stable analogues of the recently isolated natural product cyclophostin. They act as inhibitors of microbial lipases, inter alia of *Mycobacterium tuberculosis*, and may assist in understanding the mechanism of bacterial growth.[5] The 1,3-dienyl pyrophosphonate **5** has been synthesized as a mimic of natural phospho antigens with increased metabolic stability. This and several related compounds were tested for their ability to activate human lymphocytes and show immunoregulatory activity, with a perspective to treat infections and cancer (Figure 1).[6]

Several methods for the synthesis of phosphonates exist and have been covered in recent reviews.[1,2] Nevertheless, the development of alternative routes remains a subject of interest, because hitherto unexplored and more conveniently available starting materials may be used, and previously unaccessible substitution patterns and configurations can be addressed. From a synthetic point of view, vinyl phosphonates should be particularly valuable, because the double bond in conjugation with the phosphonate moiety may undergo numerous useful transformations, such as epoxidation or conjugate addition. Herein, we report a convenient and highly stereoselective approach to *Z*,*E*-configured dienyl phosphonates, which relies on a one-flask

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10.1021/ol4020078
Published on Web 08/14/2013

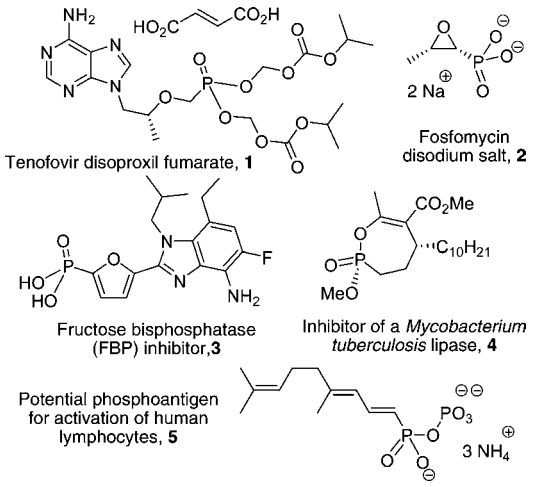
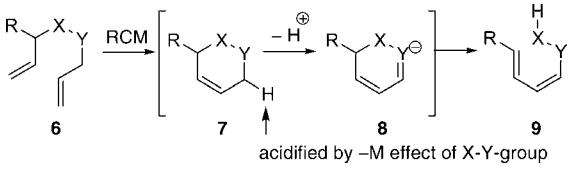


Figure 1. Drugs and medicinal chemistry test substances containing phosphonate units.

tethered ring-closing metathesis (RCM)−ring-opening reaction following the general sequence outlined in Scheme 1.

Scheme 1. General Principle of Tethered RCM−Ring-Opening Sequences



In these reactions, RCM substrates of the general structure **6** comprising an electron-withdrawing functional group Y and an acidic α-H atom are first subjected to RCM, followed by in situ deprotonation of **7** and a base-induced ring-opening of intermediate **8**. After aqueous workup, diene **9** results. In contrast to other tethered RCM reactions,[7,8] the X−Y bond remains intact, but the double bond formed during RCM is shifted and an additional functionality, i.e., a second double bond, is created. Precedence for the base-induced stereospecific ring-opening of endocyclic alkenes of the general structure **7** exists for the conversion of α,*β*-unsaturated-*δ*-lactones into (2*Z*,4*E*)-dienoic acids.[9−12] The implementation of this particular base-induced ring-opening reaction in a one-flask metathesis sequence has recently been reported by us,[13] and a related ring-opening of benzooxepines[14] and benzoazepines[15] obtained through RCM was reported by Ramachary et al.

We started our investigation into a stereoselective synthesis of dienyl phosphonates with the preparation of RCM precursor **12a** by adapting a sequence previously reported by Virieux et al.[16] To this end, allyl alcohol **10a** was treated with allyl chloro phosphonate **11** under slightly modified conditions to give the required precursor **12a** in 79% yield as a 1:1 mixture of diastereomers. We chose the second-generation catalyst **A**[17] to accomplish the cyclization of **12a**, because we suspected from previous experience with the RCM of substituted allyl butenoates that this reaction would most likely proceed slowly and in poor yield with first-generation catalysts, even if comparatively high catalyst loadings were used.[18] However, it should be noted that good yields had previously been reported for the RCM of similar allyl phosphonates[16,19,20] with sterically less demanding allylic substituents, using the first-generation Grubbs catalyst.[21] We found that **12a** underwent RCM to **13a** quantitatively as judged from the ^{1}H NMR spectrum of the crude mixture within one hour by using a comparatively low catalyst loading of 1 mol % of **A** and a conveniently manageable initial substrate concentration of 0.1 M in toluene at slightly elevated temperature. The cyclic phosphonate **13a** was isolated in 74% yield as a 1:1 mixture of diastereomers, indicating that RCM of both diastereomers of **12a** proceeds at a similar rate under these metathesis conditions. In the next step, the projected one-flask RCM−ring-opening sequence was applied to precursor **12a** by adding the base NaH to the reaction mixture upon completion of the metathesis step. Monitoring the reaction by TLC revealed that under these conditions the intermediate RCM product **13a** was completely consumed after 2 h, and upon aqueous acidic workup the hemiphosphonate **14a** was isolated as a single (1*Z*,3*E*)-diastereomer in good yield. Similarly, the alkyl-substituted phosphonates **14b**,**c** could be isolated as single diastereomers in comparable yields (Scheme 2).

At this stage we realized that the chromatographic purification of the ring-opening products **14** was very laborious, due to their high polarity. In addition, complex

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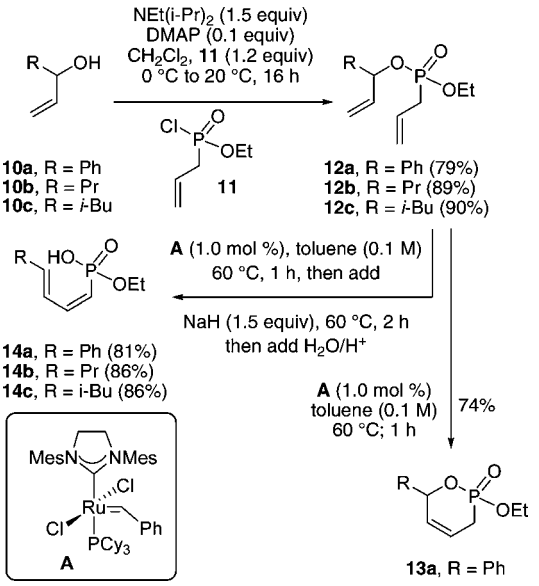
Scheme 2. Synthesis and RCM–Ring-Opening of Allyl Phosphonates **12**



NMR spectra had to be expected for derivatives with an additional stereocenter in the side chain, because in the hemi-esters **14** the phosphorus atom is still a stereocenter, leading to the formation of two diastereomers. For these reasons we decided to extend the RCM–ring-opening sequence by an O-alkylation of the sodium phosphonate obtained prior to aqueous acidic workup. In a first experiment (Table 1, entry 1), ethyl iodide was added to the reaction mixture after completed ring-opening. Under these conditions no phosphonate **15d** was formed, but only the hemi-ester **14d** was present in the crude reaction mixture obtained after aqueous workup. We reasoned that ethyl iodide is not sufficiently electrophilic to alkylate a rather weak nucleophile such as **14d**·Na^+ and therefore tested triethyl oxonium tetrafluoroborate (Meerwein's reagent).[22,23] This led to the isolation of the desired diethyl phosphonate **15d** in 44% yield (Table 1, entry 2). The reason for this moderate yield might be the comparatively low reactivity of Meerwein's reagent in an unpolar solvent such as toluene. However, more polar solvents that are commonly used for alkylation reactions, such as DMSO, DMF, or THF, have previously been reported either to be incompatible with olefin metathesis reactions due to catalyst decomposition or inhibition or to lead to a significantly decreased turnover frequency. Although the latter observation has been reported for cross metathesis reactions in THF,[24] we tested this solvent for the RCM of **12d** (Table 1, entry 3). Surprisingly, the RCM product **13d** could be isolated in very high yield with just 0.5 mol % of catalyst **A**.

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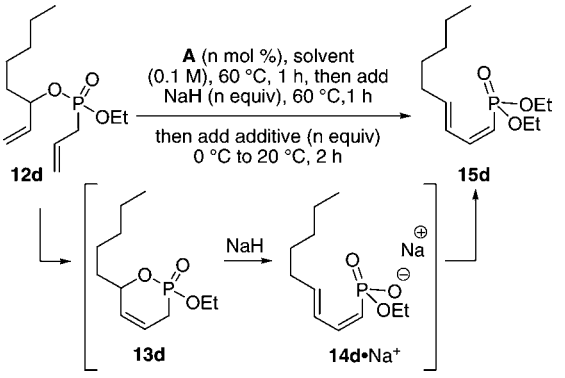
This prompted us to investigate the RCM–ring-opening–alkylation sequence for **12d** in THF, using 1.1 or 1.5 equiv of NaH and 1.0 or 0.5 mol % of catalyst (Table 1, entries 4–6).

Table 1. Optimization of RCM–Ring-Opening–Alkylation Sequence of Allyl Phosphonate **12d**



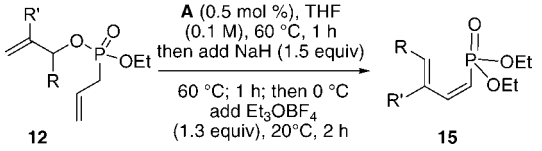
entry	cat. loading (mol %)	solvent	NaH (equiv)	additive (equiv)	product (yield)
1	1.0	toluene	1.5	C_2H_5I (4.0)	**14d** (–)
2	1.0	toluene	1.1	Et_3OBF_4 (1.3)	**15d** (44%)
3	0.5	THF			**13d** (92%)
4	1.0	THF	1.1	Et_3OBF_4 (1.3)	**15d** (62%)
5	1.0	THF	1.5	Et_3OBF_4 (1.3)	**15d** (85%)
6	0.5	THF	1.5	Et_3OBF_4 (1.3)	**15d** (88%)

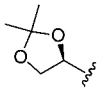
Having identified the optimized conditions listed in Table 1, entry 6, we investigated the scope of the one-flask synthesis of dienyl phosphonates **15** from allyl phosphonates **12** (Table 2).

With the exception of **12n**, all precursors were converted to defined products in synthetically useful yields. In this particular case, a complex mixture was obtained, which can most likely be explained by the presence of an additional CH-acidic position α to the ester group. An increased catalyst loading of 1.0 mol % was required for the successful conversion of precursors with a geminally disubstituted double bond (Table 2, entries 16–19). Although conversion to the intermediate RCM products proceeds quantitatively (TLC), the isolated yields of the final products **15p–s** are, for unclear reasons, significantly lower. Confirmation of the assumed 3*E*-configuration was accomplished for the example **15p**, using 2D-NOE spectroscopy. A positive NOE between the methyl group at C3 and the methylene group at C4 of the diene was indicative for the assigned double-bond configuration.

The only case in which a product other than the (1*Z*,3*E*)-configured dienyl phosphonate **15** was obtained is the benzyl-substituted precursor **12e**, which reacts with the allyl phosphonate **16** under the optimized conditions. We assume that the expected phosphonate **15e** is originally formed, but undergoes a base-catalyzed isomerization to the *E*,*E*-configured allyl phosphonate **16**, which is presumably thermodynamically preferred due to its extended conjugated π-system. With a view to the synthesis of

Table 2. Scope and Limitations of One-Flask RCM–Ring-Opening–Alkylation



entry	12	R	R'	product	yield
1	**12a**	Ph	H	**15a**	89%
2	**12b**	C_3H_7	H	**15b**	92%
3	**12c**	*iso*-Bu	H	**15c**	91%
4	**12d**	C_5H_{11}	H	**15d**	88%
5	**12e**	CH_2Ph	H	**16**	86%
6	**12f**	CH_2CH_2Ph	H	**15f**	87%
7	**12g**	H	H	**15g**	74%
8	**12h**	CH_3	H	**15h**	81%
9	**12i**	(*S*)-CH(OTBS)CH_3	H	**15i**	70%
10	**12j**	(*R*)-CH(OBoc)$CHCH_2$	H	**15j**	58%
11	**12k**	CH_2OBn	H	**15k**	78%
12	**12l**	CH_2OTBS	H	**15l**	65%
13	**12m**	CH_2OCPh_3	H	**15m**	78%
14[a]	**12n**	CH_2CO_2Et	H	**15n**	--
15	**12o**		H	**15o**	72%
16[b]	**12p**	C_5H_{11}	CH_3	**15p**	71%
17[b]	**12q**	CH_2CH_2Ph	CH_3	**15q**	51%
18[b]	**12r**	CH_2OCPh_3	CH_3	**15r**	57%
19[b]	**12s**	CH_2OTBS	CH_3	**15s**	29%

[a] Complex mixture of products. [b] 1.0 mol % of catalyst **A** was used.

products with even further extended π-systems we investigated the use of **16** in olefination reactions. Upon deprotonation using KHMDS and reaction with aldehydes **17a**,**b**, the conjugated all-*E*-trienes **18a**,**b** were obtained in high yields (Scheme 3).

Diarylhexatrienes, e.g., **18a**, have attracted attention as fluorescent probes for application in biological studies,

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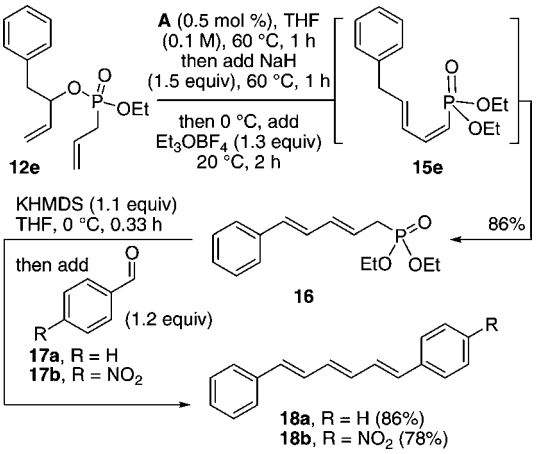
Scheme 3. RCM–Ring-Opening–Alkylation of Benzyl Derivative **12e**



and the development of alternative synthetic routes and the synthesis of novel derivatives is therefore a field of continuous interest.[25]

In summary, we developed a one-flask synthesis of *Z*,*E*-configured dienyl phosphonates starting from conveniently accessible RCM precursors. The use of these reagents for stereoselective C–C bond formation and for the synthesis of novel phosphonates or phosphonic acids with interesting biological properties is currently under investigation in our laboratory.

Acknowledgment. This work was generously supported by the Deutsche Forschungsgemeinschaft (DFG grant Schm 1095/6-3).

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

The authors declare no competing financial interest.