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Synthesis of Conjugated Polyenes via Sequential Condensation of Sulfonylphosphonates and Aldehydes

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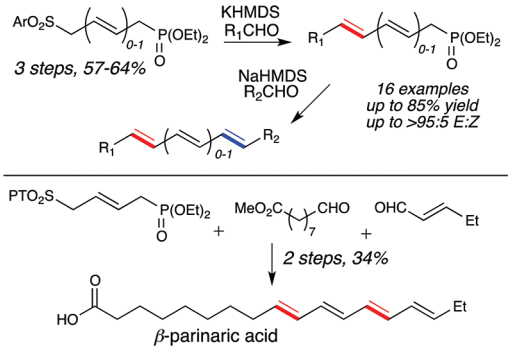
ABSTRACT



Selective metalation of sulfonylphosphonates results in sufficiently stable carbanions that undergo chemoselective Julia–Kocienski condensation with various aldehydes to provide (*E*)-allylic phosphonates in good yields and selectivities. The subsequent Horner–Wadsworth–Emmons condensation with aldehydes is used to synthesize various unsymmetrical *trans*-dienes, trienes, and tetraenes. This methodology is utilized for the concise synthesis of a naturally occurring fluorescent probe for membrane properties, β-parinaric acid.

Conjugated polyenes represent a diverse class of natural and unnatural products. The problems associated with the stereoselective syntheses of these motifs have been of great interest due to the importance of polyenes in biology, material science, and organic synthesis.[1] Although a number of different methods are available for the synthesis of conjugated polyenes, the majority of these methods are based on the use of transition-metal-catalyzed cross-couplings[1,2] or stereoselective condensations such as Wittig and Horner–Wadsworth–Emmons (HWE) olefination.[3] Traditional approaches rely on a stepwise carbon–carbon bond or carbon–carbon double bond formation and often

(1) For recent reviews of polyene synthesis refer to: (a) Thirsk, C.; Whiting, A. *J. Chem. Soc., Perkin Trans. 1* **2002**, 999–1023. (b) Krasnaya, Zh. A.; Tatikolov, A. S. *Russ. Chem. Bull., Int. Ed.* **2003**, *52* (8), 1641–1666. (c) Babudri, F.; Farinola, G. M.; Naso, F. *J. Mater. Chem.* **2004**, *14*, 11–34.

(2) Representative examples: (a) Zeng, F.; Negishi, E. *Org. Lett.* **2002**, *4*, 703–706. (b) Dominguez, B.; Iglesias, B.; de Lera, A. R. *Tetrahedron* **1999**, *55*, 15071–15098. (c) Lipshutz, B. H.; Ullman, B.; Lindsley, C.; Pecchi, S.; Buzard, D. J.; Dickson, D. *J. Org. Chem.* **1998**, *63*, 6092–6093. (d) Torrado, A.; Iglesias, B.; Lopez, S.; de Lera, A. R. *Tetrahedron* **1995**, *51*, 2435–2454.

(3) For selected reviews of Wittig and HWE reactions in the synthesis of natural products refer to: (a) Bestmann, H. J.; Vostrowsky, O. *Top. Curr. Chem.* **1983**, *109*, 85–163. (b) Nicolaou, K. C.; Harter, M. W.; Gunzner, J. L.; Nadin, A. *Liebigs Ann./Recueil* **1997**, 1283–1301.

(4) Selected examples of double cross-couplings in the synthesis of symmetrical and unsymmetrical polyenes: (a) Babudri, F.; Flandanese, V.; Mazzone, L.; Naso, F. *Tetrahedron Lett.* **1994**, *35* (47), 8847–8850. (b) Babudri, F.; Farinola, G. M.; Flandanese, V.; Mazzone, L.; Naso, F. *Tetrahedron* **1998**, *54*, 1085–1094. (c) Pihko, P. M.; Koskinen, A. M. P. *Synlett* **1999**, 1966–1968. (d) Waterson, A. G.; Kruger, A. W.; Meyers, A. I. *Tetrahedron Lett.* **2001**, *42*, 4305–4308. (e) Anderson, O. P.; Barrett, A. G. M.; Edmunds, J. J.; Hachiya, S.; Hendrix, J. A.; Horita, K.; Malecha, J. W.; Parkinson, C. J.; VanSickle, A. *Can. J. Chem.* **2001**, *79*, 1562–1592. (f) Vaz, B.; Alvarez, R.; de Lera, A. R. *J. Org. Chem.* **2002**, *67*, 5040–5043. (g) Sorg, A.; Bruckner, R. *Angew. Chem., Int. Ed.* **2004**, *43*, 4523–4526. (h) Murakami, M.; Matsuda, T.; Itami, K.; Ashida, S.; Terayama, M. *Synthesis* **2004**, *9*, 1522–1526. (i) Coleman, R. S.; Walczak, M. C. *Org. Lett.* **2005**, *7* (11), 2289–2291. (j) Denmark, S. E.; Tymonko, S. A. *J. Am. Chem. Soc.* **2005**, *127*, 8004–8005. (k) Denmark, S. E.; Fujimori, S. *J. Am. Chem. Soc.* **2005**, *127* (25), 8971–8973. (l) Lee, S. J.; Anderson, T. M.; Burke, M. D. *Angew. Chem., Int. Ed.* **2010**, *49*, 8860–8863. (m) Fujii, S.; Chang, S. Y.; Burke, M. D. *Angew. Chem., Int. Ed.* **2011**, *50*, 7862–7864.

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require multiple postcoupling manipulations in order to carry on the installation of the olefin functionality. Recently, the development of transition-metal-catalyzed double couplings and iterative cross-couplings has enabled convergent syntheses of symmetrical and unsymmetrical polyenes.[4]

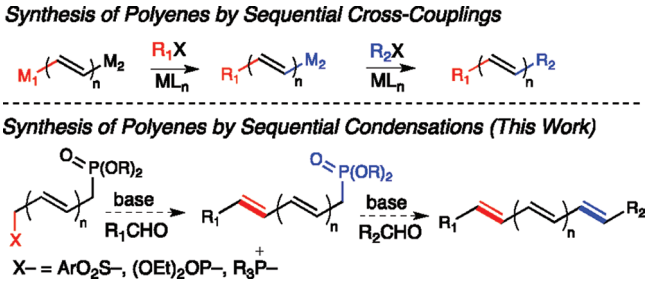


Figure 1. Cross-coupling and condensation-based convergent approaches to polyenes.

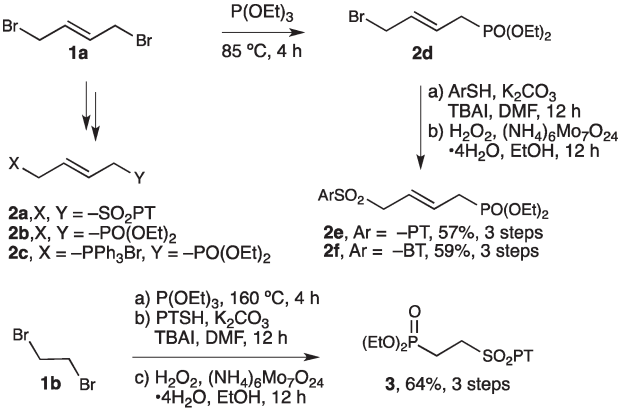
In contrast, very few sequential coupling protocols involving condensation of bifunctional reagents with aldehydes are available (Figure 1). The double condensation of vinylogous α,*β*-bisphosphonates with aldehydes has been known for many decades.[5] However, to the best of our knowledge, no condensation-based methods for the convergent two-step assembly of unsymmetrical polyenes have been reported.[6] Such a strategy might be especially valuable for the rapid generation of unsymmetrical *trans*-polyene libraries since it would avoid the additional steps required for the synthesis of various vinyl halides, boronic acids, stannanes, and silanes. Herein we now describe new, highly chemoselective, sequential condensations of sulfonylphosphonates and aldehydes that can be used for the rapid construction of conjugated unsymmetrical polyenes.

Being interested in developing new strategies for the convergent assembly of natural and unnatural polyenes, we sought to exploit various bifunctional substrates for the condensation-based synthesis of unsymmetrical polyenes (Scheme 1).

We envisioned that monodeprotonation of symmetrical *bis*-sulfone **2a**[7] or bisphosphonate **2b**, followed by condensation with 1 equiv of aldehyde, might lead to an allylic sulfone or phosphonate. These products could then undergo a second olefination upon exposure to an additional equivalent of base and aldehyde.

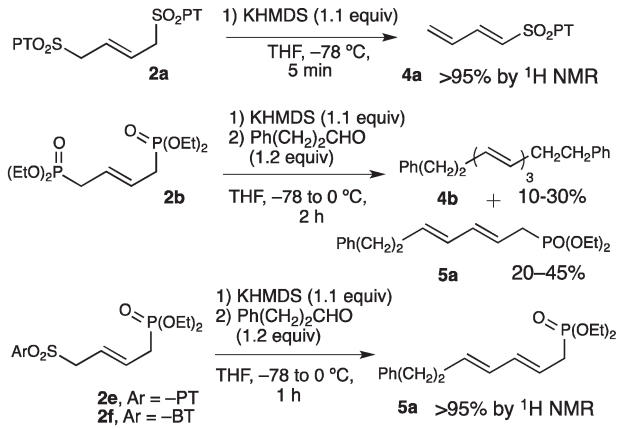
Unfortunately, the attempts to utilize substrates **2a** and **2b** for selective mono-olefination were met with limited success (Scheme 2). The deprotonation of *bis*-sulfone **2a**

Scheme 1. Synthesis of the Bifunctional Precursors for Sequential Condensation



(PT = 1-phenyl-1*H*-tetrazole; BT = 2-benzo[d]thiazole).

Scheme 2. Monocondensation of 3-Phenylpropanal and **2a**–**2f**



(PT = 1-phenyl-1*H*-tetrazole).

with KHMDS resulted in rapid elimination leading to the butadienylarylsulfone **4a**.[8] The condensation of monometalated bisphosphonate **2b** with 3-phenylpropanal (1.1 equiv) provided **5a** (20–45% yield). This reaction was sluggish and suffered from a competitive condensation leading to symmetrical triene **4b**. We surmised that the problems encountered with **2b** could be avoided if one of the phosphonates of **2b** was replaced with triphenylphosphonium or arylsulfone functionalities. The protons next to the triphenylphosphonium or arylsulfone moieties of **2c**, **2e**, or **2f** would be more acidic than the protons adjacent to diethylphosphonate. Thus, substrate **2c** may undergo chemoselective Wittig reaction, while **2e** and **2f** could undergo chemoselective Julia–Kocienski condensation[7] to provide **5a**. To test this hypothesis, the unsymmetrical bifunctional substrates **2c**, **2e** (3 steps, 57%), and **2f** (59% yield, three steps) were synthesized on a multigram scale from the commercially available (*E*)-1,4-dibromo-2-butene **1a**.

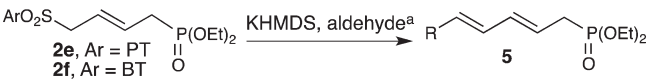
(5) Stilz, W.; Pommer, H. Germ. Pat. 1,092,472, 1958 (to BASF AG).

(6) Minami and coworkers utilized sequential Wittig/HWE condensations in the synthesis of symmetrical 1,2-bis(ylidene)cyclobutanes. However, applying this strategy to the synthesis of unsymmetrical substrates proved to be challenging: Minami, T.; Harui, N.; Taniguchi, Y. *J. Org. Chem.* **1986**, *51*, 3572–3576.

(7) (a) Blakemore, P. R.; Cole, W. J.; Kocienski, P. J.; Morley, A. *Synlett* **1998**, 26–28. (b) Blakemore, P. R. *J. Chem. Soc., Perkin Trans. 1* **2002**, 2563–2585.

(8) Hughes, S.; Griffiths, G.; Stirling, C. J. M. *J. Chem. Soc., Perkin Trans. 2* **1987**, 1253–1264.

Table 1. Reactions of Monodeprotonated **2e** and **2f** with Aldehydes



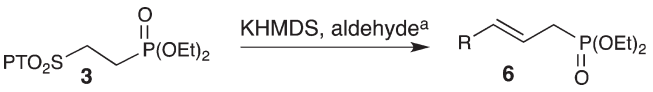
entry	substrate	aldehyde	product	yield[b] (%)	*EE*:*EZ*[c]
1	**2e**	$Ph(CH_2)_2CHO$	**5a**	85	90:10
2	**2f**			74	78:22
3	**2e**	EtCHO	**5b**	75	91:9
4	**2f**			81	75:25
5	**2e**	*n*-$C_5H_{11}CHO$	**5c**	78	>95:5
6	**2e**	*i*-PrCHO	**5d**	72	89:11
7	**2e**	*c*-$C_6H_{11}CHO$	**5e**	72	91:9
8	**2f**			61	86:14
9	**2e**	*c*-C_5H_9CHO	**5f**	67	95:5
10	**2e**	*t*-BuCHO	**5g**	70	>95:5
11	**2e**	(*E*)-$Ph(CH)_2CHO$	**5h**	39	62:38
12	**2f**			57	68:32

[a] Conditions: (i) THF, KHMDS (1.2 equiv), −78 °C, 5 min; (ii) aldehyde (1.5 equiv), −78 °C, 20 min; (iii) 0 °C, 1 h. PT = 1-phenyl-1*H*-tetrazole; BT = 2-benzo[*d*]thiazole. [b] Average of two runs. [c] Determined by ^{1}H NMR.

The attempted Wittig condensation of **2c** with 3-phenylpropanal provided only trace amounts of the desired allylic phosphonate **5a**. However, the treatment of sulfonylphosphonates **2e** and **2f** with KHMDS (1.1 equiv) followed by the addition of 3-phenylpropanal (1.2 equiv) resulted in the clean formation of **5a** (Scheme 2). Both reactions proceeded with remarkable levels of chemoselectivity, and no competing HWE condensation was detected by ^{1}H NMR analysis of the crude mixture. Neither the formation of the symmetrical triene side product nor the elimination of the arylsulfone was observed in these experiments.

Based on these encouraging results, the effect of the aldehyde structure on the yields and selectivities of this reaction was explored next (Table 1). Our general comparison of the reactions of metalated **2e** and **2f** with aldehydes illustrates that both substrates react with comparable efficiencies to provide allylic phosphonates **5**. However, olefinations with metalated 1-phenyl-1*H*-tetrazole-sulfone **2e** proceed with higher selectivities. The Julia−Kocienski condensations with metalated **2e** proceed with good yields and selectivities with both the unbranched (entries 1, 3, and 5) and β-substituted aliphatic aldehydes (entries 6−10). However, condensations with α,β-unsaturated aldehydes such as 3-phenyl-2-propenal proceed with moderate yields and selectivities (entries 11 and 12). To demonstrate that these reactions are not sensitive to scale up, a condensation of **2e** and 3-phenylpropenal was carried out on a gram scale without any erosion in yield or selectivity.

Table 2. Reactions of Monodeprotonated **3** with Aldehydes



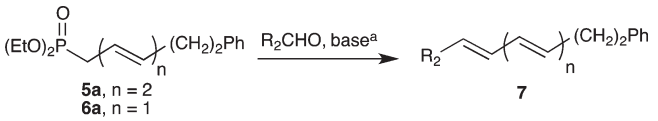
entry	aldehyde	product	yield (%)[b]	*E*:*Z*[c]
1	$Ph(CH_2)_2CHO$	**6a**	85	>95:5
2	EtCHO	**6b**	77	93:7
3	*n*-$C_5H_{11}CHO$	**6c**	82	>95:5
4	*i*-PrCHO	**6d**	72	>95:5
5	*c*-$C_6H_{11}CHO$	**6e**	79	>95:5
6	*c*-C_5H_9CHO	**6f**	80	>95:5
7	*t*-BuCHO	**6g**	40	>95:5
8	(*E*)-$Ph(CH)_2CHO$	**6h**	75	86:14

[a] Conditions: (i) **3**, THF, KHMDS (1.2 equiv), −78 °C, 5 min; (ii) aldehyde (1.5 equiv), −78 °C, 20 min; (iii) 0 °C, 1 h. PT = 1-phenyl-1*H*-tetrazole. [b] Average of two runs. [c] Determined by ^{1}H NMR.

While sulfonylphosphonates **2e** and **2f** could be eventually converted to conjugated trienes, tetraenes, or pentaenes, they cannot be used for the synthesis of dienes. In order to demonstrate that our methodology is applicable to the synthesis of dienes, sulfonylphosphonate **3** was prepared from triethylphosphite and **1b** (64%, three steps) (Scheme 1). Similar to **2e** and **2f**, **3** could be monodeprotonated with KHMDS and reacted with various aldehydes to provide allylic phosphonates **6a**−**h** (Table 2). Importantly, these reactions were completely chemoselective and no HWE or double condensation products were detected. In general, the yields and selectivities for the condensations with **3** were superior to the corresponding yields and selectivities of olefinations with **2e** and **2f**. Both the unbranched (entries 1−3) and β-substituted (entries 4−7) aliphatic aldehydes reacted with **3** to provide allylic phosphonates **6a**−**g** in 40−84% yields and excellent selectivities. Importantly, **3** could be condensed with α,β-unsaturated aldehydes such as 3-phenyl-2-propenal (entry 8). The corresponding allylic phosphonate **6h** was isolated in 75% yield with an 86:14 *E*/*Z* ratio. In addition, the condensations with **3** could be carried out on a gram scale without any erosion of yield or selectivity (entry 1).

In order to demonstrate that sulfonylphosphonates could be used for the convergent synthesis of polyenes (cf. Figure 1), the HWE condensation of phosphonates **5a** and **6a** with aldehydes was investigated (Table 3). It is known that allylic phosphonates can be utilized in the

Table 3. HWE Reactions of **5a** and **6a** with Aldehydes



5a, n = 2
6a, n = 1

7

entry	substrate	base	R_2–	product	yield[b]	$E{:}\Sigma_{(other)}$[c]
1	**5a**	KHMDS	*c*-C_6H_{11}–	**7a** (n=2)	57	60:40
2	**5a**	NaHMDS	*c*-C_6H_{11}–	**7a** (n=2)	74	85:15
3	**5a**	*n*-BuLi	*c*-C_6H_{11}–	**7a** (n=2)	80	90:10
4	**5a**	NaHMDS	*t*-Bu–	**7b** (n=2)	66	84:16
5	**5a**	*n*-BuLi	*t*-Bu–	**7b** (n=2)	81	90:10
6	**6a**	NaHMDS	*c*-C_6H_{11}–	**7c** (n=1)	95	89:11
7	**6a**	NaHMDS	*t*-Bu–	**7d** (n=1)	54	89:11

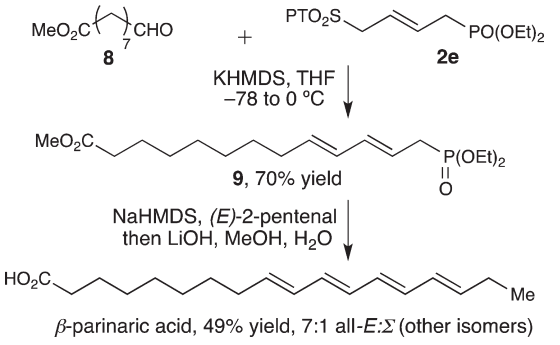
[a] Conditions: (i) **5** or **6**, THF, base (1.1 equiv), −78 °C, 20 min to 1 h; (ii) aldehyde (1.5 equiv), −78 °C, 15 min; (iii) rt, 10−15 h. [b] Average of two runs. [c] Determined by ^{1}H NMR.

(*E*)-selective HWE condensation to provide (*E*)-polyenes in good yields and selectivities, and our results reinforce these findings.[9] Our evaluation of the optimal base (entries 1−5) demonstrated that the deprotonation of dienyl phosphonates with *n*-BuLi provides superior yields and selectivities. However, NaHMDS was found to be the base of choice for the reactions of allylic phosphonate **6a** (entries 6−7).

The described method was applied to the synthesis of *β*-parinaric acid. *β*-Parinaric acid is a naturally occurring tetraene fatty acid that is a widely used fluorescent membrane probe.[10] Our synthesis commenced from known aldehyde **8** obtained in one step from the commercially available methyl oleate (Scheme 3).[11] Condensation of **8** with sulfonylphosphonate **2e** led to phosphonate **9** (70% yield, 91:9 9*E*,11*E*:9*Z*,11*E*). Phosphonate **9** could be used for the HWE condensation with commercially available (*E*)-2-pentenal. Due to the light and air sensitivity of the resultant product, the hydrolysis of the *β*-parinaric acid methyl ester was conducted *in situ* without isolation of this intermediate. The resultant acid was obtained in 49% yield and 7:1 ratio of the desired all-(*E*)-isomer to the sum of (*Z*)-olefin containing isomers.[12] Our synthesis included 5 linear steps (6 steps total) and is among the shortest approaches to *β*-parinaric acid.[13]

In summary, this report describes a new protocol for the synthesis of *trans*-dienes, trienes, and tetraenes that is based on chemoselective condensation of monometalated sulfonylphosphonates and aldehydes followed by Horner−Wadsworth−Emmons olefination of the resultant allylic phosphonates. We envision that this strategy will find its application for the rapid generation of *trans*-polyene libraries as well as for the convergent synthesis of polyene-containing natural products.

Scheme 3. Synthesis of *β*-Parinaric Acid



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Supporting Information Available. Experimental procedures and ^{1}H and ^{13}C NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

(9) Representative examples: (a) Roush, W. R.; Peseckis, S. M. *Tetrahedron Lett.* **1982**, *23* (47), 4879–4882. (b) Kerdesky, F. A. J.; Holms, J. H.; Schmidt, S. P.; Dyer, R. D.; Carter, G. W. *Tetrahedron Lett.* **1985**, *26* (18), 2143–2146. (c) Connell, R. D.; Helquist, P.; Akermark, B. *J. Org. Chem.* **1989**, *54* (14), 3359–3370. (d) Hicks, J. D.; Flamme, E. M.; Roush, W. R. *Org. Lett.* **2005**, *7* (24), 5509–5512. (e) Burke, L. T.; Dixon, D. J.; Ley, S. V.; Rodriguez, F. *Org. Biomol. Chem.* **2005**, *3*, 274–280.

(10) (a) Sklar, L. A.; Hudson, B. S.; Simoni, R. D. *Proc. Natl. Acad. Sci. U.S.A.* **1975**, *72* (5), 1649–1653. (b) Lentz, B. R. *Chem. Phys. Lipids* **1993**, *64*, 99–116.

(11) Zhang, W.; Sun, M.; Salomon, R. G. *J. Org. Chem.* **2006**, *71*, 5607–5615.

(12) Boland, W.; Schroer, N.; Sieler, C.; Feigel, M. *Helv. Chim. Acta* **1987**, *70*, 1025–1040.

(13) (a) Goerger, M. M.; Hudson, B. S. *J. Org. Chem.* **1988**, *53*, 3148–3153. (b) Kuklev, D. V.; Smith, W. L. *Chem. Phys. Lipids* **2004**, *131*, 215–222. (c) Lee, S. J.; Gray, K. C.; Paek, J. S.; Burke, M. D. *J. Am. Chem. Soc.* **2008**, *130*, 466–468.

The authors declare no competing financial interest.