ORGANIC LETTERS

2010
Vol. 12, No. 7
1460−1463

Z-Selective Intramolecular Horner−Wadsworth−Emmons Reaction for the Synthesis of Macrocyclic Lactones

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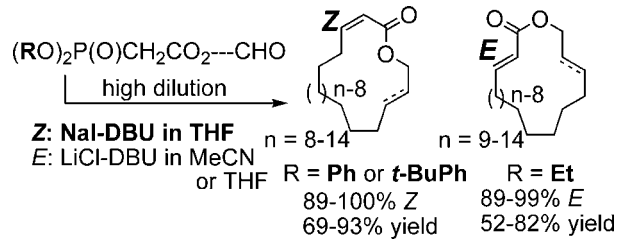
Received January 12, 2010

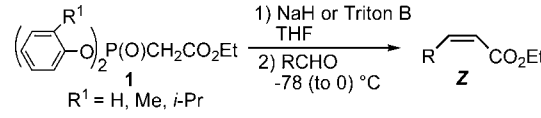
ABSTRACT



When the substrates $(ArO)_2P(O)CH_2CO_2$---CHO (Ar = Ph, *o*-*t*-BuPh) were added to a THF solution containing 3 equiv of NaH at 0 °C or NaI−DBU at rt over 1−10 h, the intramolecular Horner−Wadsworth−Emmons reaction proceeded efficiently to give the 12−18-membered-ring lactones in 69−93% yields with 89−100% *Z* selectivity. On the other hand, $(EtO)_2P(O)CH_2CO_2$---CHO gave the 13−18-membered-ring lactones in 52−82% yields with 89−99% *E* selectivity using LiCl−DBU in MeCN or THF.

Since there are a variety of macrocyclic lactones, so-called macrolides in natural products, and they have an interesting biological activity, a number of methods for their construction have been reported. After the first reports by Stork and Nakamura[1] and Nicolaou et al.[2] in 1979, the intramolecular Horner−Wadsworth−Emmons (HWE) reaction has been one of the most reliable macrocyclization procedures. These reactions gave *E*-α,β-unsaturated lactones with high selectivity. On the other hand, there are many bioactive macrolides containing a *Z*-α,β-unsaturated lactone moiety such as macrolactin A,[3] dictyostatin,[4] phorboxazoles,[5] and laulimalide.[6] In general, the HWE reaction preferentially gives more stable *E*-olefins. In order to prepare *Z*-olefins, the special HWE reagents were invented by Still et al. ($(CF_3CH_2O)_2P(O)CH_2CO_2Me$)[7] and by us (**1** in Scheme 1).[8]

Scheme 1



These reagents have been successfully applied for the synthesis of *Z*-α,β-unsaturated esters with high selectivity

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(1) Stork, G.; Nakamura, E. *J. Org. Chem.* **1979**, *44*, 4010–4011.
(2) Nicolaou, K. C.; Seitz, S. P.; Pavia, M. R.; Petasis, N. A. *J. Org. Chem.* **1979**, *44*, 4011–4013.
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(6) Quinoa, E.; Kakou, Y.; Crews, P. *J. Org. Chem.* **1988**, *53*, 3642–3644.
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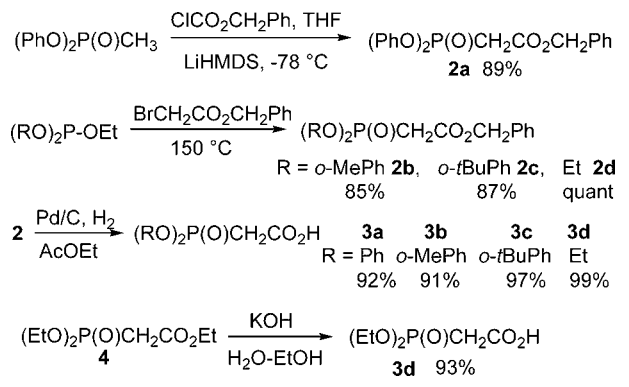
10.1021/ol100071d
Published on Web 03/01/2010

from a variety of aldehydes. However, when these reagents were applied for the intramolecular HWE reaction, low to moderate selectivity and/or low yields were generally reported.[9,10] For example, Ghosh mainly received the *E* product for the synthesis of laulimalide.[9a] The *Z*/*E* ratios were 1:1.7 and 1:2 using our reagent and Still's reagent, respectively. After Aristoff's report,[11,12] K_2CO_3 and 18-crown-6 in toluene have been used for the *Z*-selective intramolecular HWE reaction. In fact, all the intramolecular HWE reactions of ref 9 used these conditions. Since the reaction conditions for the *Z*-selective intramolecular HWE reaction have never been fully optimized, we decided to define the satisfactory reaction conditions. Here, we report our results of the intramolecular HWE reaction containing 12- to 18-membered-ring lactones.

Benzyl diphenylphosphonoacetate **2a** was prepared by treatment of diphenyl methylphosphonate with 2 equiv of LiHMDS in the presence of $ClCO_2CH_2Ph$ in THF, and the other phosphonates **2b**−**d** were obtained by heating $(RO)_2P(OEt)$[13] with $BrCH_2CO_2CH_2Ph$ in high yields (Scheme 2). The phosphonoacetic acids **3a**−**d** were prepared by

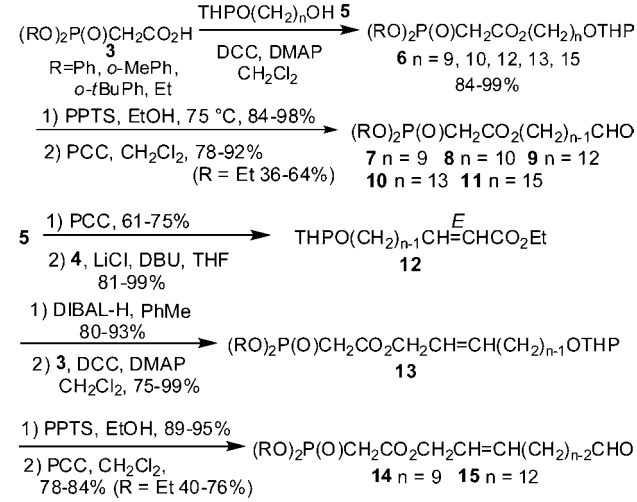
Scheme 2



hydrogenolysis of **2** with Pd/C in 91−99% yields. Diethyl phosphonoacetic acid **3d** was also obtained by hydrolysis of **4** in 93% yield.

The intramolecular HWE substrates **7**−**11** were prepared by esterification of phosphonoacetic acid **3** with mono-THP-protected diols **5**, followed by deprotection and oxidation as outlined in Scheme 3. Oxidation of **5** with PCC and the

Scheme 3



following HWE reaction with **4** using LiCl−DBU[15,14] gave *E*-α,β-unsaturated esters **12**. Reduction of **12** to the alcohols, esterification with **3**, deprotection, and then oxidation gave the intramolecular HWE subatrates **14** and **15** containing the *E*-olefin. Although the yields were not optimized, the procedure is efficient especially for the diaryl phosphonoacetate reagents.

The intramolecular HWE reaction of **9** was summarized in Table 1.[16] The HWE reaction of **9a** was performed using a procedure similar to the intermolecular HWE reaction.[8b] That is, **9a** was treated with NaH in THF at −60 °C, and then the mixture was gradually warmed to 0 °C over 1 h. Only 12% yield of the 15-membered-ring lactone ***Z*-16** was obtained. The *Z*/*E* ratio of all the obtained HWE products is 92:8 (entry 1). The main products were oligomeric (dimeric and/or trimeric) lactones (58% yield). The formation of oligomers was suppressed when a THF solution of **9a** was added to a THF solution containing 3 equiv of NaH over 4 h at 0 °C (entry 2). Gladly and somewhat surprisingly, the *Z* selectivity did not reduce even at 0 °C, and a 73% yield of ***Z*-16** was obtained. ***Z*-16** was also efficiently obtained using NaI−DBU[8e] as a base in the highest yield (84%) (entry

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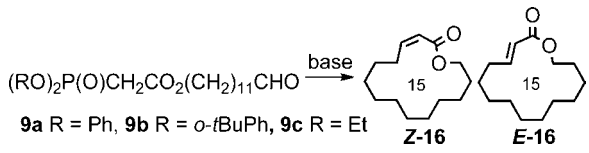
(16) All the HWE products and the reagents described in this paper were characterized by 400 MHz ^{1}H NMR spectra and mass spectroscopy. The *Z*/*E* ratios were determined by integration of the vinyl proton signals.

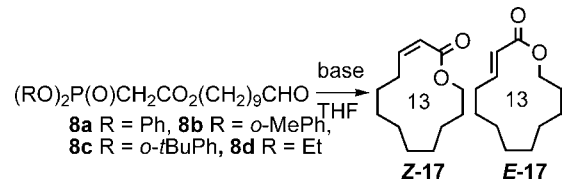
Table 1. Intramolecular HWE Reaction of **9**



entry	**9**	solvent	base[a]	conditions[b]	yield of ***Z*-16** (%)	oligomers (%)	*Z*/*E*
1	**9a**	THF	NaH	−60 to 0 °C[c]	12	58	92:8
2	**9a**	THF	NaH	0 °C, 4 h	73	1.2	92:8
3	**9a**	THF	**NaI−DBU**	**0 °C, 4 h**	**84**	2.3	**91:9**
4	**9a**	PhMe	K_2CO_3[d]	rt, 4 h	54	20	83:17
5	**9a**	THF	LiCl−DBU	rt, 1 0 h	74	*f*	81:19
6	**9b**	THF	NaI−DBU	0 °C, 10 h	70	3.5	97:3
7	**9b**	**THF**	**NaI−DBU**	**rt, 10 h**	**84**	0.2	**96:4**
8	**9b**	**THF**	**NaH**	**0 °C, 10 h**	**80**	0.2	**97:3**
9	**9b**	THF	NaH	rt, 1 0 h	60	0.1	96:4
10	**9c**	MeCN	LiCl−DBU	rt, 1 0 h	73[e]	*f*	2:98

[a] 3 equiv of base was used except for entry 1 (1.4 equiv). [b] The addition was carried out over the specified time. The final concentration was 0.01 mol L^{-1} except for entry 1 (0.05 mol L^{-1}). [c] The reaction mixture was warmed over 1 h. [d] 18-crown-6 (5 equiv). [e] Yield of ***E*-16**. [f] Not detected.

Table 2. Intramolecular HWE Reaction of **8**



entry	**8**	base[a]	conditions[b]	yield of ***Z*-17** (%)	oligomers (%)	*Z*/*E*
1	**8a**	NaH	0 °C, 4 h	52	17	94:6
2	**8a**	NaI-DBU	0 °C, 4 h	69	8	90:10
3	**8a**	**NaI−DBU**	**rt, 4 h**	**75**	7	**89:11**
4	**8b**	NaI−DBU	rt, 10 h	63	16	86:14
5	**8c**	**NaI−DBU**	**rt, 10 h**	**69**	4	**93:7**
6	**8c**	NaH	rt, 10 h	59	3	99:1
7	**8c**	**NaH**	**0 °C, 10 h**	**60**	7	**99:1**
8	**8d**	LiBr−DBU	rt, 4 h	52[d]	12	6:94
9[1]	**8d**	LiHMDS[c]	rt, 15 h	66[d]	<1	0:100

[a] 3 equiv of base was used. [b] The addition was carried out over the specified time. The final concentration was 0.01 mol L^{-1}. [c] 1.1 equiv base in the presence of 1% HMPA.[1] [d] Yield of ***E*-17**.

3). Using the standard conditions for the *Z*-selective intramolecular HWE reaction, K_2CO_3 and 18-crown-6 in toluene,[11] 54% yield of ***Z*-16** was obtained with 83:17 selectivity along with 20% oligomers (entry 4). In addition, LiCl−DBU in THF gave lower selectivity (81:19) (entry 5). Sodium base gave the highest *Z*-selectivity, the same as the intermolecular HWE reaction.[8] In our former study, we found that ortho-substituted phenyl reagents (R^1 = Me and *i*-Pr in **1**) showed higher *Z* selectivity. After that, Touchard et al. reported the improvement of selectivity at 0 °C using the *o*-*t*-BuPh reagent.[14,17] In the presence of 3 equiv of NaI−DBU, the *o*-*t*-BuPh reagent **9b** reacted to give ***Z*-16** in 70% yield with 97:3 selectivity at 0 °C. At room temperature, 84% yield was obtained with slightly reduced 96:4 selectivity (entry 7). The reaction using NaH gave similar results as NaI−DBU (entries 8−9). A better 80% yield was obtained at 0 °C with 97:3 selectivity. Thus, from the Ph reagent **9a** or *o*-*t*-BuPh reagent **9b**, ***Z*-16** was obtained in as high as 84% yield with 91−97% *Z* selectivity (entries 3, 7, and 8). On the other hand, the Et reagent **9c** was added to a solution containing 3 equiv of LiCl and DBU in MeCN to give ***E*-16** in 73% yield with 2:98 *E* selectivity (entry 10).

The results of the intramolecular HWE reaction of **8** were summarized in Table 2. Using both high dilution conditions and NaH as a base, the 13-membered-ring lactone ***Z*-17** was obtained in 52% yield with 94:6 selectivity from the Ph reagent **8a** (entry 1). Although the selectivity is lower, the highest yield of ***Z*-17** (75%) was obtained by using NaI−DBU at room temperature (entry 3). Disappointingly, *o*-MePh reagent **8b** gave lower 86:14 selectivity (entry 4). In the intermolecular HWE reaction, *o*-MePh reagent **1** (R^1 = Me) gave higher *Z*-selectivity (93−99% for a variety of aldehydes) than the Ph reagent at −78 °C or by warming from −78 to 0 °C.[8b] The *o*-*t*-BuPh reagent **8c** gave ***Z*-17** in 69% yield with 93:7 selectivity using NaI−DBU and in 60% yield with 99:1 selectivity using NaH (entries 5 and 7). Generally speaking, NaH gave the same or slightly higher *Z* selectivity than NaI−DBU. The yields were higher at 0 °C for NaH and at room temperature for NaI−DBU. Since the formation of the smaller 13-membered ring is rather difficult, the Ph reagent **8a** may be the reagent of choice because of its higher reactivity. The Et reagent **8d** gave ***E*-17** in 52% yield using LiBr−DBU in THF together with oligomers (12% yield) (entry 8). Although we did not optimize the *E*-selective reaction, slower addition might increase the yield of ***E*-17**. Stork and Nakamura reported the exclusive synthesis of ***E*-17** in 66% yield by the addition of **8d** over 15 h.[1]

Similarly, a solution of **10** (R = *o*-*t*-BuPh) was added to a THF solution containing 3 equiv of NaI and DBU at room temperature over 10 h to give the 16 membered ring lactone ***Z*-18** in 93% yield (*Z*/*E* = 94:6) (Figure 1). The addition time can be reduced for easier cases. In fact, ***Z*-18** was obtained in 89% yield (*Z*/*E* = 95:5) by the addition of **10** over 1 h. Using NaH at 0 °C gave ***Z*-18** in 76% yield with 94:6 *Z* selectivity. While, the reaction of **10** (R = Et) using 3 equiv of LiCl and DBU in MeCN gave ***E*-18** in 82% yield with 2:98 *E*-selectivity. The 18-membered-ring lactone ***Z*-19** was obtained in 71% yield (*Z*/*E* = 96:4) using NaH at 0 °C and in 77% yield (*Z*/*E* = 94:6) using NaI−DBU at room temperature from **11** (R = *o*-*t*-BuPh). On the other hand, **11** (R = Et) gave ***E*-19** in 82% yield (*Z*/*E* = 2:98). In addition, the 12-membered-ring lactone ***Z*-20** was obtained in 69% yield (*Z*/*E* = 99:1) and 67% yield (*Z*/*E* = 100:0) by the addition of **7** (R = *o*-*t*-BuPh) over 10 and 1 h, respectively. Interestingly, the *Z* selectivity obtained from 1 h addition was slightly better than the result from 10 h addition for

(17) For the amide reagents, (*o*-*t*-BuPhO)$_2$P(O)$CH_2CONR^1R^2$, see: Ando, K.; Nagaya, S.; Tarumi, Y. *Tetrahedron Lett.* **2009**, *50*, 5689–5691.

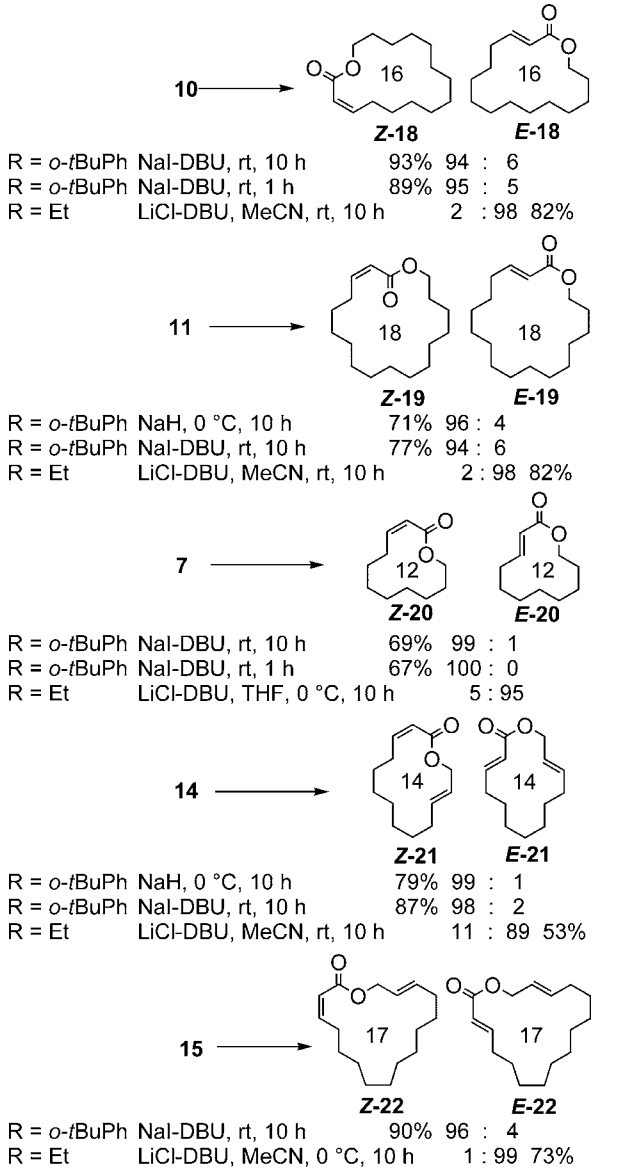


Figure 1

both **7** and **10**. Using NaH at 0 °C gave ***Z*-20** in 55% yield with 100% *Z* selectivity. The HWE reaction of **7** (R = Et) gave the HWE products E1, E2, E3, and Z1 in 92% combined yield (43:32:20:5 ratio), and the *Z*/*E* ratio of all the obtained HWE products was 5:95. Since these HWE products were not perfectly separated, the monomer ***E*-20** has not been specified yet. The 14-membered-ring lactone ***Z*-21** having an *E*-alkenyl group was prepared from **14** (R = *o*- *t*-BuPh) using either NaH at 0 °C or NaI−DBU at room temperature in 79 or 87% yield highly selectively (98−99% *Z*), while **14** (R = Et) gave ***E*-21** in 53% yield with 11:89 *E* selectivity. The 17-membered-ring lactone ***Z*-22** was also prepared from **15** (R = *o*-*t*-BuPh) using NaI−DBU in 90% yield, and ***E*-22** was obtained from **15** (R = Et) in 73% yield with 1:99 *E* selectivity.

In summary, the intramolecular HWE reaction of the substrates $(ArO)_2P(O)CH_2CO_2$----CHO (Ar = Ph, *o*-*t*-BuPh) gives the 12−18-membered-ing *Z*-lactones in good to high yields using NaI−DBU at room temperature or NaH at 0 °C in THF. The substrate should be added to a THF solution containing 3 equiv of base over 1−10 h. The 13−18-membered *E*-lactones were also selectively obtained from $(EtO)_2P(O)CH_2CO_2$----CHO. In this study, we succeeded in showing that the *Z*-selective intramolecular HWE reaction is very useful for the synthesis of simple *Z*-α,*β*-unsaturated lactones. As Stork mentioned, the most difficult cyclization will, in general, involve the least-substituted precursors because of more degrees of freedom.[1] We are planning to use this method for the synthesis of naturally occurring bioactive macrolides containing *Z*-α,*β*-unsaturated lactone moiety.

Acknowledgment. This work was partially supported by a Grant-in-Aid for Scientific Research from the Ministry of Education, Culture, Sports, Science, and Technology, Japan.

Supporting Information Available: A typical experimental procedure and compound characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

OL100071D