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Synthesis of 4-Methyldienoates Using a Vinylogous Horner−Wadsworth−Emmons Reagent. Application to the Synthesis of Trichostatic Acid

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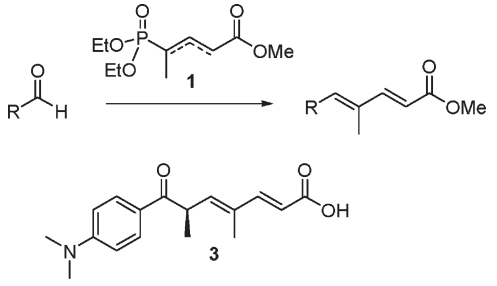
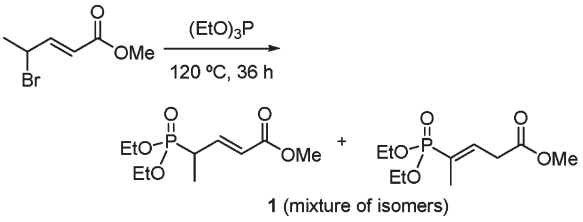


The utility of the unsaturated phosphonate **1** as a vinylogous Horner−Wadsworth−Emmons reagent was explored in reactions with aldehydes affording 4-methyldienoate esters. Factors that affect *E*/*Z* selectivity were studied. A simplified synthesis of trichostatic acid **3** was accomplished to demonstrate utility of this reagent.

The Horner−Wadsworth−Emmons (HWE) condensation[1] is a popular means of synthesizing functionalized alkenes and is commonly employed to effect subunit coupling and ring closure in complex syntheses.[2] Vinylogous HWE reagents of the type $(R^1O)_2P(O)CH_2CH{=}CHCO_2R^2$ have been employed to prepare dienes from the corresponding carbonyl substrates.[3] Several analogous reagents of various substitution patterns have been studied which produce substituted dienes.[4] However, stereoselectivity and reactivity issues may arise especially when reagents are employed bearing a substituent adjacent to the phosphorus.[5] For the present work, we chose to study the 4-methyl-substituted phosphonate **1** for the rapid construction of the 4-methyldienoate system, which constitutes a structural feature seen among several natural products arising from propionate biosynthetic pathways.

Phosphonate **1** is prepared as an inconsequential mixture of alkene positional isomers in one step through the Arbuzov reaction[6] of triethyl phosphite with (*E*)-methyl 3-bromo-2-pentenoate (eq 1). Although the dimethyl phosphonate analogue of **1** was prepared more than 20 years ago, the original authors did not report on its reactivity and applications.[7] Corresponding phosphonium ylides have seen synthetic use. Problems encountered with their use include poor or undetermined *E*/*Z* selectivity and mixtures of addition products.[8]



(1)

Our study of **1** began by examining benzaldehyde as a substrate under standard HWE conditions (Table 1). Using lithium hexamethyldisilazide (LiHMDS) in THF at low temperature, we obtained a 92:8 mixture of 2*E*,4*E*- and 2*E*,4*Z*-products with excellent purity (Table 1, entry 1). We varied the solvent and counterion, which have previously been demonstrated to affect the selectivity.[1,9] The solvent

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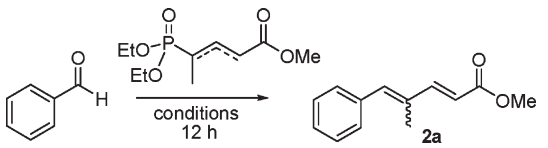
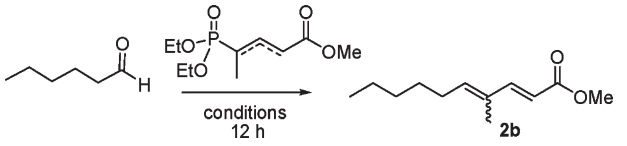
TABLE 1. Optimization of Conditions with an Aromatic Aldehyde



entry	solvent	base	temp[a] (°C)	*E*,*E*/*E*,*Z*[b]	yield[c] (%)
1	THF	LiHMDS	−78	92:8	97
2	THF/HMPA	LiHMDS	−78	88:12	98
3	$PhCH_3$	LiHMDS	−78	87:13	38
4	Et_2O	LiHMDS	−78	86:14	55
5	DME	LiHMDS	−78	91:9	94
6	DME	LiHMDS	22	87:13	69
7	THF	LiHMDS	22	86:14	69
8	THF	NaHMDS	−78	88:12	92
9	THF	KHMDS	−78	83:17	90
10	THF	KHMDS/18-C-6[d]	−78	80:20	91

[a]Temperature at which the aldehyde is added. [b]Ratios were measured from the ^{1}H NMR of the crude material. [c]Yields measured by ^{1}H NMR using mesitylene as an internal standard. [d]18-C-6 = 18-crown-6.

TABLE 2. Optimization of Conditions with an Aliphatic Aldehyde



entry	solvent	base	temp[a] (°C)	*E*,*E*/*E*,*Z*[b]	yield[c] (%)
1	THF	LiHMDS	−78	74:26	90
2	THF/HMPA	LiHMDS	−78	58:42	79
3	$PhCH_3$	LiHMDS	−78	72:28	54
4	Et_2O	LiHMDS	−78	72:28	62
5	DME	LiHMDS	−78	74:26	73
6	DME	LiHMDS	22	73:27	53
7	THF	LiHMDS	22	72:28	39
8	THF	NaHMDS	−78	49:41	71
9	THF	KHMDS	−78	46:56	69
10	THF	KHMDS/18-C-6[d]	−78	40:60	64

[a]Temperature at which the aldehyde is added. [b]Ratios were measured from the ^{1}H NMR of the crude material. [c]Yields measured by ^{1}H NMR using mesitylene as an internal standard. [d]18-C-6 = 18-crown-6.

had minimal affect on selectivity, giving approximately the same ratio of *E*,*E*- and *E*,*Z*-products. We noted decreased yields with less polar solvents (Table 1, entries 3 and 4). We investigated performing the reaction in THF and DME at elevated temperatures (Table 1, entries 6 and 7) based on Heathcock's observation that these conditions, which encourage equilibrium between the betaine and oxaphosphetane before the irreversible elimination of phosphate, lead to increased *E*-selectivity.[9] However, we noticed slightly lower selectivity and decreased yields with these conditions.

The effect of the metal ion was also investigated. It has previously been established that the use of more strongly dissociating metal ions increases the amount of the *Z*-configuration due to a lack of reversibility of reactive intermediates before the rate-limiting elimination of phosphate.[10] Thus, the highest proportion of the *E*,*Z*-product was obtained when KHMDS and 18-crown-6 were used (Table 1, entry 10).

We next performed the same study on the aliphatic aldehyde hexanal (Table 2). In general, the stereoselectivities for aliphatic aldehydes are poorer than aromatic substrates. As before, the solvent and aldehyde addition temperature had minimal effect on the diene selectivity. The same metal ion effect that was seen with benzaldehyde was again noticed. Upon use of KHMDS/18-crown-6, the amount of the *E*,*Z*-product again increased, which led in this case to a reversal of the selectivity in favor of the *E*,*Z*-product (Table 2, entry 10).

The diene configurations of **2a** and **2b** were assigned by ROESY NMR (Figure 1). More specifically, we found a NOE between the C(4) methyl group protons and the C(5) proton for the minor isomer *E*,*Z*-**2a**. This correlation was absent from the major isomer *E*,*E*-**2a**. For **2b**, a correlation was observed between the C(6) protons and the C(4) methyl group for the major isomer *E*,*E*-**2b**. This correlation was absent for the minor isomer *E*,*Z*-**2b**, which instead had a cross-peak between the C(3) and C(6) protons.

From the survey of conditions above, we judged LiHMDS in THF to be suitable for achieving modest to high *E*,*E*-selectivity and good yields. Employing these conditions, we

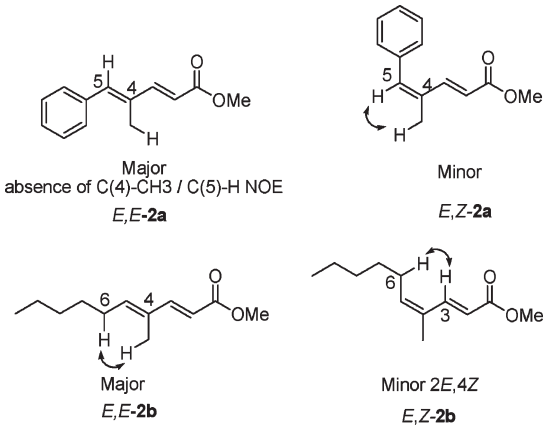


FIGURE 1. Key ROESY NMR cross-peaks for diene configuration assignments.

examined a variety of aldehydes to probe the scope of the reaction (Table 3). Again we established that aromatic aldehydes perform with good stereoselectivity while aliphatic derivatives give lower *E*,*E*-selectivity. In many cases, the minor *E*,*Z*-product could be separated by flash column chromatography.

As expected, electron-rich aldehydes react at a much slower rate than electron-poor aldehydes. Increasing the number of alkyl branches on the α carbon of the aldehyde negatively affects the *E*-selectivity (Table 3, entries 11). Not included in Table 3 are cases of aldehydes for which poor yields and products of poor purity are obtained, including a very electron-rich aromatic aldehyde (*p*-dimethylaminobenzaldehyde) and α,β-unsaturated aldehydes (acrolein, cinnamaldehyde). Additionally, a complex mixture of isomeric β-hydroxyphosphonates as addition products was isolated from the reaction with cinnamaldehyde. A ketone (cyclohexanone) gave a very low yield.

As a specific application of this reaction, we chose to develop a short synthesis of trichostatic acid **3**. This compound has been isolated from *Streptomyces sioyaensis* and induces differentiation of leukemia cells.[11] More importantly, **3** serves as a direct precursor to trichostatin A, one

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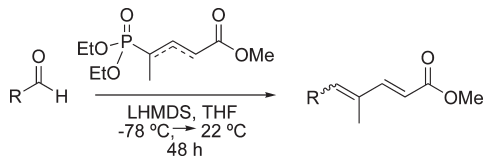
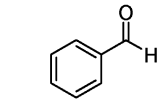
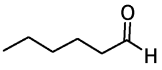
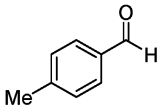
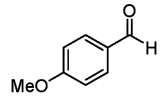
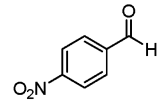
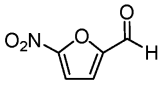
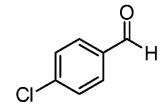
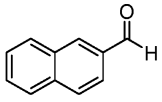
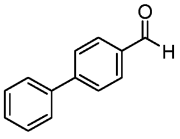
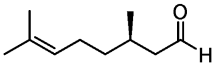
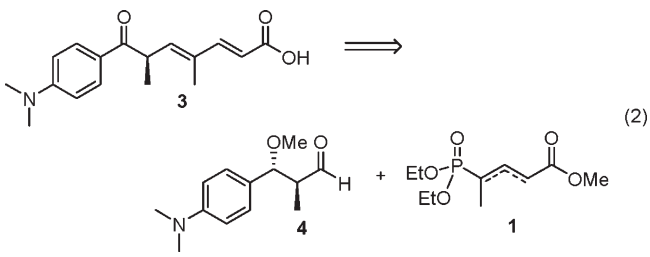
TABLE 3. Exploration of a Variety of Substrates



entry	aldehyde	product	*E,E/E,Z*[a]	yield (%)[b]
1		**2a**	92:8	82
2		**2b**	74:26	97
3		**2c**	88:22	78
4		**2d**	91:9	59
5		**2e**	89:11	82
6		**2f**	>95:5	87
7		**2g**	93:7	93
8		**2h**	93:7	91
9		**2i**	92:8	87
10		**2j**	76:24	78
11		**2k**	40:60	80

[a]Ratios were measured from the ^{1}H NMR of the crude material. [b]Yield of the purified product.

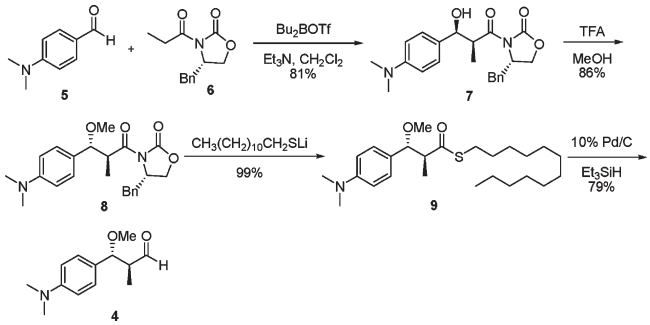
of the best known and most potent histone deacetylase inhibitors.[12] Some of the previously reported syntheses of **3** or its derivatives have tended to be somewhat long, given the only modest complexity of this system.[13] Most commonly, the diene portion has been built up linearly by sequential uses of olefination reactions, whereas the advantage of using reagent **1** would in principle be a one-step construction of the diene moiety. The pivotal compound required to reduce this plan to practice was the chiral aldehyde **4** as a substrate for reaction with **1** (eq 2).



(2)

Our synthesis of trichostatic acid[14] **3** commenced with the Evans aldol reaction[15] of *p*-dimethylaminobenzaldehyde **5** with chiral propionyloxazolidinone **6**, giving rise to a single detectable diastereomer **7** in high yield (Scheme 1). Because a base-induced retro-aldol reaction plagued subsequent steps in the synthesis, the hydroxyl group was protected as the methyl ether under solvolytic conditions. As expected, this reaction produced an inconsequential mixture of diastereomers. The major *anti*-diastereomer[16] **8** could readily be isolated by crystallization, and the minor isomer could be re-equilibrated under acidic conditions, although both diastereomers have the correct configuration at the stereogenic center that is present in trichostatic acid. Removal of the chiral auxiliary under typical reductive conditions ($LiBH_4$, Red-Al, DIBAL, etc.) proved challenging due to competing reductive ring-opening of the oxazolidinone. This problem was overcome by first converting imide **8** to thiol ester **9**. Instead of the typically used low molecular weight thiols, the long-chain dodecanethiol was employed as an essentially nonvolatile, nonodoriferous scavenger reagent that endowed the lipophilic product **9** with conveniently exploitable chromatographic properties for ease of separation from more polar impurities. The thiol ester **9** could then be reduced to the corresponding aldehyde **4** in good yield using Pd/C and Et_3SiH.[17]

SCHEME 1. Synthesis of 4



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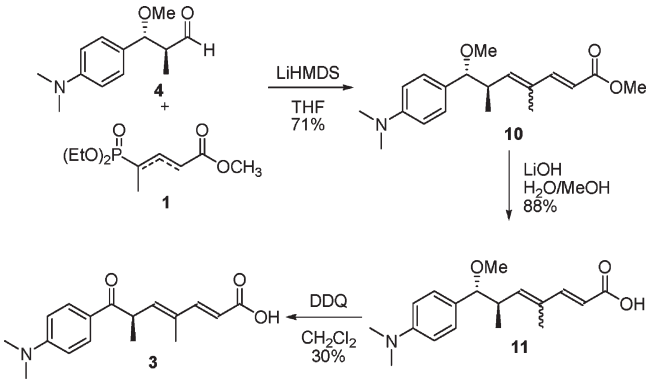
(15) Gage, J. R.; Evans, D. A.; DeRussy, D. T.; Paquette, L. A. *Org. Synth.* **1990**, *68*, 83.

(16) Assigned by X-ray diffraction (see the Supporting Information).

(17) Fukuyama, T.; Tokuyama, H. *Aldrichim. Acta* **2004**, *37*, 87.

SCHEME 2. Synthesis of Trichostatic Acid 3



In the key step of the synthesis, aldehyde **4** reacted with phosphonate **1** using LiHMDS in THF to give dienoate **10** (Scheme 2) as the product in good yield as a 2:1 mixture of *E*,*E*- and *E*,*Z*-isomers. Commonly used methods of *Z*/*E*-alkene isomerization (treatment with thiols, photochemical irradiation) were applied to no avail, which may reflect little thermodynamic preference for the desired *E*,*E*-isomer.[18] This mixture posed little difficulty in the synthesis in that it could readily be carried through the pathway, and separation of isomers could be effected at the end. Thus, the isomeric mixture of **11** was subjected to simple ester hydrolysis and benzylic ether oxidation to give trichostatic acid **3** as the corresponding mixture of isomers. At this stage, the mixture could be separated by employing flash or medium-pressure, normal-phase chromatography to give the pure, desired *E,E*-isomer with 87% ee suggesting partial loss of stereochemical integrity during the sequence of steps (see the Supporting Information regarding the sensitivity of **4**). The ^{1}H and ^{13}C NMR spectra matched the published data for trichostatic acid.[13b]

In conclusion, the reactions of vinylogous HWE reagent **1** with aldehydes provide 4-methyldienoate derivatives in one simple step. This method permits rapid access to substituted and functionalized diene subunits seen in a variety of natural products and other compounds of interest.

Experimental Section

A representative procedure for the vinylogous HWE reaction is provided here. For preparation of the reagent **1**, the other examples of its condensation, and the synthesis of trichostatic acid, see the Supporting Information.

Methyl (2*E*,4*E*)-5-(4-Chlorophenyl)-4-methylpenta-2,4-dienoate (2g). A solution of phosphonate **1** (110 mg, 0.44 mmol, 1.5 equiv) in THF (2 mL) was cooled to −78 °C, and a commercial solution of LiHMDS (0.4 mmol, 1.4 equiv)[19] was added dropwise. The solution was warmed to 22 °C for 30 min and recooled to −78 °C. A solution of the 4-chlorobenzaldehyde (42 mg, 0.30 mmol, 1.0 equiv) in THF (1 mL) was added dropwise. The solution was stirred for 12 h, and the temperature was allowed to rise to 22 °C. After the formation of product had ceased (GC monitoring), the reaction was quenched by the addition of pH 7 phosphate buffer (1 M). The solution was combined with CH_2Cl_2 and NaCl saturated aqueous solution, extracted with CH_2Cl_2, and dried with $MgSO_4$. The solvent was removed under reduced pressure to afford the crude compound which was purified using flash column chromatography (SiO_2, 0−10% EtOAc in hexanes) to yield **2g** (65 mg, 93%) of the pure 2*E*,4*E* isomer as a solid: mp = 76−77 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.49 (dd, J = 16.0, 0.8 Hz, 1H, *H*C═CC═O), 7.36 (dd J = 6.4, 2 Hz, 2H, ArH meta to Cl), 7.28 (dd, J = 6.8, 2.0 Hz, 2H, ArH ortho to Cl), 6.80 (bs, 1H, Ar-C*H*═C), 6.00 (dd, J = 15.0, 0.8 Hz, 1H, C═C*H*C═O), 3.80 (s, 3H, OCH_3) 2.03 (d, J = 1.2 Hz, 3H, C═CCH_3); (lit.[20] ^{1}H NMR) ^{13}C NMR (150 MHz, $CDCl_3$) δ 167.9, 149.8, 137.7, 135.3, 134.8, 133.8, 130.9, 128.8, 117.7, 51.8, 13.9; HMRS (ESI) for $C_{13}H_{13}O_2ClNa$ $[M + Na]^+$ calcd 237.0677, found 237.0688.

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Supporting Information Available: Further experimental procedures, spectral data, and crystallographic data. This material is available free of charge via the Internet at http://pubs.acs.org.

(18) At the B3LYP/6-211+G** + CPCM (THF)//6-31G* level of theory, the two isomers are within 0.1 kcal/mol of each other.

(19) The commercial solution was titrated prior to use following a literature procedure: Ireland, R. E.; Meissner, R. S. *J. Org. Chem.* **1991**, *56*, 4566.

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