# Asymmetric Horner-Wadsworth-Emmons Reactions Using *Meso* Dialdehydes as Substrates

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*Summary:* Asymmetric Horner-Wadsworth-Emmons reactions of the chiral phosphonate **7** with *meso* dialdehydes **1** and **4** gave the desired monoaddition products with good diastereoselectivities (87:13-97:3) and high (*E*)-selectivity.

The asymmetric transformation of a *meso* compound by reaction with a chiral reagent is a generally useful strategy for asymmetric synthesis, and in recent years several reactions of this type involving either enzymatic catalysis[1] or nonenzymatic reactions[2] have been reported. Asymmetric alkene syntheses by reaction of *meso* substrates with chiral phosphorus-based reagents[3] or chiral sulfoximines[4] have been studied for some time. Very recently, Hanessian et al.[3f] as well as Denmark et al.[3g] have reported highly selective syntheses of dissymmetric olefins from substituted cyclohexanones by such reactions. However, a compound containing two enantiotopic carbonyl groups has been used as substrate for an asymmetric alkene synthesis on only one occasion to date.[3b] We are currently investigating reactions between *meso* dialdehydes and chiral Horner-Wadsworth-Emmons reagents, and our initial results are reported in this paper.[5]

For several reasons, the dialdehydes **1** and **4** are interesting substrates. In each case, a selective reaction with one of the two enantiotopic carbonyl groups[6] will result in asymmetric induction on three stereocenters. Furthermore, the derived products **2** and **5** (or the corresponding alcohols **3** and **6**) could be used as building blocks in syntheses of several important natural products: to give specific examples, **2** corresponds to partial structures of the scytophycins[7] and the swinholide/misakinolide family of macrolides,[8] and **5** corresponds to subunits of several polyene macrolide antibiotics, e.g., roxaticin.[9]

Dialdehyde **1** has been prepared previously and isolated as its cyclic hydrate.[10] We have found that a modified (nonaqueous) workup procedure in the Swern oxidation step enables isolation of the parent dialdehyde, almost free from the corresponding hydrate. Dialdehyde **4** was prepared from 6-(benzyloxy)-1,3-cycloheptadiene[11] in five steps ((i) $Pd(OAc)_2$/benzoquinone/$MnO_2$, LiOAc, HOAc;[12] (ii) KOH; (iii) imidazole, $Bu^tPh_2SiCl$; (iv) $OsO_4$/NMMO;[13] (v) $H_5IO_6$).

Our results from reactions of **1** and **4** with the chiral phosphonate **7**,[3d,e] which is easily prepared from (-)-8-phenylmenthol,[14] are presented in Scheme I and Table I. In our first experiments, we used an excess of the dialdehyde substrate in order to suppress formation of the product from double addition of the phosphonate. To facilitate separation of the desired materials from unreacted substrate, the crude product mixture was treated with $NaBH_4$ in MeOH and the products isolated as the alcohols **3** and **6**. At -78 °C, both substrates gave essentially the same ratios (ca. 87:13) of product diastereomers, in good to excellent overall yields[15] (entries 1 and 6). Performing the reactions at -100 °C gave comparable selectivities (entries 2 and 7). Similar selectivities were also obtained when only a slight excess of the dialdehyde substrate was used (entries 3 and 8). As shown in entries 4 and 5, adjustment of stoichiometry, reaction temperature, and time can result in even higher selectivities, at the expense of a reduction in yield. A simultaneous kinetic resolution of the monoaddition product **2** explains these results.[16] In the condensations with **4**, these effects are less pronounced (entries 8 and 9). A possible explanation for this observation is that these runs might not have proceeded to complete conversion due to generally slower rates of reaction with this substrate. This could also explain the more modest yields of **6** obtained from the condensations performed at -100 °C.

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(5) Part of this work has previously been presented at the 18th IUPAC Symposium on the Chemistry of Natural Products, Strasbourg, France, Aug 30-Sept 4, 1992; Abstract 267.

(6) For a general discussion of differentiation of enantiotopic groups in a substrate and applications in two-directional chain synthesis, see: Schreiber, S. S. *Chem. Script.* **1987**, *27*, 563 and references cited therein.

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(8) Doi, M.; Ishida, T.; Kobayashi, M.; Kitagawa, I. *J. Org. Chem.* **1991**, *56*, 3629 and references cited therein.

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(13) NMMO = *N*-methylmorpholine *N*-oxide. KHMDS = potassium hexamethyl disilazide, $KN(SiMe_3)_2$.

(14) Hatakeyama, S.; Satoh, K.; Sakurai, K.; Takano, S. *Tetrahedron Lett.* **1987**, *28*, 2713.

(15) The ratios **2a:2b** and **5a:5b** have been determined on the crude condensation products; the ratios **3a:3b** and **6a:6b** refer to the products obtained after chromatography. Yields are isolated yields of compounds that are homogeneous by TLC and judged as being >95% pure by NMR.

(16) Diastereomers **2b** and **5b** are expected to react faster than **2a** and **5a** with the anion of phosphonate **7**, and consequently, increased conversion to products from double addition (**8** and **9**, Chart I) should increase the ratios **2a:2b** and **5a:5b**. See also: (a) Schreiber, S. S.; Schreiber, T. S.; Smith, D. B. *J. Am. Chem. Soc.* **1987**, *109*, 1525. (b) Reference 2e.

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**Scheme I**

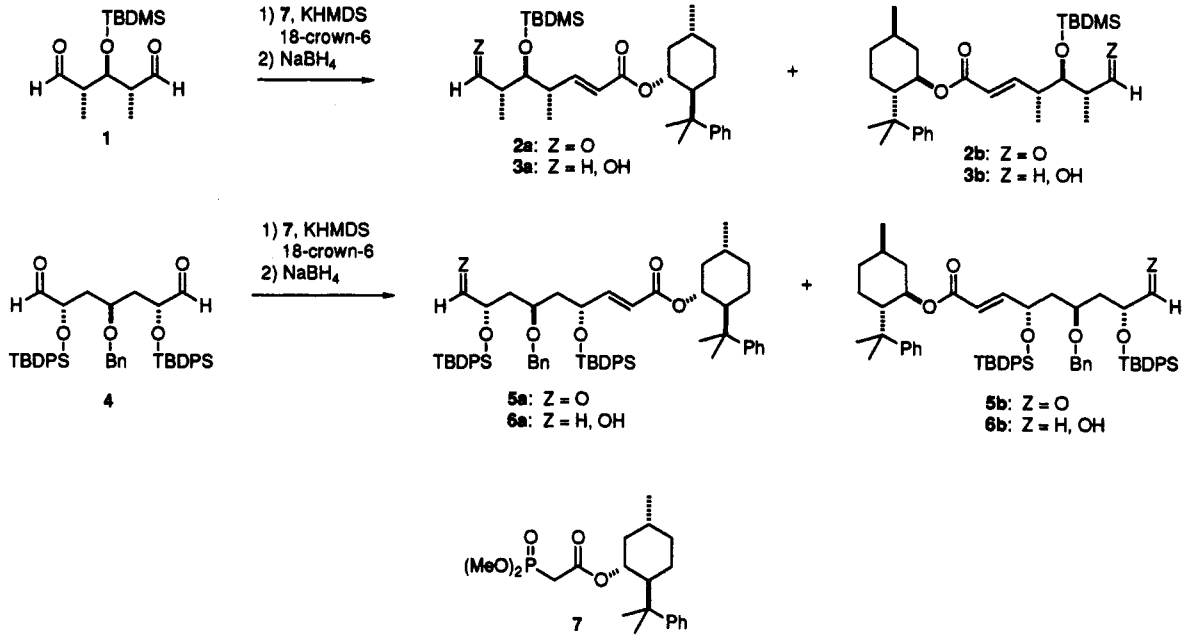



**Table I. Reactions of Phosphonate 7 with Dialdehydes 1 and 4[a]**

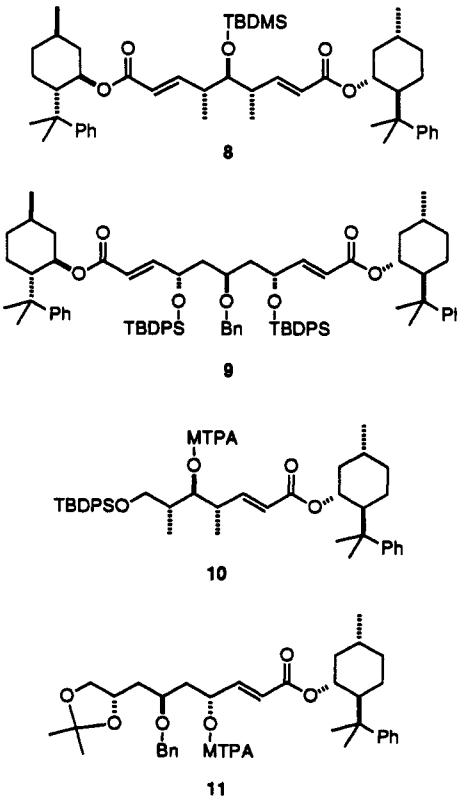
| entry | substrate (equiv) | temp (°C) | reaction time (h) | ratio 2a:2b or 5a:5b[b] | ratio 3a:3b or 6a:6b[c] | yield of 3 or 6 (%) |
|---|---|---|---|---|---|---|
| 1 | 1 (2.0) | −78 | 2.5 | 87:13 | 87:13 | 88 |
| 2 | 1 (2.1) | −100 | 5 | 90:10 | 90:10 | 87 |
| 3 | 1 (1.3) | −100 | 5 | 91:9 | 91:9 | 77 |
| 4 | 1 (1.2) | −78 | 3.5 | 97:3 | 97:3 | 36[d] |
| 5 | 1 (1.1) | −100 | 8 | 95:5[e] | not determined | 53[f] |
| 6 | 4 (2.0) | −78 | 4 | 86:14 | 87:13 | 68 |
| 7 | 4 (2.0) | −100 | 15 | 88:12 | 89:11 | 50[g] |
| 8 | 4 (1.2) | −100 | 15 | 89:11 | 92:8 | 49 |
| 9 | 4 (1.2) | −78 | 6.5 | 88:12 | 89:11 | 60[h] |

[a] General conditions: 1.1 equiv of phosphonate, 1.0 equiv of KHMDS, 5–6 equiv of 18-crown-6, ca. 0.02 M in THF. [b] Determined on the crude condensation product by $^1$H NMR at 250 or 400 MHz (integrals of aldehyde or olefin protons). [c] Determined on the product obtained after purification by chromatography by $^1$H NMR (integrals of olefin protons). [d] The double addition product 8 was also isolated, in 48% yield. [e] The same ratio was obtained before and after purification. [f] The product was isolated as the aldehyde 2. [g] The product contained small amounts (estimated as ≤3%) of a byproduct, presumably a diastereomer of 6 but different from the one obtained in entry 9. [h] Another product diastereomer (different from 6a and 6b, but not yet completely characterized) was also isolated in 17% yield.

Under certain conditions, byproducts tentatively assigned as additional product diastereomers were formed from 4 (entries 7 and 9). NMR analyses indicate that these diastereomers were formed during the reduction step and not during the initial condensation. The product from reaction of 7 with 1 can be isolated as the aldehyde 2 as well (entry 5). To avoid possible epimerization of the stereocenter α to the aldehyde carbonyl, deactivated silica[17] was used in the chromatographic purification (≤3% epimerization was observed). We are presently working on further optimization of the conditions for these reactions, including procedures that will enable isolation of aldehyde 5 in pure form. These studies will be reported upon in a forthcoming full paper.

(17) The silica was deactivated by elution with EtOAc or $CH_2Cl_2$/MeOH prior to chromatography.

**Chart I**




Our assignments of the absolute configurations of the condensation products are based on NMR analyses[18] of the Mosher ester derivatives 10 and 11 (Chart I), which were obtained from 3 and 6, respectively, by standard transformations. In all experiments in Table I, the isolated condensation products were obtained with almost complete (≥98%) (*E*)-selectivity. This is surprising, since we have used conditions (KHMDS,[13] 18-crown-6, THF) which should maximize kinetic control and as a consequence also

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favor formation of (*Z*)-product.[19] On the basis of our present knowledge, neither the (*E*)-selectivities nor the mechanistic reasons behind the observed diastereoselectivities can be rationalized in any detail; such explanations will have to await further experimental studies. The generally high (*E*)-selectivities indicate that the reactions might be under thermodynamic control.[20]

To summarize, our results show that *meso* dialdehydes are useful substrates for reactions with chiral phosphonate reagents, which in turn should broaden the synthetic potential of asymmetric alkene synthesis considerably. The selectivities obtained so far are very promising, and we are presently studying the preparation and utility of structurally modified chiral phosphonate reagents which might give even higher selectivities, as well as applications of this chemistry in synthesis. The results of these studies will be reported in due course.

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(20) For a recent review of the HWE and related reactions, including discussions of various mechanistic aspects, see: Maryanoff, B. E.; Reitz, A. B. *Chem. Rev.* **1989**, *89*, 863.

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**Supplementary Material Available:** Experimental procedures for the HWE condensations, selected analytical data for compounds **1–6**, and selected NMR data for compounds **10** and **11** (5 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.