Reagent Control of Geometric Selectivity and Enantiotopic Group Preference in Asymmetric Horner−Wadsworth−Emmons Reactions with *meso*-Dialdehydes†

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Results from asymmetric Horner−Wadsworth−Emmons reactions between chiral phosphonate reagents **3a**−**d**, which contain (1*R*,2*S*,5*R*)-8-phenylmenthol as a chiral auxiliary, and *meso*-dialdehydes **6** and **14** are presented. It was found that both the geometric selectivities and the levels of asymmetric induction depended on the structure of the phosphonate (i.e., the alkyl group R^1 in the phosphoryl unit) and to a certain extent also on the reaction conditions. Furthermore, the nature of the protecting group used on the α-oxygen substituent in dialdehydes **14** influenced the outcome somewhat. By an appropriate choice of reagent and conditions, either (*E*)- or (*Z*)-monoaddition products could be obtained geometrically pure and with good to excellent diastereoselectivities, in synthetically useful yields. Analyses of the absolute configurations of the products showed that the (*E*)-selective reagents (**3a**−**c**) and the (*Z*)-selective phosphonate **3d** reacted at opposite enantiotopic carbonyl groups in the substrates. A mechanistic model which accounts for the products formed is presented.

Introduction

Selective reaction of only one of two enantiotopic groups in a bifunctional substrate is a powerful strategy[1] for asymmetric synthesis, as witnessed by the increasing attention such processes have received in recent years; a variety of examples, using both enzymatic[2] and nonenzymatic[3] reactions, has been reported. Based on this concept, reaction types in which no additional sp^3 stereocenter is created at any of the bond-forming sites can also be used for asymmetric synthesis, since asymmetric induction is achieved by "desymmetrization" of the substrate. One such class of reactions is asymmetric Wittig-type reactions, an area which in recent years has been studied by a number of research groups,[4] with several examples of highly selective transformations being reported. In the vast majority of asymmetric Wittig-type reactions studied so far, however, monocarbonyl compounds have been utilized as substrates; only in a few cases[4f,n,q,bb] have prochiral diketones been employed, and prior to our first report[4m] the possibility

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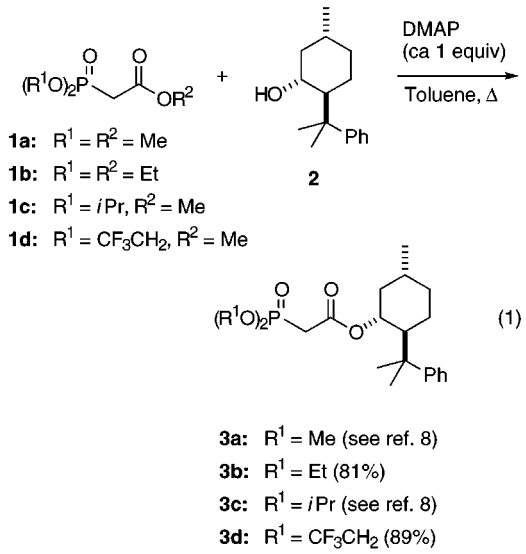
of using dialdehyde substrates[5] had not been investigated. From the viewpoint of synthetic efficiency, this alternative is appealing since the reaction product directly can take part in an additional chain-extending reaction involving the unreacted aldehyde, as exemplified in Scheme 1. Thus, relatively complex chiral structures should be quickly accessible from nonchiral precursors.

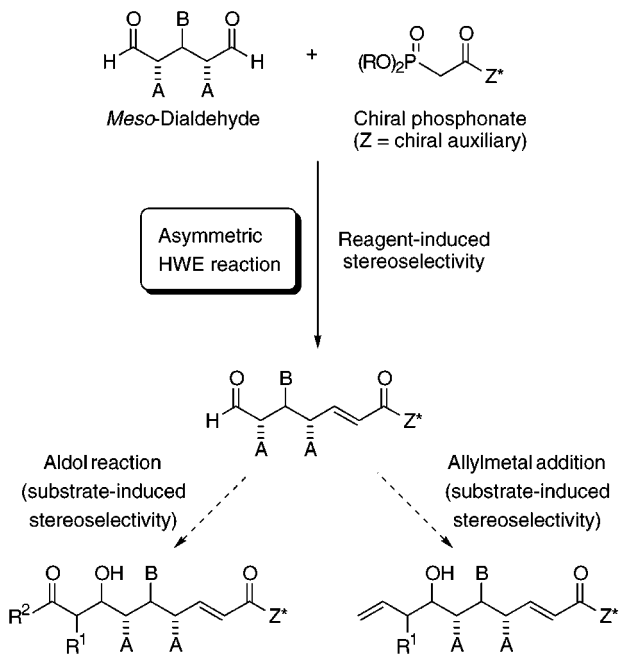
In this paper, we report results from an extension of our earlier[6] studies of asymmetric Horner−Wadsworth−Emmons (HWE) reactions[7] with dialdehydes and demonstrate that complementary product selectivities are possible by an appropriate choice of reagent: by slight structural variation in the chiral phosphonate, either (*E*)- or (*Z*)-alkenes can be obtained as products, with both high geometric selectivity and good to excellent levels of asymmetric induction. Furthermore, the (*E*)- and (*Z*)-selective reagents are complementary also in the sense that they react with opposite enantiotopic group preference.

Results

Choice and Preparation of Chiral Phosphonate Reagents. For our initial studies, we chose to examine reactions between suitable model dialdehyde substrates and the chiral phosphonates **3a**−**d**, derived from (1*R*,2*S*,5*R*)-8-phenylmenthol (eq 1). Reagent **3a** has earlier been shown to give useful levels of diastereoselectivity in reactions with a prochiral monoketone[4h,y] and with some structurally related chiral ketones.[4h,i] Furthermore, we felt that incorporation of a chiral auxiliary in the anion-stabilizing functionality rather than in the phosphorus-based functional group could give larger synthetic versatility, since choice of different alkyl groups R^1 in the reagent then might enable control of the alkene geometry in the product. This expectation was realized in practice.



Scheme 1



A procedure for preparation of the chiral phosphonates **3a** and **3c** by transesterification of the achiral precursors **1a** and **1c** with 8-phenylmenthol (**2**) has previously been reported by Takano and co-workers.[8] In the same manner, we prepared[4o] reagents **3b** and **3d** in good yields from the corresponding known phosphonates **1b** and **1d**.[9]

Choice and Preparation of Model Substrates. As our model dialdehyde substrates, we chose compounds **6**[10] and **14**. The motivation for this choice was 2-fold: (i) reactions with these substrates would give information on the influence of different types of α-substituents (CH_3 or RO) in the dialdehyde on the reaction selectivity; (ii) the expected chiral monoaddition products are potentially useful synthetic intermediates, as they correspond to partial structures of a number of natural products of biomedical interest. Thus, the products expected from dialdehyde **6** match subunits of several strongly cytotoxic macrolides,[11] whereas products derived from dialdehydes of type **14** can be envisioned as building blocks for polyene/polyol macrolide antibiotics.[12]

(5) For examples of the use of *meso*-dialdehydes as substrates for other types of asymmetric transformations, see: (a) Yamazaki, Y.; Hosono, K. *Tetrahedron Lett.* **1988**, *29*, 5769−5770. (b) Roush, W. R.; Park, J. C. *Tetrahedron Lett.* **1990**, *31*, 4707−4710. (c) Wang, Z.; Deschênes, D. *J. Am. Chem. Soc.* **1992**, *114*, 1090−1091. (d) Ward, D. E.; Liu, Y.; Rhee, C. K. *Synlett* **1993**, 561−563. (e) Ward, D. E.; Liu, Y. D.; Rhee, C. K. *Can. J. Chem.* **1994**, *72*, 1429−1446. (f) Roush, W. R.; Wada, C. K. *J. Am. Chem. Soc.* **1994**, *116*, 2151−2152. (g) Oppolzer, W.; De Brabander, J.; Walther, E.; Bernardinelli, G. *Tetrahedron Lett.* **1995**, *36*, 4413−4416. (h) De Brabander, J.; Oppolzer, W. *Tetrahedron* **1997**, *53*, 9169−9202. (i) Oppolzer, W.; Walther, E.; Balado, C. P.; De Brabander, J. *Tetrahedron Lett.* **1997**, *38*, 809−812.

(6) Part of this work has been described in an earlier communication; see ref 4m.

(7) (a) Horner, L.; Hoffman, H.; Wippel, H. G. *Chem. Ber.* **1958**, *91*, 61−63. (b) Horner, L.; Hoffman, H.; Wippel, H. G.; Klahre, G. *Chem. Ber.* **1959**, *92*, 2499−2505. (c) Wadsworth, W. S.; Emmons, W. D. *J. Am. Chem. Soc.* **1961**, *83*, 1733−1738. For reviews discussing general aspects of the HWE reaction, see: (d) Boutagy, J.; Thomas, R. *Chem. Rev.* **1974**, *74*, 87−99. (e) Wadsworth, W. S., Jr. *Org. React.* **1977**, *25*, 73−253. (f) Walker, B. J. In *Organophosphorus Reagents in Organic Synthesis*; Cadogan, J. I. G., Ed.; Academic Press: New York, 1979; pp 155−205. (g) Maryanoff, B. E.; Reitz, A. B. *Chem. Rev.* **1989**, *89*, 863−927. (h) Kelly, S. E. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon Press: Oxford, 1991; Vol. 1, pp 730−817. See also ref 4d.

(8) Hatakeyama, S.; Satoh, K.; Sakurai, K.; Takano, S. *Tetrahedron Lett.* **1987**, *28*, 2713−2716. In our hands, stoichiometric amounts of DMAP were in some cases required for the reactions to give good yields.

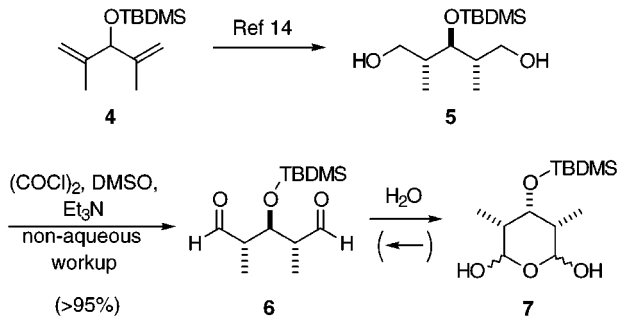
(9) Compound **1b** is commercially available. Phosphonate **1d** was prepared according to the procedure of Still: Still, W. C.; Gennari, C. *Tetrahedron Lett.* **1983**, *24*, 4405−4408.

(10) After our initial report on asymmetric HWE reactions with **6**, this dialdehyde has also been used as substrate in group-selective asymmetric aldol reactions; see refs 5g and 5h.

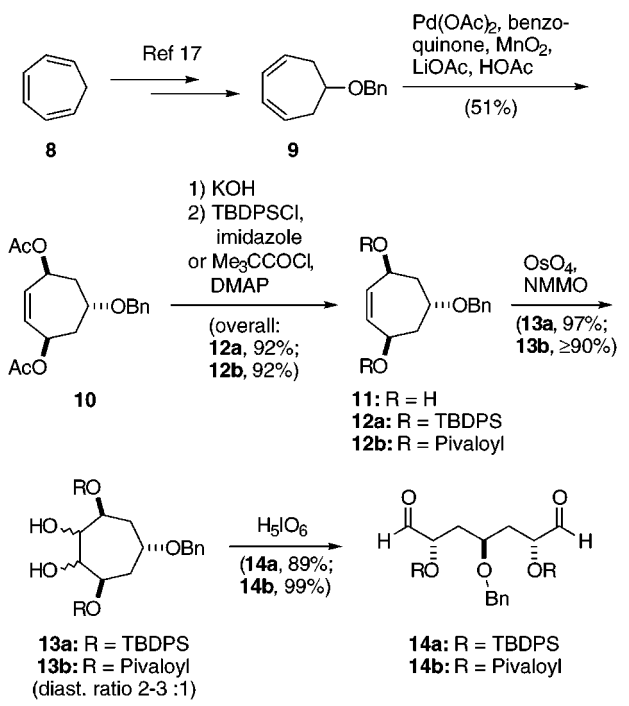
(11) Norcross, R. D.; Paterson, I. *Chem. Rev.* **1995**, *95*, 2041−2114.

(12) Rychnovsky, S. D. *Chem. Rev.* **1995**, *95*, 2021−2040.

Scheme 2



Scheme 3

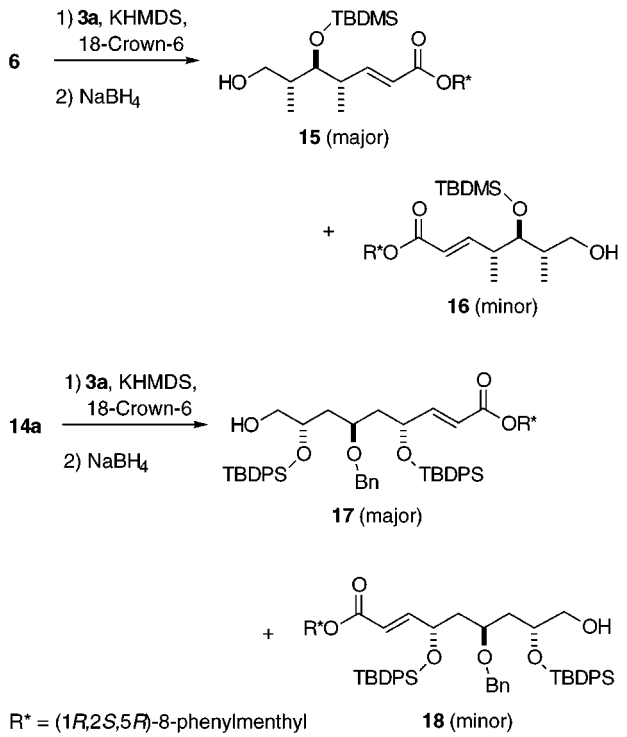


Diol **5**, the immediate precursor of dialdehyde **6**, was obtained by double hydroboration of diene **4**,[13] as described by Harada and co-workers.[14] Compound **6** could be prepared in pure form by Swern oxidation[15] of **5** if water was carefully excluded during the workup (Scheme 2). In the presence of water, the cyclic hydrate **7** was isolated as the major product,[16] and it proved difficult to regenerate **6** once the hydrate had been formed. Dialdehyde **6** is stable in solution for some time, if stored protected from water; we recommend, however, that it is freshly prepared for use.

The other model substrates, dialdehydes **14**, were synthesized in five steps from 6-(benzyloxy)-1,3-cycloheptadiene (**9**) which, in turn, is accessible from 1,3,5-cycloheptatriene[17] (Scheme 3). The relative stereochemistry of the three stereocenters in **14** was controlled by a palladium-catalyzed cis-diacetoxylation[18] of diene **9** to give diacetate **10**.[19] To gain some insight into the influence of different oxygen-protecting groups R in **14** on the outcome of the asymmetric HWE reactions, the *tert*-butyldiphenylsilyl-protected substrate **14a**, and the pivaloyl-protected **14b** were then prepared from **10** by straightforward transformations.[20]

Diols **13a** and **13b** were both formed as diastereomeric mixtures, but upon treatment with periodic acid, both diastereomers of each compound were cleanly converted to the desired dialdehyde. Dialdehyde **14a** is quite robust and stable enough to be purified by chromatography without detectable epimerization. Compound **14b**, however, is more sensitive, and is best prepared fresh immediately prior to use.

Scheme 4



Asymmetric HWE Reactions. To investigate the influence of reactant stoichiometry and reaction temperature, we first studied reactions between dimethylphosphonate **3a** and dialdehydes **6** and **14a** (Scheme 4, Table 1). Conditions which were expected to favor kinetic control in the initial addition step, by increasing the relative rate of the subsequent elimination, were chosen [potassium hexamethyldisilazide (KHMDS) as base in combination with 18-crown-6, low temperature].[21] In these initial experiments, the crude reaction product was reduced with $NaBH_4$ to facilitate separation of the products from both bis-addition products and remaining unreacted dialdehyde.

Somewhat to our surprise, essentially only (*E*)-products were obtained from both substrates, although nonasymmetric HWE reactions with dimethyl phosphonates often give (*Z*)-products under similar reaction conditions. These initial experiments demonstrated that (*E*)-alkenes **15**[22] and **17**[22] could be obtained in reasonable yields and

(13) For experimental details regarding the preparation of **4** and **5**, see Supporting Information.

(14) (a) Harada, T.; Matsuda, Y.; Uchimura, J.; Oku, A. *J. Chem. Soc., Chem. Commun.* **1990**, 21−22. (b) Harada, T.; Inoue, A.; Wada, I.; Uchimura, J.; Tanaka, S.; Oku, A. *J. Am. Chem. Soc.* **1993**, *115*, 7665−7674. For an enzyme-catalyzed desymmetrization of **5** by group-selective esterification, see: Chenevert, R.; Courchesne, G. *Tetrahedron: Asymmetry* **1995**, *6*, 2093−2096.

(15) Mancuso, A.; Huang, S.-L.; Swern, D. *J. Org. Chem.* **1978**, *43*, 2480−2482.

(16) Harada, T.; Kagamihara, Y.; Tanaka, S.; Sakamoto, K.; Oku, A. *J. Org. Chem.* **1992**, *57*, 1637−1639.

(17) Schink, H. E.; Petterson, H.; Bäckvall, J.-E. *J. Org. Chem.* **1991**, *56*, 2769−2774.

(18) Bäckvall, J.-E.; Byström, S. E.; Nordberg, R. E. *J. Org. Chem.* **1984**, *49*, 4619−4631.

Table 1. Reactions of Phosphonate 3a with Dialdehydes 6 and 14a[a]

entry	substrate (equiv)	temp (°C)	product	yield[b] (%)	diaster ratio[c]	yield of bis-addition (%)
1	**6** (2.0)	−78	**15**	88	87:13	5
2	**6** (2.1)	−100	**15**	87	90:10	−
3	**6** (1.2)	−78	**15**	36	97:3	48
4	**6** (1.3)	−100	**15**	77	91:9	6
5	**14a** (2.0)	−78	**17**	68	87:13	−
6	**14a** (2.0)	−100	**17**	50	89:11	−
7	**14a** (1.2)	−78	**17**	60[d]	88:12	*e*
8	**14a** (1.2)	−100	**17**	49	91:9	−

[a] General reaction conditions: 1.1 equiv of phosphonate, 1.0 equiv of KHMDS, 5 equiv of 18-crown-6, ca. 0.02 M in THF, 2.5−15 h. [b] Isolated yield of product judged as ≥95% pure by NMR and TLC, unless otherwise noted. [c] Ratio in isolated product; ratios in crude products were within ±2% of these values. Entries 1−4: ratio **15**:**16**; entries 5−8: ratio **17**:**18**. Geometric ratios were ≥98:2. [d] Another product, tentatively assigned as being the product of silyl group migration from the secondary to the primary hydroxyl, was isolated in 18% yield. [e] Although small amounts of bis-addition product were detected in the crude product, none were isolated after chromatography.

diastereoselectivities even when close to equimolar amounts of substrate and reagent were used (compare entries 2 and 4, 5 and 7). In addition, the reaction temperature turned out to be an important parameter, as expected. With the more reactive substrate **6**, reaction at −78 °C gave considerable amounts of bis-addition product (entry 3); this was largely suppressed by performing the reaction at −100 °C (entry 4). On the other hand, the slightly lower yields obtained from dialdehyde **14a** at the lower reaction temperature presumably resulted from incomplete conversion due to this substrate being more sterically hindered (compare entries 6 and 8 with 5 and 7).

We then embarked on a more extensive study of reactions involving dialdehydes **6**, **14a**, and **14b**. Depending on the synthetic objective, it is desirable that either (*E*)- or (*Z*)-alkenes can be prepared with high selectivity in the asymmetric HWE reactions. For this reason, we investigated the utility of reagents **3a**−**d** containing different alkyl groups R^1 in the phosphoryl unit. It is known from standard nonasymmetric HWE reactions[7,21] that the alkene geometry of the product often can be controlled by an appropriate choice of R^1 and reaction conditions. The results obtained in reactions with **6** (Scheme 5, Table 2) demonstrated that selective preparation of either (*E*)- or (*Z*)-products was indeed possible.

Phosphonates **3a**−**c** all gave essentially exclusive formation of (*E*)-products. However, the structure of

Scheme 5

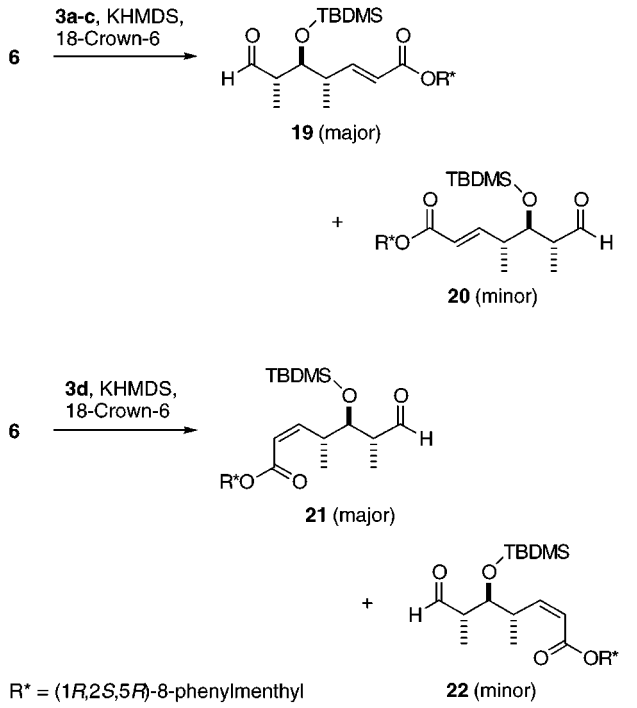


Table 2. Reactions of Phosphonates 3a−d with Dialdehyde 6[a]

entry	phosphonate	temp (°C)	product	yield[b] (%)	diaster ratio[c]	yield of bis-addition (%)
1	**3a**	−100	**19**	53	95:5[d]	*e*
2	**3b**	−90	**19**	25[f]	ca. 95:5[d]	38[f]
3	**3c**	−90	**19**	2[f]	ca. 97:3[d]	12[f]
4	**3d**	−100	**21**	74	≥98:2[g]	−
5	**3d**	−90	**21**	83	≥98:2	−
6	**3d**	−78	**21**	76	≥98:2	*e*
7	**3d**	0[h]	**21**	38[i]	≥98:2	36[i]

[a] General reaction conditions: 1.1 equiv of dialdehyde, 1.1 equiv of phosphonate, 1.0 equiv of KHMDS, 5 equiv of 18-crown-6, ca. 0.02 M in THF, 6−22 h. [b] Isolated yield of product judged as ≥95% pure by NMR and TLC, unless otherwise noted. [c] Ratio in isolated product; ratios in crude products were within ±2% of these values. Entries 1−3: ratio **19**:**20**; entries 4−7: ratio **21**:**22**. Geometric ratios were ≥98:2, unless stated otherwise. [d] Small amounts of another isomer, assigned as an epimer, were also present in the isolated product: entry 1, 3%; entry 2, 9%; entry 3, 4% (see Supporting Information). [e] Not determined. [f] (*E*)-Mono- and (*E*,*E*)-bis-addition products were obtained in the same fraction after chromatography. [g] The isolated product also contained 6% of another isomer, assigned as an epimer; this was not present in the crude, but was formed during chromatography (see Supporting Information). [h] Reaction time 2 h. [i] After chromatography, the (*Z*)-monoaddition product **21** (38% yield) and the (*E*,*Z*)-bis-addition product **28** (25% yield; see Chart 1) were obtained in the same fraction. In separate fractions, the (*Z*,*Z*)- and (*E*,*E*)-bis-addition products were isolated, in 9% and 2% yield, respectively.

R^1 did influence the yield of monoaddition product strongly: the dimethylphosphonate **3a** was clearly superior to the diethyl and diisopropyl analogues. Use of **3a** in combination with KHMDS/18-crown-6 gave the (*E*)-monoaddition product **19**[22,23] in 53% yield with a diastereomer ratio of 95:5 (entry 1).

The (*Z*)-selective reagent **3d** proved to be even more efficient than the (*E*)-selective reagents **3a**−**c** in its reactions with **6**. Together with KHMDS/18-crown-6 as

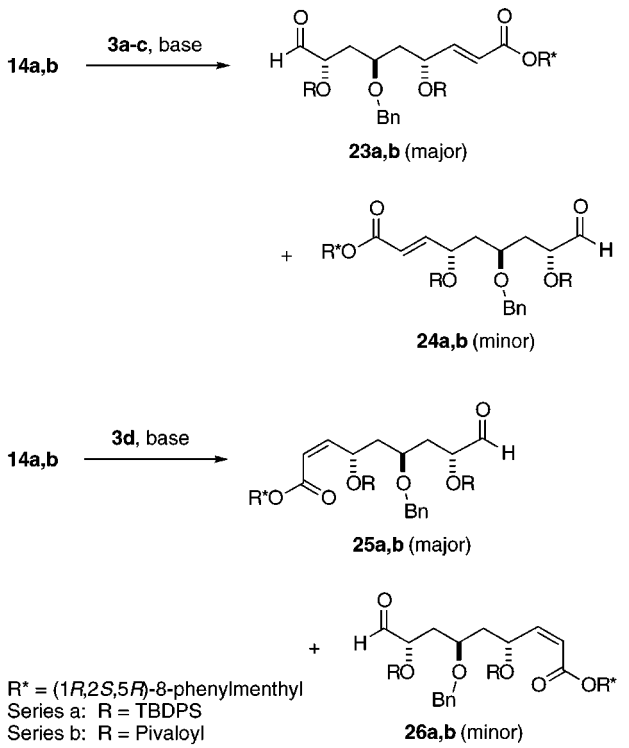
(19) Diacetate **10** was assigned as *meso*-(3*R*,5*s*,7*S*)-5-(benzyloxy)-3,7-diacetoxycyclohept-1-ene on the basis of ^{1}H NMR data, by comparison with the known[18] compound *meso*-(3*R*,5*s*,7*S*)-5-methoxy-3,7-diacetoxycyclohept-1-ene. As evidenced by NMR on the crude product, the Pd-catalyzed diacetoxylation was not completely stereoselective. However, the other product isomers could be cleanly removed by use of the MPLC system described by Baeckström: Baeckström, P.; Stridh, K.; Li, L.; Norin, T. *Acta Chem. Scand., Ser. B* **1987**, *41*, 442−447.

(20) Dihydroxylation of diacetate **10** gave a complex mixture of regioisomeric products, presumably due to facile acyl group migration in the initially formed diol. In contrast, dihydroxylation of bis-pivalate **12b** proceeded more cleanly. Upon chromatographic purification, acyl migration sometimes occurred also with diols **13b**; however, if the crude diastereomeric mixture of diols **13b** was directly cleaved with H_5IO_6, excellent yields of isomerically pure dialdehyde **14b** were reproducibly obtained. Oxidative cleavage of the alkenes **12** by ozonolysis was also attempted, but in our hands the two-step osmylation/periodic acid protocol gave much cleaner products.

(21) Thompson, S. K.; Heathcock, C. H. *J. Org. Chem.* **1990**, *55*, 3386−3388, and references therein.

(22) For details regarding how structure assignments for the HWE product isomers have been made, and how isomer ratios have been determined, see Supporting Information.

Scheme 6



base, reagent **3d** gave the (*Z*)-product **21**[22,23] in high yield, with excellent geometric selectivity and as a single detectable diastereomer (entry 5). The temperature dependence of this reaction was investigated to some extent: reactions at −78 °C and lower afforded good yields of monoaddition product, but a reaction performed at 0 °C gave a much reduced yield due to formation of substantial amounts of bisaddition products.

The reactions with the α-oxygenated substrates **14a** and **14b** (Scheme 6, Table 3) followed similar general trends as the reactions with **6**, although there are some differences worth noting.

Reagents **3a**−**c** all gave high (*E*)-selectivities in reactions with both **14a** and **14b**. The diastereoselectivities observed for the (*E*)-product **23a**[22,23] were similar for all three reagents (entries 1−3); although the amount of unreacted dialdehyde was not determined, the slightly lower yield observed in the reaction with the diisopropyl phosphonate **3c** may well be due to incomplete conversion. On the other hand, in reactions with the more reactive, pivaloyl-protected substrate **14b**, the dimethyl phosphonate **3a** performed poorly (entry 7), whereas both **3b** and **3c** gave **23b**[22,23] in much better yields and diastereoselectivities (entries 8 and 9). Thanks to the fact that the diastereomers of **23a** could be separated under optimized chromatography conditions, diastereomerically pure **23a** was obtained in a synthetically useful yield, even though the diastereoselectivity in the crude product was slightly lower than for **23b**.

The bis(trifluoroethyl)phosphonate **3d** provided access to the (*Z*)-products **25a**[22,23] and **25b**[22,23] with excellent levels of asymmetric induction and in good yields. The reactions with aldehyde **14a** proved to be special cases: both KHMDS and NaHMDS alone gave better results than our "standard" base system KHMDS/18-crown-6 (entries 4−6). The reaction between **3d** and **14b**, however, gave best selectivities under the standard conditions (entry 10).

Determination of Absolute Configurations. The assignments of absolute configurations for compounds **15** and **19** are based on ^{1}H NMR analyses of both diastereomers of the Mosher ester derivative **27** (Chart 1), according to the method introduced by Mosher and Dale and extended by Kakisawa and co-workers.[24] Compound **21** is assigned the indicated absolute configuration based on a correlation with **19**: both **19** and **21** were converted to the same mono-(*Z*)/mono-(*E*)-diastereomer **28** by reaction with **3d** and **3a**, respectively. On the basis of NMR analysis, the products from these two reactions were identical, which, in turn, implies that the monoaddition products **19** and **21** must have been formed by reaction at enantiotopic carbonyl groups in **6**. In contrast, if the (*E*)- and (*Z*)-monoaddition products were formed via reaction at the same carbonyl group, further reaction of the (*Z*)-product with **3a** would have given the diastereomeric mono-(*Z*)/mono-(*E*)-isomer **29** as product.

The assignments of absolute configurations for the products from dialdehydes **14** have been made on the basis of similar investigations. The (*E*)-product **23a** was converted to both diastereomers of the Mosher ester derivative **30**, and NMR analysis[24] of these compounds gave the assigned absolute configuration. The pivaloyl-protected (*E*)-product **23b** was correlated with **23a** by conversion of both compounds to derivative **31**; based on NMR analysis, the same diastereomer of **31** was produced in both cases. The (*Z*)-products **25a** and **25b** were correlated with **23a** and **23b**, respectively, by conversion to the mono-(*Z*)/mono-(*E*)-bisaddition products: **23a** and **25a** both formed **32a**, and **23b** and **25b** both gave **32b**.

Discussion

Our results show that the structure of the group R^1 in the chiral phosphonates **3** controls not only the (*E*)/(*Z*)-selectivity of the asymmetric HWE reactions but also which enantiotopic carbonyl group in the dialdehyde substrate reacts faster,[25] both of which factors contribute to giving these reactions increased synthetic versatility.

The bis(trifluoroethyl) reagent **3d** was found to give (*Z*)-products with excellent diastereoselectivities in good yields from all three substrates studied. The results obtained with **14a** show that the specific choice of reaction conditions is important: although the use of KHMDS/18-crown-6 as base often is the most efficient

(23) In general, the (*E*)- and (*Z*)-monoaddition products could be separated by flash chromatography. It also proved possible to separate the (*E*)-diastereomers **23a** and **24a** (Scheme 6, vide infra) by chromatography, if Amicon silica (see Experimental Section) was used; however, we have not yet found conditions which enable complete separation of other diastereomeric products (i.e., **19**/**20**, **23b**/**24b**, **25a**/**26a**). Some of the HWE products showed tendencies to undergo slight epimerization during chromatography, but this could be suppressed by use of appropriate conditions: compounds **19** and **21** could be chromatographed on Merck silica (see Experimental Section) if the silica was deactivated by elution with EtOAc or EtOAc/MeOH prior to chromatography; compounds **23b** and **25b** could be chromatographed on Amicon silica without detectable epimerization, whereas use of the Merck silica caused some epimerization. The silyl-protected products **23a** and **25a** did not undergo observable epimerization on either type of silica.

(24) (a) Dale, J. A.; Mosher, H. S. *J. Am. Chem. Soc.* **1973**, *95*, 512−519. (b) Ohtani, I.; Kusumi, T.; Kashman, Y.; Kakisawa, H. *J. Am. Chem. Soc.* **1991**, *113*, 4092−4096, and references therein. For further details regarding the preparation and NMR analyses of compounds **27** and **30**, see Supporting Information.

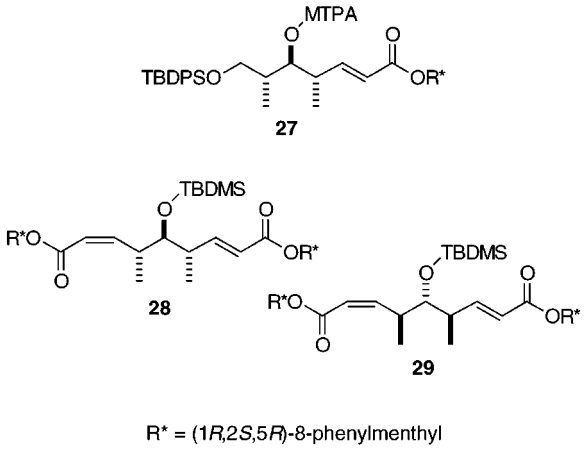
(25) We have found the same general trend to be valid also in kinetic/dynamic resolutions of racemic monoaldehydes by reaction with phosphonates **3a**−**d**; see refs 4o, 4s, and 4t.

Table 3. Reactions of Phosphonates 3a−d with Dialdehydes 14a and 14b[a]

entry	phosphonate	substrate	temp. (°C)	product	yield[b] (%)	diast. ratio[c]	yield of bis-addition (%)
1	**3a**	**14a**	−78	**23a**	65[d]	≥98:2 (87:13)	*e*
2	**3b**	**14a**	−78	**23a**	60[d]	≥98:2 (88:12)	*e*
3	**3c**	**14a**	−78	**23a**	46[d]	≥98:2 (91:9)	*e*
4	**3d**	**14a**	−78	**25a**	61[f]	86:14	24[f]
5	**3d**[g]	**14a**	−78	**25a**	76	98:2	h
6	**3d**[i]	**14a**	−78	**25a**	60	96:4	h
7	**3a**	**14b**	−90	**23b**	10	82:18	65[j]
8	**3b**	**14b**	−90	**23b**	62	95:5	35[j]
9	**3c**	**14b**	−90	**23b**	65	94:6	26[j]
10	**3d**	**14b**	−90	**25b**	62	≥98:2	29[j]

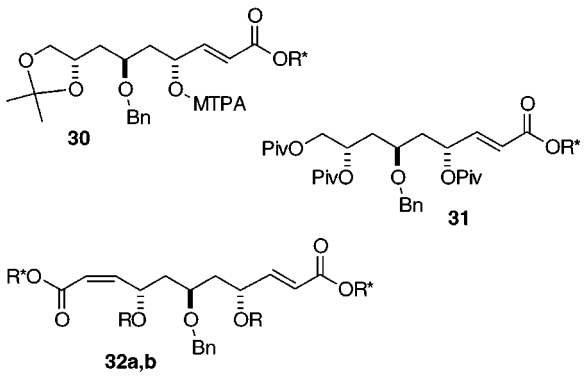
[a] General reaction conditions: 1.1−1.3 equiv of dialdehyde, 1.05−1.2 equiv of phosphonate, 1.0 equiv of KHMDS, 5 equiv of 18-crown-6, ca. 0.02 M in THF, 6−17 h. [b] Isolated yield of product judged as ≥95% pure by NMR and TLC, unless otherwise noted. [c] Ratio in isolated product. If different, the ratio in the crude product is given in parentheses. Entries 1−3: ratio **23a**:**24a**; entries 4−6: ratio **25a**:**26a**; entries 7−9: ratio **23b**:**24b**; entry 10: ratio **25b**:**26b**. Geometric ratios were ≥98:2, unless stated otherwise. [d] The isolated product also contained small amounts of unreacted dialdehyde: entry 1, 6%; entry 2, 6%; entry 3, 3%. [e] After chromatography, (*E*,*E*)-bis-addition product and the minor (*E*)-monoaddition diastereomer **24a** were obtained as a mixture; the yield of bis-addition product was not determined. [f] Some (*Z*,*E*)-bis-addition product **32a** (7% yield; see Chart 2) was obtained in the same fraction as the monoaddition product. The (*Z*,*Z*)-bis-addition product was isolated separately (17% yield). [g] Only KHMDS (no 18-crown-6) used as base. [h] Not determined. [i] NaHMDS used as base. [j] Mixture of bis-addition products.

Chart 1



R* = (1*R*,2*S*,5*R*)-8-phenylmenthyl

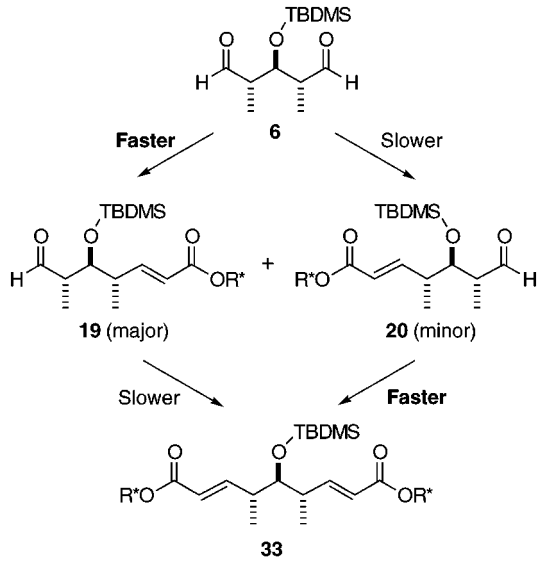
Chart 2



R* = (1*R*,2*S*,5*R*)-8-phenylmenthyl
Series a: R = TBDPS
Series b: R = Pivaloyl

with other substrates, the particular reaction between **3d** and **14a** gave best results if the crown ether was omitted. The (*E*)-selective reagents **3a**−**c**, on the other hand, generally performed best in combination with KHMDS/18-crown-6. Depending on the substrate, either **3a** or **3b** proved to be the most efficient reagent, the diisopropyl phosphonate **3c** seemingly being too sterically hindered to be generally useful. By choosing the appropriate reagent, (*E*)-products were obtained with diastereoseletivities ≥ 95:5 and in synthetically useful yields. An additional factor to take into account is the choice of protecting group in α-oxygenated substrates: although substrates **14a** and **14b** gave the same overall trends in their reactions, the structure of the protecting group clearly influenced both the yields and selectivities of the reactions.[26]

Scheme 7

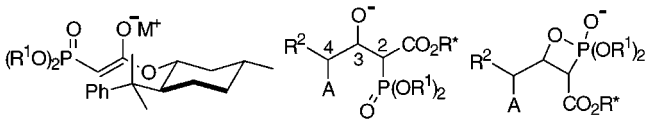


R* = (1*R*,2*S*,5*R*)-8-phenylmenthyl

As demonstrated by the results obtained in reactions with **6** (Table 1), the diastereoselectivity observed for the monoaddition product depends on the reaction stoichiometry. This outcome is to be expected, since increased conversion to the bisaddition product (e.g., **33**, Scheme 7) should increase the ratio between the diastereomeric monoaddition products (the ratio **19**:**20** in the example shown), due to the minor monoaddition diastereomer reacting faster in the second step.[27,28]

(26) A topic worthy of future investigation is whether the use of another protecting group would enable a change in the mechanism by which the α-stereocenter in the substrate influences the reaction stereochemistry (see mechanistic discussion below, and also ref 4cc); such a change could, in turn, enable complementary preparation of other product diastereomers.

Mechanism. Recent results from computational studies, using both high level *ab initio* calculations[29] and molecular mechanics methods,[30] fully support our previously reported working model[4a,cc] for rationalizing the stereochemical outcome of these asymmetric HWE reactions. This analysis is based on the postulate that phosphonates **3** form (*E*)-enolates[31] **34** under the reaction conditions used, an assumption which is reasonable based on previous studies.[32,33] Since two new stereocenters are formed at the bond-forming sites (C2 and C3) in the intermediates, and the substrate contains two enantiotopic carbonyl groups, eight different diastereomeric forms of the intermediate oxyanion **35** are theoretically possible. Our computational studies indicate that for reactions involving phosphonates **3a**−**c**, which normally are (*E*)-selective, the transition states for oxyanion formation (TS1) and for ring closure to the oxaphosphetane **36** (TS2) are close in energy, making it necessary to include appropriate models of both transition states



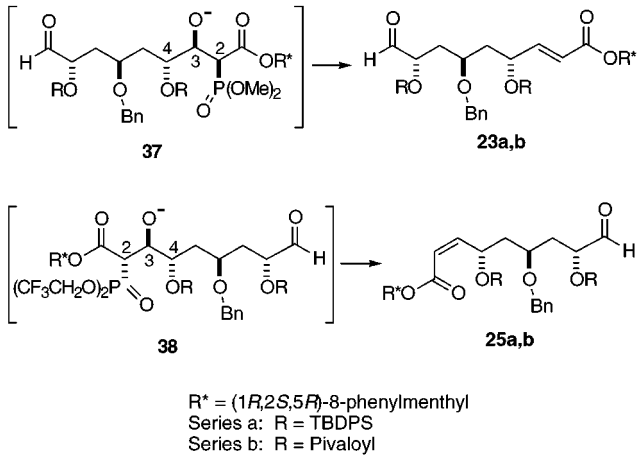
34 **35** **36**

when analyzing reaction stereoselectivities. In reactions with trifluoroethyl phosphonate **3d**, on the other hand, the initial addition step will be irreversible, and it will be sufficient to model diastereomeric forms of TS1.

The particular diastereomeric intermediates which according to our modeling studies are the precursors of the main product isomers are illustrated in Schemes 8 and 9. The formation of these intermediates is rationalized as follows. The chiral auxiliary efficiently blocks the Re-face of the phosphonate enolate **34**. Diastereomers of TS1 leading to oxyanions with (2*R*)-configuration are therefore prohibitively high in energy, leading to a very high preference for oxyanions with (2*S*)-configuration.

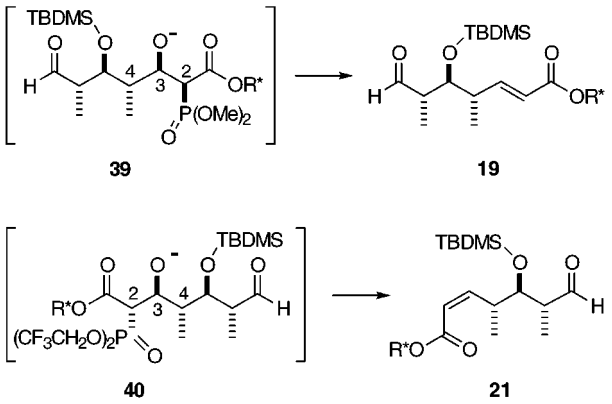
The configuration at the former aldehyde carbonyl carbon, C3, is mainly controlled by the stereochemistry at C4, the former aldehyde α-carbon. The effect can be interpreted as a formal Felkin−Anh−Eisenstein[34,35] (FAE) or anti-FAE effect in TS1, depending on the substituents

Scheme 8



R* = (1*R*,2*S*,5*R*)-8-phenylmenthyl
Series a: R = TBDPS
Series b: R = Pivaloyl

Scheme 9



R* = (1*R*,2*S*,5*R*)-8-phenylmenthyl

at C4, but is in fact even more pronounced in the tighter TS2. The overall effect is that oxyanion diastereomers with an unfavorable relative configuration at C3/C4 will revert to starting material instead of proceeding to product.

This analysis also explains the, at first perhaps puzzling, observation that the major (*E*)- and (*Z*)-products have opposite absolute configuration at the allylic stereocenter. Since the favored absolute configuration at C2 always is the same, but the configuration at C3 is controlled by the one at C4, it automatically follows that reactions at opposite enantiotopic aldehyde groups must lead to intermediates with opposite relative configuration at C2/C3 and therefore to products with opposite alkene geometry.[36]

(27) Schreiber, S. S.; Schreiber, T. S.; Smith, D. B. *J. Am. Chem. Soc.* **1987**, *109*, 1525−1529, and references therein.

(28) This expectation rests on the assumption that the unreacted aldehyde carbonyl groups in the monoaddition diastereomers show relative reactivities similar to the corresponding enantiotopic carbonyl groups in the dialdehyde substrate.

(29) Brandt, P.; Norrby, P.-O.; Martin, I.; Rein, T. *J. Org. Chem.* **1998**, *63*, 1280−1289.

(30) (a) Norrby, P.-O. In *Transition State Modelling for Catalysis*; Truhlar, D., Morokuma, K., Eds.; ACS Symposium Series, in press. (b) Norrby, P.-O.; Brandt, P.; Rein, T., manuscript in preparation. At present, modeling tools are available for reactions involving phosphonates containing simple alkyl groups (e.g., **3a**−**c**). Work toward the design of parameter sets which will allow modeling of trifluoroethyl reagents is in progress.

(31) Note that the designation of the geometry of enolate **34** as (*E*) or (*Z*) depends on whether a counterion is considered as being bonded to the anionic oxygen or not, and if so, on the CIP priority of that counterion relative to carbon.

(32) Gais and co-workers have reported[4y] that the lithium enolate formed from **3a** has (*E*)-geometry. We are presently studying the stuctures of enolates derived from reagents **3b**−**d**, as well as the dependence of the enolate ratios on the reaction conditions; these studies will be reported upon separately.

(33) (a) Bottin-Strzalko, T.; Corset, J.; Froment, F.; Pouet, M.-J.; Seyden-Penne, J.; Simmonin, M.-P. *J. Org. Chem.* **1980**, *45*, 1270−1276. (b) Seyden-Penne, J. *Bull. Soc. Chim. France* **1988 (II)**, 238−242, and references therein.

(34) (a) Chérest, M.; Felkin, H. *Tetrahedron Lett.* **1968**, 2205−2208. (b) Anh, N. T.; Eisenstein, O.; Lefour, J.-M.; Trân Huu Dâu, M. E. *J. Am. Chem. Soc.* **1973**, *95*, 6146−6147. (c) Anh, N. T.; Eisenstein, O. *Nouv. J. Chem.* **1977**, *1*, 61−70. (d) Anh, N. T. *Top. Curr. Chem.* **1980**, *88*, 145−162. (e) Lodge, E. P.; Heathcock, C. H. *J. Am. Chem. Soc.* **1987**, *109*, 2819−2820. (f) Lodge, E. P.; Heathcock, C. H. *J. Am. Chem. Soc.* **1987**, *109*, 3353−3361. For excellent discussions of different models for diastereoselection in nucleophilic additions to carbonyl compounds, see: (g) Roush, W. R. *J. Org. Chem.* **1991**, *56*, 4151−4157. (h) Evans, D. A.; Dart, M. J.; Duffy, J. L.; Yang, M. G. *J. Am. Chem. Soc.* **1996**, *118*, 4322−4343. (i) Gung, B. W. *Tetrahedron* **1996**, *52*, 5263−5301.

(35) Evans has introduced[34h] a stereochemical model which rationalizes the merged influence of α- and β-substituents in aldol-type additions to substituted aldehydes, including α-methyl-β-alkoxy-aldehydes. However, from substrates containing α- and β-substituents in an anti relationship (as in dialdehyde **6**), the Evans model also predicts formation of FAE-type products.

It should also be noted that the favored relative configuration at C3/C4 cannot easily be predicted from empirical rules. However, our recently developed molecular mechanics method[30] has been able to rationalize the product pattern.

Conclusions

In this paper, we have demonstrated that when *meso*-dialdehydes **6** and **14** are used as substrates in asymmetric HWE reactions, either (*E*)- or (*Z*)-monoaddition products can be obtained with high geometric selectivity by slight structural variation in the phosphoryl group of the chiral reagent. By an appropriate choice of chiral reagent and reaction conditions, both (*E*)- and (*Z*)-products are obtained with good to excellent diastereoselectivities and in synthetically useful yields; these results show that both α-methyl and α-oxygen substitution in the substrate enable high selectivities to be obtained. The reactions with dialdehydes **14** also show that the choice of oxygen protecting groups in the substrate can be used for fine-tuning the outcome.

Furthermore, (*E*)- and (*Z*)-products are formed with opposite enantiotopic group preference. Thus, when applying these reactions in synthesis, both enantiomeric series of a projected synthetic intermediate can be accessed using the same enantiomer of the chiral auxiliary, as long as the alkene geometry of the product is of no consequence for the particular application at hand.

The stereochemical outcome of these reactions is in all cases consistent with a mechanistic model in which the product stereochemistry is determined by the combined influence of the chiral auxiliary, the alkyl group in the phosphonate unit, and the α-stereocenters in the dialdehyde substrate. In particular, this model explains why reactions at opposite enantiotopic carbonyl groups in the substrate give products having opposite alkene geometry.

Our continuing studies in this area are aimed at further improvement and generalization of this methodology through (1) the design of even more efficient chiral reagents, (2) investigations of mechanistic details, and (3) studies of reactions with new substrates. The products obtained from the asymmetric HWE reactions have projected utility in synthetic approaches to various natural products, and several such synthetic applications are under active investigation.

Experimental Section

General. All reactions were performed in oven-dried or flame-dried glassware. Commercial reagents were used as received, unless otherwise indicated. Solvents were generally distilled before use. Potassium hexamethyldisilazide [KN(SiMe$_3$)$_2$, KHMDS] was purchased as a stock solution (0.5 M in toluene) and titrated according to the method of Ireland and Meissner.[37] 18-Crown-6 was recrystallized from anhydrous acetonitrile and dried under vacuum. Toluene, CH_2Cl_2, hexane, Et_3N, and pyridine were distilled from CaH_2. THF was distilled from sodium/benzophenone ketyl. Pd(OAc)$_2$ was recrystallized from acetic acid, and benzoquinone was recrystallized from ethanol. Dialdehydes **6** and **14b** were freshly prepared just before use. Cooling below −78 °C was effected by use of either EtOH/liquid N_2 or an immersion cooler. TLC analyses were performed on Merck aluminum-backed F254 silica gel plates, using UV light and phosphomolybdic acid for visualization. Drying of organic phases obtained from extractive workup was generally done with $MgSO_4$. Flash chromatography was performed as described by Still and co-workers[38] and medium-pressure liquid chromatography (MPLC) as described by Baeckström and co-workers,[19] in both cases using either Merck silica gel 60 (230−400 mesh) or Amicon Matrex 60 Å silica gel (35−70 μm). NMR spectra were recorded in $CDCl_3$ unless otherwise indicated, using $CHCl_3$ (δ 7.24 ppm) and $CDCl_3$ (δ 77.0 ppm) as internal references for ^{1}H and ^{13}C, respectively. (1*R*,2*S*,5*R*)-8-Phenylmenthol was prepared according to a literature procedure.[39] Tropone[40] and 1,3-cycloheptadien-6-ol[41] are intermediates in the synthetic route to diene **9** and were prepared according to literature procedures. Stereochemical descriptors for the *meso* compounds reported here have been assigned in accordance with a recent treatise.[42]

(Diethoxyphosphoryl)acetic Acid (1*R*,2*S*,5*R*)-5-Methyl-2-(1-methyl-1-phenylethyl)cyclohexyl Ester (3b). Prepared from triethyl phosphonoacetate (**1b**) and (1*R*,2*S*,5*R*)-8-phenylmenthol (**2**) in 81% yield, in analogy with the published procedure[8] for preparation of **3a**. ^{1}H NMR (400 MHz, selected data) δ 7.24−7.16 (m, 4 H), 7.08−7.03 (m, 1 H), 4.77 (ddd [app td], *J* = 10.8, 4.4 Hz, 1 H), 4.08−3.91 (m, 4 H), 2.31 (dd, *J* = 21.3, 14.4 Hz, 1 H), 2.02 (dd, *J* = 21.3, 14.4 Hz, 1 H), 0.81 (d, *J* = 6.5 Hz, 3 H); ^{13}C NMR (100 MHz) δ 165.1 (d, *J* = 5.8 Hz), 151.8, 127.9 (2 C), 125.4 (2 C), 125.1, 75.1, 62.4 (d, *J* = 5.7 Hz, 2 C), 50.3, 41.3, 39.5, 34.5, 33.9 (d, *J* = 133 Hz), 31.3, 29.2, 26.3, 23.2, 21.8, 16.3 (d, *J* = 6.1 Hz, 2 C). Anal. Calcd for $C_{22}H_{35}O_5P$: C, 64.37; H, 8.59. Found: C, 63.97; H, 8.51.

[Bis(2,2,2-trifluoroethoxy)phosphoryl]acetic Acid (1*R*,2*S*,5*R*)-5-Methyl-2-(1-methyl-1-phenylethyl)cyclohexyl ester (3d). Prepared from methyl bis(trifluoroethyl) phosphonoacetate (**1d**) and (1*R*,2*S*,5*R*)-8-phenylmenthol in 89% yield, according to the same procedure as was used for **3b**. ^{1}H NMR (400 MHz, selected data) δ 7.30−7.23 (m, 4 H), 7.17−7.07 (m, 1 H), 4.82 (ddd [app td], *J* = 10.7, 4.4 Hz, 1 H), 4.48−4.20 (m, 4 H), 2.27 (dd, *J* = 20.7, 15.9 Hz, 1 H), 2.25 (dd, *J* = 20.4, 15.9 Hz, 1 H), 1.27 (s, 3 H), 1.17 (s, 3 H), 0.86 (d, *J* = 6.4 Hz, 3 H); ^{13}C NMR (100 MHz) δ 164.0 (d, *J* = 5.8 Hz), 151.9, 128.1 (2 C), 125.3 (2 C), 125.1, 122.4 (app quartet of m, one *J* = ca 277 Hz, 2 C), 75.9, 62.4 (app quartet of m, one *J* = ca. 40 Hz, 2 C), 50.1, 41.2, 39.3, 34.4, 33.4 (d, *J* = 144 Hz), 31.2, 30.0, 26.1, 22.2, 21.7. Anal. Calcd for $C_{22}H_{29}O_5FP$: C, 50.97; H, 5.64. Found: C, 50.81; H, 5.66.

***meso*-(2*R*,3*r*,4*S*)-3-((*tert*-(Butyldimethylsilyl)oxy)-2,4-dimethylpentanedial (6).** To a solution of oxalyl chloride (136 μL, 1.55 mmol) in CH_2Cl_2 (8 mL) at −78 °C under argon was added dropwise a solution of DMSO (147 μL, 2.07 mmol) in CH_2Cl_2 (1 mL). After 30 min, a solution of **5**[14] (136 mg, 0.518 mmol) in CH_2Cl_2 (1 mL) was added dropwise followed, after 30 min, by triethylamine (722 μL, 5.18 mmol). The reaction mixture was stirred at −78 °C for 1 h and then warmed slowly to 0 °C during 1 h. After 30 min of stirring at 0 °C, the solution was diluted with dry toluene (25 mL), filtered through a dried glass frit, and concentrated. The residue was dissolved in dry hexane (25 mL), filtered again, and concentrated yielding 131 mg (quantitative crude yield) of **6** as a pale yellow oil which due to its limited stability was used without further purification in the HWE reactions: ^{1}H NMR (250 MHz) δ 9.73 (d, *J* = 2.1 Hz, 2H), 4.28 (t, *J* = 5.1 Hz, 1H), 2.59 (qdd, *J* = 7.1, 5.1, 2.0 Hz, 2H), 1.08 (d, *J* = 7.1 Hz, 6H), 0.84 (s, 9H), 0.06 (s, 6H); ^{13}C NMR (62.5 MHz) δ 203.4, 74.2, 50.8, 25.7, 18.0, 10.5, −4.5.

(36) We have observed the same general trend in all asymmetric HWE reactions studied by us to date. A similar argumentation is used by Fuji and co-workers when analyzing the results of asymmetric HWE reactions between a chiral phosphonate and a group of *meso*-diketones; see ref 4bb.

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(38) Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923−2925.

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***meso*-(3*R*,5*s*,7*S*)-5-(Benzyloxy)-3,7-diacetoxycyclohept-1-ene (10).** Diene **9**[17] (1.00 g, 5.0 mmol) was added neat to a solution of palladium(II) acetate (56 mg, 0.25 mmol), lithium acetate dihydrate (2.55 g, 25 mmol), and benzoquinone (108 mg, 1.0 mmol) in glacial acetic acid (10 mL). After addition of MnO_2 (869 mg, 10 mmol), the resulting slurry was stirred at room temperature. The reaction was followed by TLC until all starting material had been consumed (2−3 days) and then worked up by addition of water and hexane/EtOAc 1/1. The resulting emulsion was filtered through Celite, the phases were separated, and the aqueous phase was extracted with three portions of hexane/EtOAc 1/1. The combined organic phases were washed with water, 2 M NaOH, and water again and then dried and concentrated to give 1.42 g of a yellowish-brown oil. Purification was effected by MPLC (0−100% EtOAc in hexanes), yielding 811 mg (51%) of **10** as a colorless oil: ^{1}H NMR (250 MHz) δ 7.42−7.23 (5H), 5.76 (dd, J = 10.8, 2.3 Hz, 2H), 5.7 (s, 2 H), 4.65 (s, 2H), 3.92 (tt, J = 5.6, 2.7 Hz, 1H), 2.22 (ddd, J = 13.4, 5.6, 2.3 Hz, 2H), 1.86 (ddd, J = 1.4, 10.8, 2.7 Hz, 2H), 2.05 (s, 6H); ^{13}C NMR (62.5 MHz) δ 169.9, 138.3, 132.5, 128.2, 127.5, 127.3, 71.7, 70.0, 68.8, 36.6, 21.1. Anal. Calcd for $C_{18}H_{22}O_5$: C, 67.91; H, 6.97. Found: C, 67.83; H, 6.85.

***meso*-(1*R*,4*S*,6*s*)-6-(Benzyloxy)cyclohept-2-ene-1,4-diol (11).** To a solution of diacetate **10** (111 mg, 0.35 mmol) in MeOH (1.5 mL) at 0 °C was added dropwise an aqueous solution of KOH (98 mg, 1.75 mmol, in 1.5 mL of water). The resulting pale yellow solution was stirred at 0 °C until no starting material was detected by TLC (ca. 30 min). The reaction mixture was neutralized with 2 M H_2SO_4 and diluted with water. Extractive workup (CH_2Cl_2), drying, and concentration gave 82 mg of a white solid. Purification by flash chromatography (hexanes/EtOAc 1/1) gave 76 mg (93%) of white crystalline **11**: ^{1}H NMR (400 MHz, DMSO) δ 7.37−7.23 (m, 5H), 5.55 (s, 2H), 4.79 (d, J = 4.7, 2H), 4.53 (s, 2H), 4.50−4.41 (m, 2H), 3.83−3.75 (m, 1H), 2.02 (ddd, J = 13.3, 5.2, 2.4 Hz, 2H), 1.55 (ddd, J = 13.4, 11.1, 2.5 Hz, 2H); ^{13}C NMR (100 MHz, DMSO) δ 139.0, 136.1, 128.3, 127.4, 127.3, 73.2, 69.1, 64.1, 40.0. Anal. Calcd for $C_{14}H_{18}O_3$: C, 71.77; H, 7.74. Found: C, 71.88; H, 7.61.

***meso*-(3*R*,5*s*,7*S*)-5-(Benzyloxy)-3,7-bis-((*tert*-butyldiphenylsilyl)oxy)cyclohept-1-ene (12a).** To a solution of diol **11** (0.816 g, 3.35 mmol) and imidazole (1.14 g, 16.75 mmol) in dry DMF (30 mL) under argon was added *tert*-butyldiphenylsilyl chloride (2.1 mL, 8.05 mmol). The reaction mixture was stirred for 24 h at room temperature and then diluted with brine and extracted with ethyl acetate. Drying (Na_2SO_4) and concentration of the combined organic extracts followed by flash chromatography (hexanes/EtOAc 99/1) afforded 2.432 g (99%) of **12a** as a colorless oil: ^{1}H NMR (400 MHz) δ 7.72−7.64 (m, 8H), 7.44−7.23 (m, 15H), 7.00−6.93 (m, 2H), 5.78 (s, 2H), 4.75 (d, J = 9.9 Hz, 2H), 3.89 (s, 2H), 3.67−3.60 (m, 1H), 2.02 (ddd [app br dd], J = 12, 4 Hz, 2H), 1.78 (ddd [app br t], J = 12 Hz, 2H), 1.09 (s, 18H); ^{13}C NMR (100 MHz) δ 138.9, 135.8, 134.3, 134.0, 129.5, 128.0, 127.9, 127.5, 127.0, 72.6, 67.5, 69.0, 40.1, 27.0, 26.49, 19.2. Anal. Calcd for $C_{46}H_{54}O_3Si_2$: C, 77.70; H, 7.65. Found: C, 77.48; H, 7.62.

***meso*-(1*R*,2*S*,3*R*,5*s*,7*S*)-5-(Benzyloxy)-3,7-bis((*tert*-butyldiphenylsilyl)oxy)cycloheptane-1,2-diol and *meso*-(1*R*,2*S*,3*S*,5*s*,7*R*)-5-(Benzyloxy)-3,7-bis-(*tert*-butyldiphenylsilyl)oxy)cycloheptane-1,2-diol (13a; mixture of the two *meso* diols).** To a solution of silyl ether **12a** (321 mg, 0.45 mmol) and *N*-methylmorpholine *N*-oxide (53 mg, 0.45 mmol) in 5 mL of THF were added *tert*-butyl alcohol (2.5 mL) and H_2O (1.2 mL), followed by 115 μL of a 2.5 weight-% solution of OsO_4 in *tert*-butyl alcohol (0.009 mmol). The pale yellow solution was stirred for 30 h at room temperature and then quenched with 5 mL of 10% $Na_2S_2O_4$. Dilution with brine followed by extraction (EtOAc), drying, and concentration followed by flash chromatography (hexanes/EtOAc 88/12) afforded 325 mg of a mixture of diastereomeric diols **13a** (97%) as a colorless oil. The diastereomeric mixture was normally used as such for preparation of the dialdehyde **14a**; isomerically pure samples of the separate diastereomeric diols could be obtained by chromatography, however. Faster eluting isomer (R_f = 0.42, hexanes/EtOAc 8/2): ^{1}H NMR (250 MHz) δ 7.75−7.60 (m, 8H), 7.46−7.20 (m, 15H), 6.97−6.90 (m, 2H), 4.06 (br d, J = 10.2 Hz, 2H), 3.91 (s, 2H), 3.65 (br s, 2H), 3.53−3.43 (m, 1H), 3.10 (br d, J = 4.9 Hz, 2H), 2.15 (ddd, J = 14.4, 10.1, 4.1 Hz, 2H), 1.68 (ddd, J = 14.4, 5.8, 2.8 Hz, 2H), 1.06 (s, 18H); ^{13}C NMR (62.5 MHz) δ 138.6, 135.9, 133.6, 133.3, 129.8, 128.1, 127.7, 127.2, 74.7, 71.4, 70.6, 69.6, 34.8, 27.0, 19.2. Anal. Calcd for $C_{46}H_{56}O_5Si_2$: C, 74.15; H, 7.58. Found: C, 74.37; H, 7.78. Slower eluting isomer (R_f = 0.28, hexanes/EtOAc 8/2): ^{1}H NMR (250 MHz) δ 7.75−7.65 (m, 8H), 7.50−7.20 (m, 15H), 7.08−7.00 (m, 2H), 4.21 (br td, J = 7, 3 Hz, 2H), 4.01 (br dd, J = 5.9, 2.2 Hz, 2H), 3.96 (s, 2H), 3.70−3.58 (m, 1H), 2.94 (d, J = 2.4 Hz, 2H), 1.97 (ddd, J = 14.7, 6.4, 3.2 Hz, 2H), 1.88 (ddd, J = 14.7, 7.6, 4.8 Hz, 2H), 1.11 (s, 18H); ^{13}C NMR (62.5 MHz) δ 138.3, 135.9, 133.9, 133.3, 129.9, 128.2, 127.9, 127.8, 127.4, 74.7, 71.0, 70.2, 69.7, 36.2, 27.1, 19.4. Anal. Calcd for $C_{46}H_{56}O_5Si_2$: C, 74.15; H, 7.58. Found: C, 74.50; H, 7.82.

***meso*-(2*R*,4*s*,6*S*)-4-(Benzyloxy)-2,6-bis(*tert*-butyldiphenylsilyl)oxy)heptanedial (14a).** To a solution of diols **13a** (412 mg, 0.552 mmol) in THF (10 mL) was added a solution of H_5IO_6 (125 mg, 0.552 mmol) in THF (10 mL). The reaction mixture became cloudy after a few minutes. After 2.5 h at room temperature, 20 mL of pH 7 phosphate buffer was added, and the solution was extracted with ethyl acetate. Drying and concentration followed by flash chromatography (hexanes/EtOAc 9/1) yielded 365 mg (89%) of **14a** as a pale beige oil: ^{1}H NMR (400 MHz) δ 9.50 (d, J = 1.7 Hz, 2H), 7.68−7.58 (m, 8H), 7.46−7.22 (m, 15H), 7.11−7.05 (m, 2H), 4.15 (ddd [app td], J = 6.0, 1.5 Hz, 2H), 4.06 (s, 2H), 3.75−3.67 (m, 1H), 2.02 (ddd [app td], J = 14.6, 6.2 Hz, 2H), 1.78 (ddd, J = 14.6, 6.0, 4.9 Hz, 2H), 1.11 (s, 18H); ^{13}C NMR (100 MHz, some signals in the aromatic region overlap) δ 202.2, 137.8, 135.8, 135.8, 132.9, 132.8, 130.1, 128.2, 127.8, 127.7, 127.4, 76.0, 72.1, 70.1, 38.3, 26.9, 19.3. Anal. Calcd for $C_{46}H_{54}O_5Si_2$: C, 74.35; H, 7.32. Found: C, 74.12; H, 7.16.

***meso*-(3*R*,5*s*,7*S*)-5-(Benzyloxy)-3,7-bis((2,2-dimethylpropionyl)oxy)cyclohept-1-ene (12b).** To a solution of diol **11** (442 mg, 1.39 mmol) and DMAP (170 mg, 1.39 mmol) in dry pyridine (25 mL) under argon was added pivaloyl chloride (520 μL, 4.22 mmol). The reaction mixture was stirred for 16 h at reflux. After cooling and concentration, the residue was purified by flash chromatography (hexanes/EtOAc 95/5) to afford 555 mg (99%) of **12b** as white solid: ^{1}H NMR (400 MHz) δ 7.39−7.21 (m, 8H), 5.71 (br dd, J = 11, 3 Hz, 2H), 5.66 (s, 2H), 4.63 (s, 2H), 3.9 (tt [app septet], J = 5.8, 2.9 Hz, 1H), 2.18 (ddd, J = 13.4, 5.8, 2.7 Hz, 2H), 1.89 (ddd, J = 13.4, 10.7, 2.7 Hz, 2H), 1.18 (s, 18H); ^{13}C NMR (100 MHz) δ 177.2, 138.3, 132.5, 128.2, 127.5, 127.3, 71.6, 70.0, 68.5, 38.4, 36.7, 27.0. Anal. Calcd for $C_{24}H_{34}O_5$: C, 71.61; H, 8.51. Found: C, 71.61; H, 8.49.

***meso*-(1*R*,2*S*,3*R*,5*s*,7*S*)-5-(Benzyloxy)-3,7-bis((2,2-dimethylpropionyl)oxy)cycloheptane-1,2-diol and *meso*-(1*R*,2*S*,3*S*,5*s*,7*R*)-5-(Benzyloxy)-3,7-bis(2,2-dimethylpropionyl)oxy)cycloheptane-1,2-diol (13b; mixture of the two *meso* diols).** To a solution of bis-pivaloyl ester **12b** (557 mg, 1.38 mmol) and *N*-methylmorpholine *N*-oxide (162 mg, 1.38 mmol) in 16 mL of THF were added *tert*-butyl alcohol (8 mL) and H_2O (4 mL), followed by 325 μL of a 2.5 wt % solution of OsO_4 in *tert*-butyl alcohol (0.026 mmol). The reaction mixture was stirred for 4 h at room temperature and then quenched with 7 mL of 10% $Na_2S_2O_4$. Dilution with brine followed by extraction (EtOAc), drying, and concentration afforded an essentially quantitative yield of a crude mixture of diols **13b** as a colorless oil. This diastereomeric mixture could be used in the preparation of dialdehyde **14b** without further purification. Alternatively, isomerically pure samples of the separate diol diastereomers could be obtained by flash chromatography[38] (hexanes/EtOAc 7/3). Faster eluting isomer (R_f = 0.36, hexanes/EtOAc 7/3): ^{1}H NMR (400 MHz) δ 7.33−7.22 (m, 5H), 5.19 (dm, J = 10.1 Hz, 2H), 4.49 (s, 2H), 4.03 (br s, 2H), 3.82 (tt, J = 6.5, 4.4 Hz, 1H), 2.81 (br s, 2H), 2.37 (ddd, J = 14.3, 10.1, 4.6 Hz, 2H), 1.94 (ddd, J = 14.3, 6.4, 3.1 Hz, 2H), 1.18 (s, 18H); ^{13}C NMR (100 MHz) δ 177.9, 138.2, 128.3, 127.5, 73.2, 71.0, 70.5, 70.3, 38.8, 31.9, 27.0. Slower eluting

isomer (R_f = 0.22, hexanes/EtOAc 7/3): ^{1}H NMR (400 MHz) δ 7.31−7.24 (m, 5H), 5.15 (ddd [app td], J = 6.4, 4.4 Hz, 2H), 4.54 (s, 2H), 3.91 (d, J = 6.4 Hz, 2H), 3.71 (tt, J = 7.8, 2.9 Hz, 1H), 3.44 (br s, 2H), 2.30 (ddd, J = 15.0, 7.6, 4.3 Hz, 2H), 1.95 (ddd, J = 15.0, 6.1, 3.05 Hz, 2H), 1.17 (s, 18H); ^{13}C NMR (100 MHz) δ 178.1, 137.6, 128.4, 127.8, 127.7, 73.5, 71.8, 70.4, 70.2, 38.7, 35.1, 27.0. Anal. Calcd for $C_{24}H_{36}O_7$: C, 66.03; H, 8.31. Found: C, 66.02; H, 8.37.

***meso*-(2*R*,4*s*,6*S*)-4-(Benzyloxy)-2,6-bis(2,2-dimethylpropionyl)oxy)heptanedial (14b).** To a solution of diols **13b** (147 mg, 0.339 mmol) in THF (4 mL) was added a solution of H_5IO_6 (77.2 mg, 0.339 mmol) in THF (4 mL) at 0 °C. The ice bath was removed after 15 min; the reaction mixture then became cloudy in 10 min. After 1.5 h at room temperature, 3 mL of pH 7 phosphate buffer and 10 mL of brine were added. The solution was extracted with EtOAc, dried, and concentrated, and the residue was dissolved in $CHCl_3$ (2 mL) and filtered through a plug of cotton, affording 147 mg (99%) of a colorless oil after concentration. Dialdehyde **14b** was used in HWE reactions without further purification: ^{1}H NMR (400 MHz) δ 9.48 (s, 2H), 7.37−7.27 (m, 5H), 5.13 (dd, J = 9.8, 3.7 Hz, 2H), 4.38 (s, 2H), 3.69 (tt [app sept], J = 7.9, 4.0, 1H), 2.18 (ddd, J = 15.0, 7.9, 3.4 Hz, 2H), 1.95 (ddd, J = 15.0, 9.5, 4.0 Hz, 2H), 1.22 (s, 18H); ^{13}C NMR (100 MHz) δ 197.5, 177.8, 137.1, 128.6, 128.1, 75.3, 72.2, 71.5, 38.7, 34.0, 27.0.

General Procedure for the Asymmetric HWE Reactions. To a solution of the chiral phosphonate (**3a**−**d**; 1.05−1.2 equiv) and 18-crown-6 (if applicable; 5 equiv) in THF (ca 0.02 M with respect to the phosphonate) at −78 °C under argon was added 1.0 equiv of KHMDS (0.5 M in toluene). After 30 min the resulting grayish slurry was transferred via cannula to a precooled solution of the dialdehyde[43] (**6**, **14a** or **14b**; Table 1: 1.2−2.1 equiv, Tables 2 and 3: 1.1−1.3 equiv). The reaction mixture was stirred for the indicated time at the appropriate reaction temperature (monitoring by TLC) and then quenched with acetic acid (1 M in MeOH or THF). After 5 min, pH 7 phosphate buffer was added, and the reaction was slowly warmed to room temperature. After dilution with water, extractive workup (ethyl acetate), drying, and concentration gave the crude condensation products. Purification by flash chromatography or MPLC[19] using EtOAc in hexanes as eluent afforded the products as colorless oils.[23]

General Procedure for Reduction of the HWE Products. The crude condensation product was dissolved in MeOH or *i*-PrOH (THF was sometimes added to increase solubility) at 0 °C, and $NaBH_4$ (5−10 equiv) was added. After stirring at 0 °C until the reaction was finished (monitoring by TLC), the reaction mixture was diluted with water and extracted with CH_2CH_2. Drying, concentration, and purification by flash chromatography (EtOAc in hexanes) gave the alcohols as colorless oils.

(*E*)-(4*S*,5*S*,6*R*)-5-(*tert*-(Butyldimethylsilyl)oxy)-7-hydroxy-4,6-dimethylhept-2-enoic Acid (1*R*,2*S*,5*R*)-5-Methyl-2-(1-methyl-1-phenylethyl)cyclohexyl Ester (15). Prepared from **3a** and **6** in 77% overall yield; (*E*):(*Z*) = 98:2, diastereomeric ratio **15**:**16** = 91:9.[23] **15**: ^{1}H NMR (250 MHz, selected data) δ 7.27−7.19 (m, 4H), 7.13−7.06 (m, 1H), 6.72 (dd, J = 15.8, 7.7 Hz, 1H), 5.21 (dd, J = 15.7, 1.3 Hz, 1H), 4.84 (ddd [app td], J = 10.7, 4.3 Hz, 1H), 3.61−3.53 (br m, 2H), 3.57 (dd [app t], J = 5.1 Hz, 1H), 2.56−2.43 (m, 1H), 2.31 (br s, 1H), 2.00 (ddd, J = 12.1, 10.7, 3.3 Hz, 1H), 1.84−1.73 (m, 1H), 1.28 (s, 3H), 1.19 (s, 3H), 1.00 (d, J = 6.9 Hz, 3H), 0.90 (d, J = 6.8 Hz, 3H), 0.89 (s, 9H), 0.84 (d, J = 6.5 Hz, 3H), 0.09 (s, 3H), 0.06 (s, 3H); ^{13}C NMR (100 MHz) δ 165.7, 151.6, 150.4, 127.9, 125.4, 124.9, 121.5, 79.8, 74.3, 65.7, 50.6, 41.72, 39.8, 38.0, 34.6, 31.3, 27.2, 26.7, 26.0, 25.7, 21.8, 18.2, 15.6, 15.6, −4.09, −4.12. Anal. Calcd for $C_{31}H_{52}O_4Si$: C, 72.04; H, 10.14. Found: C, 71.81; H, 10.13. **16**: ^{1}H NMR (250 MHz, selected data assigned from a mixture (91:9) of diastereomers **15** and **16**) δ 6.70 (dd, J = 15.8, 7.4 Hz, 1H), 5.18 (dd, J = 15.8, 1.4 Hz, 1H).

(43) The opposite mode of addition (i.e., adding a precooled solution of the aldehyde to the phosphonate enolate) gave identical results, if the transfer was performed rapidly.

(*E*)-(4*R*,6*R*,8*S*)-6-(Benzyloxy)-4,8-bis((*tert*-butyldiphenylsilyl)oxy)-9-hydroxynon-2-enoic Acid (1*R*,2*S*,5*R*)-5-Methyl-2-(1-methyl-1-phenylethyl)cyclohexyl ester (17). Prepared from **3a** and **14a** in 60% overall yield; (*E*):(*Z*) = 98:2, diastereomeric ratio **17**:**18** = 89:11.[23] **17**: ^{1}H NMR (400 MHz, selected data) δ 6.62 (dd, J = 15.6, 5.9 Hz, 1H), 5.45 (dd, J = 15.6, 1.1 Hz, 1H), 4.83 (ddd [app td], J = 10.7, 4.3 Hz, 1H), 4.21 (app br q, J = 5.8 Hz, 1H), 4.07 (d, J = 11.1 Hz, 1H), 4.01 (d, J = 11.1 Hz, 1H), 3.77−3.70 (m, 1H), 3.46 (ddd, J = 11.6, 5.7, 3.5 Hz, 1H), 3.31 (ddd, J = 11.6, 7.23, 4.3 Hz, 1H), 3.24 (dddd [app quintet], J = ca 6 Hz, 1H), 1.27 (s, 3H), 1.24 (s, 3H), 1.05 (s, 9H), 1.02 (s, 9H), 0.87 (d, J = 6.4 Hz, 3H); ^{13}C NMR (100 MHz, some signals in the aromatic region overlap) δ 165.5, 150.8, 149.3, 138.2, 135.9, 135.7, 133.8, 133.6, 133.5, 133.2, 129.9, 129.8, 128.2, 127.9, 127.82, 127.76, 127.65, 127.57, 127.5, 127.4, 125.6, 125.2, 120.8, 74.5, 72.6, 71.6, 69.99, 69.95, 66.2, 50.7, 42.8, 41.8, 40.1, 38.7, 34.5, 31.3, 28.5, 27.04, 26.98, 25.0, 21.8, 19.3. Anal. Calcd for $C_{64}H_{80}O_6Si_2$: C, 76.76; H, 8.05. Found: C, 76.54; H, 7.96. **18**: ^{1}H NMR (400 MHz, selected data assigned from a mixture (89:11) of diastereomers **17** and **18**) δ 6.41 (dd, J = 15.6, 6.1 Hz, 1H), 5.34 (dd, J = 15.6, 1.1 Hz, 1H).

(*E*)-(4*S*,5*S*,6*S*)-5-(*tert*-(Butyldimethylsilyl)oxy)-4,6-dimethyl-7-oxo-hept-2-enoic Acid (1*R*,2*S*,5*R*)-5-Methyl-2-(1-methyl-1-phenylethyl)cyclohexyl Ester (19). Prepared from **3a** and **6** in 53% yield; (*E*):(*Z*) = 98:2, diastereomeric ratio **19**:**20** = 95:5.[23,44] **19**: ^{1}H NMR (250 MHz, selected data) δ 9.73 (d, J = 2.5 Hz, 1H), 7.27−7.19 (m, 4H), 7.14−7.05 (m, 1H), 6.68 (dd, J = 15.8, 7.7 Hz, 1H), 5.20 (dd, J = 15.8, 1.3 Hz, 1H), 4. 82 (ddd [app td]), J = 10.7, 4.3 Hz, 1H), 3.81 (dd [app t], J = 4.6 Hz, 1H), 2.52−2.39 (m, 2H), 2.01 (ddd, J = 12.1, 10.6, 3.4 Hz, 1H), 1.28 (s, 3H), 1.19 (s, 3H), 1.05 (d, J = 7.1 Hz, 3H), 0.97 (d, J = 6.9 Hz, 3H), 0.87 (s, 9H), 0.84 (d, J = 6.5 Hz, 3H), 0.05 (s, 3H), 0.04 (s, 3H); ^{13}C NMR (62.5 MHz) δ 204.3, 165.6, 151.7, 149.2, 127.9, 125.4, 124.9, 122.2, 77.2, 74.4, 50.5, 50.2, 41.7, 41.6, 39.7, 34.6, 31.3, 27.5, 26.6, 25.9, 25.4, 21.8, 18.1, 15.5, 11.7, −4.2, −4.4. Anal. Calcd for $C_{31}H_{50}O_4Si$: C, 72.32; H, 9.79. Found: C, 72.06; H, 9.74. **20**: ^{1}H NMR (250 MHz, selected data assigned from a mixture (95:5) of diastereomers **19** and **20**) δ 6.66 (dd, J = 16, 7 Hz, 1H), 5.17 (dd, J = 16, 1.5 Hz, 1H).

(*Z*)-(4*R*,5*R*,6*R*)-5-(*tert*-(Butyldimethylsilyl)oxy)-4,6-dimethyl-7-oxo-hept-2-enoic Acid (1*R*,2*S*,5*R*)-5-Methyl-2-(1-methyl-1-phenylethyl)cyclohexyl Ester (21). Prepared from **3d** and **6** in 83% yield; (*Z*):(*E*) = 98:2, diastereomeric purity = 98:2. **21**: ^{1}H NMR (400 MHz, selected data) δ 9.74 (d, J = 2.7 Hz, 1H), 7.25−7.20 (m, 4 H), 7.13−7.09 (m, 1H), 6.11 (dd, J = 11.6, 10.0 Hz, 1H), 5.18 (dd, J = 11.5, 0.6 Hz, 1H), 4.79 (ddd [app td], J = 10.7, 4.3 Hz, 1H), 3.81 (dd, J = 5.8, 3.2 Hz, 1H), 3.82 (m, 1H), 2.47 (qdd, J = 7.0, 5.8, 2.7 Hz, 1H), 1.98 (ddd, J = 12.3, 10.6, 3.2 Hz, 1H), 1.28 (s, 3H), 1.21 (s, 3H), 1.08 (d, J = 7.1 Hz, 3H), 1.00 (d, J = 6.9 Hz, 3H), 0.89 (s, 9 H), 0.84 (d, J = 6.5 Hz, 3H), 0.09 (s, 3H), 0.05 (s, 3H); ^{13}C NMR (100 MHz) δ 204.4, 165.1, 151.5, 149.9, 127.8, 125.4, 125.0, 120.4, 77.2, 73.9, 51.5, 50.5, 41.8, 39.7, 36.6, 34.6, 31.3, 26.9, 26.7, 25.8, 25.4, 21.6, 18.2, 17.6, 11.3, −4.1, −4.4. Anal. Calcd for $C_{31}H_{50}O_4Si$: C, 72.32; H, 9.79. Found: C, 72.14; H, 9.63.

(*E*)-(4*R*,6*R*,8*S*)-6-(Benzyloxy)-4,8-bis((*tert*-butyldiphenylsilyl)oxy)-9-oxonon-2-enoic Acid (1*R*,2*S*,5*R*)-5-Methyl-2-(1-methyl-1-phenylethyl)cyclohexyl Ester (23a). Prepared from **3a** and **14a** in 65% yield;[45] (*E*):(*Z*) = 98:2, diastereomeric ratio **23a**:**24a** = 98:2 (in the crude product, this diastereomer ratio was 89:11, but the diastereomers could be separated by chromatography[23]). **23a**: ^{1}H NMR (400 MHz, selected data) δ 9.45 (d, J = 1.7 Hz, 1H), 7.65−7.53 (m, 8 H),

(44) The sample also contained 3% of an isomer tentatively assigned as being epimeric at the carbon α to the aldehyde carbonyl; see Supporting Information for details.

(45) The sample obtained after flash chromatography also contained 6% of unreacted dialdehyde **14a**; this could be removed, with good material recovery, by a second chromatography. Alternatively, it was easily removed by chromatography after $NaBH_4$ reduction of the HWE product.

7.43−7.18 (m, 19H), 7.07−7.01 (m, 3H), 6.68 (dd, J = 15.6, 6.1 Hz, 1H), 5.44 (dd, J = 15.6, 1.2 Hz, 1H), 4.82 (ddd [app td], J = 10.6, 4.3 Hz, 1H), 4.28 (app br q, J = 6.2 Hz, 1H), 4.08 (ddd [app td], J = 6.0, 1.8 Hz, 1H), 4.03 (d, J = 11.1 Hz, 1H), 3.99 (d, J = 11.0 Hz, 1H), 3.54 (dddd [app br quintet], J = ca 5 Hz, 1H), 1.26 (s, 3H), 1.23 (s, 3H), 1.08 (s, 9H), 1.04 (s, 9H), 0.86 (d, J = 6.5 Hz, 3H); ^{13}C NMR (100 MHz, some signals overlap) δ 202.1, 165.5, 150.9, 149.1, 138.2, 135.97, 135.95, 135.92, 135.8, 133.6, 133.3, 133.0, 132.9, 130.2, 129.9, 128.3, 128.0, 127.9, 127.8, 127.7, 127.6, 127.4, 125.6, 125.5, 125.3, 121.1, 76.0, 74.6, 72.1, 70.3, 70.1, 50.7, 43.0, 41.8, 40.2, 38.2, 34.6, 31.4, 28.4, 27.1, 25.2, 21.9, 19.4. Anal. Calcd for $C_{64}H_{78}O_6Si_2$: C, 76.91; H, 7.87. Found: C, 76.63; H, 7.77. A sample enriched in diastereomer **24a** was obtained from a different experiment. **24a**: ^{1}H NMR (400 MHz, selected data assigned from a mixture (87:13) of diastereomers **23a** and **24a**) δ 9.42 (d, J = 1.8 Hz, 1H), 6.41 (dd, J = 15.6, 6.1 Hz, 1H), 5.38 (dd, J = 15.6, 1.4 Hz, 1H).

(*Z*)-(4*S*,6*S*,8*R*)-6-(Benzyloxy)-4,8-bis((*tert*-butyldiphenylsilyl)oxy)-9-oxonon-2-enoic Acid (1*R*,2*S*,5*R*)-5-Methyl-2-(1-methyl-1-phenylethyl)cyclohexyl Ester (25a). Prepared from **3d** and **14a**, using only KHMDS as base (i.e., no 18-crown-6), in 76% yield; (*Z*):(*E*) = 98:2, diastereomeric ratio **25a**:**26a** = 98:2. **25a**: ^{1}H NMR (400 MHz, selected data) δ 9.41 (d, J = 2.5 Hz, 1H), 7.66−7.51 (m, 8H), 7.44−7.01 (m, 22H), 5.95 (dd, J = 11.6, 8.1 Hz, 1H), 5.44 (ddd [app br quartet], J = ca 6 Hz, 1H), 4.75 (dd, J = 11.6, 1.1 Hz, 1H), 4.56 (ddd [app td], J = 10.6, 4.2 Hz, 1H), 4.26 (d, J = 11.2 Hz, 1H), 4.23 (ddd [app td], J = 6.4, 2.5 Hz, 1H), 4.11 (d, J = 11.0 Hz, 1H), 3.75−3.66 (m, 1H), 1.12 (s, 3H), 1.10 (s, 12H), 1.00 (s, 9H), 0.89 (d, J = 6.4 Hz, 3H); ^{13}C NMR (100 MHz, some signals overlapping) δ 201.8, 164.3, 151.5, 151.1, 138.5, 135.8, 134.0, 133.7, 133.3, 133.2, 129.93, 129.87, 129.7, 129.6, 128.1, 127.8, 127.7, 127.6, 127.4, 127.2, 125.4, 124.9, 118.5, 76.5, 73.9, 72.1, 69.6, 67.8, 50.4, 42.1, 41.7, 39.8, 39.6, 34.5, 31.3, 27.3, 27.0, 26.6, 25.4, 21.9, 19.4, 19.2. Anal. Calcd for $C_{64}H_{78}O_6Si_2$: C, 76.91; H, 7.87. Found: C, 77.17; H, 7.58. A sample enriched in diastereomer **26a** was obtained from a different experiment. **26a**: ^{1}H NMR (400 MHz, selected data assigned from a mixture (86:14) of diastereomers **25a** and **26a**) δ 9.38 (d, J = 2.3 Hz, 1H), 6.00 (dd, J = 11.6, 7.9 Hz, 1H), 4.93 (dd, J = 11.7, 1.3 Hz, 1H).

(*E*)-(4*R*,6*R*,8*S*)-6-(Benzyloxy)-4,8-bis((2,2-dimethylpropionyl)oxy)-9-oxonon-2-enoic Acid (1*R*,2*S*,5*R*)-5-Methyl-2-(1-methyl-1-phenylethyl)cyclohexyl Ester (23b).[46] Prepared from **3b** and **14b** in 62% yield; (*E*):(*Z*) = 98:2, diastereomeric ratio **23b**:**24b** = 95:5.[23] **23b**: ^{1}H NMR (400 MHz, selected data) δ 9.47 (s, 1H), 7.38−7.17 (m, 9H), 7.11−7.02 (m, 1H), 6.49 (dd, J = 15.8, 5.3 Hz, 1H), 5.50 (dddd, J = 9.3, 5.0, 3.5, 1.3 Hz, 1H), 5.41 (dd, J = 15.8, 1.5 Hz, 1H), 5.17 (dd, J = 9.7, 3.5, 1H), 4.83 (ddd [app td], J = 10.7, 4.3 Hz, 1H), 4.41 (d, J = 10.6 Hz, 1H), 4.35 (d, J = 10.5 Hz, 1H), 3.59 (dddd [app septet], J = 4 Hz, 1H), 1.26 (s, 3 H), 1.21 (s, 3H), 1.23 (s, 9H), 1.19 (s, 9H), 0.84 (d, J = 6.5 Hz, 3H); ^{13}C NMR (50 MHz, some peaks in the aliphatic region overlap) δ 197.3, 177.8, 177.0, 165.0, 151.3, 144.4, 137.3, 128.6, 128.2, 128.1, 127.9, 125.4, 125.1, 122.1, 75.3, 74.7, 72.6, 71.8, 69.1, 50.4, 41.6, 39.9, 38.8, 34.5, 34.1, 31.2, 27.1, 26.6, 25.9, 21.7. **24b**: ^{1}H NMR (400 MHz, selected data assigned from a mixture (95:5) of diastereomers **23b** and **24b**) δ 6.13 (dd, J = 15.8, 4.5 Hz, 1H), 5.28 (dd, J = 15.8, 1.7 Hz, 1H).

(*Z*)-(4*S*,6*S*,8*R*)-6-(Benzyloxy)-4,8-bis((2,2-dimethylpropionyl)oxy)-9-oxonon-2-enoic Acid (1*R*,2*S*,5*R*)-5-Methyl-2-(1-methyl-1-phenylethyl)cyclohexyl Ester (25b).[46] Prepared from **3d** and **14b** in 62% yield; (*Z*):(*E*) = 98:2, diastereomeric ratio **25b**:**26b** = 98:2. **25b**: ^{1}H NMR (250 MHz, selected data) δ 9.48 (s, 1H), 7.38−7.16 (m, 9H), 7.13−7.04 (m, 1H), 6.24 (dddd, J = 9.3, 7.5, 3.3, 1.3 Hz, 1H), 5.79 (dd, J = 11.6, 7.4 Hz, 1H), 5.20 (dd, J = 10.2, 3.4 Hz, 1H), 5.04 (dd, J = 11.6, 1.4 Hz, 1H), 4.82 (ddd [app td], J = 10.7, 4.3 Hz, 1H), 4.60 (d, J = 11.1 Hz, 1H), 4.40 (d J = 11.1 Hz, 1H), 3.75−3.65 (m, 1H), 1.21 (s, 9H), 1.14 (s, 9H), 0.86 (d, J = 6.5 Hz, 3H); ^{13}C NMR (125 MHz, some peaks in the aliphatic region overlap) δ 197.6, 177.7, 177.4, 164.4, 151.5, 146.7, 137.9, 128.4, 128.1, 127.9, 127.7, 125.4, 125.0, 120.9, 75.5, 74.4, 72.3, 71.7, 69.8, 50.5, 41.7, 39.7, 38.8, 34.6, 31.3, 27.7, 27.1, 26.6, 25.2, 21.8. A sample enriched in diastereomer **26b** was obtained from a different experiment. **26b**: ^{1}H NMR (250 MHz, selected data) δ 9.46 (s, 1 H), 5.82 (dd, J = 11.5, 7.5 Hz, 1H.

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Supporting Information Available: Additional experimental and characterization data (31 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.

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(46) Due to their limited stability, aldehydes **23b** and **25b** did not give satisfactory elemental analyses. The corresponding alcohols, obtained after $NaBH_4$ reduction, were fully characterized, however; see Supporting Information for details.