Remote 1,5-induction and steric approach control in Horner–Wadsworth–Emmons reactions. The stereoselective construction of trisubstituted, exocyclic double bonds from unsymmetric cyclic ketones

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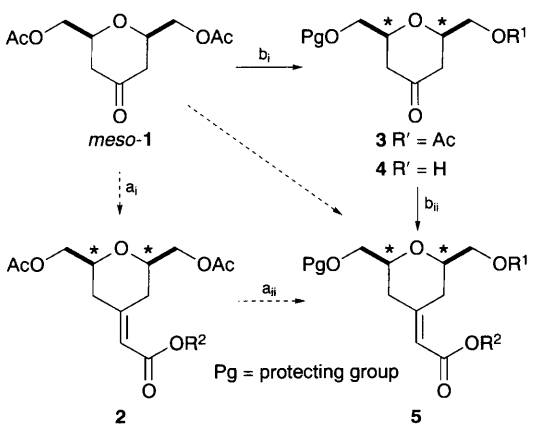
The stereoselective formation of exocyclic α,β-unsaturated ester 8b from cyclic ketone 4 has been accomplished (*E*/*Z* = 9:1).

Although the stereoselective synthesis of alkenes *via* Wittig and related reactions has been extensively investigated over the past three decades, *E*/*Z*-selective construction of trisubstituted, exocyclic double bonds from cyclic ketones remains a synthetic problem which is far from trivial.[1] In studies directed towards the synthesis of enantio- and iso-merically pure enoates such as **5** (Scheme 1) from simple *meso* configured ketones (*e.g.* **1**) we considered two distinct and straightforward strategies ($\mathbf{a_i}$–$\mathbf{a_{ii}}$ and $\mathbf{b_i}$–$\mathbf{b_{ii}}$).

Asymmetric Horner–Wadsworth–Emmons (HWE) reactions have been increasingly employed in stereoselective synthesis, *e.g.* of axially dissymmetric alkenes.[2] Applying this powerful concept, *meso* ketone **1** can be desymmetrized to chiral enoate **2** ($\mathbf{a_i}$). A subsequent chemodifferentiation of the acetoxymethyl termini ($\mathbf{a_{ii}}$) might produce **5**. However, as in the preceding step (**1** → **2**), a chiral probe, *e.g.* an enzyme, is likely to be required for step $\mathbf{a_{ii}}$ (**2** → **5**). In contrast, strategy **b** relies heavily on the *E*/*Z*-selective construction of the exocyclic double bond ($\mathbf{b_{ii}}$). Starting from *meso*-configured ketones such as **1**, the first step $\mathbf{b_i}$ has recently been accomplished by an efficient chemoenzymatic synthesis of enantiopure 2,6-difunctionalized tetrahydropyran-4-ones (*e.g.* **3** and **4**).[3,4]



Scheme 1 $\mathbf{a_i}$ = asymmetric Horner–Wadsworth–Emmons reaction, $\mathbf{a_{ii}}$ = chemoselective protection group manipulation, $\mathbf{b_i}$ = chemoenzymatic synthesis and $\mathbf{b_{ii}}$ = stereoselective olefination

In the literature a three step solution for control of remote enoate geometry by use of a tethered HWE reagent yielding a 14-membered, unsaturated bis(lactone) has been offered by Evans and Carreira.[5] Alternatively, an asymmetric HWE reaction might be employed.[6] From extensive modeling studies we assumed that a bulky protecting group (*e.g.* triphenylmethyl) should screen one side of the tetrahydropyran-4-one moiety providing an inherent bias towards *E*-selectivity. Thus, we decided on control of enoate geometry and stereoselective construction of the trisubstituted, exocyclic double bond through remote 1,5-induction[7] in the course of a HWE olefination with an achiral phosphonate. In the present study racemic ketones **3** and **4**[8] were used to optimize *E*/*Z*-selectivity to a synthetically useful level. Representative examples are shown in Table 1.

Generally, a nonpolar solvent such as toluene was superior to polar solvents (DMF, DME).[9] Ion pairing and the nature of the metal cation also come into play, sodium cation being superior to the more easily solvated lithium cation.‡ As for steric effects, maximizing the difference between CH_2OTr and CH_2OR (R = H, less satisfactory is R = Ac) improves 1,5-induction. The hydrogen atom being the smallest substituent possible affords the highest selectivity towards desired **b** isomer. Also, increasing the bulk of the HWE reagent by substituents R^1 and R^2 on the phosphonate results in higher selectivity.[10] Combining both of these effects by changing the three substituents from R = Ac, R^1 = R^2 = Me (entry 2) to R = H, R^1 = Pr^i, R^2 = Et (entry 9) improves the **b** selectivity from 1 : 1.5 to 1 : 5, *i.e.* more than four-fold. A lowering of the reaction temperature does not appear to alter the stereoselectivity for HWE reactions with normal steric demands (entries 1–3), but exerts significant stereocontrol in the presence of bulk, especially for both substrate and reagent (entries 9–11). The HWE reaction of ketone **4**, in which its trityl substituent serves as not only protecting group, but also as conformational anchor and directing group, afforded under optimal reaction conditions (entry 11) enoate **8** in 72% yield, the *E*-isomer **8b** being favoured by 9 : 1.

In order to determine the stereochemistry of the predominating diastereomer **b** (up to 90% isomerically pure), derivatives of **8b** have been prepared (Bu^tMe_2Si ether, Pr^i_3Si ether, acetate **7b**). Thanks to baseline separation of the relevant proton signals in the NMR spectrum of Bu^tMe_2Si ether **9b**§ (95% isomerically pure after column chromatography on silica gel), this compound was chosen for close spectroscopic investigation and subjected to detailed NMR experiments. The geometry of the double bond in **9b** was apparent from NOE experiments at

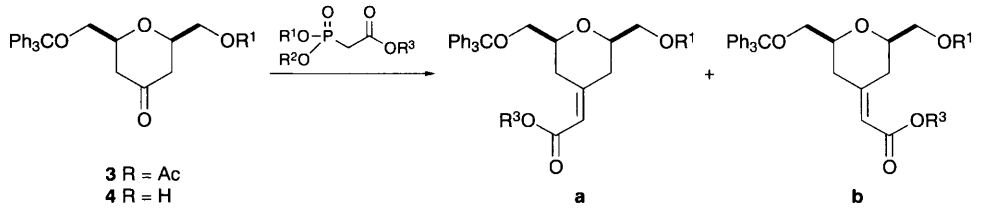


Table 1 Conditions of Horner–Wadsworth–Emmons reactions

Entry	R^1	R^2	R^3	Solvent[a]	Base[a]	T/°C	t/h	Yield (%)[b]	Product	Ratio **a** : **b**[c]
1	Ac	Me	Me	PhMe	NaH	0	o.n.	62	**6a,b**	1 : 1.5
2	Ac	Me	Me	PhMe	NaH	room temp.	2.0	60	**6a,b**	1 : 1.5
3	Ac	Me	Me	PhMe	NaH	55–60	3.5	64	**6a,b**	1 : 1.5
4	Ac	Me	Me	DME	NaH	room temp.	6.0	87	**6a,b**	1 : 1.0
5	Ac	Et	Et	PhMe	$KN(SiMe_3)_2$[d]	room temp.	2.5	50	**7a,b**	1 : 1.1
6	Ac	Et	Et	PhMe	LDA	room temp.	1.0	60	**7a,b**	1 : 1.9
7	Ac	Et	Et	PhMe	NaH	room temp.	0.5	90	**7a,b**	1 : 2.1
8	Ac	Pr^i	Et	PhMe	NaH	room temp.	0.75	71	**7a,b**	1 : 2.7
9	H	Pr^i	Et	PhMe	NaH	room temp.	1.0	70	**8a,b**	1 : 5
10	H	Pr^i	Et	PhMe	NaH	0	3.0	67	**8a,b**	1 : 7.5
11[e]	H	Pr^i	Et	PhMe	NaH	−35 to −25	18[e]	72	**8a,b**	1 : 9
12	H	Pr^i	Et	DMF	NaH	room temp.	1.5	50	**8a,b**	1 : 1.2
13	H	Pr^i	Et	PhMe	NaH–LiBr[f]	0 to room temp.	20.0	23	**8a,b**	1 : 3.2
14	H	Pr^i	Et	PhMe	BuLi	0 to room temp.	3.0	69	**8a,b**	1 : 3.5
15	H	Pr^i	Et	PhMe	NaH, 15-crown-5[g]	0 to room temp.	1.0	67	**8a,b**	1 : 1.1

[a] All reactions (except entry 11) were performed on a 0.15 to 0.3 molar scale (0.1 to 0.15 mol l^{-1}) with 1.4 equiv. of phosphonate anion. [b] Isolated yield of a pure mixture of inseparable *E*/*Z*-isomers **a,b** after column chromatography on silica gel. [c] Determined by ^{1}H NMR and/or GC analysis (280 °C, isothermal). [d] Addition of 18-crown-6 (2.4 equiv.). [e] Reaction was run on a preparative scale (6 mmol) using enantiopure (2*R*,6*S*)-2-hydroxymethyl-6-triphenylmethoxymethyltetrahydropyran-4-one, 3 h at −35 and 15 h at −25 °C. [f] Addition of anhydrous LiBr (2.6 equiv.). [g] Addition of 15-crown-5 (2.3 equiv.).

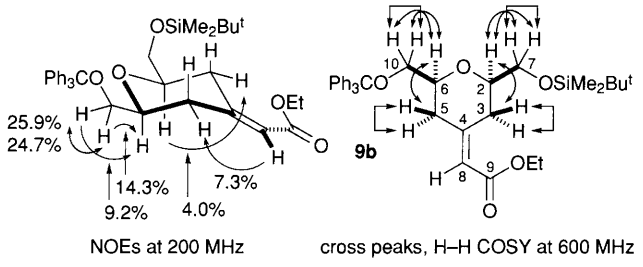


Fig. 1 Determination of alkene geometry

200 MHz in $CDCl_3$ (observed NOE's are shown in Fig. 1). A second piece of evidence came from a H–H COSY recorded at 600 MHz in $CDCl_3$. Representative cross peaks resulting from ^2J and ^3J H–H coupling are depicted in Fig. 1.

In conclusion, we have demonstrated a one step stereoselective construction of exocyclic enoates from unsymmetric ketones in the 2,6-disubstituted tetrahydropyran-4-one series. A chiral HWE reagent is unnecessary. The observed high *E*-selectivity (up to 9 : 1) arises from substrate control of axial/equatorial approach in a floppy 6-membered ketone. Reagent control by a large phosphonate is also required. Remote enoate **8b**, prepared on a multigram scale in enantiomerically pure form, serves as a key intermediate in natural product synthesis.[4]

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Footnotes

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‡ Crown ether solvation of the sodium cation as well as the use of $KN(SiMe_3)_2$–18-crown-6 greatly reduced the selectivity (entries 5 and 15, Table 1).

§ *Selected data* for **9b**; ν_{max} ($CHCl_3$)/cm^{-1} 1704, 1648, 1448, 1256, 1236, 1180, 1152, 1112, 836; ^{1}H NMR (600 MHz, $CDCl_3$, Me_4Si)¶ δ 7.46–7.44 (m, 6 H, *ortho* Ar-H), 7.30–7.27 (m, 6 H, *meta* Ar-H), 7.25–7.21 (m, 3 H, *para* Ar-H), 5.72 (s, 1 H, H-8), 4.16 (q, ^3J 7.2 Hz, 2 H, OCH_2CH_3), 3.81 (d, ^2J 14 Hz, 1 H, H_{eq}-3), 3.72 (dd, ^2J 10.7, ^3J 5.2 Hz, 1 H, H-7b), 3.67 (dd, ^2J 10.7, ^3J 4.3 Hz, 1 H, H-7a), 3.62 (m, ^3J 5.7 and 5.1 Hz, 1 H, H-6), 3.44 (m, ^3J 5.1 and 4.3 Hz, 1 H, H-2), 3.26 (dd, ^2J 9.4, ^3J 5.1 Hz, 1 H, H-10b), 3.06 (dd, ^2J 9.4, ^3J = 5.6 Hz, 1 H, H-10a), 2.29 (d, ^2J 13.2 Hz, 1 H, H_{eq}-5), 2.18 (t, $^{2/3}J$ 12 Hz, 1 H, H_{ax}-5), 1.93 (t, $^{2/3}J$ 12.6 Hz, 1 H, H_{ax}-3), 1.28 (t, ^3J 7.2 Hz, 3 H, OCH_2CH_3), 0.88 [s, 9 H, $SiC(CH_3)_3$], 0.06 and 0.05 [2 s, total 6 H, $Si(CH_3)_2$].

¶ Numbering of atoms refers to the depicted structure in Fig. 1.

References

1 For reviews concerning Wittig and related reactions, see J. Clayton and S. Warren, *Angew. Chem., Int. Ed. Engl.*, 1996, **35**, 241; M. Schlosser, *Top. Stereochem.*, 1970, **5**, 1; J. Boutagy and R. Thomas, *Chem. Rev.*, 1974, **74**, 87; B. E. Maryanoff and A. B. Reitz, *Chem. Rev.*, 1989, **89**, 863.

2 A. Abiko and S. Masamune, *Tetrahedron Lett.*, 1996, **37**, 1077; J. Mulzer, T. Speck, J. Buschmann and P. Luger, *Tetrahedron Lett.*, 1995, **36**, 7643; M. Suarez and G. B. Schuster, *J. Am. Chem. Soc.*, 1995, **117**, 6732; T. Furuta and M. Iwamura, *J. Chem. Soc., Chem. Commun.*, 1994, 2167; S. E. Denmark and C.-T. Chen, *J. Am. Chem. Soc.*, 1992, **114**, 10674; S. Hanessian and S. Beaudoin, *Tetrahedron Lett.*, 1992, **33**, 7659.

3 T. F. J. Lampe, H. M. R. Hoffmann and U. T. Bornscheuer, *Tetrahedron: Asymmetry*, 1996, **7**, 2889.

4 T. F. J. Lampe and H. M. R. Hoffmann, *Tetrahedron Lett.*, 1996, **37**, 7695; *Chem. Commun.*, 1996, 1931.

5 D. A. Evans and E. M. Carreira, *Tetrahedron Lett.*, 1990, **31**, 4703.

6 Chiral phosphonoacetates have been employed for controlling *E*/*Z*-selectivity in the synthesis of the prostacyclin analogue cicaprost: H.-J. Gais, G. Schmiedl, W. A. Ball, J. Bund, G. Hellmann and I. Erdelmeier, *Tetrahedron Lett.*, 1988, **29**, 1773; H. Rehwinkel, J. Skupsch and H. Vorbrüggen, *Tetrahedron Lett.*, 1988, **29**, 1775.

7 We define 1,*n*-induction as the distance of carbonyl carbon to the first *differing* atom (CPh_3) along alternative chain segments in **4** (R = H). For 1,*n*-induction in the olefination of cyclic ketones, see (*n* = 2): E. G. Baggiolini, J. A. Iacobelli, B. M. Hennessy, A. D. Batcho, J. F. Sereno and M. R. Uskokovic, *J. Org. Chem.*, 1986, **51**, 3098; K. Tadano, Y. Idogaki, H. Yamada and T. Suami, *J. Org. Chem.*, 1987, **52**, 1201; J. Mulzer, U. Steffen, L. Zorn, C. Schneider, E. Weinhold, W. Münch, R. Rudert, P. Luger and H. Hartl, *J. Am. Chem. Soc.*, 1988, **110**, 4640; (*n* = 3): *cf.* ref. 6; (*n* = 4): K. Ohmori, T. Suzuki, K. Miyazawa, S. Nishiyama and S. Yamamura, *Tetrahedron Lett.*, 1993, **34**, 4981.

8 The synthesis of racemic ketones **3** and **4** is described in T. Lampe, PhD thesis, University of Hannover, 1996.

9 P. A. Wender, M. A. Eissenstat and M. P. Filosa, *J. Am. Chem. Soc.*, 1979, **101**, 2196.

10 In studies on the synthesis of monensin, a significant influence of phosphonates with different steric demands on the *cis*/*trans* ratio was observed; H. Nagaoka and Y. Kishi, *Tetrahedron*, 1981, **37**, 3873 and ref. 7 therein.

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