Pergamon

Tetrahedron 56 (2000) 2491–2495

TETRAHEDRON

Synthesis of γ-Hydroxy-α,β-unsaturated Esters and Nitriles from Chiral Cyanohydrins

Jan Marcus, Pauline J. van Meurs, Adrianus M. C. H. van den Nieuwendijk, Mathieu Porchet, Johannes Brussee* and Arne van der Gen

Leiden Institute of Chemistry, Gorlaeus Laboratories, Leiden University, P.O. Box 9502, 2300 RA Leiden, The Netherlands

Received 25 October 1999; revised 4 January 2000; accepted 20 January 2000

Abstract—The Horner–Wittig reaction of cyanomethyl- and carbethoxymethyl diphenylphosphine oxides with a range of *O*-protected chiral α-hydroxy aldehydes is described. The α-hydroxy aldehydes were prepared with high enantiomeric purity from chiral *O*-protected cyanohydrins. The γ-hydroxy-α,β-unsaturated compounds formed were isolated in high enantiomeric purity and excellent yield. In all cases complete *E*-selectivity was observed. © 2000 Elsevier Science Ltd. All rights reserved.

Introduction[1]

Over the past years chiral cyanohydrins (α-hydroxynitriles) have become a versatile source for a variety of chiral building blocks. Several classes of valuable intermediates have already been synthesized, including β-hydroxy-α-amino acids,[2] α-hydroxy-β-amino acids,[3] α-hydroxy ketones[4b] and β-hydroxy nitrones.[5] Although chiral α-hydroxy aldehydes are compounds of considerable interest, their synthesis from chiral cyanohydrins has remained problematic. Some attempts towards the synthesis of chiral α-hydroxy aldehydes have been published but the results, both in yield and optical purity, seem to be contradictory.[4,6,7] It was our intention to synthesize *O*-protected chiral α-hydroxy aldehydes of high enantiomeric purity and subsequently employ these compounds in Wittig-type reactions.

The synthesis of chiral cyanohydrins is a well-studied subject in our laboratories.[8] Cyanohydrins can be prepared in excellent enantiomeric purity by asymmetric addition of hydrogen cyanide to aldehydes in a reaction catalyzed by the enzyme R-hydroxynitrile lyase (E.C. 4.1.2.10), as present in almond meal.[9] A wide variety of substrates can be employed in the R-hydroxynitrile lyase catalyzed reaction, including aromatic, heterocyclic, and saturated as well as ω- and α,β-unsaturated aliphatic aldehydes.[8b,9] The cyanohydrins **1** thus obtained are known to possess the (*R*)-configuration.[10]

To prevent decomposition and racemization in subsequent transformations the hydroxyl group of the cyanohydrin has to be protected. After protection, the nitrile moiety can be reduced with diisobutylaluminum hydride (DIBAL-H). The *O*-protected chiral α-hydroxy aldehydes formed can subsequently be used in Wittig-type reactions, thus forming chiral γ-hydroxy-α,β-unsaturated compounds. The preparation and utilization of Horner–Wittig reagents (diphenylphosphine oxides) is also part of the research in our group.[11]

We hereby report the synthesis of *O*-protected chiral α-hydroxy aldehydes starting from chiral cyanohydrins and their application in the Horner–Wittig reaction.

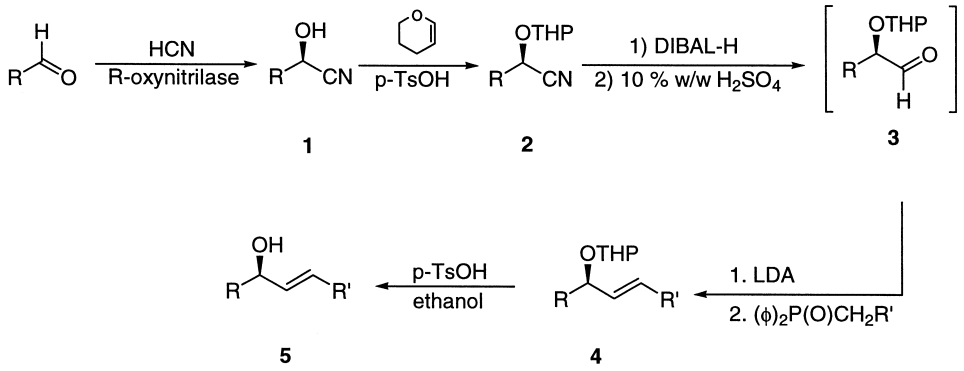
Results and Discussion

Tetrahydropyranyl (THP) protected cyanohydrins **2** were used as starting materials for the projected Horner–Wittig reaction sequence. The motive for using this protecting group was the resulting stability of the intermediate aldehydes and the ease with which it can be removed. The nitrile moiety was reduced with DIBAL-H at −78°C in a nitrogen atmosphere whereupon an imine–aluminum complex was formed. This complex was hydrolyzed to the corresponding aldehyde by stirring the reaction mixture for a brief period of time with 10% w/w sulfuric acid at −15°C. Aldehydes **3a** (R=C_6H_5) and **3f** (R=*n*-C_3H_7) were sufficiently stable to be purified by column chromatography after which they were isolated in 57% and 60% yield, respectively. The remaining aldehydes could not be purified in this way because of their air- and moisture sensitivity, and were used directly in the next step (Scheme 1).

Keywords: asymmetric synthesis; cyanohydrins; Horner–Wittig reaction; α-hydroxy aldehydes.

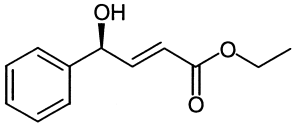
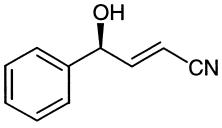
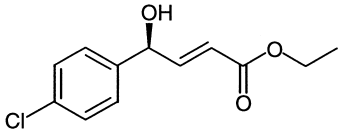
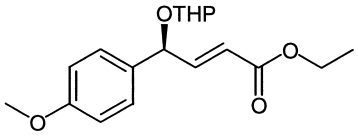
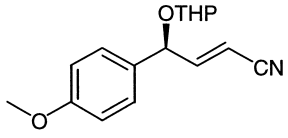
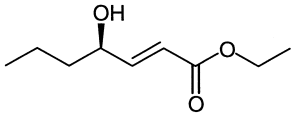
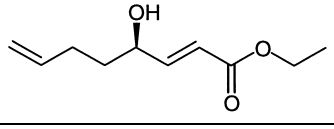
* Corresponding author. Fax: +31-71-5274537;
e-mail: brussee@chem. leidenuniv.nl

PII: S0040-4020(00)00085-5



Scheme 1. Synthesis of γ-hydroxy-α,β-unsaturated esters and nitriles from chiral cyanohydrins; **a** R=C_6H_5, R′=COOEt; **b** R=C_6H_5, R′=CN; **c** R=4-Cl–C_6H_4, R′=COOEt; **d** R=4-MeO–C_6H_4, R′=COOEt; **e** R=4-MeO–C_6H_4, R′=CN; **f** R=*n*-propyl, R′=COOEt; **g** R=3-butenyl, R′=COOEt.

Table 1. Horner–Wittig products obtained from chiral cyanohydrins

Compound	Product	e.e. (%)[a]	Yield (%)	e.e. (%)[b]	*E*/*Z*
5a		>99	86	96	*E*
5b		>99	82	96	*E*
5c		>99	86	97	*E*
4d		>99	88	96[c]	*E*
4e		>99	83	96[c]	*E*
5f		89	82	86	*E*
5g		97	79	96	*E*

[a] e.e. of cyanohydrin.
[b] e.e. of product.
[c] Racemization occurred upon deprotection.

After addition of LDA at −78°C the appropriate diphenylphosphine oxide was added. The amounts of LDA and diphenylphosphine oxide are specified in the Experimental section. After work-up the crude product was subjected to a deprotection step. The pure γ-hydroxy-α,β-unsaturated compounds were isolated upon column chromatography. NMR spectroscopy showed that the Horner–Wittig reaction had proceeded with complete *E*-selectivity.[13] Compounds **4a**–**g** were obtained in high yields and with almost no loss of enantiomeric purity. The results are shown in Table 1.

In a comparative study, the Horner–Wittig reagents (diphenylphosphine oxides) were shown to be the most successful. Application of other phosphorus compounds like the Wittig reagent carbethoxymethyl–triphenylphosphonium bromide and the Horner–Wadsworth–Emmons reagent triethylphosphono acetate resulted in lower yields and often partial racemization.

Not all *O*-protected cyanohydrins studied could be reduced to the corresponding aldehydes. The attempted synthesis of aldehydes from the *O*-protected cyanohydrins of 5-methylfurfural and crotonaldehyde were unsuccessful. For the former cyanohydrin this could be ascribed to the acid labile furan ring, which decomposed upon addition of sulfuric acid. For the latter cyanohydrin the reason for failure is not obvious. Clearly the unsaturated character of the compound is the causative factor, as compound **5f**, containing the corresponding saturated side chain, was obtained without difficulties. A similar observation has been reported in the literature.[7]

During the deprotection of compounds **4d** and **4e**, both containing a 4-methoxy substituted phenyl ring, with *para*-toluenesulfonic acid in ethanol, the hydroxyl substituent turned out to have been replaced by an ethoxy group. In addition, complete racemization had occurred. This can be explained by assuming loss of water from the initial product upon protonation of the deprotected hydroxyl group. The resulting carbocation is stabilized by the 4-methoxy phenyl substituent. Reaction with the solvent, ethanol, then gives the corresponding ethoxy compound with racemization of the chiral center. Other deprotecting reagents like $MgBr_2$ and a mixture of acetic acid, THF and water (4:2:1) failed to give better results. This impracticability to deprotect the O-THP group only occurs with strongly electron-releasing aromatic ring substituents. Compounds with electron-withdrawing ring substituents, like the unsaturated ester **4c**, could be deprotected effectively by treatment with *para*-toluenesulfonic acid in ethanol.

Conclusion

By performing a Horner–Wittig reaction on a series of chiral hydroxy aldehydes a range of different chiral γ-hydroxy-α,β-unsaturated compounds of high enantiomeric purity could be prepared in excellent yield. In all cases complete *E*-selectivity was found.

Experimental

General methods and materials

^1H and ^{13}C NMR spectra were recorded on a *Bruker DPX-200* instrument. Samples were measured in $CDCl_3$, with Me_4Si as an internal standard for ^1H NMR, and $CDCl_3$ as an internal standard for ^{13}C NMR; δ in ppm, J in Hz. Infrared spectra (neat) were recorded on a Pye Unicam SP3-200 IR spectrometer. Enantiomeric purities were determined by HPLC using a *Chiralcel OD* column (250×4.6 mm). As eluents, mixtures of hexane (H) and isopropyl alcohol (I), which are specified in each case, were applied. Flow=1 ml/min, λ=254 nm unless otherwise specified. All compounds were also prepared in racemic form to optimize the conditions for peak separation. Optical rotations were measured using a *Propol* automatic polarimeter. HRMS spectra were obtained with a Finnigan MAT ITD 700 electron impact (70 eV). The cyanohydrins were prepared as described earlier.[9] The THP protection was performed according to literature.[12] THF was distilled from $LiAlH_4$ prior to use. Diethyl ether was dried over sodium wire. The phosphine oxides were prepared via an Arbuzov reaction from ethyl diphenylphosphinite [$(C_6H_5)_2P–OC_2H_5$] and either ethyl bromoacetate or chloroacetonitrile.

Aldehyde synthesis

All reactions were carried out under a dry nitrogen atmosphere. In a three-necked reaction flask 10 mmol of a THP-protected cyanohydrin was dissolved in dry diethyl ether. At −78°C, 14 ml (14 mmol) of 1 M DIBAL-H in cyclohexane was added to the stirred solution. The cooling bath was removed and the mixture was allowed to warm to −15°C. Then 17 ml of a 10% w/w solution of H_2SO_4 in water was added. After stirring the reaction mixture vigorously for 10 min, 40 ml of an aqueous solution of saturated $NaHCO_3$ was added. The mixture was stirred for 5 min. The reaction mixture was poured into water and extracted with diethyl ether (3×100 ml). The combined organic layers were washed with brine and dried over $MgSO_4$. After evaporation of the solvent the crude aldehyde was obtained as oil. The aldehyde was used immediately in the next step.

(2*R*) 2-(tetrahydropyran-2-yloxy)-phenylacetaldehyde (3a). Prepared as described above. The crude product was chromatographed (silica gel, petroleum ether 40–60/diethyl ether 8/2) and **3a** was obtained as a pale yellow oil (yield: 57%).

Diastereoisomer A ^1H NMR: δ=1.55–1.87 (m, 6H, THP), 3.48 (m, 2H, THP), 4.66 (t, 1H, J=2.6 Hz, OC*H*O), 5.05 (d, 1H, J=1.5 Hz, CH), 7.37–7.43 (m, 5H, H-arom), 9.62 (d, 1H, J=1.5 Hz, C*H*O).

Diastereoisomer B ^1H NMR: δ=1.55–1.87 (m, 6H, THP), 3.48 (m, 2H, THP), 4.93 (t, 1H, J=2.6 Hz, OC*H*O), 5.20 (d, 1H, J=1.5 Hz, CH), 7.37–7.43 (m, 5H, H-arom), 9.65 (d, 1H, J=1.5 Hz, C*H*O).

(2*R*) 2-(tetrahydropyran-2-yloxy)-pentanal (3f). Prepared as described above. The crude product was

chromatographed (silica gel, petroleum ether 40–60/diethyl ether 8/2) and **3f** was obtained as a yellow oil (yield: 60%).

Diastereoisomer A ^{1}H NMR: δ=0.88 (t, 3H, J=7.2, CH_3), 1.43–1.61 (m, 6H, THP), 1.63–1.84 (m, 4H, 2×CH_2), 3.56 (m, 2H, THP), 4.18 (m, 1H, OC*H*O), 4.56 (m, 1H, C*H*), 9.63 (d, 1H, J=1.5 Hz, C*H*O).

Diastereoisomer B ^{1}H NMR: δ=0.96 (t, 3H, J=7.2 Hz, CH_3), 1.43–1.61 (m, 6H, THP), 1.63–1.84 (m, 4H, 2×CH_2), 3.87 (m, 2H, THP), 4.18 (m, 1H, OC*H*O), 4.69 (m, 1H, C*H*), 9.65 (d, 1H, J=1.5 Hz, C*H*O).

Horner–Wittig reaction

In a three-necked reaction flask 25 ml of dry THF was cooled to −60°C. Then diisopropylamine (DIPA) and *n*-butyllithium (BuLi) were added. The reaction mixture was allowed to warm to −20°C and then cooled to −78°C. At this temperature the diphenylphosphine oxide, dissolved in a small amount of THF, was added. After stirring the reaction mixture for 10 min, the aldehyde dissolved in THF, was added. After reaching room temperature the reaction mixture was poured into water and extracted with dichloromethane. The organic layers were combined, dried ($MgSO_4$) and concentrated in vacuo. The amounts of DPA, BuLi and diphenylphosphine oxide are case specific and are given for each compound.

Deprotection

The resulting crude product was dissolved in ethanol and a catalytic amount of *p*-toluenesulphonic acid was added. After stirring overnight at room temperature, 10 ml of an aqueous solution of saturated $NaHCO_3$ was added. The mixture was stirred vigorously for 5 min. The reaction mixture was poured into water and extracted with dichloromethane. The organic layers were combined, dried ($MgSO_4$) and concentrated in vacuo. The products were purified by column chromatography.

(4*R*) Ethyl 4-hydroxy-4-phenyl-(*E*)-but-2-enoate (5a). Prepared as described above starting from **2a**. Equivalents used: 1.2 equiv. BuLi, 1.2 equiv. (carbethoxymethyl)-diphenylphosphine oxide and 1.45 equiv. DIPA. The crude product was chromatographed (silica gel, petroleum ether 40–60/ethyl acetate; first column 9/1; second column 3/1) and **5a** was obtained as a colourless oil (yield: 86%). $[\alpha]_D^{20}$=−71.6 (c=1, $CHCl_3$); e.e. 96% (HPLC eluent H:I=95:5); IR: (liquid film) 3400 (br), 1700 cm^{-1}; ^{1}H NMR: δ=1.27 (t, 3H, J=6.9 Hz, CH_3), 2.41 (broad s, 1H, OH), 4.18 (q, 2H, J=7.0 Hz, CH_2), 5.35 (dd, 1H, J=4.6, 1.3 Hz, C*H*), 6.15 (dd, 1H, J=15.4, 1.3 Hz, CH=C*H*C(O)), 7.04 (dd, 1H, J=15.4, 4.6 Hz, C*H*=CHC(O)), 7.34 (m, 5H, H-arom). ^{13}C NMR: δ=14.02 (*C*H$_3$), 60.44 (*C*H$_2$), 73.15 (*C*H), 119.84 (*C*H=CH), 126.44, 128.01, 128.57 (C-arom), 140.86 (C$_{ipso}$), 148.86 (CH=*C*H), 166.59 (C(O)); HRMS (EI): M$^+$, found 206.0954. $C_{12}H_{14}O_3$ requires 206.0943.

(4*R*) 4-Hydroxy-4-phenyl-(*E*)-but-2-enenitrile (5b). Prepared as described above starting from **2a**. Equivalents used: 1.2 equiv. BuLi, 1.2 equiv. cyanomethyl diphenylphosphine oxide and 1.45 equiv. DIPA. The crude product was chromatographed (silica gel, petroleum ether 40–60/ethyl acetate=7/3) and **5b** was obtained as a colourless oil (yield: 82%). $[\alpha]_D^{20}$=−87.0 (c=1, $CHCl_3$); e.e. 96% (HPLC eluent H:I=95:5); IR: (liquid film) 3400 (br), 2220 cm^{-1}; ^{1}H NMR: δ=5.36 (m, 1H, C*H*O), 5.84 (dd, 1H, J=16, 2.2 Hz), 6.82 (dd, 1H, J=16, 3.7 Hz), 7.34 (m, 5H, H-arom). ^{13}C NMR: δ=73.09 (*C*HO), 98.35 (*C*H=CH), 117.21 (CN), 126.52, 128.67, 128.92 (C-arom), 139.65 (C$_{ipso}$), 155.15 (CH=*C*H); HRMS (EI): M$^+$, found 159.0681. $C_{10}H_9NO$ requires 159.0684.

(4*R*) Ethyl 4-(4-chlorophenyl)-4-hydroxy-(*E*)-but-2-enoate (5c). Prepared as described above starting from **2c**. Equivalents used: 1.2 equiv. BuLi, 1.2 equiv. (carbethoxymethyl)-diphenylphosphine oxide and 1.3 equiv. DIPA. The crude product was chromatographed (silica gel, petroleum ether 40–60/ethyl acetate=3/1) and **5c** was obtained as colourless oil (yield: 86%). $[\alpha]_D^{20}$=−52.3 (c=1, $CHCl_3$); e.e. 97% (HPLC eluent H:I=95:5); IR: (liquid film) 3400 (br), 1700, 1100 cm^{-1}; ^{1}H NMR: δ=1.29 (t, 3H, J=7.2 Hz, CH_3), 4.20 (q, 2H, J=7.2 Hz, CH_2), 5.35 (dd, 1H, J=4.6, 1.5 Hz, C*H*), 6.14 (dd, 1H, J=15.4, 1.5 Hz, CH=C*H*C(O)), 6.99 (dd, 1H, J=15.4, 4.6 Hz, C*H*=CHC(O)), 7.34 (m, 4H, H-arom). ^{13}C NMR: δ=14.02 (*C*H$_3$), 60.59 (*C*H$_2$), 72.44 (*C*H), 120.25 (*C*H=CH), 127.78, 128.07, 128.71, 128.80 (C-arom), 133.77 (C$_{ipso}$), 139.37 (Cl-C$_{ipso}$), 148.31 (CH=*C*H), 166.47 (C(O)); HRMS (EI): M$^+$, found 240.0559. $C_{12}H_{13}ClO_3$ requires 240.0553.

(4*R*) Ethyl 4-(4-methoxyphenyl)-4-(tetrahydropyran-2-yloxy)-(*E*)-but-2-enoate (4d). Prepared as described above starting from **2d**. Equivalents used: 1.2 equiv. BuLi, 1.2 equiv. (carbethoxymethyl)-diphenylphosphine oxide and 1.45 equiv. DIPA. The crude product was chromatographed (silica gel, petroleum ether 40–60/ethyl acetate=4/1 and **4d** was obtained as a colourless oil (yield: 88%). IR: (liquid film) 3400 (br), 1700 cm^{-1}; HRMS (EI): M$^+$, found 320.1623. $C_{18}H_{24}O_5$ requires 320.1624.

Diastereoisomer A ^{1}H NMR: δ=1.28 (t, 3H, J=7.3 Hz, CH_3CH$_2$O), 1.57–1.89 (m, 6H, OTHP), 3.74 (m, 2H, OTHP), 3.75 (s, 3H, MeO), 4.18 (q, 2H, J=7.3 Hz, CH$_3$CH_2O), 4.53 (m, 1H, OC*H*O), 5.27 (m, 1H, C*H*O), 6.08 (dd, 1H, J=1.5, 15.4 Hz, CH=C*H*C(O)), 6.97 (dd, 1H, J=5.1, 15.4 Hz, C*H*=CHC(O)), 7.21–7.32 (m, 4H, H-arom). ^{13}C NMR: δ=13.87 (OCH$_3$*C*H$_2$), 18.62 (THP), 25.11 (THP), 30.05 (THP), 54.80 (OCH$_3$), 59.94 (O*C*H$_3$CH$_2$), 61.45 (THP), 74.41 (CH), 94.12 (THP), 113.57 (C-arom), 119.39 (CH=*C*H), 128.15 (C-arom), 130.19 (C$_{ipso}$), 146.95 (*C*H=CH), 158.99 (C$_{ipso}$), 165.79 (C(O)).

Diastereoisomer B ^{1}H NMR: δ=1.29 (t, 3H, J=7.3 Hz, CH_3CH$_2$O), 1.57–1.89 (m, 6H, OTHP), 3.78 (m, 2H, OTHP), 3.80 (s, 3H, MeO), 4.19 (q, 2H, J=7.3 Hz, CH$_3$CH_2O), 4.80 (m, 1H, OC*H*O), 5.30 (m, 1H, C*H*O), 6.13 (dd, 1H, J=1.5, 15.4 Hz, CH=C*H*C(O)), 7.04 (dd, 1H, J=5.1, 15.4 Hz, C*H*=CHC(O)), 7.21–7.32 (m, 4H, H-arom). ^{13}C NMR: δ=13.87 (OCH$_3$*C*H$_2$), 18.71 (THP), 25.11 (THP), 30.05 (THP), 54.80 (OCH$_3$), 60.07 (O*C*H$_3$CH$_2$), 61.45 (THP), 75.36 (CH), 95.99 (THP), 113.75 (C-arom), 121.06 (CH=*C*H), 128.60 (C-arom),

131.39 (C_{ipso}), 147.80 (*C*H=CH), 159.32 (C_{ipso}), 166.15 (C(O)).

(4*R*) 4-(4-Methoxyphenyl)-4-(tetrahydropyran-2-yloxy)-(*E*)-but-2-enenitrile (4e). Prepared as described above starting from **2d**. Equivalents used: 1.2 equiv. BuLi, 1.2 equiv. cyanomethyl diphenylphosphine oxide and 1.45 equiv. DIPA. The crude product was chromatographed (silica gel, petroleum ether 40–60/ethyl acetate =3/1 and **4e** was obtained as a colourless oil (yield: 83%). IR: (liquid film) 3400 (br), 2215 cm^{-1}; HRMS (EI): M^+, found 273.1356. $C_{16}H_{19}NO_3$ requires 273.1365.

Diastereoisomer A ^{1}H NMR: δ=1.57–1.86 (m, 6H, OTHP), 3.40–3.70 (m, 2H, OTHP), 3.78 (s, 3H, MeO), 4.49 (m, 1H, OC*H*O), 5.26 (m, 1H, C*H*O), 5.67 (dd, 1H, *J*=1.5, 16 Hz, CH=C*H*CN), 6.74 (dd, 1H, *J*=5.1, 16 Hz, C*H*=CHCN), 6.88–7.26 (m, 4H, H-arom). ^{13}C NMR: δ=18.39 (THP), 24.91 (THP), 29.85 (THP), 54.77 (*Me*O), 61.38 (THP), 74.24 (*C*HO), 94.34 (THP), 97.92 (CH=*C*H), 113.69 (C-arom), 116.57 (CN), 127.91 (C-arom), 128.79 (C_{ipso}), 153.56 (*C*H=CH), 159.20 (C_{ipso}).

Diastereoisomer B ^{1}H NMR: δ=1.57–1.86 (m, 6H, OTHP), 3.40–3.70 (m, 2H, OTHP), 3.81 (s, 3H, MeO), 4.78 (m, 1H, OC*H*O), 5.30 (m, 1H, C*H*O), 5.77 (dd, 1H, *J*=1.5, 16 Hz, CH=C*H*CN), 6.78 (dd, 1H, *J*=5.1, 16 Hz, C*H*=CHCN), 6.88–7.26 (m, 4H, H-arom). ^{13}C NMR: δ=18.78 (THP), 24.91 (THP), 29.85 (THP), 54.77 (*Me*O), 61.72 (THP), 75.57 (*C*HO), 96.44 (THP), 99.13 (CH=*C*H), 113.90 (C-arom), 116.90 (CN), 128.55 (C-arom), 130.15 (C_{ipso}), 153.96 (*C*H=CH), 159.57 (C_{ipso}).

(4*R*) Ethyl 4-hydroxy-(*E*)-hept-2-enoate (5f). Prepared as described above starting from **2f**. Equivalents used: 1.02 equiv. BuLi, 1.02 equiv. (carbethoxymethyl)-diphenylphosphine oxide and 1.22 equiv. DIPA. The crude product was chromatographed (silica gel, dichloromethane/diethyl ether =8/2) and **5f** was obtained as a colourless oil (yield: 82%). $[\alpha]_D^{20}$=−16.7 (*c*=1, $CHCl_3$); e.e. 86% (HPLC eluent H:I= 95:5); IR: (liquid film) 3410 (br), 1700 cm^{-1}; ^{1}H NMR: δ=0.95 (t, 3H, *J*=7.2 Hz, C*H*$_3$), 1.30 (t, 3H, *J*= 7.2 Hz, C*H*$_3$CH$_2$O), 1.39–1.66 (m, 4H, C*H*$_2$), 4.20 (q, 2H, *J*=7.2 Hz, CH$_3$C*H*$_2$O), 4.34 (m, 1H, C*H*), 6.03 (dd, 1H, *J*=15.4, 1.5 Hz, CH=C*H*C(O)), 6.95 (dd, 1H, *J*=15.4, 5.1 Hz, C*H*=CH(CO)). ^{13}C NMR: δ=13.70 (*C*H$_3$), 13.99 (*C*H$_3$CH$_2$O), 18.31, 38.49 (*C*H$_2$), 60.30 (CH$_3$*C*H$_2$O), 70.49 (*C*H), 119.66 (*C*H=CH), 150.61 (CH=*C*H), 166.67 (C(O)); HRMS (EI): M^+, found 172.1091. $C_9H_{16}O_3$ requires 172.1099.

(4*R*) Ethyl 4-hydroxy-(*E*)-octa-2,7-dienoate (5g). Prepared as described above starting from **2g**. Equivalents used: 1.04 equiv. BuLi, 1.04 equiv. (carbethoxymethyl)-diphenylphosphine oxide and 1.23 equiv. DIPA. The crude product was chromatographed (silica gel, petroleum ether 40–60/ethyl acetate=8/2) and **5g** was obtained as a colourless oil (yield: 79%). $[\alpha]_D^{20}$=−4.5 (*c*=1, $CHCl_3$); e.e. 96% (HPLC eluent H:I=97:3 flow 0.7 ml/min); IR: (liquid film) 3420 (br), 1700 cm^{-1}; ^{1}H NMR: δ=1.30 (t, 3H, *J*=7.3 Hz, C*H*$_3$), 1.72 (m, 2H, C*H*$_2$), 2.20 (m, 2H, C*H*$_2$), 4.21 (q, 2H, *J*=7.3 Hz, CH$_3$C*H*$_2$O), 4.32 (m, 1H, C*H*), 5.02 (m, 2H, C*H*$_2$=CH), 5.83 (m, 1H, CH$_2$=C*H*), 6.05 (dd, 1H, *J*=15.4, 1.5 Hz, CH=C*H*C(O)), 6.95 (dd, 1H, *J*=15.4, 5.1 Hz, C*H*=CHC(O)). ^{13}C NMR: δ=13.89 (*C*H$_3$), 29.15, 35.21 (*C*H$_2$), 60.26 (CH$_3$*C*H$_2$O), 69.90 (*C*H), 114.94 (*C*H$_2$=CH), 119.76 (CH=*C*H(CO)), 137.50 (CH$_2$=*C*H), 150.39 (*C*H=CH(CO)), 166.61 (C(O)); HRMS (EI): M^+, found 184.1087. $C_{10}H_{16}O_3$ requires 184.1099.

References

1. Marcus, J.; Brussee, J.; van der Gen, A. In *Proceedings of ECSOC-3, The Third International Electronic Conference on Synthetic Organic Chemistry*, http://www.mdpi.org/ecsoc-3.htm, September 1–30, 1999; Pombo-Villar, E.; Neier, R.; Lin, S.-K., Eds.; CD-ROM ed.; ISBN 3-906980-04-9; 1999, MDPI, Basel.
2. Zandbergen, P.; Brussee, J.; van der Gen, A.; Kruse, C. G. *Tetrahedron: Asymmetry* **1992**, *3*, 769–774.
3. Warmerdam, E. G. J. C.; van Rijn, R. D.; Brussee, J.; Kruse, C. G.; van der Gen, A. *Tetrahedron: Asymmetry* **1996**, *7*, 1723.
4. (a) Matthews, B. R.; Gountzos, H.; Jackson, W. R.; Watson, K. G. *Tetrahedron Lett.* **1989**, *30*, 5157–5158. (b) Jackson, W. R., Jacobs, H. A.; Jayatilake, G. S.; Matthews, B. R.; Watson, K. G. *Aust. J. Chem.* **1990**, *43*, 2045–2062.
5. Hulsbos, E.; Marcus, J.; Brussee, J.; van der Gen, A. *Tetrahedron: Asymmetry* **1997**, *8*, 1061–1067.
6. Effenberger, F.; Hopf, M.; Ziegler, T.; Hudelmayer *J. Chem. Ber.* **1991**, *124*, 1651–1659.
7. Hayashi, M.; Yoshiga, T.; Nakatani, K.; Ono, K.; Oguni, N. *Tetrahedron* **1994**, *50*, 2821–2830.
8. (a) Kruse, C. G. In *Chirality in Industry*; Collins, A. N.; Sheldrake, G. N.; Crosby, J. Eds.; Wiley: New York; 1992; p 279–299. (b) Brussee, J.; van der Gen, A. In *Stereoselective Biocatalysis*; Patel, R., Ed., Marcel Dekker: New York; 1999, in press.
9. (a) Zandbergen, P.; van der Linden, J.; Brussee, J.; van der Gen, A. *Synth. Commun.* **1991**, *21*, 1387–1391. (b) Marcus, J.; Brussee, J.; van der Gen, A. *Eur. J. Org. Chem.* **1998**, 2513–2517.
10. Provided that the cyano group has priority over substituent R.
11. (a) Otten, P. A.; Davies, H. M.; van der Gen, A. *Tetrahedron Lett.* **1995**, *36*, 781. (b) Otten, P. A. *Horner–Wittig Reagents in Sulfur and Selenium Chemistry*, Ph.D. Thesis, Leiden University, 1996.
12. van den Nieuwendijk, A. M. C. H.; Warmerdam, E. G. J. C.; Brussee, J.; van der Gen, A. *Tetrahedron: Asymmetry* **1995**, *6*, 801–806.
13. Based on the coupling constant of the hydrogen atoms at the double bond formed. The observed value of 15–16 Hz is typical of an *E* double bond. No peaks belonging to the *Z* isomer could be observed. *E*-selectivity was expected since the reagents used have been shown to be *E*-selective. See: (a) Bottin-Strzalko, T. *Tetrahedron* **1973**, *29*, 4199. (b) Bottin-Strzalko, T.; Etemad-Moghadam, G.; Seyden-Penne, J. *Nouv. J. Chim.* **1982**, *7*, 155. (c) Etemad-Moghadam, G.; Seyden-Penne, J. *Synth. Commun.* **1984**, *14*, 565. (d) Etemad-Moghadam, G.; Seyden-Penne, J. *Tetrahedron* **1984**, *40*, 5153.