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# A stereoselective approach to optically active butenolides by Horner–Wadsworth–Emmons olefination reaction of α-hydroxy ketones

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**Abstract**—Di- and trisubstituted butenolides and tricyclic unsaturated lactones, of high enantiomeric excess were prepared via the efficient sequential esterification Horner–Wadsworth–Emmons reaction of enantiomerically enriched 2-hydroxy-substituted phenones and aromatic cyclic α-hydroxy ketones in good yield.


## 1. Introduction

Polysubstituted butenolides constitute as a class of compounds of high current interest due to their potential broad range of biological activities.[1] They can serve as the precursors for the synthesis of various natural products, including those bearing a chiral γ-lactone moiety.[2] As a consequence of butenolides importance, many methods have been devised for the butenolide unit preparation.[3] Among them, methodologies based on the intermediate hydroxy-substituted carbonyl compounds, such as the reactions of lactonization,[4] base catalyzed intramolecular condensation,[5] or Wittig olefination[6] have been applied with success. For the stereoselective synthesis of these target compounds[1c,2d,e,7] the asymmetric nucleophilic addition of trialkylsilyloxy furans to various electrophiles has been widely used.[7a,g,h] Also, approach to the optically active, γ-hydroxy-substituted butenolides, namely tetronic acids by intramolecular condensation reactions of accessible asymmetric α-hydroxy esters is well recognized in the literature.[2a,8] Nevertheless, the development of novel methods for the preparation of enantiomerically pure, or at least enantiomerically enriched butenolides is still an important goal in synthetic chemistry.

Recently, we elaborated the enantioselective synthesis of α-hydroxy ketones.[9] Our approach was based on the asymmetric catalytic oxidation of readily available enol phosphates by a chiral oxomanganese(III) salen complex. We have shown that the sense of asymmetric induction in this oxidation reaction depends on the substitution pattern of starting enol phosphates. Using this methodology both enantiomers of acyclic and cyclic α-hydroxy ketones **1** were obtained with high enantioselectivity up to 96% (Scheme 1).

So far only one synthesis of structures containing optically active butenolide moiety, where olefination step was accomplished by Horner–Wadsworth–Emmons (HWE) reaction of chiral α-hydroxy aldehydes, has been reported.[2c] Therefore, we decided to apply optically active α-hydroxy ketones **1**, easily obtained by our methodology, in the HWE reaction, with the purpose of the elaboration of general synthesis of chiral butenolides.

Herein, we report a stereoselective entry to enantiomerically enriched butenolides via a two-step procedure involving esterification of ketones **1** followed by an intramolecular-HWE reaction.

## 2. Results and discussion

Our initial investigations were conducted with enantiomerically enriched (*S*)-(−) and (*R*)-(+)-2-alkyl-2-hydroxy-phenones **1a–c** (see Table 1). Ketones **1a–c** were subjected to esterification with diethyl phosphonoacetic acid **3a**. Using

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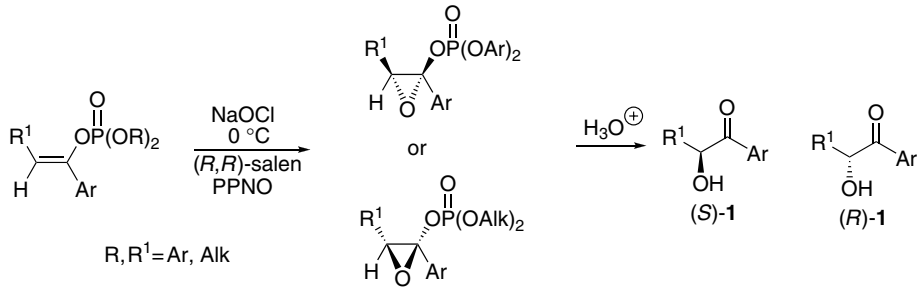



**Scheme 1.**

**Table 1.** Synthesis of optically active furanones **2** from α-hydroxy ketones **1** and phosphonates **3** or **5**[a]

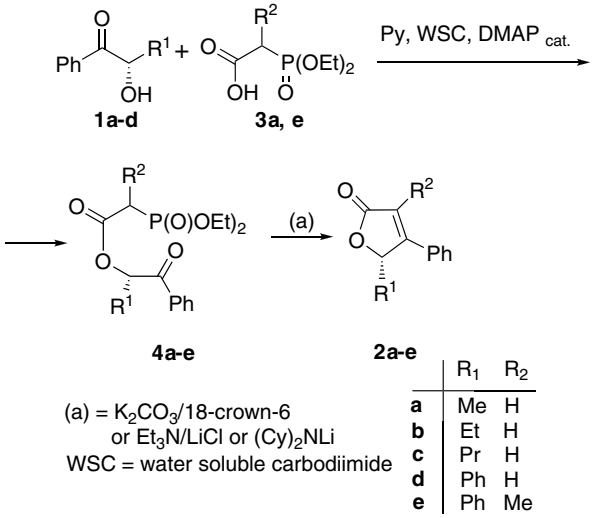
| Entry | $R^1$ | $R^2$ | Substrates | | ee[b] (%) of **1** | Route[a] | Product | ee[b] (%) | Yield[c] (%) |
|---|---|---|---|---|---|---|---|---|---|
| 1 | Me | H | (*S*)-(−)-**1a** | **3a** | 96 | A | (*S*)-(+)-**2a** | >99 | 76 |
| 2 | Et | H | (*S*)-(−)-**1b** | **3a** | 93 | A | (*S*)-(+)-**2b** | 94.0 | 75 |
| 3 | Pr | H | (*S*)-(−)-**1c** | **3a** | 88 | A | (*S*)-(+)-**2c** | 83.7 | 67 |
| 4 | Pr | H | (*R*)-(+)-**1c** | **3a** | 68 | A | (*R*)-(−)-**2c** | 67.3 | 61 |
| 5 | Pr | H | (*S*)-(−)-**1c** | **5** | 88 | B | (*S*)-(+)-**2c** | 76.5 | 35 |
| 6 | Et | H | (*S*)-(−)-**1b** | **5** | 93 | B[d] | (*S*)-(+)-**2b** | 88.8 | 60 |
| 7 | Ph | H | (*S*)-(+)-**1d** | **3a** | 83 | A[e] | (*S*)-(+)-**2d** | 74.0 | 50 |
| 8 | Ph | H | (*S*)-(+)-**1d** | **3a** | 83 | A[f] | (*S*)-(+)-**2d** | 63.3 | 89 |
| 9 | Ph | H | (*S*)-(+)-**1d** | **3a** | 83 | A[g] | (*S*)-(+)-**2d** | 76.0 | 25 |
| 10 | Ph | H | (*S*)-(+)-**1d** | **5** | 83 | B[h] | **6** | — | 30 |
| 11 | Ph | Me | (*S*)-(+)-**1d** | **3e** | 83 | A | (*S*)-(+)-**2e** | 59.0 | 40 |
| 12 | Ph | Me | (*S*)-(+)-**1d** | **3e** | 83 | A[i] | (*S*)-(+)-**2e** | 77.6 | 36 |

[a] Conditions: route A: base—$K_2CO_3$, 18-crown-6, 0 °C to +5 °C, 24 h; route B: base—$LiOH{\cdot}H_2O$, molecular sieves 4 Å, rt, 24 h.
[b] Determined by HPLC analysis (see Section 4) using racemic compounds as references.
[c] Isolated yield (not optimized).
[d] Conditions: 5 °C, 48 h.
[e] Conditions: −20 °C, 24 h.
[f] Base—$LiN(cyclohexyl)_2$, −100 °C, 1 h, warming to rt, 4 h.
[g] Base—$LiN(cyclohexyl)_2$, −100 °C, 2 h, quenching, warming to rt.
[h] Base—DBU/LiCl, −20 °C, 2 h; 5 °C, 7 h.
[i] Base—$Et_3N$/LiCl, −30 °C, 36 h.

water soluble carbodiimide (WSC) as a condensing agent in the presence of pyridine and catalytic amounts of DMAP,[6g] full conversion of **1a–c** into the desired esters **4a–c** was achieved. The next step of this synthesis involved an intramolecular-HWE reaction of **4a–c** in the presence of potassium carbonate and 18-crown-6 in toluene.[6g,10] Optically active 4-phenyl-5-alkylfuran-2-(5*H*)-ones **2a–c**, not reported in the literature, were obtained in good yields (Scheme 2, Table 1). The enantiomeric purity of **2a–c** was determined using HPLC chiral separation (Table 1, entries 1–4). According to HPLC analysis, these compounds were formed without the loss of enantiomeric purity. In the case of 4-phenyl-5-methylfuran-2-(5*H*)-one **2a** only one enantiomer was detected by chiral HPLC.

These promising results prompted us to apply the same procedure for the synthesis of optically active di- and trisubstituted 5-phenylfuranones **2d** and **2e**.

Ester **4d**, easily prepared from (*S*)-(+)-benzoin **1d** (83% ee) and phosphonoacetic acid **3a**, underwent an intramolecular-Horner–Wadsworth–Emmons reaction to give 4,5-diphenylfuran-2-(5*H*)-one **2d** in moderate yield. Due to the increased lability of the carbon stereogenic center of




**Scheme 2.**

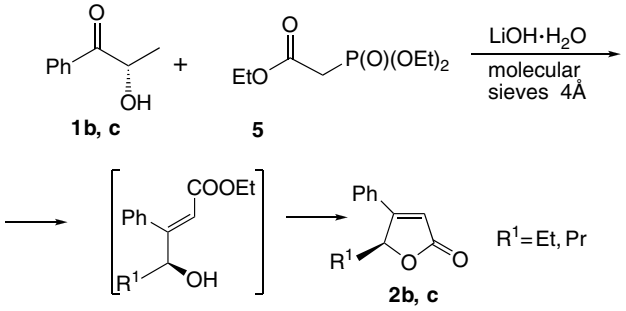
**4d** during **2d** formation, this reaction was carried out at lower temperature (−20 °C). However, even under such mild conditions, **2d** was formed with partial racemization

(74% ee) (Table 1, entry 7). To improve the enantiomeric excess and yield of **2d**, the modified reaction conditions were used. Use of the excess of $LiN(Cy)_2$[8b] under kinetically controlled conditions: −100 °C, 2 h, provided furanone **2d** with 76% ee and 25% yield and unreacted ester **4d** in 60% yield with 75% ee. The same reaction was carried out under thermodynamically controlled conditions, which means generation of an anion at −100 °C, and then warming the mixture to room temperature, afforded **2d** in high yield of 89% with 63.3% ee (Table 1, entries 8 and 9).

Methyl-substituted phosphonoacetic acid **3e** was used as a reagent for the synthesis of trisubstituted furanone. Since over the course of the esterification of (*S*)-(+) α-hydroxy ketone **1d** with acid **3e**, a new stereogenic center is formed, this reaction afforded a mixture of two diastereoisomers of ester **4e** inseparable by chromatography. However, this additional center is not important as it disappears after the HWE reaction. The conversion of **4e** to 3-methyl-4,5-diphenylfuran-2-(5*H*)-one **2e** was accomplished by this reaction performed in the presence of $K_2CO_3$/18-crown-6 or $Et_3N/LiCl$[6f,11] base systems. Furanone **2e** was formed in moderate yields and with moderate to good enantiomeric excess (Scheme 2, Table 1, entries 11 and 12). An attempt to use $LiN(Cy)_2$ for the synthesis of trisubstituted furanone **2e** from the corresponding ester **4e** failed. Starting ester **4e** was recovered with partial racemization as indicated by the measurement of the value of its optical rotation.

The enantiomeric excess values of the starting esters **4d** and **4e**, determined by chiral HPLC, were the same as those of benzoin **1d** used for their synthesis. It seems that partial racemization of esters **4d** and **4e** occurring under HWE reaction conditions is responsible for the loss of enantiomeric purity of products **2d** and **2e**.

It was of interest to compare the results of the synthesis of optically active butenolides **2** (Scheme 2) with those obtained by a 'reversed' procedure, in which the lactonization is preceded by HWE reaction of optically active α-hydroxy ketones **1** with stabilized lithium phosphonate **5** (Scheme 3).




**Scheme 3.**

Therefore, we performed the reaction of **1c** (88% ee) with **5** at room temperature using LiOH and activated 4 Å molecular sieves, according to Bonadies–Scettri[6d] (rt, 24 h) and obtained furanone **2c** in moderate yield with the partial racemization (76.5% ee) (Table 1, entry 5, route B). The reaction of ketone **1b** (93% ee) with **5**, carried out under slightly different conditions (5 °C, 48 h), provided the desired furanone **2b** with 88.8% ee in good yield (60%) (Table 1, entry 6). The other olefination procedure (LiCl, DBU, −20 °C up to 5 °C, 9 h), recommended for use with base-sensitive carbonyl compounds (mainly aldehydes),[11] was applied to the reaction of (*S*)-(+)-benzoin **1d** with phosphonate **5**. Unexpectedly, the desired furanone **2d** was not formed. Among the unidentified products γ-keto-α,β-unsaturated ester **6** (Fig. 1) and recovered benzoin **1d** were found, probably as a result of the disproportionation reaction of benzoin and consecutive reactions that occurred under the reaction condition.[12]

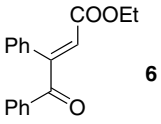
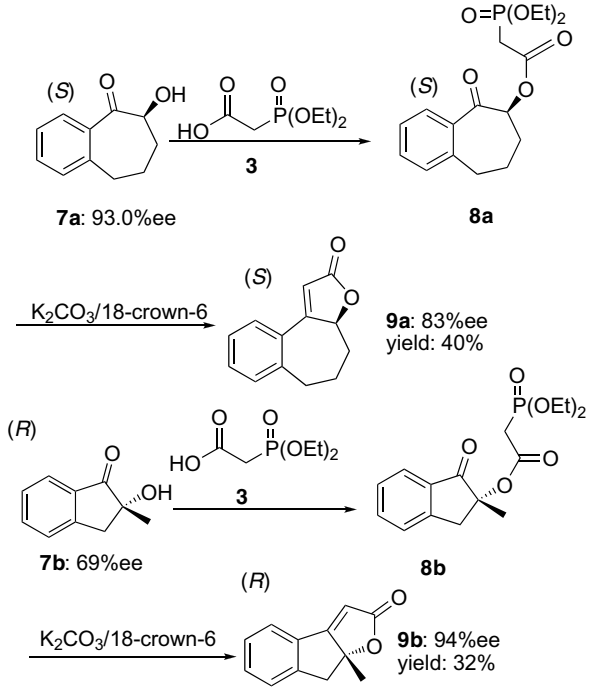



**Figure 1.**

To determine the scope of intramolecular-Horner–Wadsworth–Emmons reaction in the synthesis of optically active substituted butenolides, we studied the conversion of several other α-hydroxy ketones into the corresponding butenolides. Since the presence of a lactone functionality fused to a carbocyclic framework is common in biologically active natural products, for example, in the novel heritol family of the cadinane sesquiterpenes class,[13] we applied structurally related, optically active α-hydroxy ketones: 2-hydroxy benzosuberone **7a** and 2-hydroxy-2-methyl indanone **7b**, previously prepared by us.[9b] The preliminary results obtained are presented in Scheme 4.




**Scheme 4.**

Intramolecular Horner–Emmons reactions of esters **8a** and **8b**, obtained from ketones **7a** and **7b** by standard procedure, proceed cleanly but afford tricyclic unsaturated γ-lactones **9a** and **9b** in moderate to poor yields together with recovered starting esters **8**. The enantiomeric excesses of **7** and **9** are presented in Scheme 4. As indicated by chiral HPLC, compound **9a** was formed with good enantiomeric excess and indanone derivative **9b** in high enantiomeric excess with regard to that of substrate **7b**. This is probably the result of the recrystallization.

Further investigation concerning the scope of our approach in the synthesis of naturally occurred tricyclic lactones will be continued.

## 3. Conclusion

In conclusion, we have demonstrated that the intramolecular-Horner–Wadsworth–Emmons reaction can be successfully employed in the synthesis of enantiomerically enriched di- and trisubstituted butenolides as well as tricyclic ones starting from the corresponding α-hydroxy ketones of known enantiomeric purity. Presented by us procedure for the preparation of these target compounds, where the esterification of α-hydroxy ketones precedes the HWE step and seems to be more effective in terms of the enantiomeric purity and yield than an alternative route. Therefore, the conversion of chiral α-hydroxy ketones to optically active butenolides of known absolute configuration via intramolecular-HWE reaction can be supplementary to the previously reported methods using intramolecular Claisen condensation.[8]

## 4. Experimental

$^{1}H$, $^{13}C$, and $^{31}P$ NMR spectra were recorded on a Bruker AC 200 Spectrometer at 200.13, 50.32, and 81.02 MHz, respectively (using deuterochloroform as solvent), unless otherwise noted. IR spectra were measured on an Ati Mattson Infinity FTIR 60. MS spectra (CI and HRMS) were recorded on a Finnigan MAT 95 spectrometer. Melting points were measured with PHMK Boetius (VEB Analytik Dresden) apparatus. Optical rotation values were measured in 100 mm cell on Perkin–Elmer 241 MC under Na lamp radiation. The enantiomer ratios were determined by HPLC analysis on the commercially available column Chiracel OD, Chiralpak AS, or Chirobiotic T under condition specified.

All the reactions were carried out using anhydrous conditions and under an atmosphere of dry argon. Chemicals and solvents were obtained from commercial sources. Solvents and some of the chemicals were dried (drying reagents in brackets) and distilled prior to use: tetrahydrofuran and toluene (Na/benzophenone ketyl), acetonitrile (NaH), dichloromethane ($P_2O_5$), triethylamine ($CaH_2$), dicyclohexylamine ($CaH_2$). LiCl was dried in vacuo (0.5 torr, 24 h). Diethyl carboxymethanephosphonate **3a**[14] and diethyl carboxyethane phosphonate **3e**[15] were prepared according to the reported procedure. Activated molecular sieves 4 Å were prepared as reported.[16] Chromatographic purification was performed on silica gel columns (Merck, Kieselgel 70–230 mesh) with indicated eluent. All racemic and optically active α-hydroxy ketones **1** and **7** were prepared as described.[9] Racemic esters **4a**–**e**, **8a**,**b**, and furanones **2a**–**e** and tricyclic unsaturated lactones **9a**,**b** were prepared according to the procedure described for enantiomerically enriched compounds **2**, **4**, **8**, and **9**. Products **2**, **4**, **8**, and **9** were characterized by the comparison of their data with those of known racemic samples or by their spectral data.

### 4.1. Esterification of α-hydroxy ketones 1 and 7 by phosphonoacetic acid 3a or phosphonopropionic acid 3e. Synthesis of 4a as a general procedure

**4.1.1. (*S*)-(−)-1-Methyl-2-oxo-2-phenylethyl(diethoxyphosphoryl)acetate 4a.**[6f] To a cooled (0 °C) solution of (*S*)-(−)-2-hydroxy-1-phenyl-1-propan-1-one **1a** $[\alpha]_D^{20} = -82.7$ (*c* 3.6, $CHCl_3$), 96% ee (0.04 g, 0.26 mmol) in dichloromethane (2.5 mL) were added pyridine (21 μL, 0.26 mmol), 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (WSC) (0.1 g, 0.53 mmol), 4-dimethylaminopyridine (DMAP) (0.0096 g, 0.078 mmol). Then, a solution of diethylphosphonoacetic acid **3a** (0.104 g, 0.53 mmol) in $CH_2Cl_2$ (1 mL) was added by syringe. The mixture was stirred for 24 h at 5 °C and diluted with $CH_2Cl_2$ (5 mL). Next, the solution was washed with 0.1 M aqueous HCl to pH 5–6, extracted with additional $CH_2Cl_2$ (3 × 5 mL), organic extracts were washed with brine, dried ($MgSO_4$), and evaporated in vacuo to afford crude **4a** as a colorless oil (0.0818 g, 96%), $[\alpha]_D^{20} = -30.1$ (*c* 2.8, $CHCl_3$), $R_f = 0.29$ (hexane/EtOAc = 1.5:1); $^{1}H$ NMR ($CDCl_3$): $\delta$ 1.32 (t, $J = 7.0$ Hz, 6H, $OCH_2CH_3$), 1.54 (d, $J = 7.0$ Hz, 3H, $CH_3$), 3.06 (d(AB), $^{2}J_{HP} = 21.6$ Hz, $^{2}J_{AB} = 14.5$ Hz, 2H, $CH_2P$), 4.16 (quint, $^{3}J_{HP} = 7.1$ Hz, $^{3}J_{HH} = 7.1$ Hz, 4H, $OCH_2CH_3$), 6.01 (q, $J = 7.0$ Hz, 1H, OCH), 7.43–7.62 (m, 3H, $C_6H_5$), 7.93 (d, $J = 7.0$ Hz, 2H, $C_6H_5$); $^{13}C$ NMR ($CDCl_3$): $\delta$ 11.5 ($CH_3$), 15.3 ($OCH_2CH_3$), 35.9 (d, $^{1}J_{CP} = 135.2$ Hz, $CH_2P$), 62.9 ($OCH_2CH_3$), 76.5 (CHO), 127.3 ($C_6H_5$), 128.4 ($C_6H_5$), 129.5 ($C_6H_5$), 134.1 (C-*ipso*), 168.3 (d, $^{2}J_{CP} = 6.2$ Hz, OC(O)), 188.5 ($C_6H_5CO$); $^{31}P$ NMR ($CDCl_3$): $\delta$ 19.1; MS (CI): *m*/*z* % 329 [M+H] (100) (lit.[6f] $^{1}H$ NMR, IR, elemental analysis).

**4.1.2. (*S*)-(−)-1-Benzoylpropyl(diethoxyphosphoryl)acetate 4b.** From (*S*)-(−)-2-hydroxy-1-phenyl-1-butan-1-one **1b** $[\alpha]_D^{20} = -29.3$ (*c* 1.1, $CHCl_3$) (93% ee) (0.047 g, 0.29 mmol), ester **4b** was obtained as a light yellow oil (0.088 g, 90%), $[\alpha]_D^{20} = -16.6$ (*c* 0.2, $CHCl_3$), $R_f = 0.35$ (hexane/EtOAc = 1.2:1); IR (film) $\nu_{max}$ ($cm^{-1}$) 2971, 2906, 2870, 1722, 1595, 1512, 1449, 1230, 1212, 1118, 1027, 786; $^{1}H$ NMR ($CDCl_3$): $\delta$ 1.02 (t, $J = 7.4$ Hz, 3H, $CH_3$), 1.32 (t, $J = 7.0$ Hz, 6H, $OCH_2CH_3$), 1.78–2.00 (m, 2H, $CH_2$), 3.07 (d(AB), $^{2}J_{HP} = 21.5$ Hz, $J_{AB} = 14.5$ Hz, 2H, $CH_2P$), 4.17 (quint, $^{3}J_{HP} = 7.1$ Hz, $^{3}J_{HH} = 7.1$ Hz, 4H, $OCH_2CH_3$), 6.01 (ddd, $J = 5.9$, 4.4, 1.3 Hz, 1H, OCH), 7.31–7.61 (m, 3H, $C_6H_5$), 7.91 (d, $J = 6.8$ Hz, 2H, $C_6H_5$); $^{13}C$ NMR ($CDCl_3$): $\delta$ 9.9 ($CH_3$), 15.4 ($OCH_2CH_3$), 28.3 ($CH_2$), 35.5 (d, $^{1}J_{CP} = 135.2$ Hz, $CH_2P$), 62.8 ($OCH_2CH_3$), 78.2 (CHO), 127.7, 128.8, 129.8, ($C_6H_5$), 133.6 (C-*ipso*), 167.3 (d, $^{2}J_{CP} = 5.9$ Hz, OC(O)), 191.8 ($C_6H_5C{=}O$); $^{31}P$

NMR ($CDCl_3$): $\delta$ 19.2; MS (CI): $m/z$ % 343 [M+H] (100); HRMS $m/z$ calcd for $C_{16}H_{23}O_6P$ 342.1232; found 342.1230. HPLC analysis: Chiracel OD, 7% (*i*-PrOH/EtOH 4:1) in hexane, 0.5 mL/min; $t_R$[min] 19.6 (*R*), $t_R$[min] 25.6 (*S*), ee = 93%.

**4.1.3. (*S*)-(−)-1-Benzoylbutyl(diethoxyphosphoryl)acetate 4c.** From (*S*)-(−)-2-hydroxy-1-phenyl-1-pentan-1-one **1c** $[\alpha]_D^{20} = -19.9$ (*c* 2.4, $CHCl_3$) (88% ee) (0.042 g, 0.24 mmol), ester **4c** was obtained as a light yellow oil (0.079 g, 93%). $[\alpha]_D^{20} = -11.7$ (*c* 0.17, $CHCl_3$), $R_f = 0.4$ (hexane/EtOAc = 1.2:1); IR (film) $\nu_{max}$ ($cm^{-1}$) 3063, 2997, 2882, 1771, 1643, 1501, 1440, 1270, 1079, 954, 777; $^1$H NMR ($CDCl_3$): $\delta$ 0.94 (t, $J = 7.3$ Hz, 3H, $CH_3$), 1.33 (t, $J = 7.0$ Hz, 6H, $OCH_2CH_3$), 1.42–1.49 (m, 2H, $CH_2$), 1.85 (q, $J = 6.5$ Hz, 2H, $CH_2$), 3.08 (dd(AB), $^2J_{HP} = 21.5$ Hz, $J_{AB} = 14.5$ Hz, 2H, $CH_2P$), 4.17 (quint, $^3J_{HP} = 7.5$ Hz, $^3J_{HH} = 7.5$ Hz, 4H, $OCH_2CH_3$), 5.92 (t, $J = 6.3$ Hz, 1H, OCH), 7.43–7.59 (m, 3H, $C_6H_5$), 7.92 (d, $J = 7.1$ Hz, 2H, $C_6H_5$); $^{13}$C NMR ($CDCl_3$): $\delta$ 10.9 ($CH_3$), 16.3 ($OCH_2CH_3$), 18.2 ($CH_2$), 28.1 ($CH_2$), 35.0 (d, $^1J_{CP} = 133.7$ Hz, $CH_2P$), 62.7 ($OCH_2CH_3$), 73.5 (CHO), 128.4 ($C_6H_5$), 128.9 ($C_6H_5$), 129.6 ($C_6H_5$), 133.6, (C-*ipso*), 163.3 (d, $^2J_{CP} = 6.0$ Hz, OC(O)), 199.0 ($C_6H_5C{=}O$); $^{31}$P NMR ($CDCl_3$): $\delta$ 19.3; MS (CI): $m/z$ % 357 [M+H] (100); HRMS $m/z$ calcd for $C_{17}H_{25}O_6P$ 356.1388; found 356.1385. HPLC analysis: Chiracel OD, 7% (*i*-PrOH/EtOH 4:1) in hexane, 0.5 mL/min; $t_R$[min] 17.2 (*R*), $t_R$[min] 23.4 (*S*), ee = 85%.

**4.1.4. (*R*)-(+)-1-Benzoylbutyl(diethoxyphosphoryl)acetate 4c.** From (*R*)-(+)-2-hydroxy-1-phenyl-1-pentan-1-one **1c** $[\alpha]_D^{20} = +17.3$ (*c* 1.3, $CHCl_3$) (68% ee) (0.027 g, 0.15 mmol), ester **4c** was obtained as a light yellow oil (0.046 g, 87%). $[\alpha]_D^{20} = +5.0$ (*c* 1.0, $CHCl_3$).

**4.1.5. (*S*)-(+)-2-Oxo-1,2-diphenylethyl(diethoxyphosphoryl)acetate 4d.** From (*S*)-(+)-2-hydroxy-1,2-diphenylethanone **1d** $[\alpha]_D^{20} = +138.4$ (*c* 0.25, $CHCl_3$) (83% ee) (0.048 g, 0.23 mmol), ester **4d** was obtained as a yellow oil (0.077 g, 86%). $[\alpha]_D^{20} = +73.5$ (*c* 0.21, $CHCl_3$), $R_f = 0.35$ (hexane/EtOAc = 1.3:1); IR (film) $\nu_{max}$ ($cm^{-1}$) 2958, 2916, 2849, 1702, 1650, 1500, 1261, 1088, 1029, 801; $^1$H NMR ($CDCl_3$): $\delta$ 1.25, 1.27 (2 × t, $J = 7.0$ Hz, 6H, $OCH_2CH_3$), 3.12 (dd(AB), $^2J_{HP} = 20.2$ Hz, $J_{AB} = 14.6$ Hz, 2H, $CH_2P$), 4.12, 4.13 (2 × quint, $^3J_{HP} = 7.1$ Hz, $^3J_{HH} = 7.1$ Hz, 4H, $OCH_2CH_3$), 6.89 (s, 1H, OCH), 7.32–7.62 (m, 8H, $C_6H_5$), 7.91 (d, $J = 7.8$ Hz, 2H, $C_6H_5$); $^{13}$C NMR ($CDCl_3$): $\delta$ 16.3 ($OCH_2CH_3$), 33.9 (d, $^1J_{CP} = 134.6$ Hz, $CH_2P$), 62.8 ($OCH_2CH_3$), 78.5 (CHO), 128.7 ($C_6H_5$), 128.8 ($C_6H_5$), 129.1 ($C_6H_5$), 129.4 ($C_6H_5$), 133.2 (C-*ipso*), 134.5 (C-*ipso*), 165.3 (d, $^2J_{CP} = 5.9$ Hz, OC(O)), 192.98 ($C_6H_5C{=}O$); $^{31}$P NMR ($CDCl_3$): $\delta$ 18.8; MS (CI): $m/z$ % 391 [M+H] (100); HRMS $m/z$ calcd for $C_{20}H_{23}O_6P$ 390.1232; found 390.1237. HPLC analysis: Chiracel OD, 7% (*i*-PrOH/EtOH 4:1) in hexane, 0.5 mL/min; $t_R$[min] 30.3 (*R*), $t_R$[min] 38.2 (*S*), ee = 82%.

**4.1.6. (+)-2-Oxo-1,2-diphenylethyl-2-(diethoxyphosphoryl) propanate 4e.** From (*S*)-(+)-2-hydroxy-1,2-diphenyl-ethanone **1d** $[\alpha]_D^{20} = +138.4$ (*c* 0.25, $CHCl_3$) (83% ee) (0.032 g, 0.15 mmol), ester **4e** (two diastereoisomers in a ratio of 1:1.4) was obtained as light yellow crystals, mp 171–173 °C, (0.058 g, 96%). $[\alpha]_D^{20} = +78.2$ (*c* 1.28, $CHCl_3$); $R_f = 0.48$ (hexane/EtOAc = 1.1:1); IR (film) $\nu_{max}$ ($cm^{-1}$) 2962, 2857, 1740, 1696, 1260, 1093, 1044, 1022, 800; $^1$H NMR ($CDCl_3$): $\delta$ 1.19, 1.22, 1.27 (3 × t, $J = 7.1$ Hz, 6H, $OCH_2CH_3$), 1.47, 1.56 (2 × t, $J = 6.9$ Hz, 3H, $CH_3$), 3.14, 3.25 (2 × dq, $^2J_{HP} = 22.6$ Hz, $^3J_{HH} = 7.2$ Hz, 1H, CHP), 4.08, 4.09 (2 × dq, $^3J_{HP} = 9.5$ Hz, $^3J_{HP} = 6.8$ Hz, $^3J_{HH} = 7.2$ Hz, 4H, $OCH_2CH_3$), 6.88, 6.89 (2 × s, 1H, OCH), 7.30–7.55 (m, 8H, $C_6H_5$), 7.91 (d, $J = 7.2$ Hz, 2H, $C_6H_5$); $^{13}$C NMR ($CDCl_3$): $\delta$ 11.6 (major isomer, d, $^2J_{CP} = 6.1$ Hz, $CH_3$), 11.8 (minor isomer, d, $^2J_{CP} = 6.0$ Hz, $CH_3$), 16.1 (major isomer, d, $^3J_{CP} = 6.2$ Hz, $OCH_2CH_3$), 16.2 (minor isomer, d, $^3J_{CP} = 6.1$ Hz, $OCH_2CH_3$), 38.7 (major isomer, d, $^1J_{CP} = 133.9$ Hz, CHP), 39.3 (minor isomer, d, $^1J_{CP} = 134.4$ Hz, CHP), 62.6 (major isomer, $OCH_2CH_3$), 62.7 (minor isomer, $OCH_2CH_3$), 78.1 (major isomer, CHO), 78.2 (minor isomer, CHO), 128.5 ($C_6H_5$), 128.6 ($C_6H_5$), 128.62 ($C_6H_5$), 128.7 ($C_6H_5$), 128.98 ($C_6H_5$), 129.0 ($C_6H_5$), 129.2 ($C_6H_5$), 129.3 ($C_6H_5$), 133.1 (C-*ipso*), 133.5 (C-*ipso*), 133.8 (C-*ipso*), 134.4 (C-*ipso*), 168.8 (major isomer, OC(O)), 169.3 (minor isomer, d, $^2J_{CP} = 6.0$ Hz, OC(O)), 192.9 (minor isomer, $C_6H_5C{=}O$), 193.3 (major isomer, $C_6H_5CO$); $^{31}$P NMR ($CDCl_3$): $\delta$ 23.1 ( 58%), 22.9 (42%); MS (CI): $m/z$ % 405 [M+H] (100), 211 (64), 197 (42), 195 (26); HRMS $m/z$ calcd for $C_{21}H_{25}O_6P$ 404.1388; found 404.1385. HPLC analysis: Chiracel OD, 7% (*i*-PrOH/EtOH = 4:1) in hexane, 0.5 mL/min; major isomer $t_R$[min] 14.4, $t_R$[min] 18.2, ee = 75%; minor isomer $t_R$[min] 17.5, $t_R$[min] 28.2, ee = 85%.

**4.1.7. (*S*)-(−)-5-Oxo-6,7,8,9-tetrahydro-5*H*-benzo[7]annulen-6-yl 2-(diethoxyphosphoryl)acetate 8a.** From (*S*)-(+)-6,7,8,9-tetrahydro-6-hydroxy-5*H*-benzocyclohepten-5-one **7a** $[\alpha]_D^{20} = +44.2$ (*c* 4.4, $CHCl_3$) (94% ee) (0.096 g, 0.54 mmol), ester **8a** was obtained as a dark yellow oil, (0.174 g, 91%). $[\alpha]_D^{20} = -2.05$ (*c* 1.4, $CHCl_3$); $R_f = 0.3$ (hexane/EtOAc = 1.3:1); IR (film) $\nu_{max}$ ($cm^{-1}$) 2923, 2871, 1742, 1650, 1504, 1452, 1255, 1129, 1027, 729; $^1$H NMR ($CDCl_3$): $\delta$ 1.33 (t, $J = 7.0$ Hz, 6H, $OCH_2CH_3$), 1.78–2.35 (m, 4H, $CH_2$), 2.96–3.0 (m, 2H, $CH_2$) 3.06 (dd(AB), $^2J_{HP} = 21.5$ Hz, $J_{AB} = 14.5$ Hz, 2H, $CH_2P$), 4.17 (quint, $^3J_{HP} = 7.3$ Hz, $^3J_{HH} = 7.3$ Hz, 4H, $OCH_2CH_3$), 5.45 (dd, $J = 10.4$, 5.6 Hz, 1H, OCH), 7.18–7.43 (m, 3H, Ar), 7.71 (d, $J = 7.4$ Hz, 1H, Ar); $^{13}$C NMR ($CDCl_3$): $\delta$ 16.2 ($OCH_2CH_3$), 21.5, 23.4, 29.0 ($CH_2$), 36.0 (d, $^1J_{CP} = 130.8$ Hz, $CH_2P$), 62.8 ($OCH_2CH_3$), 89.9 (CHO), 126.8, 127.3, 129.9, 134.2 ($C_6H_4$), 154.3 (d, $^2J_{CP} = 5.9$ Hz, OC(O)), 192.98 (C=O); $^{31}$P NMR ($CDCl_3$): $\delta$ 19.2; MS (CI): $m/z$ % 355 [M+H] (100), 197 (48); HRMS $m/z$ calcd for $C_{17}H_{23}O_6P$ 354.1232; found 354.1228.

**4.1.8. (*R*)-(−)-2-Methyl-1-oxo-2,3-dihydro-1*H*-inden-2-yl 2-(diethoxyphosphoryl)acetate 8b.** From (*R*)-(+)-2-hydroxy-2-methyl 1-indanone **7b** $[\alpha]_D^{20} = +19.8$ (*c* 3.1, $CHCl_3$) (69% ee) (0.04 g, 0.25 mmol), ester **8b** was obtained as a yellow oil, (0.049 g, 56%). $[\alpha]_D^{20} = -15.0$ (*c* 0.5, $CHCl_3$), $R_f = 0.36$ (hexane/EtOAc = 1.1:1); $^1$H NMR ($CDCl_3$): $\delta$ 1.34, 1.35 (2 × t, $J = 7.0$ Hz, 6H, $OCH_2CH_3$), 1.50 (s, 3H, $CH_3$), 3.01 (d(AB), $^2J_{HP} = 24.6$ Hz, $J_{AB} = 14.3$ Hz, 2H, $CH_2P$), 3.36 (d(AB), $J_{AB} = 16.9$ Hz, 2H, $CH_2$), 4.16, 4.18

(2 × quint, $^3J_{HP} = 7.2$ Hz, $^3J_{HH} = 7.2$ Hz, 4H, OC$H_2$CH$_3$), 7.38–7.43 (m, 2H, Ar), 7.58–7.65 (m, 1H, Ar), 7.77–7.81 (m, 1H, Ar); $^{13}$C NMR ($CDCl_3$): $\delta$ 16.3(OCH$_2$*C*H$_3$), 26.7 (CH$_3$), 33.0 (d, $^1J_{CP} = 135.8$ Hz, CH$_2$P), 42.1 (CH$_2$), 63.0 (O*C*H$_2$CH$_3$), 88.8 (C(Me)O), 126.2, 128.5, 129.2, 133.5, 147.4 (C$_6$H$_4$), 160.2 (d, $^2J_{CP} = 6.1$ Hz, OC(O)), 198.98 (C=O); $^{31}$P NMR ($CDCl_3$): $\delta$ 19.1; MS (CI): *m/z* % 341 [M+H] (100), 183 (40); HRMS *m/z* calcd for $C_{16}H_{21}O_6P$ 340.1075; found 340.1077. HPLC analysis: Chiracel OD, 2% (*i*-PrOH/EtOH 4:1) in hexane, 0.5 mL/min; $t_R$[min] 23.6 (*S*), $t_R$[min] 25.8 (*R*), ee = 69.4%.

### 4.2. Intramolecular HWE reaction of 4a–e and 8a,b. Synthesis of 2a as a general procedure

**4.2.1. (*S*)-(+)-5-Methyl-4-phenylfuran-2-(5*H*)-one 2a.**[17] To a cooled (0 °C) solution of crude (*S*)-(−)-**4a** (0.08 g, 0.24 mmol) in toluene (2 mL) were added 18-crown-6 (0.111 g, 0.308 mmol) and potassium carbonate (0.021 g, 0.15 mmol). The reaction mixture was stirred for 12 h at 5 °C under an argon atmosphere, then 18-crown-6 (0,0277 g, 0.077 mmol) was added. The mixture was stirred for 1.5 h and then $K_2CO_3$ (0.0053 g, 0.038 mmol) was added. The mixture was stirred for an additional 7 h, diluted with saturated brine, and extracted with ethyl acetate. The organic layers were dried. The solvent was evaporated and the crude product was purified by column chromatography (petroleum ether/EtOAc = 6:1). Product **2a** was obtained as white crystals mp 59–60.5 °C, (0.0317 g, 76%). $[\alpha]_D^{20} = +200$ (*c* 0.35, $CHCl_3$); $R_f = 0.51$ (hexane/EtOAc = 1.5:1); $^1$H NMR ($CDCl_3$): $\delta$ 1.54 (d, $J = 6.7$ Hz, 3H, CH$_3$), 5.57 (dq, $^3J_{HH} = 6.7$ Hz, $^4J_{HH} = 1.3$ Hz, 1H, OC*H*), 6.27 (d, $^4J_{HH} = 1.2$ Hz, 1H, C=CH), 7.48 (s, 5H, C$_6$H$_5$). HPLC analysis: Chiracel OD, 5% *i*-PrOH in hexane, 0.5 mL/min; $t_R$[min] 35.5 (*S*), ee >99% (lit. mp 50–53,[17a] 55–56,[17b] 57–58,[17c] 61–63,[6f] 62.5–63.5;[17d] $^1$H NMR;[17a,b] $^{13}$C NMR;[17d] IR[17a–c]).

**4.2.2. (*S*)-(+)-5-Ethyl-4-phenylfuran-2-(5*H*)-one 2b.** From (*S*)-(−)-**4b** (0.04 g, 0.128 mmol), **2b** was obtained as a colorless oil (0.018 g, 75%). $[\alpha]_D^{20} = +160$ (*c* 0.45, $CHCl_3$); $R_f = 0.68$ (hexane/EtOAc = 1.2:1); IR (film) $\nu_{max}$ (cm$^{-1}$) 2932, 2850, 1750, 1621,1049; $^1$H NMR ($CDCl_3$): $\delta$ 0.92 (t, $^3J_{HH} = 7.3$ Hz, 3H, CH$_3$), 1.66 (septet, $^3J_{HH} = 7.2$ Hz, 1H, CH$_2$), 2.11 (ddq, $^3J_{HH} = 7.5$, 4.0, 3.4 Hz, 1H, CH$_2$), 5.50 (ddd, $^3J_{HH} = 4.6$, $^3J_{HH} = 3.4$ Hz, $^4J_{HH} = 1.2$ Hz, 1H, OC*H*), 6.29 (d, $^4J_{HH} = 1.0$ Hz, 1H, C=CH), 7.47 (s, 5H, C$_6$H$_5$); $^{13}$C NMR ($CDCl_3$): $\delta$ 8.2 (CH$_3$), 26.3 (CH$_2$), 82.9 (CHO), 114.7 (*C*H=C(C$_6$H$_5$)), 127.1 (C$_6$H$_5$), 128.5 (C$_6$H$_5$), 129.2 (C$_6$H$_5$), 130.2 (CH=*C*(C$_6$H$_5$)), 131.2 (C-*ipso*), 167.3, 172.9 (C=O); MS (CI): *m/z* % 189 [M+H] (100); HRMS *m/z* calcd for $C_{12}H_{12}O_2$ 188.0837; found 188.0835. HPLC analysis: Chirobiotic T, 25% *i*-PrOH in hexane, 0.5 mL/min; $t_R$[min] 26.4 (*R*), $t_R$[min] 28.8 (*S*), ee = 94%.

**4.2.3. (*S*)-(+)-5-Propyl-4-phenylfuran-2-(5*H*)-one 2c.**[18] From (*S*)-(−)-**4c** (0.016 g, 0.045 mmol), **2c** was obtained as a semisolid (0.006 g, 67%). $[\alpha]_D^{20} = +148$ (*c* 0.15, $CHCl_3$); $R_f = 0.72$ (hexane/EtOAc = 1.2:1); IR (film) $\nu_{max}$ (cm$^{-1}$) 2952, 2905, 2823, 1755, 1618, 1071; $^1$H NMR ($CDCl_3$): $\delta$ 0.91 (t, $^3J_{HH} = 7.1$ Hz, 3H, CH$_3$), 1.40–1.60 (m, 3H, CH$_2$), 1.82–2.05 (m, 1H, CH$_2$) 5.50 (dd, $^3J_{HH} = 4.4$ Hz, $^4J_{HH} = 1.1$ Hz, 1H, OC*H*), 6.27 (d, $^4J_{HH} = 1.2$ Hz, 1H, C=CH), 7.47 (s, 5H, C$_6$H$_5$); $^{13}$C NMR ($CDCl_3$): $\delta$ 13.7 (CH$_3$), 17.9 (CH$_2$), 35.6 (CH$_2$), 82.1 (CHO), 114.3 (*C*H=C(C$_6$H$_5$)), 127.1 (C$_6$H$_5$), 127.4 (C$_6$H$_5$), 129.2 (C$_6$H$_5$), 130.2 (CH=*C*(C$_6$H$_5$)), 131.2 (C-*ipso*), 168, 172.8 (C=O); MS (CI): *m/z* % 203 [M+H] (100); HRMS *m/z* calcd for $C_{13}H_{14}O_2$ 202.0994; found 202.0993. HPLC analysis: Chirobiotic T, 25% *i*-PrOH in hexane, 0.5 mL/min; $t_R$[min] 20.9 (*R*), $t_R$[min] 23.7 (*S*), ee = 83.7%.

**4.2.4. (*R*)-(−)-5-Propyl-4-phenylfuran-2-(5*H*)-one 2c.**[18] From (*R*)-(+)-**4c** (0.037 g, 0.1 mmol), **2c** was obtained as a semisolid (0.012 g, 61%). $[\alpha]_D^{20} = -100$ (*c* 0.36, $CHCl_3$). HPLC analysis: Chirobiotic T, 25% *i*-PrOH in hexane, 0.5 mL/min; $t_R$[min] 19.4 (*R*), $t_R$[min] 26.0 (*S*), ee = 67.3%.

**4.2.5. (*S*)-(+)-4,5-Diphenylfuran-2-(5*H*)-one 2d.**[3b] From the reaction with (*S*)-(+)-**4d** (0.05 g, 0.13 mmol), performed at −20 °C, **2d** was obtained as a white solid, mp 150 °C, (0.147 g, 50%). $[\alpha]_D^{20} = +101$ (*c* 0.1, $CHCl_3$); $R_f = 0.55$ (hexane/EtOAc = 1.3:1). HPLC analysis: Chiralpak AS, 20% (*i*-PrOH/EtOH = 4:1) in hexane, 0.5 mL/min; $t_R$[min] 37.2 (*R*), $t_R$[min] 56.8 (*S*), ee = 74% (lit. mp 151–153,[3b] 149,[19] 148;[20] $^1$H, $^{13}$C NMR;[3b] IR, MS[20]).

**4.2.6. (*S*)-(+)-3-Methyl-4,5-diphenylfuran-2-(5*H*)-one 2e.**[7e] From (+)-**4e** (mixture of diastereomers) (0.065 g, 0.16 mmol), **2e** was obtained as a white solid, mp 91–92 °C, (0.015 g, 40%). $[\alpha]_D^{20} = +102.5$ (*c* 0.16, $CHCl_3$); $R_f = 0.68$ (hexane/EtOAc = 1.1:1); $^1$H NMR ($CDCl_3$): $\delta$ 2.18 (d, $^5J_{HH} = 1.6$ Hz, 3H, CH$_3$), 6.20 (d, $^5J_{HH} = 1.6$ Hz, 1H, C=CH), 7.28–7.31 (m, 10 H, 2 × C$_6$H$_5$); MS (CI): *m/z* % 281 [M+H] (100). HPLC analysis: Chiralpak AS, 50% (*i*-PrOH/EtOH = 4:1) in hexane (50%), 0.5 mL/min; $t_R$[min] 11.6 (*S*), $t_R$[min] 17.4 (*R*), ee = 59%. (lit. mp 90 °C;[22] $^1$H, $^{13}$C NMR, IR[7e]).

**4.2.7. (*S*)-(−)-3a,4,5,6-Tetrahydro-2*H*-benzo[3,4]cyclohepta[1,2-*b*]furan-2-one 9a.**[13b,21] From (*S*)-(−)-**8a** (0.05 g, 0.138 mmol), **9a** was obtained as a white solid, mp 76 °C, (0.011 g, 40%). $[\alpha]_D^{20} = -186.5$ (*c* 0.17, $CHCl_3$); $R_f = 0.58$ (hexane/EtOAc = 1.3:1); $^1$H NMR ($CDCl_3$): $\delta$ 1.77 (q, $^3J_{HH} = 11.1$ Hz, 2H, CH$_2$), 2.73 (ddd, $^3J_{HH} = 15.6$, 13.2, 10.7 Hz, 2.5 H, CH$_2$), 2.94 (dd, $^3J_{HH} = 15$, 7.0 Hz, 1.5 H, CH$_2$), 4.99 (dd, $^3J_{HH} = 9.7$, 5.6 Hz, 1H, CHO) 6.12 (d, $^4J_{HH} = 1$ Hz, 1H, C=CH), 7.18–7.40 (m, 4H, Ar); $^{13}$C NMR ($CDCl_3$): $\delta$ 22.8, 23.4, 29.2 (CH$_2$), 84.5 (HCO), 110.3 (C=*C*H), 127.0, 128.3, 130.8, 133.1 (Ar), 139.0 (*C*=CH), 169.4 (C=O); MS (CI): *m/z* % 201 [M+H] (100). HPLC analysis: Chiralpack AS, 70% (*i*-PrOH/EtOH = 4:1) in hexane, 0.5 mL/min; $t_R$[min] 18.8 (*S*), $t_R$[min] 39.8 (*R*), ee = 83% (lit. mp 74 °C;[21] $^1$H NMR, IR, elemental analysis[21]).

**4.2.8. (*R*)-(+)-8a-Methyl-8,8a-dihydro-2*H*-inden[2,1-*b*]-furan-2-one 9b.** From (*R*)-(−)-**8b** (0.01 g, 0.027 mmol), **9b** was obtained as white crystals, mp 49 °C, (0.005 g, 32%). $[\alpha]_D^{20} = +14.0$ (*c* 0.2, $CHCl_3$); $R_f = 0.64$ (hexane/EtOAc = 1.1:1); IR (film) $\nu_{max}$ (cm$^{-1}$) 2810, 1705, 1632, 1491, 1202, 1080; $^1$H NMR ($CDCl_3$): $\delta$ 1.53 (s, 3H, CH$_3$),

3.09 (d(AB), $J_{AB} = 15.1$ Hz, 2H, $CH_2$), 5.96 (s, 1H, C=CH), 7.40–7.71 (m, 4H, Ar); $^{13}$C NMR ($CDCl_3$): $\delta$ 26.3 ($CH_3$), 42.9 ($CH_2$), 84.6 (C(Me)O), 111.8 (C=*C*H), 127.0, 128.3, 129.9, 132.8 ($C_6H_4$), 135.8 (*C*=CH), 170.5 (C=O); MS (CI): *m*/*z* % 187 [M+H] (100); HRMS *m*/*z* calcd for $C_{12}H_{10}O_2$ 186.0680; found 186.0681. HPLC analysis: Chiralpack AS, 70% (*i*-PrOH/EtOH = 4:1) in hexane (30%), 0.5 mL/min; $t_R$[min] 34.6 (*R*), $t_R$[min] 57.5 (*S*), ee = 94%.

### 4.3. Synthesis of 2d using $LiN(Cy)_2$

To a stirred solution of $LiN(Cy)_2$ (0.117 mmol) freshly prepared from $Cy_2NH$ and BuLi (2.0 M in hexane) in THF (1.5 mL), (*S*)-(+)-ester **4d** (0.0217 g, 0.056 mmol) in THF (1 mL) was added by syringe at −100 °C. The mixture was stirred at this temperature for 1 h and then allowed to warm to room temperature. Then 0.1 M HCl was added (5 mL), and the mixture was extracted with diethyl ether (3 × 5 mL), after which the organic layer was washed with brine, dried over $MgSO_4$. Evaporation followed by column chromatography (petroleum ether/EtOAc = 5:1) afforded pure (*S*)-(+)-**2d** as a white solid, mp 151 °C, (0.0117 g, 89%). $[\alpha]_D^{20} = +72.0$ (*c* 0.2, $CHCl_3$). HPLC analysis: Chiralpak AS, 20% (*i*-PrOH/EtOH = 4:1) in hexane, 0.5 mL/min; $t_R$[min] 45.5 (*R*), $t_R$[min] 66.7 (*S*), ee = 63.3%.

The reaction of (*S*)-(+)-ester **4d** in the presence of $LiN(Cy)_2$ was carried out at −100 °C for 2 h, after which it was quenched with 10% HCl (2 mL) and then allowed to warm to ambient temperature. An identical separation procedure yielded (*S*)-(+)-**2d** (25%), $[\alpha]_D^{20} = +141.0$ (*c* 0.2, $CHCl_3$), and remaining ester (*S*)-(+)-**4d** (60%), $[\alpha]_D^{20} = +70.4$ (*c* 1.2, $CHCl_3$). HPLC analysis for **2d**: Chiralpak AS, 90% (*i*-PrOH/EtOH = 4:1) in hexane (10%), 0.6 mL/min; $t_R$[min] 34.5 (*R*), $t_R$[min] 49.9 (*S*), ee = 76%. HPLC analysis for **4d**: Chiracel OD, 7% (*i*-PrOH/EtOH 4:1) in hexane, 0.5 mL/min; $t_R$[min] 30.7 (*R*), $t_R$[min] 38.9 (*S*), ee = 75.4%.

### 4.4. Synthesis of 2e using $Et_3N$/LiCl

To lithium chloride (0.012 g, 0.28 mmol) was added a solution of (+)-**4e** (mixture of diastereomers) (0.0573 g, 0.14 mmol) in THF (2 mL) at −10 °C. The mixture was stirred for 15 min at this temperature. Then, triethyl amine was added by syringe at −30 °C. Stirring was continued for 36 h at that temperature and the solution was filtered through a plug of $SiO_2$, washing with ethyl acetate. The filtrate was concentrated and the residue chromatographed using petroleum ether/EtOAc (5:1) to give (*S*)-(+)-**2e** as a solid, mp 91 °C, (0.012 g, 36%). $[\alpha]_D^{20} = +131.7$ (*c* 0.2, $CHCl_3$). HPLC analysis: Chiralpack AS, 50% (*i*-PrOH/EtOH = 4:1) in hexane, 0.5 mL/min; $t_R$[min] 12.1 (*S*), $t_R$[min] 19.1 (*R*), ee = 77.6%.

### 4.5. Sequential HWE-lactonization reaction of α-hydroxy ketones 1b, 1c, and 1d

To a suspension of activated 4 Å molecular sieves (0.5 g) in THF (3 mL), a solution of (*S*)-(−)-**1c** $[\alpha]_D^{20} = -19.9$ (*c* 2.4, $CHCl_3$) (88% ee) (0.057 g, 0.32 mmol) in THF (2 mL) and ester **5** (0.086 g, 0.38 mmol) in THF (2 mL) was added at room temperature. Then, solid $LiOH{\cdot}H_2O$ (0.016 g, 0.38 mmol) was added slowly (0.5 h). The mixture was stirred for 24 h, and then filtered through a plug of Florisil®, washing with ether. After evaporation of solvent, the residue was separated by column chromatography using petroleum ether/ethyl acetate (20:1 to 1:1, gradient elution) to give 0.022 g (35%) of **2c** together with 0.0517 g (60%) of recovered ester **5**. (*S*)-(+)-**2c**: $[\alpha]_D^{20} = +127.0$ (*c* 0.8, $CHCl_3$). HPLC analysis: Chirobiotic T, EtOH–*i*-PrOH/hexane (10:10:80), 0.5 mL/min; $t_R$[min] 13.6 (*R*), $t_R$[min] 15.2 (*S*); ee = 76.5%.

According to the modified procedure (5 °C, 48 h) from (*S*)-(−)-**1b** $[\alpha]_D^{20} = -29.3$ (*c* 1.1, $CHCl_3$) (93% ee) (0.051 g, 0.31 mmol) and **5** (0.084 g, 0.37 mmol), (*S*)-(+)-**2b** was obtained as a colorless oil, (0.035 g, 60%). $[\alpha]_D^{20} = +156.0$ (*c* 0.63, $CHCl_3$). HPLC analysis: Chirobiotic T, 25–100% *i*-PrOH in hexane, 0.5 mL/min; $t_R$[min] 15.4 (*R*), $t_R$[min] 16.9 (*S*), ee = 88.8%.

#### 4.5.1. 4-Oxo-3,4-diphenylbut-2-enoic acid ethyl ester 6.[23]

To a suspension of LiCl (0.006 g, 0.14 mmol) in THF (1 mL), a solution of **5** (0.027 g, 0.12 mmol) was added at 0 °C and the mixture was stirred for 15 min at this temperature. DBU (0.02 g, 0.13 mmol) was added and the mixture was stirred for an additional 15 min. Then, (*S*)-(+)-**1d** (0.025 g, 0.12 mmol), $[\alpha]_D^{20} = +138.4$ (*c* 0.25, $CHCl_3$) (83% ee), was added dropwise at −20 °C and the reaction mixture was stirred for 2 h at −20 °C and then 7 h at 5 °C. After quenching with 0.1 M HCl (5 mL), the mixture was diluted with diethyl ether (6 mL), aqueous layer was extracted with diethyl ether (2 × 4 mL), organic extract was dried with $MgSO_4$ and concentrated in vacuo. The residue was subjected to column chromatography using petroleum ether/ethyl acetate (25:1 to 1:2, gradient solution) to give ester **6** (0.01 g, 30%) together with recovered **1d** (0.01 g, 40%), $[\alpha]_D^{20} = +88.6$ (*c* 0.5, $CHCl_3$), and **5** (0.013 g, 50%). Compound **6**: (*E*/*Z* = 1.2/1), white solid, mp 88–89 °C; $R_f = 0.6$ (hexane/EtOAc = 1:1); $^1$H NMR ($CDCl_3$): $\delta$ 1.13, 1.15 (2 × t, $J = 7.1$ Hz, 3H, $OCH_2CH_3$), 4.11, 4.12 (2 × quint, $^3J_{HH} = 7.1$ Hz, 2H, $OCH_2CH_3$), 6.28 (s, 1H, C=CH, *E*), 6.52 (s, 1H, C=CH, *Z*), 7.37–7.60 (m, 8H, $C_6H_5$), 7.93–8.00 (m, 2H, $C_6H_5$); MS (CI): *m*/*z* % 281 [M+H] (100), 235 (10). HPLC analysis: Chiralpack AS, 5% (*i*-PrOH/EtOH: 4:1) in hexane, 0.5 mL/min; $t_R$[min] 12.1 (*Z*), $t_R$[min] 19.1 (*E*) (*E*/*Z* = 1.3:1) (lit. 91 °C;[23a] $^1$H NMR, IR, UV;[23a] $^1$H, $^{13}$C NMR, IR[23b]).

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