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# Bifuctional Amino-Squaramides Catalyzed Asymmetric Spiroannulation Cascades with Aliphatic β,γ-Unsaturated α-Keto Esters: Controlling an Aldehyde Enolate

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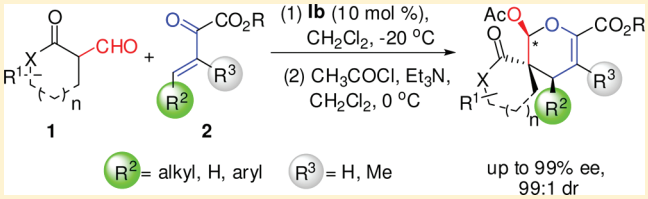
Supporting Information

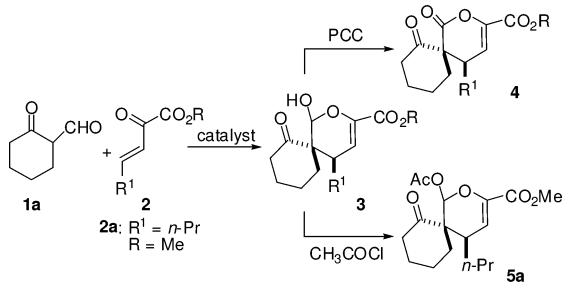
**ABSTRACT:** A quinidine-derived squaramide **Ib** catalyzed cyclization reaction of β-oxo aldehydes **1** and aliphatic or aromatic β,γ-unsaturated α-keto ester **2** is described. Using cyclic aldehyde substrates, this procedure provided a promising approach to a variety of spiro-3,4-dihydropyrans bearing three continuous quaternary and tertiary stereocenters in moderate to good yield with high stereoselectivities. Substituents on the nitrogen atoms of the squaramide moiety of the catalyst proved crucial to the reaction outcome. The stereochemistry of the three newly formed chiral centers (*trans*-selective) of the major product indicates a Micheal addition/hemiacetalization domino sequence for the present annulations.




3,4-Dihydropyrans are important structural motifs in a myriad of biologically interesting natural products and pharmaceutical targets; they also serve as versatile building blocks in organic synthesis.[1] Accordingly, asymmetric transformations enabling expeditious and stereoselective construction of dihydropyran derivatives are of particular importance in organic synthesis. Over the past few years, several elegant organocatalytic strategies based on a conjugate addition−triggered cascade reaction have been successfully developed for the asymmetric assembly of 3,4-dihydropyrans as well as their bicyclic derivatives.[2] However, the development of enatioselective synthesis of spiro-3,4-dihydropyrans having all-carbon quaternary stereocenters remains a challenging but yet scarcely explored task.[3]

We recently reported that $(DHQD)_2PYR$ (hydroquinidine-2,5-diphenyl-4,6-pyrimidinediyl diether) can catalyze the annulation reaction of cyclic β-oxo aldehydes **1** and aromatic β,γ-unsaturated α-keto esters **2** ($R^1$ = aryl), providing access to α-spiropyranones **4** with good to excellent yields and enantioselectivities after PCC oxidation (Scheme 1).[4] Unfortunately, this protocol appears to work only with aromatic α-keto esters, therefore limiting its organic synthesis application. To take on the challenge of controlling an aldehyde enolate in a Michael reaction,[5] especially for constructing a chiral all-carbon quaternary stereocenter,[6] we present herein a bifunctional amino-squaramides catalyzed approach to spirocyclic 3,4-dihydropyrans **5** from β-oxo aldehydes **1** and aliphatic or aromatic β,γ-unsaturated α-keto esters.[7]

**Scheme 1. Spiroannulation of Cyclic β-Oxo Aldehyde 1a and Aliphatic Unsaturated α-Keto Ester 2a**




Although a free hydroxyl group in quinidine, which typically participates in bifunctional catalysis, was found to be deleterious to the enatioselectivity of products **4** in our previous research, triggered by the overwhelming success of thioureas[8] as well as the recent advance of squaramides[9] in asymmetric organocatalysis, we envisaged that the replacement of the hydroxyl moiety of quinidine with a dual hydrogen-bond donor may facilitate less active aliphatic unsaturated α-keto esters to carry out this spiroannulation cascade. To verify this, we first examined the reaction of 2-oxocyclohexanecarbaldehyde (**1a**) and (*E*)-ethyl 2-oxohept-3-enoate (**2a**) in $CH_2Cl_2$ at room temperature, using $Et_3N$ as the base to generate an aldehyde enolnate. While no desired product was formed even in the presence of 1.0 equiv of $Et_3N$, to our delight, when squaramide **Ia** (10 mol %) was added, reaction of **2a** readily completed to give spirocyclic adduct **3a**, which afforded acetal **5a** in 85% yield with 98:2 dr upon subsequent treatment with acetyl chloride. On the other hand, after PCC oxidation, hemiacetal **3a** was converted to α-spiropyranone **4a** as a single diastereomer in 80% yield (Scheme 1).

Encouraged by these results, a set of bifunctional squaramide and thiourea catalysts (Figure 1) were evaluated instead of the combination of **Ia** and $Et_3N$ to catalyze the same cascade

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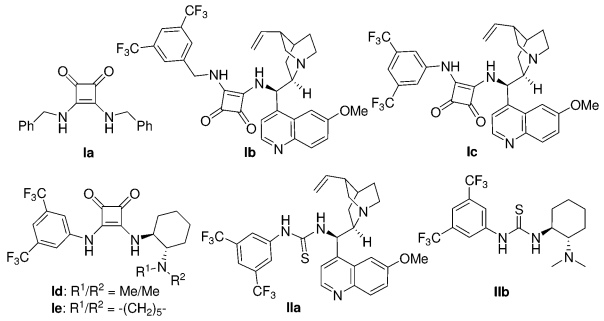



**Figure 1.** Structures of catalysts **I** and **II**.

reaction (Table 1). Both squaramides **Ib**–**Ie** and thioureas **IIa** and **IIb** could prompt the cyclization of **1a** with **2a** in $CH_2Cl_2$

**Table 1. Optimizing of the Cyclization Conditions**[a]

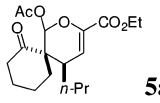
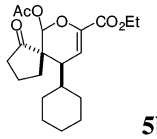
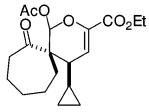
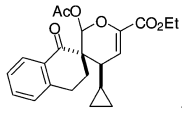
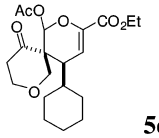
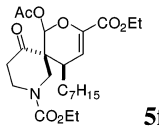
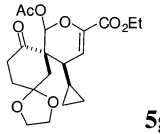
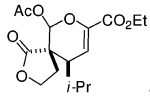
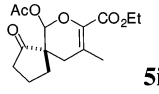
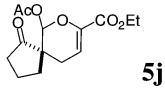
| entry | catalyst | solvent | time[b] (h) | 5a yield[c] (%) | 5a dr[d] | 5a ee[d] (%) |
|---|---|---|---|---|---|---|
| 1 | **Ib** | $CH_2Cl_2$ | 11 | 86 | 99:1 | 98 |
| 2 | **Ic** | $CH_2Cl_2$ | 12 | 24 | 99:1 | 98 |
| 3 | **Id** | $CH_2Cl_2$ | 15 | 81 | 99:1 | 96 |
| 4 | **Ie** | $CH_2Cl_2$ | 15 | 21 | 99:1 | 95 |
| 5 | **IIa** | $CH_2Cl_2$ | 36 | 17 | 99:1 | 97 |
| 6 | **IIb** | $CH_2Cl_2$ | 36 | 13 | 99:1 | 95 |
| 7 | **Ib** | THF | 14 | 86 | 87:13 | 80 |
| 8 | **Ib** | PhMe | 18 | 83 | 98:2 | 97 |
| 9[e] | **Ib** | $CH_2Cl_2$ | 36 | 84 | 99:1 | 98 |

[a]Reaction conditions: (1) **1a** (0.45 mmol), **2a** (0.30 mmol), and catalyst **I** or **II** (10 mol %) in solvent (3 mL) at −20 °C. (2) $Et_3N$ (0.75 mmol), $CH_3COCl$ (0.45 mmol) at 0 °C. [b]Time for the first cyclization step. [c]Isolated yield of **5a**. [d]Determined by chiral HPLC analysis. [e]3 mol % catalyst was used.

at −20 °C to give the hemiacetal **3a**, which after in situ acylation afforded **5a** in varying yields with excellent stereocontrol, respectively (Table 1, entries 1–6). However, the thiourea catalysts **IIa** and **IIb** did not function well for the conversion of $\alpha$-keto esters **2a**, resulting in low product yields (Table 1, entries 5 and 6). As for squaramide catalysts **Ib**–**Ie**, it was revealed that substitutents on the two nitrogen atoms of the squaramide unit play a key role in this reaction in terms of the product yield. Accordingly, squaramide **Ib** proved to be the most effective catalyst among those tested, giving access to **5a** in 86% yield with excellent stereoselectivity; however, catalysts **Ic** and **Ie**, bearing two rigid substitutents on the squaramide moiety, led to a less efficient reaction, presumably because of steric hindrance on efficient geometric arrangement of two substrates in transition state (Table 1, entries 2 and 4). With squaramide **Ib** as the catalyst, a brief survey of solvents identified $CH_2Cl_2$ to be somewhat better for this cyclization than toluene or THF (Table 1, entries 7 and 8). Catalyst loadings as low as 3 mol % could be utilized without compromising the selectivity, although a longer reaction time was required to complete the reaction (Table 1, entry 9).

With the optimal conditions in hand, the scope of this transformation is summarized in Table 2. Accordingly, aliphatic $\beta,\gamma$-unsaturated $\alpha$-keto esters are well-tolerated, rendering a variety of spiocyclic products **5** consistently as a pair of diastereomers in good yield (57–89%) with high enantioselectivities and excellent diastereoselectivities (Table 2, entries 1, 2, and 4–7). Notably, 2-oxobut-3-enoates ($R^2$ = H) were also

**Table 2. Asymmetric Synthesis of 5 from Aliphatic $\alpha$-Keto Esters 2**[a]

| entry | product **5** | time[b] (h) | yield[c] (%) | dr[d] | ee[d] (%) |
|---|---|---|---|---|---|
| 1 |  **5a** | 11 | 86 | 99:1 | 96 |
| 2 |  **5b** | 11 | 85 | 98:2 | 96 |
| 3 |  **5c** | 36 | 57 | 84:16 | 60 |
| 4 |  **5d** | 16 | 84 | 99:1 | 96 |
| 5 |  **5e** | 45 | 71 | 89:11 | 98 |
| 6 |  **5f** | 17 | 72 | 99:1 | >99 |
| 7 |  **5g** | 48 | 89 | 99:1 | >99 |
| 8 |  **5h** | 45 | 65 | 94:6 | 96 |
| 9 |  **5i** | 11 | 81 | 98:2 | 70 |
| 10 |  **5j** | 13 | 83 | >99:1 | 62 |

[a]Reaction conditions: (1) **1** (0.45 mmol), **2** (0.30 mmol), and catalyst **Ib** (10 mol %) in solvent (3 mL) at −20 °C. (2) $Et_3N$ (0.75 mmol), $CH_3COCl$ (0.45 mmol) at 0 °C for 2 h. [b]Time for the first cyclization step. [c]Yield of isolated product **5**. [d]Determined by chiral HPLC analysis.

suitable substrates, and high yield and dr values were attained. However, the lack of a substituent at the remote terminal site resulted in a less efficient stereocontrol in the Micheal addition step, thus providing the products with moderate enatioselectivities (Table 2, entries 9–10). Moreover, various cyclic $\beta$-oxo


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**Table 3. Asymmetric Synthesis of 7 from Aromatic α-Keto Esters 6[a]**


| entry | 1 | $R^1$/R | time[b] (h) | 7, yield[c] (%) | dr[d] | ee[d] (%) |
|---|---|---|---|---|---|---|
| 1 | **1a** | Ph/Me | 8 | **7a**, 81 | 99:1 | 96 |
| 2 | **1b** | 4-MeO$C_4H_6$/Me | 11 | **7b**, 83 | >99:1 | 94 |
| 3 | **1b** | 2-Me$C_4H_6$/Et | 13 | **7c**, 78 | 97:3 | 98 |
| 4 | **1b** | 4-F$C_4H_6$/Me | 7 | **7d**, 87 | 98:1 | 97 |
| 5 | **1b** | 2-furyl/Et | 15 | **7e**, 68 | 98:2 | 93 |

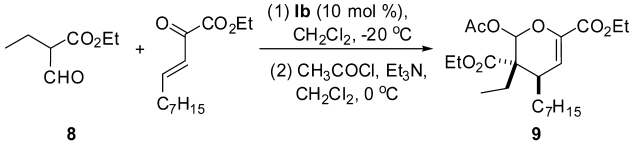
[a]Reaction conditions: (1) **1** (0.45 mmol), **6** (0.30 mmol), and catalyst **Ib** (10 mol %) in solvent (3 mL) at −20 °C. (2) $Et_3N$ (0.75 mmol), $CH_3COCl$ (0.45 mmol) at 0 °C. [b]Time for the first cyclization step. [c]Yield of isolated product **7**. [d]Determined by chiral HPLC analysis.

aldehydes were reacted with aliphatic α-keto esters to furnish the targeted heterocyclic compounds in good yields and high ee-values up to 99%, except seven-membered substrate was only in 57% yield with 60% ee and 84:16 dr (Table 2, entry 3). Substituents and heteroatom could be introduced onto the six-membered scaffolds without considerably affecting stereoinduction (Table 2, entries 4−7). In addition to ketone substrates, the cyclization of a lactone also proceeded smoothly, after an in situ acetylation, affording the desired **5h** in 65% yield with 96% ee and 94:6 dr (Table 2, entry 8).

Pleasingly, aromatic β,γ-unsaturated α-keto esters **6** with various steric and electronic properties were tolerated by the optimum catalyst **Ib** (Table 3). Use of either electron-withdrawing or electron-donating groups on the aryl moiety had virtually no effect on the cyclization cascade, leading to the formation of products **7** in either case in good yield. Indeed, the substitution pattern of the arene had little effect on the enantioselectivity, although the reactivity of the reaction may be affected a little (Table 3, 1−4). Additionally, furan-substituted ester had also successfully been employed in this process, albeit requiring an extended reaction time to obtain **7e** in acceptable yield with good diastereo- and enantioselectivity (Table 2, entry 5).

In an attempt to broaden the substrate scope for constructing an all-carbon quaternary stereocenter, acyclic aldehyde **8** with an ester substituent at the α-position was examined, as shown in Scheme 2. Under the optimized reaction conditions, the

**Scheme 2. Synthesis of 3,4-Dihydropyran Employing Acyclic Aldehyde 8**




desired 3,4-dihydropyran **9** was obtained in 67% yield and with only 57:43 dr. Fortunately, the enatioselectivties of the two diastereomers of **9** were as good as 96 and 88%, respectively.

The structure and configuration of the major enantiometric isomer was assigned by a single-crystal X-ray analysis of (−)-**5d**.[10] Mechanically, this stereochemical outcome, in which the three newly formed chiral centers of **5d** are arranged in a *trans*-configuration, probably excludes an inverse electron-demand hetero-Diels−Alder reaction[11] and indicates a Micheal addition-hemiacetalization sequence for the present procedure. Accordingly, a plausible transition state model for the Micheal addition leading to the formation of **5d** is shown here (Figure 2). It is proposed that α-keto ester is bonded to the squaramide

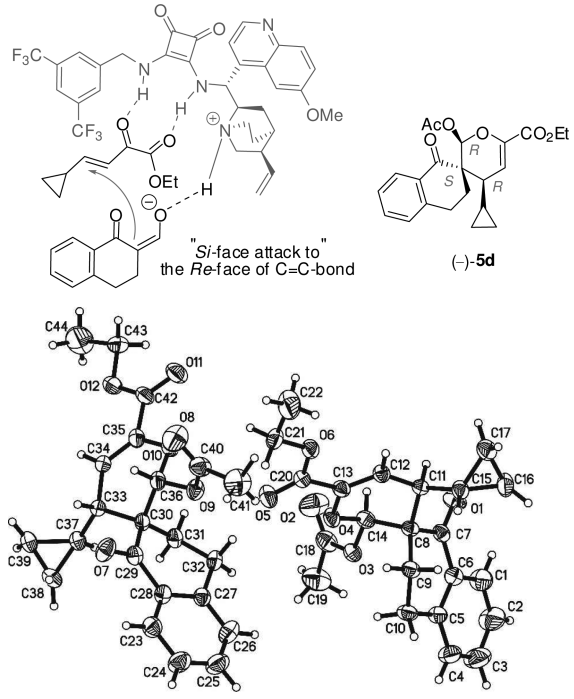



**Figure 2.** Proposed mode of action of catalyst **Ib** leading to the formation of (−)-**5d**.

motif, placing the alkene side chain away from the C-9 center of the catslyst **Ib**, while the cyclic β-oxo aldehyde is deprotonated and directed by the tertiary nitrogen atom of **Ib** for subsequent attacking onto the *Re*-face of the C=C bond.[12]

In summary, we have developed a highly stereoselective domino cyclization reaction[13] of β-oxo aldehydes and β,γ-unsaturated α-keto esters catalyzed by amino-squaramide catalyst. Using cyclic aldehyde substrates, this reaction offered a promising protocol to spiro-3,4-dihydropyrans **5** and **7** with three quaternary−tertiary stereocenters in one pot. The present annulation reaction was reasoned to proceed via an enatioselective Michael addition followed by a diastereoselective hemiacetalization. Compared with $(DHQD)_2PYR$, the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bifunctional catalyst **Ib** performed more effectively for the current reaction in view of the scope of $\beta,\gamma$-unsaturated $\alpha$-keto ester component as well as the stereocontrol. Further studies on the application of this methodology to complex natural compound syntheses are currently underway in our laboratory and will be reported in due course.

## EXPERIMENTAL SECTION

**Synthesis of Racemic Ethyl 1,7-Dioxo-5-propyl-2-oxaspiro[5.5]undec-3-ene-3-carboxylate (4a).** The aldehyde **1a** (57 mg, 0.45 mmol) and $\alpha$-keto esters **2a** (51 mg, 0.30 mmol) were dissolved in dry dichloromethane (3 mL) at −20 °C under a $N_2$ atmosphere. Catalyst **Ia** (8.7 mg, 10 mol %) and $Et_3N$ (42 μL, 0.30 mmol) were added, and the mixture was stirred at the same temperature for 12 h until complete consumption of **2a** (as observed by TLC). The reaction was quenched with 5 mL of saturated aqueous $NaHCO_3$ and extracted with dichloromethane (5 mL × 3). After being washed by brines (10 mL × 3), the organic phase was dried over $MgSO_4$ and concentrated under reduced pressure. The residue was dissolved in 5 mL of $CH_2Cl_2$, followed by the addition of pyridine chlorochromate (0.30 mmol, 65 mg), and the resulting mixture was heated at reflux for several hours. On completion of the reaction, the mixture was cooled to room temperature, diluted with ether, and quickly passed through a short pad of diatomite with ether as the eluent. The crude obtained was concentrated under vacuum and purified by column chromatography (eluting with hexane/ethyl acetate 90/10) to afford racemic **4a** as a white solid (71 mg, 80%): $^1$H NMR (500 MHz, $CDCl_3$, TMS, ppm) $\delta$ 6.47 (d, $J$ = 8.8 Hz, 1H), 4.29 (q, $J$ = 7.2 Hz, 2H), 3.12 (m, 1H), 2.59 (m, 2H), 2.27 (m, 1H), 1.90 (m, 3H), 1.73 (m, 1H), 1.45 (m, 2H), 1.34 (t, $J$ = 7.2 Hz, 3H), 1.25 (m, 1H), 0.94 (t, $J$ = 7.2 Hz, 3H); $^{13}$C NMR (125 MHz, $CDCl_3$, TMS, ppm) $\delta$ 205.7, 167.3, 159.9, 140.9, 117.6, 61.8, 58.5, 39.4, 35.8, 30.8, 30.2, 27.0, 20.6, 20.0, 14.1, 13.9; HRMS (EI) $[C_{16}H_{22}O_5]^+$, calc 294.1467, found 294.1466. Determined by HPLC with Chiralpak IA−H column at 254 nm (hexane/$i$-PrOH = 90:10, flow rate = 0.8 mL/min), $t_{R1}$ = 27.9 min, $t_{R2}$ = 30.3 min.

**General Procedure for the Synthesis of Racemic Spiro-3,4-dihydropyrans 5.** The aldehyde **1a** (57 mg, 0.45 mmol) and $\alpha$-keto esters **2a** (51 mg, 0.30 mmol) were dissolved in dry dichloromethane (3 mL) at −20 °C under a $N_2$ atmosphere. Catalyst **Ia** (8.7 mg, 10 mol %) and $Et_3N$ (42 μL, 0.30 mmol) were added, and the mixture was stirred at the same temperature for 12 h until complete consumption of **2a** (as observed by TLC). Triethylamine (62 μL, 0.45 mmol) and acetyl chloride (32 μL, 0.45 mmol) were then added at 0 °C without isolation. The resulting mixtures were stirred at 0 °C for 2 h, and then quenched with saturated aqueous $NaHCO_3$ (5 mL), and extracted with $CH_2Cl_2$ (5 mL × 3). The combined extracts were dried with anhydrous $MgSO_4$, filtered, and evaporated under reduced pressure. The residue was purified by silica gel chromatography (hexane/AcOEt = 4:1) to afford racemic **5a** (86 mg, 85%) as a white solid.

**General Procedure for the Asymmetric Synthesis of Spiro-3,4-dihydropyrans 5, 7, and 3,4-Dihydropyrans 9 Catalyzed by Ib.** The aldehydes **1** (0.45 mmol) and aliphatic $\beta,\gamma$-unsaturated $\alpha$-keto esters **2** (0.30 mmol) were dissolved in dry $CH_2Cl_2$ (3 mL) at −20 °C under a $N_2$ atmosphere. Catalyst **Ib** (19 mg, 10 mol %) was added, and the mixture was stirred at the same temperature for several hours until complete consumption of **2** (as observed by TLC). Afterward, triethylamine (104 μL, 0.75 mmol) and acetyl chloride (32 μL, 0.45 mmol) were added at 0 °C without isolation. The resulting mixtures were stirred at 0 °C for 2 h, and then quenched with saturated aqueous $NaHCO_3$ (5 mL), and extracted with dichloromethane (5 mL × 3). The combined extracts were dried with anhydrous $MgSO_4$, filtered, and evaporated under reduced pressure. The residue was purified by silica gel chromatography to afford compound **5**.

**(1*R*,5*R*,6*S*)-Ethyl 1-Acetoxy-7-oxo-5-propyl-2-oxaspiro[5.5]-undec-3-ene-3-carboxylate (5a).** The title compound was obtained according to the general procedure described above after flash column chromatography (eluting with hexane/ethyl acetate 90/10) as a white solid (87 mg, 86% yield, 99:1 dr, 98% ee): $[\alpha]_D^{20}$ −27.5 ($c$ 0.75, $CHCl_3$); $^1$H NMR (400 MHz, $CDCl_3$, TMS, ppm) $\delta$ 6.46 (s, 1H), 6.22 (d, $J$ = 3.2 Hz, 1H), 4.24 (q, $J$ = 7.2 Hz, 2H), 2.90 (m, 1H), 2.57−2.53 (m, 1H), 2.46−2.42 (m, 1H), 2.12 (s, 3H), 2.04−1.91 (m, 3H), 1.78−1.56 (m, 5H), 1.46−1.35 (m, 2H), 1.30 (t, $J$ = 7.2 Hz, 3H), 0.94 (t, $J$ = 7.2 Hz, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$, TMS, ppm) $\delta$ 210.3, 168.4, 161.6, 139.4, 115.1, 93.4, 61.2, 51.9, 40.4, 37.8, 31.3, 27.6, 25.6, 21.4, 20.8, 14.1, 14.0; HRMS (EI) $[C_{18}H_{26}O_6]^+$, calc 338.1729, found 338.1729. The dr and ee values were determined by HPLC with Chiralpack AS−H column at 254 nm (hexane/$i$-PrOH = 90:10, flow rate = 1.0 mL/min), for major diastereomer: $t_R$ = 8.6 min (minor), $t_R$ = 12.8 min (major).

**(5*S*,6*R*,10*R*)-Ethyl 6-Acetoxy-10-cyclohexyl-1-oxo-7-oxaspiro[4.5]dec-8-ene-8-carboxylate (5b).** The title compound was obtained according to the general procedure described above after flash column chromatography (eluting with hexane/ethyl acetate 90/10) as a white solid (93 mg, 85% yield, 98:2 dr, 96% ee): $[\alpha]_D^{20}$ −19.4 ($c$ 0.50, $CHCl_3$); $^1$H NMR (400 MHz, $CDCl_3$, TMS, ppm) $\delta$ 6.18 (d, $J$ = 2.0 Hz, 1H), 5.83 (s, 1H), 4.25 (q, $J$ = 7.2 Hz, 2H), 2.72 (dd, $J_1$ = 2.0 Hz, $J_1$ = 2.0 Hz 1H), 2.49−2.42 (m, 1H), 2.39−2.34 (m, 1H), 2.33−2.23 (m, 1H), 2.20−2.16 (m, 1H), 2.08 (s, 3H), 1.99−1.87 (m, 3H),1.81−1.63 (m, 3H), 1.32 (t, $J$ = 7.2 Hz, 3H), 1.29−0.96 (m, 7H); $^{13}$C NMR (100 MHz, $CDCl_3$, TMS, ppm) $\delta$ 219.7, 167.8, 161.3, 141.1, 113.9, 113.8, 95.3, 61.3, 51.9, 46.0, 38.5, 37.8, 33.4, 30.9, 26.4, 26.2, 26.0, 23.5, 20.7, 18.9, 14.1; HRMS (ESI) $[C_{20}H_{28}O_6 + Na]^+$, calc 387.1778, found 387.1766. The dr and ee values were determined by HPLC with Chiralpack AS−H column at 254 nm (hexane/$i$-PrOH = 90:10, flow rate = 1.0 mL/min), for major diastereomer: $t_R$ = 8.3 min (minor), $t_R$ = 14.4 min (major).

**(1*R*,5*R*,6*S*)-Ethyl 1-Acetoxy-5-cyclopropyl-7-oxo-2-oxaspiro[5.6]dodec-3-ene-3-carboxylate (5c).** The title compound was obtained according to the general procedure described above after flash column chromatography (eluting with hexane/ethyl acetate 90/10) as a white solid (63 mg, 60% yield, 84:16 dr, 60% ee): $[\alpha]_D^{20}$ −46.0 ($c$ 1.0, $CHCl_3$); $^1$H NMR (500 MHz, $CDCl_3$, TMS, ppm) $\delta$ 6.34 (s, 1H), 6.26 (d, $J$ = 9 Hz, 1H), 4.25 (q, $J$ = 7.0 Hz, 2H), 2.80−2.76 (m, 1H), 2.62−2.58 (m, 1H), 2.25−2.20 (m, 1H), 2.11 (s, 3H), 2.05−1.93 (m, 2H), 1.82−1.78 (m, 2H), 1.70−1.61 (m, 3H), 1.43−1.41 (m, 1H), 1.32 (t, $J$ = 7.0 Hz, 3H), 0.90−0.86 (m, 1H), 0.62−0.54 (m, 2H), 0.26−0.18 (m, 2H); $^{13}$C NMR (125 MHz, $CDCl_3$, TMS, ppm) $\delta$ 212.6, 168.8, 161.9, 139.3, 117.0, 94.1,, 61.5, 55.2, 44.6, 42.8, 31.7, 31.0, 26.7, 26.4, 25.0, 22.8, 21.1, 14.4, 14.3, 12.0, 6.3, 4.0; HRMS (EI) $[C_{19}H_{26}O_6]^+$, calc 350.1729, found 350.1729. The dr and ee values were determined by HPLC with Chiralpack AS−H column at 254 nm (hexane/$i$-PrOH = 90:10, flow rate = 1.0 mL/min), for major diastereomer: $t_R$ = 8.4 min (minor), $t_R$ = 12.0 min (major).

**(9*S*,10*R*,14*R*)-Methyl 10-Acetoxy-14-cyclopropyl-8-oxo-1,4,11-trioxadispiro[4.3.5.1]pentadec-12-ene-12-carboxylate (5d).** The title compound was obtained according to the general procedure described above after flash column chromatography (eluting with hexane/ethyl acetate 85/15) as a white solid (97 mg, 84% yield, 99:1 dr, 96% ee): $[\alpha]_D^{20}$ −174.7 ($c$ 0.50, $CHCl_3$); $^1$H NMR (400 MHz, $CDCl_3$, TMS, ppm) $\delta$ 7.93 (d, $J$ = 8.0 Hz, 1H), 7.49 (t, $J$ = 7.6 Hz, 1H), 7.30 (t, $J$ = 7.6 Hz, 1H), 7.25 (d, $J$ = 8.0 Hz, 1H), 6.23 (d, $J$ = 2.8 Hz, 1H), 6.22 (s, 1H), 4.28 (q, $J$ = 6.5 Hz, 2H), 3.28−3.20 (m, 1H), 3.10−3.03 (m, 1H), 2.50−2.41 (m, 2H), 2.28−2.21 (m, 1H), 1.89 (s, 3H), 1.31 (t, $J$ = 7.2 Hz, 3H), 0.84−0.77 (m, 1H), 0.59−0.52 (m, 1H), 0.35−0.24 (m, 2H), 0.17−0.12 (m, 1H); $^{13}$C NMR (100 MHz, $CDCl_3$, TMS, ppm) $\delta$ 198.9, 168.2, 161.5, 143.8, 140.3, 133.8, 132.8, 128.6, 127.6, 126.8, 116.1, 95.1, 6.7, 61.5, 48.9, 46.7, 26.0, 22.5, 20.7, 14.2, 11.8, 5.1, 4.3; HRMS (EI) $[C_{22}H_{24}O_6]^+$, calc 384.1573, found 384.1577. The dr and ee values were determined by HPLC with Chiralpack AS−H column at 254 nm (hexane/$i$-PrOH = 90:10, flow rate = 1.0 mL/min), for major diastereomer: $t_R$ = 11.4 min (minor), $t_R$ = 17.5 min (major).

**(1*R*,5*R*,6*R*)-Ethyl 1-Acetoxy-5-cyclohexyl-11-oxo-2,8-dioxaspiro[5.5]undec-3-ene-3-carboxylate (5e).** The title compound was obtained according to the general procedure described above after flash column chromatography (eluting with hexane/ethyl acetate 75/25) as a white solid (81 mg, 71% yield, 89:11 dr, 98% ee):


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$[\alpha]_D^{20}$ −18.1 (*c* 1.0, $CHCl_3$); $^1H$ NMR (400 MHz, $CDCl_3$, TMS, ppm) $\delta$ 6.21−6.20 (m, 2H), 4.27−4.21 (m, 2H), 4.16−4.09 (m, 2H), 4.03 (q, *J* = 6 Hz, 1H), 3.81 (t, *J* = 12 Hz, 1H), 2.92 (q, *J* = 3.2 Hz, 1H), 2.67−2.59 (m, 2H), 2.12 (s, 3H), 1.96 (d, *J* = 12 Hz, 1H), 1.78−1.72 (m, 2H), 1.64 (d, *J* = 10.4 Hz, 1H), 1.53 (d, *J* = 12.4 Hz, 1H), 1.49−1.45 (m, 1H), 1.31 (t, *J* = 7.2 Hz, 3H), 1.22−1.02 (m, 5H); $^{13}C$ NMR (100 MHz, $CDCl_3$, TMS, ppm) $\delta$ 206.9, 168.0, 161.2, 140.5, 113.6, 93.9, 66.9, 66.2, 61.4, 52.0, 44.8, 40.0, 37.3, 34.0, 30.3, 26.6, 26.4, 25.9, 20.8, 14.1; HRMS (ESI) $[C_{20}H_{28}O_7 + Na]^+$, calc 403.1727, found 403.1721. The dr and ee values were determined by HPLC with Chiralpack AS−H column at 254 nm (hexane/*i*-PrOH = 80:20, flow rate = 1.0 mL/min), for major diastereomer: $t_R$ = 10.5 min (major), $t_R$ = 11.7 min (minor).

**(1*R*,5*R*,6*R*)-Diethyl 1-Acetoxy-5-heptyl-11-oxo-2-oxa-8-azaspiro[5.5]undec-3-ene-3,8-dicarboxylate (5f).** The title compound was obtained according to the general procedure described above after flash column chromatography (eluting with hexane/ethyl acetate 80/20) as a white solid (101 mg, 72% yield, 99:1 dr, >99% ee): $[\alpha]_D^{20}$ −27.6 (*c* 1.04, $CHCl_3$); $^1H$ NMR (400 MHz, $CDCl_3$, TMS, ppm) $\delta$ 6.23 (d, *J* = 28 Hz, 1H), 6.18 (s, 1H), 4.24−4.11 (m, 5H), 4.02 (t, *J* = 5.6 Hz, 1H), 3.57 (s, 1H), 3.49 (d, *J* = 14.4 Hz, 1H), 2.97−2.74 (m, 2H), 2.53−2.44 (m, 1H), 2.12 (s, 3H), 1.51 (s, 2H), 1.35−1.25 (m, 18H), 0.89−0.83 (m, 4H); $^{13}C$ NMR (100 MHz, $CDCl_3$, TMS, ppm) $\delta$ 171.9, 171.5, 169.2, 168.8, 162.8, 133.6, 122.7, 121.4, 90.9, 90.7, 61.3, 60.9, 60.8, 48.5, 46.8, 32.4, 30.5, 28.1, 26.1, 21.0, 20.9, 19.1, 18.9, 14.2, 14.1, 14.0, 8.1, 8.1; HRMS (EI) $[C_{24}H_{37}NO_8]^+$, calc 467.2519, found 467.2517. 1721. The dr and ee values were determined by HPLC with Chiralpack AS−H column at 254 nm (hexane/*i*-PrOH = 85:15, flow rate = 0.8 mL/min), for major diastereomer: $t_R$ = 5.6 min (major), $t_R$ = 8.4 min (minor).

**(9*S*,10*R*,14*R*)-Methyl 10-Acetoxy-14-cyclopropyl-8-oxo-1,4,11-trioxadispiro[4.3.5.1]pentadec-12-ene-12-carboxylate (5g).** The title compound was obtained according to the general procedure described above after flash column chromatography (eluting with hexane/ethyl acetate 70/30) as a white solid (105 mg, 89% yield, 99:1 dr, >99% ee): $[\alpha]_D^{20}$ −25.6 (*c* 1.0, $CHCl_3$); $^1H$ NMR (400 MHz, $CDCl_3$, TMS, ppm) $\delta$ 6.81 (s, 1H), 6.23 (d, *J* = 3.2 Hz, 1H), 4.21 (q, *J* = 7.2 Hz, 2H), 4.05−3.96 (m, 4H), 2.95−2.88 (m, 1H), 2.56−2.50 (m, 1H), 2.42 (dd, $J_1$ = 2.8 Hz, $J_2$ = 15.2 Hz, 1H), 2.11 (s, 3H), 2.08−2.00 (m, 2H), 1.90 (dd, $J_1$ = 3.6 Hz, $J_2$ = 10.4 Hz, 1H), 1.30 (t, *J* = 7.2 Hz,3H), 1.01 (m, 1H), 0.88 (t, *J* = 6.4 Hz, 1H), 0.61−0.54 (m, 2H), 0.24−0.16 (m, 2H); $^{13}C$ NMR (100 MHz, $CDCl_3$, TMS, ppm) $\delta$ 208.7, 168.1, 161.6, 138.6, 116.2, 106.9, 92.3, 64.7, 64.4, 61.2, 52.1, 36.8, 33.9, 31.5, 22.5, 20.7, 14.1, 14.0, 10.8, 7.1, 3.0; HRMS (EI) $[C_{20}H_{26}O_8]^+$, calc 394.1628, found 394.1610. The dr and ee values were determined by HPLC with Chiralpack AS−H column at 254 nm (hexane/*i*-PrOH = 90:10, flow rate = 1.0 mL/min), for major diastereomer: $t_R$ = 19.3 min (minor), $t_R$ = 30.0 min (major).

**(5*S*,6*R*,10*R*)-Ethyl 6-Acetoxy-10-isopropyl-1-oxo-2,7-dioxaspiro[4.5]dec-8-ene-8-carboxylate (5h).** The title compound was obtained according to the general procedure described above after flash column chromatography (eluting with hexane/ethyl acetate 70/30) as a white solid (64 mg, 65% yield, 94:6 dr, 96% ee): $[\alpha]_D^{20}$ −52.9 (*c* 1.0, $CHCl_3$); $^1H$ NMR (500 MHz, $CDCl_3$, TMS, ppm) $\delta$ 6.15 (s, 1H), 6.01 (s, 1H), 4.47−4.40 (m, 2H), 4.30−4.25 (m, 2H), 2.73 (d, *J* = 10.0 Hz, 1H), 2.42 (m, 1H), 2.21−2.17 (m, 1H), 2.14 (s, 3H), 1.65−1.58 (m, 1H), 1.32 (t, *J* = 7.5 Hz, 3H), 1.11 (d, *J* = 6.5 Hz, 3H), 0.94 (d, *J* = 7.5 Hz, 3H); $^{13}C$ NMR (125 MHz, $CDCl_3$, TMS, ppm) $\delta$ 178.1, 167.9, 161.3, 141.5, 113.5, 94.4, 66.8, 61.8, 47.5, 45.9, 28.7, 22.0, 21.3, 21.1, 21.0, 14.3; HRMS (EI) $[C_{17}H_{24}O_6]^+$, calc 324.1573, found 324.1569. The dr and ee values were determined by HPLC with Chiralpack AS−H column at 254 nm (hexane/*i*-PrOH = 80:20, flow rate = 1.0 mL/min), for major diastereomer: $t_R$ = 11.0 min (minor), $t_R$ = 21.8 min (major).

**(5*S*,6*R*)-Ethyl 6-Acetoxy-9-methyl-1-oxo-7-oxaspiro[4.5]dec-8-ene-8-carboxylate (5i).** The title compound was obtained according to the general procedure described above after flash column chromatography (eluting with hexane/ethyl acetate 90/10) as a white solid (72 mg, 81% yield, > 99:1 dr, 70% ee): $[\alpha]_D^{20}$ +55.7 (*c* 1.0, $CHCl_3$); $^1H$ NMR (400 MHz, $CDCl_3$, TMS, ppm) $\delta$ 5.99 (s, 1H), 4.25 (q, *J* = 7.2 Hz, 2H), 2.47 (d, *J* = 18.0 Hz, 1H), 2.34 (t, *J* = 8.0 Hz, 2H), 2.10 (s, 3H), 2.06 (s, 3H), 2.00 (d, *J* = 18.0 Hz, 1H), 1.75−1.69 (m, 1H), 1.93−1.86 (m, 1H), 1.32 (t, *J* = 7.2 Hz, 3H); $^{13}C$ NMR (100 MHz, $CDCl_3$, TMS, ppm) $\delta$ 217.6, 168.6, 162.4, 136.5, 121.4, 91.5, 61.0, 49.7, 38.5, 37.9, 29.7, 20.9, 18.9, 18.5, 14.2; HRMS (EI) $[C_{15}H_{20}O_6]^+$, calc 296.1260, found 296.1257. The dr and ee values were determined by HPLC with Chiralpack AS−H column at 254 nm (hexane/*i*-PrOH = 90:10, flow rate = 0.8 mL/min), for major diastereomer: $t_R$ = 16.6 min (major), $t_R$ = 18.9 min (minor).

**(5*S*,6*R*)-Ethyl 6-Acetoxy-1-oxo-7-oxaspiro[4.5]dec-8-ene-8-carboxylate (5j).** The title compound was obtained according to the general procedure described above after flash column chromatography (eluting with hexane/ethyl acetate 90/10) as a white solid (70 mg, 83% yield, > 99:1 dr, 62% ee): $[\alpha]_D^{20}$ −37.1 (*c* 1.0, $CHCl_3$); $^1H$ NMR (500 MHz, $CDCl_3$, TMS, ppm) $\delta$ 6.16 (q, *J* = 2.0 Hz, 1H), 6.07 (s, 1H), 4.26 (m, 2H), 2.50 (dd, $J_1$ = 19 Hz, $J_2$ = 3.0 Hz, 1H), 2.34 (m, 3H), 2.12 (m, 1H), 2.10 (s, 3H), 2.09 (m, 1H), 1.90 (m, 1H), 1.74 (m, 1H), 1.33 (t, *J* = 7.0 Hz, 3H); $^{13}C$ NMR (125 MHz, $CDCl_3$, TMS, ppm) $\delta$ 217.9, 168.6, 161.6, 142.6, 110.0, 92.4, 61.7, 49.0, 38.8, 30.3, 29.6, 21.1, 19.2, 14.4; HRMS (EI) $[C_{14}H_{18}O_6]^+$, calc 282.1103, found 282.1101. The dr and ee values were determined by HPLC with Chiralpack AS−H column at 254 nm (hexane/*i*-PrOH = 90:10, flow rate = 0.8 mL/min), for major diastereomer: $t_R$ = 28.7 min (major), $t_R$ = 34.4 min (minor).

**(1*R*,5*S*,6*S*)-Methyl 1-Acetoxy-7-oxo-5-phenyl-2-oxaspiro[5.5]undec-3-ene-3-carboxylate (7a).** The title compound was obtained according to the general procedure described above after flash column chromatography (eluting with hexane/ethyl acetate 85/15) as a white solid (87 mg, 81% yield, 99:1 dr, 96% ee): $[\alpha]_D^{20}$ −60.1 (*c* 0.51, $CHCl_3$); $^1H$ NMR (400 MHz, $CDCl_3$, TMS, ppm) $\delta$ 7.30−7.19 (m, 5H), 6.70 (s, 1H), 6.37 (d, *J* = 7.6 Hz, 1H), 4.28 (d, *J* = 3.6 Hz, 1H), 3.81 (s, 3H), 2.66−2.58 (m, 1H), 2.30−2.23 (m, 1H), 2.05 (s, 3H), 1.91−1.87 (m, 1H), 1.65 (s, 3H), 1.61−1.54 (m, 1H), 1.30−1.10 (m, 2H); $^{13}C$ NMR (100 MHz, $CDCl_3$, TMS, ppm) $\delta$ 210.5, 168.3, 161.9, 140.9, 137.6, 130.1, 128.0, 127.5, 115.7, 92.8, 52.9, 52.3, 44.0, 40.6, 31.5, 28.8, 25.3, 22.6, 20.8, 20.7, 14.0; HRMS (ESI) $[C_{20}H_{22}O_6 + Na]^+$, calc 381.1309, found 381.1298. The dr and ee values were determined by HPLC with Chiralpack AS−H column at 254 nm (hexane/*i*-PrOH = 90:10, flow rate = 1.0 mL/min), for major diastereomer: $t_R$ = 18.8 min (minor), $t_R$ = 31.0 min (major).

**(5*S*,6*R*,10*S*)-Methyl 6-Acetoxy-10-(4-methoxyphenyl)-1-oxo-7-oxaspiro[4.5]dec-8-ene-8-carboxylate (7b).** The title compound was obtained according to the general procedure described above after flash column chromatography (eluting with hexane/ethyl acetate 85/15) as a white solid (93 mg, 83% yield, 99:1 dr, 94% ee): $[\alpha]_D^{20}$ −70.2 (*c* 1.0, $CHCl_3$); $^1H$ NMR (400 MHz, $CDCl_3$, TMS, ppm) $\delta$ 7.00 (d, *J* = 8.8 Hz, 2H), 6.81 (d, *J* = 8.8 Hz, 2H), 6.26 (d, *J* = 2.0 Hz, 1H), 6.14 (s, 1H), 4.23 (d, *J* = 2.0 Hz, 1H), 3.83 (s, 3H), 3.79 (s, 3H), 2.23−2.12 (m, 2H), 2.10 (s, 3H), 1.92−1.85 (m, 1H), 1.82−1.69 (m, 2H), 0.74−0.67 (m, 1H); $^{13}C$ NMR (100 MHz, $CDCl_3$, TMS, ppm) $\delta$ 219.6, 168.0, 161.6, 159.1, 142.8, 129.5, 129.2, 114.9, 114.0, 94.5, 55.2, 52.9, 52.4, 45.2, 39.5, 23.8, 20.7, 18.8; HRMS (EI) $[C_{20}H_{22}O_7]^+$, calc 374.1366, found 374.1366. The dr and ee values were determined by HPLC with Chiralcel OD−H column at 254 nm (hexane/*i*-PrOH = 85:15, flow rate = 1.0 mL/min), for major diastereomer: $t_R$ = 18.4 min (minor), $t_R$ = 34.3 min (major).

**(5*S*,6*R*,10*S*)-Ethyl 6-Acetoxy-1-oxo-10-*o*-tolyl-7-oxaspiro-[4.5]dec-8-ene-8-carboxylate (7c).** The title compound was obtained according to the general procedure described above after flash column chromatography (eluting with hexane/ethyl acetate 85/15) as a white solid (87 mg, 78% yield, 97:3 dr, 98% ee): $[\alpha]_D^{20}$ −38.1 (*c* 0.49, $CHCl_3$); $^1H$ NMR (400 MHz, $CDCl_3$, TMS, ppm) $\delta$ 7.18 (m, 4H), 6.22 (s, 1H), 6.16 (d, *J* = 2.0 Hz, 1H), 4.52 (d, *J* = 2.4 Hz, 1H), 4.29 (q, *J* = 7.2 Hz, 2H), 2.26 (m, 1H), 2.22 (s, 3H), 2.14(m, 1H), 2.09 (s, 3H), 1.90 (m, 1H), 1.73 (m, 1H), 1.33 (t, *J* = 7.2 Hz, 3H), 0.81 (m, 1H); $^{13}C$ NMR (100 MHz, $CDCl_3$, TMS, ppm) $\delta$ 219.6, 168.0, 161.2, 142.6, 136.2, 135.9, 131.1, 129.7, 127.6, 126.0, 116.5, 94.6, 61.4, 52.4, 39.0, 24.2, 20.7, 19.8, 19.0, 14.1; HRMS (ESI) $[C_{21}H_{24}O_6 + Na]^+$, calc 395.1465, found 395.1456. The dr and ee values were determined by HPLC with Chiralcel OD−H column at


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254 nm (hexane/*i*-PrOH = 85:15, flow rate = 1.0 mL/min), for major diastereomer: $t_R$ = 12.2 min (minor), $t_R$ = 13.0 min (major).

**(5*S*,6*R*,10*S*)-Methyl 6-Acetoxy-10-(4-fluorophenyl)-1-oxo-7-oxaspiro[4.5]dec-8-ene-8-carboxylate (7d).** The title compound was obtained according to the general procedure described above after flash column chromatography (eluting with hexane/ethyl acetate 85/15) as a white solid (94 mg, 87% yield, 98:2 dr, 97% ee): $[\alpha]_D^{20}$ −44.1 (*c* 1.0, $CHCl_3$); $^1H$ NMR (400 MHz, $CDCl_3$, TMS, ppm) $\delta$ 7.10−6.98 (m, 4H), 6.24 (d, *J* = 1.6 Hz, 1H), 6.14 (s, 1H), 4.28 (d, *J* = 1.2 Hz, 1H), 3.84 (s, 3H), 2.28−2.13 (m, 2H), 2.11 (s, 3H), 1.93−1.85 (m, 1H), 1.79−1.74 (m, 2H), 0.75−0.67 (m, 1H); $^{13}C$ NMR (100 MHz, $CDCl_3$, TMS, ppm) $\delta$ 219.1, 167.9, 163.5 ($J_{C-F}$ = 246.3 Hz), 161.5, 143.1, 133.2 ($J_{C-F}$ = 2.7 Hz), 130.1 ($J_{C-F}$ = 7.1 Hz), 115.7 ($J_{C-F}$ = 20.6 Hz), 114.1, 94.4, 52.8, 52.4, 45.1, 39.4, 23.7, 20.7, 18.8; HRMS (EI) $[C_{19}H_{19}FO_6]^+$, calc 362.1166, found 362.1176. The dr and ee values were determined by HPLC with Chiralcel OD−H column at 254 nm (hexane/*i*-PrOH = 85:15, flow rate = 1.0 mL/min), for major diastereomer: $t_R$ = 14.0 min (minor), $t_R$ = 24.8 min (major).

**(5*S*,6*R*,10*R*)-Ethyl 6-Acetoxy-10-(furan-2-yl)-1-oxo-7-oxaspiro[4.5]dec-8-ene-8-carboxylate (7e).** The title compound was obtained according to the general procedure described above after flash column chromatography (eluting with hexane/ethyl acetate 85/15) as a yellow solid (71 mg, 68% yield, 98:2 dr, 93% ee): $[\alpha]_D^{20}$ −36.7 (*c* 1.0, $CHCl_3$); $^1H$ NMR (400 MHz, $CDCl_3$, TMS, ppm) $\delta$ 7.32 (s, 1H), 6.33 (d, *J* = 1.6 Hz, 1H), 6.21 (d, *J* = 1.6 Hz, 1H), 6.15 (d, J = 2.8 Hz, 1H), 6.10 (s, 1H), 4.31−4.26 (m, 3H), 2.27−2.20 (m, 3H), 2.10 (s, 3H), 1.90−1.80 (m, 1H), 1.77−1.71 (m, 1H), 1.36 (t, *J* = 7.2 Hz, 3H), 1.02−0.94 (m, 1H); $^{13}C$ NMR (100 MHz, $CDCl_3$, TMS, ppm) $\delta$ 219.1, 167.9, 163.5, 161.5, 161.1, 143.1, 133.2, 133.1, 130.1, 130.0, 115.7, 115.5, 114.1, 94.4, 52.8, 52.4, 45.1, 39.4, 23.7, 20.7, 18.8; HRMS (EI) $[C_{18}H_{20}O_7]^+$, calc 348.1209, found 348.1222. The dr and ee values were determined by HPLC with Chiralcel OD−H column at 254 nm (hexane/*i*-PrOH = 85:15, flow rate = 1.0 mL/min), for major diastereomer: $t_R$ = 11.8 min (minor), $t_R$ = 14.0 min (major).

**(2*R*,3*S*,4*R*)-Diethyl 2-Acetoxy-3-ethyl-4-heptyl-3,4-dihydro-2H-pyran-3,6-dicarboxylate (9).** The title compound was obtained according to the general procedure described above after flash column chromatography (eluting with hexane/ethyl acetate 90/10) as a white solid (84 mg, 68% yield, 57:43 dr, 96% $ee_{major}$, 88% $ee_{minor}$): $[\alpha]_D^{20}$ −84.2 (*c* 1.2, $CHCl_3$); $^1H$ NMR (400 MHz, $CDCl_3$, TMS, ppm) $\delta$ 6.57 (s, 1H), 6.14 (d, *J* = 5.6 Hz, 1H), 4.27−4.12 (m, 4H), 2.88−2.80 (m, 1H), 2.02 (s, 3H), 1.71−1.52 (m, 4H), 1.34−1.22 (m, 16H), 1.02 (t, *J* = 7.6 Hz, 2H), 0.91−0.85 (m, 4H); $^{13}C$ NMR (100 MHz, $CDCl_3$, TMS, ppm) $\delta$ 171.9, 171.9, 168.7, 168.5, 162.0, 162.0, 139.2, 138.8, 115.2, 114.8, 92.9, 91.3, 61.4, 61.3, 61.2, 60.7, 51.3, 48.4, 34.8, 34.5, 31.7, 31.7, 29.6, 29.5, 29.2, 29.1, 29.1, 28.3, 27.9, 27.4, 23.3, 22.7, 22.6, 20.8, 20.7, 14.1, 14.0, 14.0, 9.3, 8.6; HRMS (EI) $[C_{17}H_{24}O_6]^+$, calc 324.1573, found 324.1569. The dr and ee values were determined by HPLC with Chiralcel OD−H column at 254 nm (hexane/*i*-PrOH = 95:5, flow rate = 1.0 mL/min), for major diastereomer: $t_R$ = 4.2 min (major), $t_R$ = 4.7 min (minor); for minor diastereomer: $t_R$ = 6.2 min (major), $t_R$ = 11.7 min (minor).

## ■ ASSOCIATED CONTENT

### Ⓢ Supporting Information

Experiment procedures, copies of HPLC chromatograms, $^1H$ and $^{13}C$ NMR spectra of the products, and X-ray crystallographic data of (−)-**5d**. This material is available free of charge via the Internet at http://pubs.acs.org.

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### Notes

The authors declare no competing financial interest.

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