An Unexpected Organocatalytic Asymmetric Tandem Michael Morita-Baylis-Hillman Reaction

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Contents

General Methods and Materials S2
Experimental Procedures and Characterizations S2
Stereochemical Assignment and Determination of the Absolute Configuration S12
**General Methods.** NMR spectra were acquired on a Varian AS 400 spectrometer, running at 400 and 100 MHz for $^1$H and $^{13}$C, respectively. Chemical shifts (δ) are reported in ppm relative to residual solvent signals (CHCl$_3$, 7.26 ppm for $^1$H NMR, CDCl$_3$, 77.0 ppm for $^{13}$C NMR). $^{13}$C NMR spectra were acquired on a broad band decoupled mode. Mass spectra were recorded on a Micromass LCT spectrometer using electrospray (ES$^+$) ionization techniques. Analytical thin layer chromatography (TLC) was performed using pre-coated aluminium-backed plates (Merck Kieselgel 60 F254) and visualized by ultraviolet irradiation or KMnO$_4$ dip. Purification of reaction products was carried out by flash chromatography (FC) using silica-gel (Fluka) or Iatrobeads 6RS-8060. Optical rotations were measured on a Perkin-Elmer 241 polarimeter. The enantiomeric excess (ee) of the products was determined by chiral stationary phase HPLC (Daicel Chiralpak AS/AD or Daicel Chiralcel OD/OJ columns).

**Materials.** Commercially available starting materials and solvents were used without further purification and catalyst 5d-e was prepared according to previously described procedures.\(^1\) The β-ketoesters 2a-c was prepared following described methods.\(^2\)

**Experimental Procedures and Characterizations:**

**General procedure for the Michael–Morita–Baylis–Hillman Reaction.** In an ordinary vial the corresponding β-ketoester 2 (0.2 mmol) was added to a stirred solution of catalyst 5e\(^1\) (0.02 mmol), benzoic acid (0.02 mmol) and the corresponding aldehyde 1a-i (0.6 mmol) in toluene (0.2 mL). After complete consumption of the β-ketoester, usually 14–18 h

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(as monitored by $^1$H NMR spectroscopy), the crude was directly charged on silica gel and subjected to FC (eluent indicated in each case).

(+)-Ethyl 2,4-dihydroxy-3-methylene-6-phenylcyclohex-1-ene-1-carboxylate (4a). The product was obtained following the general procedure as colorless oil (55% yield) after FC (eluent 4/1, hexane/Et$_2$O). The ee was determined by HPLC using a Chiralcel OD column [hexane/iPrOH (90:10)]; flow rate 1.0 mL/min; $\tau_{\text{minor}} = 18.3$ min, $\tau_{\text{major}} = 44.6$ min (94% ee). $[^{20}\alpha] = +4$ (c = 0.3, CH$_2$Cl$_2$). $^1$H NMR (CDCl$_3$) $\delta$ 12.27 (s, 1H), 7.26-7.13 (m, 5H), 6.07 (s, 1H), 5.67 (s, 1H), 4.39 (ddd, $J = 10.4$, 4.0, 2.0 Hz, 1H), 4.04-3.94 (m, 1H), 3.92-3.85 (m, 2H), 2.38-2.32 (m, 1H), 2.06-2.02 (bs, 1H), 1.76-1.68 (m, 1H), 0.78 (t, $J = 7.2$ Hz, 3H). $^{13}$C NMR (CDCl$_3$) $\delta$ 172.3, 163.4, 146.6, 142.1, 128.3 (2C), 126.7 (2C), 125.9, 115.4, 102.3, 68.6, 60.4, 41.7, 39.1, 13.5. MS (TOF ES$^+$): [M+Na]$^+$ calcd for C$_{16}$H$_{18}$NaO$_4$ 297.1103; found 297.1102.

(-)-Ethyl 2,4-dihydroxy-3-methylene-6-phenylcyclohex-1-ene-1-carboxylate (ent-4a). The product was obtained following the general procedure using 20 mol% of the enantiomer catalyst ent-5e as colorless oil (53% yield) after FC (eluent 4/1, hexane/Et$_2$O). Spectral data were identical to compound 4a. The ee was determined by HPLC using a Chiralcel OD column [hexane/iPrOH (90:10)]; flow rate 1.0 mL/min; $\tau_{\text{major}} = 18.3$ min, $\tau_{\text{minor}} = 44.6$ min (95% ee). $[^{20}\alpha] = -4$ (c = 1.0, CH$_2$Cl$_2$).

(-)-tert-Butyl 2,4-dihydroxy-3-methylene-6-phenylcyclohex-1-ene-1-carboxylate (4b). The product was obtained following the general procedure as colorless oil (68% yield) after FC (eluent 100/1, CH$_2$Cl$_2$/Et$_2$O). The ee was determined by HPLC using a Chiralcel OD column [hexane/iPrOH (90:10)]; flow rate 1.0 mL/min; $\tau_{\text{minor}} = 10.1$ min, $\tau_{\text{major}} = 24.9$ min (94% ee). $[^{20}\alpha] = -13$ (c = 1.0, CH$_2$Cl$_2$). $^1$H NMR (CDCl$_3$) $\delta$ 12.39 (s, 1H), 7.30-7.08 (m, 5H), 6.03 (s, 1H), 5.64 (s, 1H), 4.43-4.28 (m, 1H), 4.03-3.94 (m, 1H), 3.92-3.85 (m, 2H), 2.38-2.32 (m, 1H), 2.06-2.02 (bs, 1H), 1.76-1.68 (m, 1H), 0.78 (t, $J = 7.2$ Hz, 3H). $^{13}$C NMR (CDCl$_3$) $\delta$ 172.3, 163.4, 146.6, 142.1, 128.3 (2C), 126.7 (2C), 125.9, 115.4, 102.3, 68.6, 60.4, 41.7, 39.1, 13.5. MS (TOF ES$^+$): [M+Na]$^+$ calcd for C$_{16}$H$_{18}$NaO$_4$ 297.1103; found 297.1102.
3.82 (dd, J = 9.6 Hz, 1H), 2.34 (ddd, J = 12.8, 5.9, 4.0 Hz, 1H), 1.79 (bs, 1H), 1.69-1.57 (m, 1H), 1.10 (s, 9H). $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 172.0, 162.9, 147.1, 142.5, 128.2 (2C), 126.7 (2C), 125.8, 114.2, 103.5, 81.7, 68.6, 42.2, 39.6, 27.6 (3C). MS (TOF ES$^+$): [M+Na]$^+$ calcd for C$_{18}$H$_{22}$NaO$_4$ 325.1416; found 325.1412.

(-)-Allyl 2,4-dihydroxy-3-methylene-6-phenylcyclo-hex-1-ene-carboxylate (4c). The product was obtained following the standard procedure as yellow oil (45% yield) after FC (eluent 97/3, CH$_2$Cl$_2$/Et$_2$O). The ee was determined by HPLC using a Chiralcel OD column [hexane/iPrOH (90:10)]; flow rate 1.0 mL/min; $\tau$$_\text{minor}$ = 12.8 min, $\tau$$_\text{major}$ = 31.3 min (94% ee). $[^{\circ}C]$$^\alpha_{20}$D = +3 (c = 1.04, CH$_2$Cl$_2$). $^1$H NMR (CDCl$_3$) $\delta$ 12.22 (s, 1H), 7.29-7.15 (m, 5H), 6.10 (s, 1H), 5.68 (s, 1H), 5.43 (ddd, J = 22.4, 10.6, 5.4 Hz, 1H), 4.97 (d, J = 10.6 Hz, 1H), 4.85 (d, J = 17.2 Hz, 1H), 4.48-4.33 (m, 3H), 3.96 (dd, J = 8.2, 6.4 Hz, 1H), 2.36 (ddd, J = 13.0, 6.0, 4.0 Hz, 1H), 1.81-1.65 (m, 2H). $^{13}$C NMR (CDCl$_3$) $\delta$ 172.0, 163.8, 146.4, 142.0, 131.3, 128.5 (2C), 126.8 (2C), 126.1, 117.6, 116.2, 102.0, 68.8, 64.9, 41.4, 38.9. MS (TOF ES$^+$): [M+Na]$^+$ calcd for C$_{17}$H$_{18}$NaO$_4$ 309.1103; found 309.1098.

(+)-Ethyl 6-(4-chlorophenyl)-2,4-dihydroxy-3-methylene cyclohex-1-ene-1-carboxylate (4d). The product was obtained following the general procedure as colorless oil (49% yield) after FC (eluent 50/1, CH$_2$Cl$_2$/Et$_2$O). The ee was determined by HPLC using two Chiralpak AD columns in a row [hexane/iPrOH (95:5)]; flow rate 0.9 mL/min; $\tau$$_\text{major}$ = 28.1 min, $\tau$$_\text{minor}$ = 31.1 min (93% ee). $[^{\circ}C]$$^\alpha_{20}$D = +18 (c = 0.6, CH$_2$Cl$_2$). $^1$H NMR (CDCl$_3$) $\delta$ 12.29 (s, 1H), 7.22 (d, J = 8.3 Hz, 2H), 7.09 (d, J = 8.4 Hz, 2H), 6.08 (s, 1H), 5.67 (s, 1H), 4.45-4.36 (m, 1H), 4.08-3.85 (m, 3H), 2.34 (ddd, J = 12.8, 6.2, 3.9 Hz, 1H), 1.74-1.59 (m, 2H), 0.86 (t, J = 7.1 Hz, 3H). $^{13}$C NMR (CDCl$_3$) $\delta$ 172.1, 163.7, 145.2, 141.9, 131.5, 128.3 (2C), 128.2 (2C), 115.8, 101.8, 68.5, 60.5, 41.4, 38.6, 13.5. MS (TOF ES$^+$): [M+Na]$^+$ calcd for C$_{16}$H$_{17}$ClNaO$_4$ 331.0713; found 331.0705.
(+)-Ethyl 2,4-dihydroxy-6-(4-methoxyphenyl)-3-methylenecyclohex-1-ene-1-carboxylate (4e). The product was obtained following the general procedure as colorless oil (69% yield) after FC (eluent 50/1, CH₂Cl₂/Et₂O). The ee was determined by HPLC using a Chiralcel OD column [hexane/iPrOH (95:5)]; flow rate 1.0 mL/min; \( \tau_{\text{minor}} = 12.0 \) min, \( \tau_{\text{major}} = 39.0 \) min (93% ee). \([\alpha]^{20}_D = +32 \) (c = 1.0, CH₂Cl₂). \( ^1H \) NMR (CDCl₃) \( \delta \): 12.25 (s, 1H), 7.09-7.02 (m, 2H), 6.82-6.77 (m, 2H), 6.07 (s, 1H), 5.65 (s, 1H), 4.43-4.34 (m, 1H), 4.08-3.84 (m, 3H), 3.77 (s, 3H), 2.32 (ddd, \( J = 13.1, 5.9, 4.0 \) Hz, 1H), 1.79-1.68 (m, 1H), 1.64 (bs, 1H), 0.87 (t, \( J = 7.1 \) Hz, 3H). \( ^{13}C \) NMR (CDCl₃) \( \delta \): 172.3, 163.2, 157.8, 142.1, 138.6, 127.7 (2C), 115.7, 113.7 (2C), 102.5, 68.8, 60.4, 55.2, 41.5, 38.1, 13.6. MS (TOF ES⁺): [M+Na]⁺ calcd for C₁₇H₂₀NaO₅ 327.1208; found 327.1191.

(+)-Ethyl 2,4-dihydroxy-3-methylene-6-(4-nitrophenyl) cyclohex-1-ene-1-carboxylate (4f). The product was obtained following the general procedure as yellow oil (58% yield) after FC (eluent 50/1, CH₂Cl₂/Et₂O). The ee was determined by HPLC using a Chiralcel OD column [hexane/iPrOH (90:10)]; flow rate 1.0 mL/min; \( \tau_{\text{minor}} = 13.6 \) min, \( \tau_{\text{major}} = 17.3 \) min (96% ee). \([\alpha]^{20}_D = +68 \) (c = 1.0, CH₂Cl₂). \( ^1H \) NMR (CDCl₃) \( \delta \): 12.37 (s, 1H), 8.12 (d, \( J = 8.9 \) Hz, 2H), 7.33 (d, \( J = 8.8 \) Hz, 2H), 6.12 (s, 1H), 5.70 (s, 1H), 4.51-4.40 (m, 1H), 4.08-3.86 (m, 3H), 2.35 (ddd, \( J = 13.0, 6.4, 4.0 \) Hz, 1H), 1.81-1.66 (m, 2H), 0.82 (t, \( J = 7.1 \) Hz, 3H). \( ^{13}C \) NMR (CDCl₃) \( \delta \): 171.7, 164.3, 154.7, 146.1, 141.5, 127.7 (2C), 123.6 (2C), 116.6, 100.7, 68.4, 60.7, 40.7, 39.1, 13.5. MS (TOF ES⁺): [M+Na]⁺ calcd for C₁₆H₁₇NNaO₆ 342.0954; found 342.0949.
(+)-tert-Butyl 2,4-dihydroxy-3-methylene-6-(4-nitrophenyl)cyclohex-1-ene-1-carboxylate (4g). The product was obtained following the general procedure as yellow oil (51% yield) after FC (eluent 50/1, CH₂Cl₂/Et₂O). The ee was determined by HPLC using a Chiralcel OD column [hexane/iPrOH (90:10)]; flow rate 1.0 mL/min; τ<sub>minor</sub> = 16.6 min, τ<sub>major</sub> = 21.8 min (95% ee). [α]<sup>20</sup> <sub>D</sub> = +68 (c = 1.0, CH₂Cl₂). <sup>1</sup>H NMR (CDCl₃) δ 12.53 (s, 1H), 8.14 (d, J = 8.8 Hz, 2H), 7.33 (d, J = 8.7 Hz, 2H), 6.08 (s, 1H), 5.66 (s, 1H), 4.47-4.38 (m, 1H), 3.96 (dd, J = 9.0, 6.3 Hz, 1H), 2.33 (ddd, J = 13.0, 6.1, 3.9 Hz, 1H), 1.78 (bs, 1H), 1.70-1.58 (m, 1H), 1.11 (s, 9H). <sup>13</sup>C NMR (CDCl₃) δ 171.4, 164.0, 155.3, 146.1, 141.8, 127.7 (2C), 123.5 (2C), 115.6, 101.8, 82.3, 68.3, 41.0, 39.6, 27.7 (3C). MS (TOF ES<sup>+</sup>): [M+Na]<sup>+</sup> calcd for C₁₈H₂₁NNaO₆ 370.1267; found 370.1265.

(+)-Ethyl 2,4-dihydroxy-3-methylene-6-thiophenylcyclohex-1-ene-1-carboxylate (4h). The product was obtained following the general procedure as yellow oil (57% yield) after FC (eluent 95/5, CH₂Cl₂/Et₂O). The ee was determined by HPLC using a Chiralcel OD and a Chiralpak AS column in a row [hexane/iPrOH (90:10)]; flow rate 0.5 mL/min; τ<sub>minor</sub> = 37.1 min, τ<sub>major</sub> = 68.8 min (95% ee). [α]<sup>20</sup> <sub>D</sub> = +4 (c = 0.46, CH₂Cl₂). <sup>1</sup>H NMR (CDCl₃) δ 12.35 (s, 1H), 7.10 (d, J = 3.9 Hz, 1H), 6.88-6.86 (m, 1H), 6.80-6.79 (m, 1H), 6.13 (s, 1H), 5.66 (s, 1H), 4.43 (bs, 1H), 4.28 (t, J = 4.7 Hz, 1H), 4.16-4.00 (m, 3H), 2.37-2.31 (m, 1H), 2.10-2.03 (m, 1H), 1.01 (t, J = 7.2 Hz, 3H). <sup>13</sup>C NMR (CDCl₃) δ 172.1, 163.3, 150.7, 141.1, 126.6, 123.3, 123.2, 118.3, 102.1, 69.0, 60.7, 40.5, 33.5, 13.7. HRMS: C₁₄H₁₆NNaO₄S [M+Na]<sup>+</sup> calcd: 303.0667, found: 303.0677.

(+)-Ethyl 2,4-dihydroxy-3-methylene-6-furylcyclohex-1-ene-1-carboxylate (4i). The product was obtained following the general procedure as yellow oil (66% yield) after FC (eluent 95/5, CH₂Cl₂/Et₂O). The ee was determined by HPLC using a two Chiralcel OD columns in a row [hexa-
ne/iPrOH (90:10)]; flow rate 0.5 mL/min; \( \tau_{\text{minor}} = 31.6 \text{ min} \), \( \tau_{\text{major}} = 35.3 \text{ min} \) (92% ee). \([\alpha]^{20}_D = +50 \ (c = 0.45, \text{CH}_2\text{Cl}_2)\). \(^1\text{H}\) NMR (CDCl\(_3\)) \( \delta \) 12.42 (s, 1H), 7.30 (s, 1H), 6.25 (s, 1H), 6.15 (s, 1H), 5.95 (s, 1H), 5.64 (s, 1H), 4.44 (td, \( J = 4.8, 0.8 \text{ Hz} \), 1H), 4.17-4.08 (m, 3H), 2.32-2.23 (m, 1H), 2.16-2.12 (m, 1H), 1.64 (bs, 1H), 1.11 (t, \( J = 7.2 \text{ Hz} \), 3H). \(^{13}\text{C}\) NMR (CDCl\(_3\)) \( \delta \) 172.1, 163.6, 158.2, 141.1, 140.5, 120.1, 110.3, 105.7, 104.7, 69.1, 60.8, 35.4, 31.4, 13.9. HRMS: C\(_{14}\)H\(_{16}\)NaO\(_5\) [M+Na]\(^+\) calcd: 287.0895, found: 287.0904.

\( (+)\)-Diethyl 3,5-dihydroxy-4-methylene cyclohex-2-ene-1,2-dicarboxylate (4j). The product was obtained following the standard procedure using 20 mol% of catalyst 5e as a yellow solid (51% yield) after FC (elu enent 90/10, CH\(_2\)Cl\(_2\)/Et\(_2\)O). The ee was determined by HPLC using two Chiralcel AD columns [hexane/iPrOH (85:15)]; flow rate 1.0 mL/min; \( \tau_{\text{minor}} = 14.6 \text{ min} \), \( \tau_{\text{major}} = 15.8 \text{ min} \) (98% ee). \([\alpha]^{20}_D = +41 \ (c = 1.1, \text{CH}_2\text{Cl}_2)\). \(^1\text{H}\) NMR (CDCl\(_3\)) \( \delta \) 12.27 (s, 1H), 6.07 (s, 1H), 5.60 (s, 1H), 4.44-4.41 (m, 1H), 4.29-4.10 (m, 4H), 3.61 (dd, \( J = 6.0, 4.8 \text{ Hz} \), 1H), 2.60 (bs, 1H), 2.23 (dt, \( J = 13.7, 4.7 \text{ Hz} \), 1H), 2.10 (ddd, \( J = 13.7, 6.7, 3.2 \text{ Hz} \), 1H), 1.28-1.23 (m, 6H). \(^{13}\text{C}\) NMR (CDCl\(_3\)) \( \delta \) 175.4, 171.8, 163.3, 140.2, 119.7, 97.9, 68.8, 61.1, 61.0, 38.0, 32.7, 14.1 (2C). MS (TOF ES\(^+\)): [M+Na]\(^+\) calcd for C\(_{13}\)H\(_{18}\)NaO\(_6\) 293.1001; found 293.0991.

\( (+)\)-Ethyl 6-ethyl-2,4-dihydroxy-3-methylene cyclohex-1-ene-1-carboxylate (4k). The product was obtained following the general procedure using 20 mol% of catalyst 5e as colorless oil (64% yield) after FC (elu enent 6/1, hexane/Et\(_2\)O). The ee was determined by derivatization to the sulfone product 7b (86% ee) (see procedure below). \([\alpha]^{20}_D = +19 \ (c = 1.2, \text{CH}_2\text{Cl}_2)\). \(^1\text{H}\) NMR (CDCl\(_3\)) \( \delta \) 12.10 (s, 1H), 5.92 (s, 1H), 5.48 (s, 1H), 4.37-4.35 (m, 1H), 4.28-4.12 (m, 2H), 2.59-2.51 (m, 1H), 1.92-1.86 (m, 1H), 1.60-1.50 (m, 3H), 1.25 (t, \( J = 7.2 \text{ Hz} \), 3H), 0.83 (t, \( J = 7.2 \text{ Hz} \), 3H). \(^{13}\text{C}\) NMR (CDCl\(_3\)) \( \delta \) 169.4, 152.8, 134.8, 116.4, 104.1, 69.3, 60.7,
(+)-Ethyl 6-((Z)-hex-3-enyl)-2,4-dihydroxy-3-methylene cyclohex-1-ene-1-carboxylate (4l). The product was obtained following the general procedure using 20 mol% of catalyst 5e as colorless oil (51% yield) after FC (Iatrobeads) (eluent 6/1, hexane/Et₂O) as a mixture of diastereoisomers (3:2) in the allylic alcohol position. The product 4l was unstable and was transformed into the more stable sulfone 7c (see below). Major diastereoisomer: ¹H NMR (CD₃Cl) δ 12.10 (s, 1H), 5.92 (s, 1H), 5.48 (s, 1H), 5.20-5.10 (m, 2H), 4.20-4.00 (m, 3H), 3.62-2.68 (m, 1H), 2.23-1.80 (m, 9H), 1.20 (t, J = 7.1 Hz, 3H), 0.90 (t, J = 7.2 Hz, 3H). Minor diastereoisomer: ¹H NMR (CD₃Cl) δ 12.17 (s, 1H), 5.96 (s, 1H), 5.60 (s, 1H), 5.20-5.10 (m, 2H), 4.20-4.00 (m, 3H), 3.62-2.68 (m, 1H), 2.23-1.80 (m, 9H), 1.17 (t, J = 7.1 Hz, 3H), 0.90 (t, J = 7.2 Hz, 3H).

Procedure for the Isolation of the Intermediate 6. (+)-Ethyl 3-oxo-2-(3-oxo-1-phenylpropyl)pent-4-enoate (6). In an ordinary vial the β-ketoester 2a (0.6 mmol) was added to a stirred solution of catalyst 5e (0.06 mmol), benzoic acid (0.06 mmol) and cinnamaldehyde 1a (1.8 mmol) in toluene (0.6 mL) at 4 ºC. After 18 h the reaction was stopped (90% conversion, 7:1 ratio between the intermediate 6 and the tandem product 4a). The crude was directly charged on silica gel and subjected to FC in Iatrobeads (eluent 95/5, CH₂Cl₂/Et₂O) obtaining 6 (colorless oil) as a mixture of diastereoisomers (1:1) in the α-position of the ester. [α]²⁰ D = +38 (c = 0.3, CH₂Cl₂). ¹H NMR (CDCl₃) δ 9.60 (s, 1H), 9.57 (s, 1H), 7.29-7.17 (m, 10H), 6.53 (dd, J = 17.6, 10.4 Hz, 1H), 6.41 (d, J = 17.2 Hz, 1H), 6.26 (dd, J = 17.6, 10.4 Hz, 1H), 6.16 (d, J = 17.6 Hz, 1H), 5.93 (d, J = 10.4 Hz, 1H), 5.73 (d, J = 10.4 Hz, 1H), 4.21-4.08 (m, 5H), 4.00-3.85 (m, 3H), 2.89-2.86 (m, 2H), 2.76-2.74 (m, 2H), 1.25 (t, J = 7.2 Hz, 3H), 0.94 (t, J = 7.2 Hz, 3H). ¹³C NMR (CDCl₃) δ 200.3 (2C), 193.2, 193.0, 168.0, 167.2, 144.8,
139.7, 134.8, 131.0, 130.1, 129.5, 128.8, 128.6, 128.4, 128.2, 128.1, 127.44, 127.41, 127.39, 126.4, 119.7, 62.0, 61.2, 60.0, 47.4, 39.3, 39.1, 37.5, 36.6, 13.9, 13.6. MS (TOF ES'): [M+Na]^+ calcd for C_{16}H_{18}NaO_4 297.1103; found 297.1098.
General Procedure for the Preparation of the Sulfonyl derivatives 7a–c.

To a solution of the corresponding compound 4 (0.1 mmol) and acetic acid (0.1 mmol) in 0.2 mL of EtOH was added sodium p-toluensulfonate (0.15 mmol). After 12 h of stirring, water was added and the mixture was extracted with CH₂Cl₂ (2 x 5 mL). The combined organic layers were washed with saturated aqueous NaHCO₃ (2 x 5 mL), dried over MgSO₄, concentrated under vacuum, and purified by FC.

(−)-Ethyl 2-oxo-6-phenyl-3-(tosylmethyl)cyclohex-3-ene-1-carboxylate (7a). The product was obtained following the standard procedure as yellow solid (67% yield) after FC (eluent 2/1, hexane/Et₂O). The ee was determined by HPLC using a Chiralcel OJ column [hexane/iPrOH (85:15)]; flow rate 1.0 mL/min; \(\tau_{\text{major}} = 43.5\) min, \(\tau_{\text{minor}} = 60.6\) min (94% ee). [α]²⁰\(_{D}\) = +10 (c = 1.0, CH₂Cl₂). The absolute configuration of this compound was determined by X-ray crystal analysis (see below). \(^1\)H NMR (CDCl₃) δ 7.67 (d, \(J = 6.8\) Hz, 2H), 7.32–7.14 (m, 8H), 4.12 (d, \(J = 14.0\) Hz, 1H), 3.92 (d, \(J = 14.0\) Hz, 1H), 3.90–3.86 (m, 2H), 3.54–3.53 (m, 2H), 2.76–2.64 (m, 2H), 2.37 (s, 3H), 0.90 (t, \(J = 7.2\) Hz, 3H). \(^{13}\)C NMR (CDCl₃) δ 191.1, 168.3, 152.1, 144.9, 140.2, 135.6, 129.8, 129.7 (2C), 128.7 (2C), 128.4, 127.5 (2C), 127.1 (2C), 60.9, 59.6, 54.1, 34.2, 29.6, 21.6, 13.8. MS (TOF ES⁺): [M+Na]⁺ calcd for C₁₃H₂₄NaO₅S 435.1242; found 435.1239.

(−)-Ethyl 6-ethyl-2-oxo-3-(tosylmethyl)cyclohex-3-ene-1-carboxylate (7b). The product was obtained following the standard procedure as colorless oil (71% yield) after FC (eluent 2/1, hexane/Et₂O). The
ee was determined by HPLC using a Chiralcel OD column [hexane/iPrOH (80:20)]; flow rate 1.0 mL/min; \( \tau_{\text{major}} = 18.5 \) min, \( \tau_{\text{minor}} = 21.6 \) min (86% ee). \([\alpha]^{20}_{D} = -4 \) (c = 1.0, CH\(_2\)Cl\(_2\)). \(^1\)H NMR (CDCl\(_3\)) \( \delta \) 7.63 (d, \( J = 7.6 \) Hz, 2H), 7.25 (d, \( J = 7.6 \) Hz, 2H), 7.20-7.12 (m, 1H), 4.12-4.07 (m 2H), 3.83 (d, \( J = 13.6 \) Hz, 1H), 2.99 (d, \( J = 13.6 \) Hz, 1H), 2.62 (dt, \( J = 19.2 \), 4.8 Hz, 1H), 2.36 (s, 3H), 2.30-2.26 (m, 2H), 2.18-2.13 (m, 2H), 1.30-1.20 (m, 4H), 1.17 (t, \( J = 7.2 \) Hz, 3H), 0.85 (t, \( J = 7.2 \) Hz, 3H). \(^{13}\)C NMR (CDCl\(_3\)) \( \delta \) 191.9, 169.6, 152.7, 145.1, 135.8, 129.8 (2C), 128.8 (2C), 127.5, 61.3, 59.5, 54.3, 38.6, 30.5, 26.6, 23.0, 14.3, 10.6. MS (TOF ES\(^+\)): [M+Na\(^+\)] calcd for C\(_{19}\)H\(_{24}\)NaO\(_5\)S 387.1242; found 387.1245.

(-)-Ethyl 6-((Z)-hex-3-enyl)-2-oxo-3-(tosylmethyl)cyclohex-3-ene-1-carboxylate (7c). The product was obtained following the standard procedure as colorless oil (51% yield) after FC (eluent 2/1, hexane/Et\(_2\)O). The ee was determined by HPLC using a Chiralcel OD column [hexane/iPrOH (85:15)]; flow rate 1.0 mL/min; \( \tau_{\text{major}} = 15.6 \) min, \( \tau_{\text{minor}} = 17.8 \) min (94% ee). \([\alpha]^{20}_{D} = -30 \) (c = 0.9, CH\(_2\)Cl\(_2\)). \(^1\)H NMR (CDCl\(_3\)) \( \delta \) 7.69 (d, \( J = 8.4 \) Hz, 2H), 7.31 (d, \( J = 8.2 \) Hz, 2H), 7.23-7.14 (m, 1H), 5.41-5.38 (m, 1H), 5.26-5.25 (m, 1H), 4.20-4.13 (m, 2H), 3.91 (d, \( J = 14.0 \) Hz, 1H), 3.05 (d, \( J = 14.0 \) Hz, 1H), 2.71 (dt, \( J = 18.4 \), 4.4 Hz, 1H), 2.42 (s, 3H), 2.25-2.21 (m, 2H), 2.03-1.95 (m, 4H), 1.25-1.21 (m, 6H), 0.98 (t, \( J = 7.2 \) Hz, 3H). \(^{13}\)C NMR (CDCl\(_3\)) \( \delta \) 191.5, 169.2, 152.3, 144.8, 135.5, 132.7, 129.5 (2C), 128.3 (2C), 127.4, 61.1, 59.4, 54.0, 36.6 (2C), 33.5, 30.6, 29.7, 23.5, 21.6, 20.5, 14.1. MS (TOF ES\(^+\)): [M+Na\(^+\)] calcd for C\(_{23}\)H\(_{30}\)NaO\(_5\)S 441.1711; found 441.1709.

(-)Ethyl 4,8-dihydroxy-6-phenyl-1-oxaspiro[2.5]oct-4-ene-5-carboxylate (8). m-CPBA (77% pure) (63.0 mg, 1.8 equiv) was added at 0 \(^\circ\)C to a stirred solution of the ketone 4a (47.0 mg, 0.171 mmol) in CH\(_2\)Cl\(_2\) (0.45 mL). After stirring for 5 h at 0 \(^\circ\)C, the mixture was diluted with CH\(_2\)Cl\(_2\) (1.0 mL) and washed with Na\(_2\)SO\(_3\) (10%; 2 x 1 mL) and NaHCO\(_3\) (sat; 2 x 1 mL). The aqueous phases were extracted with CH\(_2\)Cl\(_2\) (2 x 1 mL).
The combined organic phases were dried (MgSO\textsubscript{4}) and the evaporation of the solvent afforded the product as a colourless solid (77% yield). Minor impurities could be removed by FC on Iatrobeads (eluent 90/10, CH\textsubscript{2}Cl\textsubscript{2}/Et\textsubscript{2}O), but the intrinsic instability of the product 8 led to a dramatically lowered yield (21% yield) but as one diastereoisomer. The relative stereochemistry is proposed on basis of the known propensity of m-CPBA to selectively afford cis-epoxidation of allylic alcohols.\textsuperscript{3} 

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\left[\alpha\right]^{20}_D = -17 \ (c = 0.8, \ CH_2Cl_2). \]

\textsuperscript{1}H NMR (CDCl\textsubscript{3}) \(\delta\) 12.14 (s, 1H), 7.28–7.15 (m, 5H), 4.06–3.92 (m, 2H), 3.88–3.80 (m, 2H), 3.66 (d, \(J = 5.7\) Hz, 1H), 3.23 (d, \(J = 5.7\) Hz, 1H), 2.39 (ddd, \(J = 13.0, 6.0, 3.6\) Hz, 1H), 1.85 (d, \(J = 10.8\) Hz, 1H), 1.69 (ddd, \(J = 13.0, 12.2, 10.5\) Hz, 1H), 0.76 (t, \(J = 7.1\) Hz, 3H). \textsuperscript{13}C NMR (CDCl\textsubscript{3}) \(\delta\) 171.4, 164.0, 146.0, 128.3 (2C), 126.7 (2C), 126.1, 107.7, 64.9, 60.6, 57.4, 48.3, 40.3, 39.4, 13.3. MS (TOF ES\textsuperscript{+}): [M+Na]\textsuperscript{+} calcd for C\textsubscript{16}H\textsubscript{18}NaO\textsubscript{3} 313.1052; found 313.1052.

\[\text{(−)-Ethyl 3-(benzylaminomethyl)-4-hydroxy-2-oxo-6-phenylcyclohexanecarboxylate (9). To a solution of 4a (15 mg, 0.05 mmol) in Et}_2O (0.2 mL) was added benzylamine (68 \mu L, 0.05 mmol). After 12 h, the white solid was filtered, washed with Et\textsubscript{2}O and dried, obtaining 9 pure (quantitative yield). \left[\alpha\right]^{20}_D = -4 \ (c = 0.31, \ CH_2Cl_2). \]

\textsuperscript{1}H NMR (CDCl\textsubscript{3}) \(\delta\) 7.34–7.23 (m, 10H), 4.06–3.95 (m, 3H), 3.87 (d, \(J = 12.8\) Hz, 1H), 3.75 (d, \(J = 12.8\) Hz, 1H), 3.67 (d, \(J = 13.2\) Hz, 1H), 3.45 (dd, \(J = 12.8, 2.8\) Hz, 1H), 3.28 (dt, \(J = 13.2, 3.6\) Hz, 1H), 2.97 (dd, \(J = 13.2, 10.8\) Hz, 1H), 2.69 (dt, \(J = 10.4, 2.8\) Hz, 1H), 2.35 (dt \(J = 13.6, 4.0\) Hz, 1H), 2.04 (ddd, \(J = 13.2, 11.2, 10.8\) Hz, 1H), 1.60 (bs, 2H), 1.04 (t, \(J = 7.2\) Hz, 3H). \textsuperscript{13}C NMR (CDCl\textsubscript{3}) \(\delta\) 203.2, 168.2, 141.1, 138.5, 128.7 (2C), 128.6, 128.2 (2C), 127.5, 127.2 (2C), 127.1 (2C), 75.5, 63.5, 60.9, 55.5, 53.9, 48.6, 41.9, 41.1, 13.9. MS (TOF ES\textsuperscript{+}): [M+H]\textsuperscript{+} calcd for C\textsubscript{23}H\textsubscript{28}NO\textsubscript{4} 382.1940; found 382.1952.

(+)-Ethyl 4-hydroxy-2-oxo-6-phenyl-3-[(phenylsulfanyl)methyl]cyclohexanecarboxylate (10). Et$_3$N (18 µL, 1.1 equiv) was added dropwise at rt to a stirred solution of 4a (26 mg, 0.1 mmol) and p-thiocresol (16 µL, 1.5 equiv) in CHCl$_3$ (0.2 mL). After 12 h, the mixture was directly purified by FC (1:1 Hexane/Et$_2$O) to give the sulfenyl compound 10 as colorless oil (65% yield). [α]$^D_{20}$ = +27 (c = 0.5, CH$_2$Cl$_2$). $^1$H NMR (CDCl$_3$) δ 7.50-7.40 (m, 2H), 7.35-7.10 (m, 8H), 4.10-3.80 (m, 3H), 3.63 (d, J = 12.8 Hz, 1H), 3.48 (dd, J = 14.0, 6.4 Hz, 1H), 3.30 (dd, J = 13.6, 4.4 Hz, 1H), 3.25 (dd, J = 12.8, 3.2 Hz, 1H), 2.80 (dt, J = 10.8, 5.6 Hz, 1H), 2.62 (bs, 1H), 2.36 (dt, J = 13.6, 4.0 Hz, 1H), 2.10-2.05 (m, 1H), 1.05 (t, J = 6.8 Hz, 3H). $^{13}$C NMR (CDCl$_3$) δ 202.0, 168.1, 140.8, 129.2 (2C), 129.1, 128.8 (2C), 127.3 (2C), 127.0 (2C), 126.4, 72.5, 62.9, 61.0, 58.0, 41.8, 41.4, 29.8, 13.9. MS (TOF ES$^+$): [M+Na]$^+$ calcd for C$_{22}$H$_{24}$NaO$_4$S 407.1293; found 407.1296.

**Stereochemical Assignment and Determination of the Absolute Configuration.**

The absolute configuration of the ethyl cyclohex-3-ene-1-carboxylates 7a-c has been determined by single-crystal X-ray analysis of ethyl 2-oxo-6-phenyl-3-((tosylmethyl)cyclohex-3-ene-1-carboxylate (7a) to be 1S and 6R (see figure below).

We assume for assigning the absolute configuration of the rest of the compounds the same approach of the nucleophile to the corresponding α,β-unsaturated aldehyde and therefore the same stereochemistry at C-6.
The stereochemical assignment of the allylic alcohol position of the tandem products 4a-1 was determined by NOESY experiments as R due to the absence of NOE cross-peak between H⁶ and H⁴. See for more details the NOESY's spectra of compounds 4a and 4g.
The anti stereochemistry of the substituents at C-3 and C-4 in compounds 9 and 10 was established by the $J_{3,4}$ value (10.4 Hz and 10.8 Hz, respectively) determined using $^1$H NMR and COSY experiments. See the CO-SYs spectra of compounds 9 and 10.