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Organocatalytic Double Michael Reaction of 7-Oxohept-2-enoates and Nitrostyrene – Formal Synthesis of (–)-α- and (–)-β-Lycorane

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Dedicated to Professor Elias J. Corey on the occasion of his 80th birthday

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Organocatalytic conjugate addition of 7-oxohept-2-enoate to nitrostyrene provided an ω-nitro-α,β-unsaturated ester. Subsequent intramolecular cyclization afforded the highly functionalized cyclohexane carboester with four stereogenic centers with high diastereoselectivity and high enantioselectivity (>99% *ee*). Some adducts were transformed into the intermediates of the synthesis of (–)-α- and (–)-β-lycorane. Application of the reactions to the corresponding dialdehyde provided bicyclo[2.2.2]octanes.

Introduction

The asymmetric organocatalytic domino reaction[1] has emerged as a powerful paradigm in accelerating the development of new methods for the synthesis of diverse chiral molecules.[2] With the benefits of ease of operation, ready availability, and low toxicity, these organocatalytic reactions are attractive methods in modern synthetic chemistry and have received remarkable attention during the past decade.[3] Among the organocatalytic reactions explored, extensive effort has been devoted to the Michael addition[4] of aldehydes to nitrostyrene.[5,6] Despite a large number of publications dealing with organocatalytic Michael reactions, however, only a few examples have focused on the domino (or tandem) reaction as a stratagem. A tour de force was demonstrated by Enders et al.: a triple cascade organocatalytic reaction for the synthesis of tetrasubstituted cyclohexenecarbaldehydes. In a Michael–Michael–aldol sequence they generated four stereogenic centers with high diastereo- and enantioselectivity (>99% *ee*).[7] In conjunction with our continuing efforts in exploring new organocatalytic annulations,[8] we investigated the domino double Michael reaction. Herein we report the development of a new domino organocatalytic nitro-Michael and conjugate addition for the diastereo- and enantioselective synthesis of highly functionalized cyclohexane derivatives with four stereocenters in a one-pot procedure.

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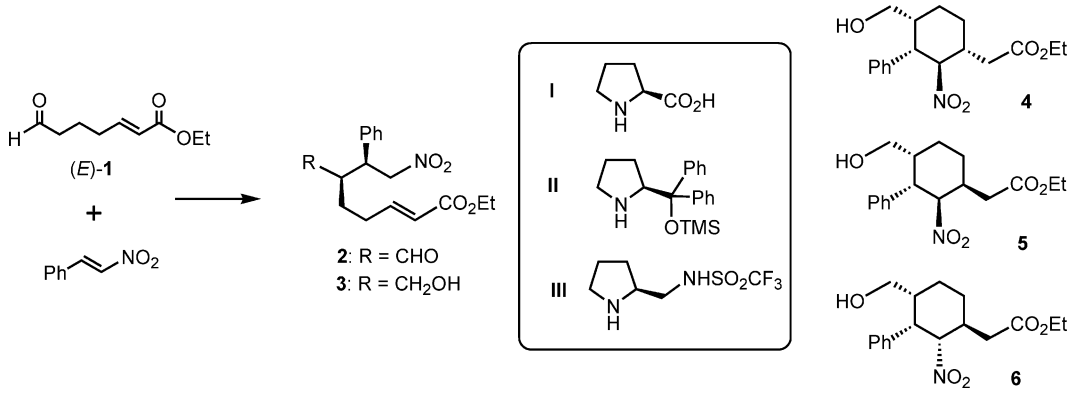
Results and Discussion

Initially, L-proline (0.2 equiv.) was added to a solution of ethyl (*E*)-7-oxohept-2-enoate (**1**) and nitrostyrene in CH_3CN (3 mL, 0.25 M) and the solution was stirred at 25 °C for 24 h until completion of reaction. The nitro-Michael product **2** was obtained in 53% yield with a diastereomeric ratio of 13:1. In a separate reaction, addition of Et_3N to the reaction mixture not only facilitated the reaction (completed in 0.5 h), but also improved the yield (75%). Recently, pyrrolidine derivatives, for example, diarylprolinol TMS ether, have emerged as promising general enamine organocatalysts.[9,10] A series of organocatalysts, additives, and various conditions were screened, and selected results are summarized in Table 1. The enantioselectivity of **2** was determined from the corresponding alcohol **3**, prepared in situ from **2** by reduction with $NaBH_4$.[11] The reduction of **2** in CH_2Cl_2 at –20 °C provided **3** in 25% *ee* and 71% yield after the two-step reaction (Table 1, entry 1). Nitro-Michael reaction of **1** and nitrostyrene catalyzed by **II**/HOAc or **II**/$C_6H_5CO_2H$ with either CH_2Cl_2 or toluene as solvent, followed by reduction at –20 °C afforded **3** in >99% *ee* (Table 1, entries 2–4). The reaction in toluene was somewhat slower and gave a lower yield than in CH_2Cl_2. On the other hand, the reaction with catalyst **III** in *i*PrOH gave only moderate enantioselectivity (41% *ee*, Table 1, entry 5). Interestingly, the products from the reduction of **2** with $NaBH_4$ were solvent- and temperature-dependent. The reaction of **2** with $NaBH_4$ in EtOH at a low temperature (–20 °C) led to the reduction of not only the aldehyde group, but also afforded the Michael cyclization adducts **4** and **5** in a ratio of 2:3 with 23 and 24% *ee*, respectively (Table 1, entry 6).[12] Apparently, the alkalinity

Table 1. Screening of the catalyst, solvent, and reaction conditions for the catalytic nitro-Michael addition reaction of 7-oxohept-2-enoate and nitrostyrene.



Entry	Cat.[a]	Additive[b]	Solvent	T [°C], t [h]	dr[c] (*syn*/*anti*)	Solvent[d]	T [°C], t [h][d]	Yield [%] [e]	Product(s) [ratio][c]	*ee* [%][f]
1	**I**	Et_3N	CH_3CN	28, 0.5	13:1	CH_2Cl_2	–20, 18	71	**3**	25
2	**II**	HOAc	CH_2Cl_2	0, 18	21:1	CH_2Cl_2	–20, 24	82	**3**	>**99**
3	**II**	HOAc	toluene	0, 30	11:1	toluene	–20, 24	75	**3**	>**99**
4	**II**	$C_6H_5CO_2H$	CH_2Cl_2	0, 18	12:1	CH_2Cl_2	–20, 24	80	**3**	>**99**
5	**III**	–	*i*PrOH	0, 36	8:1	CH_2Cl_2	–20, 24	72	**3**	41
6	**I**	Et_3N	CH_3CN	28, 0.5	13:1	EtOH	–20, 12	71	**4**, **5** [2:3]	23/24
7	**I**	Et_3N	CH_3CN	0, 1.5	13:1	EtOH	–20, 12	78	**4**, **5** [2:3]	31/31
8	**II**	HOAc	CH_3CN	0, 8	9:1	CH_3CN	–20, 12	75	**4**, **5** [1:1]	>**99**/>**99**
9	**I**	Et_3N	CH_3CN	28, 0.5	13:1	EtOH	28, 0.5	68	**4**, **6** [1:1][g]	24/22
10	**II**	HOAc	CH_3CN	0, 8	10:1	EtOH	28, 0.5	65	**4**, **6** [1:1][g]	>99/>99

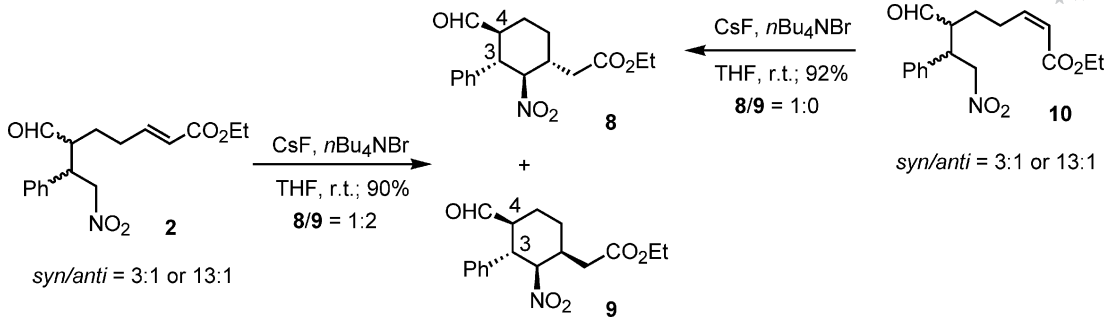
[a] 0.2 equivalents of catalysts were used. [b] 0.2 equivalents of additives were used. [c] Determined by ^1H NMR prior to work up. [d] Conditions for the reaction with $NaBH_4$. [e] Isolated yields. [f] Enantiomeric excesses (*ee* values) were determined by HPLC with a chiral column (Chiracel OD). [g] Compound **5** was obtained in less than 5% yield.

of $NaBH_4$ caused the deprotonation of the methylene proton adjacent to the nitro group of **2** and triggered the Michael reaction. The enantioselectivity was increased slightly to 31% *ee* when the first-step nitro-Michael reaction proceeded at 0 °C, and attained a maximum (>99% *ee*) in the 1st-step reaction with **II**/HOAc (Table 1, entries 7 and 8). On the other hand, performing the 2nd-step reduction process at 28 °C afforded a 1:1 ratio of **4** and **6** (not **5**) in 24 and 22% *ee*, respectively (Table 1, entry 9). The enantioselectivity was improved and reached >99% *ee* by replacing L-Pro with **II**/HOAc (Table 1, entry 10).[13]

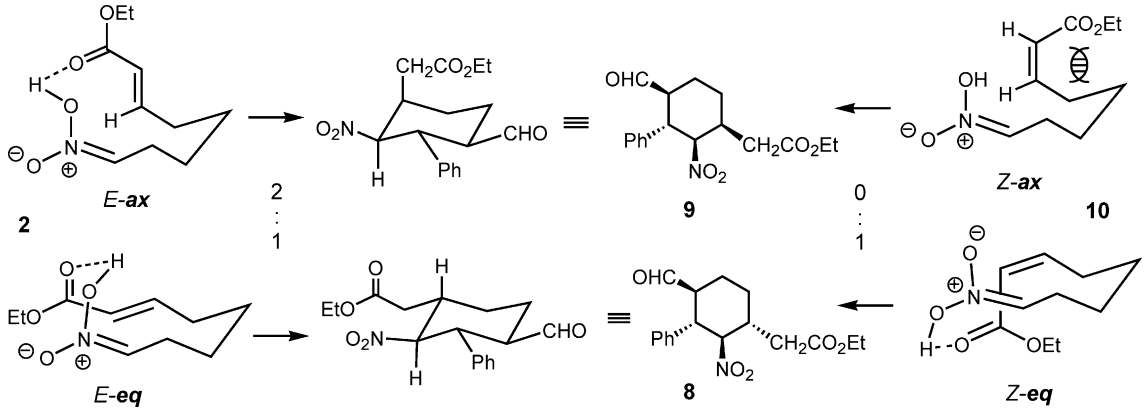
For decades, the Michael reaction has been one of the most important methodologies for ring construction.[14,15] Many fascinating examples of tandem Michael reactions have been achieved in which the first intermolecular Michael reaction was followed by an intramolecular variant leading to ring-formation. Accordingly, we attempted the intramolecular Michael cyclization of **2**. Reaction of a *syn* and *anti* mixture of **2** (3:1) with CsF and nBu$_4$NBr in THF gave a 90% yield of **8** and **9** in a ratio of 1:2 (Scheme 1). Unexpectedly, the formyl and phenyl groups at C-3 and C-4 are orientated *anti* in both **8** and **9**. As there are eight possible diastereomeric isomers, and twice as many if both enantiomers are considered, it is interesting that even modest enantioselectivity was observed. Subjecting pure *syn*-**2** to the same reaction conditions gave similar selectivity. Apparently, under basic conditions, isomerization of the formyl group occurred in the original **2** (*syn*/*anti*) and/or the formed C3–C4 *syn* adduct leading to the formation of the more stable C3–C4 *anti* product.[16,17] More interestingly, under the same reaction conditions, reaction of the *anti* and *syn* mixture of **10**, prepared from (*Z*)-**1** and nitrostyrene, gave **8** as the only observed product in 92% yield. The different stereoselectivities observed in the cyclization of the *E*/*Z* isomers **2** and **10** can be rationalized through the mechanism shown in Scheme 2.[18] A 6-*exo* cyclization of **2** (or **10**) proceeds through the chair transition state *E*-eq with an equatorial side-chain (alkene) to give **8**, or through the chair transition state *E*-ax with an axial side-chain (alkene) to give **9**. Such transition states have been shown to be close in energy, and similar effects of alkene geometry (*E* and *Z*) on the formation of ring stereochemistry have been observed in 6-*exo* radical cyclization reactions.[19]

Alternatively, the (*Z*)-alkene ester substituent on **10** raises the transition state of *Z*-ax as a result of A strain leading to the predominant formation of **8** via the *Z*-eq transition state. Based on these results, a series of nitrostyrene derivatives were treated with the (*Z*)-7-oxohept-2-enoate. The two-step reactions were carried out in one pot by reaction with catalyst **II** (0.25 equiv.) and HOAc in CH_2Cl_2 at 0 °C for 1–4 h followed by the addition of a THF solution of CsF and TBAF at 0 °C and stirring for 1–2 h (Table 2).

Significantly, all of the examples gave excellent enantioselectivity, diastereoselectivity (>30:1), and high yields (75–92%, Table 2, entries 1–7). Noteworthy, for the reaction with *ortho*-substituted nitrostyrene, for example, 1-chloro-2-(2-nitrovinyl)benzene, the C3–C4 *cis* isomer **17** was obtained when the second step of the reaction was maintained

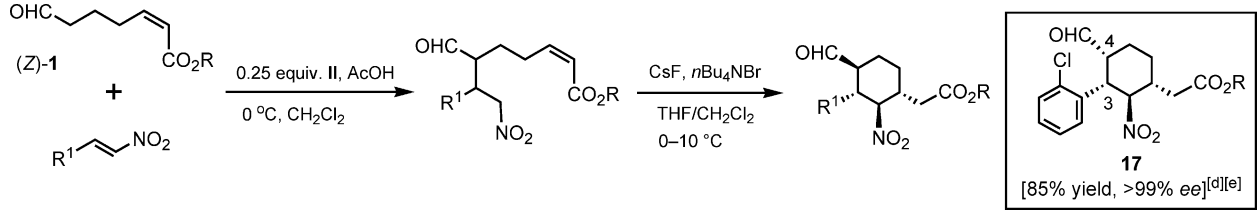


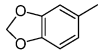
Scheme 1. Intramolecular Michael cyclization of **2** and **10**.



Scheme 2. Proposed mechanism for the cyclization reaction of **2** and **10**.

Table 2. One-pot reactions of the domino Michael reactions.

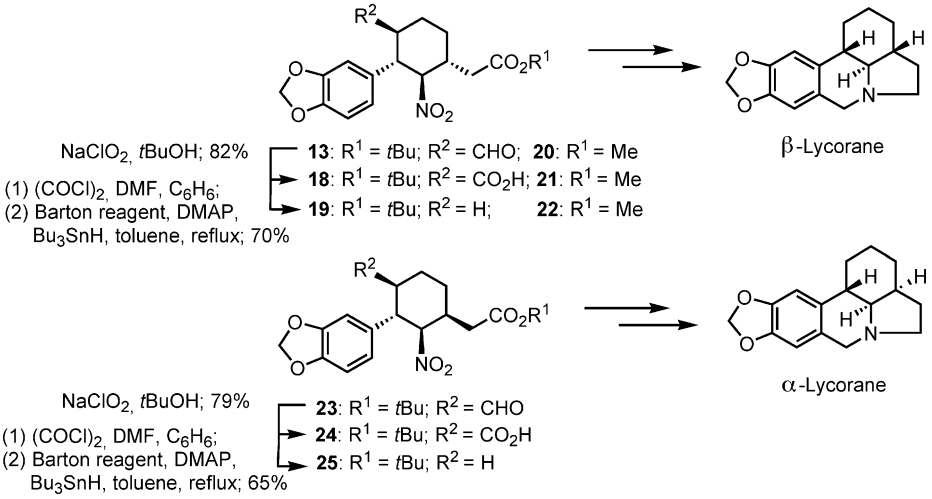


Entry	Product	*t* [h] (step 1, step 2)	Yield [%][a]	*ee* [%][b]
1	**8**: R = Et, R^1 = Ph	1, 1	92	>99[c]
2	**11**: R = Et, R^1 = *p*-OMe-C_6H_4	1, 1	80	87 (97)[d]
3	**12**: R = Et, R^1 = *p*-Br-C_6H_4	2, 1	75	>99
4	**13**: R = *t*Bu, R^1 = 	3, 1	79	98
5	**14**: R = Et, R^1 = *p*-Me-C_6H_4	2, 2	81	94
6	**15**: R = Et, R^1 = *p*-F-C_6H_4	2, 1	78	>99[e]
7	**16**: R = Et, R^1 = *o*-Cl-C_6H_4	2, 3	76	99[e,f]

[a] Isolated yield. [b] Unless otherwise noted, the enantiomeric excesses (*ee* values) were determined from the corresponding alcohol (prepared in situ with $NaBH_4$) by HPLC with a chiral column (Chiracel OD). [c] Also confirmed from the Mosher derivatives by ^1H NMR analysis. [d] The first-step reaction proceeded at –20 °C for 6 h. [e] The enantiomeric excesses (*ee* values) were determined from the aldehyde by using a Chiralpak-IA column. [f] Compound **17** was obtained exclusively in 85% yield and >99% *ee* when the second-step reaction was maintained at 0 °C for 3 h. Compound **16** was obtained exclusively in 76% yield and 99% *ee* when the second-step reaction was maintained at 28 °C for 3 h.

at 0 °C. In contrast, the C3–C4 *trans* isomer **16** was isolated when the second step of the reaction was carried out at 28 °C for 3 h. The slow isomerization of the *cis* product towards the *trans* product in this system was probably due to the congestion at C-4 around the aldehyde group, caused by the *ortho* effect of the aromatic ring.

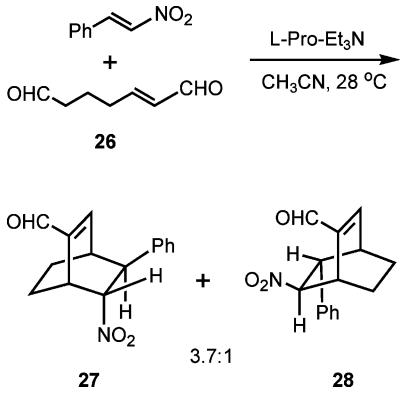
Amaryllidaceae alkaloids, for example, α-, β-, and γ-lycoranes, have attracted considerable synthetic efforts[20] due to



Scheme 3. Application of double Michael adducts in the synthesis of (–)-α- and (–)-β-lycorane.

the unique structural features of the tetracyclic galanthan skeleton and its biological activities.[21] We envisioned that the double Michael adducts would be versatile intermediates in the synthesis of amaryllidaceae alkaloids. The *tert*-butyl ester **13** was therefore transformed into **19**,[22] an intermediate used in the synthesis of (±)-β-lycorane, (Scheme 3). Chlorite oxidation of aldehyde **13** to acid **18** ($NaClO_2$, *t*BuOH, 2-methyl-2-butene, NaH_2PO_4, 25 °C; 82%) followed by transformation into the acyl chloride and esterification with 2-mercaptopyridine *N*-oxide afforded the corresponding Barton ester, which was decarboxylated (nBu_3SnH, toluene, reflux) without purification to provide **19** in 70% yield. Similarly, **22**[23] and **25**,[22] intermediates in the synthesis of β- and α-lycorane, respectively, were prepared from **20** and **23** by the same reaction sequence. Comparison of the optical rotation data obtained from (–)-**22** with literature values revealed the absolute stereochemistry of **20** as that depicted in Scheme 3.

Encouraged by the success of these results, the reaction of α,β-unsaturated dialdehyde **26** was examined. Interestingly, the reaction of **26** with L-proline and Et_3N in CH_3CN at ambient temperature for 3 h afforded two bicyclo[2.2.2]-octanes **27** and **28** in a 3.7:1 ratio in 41% yield.[24] These two bicyclic compounds may be the result of a subsequent intramolecular aldol reaction of the formylcyclohexanecarbaldehyde (Scheme 4).



Scheme 4. Domino Michael reaction of dialdehyde **26**.

Conclusions

We have developed a highly diastereoselective and enantioselective domino organocatalytic Michael addition reaction which provides expedited access to highly functionalized and enatiomerically enriched cyclohexane derivatives (>99% *ee*). Adducts **13**, **20**, and **23** were used in the formal synthesis of (–)-β- and (–)-α-lycorane, and the generality of this methodology was further demonstrated by the domino reaction of the dialdehyde **26** providing bicyclo[2.2.2]octanes. The simple experimental procedures, high enantioselectivity, and great synthetic versatility of the products render this new methodology highly appealing for asymmetric synthesis. The full scope of this methodology is currently under investigation.

Experimental Section

General Methods: All solvents were reagent grade. L-Proline (99+%) was purchased from Bachem. Other chemicals were purchased from Aldrich or Acros Chemical Co. Reactions were normally carried out under argon in flame-dried glassware. Merck silica gel 60 (particle size 0.04–0.063 mm) was employed for flash chromatography. Melting points are uncorrected. ^1H NMR and COSY spectra were obtained in $CDCl_3$ at 400 (Bruker DPX-400) or 500 MHz (Varian-Unity INOVA-500) unless otherwise noted. ^{13}C NMR spectra and HMBC, HMQC, and DEPT experiments were performed at 100 or 125 MHz. The *ee* values were measured by GC–MS (Shimadzu QP 5000, chiral capillary column, γ-cyclodextrin trifluoroacetyl, Astec Type G-TA, size 30 m × 0.25 mm, flow rate 24 mL/min, temperature range: 60–120 °C, gradient 3 °C/min) or by HPLC on a chiral column. The HPLC apparatus was equipped with ultraviolet and refractive index detectors. Samples were analyzed on a chiral column (Chiracel OD-H or Chiralpak-IA, 0.46 cm (i.d.) × 25 cm, particle size 5 μ) by elution with EtOAc/hexane or

*i*PrOH/hexane. The flow rate of the indicated eluent was maintained at 1 mL/min and the retention times were recorded accordingly.

General Procedure for the Preparation of 2: A solution of catalyst **II** (41 mg, 0.13 mmol) and acetic acid (8 mg, 0.13 mmol) in CH_2Cl_2 (1 mL) was added dropwise to a solution of (*E*)-**1** (102 mg, 0.6 mmol)[25] and *trans*-nitrostyrene (75 mg, 0.5 mmol) in CH_2Cl_2 (2 mL). The solution was stirred for 1 h, diluted with EtOAc (10 mL), washed with brine (2 mL), dried with Na_2SO_4, and concentrated in vacuo to give the crude product. The residue was purified by flash column chromatography with 10% EtOAc/hexane (R_f = 0.28 in 20% EtOAc/hexane) to give a 3:1 diastereomeric mixture of **2** as a colorless oil (149 mg, 93%). Selected spectroscopic data for **2**: $[\alpha]_D^{25}$ = +23.2 (*c* = 0.6, $CHCl_3$). IR (neat): $\tilde{\nu}$ = 2825, 1739, 1678, 1577, 1372, 1233, 1178, 1038, 790, 755 cm^{-1}. ^1H NMR ($CDCl_3$, 500 MHz): δ = 9.71 (s, 1 H), 7.38–7.05 (m, 5 H), 6.75–6.62 (m, 1 H), 5.68 (d, *J* = 15.5 Hz, 1 H), 4.70–4.58 (m, 2 H), 4.14 (q, *J* = 7.0 Hz, 2 H), 3.80–3.72 (m, 1 H), 2.18–2.08 (m, 1 H), 2.04–1.95 (m, 1 H), 1.65–1.45 (m, 3 H), 1.25 (t, *J* = 7.0 Hz, 3 H) ppm. ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 202.2 (CH), 166.1 (C), 146.3 (CH), 136.2 (C), 129.3 (2 CH), 128.4 (CH), 127.9 (2 CH), 122.5 (CH), 78.1 (CH_2), 60.3 (CH_2), 53.1 (CH), 43.0 (CH), 28.8 (CH_2), 25.6 (CH_2), 14.1 (CH_3) ppm. MS: *m*/*z* (%) = 319 (0.2) $[M]^+$, 272 (6), 225 (10), 117 (40), 104 (84), 91 (100). HRMS: calcd. for $C_{17}H_{21}NO_5$ $[M]^+$ 319.1420; found 319.1411.

General Procedure for the Preparation of 3 (Table 1, Entry 1): L-Proline (4 mg, 0.036 mmol) and Et_3N (3.6 mg, 0.036 mmol) were added to a solution of (*E*)-**1** (30 mg, 0.18 mmol) and *trans*-nitrostyrene (29 mg, 0.2 mmol) in CH_3CN (2 mL). The solution was stirred for 0.5 h, diluted with EtOAc (25 × 2 mL), washed with brine (10 mL), dried with Na_2SO_4, and concentrated in vacuo to give the crude product. $NaBH_4$ (20 mg, 0.52 mmol) was added to a solution of the residue in CH_2Cl_2 (2 mL) at –20 °C. The solution was stirred at the same temperature for 18 h, diluted with EtOAc (25 × 2 mL), washed with brine (10 mL), dried with Na_2SO_4, and concentrated in vacuo to give the crude product. The residue was purified by flash column chromatography with 20% EtOAc/hexane (R_f = 0.35 in 40% EtOAc/hexane) to give **3** as a colorless oil (41 mg, 71% yield). Spectroscopic data for **3**: $[\alpha]_D^{25}$ = –20.1 (*c* = 7.8, $CHCl_3$). IR (neat): $\tilde{\nu}$ = 3460, 2927, 1712, 1551, 1378, 1278, 1200, 1041, 703 cm^{-1}. ^1H NMR ($CDCl_3$, 500 MHz): δ = 7.36–7.30 (m, 2 H), 7.28–7.22 (m, 1 H), 7.20–7.16 (m, 2 H), 6.82–6.74 (m, 1 H), 5.72 (d, *J* = 15.5 Hz, 1 H), 4.86 (dd, *J* = 13.0, 5.5 Hz, 1 H), 4.77 (dd, *J* = 12.5, 10.0 Hz, 1 H), 4.15 (q, *J* = 7.0 Hz, 2 H), 3.78–3.72 (m, 1 H), 3.70–3.62 (m, 1 H), 3.60–3.52 (m, 1 H), 2.30–2.18 (m, 1 H), 2.12–2.02 (m, 1 H), 1.84–1.82 (m, 1 H), 1.50–1.34 (m, 2 H), 1.26 (t, *J* = 7.0 Hz, 3 H), 1.25–1.20 (m, 1 H) ppm. ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 166.4 (C), 147.8 (CH), 138.2 (C), 128.9 (2 CH), 128.1 (2 CH), 127.7 (CH), 122.0 (CH), 78.5 (CH_2), 62.0 (CH_2), 60.3 (CH_2), 45.9 (CH), 43.0 (CH), 29.7 (CH_2), 27.1 (CH_2), 14.2 (CH_3) ppm. MS: *m*/*z* (%) = 321 (1) $[M]^+$, 275 (4), 256 (12), 169 (40), 129 (44), 104 (64), 91 (100). HRMS: calcd. for $C_{17}H_{23}NO_5$ $[M]^+$ 321.1577; found 321.1572.

Representative Procedure for the Preparation of 4 and 5 (Table 1, Entry 6): L-Proline (4 mg, 0.036 mmol) and Et_3N (3.6 mg, 0.036 mmol) were added to a solution of (*E*)-**1** (30 mg, 0.18 mmol) and *trans*-nitrostyrene (29 mg, 0.2 mmol) in CH_3CN (2 mL). The solution was stirred for 0.5 h, diluted with EtOAc (25 × 2 mL), washed with brine (10 mL), dried with Na_2SO_4, and concentrated in vacuo to give the crude product. $NaBH_4$ (20 mg, 0.52 mmol) was added to a solution of the residue in EtOH (2 mL) at –20 °C. The solution was stirred at the same temperature for 12 h until completion of reaction (monitored by TLC). The solution was then diluted with EtOAc (25 × 2 mL), washed with brine (10 mL), dried with Na_2SO_4, and concentrated in vacuo to give the crude product. The residue was purified by flash column chromatography with 20% EtOAc/hexane (**4**: R_f = 0.35; **5**: R_f = 0.35; 40% EtOAc/hexane) to give a mixture of **4** and **5** which was separated by HPLC (**4**: R_t = 21.1 min; **5**: R_t = 19.0 min; 10% *i*PrOH/hexane, flow rate 1 mL/min, 210 nm) to give **4** (16 mg, 28% yield) and **5** (25 mg, 43% yield) as colorless oils. Spectroscopic data for **4**: $[\alpha]_D^{25}$ = –19.2 (*c* = 2.5, $CHCl_3$). IR (neat): $\tilde{\nu}$ = 3442, 2920, 1728, 1549, 1371, 1176, 1032, 702 cm^{-1}. ^1H NMR (C_6D_6, 500 MHz): δ = 7.08–6.97 (5 H), 5.26 (dd, *J* = 12.0, 11.0 Hz, 1 H), 3.94–3.86 (m, 2 H), 3.40 (dd, *J* = 12.0, 4.5 Hz, 1 H), 3.12–3.05 (m, 1 H), 2.94 (d, *J* = 10.5 Hz, 1 H), 2.42–2.38 (m, 2 H), 2.29 (dd, *J* = 16.5, 8.0 Hz, 1 H), 1.77 (d, *J* = 13.5 Hz, 1 H), 1.70–1.50 (m, 3 H), 1.40–1.25 (m, 1 H), 0.93 (t, *J* = 7.0 Hz, 3 H) ppm. ^{13}C NMR (C_6D_6, 125 MHz): δ = 170.8 (C), 138.9 (C), 128.7 (CH), 128.3 (CH), 128.1 (CH), 127.9 (CH), 127.4 (CH), 89.3 (CH), 61.0 (CH_2), 60.4 (CH_2), 50.1 (CH), 42.1 (CH), 39.6 (CH), 37.1 (CH_2), 27.6 (CH_2), 25.9 (CH_2), 14.1 (CH_3) ppm. MS: *m*/*z* (%) = 321 (1) $[M]^+$, 274 (4), 256 (27), 244 (32), 169 (92), 91 (100). HRMS: calcd. for $C_{17}H_{23}NO_5$ $[M]^+$ 321.1576; found 321.1582.

Spectroscopic Data for 5: $[\alpha]_D^{25}$ = –37.2 (*c* = 1.5, $CHCl_3$). IR (neat): $\tilde{\nu}$ = 3445, 2923, 2853, 1730, 1550, 1033, 757, 702 cm^{-1}. ^1H NMR ($CDCl_3$, 500 MHz): δ = 7.35–7.20 (m, 5 H), 5.23 (dd, *J* = 6.5, 5.0 Hz, 1 H), 4.11 (q, *J* = 7.0 Hz, 2 H), 3.65 (dd, *J* = 7.5, 6.5 Hz, 1 H), 3.45–3.32 (m, 2 H), 3.02–2.96 (m, 1 H), 2.55–2.40 (m, 2 H), 2.39–2.32 (m, 1 H), 2.00–1.90 (m, 1 H), 1.88–1.72 (m, 3 H), 1.75 (s, 1 H), 1.22 (t, *J* = 7.0 Hz, 3 H) ppm. ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 171.5 (C), 138.8 (C), 128.9 (2 CH), 128.1 (CH), 127.4 (2 CH), 88.0 (CH), 63.2 (CH_2), 60.8 (CH_2), 44.3 (CH), 40.0 (CH), 34.4 (CH_2), 33.7 (CH), 25.2 (CH_2), 23.0 (CH_2), 14.1 (CH_3) ppm. MS: *m*/*z* (%) = 321 (1) $[M]^+$, 256 (26), 244 (32), 169 (80), 91 (100). HRMS: calcd. for $C_{17}H_{23}NO_5$ $[M]^+$ 321.1576; 321.1577.

General Procedure for the Preparation of 4 and 6 (Table 1, Entry 9): L-Proline (4 mg, 0.036 mmol) and Et_3N (3.6 mg, 0.036 mmol) were added to a solution of (*E*)-**1** (30 mg, 0.18 mmol) and *trans*-nitrostyrene (29 mg, 0.2 mmol) in CH_3CN (2 mL). The solution was stirred for 0.5 h, diluted with EtOAc (25 × 2 mL), washed with brine (10 mL), dried with Na_2SO_4, and concentrated in vacuo to give the crude product. $NaBH_4$ (20 mg, 0.52 mmol) was added to a solution of the residue in EtOH (2 mL) at 30 °C. The solution was stirred at the same temperature for 0.5 h until completion of reaction (monitored by TLC). The solution was diluted with EtOAc (25 × 2 mL), washed with brine (10 mL), dried with Na_2SO_4, and concentrated in vacuo to give the crude product. The residue was purified by flash column chromatography with 20% EtOAc/hexane (**4**: R_f = 0.35; **6**: R_f = 0.28; 40% EtOAc/hexane) to give **4** (21 mg, 36% yield) and **6** (18 mg, 32% yield) as colorless oils. Selected spectroscopic data for **6**: $[\alpha]_D^{25}$ = –25.5 (*c* = 2.1, $CHCl_3$). IR (neat): $\tilde{\nu}$ = 3442, 2925, 1728, 1547, 1371, 1178, 1032, 704 cm^{-1}. ^1H NMR ($CDCl_3$, 500 MHz): δ = 7.28 (br. s, 5 H), 4.70 (dd, *J* = 12.0, 6.0 Hz, 1 H), 4.13 (q, *J* = 7.0 Hz, 2 H), 3.90 (dd, *J* = 6.0, 6.0 Hz, 1 H), 3.30 (dd, *J* = 10.5, 6.0 Hz, 1 H), 3.20 (dd, *J* = 10.5, 8.5 Hz, 1 H), 3.05–2.95 (m, 1 H), 2.45 (d, *J* = 15.5 Hz, 1 H), 2.30–2.10 (m, 3 H), 1.70–1.60 (m, 2 H), 1.50–1.30 (m, 2 H), 1.24 (t, *J* = 7.0 Hz, 3 H) ppm. ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 171.3 (C), 135.2 (C), 130.4 (2 CH), 128.6 (2 CH), 128.1 (CH), 91.7 (CH), 64.8 (CH_2), 60.7 (CH_2), 47.4 (CH), 43.1 (CH), 37.9 (CH_2), 31.8 (CH), 29.3 (CH_2), 22.8 (CH_2), 14.2 (CH_3) ppm. MS: *m*/*z* (%) = 321 (1) $[M]^+$, 274 (4), 256 (24), 244 (33), 169 (93). HRMS: calcd. for $C_{17}H_{23}NO_5$ $[M]^+$ 321.1576; found 321.1582.

Typical Procedure for the Preparation of 8 from 10: Tetrabutylammonium bromide (52.5 mg, 0.16 mmol) and cesium fluoride (12.4 mg, 0.08 mmol) were added to a solution of **10** (26 mg, 0.08 mmol) in THF (2 mL). The resulting mixture was stirred for 1 h. The solution was diluted with EtOAc (25 mL), washed with brine, dried with Na_2SO_4, and concentrated in vacuo to give the crude product. The residue was purified by flash column chromatography with 10% EtOAc/hexane to give **8** as a colorless oil (24 mg, 92%). Selected spectroscopic data for **8**: $[a]_D^{25}$ = –35.4 (c = 2.3, $CHCl_3$). IR (neat): $\tilde{\nu}$ = 2925, 2856, 1726, 1550, 1371, 1176, 700 cm^{-1}. ^1H NMR ($CDCl_3$, 500 MHz): δ = 9.36 (d, J = 2.5 Hz, 1 H), 7.32–7.22 (m, 3 H), 7.20–7.16 (m, 2 H), 4.68 (dd, J = 11.0, 11.0 Hz, 1 H), 4.13 (q, J = 7.0 Hz, 2 H), 3.41 (dd, J = 11.5, 12.0 Hz, 1 H), 2.80–2.72 (m, 1 H), 2.60–2.50 (m, 1 H), 2.39 (dd, J = 16.0, 3.0 Hz, 1 H), 2.30–2.22 (m, 1 H), 2.20–2.16 (m, 1 H), 2.06–2.02 (m, 1 H), 1.70–1.40 (m, 2 H), 1.24 (t, J = 7.0 Hz, 3 H) ppm. ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 200.9 (CH), 170.7 (C), 136.4 (C), 129.2 (2 CH), 128.4 (CH), 127.9 (2 CH), 94.6 (CH), 60.9 (CH_2), 53.5 (CH), 48.4 (CH), 38.2 (CH), 36.7 (CH_2), 28.7 (CH_2), 25.4 (CH_2), 14.1 (CH_3) ppm. MS: m/z (%) = 320 (10) $[M + 1]^+$, 272 (42), 242 (26), 198 (100), 167 (78), 155 (77). HRMS: calcd. for $C_{17}H_{21}NO_5$ $[M]^+$ 319.1420; found 319.1417.

Typical Procedure for the Preparation of 8 and 9 from 2: Tetrabutylammonium bromide (141 mg, 0.44 mmol) and cesium fluoride (34 mg, 0.22 mmol) were added to a solution of **2** (70 mg, 0.22 mmol) in THF (4 mL). The resulting mixture was stirred for 1 h. The solution was diluted with EtOAc (25 mL), washed with brine, dried with Na_2SO_4, and concentrated in vacuo to give the crude product. The residue was purified by flash column chromatography with 10% EtOAc/hexane to give **8** and **9** (**8**: R_f = 0.50; **9**: R_f = 0.48, 30% EtOAc/hexane) in a ratio of 1:2 as colorless oils in a combined yield of 90% (63 mg). Selected spectroscopic data for **9**: $[a]_D^{25}$ = –12.2 (c = 4, $CHCl_3$). IR (neat): $\tilde{\nu}$ = 2925, 2854, 1726, 1549, 1456, 1373, 1181, 701 cm^{-1}. ^1H NMR ($CDCl_3$, 500 MHz): δ = 9.38 (d, J = 1.5 Hz, 1 H), 7.31–7.20 (m, 5 H), 4.98 (dd, J = 12.0, 5.0 Hz, 1 H), 4.12 (q, J = 7.0 Hz, 2 H), 3.51 (dd, J = 12.0, 12.0 Hz, 1 H), 3.20–3.10 (m, 1 H), 2.75–2.62 (m, 1 H), 2.57 (d, J = 6.0 Hz, 2 H), 2.10–2.00 (m, 1 H), 1.90–1.80 (m, 2 H), 1.70–1.55 (m, 1 H), 1.23 (t, J = 7.0 Hz, 3 H) ppm. ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 200.8 (CH), 171.0 (C), 137.0 (C), 129.1 (2 CH), 128.2 (CH), 128.1 (2 CH), 91.6 (CH), 61.0 (CH_2), 54.3 (CH), 41.9 (CH), 34.0 (CH), 31.9 (CH_2), 27.9 (CH_2), 20.2 (CH_2), 14.1 (CH_3) ppm. MS: m/z (%) = 319 (1) $[M]^+$, 272 (30), 198 (57), 155 (74), 91 (100). HRMS: calcd. for $C_{17}H_{21}NO_5$ $[M]^+$ 319.1420; found 319.1415.

Typical Procedure for the Preparation of 8 from (*Z*)-1 (Two Reactions in One Pot): A solution of **II** (40 mg, 0.125 mmol) and acetic acid (7.5 mg, 0.125 mmol) in CH_2Cl_2 (1 mL) was added dropwise to a solution of (*Z*)-**1** (102.2 mg, 0.6 mmol)[26] and *trans*-nitrostyrene (75 mg, 0.5 mmol) in CH_2Cl_2 (2 mL). The resulting mixture was stirred for 2 h at 0 °C. The solution was diluted with THF (10 mL) and then tetrabutylammonium bromide (141 mg, 0.44 mmol) and cesium fluoride (34 mg, 0.22 mmol) were added. The resulting mixture was stirred for 1 h at 0–10 °C. The solution was diluted with EtOAc (30 mL), washed with brine, dried with Na_2SO_4, and concentrated in vacuo to give the crude product. The residue was purified by flash column chromatography with 10% EtOAc/hexane (R_f = 0.50 for **8** in 30% EtOAc/hexane) to give **8** as a colorless oil (147 mg, 92% yield).

Ester 10: To a solution of (*Z*)-**1** (102.2 mg, 0.6 mmol)[27] and *trans*-nitrostyrene (75 mg, 0.5 mmol) in CH_2Cl_2 (2 mL) was added dropwise a solution of (*S*)-diphenylpyrrolinol trimethylsilyl ether (**II**, 40 mg, 0.125 mmol) and acetic acid (7.5 mg, 0.125 mmol) in CH_2Cl_2 (1 mL). The resulting mixture was stirred for 1 h. The solution was diluted with EtOAc (25 mL), washed with brine, dried with Na_2SO_4, concentrate in vacuo to give the crude product. The residue was purified by flash column chromatography with 10% EtOAc/hexane (R_f = 0.38 for 10 in 20% EtOAc/hexane) to give **10** as a colorless oil (153 mg, 95% yield). Selected spectroscopic data for **10**: $[a]_D^{25}$ = +20.4 (c = 3, $CHCl_3$). ^1H NMR ($CDCl_3$, 500 MHz): δ = 9.75 (s, 1 H), 7.38–7.22 (m, 3 H), 7.18–7.10 (m, 2 H), 6.00–5.90 (m, 1 H), 5.73 (d, J = 11.5 Hz, 1 H), 4.78–4.60 (m, 2 H), 4.12 (q, J = 7.0 Hz, 2 H), 3.82–3.76 (m, 1 H), 2.78–2.70 (m, 1 H), 2.68–2.50 (m, 2 H), 1.70–1.60 (m, 1 H), 1.55–1.45 (m, 1 H), 1.23 (t, J = 7.0 Hz, 3 H) ppm. ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 202.9 (CH), 165.9 (C), 147.2 (CH), 136.5 (C), 129.1 (2 CH), 128.2 (CH), 128.0 (2 CH), 121.3 (CH), 78.1 (CH_2), 60.0 (CH_2), 53.2 (CH), 43.1 (CH), 26.6 (CH_2), 25.8 (CH_2), 14.2 (CH_3) ppm. MS: m/z (%) = 319 (4) $[M]^+$, 272 (8), 225 (16), 199 (20), 169 (30), 129 (36), 104 (96), 91 (100), 55 (16). HRMS: calcd. for $C_{17}H_{21}NO_5$ $[M]^+$: 319.1420; found 319.1412.

Ester 11: 163 mg, 80% yield. R_f = 0.29 for **11** in 30% EtOAc/hexane. Selected spectroscopic data for **11**: $[a]_D^{25}$ = –19.6 (c = 2.5, $CHCl_3$). IR (neat): $\tilde{\nu}$ = 2931, 1728, 1550, 1514, 1252, 1180, 1032, 833 cm^{-1}. ^1H NMR ($CDCl_3$, 500 MHz): δ = 9.35 (s, 1 H), 7.10 (d, J = 8.0 Hz, 2 H), 6.81 (d, J = 8.0 Hz, 2 H), 4.61 (dd, J = 11.0, 11.0 Hz, 1 H), 4.12 (q, J = 7.0 Hz, 2 H), 3.74 (s, 3 H), 3.35 (dd, J = 11.5, 11.5 Hz, 1 H), 2.75–2.68 (m, 1 H), 2.58–2.48 (m, 1 H), 2.37 (d, J = 16.0 Hz, 1 H), 2.30–2.20 (m, 1 H), 2.20–2.12 (m, 1 H), 2.05–1.95 (m, 1 H), 1.60–1.40 (m, 2 H), 1.24 (t, J = 7.0 Hz, 3 H) ppm. ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 201.1 (CH), 170.7 (C), 159.4 (C), 128.9 (2 CH), 128.2 (C), 114.6 (2 CH), 94.8 (CH), 60.8 (CH_2), 55.2 (CH_3), 53.6 (CH), 47.6 (CH), 38.2 (CH), 36.7 (CH_2), 28.7 (CH_2), 25.4 (CH_2), 14.1 (CH_3) ppm. MS: m/z (%) = 349 (55) $[M]^+$, 302 (71), 274 (40), 228 (70), 121 (100). HRMS: calcd. for $C_{18}H_{23}NO_6$ $[M]^+$: 349.1525; found 349.1526.

Ester 12: 87 mg, 75% yield. R_f = 0.26 for **12** in 30% EtOAc/hexane. Selected spectroscopic data for **12**: $[a]_D^{25}$ = –27.4 (c = 2.8, $CHCl_3$). IR (neat): $\tilde{\nu}$ = 2925, 2856, 1728, 1550, 1373, 1011, 818 cm^{-1}. ^1H NMR ($CDCl_3$, 500 MHz): δ = 9.36 (s, 1 H), 7.42 (d, J = 8.0 Hz, 2 H), 7.07 (d, J = 8.0 Hz, 2 H), 4.64 (dd, J = 11.5, 11.5 Hz, 1 H), 4.13 (q, J = 7.0 Hz, 2 H), 3.40 (dd, J = 11.5, 11.5 Hz, 1 H), 2.80–2.70 (m, 1 H), 2.58–2.44 (m, 1 H), 2.38 (dd, J = 17.0, 2.5 Hz, 1 H), 2.30–2.20 (m, 1 H), 2.19–2.12 (m, 1 H), 2.10–2.02 (m, 1 H), 1.62–1.42 (m, 2 H), 1.25 (t, J = 7.0 Hz, 3 H) ppm. ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 200.4 (CH), 170.8 (C), 135.8 (C), 132.6 (2 CH), 129.8 (2 CH), 122.7 (C), 94.5 (CH), 61.1 (CH_2), 53.7 (CH), 47.8 (CH), 38.4 (CH), 36.8 (CH_2), 28.9 (CH_2), 25.6 (CH_2), 14.4 (CH_3) ppm. MS: m/z (%) = 399 (8) $[M^+ + 2]$, 397 (8) $[M]^+$, 352 (19), 322 (20), 278 (60), 276 (55), 179 (49), 171 (81), 169 (100). HRMS: calcd. for $C_{17}H_{20}BrNO_5$ $[M]^+$: 397.0525; found 397.0522.

Ester 13: 160 mg, 79% yield. R_f = 0.40 for **13** in 30% EtOAc/hexane. Selected spectroscopic data for **13**: $[a]_D^{25}$ = –18.4 (c = 4, $CHCl_3$). IR (neat): $\tilde{\nu}$ = 2925, 1724, 1550, 1248, 1155, 1039 cm^{-1}. ^1H NMR ($CDCl_3$, 500 MHz): δ = 9.38 (s, 1 H), 6.71–6.60 (m, 3 H), 5.91 (d, J = 2.0 Hz, 2 H), 4.58 (dd, J = 13.0, 13.0 Hz, 1 H), 3.32 (dd, J = 13.0, 13.0 Hz, 1 H), 2.70–2.60 (m, 1 H), 2.50–2.40 (m, 1 H), 2.30 (d, J = 13.5 Hz, 1 H), 2.20–2.10 (m, 1 H), 2.00 (d, J = 10.5 Hz, 1 H), 1.60–1.20 (m, 3 H), 1.42 (s, 9 H) ppm. ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 200.9 (CH), 169.9 (C), 148.3 (C), 147.6 (C), 130.0 (C), 121.5 (CH), 108.8 (CH), 107.8 (CH), 101.3 (CH_2), 94.8 (CH), 81.4 (C), 53.6 (CH), 48.1 (CH), 38.4 (CH), 37.8 (CH_2), 28.6 (CH_2), 28.0 (three CH_3), 25.4 (CH_2) ppm. MS: m/z (%) = 391 (54) $[M]^+$, 318 (16), 288 (100), 199 (43), 135 (75). HRMS: calcd. for $C_{20}H_{25}NO_7$ $[M]^+$: 391.1631; found 391.1628.

Ester 14: 83 mg, 81% yield. R_f = 0.38 for **14** in 30% EtOAc/hexane. Selected spectroscopic data for **14**: $[\alpha]_D^{25}$ = –17.6 (c = 6.5, $CHCl_3$). IR (neat): $\tilde{\nu}$ = 2927, 2861, 1728, 1550, 1373, 1176, 1028, 814 cm^{-1}. ^1H NMR ($CDCl_3$, 500 MHz): δ = 9.36 (s, 1 H), 7.15–7.05 (m, 4 H), 4.66 (dd, J = 11.5, 11.0 Hz, 1 H), 4.14 (q, J = 7.0 Hz, 2 H), 3.38 (dd, J = 11.5, 11.5 Hz, 1 H), 2.80–2.70 (m, 1 H), 2.60–2.50 (m, 1 H), 2.39 (dd, J = 16.5, 3.5 Hz, 1 H), 2.30–2.20 (m, 1 H), 2.30 (s, 3 H), 2.20–2.15 (m, 1 H), 2.05–2.00 (m, 1 H), 1.65–1.40 (m, 2 H), 1.25 (t, J = 7.0 Hz, 3 H) ppm. ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 201.4 (CH), 170.9 (C), 138.4 (C), 133.5 (C), 130.1 (2 CH), 127.9 (2 CH), 95.0 (CH), 61.0 (CH_2), 53.7 (CH), 48.3 (CH), 38.5 (CH), 36.9 (CH_2), 28.9 (CH_2), 25.6 (CH_2), 21.3 (CH_3), 14.4 (CH_3) ppm. MS: m/z (%) = 333 (11) $[M]^+$, 286 (43), 258 (28), 212 (100), 181 (69), 169 (63). HRMS: calcd. for $C_{18}H_{23}NO_5$ $[M]^+$: 333.1576; found 333.1574.

Ester 15: 78 mg, 78% yield. R_f = 0.25 for **15** in 30% EtOAc/hexane. Selected spectroscopic data for **15**: $[\alpha]_D^{25}$ = –25.5 (c = 2, $CHCl_3$). IR (neat): $\tilde{\nu}$ = 2925, 2856, 1728, 1550, 1512, 1227, 1165, 839, 773 cm^{-1}. ^1H NMR ($CDCl_3$, 500 MHz): δ = 9.36 (d, J = 2.0 Hz, 1 H), 7.24–7.15 (m, 2 H), 7.00–6.95 (m, 2 H), 4.64 (dd, J = 11.5, 11.5 Hz, 1 H), 4.15–4.10 (m, 2 H), 3.42 (dd, J = 11.5, 11.5 Hz, 1 H), 2.76–2.71 (m, 1 H), 2.60–2.42 (m, 1 H), 2.40–2.36 (m, 1 H), 2.30–2.20 (m, 1 H), 2.19–2.10 (m, 1 H), 2.08–2.00 (m, 1 H); 1.60–1.42 (m, 2 H), 1.24 (t, J = 7.0 Hz, 3 H) ppm. ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 200.4 (CH), 170.6 (C), 162.4 (J = 246.3 Hz, C), 132.3 (J = 3.9 Hz, C), 129.5 (J = 7.8 Hz, two CH), 116.2 (J = 22.0 Hz, two CH), 94.6 (CH), 60.9 (CH_2), 53.6 (CH), 47.5 (CH), 38.2 (CH), 36.5 (CH_2), 28.6 (CH_2), 25.4 (CH_2), 14.1 (CH_3) ppm. MS: m/z (%) = 337 (3) $[M]^+$, 290 (12), 262 (19), 216 (81), 173 (58), 109 (100). HRMS: calcd. for $C_{17}H_{20}FNO_5$ $[M]^+$: 337.1326; found 337.1324.

Ester 16: 73 mg, 76% yield. R_f = 0.34 for **16** in 30% EtOAc/hexane. Selected spectroscopic data for **16**: $[\alpha]_D^{25}$ = –23.6 (c = 4, $CHCl_3$). IR (neat): $\tilde{\nu}$ = 2925, 2852, 1730, 1550, 1371, 1178, 1034, 758 cm^{-1}. ^1H NMR ([D$_6$]acetone, 500 MHz): δ = 9.41 (s, 1 H), 7.71 (d, J = 7.5 Hz, 1 H), 7.42–7.20 (m, 3 H), 5.07 (dd, J = 11.0, 11.0 Hz, 1 H), 4.22 (dd, J = 12.0, 15.0 Hz, 1 H), 4.11 (q, J = 7.0 Hz, 2 H), 2.95–2.80 (m, 4 H), 2.62–2.52 (m, 1 H), 2.40–2.00 (m, 1 H), 1.85–1.72 (m, 1 H), 1.70–1.60 (m, 1 H), 1.23 (t, J = 7.0 Hz, 3 H) ppm. ^{13}C NMR ([D$_6$]acetone, 125 MHz): δ = 201.4 (CH), 171.3 (C), 136.6 (C), 135.2 (C), 130.7 (CH), 130.2 (CH), 129.6 (CH), 128.8 (CH), 94.5 (CH), 61.2 (CH_2), 55.7 (CH), 44.3 (CH), 39.4 (CH), 37.7 (CH_2), 29.1 (CH_2), 26.0 (CH_2), 14.5 (CH_3) ppm. MS: m/z (%) = 353 (12) $[M]^+$, 308 (10), 261 (21), 233 (22), 215 (65), 191 (53), 189 (50), 125 (100). HRMS: calcd. for $C_{17}H_{20}ClNO_5$ $[M]^+$: 353.1030; found 353.1029.

Ester 17: 82 mg, 85% yield. R_f = 0.55 for **17** in 30% EtOAc/hexane. Selected spectroscopic data for **17**: $[\alpha]_D^{25}$ = –16.5 (c = 4.0, $CHCl_3$). IR (neat): $\tilde{\nu}$ = 2933, 2867, 1731, 1571, 1550, 1181, 1034, 755 cm^{-1}. ^1H NMR ($CDCl_3$, 500 MHz): δ = 9.46 (s, 1 H), 7.46 (d, J = 8.0 Hz, 1 H), 7.34 (d, J = 7.5 Hz, 1 H), 7.21–7.10 (m, 2 H), 5.53 (dd, J = 11.0, 11.0 Hz, 1 H), 4.12 (q, J = 7.0 Hz, 2 H), 4.07 (dd, J = 12.0, 4.0 Hz, 1 H), 3.37 (s, 1 H), 2.60–2.49 (m, 1 H), 2.43 (dd, J = 16.5, 3.5 Hz, 1 H), 2.31 (d, J = 16.5, 9.0 Hz, 1 H), 2.17 (d, J = 14.5 Hz, 1 H), 2.00–1.85 (m, 2 H), 1.39–1.30 (m, 1 H), 1.24 (t, J = 7.0 Hz, 3 H) ppm. ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 201.5 (C), 170.7 (C), 134.0 (two C), 130.1 (CH), 128.9 (CH), 128.8 (CH), 126.9 (CH), 88.2 (CH), 60.8 (CH_2), 49.4 (CH), 44.0 (CH), 39.1 (CH), 37.1 (CH_2), 26.1 (CH_2), 23.9 (CH_2), 14.1 (CH_3) ppm. HRMS: calcd. for $C_{17}H_{20}ClNO_5$ $[M]^+$: 353.1030; found 353.1032.

Ester 18: 85 mg, 82% yield. R_f = 0.58 for **18** in 80% EtOAc/hexane. Selected spectroscopic data for **18**: $[\alpha]_D^{25}$ = –24.4 (c = 0.15, $CHCl_3$). IR (neat): $\tilde{\nu}$ = 2966, 2925, 1722, 1676, 1549, 1255, 802 cm^{-1}. ^1H NMR ([D$_6$]acetone, 500 MHz): δ = 6.86 (s, 1 H), 6.73 (s, 2 H), 5.96 (s, 2 H), 4.85 (dd, J = 11.5, 11.5 Hz, 1 H), 3.33 (dd, J = 11.5, 11.5 Hz, 1 H), 3.00–2.70 (m, 4 H), 2.58–2.42 (m, 1 H), 2.30–2.10 (m, 2 H), 1.80–1.68 (m, 1 H), 1.62–1.50 (m, 1 H), 1.44 (s, 9 H) ppm. ^{13}C NMR ([D$_6$]acetone, 125 MHz): δ = 173.4 (C), 169.8 (C), 147.7 (C), 147.2 (C), 132.0 (C), 122.0 (CH), 108.2 (CH), 108.0 (CH), 101.3 (CH_2), 94.5 (CH), 80.4 (C), 49.8 (CH), 48.1 (CH), 38.7 (CH), 38.1 (CH_2), 29.4 (CH_2), 29.3 (CH_2), 27.3 (three CH_3) ppm. MS: m/z (%) = 407 (11) $[M]^+$, 334 (19), 304 (55), 258 (100), 135 (24). HRMS: calcd. for $C_{20}H_{25}NO_8$ $[M]^+$: 407.1580; found 407.1580.

Ester 19: 23 mg, 70% yield. R_f = 0.68 for **19** in 30% EtOAc/hexane. Selected spectroscopic data for **19**: $[\alpha]_D^{25}$ = –47.3 (c = 2, $CHCl_3$). IR (neat): $\tilde{\nu}$ = 2925, 1728, 1550, 1248, 1036 cm^{-1}. ^1H NMR ($CDCl_3$, 500 MHz): δ = 6.71 (d, J = 8.0 Hz, 1 H), 6.67 (s, 1 H), 6.62 (d, J = 8.0 Hz, 1 H), 5.92 (d, J = 1.5 Hz, 2 H), 4.49 (dd, J = 11.0, 11.0 Hz, 1 H), 3.60–3.10 (m, 1 H), 2.52–2.40 (m, 1 H), 2.29 (dd, J = 16.0, 3.5 Hz, 1 H), 2.14 (dd, J = 16.0, 8.5 Hz, 1 H), 2.08–1.90 (m, 2 H), 1.84–1.80 (m, 1 H), 1.44 (s, 9 H), 1.60–1.20 (m, 3 H) ppm. ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 170.2 (C), 147.9 (C), 146.9 (C), 134.0 (C), 120.6 (CH), 108.5 (CH), 107.4 (CH), 101.0 (CH2), 95.4 (CH), 81.1 (C), 48.4 (CH), 38.9 (CH), 38.3 (CH_2), 33.0 (CH_2), 30.1 (CH_2), 28.1 (three CH_3), 24.9 (CH_2).[22] MS: m/z (%) = 363 (33) $[M]^+$, 290 (10), 259 (100), 201 (37), 135 (45), 57 (36). HRMS: calcd. for $C_{19}H_{25}NO_6$ $[M]^+$: 363.1682; found 363.1684.

Ester 20: 90 mg, 90% yield. R_f = 0.20 for **20** in 30% EtOAc/hexane. Selected spectroscopic data for **20**: $[\alpha]_D^{25}$ = –36.0 (c = 3, $CHCl_3$). IR (neat): $\tilde{\nu}$ = 2951, 1730, 1550, 1248, 1038 cm^{-1}. ^1H NMR ($CDCl_3$, 500 MHz): δ = 9.37 (d, J = 2.0 Hz, 1 H), 6.70 (d, J = 8.0 Hz, 1 H), 6.66 (d, J = 1.0 Hz, 1 H), 6.62 (d, J = 8.0 Hz, 1 H), 5.91 (d, J = 2.0 Hz, 2 H), 4.60 (dd, J = 11.0, 11.0 Hz, 1 H), 3.66 (s, 3 H), 3.32 (dd, J = 11.5, 11.5 Hz, 1 H), 2.72–2.62 (m, 1 H), 2.58–2.42 (m, 1 H), 2.38 (dd, J = 16.5, 3.5 Hz, 1 H), 2.25 (dd, J = 16.5, 8.5 Hz, 1 H), 2.16–2.10 (m, 1 H), 2.02–1.96 (m, 1 H), 1.60–1.40 (m, 2 H) ppm. ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 200.8 (CH), 171.1 (C), 148.3 (C), 147.6 (C), 129.9 (C), 121.5 (CH), 108.8 (CH), 107.8 (CH), 101.3 (CH_2), 94.7 (CH), 53.5 (CH), 51.9 (CH_3), 48.1 (CH), 38.2 (CH), 36.4 (CH_2), 28.6 (CH_2), 25.4 (CH_2) ppm. MS: m/z (%) = 349 (5) $[M]^+$, 247 (10), 231 (17), 117 (100). HRMS: calcd. for $C_{17}H_{19}NO_7$ $[M]^+$: 349.1162; found 349.1160.

Ester 21: 71 mg, 85% yield. R_f = 0.33 for **21** in 80% EtOAc/hexane. Selected spectroscopic data for 21: $[\alpha]_D^{25}$ = –17.7 (c = 1, MeOH). IR (neat): $\tilde{\nu}$ = 2925, 1734, 1550, 1248, 1038 cm^{-1}. ^1H NMR ([D$_6$]-acetone, 500 MHz): δ = 6.86 (s, 1 H), 6.73 (s, 2 H), 5.95 (d, J = 2.0 Hz, 2 H), 4.87 (dd, J = 11.0, 11.0 Hz, 1 H), 3.64 (s, 3 H), 3.33 (dd, J = 11.5, 11.5 Hz, 1 H), 2.86–2.80 (m, 1 H), 2.60–2.50 (m, 1 H), 2.38–2.30 (m, 2 H), 2.18–2.02 (m, 2 H), 1.82–1.70 (m, 1 H), 1.62–1.52 (m, 1 H) ppm. ^{13}C NMR ([D$_6$]acetone, 125 MHz): δ = 172.4 (C), 171.8 (C), 148.6 (C), 148.0 (C), 132.8 (C), 122.8 (CH), 109.1 (CH), 108.8 (CH), 102.1 (CH_2), 95.3 (CH), 51.9 (CH_3), 50.6 (CH), 49.0 (CH), 39.4 (CH), 37.4 (CH_2), 30.1 (CH_2), 29.5 (CH_2) ppm. MS: m/z (%) = 365 (58) $[M]^+$, 301 (13), 272 (100), 258 (50), 199 (30), 135 (53). HRMS: calcd. for $C_{17}H_{19}NO_8$ $[M]^+$: 365.1111; found 365.1112.

Ester 22: 27 mg, 80% yield. R_f = 0.50 for **22** in 30% EtOAc/hexane. Selected spectroscopic data for **22**: $[\alpha]_D^{25}$ = –57.5 (c = 6, $CHCl_3$);[20e] IR (neat): $\tilde{\nu}$ = 2925, 2858, 1738, 1549, 1248, 1038, 933, 812 cm^{-1}. ^1H NMR ($CDCl_3$, 500 MHz): δ = 6.69 (d, J = 7.5 Hz, 1 H), 6.65 (d, J = 1.0 Hz, 1 H), 6.60 (dd, J = 8.0, 1.5 Hz, 1 H), 5.90 (d, J = 1.5 Hz, 2 H), 4.48 (dd, J = 11.0, 11.0 Hz, 1 H), 3.66 (s, 3 H), 3.10–3.00 (m, 1 H), 2.52–2.42 (m, 1 H), 2.36 (dd, J = 16.0, 3.5 Hz, 1 H), 2.23 (dd, J = 16.0, 8.5 Hz, 1 H), 2.04–1.92 (m, 2 H), 1.90–1.80 (m, 1 H), 1.60–1.48 (m, 2 H), 1.38–1.20 (m, 1 H) ppm. ^{13}C NMR

($CDCl_3$, 125 MHz): δ = 171.4 (C), 147.9 (C), 146.9 (C), 133.9 (C), 120.6 (CH), 108.5 (CH), 107.3 (CH), 101.1 (CH_2), 95.3 (CH), 51.7 (CH_3), 48.4 (CH), 38.7 (CH), 36.9 (CH_2), 32.9 (CH_2), 30.1 (CH_2), 24.8 (CH_2) ppm. HRMS: calcd. for $C_{16}H_{19}NO_6$ $[M]^+$: 321.1212; found 321.1213.

Ester 23: 40 mg, 40% yield (along with 35 mg and 35% yield of ester **13**). R_f = 0.38 for **23** in 30% EtOAc/hexane. Selected spectroscopic data for **23**: $[\alpha]_D^{25}$ = –33.1 (c = 2.5, $CHCl_3$). IR (neat): $\tilde{\nu}$ = 2923, 1724, 1610, 1550, 1489, 1369, 1255, 1155, 1039, 804, 756 cm^{-1}. ^1H NMR ($CDCl_3$, 500 MHz): δ = 9.41 (s, 1 H), 6.72–6.64 (m, 3 H), 5.91 (s, 1 H), 4.87 (dd, J = 12.0, 5.0 Hz, 1 H), 3.42 (dd, J = 11.5, 11.5 Hz, 1 H), 3.10–3.05 (m, 1 H), 2.70–2.56 (m, 1 H), 2.50–2.40 (m, 2 H), 2.08–2.00 (m, 1 H), 1.87–1.75 (m, 2 H), 1.62–1.50 (m, 2 H), 1.42 (s, 9 H) ppm. ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 200.9 (CH), 170.1 (C), 148.1 (C), 147.3 (C), 130.6 (C), 121.5 (CH), 108.7 (CH), 108.3 (CH), 101.3 (CH_2), 91.8 (CH), 81.4 (C), 54.5 (CH), 41.7 (CH), 34.0 (CH), 33.1 (CH_2), 28.1 (CH_2), 28.0 (three CH_3), 20.4 (CH_2) ppm. MS: m/z (%) = 391 (36) $[M]^+$, 344 (16), 288 (92), 200 (36), 135 (48), 57 (100). HRMS: calcd. for $C_{20}H_{25}NO_7$ $[M]^+$: 391.1631; found 391.1637.

Ester 25: 19 mg, 65% yield. R_f = 0.64 for **25** in 30% EtOAc/hexane. Selected spectroscopic data for **25**: $[\alpha]_D^{25}$ = –44 (c = 4, $CHCl_3$). IR (neat): $\tilde{\nu}$ = 2927, 2858, 1726, 1549, 1489, 1369, 1248, 1153, 1039 cm^{-1}. ^1H NMR ($CDCl_3$, 500 MHz): δ = 6.70–6.62 (m, 3 H), 5.89 (s, 2 H), 4.82 (dd, J = 12.0, 4.5 Hz, 1 H), 3.16 (ddd, J = 12.0, 12.0, 4.0 Hz, 1 H), 3.05–3.02 (m, 1 H), 2.46 (d, J = 7 Hz, 2 H), 1.96–1.85 (m, 2 H), 1.70–1.40 (m, 4 H), 1.41 (s, 9 H) ppm. ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 170.6 (C), 147.8 (C), 146.7 (C), 134.8 (C), 120.3 (CH), 108.5 (CH), 107.5 (CH), 101.0 (CH_2), 92.1 (CH), 81.1 (C), 41.7 (CH), 34.6 (CH), 33.9 (CH_2), 33.5 (CH_2), 29.3 (CH_2), 28.0 (three CH_3), 19.9 (CH_2) ppm. MS: m/z (%) = 363 (38) $[M]^+$, 290 (12), 259 (100), 201 (52), 135 (72), 71 (28), 57 (96). HRMS: calcd. for $C_{19}H_{25}NO_6$ $[M]^+$: 363.1682; found 363.1674.

Representative Procedure for the Preparation of 27 and 28: To a solution of (*E*)-**26** (30 mg, 0.24 mmol) and *trans*-nitrostyrene (43 mg, 0.29 mmol) in CH_3CN (2 mL) was added L-Proline (5 mg, 0.048 mmol) and Et_3N (5 mg, 0.048 mmol). The solution was stirred for 3 h, diluted with EtOAc (25 × 2 mL), washed with brine (10 mL), dried with Na_2SO_4, and concentrated in vacuo to give the crude product. The residue was purified by flash column chromatography with 10% EtOAc/hexane (**27**: R_f = 0.30. **28**: R_f = 0.25 in 20% EtOAc/hexane) to give **27** (20 mg, 32% yield) and **28** (6 mg, 10% yield) as colorless oils. Selected spectroscopic data for **27**: $[\alpha]_D^{25}$ = –53.6 (c = 4, $CHCl_3$). IR (neat): $\tilde{\nu}$ = 2920, 1682, 1545, 1365, 1165, 750, 700 cm^{-1}. ^1H NMR ($CDCl_3$, 500 MHz): δ = 9.60 (s, 1 H), 7.45 (d, J = 6.5 Hz, 1 H), 7.29–7.20 (m, 3 H), 7.04 (d, J = 7.5 Hz, 2 H), 4.46–4.43 (m, 1 H), 4.07 (s, 1 H), 3.92 (d, J = 5.5 Hz, 1 H), 3.18–3.15 (m, 1 H), 2.10–2.00 (m, 1 H), 1.90–1.80 (m, 1 H), 1.52–1.42 (m, 1 H), 1.30–1.20 (m, 1 H) ppm. ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 187.8 (CH), 154.5 (CH), 144.1 (C), 142.3 (C), 129.0 (2 CH), 127.4 (CH), 127.0 (2 CH), 91.4 (CH), 47.2 (CH), 38.3 (CH), 32.5 (CH), 25.7 (CH_2), 18.0 (CH_2) ppm. MS: m/z (%) = 257 (39) $[M]^+$, 210 (45), 182 (78), 108 (100), 91 (75), 79 (85). HRMS: calcd. for $C_{15}H_{15}NO_3$ $[M]^+$: 257.1052; found 257.1048. Selected spectroscopic data for **28:** $[\alpha]_D^{25}$ = –20 (c = 2.1, $CHCl_3$). IR (neat): $\tilde{\nu}$ = 2922, 1682, 1547, 1371, 1173, 702 cm^{-1}. ^1H NMR ($CDCl_3$, 500 MHz): δ = 9.57 (s, 1 H), 7.55 (d, J = 6.5 Hz, 1 H), 7.40–7.20 (m, 5 H), 5.03 (dd, J = 5.5, 2.0 Hz, 1 H), 4.01 (s, 1 H), 3.49 (dd, J = 3.0, 2.5 Hz, 1 H), 3.00 (dd, J = 3.0, 2.5 Hz, 1 H), 1.90–1.72 (m, 2 H), 1.50–1.40 (m, 1 H), 1.20–1.10 (m, 1 H) ppm. ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 188.5 (CH), 153.2 (CH), 143.1 (C), 138.1 (C), 129.1 (2 CH), 127.63 (CH), 127.59 (2 CH), 87.5 (CH), 47.5 (CH), 38.3 (CH), 32.1 (CH), 23.0 (CH_2), 17.4 (CH_2) ppm. MS (m/z, relative intensity): 257 [M^+, 3], 210 (56), 182 (100), 91 (51), 79 (50), 77 (40); HRMS: calcd. for $C_{15}H_{15}NO_3$ $[M]^+$: 257.1052; found 257.1048.

Supporting Information (see also the footnote on the first page of this article): Experimental procedures and full characterizations of products.

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