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A highly regio- and enantioselective organocatalyzed Michael addition of malonates to nitrodienes

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ABSTRACT

An organocatalyzed direct Michael addition of unsubstituted/substituted malonates, acetoacetate, or acetylacetones to conjugated nitrodienes using a cinchona alkaloid-based thiourea catalyst is disclosed. The addition products were formed in high yields and regioselectivity. The enantioselectivities of the addition products were high in most cases and could significantly be improved upon by a single recrystallization. The addition products easily undergo chemoselective nitro group reduction and subsequent lactamization with a high synthetic potential.

1. Introduction

The catalytic asymmetric Michael addition is the one to be the most frequently used C–C and C–X (X = heteroatom) bond forming reactions in organic synthesis.[1] In recent years, the organocatalytic version of this reaction has brought a renaissance in organic synthesis.[2] Amongst the organocatalyzed asymmetric Michael reactions developed, use of electron-deficient, simple olefins as Michael acceptors is well documented.[2] In comparison, extended conjugated systems such as activated dienes and enynes have rarely been used as acceptors. Asymmetric conjugate additions to such acceptors can provide intermediates with more functional groups. This would enhance the utility of the approach in the synthesis of natural products and pharmaceutical intermediates. However, in addition to the enantioselectivity, the extra conjugation in the chosen acceptors adds an additional issue of regioselectivity that is 1,4- versus 1,6-addition. The principle of vinilogy[3] states that the electronic effect of directing functional groups can propagate through a conjugated π-system. However, in practice, 1,4-additions[4] are usually preferred over 1,6-addition[5] with common electron deficient dienes.

Nitroalkenes have been well studied as Michael acceptors[2] in the field of organocatalyzed reactions because of their high electrophilicity, originating from the strong electron-withdrawing nature and hydrogen bonding ability of the nitro group. Moreover, the enantioenriched nitroalkane adducts are valuable synthons for various chiral heterocyclic skeletons found in bioactive molecules.[6] The synthetic utility can be significantly enhanced upon by the introduction of nitrodienes[7] as Michael acceptors since the additional C=C can be exploited for further synthetic maneuvers. Enamine catalysts have been used for the exclusive 1,4-addition of carbonyl compounds to nitrodienes.[8] Michael additions of 1,3-dicarbonyl compounds to nitroolefins catalyzed by bifunctional organocatalysts have been studied in detail.[9] Until now, little progress has been made with the organocatalyzed Michael reactions of 1,3-dicarbonyl compounds with nitrodiene acceptors. The only reported examples available employ acyclic or cyclic β-ketoesters as donors and bifunctional hydrogen bonding catalysts such as chiral guanidines[10] or 6′-OH *Cinchona* alkaloids[11] as promoters in Michael additions to nitrodienes. Nitroenynes have recently been used as substrates in metal-[12] or organocatalyzed[13] selective 1,4-additions of malonates, β-keto esters, and β-diketones. However, systematic studies on organocatalyzed 1,4-additions of malonates to nitrodienes have not been reported.[14,15] As part of our research efforts toward the development of organocatalyzed reactions,[16] we herein report the development of an efficient, highly regio-, and enantioselective protocol for the Michael addition of malonates, β-ketoesters, and β-diketones to nitrodienes, promoted by some *Cinchona* alkaloid-based thiourea catalysts.[17] The utility of this strategy has been exemplified by synthesizing a chiral γ-lactam, expected to be an intermediate for natural products and therapeutically useful agents.

2. Results and discussion

A number of initial experiments were performed to screen different bifunctional thiourea derived organocatalysts **1**,[18] **2**[19] and **3**–**7**[20] (Fig. 1) for the Michael addition of dimethyl malonate **8a** to nitrodiene **9a** (Table 1). These bifunctional thiourea catalysts

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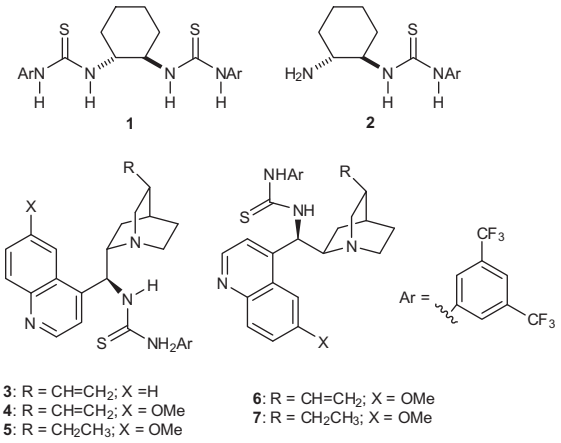
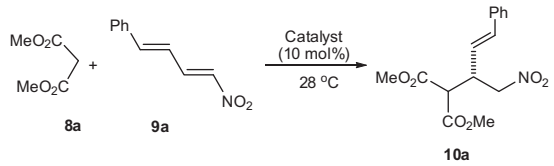


Figure 1. Bifunctional organocatalysts **1**–**7** used herein.

Table 1
Optimization of the asymmetric Michael addition of dimethyl malonate **8a** to nitrodiene **9a**[a]



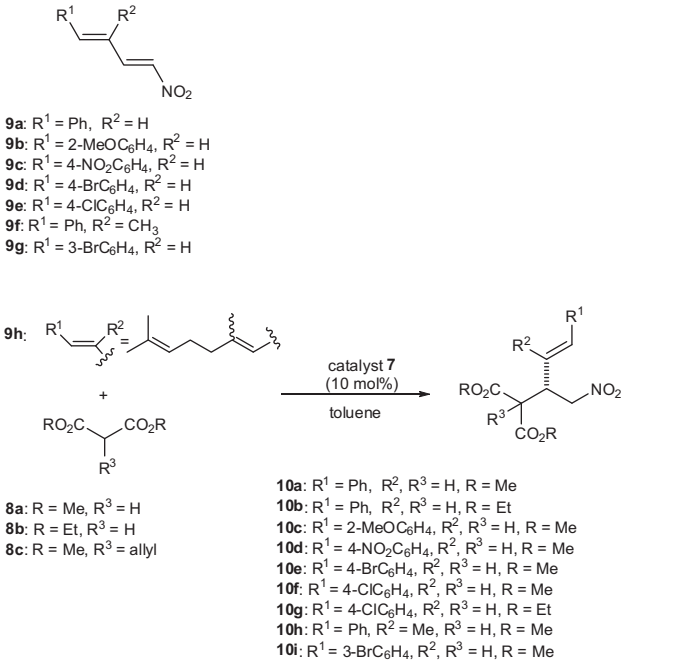
Entry	Catalyst	Solvent	Time (h)	Yield (%)[b] [ee (%)][c]
1	**1**	Toluene	48	n.r.[d]
2	**2**	Toluene	30	55[e] [49]
3	**3**	Toluene	44	72 [−42]
4	**4**	Toluene	24	83 [−50]
5	**5**	Toluene	26	82 [−70]
6	**6**	Toluene	42	88 [38]
7	**7**	Toluene	24	90 [70]
8	**7**	CH_2Cl_2	47	91 [68]
9	**7**	Et_2O	24	89 [62]
10	**7**	THF	48	90 [65]
11	**7**	DMF	72	20[e] [25]
12	**7**	CH_3CN	72	45[e] [54]
13	**7**	Toluene	72	85 [88][f]

[a] Reactions were performed with dimethyl malonate **8a** (0.5 mmol) and nitrodiene **9a** (0.25 mmol) in the presence of the respective catalysts (10 mol %) in dry solvents (0.5 mL).
[b] Yield of chromatographically homogeneous products.
[c] Determined by HPLC analysis on a Daicel chiralpak AD-H column.
[d] n.r. = no reaction.
[e] Incomplete reaction.
[f] Reaction performed at −20 °C.

are capable of playing multiple roles in a reaction. A portion of the catalyst can nucleophilically activate the methylene/methyne group of the Michael donor by proton abstraction, while H-bonding from the thiourea part of the catalyst with the nitrodiene enhances the electrophilicity of the latter. Moreover, it brings both reaction partners into close proximity (open transition state to closed transition state) for better regio- and enantiocontrol. In order to optimize the reaction conditions, a number of experiments were performed using 10 mol % each of the catalysts **1**-**7** in different solvents and at different temperatures as presented in Table 1. In toluene at room temperature (~28 °C), the *trans*-1,2-diaminocyclohexane based bis-thiourea catalyst **1** failed to produce the desired addition product **10a** (Table 1, entry 1). The monothiourea catalyst **2** showed modest activity under the same conditions to furnish **10a** in moderate yield and enantioselectivity (Table 1, entry 2). The *Cinchona* alkaloid-derived catalysts **3**–**7** showed high catalytic activity under the above reaction conditions (Table 1, entries 3–7) and the reactions were complete in all cases. Catalysts **5** and **7** showed the highest enantioselectivity (Table 1, entries 5 and 7). The enantiopreference with catalysts **3**–**5** was opposite to that of catalyst **7** and provided the adduct *ent*-**10a**.

In order to determine the influence of the solvent on the conjugate addition, other solvents were also screened using catalyst **7** (Table 1, entries 8–12) at the same temperature. Amongst the chosen solvents, dichloromethane and the ethers (Et_2O and THF)

Table 2
Michael addition of malonates **8a**–**c** to nitrodienes **9a**–**h**[a]



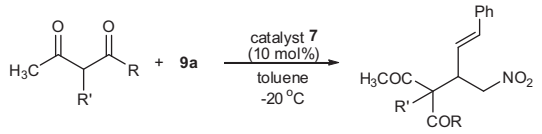
Entry	Nitrodiene	Temp (°C)/Time (d)	Product	Yield[b] (%)	ee[c] (%)
1	**9a**	−20/3	**10a**	85 (47)[d]	88 (99)[e]
2	**9a**	−20/3	*ent*-**10a**[f]	85 (48)[d]	88 (99)[e]
3[g]	**9a**	−20/6	**10b**	80	88
4	**9b**	−20/6	**10c**	75[h] (50%)[d]	89 (99)[e]
5	**9c**	28/1.5	**10d**	70	76
6	**9d**	0/1.7	**10e**	87	84
7	**9e**	0/2.5	**10f**	93	85
8[g]	**9f**	0/2.5	**10g**	91 (45%)[d]	80 (99)[e]
9	**9f**	−20/6	**10h**	66[h]	80
10	**9g**	−20/3	**10i**	95	85
11	**9h**	28/2	**10j**	76	72
12[i]	**9a**	0/6	**10k**[j]	45[h]	85

[a] Unless otherwise specified, all of the reactions were performed with nitrodiene (0.25 mmol) with malonate **8a** (0.5 mmol) in the presence of 10 mol % of the catalyst **7** in dry toluene (0.5 mL).
[b] Yield of chromatograhically homogeneous product.
[c] Determined by HPLC analysis using a chiral stationary phase.
[d] Yield after single recrystallization.
[e] Ee after a single recrystallization.
[f] Catalyst **5** was used instead of catalyst **7**.
[g] Malonate **8b** was used.
[h] Incomplete reaction.
[i] Malonate **8c** was used.
[j] 20 mol % of catalyst **7** was used.

produced similar yields and enantioselectivities of product **10a** as obtained in toluene (Table 1, entries 8–10). The reaction rate in Et_2O was comparable to that in toluene. The yield and enantioselectivity were low in polar aprotic solvents such as CH_3CN and DMF (Table 1, entries 11 and 12). This may be due to the loss of H-bonding interactions between the catalyst and the nitrodiene. When the addition reaction was performed using catalyst **7** at a lower temperature (−20 °C) in toluene, the enantioselectivity of the addition product **10a** improved significantly (88% ee, Table 1, entry 13), although the reaction took longer time to complete. Under all these conditions, the reaction furnished regioselectively the 1,4-addition product only. Based on these results, we determined the optimized reaction conditions to be: dimethyl malonate **8a** (2 equiv), nitrodiene **9a** (1 equiv), catalyst **7** (10 mol %), with toluene as the solvent at a reaction temperature of −20 °C.

Next, the scope of the optimized protocol was explored by using different nitrodienes **9a–h** and three Michael donors, dimethyl malonate **8a**, diethyl malonate **8b**, and dimethyl allylmalonate **8c** (Table 2). In these cases, the 1,4-addition products **10a–k** were formed exclusively with good to excellent yields and enantioselectivities. Substituents on the aromatic ring of the 4-aryl-1-nitrobutadienes had a minimal effect on the reactivity except for the 2-substituted aryl group where the reaction was slower, probably due to steric factors. The solubility of nitrodienes **9c–e** in toluene at −20 °C was poor. Hence, these reactions were performed at 0 °C and/or at room temperature. Nitrodiene **9f** bearing a 3-methyl group also resulted in the formation of the addition product **10h** with acceptable yield and enantioselectivity. However, the reaction was sluggish and remained incomplete (80% conversion) presumably due to unfavored interactions between the substrate and nucleophile. The 4,4-dialkyl substituted nitrodiene **9h** also underwent the Michael addition with dimethyl malonate **8a** at room temperature. The corresponding addition product **10j** was obtained in good yield and with good enantioselectivity. The majority of the addition products (Table 2, **10a–d** and **10g**) were obtained as solids and a few of them after single recrystallization provided the products with improved enantiomeric excess (Table 2, entries 1, 2, 4, and 8) of the products. The reaction of dimethyl allylmalonate **8c** with nitrodiene **9a** was very slow at −20 °C. Although the reaction rate was enhanced at 0 °C, the reaction remained incomplete (60% conversion) even after 144 h.

Table 3
Michael addition of 1,3-dicarbonyl compounds to nitrodiene **9a**[a]



11a: R = Me, R' = H
11b: R = OMe, R' = H
11c: R = OMe, R' = 2-propynyl

12a: R = Me, R' = H
12b: R = OMe, R' = H
12c: R = OMe, R' = 2-propynyl

Entry	Nucleophile	Product	Yield[b] (%)	dr[c]	ee[d] (%)
1	**11a**	**12a**	92	—	79 (96)[e]
2	**11b**	**12b**	90	1/1	83[f], 81[g]
3	**11c**	**12c**	95	7/3	54[f], 80[g]

[a] Unless otherwise specified, all the reactions were performed with nitrodiene **9a** (0.25 mmol) with the nucleophile (0.5 mmol) in the presence of 10 mol % of the catalyst **7** in dry toluene (0.5 mL) at −20 °C for 24 h.
[b] Yield of chromatographically homogeneous product.
[c] Determined from ^{1}H NMR of the crude product.
[d] Determined by HPLC analysis using a chiral stationary phase.
[e] Improved by a single recrystallization,
[f] Ee for the first or major diastereoisomer.
[g] Ee for the second or minor diastereoisomer.

The scope of this Michael addition was further explored by using nitrodiene **9a** and 1,3-dicarbonyl compounds **11a–c**. Under the optimized conditions using catalyst **7**, nitrodiene **9a** upon reaction with acetylacetone **11a** gave the addition product **12a** (Table 3) in excellent yield and with high enantioselectivity. The ee of **12a** was significantly improved (>96%) upon by a single recrystallization. As with acetylacetone, methyl acetoacetate **11b** was also added to nitrodiene **9a** to give adduct **12b** in 90% yield as an inseparable 1/1 mixture of diastereoisomers. Each diastereoisomer was also formed with high enantioselectivity as determined by HPLC. Methyl 2-propargylacetoacetate **11c** also underwent this organocatalyzed Michael addition to nitrodiene **9a** to give adduct **12c** as an inseparable mixture of diastereoisomers in a ratio of 70/30. The major diastereoisomer had moderate enantioselectivity while the minor one showed high enantioselectivity.

The absolute configuration of the Michael adduct **10b** was assigned to be (*S*) by measuring the specific rotation value {$[\alpha]_D^{23} = -23.0$ (*c* 1, $CHCl_3$); lit.[14] $[\alpha]_D^{22} = +26.1$ (*c* 1.15, $CHCl_3$) for the antipode of **10b** with 95% ee}. The absolute configurations of the other products **10a** and **10c–g** were tentatively assigned to be (*S*) in analogy with **10b**. The absolute configuration of the Michael adduct *ent*-**10a** was assigned to be (*R*), since its rotation was opposite to that of **10a**.

The stereochemical outcome for the formation of (*S*)-**10a** can be explained by the dual activation model originally proposed by Takemoto et al.[9b] and adopted by others[12,13,21] as shown in the transition state assembly depicted in Fig. 2. The NO_2 group in **9a** can complex to the thiourea moiety of the catalyst **7** by two H-bonding interactions, while the enol form of the dimethyl malonate can form an H-bond to the bridgehead-*N* as shown in **TS-1** (Fig. 2). The most favored approach would be at the *Si*-face of the nitrodiene **9a** because this route would involve the least steric interaction at the transition state for the H-bonding interaction of the enol form of dimethyl malonate **8a** to the bridgehead-*N* leading to an (*S*)-configuration for product **10a**. An alternative binding model of substrates to catalyst as proposed by Papai[22] can be

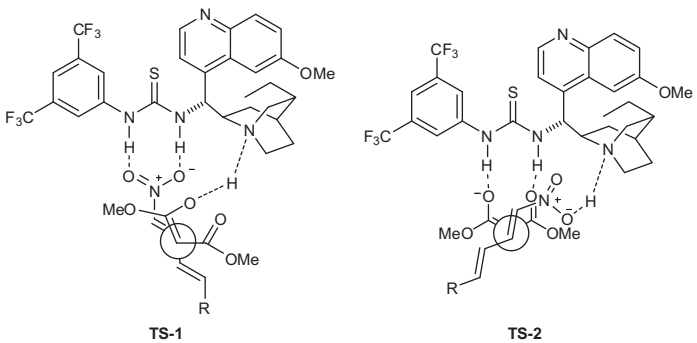
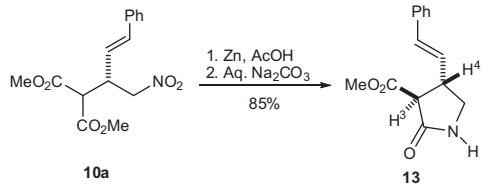


Figure 2. Transition state model.

invoked wherein the NO_2 group in **9a** can complex to the protonated bridgehead-*N* as shown in **TS-2** (Fig. 2), while the thiourea moiety of catalyst **7** can participate in two H-bonding interactions with the enolate form of dimethyl malonate. The most favored approach would be at the *Re*-face of the nitrodiene **9a** because this would involve the least steric interaction at the transition state for the H-bonding interactions, leading again to an (*S*)-configuration for product **10a**.

In order to show the utility of our method, the addition product **10a** was transformed into γ-lactam **13** (Scheme 1). The chemoselective reduction of the nitro group in **10a** using Zn and acetic acid gave the intermediate amine, which upon cyclization furnished the desired lactam **13** in very good yield. The *trans*-relative configuration of lactam **13** was confirmed by ^{1}H–^{1}H ROESY spectra wherein no nOe interactions were observed between H^3 and H^4 (Scheme 1).



Scheme 1. Synthesis of a γ-lactam.

3. Conclusion

In conclusion, we have developed an asymmetric Michael addition of malonates and 1,3-dicarbonyl compounds to obtain various substituted nitrodienes using easily accessible *cinchona* alkaloid-based thiourea organocatalysts. The addition reactions were highly regioselective providing 1,4-addition products exclusively with good to excellent yields and enantioselectivities. The addition products hold promise for the construction of stereo- and regiochemically diverse heterocyclic skeletons comprised of flexible rings and containing embedded functionalities.

4. Experimental

4.1. General

Solvent removal was carried out using a rotary evaporator connected to a dry ice condenser. TLC (0.5 mm) was carried out using homemade silica plates with fluorescence indicator. Column chromatography was performed on silica gel (230-400 mesh). ^{1}H and ^{13}C NMR spectra were recorded on a 200 MHz (^{1}H: 200 MHz, ^{13}C: 50 MHz) spectrometer. ^{1}H and ^{13}C shifts are given in ppm, δ scale and are measured relative to internal $CHCl_3$ and $CDCl_3$ as standards, respectively. High resolution mass spectra were recorded at 60–70 eV with a Q-TOF spectrometer (ESI, Ar). Enantiomeric excess (ee) determinations were carried out by HPLC using an instrument fitted with a Daicel chiralpak AD-H/OD-H/AS-H column and UV detector with λ fixed at 220 nm. Nitrodienes **9a-h** were prepared following the general procedures reported in the literature.[8c,23] Organocatalysts **1**,[18] **2**,[19] and **3**–**7**[20] were prepared by following the literature.

4.2. General procedure 1. Michael addition of 1,3-dicarbonyl compounds to nitrodienes using DBU as catalyst

1,3-Dicarbonyl compound **8a**–**c** or **11a**–**c** (0.5 mmol) was added to the corresponding nitrodiene **9a**–**h** (0.25 mmol) in toluene (0.5 mL) and the reaction mixture was stirred for 10 min. Next, DBU (8 μL, 0.05 mmol, 20 mol %) was added to the homogenous reaction mixture and stirring was continued at room temperature (~28 °C) until completion of the reaction. The resulting mixture was diluted with EtOAc and washed with water. The organic phase was dried over $MgSO_4$ and evaporated under reduced pressure. The residue was purified by column chromatography over silica gel using hexane/EtOAc as eluent to give the desired addition products *rac*-**10a**–**k** or *rac*-**12a**–**c**.

4.3. General procedure 2. Asymmetric Michael addition of 1,3-dicarbonyl compounds to nitrodienes

1,3-Dicarbonyl compound **8a**–**c** or **11a**–**c** (0.5 mmol) was added to a stirred solution of nitrodiene **9a**–**h** (0.25 mmol) and thiourea catalyst **7** (16 mg, 0.025 mmol, 10 mol %) in toluene (0.5 mL) at −20 °C. The reaction mixture was stirred at the same temperature for 14–144 h, diluted with EtOAc, and washed with water. The organic phase was dried over $MgSO_4$ and evaporated under reduced pressure. The residue was purified by column chromatography over silica gel using hexane/EtOAc as eluent to give the desired addition products **10a**–**k** and **12a**–**c**.

4.4. (*S*)-Methyl-2-carbomethoxy-3-(nitromethyl)-5-phenyl-4-pentenoate 10a

Following general procedure 2, product **10a** was obtained as a white solid. Yield: 65 mg (85%, 88% ee); Recrystallized from hexane–EtOAc; Yield: 36 mg (47%); mp 94–95 °C (hexane–EtOAc); $[\alpha]_D^{24} = -24.2$ (*c* 1.2, $CHCl_3$) 99.5% ee; ^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.26–7.33 (m, 5H), 6.57 (d, *J* = 15.8 Hz, 1H), 6.0–6.18 (m, 1H), 4.62–4.80 (m, 2H), 3.73–3.77 (m, 2H), 3.76 (s, 3H), 3.73 (s, 3H) ppm; ^{13}C NMR (50 MHz, $CDCl_3$): δ = 167.6, 167.5,135.8, 135.5, 128.6 (2C), 128.2, 126.6 (2C), 123.3, 76.9, 53.3, 52.9, 52.8, 41.2 ppm; IR (KBr): ν = 2982, 2877, 2843, 1739, 1554, 1464, 1431, 1256, 1154, 742 cm^{-1}; elemental analysis calcd (%) for $C_{15}H_{17}NO_6$: C 58.63, H 5.58, N 4.56, found: C 58.97, H 5.63, N 4.53; the enantiomeric excess of the recrystallized product was determined by HPLC with a Daicel chiralpak AD-H column [λ = 220 nm], eluent: 2-propanol/hexane (10/90), flow rate = 0.8 mL/min, t_{minor} = 21.13 min (0.33%), t_{major} = 25.85 min (99.67%).

4.5. (*R*)-Methyl-2-carbomethoxy-3-(nitromethyl)-5-phenyl-4-pentenoate *ent*-10a

Following general procedure 2 and using catalyst **5** instead of catalyst **7**, product *ent*-**10a** was obtained as a white solid. Yield: 65 mg (85%, 88% ee); Recrystallized from hexane-EtOAc; Yield: 37 mg (48%); mp 92–93 °C (hexane–EtOAc); $[\alpha]_D^{24} = +23.3$ (*c* 1.2, $CHCl_3$) >98% ee. The enantiomeric excess of the recrystallized product was determined by HPLC with a Daicel chiralpak AD-H column [λ = 220 nm], eluent: 2-propanol/hexane (10/90), flow rate = 0.8 mL/min, t_{major} = 19.04 min (99.35%), t_{minor} = 23.28 min (0.65%).

4.6. (*S*)-Ethyl-2-carboethoxy-3-(nitromethyl)-5-phenyl-4-pentenoate 10b

Yellow solid; Yield: 67 mg (80%, 88% ee); mp 48–49 °C, lit.[14] mp 49 °C; $[\alpha]_D^{25} = -23.0$ (*c* 1.0, $CHCl_3$); lit.[14] $[\alpha]_D^{22} = +26.1$ (*c* 1.15, $CHCl_3$) 95% ee; ^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.23–7.33 (m, 5H), 6.56 (d, *J* = 15.8 Hz, 1H), 6.10 (dd, *J* = 9.0, 15.8 Hz, 1H), 4.62–4.80 (m, 2H), 4.13–4.27 (q, *J* = 7.2 Hz, 4H), 3.62–3.80 (m, 2H), 1.19 (q, *J* = 7.2 Hz, 6H) ppm; ^{13}C NMR (50 MHz, $CDCl_3$): δ = 167.3, 167.1, 135.8, 135.4, 128.6 (2C), 128.2, 126.6 (2C), 123.4, 77.1, 62.0, 61.9, 53.6, 41.2, 14.0 (2C) ppm; IR ($CHCl_3$, film): ν = 3026, 2981, 2938, 2874, 1732, 1556, 1465, 1448, 1371, 1030, 970, 784, 694 cm^{-1}; the enantiomeric excess was determined by HPLC with a Daicel

chiralpak AD-H column [λ = 220 nm], eluent:2-propanol/hexane (10/90), flow rate = 0.8 mL/min, t_{minor} = 20.57 min (4.88%), t_{major} = 22.55 min (95.12%).

4.7. (*S*)-Methyl-2-carbomethoxy-3-(nitromethyl)-5-(2-methoxyphenyl)-4-pentenoate 10c

White solid; Yield: 63 mg (75%); Recrystallized from hexane–EtOAc; Yield: 42 mg (50%); mp 53–55 °C (hexane–EtOAc); $[\alpha]_D^{25} = -12.0$ (*c* 0.6, $CHCl_3$) >99% ee; ^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.18–7.36 (m, 2H), 6.81–6.92 (m, 3H), 6.01–6.17 (m, 1H), 4.63–4.81 (m, 2H), 3.81 (s, 3H), 3.76 (s, 4H), 3.73 (s, 4H) ppm; ^{13}C NMR (50 MHz, $CDCl_3$): δ = 167.8, 167.6, 156.7, 130.4, 129.3, 127.0, 124.9, 123.7, 120.6, 110.8, 77.05, 55.4, 53.5, 52.8 (2C), 41.6 ppm; IR ($CHCl_3$, film): ν = 2985, 2877, 1740, 1554, 1465, 1448, 1255, 1030, 970, 784 cm^{-1}; elemental analysis calcd (%) for $C_{16}H_{19}NO_7$: C 56.97, H 5.68, N, 4.15; found: C 57.15, H 5.50, N 4.09; the enantiomeric excess was determined by HPLC with a Daicel chiralpak AD-H column [λ = 220 nm], eluent: 2-propanol/hexane (10/90), flow rate = 0.8 mL/min, t_{minor} = 21.1 min (0.28%), t_{major} = 24.10 min (99.72%).

4.8. (*S*)-Methyl-2-carbomethoxy-3-(nitromethyl)-5-(4-nitrophenyl)-4-pentenoate 10d

Yellow solid; Yield: 62 mg (70%); mp 97–99 °C; $[\alpha]_D^{24} = -13.3$ (*c* 0.75, $CHCl_3$) 76% ee; ^{1}H NMR (200 MHz, $CDCl_3$): δ = 8.15 (d, *J* = 8.8 Hz, 2H), 7.45 (d, *J* = 8.8 Hz, 2H), 6.64 (d, *J* = 15.8 Hz, 1H), 6.30 (dd, *J* = 8.6, 15.8 Hz, 1H), 4.71–4.75 (m, 2H), 3.77 (s, 3H), 3.74 (s, 3H), 3.71–3.77 (m, 2H) ppm; ^{13}C NMR (50 MHz, $CDCl_3$): δ = 167.4 (2C), 147.4, 142.0, 133.4, 128.4, 127.3 (2C), 124.0 (2C), 76.6, 53.07, 53.02, 52.97, 41.1 ppm; IR (KBr): ν = 2985, 2843, 1740, 1600, 1552, 1515, 1438, 1348, 1322, 1262, 1163, 973, 745 cm^{-1}; HRMS (ESI): *m*/*z*: calcd for $C_{15}H_{16}N_2O_8Na$ $[M+Na]^+$: 375.0790; found: 375.0799; elemental analysis calcd (%) for $C_{15}H_{16}N_2O_8$: C 51.14, H 4.58, N 7.95; found: C, 50.97; H, 4.58; N, 8.32; The enantiomeric excess was determined by HPLC with a Daicel chiralpak OD-H column [λ = 220 nm], eluent: 2-propanol/hexane (10/90), flow rate = 1.0 mL/min, t_{minor} = 80.97 min (12.14%), t_{major} = 87.74 min (87.76%).

4.9. (*S*)-Methyl-2-carbomethoxy-3-(nitromethyl)-5-(4-bromophenyl)-4-pentenoate 10e

Light yellow oil; Yield: 84 mg (87%); $[\alpha]_D^{24} = -11.3$ (*c* 2.3, $CHCl_3$) 84% ee; ^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.39–7.43 (m, 3H); 7.17 (d, *J* = 8.4 Hz, 1H), 6.50 (d, *J* = 15.8 Hz, 1H), 6.02–6.15 (m, 1H), 4.60–4.78 (m, 2H), 3.75 (s, 3H), 3.72 (s, 3H), 3.67–3.75 (m, 2H) ppm; ^{13}C NMR (50 MHz, $CDCl_3$): δ = 167.5, 167.4, 134.7, 134.3, 131.7 (2C), 128.1 (2C), 124.1, 122.1, 76.8, 52.92, 52.9, 51.1, 41.2 ppm; IR (film): ν = 3025, 2955, 1737, 1556, 1435, 1378, 1162, 1072, 969, 753 cm^{-1}; elemental analysis calcd (%) for $C_{15}H_{16}BrNO_6$: C 46.65, H 4.18, N 3.63; found: C 46.26, H 4.05, N 3.95; The enantiomeric excess was determined by HPLC with a Daicel chiralpak OD-H column [λ = 220 nm], eluent: 2-propanol/hexane (10/90), flow rate = 0.8 mL/min, t_{minor} = 31.69 min (8.01%), t_{major} = 41.43 min (91.99%).

4.10. (*S*)-Methyl-2-carbomethoxy-3-(nitromethyl)-5-(4-chlorophenyl)-4-pentenoate 10f

Light yellow oil; Yield: 79 mg (93%); $[\alpha]_D^{27} = -15.6$ (*c* 0.9, $CHCl_3$) 86% ee; ^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.18–7.32 (m, 4H); 6.52 (d, *J* = 15.8 Hz, 1H), 6.01–6.14 (m, 1H), 4.61–4.79 (m, 2H), 3.76 (s, 3H), 3.72 (s, 3H), 3.67–3.76 (m, 2H) ppm; ^{13}C NMR (50 MHz, $CDCl_3$): δ = 167.6, 167.5, 134.3, 133.9, 129.3, 129.2, 128.7 (2C), 127.8 (2C), 124.0, 76.8, 53.2, 52.9, 41.2 ppm; IR (film): ν = 2955, 2925, 2847, 1731, 1556, 1492, 1435, 1378, 1093, 972, 753 cm^{-1}; elemental analysis calcd (%) for $C_{15}H_{16}ClNO_6$: calcd C 52.72, H 4.72, N 4.10; found: C 52.53, H 4.48, N 4.29; the enantiomeric excess was determined by HPLC with a Daicel chiralpak OD-H column [λ = 220 nm], eluent: 2-propanol/hexane (5/95), flow rate = 0.8 mL/min, t_{minor} = 41.9 min (7.33%), t_{major} = 49.09 min (92.67%).

4.11. (*S*)-Ethyl-2-carboethoxy-3-(nitromethyl)-5-(4-chlorophenyl-4-pentenoate 10g

Yellow solid; Yield: 85 mg (91%); Recrystallized from hexane–EtOAc; Yield: 42 mg (45%); mp 62–64 °C (hexane–EtOAc); $[\alpha]_D^{26} = -21.4$ (*c* 1.4, $CHCl_3$) 99% ee; ^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.20 (m, 4H), 6.52 (d, *J* = 15.8 Hz, 1H), 6.09 (dd, *J* = 8.8, 15.8 Hz, 1H), 4.61–4.80 (m, 2H), 4.16–4.27 (m, 4H), 3.62–3.79 (m, 2H), 1.24 (q, *J* = 7.2 Hz, 6H) ppm; ^{13}C NMR (50 MHz, $CDCl_3$): δ = 167.2, 167.1, 134.3, 134.2, 133.9, 128.8 (2C), 127.8 (2C), 124.2, 77.0, 62.1, 62.0, 53.5, 41.2, 14.0 (2C) ppm IR (KBr): ν = 2980, 2877, 2843, 1747, 1550, 1472, 1374, 1259, 1154, 1012, 936, 745 cm^{-1}; elemental analysis calcd (%) for $C_{17}H_{20}ClNO_6$: C 55.21, H 5.45, N 3.79; found: C 55.60, H, 5.24, N 3.98; the enantiomeric excess was determined by HPLC with a Daicel chiralpak OD-H column [λ = 220 nm], eluent: 2-propanol/hexane (5/95), flow rate = 0.8 mL/min, t_{minor} = 21.90 min (0.52%), t_{major} = 25.33 min (99.48%).

4.12. Dimethyl 2-(*R*,*E*)-3-methyl-1-nitro-4-phenylbut-3-en-2-yl) malonate 10h

Colorless oil; Yield: 53 mg (66%); $[\alpha]_D^{27} = -20.5$ (*c* 1.9, $CHCl_3$) 80% ee; ^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.25–7.35 (m, 3H); 7.12–7.24 (m, 2H), 6.43 (br s, 1H), 4.65–4.83 (m, 2H), 3.78 (s, 3H), 3.74–3.76 (m, 2H), 3.72 (s, 3H), 1.86 (d, *J* = 1.0 Hz, 3H) ppm; ^{13}C NMR (50 MHz, $CDCl_3$): δ = 168.0, 167.4, 136.6, 132.3, 131.0, 128.8 (2C), 128.1 (2C), 127.0, 75.7, 53.0, 52.9, 52.7, 46.5, 15.1 ppm; IR (film): ν = 2954, 2914, 1735, 1552, 1492, 1435, 1329, 1028, 746 cm^{-1}; elemental analysis calcd (%) for $C_{16}H_{19}NO_6$: calcd C 59.81, H 5.96, N 4.36; found: C 59.51, H 6.26, N 4.16. The enantiomeric excess was determined by HPLC with a Daicel chiralpak OD-H column [λ = 220 nm], eluent: 2-propanol/hexane (5/95), flow rate = 0.5 mL/min, t_{major} = 47.17 min (90.29%), t_{minor} = 57.25 min (9.71%).

4.13. (*S*)-Methyl-2-carbomethoxy-3-(nitromethyl)-5-(3-bromophenyl)-4-pentenoate 10i

Yellow oil; Yield: 91 mg (95%);$[\alpha]_D^{23} = -7.7$ (*c* 2.2, $CHCl_3$) 85% ee; ^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.39–7.45 (m, 1H), 7.35–7.38 (m, 1H), 7.11–7.24 (m, 2H), 6.50 (d, *J* = 15.8 Hz, 1H), 6.04–6.19 (m, 1H), 4.61–4.79 (m, 2H), 3.76 (s, 3H), 3.73 (s, 3H), 3.67–3.70 (m, 2H) ppm; ^{13}C NMR (50 MHz, $CDCl_3$): δ = 167.5, 167.5, 137.9, 134.1, 131.2, 130.1, 129.4, 126.8, 125.3, 124.9, 76.8, 53.2, 53.0, 52.95, 41.1 ppm; IR (film): ν = 3026, 2954, 1736, 1557, 1435, 1378, 1161, 1072, 970, 753 cm^{-1}; elemental analysis calcd (%) for $C_{15}H_{16}BrNO_6$: C 46.65, H 4.18, N, 3.63; found: C 46.56, H 4.04, N 4.11; the enantiomeric excess was determined by HPLC with a Daicel chiralpak AD-H column [λ = 220 nm], eluent: 2-propanol/hexane (10/90), flow rate = 0.8 mL/min, t_{minor} = 22.0 min (7.36%), t_{major} = 34.82 min (92.64%).

4.14. (4*E*)-Dimethyl 2-[(*S*)-4,8-dimethyl-1-nitronona-3,7-dien-2-yl] malonate 10j

Yellow oil; Yield: 62 mg (76%); *E*:*Z* ~ 6/4; $[\alpha]_D^{27} = -9.0$ (*c* 1.0, $CHCl_3$) 72% ee; ^{1}H NMR (200 MHz, $CDCl_3$, *E*:*Z* ~ 6/4): δ = 4.95–5.04 (m, 2H), 4.62 (dd, *J* = 4.9, 12.2 Hz, 1H), 4.44 (dd, *J* = 8.4, 12.2 Hz, 1H), 3.86–3.92 (m, 1H), 3.73 (s, 3H), 3.70 (s, 3H), 3.50 (d, *J* = 8.0 Hz, 1H), 1.97–2.04 (m, 4H), 1.66 (s, 6H), 1.55 (s, 3H) ppm;

^{13}C NMR (50 MHz, $CDCl_3$, E:Z ~ 6/4): δ = 168.0 (*E*). 167.9 (*Z*), 167.8 (*E*), 167.7 (*Z*), 143.0 (*E*), 142.8 (*Z*), 132.4 (*Z*), 131.9 (*E*), 123.6 (*Z*), 123.4 (*E*), 119.3 (*Z*), 118.7 (*E*), 77.4 (*E*), 77.3 (*Z*), 53.6 (*Z*), 53.4 (*E*), 52.7 (2 C, *E*), 52.6 (2 C, *Z*), 39.7 (*E*), 36.6 (*E*), 36.3 (*Z*), 32.0 (*Z*), 26.3, 25.6 (*Z*), 25.5 (*E*), 23.4 (*Z*), 17.6 (*E*), 17.5 (*Z*), 16.3 (*E*) ppm; IR (film): ν = 2956, 2922, 2856, 1739, 1632, 1556, 1435, 1378, 1257, 1160, 1016, 912, 733 cm^{-1}; HRMS (ESI): *m*/*z* calcd for $C_{16}H_{25}NO_6Na$ [M+Na]$^+$: 350.1575; found: 350.1574; the enantiomeric excess was determined by HPLC with a Daicel chiralpak AD-H column [λ = 220 nm], eluent: 2-propanol/hexane (5/95), flow rate = 0.5 mL/min, t_{minor} = 12.58 min (14.16%), t_{major} = 14.43 min (85.84%).

4.15. Dimethyl 2-allyl-2-((*S*,*E*)-1-nitro-4-phenylbut-3-en-2-yl) malonate 10k

Yellow oil; Yield: 40 mg (45%);$[\alpha]_D^{23} = +20.9$ (*c* 2.2, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.24–7.32 (m, 5H), 6.54 (d, *J* = 15.6 Hz, 1H), 5.62–5.77 (m, 2H), 5.07–5.18 (m, 2H), 4.90 (dd, *J* = 2.9, 12.7 Hz, 1H), 4.50 (dd, *J* = 10.8, 12.6 Hz, 1H), 3.80 (s, 3H), 3.76 (s, 3H), 3.69 (dd, *J* = 3.0, 10.4 Hz, 1H), 2.60–2.82 (m, 2H) ppm; ^{13}C NMR (50 MHz, $CDCl_3$): δ = 169.9, 169.7, 136.9, 135.8, 131.4, 128.6 (2C), 128.3, 126.6 (2C), 122.1, 120.1, 77.6, 59.5, 52.8, 52.7, 44.9, 38.5 ppm; IR (film): ν = 3081, 3027, 2954, 2846, 1729, 1641, 1556, 1495, 1434, 1378, 970, 920, 748 cm^{-1}; elemental analysis calcd (%) for $C_{18}H_{21}NO_6$: C 62.24, H 6.09, N 4.03; found: C 62.03, H 5.75, N 4.06; the enantiomeric excess was determined by HPLC with a Daicel chiralpak OD-H column [λ = 220 nm], eluent: 2-propanol/hexane (5/95), flow rate = 0.5 mL/min, t_{minor} = 25.44 min (8.51%), t_{major} = 43.74 min (91.49%).

4.16. 3-((*S*,*E*)-1-Nitro-4-phenylbut-3-en-2yl) pentane-2,4-dione 12a

White solid; Yield: 63 mg (92%); Recrystallized from hexane–EtOAc; Yield: 36 mg (53%); mp 143–145 °C (hexane–EtOAc); $[\alpha]_D^{26} = -203$ (*c* 1.0, $CHCl_3$) >96% ee; ^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.29–7.31 (m, 5H), 6.54 (d, *J* = 15.8 Hz, 1H), 6.00 (dd, *J* = 9.4Hz, 1H), 4.53 (d, *J* = 6 Hz, 2H), 4.05 (d, *J* = 11 Hz, 1H), 3.64–3.79 (m, 1H), 2.27 (s, 3H), 2.19 (s, 3H) ppm; ^{13}C NMR (50 MHz, $CDCl_3$): δ = 201.8, 201.6, 135.5, 135.5, 128.6 (2C), 128.4, 126.5 (2C), 123.1, 77.3, 68.9, 40.9, 30.5, 29.9 ppm; IR (KBr): $\bar{U}$ = 2985, 2878, 2844, 1729, 1704, 1553, 1356, 1268, 1146, 970, 744 cm^{-1}; elemental analysis calcd (%) for $C_{15}H_{17}NO_4$: C 65.44, H 6.22, N 5.09; found: C 65.39, H 5.88, N 5.05; the enantiomeric excess was determined by HPLC with a Daicel chiralpak AD-H column [λ = 220 nm], eluent: 2-propanol/hexane (5/95), flow rate = 0.5 mL/min, t_{minor} = 26.12 -min (1.84%), t_{major} = 32.61 min (98.16%).

4.17. (3*S*)-Methyl 2-acetyl-3-(nitromethyl)-5-phenylpent-4-enoate 12b

White solid; Yield: 65.5 mg (90%); ^{1}H NMR (200 MHz, $CDCl_3$, ~1:1 mixture of diastereoisomers): δ = 7.27–7.29 (m, 10H), 6.55 (dd, *J* = 2, 16 Hz, 2H), 6.07 (dd, *J* = 3, 15.8 Hz, 1H), 6.02 (dd, *J* = 3, 15.8 Hz, 1H), 4.59–4.76 (m, 4H), 3.77 (s, 3H), 3.71 (s, 3H), 3.70–3.88 (m, 4H), 2.30 (s, 3H), 2.26 (s, 3H) ppm; ^{13}C NMR (50 MHz, $CDCl_3$, ~1:1 mixture of diastereoisomers): δ = 200.9, 200.8, 168.0, 167.8, 135.8, 135.7, 135.5, 135.2, 128.6 (4C), 128.3, 128.2, 126.5 (4C), 123.4 (2C), 77.1 (2C), 60.5, 60.1, 30.3, 52.8 (2C), 40.8, 40.5, 30.1 ppm; IR ($CHCl_3$, film): ν = 3348, 3054, 3020, 2951, 1791, 1696, 1490, 1449, 1434, 1346, 1270, 1213, 1168, 1049, 997, 926, 754 cm^{-1}; HRMS (ESI): *m*/*z* calcd for $C_{15}H_{17}NO_5Na$ [M+Na]$^+$ 314.0994; found: 314.0999; the enantiomeric excess was determined by HPLC with a Daicel chiralpak AS-H column [λ = 220 nm], eluent: 2-propanol/hexane (5/95), flow rate = 0.5 mL/min, $t_{minor\ (diast\text{-}1)}$ = 52.00 min (5.17%), $t_{major\ (diast\text{-}2)}$ = 69.00 min (41.79%), $t_{minor\ (diast\text{-}2)}$ = 77.90 min (3.78%), $t_{major\ (diast\text{-}1)}$ = 142.20 min (49.26%).

4.18. (3*S*)-Methyl 2-acetyl-3-(nitromethyl)-5-phenyl-2-(prop-2-ynyl)pent-4-enoate 12c

Yellow oil; Yield: 78 mg (95%); ^{1}H NMR (200 MHz, $CDCl_3$, ~7:3 mixture of diastereoisomers): δ = 7.23–7.32 (m, 5H), 6.63 (d, 1H, *J* = 15.8 Hz, minor), 6.55 (d, 1H, *J* = 15.8 Hz, major), 6.00 (dd, 1H, *J* = 9.8, 15.6 Hz, major), 5.80 (dd, 1H, *J* = 10.2, 15.8 Hz, minor), 4.88–4.98 (m, 1H), 4.66 (dd, 1H, *J* = 10.8, 12.6 Hz, major), 4.46 (dd, 1H, *J* = 10.8, 12.6 Hz, minor), 3.84–4.01 (m, 1H), 3.83 (s, 3H, minor), 3.75 (s, 3H, major), 2.99 (dd, 1H, *J* = 2.6, 17.6 Hz, major), 2.73–2.88 (m, 1H, major, 2 H minor), 2.24 (s, 3H), 2.16 (t, 1H, *J* = 1.6 Hz) ppm; ^{13}C NMR (50 MHz, $CDCl_3$, ~7:3 mixture of diastereoisomers): δ = 202.0 (major), 201.0 (minor), 169.6, 137.1 (minor), 136.7 (major), 135.8 (major), 135.7 (minor), 128.6 (2C), 128.4 (minor), 128.3 (major), 126.7 (2 C, minor), 126.6 (2 C, major), 122.2 (major), 121.6 (minor), 78.5 (minor), 76.7 (major), 73.3, 64.4 (major), 63.7 (minor), 53.2 (major), 53.1 (minor), 45.5 (major), 43.8 (minor), 29.6, 27.8 (major), 27.1 (minor), 22.9 (minor), 22.0 (major) ppm; IR (film): ν = 3306, 2955, 2925, 2852, 2255, 1719, 1556, 1449, 1434, 1224, 970, 731 cm^{-1}; HRMS (ESI): *m*/*z* calcd for $C_{18}H_{19}NO_5Na$ [M+Na]$^+$: 352.1156; found: 352.1155; The enantiomeric excess was determined by HPLC with a Daicel chiralpak AD-H column [λ = 220 nm], eluent: 2-propanol/hexane (5/95), flow rate = 0.5 mL/min, $t_{minor\ (minor\ diast)}$ = 27.92 min (2.63%), $t_{major\ (minor\ diast)}$ = 29.35 min (24.29%), $t_{minor\ (major\ diast)}$ = 30.45 min (16.97%), $t_{major\ (major\ diast)}$ = 34.40 min (56.10%).

4.19. (3*S*,4*S*)-Methyl 2-oxo-4-styrylpyrrolidine-3-carboxylate 13

Zinc powder (570 mg, 8.8 mmol) was added portionwise to a stirred solution of nitroester **10a** (77 mg, 0.25 mmol, 88% ee) in 2:1 THF/acetic acid (3 mL) at room temperature. After 3 h, the reaction mixture was filtered through a Celite pad and the filtrate was evaporated under reduced pressure followed by high vacuum. The residue was dissolved in dichloromethane (3 mL) and an aqueous saturated solution of sodium bicarbonate (1 mL) was added into it. The reaction mixture was stirred at room temperature for 20 h, extracted with dichloromethane and the organic extract was evaporated under reduced pressure. The residue was purified by column chromatography to give lactam **13** (52 mg, 85%) as white flakes. mp 140–143 °C; $[\alpha]_D^{26} = -127.4$ (*c* 0.31, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.18–7.36 (m, 5H), 7.15 (br s, 1H), 6.53 (d, *J* = 15.6 Hz, 1H), 6.12 (dd, *J* = 7.8, 15.8 Hz, 1H), 3.79 (s, 3H), 3.53–3.75 (m, 2H), 3.35 (d, *J* = 9.2 Hz, 1H), 3.24 (t, *J* = 8.0 Hz, 1H) ppm; ^{13}C NMR (50 MHz, $CDCl_3$): δ = 172.9, 169.4, 136.1, 132.6, 128.6 (2C), 127.9, 127.2, 126.3 (2C), 53.9, 52.8, 46.2, 42.8 ppm; IR ($CHCl_3$, film): ν = 3348, 3054, 3020, 2951, 1791, 1696, 1490, 1449, 1434, 1346, 1270, 1213, 1168, 1049, 997, 926, 754 cm^{-1}; elemental analysis calcd (%) for $C_{14}H_{15}NO_3$: calcd C 68.56, H 6.16, N 5.71; found: C 68.69, H 6.46, N 5.27.

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