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Stereocontrolled Construction of Quaternary Stereocenters by Inter- and Intramolecular Nitro-Michael Additions Catalyzed by Bifunctional Thioureas

Rubén Manzano,[a] José M. Andrés,[a] María D. Muruzábal,[a] and Rafael Pedrosa[a,*]

[a] Instituto CINQUIMA and Departamento de Química Orgánica, Facultad de Ciencias, Universidad de Valladolid. 47011 Valladolid, Spain
Fax: (+34)-98-342-3013; e-mail: pedrosa@qo.uva.es

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Abstract: A highly diastereo- and enantioselective conjugate addition of β-keto esters to nitroolefins, catalyzed by a chiral thiourea prepared from L-valine is described. The formation of two contiguous tertiary and quaternary stereocenters occurs in high yield and excellent diastereo- and enantioselection with only 2 mol% of catalyst loading. The reaction is general and different β-keto esters and aryl- and alkylnitroolefins have been tested. The same catalyst has been used to promote the first intramolecular conjugate addition leading to the cyclic adduct in moderate diastereoselectivity and good enantioselectivity.

Keywords: bifunctional thioureas; Michael addition; nitroolefins; organocatalysis; quaternary stereocenters

Introduction

The stereocontrol in the construction of carbon-carbon bonds, especially the formation of quaternary stereocenters, constitutes one of the most important tasks in the asymmetric synthesis. To this end, a lot of chiral auxiliaries, reagents, and catalysts have been developed during the last two decades.[1] One of the most studied reactions is the Michael addition of easily enolizable substrates to nitroolefins because the highly functionalized nitro compounds are versatile intermediates in organic synthesis.[2] Enantioselective addition of different nucleophiles to nitroolefins catalyzed by chiral bifunctional thioureas constitutes a good approach, and a lot of organocatalysts have been developed to achieve that goal.[3]

More difficult is the stereocontrolled construction of two adjacent carbon-substituted quaternary and tertiary stereocenters, although recently some organocatalyzed processes have been described leading to the Michael adducts in good or excellent diastereo- and enantioselectivities. In this context, especially interesting are the chiral thioureas derived from *Cinchona* alkaloids,[4] *trans*-1,2-diaminocyclohexane,[5] amino alcohols,[6] guanidines,[7] or imidazolines[8] that catalyze intermolecular additions to nitroolefins, but there are no antecedents for the formation of adjacent tertiary-quaternary stereocenters intramolecularly.

Searching for easily accessible thioureas able to act as bifunctional organocatalysts, we have recently described a modular synthesis of these compounds starting from α-amino acids and their use in enantioselective transformations,[3,9] and now we describe the results obtained in both diastereo- and enantioselective inter- and intramolecular additions to nitroalkenes. For comparative purposes, we selected as nucleophiles α-substituted β-keto esters or β-diketones because they are easily enolizable substrates previously used in similar transformations.

Results and Discussion

The additions of β-keto esters **3a–f**, α-acyl lactone **3g**, β-diketone **3h** and ethyl 3-oxo-4-piperidylcarboxylate (**3i**) to *trans*-β-nitrostyrene catalyzed by thiourea **1**, derived from L-valine[3] were examined to evaluate the stereoselection in the intermolecular reaction. Initially the reaction conditions were fixed by using 10 mol% of catalyst loading, and toluene as a solvent at −18 °C, and the results are summarized in Table 1. The enantioselection for all the reactions was excel-

Table 1. Michael additions of compounds **3a–h** to *trans*-β-nitrostyrene, catalyzed by thiourea **1**.

Entry	Substrate	Time [h]	Product (Yield [%][a])	*dr*[b] (2*S*,3*R*/2*R*,3*R*)[c]	*er*[d]
1	**3a**	14	**4a** (98)	23/77	98/2
2	**3b**	0.5	**4b** (99)	98/2	95/5
3	**3c**	0.5	**4c** (99)	95/5	96/4
4	**3d**	17	**4d** (99)	98/2	97/3
5	**3e**	72	**4e** (89)	98/2[e]	98/2
6	**3f**	4	**4f** (97)	90/10	97/3
7	**3f**	9[f]	**4f** (95)	92/8	99/1
8	**3g**	0.75	**4g** (95)	70/30	96/4
9	**3g**	1.5[g]	**4g** (89)	81/19	97/3
10	**3g**	6[h]	**4g** (94)	83/17	99/1
11	**3h**	2.5	**4h** (93)	13/87	96/4
12	**3i**	20[i]	**4i** (85)	>99/1	97/3

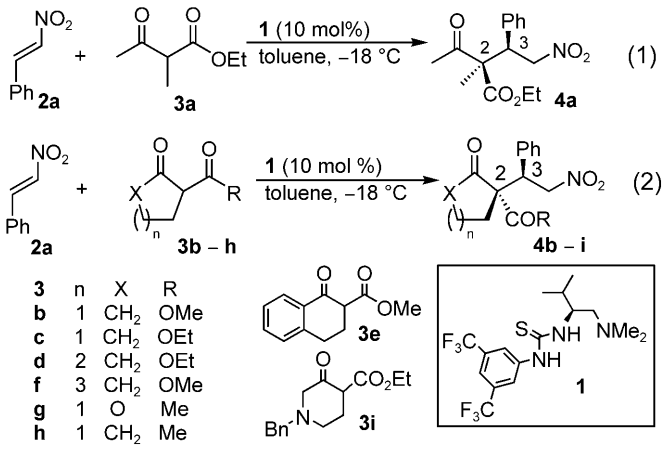
[a] Yields refer to isolated compounds.
[b] Determined by H NMR in the reaction mixture.
[c] Determined by comparison of the sign of the specific rotation previously described.
[d] Determined by chiral HPLC.
[e] Determined by X-ray diffraction analysis.
[f] The reaction was performed at −50 °C.
[g] The reaction was performed at −40 °C.
[h] The reaction was performed at −60 °C.
[i] The nitroolefin was *trans*-*p*-fluoronitrostyrene.

lent (*er* 95/5 to 99/1) while the diastereoselection varied depending on the structure of the nucleophile.

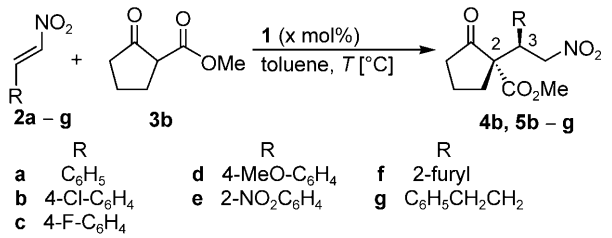
We first investigated the Michael addition of ethyl 2-methylacetoacetate to *trans*-β-nitrostyrene leading to **4a** [Scheme 1, Eq. (1)] in near quantitative yield, and excellent enantioselectivity (*er* 98/2), although moderate diasteroselectivity (*dr* 77/23). The absolute configuration of **4a** (*2R,3R*) was established by comparison of the spectral data, HPLC retention time and specific rotation with those previously described.[5c,10]

The reaction was extended to cyclic α-alkoxycarbonyl ketones **3b–f** as nucleophiles, which differ in the size or the substituents in the ring [Scheme 1, Eq. (2)]. The reactions of cyclopentanone derivatives **3a** and **3b** were faster than those of their homologous, leading to completion in 0.5 h at −18 °C in very good diastereo- and enantioselectivities (entries 2 and 3 in Table 1). The nature of the alkoxy group has little influence in the stereoselection. Cycloheptanone derivative **3f** also reacted easily (4 h) but with lower diastereo- and enantiocontrol (entry 6). Both the diastereo- and enantioselectivities were improved when the reaction temperature was lowered to −50 °C (entry 7).

The best results in terms of stereocontrol were obtained for the reaction of six-membered derivatives **3d** (98/2 *dr* and 97/3 *er*), **3e** (98/2 *dr* and 98/2 *er*), and **3i** (>99/1 *dr* and 98/2 *er*), although the reactions required longer times for completion (entries 4, 5 and 12). Diketone **3h** was also a good nucleophile, leading to the addition product in good *er* (96/4), but moderate *dr* (87/13) after 2.5 h of reaction (entry 11). Similarly, 2-acetyl butyrolactone **3g** reacted very quickly with *trans*-β-nitrostyrene at −18 °C giving **4g**[10] in good *er*, although moderate *dr* (70/30). Fortunately, by reducing the reaction temperature to −40 °C or even to −60 °C, a *dr* of 83/17 with 99/1 *er* was achieved (entries 8–10 in Table 1). As previously described, the cyclic and acyclic 2-substituted β-keto esters afforded the adducts with contrary configurations at C-2.[5c] In our case, the major diastereoisomer (**4a**) obtained from the open keto esters has the *R* configuration whereas adducts **4b–i**, prepared from cyclic substrates, have the *S* configuration at C-2.



Scheme 1. Organocatalyzed Michael additions of nucleophiles to *trans*-β-nitrostyrene by thiourea **1**.

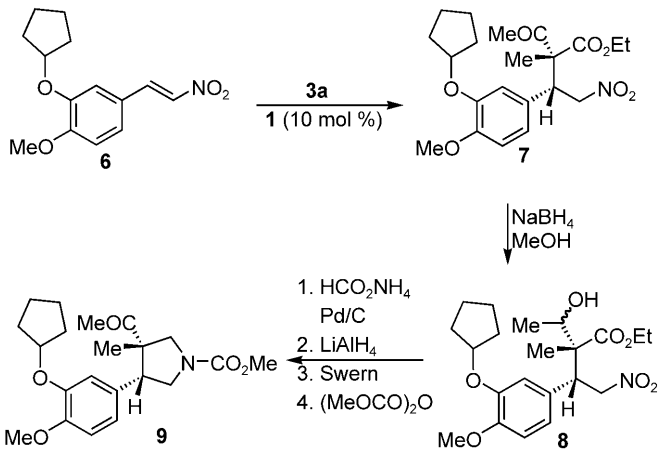


Scheme 2. Reaction of different nitroolefins with methyl 2-oxocyclopentanecarboxylate.

Next, we studied the effect of the temperature and loading of the catalyst in the process taking as a model the reaction of *trans*-β-nitrostyrene (**2a**) with methyl 2-oxocyclopentanecarboxylate (**3b**), and the results are collected in Scheme 2 and Table 2 (entries 1–4). These data showed that the lowering of the catalyst loading did not modify the diastereoselection and slightly increased the enantioselection, although at the expense of increasing the reaction time (entries 1–3). Interestingly, total diastereoselectivity and excellent enantioselectivity (97/3 *er*) were achieved with only *2 mol% of catalyst loading* when the reaction was carried out at −50 °C (entry 4).

In the same experimental conditions (toluene, −50 °C, 2 mol% of catalyst), the Michael addition was extended to nitroolefins with aryl (**2b–e**), hetaryl (**2f**), and alkyl (**2g**) substituents (Table 2, entries 5–10). The addition of β-keto ester **3a** occurred easily, furnishing the adducts **5b–g** in near quantitative yields and excellent diastereo- and enantioselectivities. Interestingly, the electronic nature of the substituent has an important effect on the reaction rate, increasing the reaction time with the electron-withdrawing effect of the substituent, but it did not modify the stereoselection appreciably. The reaction of the alkyl-substituted nitroolefin **2g** was much slower, but it went to completion after 36 h in the presence of 5 mol% of catalyst loading.

The excellent stereoselection of the reaction led us to consider the enantioselective synthesis of pyrrolidine **9** (GW3600), which is a potent inhibitor of PDE4 and closely related to rolipram. It has been demonstrated that the activity of that type of compounds is related with the presence of the acetyl group at the pyrrolidine nucleus and the stereochemistry of the substituents.[11] In our case, both the tertiary and quaternary stereocenters could be established by the diastereo- and enantioselective addition of **3a** to the corresponding β-nitrostyrene catalyzed by the chiral thiourea **1**.



Scheme 3. Enantioselective synthesis of one diastereoisomer of GW3600.

Table 2. Michael addition of **3b** to nitroolefins **2a–g** catalyzed by thiourea **1**.

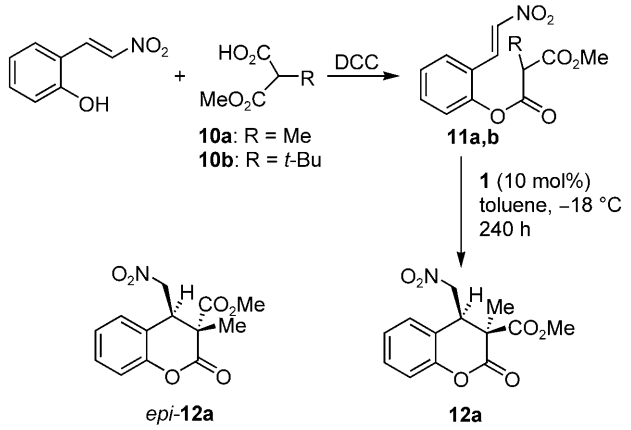
Entry	Substrate	x (mol%)	Temperature [°C]	Time [h]	Product (Yield [%][a])	*dr*[b]	*er*[c]
1	**2a**	10	−18	0.5	**4b** (99)	>98/2	95/5
2	**2a**	5	−18	1	**4b** (95)	>98/2	95/5
3	**2a**	2	−18	7	**4b** (98)	>98/2	96/4
4	**2a**	2	−50	20	**4b** (99)[d]	>98/2	97/3
5	**2b**	2	−50	24	**5b** (98)[d]	96/4	96/4
6	**2c**	2	−50	48	**5c** (98)[d]	>98/2	97/3
7	**2d**	2	−50	60	**5d** (96)[d]	96/4	96/4
8	**2e**	2	−50	16	**5e** (97)[e]	97/3	99/1
9	**2f**	2	−50	10	**5f** (99)[e]	97/3	98/2
10	**2g**	5	−50	36	**5g** (96)[e]	>98/2	96/4

[a] Yields refer to isolated compounds.
[b] Determined by H NMR in the reaction mixture.
[c] Determined by chiral HPLC.
[d] The stereochemistry of these compounds has been assigned by comparison of the physical and spectral data with those previously described.
[e] The stereochemistry of these adducts has been tentatively assigned by generalization of the stereochemical outcome of the reaction.

The known nitroolefin **6**[12] was reacted with ethyl 2-methylacetoacetate in the presence of **1** (10 mol%) at −18 °C in toluene leading to **7** (89% *ee*) and its epimer (91% *ee*) in 95% yield and 80/20 *dr* (Scheme 3). After chromatographic purification, **7** was reduced to a mixture of epimeric alcohols **8** by reaction with sodium borohydride in methanol. That mixture was transformed into **9** by reduction of the nitro group with lactamization, reduction of the lactam to the pyrrolidine derivative, Swern oxidation of the secondary alcohol, and treatment with dimethyl dicarbonate, in 31% total yield from **7**.

The stereochemistry of **9** was established on the basis of COSY and NOESY experiments.[13] Thus, the COSY experiment[13] allowed the assignation of the signals corresponding to the five protons at the pyrrolidine nucleus. In the NOESY experiment it is possible to observe signals corresponding to strong interaction between the methyl group at C-3 (quaternary stereocenter) and one proton at C-2 and the proton at C-4 (tertiary stereocenter). The last signal is clearly indicative of the *cis* relationship of the substituents at the heterocycle.

Finally, we tested the unprecedented intramolecular reaction leading to enantioenriched cyclic substrates. To this end, compounds **11a** and **11b** were prepared by reaction of *o*-hydroxy-*trans*-β-nitrostyrene[14] with the hemiesters of 2-methyl- and 2-*tert*-butyl malonic acid in the presence of DCC (Scheme 4). The intramolecular addition was much slower and less diastereo- and enantioselective than the intermolecular reaction. Compound **11a** led to **12a** in 65% yield after stirring for 240 h at −18 °C in toluene and 10 mol% of catalyst **1**. Moreover, the product was a mixture (3/2) of epimers **12a** and *epi*-**12a** at the quaternary stereocenter, and the major diastereoisomer was obtained in a moderate *er* (89/11), whereas the minor isomer was isolated as a racemate.



Scheme 4. Diastereo- and enantioselective intramolecular Michael additions to nitroolefins.

After separation by column chromatography, the relative stereochemistry was assigned by NOE experiments. The NOESY experiment[13] of **12a** showed a clear interaction between the methyl group at the quaternary carbon and the hydrogen atom at the tertiary stereocenter, indicating a *cis* relationship, while that NOE interaction did not appear for the corresponding diastereoisomer *epi*-**12a**. Interestingly, these results demonstrate that, from the stereochemical point of view, the intramolecular reaction occurs in the same way as the intermolecular process when an acyclic substrate is used as nucleophile. Unfortunately, compound **11b** did not react, and it was recovered unchanged after stirring for 1 month in the described conditions. The lack of reactivity for that compound could be attributed to the sterically encumbered transition state due to the bulkiness of the *tert*-butyl group.

Because the mechanism and stereochemical outcome of the intermolecular process are well known,[5c,6b,19] we propose a model to explain the stereoselectivity observed in the intramolecular reaction (Figure 1).

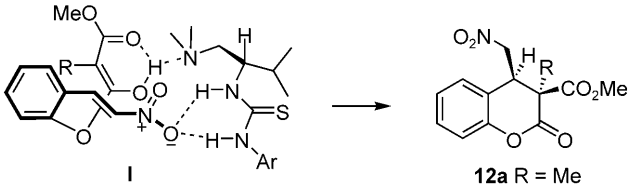


Figure 1. Proposed complex for the intramolecular reaction.

As generally accepted, the thiourea behaves as bifunctional catalyst activating both the nucleophile and the electrophile. The amino group will deprotonate the acidic hydrogen leading to an enolate near the nitrogen atom, whereas the thiourea will activate the nitroolefin by hydrogen bonding leading to complex **I**. The intramolecular attack of the enolate to the double bond yields **12a** as major stereoisomer. The proposed model could also explain why the reaction did not take place with compound **10b** (R = *t*-Bu). The sterically demanding substituent probably prevents the deprotonation of the substrate.

Conclusions

In summary, the described results show that thiourea **1**, easily prepared from natural L-valine, is an excellent catalyst for the construction of adjacent tertiary and quaternary stereocenters by enantioselective Michael addition of β-keto esters to nitroolefins. The reactions occur with very good yields and excellent diastereo- and enantioselectivities (*dr* up to >98/2 and *er*

up to 99/1). The unprecedented intramolecular Michael reaction, leading to cyclic addition products, is also catalyzed by **1** although with moderate diastereoselection and good enantioselection.

Experimental Section

General Remarks

^{1}H NMR (300 MHz or 400 MHz) and ^{13}C NMR (75 MHz) spectra were recorded in $CDCl_3$. Chemical shifts for protons are reported in ppm from tetramethylsilane with the residual $CHCl_3$ resonance as internal reference. Chemical shifts for carbons are reported in ppm from tetramethylsilane and are referenced to the carbon resonance of the solvent. Data are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, sp = septet, m = multiplet, br = broad), coupling constants in Hertz, and integration. Specific rotations were measured using a 5 mL cell with a 1-dm path length, and a sodium lamp, and concentration is given in g per 100 mL. Flash chromatography was carried out using silica gel (230–240 mesh). Chemical yields refer to pure isolated substances. TLC analysis was performed on glass-backed plates coated with silica gel 60 and an F_{254} indicator, and visualized by either UV irradiation or by staining with I_2 or phosphomolybdic acid solution. Chiral HPLC analysis was performed using a Daicel Chiralcel OD column (250×4.6 mm) or Chiralpak AS-H or AD-H column (250×4.6 mm). UV detection was monitored at 220 nm or at 254 nm. Unless otherwise indicated, all compounds were purchased from Aldrich and used as received. Nitroolefins **2g**[15] and **6**[12] were prepared according to literature procedures. β-Keto ester **3i**·HCl is commercially available and was liberated to **3i** prior to use by treatment with a saturated solution of sodium bicarbonate, and extracted with dichloromethane. Monomethyl 2-methylmalonate (**10a**) was prepared by selective mono-hydrolysis according to the literature procedure.[16] Monomethyl 2-*tert*-butylmalonate (**10b**) was prepared by α-carboxylation of methyl 3,3-dimethylbutanoate,[17a] readily prepared from 3,3-dimethylbutyric acid.[17b] Solvents were dried and stored over microwave-activated 4 Å molecular sieves.

Typical Procedure for Enantioselective Michael Addition of β-Keto Esters to Nitroolefins

To a stirred solution of *trans*-β-nitrostyrene **2a** (0.30 mmol, 45.6 mg) and catalyst **1** (0.03 mmol) in toluene (0.6 mL) was added methyl 2-oxocyclopentanecarboxylate **3b** (0.60 mmol, 0.08 mL) at −18 °C. The reaction mixture was stirred until disappearance of the nitroolefin by TLC. The solvent was removed under vacuum and the residue was purified by flash chromatography (hexane/AcOEt = 10/1 as eluent) to afford the desired product **4b**.

(2*R*,3*R*)-Ethyl 2-acetyl-2-methyl-4-nitro-3-phenylbutanoate (4a): Major diastereoisomer; $[\alpha]_D^{25}$: +43.9 (*c* 0.6, $CHCl_3$, 95% *ee*) (lit.[5c] $[\alpha]_D^{25}$: −41.0, 91% *ee*, dr > 98:2); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.19 (t, *J* = 7.2 Hz, 3H), 1.43 (s, 3H), 2.11 (s, 3H), 3.98–4.17 (m, 2H), 4.20–4.25 (m, 1H), 4.94–4.97 (m, 2H), 7.19–7.24 (m, 2H), 7.26–7.31 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 13.8 (CH_3), 18.0 (CH_3), 27.5 (CH_3), 47.3 (CH), 61.9 (C), 62.0 (CH_2), 76.9 (CH_2), 128.3 (CH), 128.7 (2 CH), 129.2 (2 CH), 135.4 (C), 170.7 (C), 205.3 (C); HPLC (Chiralcel OD, hexane/2-propanol, 90:10, 0.9 mL min^{-1}, λ = 220 nm): t_R = 12.8 min (major), 18.6 min (minor); HR-MS: *m/z* = 316.1151, calcd. for ($C_{15}H_{19}NO_5$ + Na): 316.1161.

(2*S*,3*R*)-Methyl 1-(2-nitro-1-phenylethyl)-2-oxocyclopentanecarboxylate (4b): $[\alpha]_D^{25}$: +36.4 (*c* 1.1, $CHCl_3$, 90% *ee*) (lit.[10] $[\alpha]_D^{25}$: +36.5, 99% *ee*, *dr* 95:5); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.80–2.09 (m, 4H), 2.31–2.43 (m, 2H), 3.76 (s, 3H), 4.09 (dd, *J* = 10.7, 4.0 Hz, 1H), 5.02 (dd, *J* = 13.6, 10.9 Hz, 1H), 5.17 (dd, *J* = 13.7, 4.0 Hz, 1H), 7.21–7.35 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 19.2 (CH_2), 31.0 (CH_2), 37.8 (CH_2), 46.1 (CH), 52.9 (CH_3), 62.3 (C), 76.3 (CH_2), 128.2 (CH), 128.7 (2 CH), 129.2 (2 CH), 135.2 (C), 169.7 (C), 212.2 (C); HPLC (Chiralcel OD, hexane/2-propanol, 80:20, 1.0 mL min^{-1}, λ = 220 nm): t_R (major diastereoisomer) = 10.7 min (major), 14.8 min (minor); HR-MS: *m/z* = 291.1114, calcd. for $C_{15}H_{17}NO_5$: 291.1107.

(2*S*,3*R*)-Ethyl 1-(2-nitro-1-phenylethyl)-2-oxocyclopentanecarboxylate (4c): $[\alpha]_D^{25}$: +30.8 (*c* 1.0, $CHCl_3$, 92% *ee*); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.28 (t, *J* = 7.1 Hz, 3H), 1.80–2.09 (m, 4H), 2.30–2.42 (m, 2H), 4.08 (dd, *J* = 10.8, 3.9 Hz, 1H), 4.22 (q, *J* = 7.1 Hz, 2H), 5.02 (dd, *J* = 13.5, 11.0 Hz, 1H), 5.18 (dd, *J* = 13.5, 3.9 Hz, 1H), 7.21–7.35 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 13.8 (CH_3), 19.2 (CH_2), 31.0 (CH_2), 37.8 (CH_2), 46.1 (CH), 62.1 (CH_2), 62.3 (C), 76.3 (CH_2), 128.1 (CH), 128.7 (2 CH), 129.2 (2 CH), 135.3 (C), 169.2 (C), 212.3 (C); HPLC (Chiralcel OD, hexane/2-propanol, 80:20, 1.0 mL min^{-1}, λ = 220 nm): t_R (major diastereoisomer) = 9.5 min (major), 12.9 min (minor); HR-MS: *m/z* = 305.1267, calcd. for $C_{16}H_{19}NO_5$: 305.1263.

(2*S*,3*R*)-Ethyl 1-(2-nitro-1-phenylethyl)-2-oxocyclohexanecarboxylate (4d): $[\alpha]_D^{25}$: −86.5 (*c* 1.0, $CHCl_3$, 93% *ee*) (lit.[10] $[\alpha]_D^{25}$: −91.5, 99% *ee*, *dr* > 98:2); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.26 (t, *J* = 7.1 Hz, 3H), 1.42–1.52 (m, 1H), 1.57–1.75 (m, 3H), 2.00–2.18 (m, 2H), 2.41–2.56 (m, 2H), 4.01 (dd, *J* = 11.3, 3.2 Hz, 1H), 4.22 (q, *J* = 7.1 Hz, 2H), 4.80 (dd, *J* = 13.4, 11.4 Hz, 1H), 5.07 (dd, *J* = 13.4, 3.3 Hz, 1H), 7.14–7.17 (m, 2H), 7.25–7.31 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 13.8 (CH_3), 22.2 (CH_2), 27.8 (CH_2), 36.9 (CH_2), 41.3 (CH_2), 47.6 (CH), 61.8 (CH_2), 62.8 (C), 77.4 (CH_2), 128.0 (CH),128.3 (2 CH), 129.4 (2 CH), 135.3 (C), 169.5 (C), 207.0 (C); HPLC (Chiralcel OD, hexane/2-propanol, 95:5, 1.0 mL min^{-1}, λ = 220 nm): t_R (major diastereoisomer) = 12.0 min (major), 16.7 min (minor); HR-MS: *m/z* = 319.1406, calcd. for $C_{17}H_{21}NO_5$: 319.1420.

(2*S*,3*R*)-Methyl 2-(2-nitro-1-phenylethyl)-1-oxo-1,2,3,4-tetrahydronaphthalene-2-carboxylate (4e): $[\alpha]_D^{25}$: −47.9 (*c* 1.1, $CHCl_3$, 97% *ee*) (lit.[5c] $[\alpha]_D^{25}$: +51.0, 95% *ee*, *dr* > 98:2); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.00–2.09 (m, 1H), 2.42 (dt, *J* = 13.9, 5.1 Hz, 1H), 2.96–3.00 (m, 2H), 3.65 (s, 3H), 4.22 (dd, *J* = 10.4, 4.0 Hz, 1H), 5.07 (dd, *J* = 13.5, 10.3 Hz, 1H), 5.17 (dd, *J* = 13.5, 4.1 Hz, 1H), 7.21 (d, *J* = 7.6 Hz, 1H), 7.26–7.40 (m, 6H), 7.51 (td, *J* = 7.5, 1.4 Hz, 1H), 8.05 (dd, *J* = 8.0, 1.4 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 25.5 (CH_2), 30.7 (CH_2), 47.1 (CH), 52.7 (CH_3), 59.7 (C), 77.8 (CH_2), 127.0 (CH), 128.2 (CH), 128.4 (CH), 128.6 (2 CH), 128.7 (CH), 129.8 (2 CH), 131.5 (C), 134.1 (CH), 135.9 (C), 142.4 (C), 170.2 (C), 194.2 (C); HPLC (Chiralcel OD, hexane/2-propanol, 90:10, 1.0 mL min^{-1}, λ = 254 nm): t_R

(major diastereoisomer) = 17.4 min (major), 35.6 min (minor); HR-MS: m/z = 376.1154, calcd. for ($C_{20}H_{19}NO_5$ + Na): 376.1161.

(2*S*,3*R*)-Methyl 1-(2-nitro-1-phenylethyl)-2-oxocycloheptanecarboxylate (4f): The diastereomers could not be separated. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.40–1.94 (m, 8H), 2.49–2.66 (m, 2H), 3.78 (s, 3H), 4.07 (dd, J = 9.3, 4.9 Hz, 1H), 4.88–4.99 (m, 2H), 7.14–7.21 (m, 2H), 7.27–7.34 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 24.4 (CH_2), 25.0 (CH_2), 28.8 (CH_2), 32.8 (CH_2), 41.3 (CH_2), 48.4 (CH), 52.3 (CH_3), 65.4 (C), 77.7 (CH_2), 128.2 (CH), 128.6 (2CH), 129.3 (2CH), 135.5 (C), 171.2 (C), 208.1 (C); HPLC (Chiralcel OD, hexane/2-propanol, 95:5, 1.0 mL min^{-1}, λ = 220 nm): t_R (major diastereoisomer) = 14.6 min (major), 32.8 min (minor); HR-MS: m/z = 319.1428, calcd. for $C_{17}H_{21}NO_5$: 319.1420.

(2*S*,3*R*)-2-Acetyl-2-(2-nitro-1-phenylethyl)-butyrolactone (4g): The major diastereoisomer was purified by recrystallization (hexane/AcOEt); $[\alpha]_D^{25}$: +4.2 (*c* 0.6 $CHCl_3$, 99% *ee*); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.25–2.35 (m, 1H), 2.51 (s, 3H), 2.86 (ddd, J = 13.3, 7.8, 4.1 Hz, 1H), 3.87 (td, J = 8.9, 4.1 Hz, 1H), 4.01–4.09 (m, 1H), 4.51–4.57 (m, 2H), 4.86 (dd, J = 14.2, 12.4 Hz, 1H), 7.32–7.39 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 25.6 (CH_2), 26.2 (CH_3), 45.6 (CH), 64.6 (C), 65.9 (CH_2), 74.9 (CH_2), 129.0 (CH), 129.1 (4 CH), 133.0 (C), 173.1 (C), 201.2 (C); HPLC (Chiralcel OD, hexane/2-propanol, 70:30, 1.0 mL min^{-1}, λ = 220 nm): t_R (major diastereoisomer) = 20.2 min (major), 51.0 min (minor); HR-MS: m/z = 277.0945, calcd. for $C_{14}H_{15}NO_5$: 277.0950.

(2*R*,3*R*)-2-Acetyl-2-(2-nitro-1-phenylethyl)-cyclopentanone (4h): The major diastereoisomer was purified by flash chromatography; $[\alpha]_D^{25}$: −33.3 (*c* 1.2, $CHCl_3$, 92% *ee*) (lit.[10] $[\alpha]_D^{25}$: −43.3, 99% *ee*, *dr* > 98:2); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.67–1.76 (m, 3H), 1.92–2.02 (m, 1H), 2.11–2.22 (m, 1H), 2.32 (s, 3H), 2.52–2.59 (m, 1H), 4.38 (dd, J = 11.6, 3.9 Hz, 1H), 4.50 (dd, J = 13.6, 3.9 Hz, 1H), 4.86 (dd, J = 13.5, 11.5 Hz, 1H), 7.23–7.34 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 19.3 (CH_2), 26.5 (CH_3), 27.3 (CH_2), 38.5 (CH_2), 46.2 (CH), 71.0 (C), 75.5 (CH_2), 128.3 (CH), 128.7 (2 CH), 129.4 (2 CH), 134.3 (C), 202.7 (C), 213.1 (C); HPLC (Chiralcel OD, hexane/2-propanol, 70:30, 1.0 mL min^{-1}, λ = 220 nm): t_R (major diastereoisomer) = 11.4 min (major), 39.2 min (minor); HR-MS: m/z = 275.1152, calcd. for $C_{15}H_{17}NO_4$: 275.1158.

(2*S*,3*R*)-Ethyl 1-benzyl-4-[1-(4-fluorophenyl)-2-nitroethyl]-3-oxopiperidine-4-carboxylate (4i): ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.15 (t, J = 7.1 Hz, 3H), 1.54–1.64 (m, 1H), 2.22–2.31 (m, 1H), 2.45 (ddd, J = 11.7, 7.5, 4.2 Hz, 1H), 2.70–2.80 (m, 1H), 2.97 (d, J = 16.7 Hz, 1H), 3.31 (d, J = 16.7 Hz, 1H), 3.46 (d, J = 13.0 Hz, 1H), 3.56 (d, J = 13.0 Hz, 1H), 3.95 (dd, J = 11.4, 3.5 Hz, 1H), 4.15 (q, J = 7.1 Hz, 2H), 4.73 (dd, J = 13.3, 11.7 Hz, 1H), 5.05 (dd, J = 13.3, 3.4 Hz, 1H), 6.95–7.02 (m, 2H), 7.15–7.25 (m, 4H), 7.27–7.34 (m, 3H); ^{19}F NMR (282 MHz, $CDCl_3$): δ = −114.1 (m, 1F); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 13.8 (CH_3), 31.0 (CH_2), 45.8 (CH), 48.1 (CH_2), 59.0 (C), 60.9 (CH_2), 61.9 (CH_2), 62.2 (CH_2), 77.2 (CH_2), 115.3 (d, $^2J_{C,F}$ = 22.0 Hz, 2CH), 127.5 (CH), 128.3 (2CH), 128.7 (2CH), 130.8 (C), 131.2 (d, $^3J_{C,F}$ = 8.5 Hz, 2CH), 136.6 (C), 162.4 (d, $^1J_{C,F}$ = 247.8 Hz, C), 168.4 (C), 204.3 (C); HPLC (Chiralpak AS-H, hexane/2-propanol, 90:10, 0.2 mL min^{-1}, λ = 220 nm): t_R = 69.7 min (major), 75.0 min (minor); HR-MS: m/z = 451.1634, calcd. for ($C_{23}H_{25}FN_2O_5$ + Na): 451.1645.

(2*S*,3*R*)-Methyl 1-[1-(4-chlorophenyl)-2-nitroethyl]-2-oxocyclopentanecarboxylate (5b): $[\alpha]_D^{25}$: +36.2 (*c* 1.6, $CHCl_3$, 91% *ee*) (lit.[8] $[\alpha]_D^{25}$: −39.6, 96% *ee*, *dr* > 20:1); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.82–2.13 (m, 4H), 2.35–2.45 (m, 2H), 3.75 (s, 3H), 4.04 (dd, J = 11.0, 3.9 Hz, 1H), 4.98 (dd, J = 13.6, 11.0 Hz, 1H), 5.15 (dd, J = 13.8, 4.0 Hz, 1H), 7.20–7.24 (m, 2H), 7.28–7.32 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 19.2 (CH_2), 31.2 (CH_2), 37.8 (CH_2), 45.5 (CH), 53.0 (CH_3), 62.1 (C), 76.1 (CH_2), 128.9 (2CH), 130.6 (2CH), 133.8 (C), 134.2 (C), 169.6 (C), 212.1 (C); HPLC (Chiralcel OD, hexane/2-propanol, 90:10, 1.0 mL min^{-1}, λ = 220 nm): t_R (major diastereoisomer) = 19.1 min (major), 32.2 min (minor); HR-MS: m/z = 348.0604, calcd. for ($C_{15}H_{16}ClNO_5$ + Na): 348.0615.

(2*S*,3*R*)-Methyl 1-[1-(4-fluorophenyl)-2-nitroethyl]-2-oxocyclopentanecarboxylate (5c): $[\alpha]_D^{25}$: +30.5 (*c* 1.5, $CHCl_3$, 95% *ee*) (lit.[8] $[\alpha]_D^{25}$: −31.3, 94% *ee*, *dr* > 20:1); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.81–2.11 (m, 4H), 2.32–2.44 (m, 2H), 3.75 (s, 3H), 4.05 (dd, J = 11.0, 4.0 Hz, 1H), 4.97 (dd, J = 13.6, 11.0 Hz, 1H), 5.15 (dd, J = 13.6, 4.0 Hz, 1H), 6.96–7.04 (m, 2H), 7.22–7.29 (m, 2H); ^{19}F NMR (282 MHz, $CDCl_3$): δ = −113.9 (m, 1F); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 19.2 (CH_2), 31.1 (CH_2), 37.8 (CH_2), 45.4 (CH), 53.0 (CH_3), 62.3 (C), 76.3 (CH_2), 115.7 (d, $^2J_{C,F}$ = 22.0 Hz, 2 CH), 131.0 (C), 131.0 (d, $^3J_{C,F}$ = 8.5 Hz, 2CH), 162.4 (d, $^1J_{C,F}$ = 247.8 Hz, C), 169.7 (C), 212.2 (C); HPLC (Chiralcel OD, hexane/2-propanol, 90:10, 1.0 mL min^{-1}, λ = 220 nm): t_R (major diastereoisomer) = 15.7 min (major), 28.0 min (minor); HR-MS: m/z = 332.0910, calcd. for ($C_{15}H_{16}FNO_5$ + Na): 332.0910.

(2*S*,3*R*)-Methyl 1-[1-(4-methoxyphenyl)-2-nitroethyl]-2-oxocyclopentanecarboxylate (5d): $[\alpha]_D^{25}$: +34.7 (*c* 1.5, $CHCl_3$, 92% *ee*) (lit.[8] $[\alpha]_D^{25}$: −38.9, 93% *ee*, *dr* > 20:1); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.79–2.07 (m, 4H), 2.29–2.43 (m, 2H), 3.75 (s, 3H), 3.77 (s, 3H), 4.06 (dd, J = 11.0, 4.2 Hz, 1H), 4.96 (dd, J = 13.4, 11.0 Hz, 1H), 5.11 (dd, J = 13.4, 4.0 Hz, 1H), 6.82 (ps d, J = 8.8 Hz, 2H), 7.16 (ps d, J = 8.8 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 19.2 (CH_2), 30.8 (CH_2), 37.9 (CH_2), 45.4 (CH), 52.9 (CH_3), 55.1 (CH_3), 62.5 (C), 76.4 (CH_2), 114.0 (2 CH), 126.8 (C), 130.3 (2 CH), 159.2 (C), 169.8 (C), 212.3 (C); HPLC (Chiralpak AS-H, hexane/2-propanol, 90:10, 1.0 mL min^{-1}, λ = 220 nm): t_R (major diastereoisomer) = 22.0 min (minor), 25.8 min (major); HR-MS: m/z = 344.1109, calcd. for ($C_{16}H_{19}NO_6$ + Na): 344.1110.

(2*S*,3*R*)-Methyl 1-[2-nitro-1-(2-nitrophenyl)ethyl]-2-oxocyclopentanecarboxylate (5e): $[\alpha]_D^{25}$: +108.0 (*c* 1.7, $CHCl_3$, 97% *ee*); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.87–2.07 (m, 3H), 2.15–2.23 (m, 2H), 2.42–2.52 (m, 1H), 3.73 (s, 3H), 4.65 (dd, J = 10.8, 3.5 Hz, 1H), 5.04 (dd, J = 14.3, 10.8 Hz, 1H), 5.34 (dd, J = 14.5, 3.5 Hz, 1H), 7.40–7.46 (m, 1H), 7.56–7.61 (m, 1H), 7.77–7.82 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 19.1 (CH_2), 33.2 (CH_2), 37.5 (CH_2), 38.8 (CH), 53.0 (CH_3), 61.4 (C), 76.9 (CH_2), 124.8 (CH), 129.0 (CH), 129.5 (CH), 131.4 (C), 133.2 (CH), 151.1 (C), 170.3 (C), 212.6 (C); HPLC (Chiralpak AD-H, hexane/2-propanol, 80:20, 0.2 mL min^{-1}, λ = 220 nm): t_R (major diastereoisomer) = 52.8 min (major), 66.5 min (minor); HR-MS: m/z = 359.0841, calcd. for ($C_{15}H_{16}N_2O_7$ + Na): 359.0855.

(2*S*,3*R*)-Methyl 1-[1-(furan-2-yl)-2-nitroethyl]-2-oxocyclopentanecarboxylate (5f): $[\alpha]_D^{25}$: +68.8 (*c* 1.1, $CHCl_3$, 95% *ee*); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.65–1.80 (m, 1H), 1.92–2.04 (m, 2H), 2.08–2.18 (m, 1H), 2.30–2.41 (m, 1H), 2.44–2.52 (m, 1H), 3.76 (s, 3H), 4.43 (dd, *J* = 9.1, 5.4 Hz, 1H), 4.85–4.98 (m, 2H), 6.19 (dd, *J* = 3.3, 0.4 Hz, 1H), 6.30 (dd, *J* = 3.3, 2.0 Hz, 1H), 7.33 (dd, *J* = 2.0, 0.9 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 19.3 (CH_2), 30.1 (CH_2), 37.8 (CH_2), 40.3 (CH), 53.1 (CH_3), 61.8 (C), 74.3 (CH_2), 110.0 (CH), 110.7 (CH), 142.6 (CH), 148.9 (C), 169.4 (C), 211.9 (C); HPLC (Chiralcel OD, hexane/2-propanol, 90:10, 1.0 mL min^{-1}, λ = 220 nm): t_R (major diastereoisomer) = 12.6 min (major), 19.5 min (minor); HR-MS: *m/z* = 304.0797, calcd. for ($C_{13}H_{15}NO_6$ + Na): 304.0797.

(2*S*,3*R*)-Methyl 1-(1-nitro-4-phenylbutan-2-yl)-2-oxocyclopentanecarboxylate (5g): $[\alpha]_D^{25}$: +76.1 (*c* 1.2, $CHCl_3$, 91% *ee*); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.56–1.68 (m, 1H), 1.74–2.03 (m, 4H), 2.22–2.48 (m, 2H), 2.51–2.61 (m, 2H), 2.70–2.79 (m, 1H), 2.82–2.90 (m, 1H), 3.70 (s, 3H), 4.46 (dd, *J* = 14.3, 5.3 Hz, 1H), 4.97 (dd, *J* = 14.2, 5.2 Hz, 1H), 7.13–7.32 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 19.2 (CH_2), 31.1 (CH_2), 32.4 (CH_2), 33.8 (CH_2), 38.0 (CH_2), 39.9 (CH), 52.7 (CH_3), 62.7 (C), 76.1 (CH_2), 126.3 (CH), 128.3 (2 CH), 128.5 (2 CH), 140.5 (C), 169.8 (C), 213.2 (C); HPLC (Chiralpak AS-H, hexane/2-propanol, 90:10, 1.0 mL min^{-1}, λ = 220 nm): t_R = 11.6 min (major), 12.8 min (minor); HR-MS: *m/z* = 342.1327, calcd. for ($C_{17}H_{21}NO_5$ + Na): 342.1317.

Conjugate Addition of β-Keto Ester 2a to Nitroolefin 6

Product **7** was obtained following the general procedure for nitro-Michael additions described above for **4b** starting from 3-cyclopentyloxy-4-methoxy-β-nitrostyrene (**6**)[12] and ethyl 2-methylacetoacetate (**3a**), and using thiourea **1** as catalyst (48 h). The mixture of diasteroisomers was obtained with 95% yield and the major diastereoisomer (**7**) was separated (*ca.* 80:20) by flash chromatography (hexane/ethyl acetate 8:1 to 4:1).

(2*R*, 3*R*)-Ethyl 2-acetyl-3-[3-(cyclopentyloxy)-4-methoxyphenyl]-2-methyl-4-nitrobutanoate (7): ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.22 (t, *J* = 7.1 Hz, 3H), 1.44 (s, 3H), 1.59–1.66 (m, 2H), 1.79–1.97 (m, 6H), 2.11 (s, 3H), 3.81 (s, 3H), 4.02–4.22 (m, 1H), 4.69–4.74 (m, 1H), 4.93 (ABX, *J* = 14.6, 13.3 Hz, 1H), 4.96 (ABX, *J* = 19.5, 13.2 Hz, 1H), 6.71–6.78 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 13.6 (CH_3), 18.3 (CH_3), 23.8 (2 CH_2), 27.6 (CH_3), 32.5 (CH_2), 32.5 (CH_2), 47.1 (CH), 55.6 (CH_3), 61.7 (CH_2), 61.8 (C), 77.4 (CH_2), 80.2 (CH), 111.5 (CH), 115.9 (CH), 121.5 (CH), 127.2 (C), 147.1 (C), 149.7 (C), 170.8 (C), 205.6 (C); HPLC (Chiralpak OD, hexane/2-propanol, 90:10, 1.0 mL min^{-1}, λ = 220 nm): t_R = 11.7 min (major), 14.3 min (minor); HR-MS: *m/z* = 430.1823, calcd. for ($C_{21}H_{29}NO_7$ + Na): 430.1842.

Synthesis of 9

To a solution of β-keto ester **7** (407 mg, 1 mmol) in methanol (8 mL) at 0 °C was added $NaBH_4$ (76 mg, 2 mmol). The reaction mixture was stirred until disappearance of starting material (TLC, about 1 hour), and then acidified with HCl (2 M). The volatiles were removed under vacuum and the residue was partitioned between H_2O (2 mL) and EtOAc (2 mL). The organic phase was separated and the aqueous phase was extracted with EtOAc (3 × 3 mL). The combined organic extracts were dried over anhydrous $MgSO_4$. After removal of the solvent at reduced pressure the crude product was passed through a plug of silica gel to afford **8** as colorless oil; yield: 75%. The diastereoisomers could be separated by flash chromatography (hexane/ethyl acetate 5:1).

Ethyl 3-[3-(cyclopentyloxy)-4-methoxyphenyl]-2-(1-hydroxyethyl)-2-methyl-4-nitrobutanoate (8a): ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.09 (s, 3H), 1.21 (d, *J* = 6.4 Hz, 3H), 1.24 (t, *J* = 7.1 Hz, 3H), 1.57–1.64 (m, 2H), 1.77–1.98 (m, 6H), 3.12 (br d, *J* = 11.0 Hz, 1H), 3.61–3.71 (m, 1H), 3.82 (s, 3H), 4.04 (dd, *J* = 11.9, 4.0 Hz, 1H), 4.15 (q, *J* = 7.2 Hz, 1H), 4.72–4.79 (m, 1H), 4.78 (dd, *J* = 12.8, 3.8 Hz, 1H), 5.04 (ps t, *J* = 12.4 Hz, 1H), 6.69–6.80 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.1 (CH_3), 18.1 (CH_3), 19.2 (CH_3), 24.0 (2 CH_2), 32.7 (2 CH_2), 48.5 (CH), 53.6 (C), 55.9 (CH_3), 61.3 (CH_2), 69.9 (CH), 77.0 (CH_2), 80.4 (CH), 111.5 (CH), 116.2 (CH), 121.6 (CH), 127.1 (C), 147.2 (C), 149.8 (C), 175.1 (C); HR-MS: *m/z* = 432.1975, calcd. for ($C_{21}H_{31}NO_7$ + Na): 432.1998.

To a mixture of epimers **8** (286 mg, 0.7 mmol) and 10% Pd-C (80 mg) in methanol (2 mL) anhydrous ammonium formate (442 mg, 7 mmol) was added in a single portion.[18] The resulting reaction mixture was stirred at room remperature for 2–3 h (TLC) under nitrogen, and then it was refluxed for 20 min. The catalyst was removed by filtration through a celite pad and washed with dry methanol. The filtrate was evaporated under reduced pressure and the resulting residue was partitioned between water (1 mL) and dichloromethane (2 mL). The aqueous phase was extracted with dichloromethane (4 × 2 mL) and the combined organic layers were dried over anhydrous $MgSO_4$. After removal of the solvent, the crude diastereoisomeric hydroxy lactams were subjected to further reduction with lithium aluminum hydride, as follows.

To a suspension of $LiAlH_4$ (106 mg, 2.8 mmol, 4 equiv.) in dry tetrahydrofuran (7 mL) at 0 °C a solution of the previously obtained hydroxylactams in THF (3 mL) was added. The reaction mixture was refluxed for 16 h until disappearance of the starting material and carefully quenched by sequential addition of water (0.11 mL), 15% NaOH (0.11 mL) and water (0.32 mL). The solids were filtered off and washed with ethyl acetate, and the filtrate was dried over anhydrous $MgSO_4$. The solvent was removed in vacuo and the crude product was subjected to the Swern oxidation conditions.

To a stirred solution of 0.08 mL (0.95 mmol) of oxalyl chloride in 2 mL of dichloromethane at −78 °C under nitrogen was added 0.14 mL (2.0 mmol) of dimethyl sulfoxide. After 15 min, a solution of the hydroxypirrolydine in 2 mL of dichloromethane was added. After 30 min, 0.28 mL of triethylamine (2.0 mmol) was added and the resulting mixture was gradually warmed to room temparature. The mixture was partitioned between dichloromethane and water. The organic phase was dried over anhydrous $MgSO_4$ and then evaporated to yield the crude keto lactam, which was redissolved in dichloromethane and treated with 1.5 equiv. of dimethyl pyrocarbonate at room temperature for 30 min. The solvent was removed at reduced pressure and the product was purified by flash chromatography (hexane/ethyl acetate 1:3) to afford desired product **9**; overall yield: 31% (4 steps).

(3*S*,4*R*) Methyl 3-acetyl-4-[3-(cyclopentyloxy)-4-methoxyphenyl]-3-methylpyrrolidine-1-carboxylate (2 conformers) (9): ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 1.44$ (s, 3H), 1.61–1.71 (m, 2H), 1.69 (s, 3H), 1.75–1.97 (m, 6H), 3.17 (t, 1H), 3.20–3.33 (m, 1H), 3.62–3.94 (m, 2H), 3.74 (s, 1.5H), 3.75 (s, 1.5H), 3.82 (s, 3H), 4.04 (t, $J = 10.8$ Hz, 1H), 4.71 (br s, 1H), 6.62–6.69 (m, 2H), 6.78 (d, $J = 8.3$ Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 23.1$ (CH_3), 24.1 (2CH_2), 28.1 (CH_3), 28.4 (CH_3), 32.8 (2 CH_2), 50.4 (CH_2), 50.8 (CH_2), 52.5 (CH_3), 52.7 (CH), 53.6 (CH), 54.0 (CH_2), 54.6 (CH_2), 55.9 (CH_3), 57.5 (C), 58.6 (C), 80.4 (CH), 111.8 (CH), 114.3 (CH), 120.0 (CH), 129.8 (C), 130.0 (C), 147.6 (C), 149.4 (C), 155.4 (C), 210.1 (C); HR-MS: $m/z = 398.1931$, calcd. for ($C_{21}H_{29}NO_5$+Na): 398.1943.

Synthesis of 2-(2-Nitrovinyl)phenyl Malonates

To a solution of *trans*-2-hydroxy-β-nitrostyrene (510 mg, 3 mmol) and monomethyl 2-methylmalonate **10a** (436 mg, 3.3 mmol)[16] in dry THF (30 mL), DCC (681 mg, 3.3 mmol) was added at −20 °C in one portion.[14] After stirring for 15 min at this temperature, the reaction mixture was allowed to warm to room temperature and stirred for 7 days. During that time a white precipitate of dicyclohexylurea was formed. The white solid was filtered off and the solvent was removed in vacuo. The crude product was purified by flash chromatography (CH_2Cl_2) to afford compound **11a** as a yellow solid; yield: 272 mg (0.97 mmol, 32%).

(*E*)-1-Methyl 3-[2-(2-nitrovinyl)phenyl] 2-methylmalonate (11a): ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 1.62$ (d, $J = 7.2$ Hz, 3H), 3.81 (q, $J = 7.2$ Hz, 1H), 3.89 (s, 3H), 7.21–7.24 (m, 1H), 7.32–7.37 (m, 1H), 7.51–7.57 (m, 1H), 7.61 (d, $J = 13.8$ Hz, 1H), 7.61–7.64 (m, 1H), 8.13 (d, $J = 13.6$ Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 13.5$ (CH_3), 45.9 (CH), 53.0 (CH_3), 123.0 (C), 123.2 (CH), 126.8 (CH), 128.4 (CH), 132.4 (CH), 132.9 (CH), 138.5 (CH), 149.7 (C), 168.1 (C), 169.6 (C); HR-MS: $m/z = 302.0637$, calcd. for ($C_{13}H_{13}NO_6$+Na): 302.0641.

(*E*)-1-Methyl 3-[2-(2-nitrovinyl)phenyl] 2-*tert*-butylmalonate (11b): ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 1.25$ (s, 9H), 3.61 (s, 1H), 3.87 (s, 3H), 7.21 (dd, $J = 8.2$, 1.1 Hz, 1H), 7.32–7.36 (m, 1H), 7.51–7.56 (m, 1H), 7.60 (d, $J = 13.8$ Hz, 1H), 7.61–7.63 (m, 1H), 8.12 (d, $J = 13.8$ Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 27.8$ (3 CH_3), 33.9 (C), 52.4 (CH_3), 60.9 (CH), 123.1 (C), 123.2 (CH), 126.8 (CH), 128.4 (CH), 132.5 (CH), 132.9 (CH), 138.5 (CH), 149.6 (C), 166.4 (C), 167.9 (C); HR-MS: $m/z = 344.1108$, calcd. for ($C_{16}H_{19}NO_6$+Na): 344.1110.

Procedure for Intramolecular Michael Addition

A mixture of **11a** (84 mg, 0.3 mmol) and catalyst **1** (10 mol%) in toluene (0.6 mL) was stirred at −18 °C until disappearance of starting material (TLC, 9 days). During this time the turbid mixture became a solution. The solvent was removed under vacuum and the residue was purified by flash chromatography (hexane/AcOEt = 6/1 to 4/1 as eluent) to afford diasteromeric products; yield: 55 mg (65%).

(3*S*,4*R*)-Methyl 3-methyl-4-(nitromethyl)-2-oxochroman-3-carboxylate (12a): ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 1.68$ (s, 3H), 3.63 (s, 3H), 3.98 (dd, $J = 8.4$, 4.4 Hz, 1H), 4.92 (dd, $J = 14.7$, 8.4, 1H), 5.05 (dd, $J = 14.7$, 4.4 Hz, 1H), 7.10–7.21 (m, 3H), 7.35–7.39 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 19.7$ (CH_3), 41.5 (CH), 51.7 (C), 53.3 (CH_3), 74.9 (CH_2), 117.2 (CH), 121.3 (C), 125.6 (CH), 126.2 (CH), 130.1 (CH), 150.2 (C), 166.0 (C), 169.4 (C); HPLC (Chiralpak AD-H, hexane/2-propanol, 90:10, 1.0 mL min^{-1}, $\lambda = 220$ nm): t_R = 14.8 min (major), 16.3 min (minor); HR-MS: $m/z = 302.0637$, calcd. for ($C_{13}H_{13}NO_6$+Na): 302.0641.

(3*R*, 4*R*)-Methyl 3-methyl-4-(nitromethyl)-2-oxochroman-3-carboxylate (*epi*-12a): ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.66 (s, 3H), 3.58 (s, 3H), 4.25 (dd, $J = 9.7$, 5.2 Hz, 1H), 4.37 (dd, $J = 12.6$, 9.8, 1H), 4.69 (dd, $J = 12.6$, 5.0 Hz, 1H), 7.10–7.21 (m, 3H), 7.34–7.39 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 18.2$ (CH), 42.0 (CH_3), 52.2 (C), 53.6 (CH), 75.4 (CH_2), 117.3 (CH), 120.7 (C), 125.5 (CH), 128.7 (CH), 130.6 (CH), 150.5 (C), 166.1 (C), 169.7 (C); HPLC (Chiralpak AD-H, hexane/2-propanol, 90:10, 1.0 mL min^{-1}, $\lambda = 220$ nm): $t_R = 13.1$ min (minor), 14.7 min (major); HR-MS: m/z = 302.0627, calcd. for ($C_{13}H_{13}NO_6$+Na): 302.0641.

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