Asymmetric Synthesis of Functionalized Chromans via a One-Pot Organocatalytic Domino Michael–Hemiacetalization or –Lactonization and Dehydration Sequence

Dieter Enders,* Gregor Urbanietz, Robert Hahn, Gerhard Raabe

Institute of Organic Chemistry, RWTH Aachen University, Landoltweg 1, 52074 Aachen, Germany
Fax +49(241)8092127; E-mail: enders@rwth-aachen.de

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Abstract: Starting from 2-(nitrovinyl)phenols and various cyclic dicarbonyl nucleophiles, a one-pot thiourea-catalyzed diastereo- and enantioselective synthesis of polyfunctionalized chroman derivatives via a domino Michael–hemiacetalization and dehydration sequence as well as via a domino Michael–lactonization reaction is reported. Cyclopenta[*b*]chromenes, tricyclic spirochromans, and tetrahydro-1*H*-xanthenes bearing a variety of functional groups can be synthesized in this way in good to excellent yields (56–91%) and with very good diastereo- (88–99% de) and enantioselectivities (83–99% ee).

Key words: organocatalysis, domino reaction, thiourea, one-pot reaction, chromans

In recent years, great progress has been made in the asymmetric organocatalytic synthesis of stereochemically defined complex molecular structures via the concept of multi-component domino reactions.[1] Owing to the importance of the benzopyran framework, its construction has attracted considerable attention, and various synthetic methods have been reported.[2] Chiral benzopyrans represent a privileged structural motif that is found in a range of natural products and drug candidates with broad biological implications (Figure 1).[3]

Thus, it is crucial to develop asymmetric strategies to construct highly enantioenriched scaffolds like dihydrocoumarins and chromenes. For the stereoselective synthesis

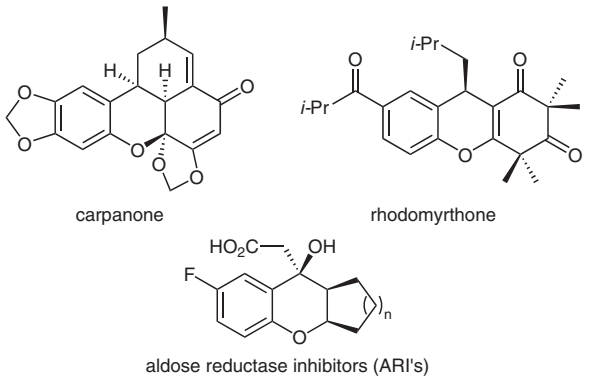

Figure 1 Natural product and bioactive compounds with chroman and chromene cores

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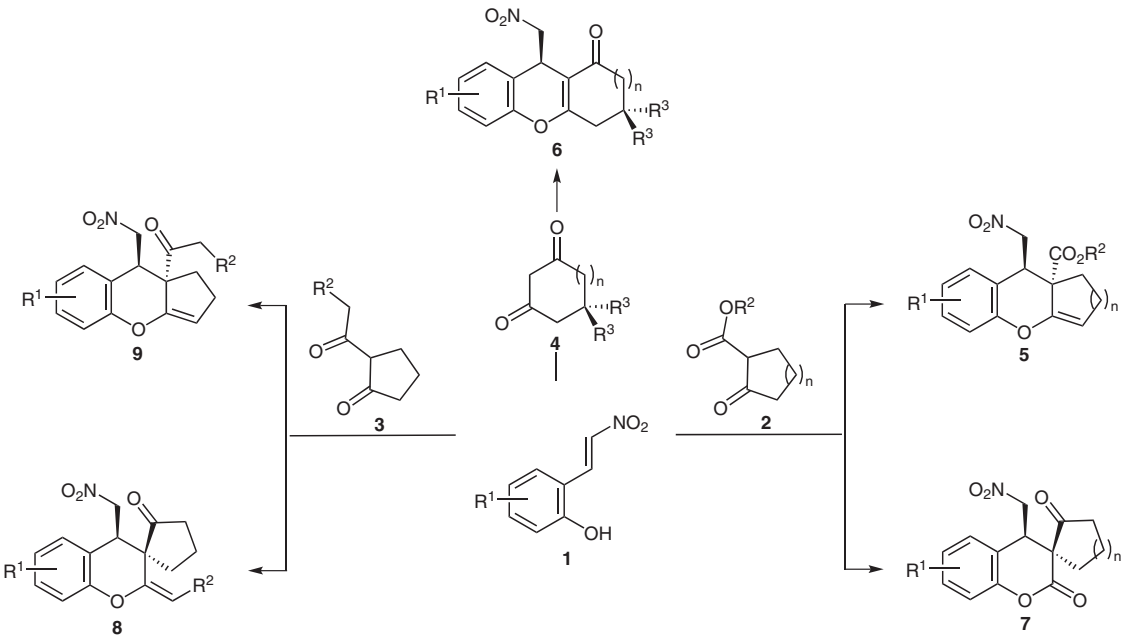
of these oxygen-containing heterocycles, (nitrovinyl)phenols are important starting materials. During our investigations of new reactive species for developing new organocatalytic cascade reactions, we decided to expand the potential ability of 2-(2-nitrovinyl)phenols **1** to participate in the thiourea amine-catalyzed domino Michael–hemiacetalization reaction[4] with easily enolizable nucleophiles like cyclic β-keto esters **2** as well as cyclic 1,3-diketones **3**,**4**. Quite recently, we have developed a novel bifunctional thiourea catalyst, which promotes the asymmetric Michael addition of acyclic β-keto esters to (nitrovinyl)phenols as well as nitrostryrenes with great efficiency. On the basis of this observation we envisaged that polycyclic chromanols, versatile intermediates to complex chromenes, spirochromans and tetrahydro-1*H*-xanthenes, could be generated by Michael addition and subsequent intramolecular hemiacetalization if 2-(2-nitrovinyl)phenol served as substrate. The phenolic hydroxy group participates in this process through carbonyl addition and makes this sequence a powerful tool among the existing annulation methodologies. Hemiacetals can be subsequently transformed into many useful chroman core structures. However, different pathways are possible if prochiral nucleophiles bear more than one carbonyl group and thus the chemoselectivity of the reaction becomes an important issue. Cyclization would either afford chromenes or xanthenes **5**, **6**, and **9** or spiranes **7** and **8** as shown in Scheme 1. Herein, we report our findings regarding these sequential one-pot reactions.

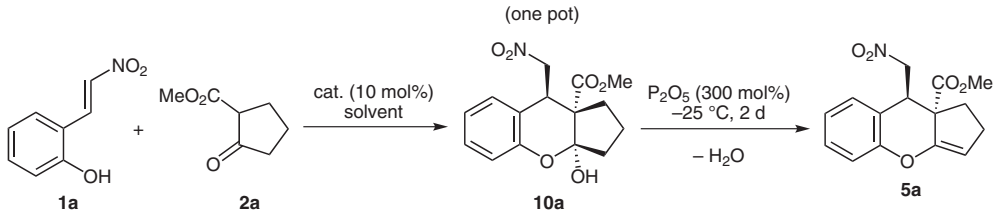
The studies of the domino Michael–hemiacetalization reactions were started by screening the organocatalysts **A**, **B**, and **C** for the Michael reaction of 2-(2-nitrovinyl)phenol[5] (**1a**) with one equivalent of methyl 2-oxocyclopentanecarboxylate (**2a**). The intermediate chromanol **10a** was directly dehydrated to the tetrahydrocyclopenta[*b*]chromenecarboxylate **5a** in a one-pot procedure (see Table 1). It turned out that 300 mol% P_2O_5 in dichloromethane at –25 °C for two days is the best reaction condition for the dehydration process, which succeeded in good yields and no lactonization occurred.

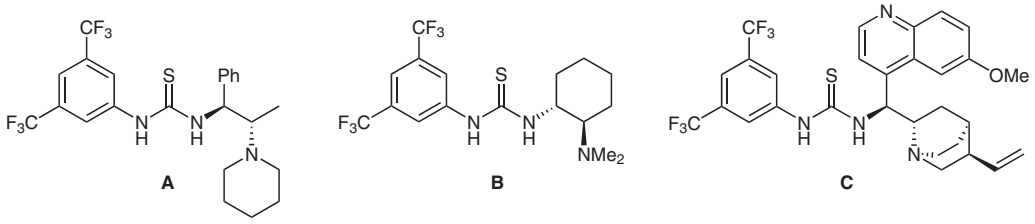
While the ephedrine derived catalyst **A** showed excellent stereoselectivities for acyclic β-keto esters[2b] in toluene, low enantioselectivities were obtained when methyl 2-oxocyclopentanecarboxylate (**2a**) was used as nucleophile (Table 1, entry 1). The diastereo- and enantioselectivity could be improved slightly by using Takemoto's catalyst



Scheme 1 Domino Michael–hemiacetalization or –lactonization and dehydration sequences to tricyclic chroman scaffolds

Table 1 Optimization of Conditions for the Domino Michael-Hemiacetalization and Subsequent Dehydration Sequence





Entry[a]	Catalyst	Solvent	Temp (°C)	Time (h)	Yield (%)[b]	de (%)[c]	ee (%)[d]
1	A	PhMe	r.t.	7	76	84	77 (58)
2	B	PhMe	r.t.	7	71	86	80 (27)[e]
3	C	PhMe	r.t.	7	81	99	93 (67)
4	C	PhMe	5	16	84	92	86 (50)
5	C	PhMe	–25	48	86	93	86 (8)
6	C	CH_2Cl_2	r.t.	9	74	89	92 (79)
7	C	THF	r.t.	9	72	94	91 (87)
8[f]	C	PhMe	r.t.	48	77	87	76 (56)

[a] All reactions were performed on a 1.0 mmol scale.
[b] Yield of isolated product **5a**.
[c] Determined by HPLC analysis on a chiral stationary phase.
[d] The enantiomeric excess of the minor diastereomer is given in parentheses.
[e] The opposite enantiomer *ent*-**5a** was obtained.
[f] The reaction was performed with 5 mol% catalyst loading.

B,[6] but still did not give satisfactory asymmetric inductions (Table 1, entry 2). In contrast to catalyst **A** the opposite enantiomer was obtained with catalyst **B**. While catalyst **A** and **B** showed moderate to good diastereo- and enantioselectivity, the quinine thiourea catalyst **C**[7] led to the best stereoselectivity (Table 1, entry 3). With a suitable catalyst in hand, we tried to improve the stereoselectivity as well as the yield of the reaction by decreasing the temperature. The domino Michael–hemiacetalization reaction proceeds at 5 °C as well as at –25 °C (Table 1, entries 4, 5). While decreasing the temperature to –25 °C or +5 °C results in a slight decrease in enantioselectivity, the diastereoselectivity and yield could be improved, yet longer reaction times were necessary. Therefore, it was decided to change the catalyst loading from 10 mol% to 5 mol% at ambient temperature. The selectivity decreased while the loading did not have an effect on the yield (Table 1, entry 8). Next, solvents like dichloromethane and THF were examined in the domino Michael–hemiacetalization reaction of **1a** and **2a**, which had no big impact on yield, reaction time, and selectivity (Table 1, entries 6, 7). It turned out that the bulky quinine motif attached to the 3,5-bis(trifluoromethyl)phenylthiourea moiety is the best catalyst for the addition of cyclic β-keto esters to (nitrovinyl)phenols and afforded after dehydration tricyclic derivatives of the chroman skeleton with two adjacent stereocenters, one being an all carbon quarternary center.

In order to determine the scope of the organocatalytic domino dehydration one-pot reaction, the cyclic carbonyl containing nucleophiles **2**–**4** were tested. A series of substituted (nitrovinyl)phenols **1a**–**e** were reacted with one equivalent of cyclic β-keto esters **2a**–**d** or with one equivalent of cyclic 1,3-diketones **4a**–**d** in the presence of 10 mol% of catalyst **C** at ambient temperature in toluene followed by dehydration of the crude products with P_2O_5 in dichloromethane. The tricyclic products **5a**–**h** and **6a**–**d** were obtained in good yields and stereoselectivities (Table 2). Electronic factors had little influence: both, neutral and electron-withdrawing group substituted 2-(2-nitrovinyl)phenols **1a**–**e** led to the expected products in good yields (72–86%) and stereoselectivities (83–99% ee). While with five-membered nucleophiles **2a**,**b** cyclopenta[*b*]chromenes **5a**–**f** were obtained, the six-membered nucleophiles **2c**,**d** afforded tetrahydro-1*H*-xanthenes **5g**,**h** in moderate yields (61–62%) but with good enantioselectivities (83–88%). In the case of cyclic 1,3-diketones **4a**–**c** as nucleophiles the dehydration occurred regioselective to tetrahydro-1*H*-xanthen-1-ones **6b**,**c** or 2,3-dihydrocyclopenta[*b*]chromen-1(9*H*)-one **6a** depending on the ring size bearing one stereogenic center. The absolute configuration was determined by X-ray crystal structure analysis in the case of **5d** (Figure 2).

Using cyclic prochiral 1,3-diketones like **3a** (R^2 = H), **3b** (R^2 = Me) as nucleophiles, two possibilities for the intramolecular hemiacetalization exist. Either the acyclic or the cyclic carbonyl group might react followed by dehy-

Table 2 Scope of the Asymmetric Synthesis of Chroman Derivatives via One-Pot Domino Michael–Hemiacetalization and Dehydration[a]

Product	R^1	R^2	R^3	n	Time (h)	Yield (%)[b]	de (%)[c]	ee (%)[d,e]
5a	H	Me	–	1	7	81	99	93 (67)
5b	2-OMe	Me	–	1	5	86	90	96 (73)
5c	3-Me	Me	–	1	8	83	92	90 (67)
5d	4-Br	Me	–	1	6	78	91	89 (2)
5e	4-Br-2-OMe	Me	–	1	5	72	97	99 (99)
5f	H	Et	–	1	7	88	88	96 (48)
5g[f]	H	Me	–	2	24	61	99	83
5h[f]	H	Et	–	2	24	62	95	88 (47)
6a	H	–	H	0	12	64	–	99
6b	H	–	H	1	16	61	–	89
6c	H	–	Me	1	16	55	–	95
8a	H	H	–	1	5	76	98	93 (43)
8b	H	Me	–	1	5	71	99	91

[a] All reactions were performed on a 1.0 mmol scale with catalyst **C**.
[b] Yield of isolated product.
[c] Determined by HPLC analysis.
[d] Determined by HPLC analysis on a chiral stationary phase.
[e] The enantiomeric excess of the minor diastereomer is given in parentheses.
[f] The reaction was performed without any solvent.

dration. In fact, the less hindered exocyclic carbonyl group reacted chemoselectively and after dehydration an exocyclic double bond was generated (Table 2, product **8a**). In the case of **3b** under thermodynamic control the corresponding *E*-enol ether could be isolated (Table 2, product **8b**). In addition, changing the reaction conditions to protic acids (20 mol% PTSA in toluene) resulted in no change in chemoselectivity. Only with **2a** the reaction conditions had a significant effect on the reaction pathway between the Michael–hemiacetalization–dehydration sequence and the Michael–lactonization cascade. In contrast, the six-membered cyclic β-keto esters gave only xanthenes and no lactonization occurred as observed with the five-membered cyclic β-keto ester **2a** by varying the reaction conditions between P_2O_5 and PTSA (not shown in Table 2).

Next, the follow-up reactions of the intermediate Michael adduct **10** were investigated to emphasize the value of this approach, for example, towards the synthesis of bioactive compounds such as pharmaceuticals. It is well known that the hemiacetal unit can be oxidized, reduced, methylated, or dehydrated to the corresponding chroman derivatives. A dynamic equilibrium in $CDCl_3$ (3:2) was observed between the hemiacetal **10a** and the hydroxy ketone **10b** (Scheme 2). The relative configuration of **10** was determined by NOE measurements, showing the cyclopentane moiety exclusively in the *cis*-configuration. By treatment with 20 mol% PTSA in methanol for eight hours at room temperature, **10** was converted into the acetal **13** in moderate yield (56%), however, with excellent diastereomeric (93%) and enantiomeric excess (92%/70%). The high stereoselectivity of our approach is evident from the fact that only two diastereomers are formed while building up three contiguous stereocenters, two of which are quaternary. The intermediate **10** could be reduced to **12** with three equivalents of $HSiEt_3$ in dichloromethane at –78 °C in moderate yield (62%) and again with excellent diastereo- (88% de) and enantioselectivity (99%/94% ee). The configuration was determined by NOE measurements and showed that the cyclopentane moiety is exclusively *cis*-annulated. A lactonization could be observed when **10** was treated with 20 mol% PTSA in toluene for two hours at 100 °C. Compound **11** was isolated in very good yield (88%) and with virtually complete diastereo- and enantioselectivity (de, ee = 99%).

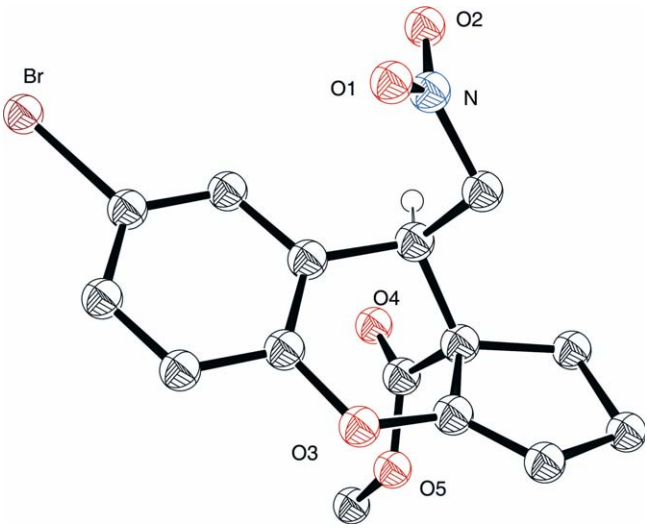


Figure 2 X-ray crystal structure of (9*R*,9a*S*)-**5d**[8]

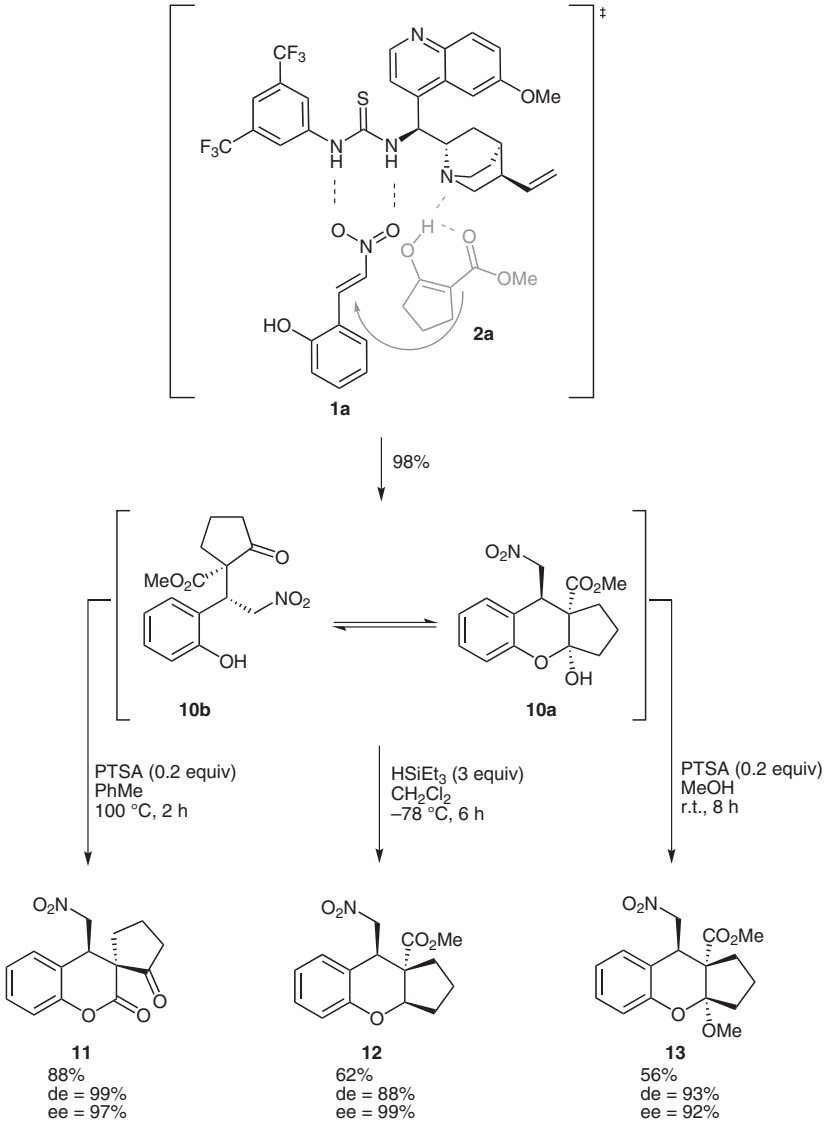
The various transformations performed with the hemiacetal **10a** underpin the stereochemical outcome of the Michael reaction. In the case of the addition of **1a** to **2a**, we can rationalize the observed configuration through a favored transition state where **2a** approaches **1a** from the *Si* face. The *anti*- configuration of the nitro methyl group and the methyl ester group can be explained by their steric demand. A potentially favorable electrostatic interaction between the partially positive nitro group and the partially negative hydroxy group could not be detected. In all cases a *cis*-configuration of the cyclopentane moiety was observed. 1,3-Diaxial interactions may explain the favored diastereoselectivity.

In conclusion, we have developed diastereo- and enantioselective one-pot reactions producing polyfunctionalized chromans by employing a thiourea-catalyzed domino Michael–hemiacetalization reaction. Subsequent transformations of the intermediate chromanols gave acetals, lactones, and hexahydrocyclopenta[*b*]chromenes bearing up to three contiguous stereocenters. The title compounds are important heterocycles due to their widespread occurrence in nature and as privileged scaffolds in medicinal chemistry. They were obtained in good to excellent yields of 56–88% and enantiomeric excess values of 83–99% ee. In addition, our protocol allows for the introduction of several functional groups, such as the nitromethyl, ester, and keto groups as well as double bonds and various substituents at the aromatic ring.

Starting materials and reagents were purchased from commercial suppliers and used without further purification, unless stated otherwise. All solvents were dried by conventional methods. Preparative column chromatography: Merck silica gel 60, particle size 0.040–0.063 mm (230–240 mesh, flash). Analytical TLC: silica gel 60 F254 plates from Merck, Darmstadt. Visualization of the developed TLC plates was performed by ultraviolet irradiation (254 nm) or by staining with a solution of $KMnO_4$. Analytical HPLC was carried out on a Hewlett-Packard 1100 Series instrument using chiral stationary phases. ^1H and ^{13}C NMR spectra were recorded at r.t. on Varian Mercury 300, Varian Inova 400, or Varian Inova 600 instrument. Mass spectra were acquired on a Finnigan SSQ7000 (EI 70 eV) spectrometer, high-resolution mass spectra on a Finnigan MAT 95, and high-resolution ESI spectra on a Thermo Fisher Scientific LTQ-Orbitrap XL. IR spectra were recorded on a Perkin-Elmer 100 FT-IR Spectrum instrument. Microanalyses were performed with a Vario EL element analyzer. Melting points were determined with a Büchi melting point B-540 apparatus. Optical rotation values were measured on a Perkin-Elmer 241 polarimeter.

One-Pot Domino Michael-Hemiacetalization and Dehydration Reaction; General Procedure

In a glass vial equipped with a magnetic stirring bar, catalyst **C** (10 mol%) was added to a mixture of cyclic β-keto ester **2**, or 1,3-diketones **3**, **4** (1.0 mmol, 1.0 equiv) and (*E*)-2-(2-nitrovinyl)phenol **1** (1.0 mmol, 1 equiv) in toluene (6.0 mL per mmol) at r.t. The reac-



Scheme 2 Various transformations of chromanol **10**

tion was monitored by TLC (eluent: *n*-pentane–Et_2O, 1:1). After complete conversion of the starting material, the solvent was evaporated and CH_2Cl_2 (6 mL per mmol) and P_2O_5 (3.0 mmol, 3 equiv) were added and stirred for 2 d at –25 °C. After completion of the reaction, the crude reaction mixture was filtered through a small plug of silica gel. Products **5**, **6**, and **8** were isolated after column chromatography as pale yellow to colorless solids (Table 2).

Methyl (9*R*,9a*S*)-9-(Nitromethyl)-1,2,9,9a-tetrahydrocyclopenta[*b*]chromene-9a-carboxylate (5a)

Compound **5a** was synthesized according to the general procedure to yield 234 mg (81%) of a colorless solid; mp 158 °C; R_f = 0.26 (*n*-pentane–Et_2O, 4:1); $[\alpha]_D^{20}$ –85.0 (*c* 1.0, $CHCl_3$); ee (major) = 93%, ee (minor) = 67%; de = 99%. The enantiomeric excess was determined by chiral stationary phase HPLC using a Chiralcel AD column [*n*-heptane–EtOH (98:2), flow rate 0.5 mL/min, λ = 254 nm], t_R = 22.79 min (major), t_R = 24.95 min (minor), t_R = 19.61 min (major), t_R = 29.22 min (minor).

IR (film): 2964, 2923, 2864, 1723, 1676, 1606, 1550, 1478, 1453, 1377, 1353, 1277, 1227, 1176, 1112, 1032, 984, 905, 863, 803, 764, 662 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 1.97–2.06 (m, 1 H, CH_2), 2.20–2.33 (m, 2 H, CH_2), 2.44 (dddd, *J* = 2.0, 6.7, 9.0, 15.8 Hz, 1 H, CH_2), 3.49 (s, 3 H, CH_3), 4.18 (dd, *J* = 8.3, 12.3 Hz, 1 H, CH_2), 4.26 (dd, *J* = 6.0, 8.3 Hz, 1 H, CH), 4.60 (dd, *J* = 6.0, 12.3 Hz, 1 H, CH_2), 5.32 (dd, *J* = 2.3, 2.7 Hz, 1 H, CH_{arom}), 6.85–6.90 (m, 2 H, CH_{arom}), 7.00–7.04 (m, 1 H, CH_{arom}), 7.13–7.18 (m, 1 H, CH_{arom}).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 25.8 (CH_2), 30.1 (CH_2), 40.3 (CH), 52.8 (CH_3), 54.5 (C), 77.8 (CH_2), 106.0 (CH_{olef}), 116.7 (CH_{arom}), 120.5 (C_{arom}), 122.7 (CH_{arom}), 129.8 (CH_{arom}), 129.9 (CH_{arom}), 148.5 ($C_{arom}O$), 151.9 ($C_{olef}O$), 172.9 (CO_2Me).

MS (EI, 70 eV): *m*/*z* (%) = 289 ([M^+], 26), 242 (10), 184 (24), 183 (100), 169 (26).

Anal. Calcd for $C_{15}H_{15}NO_5$: C, 62.28; H, 5.23; N, 4.84. Found: C, 62.28; H, 5.28; N, 4.90.

Methyl (9*R*,9a*S*)-5-Methoxy-9-(nitromethyl)-1,2,9,9a-tetrahydrocyclopenta[*b*]chromene-9a-carboxylate (5b)

Compound **5b** was synthesized according to the general procedure to yield 274 mg (86%) of a colorless solid; mp 183 °C; R_f = 0.40 (*n*-pentane–Et_2O, 1:1); $[\alpha]_D^{20}$ –71.3 (*c* 1.0, $CHCl_3$); ee (major) = 96%, ee (minor) = 73%; de = 90%. The enantiomeric excess was deter-

mined by chiral stationary phase HPLC using a Chiralcel AS column [*n*-heptane–*i*-PrOH (9:1), flow rate 1.0 mL/min, λ = 254 nm], t_R = 12.86 min (major), t_R = 17.48 min (minor), t_R = 11.31 min (major), t_R = 10.28 min (minor).

IR (film): 2965, 2933, 2867, 1716, 1678, 1585, 1549, 1477, 1436, 1376, 1351, 1322, 1214, 1079, 983, 894, 847, 776, 733 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 1.99–2.11 (m, 1 H, CH_2), 2.24–2.38 (m, 2 H, CH_2), 2.45–2.56 (m, 1 H, CH_2), 3.55 (s, 3 H, CH_3), 3.86 (s, 3 H, OCH_3), 4.23 (dd, *J* = 8.3, 12.3 Hz, 1 H, CH_2), 4.32 (dd, *J* = 6.0, 8.3 Hz, 1 H, CH), 4.64 (dd, *J* = 6.0, 12.3 Hz, 1 H, CH_2), 5.49 (dd, *J* = 2.3, 2.3 Hz, 1 H, CH_{olef}), 6.66–6.70 (m, 2 H, CH_{arom}), 6.79–6.83 (m, 1 H, CH_{arom}), 6.85–6.91 (m, 1 H, CH_{arom}).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 25.9 (CH_2), 30.2 (CH_2), 40.3 (CH), 52.8 (CH_3), 54.5 (C_q), 56.0 (CH_3), 77.7 (CH_2), 106.9 (CH_{olef}), 111.9 (CH_{arom}), 121.2 (CH_{arom}), 121.5 (C), 122.6 (CH_{arom}), 141.3 (C_{arom}), 147.8 ($C_{arom}O$), 148.2 ($C_{olef}O$), 172.9 (CO_2Me).

MS (EI, 70 eV): *m*/*z* (%) = 319.1 ([M^+], 61), 272.1 (10), 213.1 (100), 199.1 (26), 153.1 (10), 128.1 (10).

HRMS: *m*/*z* calcd for $C_{16}H_{17}NO_6$: 320.1125; found: 320.1129.

Methyl (9*R*,9a*S*)-6-Methyl-9-(nitromethyl)-1,2,9,9a-tetrahydrocyclopenta[*b*]chromene-9a-carboxylate (5c)

Compound **5c** was synthesized according to the general procedure to yield 252 mg (83%) of a colorless solid; mp 131 °C; R_f = 0.42 (*n*-pentane–Et_2O, 2:1); $[\alpha]_D^{20}$ –64.4 (*c* 1.0, $CHCl_3$); ee (major) = 90%, ee (minor) = 67%; de = 92%. The enantiomeric excess was determined by chiral stationary phase HPLC using a Chiralcel AD column [*n*-heptane–*i*-PrOH (95:5), flow rate 0.5 mL/min, λ = 254 nm], t_R = 16.92 min (major), t_R = 20.36 min (minor), t_R = 18.02 min (major), t_R = 14.58 min (minor).

IR (film): 2958, 2919, 2861, 1725, 1677, 1619, 1585, 1503, 1430, 1377, 1345, 1306, 1250, 1163, 1123, 1074, 940, 806, 674 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$,): δ = 1.95–2.05 (m, 1 H, CH_2), 2.21 (s, 3 H, CH_3), 2.16–2.32 (m, 2 H, CH_2), 2.36–2.48 (m, 1 H, CH_2), 3.50 (s, 3 H, CH_3), 4.16 (dd, *J* = 8.3, 11.6 Hz, 1 H, CH_2), 4.21 (dd, *J* = 5.3, 8.3 Hz, 1 H, CH), 4.58 (dd, *J* = 5.3, 11.6 Hz, 1 H, CH_2), 5.49 (dd, *J* = 2.3, 2.7 Hz, 1 H, CH_{olef}), 6.65–6.70 (m, 2 H, CH_{arom}), 6.85–6.90 (m, 1 H, CH_{arom}).

^{13}C NMR (100 MHz, $CDCl_3$,): δ = 21.0 (CH_3), 25.8 (CH_2), 30.0 (CH_2), 40.0 (CH), 52.8 (CH_3), 54.6 (C_q), 77.9 (CH_2), 105.8 (CH_{olef}), 117.1 (C_{arom}), 117.4 (CH_{arom}), 123.7 (CH_{arom}), 129.4 (CH_{arom}), 140.2 (C_{arom}), 148.7 ($C_{arom}O$), 151.7 ($C_{olef}O$), 173.0 (CO_2Me).

MS (EI, 70 eV): *m*/*z* (%) = 303 ([M^+], 39), 256 (20), 213 (100), 197 (100), 183 (25), 115 (14).

HRMS: *m*/*z* calcd for $C_{16}H_{17}NO_5$: 304.1180; found: 304.1179.

Methyl (9*R*,9a*S*)-7-Bromo-9-(nitromethyl)-1,2,9,9a-tetrahydrocyclopenta[*b*]chromene-9a-carboxylate (5d)

Compound **5d** was synthesized according to the general procedure to yield 387 mg (78%) of a colorless solid; mp 125 °C; R_f = 0.36 (*n*-pentane–Et_2O, 2:1); $[\alpha]_D^{20}$ –62.4 (*c* 1.0, $CHCl_3$); ee (major) = 89%, ee (minor) = 2%; de = 91%. The enantiomeric excess was determined by chiral stationary phase HPLC using a Chiralcel OD column [*n*-heptane–*i*-PrOH (9:1), flow rate 0.5 mL/min, λ = 254 nm], t_R = 18.91 min (major), t_R = 21.16 min (minor), t_R = 28.08 min (major), t_R = 32.31 min (minor).

IR (film) 2956, 2921, 2864, 1729, 1678, 1560, 1471, 1435, 1380, 1349, 1274, 1229, 1176, 1121, 1083, 1030, 990, 921, 886, 820, 757, 723, 670 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 1.98–2.10 (m, 1 H, CH_2), 2.24–2.38 (m, 2 H, CH_2), 2.42–2.53 (m, 1 H, CH_2), 3.57 (s, 3 H, CH_3), 4.23 (dd, *J* = 8.3, 12.3 Hz, 1 H, CH_2), 4.28 (dd, *J* = 5.6, 8.3 Hz, 1 H, CH), 4.64 (dd, *J* = 5.6, 12.3 Hz, 1 H, CH_2), 5.39 (dd, *J* = 2.3, 2.3 Hz, 1 H, CH_{olef}), 6.82 (d, *J* = 8.6 Hz, 1 H, CH_{arom}), 7.22–7.26 (m, 1 H, CH_{arom}), 7.30–7.34 (m, 1 H, CH_{arom}).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 25.9 (CH_2), 30.1 (CH_2), 40.0 (CH), 53.0 (CH_3), 54.3 (C_q), 77.4 (CH_2), 106.9 (CH_{olef}), 114.9 (C_{arom}), 118.5 (CH_{arom}), 122.7 (C_{arom}), 132.3 (CH_{arom}), 132.9 (CH_{arom}), 148.0 ($C_{arom}O$), 151.0 ($C_{olef}O$), 172.6 (CO_2CH_3).

MS (EI, 70 eV): *m*/*z* (%) = 369 ([M^+], 70), 367 (76), 322 (22), 263 (100), 249 (17), 182 (23), 124 (15).

Anal. Calcd for $C_{15}H_{14}BrNO_5$: C, 48.93; H, 3.83; N, 3.80. Found: C, 49.15; H, 3.66; N, 3.74.

Methyl (9*R*,9a*S*)-7-Bromo-5-methoxy-9-(nitromethyl)-1,2,9,9a-tetrahydrocyclopenta[*b*]chromene-9a-carboxylate (5e)

Compound **5e** was synthesized according to the general procedure to yield 286 mg (72%) of a colorless solid; mp 127 °C; R_f = 0.43 (*n*-pentane–Et_2O, 1:1); $[\alpha]_D^{20}$ –38.4 (*c* 1.0, $CHCl_3$); ee (major) = 99%, ee (minor) = 99%; de = 97%. The enantiomeric excess was determined by chiral stationary phase HPLC using a Chiralcel OD column [*n*-heptane–*i*-PrOH (95:5), flow rate 0.7 mL/min, λ = 254 nm], t_R = 25.23 min (major), t_R = 22.66 min (minor), t_R = 28.80 min (major), t_R = 34.79 min (minor).

IR (film): 3097, 2949, 2860, 1725, 1685, 1552, 1478, 1433, 1378, 1348, 1319, 1215, 1174, 1109, 1081, 1033, 980, 899, 846, 798, 672 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 1.98–2.08 (m, 1 H, CH_2), 2.24–2.39 (m, 2 H, CH_2), 2.46–2.46 (m, 1 H, CH_2), 3.58 (s, 3 H, CH_3), 3.84 (s, 3 H, OCH_3), 4.22 (dd, *J* = 7.6, 12.9 Hz, 1 H, CH_2),), 4.29 (dd, *J* = 7.6, 6.0 Hz, 1 H, CH), 4.61 (dd, *J* = 6.0, 12.9 Hz, 1 H, CH_2), 5.50 (dd, *J* = 2.3, 2.3 Hz, 1 H, CH_{olef}), 6.84 (d, *J* = 2.0 Hz, 1 H, CH_{arom}), 6.90 (d, *J* = 2.0 Hz, 1 H, CH_{arom}).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 25.9 (CH_2), 30.2 (CH_2), 40.0 (CH), 53.0 (CH_3), 54.2 (C_q), 56.3 (CH_3), 77.4 (CH_2), 107.6 (CH_{olef}), 115.4 (CH_{arom}), 123.0 (C_{arom}), 123.6 (CH_{arom}), 128.3 (C_{arom}), 140.7 (C_{arom}), 147.7 ($C_{arom}O$), 148.4 ($C_{olef}O$), 172.6 (CO_2Me).

MS (EI, 70 eV): *m*/*z* (%) = 397 ([M^+], 100), 352 (16), 350 (17), 337 (10), 293 (94), 291 (97), 279 (22), 212 (19), 197 (13), 168 (10), 141 (11).

HRMS: *m*/*z* calcd for $C_{16}H_{16}BrNO_6$: 398.0234; found: 398.0234.

Ethyl (9*R*,9a*S*)-9-(Nitromethyl)-1,2,9,9a-tetrahydrocyclopenta[*b*]chromene-9a-carboxylate (5f)

Compound **5f** was synthesized according to the general procedure to yield 267 mg (88%) of a colorless solid; mp 91 °C; R_f = 0.32 (*n*-pentane–Et_2O, 4:1); $[\alpha]_D^{20}$ –24.0 (*c* 0.5, $CHCl_3$); ee (major) = 96%, ee (minor) = 48%; de = 88%. The enantiomeric excess was determined by chiral stationary phase HPLC using a Chiralcel OD column [*n*-heptane–*i*-PrOH (97:3), flow rate 0.5 mL/min, λ = 254 nm], t_R = 24.43 min (major), t_R = 44.37 min (minor), t_R = 19.70 min (major), t_R = 22.07 min (minor).

IR (film): 2989, 2942, 2868, 1723, 1678, 1609, 1549, 1484, 1453, 1367, 1297, 1250, 1220, 1175, 1114, 1092, 1050, 1008, 912, 861, 8014, 759, 664 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 0.95 (t, *J* = 6.7 Hz, 3 H, CH_3), 1.92–2.11 (m, 1 H, CH_2), 2.24–2.37 (m, 2 H, CH_2), 2.42–2.55 (m, 1 H, CH_2), 3.97 (m, 2 H, CH_2), 4.22 (dd, *J* = 8.7, 11.3 Hz, 1 H, CH_2), 4.25 (dd, *J* = 4.3, 8.7 Hz, 1 H, CH), 4.65 (dd, *J* = 4.3, 11.3 Hz, 1 H, CH_2), 5.35 (dd, *J* = 2.3, 2.3 Hz, 1 H, CH_{olef}), 6.88–6.95 (m, 2 H, CH_{arom}), 7.02–7.08 (m, 1 H, CH_{arom}), 7.17–7.23 (m, 1 H, CH_{arom}).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 13.8 (CH_3), 25.8 (CH_2), 30.0 (CH_2), 40.5 (CH), 54.6 (C_q), 61.5 (CH_2), 77.8 (CH_2), 105.6 (CH_{olef}), 116.7 (CH_{arom}), 120.6 (C_{arom}), 122.6 (CH_{arom}), 129.8 (CH_{arom}), 129.9 (CH_{arom}), 148.7 ($C_{arom}O$), 152.0 ($C_{olef}O$), 172.3 (CO_2Et).

MS (EI, 70 eV): *m*/*z* (%) = 303 ([M$^+$], 66), 256 (39), 183 (100), 169 (45).

HRMS: *m*/*z* calcd for $C_{16}H_{17}NO_5$ + Na: 326.0999; found: 326.0998.

Methyl (9*R*,9a*S*)-9-(Nitromethyl)-2,3,9,9a-tetrahydro-1*H*-xanthene-9a-carboxylate (5g)

Compound **5g** was synthesized according to the general procedure to yield 184 mg (61%) of a colorless solid; mp 78 °C; R_f = 0.28 (*n*-pentane–Et_2O, 8:1); $[\alpha]_D^{20}$ –69.4 (*c* 1.0, $CHCl_3$); ee = 83%; de >99%. The enantiomeric excess was determined by chiral stationary phase HPLC using a Chiralcel OD column [*n*-heptane–*i*-PrOH (7:3), flow rate 0.7 mL/min, λ = 254 nm], t_R = 7.48 min (major), t_R = 10.17 min (minor).

IR (film): 3009, 2933, 2860, 1727, 1684, 1553, 1485, 1455, 1380, 1279, 1237, 1149, 1119, 1098, 988, 847, 760, 693 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.46–1.80 (m, 3 H, 1.5 × CH_2), 2.18–2.28 (m, 3 H, 1.5 × CH_2), 3.50 (s, 3 H, CH_3), 4.09 (dd, *J* = 5.9, 8.7 Hz, 1 H, CH_2), 4.27 (dd, *J* = 8.7, 12.6 Hz, 1 H, CH_2), 4.69 (dd, *J* = 5.9, 12.6 Hz, 1 H, CH), 5.57 (dd, *J* = 4.0, 4.2 Hz, 1 H, CH_{olef}), 6.84–6.93 (m, 2 H, CH_{arom}), 6.98–7.03 (m, 1 H, CH_{arom}), 7.17–7.25 (m, 1 H, CH_{arom}).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 20.0 (CH_2), 23.4 (CH_2), 30.3 (CH_2), 40.5 (CH), 49.2 (C_q), 52.9 (CH_3), 77.5 (CH_2), 106.7 (CH_{olef}), 116.4 (CH_{arom}), 120.5 (C_{arom}), 122.1 (CH_{arom}), 128.8 (CH_{arom}), 130.1 (CH_{arom}), 145.8 ($C_{arom}O$), 151.6 ($C_{olef}O$), 172.8 (*C*O_2Me).

MS (EI, 70 eV): *m*/*z* (%) = 303 ([M$^+$], 30), 197 (100), 183 (23), 77 (10).

HRMS: *m*/*z* calcd for $C_{16}H_{17}NO_5$ + Na: 326.0999; found: 326.0999.

Ethyl (9*R*,9a*S*)-9-(Nitromethyl)-2,3,9,9a-tetrahydro-1*H*-xanthene-9a-carboxylate (5h)

Compound **5h** was synthesized according to the general procedure to yield 197 mg (62%) of a colorless solid; mp 100 °C; R_f = 0.34 (*n*-pentane–Et_2O, 8:1); $[\alpha]_D^{20}$ –71.0 (*c* 1.0, $CHCl_3$); ee (major) = 88%, ee (minor) = 47%; de = 95%. The enantiomeric excess was determined by chiral stationary phase HPLC using a Chiralcel AD column [*n*-heptane–*i*-PrOH (98:2), flow rate 0.3 mL/min, λ = 254 nm], t_R = 30.05 min (major), t_R = 32.50 min (minor), t_R = 36.39 min (major), t_R = 39.57 min (minor).

IR (film): 2965, 2933, 2851, 1720, 1682, 1549, 1487, 1456, 1372, 1277, 1233, 1198, 1145, 1093, 1012, 939, 855, 819, 755, 688 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.89 (t, *J* = 7.2 Hz, 3 H, CH_3), 1.55–1.64 (m, 2 H, CH_2), 1.66–1.81 (m, 2 H, CH_2), 2.17–2.31 (m, 2 H, CH_2), 3.85–4.09 (m, 3 H, CH, CH_2), 4.29 (dd, *J* = 8.8, 12.6 Hz, 1 H, CH_2), 4.74 (dd, *J* = 5.7, 12.6 Hz, 1 H, CH), 5.58 (dd, *J* = 4.0, 7.9 Hz, 1 H, CH_{olef}), 6.83–6.94 (m, 2 H, CH_{arom}), 6.97–7.04 (m, 1 H, CH_{arom}), 7.17–7.28 (m, 1 H, CH_{arom}).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 13.7 (CH_3), 20.6 (CH_2), 23.4 (CH_2), 30.2 (CH_2), 40.6 (CH), 49.1 (C_q), 61.6 (CH_2), 77.5 (CH_2), 106.4 (CH_{olef}), 116.4 (CH_{arom}), 120.6 (C_{arom}), 122.0 (CH_{arom}), 128.9 (CH_{arom}), 130.1 (CH_{arom}), 146.0 ($C_{arom}O$), 151.8 ($C_{olef}O$), 172.2 (*C*O_2Et).

MS (EI, 70 eV): *m*/*z* (%) = 317 ([M$^+$], 76), 270 (10), 243 (10), 213 (100), 197 (100), 183 (53), 169 (23), 157 (14).

Anal. Calcd for $C_{17}H_{19}NO_5$: C, 64.34; H, 6.03; N, 4.41. Found: C, 64.63; H, 6.25; N, 4.33.

(*R*)-9-(Nitromethyl)-2,3-dihydrocyclopenta[*b*]chromen-1(9*H*)-one (6a)

Compound **6a** was synthesized according to the general procedure to yield 157 mg (64%) of a pale yellow solid; mp 130 °C; R_f = 0.26 (*n*-pentane–Et_2O, 4:1); $[\alpha]_D^{20}$ –18.6 (*c* 0.9, $CHCl_3$); ee = 99%. The enantiomeric excess was determined by chiral stationary phase HPLC using a Chiralcel AD column [*n*-heptane–EtOH (7:3), flow rate 0.7 mL/min, λ = 254 nm], t_R = 14.45 min (major), t_R = 18.68 min (minor).

IR (film): 2929, 2853, 1695, 1649, 1577, 1534, 1487, 1432, 1387, 1248, 1160, 1122, 1022, 981, 839, 766, 682 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.55–2.62 (m, 2 H, CH_2), 2.75–2.85 (m, 2 H, CH_2), 4.40 (m, 1 H, CH), 4.72 (dd, *J* = 3.7, 12.4 Hz, 1 H, CH_2), 4.82 (dd, *J* = 5.5, 12.4 Hz, 1 H, CH_2), 7.08–7.30 (m, 4 H, CH_{arom}).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 26.0 (CH_2), 31.9 (CH), 33.6 (CH_2), 81.1 (CH_2), 118.0 (CH_{arom}), 119.1 (C_{arom}), 126.2 (CH_{arom}), 129.0 (CH_{arom}), 129.8 (CH_{arom}), 151.2 ($C_{olef}O$), 172.5 ($C_{olef}O$), 181.0 ($C_{arom}O$), 202.9 (C=O).

MS (EI, 70 eV): *m*/*z* (%) = 198 ([M – HNO_2]$^+$, 100), 185 (39), 128 (13), 115 (10).

Anal. Calcd for $C_{13}H_{11}NO_4$: C, 63.67; H, 4.52; N, 5.71. Found: C, 63.43; H, 4.45; N, 5.53.

(*R*)-9-(Nitromethyl)-2,3,4,9-tetrahydro-1*H*-xanthen-1-one (6b)

Compound **6b** was synthesized according to the general procedure to yield 158 mg (61%) of a colorless solid; mp 142 °C; R_f = 0.30 (*n*-pentane–Et_2O, 1:1); $[\alpha]_D^{20}$ –88.4 (*c* 1.0, $CHCl_3$); ee = 89%. The enantiomeric excess was determined by chiral stationary phase HPLC using a Chiralcel AD column [*n*-heptane–EtOH (9:1), flow rate 1.0 mL/min, λ = 254 nm], t_R = 6.32 min (major), t_R = 7.14 min (minor).

IR (film): 3019, 2953, 1644, 1582, 1584, 1488, 1457, 1427, 1385, 1235, 1183, 1137, 1003, 959, 759 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.03–2.15 (m, 2 H, CH_2), 2.36–2.76 (m, 4 H, 2 × CH_2), 4.56–4.71 (m, 3 H, CH, CH_2), 7.04–7.32 (m, 4 H, CH_{arom}).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 20.4 (CH_2), 28.0 (CH_2), 31.7 (CH), 36.8 (CH_2), 79.6 (CH_2), 108.8 (C_{olef}), 117.0 (CH_{arom}), 120.0 (C_{arom}), 125.5 (CH_{arom}), 128.5 (CH_{arom}), 129.0 (CH_{arom}), 150.2 ($C_{arom}O$), 169.6 ($C_{olef}O$), 197.3 (C=O).

MS (EI, 70 eV): *m*/*z* (%) = 212 ([M – HNO_2]$^+$, 100), 199 (77), 171 (11), 128 (21), 115 (25).

Anal. Calcd for $C_{14}H_{13}NO_4$: C, 64.86; H, 5.05; N, 5.40. Found: C, 64.80; H, 4.83; N, 5.40.

(*R*)-3,3-Dimethyl-9-(nitromethyl)-2,3,4,9-tetrahydro-1*H*-xanthen-1-one (6c)

Compound **6c** was synthesized according to the general procedure to yield 143 mg (55%) of a colorless solid; mp 96 °C; R_f = 0.29 (*n*-pentane–Et_2O, 1:1); $[\alpha]_D^{20}$ –61.1 (*c* 1.0, $CHCl_3$); ee = 95%. The enantiomeric excess was determined by chiral stationary phase HPLC using a Chiralcel AD column [*n*-heptane–*i*-PrOH (8:2), flow rate 1.5 mL/min, λ = 254 nm], t_R = 4.40 min (major), t_R = 5.24 min (minor).

IR (film): 2951, 2168, 1982, 1633, 1583, 1490, 1439, 1380, 1335, 1233, 1181, 1038, 959, 923, 852, 760, 659 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.13 (s, 6 H, 2 × CH_3), 2.35 (s, 2 H, CH_2), 2.50 (s, 2 H, CH_2), 4.53 (m, 1 H, CH), 4.60 (dd, *J* = 3.7, 11.6 Hz, 1 H, CH_2), 4.74 (dd, *J* = 5.5, 11.6 Hz, 1 H, CH_2), 7.00–7.07 (m, 1 H, CH_{arom}), 7.11–7.18 (m, 1 H, CH_{arom}), 7.21–7.30 (m, 2 H, CH_{arom}).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 27.5 (CH_3), 29.6 (CH_3), 32.0 (CH), 32.3 (C_q), 41.8 (CH_2), 50.9 (CH_2), 79.6 (CH_2), 107.8 (C_{olef}), 117.2 (CH_{arom}), 120.1 (C_{arom}), 125.7 (CH_{arom}), 128.7 (CH_{arom}), 129.3 (CH_{arom}), 150.5 ($C_{arom}O$), 168.2 ($C_{olef}O$), 197.5 (C=O).

MS (EI, 70 eV): *m*/*z* (%) = 240 ([M – HNO_2]$^+$, 100), 227 (48), 184 (14), 171 (33), 128 (9), 115 (12).

Anal. Calcd for $C_{16}H_{17}NO_4$: C, 66.89; H, 5.96; N, 4.88. Found: C, 66.74; H, 6.03; N, 4.95.

(1′*S*,4*R*)-2-Methylene-4-(nitromethyl)spiro[chroman-3,1′-cyclopentan]-2′-one (8a)

Compound **8a** was synthesized according to the general procedure to yield 208 mg (76%) of a colorless solid; mp 109 °C; R_f = 0.26 (*n*-pentane–Et_2O, 4:1); $[\alpha]_D^{20}$ –7.1 (*c* 1.0, $CHCl_3$); ee (major) = 93%, ee (minor) = 43%; de = 98%. The enantiomeric excess was determined by chiral stationary phase HPLC using a Chiralcel AD column [*n*-heptane–*i*-PrOH (95:5), flow rate 1.0 mL/min, λ = 254 nm], t_R = 7.55 min (major), t_R = 9.44 min (minor), t_R = 3.24 min (major), t_R = 4.25 min (minor).

IR (film): 2980, 2916, 2869, 1726, 1651, 1544, 1486, 1455, 1381, 1334, 1289, 1234, 1187, 1166, 1113, 1036, 843, 760, 691 cm^{-1}.

^1H NMR (600 MHz, $CDCl_3$): δ = 1.68–1.78 (m, 1 H, CH_2), 1.90–2.07 (m, 3 H, CH_2), 2.43–2.57 (m, 2 H, CH_2), 3.61 (dd, *J* = 5.3, 9.3 Hz, 1 H, CH_2), 3.99 (d, *J* = 2.3 Hz, 1 H, CH_2), 4.27 (dd, *J* = 9.3, 13.6 Hz, 1 H, CH), 4.82 (d, *J* = 2.3 Hz, 1 H, CH_2), 5.43 (dd, *J* = 5.3, 13.6 Hz, 1 H, CH_2), 6.84–6.94 (m, 2 H, CH_{arom}), 7.01–7.07 (m, 1 H, CH_{arom}), 7.18–7.27 (m, 1 H, CH_{arom}).

^{13}C NMR (150 MHz, $CDCl_3$): δ = 18.2 (CH_2), 36.4 (CH_2), 39.7(CH_2), 41.1 (CH), 51.9 (C_q), 77.0 (CH_2), 93.2 (CH_2), 116.3 (CH_{arom}), 120.6 (C_{arom}), 122.3 (CH_{arom}), 129.1 (CH_{arom}), 129.9 (CH_{arom}), 151.4 ($C_{arom}O$), 152.4 ($C_{olef}O$), 217.0 (C=O).

MS (EI, 70 eV): *m*/*z* (%) = 273 ([M^+], 15), 226 (66), 213 (100), 185 (83), 169 (15), 158 (12), 128 (30), 115 (23), 77 (31).

HRMS: *m*/*z* calcd for $C_{15}H_{15}NO_4$: 273.0996; found: 273.0998.

(1′*R*,4*R*,*E*)-2-Ethylidene-4-(nitromethyl)spiro[chroman-3,1′-cyclopentan]-2′-one (8b)

Compound **8b** was synthesized according to the general procedure to yield 204 mg (71%) of a colorless oil; R_f = 0.38 (*n*-pentane–Et_2O, 4:1); $[\alpha]_D^{20}$ –11.3 (*c* 1.0, $CHCl_3$); ee = 91%; de = 99%. The enantiomeric excess was determined by chiral stationary phase HPLC using a Chiralcel AD column [*n*-heptane–*i*-PrOH (95:5), flow rate 1.0 mL/min, λ = 254 nm], t_R = 6.08 min (major), t_R = 7.10 min (minor).

IR (film): 3442, 2969, 1732, 1601, 1550, 1491, 1451, 1376, 1259, 1212, 1173, 756, 706 cm^{-1}.

^1H NMR (600 MHz, $CDCl_3$): δ = 1.64–1.74 (m, 1 H, CH_2), 1.77 (d, *J* = 6.7 Hz, 3 H, CH_3), 1.87–1.96 (m, 2 H, CH_2), 1.99–2.07 (m, 1 H, CH_2), 2.36–2.54 (m, 2 H, CH_2), 3.59 (dd, *J* = 5.1, 9.2 Hz, 1 H, CH), 4.25 (dd, *J* = 9.2, 13.4 Hz, 1 H, CH_2), 4.47 (q, *J* = 6.7 Hz, 1 H, CH), 5.46 (dd, *J* = 5.1, 13.4 Hz, 1 H, CH_2), 6.89–6.94 (m, 1 H, CH_{arom}), 6.97–7.05 (m, 2 H, CH_{arom}), 7.24–7.29 (m, 1 H, CH_{arom}).

^{13}C NMR (150 MHz, $CDCl_3$): δ = 10.0 (CH_3), 18.2 (CH_2), 36.4 (CH_2), 39.8 (CH_2), 41.6 (CH), 52.2 (C_q), 77.5 (CH_2), 103.9 (CH), 116.3 (CH_{arom}), 120.8 (C_{arom}), 122.0 (CH_{arom}), 129.2 (CH_{arom}), 129.8 (CH_{arom}), 145.0 ($C_{arom}O$), 151.7 ($C_{olef}O$), 217.7 (C=O).

MS (EI, 70 eV): *m*/*z* (%) = 287 ([M^+], 25), 240 (82), 227 (100), 199 (46), 183 (25), 128 (12), 116 (14), 91 (21), 77 (25).

HRMS: *m*/*z* calcd for $C_{16}H_{17}NO_4$ + Na: 310.1049; found: 310.1044.

Methyl (3a*R*,9*R*,9a*S*)-3a-Hydroxy-9-(nitromethyl)-1,2,3,3a,9,9a-hexahydrocyclopenta[*b*]chromene-9a-carboxylate (10a) and Methyl (*S*)-1-[(*R*)-1-(2-Hydroxyphenyl)-2-nitroethyl]-2-oxocyclopentanecarboxylate (10b)

In a glass vial equipped with a magnetic stirring bar, catalyst **C** (10 mol%) was added to a mixture of methyl 2-oxocyclopentanecarboxylate (**2a**; 135 μL, 1.0 mmol) and (*E*)-2-(2-nitrovinyl)phenol (**1a**; 165 mg, 1.0 mmol) in toluene (6.0 mL) at r.t. The reaction was monitored by TLC (eluent: *n*-pentane–Et_2O, 1:1). After completion of the reaction, the solvent was evaporated and compound **10** was isolated as a mixture of hydroxy ketone **10b** and hemiacetal **10a** by column chromatography (silica gel, *n*-pentane–Et_2O, 1:1) as a colorless solid (301 mg, 98%); mp 150 °C; R_f = 0.31 (*n*-pentane–Et_2O, 1:1); $[\alpha]_D^{20}$ –92.4 (*c* 1.0, $CHCl_3$). Ratio **10a**/**10b** = 3:2.

IR (film): 3368, 2967, 2891, 1727, 1598, 1548, 1458, 1431, 1339, 1233, 1152, 1108, 994, 840, 765, 665 cm^{-1}.

^1H NMR (600 MHz, $CDCl_3$): δ = 1.17–1.87 (m, 4 H, CH_2, **10b**), 1.49–1.57 (m, 2 H, CH_2, **10b**), 2.00–2.14 (m, 2 H, CH_2, **10a**, **10b**), 2.21–2.33 (m, 2 H, CH_2, **10a**), 2.34–2.45 (m, 2 H, CH_2, **10a**), 3.74 (s, 3 H, CH_3, **10a**), 3.77 (s, 3 H, CH_3, **10b**), 3.95 (dd, *J* = 4.5, 8.4 Hz, 1 H, CH, **10b**), 4.34 (br s, 1 H, OH, **10a**), 4.71 (dd, *J* = 4.5, 13.4 Hz, 1 H, CH, **10a**, **10b**), 4.78 (dd, *J* = 8.4, 13.4 Hz, 1 H, CH, **10a**), 4.88 (dd, *J* = 3.5, 13.4 Hz, 1 H, CH, **10b**), 5.28 (dd, *J* = 10.9, 13.4 Hz, 1 H, CH, **10a**), 5.87 (br s, 1 H, OH, **10a**), 6.75–6.79 (m, 1 H, CH_{arom}, **10a**), 6.84–6.88 (m, 1 H, CH_{arom}, **10a**), 6.90–6.93 (m, 1 H, CH_{arom}, **10b**), 6.94–6.98 (m, 1 H, CH_{arom}, **10b**), 7.06–7.10 (m, 1 H, CH_{arom}, **10a**, **10b**), 7.11–7.15 (m, 1 H, CH_{arom}, **10a**), 7.21–7.25 (m, 1 H, CH_{arom}, **10b**).

^{13}C NMR (150 MHz, $CDCl_3$): δ = 19.3 (CH_2, **10b**), 19.8 (CH_2, **10a**), 33.3 (CH_2, **10b**), 33.4 (CH_2, **10a**), 38.4 (**10b**), 39.1 (CH_2, **10a**), 39.3 (CH_2, **10b**), 40.4 (CH_3, **10b**), 52.9 (CH_3, **10a**), 53.1 (CH, **10b**), 53.2 (CH, **10a**), 56.1 (C_q, **10a**), 62.1 (C_q, **10b**), 76.3 (CH_2, **10a**), 77.5 (CH_2, **10b**), 107.5 (C_{acetal}, **10a**), 116.4 (CH_{arom}, **10a**), 117.6 (CH_{arom}, **10b**), 120.5 (CH_{arom}, **10a**), 121.3 (CH_{arom}, **10b**), 122.2 (CH_{arom}, **10b**), 122.3 (C_{arom}, **10a**), 127.8 (CH_{arom}, **10a**), 129.4 (CH_{arom}, **10a**), 129.5 (CH_{arom}, **10b**), 151.0 ($C_{arom}OH$, **10b**), 154.4 ($C_{arom}O$, **10a**), 172.0 (CO_2CH_3, **10a**), 174.3 (CO_2CH_3, **10b**), 216.3 (C=O, **10b**).

MS (EI, 70 eV): *m*/*z* (%) = 307 ([M^+], 53), 216 (25), 183 (22), 159 (30), 142 (100), 119 (38), 91 (64), 77 (33), 55 (69).

Anal. Calcd for $C_{15}H_{17}NO_6$: C, 58.63; H, 5.58; N, 4.56. Found: C, 58.76; H, 5.59; N, 4.45.

One-Pot Domino Michael–Lactonization Reaction; (1′*R*,4*R*)-4-(Nitromethyl)spiro[chroman-3,1′-cyclopentane]-2,2′-dione (11)

In a glass vial equipped with a magnetic stirring bar, catalyst **C** (10 mol%) was added to a mixture of cyclic β-keto ester **2a** (135 μL, 1.0 mmol) and (*E*)-2-(2-nitrovinyl)phenol (**1a**; 165 mg, 1.0 mmol) in toluene (6.0 mL) at r.t. The reaction was monitored by TLC (eluent: *n*-pentane–Et_2O, 1:1). After completion of the reaction, PTSA monohydrate (20 mol%, 38 mg) was added and the reaction mixture was heated to 100 °C for 2 h. Product **11** was obtained after column chromatography (silica gel, *n*-pentane–EtOAc, 4:1) as a colorless solid (242 mg, 88%); mp 159 °C; R_f = 0.36 (*n*-pentane–EtOAc, 4:1); $[\alpha]_D^{20}$ –42.4 (*c* 1.0, $CHCl_3$); ee (major) = 99%; de = 99%. The enantiomeric excess was determined by chiral stationary phase HPLC using a Chiralpak IA column [*n*-heptane–EtOH (9:1), flow rate 1.2 mL/min, λ = 254 nm], t_R = 24.06 min (major), t_R = 21.80 min (minor).

IR (film): 3017, 2968, 2890, 1738, 1549, 1487, 1458, 1380, 1345, 1219, 1158, 1131, 1028, 1001, 943, 823, 763, 686 cm^{-1}.

^1H NMR (600 MHz, $CDCl_3$): δ = 1.94–2.08 (m, 3 H, CH_2), 2.16–2.22 (m, 1 H, CH_2), 2.43–2.50 (m, 1 H, CH_2), 2.64–2.72 (m, 1 H, CH_2), 3.77 (dd, *J* = 5.0, 9.9 Hz, 1 H, CH_2), 4.40 (dd, *J* = 9.9, 13.9 Hz, 1 H, CH), 5.54 (dd, *J* = 5.0, 13.9 Hz, 1 H, CH_2), 7.00–7.20 (m, 3 H, CH_{arom}), 7.35–7.40 (m, 1 H, CH_{arom}).

^{13}C NMR (150 MHz $CDCl_3$): δ = 18.7 (CH_2), 35.7 (CH_2), 39.1 (CH_2), 41.6 (CH), 54.9 (C_q), 75.5 (CH_2), 117.2 (CH_{arom}), 120.6 (C_{arom}), 125.6 (CH_{arom}), 168.8 (CH_{arom}), 130.4 (CH_{arom}), 150.3 ($C_{arom}O$), 166.5 (CO_2), 212.5 (C=O).

MS (EI, 70 eV): *m*/*z* (%) = 275 ([M^+], 13), 215 (78), 200 (94), 187 (82), 159 (100), 115 (71), 91 (58), 77 (43).

Anal. Calcd for $C_{14}H_{13}NO_5$: C, 61.09; H, 4.76; N, 5.09. Found: C, 61.06; H, 4.73; N, 4.98.

One-Pot Domino Michael–Hemiacetalization and Reduction Reaction; Methyl (3a*R*,9*R*,9a*S*)-9-(Nitromethyl)-1,2,3,3a,9,9a-hexahydrocyclopenta[*b*]chromene-9a-carboxylate (12)

In a glass vial equipped with a magnetic stirring bar, catalyst **C** (10 mol%) was added to a mixture of cyclic β-keto ester **2a** (135 μL, 1.0 mmol) and (*E*)-2-(2-nitrovinyl)phenol (**1a**; 165 mg, 1.0 mmol) in toluene (6.0 mL) at r.t. The reaction mixture was monitored by TLC. After completion of the reaction, the solvent was evaporated, and CH_2Cl_2 (6 mL), $HSiEt_3$ (240 μL, 1.5 mmol), and $BF_3{\cdot}OEt_2$ (130 μL, 1.0 mmol) were added at –78 °C. After stirring for 6 h, the reaction mixture was warmed up to r.t. The crude mixture was quenched with sat. aq $NaHCO_3$ (5 mL), the organic phase was separated, and the aqueous phase was extracted with EtOAc (3 × 5 mL). The organic extracts were combined and dried (Na_2SO_4), and concentrated under reduced pressure. The residue was purified after chromatography (silica gel, *n*-pentane–EtOAc, 6:1) to afford **12** as a colorless solid (181 mg, 62%); mp 161 °C; R_f = 0.45 (*n*-pentane–EtOAc, 6:1); $[\alpha]_D^{20}$ –13.4 (*c* 1.0, $CHCl_3$); ee (major) = 94%, ee (minor) = 99%; de = 88%. The enantiomeric excess was determined by chiral stationary phase HPLC using a Chiralcel OD column [*n*-heptane–*i*-PrOH (95:5), flow rate 0.7 mL/min, λ = 254 nm], t_R = 13.36 min (major), t_R = 27.32 min (minor), t_R = 21.13 min (major), t_R = 44.50 min (minor).

IR (film): 2982, 2951, 2875, 1723, 1543, 1482, 1447, 1373, 1326, 1223, 1151, 1105, 1035, 996, 804, 757, 660 cm^{-1}.

^1H NMR (600 MHz, $CDCl_3$): δ = 1.51–1.61 (m, 1 H, CH_2), 1.81–1.90 (m, 1 H, CH_2), 1.99–2.22 (m, 2 H, CH_2), 2.34–2.40 (m, 1 H, CH_2), 2.64–2.72 (m, 1 H, CH_2), 3.93 (dd, *J* = 6.0, 6.4 Hz, 1 H, CH), 4.14 (dd, *J* = 7.4, 11.4 Hz, 1 H, OCH), 4.68 (dd, *J* = 6.0, 13.4 Hz, 1 H, CH_2), 5.00 (dd, *J* = 6.4, 13.4 Hz, 1 H, CH_2), 6.87 (d, *J* = 7.0 Hz, 1 H, CH_{arom}), 6.96 (t, *J* = 7.4 Hz, 1 H, CH_{arom}), 7.05 (d, *J* = 8.0 Hz, 1 H, CH_{arom}), 7.16 (t, *J* = 8.0 Hz, 1 H, CH_{arom}).

^{13}C NMR (150 MHz, $CDCl_3$): δ = 19.2 (CH_2), 26.4 (CH_2), 31.1 (CH_2), 46.2 (CH), 52.1 (CH_3), 52.2 (C_q), 77.9 (CH_2), 83.8 (OCH), 117.3 (CH_{arom}), 121.8 (CH_{arom}), 122.9 (C_{arom}), 126.0 (CH_{arom}), 128.2 (CH_{arom}), 155.5 ($C_{arom}O$), 171.9 (CO_2CH_3).

MS (EI, 70 eV): *m*/*z* (%) = 291 ([M^+], 52), 244 (80), 200 (94), 185 (100), 157 (11), 115 (71), 91 (42), 77 (20).

Anal. Calcd for $C_{15}H_{17}NO_5$: C, 61.85; H, 5.88; N, 4.81. Found: C, 61.50; H, 5.87; N, 4.74.

One-Pot Domino Michael–Hemiacetalization and Acetalization Reaction; Methyl (3a*R*,9*R*,9a*S*)-3a-Methoxy-9-(nitromethyl)-1,2,3,3a,9,9a-hexahydrocyclopenta[*b*]chromene-9a-carboxylate (13)

In a glass vial equipped with a magnetic stirring bar, catalyst **C** (10 mol%) was added to a mixture of cyclic β-keto ester (**2a**; 135 μL, 1.0 mmol) and (*E*)-2-(2-nitrovinyl)phenol (**1a**; 165 mg, 1.0 mmol) in toluene (6.0 mL) at r.t. The reaction was monitored by TLC. After completion of the reaction, the solvent was evaporated and MeOH (6 mL) and PTSA monohydrate (20 mol%, 38 mg) were added and the mixture was stirred for 8 h at r.t. After completion, the crude reaction mixture was filtered through a small plug of silica gel. Product **13** was isolated after column chromatography (silica gel, *n*-pentane–Et_2O, 6:1) as a colorless oil (180 mg, 56%); R_f = 0.45 (*n*-pentane–Et_2O, 6:1); $[\alpha]_D^{20}$ –23.5 (*c* 1.0, $CHCl_3$); ee (major) = 92%, ee (minor) = 70%; de = 93%. The enantiomeric excess was determined by chiral stationary phase HPLC using a Chiralcel OD column [*n*-heptane–EtOH (9:1), flow rate 1.0 mL/min, λ = 254 nm], t_R = 6.02 min (major), t_R = 9.90 min (minor), t_R = 5.46 min (major), t_R = 7.13 min (minor).

IR (film): 2954, 2847, 1730, 1556, 1492, 1452, 1379, 1322, 1246, 1133, 1083, 1029, 973, 912, 840, 803, 756, 663 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$,): δ = 1.48–1.59 (m, 1 H, CH_2), 1.72–1.88 (m, 1 H, CH_2), 2.02–2.15 (m, 3 H, CH_2), 2.18–2.26 (m, 1 H, CH_2), 3.34 (s, 3 H, CH_3), 3.75 (s, 3 H, OCH_3), 4.47 (dd, *J* = 4.7, 13.3 Hz, 1 H, CH_2), 4.60 (dd, *J* = 4.7, 6.3 Hz, 1 H, CH), 4.68 (dd, *J* = 6.3, 13.3 Hz, 1 H, CH_2), 6.86–6.90 (m, 1 H, CH_{arom}), 6.94–7.00 (m, 1 H, CH_{arom}), 7.04–7.13 (m, 1 H, CH_{arom}), 7.16–7.22 (m, 1 H, CH_{arom}).

^{13}C NMR (100 MHz, $CDCl_3$,): δ = 19.5 (CH_2), 27.8 (CH_2), 32.0 (CH_2), 35.3 (CH), 52.0 (OCH_3), 52.7 (CH_3), 56.2 (C_q), 78.1 (CH_2), 108.9 (CH_{olef}), 117.6 (CH_{arom}), 120.4 (C_{arom}), 122.2 (CH_{arom}), 126.8 (CH_{arom}), 128.6 (CH_{arom}), 150.2 ($C_{olef}O$), 173.0 (CO_2CH_3).

MS (EI, 70 eV): *m*/*z* (%) = 321 ([M^+], 13), 274 (56), 243 (65), 215 (44), 183 (42), 156 (100), 141 (41), 124 (20), 109 (26).

HRMS: *m*/*z* calcd for $C_{16}H_{19}NO_6$ + Na: 344.1105; found: 344.1104.

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