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79-99% vield

93–99% *ee* 14 examples

31-94% yield

88-94% ee

3 examples

5-exo-dig

٥r

6-endo-dig

NO₂

Asymmetric Synthesis of Tetrahydrobenzofurans and Annulated Dihydropyrans via Cooperative One-Pot Organo- and Silver-Catalysis

cat

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In memory of Professor lean Normant

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Abstract A low catalyst loading of a squaramide (0.5 mol%) and a silver(I) salt (1 mol%) efficiently catalyzes a one-pot asymmetric Michael addition/hydroalkoxylation reaction between 1,3-diketones and alkynetethered nitroalkenes. Depending on the 1,3-dicarbonyl substrate this cooperative catalytic approach opens access to tetrahydrobenzofurans or annulated dihydropyrans in moderate to excellent yields and very good to excellent enantioselectivities.

Key words asymmetric synthesis, organocatalysis, one-pot synthesis, silver catalysis, annulation

Benzofuran and its partially hydrogenated analogues are important heterocyclic building blocks and very common structures in natural products with interesting biological and pharmaceutical properties. This is also true for structurally isomeric annulated dihydropyrans.¹ Natural products such as the furanomonoterpene evodone (**I**), which has been isolated from *Evodia hortensis*, exhibits significant inhibitory activity on the seed germination of certain species.² Curzerenone (**II**) and bisabolangelone (**III**) are other natural products with antibacterial and anti-inflammatory activities,^{3,4} respectively, whereas the diterpenoid maoecrystal V (**IV**) is a potent selective HeLa cell inhibitor.⁵ The dihydropyran-type natural product crolibulin (**V**) and the pharmaceutical HA14-1 (**VI**) show anticancer properties (Figure 1).⁶

Recently, much effort has been invested in the synthesis of tetrahydrobenzofuran and dihydropyran core structures.⁷ Singh and co-workers developed a silver-catalyzed



cat. (0.5 mol%)

Ag₂O (1 mol%)

CH₂Cl₂, r.t.

Ag

H-Do

Figure 1 Bioactive natural products and pharmaceuticals containing the partially hydrogenated benzofuran and dihydropyran moieties

interrupted Feist–Bénary reaction between ynones and βdiketones to provide dihydrofurans in moderate to good yields and good to excellent enantioselectivities (Scheme 1).⁸ Feng and co-workers reported an asymmetric domino Michael addition/O-alkylation reaction between cyclohexane-1,3-dione derivatives and bromonitrostyrenes catalyzed by a bifunctional *N*,*N'*-dioxide organocatalyst to afford polysubstituted bicyclic dihydrofurans.⁹ Calter's group published another interesting synthesis of highly substituted furanoids via an organocatalytic asymmetric aldol/oxa-Michael addition sequence between 2-ene-1,4-diketones and dimedone in the presence of a bis(cinchona alkaloid)pyrimidine catalyst.¹⁰ The Schneider group developed an interesting enantioselective phosphoric acid-catalyzed syn-



thesis of 4-aryl-4*H*-chromenes via a conjugate addition of 1,3-diketones to in situ generated ortho-quinone methides followed by a cyclodehydration reaction.¹¹



Scheme 1 Approaches for the asymmetric synthesis of tetrahydrobenzofurans and annulated dihydropyran derivatives

The activation of alkynes for subsequent transformations has become an important tool in organic chemistry to develop new and valuable reactions. Alkyne functionalization can be achieved in two crucial routes: σ -activation (σ bond metathesis or σ -coordination) and π -activation (π complex formation).¹² The coinage metals (Cu, Ag and Au) are suitable candidates for alkyne functionalization due to their good alkynophilicity.¹³ Especially, silver(I) salts have emerged as powerful activators of alkynes. The advantages of stability, nontoxicity, low price, or catalyst compatibility with organocatalysts favor the choice of silver in C=C bond activation reactions such as alkynylation, cycloaddition, cycloisomerization, or hydrofunctionalization.¹⁴

Merging organocatalysis and metal catalysis enables multiple unique transformations in one-pot and this catalytic approach has become a powerful strategy in asymmetric synthesis. Particularly cooperative, relay, synergistic, and dual catalysis variations, where all reactants and catalysts are present from the beginning, is challenging and require high compatibility of the combined catalysts.¹⁵

In search of new methods for acquiring valuable bioactive heterocyclic compounds and our interest in the combination of organocatalysts and silver(I) salts,¹⁶ we investigated an asymmetric Michael addition/hydroalkoxylation sequence between 1,3-diketones and alkyne-tethered nitroalkenes catalyzed by a bifunctional squaramide¹⁷ and a silver(I) salt to provide the desired tetrahydrobenzofurans. We began our investigation by choosing dimedone (1) and nitroalkene 2a as model substrates. To our delight, the onepot reaction of 1 and 2a in CH₂Cl₂ at room temperature catalyzed by squaramide **A** and Ag₂O afforded the desired 5exo-dig cyclization product 3a in 98% vield and 94% enantiomeric excess (Scheme 2). Inspired by these excellent results, the reaction was carried out with different squaramide and thiourea catalysts A-I along with Ag₂O as silver(I) salt. All squaramide catalysts as well as thiourea catalysts provided the tetrahydrobenzofuran in high yields and moderate to very good enantioselectivities. The best result was obtained with squaramide A, which gave 98% yield and 94% ee.



Scheme 2 Catalyst screening for the Michael addition/hydroalkoxylation reaction of 1 with 2a

The reaction conditions were optimized further by varying the solvent (Table 1). The solvent screening indicated that the chlorinated solvents and Et_2O gave very good results. The best yields were obtained with CH_2Cl_2 and $CHCl_3$. We chose CH_2Cl_2 over $CHCl_3$ on the basis of its lower toxici-

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ty. Further optimization studies were carried out by screening transition metal catalysts for the hydroalkoxylation reaction. Ag₂CO₃ provided the annulated product with 99% yield and 95% *ee*. The cost aspect led to our decision to use Ag₂O instead of Ag₂CO₃. After carrying out the reaction at different temperatures and catalyst loadings of the squaramide and the silver(I) salt, we determined the optimal reaction conditions, these being 0.5 mol% of the squaramide **A**, 1 mol% of Ag₂O, and CH₂Cl₂ as solvent at room temperature.

Table 1 Further Optimization Studies^a

H ₃ C H ₃ C ¹	0 + 1 +	NO2 Cat. A (1 mol M-cat. (10 mo solvent (0.1 M)	$(h_{1}^{(6)}) \xrightarrow{(h_{1})}_{H_{3}C} (h_{3}^{(6)}) \xrightarrow{(h_{1})}_{H_{3}C} (h_{1})$	NO ₂
Entry	M-catalyst	Solvent	Yield (%) ^b	ee (%)°
1	Ag ₂ O	toluene	90	92
2	Ag ₂ O	Et ₂ O	99	92
3	Ag ₂ O	CHCl ₃	99	95
4	Ag ₂ O	DCE	99	94
5	Ag ₂ O	CH ₂ Cl ₂	99	95
6	PtCl ₂	CH ₂ Cl ₂	traces	-
7	CuCl	CH ₂ Cl ₂	37	94
8	AgOTf	CH ₂ Cl ₂	25	22
9	AgBF ₄	CH ₂ Cl ₂	20	47
10	Ag ₂ CO ₃	CH_2CI_2	99	95
11	AuClPPh ₃	CH_2CI_2	n.d.	-
12 ^d	Ag ₂ O	CH_2CI_2	99	96
13 ^e	Ag ₂ O	CH_2CI_2	99	95
14 ^f	Ag ₂ O	CH_2CI_2	99	96
15 ^g	Ag ₂ O	CH ₂ Cl ₂	99	97

^a Reaction conditions: Dimedone (1; 0.25 mmol), nitroalkene 2a (1.1

equiv), cat. A (1 mol%), Ag₂O (10 mol%), solvent (2.5 mL, 0.1 M).

^b Yield of **3a** after flash chromatography.

^c The enantiomeric excess was determined by HPLC on a chiral stationary phase.

d The reaction was carried out with **A** (0.5 mol%).

 $^{\rm e}$ The reaction was carried out with Ag₂O (5 mol%) and **A** (0.5 mol%).

^f The reaction was carried out with $Ag_2O(1 \text{ mol}\%)$ and **A** (0.5 mol%).

 g The reaction was carried out with Ag_O (1 mol%) and \bm{A} (0.5 mol%) at 0 °C.

The substrate scope of the cooperative organo- and silver-catalyzed asymmetric one-pot reaction was then explored for the reaction of dimedone (1) with various alkyne-tethered nitroalkenes 2 under optimal reaction conditions (Table 2). The nitroalkenes with electron-withdrawing and electron-donating groups worked smoothly under the cooperative catalysis condition to provide tetrahydrobenzofurans **3b-f** in excellent yields and very good enantio-selectivities. The sterically encumbered 1-naphthyl- and 2-naphthyl-substituted nitroalkenes led to the formation of the desired tetrahydrobenzofurans **3g,h** in very good yields

and excellent enantiomeric excesses (Table 2). Furthermore, the one-pot Michael addition/hydroalkoxylation sequence with heteroaryl-substituted nitroalkenes provided the desired annulated product **3i** in excellent yields and enantio-selectivity.

Table 2 Substrate Scope^a

	NO ₂	cat. A (0.5 mol%) Ag ₂ O (1 mol%) CH ₂ Cl ₂ (0.1 M), r.t. H ₃ C	
3	R	Yield (%) ^b	ee (%) ^c
а	Ph	99	96
Ь	3-MeOC ₆ H ₄	98	96
c	2-CIC ₆ H ₄	97	95
d	$4-F_3CC_6H_4$	93	94
e	$3-MeC_6H_4$	97	95
f	3,4-(OCH ₂ O)C ₆ H ₃	97	95
g	2-naphthyl	94	97
h	1-naphthyl	90	95
i	2-furanyl	96	96

^a Reaction conditions: Dimedone (**1**; 0.25 mmol), nitroalkene **2** (1.1 equiv), cat. **A** (0.5 mol%), Ag_2O (1 mol%), solvent (2.5 mL, 0.1 M).

^b Yield of **3a** after flash chromatography.

^c The enantiomeric excess was determined by HPLC on a chiral stationary phase.

An extended substrate scope was investigated using different cyclic 1,3-diketones based on five- and six-membered rings. The reaction with 1,3-cyclohexanedione led to the tetrahydrobenzofuran product in good yield and excellent enantioselectivity (Scheme 3, 5a) Interestingly, a dihydropyran derivative **5b** could be obtained in moderate yield and good enantiomeric excess using 1,3-cyclopentanedione. The substrate scope of the cooperative catalytic reaction was extended further to 1,3-diketones bearing heteroatoms, which also provided dihydropyran derivatives in moderate to very good yields and high enantioselectivities (Scheme 3, 5c, d).

The developed one-pot asymmetric transformation was also conducted with various 5-substituted 1,3-cyclohexanediones to introduce another stereocenter via desymmetrization. The desired tetrahydrobenzofurans could be obtained in very good yields and enantioselectivities, but the diastereomeric ratio was virtually 1:1 in all attempts (Scheme 4, 7a–d).

To evaluate the efficiency and synthetic utility of the current Michael addition/hydroalkoxylation strategy, tetrahydrobenzofuran **3a** was prepared on a gram-scale maintaining the excellent yield and *ee* value (Scheme 5).





Scheme 3 Extended substrate scope to annulated dihydropyrans





The absolute configuration of the tetrahydrobenzofurans was determined by X-ray crystal structure analysis of compound **5a** (Figure 2)¹⁸ in combination with a CD measurement and calculation (Figure 3).

The absolute configuration of the dihydropyran derivatives is based on an X-ray crystallographic analysis of compound **5d** (Figure 4).¹⁸



Figure 2 X-ray crystal structure of tetrahydrobenzofuran 5a

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Figure 3 Measured (red) CD spectrum of **5a**. The black curve is the calculated CD spectrum of **5a** with the S-configuration at carbon atom C3. $\Delta\epsilon$ in 1000 cm²mol⁻¹ and λ in nm. For details, see the Supporting Information.



Figure 4 X-ray crystal structure of dihydropyran derivative 5d

This one-pot Michael addition/hydroalkoxylation protocol is proposed to proceed via two catalytic cycles (Scheme 6). The first organocatalytic cycle involves the synergistic activation of the 1,3-diketone **1** and the nitroalkene **2** by the bifunctional squaramide **A**, where the squaramide moiety activates the nitroalkene **2** through the formation of hydrogen bonds to the nitro group and simultaneously the 1,3-diketone undergoes activation by the tertiary amine to promote the Michael addition from the *Re*-face. In the second catalytic cycle the silver forms a π -complex for the electrophilic activation of the internal alkyne to facilitate a 5-*exo*-dig or a 6-*endo*-dig annulation reaction leading to the vinylsilver intermediate. The latter undergoes a fast protodeargentation to provide the desired product **3**, **5** and **7**.

In conclusion, we have developed a one-pot asymmetric Michael addition/hydroalkoxylation protocol by merging a bifunctional squaramide and a silver(I) salt at a very low





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 $Ag_{2}O$ $Ag_{$

Scheme 6 Proposed mechanism of the one-pot Michael addition/ hydroalkoxylation reaction

catalyst loading. The combination of both catalytic systems enabled the formation of the desired tetrahydrobenzofurans and annulated dihydropyranes in moderate to excellent yields and good to excellent enantiomeric excesses.

Unless otherwise noted, all commercially available chemicals were used without purification. All solvents were distilled and purified according to standard procedures. Analytical TLC was performed using SIL G-25 UV₂₅₂ from Macherey & Nagel (particle size 0.040–0.063 nm; 230–240 mesh. flash) and visualized with ultraviolet radiation at 254 nm. ¹H, ¹³C, and ¹⁹F NMR spectra were recorded at ambient temperature on a Varian Innova 400 or Innova 600 spectrometer. Chemical shifts for ¹H NMR and ¹³C NMR spectra are reported in parts per million (ppm) and coupling constants in hertz (Hz). Standard abbreviations are used for the spin multiplicity (qi = quintet). Optical rotations

were measured on a PerkinElmer 241 polarimeter. Melting points were measured on a LLG MPM-H2 melting point instrument. Mass spectra were acquired on a Finnigan SSQ7000 (EI, 70 eV) spectrometer and on a ThermoFinnigan LCQ Deca XP plus (ESI) spectrometer and high-resolution ESI spectra on a ThermoFisher Scientific LTQ Orbitrap XL. Analytical HPLC was performed on a Aligent 1100, Aligent 1260, or Hewlett-Packard 1100 Series instrument using chiral stationary phases (Daicel Chiralpak IC, Daicel Chiralpak IA, Daicel Chiralpak AD, Daicel Chiralpak AS, Daicel Chiralpak IB columns). Analytical SFC was performed on a THAR-SFC MethodStation II with a WATERS 2998 Photodiode Array Detector using chiral stationary phases (Daicel Chiralcel OJ-H). Catalyst **A** and **B**,¹⁹ **D**–**I**²⁰ and the nitroalkenes **2**^{16c} were prepared according to known procedures.

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Tetrahydrobenzofurans and Annulated Dihydropyrans; General Procedure

A mixture of 1,3-diketones **1,4**, or **6** (0.25 mmol), nitroalkene **2** (0.275 mmol, 1.1 equiv), catalyst **A** (0.5 mol%), and Ag₂O (1 mol%) in CH₂Cl₂ (2.5 mL, 0.1 M) was stirred at r.t. until the intermediate Michael adduct was completely converted as indicated by TLC. The crude product was directly subjected to flash chromatography on silica (*n*-pentane/Et₂O or *n*-pentane/CH₂Cl₂) to afford the corresponding product **3**, **5**, or **7**.

(*R*)-(*Z*)-2-Benzylidene-6,6-dimethyl-3-(nitromethyl)-3,5,6,7-tet-rahydrobenzofuran-4(2*H*)-one (3a)

Compound **3a** was isolated after flash chromatography (*n*-pentane/Et₂O, 1:1); yield: 75 mg (96%); colorless solid; mp 136–138 °C; $R_f = 0.22$ (*n*-pentane/Et₂O, 1:1); $[\alpha]_D^{24}$ +96.6 (*c* = 0.6, MeOH).

HPLC: Daicel Chiralpak IC, *n*-heptane/*i*-PrOH (7:3), 1.0 mL/min, λ = 254 nm, t_R (minor) = 7.6 min, t_R (major) = 6.4 min; 96% *ee*.

IR (ATR): 2955, 2330, 2086, 1900, 1645, 1546, 1492, 1397, 1335, 1286, 1219, 1174, 1140, 1092, 998, 917, 849, 755, 694 $\rm cm^{-1}.$

¹H NMR (600 MHz, C₆D₆): δ = 7.52 (d, *J* = 7.4 Hz, 2 H, ArH), 7.19 (t, *J* = 7.8 Hz, 2 H, ArH), 7.04 (t, *J* = 7.4 Hz, 1 H, ArH), 5.42 (d, *J* = 2.0 Hz, 1 H, OC=CH), 4.36 (dd, *J* = 13.1, 6.3 Hz, 1 H, CHHNO₂), 4.17 (dd, *J* = 13.1, 4.7 Hz, 1 H, CHHNO₂), 3.92 (s, 1 H, CHCH₂), 1.93 (d, *J* = 16.0 Hz, 1 H, CH₂), 1.85 (d, *J* = 16.0 Hz, 1 H, CH₂), 1.66 (d, *J* = 17.9 Hz, 1 H, CH₂), 1.58 (d, *J* = 17.9 Hz, 1 H, CH₂), 0.64 (s, 3 H, CH₃), 0.58 (s, 3 H, CH₃).

 ^{13}C NMR (151 MHz, C₆D₆): δ = 191.6 (C=O), 173.4 (C_q), 153.4 (C_q), 133.9 (C_q), 128.7 (2 C, ArC), 128.3 (2 C, ArC), 127.0 (ArC), 111.1 (C_q), 106.0 (OC=CH), 75.3 (CH₂NO₂), 50.5 (CH₂), 41.9 (CHCH₂), 36.1 (CH₂), 33.2 [C(CH₃)₂], 28.4 (CH₃), 27.2 (CH₃).

$$\begin{split} \mathsf{MS} \;(\mathsf{EI}, 70 \; \mathsf{eV}): \; m/z \; (\%) &= 313.1 \; (1, [\mathsf{M}]^*), 267.1 \; (17, [\mathsf{M}-\mathsf{NO}_2]^*), 253.0 \\ (7, [\mathsf{M}-\mathsf{CH}_2\mathsf{NO}_2]^*), 90.1 \; (38, [\mathsf{CH}_2\mathsf{C}_6\mathsf{H}_5]^*), 77.1 \; (27, [\mathsf{C}_6\mathsf{H}_5]^*). \end{split}$$

HRMS (ESI⁺): m/z [M + Na]⁺ calcd for C₁₈H₁₉NO₄Na: 336.1206; found: 336.1195.

(*R*)-(*Z*)-2-(3-Methoxybenzylidene)-6,6-dimethyl-3-(nitromethyl)-3,5,6,7-tetrahydrobenzofuran-4(2*H*)-one (3b)

Compound **3b** was isolated after flash chromatography (*n*-pentane/Et₂O, 2:1); yield: 84 mg (98%); colorless solid; mp 127–129 °C; $R_f = 0.17$ (*n*-pentane/Et₂O, 1:1); [α]_D²⁴+67.7 (*c* = 0.4, benzene).

HPLC: Daicel Chiralpak IC, *n*-heptane/*i*-PrOH (7:3), 0.7 mL/min, $\lambda = 254$ nm, t_R (minor) = 14.0 min, t_R (major) = 15.4 min; 96% ee.

IR (ATR): 2934, 2293, 2090, 1891, 1649, 1566, 1399, 1232, 1015, 840, 692 $\rm cm^{-1}.$

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¹H NMR (600 MHz, CDCl₃): δ = 7.25 (m, 1 H, ArH), 7.11 (m, 2 H, ArH), 6.83–6.78 (m, 1 H, ArH), 5.71 (d, *J* = 2.2 Hz, 1 H, OC=CH), 4.89 (dd, *J* = 13.3, 3.9 Hz, 1 H, CHHNO₂), 4.73 (dd, *J* = 13.3, 7.1 Hz, 1 H, CHHNO₂), 4.58–4.53 (m, 1 H, CHCH₂), 3.82 (s, 3 H, OCH₃), 2.54 (m, 2 H, CH₂), 2.31 (m, 2 H, CH₂), 1.17 (s, 3 H, CH₃), 1.16 (s, 3 H, CH₃).

¹³C NMR (151 MHz, CDCl₃): δ = 193.6 (C=O), 175.0 (C_q), 159.6 (C_q), 153.3 (C_q), 134.5 (C_q), 129.4 (ArC), 121.3 (ArC), 114.2 (ArC), 112.8 (ArC), 111.3 (C_q), 106.7 (OC=CH), 75.7 (CH₂NO₂), 55.2 (OCH₃), 51.0 (CH₂), 41.7 (CHCH₂), 37.2 (CH₂), 34.4 [C(CH₃)₂], 29.0 (CH₃), 28.3 (CH₃). MS (EI, 70 eV): m/z (%) = 343.3 (5, [M]⁺), 297.3 (34, [M – NO₂]⁺), 283.3 (12, [M – CH₂NO₂]⁺).

HRMS (ESI⁺): m/z [M + Na]⁺ calcd for C₁₉H₂₁NO₅Na: 366.1312; found: 366.1310.

(*R*)-(*Z*)-2-(2-Chlorobenzylidene)-6,6-dimethyl-3-(nitromethyl)-3,5,6,7-tetrahydrobenzofuran-4(2*H*)-one (3c)

Compound **3c** was isolated after flash chromatography (*n*-pentane/Et₂O, 1:1); yield: 84 mg (97%); colorless solid; mp 130–132 °C; $R_f = 0.36$ (*n*-pentane/Et₂O, 1:1); $[\alpha]_D^{24} = 115.8$ (*c* = 0.5, benzene).

HPLC: Daicel Chiralpak IA, *n*-heptane/*i*-PrOH (7:3), 0.7 mL/min, λ = 230 nm, t_R (minor) = 8.4 min, t_R (major) = 9.0 min; 95% *ee*.

IR (ATR): 2956, 2314, 2084, 1648, 1552, 1396, 1284, 1214, 1017, 972, 852, 754, 692 $\rm cm^{-1}.$

¹H NMR (600 MHz, C_6D_6): δ = 7.95 (dd, *J* = 7.9, 1.6 Hz, 1 H, ArH), 7.17 (dd, *J* = 8.1, 1.2 Hz, 1 H, ArH), 6.97 (m, 1 H, ArH), 6.73 (m, 1 H, ArH), 6.04 (d, *J* = 2.3 Hz, 1 H, OC=CH), 4.48 (dd, *J* = 13.2, 5.3 Hz, 1 H, CHH-NO₂), 3.99 (dd, *J* = 13.2, 3.6 Hz, 1 H, CHHNO₂), 3.69 (s, 1 H, CHCH₂), 1.92 (d, *J* = 16.0 Hz, 1 H, CH₂), 1.83 (d, *J* = 16.0 Hz, 1 H, CH₂), 1.67 (d, *J* = 17.9 Hz, 1 H, CH₂), 1.57 (d, *J* = 17.9 Hz, 1 H, CH₂), 0.64 (s, 3 H, CH₃), 0.56 (s, 3 H, CH₃).

 ^{13}C NMR (151 MHz, C₆D₆): δ = 191.6 (C=O), 173.2 (C_q), 155.4 (C_q), 132.7 (C_q), 131.9 (C_q), 130.2 (ArC), 129.4 (ArC), 128.1 (ArC), 126.5 (ArC), 111.4 (C_q), 101.5 (OC=CH), 75.2 (CH₂NO₂), 50.5 (CH₂), 42.0 (CHCH₂), 36.1 (CH₂), 33.2 [C(CH₃)₂], 28.4 (CH₃), 27.2 (CH₃).

MS (EI, 70 eV): m/z (%) = 348.3 (1, [M + H]⁺), 303.3 (7, [M - NO₂, ³⁷Cl]⁺), 301.2 (37, [M - NO₂, ³⁵Cl]⁺), 289.2 (2, [M - CH₂NO₂, ³⁷Cl]⁺), 287.2 (6, [M - NO₂, ³⁵Cl]⁺).

HRMS (ESI⁺): m/z [M + Na]⁺ calcd for C₁₈H₁₈ClNO₄Na: 370.0812; found: 370.0813.

(*R*)-(*Z*)-6,6-Dimethyl-3-(nitromethyl)-2-[4-(trifluoromethyl)benzylidene]-3,5,6,7-tetrahydrobenzofuran-4(2*H*)-one (3d)

Compound **3d** was isolated after flash chromatography (*n*-pentane/Et₂O, 1:2); yield: 106 mg (93%); colorless solid; mp 54–56 °C; $R_f = 0.14$ (*n*-pentane/Et₂O, 1:1); $[\alpha]_D^{24}$ +49.2 (c = 0.3, benzene).

HPLC: Daicel Chiralpak IC, *n*-heptane/*i*-PrOH (8:2), 1.0 mL/min, λ = 254 nm, t_R (minor) = 7.9 min, t_R (major) = 6.1 min; 94% *ee*.

IR (ATR): 2962, 1949, 1692, 1651, 1615, 1552, 1400, 1321, 1219, 1166, 1116, 1067, 1014, 917, 862, 834, 791, 758, 703 $\rm cm^{-1}.$

¹H NMR (400 MHz, CDCl₃): δ = 7.59 (m, 4 H, ArH), 5.76 (d, *J* = 2.2 Hz, 1 H, OC=CH), 4.90 (dd, *J* = 13.4, 3.9 Hz, 1 H, CHHNO₂), 4.75 (dd, *J* = 13.4, 6.9 Hz, 1 H, CHHNO₂), 4.55 (m, 1 H, CHCH₂), 2.55 (m, 2 H, CH₂), 2.31 (s, 2 H, CH₂), 1.17 (s, 3 H, CH₃), 1.16 (s, 3 H, CH₃).

 ^{13}C NMR (101 MHz, CDCl₃): δ = 193.5 (C=O), 174.7 (C_q), 155.0 (C_q), 136.8 (C_q), 128.7 (3 C, ArC), 125.3 (2 C, ArC), 122.7 (CF₃), 111.4 (C_q), 105.4 (OC=CH), 75.4 (CH₂NO₂), 51.0 (CH₂), 41.9 (CHCH₂), 37.2 (CH₂), 34.4 [C(CH₃)₂], 28.9 (CH₃), 28.2 (CH₃).

¹⁹F NMR (376 MHz, CDCl₃): δ = -62.61 (s).

MS (EI, 70 eV): *m*/*z* (%) = 382.3 (3, [M + H]⁺), 335.3 (29, [M - NO₂]⁺), 321.2 (9, [M - CH₂NO₂]⁺).

HRMS (ESI*): $m/z \, [M + Na]^+$ calcd for $C_{19}H_{18}F_3NO_4Na$: 404.1080; found: 404.1069.

(*R*)-(*Z*)-6,6-Dimethyl-2-(3-methylbenzylidene)-3-(nitromethyl)-3,5,6,7-tetrahydrobenzofuran-4(2*H*)-one (3e)

Compound **3e** was isolated after flash chromatography (*n*-pentane/Et₂O, 1:1); yield: 79 mg (97%); colorless solid; mp 138–140 °C; $R_f = 0.26$ (*n*-pentane/Et₂O, 1:1); $[\alpha]_D^{24}$ +71.2 (*c* = 0.4, benzene).

HPLC: Daicel Chiralpak IB, *n*-heptane/*i*-PrOH (7:3), 0.7 mL/min, $\lambda = 254$ nm, t_R (minor) = 11.0 min, t_R (major) = 10.0 min; 95% ee.

IR (ATR): 2957, 2290, 2086, 1644, 1547, 1474, 1403, 1328, 1280, 1214, 1171, 1093, 1006, 891, 840, 781, 697 $\rm cm^{-1}.$

¹H NMR (600 MHz, CDCl₃): δ = 7.37 (d, *J* = 7.8 Hz, 1 H, ArH), 7.32 (s, 1 H, ArH), 7.23 (t, *J* = 7.7 Hz, 1 H, ArH), 7.06 (d, *J* = 7.5 Hz, 1 H, ArH), 5.70 (d, *J* = 2.2 Hz, 1 H, OC=CH), 4.89 (dd, *J* = 13.2, 3.9 Hz, 1 H, CHHNO₂), 4.73 (dd, *J* = 13.3, 7.1 Hz, 1 H, CHHNO₂), 4.55 (m, 1 H, CHCH₂), 2.55 (m, 2 H, CH₂), 2.35 (s, 3 H, CH₃), 2.32 (m, 2 H, CH₂), 1.17 (s, 3 H, CH₃), 1.16 (s, 3 H, CH₃).

 ^{13}C NMR (151 MHz, CDCl₃): δ = 193.6 (C=O), 175.1 (Cq), 152.8 (Cq), 138.0 (Cq), 133.2 (Cq), 129.4 (ArC), 128.4 (ArC), 128.2 (ArC), 125.7 (ArC), 111.3 (Cq), 106.9 (OC=CH), 75.7 (CH_2NO_2), 51.0 (CH_2), 41.7 (CHCH_2), 37.3 (CH_2), 34.4 [C(CH_3)_2], 29.0 (CH_3), 28.3 (CH_3), 21.5 (ArCH_3).

MS (EI, 70 eV): *m*/*z* (%) = 327.2 (2, [M]⁺), 328.2 (9, [M + H]⁺), 281.3 (26, [M - NO₂]⁺), 267.3 (17, [M - CH₂NO₂]⁺).

HRMS (ESI⁺): m/z [M + Na]⁺ calcd for C₁₉H₂₁NO₄Na: 350.1363; found: 350.1356.

(*R*)-(*Z*)-2-(Benzo[*d*][1,3]dioxol-5-ylmethylene)-6,6-dimethyl-3-(nitromethyl)-3,5,6,7-tetrahydrobenzofuran-4(2*H*)-one (3f)

Compound **3f** was isolated after flash chromatography (*n*-pentane/Et₂O, 1:2); yield: 87 mg (97%); colorless solid; mp 138–140 °C; $R_f = 0.21$ (*n*-pentane/Et₂O, 1:1); $[\alpha]_D^{24}$ +72.8 (*c* = 0.4, benzene).

HPLC: Daicel Chiralpak IB, *n*-heptane/EtOH (7:3), 1.0 mL/min, λ = 254 nm, $t_{\rm R}$ (minor) = 9.8 min, $t_{\rm R}$ (major) = 13.8 min; 95% *ee*.

IR (ATR): 2960, 1650, 1549, 1493, 1398, 1292, 1239, 1097, 1027, 928, 875, 804, 697 $\rm cm^{-1}$.

¹H NMR (600 MHz, C₆D₆): δ = 7.42 (m, 1 H, ArH), 6.72 (m, 1 H, ArH), 6.64 (m, 1 H, ArH), 5.36 (d, *J* = 2.1 Hz, 1 H, OC=CH), 5.27 (m, 2 H, OCH₂O), 4.31 (dd, *J* = 12.9, 6.4 Hz, 1 H, CHHNO₂), 4.18 (dd, *J* = 13.0, 3.8 Hz, 1 H, CHHNO₂), 3.94 (s, 1 H, CHCH₂), 1.92 (d, *J* = 16.0 Hz, 1 H, CH₂), 1.84 (d, *J* = 16.0 Hz, 1 H, CH₂), 1.56 (d, *J* = 17.9 Hz, 1 H, CH₂), 1.48 (d, *J* = 17.9 Hz, 1 H, CH₂), 0.63 (s, 3 H, CH₃), 0.57 (s, 3 H, CH₃).

¹³C NMR (151 MHz, C_6D_6): δ = 191.7 (C=O), 173.4 (C_q), 151.9 (C_q), 148.1 (C_q), 146.8 (C_q), 128.1 (C_q), 123.1 (ArC), 111.0 (C_q), 108.6 (ArC), 108.2 (ArC), 106.0 (OC=CH), 100.8 (OCH₂O), 75.4 (CH₂NO₂), 50.5 (CH₂), 41.8 (CHCH₂), 36.0 (CH₂), 33.1 [*C*(CH₃)₂], 28.3 (CH₃), 27.2 (CH₃).

MS (EI, 70 eV): m/z (%) = 358.3 (5, $[M + H]^+$), 357.3 (17, $[M]^+$), 311.3 (24, $[M - NO_2]^+$), 297.3 (28, $[M - CH_2NO_2]^+$).

HRMS (ESI⁺): m/z [M + Na]⁺ calcd for C₁₉H₁₉NO₆Na: 380.1105; found: 380.1094.



(*R*)-(*Z*)-6,6-Dimethyl-2-(naphthalen-2-ylmethylene)-3-(nitromethyl)-3,5,6,7-tetrahydrobenzofuran-4(2*H*)-one (3g)

Compound **3g** was isolated after flash chromatography (*n*-pentane/Et₂O, 1:1 to 1:2); yield: 85 mg (94%); colorless solid; mp 133– 135 °C; R_f = 0.24 (*n*-pentane/Et₂O, 1:1); $[\alpha]_D^{24}$ +93.9 (*c* = 0.4, benzene).

HPLC: Daicel Chiralpak IA, *n*-heptane/*i*-PrOH (7:3), 0.7 mL/min, λ = 254 nm, t_R (minor) = 11.1 min, t_R (major) = 11.7 min; 97% ee.

IR (ATR): 2956, 2313, 2073, 2002, 1646, 1549, 1463, 1401, 1290, 1218, 1173, 1140, 1090, 1019, 900, 862, 821, 749, 699 $\rm cm^{-1}.$

¹H NMR (600 MHz, CDCl₃): δ = 7.94 (s, 1 H, ArH), 7.84–7.77 (m, 3 H, ArH), 7.72 (dd, *J* = 8.6, 1.7 Hz, 1 H, ArH), 7.50–7.43 (m, 2 H, ArH), 5.90 (d, *J* = 2.1 Hz, 1 H, OC=CH), 4.94 (dd, *J* = 13.3, 3.9 Hz, 1 H, CHHNO₂), 4.77 (dd, *J* = 13.3, 7.2 Hz, 1 H, CHHNO₂), 4.62 (m, 1 H, CHCH₂), 2.60 (m, 2 H, CH₂), 2.34 (s, 2 H, CH₂), 1.19 (s, 3 H, CH₃), 1.18 (s, 3 H, CH₃).

 ^{13}C NMR (151 MHz, CDCl₃): δ = 193.6 (C=O), 175.0 (Cq), 153.3 (Cq), 133.4 (Cq), 132.4 (Cq), 130.9 (Cq), 128.1 (ArC), 128.0 (ArC), 127.8 (ArC), 127.6 (ArC), 126.5 (ArC), 126.3 (ArC), 126.1 (ArC), 111.4 (Cq), 106.9 (OC=CH), 75.7 (CH_2NO_2), 51.1 (CH_2), 41.8 (CHCH_2), 37.3 (CH_2), 34.4 [C(CH_3)_2], 29.0 (CH_3), 28.3 (CH_3).

 $MS (EI, 70 \text{ eV}): m/z (\%) = 364.3 (2, [M + H]^+), 363.3 (4, [M]^+), 317.3 (27, [M - NO_2]^+), 303.3 (12, [M - CH_2NO_2]^+).$

HRMS (ESI⁺): m/z [M + Na]⁺ calcd for C₂₂H₂₁NO₄Na: 386.1363; found: 386.1351.

(*R*)-(*Z*)-6,6-Dimethyl-2-(naphthalen-1-ylmethylene)-3-(nitromethyl)-3,5,6,7-tetrahydrobenzofuran-4(2*H*)-one (3h)

Compound **3h** was isolated after flash chromatography (*n*-pentane/Et₂O, 1:1); yield: 82 mg (90%); colorless solid; mp 165–167 °C; $R_f = 0.23$ (*n*-pentane/Et₂O, 1:1); $[\alpha]_D^{24}$ +110.1 (c = 0.4, benzene).

HPLC: Daicel Chiralpak IB, *n*-heptane/EtOH (7:3), 0.5 mL/min, λ = 230 nm, $t_{\rm R}$ (minor) = 15.9 min, $t_{\rm R}$ (major) = 16.9 min; 95% *ee*.

IR (ATR): 3056, 2959, 1648, 1550, 1398, 1294, 1218, 1172, 1141, 1089, 1019, 975, 915, 838, 780, 699 cm⁻¹.

¹H NMR (600 MHz, CDCl₃): δ = 7.98 (d, *J* = 8.3 Hz, 1 H, ArH), 7.87–7.77 (m, 3 H, ArH), 7.56–7.46 (m, 3 H, ArH), 6.41 (d, *J* = 2.1 Hz, 1 H, OC=CH), 5.02 (dd, *J* = 13.1, 3.9 Hz, 1 H, CHHNO₂), 4.83 (dd, *J* = 13.1, 7.2 Hz, 1 H, CHHNO₂), 4.72–4.66 (m, 1 H, CHCH₂), 2.48 (m, 2 H, CH₂), 2.32 (m, 2 H, CH₂), 1.16 (s, 3 H, CH₃), 1.15 (s, 3 H, CH₃).

¹³C NMR (151 MHz, CDCl₃): δ = 193.6 (C=O), 175.2 (C_q), 154.2 (C_q), 133.6 (C_q), 131.1 (C_q), 129.4 (C_q), 128.6 (ArC), 128.1 (ArC), 127.1 (ArC), 126.4 (ArC), 125.9 (ArC), 125.3 (ArC), 123.8 (ArC), 111.5 (C_q), 103.5 (OC=*C*H), 76.0 (CH₂NO₂), 51.0 (CH₂), 41.7 (CHCH₂), 37.2 (CH₂), 34.4 [C(CH₃)₂], 29.0 (CH₃), 28.3 (CH₃).

MS (EI, 70 eV): m/z (%) = 364.4 (2, [M + H]⁺), 363.3 (7, [M]⁺), 317.3 (24, [M - NO₂]⁺), 303.3 (6, [M - CH₂NO₂]⁺).

HRMS (ESI⁺): m/z [M + Na]⁺ calcd for C₂₂H₂₁NO₄Na: 386.1323; found: 386.1345.

(*R*)-(*Z*)-2-(Furan-2-ylmethylene)-6,6-dimethyl-3-(nitromethyl)-3,5,6,7-tetrahydrobenzofuran-4(2*H*)-one (3i)

Compound **3i** was isolated after flash chromatography (*n*-pentane/Et₂O, 1:1); yield: 73 mg (96%); colorless solid; mp 103–105 °C; $R_f = 0.31 (n$ -pentane/Et₂O, 1:1); $[\alpha]_D^{24}$ +85.7 (c = 0.4, benzene).

HPLC: Daicel Chiralpak IB, *n*-heptane/EtOH (7:3), 0.7 mL/min, λ = 254 nm, t_R (minor) = 9.3 min, t_R (major) = 10.3 min; 96% *ee*.

 $IR \ (ATR): 2960, 2876, 2081, 1988, 1649, 1554, 1466, 1374, 1292, 1228, 1167, 1089, 1049, 1016, 989, 920, 884, 816, 747, 700, 671\ cm^{-1}.$

¹H NMR (600 MHz, C_6D_6): δ = 7.05 (d, *J* = 1.6 Hz, 1 H, OCH), 6.59 (d, *J* = 3.3 Hz, 1 H, CH), 6.19 (dd, *J* = 3.3, 1.8 Hz, 1 H, CH), 5.61 (d, *J* = 2.3 Hz, 1 H, OC=CH), 4.29 (dd, *J* = 13.2, 6.1 Hz, 1 H, CHHNO₂), 4.04 (dd, *J* = 13.2, 3.7 Hz, 1 H, CHHNO₂), 3.79 (s, 1 H, CHCH₂), 1.90 (d, *J* = 16.0 Hz, 1 H, CH₂), 1.82 (d, *J* = 16.0 Hz, 1 H, CH₂), 1.71 (d, *J* = 17.8 Hz, 1 H, CH₂), 1.63 (d, *J* = 17.8 Hz, 1 H, CH₂), 0.62 (s, 3 H, CH₃), 0.57 (s, 3 H, CH₃).

 ^{13}C NMR (151 MHz, C₆D₆): δ = 191.6 (C=O), 173.2 (C_q), 152.1 (C_q), 149.1 (C_q), 141.2 (OCH), 111.6 (CH), 111.3 (C_q), 109.5 (CH), 96.2 (OC=CH), 74.8 (CH_2NO_2), 50.5 (CH_2), 41.4 (CHCH_2), 36.2 (CH_2), 33.2 [C(CH_3)_2], 28.3 (CH_3), 27.2 (CH_3).

MS (EI, 70 eV): m/z (%) = 304.1 (1, [M + H]⁺), 303.1 (5, [M]⁺), 257.1 (24, [M - NO₂]⁺), 243.0 (13, [M - CH₂NO₂]⁺).

HRMS (ESI⁺): m/z [M + Na]⁺ calcd for C₁₆H₁₇NO₅Na: 326.0999; found: 326.0990.

(*R*)-(*Z*)-2-Benzylidene-3-(nitromethyl)-3,5,6,7-tetrahydrobenzo-furan-4(2*H*)-one (5a)

Compound **5a** was isolated after flash chromatography (*n*-pentane/Et₂O, 1:2); yield: 56 mg (79%); colorless solid; mp 117–119 °C; $R_f = 0.14$ (*n*-pentane/Et₂O, 1:1); $[\alpha]_D^{24}$ +74.9 (*c* = 0.5, benzene).

HPLC: Daicel Chiralpak AS, *n*-heptane/EtOH (7:3), 0.7 mL/min, λ = 254 nm, t_R (minor) = 13.3 min, t_R (major) = 15.9 min; 98% *ee*.

IR (ATR): 2953, 2322, 2087, 1892, 1641, 1547, 1384, 1217, 1176, 1051, 974, 841, 696 $\rm cm^{-1}.$

¹H NMR (600 MHz, CDCl₃): δ = 7.54 (d, J = 7.4 Hz, 2 H, ArH), 7.34 (t, J = 7.8 Hz, 2 H, ArH), 7.24 (t, J = 7.4 Hz, 1 H, ArH), 5.73 (d, J = 2.1 Hz, 1 H, OC=CH), 4.92 (dd, J = 13.2, 3.8 Hz, 1 H, CHHNO₂), 4.67 (dd, J = 13.2, 7.6 Hz, 1 H, CHHNO₂), 4.58 (m, 1 H, CHCH₂), 2.72–2.65 (m, 2 H, CH₂), 2.47–2.42 (m, 2 H, CH₂), 2.16 (qi, J = 6.4 Hz, 2 H, CH₂).

 ^{13}C NMR (151 MHz, CDCl₃): δ = 194.1 (C=O), 176.0 (Cq), 152.8 (Cq), 133.3 (Cq), 128.7 (ArC), 128.5 (ArC), 127.3 (ArC), 112.7 (Cq), 106.8 (OC=CH), 75.9 (CH_2NO_2), 41.7 (CHCH_2), 36.6 (CH_2), 23.4 (CH_2), 21.5 (CH_2).

MS (EI, 70 eV): m/z (%) = 286.3 (13, [M + H]⁺), 285.2 (2, [M]⁺), 239.3 (21, [M - NO₂]⁺), 225.2 (19, [M - CH₂NO₂]⁺).

HRMS (ESI⁺): m/z [M + Na]⁺ calcd for C₁₆H₁₅NO₄Na: 308.0893; found: 308.0893.

(*R*)-4-(Nitromethyl)-2-phenyl-6,7-dihydrocyclopenta[*b*]pyran-5(4*H*)-one (5b)

Compound **5b** was isolated after flash chromatography (*n*-pentane/Et₂O, 1:2); yield: 43 mg (63%); colorless solid; mp 153–155 °C; $R_f = 0.19 (n$ -pentane/Et₂O, 1:1); $[\alpha]_D^{24}$ –162.9 (c = 0.4, benzene).

HPLC: Daicel Chiralpak IC, *n*-heptane/EtOH (7:3), 0.7 mL/min, λ = 230 nm, t_R (minor) = 10.7 min, t_R (major) = 8.8 min; 94% *ee*.

IR (ATR): 3075, 2922, 2308, 2096, 1902, 1665, 1543, 1393, 1234, 991, 856, 764, 696 $\rm cm^{-1}.$

¹H NMR (600 MHz, C₆D₆): δ = 7.32 (m, 2 H, ArH), 7.04 (m, 3 H, ArH), 5.09 (d, J = 3.6 Hz, 1 H, OC=CH), 4.20 (m, 2 H, CH₂NO₂), 3.47 (m, 1 H, CHCH₂), 1.89 (ddd, J = 17.8, 7.4, 2.8 Hz, 1 H, CH), 1.81 (ddd, J = 17.9, 7.4, 2.5 Hz, 1 H, CH), 1.75 (m, 1 H, CH), 1.68 (m, 1 H, CH).

MS (EI, 70 eV): m/z (%) = 272.2 (3, [M + H]⁺), 225.2 (27, [M - NO₂]⁺), 211.2 (84, [M - CH₂NO₂]⁺).

HRMS (ESI⁺): m/z [M + Na]⁺ calcd for C₁₅H₁₃NO₄Na: 294.0737; found: 294.0732.

(*R*)-4-(Nitromethyl)-2-phenyl-4,8-dihydropyrano[3,4-*b*]pyran-5(6*H*)-one (5c)

Compound **5c** was isolated after flash chromatography (*n*-pen-tane/Et₂O, 1:1 to 1:2); yield: 22 mg (31%); colorless solid; mp 113–115 °C; $R_f = 0.43$ (*n*-pentane/Et₂O, 1:1); $[\alpha]_D^{24}$ –213.5 (*c* = 0.4, ben-zene).

HPLC: Daicel Chiralpak IA, *n*-heptane/*i*-PrOH (7:3), 0.7 mL/min, λ = 254 nm, t_R (minor) = 14.2 min, t_R (major) = 11.9 min; 90% *ee*.

IR (ATR): 2962, 1675, 1635, 1546, 1494, 1439, 1393, 1270, 1229, 1139, 1056, 994, 952, 873, 814, 764, 677 $\rm cm^{-1}.$

¹H NMR (600 MHz, C₆D₆): δ = 7.22–7.19 (m, 2 H, ArH), 7.05–7.02 (m, 3 H, ArH), 5.10 (d, *J* = 4.3 Hz, 1 H, OC=CH), 4.06 (dd, *J* = 11.7, 7.0 Hz, 1 H, CHHNO₂), 4.01 (dd, *J* = 11.7, 3.8 Hz, 1 H, CHHNO₂), 3.92 (d, *J* = 15.9 Hz, 1 H, CH₂), 3.75 (d, *J* = 16.2 Hz, 1 H, CH₂), 3.67–3.63 (m, 1 H, CHCH₂), 3.59 (dd, *J* = 15.9, 1.7 Hz, 1 H, CH₂), 3.52 (dd, *J* = 16.1, 1.4 Hz, 1 H, CH₂).

 ^{13}C NMR (151 MHz, C₆D₆): δ = 192.1 (C=O), 165.3 (C_q), 149.2 (C_q), 131.9 (C_q), 129.2 (ArC), 128.3 (ArC), 124.6 (ArC), 106.1 (C_q), 99.1 (OC=CH), 77.6 (CH₂NO₂), 71.1 (CH₂), 63.5 (CH₂), 28.4 (CHCH₂).

MS (EI, 70 eV): m/z (%) = 241.1 (17, $[M - NO_2]^+$), 227.1 (45, $[M - CH_2NO_2]^+$).

HRMS (ESI⁺): m/z [M + Na]⁺ calcd for C₁₅H₁₃NO₅Na: 310.0686; found: 310.0686.

(*R*)-1,3-Dimethyl-5-(nitromethyl)-7-phenyl-1,5-dihydro-2*H*-pyrano[2,3-*d*]pyrimidine-2,4(3*H*)-dione (5d)

Compound **5d** was isolated after flash chromatography [*n*-pen-tane/CH₂Cl₂ (1:4) to pure CH₂Cl₂]; yield: 77 mg (94%); bright yellow solid; mp 224–226 °C; R_f = 0.26 (CH₂Cl₂/Et₂O, 20:1); [α]_D²⁴ –144.5 (*c* = 0.4, CHCl₃).

HPLC: Daicel Chiralpak AS, *n*-heptane/EtOH (7:3), 1.0 mL/min, λ = 254 nm, t_R (minor) = 10.3 min, t_R (major) = 7.5 min; 88% *ee*.

IR (ATR): 2954, 2324, 2107, 1645, 1476, 1375, 1203, 1003, 753, 690 $\rm cm^{-1}.$

¹H NMR (600 MHz, CDCl₃): δ = 7.58–7.52 (m, 2 H, ArH), 7.45–7.41 (m, 3 H, ArH), 5.71 (d, J = 4.4 Hz, 1 H, OC=CH), 4.83–4.74 (m, 2 H, CH₂NO₂), 4.24 (dt, J = 6.1, 4.3 Hz, 1 H, CHCH₂), 3.54 (s, 3 H, CH₃), 3.39 (s, 3 H, CH₃).

 ^{13}C NMR (151 MHz, CDCl₃): δ = 162.0 (C=O), 154.3 (C=O), 150.5 (Cq), 149.7 (Cq), 131.2 (Cq), 130.0 (ArC), 128.8 (2 C, ArC), 124.8 (2 C, ArC), 99.2 (OC=CH), 84.0 (Cq), 77.9 (CH_2NO_2), 30.9 (CHCH_2), 29.2 (CH_3), 28.2 (CH_3).

MS (EI, 70 eV) m/z (%) = 283.1 (20, [M - NO₂]⁺), 269.0 (71, [M - CH₂NO₂]⁺).

HRMS (ESI⁺): m/z [M + Na]⁺ calcd for C₁₆H₁₅N₃O₅Na: 352.0904; found: 352.0894.

(*R*)-(*Z*)-2-Benzylidene-6-methyl-3-(nitromethyl)-3,5,6,7-tetrahydrobenzofuran-4(2*H*)-one (7a)

Compound **7a** was isolated after flash chromatography (*n*-pentane/Et₂O, 1:1 to 1:2); yield: 73 mg (98%); colorless solid; mp 175– 177 °C; R_f = 0.24 (*n*-pentane/Et₂O, 1:1); [α]_D²⁴ +85.5 (*c* = 0.5, MeOH). HPLC: Daicel Chiralpak IC, *n*-heptane/*i*-PrOH (7:3), 0.5 mL/min, $\lambda = 254$ nm, t_R (minor) 1 = 27.5 min, t_R (major) 1 = 16.6 min; t_R (minor) 2 = 29.9 min, t_R (major) 2 = 18.2 min; 94% *ee*, dr = 1:1.

IR (ATR): 2951, 2925, 2871, 2153, 2086, 2048, 1989, 1735, 1691, 1650, 1549, 1389, 1288, 1205, 1163, 1099, 1016, 973, 914, 873, 847, 811, 752, 694 $\rm cm^{-1}.$

¹H NMR (600 MHz, C₆D₆): δ = 7.51 (m, 4 H, ArH, ArH_{Diast.}), 7.18 (m, 4 H, Ar-H, ArH_{Diast.}), 7.03 (m, 2 H, ArH, ArH_{Diast.}), 5.44 (d, *J* = 2.2 Hz, 1 H, OC=CH), 5.42 (d, *J* = 2.2 Hz, 1 H, OC=CH_{Diast.}), 4.34 (dd, *J* = 13.1, 6.4 Hz, 1 H, CH₂NO₂), 4.28 (dd, *J* = 13.0, 6.6 Hz, 1 H, CH₂NO₂_{Diast.}), 4.22 (ddd, *J* = 13.0, 7.9, 3.8 Hz, 2 H, CH₂NO₂, CH₂NO₂_{Diast.}), 3.94 (m, 2 H, CHCH₂, CHCH₂_{Diast.}), 2.07 (m, 4 H, CH₂, CH₂_{Diast.}), 1.65 (m, 4 H, CH₂, CHCH₃_{Diast.}), 0.50 (d, *J* = 6.6 Hz, 3 H, CH₃), 0.46 (d, *J* = 6.3 Hz, 3 H, CH₃_{Diast.}).

MS (EI, 70 eV): m/z (%) = 300.0 (3, [M + H]⁺), 253.1 (19, [M - NO₂]⁺), 239.0 (11, [M - CH₂NO₂]⁺).

HRMS (ESI⁺): m/z [M + Na]⁺ calcd for C₁₇H₁₇NO₄Na: 322.1050; found: 322.1049.

(*R*)-(*Z*)-2-Benzylidene-6-isopropyl-3-(nitromethyl)-3,5,6,7-tetrahydrobenzofuran-4(2*H*)-one (7b)

Compound **7b** was isolated after flash chromatography (*n*-pentane/Et₂O, 1:1 to 1:2); yield: 67 mg (82%); colorless solid; mp 141– 143 °C; $R_f = 0.33$ (*n*-pentane/Et₂O, 1:1); $[\alpha]_D^{24}$ +52.7 (*c* = 0.5, benzene).

HPLC: Daicel Chiralpak IA, *n*-heptane/EtOH (97:3), 1.0 mL/min, λ = 254 nm, t_R (minor) 1 = 41.7 min, t_R (major) 1 = 63.8 min; t_R (minor) 2 = 50.4 min, t_R (major) 2 = 58.3 min; 93% *ee*, dr = 1:1.

IR (ATR): 3352, 2956, 2325, 2096, 1649, 1546, 1381, 1100, 958, 842, 756, 687 cm⁻¹.

¹H NMR (600 MHz, C₆D₆): δ = 7.53 (m, 4 H, ArH, ArH _{Diast}.), 7.20 (m, 4 H, ArH, ArH, ArH_{Diast}.), 7.05 (m, 2 H, ArH, ArH_{Diast}.), 5.49 (d, *J* = 2.1 Hz, 1 H, OC=CH), 5.47 (d, *J* = 2.1 Hz, 1 H, OC=CH_{Diast}.), 4.35 (m, 1 H, CHHNO₂), 4.30 (m, 3 H, CH₂NO₂, CH₂NO₂ _{Diast}.), 4.05 (m, 1 H, CHCH₂), 4.01 (m, 1 H, CHCH₂ _{Diast}.), 2.17 (m, 2 H, CHH, CHH_{Diast}.), 1.79 (m, 3 H, CHH, CHH_{Diast}.), 1.59 [m, 2 H, CHCH(CH₃)₂, CHCH(CH₃)₂ _{Diast}.], 1.43 (m, 2 H, CHH, CHH_{Diast}.), 1.31 (m, 1 H, CHH), 1.01 [m, 2 H, CH(CH₃)₂, CH(CH₃)₂ _{Diast}.], 0.48 [m, 12 H, CH(CH₃)₂, CH(CH₃)₂ _{Diast}.].

 13 C NMR (151 MHz, C₆D₆): δ = 192.1 (C=O), 192.1 (C=O $_{\rm Diast.}$), 174.7 (C_q), 174.7 (C_q)_{Diast.}), 153.4 (C_q), 153.4 (C_q)_{Diast.}), 133.9 (C_q), 133.9 (C_q)_{Diast.}), 128.7 (4 C, ArC, ArC_{Diast.}), 128.4 (4 C, ArC, ArC_{Diast.}), 127.1 (2 C, ArC, ArC $_{\rm Diast.}$), 112.2 (C_q), 112.0 (C_q _{Diast.}), 106.1 (OC=CH), 106.0 (OC=CH_{Diast.}), 75.8 (CH₂NO₂), 75.1 (CH₂NO₂ _{Diast.}), 41.9 (CHCH₂), 41.9 (CHCH₂ _{Diast.}), 40.7 (CH₂), 40.4 (CH₂ _{Diast.}), 40.3 [CHCH(CH₃)₂], 40.2 [CHCH(CH₃)₂] _{Diast.}], 31.4 [CH(CH₃)₂], 31.3 [CH(CH₃)₂ _{Diast.}], 26.1 (CH₂), 25.9 (CH₂ _{Diast.}), 19.3 (CH₃), 19.1 (CH₃ _{Diast.}), 18.8 (CH₃), 18.7 (CH₃ _{Diast.}).

MS (EI⁺, 70 eV): m/z (%) = 328.1 (3, [M + H]⁺), 327.1 (1, [M]⁺), 281.1 (33, [M - NO₂]⁺), 267.1 (8, [M - CH₂NO₂]⁺).

HRMS (ESI⁺): m/z [M + Na]⁺ calcd for C₁₉H₂₁NO₄Na: 350.1363; found: 350.1362.



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(*R*)-(*Z*)-2-Benzylidene-3-(nitromethyl)-6-phenyl-3,5,6,7-tetrahyd-robenzofuran-4(2*H*)-one (7c)

Compound **7c** was isolated after flash chromatography (*n*-pentane/Et₂O, 1:1 to 1:2); yield: 85 mg (94%); colorless solid; mp 128– 130 °C; $R_f = 0.24$ (*n*-pentane/Et₂O, 1:1); $[\alpha]_D^{24}$ +64.8 (*c* = 0.5, benzene).

HPLC: Daicel Chiralpak AD, *n*-heptane/EtOH (1:1), 1.0 mL/min, $\lambda = 254$ nm, t_R (minor) 1 = 9.2 min, t_R (major) 1 = 17.1 min; t_R (minor) 2 = 11.0 min, t_R (major) 2 = 13.9 min; 94% *ee*, dr = 1:1.

IR (ATR): 3027, 2305, 2102, 1910, 1735, 1647, 1546, 1397, 1204, 1002, 909, 853, 753, 694 $\rm cm^{-1}.$

¹H NMR (600 MHz, C₆D₆): δ = 7.51 (m, 4 H, ArH, ArH_{Diast.}), 7.19 (m, 4 H, ArH, ArH_{Diast.}), 7.04 (m, 8 H, ArH, _{Diast.}), 6.72 (m, 4 H, ArH, ArH_{Diast.}), 5.48 (s, 2 H, OC=CH, OC=CH_{Diast.}), 4.32 (m, 4 H, CH₂NO₂, CH₂NO₂ _{Diast.}), 4.06 (m, 1 H, CHCH₂), 4.00 (m, 1 H, CHCH₂ _{Diast.}), 2.83 (m, 1 H, CHC₆H₅), 2.70 (m, 1 H, CHC₆H₅ _{Diast.}), 2.36 (m, 2 H, CH₂ _{Diast.}), 2.23 (dd, *J* = 16.2, 12.5 Hz, 1 H, CHH), 2.11 (dd, *J* = 16.2, 12.9 Hz, 1 H, CHH), 1.92 (m, 4 H, CH₂, CH₂ _{Diast.}).

 $\label{eq:stars} \begin{array}{l} {}^{13}\text{C NMR (151 MHz, C_6D_6): } \delta = 191.0 (C=O), 190.9 (C=O_{\text{Diast.}}), 173.8 (C_q), \\ 173.8 (C_q \, \text{Diast.}), 153.3 (C_q), 153.2 (C_q \, \text{Diast.}), 142.0 (C_q), 142.0 (C_q \, \text{Diast.}), \\ 133.8 (C_q), 133.8 (C_q \, \text{Diast.}), 128.7 (4 C, ArC, ArC_{\text{Diast.}}), 128.5 (4 C, ArC, ArC_{\text{Diast.}}), 128.4 (4 C, ArC, ArC_{\text{Diast.}}), 127.1 (2 C, ArC, ArC_{\text{Diast.}}), 127.0 (2 C, ArC, ArC_{\text{Diast.}}), 126.6 (4 C, ArC, ArC_{\text{Diast.}}), 112.3 (C_q), 112.2 (C_q \, \text{Diast.}), 106.3 (OC=CH_{\text{Diast.}}), 75.7 (CH_2NO_2), 75.0 (CH_2NO_2 \, \text{Diast.}), 43.7 (CH_2), 43.6 (CH_2 \, \text{Diast.}), 41.9 (CHCH_2), 41.8 (CHCH_2 \, \text{Diast.}), 39.7 (CHPh), \\ 39.6 (CHPh_{\text{Diast.}}), 30.1 (CH_2), 30.0 (CH_2 \, \text{Diast.}). \end{array}$

MS (El⁺, 70 eV): m/z (%) = 361.1 (1, [M + H]⁺), 315.1 (38, [M - NO₂]⁺), 301.1 (7, [M - CH₂NO₂]⁺).

HRMS (ESI⁺): m/z [M + Na]⁺ calcd for C₂₂H₁₉NO₄Na: 384.1206; found: 384.1207.

(*R*)-(*Z*)-2-Benzylidene-6-(furan-2-yl)-3-(nitromethyl)-3,5,6,7-tet-rahydrobenzofuran-4(2*H*)-one (7d)

Compound **7d** was isolated after flash chromatography (*n*-pentane/Et₂O, 1:1); yield: 86 mg (98%); colorless solid; mp 143–145 °C; $R_f = 0.21 (n$ -pentane/Et₂O, 1:1); $[\alpha]_D^{24}$ +64.8 (c = 0.4, MeOH).

SFC: Daicel Chiralcel OJ-H, CO₂/MeCN (8:2), 4.0 mL/min, λ = 222 nm, t_R (minor) 1 = 3.9 min, t_R (major) 1 = 5.2 min; t_R (minor) 2 = 7.1 min, t_R (major) 2 = 9.7 min; 99% *ee*, dr = 1:1.

IR (ATR): 2914, 2327, 2098, 1647, 1547, 1393, 1201, 1009, 849, 752 $\rm cm^{-1}.$

¹H NMR (600 MHz, $C_{6}D_{6}$): δ = 7.47 (t, *J* = 6.9 Hz, 4 H, ArH, ArH_{Diast}.), 7.17 (m, 4 H, ArH, ArH_{Diast}.), 7.03 (m, 2 H, ArH, ArH_{Diast}.), 6.96–6.93 (m, 2 H, OCH, OCH_{Diast}.), 5.97 (ddd, *J* = 6.6, 3.2, 1.9 Hz, 2 H, ArH, ArH_{Diast}.), 5.65 (d, *J* = 3.2 Hz, 2 H, ArH, ArH_{Diast}.), 5.44 (d, *J* = 2.2 Hz, 1 H, OC=CH), 5.41 (d, *J* = 2.2 Hz, 1 H, OC=CH_{Diast}.), 4.25 (m, 2 H, CHHNO₂, CHHNO₂ Diast.), 4.17 (m, 2 H, CHHNO₂, CHHNO₂ Diast.), 4.01 (m, 1 H, CHCH₂), 3.89 (m, 1 H, CHCH₂ Diast.), 2.21 (m, 2 H, CH₂ Diast.), 2.07 (m, 4 H, CH₂, CH₂ Diast.).

¹³C NMR (151 MHz, C_6D_6): δ = 190.2 (2 C, C=O, C=O_{Diast.}), 172.9 (C_q), 172.8 (C_{q Diast.}), 155.1 (C_q), 155.0 (C_{q Diast.}), 153.1 (C_q), 153.0 (C_{q Diast.}), 141.4 (2 C, OCH_{furanyl}, OCH_{furanyl}, Diast.), 133.7 (C_q), 133.7 (C_{q Diast.}), 128.7 (4 C, ArC, ArC_{Diast.}), 128.3 (4 C, ArC, ArC_{Diast.}), 127.1 (2 C, ArC, ArC_{Diast.}), 112.3 (C_q), 112.2 (C_{q Diast.}), 110.1 (CH_{furanyl}), 110.1 (CH_{furanyl}, Diast.), 106.3 (OC=CH), 106.3 (OC=CO _{Diast.}), 104.9 (CH_{furanyl}), 104.8 (CH_{furanyl}, Diast.), 75.4 (CH₂NO₂), 75.0 (CH₂NO₂ _{Diast.}), 41.8 (CHCH₂), 41.7 (CHCH₂ _{Diast.}), 27.4 (2 C, CH₂, 40.7 (CH₂ _{Diast.}), 33.0 (CH_{furanyl}), 32.8 (CH_{furanyl}, Diast.), 27.4 (2 C, CH₂, CH₂ _{Diast.}). MS (EI, 70 eV): m/z (%) = 351.1 (1, [M]⁺), 305.1 (44, [M - NO₂]⁺), 291.1 (7, [M - CH₂NO₂]⁺).

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HRMS (ESI⁺): m/z [M + Na]⁺ calcd for C₂₀H₁₇NO₅Na: 374.0999; found: 374.0997.

Acknowledgment

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Supporting Information

Supporting information for this article is available online at http://dx.doi.org/10.1055/s-0035-1561468.

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