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Synthesis of non-racemic dihydrofurans via Ni(II)-catalyzed asymmetric Michael addition

Dmitry S. Nikerov [a, *], Maria A. Ashatkina [a], Vadim A. Shiryaev [a], Ilya M. Tkachenko [a], Victor B. Rybakov [b], Alexander N. Reznikov [a], Yuri N. Klimochkin [a]

[a] Department of Organic Chemistry, Samara State Technical University, Molodogvardeyskaya Str., 244, 443100, Samara, Russian Federation
[b] Department of Chemistry, Moscow State University, Leninskie Gory, 1, 119991, Moscow, Russian Federation

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ABSTRACT

A highly efficient strategy for the enantio- and diastereoselective synthesis of 4,5-dihydrofuran derivatives was developed. Addition of carbonyl compounds which contain bulky adamantyl substituent and β-keto or phosphonate group to conjugated α-bromonitroolefins in the presence of a chiral Ni(II) complex gave corresponding non-racemic products of Michael reaction. These adducts were used for intramolecular cyclization leading to *trans*-4,5-dihydrofurans with two stereocenters. Resulting *trans*-4,5-dihydrofurans were obtained in good yields with moderate to high enantioselectivities (84–99% *ee*) and excellent diastereoselectivities (*dr* >99%).

1. Introduction

Dihydrofurans and their derivatives are often key building blocks in organic syntheses. Such heterocycle moiety is present in numerous natural products, agrochemicals and pharmaceuticals: cheimonophyllal (nematicidal activity) [1], jiadifenlactone A (antiviral activity) [2], colletofragarones A1 (germination self-inhibitors from the fungus) [3] and inoscavin A (antioxidative activity) [4] (Fig. 1).

Non-racemic dihydrofurans represents important subunits of different biologically active compounds and precursors for the preparation of some biologically active tetrahydrofurans. For example, deoxy-C-nucleosides (potential therapeutic agents and Biochemical probes) [5], virgatusin (antifungal) [6] and nymphone (cytotoxin) [6a,7] are prepared directly from non-racemic dihydrofurans. Some xyloketals, exhibiting a broad range of biological activity (Fig. 2) could be obtained from dihydrofurans [8].

Dihydrofurans readily react with electrophiles [9] and nucleophiles [10]. Thus, dihydrofurans represents an excellent synthetic precursors for broad range of useful compounds with diverse pharmacological properties.

The pioneer work of Dauzonne and co-workers for the one-pot preparation of racemic dihydrofurans includes the Michael reaction as a key stage [11]. Asymmetric synthesis of such dihydrofurans has attracted extensive attention. A number of synthetic strategies have been developed in recent years, including rearrangement [12], cycloaddition [13] and modified Feist–Bénary reaction [14]. The application of these methods is limited by their relatively narrow substrate scope and comparatively poor enantioselectivity. It is highly desirable to develop an efficient pathway to chiral dihydrofurans. Several non-racemic 4,5-dihydrofurans could be obtained using organocatalysis [6a,15]. However this method requires the use of a large amount of organocatalyst (≥10 mol %). In addition, organocatalysts, such as cinchona alkaloids-derived thioureas and squaramides are expensive and have low synthetical access which reduces the practical value of these methods. Therefore, a synthetically available and inexpensive nickel complex **3,** successfully applied in the construction of chiral substrates by the Michael reaction [16], was used in this work.

The presence of the dihydrofuran subunits and lipophilic adamantate scaffold could be presubposition to some interesting biological properties [17]. This will allow the use of these chemical

* Corresponding author.
E-mail address: d.nikerov@mail.ru (D.S. Nikerov).

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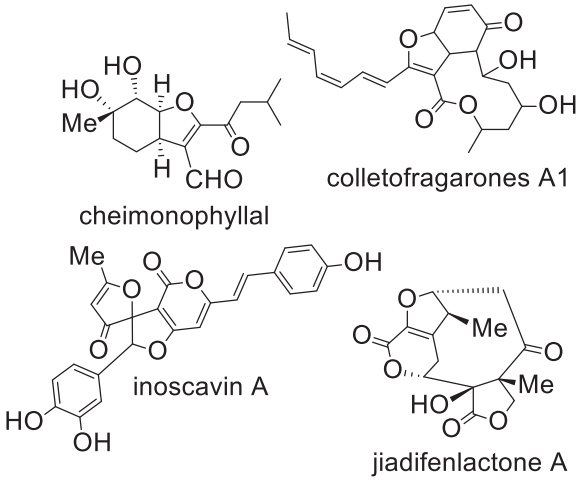


Fig. 1. Biologically active substances based on the dihydrofurans.

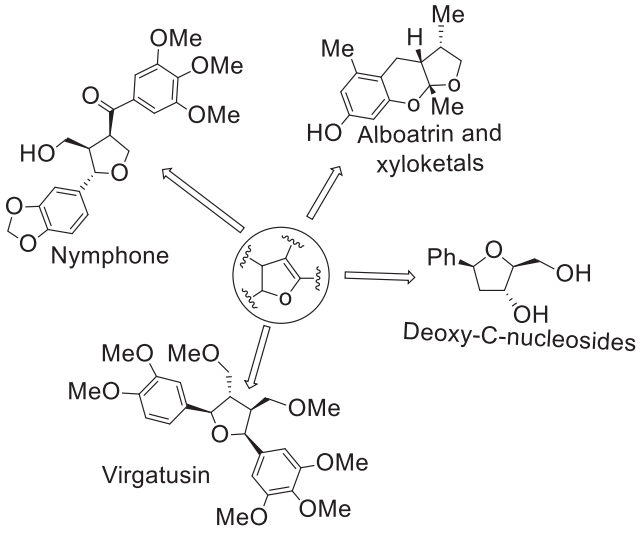
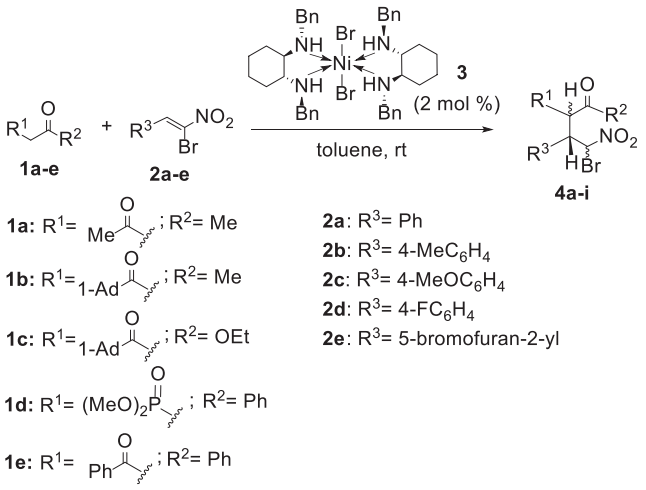


Fig. 2. Some examples of biologically active compounds derived from dihydrofurans.

objects in the drug development. The use of atom-efficient methods of asymmetric catalysis for the synthesis of such compounds is extremely relevant. The transition metal catalyzed [16] or organocatalyzed [18] asymmetric Michael reaction is one of the most important synthetic tools for the asymmetric formation of a C–C bond. A possibility to create one stereocenter with a given configuration during the catalytic process could be the starting point of complex enantioselective syntheses of compounds with several new stereocenters. Our work reports the synthesis of non-racemic adamantyl 4,5-dihydrofurans via Ni(II)-catalyzed asymmetric Michael addition of β-diketone, β-ketoester or β-keto phosphonate to conjugated α-bromonitroolefins, where bromide is a good leaving group which promote subsequent intramolecular cyclization.

2. Results and discussion

The Michael addition of 1,3-dicarbonyl compounds to α-bromonitroolefins was carried out in the presence of 2 mol % Ni(II) complex **3** (Scheme 1). This complex was previously successfully



Scheme 1. Synthesis of chiral precursors of 4,5-dihydrofurans by the asymmetric Michael reaction catalyzed by a Ni(II)-complex.

used in the asymmetric addition of 1,3-dicarbonyl compounds [19], β-keto phosphonates [16c,20] and β-ketosulfones [16d] to nitroolefins. In a number of cases, these reactions proceeded enantio- and diastereoselectively. The reaction with α-bromonitroolefins in most cases led to the formation of four diastereomers according to ^{1}H and ^{31}P NMR (Table 1). However, in some experiments formation of only two diastereoisomers was observed. Subsequent recrystallization of Michael adducts led to some diastereomeric enrichment.

The stereocenter at 3 position of the resulting nitroketones **4a-i** can be attributed to the (*S*)-configuration according to absolute configuration of the previously reported cyclization product **5a** [15e].

At the next step the obtained adducts **4a-i** were subjected to cyclization with the formation of 4,5-dihydrofurans **5a-i**. Initially, the cyclization of 3-(2-bromo-2-nitro-1-phenylethyl) pentane-2,4-dione (**4a**) was chosen as a model reaction to find the optimal reaction conditions. The cyclization product **5a** was previously obtained using reaction conditions for one-pot Michael addition/I_2-mediated cyclization sequence [15e]. The cyclization of compound **4a** in the presence of potassium carbonate (1.0 equiv.) gave 4,5-dihydrofuran **5a** in 85% yield. The configuration **5a** (4*R*,5*R*) is the same as of 4,5-dihydrofuran obtained by Zhang et al. [15e].

However, the synthesis of 4,5-dihydrofuran **5b** from adamantyl containing compound **4b** wasn't successful when the same

Table 1
The yields of the products **4a-i** and their diastereomeric ratio.

Entry	1	2	Product 4	Yield[b] of 4, %	*dr* of 4[c]
1	**1a**	**2a**	**4a**	95	1.1:1.0
2	**1b**	**2a**	**4b**	56	5.0:1.0
3	**1b**	**2b**	**4c**	70	1.6:1.0
4	**1b**	**2c**	**4d**	71	3.7:2.4:1.1:1.0
5	**1b**	**2d**	**4e**	64	4.1:3.9:2.1:1.0
6	**1c**	**2a**	**4f**	40	1.6:1.0
7	**1d**	**2a**	**4g**	58	23:22:3:1
8	**1e**	**2a**	**4h**	58	1.3:1.0
9	**1b**	**2e**	**4i**	40	1.5:1.0

[a]Reaction conditions: carbonyl compounds **1a-e** (2.2 mmol), α-bromonitroolefins **2a-e** (2.2 mmol), toluene (2 mL), Ni(II) complex **3** (0.044 mmol), rt, 24 h.
[b] After recrystallization from MeOH (entries 2,3,6), toluene (entry 8) or purification by column chromatography on silica gel (eluent CCl_4, entries 1,4,5,7,9).
[c] Determined by ^{1}H NMR.

conditions were used. For this reason, further optimization of the cyclization was required for adamantyl Michael adducts (Table 2). The cleavage of β-diketone moiety was observed while using aqueous NaOH leading to **6** (entry 4). When DMAP was used as a base in acetonitrile cyclization product **5b** was formed after 24 h in 74% yield.

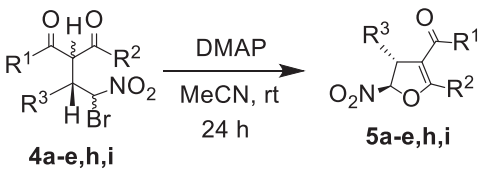
The structure **5b** was confirmed by ^{1}H, ^{13}C NMR, NOESY, HMQC and HMBC spectra. The vicinal spin-spin coupling constants of two methine protons compound **5b** is 1.2 Hz. Vicinal coupling constants of two methine protons in *cis*-dihydrofuran are J_{cis} 7–10 Hz [21], while in *trans*-dihydrofurans vicinal coupling constants are J_{trans} 2.5–7.5 Hz [22]. In the NOESY spectrum, there are no cross peaks between H-4 and H-5 of the dihydrofuran ring. These facts also prove the *trans* configuration of substituents at the 4 and 5 positions of the dihydrofuran ring.

Non-racemic 4,5-dihydrofurans **5a-e,h,i** were obtained using optimized reaction conditions (Scheme 2). Compounds **5a-e,h,i** were obtained as *trans*-isomer in 50–85% yields and 84–99% *ee* (Table 3). The vicinal spin-spin coupling constants for the compounds **5a-e,h,i** are J_{trans} 1.0–2.0 Hz between H-4 and H-5 of the dihydrofuran ring. The configuration of *trans*-4,5-dihydrofurans **5a-e,h,i** was suggested analogically to **5b**.

It is noteworthy that reaction of nitroketoester **4f** leads to 4,5-dihydrofuran **5f**, despite steric hindrance of adamantly group. Compound **5f** was obtained as *trans*-isomer in 60% yield and >99% *ee* (Scheme 3). The vicinal spin-spin coupling constants for the compound **5f** between H-4 and H-5 of the dihydrofuran ring is J_{trans} 1.2 Hz.

Unfortunately, we were unable to grow a single crystal of phosphorylated dihydrofuran **5g**, therefore we could't establish the absolute configuration of this compound using X-ray structural analysis. However, we succeed in growing a single crystal of the compound **5f** that was suitable for X-ray determination of the relative configuration of 4,5-dihydrofuran **5f**. An X-ray diffraction study of the 4,5-dihydrofuran **5f** showed its *trans*-configuration (Fig. 3) [23]. The relative configurations of dihydrofurans **5a-i** were assigned by analogy.

Therefore, to determine the absolute configuration of the compound **5f**, we selected a method that is based on correlation of computed specific rotation with experimental values. This method allows the absolute configuration of molecules having [α] more than 25° to be correlated [24]. The calculations were performed for the *trans*-isomer of dihydrofuran (4*R*,5*R*)-**5f**. The conformational analysis showed high rigidity of this molecule. The optimization of geometry and calculation of specific rotation were performed using the 6–311++G(2d,2p)/B3LYP basis set with solvation model IEFPCM in chloroform. The obtained results showed a correlation of the sign of specific rotation and the behavior of ORD curve of



5a: R^1= Me; R^2= Me; R^3= Ph
5b: R^1= 1-Ad; R^2= Me; R^3= Ph
5c: R^1= 1-Ad; R^2= Me; R^3= 4-MeC_6H_4
5d: R^1= 1-Ad; R^2= Me; R^3= 4-$MeOC_6H_4$
5e: R^1= 1-Ad; R^2= Me; R^3= 4-FC_6H_4
5h: R^1= Ph; R^2= Ph; R^3= Ph
5i: R^1= 1-Ad; R^2= Me; R^3= 5-bromofuran-2-yl

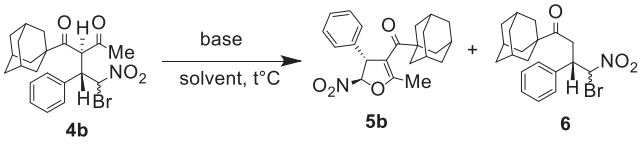
Scheme 2. Synthesis of non-racemic 4,5-dihydrofurans by the reaction of intramolecular cyclization from Michael adducts.

Table 3
The yields of the products **5a-e,h,i** and their diastereomeric ratio, enantiomeric excesses[a].

Entry	Product	Yield, %	dr[b]	*ee*[d]
1	**5a**	56	1/-	94
2	**5b**	77	1/-	99
3	**5c**	57	1/-[c]	89
4	**5d**	61	1/-[c]	92
5	**5e**	56	1/-	90
6	**5h**	85	1/-	96
7	**5i**	50	9.0:1.0	84[e]

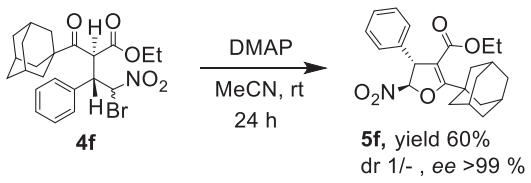
[a] Reaction conditions: compounds **4a-e,h,i** (0.94 mmol), DMAP (0.94 mmol), MeCN (5 mL), rt, 24 h.
[b] Determined by ^{1}H NMR.
[c] Two diastereomers according to HPLC analysis. The second diastereomer is formed by epimerization in a chromatographic column.
[d] *ee* of products **5a-e,h,i** was determined by HPLC; [e]*ee* of major diastereomer **5i**.

Table 2
Optimization of the conditions of intramolecular cyclization reaction with substance **4b**[a].



Entry	Base	Phase- transfer catalyst[c]	Solvent	t°C	time, h	Yield of 5b, %	Yield of 6, %
1	K_2CO_3	–	THF	20	24	–	–
2	KOH	18-crown-6	benzene	20	36	–	–
2	NaOAc	TBAB	H_2O	70	6	–	–
3	K_2CO_3	KI/18-crown-6	MeCN	20	5	–	–
4	NaOH[b]	–	H_2O	20	6	–	50[d]
5	DMAP	–	CH_2Cl_2	20	72	74[d]	–
6	DMAP	–	MeCN	20	24	74[d]	–

[a] Reaction conditions: compound **4b** (0.94 mmol), base (0.94 mmol), solvent (5 mL).
[b] NaOH (2.10 mmol).
[c] Phase-transfer catalyst (0.094 mmol).
[d] After recrystallization from MeOH.



Scheme 3. Synthesis of non-racemic 4,5-dihydrofuran **5f** by the reaction of intramolecular cyclization from nitroketoester **4f**.

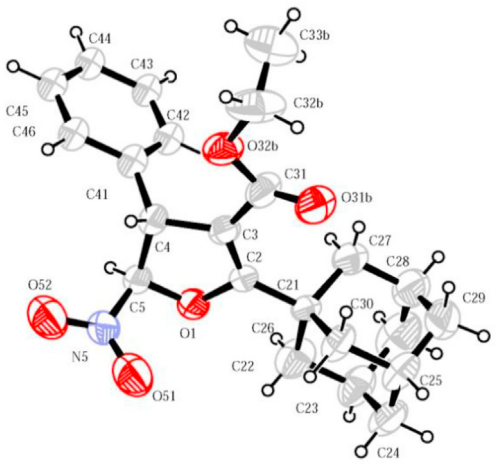
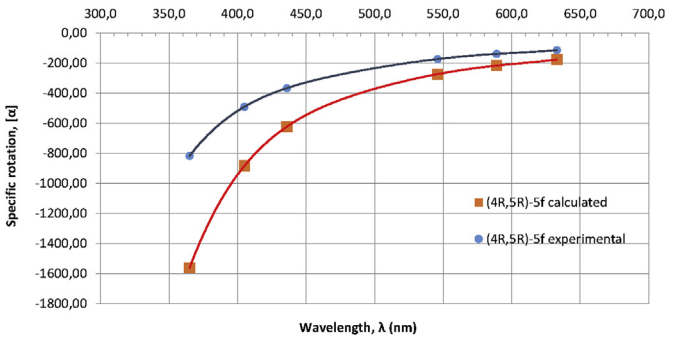


Fig. 3. ORTEP diagram of (4*R*,5*R*)-**5f**.

(4*R*,5*R*)-**5f** with experimental values that allow this configuration to be confirmed (Table 4). Therefore, the absolute configuration of the compound **5f** is (4*R*,5*R*). The absolute configurations of the other dihydrofurans **5a-i** are similar.

The cyclization of adduct **4g** using optimal reaction conditions leads to formation of non-racemic phosphoryl-substituted 4,5-dihydrofuran **5g** in 90% yield after 24 h (Table 4, entry 1) despite the poor solubility of phosphonate **4g** in acetonitrile. Other combinations of bases and solvents leads to significant decrease in yield

Table 4
Experimental and calculated values for the specific rotation of (4*R*,5*R*)-**5f**.



Wavelength, λ (nm)	(4*R*,5*R*)-5f $[\alpha]^{20}$ exp.	(4*R*,5*R*)-5f $[\alpha]^{20}$ calc.
365	−817.40	−1559.96
405	−491.80	−883.60
436	−368.00	−623.47
546	−174.90	−274.92
589	−140.50	−218.28
633	−115.70	−178.16

(Table 5, entries 2–4). The structure **5g** was confirmed by ^{1}H, ^{13}C NMR, NOESY, HMQC and HMBC spectra. The vicinal spin-spin coupling constants of two methine protons compound **5g** is 1.6 Hz. In the NOESY spectrum, there are no cross peaks between H-4 and H-5 of the dihydrofuran ring, indicating the *trans*-isomer of dihydrofuran **5g**.

To improve the method of obtaining 4,5-dihydrofurans, we have developed a Ni-catalyzed one-pot procedure, with a base additive, avoiding the isolation of the Michael adduct (Scheme 4). The application of this procedure to simple starting compound, such as acetylacetone and 1,3-diphenylpropane-1,3-dione, allows to obtain 4,5-dihydrofurans **5a,h**. Unfortunately, shift to more complex adamantyl-containing 1,3-diketones and, especially, ketophosphonates lead to the formation of numerous byproducts. Therefore, in the case of sterically hindered substrates there is needed to isolate the Michael adducts before their cyclization to 4,5-dihydrofurans.

Pyrroles are an important class of compounds in the pharmaceutical [25] and material sciences [26]. In the course of our study, polysubstituted pyrrole **7** was obtained in 90% yield from dihydrofuran **5a** by reduction with H_2 on Pd/C (10%) catalyst (Scheme 5).

3. Conclusions

In summary, a convenient protocol for the synthesis of non-racemic *trans*-4,5-dihydrofurans was developed. Synthetic strategy consist of asymmetric Michael addition in the presence of readily available Ni(II) complex and subsequent intramolecular cyclization of enantioenriched adducts. The applicability of the method was shown through the synthesis of novel enantioenriched adamantyl-substituted dihydrofurans using the Ni(II) complex as a catalyst at the key step. DMAP-promoted cyclization of intermediate bromonitroketones leads to formation of *trans*-isomers in good yields and moderate to high enantioselectivities (84–99% *ee*). The obtained 4,5-dihydrofurans also could be used as precursors of aromatic pyrroles and furans.

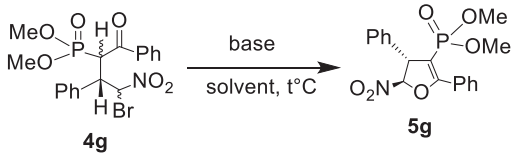
4. Experimental section

4.1. General methods

All commercially obtained reagents were used without further purification. All solvents were distilled prior to use. α-Bromonitroalkenes [27], dimethyl (2-oxo-2-phenylethyl)phosphonate [16c], 1-(adamantan-1-yl)butane-1,3-dione [28], ethyl 3-(adamantan-1-yl)-3-oxopropanoate [29] were obtained according to reported procedures. Bis[(1*R*,2*R*)-*N*,*N*`-dibenzylcyclohexane-1,2-diamine-κ$^2$*N*,*N*`](dibromo)nickel was obtained according to a reported procedure [19a]. Melting points were measured with an OptiMelt automated melting point system. All the reactions were monitored by TLC, performed on precoated silica gel plates (Sorbfil); (display with iodine vapour). ^{1}H, ^{13}C, ^{19}F and ^{31}P NMR spectra were recorded with a JEOL JNM-ECX400 spectrometer at 399.78, 100.53, 376.17 and 161.83 MHz, respectively, in $CDCl_3$ solution. Elemental analysis was performed with an EuroVector EA-3000 analyzer. Optical rotations were measured with Rudolph Research Analytical (Autopol V Plus Automatic Polarimeter). The enantiomeric purity of the products was determined by HPLC analysis on Shimadzu Prominence LC-20AD (Spd-20auv vis detector, Cto-20a column over, Dgu-20a degasing unit) equipped with a chiral stationary phase column (ChiralPAK AD-3) with hexane/2-propanol as eluent. Column chromatography was performed on Silica gel 60, Merck (230–400 mesh). The X-ray studies were fulfilled using a STOE STADI VARI PILATUS-100K diffractometer.

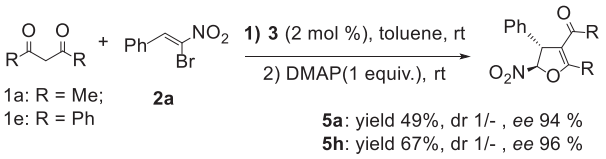
The initial modelling of structure was performed with Avogadro 1.1.1 [30] in force field MMFF94s, optimization of structure and

Table 5
Optimization of the conditions of intramolecular cyclization reaction with substance **4g**[a].

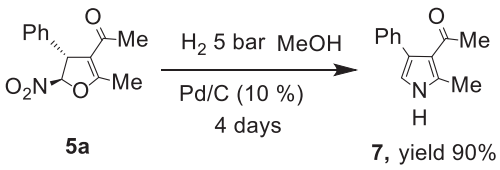


Entry	Base	Phase- transfer catalyst[b]	Solvent	t°C	time, h	Yield[c] of 5g, %	dr[d]	*ee*[e]
1	DMAP	–	MeCN	20	24	90	1/-	98
2	KOH	18-crown-6	benzene:toluene 2:1	0	36	40	1/-	98
3	KOH	18-crown-6	benzene	20	36	51	1/-	98
4	NaOAc	TBAB	H_2O	70	7	42	1/-	97

[a] Reaction conditions: compound **4g** (1.10 mmol), base (1.10 mmol), solvent (9 mL).
[b] Phase-transfer catalyst (0.11 mmol).
[c] After purification by column chromatography on silica gel (eluent – petroleum ether: ethyl acetate 5:1).
[d] determined by ^{1}H NMR.
[e] *ee* of product **5g** was determined by HPLC.



Scheme 4. One-Pot synthesis of non-racemic 4,5-dihydrofurans **5a,h**.



Scheme 5. Synthesis of pyrrole **7** by reduction from 4,5-dihydrofuran **5a**.

optical rotation calculations were performed with Gaussian G.09 Rev A.02 [31] in 6–311++G(2d,2p) basis set with solvation model IEFPCM in chloroform.

4.2. General procedure for the preparation of adducts Michael

A mixture of β-diketone **1a,b,e**, β-ketoester **1c** or β-keto phosphonate **1d** (2.2 mmol), α-bromonitroalkene **2a-e** (2.2 mmol) and bis[(1*R*,2*R*)-*N*,*N*`-dibenzylcyclohexane-1,2-diamine-κ$^2$*N*,*N*`](dibromo)nickel (**3**) (0.044 mmol) in 2 mL of toluene was stirred at rt for 24 h. The formed crystalline compounds **4b**,**c**,**f** were filtered and recrystallized from MeOH, and the crystalline compound **4h** filtered and recrystallized from toluene. If no precipitate was formed, then the solvent was distilled off under reduced pressure, and the compounds **4a**,**d**,**e**,**g**,**i** were purified by column chromatography on silica gel (eluent CCl_4).

4.2.1. 3-[(1S)-2-Bromo-2-nitro-1-phenylethyl]pentane-2,4-dione (*4a*)

Yield: 0.68 g (95%), colorless oil [mixture of diastereomers *dr* 1:1], $[\alpha]_D^{20} = +126.1$ (*c* 1.0, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.89 (s, 3H - first diastereomer, Me), 1.91 (s, 3H - first diastereomer, Me), 2.31 (s, 3H – second diastereomer, Me), 2.32 (s, 3H – second diastereomer, Me), 4.35 (dd, $^3J_{HH}$ = 10.4, 5.6 Hz, 1H – first diastereomer, CHPh), 4.55–4.66 (m, 3H, CHC(O), CHPh), 6.39 (d, $^3J_{HH}$ = 5.6 Hz, 1H – first diastereomer, CHBr), 6.52 (d, $^3J_{HH}$ = 5.6 Hz, 1H – second diastereomer, CHBr), 7.12–7.31 (m, 5H – first diastereomer, 5H – second diastereomer, aromatic); ^{13}C NMR (101 MHz, $CDCl_3$): δ = 29.4 (Me, first diastereomer), 29.5 (Me, second diastereomer), 30.5 (Me, first diastereomer), 30.7 (Me, second diastereomer), 48.2 (CHPh, first diastereomer), 50.1 (CHPh, second diastereomer), 70.5 (CHC(O), first diastereomer), 71.9 (CHC(O), second diastereomer), 83.1 (CHBr, first diastereomer), 86.2 (CHBr, second diastereomer), 127.3 (aromatic), 129.0 (aromatic), 129.1 (aromatic), 129.2 (aromatic), 129.4 (aromatic), 129.5 (aromatic), 129.6 (aromatic), 131.9 (aromatic), 132.9 (aromatic), 199.9 (C=O), 200.6 (C=O), 201.1 (C=O), 201.5 (C=O). Anal. calcd for $C_{13}H_{14}BrNO_4$: C, 47.58; H, 4.30; N, 4.27. Found: C, 47.64; H, 4.33; N, 4.36.

4.2.2. 1-(Adamantan-1-yl)-2-[(1S)-2-bromo-2-nitro-1-phenylethyl]butane-1,3-dione (*4b*)

Yield: 0.55 g (56%), white crystals [mixture of diastereomers *dr* 5:1], mp 156–157 °C (methanol), $[\alpha]_D^{20} = -39.8$ (*c* 1.0. $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.48–1.66 (m, 12H – first diastereomer, 12H – second diastereomer, Ad), 1.93 (br s, 3H – first diastereomer, 3H – second diastereomer, Ad), 2.29 (s, 3H – first diastereomer, 3H – second diastereomer, Me), 4.30–4.31 (m, 1H – second diastereomer, CHPh), 4.58–4.62 (m, 1H – first diastereomer, CHPh), 4.83 (d, $^3J_{HH}$ = 10.4 Hz, 1H - first diastereomer, CHC(O)), 4.95 (d, $^3J_{HH}$ = 10.0 Hz, 1H – second diastereomer, CHC(O)), 6.34 (d, $^3J_{HH}$ = 5.2 Hz, 1H – first diastereomer, CHBr), 6.44 (d, $^3J_{HH}$ = 6.4 Hz, 1H - second diastereomer, CHBr), 7.17–7.33 (m, 5H – first diastereomer, 5H – second diastereomer, aromatic); ^{13}C NMR (101 MHz, $CDCl_3$): δ = 27.7 (Ad, first diastereomer), 27.8 (Ad, second diastereomer), 29.3 (Me, first diastereomer), 30.5 (Me, second diastereomer), 36.1 (Ad, first diastereomer), 36.3 (Ad, second diastereomer), 38.1 (Ad, fist diastereomer), 38.4 (Ad, second diastereomer), 48.1 (Ad, second diastereomer), 48.3 (Ad, first diastereomer), 50.2 (CHPh, first diastereomer), 52.7 (CHPh, second diastereomer), 64.4 (CHC(O), second diastereomer), 65.3 (CHC(O), first diastereomer), 82.3 (CHBr, second diastereomer), 85.2 (CHBr, first diastereomer), 128.7 (aromatic), 128.9 (aromatic), 129.2 (aromatic), 129.7 (aromatic), 129.9 (aromatic), 133.2 (aromatic), 133.7 (aromatic), 201.3 (C=O, first diastereomer), 201.7 (C=O, second diastereomer), 207.2 (C=O, first diastereomer), 208.3 (C=O,

second diastereomer). Anal. calcd for $C_{22}H_{26}BrNO_4$: C, 58.94; H, 5.85; N, 3.12. Found: C, 58.99; H, 5.91; N, 3.21.

4.2.3. 1-(Adamantan-1-yl)-2-[(1S)-2-bromo-2-nitro-1-(4-methylphenyl)ethyl]butane-1,3-dione (**4c**)

Yield: 0.71 g (70%), white crystals [mixture of diastereomers *dr* 1.6:1], mp 95.1–96.4 °C (CCl_4), $[\alpha]_D^{20} = -20.2$ (*c* 1.0, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.67–1.73 (m, 12H, Ad), 1.79 (s, 3H – second diastereomer, Me), 1.82 (s, 3H – first diastereomer, Me), 1.86–1.89 (m, 12H, Ad), 2.07 (br s, 3H – first diastereomer, 3H – second diastereomer, Ad), 2.29 (s, 3H – first diastereomer, Me), 2.30 (s, 3H – second diastereomer, Me), 4.32 (dd, $^3J_{HH}$ = 10.3, 5.0 Hz, 1H – first diastereomer, CHAr), 4.65 (dd, $^3J_{HH}$ = 11.2, 4.0 Hz, 1H – second diastereomer, CHAr), 4.79 (d, $^3J_{HH}$ = 11.0 Hz, 1H – first diastereomer, CHC(O)), 4.92 (d, $^3J_{HH}$ = 10.3 Hz, 1H – second diastereomer, CHC(O)), 6.24–6.27 (m, 1H – first diastereomer, 1H – second diastereomer, CHBr), 7.04–7.13 (m, 4H – first diastereomer, 4H – second diastereomer, aromatic); ^{13}C NMR (101 MHz, $CDCl_3$): δ = 21.3 (Me), 27.9 (Ad, first diastereomer), 28.0 (Ad, second diastereomer), 28.2 (Me, first diastereomer), 28.6 (Me, second diastereomer), 36.2 (Ad, first diastereomer), 36.3 (Ad, second diastereomer), 38.4 (Ad, first diastereomer), 38.6 (Ad, second diastereomer), 48.6 (Ad, second diastereomer), 48.7 (Ad, first diastereomer), 49.2 (CHAr, first diastereomer), 51.1 (CHAr, second diastereomer), 64.7 (CHC(O), second diastereomer), 66.0 (CHC(O), first diastereomer), 83.5 (CHBr, second diastereomer), 86.6 (CHBr, first diastereomer), 128.2 (aromatic, first diastereomer), 129.3 (aromatic, second diastereomer), 129.6 (aromatic), 129.7 (aromatic), 129.8 (aromatic), 139.3 (aromatic), 139.4 (aromatic), 200.5 (C=O, first diastereomer), 201.4 (C=O, second diastereomer), 208.8 (C=O, first diastereomer), 209.2 (C=O, second diastereomer). Anal. calcd for $C_{23}H_{28}BrNO_4$: C, 59.75; H, 6.10; N, 3.03. Found: C, 59.83; H, 6.15; N, 3.18.

4.2.4. 1-(Adamantan-1-yl)-2-[(1S)-2-bromo-1-(4-methoxyphenyl)-2-nitroethyl]butane-1,3-dione (**4d**)

Yield: 0.75 g (71%), yellow oil [mixture of diastereomers *dr* 3.7:2.4:1.1:1], $[\alpha]_D^{20} = -2.2$ (*c* 1.0, $CHCl_3$). ^{1}H NMR (400 MHz.

$CDCl_3$): δ = 1.50–1.56 (m, 12H – second diastereomer, Ad), 1.63–1.76 (m, 12H – first diastereomer, Ad), 1.79 (s, 3H – second diastereomer, Me), 1.82 (s, 3H – first diastereomer, Me), 1.85–1.88 (m, 12H – third diastereomer, 12H – fourth diastereomer, Ad), 1.94 (br s, 3H – third diastereomer, 3H – fourth diastereomer, Ad), 2.07 (br s, 3H – third diastereomer, 3H – fourth diastereomer, Ad), 2.25 (s, 3H – fourth diastereomer, Me), 2.28 (s, 3H – third diastereomer, Me), 3.75–3.76 (m, 3H – first diastereomer, 3H – second diastereomer, 3H – third diastereomer, 3H – fourth diastereomer, MeO), 4.21–4.26 (m, 1H – third diastereomer, CHAr), 4.30 (dd, $^3J_{HH}$ = 10.8, 4.8 Hz, 1H – second diastereomer, CHAr), 4.55 (dd, $^3J_{HH}$ = 10.8, 5.2 Hz, 1H – fourth diastereomer, CHAr), 4.63 (dd, $^3J_{HH}$ = 10.8, 6.0 Hz, 1H – first diastereomer, CHAr), 4.75–4.80 (m, 1H – first diastereomer, 1H – third diastereomer, 1H – fourth diastereomer, CHC(O)), 4.90 (d, $^3J_{HH}$ = 9.6 Hz, 1H – second diastereomer, CHC(O)), 6.24–6.25 (m, 1H – first diastereomer, 1H – second diastereomer, CHBr), 6.29 (d, $^3J_{HH}$ = 5.2 Hz, 1H – second diastereomer, CHBr), 6.39 (d, $^3J_{HH}$ = 7.2 Hz, 1H – fourth diastereomer, CHBr), 6.78–6.89 (m, 4H – first diastereomer, aromatic), 7.07–7.12 (m, 4H – third diastereomer, 4H – fourth diastereomer, aromatic), 7.17–7.19 (m, 4H – second diastereomer, aromatic); ^{13}C NMR (101 MHz, $CDCl_3$): δ = 27.7 (Ad), 27.8 (Ad), 27.9 (Ad), 28.0 (Me, first diastereomer), 28.6 (Me, second diastereomer), 29.2 (Me, third diastereomer), 30.4 (Me, fourth diastereomer), 36.1 (Ad, fourth diastereomer), 36.2 (Ad, third diastereomer), 36.3 (Ad, first diastereomer.), 36.4 (Ad, second diastereomer), 38.1 (Ad, third diastereomer), 38.4 (Ad, first diastereomer), 38.5 (Ad, second diastereomer.), 48.1 (Ad, third diastereomer), 48.3 (Ad, fourth diastereomer), 48.6 (Ad, second diastereomer), 48.7 (Ad, first diastereomer), 48.8 (MeO, first diastereomer), 49.6 (MeO, third diastereomer), 50.7 (MeO, second diastereomer), 51.9 (MeO, fourth diastereomer.), 55.3 (CHAr), 64.3 (CHC(O), third diastereomer), 64.7 (CHC(O), second diastereomer), 65.3 (CHC(O), fourth diastereomer), 66.0 (CHC(O), first diastereomer), 82.4 (CHBr, third diastereomer), 83.6 (CHBr, second diastereomer), 85.6 (CHBr, fourth diastereomer), 86.8 (CHBr, first diastereomer), 114.0 (aromatic), 114.4 (aromatic), 114.4 (aromatic), 123.0 (aromatic, first diastereomer), 124.0 (aromatic, second diastereomer), 124.9 (aromatic, first diastereomer), 125.2 (aromatic, fourth diastereomer), 130.9 (aromatic), 131.0 (aromatic), 160.0 (aromatic, fourth diastereomer.), 160.1 (aromatic, third diastereomer), 160.2 (aromatic, second diastereomer), 160.3 (aromatic, first diastereomer), 200.5 (C=O, first diastereomer), 201.4 (C=O, second diastereomer), 201.5 (C=O, fourth diastereomer), 201.9 (C=O, third diastereomer), 207.2 (C=O, fourth diastereomer), 208.6 (C=O, third diastereomer), 208.8 (C=O, first diastereomer), 209.2 (C=O, second diastereomer). Anal. calcd for $C_{23}H_{28}BrNO_5$: C, 57.75; H, 5.90; N, 2.93. Found: C, 57.82; H, 5.93; N, 3.08.

4.2.5. 1-(Adamantan-1-yl)-2-[(1S)-2-bromo-1-(4-fluorophenyl)-2-nitroethyl]butane-1,3-dione (**4e**)

Yield: 0.66 g (64%), white crystals [mixture of diastereomers *dr* 4.1:3.9:2.1:1], mp 60–61 °C (CCl_4), $[\alpha]_D^{20} = -5.3$ (*c* 1.0.

$CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.49–1.77 (m, 12H – first diastereomer, 12H – second diastereomer, 12H – third diastereomer, 12H – fourth diastereomer, Ad), 1.81 (s, 3H – fourth diastereomer, Me), 1.83 (s, 3H – third diastereomer, Me), 1.85 (br s, 3H – second diastereomer, Ad), 1.88 (br s, 3H – third diastereomer, Ad), 1.95 (br s, 3H – first diastereomer, Ad), 2.07 (br s, 3H – fourth diastereomer, Ad), 2.28 (br s, 3H – second diastereomer, Me), 2.30 (br s, 3H – first diastereomer, Me), 4.27–4.33 (m, 1H – first diastereomer, 1H – fourth diastereomer, CHAr), 4.60 (dd, $^3J_{HH}$ = 10.8, 4.8 Hz, 1H – second diastereomer, CHAr), 4.66 (dd, $^3J_{HH}$ = 10.8, 4.0 Hz, 1H – first diastereomer, CHAr), 4.74–4.79 (m, 1H – first diastereomer, 1H – third diastereomer, CHC(O)), 4.90–4.93 (m, 1H – second diastereomer, 1H – fourth diastereomer, CHC(O)), 6.25 (d, $^3J_{HH}$ = 4.0 Hz, 1H – third diastereomer, CHBr), 6.28–6.31 (m, 1H – first diastereomer, 1H – fourth diastereomer, CHBr), 6.40 (d, $^3J_{HH}$ = 6.8 Hz, 1H – second diastereomer, CHBr), 6.95–7.02 (m, 8H, aromatic), 7.15–7.20 (m, 4H, aromatic), 7.25–7.29 (m, 4H, aromatic); ^{13}C NMR (101 MHz, $CDCl_3$): δ = 27.7 (Ad, first diastereomer), 27.8 (Ad, second diastereomer), 27.8 (Ad, third diastereomer), 27.9 (Ad, fourth diastereomer), 28.2 (Me, third diastereomer), 28.7 (Me, fourth diastereomer), 29.3 (Me, first diastereomer), 30.5 (Me, second diastereomer), 36.1 (Ad, first diastereomer), 36.2 (Ad, second diastereomer), 36.3 (Ad, fourth diastereomer), 38.1 (Ad, first diastereomer), 38.4 (Ad, third diastereomer), 38.5 (Ad, second diastereomer), 38.5 (Ad, fourth diastereomer), 48.1 (Ad, second diastereomer), 48.2 (Ad, first diastereomer), 48.6 (Ad, fourth diastereomer), 48.7 (CHAr, second diastereomer), 49.5 (CHAr, first diastereomer), 50.7 (CHAr, fourth diastereomer), 51.9 (CHAr, third diastereomer), 64.1 (CHC(O), second diastereomer), 64.5 (CHC(O), fourth diastereomer), 65.3 (CHC(O), first diastereomer), 65.9 (CHC(O), third diastereomer), 82.1 (CHBr, second diastereomer), 83.1 (CHBr, fourth diastereomer), 85.2 (CHBr, first diastereomer), 86.4 (CHBr, third diastereomer), 115.8 (d, $^2J_{CF}$ = 42.9 Hz, aromatic), 116.0 (d, $^2J_{CF}$ = 22 Hz, aromatic), 115.8 (aromatic), 127.2 (d, $^4J_{CF}$ = 3.8 Hz, aromatic, third diastereomer), 128.1 (d, $^4J_{CF}$ = 2.8 Hz, aromatic, fourth diastereomer), 129.0 (d, $^4J_{CF}$ = 2.8 Hz, aromatic, third diastereomer), 129.4 (d, $^4J_{CF}$ = 3.8 Hz, aromatic, second diastereomer), 131.5 (d, $^3J_{CF}$ = 7.6 Hz, aromatic second diastereomer),

131.7 (d, $^3J_{CF}$ = 9.5 Hz, aromatic, first diastereomer), 131.6 (aromatic, third diastereomer), 162.9 (d, $^1J_{CF}$ = 247.9 Hz, aromatic, second diastereomer), 163.1 (d, $^1J_{CF}$ = 247 Hz, aromatic, first diastereomer), 163.3 (d, $^1J_{CF}$ = 247.9 Hz, aromatic third diastereomer), 200.2 (C═O, third diastereomer), 201.0 (C═O, first diastereomer), 201.2 (C═O, fourth diastereomer), 201.5 (C═O, second diastereomer), 206.9 (C═O, first diastereomer), 208.3 (C═O, second diastereomer), 208.5 (C═O, third diastereomer), 209.0 (C═O, fourth diastereomer); ^{19}F NMR (376 MHz, $CDCl_3$): −111.3 (third diastereomer), −111.4 (fourth diastereomer), −111.7 (first diastereomer), −111.8 (second diastereomer). Anal. calcd for $C_{22}H_{25}BrFNO_4$: C, 56.66; H, 5.40; N, 3.00. Found: C, 56.71; H, 5.44; N, 3.19.

4.2.6. Ethyl (3S)-2-[(adamantane-1-carbonyl]-4-bromo-4-nitro-3-phenylbutanoate (**4f**)

Yield: 0.4 g (40%), white crystals [mixture of diastereomers *dr* 1.6:1], mp 136–138 °C (methanol), $[\alpha]_D^{20}$ = − 19.6 (*c* 1.0.

$CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.16 (t, $^3J_{HH}$ = 6.8 Hz, 3H − second diastereomer, Me), 1.27 (t, $^3J_{HH}$ = 6.8 Hz, 3H − first diastereomer, Me), 1.51–1.65 (m, 12H − first diastereomer, 12H − second diastereomer, Ad), 1.92 (s, 3H − first diastereomer, 3H − second diastereomer, Ad), 4.06–4.09 (m, 2H − second diastereomer, O<u>CH</u>$_2$), 4.23 (q, $^3J_{HH}$ = 7.4 Hz, 2H − first diastereomer, O<u>CH</u>$_2$), 4.24–4.28 (m, 1H − second diastereomer, <u>CH</u>Ph), 4.61–4.62 (m, 1H − first diastereomer, 1H − first diastereomer, <u>CH</u>Ph, <u>CH</u>C(O)), 4.73 (d, $^3J_{HH}$ = 10.0 Hz, 1H − second diastereomer, <u>CH</u>C(O)), 6.68–6.70 (m, 1H − first diastereomer, 1H − second diastereomer, <u>CH</u>Br), 7.22–7.29 (m, 5H − first diastereomer, 5H − second diastereomer, aromatic); ^{13}C NMR (101 MHz, $CDCl_3$): δ = 13.9 (Me, second diastereomer), 14.1 (Me, first diastereomer), 27.8 (Ad, second diastereomer), 27.9 (Ad, first diastereomer), 36.2 (Ad, first diastereomer), 36.3 (Ad, second diastereomer), 38.1 (Ad, first diastereomer), 38.4 (Ad, second diastereomer), 47.7 (Ad), 49.4 (<u>CH</u>Ph, first diastereomer), 51.9 (<u>CH</u>Ph, second diastereomer), 55.4 (<u>CH</u>C(O), second diastereomer), 55.9 (CHC(O), first diastereomer), 62.2 (O<u>CH</u>$_2$, first diastereomer), 62.4 (O<u>CH</u>$_2$, second diastereomer), 82.6 (<u>CH</u>Br, first diastereomer), 85.7 (<u>CH</u>Br, second diastereomer), 128.6 (aromatic, first diastereomer), 128.7 (aromatic, second diastereomer), 129.0 (aromatic, second diastereomer), 129.1 (aromatic, first diastereomer), 129.7 (aromatic, first diastereomer), 130.0 (aromatic, second diastereomer), 133.3 (aromatic, first diastereomer), 133.7 (aromatic, second diastereomer), 167.1 (C(O)O, first diastereomer), 167.4 (C(O)O, second diastereomer), 206.5 (C═O, first diastereomer), 207.7 (C═O, second diastereomer). Anal. calcd for $C_{23}H_{28}BrNO_5$: C, 57.75; H, 5.90; N, 2.93. Found: C, 57.84; H, 5.95; N, 3.01.

4.2.7. Dimethyl [(3R)-4-bromo-4-nitro-1-oxo-1,3-diphenylbutan-2-yl]phosphonate (**4g**)

Yield: 0.58 g (58%), white crystals [mixture of diastereomers *dr* 23:22:3:1], mp 136–138 °C (methanol), $[\alpha]_D^{20}$ = − 35.5 (*c* 1.0.

$CHCl_3$). NMR data are presented for two main diastereomers. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.19 (d, $^3J_{HP}$ = 11.2 Hz, 3H − first diastereomer, MeO), 3.27 (d, $^3J_{HP}$ = 11.2 Hz, 3H − first diastereomer, MeO), 3.73 (d, $^3J_{HP}$ = 11.2 Hz, 3H − second diastereomer, MeO), 3.86 (d, $^3J_{HP}$ = 11.2 Hz, 3H − second diastereomer, MeO), 4.78–4.95 (m, 2H − first diastereomer, 2H − second diastereomer, <u>CH</u>P(O), <u>CH</u>Ph), 6.44–6.48 (m, 1H − first diastereomer,<u>CH</u>NO$_2$), 7.10–7.78 (m, 16H aromatic, 1H − second diastereomer <u>CH</u>NO$_2$), 7.79 (d, $^3J_{HH}$ = 7.2 Hz, 1H − first diastereomer, aromatic), 8.10 (d, $^3J_{HH}$ = 7.2 Hz, 1H − second diastereomer, aromatic); ^{13}C NMR (101 MHz, $CDCl_3$): δ = 48.4 (<u>CH</u>Ph, first diastereomer), 48.8 (d, $^2J_{CP}$ = 3.8 Hz, CHPh, second diastereomer), 48.9 (d, $^1J_{CP}$ = 124 Hz, CHP(O), first diastereomer), 50.7 (d, $^1J_{CP}$ = 128 Hz, CHP(O), second diastereomer), 53.3 (d, $^2J_{CP}$ = 6.7 Hz, MeO, first diastereomer), 53.4 (d, $^2J_{CP}$ = 6.7 Hz, MeO, first diastereomer), 53.8 (d, $^2J_{CP}$ = 7.6 Hz, MeO, second diastereomer), 54.4 (d, $^2J_{CP}$ = 6.7 Hz, MeO, second diastereomer), 86.9 (d, $^3J_{CP}$ = 19.2 Hz, <u>CH</u>NO$_2$, first diastereomer), 88.5 (<u>CH</u>NO$_2$, second diastereomer), 128.4 (aromatic), 128.5 (aromatic), 128.8 (aromatic), 128.9 (aromatic), 129.0 (aromatic), 129.3 (aromatic), 129.4 (aromatic), 129.8 (aromatic), 130.0 (aromatic), 130.1 (aromatic), 132.2 (aromatic), 132.8 (aromatic), 132.9 (aromatic), 133.8 (aromatic), 134.1 (aromatic), 134.2 (aromatic), 136.8 (aromatic), 137.1 (aromatic), 192.8 (d, $^2J_{CP}$ = 5.7 Hz, C(O), first diastereomer), 194.3 (d, $^2J_{CP}$ = 5.7 Hz, C(O), second diastereomer); ^{31}P NMR (161 MHz, $CDCl_3$): δ = 22.3 (fourth diastereomer), 21.9 (first diastereomer), 21.6 (third diastereomer), 21.3 (second diastereomer). Anal. calcd for $C_{18}H_{19}BrNO_6P$: C, 47.39; H, 4.20; N, 3.07. Found: C, 47.44; H, 4.27; N, 3.18.

4.2.8. [(1S)-2-Bromo-2-nitro-1-phenylethyl]-1,3-diphenylpropane-1,3-dione (**4h**)

Yield: 0.58 g (58%), white crystals [mixture of diastereomers *dr* 1.3:1], mp 163–164 °C (toluene), $[\alpha]_D^{20}$ = +35.2 (*c* 1.0, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.67 (dd, $^3J_{HH}$ = 8.4, 7.2 Hz, 1H − first diastereomer, <u>CH</u>Ph), 5.05 (dd, $^3J_{HH}$ = 10.4, 5.2 Hz, 1H − second diastereomer, <u>CH</u>Ph), 6.09 (d, $^3J_{HH}$ = 10.4, 1H − second diastereomer, <u>CH</u>C(O)), 6.27 (d, $^3J_{HH}$ = 8.8, 1H − first diastereomer, <u>CH</u>C(O)), 6.80 (d, $^3J_{HH}$ = 5.2 Hz, 1H − first diastereomer, 1H − second diastereomer, <u>CH</u>Br), 7.28–7.48 (m, 10H − first diastereomer, 10H − second diastereomer, aromatic), 7.54–7.58 (m, 1H − first diastereomer, 1H − second diastereomer, aromatic), 7.70–7.74 (m, 2H − first diastereomer, 2H − second diastereomer, aromatic), 7.98 (d, $^3J_{HH}$ = 7.6, 2H − first diastereomer, aromatic), 8.04 (d, $^3J_{HH}$ = 7.6, 2H − second diastereomer, aromatic); ^{13}C NMR (101 MHz, $CDCl_3$): δ = 50.3 (<u>CH</u>Ph, second diastereomer), 52.2 (<u>CH</u>Ph, first diastereomer), 59.2 (<u>CH</u>C(O), first diastereomer), 61.1 (<u>CH</u>C(O), second diastereomer), 83.0 (<u>CH</u>Br, first diastereomer), 85.9 (<u>CH</u>Br, second diastereomer), 128.5 (aromatic), 128.6 (aromatic), 128.7 (aromatic), 128.8 (aromatic), 128.9 (aromatic), 129.0 (aromatic), 129.1 (aromatic), 129.1 (aromatic), 129.2 (aromatic), 129.8 (aromatic), 130.0 (aromatic), 132.4 (aromatic), 132.7 (aromatic), 133.7 (aromatic), 133.8 (aromatic), 134.2 (aromatic), 134.4 (aromatic), 135.9 (aromatic), 136.0 (aromatic), 136.3 (aromatic), 192.6 (C═O, second diastereomer), 193.4 (C═O, second diastereomer), 193.9 (C═O, first diastereomer), 194.1 (C═O, first diastereomer). Anal. calcd for $C_{23}H_{18}BrNO_4$: C, 61.08; H, 4.01; N, 3.10. Found: C, 61.12; H, 4.05; N, 3.29.

4.2.9. 1-(adamantan-1-yl)-2-((1S)-2-bromo-1-(5-bromofuran-2-yl)-2-nitroethyl)butane-1,3-dione (**4i**)

Yield: 0.45 g (40%), yellow oil [mixture of diastereomers *dr* 1.5:1.0], $[\alpha]_D^{20}$ = +66.0 (*c* 1.0, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.66–1.86 (m, 12H − first diastereomer, 12H − second diastereomer, Ad), 1.95 (s, 3H − first diastereomer, Me), 1.98 (s, 3H − second diastereomer, Me), 2.07 (br s, 3H − first diastereomer, 3H − second diastereomer, Ad), 4.31 (dd, $^3J_{HH}$ = 9.6 Hz, $^3J_{HH}$ = 4.8 Hz, 1H − first diastereomer, <u>CH</u>(5-bromofuran-2-yl)), 4.72–4.78 (m, 1H − second diastereomer, <u>CH</u>(5-bromofuran-2-yl), 1H − second diastereomer, <u>CH</u>C(O)), 4.88 (d, $^3J_{HH}$ = 9.6 Hz, 1H - first diastereomer, <u>CH</u>C(O)), 6.14 (d, $^3J_{HH}$ = 3.2 Hz, 1H − first diastereomer, aromatic), 6.23–6.26 (m, 1H − first diastereomer, <u>CH</u>Br, 2H − second diastereomer, aromatic), 7.25 (d, $^3J_{HH}$ = 0.4 Hz, 1H − second diastereomer, <u>CH</u>Br); ^{13}C NMR (101 MHz, $CDCl_3$): δ = 27.7 (Ad, second diastereomer), 27.8 (Ad, first diastereomer), 28.8 (Me, second diastereomer), 29.4 (Me, first diastereomer), 36.2 (Ad, second diastereomer), 36.3 (Ad, first

diastereomer), 38.3 (Ad, second diastereomer), 38.4 (Ad, first diastereomer), 44.5 (CH(5-bromofuran-2-yl, second diastereomer), 45.9 (CH(5-bromofuran-2-yl, first diastereomer), 48.1 (Ad, first diastereomer), 48.3 (Ad, second diastereomer), 61.8 (CHC(O), first diastereomer), 63.1 (CHC(O), second diastereomer), 80.8 (CHBr, first diastereomer), 83.4 (CHBr, second diastereomer), 112.6 (aromatic, second diastereomer), 112.7 (aromatic, first diastereomer), 114.7 (aromatic, second diastereomer), 115.0 (aromatic, first diastereomer), 123.2 (aromatic, CBr, first diastereomer), 123.4 (aromatic, CBr, second diastereomer), 148.0 (aromatic, second diastereomer), 148.1 (aromatic, first diastereomer), 199.8 (C=O, second diastereomer), 200.6 (C=O, first diastereomer), 207.6 (C=O, second diastereomer), 208.2 (C=O, first diastereomer). Anal. calcd for $C_{20}H_{23}Br_2NO_5$: C, 46.44; H, 4.48; N, 2.71. Found: C, 46.50; H, 4.52; N, 2.73.

4.3. General procedure for the synthesis of 4,5-dihydrofurans

To a mixture of compound **4a-i** (0.94 mmol) in 5 mL acetonitrile was added (0.94 mmol). The reaction mixture was kept at rt for 24 h, then washed with a solution of ammonium chloride. The aqueous layer was extracted with $CHCl_3$ (3x20 mL). The organic phase was separated, dried over Na_2SO_4. The solvent was distilled off under reduced pressure. The residue was purified by column chromatography on silica gel (eluent CCl_4).

4.3.1. One-pot procedure for the synthesis of 4,5-dihydrofurans *5a* and *5h*

A mixture of β-diketone **1a,e** (2.2 mmol), α-bromonitroalkene **2a** (2.2 mmol) and bis[(1*R*,2*R*)-*N*,*N*`-dibenzylcyclohexane-1,2-diamine-κ$^2$*N*,*N*`](dibromo)nickel (**3**) (0.044 mmol) in 2 mL of toluene was stirred at rt for 24 h. Then DMAP (2.2 mmol) was added to this reaction medium and kept at rt for 24 h. The reaction mixture was washed with a solution of ammonium chloride. The aqueous layer was extracted with $CHCl_3$ (3x20 mL). The organic phase was separated, dried over Na_2SO_4. The solvent was distilled off under reduced pressure. The residue was purified by column chromatography on silica gel (eluent CCl_4).

*4.3.1.1. 1-[(4R,5R)-2-Methyl-5-nitro-4-phenyl-4,5-dihydrofuran-3-yl]ethan-1-one (**5a**).* **General procedure:** Yield: 0.13 g (56%), 94% *ee* (4*R*,5*R*). **One-pot procedure:** Yield: 0.26 g (49%), 94% *ee* (4*R*,5*R*). HPLC analysis (CHIRALPAK AD-3 column; hexane/2-propanol, 97:3; flow rate 1.2 mL/min; wavelength 210 nm): t_R = 9.8 (4*R*,5*R*), 10.4 (4*S*,5*S*). White crystals, mp 70.2–72.3 °C (CCl_4), $[\alpha]_D^{20}$ = − 199.4(c 1.0, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.01 (s, 3H, Me), 2.52 (d, $^3J_{HH}$ = 1.2 Hz, 3H, Me), 4.65 (s, 1H, H-4), 5.72 (d, $^3J_{HH}$ = 2.0 Hz, 3H, H-5), 7.21–7.26 (m, 2H, aromatic), 7.31–7.40 (m, 3H, aromatic); ^{13}C NMR (101 MHz, $CDCl_3$): δ = 14.6 (Me), 29.8 (Me), 56.4 (C-4), 109.6 (C-5), 115.7 (C-3), 127.2 (aromatic), 128.8 (aromatic), 129.6 (aromatic), 137.6 (aromatic), 166.9 (C-2), 193.2 (C=O). Anal. calcd for $C_{13}H_{13}NO_4$: C, 65.13; H, 5.30; N, 5.67. Found: C, 65.23; H, 5.33; N, 5.83.

*4.3.1.2. (Adamantan-1-yl)[(4R,5R)-2-methyl-5-nitro-4-phenyl-4,5-dihydrofuran-3-yl])methanone (**5b**).* Yield: 0.26 g (77%), 99% *ee* (4*R*;5*R*). HPLC analysis (CHIRALPAK AD-3 column; hexane/2-propanol, 97:3; flow rate 1.2 mL/min; wavelength 210 nm): t_R = 10.8 (4*R*,5*R*), 12.4 (4*S*,5*S*) min. White crystals, mp 93.5–95.0 °C (CCl_4), $[\alpha]_D^{20}$ = − 94.8 (c 1.0, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.73–1.84 (m, 6H, Ad), 1.90 (s, 3H, Me), 2.06 (s, 3H, Ad), 2.18 (s, 6H, Ad), 4.63 (d, $^3J_{HH}$ = 1.2 Hz, 1H, H-4), 5.60 (d, $^3J_{HH}$ = 1.2 Hz, 1H, H-5), 7.23–7.36 (m, 2H, aromatic), 7.38–7.43 (m, 3H, aromatic); ^{13}C NMR (101 MHz, $CDCl_3$): δ = 28.2 (Ad), 31.1 (Me), 36.6 (Ad), 37.4 (Ad), 37.6 (Ad), 57.8 (C-4), 108.6 (C-5), 113.0 (C-3), 127.2 (aromatic), 128.9 (aromatic), 129.8 (aromatic), 137.4 (aromatic), 175.1 (C-2), 193.8 (C = O). Anal. calcd for $C_{22}H_{25}NO_4$: C, 71.91; H, 6.86; N, 3.81. Found: C, 71.97; H, 6.89; N, 3.99.

*4.3.1.3. (Adamantan-1-yl)[(4R,5R)-2-methyl-5-nitro-4-(4-methylphenyl)-4,5-dihydrofuran-3-yl]methanone (**5c**).* Yield: 0.20 g (57%), 89% *ee* (4*R*,5*R*). HPLC analysis (CHIRALPAK AD-3 column; hexane/2-propanol, 97:3; flow rate 1.2 mL/min; wavelength 210 nm): t_R = 5.0 (4*S*,5*R*), 5.9 (4*R*,5*S*), 9.3 (4*R*,5*R*), 11.1 (4*S*,5*S*) min. The HPLC chromatogram shows two diastereomers. The second diastereomer is formed by epimerization in a chromatographic column. Yellow oil, $[\alpha]_D^{20}$ = −88.6 (*c* 1.0, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.73–1.86 (m, 6H, Ad), 1.90 (s, 3H, Me), 2.05 (s, 3H, Ad), 2.18 (s, 6H, Ad), 2.35 (s, 3H, Me), 4.59 (s, 1H, H-4), 5.57 (d, $^3J_{HH}$ = 1.6 Hz, 1H, H-5), 7.11 (d, $^3J_{HH}$ = 8.0 Hz, 2H, aromatic), 7.20 (d, $^3J_{HH}$ = 8.0 Hz, 2H, aromatic). ^{13}C NMR (101 MHz, $CDCl_3$): 21.2 (Me), 28.2 (Ad), 31.1 (Me), 36.6 (Ad), 37.6 (Ad), 38.4 (Ad), 57.5 (C-4), 108.8 (C-5), 113.6 (C-3), 127.1 (aromatic), 129.7 (aromatic), 134.4 (aromatic), 138.8 (aromatic), 174.9 (C-2), 193.9 (C = O). Anal. calcd for $C_{23}H_{27}NO_4$: C, 72.42; H, 7.13; N, 3.67. Found: C, 72.48; H, 7.20; N, 3.80.

*4.3.1.4. (Adamantan-1-yl)[(4R,5R)-4-(4-methoxyphenyl)-2-methyl-5-nitro-4,5-dihydrofuran-3-yl]methanone (**5d**).* Yield: 0.23 g (61%), 92% *ee* (4*R*,5*R*). HPLC analysis (CHIRALPAK AD-3 column; hexane/2-propanol, 97:3; flow rate 1.2 mL/min; wavelength 210 nm): t_R = 6.5 (4*S*,5*R*), 8.8 (4*R*,5*S*), 12.4 (4*R*,5*R*), 13.9 (4*S*,5*S*) min. The HPLC chromatogram shows two diastereomers. The second diastereomer is formed by epimerization in a chromatographic column. Yellow oil, $[\alpha]_D^{20}$ = −100.0 (*c* 1.0, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.73–1.83 (m, 6H, Ad), 1.90 (s, 3H, Ad), 2.05 (s, 3H, Ad), 2.17 (s, 6H, Ad), 3.80 (s, 3H, MeO), 4.58 (s, 1H, H-4), 5.57 (d, $^3J_{HH}$ = 1.2 Hz, 1H, H-5), 6.91 (d, $^3J_{HH}$ = 8.8 Hz, 1H, aromatic), 7.14 (d, $^3J_{HH}$ = 8.8 Hz, 1H, aromatic); ^{13}C NMR (101 MHz, $CDCl_3$): 27.9 (Ad), 31.1 (Me), 36.6 (Ad), 37.7 (Ad), 38.1 (Ad), 55.5 (OMe), 57.2 (C-4), 108.8 (C-5), 113.4 (C-3), 115.1 (aromatic), 128.4 (aromatic), 129.2 (aromatic), 159.9 (aromatic), 174.8 (C-2), 193.9 (C = O). Anal. calcd for $C_{23}H_{27}NO_5$: C, 69.50; H, 6.85; N, 3.52. Found: C, 69.58; H, 6.89; N, 3.64.

*4.3.1.5. (Adamantan-1-yl)[(4R,5R)-4-(4-fluorophenyl)-2-methyl-5-nitro-4,5-dihydrofuran-3-yl]methanone (**5e**).* Yield: 0.22 g (56%), 90% *ee* (4*R*,5*R*). HPLC analysis (CHIRALPAK AD-3 column; hexane/2-propanol, 97:3; flow rate 1.2 mL/min; wavelength 210 nm): t_R = 9.5 (4*R*,5*R*), 11.1 (4*S*,5*S*) min. Yellow oil, $[\alpha]_D^{20}$ = − 62.2 (c 1.0, $CHCl_3$). ^{1}H NMR (400.

MHz, $CDCl_3$): δ = 1.73–1.83 (m, 6H, Ad), 1.90 (s, 3H, Me), 2.05 (s, 3H, Ad), 2.17 (br s, 6H, Ad), 4.63 (s, 1H, H-4), 5.57 (d, $^3J_{HH}$ = 0.8 Hz, 1H, H-5), 7.08–7.12 (m, 2H, aromatic), 7.20–7.25 (m, 2H, aromatic); ^{13}C NMR (101 MHz, $CDCl_3$): δ = 28.2 (Ad), 31.1 (Me), 36.5 (Ad), 37.3 (Ad), 37.7 (Ad), 57.1 (C-4), 108.4 (C-5), 113.0 (C-3), 116.8 (d, $^2J_{CF}$ = 22.0 Hz, aromatic), 129.0 (d, $^3J_{CF}$ = 8.6 Hz, aromatic), 133.1 (d, $^4J_{CF}$ = 3.8 Hz, aromatic), 162.9 (d, $^1J_{CF}$ = 247.9 Hz, aromatic), 175.1 (C-2), 193.6 (C = O); ^{19}F NMR (376 MHz, $CDCl_3$): δ = −112.4. Anal. calcd for $C_{22}H_{24}FNO_4$: C, 68.56; H, 6.28; N, 3.63. Found: C, 68.61; H, 6.32; N, 3.78.

*4.3.1.6. Ethyl (4R,5R)-2-(adamantan-1-yl)-5-nitro-4-phenyl-4,5-dihydrofuran-3-carboxylate (**5f**).* Yield: 0.22 g (60%), >99% *ee* (4*R*;5*R*). HPLC analysis (CHIRALPAK AD-3 column; hexane/2-propanol, 92:8; flow rate 1.2 mL/min; wavelength 210 nm): t_R = 3.4 (4*R*,5*R*), 3.9 (4*S*,5*S*) min. White crystals, mp 125–126 °C (methanol), $[\alpha]_D^{20}$ = − 140 (*c* 1.0, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.04 (t, $^3J_{HH}$ = 7.1 Hz, 3H, Me), 1.74–1.84 (m, 6H, Ad), 2.07 (s, 3H, Ad), 2.25 (s, 6H, Ad), 3.98 (q, $^3J_{HH}$ = 7.1 Hz, 2H, OCH_2), 4.61 (d, $^3J_{HH}$ = 1.2 Hz, 1H, H-4), 5.66 (d, $^3J_{HH}$ = 1.2 Hz, 1H, H-5), 7.18–7.20 (m, 2H, aromatic), 7.28–7.37 (m, 3H, aromatic); ^{13}C NMR (101 MHz, $CDCl_3$): δ = 13.9 (Me), 28.3 (Ad), 36.6 (Ad), 37.0 (Ad), 38.2 (Ad), 57.5 (C-4), 60.4 (OCH_2), 106.3 (C-3), 108.6 (C-5), 127.1 (aromatic), 128.3 (aromatic), 129.2 (aromatic), 138.4 (aromatic), 162.9 (C(O)O), 175.3 (C-2). Anal. calcd for $C_{23}H_{27}NO_5$: C, 69.50; H, 6.85; N, 3.52. Found: C, 69.58; H, 6.89; N, 3.64. The single crystal of compound **5f** was grown by slow evaporation of methanol. The compound crystallizes in the orthorhombic crystal system, space group $P2_12_12_1$, a = 9.8066(3) Å, b = 13.2489(4) Å, c = 16.3828(6) Å, α = 90°, β = 90°, γ = 90°, V = 2128.56(12) Å^3, Z = 4, d_{calcd}=1.240 g/cm^3, F(000) = 848, Theta range 4.292–72.775°, R indices (all data) R1 = 0.0897 wR2 = 0.1490.

*4.3.1.7. Dimethyl [(4S,5R)-5-nitro-2,4-diphenyl-4,5-dihydrofuran-3-yl]phosphonate (**5g**).* Yield: 0.37 g (90%), 98% *ee* (4*S*;5*R*). HPLC analysis (CHIRALPAK AD-3 column; hexane/2-propanol, 93:7; flow rate 1.2 mL/min; wavelength 210 nm): t_R = 25.0 (4*R*,5*S*), 28.8 (4*S*,5*R*) min. $[\alpha]_D^{20}$ = − 38.5 (*c* 1.0, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.31 (d, $^3J_{HH}$ = 12.0 Hz, 3H, MeO), 3.39 (d, $^3J_{HH}$ = 12.0 Hz, 3H, MeO), 4.76 (dd, $^3J_{HP}$ = 4.0 Hz, $^3J_{HH}$ = 1.6 Hz, 1H, H-4), 5.91 (d, $^3J_{HH}$ = 1.6 Hz, 1H, H-5), 7.34–7.40 (m, 5H, aromatic), 7.45–7.53 (m, 3H, aromatic), 8.04–8.07 (m, 2H, aromatic); ^{13}C NMR (101 MHz, $CDCl_3$): δ = 52.4 (d, $^2J_{CP}$ = 4.8 Hz, MeO), 52.6 (d, $^2J_{CP}$ = 4.8 Hz, MeO), 59.7 (d, $^2J_{CP}$ = 10.5 Hz, C-4), 100.7 (d, $^1J_{CP}$ = 213.5 Hz, C-3), 109.2 (d, $^2J_{CP}$ = 10.5 Hz, C-5), 127.4 (aromatic), 127.6 (aromatic), 128.4 (aromatic), 128.8 (aromatic), 129.4 (aromatic), 129.6 (aromatic), 132.0 (aromatic), 137.4 (aromatic), 165.0 (d, $^2J_{CP}$ = 25.7 Hz, C-2): ^{31}P NMR (161 MHz, $CDCl_3$): δ = 16.3. Anal. calcd for $C_{18}H_{18}NO_6P$: C, 57.60; H, 4.83; N, 3.73. Found: C, 57.66; H, 4.86; N, 3.84.

*4.3.1.8. [(4R,5R)-5-nitro-2,4-diphenyl-4,5-dihydrofuran-3-yl](phenyl)methanone (**5h**).* **General procedure:** Yield: 0.21 g (61%), 96% *ee* (4*R*,5*R*). **One-pot procedure:** Yield: 0.54 g (67%), 96% *ee* (4*R*,5*R*). HPLC analysis (CHIRALPAK AD-3 column; hexane/2-propanol, 93:7; flow rate 1.2 mL/min; wavelength 210 nm): t_R = 12.9 (4*R*,5*R*), 18.3 (4*S*,5*S*) min. White crystals, mp 77–78 °C (CCl_4), $[\alpha]_D^{20}$ = − 124.3 (*c* 1.0.

$CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.94 (d, $^3J_{HH}$ = 1.2 Hz, 1H, H-4), 5.98 (d, $^3J_{HH}$ = 1.2 Hz, 1H, H-5), 7.10–7.51 (m, 15H, aromatic); ^{13}C NMR (101 MHz, $CDCl_3$): δ = 59.2 (C-4), 109.3 (C-5), 114.4 (C-3), 127.3 (aromatic), 127.8 (aromatic), 128.1 (aromatic), 128.2 (aromatic), 128.6 (aromatic), 129.2 (aromatic), 129.4 (aromatic), 129.7 (aromatic), 131.4 (aromatic), 132.4 (aromatic), 137.6 (aromatic), 162.9 (C-2), 191.4 (C = O). Anal. calcd for $C_{23}H_{17}NO_4$: C, 74.38; H, 4.61; N, 3.77. Found: C, 74.44; H, 4.65; N, 3.80.

*4.3.1.9. (Adamantan-1-yl)[(4S,5R)-2-methyl-5-nitro-4-(5-bromofuran-2-yl)-4,5-dihydrofuran-3-yl]methanone (**5i**).* Yield: 0.21 g (50%), yellow oil [mixture of diastereomers *dr* 9.0:1.0], 84% *ee* (4*S*;5*R*). HPLC analysis (CHIRALPAK AD-3 column; hexane/2-propanol, 97:3; flow rate 1.2 mL/min; wavelength 210 nm): t_R = 12.2 (4*S*,5*R*), 17.2 (4*R*,5*S*) min. $[\alpha]_D^{20}$ = − 47.1 (c 1.0, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.63–1.80 (m, 6H, Ad), 2.02 (s, 3H, Me), 2.04 (s, 3H, Ad), 2.11 (s, 6H, Ad), 4.74 (s, 1H, H-4), 5.75 (s, 1H, H-5), 6.17 (d, $^3J_{HH}$ = 3.2 Hz, 1H, aromatic), 6.29 (d, $^3J_{HH}$ = 3.2 Hz, 1H, aromatic); ^{13}C NMR (101 MHz, $CDCl_3$): δ = 28.1 (Ad), 30.7 (Me), 36.4 (Ad), 37.4 (Ad), 37.6 (Ad), 51.3 (C-4), 105.6 (C-5), 109.9 (C-3), 111.3 (aromatic), 112.7 (aromatic), 123.2 (aromatic, CBr), 151.9 (aromatic), 176.1 (C-2), 192.9 (C = O). Anal. calcd for $C_{20}H_{22}BrNO_5$: C, 55.06; H, 5.08; N, 3.21. Found: C, 55.10; H, 5.12; N, 3.25.

*4.4. (3S)-1-(adamantan-1-yl)-4-bromo-4-nitro-3-phenylbutan-1-one (**6**)*

A mixture of compound **4b** (0.5 g, 1.12 mmol), sodium hydroxide (0.1 g, 2.50 mmol) in 5 mL of water was stirred at rt for 6 h until complete dissolution. Then the reaction mass was acidified with 5% HCl solution, extracted with $CHCl_3$ (3 × 20 mL). The organic phase was separated, dried over Na_2SO_4. The solvent was distilled off under reduced pressure. The formed crystalline product (**6**) was filtered and recrystallized from MeOH. Yield: 0.24 g (50%), brown crystals [mixture of diastereomers *dr* 1.0:0.4], mp 119.2–119.8 °C (MeOH). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.62–1.73 (м, 12H − first diastereomer, 12H −second diastereomer, Ad), 4.43 (br s, 3H − first diastereomer, 3H − second diastereomer, Ad), 2.98 (d, $^3J_{HH}$ = 5.6 Hz, 1H − second diastereomer., $\underline{CH_2}C(O)$), 3.02 (d, $^3J_{HH}$ = 6 Hz, 1H − second diastereomer, $\underline{CH_2}C(O)$), 3.08–3.17 (m, 2H −first diastereomer, $\underline{CH_2}C(O)$), 4.13–4.21 (m, 1H − first diastereomer, 1H − second diastereomer, $\underline{CH}$Ph), 6.29 (d, $^3J_{HH}$ = 8.8 Hz, 1H − second diastereomer, $\underline{CH}$Br), 6.38 (d, $^3J_{HH}$ = 6.8 Hz, 1H − first diasteromer, $\underline{CH}$Br), 7.20–7.31 (m, 5H − first diastereomer, 5H − second diastereomer, aromatic). ^{13}C NMR (101 MHz, $CDCl_3$): δ = 27.9 (Ad), 36.5 (Ad), 37.9 (Ad, second diastereomer), 38.0 (Ad, first diastereomer), 38.6 (CH_2, first diastereomer), 38.9 (CH_2, second diastereomer), 39.3 (Ad), 45.9 ($\underline{CH}$Ph, first diastereomer), 46.5 ($\underline{CH}$Ph, second diastereomer), 84.2 ($\underline{CH}$Br, second diastereomer), 85.4 ($\underline{CH}$Br, first diastereomer), 127.5 aromatic, first diastereomer), 127.8 (aromatic, second diastereomer), 128.4 (aromatic, second diastereomer), 128.6 (aromatic, first diastereomer), 128.9 (aromatic, first diastereomer), 129.0 (aromatic, second diastereomer), 136.4 (aromatic, first diastereomer), 136.6 (aromatic, second diastereomer), 211.4 (C═O, first diastereomer), 211.6 (C═O, second diastereomer). Anal. calcd for $C_{20}H_{24}BrNO_3$: C, 59.12; H, 5.95; N, 3.45. Found: C, 59.20; H, 5.99; N, 3.64.

4.5. General procedure for the preparation of 1-(2-methyl-4-phenyl-1H-pyrrol-3-yl)ethan-1-one (7)

To a solution of compound **5a** (0.25 mg, 1.01 mmol) in methanol (1.5 mL) was added 10% Pd/C (25 mg). The reaction mixture was stirred under an atmosphere of H_2 (5 bar) at rt for 4 days. The solvent was distilled off under reduced pressure. The product was filtered through a layer of silica gel ($CHCl_3$).

Yield: 0.18 g (90%), purple crystals, mp 151.2–152.6 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.06 (s, 3H, Me), 2.51 (s,3H, Me), 6.52 (d, $^3J_{HH}$ = 2.4 Hz, 1H, H-5), 7.29–7.36 (m, 5H, aromatic), 9.12 (s, 1H, NH); ^{13}C NMR (101 MHz, $CDCl_3$): δ = 14.3 (Me), 30.9 (Me), 115.7 (C-5), 120.8 (C-4), 126.8 (aromatic), 126.9 (C-3), 128.3 (aromatic), 129.6 (aromatic), 135.7 (C-2), 136.9 (aromatic), 197.7 (C═O). Anal. calcd for $C_{13}H_{13}NO$: C, 78.36; H, 6.58; N, 7.03. Found: C, 78.41; H, 6.63; N, 7.15.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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0778-2020-0005), Russia. The X-ray studies were fulfilled using a STOE STADI VARI PILATUS-100K diffractometer purchased by MSU Development Program.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.tet.2021.132029.

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