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STEREOSELECTIVE AZA-HENRY REACTION OF CHIRAL *tert*-BUTANESULFINYL IMINES WITH METHYL OR ETHYL 4-NITROBUTANOATE: EASY ACCESS TO ENANTIOENRICHED 6-SUBSTITUTED PIPERIDINE-2,5-DIONES

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Abstract – The base-catalyzed addition of 4-nitrobutanoates **6** to *N*-*tert*-butanesulfinyl imines **8** under solvent-free reaction conditions proceeded with high face diastereoselectivity. The resulting β-nitroamine derivatives **9** were easily transformed into 6-substituted piperidine-2,5-diones **11** upon removal of the sulfinyl group with concomitant δ-lactam formation and functional group transformation under Nef reaction conditions.

Substituted piperidine-2,5-diones are versatile building blocks in organic synthesis because they can be transformed very easily into substituted piperidin-3-ols with high control of the stereochemistry. It is known that the piperidine ring is widely represented in many natural products and can exhibit broad range of biological activities.[1] Particularly, systems with the piperidin-2-ol skeleton having substituents at 2-position[2] and 6-position[3] are of great pharmacological interest. For instance, (+)-febrifugine (**1**) is a natural product isolated from *Dichroa febrifuga*,[4] a plant used in traditional Chinese medicine to treat malaria (Figure 1). A synthetic propanoic acid derivative **2**, with a 3-hydroxyl-2-piperidinyl unit, showed a potent in vitro activity as a GABA receptor binder, similar to that displayed by baclofen.[5] Several 2,6-disubstituted piperidin-3-ols have been isolated from the African savanna plant, *Prosopis africana*. Among them, (+)-prosophylline (**3**) displays antibiotic and anesthetic properties (Figure 1).[6]

This paper is dedicated to Professor Isao Kuwajima on occasion of his 77th birthday.

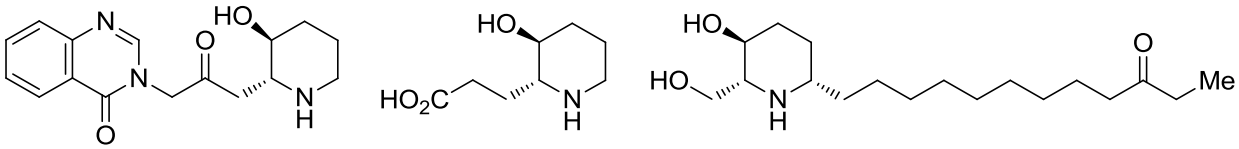
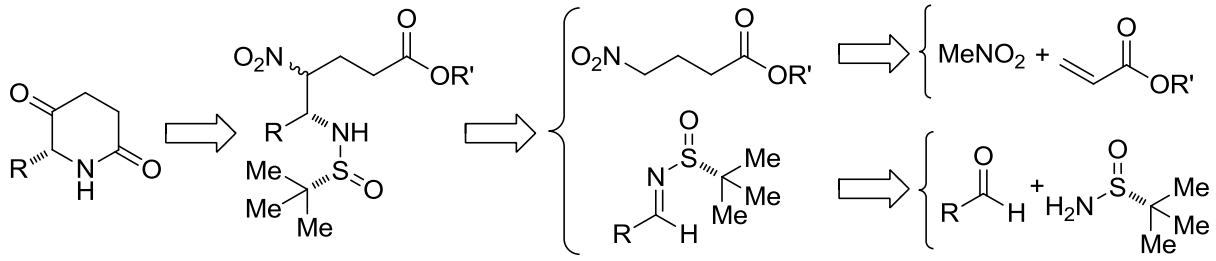


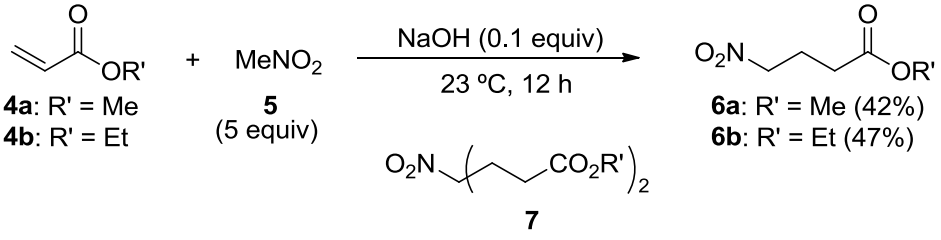
Figure 1

Most of the enantioselective syntheses of substituted piperidin-3-ols reported until today are based on the chiral pool synthesis using amino acid and sugar derivatives as starting materials.[7] Other stereoselective syntheses included as key steps nucleophilic additions of organomagnesium compounds to chiral oximes[8] and enzymatic resolution of racemic compounds.[2,9] Continuing our interest in the use of *N-tert*-butanesulfinyl imines[10] as electrophiles, we envisioned a straightforward synthesis of 6-substituted piperidin-2,5-diones, based on the diastereoselective aza-Henry reaction of methyl or ethyl 4-nitrobutanoate and these chiral imines.[11] Our retrosynthentic analysis for the preparation of target 6-substituted piperidin-2,5-diones is depicted on Scheme 1.



Scheme 1

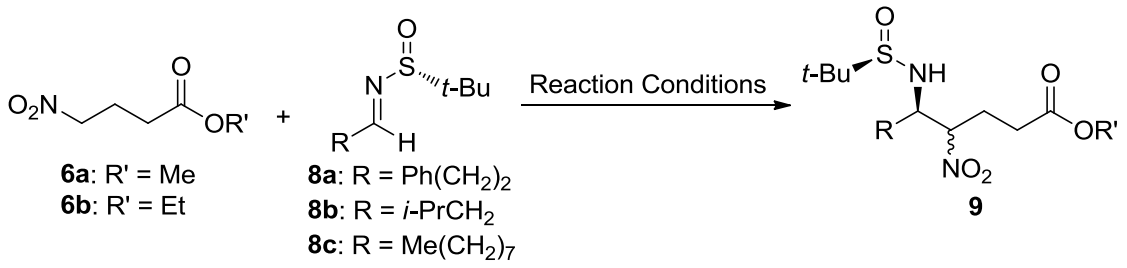
Methyl and ethyl 4-nitrobutanoate (**6a** and **6b**, respectively) were prepared in reasonable yields (42 and 47%, respectively) from the corresponding acrylate **4** and an excess of nitromethane (**5**) in the presence of 0.1 equivalents of sodium hydroxide at 0 to 23 ºC for 12 h. The reaction is performed without an additional solvent. In spite of working with an excess of nitromethane (**5**), compounds resulting from double conjugate addition **7** were also isolated as undesirable side reaction products (Scheme 2).



Scheme 2

As depicted in Scheme 1, our approach to the synthesis of target 6-substituted piperidine-2,5-diones commenced with the diastereoselective aza-Henry reaction of methyl or ethyl 4-nitrobutanoate (**6a** or **6b**, respectively) with *N*-*tert*-butanesulfinyl imines **8**. These chiral imines **8** were easily accessible from (*R*)-*tert*-butanesulfinamide and the corresponding aldehyde.[12] First, imine **8a** (derived from 3-phenylpropanal) was taken as the model compound in order to determine the optimal reaction conditions to carry out the coupling of nitro compounds **6** with chiral imines **8**. Sodium bicarbonate has recently been used successfully in our group as a promoter of the condensation of nitromethane (**5**) and nitroethane with sulfinyl imines **8**.[10t] The reaction of 3 equivalents of methyl 4-nitrobutanoate (**6a**) with **8a** in the presence of 2 equivalents of sodium bicarbonate at 60 ºC for 3 days led to the expected aza-Henry product **9aa** in relatively low yield (Table 1, entry 1). Ethyl 4-nitrobutanoate (**6b**), under the same reaction conditions, produced **9ab** even in lower yield (Table 1, entry 2). Very low yield was also obtained when the reaction was performed under sonication for 7 h, using the same reaction mixture of **6a, 8a** and sodium bicarbonate (Table 1, entry 3). Interestingly, yield was significantly improved (from 37 to 80%) when the coupling of **6a** and **8a** was performed in the presence of 0.2 equivalents of sodium hydroxide as a base at 40 °C for 24 h (Table 1, entry 4). Fortunately, the sodium hydroxide promoted reaction of imine **8a** with ethyl 4-nitrobutanoate (**6b**) led to expected adduct **9ab** in a satisfactory 76% isolated yield (Table 1, entry 5). In order to broaden the scope of the sodium hydroxide promoted aza-Henry reaction, we applied the optimized conditions depicted in Table 1, entries 4 and 5, to *N*-*tert*-butanesulfinyl imines **8b** and **8c**. Thus, the reaction of imine **8b** derived from isovaleraldehyde with methyl and ethyl 4-nitrobutanoate (**6**) gave compounds **9ba** and **9bb** in 69 and 50% yield, respectively (Table 1, entries 6 and 7). Meanwhile, the reactions of nitro compounds **6** with chiral imine **8c** derived from nonanal produced the expected adducts **9ca** and **9cb** in near 50% yield (Table 1, entries 8 and 9). In these reactions, two stereogenic centers are generated, and diastereomeric ratios shown on Table 1 refer to the face selectivity. Regarding the second stereogenic center, an almost 1:1 mixture of epimers were always obtained, due probably to the reaction conditions (prolonged reaction times in the presence of a base), considering that an acidic proton remains in **9**, so epimerization could take place rapidly. Nucleophilic additions of nitro compounds **6** to chiral imines **8** takes place with relatively high diastereoselectivity, diastereomeric ratios ranging in all cases from 87:13 (Table 1, entry 5) to 98:2 (Table 1, entry 6). The stereochemical pathway of these nucleophilic additions to chiral sulfinyl imines was previously studied in depth by us[10t] and others.[13] It was always found that in the case of chiral imines **8** with *R* configuration at the sulphur atom, the attack of the nucleophile occurs predominantly to the *Si*-face of the imine, so the configuration assigned to the newly created stereogenic center bonded to the nitrogen atom in compounds **9** is based in this assumption.

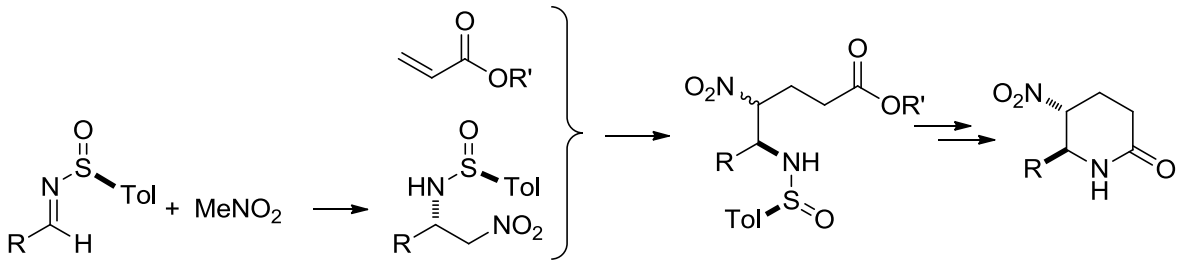
Table 1. Aza-Henry reaction of chiral imines **8** with alkyl 4-nitrobutanoates **6**[a]



Entry	Reaction Conditions	Compound **9** R	R'	No. (Yield)[b]	dr[c]
1	**8a**, **6a** (3 equiv), $NaHCO_3$ (2 equiv), 60 ºC, 3 d	$Ph(CH_2)_2$	Me	**9aa** (37%)	ND
2	**8a**, **6b** (3 equiv), $NaHCO_3$ (2 equiv), 60 ºC, 3 d	$Ph(CH_2)_2$	Me	**9ab** (<10%)	ND
3	**8a**, **6a** (3 equiv), $NaHCO_3$ (2 equiv),))))), 7 h	$Ph(CH_2)_2$	Me	**9aa** (<10%)	ND
4	**8a**, **6a** (3 equiv), NaOH (0.2 equiv), 40 ºC, 24 h	$Ph(CH_2)_2$	Me	**9aa** (80%)	95:5
5	**8a**, **6b** (3 equiv), NaOH (0.2 equiv), 40 ºC, 24 h	$Ph(CH_2)_2$	Et	**9ab** (76%)	87:13
6	**8b**, **6a** (3 equiv), NaOH (0.2 equiv), 40 ºC, 24 h	*i*-$PrCH_2$	Me	**9ba** (69%)	98:2
7	**8b**, **6b** (3 equiv), NaOH (0.2 equiv), 40 ºC, 24 h	*i*-$PrCH_2$	Et	**9bb** (50%)	95:5
8	**8c**, **6a** (3 equiv), NaOH (0.2 equiv), 40 ºC, 24 h	$Me(CH_2)_7$	Me	**9ca** (45%)	92:8
9	**8c**, **6b** (3 equiv), NaOH (0.2 equiv), 40 ºC, 24 h	$Me(CH_2)_7$	Et	**9cb** (49%)	90:10

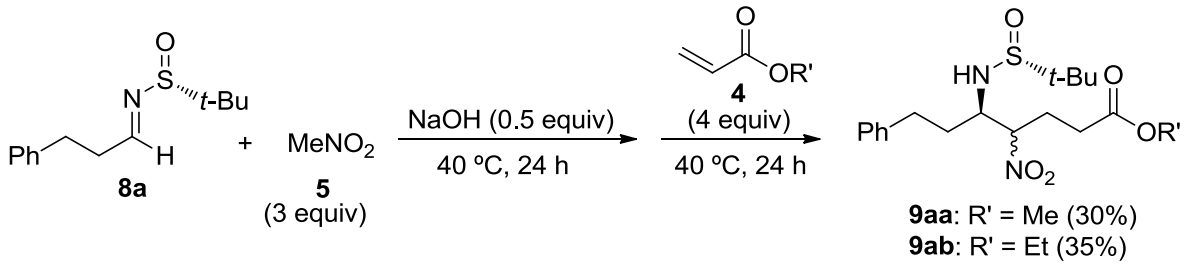
[a] All the reactions were carried out with 0.2 mmol of aldimine **8**. [b] Yield was determined for isolated compound after column chromatography. [c] The diastereomeric ratio was determined by ^{1}H NMR of the crude reaction mixture and refers to the facial selectivity.

Compounds of type **9** were previously prepared by García Ruano, Cid and co-workers, following a slightly different strategy. They performed first the nucleophilic addition of nitromethane (**5**) to a chiral *N*-*p*-toluenesulfinyl imine, and subsequently, the DBU-promoted Michael addition of the resulting β-nitroamino derivative to the corresponding acrylate. These compounds were later transformed into the 6-substituted 5-nitropiperidin-2-ones as shown in Scheme 3.[14]



Scheme 3

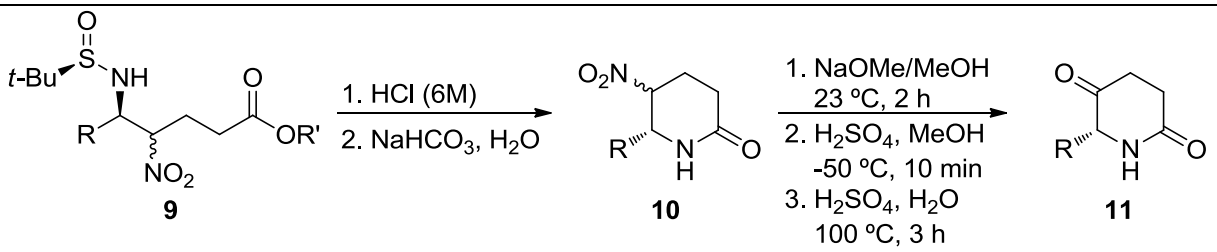
We found also of interest, to reach compounds **9** through a one-pot multicomponent assembling of nitromethane (**5**), chiral imines **8** and acrylates **4**. Benefits of the multicomponent processes use to include decreased operational costs associated with time and labor. For that reason we studied first this reaction with chiral aldimine **8a** as a model imine. Different reaction conditions were applied (stoichiometry, temperature, reaction time, base, reagents addition order, solvent) and the highest yield of the expected adducts **9aa** and **9ab** were obtained when the imine **8a** reacted first with 3 equivalents of nitromethane (**5**) in the presence of 0.5 equivalents of sodium hydroxide at 40 ºC for 24 h, and after that, 4 equivalents of the corresponding acrylate **4** were added maintaining the reaction mixture at the same temperature for 24 additional hours. The methyl ester derivative **9aa** was obtained in 30% yield and the ethyl derivative **9ab** in 35% yield (Scheme 4). The here described one-pot methodology does not seem to be superior to the multistep strategy previously commented.



Scheme 4

Removal of the *tert*-butanesulfinyl group in compounds **9** was achieved under acidic conditions. Further treatment of the initially formed ammonium chloride salt with an aqueous saturated solution of sodium bicarbonate produced the free amine, which underwent rapid intramolecular cyclization to give 6-substituted 5-nitropiperidin-2-one **10** as a mixture of diastereoisomers in an almost 3:1 ratio, *trans*-isomer being the major component of the mixture. Pure diastereoisomers were obtained after column chromatography purification. In general, yields were slightly higher in the case of the methyl ester derivatives (Table 2). Finally, compounds **10**, as a diastereomeric mixture, were transformed into piperidine-2,5-diones **11** under typical Nef reaction conditions. First treatment with sodium methoxide in methanol to generate the corresponding nitronate at room temperature, followed by addition of a methanolic solution of sulfuric acid and final hydrolysis at low temperature. After that, the expected dione **11** was formed along with the corresponding dimethyl acetal, since the protonation of the nitronate was performed in a mixture of methanol and water. A second hydrolysis at 100 ºC in water under acidic conditions of the residue resulting after removing of volatile solvents gave the expected piperidine-2,5-dione **11** as a single isomer (Table 2).

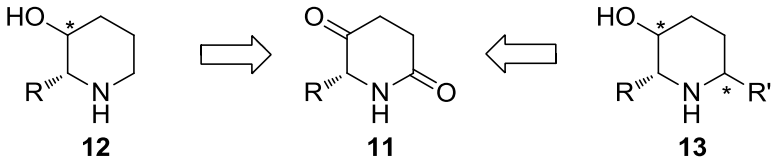
Table 2. Synthesis of 6-substituted piperidine-2,5-diones **11** from compounds **9**



	Starting Compound **9**			Compound **10**		Compound **11**	
Entry	R	R'	No.	R	No. (Yield)[a]	R	No. (Yield)[b]
1	$Ph(CH_2)_2$	Me	**9aa**	$Ph(CH_2)_2$	**10a** (40%)	$Ph(CH_2)_2$	**11a** (66%)
2	$Ph(CH_2)_2$	Et	**9ab**	$Ph(CH_2)_2$	**10a** (23%)		
3	*i*-$PrCH_2$	Me	**9ba**	*i*-$PrCH_2$	**10b** (43%)	*i*-$PrCH_2$	**11b** (55%)
4	*i*-$PrCH_2$	Et	**9bb**	*i*-$PrCH_2$	**10b** (47%)		
5	$Me(CH_2)_7$	Me	**9ca**	$Me(CH_2)_7$	**10c** (60%)	$Me(CH_2)_7$	**11c** (50%)
6	$Me(CH_2)_7$	Et	**9cb**	$Me(CH_2)_7$	**10c** (50%)		

[a] Combined yield was determined for the mixture of diastereoisomers after column chromatography purification. [b] Yield was determined for isolated compounds after column chromatography.

In summary, enantioenriched 6-substituted piperidine-2,5-diones **11** were prepared in few synthetic operations from commercially available starting materials. The methodology presented here comprised as key steps a diastereoselective addition of a 4-nitrobutanoate to a chiral sulfinyl imine, and a Nef reaction for the transformation of the nitro group into ketone. Studies are currently in progress trying to find reaction conditions for the stereoselective transformation of 6-substituted piperidine-2,5-diones **11** into 2-substituted piperidin-3-ols **12** and 2,6-disubstituted piperidin-3-ols **13** (Scheme 5), compounds of potential biological activity.



Scheme 5

EXPERIMENTAL

All chemicals were commercially available (Acros, Aldrich). TLC was performed on Merck silica gel 60 F_{254}, using aluminum plates and visualized with phosphomolybdic acid (PMA) stain. Chromatographic purification was performed by flash chromatography using Merck silica gel 60 (0.040-0.063 mm) and

hexane/EtOAc as eluent. Low-resolution electron impact (EI) mass spectra were obtained at 70eV on Agilent GC/MS-5973N apparatus equipped with a HP-5MS column (Agilent technologies, 30 m × 0.25 mm) and high resolution mass spectra (HRMS-ESI) were obtained on a Waters LCT Premier XE apparatus equipped with a time of flight (TOF) analyzer and the samples were ionized by ESI techniques and introduced through an ultra-high pressure liquid chromatograph (UPLC) model Waters ACQUITY H CLASS. IR spectra were measured (film) with a Nicolet Impact 510 P-FT Spectrometer. NMR spectra were recorded with a Bruker AC-300 using $CDCl_3$ as the solvent and TMS as internal standard. Optical rotations were measured on a Perkin Elmer 341 polarimeter. Starting aldimines **8a**,[15] **8b**[16] and **8c**[17] were prepared according to the procedures reported in the literature from (*R*)-*tert*-butanesulfinamide and the corresponding aldehyde.

Preparation of 4-nitrobutanoates 6. General procedure.

To a solution of NaOH (20 g, 0.5 mmol) in nitromethane (1.525 g, 1.3 mL, 25 mmol) was added the corresponding acrylate **4** (5 mmol) at 0 ºC. The reaction mixture was stirred for 12 h and the system was allowed to reach room temperature. Then, the resulting mixture was hydrolyzed with H_2O (20 mL) and extracted with EtOAc (3 × 15 mL). The organic layer was washed with brine (2 × 10 mL), dried over anhydrous $MgSO_4$ and evaporated (15 Torr). The resulting residue was purified by distillation under vacuum to give pure products **6**. Yields are given in Scheme 2. Physical and spectroscopic data follow.

Methyl 4-nitrobutanonate (6a).[18] Colourless oil; bp 120-122 ºC (2,4 mbar); R_f 0.45 (hexane/EtOAc: 3/1); IR ν (film) 2991, 2951, 1731, 1548, 1436, 1372, 1200, 1171 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 4.49 (2H, t, J = 6.6 Hz, CH_2), 3.71 (3H, s, Me), 2.48 (2H, t, J = 6.8 Hz, CH_2), 2.40-2.21 (2H, m, CH_2); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.3 (C), 74.3 (CH_2), 51.9 (Me), 30.2, 22.3 (CH_2); LRMS (EI) *m/z* 116 (M^+-MeO, 35%), 100 (9), 88 (11), 69 (10), 59 (100).

Ethyl 4-nitrobutanonate (6b).[19] Colourless oil; bp 123-125 ºC (2,4 mbar); R_f 0.46 (hexane/EtOAc: 3/1); IR ν (film) 2983, 2946, 2908, 1728, 1550, 1435, 1376, 1177, 1027 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 4.49 (2H, t, J = 6.6 Hz, CH_2), 4.16 (2H, q, J = 7.1 Hz, CH_2), 2.47 (2H, t, J = 6.8 Hz, CH_2), 2.32 (2H, quint, J = 6.8 Hz, CH_2), 1.27 (3H, t, J = 7.1 Hz, Me); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.8 (C), 74.3, 60.9, 30.5, 22.4 (CH_2), 14.1 (Me); LRMS (EI) *m/z* 116 (M^+-MeO, 35%), 100 (9), 88 (11), 69 (10), 59 (100).

Preparation of β-nitroamine derivatives 9 from nitrobutanoates 6 and chiral imines 8. General procedure.

A mixture of the corresponding nitrocompound **6** (6.0 mmol), NaOH (16 mg, 0.4 mmol), and the corresponding *N*-*tert*-butanesulfinyl imine **8** (2.0 mmol) was stirred at 40 ºC for 24 h. The resulting

mixture was hydrolyzed with H_2O (15 mL) and extracted with EtOAc (3 × 15 mL). The organic layer was washed with brine (2 × 10 mL), dried over anhydrous $MgSO_4$, and evaporated (15 Torr). The residue was purified by column chromatography (silica gel) to yield pure compounds **9**. Yields are given in Table 1. Physical and spectroscopic data follow.

(4*R,5*R*,*R*$_S$)-Methyl *N*-(*tert*-butanesulfinyl)-5-amino-4-nitro-7-phenylheptanoate (9aa)**. Mixture of diastereoisomers (1:1); yellow oil; R_f 0.31 (hexane/EtOAc: 1/1); IR ν (film) 2947, 2927, 2868, 1734, 1546, 1454, 1437, 1364, 1174, 1052, 749, 700 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.35-7.10 (10H, m, ArH), 5.00-4.91 (1H, m, CH), 4.90-4.82 (1H, m, CH), 4.32 (1H, d, *J* = 8.6 Hz, NH), 4.27 (1H, d, *J* = 9.5 Hz, NH), 3.69 (3H, s, Me), 3.68 (3H, s, Me), 3.64-3.46 (2H, m, CH_2), 2.97-2.77 (2H, m, CH_2), 2.77-2.56 (2H, m, CH_2), 2.54-2.19 (8H, m, 4 × CH_2), 1.95-1.78 (4H, m, 2 × CH_2) , 1.31 [9H, s, Me_3C], 1.28 [9H, s, Me_3C]; ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.3, 140.2 (C), 128.6, 128.4, 128.3, 126.3, 90.6, 89.6, 58.5, 57.8 (CH), 56.8, 56.7 (C), 51.9 (Me), 35.6, 32.4, 32.0, 31.8, 30.2, 29.6, 26.1, 25.0 (CH_2), 22.8, 22.7 (Me); LRMS (EI) *m/z* 264 [M^+-Ph(CH_2)$_2$-Me, 33%], 232 (11), 231 (16), 218 (25), 217 (58), 207 (12), 185 (27), 183 (19), 158 (15), 143 (37), 141 (16), 139 (28), 133 (21), 132 (29), 129 (22), 128 (20), 115 (26), 91 (100), 77 (20), 65 (16), 55 (21); HRMS (ESI) calcd for $C_{18}H_{29}N_2O_5S$ (M+H) 385.1797, found 385.1791.

(4*R,5*R*,*R*$_S$)-Ethyl *N*-(*tert*-butanesulfinyl)-5-amino-4-nitro-7-phenylheptanoate (9ab)**. Mixture of diastereoisomers (1:1); yellow oil; R_f 0.28 (hexane/EtOAc: 1/1); IR ν (film) 2981, 2958, 2918, 1731, 1547, 1455, 1368, 1241, 1182, 1047, 700 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.36-7.07 (10H, m, ArH), 4.93 (1H, ddd, *J* = 9.0, 6.2, 2.5 Hz, CH), 4.87 (1H, dt, *J* = 6.9, 4.2 Hz, CH), 4.31 (1H, d, *J* = 8.6 Hz, NH), 4.24 (1H, d, *J* = 9.5 Hz, NH), 4.13 (2H, q, *J* = 7.1 Hz, CH_2), 4.12 (2H, q, *J* = 7.1 Hz, CH_2), 3.66-3.43 (2H, m, 2 × CH), 2.95-2.74 (2H, m, CH_2), 2.76-2.53 (2H, m, CH_2), 2.52-2.15 (7H, m, 3 × CH_2, C*H*H), 2.14-1.97 (1H, m, CH*H*), 1.95-1.77 (3H, m, CH_2, C*H*H), 1.73-1.58 (1H, m, CH*H*), 1.30 [9H, s, Me_3C], 1.27 [9H, s, Me_3C], 1.24 (6H, t, *J* = 7.2 Hz, 2 × Me); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.9, 140.3 (C), 128.6, 128.4, 128.3, 126.3, 90.6, 89.6 (CH), 60.9, 60.8 (CH_2), 58.5, 57.8 (CH), 56.8, 56.6 (C), 35.7, 32.4, 32.0, 31.8, 30.4, 29.7, 26.1, 25.0 (CH_2), 22.8, 22.7, 14.1 (Me); LRMS (EI) *m/z* 313 [M^+-Me_2C=CH_2-Et, 1%], 182 (47), 157 (20), 144 (14), 143 (100), 141 (25), 129 (32), 128 (28), 115 (20), 111 (13), 91 (67); HRMS (ESI) calcd for $C_{19}H_{31}N_2O_5S$ (M+H) 399.1954, found 399.1941.

(4*R,5*R*,*R*$_S$)-Methyl *N*-(*tert*-butanesulfinyl)-5-amino-7-methyl-4-nitrooctanoate (9ba)**. Mixture of diastereoisomers (1:1); yellow oil; R_f 0.30 (hexane/EtOAc: 1/1); IR ν (film) 3193, 2957, 2929, 2870, 1736, 1548, 1438, 1173, 1028 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.99-4.90 (1H, m, CH), 4.86-4.77 (1H, m, CH), 4.19 (1H, d, *J* = 9.1 Hz, NH), 4.15 (1H, d, *J* = 9.9 Hz, NH), 3.71 (3H, s, Me), 3.70 (3H, s, Me), 3.67-3.56 (2H, m, CH), 2.60-2.34 (6H, m, 3 × CH_2), 2.33-2.20 (1H, m, C*H*H), 2.20-2.09 (1H, m, CH*H*), 1.88-1.70 (2H, m, CH_2), 1.55-1.42 (2H, m, CH_2), 1.34-1.28 (2H,m, 2 × CH), 1.26 [9H, s, Me_3C], 1.25[9H,

s, Me_3C], 0.93 (3H, d, *J* = 0.9 Hz, Me), 0.92 (3H, d, *J* = 0.9 Hz, Me), 0.90 (3H, d, *J* = 1.9 Hz, Me), 0.89 (3H, d, *J* = 1.9 Hz, Me); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.4, 172.3 (C), 91.1, 90.0, 57.8 (CH), 56.8 (C), 56.7 (CH), 56.6 (C), 52.0, 51.9 (Me), 42.6, 39.3, 30.5, 29.7, 26.0, 25.0 (CH_2), 24.3, 24.2 (CH), 23.4, 23.0, 22.8, 22.7, 21.3, 21.0 (Me); LRMS (EI) *m/z* 280 (M^+-C_4H_8, 1%), 153 (29), 143 (15), 138 (11), 111 (100), 97 (83), 84 (13), 83 (19), 82 (19), 69 (18), 55 (27); HRMS (ESI) calcd for $C_{14}H_{29}N_2O_5S$ (M+H) 337.1797, found 337.1790.

(4*R,5*R*,*R*$_S$)-Ethyl *N*-(*tert*-butanesulfinyl)-5-amino-7-methyl-4-nitrooctanoate (9bb)**. Mixture of diastereoisomers (1:1); yellow oil; R_f 0.31 (hexane/EtOAc: 1/1); IR ν (film) 3218, 2958, 2870, 1732, 1546, 1365, 1181, 1051 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.00-4.90 (1H, m, CH), 4.88-4.78 (1H, m, CH), 4.25-4.78 (6H, m, 2 × NH, 2 × CH_2), 3.71-3.55 (2H, m, 2 × CH), 2.62-2.18 (10H, m, 5 × CH_2), 1.87-1.72 (2H, m, 2 × CH), 1.56-1.38 (2H, m, CH_2), 1.35-1.16 [24H, m, 2 × Me_3C, 2 × Me] 1.01-0.84 (12H, 4 × Me); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.0, 171.9 (C), 91.1, 89.9 (CH), 60.9, 60.8 (CH_2), 57.7 (CH), 56.7 (C), 56.6 (CH), 56.5 (C), 42.5, 39.3, 30.6, 29.9, 26.0, 25.0 (CH_2), 24.2, 24.1 (CH), 23.3, 23.0, 22.7, 22.6, 21.2, 21.0, 14.1 (Me); LRMS (EI) *m/z* 335 (M^+-Me, 1%), 216 (38), 185 (10), 170 (56), 169 (71), 157 (20), 141 (100), 124 (13), 123 (94), 113 (47), 111 (29), 99 (44), 95 (40), 71 (67), 67 (37), 60 (16), 55 (53); HRMS (ESI) calcd for $C_{15}H_{31}N_2O_5S$ (M+H) 351.1954, found 351.1950.

(4*R,5*R*,*R*$_S$)-Methyl *N*-(*tert*-butanesulfinyl)-5-amino-4-nitrotridecanoate (9ca)**. Mixture of diastereoisomers (1:1); pale yellow oil; R_f 0.40 (hexane/EtOAc: 1/1); IR ν (film) 3242, 2953, 2925, 2925, 2855, 1736, 1547, 1056, 733 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.97-4.78 (2H, m, 2 × CH), 4.23 (1H, d, *J* = 8.7 Hz, NH), 4.14 (1H, d, *J* = 8.3 Hz, NH), 3.71 (3H, s, Me), 3.71 (3H, s, Me), 3.64-3.46 (2H, m, 2 × CH), 2.61-2.15 (8H, m, 4 × CH_2), 1.61-1.44 (8H, m, 4 × CH_2), 1.40-1.14 [38H, m, 10 × CH_2, 2 × Me_3C], 0.89 (6H, t, *J* = 6.6 Hz, 2 × Me); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.4 (C), 90.8, 89.7, 59.4, 58.6 (CH), 56.7, 56.6 (C), 52.0, 51.9 (Me), 33.8, 31.8, 30.4, 29.7, 29.3, 29.1, 29.0, 26.1, 25.9, 25.8 (CH_2), 22.8, 22.7 (Me), 22.6 (CH_2), 14.05 (Me); LRMS (EI) *m/z* 317 (M^+-$C_2H_3O_3$, 3%), 270 (17), 256 (16), 238 (19), 224 (16), 208 (21), 196 (17), 187 (19), 140 (17), 110 (34), 97 (33), 96 (57), 95 (24), 85 (16), 83 (44), 82 (100), 81 (33), 80 (17), 79 (17), 71 (20), 69 (42), 68 (30), 67 (42), 64 (46), 59 (35), 57 (55), 56 (44), 55 (82), 54 (67), 53 (25); HRMS (ESI) calcd for $C_{18}H_{37}N_2O_5S$ (M+H) 393.2423, found 393.2418.

(4*R,5*R*,*R*$_S$)-Ethyl *N*-(*tert*-butanesulfinyl)-5-amino-4-nitrotridecanoate (9cb)**. Mixture of diastereoisomers (1:1); colourless oil; R_f 0.41 (hexane/EtOAc: 1/1); IR ν (film) 2957, 2925, 2856, 1734, 1547, 1365, 1181, 1053 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.97-4.78 (2H, m, CH), 4.27-4.02 (6H, m, 2 × NH, 2 × CH_2), 3.61-3.46 (2H, m, 2 × CH), 2.59-2.18 (10H, m, 5 × CH_2), 1.64-1.41 (6H, m, 3 × CH_2), 1.38-1.13 [44H, 10 × CH_2, 2 × Me, 2 × Me_3C], 0.88 (6H, t, *J* = 6.7 Hz, 2 × Me); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.9 (C), 90.8, 89.6 (CH), 60.9, 60.8 (CH_2), 59.3, 58.5 (CH), 56.6, 56.5 (C), 33.7, 31.7, 29.8,

29.3, 29.2, 29.1, 29.0, 28.9, 26.1, 25.8, 25.7, 25.0 (CH_2), 23.0, 22.7, 22.6 (Me), 22.5 (CH_2), 14.1, 14.0 (Me); LRMS (EI) *m/z* 335 (M^+-C_4H_8-Me, 1%), 187 (18), 170 (11), 143 (20), 140 (20), 129 (50), 113 (19), 110 (24), 100 (49), 97 (30), 96 (43), 95 (31), 90 (24), 83 (35), 82 (42), 81 (42), 71 (22), 70 (14), 69 (55), 68 (17), 67 (39), 64 (36), 63 (18), 57 (63), 56 (37), 55 (100), 54 (27), 53 (16); HRMS (ESI) calcd for $C_{19}H_{39}N_2O_5S$ (M+H) 407.2580, found 407.2573.

Preparation of β-nitroamine derivatives 9aa and 9ab from nitromethane 5, acrylates 4 and chiral imine 8a. General procedure.

A mixture of NaOH (6 mg, 0.15 mmol), nitromethane (55 mg, 0.049 mL, 0.9 mmol) and the chiral imine **8a** (71 mg, 0.3 mmol) was stirred at 40 ºC for 24 h. After that, the excess of nitromethane (**5**) is removed under vacuum (15 Torr). To the resulting residue the corresponding acrylate **4** (1.2 mmol) was added and the reaction mixture was stirred at 40 ºC for additional 24 h. Then, the resulting mixture was hydrolyzed with H_2O (10 mL) and extracted with EtOAc (3 × 10 mL). The organic layer was washed with brine (2 × 10 mL), dried over anhydrous $MgSO_4$ and evaporated (15 Torr). The residue was purified by column chromatography (silica gel, hexane/EtOAc) to yield pure compounds **9aa** and **9ab**. Yields are given in Scheme 4. Physical and spectroscopic data are given above.

Preparation of 6-substituted-5-nitropiperidin-2-ones 10. General procedure.

To a solution of the corresponding β-nitroamino derivative **9** (0.5 mmol) in THF (0.5 mL) was added dropwise a 6M solution of HCl (0.25 mL, 1.5 mmol) at 0 ºC. The reaction mixture was stirred at this temperature for 4 h and after that basified with saturated aqueous solution of $NaHCO_3$. Then stirring was continued at room temperature for 20 min. Then, the resulting mixture was extracted with EtOAc (3 × 10 mL). The organic layer was washed with brine (2 × 10 mL), dried over anhydrous $MgSO_4$ and evaporated (15 Torr). The residue was purified by column chromatography (silica gel, hexane/EtOAc) to yield pure compounds **10**. Yields are given in Table 2. Physical and spectroscopic data follow.

(5*S*,6*R*)-5-Nitro-6-(2-phenylethyl)piperidin-2-one *trans*-(10a). White solid; mp 110-112 ºC (hexane/CH_2Cl_2); $[\alpha]^{20}_D$ +71 (*c* 0.79, CH_2Cl_2); R_f 0.25 (hexane/EtOAc: 1/2); IR ν (KBr) 3182, 3025, 2918, 2858, 1656, 1555, 1348, 1349, 802, 747, 698 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.41-7.08 (5H, m, ArH), 6.30 (1H, s, NH), 4.71-4.47 (1H, m, CH), 4.25-3.97 (1H, m, CH), 2.91-2.75 (1H, m, C*H*H), 2.76-2.63 (1H, m, CH*H*), 2.63-2.41 (3H, m, CH_2, C*H*H), 2.41-2.25 (1H, m, CH*H*), 2.00-1.82 (2H, m, CH_2); ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.7, 139.4 (C), 128.9, 128.2, 126.7, 82.7, 54.0 (CH), 36.3, 31.2, 27.7, 23.8 (CH_2); LRMS (EI) *m/z* 248 (M^+, 0.5%), 202 (22), 201 (100), 143 (13), 105 (13), 97 (59), 92 (16), 91 (96), 69 (11), 65 (11), 55 (14); HRMS (ESI) calcd for $C_{13}H_{17}N_2O_3$ (M+H) 249.1239, found

249.1227.

(5*R*,6*R*)-5-Nitro-6-(2-phenylethyl)piperidin-2-one *cis*-(10a). White solid; mp 108-113 ºC (hexane/CH_2Cl_2); $[\alpha]^{20}_D$ +85 (*c* 1.04, CH_2Cl_2); R_f 0.12 (hexane/EtOAc: 1/2); IR ν (KBr) 3187, 3070, 2941, 2922, 1655, 1540, 1405, 747, 704 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.40-7.14 (5H, m, ArH), 6.84 (1H, s, NH), 4.87 (1H, dd, *J* = 9.7, 4.5 Hz, CH), 3.86-3.68 (1H, m, CH), 2.94-2.60 (3H, m, CH_2, C*H*H), 2.60-2.38 (2H, m, CH_2), 2.30-2.14 (1H, m, C*H*H), 1.89 (2H, dd, *J* = 14.8, 7.6 Hz, CH_2); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.7, 139.5 (C), 128.7, 128.3, 126.6, 80.8, 53.0 (CH), 33.2, 31.4, 27.2, 22.9 (CH_2); LRMS (EI) *m/z* 248 (M^+, 1%), 202 (24), 201 (100), 143 (16), 105 (11), 97 (63), 92 (14), 91 (93), 69 (14), 55 (17); HRMS (ESI) calcd for $C_{13}H_{17}N_2O_3$ (M+H) 249.1239, found 249.1229.

(5*S*,6*R*)-6-Isobutyl-5-nitropiperidin-2-one *trans*-(10b). White solid; mp 127-129 ºC (hexane/CH_2Cl_2); $[\alpha]^{20}_D$ +49 (*c* 0.78, CH_2Cl_2); R_f 0.21 (hexane/EtOAc: 1/3); IR ν (KBr) 3193, 3074, 2957, 2927, 2868, 1657, 1555, 1406, 1375, 1353, 779 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 6.48 (1H, s, NH), 4.51 (1H, dt, *J* = 6.8, 4.8 Hz, CH), 4.13 (1H, ddd, *J* = 9.8, 6.2, 2.0 Hz, CH), 2.63-2.50 (3H, m, CH_2, C*H*H), 2.50-2.41 (1H, m, CH*H*), 2.39-2.28 (1H, m, C*H*H), 1.83-1.63 (1H, m, CH), 1.54 (1H, ddd, *J* = 14.5, 9.3, 5.3 Hz, C*H*H), 1.37 (1H, m, *J* = 13.7, 9.2, 4.4 Hz, CH*H*), 0.98 (3H, d, *J* = 6.6 Hz, Me), 0.95 (3H, d, *J* = 6.6 Hz, Me); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.0 (C), 83.3, 52.5 (CH), 43.8, 27.6 (CH_2), 24.2 (CH), 23.6 (CH_2), 23.1, 21.3 (Me); LRMS (EI) *m/z* 157 (M^+-C_3H_7, 1%), 153 (44), 138 (16), 112 (13), 111 (100), 97 (96), 83 (15), 82 (15), 69 (13), 55 (16); HRMS (ESI) calcd for $C_9H_{17}N_2O_3$ (M+H) 201.1239, found 201.1229.

(5*S*,6*R*)-5-Nitro-6-octylpiperidin-2-one *trans*-(10c). White solid; mp 96-99 ºC (hexane/CH_2Cl_2); $[\alpha]^{20}_D$ +44 (*c* 0.93, CH_2Cl_2); R_f 0.38 (hexane/EtOAc: 1/3); IR ν (KBr) 3203, 2919, 2848, 1656, 1556, 1405, 1352, 793, 626 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 6.49 (1H, s, NH), 4.56 (1H, dt, *J* = 11.1, 5.5 Hz, CH), 4.06 (1H, td, *J* = 7.6, 1.8 Hz, CH), 2.63-2.40 (3H, m, CH_2, C*H*H), 2.39-2.28 (1H, m, CH*H*), 1.61-1.56 (2H, m, CH_2), 1.48-1.44 (1H, m, C*H*H), 1.37-1.27 (11H, m, CH*H*, 5 × CH_2), 0.88 (3H, t, *J* = 6.9 Hz, Me); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.0, 82.8, 54.5 (CH), 34.5, 31.7, 29.2, 29.1, 29.05, 27.6, 24.8, 23.8, 22.6 (CH_2), 14.0 (Me); LRMS (EI) *m/z* 210 (M^+-NO_2, 7%), 143 (13), 124 (37), 111 (100), 97 (52), 83 (13), 82 (13), 56 (22); HRMS (ESI) calcd for $C_{13}H_{25}N_2O_3$ (M+H) 257.1865, found 257.1853.

(5*R*,6*R*)-5-Nitro-6-octylpiperidin-2-one *cis*-(10c). White solid; mp 99-103 ºC (hexane/CH_2Cl_2); $[\alpha]^{20}_D$ +84 (*c* 0.44, CH_2Cl_2); R_f 0.23 (hexane/EtOAc: 1/3); IR ν (KBr) 3198, 2918, 2850, 1660, 1537, 1411, 1346, 807 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 6.35 (1H, s, NH), 4.98-4.80 (1H, m, CH), 3.88-3.70 (1H, m, CH), 2.85-2.61 (1H, m, C*H*H), 2.57-2.40 (2H, m, CH_2), 2.28 (1H, ddd, *J* = 15.6, 9.7, 7.4 Hz, CH*H*), 1.64-1.48 (2H, m, CH_2), 1.46-1.14 (12H, m, CH*H*, 6 × CH_2), 0.88 (3H, t, *J* = 6.9 Hz, Me); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.6, 80.7, 54.1 (CH), 31.7, 31.6, 29.2, 29.1, 29.05, 27.2, 25.5, 23.0, 22.6 (CH_2), 14.05 (Me); LRMS (EI) *m/z* 210 (M^+-NO_2, 23%), 208 (15), 143 (51), 112 (13), 98 (15), 97 (100), 96 (14), 69

(17), 56 (17), 55 (34); HRMS (ESI) calcd for $C_{13}H_{25}N_2O_3$ (M+H) 257.1865, found 257.1857.

Preparation of 6-substituted piperidine-2,5-diones 11. General procedure.

To a solution of the corresponding nitropiridinone **10** (0.2 mmol) in MeOH (0.5 mL) was added dropwise a 1M solution of NaOMe in MeOH (0.3 mL, 0.3 mmol) at room temperature. The reaction mixture was stirred at this temperature for 2 h and after that, it was cooled down to -50 ºC. To the resulting reaction mixture was added first a 1M solution of H_2SO_4 in MeOH (0.6 mL, 0.6 mmol) and after 10 min, H_2O (1.0 mL). The reaction mixture was allowed to reach room temperature, basified with saturated aqueous solution of $NaHCO_3$, extracted with EtOAc (3 × 10 mL), dried over anhydrous $MgSO_4$ and evaporated (15 Torr). The resulting residue was suspended in H_2O and then a 1M solution of H_2SO_4 in H_2O (0.02 mL, 0.02 mmol) was added. The reaction mixture was stirred at 100 ºC for 3 h and after that it was cooled down to room temperature, basified with saturated aqueous solution of $NaHCO_3$ and extracted with EtOAc (3 × 10 mL). The organic layer was washed with brine (2 × 10 mL), dried over anhydrous $MgSO_4$ and evaporated (15 Torr). The resulting white solid was purified by column chromatography (silica gel, hexane/EtOAc) to yield pure compounds **11**. Yields are given in Table 2. Physical and spectroscopic data follow.

(*S*)-6-(2-Phenylethyl)piperidine-2,5-dione (11a). White solid; mp 99-102 ºC (hexane/CH_2Cl_2); $[\alpha]^{20}_D$ +29 (*c* 1.02, CH_2Cl_2); R_f 0.24 (hexane/EtOAc: 1/3); IR ν (KBr) 3193, 2957, 2927, 1717, 1663, 1417, 1318, 749, 703 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.33-7.25 (2H, m, ArH), 7.24-7.15 (3H, m, ArH), 6.76 (1H, s, NH), 3.90-3.74 (1H, m, CH), 2.79-2.69 (2H, m, CH_2), 2.69-2.62 (4H, m, 2 × CH_2), 2.25-2.12 (1H, m, C*H*H), 2.10-1.98 (1H, m, CH*H*); ^{13}C NMR (75 MHz, $CDCl_3$) δ 206.1, 172.2, 139.9 (C), 128.7, 128.4, 126.5, 60.1 (CH), 35.3, 34.2, 31.1, 29.0 (CH_2); LRMS (EI) *m/z* 217 (M^+, 100%), 134 (12), 132 (27), 117 (21), 113 (66), 98 (15), 91 (78), 84 (56); HRMS (ESI) calcd for $C_{13}H_{16}NO_2$ (M+H) 218.1181, found 218.1172.

(*S*)-6-Isobutylpiperidine-2,5-dione (11b). White solid; mp 136-139 ºC (hexane/CH_2Cl_2); $[\alpha]^{20}_D$ +23 (*c* 0.23, CH_2Cl_2); R_f 0.21 (hexane/EtOAc: 1/3); IR ν (KBr) 3203, 2957, 2927, 2868, 1719, 1659, 1426, 1314 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 6.37 (1H, s, NH), 3.95-3.76 (1H, m, CH), 2.70-2.66 (4H, m, 2 × CH_2), 1.88-1.65 (2H, m, CH_2), 1.65-1.45 (1H, m, CH), 0.97 (3H, d, *J* = 6.0 Hz, Me), 0.94 (3H, d, *J* = 5.9 Hz, Me); ^{13}C NMR (75 MHz, $CDCl_3$) δ 206.5, 172.0 (C), 59.2 (CH), 41.5, 35.0, 29.1 (CH_2), 24.3 (CH), 23.1, 21.2 (Me); LRMS (EI) *m/z* 141 (M^+-CO, 6%), 126 (6), 112 (9), 86 (26), 84 (100), 57 (9); HRMS (ESI) calcd for $C_9H_{16}NO_2$ (M+H) 170.1181, found 170.1173.

(*R*)-6-Octylpiperidine-2,5-dione (11c). White solid; mp 83-85 ºC (hexane/CH_2Cl_2); $[\alpha]^{20}_D$ +47 (*c* 0.60, CH_2Cl_2); R_f 0.31 (hexane/EtOAc: 1/3); IR ν (KBr) 3222, 2917, 2849, 1717, 1669, 1420, 1328, 724 cm^{-1};

^{1}H NMR (300 MHz, $CDCl_3$) δ 6.26 (1H, s, NH), 3.89-3.74 (1H, m, CH), 2.76-2.61 (4H, m, 2 × CH_2), 1.89-1.64 (2H, m, CH_2), 1.30-1.23 (12H, m, 6 × CH_2), 0.88 (3H, t, *J* = 6.9 Hz, Me); ^{13}C NMR (75 MHz, $CDCl_3$) δ 206.2, 172.0 (C), 60.9 (CH), 35.3, 32.9, 31.8, 29.3, 29.2, 29.1, 29.0, 25.0, 22.6 (CH_2), 14.1, (Me); LRMS (EI) *m/z* 225 (M^+, 1%), 142 (13), 84 (100), 56 (10); HRMS (ESI) calcd for $C_{13}H_{24}NO_2$ (M+H) 226.1807, found 226.1798.

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REFERENCES

1. M. Schneider, *Alkaloids: Chemical and Biological Perspectives*, Vol. 10, ed. by S. W. Pelletier, Pergamon: Oxford, 1996, pp. 55–299.
2. M. A. Wijdeven, F. L. van Delft, and F. P. J. T. Rutjes, *Tetrahedron*, 2010, **66**, 5623.
3. D. Enders, B. Nolte, and J. Runsink, *Tetrahedron: Asymmetry*, 2002, **13**, 587.
4. J. B. Koepeli, J. F. Mead, and J. Brockman, *J. Am. Chem. Soc.*, 1947, **69**, 1837.
5. N. Desideri, A. Galli, J. Sestili, and M. L. Stein, *Arch. Pharm.*, 1992, **325**, 29.
6. (a) G. Ratle, X. Monseur, B. C. Das, J. Yassi, Q. Khuong-Huu, and R. Goutarel, *Bull. Soc. Chim. Fr.*, 1966, 2945; (b) Q. Khuong-Huu, G. Ratle, X. Monseur, and R. Goutarel, *Bull. Soc. Chim. Belg.*, 1972, **81**, 425; (c) Q. Khuong-Huu, G. Ratle, X. Monseur, and R. Goutarel, *Bull. Soc. Chim. Belg.*, 1972, **81**, 443.
7. (a) J. Löfstedt, H. Pettersson-Fasth, and J.-E. Bäckvall, *Tetrahedron*, 2000, **56**, 2225; (b) P. N. M. Botman, F. J. Dommerholt, R. de Gelder, Q. B. Broxterman, H. E. Schoemaker, F. P. J. T. Rutjes, and R. H. Blaauw, *Org. Lett.*, 2004, **6**, 4941; (c) J.-C. Jung and M. A. Avery, *Tetrahedron: Asymmetry*, 2006, **17**, 2479.
8. C. J. Moody, A. P. Lightfoot, and P. T. Gallagher, *J. Org. Chem.*, 1997, **62**, 746.
9. H. Sakagami, T. Kamikubo, and K. Ogasawara, *J. Chem. Soc., Chem. Commun.*, 1996, 1433.
10. (a) F. Foubelo and M. Yus, *Tetrahedron: Asymmetry*, 2004, **15**, 3823; (b) J. C. González-Gómez, F. Foubelo, and M. Yus, *Synlett*, 2008, 2777; (c) M. Medjahdi, J. C. González-Gómez, F. Foubelo, and M. Yus, *Heterocycles*, 2008, **76**, 569; (d) M. Medjahdi, J. C. González-Gómez, F. Foubelo, and M. Yus, *J. Org. Chem.*, 2009, **74**, 7859; (e) H. K. Dema, F. Foubelo, and M. Yus, *Heterocycles*, 2010, **80**, 125; (f) J. C. González-Gómez, M. Medjahdi, F. Foubelo, and M. Yus, *J. Org. Chem.*, 2010, **75**,

6308; (g) H. K. Dema, F. Foubelo, and M. Yus, *Heterocycles*, 2011, **82**, 1411; (h) M. Medjahdi, J. C. González-Gómez, F. Foubelo, and M. Yus, *Eur. J. Org. Chem.*, 2011, 2230; (i) H. K. Dema, F. Foubelo, and M. Yus, *Jordan J. Chem.*, 2011, **6**, 247; (j) J. C. González-Gómez, F. Foubelo, and M. Yus, *Org. Synth.*, 2012, **89**, 88; (k) I. Bosque, J. C. González-Gómez, F. Foubelo, and M. Yus, *J. Org. Chem.*, 2012, **77**, 780 (correction: I. Bosque, J. C. González-Gómez, F. Foubelo, and M. Yus, *J. Org. Chem.*, 2012, **77**, 4190); (l) I. Bosque, J. C. González-Gómez, A. Guijarro, F. Foubelo, and M. Yus, *J. Org. Chem.*, 2012, **77**, 10340; (m) J. A. Sirvent, F. Foubelo, and M. Yus, *Chem. Commun.*, 2012, **48**, 2543; (n) H. K. Dema, F. Foubelo, and M. Yus, *Helv. Chim. Acta*, 2012, **95**, 1790; (o) M. Medjahdi, J. C. González-Gómez, F. Foubelo, and M. Yus, *Heterocycles*, 2012, **86**, 727; (p) M. J. García-Muñoz, F. Zacconi, F. Foubelo, and M. Yus, *Eur. J. Org. Chem.*, 2013, 1287; (q) J. A. Sirvent, F. Foubelo, and M. Yus, *Eur. J. Org. Chem.*, 2013, 2461; (r) J. A. Sirvent, F. Foubelo, and M. Yus, *Heterocycles*, 2018, **88**, 1163; (s) J. A. Sirvent, F. Foubelo, and M. Yus, *J. Org. Chem.*, 2014, **79**, 1356; (t) M. J. García-Muñoz, H. K. Dema, F. Foubelo, and M. Yus, *Tetrahedron: Asymmetry*, 2014, **25**, 362; (u) O. S. R. Barros, J. A. Sirvent, F. Foubelo, and M. Yus, *Chem. Commun.*, 2014, **50**, 6898.

11. For reviews, see: (a) G.-Q. Lin, M.-H. Xu, Y.-W. Zhong, and X.-W. Sun, *Acc. Chem. Res.*, 2008, **41**, 831; (b) F. Ferreira, C. Botuha, F. Chemla, and A. Pérez-Luna, *Chem. Soc. Rev.*, 2009, **38**, 1162; (c) M. A. T. Robak, M. A. Herbage, and J. A. Ellman, *Chem. Rev.*, 2010, **110**, 3600; (d) F. Foubelo and M. Yus, *Eur. J. Org. Chem.*, 2014, 485.
12. T. P. Tang and J. A. Ellman, *J. Org. Chem.*, 1999, **64**, 12.
13. (a) J. L. García Ruano, M. Topp, J. López-Cantarero, J. Alemán, M. J. Remuiñán, and M. B. Cid, *Org. Lett.*, 2005, **7**, 4407; (b) J. L. García Ruano, J. López-Cantarero, T. De Haro, J. Alemán, and M. B. Cid, *Tetrahedron*, 2006, **62**, 12197.
14. J. L. García Ruano, T. de Haro, R. Singh, and M. B. Cid, *J. Org. Chem.*, 2008, **73**, 1150.
15. L. B. Schenkel and J. A. Ellman, *Org. Lett.*, 2004, **6**, 3621.
16. L. Nielsen, K. B. Lindsay, J. Faber, N. C. Nielsen, and T. Skrydstrup, *J. Org. Chem.*, 2007, **72**, 10035.
17. R. Almansa, D. Guijarro, and M. Yus, *Tetrahedron: Asymmetry*, 2008, **19**, 2484.
18. J. Escalante and F. D. Díaz-Coutiño, *Molecules*, 2009, **14**, 1595.
19. B. M. Choudary, M. Lakshmi Kantam, B. Kavita, C. Venkat Reddya, and F. Figueras, *Tetrahedron*, 2000, **56**, 9357.