Synthesis of Substituted 5-(3-Hydroxypropyl)pyrrolidin-2-ones and Pyrrolizidinones from Nitroethane via C3 Functionalized 5,6-Dihydro-4*H*-1,2-oxazines: A Novel Approach to Some Analogues of the Antidepressant Rolipram

Alexey Yu. Sukhorukov, Alexey V. Lesiv, Yulia A. Khomutova, Sema L. Ioffe,* Vladimir A. Tartakovsky

N. D. Zelinsky Institute of Organic Chemistry, Russian Academy of Sciences, Leninsky prosp. 47, 119991 Moscow, Russian Federation
Fax +7(499)1355328; E-mail: iof@ioc.ac.ru

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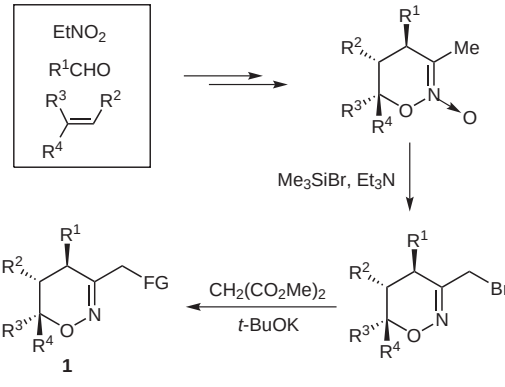
Abstract: Easily accessible [(5,6-dihydro-4*H*-1,2-oxazin-3-yl)methyl]malonates **1** were converted into substituted 5-(3-hydroxypropyl)pyrrolidin-2-ones **2** and pyrrolizidinones **3**, which are versatile products and intermediates for organic and bioorganic chemistry. The synthetic sequence suggested includes stereoselective two-step reduction of an oximino fragment, followed by intramolecular cyclization involving one of the CO_2Me groups and decarboxylation in the last stage. The efficiency of this strategy was demonstrated by the stereoselective synthesis of pyrrolizidinone *rac*-**4**, a highly efficient analogue of antidepressant Rolipram, from nitroethane.

Key words: 5,6-dihydro-4*H*-1,2-oxazines, reduction, pyrrolidones, pyrrolizidinones, Rolipram

Recently we reported a simple and efficient approach to the synthesis of diastereomerically pure 5,6-dihydro-4*H*-1,2-oxazines **1**, bearing a fragment CH_2FG [FG = $CH(CO_2Me)_2$, Scheme 1] at C3, starting from nitroethane and other simple precursors.[1] The resulting six-membered cyclic oxime ethers **1** can be considered as perspective reagents for the preparation of a variety of versatile polyfunctionalized products.

We have now demonstrated the application of dihydrooxazines **1** in the synthesis of unnatural γ-amino acids derivatives,[2] oxaazaspirononanones,[3] substituted dihydrofurans,[4] and pyrroles.[3] However, it is evident that the synthetic potential of dihydrooxazines **1** is not exhausted by these examples. Herein we would like to report the use of dihydrooxazines **1** in the synthesis of diastereomerically pure 5-(3-hydroxypropyl)pyrrolidin-2-ones **2** and pyrrolizidinones **3** (Figure 1).[5]



Scheme 1

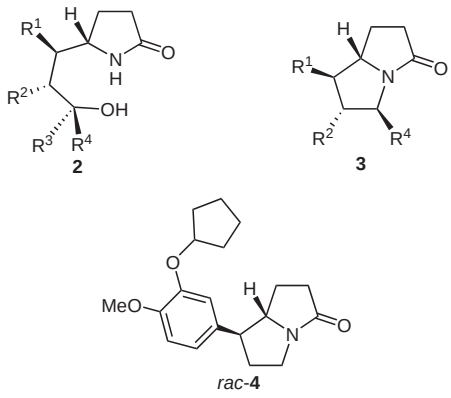


Figure 1

Products of types **2** and **3** have considerable interest as valuable intermediates for the total synthesis of pyrrolizidine alkaloids, such as pseudoheliotridane,[6] isoretronecanol,[7] and platynecine,[8] as well as some biologically active products (e.g., highly selective EP4 antagonists[9]). Furthermore, many heterocycles of types **2** and **3** possess their own high biological activity.[10] Thus, racemic pyrrolizidinone **4** (Figure 1) is several times more active as a cAMP-specific phosphodiesterase (PDE IV) inhibitor than the known antidepressant Rolipram.[11]

Scheme 2 shows the proposed three-step sequence for the transformation of cyclic oxime ethers **1** into pyrrolidinones **2** or pyrrolizidinones **3** (depending on the nature of the substituents at C6 of the oxazine ring). This method includes the selective reduction of a C=N bond (step 1), the subsequent hydrogenolysis of an N–O bond in intermediates **5**, followed by pyrrolidinone ring closure (step 2) and, finally, removal of a CO_2Me group, attached to the pyrrolidinone ring (step 3).

Ring contraction of 5,6-dihydrooxazines to pyrrolidines is known to occur during the hydrogenolysis of six-membered cyclic oxime ethers, bearing an alkoxy group at C6.[12] However, in the synthetic scheme suggested here another process, an intramolecular cyclization involving

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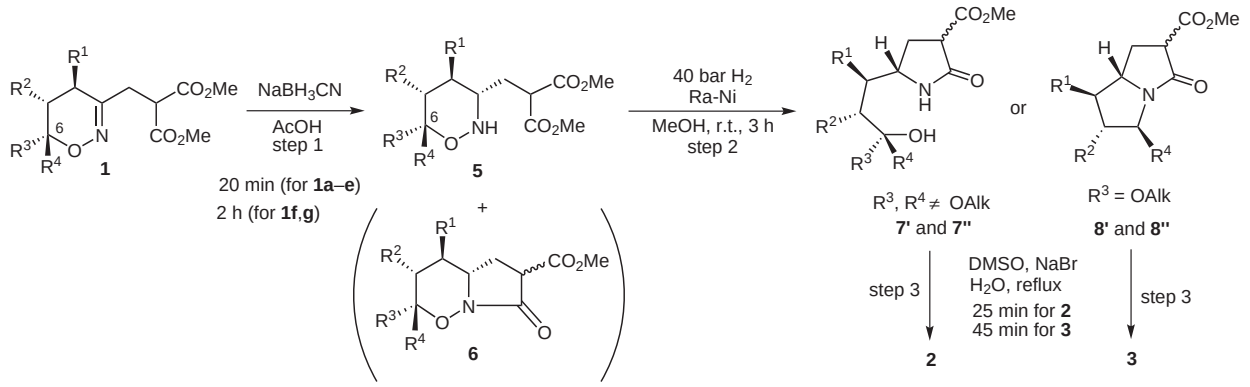


Scheme 2

one of the CO_2Me groups of the FG fragment, is used (Schemes 1 and 2).

As for the formation of the bicyclic skeleton in products **3**, single examples of their synthesis using an approach similar to that indicated in Scheme 2 are known in the literature.[5]

The yields of target and intermediate products are collected in Table 1 and the optimized procedures for the synthesis are illustrated in Scheme 2.

Stereoselective reduction of the C=N bond in dihydrooxazines **1** (step 1, Scheme 2) was accomplished with sodium cyanoborohydride in acetic acid.[2] Recently it was shown,[2] that the products of this transformation, 3,4-*trans*-tetrahydrooxazines **5**, are unstable under the reduction conditions, undergoing an intramolecular ring closure between the nitrogen atom and CO_2Me group to give bicyclic derivatives **6**.[13] Now by decreasing the reaction time from two hours to 20 minutes we were able to obtain individual products **5** in good to high yields. Over the indicated reaction time nearly full conversion of the starting material was observed in most of the examples with the amount of cyclization products being very small. Tetrahydrooxazines **5f**,**g** with R^3 = OAlkyl, which are more stable towards the intramolecular cyclization to **6**, were prepared according to a known procedure ($NaBH_3CN$, AcOH, 2 h).[2]

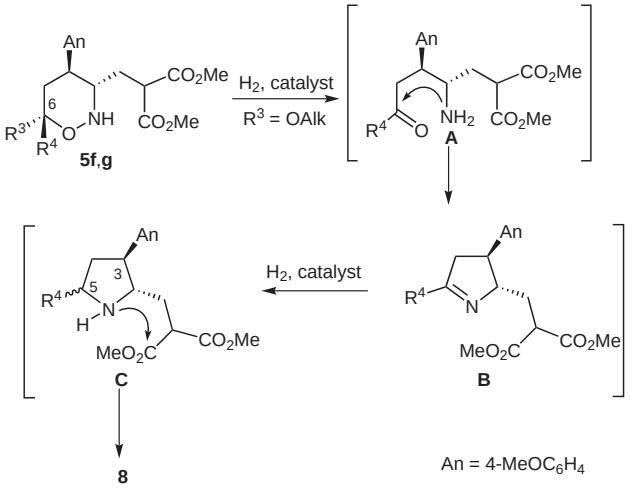
Selective catalytic hydrogenation of the N–O bond in oxazines **5** (step 2, Scheme 2) furnishes products **7** or **8**, which differ from the target heterocycles **2** and **3** in the presence of an additional CO_2Me group. The nature of the resulting product, **7** or **8**, depends on the structure of the tetrahydrooxazine **5**. Catalytic hydrogenation of tetrahydrooxazines **5a**–**e**, which do not possess an alkoxy substituent at C6 (R^3, R^4 ≠ OAlkyl), in the presence of Raney nickel in methanol causes the reductive cleavage of the N–O bond and subsequent intramolecular cyclization of the corresponding amine with one of the CO_2Me groups. Due to these transformations, hydroxy-pyrrolidinones **7** are formed as nearly equimolar mixtures of diastereomers (**7′** and **7″**) differing in the configuration of the stereocenter at C3 bearing the CO_2Me group. In the hydrogenation of oxazine **5d** reductive dehalogenation of a chlorine atom in the aromatic ring also occurs (see Table 1, entry 4).

Catalytic hydrogenation of tetrahydrooxazines **5f**,**g**, bearing an alkoxy substituent at C6 (R^3 = OAlkyl), results in consecutive closures of pyrrolidine and pyrrolidinone rings (Schemes 2 and 3).

Table 1 Synthesis of Products **2** and **3**

Entry	Dihydrooxazine	R^1	R^2	R^3	R^4	Final product [yield[a] (%)]	Product [yield (%)] Step 1	Step 2	Step 3
1	**1a**	Me	H	Me	Me	**2a** [58]	**5a** [82]	**7a** [75]	**2a** [94]
2	**1b**	Ph	H	Me	Me	**2b** [65]	**5b** [76]	**7b** [94]	**2b** [91]
3	**1c**	4-$MeOC_6H_4$	H	Me	Me	**2c** [60]	**5c** [83]	**7c** [87]	**2c** [83]
4	**1d**	4-ClC_6H_4	H	Me	Me	–	**5d** [70]	**7b**[b] [69]	–
5	**1e**	4-$MeOC_6H_4$	$(CH_2)_4$		H	**2e** [39]	**5e** [47[c]]	**7e** [84]	**2e** [99]
6	**1f**	4-$MeOC_6H_4$	H	OEt	H	**3f** [41]	**5f** [82]	**8f** [57]	**3f** [87]
7	**1g**	4-$MeOC_6H_4$	H	OMe	Me	**3g** [42]	**5g** [81]	**8g** [60]	**3g** [86]

[a] Yield of isolated product based on **1**.
[b] The product of hydrogenation is **7b** due to reductive dehalogenation of the chlorine attached to the phenyl ring.
[c] Yield of isolated product based on converted **1e** (conversion of **1e**: 56%).



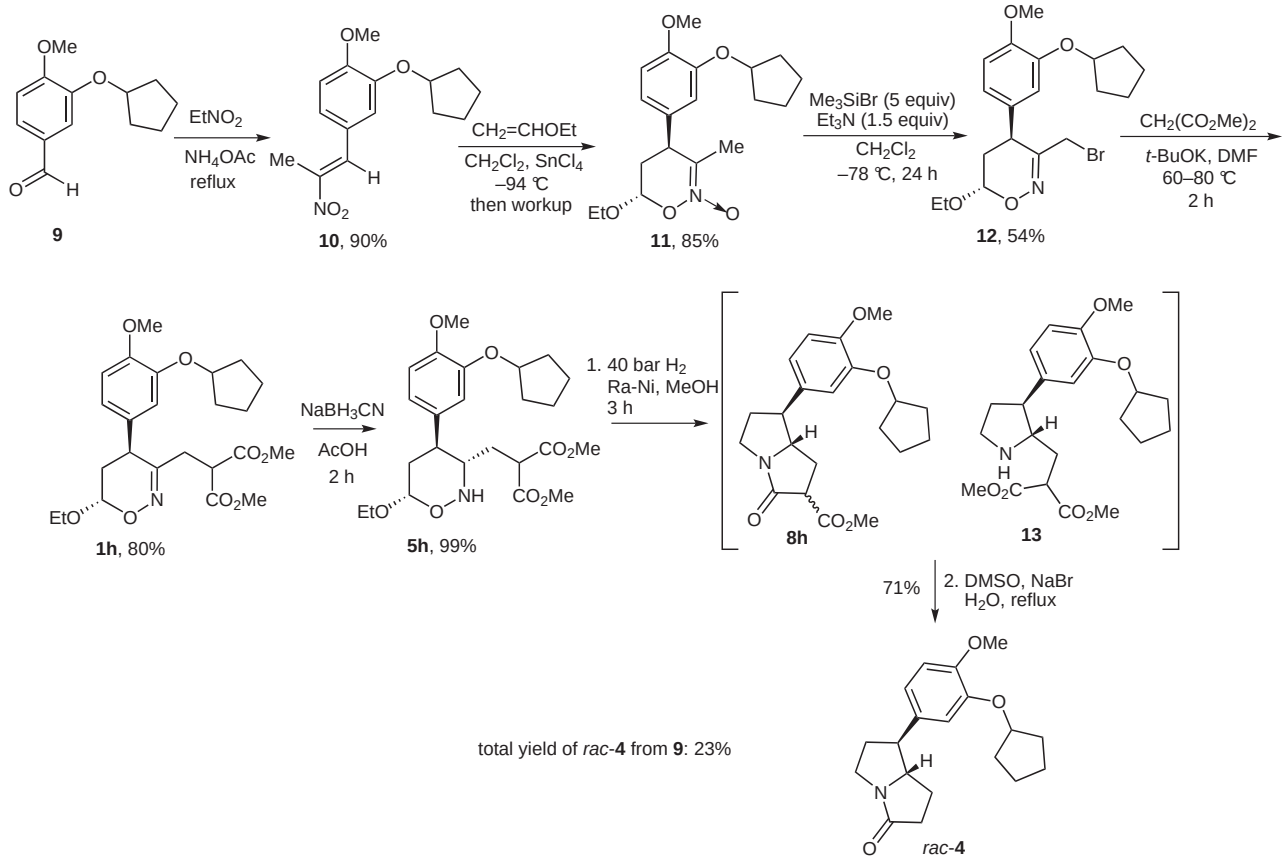
Scheme 3

In the transformation **5f**,**g** into **8f**,**g** the reductive oxazine ring contraction to pyrrolidine, apparently, is a multistep process (Scheme 3), which involves the hydrogenolysis of an N–O bond, leading to intermediate **A**, subsequent recyclization of **A** to dihydropyrrolidine **B** and the reduction of **B** to pyrrolidine **C**.[2,14] Intramolecular cyclization of **C** furnishes a mixture of diastereomeric pyrrolizidinones **8′** and **8″** isolated in good yield by column chromatography.[15]

The final stage, removal of the CO_2Me group (step 3, Scheme 2), was realized by refluxing the products **7** or **8** in wet dimethyl sulfoxide in the presence of sodium bromide.[16] As a result, the target 5-(3-hydroxypropyl)pyrrolidin-2-ones **2** and pyrrolizidinones **3** were obtained from products **7** and **8**, respectively. Thus, dihydrooxazines **1** were converted into target products **2** or **3** in 39–65% overall yields in three steps.

The efficiency of the suggested approach towards the synthesis of α-pyrrolidone derivatives from simple molecules was demonstrated by the stereoselective total synthesis of racemic product **4** (Figure 1). Pyrrolizidinone **4** was shown to be four times more active than the known drug Rolipram.[17]

Details of our strategy for the synthesis of pyrrolizidinone **4** are illustrated in Scheme 4. We started from the known aldehyde **9** available from isovanillin,[18] nitroethane, and ethyl vinyl ether. These reagents were converted into cyclic nitronate **11** according to the two-step protocol developed by S. E. Denmark.[19a,b] The nitronate **11** was isolated as the diastereomerically pure 4,6-*trans*-isomer (trace amount of the corresponding 4,6-*cis*-isomer can be separated from **11** by column chromatography). Silylation of nitronate **11** with excess bromotrimethylsilane/triethylamine mixture and subsequent nucleophilic substitution of bromine with the $CH(CO_2Me)_2$ fragment according to a literature method[1a] provided dihydrooxazine **1h**, the key intermediate in the synthesis of *rac*-**4**, possessing the



Scheme 4

whole carbon skeleton of the target molecule. Diastereoselective reduction of the C=N bond in **1h** with sodium cyanoborohydride in acetic acid according to the procedure listed in Scheme 2 and Table 1 provided the expected 3,4-*trans*-tetrahydrooxazine **5h** in quantitative yield. However, we failed to realize selective hydrogenation of product **5h** to **8h** under the conditions applied for the reduction of oxazines **5f**,**g** (Scheme 2). Here in addition to the desired pyrrolizidinone **8h**, pyrrolidine **13** was detected in the reaction mixture (ration **8h**/**13** ~1.9:1.0). Apparently, this indicates that the cyclization of **13** to **8h** is slower than the corresponding transformation in case of model oxazines **5f**,**g**.

Fortunately, under the decarboxylation conditions both products **13** and **8h** were converted smoothly into the target pyrrolizidinone *rac*-**4**. This allows the transformation of **5h** to *rac*-**4** to be performed in one technological step in 71% yield without isolation of intermediate heterocycle **8h**. Thus, target pyrrolizidinone *rac*-**4** was obtained in seven steps in 23% overall yield from aldehyde **9** and nitroethane.

The previous synthesis of *rac*-**4** from aldehyde **9** is also quite efficient (6 steps, 16.9% yield),[11] but it is not stereoselective and requires a chromatographic separation of diastereomers (c.a. 2:1 in favor of *rac*-**4**) in the last step of the synthesis.

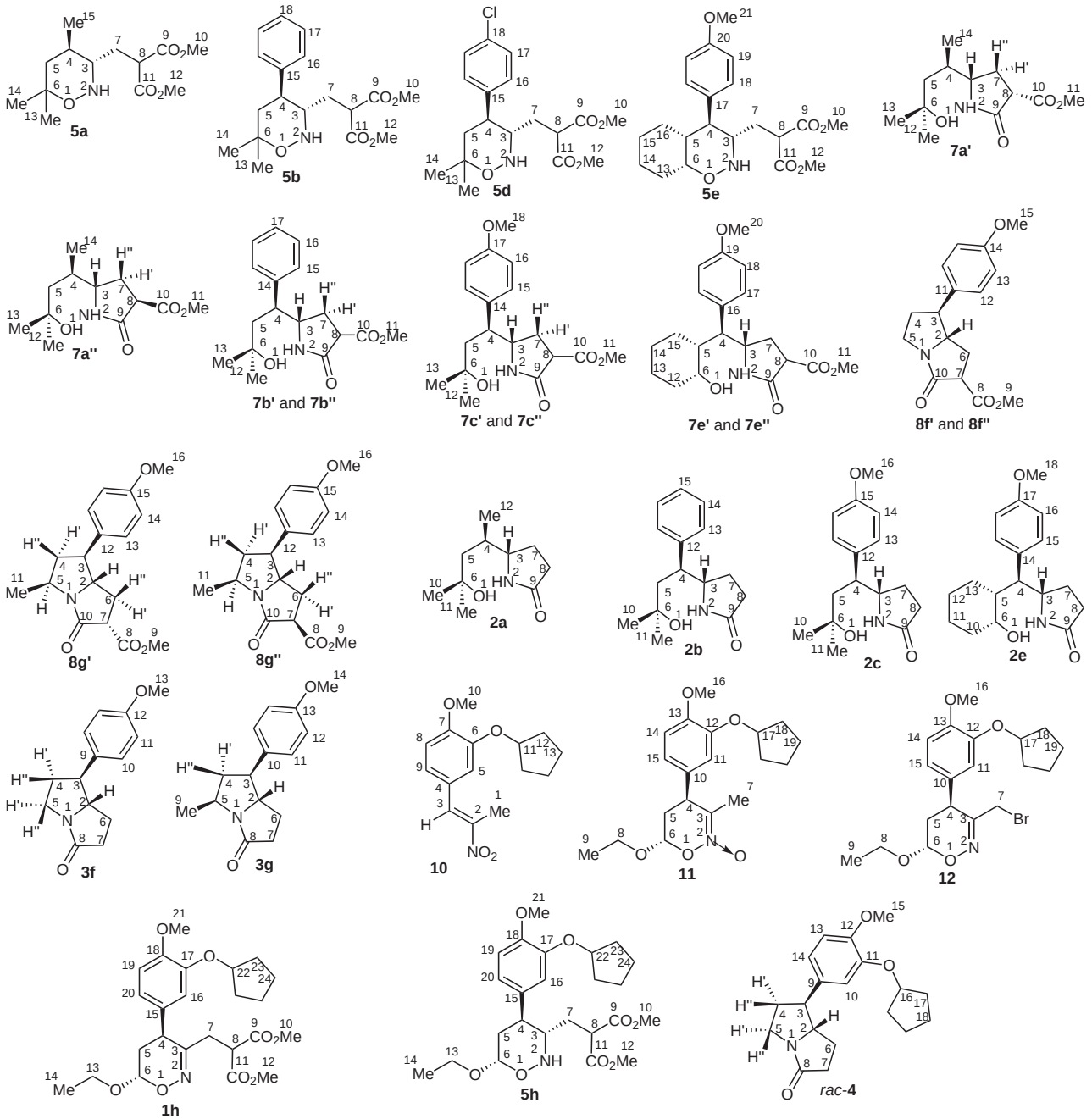


Figure 2

It is likely that the synthesis of *rac*-**4** presented here can be realized in an asymmetric variant by generation of an analogue of nitronate **11** with a chiral auxiliary at C6. This can be achieved by employing a chiral vinyl ether in the [4+2] cycloaddition with nitroalkene **10**; preparations of chiral six-membered cyclic nitronates and dihydrooxazines are given in the literature.[19]

The structure of final (**2**–**4**) and intermediate (**1h**, **5**, **7**, **8**, **10**–**12**) products was confirmed by elemental analysis and NMR spectroscopy data (^{1}H, ^{13}C, INEPT, for numbering see Figure 2), as well as by the chemical transformations depicted in Schemes 2 and 4. The 3,4-*trans*-configuration of tetrahydrooxazines **5a**–**h** was established from the analysis of coupling constants of protons at C3 and C4 under the standard hypothesis that tetrahydrooxazine ring occupies a chair-type conformation. In further transformations of products **5a**–**h** (Schemes 2 and 4), the relative configuration of substituents at C3 and C4 is not affected. This was confirmed by 2D NOESY experiments for products **3g** and **8g**. The unambiguous assignment of signals in NMR spectra of diastereomers **7** and **8** was guided by 2D NMR experiments COSY, HSQC, and NOESY (for characteristic correlations see the experimental section).

In conclusion, stepwise reduction of readily available dihydrooxazines **1** bearing the $CH_2CH(CO_2Me)_2$ fragment at C3 can be considered as an efficient approach to the synthesis of diastereomerically pure substituted 5-(3-hydroxypropyl)pyrrolidin-2-ones **2** and pyrrolizidinones **3**, versatile products and precursors of biologically active molecules. Great synthetic potential of the above-mentioned approach was demonstrated by the synthesis of pyrrolizidinone *rac*-**4**, a highly active analogue of the antidepressant Rolipram. It is evident that other analogues of *rac*-**4** should be available by this synthetic route as well.

1D and 2D NMR spectra were recorded at r.t. on Bruker DRX-500 (^{1}H (500.13 MHz), ^{1}H-^{1}H COSY, HSQC (J = 145 Hz), NOESY (mixing time 900 ms), Bruker AM-300 (^{13}C 75.13 MHz, INEPT) and WM-250 (^{13}C 62.9 MHz, INEPT) NMR spectrometers for 0.1–0.2 M solns in $CDCl_3$. The chemical shifts (^{1}H and ^{13}C) are given in relative to the solvent signal.[20] All NMR experiments were performed using standard methods and Bruker NMR technique software. Elemental analyses were performed by the Analytical Center of the Moscow Chemical Lyceum and Analytical Laboratory of Institute of Organic Chemistry. Melting points were determined on a Kofler melting point apparatus (uncorrected). Analytical TLC was performed on Merck silica gel plates with QF-254. Visualization was accomplished with UV light or with soln of ninhydrin in EtOH. Glacial AcOH and DMSO were recrystallized twice. CH_2Cl_2 (technical grade), MeCN (technical grade), Et_3N, and Me_3SiBr were redistilled from CaH_2. Hexane and EtOAc for chromatography and extractions and MeOH for hydrogenation were technical grade and distilled without drying agents. Column chromatography was performed using Merck Kieselgel 40–60 μm 60A silica gel. $NaBH_3CN$ (Sigma-Aldrich), Raney Nickel (50% slurry in H_2O) (Acros), ethyl vinyl ether (Acros), dimethyl malonate (Acros), nitroethane (Acros), $SnCl_4$ (Acros) were purchased from commercial sources and used as received. Initial oxazines **1a**–**g**[1] and **5f**,**g**[2] were prepared according to literature procedures. Catalytic hydrogenations were carried out in a steel autoclave (Parr instrument) with external stirring.

Tetrahydrooxazines 5; General Procedure

$NaBH_3CN$ (0.19 g, 3 mmol for **1a**–**d**, 0.57 g, 9 mmol for **1e**) was added to a stirred soln of oxazine **1** (1 mmol) in AcOH (4.4 mL) under argon. The mixture was kept stirring at r.t. for 20 min (for **1a**–**e**) or 2 h (for **1h**) and poured into a mixture of EtOAc (200 mL) and sat. aq K_2CO_3 (200 mL). The aqueous phase was back-extracted with EtOAc (2 × 50 mL); the combined organic layers were washed brine (50 mL) and dried (Na_2SO_4). The solvent was evaporated in vacuo and the residue was immediately subjected to column chromatography (silica gel, EtOAc–hexane, 1:5 to 1:3). Yields of products are presented in Table 1.

Dimethyl *rel*-2-{[(3*S*,4*R*)-4,6,6-Trimethyltetrahydro-2*H*-1,2-oxazin-3-yl]methyl}malonate (5a)

Mp 35–37 °C; R_f = 0.52 (EtOAc–hexane, 1:1).

^{1}H NMR (500 MHz, COSY, $CDCl_3$): δ = 0.91 (d, J = 5.9 Hz, 3 H, 15-CH_3), 1.16 and 1.25 (2 s, 6 H, 13-CH_3, 14-CH_3), 1.26 (m, 1 H, $H5_{ax}$), 1.50 (m, 1 H, H4), 1.58 (dd, J = 12.5, 3.7 Hz, 1 H, H5), 1.69 (ddd, J = 14.9, 9.6, 5.9 Hz, 1 H, H7), 2.34 (ddd, J = 14.9, 8.5, 3.0 Hz, 1 H, H7), 2.53 (ddd, 1 H, J = 9.6, 9.6, 3.0 Hz, $H3_{ax}$), 3.66 (dd, J = 8.8, 5.9 Hz, 1 H, H8), 3.73 and 3.74 (2 s, 6 H, 10-CH_3, 12-CH_3), 5.90 (br, 1 H, 2-NH).

^{13}C NMR (75 MHz, HSQC, $CDCl_3$): δ = 18.2 (C15), 21.6 and 29.3 (C13, C14), 29.3 (C7), 31.1 (C4), 44.2 (C5), 48.7 (C8), 52.5 and 52.6 (C10, C12), 62.1 (C3), 74.7 (C6), 169.8 and 170.2 (C9, C11).

Anal. Calcd for $C_{13}H_{23}NO_5$: H, 8.48; C, 57.13; N, 5.12. Found: H, 8.29; C, 57.22; N, 5.09.

Dimethyl *rel*-2-{[(3*S*,4*S*)-6,6-Dimethyl-4-phenyltetrahydro-2*H*-1,2-oxazin-3-yl]methyl}malonate (5b)

Oil; R_f = 0.60 (EtOAc–hexane, 1:1).

^{1}H NMR (500 MHz, COSY, $CDCl_3$): δ = 1.19 and 1.33 (2 s, 6 H, 13-CH_3, 14-CH_3), 1.62 (ddd, J = 15.0, 10.0, 6.1 Hz, 1 H, H7), 1.72 (dd, J = 13.3, 5.3 Hz, 1 H, H5), 1.76 (dd, J = 13.3, 11.1 Hz, 1 H, H5), 1.92 (ddd, J = 15.0, 8.1, 3.2 Hz, 1 H, H7), 2.60 (ddd, J = 11.1, 10.5, 5.3 Hz, 1 H, $H4_{ax}$), 3.14 (ddd, J = 10.5, 10.0, 3.0 Hz, 1 H, $H3_{ax}$), 3.50 (dd, J = 8.1, 6.1 Hz, 1 H, H8), 3.62 and 3.64 (2 s, 6 H, 10-CH_3, 12-CH_3), 4.85 (br, 1 H, 2-NH), 7.14–7.28 (m, 5 H, H16, H17, H18).

^{13}C NMR (75 MHz, HSQC, $CDCl_3$): δ = 21.5 and 29.3 (C13, C14), 29.5 (C7), 44.2 (C5), 44.4 (C4), 48.6 (C8), 52.5 and 52.6 (C10, C12), 60.2 (C3), 74.6 (C6), 126.9, 127.6 and 128.8 (C14, C15, C16), 142.1 (C15), 169.5 and 170.1 (C9, C11).

Anal. Calcd for $C_{18}H_{25}NO_5$: H, 7.51; C, 64.46; N, 4.18. Found: H, 7.67; C, 64.29; N, 4.06.

Dimethyl *rel*-2-{[(3*S*,4*S*)-4-(4-Methoxyphenyl)-6,6-dimethyltetrahydro-2*H*-1,2-oxazin-3-yl]methyl}malonate (5c)

^{1}H and ^{13}C NMR data are consistent with previously reported data.[2]

Dimethyl *rel*-2-{[(3*S*,4*S*)-4-(4-Chlorophenyl)-6,6-dimethyltetrahydro-2*H*-1,2-oxazin-3-yl]methyl}malonate (5d)

Oil; R_f = 0.60 (EtOAc–hexane, 1:1).

^{1}H NMR (500 MHz, COSY, $CDCl_3$): δ = 1.19 and 1.33 (2 s, 6 H, 13-CH_3, 14-CH_3), 1.60 (ddd, J = 14.7, 10.3, 6.2 Hz, 1 H, H7), 1.71 (d, J = 8.5 Hz, 2 H, H5), 1.90 (ddd, J = 14.7, 8.5, 3.1 Hz, 1 H, H7), 2.58 (ddd, J = 10.3, 8.5, 8.5 Hz, 1 H, H4), 3.10 (ddd, J = 10.3, 10.3, 3.1 Hz, 1 H, H3), 3.51 (dd, J = 8.5, 6.2 Hz, 1 H, H8), 3.64 and 3.66 (2 s, 6 H, 10-CH_3, 12-CH_3), 4.80 (br, 1 H, 2-NH), 7.09 and 7.27 (2 d, J = 8.9 Hz, 4 H, H16, H18).

^{13}C NMR (75 MHz, HSQC, $CDCl_3$): δ = 21.5 and 29.3 (C13, C14), 29.5 (C7), 43.9 (C4), 44.2 (C5), 48.5 (C8), 52.6 and 52.7 (C10, C12), 60.1 (C3), 74.6 (C6), 129.0 (C16, C17), 132.6 and 140.6 (C15, C18), 169.5 and 170.1 (C9, C11).

Anal. Calcd for $C_{18}H_{24}ClNO_5$: H, 6.54; C, 58.46; N, 3.79. Found: H, 6.52; C, 58.47; N, 3.77.

Dimethyl *rel*-2-{[(3*S*,4*S*,4a*R*,8a*R*)-4-(4-Methoxyphenyl)octahydro-2*H*-1,2-benzoxazin-3-yl]methyl}malonate (5e)

Mp 127–128 °C; R_f = 0.43 (EtOAc–hexane, 1:1).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.05–1.21, 1.24–1.36, 1.65–1.68, 1.84–1.90, 2.03–2.10 (5 m, 1 H, 4 H, 1 H, 1 H, 1 H, H13, H14, H15, H16), 1.60 (ddd, *J* = 14.7, 9.9, 6.0 Hz, 1 H, H7), 1.84 (ddd, *J* = 14.7, 8.1, 3.1 Hz, 1 H, H7), 2.26 (ddd, *J* = 11.4, 5.9, 4.4 Hz, 1 H, H5), 2.61 (dd, *J* = 11.4, 10.6 Hz, 1 H, H4), 3.19 (ddd, *J* = 10.6, 9.9, 3.1 Hz, 1 H, H3), 3.48 (dd, *J* = 8.1, 6.0 Hz, 1 H, H8), 3.63 and 3.65 (2 s, 6 H, 10-CH_3, 12-CH_3), 3.77 (s, 3 H, 21-CH_3), 3.92 (ddd, *J* = 12.5, 5.1, 4.8 Hz, 1 H, H6), 4.86 (br, 1 H, 2-NH), 6.84 (d, *J* = 8.1 Hz, 2 H, H19), 7.04 (d, *J* = 8.1 Hz, 2 H, H18).

^{13}C NMR (62 MHz, INEPT, $CDCl_3$): δ = 19.8, 24.1, 25.0, 26.8 and 29.9 (C7, C13, C14, C15, C16), 40.3 and 44.3 (C4, C5), 48.6 (C8), 52.4 and 52.5 (C10, C12), 55.1 (C21), 61.1 (C3), 77.5 (C6), 114.0 (C19), 128.7 (br, C18), 132.1 (C17), 158.3 (C20), 169.5 and 170.1 (C9, C11).

Anal. Calcd for $C_{21}H_{29}NO_6$: H, 7.47; C, 64.43; N, 3.58. Found: H, 7.78; C, 64.26; N, 3.64.

Hydrogenation of Tetrahydrooxazines 5; General Procedure

Raney nickel (c.a. 0.05 g, washed with MeOH) was placed in a test tube equipped with a magnetic stirrer and charged with a soln of oxazine **5** (0.47 mmol) in MeOH (5.0 mL). The test tube was placed in steel autoclave which was then flushed and filled with H_2 to a pressure of 40 bar. After stirring the mixture at r.t. for 3 h, the autoclave was slowly depressurized and the catalyst was filtered off. The solvent was evaporated in vacuo and the residue was subjected to column chromatography (for products **8f** and **8g**, silica gel, EtOAc–hexane, 1:5 to 1:3 to 1:1 to 1:0) or filtered thorough a short pad of silica gel (for products **7a**–**c**,**e**, EtOAc–hexane, 1:1 to EtOAc to MeOH). Yields of products are presented in Table 1.

Pyrrolidones 7a

Mp 114–119 °C; mixture of diastereomers, **7a′**/**7a″**, 1.3:1.0.

Anal. Calcd for $C_{12}H_{21}NO_4$: H, 8.70; C, 59.24; N, 5.76. Found: H, 9.04; C, 59.28; N, 5.76.

Methyl *rel*-(3*S*,5*S*)-5-[(1*R*)-3-Hydroxy-1,3-dimethylbutyl]-2-oxopyrrolidine-3-carboxylate (7a′)

^{1}H NMR (500 MHz, COSY, NOESY, $CDCl_3$): δ (selected signals) = 0.91 (d, *J* = 6.6 Hz, 3 H, 14-CH_3), 1.18 and 1.22 (2 s, 6 H, 12-CH_3, 13-CH_3), 1.31 (m, 1 H, H5), 1.57 (dd, *J* = 14.5, 13.8 Hz, 1 H, H5), 1.78 (m, 1 H, H4), 2.09 (ddd, *J* = 12.7, 11.0, 9.1 Hz, 1 H, H7′), 2.32 (ddd, *J* = 12.7, 8.6, 6.6 Hz, 1 H, H7″), 3.00 (br, 1 H, 1-OH), 3.28 (ddd, *J* = 9.1, 8.6, 6.6 Hz, 1 H, H3), 3.39 (dd, *J* = 11.0, 8.6 Hz, 1 H, H8), 8.36 (br, 1 H, 2-NH).

^{13}C NMR (75 MHz, HSQC, $CDCl_3$): δ (selected signals) = 18.5 (C14), 28.1 and 31.9 (C12, C13), 30.5 (C7), 34.8 (C4), 48.5 (C5), 48.8 (C8), 52.5 (C11), 59.1 (C3), 70.3 (C6).

Characteristic 2D-NOESY correlations: H3/H7″, H7″/H8.

Methyl *rel*-(3*R*,5*S*)-5-[(1*R*)-3-Hydroxy-1,3-dimethylbutyl]-2-oxopyrrolidine-3-carboxylate (7a″)

^{1}H NMR (500 MHz, COSY, NOESY, $CDCl_3$): δ (selected signals) = 0.86 (d, *J* = 7.4 Hz, 3 H, 14-CH_3), 1.18 and 1.22 (2 s, 6 H, 12-CH_3, 13-CH_3), 1.31 (m, 1 H, H5), 1.55 (dd, *J* = 14.4, 13.6 Hz, 1 H, H5), 1.70 (m, 1 H, H4), 1.90 (ddd, *J* = 13.3, 9.6, 7.7 Hz, 1 H, H7′), 2.43 (ddd, *J* = 13.3, 7.2, 3.3 Hz, 1 H, H7″), 3.00 (br, 1 H, 1-OH), 3.36 (dd, *J* = 9.6, 3.3 Hz, 1 H, H8), 3.53 (ddd, *J* = 7.7, 7.5, 7.2 Hz, 1 H, H3), 8.19 (br, 1 H, 2-NH).

^{13}C NMR (75 MHz, HSQC, $CDCl_3$): δ (selected signals) = 18.3 (C14), 28.3 and 31.7 (C12, C13), 30.1 (C7), 34.8 (C4), 48.5 (C5), 48.8 (C8), 52.5 (C11), 59.7 (C3), 70.3 (C6).

Characteristic 2D-NOESY correlations: H3/H7″, H7′/H8.

Unassigned signals for both isomers:

^{1}H NMR (500 MHz, $CDCl_3$): δ = 3.72 and 3.73 (2 s, 3 H, 11-CH_3).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 170.4, 170.5, 172.6 and 172.7 (C9, C10).

Pyrrolidones 7b

Oil; mixture of diastereomers, **7b′**/**7b″**, 1.2:1.0. ^{1}H and ^{13}C NMR spectra are consistent with those previously reported for **7b** prepared directly from dihydrooxazine **2b**.[3]

Methyl *rel*-(3*S*,5*S*)-5-[(1*S*)-3-Hydroxy-3-methyl-1-phenylbutyl]-2-oxopyrrolidine-3-carboxylate (7b′)

^{1}H NMR (500 MHz, COSY, NOESY, $CDCl_3$): δ (selected signals) = 1.80 (m, 1 H, H7″), 1.89 (m, 1 H, H7), 1.95 (m, 1 H, H7′), 2.05 (dd, *J* = 14.8, 5.2 Hz, 1 H, H5), 2.90 (ddd, *J* = 9.5, 5.9, 5.2 Hz, 1 H, H4), 3.05 (br, 1 H, 1-OH), 3.35 (dd, *J* = 10.3, 9.1 Hz, 1 H, H8), 3.70 (m, 1 H, H3), 7.15–7.31 (m, 5 H, H15, H16, H17).

^{13}C NMR (75 MHz, HSQC, $CDCl_3$): δ (selected signals) = 31.4 (C7), 47.8 (C4), 48.8 (C8), 52.6 (C11), 59.0 (C3), 70.6 (C6), 126.9 (C17).

Characteristic 2D-NOESY correlations: H3/H7″, H7″/H8.

Methyl *rel*-(3*R*,5*S*)-5-[(1*S*)-3-Hydroxy-3-methyl-1-phenylbutyl]-2-oxopyrrolidine-3-carboxylate (7b″)

^{1}H NMR (500 MHz, COSY, NOESY, $CDCl_3$): δ (selected signals) = 1.80 (m, 1 H, H7′), 1.89 (m, 1 H, H5), 1.92 (m, 1 H, H5), 2.08 (m, 1 H, H7″), 2.80 (ddd, *J* = 9.2, 6.1, 5.0 Hz, 1 H, H4), 3.05 (br, 1 H, 1-OH), 3.22 (dd, *J* = 9.5, 4.2 Hz, 1 H, H8), 3.86 (ddd, *J* = 9.2, 7.0, 7.0 Hz, 1 H, H3), 7.15–7.31 (m, 5 H, H15, H16, H17).

^{13}C NMR (75 MHz, HSQC, $CDCl_3$): δ (selected signals) = 30.6 (C7), 47.7 (C4), 48.4 (C8), 52.6 (C11), 59.5 (C3), 70.6 (C8), 126.9 (C17).

Characteristic 2D-NOESY correlations: H3/H7″, H7′/H8.

Unassigned signals for both isomers:

^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.01, 1.08, 1.19 and 1.20 (4 s, 6 H, 12-CH_3, 13-CH_3), 3.68 and 3.72 (2 s, 3 H, 11-CH_3), 8.45 and 8.70 (2 br, 1 H, 2-NH).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 27.8, 28.0 and 31.9 (C12, C13), 48.2 and 48.7 (C5), 128.1, 128.2, 128.9 (C15, C16), 142.9 and 143.0 (C14), 170.4, 173.3 and 173.4 (C9, C10).

Pyrrolidones 7c

Oil; mixture of diastereomers, **7c′**/**7c″**, 1.0:1.1.

Anal. Calcd for $C_{18}H_{25}NO_5$: H, 7.51; C, 64.46; N, 4.18. Found: H, 7.63; C, 64.33; N, 4.10.

Methyl *rel*-(3*S*,5*S*)-5-[(1*S*)-3-Hydroxy-1-(4-methoxyphenyl)-3-methylbutyl]-2-oxopyrrolidine-3-carboxylate (7c′)

^{1}H NMR (500 MHz, COSY, NOESY, $CDCl_3$): δ (selected signals) = 1.80 (m, 1 H, H7″), 1.85–1.90 (m, 2 H, H5), 1.98 (m, 1 H, H7′), 2.70 (br, 1 H, 1-OH), 2.82 (ddd, *J* = 8.8, 6.4, 6.4 Hz, 1 H, H4), 3.33 (dd, *J* = 9.1, 10.1 Hz, 1 H, H8), 3.63 (ddd, *J* = 8.8, 8.7, 6.9 Hz, 1 H, H3), 3.75 (s, 3 H, 18-CH_3).

^{13}C NMR (75 MHz, HSQC, $CDCl_3$): δ (selected signals) = 31.3 (C7), 46.9 (C4), 48.6 (C8), 52.6 (C11), 55.2 (C18), 59.1 (C3), 70.6 (C6), 114.2 (C16).

Characteristic 2D-NOESY correlations: H3/H7″, H7″/H8.

Methyl *rel*-(3*R*,5*S*)-5-[(1*S*)-3-Hydroxy-1-(4-methoxyphenyl)-3-methylbutyl]-2-oxopyrrolidine-3-carboxylate (7c″)

^{1}H NMR (500 MHz, COSY, NOESY, $CDCl_3$): δ (selected signals) = 1.80 (m, 1 H, H7′), 1.85–1.90 (m, 2 H, H5), 2.04 (m, 1 H, H7″), 2.70 (br, 1 H, 1-OH), 2.73 (ddd, *J* = 8.9, 7.0, 4.6 Hz, 1 H, H4), 3.20 (dd, *J* = 9.5, 4.4 Hz, 1 H, H8), 3.75 (s, 3 H, 18-CH_3), 3.85 (ddd, *J* = 8.9, 7.3, 7.0 Hz, 1 H, H3).

^{13}C NMR (75 MHz, HSQC, $CDCl_3$): δ (selected signals) = 30.4 (C7), 46.8 (C4), 48.3 (C8), 52.6 (C11), 55.2 (C18), 59.5 (C3), 70.6 (C6), 114.2 (C16).

Characteristic 2D-NOESY correlations: H3/H7″, H7′/H8.

Unassigned signals for both isomers:

^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.02, 1.05 and 1.15 (3 s, 6 H, 12-CH_3, 13-CH_3), 3.68 and 3.71 (2 s, 3 H, 11-CH_3), 6.83 (d, *J* = 8.8 Hz, 2 H, H16), 7.08 and 7.10 (2 d, *J* = 8.8 Hz, 2 H, H15), 8.29 and 8.54 (2 br, 1 H, 2-NH).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 27.9, 28.1, 31.7 and 31.8 (C12, C13), 48.0 and 48.5 (C5), 129.0, 129.1 (C15), 134.6 and 134.9 (C14), 158.3 and 158.4 (C17), 170.4, 173.2 and 173.3 (C9, C10).

Methyl *rel*-(3*S*,5*S*)-5-{(*S*)-[(1*R*,2*R*)-2-Hydroxycyclohexyl](4-methoxyphenyl)methyl}-2-oxopyrrolidine-3-carboxylate (7e′) and Methyl *rel*-(3*R*,5*S*)-5-{(*S*)-[(1*R*,2*R*)-2-Hydroxycyclohexyl](4-methoxyphenyl)methyl}-2-oxopyrrolidine-3-carboxylate (7e″)

Mp 193–198 °C; mixture of isomers, 1.3:1.0.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.98–1.34, 1.44–1.65, 1.73–1.83, 1.90–1.99 (4 m, 11 H, H7, H12, H13, H14, H15, H5, both isomers), 2.50 (m, 1 H, H4, both isomers), 3.05–3.12 (m, 2 H, H8, minor isomer and 1-OH, major isomer), 3.31 (dd, *J* = 11.0, 8.8 Hz, 1 H, H8, major isomer), 3.47 (br, 1 H, 1-OH, minor isomer), 3.69 and 3.70 (2 s, 3 H, 11-CH_3, both isomers), 3.78 (s, 3 H, 20-CH_3, both isomers), 3.86 (ddd, *J* = 9.2, 8.4, 6.6 Hz, 1 H, H3, major isomer), 4.19 (m, 2 H, H6, both isomers and H3, minor isomer), 6.83 (d, *J* = 7.9 Hz, 2 H, H18, both isomers), 7.02 (d, *J* = 7.9 Hz, 2 H, H17, both isomers), 7.72 (br, 1 H, 2-NH, minor isomer), 7.95 (br, 1 H, 2-NH, major isomer).

^{13}C NMR (75 MHz, INEPT, $CDCl_3$): δ = 19.7, 25.3, 25.9, 31.8, 33.0, 33.6 (C7, C12, C13, C14, C15), 46.9, 47.8, 48.1, 48.3 (C4, C8), 52.4, 52.5, 53.0, 53.2 (C5, C11), 55.2 (C20), 55.4 and 55.7 (C3), 66.6 and 66.8 (C6), 113.8 (C18), 129.4 and 129.6 (C17), 132.9 and 133.3 (C16), 158.3 (C19), 170.4, 170.5, 172.5 and 172.8 (C9, C10).

Anal. Calcd for $C_{20}H_{27}NO_5$: H, 7.53; C, 66.46; N, 3.88. Found: H, 7.53; C, 66.49; N, 3.91.

Methyl *rel*-(2*S*,7*R*,7a*R*)-7-(4-Methoxyphenyl)-3-oxohexahydro-1*H*-pyrrolizine-2-carboxylate (8f′) and Methyl *rel*-(2*R*,7*R*,7a*R*)-7-(4-Methoxyphenyl)-3-oxohexahydro-1*H*-pyrrolizine-2-carboxylate (8f″)

Mp 63–66 °C; R_f = 0.11 (EtOAc–hexane = 1:1); mixture of isomers, 1.2:1.0.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.04 (ddd, *J* = 13.2, 9.5, 7.3 Hz, 1 H, H6, major isomer), 2.17–2.31, 2.34–2.42 and 2.44–2.58 (3 m, 4 H, H4, H6, both isomers), 2.69 (ddd, *J* = 11.4, 9.5, 7.3 Hz, 1 H, H3, minor isomer), 2.84 (ddd, *J* = 11.4, 9.5, 7.0 Hz, 1 H, H3, major isomer), 3.32 (m, 1 H, H5, both isomers), 3.53–3.68 (m, 2 H, H8, H5, both isomers), 3.72, 3.76 and 3.77 (3 s, 6 H, 9-CH_3, 15-CH_3, both isomers), 3.82 (ddd, *J* = 9.9, 9.5, 9.5 Hz, 1 H, H2, major isomer), 4.08 (ddd, *J* = 9.9, 9.5, 9.5 Hz, 1 H, H2, minor isomer), 6.86 (d, *J* = 8.4 Hz, 2 H, H13, both isomers), 7.12 (d, *J* = 8.4 Hz, 2 H, H12, minor isomer), 7.15 (d, *J* = 8.4 Hz, 2 H, H12, major isomer).

^{13}C NMR (75 MHz, INEPT, $CDCl_3$): δ = 29.4, 29.8, 35.0 and 35.4 (C4, C6), 41.2 and 41.3 (C5), 50.2, 50.5, 52.1, 52.4, 52.5 and 53.1 (C3, C7, C9), 55.1 (C15), 65.7 and 66.6 (C2), 114.1 (C13), 128.0 and 128.1 (C12), 130.4 and 130.5 (C11), 158.7 (C14), 168.7, 169.0, 170.2 and 170.3 (C8, C10).

Anal. Calcd for $C_{16}H_{19}NO_4$: H, 6.62; C, 66.42; N, 4.84. Found: H, 6.88; C, 66.34; N, 4.69.

Pyrrolizidinones 8g

Oil; R_f = 0.22 (EtOAc–hexane, 1:1); mixture of diastereomers, **8g′**/**8g″**, 1.4:1.0.

Anal. Calcd for $C_{17}H_{21}NO_4$: H, 6.98; C, 67.31; N, 4.62. Found: H, 7.28; C, 66.73; N, 4.36.

Methyl *rel*-(2*S*,5*S*,7*S*, 7a*S*)-7-(4-Methoxyphenyl)-5-methyl-3-oxohexahydro-1*H*-pyrrolizine-2-carboxylate (8g′)

^{1}H NMR (500 MHz, COSY, NOESY, $CDCl_3$): δ (selected signals) = 1.86 (ddd, *J* = 12.4, 12.2, 9.1 Hz, 1 H, H4″), 2.28 (ddd, *J* = 12.9, 10.9, 7.3 Hz, 1 H, H6′), 2.38 (ddd, *J* = 12.9, 8.8, 6.9 Hz, 1 H, H6″), 2.67 (ddd, *J* = 12.4, 6.9, 6.5 Hz, 1 H, H4′), 2.87 (ddd, *J* = 12.2, 9.8, 6.9 Hz, 1 H, H3), 3.77 (m, 1 H, H7), 3.87 (ddd, *J* = 9.8, 7.3, 6.9 Hz, 1 H, H2), 3.99 (m, 1 H, H5).

^{13}C NMR (75 MHz, HSQC, $CDCl_3$): δ (selected signals) = 21.1 (C11), 29.6 (C6), 44.5 (C4), 50.3 (C5), 51.0 (C3), 52.8 (C7), 55.3 (C16), 66.0 (C2), 114.2 (C14), 128.1 (C13), 158.7 (C15).

Characteristic 2D-NOESY correlations: H2/H6″, H6″/H7, H6′/H3, H3/H4′, H4′/H5, H4″/11-CH_3.

Methyl *rel*-(2*R*,5*S*,7*S*,7a*S*)-7-(4-Methoxyphenyl)-5-methyl-3-oxohexahydro-1*H*-pyrrolizine-2-carboxylate (8g″)

^{1}H NMR (500 MHz, COSY, NOESY, $CDCl_3$): δ (selected signals) = 1.86 (m, 1 H, H4″), 2.01 (ddd, *J* = 13.1, 9.5, 7.3 Hz, 1 H, H6′), 2.53 (ddd, *J* = 13.1, 6.9, 1.7 Hz, 1 H, H6″), 2.67 (ddd, *J* = 12.4, 6.9, 6.5 Hz, 1 H, H4′), 2.72 (ddd, *J* = 9.9, 7.3, 6.9 Hz, 1 H, H3), 3.55 (dd, *J* = 9.5, 1.7 Hz, 1 H, H7), 3.99 (m, 1 H, H5), 4.15 (ddd, *J* = 9.9, 7.3, 6.9 Hz, 1 H, H2).

^{13}C NMR (75 MHz, HSQC, $CDCl_3$): δ (selected signals) = 21.0 (C11), 29.8 (C6), 44.9 (C4), 50.3 (C5), 51.3 (C3), 53.2 (C7), 55.3 (C16), 65.1 (C2), 114.2 (C14), 128.1 (C13), 158.7 (C15).

Characteristic 2D-NOESY correlations: H2/H6″, H6′/H7, H3/H4′, H4′/H5, H4″/11-CH_3.

Unassigned signals for both isomers:

^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.34 and 1.36 (2 d, *J* = 6.6 Hz, *J* = 6.0 Hz, 3 H, 11-CH_3), 3.77 and 3.80 (2 s, 6 H, 9-CH_3, 16-CH_3), 6.88 (d, *J* = 9.2 Hz, 2 H, H14), 7.14 and 7.16 (2 d, *J* = 9.2 Hz, *J* = 8.5 Hz, 2 H, H13).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 52.2 and 52.6 (C9), 130.4 and 130.5 (C12), 168.9, 169.1, 170.4 and 170.5 (C8, C10).

Decarboxylation of Products 7 and 8; General Procedure

H_2O (0.018 mL, 1.0 mmol) was added to a soln of **7** or **8** (0.5 mmol) and NaBr (0.052 g, 0.5 mmol) in DMSO (7.0 mL) and the mixture was gently refluxed for 25 min (for **7**) or 45 min (for **8**). Then the solvent was evaporated in vacuo (100 °C/0.67 mbar) and the residue was subjected to column chromatography (silica gel, EtOAc–hexane, 1:3 to 1:1 to 1:0 to EtOAc–MeOH, 10:1 to 5:1). Yields of products are presented in Table 1.

***rel*-(5*S*)-5-[(1*R*)-3-Hydroxy-1,3-dimethylbutyl]pyrrolidin-2-one (2a)**

Mp 59–63 °C; R_f = 0.51 (EtOAc–MeOH, 3:1).

^{1}H NMR (300 MHz, COSY, HSQC, $CDCl_3$): δ = 0.90 (d, *J* = 6.6 Hz, 3 H, 12-CH_3), 1.18 and 1.23 (2 s, 6 H, 10-CH_3, 11-CH_3), 1.33 (dd, *J* = 14.9, 5.1 Hz, 1 H, H5), 1.58 (dd, *J* = 14.9, 4.8 Hz, 1 H, H5), 1.69 (m, 2 H, H4, H7), 2.10 (m, 1 H, H7), 2.28 (m, 2 H, H8), 3.36 (ddd, *J* = 8.1, 7.7, 7.3 Hz, 1 H, H3), 3.44 (br, 1 H, 1-OH), 8.11 (br, 1 H, 2-NH).

^{13}C NMR (75 MHz, INEPT, HSQC, $CDCl_3$): δ = 18.3 (C12), 26.0 (C7), 31.3 (C8), 28.1 and 31.7 (C10, C11), 34.8 (C4), 48.6 (C5), 61.1 (C3), 70.1 (C6), 178.5 (C9).

Anal. Calcd for $C_{10}H_{19}NO_2$: H, 10.34; C, 64.83; N, 7.56. Found: H, 10.41; C, 64.67; N, 7.75.

***rel*-(5*S*)-5-[(1*S*)-3-Hydroxy-3-methyl-1-phenylbutyl]pyrrolidin-2-one (2b)**

Mp 118–121 °C; R_f = 0.64 (EtOAc–MeOH, 3:1).

^{1}H NMR (300 MHz, COSY, HSQC, $CDCl_3$): δ = 1.08 and 1.21 (2 s, 6 H, 10-CH_3, 11-CH_3), 1.51–1.70 (m, 2 H, H7), 1.96 (dd, *J* = 14.7, 6.6 Hz, 1 H, H5), 2.06 (dd, *J* = 14.7, 4.4 Hz, 1 H, H5), 2.16–2.24 (m, 2 H, H8), 2.83 (ddd, *J* = 9.6, 6.6, 4.4 Hz, 1 H, H4), 3.35 (br, 1 H, 1-OH), 3.77 (ddd, *J* = 9.6, 7.3, 7.3 Hz, 1 H, H3), 7.16–7.32 (m, 5 H, H13, H14, H15), 8.33 (br, 1 H, 2-NH).

^{13}C NMR (75 MHz, INEPT, $CDCl_3$): δ = 26.8 (C7), 30.9 (C8), 27.9 and 31.9 (C10, C11), 47.8 (C4), 48.3 (C5), 60.9 (C3), 70.4 (C6), 126.6, 128.1 and 128.6 (C13, C14, C15), 143.4 (C12), 178.9 (C9).

Anal. Calcd for $C_{15}H_{21}NO_2$: H, 8.56; C, 72.84; N, 5.66. Found: H, 8.56; C, 72.74; N, 5.33.

***rel*-(5*S*)-5-[(1*S*)-3-Hydroxy-1-(4-methoxyphenyl)-3-methylbutyl]pyrrolidin-2-one (2c)**

Mp 128–132 °C; R_f = 0.61 (EtOAc–MeOH, 3:1).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.03 and 1.15 (2 s, 6 H, 10-CH_3, 11-CH_3), 1.48–1.68 (m, 2 H, H7), 1.88 (dd, *J* = 14.7, 7.0 Hz, 1 H, H5), 1.97 (dd, *J* = 14.7, 4.0 Hz, 1 H, H5), 2.10–2.22 (m, 2 H, H8), 2.74 (ddd, *J* = 9.2, 7.0, 4.0 Hz, 1 H, H4), 3.29 (br, 1 H, 1-OH), 3.67 (ddd, *J* = 9.2, 7.3, 7.0 Hz, 1 H, H3), 3.74 (s, 3 H, 16-CH_3), 6.80 (d, *J* = 8.4 Hz, 2 H, H14), 7.06 (d, *J* = 8.4 Hz, 2 H, H13), 8.16 (br, 1 H, 2-NH).

^{13}C NMR (75 MHz, INEPT, $CDCl_3$): δ = 26.5 (C7), 30.8 (C8), 27.9 and 31.7 (C10, C11), 46.8 (C4), 48.0 (C5), 55.1 (C16), 60.8 (C3), 70.3 (C6), 113.9 (C14), 128.9 (C13), 135.1 (C12), 158.1 (C15), 178.8 (C9).

Anal. Calcd for $C_{16}H_{23}NO_3$: H, 8.36; C, 69.29; N, 5.05. Found: H, 8.45; C, 69.15; N, 5.05.

***rel*-(5*S*)-5-{(*S*)-[(1*R*,2*R*)-2-Hydroxycyclohexyl](4-methoxyphenyl)methyl}pyrrolidin-2-one (2e)**

Mp 213–218 °C; R_f = 0.61 (EtOAc–MeOH, 3:1).

^{1}H NMR (300 MHz, COSY, HSQC, $CDCl_3$): δ = 1.10–1.18 (m, 1 H, H12), 1.25–1.36 (m, 2 H, H7, H12), 1.46 (m, 1 H, H11), 1.54–1.69 (m, 6 H, H5, H7, H10, H11, H13), 1.92–2.00 (m, 1 H, H10), 2.03–2.10 (m, 1 H, H8), 2.12–2.24 (m, 1 H, H8), 2.49 (dd, *J* = 9.2, 9.0 Hz, 1 H, H4), 3.78 (s, 3 H, 18-CH_3), 3.95 (ddd, *J* = 9.0, 7.0, 5.9 Hz, 1 H, H3), 3.99 (br, 1 H, 1-OH), 4.19 (s, 1 H, H6), 6.82 (d, *J* = 8.2 Hz, 2 H, H16), 7.00 (d, *J* = 8.2 Hz, 2 H, H15), 7.73 (br, 1 H, 2-NH).

^{13}C NMR (75 MHz, INEPT, HSQC, $CDCl_3$): δ = 19.8 (C11), 25.3 (C12), 26.0 (C13), 28.4 (C7), 30.8 (C8), 33.6 (C10), 47.5 (C5), 53.4 (C4), 55.1 (C18), 57.3 (C3), 66.0 (C6), 113.7 (C16), 129.5 (C15), 133.7 (C14), 158.2 (C17), 178.4 (C9).

Anal. Calcd for $C_{18}H_{25}NO_3$: H, 8.31; C, 71.26; N, 4.62. Found: H, 8.14; C, 71.12; N, 4.68.

***rel*-(7*S*,7a*S*)-7-(4-Methoxyphenyl)hexahydro-3*H*-pyrrolizin-3-one (3f)**

Mp 79–81 °C; R_f = 0.65 (EtOAc–MeOH, 3:1).

^{1}H NMR (300 MHz, COSY, NOESY, HSQC, $CDCl_3$): δ = 1.83 (dddd, *J* = 12.8, 10.3, 9.5, 7.0 Hz, 1 H, H6), 2.15–2.19 (m, 2 H, H4″, H6), 2.42–2.53 (m, 2 H, H4′, H7), 2.64–2.79 (m, 2 H, H3, H7), 3.31 (dd, *J* = 11.2, 10.3 Hz, 1 H, H5″), 3.61 (ddd, *J* = 11.2, 10.3, 8.1 Hz, 1 H, H5′), 3.78 (s, 3 H, 13-CH_3), 3.89 (ddd, *J* = 9.9, 7.3, 7.0 Hz, 1 H, H2), 6.86 (d, *J* = 8.6 Hz, 2 H, H11), 7.13 (d, *J* = 8.6 Hz, 2 H, H10).

^{13}C NMR (75 MHz, INEPT, HSQC, $CDCl_3$): δ = 25.5 (C6), 34.8 (C7), 35.4 (C4) 40.9 (C5), 50.6 (C3), 55.2 (C13), 67.8 (C2), 114.1 (C11), 128.1 (C10), 131.0 (C9), 158.6 (C12), 174.7 (C8).

Characteristic 2D-NOESY correlations: H2/H10, H4″/H10, H4″/H5″, H4′/H5′C.

Anal. Calcd for $C_{14}H_{17}NO_2$: H, 7.41; C, 72.70; N, 6.06. Found: H, 7.62; C, 72.05; N, 6.05.

***rel*-(5*S*,7*S*,7a*S*)-7-(4-Methoxyphenyl)-5-methylhexahydro-3*H*-pyrrolizin-3-one (3g)**

Oil; R_f = 0.64 (EtOAc–MeOH, 3:1).

^{1}H NMR (300 MHz, COSY, NOESY, $CDCl_3$): δ = 1.34 (d, *J* = 5.9 Hz, 3 H, 9-CH_3), 1.75–1.90 (m, 2 H, H6, H4″), 2.15–2.25 (dddd, *J* = 13.2, 9.5, 6.6, 2.2 Hz, 1 H, H6), 2.45 (ddd, *J* = 16.1, 9.5, 2.2 Hz, 1 H, H7), 2.63–2.78 (m, 3 H, H3, H4′, H7), 3.79 (s, 3 H, 14-CH_3), 3.97 (ddd, *J* = 9.5, 7.3, 7.3 Hz, 1 H, H2), 4.01 (m, 1 H, H5), 6.86 (d, *J* = 8.2 Hz, 2 H, H12), 7.14 (d, *J* = 8.2 Hz, 2 H, H11).

^{13}C NMR (75 MHz, INEPT, $CDCl_3$): δ = 21.3 (C9), 25.4 (C6), 34.8 (C7), 44.7 (C4), 49.7 and 51.3 (C3, C5), 55.3 (C14), 67.0 (C2), 114.1 (C12), 128.1 (C11), 131.0 (C10), 158.6 (C13), 174.8 (C8).

Characteristic 2D-NOESY correlations: H11/H2, H11/H4″, H4″/9-CH_3.

Anal. Calcd for $C_{15}H_{19}NO_2$: H, 7.81; C, 73.44; N, 5.71. Found: H, 7.62; C, 73.14; N, 5.43.

Cyclopentyl 2-Methoxy-5-[(*E*)-2-nitroprop-1-enyl]phenyl Ether (10)

To a soln of aldehyde **9h**[18] (5.5 g, 25.0 mmol) in nitroethane (50 mL) was added NH_4OAc (1.9 g, 25.0 mmol) and AcOH (22.5 mL). The mixture was heated at 90 °C with vigorous stirring for 7 h, then cooled to r.t. and poured into a mixture of H_2O (25 mL) and EtOAc (50 mL). The aqueous phase was back-extracted with EtOAc (3 × 50 mL); the combined organic layers were washed with H_2O (25 mL) and brine (50 mL) and dried (Na_2SO_4). The solvent was evaporated in vacuo and the crude product was recrystallized (MeOH) to give **10** (6.23 g, 90%) as yellow crystals; mp 69–73 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.56–1.69 and 1.76–1.98 (2 m, 2 H, 6 H, H12, H13), 2.46 (s, 3 H, 1-CH_3), 3.87 (s, 3 H, 10-CH_3), 4.76 (m, 1 H, H11), 6.91 (d, *J* = 8.3 Hz, 1 H, H8), 6.95 (s, 1 H, H5), 7.04 (d, *J* = 8.3 Hz, 1 H, H9), 8.02 (s, 1 H, H3).

^{13}C NMR (75 MHz, INEPT, $CDCl_3$): δ = 14.0 (C1), 24.0 and 32.7 (C12, C13), 55.9 (C10), 80.5 (C11), 111.6 (C8), 116.3 (C5), 123.9 (C9), 124.7 (C4), 133.9 (C3), 145.5, 147.6 and 151.7 (C2, C6, C7).

Anal. Calcd for $C_{15}H_{19}NO_4$: H, 6.91; C, 64.97; N, 5.05. Found H, 6.82; C, 64.93; N, 5.14.

***rel*-(4*S*,6*S*)-4-[3-(Cyclopentyloxy)-4-methoxyphenyl]-6-ethoxy-3-methyl-5,6-dihydro-4*H*-1,2-oxazin-2-ium-2-olate (11)**

To a soln of nitroalkene **10** (1.5 g, 5.4 mmol) in CH_2Cl_2 (50 mL) at –94 °C was added $SnCl_4$ (0.63 mL, 5.4 mmol) under a dry argon atmosphere followed by ethyl vinyl ether (1.0 mL, 10.8 mmol). After 10 min at –94 °C an additional portion of ethyl vinyl ether (0.5 mL, 5.4 mmol) was added and the resulting mixture was poured into a

mixture of sat. aq K_2CO_3 (200 mL) and EtOAc (200 mL). The aqueous phase was back-extracted with EtOAc (2 × 50 mL); the combined organic layers were washed with H_2O (50 mL) and brine (50 mL) and dried (Na_2SO_4). The solvent was evaporated in vacuo and the residue was subjected to column chromatography (silica gel, EtOAc–hexane, 1:5 to 1:3 to 1:1) to give nitronate **11** (1.6 g, 85%) as a white solid. The minor fraction (0.19 g, R_f = 0.15, EtOAc–hexane, 1:1) contained a mixture of **11** and the corresponding 4,6-*cis*-isomer (~1.7:1.0).

Mp 90–92 °C; R_f = 0.23 (EtOAc–hexane, 1:1).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.20 (t, *J* = 7.0 Hz, 3 H, 9-CH_3), 1.49–1.61 and 1.71–1.87 (2 m, 8 H, H18, H19), 1.79 (s, 3 H, 7-CH_3), 2.02 (ddd, *J* = 14.1, 11.0, 2.6 Hz, 1 H, H5), 2.18 (ddd, *J* = 14.1, 7.3, 2.2 Hz, 1 H, H5), 3.60–3.72 (m, 2 H, H4, H8), 3.75 (s, 3 H, 16-CH_3), 3.99 (m, 1 H, H8), 4.68 (m, 1 H, H17), 5.29 (dd, *J* = 2.9, 2.2 Hz, 1 H, H6), 6.58 (d, *J* = 2.2 Hz, 1 H, H11), 6.65 (dd, *J* = 8.3, 2.2 Hz, 1 H, H15), 6.75 (d, *J* = 8.3 Hz, 1 H, H14).

^{13}C NMR (75 MHz, INEPT, $CDCl_3$): δ = 14.8 (C9), 17.3 (C7), 23.8, 32.5 and 34.1 (C5, C18, C19), 39.9 (C4), 55.8 (C16), 64.7 (C8), 80.2 (C17), 100.8 (C6), 112.1, 114.1 and 120.1 (C11, C14, C15), 123.3 (C3), 132.0 (C10), 147.9 and 149.4 (C12, C13).

Anal. Calcd for $C_{19}H_{27}NO_5$: H, 7.79; C, 65.31; N, 4.01. Found: H, 7.79; C, 65.21; N, 4.06.

rel-(4*S*,6*S*)-3-(Bromomethyl)-4-[3-(cyclopentyloxy)-4-methoxyphenyl]-6-ethoxy-5,6-dihydro-4*H*-1,2-oxazine (12)

To a soln of nitronate **11** (0.345 g, 0.989 mmol) and Et_3N (0.21 mL, 1.48 mmol) in CH_2Cl_2–MeCN (10:1, 2.0 mL) was added Me_3SiBr (0.65 mL, 4.94 mmol) at –78 °C under a dry argon atmosphere. The mixture was kept with occasional shaking at –78 °C for 24 h, then poured into a mixture of sat. aq K_2CO_3 (100 mL) and EtOAc (100 mL). The aqueous phase was back-extracted with EtOAc (1 × 80 mL); the combined organic layers were washed with H_2O (50 mL) and brine (50 mL) and dried (Na_2SO_4). The solvent was evaporated in vacuo and the residue was subjected to column chromatography (silica gel, EtOAc–hexane, 1:10 to 1:5) to give **12** (0.22 g, 54%). Further elution (EtOAc–hexane, 1:1) provided unreacted nitronate **11** (0.11 g, 34%).

Mp 60–62 °C; R_f = 0.70 (EtOAc–hexane, 1:1).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.25 (t, *J* = 7.0 Hz, 3 H, 9-CH_3), 1.58–1.69 and 1.79–1.96 (2 m, 8 H, H18, H19), 2.11 (ddd, *J* = 13.2, 10.6, 2.6 Hz, 1 H, H5), 2.25 (ddd, *J* = 13.2, 8.1, 2.4 Hz, 1 H, H5), 3.63 (m, 1 H, H8), 3.64 (d, *J* = 9.9 Hz, 1 H, H7), 3.83 (s, 3 H, 16-CH_3), 3.86–4.00 (m, 2 H, H4, H8), 3.91 (d, *J* = 9.9 Hz, 1 H, H7), 4.75 (m, 1 H, H17), 5.18 (dd, *J* = 2.6, 2.2 Hz, 1 H, H6), 6.74 (s, 1 H, H11), 6.76 (d, *J* = 8.1 Hz, 1 H, H15), 6.83 (d, *J* = 8.1 Hz, 1 H, H14).

^{13}C NMR (75 MHz, INEPT, $CDCl_3$): δ = 15.0 (C9), 24.0, 30.9, 32.5 and 32.7 (C5, C7, C18, C19), 33.4 (C4), 56.0 (C16), 63.6 (C8), 80.3 (C17), 96.1 (C6), 112.4, 115.0 and 120.4 (C11, C14, C15), 130.8 (C10), 148.0 and 149.4 (C12, C13), 158.3 (C3).

Anal. Calcd for $C_{19}H_{26}BrNO_4$: H, 6.36; C, 55.35; N, 3.40. Found: H, 6.50; C, 55.36; N, 3.54.

Dimethyl *rel*-2-{[(4*S*,6*S*)-4-[3-(Cyclopentyloxy)-4-methoxyphenyl]-6-ethoxy-5,6-dihydro-4*H*-1,2-oxazin-3-yl]methyl}malonate (1h)

Dihydrooxazine **1h** was prepared from bromide **12** in 80% yield by general procedure described in ref. 1a.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.22 (t, *J* = 7.3, 7.0 Hz, 3 H, 14-CH_3), 1.55–1.64 and 1.79–1.94 (2 m, 8 H, H23, H24), 2.03 (ddd, *J* = 13.6, 9.9, 2.2 Hz, 1 H, H5), 2.20 (ddd, *J* = 13.6, 7.3, 2.6 Hz, 1 H, H5), 2.53 (dd, *J* = 16.9, 7.7 Hz, 1 H, H7), 2.63 (dd, *J* = 16.9, 7.7 Hz, 1 H, H7), 3.47 and 3.59 (2 m, 2 H, H13), 3.69 (s, 6 H, 10-CH_3, 12-CH_3), 3.79 (dd, *J* = 9.9, 7.3 Hz, 1 H, H4), 3.83 (s, 3 H, 21-CH_3), 3.91 (dd, *J* = 7.7, 7.7 Hz, 1 H, H8), 4.77 (m, 1 H, H22), 5.10 (dd, *J* = 2.6, 2.2 Hz, 1 H, H6), 6.68 (d, *J* = 1.8 Hz, 1 H, H16), 6.73 (dd, *J* = 8.3, 1.8 Hz, 1 H, H20), 6.83 (d, *J* = 8.3 Hz, 1 H, H19).

^{13}C NMR (75 MHz, INEPT, $CDCl_3$): δ = 15.0 (C14), 24.0, 32.6, 32.7 and 33.5 (C5, C7, C23, C24), 36.6 (C4), 47.9 (C8), 52.5 (C10, C12), 56.0 (C21), 63.5 (C13), 80.4 (C22), 95.5 (C6), 112.4, 114.8 and 120.6 (C16, C19, C20), 131.9 (C15), 148.1 and 149.3 (C17, C18), 157.8 (C3), 169.3 and 169.4 (C9, C11).

Anal. Calcd for $C_{24}H_{33}NO_8$: H, 7.18; C, 62.19; N, 3.02. Found: H, 7.16; C, 62.40; N, 3.07.

Dimethyl *rel*-2-{[(3*S*,4*S*,6*S*)-4-[3-(Cyclopentyloxy)-4-methoxyphenyl]-6-ethoxytetrahydro-2*H*-1,2-oxazin-3-yl]methyl}malonate (5h)

Tetrahydrooxazine **5h** was prepared in 99% yield according to the same procedure used for the reduction of dihydrooxazines **1f**,**g**;[2] mp 99–102 °C; R_f = 0.47 (EtOAc–hexane, 1:1).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.28 (t, *J* = 7.3, 7.0 Hz, 3 H, 14-CH_3), 1.52–1.66 and 1.76–2.01 (2 m, 12 H, H5, H7, H23, H24), 2.66 (ddd, *J* = 11.0, 10.6, 5.5 Hz, 1 H, H4), 3.20 (ddd, *J* = 11.0, 10.6, 2.2 Hz, 1 H, H3), 3.54 (m, 1 H, H13), 3.64 and 3.67 (s and m, s, 7 H, H8, 10-CH_3, 12-CH_3), 3.79 (m, 1 H, H13), 3.80 (s, 3 H, 21-CH_3), 4.76 (m, 1 H, H22), 4.84 (s, 1 H, H6), 5.26 (br, 1 H, 2-NH), 6.67 (s, 1 H, H16), 6.69 (d, *J* = 8.8 Hz, 1 H, H20), 6.80 (d, *J* = 8.8 Hz, 1 H, H20).

^{13}C NMR (75 MHz, INEPT, $CDCl_3$): δ = 15.1 (C14), 23.9, 29.7, 32.7, and 37.1 (C5, C7, C23, C24), 41.9 (C4), 48.4 (C8), 52.3 and 52.5 (C10, C12), 56.0 (C21), 60.1 (C3), 63.5 (C13), 80.3 (C22), 98.0 (C6), 112.1, 114.3 and 119.3 (C16, C19, C20), 134.1 (C15), 147.6 and 148.8 (C17, C18), 169.4 and 170.2 (C9, C11).

Anal. Calcd for $C_{24}H_{35}NO_8$: H, 7.58; C, 61.92; N, 3.01. Found: H, 7.68; C, 62.02; N, 3.21.

rel-(7*S*,7a*S*)-7-[3-(Cyclopentyloxy)-4-methoxyphenyl]hexahydro-3*H*-pyrrolizin-3-one (*rac*-4)

Reduction of **5h** (0.205 g, 0.44 mmol) was accomplished by the procedure for hydrogenation of oxazines **5a**–**g** listed above. ^{1}H NMR analysis of the crude product obtained after filtration of the mixture and evaporation showed the presence of pyrrolizidinone **8h** (ratio of isomers 1.2:1.0) and pyrrolidine **13**, ca. 1.9:1.0, respectively. This mixture was dissolved in DMSO (6.2 mL) and the soln was heated at 100–140 °C for 30 min. Then it was cooled and NaBr (0.045 g, 0.44 mmol) and H_2O (0.016 mL, 0.88 mmol) were added. The mixture was gently refluxed for 45 min. The solvent was evaporated in vacuo (100 °C/0.67 mbar) and the residue was subjected to column chromatography (silica gel, EtOAc–hexane, 1:3 to 1:1 to 1:0 to EtOAc–MeOH, 10:1) to give pyrrolizidinone **4** (0.098 g, 71%); mp 65–66 °C (Lit.[11] 64–66 °C); R_f = 0.71 (EtOAc–MeOH, 1:3). The ^{1}H NMR spectrum is consistent with that previously reported for pyrrolizidinone *rac*-**4**.[11]

^{1}H NMR (300 MHz, COSY, NOESY, HSQC, $CDCl_3$): δ = 1.54–1.65 and 1.76–1.95 (2 m, 2 H, 7 H, H6, H17, H18), 2.15–2.30 (m, 2 H, H4″, H6), 2.43–2.53 (m, 2 H, H4′, H7), 2.63–2.79 (m, 2 H, H3, H7), 3.31 (dd, *J* = 11.0, 10.3 Hz, 1 H, H5″), 3.61 (ddd, *J* = 11.0, 9.2, 8.8 Hz, 1 H, H5′), 3.81 (s, 3 H, 13-CH_3), 3.89 (ddd, *J* = 9.5, 7.3, 7.0 Hz, 1 H, H2), 4.75 (m, 1 H, H16), 6.72 (s, 1 H, H10), 6.73 (d, *J* = 8.1 Hz, 1 H, H14), 6.82 (d, *J* = 8.1 Hz, 1 H, H13).

^{13}C NMR (75 MHz, INEPT, HSQC, $CDCl_3$): δ = 23.9 (C18), 25.5 (C6), 32.7 (C17), 34.7 (C7), 35.2 (C4), 40.9 (C5), 50.8 (C3), 56.0 (C15), 67.7 (C2), 80.5 (C16), 112.1, 114.3 and 119.1 (C10, C13, C14), 131.5 (C9), 147.7 and 149.1 (C11, C12), 174.7 (C8).

Characteristic 2D-NOESY correlations: H10/H2, H10/H4″, H4″/H5″, H4′/H5′.

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