5,6-Dihydro-4*H*-1,2-oxazines in Organic Synthesis: Catalytic Hydrogenation of [(5,6-Dihydro-4*H*-1,2-oxazin-3-yl)methyl]malonates to Methyl 7-Oxo-1-oxa-6-azaspiro[4.4]nonane-8-carboxylates

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Dedicated to Professor H. Mayr on the occasion of his 60th birthday

Abstract: [(5,6-Dihydro-4*H*-1,2-oxazin-3-yl)methyl]malonates undergo a cascade transformation into substituted methyl 7-oxo-1-oxa-6-azaspiro[4.4]nonane-8-carboxylates under catalytic hydrogenation conditions over Raney nickel. A mechanistic scheme involving initial N–O bond cleavage with the formation of imines as key intermediates is suggested.

Key words: 5,6-dihydro-4*H*-1,2-oxazines, reduction, oxaazaspirononanones, imines

Six-membered cyclic ethers of oximes, 5,6-dihydro-1,2-dihydro-4*H*-oxazines **1** and **1′**, can be considered as convenient precursors of natural and biologically active compounds (e.g., alkaloids,[1] unnatural α-amino acids,[2] and aminocarbohydrates[3]). The main significance of the oxazine ring in these syntheses is the stereoselective design of the carbon skeleton of the target molecule; subsequent reduction allows the preparation of individual stereoisomers of substituted pyrrolidines **2** or 1,4-amino alcohols **3** (Scheme 1).[4]

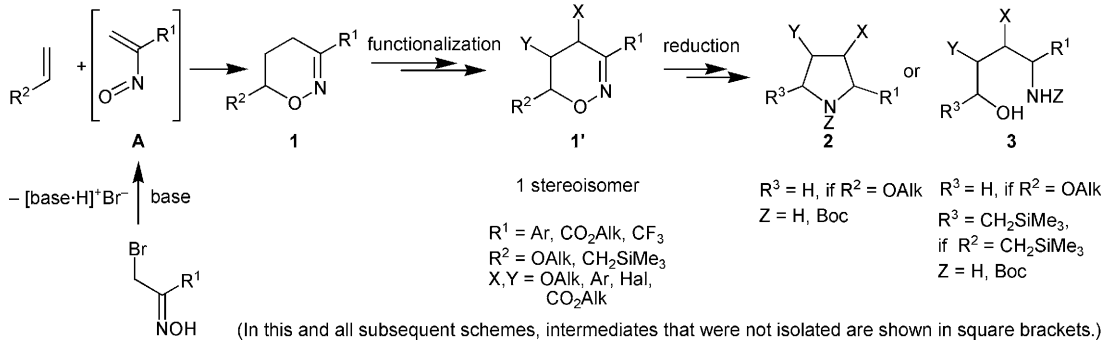
According to this strategy, dihydrooxazines **1** are generated via [4+2] cycloaddition of highly unstable nitrosoalkenes **A** to the corresponding alkenes. Further functionalization gives diastereomerically pure dihydrooxazines **1′** that can be reduced to give target products **2** or **3**. Apart from the instability of intermediates **A**, this approach possesses another significant disadvantage, which is that there is a very limited scope for the substituents at C3 because the range of available, appropriate nitrosoalkenes **A** is very small.[5]

Recently[6] we developed a novel strategy for the synthesis of polysubstituted 5,6-dihydro-4*H*-1,2-oxazines **4** from available and absolutely stable nitroethane (Scheme 2). In contrast to previously reported methodology,[1–4] the unique feature of this approach is the diversity of substituents that can be introduced at the C3 position of the oxazine ring after functionalization of the methyl group originating from nitroethane.

This may result in new types of products at the step of hydrogenolysis of the oxazines **4**. In particular, intramolecular cyclizations of intermediates or products of catalytic hydrogenation can also involve the group FG.

Recently[7] we reported a novel result of the hydrogenation of oxazines **4** in acetic acid. If the above-mentioned oxazines do not contain an alkoxy group at C6, the dihydrofuran derivatives **5** or **5′** can be obtained instead of the expected amino alcohols **3** (cf., Schemes 1 and 2).

Herein we demonstrate that changing the solvent from acetic acid to methanol for the catalytic hydrogenation of oxazines **4** with Raney nickel results in the formation of other furan derivatives, oxaazaspirononanones **6**$^{I–IV}$, i.e. the FG is involved in the cyclization (Scheme 3, Table 1).



Scheme 1

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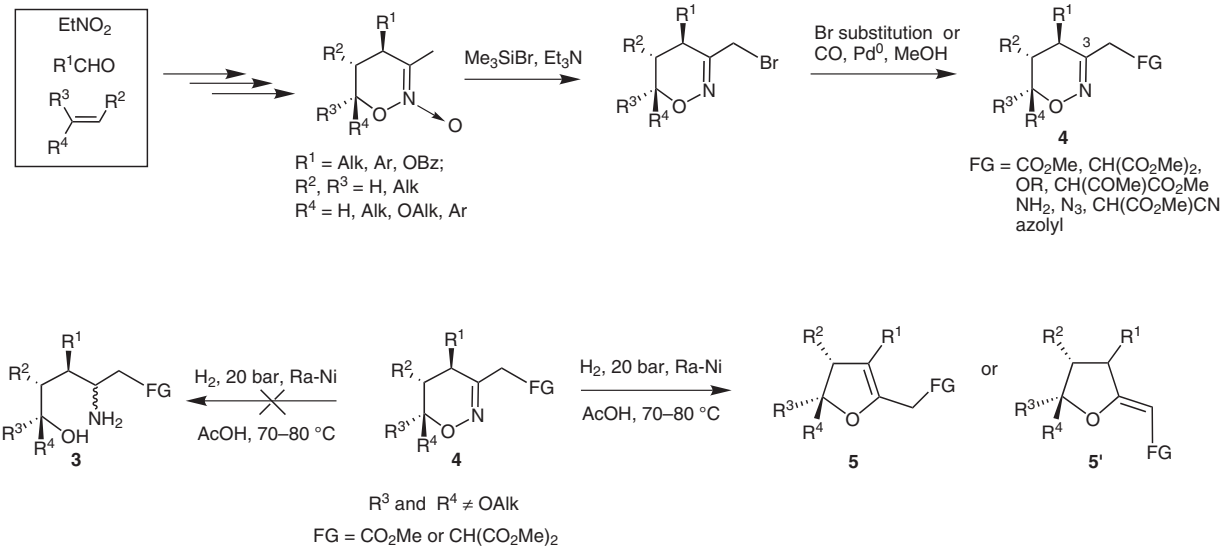
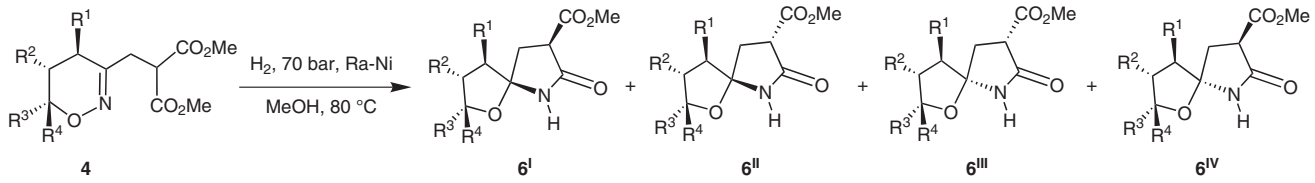


Scheme 2

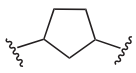


Scheme 3

The optimal procedure for the transformation of **4** into **6** is illustrated in Scheme 3 (the conditions of the process were optimized for model oxazine **4b**). A decrease of the hydrogen pressure as well as performing the hydrogenation in other solvents (THF, EtOAc) or with palladium-on-carbon instead of Raney nickel resulted in reduced yields of target **6b** and in lower conversion of the initial oxazine **4b**.[8]

The treatment of **4b** with sodium borohydride/cobalt(II) chloride in methanol at ambient temperature allows the use of atmospheric pressure of hydrogen, but in this case a great excess of reagents [$NaBH_4$ (10 equiv), $CoCl_2$ (1.5

Table 1 Synthesis of Oxaazaspirononanones **6**

Entry	**4**, **6**	R^1	R^2	R^3	R^4	Yield of **6** (%)	Ratio of isomers[a] $\mathbf{6^I/6^{II}/6^{III}/6^{IV}}$
1	**a**	Me	H	Me	Me	77	5.4:1.1:4.1:1.0
2	**b**	Ph	H	Me	Me	66	1.3:1.0:2.2:2.2
3	**c**	4-$MeOC_6H_4$	H	Me	Me	86	1.0:1.0:2.3:2.1
4	**d**	4-ClC_6H_4	H	Me	Me	80	1.4:1.0:1.8:1.8
5	**e**	Ph	$-(CH_2)_4-$		H	76	1.6:1.0:1.4:1.2
6	**f**	4-$MeOC_6H_4$	$-(CH_2)_4-$		H	61	1.7:1.0:1.2:1.1
7	**g**	Ph	$-(CH_2)_3-$		H	94	1.8:1.3:1.2:1.0
8	**h**	Ph			H	86	3.4:1.2:1.6:1.0
9	**i**	4-$MeOC_6H_4$	H	OEt	H	41[b]	2.9:1.9:2.5:1.0
10	**j**	4-$MeOC_6H_4$	H	OMe	Me	0[c]	–

[a] From NMR data after elution of the crude product (EtOAc–hexane, 1:1) through a short pad of silica gel.
[b] H_2 (45 bar), Raney Ni, MeOH, 80 °C, Boc_2O, Et_3N; the second product is pyrrolidine **7** (33%) (see Scheme 4).
[c] Only pyrrole **8** is obtained (78%) (see Scheme 4).

equiv)] is required to reach full conversion of **4b** (the yield of spiranonanone **6b** is 55% and it is lower than that by standard catalytic hydrogenation, see Table 1, entry 2).

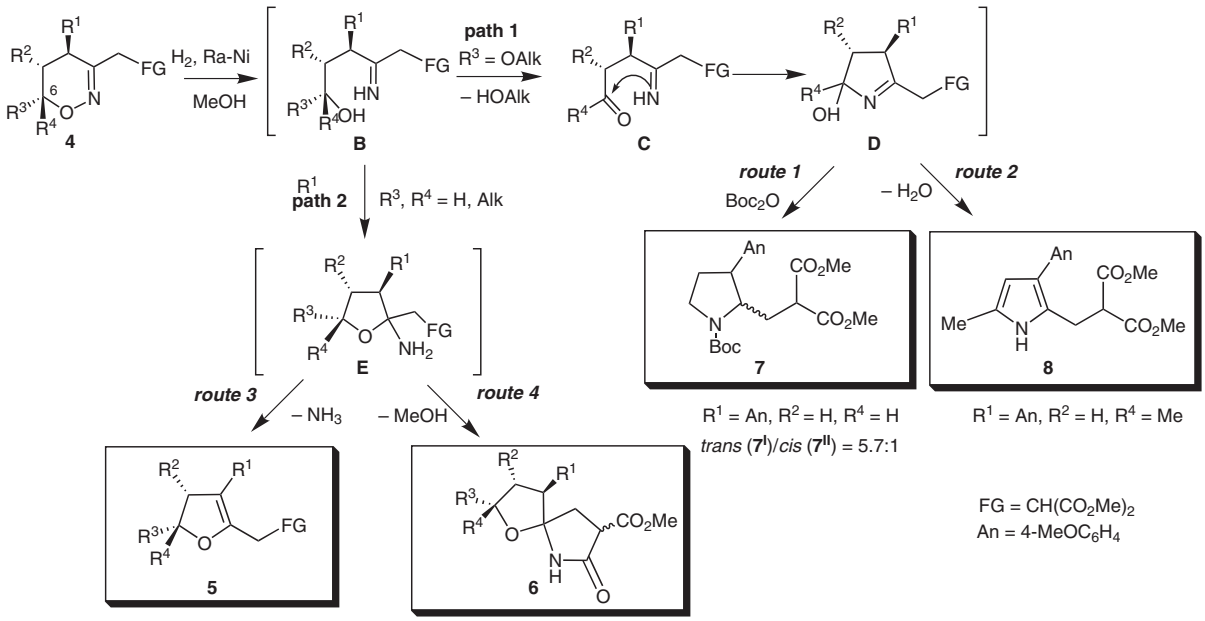
Traces of water in the reaction mixture decrease the yield of the target spiranone **6b** (up to 54%) owing to generation of lactam **9** (for details see discussion of Scheme 11). If hydrogenation of **4b** is carried out with ten equivalents of water using 'nondried' Raney nickel (for preparation see procedure b in experimental part) quick conversion of **4b** can be achieved at a lower pressure of hydrogen (40 bar, 80 °C, 1 h); however, lactam **9** dominates under these conditions (~50% yield). Therefore, the transformation of **4** into **6** should be realized only under anhydrous conditions and in the presence of a specially dried catalyst (see experimental part).[9]

The spiranones **6** can be prepared in good to excellent yields only for oxazines **4a–h** without an alkoxy group at C6. However, the hydrogenation of oxazine **4i** in the presence of di-*tert*-butyl dicarbonate provides the respective spiranone **6i** in 41% yield and the desired formation of **6i** is accompanied by the formation of pyrrolidine **7** (Scheme 4). The catalytic hydrogenation of another oxazine **6j** containing an alkoxy group at C6 furnished only the corresponding pyrrole derivative **8**. Interestingly, our attempts to change the course of the reduction by performing the reaction under milder, as well as more robust conditions, or by using palladium-on-carbon instead of Raney nickel were unsuccessful.

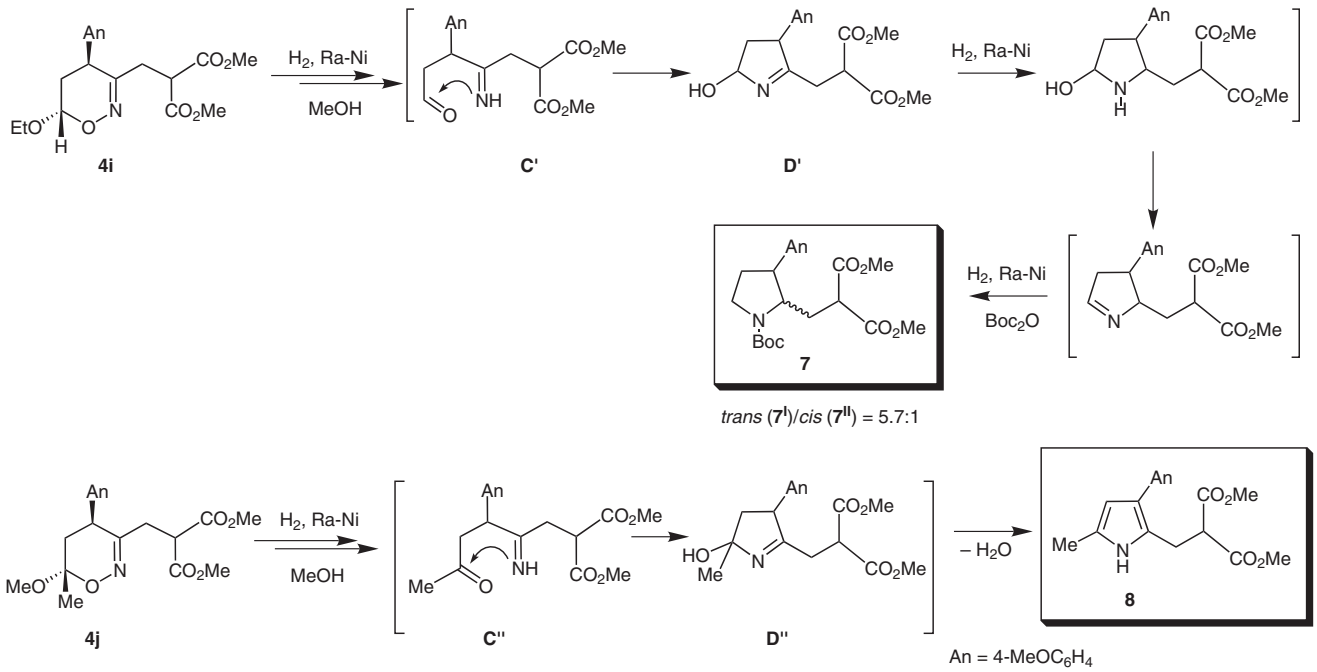
The mechanistic aspects of the formation of spiranones **6** should be discussed in the context of a general consideration of heterogeneous catalytic hydrogenation of oxazines **4** bearing a functional substituent CH_2FG at C3 (Scheme 4). The sequence demonstrated in Scheme 4 explains the known literature data and is in good agreement with results previously obtained in our studies[7] and in the present investigation.

We believe that the first stage of this multistep process involves reductive cleavage of the N–O bond leading to the formation of imine **B** (this conclusion is in line with published data on the hydrogenation of six-membered cyclic ethers of oximes,[4] as well as the oximes themselves[10]). The high reactivity of imines **B** allows them to be transformed into a diverse number of possible final products, but also it makes predictions of the results of these transformations problematic. In addition to C=N bond hydrogenation, the imino fragment in intermediate **B** can either act as an electrophile or act as a nucleophile depending on its structure. In these reactions, the presence (or absence) of an alkoxy group at C6 can be considered as the main determining criterion. If the oxazine **4** bears an alkoxy group at C6 (R^4 = OAlk), the initial semiacetal **B** transforms rapidly into the corresponding carbonyl-containing imine **C** (Scheme 4, Path 1). The latter undergoes intramolecular recyclization to achieve pyrroline **D**, which gives, after hydrogenation of the C=N bond, the final pyrrolidine **7** (route 1), or after elimination of water, pyrrole **8** (route 2).

The character of the resulting product (**7** or **8**) depends on the relative rates of different processes: cyclization of **C** to **D**, the hydrogenations of **C** and **D**, and elimination of water from **D**. Examples of the reduction of 5,6-dihydro-4*H*-1,2-oxazines to pyrroles[11a–c] and the reduction of 5,6-dihydro-4*H*-1,2-oxazines to pyrrolidines and fused pyrrolidines[1a,b,12] are available in the literature. There is clear evidence, that pyrroles arise from intermediates **D**, such as in the well-known Paal–Knorr reaction.[11d] Also, it was proposed[1b,12a] that the formation of pyrrolidines occurs via initial hydrogenolysis of the C=N bond in imines **C**. Thus pyrroles and pyrrolidines should have different precursors (**D** and **C**, respectively). By contrast, we believe that the reduction of the C=N bond occurs only after



Scheme 4



Scheme 5

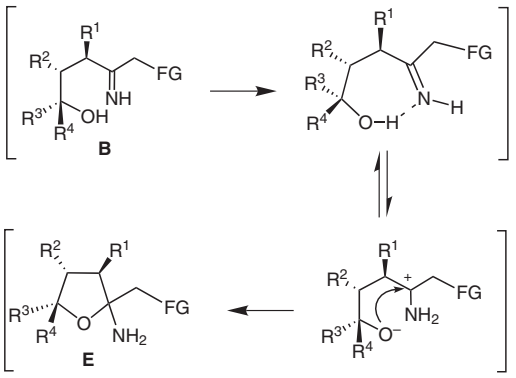
the cyclization of **C** to **D**, e.g. in cyclic imine **D** (Scheme 4).

This suggestion is supported with data shown in Scheme 5. Indeed, intermediates **C′** and **C″** lead to quite different products, pyrrolidine **7** and pyrrole **8**, respectively. At the same time, the iminium fragments of these intermediates are practically identical and, hence, it is difficult to conceive their different behavior during the hydrogenolysis of the C=N bond. However, the electrophilicity of carbonyl group in the above-mentioned intermediates **C′** and **C″** is quite different and owing to a combination of electronic and steric factors, the rate of cyclization of **C′** to **D′** could be significantly higher than the rate of cyclization of **C″** to **D″**.

By this consideration one could underline that the stereochemical outcome of hydrogenation of 5,6-dihydro-4*H*-1,2-oxazines should depend on the stereochemistry of the reduction of cyclic intermediate **D** (Scheme 4). However, earlier it was proposed that this outcome depends on the stereochemistry of the hydrogenation of acyclic intermediates **C**.[1b]

Thus, the catalytic hydrogenation of dihydrooxazines **4** bearing an alkoxy group at C6 results in recyclization with ring contraction after initial N–O bond cleavage. As a result of this process, the oxygen atom becomes exocyclic and is later eliminated to give the final heterocycle.

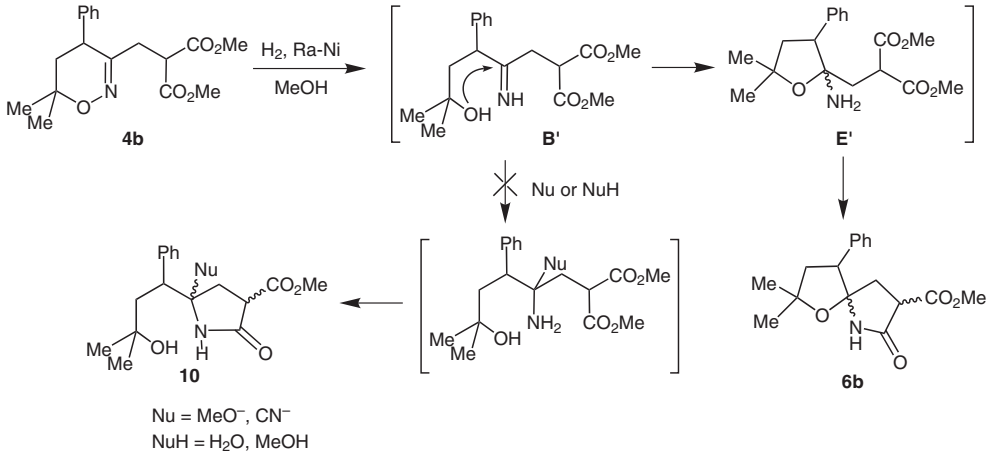
The hydrogenation of dihydrooxazines **4** that do not contain an alkoxy group at C6, also begins with initial N–O bond cleavage. However, in this case another recyclization is observed and the imine fragment is involved in the process as an electrophilic center to give intermediate **E** (Scheme 4, Path 2); an alternative pathway for the formation of amino acetals **E** involves the initial nucleophilic attack of imine group at the OH-proton in the imine intermediate **E** (Scheme 6). After this transformation the NH_2 fragment becomes exocyclic. Under acidic catalysis intermediates **E** are able to eliminate ammonia furnishing the respective dihydrofurans **5** (Scheme 4, route 3). By contrast, under neutral conditions derivatives **E** undergo intramolecular cyclization with participation of one of methoxycarbonyl groups to afford oxaazaspirononanones **6** (Scheme 4, route 4).



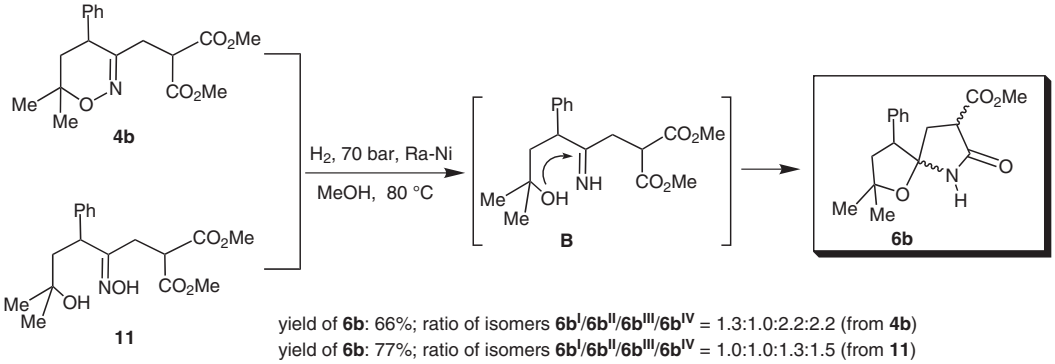
Scheme 6

Attempts to isolate α-aminofuran **E′** or to trap its precursor imine **B** with an external nucleophile (H_2O, MeOH, NaOMe, NaCN) to give lactam **10** were unsuccessful (Scheme 7).

In the scheme of generation of spiranones **6** (Scheme 7) the cyclization of **B** to **E** seems to be the most intriguing. The participation of imine intermediate **B** in the catalytic hydrogenation of oxazines **4** was indirectly confirmed by the similarity of the results of hydrogenation of the dihydrooxazine **4b** and specially obtained related oxime **11** (Scheme 8); it is well known that catalytic reduction of



Scheme 7



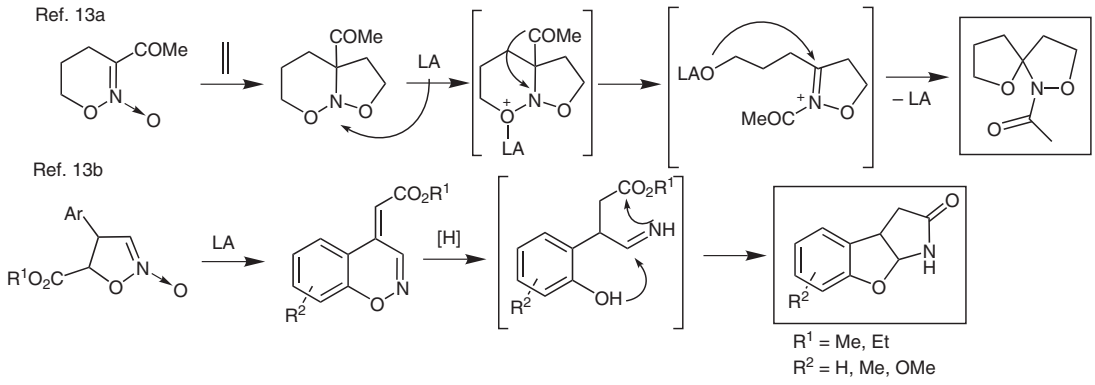
Scheme 8

oximes proceeds through the formation of the respective imines.[10]

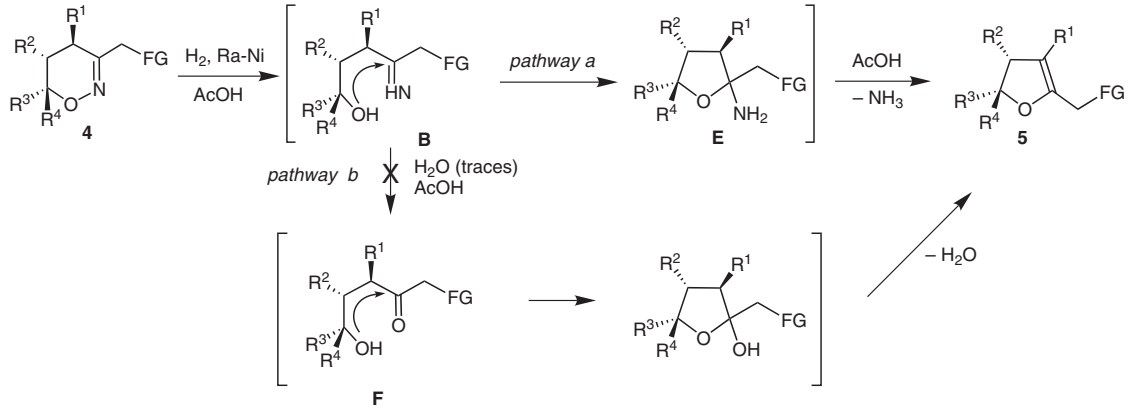
Several examples of processes involving intramolecular trapping of imines or iminium cations by hydroxy or related groups are known[13] (Scheme 9), although the mechanistic schemes suggested for these reactions are hypothetical.

For a comprehensive picture, the sequence leading to dihydrofurans **5**, which is an alternative to the conversion of **B** to **E** and then **5**, should be discussed (Scheme 10, pathway *b*). This pathway includes the hydrolysis of imines **B** with traces of water into the respective γ-hydroxycarbonyl derivatives **F**, which undergo successive intramolecular cyclization and elimination of water affording dihydrofurans **5**. Acid-mediated hydrolysis of imines, as well as oximes and their six-membered cyclic ethers is a well-known process.[14] However, this pathway seems unlikely, because upon hydrogenation of oxazine **4b** in aqueous acetic acid, neither the rate of reaction nor the yield of target dihydrofuran **5b** were increased.[7]

Attempts to perform the hydrogenation of oxazine **4b** with an acid that is stronger than acetic acid (HCl in dioxane–MeOH) resulted in the predominant formation of lactam **9** (55%), while the yield of oxaazaspirononanone **6b** decreased to 17% (Scheme 11).



Scheme 9



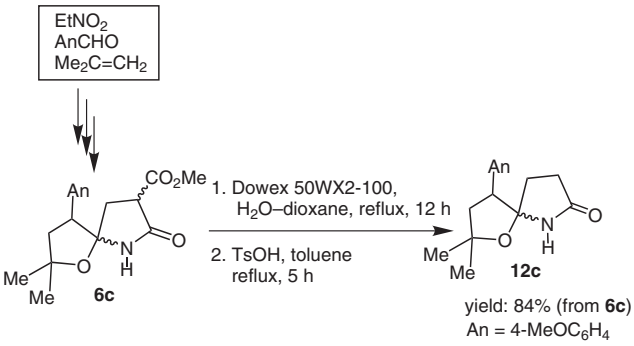
Scheme 10

Since acid-induced catalytic hydrogenation of amido acetals of type **6** is known,[15] the assumption that lactam **9** could be generated from the corresponding spirononanone **6b** needs to be taken into consideration. However, attempts to reduce the C–O bond in spirononanone **6b** under the conditions depicted in Scheme 11 were unsuccessful. Therefore, we believe that lactam **9** arises from oxazinium cation **G** after the hydrogenation of the C=N bond, e.g. the protonation of oxazine **4b** leads to initial reduction of the C=N bond in the oximino fragment.

In conclusion of the discussion related to the mechanism of the catalytic hydrogenation of oxazines **4**, it should be emphasized that Scheme 4 is only hypothetic and it undoubtedly requires further consideration.

As shown for the example of the spirononanone **6c**, spiranes of type **12**, possessing an unsubstituted pyrrolidone ring, can easily be obtained from simple and available precursors, nitroethane and the corresponding alkenes and aldehydes (Scheme 12).

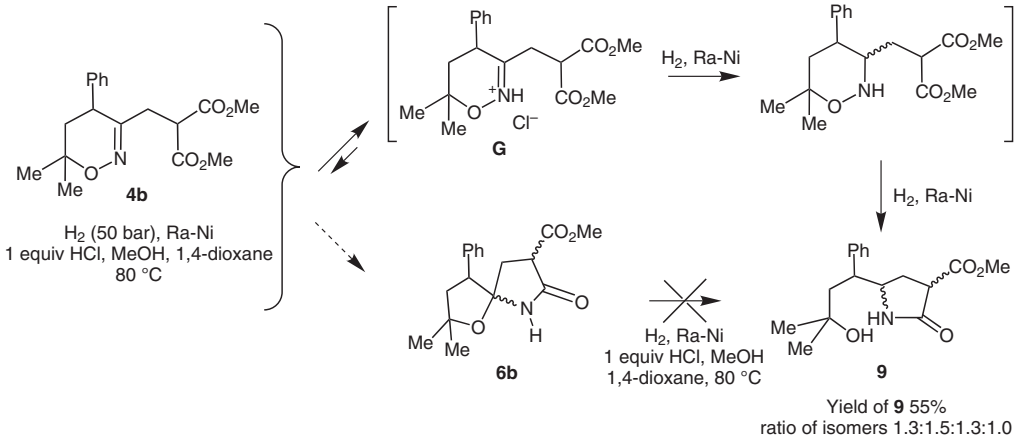
Close analogues of **6** and **12** are known as intermediates in the total syntheses of alkaloids (±)-isostemonamide[16] and cephalotaxine.[17] However, literature approaches[16–18] towards the synthesis of spiranes of type **12** seem to be less efficient owing to a greater number of steps and lower yields of the target compounds.



Scheme 12

As evident from Table 1, the compounds **6** are generated as mixtures of four diastereomers that differ in the configuration at C5 and C8 (Scheme 3, Table 1).

Confirmation of the structure of spiranones **6** and determination of the stereochemistry of individual isomers requires special discussion. The structure of products **6** was supported by elemental analysis and X-ray data, as well as by chemical transformation – decarboxylation of **6c** to give **12c**. The presence of major structural fragments of



Scheme 11

oxaazaspirononanones **6** was confirmed by ^{1}H and ^{13}C NMR. X-ray crystal data of **6b^{III}** are demonstrated in Figure 1.[19]

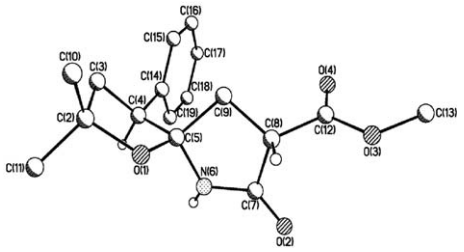


Figure 1 General view of the compound **6b^{III}** according to X-ray diffraction data, $C_{17}H_{21}NO_4$, M = 303.35, triclinic, space group $P\bar{1}$, at 100 K: a = 9.2027(18), b = 9.4230(19), c = 10.645(2) Å, α = 111.65(3), β = 98.67(3), γ = 103.91(3)°, V = 803.0(4) Å^3, Z = 2 (Z' = 1), d_{calc} = 1.255 g·cm^{-3}, μ(MoKα) = 0.89 cm^{-1}, F(000) = 324. Intensities of 3718 reflections were measured with a Bruker SMART APEX2 CCD diffractometer [λ(MoKα) = 0.71072 Å, ω-scans, 2θ < 54°] and 3496 independent reflections [R_{int} = 0.0249] were used in further refinement. The structure was solved by direct method and refined by the full-matrix least-squares technique against F^2 in the anisotropic-isotropic approximation. The hydrogen atom of the NH group was located from the Fourier synthesis of the electron density. The positions of H(C) atoms were calculated. All hydrogen atoms were refined in the isotropic approximation in the riding model. For **6b^{III}** the refinement converged to $wR2$ = 0.1005 and GOF = 1.002 for all independent reflections [$R1$ = 0.0475 was calculated against F for 2422 observed reflections with $I > 2\sigma(I)$]. All calculations were performed using SHELXTL PLUS 5.0.

The geometrical parameters of **6b^{III}** fall in the range common for this type of compounds. In the molecule, two heterocyclic fragments are bonded together through C5. The 'tetrahydrofuran' fragment is characterized by the envelope conformation with the deviation of C4 by 0.62 Å from the plane formed by other atoms of the ring. The same trend is observed for the nitrogen-containing heterocycle. In this case the C9 atom deviates by 0.47 Å. These two planes are practically perpendicular to each other and corresponding dihedral angle is equal to 93.8(2)°. The analysis of the crystal packing of **6b^{III}** revealed that the molecules are assembled into centrosymmetric dimers by N–H···O hydrogen bonds of intermediate strength (N···O separation and NHO angle are 2.910(2) Å and 165.1(1)°, respectively) through the formation of six-membered hydrogen-bonded rings. The above associates are held together by a number of weak C–H···O and C–H···π contacts thus resulting in the 3D-framework.

The configuration of the stereocenters in the tetrahydrofuran unit is identical for all isomers **6$^{I–IV}$** since it is governed by the 'architecture' of the initial diastereomerically pure oxazines **4a–i**. In most cases, mixtures of **6$^{I–IV}$** can be separated by column chromatography to give two fractions, containing pairs of isomers, **6^{I}** and **6^{II}**, **6^{III}** and **6^{IV}** respectively. These pairs differ in the configuration of the stereocenter at C5, while the isomers constituting one pair have different configuration at the C8 stereocenter. Isomer pairs cannot be separated into individual stereoisomers, though isomers **6b^{III}** and **6f^{I}** can be isolated from the corresponding pairs by crystallization.[20]

The relative configuration of stereocenters in **6$^{I–IV}$** was determined by various NMR techniques (^{1}H, ^{13}C, COSY, HSQC, DEPT, NOESY), which allowed signals in ^{1}H and ^{13}C spectra to be unambiguously assigned. The stereochemical disposition of protons and other substituents were established mainly from the results of 2D-NMR NOESY experiments. Figure 2 represents the main characteristic NOESY correlations for each of four isomers **6$^{I–IV}$**.

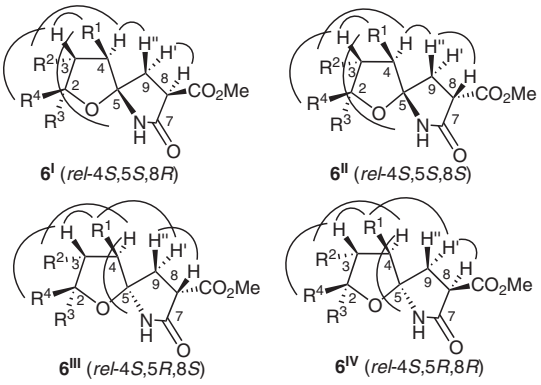


Figure 2 Characteristic NOE correlations in spirononanones **6a–i**.

In these spectra correlations of protons attached to C9 and C8, as well as the correlations (or their absence) between H9 and H4 were found to be the most important for determination of configuration. X-ray diffraction analysis of spirononanone **6b^{III}** revealed the same configuration as deduced for this stereoisomer by NMR spectroscopy. This circumstance confirms the correctness of all NMR assignments (see Figures 1– 3).

Chemical shifts of protons related to 'tetrahydrofuran' cycle of spiranes **6** do not depend on the configuration of stereocenters. At the same time, chemical shifts of protons H9 and, especially, H8 were very informative in the stereochemical assignment of isomers in their mixtures. The diagnostic ^{1}H NMR spectroscopic data for **6a–i** are collected in Table 2.

These data clearly indicate that H8 of isomers **6^{I}** and **6^{III}** have a chemical shift in the small range (δ = 3.6 to 3.7), whereas these signals of isomers **6^{II}** and **6^{IV}** are shifted to lower field. This effect becomes especially significant when R^1 is an aryl substituent. In this case the diamagnetic shift is nearly 1.5 ppm. We believe, that the diamagnetic shift of the H9 signal, is substantially connected with anisotropic effects of the aromatic ring. Analysis of atomic models of spiranes **6** clearly shows that the distance from H8 to the plane of aromatic ring in isomers **6^{I}** and **6^{III}** is almost one and a half times greater than the same distance in isomers **6^{II}** and **6^{IV}**.

In conclusion, catalytic hydrogenation of 5,6-dihydro-4*H*-1,2-oxazines **4** that have the $CH_2CH(CO_2Me)_2$ fragment at C3 and do not contain an alkoxy group at C6 with

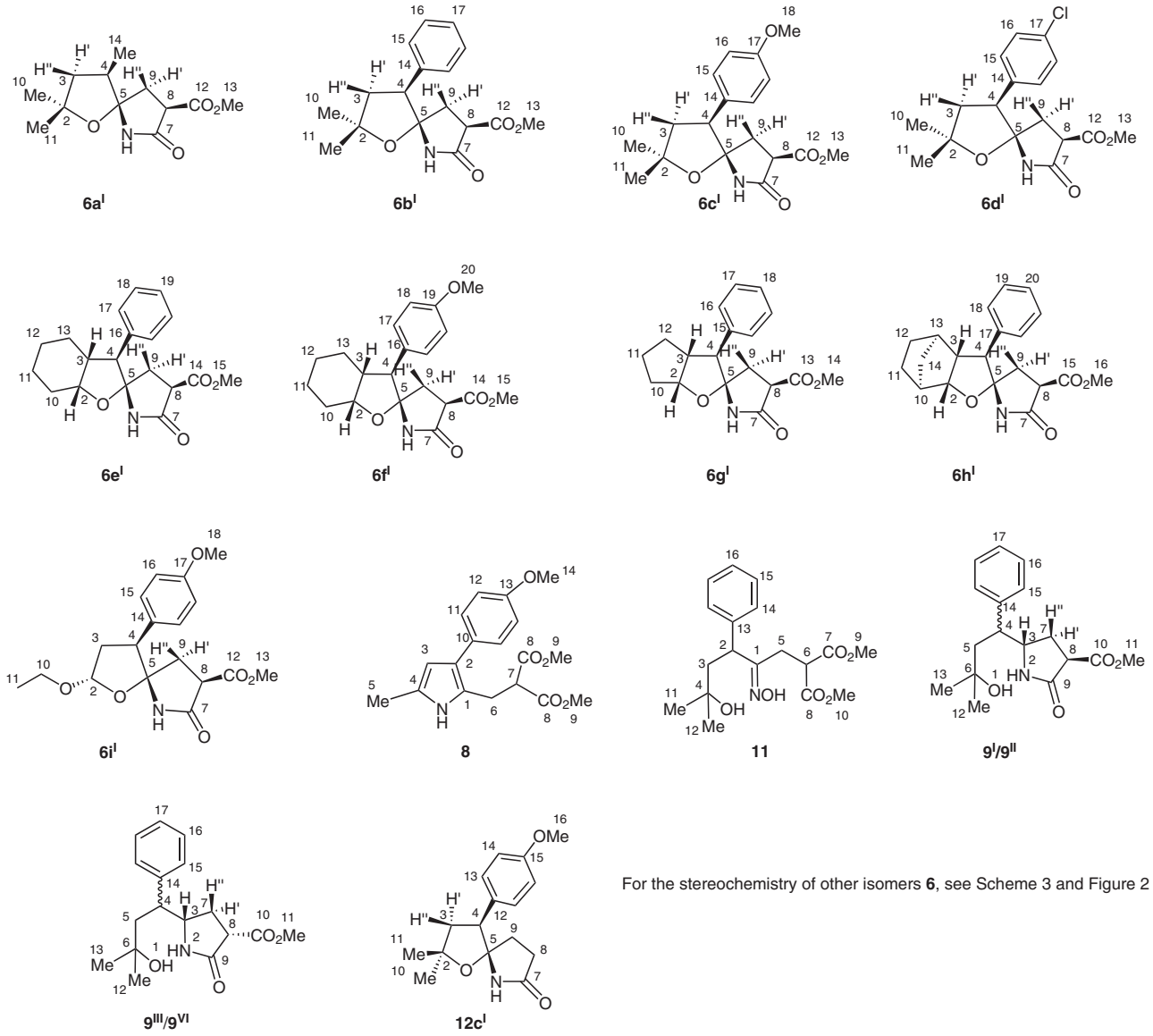


Figure 3

Raney nickel in methanol is an efficient method for the synthesis of previously unknown oxaazaspirononanones **6**.

NMR spectra were measured for pairs of isomers $\mathbf{6^I}$, $\mathbf{6^{II}}$ and $\mathbf{6^{III}}$, $\mathbf{6^{IV}}$, obtained after column chromatography of crude products **6** (for **6b** and **6f** NMR spectra were also measured for individual isomers $\mathbf{6b^{III}}$ and $\mathbf{6f^I}$; isomer pairs $\mathbf{6g^{III}}$ and $\mathbf{6g^{IV}}$, $\mathbf{6h^{III}}$ and $\mathbf{6h^{IV}}$, $\mathbf{6i^I}$ and $\mathbf{6i^{II}}$, respectively, could not be fully separated from the corresponding isomer pairs and were characterized in mixtures). 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 and WM-250 (^{13}C 75.13 or 62.5 MHz, INEPT, JMOD) NMR spectrometers in $CDCl_3$ (0.2 M solns). The chemical shifts (^{1}H and ^{13}C) are given relative to the solvent signal.[21] All 1D and 2D NMR experiments were performed using standard methods and Bruker NMR technique software. Atom-numbering is shown in Figure 3. Ratios of isomers $\mathbf{6^I}$, $\mathbf{6^{II}}$, $\mathbf{6^{III}}$, $\mathbf{6^{IV}}$ were determined by ^{1}H NMR (from the relative integral intensity of characteristic signals) for samples, obtained by filtration of the corresponding reaction mixtures through a short pad of silica gel to remove the traces of the catalyst.

Elemental analyses were performed by Analytical Laboratory of Institute of Organic Chemistry and the Analytical Center of the Moscow Chemical Lyceum. For diastereomeric mixtures $\mathbf{6^I}$–$\mathbf{6^{IV}}$ elemental analyses was performed for one of the middle fractions of chromatographic separation (consisting of all four isomers) after evaporation of the solvent and verification of the sample in vacuum. Melting points were determined on a Koffler 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.

High-pressure hydrogenation was carried out in a steel autoclave. The following reaction solvents and reagents were distilled from the indicated drying agents: toluene (CaH_2), 1,4-dioxane (CaH_2), THF ($LiAlH_4$), Et_3N (CaH_2). Anhyd MeOH (for Raney Ni preparation, procedure a and hydrogenation of oxazines **4a–h**) was prepared by distillation under Mg.

Table 2 Characteristic ^{1}H NMR Chemical Shifts for **6** [δ (500.13 MHz, $CDCl_3$)]

	Isomer			
6	**6^{I}**	**6^{II}**	**6^{III}**	**6^{IV}**
6a	H8: 3.64 H9′: 2.28 H9″: 2.57	H8: 3.34 H9′: 2.60 H9″: 2.33	H8: 3.66 H9′: 2.59 H9″: 2.11	H8: 3.33 H9′: 2.33 H9″: 2.47
6b	H8: 3.62 H9′: 2.40 H9″: 2.71	H8: 2.74 H9′: 2.74 H9″: 2.51	H8: 3.62 H9′: 2.14 H9″: 2.07	H8: 2.36 H9′: 2.21 H9″: 2.28
6c	H8: 3.64 H9′: 2.37 H9″: 2.69	H8: 2.77 H9′: 2.76 H9″: 2.49	H8: 3.68 H9′: 2.22 H9″: 2.15	H8: 2.41 H9′: 2.22 H9″: 2.31
6d	H8: 3.63 H9′: 2.41 H9″: 2.64	H8: 2.78 H9′: 2.73 H9″: 2.49	H8: 3.63 H9′: 2.32 H9″: 2.32	H8: 2.49 H9′: 2.13 H9″: 2.32
6e	H8: 3.65 H9′: 2.49 H9″: 2.80	H8: 2.90 H9′: 2.80 H9″: 2.56	H8: 3.60 H9′: 2.07 H9″: 2.07	H8: 2.36 H9′: 2.18 H9″: 2.31
6f	H8: 3.64 H9′: 2.45 H9″: 2.75	H8: 2.89 H9′: 2.78 H9″: 2.51	H8: 3.58 H9′: 2.04 H9″: 2.04	H8: 2.37 H9′: 2.16 H9″: 2.25
6g	H8: 3.63 H9′: 2.41 H9″: 2.55	H8: 2.84 H9′: 2.69 H9″: 2.41	H8: 3.63 H9′: 2.14 H9″: 2.14	H8: 2.58 H9′: 2.21 H9″: 2.35
6h	H8: 3.63 H9′: 2.40 H9″: 2.56	H8: 2.87 H9′: 2.72 H9″: 2.33	H8: 3.60 H9′: 2.12 H9″: 2.12	H8: 2.55 H9′: 2.19 H9″: 2.28
6i	H8: 3.68 H9′: 2.64 H9″: 2.75	H8: 3.14 H9′: 2.89 H9″: 2.58	H8: 3.58 H9′: 2.13 H9″: 1.97	H8: 2.85 H9′: 2.12 H9″: 2.31

MeOH, hexane, EtOAc, and DMF were technical grade and distilled without drying agents. Column chromatography was performed using Merck Kieselgel 60 (230–400 mesh) silica gel.

The following chemicals were purchased from the indicated sources: Raney Ni (50% slurry in H_2O) (Acros), Dowex 50WX2-100 (Sigma-Aldrich), TsOH·H_2O (Fluka), dimethyl malonate (Acros), *t*-BuOK (Fluka), Boc_2O (Acros), 5% Pd-C (Acros).

Initial malonates **4** were prepared according to literature procedure in four steps from nitroethane.[6a]

Preparation of Raney Nickel; Procedure a

A 50% slurry of Raney Ni in H_2O (100 mL) was washed with anhyd MeOH (5 × 50 mL), dried in vacuo (0.4 Torr) at 100 °C for 1 h and at r.t. for 2 h. The catalyst was stored under anhyd MeOH.

Preparation of Raney Nickel; Procedure b

A 50% slurry of Raney Ni in H_2O (5 mL) was washed with MeOH (5 × 10 mL). The catalyst was used immediately after preparation.

Oxaazaspirononanones 6a–h; General Procedure

To a soln of oxazine **4** (1.0 mmol) or oxime **11** (1.0 mmol) in anhyd MeOH (5.0 mL) was added Raney Ni (ca. 0.1 g in MeOH, prepared using procedure a). The suspension was hydrogenated at 70 bar H_2 and 80 °C with intensive stirring for 2 h and then filtered and concentrated in vacuum. The residue was purified by column chromatography (silica gel). Yields are presented in Table 1.

Methyl 2,2,4-Trimethyl-7-oxo-1-oxa-6-azaspiro[4.4]nonane-8-carboxylate (6a)

Anal. Calcd for $C_{12}H_{19}NO_4$: H, 7.94; C, 59.73; N, 5.81. Found: H, 7.62; C, 59.62; N, 5.84.

Mixture of 6a^{I} and 6a^{II}

Oil; ratio **6a^{I}/6a^{II}** 85:15; R_f = 0.13 (EtOAc–hexane, 1:1).

(4*R**,5*S**,8*R**)-Isomer 6a^{I}

^{1}H NMR (500.13 MHz, $CDCl_3$): δ = 0.98 (d, *J* = 6.2 Hz, 3 H, 14-CH_3), 1.15 (s, 3 H, 10-CH_3), 1.24 (s, 3 H, 11-CH_3), 1.56 (dd, *J* = 12.7, 12.7 Hz, 1 H, H3″), 1.96 (dd, *J* = 12.7, 7.0 Hz, 1 H, H3′), 2.28 (dd, *J* = 13.6, 9.2 Hz, 1 H, H9′), 2.32 (m, 1 H, H4), 2.57 (dd, *J* = 13.6, 8.8 Hz, 1 H, H9″), 3.64 (dd, *J* = 8.8, 9.2 Hz, 1 H, H8), 3.72 (s, 3 H, 13-CH_3), 7.75 (br, 1 H, NH).

^{13}C NMR ($CDCl_3$): δ = 13.1 (C14), 28.9 (C10), 30.1 (C11), 36.1 (C9), 41.5 (C4), 45.5 (C3), 47.3 (C8), 52.5 (C13), 80.1 (C2), 97.8 (C5), 170.1 (C12), 172.7 (C7).

Characteristic 2D-NOESY correlations: NH/11-CH_3, NH/14-CH_3, NH/H3″, H4/H3′, H8/H9′, H4/H9″.

(4*R**,5*S**,8*S**)-Isomer 6a^{II}

^{1}H NMR (500.13 MHz, $CDCl_3$): δ (selected signals) = 0.92 (d, *J* = 7.0 Hz, 3 H, 14-CH_3), 2.33 (m, 1 H, H9″), 2.60 (dd, *J* = 12.4, 6.6 Hz, 1 H, H9′), 3.37 (dd, *J* = 10.9, 6.6 Hz, 1 H, H8).

^{13}C NMR ($CDCl_3$): δ (selected signals from HSQC) = 35.9 (C9), 42.0 (C4), 44.8 (C3), 47.4 (C8).

Characteristic 2D-NOESY correlations: H9′/H9″, H8/H9″.

Mixture of 6a^{III} and 6a^{IV}

Oil; ratio **6a^{III}/6a^{IV}** 7.0:2.0; R_f = 0.09 (EtOAc–hexane, 1:1).

(4*R**,5*R**,8*S**)-Isomer 6a^{III}

^{1}H NMR (500.13 MHz, $CDCl_3$): δ = 1.08 (d, *J* = 7.2 Hz, 3 H, 14-CH_3), 1.22 and 1.25 (2 s, 6 H, 10-CH_3, 11-CH_3), 1.54 (dd, *J* = 12.4, 10.0 Hz, 1 H, H3″), 2.03 (dd, *J* = 12.4, 7.3 Hz, 1 H, H3′), 2.11 (dd, *J* = 13.2, 8.7 Hz, 1 H, H9″), 2.42 (ddq, *J* = 10.0, 7.3, 7.2 Hz, 1 H, H4), 2.59 (dd, *J* = 13.2, 8.1 Hz, 1 H, H9′), 3.66 (dd, *J* = 8.7, 8.1 Hz, 1 H, H8), 3.72 (s, 3 H, 13-CH_3), 7.25 (br, 1 H, NH).

^{13}C NMR ($CDCl_3$): δ = 14.9 (C14), 29.7 and 30.3 (C10, C11), 34.0 (C9), 40.5 (C4), 45.8 (C3), 47.0 (C8), 52.5 (C13), 79.2 (C2), 98.0 (C5), 170.1 (C12), 172.7 (C7).

Characteristic 2D-NOESY correlations: NH/H4, 14-CH_3/H3″, H3′/H3″, H8/H9″, 14-CH_3/H9′.

(4*R**,5*R**,8*R**)-Isomer 6a^{IV}

^{1}H NMR (500.13 MHz, $CDCl_3$): δ (selected signals) = 1.03 (d, *J* = 7.0 Hz, 3 H, 14-CH_3), 1.56 (dd, *J* = 13.0, 13.0 Hz, 1 H, H3), 2.25 (m, 1 H, H4), 2.33 (m, 1 H, H9′), 2.47 (dd, *J* = 13.5, 8.9 Hz, 1 H, H9″), 3.33 (dd, *J* = 8.9, 8.1 Hz, 1 H, H8), 6.07 (br, 1 H, NH).

^{13}C NMR ($CDCl_3$): δ (selected signals from HSQC) = 13.4 (C14), 33.8 (C9), 42.6 (C4), 45.6 (C3), 47.6 (C8).

Characteristic 2D-NOESY correlations: H9′/H9″, H9′/14-CH_3, H8/H9′.

Methyl 2,2-Dimethyl-4-phenyl-7-oxo-1-oxa-6-aza-spiro[4.4]nonane-8-carboxylate (6b)

Mixture of 6b^{I} and 6b^{II}

Oil; ratio **6b^{I}/6b^{II}** 1.0:1.0; R_f = 0.24 (EtOAc–hexane, 1:1).

(4*S**,5*S**,8*R**)-Isomer 6b^{I}

^{1}H NMR (500.13 MHz, $CDCl_3$): δ (selected signals) = 2.32 (m, 1 H, H3″), 2.40 (dd, *J* = 13.5, 9.0 Hz, 1 H, H9′), 2.71 (dd, *J* = 13.5, 9.4

Hz, 1 H, 1 H, H9″), 3.44 (m, 1 H, H4), 3.62 (dd, *J* = 9.4, 9.0 Hz, 1 H, H8).

^{13}C NMR ($CDCl_3$): δ (selected signals from HSQC) = 35.9 (C9), 47.1 (C8).

Characteristic 2D-NOESY correlations: NH/11-CH_3, NH/H3″, H4/H9″, H9′/H8, H4/10-CH_3, H4/H3′, H3″/11-CH_3.

(4*S,5*S**,8*S**)-Isomer 6b^{II}**

^{1}H NMR (500.13 MHz, $CDCl_3$): δ (selected signals) = 2.32 (m, 1 H, H3″), 2.51 (dd, *J* = 12.2, 6.2 Hz, 1 H, H9″), 2.74 (m, 2 H, H8, H9′), 3.44 (m, 1 H, H4).

^{13}C NMR ($CDCl_3$): δ (selected signals from HSQC) = 35.9 (C9), 47.7 (C8).

Characteristic 2D-NOESY correlations: NH/11-CH_3, NH/H3″, H4/H9″, H9″/H8, H4/10-CH_3, H4/H3′, H3″/11-CH_3.

Unassigned signals of both isomers:

^{1}H NMR (500.13 MHz, $CDCl_3$): δ = 1.29 and 1.30 (2 s, 6 H, 10-CH_3), 1.34 and 1.37 (2 s, 6 H, 11-CH_3), 2.06 and 2.11 (2 dd, *J* = 12.8, 6.8 Hz, 2 H, H3′), 3.56 and 3.70 (2 s, 6 H, 13-CH_3), 7.10–7.45 (m, 5 H, H15, H16, H17), 8.00 and 8.40 (2 br, 2 H, NH).

^{13}C NMR ($CDCl_3$): δ = 29.0 and 29.1 (C10), 29.8 and 30.1 (C11), 42.5 and 42.9 (C3), 52.5, 52.6, and 54.3 (C4 and C13), 79.8 and 80.3 (C2), 97.3 and 97.4 (C5), 127.6 and 127.8 (C15), 128.5, 128.6, 128.7, and 128.8 (C16 and C17), 135.5 and 135.6 (C14), 169.4 and 169.5 (C12), 171.5 and 172.6 (C7).

Mixture of 6b^{III} and 6b^{IV}

Oil; ratio **6b^{III}/6b^{IV}** 1.0:1.0; R_f = 0.20 (EtOAc–hexane, 1:1).

(4*S,5*R**,8*S**)-Isomer 6b^{III}**

Crystallized from mixture with **6b^{IV}**; mp 152–155 °C.

^{1}H NMR (500.13 MHz, $CDCl_3$): δ = 1.33 (s, 3 H, 10-CH_3), 1.38 (s, 3 H, 11-CH_3), 2.07 (dd, *J* = 9.2, 11.0 Hz, 1 H, H9″), 2.14 (dd, *J* = 9.2, 11.0 Hz, 1 H, H9′), 2.18 (dd, *J* = 13.0, 6.9 Hz, 1 H, H3′), 2.29 (dd, *J* = 13.3, 13.0 Hz, 1 H, H3″), 3.53 (s, 3 H, 13-CH_3), 3.62 (dd, *J* = 9.2, 9.2 Hz, 1 H, H8), 3.71 (dd, *J* = 13.3, 6.9 Hz, 1 H, H4), 7.10–7.45 (m, 5 H, H15, H16, H17), 7.70 (br, 1 H, NH).

^{13}C NMR ($CDCl_3$): δ = 29.2 (C10), 30.4 (C11), 35.3 (C9), 42.5 (C3), 47.1 (C8), 52.5 (C4), 52.6 (C13), 79.0 (C2), 97.8 (C5), 127.9 (C17), 128.3 and 128.9 (C15 and C16), 135.9 (C14), 169.6 (C12), 171.3 (C7).

Characteristic 2D-NOESY correlations: NH/H4, H8/H9″, H15/H9′, H4/H3′, H15/H3″, H4/10-CH_3.

Anal. Calcd for $C_{17}H_{21}NO_4$: H, 6.98; C, 67.31; N, 4.62. Found: H, 6.80; C, 67.41; N, 4.65.

(4*S,5*R**,8*R**)-Isomer 6b^{IV}**

Described in mixture with **6b^{III}**.

^{1}H NMR (500.13 MHz, $CDCl_3$): δ = 1.34 (s, 3 H, 10-CH_3), 1.40 (s, 3 H, 11-CH_3), 2.09 (m, 1 H, H3), 2.21 (dd, *J* = 13.1, 9.3 Hz, 1 H, H9′), 2.28 (dd, *J* = 13.1, 7.5 Hz, 1 H, H9″), 2.31 (m, 1 H, H3), 2.36 (dd, *J* = 9.3, 7.5 Hz, 1 H, H8), 3.61 (m, 1 H, H4), 3.63 (s, 3 H, 13-CH_3), 7.10–7.45 (m, 5 H, H15, H16 and H17), 7.35 (br, 1 H, NH).

^{13}C NMR ($CDCl_3$): δ = 28.8 (C10), 30.6 (C11), 35.3 (C9), 41.2 (C3), 47.9 (C8), 50.7 (C4), 52.1 (C13), 79.0 (C2), 98.2 (C5), 127.5 (C17), 128.5 and 128.7 (C15 and C16), 137.1 (C14), 169.5 (C12), 173.2 (C7).

Characteristic 2D-NOESY correlations: NH/H4, H8/H9′, H15/H9′, H4/10-CH_3.

Methyl 4-(4-Methoxyphenyl)-2,2-dimethyl-7-oxo-1-oxa-6-azaspiro[4.4]nonane-8-carboxylate (6c)

Anal. Calcd for $C_{18}H_{23}NO_5$: H, 6.95; C, 64.85; N, 4.20. Found: H, 7.08; C, 64.96; N, 4.18.

Mixture of 6c^{I} and 6c^{II}

Oil; ratio **6c^{I}/6c^{II}** 1.5:1.0; R_f = 0.20 (EtOAc–hexane, 1:1).

(4*S,5*S**,8*R**)-Isomer 6c^{I}**

^{1}H NMR (500.13 MHz, $CDCl_3$): δ = 1.27 (s, 3 H, 10-CH_3), 1.35 (s, 3 H, 11-CH_3), 2.05 (m, 1 H, H3′), 2.30 (m, 1 H, H3″), 2.37 (dd, *J* = 13.6, 9.4 Hz, 1 H, H9′), 2.69 (dd, *J* = 13.6, 9.8 Hz, 1 H, H9″), 3.37 (dd, *J* = 13.7, 7.0 Hz, 1 H, H4), 3.60 (s, 3 H, 13-CH_3), 3.64 (dd, *J* = 9.8, 9.4 Hz, 1 H, H8), 3.74 (s, 3 H, 18-CH_3), 6.76 (d, *J* = 7.9 Hz, 2 H, H16), 7.15 (d, *J* = 7.9 Hz, 2 H, H15), 8.52 (br, 1 H, NH).

^{13}C NMR ($CDCl_3$): δ = 29.1, 30.0 (C10, C11), 35.6 (C9), 43.1 (C3), 47.3 (C8), 51.9 (C4), 52.5 (C13), 55.1 (C18), 79.7 (C2), 97.6 (C5), 113.9 (C16), 127.5 (C14), 129.9 (C15), 158.9 (C17), 169.7 (C12), 172.3 (C7).

Characteristic 2D-NOESY correlations: NH/H15, NH/11-CH_3, NH/H3″, H4/H9″, H9′/H8.

(4*S,5*S**,8*S**)-Isomer 6c^{II}**

^{1}H NMR (500.13 MHz, $CDCl_3$): δ = 1.29 (s, 3 H, 10-CH_3), 1.31 (s, 3 H, 11-CH_3), 2.05 (m, 1 H, H3′), 2.30 (m, 1 H, H3″), 2.49 (dd, *J* = 13.5, 9.6 Hz, 1 H, H9″), 2.76 (dd, *J* = 13.5, 9.8 Hz, 1 H, H9′), 2.77 (dd, *J* = 9.8, 9.6 Hz, 1 H, H8), 3.37 (dd, *J* = 13.7, 7.0 Hz, 1 H, H4), 3.69 (s, 3 H, 13-CH_3), 3.78 (s, 3 H, 18-CH_3), 6.82 (d, *J* = 8.1 Hz, 2 H, H16), 7.19 (d, *J* = 8.1 Hz, 2 H, H15), 8.78 (br, 1 H, NH).

^{13}C NMR ($CDCl_3$): δ = 29.7, 29.3 (C10, C11), 35.7 (C9), 42.6 (C3), 47.8 (C8), 52.5 (C13), 53.6 (C4), 55.1 (C18), 80.2 (C2), 97.5 (C5), 114.1 (C16), 127.6 (C14), 129.8 (C15), 159.1 (C17), 169.6 (C12), 171.8 (C7).

Characteristic 2D-NOESY correlations: NH/H15, NH/11-CH_3, NH/H3″, H4/H9″.

Mixture of 6c^{III} and 6c^{IV}

Oil; ratio **6c^{III}/6c^{IV}** 1.0:1.0; R_f = 0.16 (EtOAc–hexane, 1:1).

(4*S,5*R**,8*S**)-Isomer 6c^{III}**

^{1}H NMR (500.13 MHz, $CDCl_3$): δ (selected signals) = 2.15 (dd, *J* = 13.5, 9.7 Hz, 1 H, H9″), 2.22 (dd, *J* = 13.5, 10.9 Hz, 1 H, H9′), 3.68 (dd, *J* = 11.0, 9.4 Hz, 1 H, H8), 3.78 (s, 3 H, 18-CH_3), 7.14 (d, *J* = 7.5 Hz, 2 H, H15).

^{13}C NMR ($CDCl_3$): δ (selected signals from HSQC) = 35.1 (C9), 47.1 (C8), 55.2 (C18).

Characteristic 2D-NOESY correlations: NH/H4.

(4*S,5*R**,8*R**)-Isomer 6c^{IV}**

^{1}H NMR (500.13 MHz, $CDCl_3$): δ (selected signals) = 2.22 (dd, *J* = 13.4, 10.0 Hz, 1 H, H9′), 2.31 (m, 1 H, H9″), 2.41 (dd, *J* = 9.2, 9.2 Hz, 1 H, H8), 3.78 (s, 3 H, 18-CH_3), 7.18 (d, *J* = 7.5 Hz, 2 H, H15).

^{13}C NMR ($CDCl_3$): δ (selected signals from HSQC) = 35.1 (C9), 47.9 (C8), 55.2 (C18).

Characteristic 2D-NOESY correlations: NH/H4, H9′/H8, H9′/H15.

Unassigned signals of both isomers:

^{1}H NMR (500.13 MHz, $CDCl_3$): δ = 1.33 and 1.34 (2 s, 6 H, 10-CH_3), 1.37 and 1.40 (2 s, 6 H, 11-CH_3), 2.08, 2.15, and 2.24 (m, 1 H, 1 H and 2 H, 2 H3), 3.60 and 3.63 (dd, *J* = 13.5, 6.8 Hz, and dd, *J* = 9.4, 9.4 Hz, 2 H, H4), 3.55 and 3.64 (2 s, 6 H, 13-CH_3), 6.85 and 6.86 (2 d, *J* = 7.5, 4 H, H16), 7.60 and 7.87 (br, 2 H, NH).

^{13}C NMR ($CDCl_3$): δ = 28.7 and 29.2 (C10), 30.2 and 30.5 (C11), 41.2 and 42.6 (C3), 49.8 and 51.3 (C4), 52.4 and 52.5 (C13), 78.8 and 78.9 (C2), 97.6 and 98.1 (C5), 114.0 and 114.2 (C16), 127.6 and 128.9 (C14), 128.7 and 129.2 (C15), 158.8 and 159.0 (C17), 169.4 and 169.5 (C12), 171.2 and 173.2 (C7).

Methyl 4-(4-Chlorophenyl)-2,2-dimethyl-7-oxo-1-oxa-6-aza-spiro[4.4]nonane-8-carboxylate (6d)

Anal. Calcd for $C_{17}H_{20}NO_4Cl$: H, 5.97; C, 60.45; N, 4.15. Found: H, 6.55; C, 60.93; N, 3.99.

Mixture of 6d^{I} and 6d^{II}

Oil; ratio **6d^{I}/6d^{II}** 1.0:1.0; R_f = 0.20 (EtOAc–hexane, 1:1).

(4*S,5*S**,8*R**)-Isomer 6d^{I}**

^{1}H NMR (500.13 MHz, $CDCl_3$): δ = 1.28 (s, 3 H, 10-CH_3), 1.35 (s, 3 H, 11-CH_3), 2.10 (m, 1 H, H3′), 2.32 (m, 1 H, H3″), 2.41 (dd, *J* = 13.5, 9.6 Hz, 1 H, H9′), 2.64 (dd, *J* = 13.5, 8.5 Hz, 1 H, H9″), 3.40 (dd, *J* = 13.2, 7.4 Hz, 1 H, H4), 3.59 (s, 3 H, 15-CH_3), 3.63 (dd, *J* = 9.6, 8.5 Hz, 1 H, H8), 7.10–7.45 (m, 4 H, H15, H16), 8.81 (br, 1 H, NH).

^{13}C NMR ($CDCl_3$): δ = 29.0 and 29.7 (C10, C11), 35.6 (C9), 42.9 (C3), 47.3 (C8), 52.6 (C13), 52.3 (C4), 80.0 (C2), 97.5 (C5), 128.7 and 130.4 (C15, C16), 132.3 and 134.1 (C14, C17), 168.5 (C12), 173.2 (C7).

Characteristic 2D-NOESY correlations: NH/11-CH_3, NH/H3″, H15/H3″, H4/H9″, H8/H9′, H4/10-CH_3, H3′/10-CH_3, H3″/11-CH_3.

(4*S,5*S**,8*S**)-Isomer 6d^{II}**

^{1}H NMR (500.13 MHz, $CDCl_3$): δ = 1.25 (s, 3 H, 10-CH_3), 1.31 (s, 3 H, 11-CH_3), 2.10 (m, 1 H, H3′), 2.32 (m, 1 H, H3″), 2.49 (dd, *J* = 13.4, 9.2 Hz, 1 H, H9″), 2.73 (dd, *J* = 13.4, 9.5 Hz, 1 H, H9′), 2.78 (dd, *J* = 9.5, 9.2 Hz, 1 H, H8), 3.40 (dd, *J* = 13.2, 7.4 Hz, 1 H, H4), 3.71 (s, 3 H, 15-CH_3), 7.10–7.45 (m, 4 H, H15, H16), 9.10 (br, 1 H, NH).

^{13}C NMR ($CDCl_3$): δ = 29.0 and 29.7 (C10, C11), 35.7 (C9), 42.7 (C3), 47.8 (C8), 52.6 (C13), 53.7 (C4), 80.5 (C2), 97.5 (C5), 128.9 and 130.2 (C15, C16), 132.4 and 134.3 (C14, C17), 168.5 (C12), 172.1 (C7).

Characteristic 2D-NOESY correlations: NH/11-CH_3, NH/H3″, H15/H3″, H4/H9″, H8/H9″, H4/10-CH_3, H3′/10-CH_3, H3″/11-CH_3.

Mixture of 6d^{III} and 6d^{IV}

Oil; ratio **6d^{III}/6d^{IV}** 1.0:1.0; R_f = 0.13 (EtOAc–hexane, 1:1).

(4*S,5*R**,8*S**)-Isomer 6d^{III}**

^{1}H NMR (500.13 MHz, $CDCl_3$): δ (selected signals) = 2.23 (m, 2 H, H3), 2.32 (m, 2 H, H9), 3.56 (s, 3 H, 13-CH_3), 3.63 (m, 1 H, H8), 3.72 (dd, *J* = 12.4, 7.0 Hz, 1 H, H4), 7.18 (d, *J* = 7.9 Hz, 2 H, H15), 7.30–7.35 (m, 2 H, H16), 8.21 (br, 1 H, NH).

^{13}C NMR ($CDCl_3$): δ (selected signals from HSQC) = 42.3 (C3), 50.0 (C4), 79.1 (C2).

Characteristic 2D-NOESY correlations: NH/10-CH_3, NH/H4.

(4*S,5*R**,8*R**)-Isomer 6d^{IV}**

^{1}H NMR (500.13 MHz, $CDCl_3$): δ (selected signals) = 2.06 (m, 1 H, H3′), 2.10 (m, 1 H, H3″), 2.13 (m, 1 H, H9′), 2.32 (dd, *J* = 13.9, 8.8 Hz, 1 H, H9″), 2.49 (dd, *J* = 8.8, 8.8 Hz, 1 H, H8), 3.61 (m, 1 H, H4), 3.66 (s, 3 H, 13-CH_3), 7.21 (d, *J* = 8.5 Hz, 2 H, H15), 7.30–7.35 (m, 2 H, H16), 7.95 (br, 1 H, NH).

^{13}C NMR ($CDCl_3$): δ (selected signals from HSQC) = 41.1 (C3), 51.3 (C4), 79.1 (C2).

Characteristic 2D-NOESY correlations: NH/10-CH_3, NH/H4, H9′/H8, H4/10-CH_3, H9′/H15, H3′/10-CH_3.

Unassigned signals of both isomers:

^{1}H NMR (500.13 MHz, $CDCl_3$): δ = 1.35 and 1.36 (2 s, 3 H, 10-CH_3), 1.39 and 1.41 (2 s, 3 H, 11-CH_3).

^{13}C NMR ($CDCl_3$): δ = 28.7 and 29.1 (C10), 30.4 and 30.2 (C11), 35.1 and 35.0 (C9), 47.8 and 47.0 (C8), 52.6 and 52.5 (C13), 97.9 and 97.5 (C5), 129.6, 129.1, 129.0, and 128.8 (C15, C16), 135.4, 134.4, 133.7, and 133.3 (C14, C17), 169.3 and 169.1 (C12), 171.7 and 173.6 (C7).

Methyl 5′-Oxo-3-phenyl-hexahydro-3*H*-spiro[1-benzofuran-2,2′-pyrrolidine]-4′-carboxylate (6e)

Anal. Calcd for $C_{19}H_{23}NO_4$: H, 7.04; C, 69.28; N, 4.25. Found: H, 7.31; C, 69.13; N, 3.98.

Mixture of 6e^{I} and 6e^{II}

Oil; ratio **6e^{I}/6e^{II}** 1.3:1.0; R_f = 0.16 (EtOAc–hexane, 1:1).

(2*S,3*S**,3a*R**,4′*R**,7a*R**)-Isomer 6e^{I}**

^{1}H NMR (500.13 MHz, $CDCl_3$): δ = 1.15–1.25 (m, 1 H, H11), 1.30–1.45 (m, 2 H, H12), 1.48–1.53 (m, 2 H, H10, H13), 1.60–1.65 (m, 2 H, H11, H13), 1.85 (m, 1 H, H10), 2.49 (dd, *J* = 13.3, 8.7 Hz, 1 H, H9′), 2.70 (m, 1 H, H3), 2.80 (m, 1 H, H9″), 3.31 (d, *J* = 11.9 Hz, 1 H, H4), 3.65 (dd, *J* = 8.7, 9.6 Hz, 1 H, H8), 3.68 (s, 3 H, 15-CH_3), 4.23 (m, 1 H, H2), 7.10–7.30 (m, 6 H, H17, H18, H19, NH).

^{13}C NMR ($CDCl_3$): δ = 21.0 (C12), 22.2 (C11), 25.2 (C13), 28.2 (C10), 38.1 (C9), 41.3 (C3), 46.9 (C8), 52.5 (C15), 54.9 (C4), 76.3 (C2), 96.7 (C5), 127.7 (C19), 128.4 and 128.8 (C17, C18), 135.6 (C16), 169.5 (C14), 171.8 (C7).

Characteristic 2D-NOESY correlations: H3/H2, H17/H2, H17/H3, H4/H9″, H8/H9′.

(2*S,3*S**,3a*R**,4′*S**,7a*R**)-Isomer 6e^{II}**

^{1}H NMR (500.13 MHz, $CDCl_3$): δ = 1.15–1.25 (m, 1 H, H11), 1.30–1.45 (m, 3 H, H10, H12), 1.48–1.53 (m, 1 H, H13), 1.61–1.65 (m, 2 H, H11, H13), 1.95 (m, 1 H, H10), 2.56 (dd, *J* = 13.7, 9.5 Hz, 1 H, H9″), 2.70 (m, 1 H, H3), 2.80 (m, 1 H, H9′), 2.90 (dd, *J* = 9.5, 7.3 Hz, 1 H, H8), 3.31 (d, *J* = 11.9 Hz, 1 H, H4), 3.70 (s, 3 H, 15-CH_3), 4.23 (m, 1 H, H2), 6.80 (br, 1 H, NH), 7.10–7.40 (m, 5 H, H17, H18, H19).

^{13}C NMR ($CDCl_3$): δ = 20.5 (C12), 22.6 (C11), 24.1 (C13), 30.3 (C10), 37.6 (C9), 40.4 (C3), 47.5 (C8), 53.2 (C15), 55.2 (C4), 76.3 (C2), 96.6 (C5), 127.8 (C19), 128.4 and 128.8 (C17, C18), 135.2 (C16), 169.5 (C14), 171.8 (C7).

Characteristic 2D-NOESY correlations: H3/H2, H17/H2, H17/H3, NH/H3, H4/H9″, H8/H9″.

Mixture of 6e^{III} and 6e^{IV}

Oil; ratio **6e^{III}/6e^{IV}** 1.0:1.0; R_f = 0.19 (EtOAc–hexane, 1:1).

(2*R,3*S**,3a*R**,4′*S**,7a*R**)-Isomer 6e^{III}**

^{1}H NMR (500.13 MHz, $CDCl_3$): δ = 1.10–1.60 (m, 7 H, H10, H11, H12, H13), 1.81–1.98 (m, 1 H, H10), 2.07 (m, 2 H, H9), 2.73 (m, 1 H, H3), 3.48 (d, *J* = 11.9 Hz, 1 H, H4), 3.55 (s, 3 H, 15-CH_3), 3.60 (dd, *J* = 8.9, 8.9 Hz, 1 H, H8), 4.17 (m, 1 H, H2), 7.10–7.30 (m, 5 H, H17, H18, H19), 7.79 (br, 1 H, NH).

^{13}C NMR ($CDCl_3$): δ = 20.4 (C12), 22.7 (C11), 25.1 (C13), 30.3 (C10), 35.7 (C9), 40.7 (C3), 46.9 (C8), 52.8 and 52.9 (C4, C15), 76.5 (C2), 98.1 (C5), 127.5 (C19), 128.4 and 128.8 (C17, C18), 136.6 (C16), 169.4 (C14), 173.2 (C7).

Characteristic 2D-NOESY correlations: NH/H4, 9-CH_2/H17, 9-CH_2/H8, H2/H3.

(2*R,3*S**,3a*R**,4′*R**,7a*R**)-Isomer 6e^{IV}**

^{1}H NMR (500.13 MHz, $CDCl_3$): δ = 1.10–1.60 (m, 7 H, H10, H11, H12, H13), 1.81–1.98 (m, 1 H, H10), 2.18 (dd, *J* = 13.0, 9.2 Hz, 1 H, H9′), 2.31 (dd, *J* = 13.0, 8.3 Hz, 1 H, H9″), 2.36 (dd, *J* = 8.3, 9.2 Hz, 1 H, H8), 2.73 (m, 1 H, H3), 3.48 (d, *J* = 13.2 Hz, 1 H, H4), 3.68 (s, 3 H, 15-CH_3), 4.17 (m, 1 H, H2), 7.10–7.40 (m, 5 H, H17, H18, H19), 7.72 (br, 1 H, NH).

^{13}C NMR ($CDCl_3$): δ = 20.9 (C12), 23.1 (C11), 24.1 (C13), 30.3 (C10), 37.6 (C9), 38.9 (C3), 47.6 (C8), 52.3 and 52.4 (C4, C15), 76.2 (C2), 97.7 (C5), 127.5 (C19), 128.4 and 128.8 (C17, C18), 135.4 (C16), 169.5 (C14), 173.2 (C7).

Characteristic 2D-NOESY correlations: H4/NH, H2/H3, H17/H9′, H8/H9′.

Methyl 3-(4-Methoxyphenyl)-5′-oxo-hexahydro-3*H*-spiro[1-benzofuran-2,2′-pyrrolidine]-4′-carboxylate (6f)

Mixture of 6f^{I} and 6f^{II}

Oil; ratio **6f^{I}/6f^{II}** 1.5:1.0; R_f = 0.12 (EtOAc–hexane, 1:1).

(2*S,3*S**,3a*R**,4′*R**,7a*R**)-Isomer 6f^{I}**

Crystallized from mixture with **6f^{II}**; mp 159–165 °C.

^{1}H NMR (500.13 MHz, $CDCl_3$): δ = 1.10–1.70 (m, 7 H, H10, H11, H12, H13), 1.87 (m, 1 H, H10), 2.45 (dd, *J* = 13.1, 8.5 Hz, 1 H, H9′), 2.63 (m, 1 H, H3), 2.75 (dd, *J* = 13.1, 9.6 Hz, 1 H, H9″), 3.24 (d, *J* = 11.1 Hz, 1 H, H4), 3.64 (dd, *J* = 8.5, 9.6 Hz, 1 H, H8), 3.66 (s, 3 H, 15-CH_3), 3.74 (s, 3 H, 20-CH_3), 4.20 (ddd, *J* = 9.9, 7.2, 2.5 Hz, 1 H, H2), 6.79 (d, *J* = 8.4 Hz, 2 H, H18), 7.08 (d, *J* = 8.4 Hz, 2 H, H17), 7.35 (br, 1 H, NH).

^{13}C NMR ($CDCl_3$): δ = 20.8 (C12), 22.4 (C11), 24.8 (C13), 29.8 (C10), 37.7 (C9), 41.2 (C3), 47.0 (C8), 51.8 (C15), 53.5 (C4), 55.2 (C20), 76.3 (C2), 96.7 (C5), 114.2 (C18), 127.2 (C16), 129.6 (C17), 158.9 (C19), 169.6 (C14), 172.2 (C7).

Characteristic 2D-NOESY correlations: H3/H2, H17/H3, H4/H9″, H8/H9′.

Anal. Calcd for $C_{20}H_{25}NO_5$: H, 7.01; C, 66.83; N, 3.90. Found: H, 6.91; C, 67.15; N, 3.81.

(2*S,3*S**,3a*R**,4′*S**,7a*R**)-Isomer 6f^{II}**

Described in mixture with **6f^{I}**.

^{1}H NMR (500.13 MHz, $CDCl_3$): δ = 1.10–1.70 (m, 7 H, H10, H11, H12, H13), 1.97 (m, 1 H, H10), 2.51 (dd, *J* = 13.7, 9.3 Hz, 1 H, H9″), 2.63 (m, 1 H, H3), 2.78 (dd, *J* = 13.7, 7.5 Hz, 1 H, H9′), 2.89 (dd, *J* = 9.3, 7.5 Hz, 1 H, H8), 3.24 (d, *J* = 11.1 Hz, 1 H, H4), 3.71 (s, 3 H, 15-CH_3), 3.76 (s, 3 H, 20-CH_3), 4.20 (ddd, *J* = 9.9, 7.2, 2.5 Hz, 1 H, H2), 6.83 (d, *J* = 8.5 Hz, 2 H, H18), 7.09 (d, *J* = 8.5 Hz, 2 H, H17), 7.42 (br, 1 H, NH).

^{13}C NMR ($CDCl_3$): δ = 20.4 (C12), 22.7 (C11), 24.0 (C13), 30.5 (C10), 37.4 (C9), 40.3 (C3), 47.6 (C8), 52.6 (C15), 54.2 (C4), 55.2 (C20), 76.4 (C2), 96.7 (C5), 114.3 (C18), 126.8 (C16), 129.9 (C17), 158.9 (C19), 169.6 (C14), 170.9 (C7).

Characteristic 2D-NOESY correlations: H3/H2, H17/H2, H17/H3, NH/H3, H4/H9″, H8/H9″.

Mixture of 6f^{III} and 6f^{IV}

Oil; ratio **6f^{III}/6f^{IV}** 3.4:3.8; R_f = 0.16 (EtOAc–hexane, 1:1).

(2*R,3*S**,3a*R**,4′*S**,7a*R**)-Isomer 6f^{III}**

^{1}H NMR (500.13 MHz, $CDCl_3$): δ = 1.10–1.70 (m, 8 H, H10, H11, H12, H13), 2.04 (m, 2 H, H9), 2.70 (m, 1 H, H3), 3.41 (d, *J* = 12.0 Hz, 1 H, H4), 3.53 (s, 3 H, 15-CH_3), 3.58 (dd, *J* = 8.9, 8.9 Hz, 1 H, H8), 3.75 (s, 3 H, 20-CH_3), 4.13 (m, 1 H, H2), 6.85 (d, *J* = 8.4 Hz, 2 H, H18), 7.05 (d, *J* = 8.4 Hz, 2 H, H17), 7.66 (br, 1 H, NH).

^{13}C NMR ($CDCl_3$): δ (selected signals from HSQC) = 37.6 (C9), 40.7 (C3), 47.0 (C8).

Characteristic 2D-NOESY correlations: 9-CH_2/H17, 9-CH_2/H8, H2/H3.

(2*R,3*S**,3a*R**,4′*R**,7a*R**)-Isomer 6f^{IV}**

^{1}H NMR (500.13 MHz, $CDCl_3$): δ = 1.10–1.70 (m, 8 H, H10, H11, H12, H13), 2.16 (dd, *J* = 13.5, 9.0 Hz, 1 H, H9′), 2.25 (dd, *J* = 13.5, 8.3 Hz, 1 H, H9″), 2.37 (dd, *J* = 8.3, 9.0 Hz, 1 H, H8), 2.70 (m, 1 H, H3), 3.41 (d, *J* = 12.0 Hz, 1 H, H4), 3.66 (s, 3 H, 15-CH_3), 3.75 (s, 3 H, 20-CH_3), 4.13 (m, 1 H, H2), 6.83 (d, *J* = 8.3 Hz, 2 H, H18), 7.10 (d, *J* = 8.3 Hz, 2 H, H17), 7.74 (br, 1 H, NH).

^{13}C NMR ($CDCl_3$): δ (selected signals from HSQC) = 37.6 (C9), 40.7 (C3), 47.7 (C8).

Characteristic 2D-NOESY correlations: H4/NH, H2/H3, H17/H9′, H8/H9′.

Unassigned signals of both isomers:

^{13}C NMR ($CDCl_3$): δ = 20.4 and 20.8 (C12), 22.8 and 23.2 (C11), 24.1 and 24.9 (C13), 30.2 and 30.4 (C10), 47.0 (C8), 51.6 and 51.8 (C4), 52.4 and 52.5 (C15), 55.2 (C20), 76.3 and 76.5 (C2), 97.8 and 98.2 (C5), 114.2 and 114.4 (C18), 126.9 and 128.3 (C16), 129.4 and 129.7 (C17), 158.9 and 159.0 (C19), 169.5 and 169.6 (C14), 171.4 and 173.4 (C7).

Methyl 5′-Oxo-3-phenyl-hexahydrospiro[2*H*-cyclopenta[*b*]furan-2,2′-pyrrolidine]-4′-carboxylate (6g)

Anal. Calcd for $C_{18}H_{21}NO_4$: H, 6.71; C, 68.55; N, 4.44. Found: H, 6.74; C, 68.29; N, 4.15.

Mixture of 6g^{I} and 6g^{II}

Oil; ratio **6g^{I}/6g^{II}** 1.4:1.0; R_f = 0.16 (EtOAc–hexane, 1:1).

(2*S,3*S**,3a*R**,4′*R**,6a*R**)-Isomer 6g^{I}**

^{1}H NMR (500.13 MHz, $CDCl_3$): δ = 1.48–1.53 (m, 3 H, H10, H12), 1.55–1.75 (m, 2 H, H11), 1.80–1.90 (m, 1 H, H10), 2.41 (dd, *J* = 13.6, 8.8 Hz, 1 H, H9′), 2.55 (dd, *J* = 13.6, 9.0 Hz, 1 H, H9″), 2.74 (d, *J* = 9.6 Hz, 1 H, H4), 3.07 (m, 1 H, H3), 3.57 (s, 3 H, 14-CH_3), 3.63 (dd, *J* = 8.8, 9.0 Hz, 1 H, H8), 4.61 (dd, *J* = 8.6, 8.6 Hz, 1 H, H2), 7.10–7.40 (m, 5 H, H16, H17, H18), 8.84 (br, 1 H, NH).

^{13}C NMR ($CDCl_3$): δ = 23.2 (C11), 31.7 (C12), 33.6 and 33.9 (C9, C10), 47.3 (C8), 48.1 (C3), 52.5 (C14), 59.3 (C4), 82.3 (C2), 98.5 (C5), 127.5 (C18), 128.5 and 129.2 (C16, C17), 136.2 (C15), 169.5 (C13), 173.7 (C7).

Characteristic 2D-NOESY correlations: H2/H3, NH/H16, NH/H2, NH/H3, H16/H2, H16/H3, H4/H9″, H8/H9′.

(2*S,3*S**,3a*R**,4′*S**,6a*R**)-Isomer 6g^{II}**

^{1}H NMR (500.13 MHz, $CDCl_3$): δ = 1.48–1.53 (m, 3 H, H10, H12), 1.55–1.75 (m, 2 H, H11), 1.80–1.90 (m, 1 H, H10), 2.41 (dd, *J* = 13.9, 9.6 Hz, 1 H, H9″), 2.69 (dd, *J* = 13.9, 6.2 Hz, 1 H, H9′), 2.76 (d, *J* = 9.6 Hz, 1 H, H4), 2.84 (dd, *J* = 9.6, 6.2 Hz, 1 H, H8), 3.07 (m, 1 H, H3), 3.70 (s, 3 H, 14-CH_3), 4.63 (dd, *J* = 8.6, 8.6 Hz, 1 H, H2), 7.10–7.40 (m, 5 H, H16, H17, H18), 8.78 (br, 1 H, NH).

^{13}C NMR ($CDCl_3$): δ = 23.2 (C11), 31.4 (C12), 33.6 and 33.9 (C9, C10), 47.6 (C8), 47.9 (C3), 52.6 (C14), 60.6 (C4), 83.1 (C2), 98.5 (C5), 127.6 (C18), 128.6 and 129.2 (C16, C17), 136.4 (C15), 169.5 (C13), 172.5 (C7).

Characteristic 2D-NOESY correlations: H2/H3, NH/H16, NH/H2, NH/H3, H16/H2, H16/H3, H4/H9″, H8/H9″.

Mixture of 6g^{I}, 6g^{II}, 6g^{III}, and 6g^{IV}

Oil; ratio **6g^{I}/6g^{II}/6g^{III}/6g^{IV}** 1.0:1.7:0.8:0.6; R_f = 0.14 (EtOAc–hexane, 1:1).

(2*R,3*S**,3a*R**,4′*S**,6a*R**)-Isomer 6g^{III}**

^{1}H NMR (500.13 MHz, $CDCl_3$): δ = 1.48–1.53 (m, 3 H, H10, H12), 1.55–1.75 (m, 2 H, H11), 1.80–1.90 (m, 1 H, H12), 2.14 (m, 2 H, H9), 3.01 (d, *J* = 8.8 Hz, 1 H, H4), 3.07 (m, 1 H, H3), 3.57 (s, 3 H, 14-CH_3), 3.63 (m, 1 H, H8), 4.54 (m, 1 H, H2), 7.10–7.40 (m, 5 H, H16, H17, H18), 7.35 (br, 1 H, NH).

^{13}C NMR ($CDCl_3$): δ = 23.5 (C11), 30.2 (C9), 31.5 (C12), 33.6 (C10), 46.5 (C3), 48.1 (C8), 52.6 (C14), 56.9 (C4), 81.2 (C2), 98.5 (C5), 127.6 (C18), 128.7 and 129.2 (C16, C17), 136.9 (C15), 169.5 (C13), 173.1 (C7).

Characteristic 2D-NOESY correlations: NH/H4, H2/H3.

(2*R,3*S**,3a*R**,4′*R**,6a*R**)-Isomer 6g^{IV}**

^{1}H NMR (500.13 MHz, $CDCl_3$): δ = 1.48–1.53 (m, 3 H, H10, H12), 1.55–1.75 (m, 2 H, H11), 1.80–1.90 (m, 1 H, H12), 2.21 (dd, *J* = 13.7, 9.6 Hz, 1 H, H9′), 2.35 (dd, *J* = 13.7, 6.4 Hz, 1 H, H9″), 2.58 (m, 1 H, H8), 2.90 (d, *J* = 9.0 Hz, 1 H, H4), 3.12 (m, 1 H, H3), 3.68 (s, 3 H, 14-CH_3), 4.54 (m, 1 H, H2), 7.10–7.40 (m, 6 H, H16, H17, H18, NH).

^{13}C NMR ($CDCl_3$): δ = 23.4 (C11), 31.6 (C12), 32.1 (C9), 33.6 (C10), 46.9 (C3, C8), 52.6 (C14), 57.9 (C4), 80.6 (C2), 98.5 (C5), 127.5 (C18), 128.3 and 129.2 (C16, C17), 136.9 (C15), 169.5 (C13), 173.1 (C7).

Characteristic 2D-NOESY correlations: H2/H3, H16/H9′, H8/H9′.

Methyl 5′-Oxo-5-phenylspiro[3-oxatricyclo[5.2.1.0^{2,6}]decane-4,2′-pyrrolidine]-4′-carboxylate (6h)

Anal. Calcd for $C_{20}H_{23}NO_4$: H, 6.79; C, 70.36; N, 4.10. Found: H, 6.97; C, 70.17; N, 4.10.

Mixture of 6h^{I} and 6h^{II}

Oil; ratio **6h^{I}/6h^{II}** 1.4:1.0; R_f = 0.22 (EtOAc–hexane, 1:1).

(1*R,2*R**,4*S**,4′*R**,5*S**,6*R**,7*R**)-Isomer 6h^{I}**

^{1}H NMR (500.13 MHz, $CDCl_3$): δ = 1.02 (m, 2 H, H11, H12), 1.10 (m, 1 H, H14$_{anti}$), 1.42 (m, 1 H, H12), 1.45 (m, 1 H, H11), 1.63 (m, 1 H, H14$_{syn}$), 2.02 (d, *J* = 3.6 Hz, 1 H, H13), 2.27 (d, *J* = 4.7 Hz, 1 H, H10), 2.40 (m, 2 H, H3, H9′), 2.56 (dd, *J* = 13.7, 9.7 Hz, 1 H, H9″), 2.71 (d, *J* = 8.5 Hz, 1 H, H4), 3.60 (s, 3 H, 16-CH_3), 3.63 (dd, *J* = 8.8, 9.7 Hz, 1 H, H8), 3.94 (d, *J* = 6.2 Hz, 1 H, H2), 7.20–7.40 (m, 5 H, H18, H19, H20), 8.39 (br, 1 H, NH).

^{13}C NMR ($CDCl_3$): δ = 23.4 (C11), 27.7 (C12), 31.1 (C14), 33.8 (C9), 39.7 and 40.2 (C10, C13), 47.2 (C8), 52.4 and 52.5 (C3, C16), 57.5 (C4), 83.5 (C2), 97.6 (C5), 127.5 (C20), 128.5 and 129.2 (C18, C19), 136.4 (C17), 169.4 (C15), 173.4 (C7).

Characteristic 2D-NOESY correlations: NH/H2, NH/H3, NH/H18, H2/H3, H18/H3, H2/H11, H4/H14$_{syn}$, H4/H13, H2/H10, H4/H9″, H8/H9′.

(1*R,2*R**,4*S**,4′*S**,5*S**,6*R**,7*R**)-Isomer 6h^{II}**

^{1}H NMR (500.13 MHz, $CDCl_3$): δ = 1.02 (m, 2 H, H11, H12), 1.10 (m, 1 H, H14$_{anti}$), 1.42 (m, 1 H, H12), 1.45 (m, 1 H, H11), 1.63 (m, 1 H, H14$_{syn}$), 2.01 (d, *J* = 3.9 Hz, 1 H, H13), 2.32 (d, *J* = 4.3 Hz, 1 H, H10), 2.33 (m, 2 H, H3, H9″), 2.71 (d, *J* = 8.5 Hz, 1 H, H4), 2.72 (dd, *J* = 13.0, 9.7 Hz, 1 H, H9′), 2.87 (dd, *J* = 9.7, 6.2 Hz, 1 H, H8), 3.70 (s, 3 H, 16-CH_3), 3.94 (d, *J* = 6.2 Hz, 1 H, H2), 7.20–7.40 (m, 5 H, H18, H19, H20), 8.56 (br, 1 H, NH).

^{13}C NMR ($CDCl_3$): δ = 23.4 (C11), 27.7 (C12), 31.1 (C14), 33.8 (C9), 39.4 and 40.2 (C10, C13), 47.4 (C8), 52.4 and 52.5 (C3, C16), 59.1 (C4), 84.3 (C2), 97.6 (C5), 127.5 (C20), 128.6 and 129.0 (C18, C19), 136.7 (C17), 169.4 (C15), 172.2 (C7).

Characteristic 2D-NOESY correlations: NH/H2, NH/H3, NH/H18, H4/H14$_{syn}$, H18/H3, H2/H10, H4/H9″, H8/H9″.

Mixture of 6h^{I}, 6h^{II}, 6h^{III}, and 6h^{IV}

Oil; ratio **6h^{I}/6h^{II}/6h^{III}/6h^{IV}** 3.1:1.0:10.0:4.7; R_f = 0.19 (EtOAc–hexane, 1:1).

(1*R,2*R**,4*R**,4′*S**,5*S**,6*R**,7*R**)-Isomer 6h^{III}**

^{1}H NMR (500.13 MHz, $CDCl_3$): δ = 0.90–1.10 (m, 3 H, H11, H12, H14$_{anti}$), 1.45 (m, 1 H, H12), 1.64 (m, 1 H, H11), 1.72 (m, 1 H, H14$_{syn}$), 2.05 (m, 1 H, H13), 2.12 (d, *J* = 9.2 Hz, 2 H, H9), 2.35 (d, *J* = 3.0 Hz, 1 H, H10), 2.45 (m, 1 H, H3), 2.93 (d, *J* = 8.8 Hz, 1 H, H4), 3.57 (s, 3 H, 16-CH_3), 3.60 (t, *J* = 9.2 Hz, 1 H, H8), 3.84 (d, *J* = 6.8 Hz, 1 H, H2), 7.20–7.40 (m, 5 H, H18, H19, H20), 7.52 (br, 1 H, NH).

^{13}C NMR ($CDCl_3$): δ = 23.5 (C11), 27.7 (C12), 31.9 and 32.2 (C9, C14), 39.4 and 40.1 (C10, C13), 46.9 (C8), 50.6 (C3), 52.6 (C16), 54.8 (C4), 81.8 (C2), 97.5 (C5), 127.5 (C20), 128.7 and 129.2 (C18, C19), 136.7 (C17), 169.2 (C15), 173.4 (C7).

Characteristic 2D-NOESY correlations: NH/H4, H2/H3, H18/H3, H13/H4, H4/H14$_{syn}$, H_2C(9)/H8.

(1*R,2*R**,4*R**,4′*R**,5*S**,6*R**,7*R**)-Isomer 6h^{IV}**

^{1}H NMR (500.13 MHz, $CDCl_3$): δ = 0.90–1.10 (m, 3 H, H11, H12, H14$_{anti}$), 1.45 (m, 1 H, H12), 1.64 (m, 1 H, H11), 1.72 (m, 1 H, H14$_{syn}$), 2.05 (m, 1 H, H13), 2.19 (dd, *J* = 13.0, 9.8 Hz, 1 H, H9′), 2.28 (m, 1 H, H9″), 2.35 (d, *J* = 3.7 Hz, 1 H, H10), 2.45 (m, 1 H, H3), 2.55 (dd, *J* = 9.8, 6.2 Hz, 1 H, H8), 2.84 (d, *J* = 9.2 Hz, 1 H, H4), 3.68 (s, 3 H, 16-CH_3), 3.90 (d, *J* = 6.8 Hz, 1 H, H2), 7.20–7.40 (m, 6 H, H18, H19, H20, NH).

^{13}C NMR ($CDCl_3$): δ = 23.5 (C11), 27.7 (C12), 31.9 and 32.2 (C9, C14), 39.4 and 40.1 (C10, C13), 47.5 (C8), 49.5 (C3), 52.6 (C16), 56.1 (C4), 81.7 (C2), 97.1 (C5), 127.6 (C20), 128.7 and 129.2 (C18, C19), 136.5 (C17), 169.2 (C15), 171.5 (C7).

Characteristic 2D-NOESY correlations: NH/H4, H2/H3, H13/H4, H4/H14$_{syn}$, H18/H9′, H8/H9′.

Methyl 2-Ethoxy-4-(4-methoxyphenyl)-7-oxo-1-oxa-6-aza-spiro[4.4]nonane-8-carboxylate (6i) and Dimethyl {[1-(*tert*-Butoxycarbonyl)-3-(4-methoxyphenyl)pyrrolidin-2-yl]methyl}malonate (7)

Oxaazaspirononane **6i** can be obtained as byproduct (20%) using the previously reported procedure for the hydrogenation of **4i**.[6a] The optimized procedure is given below.

To a soln of **4i** (0.3 g, 0.79 mmol) in MeOH (5 mL) was added Boc_2O (0.28 g, 1.28 mmol), Et_3N (0.11 mL, 0.79 mmol), and Raney Ni (c.a. 0.1 g in MeOH, prepared using procedure b). The mixture was hydrogenated at 45 bar H_2 and 80 ° C for 2 h. The resulting soln was filtered and evaporated under reduced pressure. The products were separated by column chromatography (silica gel, EtOAc–hexane, 1:5 to 1:3 to 1:1).

Dimethyl {[1-(*tert*-Butoxycarbonyl)-3-(4-methoxyphenyl)pyrrolidin-2-yl]methylmalonate (7)

Oil; mixture of *trans*- and *cis*-isomers (**7^{I}/7^{II}** 5.7:1); R_f = 0.75 (EtOAc–hexane, 1:1); yield: 0.11 g (33%).

The NMR spectroscopic data are in agreement with the published data for **7**.[6a]

Methyl 2-Ethoxy-4-(4-methoxyphenyl)-7-oxo-1-oxa-6-aza-spiro[4.4]nonane-8-carboxylate (6i)

Anal. Calcd for $C_{18}H_{23}NO_6$: H, 6.64; C, 61.88; N, 4.01. Found: H, 6.81; C, 61.76; N, 3.80.

Mixture of 6i^{I}, 6i^{II}, and 6i^{III}

Oil; ratio **6i^{I}/6i^{II}/6i^{III}** 3.1:1.6:1.0; R_f = 0.29 (EtOAc–hexane, 1:1).

(2*S,4*S**,5*S**,8*R**)-Isomer 6i^{I}**

^{1}H NMR (500.13 MHz, $CDCl_3$): δ = 1.23 (t, *J* = 7.3 Hz, 3 H, 11-CH_3), 2.26–2.48 (m, 2 H, H3), 2.64 (dd, *J* = 8.5, 13.3 Hz, 1 H, H9′), 2.75 (dd, *J* = 9.6, 13.3 Hz, 1 H, H9″), 3.51 and 3.81 (2 m, 2 H, H10), 3.60 (m, 1 H, H4), 3.68 (dd, *J* = 8.5, 9.6 Hz, 1 H, H8), 3.74 (s, 3 H, 13-CH_3), 3.77 (s, 3 H, 18-CH_3), 5.27 (m, 1 H, H2), 6.03 (br, 1 H, NH), 6.84 (d, *J* = 8.1 Hz, 2 H, H16), 7.08 (d, *J* = 8.5 Hz, 2 H, H15).

^{13}C NMR ($CDCl_3$): δ = 15.2 (C11), 38.3 (C9), 38.7 (C3), 47.1 (C8), 49.8 (C4), 52.7 (C13), 55.3 (C18), 63.5 (C10), 97.5 (C5), 101.8 (C2), 114.4 (C16), 129.0 (C15), 130.2 (C14), 159.1 (C17), 169.6 and 171.7 (C7, C12).

Characteristic 2D-NOESY correlations: NH/H15, H2/H15, H4/H9″, H9′/H8.

(2*S,4*S**,5*S**,8*S**)-Isomer 6i^{II}**

^{1}H NMR (500.13 MHz, $CDCl_3$): δ = 1.24 (t, *J* = 7.3 Hz, 3 H, 11-CH_3), 2.26–2.48 (m, 2 H, H3), 2.58 (dd, *J* = 9.7, 13.8 Hz, 1 H, H9″), 2.89 (dd, *J* = 5.8, 13.8 Hz, 1 H, H9′), 3.14 (dd, *J* = 5.8, 9.7 Hz, 1 H, H8), 3.51 and 3.81 (2 m, 2 H, H10), 3.60 (m, 1 H, H4), 3.76 and 3.77 (2 s, 6 H, 13-CH_3, 18-CH_3), 5.27 (m, 1 H, H2), 6.42 (br, 1 H, NH), 6.84 (d, *J* = 8.1 Hz, 2 H, H16), 7.08 (d, *J* = 8.5 Hz, 2 H, H15).

^{13}C NMR ($CDCl_3$): δ = 15.2 (C11), 38.0 (C9), 38.7 (C3), 47.5 (C8), 50.7 (C4), 52.7 (C13), 55.3 (C18), 63.4 (C10), 97.6 (C5), 101.6 (C2), 114.4 (C16), 129.2 (C15), 130.2 (C14), 159.1 (C17), 169.6 and 170.9 (C7, C12).

Characteristic 2D-NOESY correlations: NH/H15, H2/H15, H4/H9″, H9″/H8.

Mixture of 6i^{III} and 6i^{IV}

Ratio **6i ^{III}/6i^{IV}** 1.3:1.0; mp 135–141 °C; R_f = 0.33 (EtOAc–hexane, 1:1).

(2*S,4*S**,5*R**,8*S**)-Isomer 6i^{III}**

^{1}H NMR (500.13 MHz, $CDCl_3$): δ = 1.20 (t, *J* = 7.3 Hz, 3 H, 11-CH_3), 1.97 (dd, *J* = 8.7, 13.8 Hz, 1 H, H9″), 2.13 (dd, *J* = 8.8, 13.8 Hz, 1 H, H9′), 2.40 (m, 2 H, H3), 3.49 and 3.80 (2 m, 2 H, H10), 3.58 (m, 2 H, H8, H4), 3.67 (s, 3 H, 13-CH_3), 3.78 (s, 3 H, 18-CH_3), 5.33 (dd, *J* = 2.3, 4.7 Hz, 1 H, H2), 6.61 (br, 1 H, NH), 6.85 (d, *J* = 8.1 Hz, 2 H, H16), 7.05 (d, *J* = 8.5 Hz, 2 H, H15).

^{13}C NMR ($CDCl_3$): δ = 15.2 (C11), 34.7 (C9), 40.4 (C3), 47.1 and 50.8 (C4, C8), 52.7 (C13), 55.2 (C18), 63.6 (C10), 98.6 (C5), 103.3 (C2), 114.1 (C16), 129.1 (C15), 131.7 (C14), 158.9 (C17), 169.7 and 171.8 (C7, C12).

Characteristic 2D-NOESY correlations: NH/H4, H2/H15, H15/H9′, H9″/H8.

(2*S,4*S**,5*R**,8*R**)-Isomer 6i^{IV}**

^{1}H NMR (500.13 MHz, $CDCl_3$): δ = 1.21 (t, *J* = 7.3 Hz, 3 H, 11-CH_3), 2.12 (dd, *J* = 9.4, 13.9 Hz, 1 H, H9′), 2.31 (dd, *J* = 7.0, 13.9 Hz, 1 H, H9″), 2.40 (m, 2 H, H3), 2.85 (dd, *J* = 7.0, 9.4 Hz, 1 H, H8), 3.49 and 3.80 (2 m, 2 H, H10), 3.58 (m, 1 H, H4), 3.71 (s, 3 H, 13-CH_3), 3.78 (s, 3 H, 18-CH_3), 5.26 (d, *J* = 6.4 Hz, 1 H, H2), 6.61 (br, 1 H, NH), 6.85 (d, *J* = 8.1 Hz, 2 H, H16), 7.08 (d, *J* = 8.5 Hz, 2 H, H15).

^{13}C NMR ($CDCl_3$): δ = 15.2 (C11), 34.2 (C9), 38.7 (C3), 47.0 (C4), 51.1 (C8), 52.7 (C13), 55.2 (C18), 63.5 (C10), 98.3 (C5), 102.4 (C2), 114.3 (C16), 128.8 (C15), 130.0 (C14), 159.1 (C17), 169.3 and 171.0 (C7, C12).

Characteristic 2D-NOESY correlations: NH/H4, H2/H15, H15/H9′, H9′/H8.

Dimethyl {[3-(4-Methoxyphenyl)-5-methyl-1*H*-pyrrol-2-yl]methyl}malonate (8)

Product **8** can be obtained using the procedure for hydrogenation of **4a–h** in 78% yield. Best result was obtained using the procedure given below.

To a soln of **4j** (0.3 g, 0.79 mmol) in MeOH (15 mL) was added Pd/C (5% Pd, 0.05 g) and the mixture was hydrogenated at 110 bar H_2 and 100 ° for 4 h and at 100 bar H_2 and r.t. for 18 h. The resulting soln was filtered and evaporated under reduced pressure. The crude product was purified by column chromatography (silica gel) to give an oil that was unstable (oxidized in air); yield: 0.26 g (99%); R_f = 0.59 (EtOAc–hexane, 1:1).

^{1}H NMR (300.13 MHz, $CDCl_3$): δ = 2.24 (s, 3 H, 5-CH_3), 3.25 (d, *J* = 6.6 Hz, 2 H, H6), 3.68 (t, *J* = 6.6 Hz, 1 H, H7), 3.74 (s, 6 H, 9-CH_3), 3.83 (s, 3 H, 14-CH_3), 5.90 (d, *J* = 2.2 Hz, 1 H, H3), 6.92 (d, *J* = 8.8 Hz, 2 H, H12), 7.26 (d, *J* = 8.8 Hz, 2 H, H11), 8.35 (br, 1 H, NH).

^{13}C NMR ($CDCl_3$): δ = 12.9 (C5), 25.3 (C6), 36.8 (C7), 52.7 (C9), 55.3 (C14), 106.6 (C3), 113.9 (C12), 121.9, 122.6, and 126.8 (C1, C2, C4), 128.9 (C11), 129.4 (C10), 157.7 (C13), 170.0 (C8).

Dimethyl (5-Hydroxy-2-(hydroxyimino)-5-methyl-3-phenylhexyl)malonate (11)

t-BuOK (0.13 g, 1.2 mmol) was added to a stirred soln of dimethyl malonate (0.16 g, 1.2 mmol) in DMF (1 mL) at 0 °C. After 5 min, a soln of 1-bromo-5-hydroxy-5-methyl-3-phenylhexan-2-one oxime[6b] (0.30 g, 1.0 mmol) in DMF (1.5 mL) was carefully added. The resulting mixture was stirred at 60 °C for 2 h and poured into a mixture of EtOAc (100 mL) and H_2O (100 mL). The aqueous phase was back-extracted with EtOAc (2 × 50 mL) and the combined organic layers were washed with brine (50 mL) and dried (Na_2SO_4). The solvent was evaporated in vacuo and the residue was subjected to column chromatography (silica gel) to give the corresponding oxime as one isomer; yield: 0.28 g (78%); mp 95–103 °C; R_f = 0.23 (EtOAc–hexane, 1:1).

^{1}H NMR (300.13 MHz, $CDCl_3$): δ = 1.23 (s, 6 H, 11-CH_3, 12-CH_3), 1.76 (dd, *J* = 3.5, 15.8 Hz, 1 H, H3), 2.20 (m, 1 H, H3), 2.39 (m, 3 H, H5, OH), 3.66 and 3.74 (2 s, 6 H, 9-CH_3, 10-CH_3), 3.87 (dd, *J* = 3.5, 10.5 Hz, 1 H, H2), 4.06 (m, 1 H, H6), 7.20–7.35 (m, 5 H, H14, H15, H16), 10.35 (br, 1 H, NOH).

^{13}C NMR ($CDCl_3$): δ = 28.2 and 29.0 (C11, C12), 30.5 (C5), 45.0 (C2), 47.9 (C3), 48.7 (C6), 52.6 (C9, C10), 70.3 (C4), 127.1, 128.2, and 128.9 (C14, C15, C16), 142.1 (C13), 159.5 (C1), 169.5 (C9, C10).

Anal Calcd for $C_{18}H_{25}NO_6$: H, 7.17; C, 61.52; N, 3.99. Found: H, 7.10; C, 61.36; N, 4.05.

Methyl 5-[(1*R*/*S*)-3-Hydroxy-3-methyl-1-phenylbutyl]-2-oxopyrrolidine-3-carboxylate (9)

To a soln of oxazine **4b** (0.1 g, 0.3 mmol) in MeOH (2.0 mL) was added 4 M HCl in 1,4-dioxane (0.076 mL, 0.3 mmol) and Raney Ni (c.a. 0.05 g in MeOH, prepared using procedure b). The suspension was hydrogenated at 50 bar H_2 and 70–80 °C with intensive stirring for 2 h and then filtered and concentrated in vacuo. The residue was purified by flesh chromatography (silica gel, EtOAc then MeOH). The EtOAc fraction contained **6b** [yield: 0.015 g (17%)], the MeOH fraction contained **9** [yield: 0.05 g (55%)]; oil; mixture of isomers, ratio **9^{I}/9^{II}/9^{III}/9^{IV}** 1.3:1.5:1.3:1.0. Isomers **9^{I}/9^{II}** and **9^{III}/9^{IV}**, respectively, cannot be unambiguously assigned by NMR.

Anal. Calcd for $C_{17}H_{23}NO_4$: H, 7.59; C, 66.86; N, 4.59. Found: H, 7.68; C, 66.02; N, 4.83.

Isomer 9^{I} (1′*R,3*R**,5*S**) or (1′*S**,3*R**,5*S**)**

^{1}H NMR (300.13 MHz, $CDCl_3$): 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), 3.22 (dd, *J* = 9.5, 4.2 Hz, 1 H, H8), 3.92 (ddd, *J* = 9.2, 7.0, 7.0 Hz, 1 H, H3), 5.05 (br, 1 H, 1-OH), 7.15–7.31 (m, 5 H, H15, H16, H17).

^{13}C NMR (62.5 MHz, $CDCl_3$): δ (selected signals) = 30.6 (C7), 47.7 (C4), 48.4 (C8), 59.5 (C3), 70.6 (C8).

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

Isomer 9^{II} (1′*R,3*R**,5*S**) or (1′*S**,3*R**,5*S**)**

^{1}H NMR (300.13 MHz, $CDCl_3$): δ (selected signals) = 1.97 (m, 2 H, H5), 2.05 (m, 1 H, H7′), 2.59 (ddd, *J* = 5.9, 6.6, 13.2 Hz, 1 H, H7″), 2.82 (m, 1 H, H8), 2.89 (m, 1 H, H4), 4.11 (m, 1 H, H3), 5.05 (br, 1 H, 1-OH), 7.15–7.31 (m, 5 H, H15, H16, H17).

^{13}C NMR (62.5 MHz, $CDCl_3$): δ (selected signals) = 29.5 (C7), 47.2 (C4), 47.6 (C8), 57.5 (C3).

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

Isomer 9^{III} (1′*R,3*S**,5*S**) or (1′*S**,3*S**,5*S**)**

^{1}H NMR (300.13 MHz, $CDCl_3$): δ (selected signals) = 1.80 (m, 1 H, H7″), 1.89 (m, 1 H, H5), 1.95 (m, 1 H, H7′), 2.05 (m, 1 H, H5), 2.90 (ddd, *J* = 9.5, 5.9, 5.2 Hz, 1 H, H4), 3.35 (dd, *J* = 10.3, 9.1 Hz, 1 H, H8), 3.70 (m, 1 H, H3), 5.05 (br, 1 H, 1-OH), 7.15–7.31 (m, 5 H, H15, H16, H17).

^{13}C NMR (62.5 MHz, $CDCl_3$): δ (selected signals) = 31.4 (C7), 47.8 (C4), 48.8 (C8), 59.0 (C3), 70.6 (C6), 126.9 (C17).

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

Isomer 9^{IV} (1′*R,3*S**,5*S**) or (1′*S**,3*S**,5*S**)**

^{1}H NMR (300.13 MHz, $CDCl_3$): δ (selected signals) = 1.93 (m, 2 H, H5), 2.31 (ddd, *J* = 8.1, 9.5, 12.7 Hz, 1 H, H7′), 2.44 (ddd, *J* = 7.3, 8.8, 12.7 Hz, 1 H, H7″), 2.96 (ddd, *J* = 2.2, 8.1, 11.4 Hz, 1 H, H4), 3.44 (dd, *J* = 9.5, 8.8 Hz, 1 H, H8), 3.76 (m, 1 H, H3), 5.05 (br, 1 H, 1-OH), 7.15–7.31 (m, 5 H, H15, H16, H17).

^{13}C NMR (62.5 MHz, $CDCl_3$): δ (selected signals) = 29.2 (C7), 47.2 (C4), 48.2 (C8), 58.0 (C3).

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

Unassigned signals of 4 isomers:

^{1}H NMR (300.13 MHz, $CDCl_3$): δ = 1.04, 1.06, 1.08, 1.09, 1.12, 1.15, 1.19 (7 s, 12 H, 12-CH_3, 13-CH_3), 3.68, 3.72, and 3.76 (3 s, 3 H, 11-CH_3), 6.10, 6.83, 8.41, and 8.61 (4 br, 1 H, 2-NH).

^{13}C NMR (62.5 MHz, $CDCl_3$): δ = 27.8, 27.9, 28.5, 29.6, 30.8, 31.5, 31.8, and 31.9 (C12, C13), 43.8, 44.5, 48.0, and 48.6 (C5), 52.5, 52.6, and 52.7 (C11), 70.6 and 70.8 (C6), 126.7, 127.2, 128.0, 128.2, 128.3, 128.7, 128.9, and 129.0 (C15, C16, C17), 141.3, 142.0, 142.7, and 143.0 (C14), 170.4, 170.5, 173.1, 173.3, and 173.4 (C9, C10).

4-(4-Methoxyphenyl)-2,2-dimethyl-1-oxa-6-aza-spiro[4.4]nonan-7-one (12c)

To a stirred soln of **6c** (mixture of isomers **6c^{I}/6c^{II}/6c^{III}/6c^{IV}** 1.0:1.0:2.3:2.1, 0.29 g, 0.87 mmol) in 1,4-dioxane–H_2O (1:1, 2 mL) was added Dowex 50WX2-100 (0.29 g), the mixture was refluxed for 12 h and then the solvent was evaporated. The residue was dissolved in toluene (5 mL) and TsOH·H_2O (0.02 g, 0.1 mmol) was added. The resulting mixture was refluxed for 5 h, then concentrated in vacuum and the residue was subjected to column chromatography (silica gel, hexane–EtOAc, 5:1 to 1:1 to 0:1) to give **12c** 0.19 g (79% from **6c**) as a white solid.

Mixture of 12c^{I} and 12c^{II}

Ratio **12c^{I}/12c^{II}** 1.0:2.5; mp 202–208 °C R_f = 0.11 (EtOAc–hexane, 1:1).

(4*S,5*S**)-Isomer 12c^{I}**

^{1}H NMR (500.13 MHz, $CDCl_3$): δ = 1.31 (s, 3 H, 10-CH_3), 1.38 (s, 3 H, 11-CH_3), 1.63 (ddd, *J* = 17.6, 9.8, 5.5 Hz, 1 H, H8), 1.80 (m, 2 H, H9), 2.09 (dd, *J* = 12.8, 7.1 Hz, 1 H, H3′), 2.25 (m, 1 H, H3″), 2.31 (m, 1 H, H8), 3.55 (dd, *J* = 13.4, 7.1 Hz, 1 H, H4), 3.77 (s, 3 H, 16-CH_3), 6.84 (d, *J* = 8.4 Hz, 2 H, H14), 7.14 (d, *J* = 8.4 Hz, 2 H, H13), 7.95 (br, 1 H, NH).

^{13}C NMR ($CDCl_3$): δ = 29.0 (C10), 29.8 (C8), 29.9 (C11), 31.0 (C9), 41.8 (C3), 50.8 (C4), 55.2 (C16), 78.3 (C2), 99.1 (C5), 114.0 (C14), 128.1 (C12), 128.2 (C13), 158.9 (C15), 177.5 (C7).

Characteristic 2D-NOESY correlations: NH/H13, H4/10-CH_3, H13/H3″, H4/H3′.

(4*R,5*S**)-Isomer 12c^{II}**

^{1}H NMR (500.13 MHz, $CDCl_3$): δ = 1.28 (s, 3 H, 10-CH_3), 1.37 (s, 3 H, 11-CH_3), 1.89 (ddd, *J* = 17.3, 9.8, 4.9 Hz, 1 H, H8), 2.06 (dd, *J* = 12.4, 7.1 Hz, 1 H, H3′), 2.21 (m, 2 H, H9), 2.31 (m, 1 H, H3″), 2.39 (ddd, *J* = 17.3, 9.8, 7.5 Hz, 1 H, H8), 3.35 (dd, *J* = 13.7, 7.1 Hz, 1 H, H4), 3.76 (s, 3 H, 16-CH_3), 6.81 (d, *J* = 8.5 Hz, 2 H, H14), 7.18 (d, *J* = 8.5 Hz, 2 H, H13), 8.00 (br, 1 H, NH).

^{13}C NMR ($CDCl_3$): δ = 29.0 (C10), 29.8 (C8), 29.9 (C11), 31.8 (C9), 43.2 (C3), 52.6 (C4), 55.2 (C16), 79.4 (C2), 99.1 (C5), 114.0 (C14), 128.1 (C12), 129.8 (C13), 158.9 (C15), 177.7 (C7).

Characteristic 2D-NOESY correlations: H4/10-CH_3, H13/H3″, H4/H3′.

Anal. Calcd for $C_{16}H_{21}NO_3$: H, 7.69; C, 69.79; N, 5.09. Found: H, 7.73; C, 69.71; N, 4.98.

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References

(1) (a) Angermann, J.; Homann, K.; Reissig, H.-U.; Zimmer, R. *Synlett* **1995**, 1014. (b) Buchholz, M.; Reissig, H.-U. *Eur. J. Org. Chem.* **2003**, 3524. (c) Gallos, J. K.; Sarli, V. C.; Stathakis, C. I.; Koftis, T. V.; Nachmia, V. R.; Coutouli-Argyropoulou, E. *Tetrahedron* **2002**, *58*, 9351.

(2) (a) Gallos, J. K.; Sarli, V. C.; Varvogli, A. C.; Papadoyanni, C. Z.; Papaspyrou, S. D.; Argyropoulos, N. G. *Tetrahedron Lett.* **2003**, *44*, 3905. (b) Gallos, J. K.; Sarli, V. C.; Massen, Z. S.; Varvogli, A. C.; Papadoyanni, C. Z.; Papaspyrou, S. D.; Argyropoulos, N. G. *Tetrahedron* **2005**, *61*, 565.

(3) (a) Best, W. M.; MacDonald, J. M.; Skelton, B. W.; Stick, R. V.; Tilbrook, M. G.; White, A. H. *Can. J. Chem.* **2002**, *80*, 857. (b) Humphrey, A. J.; Parsons, S. F.; Smith, M. E. B.; Turner, N. J. *Tetrahedron Lett.* **2000**, *41*, 4481. (c) Joubert, M.; Defoin, A.; Tarnus, C.; Streith, J. *Synlett* **2000**, 1366.

(4) Tsoungas, P. G. *Heterocycles* **2002**, *57*, 915.

(5) (a) Lyapkalo, I. M.; Ioffe, S. L. *Russ. Chem. Rev.* **1998**, *67*, 467. (b) Francotte, E.; Merenyi, R.; Vandenbulcke-Coyette, B.; Vieche, H.-G. *Helv. Chim. Acta* **1981**, *64*, 1208.

(6) (a) Sukhorukov, A. Yu.; Klenov, M. S.; Ivashkin, P. E.; Lesiv, A. V.; Khomutova, Yu. A.; Ioffe, S. L. *Synthesis* **2007**, 97. (b) Klenov, M. S.; Lesiv, A. V.; Khomutova, Yu. A.; Nesterov, I. D.; Ioffe, S. L. *Synthesis* **2004**, 1159. (c) Eliseev, O. L.; Ivashkin, P. E.; Ostapenko, A. G.; Lesiv, A. V.; Khomutova, Yu. A.; Ioffe, S. L.; Lapidus, A. L. *Synlett* **2006**, 2239.

(7) Sukhorukov, A. Yu.; Lesiv, A. V.; Eliseev, O. L.; Khomutova, Yu. A.; Bondarenko, T. N.; Lapidus, A. L.; Ioffe, S. L. *Mendeleev Commun.* **2007**, 122.

(8) Hydrogenolysis of oxazine **4b** with Pd/C (70 bar H_2, MeOH, 80 °C, 2 h) resulted in low conversion of starting material (40%) and the formation of two major products: oxaazaspirononanone **6b** (yield: 20%) and lactam **9** (Scheme 11, yield: 17%). When the reaction is performed under more robust conditions [H_2 (150 bar), MeOH, 100 °C, 6 h] in addition to products **6b** and **9** the corresponding dihydrofuran **5b** was obtained in 11% yield [Scheme 2, R^1 = Ph, R^2 = H, R^3 = R^4 = Me, FG = $CH(CO_2Me)_2$].

(9) When the hydrogenation is carried out in the presence of undried Raney nickel the yields of target spirononanones decrease by 10–25% for the whole series of oxazines **4a**–**h**.

(10) (a) Curran, D. P.; Brill, J. F.; Rakiewicz, D. M. *J. Org. Chem.* **1984**, *49*, 1654. (b) Rylander, P. N. *Catalytic Hydrogenation in Organic Synthesis*; Academic Press: New York, **1979**, 153. (c) Nishimura, S. *Handbook of Heterogeneous Catalytic Hydrogenation for Organic Synthesis*; Wiley: New York, **2001**, 290–291.

(11) (a) Hippeli, C.; Zimmer, R.; Reissig, H.-U. *Liebigs Ann. Chem.* **1990**, 469. (b) Nakanishi, S.; Otsuji, Y.; Itoh, K.; Hayashi, N. *Bull. Chem. Soc. Jpn.* **1990**, *63*, 3595. (c) Nakanishi, S.; Shirai, Y.; Takahashi, K.; Otsuji, Y. *Chem. Lett.* **1981**, 869. (d) Amarnath, V.; Anthony, D. C.; Amarnath, K.; Valenyine, W. M.; Watterau, L. A.; Graham, D. G. *J. Org. Chem.* **1991**, *56*, 6924; and references cited therein.

(12) (a) Chrystal, E. J. T.; Gilchrist, T. L.; Stretch, W. *J. Chem. Res., Synop.* **1987**, 180. (b) Henning, R.; Lerch, U.; Urbah, H. *Synthesis* **1989**, 265. (c) Hippeli, C.; Reissig, H.-U. *Liebigs Ann. Chem.* **1990**, 475. (d) Tishkov, A. A.; Reissig, H.-U.; Ioffe, S. L. *Synlett* **2002**, 863.

(13) (a) Chlenov, I. E.; Salamonov, Yu. V.; Tartakovsky, V. A. *Bull. Acad. Sci. USSR, Div. Chem. Sci. (Engl. Transl.)* **1976**, *25*, 1788. (b) Harada, K.; Kaji, E.; Takahashi, K.; Zen, S. *Chem. Pharm. Bull.* **1994**, 1562.

(14) For hydrolysis of imines see: (a) Pickard, P. L.; Vaughan, D. J. *J. Am. Chem. Soc.* **1950**, *72*, 5017. For hydrolysis of oximes see: (b) Buhler, D. R.; Schroeter, L. C.; Wechter, W. J. *J. Med. Chem.* **1965**, *8*, 215. For reductive hydrolysis of oximes see: (c) Monti, D.; Gramatica, P.; Speranza, G.; Tagliapietra, S.; Manitto, A. *Synth. Commun.* **1986**, *16*, 803. (d) Timms, G. H.; Wildsmith, E. *Tetrahedron Lett.* **1971**, *12*, 195. For reductive hydrolysis of 5,6-dihydro-4*H*-1,2-oxazines see: (e) Zimmer, R.; Collas, M.; Roth, M.; Reissig, H.-U. *Liebigs Ann. Chem.* **1992**, 709.

(15) Meyers, A. I.; Fray, A. H. *Bull. Soc. Chim. Fr.* **1997**, *134*, 283.

(16) Kende, A. S.; Hernando, I. J.; Milbank, J. B. *Tetrahedron* **2002**, *57*, 61.

(17) Koseki, Y.; Sato, H.; Watanabe, Y.; Nagasaka, T. *Org. Lett.* **2002**, *4*, 885.

(18) Martin, A.; Perez-Martin, I.; Suarez, E. *Org. Lett.* **2005**, *7*, 2027.

(19) CCDC 642140 contains the supplementary crystallographic data for **6b**^{III}. These data can be obtained free of charge via http://www.ccdc.cam.ac.uk, by e-mailing or faxing a request to deposit@ccdc.cam.ac.uk or +44(1223)336033, respectively, or by writing to the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK.

(20) Treatment of the mixture of oxaazaspirononanones **6c**^{III} and **6c**^{IV} (1:1) with some bases (Et_3N, *t*-BuOK in THF at r.t.) does not influence the ratio of isomers.

(21) Gottlieb, H. E.; Kotlyar, V.; Nudelman, A. *J. Org. Chem.* **1997**, *62*, 7512.