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Catalytic Hydrogenation of 5,6-Dihydro-4*H*-1,2-oxazines Bearing a Functionalized Methylene Group at C-3

Alexey Yu. Sukhorukov,[a] Alexey V. Lesiv,[a] Oleg L. Eliseev,[a] Yulia A. Khomutova,[a] Sema L. Ioffe,*[a] and Alexandra O. Borissova[b]

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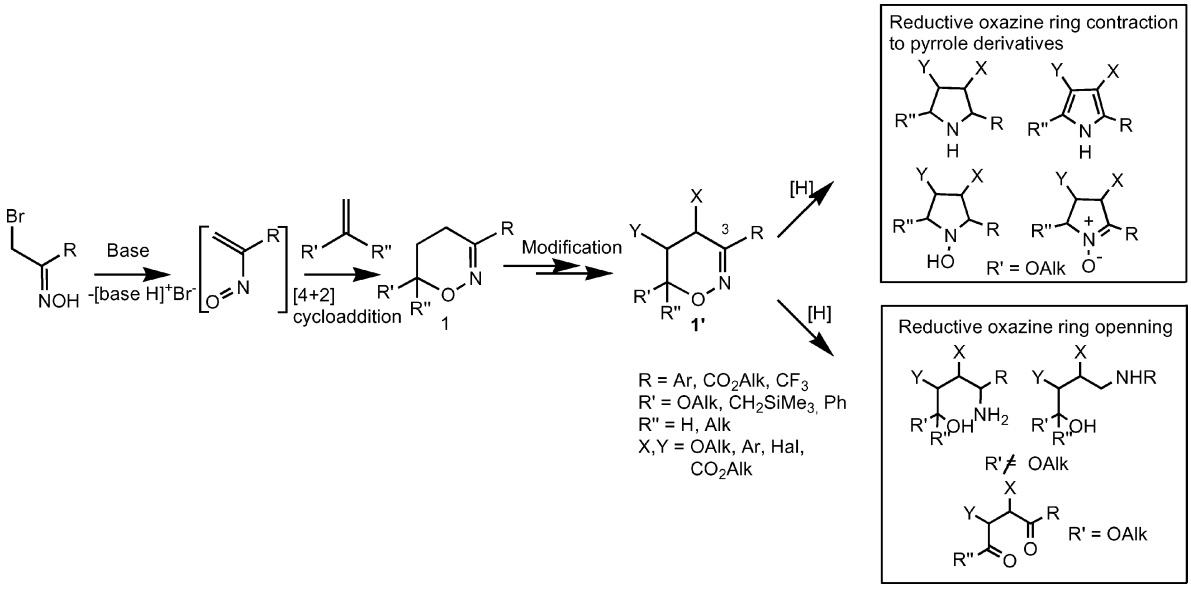
The catalytic hydrogenation of readily available methyl 2-(5,6-dihydro-4*H*-1,2-oxazin-3-yl)acetates **6** has been studied. Dihydrooxazines **6** without an alkoxy substituent at C-6 under mild hydrogenation conditions in methanol produce a dynamic mixture of enamines **7** and tetrahydro-2-furanamines **7′**(α+β). These products can be transformed into 1,4-amino alcohols **8** under more robust hydrogenation conditions or into isomeric dihydrofurans **9** and **10** if the reduction is carried out in glacial acetic acid. Reduction of dihydrooxazines **6h**,**i**, which possess an alkoxy substituent at C-6, under similar conditions affords pyrrolidine derivatives **12**, **13** and **14**. A general mechanistic scheme for the hydrogenation reaction that involves an initial N–O bond cleavage has been suggested.

Introduction

Six-membered cyclic oxime ethers, 5,6-dihydro-4*H*-1,2-oxazines **1** or **1′** (Scheme 1), have found numerous applications in the total synthesis of natural and biologically active nitrogen-containing compounds, for example, alkaloids,[1] unnatural amino acids[2] and amino sugars.[3]



Scheme 1. 5,6-Dihydro-4*H*-1,2-oxazines in organic synthesis.

[a] N. D. Zelinsky Institute of Organic Chemistry, Russian Academy of Sciences,
Leninsky prosp. 47, 119991 Moscow, Russian Federation
Fax: +7-495-1355328
E-mail: iof@ioc.ac.ru
[b] A. N. Nesmeyanov Institute of Organoelement Compounds, Vavilov Str. 28, 119991 Moscow, Russian Federation
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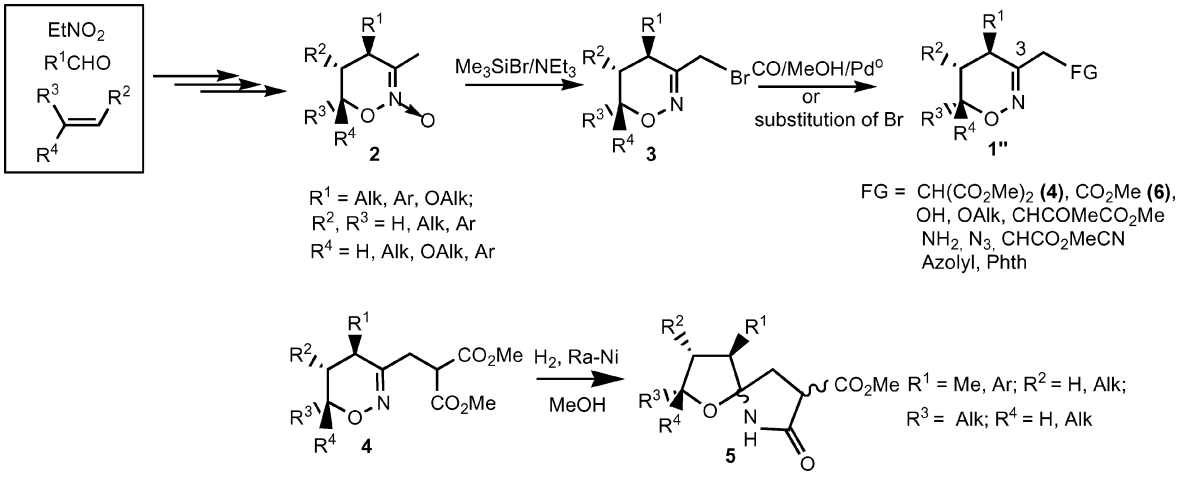
In these syntheses, the reduction of the oximino fragment is the key to the transformation of oxazines **1** and **1′** into a wide range of heterocyclic and acyclic products. Thus, depending on the structures of oxazines **1** and **1′** and the reaction conditions, the reduction can lead to substituted[4a–4d] and fused[5] pyrrolidines, pyrroles,[4e–4g] five-membered cyclic nitrones,[4b] δ-amino alcohols[2,6] and diketones[7]



Scheme 2. Synthesis and hydrogenation of 5,6-dihydro-4*H*-1,2-oxazines with a functionalized methylene group at C-3.

(Scheme 1). The major disadvantage of this strategy is the limited accessibility of oxazines **1** and **1′**. Until recently, the only route to their synthesis was the [4+2] cycloaddition of highly unstable α-nitroso olefins to electron-rich alkenes[8] (Scheme 1). In particular, this strategy seems ineffective for the preparation of oxazines bearing functionalized alkyl substituents at the C-3 atom. However, just recently, a quite original approach to the synthesis of oxazines **1** from available nitroethane was suggested[9] (Scheme 2).

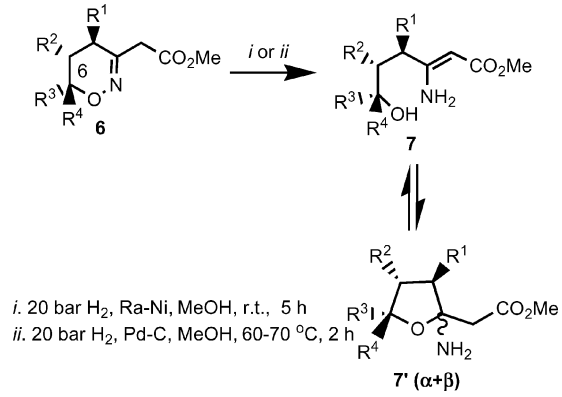
This approach seems to be the most attractive for the preparation of dihydrooxazines **1′′** bearing a CH_2FG (FG = functional group) substituent at the C-3 carbon atom. Oxazines **1′′** with FG = CO_2Me and $CH(CO_2Me)_2$ are currently of particular interest because the functional group can be involved in the reduction process, giving new types of polyfunctionalized products. Accordingly we recently reported[10] the synthesis of substituted oxaazaspirononanones **5** by the catalytic hydrogenation of dihydrooxazines **4** with FG = $CH(CO_2Me)_2$ (Scheme 2).

In this work we have studied the catalytic hydrogenation of 2-(5,6-dihydro-4*H*-1,2-oxazin-3-yl)acetates **6** (FG = CO_2Me).[11]

Results and Discussion

Catalytic Hydrogenation of Dihydrooxazines 6

It was discovered (Scheme 3, Table 1) that mild catalytic hydrogenation of dihydrooxazines **6a**–**g**, which do not contain an alkoxy substituent at C-6, in the presence of Raney nickel (20 bar H_2, MeOH, room temp., 5 h) or Pd-C (20 bar H_2, MeOH, 60–70 °C, 2 h) furnishes a dynamic mixture of enamines **7** and tetrahydro-2-aminofurans **7′**(α + β) (hereinafter these mixtures are referred as enamines **7** for brevity). It is evident that these products arise from the selective hydrogenolysis of the N–O bond in oxazines **6** and a subsequent 1,3-proton shift of the activated proton from the CH_2CO_2Me fragment (the mechanism of the catalytic hydrogenation will be discussed below, see Scheme 8). Enamines **7** were isolated from the reaction mixtures in analytically pure form by column chromatography on silica gel. The flexible equilibrium between compounds **7** and **7′** was confirmed by the solvent dependence of the ratio **7**/**7′** (see below).[12]



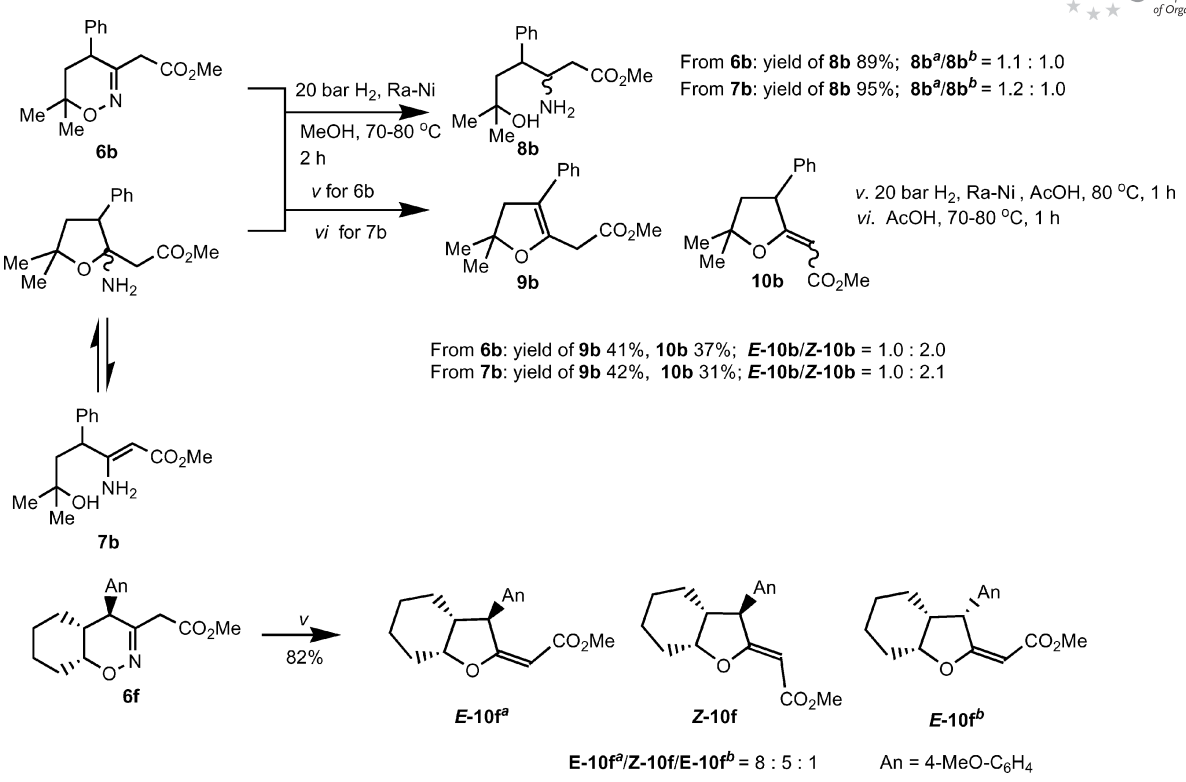
Scheme 3. Hydrogenation of dihydrooxazines **6** to enamines **7**.

Table 1. Preparation of enamines **7** from dihydrooxazines **6a**–**g**.

Entry	**6**	R^1	R^2	R^3	R^4	Yield of **7**+**7′** [%] *i*	*ii*
1	**a**	Me	H	Me	Me	62	75
2	**b**	Ph	H	Me	Me	70[a]	70
3	**c**	4-MeO-C_6H_4	H	Me	Me	59	81
4	**d**	4-Cl-C_6H_4	H	Me	Me	84	–[b]
5	**e**	4-MeO-C_6H_4	H	H	*n*Pr	77	94
6	**f**	4-MeO-C_6H_4	–$(CH_2)_4$–		H	85	54
7	**g**	Ph	–$(CH_2)_3$–		H	84	86

[a] In the hydrogenation at 40 bar H_2, the total yield of **8b** = 25% (**8b**^{a}/**8b**^{b} = 1.1:1.0). [b] For more details, see Scheme 5.

The conditions for the transformation **6**→**7**, optimized for model oxazine **6b**, are presented in Scheme 3 (procedures *i* and *ii*). The hydrogenation of **6b** in the presence of Raney nickel at a lower hydrogen pressure (e.g. 10 bar) resulted in incomplete conversion of the starting material. An increase of the hydrogen pressure up to 40 bar resulted



Scheme 4. Comparison of the catalytic hydrogenation of oxazines **6b** and **6f** with the hydrogenation of enamine **7b**.

in a lowering of the yield of the mixture **7b**⇆**7′b** to 65% owing to the formation of products from exhaustive hydrogenation, i.e. diastereomeric amino alcohols **8b**^{a} and **8b**^{b} (see entry 2 in Table 1 and Scheme 4).

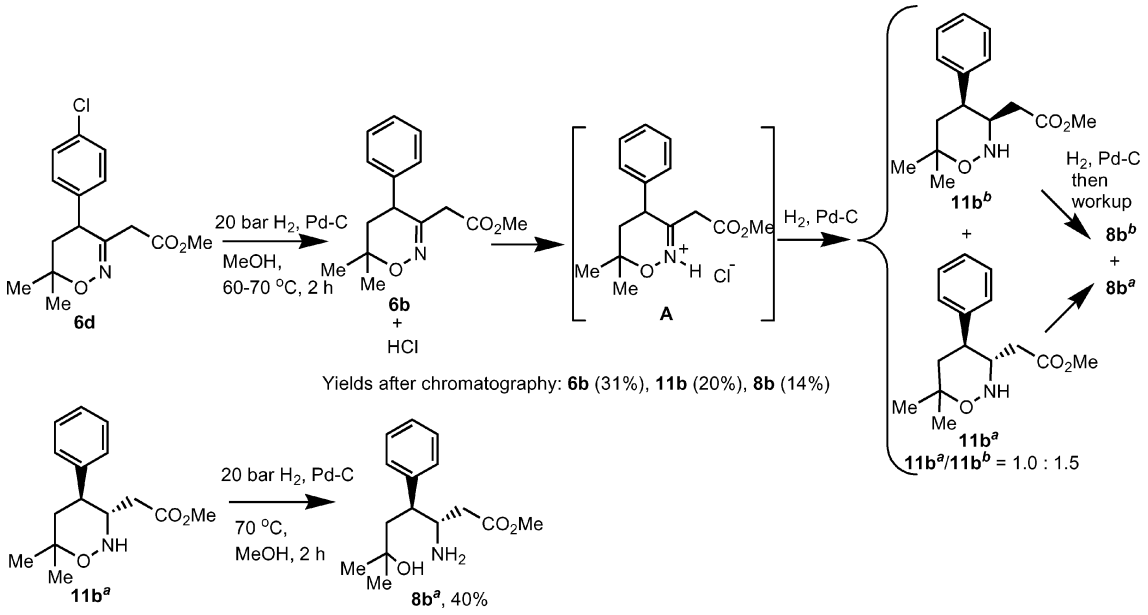
When the temperature used during hydrogenation was increased (20 bar H_2, 70–80 °C, 2 h) only amino alcohols **8b** were obtained (yield 89%). The catalytic hydrogenation of the corresponding enamine **7b** under identical reaction conditions afforded amino alcohol **8b** in a similar isomeric ratio.

At the same time, hydrogenations of **6b** carried out in glacial acetic acid furnished only a mixture of isomeric furans **9b** and **10b** (*E*/*Z* = 1:2, see also ref.[11]). Moreover, heating enamine **7b** in AcOH (70–80 °C, 1 h) led to a similar result (see Scheme 4).

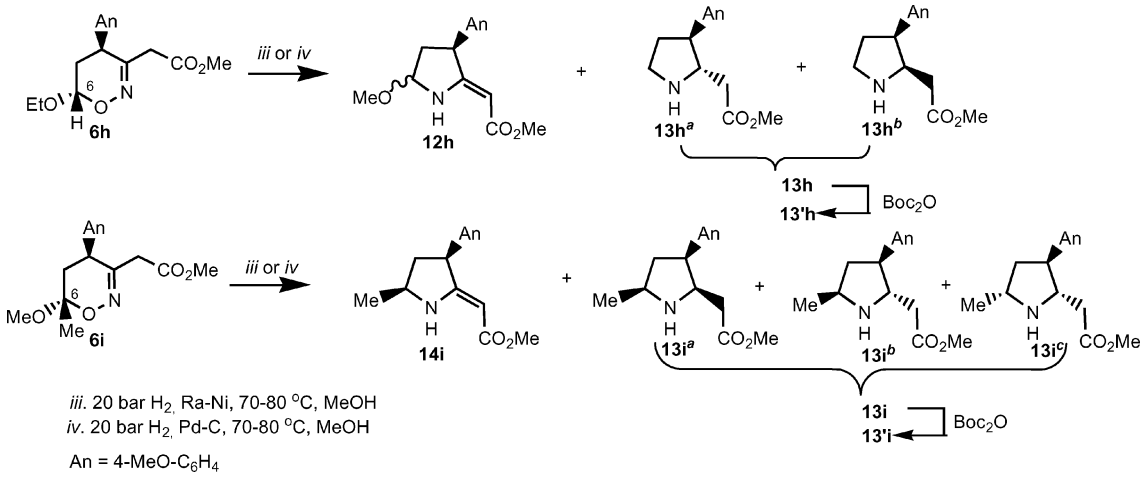
The reduction of bicyclic oxazine **6f** under similar conditions afforded only one regioisomer, tetrahydrofuran **10f** (yield: 82%), as a mixture of three isomers (*E*-**10f**^{a}/*Z*-**10f**/*E*-**10f**^{b} = 8:5:1). Isomers *E*-**10f**^{a} and Z-**10f** have a different configuration of the C=C double bond, whereas the minor isomer *E*-**10f**^{b} differs from *E*-**10f**^{a} in the relative configuration of the stereocentre at C-3. Dihydrofuran **9f** (similar to **9b**) was not generated in the hydrogenation of dihydrooxazine **6f**. However, the production of furan *E*-**10f**^{b} with an inverse configuration of the stereocentre at C-3 indicates the intermediacy of **9f** in the hydrogenation of dihydrooxazine **6f**.

In the hydrogenation of dihydrooxazine **6b**, Pd-C proved to be less active than Raney nickel. When the hydrogenation with Pd-C was carried out at room temp. (20 bar H_2, MeOH, 5 h), no conversion of **6b** was observed, although if the reduction of derivatives **6** was performed at 60–70 °C (procedure *ii* in Table 1) the yields of the respective mixtures **7**⇆**7′** were in most cases similar to those obtained by procedure *i*. However, hydrogenolysis of dihydrooxazine **6d** in the presence of Pd-C proceeds in a more complicated manner (Scheme 5). The resulting reaction mixture is strongly acidic. After aqueous work-up and column chromatography on silica gel, five products were identified: **6b** (31%), diastereomers **11b**^{a} and **11b**^{b} (yield: 20%, **11b**^{a}/**11b**^{b} = 1.0:1.5) and amino alcohols **8b**^{a} and **8b**^{b} (yield 14%, **8b**^{a}/**8b**^{b} = 1.0:1.3). None of these products possess a chlorine atom on the aromatic ring. Tetrahydrooxazine **11b**^{a} itself can be hydrogenated to give diastereomerically pure amino alcohol **8b**^{a} (20 bar H_2, MeOH, 70 °C, 2 h, conversion of **11b**^{a} 43%, yield of **8b**^{a} 40%).[13] We believe that in the hydrogenolysis of **6d** under these conditions the reductive dehalogenation takes place with the initial formation of dihydrooxazine **6b** and hydrogen chloride (Scheme 5). Subsequent protonation of the nitrogen atom in **6b** by HCl furnishes cation **A**.[14] Hydrogenation of intermediate **A** leads to the products depicted in Scheme 5.

The presence or absence of the alkoxy group at C-6 can be considered as the major factor that determines the type of product in the hydrogenation of 5,6-dihydro-4*H*-1,2-oxazines (for example, see ref.[10]). Dihydrooxazines that do not contain an alkoxy group at C-6 tend to form furan derivatives or δ-amino alcohols, whereas dihydrooxazines with an alkoxy substituent at C-6 produce pyrrolidine and pyrrole derivatives. In this context, it seems reasonable to dis-



Scheme 5. Hydrogenation of dihydrooxazine **6d** in the presence of Pd-C.



Scheme 6. Catalytic hydrogenation of dihydrooxazines **6h**,**i**.

cuss the catalytic hydrogenation of oxazines **6h**,**i** that bear a CH_2CO_2Me substituent at C-3 and an alkoxy group at C-6 (see Scheme 6 and Table 2).

Table 2. Hydrogenation of oxazines **6h**,**i**.

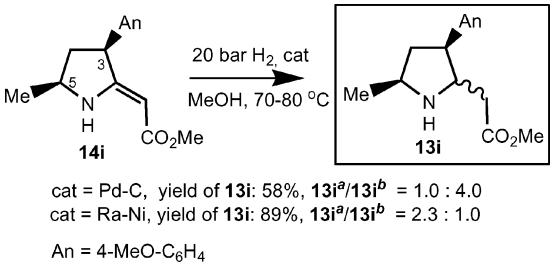
Entry	**6**	Yields of pyrrolidines [%]						
		12h		**14i**			**13**	
		iii	*iv*	*iii*	*iv*		*iii*	*iv*
1	**h**	11[a]	53[b]	–	–	**13h**	87[c]	–
2	**i**	–	–	28	31	**13i**	52[d]	51[e]

[a] Mixture of 3,5-*trans* (**12h**^{a}) and 3,5-*cis* (**12h**^{b}) isomers in a 4.0:1.0 ratio. [b] **12h**^{a}/**12h**^{b} = 3.0:1.0. [c] **13h**^{a}/**13h**^{b} = 2.5:1.0. [d] **13i**^{a}/**13i**^{b}/**13i**^{c} = 8.5:3.3:1.0. [e] **13i**^{a}/**13i**^{b} = 1.0:3.7.

As one can see, apart from the usual hydrogenation products, pyrrolidines of type **13**, enamines **12h** and **14i** were also obtained. Their formation will be discussed in the next section. Here it is worth mentioning that the employment of the less active Pd-C catalytic system instead of Raney nickel increases the yield of enamine **12h** or **14i**. Because the free pyrrolidines **13h**,**i** are labile and cannot be isolated in an analytically pure form, they were transformed into stable *N*-Boc derivatives **13′h**,**i**, which were then characterized. Also, product **13′i** can be obtained directly from **6i** by hydrogenation in the presence of Boc_2O (see Exp. Sect.).

It is evident that enamines **12h** and **14i** have a different relationship with the corresponding pyrrolidines **13h**,**i**. Indeed, the hydrogenation of enamine **12h** under similar conditions to those used for the hydrogenation of dihydrooxaz-

ine **6h** (20 bar H_2, Raney nickel, MeOH, 70–80 °C, 2 h) leads to a complex mixture of unidentified products. Pyrrolidine **13h** was not identified in this mixture. However, the hydrogenation of pyrrolidine **14i** (single stereoisomer) yields a mixture of pyrrolidines **13i**^{a} and **13i**^{b} (Scheme 7). Remarkably, the ratio of **13i**^{a}/**13i**^{b} is similar to that observed in the hydrogenation reaction of the corresponding dihydrooxazine **6i** under the same conditions with H_2/Raney nickel and H_2/Pd-C (cf. footnotes to Table 2 and Scheme 7).



Scheme 7. Catalytic hydrogenation of enamine **14i**.

Mechanistic Consideration of the Hydrogenation of Oxazines 6

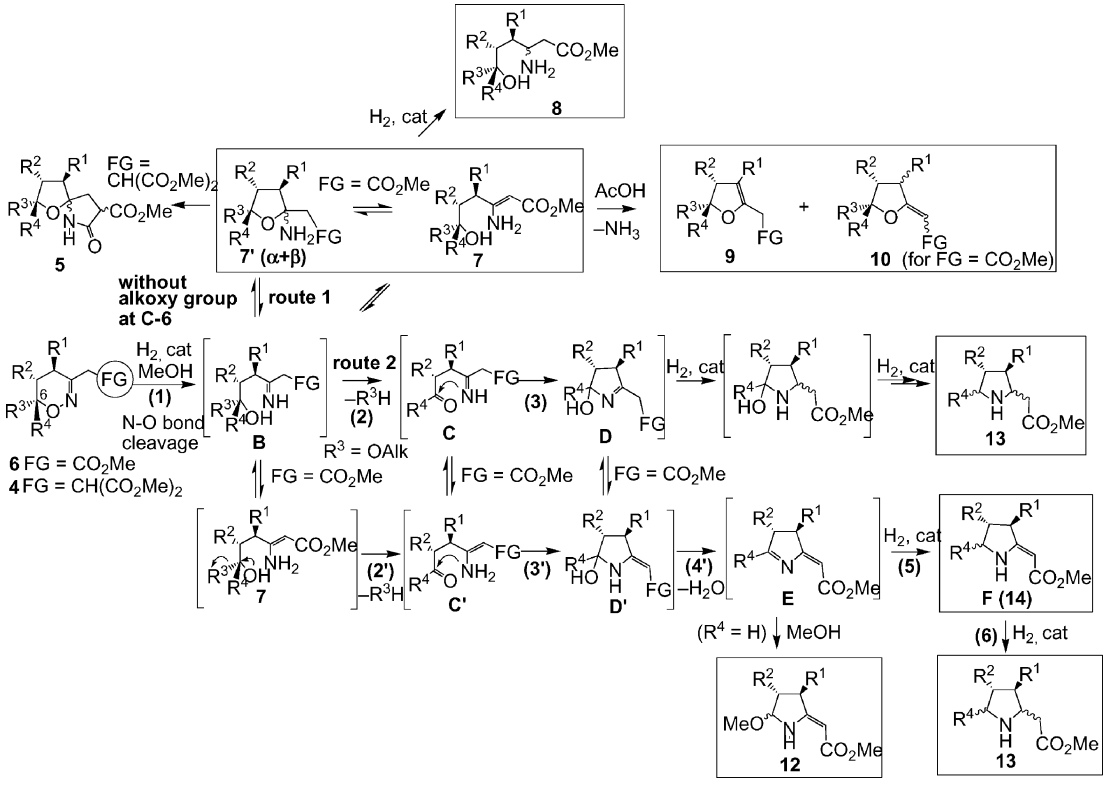
Scheme 8 depicts a general mechanism for the catalytic hydrogenation of 5,6-dihydro-4*H*-1,2-oxazines that explains completely the data obtained in this study, as well as the results presented in previous reports on the hydrogenation of dihydrooxazines **4** and **6**.[10,11]

According to this scheme the hydrogenation of **4** and **6** starts with the initial cleavage of the endocyclic N–O bond [step (1)] and the formation of imine **B**. A similar view concerning the hydrogenation of six-membered cyclic oxime ethers has been suggested previously.[15] However, in a recent report,[5] the reduction of the oximino group in 5,6-dihydro-4*H*-1,2-oxazines under catalytic hydrogenation conditions was postulated to occur in the reverse order (i.e., with initial reduction of the C=N double bond).

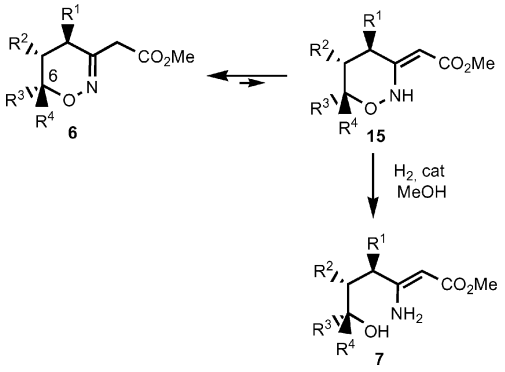
Note that intermediates **B** have never previously been isolated or fixed. In this study the tautomers of **B** (as mixtures **7**+**7′**) were obtained. These compounds are probably thermodynamically more stable than imines **B**. The formation of **7**+**7′** is preferable owing to the activation of CH_2 protons with an adjacent electron-withdrawing CO_2Me group.[16] However, it cannot be ruled out that the enamines **7** are generated by catalytic hydrogenation of tautomers **15** (Scheme 9). The latter results from 1,3-C,N migration of a flexible proton from the CH_2CO_2Me group.

It is evident that other isolated products from the hydrogenation of oxazines **4** and **6** (**5**, **8**, **9**, **10**) arise from the imines **B** or their tautomers **7** and **7′** (Scheme 8, route 1). This conclusion is confirmed by the identical transformations of dihydrooxazine **6b** and intermediate **7b** upon treatment with some reagents (see Scheme 4).

If the oxazines **4** and **6** possess an alkoxy group at C-6 (R^3 = OAlk), the initially formed imines **B** can be transformed consequently into intermediates **C** and **D** [route 2, steps (2) and (3), Scheme 8]. Hydrogenolysis of pyrrolines



Scheme 8. General mechanistic scheme for the catalytic hydrogenation of 5,6-dihydro-4*H*-1,2-oxazines bearing a functionalized methylene group at C-3.



Scheme 9. Possible route to enamines **7** from dihydrooxazines **6**.

D may lead to the final pyrrolidines **13**, yet this does not provide an explanation of how enamines **12** and **14** are formed. At the same time, the presence of the CH_2CO_2Me fragment at C-3 results in activation of the CH_2 protons. Therefore isomerization of the imines (**B**⇆**7**) becomes possible. Subsequent elimination of R^3H [step (2′)], cyclization [step (3′)] and elimination of H_2O [step (4′)] furnish intermediates **E**. Hydrogenolysis of pyrrolines **E** [step (5)] yields pyrrolines **F** (compare with product **14i**). Finally, hydrogenation of the C=C double bond in **F** [step (6)] affords pyrrolidines **13** as the final product of this multistep process. Note that the key intermediates in the process, pyrrolines **D**′, can be generated through alternative mechanistic pathways involving the reversible isomerization of intermediates **C** (**C**⇆**C**′) or **D** (**D**⇆**D**′).

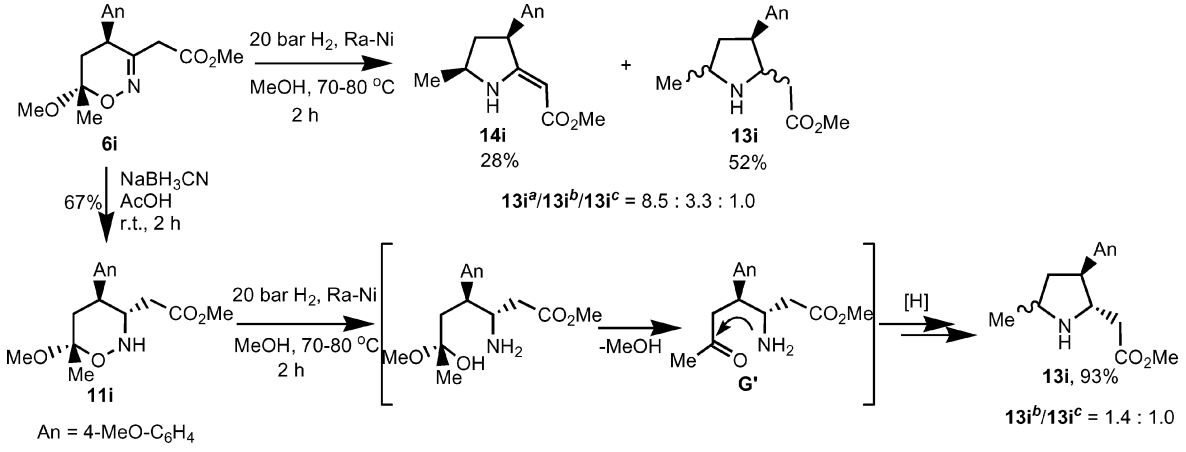
As is illustrated in Scheme 8, of the isolated pyrrolidines **12h** and **14i**, only the latter is involved in the pathway that leads to the target pyrrolidines **13**. Pyrroline **12h** is not a part of this sequence and presumably arises from the intermolecular trapping of the intermediate **E** with methanol (R^4 = H, generated from oxazine **6h**). It is assumed that intermediate **E** (R^4 = Me), which arises from the hydrogenolysis of oxazine **6i**, is not trapped with methanol because of the lower electrophilicity of the carbon atom in the imine fragment and the steric hindrance of the methyl group at C-5.

The different results of the hydrogenation of the oximino ether **6h** and enamine **12h** on the one hand, and the similarity of results of the hydrogenation of **6i** and **14i** (cf. Scheme 7 and Table 2) on the other, support this interpretation. The only difference was the absence of isomer **13i**^{c} among the products of the hydrogenation of **14i** in the presence of the Raney nickel catalyst. It is evident that this isomer cannot arise from the diastereomerically pure 3,5-*cis* isomer of enamine **14i**. Perhaps step (5) of the catalytic hydrogenation of **6i** with H_2/Raney nickel (Scheme 8) is not completely stereoselective. Therefore, besides 3,5-*cis*-**14i**, a small amount of the corresponding 3,5-*trans*-isomer **14i** is generated. Yet this substance was never isolated or observed in the reaction mixtures. The rate of transformation 3,5-*trans*-**14i**→**13i**^{c} is probably greater than the rate of hydrogenation of the corresponding 3,5-*cis* isomer **14i**.

Scheme 10 demonstrates that the catalytic hydrogenation of dihydrooxazine **6i** starts with the selective reduction of the weak N–O bond. Indeed, specially obtained tetrahydrooxazine **11i** yields only pyrrolidine **13i** (as a mixture of two isomers), whereas dihydrooxazine **6i** affords two types of pyrrolidines (**13i** and **14i**) under the same conditions. Therefore, products similar to **11i** cannot be considered as intermediates in the hydrogenation of the cyclic ethers of oximes. In other words, the hydrogenation of derivatives **6** does not start with the reduction of the C=N double bond. Furthermore, participation of the intermediate **G**′ in the sequence leading from **6i** to pyrrolidine **13i** seems unlikely because otherwise the ratios of isomers **13i**^{b} and **13i**^{c} in both reactions (the hydrogenation reactions of **6i** and **11i**) would have been equal.

In this manner, according to Scheme 8, the key processes of the catalytic hydrogenation of **6** are the cyclization and isomerization of intermediate imines **B**. Previously, however, the hydrogenation of the C=N double bond in imines **B** was considered as the only transformation leading to the final pyrrolidines.[15]

Thus, the general sequence for the reduction of the oximino fragment in the cyclic ethers of oximes includes the initial hydrogenolysis of the N–O bond. It is evident that the



Scheme 10. Comparison of the hydrogenation reactions of oxazine **6i** and tetrahydrooxazine **11i**.

initial protonation of the nitrogen atom with acids can drastically change the sequence of bond reduction (cf. Scheme 5).

Support for the Structures of the Target Products

The structures and configurations of the stereocentres in products **7a**–**g**, **8b**, **9b**, **10b**, **10f**, **11b**, **11i**, **12h**, **13′h**–**i** and **14i** were established by elemental analysis, NMR (^{1}H, ^{13}C, DEPT, COSY, HSQC, NOESY) and IR spectroscopy, as well as by the chemical transformations illustrated in Schemes 4, 5, 7 and 10.

The flexible equilibrium **7**⇆**7′** was established from the solvent dependence of the ratio of **7**/**7′** (see Table 3). In $CDCl_3$ solutions, cyclic form **7′** is dominant for substrates **7a**–**d** containing a tertiary alcohol moiety. In contrast, in CD_3CN, the predominant tautomeric form is the open-chain enamine **7** (in CD_3OD compound **7b** exists solely as an acyclic enamine).

Table 3. Ratio of tautomers **7** and **7′** in $CDCl_3$ and CD_3CN.

Products 7+7′	$CDCl_3$		CD_3CN	
	Ratio	Ratio	Ratio	Ratio
	7/**7′**	α/β (for **7′**)	**7**/**7′**	α/β (for **7′**)
a	1.0:2.7	1.0:1.0	4.2:1.0	1.5:1.0
b	1.0:2.5	1.2:1.0	4.2:1.0	1.2:1.0
c	1.0:4.4	1.8:1.0	3.5:1.0	1.2:1.0
d	1.0:3.7	1.5:1.0	5.2:1.0	1.3:1.0
e	3.8:1.0	1.4:1.0 or 1.0:1.4[a]	**7** only	–
f	5.7:1.0	1.3:1.0 or 1.0:1.3[a]	**7** only	–
g	1.0:12.1	1.0:1.0	1.2:1.0	1.0:1.0

[a] The isomers were not assigned unambiguously due to their low concentration and the overlapping of characteristic signals in the ^{1}H NMR spectra with signals from the dominant acyclic tautomeric form.

Compounds **7e**,**f**, which contain a secondary alcohol moiety (R^4 = H), in CD_3CN and $CDCl_3$ exist mainly in the acyclic tautomeric form **7**. In contrast, for compound **7g**, which bears a fused cyclopentane ring, the cyclic form **7′g**(α+β) was found to be predominant in $CDCl_3$ (Table 3).

The acyclic tautomeric form **7** was detected as a single geometrical isomer with a *Z* configuration of the double bond that is stabilized by an intramolecular hydrogen bond [this configuration was originally established from the characteristic correlations between the protons at C-3 and C-9 in the 2D NOESY spectra (Figure 1)].

The relative configuration of the stereocentre at C-2 in the mixtures of tautomers **7′α** and **7′β** was determined on the basis of 2D NOESY experiments (characteristic NOE correlations are depicted in Figure 1). The configurations of the stereocentres at C-3, C-4 and C-5 in the furan unit are identical for both isomers **7′α** and **7′β** as it is governed by the "architecture" of the initial diastereomerically pure oxazines **6**. This was confirmed by the results of 2D NOESY experiments for a mixture of **7g**+**7′g**(α+β) in $CDCl_3$.

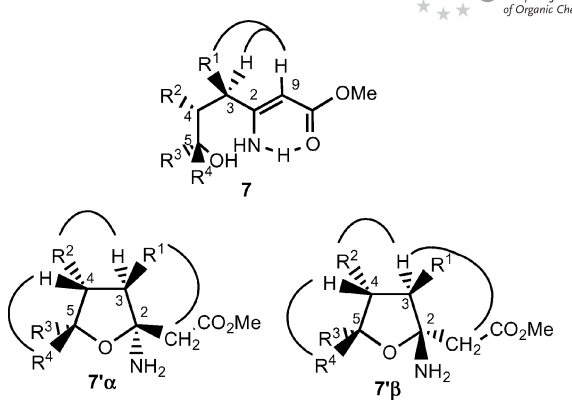


Figure 1. Characteristic 2D NOESY correlations in **7** and **7′**.

Additional information on the structure of **7** was obtained from the IR spectra recorded in CH_3CN. Note that these spectroscopic data are in close agreement with the previously reported spectroscopic studies of 3-aminocrotonic esters.[17] First, the IR data support the existence of the main functional groups in the structure of **7** (C=O ≈ 1670 cm^{-1}, C=CNH$_2$ ≈ 1620 and ≈ 1560 cm^{-1}, OMe ≈ 1170 cm^{-1}, C=*C*–*H* ≈ 795 cm^{-1}; see ref.[17]). Secondly, all the compounds studied (**7a**–**g**) presented four (or sometimes three) bands in the ν(N–H) region (ca. 3630, ca. 3520, ca. 3450 and ca. 3330 cm^{-1}). Unlike the first three ones, the fourth band was almost insensitive to changes in concentration (studied for compound **7b**) and therefore was attributed to the N–H bond intramolecularly bonded to the carboxylic group (literature values for such bonding in methyl 3-aminocrotonates are 3310–3340 cm^{-1} [17]). Also, the large displacement of the ν(C=O) band to lower frequencies in **7** must be due to chelation.[18] This intramolecular hydrogen bond can only exist in the *Z* isomers of enamines **7** (see Figure 1). In addition, the ^{1}H NMR spectra of enamines **7** in CD_3CN show two signals arising from the NH_2 group (ca. 5.5 and ca. 7.8 ppm), which can be assigned to the chelated and free NH protons.

The configuration of the C=C double bond in the pyrrolidine **14i** was similarly revealed. Among the characteristic parameters the low-frequency shift of ν(C=O) band should be noted.

The structure and the configuration of the double bond in furan *E*-**10f**[a] were unambiguously determined by single-crystal X-ray diffraction analysis (Figure 2).[19] The geometrical parameters of *E*-**10f**[a] fall in the range common for this type of compounds. In this molecule two cyclic fragments are annelated through C-4 and C-5 atoms. The "tetrahydrofuran" fragment is characterized by the envelope conformation with a deviation of C-4 from the plane formed by other atoms of the ring of 0.67 Å [torsion angle C(5) O(1)C(2)C(3) is 1°].

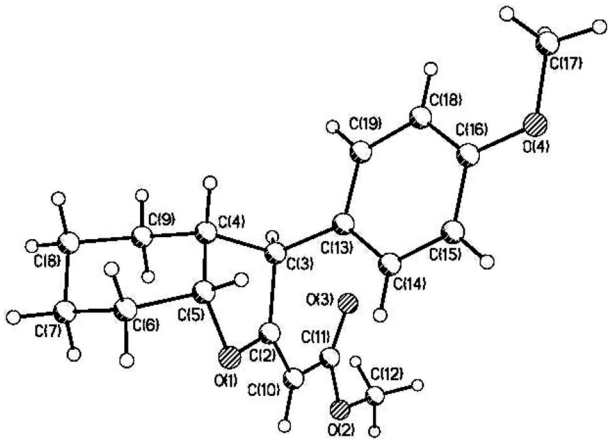


Figure 2. X-ray crystal structure of compound *E*-**10f***[a]* recorded at 293(2) K.

Conclusions

The products of the reduction of oxazines **6**, i.e. enamines **7**, amines **8** and pyrrolidines **13**, can be considered as the esters of previously unknown β-amino acids (β-amino acids are widely applied in modern bioorganic chemistry, e.g., in the synthesis of β-peptides[20]). The incorporation of fused furanosyl β-amino acids, related to the cyclic tautomers **7′**, into the structure of small peptides has been reported recently.[12,21]

In conclusion, a convenient method for the preparation of substituted 5,6-dihydro-4*H*-1,2-oxazines **6** bearing a CH_2CO_2Me group at C-3[9c] as well as effective procedures for their reduction that have been developed here can be assumed to be the basis of a novel strategy for the synthesis of unnatural β-amino acids from nitroethane and other simple precursors.

Experimental Section

General Remarks: 1D and 2D NMR spectra were recorded at room temperature with Bruker DRX-500 [^{1}H (500.13 MHz), ^{1}H–^{1}H COSY, HSQC (J = 145 Hz), NOESY (mixing time 900 ms)], AM-300 (^{13}C (75.13 MHz), INEPT, JMOD, ^{1}H–^{1}H COSY, HSQC, NOESY) NMR spectrometers for 0.1–0.2 M solutions in $CDCl_3$ or CD_3CN. The chemical shifts (^{1}H and ^{13}C) are given in ppm relative to the solvent signal.[22] All 1D and 2D NMR experiments were performed using standard methods and Bruker NMR software. Ratios of tautomers **7**/**7′**(α + β) and stereoisomers **7′**(α)/**7′**(β) were determined from the relative integral intensity of characteristic signals in the ^{1}H NMR spectra for samples obtained after column chromatography. Acyclic tautomers **7** were characterized by NMR in CD_3CN, whereas cyclic tautomers **7′**(α + β) were characterized by NMR in $CDCl_3$ as mixtures with acyclic tautomers. The ratios of the stereoisomers of **9**, **10**, **11**, **12** and **13** (prepared by catalytic hydrogenation) were determined from the relative integral intensity of characteristic signals in the ^{1}H NMR spectra for samples obtained after column chromatography or after filtration of the corresponding reaction mixtures through a short pad of silica gel to remove traces of catalyst. FTIR spectra were recorded with the Bruker VECTOR-22 instrument for 0.1 M solutions in CH_3CN. Peaks are reported in cm^{-1} with the following relative intensities: s (strong), m (medium), w (weak), br (broad), sh (shoulder). Elemental analyses were performed by the Analytical Laboratory of the Institute of Organic Chemistry and Analytical Laboratory of the Institute of Organoelement Compounds. Melting points (uncorrected) were determined with a Kofler apparatus. Analytical thin-layer chromatography was performed with Merck silica gel plates with QF-254. Visualization was accomplished with UV light or with a solution of ninhydrin in ethanol. Column chromatography was performed using Merck Kieselgel 60, 230–400-mesh silica gel. MeOH, hexane and AcOEt were distilled without drying agents. Glacial acetic acid was recrystallized twice. The following chemicals were purchased from Acros: Raney-Ni (50% slurry in water), 5% palladium on charcoal, $NaBH_3CN$, $(t\text{BuOCO})_2O$. Starting oxazines **6b**–**d**,**f**,**g** were prepared from nitroethane according to the literature procedure.[9a,9c] Previously unknown oxazines **6a**,**e** were prepared by a procedure described in ref.[9c] from nitroethane, acetaldehyde, isobutylene or nitroethane, anisaldehyde and *n*-pentene (15 and 14% yields, respectively). High-pressure hydrogenation was carried out in a steel autoclave with the external heating and stirring.

Preparation of Raney Nickel: A 50% slurry of Raney-Ni in water (5 mL) was washed with methanol (5 × 10 mL). The catalyst was used immediately after preparation.

General Procedures for the Preparation of Dynamic Mixtures of Enamines 7 and Tetrahydrofurans 7′

Procedure *i*: Raney-Ni (ca. 0.1 g in methanol) was added to a solution of oxazine **6** (1.0 mmol) in methanol (8.0 mL) was added. The suspension was hydrogenated with vigorous stirring for 5 h at room temp. (20 bar H_2), filtered and concentrated in vacuo. The residue was purified by column chromatography on silica gel (eluent: AcOEt/hexane, 1:5→1:3→1:1). The yields of the target products **7** are presented in Table 1.

Procedure *ii*: Pd-C (0.084 g) was added to a solution of oxazine **6** (1.0 mmol) in methanol (8.0 mL) . The suspension was hydrogenated with vigorous stirring for 2 h at 60–70 °C (20 bar H_2), filtered and concentrated in vacuo. The residue was purified by column chromatography on silica gel (eluent: AcOEt/hexane, 1:5→1:3→1:1). The yields of the target products **7** are presented in Table 1.

Methyl 3-Amino-6-hydroxy-6-methyl-4-phenylheptanoate (8b): Raney-Ni (ca. 0.1 g in methanol) was added to a solution of dihydrooxazine **6b** (0.131 g, 0.5 mmol) in methanol (4.0 mL). The suspension was hydrogenated with vigorous stirring for 2 h at 70–80 °C (20 bar H_2), filtered and concentrated in vacuo. The residue was purified by filtration through a short pad of silica gel (eluent: AcOEt/hexane, 1:5→1:3→1:1→MeOH). Evaporation of the methanol fraction gave a mixture of amino alcohols **8b***[a]* and **8b***[b]* as a colourless oil (0.118 g, 89%, **8b***[a]*/**8b***[b]* = 1.1:1.0).

Hydrogenation of Oxazine 6d over Pd-C: Hydrogenation of oxazine **6d** was realized by procedure *ii* (per 0.5 mmol). The resulting reaction mixture was filtered to remove the catalyst and concentrated in vacuo. The residue was dissolved in $CHCl_3$ (50 mL) and washed with a saturated solution of K_2CO_3 (2 × 30 mL). The aqueous phase was back-extracted with $CHCl_3$ (30 mL) and the combined organic layers were washed with brine (30 mL) and dried (Na_2SO_4). The solvent was evaporated in vacuo and the residue was subjected to column chromatography on silica gel (eluent: AcOEt/hexane, 1:5→1:3→1:1→AcOEt/MeOH, 3:1). Three fractions were collected after chromatographic separation. The first one contained a mixture of dihydrooxazine **6b** and tetrahydrooxazines **11b***[a]* and

11b^b [R_f = 0.63 (AcOEt/hexane, 1:1)]. The second contained pure oxazine **11b^a** [R_f = 0.61 (AcOEt/hexane, 1:1)]. The methanol/AcOEt fraction contained a mixture of amino alcohols **8b^a** and **8b^b**. Total yields: **6b** (31%), **11b^a** (8%), **11b^b** (12%), **8b** (14%, **8b^a/8b^b** = 1.0:1.5).

Hydrogenation of Tetrahydrooxazine 11b^a to Amino Alcohol 8b^a: Pd-C (0.008 g) was added to a solution of tetrahydrooxazine **11b^a** (0.036 g, 0.1 mmol) in methanol (1.0 mL). The suspension was hydrogenated with vigorous stirring for 2 h at 70 °C (20 bar H_2). The resulting mixture was filtered and the solvents evaporated in vacuo. The residue was subjected to flash chromatography on silica gel (eluent: AcOEt/hexane, 1:1→methanol) to give two fractions. The first fraction contained the initial tetrahydrooxazine **11b^a** (0.0205 g, 57%). The methanol fraction contained amino alcohol **8b^a** (0.014 g, 40%).

General Procedure for the Synthesis of Furan Derivatives 9 and 10 from Oxazines 6 (Procedure *v*): Raney-Ni (ca. 0.1 g in methanol) was added to a solution of oxazine **6b** or **6f** (1.0 mmol) in acetic acid (6.6 mL). The suspension was hydrogenated with vigorous stirring for 1 h at 80 °C (20 bar H_2). The resulting mixture was poured into a mixture of EtOAc (100 mL) and a saturated solution of Na_2CO_3 in water (100 mL). The aqueous phase was back-extracted with EtOAc (50 mL) and the combined organic layers were washed with brine (50 mL) and dried with Na_2SO_4. The solvent was evaporated in vacuo and the residue was subjected to column chromatography on silica gel (eluent: AcOEt/hexane, 1:10→1:5). Several fractions were collected after chromatographic separation (for details see below).

Furan Derivatives 9b and 10b: Two fractions were collected after chromatographic separation (procedure *v*). The first one [R_f = 0.78 (AcOEt/hexane, 1:1)] contained a mixture of **9b** (total yield: 41%) and *E*-**10b** (total yield: 12%), the second one [R_f = 0.61 (AcOEt/hexane, 1:1)] contained only *Z*-**10b** (total yield: 25%).

For the characterization of the dihydrofurans **9b** and *Z*-**10b** see ref.[11]

Furan Derivatives 10f: Two fractions were collected after chromatographic separation (procedure *v*). The first one [R_f = 0.69 (AcOEt/hexane, 1:1)] contained isomer *E*-**10f^a** (yield: 47%), the second [R_f = 0.51 (AcOEt/hexane, 1:1)] contained a mixture of *Z*-**10f** (yield: 29%) and *E*-**10f^b** (yield: 6%).

Crystals of *E*-**10f^a** were obtained of sufficient quality for X-ray crystallographic analysis. $C_{18}H_{22}O_4$, M = 302.36, orthorhombic, space group $Pna2_1$, a = 9.1511(18), b = 19.428(4), c = 9.0557(18) Å, V = 1610.0(6) Å^3, Z = 4, $d_{calcd.}$ = 11.247 g cm^{-3}, μ(Mo-K_α) = 0.087 cm^{-1}, F(000) = 648. The intensities of 2136 reflections were measured with a "CAD4 Enraf-Nonius" diffractometer ($\theta/2\theta$-scan, graphite monochromator, $2\theta_{max} \leq 52°$) and 1857 independent reflections [R_{int} = 0.0431] were used in further refinement. The refinement converged to wR_2 = 0.1042 and GOF = 1.000 for all independent reflections [R_1 = 0.0426 was calculated against F for 1491 observed reflections with $I > 2\sigma(I)$].[19] All calculations were performed by using SHELXTL PLUS 5.0.[23]

Synthesis of Furan Derivatives 9b and 10b from Enamine 7b (Procedure *vi*): A solution of enamine **7b** (0.11 mmol) in acetic acid (1.0 mL) was heated for 1 h at 70–80 °C with stirring and then evaporated in vacuo. The ^{1}H NMR spectrum of the residue (with hexamethyldisiloxane as the internal standard) showed the presence of dihydrofuran **9b** (42%) and tetrahydrofurans *Z*-**10b** and *E*-**10b** (total yield: 31%, ration 2.1:1.0) as the major products.

Hydrogenation of 6-Alkoxy-Substituted Oxazines 6h,i

Procedure *iii*: Raney-Ni (ca. 0.1 g in methanol) was added to a solution of oxazine **6h** or **6i** (0.154 g, 0.5 mmol) in methanol (4.0 mL). The suspension was hydrogenated with vigorous stirring for 2 h at 70–80 °C (20 bar H_2), filtered and concentrated in vacuo. The residue was subjected to column chromatography on silica gel (eluent: AcOEt/hexane, 1:5→1:3→1:1→MeOH). The products were isolated as indicated below.

Procedure *iv*: Pd-C (0.04 g) was added to a solution of oxazine **6h** or **6i** (0.154 g, 0.5 mmol) in methanol (4.0 mL). The suspension was hydrogenated with vigorous stirring for 2 h at 70–80 °C (20 bar H_2) and then filtered and concentrated in vacuo. The residue was subjected to column chromatography on silica gel (eluent: AcOEt/hexane, 1:5→1:3→1:1→MeOH). The products were isolated and characterized as indicated below.

Mixture of Pyrrolidines 12h^a and 12h^b: Pyrrolidine **12h** was isolated as the only product (yield: 53%, ratio **12h^a/12h^b** = 3.0:1.0) from the hydrogenation of **6h** by procedure *iv* (eluent: for column chromatography AcOEt/hexane, 1:5→1:3). However, pyrrolidine **12h** was isolated as a minor product from the hydrogenation of **6h** by procedure *iii* (yield: 11%, **12h^a/12h^b** = 4.0:1.0).

Pyrrolidines 13h and 13′h: Unstable crude pyrrolidine **13h** (oil, structure supported by ^{1}H and ^{13}C NMR) was obtained as the major product (yield: 87%, mixture of isomers, **13h^a/13h^b** = 2.5:1.0) from the hydrogenation of oxazine **6h** by procedure *iii* (methanol fraction).

Transformation of 13h to the Boc-Protected Pyrrolidine 13′h: Pyrrolidine **13h** was dissolved in CH_2Cl_2 (11 mL) and treated with Boc_2O (0.140 g, 0.65 mmol). The resulting mixture was kept for 48 h with occasional shaking, concentrated in vacuo and the residue was subjected to column chromatography on silica gel (eluent: AcOEt/hexane, 1:10→1:5) to give a mixture of pyrrolidines **13′h^a** and **13′h^b** (0.065 g, 37% from **6h**, ratio **13′h^a/13′h^b** = 2.8:1.0).

Methyl 2-[*rel*-(*Z*)-(3*S*,5*S*)-5-Methyl-3-[4-(methoxy)phenyl]tetrahydro-2*H*-pyrrol-2-ylidene]acetate (14i): Pyrrolidine **14i** was obtained by procedure *iii* (yield: 28%) or *iv* (yield: 31%) from oxazine **6i** (AcOEt/hexane fraction in the chromatographic separation).

Pyrrolidines 13i and 13′i: Crude unstable mixtures of pyrrolidines **13i** were obtained as oils by hydrogenation of oxazine **6i** over Raney-Ni (procedure *iii*, methanol fraction, yield: 52%, ratio of isomers **13i^a/13i^b/13i^c** = 8.5:3.3:1.0) or over Pd-C (procedure *iv*, methanol fraction, yield: 51%, ratio of isomers **13i^a/13i^b** = 1.0:3.7). The two major isomers (**13i^a** and **13i^b**) were characterized by NMR analysis.

Transformation of 13i to the Boc-Protected Pyrrolidine 13′i: Boc_2O (0.065 g, 0.3 mmol) was added to a solution of crude pyrrolidine **13i** (0.053 g, 0.2 mmol, mixture of isomers **13i^a/13i^b** = 1.0:3.7) in CH_2Cl_2 (5 mL). The mixture was kept for 48 h with occasional shaking. The solvent was evaporated in vacuo and the residue was subjected to column chromatography on silica gel (eluent: AcOEt/hexane, 1:10→1:5) to give pyrrolidine **13′i** as an oil (0.052 g, 71%, ratio of isomers **13′i^a/13′i^b** = 1.0:3.0).

Procedure for the Direct Hydrogenation 6i→13′i: Boc_2O (0.16 g, 0.73 mmol) and Raney-Ni (ca. 0.1 g in methanol) were added to a solution of oxazine **6i** (0.15 g, 0.49 mmol) in methanol (4.0 mL). The suspension was hydrogenated with vigorous stirring for 2 h at 70–80 °C (20 bar H_2), filtered, concentrated in vacuo and subjected to column chromatography on silica gel (eluent: AcOEt/hexane, 1:10→1:5) to give pyrrolidine **13′i** as an oil (0.11 g, 62%, mixture of isomers **13′i^a/13′i^b/13′i^c** = 8.1:2.5:1.0).

Methyl *rel*-[(3*S*,4*S*,6*S*)-6-Methoxy-4-(4-methoxyphenyl)-6-methyl-1,2-oxazinan-3-yl]acetate (11i): $NaBH_3CN$ was added to a stirred solution of oxazine **6i** (0.10 g, 0.33 mmol) in AcOH (1.5 mL) and vigorously stirred for 2 h. Then the reaction mixture was diluted with AcOEt (30 mL) and poured into a mixture of AcOEt (20 mL) and a saturated solution of K_2CO_3 in water (50 mL). The aqueous phase was back-extracted with EtOAc (2 × 20 mL) and the combined organic layers were washed with brine (50 mL) and dried with Na_2SO_4. The solvent was evaporated in vacuo and the residue was subjected to column chromatography on silica gel (eluent: AcOEt/hexane, 1:10 → 1:5) to give tetrahydrooxazine **11i** as a single diastereomer (0.069 g, 67%).

Hydrogenation of Tetrahydrooxazine 11i to Pyrrolidine 13i: Raney-Ni (ca. 30 mg) was added to a solution of tetrahydrooxazine **11i** (0.037 g, 0.12 mmol) in methanol (1.0 mL). The suspension was hydrogenated with vigorous stirring for 2 h at 70–80 °C (20 bar H_2). The resulting mixture was filtered and evaporated under reduced pressure. The residue was purified by flash chromatography on silica gel (eluent: AcOEt/hexane, 1:5 → 1:1 → MeOH). The methanolic fraction contained **13i** (0.027 g, 93%, **13i*b*/13i*c*** = 1.4:1.0). The crude **13i** was transformed into derivative **13′i** by the procedure described above (0.028 g, 64% from **11i**, ratio **13i′*b*/13′i*c*** = 1.6:1.0).

Supporting Information (see also the footnote on the first page of this article): Characterization data for all new compounds (m.p., R_f, ^1H, ^{13}C, INEPT, COSY, HSQC, NOESY NMR spectra, FTIR and elemental analyses).

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