



Simple Synthesis of 2*H*-1,3-Oxazines and Their Stereoselective Transformation into 1,3-Aminoalcohols and Azetidines

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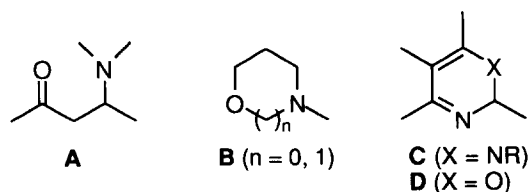
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Abstract: 4-Amino-1-azadienes **1** undergo cyclization at 20-50° C with esters of glyoxylic acid giving rise to 2*H*-1,3-oxazines **3**. These compounds are reduced with NaBH₃CN / AcOH affording stereoselectively *syn*, *syn*-1,3-aminoalcohols **4**, which are further *O*-mesylated and cyclized to yield azetidines **7** with a *cis*, *trans* stereochemistry.

INTRODUCTION

Functionalized molecules containing the 1,3-aminoalcohol structural unit have attracted a great deal of attention because of their pharmacological properties and their utility as building blocks in natural products synthesis.¹ Two general routes starting from structures **A** and **B** have been described to produce efficiently 1,3-aminoalcohols (Figure 1). The first one involves reduction of β -aminoketones and β -aminoacid derivatives of type **A** using most frequently metal hydrides as the reducing agents; in general, one or two chiral centers are generated and the γ -aminoalcohols are obtained with moderate to good stereoselectivity.² The second approach to these difunctional compounds requires the ring cleavage of heterocycles containing nitrogen and oxygen; thus, the reductive cleavage of the isoxazolidine ring **B** ($n = 0$) and the acid hydrolysis of the 1,3-oxazine ring **B** ($n = 1$) represent other common strategies.^{1c,3}

Figure 1

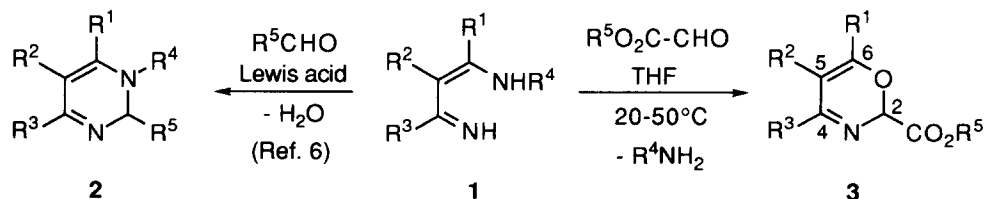


For several years, we have been engaged in the synthesis of novel heterocyclic compounds starting from various heterodienes, particularly azadienes, and have studied in some cases their applications for the construction of acyclic functionalized molecules.⁴ For instance, we have reported the diastereo- and enantioselective preparation of γ -aminoalcohols from 4-amino-1-azabutadienes **1**; the whole protocol entails condensation of such systems with an aliphatic or aromatic aldehyde to form dihydropyrimidines **C** followed by imine reduction and hydrolysis to give β -aminoketones **A** which are finally subjected to LiAlH_4 reduction.⁵ Then, we realized that this synthetic sequence, 4-amino-1-azabutadiene $\rightarrow$ 1,3-aminoalcohol, might be greatly shortened and the stereoselectivity enhanced if the reduction were accomplished on the 1,3-oxazine species **D** rather than on **C**.^{6,7} On the basis of this thought, we report herein the preparation of 2*H*-1,3-oxazines **3** by reaction of azadienes **1** with glyoxylic acid esters as well as their consecutive transformation into 1,3-aminoalcohols **4** and substituted azetidines **7**.

RESULTS AND DISCUSSION

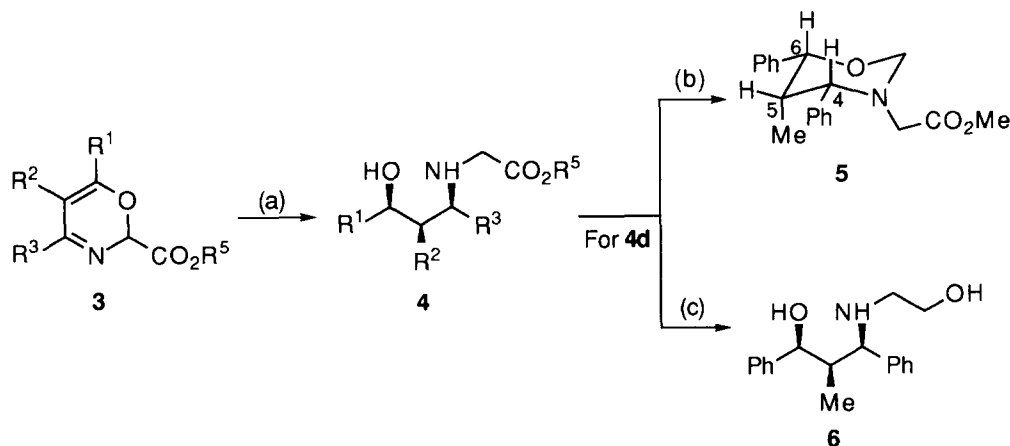
Synthesis of 2*H*-1,3-oxazines **3** (Scheme 1). Some years ago we found that 4-amino-1-azadienes **1** cyclocondensed with aliphatic and aromatic aldehydes in the presence of a Lewis acid catalyst to give 1,2-dihydropyrimidines **2**.^{4,8} Now, we have employed more reactive aldehydes and observed the chemoselective cyclization involving displacement of the amino group R^4NH_2 when the reaction is run under uncatalyzed conditions.⁹ Thus, when 4-amino-1-azadienes **1** were treated overnight with esters of glyoxylic acid at 20–50° *C*-substituted 2*H*-1,3-oxazines **3** were isolated in very high yields (Table 1). The ^1H and ^{13}C NMR of **3** are in agreement with the proposed structure; for instance, the following chemical shifts (δ , ppm) of **3j** are representative: H-2 (6.1), H-5 (6.6), C-2 (86.6), C-5 (95.5), C-4 and C-6 (161.4 and 163.6).

Scheme 1



Synthesis of 1,3-aminoalcohols **4 from oxazines **3**** (Scheme 2). In previous work we have achieved the stereoselective preparation of 1,3-disubstituted propanediamines and polyamines from 1,2-dihydropyrimidines **2** ($R^2 = H$); in that event $\text{NaBH}_4/\text{MeOH}$ worked well and enabled us to perform in one step the reduction of both the imine and enamine groups and the regioselective reductive cleavage of the carbon-substituted nitrogen bond.¹⁰ Accordingly, we have applied this methodology to the reduction of the closely related 2*H*-1,3-oxazine derivatives **3**; however, the initial attempted reduction of **3** following the standard procedure ($\text{NaBH}_4/\text{MeOH}/\text{THF}$) failed and led to a complex mixture from which no defined compounds could be isolated.¹¹ On the contrary, sodium cyanoborohydride was found very suitable to accomplish the reduction in a satisfactory way; thus, oxazines **3** were reacted overnight with NaBH_3CN (molar ratio 1:2.5) in THF/AcOH ($\text{pH} = 5\text{--}6$) at $20\text{--}50^\circ\text{C}$ to furnish, after basic hydrolysis and column chromatography, high yields of 1,3-aminoalcohols **4** as single stereoisomers (^1H NMR 300MHz of the reaction crude) (Table 2). The stereochemical assignment was based on the NMR data of the tetrahydrooxazine derivative **5** obtained by cyclocondensation of **4d** with aqueous formaldehyde (95% yield). Thus, the H-4 and H-6 hydrogen atoms appear as doublets at 4.1 ($J_{\text{H-4}/\text{H-5}} = 3.2\text{ Hz}$) and 4.8 ($J_{\text{H-5}/\text{H-6}} = 2.4\text{ Hz}$) ppm, respectively, which confirms their *cis* relationship. Further reduction of **4d** with LiAlH_4 (molar ratio 1:3, THF , 20°C) yielded the aminodiols derivative **6** (92%).

Scheme 2



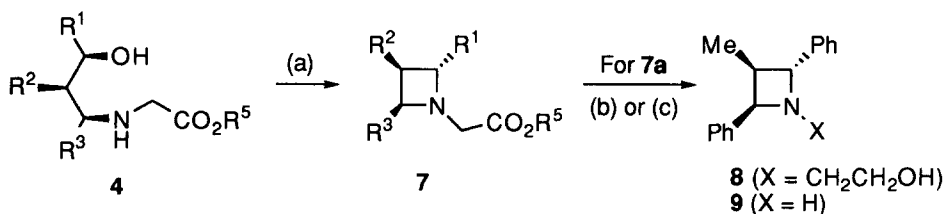
Reagents and conditions: (a) NaBH_3CN / THF / AcOH , 20°C (for $R^2 \neq H$) or 50°C (for $R^2 = H$). (b) H_2CO / Et_2O / 20°C . (c) LiAlH_4 / THF / 20°C .

Table 1. 2*H*-1,3-oxazines **3** from 4-Amino-1-azabutadienes **1**

Compound	R ¹	R ²	R ³	R ⁵	Yield (%)
3a	Ph	Me	Ph	Me	93
3b	Ph	Me	Ph	Et	91
3c	Ph	Me	4-Me-C ₆ H ₄	Et	90
3d	Ph	Me	<i>c</i> -C ₆ H ₁₁	Et	84
3e	4-MeO-C ₆ H ₄	Me	2-Furyl	Et	80
3f	Ph	allyl	Ph	Et	94
3g	Ph	allyl	4-Me-C ₆ H ₄	Et	91
3h	Ph	Ph-CH ₂	Ph	Et	88
3i	Ph	Ph-CH ₂	4-Me-C ₆ H ₄	Et	85
3j	Ph	H	Ph	Et	87
3k	Ph	H	4-Me-C ₆ H ₄	Et	90

Synthesis of azetidines **7 from aminoalcohols **4**** (Scheme 3). Because of the interest of azetidines in terms of reactivity and potential biological activity as well as of the difficulties associated with their preparation¹² we thought on synthesizing stereochemically defined, polysubstituted azetidines from aminoalcohols **4**. To this end, compounds **4a-c** were mesylated at 0°C for 2 h (MsCl, NEt₃/DMAP cat., CH₂Cl₂) and the mixture hydrolyzed with base and chromatographed furnishing azetidines **7a-c** in 60-68% after purification (Table 2). Compounds **7** were isolated as single isomers and the resulted stereochemistry is a consequence of the inversion of configuration at the hydroxyl carbon in the cyclization. Further LiAlH₄ reduction of the ester function of **7a** gave the *N*-(2-hydroxyethyl) derivative **8** (91%) with the azetidine skeleton remaining unaltered. The nitrogen substituent could be cleanly removed by α -hydroxylation of the ester followed by hydrolysis of the resulting aminal; this amine deprotection was accomplished by forming the enolate with NaN(SiMe₃)₂ and treated it at low temperature with the molybdenum peroxide complex MoO₅.py.HMPA¹³ to afford **9** in 90% yield.

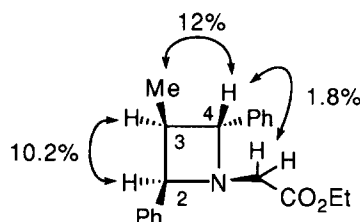
Scheme 3



Reagents and conditions: (a) MsCl / NEt₃ / DMAP cat / CH₂Cl₂ / 0°C. (b) LiAlH₄ / THF / 20°C. (c) NaN(SiMe₃)₂ -78°C / THF; then MoO₅.Py.HMPA / -40°C; then 1M H₂SO₄.

The *syn,anti* stereochemistry of compounds **7-9** was readily ascertained from the ^1H NMR spectrum of **7a**, which shows the coupling constants $J_{\text{cis H-2/H-3}}$ and $J_{\text{trans H-3/H-4}}$ to be 8.6 and 4.3 Hz, respectively, as expected for an azacyclobutane structure;¹⁴ moreover, the relative configuration was confirmed by NOE experiments as shown in Figure 2.

Figure 2

Table 2. Aminoalcohols **4** and Azetidines **7** prepared

Entry	R ¹	R ²	R ³	R ⁵	4 (%)	7 (%)
a	Ph	Me	Ph	Et	82	68
b	4-MeO-C ₆ H ₄	Me	2-Furyl	Et	79	60
c	Ph	H	Ph	Et	81	65
d	Ph	Me	Ph	Me	78	--
e	Ph	allyl	4-Me-C ₆ H ₄	Et	85	--
f	Ph	H	4-Me-C ₆ H ₄	Et	75	--

Conclusions. A facile synthesis of uncommon 2*H*-1,3-oxazines is straightforward achieved by [4+2] cyclization of 1-azadiene derivatives and glyoxylic acid esters. These oxazines undergo sodium cyanoborohydride reduction allowing the preparation of 1,3-aminoalcohols in a fully stereoselective fashion; it is worth noting that two or three chiral centers are created in this simple reduction and the easy synthesis of the *syn,syn*-stereoisomers is achieved which are hardly available by other methods.^{5d} These aminoalcohols have been ultimately used as valuable precursor materials for polysubstituted azetidines. Further work is in progress in order to develop the enantioselective version of this synthesis of aminoalcohols by using optically active glyoxylic acid esters.

EXPERIMENTAL SECTION

General Considerations:

All common reagents were obtained from commercial suppliers and used without further purification unless otherwise indicated. THF was distilled from sodium benzophenone ketyl under a N₂ atmosphere prior to use. Hexane, ethyl acetate, diethyl ether, triethylamine and hexamethylphosphoramide (HMPA) were distilled before use. Flash column chromatography was carried out on silica gel 60 (230-400 mesh). NMR spectra were run on Bruker AC200 and AC300 spectrometers. Mass spectra were determined on HP 5987A (EIMS) and Finnigan MAT 95 (HRMS) spectrometers

General procedure for the preparation of oxazines 3:

To a solution of 4-amino-1-azadiene **1** (1.5 mmol) in THF (25 mL) was added a solution of the glyoxylic acid ester¹⁵ (1.5 mmol) in THF (10 mL) at room temperature and stirred at the same temperature (R² ≠ H) or 50°C (R² = H) overnight. The reaction mixture was treated with 1M H₂SO₄, extracted with Et₂O (3 x 20 mL) and the combined organic layers washed with brine and dried over Na₂SO₄. The solvents were removed under vacuum and the residue subjected to column chromatography (SiO₂, hexane / ethyl acetate 4:1) furnishing pure oxazines **3** (Table 1, Scheme 1).

2-Methoxycarbonyl-5-methyl-4,6-diphenyl-2H-1,3-oxazine 3a

¹H-NMR (300 MHz, CDCl₃): δ 1.95 (s, 3H), 3.9 (s, 3H), 5.8 (s, 1H), 7.4-7.5 (m, 6H), 7.5-7.6 (m, 2H), 7.7-7.8 (m, 2H). ¹³C-NMR (75 MHz, CDCl₃): δ 169.6 (s), 168.8 (s), 157.7 (s), 137.2 (s), 131.9 (s), 130.2 (d), 129.8 (d), 129.5 (d), 128.3 (d), 128.0 (d), 107.5 (s), 85.0 (d), 52.6 (q), 15.1 (q). IR (neat): 1741, 1670 cm⁻¹. Anal.: Found: C, 74.34; H, 5.64; N, 4.54 %; Calcd. for C₁₉H₁₇NO₃, C, 74.25; H, 5.58; N, 4.58 %.

2-Ethoxycarbonyl-5-methyl-4,6-diphenyl-2H-1,3-oxazine 3b

¹H-NMR (300 MHz, CDCl₃): δ 1.3 (t, *J* = 7.1 Hz, 3H), 1.9 (s, 3H), 4.3 (q, *J* = 7.1 Hz, 2H), 5.9 (s, 1H), 7.4-7.5 (m, 6H), 7.5-7.6 (m, 2H), 7.7-7.8 (m, 2H). ¹³C-NMR (75 MHz, CDCl₃): δ 169.3 (s), 168.3 (s), 157.6 (s), 137.2 (s), 132.0 (s), 130.1 (d), 129.7 (d), 129.3 (d), 128.2 (d), 127.9 (d), 107.3 (s), 84.8 (d), 61.5 (t), 15.0 (q), 13.9 (q). IR (neat): 1740, 1692 cm⁻¹. Anal.: Found: C, 74.82; H, 5.91; N, 4.30 %; Calcd. for C₂₀H₁₉NO₃, C, 74.75; H, 5.96; N, 4.36 %.

2-Ethoxycarbonyl-5-methyl-4-(4-methylphenyl)-6-phenyl-2H-1,3-oxazine 3c

¹H-NMR (300 MHz, CDCl₃): δ 1.3 (t, *J* = 7.1 Hz, 3H), 1.9 (s, 3H), 2.4 (s, 3H), 4.3 (q, *J* = 7.1 Hz, 2H), 5.9 (s, 1H), 7.2 (d, *J* = 7.7 Hz, 2H), 7.4-7.6 (m, 5H), 7.7-7.8 (m, 2H). ¹³C-NMR (75 MHz, CDCl₃): δ 169.3 (s), 168.5 (s), 157.7 (s), 139.6 (s), 134.4 (s), 132.1 (s), 130.1 (d), 129.8 (d), 128.7 (d), 128.3 (d), 128.0 (d), 107.5 (s), 84.8 (d), 61.6 (t), 21.2 (q), 15.2 (q), 14.0 (q). IR (neat): 1730, 1665 cm⁻¹. Anal.: Found: C, 75.20; H, 6.31; N, 4.18 %; Calcd. for C₂₁H₂₁NO₃, C, 75.31; H, 6.37; N, 4.11 %.

4-Cyclohexyl-2-ethoxycarbonyl-5-methyl-6-phenyl-2H-1,3-oxazine 3d

¹H-NMR (300 MHz, CDCl₃): δ 1.1-1.8 (m, 10 H), 1.2 (t, *J* = 7.1 Hz, 3H), 1.9 (s, 3H), 2.4 (m, 1H), 4.2 (q, *J* = 7.1 Hz, 2H), 5.7 (s, 1H), 7.3-7.4 (m, 3H), 7.5-7.6 (m, 2H). ¹³C-NMR (75 MHz, CDCl₃): δ 173.6 (s), 169.0 (s), 155.7 (s), 132.4 (s), 129.9 (d), 129.8 (d), 127.9 (d), 107.4 (s), 84.6 (d), 61.3 (t), 41.7 (d), 30.7 (t), 30.5 (t), 26.3

(t), 26.2 (t), 25.8 (t), 14.0 (q), 12.6 (q). IR (neat): 1715, 1661 cm^{-1} . HRMS: m/z , 327.1825; Calcd. for $\text{C}_{20}\text{H}_{25}\text{NO}_3$, 327.1834 (M^+).

2-Ethoxycarbonyl-4-(2-furyl)-6-(4-methoxyphenyl)-5-methyl-2*H*-1,3-oxazine 3e

^1H -NMR (300 MHz, CDCl_3): δ 1.3 (t, $J = 7.1$ Hz, 3H), 2.2 (s, 3H), 3.8 (s, 3H), 4.2-4.5 (m, 2H), 5.8 (s, 1H), 6.5 (m, 1H), 7.0 (d, $J = 10$ Hz, 2H), 7.1 (m, 1H), 7.6 (m, 1H), 7.7 (d, $J = 10$ Hz, 2H). ^{13}C -NMR (75 MHz, CDCl_3): δ 168.1 (s), 160.7 (s), 157.8 (s), 150.2 (s), 143.9 (d), 143.6 (s), 131.4 (d), 129.0 (d), 114.5 (d), 112.9 (d), 111.0 (s), 105.2 (s), 84.2 (d), 61.2 (t), 54.6 (q), 14.5 (q), 13.5 (q). IR (neat): 1740, 1675 cm^{-1} . Anal.: Found: C, 66.92; H, 5.67; N, 4.13 %; Calcd. for $\text{C}_{19}\text{H}_{19}\text{NO}_5$, C, 66.85; H, 5.61; N, 4.10 %.

2-Ethoxycarbonyl-4,6-diphenyl-5-(2-propenyl)-2*H*-1,3-oxazine 3f

^1H -NMR (300 MHz, CDCl_3): δ 1.3 (t, $J = 7.1$ Hz, 3H), 3.2 (m, 2H), 4.3 (q, $J = 7.1$ Hz, 2H), 4.6 (dd, $J_1 = 17.1$ Hz, $J_2 = 1.6$ Hz, 1H), 4.7 (dd, $J_1 = 10.2$ Hz, $J_2 = 1.6$ Hz, 1H), 5.4 (m, 1H), 5.9 (s, 1 H), 7.3-7.6 (m, 8H), 7.7-7.8 (m, 2H). ^{13}C -NMR (75 MHz, CDCl_3): δ 169.2 (s), 168.4 (s), 159.2 (s), 137.5 (s), 135.3 (d), 131.8 (s), 130.3 (d), 129.8 (d), 129.2 (d), 128.1 (d), 127.9 (d), 115.5 (t), 111.0 (s), 84.9 (d), 61.7 (t), 31.3 (t), 14.0 (q). IR (neat): 1728, 1642 cm^{-1} . Anal.: Found: C, 76.00; H, 5.99; N, 4.01 %; Calcd. for $\text{C}_{22}\text{H}_{21}\text{NO}_3$, C, 76.06; H, 6.09; N, 4.03 %.

2-Ethoxycarbonyl-4-(4-methylphenyl)-6-phenyl-5-(2-propenyl)-2*H*-1,3-oxazine 3g

^1H -NMR (300 MHz, CDCl_3): δ 1.3 (t, $J = 7.2$ Hz, 3H), 2.3 (s, 3H), 3.2 (m, 2H), 4.3 (m, 2H), 4.6 (dd, $J_1 = 14.8$ Hz, $J_2 = 1.3$ Hz, 1H), 4.7 (dd, $J_1 = 10.3$ Hz, $J_2 = 1.3$ Hz, 1H), 5.3-5.4 (m, 1H), 5.9 (s, 1 H), 7.2 (d, $J = 7.7$ Hz, 2H), 7.4-7.5 (m, 5H), 7.7-7.8 (m, 2H). ^{13}C -NMR (75 MHz, CDCl_3): δ 169.0(s), 168.4 (s), 159.0 (s), 139.2 (s), 135.3 (d), 134.5 (s), 131.7 (s), 130.2 (d), 129.7 (d), 128.5 (d), 128.0 (d), 115.3 (t), 111.1 (s), 84.8 (d), 61.6 (t), 31.3 (t), 21.1 (q), 13.9 (q). IR (neat): 1730, 1682 cm^{-1} . Anal.: Found: C, 76.49; H, 6.48; N, 3.86 %; Calcd. for $\text{C}_{23}\text{H}_{23}\text{NO}_3$, C, 76.43; H, 6.41; N, 3.88 %.

5-Benzyl-2-ethoxycarbonyl-4,6-diphenyl-2*H*-1,3-oxazine 3h

^1H -NMR (300 MHz, CDCl_3): δ 1.2 (t, $J = 7.1$ Hz, 3H), 3.6 (d, $J = 15.6$ Hz, 1H), 3.7 (d, $J = 15.6$ Hz, 1H), 4.1-4.3 (m, 2 H), 5.8 (s, 1 H), 6.4-6.5 (m, 2 H), 6.8-6.9 (m, 3 H), 7.2-7.4 (m, 8 H), 7.7-7.8 (m, 2 H). ^{13}C -NMR (75 MHz, CDCl_3): δ 169.0 (s), 168.4 (s), 159.1 (s), 139.3 (s), 137.4 (s), 131.7 (s), 130.4 (d), 130.1 (d), 129.0 (d), 128.1 (d), 127.8 (d), 127.7 (d), 127.6 (d), 125.6 (d), 112.8 (s), 84.8 (d), 61.6 (t), 33.2 (t), 13.8 (q). IR (neat): 1738, 1694 cm^{-1} . Anal.: Found: C, 78.62; H, 5.89; N, 3.49 %; Calcd. for $\text{C}_{26}\text{H}_{23}\text{NO}_3$, C, 78.57; H, 5.83; N, 3.52 %.

5-Benzyl-2-ethoxycarbonyl-4-(4-methylphenyl)-6-phenyl-2*H*-1,3-oxazine 3i

^1H -NMR (200 MHz, CDCl_3): δ 1.2 (t, $J = 7.2$ Hz, 3H), 2.4 (s, 3H), 3.7 (d, $J = 15.6$ Hz, 1H), 3.8 (d, $J = 15.6$ Hz, 1H), 4.2-4.3 (m, 2 H), 5.9 (s, 1 H), 6.5-6.6 (m, 2 H), 6.9-7.0 (m, 3 H), 7.1 (d, $J = 7.7$ Hz, 2H), 7.3 (d, $J = 7.7$ Hz, 2H), 7.4-7.5 (m, 3 H), 7.7-7.8 (m, 2 H). ^{13}C -NMR (50 MHz, CDCl_3): δ 168.7 (s), 168.4 (s), 159.0 (s), 139.4 (s), 138.9 (s), 134.5 (s), 131.7 (s), 130.2 (d), 130.0 (d), 128.3 (d), 128.0 (d), 127.8 (d), 127.7 (d), 127.5 (d), 125.4 (d), 112.9 (s), 84.6 (d), 61.4 (t), 33.1 (t), 21.0 (q), 13.7 (q). IR (neat): 1740, 1684 cm^{-1} . Anal.: Found: C, 78.89; H, 6.17; N, 3.43 %; Calcd. for $\text{C}_{27}\text{H}_{25}\text{NO}_3$, C, 78.81; H, 6.12; N, 3.40 %.

2-Ethoxycarbonyl-4,6-diphenyl-2H-1,3-oxazine 3j

¹H-NMR (300 MHz, CDCl₃): δ 1.3 (t, *J* = 7.1 Hz, 3H), 4.3-4.4 (m, 2H), 6.1 (s, 1H), 6.6 (s, 1H), 7.4-7.6 (m, 6H), 7.8-8.0 (m, 4 H). ¹³C-NMR (75 MHz, CDCl₃): δ 168.1 (s), 163.6 (s), 161.4 (s), 136.3 (s), 131.6 (s), 131.2 (d), 130.7 (d), 128.5 (d), 128.4 (d), 126.8 (d), 126.3 (d), 95.5 (d), 86.6 (d), 61.8 (t), 14.0 (q). IR (neat): 1728, 1650 cm⁻¹. HRMS: *m* / *e*, 307.1218; Calcd. for C₁₉H₁₇NO₃, 307.1208 (M)⁺.

2-Ethoxycarbonyl-4-(4-methylphenyl)-6-phenyl-2H-1,3-oxazine 3k

¹H-NMR (300 MHz, CDCl₃): δ 1.2 (t, *J* = 7.1 Hz, 3H), 2.2 (s, 3H), 4.1-4.3 (m, 2H), 5.9 (s, 1H), 6.5 (s, 1H), 7.1 (d, *J* = 7.6 Hz, 2H), 7.2-7.3 (m, 3H), 7.6-7.7 (m, 4 H). ¹³C-NMR (75 MHz, CDCl₃): δ 167.9 (s), 162.9 (s), 160.9 (s), 140.7 (s), 133.2 (s), 131.4 (s), 130.8 (d), 128.8 (d), 128.1 (d), 126.5 (d), 125.9 (d), 95.1 (d), 86.4 (d), 61.3 (t), 20.9 (q), 13.7 (q). IR (neat): 1732, 1670 cm⁻¹. Anal.: Found: C, 74.77; H, 6.00; N, 4.33 %; Calcd. for C₂₀H₁₉NO₃, C, 74.75; H, 5.96; N, 4.36 %.

General procedure for the preparation of aminoalcohols 4:

To a solution of oxazine **3** (1 mmol) in THF (20 mL) at 0°C was added NaBH₃CN (160 mg, 2.5 mmol) and acetic acid (1.5 mL); stirring was continued at room temperature (*R*² ≠ H) or at 50°C (*R*² = H) overnight. The resulting mixture was treated with 2M NaOH (20 mL), extracted with Et₂O (3 x 20 mL) and the combined organic layers washed with brine and dried over Na₂SO₄. The solvents were removed under vacuum and the residue chromatographed (SiO₂, hexane / ethyl acetate 2:1) to yield pure aminoalcohols **4** (Table 2, Scheme 2).

(1S,2R,3R/1R,2S,3S)-3-Ethoxycarbonylmethylamino-2-methyl-1,3-diphenyl-1-propanol 4a

¹H-NMR (300 MHz, CDCl₃): δ 0.6 (d, *J* = 7.1 Hz, 3H), 1.2 (t, *J* = 7.2 Hz, 3H), 1.9 (m, 1 H), 3.35 (s, 2 H), 4.1 (m, 3 H), 5.2 (d, *J* = 2.0 Hz, 1H), 7.1-7.3 (m, 10 H). ¹³C-NMR (75 MHz, CDCl₃): δ 171.8 (s), 143.4 (s), 140.8 (s), 128.5 (d), 127.8 (d), 127.1 (d), 126.5 (d), 126.4 (d), 125.5 (d), 77.7 (d), 66.8 (d), 60.9 (t), 48.4 (t), 46.2 (d), 14.0 (q), 4.4 (q). IR (neat): 3335, 1730 cm⁻¹. HRMS: *m* / *e*, 327.1835; Calcd. for C₂₀H₂₅NO₃, 327.1834 (M)⁺.

(1S,2R,3R/1R,2S,3S)-3-Ethoxycarbonylmethylamino-3-(2-furyl)-1-(4-methoxyphenyl)-1-propanol 4b

¹H-NMR (300 MHz, CDCl₃): δ 0.7 (d, *J* = 7.1 Hz, 3H), 1.2 (t, *J* = 7.2 Hz, 3H), 2.1 (m, 1H), 3.4 (s, 2H), 3.8 (s, 3H), 4.1-4.2 (m, 3H), 5.1 (d, *J* = 2.1 Hz, 1H), 6.15 (m, 1H), 6.3 (m, 1H), 6.9 (d, *J* = 9.8 Hz, 2H), 7.3 (d, *J* = 9.8 Hz, 2H), 7.4 (m, 1H). ¹³C-NMR (75 MHz, CDCl₃): δ 171.5 (s), 158.1 (s), 154.7 (s), 141.7 (d), 135.4 (s), 126.6 (d), 113.1 (d), 109.9 (d), 106.2 (d), 76.9 (d), 61.0 (d), 60.9 (t), 55.0 (q), 48.7 (t), 43.8 (d), 14.0 (q), 5.2 (q). IR (neat): 3348, 1730 cm⁻¹. Anal.: Found: C, 65.72; H, 7.31; N, 4.00 %; Calcd. for C₁₉H₂₅NO₅, C, 65.69; H, 7.25; N, 4.03 %.

(1S,3R/1R,3S)-3-Ethoxycarbonylmethylamino-1,3-diphenyl-1-propanol 4c

¹H-NMR (200 MHz, CDCl₃): δ 1.25 (t, *J* = 7.0 Hz, 3H), 1.9-2.2 (m, 2H), 3.25 (d, *J* = 17.0 Hz, 1H), 3.35 (d, *J* = 17.0 Hz, 1H), 3.8-4.0 (br, NH, OH), 3.95 (dd, *J*₁ = 9.8 Hz, *J*₂ = 3.8 Hz, 1H), 4.15 (q, *J* = 7.0 Hz, 2H), 5.0 (dd, *J*₁ = 10.2 Hz, *J*₂ = 2.8 Hz, 1H), 7.2-7.4 (m, 10 H). ¹³C-NMR (50 MHz, CDCl₃): δ 171.6 (s), 144.7 (s), 142.2 (s), 128.6 (d), 128.1 (d), 127.5 (d), 127.0 (d), 126.5 (d), 125.4 (d), 74.6 (d), 62.9 (d), 60.8 (t), 48.0 (t),

46.2 (t), 14.0 (q). IR (neat): 3340, 1735 cm^{-1} . HRMS: m/e , 313.1665; Calcd. for $\text{C}_{19}\text{H}_{23}\text{NO}_3$, 313.1677 (M)⁺.

(1S,2R,3R/1R,2S,3S)-3-Methoxycarbonylmethylamino-2-methyl-1,3-diphenyl-1-propanol **4d**

¹H-NMR (300 MHz, CDCl_3): δ 0.7 (d, $J = 7.1$ Hz, 3H), 2.0 (m, 1 H), 3.35 (s, 2 H), 3.7 (s, 3 H), 4.15 (d, $J = 3.2$ Hz, 1H), 5.2 (d, $J = 2.1$ Hz, 1H), 7.2-7.4 (m, 10 H). ¹³C-NMR (75 MHz, CDCl_3): δ 172.3 (s), 143.4 (s), 140.8 (s), 128.5 (d), 127.8 (d), 127.1 (d), 126.6 (d), 126.5 (d), 125.5 (d), 77.6 (d), 66.8 (d), 51.8 (q), 48.3 (t), 46.3 (d), 4.5 (q). IR (neat): 3333, 1740 cm^{-1} . Anal.: Found: C, 72.93; H, 7.45; N, 4.43 %; Calcd. for $\text{C}_{19}\text{H}_{23}\text{NO}_3$, C, 72.82; H, 7.40; N, 4.47 %.

(1S,2R,3R/1R,2S,3S)-3-Ethoxycarbonylmethylamino-3-(4-methylphenyl)-1-phenyl-2-(2-propenyl)-1-propanol **4e**

¹H-NMR (300 MHz, CDCl_3): δ 1.25 (t, $J = 7.3$ Hz, 3H), 2.0-2.3 (m, 3H), 2.35 (s, 3H), 3.2 (d, $J = 17.2$ Hz, 1H), 3.3 (d, $J = 17.2$ Hz, 1H), 3.5 (br, NH, OH), 4.1 (d, $J = 3.9$ Hz, 1H), 4.2 (q, $J = 7.3$ Hz, 2H), 4.6-4.8 (m, 2H), 5.2 (d, $J = 1.9$ Hz, 1H), 5.4-5.6 (m, 1H), 7.1-7.4 (m, 9H). ¹³C-NMR (75 MHz, CDCl_3): δ 171.9 (s), 143.4 (s), 138.7 (d), 137.6 (s), 136.7 (d), 129.2 (d), 127.8 (d), 126.8 (d), 126.5 (d), 125.5 (d), 114. (t), 76.4 (d), 65.7 (d), 60.7 (t), 51.7 (d), 48.6 (t), 27.3 (t), 20.9 (q), 14.0 (q). IR (neat): 3338, 1735 cm^{-1} . Anal.: Found: C, 75.11; H, 7.90; N, 3.78 %; Calcd. for $\text{C}_{23}\text{H}_{29}\text{NO}_3$, C, 75.17; H, 7.95; N, 3.81 %.

(1S,2R,3R/1R,2S,3S)-3-Ethoxycarbonylmethylamino-3-(4-methylphenyl)-1-phenyl-1-propanol **4f**

¹H-NMR (200 MHz, CDCl_3): δ 1.2 (t, $J = 7.2$ Hz, 3H), 1.8-2.1 (m, 2 H), 2.4 (s, 3H), 3.2 (d, $J = 17.0$ Hz, 1H), 3.25 (d, $J = 17.0$ Hz, 1H), 3.7-4.0 (br, NH, OH), 3.85 (dd, $J_1 = 10.0$ Hz, $J_2 = 3.6$ Hz, 1H), 4.1 (q, $J = 7.2$ Hz, 2H), 4.9 (dd, $J_1 = 10.3$ Hz, $J_2 = 2.1$ Hz, 1H), 7.1-7.4 (m, 9 H). ¹³C-NMR (50 MHz, CDCl_3): δ 171.5 (s), 144.7 (s), 139.0 (s), 137.0 (s), 129.2 (d), 128.0 (d), 126.9 (d), 126.4 (d), 125.4 (d), 77.4 (d), 62.5 (d), 60.7 (t), 47.9 (t), 46.0 (t), 20.8 (q), 13.9 (q). IR (neat): 3325, 1738 cm^{-1} . Anal.: Found: C, 73.47; H, 7.81; N, 4.25 %; Calcd. for $\text{C}_{20}\text{H}_{25}\text{NO}_3$, C, 73.37; H, 7.70; N, 4.28 %.

Preparation of (4R,5R,6S/4S,5S,6R)-tetrahydro-3-methoxycarbonylmethyl-5-methyl-4,6-diphenyl-1,3-oxazine 5:

A solution of **4d** (156 mg, 0.5 mmol) in Et_2O (20 mL) was treated at room temperature with aqueous 38-40% CH_2O (1 mL) for 12 h. The reaction mixture was washed with H_2O (3 x 5 mL) and the organic layer dried over Na_2SO_4 . Removal of the solvents at reduced pressure gave pure **5** (154 mg, 95%) (Scheme 2). ¹H-NMR (300 MHz, CDCl_3): δ 0.5 (d, $J = 7.0$ Hz, 3H), 1.95 (m, 1 H), 3.0 (d, $J = 17.1$ Hz, 1H), 3.35 (d, $J = 17.1$ Hz, 1H), 3.6 (s, 3 H), 4.1 (d, $J = 3.2$ Hz, 1H), 4.3 (d, $J = 7.8$ Hz, 1H), 4.8 (d, $J = 2.4$ Hz, 1H), 4.85 (d, $J = 7.8$ Hz, 1H), 7.1-7.3 (m, 10 H). ¹³C-NMR (75 MHz, CDCl_3): δ 170.9 (s), 140.6 (s), 139.6 (s), 128.3 (d), 128.2 (d), 128.0 (d), 127.2 (d), 126.7 (d), 125.1 (d), 85.8 (t), 82.8 (d), 68.6 (d), 51.4 (q), 50.7 (t), 40.4 (d), 7.3 (q). IR (neat): 1738 cm^{-1} . Anal.: Found: C, 73.97; H, 7.19; N, 4.25 %; Calcd. for $\text{C}_{20}\text{H}_{23}\text{NO}_3$, C, 73.82; H, 7.12; N, 4.30 %.

Preparation of (1S,2R,3R/1R,2S,3S)-3-(2-hydroxyethylamino)-2-methyl-1,3-diphenyl-1-propanol **6:**

To a solution of **4d** (156 mg, 0.5 mmol) in THF (20 mL) was added at 0°C LiAlH_4 (55 mg, 1.5 mmol). Then the mixture was stirred at room temperature for 2 h and treated successively with MeOH (5 mL) and 2M

NaOH (20 mL). The organic layer was extracted with Et₂O (2 x 15 mL) and dried over Na₂SO₄; the solvents were eliminated under vacuum leaving behind an oil which was chromatographed (SiO₂, hexane / ethyl acetate 1:2) yielding **6** (131 mg, 92%) (Scheme 2). ¹H-NMR (300 MHz, CDCl₃): δ 0.5 (d, *J* = 7.2 Hz, 3H), 1.9 (m, 1 H), 2.5 (m, 1 H), 2.7 (m, 1 H), 3.6-4.0 (m, 3H, NH, OH), 4.1 (d, *J* = 3.0 Hz, 1H), 5.2 (d, *J* = 2.2 Hz, 1H), 7.1-7.3 (m, 10 H). ¹³C-NMR (75 MHz, CDCl₃): δ 143.2 (s), 141.1 (s), 128.4 (d), 127.9 (d), 126.9 (d), 126.6 (d), 126.4 (d), 125.5 (d), 78.4 (d), 67.2 (d), 61.7 (t), 49.1 (t), 45.8 (d), 4.2 (q). IR (neat): 3412, 3260 cm⁻¹. Anal.: Found: C, 75.87; H, 8.20; N, 4.87 %; Calcd. for C₁₈H₂₃NO₂, C, 75.76; H, 8.12; N, 4.90 %.

General procedure for the preparation of azetidines 7:

A mixture of 1,3-aminoalcohol **4** (0.5 mmol), Et₃N (202 mg, 2 mmol) and DMAP (6.1 mg, 0.05 mmol) in CH₂Cl₂ (20 mL) was treated at 0°C with CF₃SO₂Cl (337 mg, 2 mmol); after stirring for 2 h the resulting mixture was hydrolyzed with saturated NaHCO₃ (15 mL), extracted with CH₂Cl₂ (3 x 20 mL), washed with H₂O and dried over Na₂SO₄. After removing the solvents, Et₂O (5 mL) was added to the residue and the solid filtered off; the filtrate was concentrated and chromatographed (SiO₂, hexane / ethyl acetate 4:1) to afford pure azetidines **7** (Table 2, Scheme 3).

(2R,3R,4R/2S,3S,4S)-1-Ethoxycarbonylmethyl-3-methyl-2,4-diphenylazetidine 7a

¹H-NMR (300 MHz, CDCl₃): δ 0.95 (d, *J* = 7.3 Hz, 3H), 1.05 (t, *J* = 7.3 Hz, 3H), 3.0 (m, 1H), 3.1 (s, 2H), 3.9 (q, *J* = 7.3 Hz, 2H), 4.5 (d, *J* = 4.3 Hz, 1H), 4.95 (d, *J* = 8.6 Hz, 1H), 7.2-7.5 (m, 10H). ¹³C-NMR (75 MHz, CDCl₃): δ 170.9 (s), 139.6 (s), 138.9 (s), 128.6 (d), 128.4 (d), 128.0 (d), 127.9 (d), 127.7 (d), 127.0 (d), 72.5 (d), 68.9 (d), 60.1 (t), 51.1 (t), 39.0 (d), 15.0 (q), 13.9 (q). IR (neat): 1740 cm⁻¹. Anal.: Found: C, 77.53; H, 7.40; N, 4.49 %; Calcd. for C₂₀H₂₃NO₂, C, 77.64; H, 7.49; N, 4.53 %. MS: *m* / *e*, 309 (M⁺, 1).

(2R,3R,4R/2S,3S,4S)-1-Ethoxycarbonylmethyl-2-furyl-4-(4-methoxyphenyl)-3-methylazetidine 7b

¹H-NMR (300 MHz, CDCl₃): δ 1.0 (d, *J* = 7.2 Hz, 3H), 1.1 (t, *J* = 7.0 Hz, 3H), 3.0 (m, 1H), 3.2 (s, 2H), 3.8 (s, 3H), 4.0 (q, *J* = 7.0 Hz, 2H), 4.4 (d, *J* = 6.5 Hz, 1H), 5.0 (d, *J* = 8.1 Hz, 1H), 6.4 (m, 2H), 6.9 (d, *J* = 9.6 Hz, 2H), 7.4 (d, *J* = 9.6 Hz, 2H), 7.5 (m, 1H). ¹³C-NMR (75 MHz, CDCl₃): δ 170.4 (s), 158.8 (s), 152.9 (s), 142.5 (d), 133.2 (s), 127.9 (d), 113.3 (d), 111.3 (d), 109.8 (d), 74.0 (d), 61.5 (d), 59.9 (t), 54.8 (q), 51.5 (t), 41.5 (d), 13.6 (q), 12.8 (q). IR (neat): 1738 cm⁻¹. Anal.: Found: C, 69.35; H, 7.11; N, 4.22 %; Calcd. for C₁₉H₂₃NO₄, C, 69.28; H, 7.04; N, 4.25 %.

(2R,4R/2S,4S)-1-Ethoxycarbonylmethyl-2,4-diphenylazetidine 7c

¹H-NMR (300 MHz, CDCl₃): δ 1.0 (t, *J* = 7.3 Hz, 3H), 2.75 (t, *J* = 6.9 Hz, 2H), 2.9 (d, *J* = 16.8 Hz, 1H), 2.95 (d, *J* = 16.8 Hz, 1H), 3.9 (q, *J* = 7.3 Hz, 2H), 4.9 (t, *J* = 6.9 Hz, 2H), 7.2-7.6 (m, 10H). ¹³C-NMR (75 MHz, CDCl₃): δ 170.8 (s), 140.7 (s), 128.3 (d), 127.8 (d), 127.6 (d), 65.6 (d), 60.2 (t), 52.1 (t), 34.3 (t), 13.9 (q). IR (neat): 1740 cm⁻¹. Anal.: Found: C, 77.32; H, 7.21; N, 4.73 %; Calcd. for C₁₉H₂₁NO₂, C, 77.26; H, 7.17; N, 4.74 %.

Preparation of (2R,3R,4R/2S,3S,4S)-1-(2-hydroxyethyl)-3-methyl-2,4-diphenylazetidine 8:

To a solution of **7a** (154 mg, 0.5 mmol) in THF (15 mL) was added at 0°C LiAlH₄ (55 mg, 1.5 mmol). Then the mixture was stirred at room temperature for 2 h and treated successively with MeOH (5 mL) and 2M NaOH (20 mL). The organic layer was extracted with Et₂O (2 x 15 mL) and dried over Na₂SO₄; the solvents

were eliminated under vacuum leaving behind pure azetidine **8** (121 mg, 91%) (Scheme 3). ¹H-NMR (300 MHz, CDCl₃): δ 0.85 (d, *J* = 7.1 Hz, 3H), 2.4-2.5 (m, 2H), 2.8-3.0 (m, 1H), 3.1-3.2 (m, 2H), 3.5-3.7 (br, OH), 4.3 (d, *J* = 4.7 Hz, 1H), 4.8 (d, *J* = 8.6 Hz, 1H), 7.1-7.4 (m, 10H). ¹³C-NMR (75 MHz, CDCl₃): δ 140.5 (s), 139.2 (s), 128.4 (d), 128.2 (d), 128.0 (d), 127.9 (d), 127.6 (d), 127.0 (d), 72.7 (d), 69.1 (d), 59.5 (t), 51.7 (t), 39.2 (d), 14.9 (q). IR (neat): 3380 cm⁻¹. Anal.: Found: C, 80.94; H, 7.99; N, 5.29 %; Calcd. for C₁₈H₂₁NO, C, 80.86; H, 7.92; N, 5.24 %. MS: *m/e*, 267 (M⁺, 2).

Preparation of (2*R*,3*R*,4*R*/2*S*,3*S*,4*S*)-3-methyl-2,4-diphenylazetidine **9:**

A solution of **7a** (154 mg, 0.5 mmol) in THF (20 mL) was cooled to -78°C and a THF solution of NaN(SiMe₃)₂ (1M, 0.75 mL, 0.75 mmol) and HMPA (358 mg, 2 mmol) added. The mixture was allowed to reach -55°C for 2 h, MoO₅.py.HMPA (868 mg, 2 mmol) added and the resulting solution stirred at -45°C for 1.5 h. The mixture was treated with aqueous Na₂SO₃, acidified with 1M H₂SO₄ and the organic layer discarded. The aqueous layer was made basic with 2N NaOH, extracted with Et₂O (2 x 20 mL), washed with H₂O and dried over Na₂SO₄. The solvents were removed under reduced pressure to give pure azetidine **9** (100 mg, 90%) (Scheme 3). ¹H-NMR (300 MHz, CDCl₃): δ 0.7 (d, *J* = 7.0 Hz, 3H), 2.2-2.8 (br, NH), 3.0 (m, 1H), 4.5 (d, *J* = 6.7 Hz, 1H), 5.0 (d, *J* = 8.6 Hz, 1H), 7.2-7.6 (m, 10H). ¹³C-NMR (75 MHz, CDCl₃): δ 144.5 (s), 141.5 (s), 128.5 (d), 128.2 (d), 127.1 (d), 126.8 (d), 126.6 (d), 125.8 (d), 67.1 (d), 62.0 (d), 42.4 (d), 15.1 (q). IR (neat): 3443 cm⁻¹. Anal.: Found: C, 85.96; H, 7.61; N, 6.22 %; Calcd. for C₁₆H₁₇N, C, 86.06; H, 7.67; N, 6.27 %. MS: *m/e*, 223 (M⁺, 3).

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