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1,2-Oxazines as Building Blocks for Stereoselective Synthesis: Preparation of Oxygen-Substituted 1,2-Oxazines, either by Alcohol Addition or by Epoxidation, and Subsequent Hydrogenation Leading to 1,2-Amino Alcohols and Pyrrolidines

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Keywords: N,O Heterocycles / Epoxidation / Hydrogenation / Amino alcohols / 1,2-Oxazines / Proline esters

Stereodefined oxygen-substituted 1,2-oxazines were prepared by three different routes. The cycloaddition of enol ethers such as **1** with α-nitrosoalkenes generated in situ gave the heterocycles **3** and **4**. Acid-catalysed additions of alcohols to the 6*H*-1,2-oxazines **5** led to mixtures of the adducts **6** and the substitution products **7** with moderate chemoselectivity. Epoxidation of the 6*H*-1,2-oxazines **5** proceeded more efficiently and furnished the corresponding epoxides **25** and **32** in reasonable to excellent yields. It was demonstrated that the resulting oxygen-substituted 1,2-oxazines were suitable precursors for the preparation of cyclic or acyclic primary and secondary amines in racemic or enantiopure form. Hydrogenation of the 3-phenyl-substituted 1,2-oxazines **3** and **25a** and of (6*S*)- and (6*R*)-**32** preferentially furnished the 1,2-amino alcohols **15**, *rac*-**29** and (2*S*)- and (2*R*)-**29**. On the other hand, reduction of the 3-ethoxycarbonyl-substituted 1,2-oxazines **4**, **6d** and **20** led to the formation of the *N*-protected proline esters **21**–**24** in moderate yields. It was also found that the 5-methyl-6*H*-1,2-oxazine **10** was a good precursor for the propargylic ether **11**, which allowed a Pauson–Khand reaction leading to the tricyclic compounds **13** and **14**. Hydrogen peroxide converted **10** into a hydroperoxide intermediate, which was further transformed into the 1,2-oxazin-6-one **28b**. Overall, the results demonstrate the remarkable potential of suitably substituted 1,2-oxazine derivatives for the stereoselective synthesis of amines.

Introduction

Since the first systematic studies in the 1970s, the synthesis of 1,2-oxazine derivatives and their subsequent transformations into a variety of acyclic and cyclic nitrogen-containing compounds have been the subjects of constantly increasing attention.[1] This ongoing interest is also due to the occurrence of the 1,2-oxazine skeleton in natural products, such as trichodermamides A–C or penicillazine.[2] Polyhydroxylated 1,2-oxazines are particularly useful precursors in the synthesis of oxygen-substituted heterocycles of different ring sizes.[1d,3] In this context, polyhydroxylated pyrrolidine and piperidine derivatives are of great interest because of their potential biological activities – as specific glycosidase inhibitors, for example – and hence as lead compounds for novel drugs.[4] Consequently, a wide variety of methods to enable the efficient and stereoselective synthesis of 1,2-oxazine derivatives, in particular of the polyhydroxylated tetrahydro-2*H*-1,2-oxazines **A** (Figure 1), have been developed.[5] In contrast with the various syntheses and applications of oxygen-substituted 1,2-oxazines, the related 5,6-dihydro-4*H*-1,2-oxazines **B** have gained less attention.[6] To the best of our knowledge, there is only one report, from our group, systematically dealing with the *cis*-dihydroxylation of the easily accessible 6*H*-1,2-oxazines.[7] Here we describe the synthesis of stereodefined oxygen-substituted dihydro-4*H*-1,2-oxazines (type **B**), mainly through the employment of 6*H*-1,2-oxazines as ideal precursors,[8] and their subsequent transformations into synthetically useful amino alcohols and pyrrolidine derivatives.

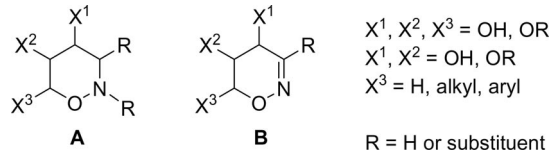

Figure 1. Substitution patterns of the tetrahydro-2*H*-1,2-oxazines **A** and the dihydro-4*H*-1,2-oxazines **B**.

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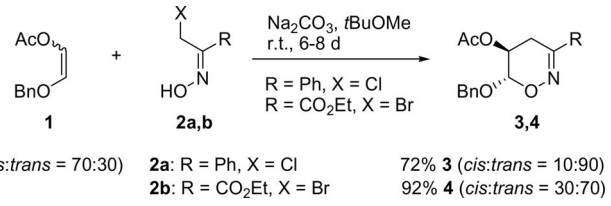
Synthesis of Oxygen-Substituted 1,2-Oxazines

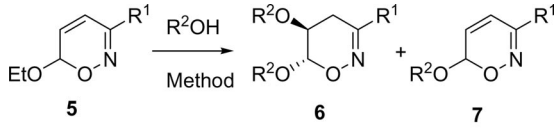
One straightforward synthesis of oxygen-substituted 1,2-oxazines would seem to be the direct approach, through hetero-Diels–Alder reactions between enediol derivatives and α-nitrosoalkenes, generated in turn from the corresponding α-haloketoximes. Despite this obvious means of access, only a few examples have been reported, with the use of symmetrical 1,2-bis-*O*-substituted olefins such as 1,2-bis(trimethylsiloxy)ethene.[9] An alternative good dienophile candidate in such cycloadditions would be 1-acetoxy-2-(benzyloxy)ethene (**1**).[10] Treatment of the oxime **2a** with **1** in excess (*cis*/*trans* = 70:30) under typical reaction conditions exclusively furnished 5-acetoxy-6-benzyloxy-4*H*-1,2-oxazine (**3**) in good yield (Scheme 1). The observed excellent *trans* selectivity was expected and consistent with previous results demonstrating that *E*-configured alkenes generally react more rapidly than the corresponding *Z*-configured alkenes with α-nitrosoalkenes generated in situ.[11] The reaction between the pyruvate oxime **2b** and the olefin **1** afforded the corresponding 4*H*-1,2-oxazine **4** in excellent yield but with lower *trans*/*cis* selectivity. This result shows that the α-nitrosoalkene derived from **2b** is significantly more reactive than that generated from **2a**, as also already observed in previous studies with **2b** as a heterodiene precursor.[11] Nevertheless, this direct route to oxygen-functionalized 1,2-oxazines suffers from the restriction that no substituent can be installed at C–4.



Scheme 1. Synthesis of the oxygen-substituted 1,2-oxazines **3** and **4** through hetero-Diels–Alder reactions.

We next focused our efforts on a two-step route to oxygen-functionalized 1,2-oxazines. Encouraged by our previously published synthetic applications of the 6*H*-1,2-oxazines **5**,[12] we chose these heterocycles as reliable starting materials for addition reactions to the C-4,C-5 double bond. We first examined additions of alcohols to the double bonds of compounds **5** (Table 1). The heterocycles **5a** and **5b** were each treated with catalytic amounts of sulfuric acid in various alcohols R^2OH at room temperature (Table 1, Entries 1–4). In general, mixtures of the desired addition products **6a**–**6d** and the transacetalization products **7a**–**7c** were formed, and in some cases the mixtures could be separated by fractional distillation (**6a**/**7a**) or by chromatography (**6b**/**7b**). In all products **6a**–**6d** the 6-ethoxy group had been replaced by the 6-OR^2 group, which indicates that the exchange at the 6-position is faster than the addition of the alcohol to the C,C-double bond.[13] The isolation of the 6*H*-1,2-oxazines **7** also indicates that the exchange at the 6-position is faster than the addition of the corresponding alcohol to the C,C-double bond.

Table 1. Addition reactions of alcohols R^2OH to 6*H*-1,2-oxazines.



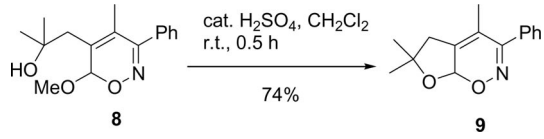
Method A: concd. H_2SO_4 (cat), R^2OH, r.t.
Method B: 8N NaOH, R^2OH, THF, r.t.

Entry[a]	5	R^1	R^2	6	% Yield[b]	7 or 5	% Yield
1	**5a**	Ph	Me	**6a**	73	**7a**	13
2	**5a**	Ph	$CH_2C{\equiv}CH$	**6b**	62	**7b**	27
3	**5a**	Ph	Bn	**6c**	19 (34:66)	**7c**	46
4	**5b**	CO_2Et	Et	**6d**	57 (13:87)	**5b**	17
5	**5a**	Ph	Me	**6a**	44 (43:57)[c]		[c]

[a] Entries 1–4: Method A; Entry 5: Method B. [b] *cis*/*trans* ratio given in brackets. [c] Calculated yield; mixture of **5a** and *trans*-**6a**.

The 5,6-dihydro-4*H*-1,2-oxazines **6** were obtained either as single *trans* diastereomers (Entries 1 and 2) or predominantly with *trans* configurations (Entries 3 and 4). Taking into account that the addition of R^2OH to **5** is a reversible process, we also changed the reaction conditions. When the reaction of **5b** in ethanol was performed at high pressure (6–13 kbar) and with prolonged reaction times (1–7 d), better product to precursor ratios (up to 87:13) could be achieved but the yields were significantly lower.[14] Finally, an attempt to add methanol to **5a** under basic conditions (Method B) resulted in incomplete conversion and only an inseparable mixture of **5a** and **6a** (ca. 1:1) was obtained (Entry 5).

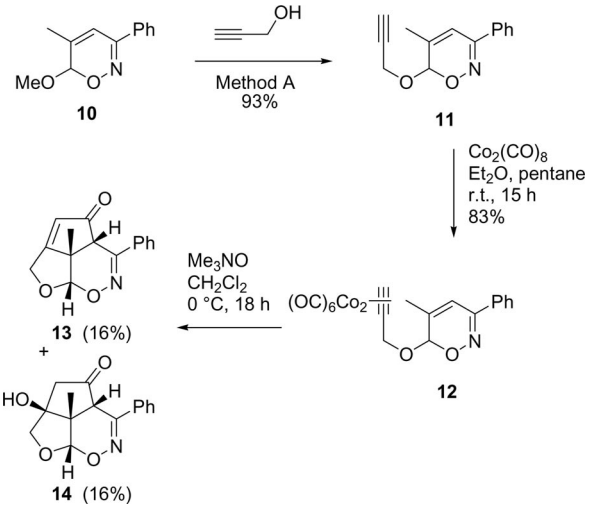
An interesting intramolecular version of the alkoxy exchange reaction by Method A was observed with the easily accessible 6*H*-1,2-oxazine **8**[15] (Scheme 2). Treatment of **8** with a catalytic amount of sulfuric acid in dichloromethane at room temperature furnished the bicyclic product **9** in 74% yield.



Scheme 2. Intramolecular acetal formation leading to the bicyclic 6*H*-1,2-oxazine derivative **9**.

When the 5-methyl-6*H*-1,2-oxazine **10**[8a] (Scheme 3) was treated with a catalytic amount of sulfuric acid in propargyl alcohol (Method A), we could not achieve the addition of the alcohol to the C=C double bond but we did observe a clean transacetalization, forming the 6-propargyloxy-substituted 1,2-oxazine **11** in excellent yield. This reaction outcome is clearly due to the 5-methyl group, which hampers the 1,4-addition of the alcohol. Compound **11**, bearing C≡C and C=C units, is an interesting candidate for further synthetic manipulation such as the Pauson–Khand reaction.[16] The addition of $Co_2(CO)_8$ to the triple bond in **11** cleanly furnished the expected cobalt complex **12** in high yield. A subsequent Pauson–Khand reaction was carried

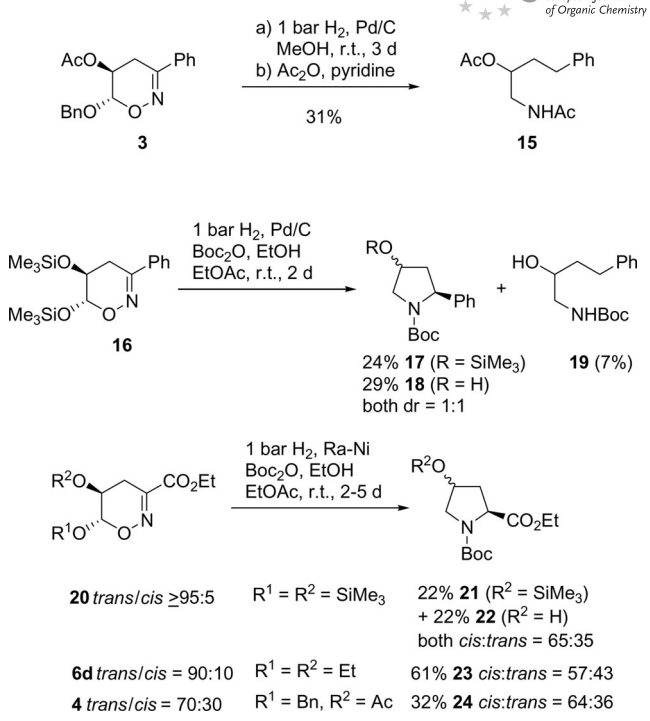
out by treatment of **12** with trimethylamine *N*-oxide at 0 °C[16e] and afforded the expected tricyclic heterocycle **13** as a single diastereomer together with compound **14**, both in low yields. The formation of **14** probably occurs during workup with dilute HCl solution through addition of water to the α,β-unsaturated precursor **13**. We do not have unambiguous proof of the given relative configurations of **13** and **14**, but the depicted structures should be most likely, due to the considerably higher strain of alternative isomers.



Scheme 3. Formation of the 6*H*-1,2-oxazine **11** by transacetalization and subsequent Pauson–Khand reaction.

Hydrogenations of Oxygen-Substituted 1,2-Oxazines

The most commonly employed subsequent transformations of 1,2-oxazines involve palladium- and nickel-catalysed hydrogenations, leading to acyclic and cyclic nitrogen-containing products. The outcome of these reactions strongly depends on the substitution pattern of the substrates.[17] In order to address the role of the C-5 oxygen substituent, the ring cleavage was examined with the 3-phenyl-substituted 1,2-oxazines **3** and **16** (Scheme 4),[9a] as well as with the 3-ethoxycarbonyl-substituted compounds **4**, **6d** and **20**. Treatment of **3** with hydrogen in the presence of palladium on charcoal and subsequent acetylation furnished the ring-opened product **15** in low yield (31%). Subsequent acetylation to afford the *N*,*O*-bisacetylated product was necessary because the primary hydrogenated product was obtained as a mixture of *N*- and *O*-monoacetylated 1,2-amino alcohols as a result of a partial O-to-N acetyl shift. In contrast, we were not able to convert the 3-phenyl-5,6-bis(trimethylsiloxy)-substituted 4*H*-1,2-oxazine **16** completely into the corresponding 1,2-amino alcohol. The hydrogenation of this compound in the presence of Boc anhydride led to a mixture of the *O*-silylated pyrrolidine **17**, its desilylated derivative **18** as main component and the amino alcohol **19** as by-product (7%). The obtained products could easily be separated by column chromatography on alumina.



Scheme 4. Palladium-catalysed hydrogenations of 3-phenyl- and 3-ethoxycarbonyl-substituted 4*H*-1,2-oxazines.

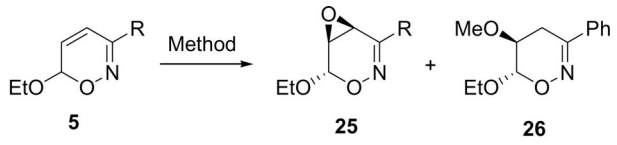
We then examined the reductive ring-contraction of the *trans*-enriched ethoxycarbonyl-substituted 4*H*-1,2-oxazines **4**, **6d** and **20** (Scheme 4). Hydrogenation of these compounds in the presence of Raney nickel and Boc anhydride exclusively produced the hydroxyproline derivatives **21**–**24** in moderate to good yields, but with low diastereoselectivity. The low stereocontrol is not surprising in view of related previous results.[7a,17b,17e] Like the bis(siloxy)-substituted 1,2-oxazine **16** the 3-ethoxycarbonyl-substituted analogue **20** also underwent a partial desilylation leading to the proline esters **21** and **22**, both in a *cis*/*trans* ratio close to 2:1. It should be mentioned that the hydrogenation of the 4*H*-1,2-oxazine **4** was also carried out under high-pressure conditions (50 bar), but the yield and the *cis*/*trans* ratio were very similar to those observed under atmospheric pressure.[14]

Epoxidations of 6*H*-1,2-Oxazines

In our search for alternative procedures suitable for functionalization of the C=C bond of 6*H*-1,2-oxazines we examined epoxidation methods. The results are compiled in Table 2. Because the double bond in a 6*H*-1,2-oxazine is moderately electron-deficient we first applied a typical epoxidation protocol by treating the 3-phenyl-substituted precursor **5a** with hydrogen peroxide and aqueous NaOH (8 N) in a methanol/THF mixture (3:1) at 0 °C. This procedure gave the epoxide **25a** and the methanol adduct **26** as a ca. 1:1 mixture in moderate yield (Entry 1, Method A). To overcome the competing alcohol addition, we modified the conditions and avoided the use of methanol as solvent.

When the epoxidation was performed with *tert*-butyl hydroperoxide and DBU in dichloromethane[18] the reaction proceeded chemoselectively and the desired epoxides **25a**–**25d** could be obtained in moderate to good yields (Entries 2–5, Method B). The best results for the epoxidation of the 3-aryl-substituted 6*H*-1,2-oxazines **5a** and **5c** were obtained by a protocol developed by Yadav and Kapoor with *tert*-butyl hydroperoxide in the presence of KF on alumina in acetonitrile (Entries 6 and 8).[19] In contrast, the 3-ethoxycarbonyl- or 3-trifluoromethyl-substituted 1,2-oxazines **5b** and **5d** did not undergo epoxidation when exposed to the conditions of Method C, leading either to no reaction or to complete decomposition (Entries 7 and 9). Finally, Method C was also suitable for the epoxidation of the 6*H*-1,2-oxazine **5e** with a (diethoxy)methyl group at C-3 (Entry 10). It should be noted that very high (here exclusive) *trans* selectivity of the addition reaction was again observed. The axially orientated 6-alkoxy groups in 1,2-oxazines such as **5** strongly steer the incoming reagent to the opposite face of the heterocyclic core, as also observed in several previously studied addition reactions.[5d,6b,7b,20]

Table 2. Epoxidation of the 6*H*-1,2-oxazines **5**.



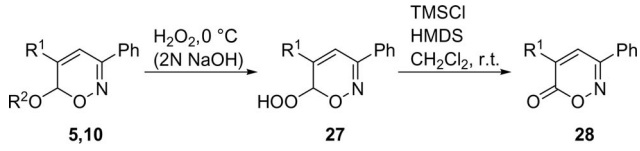
5 **25** **26**

Method A: H_2O_2, 8N NaOH, MeOH/THF, 0 °C
Method B: *t*BuOOH, DBU, CH_2Cl_2, r.t.
Method C: *t*BuOOH, KF-Al_2O_3, MeCN, r.t.

Entry	5	R	Method	25	% Yield
1	**5a**	Ph	A	**25a**	39[a]
2	**5a**	Ph	B	**25a**	71
3	**5b**	CO_2Et	B	**25b**	48[b]
4	**5c**	3-$CF_3C_6H_4$	B	**25c**	67
5	**5d**	CF_3	B	**25d**	24
6	**5a**	Ph	C	**25a**	91
7	**5b**	CO_2Et	C	**25b**	0
8	**5c**	3-$CF_3C_6H_4$	C	**25c**	70
9	**5d**	CF_3	C	**25d**	[c]
10	**5e**	$CH(OEt)_2$	C	**25e**	52[d]

[a] Mixture of **25a**/**26** 54:46. [b] Crude product. [c] Decomposition. [d] In addition, **5e** (19%) was recovered.

Remarkably, the reaction outcome was completely changed when we applied hydrogen peroxide as in Method A, but without NaOH (8 N). Instead of the epoxides **25** we obtained the 6-hydroperoxy-substituted 6*H*-1,2-oxazines **27a** and **27b** (Scheme 5) as the only products and in good yields. When the reaction of **10** was performed in the presence of dilute NaOH solution (2 N) a better yield was obtained for **27b**. The hydroperoxide intermediates **27** underwent subsequent dehydration on treatment with trimethylsilyl chloride and hexamethyldisilazene in dichloromethane at room temperature, furnishing the 6*H*-1,2-oxazin-6-ones **28a** and **28b** in 54–79% yields. Overall, oxidation of 1,2-oxazines at C-6 has thus been achieved. 6*H*-1,2-Oxazin-6-ones are versatile compounds that can be converted into γ-amino acids or into γ-keto carboxylic acids. It has already demonstrated with **28b** that the outcomes of palladium-catalysed hydrogenation of this compound strongly depend on the solvent.[17c]



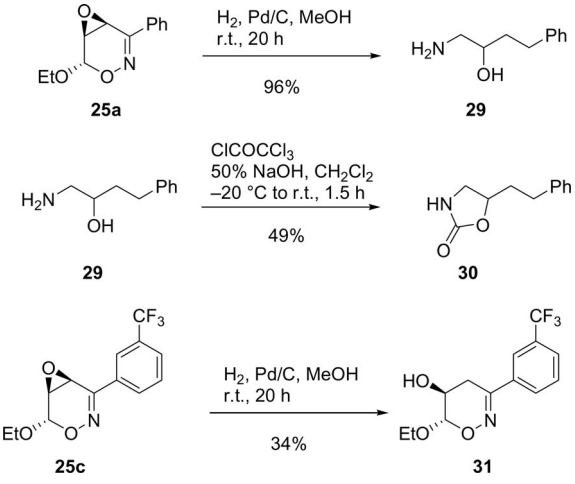
5,10 **27** **28**

5a: R^1 = H, R^2 = Et:[a] 59% **27a** 54% **28a**
10: R^1 = R^2 = Me:[a] 58% **27b** 79% **28b**
10: R^1 = R^2 = Me:[b] 73% **27b**
[a] without NaOH; [b] with NaOH.

Scheme 5. Synthesis of the 6*H*-1,2-oxazin-6-ones **28**.

Hydrogenations of Epoxides

The hydrogenation of the epoxide **25a** (Scheme 6) proceeded cleanly and resulted in regioselective formation of the 1,2-amino alcohol **29** in excellent yield. The outcome of this reduction could be confirmed by conversion of **29** into compound **30** in 49% yield on treatment with diphosgene. The NMR spectroscopic data for **30** are in agreement with an oxazolidin-2-one structure and not with a conceivable six-membered heterocycle derived from a 1,3-amino alcohol.

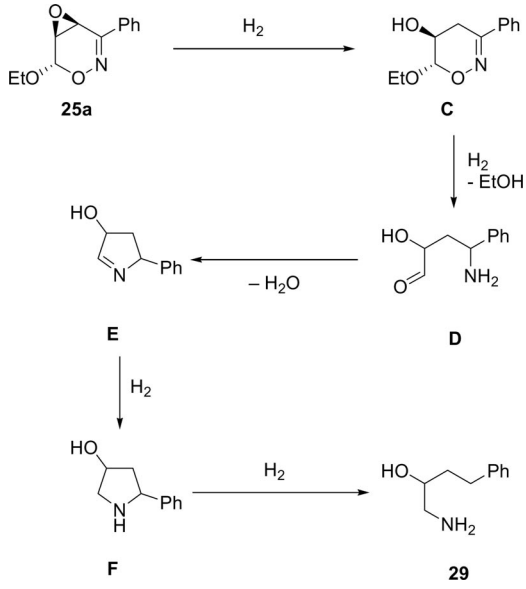


25a **29** **30** **25c** **31**

Scheme 6. Catalytic hydrogenation of the epoxides **25a** and **25c**.

When the epoxide **25c** (Scheme 6) was subjected to the catalytic hydrogenation protocol, we were able to isolate the *trans*-configured 5-hydroxy-substituted 1,2-oxazine derivative **31** as a single diastereomer in moderate yield. Currently it is not clear why the change from **25a** to **25c** (Ph vs. the more electron-deficient *m*-CF_3-C_6H_4) considerably slowed down the reduction steps. Nevertheless, the isolation of a primary reduction product such as **31** provides additional evidence for the proposed mechanistic pathway involving a regioselective ring-opening of the epoxide moiety (see below).

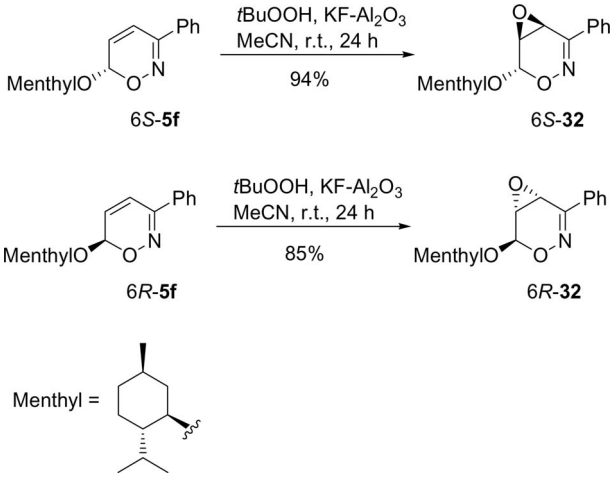
A plausible mechanism for the formation of 1,2-amino alcohols is illustrated in Scheme 7. The first step probably involves the regioselective reduction of the epoxide unit of **25a** to provide compound **C**.[21] Subsequent reductive cleavage of the N–O bond followed by the reduction of the C=N bond leads to the intermediate **D**. Ring closure of **D** and subsequent water elimination to give the cyclic imine **E**, followed by reduction of the C=N unit and finally by reductive cleavage of the benzylic bond of the pyrrolidine **F**, furnish the isolated 1,2-amino alcohol **29**.



Scheme 7. Plausible mechanism for the conversion of the epoxide **25a** into the 1,2-amino alcohol **29**.

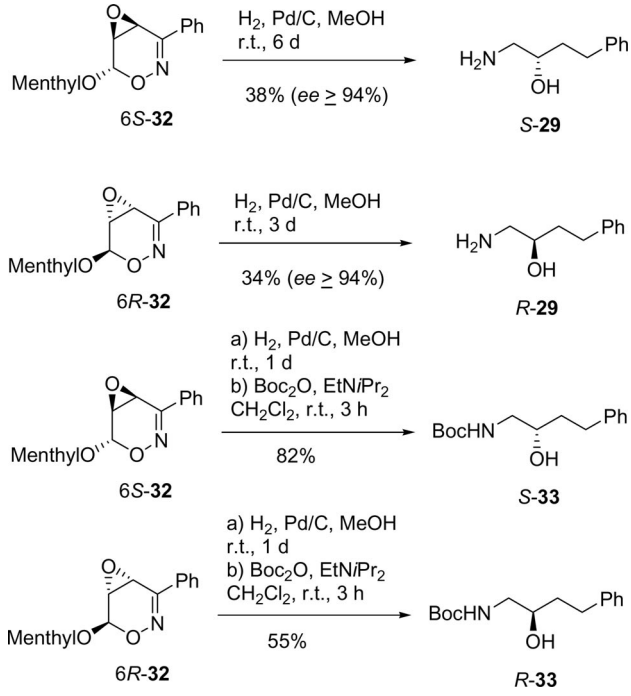
Synthesis of Enantiopure Compounds

The easily accessible enantiopure 6-menthyloxy-substituted 6*H*-1,2-oxazines (6*S*)-**5f** and (6*R*)-**5f**[22] (Scheme 8) also served as suitable substrates for the optimized epoxidation protocol (Method C) described above. The reactions again proceeded with excellent degrees of diastereoselectivity, providing the expected epoxides (6*S*)-**32** and (6*R*)-**32** as single diastereomers and in very good yields. Unlike in the case of Method C, epoxidations of (6*S*)-**5f** or (6*R*)-**5f** by Method B afforded the expected products only in moderate yields (32–42%).



Scheme 8. Epoxidation of the enantiopure 6-menthyloxy-substituted 6*H*-1,2-oxazines **5f**.

Subsequent catalytic hydrogenation of the epoxides (6*S*)-**32** and (6*R*)-**32** with palladium on charcoal led to the expected 1,2-amino alcohols (*S*)-**29** and (*R*)-**29** (Scheme 9) in moderate yields but with excellent enantiomeric excesses (≥94%).[23] The levels of conversion in these hydrogenations were high, but the yields suffered from inefficient purification caused by difficulties in completely removing liberated menthol from the products. This problem could be solved by converting the crude amino alcohols directly into their *N*-Boc-protected derivatives. Under these conditions the hydrogenation of (6*S*)-**32** and (6*R*)-**32** provided (2*S*)-**33** and (2*R*)-**33**, respectively, in good overall yields. The measured optical rotation of (2*S*)-**33** is almost identical to the already known value, thus confirming the high optical purity of the compound.[26]



Scheme 9. Reductive ring opening of enantiopure 1,2-oxazines **32**.

Reductive cleavage of epoxy-1,2-oxazines is just one option for use of these polyfunctionalized heterocycles. Ring opening by attack of nucleophiles followed by transformations of the oxime ether and acetal groups would certainly lead to more complex compounds, either in racemic or in enantioenriched form.

Conclusions

We have presented three different approaches for the synthesis of stereodefined oxygen-substituted 1,2-oxazines:

a) direct synthesis through cycloadditions between α-nitrosoalkenes and appropriate electron-rich olefins such as **1**, b) acid-catalysed additions of various alcohols to the 6*H*-1,2-oxazines **5**, which often led to mixtures of the addition products **6** and the substitution products **7** with moderate chemoselectivities, and c) the efficient epoxidation of the 6*H*-1,2-oxazines **5** which afforded the epoxides **25** in moderate to excellent yields. Reactions of 5-methyl-substituted 6*H*-1,2-oxazine **10** often resulted in different outcomes, leading to products such as **11**, **13** or **28**. Furthermore, we have successfully demonstrated that oxygen-substituted 1,2-oxazines such as **3**, **4**, **6**, **16**, **20**, **25** and **32** are useful key compounds that can be converted into 1,2-amino alcohols and hydroxyproline derivatives. The developed epoxidation/ring-cleavage sequence leading to 1,2-amino alcohols was successfully expanded to the synthesis of optically pure substrates such as (6*S*)- and (6*R*)-**32**, hence smoothly allowing the preparation of enantiopure 1,2-amino alcohols.

Experimental Section

General: Unless otherwise stated all reactions were performed under argon in flame-dried flasks with addition of the components by syringe. All solvents were dried by standard procedures. ^{1}H and ^{13}C NMR spectra were recorded with Bruker instruments (AC 500, AC 300, WH 270, AC 250) in $CDCl_3$ or C_6D_6. The chemical shifts are given relative to the TMS or to the $CDCl_3$ signal (δ_H = 7.27 ppm, δ_C = 77.0 ppm). Higher-order NMR spectra were approximately interpreted as first-order spectra if possible. Missing signals of minor isomers were either hidden by signals of major isomers or could not be unambiguously identified due to low intensity. IR spectra were measured with a Nicolet 5 SXC FT-IR spectrometer. The MS and HRMS spectra were recorded with a Varian MAT 711 instrument. Neutral aluminium oxide (activity III, Fluka/Merck) or silica gel (0.040–0.063 mm, Fluka) were used for column chromatography. Nucleosil 50-5 (Macherey–Nagel) was used for HPLC. Melting points (uncorrected) were measured with a Thermovar melting point microscope from Reichert. Optical rotations were determined with a Perkin–Elmer 241 polarimeter. The starting materials **1**,[10] **2a** and **2b**,[24] **5a**–**d**,[8c] **5e**,[12b] **5f**,[22] **10**[8a] and **16**[9a] were prepared by literature procedures. All other chemicals were commercially available and were used as received.

Hetero Diels–Alder Reaction. General Procedure 1 (GP 1): Freshly ground Na_2CO_3 (6 equiv.) was added to a solution of 1-acetoxy-2-(benzyloxy)ethene (**1**, 5.3–5.7 equiv.) and the corresponding α-halo ketoxime **2** (1 equiv.) in MeO*t*Bu (20 mL/mmol **1**). After the system had been stirred at room temp. for the time indicated under the individual reaction, the suspension was filtered through a pad of Celite to remove inorganic salts. The resulting filtrate was concentrated in vacuo and the residue was purified by column chromatography.

5-Acetoxy-6-(benzyloxy)-3-phenyl-5,6-dihydro-4*H*-1,2-oxazine (3): A mixture of the oxime **2a** (0.680 g, 4.01 mmol), the alkene **1** (4.97 g, 21.0 mmol, *cis*/*trans* = 70:30) and Na_2CO_3 (2.54 g, 24.0 mmol) in MeO*t*Bu (80 mL) was stirred for 8 d as described in GP 1. The resulting crude product was purified by column chromatography (alumina, hexane/EtOAc, 4:1) to give the 5-acetoxy-4*H*-1,2-oxazine **3** (0.940 g, 72%, *cis*/*trans* = 10:90) as a colourless oil. *trans*-**3**: ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.07 (s, 3 H, CH_3), 2.64 (dd, J = 1.0, 18.4 Hz, 1 H, 4-H), 2.97 (dd, J = 5.3, 18.4 Hz, 1 H, 4-H), 4.69, 4.88 (2 × d, J = 11.7 Hz, 1 H each, CH_2Ph), 5.12–5.21 (m, 2 H, 5-H, 6-H), 7.27–7.34, 7.37–7.44 (2 × m, 8 H, Ph), 7.69–7.74 (m, 2 H, Ph) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 21.0 (q, CH_3), 23.0 (t, C-4), 63.2 (d, C-5), 69.6 (t, *C*H_2Ph), 92.8 (d, C-6), 125.4, 128.0, 128.1, 128.5, 128.6, 130.0, 135.2, 136.7 (6 × d, 2 × s, Ph), 154.2 (s, C-3), 170.3 (s, C=O) ppm. Additional signals for *cis*-**3**: ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.12 (s, 3 H, CH_3), 5.31–5.32 (m, 2 H, 5-H, 6-H) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 20.9 (q, CH_3), 65.3 (d, C-5), 69.5 (t, *C*H_2Ph), 92.9 (d, C-6), 125.6, 127.9, 128.4, 130.1, 137.0 (4 × d, s, Ph), 155.3 (s, C-3), 170.2 (s, C=O) ppm. *cis*/*trans*-**3**: IR (neat): $\tilde{\nu}$ = 3085–2880 (=C–H, C–H), 1740 (C=O), 1610 (C=N) cm^{-1}. $C_{19}H_{19}NO_4$ (325.4): calcd. C 70.14, H 5.89, N 4.31; found C 69.79, H 6.01, N 4.60.

Ethyl 5-Acetoxy-6-(benzyloxy)-5,6-dihydro-4*H*-1,2-oxazine-3-carboxylate (4): A mixture of the oxime **2b** (0.630 g, 3.00 mmol), the alkene **1** (3.26 g, 17.0 mmol, *cis*/*trans* = 70:30), and Na_2CO_3 (1.91 g, 18.0 mmol) in MeO*t*Bu (60 mL) was stirred for 6 d as described in GP 1. The resulting crude product was purified by column chromatography (alumina, hexane/EtOAc, 4:1) to give the 5-acetoxy-4*H*-1,2-oxazine **4** (0.887 g, 92%, *cis*/*trans* = 30:70) as a colourless oil. *trans*-**4**: ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.35 (t, J = 7 Hz, 3 H, CH_3), 2.05 (s, 3 H, CH_3), 2.66–2.68 (m, 2 H, 4-H), 4.32–4.39 (m, 2 H, CH_2O), 4.66, 4.85 (2 × d, J = 11.7 Hz, 1 H each, CH_2Ph), 5.11–5.14 (m, 1 H, 5-H), 5.18 (d, J = 2.4 Hz, 1 H, 6-H), 7.30–7.39 (m, 5 H, Ph) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 14.1 (q, CH_3), 20.8 (q, CH_3), 21.9 (t, C-4), 62.2 (t, CH_2O), 61.9 (d, C-5), 70.1 (t, *C*H_2Ph), 93.2 (d, C-6), 128.1, 128.2, 128.5, 136.1 (3 × d, s, Ph), 149.3 (s, C-3), 162.8, 169.9 (2 × s, C=O) ppm. Additional signals for *cis*-**4**: ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.41 (t, J = 7 Hz, 3 H, CH_3), 2.09 (s, 3 H, CH_3), 2.62, 2.93 (2 × dd, J = 7.0, 18.4 Hz, 1 H each, 4-H), 4.67, 4.87 (2 × d, J = 11.7 Hz, 2 H each, CH_2Ph), 4.94–5.01 (m, 1 H, 5-H), 5.32 (d, J = 2.8 Hz, 1 H, 6-H) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 20.7 (q, CH_3), 23.2 (t, C-4), 62.3 (t, CH_2O), 64.0 (d, C-5), 70.0 (t, *C*H_2Ph), 93.4 (d, C-6), 127.9, 128.4, 136.4 (2 × d, s, Ph), 150.1 (s, C-3), 162.2 (s, C=O) ppm. *cis*/*trans*-**4**: IR (neat): $\tilde{\nu}$ = 3065–2880 (=C–H, C–H), 1745, 1720 (C=O), 1605 (C=N) cm^{-1}. $C_{16}H_{19}NO_6$ (321.3): calcd. C 59.81, H 5.96, N 4.36; found C 60.33, H 6.04, N 4.52.

Treatment of 6*H*-1,2-Oxazines with Alcohol in the Presence of Sulfuric Acid. General Procedure 2 (GP 2): Concd. H_2SO_4 (1 drop/mmol of **5**) was added to a solution of the 6*H*-1,2-oxazine **5** in the corresponding alcohol (5 mL/mmol of **5**) and the mixture was stirred at room temp. for the time indicated in the individual experiment. The solution was then neutralized with solid $NaHCO_3$, the alcohol was removed in vacuo, and the residue was dissolved in *t*BuOMe and filtered. The crude product was purified either by kugelrohr distillation or by column chromatography.

***trans*-5,6-Dimethoxy-3-phenyl-5,6-dihydro-4*H*-1,2-oxazine (6a):** The 6*H*-1,2-oxazine **5a** (0.406 g, 2.00 mmol) dissolved in MeOH (10 mL) was treated with concd. H_2SO_4 for 4 h at room temp. as described in GP 2. The resulting crude product was purified by kugelrohr distillation: the first fraction (110 °C/0.02 mbar) gave a mixture of **6a** and **7a** (2:1, 0.128 g) and the second fraction (120 °C/0.01 mbar) gave pure **6a** (0.246 g, 56%) as a colourless oil, which slowly crystallized (m.p. 53–55 °C). Calculated yields: 73% (**6a**) and 13% (**7a**). 5,6-*trans*-Configured 4*H*-1,2-oxazine **6a**: ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.60 (dd, J = 2.5, 18 Hz, 1 H, 4-H_{eq}), 2.77 (dd, J = 5, 18 Hz, 1 H, 4-H_{ax}), 3.45, 3.51 (2 × s, 3 H each, OCH_3), 3.68 (m_c, 1 H, 5-H), 4.98 (d, J = 2.5 Hz, 1 H, 6-H), 7.35–7.39, 7.67–7.72 (2 × m, 3 H, 2 H, Ph) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 23.4 (t, C-4), 55.9, 57.1 (2 × q, OCH_3), 70.5 (d, C-5), 96.2 (d, C-

6), 125.6, 128.2, 129.8, 135.8 (3 × d, s, Ph), 155.0 (s, C-3) ppm. IR (neat): ṽ = 3200–2720 (=C–H, C–H), 1575 (C=N) cm^{-1}. $C_{12}H_{15}NO_3$ (221.3): calcd. C 65.14, H 6.83, N 6.33; found C 65.09, H 6.84, N 6.31. Additional spectroscopic data for 6-methoxy-3-phenyl-6*H*-1,2-oxazine (**7a**): ^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.48 (s, 3 H, OCH_3), 5.49 (d, *J* = 4.5 Hz, 1 H, 6-H), 6.39 (dd, *J* = 4.5, 10 Hz, 1 H, 5-H), 6.58 (d, *J* = 10 Hz, 1 H, 4-H) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 55.8 (q, OCH_3), 93.2 (d, C-6), 116.3 (d, C-4), 126.1, 125.6, 128.6, 130.1, 133.9 (4 × d, s, Ph, C-5), 154.3 (s, C-3) ppm.

5-Methyl-3-phenyl-6-(prop-2-yn-1-oxy)-6*H*-1,2-oxazine (11): The 6*H*-1,2-oxazine **10** (0.406 g, 2.00 mmol) dissolved in propargyl alcohol (10 mL) was treated with concd. H_2SO_4 for 3 h at room temp. as described in GP 2. Purification by column chromatography (alumina, hexane/EtOAc, 4:1) afforded **11** (0.420 g, 93%) as a colourless oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.09 (d, *J* = 1.4 Hz, 3 H, CH_3), 2.48 (t, *J* = 2 Hz, 1 H, ≡CH), 4.30, 4.48 (AB part of ABX system, J_{AB} = 15.4, J_{AX} = J_{BX} = 2 Hz, 2 H, 1 H each, OCH_2), 5.65 (s, 1 H, 6-H), 6.36 (q, *J* = 1.4 Hz, 1 H, 4-H), 7.36–7.47, 7.64–7.75 (2 × m, 3 H, 2 H, Ph) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 18.8 (q, CH_3), 54.6 (t, OCH_2), 75.2, 78.7 (d, s, C≡CH), 93.5 (d, C-6), 112.1 (d, C-4), 126.1, 128.5, 129.8, 133.7 (3 × d, s, Ph), 137.3 (s, C-5), 154.1 (s, C-3) ppm. IR (neat): ṽ = 3120–2780 (≡C–H, =C–H, C–H), 2115 (C≡C), 1660 (C=C), 1580 (C=N) cm^{-1}. $C_{14}H_{13}NO_2$ (227.3): calcd. C 73.99, H 5.77, N 6.16; found C 73.83, H 5.84, N 5.64.

Treatment of 11 with Octacarbonyldicobalt: The 1,2-oxazine **11** (0.227 g, 1.00 mmol) was dissolved in a diethyl ether/pentane mixture (3 mL/3 mL). After addition of $Co_2(CO)_8$ (0.342 g, 1.00 mmol), the solution was stirred for 15 h at room temp. It was then filtered through neutral alumina (hexane/EtOAc, 9:1) and the filtrate was concentrated to a third of the volume. After the solution had been kept at –10 °C, the resulting crystals were separated and dried in vacuo (0.01 mbar) to give **12** (0.428 g, 83%) as red-brown crystals, m.p. 90–91 °C. ^{1}H NMR ($CDCl_3$, 60 MHz): δ = 2.00 (m_c, 3 H, CH_3), 4.50–6.35 (m, 5 H, 4-H, 6-H, ≡CH, OCH_2), 7.45 (m_c, 5 H, Ph) ppm. IR (KBr): ṽ = 3050–2840 (≡C–H, =C–H, C–H), 2055, 2030, 1995 (C≡O), 1655 (C=C), 1560 (C=N) cm^{-1}. MS (EI, 70 eV): *m*/*z* (%) = 457 (7) $[M - 2CO]^+$, 429 (11) $[M - 3CO]^+$, 401 (1) $[M - 4CO]^+$, 373 (15) $[M - 5CO]^+$, 355 (18) $[M - 6CO]^+$, 315 (100) $[M - 6CO - NO]^+$, 143 (33) $[Co(CO)_3]^+$, 115 (15) $[Co(CO)_2]^+$, 87 (24) $[Co(CO)]^+$, 77 (30) $[Ph]^+$, 59 (60), 51 (22) $[C_4H_3]^+$. $C_{20}H_{13}Co_2NO_8$ (513.2): calcd. C 46.81, H 2.55, N 2.73; found C 46.72, H 2.58, N 2.70.

Pauson–Khand Reaction of 12: Me_3NO (0.316 g, 4.21 mmol) was added in one portion at 0 °C to a solution of the 1,2-oxazine **12** (0.216 g, 0.421 mmol) in CH_2Cl_2 (5 mL). The solution was stirred at this temperature for 18 h and then treated with HCl solution (10%, 1 mL). The separated organic phase was washed with brine (2 × 2 mL) and dried (Na_2SO_4). After removal of the solvent under reduced pressure, the residue was purified by preparative TLC (hexane/EtOAc, 4:1) to afford the tricyclic heterocycles **13** (0.017 g, 16%) as a colourless oil and **14** (0.018 g, 16%) as a colourless solid, m.p. 136–139 °C (dec.).

7b-Methyl-5-phenyl-7a,7b-dihydro-2*H*,4a*H*-1,7-dioxa-6-azacyclopenta[*cd*]inden-4-one (13): ^{1}H NMR ($CDCl_3$, 250 MHz): δ = 1.15 (s, 3 H, CH_3), 3.79 (s, 1 H, 4a-H), 4.84, 4.92 (AB system, J_{AB} = 14.6 Hz, 1 H each, 2-H), 5.09 (s, 1 H, 7a-H), 6.19 (s, 1 H, 3-H), 7.35–7.55, 7.93–8.02 (2 × m, 3 H, 2 H, Ph) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 20.8 (q, CH_3), 53.9 (d, C-4a), 54.6 (s, C-7b), 65.3 (t, C-2), 100.7 (d, C-7a), 126.5 (d, C-3), 127.3, 128.5, 128.7, 130.5 (3 × d, s, Ph), 156.4 (s, C-5), 181.5 (s, C-2a), 199.9 (s, C-4) ppm. IR (ATR): ṽ = 3060–2850 (=C–H, C–H), 1710 (C=O), 1650 (C=C), 1555 (C=N) cm^{-1}. HRMS (ESI): calcd. for $C_{15}H_{14}NO_3$ $[M]^+$: 256.0974; found 256.0965.

2a-Hydroxy-7b-methyl-5-phenyl-2a,3,7a,7b-tetrahydro-2*H*,4a*H*-1,7-dioxa-6-azacyclopenta[*cd*]inden-4-one (14): ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 1.31 (s, 3 H, CH_3), 1.98 (s, 1 H, OH), 2.90, 3.13 (dd, d, *J* = 1.6, 17.6 Hz, *J* = 17.6 Hz, 1 H each, 3-H), 3.67 (d, *J* = 1.6 Hz, 1 H, 4a-H), 4.10, 4.35 (AB system, J_{AB} = 9.4 Hz, 1 H each, 2-H), 4.88 (s, 1 H, 7a-H), 7.38–7.53, 7.77–7.82 (2 × m, 3 H, 2 H, Ph) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 17.0 (q, CH_3), 53.4 (t, C-3), 55.8 (d, C-4a), 56.7 (s, C-7b), 77.4 (t, C-2), 78.4 (s, C-2a), 108.3 (d, C-7a), 127.0, 128.7, 131.2, 133.3 (3 × d, s, Ph), 168.8 (s, C-5), 207.5 (s, C-4) ppm. IR (ATR): ṽ = 3060–2860 (=C–H, C–H), 1730 (C=O), 1670 (C=C), 1570 (C=N) cm^{-1}. HRMS (ESI): calcd. for $C_{15}H_{16}NO_4$ $[M + Na]^+$: 276.0899; found 276.0925.

Hydrogenation of 1,2-Oxazines with Palladium on Charcoal. General Procedure 3 (GP 3): A suspension of Pd/C (10%, 0.100–0.300 g/mmol of 1,2-oxazine) in MeOH or in a mixture (1:1) of MeOH/EtOAc (10 mL/mmol of 1,2-oxazine) was saturated with H_2. The corresponding 1,2-oxazine was added and the mixture was stirred at room temp. under H_2 at atmospheric pressure for the time indicated in the individual experiment. The suspension was then filtered through a pad of Celite with elution with EtOAc. The filtrate was concentrated in vacuo and the crude product was purified either by filtration or by kugelrohr distillation.

2-Acetoxy-(4-phenylbutyl)acetamide (15): The 1,2-oxazine **3** (0.325 g, 1.00 mmol, *cis*/*trans* = 10:90) was treated with Pd/C (10%, 0.100 g) in MeOH (40 mL) under H_2 for 3 d. After workup as described in GP 3, the crude product was dissolved in CH_2Cl_2 (5 mL), acetic acid anhydride (200 μL, 2.10 mmol) and pyridine (0.25 mL, 3.10 mmol) were added, and the mixture was stirred under reflux for an additional 3 h. The solution was then cooled to room temp. and washed with HCl solution (2 N), and the organic phase was dried (Na_2SO_4). Removal of the solvent in vacuo and purification by column chromatography (alumina, EtOAc) afforded **15** (0.077 g, 31%) as a colourless oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.76–2.00 (m, 2 H, 3-H), 1.98, 2.07 (2 × s, 3 H each, CH_3), 2.59–2.72 (m, 2 H, 4-H), 3.44–3.48 (m, 2 H, 1-H), 4.90–4.98 (m, 1 H, 2-H), 5.76 (br s, 1 H, NH), 7.15–7.22, 7.26–7.34 (2 × m, 5 H, Ph) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 21.0, 23.0 (2 × q, CH_3), 33.3, 35.4 (2 × t, C-3, C-4), 42.8 (t, C-1), 72.8 (d, C-2), 126.0, 128.3, 128.4, 140.8 (3 × d, s, Ph), 170.2, 171.1 (2 × s, C=O) ppm. IR (neat): ṽ = 3410 (N–H), 3030–2865 (C–H), 1700, 1640 (C=O) cm^{-1}. $C_{14}H_{18}NO_3$ (248.3): calcd. C 67.72, H 7.31, N 5.64; found C 67.21, H 7.88, N 5.98.

Hydrogenation of 1,2-Oxazines with Raney nickel. General Procedure 4 (GP 4): Raney nickel (suspension in H_2O; 0.200 g/mmol of 1,2-oxazine) was washed several times with ethanol and finally suspended in dry ethanol or ethanol/EtOAc (20–60 mL/mmol of 1,2-oxazine). This suspension was saturated with H_2 for 30 min at room temp. The corresponding 1,2-oxazine dissolved in ethanol (or in ethanol/EtOAc) and Boc_2O dissolved in EtOAc were added and the mixture was stirred at room temp. under H_2 at atmosphere pressure for the time indicated in the individual experiment. The suspension was then filtered through a pad of Celite by elution with EtOAc. The filtrate was concentrated in vacuo and the crude product was purified by column chromatography.

1-*tert*-Butyl 2-Ethyl 4-(Trimethylsiloxy)pyrrolidine-1,2-dicarboxylate (21) and 1-*tert*-Butyl 2-Ethyl 4-Hydroxypyrrolidine-1,2-dicarboxylate (22): The 1,2-oxazine **20** (0.451 g, 1.26 mmol, *trans*/*cis* >95:5) was treated with Raney nickel (0.250 g) and Boc_2O (0.413 g, 1.89 mmol) in ethanol/EtOAc (10 mL/4 mL) under H_2 for 5 d as

described in GP 4, followed by workup and purification by column chromatography (alumina, hexane/EtOAc, 8:1) to give **21** (0.086 g, 22%, *cis*/*trans* = 65:35) and **22** (0.067 g, 22%, *cis*/*trans* = 65:35) as colourless oils.

Pyrrolidine 21 (two rotamers): ^{1}H NMR (250 MHz, $CDCl_3$): δ = 0.09, 0.11 (2×s, 9 H, $SiMe_3$), 1.25–1.30 (m, 3 H, CH_3), 1.44–1.51 [m, 9 H, $C(CH_3)_3$], 2.00–2.35 (m, 2 H, 3-H), 3.27–3.39, 3.61–3.71 (2×m, 1 H each, 5-H), 4.14–4.39 (m, 4 H, OCH_2, 2-H, 4-H) ppm. ^{13}C NMR (62.9 MHz, $CDCl_3$): δ = –0.3, –0.2 (2×q, $SiMe_3$), 14.0, 14.1 (2×q, CH_3), 28.2, 28.3 [2×q, $C(CH_3)_3$], 38.5,* 38.6,* 39.3, 39.6 (4×t, C-3), 53.6, 54.2, 54.4,* 54.3* (4×t, C-5), 57.3,* 57.7, 57.9 (3×d, C-2), 60.7 (t, OCH_2), 69.1, 69.2, 69.9,* 70.0* (4×d, C-4), 79.9 [s, $C(CH_3)_3$], 153.7 (s, C=O), 173.1, 172.3 (2×s, C=O) ppm. Signals of the minor rotamer are marked with *. IR (neat): $\tilde{\nu}$ = 2980–2900 (C–H), 1750, 1705 (C=O) cm^{-1}. $C_{15}H_{29}NO_5Si$ (311.5): calcd. C 54.35, H 8.82, N 4.23; found C 54.29, H 8.51, N 4.38.

Pyrrolidine 22 (two rotamers): ^{1}H NMR (250 MHz, $CDCl_3$): δ = 1.15–1.26 (m, 3 H, CH_3), 1.34–1.38 [m, 9 H, $C(CH_3)_3$], 1.97–2.34 (m, 2 H, 3-H), 3.14–3.62 (m, 3 H, 5-H, OH), 4.00–4.40 (m, 4 H, OCH_2, 2-H, 4-H) ppm. ^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 13.9, 14.0 (2×q, CH_3), 28.15, 28.24 [2×q, $C(CH_3)_3$], 37.6,* 38.3,* 38.5, 39.0 (4×t, C-3), 54.3, 55.2, 55.7* (3×t, C-5), 57.5,* 57.7, 57.9 (3×d, C-2), 60.9, 61.5, 61.7* (3×t, OCH_2), 69.1, 69.2,* 70.0, 71.0* (4×d, C-4), 80.1, 80.3 [2×s, $C(CH_3)_3$], 153.6, 153.9, 154.3 (3×s, C=O), 173.0, 174.8 (2×s, C=O) ppm. Signals of the minor rotamer are marked with *. IR (neat): $\tilde{\nu}$ = 3445 (O–H), 2980–2935 (C–H), 1750, 1700 (C=O) cm^{-1}. The spectroscopic data are in agreement with those given in ref.[25]

Epoxidation of 1,2-Oxazines with Hydrogen Peroxide. General Procedure 5 (GP 5): NaOH solution (8 N, 10 mL/mmol **5**) and H_2O_2 solution (30%, 5 mL/mmol **5**) were added dropwise at 0 °C to a vigorously stirred solution of the appropriate 6*H*-1,2-oxazine **5** in a 3:1 mixture of MeOH and THF (20 mL/mmol **5**). The mixture was stirred at 0 °C for 2.5 h and diluted with H_2O (50 mL/mmol **5**). The solution was then carefully quenched with aqueous sodium hydrogen sulfite (40%, 10 mL/mmol **5**) to destroy excess H_2O_2. The aqueous phase was separated and extracted with CH_2Cl_2 (3×40 mL/mmol **5**), and the combined organic extracts were dried (Na_2SO_4). The crude product was purified as described in the individual experiment.

Epoxidation of 1,2-Oxazines with *tert*-Butyl Hydroperoxide. General Procedure 6 (GP 6): *tert*-Butyl hydroperoxide (1.2–10 equiv.) and DBU (1.2 equiv.) were added to a solution of the 6*H*-1,2-oxazine **5** (1 equiv.) in CH_2Cl_2 (3–5 mL/mmol **5**) and the mixture was stirred at room temp. for 2 d. It was then diluted with CH_2Cl_2 (3–5 mL/mmol **5**), aqueous sodium hydrogen sulfite solution (40%, 3–5 mL/mmol **5**) was added, and the mixture was stirred for an additional 1 h at room temp. The organic layer was washed with H_2O and brine (1×10 mL each/mmol **5**) and dried (Na_2SO_4). The crude product was purified as described in the individual experiment.

Epoxidation of 1,2-Oxazines with *tert*-Butyl Hydroperoxide and KF·Al_2O_3. General Procedure 7 (GP 7): *tert*-Butyl hydroperoxide (2 equiv.) and the corresponding 1,2-oxazine **5** (1 equiv.), dissolved in MeCN (0.5 mL/mmol **5**), were added to a suspension of KF·Al_2O_3 (1.5 mmol KF/mmol **5**) in MeCN (3 mL/mmol **5**). The mixture was stirred for the time indicated in the individual experiment at room temp. The suspension was then filtered through Celite with elution with EtOAc and the filtrate was concentrated in vacuo. The crude product was purified as described in the individual experiment.

***t*-4,*t*-5-Epoxy-*r*-6-ethoxy-3-phenyl-5,6-dihydro-4*H*-1,2-oxazine (25a):** The 6*H*-1,2-oxazine **5a** (0.812 g, 4.00 mmol), dissolved in a MeOH/THF mixture (80 mL), was treated with NaOH solution (8 N, 40 mL) and H_2O_2 solution (30%, 20 mL) as described in GP 5. Workup and purification by recrystallization (Et_2O) gave a 56:44 mixture of **25a** and **26** (39%).

The 6*H*-1,2-oxazine **5a** (0.609 g, 3.00 mmol), dissolved in CH_2Cl_2 (15 mL), was treated with *t*BuOOH (6 M in decane, 5.0 mL, 30.0 mmol) and DBU (547 mg, 3.60 mmol) as described in GP 6. Workup and purification by chromatography (alumina, hexane/EtOAc, 4:1) gave **25a** (0.469 g, 71%) as a colourless solid.

The 6*H*-1,2-oxazine **5a** (0.609 g, 3.00 mmol), dissolved in MeCN (9 mL), was treated with *t*BuOOH (6 M in decane, 1.00 mL, 6.00 mmol) and KF·Al_2O_3 (0.720 g, 4.50 mmol KF) for 17 h at room temp. as described in GP 7. After workup and purification by chromatography (alumina, hexane/EtOAc, 6:1) **25a** (0.600 g, 91%) was obtained as a colourless solid, m.p. 110–112 °C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 1.24 (t, J = 7 Hz, 3 H, Me), AB part of ABX_3 system (δ_A = 3.69, δ_B = 3.96, J_{AX} = J_{BX} = 7, J_{AB} = 9.5 Hz, 2 H, OCH_2), 3.83 (s, 2 H, 4-H, 5-H), 5.42 (s, 1 H, 6-H), 7.38–7.49, 7.73–7.83 (2×m, 3 H, 2 H, Ph) ppm. ^{1}H NMR (C_6D_6, 200 MHz): δ = 0.98 (t, J = 7 Hz, 3 H, Me), AB part of ABX_3 system (δ_A = 3.23, δ_B = 3.30, J_{AX} = J_{BX} = 1.2, J_{AB} = 4.6 Hz, 2 H, 4-H, 5-H), 3.19–3.34, 3.70–3.85 (2×m, 1 H each, OCH_2), 5.03 (d, J = 1.2 Hz, 1 H, 6-H), 6.97–7.06, 7.54–7.59 (2×m, 3 H, 2 H, Ph) ppm. ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ = 14.9 (q, Me), 41.2 (d, C-4), 55.5 (d, C-5), 64.8 (t, OCH_2), 93.6 (d, C-6), 126.2, 128.7, 130.4, 133.5 (3×d, s, Ph), 158.3 (s, C-3) ppm. IR (Nujol): $\tilde{\nu}$ = 3250–2550 (=C–H, C–H), 1560 (C=N) cm^{-1}. $C_{20}H_{27}NO_3$ (329.4): calcd. C 72.92, H 8.26, N 4.25; found C 72.93, H 8.27, N 4.39.

***trans*-6-Ethoxy-5-methoxy-3-phenyl-5,6-dihydro-4*H*-1,2-oxazine (26):** ^{1}H NMR ($CDCl_3$, 200 MHz): δ = 1.20 (t, J = 7 Hz, 3 H, Me), 2.61 (dd, J = 2.3, 18 Hz, 1 H, 4-H_{eq}), 2.80 (dd, J = 5.2, 18 Hz, 1 H, 4-H_{ax}), 3.47 (s, 3 H, OMe), 3.64–3.74, 3.89–4.03 (2×m, 2 H, 1 H, 5-H, OCH_2), 5.09 (d, J = 2.8 Hz, 1 H, 6-H), 7.37–7.43, 7.68–7.74 (2×m, 3 H, 2 H, Ph) ppm. ^{13}C NMR ($CDCl_3$, 50.3 MHz): δ = 15.0 (q, Me), 23.5 (t, C-4), 57.0 (q, OMe), 63.9 (t, OCH_2), 70.7 (d, C-5), 94.9 (d, C-6), 125.4, 128.4, 129.9, 135.7 (3×d, s, Ph), 154.8 (s, C-3) ppm.

6-Hydroperoxy-3-phenyl-6*H*-1,2-oxazine (27a): H_2O_2 (30% in H_2O, 10 mL) was added to a solution of the 6*H*-1,2-oxazine **5a** (0.406 g, 2.00 mmol) dissolved in MeOH/THF (15 mL/5 mL) and the mixture was stirred for 5 h at 0 °C. It was then slowly poured into aqueous sodium hydrogen sulfite solution (40%) and saturated aqueous $NaHCO_3$ solution (20 mL each) and the mixture was stirred for an additional 0.5 h at room temp. The aqueous layer was extracted with diethyl ether (3× 20 mL) and dried ($MgSO_4$). Purification by recrystallization (CH_2Cl_2/hexane) gave **27a** (0.224 g, 59%) as a colourless solid, m.p. 116–117.5 °C (dec.). ^{1}H NMR ([D$_6$]acetone, 300 MHz): δ = 3.05 (s, 1 H, OOH), 6.12 (m_c, 1 H, 6-H), 6.50 (dd, J = 5, 10 Hz, 1 H, 5-H), 6.91 (dd, J = 0.5, 10 Hz, 1 H, 4-H), 7.44–7.49, 7.74–7.80 (2×m, 3 H, 2 H, Ph) ppm. ^{13}C NMR ([D$_6$]acetone, 75.5 MHz): δ = 96.6 (d, C-6), 119.1 (d, C-4), 123.8, 126.7, 129.6, 130.8, 134.7 (4×d, s, Ph, C-5), 154.2 (s, C-3) ppm. IR (KBr): $\tilde{\nu}$ = 3120 (O–H), 3080–2700 (=C–H, C–H), 1645 (C=C), 1535 (C=N) cm^{-1}. $C_{10}H_9NO_3$ (191.2): calcd. C 62.82, H 4.75, N 7.33; found C 62.57, H 4.67, N 7.22.

3-Phenyl-6*H*-1,2-oxazin-6-one (28a): TMSCl (1 mL) was added to a suspension of the 6*H*-1,2-oxazine **27a** (0.147 g, 0.770 mmol) in HMDS (10 mL) and the system was stirred for 1 d at room temp. The solvent was then removed under reduced pressure and the residue was purified by recrystallization to afford the 1,2-oxazin-6-one

28a (0.072 g, 54%) as colourless crystals, m.p. 152–153 °C. ^{1}H NMR ([D$_6$]acetone, 300 MHz): δ = 6.96 (d, J = 10 Hz, 1 H, 5-H), 7.52–7.63, 7.87–7.93 (2 × m, 3 H, 2 H, Ph), 7.91 (d, J = 10 Hz, 1 H, 4-H) ppm. ^{13}C NMR ([D$_6$]acetone, 75.5 MHz): δ = 126.2, 127.6, 130.0, 131.9, 132.6, 133.4 (4 × d, s, d, Ph, C-4, C-5), 154.7 (s, C-3), 163.1 (s, C-6) ppm. IR (KBr): $\tilde{\nu}$ = 3080–2900 (=C–H, C–H), 1745 (C=O), 1620 (C=C), 1520 (C=N) cm^{-1}. $C_{10}H_7NO_2$ (173.2): calcd. C 69.36, H 4.01, N 8.09; found C 69.34, H 4.04, N 8.19.

1-Amino-4-phenylbutan-2-ol (29): The 1,2-oxazine **25a** (0.327 g, 1.49 mmol) was treated with Pd/C (10%, 0.150 g) in MeOH/EtOAc (15 mL) under H_2 for 20 h as described in GP 3, followed by workup and purification by filtration (alumina, hexane/EtOAc, 2:1) to give **29** (0.236 g, 96%) as a colourless oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.62–1.78 (m, 2 H, CH_2), 2.52–2.85 (m, 4 H, CH_2), 2.89 (br s, 3 H, OH, NH_2), 3.51–3.58 (m, 1 H, 2-H), 7.14–7.29 (m, 5 H, Ph) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 31.9, 36.3 (2 × t, C-3, C-4), 47.3 (t, C-1), 71.1 (d, C-2), 125.7, 128.28, 128.30, 141.9 (3 × d, s, Ph) ppm. Complete characterization was performed after the following protection step.

5-(2-Phenylethyl)oxazolidin-2-one (30): Aqueous NaOH solution (50%, 5 mL) and diphosgene (324 μL, 2.67 mmol) were slowly added at –20 °C to a solution of the amino alcohol **29** (0.230 g, 1.39 mmol) in CH_2Cl_2 (5 mL) and the mixture was stirred for 1.5 h at room temp. For the subsequent hydrolysis of excess diphosgene, water (5 mL) was added. After separation of the phases, the aqueous phase was extracted with CH_2Cl_2 (3 × 5 mL) and the combined organic phases were dried (Na_2SO_4), and concentrated in vacuo. The resulting residue was purified by column chromatography (SiO_2, hexane/EtOAc, 1:2, then EtOAc/MeOH, 1:1) to yield **30** (0.130 g, 49%) as colourless crystals, m.p. 82–84 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.89–1.96, 2.08–2.16 (2 × m, 1 H each, CH_2), 2.69–2.75, 2.80–2.86 (2 × m, 1 H each, CH_2Ph), 3.20–3.23, 3.56–3.66 (2 × m, 1 H each, NCH_2), 4.56–4.62 (m, 1 H, OCH), 6.06 (br s, 1 H, NH), 7.15–7.32 (m, 5 H, Ph) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 31.9 (t, *C*H$_2$Ph), 36.6 (t, CH_2), 45.8 (t, NCH_2), 76.0 (d, OCH), 126.2, 128.4, 128.5, 140.4 (3 × d, s, Ph), 160.0 (s, C=O) ppm. IR (KBr): $\tilde{\nu}$ = 3290 (N–H), 3090–2860 (=C–H, C–H), 1720 (C=O) cm^{-1}. $C_{11}H_{13}NO_2$ (191.2): calcd. C 69.09, H 6.87, N 7.32; found C 69.70, H 7.01, N 7.15.

6-Ethoxy-5-hydroxy-3-(3-trifluoromethylphenyl)-5,6-dihydro-4*H*-1,2-oxazine (31): The 1,2-oxazine **25c** (0.458 g, 1.59 mmol) was treated with Pd/C (10%, 0.160 g) in MeOH (15 mL) under H_2 for 20 h as described in GP 3, followed by workup and purification by column chromatography (alumina, hexane/EtOAc, 4:1) to give **31** (0.155 g, 34%) as a brownish resin. ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 1.21 (t, J = 7 Hz, 3 H, Me), 2.27 (dd, J = 2.3, 18 Hz, 1 H, 4-H$_{eq}$), 2.36 (s, 1 H, OH), 2.89 (dd, J = 5.2, 18 Hz, 1 H, 4-H$_{ax}$), 3.64–3.74, 3.87–3.98 (2 × m, 1 H each, OCH_2), 4.12 (m$_c$, 1 H, 5-H), 4.99 (d, J = 3 Hz, 1 H, 6-H), 7.52 (t, J = 7.8 Hz, 1 H, Ar), 7.66, 7.88 (2 × d, J = 7.8 Hz each, 2 H, Ar), 7.97 (s, 1 H, Ar) ppm. ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ = 14.9 (q, Me), 26.7 (t, C-4), 61.6 (d, C-5), 64.4 (t, OCH_2), 97.5 (d, C-6), 123.9 (q, $^1J_{C,F}$ = 274 Hz, CF_3), 122.3, 126.4 (2 × dq, $^3J_{C,F}$ = 3.8 Hz each, Ar), 128.6 (q, $^4J_{C,F}$ = 1 Hz, Ar), 129.1 (d, Ar), 131.0 (q, $^2J_{C,F}$ = 33 Hz, Ar), 136.2 (s, Ar), 154.4 (s, C-3) ppm. IR (neat): $\tilde{\nu}$ = 3400 (O–H), 3040–2930 (=C–H, C–H), 1600 (C=N), 1170, 1130 (C–F) cm^{-1}. $C_{13}H_{14}F_3NO_3$ (289.3): calcd. C 53.97, H 4.89, N 4.84; found C 54.32, H 5.11, N 4.96.

(4*S*,5*S*,6*S*)-6-[(1′*R*,2′*S*,5′*R*)-2′-Isopropyl-5′-methylcyclohexyloxy]-4,5-epoxy-3-phenyl-5,6-dihydro-4*H*-1,2-oxazine [(6*S*)-32]: The 6*H*-1,2-oxazine (6*S*)-**5f** (0.057 g, 0.18 mmol), dissolved in MeCN (1 mL), was treated with *t*BuOOH (6 M in decane, 59 μL, 0.36 mmol) and KF·Al_2O_3 (0.043 g, 0.27 mmol KF) for 22 h at room temp. as described in GP 7. Workup and purification by chromatography (alumina, hexane/EtOAc, 8:1) gave (4*S*,5*S*,6*S*)-**32** (0.056 g, 94%) as colourless crystals, m.p. 146–147 °C, $[\alpha]_D^{25}$ = –16.0 (c = 0.10, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 0.76–1.70 [m, 16 H, 3′-H, 4′-H, 5′-H, 6′-H, 5′-CH_3, CH(C*H*$_3$)$_2$], 2.09 [m$_c$, 1 H, C*H*(CH$_3$)$_2$], 2.21–2.28 (m, 1 H, 2′-H), 3.57 (dt, J = 4.5, 10.5 Hz, 1 H, 1′-H), 3.83 (s, 2 H, 4-H, 5-H), 5.44 (s, 1 H, 6-H), 7.41–7.51, 7.68–7.77 (2 × m, 3 H, 2 H, Ph) ppm. ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ = 16.3, 21.1 [2 × q, CH(CH$_3$)$_2$], 22.1 (q, 5′-CH_3), 23.2 (t, C-3′), 25.7 [d, CH(CH$_3$)$_2$], 31.6 (d, C-5′), 34.2 (t, C-4′), 42.4 (t, C-6′), 41.6 (d, C-4), 48.6 (d, C-2′), 55.5 (d, C-5), 80.9 (d, C-1′), 94.9 (d, C-6), 126.4, 128.8, 130.4, 133.7 (3 × d, s, Ph), 158.2 (s, C-3) ppm. IR (KBr): $\tilde{\nu}$ = 3050–2800 (=C–H, C–H), 1620 (C=N) cm^{-1}. $C_{20}H_{27}NO_3$ (329.4): calcd. C 72.92, H 8.26, N 4.25; found C 72.45, H 7.78, N 4.29.

(4*R*,5*R*,6*R*)-6-[(1′*R*,2′*S*,5′*R*)-2′-Isopropyl-5′-methylcyclohexyloxy]-4,5-epoxy-3-phenyl-5,6-dihydro-4*H*-1,2-oxazine [(6*R*)-32]: The 6*H*-1,2-oxazine (6*R*)-**5f** (0.846 g, 2.70 mmol), dissolved in MeCN (12 mL), was treated with *t*BuOOH (6 M in decane, 0.90 mL, 5.40 mmol) and KF·Al_2O_3 (0.646 g, 4.05 mmol KF) for 24 h at room temp. as described in GP 7. Workup and purification by chromatography (alumina, hexane/EtOAc, 8:1) gave (4*R*,5*R*,6*R*)-**32** (0.756 g, 85%) as colourless crystals, m.p. 141–143 °C, $[\alpha]_D^{28}$ = –42.4 (c = 0.50, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 0.71–1.74 [m, 16 H, 3′-H, 4′-H, 5′-H, 6′-H, 5′-CH_3, CH(CH$_3$)$_2$], 2.06 [m$_c$, 1 H, CH(CH$_3$)$_2$], 2.09–2.20 (m, 1 H, 2′-H), 3.72 (dt, J = 4, 10.5 Hz, 1 H, 1′-H), 3.77 (dd, J = 1, 4.5 Hz, 1 H, 5-H), 3.81 (d, J = 4.5 Hz, 1 H, 4-H), 5.58 (d, J = 1 Hz, 1 H, 6-H), 7.41–7.54, 7.63–7.76 (2 × m, 3 H, 2 H, Ph) ppm. ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ = 15.9, 21.0 [2 × q, CH(*C*H$_3$)$_2$], 22.3 (q, 5′-CH_3), 22.8 (t, C-3′), 25.2 [d, *C*H(CH$_3$)$_2$], 31.3 (d, C-5′), 34.3 (t, C-4′), 40.2 (t, C-6′), 41.3 (d, C-4), 47.9 (d, C-2′), 56.2 (d, C-5), 76.6 (d, C-1′), 93.7 (d, C-6), 126.1, 128.8, 130.4, 133.8 (3 × d, s, Ph), 158.3 (s, C-3) ppm. IR (KBr): $\tilde{\nu}$ = 3050–2800 (=C–H, C–H), 1630 (C=N) cm^{-1}. $C_{20}H_{27}NO_3$ (329.4): calcd. C 72.92, H 8.26, N 4.25; found C 72.93, H 8.27, N 4.39.

***tert*-Butyl (2*S*)-(2-Hydroxy-4-phenylbutyl)carbamate (33):** The 1,2-oxazine (6*S*)-**32** (0.151 g, 0.458 mmol) was treated with Pd/C (10%, 0.080 g) in MeOH/EtOAc (10 mL/4 mL) under H_2 for 1 d as described in GP 3, followed by workup and removal of the liberated menthol by sublimation (50 °C, 0.05 mbar). The crude (2*S*)-**29** (0.088 g) was directly dissolved in CH_2Cl_2 (4.5 mL), and Hünig base (162 μL, 0.916 mmol) and Boc_2O (0.111 g, 0.505 mmol) were subsequently introduced into the reaction mixture. After 3 h at room temp., the mixture was diluted with EtOAc (5 mL), washed with satd. aq. NH_4Cl solution, water and brine (3 mL each) and dried ($MgSO_4$), and the solvent was removed under reduced pressure. The crude product was purified by column chromatography (silica gel, hexane/EtOAc, 2:1) to afford (2*S*)-**33** (0.100 g, 82%) as a colourless oil, $[\alpha]_D^{23}$ = –8.8 (c = 0.63, CH_2Cl_2); ref.[26]: $[\alpha]_D^{25}$ = –8.86 (c = 0.56, CH_2Cl_2). The spectroscopic data agree with the data given in the literature.[26]

***tert*-Butyl (2*R*)-(2-Hydroxy-4-phenylbutyl)carbamate (33):** The 1,2-oxazine (6*R*)-**32** (0.115 g, 0.348 mmol) was treated with Pd/C (10%, 0.061 g) in MeOH/EtOAc (8 mL/3 mL) under H_2 for 1 d as described in GP 3, followed by workup and removal of the liberated menthol by sublimation (50 °C, 0.05 mbar). The crude (2*R*)-**29** (0.053 g) was directly dissolved in CH_2Cl_2 (4 mL), and Hünig base (123 μL, 0.696 mmol) and Boc_2O (0.084 g, 0.384 mmol) were subsequently introduced into the reaction mixture. After 3 h at room temp., the mixture was diluted with EtOAc (4 mL), washed with satd. aq. NH_4Cl solution, water and brine (3 mL each) and dried

($MgSO_4$), and the solvent was removed under reduced pressure. The crude product was purified by column chromatography (silica gel, hexane/EtOAc, 3:1) to afford (2*R*)-**33** (0.050 g, 55%) as a colourless oil, $[\alpha]_D^{23} = +8.6$ ($c = 0.64$, CH_2Cl_2).

Supporting Information (see also the footnote on the first page of this article): Procedures for the synthesis of **6b–d**, **9**, **17**, **18**, **23**, **24**, **25b–e**, **27b**, **28b**, (2*R*)-**29** and (2*S*)-**29**.

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