A Stereoselective Access to Dihydroxylated Pyrrolidines by Reductive Ring Contraction of 1,2-Oxazines

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Received 30 March 2007; revised 22 May 2007

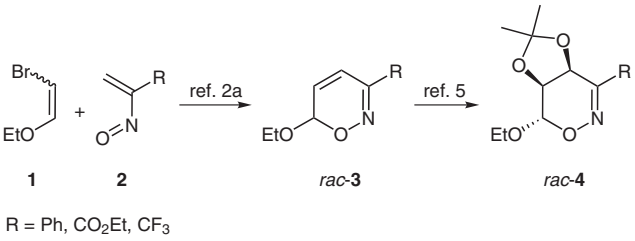
This paper is dedicated with respect to Dr. Maximilian A. Grassberger on the occasion of his 70th birthday.

Abstract: Protected dihydroxylated 1,2-oxazine derivatives such as *rac*-**4** were converted into tetrahydro-1,2-oxazines *rac*-**7** by employing BH_3·THF for the stereoselective reduction of the C=N bond. Compound **7a** underwent a reductive ring contraction on hydrogenation in the presence of palladium on charcoal to provide *rac*-**5** in good yield. Enantiopure 1,2-oxazine derivatives **13** and **14** were prepared using (–)-menthol as chiral auxiliary. Their diastereoselective dihydroxylation and BH_3·THF reduction furnished enantiopure tetrahydro-2*H*-1,2-oxazine derivatives **17** and **18** in good overall yield. Enantiomers (6*R*)-**18** and (6*S*)-**18** were transformed into the two enantiomeric hydroxylated pyrrolidine derivatives **5** in moderate yield.

Key words: cycloaddition, 1,2-oxazines, pyrrolidines, hydrogenation, ring contraction

Among the six-membered heterocycles, 1,2-oxazine derivatives are very versatile building blocks since they allow stereoselective synthesis of a variety of cyclic or acyclic nitrogen-containing compounds.[1] 6*H*-1,2-Oxazines **3** possessing an additional 4,5-C=C bond are particularly important.[2,3] These unsaturated N,O-heterocycles have been used successfully as starting materials by employing the C=C bond as handle for introduction of substituents or functional groups, e.g., by addition of nucleophilic and electrophilic agents,[4] dihydroxylations,[5] epoxidations,[6] and 1,3-dipolar cycloadditions.[7] All these transformations furnish a variety of highly functionalized 5,6-dihydro-4*H*-1,2-oxazines and they generally proceed with high stereoselectivity, since the 6-alkoxy group leads to strongly preferred attack of reagents *trans* to this substituent. In the last years, we and others have reported numerous applications of 5,6-dihydro-4*H*-1,2-oxazines as useful key intermediates for preparation of pyrroles,[4d,8] proline derivatives,[8c,9] azasugars,[10] tetrahydrofurans,[11] as well as acyclic primary and secondary amines.[2b,4c,5a,9c,12] Many of these products belong to compound classes with potential biological activity. In this report, we demonstrate the viability of this route, by first focusing on the diastereoselective synthesis of racemic pyrrolidine derivatives and then expanding this methodology to enantiopure heterocycles.

Previously, we have described the synthesis of racemic acetal-protected 1,2-oxazines *rac*-**4** in a short reaction sequence involving a hetero Diels–Alder reaction of 2-bromo enol ether **1** and α-nitrosoalkenes **2** (generated in situ from the corresponding α-halogen-substituted oximes).[2a] The resulting 1,2-oxazines were converted into *rac*-**4** by diastereoselective *cis*-dihydroxylation either by treatment with $KMnO_4$ or with $RuCl_3/NaIO_4$ and finally protection as acetal with 2,2-dimethoxypropane (Scheme 1).[5]



Scheme 1 Synthesis of protected 4,5-dihydroxylated 1,2-oxazines

We first examined the reductive ring contraction of 1,2-oxazines **4** by performing the synthesis of racemic pyrrolidines *rac*-**5** and *rac*-**6**, respectively (Scheme 2). Hydrogenation of 1,2-oxazines *rac*-**4** in the presence of Pd/C produced pyrrolidines *rac*-**5** and *rac*-**6** in good to excellent yields. The hydrogenation of *rac*-**4** with R = CO_2Et was carried out by addition of dilute HCl solution suppressing unidentified side products which were observed during reduction in the absence of acid.[13] Under these acidic conditions a re-protection of the partially deprotected hydroxyl groups was necessary.

rac-**4**
R = Ph 94% (*cis*/*trans* = 33:67)
R = CO_2Et 63% (*cis*/*trans* = 52:48)

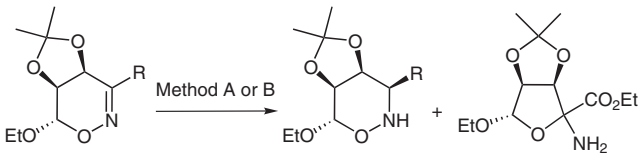
rac-**5** (R = Ph)
rac-**6** (R = CO_2Et)

Scheme 2 Hydrogenation of racemic 5,6-dihydro-4*H*-1,2-oxazines *rac*-**4** providing pyrrolidine derivatives *rac*-**5** and *rac*-**6**

SYNTHESIS 2007, No. 17, pp 2681–2689
Advanced online publication: 24.07.2007
DOI: 10.1055/s-2007-983802; Art ID: T06307SS

The transformation of 5,6-dihydro-4*H*-1,2-oxazines into acyclic amines or pyrrolidines by catalytic hydrogenation is well investigated. A plausible mechanism of this multistep process has already been discussed in previous reports. It involves reductive N–O bond cleavage as the first step, followed by imine reduction, formation of the pyrrolidine ring by cyclization of an acyclic γ-amino aldehyde and final reduction of the intermediate 3,4-dihydro-2*H*-pyrrole.[9a,12a,14]

In agreement with this sequence of steps, it is not surprising that products *rac*-**5** and *rac*-**6** were formed either with moderate or no diastereoselectivity. Low stereocontrol can be expected for the reduction of the intermediate acyclic imine. To overcome this problem, we decided to prepare the pyrrolidines in an alternative two steps route inverting the sequence of reductive processes. The stereocontrolled reduction of the C=N bond should be achieved at the cyclic stage and then followed by the N–O cleavage and reductive ring contraction. The borane-tetrahydrofuran complex is a powerful reducing agent for C=N bonds and has been frequently applied for reductions of oximes or oxime ethers.[15] Reduction of 1,2-oxazines *rac*-**4** with BH_3·THF followed by treatment with aqueous 2 N NaOH solution furnished the tetrahydro-2*H*-1,2-oxazines *rac*-**7** in moderate to good yields and with high *cis-trans* selectivity (Scheme 3). Whereas the reduction of 3-phenyl- and 3-trifluoromethyl-substituted compounds *rac*-**4a** and *rac*-**4c** exclusively led to the expected products *rac*-**7a** and *rac*-**7c**, the reduction of ethoxycarbonyl-substituted 1,2-oxazine *rac*-**4b** was less chemoselective and led to the unexpected formation of furan derivative **8** as major product in 49% yield. As published previously, the reduction of the C=N unit in *rac*-**4b** could be performed more successfully by employing sodium cyanoborohydride as reducing agent,[16] which afforded only tetrahydro-2*H*-1,2-oxazine *rac*-**7b** in 48% yield and with high *cis-trans* selectivity.[17] The reduction of phenyl-substituted precursor *rac*-**4a** with $NaBH_3CN$ in acetic acid gave a better yield (77%), but the diastereoselectivity was only moderate.[18] In all examples



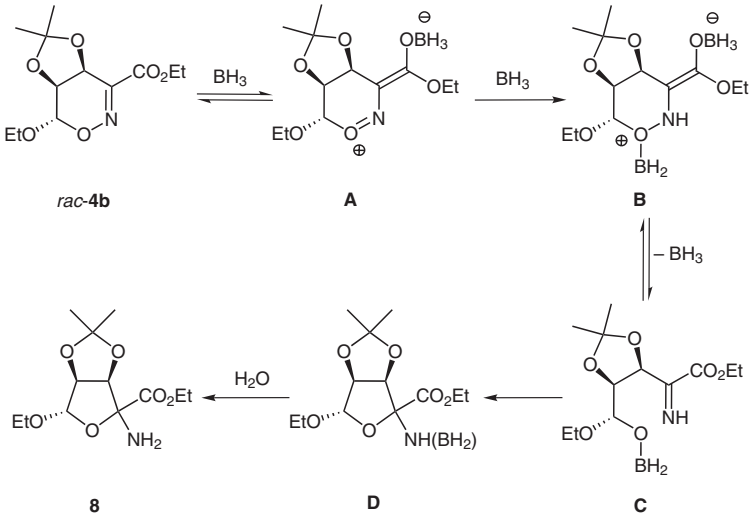
Method A: **a**: R = Ph 75% (*cis*/*trans* = 89:11)
b: R = CO_2Et 21% (*cis*/*trans* = 79:21) + 49% of **8**
c: R = CF_3 69% (only 1 diastereomer)
Method B: **a**: R = Ph 77% (*cis*/*trans* = 65:35)
b: R = CO_2Et 48% (*cis*/*trans* = 89:11)[17]

Scheme 3 Stereoselective conversion of *rac*-**4** into tetrahydro-2*H*-1,2-oxazines **7**. *Reagents and conditions*: Method A: (a) BH_3·THF, THF, r.t.; (b) 2 N NaOH, r.t.; Method B: $NaBH_3CN$, AcOH, r.t., 6 h.

presented in Scheme 3, the hydride was delivered to the sterically better available *exo*-side of the fairly rigid bicyclic compounds **4**.

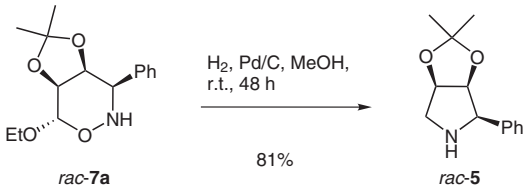
The observed side product **8** is very similar to an interesting class of structurally related furanose derivatives. These are known precursors of hydantoins, which are pharmacophores with a wide range of biological activities.[19] The formation of **8** probably starts with a reversible addition of the Lewis acid borane to the ethoxycarbonyl group to form intermediate **A** as illustrated in Scheme 4. Thereby, activation of the N–O bond resulted in reduction of this unit to give the acyclic imine **C** via **B**. Ring closure of **C** to the furan intermediate **D** followed by hydrolysis (during workup) affords the isolated compound **8**.

The major *cis*-isomer *rac*-**7a**, which is easily separable from the minor *trans*-isomer by chromatography, was reduced with hydrogen/palladium on charcoal under standard conditions and furnished the 2-phenyl-substituted pyrrolidine *rac*-**5** as single *cis-cis*-diastereomer in good yield (Equation 1). Thus, the two-step route to pyrro-



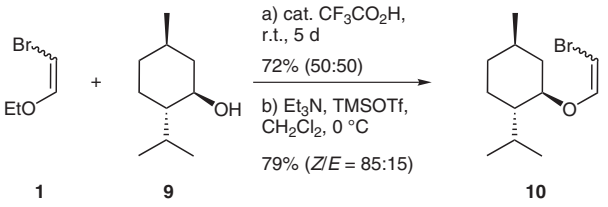
Scheme 4 Proposed mechanism for formation of furan derivative **8**

lidines proceeds with significantly higher diastereoselectivity than the one-step route.



Equation 1 Reductive ring contraction of tetrahydro-2*H*-1,2-oxazine *rac*-**7a** to *cis-cis rac*-**5**

We then focused on the extension of these reductions to enantiopure 1,2-oxazine derivatives. To this end, conversion of 2-bromo enol ether **1** into the chiral enol ether **10** was performed in two simple steps. Addition of (–)-menthol (**9**) to **1** in the presence of catalytic amounts of trifluoroacetic acid formed an acetal intermediate which was subsequently treated with trimethylsilyl triflate and triethylamine analogously to a protocol developed by Dujardin et al.[20] This method afforded menthyloxy-substituted bromo enol ether **10** in good yield as a 85:15 *Z*/*E* mixture (Scheme 5).

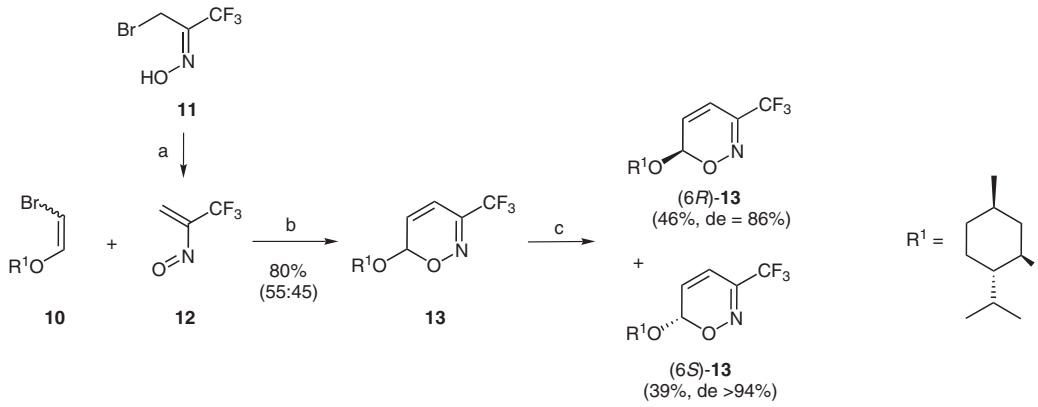


Scheme 5 Preparation of the chiral bromo enol ether **10**

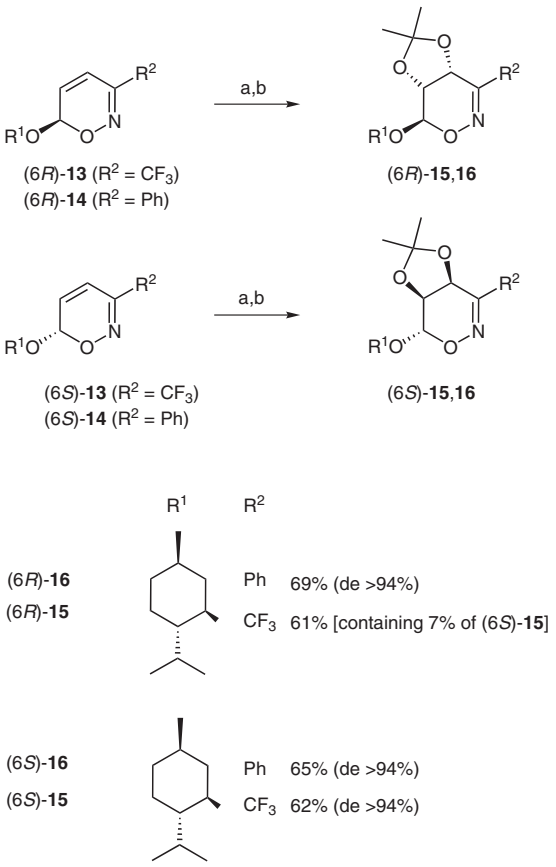
According to the route described above, the chiral enol ether **10** served as dienophile in the hetero Diels–Alder reaction with α-nitrosoalkene **12**, in situ generated from **11**,[21] to furnish 6-menthyloxy-substituted 6*H*-1,2-oxazine **13** in 80% yield as a 1:1 mixture of 6*R*- and 6*S*-diastereomers (Scheme 6). Separation of the isomers by flash chromatography allowed isolation of essentially pure (6*S*)-**13** and diastereomerically highly enriched (6*R*)-**13**. Similarly, the corresponding 3-ethoxycarbonyl-6*H*-1,2-oxazine could be prepared under analogous conditions, but the yield amounted only to 21%. However, when the hetero Diels–Alder reaction of **10** and α-nitrosoalkene **2** with R = CO_2Et was performed in the absence of solvent the yield improved to 72% with dr = 56:44. Unfortunately, separation of both diastereomers of the resulting 3-ethoxycarbonyl-6*H*-1,2-oxazine was not possible either by flash chromatography nor by HPLC.[22] The already described synthesis of 6-menthyloxy-3-phenyl-6*H*-1,2-oxazine (**14**) employs an alternative route in which (–)-menthol (**9**) was added to an easily available phenyl-substituted azapyrylium intermediate.[4c] The absolute configuration of (6*S*)-**14** at C-6 was unambiguously determined by an X-ray analysis.[23] The assignments of configuration for (6*S*)-**13** and (6*R*)-**13** are based on comparison of the NMR data.

All 6-menthyloxy-substituted 6*H*-1,2-oxazines (6*R*)-**13**/(6*S*)-**13** and (6*R*)-**14**/(6*S*)-**14** underwent dihydroxylation using the typical protocol employing $RuCl_3/NaIO_4$ followed by standard protection of the 4,5-diol unit with 2,2-dimethoxypropane (Scheme 7). The reactions again proceeded with excellent degrees of diastereoselectivity providing (6*S*)-**15**, (6*S*)-**16** and (6*R*)-**16** as single isomers. The only exception is the case of (6*R*)-**15**, where the starting material was contaminated with the minor isomer (6*S*)-**13**.

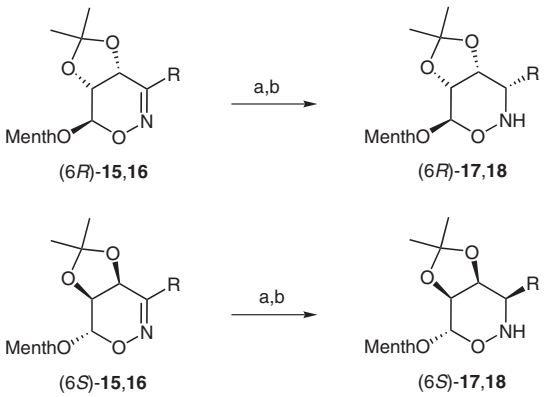
Subsequent treatment of the bicyclic compounds (6*R*)-**15**, (6*R*)-**16** and (6*S*)-**15**, (6*S*)-**16** with BH_3·THF complex led to diastereoselective reduction of the C=N bond to give the expected products (6*R*)-**17**, (6*R*)-**18** and (6*S*)-**17**, (6*S*)-**18** in moderate to good yields (Scheme 8). With the exception of trifluoromethyl-substituted 1,2-oxazine (6*R*)-**17**, all other products were diastereomerically pure (de >94%). The menthyloxy group thus leads to higher diastereoselectivity compared to the ethoxy compounds (Scheme 3) although this more bulky substituent is at the face where the hydride reagent attacks.



Scheme 6 Synthesis and separation of diastereomeric 6*H*-1,2-oxazines **13**. *Reagents and conditions*: (a) Na_2CO_3, *t*-BuOMe, r.t., 6 d; (b) DBU, r.t., 4 h; (c) separation by flash chromatography.



Scheme 7 Dihydroxylations of diastereomerically pure 6*H*-1,2-oxazines **13** and **14**. *Reagents and conditions*: (a) $RuCl_3 \cdot 3H_2O$, $NaIO_4$, MeCN–(EtOAc)–H_2O, 0 ° C, 3–4 min; (b) 2,2-DMP, *p*-TsOH, acetone, r.t., 4 h.

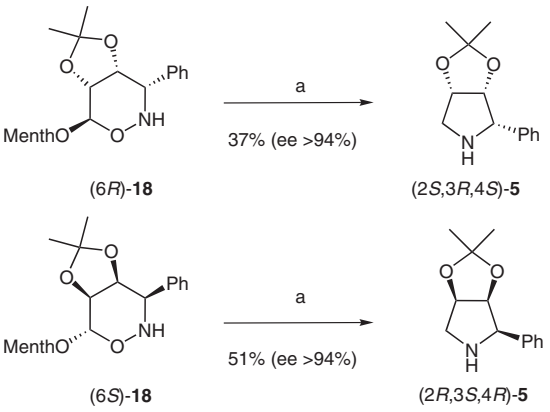


(6*R*)-**18**	R = Ph	43% (de >94%)
(6*R*)-**17**	R = CF_3[a]	68% [containing 9% of (6*S*)-**17**]
(6*S*)-**18**	R = Ph	71% (de >94%)
(6*S*)-**17**	R = CF_3	67% (de >94%)

[a] containing 7% of (6*S*)-**15**

Scheme 8 Reduction of 5,6-dihydro-4*H*-1,2-oxazines with borane-tetrahydrofuran complex. *Reagents and conditions*: (a) $BH_3 \cdot THF$, THF, r.t.; (b) 2 N NaOH, r.t.

Hydrogenations of 3-phenyl-substituted tetrahydro-2*H*-1,2-oxazines (6*R*)-**18** and (6*S*)-**18** proceeded under standard conditions and furnished pyrrolidines (2*S*,3*R*,4*S*)-**5** and (2*R*,3*S*,4*R*)-**5**, respectively, in moderate yields (Scheme 9). We assume that the excellent diastereoselectivity achieved at the level of **18** is completely transferred to pyrrolidine derivatives **5** which should be essentially enantiopure (ee >94%). Unfortunately, the corresponding 3-trifluoromethyl-substituted tetrahydro-2*H*-1,2-oxazines (6*R*)-**17** and (6*S*)-**17** could not be hydrogenated under these conditions – even after prolonged reaction times only starting material was recovered.[22]



Scheme 9 Reductive ring contraction of tetrahydro-2*H*-1,2-oxazines **18** into enantiopure pyrrolidines **5**. *Reagents and conditions*: (a) H_2, Pd/C, MeOH, r.t., 24–48 h.

In summary, we could demonstrate that the standard reductive ring contractions of 5,6-dihydro-4*H*-1,2-oxazines derivatives by directly employing hydrogen/palladium on charcoal could strongly be improved by development of a two step sequence. The highly diastereoselective reduction of 5,6-dihydro-4*H*-1,2-oxazines by the borane-tetrahydrofuran complex was the crucial step in this sequence. The resulting tetrahydro-1,2-oxazines were then reductively ring contracted to diastereomerically pure pyrrolidines. This sequence was applied to the preparation of racemic dihydroxylated pyrrolidines and it could successfully be extended to the synthesis of enantiopure compounds such as **17**, **18** and **5**. The dihydroxylated 1,2-oxazines and pyrrolidines are compounds which should have biological activity since several glycosidase inhibitors with these structural features are well known.[24]

All reactions were performed under argon in flame-dried flasks, and the components were added by means of syringes. All solvents were dried by standard methods. IR spectra were measured with a Nicolet 205 FT-IR spectrophotometer. MS spectra were recorded with a Varian MAT 711 spectrometer. Optical rotations were measured using a Perkin-Elmer 241 polarimeter at 22 °C. ^1H and ^{13}C NMR spectra were recorded on Bruker instruments (AC 200, AC 300 or DXR 500) in $CDCl_3$ solution. The chemical shifts are given relative to the TMS or to the $CDCl_3$ signal ($\delta_H = 7.27$, $\delta_C = 77.0$). Higher order NMR spectra were approximately interpreted as first-order spectra if possible. Silica gel 60 (0.04–0.063 mm, Merck-Schuchardt) was used for column chromatography. Melting points (uncorrected) were measured with an apparatus from Gallenkamp (MPD 350).

Starting materials and reagents **1**,[25] *rac*-**4a**,**b**,[2a,5] and **11**[21] were prepared by literature procedures. All other chemicals were commercially available and were used as received.

rac-3,4-*O*-Isopropylidene-2-phenylpyrrolidine (5)

A suspension of 10% Pd/C (0.290 g) in EtOH (29 mL) was saturated with H_2. 1,2-Oxazine *rac*-**4a** (0.804 g, 2.90 mmol) was added and the mixture was stirred at r.t. under H_2 at atmospheric pressure for 24 h. The suspension was then filtered through Celite, eluting with EtOAc. The filtrate was concentrated in vacuo and the crude product was purified by filtration (alumina, *t*-BuOMe) and Kugelrohr distillation (110 °C/0.01 mbar) to yield a mixture of *cis*/*trans* isomers (33:67) (0.597 g, 94%). The mixture of diastereomers was separated by chromatography using a chromatotron (hexane–EtOAc, 1:3).

cis-**5**

Colorless oil.

^{1}H NMR ($CDCl_3$, 300 MHz): δ = 1.29, 1.44 (2 s, 3 H each, 2 × CH_3), 2.59 (s, 1 H, NH), 2.78 (dd, *J* = 3, 12.5 Hz, 1 H, 5-H), 3.23 (d, *J* = 12.5 Hz, 1 H, 5-H), 3.80 (d, *J* = 3 Hz, 1 H, 2-H), 4.75 (m_c, 2 H, 3-H, 4-H), 7.24–7.45 (m, 5 H, C_6H_5).

^{13}C NMR ($CDCl_3$, 75.5 MHz): δ = 23.9, 25.8 (2 q, 2 × CH_3), 53.0 (t, C-5), 67.3 (d, C-2), 81.8 (d, C-4), 82.3 (d, C-3), 110.7 (s, *C*Me_2), 127.3, 127.5, 128.1, 137.0 (3 d, s, C_6H_5).

trans-**5**

Colorless oil.

^{1}H NMR ($CDCl_3$, 300 MHz): δ = 1.34, 1.53 (2 s, 3 H each, 2 × CH_3), 2.64 (s, 1 H, NH), 2.93 (dd, *J* = 4, 13.5 Hz, 1 H, 5-H), 3.10 (d, *J* = 13.5 Hz, 1 H, 5-H), 4.35 (s, 1 H, 2-H), 4.67, 4.82 (2 m_c, 1 H each, 3-H, 4-H), 7.23–7.40 (m, 5 H, C_6H_5).

^{13}C NMR ($CDCl_3$, 75.5 MHz): δ = 24.1, 26.4 (2 q, 2 × CH_3), 52.7 (t, C-5), 67.6 (d, C-2), 82.2 (d, C-4), 88.1 (d, C-3), 111.1 (s, *C*Me_2), 126.7, 126.8, 128.4, 139.6 (3 d, s, C_6H_5).

Further data obtained from the mixture:

IR (neat): 3340 (N–H), 3090–2860 cm^{-1} (=C–H, C–H).

Anal. Calcd for $C_{13}H_{17}NO_2$ (219.3): C, 71.21; H, 7.82; N, 6.39. Found: C, 71.22; H, 7.97; N, 6.28.

rac-Ethyl 3,4-*O*-Isopropylidenepyrrolidine-2-carboxylate (6)

A suspension of 10% Pd/C (0.553 g) in EtOH (55 mL) was saturated with H_2. 1,2-Oxazine *rac*-**4b** (1.51 g, 5.53 mmol) and aq 2 N HCl (1 mL) were added and the mixture was stirred at r.t. under H_2 at atmospheric pressure for 24 h. The suspension was then filtered through Celite, eluting with EtOAc. After addition of aq sat. $NaHCO_3$ solution (10 mL), the mixture was concentrated in vacuo. The residue was extracted with EtOAc (3 × 20 mL) and the combined organic extracts were dried (Na_2SO_4), and concentrated in vacuo. The resulting crude product was dissolved in anhyd acetone (10 mL) and treated with 2,2-dimethoxypropane (2,2-DMP, 2 mL) and a catalytic amount of *p*-toluenesulfonic acid for 4 h at r.t. Then an excess of solid $NaHCO_3$ was added to the mixture, the suspension was filtered, and the volatile components were removed in vacuo. The residue was purified by Kugelrohr distillation (95 °C/0.01 mbar) to yield a mixture of *cis*/*trans* isomers (52:48) (0.746 g, 63%). The mixture of diastereomers was separated by flash chromatography (silica gel, *t*-BuOMe–MeOH, 20:1).

cis-**6**

Colorless crystals; mp 67–68.5 °C.

^{1}H NMR ($CDCl_3$, 300 MHz): δ = 1.27 (t, *J* = 7 Hz, 3 H, CH_3), 1.27, 1.40 (2 s, 3 H each, 2 × CH_3), 2.57 (br s, 1 H, NH), 2.64 (dd, *J* = 3.5, 13.5 Hz, 1 H, 5-H), 3.20 (d, *J* = 13.5 Hz, 1 H, 5-H), 3.54 (d, *J* = 5 Hz, 1 H, 2-H), 4.22, 4.26 (AB part of ABX_3 system, $J_{A,X} = J_{B,X}$ = 7 Hz, $J_{A,B}$ = 11.5 Hz, 2 H, OCH_2), 4.70 (m_c, 1 H, 4-H), 4.82 (t, *J* = 5 Hz, 1 H, 3-H).

^{13}C NMR ($CDCl_3$, 75.5 MHz): δ = 14.0, 23.9, 25.4 (3 q, 3 × CH_3), 51.8 (t, C-5), 60.8 (t, OCH_2), 66.2 (d, C-2), 81.5 (d, C-4), 82.3 (d, C-3), 111.3 (s, *C*Me_2), 168.6 (s, *C*O_2Et).

trans-**6**

Colorless oil.

^{1}H NMR ($CDCl_3$, 300 MHz): δ = 1.29 (t, *J* = 7 Hz, 3 H, CH_3), 1.33, 1.49 (2 s, 3 H each, 2 × CH_3), 2.57 (br s, 1 H, NH), 2.95 (dd, *J* = 4, 13 Hz, 1 H, 5-H), 3.14 (d, *J* = 13 Hz, 1 H, 5-H), 3.84 (s, 1 H, 2-H), 4.19 (q, *J* = 7 Hz, 2 H, OCH_2), 4.72 (m_c, 1 H, 4-H), 4.89 (d, *J* = 5.5 Hz, 1 H, 3-H).

^{13}C NMR ($CDCl_3$, 75.5 MHz): δ = 14.0, 23.9, 26.1 (3 q, 3 × CH_3), 52.6 (t, C-5), 61.0 (t, OCH_2), 67.1 (d, C-2), 81.2 (d, C-4), 83.9 (d, C-3), 111.3 (s, *C*Me_2), 171.5 (s, *C*O_2Et).

Further data obtained from the mixture:

IR (neat): 3320 (N–H), 2990–2870 (C–H), 1740 cm^{-1} (C=O).

Anal. Calcd for $C_{10}H_{17}NO_4$ (215.3): C, 55.80; H, 7.96; N, 6.51. Found: C, 55.93; H, 8.05; N, 6.28.

Reduction of 1,2-Oxazines with BH_3·THF; General Procedure 1

Under argon, the corresponding 1,2-oxazine dissolved in THF (10 mL/mmol of 1,2-oxazine) was treated with BH_3·THF (1 M in THF, 3–4 equiv) at r.t. The solution was stirred for 24–48 h, then aq 2 N NaOH solution (10 mL/mmol of 1,2-oxazine) was added. After an additional 2 h at r.t., the phases were separated and the aqueous phase was extracted with EtOAc (2 × 10 mL/mmol of 1,2-oxazine). The combined organic phases were dried (Na_2SO_4) and concentrated in vacuo. The crude product was purified by column chromatography or by Kugelrohr distillation.

rac-3,4,5,6-Tetrahydro-4,5-*O*-isopropylidene-3-phenyl-2*H*-1,2-oxazine (7a)

According to general procedure 1, 1,2-oxazine *rac*-**4a** (1.09 g, 3.93 mmol) was treated with BH_3·THF (16.0 mL, 16.0 mmol) in THF (40 mL), followed by workup and purification using column chromatography (alumina, hexane–EtOAc, 5:1) to give **7a** (0.667 g, 75%; *cis*/*trans* = 89:11) as colorless crystals; mp 131–133.5 °C.

^{1}H NMR ($CDCl_3$, 300 MHz): δ = 1.28 (t, *J* = 7 Hz, 3 H, CH_3), 1.31, 1.57 (2 s, 3 H each, 2 × CH_3), 3.72, 3.97 (AB part of ABX_3 system, $J_{A,X} = J_{B,X}$ = 7 Hz, $J_{A,B}$ = 9.5 Hz, 2 H, OCH_2), 4.00, 4.46 (2 m_c, 1 H, 2 H, 3-H, 4-H, 5-H), 4.78 (d, *J* = 7 Hz, 1 H, 6-H), 5.49 (br s, 1 H, NH), 7.31–7.38, 7.43–7.47 (2 m, 3 H, 2 H, C_6H_5).

^{13}C NMR ($CDCl_3$, 75.5 MHz): δ = 15.3, 26.1, 28.1 (3 q, 3 × CH_3), 62.9 (d, C-3), 65.9 (t, OCH_2), 75.5, 75.9 (2 d, C-4, C-5), 103.8 (d, C-6), 110.2 (s, *C*Me_2), 128.3, 128.7, 135.4 (2 d, s, C_6H_5).

Additional signals assigned to *trans*-isomer:

^{1}H NMR ($CDCl_3$, 300 MHz): δ = 1.10, 1.48 (2 s, 3 H each, 2 × CH_3), 1.13 (t, *J* = 7 Hz, 3 H, CH_3), 3.57, 3.95 (AB part of ABX_3 system, $J_{A,X} = J_{B,X}$ = 7 Hz, $J_{A,B}$ = 9.5 Hz, 2 H, OCH_2), 4.05, 4.13 (2 × m_c, 2 H, 1 H, 3-H, 4-H, 5-H), 4.96 (d, *J* = 6.5 Hz, 1 H, 6-H), 5.14 (br s, 1 H, NH), 7.06–7.16, 7.37–7.39 (2 × m, 3 H, 2 H, C_6H_5).

^{13}C NMR ($CDCl_3$, 75.5 MHz): δ = 14.9, 26.2 (2 q, 2 × CH_3), 63.0 (d, C-3), 63.8 (t, OCH_2), 73.4, 74.6 (2 d, C-4, C-5), 99.1 (d, C-6), 109.4 (s, *C*Me_2), 137.3 (s, C_6H_5).

cis/*trans*-**7a**

IR (Nujol): 3410, 3300 (N–H), 3140–2720 cm^{-1} (C–H).

Anal. Calcd for $C_{15}H_{21}NO_4$ (279.3): C, 64.50; H, 7.58; N, 5.01. Found: C, 64.51; H, 7.68; N, 4.96.

rac-Ethyl 3,4,5,6-Tetrahydro-4,5-*O*-isopropylidene-3-phenyl-2*H*-1,2-oxazine-3-carboxylate (7b) and *rac*-Ethyl 4-Amino-6-ethoxy-2,2-dimethyltetrahydrofuro[3,4-*d*][1,3]dioxole-4-carboxylate (8)

According to general procedure 1, 1,2-oxazine *rac*-**4b** (0.273 g, 1.00 mmol) was treated with BH_3·THF (3.3 mL, 3.30 mmol) in THF (10 mL), followed by workup and filtration (alumina, hexane–EtOAc, 5:1) to give a mixture of **7b** (*cis*/*trans* = 79:21) and **8** (0.188 g, 21% of **7b**; 49% of **8**).

The spectroscopic data of **7b** are in agreement with those given in ref. 17.

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IR (neat): 3420, 3340 (N–H), 3040–2810 (C–H), 1740 cm^{-1} (C=O).

^1H NMR ($CDCl_3$, 300 MHz): δ = 1.11, 1.32 (2 t, *J* = 7 Hz, 3 H each, 2 × CH_3), 1.37, 1.51 (2 s, 3 H each, 2 × CH_3), 2.47 (br s, 2 H, NH_2), 3.40, 3.70 (AB part of ABX_3 system, $J_{A,X} = J_{B,X}$ = 7 Hz, $J_{A,B}$ = 10 Hz, 2 H, OCH_2), 4.21 (m_c, 2 H, OCH_2), 4.62 (d, *J* = 6 Hz, 1 H, 4-H), 4.93 (s, 1 H, 5-H), 5.15 (d, *J* = 6 Hz, 1 H, 3-H).

^{13}C NMR ($CDCl_3$, 75.5 MHz): δ = 14.0, 14.7, 24.9, 26.3 (4 q, 4 × CH_3), 61.6, 63.2 (2 t, 2 × OCH_2), 79.8 (d, C-4), 84.8 (d, C-3), 93.6 (s, C-2), 105.3 (d, C-5), 112.6 (s, *C*Me_2), 169.7 (s, *C*O_2Et).

MS (EI, 70 eV): *m*/*z* = 261 (4), 231 (11), 203 (55), 144 (36), 129 (37), 119 (75), 115 (79), 114 (80), 100 (76), 85 (51), 71 (76), 59 (79), 56 (59), 43 (100), 31 (61).

Anal. Calcd for $C_{12}H_{21}NO_6$ (275.3): C, 52.35; H, 7.69; N, 5.09. Found: C, 52.23; H, 7.64; N, 4.94.

rac-3,4,5,6-Tetrahydro-4,5-*O*-isopropylidene-3-trifluoromethyl-2*H*-1,2-oxazine (7c)

According to general procedure 1, 1,2-oxazine *rac*-**4c** (0.226 g, 0.84 mmol) was treated with BH_3·THF (3.4 mL, 3.40 mmol) in THF (8 mL), followed by workup and purification using Kugelrohr distillation (85 °C/0.01 mbar) to give **7c** (0.157 g, 69%; single diastereomer) as colorless crystals; mp 88–89.5 °C.

IR (KBr): 3260 (N–H), 3090–2810 cm^{-1} (C–H).

^1H NMR ($CDCl_3$, 300 MHz): δ = 1.23 (t, *J* = 7 Hz, 3 H, CH_3), 1.38, 1.55 (2 s, 3 H each, 2 × CH_3), 3.64, 3.91 (AB part of ABX_3 system, $J_{A,X} = J_{B,X}$ = 7 Hz, $J_{A,B}$ = 9.5 Hz, 2 H, OCH_2), 3.95 (m_c, 1 H, 3-H), 4.02 (dd, *J* = 5.5, 6 Hz, 1 H, 5-H), 4.48 (dd, *J* = 3, 5.5 Hz, 1 H, 4-H), 4.61 (d, *J* = 6 Hz, 1 H, 6-H), 5.45 (br s, 1 H, NH).

^{13}C NMR ($CDCl_3$, 75.5 MHz): δ = 15.0, 25.7, 27.5 (3 q, 3 × CH_3), 59.3 (dq, $J_{C,F}$ = 29 Hz, C-3), 66.9 (t, OCH_2), 69.5 (d, C-5), 74.9 (d, C-4), 103.0 (d, C-6), 111.3 (s, *C*Me_2), 122.9 (q, $J_{C,F}$ = 281 Hz, CF_3).

Anal. Calcd for $C_{10}H_{16}F_3NO_4$ (271.2): C, 44.28; H, 5.95; N, 5.16. Found: C, 44.22; H, 5.81; N, 5.08.

Reduction of 1,2-Oxazine 4a with $NaBH_3CN$

1,2-Oxazine **4a** (0.205 g, 0.74 mmol) was dissolved in AcOH (7 mL) and $NaBH_3CN$ (0.187 g, 2.96 mmol) was added in portions under argon. The solution was stirred mechanically at r.t. for 6 h. After consumption of the starting material, the solution was slowly added to an aq sat. Na_2CO_3 solution (60 mL) and extracted with EtOAc (3 × 60 mL). The combined organic layers were concentrated in vacuo, and the crude product (*cis*:*trans* = 87:13) was purified by column chromatography (alumina, hexane–*t*-BuOMe, 5:1) to give **7a** (0.160 g, 77%).

Hydrogenolysis of *rac*-7a

A suspension of 10% Pd/C (0.100 g) in MeOH (10 mL) was saturated with H_2. 1,2-Oxazine *rac*-**7a** (0.279 g, 1.00 mmol) was added and the mixture was stirred at r.t. under H_2 at atmospheric pressure for 48 h. The suspension was then filtered through Celite, eluting with EtOAc. The filtrate was concentrated in vacuo and the crude product was purified by filtration (alumina, *t*-BuOMe) and Kugelrohr distillation (110 °C/0.01 mbar) to yield *rac*-**5a** as the all *cis*-configured diastereomer (0.178 g, 81%).

(1*S*,2*R*,4*R*)-2-(2-Bromovinyloxy)-1-isopropyl-4-methylcyclohexane (10)

To a solution of (–)-menthol (**9**; 39.1 g, 0.25 mol) in 1-bromo-2-ethoxyethene (**1**; 37.8 g, 0.25 mol), was added trifluoroacetic acid (1.0 mL) and the mixture was stirred for 5 d at r.t. The mixture was diluted with CH_2Cl_2 (100 mL) and washed once with aq sat. $NaHCO_3$ solution (30 mL). Separation of the layers, drying of the organic layer (Na_2SO_4) and concentration in vacuo gave the bromoacetal intermediate (69.5 g). The crude product was purified by Kugelrohr distillation (120 °C/0.06 mbar) to furnish the bromoacetal intermediate (51.1 g, 72%; two diastereomers = 1:1). Under argon, the bromoacetal (41.5 g, 0.135 mol) and Et_3N (19.1 g, 0.189 mol) were dissolved in CH_2Cl_2 (135 mL) and TMSOTf (33.1 g, 0.149 mmol) was added dropwise at 0 °C. After 16 h at 0 °C, aq 1 N NaOH solution (65 mL) and pentane (65 mL) were added, the layers were separated and the organic layer was dried (Na_2SO_4). Removal of the solvent, filtration through alumina (hexane), followed by Kugelrohr distillation of the crude product led to bromo enol ether **10** as a colorless oil (26.9 g, 79%; *Z*/*E* = 85:15).

(*Z*)-**10**

^1H NMR ($CDCl_3$, 200 MHz): δ = 0.72–1.74 (m, 16 H, 3-H, 4-H, 5-H, 6-H, 3 × CH_3), 1.94–2.24 (m, 2 H, 2-H, C*H*Me_2), 3.57 (dt, *J* = 4.5, 10.5 Hz, 1 H, 1-H), 5.05 (d, *J* = 4 Hz, 1 H, =CH), 6.65 (d, *J* = 4 Hz, 1 H, =CH).

^{13}C NMR ($CDCl_3$, 50.3 MHz): δ = 16.45, 20.6, 22.0 (3 q, 3 × CH_3), 23.6 (t, C-3), 25.9 (d, *C*HMe_2), 31.6 (d, C-5), 34.23 (t, C-4), 41.5 (t, C-6), 47.5 (d, C-2), 81.6 (d, C-1), 83.3 (d, =CH), 146.7 (d, =CH).

Additional signals assigned to (*E*)-**10**:

^1H NMR ($CDCl_3$, 200 MHz): δ = 0.78 (d, *J* = 7 Hz, 3 H, CH_3), 5.47 (d, *J* = 11.5 Hz, 1 H, =CH), 6.76 (d, *J* = 11.5 Hz, 1 H, =CH).

^{13}C NMR ($CDCl_3$, 50.3 MHz): δ = 16.39, 22.3 (2 q, 2 × CH_3), 23.5 (t, C-3), 31.5 (d, C-5), 34.19 (t, C-4), 40.9 (t, C-6), 47.7 (d, C-2), 81.7 (d, C-1), 84.2 (d, =CH), 149.8 (d, =CH).

(*Z*/*E*)-**10**

IR (neat): 2960–2870 (C–H), 1640 cm^{-1} (C=C).

Anal. Calcd for $C_{12}H_{21}BrO$ (261.2): C, 55.18; H, 8.10. Found: C, 55.30; H, 7.86.

(6*R*)- and (6*S*)-[(1*R*,2*S*,5*R*)-2-Isopropyl-5-methylcyclohexyloxy]-3-trifluoromethyl-6*H*-1,2-oxazine (13)

A solution of 2-bromo enol ether **10** (18.3 g, 70.0 mmol; *E*/*Z* = 85:15) and oxime **11** (1.44 g, 7.00 mmol) in *t*-BuOMe (175 mL) were stirred with freshly ground Na_2CO_3 (4.45 g, 42.0 mmol). After stirring at r.t. for 6 d, the suspension was filtered through a pad of Celite to remove the inorganic salts. To the resulting filtrate was added DBU (1.07 g, 70.0 mmol) and the solution was stirred at r.t. for 4 h. The organic layer was washed with H_2O (3 × 30 mL) and dried (Na_2SO_4). The solvent was removed in vacuo, and the excess of **10** was distilled off by Kugelrohr distillation (20–60 °C/15 mbar). The residue was filtered through alumina (hexane–EtOAc, 4:1) to furnish **13** (1.71 g, 80%, 6*R*/6*S* = 55:45). Separation of **13** (0.870 g) by flash chromatography (silica gel; hexane–EtOAc, 15:1) gave (6*S*)-**13** (0.336 g, 39%, de >94%) as colorless crystals; mp 64–71 °C, and (6*R*)-**13** (0.403 g, 46%, de = 86%) as a colorless oil.

(1′*R*,2′*S*,5′*R*,6*S*)-**13**

$[\alpha]_D$ +128 (*c* = 0.47, $CHCl_3$).

IR (KBr): 2980–2820 (C–H), 1630 (C=C), 1570 cm^{-1} (C=N).

^{1}H NMR ($CDCl_3$, 200 MHz): δ = 0.75–1.72 (m, 16 H, 3-H, 4′-H, 5′-H, 6′-H, 3 × CH_3), 1.95–2.27 (m, 2 H, 2′-H, C*H*Me_2), 3.60 (dt, *J* = 4.5, 10.5 Hz, 1 H, 1′-H), 5.70 (d, *J* = 4 Hz, 1 H, 6-H), 6.29 (d, *J* = 10 Hz, 1 H, 4-H), 6.38 (dd, *J* = 4, 10 Hz, 1 H, 5-H).

^{13}C NMR ($CDCl_3$, 50.3 MHz): δ = 16.3, 22.1, 23.2 (3 q, 3 × CH_3), 23.2 (t, C-3′), 25.7 (d, *C*HMe_2), 31.7 (d, C-5′), 34.2 (t, C-4′), 42.2 (t, C-6′), 48.3 (d, C-2′), 81.2 (d, C-1′), 94.0 (d, C-6), 111.9 (d, C-4), 120.3 (q, J_{C-F} = 274 Hz, CF_3), 126.2 (d, C-5), 147.1 (q, $J_{C,F}$ = 35 Hz, C-3).

(1′*R*,2′*S*,5′*R*,6*R*)-**13**

$[\alpha]_D$ –174 (*c* = 0.43, $CHCl_3$).

IR (neat): 2970–2820 (C–H), 1630 (C=C), 1575 cm^{-1} (C=N).

^{1}H NMR ($CDCl_3$, 200 MHz): δ = 0.74–1.72 (m, 16 H, 3-H, 4′-H, 5′-H, 6′-H, 3 × CH_3), 1.89, 2.08–2.20 (m_c, m, 1 H each, 2′-H, C*H*Me_2), 3.81 (dt, *J* = 4, 10.5 Hz, 1 H, 1′-H), 5.81 (d, *J* = 3.5 Hz, 1 H, 6-H), 6.25 (d, *J* = 9.5 Hz, 1 H, 4-H), 6.35 (dd, *J* = 3.5, 9.5 Hz, 1 H, 5-H).

^{13}C NMR ($CDCl_3$, 50.3 MHz): δ = 15.7, 20.7, 22.2 (3 q, 3 × CH_3), 23.3 (t, C-3′), 25.3 (d, *C*HMe_2), 31.4 (d, C-5′), 34.3 (t, C-4′), 40.1 (t, C-6′), 48.0 (d, C-2′), 75.7 (d, C-1′), 89.2 (d, C-6), 112.0 (d, C-4), 120.4 (q, $J_{C,F}$ = 274 Hz, CF_3), 126.9 (d, C-5), 147.6 (q, $J_{C,F}$ = 35 Hz, C-3).

Anal. Calcd for $C_{15}H_{22}F_3NO_2$ (305.3) from a mixture of (6*S*)- and (6*R*)-**13**: C, 59.00; H, 7.26; N, 4.59. Found: C, 58.93; H, 7.29; N, 4.95.

Dihydroxylation and Acetalization of 1,2-Oxazines, General Procedure 2

To a vigorously stirred solution of the corresponding 1,2-oxazine in a mixture of EtOAc and MeCN (18 mL each/mmol of 1,2-oxazine) at 0 °C, was added a solution of $RuCl_3·3H_2O$ (0.07 equiv) and $NaIO_4$ (1.5 equiv) in H_2O (5 mL/mmol of 1,2-oxazine). The mixture was stirred vigorously for 3–4 min and then quenched with aq sat. $Na_2S_2O_3$ solution (10 mL/mmol of 1,2-oxazine). The aqueous phase was separated, extracted with EtOAc (3 × 20 mL/mmol of 1,2-oxazine) and the combined organic extracts were dried ($MgSO_4$). Evaporation of the solvent under reduced pressure gave the 4,5-dihydroxylated 1,2-oxazine, which was directly protected without further purification.

To a solution of the dried 4,5-dihydroxylated 1,2-oxazine in acetone (4–20 mL/mmol of 1,2-oxazine) were added 2,2-DMP (1–10 mL/mmol of 1,2-oxazine) and *p*-TsOH (40 mg/mmol of 1,2-oxazine). The mixture was stirred for 4 h at r.t., then an excess of solid $NaHCO_3$ was added. The suspension was filtered, the solvent was removed in vacuo, and the resulting crude product was purified by column chromatography.

(4*R*,5*R*,6*R*)-6-[(1*R*,2*S*,5*R*)-2-Isopropyl-5-methylcyclohexyloxy]-4,5-isopropylidene-3-phenyl-5,6-dihydro-4*H*-1,2-oxazine [(6*R*)-16]

According to general procedure 2, 1,2-oxazine (6*R*)-**14** (0.940 g, 3.00 mmol) was treated with $RuCl_3·3H_2O$ (0.054 g, 0.21 mmol) and $NaIO_4$ (0.963 g, 4.50 mmol), followed by acetalization with 2,2-DMP (20 mL) in the presence of *p*-TsOH (0.120 g). Workup and column chromatography (alumina, hexane–EtOAc, 8:1) afforded (6*R*)-**16** (0.800 g, 69%, de >94%) as colorless crystals; mp 124–127 °C;

$[\alpha]_D$ –72.3 (*c* = 0.51, $CHCl_3$).

IR (KBr): 3100–2775 (=C–H, C–H), 1580 cm^{-1} (C=N).

^{1}H NMR ($CDCl_3$, 200 MHz): δ = 0.68–1.73 (m, 22 H, 3-H, 4′-H, 5′-H, 6′-H, 5 × CH_3), 1.93–2.22 (m, 2 H, 2′-H, C*H*Me_2), 3.71 (dt, *J* = 4, 10.5 Hz, 1 H, 1′-H), 4.36 (dd, *J* = 4, 7 Hz, 1 H, 5-H), 4.94 (d, *J* = 7 Hz, 1 H, 4-H), 5.16 (d, *J* = 4 Hz, 1 H, 6-H), 7.36–7.46, 7.78–7.88 (2 m, 3 H, 2 H, C_6H_5).

^{13}C NMR ($CDCl_3$, 50.3 MHz): δ = 15.8, 20.9, 22.3, 26.0, 27.0 (5 q, 5 × CH_3), 23.2 (t, C-3′), 25.4 (d, *C*HMe_2), 31.3 (d, C-5′), 34.4 (t, C-4′), 39.5 (t, C-6′), 47.9 (d, C-2′), 65.6 (d, C-1′), 72.7 (d, C-4), 75.9 (d, C-5), 94.6 (d, C-6), 110.9 (s, *C*Me_2), 126.6, 128.4, 129.9, 133.7 (3 d, s, C_6H_5), 157.1 (s, C-3).

Anal. Calcd for $C_{23}H_{33}NO_4$ (387.5): C, 71.30; H, 8.58; N, 3.61. Found: C, 71.40; H, 8.79; N, 3.45.

(4*S*,5*S*,6*S*)-6-[(1*R*,2*S*,5*R*)-2-Isopropyl-5-methylcyclohexyloxy]-4,5-isopropylidene-3-phenyl-5,6-dihydro-4*H*-1,2-oxazine [(6*S*)-16]

According to general procedure 2, 1,2-oxazine (6*S*)-**14** (0.313 g, 1.00 mmol) was treated with $RuCl_3·3H_2O$ (0.018 g, 0.07 mmol) and $NaIO_4$ (0.321 g, 1.50 mmol), followed by acetalization with 2,2-DMP (7 mL) in the presence of *p*-TsOH (0.040 g). Workup and column chromatography (alumina, hexane–EtOAc, 8:1) afforded (6*S*)-**16** (0.250 g, 65%, de >94%) as colorless crystals; mp 138–140 °C;

$[\alpha]_D$ +28.0 (*c* = 0.51, $CHCl_3$).

IR (KBr): 3100–2750 (=C–H, C–H), 1575 cm^{-1} (C=N).

^{1}H NMR ($CDCl_3$, 200 MHz): δ = 0.75–1.70 (m, 22 H, 3-H, 4′-H, 5′-H, 6′-H, 5 × CH_3), 2.09–2.32 (m, 2 H, 2′-H, C*H*Me_2), 3.56 (dt, *J* = 4.5, 10.5 Hz, 1 H, 1′-H), 4.37 (dd, *J* = 4.5, 6.5 Hz, 1 H, 5-H), 4.92 (d, *J* = 4.5 Hz, 1 H, 6-H), 4.95 (d, *J* = 6.5 Hz, 1 H, 4-H), 7.37–7.47, 7.80–7.90 (2 m, 3 H, 2 H, C_6H_5).

^{13}C NMR ($CDCl_3$, 50.3 MHz): δ = 16.2, 21.1, 22.1, 26.0, 27.1 (5 q, 5 × CH_3), 23.1 (t, C-3′), 25.4 (d, *C*HMe_2), 31.7 (d, C-5′), 34.3 (t, C-4′), 42.6 (t, C-6′), 48.8 (d, C-2′), 66.2 (d, C-1′), 72.4 (d, C-4), 81.3 (d, C-5), 99.8 (d, C-6), 110.6 (s, *C*Me_2), 126.7, 128.5, 130.0, 133.6 (3 d, s, C_6H_5), 156.7 (s, C-3).

Anal. Calcd for $C_{23}H_{33}NO_4$ (387.5): C, 71.30; H, 8.58; N, 3.61. Found: C, 71.48; H, 8.82; N, 3.54.

(4*R*,5*R*,6*R*)-6-[(1*R*,2*S*,5*R*)-2-Isopropyl-5-methylcyclohexyloxy]-4,5-isopropylidene-3-trifluoromethyl-5,6-dihydro-4*H*-1,2-oxazine [(6*R*)-15]

According to general procedure 2, 1,2-oxazine (6*R*)-**13** (0.305 g, 1.00 mmol, de = 86%) was treated with $RuCl_3·3H_2O$ (0.018 g, 0.07 mmol) and $NaIO_4$ (0.321 g, 1.50 mmol), followed by acetalization with 2,2-DMP (7 mL) in the presence of *p*-TsOH (0.040 g). Workup and column chromatography (alumina, hexane–EtOAc, 15:1) afforded (6*R*)-**15** [0.232 g, 61%, de >94%, containing 7% of (6*S*)-**15**] as colorless crystals; mp 90–95 °C; $[\alpha]_D$ –203 (*c* = 0.42, $CHCl_3$).

IR (KBr): 2960–2870 (=C–H, C–H), 1640 cm^{-1} (C=N).

^{1}H NMR ($CDCl_3$, 300 MHz): δ = 0.68–1.72 (m, 22 H, 3-H, 4′-H, 5′-H, 6′-H, 5 × CH_3), 1.88, 2.08–2.15 (m_c, m, 1 H each, 2′-H, C*H*Me_2), 3.64 (dt, *J* = 4, 10.5 Hz, 1 H, 1′-H), 4.32 (dd, *J* = 2.5, 6.5 Hz, 1 H, 5-H), 4.65 (d, *J* = 6.5 Hz, 1 H, 4-H), 5.37 (d, *J* = 2.5 Hz, 1 H, 6-H).

^{13}C NMR ($CDCl_3$, 50.3 MHz): δ = 15.5, 20.8, 22.2, 26.1, 26.9 (5 q, 5 × CH_3), 23.0 (t, C-3′), 25.4 (d, *C*HMe_2), 31.2 (d, C-5′), 34.3 (t, C-4′), 39.1 (t, C-6′), 47.8 (d, C-2′), 62.2 (d, C-1′), 71.0 (d, C-4), 76.2 (d, C-5), 93.4 (d, C-6), 112.3 (s, *C*Me_2), 120.1 (q, $J_{C,F}$ = 276 Hz, CF_3), 149.6 (q, $J_{C,F}$ = 33 Hz, C-3).

Anal. Calcd for $C_{18}H_{28}F_3NO_4$ (379.4): C, 56.98; H, 7.44; N, 3.69. Found: C, 57.35; H, 7.79; N, 3.60.

(4*S*,5*S*,6*S*)-6-[(1*R*,2*S*,5*R*)-2-Isopropyl-5-methylcyclohexyloxy]-4,5-isopropylidene-3-trifluoromethyl-5,6-dihydro-4*H*-1,2-oxazine [(6*S*)-15]

According to general procedure 2, 1,2-oxazine (6*S*)-**13** (0.305 g, 1.00 mmol) was treated with $RuCl_3·3H_2O$ (0.018 g, 0.07 mmol) and $NaIO_4$ (0.321 g, 1.50 mmol), followed by acetalization with 2,2-DMP (7 mL) in the presence of *p*-TsOH (0.040 g). Workup and column chromatography (alumina, hexane–EtOAc, 15:1) afforded

(6*S*)-**15** (0.237 g, 62%, de >94%) as colorless crystals; mp 109–113 °C; $[\alpha]_D$ +131 (*c* = 0.40, $CHCl_3$).

IR (KBr): 2960–2870 (=C–H, C–H), 1640 cm^{-1} (C=N).

^1H NMR ($CDCl_3$, 300 MHz): δ = 0.65–1.68 (m, 22 H, 3-H, 4′-H, 5′-H, 6′-H, 5 × CH_3), 1.96–2.11 (m, 2 H, 2′-H, C*H*Me_2), 3.53 (dt, *J* = 4.5, 10.5 Hz, 1 H, 1′-H), 4.34 (dd, *J* = 3, 6.5 Hz, 1 H, 5-H), 4.64 (d, *J* = 6.5 Hz, 1 H, 4-H), 5.14 (d, *J* = 3 Hz, 1 H, 6-H).

^{13}C NMR ($CDCl_3$, 50.3 MHz): δ = 16.2, 21.1, 22.0, 26.1, 27.0 (5 q, 5 × CH_3), 23.1 (t, C-3′), 25.6 (d, *C*HMe_2), 31.6 (d, C-5′), 34.1 (t, C-4′), 42.0 (t, C-6′), 48.6 (d, C-2′), 62.7 (d, C-1′), 70.6 (d, C-4), 81.9 (d, C-5), 98.9 (d, C-6), 112.2 (s, *C*Me_2), 120.2 (q, $J_{C,F}$ = 276 Hz, CF_3), 149.9 (q, $J_{C,F}$ = 33 Hz, C-3).

Anal. Calcd for $C_{18}H_{28}F_3NO_4$ (379.4): C, 56.98; H, 7.44; N, 3.69. Found: C, 57.15; H, 7.50; N, 3.62.

(3*S*,4*R*,5*R*,6*R*)-6-[(1*R*,2*S*,5*R*)-2-Isopropyl-5-methylcyclohexyloxy]-4,5-isopropylidene-3-phenyl-3,4,5,6-tetrahydro-2*H*-1,2-oxazine [(6*R*)-18]

According to general procedure 1, 1,2-oxazine (6*R*)-**16** (0.194 g, 0.50 mmol) was treated with BH_3·THF (2.0 mL, 2.00 mmol) in THF (5 mL). Workup and purification using column chromatography (alumina, hexane–EtOAc, 6:1) afforded (6*R*)-**18** (0.081 g, 43%; de >94%) as colorless crystals; mp 42–45 °C; $[\alpha]_D$ –40.7 (*c* = 0.30, $CHCl_3$).

IR (KBr): 3440 (N–H), 2985–2870 (=C–H, C–H) cm^{-1}.

^1H NMR ($CDCl_3$, 300 MHz): δ = 0.75–1.70 (m, 22 H, 3-H, 4′-H, 5′-H, 6′-H, 5 × CH_3), 2.06–2.32 (m, 2 H, 2′-H, C*H*Me_2), 3.55 (dt, *J* = 4.5, 10.5 Hz, 1 H, 1′-H), 3.98 (dd, *J* = 5, 7 Hz, 1 H, 5-H), 4.46 (dd, *J* = 2.5, 5 Hz, 1 H, 4-H), 4.49 (br s, 1 H, 3-H), 4.88 (d, *J* = 7 Hz, 1 H, 6-H), 5.43 (br s, 1 H, NH), 7.27–7.38, 7.41–7.49 (2 m, 3 H, 2 H, C_6H_5).

^{13}C NMR ($CDCl_3$, 75.5 MHz): δ = 15.8, 20.9, 22.3, 26.2, 28.1 (5 q, 5 × CH_3), 23.2 (t, C-3′), 25.3 (d, *C*HMe_2), 31.6 (d, C-5′), 34.4 (t, C-4′), 40.3 (t, C-6′), 47.5 (d, C-2′), 62.9 (d, C-1′), 75.6, 76.0, 77.5 (3 d, C-3, C-4, C-5), 100.7 (d, C-6), 110.1 (s, *C*Me_2), 128.27, 128.31, 128.7, 135.4 (3 d, s, C_6H_5).

Anal. Calcd for $C_{23}H_{35}NO_4$ (389.5): C, 70.92; H, 9.06; N, 3.60. Found: C, 70.86; H, 9.07; N, 3.71.

(3*R*,4*S*,5*S*,6*S*)-6-[(1*R*,2*S*,5*R*)-2-Isopropyl-5-methylcyclohexyloxy]-4,5-isopropylidene-3-phenyl-3,4,5,6-tetrahydro-2*H*-1,2-oxazine [(6*S*)-18]

According to general procedure 1, 1,2-oxazine (6*S*)-**16** (0.194 g, 0.50 mmol) was treated with BH_3·THF (2.0 mL, 2.00 mmol) in THF (5 mL). Workup and purification using column chromatography (alumina, hexane–EtOAc, 6:1) afforded (6*S*)-**18** (0.130 g, 71%; de >94%) as a colorless resin; $[\alpha]_D$ –55.4 (*c* = 0.57, $CHCl_3$).

IR (KBr): 3450 (N–H), 2960–2870 cm^{-1} (=C–H, C–H).

^1H NMR ($CDCl_3$, 300 MHz): δ = 0.75–1.70 (m, 22 H, 3-H, 4′-H, 5′-H, 6′-H, 5 × CH_3), 2.12–2.21, 2.38 (m, m_c, 1 H each, 2′-H, C*H*Me_2), 3.45 (dt, *J* = 4.5, 10.5 Hz, 1 H, 1′-H), 4.01 (dd, *J* = 5, 7 Hz, 1 H, 5-H), 4.43–4.49 (m, 2 H, 3-H, 4-H), 4.82 (d, *J* = 7 Hz, 1 H, 6-H), 5.45 (br s, 1 H, NH), 7.28–7.38, 7.42–7.50 (2 m, 3 H, 2 H, C_6H_5).

^{13}C NMR ($CDCl_3$, 75.5 MHz): δ = 16.1, 21.1, 23.1, 26.3, 28.1 (5 q, 5 × CH_3), 23.1 (t, C-3′), 24.8 (d, *C*HMe_2), 31.8 (d, C-5′), 34.3 (t, C-4′), 43.8 (t, C-6′), 48.7 (d, C-2′), 62.7 (d, C-1′), 75.5, 76.3, 82.5 (3 d, C-3, C-4, C-5), 105.6 (d, C-6), 110.1 (s, *C*Me_2), 128.2, 128.3, 128.6, 135.4 (3 d, s, C_6H_5).

Anal. Calcd for $C_{23}H_{35}NO_4$ (389.5): C, 70.92; H, 9.06; N, 3.60. Found: C, 71.23; H, 9.43; N, 3.42.

(3*R*,4*R*,5*R*,6*R*)-6-[(1*R*,2*S*,5*R*)-2-Isopropyl-5-methylcyclohexyloxy]-4,5-isopropylidene-3-trifluoromethyl-3,4,5,6-tetrahydro-2*H*-1,2-oxazine [(6*R*)-17]

According to general procedure 1, 1,2-oxazine (6*R*)-**15** [0.189 g, 0.50 mmol, containing 7% of (6*S*)-**15**] was treated with BH_3·THF (2.0 mL, 2.00 mmol) in THF (5 mL). Workup and purification using column chromatography (alumina, hexane–EtOAc, 6:1) afforded (6*R*)-**17** [0.130 g, 68%, de >94%, containing 9% of (6*S*)-**17**] as a colorless oil; $[\alpha]_D$ –89.1 (*c* = 0.29, $CHCl_3$).

IR (neat): 3250 (N–H), 2970–2870 cm^{-1} (C–H).

^1H NMR ($CDCl_3$, 300 MHz): δ = 0.75–1.71 (m, 22 H, 3-H, 4′-H, 5′-H, 6′-H, 5 × CH_3), 2.00–2.20 (m, 2 H, 2′-H, C*H*Me_2), 3.52 (dt, *J* = 4.5, 11 Hz, 1 H, 1′-H), 3.95–4.09 (m, 2 H, 3-H, 5-H), 4.49 (dd, *J* = 3, 5.5 Hz, 1 H, 4-H), 4.73 (d, *J* = 6.5 Hz, 1 H, 6-H), 5.39 (d, *J* = 9 Hz, 1 H, NH).

^{13}C NMR ($CDCl_3$, 75.5 MHz): δ = 15.7, 20.9, 22.2, 26.0, 27.7 (5 q, 5 × CH_3), 23.1 (t, C-3′), 25.3 (d, *C*HMe_2), 31.4 (d, C-5′), 34.3 (t, C-4′), 40.1 (t, C-6′), 47.5 (d, C-2′), 59.7 (q, $J_{C,F}$ = 29 Hz, C-3), 70.0, 75.3, 77.7 (3 d, C-4, C-5, C-1′), 100.3 (d, C-6), 111.2 (s, *C*Me_2), 123.0 (q, $J_{C,F}$ = 281 Hz, CF_3).

Anal. Calcd for $C_{18}H_{30}F_3NO_4$ (381.4): C, 56.68; H, 7.93; N, 3.67. Found: C, 56.51; H, 8.19; N, 3.73.

(3*S*,4*S*,5*S*,6*S*)-6-[(1*R*,2*S*,5*R*)-2-Isopropyl-5-methylcyclohexyloxy]-4,5-isopropylidene-3-trifluoromethyl-3,4,5,6-tetrahydro-2*H*-1,2-oxazine [(6*S*)-17]

According to general procedure 1, 1,2-oxazine (6*S*)-**15** (0.172 g, 0.45 mmol) was treated with BH_3·THF (1.8 mL, 1.80 mmol) in THF (5 mL). Workup and purification using column chromatography (alumina, hexane–EtOAc, 8:1) afforded (6*S*)-**17** (0.165 g, 67%, de >94%) as colorless crystals; mp 77–80 °C; $[\alpha]_D$ –15.2 (*c* = 0.48, $CHCl_3$).

IR (KBr): 3450 (N–H), 2980–2875 cm^{-1} (C–H).

^1H NMR ($CDCl_3$, 300 MHz): δ = 0.74–1.68 (m, 22 H, 3-H, 4′-H, 5′-H, 6′-H, 5 × CH_3), 2.09–2.18, 2.27 (m, m_c, 1 H each, 2′-H, C*H*Me_2), 3.40 (dt, *J* = 4.5, 10.5 Hz, 1 H, 1′-H), 3.92–4.07 (m, 2 H, 3-H, 5-H), 4.47 (dd, *J* = 2.5, 5.5 Hz, 1 H, 4-H), 4.65 (d, *J* = 6.5 Hz, 1 H, 6-H), 5.40 (d, *J* = 9.5 Hz, 1 H, NH).

^{13}C NMR ($CDCl_3$, 75.5 MHz): δ = 16.1, 21.0, 22.1, 26.1, 27.7 (5 q, 5 × CH_3), 23.1 (t, C-3′), 25.0 (d, *C*HMe_2), 31.7 (d, C-5′), 34.2 (t, C-4′), 43.5 (t, C-6′), 48.6 (d, C-2′), 59.7 (q, $J_{C,F}$ = 29 Hz, C-3), 70.0, 75.5, 82.7 (3 d, C-4, C-5, C-1′), 105.4 (d, C-6), 111.2 (s, *C*Me_2), 122.9 (q, $J_{C,F}$ = 281 Hz, CF_3).

Anal. Calcd for $C_{18}H_{30}F_3NO_4$ (381.4): C, 56.68; H, 7.93; N, 3.67. Found: C, 56.83; H, 8.10; N, 3.48.

Hydrogenolysis of (6*R*)-18

Following the procedure for the hydrogenolysis of *rac*-**4a**, 1,2-oxazine (6*R*)-**18** (0.097 g, 0.25 mmol) was treated with H_2 and 10% Pd/C (0.025 g) in MeOH (2.5 mL). Removal of (–)-menthol (**9**) by Kugelrohr distillation (110 °C/0.01 mbar) and purification of the residue by column chromatography (alumina, hexane–EtOAc, 1:2) provided (2*S*,3*R*,4*S*)-**5** (0.018 g, 37%, de, ee >94%) as colorless crystals; mp 49–53 °C; $[\alpha]_D$ +138 (*c* = 0.21, $CHCl_3$).

Hydrogenolysis of (6*S*)-18

Following the procedure for the hydrogenolysis of *rac*-**4a**, 1,2-oxazine (6*S*)-**18** (0.077 g, 0.20 mmol) was treated with H_2 and 10% Pd/C (0.020 g) in MeOH (2 mL). Removal of (–)-menthol (**9**) by Kugelrohr distillation (110 °C/0.01 mbar) and purification by column chromatography (alumina, hexane–EtOAc, 1:2) provided (2*R*,3*S*,4*R*)-**5** (0.021 g, 51%, de, ee >94%) as colorless crystals; mp 50–54 °C; $[\alpha]_D$ –130 (*c* = 0.30, $CHCl_3$).

Acknowledgment

Generous support by the Deutsche Forschungsgemeinschaft (Graduiertenkolleg 'Struktur-Eigenschafts-Beziehungen bei Heterocyclen'), the Fonds der Chemischen Industrie, and the Schering AG is most gratefully acknowledged. We also thank Dr. Robert Pulz for experimental assistance.

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