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

Hans-Ulrich Reissig,*a Kai Homann,b Florian Hillerb, Reinhold Zimmer*a

a Institut für Chemie und Biochemie, Freie Universität Berlin, Takustraße 3, 14195 Berlin, Germany
Fax +49(30)83855367; E-mail: hans.reissig@chemie.fu-berlin.de
b Institut für Organische Chemie, Technische Universität Darmstadt, 64287 Darmstadt, Germany

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 BH₃·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 dihydroxylaton and BH₃·THF reduction furnished enantiopure tetrahydro-2H-1,2-oxazine derivatives 17 and 18 in good overall yield. Enantiomers (6R)-18 and (6S)-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 6H-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-4H-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-4H-1,2-oxazines as useful key intermediates for preparation of pyroles,8,9 proline derivatives,10 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 KMnO₄ or with RuCl₃/NaIO₄ and finally protection as acetal with 2,2-dimethoxypropane (Scheme 1).5

![Scheme 1](image)

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 = CO₂Et 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.

![Scheme 2](image)
The transformation of 5,6-dihydro-4H-1,2-oxazines into acyclic amines or pyrrolidines by catalytic hydrogenation is well investigated. A plausible mechanism of this multi-step 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-2H-pyrrrole.\textsuperscript{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 sterecontrol 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.\textsuperscript{15} Reduction of 1,2-oxazines rac-4 with BH\textsubscript{3}·THF followed by treatment with aqueous 2 N NaOH solution furnished the tetrahydro-2H-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,\textsuperscript{16} which afforded only tetrahydro-2H-1,2-oxazine rac-7b in 48% yield and with high cis-trans selectivity.\textsuperscript{17} The reduction of phenyl-substituted precursor rac-4a with NaBH₃CN in acetic acid gave a better yield (77%), but the diastereoselectivity was only moderate.\textsuperscript{18} In all examples 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.\textsuperscript{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-
Reductive Ring Contraction of 1,2-Oxazines to Pyrrolidines

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. This method afforded menthyloxy-substituted bromo enol ether 10 in good yield as a 85:15 Z/E mixture (Scheme 5).

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, to furnish 6-menthlyoxy-substituted 6H-1,2-oxazine 13 in 80% yield as a 1:1 mixture of 6R- and 6S-diastereomers (Scheme 6). Separation of the isomers by flash chromatography allowed isolation of essentially pure (6S)-13 and diastereomerically highly enriched (6R)-13. Similarly, the corresponding 3-ethoxycarbonyl-6H-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 = CO₂Et 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-6H-1,2-oxazine was not possible either by flash chromatography nor by HPLC. The already described synthesis of 6-menthlyoxy-3-phenyl-6H-1,2-oxazine (14) employs an alternative route in which (–)-menthol (9) was added to an easily available phenyl substituted azapyrylium intermediate. The absolute configuration of (6S)-14 at C-6 was unambiguously determined by an X-ray analysis. The assignments of configuration for (6S)-13 and (6R)-13 are based on comparison of the NMR data.

Subsequent treatment of the bicyclic compounds (6R)-15, (6R)-16 and (6S)-15, (6S)-16 with BH₃/THF complex led to diastereoselective reduction of the C=N bond to give the expected products (6R)-17, (6R)-18 and (6S)-17, (6S)-18 in moderate to good yields (Scheme 8). With the exception of trifluoromethyl-substituted 1,2-oxazine (6R)-17, all other products were diastereomerically pure (de >94%). The menthlyoxy 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.

Synthesis 2007, No. 17, 2681–2689 © Thieme Stuttgart · New York
Scheme 7 Dihydroxylations of diastereomerically pure 6H-1,2-oxazines 13 and 14. Reagents and conditions: (a) RuCl₃·3H₂O, NaIO₄, MeCN–(EtOAc)–H₂O, 0 °C, 3–4 min; (b) 2,2-DMP, oxazines 17.

Scheme 8 Reduction of 5,6-dihydro-4H-1,2-oxazines with borane-tetrahydrofuran complex. Reagents and conditions: (a) BH₃·THF, THF, r.t.; (b) 2 N NaOH, r.t.

Scheme 9 Reductive ring contraction of tetrahydro-2H-1,2-oxazines into enantiopure pyrrolidines. Reagents and conditions: (a) H₂, Pd/C, MeOH, r.t., 24–48 h.

In summary, we could demonstrate that the standard reductive ring contractions of 5,6-dihydro-4H-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-4H-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.

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 ¹³C NMR spectra were recorded on Bruker instruments (AC 200, AC 300 or DXR 500) in CDCl₃ solution. The chemical shifts are given relative to the TMS or to the CDCl₃ signal (δH = 7.27, δC = 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 1,2,3rac-4a,b,2,5 and 11 were prepared by literature procedures. All other chemicals were commercially available and were used as received.

rac-3,4,4-O-Isopropylidene-2-pheny pyrrolidine (5)
A suspension of 10% Pd/C (0.290 g) in EtOH (29 mL) was saturated with H₂, 1,2-oxazine rac-4a (0.804 g, 2.90 mmol) was added and the mixture was stirred at r.t. under H₂ 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 chromatography using a chromatotron (hexane–EtOAc, 5:1) to yield a mixture of cis/trans isomers (33:67) (0.597 g, 94%). The mixture of diastereomers was separated by chromatography using a hexamethylenediamine–EtOAc eluent.

cis-5
Colorless oil.

IR (neat): 3340 (N–H), 3090–2860 cm⁻¹ (=C–H, C–H).


Found: C, 55.93; H, 8.05; N, 6.28.

Reduction of 1,2-Oxazines with BH₃·THF; General Procedure 1
Under argon, the corresponding 1,2-oxazine dissolved in THF (10 mL/mmol of 1,2-oxazine) was treated with BH₃·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 (Na₂SO₄) 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-2H-1,2-oxazine (7a)
According to general procedure 1, 1,2-oxazine rac-4a (1.09 g, 3.93 mmol) was treated with BH₃·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.

'H NMR (CDCl₃, 300 MHz): δ = 1.28 (t, J = 7 Hz, 3 H, CH₃), 1.31, 1.57 (2 s, 3 H each, 2 × CH₃), 3.72, 3.97 (AB part of ABX₃ system, Jₓₓ = Jₓₓ = 7 Hz, Jₓₓ = 9.5 Hz, 2 H, OCH₃), 4.00, 4.46 (2 m, 1 H, 2 H, 3–4, 4–5, 5–6), 4.78 (dd, J = 7 Hz, 1 H, 6–5), 5.49 (br s, 1 H, NH), 7.31–7.38, 7.43–7.47 (2 m, 3 H, 2 H, C₆H₅).

'C NMR (CDCl₃, 75.5 MHz): δ = 15.3, 26.1, 28.3 (3 q, 3 CH₃), 62.9 (d, C-3), 65.9 (t, OCH₃), 75.5, 75.9 (2 d, C-4, C-5), 103.8 (d, C-6), 110.2 (s, C-15), 128.3, 128.7, 135.4 (2 d, s, C₆H₅).

Additional signals assigned to trans-isomer:

'H NMR (CDCl₃, 300 MHz): δ = 1.10, 1.48 (2 s, 3 H each, 2 × CH₃), 1.13 (t, J = 7 Hz, 3 H, CH₃), 3.57, 3.95 (AB part of ABX₃ system, Jₓₓ = Jₓₓ = 7 Hz, Jₓₓ = 9.5 Hz, 2 H, OCH₃), 4.05, 4.13 (2 m, 1 H, 2 H, 3–4, 4–5, 5–6), 4.96 (d, J = 6.5 Hz, 1 H, 6–5), 5.14 (br s, 1 H, NH), 7.06–7.16, 7.37–7.39 (2 m, 3 H, 2 H, C₆H₅).

'C NMR (CDCl₃, 75.5 MHz): δ = 14.9, 26.2 (2 q, 2 H, OCH₃), 63.0 (d, C-3), 63.8 (t, OCH₃), 73.4, 74.6 (2 d, C-4, C-5), 99.1 (d, C-6), 110.9 (s, C-15), 137.3 (s, C₆H₅).

cis/trans-7a
IR (Nujol): 3410, 3300 (N–H), 3140–2720 cm⁻¹ (C–H).

Synthesis 2007, No. 17, 2681–2689 © Thieme Stuttgart · New York
rac-Ethyl 3,4,5,6-Tetrahydro-4,5-O-isopropylidene-3-phenyl-2H-1,2-oxazine-3-carboxylate (7b) and rac-Ethyl 4-Amino-6-ethoxy-2,2-dimethyltetrahydrofurano[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 BH₃·THF (3.4 mL, 3.40 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.

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

According to general procedure 1, 1,2-oxazine rac-4c (0.226 g, 0.84 mmol) was treated with BH₃·THF (3.4 mL, 3.40 mmol) in THF (8 mL), followed by workup and purification using Kugelrohr distillation (120 °C/0.01 mbar) to furnish the bromoacetate intermediate (51.5 g, 72%; two diastereomers = 1:1). Under argon, the bromoacetate (41.5 g, 0.135 mol) and Et,N (19.1 g, 0.189 mol) were dissolved in CH₂Cl₂ (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 (Na₂SO₄). 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).

1H NMR (CDCl₃, 200 MHz): δ = 0.72–1.74 (m, 16 H, 3–CH₃, 4–CH₃, 5–CH₃), 1.94–2.24 (m, 2 H, 2–H, CH₂Me), 3.57 (dt, J = 4.5, 10.5 Hz, 1 H, 1-H), 5.05 (d, J = 4 Hz, 1 H, =CH).

Additional signals assigned to (E)-10:

1H NMR (CDCl₃, 200 MHz): δ = 0.78 (d, J = 7 Hz, 3 CH₃), 5.47 (d, J = 11.5 Hz, 1 H, =CH), 6.76 (d, J = 11.5 Hz, 1 H, =CH). 13C NMR (CDCl₃, 50.3 MHz): δ = 16.45, 20.6, 22.0 (3 q, 3 × CH₃), 23.6 (t, C-6), 25.9 (t, CHMe₂), 31.6 (d, C-5), 34.2 (t, C-4), 41.5 (t, C-6), 47.5 (d, C-2), 81.6 (d, C-1), 85.3 (d, =CH), 146.7 (d, =CH).

Reduction of 1,2-Oxazine 4a with NaBH₄CN

A suspension of 10% Pd/C (0.100 g) in MeOH (10 mL) was saturated with H₂, 1,2-Oxazine rac-7a (0.279 g, 1.00 mmol) was added and the mixture was stirred at r.t. under H₂ 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%).
1H NMR (CDCl₃, 200 MHz): δ = 0.75–1.72 (m, 16 H, 3-H, 4′-H, 5′-H, 6′-H, 3 × CH₃), 1.95–2.27 (m, 2 H, 2′-H, CHMe₃), 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).

13C NMR (CDCl₃, 50.3 MHz): δ = 16.3, 22.1, 23.2 (3 q, 3 × CH₃), 23.2 (t, C-3′), 25.7 (d, CHMe₃), 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, JCF = 274 Hz, CF₃), 126.2 (d, C-5), 147.1 (q, JCF = 35 Hz, C-3).

(1′R,2′S,5′R,6′S)-13
[a]D = 174 (c = 0.43, CHCl₃).

IR (neat): 2970–2820 (C–H), 1630 (C=O), 1575 cm⁻¹ (C=–N).

1H NMR (CDCl₃, 200 MHz): δ = 0.74–1.72 (m, 16 H, 3-H, 4′-H, 5′-H, 6′-H, 3 × CH₃), 1.89, 20.8–20.20 (m, m, 1 H each, 2′-H, CHMe₃), 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).

13C NMR (CDCl₃, 50.3 MHz): δ = 15.7, 20.7, 22.2 (3 q, 3 × CH₃), 23.3 (t, C-3′), 25.3 (d, CHMe₃), 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, JCF = 274 Hz, CF₃), 126.9 (d, C-5), 147.6 (q, JCF = 35 Hz, C-3).

Anal. Calcd for C₁₅H₂₂F₃NO₂ (305.3): C, 66%; H, 9.2%.

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 RuCl₃·3H₂O (0.07 equiv) and NaIO₄ (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 (6S)-16 (0.250 g, 65%, de >94%) as colorless crystals; mp 138–140 °C; [a]D +28.0 (c = 0.51, CHCl₃).

IR (KBr): 3100–2780 (s = C–C, H–C), 1575 cm⁻¹ (C=–N).

1H NMR (CDCl₃, 200 MHz): δ = 0.75–1.70 (m, 22 H, 3-H, 4′-H, 5′-H, 6′-H, 5 × CH₃), 2.09–2.32 (m, 2 H, 2′-H, CHMe₃), 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, 4-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, CH₂).

13C NMR (CDCl₃, 50.3 MHz): δ = 16.2, 21.1, 22.1, 26.0, 27.1 (5 q, 5 × CH₃), 23.1 (t, C-3′), 25.4 (d, CHMe₃), 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, CMe₂), 126.7, 128.5, 130.0, 133.6 (3 d, s, C₆H₅), 156.7 (s, C-3).

Anal. Calcd for C₁₇H₂₅F₃NO₄ (387.5): C, 71.30; H, 8.58; N, 3.61. Found: C, 71.48; H, 8.82; N, 3.54.

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

According to general procedure 2, 1,2-oxazine (6R)-13 (0.305 g, 1.00 mmol) was treated with RuCl₃·3H₂O (0.018 g, 0.07 mmol) and NaIO₄ (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 (6R)-15 (0.232 g, 61%, de >94%), containing 7% of (6S)-16 as colorless crystals; mp 90–95 °C; [a]D +203 (c = 0.42, CHCl₃).

IR (KBr): 2960–2870 (s = C–C, H–C), 1640 cm⁻¹ (C=–N).

1H NMR (CDCl₃, 300 MHz): δ = 0.68–1.72 (m, 22 H, 3-H, 4′-H, 5′-H, 6′-H, 5 × CH₃), 1.88, 20.8–21.55 (m, m, 1 H each, 2′-H, CHMe₃), 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).

13C NMR (CDCl₃, 50.3 MHz): δ = 15.5, 20.8, 22.2, 26.1, 26.9 (5 q, 5 × CH₃), 23.0 (t, C-3′), 25.4 (d, CHMe₃), 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, CMe₂), 120.1 (q, JCF = 276 Hz, CF₃), 149.6 (q, JCF = 35 Hz, C-3).

Anal. Calcd for C₁₇H₂₂F₃NO₄ (397.4): C, 56.98; H, 7.44; N, 3.69. Found: C, 57.35; H, 7.79; N, 3.60.

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

According to general procedure 2, 1,2-oxazine (6S)-13 (0.305 g, 1.00 mmol) was treated with RuCl₃·3H₂O (0.018 g, 0.07 mmol) and NaIO₄ (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

Synthesis 2007, No. 17, 2681–2689 © Thieme Stuttgart · New York
(6S)-15 (0.237 g, 62%, de >94%) as colorless crystals; mp 109–113 °C; [α]D +131 (c 0.40, CHCl3).

IR (KBr): 2960–2870 (=C–H, C–H), 1640 cm–1 (C≡N).

1H NMR (CDCl3, 300 MHz): δ = 0.65–1.68 (m, 22 H, 3-H, 4′-H, 5′-H, 6′-H, 5 x CH3), 1.96–2.11 (m, 2 H, 2′-H, CHMe2), 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).

13C NMR (CDCl3, 75.5 MHz): δ = 16.2, 21.1, 22.0, 26.1, 27.0 (5 q, 5 x CH3), 23.1 (t, C-3′), 25.6 (d, CHMe2), 31.6 (d, C-3′, 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, 2 C-Me), 112.2 (s, C-Me2), 120.2 (q, JCF = 276 Hz, CF3), 149.9 (q, JCF = 33 Hz, C-3).


(3R,4S,5R,6R)-6-[1(R,2S,5R)-2-Isopropyl-5-methylcyclohexyl-oxyl]-4,5-isopropylidened-3-phenyl-3,4,5,6-tetrahydro-2H-1,2-oxazine [[6R]–18]

According to general procedure 1, 1,2-oxazine (6R)-16 (0.194 g, 0.50 mmol) was treated with BH3·THF (2.0 mL, 2.00 mmol) in THF (5 mL).

Workup and purification using column chromatography (alumina, hexane–EtOAc, 6:1) afforded (6R)-18 (0.081 g, 43%; de >94%) as colorless crystals; mp 42–45 °C; [α]D –40.7 (c 0.30, CHCl3).

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

1H NMR (CDCl3, 300 MHz): δ = 0.75–1.70 (m, 22 H, 3-H, 4′-H, 5′-H, 6′-H, 5 x CH3), 2.06–2.32 (m, 2 H, 2′-H, CHMe2), 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, C6H3).

13C NMR (CDCl3, 75.5 MHz): δ = 15.8, 20.9, 22.3, 26.2, 28.1 (5 q, 5 x CH3), 23.2 (t, C-3′), 25.3 (d, CHMe2), 31.6 (d, C-3′, C-4′), 40.3 (t, C-6′), 47.5 (d, C-2′), 62.9 (d, C-1′), 75.5, 76.0, 77.5 (3 d, C-3, C-4, C-5), 100.7 (d, C-6), 110.1 (s, C-Me2), 128.7, 128.31, 128.7, 135.4 (5 q, 5 x C6H3).

Anal. Calcéd for C18H22F2NO4 (348.5): C, 70.92; H, 9.06; N, 3.60. Found: C, 70.86; H, 9.07; N, 3.71.

(3R,4S,5S,6S)-6-[1(R,2S,5R)-2-Isopropyl-5-methylcyclohexyl-oxyl]-4,5-isopropylidened-3-phenyl-3,4,5,6-tetrahydro-2H-1,2-oxazine [[6S]-18]

According to general procedure 1, 1,2-oxazine (6S)-16 (0.194 g, 0.50 mmol) was treated with BH3·THF (2.0 mL, 2.00 mmol) in THF (5 mL).

Workup and purification using column chromatography (alumina, hexane–EtOAc, 6:1) afforded (6S)-18 (0.130 g, 71%; de >94%) as colorless crystals; mp 77–80 °C; [α]D +52.0 (c 0.48, CHCl3).

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

1H NMR (CDCl3, 300 MHz): δ = 0.74–1.68 (m, 22 H, 3-H, 4′-H, 5′-H, 6′-H, 5 x CH3), 2.09–2.18, 2.27 (m, 1 H each, 2′-H, CHMe2), 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).

13C NMR (CDCl3, 75.5 MHz): δ = 16.1, 21.0, 22.1, 26.1, 27.7 (5 q, 5 x CH3), 23.1 (t, C-3′), 25.0 (d, CHMe2), 31.7 (d, C-5′), 34.2 (t, C-4′), 43.5 (t, C-6′), 48.6 (d, C-2′), 59.7 (q, JCF = 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-Me2), 122.9 (q, JCF = 281 Hz, CF3).

Anal. Calcéd for C18H22F2NO4 (381.4): C, 56.68; H, 7.93; N, 3.67. Found: C, 56.51; H, 8.19; N, 3.73.

Hydrogenolysis of (6R)-18

Following the procedure for the hydrogenolysis of rac-4a, 1,2-oxazine (6R)-18 (0.097 g, 0.25 mmol) was treated with H2 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 (2S,3R,4S)-5 (0.018 g, 37%, de, ee >94%) as colorless crystals; mp 49–53 °C; [α]D +138 (c 0.21, CHCl3).

Hydrogenolysis of (6S)-18

Following the procedure for the hydrogenolysis of rac-4a, 1,2-oxazine (6S)-18 (0.077 g, 0.20 mmol) was treated with H2 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 (2R,3S,4R)-5 (0.021 g, 51%, de, ee >94%) as colorless crystals; mp 50–54 °C; [α]D –130 (c 0.30, CHCl3).
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.

References


(13) The hydrogenation of ethoxycarbonyl-substituted rac-4 was carried out in EtOH as solvent. The reaction in MeOH led to transesterification: see ref. 6a.


(18) It should be noted that the reduction of the corresponding 3-trifluoromethyl-substituted 1,2-oxazine rac-4c with NaBH₃CN failed. This may be due to the electron-withdrawing ability of the trifluoromethyl group which prevents protonation of the C=N unit.


(22) Hiller, Ph.D. Thesis; Technische Universität Dresden: Germany, 1997.

