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Formation of Enantiopure Tricyclic Compounds by Intramolecular 1,3-Dipolar Cycloaddition of Nitrones

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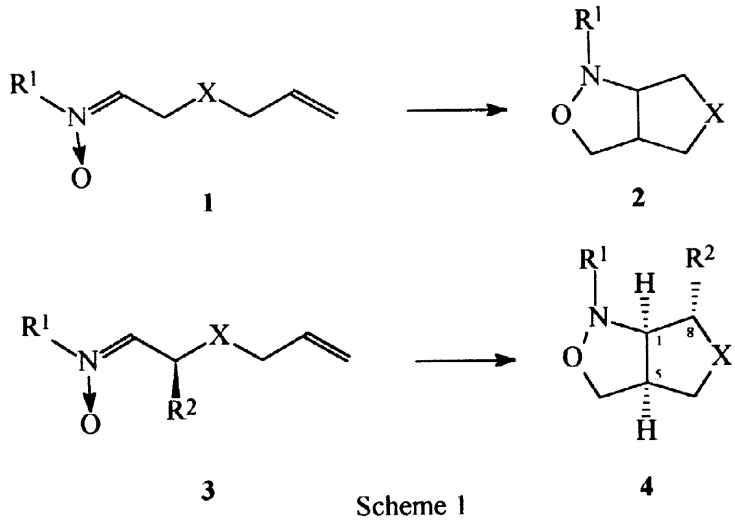
Abstract: Nitrones **6** prepared from ester **5** underwent an intramolecular cycloaddition affording diastereomeric mixtures of tricyclic compounds **7A/B**. These were separated to give the enantiopure compounds **7A** and **7B**. Starting from aminoalcohol **8** compounds **10A** and **10B** were formed via nitrones **9**. Nitrone **9a** yielded the *trans*-product **10aC** in addition. X-ray analyses confirm the structure of **7aB** and **10aA**. Catalytic hydrogenation of compounds **7A** and **7B** yielded the bicyclic γ-aminoalcohols, which were tested as ligands in the enantioselective addition of diethylzinc to benzaldehyde.

INTRODUCTION

The intramolecular cycloaddition of alkenyl nitrones is a powerful method in synthetic organic chemistry. Bicyclic and polycyclic compounds accessible by this method can be easily converted to cyclic γ-aminoalcohols by reductive cleavage of the NO-bond.[1] In particular, C-5-hexenylnitrones **1a** are useful preparative tools, since they undergo intramolecular cycloaddition yielding 3-oxa-2-azabicyclo[3.3.0]octanes **2a** under relative mild conditions with high regio- and stereoselectivity.[1]



1,2	X
a	CH_2
b	O
c	NR

R^1 = alkyl

3,4	X
a	O
b	NR^3

R^1 = alkyl, aryl
R^2 = alkyl, phenyl
R^3 = allyl, benzyl

Scheme 1

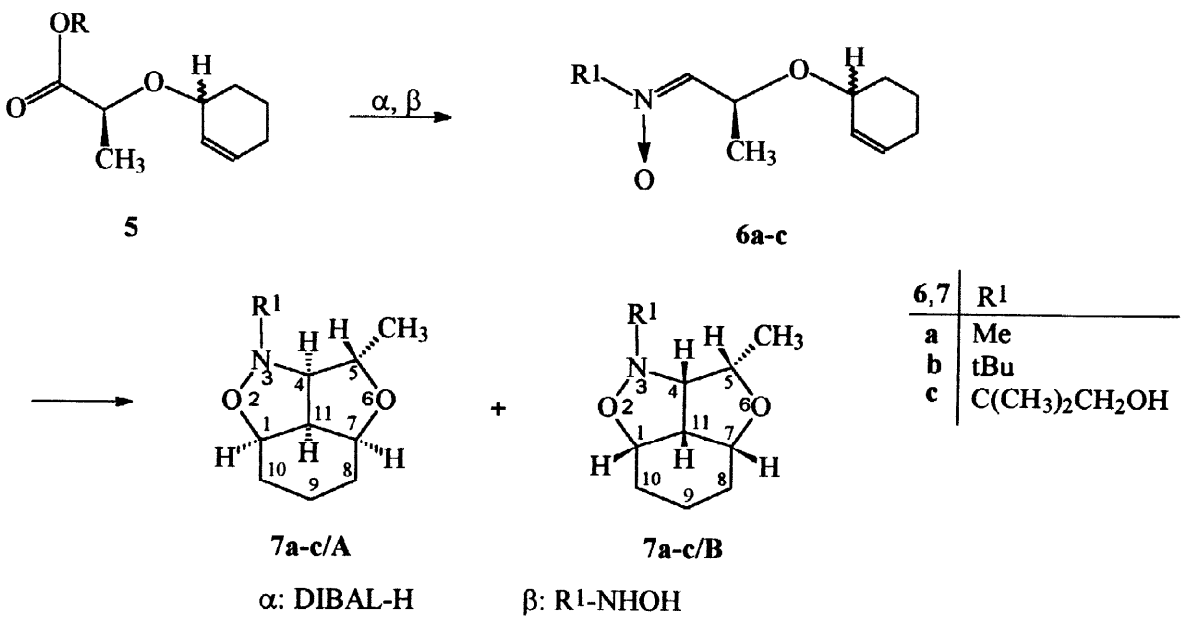
PII: S0040-4020(98)00064-7

If the 5-hexenyl nitrone is partly integrated in a ring system tricyclic or even higher polycyclic compounds can be synthesized by their intramolecular cycloaddition. In 1965 LeBel reported the synthesis of a 2-oxa-3-azatricyclo[5.3.1.$0^{4,11}$]undecane utilizing this method.[2] Some other similar tricyclic compounds were synthesized in the meantime.[3]

The intramolecular cycloaddition of nitrones of the 5-hexenyl type in which the C-atom in 3-position is replaced by a heteroatom (**1b,c**) was studied by various groups.[4] We synthesized enantiopure 3,7-dioxa-2-azabicyclo[3.3.0]octanes **4a** and 3-oxa-2,7-diazabicyclo[3.3.0]octanes **4b** by intramolecular cycloaddition via the corresponding nitrones **3** starting from enantiopure natural products. In this way, formation of bicyclic compounds with at least three contiguous stereogenic centers occurred (Scheme 1).[5] Such compounds revealed not only interesting conformational properties, but some of them could also be used as chiral ligands in enantioselective catalytic reactions, in particular those which bear an β-hydroxyalkyl group at the nitrogen atom.[5c]

RESULTS AND DISCUSSION

In continuation of these studies, we attempted to prepare enantiopure tricyclic compounds **7** and **10** (Scheme 2, 3) by intramolecular cycloaddition of corresponding nitrones.[6] For this reason we synthesized the ester **5** as a diastereomeric mixture from (*S*)-ethyl lactate and racemic 3-bromocyclohexene in the presence of silver-I-oxide. Reduction with diisobutyl aluminium hydride (DIBAL-H) to the corresponding aldehyde followed by treatment with *N*-alkylhydroxylamines afforded the nitrones **6** which underwent an intramolecular cycloaddition either spontaneously or by refluxing in toluene. The tricyclic compounds were formed as a mixture of two diastereomers **7A** and **7B** (Scheme 2) which could be separated by column chromatography.

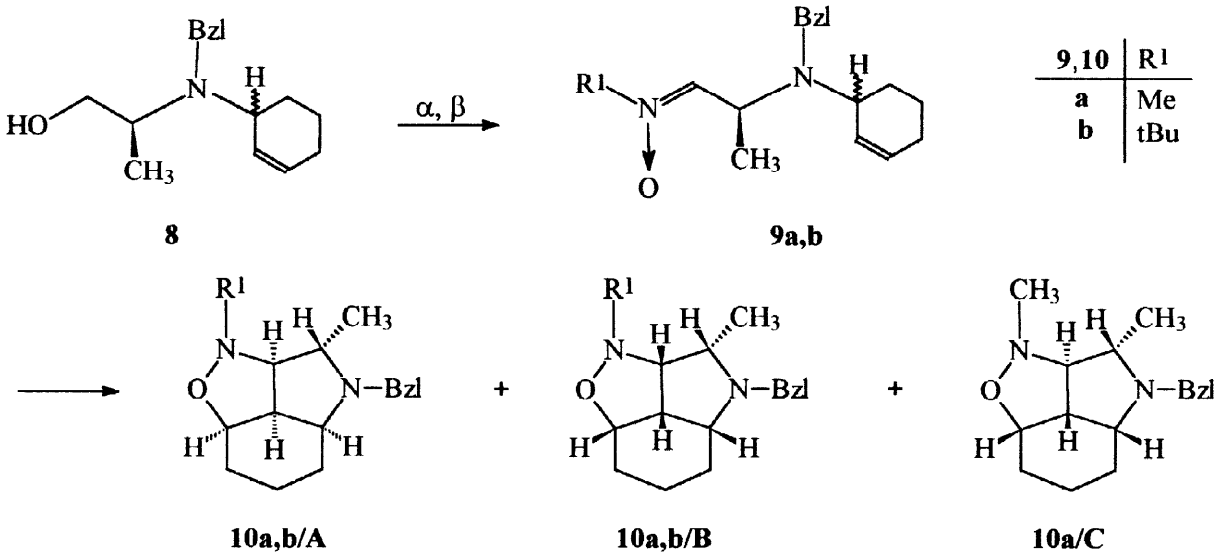


6,7	R1
a	Me
b	tBu
c	$C(CH_3)_2CH_2OH$

Scheme 2

The β-aminoalcohol **8** was prepared from (*S*)-N-benzyl alaninol[7a] and racemic 3-bromocyclohexene. Swern oxidation of **8** furnished the corresponding aldehyde, which afforded nitrones **9** upon treatment with *N*-methyl or *N*-tert-butylhydroxylamine, respectively. Spontaneous intramolecular cycloaddition of **9** yielded diastereomeric mixtures of compounds **10** which were separated by column chromatography (Scheme 3).

The tricyclic compounds **7** and **10** were shown to be optically active. Since the formation of the corresponding bicyclic products under the same reaction conditions proceeded without racemization,[5] it was assumed that this is also true for the formation of compounds **7** and **10**. To confirm this assumption compound **7cA** was treated with enantiopure (*S*)-(+)-*O*-acetylmandelic acid in the presence of *N,N'*-dicyclohexyl carbodiimide and 4-dimethylaminopyridine. The resulting ester was diastereomerically pure as was indicated by comparison of the ^{1}H NMR spectrum with the spectrum of the ester derived from racemic *O*-acetylmandelic acid. Thus, **7** and **10** were obtained as enantiopure compounds.



Scheme 3

In addition to the two stereogenic centers originating from the starting compounds, in the tricyclic compounds **7** and **10** three new stereogenic centers were formed by the intramolecular cycloaddition of the nitrones **6** and **9**, respectively. In compounds **7B** and **10B** the hydrogen atoms at the stereogenic centers C-1, C-4, C-5, C-7 and C-11 are all *cis*-orientated whereas in compounds **7A** and **10A** this is only true for the protons at C-1, C-4, C-7 and C-11. In the latter case the proton 5-H is in *trans*-position with respect to 4-H. Finally, in compound **10aC** the 4-H is in *trans*-position to 5-H as well as to 11-H.

In any case the asymmetric induction by the intramolecular cycloaddition is primarily controlled by the stereogenic center at the 3-position of the cyclohexene ring. It is obvious that the approach of the nitrone group to the cyclohexene double bond can only occur from the face at which the heteroatom is attached to the ring

(Figure 1). An attack from the opposite face would be impossible due to severe strain in the transition state and the product. Thus, in all the products **7** and **10** the hydrogen atoms 1-H, 11-H and 7-H are *cis*-configurated.

On the other hand, the *Re*-face of the *Z*-configurated nitrone group is the favored face for its approach to the alkene moiety due to less destabilization by 1,3-interaction between the nitrone oxygen atom and the hydrogen atom (Figure 1A) as compared to the larger destabilization by the interaction between oxygen atom and methyl group in the case of an approach from the *Si*-face (Figure 1B).[7,8]

Thus, both stereogenic centers of nitrones **6A** and **9A** (*S*-configuration at C-3 of the cyclohexene ring) favor the formation of diastereomers A (Figure 1A). In contrast, the reaction pathway from nitrones **6B** and **9B** (*R*-configuration at C-3 of the cyclohexene ring) to the tricyclic compounds **7B** and **10B**, respectively, suffers from the stronger destabilizing effect of the *Z*-configurated nitrone moiety caused by the 1,3-interaction between the oxygen atom and the methyl group (Figure 1B).[7,8] Obviously, formation of the compound **10aC** becomes an appropriate alternative in the latter case. This compound must be formed from the *E*-configurated nitrone **9aC** (Figure 1C).in which the 1,3-interaction between the *N*-methyl group and the hydrogen atom at the *quasi*-allylic position minimizes the destabilization.

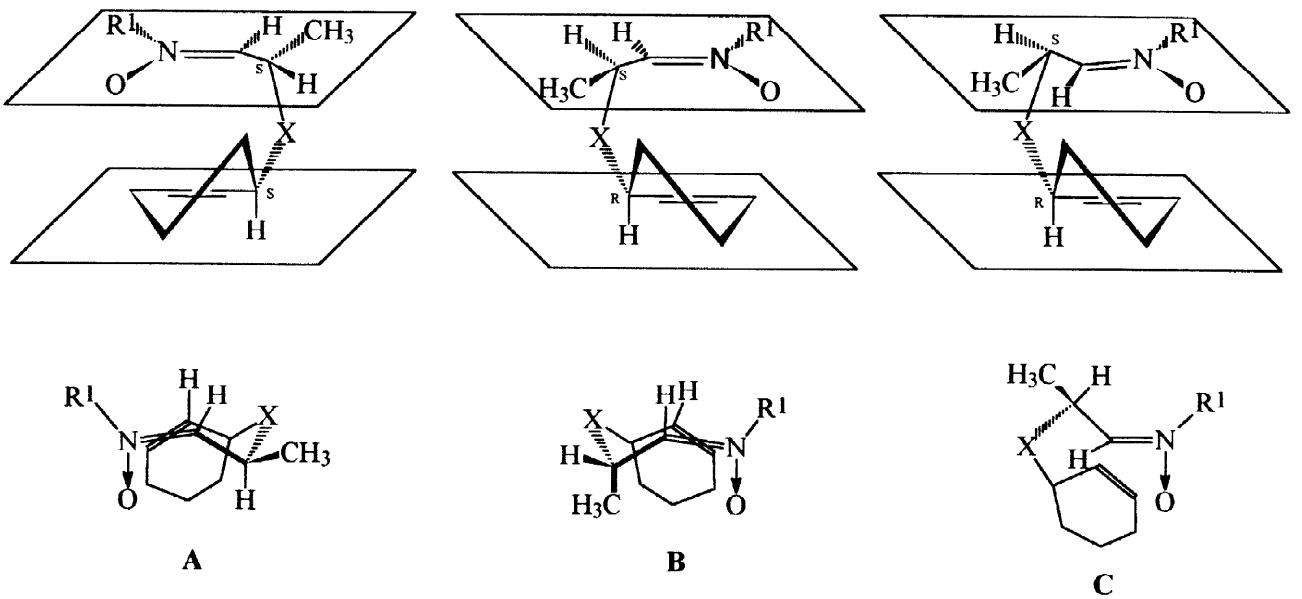


Fig. 1 Schematic presentation of the cyclohexene moiety approaching to the nitrone group:
(**A**) *Re*-face of the *Z* nitrone, (**B**) *Si*-face of the *Z* nitrone, (**C**) *Re*-face of the *E* nitrone

The structure determination of the tricyclic compounds is mainly based on the X-ray analyses[9] of the compounds **7aB** (Figure 2) and **10aA** (Figure 3) and the ^{1}H and ^{13}C NMR data. In Table 1 the torsional angles formed by the hydrogen atoms of the tricyclic frame are given. With the aid of the Karplus equation[10] ^{1}H coupling constants ^{3}J for vicinal protons are calculated which agree well with the coupling constants experimentally found, although the Karplus equation was developed for pure carbon compounds.[11] Thus, it can be concluded that the conformations of the molecules in solution resemble those in the solid state.

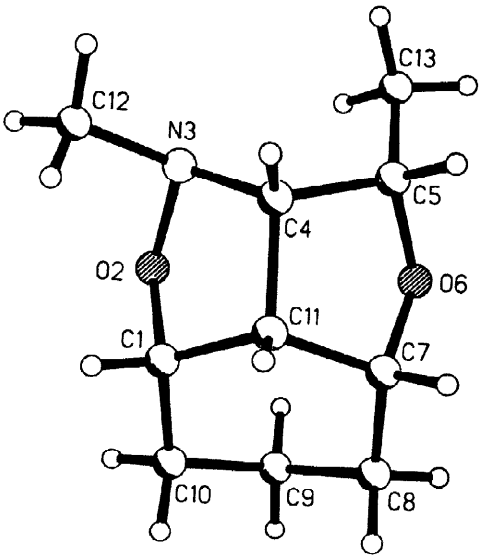


Figure 2. Molecular plot of (1*S*,4*S*,5*S*,7*R*,11*R*)-(+)-3,5-dimethyl-2,6-dioxa-3-azatricyclo[5.3.1.$0^{4,11}$]-undecane (**7aB**). Selected bond lengths [Å]: C1-O2 1.438(3), C1-C11 1.522(3), O2-N3 1.439(3), N3-C4 1.472(3), C4-C5 1.542(3), C4-C11 1.545(3), C5-O6 1.422(3), O6-C7 1.428(3), C7-C11 1.536(3) - Selected bond angles [°]: C1-O2-N3 107.1(2), O2-N3-C4 104.4(2), N3-C4-C5 113.2(2), N3-C4-C11 107.2(2), C4-C5-O6 105.3(2), C5-O6-C7 105.7(2), O6-C7-C11 105.5(2), C7-C11-C1 115.7(2), C7-C11-C4 103.9(2).

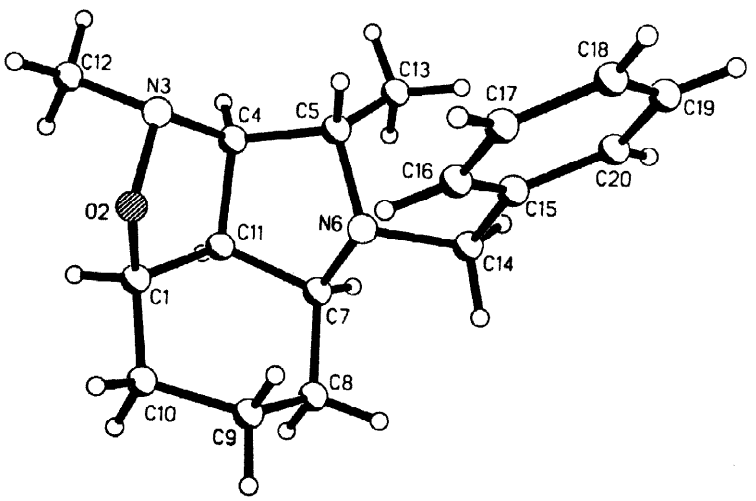


Figure 3. Molecular plot of (1*R*,4*R*,5*S*,7*S*,11*R*)-(+)-6-benzyl-3,5-dimethyl-2-oxa-3,6-diazatricyclo-[5.3.1.$0^{4,11}$]undecane (**10aA**). Selected bond lengths [Å]: C1-O2 1.438(3), C1-C11 1.533(3), O2-N3 1.447(2), N3-C4 1.468(3), C4-C5 1.530(3), C4-C11 1.551(3), C5-N6 1.469(3), N6-C7 1.462(3), C7-C11 1.538(3). - Selected bond angles [°]: C1-O2-N3 107.30(14), O2-N3-C4 104.20(14), N3-C4-C5 112.6(2), N3-C4-C11 107.1(2), C4-C5-N6 103.4(2), C5-N6-C7 106.6(2), N6-C7-C11 102.5(2), C7-C11-C1 115.7(2), C7-C11-C4 105.0(2).

Table 1. Selected Torsional Angles of Compounds **7aB** and **10aA** [°] and Comparison of ^{1}H NMR Coupling Constants ^{3}J (Hz) with Theoretical Values Calculated from the Torsional Angles.

Torsional Angles φ	**7aB**			**10aA**		
	[°]	$^3J_{calcd}$ [a]	$^3J_{found}$	[°]	$^3J_{calcd}$ [a]	$^3J_{found}$
H1-C1-C11-H11	26.6	6.5	6.5	-23.1	6.9	5.9
H4-C4-C5-H5	28.2	6.2	5.4	102.7	0.2	<1
H4-C4-C11-H11	-0.8	8.2	7.6	-3.5	8.2	7.9
H7-C7-C11-H11	-25.2	6.7	6.3	30.3	6.1	7.2

[a] Calculated with the aid of the Karplus equation: $^3J = 8.5 \cdot \cos^2\varphi - 0.28$ for 0°-90° and $^3J = 9.5 \cdot \cos^2\varphi - 0.28$ for 90°-180°.

The selected NMR data given in Tables 2/3 confirm the assignment of structure A or structure B to the various tricyclic compounds **7** and **10**. The most striking differences between these two types of diastereomers are found for the chemical shifts for protons 5-H and 7-H, as well as for the coupling constants J 4/5. The data of the third diastereomer of compound **10a**, however, deviate clearly from those of diastereomers **10A** as well as from those of diastereomers **10B**. In particular, this is true for the large coupling constant ^{3}J 4/11 = 11.7 Hz,

Table 2. Selected NMR Data of Compounds **7** (in $CDCl_3$). Chemical Shifts δ (in ppm), Coupling Constants ^{3}J (in Hz)[a]

Compound		**7aA**	**7bA**	**7cA**	**7aB**	**7bB**	**7cB**
δ	1-H	4.33	4.26	4.25	4.31	4.19	4.14
	4-H	3.40	3.68	3.70	3.44	3.82	3.84
	5-H	4.26	4.15	4.15	3.73	3.70	3.67
	7-H	4.15	4.19	4.16	3.77	3.75	3.73
	11-H	2.99	3.00	2.99	2.91	2.91	2.90
	CH_3(5)	1.18	1.11	1.15	1.34	1.33	1.29
δ	C-1	70.9[b]	76.7	76.8	70.8	76.2	76.4
	C-4	81.3	73.1	72.7	77.8	68.2	67.9
	C-5	80.7[b]	81.7	81.7	74.3[b]	78.5	78.2
	C-7	72.9	73.3	73.0	76.6[b]	74.4	74.2
	C-11	46.4	48.9	48.7	48.2	50.1	50.1
	CH_3(5)	19.3	18.4	18.1	15.1	15.5	15.4
^{3}J	1-H/11-H	7.1	7.5	7.4	6.5	7.1	6.8
	4-H/5-H	<1	3.0	2.4	5.4	4.8	4.7
	4-H/11-H	7.1	8.0	8.3	7.6	7.9	7.9
	7-H/11-H	7.1	7.4	7.1	6.3	6.1	6.4

[a] Additional chemical shifts and coupling constants see **Experimental Part** [b] An opposite assignment of the two numbers is possible.

as well as for the chemical shifts of the proton 11-H and the carbon atoms C-11 and 5-CH_3. Its NOESY spectrum shows cross-peaks for the protons 4-H/CH_3, 1-H/11-H, and 7-H/11-H but not for the protons 4-H/11-H indicating the *trans*-position of the protons 4-H and 11-H. Based on these data structure **10aC** was assigned to this diastereomer. The good agreement of the data for compounds **7A** as well as **10A** on one hand, and for compounds **7B** as well as **10B** on the other hand, indicates that the conformation within these two groups of diastereomers is very similar. Thus, the conformation of the molecules of group A is reflected by the crystal structure of **10aA** (Figure 3), that of group B by the crystal structure of **7aB** (Figure 2), respectively.

Table 3. Selected NMR Data of Compounds **10** (in $CDCl_3$). Chemical Shifts δ (in ppm), Coupling Constants ^3J (in Hz)[a)]

Compound		**10aA**	**10bA**	**10aB**	**10bB**	**10aC**
δ	1-H	4.41	4.25	4.30	4.15	4.08
	4-H	3.13	3.46	3.16	3.64	3.07
	5-H	3.35	3.14	2.40	2.40	2.95
	7-H	2.94	2.90	2.43	2.42	2.88
	11-H	3.02	2.90	2.75	2.75	3.21
	CH_3(5)	0.86	0.92	1.12	1.20	1.26
	CH_2Ph	3.29	3.41	3.54	3.68	3.69
	CH_2Ph	3.87	3.85	3.62	3.74	4.00
δ	C-1	71.5	77.2	71.2	76.2	73.5
	C-4	78.0	71.0	74.8	65.9	76.4
	C-5	61.4	63.0	63.8	63.7	60.3
	C-7	55.4	56.6	60.4	59.6	57.7
	C-11	46.4	49.0	46.6	48.2	55.9
	CH_3(5)	11.1	12.4	15.2	15.5	18.4
	CH_2Ph	50.2	51.0	54.6	53.8	58.1
^3J	1-H/11-H	5.9	nd	6.2	7.1	7.9
	4-H/5-H	<1	2.2	8.0	5.6	8.9
	4-H/11-H	7.9	8.2	7.6	7.7	11.7
	7-H/11-H	7.2	nd	7.7	7.8	8.0

[a)] Additional chemical shifts and coupling constants see **Experimental Part**

Most of the corresponding bicyclic compounds **4** adopt a pseudo-chair conformation I (Figure 4) with the O-atom of the isoxazolidine ring *anti* and the heteroatom X *syn* to the hydrogen atoms at the brigdehead positions 1 and 5. Obviously, this conformation benefits from the favorable *quasi*-equatorial position of the substituent R^2 at C-8 as well as from the gauche arrangement of the free electron pairs of the N-atom and the O-atom of the isoxazolidine moiety.[5b,c] In contrast, compounds substituted at 4α or 5-position exist in an inverted pseudo-chair conformation II with the heteroatom X in *anti*-position to the hydrogen atoms at the bridgehead positions.[12] In none of the bicyclic compounds **4** conformation III or IV could be observed in which the heteroatoms O-3 and X-7 protrude in the same direction from the respective plane.

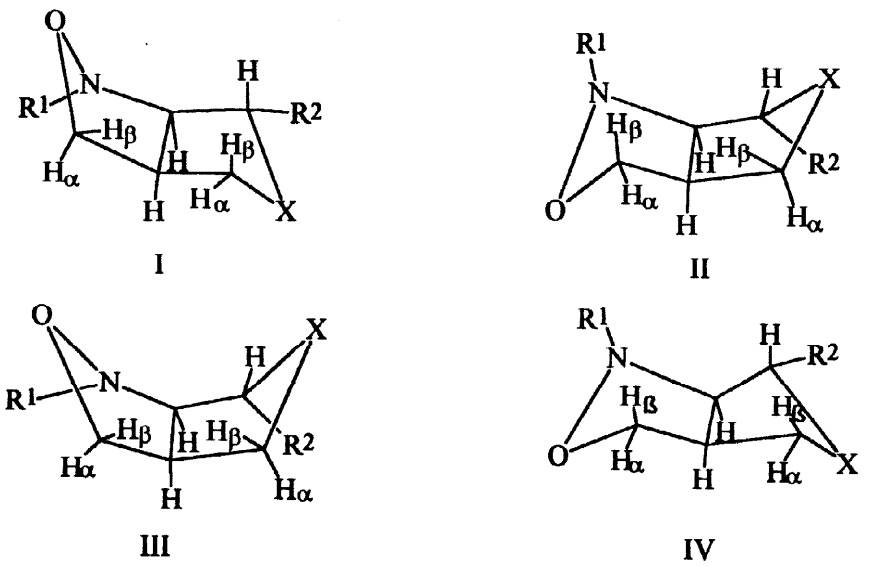


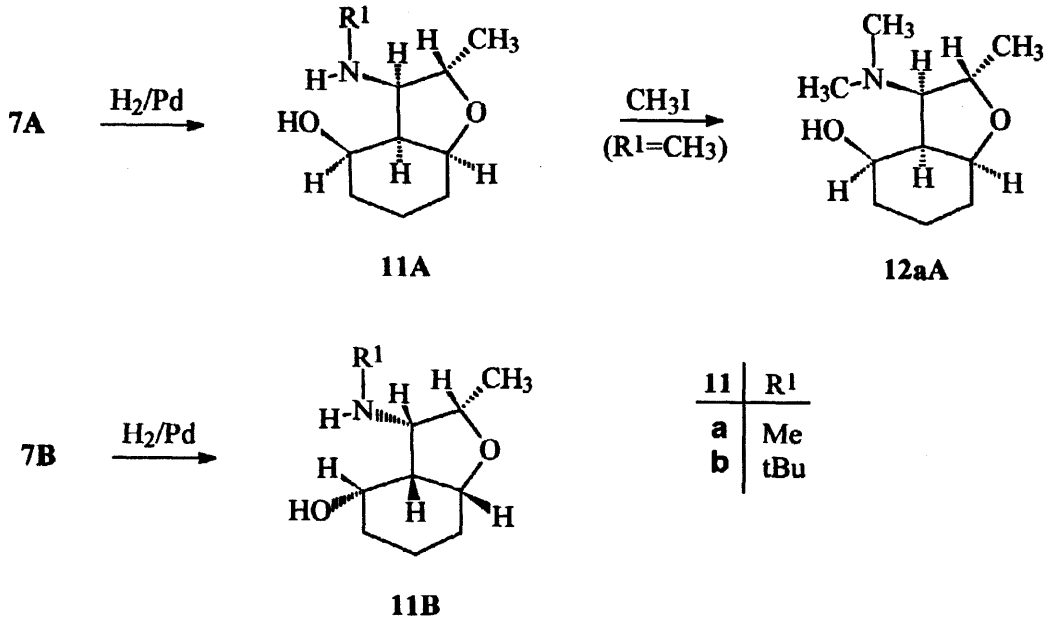
Figure 4: Possible half-chair conformations of compounds **4a** (X=O) and **4b** (X=NR^3), R^1 and R^2 = alkyl

These conformations would suffer, in particular, from destabilization by unfavorable effects such as *trans*-annular interaction between the protons 4β-H and 6β-H and the almost *syn*-periplanar arrangement of protons 4α-H/5-H and 5-H/6α-H, respectively, which are avoided or minimized in conformations I or II. The pseudo-boat conformation III would be additionally destabilized by electron-pair repulsion between O and X, whereas in conformation IV an unfavorable 1,3-*syn* interaction between substitutents R^1 and R^2 would appear.

In the tricyclic compounds **7A** and **B** as well as **10A** and **B**, however, the heteroatom-substituted bicyclo[3.3.0]octane moiety adopts a pseudo-boat conformation with O-2 and X-6 *anti* to the hydrogen atoms at the brigdehead positions 4 and 11 (Figures 2 and 3). Thus, the fused cyclohexane part of the molecule can exist in a chair conformation almost free of strain, whereas in conformations derived from bicyclic structures I or II a considerable amount of strain would arise in the cyclohexane part. Furthermore, the unfavorable *trans*-annular interaction between 4β-H and 6β-H in conformation III of bicyclic compounds **4** does no longer exist, since these atoms are substituted by the $(CH_2)_3$ unit of the six-membered ring. These effects seem to compensate the enhanced electron-pair repulsion of the heteroatoms O and X.

Catalytic hydrogenation of the compounds **7a,b** afforded the 9-amino-8-methyl-7-oxabicyclo[4.3.0]nonan-2-ols **11a,b** in 83-93% yield. The *N*-methyl compound **11aA** could be converted to the *N,N*-dimethyl compound **12aA** by treatment with methyl iodide, whereas methylation of the *N*-tert butyl compound **11bA** did not occur using the same method.

The bicyclic compounds **11A, 11B** and **12aA** were tested as ligands in the enantioselective reaction between benzaldehyde and diethylzinc. Although with the γ-aminoalcohols **11aA** and **11aB** only moderate enantioselectivities were found (ee = 64% (*R*), and 63% (*S*), respectively), they exceed those of the β-aminoalcohols **7cA** and **7cB** (ee = 46% (*R*) and 45% (*S*), respectively).[5c] Surprisingly, with the sterically more hindered *N*-tert-butyl compounds **11b** the enantiomeric excess is not only dramatically diminished but the other enantiomer is preferably formed (**11bA**: ee = 42% (*S*); **11bB**: ee = 10% (*R*)). The same effect is observed by the introduction of the second methyl group (compound **12aA**: 28% ee (*S*)).



Scheme 4

EXPERIMENTAL PART

Elemental analyses were performed by the division Routine-Analytik, Fachbereich Chemie, University of Marburg. Spectra were recorded with following instruments: NMR: Bruker AMX 500 and Bruker AC 300 using the residues of ^1H (δ = 7.24) or of ^{13}C (δ = 77.0 ppm) of the solvent $CDCl_3$ as internal standard. As far as not stated otherwise ^1H NMR spectra were recorded at 300 MHz, the ^{13}C-NMR spectra at 75 MHz. - MS: Varian CH 7 (EI) and 711 (FD). - IR: Beckman IR 33 and Bruker IFS 88-FT-IR. Optical rotations: Polarimeter Perkin Elmer 241, at 589 nm.- X-ray: 4-circle diffractometer (Enraf-Nonius CAD4).

Ethyl (2S,3'R/S)-2-(cyclohexen-3'-yloxy)propionate (**5**): *rac*-3-Bromocyclohexene (15.7 g, 99 mmol) was added to a solution of ethyl (*S*)-(-)-lactate (7.8 g, 66 mmol) in diethyl ether (100 mL) under nitrogen with exclusion of light. The reaction mixture was refluxed. Anhydrous silver-(I)-oxide (20 g, 86 mmol) was added during 10 min. Refluxing was continued for 2 h. Then the reaction mixture was stirred for 20 h at room temperature. After filtration the solid residue was thoroughly washed with diethyl ether. The combined ether solutions were washed with water (10 x 50 mL) and dried with $MgSO_4$. After removal of the solvent the crude product was purified by column chromatography (SiO_2, petroleum ether/Et_2O 5:1, R_f = 0.44). Fade-yellow liquid, 20% yield (2.61 g). - $C_{11}H_{18}O_3$ (198.3) Calcd. C 66.38 H 9.15 Found C 66.49 H 9.16. - MS (EI): m/z (%) = 198 (10) [M^+]. - IR (neat): 1749 cm^{-1}. - ^1H NMR δ = 1.21 (t, ^3J = 7.2 Hz, 3 H, OCH_2CH_3), 1.34 (d, ^3J = 6.9 Hz, 3 H, $CHCH_3$), 1.40-2.10 (m, 6 H, cyclohexenyl-H), 3.84 (m, 1 H, 3'-cyclohexenyl-H), 4.05 (qd, ^3J = 6.9, ^4J = 1.2 Hz, 1 H, 2-H), 4.13 (m, 2H, CH_2-CH_3), 5.74 (m, 2 H, 1'- and 2'-cyclohexenyl-H). - ^{13}C NMR: δ = 14.0 (CH_2CH_3), 19.1 (C-3), 24.9, 27.8, 29.3 (cyclohexenyl-C), 60.5 (OCH_2), 72.3, 72.8 (C-2 and C-3'), 126.8 (C-2'), 130.9 (C-1'), 173.1 (C=O).

(2S,3'RS)-2-[N-Benzyl-(cyclohexen-3-yl)amino]-propan-1-ol (**8**): A solution of (*S*)-2-benzylamino-propan-1-ol (1.65 g, 10 mmol) and *rac*-3-bromocyclohexene in diethyl ether (50 mL) was stirred at room temperature for 48 h. Subsequently, the solution was extracted with 2 N-HCl (50 mL). The aqueous layer was brought to pH 8 by addition of Na_2CO_3 and extracted with diethyl ether (3 x 100 mL). After the combined organic solutions had been dried with $MgSO_4$ the solvent was removed affording **8** as a colourless oil in 26% yield. (0.64 g). - $C_{16}H_{23}NO$ (245.2) Calcd. C 78.41 H 9.38 N 5.71 Found C 78.38 H 9.40 N 5.80.- MS (EI): m/z (%) = 245 (11) [M$^+$]- ^{13}C NMR = 12.8/14.8 (CH_3), 21.7, 22.2, 25.0, 25.1, 25.4, 29.6 (cyclohexenyl-C), 48.0/49.6 (3'-cyclohexenyl-C) 52.7/53.1 ($CH_2C_6H_5$), 54.1/54.8 (C-2), 61.1 (C-1), 129.2, 130.2, 130.3, 132.3 (CH=CH_2), 140.1/140.6 (Ar-C). The other Ar-C could not be identified.

General procedure for the preparation of the N-Alkyl 5-methyl-2,6-dioxa-3-azatricyclo[5.3.1.0^{4,11}]undecanes **7**. A solution of diisobutyl aluminium hydride (DIBAH) in hexane (15 mL, 1 mol/L) was added to a solution of compound **5** (10 mmol) in diethyl ether (30 mL) at -72°C under argon during 30 min. Subsequently the reaction mixture was stirred for 2 h at -72°C. After addition of methanol (0.2 mL) the temperature was brought to 0°C, followed by addition of water (1.5 mL). Aluminium oxide gave a white gelatinous precipitate after approximately 10 min. Then a solution of the *N*-alkyl hydroxylamine (11 mmol), prepared from the hydrochloride and triethylamine (1.5 mL) in 30 mL of dichloromethane was added at 0°C. After addition of molecular sieves (5 g, 4 Å) stirring was continued for 24 h at room temperature. The reaction mixture was filtered through a filter that contained some $MgSO_4$. The solid was washed thoroughly with diethyl ether. The filtrate was concentrated at a rotavapor, the rests of the solvent were removed in vacuum.

Separation of the diastereomers **7a** was performed by column chromatography (SiO_2, Et_2O).

(1R,4R,5S,7S,11S)-(-)-3,5-Dimethyl-2,6-dioxa-3-azatricyclo[5.3.1.0^{4,11}]undecane (**7aA**): R_f = 0.36, colourless crystals, 25 % yield, mp 43° C (Et_2O). $[\alpha]_D^{22}$ = -23.2 (c = 0.0024 g/mL, EtOH).- $C_{10}H_{17}NO_2$ (183.2) Calcd C 65.54 H 9.35 N 7.64 Found C 66.02 H 9.77 N 7.37. - MS(FD): m/z (%) = 183 (100) [M$^+$] - IR (KBr): 2964, 2935, 1457, 1440, 1295 cm^{-1}. - ^{1}H NMR (500 MHz): see Table 2. Additional signals: δ 1.30 (m, ^{2}J = 14.0, ^{3}J = 3.5, 3.5, 3.5, 3.5 Hz, 1 H, 9-H_{eq}); 1.47 (m, ^{2}J = 14.0, ^{3}J = 14.0, 3.5, 3.5 Hz, 1 H, 8-H_{ax}); 1.61 (m, ^{2}J = 14.0, ^{3}J = 14.0, 4.0, 4.0 Hz, 1 H, 10-H_{ax}); 1.72 (m, ^{2}J = 16.0, ^{3}J = 14.0, 14.0, 3.5, 3.5 Hz, 1 H, 9-H_{ax}), 2.00 (d, ^{2}J = 14.5 Hz, 1 H, 8-H_{eq}); 2.00 (d, 14.5 Hz, 1 H, 10-H_{eq}); 2.66 (s, 3 H, N-CH_3). Additional coupling constants: ^{3}J = 7/8$_{eq}$ = 3.5, 7/8$_{ax}$ = 3.5, 5/CH_3 = 6.6 Hz. ^{13}C NMR: see Table 2. Additional signals: δ = 13.1 (C-9), 19.3 ((5)-CH_3), 25.4 (C-10), 28.0 (C-8), 44.9 (NCH_3).

(1S,4S,5S,7R,11R)-(+)-3,5-Dimethyl-2,6-dioxa-3-azatricyclo[5.3.1.0^{4,11}]undecane (**7aB**): R_f = 0.76, colourless crystals, 27 % yield, mp 72° C (Et_2O). $[\alpha]_D^{22}$ = +54.5 (c = 0.0018 g/mL, EtOH).- $C_{10}H_{17}NO_2$ (183.2) Calcd C 65.54 H 9.35 N 7.64 Found C 65.93 H 9.70 N 7.48. - MS(FD): m/z (%) = 183 (100) [M$^+$] - IR (KBr): 2988, 2944, 2923, 2770, 1264, 1119 cm^{-1}. - 1H NMR (500 MHz): see Table 2. Additional signals: δ 1.24 (m, ^{2}J = 13.1, ^{3}J = 3.4, 3.4, 3.4, 3.8 Hz, 1 H, 9-H_{eq}); 1.47 (m, ^{2}J = 14.5, ^{3}J = 13.4, 3.4, 3.2 Hz, 1 H, 8-H_{ax}); 1.61 (m, ^{2}J = 14.5, ^{3}J = 13.7, 3.8, 3.8 Hz, 1 H, 10-H_{ax}); 1.76 (m, ^{2}J = 13.1, ^{3}J = 13.7, 13.4, 3.2, 3.2 Hz, 1 H, 9-H_{ax}), 1.99 (m, ^{2}J = 14.5 ^{3}J = 3.4, 3.2, 2.8 Hz, 1 H, 8-H_{eq}); 2.07 (m, ^{2}J =14.5 ^{3}J = 3.4, 3.2, 2.1 Hz, 1 H, 10-

H_{eq}); 2.64 (s, 3 H, N-CH_3). Additional coupling constants: ^3J = 5/CH_3 = 6.3, 1/10_{eq} = 2.1, 1/10_{ax} = 3.8, 7/8_{eq} = 2.8, 7/8_{ax} = 3.2 Hz. ^{13}C NMR: see Table 2. Additional signals: δ = 13.3 (C-9), 25.6, 27.7 (C-8, C-10), 45.6 (N-CH_3).

The reaction of the tricyclic diastereomers **7b** contains a considerable amount of nitrone **6b** (^{13}C NMR signals: δ = 27.9 (C(CH_3)$_3$), 69.4 (*C*(CH_3)$_3$), 127.9 and 131.3 (C=C), 137.8 (N=CH). The cycloaddition was completed by refluxing the mixture in toluene for 2 h.

Separation of the diastereomers **7b** was performed by column chromatography (SiO_2, Et_2O/petroleum ether 1:1).

(1R,4R,5S,7S,11S)-(+)-3-tert-Butyl-5-methyl-2,6-dioxa-3-azatricyclo[5.3.1.0^{4,11}]undecane (**7bA**): R_f = 0.55, yellow oil, 20% yield, $[\alpha]_D^{22}$ = +25.4 (c = 0.0041 g/mL, EtOH).- $C_{13}H_{23}NO_2$ (225.3) Calcd C 69.29 H 10.29 N 6.22 Found C 69.02 H 10.36 N 6.20. - MS(EI): m/z (%) = 225 (32) [M^+] - IR (neat): 2968, 2935, 2762, 1453, 1390, 1362, 1219 cm^{-1}. - ^1H NMR (500 MHz): see Table 2. Additional signals: δ = 1.04 (s, 9 H, C(CH_3)$_3$), 1.22 (m, ^2J = 13.4, ^3J = 3.9, 3.9, 3.9, 3.9 Hz, 1 H, 9-H_{eq}), 1.45 (m, 2 H, 8-H_{ax}, 10-H_{ax}), 1.74 (m, ^2J = 13.2, ^3J = 16.5, 12.6, 3.3, 3.3 Hz, 1 H, 9-H_{ax}), 2.00 (d, ^2J = 12.7 Hz, 1 H, 8-H_{eq}), 2.00 (d, ^2J = 12.7 Hz, 1 H, 10-H_{eq}). - Additional coupling constants ^3J 5/CH_3 = 6.6, 1/10_{eq} = 1.8, 1/10_{ax} = 4.5, 7/8_{ax} = 3.9 Hz. ^{13}C NMR: see Table 2. Additional signals: δ = 13.9 (C-9), 26.8, 28.6 (C-8, C-10), 27.1 (C(CH_3)$_3$), 59.4 (*C*(CH_3)$_3$).

(1S,4S,5S,7R,11R)-(-)-3-tert-Butyl-5-methyl-2,6-dioxa-3-azatricyclo[5.3.1.0^{4,11}]undecane (**7bB**): R_f = 0.78, yellow oil, 19% yield, $[\alpha]_D^{22}$ = -23.1 (c = 0.00225 g/mL, EtOH).- $C_{13}H_{23}NO_2$ (225.3) Calcd C 69.29 H 10.29 N 6.22 Found C 69.14 H 10.22 N 6.32. - MS(EI): m/z (%) = 225 (32) [M^+] - IR (neat): 2972, 2934, 1453, 1390, 1362, 1219 cm^{-1}. - ^1H NMR (500 MHz): see Table 2. Additional signals: δ = 1.09 (s, 9 H, C(CH_3)$_3$), 1.21 (m, ^2J = 13.5, ^3J = 3.4, 3.4, 3.3, 3.3 Hz, 1 H, 9-H_{eq}), 1.45 (m, 2 H, 8-H_{ax}, 10-H_{ax}), 1.76 (m, 1 H, 9-H_{ax}), 2.02 (dd, ^2J = 14.6, ^3J = 1.9 Hz, 8-H_{eq}), 2.09 (dd, ^2J = 14.5 Hz, ^3J = 2.9 Hz, 1 H, 10-H_{eq}). - Additional coupling constants ^3J 1/10_{eq} = 2.9, 1/10_{ax} = 3.2, 7/8_{eq} = 1.8, 7/8_{ax} = 3.0, 5/CH_3 = 6.2 Hz. ^{13}C NMR : see Table 2. Additional signals: δ = 13.1(C-9), 26.7, 27.8 (C-8, C-10), 27.3 (C(CH_3)$_3$), 59.4 (*C*(CH_3)$_3$).

Separation of the diastereomers **7c** was performed by column chromatography (SiO_2, diethyl ether/petroleum ether 3:1.

(1'R,4'R,5'S,7'S,11'S)-(+)-2-Methyl-2-(5'-methyl-2',6'-dioxa-3'-azatricyclo[5.3.1.0^{4,11}]undec-3'yl)-propan-1-ol (**7cA**): R_f = 0.27, colourless crystals, 38% yield, mp. 53°C (Et_2O/petroleum ether). - $[\alpha]_D^{22}$ = +28.6 (c = 0.0034 g/mL, EtOH).- $C_{13}H_{23}NO_3$ (241.3) Calcd C 64.70 H 9.61 N 5.80 Found C 64.36 H 9.57 N 5.62. - MS(EI): m/z (%) = 241 (2.5) [M^+] - IR (KBr): 3447, 2966, 2935, 1453, 1441, 1292 cm^{-1}. - ^1H NMR (500 MHz): see Table 2. Additional signals: δ = 0.99 (s, 3 H, C(CH_3)$_2$), 1.07 (s, 3H, C(CH_3)$_2$), 1.27 (m, ^2J = 13.4, ^3J = 4.0, 4.0, 4.0 Hz, 1 H, 9'-H_{eq}), 1.45 (m, 2 H, 8'-H_{ax}, 10'-H_{ax}), 1.69 (m, ^2J = 13.1, ^3J = 16.6, 13.1, 3.4, 3.4 Hz, 1 H, 9'-H_{ax}), 1.97 (dd, ^2J = 16.6, ^3J = 1.8 Hz, 1 H, 8'-H_{eq}), 2.00 (dd, ^2J = 16.1, ^3J = 1.7 Hz 1 H, 10'-H_{eq}), 2.87 (s, broad, 1 H, OH), 3.42 (dd, ^2J = 10.6, ^3J = 3.9 Hz, 1 H, 1-H), 3.46 (dd, ^2J = 10.7, ^3J = 3.9 Hz, 1 H, 1-H'). - Additional coupling constants ^3J 1'/10'$_{eq}$ = 4.1, 1'/10'$_{ax}$ = 4.1, 5/CH_3 = 6.6 Hz. ^{13}C NMR: δ = 13.6(C-9'), 19.1 (C(CH_3)$_2$), 23.5 (*C*(CH_3)$_2$), 26.5, 27.9 (C-8', C-10'), 62.2 (C-2), 70.6 (C-1).

(1'S,4'S,5'S,7'R,11'R)-(-)-2-Methyl-2-(5'-methyl-2',6'-dioxa-3'-azatricyclo[5.3.1.0^{4,11}]undec-3'-yl)-propan-1-ol (**7cB**): R_f = 0.39, colourless oil, 10% yield. - $[\alpha]_D^{22}$ = -18.0 (c = 0.001 g/mL, EtOH). - $C_{13}H_{23}NO_3$ (241.3) Calcd C 64.70 H 9.61 N 5.80 Found C 64.53 H 9.56 N 5.62. - MS(EI): m/z (%) = 241 (3.5) [M$^+$] - IR (neat): 3447, 2969, 2930, 1476, 1375 cm^{-1}. - ^{1}H NMR (500 MHz): see Table 2. Additional signals: δ = 0.96 (s, 3 H, C(CH$_3$)$_2$), 1.02 (s, 3 H, C(CH$_3$)$_2$), 1.19 (m, ^{2}J = 13.3, ^{3}J = 3.5, 3.4, 3.4 Hz, 1 H, 9'-H$_{eq}$), 1.44 (m, 2 H, 8'-H$_{ax}$, 10'-H$_{ax}$), 1.68 (m, 1 H, 9'-H$_{ax}$), 1.93 (dd, ^{2}J = 14.5, ^{3}J = 1.9 Hz, 1 H, 8'-H$_{eq}$), 2.04 (dd, ^{2}J = 14.5, ^{3}J = 2.2 Hz 1 H, 10'-H$_{eq}$), 2.96 (s, broad, 1 H, OH), 3.37 (dd, ^{2}J = 10.7 Hz, 1 H, 1-H), 3.50 (dd, ^{2}J = 10.7 Hz, 1 H, 1-H'). - Additional coupling constants ^{3}J 1'/10'$_{eq}$ = 3.6, 1'/10'$_{ax}$ = 7.4, 5/CH$_3$ = 6.2 Hz. ^{13}C NMR: δ = 12.9 (C-9'), 19.3 (C(*C*H$_3$)$_2$), 23.9 (*C*(CH$_3$)$_2$), 26.4, 27.5 (C-8', C-10'), 62.3 (C-2), 70.6 (C-1).

(1'R,4'R,5'S,7'S,11'S)-(+)-2-Methyl-2-(5'methyl-2',6'-dioxa-3'-azatricyclo[5.3.1.0^{4,11}]undec-3'-yl)-1-propyl (S)-O-acetylmandelate

Esterification of compound **7cA** with (*S*)-(+)-*O*-acetylmandelic acid and (*R/S*)-*O*-acetylmandelic acid chloride was performed as described earlier.[5c] The enantiomeric excess of **7cA** was found to be more than 94%, because in the ^{1}H NMR spectrum of the (*S*)-compound additional signals due to the (*R/S*)-ester did not appear. The additional signals of the *R/S* ester are given in brackets.

^{1}H NMR: δ = 0.91 (s, 3H, C(CH$_3$)$_2$), 0.92 (s, 3H, C(CH$_3$)$_2$), 1.10 [1.16] (d, 3 H, (5')-CH$_3$), 1.20 [1.19] (m, 1 H, 9'-H$_{eq}$), 1.39 [1.36] (m, 2 H, 8'-H$_{ax}$, 10'-H$_{eq}$), 1.61 [1.60] (m, 1 H, 9'-H$_{ax}$), 1.91 [1.90] (m, 2 H, 8'-H$_{eq}$, 10'-H$_{eq}$), 2.12 [2.11] (s, 3 H, CH$_3$-C=O), 2.86 [2.56] (ddd, 1 H, 11'-H), 3.60 [3.62] (dd, 4'-H), 3.98 [3.92] (d, 1H, 1-H), 4.00 (m, 5-H'), 4.07 (m, 2H, 1'H, 7'-H), 4.10 [4.15] (d, 1 H, 1-H'), 5.86 [5.89] (s, 1H, C$_6$H$_5$-C*H*), 7.21-7.42 (m, Ar-H).

General procedure for the preparation of the *N-Alkyl 6-benzyl-5-methyl-2-oxa-3,6-diaza-tricyclo[5.3.1.0^{4,11}]undecanes* **10**.

A solution of dimethyl sulfoxide (1.15 g, 14.6 mmol) in dichloromethane was added dropwise to a solution of oxalyl chloride (0.96 g, 7.6 mmol) in dichloromethane (50 mL) at -78°C under nitrogen. After 10 min aminoalcohol **8** (1.79 g, 7.3 mmol) in dichloromethane (10 mL) was added dropwise. Stirring was continued for 2 h at -78°C before triethylamine (1.9 g, 18.2 mmol) was added. Subsequently the temperature was raised to 0°C before hydrolysis was performed by addition of water (0.25 mL). Successively $MgSO_4$ (approxim. 3 g) and the *N*-alkylhydroxylamine hydrochloride (7.3 mmol) were added. The reaction mixture was stirred for 3 d at room temperature. After filtration the organic layer was washed twice with water and then dried with $MgSO_4$. Removal of the solvent was followed by column chromatography.

Diastereomers **10a** were separated by chromatography on Al_2O_3 (solvent: *tert*-butylmethyl ether).

(1R,4R,5S,7S,11R)-(+)-6-Benzyl-3,5-dimethyl-2-oxa-3,6-diazatricyclo[5.3.1.0^{4,11}]undecane (**10aA**):

R_f = 0.58, colourless crystals, 24% yield melting range 52-58°C (hexane). - $[\alpha]_D^{22}$ = 61.9 (c = 0.01 g/mL, EtOH). - $C_{17}H_{24}N_2O$ (272.2) Calcd C 74.96 H 8.88 N 10.28 Found C 74.03 H 9.32 N 10.11. - MS(FD): m/z (%) = 272 (100) [M$^+$] - IR (KBr): 2944, 1453, 1148, 742 cm^{-1}. - ^{1}H NMR (500 MHz, 233 K): see Table 3. Additional signals: δ = 1.16 (m, ^{2}J = 14.0, ^{3}J = 4.0, 4.0 Hz, 1 H, 9-H$_{eq}$), 1.40 (dd, ^{2}J = 14.0, ^{3}J = 13.0 Hz, 1H, 8-H$_{ax}$), 1.69 (m, ^{2}J = 14.5, ^{3}J = 13.0 Hz, 1 H, 10-H$_{ax}$), 1.89 (m, ^{2}J = 14.0, ^{3}J = 13.0, 13.0 Hz, 1 H, 9-H$_{ax}$,),

1.89 (m, 1 H, 8-H_{eq}), 2.03 (d, ^2J = 14.5 Hz, 1 H, 10-H_{eq}), 2.70 (s, 1 H, N-CH_3), 7.35 (m, 5 H, Ar-H). - Additional coupling constants: ^2J CH_2Ph = 14.0, ^3J $1/10_{eq}$ = 4.0, $1/10_{ax}$ = nd, $7/8_{eq}$ = nd, $7/8_{ax}$ = nd, $5/CH_3$ = 6.7 Hz. ^{13}C NMR:see Table 3. Additional signals: δ = 13.4 (C-9), 24.8, 25.8 (C-8, C-10), 45.7 (NCH_3), 126.2, 128.0, 128.1, 139.6 (Ar-C).

(1S,4S,5S,7R,11S)-(+)-6-Benzyl-3,5-dimethyl-2-oxa-3,6-diazatricyclo[5.3.1.0^{4,11}]undecane (**10aB**): R_f = 0.63, colourless oil, 22% yield. - $[\alpha]_D^{22}$ = 56.9 (c = 0.018 g/mL, EtOH). - $C_{17}H_{24}N_2O$ (272.2) Calcd C 74.96 H 8.88 N 10.28 Found C 74.86 H 8.93 N 10.36. - MS(EI): m/z (%) = 272 (57) [M^+] - IR (neat): 3035, 2990, 1450, 1290 cm^{-1}. - ^1H NMR (500 MHz): see Table 3. Additional signals: δ = 1.09 (m, ^2J = 12.6, ^3J = 3.6, 2.0, <2.0 Hz, 1 H, 9-H_{eq}), 1.28 (m, ^2J = 14.1, ^3J = 13.0, 3.6, 2.0 Hz, 1 H, 8-H_{ax}), 1.59 (m, ^2J = 14.6, ^3J = 13.4, 4.1, 4.1 Hz, 1 H, 10-H_{ax}), 1.82 (m, ^2J = 12.6, ^3J = 13.4, 13.0, 2.0, <2.0 Hz, 1 H, 9-H_{ax},), 1.88 (dq, ^2J = 14.1, ^3J = <2, <2, <2 Hz, 1 H, 8-H_{eq}), 1.99 (dq, ^2J = 14.6, ^3J <2 <2 <2 Hz, 1 H, 10-H_{eq}), 2.62 (s, 3 H, N-CH_3), 7.17-7.32 (m, 5 H, Ar-H). - Additional coupling constants: ^2J CH_2Ph = 15.5, ^3J $1/10_{eq}$ = 2.0, $1/10_{ax}$ = 4.1, $7/8_{eq}$ <2.0, $7/8_{ax}$ = 3.6, $5/CH_3$ = 6.3 Hz. ^{13}C NMR:see Table 3. Additional signals: δ = 13.8 (C-9), 25.9, 26.1 (C-8, C-10), 46.0 (N-CH_3), 126.3, 127.8, 128.5, 139.3 (Ar-C).

(1S,4R,5S,7R,11S)-(+)-6-Benzyl-3,5-dimethyl-2-oxa-3,6-diazatricyclo[5.3.1.0^{4,11}]undecane (**10aC**): Additional chromatography (Al_2O_3, EtOAc, R_f = 0.39), colourless oil, 19% yield. - $[\alpha]_D^{22}$ = 85.6 (c = 0.01 g/mL, EtOH). - $C_{17}H_{24}N_2O$ (272.2) Calcd C 74.96 H 8.88 N 10.28 Found C 74.43 H 9.30 N 10.16. - MS(FD): m/z (%) = 272 (100) [M^+] - IR (neat): 2980, 1480, 950, 725 cm^{-1}. - ^1H NMR (500 MHz): see Table 3. Additional signals: δ = 0.91 (m, ^2J = 13.4, 2.5 Hz, 1 H, 9-H_{eq}), 1.23 (^3J = 10.6, Hz, 1H, 8-H_{ax}), 1.39 (m, ^2J = 13.4, ^3J = 10.6, 1.6 Hz, 1 H, 9-H_{ax}), 1.41 (m, 2 H, 8-H_{eq}, 10-H_{ax}), 1.93 (m, ^2J = 15.0, ^3J = 2.5, 1.6 Hz, 1 H, 10-H_{eq}), 2.83 (s, 3 H, N-CH_3), 7.30 (m, 5 H, Ar-H). - Additional coupling constants: ^2J CH_2Ph = 13.7, ^3J $1/10_{eq}$ = 9.2, $1/10_{ax}$ = 7.2, $7/8_{eq}$ = 9.1, $7/8_{ax}$ = 9.1, $7/8_{eq}$ nd., $5/CH_3$ = 5.8 Hz. ^{13}C NMR: see Table 3. Additional signals: δ = 21.6 (C-9),31.9, 33.1 (C-8, C-10), 47.6 (N-CH_3), 126.9, 128.1, 128.9, 140.6 (Ar-C).

Diastereomers **10b** were separated by chromatography on SiO_2 (solvent Et_2O/petroleum ether 1:5)

(1R,4R,5S,7S,11R)-6-Benzyl-3-tert-butyl-5-methyl-2-oxa-3,6-diazatricyclo[5.3.1.0^{4,11}]undecane (**10bA**): R_f = 0.23), brown oil, 12% yield. - $C_{20}H_{30}N_2O$ (330.2) Calcd C 72.77 H 9.08 N 8.48 Found C 72.23 H 9.24 N 8.25. - MS(EI): m/z (%) = 330 (5) [M^+] - IR (neat): 3025, 1620, 1445, 1280 cm^{-1}. - ^1H NMR: see Table 3. Additional signals: δ = 1.10 (s, 9 H, $C(CH_3)_3$). 1.36 (m, 1H), 1.51 (m, 2 H), 1.81 (m, 2 H), 1.94 (m, 1 H), 7.12-7.46 (m, 5 H, Ar-H). - Additional coupling constants: ^2J CH_2Ph = 14.1, ^3J $5/CH_3$ = 6.6 Hz. ^{13}C NMR:see Table 3. Additional signals: δ = 14.8 (C-9), 23.9, 26.5 (C-8, C-10), 27.1 ($C(CH_3)_3$), 59.5 ($C(CH_3)_3$), 126.5, 128.1, 128.5, 140.3 (Ar-C).

(1S,4S,5S,7R,11S)-6-Benzyl-3-tert-butyl-5-methyl-2-oxa-3,6-diazatricyclo[5.3.1.0^{4,11}]undecane (**10bB**): R_f = 0.63), brown oil, 12% yield. - $C_{20}H_{30}N_2O$ (330.2) Calcd C 72.77 H 9.08 N 8.48 Found C 72.69 H 9.21 N 8.37. - MS(EI): m/z (%) = 330 (10) [M^+] - IR (neat): 3030, 1615, 1455, 1280 cm^{-1}. - ^1H NMR: see Table 3. Additional signals: δ = 1.08 (s, 9 H, $C(CH_3)_3$), 1.26 (dd, ^2J = 13.3, ^3J = 13.0 Hz, 1 H, 8-H_{ax}), 1.44 (m, ^2J = 13.1, ^3J = 4.1, 3.6 Hz, 1 H, 9-H_{eq}), 1.46 (m, ^2J = 14.6, ^3J = 13.2, 4.1, 4.0 Hz, 1 H, 10-H_{ax}), 1.78 (m, ^2J = 13.1, ^3J = 13.3, 13.0, 3.0 Hz, 1 H, 9-H_{ax}), 1.96 (dd, ^2J = 13.3, ^3J = 3.0 Hz, 1 H, 8-H_{eq}), 2.00 (dd, ^2J = 14.6, ^3J = 3.0

Hz, 1 H, 10-H_{eq}), 7.12-7.25 (m, 5 H, Ar-H). - Additional coupling constants: ^2J CH_2Ph = 15.5, 3J $1/10_{ax}$ = 4.0, $1/10_{eq}$ = <2, $7/8_{ax}$ = <2, $7/8_{eq}$ <2, $5/CH_3$ = 6.3 Hz. ^{13}C NMR:see Table 3. Additional signals: δ = 13.8 (C-9), 25.8, 27.3 (C-8, C-10), 27.6 ($C(CH_3)_3$), 59.7 ($C(CH_3)_3$), 126.6, 127.9, 129.1, 138.3 (Ar-C).

General procedure for the reductive opening of the isoxazolidine ring.

A solution of the tricyclic compounds 7 (2 mmol) in ethanol (50mL) was hydrogenated in the presence of $Pd(OH)_2$ on charcoal (0.5 g) in an autoclave at 100°C under a hydrogen pressure of 100-150 bar for 1-3 days. After separation from the catalyst the solvent was removed under reduced pressure.

(1R,2R,6S,8S,9R)-(-)-8-Methyl-9-methylamino-7-oxabicyclo[4.3.0]nonan-2-ol (**11aA**): Reaction time 2 d, 93% yield, white solid, mp 95°C (EtOH). - $[\alpha]_D^{20}$ = -57.28 (c = 0.0033 g/mL, EtOH. - $C_{10}H_{19}NO_2$ (185.3) Calcd. C 64.83 H 10.34 N 7.56 Found C 64.65 H 10.25 N 7.24. - MS (EI): m/z (%) = 185 (16) [M^+]. IR (KBr): 3389, 3310, 3159, 2938, 1448, 1368, 1119 cm^{-1}. - ^1H NMR (500MHz): δ = 1.30 (d, ^3J = 6.8 Hz, 3 H, CH_3), 1.38 (m, 1 H, 4-H_{eq}), 1.44 (m, 1 H, 3-H_{ax}), 1.55 (m, 1 H, 5-H_{ax}), 1.82 (m, 1 H, 4-H_{ax}), 1.89 (m, 1 H, 3-H_{eq}), 1.97 (m, 1 H, 5-H_{eq}), 2.13 (dt, ^3J = 7.1, 4.3, 4.3 Hz, 1 H, 1-H), 2.51 (s, 3H, N-CH_3), 2.95 (s, br, 2 H, NH, OH), 3.06 (dd, ^3J = 7.1, 6.5 Hz, 1 H, 9-H), 3.94 (quint., 6.3 Hz, 1 H, 8-H), 4.06 (ddd, ^3J = 4.3, 3.5, 2.5 Hz, 1 H, 2-H or 6-H), 4.06 (dt, ^3J = 4.3, 3.5, 3.5 Hz, 1 H, 6-H or 2-H). - ^{13}C NMR: δ = 13.9 (C-4), 21.8 (CH_3), 27.8 (C-5), 31.4 (C-3), 36.1 (N-CH_3), 44.3 (C-1), 65.5, 74.9 (C-2, C-6), 71.5 (C-9), 80.2 (C-8).

(1S,2S,6R,8S,9S)-(+)-8-Methyl-9-methylamino-7-oxabicyclo[4.3.0]nonan-2ol (**11aB**): Reaction time 3 d at 150 bar, 93% yield, colourless oil. $[\alpha]_D^{20}$ = +27.51 (c = 0.0004 g/mL, EtOH. - $C_{10}H_{19}NO_2$ (185.3) Calcd. C 64.83 H 10.34 N 7.56 Found C 64.56 H 10.59 N 7.33. - MS (EI): m/z (%) = 185 (21) [M^+]. IR (neat): 3357, 2932, 2865, 2749, 1448, 1117 cm^{-1}. - ^1H NMR: δ = 1.19 (d, ^3J = 6.6 Hz, 3 H, CH_3), 1.36 (m, 2 H, 3-H_{ax}, 4-H_{eq}), 1.41 (m, 1 H, 5-H_{ax}), 1.62 (m, 2 H, 4-H_{ax}, 3-H_{eq}), 1.96 (m, 1 H, 5-H_{eq}), 2.10 (ddd, ^3J = 7.6, 4.5, 3.9 Hz, 1 H, 1-H), 2.45 (s, 3 H, N-CH_3), 2.89 (s br., 2 H, NH, OH), 3.38 (dd, ^3J = 7.7, 3.8 Hz, 1 H, 9-H), 3.70 (qd, ^3J = 6.6, 3.8 Hz, 1 H, 8-H), 3.97 (ddd, ^3J = 6.6, 3.9, 2.1, Hz, 1 H, 2-H or 6-H), 4.06 (ddd, ^3J = 6.6, 4.5, 1.8 Hz, 1 H, 6-H or 2-H), - ^{13}C NMR: δ = 13.9 (C-4), 14.1 (CH_3), 27.2 (C-5), 31.2 (C-3), 36.4 (N-CH_3), 43.8 (C-1), 65.3, 65.4, 75.4 (C-2, C-6, C-9), 76.1 (C-8).

(1R,2R,6S,8S,9R)-(-)-9-tert-Butylamino-8-methyl-7-oxabicyclo[4.3.0]nonan-2-ol (**11bA**): Reaction time 1 d at 150 bar, 83% yield, yellow oil. $[\alpha]_D^{20}$ = -56.48 (c = 0.0034 g/mL, EtOH. - $C_{13}H_{25}NO_2$ (227.4) Calcd. C 68.68 H 11.08 N 6.16 Found C 68.92 H 10.97 N 6.30. - MS (EI): m/z (%) = 227 (15) [M^+]. IR (neat): 3481,3375, 2974, 2961, 1453, 1444, 1375, 1231 cm^{-1}. - ^1H NMR: δ = 1.07 (s, 9 H, $C(CH_3)_3$), 1.20 (d, ^3J = 6.2 Hz, 3 H, CH_3), 1.26-1.52 (m, 3 H, 3-H_{ax}, 4-H_{eq}, 5-H_{ax}), 1.66-1.82 (m, 3 H, 3-H_{eq}, 4-H_{ax}, 5-H_{eq}), 1.86 (ddd, ^3J = 7.1, 6.6, 4.7 Hz, 1 H, 1-H), 2.72 (s br., 2 H, NH, OH), 3.15 (dd, ^3J = 7.1, 6.9 Hz, 1 H, 9-H), 3.74 (dq, ^3J = 6.8, 6.2 Hz 1 H, 8-H), 4.04 (dd, ^3J = 4.7, 3.3 Hz, 1 H, 2-H or 6-H), 4.06 (dd, ^3J = 6.6, 3.7 Hz, 1 H, 6-H or 2-H), - ^{13}C NMR: δ = 13.7 (C-4), 20.1 (CH_3), 27.8, 31.2 (C-3, C-5), 29.6 ($C(CH_3)_3$), 45.4 (C-1), 50.6 ($C(CH_3)_3$), 63.9 (C-9), 65.6, 75.3 (C-2, C-6), 80.8 (C-8).

(1S,2S,6R,8S,9S)-(+)-9-tert-Butylamino-8-methyl-7-oxabicyclo[4.3.0]nonan-2-ol (**11bB**): Reaction time 3 d at 150 bar, CC (SiO_2, EtOAc/petroleum ether 1:1), 88% yield, bright-yellow solid, mp 82°C

(EtOAc/petroleum ether). $[\alpha]_D^{20}$ = +40.01 (c = 0.0012 g/mL, EtOH. - $C_{13}H_{25}NO_2$ (227.4) Calcd. C 68.68 H 11.08 N 6.16 Found C 68.41 H 10.83 N 5.86. - MS (EI): m/z (%) = 227 (19) [M^+]. IR (KBr): 3413, 3360, 2961, 1477, 1453, 1389, 1231 cm^{-1}. - ^1H NMR: δ = 1.04 (s, 9 H, $C(CH_3)_3$), 1.13 (d, ^3J = 6.6 Hz, 3 H, CH_3), 1.35-1.80 (m, 5 H, cyclohexyl-H), 1.85 (ddd, ^3J = 7.7, 3.5, 2.1 Hz, 1 H, 1-H), 2.00 (m, 1 H, 5-H_{eq}), 3.20 (s br., 2 H, NH, OH), 3.52 (dd, ^3J = 7.7, 4.9 Hz, 1 H, 9-H), 3.70 (qd, ^3J = 6.6, 4.9 Hz 1 H, 8-H), 3.92 (dd, ^3J = 6.6, 2.1 Hz, 1 H, 2-H or 6-H), 4.02 (dd, ^3J = 6.6, 3.6 Hz, 1 H, 6-H or 2-H), - ^{13}C NMR: δ = 14.1 (C-4), 14.9 (CH_3), 26.5, 29.5 (C-3, C-5), 30.3 ($C(CH_3)_3$), 45.5 (C-1), 50.2 ($C(CH_3)_3$), 57.2 (C-9), 65.9, 75.6 (C-2, C-6), 76.6 (C-8).

Methylation of compound **11aA**

(1R,2R,6S,8S,9R)-(-)-9-Dimethylamino-8-methyl-7-oxabicyclo[4.3.0]nonan-2-ol (**12aA**): Methyl iodide (0.18 g, 1.25 mmol) was added to a solution of compound **11aA** (0.18 g, 1 mmol) and diisopropylamine (0.13 g, 1.25 mmol). The reaction mixture was stirred for 20 h. After addition of water (10 mL) the organic layer was separated and washed with water (3 x 5mL). Then it was dried with $MgSO_4$. Subsequently the solvent was removed under reduced pressure. Yellow oil, 56% yield. $[\alpha]_D^{20}$ = -11.67 (c = 0.0018 g/mL, EtOH. - $C_{11}H_{21}NO_2$ (199.3) Calcd. C 66.29 H 10.62 N 7.03 Found C 65.82 H 10.61 N 6.52. - MS (EI): m/z (%) = 199 (29) [M^+]. IR (neat): 3312, 3150, 2930, 1450, 1368, 1120 cm^{-1}. - ^1H NMR (500 MHz): δ = 1.23 (d, ^3J = 6.2 Hz, 3 H, CH_3), 1.24-1.46, 1.78-1.93 (m, 6 H, 3-H, 4-H, 5-H), 2.03 (dt, ^3J = 6.6, 4.4, 4.4 Hz, 1 H, 1-H), 2.23 (s, 6 H, $N(CH_3)_2$), 2.55 (t, ^3J = 6.7 Hz, 1 H, 9-H), 4.10 (ddd, ^3J = 4.4, 3.5, 3.0 Hz, 1 H, 2-H or 6-H), 4.11 (dq, ^3J = 6.7, 6.3 Hz, 1 H, 8-H), 4.13 (ddd, ^3J = 4.5, 3.5, 3.3 Hz, 1 H, 6-H or 2-H), - ^{13}C NMR: δ = 13.5 (C-4), 22.8 (CH_3), 28.1, 31.1 (C-3, C-5), 45.5 (C-1), 45.9 ($N(CH_3)_2$), 64.7, 77.6 (C-2, C-6), 74.0 (C-9), 78.1 (C-8).

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REFERENCES AND FOOTNOTES

1. Tufariello, J.J. in *1.3 Dipolar Cycloaddition Chemistry*, Padwa, A. (Ed.), Wiley - Interscience: New York, **1984**, Chapter 9, pp. 116-122, 140-153; b) Wade, P.A. in *Comprehensive Organic Synthesis*; Trost, B.M.; Fleming, I; Semmelhack, M.F. Eds., Pergamon: Oxford **1991**, Vol. 4, pp. 1113-1124; c) Breuer, E. in *Nitrones, Nitronates and Nitroxides*, Patai, S.; Rappoport, Z. Eds.; Wiley: Chichester **1989**, pp. 182-186, 264-277; d) Torsell, K.B.G. *Nitrile Oxides, Nitrones, and Nitronates*, VCH Publishers Inc.: Weinheim **1988**, pp. 194-254.
2. LeBel, N.A. *Trans. N.Y. Acad. Sci.* **1965**, *27*, 858-867, (*C.A.* **1966**, *64*, 548h).
3. a) Walts, A.E.; Roush, W.R. *Tetrahedron* **1985**, *41*, 3463-3478; b) Stanssens, D.; De Keukeleire, D.; Vandewalle, M. *Tetrahedron Asymm.* **1990**, *1*, 547-560; c)Tamura, O.; Okabe, T.; Yamaguchi, T.; Gotanda, K.; Noe, K., Sakamoto, M. *Tetrahedron* **1995**, *51*, 107-118.
4. a) Hassner, A.; Maurya, R.; Friedman, O.; Gottlieb, H.E.; Padwa, A.; Austin, D. *J. Org. Chem.* **1993**, *58*, 4539-4546; b) Chiacchio, U.; Casuscelli, F.; Corsaro, A.; Librando, V.; Rescifina, A.; Romeo, R.; Romeo, G. *Tetrahedron*, **1995**, *51*, 5689-5700; c) see also references 6-16 in Aurich, H.G.; Biesemeier, F. *Synthesis* **1995**, 1171-1178.

5. a) Aurich, H.G.; Biesemeier, F. *Synthesis* **1995**, 1171-1178; b) Aurich, H.G.; Gentes, C.; Harms, K. *Tetrahedron* **1995**, *51*, 10497-10512; c) Aurich, H.G.; Biesemeier, F.; Geiger, M.; Harms, K. *Liebigs Ann. / Recueil* **1997**, 423-434; d) Aurich, H.G.; Geiger, M.; Sievers, U. *Synlett* **1997**, 1004-1006. - See also references cited in 5a-d.
6. Preliminary communication: Aurich, H.G.; Geiger, M.; Gentes, C.; Köster, H. *Tetrahedron Lett.* **1996**, *37*, 841-844.
7. a) Aurich, H.G.; Frenzen, G.; Gentes, C. *Chem.* Ber. **1993**, *126*, 787-795; b) Aurich, H.G.; Biesemeier, F.; Boutahar, M. *Chem. Ber.* **1991**, *124*, 2329-2334.
8. Concerning allylic 1,3-strain see: Hoffmann, R.W. *Chem. Rev.* **1989**, *89*, 1841-1860.
9. The atomic coordinates and additional data such as bond lengths and angles for this work are available on request from the Director of the Cambridge Crystallographic Data Centre, University Chemical Laboratory, Lensfield Road, Cambridge, CB2 1EW. Any request should be accompanied by the full literature citation for this communication.
10. Hesse, M., Meier, H., Zeeh, B. *Spektroskopische Methoden in der organischen Chemie*. Thieme: Stuttgart, **1991**, p. 105.
11. See also references 5b and c.
12. Aurich, H.G.; Köster, H. *Tetrahedron* **1995**, *51*, 6285-6292, see also ref. 5b and 5c.