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Resolution and enantioselective rearrangements of amino group-containing oxiranyl ethers

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Abstract—Resolution protocols for 2-benzyloxymethyl-3-diethylaminomethyloxirane and 2-benzyloxymethyl-3-piperidinomethyloxirane have been developed. In the presence of organometallic bases enantioselective rearrangement of the newly separated oxirane enantiomers provides chiral oxetanes or *cis*-but-2-ene-1,4-diol derivatives without any racemization. The stereochemistry of the oxetanes was investigated by ^{1}H NMR and molecular modeling. A novel method using an atropisomeric dicarboxylic acid as a chiral solvating agent in ^{1}H NMR for the determination of the enantiomeric excess of the products is also reported.

1. Introduction

Optically active oxiranes are useful intermediates for the synthesis of compounds of practical importance. Thus, regio- and stereospecific opening of chiral 2,3-disubstituted oxiranes is a well-known route to a large variety of optically active alcohols, diols and other compounds.[1,2] Biocatalytic asymmetric hydrolysis has also been reported as a convenient access to non-racemic vicinal diols.[3]

During our studies we have investigated extensively the base-catalyzed rearrangement reactions of methoxymethyl, benzyl or substituted benzyl group-containing oxiranyl ethers for preparing substituted hydroxy vinyl ethers,[4] tetrahydrooxepines,[5] hydroxy oxetanes[6] and *cis*-but-2-ene-1,4-diols.[7]

Recently we reported that hydroxy oxetanes **2** and *cis*-but-2-ene-1,4-diols **3** can be obtained from 3-alkoxymethyl-, 3-trialkylsilylmethyl- or 3-dialkylaminomethyl-2-benzyloxymethyloxiranes[8] **1** (Scheme 1) in the presence of potassium *tert*-butoxide activated lithium diisopropylamide (LDA-KO*t*Bu reagent[9]) at low or ambident temperature, respectively. Furthermore, an improved method for the rearrangement of oxetanes **2** into the diols **3** has been developed by the use of large excess of *n*-butyllithium (*n*-BuLi).[8]

The enantioselective formation of the corresponding 2,3-substituted *anti*-oxetane derivative from optically active 2-benzyloxymethyl-3-pentyloxirane has already been demonstrated[6] when the chiral oxirane was synthesized by the Sharpless-epoxidation method. However, the enantioselectivity of the rearrangement of **1** or **2** into substituted *cis*-but-2-ene-1,4-diols **3** has never been investigated. In order to determine the enantioselectivity of the above-mentioned reactions, a systematic study on the resolutions of (±)-2-benzyloxymethyl-3-diethylaminomethyloxirane **4** and (±)-2-benzyloxymethyl-3-piperidinomethyloxirane **5** was carried out in our laboratory with the aim of yielding optically active starting materials for the rearrangement reactions. On the other hand the optically active oxiranes **4** and **5** may be used as valuable chiral building blocks in the synthesis of amino alcohols and amino polyols, many of which have interesting biological activities.[10,11]

2. Results and discussion

The racemic *cis*-oxiranyl ethers **4** and **5** were prepared from *cis*-2-buten-1,4-diol via monobenzylation followed by epoxidation, tosylation and nucleophilic displace-

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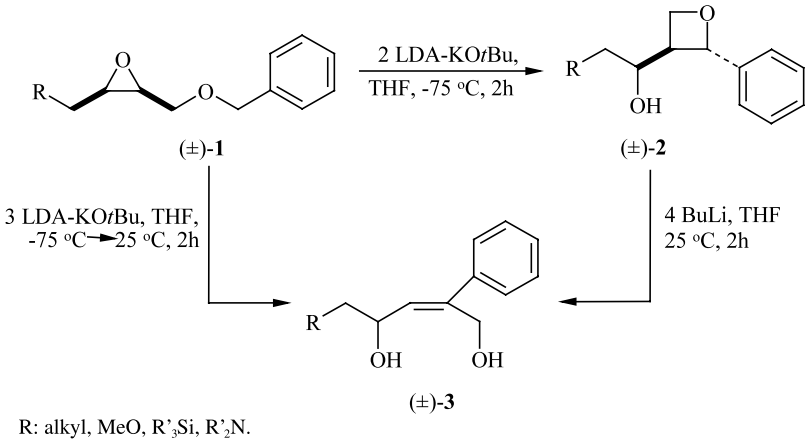


Scheme 1.

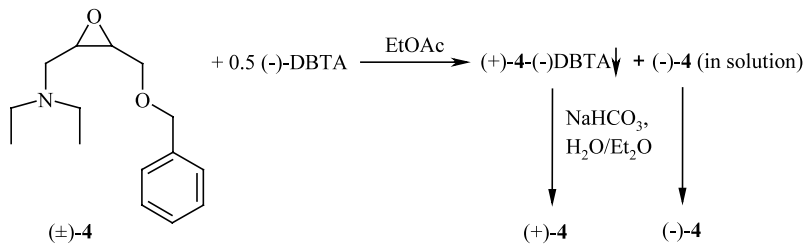
ment of the tosyl group by the required amine according to known procedures.[7,8]

2.1. Resolution of (±)-4 and (±)-5

Enantiomer separation of racemic oxirane derivatives is complicated by the reactivity of the three-membered ring. In the case of **4** and **5** the tertiary amino group is suitable for salt formation, however, mild conditions have to be used to avoid ring-opening reactions during the formation and decomposition of the diastereoisomeric salts. Several chiral acids (tartaric acid and its *O*,*O*′-diacylated derivatives, mandelic acid) and different conditions (solvents, molar ratios) were tested for preparing crystalline diastereoisomeric salts of **4** and **5**. The best results were achieved with *O*,*O*′-dibenzoyl-(*R*,*R*)-tartaric acid monohydrate ((−)-DBTA) in ethyl acetate.

In the case of (±)-**4**, a half equivalent amount of DBTA resulted in crystallization of the less soluble (+)-**4**-(−)-DBTA salt in good yield (64%) and enantiomeric purity (84%), while an excess of the (−)-enantiomer remained in solution (Scheme 2). Using an equivalent amount of (−)-DBTA gave much worse separation. We avoided recrystallization of the diastereoisomeric salt because of the reactivity of **4**.

However, repeated resolution of (+)-**4** with (−)-DBTA was carried out successfully to obtain the enantiomerically pure sample. Again, the molar amount of the resolving agent was about equal to the molar amount of the (+)-**4** isomer in the enantiomeric mixture. Enrichment of (−)-**4** was achieved in a similar way by using *O*,*O*′-dibenzoyl-(*S*,*S*)-tartaric acid monohydrate ((+)-DBTA) as resolving the agent. The results are summarized in Table 1.



Scheme 2.

Table 1. Results from resolutions of **4** and **5** in ethyl acetate

Starting material (e.e.%)	Resolving agent (equiv.)	Product from the crystalline			S[a]	Product from the filtrate		
		Isomer	Yield[b] (%)	E.e. (%)		Isomer	Yield[b] (%)	E.e. (%)
(±)-**4** (0)	(−)-DBTA (0.50)	(+)-**4**	53	84	0.45	(−)-**4**	134	77
(−)-**4** (77)	(+)-DBTA (0.78)	(−)-**4**	77	95	0.73	(+)-**4**	140	23
(+)-**4** (65)	(−)-DBTA (0.75)	(+)-**4**	69	99	0.68	(+)-**4**	52	17
(±)-**5** (0)	(−)-DBTA (1.00)	(−)-**5**	100	75	0.75	(+)-**5**	70	65
(−)-**5** (75)	(−)-DBTA (0.80)	(−)-**5**	81	89	0.72	(−)-**5**	28	40

[a] Efficiency of the resolution **S** = yield×e.e.×10^{-4}.[12]
[b] Yields are calculated on the basis of the starting amount of the given enantiomer.

It was interesting to observe that 1 molar equivalent of (−)-DBTA was necessary for the resolution of (±)-**5** (Scheme 3). The less soluble (+)-**5**-(−)-DBTA salt crystallized from ethyl acetate, the (−)-**5**-(−)-DBTA salt remained in solution. The efficiency[12] (**S**) of this resolution was higher than that of (±)-**4**. Repeated resolution of the (−)-**5** enriched enantiomeric mixture gave (−)-**5** in 89% e.e. (the results are summarized in Table 1).

Unfortunately, the resolved products are oils and our attempts to prepare single crystals from salts of **4** and **5** enantiomers have also failed. Therefore, we have not been able to determine the absolute configurations of these products by X-ray crystallography.

2.2. Enantioselective rearrangement of 4 and 5 into oxetanes 6 and 7 and diols 8 and 9

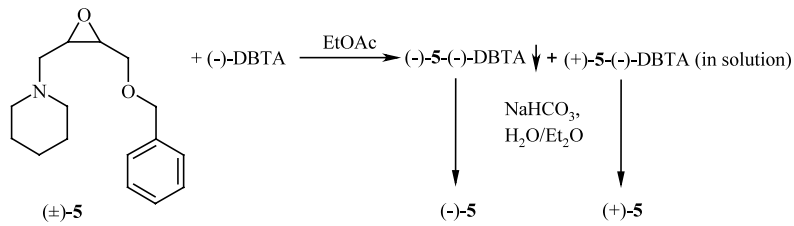
In order to investigate the enantioselectivities of the rearrangement processes, (+)-**4** and (−)-**5** were converted into the corresponding oxetanes **6** and **7** and *cis*-but-2-ene-1,4-diols **8** and **9**, respectively, by using LDA-KO*t*Bu reagent. The two-step rearrangement process was tested by treating the chiral oxetanes **6** or **7** with an excess of butyllithium to yield the diols **8** and **9**, respectively (Scheme 4).

We obtained optically active products in all cases. Moreover, the enantiomeric purity was maintained throughout the whole reaction sequence. The results indicate that both the single-step and the two-step rearrangements of our model compounds are highly stereo- and enantioselective reactions. Consequently, these routes can serve as new methods for the preparation of optically active oxetane and *cis*-but-2-ene-1,4-diol derivatives.

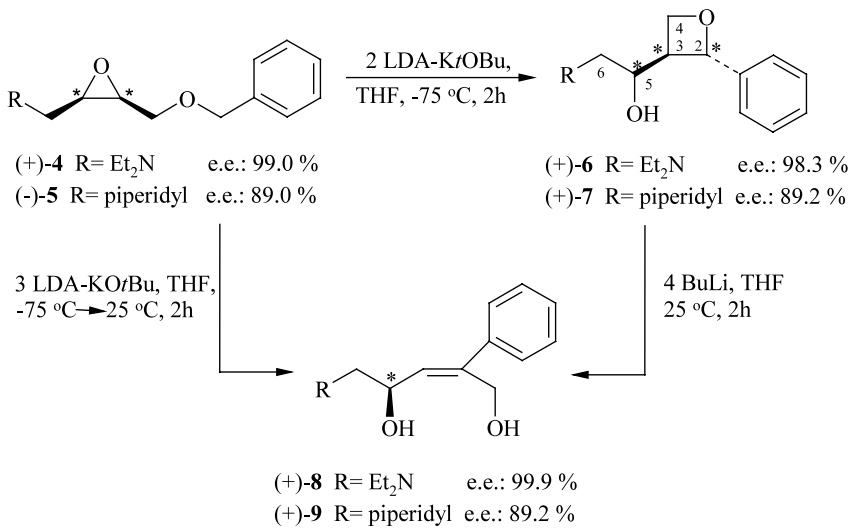
2.3. Stereochemical analysis of oxetanes 6–7

The structures of compounds **6** and **7** were verified by the concerted use of one- and two-dimensional homonuclear ^{1}H–^{1}H and ^{1}H–^{13}C shift correlation NMR. The assignment of the relative configuration of the C(2), C(3) and C(5) stereogenic centers (see Scheme 4) was based on the analysis of the dipolar connectivities (Table 2) and the interpretation of the vicinal scalar coupling constants (Table 3) with the combination of force-field based molecular modeling and potential energy calculations (Table 4).

Because structures **6** and **7** showed identical through-space and through-bond connectivities, in the following we report the line of thought leading to the configurational assignment of **6** only. As reported previously,[8] substituted 2,3-*anti*-oxetanes were expected from the LDA-KO*t*Bu-induced rearrangement of oxiranes **4** and **5**; in the case of **6** this corresponds to the relative configurations (2*S*,3*S*) or (2*R*,3*R*). This anticipation was confirmed by the massive NOE[13] enhancement observed between H_3 and the aromatic protons (Ar), indicating a spatial proximity between those protons. The lack of $H_5\cdots$Ar and $H_6x\cdots$Ar NOEs and the rela-



Scheme 3.



Scheme 4.

Table 2. Observed dipolar connectivities (NOE) in **6**. Some relevant NOEs are highlighted. Classification of the relative NOE intensities are according to: S = small, M = medium, L = large, T = tocsy

Protons	H_2	H_3	H_4x	H_4y	H_5	H_6x	H_6y	Et	Ar
H_2	–	T		M	**L**	No effect	**M**		L
H_3	T	–	L	T	**L**	**M**	**L**	No effect	L
H_4x		T	–	T					S
H_4y	M	T	T	–	**L**	**M**			
H_5	L	L		L	–	**L**	T	M	
H_6x		M	S	L	L	–	T	L	
H_6y	M	L			T	T	–	L	**S**

Table 3. Vicinal scalar coupling constants (in Hz) in **6**. The relevant coupling constants are highlighted

Protons	H_2	H_3	H_4x	H_4y	H_5	H_6x	H_6y
H_2	–	6.2	–	–	–	–	–
H_3	6.2	–	8.5	7.1	**7.1**	–	–
H_4x	–	8.5	–	–	–	–	–
H_4y	–	7.1	–	–	–	–	–
H_5	–	**7.1**	–	–	–	**3.3**	**10.5**
H_6x	–	–	–	–	**3.3**	–	–
H_6y	–	–	–	–	**10.5**	–	–

Table 4. Calculated relative potential energies (kcal/mol) of the rotamers of **6** (2*S*,3*S*,5*S*) and (2*S*,3*S*,5*R*). Energy minima are highlighted

Rotamer	B_1	B_2	B_3
A_1	82.9	87.2	88.2
A_2	**81.4**	84.5	85.7
A_3	**80.0**	82.7	84.0
	B_4	B_5	B_6
A_4	82.6	89.1	85.9
A_5	**79.7**	84.7	**80.6**
A_6	81.9	86.8	84.7

tively small NOE observed between H_6y and Ar also suggested that the phenyl group and the (2-amino-1-hydroxy)ethyl group occupy the opposite side of the oxetane ring (Figs. 1 and 2). The mutually observable NOEs between $H_2\cdots H_4y$ and $H_4x\cdots Ar$ allowed the unambiguous assignment of the diasterotopic hydrogens H_4x and H_4y.

Due to the flexibility of the (2-amino-1-hydroxy)ethyl group the assessment of the relative configuration of the third stereogenic center C(5) requires a systematic search for the most populated conformational species in both (2*S*,3*S*,5*S*)- and (2*S*,3*S*,5*R*)-2,3-*anti*-oxetane epimers. Scheme 5 and Scheme 6 show the Newman projections of the staggered rotamers about the C(3)–C(5) (A series) and C(5)–C(6) (B series) bonds of the side chain for the two epimers (2*S*,3*S*,5*S*) and (2*S*,3*S*,5*R*), respectively.

We note that the stereochemical analysis involved an initial ambiguity regarding the assignment of the diastereotopic side-chain protons H_6x and H_6y. These protons were interchangeably assigned to the resonances at 2.18 ppm (1H, dd, $J = 12.6$, 10.5) and 2.32 ppm (1H, dd, $J = 12.6$, 3.3); their assignment was verified at later stages of the conformational analysis.

Each epimer gives rise to nine different conformational families (see Figs. 1 and 2) in which the nitrogen lone pair occupies the energetically most favorable position, forming a hydrogen bond, where possible, with the hydroxyl group. The conformers in Figs. 1 and 2 are denoted as A_1B_1, $A_1B_2 \ldots A_6B_6$ following the notation used for the description of the C(3)–C(5) and C(5)–C(6) rotamers in Schemes 5 and 6. Since the interpretation of the observed NOEs often requires the consideration of the contribution of two or more rotamers due to the rapid interconversion of the conformational species on the relaxation time scale,[13] additional constraints were needed to interpret the NOEs and decide between epimers. The criteria introduced into the conformational analysis are: (1) energy criteria and (2) torsion angle criteria. By the introduction of energy constraints we assumed that the main conformational species responsible for the appearance of the NOEs in Table 2 are among the low-energy conformers of the applied molecular simulation method (Table 4). For the purposes of the present discussion we define low-energy conformers as those within the 4 kcal/mol range relative to the absolute minimum energies in A_3B_1 and A_5B_4.

Incorporation of the torsion angles into the conformational analysis is based on the torsional angle dependence of the vicinal proton–proton coupling constants, usually referred to as a Karplus-type relation.[14] For compound **6**, the vicinal ^1H–^1H coupling constants $^3J_{(H3–H5)}$, $^3J_{(H5–H6x)}$, $^3J_{(H5–H6y)}$ that were found useful in determining the C(3)–C(5) and C(5)–C(6) rotamer population are highlighted in Table 3. According to the refined Karplus relation parametrized by Altona et al.,[15] the markedly different experimental vicinal coupling constants (3.3 versus 10.5 Hz) of the diastereotopic hydrogens H_6x and H_6y indicate a preferred conformational species among the C(5)–C(6) rotamers in which one of the hydrogens attached to the C(6) carbon is *anti-periplanar* to proton H_5, while the other is necessarily gauche to it (see Scheme 5 rotamers B_1,B_3 and Scheme 6 rotamers B_4,B_5). The initially arbitrary x,y labeling of the H–C(6)–H diastereotopic hydrogens inevitably leads to simultaneous assignment routes, where interchanging the role of the x,y protons requires

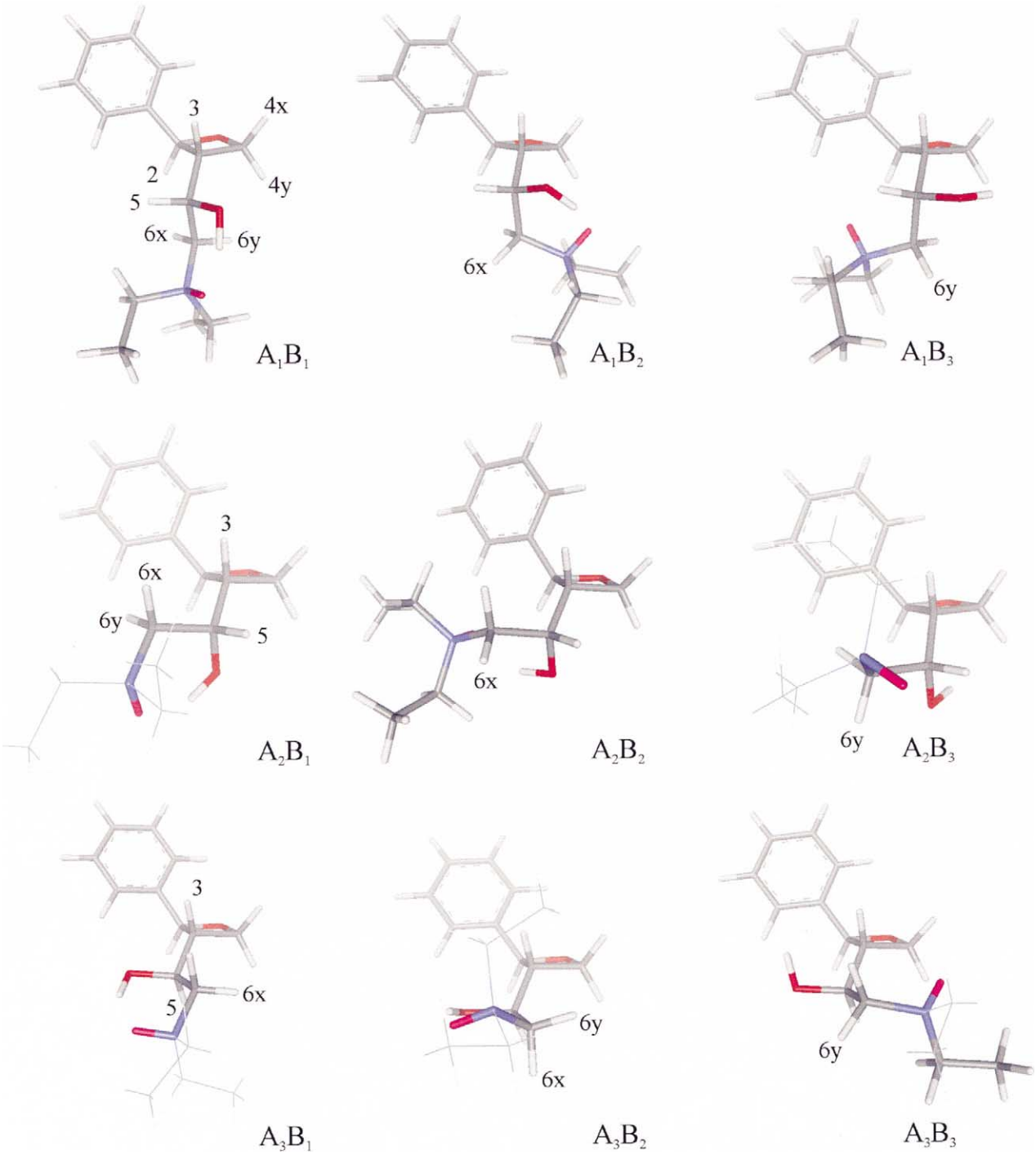


Figure 1. Conformers of (2*S*,3*S*,5*S*) epimer of **6** used for the interpretation of the NOEs.

the re-interpretation of the observed NOE connectivities.

This initial uncertainty in the assignment of protons H_6x and H_6y can be overridden by the introduction of energy constraints. According to this, by taking one of the epimers, say (2*S*,3*S*,5*S*), the potential energies of all six conformers, where one of the H_6 protons is *anti-periplanar* with H_5 (the $A_1\ldots{}_3B_1$ and $A_1\ldots{}_3B_3$ conformers), are compared from the point of view of whether the $A_1\ldots{}_3B_1$ or $A_1\ldots{}_3B_3$ conformers are of lower energy. Comparison of the relative potential energies in Table 4 indicate that the B_1 conformers are systematically lower in energy by at least 4 kcal/mol than the corresponding B_3 conformers. Since the average value of the observed vicinal $^3J_{(H5-H6x)}$, $^3J_{(H5-H6y)}$ coupling constants stems from the relatively highly populated 'low energy' conformers, we may assign the resonance at 2.18 ppm ($J=12.6$, 10.5) to the proton that is *anti-periplanar* to H_5 in the B_1 rotamers (H_6y). The above assignment of H_6y is in perfect accordance with the fact that H_5 gives large NOE enhancement only into H_6x, the geminal partner of H_6y. Since all the $A_4\ldots{}_6B_4$ rotamers in the (2*S*,3*S*,5*R*) epimer are lower in energy than the corre-

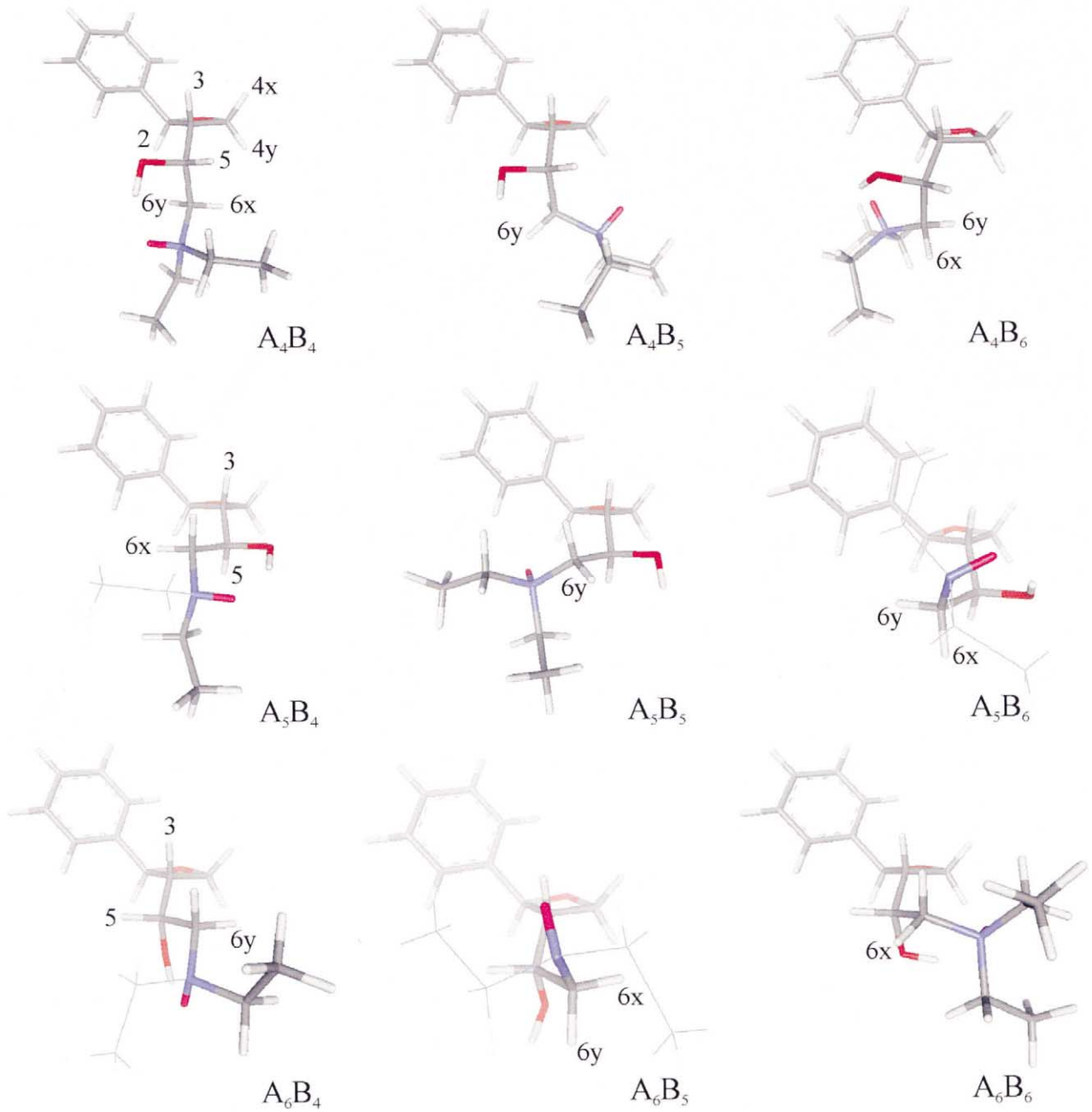
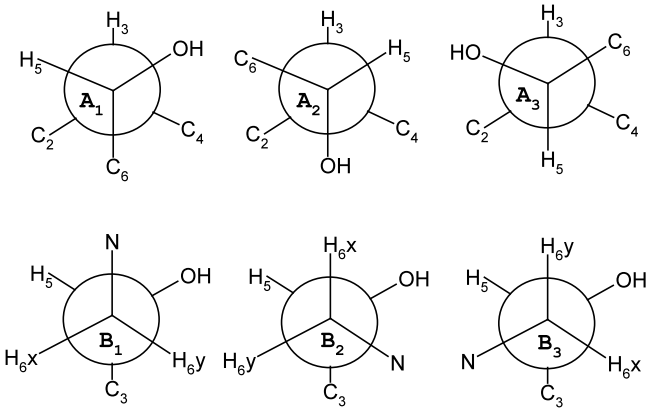


Figure 2. Conformers of (2*S*,3*S*,5*R*) epimer of **6** used for the interpretation of the NOEs.

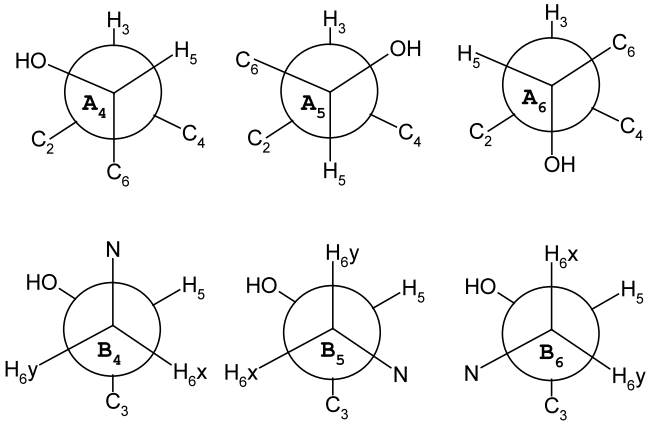
sponding $A_4\ldots_6B_5$ rotamers, the assignment of the proton at 2.18 ppm ($J=12.6$, 10.5) was carried out in an analogous way as in (2*S*,3*S*,5*S*). According to the applied torsion angle and energy constraints, the Newman projections of (2*S*,3*S*,5*R*) and (2*S*,3*S*,5*S*) not only differ in the configuration of the C(5) carbon but also in the reversed labeling of H_6 protons.

On the basis of the proposed assignment of the H_6x and H_6y diastereotopic hydrogens the interpretation of the observed NOE connectivities between each and every pair of nuclei gains importance in the following discussion. Close inspection of the perspective view of the stereostructures in Figs. 1 and 2 reveals that the highlighted network of existing and absent NOE connections in Table 2 cannot be described by the presence of a single predominant conformer in either epimer. Since the theoretical $^3J_{(H3-H5)}$ vicinal coupling constants vary from 12.4 Hz (*anti-periplanar*, e.g. A_3B_1) to as low as 0.6 Hz (gauche, e.g. A_2B_1), the measured 7.1 Hz value suggests a more evenly populated conformational equilibrium around the C(3)–C(5) bond than around the C(5)–C(6) bond where B_1 and B_4 were found dominant over the rest of the rotamers.

In conclusion, by taking all the measured and calculated constraints into account, the observed NOEs can be rationalized only in terms of a conformational equilibrium of the most dominant species: $A_2B_1 \rightleftharpoons A_3B_1$, as being slightly shifted towards A_3B_1. This allows us to state confidently that the LDA-KO*t*Bu induced rearrangement of **4** and **5** *cis*-oxiranes yields **6** and **7**



Scheme 5.



Scheme 6.

anti-phenyloxetanes with (2*S**,3*S**,5*S**)-relative configuration.

2.4. Determination of the enantiomeric excess of compounds 4–9

The samples underwent rapid decomposition in aqueous medium, which prevented us from developing a successful reversed phase chiral chromatographic system for the analysis of their enantiomeric composition, therefore we decided to determine the enantiomeric excess of structures **4**–**9** by ^{1}H NMR, using optically active chiral solvating agents (CSA).[16] The application of CSAs in NMR is often a method of choice when other chiral selectors (e.g. lanthanide shift reagents[16] or cyclodextrins[17]) fail to work properly. In the case of oxiranes (**4** and **5**), (−)-quinine, a commonly used CSA[18] was used for the enantiomeric discrimination which yielded satisfactory shift non-equivalence ($\Delta\delta$) at the benzyl-protons of the enantiomers. The NMR resonances suffered negligible exchange broadening[19] due to the presence of the CSA, and identical results were obtained both from the ratio of the integrals and from that of the intensities of the pertinent lines.

For the determination of the enantiomeric excess of oxetanes **6** and **7** and the *cis*-but-2-ene-1,4-diol derivatives **8** and **9**, we employed (+)-1-[2-carboxy-6-(trifluoromethyl)phenyl]pyrrole-2-carboxylic acid (**10**, Scheme 7), a new CSA synthesized recently by our group.[20] Although a few atropisomers have been reported[18,21] as being successful CSAs in NMR, the application of atropisomeric bifunctional carboxylic acid derivatives has no reported precedent. Preliminary molecular modeling studies indicated that the lone pair of the nitrogen and the neighboring hydroxyl group in the N–CH_2–CH–OH moiety of compounds **6**–**9** are in favorable spatial proximity to form two-point hydrogen bonds with the carboxylic groups of **10**, fulfilling one of the criteria of successful chiral recognition. Moreover, for *cis*-but-2-ene-1,4-diol derivatives **8** and **9** the possibility for the formation of a third and fourth hydrogen bond was also predicted. Fig. 3 shows the enantiomeric splitting of C(2)H–Ar (in **6** and **7**) and –CH= in **8** and **9** in the presence of **10**. Although other resonances showed enantiomeric splitting as well, because of their simple scalar coupling patterns the doublets of C(2)H–Ar and –CH= (both at ca. 5.60 ppm) were found to be the most adequate for the determination of e.e. The addition of 1 molar equivalent of **10** yielded only a slight broadening of the resonances and no decomposition of the samples was observed upon the addition of the chiral selector **10**. Further investigation of the underlying enantiodiscrimination mechanism and the possibility of assessing the absolute configuration of **6**–**9** using **10** is currently under way.

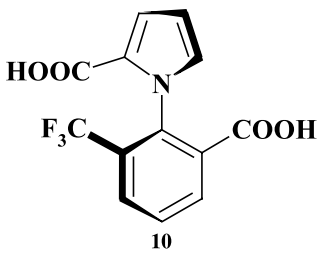
3. Experimental

3.1. General

Commercial starting materials were purchased from FLUKA AG and were used without further purification. Butyllithium was supplied by Chemetall GmbH Lithium Division, Frankfurt.

Tetrahydrofuran was obtained anhydrous by distillation from sodium wire after the characteristic blue color of in situ generated sodium diphenylketyl had been found to persist. Diisopropylamine was freshly distilled and kept under dry inert gas atmosphere. The concentration of the butyllithium solution was determined by double titration method.[22] All experiments were carried out in Schlenk-flasks under a dry nitrogen atmosphere.

The NMR measurements were carried out at 22°C in $CDCl_3$ on a Varian INOVA-500 spectrometer (operating at 500 MHz for ^{1}H) equipped with a waveform generator, using a ^{1}H{^{13}C,^{15}N} PFG-triple resonance 5 mm probe. ^{1}H chemical shifts are given relative to $\delta_{TMS}=0.00$ ppm. The applied pulse sequences (gDQF-



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Scheme 7.

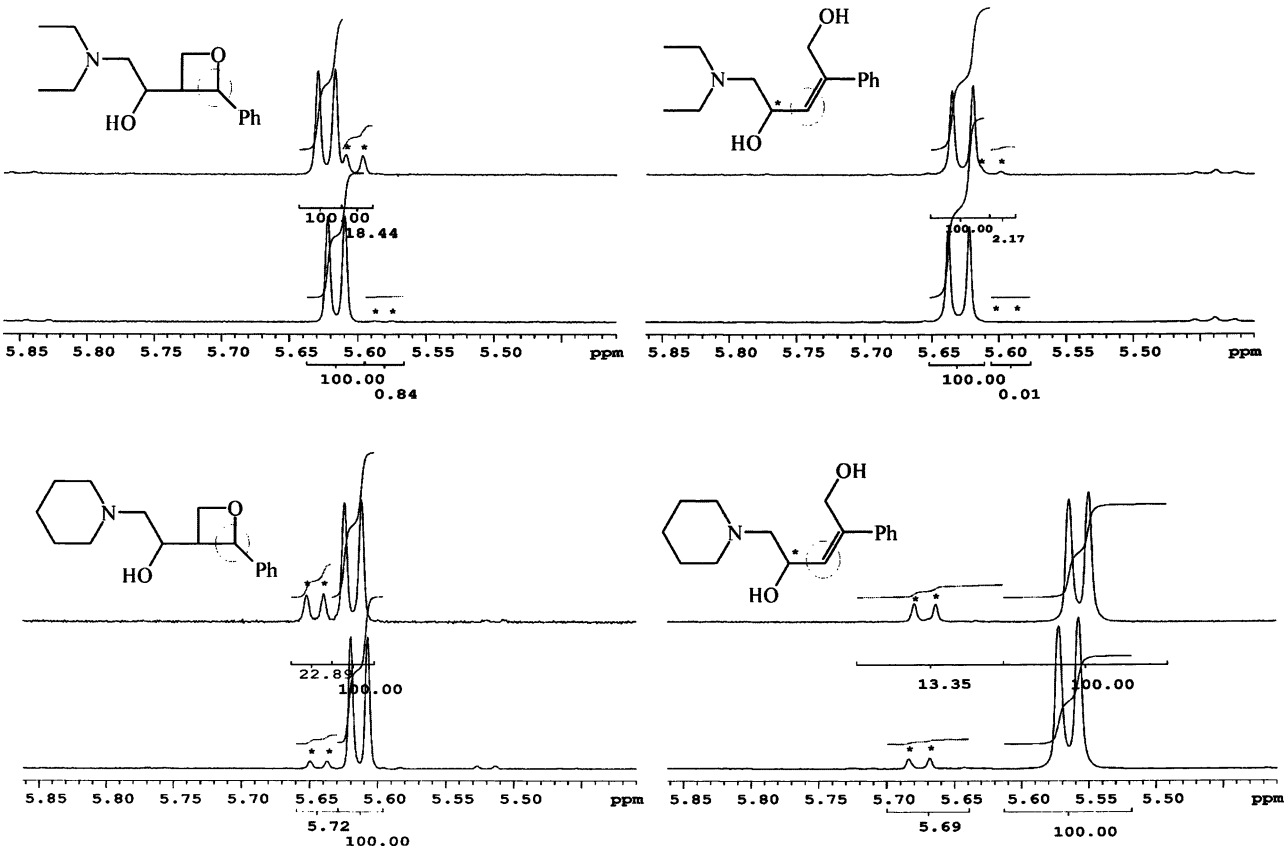

Figure 3. Determination of e.e. values for compounds **6**–**9** by ^{1}H NMR analysis. Spectra were recorded in the presence of **10**. The racemate was added to the solution in each case (upper spectra) to check the validity of the NMR method and to confirm the chemical shift and the enantiomeric purity.

COSY, TOCSY-1D, gDPFGSE-NOE, gHSQC) were part of the standard spectrometer software package. We used iBurp2 selective inversion pulses and 1 s mixing time for the gDPFGSE-NOE experiments. E.e. measurements were obtained in $CDCl_3$ for compounds **4** and **5** and in $CDCl_3$:acetone = 10:1 for **6**–**9** at 22°C. For the determination of e.e. (−)-quinine was used in 268 mM concentration whereas the concentration of the chiral selector **10** varied between 42 and 49 mM. The applied sample concentrations for **4**–**9** were: 86, 94, 10, 27, 64, 143 mM, respectively.

Molecular modeling calculations were carried out by using the Discover module of InsightII from Molecular Simulations Inc., licensed to Gedeon Richter Ltd. We applied in vacuo molecular mechanics calculations using CVFF force-field with atomic-charges and explicit nitrogen lone-pair.

Racemic **4** and **5** are known compounds, they were synthesized according to the literature procedure.[7,8]

3.2. Optical resolution of (±)-4 and (±)-5

3.2.1. Resolution of (±)-4. *O,O′*-Dibenzoyl-(*R,R*)-tartaric acid monohydrate (1.57 g, 4.16 mmol) was added to an ethyl acetate (100 mL) solution of (±)-**4** (2.08 g, 8.33 mmol) and the mixture was stirred for 16 h at 25°C. The precipitate was filtered off, washed with cold ethyl acetate (3×5 mL) and dried to afford (+)-**4**-*O,O′*-dibenzoyl-(*R,R*)-tartarate (1.61 g, 64%). The filtrate was concentrated in vacuo to give a mixture of (−)-**4** and (+)-**4**-*O,O′*-dibenzoyl-(*R,R*)-tartrate salt (2.00 g).

A suspension of (+)-**4**-*O,O′*-dibenzoyl-(*R,R*)-tartarate (1.61 g) in diethyl ether (30 mL) was stirred with saturated aqueous sodium hydrogen carbonate (30 mL). The aqueous phase was extracted with diethyl ether (20 mL). The combined organic extracts were washed with brine (20 mL) then dried and concentrated in vacuo to yield (+)-**4** as an oil (0.55 g, 2.21 mmol), $[\alpha]_D = +5.5$ ($c = 0.7$; chloroform); e.e. 83.5%. Using the same workup procedure for the mixture of (−)-**4** and (+)-**4**-*O,O′*-dibenzoyl-(*R,R*)-tartrate resulted in (−)-**4** (1.40 g, 5.61 mmol), $[\alpha]_D = -5.0$ ($c = 0.7$; chloroform); e.e. 77.2%.

To obtain a higher enantiomeric excess for (−)-**4** repeated resolution was carried out starting from (−)-**4** (1.36 g, 5.44 mmol, e.e. 77.2%) and *O,O′*-dibenzoyl-(*S,S*)-tartaric acid monohydrate (1.60 g, 4.24 mmol) to afford (−)-**4**-*O,O′*-dibenzoyl-(*S,S*)-tartrate (2.17 g, 66%) and, after workup, (−)-**4** (0.92 g, 3.68 mmol), $[\alpha]_D = -6.2$ ($c = 0.7$; chloroform); e.e. 95%. The filtrate was concentrated in vacuo and the residue contained the salt and the oxirane (0.64 g). It was converted into the free oxirane derivative (+)-**4** following the procedure above (0.24 g, 0.96 mmol), $[\alpha]_D = +1.5$ ($c = 0.7$; chloroform); e.e. 23%.

Enantiomerically pure (+)-**4** was prepared by repeated resolution of (+)-**4** (0.79 g, 3.17 mmol, e.e. 65%) with *O*,*O*′-dibenzoyl-(*R*,*R*)-tartaric acid monohydrate (0.91 g, 2.41 mmol) in ethyl acetate (35 mL) to obtain (+)-**4**-*O*,*O*′-dibenzoyl-(*R*,*R*)-tartrate (1.16 g, 60%). The usual workup procedure afforded (+)-**4** (0.45 g, 1.80 mmol), $[\alpha]_D = +6.5$ ($c = 0.7$; chloroform); e.e. 99%.

3.2.2. Resolution of (±)-5. *O*,*O*′-Dibenzoyl-(*R*,*R*)-tartaric acid monohydrate (4.15 g, 11.02 mmol) was added into an ethyl acetate (70 mL) solution of (±)-**5** (2.88 g, 11.02 mmol) and the mixture was stirred for 16 h at 25°C. The precipitate was filtered off, washed with cold ethyl acetate (3×5 mL) and dried to get (−)-**5**-*O*,*O*′-dibenzoyl-(*R*,*R*)-tartarate (3.70 g, 53%). The filtrate was concentrated in vacuo to yield a mixture of (+)-**5** and (−)-**5**-*O*,*O*′-dibenzoyl-(*R*,*R*)-tartrates (3.23 g).

A suspension of (−)-**5**-*O*,*O*′-dibenzoyl-(*R*,*R*)-tartarate (3.61 g) in diethyl ether (30 mL) was stirred with saturated aqueous sodium hydrogen carbonate (45 mL). The aqueous phase was extracted with diethyl ether (20 mL). The collected organic phases were washed with brine (20 mL) then dried and concentrated in vacuo to yield (−)-**5** as an oil (1.45 g, 5.55 mmol), $[\alpha]_D = -11.7$ ($c = 0.7$; chloroform); e.e. 75.0%. Using the same workup procedure for the mixture of (+)-**5** and (−)-**5**-*O*,*O*′-dibenzoyl-(*R*,*R*)-tartrates resulted in (+)-**5** (1.01 g, 3.87 mmol), $[\alpha]_D = +10.2$ ($c = 0.7$; chloroform); e.e. 65.0%.

To obtain a higher enantiomeric excess we repeated the resolution above starting from (−)-**5** (1.42 g, 5.43 mmol, e.e. 75%) and *O*,*O*′-dibenzoyl-(*R*,*R*)-tartaric acid monohydrate (1.64 g, 4.35 mmol) to afford (−)-**5**-*O*,*O*′-dibenzoyl-(*R*,*R*)-tartrate (2.75 g, 82%) and, after workup, (−)-**5b** (1.01 g, 3.87 mmol), $[\alpha]_D = -13.9$ ($c = 0.7$; chloroform); e.e. 89%. The filtrate of this repeated resolution was concentrated in vacuo, the residue was treated with diethyl ether (20 mL) and saturated aqueous sodium hydrogen carbonate (25 mL), then the organic phase was separated, dried and concentrated in vacuo to yield a mixture of (−)-**5** and (+)-**5** (0.35 g, 1.34 mmol), $[\alpha]_D = -6.4$ ($c = 0.7$; chloroform); e.e. 41%.

3.3. LDA-KO*t*Bu-induced rearrangement (general procedure)

A solution of potassium *tert*-butoxide (0.37 g, 3.28 mmol) in tetrahydrofuran (5 mL) was cooled to −78°C then diisopropylamine (0.33 g, 3.28 mmol) and a 15% solution of butyllithium in hexane (4.92 mmol) were added and the mixture was stirred for 30 min. After addition of (+)-**4** or (−)-**5** (1.64 mmol) the reaction mixture was stirred for 3 h at −78°C then diluted with diethyl ether (15 mL) and treated with distilled water (20 mL). The aqueous phase was extracted with diethyl ether (4×15 mL) then the organic phase was washed with distilled water (4×15 mL) and brine (2×15 mL) and dried. After removal of the solvent, the oxetane **6** or **7** was obtained. The crude products were purified by column chromatography on Florisil, eluent hexane/ethyl acetate 2/1.

3.3.1. (3*S)-[2-Diethylamino-(1*S**)-hydroxyethyl]-(2*S**)-phenyloxetane 6**[8]. Oil, 75% (from (+)-**4**, e.e. 99%). ^{1}H NMR ($CDCl_3$, 22°C): δ 1.02 (6H, t, $J = 7.0$, $C\underline{H}_3$); 2.18 (1H, dd, $J = 12.6$, 10.5, H_y-6); 2.32 (1H, dd, $J = 12.6$, 3.3, H_x-6); 2.44–2.51 (2H, m, -N-$C\underline{H}_2$-); 2.61–2.68 (2H, m, -N-$C\underline{H}_2$-); 2.82 (1H, dddd, $J = 8.5$, 7.1, 7.1, H-3); 3.90 (1H, s, broad, -OH); 4.00 (1H, ddt, $J = 10.5$, 7.1, 3.3, H-5); 4.63 (1H, dd, $J = 7.1$, 6.1, H_y-4); 4.68 (1H, dd, $J = 8.5$, 6.1, H_x-4); 5.79 (1H, d, $J = 6.2$, H-2); 7.26–7.31 (1H, m, Ph); 7.36–7.41 (2H, m, Ph); 7.46–7.50 (2H, m, Ph). $[\alpha]_D = +8.1°$ ($c = 0.9$; chloroform); e.e. 98.3%.

3.3.2. (3*S)-[(1*S**)-Hydroxy 2-piperidinoethyl]-(2*S**)-phenyloxetane 7**[8]. Oil, 69% (from (−)-**5**, e.e. 89.0%). ^{1}H NMR ($CDCl_3$): δ 1.40–1.48 (2H, m, ring -CH_2-); 1.51–1.64 (4H, m, ring -CH_2-); 2.12 (1H, dd, $J = 12.3$, 10.4, H_y-6); 2.19 (1H, dd, $J = 12.3$, 3.4, H_x-6); 2.22–2.34 (2H, m, broad, ring -N-$C\underline{H}_2$-); 2.55–2.65 (2H, m, broad, ring -N-CH_2-); 2.81 (1H, dddd, $J = 8.6$, 7.1, 7.1, 6.3, H-3); 3.50 (1H, s, broad, -OH); 4.06 (1H, ddt, $J = 10.4$, 7.1, 3.4, H-5); 4.61 (1H, dd, $J = 7.1$, 6.1, H_y-4); 4.67 (1H, dd, $J = 8.6$, 6.1, H_x-4); 5.78 (1H, d, $J = 6.3$, H-2); 7.25–7.30 (1H, m, Ph); 7.36–7.40 (2H, m, Ph); 7.45–7.49 (2H, m, Ph). $[\alpha]_D = +5.0°$ ($c = 1.0$; chloroform); e.e. 89.2%.

3.4. *n*-Butyllithium-induced rearrangement (general procedure)

A solution of **6** or **7** (0.56 mmol) in tetrahydrofuran (3 mL) was cooled to 0°C and a 15% solution of butyllithium in hexane (2.24 mmol) was added. The mixture was allowed to warm up to 25°C and stirred for 3 h at this temperature. After being diluted with diethyl ether (20 mL) the mixture was treated with distilled water (20 mL). The aqueous phase was extracted with diethyl ether (3×25 mL) then the organic phase was washed with brine (3×15 mL) and dried. After removal of the solvent the residue was purified by column chromatography on Florisil, eluent hexane/ethyl acetate 2/1.

3.4.1. (*Z*)-5-Diethylamino-2-phenyl-2-penten-1,4-diol 8[8]. Oil, 39% (from (+)-**6**, e.e. 98.3%). ^{1}H NMR ($CDCl_3$): δ 1.04 t (6H, t, $J = 7.1$ Hz, -CH_3); 2.52 dd (1H, dd, $J = 13.1$, 7.6) and 2.59 (1H, dd, $J = 13.1$, 6.5) (N-$\underline{CH}_2$-CHOH); 2.60 (4H, q, $J = 7.1$, N-$\underline{CH}_2$-CH_3); 4.37 (1H, d, $J = 12.3$) and 4.47 (1H, dd, $J = 12.3$, 0.7) (-$\underline{CH}_2$-OH); 4.59 (1H, ddt, $J = 7.8$, 7.6, 6.5, -$\underline{CH}$-OH); 5.75 (1H, dd, $J = 7.8$, 0.7); 7.24–7.29 (1H, m, Ph); 7.30–7.35 (2H, m, Ph); 7.45–7.48 (2H, m, Ph). $[\alpha]_D = +5.8$ ($c = 0.5$; chloroform); e.e. 99.9%.

3.4.2. (*Z*)-2 Phenyl-5-piperidino-2-penten-1,4-diol 9[8]. Oil, 39% (from **7**, e.e. 89.2%). ^{1}H NMR ($CDCl_3$): δ 1.38–1.47 (2H, m) and 1.52–1.64 (4H, m) and 2.46–2.56 (4H, m) (piperidine -CH_2-); 2.40 dd (1H, dd, $J = 12.7$, 7.5) and 2.59 (1H, dd, $J = 12.7$, 6.4) (N-$\underline{CH}_2$-CHOH); 4.37 (1H, d, $J = 12.3$) and 4.46 (1H, d, $J = 12.3$) (-$\underline{CH}_2$-OH); 4.65 (1H, ddt, $J = 7.9$, 7.5, 6.4, -$\underline{CH}$-OH); 5.77 (1H, d, $J = 7.9$); 7.24–7.29 (1H, m, Ph); 7.30–7.35 (2H, m, Ph); 7.45–7.48 (2H, m, Ph). $[\alpha]_D = +8.3°$ ($c = 1.0$; chloroform); e.e. 89.2%.

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