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2-Vinyl-*trans*-octahydro-1,3-benzoxazine: Cyclization and 1,3-Dipolar Cycloaddition of Nitrile Oxides

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Abstract: A study of the stereochemistry of the acid-catalyzed cyclization between (-)-8-tosylaminomenthol (derived from (+)-pulegone) and acrolein diethyl acetal afforded two novel chiral perhydro-1,3-benzoxazine isomers **4a** and **4b**. Catalyst type as well as the reaction conditions dramatically affected the isomeric ratio. An X-ray crystal structure of **4a** established a chair-boat conformation. The usefulness of this auxiliary was demonstrated by highly diastereoselective (i.e. 90% *de*) 1,3-dipolar cycloadditions with nitrile oxides.

Keywords: Asymmetric induction, benzoxazines, cycloadditions, isoxazolines.

As part of a research program aimed at the asymmetric synthesis of 2-isoxazolines for their application in the total synthesis of natural products, we envisaged the use of 2-vinyloxazines to control both the regio- and stereoselectivity of the 1,3-cycloaddition reaction involving nitrile oxides. We have previously described the use of 2-vinyl-N-benzyl-4,4,7α-trimethyl-*trans*-octahydro-1,3-benzoxazine in the 1,3-dipolar cycloaddition of acetonitrile oxide which resulted in a process up to 90% *de*.[1] Then we wished to study structural modifications of **1** to investigate if higher stereoselectivity could be induced. To this end, we prepared the N-tosyl derivative **3**, since the same derivative was found to give a significant levels of asymmetric induction in the (±)-norephedrine model. Futhermore, these heterocycles can easily be obtained and feature the necessary water and silica gel stability.[1,2] These experiments also led to the discovery of new isomeric dipolarophiles issued from the same auxiliary.

(-)-8-Tosylaminomenthol, **3**, was prepared as shown in scheme **1**. Debenzylation of compound **1** under reductive conditions gave the amino alcohol **2**.[3] Unfortunately, attempts to selectively tosylate the amine function using the Scotten-Baumann conditions[4] or with tosyl chloride and Et_3N, gave substantial amounts of the *O*-tosyl by-product. Therefore we chose to protect the alcohol function as a TBDMS ether, and followed this with a N-tosylation. Upon treatment with fluoride ion (TBAF•H_2O) we obtained the chiral auxiliary **3** in 75% overall yield.

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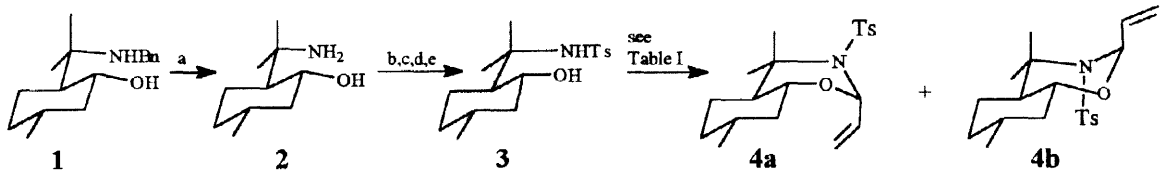


Scheme 1 Conditions: a) HCO_2NH_4, Pd/C, MeOH, H_2O; b) *n*-BuLi, Et_2O, -78°C; c) TBDMSCl, Et_2O, -78°C→rt; d) TsCl, Et_3N, CH_2Cl_2, Δ, 12 hrs; e) TBAF•$3H_2O$, THF, rt.

Condensation of **3** with acrolein diethyl acetal in the presence of a Lewis acid afforded two isomers: **4a** and **4b**.[5] The absolute configuration at the nitrogen and C-2 stereocenters of **4a** and **4b** was determined by nOe difference measurements (***Figure 1***). Irradiation of the axial proton at C-9 of **4a** gave rise to positives nOe's for the signals attributed to the axial Me-4_{ax}, H-7, H-8_{eq}, H-2_{weak}, and the *ortho* protons of the tosyl group. The last two results support a *cis*, but distant, relationship between H-9 and H-2, as well as a spatial proximity between H-9 and the tosyl group. Surprisingly, irradiation of the olefinic proton H-1' enhanced the signals assigned to H-10, H-2 and H-$8_{ax,\ weak}$. Thus, these results support a boat conformation for the oxazine ring. Keeping in mind the striking structural differences observed for the N-benzyl derivative,[1] the absolute configuration of **4a** was confirmed by X-ray diffraction analysis (***Figure 1***).[5] The conformation of **4a** in solution correlates well with the X-ray structure except for the C-2 vinyl group, which projects for the most part towards the N-tosyl appendage.

In the case of isomer **4b**, irradiation of the axial proton at C-9 gave rise to an nOe for the two signals attributed to olefinic protons H-1' and H-2' and none was observed for the signal corresponding to H-2. Positive nOe's were observed for the olefinic H-1' and the *ortho* protons of the tosyl group upon irradiation at H-2. These results support a chair-chair conformation for **4b** in which the C-2 vinyl group is *cis* to H-9 and the N-tosyl group is *cis* to H-2.

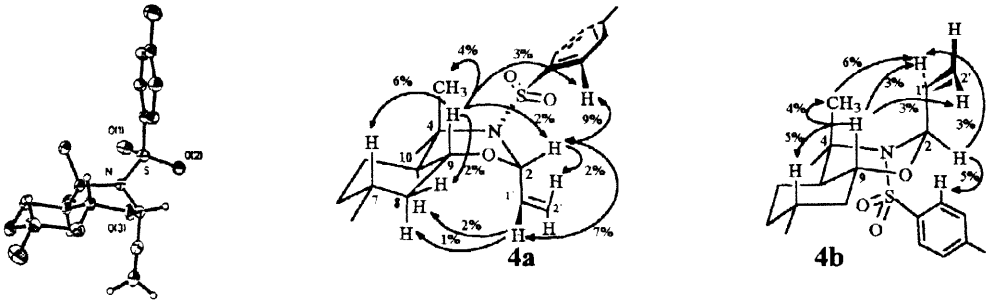


Figure 1 Left: X-ray crystal structure of **4a**. Right: Relevant nOe enhancement in **4a** and **4b**.

Several Lewis acids were investigated and the reaction conditions were varied in order to control the formation of **4a** or **4b**, and the results[6] are summarized in Table 1. Of the various acids investigated (entry 1-4), the weak Lewis acid $MgBr_2$•Et_2O was found to be incapable of catalyzing the reaction, while a too strong acid such as $AlCl_3$ resulted in a poor chemical yield. A good conversion yield was observed when the reaction was catalyzed by PPTS, BF_3•Et_2O and BBr_3 (entry 2,6,9). Isomer **4a** could be obtained with better 95% selectivity (entry 5-8) using

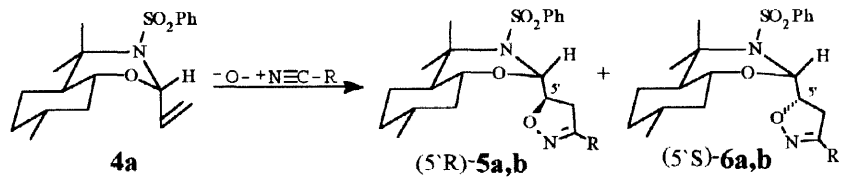
Table 1 The stereoselectivity of the cyclization of 3 to isomers 4a and 4b.[a]

Entry	Acrolein diethyl acetal (Eq.)	Catalyst	Solvent	T (°C)	Time hrs	4a[b] (%)	4b[b] (%)	Yield (%)[c]
1	1.5	$MgBr_2 \bullet Et_2O$	Et_2O	20	4	0	0	0
2	1	PPTS	Bz	80	5	64	36	83
3	1.5	$AlCl_3$	Et_2O	20	4	80	20	14
4	2	BF_3	Et_2O	20	4	80	20	66
5	5	BF_3	Et_2O	20	4	95	5	71
6	10	BF_3	Et_2O	20	4	95	5	80
7	5	BF_3	Et_2O	-15	4	98	2	60
8	5	BF_3	Et_2O	0	4	98	2	69
9	5	BBr_3	CH_2Cl_2	20	4	11	89	81

a) The acid was added to a solution of **3** and acrolein diethyl acetal at -30°C and then the mixture was allowed to reach the indicated temperature; b) Product ratio were determined by ^1H NMR analysis of the reaction mixture[6]; c) Isolated yields.

$BF_3 \bullet Et_2O$ with 5 to 10 equivalents of acrolein diethyl acetal starting at -30°C and rising to room temperature.[7] Futhermore, isomer **4a** readily crystallized from pentane in pure form. On the other hand, isomer **4b** was obtained in good yield but with lower selectivity using a milder Lewis acid, BBr_3 (entry 9). This isomer was found to be unstable in the presence of $BF_3 \bullet Et_2O$, and attempts to induce isomerization of **4b** in the absence of acrolein diethyl acetal yielded **3** only.

The reaction between isomer **4a** and an excess (i.e., 10eq) of acetonitrile oxide or benzonitrile oxide, generated from their corresponding oxime[8] resulted, in each case, in a mixture of two diastereomers, **5** and **6**.[5,9] This cycloaddition was found to be stereoselective (i.e., up to 90% *de* in favor of **5**)[10] and efficient (**Scheme 2,** Table 2). The stereochemistry for the epimeric 2-isoxazolines products, **5** and **6**, is supported by nOe`s.[11] Due to increased steric constraints imposed by the 2-isoxazoline ring, the preferred conformation of the cycloadducts is close to a half-chair in which the C-2 center is nearly coplanar with the N,O heteroatoms. Taking into account that the reactive conformer of the dipolarophile **4a** is that observed in solution, the absolute configuration ***R*** at the C-5` center of the major isomer, **5**, can be explained by a cycloaddition on the exposed *Re* face of the alkene function. The cycloaddition of benzonitrile oxide led to a slightly higher level of asymmetric induction.



4a (5`R)-**5a,b** (5`S)-**6a,b**

Scheme 2

Table 2 Diastereoselectivity in 1,3-dipolar cycloaddition of nitrile oxides with isomer **4a**.

Entry	R	Yield %[a]	% *de*[b] (conf)[c]
1	**a**: CH_3	75	86 (5'R)
2	**b**: Ph	70	90 (5'R)

a) Isolated yields; b) Determined by ^1H NMR and ^{13}C NMR; c) Determined by nOe experiments.

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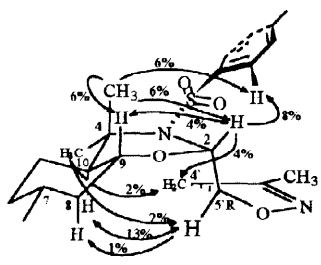
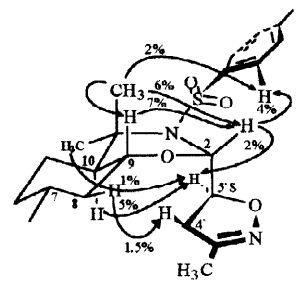
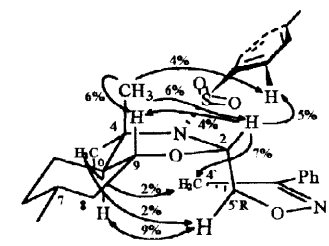
3. Eliel E.L.; He X.C. *J. Org. Chem.* **1990**, *55*, 2114-2119.
4. Belvisi L.; Gennari C.; Poli G.; Scolastico C.; Salom B.; Vassallo M. *Tetrahedron* **1992**, *48*, 19, 3945-3960.
5. All new compounds gave the correct mass spectra and suitable spectroscopic data (IR, NMR, MS). The crystallographic structure for **4a** will be published in *Acta Crystallographica*.
6. The isomeric ratios were determined by the integration of the signals arising from protons H-9 and H-2. The signals are as follows ($CDCl_3$): **4a**: 3.53 (dt, *J*=11.0 and 4.4 Hz, H-9), 5.95 (dd, *J*=2.2 and 1.1 Hz, H-2), **4b**: 3.81 (dt, *J*=10.5 and 4.4Hz, H-9), 6.36 (dd, *J*=2.4 and 1.2Hz, H-2).
7. General procedure for **4a**: To a solution of dimethyl acetal (1.5-10eq see Table 1) and the N-tosyl amino alcohol **3** (160 mg, 0.5 mmole) in 15 mL of dry diethyl ether was added $BF_3 \bullet Et_2O$ (22 mg, 0.15 mmole) at -30°C and then the reaction was allowed to rise to room temperature. The reaction mixture was stirred at room temperature for the specified time (see Table 1). The reaction mixture was quenched with a 5% aqueous $NaHCO_3$ solution (10 mL), extracted into CH_2Cl_2 (2 X 10 mL), dried over $MgSO_4$, then filtered and the solvent evaporated under reduced pressure. Purification by circular chromatography using Hex-CH_2Cl_2-EtOAc; 8:1:1 gave a mixture of **4a** and **4b**. Crystallization from pentane afforded pure **4a**.
8. Mukerji, S.K.; Sharma, K.K.; Torsell, K.B.G. *Tetrahedron* **1983**, *39*, 2231-2235.
9. Spectroscopic data for **5a**; ^{1}H-NMR (300 MHz, $CDCl_3$): 0.76 (m, 1H, H-2), 0.84 (d, J=6.3 Hz, 3H, CH_3-7), 0.87 (m, 1H, H-5_{ax}), 1.02 (q, J=11.8 Hz, 1H, H-8_{ax}), 1.11 (s, 3H, Me-4_{ax}), 1.31 (m, 1H, H-7), 1.43 (s, 3H, Me-4_{eq}), 1.49 (m, 1H, H-5_{eq}), 1.54 (m, 1H, H-6_{eq}), 1.66 (td, J=11.1 and 3.0 Hz, 1H, H-10), 1.94 (s, 3H, Me-3'), 2.05 (m, 1H, H-8_{eq}), 2.35 (s, 3H, CH_3-Ar), 3.03 (dd, J=17.6 and 10.4 Hz, 1H, H-4'), 3.21 (dd, J=17.6 and 6.5 Hz, 1H, H-4'), 3.42 (td, J=11.1 and 4.3 Hz, 1H, H-9), 5.01 (ddd, J=10.4, 8.0 and 6.5 Hz, 1H, H-5'), 5.28 (d, J=8.0 Hz, 1H, H-2), 7.21 (d, J=8.5 Hz, 2H, H-*m*-Ar), 7.72 (d, J=8.5 Hz, 2H, H-*o*-Ar).
10. The *d.e.*'s were determined by integration of the ddd signal corresponding to H-5' for **5a** (δ 5.01) and **6a** (δ 5.20) in the ^{1}H-NMR spectrum of the crude product mixture and the C-4' signals of isomers **5a** (δ41.34) and **6a** (δ41.64) in the ^{13}C spectrum of the crude mixture. For isomers **5b** and **6b**, the ratio was determined by the integration of the signal assigned to C-10; **5b** (δ47.19) and **6b** (δ48.21).
11. The stereochemistry of the isoxazolines products is based on the nOe results shown below. In all products, irradiation of the signal attributed to H-9 enhanced the signals assigned to H-2, H-*o*-Ts, CH_3-4_{ax} and H-7. Irradiation of H-2 cause an enhancement of the signals corresponding to CH_3-4_{ax}, H-9 and H-*o*-Ts. Interestingly, the intensity of the nOe between H-2 and H-9 is twice that observed for the chair-boat structure **4a** and is half of that observed for the chair-chair structure of N-benzyl derivative of **4a**.[1] A strong nOe was also observed between the H-5' and H-10. These results support a chair-half chair conformation for the octahydrobenzoxazine moiety. The absence of an nOe between protons H-2 and H-5' for isomer **5a** and a



5a



6a



5b

coupling constant of 8Hz supports an anti spatial arrangement between these two protons. Since an nOe enhancement of the protons corresponding to C-4' was observed upon irradiation of the Me-4_{eq}, the methylene C-4' points towards the Me-4_{eq} which gives an R absolute configuration at the C5' center. The 5'(S)-isomer **6a** is characterized by an nOe between the protons H-2 and H-5' and a coupling constant of 4.6 Hz, which supports a gauche relationship between these two protons. Since an nOe enhancement was observed between the proton H-4'$_\alpha$ and H-8_{eq} and none was observed with the signal attributed to the Me-4_{eq} protons; the methylene C-4' is oriented towards C-8. The results of the nOe experiments for **5b** and **6b** are very similar to those observed for **5a** and **6a** (*e.g.* compare **5a** and **5b** above).