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

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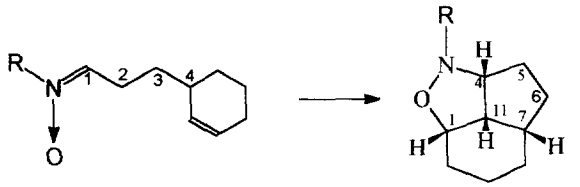
Abstract: 3-Oxanitrones **10** and 3-azanitrones **11** were prepared starting from (*S*)-ethyl lactate **5** and (*S*)-N-benzyl alaninol **8**, respectively. Both nitrones underwent spontaneously an intramolecular cycloaddition affording the tricyclic compounds **12** and **13**. The diastereomeric forms of **12** and of **13** were separated by column chromatography and identified by NMR spectroscopy.

The intramolecular 1,3-dipolar cycloaddition of δ-unsaturated nitrones makes 3-oxa-2-azabicyclo[3.3.0]octanes easily accessible.[1] Tricyclic compounds are formed by an analogous reaction if either the nitrone group or the unsaturated moiety or the tether between these two functional groups is part of a ring system. Thus, LeBel prepared 2-oxa-3-azatricyclo[5.3.1.$0^{4,10}$]undecane **2** (R = CH_3) by intramolecular cycloaddition of nitrone **1** in 1965.[2]

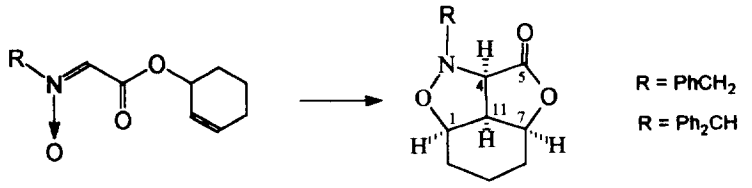


1 **2**

Roush et al. obtained a corresponding tricyclic compound **2** (R = Bzl)substituted by a methyl and a butyl group at positions 9 and 10, respectively, in the synthesis of (-)-ptilocauline. As they found, the reaction proceeds with high asymmetric induction by the stereogenic center at position 4 of the nitrone giving an enantiomerically pure product in which the four protons at the bridgehead C-atoms are cis-orientated.[3] Analogous nitrones with a cross-conjugated cyclohexadiene moiety afforded again an enantiomerically pure tricyclic compound as **2** with an additional double bond.[4]

Similar intramolecular cycloadditions were also performed with corresponding nitrile oxides giving tricyclic compounds with the same core including a C=N double bond function.[5] Hassner et al. prepared the first compound of this type containing an additional O-atom in 6-position.[6]

Only recently, it was found that nitrones **3** formed in situ by a transesterification reaction give racemic tricyclic lactones **4** as single diastereomers.[7]



3 4

Our goal was the preparation of non-racemic 2.6-dioxa-3-azatricyclo[5.3.1.$0^{4,10}$]undecanes **12** and 2-oxa-3.6-diazatricyclo[5.3.1.$0^{4,10}$]undecanes **13**.[8] Thus the ester **7** was prepared as diastereomeric mixture by reaction of (*S*)-ethyl lactate with racemic 1-bromo-2-cyclohexene in the presence of silver(I)-oxide. Reduction of **7** with DIBAL-H afforded the corresponding aldehyde which was treated with N-methylhydroxylamine to give nitrone **10**. Compound **10** underwent spontaneously an intramolecular cycloaddition yielding a mixture of the two diastereomers **12A** and **12B**. These could be separated by column chromatography. Reaction of aminoalcohol **8** with racemic 1-bromo-2-cyclohexene afforded compound **9**, which was subjected to Swern oxidation. Without isolation the aldehyde was treated with methylhydroxylamine to give nitrone **11**. This underwent an intramolecular cycloaddition yielding a mixture of three diastereomers **13A, B** and **C**. The diastereomers could be separated by chromatography.[9]

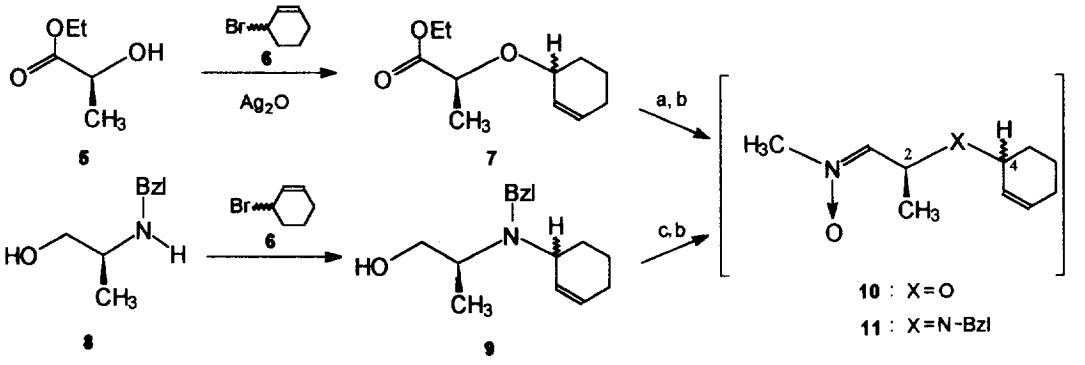
The tricyclic compounds **12** and **13** were shown to be optically active (**12A**: $[\alpha]_D^{22}$ = -23.2°; **12B**: $[\alpha]_D^{22}$ = +54.5°; **13A**: $[\alpha]_D^{22}$ = +61.9°; **13B**: $[\alpha]_D^{22}$ = +56.9°; **13C**: $[\alpha]_D^{22}$ = 85.6°, in ethanol). Since the formation of the corresponding bicyclic products under the same reaction conditions proceeded without racemization,[9] it can be assumed that this is also true for the formation of compounds **12** and **13**. Thus, these compounds should be enantiomerically pure. There are two stereogenic centers at C-2 and C-4 in the nitrones **10** and **11** formed as intermediates. Whereas in both diastereomers **A** and **B** the configuration at C-2 is equal they differ by their configuration at C-4. Certainly, the configuration at C-4 determines the side from which the cyclohexene ring is attacked by the nitrone group. Thus, the cis-relationship of protons 1-H, 11-H, 7-H and 4-H in the cycloadducts **12A/13A** and **12B/13B** results from an exo-approach of the Z-nitrone group.

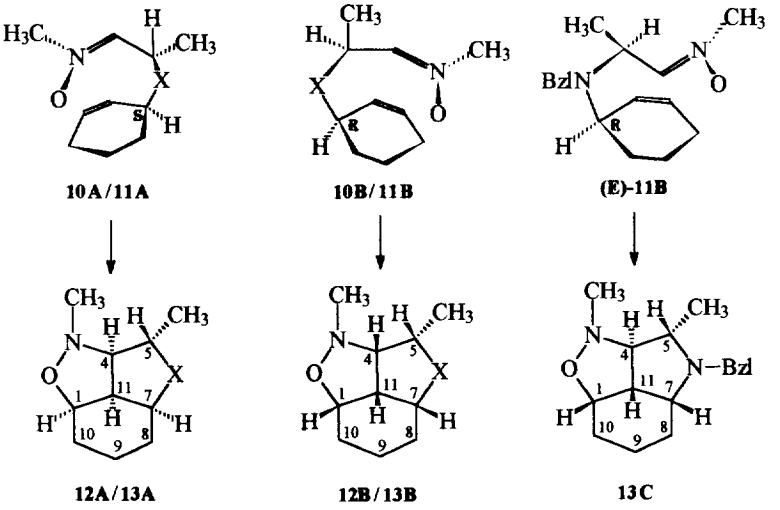
The cis-relationship of 4-H and 5-H in compounds **12B/13B** is unusual, since in the cycloadducts of nitrones with only one stereogenic center adjacent to the nitrone carbon atom the relative configuration at the comparable positions is opposite.[10] However, in the case of diastereomers **B** the *cis*-relationship of 4-H and 5-H is caused by the dominating effect of the stereogenic center of the cyclohexene ring.

As models reveal an endo-approach of the nitrone group would be severely strained. Consequently, the trans-annulation of the two five-membered rings in **13C** must be assumed to result from the attack of an E-nitrone group. The structural assignment of the tricyclic compounds **12** and **13** is based on the NMR spectra (^{1}H NMR data see Table 1). It is further confirmed by an X-ray analysis of **13A**.[11]

The ^{1}H NMR spectra of diastereomers **A** and **B** differ in particular by the coupling constants ^{3}J 4-H/5-H and the chemical shifts of the protons 5-H, 7-H and the methyl groups at C-5 according to different conformations. Thus, the coupling constants J 4/5 <1 Hz of **12A** and **13A** certainly indicate the trans-configuration of 4-H and

5-H. In **12A** and **13A** the proton 5-H occupies a quasi-equatorial position according to the down-field shift of its





signal compared to the signal of the quasi-axial position of 5-H in **12B** and **13B**. For the methyl group at C-5 the situation is opposite.

The most striking data of **13C** are the high coupling constant J 4/11 = 11.7 Hz and the signal of C-11 at lower field (55.9 ppm) compared to **13A** and **B** (46.8 and 46.6 ppm, resp.). The trans-annulation of the two five-membered rings in **13C** is confirmed by a NOESY spectrum which shows cross-peaks for the protons 4/CH_3, 1/11 and 7/11 but not for the protons 4/11.[12]

Table 1. Characteristic ^1H NMR data of compounds **12** and **13** (in $CDCl_3$, δ in ppm, J in Hz)

δ	12A	12B	13A	13B	13C
1-H	4.33	4.31	4.41	4.30	4.08
4-H	3.40	3.44	3.13	3.16	3.07
5-H	4.26	3.73	3.35	2.40	2.95
7-H	4.15	3.77	2.94	2.43	2.88
11-H	2.99	2.91	3.02	2.75	3.21
CH_3(5)	1.18	1.35	0.86	1.12	1.26
$^3J_{H-H}$					
1/11	7.1	6.5	~7	6.2	7.9
4/5	<1	5.4	<1	8.0	8.9
4/11	7.1	7.6	7.9	7.6	11.7
7/11	7.1	6.3	~7	7.7	8.0

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11. The results of the X-ray analysis performed by Dr. K. Harms will be published later.
12. To the best of our knowledge only one example of two trans-fused five-membered rings containing an isoxazolidine moiety comparable to **13C** has been described: Armstrong, P; Grigg, R.; Heaney, F.; Surendrakumar, S.; Warnock, W.J. *Tetrahedron* **1991**, *47*, 4495-4518.

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