FIRST ASYMMETRIC DIELS-ALDER REACTIONS IN THE VINYLHETARENE SERIES: CYCLOADDITIONS WITH VINYLINDOLES TO ENANTIOMERICALLY PURE CARBAZOLE DERIVATIVES

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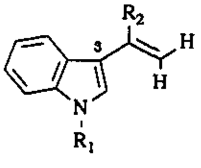
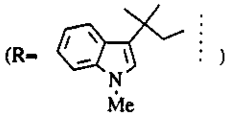
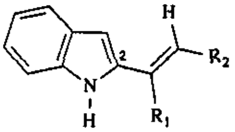
Abstract —— The first asymmetric Diels-Alder reactions of some 3- and 2-vinylindoles with (*N*-propenoyl)bornane-10,2-sultam are described. The experimental results are indicative of high to sufficient π-facial diastereoselectivity.

The strict demands for biologically selective and degradable drugs have prompted much research work directed at the development of stereoselective syntheses. Because of the inherent diastereoselectivity of concerted cycloaddition reactions, the Diels-Alder reaction provides a valuable method for highly stereoselective syntheses of cyclic and polycyclic compounds. A number of such routes for the diastereo-[1] and enantioselective[2] formation of chiral products have been developed and, in the vinylhetarene series, 2- and 3-vinylindoles have been used as versatile diene components in some highly regio- and stereoselective HOMO(diene)-LUMO(dienophile)-controlled [4 + 2] cycloaddition reactions for the construction of (racemic) annellated indoles and alkaloids of pharmacological interest.[3-5] However, there are no reports of asymmetric Diels-Alder reactions of vinylheterocycles for the construction of enantiomerically pure annellated polycyclic systems containing hetarene skeletons. Thus, in continuation of our work on pericyclic 6-electron processes with vinylhetarenes,[6] we now describe the first π-facial diastereoselective [4 + 2] cycloadditions of 3- and 2-vinylindoles with a chiral acrylamide.

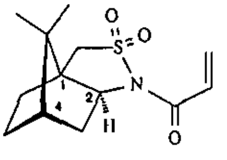


	R1	R2
1	$PhSO_2$	Me
2	Me	Me
3	Me	Ph
4	Me	R





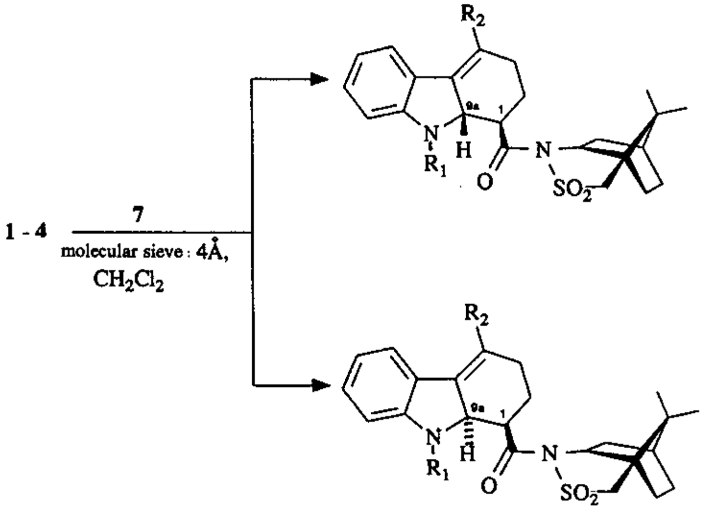
	R1	R2
5	H	Me
6	Me	Me



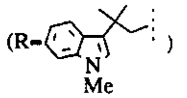
(1R, 2S, 4S)-7
(and enantiomer)

The antipodal, camphor-derived bornane-10,2-sultams have proved to be versatile chiral auxiliaries for asymmetric Diels-Alder reactions and a high π-face stereoselectivity has been reported.[7] This prompted us to test the [4 + 2] cycloaddition reactions of the 3- and 2-vinylindoles (**1-6**) with the 1*R*,2*S*,4*S*-(*N*-propenoyl)bornane-10,2-sultam (**7**) as well as those of its enantiomer. Thus, the 3-vinylindoles (**1-4**) reacted with **7** under molecular sieve catalysis to yield the enantiomerically pure diastereomeric tetrahydrocarbazoles (**8a-d**). Only in the Diels-Alder reaction of **2** with **7** was the additionally formed diastereomer (**9b**) detected as a minor product (Scheme 1). However, the chemical yields were unsatisfactory although the π-face diastereoselectivity in the reactions of **1**, **3**, and **4** had reached a maximum, as shown by hplc and nmr data (Table 1). The relative configurational analyses were performed by 400 MHz ^{1}H-nmr spectrometry including H,H-COSY, nOe, and ^{13}C-APT techniques.[10] The absolute configuration was elucidated by an X-ray crystallographic analysis of the carbazole (**8c**) (Figure 1b).[8] Cd spectral data of compounds (**8a**) and (**8c**) in combination with the X-ray analysis and conformational considerations are in accord with the postulated absolute configurations given here for **8a**, **b**, and **d** (and the enantiomers obtained with the enantiomer of **7**).

Scheme 1



8	R$_1$	R$_2$
a	PhSO$_2$	Me
b	Me	Me
c	Me	Ph
d	Me	R



9	R$_1$	R$_2$
a	PhSO$_2$	Me
b	Me	Me
c	Me	Ph
d	Me	R

Thus, in the [4 + 2] cycloadditions of 3-vinylindoles with **7**, an *exo*-orientation in the transition state should be preferred under the given reaction conditions (Table 1). On the basis of Dreiding models, MMX molecular mechanics calculations,[9] and ^{1}H-nOe measurements, the dienophile should adopt a preferred conformation (Figure 1a) which induces an efficient shielding of the C(α)-*Re*-face. However, in spite of the rigidity of the bulky bornane-sultam unit, the SO$_2$ group, above all, exerts a powerful stereodifferentiation in these reactions.

Table 1. Reactions of **1-4** with the acrylamide (1*R*,2*S*,4*S*)-**7**[a]

Diene	Temp. (°C)	Time	Product	Chemical yield (%)[b]	Ratio of diastereomers (*exo*:*endo*)[c]
1	40	5 d	**8a,9a**[d]	14	>99:1
2	20	3 d	**8b,9b**	11	74:24[e]
3	20	18 h	**8c,9c**[d]	27	>99:1
4	20	3 d	**8d,9d**[d]	2	>99:1

[a] Solvent CH_2Cl_2 in the presence of 4Å molecular sieves.

[b] Total yield of products isolated by flash chromatography. The crude yields (by tlc) were significantly larger but substantial losses occurred during chromatographic work-up.

[c] By hplc and ^{1}H-nmr analyses. According to considerations of Dreiding models, the minor isomer (not detected in the reactions of **1**, **3**, and **4**) should have *endo*-stereochemistry at C1 and C9a of **9**.

[d] Compounds (**9a**, **c**, and **d**) were not detected within the limits of the hplc analysis.

[e] Ratio of *exo*:*endo* or *endo*:*exo* stereochemistry.

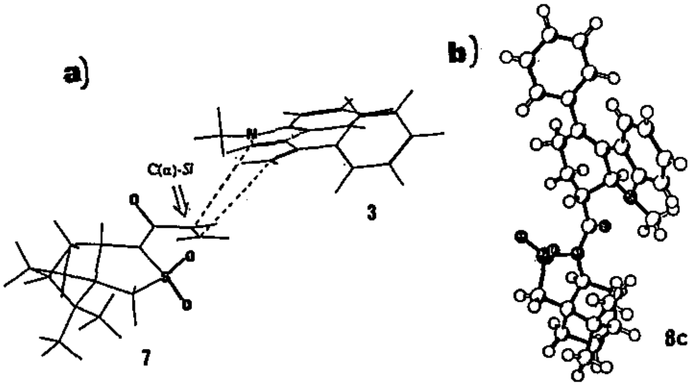


Figure 1. (a) Orientation of MMX-minimized ground state conformations of **7** and **3** for the creation of the transition state to give **8c**. (b) X-ray crystal structure of **8c** (SCHAKAL plot)[8]

In the case of the reactions with 3-vinylindoles (**1** and **3**), [4 + 2]-cycloadditions with the 1*S*,2*R*,4*R*-enantiomer of **7** were also investigated. The enantiomers of **8a** and **c** were formed with more than 99% d.e. (by hplc, cd, and nmr; yields: 16%, 27%). The 2-vinylindoles (**5**) and (**6**) were also subjected to Diels-Alder reactions with **7**. However, the formed carbazoles were obtained as inseparable mixtures of diastereomers. Furthermore, the regio- and stereochemistry could not be analysed satisfactorily in the mixture as a result of the overlapping of the diagnostically relevant signals in the nmr spectra.

In summary, the first Diels-Alder reactions of some vinylindoles with a chiral acrylamide have been achieved and the products are characterized by a high to sufficient π-facial diastereoselectivity. Encouraged by these results, further asymmetric Diels-Alder reactions with other chiral carbo- and heterodienophiles are now being studied in our laboratory.

ACKNOWLEDGEMENTS

We thank the Deutsche Forschungsgemeinschaft (Bonn) for financial support of this work (Project Pi 135-7) and we are indebted to the late Prof. G. Snatzke, University of Bochum, for the cd spectra.

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8. Crystal data: $C_{30}H_{34}N_2O_3S$ (502.64), space group $P2_12_12_1$, Z = 4, a = 10.416(1), b = 12.429(1), c = 20.349(1) Å, D_c = 1.267 $g{\cdot}cm^{-3}$, R = 0.034, wR = 0.028 for 3643 observed reflections. The alternative enantiomer could be discounted by the significantly higher residuals for the inverted structure (R = 0.045, wR = 0.041, Friedel pairs measured).
9. MMX molecular mechanics calculations (enhanced MM2 variant): J. J. Gajewski, K. E. Gilbert, and J. McKelevey, *Adv. Mol. Mod.*, 1990, **2**, 65.
10. For example, 400 MHz ^{1}H-nmr spectrum of product **8a** in CD_2Cl_2: δ (ppm) = 0.98 (s, 3H, C7'-CH_3), 1.30 (s, 3H, C7'-CH_3), 1.34-1.48 (m, 2H, C6'-H), 1.81-1.94 (m, 5H, C3-H, C2-H, C5'-H), 2.0 (d, 3H, J = 1 Hz, C4-CH_3), 2.05-2.13 (m, 2H, C3'-H), 2.22 (m, 1H, C3-H), 2.55 (m, 1H, C4'-H), 3.41 (m, 1H, C1-H), 3.43 (d, 1H, ^2J = 13.9 Hz, C10'-H), 3.55 (d, 1H, ^2J = 13.9 Hz, C10'-H), 4.01 (m, 1H, C2'-H), 4.75 (m, 1H, C9a-H), 7.03 (d, pseudo-t, 1H, J = 0.6 Hz, C4-H or C7-H), 7.21 (pseudo-t, 1H, C6-H or C7-H), 7.39-7.45 (m, 3H, C5-H or C8-H, C3"-H, C5"-H), 7.55 (pseudo-t, 1H, C4"-H), 7.78 (d, 2H, ^3J = 7.62 Hz, C2"-H, C6"-H), 7.83 (d, 1H, ^3J = 8.2 Hz, C8-H or C5-H).

Received, 6th November, 1992