SYNTHESIS OF 4,5-DISUBSTITUTED 1*H*-1,3,4,5-TETRAHYDRO-BENZ[*cd*]INDOLE DERIVATIVES

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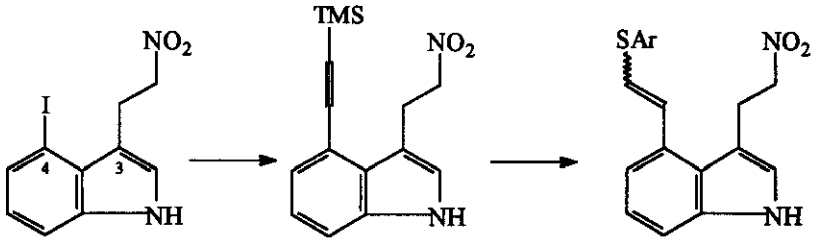
Abstract - 4,5-Disubstituted 1*H*-1,3,4,5-tetrahydrobenz[*cd*]indole derivatives are prepared through intramolecular Michael addition.

Recently we have disclosed two accounts[1] on the preparation of indoles functionalized properly at C-3 and C-4 for further transformations (Scheme 1). Our final goal in this line is the construction of naturally occurring alkaloids, and we present here the preliminary results about the synthesis of tricyclic key intermediates (**6**) to (**9**).[2]

Scheme 1

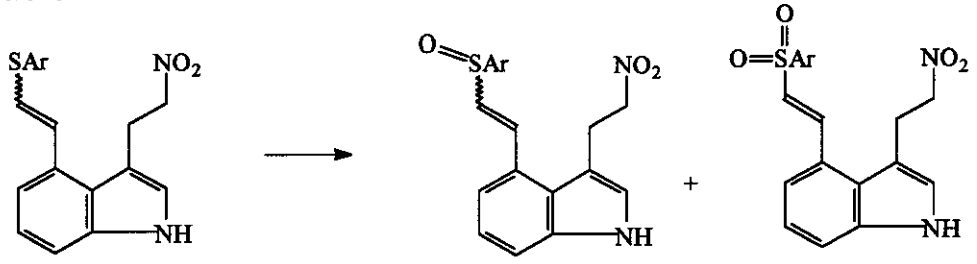


1 **2** **3**

Since we intended to perform a ring closure between the two side chains *via* an intramolecular Michael addition,[3] first we studied the preparation of the corresponding sulfoxides (**4**) in which the electron density of the double bond is properly adjusted to such a reaction (Scheme 2).

Treatment of **3b** (*ca.* 4:1 mixture of *E* and *Z* isomers[1b]) with sodium metaperiodate [10 mg sulfide/ml mixed solvent of $CHCl_3$/EtOH/H_2O (3:6:1), 4.0 equiv of $NaIO_4$, room temperature] resulted in an easily separable mixture of 2% of sulfone (*E*)-**5b**[2,4] in addition to sulfoxides (*E*)-**4b**[2,4] and (*Z*)-**4b**[2,4] (in 42% and 11% yields, respectively). These results indicate that no isomerization of the double bond occurred during the oxidation.[5] Performing the reaction with *m*-CPBA (30 mg of sulfide/ml of $CHCl_3$, 1.2 equiv of oxidant, 5.0 equiv of $NaHCO_3$, 0°C) afforded 9% of (*E*)-**5b** and 75% combined yield of **4b** isomers in the same ratio as before. Turning our attention to **3a** (*ca.* 5:1 mixture of *E* and *Z* isomers[1b]) we were satisfied to establish that *m*-CPBA

Scheme 2



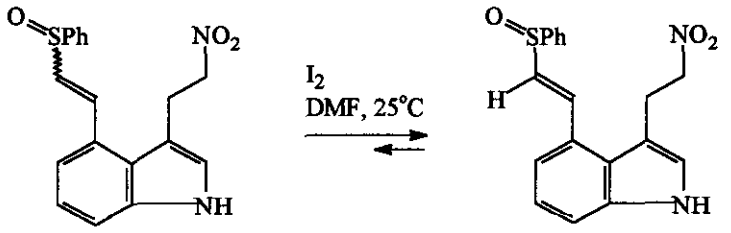
3	Ar	**4**	Ar	**5**	Ar
a	Ph	**a**	Ph	**a**	Ph
b	4-Me-C_6H_4	**b**	4-Me-C_6H_4	**b**	4-Me-C_6H_4

oxidation executed as before gave 4% of sulfone (*E*)-**5a**,[2,4] 74% of (*E*)-, and 17% of (*Z*)-**4a**.[2,4] We were unable to detect (*Z*)-sulfone by-products in the reaction mixtures. It is in good agreement with our findings that there is a slight difference in the oxidation rates of the (*E*)- and (*Z*)-vinyl sulfides in favor of the sterically less hindered (*E*)-one.[6]

During chromatographic purification of the products, however, we could not prepare completely pure sulfoxide isomers: the minor (*Z*)-isomer was inevitably contaminated with the major (*E*)-one, even after repeated chromatography. We attributed this failure of purification to isomerization under the chromatographic conditions, and decided to examine this equilibrating process. Preparatively, iodine catalyzed transformation (~ 60 mg of olefinic isomers/ml of CH_2Cl_2 or DMF, 0.3 equiv of iodine, room temperature) was found to be

superior to the acid promoted one (Scheme 3). This equilibration gave (*E*)-**4a** in good isolated yield and the product contained only trace amounts of the thermodynamically less stable (*Z*)-isomer.

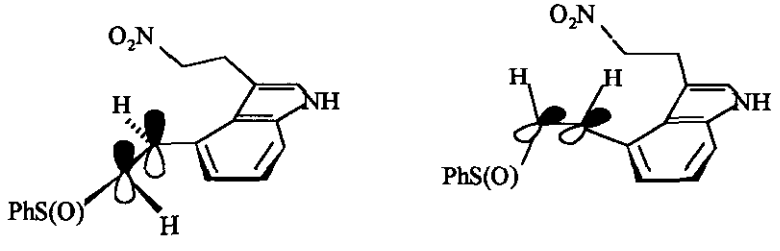
Scheme 3



(*E,Z*)-**4a** (*E*)-**4a**, 89%

This extremely high selectivity in the equilibrating process can be rationalized by taking into account the preferred conformations of the isomers (Scheme 4). While the (*E*) double bond is in the plane of the aromatic ring, thus ensuring maximal overlap of π electrons, the optimal position of the (*Z*) double bond is perpendicular to the ring system. The calculated difference between the heats of formation of the two isomers is more than 25 kcal/mol.[7]

Scheme 4

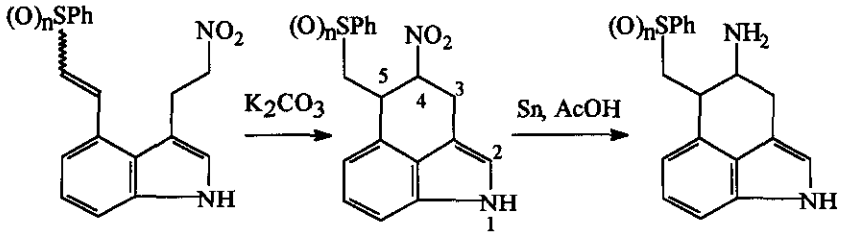


(E)-**4a** *(Z)*-**4a**

In the possession of the necessary information about the behaviour of oxygenated thio enol ethers next we turned our attention to cyclization.[3] In preliminary experiments we found that thiophenol derivative (**4a**) gives slightly more promising results than the corresponding substituted (**4b**), therefore we restricted our experiments to the former compound. Gratifyingly, potassium carbonate initiated ring closure (50 mg of indole/ml of DMF, 0.2 equiv of K_2CO_3, room temperature) gave useful yields of intramolecular Michael addition (Scheme 5).

Other bases examined (dry TBAF, DBU, KF on basic alumina) proved to be inferior to this method. With this procedure both sulfoxide (**4**) and sulfone (**5**) could be transformed to the hardly separable stereo isomeric mixtures of the corresponding tricyclic compounds (**6**)[2,4] and (**7**),[2,4] respectively. Sulfone (**7**) is a *ca.* 7:3 mixture of two isomers,[2,4] the major one is probably the *trans* disubstituted compound. Sulfoxide (**4**) gave all the possible four isomers.[2,4]

Scheme 5



4a (n=1) **6** (n=1), 93% **8** (n=1), 65-70%

5a (n=2) **7** (n=2), 74% **9** (n=2), 60%

Being satisfied with the properly oxidized sulfide substituents we attempted to reduce the nitro functionality without affecting other parts of the molecule. Not unexpectedly, the sulfoxide group exerted a catalyst poisoning effect, so we failed to achieve the desired transformation with palladium or platinum catalyzed hydrogenations. Qualitative testing of alternative methods ($SnCl_2$, $LiAlH_4$, $Na_2S_2O_4$, Zn/AcOH, Zn/aq. HCl, Fe/AcOH, Fe/aq. HCl, Sn/AcOH, Sn/aq. HCl) indicated the Sn/AcOH system to be the most promising one. As depicted in Scheme 5, both amines (**8**) and (**9**) could be produced as a mixture of isomers in preparatively acceptable yields[2,4] simply by vigorous stirring of the nitro compound (15 mg/ml of ethanol) with tin powder (~1.2 mg of tin/mg of nitro compound) in the presence of acetic acid (~150 mg of indole/ml of AcOH). The partial separation of isomers could be achieved at this stage.

In conclusion, we have worked out a procedure for the transformation of iodo compound (**1**)[8] to tricyclic compounds (**6**) and (**8**) in five steps in *ca.* 35% overall yield.

Full paper about the preparative details and stereochemical evaluations will be published in due course.[9]

REFERENCES and NOTES

1. **a.** G. Galambos, Cs. Szántay, Jr., J. Tamás, and Cs. Szántay, *Heterocycles* **1993,** *36*, 2241. **b.** G. Galambos, P. Csókási, Cs. Szántay, Jr., G. Czira, and Cs. Szántay, *Heterocycles*, accepted for publication.
2. All new compounds were characterized by ir, ^{1}H nmr, ^{13}C nmr (Varian VXR-300), EI-ms, and FAB-ms (Kratos MS-902) spectroscopy. Selected physical and spectroscopical data are given below.[4] The following abbreviations are used with the data given[4]: mp: melting point in °C; R_f: tlc in the following eluents: $CHCl_3$: K, MeOH: M; ^{1}H nmr: δ (ppm in $CDCl_3$ solution with TMS internal standard; ms: m/z value of base peak, % abundance of M^+/z in the 70 eV EI mass spectra. Since we could not detect any difference in the fragmentation of isomers, the values are given for one isomer only. In the case of thermally labile compounds FAB mass spectra (in nitrobenzyl alcohol matrix) always gave the expected M^++1 ion, which are not indicated separately.
3. A similar Michael addition of chiral (*E*)-**4b** has been described in the literature: M. Somei, F Yamada, H. Okinishi, Y. Makita, and M. Kuriki, *Heterocycles*, **1987**, *26*, 2823. In that publication (*E*)-**4b** was prepared by direct Heck coupling of **1** with (+)-(R)-*para*-tolylvinylsulfoxide in 45% yield, then cyclisation to the tricyclic ring system was performed in the presence of $NaBH_4$ as a base (isolated yield: 74%).
4. (*E*)-**4a**: mp 121-123°C; R_f: 0.40 (30 K-1 M); ^{1}H nmr: 6.86 [d, J= 15.0 Hz, ArS(O)C<u>H</u>=CH], 7.99 [ArS(O)CH=C<u>H</u>];(*Z*)-**4a:** mp: 186-189°C, R_f: 0 31 (30 K-1 M);^{1}H nmr: 6.92 [d, J= 10.0 Hz, PhS(O)C<u>H</u>=CH], 7.96 [PhS(O)CH=C<u>H</u>]; (*E*)-**4b:** mp. 127-132°C, R_f: 0.34 (20 K-1 M); ^{1}H nmr: 6.88 [d, J= 15.1 Hz, ArS(O)C<u>H</u>=CH], 8.27 [ArS(O)CH=C<u>H</u>]; ms: base peak: 168, % of M^+/z: 8; (*Z*)-**4b:** mp. 195-198°C (decomp.), R_f: 0.26 (20 K-1 M); ^{1}H nmr: 6.65 [d, J= 10.0 Hz, ArS(O)C<u>H</u>=CH], 7.52 [ArS(O)CH=C<u>H</u>]; **5a**: oil; R_f: 0.50 (30 K-1 M); ^{1}H nmr: 6.89 [d, J= 15.0 Hz, $ArS(O)_2C\underline{H}$=CH], 8 29 [$ArS(O)_2CH$=C<u>H</u>]; ms· base peak: 167, M^+/z: 15; **5b**: mp: 162-165°C, R_f: 0.46 (20 K-1 M); ^{1}H nmr: 6.88 [d, J= 15.1 Hz, $ArS(O)_2C\underline{H}$=CH], 8.27 [$ArS(O)_2CH$=C<u>H</u>]; **6:** oil; R_f: 0.45 (20 K-1 M); ^{1}H nmr (major component): 3.08 [dd, J_1= 4.4 Hz, J_2= 14.3 Hz, S(O)C<u>H</u>H], 3.17 [dd, J_1= 8.9 Hz, J_2= 14.3 Hz, S(O)CH<u>H</u>], 4.35 [ddd, J_1= J_2= 4.4 Hz, J_3= 8.9 Hz, $S(O)CH_2C\underline{H}$], 5.70 (ddd, J_1= 4.8 Hz, J_2= 4.3 Hz, J_3= 4 4 Hz, C<u>H</u>NO_2), 3.45 (ddd, J_1= 1.3 Hz, J_2= 5.3 Hz, J_3= 16.7 Hz, $NO_2CHC\underline{H}H$), 3.82 (dd, J_1= 4.8 Hz, J_2= 16.7 Hz $NO_2CHCH\underline{H}$); **7:** mp: 166-169°C; R_f: 0.32 (30 K-1 M); ^{1}H nmr (major component): 3.32 [dd, J_1= 10.1 Hz, J_2= 14.0 Hz, $S(O)_2C\underline{H}H$], 3.42 [dd, J_1= 3.4 Hz, J_2= 14.0 Hz, $S(O)_2CH\underline{H}$], 4.56 [ddd, J_1= J_2= 3.4 Hz, J_3= 10.1 Hz, $S(O)_2CH_2C\underline{H}$], 5.66 (ddd, J_1= J_2= 3.2 Hz, J_3= 3.4 Hz, C<u>H</u>NO_2), 3.42 (ddd, J_1= 1.3 Hz, J_2= 3.2 Hz, J_3= 14.0 Hz, $NO_2CHC\underline{H}H$), 3.97 (dd, J_1= 3.2 Hz, J_2= 17.3 Hz, $NO_2CHCH\underline{H}$); **8** (major component):

mp: 100-104°C; R_f: 0.12 (5 K-1 M); ^{1}H nmr: 2.98 [dd, J_1= 9.2 Hz, J_2= 13.7 Hz, S(O)CH<u>H</u>], 3.14 [dd, J_1= 4.5 Hz, J_2= 13.7 Hz, S(O)CH<u>H</u>], 3.46 [ddd, J_1= 4 Hz, J_2= 4.5 Hz, J_3= 9.2 Hz, S(O)CH_2C<u>H</u>], 3.89, (brddd, J_1= 4 Hz, J_2= 4.1 Hz, J_3= 3.9 Hz, C<u>H</u>NH_2), 3.13 (ddd, J_1= 1.3 Hz, J_2= 3.9 Hz, J_3= 15.9 Hz, NH_2CHC<u>H</u>H), 2.93 (dd, J_1= 4.1 Hz, J_2= 15.9 Hz, NH_2CHCH<u>H</u>); **9** (major component): mp: 61-66°C; R_f: 0.15 (10 K-1 M); ^{1}H nmr: 3.30 [dd, J_1= 7.6 Hz, J_2= 14.4 Hz, S(O)$_2$C<u>H</u>H], 3.40 [dd, J_1= 4.7 Hz, J_2= 14.4 Hz, S(O)$_2$CH<u>H</u>], 3.56 [ddd, J_1= 3.8 Hz, J_2= 4.7 Hz, J_3= 7.6 Hz, S(O)$_2$$CH_2$C<u>H</u>], 3.82 (brddd, J_1= 3.8 Hz, J_2= 3.7 Hz, J_3= 3.9 Hz, C<u>H</u>NH_2), 3.11 (ddd, J_1= 1.6 Hz, J_2= 3.9 Hz, J_3= 16.1 Hz, NO_2CHC<u>H</u>H), 2.86 (dd, J_1= 3.7 Hz, J_2= 16.1 Hz, NH_2CHCH<u>H</u>); ms: base peak: 185, M^+/z: 9.

5. In every oxidation reaction the *E/Z* isomer ratio of **3** determined by nmr was in good agreement with the ratios of the isolated sulfoxide isomers (**4**).
6. In one experiment the oxidation of **3b** (5 mg/ml in the mixed solvent given in the text, 5 equiv of $NaIO_4$, room temperature) was followed by hplc [Hypersil ODS, MeOH/H_2O (3:1)]. The ratios of the isomers of unreacted **3b** changed according to the table below:

Conversion(%)	**E/Z(in unreacted 3b)**
0	1.9
17	1.6
30	1.5
90	0.5

7. Approximative calculations were carried out using the MM+ facility of HyperChem.
8. **a.** S. Hamabuchi, H. Hamada, A. Hironaka, and M. Somei, *Heterocycles*, **1991,** *32*, 443. **b.** M. Somei, F. Yamada, H. Yamada, and T. Kawasaki, *Heterocycles*, **1989,** *29*, 643. **c.** M Somei, F. Yamada, M. Kunimoto, and C. Kaneko, *Heterocycles*, **1984,** *22*, 797. **d.** F. Nakagawa, and M. Somei, *Heterocycles*, **1991,** *32*, 873. **e.** M. Somei, and F. Yamada, *Chem. Pharm. Bull.* **1984,** *32*, 5064. **f.** M. Somei, F. Yamada, and Y. Makita, *Heterocycles*, **1987,***26*, 895. **g.** M. Somei, F. Yamada, and K. Naka, *Chem. Pharm. Bull.*, **1987**, *35*, 1322. **h.** R. A. Hollins, L. A. Colnago, V. M. Salim, and M. C. Seidl, *J. Heterocycl.Chem.* **1979,** *16*, 993.
9. Part of the mass spectroscopy was performed by Prof. J. Tamás deceased in 1993. We are grateful to Dr. E. Simon-Trompler, who evaluated the stereochemistry of the oxidation of vinyl sulfide.[6] Technical assistance of É. Papp-Borsos and K. Welker-Kardulesz is acknowledged here.

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