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Asymmetric Synthesis of Highly Functionalized Tetracyclic Indole Bases Embodying the Basic Skeleton of Yohimbine- and Reserpine Type Alkaloids

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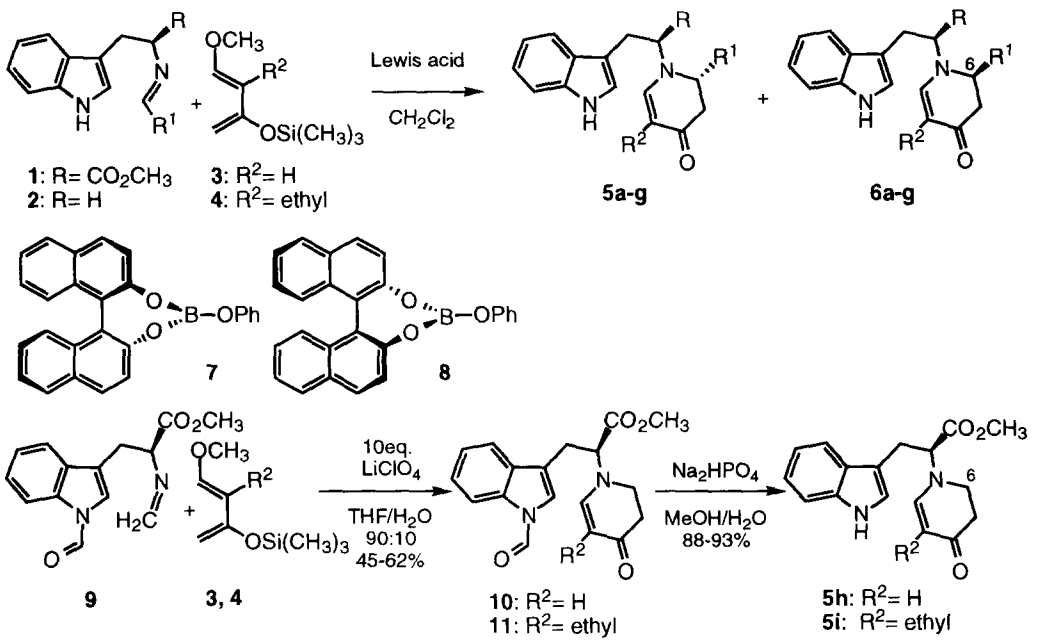
Abstract: Schiff bases derived from tryptophan methyl ester react with differently substituted electron-rich siloxy dienes in the presence of achiral or chiral boric acid esters to give enaminones **5** and **6** with high diastereomer ratios (up to >98:2). These intermediates are converted into highly functionalized indoloquinolizines **14** and **15** by means of a new method which employs the transformation of vinylogous amides to vinylogous chloromethyl amines and their subsequent conversion to vinylogous imidoyl chlorides as the key step.

The polycyclic indole alkaloids e.g. of the yohimbine- and the reserpine class mediate a variety of interesting physiological effects which can advantageously be exploited for pharmaceutical purposes. Therefore, the stereoselective synthesis of these natural products and analogs thereof with modified biological properties is of great interest to organic synthesis in general and to natural product, heterocyclic and medicinal chemistry in particular.[1)] For the construction of the underlying polycyclic framework of these complex alkaloids, the strategy to build up appropriately functionalized derivates of indoloquinolizidine and to elaborate them further into the different target compounds, has proven to be particularly viable.[1-4)] It depends, however, on the availability of convenient routes to these intermediates in enantiomerically pure form.

In this paper we report on a new method for the asymmetric synthesis of indoloquinolizines which on the one hand are selectively functionalized in the 1-position, i. e. at the C-atom which carries further substituents in many alkaloids, and which on the other hand embody a vinyl halide, i. e. a functional group which opens up new opportunities for the selective introduction of additional substituents or the attachment of further rings.

For the construction of the desired chiral heterocycles we have drawn from our previous experience in this field[3,4)] and employed tryptophan-derived enaminones **5a-i** as central intermediates (Scheme 1). These vinylogous amides were readily obtained from the Schiff bases **1** and **2** and the electron rich siloxy dienes **3** and **4**[5)] in a domino Mannich-Michael process. In this sequential transformation the silylenol ether of the diene attacks the imine first to give rise to a vinylogous ester which cyclizes by conjugate attack of the amine on the carbonyl group.[6)] Whereas in the case of the diene **3** (R^2= H) this transformation could be catalyzed by $ZnCl_2$ in THF at 0°C to give the desired enaminones in moderate yield and with diastereomer ratios ranging from 66:34 to 88:12, these conditions could not be applied for the ethyl-substituted diene **4** (R^2= ethyl). In this case, however, the use of boric acid triphenyl ester at -78°C in dichloromethane as recommended by Yamamoto et al.[7)] for related transformations, proved to be successful (Scheme 1, Table 1). In the presence of this Lewis acid the vinylogous amides **5a-g** were smoothly formed in yields up to 61% (for 2 steps, i. e. from tryptophan methyl ester hydrochloride) and with diastereomer ratios of 90:10 up to >98:2 (Table 1, entries 4 and 7-10). Even more gratifyingly, the preferable use of a boric acid phenyl ester opened up the possibility to further enhance the stereoselectivity by double diastereoselection.[8)] To this end, enantiomerically pure boric acid binaphthyl esters **7** and **8** were prepared from triphenoxy borane and (R)- or (S)-binaphthol as described by Yamamoto et al.[7)] In the presence of these chiral Lewis acids for both electron rich dienes **3** and **4** a significant enhancement of the stereoselectivity was



Scheme 1

Table 1: Results of the Mannich-Michael reactions employing the imines **1**, **2** and **9** and the dienes **3** and **4**.

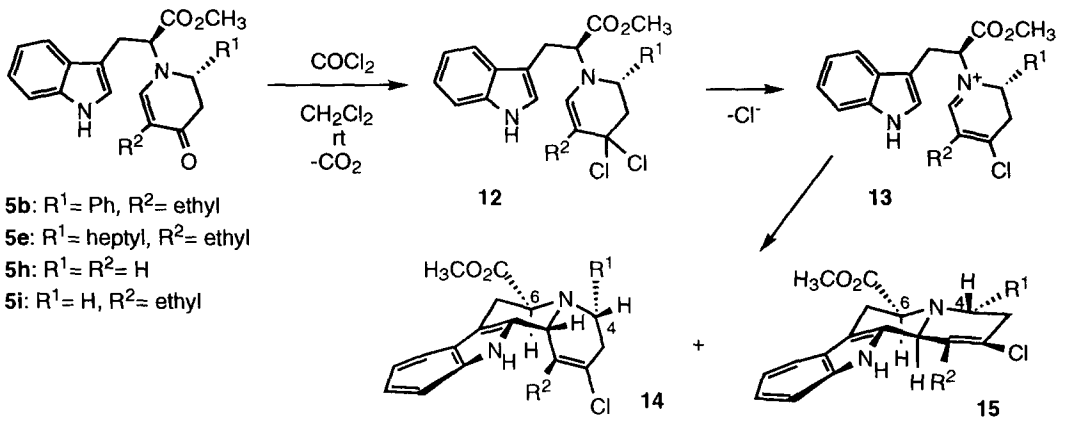
entry	5,6	R	R^1	R^2	temp. [°C]	Lewis acid	δ of 6-H [ppm] [a]	yield [%] [b]	5:6 [a,c]
1	**a**	CO_2CH_3	phenyl	H	-78	$B(OPh)_3$	4.6	51	88:12
2	**a**	CO_2CH_3	phenyl	H	-40	**7**	4.6	34	95:5
3	**a**	CO_2CH_3	phenyl	H	-40	**8**	4.6	24	91:9
4	**b**	CO_2CH_3	phenyl	ethyl	-78	$B(OPh)_3$	4.57	61[g]	93:7
5	**b**	CO_2CH_3	phenyl	ethyl	-40	**7**[d]	4.57	53	96:4
6	**b**	CO_2CH_3	phenyl	ethyl	-40	**8**	4.57	40	94:6
7	**c**	CO_2CH_3	4-Cl-phenyl	ethyl	-78	$B(OPh)_3$	4.54	38	91:9
8	**d**	CO_2CH_3	4-NO_2-phenyl	ethyl	-78	$B(OPh)_3$	4.64	35	94:6
9	**e**	CO_2CH_3	heptyl	ethyl	-78	$B(OPh)_3$	3.44-3.36	31[g]	90:10
10	**f**	CO_2CH_3	2-propyl	ethyl	-78	$B(OPh)_3$	3.22	29[g]	>98:2
11	**g**	H	phenyl	ethyl	-60	**7**[d]	4.53	62	37:63[e]
12	**10**	CO_2CH_3	H	H	20	$LiClO_4$	3.62-3.35	45[f,g]	_
13	**11**	CO_2CH_3	H	ethyl	20	$LiClO_4$	3.58-3.32	62[f,g]	_

[a] All didehydropiperidinones were characterized by means of their 250- or 400-MHz-^{1}H and 62.9- or 100.6-MHz-^{13}C NMR spectra (in $CDCl_3$). The elemental analyses are in accord with the calculated values. [b] All yields refer to tryptophan methyl ester hydrochloride. [c] Determined by integration of the respective signals found in the NMR spectra for 6-H and α-H of the diastereomeres **5**, **6**. [d] 0.5 Equivalents of the Lewis acid were used. [e] Determined by HPLC with a chiral column (ZWE 376A), kindly supplied by the Bayer AG, see ref. 9). [f] Yields refer to N^{ind}-formyl protected tryptophan methyl ester hydrochloride. [g] Specific rotations of selected examples in CH_2Cl_2: **5b**: $[\alpha]_D^{20}$= -65.2° (c= 1.05), **5e**: $[\alpha]_D^{20}$= -204.1° (c= 0.7), **5f**: $[\alpha]_D^{20}$= -187.1° (c= 1), **10**: $[\alpha]_D^{20}$= -131.5° (c= 1), **11**: $[\alpha]_D^{20}$= -139.7° (c= 1).

observed. If the reaction of the diene **3** with the imine **1a** (R^1= Ph) derived from L-tryptophan methyl ester and benzaldehyde was mediated by the boric acid ester **7** obtained from (R)-binaphthol, the enaminones **5a** and **6a** were formed in a ratio of 95:5, as compared to 88:12 with $B(OPh)_3$ (Table 1, entries 1 and 2), if (S)-binaphthol was incorporated into the Lewis acid the ratio was lower (Table 1, entry 3). Similarly, in the analogous transformations employing the ethyl-substituted diene **4** the selectivity was raised from 93:7 to 96:4 if (R)-binaphthol was used for its steric steering whereas only a slight enhancement (94:6) was recorded for the (S)-binaphthol derived catalyst (Table 1, entries 4-6). In the presence of the binaphthol Lewis acids **7** and **8** the reaction proceeded with a lower velocity, so the reaction temperature was raised to -40°C. The achiral imine **2**, was converted to the enaminones **5g** and **6g** in the presence of the boric acid ester **7** only with low enantioselectivity (Table 1, entry 11). Thus, clearly in these transformations the principle of double diastereoselectivity is operative with the L-tryptophan-derived imines and the (R)-binaphthol catalyst forming the "matched" pair. The presence of the substituent R^1 in the enaminones opens up the possibility to construct various 4-substituted indoloquinolizines (*vide infra*) which may be converted into analogs of natural products. But for the construction of polycyclic indole alkaloids themselves, a hydrogen is needed in this positon since the naturally occurring nitrogen bases do not carry an alkyl or aryl residue at this carbon atom. Unfortunately, under the conditions described above the dienes **3** and **4** did not react with the respective formaldehyde imine. However, the desired enaminones **5h** and **5i** were obtained in satisfactory yield by treatment of the formaldimine of N^{ind}-formyl protected[10] tryptophan methyl ester **9** with these dienes in aqueous tetrahydrofuran in the presence of 10 equivalents of $LiClO_4$ (Scheme 1, Table 1, entries 12 and 13), followed by removal of the formamide from the intermediary formed **10** and **11** under basic conditions.

To build up the basic tetracyclic indoloquinolizine ring system of polycyclic indole alkaloids from the enaminones **5**, the ring closure by attack of the electron rich indole nucleus on the double bond of the vinylogous amide had to be induced. For this cyclization we investigated a new method which exploits the conversion of the carbonyl group of amides to geminal dichlorides described previously in a different context.[11] Upon treatment of the enaminones **5b**, **5e**, **5h** and **5i** with phosgene the vinylogous chloromethyl amines **12** were formed. These unstable intermediates readily eliminated a chloride ion and thereby gave rise to the vinylogous imidoyl chlorides **13**. These iminium intermediates then were subject to a rapidly occurring intramolecular attack by the indole nucleus leading to the desired formation of the heterocycles **14** and **15** (Scheme 2, Table 2). If R^1 was H or phenyl the indole preferably approached the si-side of the $C=N^+$ double bond and the isomers **14a-c** were formed in excess, if R^1 was heptyl the diastereomer **15d** was generated preferably. The analysis of the conformation of the indoloquinolizines by ^{1}H-NMR- and NOE techniques revealed that in **14** the two rings are in a cis-orientation, whereas the products **15** are present as trans-conformers (Scheme 2). This was indicated by the different chemical shifts of 12b-H in **14** and **15**.[4] Furthermore, an NOE signal enhancement between 12b-H and 4-H was observed for **14**, wheras in **15** 12b-H and 6-H are in close vicinity to each other.

Overall, the two step reaction sequence illustrated in schemes 1 and 2 makes the desired selectively functionalized indolizines available in enantiomerically pure form in a straightforward and efficient manner. A particularly attractive feature of this approach is that by means of an appropriately substituted diene different substituents can be incorporated directly into the 1-position of the tetracyclic nitrogen base, i. e. a subsequent regioselective derivatization of the alkaloid precursor is not necessary. In addition, the vinyl chloride generated in the terminal ring opens up many possibilities for the rapid and selective introduction of further substituents, i. e. via Heck-type processes or after hydrolysis to the ketone.



Scheme 2

Table 2: Cyclization of the didehydropiperidin-4-ones to indolo[2,3-*a*]quinolizines

entry	**14,15**	R^1	R^2	yield [%][a]	cis : trans [b]		δ 12b-H [ppm][a]	
					14	**15**	**14**	**15**
1	**a**	H	H	46	3.6[c]	1	5.00	4.85
2	**b**	H	ethyl	54	2[c]	1	5.07	4.88
3	**c**	Ph	ethyl	59	1.5	1[c]	5.19	5.09
4	**d**	heptyl	ethyl	49	1	2.5[c]	5.11	4.93

[a] All indolo[2,3-*a*]quinolizines **14, 15** were characterized by 250- or 400-MHz-^{1}H and 62.9- or 100.6-MHz-^{13}C NMR spectra (in $CDCl_3$). The elemental analyses are in accord with the calculated values. [b] Determined from the 250- and 400- MHz-^{1}H NMR spectra. [c] Specific rotations of selected examples in CH_2Cl_2: **14a**: $[\alpha]_D^{20}$= +119.6° (c= 0.25), **14b**: $[\alpha]_D^{20}$= +57.4° (c= 0.35), **15c**: $[\alpha]_D^{20}$= -11.8° (c= 0.4), **15d**: $[\alpha]_D^{20}$= -126.7° (c= 0.3).

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