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A Novel Access to Tetrahydro-β-Carbolines via One-Pot Hydroformylation/Fischer Indole Synthesis: Rearrangement of 3,3-Spiroindoleninium Cations

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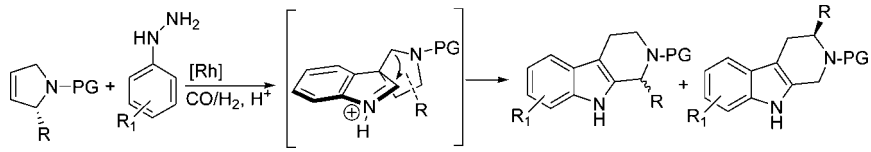
ABSTRACT



The two component one-pot hydroformylation/Fischer indole synthesis sequence of 2,5 dihydropyrroles and phenyl hydrazines allows a facile and convenient access to tetrahydro-β-carbolines in moderate to good yields.

The tetrahydro-β-carboline (THBC) ring system is present in many synthetic and naturally occurring indole alkaloids, possessing a wide diversity of structural types and displaying a variety of important biological activities.[1] Traditional strategies for the synthesis of functionalized variants of this "privileged" moiety have relied largely upon cyclocondensation of appropriately substituted tryptophan or tryptamine derivatives with carbonyl compounds under aprotic or acidic conditions, known as the Pictet-Spengler (PS) reaction.[2] However, despite the wide scope of the PS condensation and its continuous development, it turns out to be less applicable when 3- or 4-substituted THBC systems are targeted. In these cases syntheses of appropriate α or β substituted tryptamine precursors are required, which can be a very laborious and time-demanding process especially when enantiomerically pure molecules are targeted. Most of the known 3-substituted THBCs are tryptophan derivatives and are synthesized starting from this essential amino acid. As a part of our research interest adressed toward the investigation of new tandem reactions involving regio-, and/or stereocontrolled Rh catalyzed hydroformylation,[3] we have recently reported on the use of carbo- and heterocyclic olefins in tandem hydroformylation/Fischer indole synthesis sequence yielding carbazoles, sila-carbazoles and β-carboline.[4] We envisaged using this strategy for the synthesis of substituted carboline derivatives starting from enantiopure 2-substituted 2,5-dihydropyrroles. These substrates possess two available

(1) (a) Greeberger, L. M. *Cancer Res.* **1998**, *58*, 5850. (b) *Introduction to Alkaloids: A Biosynthetic Approach*; Cordell, G. A., Ed.; Wiley: New York, 1981. (c) Ulven, T.; Kostenis, E. *J. Med. Chem.* **2005**, *48*, 898. (d) Schott, Y.; Decker, M.; Rommelspacher, H.; Lehmann, J. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 5840–5843. (e) Bentley, K. W. *Nat. Prod. Rep* **2001**, *18*, 148.

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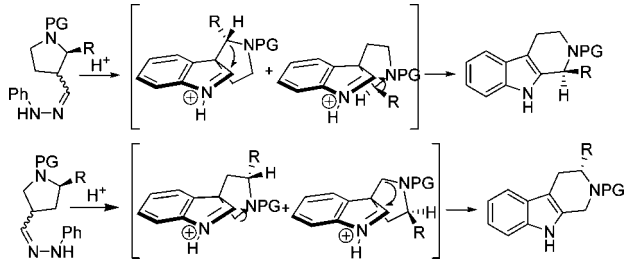
positions for the hydroformylation and, in the presence of phenyl hydrazines the aldehydes formed, can yield in two diastereomeric pairs of regioisomeric phenyl hydrazones. After acidic indolization 3,3-spiroindolenine intermediates are undergoing rearrangement to form the THBC products.[4] If the rearrangement selectively occurs with retention of the precursor configuration both diastereomers of each pair should give the same configuration in the final regioisomeric product independently from the second stereogenic center formed during hydroformylation (Scheme 1). Since under

Scheme 1. Envisaged Reaction Pathway Hydrazones Formed after Hydroformylation Are Depicted to Undergo Acid Promoted Indolization and Rearrangement



hydroformylation conditions primary and secondary amines undergo hydroaminomethylation reaction,[3] use of *N*-protected starting materials was required. For the synthesis of the enantiopure 2-substituted 2,5-dihydropyrroles Ir catalyzed allylic amination/ring closing metathesis (RCM) strategy was applied.[6c] Ir catalyzed intramolecular allylic substitution, as well as combination of intermolecular version of the latter with RCM have recently allowed asymmetric syntheses of various carbo-[5] and heterocycles.[6] For our synthesis, we used phosphoramidite type ligand **L1**. Good yields and excelent enantioselectivities were obtained in all cases (Scheme 2).[7]

Next, we focused on optimization of reaction conditions and investigation of the product distribution in the hydroformylation/indolization sequence. A stepwise procedure[4] involving tandem hydroformylation/ hydrazone formation using 1 mol % $Rh(acac)(CO)_2$ under 50/10 bar CO/H_2 in THF at 100 °C for 3 days with subsequent indolization in 4

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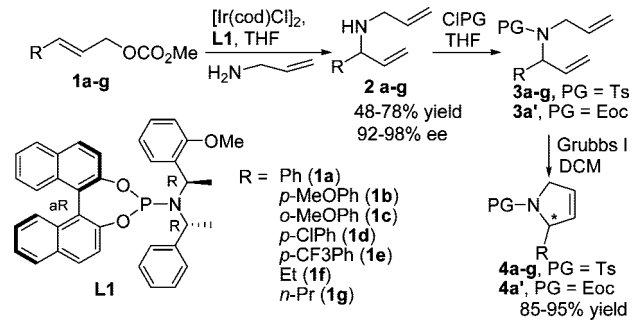
(8) See for instance: (a) *Rhodium Catalyzed Hydroformylation*; van Leeuwen, P. W. N. M., Claver, C., Eds.; Kluwer Academic Publishers: Dordrecht, 2000.

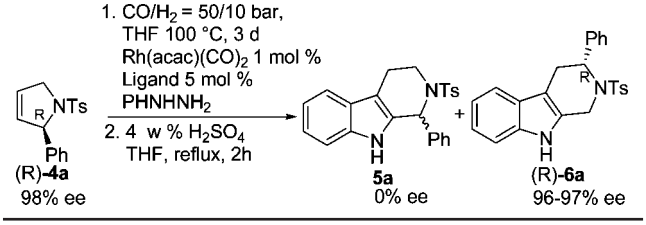
Scheme 2. Synthesis of 2-Substituted 2,5-Dihydropyrroles via Ir Catalyzed Allylic Amination/Ring Closing Metathesis Sequence[a]



[a] See Supporting Information for details.

wt % H_2SO_4 has been applied for the test reaction with substrate **4a**. Unmodified Rh catalyst yielded in two products **5a** and **6a**, in good yield of 87% and ratio of 1/1.3 in favor of **6a** (Table 1, entry 1). Tetrahydro-β-carbolines were

Table 1. Testing of Ligands in Sequential Hydroformylation/ Tetrahydro-β-carboline Synthesis



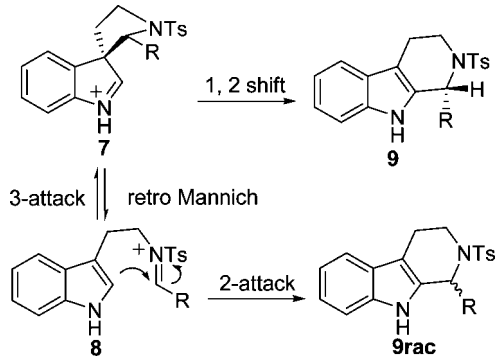
entry	ligand	olefin convn %[a]	yield, %[b] 5a + 6a	ratio[c] 5a/6a	ee, %[d] 5a	ee, %[d] 6a
1	/	full	87	1:1.3	0	97
2	PPh_3	full	85	1:2.7	0	96
3	DPPF	0	/	/	/	/
4	DPPB	30	22	1:1.3	nd[e]	nd[e]
5	BINAP	0	/	/	/	/
6	XANTPHOS	full	37	1: 5.2	nd[e]	nd[e]
7	$P(OPh)_3$	full	72	1:1.6	0	96
8	BIPHEPHOS	full	81	1:1.4	0	96

[a] Determined by 1H-NMR of crude reaction mixture. [b] Isolated yield after column chromatography. [c] Based on isolated product. [d] Determined by HPLC on chiral column. [e] Not determined.

obtained exclusively, no rearrangement toward γ-carboline was observed, in contrast to carbocyclic and cyclic silyl olefins which are known to give γ-carboline analogues.[4] To selectively obtain the desired 3-substituted THBCs, regioselective hydroformylation step is required (Scheme 1). Modifications of the rhodium catalyst with phosphine and phosphite ligands are well-known to influence regioselectivity of the hydroformylation.[8] Reaction with PPh_3 modified catalyst (Table 1, entry 1), gave 1/2.7 ratio of **5a**/**6a** in 85% yield. Rh catalyst modified with diphosphine ligands such as DPPF, BINAP, and DPPB gave no aldehyde at all or gave

low conversions of substrate (Table 1, entries 3−5). Bulky diphosphine ligand XANTPHOS usually used for *n*-selective hydroformylations of terminal olefins yielded in 1/5.2 ratio of **5a**/**6a** but in poor yield of 37%. Phosphite ligand $P(OPh)_3$ and bulky diphosphite BIPHEPHOS gave good yields but had low influence on regioselectivity of the reaction (Table 1, entries 7 and 8). Because PPh_3 appeared to be the best compromise between yield and selectivity of hydroformylation step, this ligand was chosen for further investigations. Surprisingly, in all cases, 1-substituted carboline **5a** was isolated as racemate while 3-substituted **6a** retained enantiopurity of substrate. Racemization of the 1-substituted carbolines was also observed by Danishevsky et al. during their investigation on this type of rearrangement. The authors proposed two possible rearrangement pathways of the intermediate enantiopure 3,3-spiroindoleninium cations **7** (Scheme 3).[9f] Wagner-Meerwein like 1,2 shift proceeds in

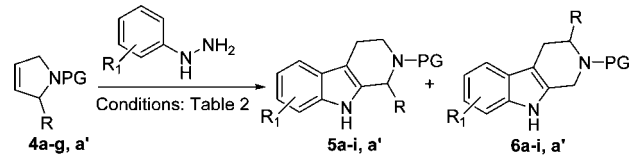
Scheme 3. Possible Rearrangement Pathways



a suprafacial fashion,[10] and leads to preservation of the stereochemical information. A second mechanistic pathway involves retro Mannich reaction of **7** to give the achiral, ring opened intermediate **8**, followed by subsequent cyclization directly yielding **9rac**. However, attack of the iminium ion **8** can also occur at position 3[11] of indole core, giving back **7**. This implies that an equilibrium between **7** and **8** might exist, leading to racemization of the spiroindoleninium cation **7** as a consequence. In addition, another factor that has to be taken into consideration is the acid-promoted racemization of 1-substituted THBCs. This is a well-documented process and occurs presumably via C1−Nb bond scission.[2b] To test whether racemization in our case is promoted by the acid used in indolization step, stepwise procedure involving thermally induced indolization[9c] was attempted starting from **4a**, but no products were obtained. Lewis acid catalyzed indolization with the same substrate gave the desired products **5a** and **6a** but again 1-substituted THBC was isolated as a racemate. Stereochemical outcome is also determined by the rearrangement pathway. To resolve whether retro Mannich reaction or 1,2 shift are occurring, a crossover experiment with a mixture of the acyclic, symmetric allylic amines was performed.[12] This experiment indicates that the rearrangement occurs in an intramolecular fashion. This is in accordance with previous studies, which also showed that the rearrangement of the 3,3-spiroindoleninium cations is an intramolecular proces.[9a] This observation therefore excludes the retro Mannich pathway and indicates that racemization is most probably a post rearrangment event, in this case caused by the acid used for indolization. The stereocenter of 3-substituted carboline product is not influenced by any of the possible reaction pathways; therefore, it stays intact.

We next turned our attention to the scope of the reaction (Table 2). Several substrates with various alkyl or aromatic groups at the pyrrole ring were tested using the optimized conditions in the presence of unsubstituted phenyl hydrazines

Table 2. Syntheses of THBCs from Substrates **4a**−**g**, **a′**



	olefin			yield		ee, %[e]	
entry	R	PG	R_1	**5** + **6**[c]	**5**: **6**[d]	**5**	**6**
1	Ph	Ts	H[a]	85 (**a**)	1:2.7	0	97
2	Ph	Eoc	H[a]	63 (**a′**)	1:2.1	0	98
3	*p*-MeO-Ph	Ts	H[a]	76 (**b**)	1:5.5	0	96
4	*o*-MeO-Ph	Ts	H[a]	71 (**c**)	1:5.2	0	95
5	*p*-Cl-Ph	Ts	H[a]	74 (**d**)	1:2.4	0	nd[g]
6	*p*-CF_3-Ph	Ts	H[a]	58 (**e**)	1:1.4	0	nd[g]
7	Et	Ts	H[a]	65 (**f**)	1:3.3	0	94
8	^{n}Pr	Ts	H[a]	69 (**g**)	1:3.6	0	93
9	Ph	Ts	*o*-Me[b]	45 (**h**)	/[f]	/	95
10	Ph	Ts	*p*-Cl[b]	41 (**i**)	1:4.4	0	95

[a] Conditions: 1 equiv **4**, 1 equiv phenyl hydrazine, 1 mol % Rh(acac)-$(CO)_2$, 5 mol % PPh_3, 50/10 bar CO/H_2, THF, 100 °C, 3 d then 4 w % H_2SO_4, THF, 80 °C. [b] Tandem reaction run with 1 equiv of PTSA and 1 equiv of benzhydrylidene protected phenyl hydrazine. [c] Isolated yield after column chromatography. [d] Determined by isolation. [e] Determined by HPLC on chiral column. [f] Only 3-substituted product isolated. [g] Not determined.

(9) For some previous work considering this type of rearrangement, see: (a) Jackson, A. H.; Smith, A. E. *Tetrahedron* **1968**, *24*, 403. (b) Jackson, A. H.; Smith, P. *Tetrahedron* **1968**, *24*, 222. (c) Benito, Y.; Temporano, F.; Rodriguez, J. G. *J. Heterocyclic Chem*, **1985**, *22*, 1207. (d) Benito, Y.; Canoira, L.; Martinez-Lopez, N.; Temporano, F.; Rodriguez, J. G. *J. Heterocyclic Chem*, **1987**, *24*, 623. (e) Lynch, P. P.; Jackson, A. H. *J. Chem. Soc., Perkin Trans. 1* **1987**, 1215. (f) Li, C.; Chan, K.; Heimamm, A. C.; Danishefsky, S. J. *Angew. Chem., Int. Ed.* **2007**, *46*, 1444–7. (g) Liu, K. G.; Robichaud, A. J.; Lo, J. R.; Mattes, J. F.; Cai, Y. *Org. Lett.* **2006**, *8*, 5769–71.

(10) Starling, S. M.; Vonwiller, S. C.; Reek, J. N. H. *J. Org. Chem.* **1998**, *63*, 2262.

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(12) See Supporting Information for details on crossover experiment.

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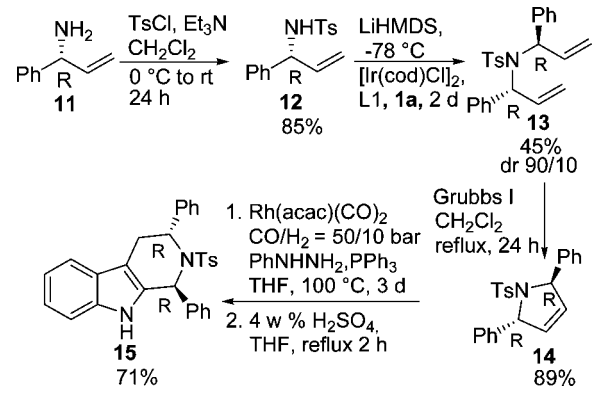
(Table 2, entries 1−8). Ts-protected **4a** gave better yields in this sequence than Eoc-protected **4a′** (Table 2, entries 1, 2); hence, Ts-protected substrates were preferably investigated. In all cases, 3-substituted THBCs were obtained as the major products. Pyrroles containing both electron-donating and electron-withdrawing aromatic substituents were included. Regioselectivities of products ranged from 1/2.7 to 1/5.5 in favor of **6**. Electron donating substituents on the substrate shifted the regioselectivity toward 3-substituted product (Table 2, Entries 3 and 4) in contrast to electron withdrawing ones (Table 2, entries 5 and 6). Pyrroles possessing alkyl substituents (Table 2, entries 7 and 8) gave THBCs in good overall yields of 65 and 69%, respectively, and in moderate selectivities. 3-Substituted products retained the enantiopurity of starting material in all cases whereas 1-substituted products were obtained as racemates. To introduce substituents in the indole part of the molecule, substituted hydrazines were used. For this purpose, benzhydrylidene-protected aryl hydrazones have been synthesized via Buchwald's method.[13] These substrates are known to undergo high-yielding Fischer indolization in the presence of olefins under hydroformylation conditions.[14] Because the benzhydrylidene group is stable under hydroformylation conditions, reactions were conducted in the presence of 1 equiv of PTSA.[14] In general, lower yields than with unprotected hydrazines were observed. Tandem reaction of **4a** with *o*-Me substituted benzhydrylidene hydrazone yielded exclusively the 3-substituted product although in moderate yield of 45% (Table 2, Entry 9), whereas *p*-Cl substituted hydrazone gave only 41% yield of products in 1/4.4 ratio (Table 2, entry 10).

To simultaneously introduce two substituents in the final carboline molecule, it was necessary to synthesize 2,5-disubstituted pyrroles. This was achieved by a modified procedure of Helmchen (Scheme 4).[6d] Enantiopure (*R*)-**10** was thus obtained in 98% ee. This was tosylated to give **11**, which was converted to Li anion and submitted to an Ir catalyzed amination reaction with cinnamyl carbonate in the presence of ligand **L1.** Product **12** was obtained in 45% yield as a 90/10 mixture of diastereoisomers. After ring-closing metathesis, **13** was obtained in 89% yield. Pyrrole **13** was submitted to standard reaction conditions in a stepwise manner in the presence of phenylhydrazine to yield **14** as single diastereoisomer in 71% yield. Disubstituted pyrroles

Scheme 4. Synthesis of Enantiopure 1,3-Disubstituted Tetrahydro-β-carboline **14**



such as **13** thus allow fast access to enantiopure 1,3-disubstituted tetrahydro-β-carbolines. Substrates of this type are particularly promising due to the fact that they are not suffering from problems with regioselectivity of hydroformylation.

In summary, this convergent, one-pot strategy offers a convenient approach toward 1- and 3-substituted tetrahydro-β-carbolines independent from the usual indole precursors such as tryptophane and tryptamines. Highly functionalized building blocks are assembled to simultaneously form the indole and carboline core in the final synthetic step. This allows flexible determination of the substitution pattern in the products. The outcome of the reaction sequence depends on two factors, the regioselective hydroformylation to yield desired aldehyde and the selective migration of one of the two available positions. For both factors clear tendencies are observed.

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Supporting Information Available: Experimental procedures and full spectroscopic data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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