in iodine-containing by-products, hydrogenolysis of the allylic alcohol, and/or olefin saturation.

Methyl benzoate **23**, aliphatic ester **25**, and phenolic ether **27** readily afforded alcohols **24**–**28** (Table 2, entries 5–7), respectively. However, it was necessary to reduce the temperature and increase the reaction times for methyl ether **29**, tetrahydropyran (THP) **31**, and silyl ether **33** (Table 2, entries 8–10) to avoid any concomitant loss of these functional groups. 1,1,1,3,3,3-Hexafluoro-2-phenylisopropyl (HIP) ethers,[13] although classified as benzyl ethers, were stable to $CrCl_2$/LiI treatment, for example, **35** was converted into **36** (Table 2, entry 11). On the other hand, amines such as **37** tended to retard de-*O*-benzylation, but this could be surmounted with the use of excess reagent (Table 2, entry 12).

Experimental Section

De-*O*-benzylation procedure: An arylmethyl ether (1 equiv) was added to a purple suspension of $CrCl_2$ (3 equiv) and LiI (4 equiv; Aldrich Chem. Co, 99.99%) in a solution of EtOAc/H_2O (1:0.005 v/v, 10 mL/100 mg arylmethyl ether). The reaction was heated at the indicated temperature (Tables 1 and 2) for 2–24 h, then cooled to room temperature, quenched with water, and extracted three times with Et_2O. The combined organic extracts were washed with saturated sodium sulfite solution and water, then dried and evaporated in vacuo. Chromatographic purification of the residue afforded the corresponding free alcohol.

Preparation of 2,6-dimethoxybenzyl bromide:[3] 2,6-Dimethoxytoluene (1 equiv) was heated at reflux with *N*-bromosuccinimide (NBS; 1.1 equiv) and benzoyl peroxide (2 mol%) in carbon tetrachloride (10 mL/1.5 g 2,6-dimethoxytoluene) for 30 min. After cooling the reaction mixture to room temperature, the precipitated succinimide was removed by filtration and the solvent was evaporated in vacuo to give crude 2,6-dimethoxybenzyl bromide (95%), which was sufficiently pure to be used without further purification.

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[4] At less than $1.00/g from Aldrich Chem. Co., 2,6-dimethoxytoluene, from which 2,6-dimethoxybenzyl bromide is directly obtained by NBS bromination (see Experimental Section), is competitively priced with respect to the precursors of other methoxy-substituted benzylation reagents.

[5] Anhydrous LiI (99.99%) from Aldrich gave a consistently good result, whereas samples purchased from Acros were inconsistent.

[6] 1:0.005 v:v EtOAc:H_2O. The reaction is impeded by ratios above 1:0.01.

[7] Inorganic iodides have been used for dealkylations and debenzylations of phosphate triesters: R. J. W. Cremlyn, G. W. Kenner, Sir A. Todd, *J. Chem. Soc.* **1958**, 528–530.

[8] $Cr^{III}Cl_3$ (6 equiv)/LiI (10 equiv) gave comparable or, in some cases, higher yields than $Cr^{II}Cl_2$ (3 equiv)/LiI (4 equiv). Evidently, Cr^{III} is reduced by LiI to Cr^{II} under the reaction conditions.

[9] *p*-Phenylbenzyl ethers are also cleaved by $FeCl_3$: M. H. Park, R. Takeda, K. Nakanishi, *Tetrahedron Lett.* **1987**, *28*, 3823–3824.

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Indoloparacyclophanes: Synthesis and Dopamine Receptor Binding of a Novel Arylbioisostere**

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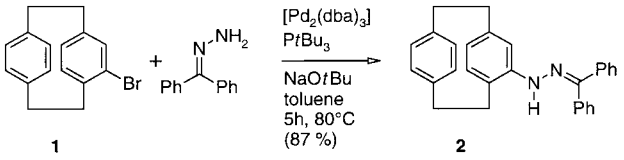
Dedicated to Professor Dieter Sellmann on the occasion of his 60th birthday

Investigating the reaction of arylhydrazines with ketones in his laboratory in Erlangen, Emil Fischer discovered the formation of indoles.[1, 2] Very recent work published by Buchwald et al. and also by Hartwig further extended the scope of the Fischer indole synthesis.[3, 4] The major improvement of this variant is the Pd-catalyzed preparation of *N*-arylbenzophenone hydrazones used as key intermediates. As part of our exploration of novel types of pharmacophoric elements, we recently found that enyne moieties and aza-derivatives thereof can serve as nonaromatic arylbioisosteres.[5] Furthermore, the pyrazolo[1,5]pyridine nucleus turned out as an effective indole bioisostere.[6] As an extension of these studies, we were intrigued by the question whether a double-layered [2.2](4,7)indoloparacyclophane system with its close proximity of the face-to-face aromatic rings coupled to the rigid and highly strained skeleton could be exploited as a pharmacophoric element being able to coordinate to highly specific receptor binding sites.[7]

For the preparation of the hitherto unknown [2.2]indoloparacyclophane ring system,[8, 9] we planned to take advantage of Buchwald's variant of the Fischer indole synthesis.[3] Thus, we tried to prepare the *N*-([2.2]paracyclophanyl)benzophenone hydrazone **2** by Pd-catalyzed cross-coupling reaction of benzophenone hydrazone with 2-bromo[2.2]paracyclophane **1**, readily available by bromination of [2.2]paracyclophane [Eq. (1)].[10] Our initial attempts using 1.0 mol% $Pd(OAc)_2$



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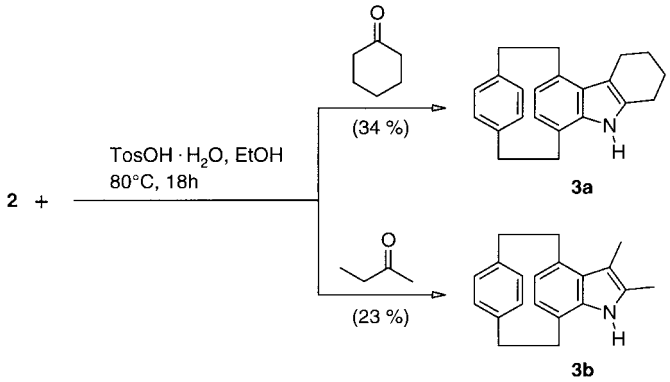
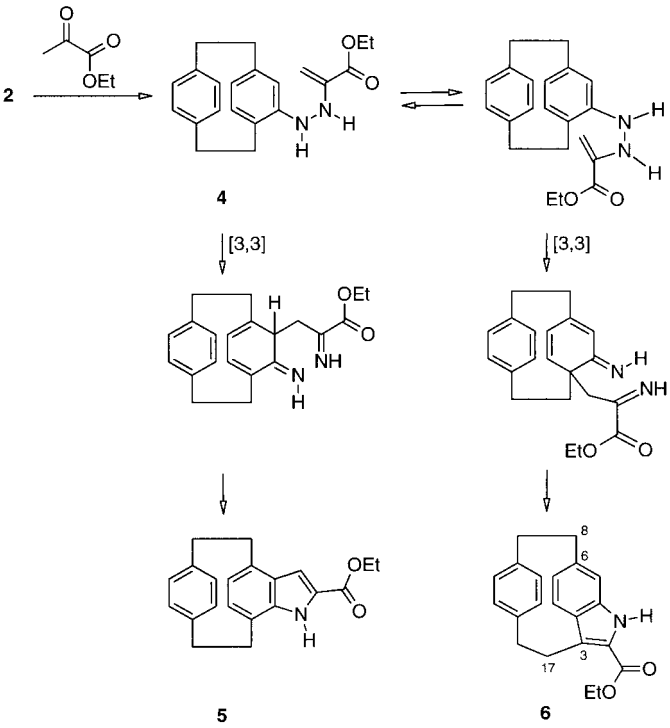
and 4.0 mol % PPh_3 failed to promote cross-coupling. Further investigations examining the utility of catalysts based on the reagents $Pd(OAc)_2$ (or $[Pd_2(dba)_3]$, dba = dibenzylideneacetone) and P(*o*-Tol)$_3$ (or DPPF 1,1′-bis(diphenylphosphanyl)-ferrocene) furnished small amounts of the desired coupling product **2**.[11] Further improvement was observed with the Pd/BINAP catalyst system resulting in formation of the cyclophanyl hydrazone **2** in 20 % yield. Superior activity resulted with a catalyst composed of $[Pd_2(dba)_3]$ and the sterically demanding P*t*Bu$_3$[12] ligand facilitating a clean conversion of the starting material to the coupling product **2** in 87 % yield.

We next turned our attention to the following reaction steps involving cleavage of the hydrazone, condensation of the resulting paracyclophanylhydrazine with an enolizable ketone and, finally, Fischer cyclization. Employing Buchwald's one-pot protocol, the benzophenone hydrazone **2** was treated with cyclohexanone and TosOH in refluxing EtOH, which led to the formation of the fused [2.2](4,7)indoloparacyclophane **3a** in 34 % yield (Scheme 1). Analogously, the 2,3-dimethyl derivative **3b** could be synthesized starting from the central precursor **2** and butanone.



Scheme 1. Synthesis of the double-layered indoles **3a** and **3b**. Tos = *para*-Toluenesulfonyl.

Subjecting ethyl pyruvate and the hydrazone **2** to identical conditions gave a 1:1 reaction mixture separable by preparative HPLC (10-μ silica gel, hexane/EtOAc 9/1). Depending on the direction of cyclization, both the typical Fischer cyclization product **5** and the rearranged (3,6)indoloparacyclophane **6** were formed, as depicted in Scheme 2. Atypical Fischer indolizations of *ortho*-substituted phenylhydrazones including *ipso*-cyclization paired with [1,2], [1,3], [1,4], and [1,5] alkyl shifts are reported in the literature.[13] Only one rearrangement is described from the benzene ring to the C3 position of the pyrrole moiety.[14] Obviously, the reaction sequence leading to the atypical cyclization product **6** involves an *ipso*-directed [3.3] sigmatropic rearrangement of the intermediate ene – hydrazine followed by imine/enamine tautomerization, alkyl shift and cyclization under loss of ammonia. Since we did not observe atypical indolizations for the synthesis of the indoloparacyclophanes **3a** and **3b**, we reason that the carboxylic ester functionality, favoring the formation of an enamine intermediate, facilitates the alternative reaction pathway.



Scheme 2. Typical and atypical indolizations. One-pot synthesis: TosOH · H_2O (2 equiv), ethyl pyruvate, EtOH (1 equiv), reflux, 18 h (**5**: 23 %; **6**: 23 %). Synthesis step by step: 1. TosOH · H_2O (5 equiv), $HOCH_2CH_2OH$, HCl/EtOH, reflux, 18 h; 2. ethyl pyruvate (1 equiv), EtOH, 70 °C, 5 h (61 %); 3. TosOH (1.5 equiv), C_6H_6, reflux, 45 min (42 % **5**).

Careful NMR studies including HMQC, HMBC, and NOE experiments unambiguously proved the structures of the double-layered indoles **5** and **6**. Multiple bond correlations between the methylene protons and the neighbored aromatic carbon atoms demonstrated the substitution pattern of the aromatic ring systems. In detail, the connectivities of the rearranged (3,6)indolocyclophane **6** were unambiguously proved by heteronuclear correlations between $H17_{anti}$ and C2, C3, and C3a and between $H8_{anti}$ and C5, C6, and C7, respectively. Based on the aromatic protons H4, H5, and H7, three-bond correlations to the respective aromatic carbon atoms C6/C7a, C3a/C7, and C3a/C5 were diagnostic for localizing the quaternary carbon atoms. In combination with difference NOE measurements the heteronuclear correlation experiments enabled us to assign all ^1H and ^{13}C NMR resonances of the structural isomers **5** and **6** completely. Quantum mechanical calculations of the indolocyclophanes **5** and **6** choosing the AM1 parameter set[15] in MOPAC gave minimal-energy structures clearly demonstrating boat shapes for the benzene moieties and a significantly crooked indole nucleus for the (3,6)-isomer **6**. It is interesting to note that the final heats of formation obtained by the SCF calculations were similar ($\Delta\Delta H = 1.2$ kcal mol^{-1}) when the rearranged isomer **6** was predicted more stable.

To circumvent the difficult purification process involved in the preparation of pure **5**, which should be used as an intermediate for the synthesis of bioactive compounds, we tried to avoid the formation of the side product **6**. It turned out to be useful to perform the synthesis step by step (see

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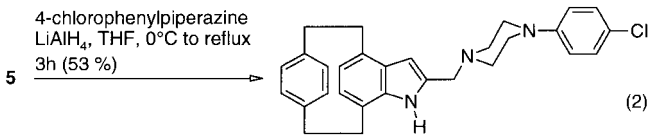
legend to Scheme 2). Deprotection of the benzophenone hydrazone **2** under acidic conditions was facilitated by ethylene glycol which effectively traps benzophenone. After extraction, the liberated hydrazine was reacted with ethyl pyruvate to furnish the condensation product **4**. Finally, cyclization of pure **4** under relatively mild conditions resulted in formation of the typical indolization product **5** without rearrangement.

In order to investigate whether the double-layered [2.2](4,7)indoloparacyclophane moiety can serve as an indole bioisostere, we envisioned to synthesize the test compound **7** which is structurally related to piperazinylmethylindoles that were recently described as strong and selective dopamine D4 receptor ligands.[16] Employing a one-step process, pre-treatment of (4-chlorophenyl)piperazine with $LiAlH_4$ and subsequent addition of the carboxylic ester **5** resulted in formation of the reductive amination product **7** [Eq. (2)].



(2)

7

The test compound **7** and the dopamine receptor antagonist clozapine, known as a valuable antipsychotic drug, were evaluated in vitro for their abilities to displace [^{3}H]spiperone from the cloned human dopamine receptors $D2_{long}$, $D2_{short}$,[17] D3,[18] and D4.4[19] being stably expressed in CHO cells (Table 1).[5a] The D1 affinities were determined by employing bovine striatal membrane preparations and the D1 selective antagonist [^{3}H]SCH 23390. The data prove that the double-layered indolocyclophane **7** displays strong and selective affinity for the dopamine D4 receptor subtype which is of special interest for the treatment of neuropsychiatric disorders. These results clearly demonstrate that sterically demanding cyclophane derivatives are, in fact, capable of approaching and recognizing highly specific transmembrane receptor binding sites. Further investigations including enantiopure indolocyclophanes are currently in progress.

Table 1. Dopamine receptor binding (K_i values (nM)) of the test compound **7** compared to the antipsychotic drug clozapine.[a]

compound	D1	$D2_{long}$	$D2_{short}$	D3	D4.4
7	1500	2500	1100	410	35
clozapine	420	41	28	960	16

[a] Data are based on the means of 2–4 experiments performed in triplicate at eight concentrations.

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