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Synthesis of Pharmacologically Relevant Indoles with Amine Side Chains via Tandem Hydroformylation/Fischer Indole Synthesis

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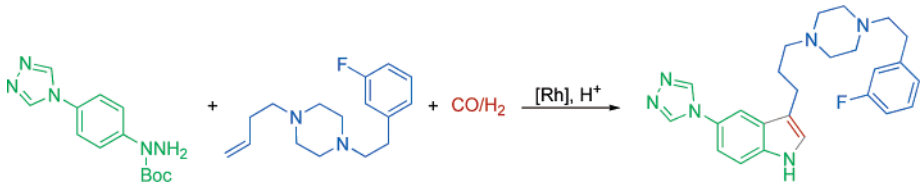


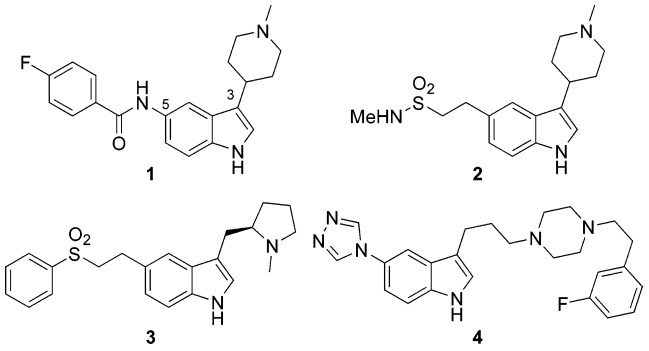
The sequence of hydroformylation and Fischer indole synthesis starting from amino olefins and aryl hydrazines is described. In a convergent manner, the two units bearing pharmacologically relevant substituents are assembled in the final indolization step. This modular and diversity-oriented approach to tryptamines and homotryptamines can be conducted in water and allows synthesis of branched and nonbranched tryptamines as well as tryptamine-based pharmaceuticals such as the 5-HT_{1D} agonist L 775 606.

Introduction

Tryptamines are involved in various biological processes. Serotonin, for example, is a neurotransmitter and influences the human nervous system. It controls the state of mind, affects circadian rhythm, sexual urge, and body temperature and seems to play a key role in neurological disorders such as migraine. Tailored serotonin-type tryptamines are therapeutically used to influence these systems by addressing the responsible receptors selectively. In the past few years, it was found that in addition to appropriate substituents at C5, more sophisticated amine moieties have to be attached with varying distances at C3 to achieve high selectivities toward subtypes of the serotonin receptor family in addition to extended substituents at the 5-position (Scheme 1).[1−3]

From a synthetic chemist's point of view, these and additional features such as the occurrence of branching in the α- and β-positions or stereochemical issues, as well as the fact that the nitrogen might be embedded in a cyclic system such as piperidines, pyrrolidines, or piperazines, are interesting. All these features demand synthetic strategies that give convenient and fast access

SCHEME 1. Recent Drug Developments



to highly diverse libraries of tryptamines and their homologues. Therefore, a general protocol is required that allows simultaneous variations in all medicinally important positions. For a modular approach with high diversity, fusion of all building blocks in a late synthetic step would be desirable with flexible determination of the chain length and the substitution pattern in the side chain. Such a convergent strategy should preferably include the construction of the indole core from building blocks (amine moiety, side chain fragment, properly substituted aromatic indole precursor), which are easily available in large amounts from previous synthetic steps.

Fischer's method and Larock's method are the most common methods used to construct indoles. In the Larock indole synthesis, *o*-halo anilines are connected with a functionalized alkyne under palladium catalysis.[4] Syn-

(1) Johnson, K. W.; Schaus, J. M.; Durkin, M. M.; Audia, J. E.; Kaldor, S. W.; Flaugh, M. E.; Adham, N.; Zgombick, J. M.; Cohen, M. L.; Branchek, T. A.; Phebus, L. A. *NeuroReport* **1997**, 8, 2237−2240.
(2) Harding, V. D.; Macrae, R. J.; Ogilvie, R. J. PCT Int. Appl. WO9606842A1, 1996.
(3) MacLeod, A. M.; Street, L. J.; Reeve, A. J.; Jelley, R. A.; Sternfeld, F.; Beer, M. S.; Stanton, J. A.; Watt, A. P.; Rathbone, D.; Matassa, V. G. *J. Med. Chem.* **1997**, *22*, 3501−3503.

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thesis of additionally substituted *o*-halo anilines, however, requires further steps and is not always easily achieved. Similarly, the alkyne unit may require laborious synthetic procedures. If the final product bears additional substituents on the six-membered ring of the indole core, the substituted *o*-halo anilines subjected to the Larock synthesis can cause steric hindrance. Similarly, obtaining the starting materials for Fischer's indole synthesis can be laborious. Here carbonyl compounds are reacted with aryl hydrazines under acid catalysis.[5] While a number of different approaches have been reported for the synthesis of substituted aryl hydrazines (the degree of substitution is reduced by one as compared to the aryl halide required for a Larock synthesis of the same compound), synthesis of the carbonyl compound very often requires a large number of simple functional group transformations (e.g., homologization of the carbon chain, reduction, oxidation). If aldehydes are needed for the indolization step, these have to be protected as acetals, aminals, enol ethers, or bisulfite adducts in order to prevent aldol condensation and oligomerization under the harsh conditions of Fischer indole synthesis. This requires additional steps and reagents and may hamper a general application with broad diversity as demanded for an ideal synthesis[6] and the medicinal chemist's needs.

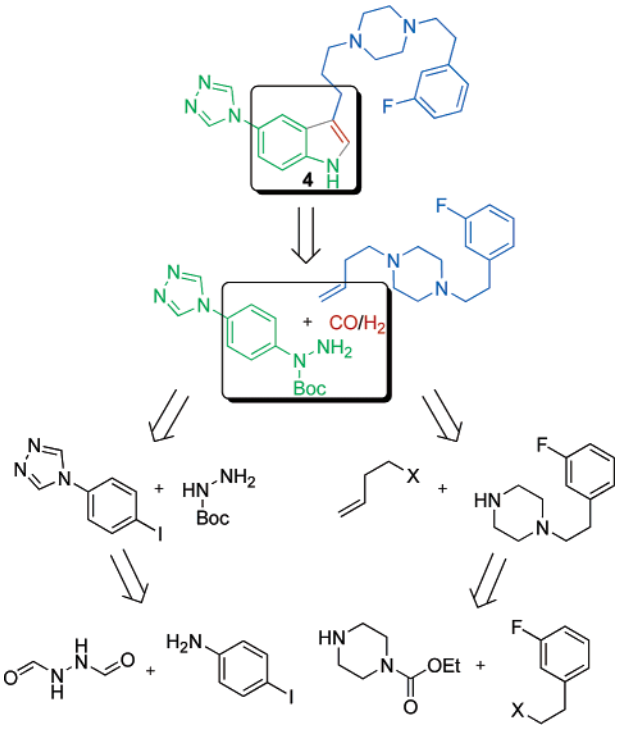
Recently, we have given a preliminary report on a new approach to indoles starting from alkenes and hydrazines via a combination of rhodium-catalyzed hydroformylation and Brønsted acid-catalyzed Fischer indole synthesis.[7] The aldehyde is generated in situ from the alkene and trapped by the hydrazine to form the hydrazone, which is cyclized to the indole product. This one-pot procedure offers a convenient modular approach toward side chain-functionalized indoles with high diversity, if the broad availability of substituted aryl hydrazines and functionalized alkenes is considered. If amino olefins are used, aryl- and side chain-functionalized indoles such as tryptamines and their homologues should be obtainable from, respectively, two and three easily available building blocks and CO/H_2 (Scheme 2).

We here wish to demonstrate the efficiency of this new tandem procedure in modular syntheses of linear and branched tryptamines and their homologues.

Results and Discussion

A modular one-pot synthesis of tryptamine-type indoles according to the above-described protocol requires efficient hydroformylation, hydrazone formation, and indolization under optimized conditions for all steps. Hydroformylation of nonprotected amino olefins and especially of allylic amines, however, is not trivial since various unwanted side reactions can occur. It is well

SCHEME 2. Retrosynthesis for L775 606 (4) via Tandem Hydroformylation/Fischer Indole Synthesis



documented that the hydrogenation activity of rhodium catalysts is increased in the presence of catalytic amounts of tertiary amines.[8] In using amino olefins, the amine as part of the substrate is present in a large excess relative to the catalyst. Therefore, hydrogenation of the olefin can result in loss of starting material, while subsequent hydrogenation of the hydroformylation product leads to the corresponding alcohol. On the other hand, rhodium catalysts exhibit double-bond isomerization activity. It has been reported that allylic amines isomerize to enamines under rhodium catalysis at mild temperatures,[9] and according to our own experience with hydroaminomethylation, such enamines are easily hydrogenated under hydroformylation conditions.[10] Furthermore, even amine bases can induce aldol condensation reactions of the aldehydes. All these side reactions may be prevented, if hydroformylation of amino olefins is conducted in the presence of hydrazines with trapping of the aldehydes as hydrazones. Therefore, we started our investigation with studies of the hydroformylation of amino olefins in the presence of hydrazines.

Hydroformylation of Amino Olefins in the Presence of Aryl Hydrazines. As expected, hydroformylation of *N*-allylic, *N*,*N*-dimethylamine (**5a**) and of

(4) (a) Larock, R. C.; Yum, E. K. *J. Am. Chem. Soc*. **1991**, *113*, 6689. (b) Larock, R. C.; Yum, E. K.; Refvik, M. D. *J. Org. Chem*. **1998**, *63*, 7652.

(5) (a) Robinson, B. *Chem. Rev*. **1963**, *3*, 373. (b) Ishii, H. *Acc. Chem. Res*. 1981, *14*, 233−247. (c) Robinson, B. *The Fischer Indole Synthesis*; Wiley: New York, 1982. (d) Hughes, D. L. *Org. Prep. Proced. Int*. **1993**, *25*, 607−632. (e) Gribble, G. W. *J. Chem. Soc., Perkin Trans. 1* **2000**, 1045.

(6) Wender, P. A.; Handy, S. T.; Wright, D. L. *Chem. Ind*. **1997**, 765−769.

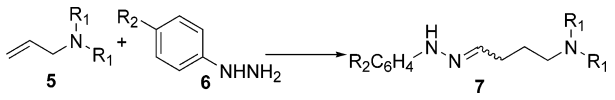
(7) (a) Köhling, P.; Schmidt, A. M.; Eilbracht, P. *Org. Lett*. **2003**, *5*, *18*, 3213−3216. (b) Schmidt, A. M.; Eilbracht, P. *Org. Biomol. Chem*. **2005**, *3*, 124−134.

(8) (a) Kaneda, K.; Yasumura, M.; Hiraki, M.; Imanaka, T.; Teranishi, S. *Chem. Lett*. **1981**, 1763. (b) Kaneda, K.; Imanaka, T.; Teranishi, S. *Chem. Lett*. **1983**, 1465.

(9) Tani, K.; Yamagata, T.; Akutagawa, S.; Kumobayashi, H.; Taketomi, T.; Takaya, H.; Miyashita, A.; Noyori, R.; Otsuka, S. *J. Am. Chem. Soc*. **1984**, *18*, 106, 5208−5217.

(10) (a) Eilbracht, P.; Bärfacker, L.; Buss, C.; Hollmann, C.; Kitsos-Rzychon, B. E.; Kranemann, C. L.; Rische, T.; Roggenbuck, R.; Schmidt, A. *Chem. Rev*. **1999**, *99*, 3329−3366. (b) Schmidt, A. M.; Eilbracht, P. In *Transition Metals for Organic Synthesis: Building Blocks and Fine Chemicals*, 2nd ed.; Beller, M., Bolm, C., Eds.; Wiley-VCH: Weinheim, 2004, pp 57−111.

TABLE 1. Tandem Hydroformylation/Hydrazone Formation[a]



entry	olefin **5**	hydrazine **6**	yield
1	**5a** ($R_1 = CH_3$)	**6a** ($R_2 = H$)	quant. (**7a**)
2	**5b** ($R_1 = (CH_2)_5$)	**6a** ($R_2 = H$)	97% (**7b**)
3	**5b** ($R_1 = (CH_2)_5$)	**6b** ($R_2 = OMe$)	93% (**7c**)
4	**5a** ($R_1 = CH_3$)	**6c** ($R_2 = CN$)	90% (**7d**)
5	**5b** ($R_1 = (CH_2)_5$)	**6d** ($R_2 = NO_2$)	80% (**7e**)

[a] Conditions: 1 equiv of **5**, 1 equiv of **6**, 0.3 mol % $Rh(acac)(CO)_2$, 1.5 mol % XANTPHOS, 10 bar CO, 10 bar H_2, THF, 3 days, 70 °C.

4-methylene, *N*-methyl piperidine (**5l**) does not selectively lead to amino aldehydes even if phosphane ligands such as XANTPHOS are added. If, however, hydroformylation of the same allylic amines is conducted in the presence of phenylhydrazine (**6a**), the expected aryl hydrazones **7** can be isolated in almost quantitative yields (Table 1). No purification is needed; the products can be used for indolization directly without further purification.[11] Under the chosen conditions, electron-withdrawing as well as electron-donating substituents at the aromatic hydrazine are tolerated. Even nitro groups are stable under the reductive conditions.[12] It is also important to mention that the use of a Rh/XANTPHOS system grants high *n*-selectivity in the hydroformylation of terminally monosubstituted amino olefins.

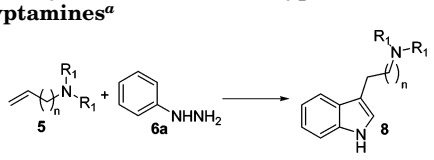
In all cases, hydrogenation products are not observed, neither the olefin nor the aldehyde, which is immediately trapped by the hydrazine. Also, the aryl hydrazone double bond is not hydrogenated, so a higher stability of aryl hydrazones toward hydrogenation can be assumed as compared to the aldehyde precursors. In summary, the hydrazone group acts as an efficient protecting group for aldehydes. In contrast to other protection groups, the aryl hydrazone at the same time is a building block for the final indole product.

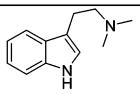
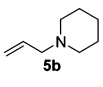
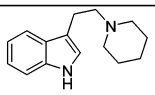
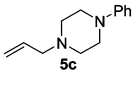
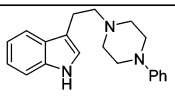
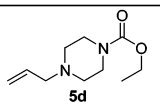
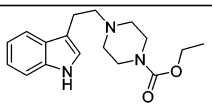
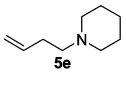
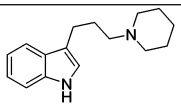
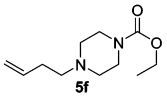
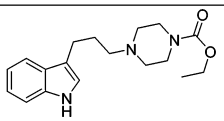
Fischer Indolization. While the hydroformylations described above are performed in THF, Fischer indolization requires a more polar solvent in order to prevent precipitation of salts formed by protonation of the amino and/or hydrazine/hydrazone groups. Alcohols are common solvents in Fischer indole syntheses. However, indolization of **7a** in ethanol gives tryptamine **8a** only in an unselective conversion with poor yields. Reaction in methanol does not lead to any improvements, whereas in aqueous sulfuric acid, fast and highly selective conversion toward indole **8a** is found with quantitative yields. Surprisingly, this method proceeds with such a high degree of selectivity that a purification of the reaction product is not required.

(11) Beller et al. have simultaneously found that aldehydes can be trapped as aryl hydrazones under hydroformylation conditions. Subsequent indolization was verified by the addition of $ZnCl_2$ to the crude mixture, but in contrast to our protocol this procedure appears to be limited to simple alkyl indoles. For further details, see: Ahmed, M.; Jackstell, R.; Seayad, A. M. Klein, H.; Beller, M. *Tetrahedron Lett.* **2004**, 45, *4*, 869−873.

(12) In our experience, aromatic nitro groups can be reduced under harsh hydroformylation conditions, allowing them to be used as aniline precursors in hydroaminomethylations. Unpublished results; Rische, T.; Eilbracht, P.; 1999.

TABLE 2. Synthesis of Linear Tryptamines and Homotryptamines[a]



entry	olefin **5**	product	yield
1			quant. (**8a**)
2			97% (**8b**)
3			96%[b] (**8c**)
4			94% (**8d**)
5			91% (**8e**)
6			91% (**8f**)

[a] Conditions: (i) 1 equiv of **5**, 1 equiv of phenylhydrazine **6a**, 0.3 mol % $Rh(acac)(CO)_2$, 1.5 mol % XANTPHOS, 10 bar CO, 10 bar H_2, THF, 3 days, 70 °C; (ii) 4 wt % H_2SO_4, 2 h, 100 °C. Yield is given for the tandem reaction starting with the olefin. [b] Precipitated as hydrochloride salt.

Tandem Hydroformylation/Hydrazone Formation/Fischer Indolization. A combination of both steps therefore seems to be a suitable protocol for the synthesis of tryptamines directly from olefins, if after a hydroformylation of the amino olefin in the presence of an aryl hydrazine the solvent is removed and the remaining aryl hydrazone is taken up in aqueous sulfuric acid for the final indolization. The reliability of this protocol is tested with a number of different allylic and homoallylic amines as compiled in Table 2.

Without any exception, all indoles are obtained in excellent yields, and no products stemming from *iso*-aldehydes are detected. Thus, the Rh/XANTPHOS system is a powerful hydroformylation catalyst for the regioselective conversion of amino olefins, and in contrast to other observations[13] the positive effect of the ligand is not suppressed in the presence of the amine and hydrazine units. The stability of the carbamate protection group in **8d** and **8f** is also surprising. After removal of this group, the nitrogen is activated for further derivatization as required for target molecules such as pharmaceutical compound L 775 606 (**4**, Scheme 1). While tryptamine **8a** (Table 2, entry 1) is known as a prominent

(13) Angelovski, G.; Eilbracht, P. *Tetrahedron* **2003**, *59*, 8265−8274.

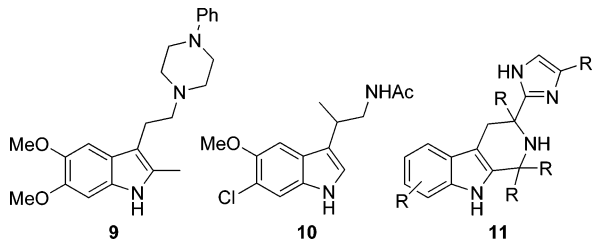


FIGURE 1.

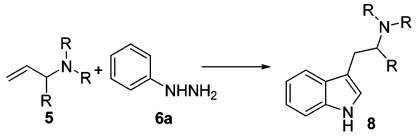
structural element in many biologically active indole derivatives, tryptamines with the nitrogen as part of a cyclic moiety have become more and more interesting. Especially the piperazine moiety seems to be very attractive for pharmaceutical use. The structural element of **8c**, for example, is found in the antipsychotic Oxypertine (**9**, Figure 1). For targets of this type, it was important to prove that both allylic piperazines as well as homoallylic piperazines are tolerated under the conditions used to allow the attachment of amines in varying distances to different indole cores (Table 2, entries 3, 4, 6). In general, allylation and homoallylation of amines proceed with excellent yields, thus allowing a modular approach using the method described above.

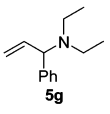
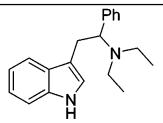
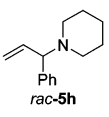
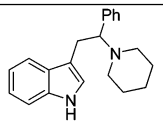
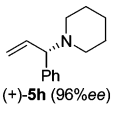
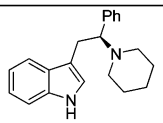
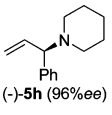
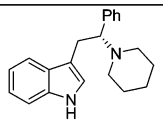
Apart from tryptamine analogues with linear side chains as prepared above, also derivatives with branched side chains have come into the focus of medicinal chemistry. In the past few years, the first examples of such branched tryptamines possessing pharmacologically interesting properties have been developed. The α-branched tryptamine LY 156 735 (**10**, Figure 1), for example, is a melatonin agonist that helps to alleviate the symptoms of time shift lag and enhances readaptation of desynchronized circadian rhythms to a new time zone.[14]

Tryptamines with branches at the *β*-carbon as found in various *β*-carboline derivatives (**11**) act as potential drugs against depression anxiety. Most of the known *β*-branched tryptamines are tryptophan derivatives and can be synthesized starting from this essential amino acid. Therefore, not surprisingly, only a few examples of *β*-branched tryptamines are reported, with substituents not possessing the oxidation level of the carboxylic group or with substituents not obtainable from this function. Obviously, there is a need for a method that allows fast access to branched tryptamines as well.

We have previously demonstrated[7] that α-branched tryptamines can be obtained by using terminally disubstituted olefins such as methallylic amines, which can easily be prepared by simple allylation with methallylic chloride. The allylic amines required for the synthesis of *β*-branched tryptamines are obviously less conveniently obtained, and in addition, they bear a stereogenic center. Simple allylation of amines may fail due to poor regioselectivity and problems to control the configuration of the newly formed stereocenter, if required. A well-described access toward chiral allylic amines is the Overman rearrangement of allylic trihalo acetimidates giving protected primary amines.[15] After alkylation, the tertiary

TABLE 3. Synthesis of Branched Tryptamines



entry	olefin **5**	product	yield
1	 **5g**		85% (**8g**)
2	 *rac*-**5h**		54%[b] (*rac*-**8h**)
3	 (+)-**5h** (96%*ee*)		54%[b], 95%*ee*[c] ((+)-**8h**)
4	 (-)-**5h** (96%*ee*)		54%[b], 95%*ee*[c] ((-)-**8h**)

[a] Conditions: (i) 1 equiv of **5**, 1 equiv of phenylhydrazine **6a**, 1 mol % $Rh(acac)(CO)_2$, 5 mol % XANTPHOS, 10 bar CO, 10 bar H_2, THF, 3 days, 80 °C; (ii) 4 wt % H_2SO_4, 2 h, 100 °C. Yield is given for the tandem reaction starting with the olefin. [b] Average of all reactions with **5h**. [c] Determined by HPLC with a Daicel Chiracel OJ.

chiral amine **5g** can be obtained as a racemate. An alternative method to obtain chiral allylic amines was published in 2001 by Takeuchi et. al.[17] Here, regioselective allylic amination of allylic carbonates and acetates has been achieved with an $Ir/P(OPh)_3$ catalyst. In 2002, Hartwig published the first regio- and enantioselective allylic amination.[18] With this methodology, a large number of different allylic amines such as **5h** are accessible with varying amine functionalities, as well as alkyl, homoaryl, and heteroaryl substituents tolerable at the stereocenter. Use of these methods (Overman rearrangement, allylic amination) for selected examples and the tandem hydroformylation/Fischer indole procedure affords *β*-branched indoles in good to excellent yields (Table 3).

While the allylic amination proceeds with high enantiomeric excesses, the stereocenter may epimerize during a tandem hydroformylation/Fischer indolization via reversible double-bond isomerization either by the transition metal catalyst or the acid. The tryptamines obtained from enantiomerically pure allylic amines, however, reveal complete retention of chirality under hydroformylation conditions. This combination of iridium-catalyzed enantioselective allylic amination and tandem hydro-

(14) Nickelsen, T.; Samel, A.; Vejvoda, M.; Wenzel, J.; Smith, B.; Gerzer, R. *Chronobiol. Int.* **2002**, 9, *5*, 915−936.
(15) Overman, L. E. *J. Am. Chem. Soc.* **1974**, *96*, 597.
(16) Anderson, C. E.; Overman, L. E. *J. Am. Chem. Soc*. **2003**, *125*, 12412−12413.
(17) Takeuchi, R.; Ue, N.; Tanabe, K.; Yamashita, K.; Shiga, N. *J. Am. Chem. Soc.* **2001**, *123*, 9525−9534.
(18) Ohmura, T.; Hartwig, J. F. *J. Am. Chem. Soc*. **2002**, *124*, 15164−15165.

formylation/Fischer indole synthesis, in contrast to other methods reported, gives fast access to β-branched tryptamines, which cannot be derived from tryptophan, and therefore opens access to a new class of tryptamine derivatives for biological screenings.

Using the same protocol with branched homoallylic amines leads to branched homotryptamines. The required amines are easily obtained via a combination of Mannich reaction and Wittig olefination or by simple Barbier-type reactions. For the latter a number of different methods have been published to control the absolute configuration of stereocenters. The homoallylic moiety can also be embedded in an exocyclic olefin. If piperidines with an exocyclic double bond are used, 3-(*N*-methyl piperdiyl)-indoles are obtained, containing an important structural element of active agents such as the antimigraine drug LY 334 370 (**1**) or Naratriptan (**2**, Scheme 1).

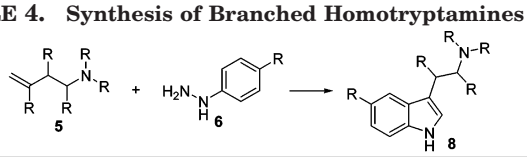
As it can be seen from Table 4, most homotryptamines can be obtained in good to excellent yields. Halide substituents are tolerated, allowing further derivatization with common cross-coupling methodologies. In this respect, substrate **8o** may act as a valuable intermediate for the synthesis of Naratriptan (**2**).

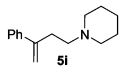
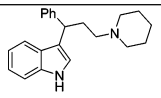
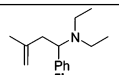
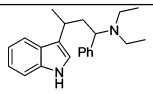
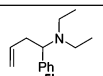
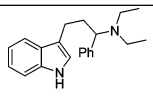
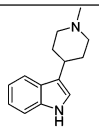
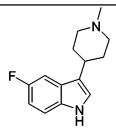
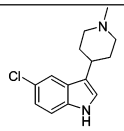
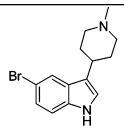
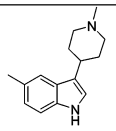
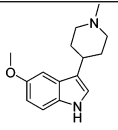
Second-Generation Protocol for the Tandem Hydroformylation/Fischer Indolization. So far, our protocol for tandem hydroformylation/Fischer indole synthesis gives fast and convenient access to a large number of differently substituted tryptamines. However, the method requires a change of solvent to complete the procedure, although there is no need for a purification of the aryl hydrazones obtained. Therefore, it is desirable to develop a protocol that allows direct access to tryptamine derivatives from amino olefins. This requires a solvent with good solubility for all reagents and reactants. Since alcohol solvents failed in test reactions, we concentrated on water as the solvent of choice. Sulfuric acid in water allows a smooth conversion of the aryl hydrazones to tryptamines and has the advantage of being environmentally benign. Solubility of the rhodium-based hydroformylation catalyst in water and even in aqueous sulfuric acid can be achieved by using sulfonated ligands such as TPPTS (**12**) or the analogous derivative **13** of XANTPHOS.We tested this modification with allylic and homoallylic substrates mostly containing the piperidyl or the piperazinyl moiety duo to their pharmacological relevance. As shown in Table 5, tandem hydroformylation/Fischer indole synthesis in water gives in all cases excellent results. For 3-piperidyl indoles (entries 1−5), no further purification is required. It is worth mentioning that sensitive bromine substituents are known to be cleaved under Fischer indole conditions. Under the conditions used here the bromine substituent is maintained, even at prolonged reaction times during which the aryl halide is treated with mineral acid under harsh conditions. Clearly, regioselective tandem hydroformylation/Fischer indole synthesis in water is not limited to disubstituted terminal olefins as the substrate. Conversion of allylic and homoallylic amines also gives good to excellent yields of the desired tryptamine analogues. High regioselectivities can also be achieved with sulfonated XANTPHOS **13**.

Pharmaceuticals. Finally, we tested the tandem hydroformylation/Fischer indole procedure in the synthesis of the three antimigraine drugs LY 349 950 (**14**), LY 334 370 (**1**), and L 775 606 (**4**). The results are compiled in Table 6.

Although synthesis of the required aryl hydrazines has been reported,[19,20] it turned out to be difficult to obtain the products with sufficient purity. Obviously, the clas-

TABLE 4. Synthesis of Branched Homotryptamines



entry	olefin **5**	hydrazine **6**	product	yield
1	 **5i**	**6a** (R=H)		41% (**8i**)
2	 **5j**	**6a** (R=H)		51%[a] (**8j**)
3	 **5k**	**6a** (R=H)		81%[b] (**8k**)
4	 **5l**	**6a** (R=H)		78%[c] (**8l**)
5	 **5l**	**6e** (R=F)		65%[c] (**8m**)
6	 **5l**	**6f** (R=Cl)		85%[c] (**8n**)
7	 **5l**	**6g** (R=Br)		quant.[c] (**8o**)
8	 **5l**	**6h** (R=CH_3)		66%[c] (**8p**)
9	 **5l**	**6b** (R=OCH_3)		85%[c] (**8q**)

[a] Conditions: (i) 1 equiv of **5**, 1 equiv of **6**, 1 mol % $Rh(acac)(CO)_2$, 50 bar CO, 10 bar H_2, THF, 3 days, 120 °C; (ii) 4 wt % H_2SO_4, 2 h, 100 °C. Yield is given for the tandem reaction starting with the olefin. [b] Conditions: (i) 1 equiv of **5**, 1 equiv of **6**, 0.3 mol % $Rh(acac)(CO)_2$, 1.5 mol % XANTPHOS, 10 bar CO, 10 bar H_2, THF, 3 days, 70 °C; (ii) 4 wt % H_2SO_4, 2 h, 100 °C. Yield is given for the tandem reaction starting with the olefin. [c] Conditions: (i) 1 equiv of **5**, 1 equiv of **6**, 0.3 mol % $Rh(acac)(CO)_2$, 50 bar CO, 10 bar H_2, THF, 3 days, 100 °C; (ii) 4 wt % H_2SO_4, 2 h, 100 °C. Yield is given for the tandem reaction starting with the olefin.

SCHEME 3. Ligands for the Tandem Reaction in Water

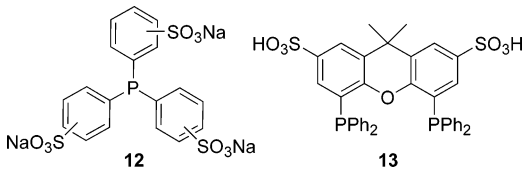
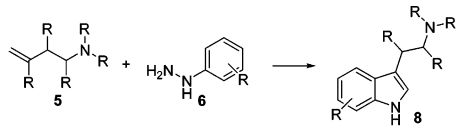
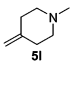
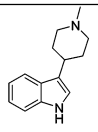
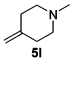
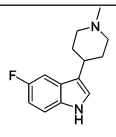
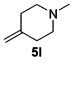
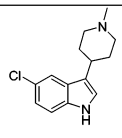
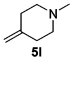
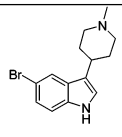
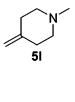
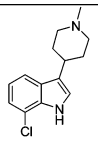
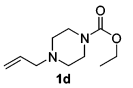
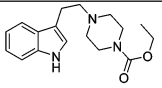
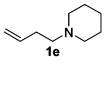
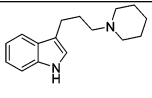
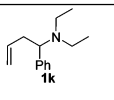
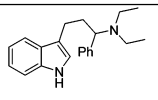


TABLE 5. Tandem Hydroformylation/Fischer Indole Synthesis in Water

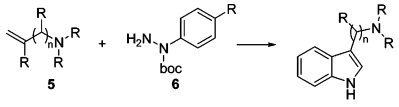


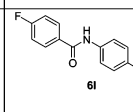
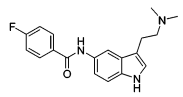
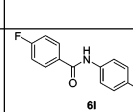
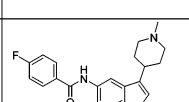
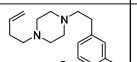
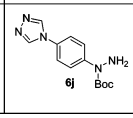
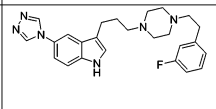
entry	olefin **5**	hydrazine **6**	product	yield
1		**6a** (R=4-H)		80% (**8l**)
2		**6e** (R=4-F)[a]		95%[b] (**8m**)
3		**6f** (R=4-Cl)[a]		quant.[b] (**8n**)
4		**6g** (R=4-Br)[a]		96%[b] (**8o**)
5		**6h** (R=2-Cl)[a]		96%[b] (**8r**)
6		**6a** (R=4-H)		quant.[c] (**8d**)
7		**6a** (R=4-H)		50%[c] (**8e**)
8		**6a** (R=4-H)		quant.[c] (**8k**)

[a] Hydrochlorides were used directly. [b] Conditions: 1 equiv of **5**, 1 equiv of **6**, 0.3 mol % $Rh(acac)(CO)_2$, 1.5 mol % **12**, 50 bar CO, 10 bar H_2, 4 wt % H_2SO_4, 3 days, 100 °C. [c] Conditions: 2 equiv of **5**, 1 equiv of **6**, 0.3 mol % $Rh(acac)(CO)_2$, 3 mol % **13**, 10 bar CO, 10 bar H_2, 4 wt % H_2SO_4, 3 days, 100 °C.

sical approach of aniline diazotation and reduction of the resulting diazonium salts with bisulfites or tin dichloride suffers from low selectivity. Furthermore, purification of aryl hydrazines is hard to manage. Therefore, we decided to use the Goldberg reaction to synthesize the required hydrazines starting from the corresponding aryl iodides

TABLE 6. Synthesis of Migraine Drug Candidates



entry	olefin **5**	hydrazine **6**	product	yield
1				44%[a] (**14**)
2				95%[b] (**1**)
3				51%[a] (**4**)

[a] Conditions: (i) 1 equiv of **5**, 1 equiv of **6**, 1 mol % $Rh(acac)(CO)_2$, 5 mol % XANTPHOS, 10 bar CO, 10 bar H_2, THF, 3 days, 70 °C; (ii) 4 wt % H_2SO_4, 2 h, 100 °C. Yield is given for the tandem reaction starting with the olefin. [b] Conditions: 1 equiv of **5**, 1 equiv of **6**, 0.3 mol % $Rh(acac)(CO)_2$, 1.5 mol % TPPTS, 50 bar CO, 10 bar H_2, 4 wt % H_2SO_4, 3 days, 100 °C.

under copper catalysis in good yields. The α-Boc-protected aryl hydrazines are no longer prone to oxidation and can easily be purified by LC. Olefin (**5**) and hydrazine (**6**) are assembled in the tandem hydroformylation/Fischer indole synthesis as the final step, giving the desired drug candidates in good to excellent yield. Neither hydrolysis of the amide bonds in LY 334 950 (**14**) and LY 334 370 (**1**) nor hydrogenation of the imine−enamine pattern in L 775 606 (**4**) is observed.

Conclusion

The combination of modern allylation chemistry with the tandem hydroformylation/Fischer indolization is an efficient and highly diversity-oriented strategy for the synthesis of tryptamine analogues. Both linear as well as branched olefins can be used, giving nonbranched and branched tryptamines and homotryptamines. Stereocenters close to the olefinic bond can be tolerated and do not epimerize, leading to enantiomerically pure β-branched tryptamines. In many cases, the obtained products do not require further purification, since tandem hydroformylation/Fischer indole synthesis proceeds with high selectivity. The use of sulfonated ligands allows this tandem reaction to be conducted in water, making it environmentally benign. With this new methodology, simple model tryptamines as well as recent drug development candidates can be synthesized more conveniently than with previously reported methodologies. Usually, the number of required steps is reduced, since simple functional group transformations (e.g., hydrogenations, homologization, reduction, oxidation, protection) are re-

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duced to a minimum. A protection of the in situ-generated aldehyde is achieved by trapping the aldehyde as a hydrazone. This modular approach is remarkable since substituents at C3 and C5, the type of the amine moiety, and the distance from the amine moiety to the indole core are assembled in the final synthetic step. Therefore, this approach is valuable for the synthesis of substance libraries with high diversity.

Experimental Section

Materials. All reagents and solvents were dried and purified before use by the usual procedures. $Rh(acac)(CO)_2$, XANTPHOS, *N*,*N*-dimethylprop-2-en-1-amine, and phenylhydrazine were purchased.

Tandem Hydroformylation/Hydrazone Formation. Dimethyl-[4-(phenyl-hydrazono)-butyl]-amine (7a). In a typical procedure *N*,*N*-dimethylprop-2-en-1-amine (679 mg, 7.97 mmol), phenylhydrazine (862 mg, 7.97 mmol), $Rh(acac)(CO)_2$ (6.2 mg, 0.3 mol %), and XANTPHOS (69 mg, 0.15 mol %) in anhydrous THF (6.1 g, 10 wt % olefin) were added in an autoclave. The autoclave was pressurized with 10 bar H_2 and 10 bar CO. After the mixture was stirred for 68 h (the reaction is stirred magnetically; with a stirrer that mixes the gas phase and the liquid phase intensively, the reaction time can be reduced greatly according to our experience) at 70 °C, the solvent was removed to give dimethyl-[4-(phenyl-hydrazono)-butyl]-amine (1.64 g, 100%) without further purification. Analytical data was obtained from an inseparable mixture of *E*/*Z* isomers. ^{1}H NMR: ($CDCl_3$, 400 MHz) δ = 1.69−1.72 (2H, CH_2); 2.22 (s, 3H, CH_3); 2.28−2.33 (4H, 2 x CH_2); 6.52−6.81 (1H, CH); 6.97−7.03 (3H, 3 x CH); 7.20−7.23 (2H, 2 x CH). Major isomer: ^{13}C NMR: ($CDCl_3$, 100 MHz) δ = 23.6 (CH_2); 29.8 (CH_2); 44.8 (2 x CH_3); 56.4 (CH_2); 112.2 (2 x CH); 118.8 (CH_2); 128.8 (2 x CH); 140.6 (CH); 146.1 (C). Minor isomer: ^{13}C NMR: ($CDCl_3$, 100 MHz) δ = 23.6 (CH_2); 24.8 (CH_2); 45.3 (2 x CH_3); 58.9 (CH_2); 112.2 (2 x CH); 119.0 (CH_2); 128.8 (2 x CH); 140.1 (CH); 145.3 (C). IR: $\tilde{\nu}$ [cm^{-1}] = 2943 (vs), 2779 (s), 1603 (vs), 1496 (vs), 1259 (vs), 1115 (s), 750 (vs), 694 (vs). HRMS: found M^+ 205.1580, $C_{12}H_{19}N_3$ requires M^+, 205.1579. Elementary analysis: found C 69.67, H 9.14, N 19.72; $C_{12}H_{19}N_3$ requires C 70.20, H 9.33, N 20.47.

First-Generation Protocol of Tandem Hydroformylation/Fischer Indole: [2-(1*H*-Indol-3-yl)-ethyl]-dimethyl-amine (8a). In a typical procedure, *N*,*N*-dimethylprop-2-en-1-amine (679 mg, 7.97 mmol), phenylhydrazine (862 mg, 7.97 mmol), $Rh(acac)(CO)_2$ (6 mg, 0.3 mol %), and XANTPHOS (69 mg, 1.5 mol %) in anhydrous THF (6.1 g, 10 wt % olefin) were added in an autoclave. The autoclave was pressurized with 10 bar H_2 and 10 bar CO. After the mixture was stirred for 3 days (the reaction is stirred magnetically; with a stirrer that mixes the gas phase and the liquid phase intensively, the reaction time can be reduced greatly according to our experience) at 70 °C, the solvent was evaporated, and the residue was taken up in H_2SO_4 (30 mL, 4 wt % in water). After the mixture was stirred for 2 h under reflux, NH_3 (10 mL, 30 wt % in water) was added, and the mixture was extracted with EtOAc. The solvent was evaporated to give [2-(1*H*-indol-3-yl)-ethyl]-dimethyl-amine (1.5 g, 100%) without further purification. NMR data fit with literature.[21]

Second-Generation Protocol for the Tandem Hydroformylation/Fischer Indole Synthesis in Water. In a typical experiment, 1-methyl-4-methylenepiperidine (259 mg, 2.33 mmol), phenylhydrazine (252 mg, 2.33 mmol), $Rh(acac)(CO)_2$ (1.8 mg, 0.3 mol %), and TPPTS (20 mg, 1.5 mol %) in H_2SO_4 (9.3 g, 4 wt % in water, 2.5 wt % olefin) were added in an autoclave. The autoclave was pressurized with 10 bar H_2 and 50 bar CO. After the mixture was stirred for 3 days (the reaction is stirred magnetically; with a stirrer that mixes the gas phase and the liquid phase intensively, the reaction time can be reduced greatly according to our experience) at 100 °C, NH_3 (10 mL, 30 wt % in water) was added, and the mixture was extracted with EtOAc. The solvent was evaporated to give 3-(1-methylpiperidin-4-yl)-1*H*-indole (400 mg, 80%) without further purification.

***N*-[3-(2-Dimethylamino-ethyl)-1*H*-indol-5-yl]-4-fluoro-benzamide (14).** The first-generation protocol was followed with *N*,*N*-dimethylprop-2-en-1-amine (262 mg, 3.1 mmol), *N*-[4-(4-fluoro-benzoylamino)-phenyl]-hydrazinecarboxylic acid *tert*-butyl ester (1.06 g, 3.1 mmol), $Rh(acac)(CO)_2$ (8 mg, 1 mol %), and XANTPHOS (89 mg, 5 mol %). The crude product was purified by chromatography (silica, CH_2Cl_2, cyclohexane, NEt_3) to give *N*-[3-(2-(dimethylamino)-ethyl)-1*H*-indol-5-yl]-4-fluoro-benzamide (440 mg, 44%). ^{1}H NMR: ($CDCl_3$, 500 MHz) δ = 2.30 (s, 6H, 2 x CH_3); 2.62 (t, 2H, J = 8.0 Hz, CH_2); 2.87 (t, 2H, J = 8.0 Hz, CH_2); 6.94 (s, 1H, CH); 7.11 (dd, 2H, J = 8.7 Hz, J = 8.2 Hz, 2 x CH); 7.20 (d, 1H, J = 8.7 Hz, CH); 7.26 (s, 1H, CH); 7.81 (s, 1H, CH); 7.90 (bs, 2H, 2 x CH); 8.13 (s, 1H, NH); 8.59 (s, 1H, NH). ^{13}C NMR: ($CDCl_3$, 125 MHz) δ = 23.4 (CH_2); 45.3 (2 x CH_3); 60.0 (CH_2); 114.0 (CH); 111.6 (CH); 114.2 (C); 115.6 (d, 2C, J_{C-F} = 21 Hz, 2 x CH); 116.9 (CH); 122.8 (CH); 127.6 (C); 129.4 (d, 2C, J_{C-F} = 8 Hz, 2 x CH); 129.7 (C); 131.4 (C); 134.0 (C); 163.7 (C); 165.3 (d, 1C, J_{C-F} = 251 Hz, C). IR: $\tilde{\nu}$ [cm^{-1}] = 3291 (s); 2942 (m); 2823 (m); 1644 (vs); 1602 (vs); 1540 (s); 1481 (vs); 1330 (m); 1232 (s); 1159 (s); 850 (s); 796 (m). HRMS: found $[M + H]^+$ 326.1689 $C_{19}H_{20}FN_3O$ requires $[M + H]^+$, 326.1709.

4-Fluoro-*N*-[3-(1-methyl-piperidin-4-yl)-1*H*-indol-5-yl]-benzamide (1). The second-generation protocol was followed with 1-methyl-4-methylene-piperidine (158 mg, 1.42 mmol), *N*-[4-(4-fluoro-benzoylamino)-phenyl]-hydrazinecarboxylic acid *tert*-butyl ester (491 mg, 1.42 mmol), $Rh(acac)(CO)_2$ (3.7 mg, 1 mol %), and TPPTS (40 mg, 5 mol %) to give 4-fluoro-*N*-[3-(1-methyl-piperidin-4-yl)-1*H*-indol-5-yl]-benzamide (474 mg, 95%) without further purification.^{1}H NMR: ($CDCl_3$, 500 MHz) δ = 1.68 (q, 2H, J = 11.8 Hz, 2 x CH_2); 1.86 (d, 2H, J = 11.2 Hz, CH_2); 1.96 (t, 2H, J = 11.7 Hz, CH_2); 2.23 (s, 3H, CH_3); 2.60 (t, 1H, J = 11.0 Hz, CH); 2.82 (d, 2H, J = 9.7 Hz, CH_2); 6.71 (s, 1H, CH); 6.98 (bs, 2H, 2 x CH); 7.11 (d, 1H, J = 8.3 Hz, CH); 7.18 (d, 1H, J = 8.3 Hz, CH); 7.84 (bs, 2H, 2 x CH); 7.88 (s, 1H, CH); 8.61 (bs, 1H, NH); 9.27 (s, 1H, NH). ^{13}C NMR: ($CDCl_3$, 125 MHz) δ = 32.4 (CH); 32.5 (2 x CH_2); 46.1 (CH_3); 56.0 (2 x CH_2); 111.5 (CH); 112.2 (CH); 115.4 (d, 2C, J_{C-F} = 21 Hz, 2 x CH_2); 116.8 (CH); 120.6 (C); 121.1 (CH); 126.6 (C); 129.3 (C); 129.4 (d, 2C, J_{C-F} = 8 Hz, 2 x CH); 131.2 (C); 134.2 (C); 164.5 (d, 1C, J = 251 Hz, CC); 165.3 (C). IR: $\tilde{\nu}$ [cm^{-1}] = 3291 (s); 2933 (s); 2850 (m); 1646 (vs); 1602 (s); 1540 (s); 1481 (vs); 1328 (m); 1232 (s); 1159 (s); 850 (s); 796 (m). HRMS found $[M]^+$ 351.1729 $C_{21}H_{22}FN_3O$ requires $[M]^+$, 351.1711.

3-(3-{4-[2-(3-Fluoro-phenyl)-ethyl]-piperazin-1-yl}-propyl)-5-[1,2,4]triazol-4-yl-1*H*-indole (4). The first-generation protocol was followed with 1-but-3-enyl-4-[2-(3-fluoro-phenyl)-ethyl]-piperazine (455 mg, 1.7 mmol), *N*-(4-[1,2,4]triazol-4-yl-phenyl)-hydrazinecarboxylic acid *tert*-butyl ester (477 mg, 1.7 mmol), $Rh(acac)(CO)_2$ (4.5 mg, 1 mol %), and XANTPHOS (50 mg, 5 mol %). The crude product was purified by chromatography (silica, CH_2Cl_2, EtOH, NEt_3) to give 3-(3-{4-[2-(3-fluoro-phenyl)-ethyl]-piperazin-1-yl}-propyl)-5-[1,2,4]triazol-4-yl-1*H*-indole (382 mg, 51%). ^{1}H NMR: ($CDCl_3$, 500 MHz) δ = 1.27 (t, 2H, J = 7.2 Hz, CH_2); 1.41 (t, 2H, J = 7.2 Hz, CH_2); 1.89 (p, 2H, J = 7.5 Hz, CH_2); 2.44 (t, 2H, J = 7.5 Hz, CH_2); 2.55−2.58 (4H, 2 x CH_2); 2.74−2.78 (6H, 3 x CH_2); 6.84 (d, 1H, J = 8.5 Hz, CH); 6.88 (d, 1H, J = 8.5 Hz, CH); 6.94 (d, 1H, J = 7.5 Hz, CH); 7.05 (d, 1H, J = 8.5 Hz, CH); 7.14 (s, 1H, CH); 7.19 (d, 1H, J = 7.5 Hz, CH); 7.47 (d, 1H, J = 8.5 Hz, CH); 7.52 (s, 1H, CH); 8.44 (s, 2H, 2 x CH); 9.51 (s, 1H, NH).^{13}C NMR: ($CDCl_3$, 125 MHz) δ = 22.6 (CH_2); 27.0 (CH_2); 33.0 (CH_2); 52.8

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(2 x CH_2); 53.0 (2 x CH_2); 58.0 (CH_2); 59.7 (CH_2); 112.6 (CH); 112.6 (d, 1C, J_{C-F} = 21 Hz, CH); 113.2 (CH); 115.4 (d, 1C, J_{C-F} = 19 Hz, CH); 116.4 (C); 116.5 (CH); 124.3 (CH); 125.8 (C); 127.9 (C); 128.1 (d, 1C, J_{C-F} = 11 Hz, CH); 129.7 (d, 1C, J_{C-F} = 8 Hz, CH); 136.1 (C); 142.5 (2 x CH); 142.8 (d, 1C, J_{C-F} = 6 Hz, C); 162.6 (d, 1C, J_{C-F} = 246 Hz, C). IR: $\tilde{\nu}$ [cm^{-1}] = 3126 (s); 2940 (vs); 2811 (vs); 2773 (s); 1616 (s); 1587 (vs); 1488 (vs); 1448 (vs); 1267 (s); 1249 (vs); 1157 (s); 1139 (vs); 1093 (vs); 784 (s); 730 (vs).

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Supporting Information Available: Full experimental data for all starting material and all indoles. This material is available free of charge via the Internet at http://pubs.acs.org.

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