Asymmetric Synthesis

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Asymmetric Synthesis of Tetracyclic Pyrroloindolines and Constrained Tryptamines by a Switchable Cascade Reaction

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Abstract: *The interrupted Fischer indole synthesis of arylhydrazines and biocatalytically generated chiral bicyclic imines selectively affords either tetracyclic pyrroloindolines or tricyclic tryptamine analogues depending on the reaction conditions. We demonstrate that the reaction is compatible with a variety of functional groups. The products are obtained in high optical purity and in reasonable to good yield. We present a plausible reaction mechanism to explain the observed reaction outcome depending on the stoichiometry of the acid mediator. To demonstrate the synthetic utility of our method, pharmaceutically relevant examples of both product classes were synthesized in highly efficient reaction sequences, including a phenserine analogue as a potential cholinesterase inhibitor and constrained tryptamine derivatives as selective inhibitors of the 5-HT$_6$ serotonin receptor and the TRPV1 ion channel.*

Since the dawn of modern chemistry, nature has served as an inspiration for the development of new reactions, molecules, and materials. In a chemical biology context, the biology-oriented synthesis (BIOS) concept was introduced by Waldmann et al. to suggest natural product scaffolds as starting points in the quest to find novel bioactive compounds.[1] Indeed, this strategy has provided several new molecular probes for the selective and reversible modulation of cellular functions.[2] On the other hand, nature also provides essential tools for the efficient synthesis of complex bioactive compounds in the form of enzymes that offer unrivaled chemo-, regio-, and stereoselectivity. For example, we recently employed an engineered monoamine oxidase[3] in an efficient synthesis of the hepatitis C drug telaprevir (Scheme 1).[4] Our success in this area prompted us to investigate the utility of biocatalytically generated chiral building blocks such as **2** in other cascade-type reactions by considering them as amino aldehyde synthons.

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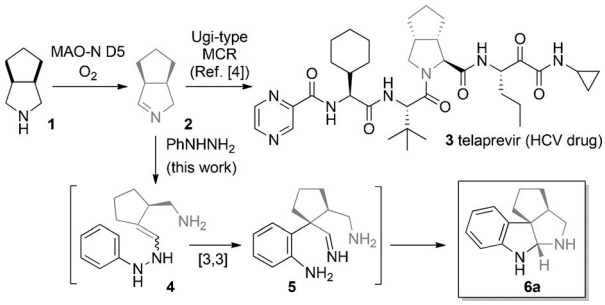

Scheme 1. Biocatalytic generation of chiral bicyclic imine (−)-**2** and conversion into telaprevir (**3**) and tetracyclic pyrroloindolines **6**. MCR = multicomponent reaction. HCV = hepatitis C virus.

Within the rich molecular diversity of natural products, indole derivatives take a privileged position.[5] From a synthetic perspective, the available range of synthetic strategies to construct and modify indoles led us to investigate the possibilities to combine readily available reactants in novel cascade reactions to directly access complex polycyclic, natural-product-inspired compounds in a stereoselective fashion.

Regarding **2** as a masked amino aldehyde, we hypothesized its reaction with arylhydrazines would result in an interrupted Fischer indole synthesis[6] via intermediate **5**, which would undergo a double cyclization to afford **6** with a *cis* junction of both [3.3.0] bicyclic systems (Scheme 1).[7] Thus, we started our investigations with the benchmark reaction between cyclic imine **2** and phenylhydrazine (**7a**). To our delight, the envisioned stereoselective interrupted Fischer indolization proceeded smoothly in various solvents with a range of Brønsted acids (for details, see the Supporting Information Table S1). Optimal conversion of (±)-**2** into the desired tetracyclic pyrroloindoline **6a** was achieved with phenylhydrazine hydrochloride (**7b**) and TsOH (1.0 equiv) in toluene with microwave heating to 130 °C for 30 min. We next explored the scope of the reaction with respect to the arylhydrazine employing (±)-**2**[3] (Scheme 2).[8] Gratifyingly, we found that various *para*-substituted arylhydrazines could be converted into the corresponding pyrroloindolines **6b–g** in modest to good yield (18–73 %). Electron-deficient arylhydrazines typically led to lower yields of product, most likely because of slower formation of the hydrazone intermediate and/or slower sigmatropic rearrangement. Additionally, *meta*-substituted arylhydrazines could be used to obtain the corresponding pyrroloindolines in modest to reasonable yield (26–52 %). In all cases, the 6-substituted regioisomers **6h–k** were the major products, accompanied by varying amounts of the 4-substituted isomers **6h′–k′**. We recognized that the regioselectivity is mainly governed by the steric

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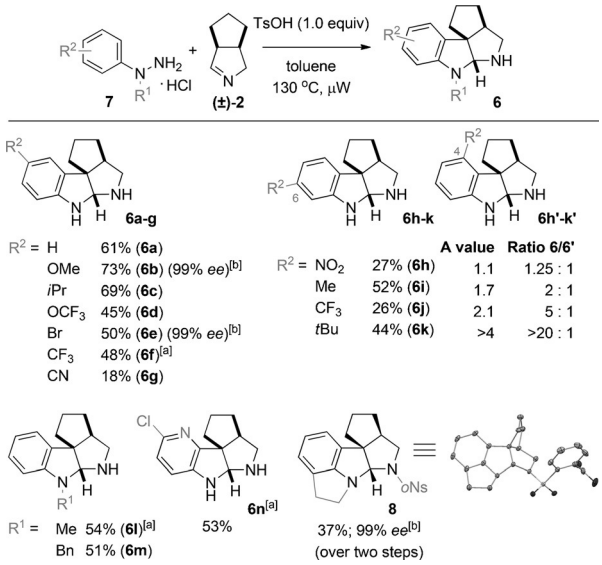
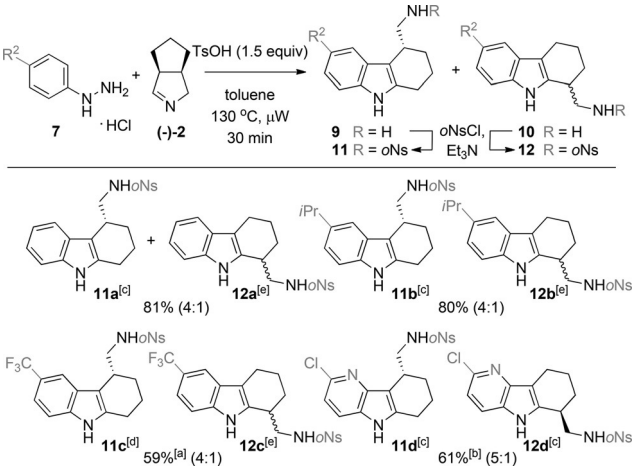


Scheme 2. Synthesis of diverse pyrroloindolines **6**. [a] Free hydrazine used (instead of HCl salt) in combination with TsOH (2.0 equiv). [b] (−)-**2** was used. Bn = benzyl.

properties of the *meta* substituents, most accurately described as the Winstein–Holness A values.[9] Also N_α-substituted arylhydrazines could be used to obtain the corresponding pyrroloindolines **6l**,**m** in reasonable yield (51–54 %). Notably, also the pyrroloazaindoline **6n** was accessible as a single regioisomer via this route in reasonable yield. As expected, the use of enantiopure (−)-**2** (99 % *ee*) led to the formation of **6b** and **6e** in excellent optical purity (99 % *ee*). Finally, the pentacyclic derivative **8** could be isolated and crystallized in optically pure form after *o*-nosylation and its structure was corroborated by X-ray crystallography.[10]

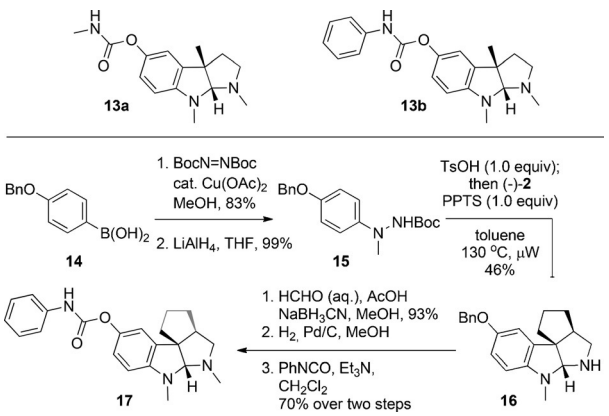
During our optimization of the reaction between **2** and **7** we discovered that the yield of **6** is highly dependent on the stoichiometry of the acid mediator. We found that, under otherwise identical conditions, the use of 1.5 equiv of TsOH (instead of 1.0 equiv) led to full conversion into a different product, that is, tricyclic tryptamine derivative **9**, along with its regioisomer **10** (Scheme 3). Compounds **9** and **10** were most likely formed through a rearrangement of **6** (see below). Under these conditions, **6** was not detected in the crude reaction product. We soon discovered that the poorly separable regioisomeric mixture of **9** and **10** could be subjected to in situ *o*-nosylation to afford compounds **11** and **12** in a ratio of about 4:1, which were found to be readily separable by flash chromatography (Scheme 3). This rearrangement proved quite general, as demonstrated for compounds **11a–d**/**12a–d** (Scheme 3). In addition to relatively electron-rich systems (**11a,b**/**12a,b**), also the electron-deficient products **11c**/**12c** and even the heterocyclic derivatives **11d**/**12d** were isolated after this two-step procedure in very good yields, considering the complexity of the transformation. Interestingly, while products **11a–d** and **12d** were isolated in excellent optical purity (98–99 % *ee*), the regioisomers **12a–c** were found to be partially or completed racemized.[11]

With selective routes to both **6** and **9** in hand, we set out to investigate applications of our method to the synthesis of pharmaceutically relevant compounds. Pyrroloindolines are



Scheme 3. Synthesis of tricyclic tryptamine analogues **11** and regioisomers **12**. [a] Free hydrazine used (instead of the HCl salt) in combination with TsOH (2.5 equiv). [b] Free hydrazine used; TsOH (3.5 equiv), 150 °C, 60 min. [c] *ee* = 99 % (**11a**,**b**), 98 % (**11d**, **12d**). Determined by comparison with the racemate using HPLC on a chiral stationary phase. [d] Presumed optically pure by detection of a single peak by HPLC (on a chiral stationary phase) and in analogy to **11a**, **11b**, and **11d**. [e] (Partially) racemized as determined by detection of two peaks by HPLC analysis (chiral stationary phase). *o*Ns = 2-nitrobenzenesulfonyl.

frequent structural motifs in naturally occurring alkaloids such as the acetylcholine esterase inhibitor physostigmine (**13a**; Scheme 4). Its semisynthetic derivative phenserine (**13b**) advanced as far as phase III clinical trials for the treatment of Alzheimer's disease (AD).[12] We soon realized that our method provided rapid and efficient stereoselective access to the novel ring-fused physostigmine/phenserine analogue **17**. As initial studies revealed that post-cascade methylation of the aromatic NH is challenging, we opted to employ an N_α-methylated hydrazine derivative in the cascade process. We discovered that mono-N_β-Boc-protected N_α-methylhydrazine **15** (Boc = *tert*-butoxycarbonyl) could be conveniently prepared by Cu^{II}-catalyzed addition of commercial boronic acid **14** to di-*tert*-butyl azodicarboxylate[13] followed by chemoselective reduction of the N_α-Boc group. After in situ Boc deprotection (1.0 equiv TsOH, 60 °C, 1 h), the cascade reaction proceeded smoothly, in this case with



Scheme 4. Synthesis of phenserine analogue **17**.

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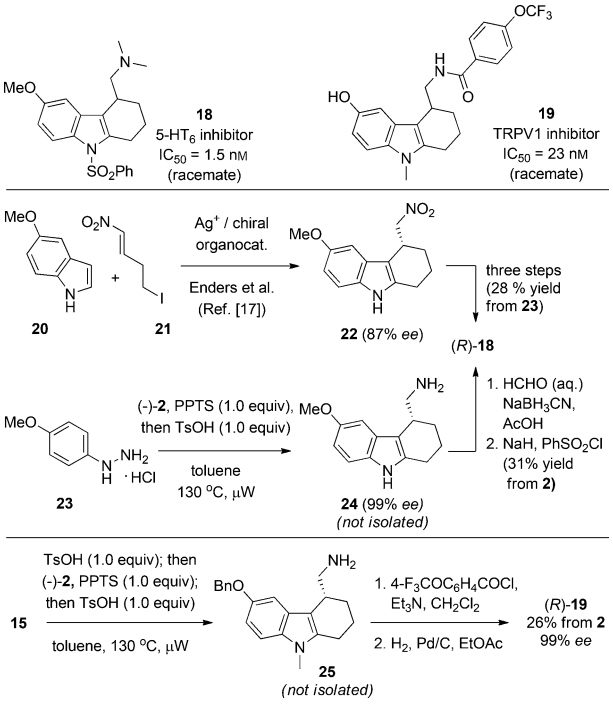
1.0 equiv of PPTS (pyridinium *p*-toluenesulfonate) to provide a cleaner conversion into **16**. Subsequent *N*-methylation, hydrogenolysis of the benzyl ether, and carbamate formation afforded phenserine analogue **17**.

Tricyclic constrained tryptamine analogues have been reported as potent and selective inhibitors of serotonin[14] and melatonin[15] receptors as well as the TRPV1 (transient receptor potential vanilloid 1) ion channel,[16] leading to several conceivable therapeutic applications of this compound class. Compound (±)-**18** (Scheme 5), a constrained analogue of the lead compound MS-245 (1-benzenesulfonyl-3-(2-dimethylamino)ethyl-5-methoxyindole), is a potent 5-HT_6 receptor inhibitor ($IC_{50} = 1.5$ nM).[14] Recently, Enders and co-workers described the asymmetric synthesis of (*R*)-**18** by an organocatalytic cascade reaction of 5-methoxyindole (**20**) and iodonitroalkene **21** to give **22**, which could be converted in a three-step sequence into (*R*)-**18** (Scheme 5).[17] We envisioned that we could access (*R*)-**18** in an efficient three-step sequence using our novel cascade process. Thus, arylhydrazine **23** was reacted with (−)-**2** to give tricyclic tryptamine derivative **24**. In this case, we found the reaction proceeded most smoothly in a one-pot, two-stage process involving the interrupted Fischer indolization (1.0 equiv PPTS, 130 °C, 30 min) and the rearrangement (1.0 equiv TsOH, 130 °C, 30 min). The resulting tryptamine derivative **24** was then converted into (*R*)-**18** (99% *ee*) by *N*-methylation and sulfonylation of the indole nucleus. Notably, our route afforded (*R*)-**18** in higher yield, with a higher *ee* value, and in a more time- and step-efficient manner than the route of Enders et al.

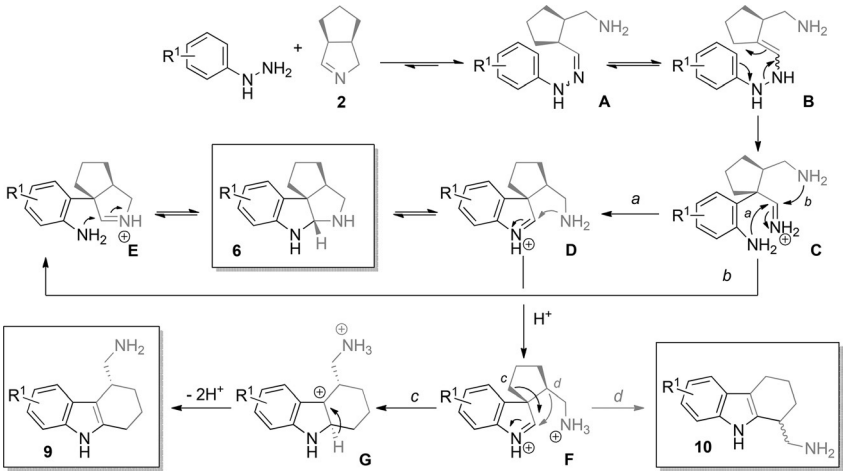
Tricyclic tryptamine derivative (±)-**19** has been reported as a potent and selective inhibitor of the TRPV1 ion channel, which has been implicated in the treatment of neuropathic pain.[16] We envisioned the application of our cascade method to the stereoselective synthesis of (*R*)-**19**. Indeed, the cascade reaction of **15** and (−)-**2** with in situ Boc deprotection (1.0 equiv TsOH, toluene, 60 °C, 1 h) followed by the conditions developed for **24** (1.0 equiv PPTS, 130 °C, 30 min, then 1.0 equiv TsOH, 130 °C, 30 min) afforded **25**. Acylation followed by hydrogenolysis of the benzyl ether then furnished (*R*)-**19** in 26 % overall yield from **2** with 99 % *ee*.

Based on our experimental observations we propose the following mechanism for the switchable cascade reaction described above (Scheme 6). As envisioned, imine **2** undergoes a "transimination" reaction with the arylhydrazine to afford hydrazone intermediate **A** which is in tautomeric equilibrium with enehydrazine intermediate **B**.[18] A subsequent [3,3]-sigmatropic rearrangement produces **C** which undergoes intramolecular addition of either the aromatic (pathway *a*) or aliphatic (pathway *b*) amine to the iminium moiety to give possible intermediates **D** and **E**, respectively, with loss of an ammonium ion. Both **D** and **E** may undergo a second intramolecular addition to give (protonated) **6**. Plausibly, the latter three species (**D**, **E**, and protonated **6**) are in dynamic equilibrium under the reaction conditions. Only when additional strong acid is present, intermediate **D** can undergo a second protonation to bivalent cation **F**.[19] This highly reactive intermediate can undergo a Plancher rearrangement[20] via either pathway *c* or *d*, with both sterics and electronics favoring pathway *c* leading to carbocationic intermediate **G**. Loss of two protons finally affords **9**. A similar mechanism following pathway *d* produces isomer **10**.[11]

In conclusion, we have developed a cascade reaction of arylhydrazines and chiral bicyclic imine **2** involving an interrupted Fischer indolization. The reaction selectively affords either tetracyclic pyrroloindolines **6** or tricyclic tryptamine derivatives **9** depending on the stoichiometry of the acid mediator. Biocatalytic production of imine **2** allows efficient control over the overall asymmetry of the reaction.



Scheme 5. Stereoselective synthesis of serotonin receptor inhibitor **18** and TRPV1 inhibitor **19**.



Scheme 6. Proposed mechanism for the formation of **6**, **9**, and **10**.

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Medicinally relevant examples of both product classes were produced in excellent optical purity by short reaction sequences. These findings underline the importance of both rational design and serendipity in the development of novel reactions for the efficient construction of complex molecular targets.

Experimental Section

General procedure for the synthesis of pyrroloindolines **6**: Hydrazine hydrochloride **7** (0.26 mmol, 1.05 equiv) and *p*-toluenesulfonic acid monohydrate (0.25 mmol, 1.0 equiv) were added to a solution of 1-pyrroline **2** (0.25 mmol, 1.0 equiv) in toluene (0.1M). The reaction mixture was stirred for 30 min at 130 °C under microwave irradiation. The suspension was cooled to RT, washed with saturated aqueous Na_2CO_3/brine (3:1, 20 mL), extracted with CH_2Cl_2 (2 × 10 mL), dried over Na_2SO_4, and concentrated under reduced pressure. The crude product was purified by flash chromatography.

General procedure for the synthesis of tryptamine analogues **11** *and* **12**: Hydrazine hydrochloride **7** (0.53 mmol, 1.05 equiv) and *p*-toluenesulfonic acid monohydrate (0.75 mmol, 1.5 equiv) were added to a solution of 1-pyrroline **2** (0.50 mmol, 1.0 equiv) in toluene (0.1M). The reaction mixture was stirred for 30 min at 130 °C under microwave irradiation. The suspension was cooled to RT, dissolved in methanol (3 mL), washed with saturated aqueous Na_2CO_3 (20 mL), extracted with CH_2Cl_2 (3 × 15 mL), dried over Na_2SO_4, and concentrated under reduced pressure. The crude product was dissolved in CH_2Cl_2 (0.1M), after which Et_3N (1.2 equiv) and *o*-nosyl chloride (1.2 equiv) were added. The reaction mixture was stirred for 2 h at RT, washed with brine (20 mL), extracted with CH_2Cl_2 (3 × 15 mL), dried over Na_2SO_4, and concentrated under reduced pressure. The crude product was impregnated on SiO_2 and purified by flash chromatography.

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