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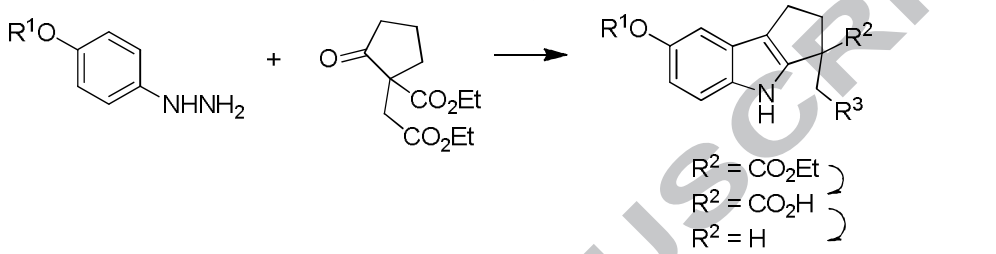

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ABSTRACT

A novel Fischer pseudo-benzylic decarboxylation approach to the 1,2,3,4-tetrahydrocyclopenta[b]indol-3-yl system was developed starting from geminally substituted cyclopentanone derivatives and appropriately substituted phenyl hydrazines. In addition, we demonstrate that substituents at the 3- and 7-positions can, for example, be useful synthetic handles for further functionalization.

Over ten thousand biologically active indole derivatives have been identified to date. Of those, over 200 are currently marked as drugs or undergoing clinical trials.[1] As such, new or improved methods for the construction of this heterocyclic system are constantly needed. This is particularly true for the development of safe and efficient large scale preparations, given the ubiquitous characteristics of indoles among bioactive molecules and natural products.[2] As part of our pharmacological compound evaluation, we were interested in synthesizing 7-alkoxy-1,2,3,4-tetrahydro-cyclopenta[b]-indol-3-yl derivatives (see Fig. 1 for numbering of the 1,2,3,4-tetrahydrocyclopenta[b]indole ring system). One of

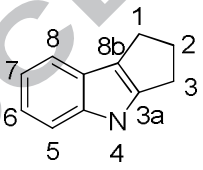


Figure 1. 1,2,3,4-Tetrahydrocyclopenta[b]indole numbering system.

these compounds, APD334[3,8] (Fig. 2), was selected as a clinical candidate for the potential treatment of autoimmune diseases. Although a variety of ring-substituted indoles are accessible through classical methods such as the Fischer, Bischler, Madelung, Reissert, Nenitzescu and Gassman procedures,[4] limitations can arise from difficult to obtain precursors and/or low reaction conversions.[5] Our attempts to synthesize 7-oxo-1,2,3,4-tetrahydrocyclopenta[b]-indol-3-yl derivatives using the Nenitzescu reaction, for example, led only to multicomponent mixtures. A telescoped condensation intramolecular Heck cyclization strategy (Scheme 1),[6,8] on the other hand, proved more successful but was still restrictive. As expected, iodides (Table 1, Entries 1-3) were superior to bromides (Table 1, Entries 4-6) in the cyclization step. The benzyloxy derivative **4** (R = Bn), however, could not be obtained

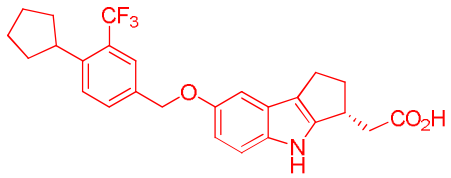
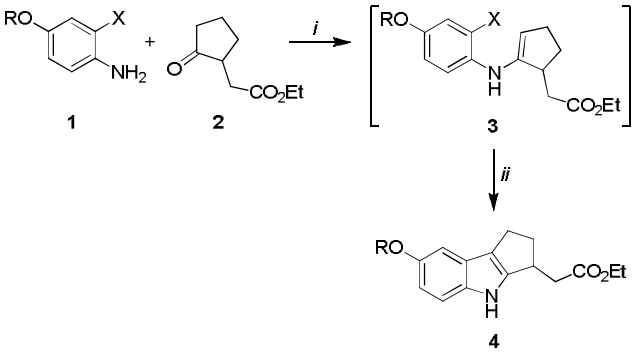


Figure 2. APD334



Scheme 1. (i) $Si(OEt)_4$, PPTS, DMF. (ii) Pd-catalyst, DIEA.

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under a variety of conditions and palladium catalysts (e.g. $Pd(dppb)Cl_2$, $Pd(dppp)Cl_2$, Table 1, Entries 7-12).[7] Conversely, the methoxy analogue **4** (R = Me) formed as the major product, as determined by LC-MS, but due to **4** co-eluting with $Si(OEt)_4$ or products derived therefrom, it could only be isolated in modest yields after extensive column chromatography on silica (Table 1, Entries 1-3). These results made us question the generality

Table 1. Formation of **4** under the conditions described in Scheme 1 utilizing different Pd-catalysts

Entry	R	X	Pd-catalyst	Yield %
1	Me	I	$Pd(OAc)_2$	32 (**4a**)
2	Me	I	$Pd(dppb)Cl_2$	29 (**4a**)
3	Me	I	$Pd(dppp)Cl_2$	44 (**4a**)
4	Me	Br	$Pd(OAc)_2$	5 (**4a**)
5	Me	Br	$Pd(dppb)Cl_2$	6 (**4a**)
6	Me	Br	$Pd(dppp)Cl_2$	6 (**4a**)
7	Bn	I	$Pd(OAc)_2$	decomposition
8	Bn	I	$Pd(dppb)Cl_2$	decomposition
9	Bn	I	$Pd(dppp)Cl_2$	decomposition
10	Bn	Br	$Pd(OAc)_2$	no reaction
11	Bn	Br	$Pd(dppb)Cl_2$	no reaction
12	Bn	Br	$Pd(dppp)Cl_2$	no reaction

and scalability of this approach and prompted us to explore other routes. Thus, herein we now report a novel and more scalable approach to the 7-oxo-1,2,3,4-tetrahydrocyclopenta[b]-indol-3-yl system with broader application

We first evaluated the condensation/cyclization reaction of 4-substituted phenylhydrazines **5** with ethyl 2-(2-oxocylopentyl)acetate (**2**) (Figure 3). Although the correspon-

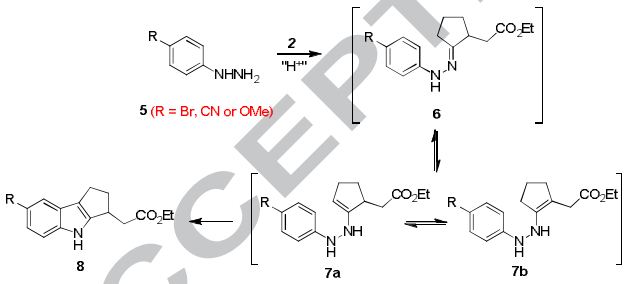
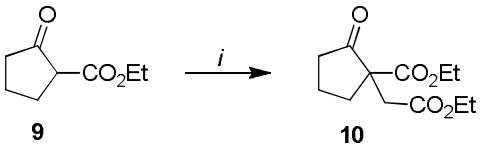


Figure 3. Fischer Indolization of **2** with various 4-substituted phenyl hydrazines.

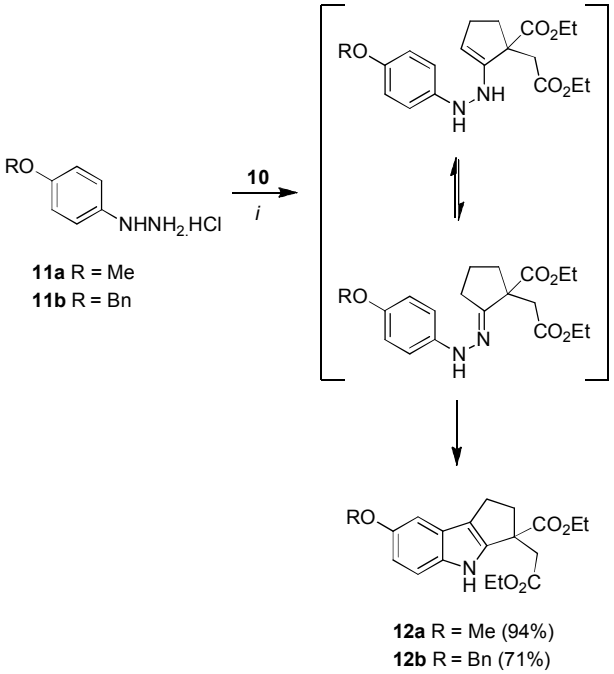
ding phenylhydrazones **6** formed successfully *in-situ*, subsequent cyclization, independent of the electronic nature of the R-groups investigated, invariably led to product mixtures in which the desired indoles **8** were only minor components.[9] Similar results were obtained with the isolated phenylhydrazones **6** under a variety of conditions. We reasoned that failure to mainly produce the indoles (**8**) of interest was, in part, due to non-selective tautomerization of the phenylhydrazones **6** to ene-hydrazines **7**.[10] Consequently, we decided to block one side of the cyclopentanone derivative to tautomerization by introducing a second functional group at the same carbon, with the potential for removal at a later stage. Thus, **10**[11] was obtained quantitatively,



Scheme 2. (i) K_2CO_3, Acetone , reflux.

in g to kg scale, after commercially available ethyl 2-oxocyclopentanecarboxylate (**9**) was alkylated with ethyl 2-bromoacetate in the presence of potassium carbonate in acetone (Scheme 2). Alkylation of **9** with other 2-bromo-esters and -nitriles worked similarly well.

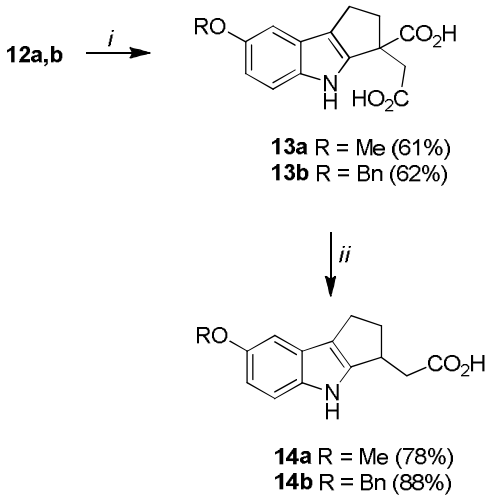
To test our hypothesis, 4-methoxyphenyl hydrazine (**11a**) and **10** were subjected to acid catalyzed Fischer indolization. To our delight, the corresponding indole derivative formed under a variety of conditions, and in the most promising iteration, merely heating the two precursors in the presence of stoichiometric amounts of acetic acid in ethanol gave the corresponding product **12a** in high yield (Scheme 3).[12] Under the established parameters, this procedure was deemed safe and operationally simple enough to be carried out in hundreds of grams. Interestingly, reaction of 4-benzyloxyphenyl hydrazine (**11b**) with **10** also resulted in the successful formation of the indole derivative **12b**. This was particularly pleasing since, for unknown reasons to us, the condensation intramolecular Heck cyclization strategy (*vide supra*) of the respective benzyloxy aniline **1** failed, in our laboratory, to yield the corresponding indole derivative **4** (Scheme 1, Table 1, Entries 7-12).



Scheme 3. (i) 1 equiv AcOH, EtOH, 75 °C.

Next, we focused our attention to the removal of the ester dummy group. We reasoned that, after hydrolysis, decarboxylation should be feasible due to the 1,3 relationship of

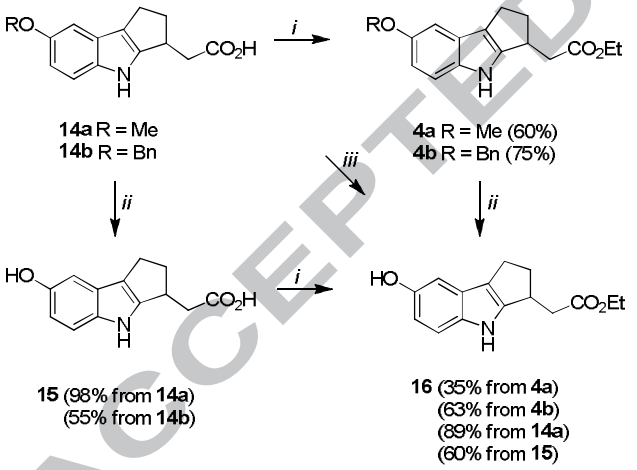
the resulting pseudo-benzylic acid with the indole double bond. Thus, treatment of diester **12a** with 50% aq NaOH in ethanol/water gave the corresponding diacid **13a** in 61% yield (Scheme 4). As expected and in analogy to *β*-ketoacids, simply



Scheme 4. (i) 50% aq NaOH, EtOH/H_2O then 6 N HCl. (ii) AcOH, 60 °C.

heating **13a** in acetic acid resulted in smooth decarboxylation to the corresponding tricycle **14a**.[13] Similarly, **12b** gave after hydrolysis (**13b**) and decarboxylation the corresponding acid **14b** in 55% overall yield.

Fischer re-esterification of **14a,b** and **15** to **4a,b** and **16**, respectively, was easily achieved *via* refluxing the corresponding acids in ethanol with a catalytic amount of sulfuric acid (Scheme 5). Acid catalyzed reaction with other alcohols also succeeded



Scheme 5. (i) EtOH, H_2SO_4 (0.6 equiv), reflux. (ii) 3 equiv BBr_3, CH_2Cl_2, -5 to 0 °C or EtOH/H_2O, $NH_4^+HCO_2^-$, 10% Pd/C, 40 °C. (iii) 3 equiv BBr_3, CH_2Cl_2, -5 to 0 °C then EtOH, 40 °C.

neat or by using solvents such as chloroform or toluene. De-methylation of **14a**, on the other hand, was best achieved with BBr_3 whereas transfer hydrogenation[14] of **14b** using ammonium formate in the presence of palladium-on-carbon (10% Pd/C) gave the same product **15** without significant reduction of the indole to the indoline.[15] De-methylation of **4a** or de-benzylation of **4b** using the respective conditions described above, gave indole **16** in modest yield. **16** could also be conveniently obtained from **14a** *via* a one pot de-methylation/re-esterification procedure using excess BBr_3 and quenching of the resulting reaction mixture with ethanol.[16]

In summary, we have developed a new entry into the 1,2,3,4-tetrahydrocyclopenta[b]-indol-3-yl core by utilizing a Fischer indolization of geminally substituted cyclopentanone derivatives followed by a pseudo-benzylic decarboxylation of the resulting acids. Furthermore, we demonstrate that substituents at the 3- and 7-positions can, for example, be useful synthetic handles for further functionalization. We are now evaluating the asymmetric version of the pseudo-benzylic decarboxylation step and general applicability of this methodology.

Acknowledgments

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12. *Procedure for the preparation* of indole derivative **12a**: To a suspension of (4-methoxyphenyl)hydrazine hydrochloride (379.5 g, 2.17 mol) and ethyl 1-(2-ethoxy-2-oxoethyl)-2-oxocyclopenta-necarboxylate (526 g, 2.17 mol) in EtOH (2.0 L) AcOH (131 g, 124 mL, 2.17 mol) was added and the mixture stirred at 75 °C for 18 h under N_2. The fine dark brown suspension was allowed to cool and neutralized with saturated aqueous $NaHCO_3$. The solvent was evaporated under reduced pressure, the brown oily residue

taken up in EtOAc (2 L), filtered and the organics washed with water (3 x 500 mL) and brine (2 x 500 mL). The combined aqueous layers were re-extracted with EtOAc. The combined organics were dried ($MgSO_4$) and the solvent was evaporated under reduced pressure to afford ethyl 3-(2-ethoxy-2-oxoethyl)-7-methoxy-1,2,3,4-tetrahydrocyclopenta[β]indole-3-carboxylate (703.4 g, 94%) as a thick dark brown oil. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 10.57 (s, 1H), 7.21 (d, *J* = 8.7 Hz, 1H), 6.85 (d, *J* = 2.4 Hz, 1H), 6.67 (dd, *J* = 8.8, 2.5 Hz, 1H), 4.12 – 4.00 (m, 4H), 3.73 (s, 3H), 3.18 (d, *J* = 16.6 Hz, 1H), 3.05 – 2.99 (m, 1H), 2.81 (d, *J* = 16.6 Hz, 1H), 2.82 – 2.70 (m, 2H), 2.48 – 2.42 (m, 1H), 1.17 (t, *J* = 7.2 Hz, 3H), 1.15 (t, *J* = 7.2 Hz, 3H). LCMS *m/z* = 346.2 $[M + H]^+$.

13. *Procedure for the preparation of indole derivative* **14a**: A solution of **13a** (191 g, 0.66 mol) in AcOH (1.0 L) was stirred at 60 °C for 4.5 h under N_2. The dark brown solution was concentrated, the precipitate collected under suction, washed with H_2O (3 x 500 mL) and dried at 40 °C under vacuum overnight to afford 2-(7-methoxy-1,2,3,4-tetrahydrocyclopenta[β]indol-3-yl)acetic acid (126.4 g, 78%) as a brown solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 12.16 (s, 1H), 10.42 (s, 1H), 7.18 (d, *J* = 8.7 Hz, 1H), 6.81 (d, *J* = 2.3 Hz, 1H), 6.62 (dd, *J* = 8.8, 2.5 Hz, 1H), 3.72 (s, 3H), 3.50 – 3.43 (m, 1H), 2.77 – 2.60 (m, 4H), 2.35 (dd, *J* = 16.0, 9.1 Hz, 1H), 2.12 – 2.04 (m, 1H). LCMS *m/z* = 246.1 $[M + H]^+$.
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15. *Procedure for the preparation of indole derivative* **15** *via debenzylation*: To a solution of **14b** (1.02 g, 3.17 mmol) in EtOH (10 mL) and water (0.5 mL), ammonium formate (1.20 g, 19.04 mmol) and wet palladium-on-carbon (10%wt, 0.10 g, 0.094 mmol) were added under N_2. The dark purple reaction mixture was heated to 40 °C. Conversion by HPLC after stirring for 4.5 h at 40 °C was determined to be 75%. Additional ammonium formate (1.20 g, 19.04 mmol) and wet palladium-on-carbon (10%wt, 0.10 g, 0.094 mmol) were added. Reaction completion was achieved after stirring under N_2 at 40 °C for further 5 h. The reaction mixture was allowed to cool, filtered through celite and the filter cake washed with EtOH (3 X 3 mL). The combined filtrates were concentrated, the greenish residue taken up in H_2O and the pH adjusted to ~2 with 6 N HCl. The aqueous mixture was extracted with EtOAc (10 mL), the layers separated and the aqueous layer back extracted with EtOAc (2 x 5 mL). The combined organic layers were dried (Na_2SO_4), filtered and concentrated to give the title compound (0.40 g, 55%) as a purple solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 12.15 (s, 1H), 10.26 (s, 1H), 8.48 (s, 1H), 7.08 (d, *J* = 8.6 Hz, 1H), 6.63 (d, *J* = 2.3 Hz, 1H), 6.49 (dd, *J* = 8.6, 2.4 Hz, 1H), 3.49 – 3.39 (m, 1H), 2.72 (dd, *J* = 15.9, 5.3 Hz, 1H), 2.69 – 2.56 (m, 3H), 2.34 (dd, *J* = 15.9, 9.2 Hz, 1H), 2.11 – 2.02 (m, 1H). LCMS *m/z* = 232.0 $[M + H]^+$.
16. *Telescoped procedure for the preparation of indole devirative* **16**: To a solution of BBr_3 (115 g, 43.3 mL, 458 mmol, 3 equiv) in CH_2Cl_2 (70 mL) a suspension of 2-(7-methoxy-1,2,3,4-tetrahydrocyclopenta[b]indol-3-yl)acetic acid (**14a**, 37.44 g, 153 mmol) in CH_2Cl_2 (300 mL) was added slowly while maintaining the reaction temperature between -5 to 0 °C. The resulting dark brown suspension was stirred at -5 to 0 °C for an additional 1 h. EtOH (187 mL) was added dropwise to the reaction mixture while maintaining the temperature between 0 - 10 °C. The resulting solution was heated at 40 °C for 30 min. The solution was cooled and the pH adjusted to 8 by adding 10 N NaOH (142.9 mL, 1.43 mol) slowly while maintaining the temperature between 0 - 3 °C. The solvent was removed under reduced pressure until about 200 mL of concentrate remained. The pH was adjusted to about 7 with concentrated HCl, the suspension filtered, the solids washed with H_2O (3 x 200 mL) and dried under vacuum at ambient temperature overnight. The light brown material was dissolved in EtOAc (200 mL), and filtered washing the solids with EtOAc. The combined organics were washed with saturated aqueous $NaHCO_3$.(2 x 200 mL), brine (200 mL), dried (Na_2SO_4) and the solvent rotary evaporated to afford ethyl 2-(7-hydroxy-1,2,3,4-tetrahydrocyclopenta[β]indol-3-yl)acetate (35.2 g, 88.9 %) as a light brown solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 10.25 (s, 1H), 8.47 (s, 1H), 7.07 (d, *J* = 8.6 Hz, 1H), 6.62 (d, *J* = 2.1 Hz, 1H), 6.49 (dd, *J* = 8.6, 2.3 Hz, 1H), 4.11 (q, *J* = 7.1 Hz, 2H), 3.49 – 3.42 (m, 1H), 2.76 (dd, *J* = 15.7, 5.5 Hz, 1H), 2.71 – 2.55 (m, 3H), 2.42 (dd, *J* = 15.7, 8.9 Hz, 1H), 2.11 – 2.03 (m, 1H), 1.20 (t, *J* = 7.1 Hz, 3H). LCMS *m/z* = 260.1 $[M + H]^+$.