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Efficient and Diverse Synthesis of Indole Derivatives

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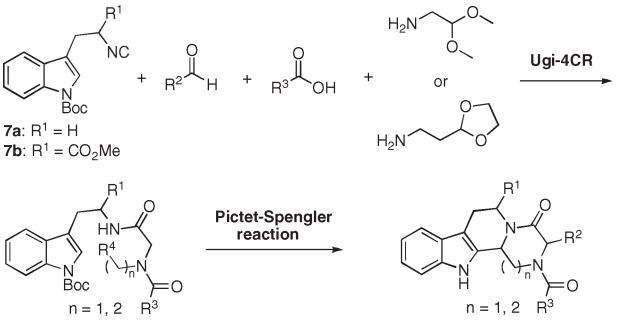

A convergent 2-step procedure toward an array of indole derivatives involving an Ugi reaction and a Pictet−Spengler reaction is described. The reactions are versatile regarding different starting materials. Hexacyclic **24** can be produced with unprecedented complexity.

Indole alkaloids are the main group of bioactive alkaloids, including, for example, hypertensive reserpine, antiproliferative vinblastine, or antiprotocoal apicidin.[1] The basic skeleton of indole alkaloids, however, is often only accessible via lengthy sequential synthesis. To optimize the properties of natural products or to efficiently discover novel unrelated biological activities, flexible synthetic approaches are in high demand. An efficient synthesis should lead into a target scaffold in a few synthetic steps, in good yields, and allowing for extensive variation of the different starting materials to broadly cover the respective chemical space. A stereoselective procedure should be possible as well. Multicomponent reaction (MCR) chemistry is a technique that allows for efficient and diverse access to multiple bioactive scaffolds.[2] This technique recently led to multiple biological active compounds currently undergoing clinical evaluation or even being marketed.[3] As part of our ongoing program to identify new and efficient access to scaffolds of biological interest, we herein report a new and versatile MCR synthesis of tetrahydro-β-carboline (Figure 1).[4]

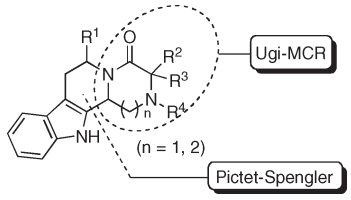

FIGURE 1. New synthetic access to the tetrahydro-β-carboline scaffold.

Tetrahydro-β-carboline ring systems are usually formed from tryptophan or its derivative tryptamine and an aldehyde via the classical Pictet−Spengler condensation.[5] The reaction products then serve for further derivatizations in sequential multistep processes.[6] A combination of MCR and Pictet−Spengler reaction has been described in the past, however, leading to different types of scaffolds.[2a,7] We figured that our herein described MCR process might be suitable to rapidly assemble tetrahydro-β-carboline scaffolds and would thus be complementary to previously reported methods. Toward this end, we synthesized tryptophan and tryptamine derived isocyanides and reacted them in the Ugi 4-CR with aldehydes, primary amines, and carboxylic acids. As a bifunctional amine component we used aminoacetaldehyde dimethylacetal, which in a subsequent step would undergo the Pictet−Spengler reaction to afford highly substituted tetrahydro-β-carbolines. Such a two-step process could have advantages over currently sequential processes,

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(5) (a) Pictet, A.; Spengler, T. *Ber*. **1911**, *44*, 2030–2036. (b) Whaley, G. In *Organic Reactions*; Wiley: New York, 1951; Vol. 6, pp 151−190.

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(7) (a) Sapi, J.; Laronze, J.-Y. *ARKIVOC* **2004**, 208–222. (b) El Kaim, L.; Gageat, M.; Gaultier, L.; Grimaud, L. *Synlett* **2007**, 500–502.

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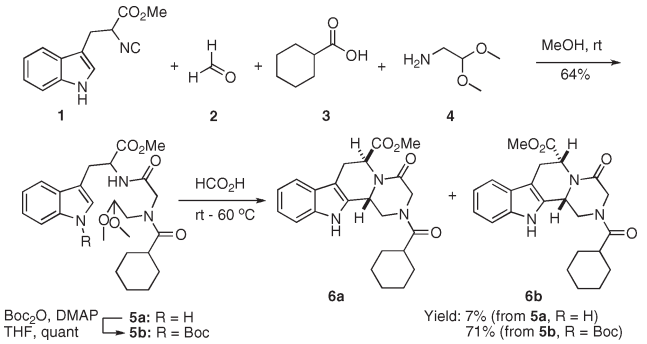
SCHEME 1. Stepwise Ugi-4CR and Pictet−Spengler Reaction

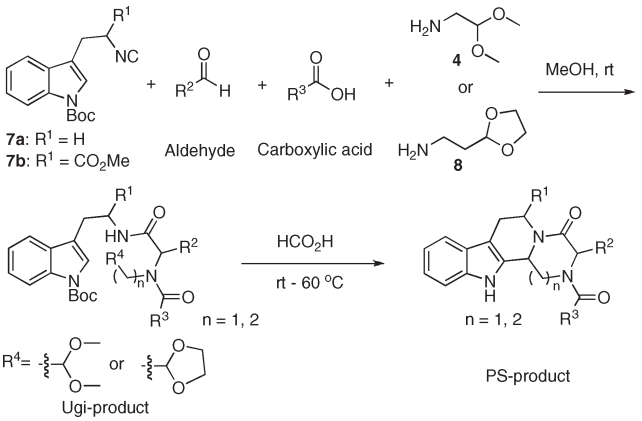


since the product diversity should be much larger and the effort to synthesize the compound should be drastically reduced.[8]

As a model, we first reacted tryptophan derivative **1**, aldehyde **2**, carboxylic acid **3**, and bifunctional amine **4** in methanol at room temperature as shown in Scheme 1. The Ugi 4-CR proceeded well and the desired product **5a** was isolated in good yield. To our surprise, however, the subsequent Pictet−Spengler reaction of **5a** was very sluggish and the desired product **6** could only be found in traces. Variation of the reaction conditions including the acid (formic acid, methane sulfonic acid, PTSA, CSA), solvent, and temperature did not greatly improve the reaction performance. This was surprising since the electron-rich indole ring systems are the archetypical substrates for Pictet−Spengler reactions.[5] We reasoned that the unprotected indole proton could interfere with the reaction and undergo side reactions, and we decided to prepare N-protected derivatives. Already the first protecting group we tried, *tert*-butyloxycarbonyl (Boc) in compound **5b**, proved to be highly superior and afforded the product **6** in a clean reaction in good yield (Scheme 1). The two-step reaction sequence was running very smoothly and the isolation of the desired compound proved to be very simple and therefore we went on to try different variations and to find out the scope and limitations of the reactions.

Two different N-Boc protected indole-containing isocyanides derived from tryptophan[9] and tryptamine were prepared.[10] Both can be efficiently synthesized on a multigram scale and react nicely in all reactions investigated herein. First, we made variations in the carboxylic acid, and as expected a range of carboxylic acids with different properties reacted nicely, e.g., aliphatic (Table 1, entries 1−2, 5−6, and 7), aromatic (Table 1, entries 3−4, and 8), and cyclic (Table 1, entries 1−2, 5−6, and 9). Next, we tried different aldehydes. Besides formaldehyde we reacted sterically hindered ortho, ortho-disubstituted difluoro benzaldehyde, which resulted in product **17** formation in good yield (48%, over two steps) as two diastereomers (1:1 by ^{1}H NMR) (Table 1, entry 10). We also tried valeraldehyde (entry 11), which gave two diastereomers in a ratio of 2:1 which can be separated by preparative TLC. Finally a different bifunctional primary amino aldehyde **8** (entries 12−15) was used to give corresponding 7-membered-ring products after the Pictet−Spengler reaction, however, in poor yields. The product of 4-fluoro-3-nitrobenzoic acid can be potentially further derivatized by aromatic nucleophilic substitutions (Table 1, entry 15; Scheme 2).

SCHEME 2. Versatile Synthesis of Indole Derivatives



In the case of tryptophan-derived isocyanide and formaldehyde, two products are formed in a ratio of approximately 2:1 (Table 1, entries 1−4); the major compound is the trans diastereomer (**6a**, **9a**−**11a**), which can be separated by column chromatography on silica gel. The stereochemical assignment of these diastereomers is generally done by 2D NOESY experiments (Figure 2).

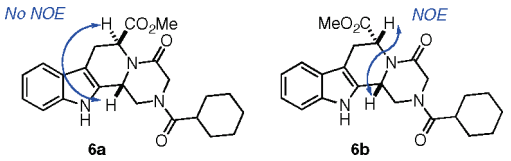
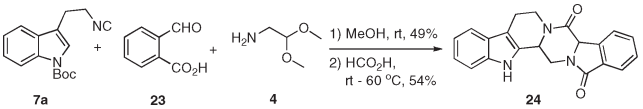


FIGURE 2. Relative configuration of **6a** and **6b** by NOESY.

The bifunctinal 2-formylbenzoic acid **23** was also investigated, which reacts with tryptophan-derived isocyanide **7** and bifunctional amine **4** under HCO_2H-mediated conditions in a two-step manner to give polycyclic indole alkaloid **24** in decent yield with 6 condensed rings in a row (Scheme 3). This is a remarkable example of an efficient synthesis of a complex compound containing six annulated rings and concomitant formation of three new C−C bonds and four new N−C bonds in just two steps from simple and commercial precursors.

SCHEME 3. One-Pot Formation of Polycyclic Indole Derivative 24



In summary, a new and efficient 2-step sequence to assemble highly substituted tetrahydro-β-carbolines has been developed. The sequence comprises an Ugi-4CR followed by a Pictet−Spengler ring closure. Using tryptophan-derived isocyanide yields two diastereomers, slightly favoring

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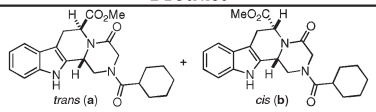
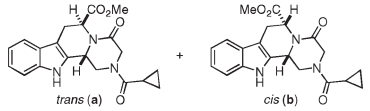
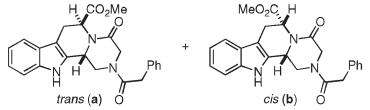
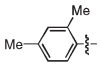
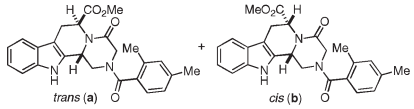
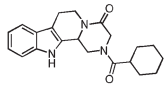
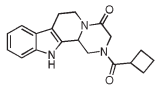
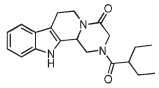
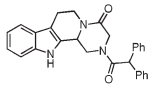
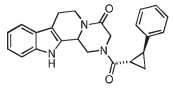
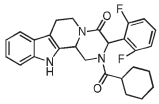
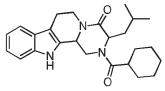
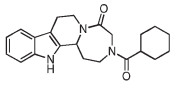
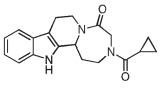
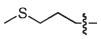
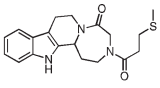
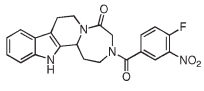
(9) For previous uses of indole-derived isocyanides in MCR see: (a) Beck, B.; Dömling, A. *Bioorg. Med. Chem. Lett.* **2000**, *10*, 1701–1705. (b) Beck, B.; Dömling, D. E. *19943508*. (c) Gulevich, A. V.; Shevchenko, N. E.; Balenkova, E. S.; Röschenthaler, G.-V.; Nenajdenko, V. G. *Tetrahedron* **2008**, *64*, 11706–11712.

(10) See the Supporting Information for the synthesis of indole-containing isocyanides.

TABLE 1. Synthesis of Indole Derivatives

Entry	R^1	R^2	R^3	Product	Comp.	Yield
1[a]	-CO_2Me	-H			**6** *trans*/*cis* 2.4/1	64%[e], 71%[f]
2[a]	-CO_2Me	-H			**9** *trans*/*cis* 2.0/1	70%[e], 64%[f]
3[b]	-CO_2Me	-H			**10** *trans*/*cis* 1.6/1	45%
4[b]	-CO_2Me	-H			**11** *trans*/*cis* 1.7/1	44%
5[a]	-H	-H			**12**	73%[e], 64%[f]
6[b]	-H	-H			**13**	41%
7[b]	-H	-H			**14**	42%
8[b]	-H	-H			**15**	39%
9[b]	-H	-H			**16**	42%
10[b]	-H				**17**[c] *d.r.*=1/1	48%
11[b]	-H				**18**[d] *d.r.*=2/1	54%
12[b]	-H	-H			**19**	15%
13[b]	-H	-H			**20**	13%
14[b]	-H	-H			**21**	17%
15[b]	-H	-H			**22**	10%

[a] Ugi-4CR intermediates separated and yields refer to the Pictet−Spengler reactions. [b] Overall yield in two steps (crude Ugi reaction product was directly used for the Pictet−Spengler reaction). [c] Unseparable diastereomers, d.r. determined by ^{1}H NMR. [d] Separable diastereomers by chromatography, d.r. determined by ^{1}H NMR. [e] Yield for the Ugi reaction. [f] Yield for the Pictet−Spengler reaction.

the trans stereoisomer. The developed short sequence not only allows for efficient production of many derivatives for screening purposes, but it also can be potentially used to efficiently assemble indole alkaloids type natural products.

Experimental Section

General Procedure for the Ugi-4CR Reaction. To a mixture of aldehyde (1.2 mmol), amine **4** or **10** (1.0 mmol), and carboxylic acid (1.0 mmol) in MeOH (3.0 mL) was added isocyanide **7a** or

7b (1.0 mmol) at 0 °C and the reaction was stirred at rt for 24 h. The resulting solution was concentrated under reduced pressure and the residue was purified by column chromatography on silica gel or used directly in the next step without further purification.

General Procedure for the Pictet−Spengler Reaction. The above Ugi reaction product (150−200 mg) was dissolved in cold HCO_2H (1.5 mL). After being stirred at rt for 30 min, the mixture was warmed to 60 °C and stirred for 2 h. The reaction mixture was diluted with EtOAc and neutralized by carefully adding sat. $NaHCO_3$ solution. The organic layer was separated, washed once with brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel to afford corresponding Pictet−Spengler products in decent yield. Characterization of **6a**: ^{1}H NMR (600 MHz, $CDCl_3$) δ 9.04 (s, 1H), 7.54 (d, J = 7.8 Hz, 1H), 7.37 (d, J = 7.8 Hz, 1H), 7.23 (t, J = 7.8 Hz, 1H), 7.15 (t, J = 7.8 Hz, 1H), 5.98 (d, J = 5.4 Hz, 1H), 5.26 (d, J = 13.2 Hz, 1H), 5.18 (d, J = 10.8 Hz, 1H), 4.61 (d, J = 17.4 Hz, 1H), 4.23 (d, J = 17.4 Hz, 1H), 3.64 (s, 3H), 3.52 (d, J = 16.2 Hz, 1H), 3.15 (dd, J = 5.4, 16.2 Hz, 1H), 2.88 (dd, J = 13.2, 10.8 Hz, 1H), 2.51 (tt, J = 11.4, 3.0 Hz, 1H), 1.82 (m, 3H), 1.53 (m, 2H), 1.27 (m, 5H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$) δ 175.2, 170.7, 165.1, 136.7, 128.2, 126.3, 122.7, 119.9, 118.4, 111.3, 107.3, 52.7, 50.8, 50.1, 49.0, 44.3, 40.9, 30.6, 29.1, 28.9, 25.7, 25.6, 22.8 ppm; HPLC-MS r_t 10.67, 11.12 min, m/z $[M + H]^+$ 410; HRMS (EI) m/z calcd for $C_{23}H_{27}N_3O_4$ $[M^+]$ 409.2002, found 409.2009. Characterization of **6b**: ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.87 (s, 1H), 7.50 (d, J = 7.8 Hz, 1H), 7.36 (d, J = 7.8 Hz, 1H), 7.20 (t, J = 7.8 Hz, 1H), 7.13 (t, J = 7.8 Hz, 1H), 5.03 (m, 1H), 4.65 (dd, J = 6.6, 6.0 Hz, 1H), 4.47 (dd, J = 13.2, 3.0 Hz, 1H), 4.28 (dd, J_{AB} = 24.6, 16.2 Hz, 2H), 4.05 (dd, J = 13.2, 8.4 Hz, 1H), 3.71 (s, 3H), 3.49 (dd, J = 15.6, 6.6 Hz, 1H), 3.10 (dd, J = 15.6, 6.0 Hz, 1H), 2.40 (tt, J = 11.4, 3.0 Hz, 1H), 1.69 (m, 3H), 1.54 (m, 2H), 1.26 (m, 5H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$) δ 175.3, 170.0, 166.7, 136.6, 129.5, 126.4, 122.7, 120.0, 118.2, 111.6, 109.1, 56.3, 53.7, 52.6, 49.3, 42.9, 40.7, 29.7, 29.0, 25.6, 25.5, 22.5 ppm; HPLC-MS r_t 10.67, 11.12 min, m/z $[M + H]^+$ 410; HRMS (EI) m/z calcd for $C_{23}H_{27}N_3O_4$ $[M^+]$ 409.2002, found 409.2002.

Synthesis of Polycyclic Indole Derivative 24. To a mixture of formylbenzoic acid **23** (1.2 mmol) and amine **4** (1.0 mmol) in MeOH (3.0 mL) was added isocyanide **7a** (1.0 mmol) at 0 °C. The reaction mixture was stirred at rt for 24 h. The resulting solution was concentrated under reduced pressure and the residue was purified by column chromatography on silica gel to give the Ugi product (252 mg, 49%). The above Ugi reaction product (100 mg, 0.20 mmol) was dissolved in cold HCO_2H (1.5 mL). After being stirred at rt for 30 min, the mixture was warmed to 60 °C and stirred for 2 h. The reaction mixture was diluted with EtOAc and neutralized by carefully adding sat. $NaHCO_3$ solution. The organic layer was separated, washed once with brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel affording compound **24** (67 mg, 54%) as a white solid. ^{1}H NMR (600 MHz, $CDCl_3$) δ 9.45 (s, 1H), 8.12 (d, J = 7.8 Hz, 1H), 7.95 (d, J = 7.8 Hz, 1H), 7.71 (t, J = 7.8 Hz, 1H), 7.61 (t, J = 7.8 Hz, 1H), 7.57 (d, J = 7.8 Hz, 1H), 7.46 (d, J = 7.8 Hz, 1H), 7.27 (t, J = 7.8 Hz, 1H), 7.18 (t, J = 7.8 Hz, 1H), 5.50 (dd, J = 4.8, 13.2 Hz, 1H), 5.33 (s, 1H), 5.15 (dd, J = 4.8, 13.2 Hz, 1H), 5.07 (m, 1H), 3.49 (dd, J = 11.4, 13.2 Hz, 1H), 2.97 (m, 1H), 2.86 (m, 2 H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 168.6, 164.4, 140.5, 136.6, 132.8, 131.4, 129.3, 126.4, 125. 1, 123.4, 122.6, 119.8, 118.5, 111.2, 110.2, 106.4, 60.6, 53.9, 42.5, 40.0, 21.0; HPLC-MS r_t 10.13, 10.62 min; m/z $[M + H]^+$ 344.

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Supporting Information Available: Detailed experimental procedures, and spectral data for all new compounds, including ^{1}H, ^{13}C. This material is available free of charge via the Internet at http://pubs.acs.org.