Polycyclic indole alkaloid-type compounds by MCR†

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Polycyclic indole moieties are often part of bioactive natural or synthetic products, however traditionally have to be synthesized over several steps involving time consuming sequential multi-step syntheses. We herein communicate an efficient and flexible 2-step procedure to complex multicyclic indole alkaloid-type compounds involving Ugi MCR and Pictet–Spengler reaction.

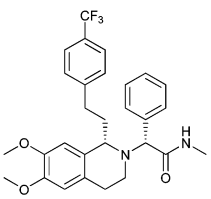
The Pictet–Spengler reaction (PS-2CR) is an intramolecular variant of the Mannich three component reaction and is very useful for the assembly of natural products and biopharmaceutical compounds.[1] Several years ago we reported on the combination of the Ugi and PS-2CR[2] and in the meantime the combination of MCRs and PS-2CR became quite popular to rapidly assemble molecular diversity.[3] For example the orexin I antagonist almorexant (Fig. 1) currently undergoing phase III clinical trials for sleeping disorders has been discovered by a combination of the Ugi-3CR and a subsequent PS-2CR.[4] Herein we wish to report on the first Ugi–PS combination where electron rich indolethylamine-derived isocyanides react in the Ugi–PS reactions with a diversity of bifunctional ketocarboxylic acid derivatives and orthogonally protected aminoacetaldehyde, to yield structurally intriguing polycyclic indole alkaloid-type compounds.

We recently introduced tryptophane-derived isocyanides for use in Ugi reactions with the aim to use the resulting molecules for further transformations involving indoles.[5] Specifically, we are interested in the reaction of the intermediate Ugi products in the PS reaction to build-up polycyclic indole alkaloid-type compounds. We initially reported one case of the Ugi–Pictet–Spengler transformation cascade leading to a polycyclic product and would like to report here details on this synthesis strategy.[5a] Additionally we also introduce here aliphatic and cyclic oxocarboxylic acids leading to a much greater diversity of products.

Ketocarboxylic acids are known to be bifunctional substrates in Ugi chemistry yielding lactams of varying ring sizes. However in order to perform a PS reaction an oxo component has to react with an indolethylamine fragment. Thus we introduced a protected aldehyde fragment the amine component in the Ugi reaction by employing aminoacetaldehyde dimethyl acetal **4**.‡ In a first example we reacted unprotected 2-isocyanoethylindole **1** with 2-formyl benzoic acid **3** and aminoacetaldehyde dimethyl acetal **4** and the Ugi product of this transformation can be isolated in 65% yield. Acid-mediated PS reaction, however, yielded only very poor yields of the expected product **7** despite extensively varying the conditions including temperature, solvent and acid catalyst (Scheme 1). Interestingly, protection of the indole proton by a Boc group **2** increased the yield of the PS reaction to 80% **7** upon treatment of the Ugi product **6** with formic acid at room temperature. Two diastereomers of **7** were separated in the following PS reaction with a 3 : 1 ratio.

We investigated the reaction and introduced different starting materials to find out scope and limitations (Scheme 2). Not to our surprise the Ugi reaction in most cases went very well despite the fact that in several cases quaternary carbon centres and sterically encumbered products are formed. Only with the 6-oxoheptanoic acid **9**, the Ugi product could not be produced presumably due to intermolecular reactions. The other oxo components reacted in mostly good to very good yields (Table 1). Even hindered cyclic ketones (**10** 2-(2-oxocyclopentyl)acetic acid) reacted satisfactorily. The Ugi products were isolated and purified before subjecting them to the PS procedure. Typically the Ugi products were formed as mixtures of enantiomers or diastereomers in equal or almost equal ratio, respectively.

Ugi–PS compound **16** contains three stereocenters and gives rise to 8 stereoisomers. The intermediate Ugi products **21** and **22** have only two stereocenters and could be separated by chromatography in 45% and 15% yields, respectively. The subsequent PS reactions yielded a third stereocenter. Starting from Ugi product **21** PS products **16a** and **16b** could be separately isolated in 58% and 38% yields, respectively; whereas Ugi product **22** yielded an inseparable 1 : 1 mixture of PS product **16c** in 70% yield. The relative stereochemistry of the separate diastereomers **16a** and **16b** has been assigned by 2D NMR experiments (ESI†). Fortunately, the polar diastereomer of **16b**, a hexacyclic indole derivative also crystallized and yielded X-ray diffraction suitable crystals. The structure of **16b** in the solid state is shown in Fig. 2.



Almorexant

Fig. 1 Almorexant® as an example of a compound discovered by the efficient sequence Ugi-3CR and PS-2CR.

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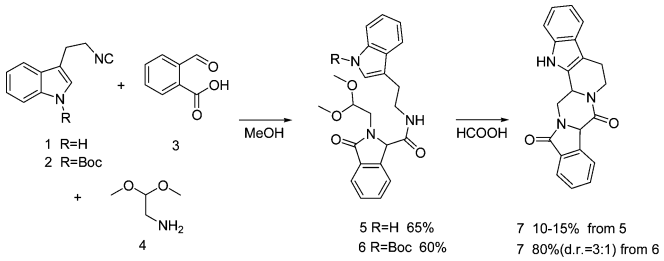
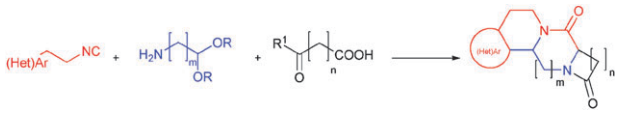
† Electronic supplementary information (ESI) available: 1D and 2D NMRs of novel compounds, crystallographic details. CCDC 749252. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/b917660h



Scheme 1 Synthesis sequence involving an intramolecular U-4CR and a subsequent PS-2CR.



Scheme 2 General structure scheme of Ugi–PS sequence.

The X-ray structure is fully consistent with the relative stereochemistry assigned by 2D NMR analysis (Fig. 3).

The ease of synthesis and the increase in molecular complexity during the 2-step sequence are worthwhile mentioning, *e.g.* **16** could be formed in 50% yield over two steps, which is excellent when considering that six new bonds are formed (2 C–C, 1 C–O, 3 C–N). In fact, the yield per bond formation is 89%. **16** is a highly complex molecule containing in total 6 cycles, 4 heterocycles (pyrrole, piperazinone, hydropyridine, γ-lactam) and two carbocyles (benzene, cyclopentane). Three cycles are annulated, and three cycles, however are connected to each other *via* a common quaternary carbon which is formed during the Ugi reaction. The ring sizes comprise three 5-membered and three 6-membered rings.

In summary we have described a very efficient two step sequence towards highly complex polycyclic indole alkaloid-type

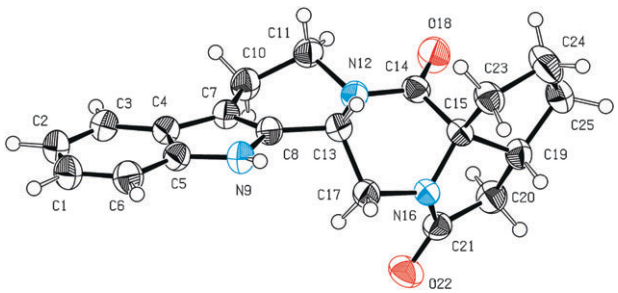


Fig. 2 ORTEP style plot of compound **16b** in the solid state. Thermal ellipsoids are drawn at the 50% probability level.

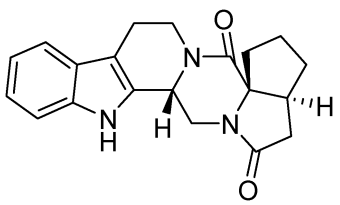
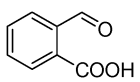
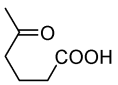
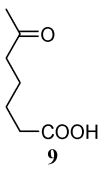
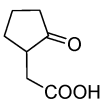
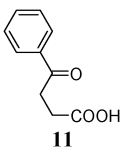
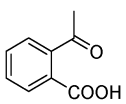
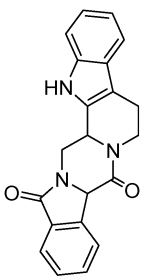
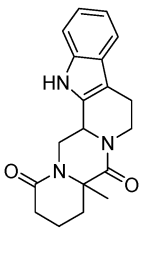
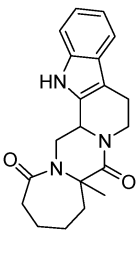
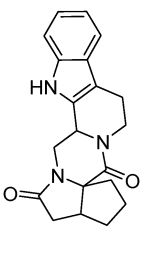
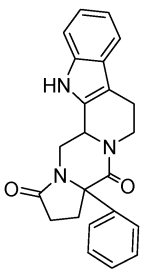
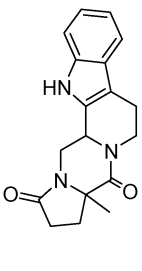
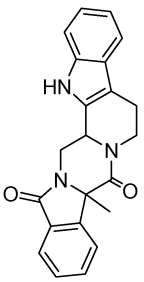


Fig. 3 Relative configuration of **16b** as of X-ray analysis.

Table 1 Polycyclic indole product results

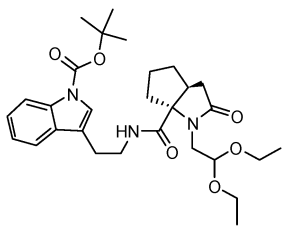
Oxo carboxylic acid	 **3**	 **8**	 **9**	 **10**	 **11**	 **12**	 **13**
Polycyclic indole product	 **7**	 **14**	 **15**	 **16**	 **17**	 **18**	 **19**
Ugi product	**6** 60%[a]	**20** 80%[b]	No	Diastereomer **21** 45% + **22** 15%[b,d]	**23** 55%[b]	**24** 53%[b]	**25** 60%[a]
PS product	**7a** 60% + **7b** 20%[d]	**14** 63% (3 : 1)[c]	No	**16a** 58% + **16b** 38%[d]	**16c** 70% (1 : 1)[c]	**17** 48% (1 : 1.58)[c]	**18** 48% (1 : 1)[c]	**19a** 45% + **19b** 50%[d]

All yields refer to isolated yields.[a] Reaction with aminoacetaldehyde dimethyl acetal. [b] Reaction with aminoacetaldehyde diethyl acetal. [c] The products are the two diastereomer mixtures, the ratio of diastereomer is shown. [d] The two diastereomers are separated.

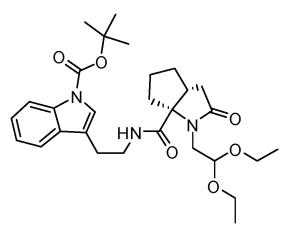
molecules involving an Ugi-4CR and a subsequent PS reaction. Significantly, aliphatic acyclic and cyclic as well as aromatic oxo acids are substrates for this reaction sequence. Scope and limitation of the sequence are described. Further work is being performed in our laboratory to investigate the intriguing biological activities of these molecules and will be reported in due course.

Notes and references

‡ General procedure for Ugi reaction: 1 mmol of aldehyde or ketone acid was dissolved in 1 mL MeOH, 1 mmol of isocyanide and 1mmol amino acetal were added into the solution. The solution was stirred for 24 hours at rt. The solution was evaporated and purified by SiO_2 column chromatography to give the Ugi product.Ugi product **21**, 3-(2-{[1-(2,2-diethoxy-ethyl)-2-oxo-hexahydro-cyclopenta[*b*]pyrrole-6a-carbonyl]-amino-ethyl)-indole-1-carboxylic acid *tert*-butyl ester, $C_{29}H_{41}N_3O_6$, M_w: 527.65 g mol^{-1}; HRMS (ESI-TOF) m/z (calc.): 527.2995, (found) $[M]^+$: 527.3001; HPLC-MS rt: 12.06, m/z $[M - Boc]^+$: 426.0. ^{1}H-NMR ($CDCl_3$, 600 MHz): δ = 1.17 (t, J = 7.02 Hz, 3 H), 1.19 (t, J = 7.02 Hz, 3 H), 1.68 (s, 9 H), 1.80 (m, 1 H), 2.10 (m, 2 H), 2.22 (m, 2 H), 2.29 (dd, J = 6.17, 14.83 Hz, 1 H), 2.39 (t, J = 14.57 Hz, 1 H), 2.91 (dt, J = 1.56, 3.62 Hz, 1 H), 3.36 (q, J = 7.02 Hz, 1 H), 3.45 (dd, J = 7.10, 9.24 Hz, 1 H), 3.54 (m, J = 6.80 Hz, 1 H), 3.61 (m, 3 H), 3.72 (q, J = 5.47 Hz, 1 H), 4.61 (t, J = 4.72 Hz, 1 H), 6.69 (t, J = 5.48 Hz, 1 H), 7.26 (t, J = 7.74 Hz, 1 H), 7.33 (t, J = 7.50 Hz, 1 H), 7.41 (s, 1 H), 7.55 (d, J = 7.55 Hz, 2 H), 8.16 (s, 1 H). ^{13}C-NMR ($CDCl_3$, 150.92 MHz): δ = 15.2, 15.3, 22.4, 25.0, 26.5, 28.2, 30.5, 33.8, 39.6, 44.8, 52.4, 62.8, 62.9, 100.1, 115.3, 117.5, 118.8, 122.6, 123.0, 124.5, 130.5, 172.0, 180.2.

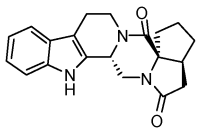


Ugi product **22**, 3-(2-{[1-(2,2-diethoxy-ethyl)-2-oxo-hexahydro-cyclopenta[*b*]pyrrole-6a-carbonyl]-amino}-ethyl)-indole-1-carboxylic acid tert-butyl ester, $C_{29}H_{41}N_3O_6$, M_w: 527.65 g mol^{-1}; HRMS (ESI-TOF) m/z (calc.): 527.2995, (found) $[M]^+$: 527.3001; HPLC-MS rt: 12.04, m/z $[M + H]^+$: 426.2. ^{1}H-NMR ($CDCl_3$, 600 MHz): δ = 1.05 (t, J = 7.08 Hz, 3 H), 1.17 (t, J = 7.02 Hz, 3 H), 1.43 (m, 1 H), 1.59 (m, 1 H), 1.65 (m, 1 H), 1.77 (m, 1 H), 1.87 (m, 1 H), 2.02 (dd, J = 1.77, 17.43 Hz, 1 H), 2.08 (m, 1 H), 2.34–2.38 (m, 2 H), 2.60 (dd, J = 17.4, 9.78 Hz, 1 H), 2.72 (w, 1 H), 2.79 (dd, J = 7.41, 14.01 Hz, 1 H), 2.93 (t, J = 7.29 Hz, 2 H), 3.39 (dd, J = 4.21, 13.92 Hz, 1 H), 3.47 (m, 2 H), 3.52 (m, 1 H), 3.57 (dt, J = 7.02, 6.57 Hz, 1 H), 3.66 (dt, J = 7.16, 7.96 Hz, 1 H), 3.68 (dd, J = 5.48, 16.05 Hz, 1 H), 5.33 (dd, J = 4.32, 7.32 Hz, 1 H), 7.22 (t, J = 7.44 Hz, 1 H), 7.29 (dd, J = 6.69, 14.25 Hz, 1 H), 7.37 (s, 1 H), 7.55 (d, J = 7.93 Hz, 2 H), 7.98 (t, J = 5.67 Hz, 1 H), 8.12 (s, 1 H). ^{13}C-NMR ($CDCl_3$, 150.92 MHz): δ = 15.2, 15.5, 24.8, 25.5, 28.2, 34.1, 35.0, 37.0, 39.7, 43.7, 46.2, 63.8, 64.9, 78.6, 83.4 (rotamer), 99.4, 115.3, 117.8, 118.8, 122.4, 123.0, 124.4, 130.5, 135.5 (rotamer), 149.6 (rotamer), 174.0, 177.1.

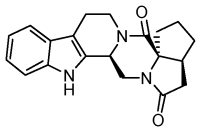


General procedure for Pictet–Spengler reaction: 0.1 mmol of Ugi product was dissolved in 0.5 ml of HCOOH and stirred for 4 h at rt. Evaporation and purification by preparative TLC or column chromatography gave the corresponding polycyclic product.

Less polar product **16a**, $C_{20}H_{21}N_3O_2$, M_w: 335.40 g mol^{-1}; HRMS (ESI-TOF) m/z (calc.): 335.1634, (found) $[M]^+$: 335.1598, m/z $[M + H]^+$: 336.2. ^{1}H-NMR ($CDCl_3$, 600 MHz): δ = 1.62 (dt, J = 7.98, 5.63 Hz, 1 H), 1.91 (dd, J = 8.24, 14.42 Hz, 1 H), 1.95 (dd, J = 8.24, 11.20 Hz, 1 H), 2.22 (m, 1 H), 2.35 (m, 4 H), 2.59 (dd, J = 4.22, 14.29 Hz, 1 H), 2.75 (ddd, J = 3.81, 10.21, 22.61 Hz, 1 H), 2.80 (m, 1 H), 2.86 (ddt, J = 2.58, 5.85, 6.75 Hz, 1 H), 3.27 (dd, J = 11.31, 13.11 Hz, 1 H), 4.96 (dd, J = 5.94, 13.32 Hz, 1 H), 5.11 (dd, J = 4.42, 12.76 Hz, 1 H), 5.20 (dd, J = 5.92, 11.08 Hz, 1 H), 7.14 (t, J = 7.32 Hz, 1 H), 7.22 (t, J = 7.59 Hz, 1 H), 7.37 (d, J = 8.10 Hz, 1 H), 7.53 (d, J = 7.80 Hz, 1 H), 9.03 (s, 1 H). ^{13}C-NMR ($CDCl_3$, 150.92 MHz): δ = 21.2, 22.9, 26.4, 32.7, 34.9, 40.2, 43.2, 50.2, 51.3, 73.7, 110.1, 111.2, 118.4, 119.9, 122.4, 126.4, 130.5, 136.6, 169.7, 183.2.



More polar product **16b**, $C_{20}H_{21}N_3O_2$, M_w: 335.40 g mol^{-1}; HRMS (ESI-TOF) m/z (calc.): 335.1634, (found) $[M]^+$: 335.1598; HPLC-MS rt: 10.05, m/z $[M + H]^+$: 336.2. ^{1}H-NMR ($CDCl_3$, 600 MHz): δ = 1.83–1.91 (m, 2 H), 2.01 (dd, J = 13.22, 7.93, 1 H), 2.03–2.16 (m, 3 H), 2.35 (t, J = 14.52 Hz, 1 H), 2.44 (dd, J = 6.00, 15.12 Hz, 1 H), 2.48–2.55 (m, 1 H), 2.78 (ddd, J = 1.67, 4.87, 15.63 Hz, 1 H), 2.84–2.86 (m, 1 H), 3.05 (ddd, J = 4.33, 12.84, 11.16 Hz, 1 H), 3.79 (dd, J = 6.06, 12.30 Hz, 1 H), 3.94 (dd, J = 10.06, 12.20 Hz, 1 H), 4.67 (ddd, J = 2.48, 5.09, 12.86 Hz, 1 H), 5.03 (dd, J = 6.18, 9.96 Hz, 1 H), 7.15 (t, J = 7.46 Hz, 1 H), 7.20 (t, J = 7.07 Hz, 1 H), 7.33 (d, J = 8.10 Hz, 1 H), 7.52 (d, J = 7.93 Hz, 1 H), 8.16 (s, 1 H). ^{13}C-NMR ($CDCl_3$, 150.92 MHz): δ = 20.2, 22.0, 25.2, 31.8, 33.9, 39.3, 46.6, 48.8, 49.5, 72.0, 110.2, 111.2, 118.5, 120.0, 122.6, 126.5, 129.4, 136.7, 171.4, 182.3.



X-Ray single crystal structure analysis of compound **16b**: $C_{20}H_{21}N_3O_2$, M_r = 335.40, colorless fragment, monoclinic, $P2_1/c$ (no.: 14), a = 11.3899(5), b = 8.9061(4), c = 16.9450(7) Å, β = 94.3181(18)°, V = 1714.02(13) Å^3, Z = 4, d_{calc} = 1.300 g cm^{-3}, F_{000} = 712, μ = 0.686 mm^{-1}, 11 088 reflections, R_{int} = 0.023, 2862 independent data [2665: $I_o > 2\sigma(I_o)$], R_1 = 0.0329 [$I_o > 2\sigma(I_o)$], wR_2 = 0.0817 [all data]. For more detailed information see the ESI.†

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