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Solid-phase synthesis of new fused tetra, penta and hexacyclic β-carboline derivatives

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This paper is dedicated to Professor Manfred Mutter on the occasion of his 60th birthday

Abstract—The parallel synthesis of new fused tetra, penta and hexacyclic β-carbolines via the functionalization of resin-bound tetrahydro-β-carboline derivatives is described. Reduction of the amide bonds and/or nitro group is the key step in the formation of different described fused heterocycles.

We report an efficient method for the parallel solid-phase synthesis[1] of new classes of tetrahydro-β-carboline derivatives. The tetrahydro-β-carboline scaffold is known to exhibit a wide range of pharmacological properties. Such compounds inhibit monoamine oxidase A[2] and, in the case of the tetrahydro-β-carboline yohimbine, bind with nanomolar affinity to serotonin receptors.[3] They also bind to the $GABA_A$ receptor ion channel and modulate molecular mechanisms controlling anxiety, convulsions and sleep.[4] Recently, the β-carboline alkaloid flavopereirine has been isolated from *Geissospermum* and has been studied for the treatment of malaria.[5] The activities of tryprostatin B and demethoxyfumitremorgin, which combines features of tetrahydro-β-carbolines and diketopiperazines,[6] have also been reported and demonstrate the usefulness of the fumitremorgin skeleton as a template for drug discovery.

Our approach is based on the Pictet–Spengler reaction, which has been used for the synthesis of isoquinoline and indole alkaloids.[7,8] It has been shown that tryptophan analogues react with aldehydes to give tetrahydro-β-carboline derivatives.[9–11] We were interested in preparing functionalized tetrahydro-β-carboline derivatives. First, Fmoc-L-tryptophan was coupled to 4-methyl-benzhydrylamine (MBHA) resin, followed by removal of the Fmoc group with 20% piperidine in dimethylformamide. In order to avoid *t*-butyl alkylation of the indole ring during the deprotection, the Boc-protected analogue was avoided. The solid-phase Pictet–Spengler reaction was carried out using various aldehydes in the presence of 2% TFA in dichloromethane at room temperature overnight. Our first approach was to derive different tetracyclic β-carboline derivatives from compound **2** (Scheme 1). Benzaldehyde, 4-fluoro-benzaldehyde, valeraldehyde and *p*-anisaldehyde were used to study various aldehydes. The reduced β-carboline **2** was obtained from the β-carboline carboxamide **1** using BH_3–THF.[12] Treatment of the resin-bound tetrahydro-β-carboline **2** with oxalyldiimidazole, carbonyldiimidazole, and thiocarbonyldiimidazole afforded following cleavage from the solid support, respectively, compounds **3**, **4** and **5**.[13] Introduction of the guanidine moiety on these derivatives was also desired. This was accomplished using cyanogen bromide[14] on the resin-bound tetrahydro-β-carboline **2** to generate the cyclic guanidino β-carboline **6**. This compound was treated with phenylacetic acid in the presence of 2-(1*H*-benzotriazole-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate (HBTU) and *N*,*N*′-diisopropylethylamine (DIEA) to afford the corresponding *N*-acylated guanidine **7**.

Our second approach was to derive different pentacyclic β-carboline derivatives from compound **9** (Scheme 2) in which *o*-nitrobenzaldehyde derivatives were chosen for the Pictet–Spengler condensation. The reduction of the nitro group was carried out with tin(II) chloride dihydrate ($SnCl_2 \cdot 2H_2O$) to generate **9**, which was treated with oxalyldiimidazole, carbonyldiimidazole, and thiocarbonyldiimidazole, respectively, to afford compounds **10**, **11** and **12**. Using the same approach, the cyclic guanidino β-carboline **13** was obtained with a side product that appeared to be a

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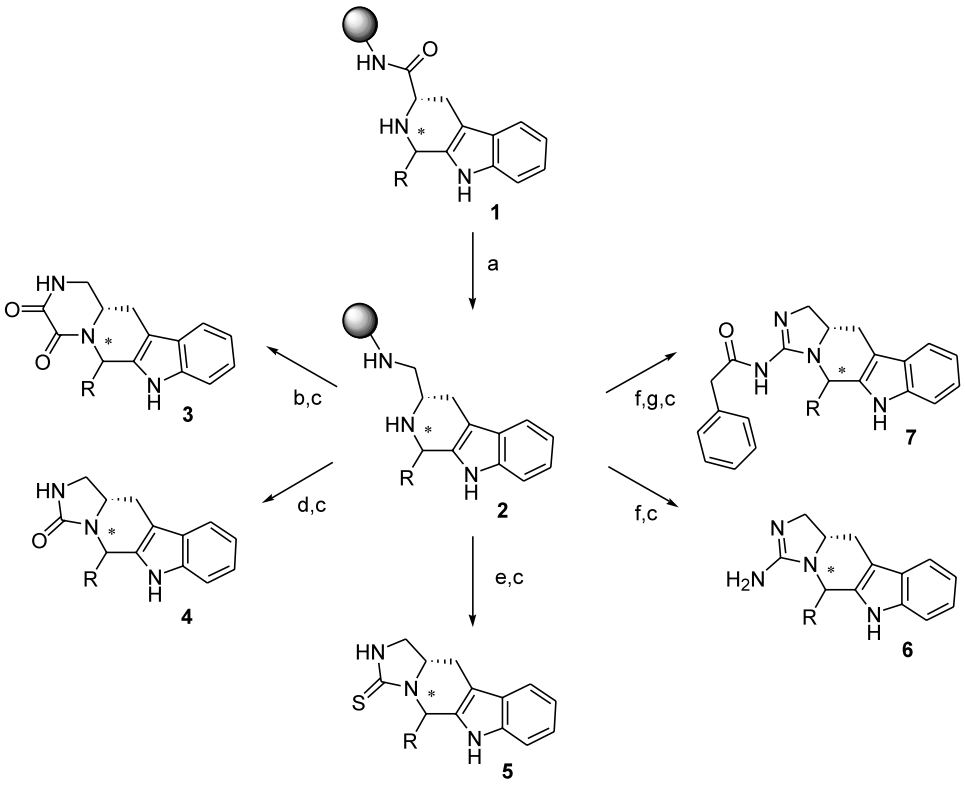
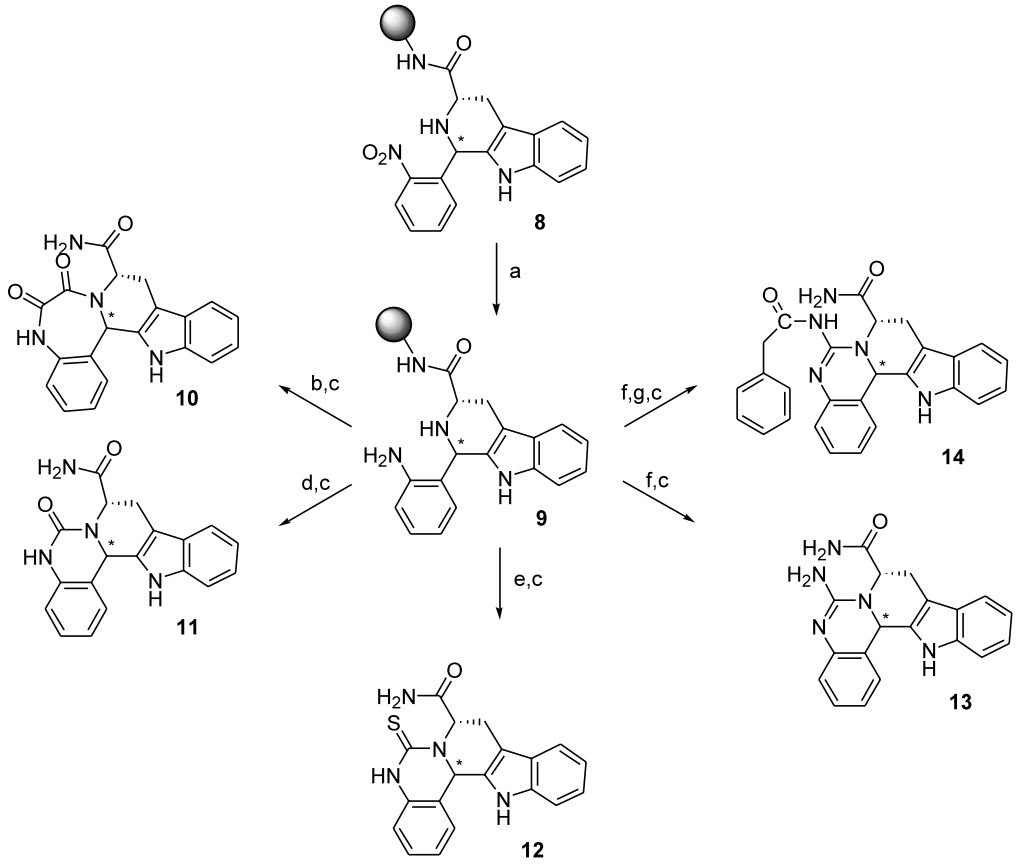
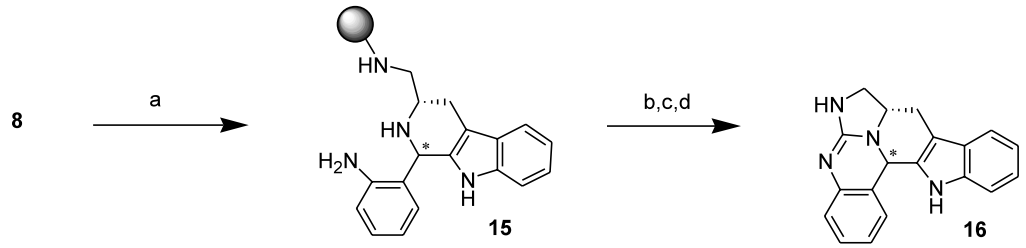


Scheme 1. *Reagents and conditions*: (a) BH_3–THF, 65°C, 48 h; (b) 10 equiv. $(COIm)_2$ in DMF overnight; (c) HF, 0°C, 7 h; (d) 10 equiv. $COIm_2$ in DCM overnight; (e) 10 equiv. $CSIm_2$ in DCM overnight; (f) 10 equiv. CNBr in DCM overnight; (g) 25 equiv. $C_6H_5CH_2$ COOH, 25 equiv. HBTU, 50 equiv. DIEA, 24 h in DMF.



Scheme 2. *Reagents and conditions*: (a) 20 equiv. $SnCl_2$ in DMF, overnight; (b) 10 equiv. $(COIm)_2$ in DMF overnight; (c) HF, 0°C, 1.5 h; (d) 10 equiv. $COIm_2$ in DCM overnight; (e) 10 equiv. $CSIm_2$ in DCM overnight; (f) 10 equiv. CNBr in DCM overnight; (g) 25 equiv. R_2 COOH, 25 equiv. HBTU, 50 equiv. DIEA, 24 h in DMF.



Scheme 3. *Reagents and conditions*: (a) BH_3–THF, 65°C, 48 h; (b) 10 equiv. $CSIm_2$ in DCM overnight; (c) 10 equiv. $Hg(OAc)_2$ in DMF overnight; (d) HF, 0°C, 7 h.

dimer. The *N*-acylated derivative **14** was then obtained in low purity.

We were also interested in forming a bicyclic guanidine leading to a fused hexacyclic β-carboline derivative (Scheme 3). Following Pictet–Spengler condensation of the 2-nitro benzaldehyde with the resin-bound tryptophan, both the amide bond and nitro group were reduced using borane–THF to generate compound **15** containing two secondary amines and one primary aniline. This compound was treated with thiocarbonyldiimidazole ($CSIm_2$), followed by mercuric acetate ($Hg(OAc)_2$),[14] to afford the fused hexacyclic β-carboline derivative **16** after HF cleavage.

The purity of all intermediates was determined following HF cleavage of small amounts of the resin and analysis by LC–MS. The final products were also analyzed by LC–MS (Table 1).[15] Figure 1 illustrates a typical LC–MS spectra of a pentacyclic urea fused cyclic β-carboline.

In summary, an efficient approach for the synthesis of new fused tetra, penta and hexacyclic containing β-carbolines was described. Using different commercially available tryptophan analogues, and different benzaldehydes, we elaborated the synthesis of different fused β-carboline libraries.

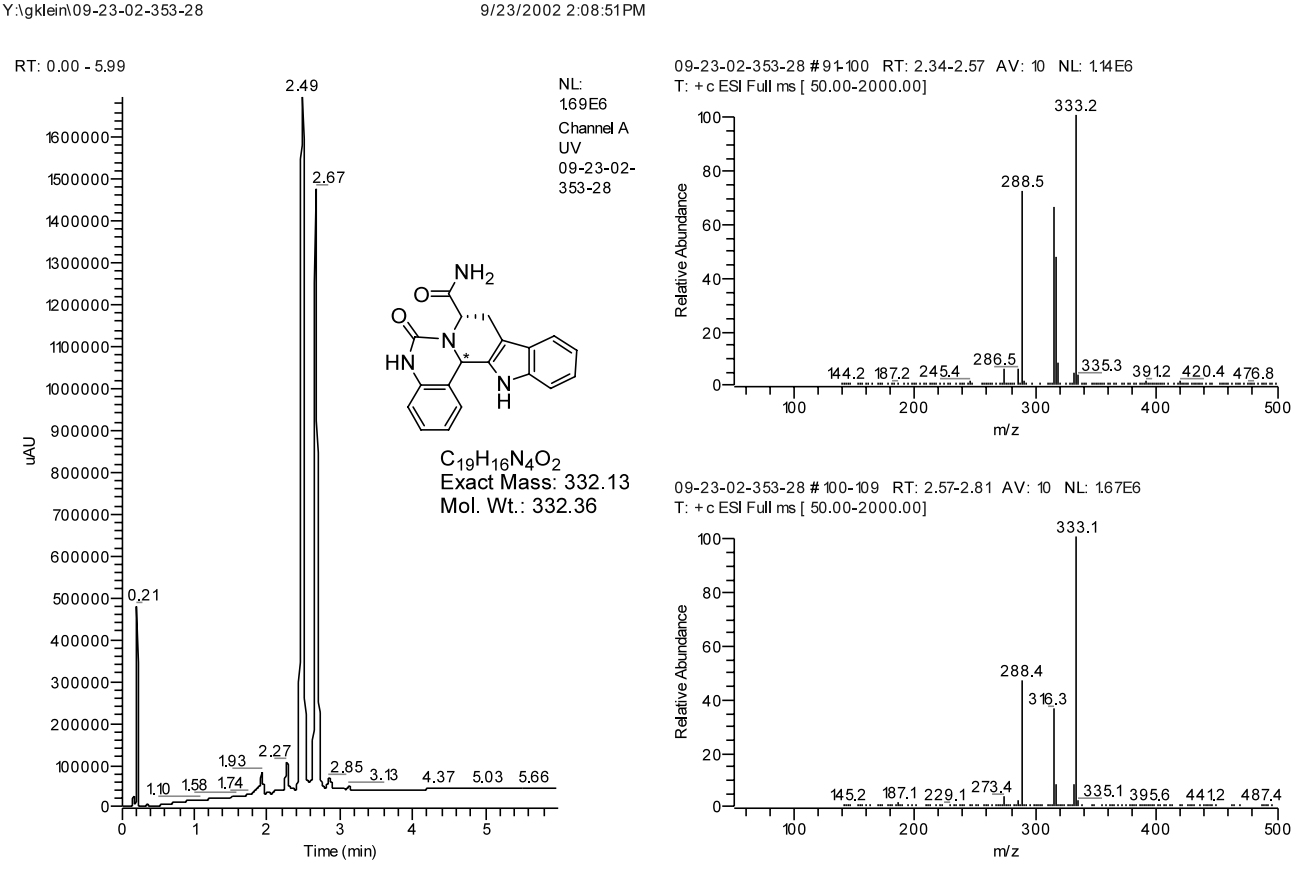


Figure 1. LC–MS of crude cyclic urea β-carboline derivative **11**

Table 1. MW and RP-HPLC purity found for the fused tetra, penta and hexacyclic β-carbolines

Entry	R	Yield[a]	Purity[b]	MW (calcd)[c]	MW (found)
3a	$-C_6H_4$(4-F)	90	80[c]	349.1	350.2 ($[M+H]^+$)
3b	$-C_6H_5$	70	82[c]	331.1	332.2 ($[M+H]^+$)
3c	$-C_6H_4$(4-OCH_3)	91	75[c]	361.1	362.2 ($[M+H]^+$)
4c	$-C_6H_4$(4-OCH_3)	72	40[c]	333.1	334.3 ($[M+H]^+$)
5a	$-C_6H_4$(4-F)	87	70[c]	337.1	338.3 ($[M+H]^+$)
5b	$-C_6H_5$	92	72[c]	319.1	320.2 ($[M+H]^+$)
6b	$-C_6H_5$	85	75[c]	302.1	303.3 ($[M+H]^+$)
7a	$-C_6H_4$(4-F)	72	75 (69–31)	438.2	439.3 ($[M+H]^+$)
7b	$-C_6H_5$	65	80 (68–32)	420.2	421.2 ($[M+H]^+$)
10		69	62[c]	360.1	361.1 ($[M+H]^+$)
11		85	90 (66–34)	332.1	333.2 ($[M+H]^+$)
12		82	70[c]	348.1	349.1 ($[M+H]^+$)
13		75	60 (58–42)	331.1	332.4 ($[M+H]^+$)
14		72	40[c]	449.2	450.4 ($[M+H]^+$)
16		80	60 (66–34)	300.1	301.1 ($[M+H]^+$)

[a] Yields (in %) are based on the weight of crude material and are relative to the initial loading of the resin (1.15 mequiv./g).

[b] The combined purity of the crude diastereoisomers was determined from the relative peak areas (%) of RP-HPLC chromatograms run with a gradient of 5–95% acetonitrile in water (0.05% TFA) for 30 min at $\lambda = 214$ nm. Percent of each individual diastereoisomers is shown in parentheses when resolved.

[c] No diastereoisomeric resolution was observed under these HPLC conditions.

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15. Typical procedure for the synthesis of cyclic urea β-carboline **11**: 50 mg of MBHA resin was contained in a polypropylene mesh packet.[16] Following neutralization with 5% diisopropylethylamine (DIEA) in dichloromethane (DCM), the resin was washed with DCM. Fmoc-L-tryptophan (6 equiv., 0.1 M) was coupled using hydroxybenzotriazole (HOBt, 6 equiv., 0.1 M) and diisopropylcarbodiimide (DICI, 6 equiv., 0.1 M) in DMF for 2 h. Upon removal of the Fmoc group with 20% piperidine in DMF (30 min), the packet was washed with DMF and DCM. The resin-bound amide was reacted with 2-nitrobenzaldehyde (10 equiv., 0.2 M) overnight in 2% TFA/DCM to generate **9**. The resin was then treated with tin(II) chloride dihydrate (20 equiv., 0.5 M) overnight in DMF. The resin was washed with DMF (eight times), IPA (three times), DCM (three times) to generate the dianilino analogue. The cyclic urea was formed using $COIm_2$ (10 equiv., 0.1 M) overnight in DCM. The resin was then washed with DCM (three times), IPA (three times) and DCM (three times), dried and cleaved with HF/anisole (95/5) at 0°C for 1.5 h. The desired product was extracted with acetic acid/water (95/5), and lyophilized. The product was characterized by electrospray LC–MS under ESI conditions and by NMR (single diastereoisomer after separation; absolute configu-

ration not determined): ^{1}H NMR (500 MHz, DMSO-d_6) δ 2.83–2.87 (m, 2H), 4.02–4.05 (m, 1H), 6.12 (s, 1H), 6.82–6.88 (m, 2H), 6.95–7.03 (m, 2H), 7.07–7.11 (m, 2H), 7.28–7.28 (m, 2H), 7.42 (d, $J=7.70$ Hz, 1H), 7.50 (d, $J=7.35$ Hz, 1H), 9.55 (s, 1H), 10.26 (s, 1H).

Reduction procedure: To obtain compounds **2** and **15**, the reduction was achieved following the conditions described in Ref. 12. Low purities for compounds **4** and **10** are due to incomplete cyclization and other undetermined side reactions. Attempts to optimize the reaction conditions to drive cyclization to completion are under investigation.

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