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Diversity-oriented reconstruction of primitive diketopiperazine-fused tetrahydro-β-carboline ring system *via* Pictet-Spengler/Ugi-4CR/ deprotection-cyclization reactions

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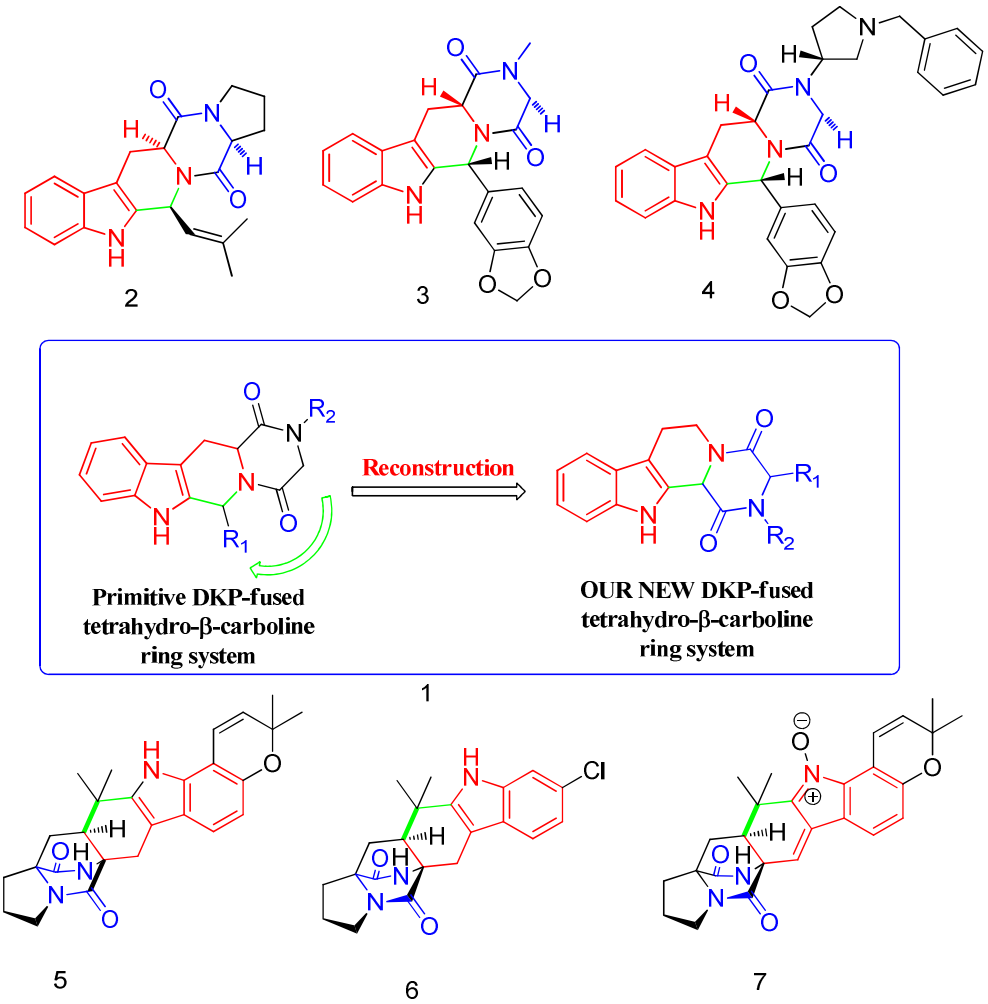
Abstract: An expedient construction of tetrahydro-β-carbolinediketopiperazines ring system which presents in various indole alkaloids has been documented. The synthetic strategy proceeds through Pictet-Spengler reaction with Ugi-4CR followed by deprotection-cyclization reactions. It is the first report on Pre Ugi-multicomponent reaction modification using 2,3,4,9-tetrahydro-1*H*-Pyrido[3,4-*b*]indole-1-carboxylic acid as acidic partner. This novel approach not only provided highly diverse reconstruct novel tetrahydro-β-carbolinediketopiperazines derivatives, but also it can be used as privileged structure in medicinal chemistry.

Key words: Tetrahydro-β-carbolinediketopiperazines, Multicomponent reactions, Pictet-spengler reaction, Ugi reaction, Deprotection-cyclization reactions.

Introduction

The tetrahydro-β-carbolinediketopiperazine ring system (**1**) is a common motif frequently encountered within a large family of indole alkaloids.[1] This alkaloids family have attracted much attention due to its wide range of biological activities, complex molecular structure and limited availability in nature. For example, demethoxyfumitremorgin C (**2**) showed antifungal activity, Tadalafil (**3**) and its analogues (**4**) showed antimalarial activity, further Stephacidins A (**5**), malbrancheamide B (**6**), and avrainvillamide (**7**) are a complex Diketopiperazines (DKP) natural product with potent anticancer activities (Figure 1.).[2]

Figure1. Some biologically active tetrahydro β-carboline fused 2, 5-diketopiperazine and our modernize prototype.



Molecular frameworks constantly have an effect on medicinal chemistry. Diversity-oriented of bioactive molecular frameworks have enhanced our vision towards structure-activity relationships, absorption, distribution, metabolism, elimination and toxicity. The selected structures might symbolize potential replacements of frequently occurring structural motifs. The development of efficient methodologies for the synthesis of the novel tetrahydro-β-carbolinediketopiperazines ring system has provided the suitable tools to open up an

investigation about the behaviour of such a kind of molecules towards biological systems. Several synthetic strategies for the construction of this motif has been established, but most of them involve time consuming complex reaction sequence, offer less structural and point diversity, suffer from low yields and use of expensive starting materials.[3] The development of general and inexpensive methodologies to generate the diverse scaffolds structurally related to these indole alkaloids would advance the finding of new agents in drug discovery.

Further , the post multicomponent reaction (MCR) has been proven as a powerful tool for the construction of complex molecules in few steps, and generally from readily available starting materials.[4] Among these MCRs, the isocyanide based Ugi multicomponent reaction (IMCR) especially useful for the synthesis of complex molecules due to its convergent character, atom economy, operational simplicity, high variability and provide the possibility of further transformations including condensation, an intramolecular SNAr reaction, ring-closure metathesis, cycloaddition, and macrolactonization etc.[5] Currently, much attention has been paid for the arrangement of Ugi-MCR and Pictet-Spengler reactions to the construct of natural product-like compounds. In this context, Domling *et. al.* reported the synthesis of polycyclic indole and schistosomiasis drug praziquantel (PZQ) by the coupling of Ugi-4CR and Pictet-Spengler reactions.[6] EI Kaim and co-workers describe an interesting methodology to obtain 2, 5-diketopiperazine by the Ugi reaction between amines, aldehydes, α-ketocarboxylic acid and homoaveratryl isocyanide followed by Pictet-Spengler reaction.[7] The most recent papers by Miranda and co-workers report the synthesis of piperazineohydroisoquinoline ring system using the combination of Ugi and Pictet-Spengler reactions.[8]

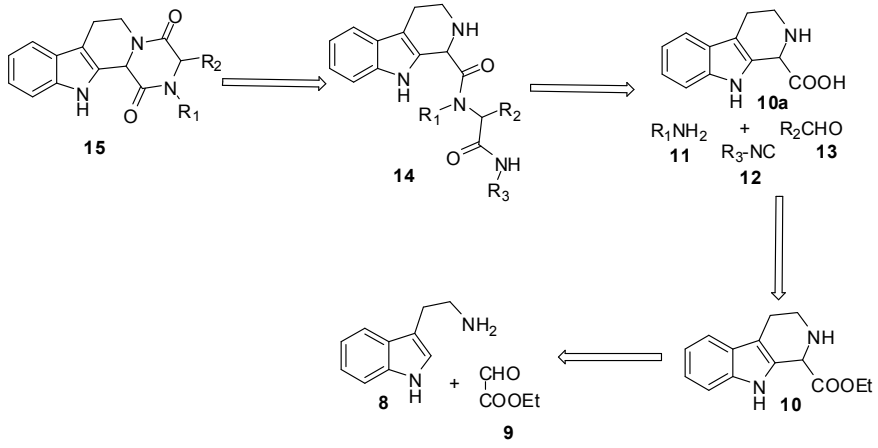
As a part of our program to synthesize the natural product inspired heterocycles through IMCR with other synthetic transformation, we wish to report our effort towards the synthesis of diverse tetrahydro-β-carbolinediketopiperazines ring system using Pictet-Spengler reaction

followed by Ugi condensation with deprotection-cyclization reactions.[9] To the best of our knowledge, it is first report on Ugi-multicomponent reaction using 2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indole-1-carboxylic acid as acidic partner, which is synthesized by Pictet-Spengler reaction. Our protocol (Pictet-Spengler/Ugi-4CR/ deprotection-cyclization reactions) is altered from documented protocol (Ugi-4CR/ Pictet-Spengler/ deprotection-cyclization reactions).

Results and discussion

It was envisaged that the acidic precursor 2,3,4,9-tetrahydro-1*H*-Pyrido[3,4-*b*]indole-1-carboxylic acid **10a** of Ugi product **14** might be constructed using Pictet-Spengler cyclization of tryptamine **8** and ethyl glyoxalate **9** followed by de-esterification reaction. The Ugi product **14,** which can be obtained by the reaction of acid **10a,** amine **11**, isocyanide **12** and aldehyde **13,** undergo tandem deprotection-cyclization reaction to genrate tetrahydro-β-carbolinediketopiperazines ring system **15** (Figure 2).

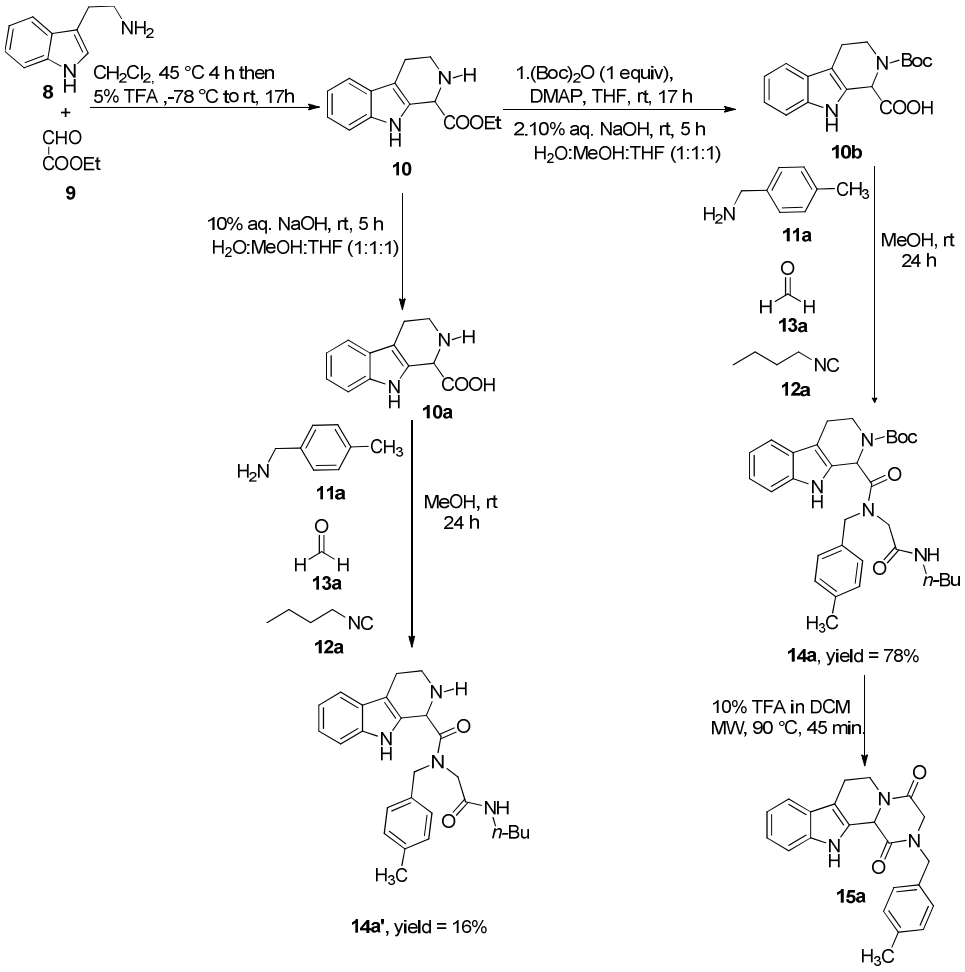
Figure 2. Retrosynthetic analysis



To actualize this design, we started with the Pictet-Spengler cyclization of tryptamine **8** with ethyl glyoxalate **9** to obtain ethyl 2,3,4,9-tetrahydro-1*H*-Pyrido[3,4-*b*]indole-1-carboxylate, which gave the hydrolysis reaction in the basic conditions to provide 2,3,4,9-tetrahydro-1*H*-

Pyrido[3,4-*b*]indole-1-carboxylic acid **10a** (scheme 1), one of the four inputs in the Ugi-MCR for the synthesis of tetrahydro-β-carbolinediketopiperazines ring system.

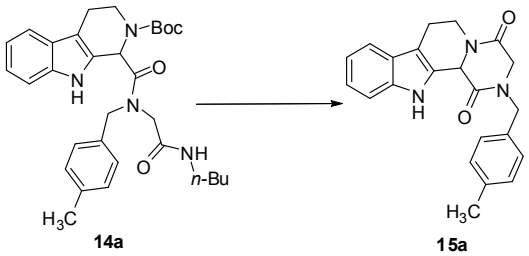
Scheme 1. Pictet-Spengler/Ugi-4CR/deprotection-cyclization sequence



Once Pictet-Spengler type product **10a** was synthesized, we first used aldehyde **13a**, amine **11a**, and isocyanide **12a** with acid **10a** in methanol at room temperature for the synthesis of Ugi product **14a'** (Scheme 1).[11] Unfortunately, the sequential Ugi reaction using **10a** as acid input, furnished the product **14a'** in very poor yield. Variation in the temperature and solvent did not improve the yield of product **14a'**. It may be due to the low solubility of **10a** in the used solvent or the result of a competitive reaction between the secondary amine in **10a** and formaldehyde **13a**. Further, we used pyrido *N*-Boc (*tert*-butyloxycarbonyl) protected

derivatives **10b** as acid input for Ugi reaction, [11] which provides Ugi product **14a** in very good yield. In the next step we used Ugi product **14a** as a model substrate to optimize the reaction conditions for tandem deprotection-cyclization reaction. It has been found that 10% TFA in DCE at reflux was the optimal condition for the tandem deprotection-cyclization reaction (Table 1, entry 4). It is interesting to note that under conventional heating the reaction took 12-15 h to reach the completion, while the reaction was finished in a 45-50 min when the reaction conceded out at 90°C using microwave irradiation.

Table 1. Optimization of acidic protocols for tandem deprotection-cyclization reaction



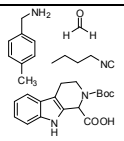
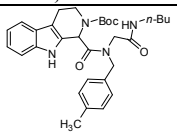
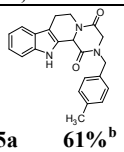
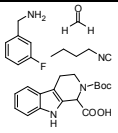
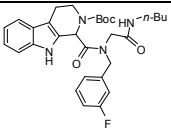
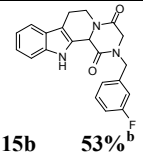
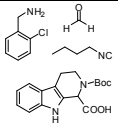
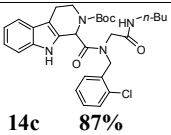
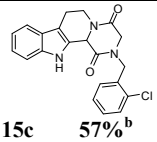
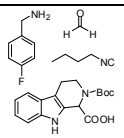
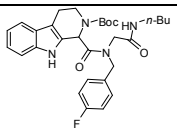
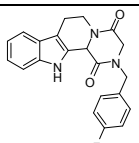
entry	Solvent	TFA %	yields (%)
1	DCM	5	23
2	DCM	10	30
3	DCE	5	26
4	**DCE**	**10**	**61**
5	THF	10	51

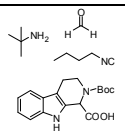
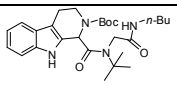
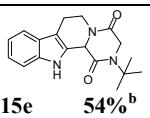
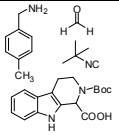
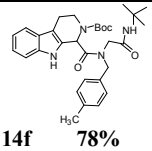
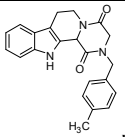
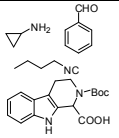
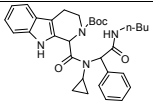
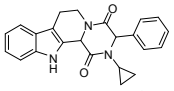
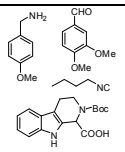
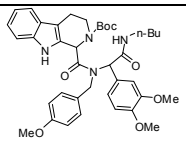
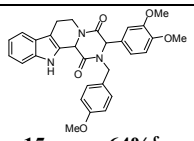
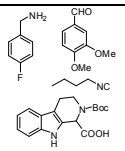
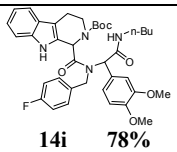
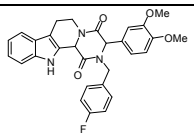
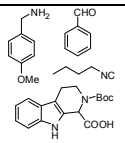
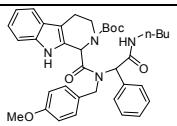
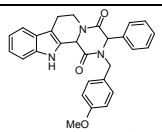
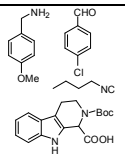
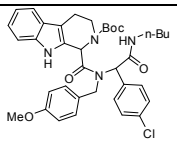
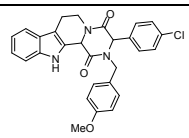
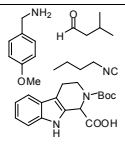
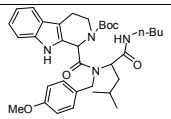
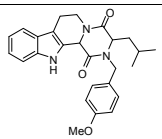
To test the scope and limitation of the proposed reactions, we introduced the commercially available aldehydes, amines, and isocyanides to identify the proper substrates that can generate the Ugi products with the structural features of deprotection-cyclization.

First, we made variations in the amines, and as expected the Ugi-product formed smoothly with different properties of amine (Table 2). Next, we used different aromatic aldehydes including formaldehyde also, which furnished the Ugi products in very good yields. However, when folmaldehyde was used in the Ugi reaction, the products have just one point chirality, but in case of other aldehydes the products were formed as a mixture of two distereoisomers (**14g-l**, Table 2), which was not separated in this step and used for next step i.e. deprotection-cyclization. The major diastereoisomer of adduct formed after deproection-cyclization was separated by column chromatography on silica gel.

Further, we used commercially available *n-butyl* isocyanide and *tert*-butyl isocyanide as convertible isocyanide in the Ugi reactions (Table 2, entry 6), but unfortunately the acid catalyzed tandem deprotection-cyclization reaction went properly only with *n-butyl* isocyanide (Table 2). It may be due to the steric hindrance of *tert*-butyl group in deproection-cyclization reaction.

Table 2. Synthesis of tetrahydro-β-carbolinediketopiperazines ring system

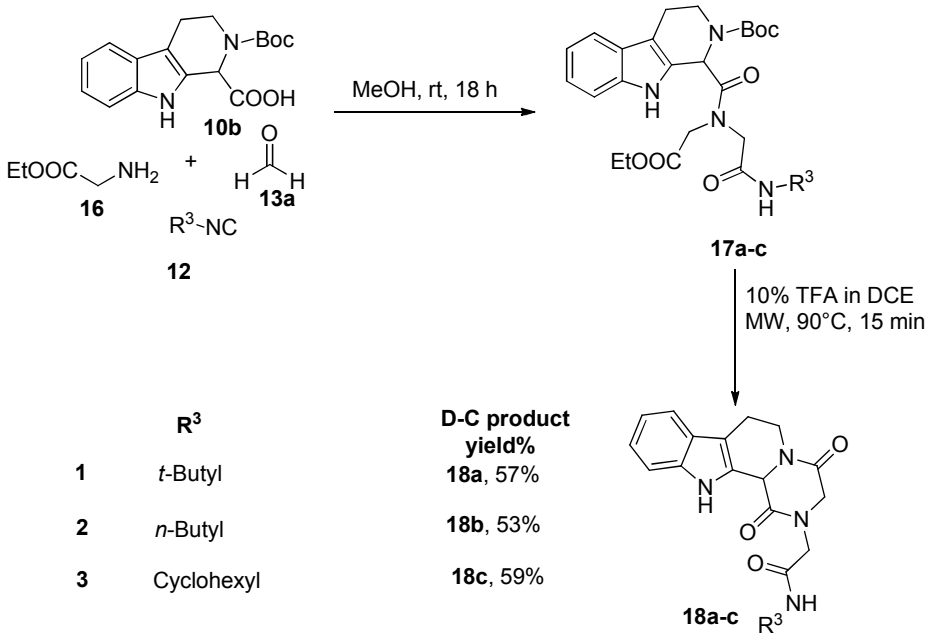
entry	Starting material	Ugi product 14, Yield%[a]	D-C product 15, Yield %[b]
1		 **14a 78%**	 **15a 61%[b]**
2		 **14b 85%**	 **15b 53%[b]**
3		 **14c 87%**	 **15c 57%[b]**
4		 **14d 82%**	 **15d 49%[b]**

5		 **14e 69%**	 **15e 54%**[b]
6		 **14f 78%**	 **15a 16%**[b]
7[c]		 **14g 71%** [g]d:r = 80:20	 **15f 70%**[c] [f]d:r = 80:20
8[c]		 **14h 82%** [g]d:r = 88:12	 **15g 64%**[c] [f]d:r = 88:12
9[d]		 **14i 78%** [g]d:r = 95:5	 **15h 55%**[c] [f]d:r = 95:5
10[c]		 **14j 84%** [g]d:r = 75:25	 **15i 68%**[c] [f]d:r = 75:25
11[c]		 **14k 87%** [g]d:r = 80:20	 **15j 60%**[c] [f]d:r = 80:20
12[e]		 **14l 61%** [g]d:r = 50:50	 **15k 47%** [f]d:r = 50:50

[a]Isolated yield of Ugi products, [b]Isolated yield of D-C products (**7-12**, yields refer to the mixture of diasteromers), [c]only major diasteromer was separated, [d]both diasteromers was separated, [e]unseparable diastereomers, [f]d:r determined by ^{1}H NMR, D-C = deprotection-cyclization reactions.

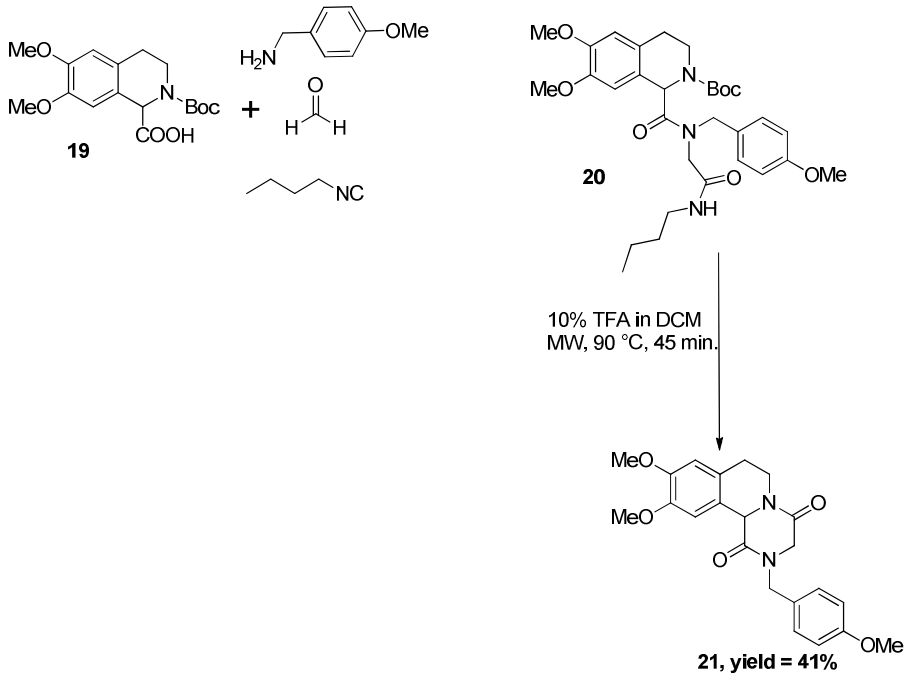
Subsequently, to increase the isocyanides diversity, we used the glycine ester **16** as amine input with acid **10b**, formaldehyde **13a**, and different isocyanides in Ugi-4CR condensation (Scheme 2, **17a-c**). To our pleasure good results of cyclized products **18a-c** were obtained through deprotection-cyclization reactions when the Ugi products were directly employed with 10% TFA in DCE under the microwave irradiation (Scheme 2, **18a-c**). Furthermore, *L*-alanine ester was used instead of glycine ester as amine input in Ugi-MCR. Unfortunately, deprotection-cyclization product was formed in trace amount when this Ugi product was employed with 10% TFA in DCE under the irradiation of microwave.

Scheme 2. Versatile synthesis of tetrahydro-β-carbolinediketopiperazines ring system



Interestingly, the tetrahydro-isoquinoline acid **19** was also investigated, which reacts with *n*-butyl-isocyanide, formaldehyde, 4-methoxybenzylamine in a same manner as described in the synthesis of products **15a-j**. This is a remarkable example of an efficient synthesis of isoquinoline fused diketopiperazine, which are the analogues of schistosomiasis drug praziquantel (PZQ).[6d]

Scheme3. Synthesis of isoquinolinediktopiperazine ring system



Conclusions

In summary, we have documented a convenient approach towards the synthesis and reconstructions of the primitive tetrahydro-β-carbolinediketopiperazines ring system. This synthetic strategy involves Pictet-Spengler reaction with Ugi-4CR followed by deprotection/cyclization reaction. We believe that this novel strategy not only provided the new pharmacologically active tetrahydro-β-carbolinediketopiperazines derivative in high diversity, but it can also be used to economically collect indole alkaloids type natural product.

Experimental

General information:

All reagents and solvents were purchased from commercial sources and used without purification. NMR spectra were recorded with 200, 300, 400 MHz spectrometers for ^{1}H NMR and 50, 75, 100 MHz for ^{13}C NMR on Bruker Supercon Magnet Avance DRX-300 spectrometers in deuterated solvents with TMS as internal reference (chemical shifts δ in ppm, coupling constant *J* in Hz.). Multiplicities are reported as follows: singlet (s), doublet

(d), triplet (t), multiplet (m), double doublet (dd), quartet (q) and broad singlet (br s). Melting points were determined in open capillary tubes on an electrically heated block and are uncorrected. Mass spectra and HRMS were taken in the ESI positive ion mode. Microwave reactions were conducted using a Biotage Initiator in 10-mL glass tubes, sealed with Teflon septum and placed in the microwave cavity. The reaction progress was monitored by thin layer chromatography (TLC) on pre-coated silica gel plates. Column chromatography was performed over Merck silica gel (230-400 flash). All compounds were characterized by TLC, ^{1}H NMR and ^{13}C NMR, MS and HRMS.

General procedure for the synthesis of Ugi products (14a-l), (17a-c) and 20: To the solution of the amines **11** or glycine ester **16** (1 mmol), 2,3,4,9-tetrahydro-*1H*-Pyrido[3,4-*b*]indole-1-carboxylic acid **10b** or 2-(tert-butoxycarbonyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline-1-carboxylic acid **19,** (1 mmol), and Paraformaldehyde or other aromatic aldehydes **13** (1.2 mmol) in methanol (3 mL) was added isocyanides (1 mmol) through a microsyringe at room temperature. After being stirring at rt for 24 hr, the mixture was concentrated and the Ugi-4CR reaction products were purified by column chromatography or used directly in the next step without further purification.

General procedure for the synthesis of D-C products 15a-k, 18a-c, 21: The Ugi-4CR products were dissolved in 10% TFA in DCE (5mL) in a 10 mL reaction glass vial containing a stirring bar, the vial was sealed tightly with a Teflon cap and placed in microwave cavity for 45-50 min (for 15a-j and 21) or 15 min (for 18a-c) at a pre-selected temperature of 90 $^{\circ}$C. After completion of the reaction as indicated by TLC, the solvent was evaporated under reduced pressure and the residue was purified by flash column chromatography on silica gel (eluent: hexane/ EtOAc) affording the corresponding products.

Characterization data of compounds:

Compound 14a:

White Solid, Yield 78% (414 mg), mp = 163-165 ^{0}C, FT-IR (KBr) ν (cm^{-1}): 3788, 3660, 3372, 1616, 1410, 1216, 1053, 769, 669; ^{1}H NMR (300 MHz, $CDCl_3$): 10.13 (s, 1H), 7.53 (d, *J* = 7.5 Hz, 1H), 7.45 (d, *J* = 7.5 Hz, 1H), 7.30 (d, *J* = 4.8 Hz, 2H), 7.17-7.09 (m, 4H), 5.90 (s, 1H), 5.79 (br s, 1H), 5.23-5.10 (m, 1H), 4.11-3.95 (m, 3H) 3.75 (d, *J* = 17.7 Hz, 1H), 3.29 (br s, 2H), 2.88 (br s, 2H), 2.35 (s, 3H), 1.55 (s, 9H), 1.44-1.29 (m, 4H), 0.95 (t, *J* = 6.3 Hz, 3H) ppm, ^{13}C NMR (75 MHz, $CDCl_3$): δ 172.3, 169.4, 155.9, 137.1, 136.3, 133.2, 130.2, 129.2, 129.1, 128.0, 127.6, 126.6, 121.6, 118.9, 118.0, 111.5, 109.5, 80.5, 60.4, 53.4, 50.7, 41.0, 39.7, 31.4, 28.4, 21.0, 19.9, 14.1, 13.6 ppm, HRMS (ESI) Calcd. for $C_{31}H_{41}N_4O_4$ $[M+H]^+$ 533.3128 Found 533.3122.

Compound 14b:

White Solid, Yield 85% (455 mg), mp = 134-136 ^{0}C, FT-IR (KBr) ν (cm^{-1}): 3374, 2926, 1609, 1387, 1220, 1030, 766; ^{1}H NMR (400 MHz, $CDCl_3$): 10.17 (s, 1H), 7.52 (d, *J* = 7.6 Hz, 1H), 7.47 (d, *J* = 11.2 Hz, 1H), 7.35-7.28 (m, 2H), 7.19 (t, *J* = 7.6 Hz, 2H), 7.11-7.05 (m, 2H), 5.97 (br s, 1H), 5.85 (s, 1H), 5.26 (d, *J* = 17.6 Hz, 1H), 4.98 (d, *J* = 15.2 Hz, 1H), 4.35 (d, *J* = 10.4 Hz, 1H), 4.08 (d, *J* = 15.6 Hz, 1H), 3.98-3.91 (m, 1H), 3.68 (d, *J* = 18.0 Hz, 1H), 3.26-3.14 (m, 2H), 2.92-2.81 (m, 2H), 1.57 (s, 9H), 1.47-1.24 (m, 4H), 0.92 (t, *J* = 7.2 Hz, 3H) ppm, ^{13}C NMR (75 MHz, $CDCl_3$): δ 172.6, 169.0, 156.0, 136.8, 136.3, 132.6, 131.5, 130.5, 129.5, 128.8, 127.2, 126.5, 121.8, 119.0, 118.1, 111.5, 109.6, 80.8, 50.8, 50.1, 49.7, 41.1, 39.8, 31.4, 28.4, 21.1, 19.9, 13.6 ppm, HRMS (ESI) Calcd. for $C_{30}H_{38}FN_4O_4$ $[M+H]^+$ 537.2877 Found 537.2870.

Compound 14c:

White Solid, Yield 69% (480 mg), mp = 167-169 ^{0}C, FT-IR (KBr) ν (cm^{-1}): 3319, 3071, 1672, 1550, 1365,1163,1098, 928, 757, 669; ^{1}H NMR (300 MHz, $CDCl_3$): 10.37 (s, 1H), 7.54 (d, *J* = 7.5 Hz, 1H), 7.45 (d, *J* = 7.8 Hz, 1H), 7.38-7.28 (m, 2H), 7.21-7.16 (m, 3H), 7.12 (t, *J*

= 7.5 Hz, 1H), 5.90 (s, 1H), 5.60 (s, 1H), 5.35-5.29 (m, 1H), 5.22 (d, *J* = 16.2 Hz, 1H), 4.37 (d, *J* = 16.2 Hz, 1H), 4.06-3.95 (m, 1H), 3.73 (d, *J* = 16.2 Hz, 1H), 3.48 (s, 1H), 2.89-2.81 (m, 2H), 1.56 (s, 9H), 1.42-1.33 (m, 2H), 1.30-1.29 (m, 2H), 0.95 (t, *J* = 6.9 Hz, 3H) ppm, 172.5, 168.4, 156.0, 136.3, 133.9, 133.5, 129.4, 129.0, 128.6, 127.1, 126.5, 121.6, 118.8, 118.1, 111.4, 109.5, 80.6, 60.4, 53.4, 52.3, 51.6, 50.7, 49.9, 48.2, 41.1, 28.6, 21.1, 14.1 ppm, HRMS (ESI) Calcd. for $C_{30}H_{38}ClN_4O_4$ $[M+H]^+$ 553.2582 Found 553.2578.

Compound 14d:

White Solid, Yield 82% (439 mg), mp = 155-157 ^{0}C, FT-IR (KBr) ν (cm^{-1}): 3325, 3015, 1675, 1512, 1457, 1218, 1100, 928, 669; ^{1}H NMR (300 MHz, $CDCl_3$): 10.15 (s, 1H), 7.53 (d, *J* = 7.5 Hz, 1H), 7.44 (d, *J* = 7.8 Hz, 1H), 7.28-7.15 (m, 3H), 7.02-6.97 (m, 3H), 5.83 (s, 1H), 5.70 (s, 1H), 5.31 (s, 1H), 5.22 (t, *J* = 17.4 Hz, 2H), 4.37 (d, *J* = 13.8 Hz, 1H), 4.15 (d, *J* = 15.6 Hz, 1H), 4.02-3.96 (m, 1H), 3.70 (d, *J* = 17.7 Hz, 1H), 2.89 (br s, 3H), 1.81 (br s, 2H), 1.55 (s, 9H), 1.46-1.29 (m, 4H), 0.95 (t, *J* = 6.9 Hz, 3H) ppm, ^{13}C NMR (75 MHz, $CDCl_3$): δ 172.5, 168.6, 156.0, 136.3, 132.2, 132.1, 129.5, 129.4, 128.9, 126.5, 121.7, 118.9, 118.1, 115.5, 115.2, 111.4, 109.5, 80.7, 53.4, 52.2, 51.1, 50.7, 50.1, 50.0, 41.1, 28.6, 21.1 ppm, HRMS (ESI) Calcd. For $C_{30}H_{38}FN_4O_4$ $[M+H]^+$ 537.2877 Found 537.2873.

Compound 14e:

White Solid, Yield 69% (333 mg), mp = 148-150 ^{0}C, FT-IR (KBr) ν (cm^{-1}): 3430, 2957, 2823, 1721, 1664, 1487, 1067, 757, ^{1}H NMR (300 MHz, $CDCl_3$): 10.34 (s, 1H), 7.52-7.45 (m, 2H), 7.19-7.06 (m, 2H), 6.14 (br s, 1H), 5.66 (s, 1H), 5.18 (d, *J* = 18.6 Hz, 1H), 4.34 (d, *J* = 10.2 Hz, 1H), 4.07 (d, *J* = 18.0 Hz, 2H), 3.44-3.17 (m, 2H), 2.89-2.76 (m, 2H), 1.52 (s, 9H), 1.48-1.42 (m, 2H), 1.36 (s, 9H), 1.33-1.29 (m, 2H), 0.92 (t, *J* = 7.2 Hz, 3H) ppm, ^{13}C NMR (75 MHz, $CDCl_3$): δ 174.0, 171.4, 156.1, 136.2, 129.8, 126.6, 121.5, 118.8, 118.0,

111.5, 108.8, 80.5, 58.3, 52.6, 48.2, 41.2, 39.7, 31.4, 28.4, 27.9, 21.0, 19.9, 13.6 ppm, HRMS (ESI) Calcd. for $C_{27}H_{41}N_4O_4$ $[M+H]^+$ 485.3128 Found 485.3120.

Compound 14f:

White Solid, Yield 78% (414 mg), mp = 142-144 ^{0}C, FT-IR (KBr) ν (cm^{-1}): 3345, 3019, 1663, 1411,1215, 1045,929,757; ^{1}H NMR (400 MHz, $CDCl_3$): 10.2 (s, 1H), 7.54 (d, *J* = 7.6 Hz, 1H), 7.44 (d, *J* = 8.0 Hz, 1H), 7.28-7.05 (m, 6H), 5.90 (s, 1H), 5.63 (d, *J* = 19.6 Hz, 1H), 5.21 (d, *J* = 17.6 Hz, 1H), 4.39 (d, *J* = 12.8 Hz, 1H), 4.12-4.04 (m, 1H), 3.72 (d, *J* = 17.6 Hz, 1H), 2.93-2.87 (m, 2H), 2.35 (s, 3H), 1.57 (s, 9H), 1.35 (s, 9H) ppm, ^{13}C NMR (100 MHz, $CDCl_3$): 172.4, 168.7, 155.9, 138.3, 136.4, 136.3, 129.2, 129.0, 128.5, 128.4, 128.2, 126.6, 124.9, 121.6, 118.9, 111.4, 109.5, 80.5, 52.2, 51.0, 50.4, 50.1, 41.1, 28.6, 28.4, 21.4, 21.2 ppm, HRMS (ESI) Calcd. for $C_{31}H_{41}N_4O_4$ $[M+H]^+$ 533.3128 Found 533.3126.

Compound 15a:

Bright yellow solid, Yield 61% (218 mg), mp = 130-132 ^{0}C, FT-IR (KBr) ν (cm^{-1}): 3327, 2921, 2162, 1567, 1439, 1210, 760, ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.38 (s, 1H), 7.50 (d, *J* = 8.0 Hz, 1H), 7.40 (d, *J* = 8.4 Hz, 1H), 7.23 (t, *J* = 7.2 Hz, 1H), 7.15-7.11 (m, 5H), 5.43 (s, 1H), 5.02 (q, *J* = 4.4 Hz, 1H), 4.66 (d, *J* = 14.4 Hz, 1H), 4.46 (d, *J* = 14.4 Hz, 1H), 3.98 (dd, *J* = 17.8, 39.5 Hz, 2H), 3.01-2.92 (m, 2H), 2.82-2.74 (m, 1H), 2.33(s, 3H) ppm, ^{13}C NMR (75 MHz, $CDCl_3$): δ 162.4, 161.1, 137.5, 135.3, 130.6, 128.9, 127.9, 126.5, 125.8, 121.8, 118.9, 117.5, 110.7, 108.8, 54.8, 48.5, 48.1, 40.1, 20.4, 19.6 ppm, HRMS (ESI) Calcd. for $C_{22}H_{22}N_3O_2$ $[M+H]^+$ 360.1712 Found 360.1700.

Compound 15b:

Yellow solid, Yield 53% (192 mg), mp = 125-127 ^{0}C, FT-IR (KBr) ν (cm^{-1}): 3430, 2829, 2420, 1660, 1610, 1343, 675, ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.27 (s, 1H), 7.51 (d, *J* = 8.0 Hz, 1H), 7.40 (d, *J* = 8.0 Hz, 1H), 7.34-7.28 (m, 1H), 7.23 (t, *J* = 7.2 Hz, 1H), 7.14 (t, *J* = 7.2 Hz, 1H), 7.06-6.94 (m, 3H), 5.53 (s, 1H), 5.05 (d, *J* = 7.6 Hz, 1H), 4.74 (d, *J* = 14.8 Hz, 1H), 4.52 (d, *J* = 14.4 Hz, 1H), 4.04 (q, *J* = 17.6 Hz, 2H), 3.01-2.95 (m, 2H), 2.83-2.80 (m, 1H) ppm, ^{13}C NMR (75 MHz, $CDCl_3$): δ , 163.4, 161.5, 136.8, 136.0, 130.7, 130.6, 130.1, 130.0, 126.9, 126.5, 124.1, 123.6, 122.6, 119.7, 118.3, 111.5, 109.7, 55.6, 49.1, 40.9, 28.7, 20.3 ppm, HRMS (ESI) Calcd. for $C_{21}H_{19}FN_3O_2$ $[M+H]^+$ 364.1461 Found 364.1454.

Compound 15c:

Pale yellow solid, Yield 57% (216 mg), mp = 142-144 ^{0}C, FT-IR (KBr) ν (cm^{-1}): 3445, 2428, 1529, 1437, 1379, 671, ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.28 (s, 1H), 7.51 (d, *J* = 8.0 Hz, 1H), 7.40-7.37 (m, 2H), 7.31-7.19 (m, 4H), 7.14 (t, *J* =7.6 Hz, 1H), 5.53 (s, 1H), 5.05 (d, *J* = 8.0 Hz, 1H), 4.88 (d, *J* = 14.8 Hz, 1H), 4.76 (d, *J* = 14.8 Hz, 1H), 4.06 (q, *J* = 18.0 Hz, 2H), 3.05- 2.96 (m, 2H), 2.95-2.80 (m, 1H) ppm, ^{13}C NMR (75 MHz, $CDCl_3$): δ 162.8, 161.0, 135.4, 133.5, 131.3, 129.6, 129.3, 129.1, 126.8, 126.3, 125.9, 121.9, 119.1, 117.7, 110.8, 109.0, 54.9, 48.6, 46.0, 40.3, 19.6 ppm, HRMS (ESI) Calcd. for $C_{21}H_{19}ClN_3O_2$ $[M+H]^+$ 380.1166 Found 380.1151.

Compound 15d:

Light yellow solid, Yield 49% (177 mg), mp = 190-192 ^{0}C, FT-IR (KBr) ν (cm^{-1}): 3427, 2927, 2364, 1660, 1439, 1219, 771, 675, ^{1}H NMR (300 MHz, $CDCl_3$): δ 9.31 (s, 1H), 7.53 (d, *J* = 7.5 Hz, 1H), 7.42 (d, *J* = 7.8 Hz, 1H), 7.24-7.02 (m, 6H), 5.53 (s, 1H), 5.07 (d, *J* = 8.1 Hz, 1H), 4.71 (d, *J* = 14.4 Hz, 1H), 4.56 (d, *J* = 14.4 Hz, 1H), 4.05 (q, *J* = 17.7 Hz, 2H), 3.06-2.81 (m, 3H) ppm, ^{13}C NMR (75 MHz, $CDCl_3$): δ 164.5, 162.6, 160.9, 135.4, 129.8, 129.6, 129.5,

126.3, 125.8, 121.9, 119.1, 117.7, 115.6, 115.1, 110.8, 109.0, 54.9, 48.2, 48.1, 40.2, 29.0, 19.7 ppm, HRMS (ESI) Calcd. for $C_{21}H_{19}FN_3O_2$ $[M+H]^+$ 364.1461 Found 364.1464.

Compound 15e:

White Solid, Yield 54% (167 mg), mp = 130-132 ^{0}C, FT-IR (KBr) ν (cm^{-1}): 3436, 3018, 2927, 1821, 1664, 1385, 1096, 757, ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.28 (s, 1H), 7.50 (d, *J* = 8.0 Hz, 1H), 7.38 (d, *J* = 8.0 Hz, 1H), 7.21 (t, *J* = 7.2 Hz, 1H), 7.12 (t, *J* = 7.2 Hz, 1H), 5.36 (s, 1H), 4.99 (d, *J* = 7.6 Hz, 1H), 4.08 (s, 2H), 3.00 (d, *J* = 9.2 Hz, 2H), 2.81 (d, *J* = 11.2 Hz, 1H), 1.49 (s, 9H) ppm, ^{13}C NMR (75 MHz, $CDCl_3$): δ 163.5, 162.1, 135.2, 127.1, 125.9, 121.8, 118.9, 117.6, 110.7, 108.7, 57.9, 55.7, 46.3, 39.9, 27.0, 19.6 ppm, HRMS (ESI) Calcd. for $C_{18}H_{22}N_3O_2$ $[M+H]^+$ 312.1712 Found 360.1710.

Compound 15f:

Yellow-green solid, Yield 70% (259 mg), data for major isomer: mp = 150-152 ^{0}C, FT-IR (KBr) ν (cm^{-1}): 3421, 2813, 2457, 1621, 1441, 928, ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.36 (s, 1H), 7.51 (d, *J* = 7.6 Hz, 1H), 7.45-7.38 (m, 6H), 7.23 (t, *J* = 7.2 Hz, 1H), 7.14 (t, *J* = 8.0 Hz, 1H), 5.55 (s, 1H), 5.09 (s, 1H), 4.96 (d, *J* = 7.6 Hz, 1H), 2.97 (d, *J* = 2.4 Hz, 2H), 2.82 (d, *J* = 11.2 Hz, 1H), 2.53-2.51 (m, 1H), 1.05-1.01 (m, 1H), 0.80-0.77 (m, 1H), 0.66-0.58 (m, 2H) ppm, ^{13}C NMR (75 MHz, $CDCl_3$): δ 166.5, 163.4, 135.6, 135.5, 128.7, 128.2, 126.3, 125.9, 125.7, 121.9, 119.0, 117.7, 110.8, 109.3, 64.8, 54.9, 40.3, 27.8, 19.6, 8.4, 4.6 ppm, HRMS (ESI) Calcd. for $C_{23}H_{22}N_3O_2$ $[M+H]^+$ 372.1712 Found 372.1706.

Compound 15g:

Bright yellow solid, Yield 64% (327 mg), data for major isomer: mp = 182-184 ^{0}C, FT-IR (KBr) ν (cm^{-1}): 3419, 2975, 2401, 1606, 1518, 1423, 928, 759 ^{1}H NMR (300 MHz, $CDCl_3$): δ 9.58 (s, 1H), 7.55 (d, *J* = 8.1 Hz, 1H), 7.46 (d, *J* = 8.1 Hz, 1H), 7.23-7.11 (m, 2H), 7.04 (d, *J* = 8.7 Hz, 2H), 6.95-6.87 (m, 3H), 6.82 (d, *J* = 8.4 Hz, 2H), 5.65 (s, 1H), 5.49 (d, *J* = 14.7

Hz, 1H), 4.94-4.86 (m, 2H), 3.92 (s, 6H), 3.90-3.80 (m, 1H), 3.77 (s, 3H), 3.60 (d, *J* = 14.1 Hz, 1H), 3.01-2.80 (m, 2H) ppm, ^{13}C NMR (75 MHz, $CDCl_3$): δ 163.7, 163.1, 158.8, 148.9, 135.7, 129.3, 127.4, 126.5, 125.8, 125.6, 121.8, 118.9, 117.9, 117.6, 113.6, 110.8, 109.9, 109.4, 61.6, 55.4, 55.3, 54.6, 54.5, 46.0, 40.6, 19.5 ppm, HRMS (ESI) Calcd. for $C_{30}H_{30}N_3O_5$ $[M+H]^+$ 512.2185 Found 512.2191.

Compound 15h:

White Solid, Yield 55% (274 mg), data for major isomer: mp = 188-190 ^{0}C, FT-IR (KBr) ν (cm^{-1}): 2926, 2365, 1660, 1440, 1221, 771, ^{1}H NMR (200 MHz, $CDCl_3$): δ 9.45 (s, 1H), 7.54-7.41 (m, 2H), 7.21-6.84 (m, 9H), 5.65 (s, 1H), 5.48 (d, *J* = 14.8 Hz, 1H), 4.94 (d, *J* = 7.6 Hz, 1H), 4.84 (s, 1H), 3.91 (s, 6H), 3.66 (d, *J* = 14.6, 1H), 3.01-2.78(m, 3H) ppm, ^{13}C NMR (50 MHz, $CDCl_3$): δ 163.9, 162.9, 149.1, 149.1, 135.7, 129.7, 129.6, 127.2, 126.3, 125.8, 121.9, 119.0, 117.9, 117.7, 115.3, 115.0, 110.9, 110.8, 109.9, 109.5, 62.0, 55.4, 55.3, 54.5, 46.0, 40.6, 19.5 ppm. HRMS (ESI) Calcd. for $C_{29}H_{27}FN_3O_4$ $[M+H]^+$ 500.1985 Found 500.1971.data for minor isomer: ^{1}H NMR (300 MHz, $CDCl_3$): δ 9.12 (s, 1H), 7.50 (d, *J* = 8.1 Hz, 1H), 7.42 (d, *J* = 7.2 Hz, 1H), 7.25-7.22 (m, 5H), 7.17-7.05 (m, 3H), 6.80-6.68 (m, 2H), 5.73 (s, 1H), 5.47 (d, *J* = 15.0 Hz, 1H), 4.99-4.94 (m, 1H), 4.78 (s, 1H), 3.80 (s, 3H), 3.47 (d, *J* = 14.7 Hz, 1H), 3.12-2.88 (m, 1H), 2.37 (s, 3H), 2.34-2.06 (m, 2H) ppm, HRMS (ESI) Calcd. for $C_{29}H_{27}FN_3O_4$ $[M+H]^+$ 500.1985 Found 500.1978.

Compound 15i:

White solid, Yield 68% (306 mg), data for major isomer: mp = 198-200 ^{0}C, FT-IR (KBr) ν (cm^{-1}): 3422, 2931, 2365, 1650, 1456, 1243, 1030, 769, 518, ^{1}H NMR (200 MHz, $CDCl_3$): δ 8.12 (s, 1H),7.68 (d, J = 7.6 Hz, 1H), 7.39 (d, *J* = 7.4 Hz, 1H), 7.23-7.06 (m, 7H), 6.94 (d, *J* = 8.6 Hz, 2H), 6.81 (d, *J* = 8.6 Hz, 2H), 5.91 (s, 1H), 5.52 (d, *J* = 14.4 Hz, 1H), 4.74 (s, 1H), 4.51 (d-d, *J* = 9.8, 3.4 Hz, 1H), 3.85-3.76 (m, 4H), 3.50 (d, *J* = 14.4 Hz, 1H), 3.21 (d-d, *J* =

14.8, 9.8 Hz, 1H), 2.98-2.82 (m, 1H), ^{13}C NMR (50 MHz, $CDCl_3$): δ 163.7, 162.9, 158.9, 135.7, 135.2, 129.3, 128.7, 128.4, 126.6, 126.4, 125.8, 125.6, 121.9, 118.9, 117.7, 113.7, 110.9, 109.5, 61.9, 54.6, 54.5, 46.0, 40.6,19.6 ppm, HRMS (ESI) Calcd. for $C_{28}H_{26}N_3O_3$ $[M+H]^+$ 452.1974 Found 452.1961.

Compound 15j:

Pale yellow solid, Yield 60% (291 mg), data for major isomer: mp = 202-204 ^{0}C, FT-IR (KBr) ν (cm^{-1}): 3359, 2920, 2365, 1656, 1457, 1249, 1093, 767, 514, ^{1}H NMR (300 MHz, $CDCl_3$): δ 9.47 (s, 1H), 7.53 (d, *J* = 8.1 Hz, 1H), 7.45-7.41 (m, 3H), 7.31-7.22 (m, 3H), 7.16 (t, *J* = 7.2 Hz, 1H), 6.99 (d, *J* = 8.7 Hz, 2H), 6.79 (d, *J* = 8.7 Hz, 2H), 5.65 (s, 1H), 5.49 (d, *J* = 14.4 Hz, 1H), 4.88 (s, 2H), 3.75 (s, 3H), 3.52 (d, *J* = 14.4 Hz, 1H), 3.02-2.79 (m, 3H), ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ 163.6, 162.5, 159.0, 135.7, 134.5, 133.7, 129.3, 128.9, 127.7, 126.4, 125.8, 125.3, 122.0, 119.0, 117.7, 113.8, 110.9, 109.5, 61.4, 54.6, 54.6, 46.1, 40.7, 19.5 ppm, HRMS (ESI) Calcd. for $C_{28}H_{25}ClN_3O_3$ $[M+H]^+$ 486.1584 Found 486.1604.

Compound 15k:

Yellow solid, Yield 47% (291 mg), obtained as two unseparable isomer mixtures, FT-IR (KBr) ν (cm^{-1}): 3363, 3010, 2910, 2360, 1734, 1643, 1444, 1263, 1103, 753, 510 ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.22 (br s, 2H), 7.49-7.41 (m, 5H), 7.23 (d, J = 8.1 Hz, 2H), 7.14-7.06 (m, 5H), 7.02-6.88 (m, 4H), 6.21 (s, 1H), 5.82 (s, 1H), 5.26 (br s, 2H), 4.53 (d, *J* = 17.1 Hz, 1H), 4.23 (d, *J* = 12.0 Hz, 1H), 4.10-4.03 (m, 2H), 3.86 (s, 3H), 3.82 (s, 3H), 3.29-3.17 (m, 5H), 2.85-2.78 (m, 3H), 2.33-2.19 (m, 2H), 1.06-0.86 (m, 18H) ppm. HRMS (ESI) Calcd. for $C_{26}H_{30}N_3O_3$ $[M+H]^+$ 432.2287 Found 432.2270.

Compound 18a:

White solid, Yield 57% (309 mg), mp = 180-182 ^{0}C, FT-IR (KBr) ν (cm^{-1}): 3429, 3019, 2927, 1664, 1439, 1215, 1097, 757, 669, ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.24 (s, 1H), 7.51 (

d, *J* = 7.5 Hz, 1H), 7.37 (d, *J* = 8.1 Hz, 1H), 7.28 (s, 1H), 7.23-7.09 (m, 1H), 5.74 (s, 1H), 5.51 (s, 1H), 5.11-5.02 (m, 1H), 4.43 (d, *J* = 17.1 Hz, 1H), 4.26 (d, *J* = 15.3 Hz, 1H), 4.10 (d, *J* = 17.4 Hz, 1H), 3.64 (d, *J* = 15.3 Hz, 1H), 3.05-2.80 (m, 3H),1.36 (s, 9H) ppm, ^{13}C NMR (75 MHz, $CDCl_3$): δ 166.0, 164.6, 136.4, 127.2, 126.8, 122.9, 120.0, 118.6, 111.8, 110.0, 55.6, 52.2, 51.5, 50.1, 41.1, 29.0, 20.6 ppm, HRMS (ESI) Calcd. for $C_{20}H_{25}N_4O_3$ $[M+H]^+$ 369.1927 Found 369.1920.

Compound 18b:

White solid, Yield 53% (290 mg), mp = 160-162 ^{0}C, FT-IR (KBr) ν (cm^{-1}): 3424, 2929, 1657, 1387, 1218, 1111, 762, ^{1}H NMR (300 MHz, $CDCl_3$): δ 9.24 (s, 1H), 7.51 (d, *J* = 7.5 Hz, 1H), 7.38 (d, *J* = 8.1 Hz, 1H), 7.23 (t, *J* = 7.5 Hz, 1H), 7.14 (t, *J* = 7.2 Hz, 1H), 6.05 (s, 1H), 5.49 (s, 1H), 5.07 (d, *J* = 7.5 Hz, 1H), 4.41 (d, *J* = 17.4 Hz, 1H), 4.24 (q, *J* = 15.3 Hz, 2H), 3.79 (d, *J* = 15.3 Hz, 1H), 3.29-3.23 (m, 2H), 3.04-2.80 (m, 3H), 1.54-1.30 (m, 4H), 0.93 (t, *J* = 7.2 Hz, 3H) ppm, ^{13}C NMR (75 MHz, $CDCl_3$): δ 166.5, 164.4, 163.7, 137.0, 128.7, 126.7, 122.0, 119.4, 118.5, 112.8, 108.9, 55.8, 51.5, 48.7, 48.4, 33.1, 25.9, 25.3, 20.8 ppm, HRMS (ESI) Calcd. for $C_{20}H_{25}N_4O_3$ $[M+H]^+$ 369.1927 Found 369.1923.

Compound 18c:

White solid, Yield 59% (346 mg), mp = 210-212 ^{0}C, FT-IR (KBr) ν (cm^{-1}): 3299, 2928, 2399, 1651, 1095, 928, 757, ^{1}H NMR (300 MHz, $CDCl_3$): δ 10.6 (s, 1H), 7.95 (d, *J* = 7.2 Hz, 1H), 7.48-7.41 (m, 2H), 7.09-6.95 (m, 2H), 5.67 (s, 1H), 4.80 (d, *J* = 12.0 Hz, 1H), 4.25 (d, *J* = 17.4 Hz, 1H), 4.08-3.91 (m, 3H), 3.62-3.52 (m, 1H), 3.12-2.94 (m, 1H), 2.76 (s, 2H), 1.70-1.53 (m, 5H), 1.20-1.13 (m, 5H) ppm, ^{13}C NMR (75 MHz, $CDCl_3$): δ 166.5, 164.4, 163.7, 137.0, 128.7, 126.7, 122.0, 119.4, 118.4, 112.8, 108.9, 55.8, 51.5, 48.7, 48.4, 33.1, 25.9, 25.3, 20.8 ppm, HRMS (ESI) Calcd. for $C_{22}H_{26}N_4O_3$ $[M+H]^+$ 394.2005 Found 394.1994.

Compound 21:

Semi-solid, Yield 41% (162 mg), FT-IR (Neat) ν (cm^{-1}): 3421, 3019, 2932, 1654, 1401, 1215, 1096, 757, 669, ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.30 (s, 1H), 7.22 (d, *J* = 8.4 Hz, 2H), 6.85 (d, *J* = 8.7 Hz, 2H), 6.61 (s, 1H), 5.25 (s, 1H), 4.68-4.61 (m, 2H), 4.53 (d, *J* = 14.4 Hz, 1H), 3.93 (s, 3H), 3.88 (s, 3H), 3.87-3.82 (m, 2H), 3.78 (s, 3H), 3.14-2.95 (m, 2H), 2.70 (d, *J* = 14.1 Hz, 1H), ^{13}C NMR (75 MHz, $CDCl_3$): δ 164.1, 163.9, 159.5, 148.7, 147.4, 129.8, 127.1, 126.7, 122.9, 114.3, 111.8, 109.0, 59.1, 56.0, 55.9, 55.3, 49.1, 48.9, 41.0, 26.9 ppm, HRMS (ESI) Calcd. for $C_{22}H_{25}N_2O_5$ $[M+H]^+$ 379.1763 Found 379.1760.

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Supporting Information Available: Copies of ^{1}H and ^{13}C NMR spectra of the all compounds will be available as supplementary data

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Graphical abstract:

Diversity-oriented reconstruction of primitive diketopiperazine-fused tetrahydro-β-carboline ring system *via* Pictet-Spengler/Ugi-4CR/ deprotection-cyclization reactions

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