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Cite this: DOI: 10.1039/xoxxoooooox

Highly stereoselective one-pot construction of trisubstituted tetrahydro-β-carboline-fused diketopiperazines: A synthetic route towards cialis analogues

Received ooth January 2012,
Accepted ooth January 2012
DOI: 10.1039/xoxxoooooox

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A facile and efficient synthetic method for the stereoselective preparation of trisubstituted tetrahydro-β-carboline-fused diketopiperazine derivatives is reported. The methodology represents a one-pot four-step reaction, employing the Ugi four-component condensation which is followed by a Boc-deprotection, a Pictet-Spengler reaction and a final lactamization. All THBC-DKPs were obtained in good yields and excellent diastereomeric excess.

Over the past decades, the synthesis of novel tetrahydro-β-carbolines (THBCs) has attracted considerable interest due to the prevalence of indoles in medicinal products.[1] Indoles that are fused with a diketopiperazine **1** moiety form an interesting motif which is found in several natural products and which proves to possess a wide diversity of biological activities. Tadalafil **2** (Cialis™, Icos/Lilly), for example, is a potent and selective phosphodiesterase type 5 (PDE5) enzyme inhibitor discovered by GlaxoSmithKline and used as a drug for the management of erectile dysfunction.[2] The analogous structure **3** exhibits antiplasmodial activity.[3] While Fumitremorgin C **4** showed to be a selective inhibitor of the breast cancer resistance protein (BCRP/ABCG2),[4] THBC-DKP **5** serves as an anti-cancer agent,[5] and anti-thrombotic activity after oral administration can also be targeted by use of this core scaffold[6] (**6,** Fig. 1).

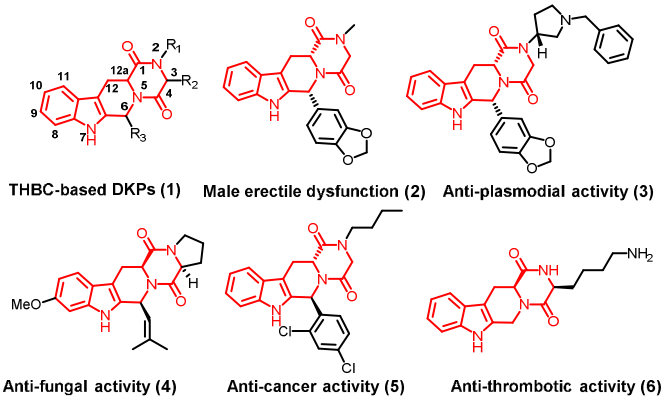


Fig. 1 Structurally related bioactive and naturally occurring THBC-based DKPs compounds.

Several methods have been developed for the synthesis of tetrahydro-β-carboline (THBC) scaffolds.[1] One of the most straightforward ways involves a Pictet–Spengler reaction between a tryptamine derivative and an aldehyde.[7] Similarly, diketopiperazines (DKPs) represent an important class of interesting bioactive molecules.[8] Multicomponent reactions (MCRs) are especially amenable to produce diketopiperazines in a straightforward manner.[9,10] One of the most explored MCRs is the Ugi reaction.[11]

Moreover, a variety of elegant Ugi-post-condensation modifications have been reported in literature (e.g. Ugi/Diels Alder,[12] Ugi/Buchwald–Hartwig,[13] Ugi/Heck,[14] Ugi/nucleophilic additions/substitutions,[15] Ugi/ring-closing metathesis,[16] Ugi/Aldol sequences,[17] Ugi/deprotection/cyclization[18] and Ugi/Pictet-Spengler).[19] *N*-fused polycyclic THBC-DKP alkaloid analogues of type **1** can be derived by unification of the THBC and DKP pharmacophores through the combination of Ugi and Pictet-Spengler reactions, a unification that belongs to the so-called post-Ugi Pictet-Spengler condensations procedures.[19] In all reported cases, the THBC-DKPs were isolated in low yield and with poor diastereoselectivity. A mixture of two diastereomers was for example obtained after a Ugi/deprotection/amine-ester cyclisation/Pictet-Spengler sequence, [19e] but other protocols have also been developed to generate the polycyclic THBC-DKPs.[20,21] However, these methods often require multi-step synthesis and result in low product yields. In order to obtain chiral THBC precursors a separation of the diastereomeric mixtures and crystallization-induced asymmetric transformation are needed.[2,3,21] Recently, we have reported the preparation of *N*-benzyl-2-substituted piperazines in racemic form and derived from DKPs by a Ugi-4CR/deprotection/lactamization/reduction reaction.[22] In pursuit of this work, a retrosynthetic approach to synthesize THBC-based DKP derivatives of type **1** by a one-pot four step Ugi/deprotection/Pictet-Spengler/lactamization is shown in Fig. 2.

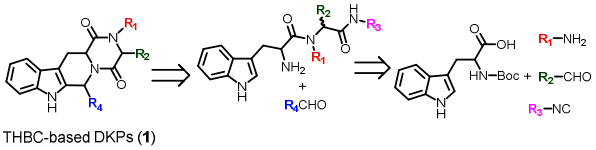
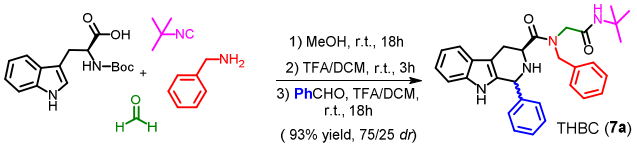


Fig. 2 Retrosynthetic strategy

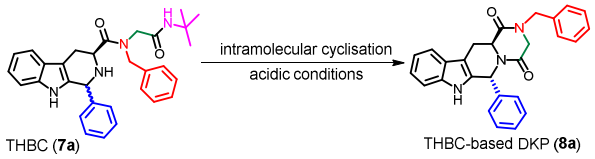
Herein, we report a new synthetic method to stereoselectively obtain functionalized THBC-based DKPs. It allows the synthesis of novel, optically pure Tadalafil (compound **2** in Fig. 1) analogues by a one-pot four-step procedure. In order to study the feasibility of the proposed protocol and to find the best reaction conditions for the synthesis of the prototype THBC-based DKP derivatives, *N*-Boc-L-tryptophan, benzylamine, formaldehyde and *tert*-butyl isocyanide were chosen as model substrates. The Ugi-4CR reaction was first carried out at room temperature in MeOH for 18 h, affording the classical Ugi products in excellent purity as judged by HPLC at UV 215 nm and LCMS analysis. Then, a TFA-promoted Boc removal (30% TFA in DCM at room temperature for 3 h), followed by a Pictet-Spengler reaction between the deprotected peptoid products and benzaldehyde (3 equiv of TFA in DCM at room temperature for 18 h) was carried out, yielding the desired THBC **7** in excellent overall yield as a mixture of 2 diastereomers (93% yield, 75/25 dr) with 4 rotamers being present in total (Scheme 1).



Scheme 1 Sequential Ugi/deprotection/Pictet–Spengler reaction for the synthesis of THBC **7a**.

Because we recently investigated microwave-assisted conversions,[23] the development of such conditions was of particular interest to optimize the subsequent lactamization step towards the desired THBC-DKPs. The results are summarized in Table 1.

Table 1 Optimization of the lactamization step[a]



Entry[a]	temp (°C)	time (h/min)	conv (%)[b]
1[c]	100	18 h	traces
2[c]	130	18 h	7
3[d]	100	10 min	6
4[d]	120	10 min	10
5[d]	150	10 min	20
6[d]	150	30 min	39
7[d]	150	60 min	70
8[d]	150	120 min	100
9[d]	150	90 min	91
10[d]	180	90 min	100
11[d,e]	**180**	**80 min**	**100**
12[d]	180	60 min	92
13[d]	180	70 min	98
14[f]	180	80 min	100
15[g]	180	18 h	91

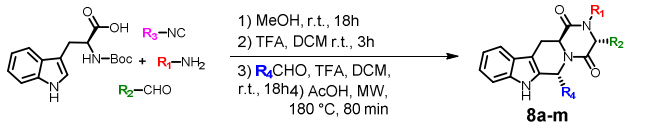
[a]Reaction conditions: **7a** (0.5 mmol), AcOH (3 mL). [b]Determined by HPLC of the crude reaction mixture. [c]The reaction was performed under classical heating conditions. [d]The reaction was performed in AcOH (0.17 M) under microwave irradiation. [e] Isolated in 95% yield as a single *trans* diastereomer. [f]The reaction was performed in TFA under microwave irradiation. [g]The reaction was performed in a sealed vial placed in an oil bath.

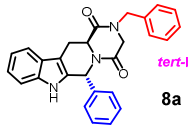
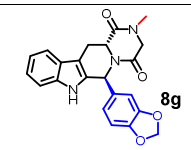
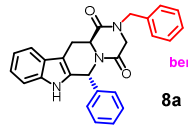
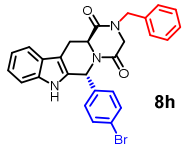
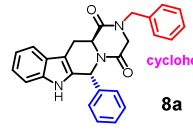
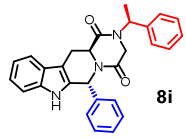
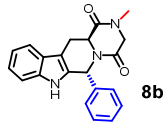
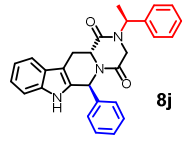
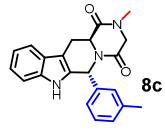
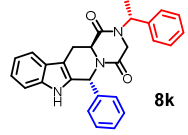
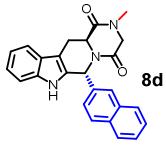
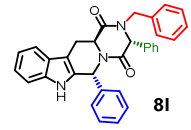
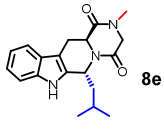
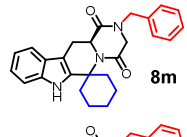
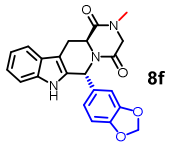
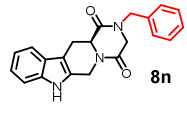
Under classical heating conditions in glacial acetic acid, the reaction did not proceed when the mixture was heated at 100 °C in an oil bath for 18 hours (entry 1, Table 1). Performing the reaction at 130 °C slightly increased the conversion (7% conversion as detected by RP-HPLC, entry 2, Table 1). We thus turned our attention to explore the microwave irradiation parameters to optimize the reaction. When the reaction was carried out under microwave conditions, only a limited conversion (6%) was observed after 10 minutes (entry 3, Table 1). To our satisfaction, more of the desired product was observed upon further increase of the temperature (entries 4 and 5, Table 1). Ensuing optimization showed that increased reaction time and temperature was appropriate for a cyclization in good to excellent yield (Table 1, entries 6–13). Successive temperature increase from 100°C to 180°C and applying a reaction time of 10 to 80 min afforded total conversion to **8a** (100% conversion, 95% isolated yield, entry 11, Table 1). Gratifyingly, only a single diastereomer, characterized as the *trans* isomer by NOESY studies (*see supporting information*) was observed by RP-HPLC. When using TFA instead of AcOH, the full conversion obtained at 180 °C for 80 minutes was accompanied by the formation of by-products in the reaction mixture (entry 14, Table 1). Although much longer reaction times were needed, a good conversion (91 %) was also obtained in sealed vials, which were placed in an oil bath at 180 °C for 18 h. (entry 15, Table 1). Next, the optimal conditions (entry 11, Table 1) were chosen to explore the substituent scope of this methodology. At this temperature and reaction time, full conversion and high diastereomeric excesses were obtained for a wide array of enantiopure THBC-based DKP scaffolds, as summarized in Table 2. This amine-amide cyclisation mode provides an alternative for the amine-ester DKP formation, as reported by Tyagi,[19e] and has the advantage to give a single diastereomer in high yield. In contrast to reported methodologies, this method allows to prepare cialis derivatives with high diversity.

With enantiopure Boc-(L/D)-Trp-OH as chiral amino acids in hand, we initiated a study to explore the scope of the one-pot four-step Ugi/deprotection/Pictet-Spengler/lactamization sequence. The reaction of three different isocyanides with Boc-L-Trp-OH, benzylamine and benzaldehyde was examined (entries 1-3, Table 2) and the desired products **8a** were isolated with high yields and excellent diastereomeric excess. We herewith demonstrated for the first time that in the microwave-assisted intramolecular-cyclization process, the readily available cyclohexyl- and benzyl isocyanide (entries 2 and 3, Table 2) can also be used as convertible isocyanides (with total conversion) when an intramolecular nucleophile is present, thus offering a cost effective alternative to Armstrong's isocyanide[24]. The electron-donating or electron-withdrawing properties of substituents in the aldehyde component, involved in the Pictet-Spengler reaction, were well tolerated and have no influence on the yield and diastereomeric excess of the reaction, as compounds (**8b-h**) were isolated in an enantiopure form in good yields (entries 4-10, Table 2). Interestingly, 12a-*epi*-tadalafil **8f** and its enantiomer 6-*epi*-tadalafil **8g** could be accessed starting from either L- or D-Trp-OH (entries 8 and 9, Table 2). Next, chiral α-branched amines were used in the Ugi reaction and gave the expected compounds (**8i-k**) in excellent yields and d.e.(%) (entries 11-13, Table 2).The reaction with (*S*)-1-methyl benzylamine and (*R*)-1-methyl benzylamine allowed to identify a double stereochemical change at C-6 and C-12a. When using (*S*)-1-methyl benzylamine, product **8i** was obtained with a minor amount of epimer **8i**' (3-4%) (entry 11, Table 2). In contrast, only single THBC-DKP diastereoisomers **8j** and **8k** were observed by ^{1}H NMR and HPLC (entries 12 and 13, Table 2). Using benzaldehyde in the Ugi reaction, an excellent d.e.(%) was obtained for the compound **8l**, and the product was isolated as a single diastereomer (*3R*, *6R*, *12aS*) (entry 14, Table 2). An epimerization at C-3, probably occurring through enolization of the initially formed diastereomeric mixture in glacial acetic acid, yields the single, more

stable, *trans* diastereomer **8l**. The configuration of **8l** was confirmed by NOESY studies (see supporting information). Application of the Pictet–Spengler reaction with cyclohexanone produced the spirocyclic-tetrahydro-*β*-carbolines and finally led to THBC-DKP **8m** in good yield (entry 15, Table 2). In addition, the Pictet-Spengler reaction with formaldehyde afforded the desired compound **8n** in good yield (entry 16, Table 2).

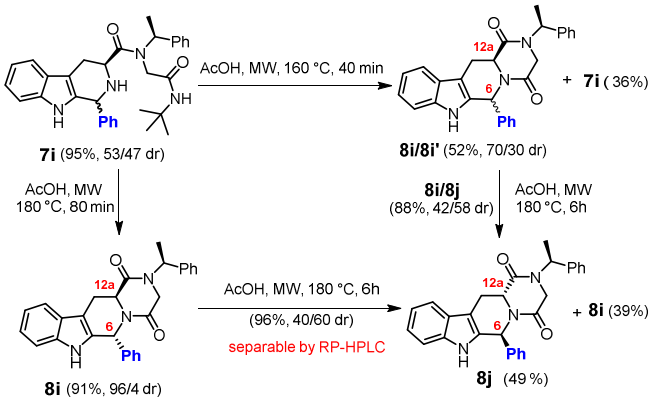
Table 2 Substrate scope



entry	THBC-DKP product	yield (%)[a] de (%)[b]	entry	THBC-DKP product	yield (%)[a] de (%)[b]
1	 **8a**	81 (> 98) *via tert*-butyl isocyanide	9[c,d]	 **8g**	73 (> 98)
2	 **8a**	77 (> 98) *via* benzyl isocyanide	10	 **8h**	74 (> 98)
3	 **8a**	75 (> 98) *via* cyclohexyl isocyanide	11	 **8i**	73 (> 92)
4[c]	 **8b**	70 (> 98)	12[d]	 **8j**	75 (> 98)
5[c]	 **8c**	76 (> 98)	13	 **8k**	79 (> 98)
6[c]	 **8d**	71 (> 98)	14	 **8l**	72 (> 98)
7[c]	 **8e**	73 (> 98)	15	 **8m**	80
8[c]	 **8f**	68 (> 98)	16	 **8n**	75

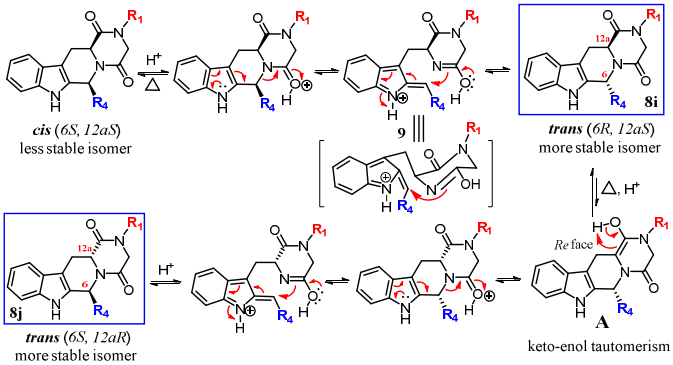
[a]Isolated yields after silica gel column chromatography. [b]Diastereomeric excess determined by ^{1}H and ^{13}C NMR spectra or HPLC. [c]One equiv of Et_3N was added to neutralize the methylamine hydrochloride. [d]Isolated yields from Boc-D-Trp-OH.

In order to gain a better insight into the observed acid-catalyzed epimerization in the tetracyclic compound **8i**, we decided to study the origin of the observed stereoselectivity after the lactamization step (Scheme 2). Using the reaction conditions of the above described Ugi/deprotection/Pictet-Spengler sequence intermediate **7i** (Scheme 2) was isolated in excellent yield as a mixture of two diastereomers (95% yield, 53/47 dr). When the lactamization was carried out in glacial acetic acid, applying the optimal reaction conditions (microwave irradiation, 180°C, 80 min), the desired compound **8i**, THBC-based DKP derivative, was obtained in high diastereomeric excess (91% yield, 96/4 dr), in favour of the *trans* (*6R*, *12aS*) diastereomer. However, performing the reaction at 160 °C for 40 min, a moderate conversion was obtained and the desired product **8i/8i'** was isolated as a mixture of *trans* and *cis* diastereomers (52 % yield, 70/30 dr). Prolonged heating of the isolated mixture **8i/8i'** for 6 hours at 180 °C afforded a mixture of *trans* diastereomer **8i** (*6R*, *12a*S) and its stereoisomer **8j** (*6S, 12aR*) (88 % yield, 42/58 dr). To understand the epimerization of **8i** at the C-12a and C-6 positions, heating compound **8i** under the same conditions (180 °C, 6 hours) led to a separable mixture of *trans* diastereomer **8j** (*6S, 12aR*) in 49 % yield and **8i** (39%) (Scheme 2).



Scheme 2 Epimerization study

The mechanism by which the conversion of the *cis* diastereomers into the more thermodynamically stable *trans* diastereomers takes place is tentatively rationalized (Scheme 3).



Scheme 3 Proposed mechanism for the acid-catalyzed epimerization at the C-6 and C-12a positions

Under microwave irradiation in acidic conditions, the Pictet-Spengler reaction is reversible through a retro process in which a C-N bond is broken,[25] allowing the *cis*-isomer (*6S*, *12aS*) to isomerize

to the thermodynamically more stable *trans* isomer **8i** (*6R*, *12aS*). This is realized by an intramolecular addition of the adjacent double bond of the lactim onto the Re-face (top side) of the olefin iminium intermediate **9** in which the fused THBC-DKP have a *trans* chair–chair junction (less strained and more stable conformation).[20c,d] Furthermore, under microwave conditions, in the presence of an acid and upon prolonged heating, this *trans* isomer **8i** could be converted into enol form **A,** through enolization in which the hydrogen-transfer of the hydroxyl group to the *Si*-face of sp2-hybridized C-12a is able to regenerate compound **8i** (more stable). The hydrogen-transfer to the *Re*-face of C-12a in enol **A** produces intermediate *cis* (*6R, 12aR*), which ultimately leads to the more stable *trans* isomer **8j** (*6S, 12aR*) *via* a tandem ring-opening and stereoselective intramolecular addition process.

In summary, we have developed an efficient and novel stereoselective strategy for the preparation of various optically pure and trisubstituted tetrahydro-*β*-carboline-fused diketopiperazines (THBC-DKPs), containing three potential points of diversity, by a one-pot tandem Ugi/Boc-deprotection /Pictet-Spengler/lactamization sequence. We demonstrated for the first time that the readily available cyclohexyl- and benzyl isocyanide applied in the Ugi-4CR can used as convertible isocyanides in post-condensation Ugi modifications when an intramolecular nucleophile is present. This original procedure is suitable for the synthesis of 12a-*epi*-cialis **8f** and its enantiomer 6-*epi*-cialis **8g** in an enantiopure form, and should prove useful for the synthesis of new compound libraries with a wide structural diversity.

Acknowledgements

This work was supported by a collaboration convention between the Ministère du Développement Economique, de l'Innovation et de l'Exportation du Québec and the Research Foundation – Flanders (FWO Vlaanderen) (PSR-SIIRI-417 & FWOAL570).

Notes and references

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Electronic Supplementary Information (ESI) available. See DOI: 10.1039/b000000x/

Author Contributions

MJ was in charge of the design and synthesis of all compounds. MJ, DT and SB contributed equally to the manuscript preparation.

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