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Synthesis of C-1 indol-3-yl substituted tetrahydroisoquinoline derivatives via a Pictet–Spengler approach

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ABSTRACT

A protocol for the diastereoselective synthesis of C-1 indol-3-yl substituted tetrahydroisoquinoline derivatives via Pictet–Spengler condensation with L-DOPA or L-DOPA derivatives and 1*H*-indole-3-carbaldehydes is presented. The protocol is used for the successful synthesis of several tetrahydroisoquinolines as well as diketopiperazine fused analogues.

Tetrahydroisoquinolines have received considerable interest as synthetic targets in the field of medicinal chemistry due to their biological activities, for example, antitumor and antimicrobial activities.[1]

The most widely used, and probably the most convenient, reaction for the synthesis of substituted tetrahydroisoquinolines is the Pictet–Spengler condensation,[2] first described in 1911 by Amé Pictet and Theodore Spengler.[3] Since its discovery its usefulness has been demonstrated in numerous syntheses of biologically active compounds, natural products and synthetic compounds.[4] Although the reaction has been known for 100 years, reports on successful Pictet–Spengler condensations between L-3,4-dihydroxyphenylalanine (L-DOPA) and heteroaromatic aldehydes resulting in tetrahydroisoquinolines substituted with a heteroaromatic moiety at the C-1 position are scarce. In 2006, Aubry and coworkers reported the successful synthesis of thiophene substituted tetrahydroisoquinolines, from, among others, L-DOPA via a Pictet–Spengler condensation,[2] in moderate to good yields. The scope of that investigation was limited to substituted phenyl and thiophene aldehydes, and there is obviously a need for further studies with *N*-heteroaromatic aldehydes. As we were studying the biological effects of compounds possibly formed via C-1 indol-3-yl substituted tetrahydroisoquinolines, Pictet–Spengler condensations with 1*H*-indole-3-carbaldehydes were of particular interest to us.

An indication of the usefulness of the Pictet–Spengler approach towards the synthesis of C-1 indol-3-yl substituted tetrahydroisoquinolines was reported by Bogza and coworkers,[5]who described the synthesis of an elimination product, possibly formed after elimination of the indole moiety following a Pictet–Spengler condensation between an aminopyrazole derivative and a substituted indole-3-carboxaldehyde. Numa and coworkers[6] reported the successful condensation between the HCl salt of 5-hydroxydopamine and indole-3-carboxaldehyde, however, without isolating or providing any analytical data for the claimed product. Additional research is therefore needed, and we decided to develop a protocol for the synthesis of C-1 indol-3-yl substituted tetrahydroisoquinolines via a Pictet–Spengler approach (see Scheme 1), that could provide derivatives which would enable our synthesis of diketopiperazine fused analogues and a subsequent structure–activity relationship study.

The diastereoselectivity of the Pictet–Spengler condensation has been discussed in several reports[7] and reviews,[8] and it has been demonstrated that the formation of the *cis* diastereomer is favoured over the thermodynamically more stable *trans* diastereomer when the reaction is under kinetic control in acidic media,[9] and that the *cis*/*trans* ratio depends on the nature of the aldehyde employed[3,9] and the substitution pattern at C-3.[10] Also, *cis* to *trans* epimerisation at C-1 has been observed, and is a key step in Cook's synthesis of mitragunine[11] via a Pictet–Spengler reaction.

L-DOPA (**1**) was converted into its corresponding methyl ester according to a standard procedure leading directly to the Pictet–Spengler precursor **2** (see Scheme 2). However, stirring **2**, NaOAc

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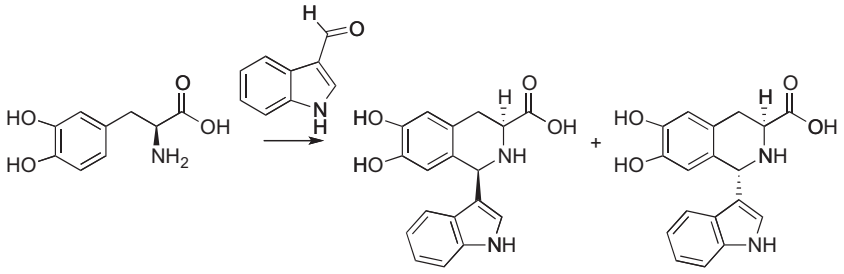
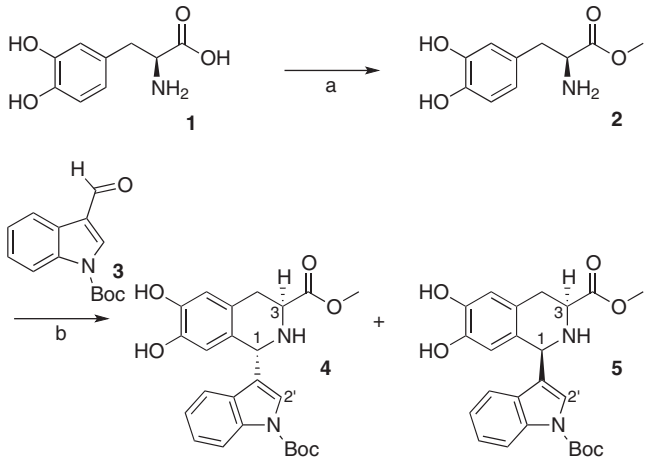
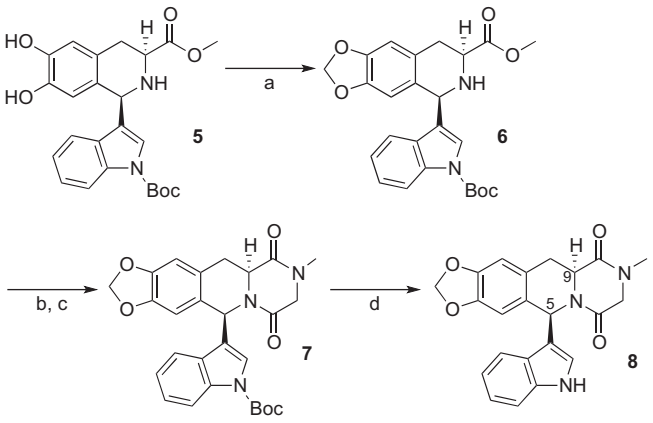


Scheme 1. C-1 indol-3-yl substituted tetrahydroisoquinolines formed via a Pictet–Spengler condensation.



Scheme 2. Reagents and conditions: (a) $SOCl_2$, MeOH, 0 °C – room temperature, (b) NaOAc, AcOH, room temperature, overnight, 67% (1:9, *trans*:*cis*).



Scheme 3. Reagents and conditions: (a) $BrCH_2Cl$, Cs_2CO_3, DMF, 95 °C, 5 h, 40%. (b) chloroacetyl chloride, pyridine, DMAP, CH_2Cl_2, room temperature, overnight. (c) $MeNH_2$, MeOH, 50 °C, overnight, 23% (over two steps). (d) DMF, 150 °C, 3 h, 15%.

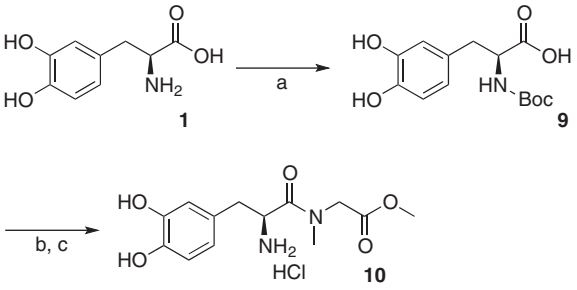
and indole-3-carboxaldehyde[12] in AcOH at room temperature for 24 h failed to give the desired product. Reasoning that protecting the nitrogen on indole-3-carboxaldehyde with an electron-withdrawing group would facilitate both the formation of the intermediate Schiff base and the subsequent ring-closure, we tried the same reaction with *N*-Boc-protected indole-3-carboxaldehyde **3** (see Scheme 2). The desired indolyl substituted tetrahydroisoquinoline was isolated as a separable 1:9 (*trans*:*cis*) diastereomeric mixture in a total yield of 67%. The configurations of **4** and **5** were determined by NMR NOESY experiments; a correlation between 2′-H and 3-H was observed for diastereomer **4**, demonstrating that the protons were on the same face of the tetrahydroisoquinoline ring, while no correlation was observed between 1-H and 3-H. With **5**, no correlation was observed between 2′-H and 3-H, demonstrating that these protons were on opposite faces, while a strong correlation was observed between 1-H and 3-H. The diastereomeric outcome was in full agreement with previous observations which indicated that the *cis* isomer was the preferred diastereomer under the reaction conditions used.[9]

We were interested in the further derivatisation of the tetrahydroisoquinoline scaffold via the introduction of a fused diketopiperazine ring, as well as protection of the catechol moiety with a methylene dioxy bridge, to obtain diketopiperazine fused tetrahydroisoquinoline derivatives such as **8** after removal of the *N*-Boc protecting group.

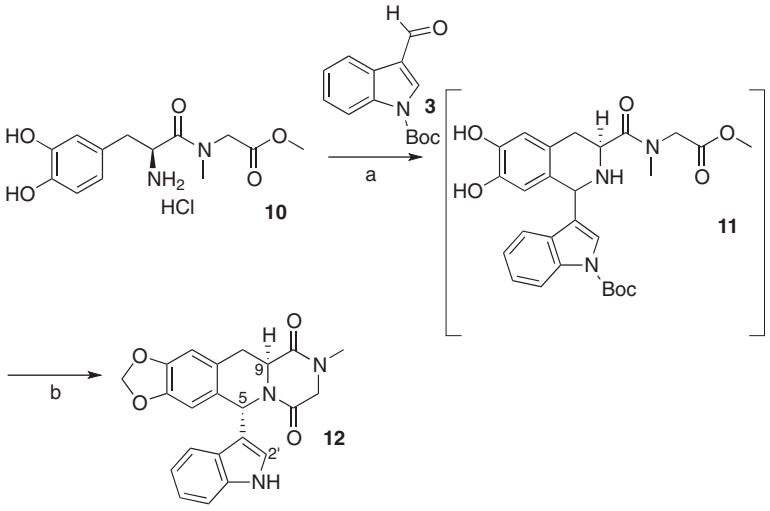
Treating **5** with bromochloromethane at 95 °C in DMF yielded the methylene dioxy protected tetrahydroisoquinoline **6** (Scheme 3). The diketopiperazine ring was formed in moderate yield via *N*-acylation with chloroacetyl chloride, followed by treatment with methylamine and heating overnight to give the *N*-Boc protected intermediate **7**. The Boc protecting group was resilient to removal. Heating **7** with Cs_2CO_3 in DMF at 150 °C, stirring **7** in 2 M HCl in Et_2O or TFA in CH_2Cl_2 at room temperature only led to the total degradation of the starting material. However, we found that heating **7** for 3 h in DMF at 150 °C afforded **8** as a single diastereomer. The relative configuration of **8** was determined by NOESY experiments in the same way as discussed for **4** and **5**. Compound **8** was optically active ($[\alpha]_D = -34$ ($c = 0.43$, DMSO)), and as the absolute configuration at C-9 is determined from L-DOPA the absolute configuration of **8** is 5*R*, 9*S*.

As the synthesis of **8** from **5** only proceeded in moderate yields, we decided to investigate an alternative route.

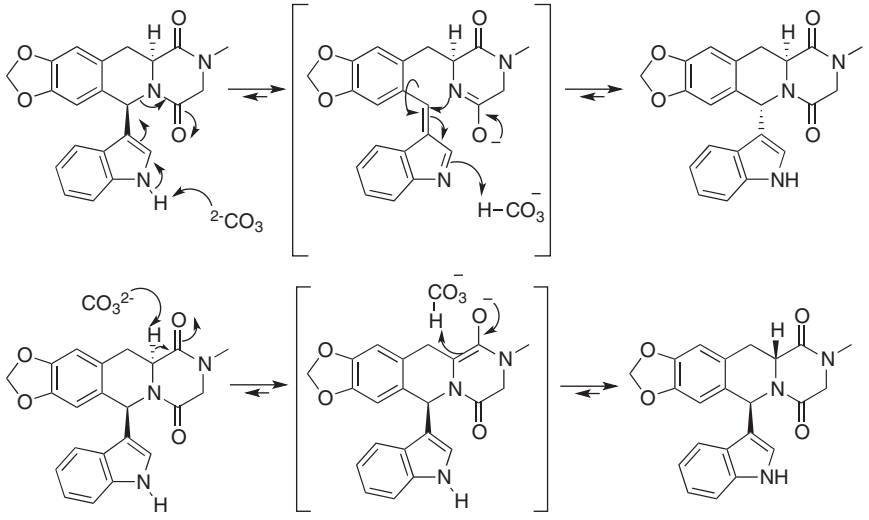
N-Boc protection of L-DOPA (**1**) (Scheme 4), according to standard procedure gave **9** in excellent yield. BOPCl mediated amide coupling between **9** and methyl sarcosine, followed by non-aqueous (due to the hydrophilic nature of **10**) Boc deprotection yielded the optically active ($[\alpha]_D = 50$ ($c = 0.86$, MeOH)) Pictet–Spengler precursor **10**.



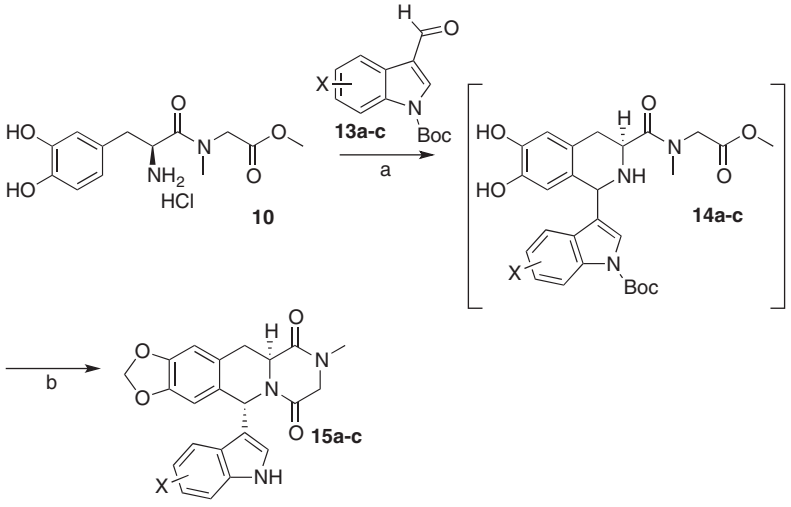
Scheme 4. Reagents and conditions: (a) Boc_2O, NaOH, 1,4-dioxane/H_2O, room temperature, quant. (b) Sarcosine methyl ester hydrochloride, BOPCl, Et_3N, $NaHCO_3$, CH_2Cl_2, room temperature, overnight, (c) 2 M HCl in Et_2O, 0 °C, 1 h, 21% (over two steps).



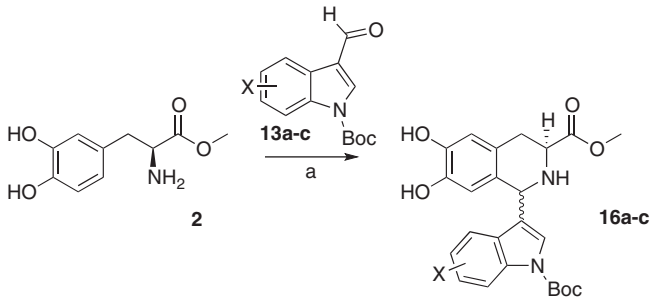
Scheme 5. Reagents and conditions: (a) NaOAc, AcOH, room temperature, overnight, 50%. (b) $BrCH_2Cl$, Cs_2CO_3, DMF, 150 °C, 2.5 h, 31%.



Scheme 6. Suggested mechanism for the racemisation of **12**.



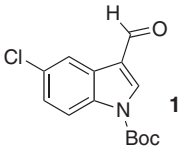
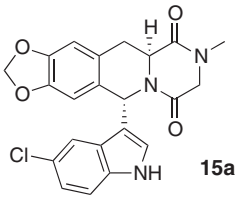
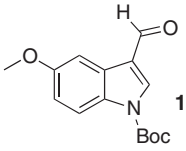
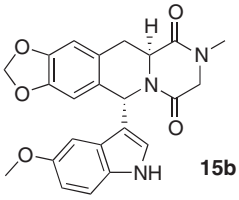
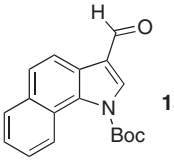
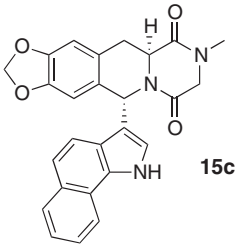
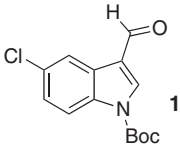
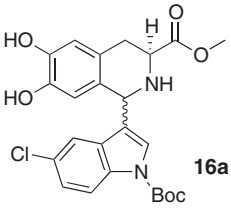
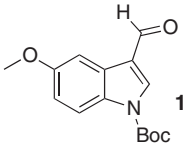
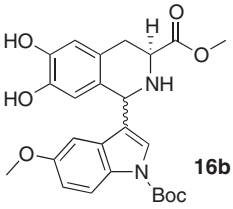
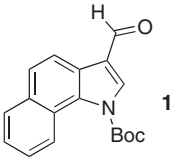
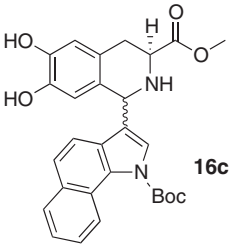
Scheme 7. Reagents and conditions: (a) NaOAc, AcOH, room temperature, overnight, (b) $BrCH_2Cl$, Cs_2CO_3, DMF, 150 °C, 2.5 h.



Scheme 8. Reagents and conditions: (a) NaOAc, AcOH, room temperature, overnight.

Stirring a mixture of **10**, *N*-Boc protected indole-3-carboxaldehyde **3** and NaOAc in AcOH at room temperature overnight resulted in the formation of a new product (Scheme 5). We propose the structure to be that of tetrahydroisoquinoline **11**, but its identification proved difficult as we could not obtain good quality NMR spectra (possibly due to the existence of rotamers). Assuming that the product we obtained was in fact the Pictet–Spengler condensation product **11** between **10** and *N*-Boc protected indole-3-carboxaldehyde **3**, we applied the previously described conditions for the protection of the catechol moiety and deprotection of the *N*-Boc group. Heating **11**, $BrCH_2Cl$ and Cs_2CO_3 in DMF at 150 °C for 2.5 h yielded **12** as a single diastereomer, although the yield was still only moderate. The configuration

Table 1
Analogue synthesis

Pictet–Spengler precursor	Indole derivative	Product	Yield (%)
10	 **13a**	 **15a**	16[a]
10	 **13b**	 **15b**	31[a]
10	 **13c**	 **15c**	5[a]
2	 **13a**	 **16a**	72 (8:1) (*cis*/*trans*)
2	 **13b**	 **16b**	66 (5:1) (*cis*/*trans*)
2	 **13c**	 **16c**	75 (3:1) (*cis*/*trans*)

[a] The low yield is mainly due to the Boc deprotection step.

of **12** was determined by the NOESY correlation between proton 2′-H and 9-H (Scheme 5). No trace of **8** was observed. Interestingly, product **12** was optically inactive.

The racemisation of **12** could be explained by considering two mechanisms, base-catalysed breaking of the C-5–N bond (Scheme 6, top) leading to a ring-opening/closure to the thermodynamically most stable diastereomer (*trans*), and a base-catalysed keto–enol tautomerisation of C-9 (Scheme 6, bottom), resulting in **12** as a racemate. It is possible that somewhat milder conditions for the transformation of **11** into **12** would avoid the racemisation, but this was not investigated.

To investigate further the usefulness of the Pictet–Spengler protocol with 1*H*-indole-3-carbaldehydes, we attempted the reaction with both Pictet–Spengler precursors **2** and **10** and the three additional *N*-Boc protected 1*H*-indole-3-carbaldehydes **13a**, **13b** and **13c** (Schemes 7 and 8, Table 1).

The initial Pictet–Spengler condensation products obtained from **10**, and believed to be **14a–c** were not isolated, but after a simple filtration through SiO_2 were further reacted to yield **15a–c** (see Scheme 7 and Table 1). The corresponding reactions with **2** yielded the substituted tetrahydroisoquinolines **16a–c** (see Scheme 8 and Table 1).

In conclusion we have developed a protocol for the Pictet–Spengler condensation between the methyl ester of L-DOPA and various *N*-Boc protected 1*H*-indole-3-carbaldehydes which gives C-1 indolyl substituted tetrahydroisoquinolines **4**/**5**, **16a**, **16b** and **16c** in good yields. The condensation products were obtained as *cis*/*trans* diastereomeric mixtures, but the components could be isolated and the procedure gives access to both isomers. A general limitation that remains to be improved is the cleavage of the Boc group which requires harsh conditions and only gives moderate yields at best. We have also shown that condensation products such as **5** can be transformed into optically active diketopiperazine fused tetrahydroisoquinoline derivatives such as **8**, in a process that retains the configuration of the stereogenic carbons. An alternative way of preparing the diketopiperazine fused tetrahydroisoquinoline derivatives involved the transformation of L-DOPA into the Pictet–Spengler precursor **10** and the condensation of this with *N*-Boc protected 1*H*-indole-3-carbaldehydes.

Acknowledgements

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Supplementary data

Supplementary data (^{1}H NMR, ^{13}C NMR HRMS, optical activity) associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2012.07.017.

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