Syntheses of tetrahydro-β-carbolines *via* a tandem hydroformylation–Pictet–Spengler reaction. Scope and limitations†

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A novel one-pot synthesis of tetrahydro-β-carboline systems *via* tandem hydroformylation–Pictet–Spengler reaction starting from olefins and aryl ethylamines is described. This tandem procedure allows fast and convenient synthesis of various substituted tetrahydro-β-carbolines.

Introduction

The Pictet–Spengler reaction[1] is one of the most widely used methods for building tetrahydroisoquinoline and tetrahydro-β-carboline (THBC) ring systems, present in numerous natural and synthetic organic compounds, many of which display useful and interesting biological activities (Fig. 1).[2] In general, the Pictet–Spengler (PS) reaction comprises an acid catalyzed cyclocondensation of β-arylethyl amine derivatives with aldehydes or ketones involving an iminium ion intermediate.[3] Tetrahydro-β-carbolines, covering a wide range of structural types, are very attractive targets for synthesis and have stimulated the development of new synthetic approaches and methodologies, especially in the Pictet–Spengler reaction. Although the classical version of this reaction is well established as a method of choice for construction of THBC frameworks, original strategy has been modified over the past decades, allowing *N*-acyl, *N*-sulfinyl and *N*-sulfonyl β-arylethylamines to be used as nucleophilic components.[4] On the other hand, masked ketones, aldehydes and aldehyde equivalents such as acetals, ketals, enol ethers, thioortho esters, oxazines and oxazolidines[5] as well as acetylene sulfoxides, enamines and azalactones[6] have been employed as electrophilic components.

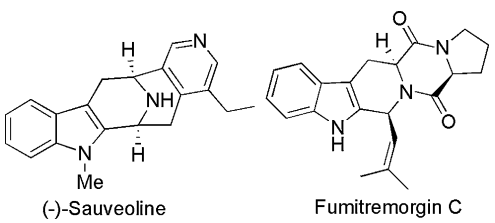
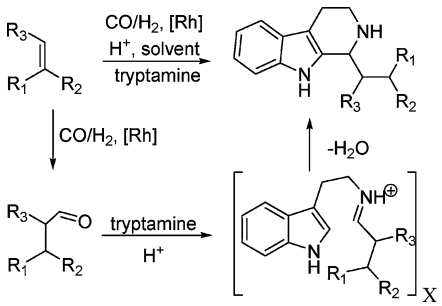


Fig. 1 Naturally occurring, bioactive tetrahydro-β-carbolines.

Results and discussion

Based on our general interest in tandem hydroformylation sequences,[7] we wanted to explore the possibility of combining a Rh catalyzed olefin hydroformylation reaction and a Pictet–Spengler reaction into a tandem reaction sequence, involving olefins as precursors of the electrophilic component. In this reaction sequence, the hydroformylation reaction in the presence of a rhodium catalyst is used to synthesize the aldehyde *in situ* from an olefin, thus reducing the functional group transformations to a minimum. In the presence of a β-arylethyl amine (and a Brønsted acid), this aldehyde is directly converted to a Schiff base, which subsequently cyclizes to form tetrahydro-β-carboline or tetrahydro-isoquinoline ring systems (Scheme 1). To the best of our knowledge, up to now there is only one precedent in the literature, where Taddei *et al.* have used this sequence in solid phase synthesis of a carboline.[8] Here, we describe the first examples of this reaction in solution, and discuss scope and limitations for further applications. This methodology allows introduction of various substituents at C_1 without the need of sensitive and sometimes costly aldehyde components. Furthermore, high concentrations of the aldehyde are avoided due to the slower hydroformylation step, which prevents competitive aldehyde self-condensation reactions resulting in low yields.[9] Thus some of the primary limitations of the conventional Pictet–Spengler reaction are avoided. For high yields of the desired product, high chemoselectivities are required in each step of the tandem process. To achieve this, it is important that all reagents and reactants as well as all intermediates are compatible and do not affect each other.



Scheme 1 Tandem hydroformylation–Pictet–Spengler reaction.

Hydroformylation of the olefins, however, in the presence of amines may yield a variety of products. Primary and secondary amines are condensing with the aldehydes followed by hydrogenation of the resulting imines or enamines to amines in an overall hydroaminomethylation.[7] It is also known that the rhodium acyl species, instead of hydrogenolysis to form the aldehyde, are also undergoing nucleophilic addition of the amine to form the amide.[10] Therefore a synthesis of tetrahydro-β-carbolines under

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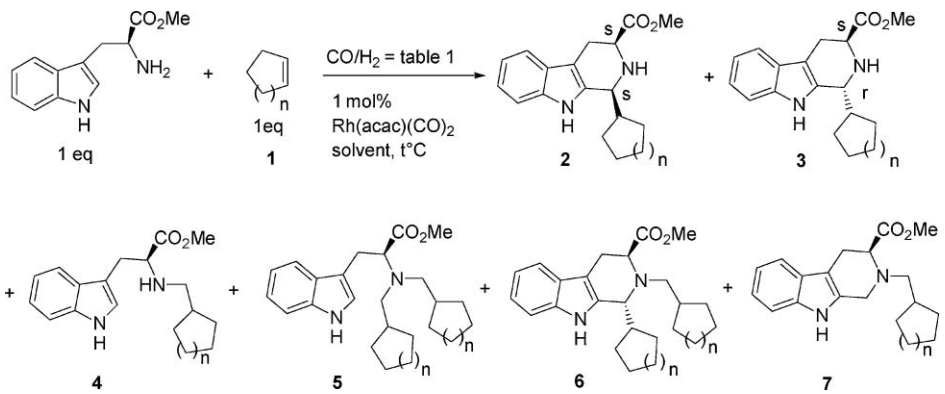
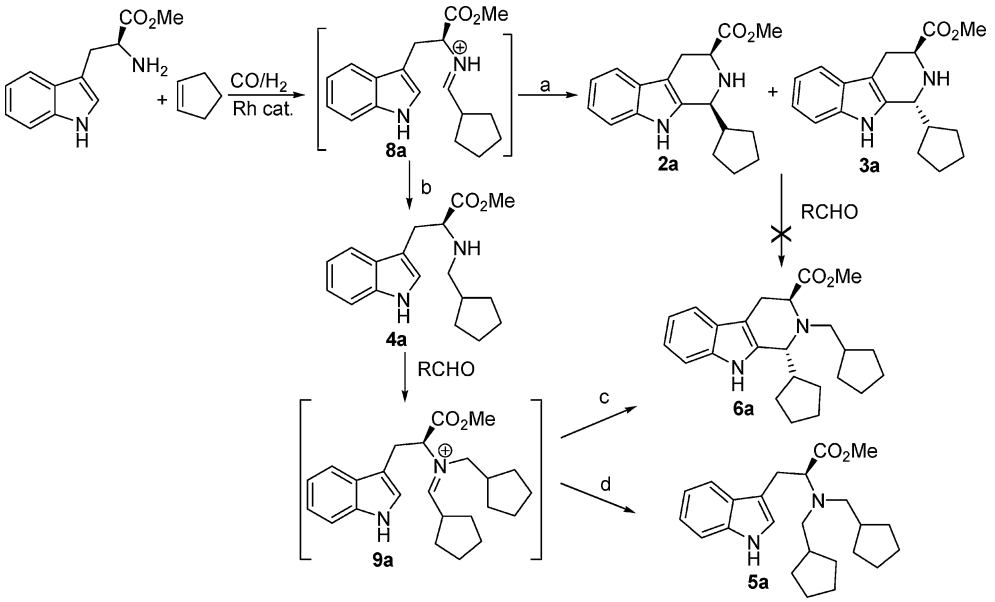
hydroformylation conditions according to the above described limitations has to consist of an efficient hydroformylation step leading exclusively to the aldehyde. This without isolation or side reactions must condense under the same reaction conditions with β-arylethyl amine to form the imine, while reduction and self condensation of aldehydes must be avoided. The intermediate imine must cyclize so that no reduction leading to hydroaminomethylation products occurs. Since hydroformylation of terminal olefins usually results in a mixture of linear and branched aldehydes, in our initial investigations, disubstituted terminal olefins like 1,1′-diphenylethylene or cyclic olefins were preferably used. The former undergo regioselective hydroformylation to form linear aldehydes and make the use of *n*-directing ligands obsolete, whereas the latter are symmetric compounds and yield only one aldehyde isomer. To prevent hydrogenation of the starting olefin, and/or of the intermediate Schiff base, high carbon monoxide partial pressures were chosen in order to support the rate determining carbon monoxide insertion. Since it is well known that esters of tryptophan undergo Pictet–Spengler reaction with aldehydes in aprotic conditions,[3b] the conversion of tryptophan methyl ester and cyclopentene as electrophile precursor under hydroformylation conditions was chosen as a first model reaction. Cyclopentene is a cheap and readily available olefin, and hydroformylation of cyclopentene is well known and described, with conditions usually involving temperatures of 40–80 °C and pressures of 40–80 bar of syngas.[8,11] Therefore, cyclopentene is mixed with (*S*)-tryptophan methyl ester in toluene, which is the most commonly used solvent in conventional PS reactions and a convenient solvent for hydroformylation reaction as well. This solution is submitted to hydroformylation in the presence of 1 mol% of $Rh(acac)(CO)_2$ at 80 °C and at 30 : 10 bar of $CO–H_2$ pressure. After workup, however, no Pictet–Spengler products were observed, and only products **4a** and **5a** were isolated (Table 1, entry 1), which arise from mono and double hydroaminomethylation reactions respectively (*vide infra*). Obviously, reduction of the intermediate Schiff base under these conditions is faster than electrophilic attack of the imine to the aromatic ring of the indole (Scheme 2, pathways **b** and **d**). The same products were isolated in a reaction with cyclohexene (Table 1, entry 2), although this olefin required higher temperature for hydroformylation as compared to cyclopentene. Since in toluene only hydroaminomethylation products were obtained, the reaction was performed in more polar solvents such as CH_2Cl_2, THF or MeOH. In these solvents, Pictet–Spengler products **2a** (*cis*) and **3a** (*trans*) were isolated in all cases. When starting from cyclopentene and (*S*)-tryptophan methyl ester in CH_2Cl_2 (Table 1, entry 3), **2a** and **3a** were isolated in relative ratios of approximately 1 : 1 and overall yield of 67%. Under these conditions, reduction of the intermediate Schiff base was widely suppressed, but formation of two additional side products **6a** and **7a** was observed. The same reactants in THF under similar conditions gave rise exclusively

Table 1 Tandem hydroformylation–Pictet–Spengler reaction in aprotic conditions



Entry	$CO–H_2$ bar	T/°C, time/d	Solvent	n (**1**)	Yield (%)[a] **2** + **3**	Ratio[b] **2** : **3**	Yield (%)[a] **4**	**5**	**6**	**7**
1	30 : 10	80 °C, 3 d	Toluene	1 (**1a**)	—	—	65 (**4a**)	10 (**5a**)	—	—
2	30 : 10	120 °C, 3 d	Toluene	2 (**1b**)	—	—	60 (**4b**)	12 (**5a**)	—	—
3	30 : 10	80 °C, 3 d	CH_2Cl_2	1 (**1a**)	67 (**a**)	48 : 52	3 (**4a**)	7 (**5a**)	4 (**6a**)	—
4	30 : 10	80 °C, 3 d	THF	1 (**1a**)	45 (**a**)	49 : 51	—	—	—	—
5	30 : 10	80 °C, 4 d	THF	1 (**1a**)	52 (**a**)	47 : 53	10 (**4a**)	—	—	—
6	30 : 10	80 °C, 3 d	MeOH	1 (**1a**)	15 (**a**)	50 : 50	48 (**4a**)	—	—	—
7	50 : 10	80 °C, 3 d	CH_2Cl_2	1 (**1a**)	79 (**a**)	48 : 52	1 (**4a**)	5 (**5a**)	3 (**6a**)	—
8	70 : 10	80 °C, 3 d	CH_2Cl_2	1 (**1a**)	72 (**a**)	51 : 49	—	6 (**5a**)	5 (**6a**)	—
9	50 : 10	120 °C, 3 d	CH_2Cl_2	2 (**1b**)	63 (**b**)	45 : 55	—	11 (**5b**)	5 (**6b**)	5 (**7b**)
10	50 : 10	80 °C, 3 d	CH_2Cl_2	3 (**1c**)	71 (**c**)	44 : 56	22 (**4c**)	—	—	—
11	50 : 10	80 °C, 3 d	CH_2Cl_2	4 (**1d**)	—	—	43 (**4d**)	—	—	—
12	50 : 10	120 °C, 3 d	CH_2Cl_2	Stilbene (**1e**)	48 (**e**)	51 : 49	41 (**4e**)	—	—	—
13	50 : 10	120 °C, 3 d	CH_2Cl_2	1,1′-diphenyl ethylene (**1f**)	67 (**f**)[c]	54 : 46	17 (**4f**)	—	—	—

[a] Yield of isolated product after column chromatography. [b] Ratio based on isolated products after column chromatography. [c] Isolated as mixture of inseparable diastereoisomers.



Scheme 2 Tandem hydroformylation–Pictet–Spengler reaction and formation of side products.

to Pictet–Spengler products **2a** and **3a** in 45% yield (Table 1, entry 4), albeit in a lower yield as compared to CH_2Cl_2 due to incomplete conversion of 80% in this case. Prolonged reaction time of 4 days allowed full conversion of the olefin and increased the yields of **2a** and **3a** to some extent but also yielded in reduction product **4a** (Table 1, entry 5). Acetals, which are often used as protected aldehydes in PS reactions, are also formed *in situ* under hydroformylation conditions in the presence of alcohols.[12] The use of alcohols as a solvent in the hydroformylation step is therefore a further option and would provide low stationary aldehyde concentrations. However, when the reaction was run in MeOH, only 15% overall yield of Pictet–Spengler adducts were isolated accompanied by **4a** as a main product in 48% yield (Table 1, entry 6). It is obvious that polarity of solvents plays a crucial role in the distribution of products. In non-polar solvents, such as toluene, reduction of the intermediate Schiff base is favoured. The more polar solvents stabilize cationic intermediates and promote electrophilic attack, hence, the rate of cyclization is by far higher than that of reduction. As already noted, **4a** is formed by reduction of iminium ion **8a** while formation of **5a** and **6a** can be explained as depicted in Scheme 2 (pathways **c** and **d**). Here the monoalkylated tryptophan methyl ester **4a** reacts with another molecule of aldehyde giving Schiff base **9a**, which undergoes hydrogenation giving **5a** or cyclization giving **6a**. This assumption was tested by control experiments. Isolated products **2a**, **3a** and **4a** were separately submitted to the hydroformylation conditions in the presence of cyclopentene and indeed, only **4a** yielded **6a** in 47% yield accompanied with dihydroaminomethylation product **5a**, in 22% yield. On the other hand, **2a** and **3a** gave no product of hydroaminomethylation presumably due to a higher steric hindrance at the ring *N* atom in these cases. Based on these observations, formation of **6a** from **2a** or **3a** can be ruled out. It is noteworthy to mention that **6a** was isolated exclusively as the *trans* isomer. According to earlier reports, the formation of the *trans* isomer in this case is both kinetically and thermodynamically favored, and was explained by a Felkin–Ahn-like attack of the *E*-iminium from the face opposite to the ester group (Fig. 2).[3b] Cook *et al.* have demonstrated that if the side chain nitrogen of tryptophan esters is monoprotected with sterically demanding Bn or Cbz groups and as such submitted to conventional PS reaction, the *trans* adduct will exclusively be formed. Apparently, this is also the case with monohydroaminomethylated tryptophan esters **4a** or **4b** when cyclic olefins such as cyclopentene or cyclohexene are used as aldehyde precursors. By-product **7a** was only observed when CH_2Cl_2 was used as a solvent and the CH_2 fragment that inserts between the iminium carbon and the indole stems most probably from the solvent. Since the best yields of **2a** and **3a** were obtained in CH_2Cl_2, this solvent was chosen for further optimization of reaction conditions. In order to lower the extent of reduction, carbon monoxide pressure and the CO–H_2 ratio was increased to 50 : 10 and 70 : 10 bar. While a 50 : 10 ratio of syngas gave 79% yield of **2a** and **3a** and lower yields of by-products (Table 1, entry 7), a ratio of 70 : 10 gave slightly lower yields of Pictet–Spengler adducts (Table 1, entry 8). Therefore, operating pressures of 50 bar CO and 10 bar H_2 were chosen for other substrates (Table 1, entries 9–13). In the reaction of cyclohexene and tryptophan methyl ester at 120 °C (Table 1, entry 9), **2b** and **3b** were obtained in a yield of 63% and in a ratio of approximately 1 : 1. Cycloheptene was hydroformylated at 80 °C and the products **2c** and **3c** were obtained in slightly higher yields than in case of cyclohexene (Table 1, entry 10). Surprisingly, when cyclooctene was reacted, no Pictet–Spengler products were observed and the main product was that of mono hydroaminomethylation reaction, **4d**, obtained in 43% yield (Table 1, entry 11). A trend from cyclopentene to cyclooctene can be observed: the yields of

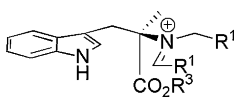


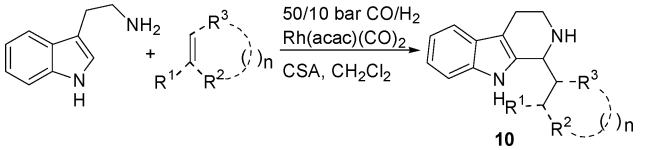
Fig. 2 Felkin–Ahn model of stereochemical course of Pictet–Spengler reactions of *Nb* protected tryptophanes.

Pictet–Spengler products decrease until they finally disappear. This is most probably connected with steric hindrance of the aldehydes formed, *i.e.* higher steric hindrance lowers the rate of cyclization and hence reduction becomes a more competitive reaction, exclusively yielding the hydroaminomethylation product. Cyclohexene is an exception here, most probably due to the harsher reaction conditions required for hydroformylation of this compound. This trend was also observed when acyclic olefins *trans* stilbene **1e** and 1,1′-diphenylethylene **1f** were reacted with (*S*)-tryptophan methyl ester under hydroformylation conditions. The former, bearing one Ph group in the α position and one in the β position, gives PS products **2e** and **3e** in 48% yield accompanied by mono hydroaminomethylated by-product **4e** (Table 1, entry 12). The latter, having two Ph groups in the β position of the aldehyde due to lower steric compression, gives Pictet–Spengler products **2f** and **3f** in a higher yield of 67% as a mixture of inseparable diastereoisomers accompanied by mono hydroaminomethylated by-product **13** in 17% yield (Table 1, entry 13). In summary, a tandem hydroformylation–Pictet–Spengler reaction performed under aprotic conditions using tryptophan methyl ester as nucleophilic component proved to be useful tool for the synthesis of simple tetrahydro-β-carbolines starting from readily available and cheap olefins.

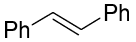
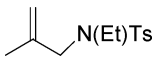
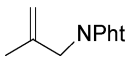
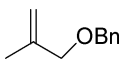
In order to expand the scope of this sequence, we tested the feasibility of tryptamine as a nucleophilic component in a tandem sequence. PS reactions of tryptamine often feature harsher conditions than their tryptophan counterparts. This is due to the absence of the inductively electron-withdrawing carbonyl group in tryptophan and thus lower pK_a values of tryptamine based Schiff bases.[3i] Tryptamine imines are significantly less reactive towards electrophilic attack, and hence the presence of acid (Brønsted or Lewis) is required. Brønsted acids such as sulfuric acid (1 eq), trifluoroacetic acid (TFA) (1 eq), *p*-toluenesulfonic acid (*p*TsOH) (1 eq), and camphorsulfonic acid (CSA) (1 eq) were tested in the reaction of tryptamine and cyclopentene under optimized conditions for tryptophan methyl ester. Lewis acids $ZnCl_2$, and BF_3 were tested as well. All reactions were carried out under the same conditions for 72 hours and yields of products were determined by isolation. The best results were obtained with CSA while *p*-TSOH, sulfuric and trifluoroacetic acid yielded mainly mixtures of products. In the presence of Lewis acids, no product was formed. In the absence of acid, no product of Pictet–Spengler cyclization was observed either. Conditions optimized for tryptophan methyl ester with addition of 1 eq of CSA were applied in the reaction of tryptamine with selected olefins and the results are summarized in Table 2. Here, 5, 7, and 8 membered carbocyclic olefins required milder conditions for hydroformylation as compared to other olefins applied. The reactions were run at 80 °C and full conversions of olefins were observed after 3 days, with good yields of isolated products (Table 2, entries 1, 2 and 4). Surprisingly, and in contrast to the aprotic conditions, here we were able to isolate PS product from the reaction of tryptamine and cyclooctene.

All other substrates gave moderate to good yields in the presence of 1 eq of camphorsulfonic acid. 1,1-Disubstituted substrates, as well as hindered internal olefins such as *trans* stilbene (Table 2, entry 5), required harsher conditions for hydroformylation, therefore, a temperature of 110 °C for 3 days was applied. Hydroformylation of 1,1′-diphenylethylene at 80 °C after 3 days

Table 2 Tandem hydroformylation–Pictet–Spengler reaction of tryptamine and selected olefins under protic conditions



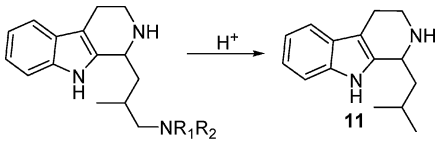
10

Entry	Substrate	T/°C	t/h	Alkene conversion (%)[b]	Yield[c](%), **10**
1		80	72	>99	65 (**10a**)
2		110	80	>95	46 (**10b**)
3		80	68	>99	68 (**10c**)
4		80	72	>99	59 (**10d**)
5		110	72	>95	64 (**10e**)
6		110	72	>99	49 (**10f**)
7		110	72	>99	74 (**10g**)
8		110	72	>99	82 (**10h**)
9		110	72	>99	51 (**10i**)

[a] Reactions were conducted at room temperature on a 1 mmol scale in CH_2Cl_2 (10 ml) with a relative mol ratio of tryptamine–olefin–catalyst of 100 : 100 : 1; 1 mol% of $Rh(acac)(CO)_2$, 1 eq CSA, 50 bar CO, 10 bar H_2, CH_2Cl_2. [b] Determined by analysis of ^{1}H-NMR spectra of crude reaction mixture. [c] Yield of isolated product after column chromatography.

yielded only 20% conversion of the olefin as determined by ^{1}H-NMR of the crude reaction mixture. The same substrate at 110 °C after 3 days was almost quantitatively consumed and gave product in quite a fair yield of 64% (Table 2, entry 5). Cyclohexene and methallylic amines required harsher conditions, therefore temperatures of 110 °C were applied in order to achieve full conversions of these olefins (Table 2, entries 2, 7 and 8). Substrates possessing allylic amino functionality had to be protected and used in the form of tertiary amines in order to prevent intramolecular cyclizations and formation of lactams under hydroformylation conditions.[10] Yields varied from a moderate 46% for cyclohexane to very good 74 and 82% yields respectively for methallylic amines (Table 2, entries 7 and 8). In the reaction mixture of methallylic amines, products **10g** and **10h** were accompanied by product **11**, which was isolated in 8% and 12% yield respectively (Scheme 3).

Methallylic alcohol (Table 2, entry 9) required harsher conditions as well; product **10i** was isolated in a moderate 51% yield.



Scheme 3 Byproduct isolated after tandem hydroformylation–Pictet–Spengler reaction with tertiary metallylic amines.

Conclusions

In summary, we have demonstrated that a reaction sequence of tandem hydroformylation and Pictet–Spengler cyclization can be applied in the synthesis of various THBCs involving both aprotic and protic conditions. Problems arise with formation of reduction byproducts, however, yields of products are synthetically useful in most cases. The fact that intermediates do not have to be isolated or purified clearly saves time and resources. Further investigation in using more complex olefinic structures and possible application in the synthesis of more complex structures is currently under way.

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