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Synthesis of β-carbolines from aldehydes and ketones via the α-siloxy α,β-unsaturated esters

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ABSTRACT

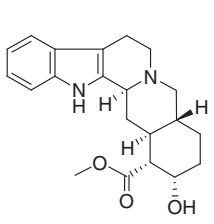
We report an efficient method for the synthesis of β-carbolines from α-siloxy α,β-unsaturated esters, which are accessible from a variety of aldehydes and ketones.

Since its original description in the literature, the Pictet–Spengler reaction has become one of the most powerful reactions for the preparation of tetrahydro-β-carbolines and tetrahydro-isoquinolines.[1] Through this reaction, structures of a high degree of molecular complexity can be constructed from relatively simple starting materials. Tetrahydro-β-carboline, in particular, has been featured as an important pharmacophore in many biologically active natural products and drugs (e.g., yohimbine and tadalafil) (Fig. 1). The method development and the total synthesis of natural products based on the Pictet–Spengler reaction remain an active area of research.[2]

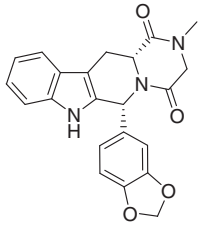
In a medicinal chemistry research program, we were particularly interested in the tetrahydro-β-carbolines prepared from the reaction of a substituted tryptamine with α-ketoesters (Scheme 1). To facilitate our SAR studies, we needed to synthesize a series of compounds with different R groups. Therefore, we were seeking a convenient method for the preparation of α-ketoesters.

α-Ketoesters have been prepared by many methods,[3] including the reaction of organometallic reagents with oxalic ester derivatives, the Friedel–Crafts acylation of arenes, oxidation of α-hydroxy esters prepared from the hydrolysis of the Strecker reaction products followed by the esterification, ozonolysis of cyano keto phosphoranes or α-keto vinyl ethers,[4] the oxidation of hydroxyl alkynyl ethers by potassium permanganate,[5] and desilylation of the α-siloxy α,β-unsaturated ester, which was prepared from the reaction of an aldehyde with a Horner–Emmons reagent (Scheme 2).[6]

We became interested in the last method listed above. We considered the possibility of using the intermediate α-siloxy α,β-unsaturated ester directly in Pictet–Spengler reaction bypassing the isolation of α-ketoesters (Scheme 3). Since the Pictet–Spengler reaction is typically facilitated by a strong acid, we envisioned that a strong acid would deprotect the silyl enol ether, generating the required α-ketoester in situ for the Pictet–Spengler reaction. Furthermore, we were surprised to find that although the preparation



Yohimbine



Tadalafil

Figure 1. Structures of yohimbine and tadalafil (Cialis®).

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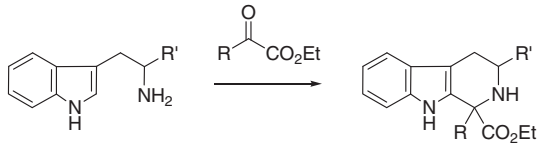
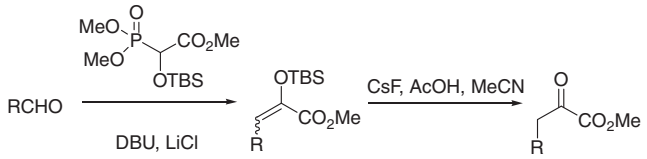
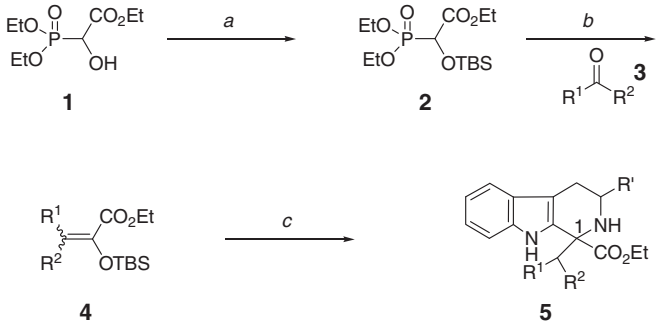


Scheme 1. Pictet–Spengler reaction of tryptamine with α-ketoester.



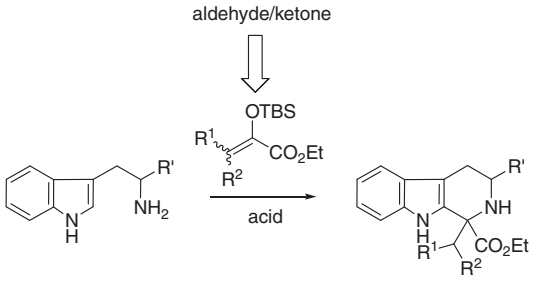
Scheme 2. Preparation of the α-ketoester from an aldehyde via α-siloxy α,β-unsaturated esters.



Scheme 4. Reagents and conditions: (a) TBSCl, imidazole, DMF, 52%; (b) LiHMDS, THF, −78 °C 30 min; then ketone or aldehyde, −78 °C to rt overnight; (c) method A: tryptamine HCl salt (1 equiv), *p*-TsOH monohydrate (1 equiv), 80 °C, EtOH, overnight; method B: *p*-TsOH monohydrate (2 equiv), 80 °C, EtOH, 5 h, then: tryptamine HCl salt added (1 equiv), 80 °C, overnight.

of α-siloxy α,β-unsaturated esters from ketones was known in the literature,[7] there has been no report on the desilylation to generate the corresponding α-ketoesters. Herein, we describe a novel method using α-siloxy α,β-unsaturated esters derived from aldehydes and ketones as surrogates to α-ketoesters in the Pictet–Spengler reaction with tryptamine.

The α-siloxy α,β-unsaturated esters **3** were prepared conveniently from the phosphonate reagent **2** and the aldehyde or ketone by the Horner–Emmons reaction[6,7] (Scheme 4). The phosphonate **2** was prepared from commercially available **1** following a known procedure.[8,9] A variety of ketones and aldehydes participated in this Horner–Emmons reaction efficiently to give the corresponding α-siloxy α,β-unsaturated esters (Table 1).[10] To demonstrate the utility of the current method, we chose to prepare α-siloxy α,β-unsaturated esters whose corresponding α-ketoesters are not commercially available and not easily accessible by other methods. We were gratified to find that even **4g** can be prepared efficiently from 2-indanone **3g**, which is well known to be prone to enolization. The α-siloxy α,β-unsaturated esters **4** are generally a mixture of two geometric isomers when R^1 and R^2 are different groups. However, it is interesting to note that aldehyde **3a** gives exclusively one isomer **4a** due to the steric bulk of both the OTBS group and the tetrahydropyran ring. The product **4a** most likely has *E* configuration.[6b] Since the cyclopropyl ring in aldehyde **3b** is sterically less demanding, the product **4b** is a mixture of two isomers in a ratio of 17:1. The mixture of geometric isomers is of little significance because under the subsequent Pictet–Spengler reaction conditions, both isomers will be desilylated to converge to the same α-ketoester. Since aldehydes and ketones are among the most accessible starting materials in organic synthesis, a variety of α-siloxy α,β-unsaturated esters should be accessible as the surrogates for the α-ketoester.



Scheme 3. Pictet–Spengler reaction of tryptamine with α-siloxy α,β-unsaturated esters.

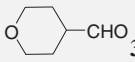
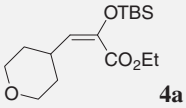
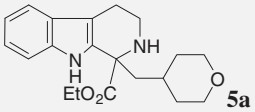
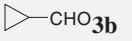
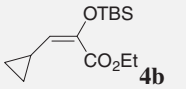
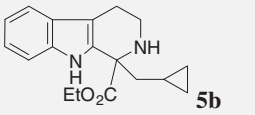
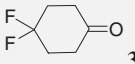
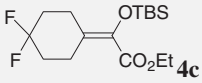
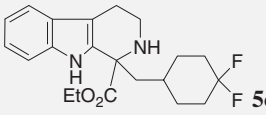
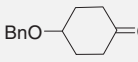
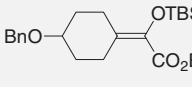
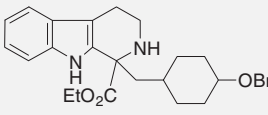
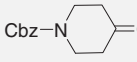
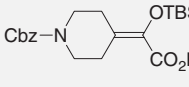
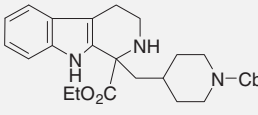
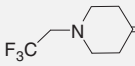
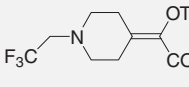
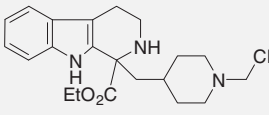
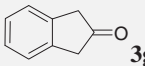
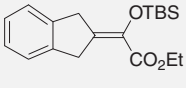
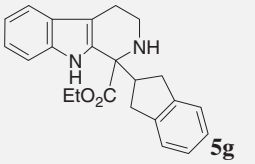
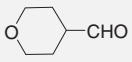
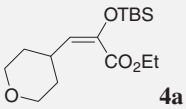
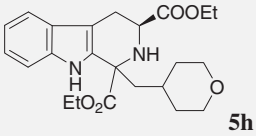
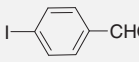
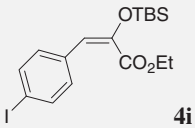
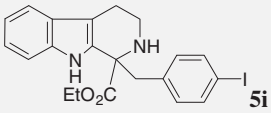
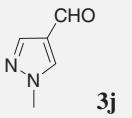
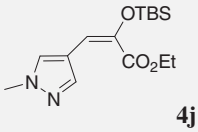
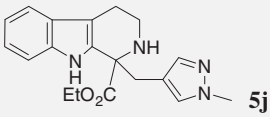
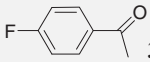
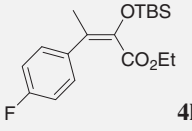
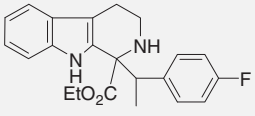
We carried out the Pictet–Spengler reaction of these α-siloxy α,β-unsaturated esters with tryptamine HCl salt to prepare the corresponding β-carbolines (Table 1). As an example, simply heating a mixture of **4a** with tryptamine HCl salt and 1 equiv of *p*-TsOH monohydrate each in ethanol overnight at 80 °C gave the β-carboline product **5a** in good yield (Method A).[11] Compound **5c** with an interesting difluoro substitution on the cyclohexyl ring was prepared accordingly. Compound **4d** gave β-carboline **5d** as a 1.6:1 cis/trans mixture in respect to the cyclohexyl ring. Compounds **5e** and **5f** with a piperidine ring were prepared conveniently from the piperidone starting materials **3e** and **3f**, respectively. Compound **4g** prepared from 2-indanone gave β-carboline **5g** containing indane in good yield. More interestingly, when L-tryptophan ester was used instead of tryptamine, the product **5h** was also produced as a diastereomeric mixture (1.4:1) in good yield (entry 8). Method A worked well with α-siloxy α,β-unsaturated esters derived from aliphatic aldehydes and ketones. However, when the exact method was applied to the α-siloxy α,β-unsaturated esters prepared from aromatic carbonyl compounds, the yield of the Pictet–Spengler products was low. Method B, a slight modification of Method A, whereby the α-siloxy α,β-unsaturated ester was heated with 2 equiv of *p*-TsOH in ethanol for 6 h to achieve complete desilylation before tryptamine HCl salt was added, circumvented this problem.[12] In this way, β-carbolines **5i–k** were prepared in good yields. As demonstrated by the examples, the current method for the synthesis of carbolines is quite general. However, this method is limited to the structure of **5** (Scheme 4) with a methyne carbon attached to the C1 carbon of the β-carboline.

In summary, we describe a novel efficient method for the preparation of β-carbolines from a variety of aldehydes and ketones via α-siloxy α,β-unsaturated esters. Since ketones and aldehydes are widely available starting materials, we believe that this novel method will complement known methods in the synthesis of β-carbolines.

Supplementary data

Supplementary data (the supplementary material contains the ^{1}H NMR spectra for all new compounds) associated with this

Table 1
Synthesis of tetrahydro-β-carbolines **5** from aldehydes/ketones **3** via α-siloxy α,β-unsaturated esters **4**

Entry	Aldehyde/ketone **3**	α-Siloxy α,β-unsaturated esters **4**	Yield (%) of **4**[a]	Pictet–Spengler product **5**	Method for Pictet–Spengler reaction[c]	Yield (%) of **5**[b]
1	 **3a**	 **4a**	91 (Single isomer)	 **5a**	A	78
2	 **3b**	 **4b**	81 (17:1)	 **5b**	A	88
3	 **3c**	 **4c**	88	 **5c**	A	84
4	 **3d**	 **4d**	78	 **5d**	A	74 (1.6:1)
5	 **3e**	 **4e**	93	 **5e**	A	67
6	 **3f**	 **4f**	81	 **5f**	A	81
7	 **3g**	 **4g**	83	 **5g**	A	78
8	 **3a**	 **4a**	91 (Single isomer)	 **5h**	A	80 (1.4:1)
9	 **3i**	 **4i**	78 (3.6:1)	 **5i**	B	84
10	 **3j**	 **4j**	99 (3.9:1)	 **5j**	B	78
11	 **3k**	 **4k**	62 (11:1)	 **5k**	B	77 (1:1)

[a] The ratio of the geometric isomers is noted in the parentheses.
[b] The diastereomeric ratio is noted in the parentheses.
[c] Method A: tryptamine HCl salt (1 equiv), *p*-TsOH monohydrate (1 equiv), 80 °C, EtOH, overnight; method B: *p*-TsOH monohydrate (2 equiv), 80 °C, EtOH, 5 h, then: tryptamine HCl salt added (1 equiv), 80 °C, overnight.

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References and notes

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9. *Preparation of phosphonate* **2**: To a solution of ethyl 2-(diethoxyphosphoryl)-2-hydroxyacetate **1** (50 g, 208 mmol) (purchased from Toronto Research Chemicals, Ontario, Canada) in DMF (170 mL) at 0 °C was added imidazole (35.4 g, 520 mmol) followed by TBSCl (37.7 g, 250 mmol). The reaction mixture was warmed to rt and stirred overnight under N_2. The reaction mixture was partitioned between water and ethyl acetate. The organic layer was separated, dried (Na_2SO_4), and concentrated. The residue was purified by silica gel column eluted by a gradient of hexanes to ethyl acetate to afford phosphonate **2** (38.43 g, 52%) as a colorless oil. LC–MS: M+H = 355.12. ^{1}H NMR ($CDCl_3$, 500 MHz) δ = 0.083 (3H, s), 0.091 (3H, s), 0.902 (9H, s), 1.30 (9H, m), 4.21 (6H, m), 4.56 (1H, d, *J* = 18 Hz).
10. *Preparation of* α*-siloxy* α,β*-unsaturated esters from phosphonate* **2** *exemplified by* **4a**: Phosphonate **2** (3.73 g, 10.51 mmol) was dissolved in THF (16 mL) and cooled to −78 °C. LiHMDS (1 M solution in THF, 9.64 mL, 9.64 mmol) was added. The reaction mixture was stirred at −78 °C for 30 min. Aldehyde **3a** (1 g, 8.76 mmol) was added. The reaction mixture was allowed to warm to rt overnight. The reaction was quenched by satd aqueous NH_4Cl solution. The mixture was extracted with CH_2Cl_2 and extracts were dried (Na_2SO_4). The extracts were concentrated and the residue was purified by silica gel chromatography eluted by a gradient of hexanes to 30% ethyl acetate to afford **4a** (2.5 g, 91%) as an oil. ^{1}H NMR ($CDCl_3$, 500 MHz) δ = 0.15 (6H, s), 0.97 (9H, s), 1.35 (3H, t, *J* = 7 Hz), 1.46 (2H, qd, *J* = 12 Hz, 4.5 Hz), 1.67 (2H, d, *J* = 12 Hz), 3.25 (1H, m), 3.48 (2H, t, *J* = 12 Hz), 3.96 (2H, d, *J* = 12 Hz), 4.25 (2H, q, *J* = 7 Hz), 5.33 (1H, d, *J* = 10 Hz).
11. *Pictet–Spengler reactions with* α*-siloxy* α,β*-unsaturated ester* **4**, *Method A exemplified by the synthesis of* β*-carboline* **5a**: A mixture of tryptamine hydrochloride (125 mg, 0.636 mmol), *p*-TsOH monohydrate (121 mg, 0.636 mmol), and silyl enol ether **4a** (200 mg, 0.636 mmol)in ethanol (8 mL) was stirred at 80 °C under N_2 overnight. The reaction mixture was cooled to rt and treated with solid $NaHCO_3$ (534 mg, 6.36 mmol). The solvent was removed and the residue was dry-loaded on a silica gel column. Elution by a gradient to CH_2Cl_2 to 50% acetone afforded the product **5a** (170 mg, 78%) as a solid. LC–MS: M+H = 343.21. ^{1}H NMR (CD_3OD, 500 MHz) δ = 1.26 (3H, t, *J* = 7 Hz), 1.26 (1H, m), 1.32 (1H, m), 1.39 (1H, d, *J* = 12.5 Hz), 1.65 (1H, d, *J* = 12.5 Hz), 1.84 (1H, m), 1.93 (1H, dd, *J* = 14 Hz, 5 Hz), 2.18 (1H, dd, *J* = 14 Hz, 6.5 Hz), 2.64 (1H, dt, *J* = 15 Hz, 3.1 Hz), 2.76 (1H, m), 3.13 (1H, m), 3.21 (1H, dq, *J* = 12 Hz, 3.1 Hz), 3.33 (2H, m), 3.76 (1H, d, *J* = 12 Hz), 3.84 (1H, d, *J* = 12 Hz), 4.19 (2H, m), 6.96 (1H, t, *J* = 8 Hz), 7.06 (1H, d, *J* = 8 Hz), 7.32 (1H, d, *J* = 8 Hz), 7.38 (1H, d, *J* = 8 Hz).
12. *Pictet–Spengler reactions with* α*-siloxy* α,β*-unsaturated ester* **4**, *Method B exemplified by the synthesis of* β*-carboline* **5i**: A mixture of *p*-TsOH monohydrate (164 mg, 0.86 mmol) and silyl enol ether **4i** (186 mg, 0.43 mmol) in ethanol (5 mL) was stirred at 80 °C under N_2 for 6 h. LC–MS indicated that 4 g was consumed. The mixture was treated with tryptamine hydrochloride (85 mg, 0.43 mmol) and then stirred at 80 °C under N_2 overnight. Further processing as described for Method A afforded product **5g** (166 mg, 84%) as a solid. LC–MS: M+H = 460.99. ^{1}H NMR (CD_3OD, 500 MHz) δ = 1.23 (3H, t, *J* = 7 Hz), 2.66 (1H, dt, *J* = 15 Hz, 3.9 Hz), 2.68 (1H, m), 3.04 (1H, m,), 3.10 (1H, m,), 3.14 (1H, d, *J* = 13.5 Hz), 3.54 (1H, d, *J* = 13.5 Hz), 4.17 (2H, dd, m), 6.93 (2H, d, *J* = 8 Hz), 6.98 (1H, d, *J* = 7.5 Hz), 7.10 (1H, t, *J* = 7.5 Hz), 7.38 (1H, d, *J* = 7.5 Hz), 7.41 (1H, d, *J* = 7.5 Hz), 7.58 (2H, d, *J* = 8 Hz).