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Influence of reaction conditions on products of the Pictet–Spengler condensation

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ABSTRACT

The Pictet–Spengler reaction with *N*-protected α-amino aldehydes was found to be very sensitive to reaction conditions. The outcome of the reaction can be controlled mainly by choice of solvent. Tetrahydro-β-carbolines were obtained in apolar solvents, while in polar media octahydro-bipyrroloindoles were the main compounds. Temperature, amount of acid and reaction time also influenced the final results of the PS reaction. Depending on conditions, products with opposite configuration of stereogenic centre, descended from amino aldehydes, were formed as byproducts.

1. Introduction

The Pictet–Spengler (PS) reaction[1] is widely applied in the synthesis of tetrahydroisoquinoline and tetrahydro-β-carboline skeletons, which are found in many alkaloids.[2–4] Such moieties are also useful in peptide chemistry as constrained analogs of aromatic amino acids. There are known examples of biological active peptides where the incorporation of a tetrahydroisoquinoline or tetrahydro-β-carboline moiety into the peptide chain changes the physico-chemical properties and the biological activity of the parent peptide.[5,6]

In recent years, α-amino aldehydes derived from α-amino acids have been widely used as carbonyl components in the Pictet–Spengler reaction.[7–10] If such compounds are condensed with tryptophan, a mixture of diastereomers is formed.[11] Additionally, the tetrahydro-β-carbolines obtained have carboxyl and amine groups, which make them useful in further transformations and libraries of new analogs might be formed.[12]

Our laboratory recently studied the influence of the stereogenic centre of the α-amino aldehyde on the ratio of *cis*/*trans* products.[11] We found that an intramolecular hydrogen bond, formed during the PS reaction, may be responsible for the distribution of products. In the literature, there are other examples of the Pictet–Spengler reaction with the use of amino aldehydes;[10,13] comparison of those results shows that the ratio of the formed products strongly depends on the conditions of PS reaction.[10,13] During the PS reaction, racemisation on the stereogenic centre descended from amino aldehydes may occur and it could lead to mistaken conclusion about the ratio of *cis*/*trans* products.

This induced us to investigate in greater detail the influence of reaction conditions on the products of the Pictet–Spengler condensation. To our knowledge, no such detailed studies have yet been reported in the literature.

2. Results and discussion

During the PS reaction with amino aldehydes two types of products may be formed: **3**,**4** and **5**,**6** (Scheme 1).[10,14]

We investigated the influence of temperature, solvents, reaction time, and equivalents of added acid on the ratio of possible products. *N*-Cbz protected amino aldehydes derived from L-Leu, D-Leu and L-Phe, D-Phe were used as carbonyl components. Our earlier studies have shown that for L-amino aldehydes, compounds **3a** and **3b** are formed and compound **3b** is the main product; for D-amino aldehydes only compound **4a** is formed.[11] We have never observed compound **4b** in the reaction mixture; however, Grieco et al.[10] did describe products of this type. We speculate that racemisation of the starting aldehydes might be one of the causes for obtaining the *trans* diastereomer, because chiral amino aldehydes are well-known to easily undergo such a transformation.[15–17] At the beginning of our studies, the main goal was to investigate the influence of the PS reaction conditions on amino aldehydes racemisation. Therefore, we first attempted to study the susceptibility to racemisation directly, using optical rotation measurement. Samples were prepared in

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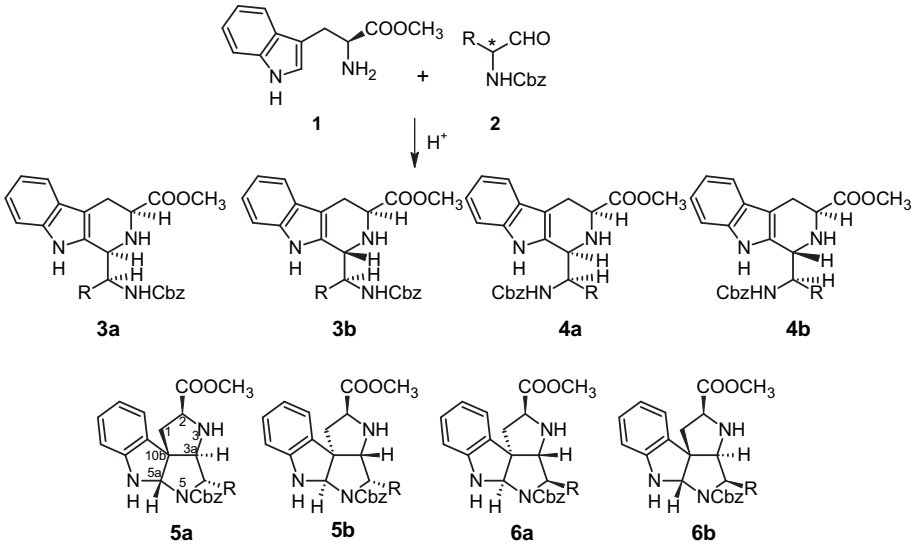
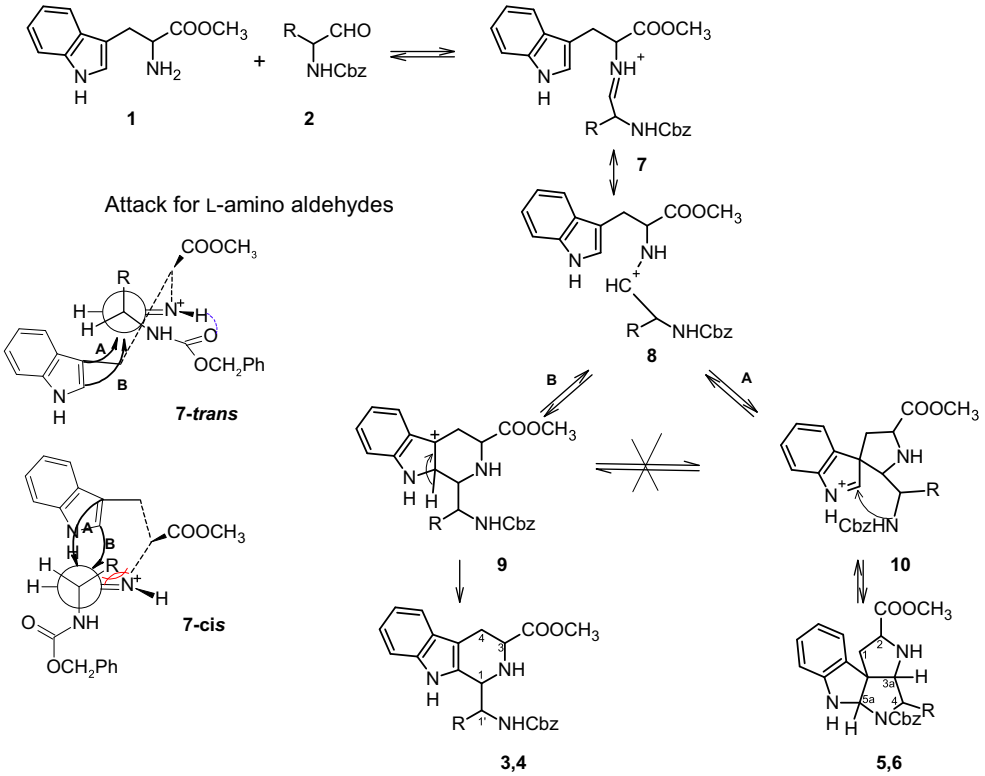


Scheme 1. Possible products of the Pictet–Spengler reaction.

solvents with acid addition, but it proved to be impossible to calculate the racemisation ratio by measuring optical rotation. In the presence of acid, amino aldehydes condensed to form dehydrated aldol products, which were confirmed by MS analysis. The determination of the racemisation ratio of **2** was instead performed indirectly, by analyzing the products of the PS reaction.

Regarding the PS reaction, we interpreted all our results on the basis of a known mechanism (Scheme 2). It was postulated that the reaction could go through two possible paths: **A** and **B**. Kowalski et al.[18] and recently Maresh et al.[19] showed that path **A** does not lead to 'normal' Pictet–Spengler products with a six-membered ring. Spiroindolenine **10** is formed via C-3 attack of the indol ring on the iminium ion **7**. It may react further to form compounds of type **5** and **6**. However, conversion of **10** by alkyl shift into the six-membered carbocation **9** is energetically unfavorable. The six-membered products of the PS reaction are formed through path **B**. Six-membered carbocation **9** is formed by a direct attack of C-2. It was also confirmed that the formation of spiroindolenine **10** is reversible, so iminium cation may react through path **B** to form the required products.[8,18,19]

We performed the Pictet–Spengler reaction in two types of solvents: aprotic (CH_2Cl_2) and protic (CH_3OH) with 5 equiv of TFA.



Scheme 2. The Pictet–Spengler reaction mechanism.

The reaction mixtures were stirred for the first 5 h at −30, 0 or rt and then at rt overnight. The results are given in Table 1. In CH_2Cl_2 we observed the formation of products **3a**,**b** for L-amino aldehydes and **4a** for D-amino aldehydes as main products. We also observed the products with an opposite configuration at C-1′ depending on the temperature (Fig. 1a). This is caused by racemisation due to the keto-enol tautomerism of parent aldehyde or iminium–enamine in iminium ion **7**. At higher temperature, higher amounts of product **4a** for L- and products **3a**,**b** for D-amino aldehydes were observed. Experiments at different temperatures were also performed in CH_3OH, with surprising results: the reaction was much slower and Trp–OMe **1** was still present after 24 h. The main product was compound **5a** for L- and **6a** for D-amino aldehydes (Fig. 1b). The intramolecular hydrogen bond in cation **7**-*trans*, which, in our opinion, favors diastereomer *trans* **3b** (and *cis* **4a**)[11] was probably broken by the solvent and the attack of C-3 (path **A**) on the cation **7**-*cis* occurred on the other, less hindered face of the iminium, forming spiroindolenine **10** (Scheme 2). It did not undergo a reversible reaction to iminium cation **7** because a topographical relation of reacting groups was suitable for further conversion into compound **5a**. Spiroindolenine **10** did not also convert into cation **9**, because such transformation was found to be energetically unfavorable.[18] Cation **7**-*trans* cannot react via spiroindolenine **10** to compound **5b**, because of the unfavorable topographical relation of the reacting centers. Additionally, in CH_3OH some other products (marked grey in Fig. 1b) were formed, which were not analyzed in detail but were shown by LC-MS analysis to be formed from dehydrated aldol.

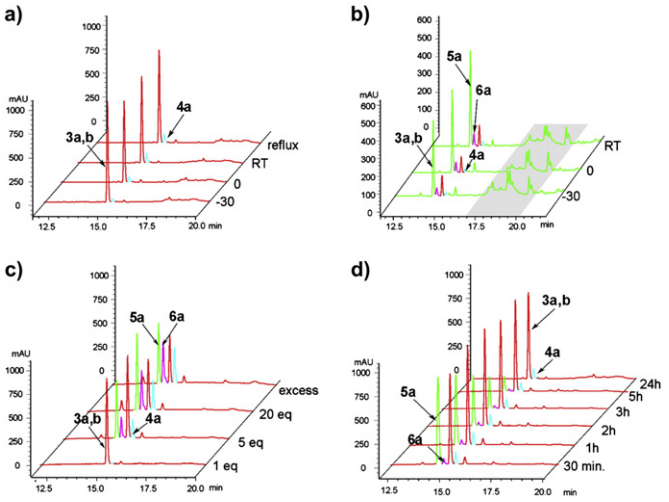


Fig. 1. HPLC of reaction mixtures with Cbz-L-Phe-H, in the presence of 5 equiv TFA (a) in CH_2Cl_2; (b) in CH_3OH; (c) with DMSO addition (d) at different time intervals.

The hydrogen bond in cation **7** is broken and there is a possibility to form higher amounts of compound **3a** and spiroindolenine **10** and, further, compound **5**. DMSO, as a polar co-solvent, has also a strong influence on racemisation of the aldehydes stereogenic centre.

The next experiment was based on kinetic studies of reaction of Cbz-L-Phe-H in CH_2Cl_2 (Fig. 1d, Table 3). The reaction was performed at rt with 5 equiv TFA. We analyzed a mixture of products after 30 min, 1 h, 2 h, 3 h, 5 h and 24 h. After 30 min the ratio of products **3a**,**b** to **5a** was almost 1:1 and small amounts of products **4a** and **6a** were also observed.

Table 1
Ratio of the Pictet–Spengler reaction products determined by HPLC

Aldehyde **2**	T [°C]	Solvent	TFA [equiv]	**3a**,**b**[%] (**3a**/**3b**)[a,b]	**4a** [%][a]	**5a**/**6a** [%][c]
Cbz-L-Phe-H[d]	−30	CH_2Cl_2	5	97.7 (14/86)	2.3	0
	0	CH_2Cl_2	5	94.3 (26/74)	5.7	0
	rt	CH_2Cl_2	5	90.8 (27/73)	9.2	0
	reflux	CH_2Cl_2	5	92.0 (30/70)	8.0	0
	rt	CH_2Cl_2	1	26.4	21.8	36.1/15.7
	−30	CH_3OH	5	18.7	6.8	68.6/5.8
	0	CH_3OH	5	13.8	3.7	74.8/7.7
	rt	CH_3OH	5	15.8	3.8	72.2/8.2
	rt	CH_3OH	1	19.1	10.5	50.0/20.4
Cbz-L-Leu-H	−30	CH_2Cl_2	5	97.9 (20/80)	2.1	0
	0	CH_2Cl_2	5	97.4 (26/74)	2.6	0
	rt	CH_2Cl_2	5	94.1 (27/73)	5.9	0
	−30	CH_3OH	5	13.0	4.6	82.4
	0	CH_3OH	5	17.0	4.7	78.3
	rt	CH_3OH	5	11.8	5.8	82.4

[a] Ratio of **3a**/**3b** obtained in CH_2Cl_2 was determined by ^1H NMR, in the case of reaction with D-amino aldehydes only product *cis* was observed.
[b] It was not possible to determine the ratio of **3a**/**3b** for reactions performed in CH_3OH, due to overlap with signals of **5a** and **6a** in ^1H NMR spectrum.
[c] In the case of reaction with L and D-Leu it was not possible to determined the ratio of **5a**/**6a**.
[d] Data for Cbz-D-Phe-H and Cbz-D-Leu-H are given as the Supplementary data.

We also performed the reaction in CH_2Cl_2 with a smaller amount of acid (1 equiv) and the results were completely different from those with 5 equiv (Table 1). The ratio of compounds **3a**,**b** to **4a** was almost 1:1 and, additionally, compounds **5a** and **6a** were formed. This means that the reaction proceeded by both paths **A** and **B** (Scheme 2). The higher percent of epimeric products in the reaction performed with 1 equiv of acid in comparison to 5 equiv (21.8 versus 9.2%) indicates that to maintain stereogenic integrity of products excess of acid should be used.

To verify the importance of the intramolecular hydrogen bond in the formation of the Pictet–Spengler reaction products, we performed this reaction with different amounts of DMSO (as a hydrogen bond breaker) added to CH_2Cl_2 (Fig. 1c, Table 2).

The results indicate that the hydrogen bond is responsible for the formation of compounds **3b** and **4a**.

Table 2
Experiment with different amounts of DMSO (related to Trp–OMe) added to CH_2Cl_2 (model reaction with Cbz-L-Phe-H, −30 °C, 5 equiv TFA). Ratio of products determined by HPLC

DMSO (equiv)	**3a**,**b** [%](**3a**/**3b**)[a]	**4a** [%]	**5a** [%]	**6a** [%]
1	98.9 (17/83)	1.1	0	0
5	46.8 (26/74)	9.8	33.0	10.4
20	25.6 (40/60)	14.6	39.0	20.8
Excess	25.5 (43/57)	18.6	31.7	24.2

[a] Ratio of **3a**/**3b** was determined by ^1H NMR.

Table 3
Kinetic experiment in CH_2Cl_2 at rt (model reaction with Cbz-L-Phe-H, 5 equiv TFA). Ratio of products determined by HPLC

Time intervals	**3a**,**b** [%]	**4a** [%]	**5a** [%]	**6a** [%]
30 min	43.1	5.1	49.8	2.0
1 h	50.6	5.7	41.9	1.8
2 h	60.3	6.2	32.0	1.5
3 h	68.7	6.3	23.7	1.3
5 h	80.0	6.6	12.4	1.0
24 h	90.8	9.2	0	0

In time, we observed decreasing amounts of products **5a**,**6a** and increasing amounts of products with the six-membered ring. This confirmed that the formation of product **5a**,**6a** is reversible and the direct attack of C-2 of the indole moiety, forming the six-membered ring, is the driving force of the Pictet–Spengler reaction in aprotic solvents. The rate of formation of spiroindolenine **10** and six-membered carbocation **9** is probably similar, but the reaction equilibrium is shifted into products **3**,**4** because they are thermodynamically favored and do not easily undergo reversible conversion into iminium cation **7**.

To prove the reversibility of formation of compounds **5a** and **6a**, we attempted to convert products **5a** or **6a** formed in CH_3OH into **3**,**4** (Fig. 2). Acid and aprotic solvent were necessary for this conversion. Products **5a** or **6a** dissolved in CH_2Cl_2 without acid, or in CH_3OH with acid addition, were stable. However, when the mixture obtained in the reaction with L-amino aldehydes in CH_3OH, was redissolved at rt in CH_2Cl_2 and 5 equiv of TFA was added, we observed both compounds **3a** and **3b** in a ratio similar to that obtained in CH_2Cl_2 at the same temperature (Table 1). This confirmed that the formation of spiroindolenine **10** has to be reversible, otherwise only compound *cis* **3a** should be observed.

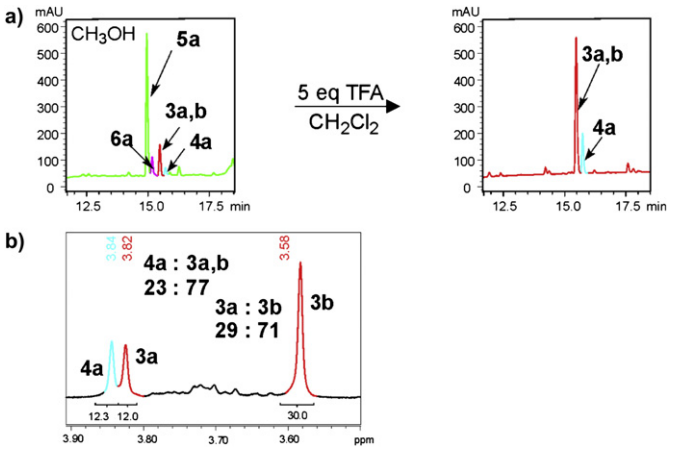


Fig. 2. a) Conversion of 5a (four rings system) into 3,4 (three rings system); (b) ^{1}H NMR spectrum of the mixture after conversion.

Compounds **3a**,**b** and **4a** were stable under conditions mentioned above. They did not undergo any conversion in CH_2Cl_2 or CH_3OH with acid addition, which was confirmed by ^{1}H NMR.

3. Conclusion

In conclusion, our studies have shown that differently structured products may be obtained depending on PS reaction conditions. We have also confirmed, in greater detail, the well-known fact that α-amino aldehydes are very sensitive to reaction conditions and easily undergo racemisation. Better stereochemistry control of the PS reaction with α-amino aldehydes is obtained at lower temperature. The excess of acid used is also crucial, because in the equimolar condition it is not possible to obtain the desired selectivity of this reaction. Aprotic solvents favor the formation of six-membered products (tetrahydro-β-carbolines), whereas protic and polar solvents (or co-solvents) favor five-membered products (octahydro-bipyrolloindoles).

Our results have shown that the Pictet–Spengler reaction with α-amino aldehydes opens up a broad spectrum of synthetic possibilities. We can control the outcome of the reaction depending on the solvent used.

4. Experimental section

4.1. General procedure

RP-HPLC was performed using an RP C-12 column (Jupiter 4u Proteo 90A, ID=0.46 cm, *L*=25 cm). 'Gradient 1' for analogs of Cbz-L-Phe-H: *t*=0 min, 80% A, 20% B, *t*=20 min, 3% A, 97% B; the mobile phases (water, acetonitrile) contained 0.05% TFA. For analogs of Cbz-L-Leu an isocratic program was used 'gradient 2' *t*=0–15 min, 55% A, 45% B, the mobile phase (water, acetonitrile) contained 0.05% HCOOH. For both programs the flow rate was 1 mL min^{-1} and λ=210 nm. All 1H and 2D NMR spectra were acquired using a 700 MHz spectrometer. For ROESY measurements the standard pulse sequence was applied with ms mixing time. Mass spectra were recorded on an LCT TOF spectrometer using electrospray ionization (positive ion mode) or LC-MS.

4.2. General procedure for Pictet–Spengler reaction

All reactions were performed as previously reported[11] with the exception of solvents and temperature. α-Amino aldehyde (0.36 mmol) dissolved in 2 mL CH_2Cl_2 (or CH_3OH) was added to 0.33 mmol of Trp–OCH_3 in 2 mL CH_2Cl_2 (or CH_3OH). 5 equiv (0.127 mL) of TFA in 1 mL CH_2Cl_2 (or CH_3OH) was added in three portions. The reaction mixtures were stirred for 5 h at −30 °C, 0 °C, rt, or reflux and then at rt overnight. Then the mixture was diluted with CH_2Cl_2 and saturated solution of $NaHCO_3$ was used to neutralize TFA. For reactions performed in CH_3OH, the solvent was evaporated and the mixture was redissolved in CH_2Cl_2 and neutralized with satd $NaHCO_3$. Organic phases were extracted with satd $NaHCO_3$, washed with brine and dried over $MgSO_4$. For experiments with DMSO addition, the co-solvent was added immediately after the mixing of aldehyde with tryptophan.

The reaction mixtures were analyzed by HPLC. In four cases the reaction mixtures prepared in CH_3OH were purified by semi-preparative HPLC (*t*=0 min, 97% A, 3% B, *t*=40 min, 3% A, 97% B; the mobile phases (water, acetonitrile) contained 0.05% TFA) to obtain 20–30 mg of standards for compounds of type **5a** and **6a**.

Compounds **3a**,**b** and **4a** have been isolated and fully characterized before.[11]

*4.2.1. 5-Benzyl 2-methyl (2S,3aR,4S,5aS,10bR)-4-benzyl-1,2,3,3a,4,5,5a,6-octahydropyrrolo[3′,2′:3,4]pyrrolo[2,3-b]indole-2,5-dicarboxylate (**5a** Phe).* Yellow solid, t_R (gradient 1)=14.76 min. Duplicated signals in NMR resulted from *cis*/*trans* isomerisation of amide (urethane–Cbz) bond. ^{1}H NMR (700 MHz, $CDCl_3$) δ_H 7.44–6.61 (14H, m, Ar), 5.43 and 5.37 (1H, s, H-5a), 5.24 (q, *J* 12.3 Hz, CH_2Cbz) and 5.13 (2H, q, *J* 12.2 Hz, CH_2Cbz), 4.26 (dd, *J* 11.6, 4.5 Hz, H-4) and 4.18 (1H,dd, *J* 10.9, 4.9 Hz, H-4), 4.00–3.96 (1H, 2×dd, *J* 9.8, 9.3, 5.1, 4.9 Hz, H-2), 3.71 and 3.66 (3H s, OCH_3), 3.65 and 3.64 (1H, s, H-3a), 2.59–2.53 (1H, 2×dd, *J* 14.0, 5.1, 4.9, H-1), 2.48–2.41 (1H, 2×dd, *J* 14.0, 9.4, 9.3 Hz, H-1), 1.96 (1H, dd, *J* 13.3, 11.0 Hz, H-4′) and 1.87 (dd, *J* 12.7, 12.1 Hz, H-4′); ^{13}C NMR (125 MHz, $CDCl_3$) δ_C 174.0 and 173.9, 155.2 and 154.3, 149.0 and 148.6, 138.1–109.4, 83.1 and 82.4, 72.3 and 71.2, 67.2 and 67.2, 66.7 and 66.3, 63.6 and 62.4, 60.4 and 60.3, 52.4 and 52.3, 42.6 and 42.5, 39.7 and 38.7. COSY (700 MHz, $CDCl_3$) H-1 (H-1, H-2), H-2 (2×H-1), H-4 (2×H-4′). HSQC (700 MHz, $CDCl_3$)

Ar (129–109), H-5a (83.0 and 82.2), H-3a (72.2 and 71.1), CH_2Cbz (67.10), H-4 (66.6 and 66.2), H-2 (60.3), OCH_3 (52.2), H-1 (42.5), H-4′ (39.6 and 38.6). ROESY (700 MHz, $CDCl_3$) H-1 (H-2, H-5a), H-2 (H-1), H-4 (H-4′), H-4′(H-4), H-5a (H-1). LC-MS (ESI^+) *m/z* 484 $[M+H]^+$, 506 $[M+Na]^+$. Exact mass calcd for $C_{29}H_{29}N_3O_4Na$ $[M+Na]^+$: 506.2056, found: 506.2079.

*4.2.2. 5-Benzyl 2-methyl (2S,3aS,4R,5aR,10bS)-4-benzyl-1,2,3,3a,4,5,5a,6-octahydropyrrolo[3′,2′:3,4]pyrrolo[2,3-b]indole-2,5-dicarboxylate (**6a** Phe).* Yellow solid, t_R (gradient 1)=15.00 min. Duplicated, broad signals in NMR resulted from *cis*/*trans* isomerisation of amide (urethane–Cbz) bond. ^{1}H NMR (700 MHz, $CDCl_3$) δ_H 7.40–6.64 (14H, m, Ar), 5.69 and 5.63 (1H, s, H-5a), 5.26 and 5.10–4.99 (2H, m, CH_2Cbz), 4.77–4.72 (m, H-2 and H-4), 4.68 (1H, dd, *J* 9.7, 5.8 Hz, H-4), 4.53 (1H, dd, *J* 10.3, 6.7 Hz, H-2), 4.22 and 4.20 (1H, s, H-3a), 3.73 and 3.65 (3H, s, OCH_3), 2.96 (br d, *J* 12.1 Hz, H-4′), 2.89 (dd, *J* 13.3, 7.1 Hz, H-1), 2.80–2.75 (1H, m, H-1 and H-4′), 2.56 (1H, dd, *J* 13.3, 11.6 Hz, H-1) and 2.49 (dd, *J* 13.9, 8.4 Hz, H-1). 2.12 (1H, dd, *J* 12.9, 9.9 Hz, H-4′) and 1.99 (br t, *J* 11.9 Hz, H-4′); ^{13}C NMR (125 MHz, $CDCl_3$) δ_C 169.0 and 168.2, 154.9 and 154.7, 148.8 and 148.4, 137.3–109.9, 81.7 and 81.4, 70.1 and 69.3, 67.8 and 67.2, 63.4 and 63.3, 60.0, 59.0 and 58.9, 53.5 and 53.4, 40.3 and 40.0, 39.6 and 38.6. COSY (700 MHz, $CDCl_3$), H-1 (H-1, H-2), H-2 (2×H-1), H-4 (2×H-4′). HSQC (700 MHz, $CDCl_3$) Ar (110–130), H-5a (81.3 and 81.7), H-3a (69.2 and 70.1), CH_2Cbz (67.6), H-4 (63.4), H-2 (58.7), OCH_3 (53.4), H-1 (40.0 and 40.3), H-4′ (38.6 and 39.6). ROESY ($CDCl_3$, 700 MHz) H-1 (H-2, H-5a), H-2 (H-1, H-5a), H-3a (H-4′), H-4 (H-4′), H-4′(H-3a, H-4), H-5a (H-1, H-2). LC-MS (ESI^+) *m/z* 484 $[M+H]^+$, 506 $[M+Na]^+$. Exact mass calcd for $C_{29}H_{30}N_3O_4$ $[M+H]^+$: 484.2236, found: 484.2213.

*4.2.3. 5-Isobuthyl 2-methyl (2S,3aR,4S,5aS,10bR)-4-benzyl-1,2,3,3a,4,5,5a,6-octahydropyrrolo[3′,2′:3,4]pyrrolo[2,3-b]indole-2,5-dicarboxylate (**5a** Leu).* White solid, t_R (gradient 2)=6.11 min. Duplicated, broad signals in NMR resulted from *cis*/*trans* isomerisation of amide (urethane–Cbz) bond. ^{1}H NMR (700 MHz, $CDCl_3$) δ_H 7.39–6.57 (9H, m, Ar), 5.45 and 5.43 (1H, s, H-5a), 5.23 and 5.16 and 5.10 (2H, s+dd, *J* 11.9 Hz, CH_2Cbz), 4.73–4.69 (1H, m, H-2), 4.61 (dd, *J* 9.3, 6.0 Hz, H-4), 4.47 (1H, dd, *J* 9.4, 5.7 Hz, H-4), 4.21 and 4.18 (1H, s, H-3a), 3.80 and 3.66 (3H, s, OCH_3), 2.89 (dd, *J* 14.3, 9.5 Hz, H-1) and 2.81–2.80 (2H, m, H-1), 1.47–1.43 and 1.40–1.37 (1H, m, H-5′), 1.31–1.20 (1H, m, H-4′), 0.89–0.82 (1H, m, H-4′), 0.78 (d, *J* 6.5 Hz, H-6′) and 0.71 (d, *J* 6.5 Hz, H-6′) and 0.69 (3H, d, *J* 6.5 Hz, H-6′) and 0.62 (3H, d, *J* 6.6 Hz, H-6′); ^{13}C NMR (125 MHz, $CDCl_3$) δ_C 169.5 and 168.9, 154.5 and 153.6, 148.3 and 148.1, 135.6–110.7, 81.7 and 81.3, 72.5 and 71.3, 67.6 and 67.3, 62.9 and 62.7, 61.2 and 60.4, 59.8 and 59.6, 53.7 and 53.6, 42.9 and 42.6, 40.2 and 40.0, 25.2 and 24.9, 22.4 and 21.4. COSY (700 MHz, $CDCl_3$) H-1 (H-2), H-2 (H-1), H-4 (H-4′), H-4′ (H-4, H-5′), H-5′(H-4′, H-6′), H-6′ (H-5′). HSQC (700 MHz, $CDCl_3$) Ar (109–130), H-5a (81.7 and 81.5), H-3a (72.6 and 71.6), CH_2Cbz (67.6), H-4 (61.3 and 60.5), H-2 (59.7), OCH_3 (54.1 and 53.5), H-4′ (42.7 and 42.3), H-1 (40.1), H-5′ (25.1), H-6′ (22.7 and 21.6). ROESY (700 MHz, $CDCl_3$) H-1 (H-2, H-5a), H-2 (H-1), H-3a (H-4′, H-5′), H-4 (H-4′, H-5′), H-4′(H-3a, H-4, H-5′), H-5′(H-6′), H-6′(H-4′, H-5′), H-5a (H-1). LC-MS (ESI^+) *m/z* 450 $[M+H]^+$, 472 $[M+Na]^+$. Exact mass calcd for $C_{26}H_{32}N_3O_4$ $[M+H]^+$: 450.2393, found: 450.2400.

*4.2.4. 5-Isobuthyl 2-methyl (2S,3aS,4R,5aR,10bS)-4-benzyl-1,2,3,3a,4,5,5a,6-octahydropyrrolo[3′,2′:3,4]pyrrolo[2,3-b]indole-2,5-dicarboxylate (**6a** Leu).* White solid, t_R (gradient 2)=6.23 min. Duplicated, broad signals in NMR resulted from *cis*/*trans* isomerisation of amide (urethane–Cbz) bond. ^{1}H NMR (700 MHz, $CDCl_3$) δ_H 7.40–6.57 (9H, m, Ar), 5.68 and 5.60 (1H, s, H-5a), 5.28 and 5.24 and 5.10 and 5.00 (2H, d, *J* 12.1 Hz, CH_2Cbz), 4.71 (br t, *J* 8 Hz, H-2), 4.61 (br t, *J* 7 Hz, H-4) and 4.53 (1H, dd, *J* 9.9 Hz, 4.9 Hz, H-4), 4.50 (1H, dd, *J* 11.2, 7.7 Hz, H-2), 4.28 and 4.24 (1H, s, H-3a), 3.80 and 3.74 (3H, s, OCH_3), 2.87 (dd, *J* 14.0, 8.0 Hz, H-1) and 2.73–2.67 (2H, m, H-1) and 2.58 (dd, *J* 14.2, 8.7 Hz, H-1), 1.43–1.39 and 1.52–1.46 (1H, m, H-5′), 1.30–1.21 (1H, m, H-4′), 0.92–0. 81 (1H, m, H-4′), 0.79 (d, *J* 6.3 Hz, H-6′) and 0.70 (d, *J* 6.3 Hz, H-6′) and 0.64 (3H, d, *J* 6.5 Hz, H-6′) and 0.57 (3H, d, *J* 6.5 Hz, H-6′); ^{13}C NMR (125 MHz, $CDCl_3$) δ_C 169.3 and 168.7, 154.8 and 154.1, 148.9 and 148.6, 137.6–109.8, 82.3 and 81.8, 72.0 and 71.3, 68.0 and 67.4, 64.1 and 63.5, 60.9 and 60.7, 59.3 and 59.2, 53.7 and 53.6, 43.4 and 42.5, 40.7 and 40.2, 25.2 and 23.2, 21.7 and 21.3. COSY (700 MHz, $CDCl_3$) H-1 (H-2), H-2 (H-1), H-4 (H-4′), H-4′ (H-4, H-5′), H-5′(H-4′, H-6′), H-6′ (H-5′). HSQC (700 MHz, $CDCl_3$) Ar (109.5–130), H-5a (81.47 and 81.9), H-3a (71.0 and 71.6), CH_2Cbz (67.6), H-4 (60.5), H-2 (59.0), OCH_3 (53.3), H-4′ (43.1 and 42.2), H-1 (40.4 and 39.8), H-5′ (24.9), H-6′ (22.8 and 21.4). ROESY (700 MHz, $CDCl_3$) H-1 (H-2, H-5a), H-2 (H-1. H-5a), H-3a (H-4′, H-5′), H-4 (H-4′, H-6′), H-4′(H-3a, H-4,), H-5′(3a, H-6′), H-6′(H-4′, H-5′), H-5a (H-1, H-2). LC-MS (ESI^+) *m/z*=450 $[M+H]^+$, 472 $[M+Na]^+$. Exact mass calcd for $C_{26}H_{32}N_3O_4$ $[M+H]^+$: 450.2393, found: 450.2400.

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Supplementary data

Data obtained for Cbz-D-Phe-H and Cbz-D-Leu-H are given as the Supplementary data. Supplementary data related to this article can be found online at doi:10.1016/j.tet.2011.01.018. These data include MOL files and InChIKeys of the most important compounds described in this article.

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