An Unusual Diastereoselective Pictet–Spengler Reaction: Synthesis of Novel Tetrahydro-β-Carboline Glycosides

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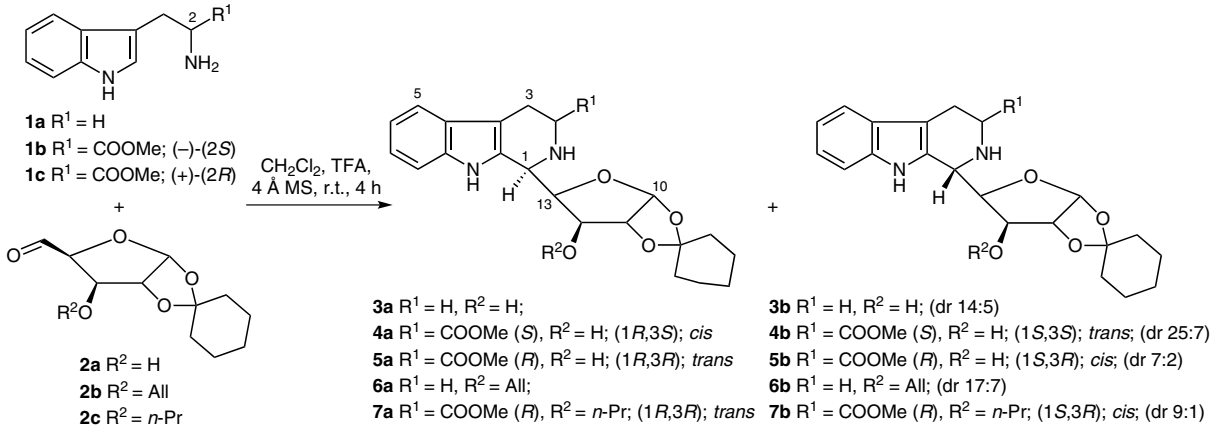
Abstract: An unusual kinetic approach to the Pictet–Spengler reaction was investigated, in which L- or D-tryptophan methyl ester reacted with aldehydes of 1,2-*O*-cyclohexylidene-3-allyloxy-α-D-xylofuranose, yielding exclusively the *cis* or *trans* diastereomer of tetrahydro-β-carboline glycoside, respectively, with complete stereocontrol.

Keywords: Pictet–Spengler reaction, stereoselectivity, diastereoselectivity, stereocontrol, glycosides, imines, π-stacking interactions

The Pictet–Spengler condensation[2] is one of the most widely used methods for preparing 1,2,3,4-tetrahydro-β-carbolines and tetrahydroisoquinolines. The reaction has been extensively used for the synthesis of isoquinoline and indole alkaloids[3] and has been studied both under acidic conditions,[4] including under microwave irradiation,[5] and without the aid of an acid or protic solvent.[6] The importance of this reaction has led organic chemists to focus on the development of stereoselective synthetic routes[7] that involve either chiral substrates or chiral reagents, including chiral catalysts.

Here, we report a new methodology in which complete stereocontrol of the Pictet–Spengler conditions results in the formation of 100% *cis* or *trans* diastereomeric tetrahydro-β-carboline glycosides from either L- or D-tryptophan methyl ester. The tetrahydro-β-carboline glycosides are important as intermediates in the synthesis of indolo[2,3-*a*]quinolizine alkaloids[8] and tetrahydro-β-carboline nucleosides,[9] which have the ability to bind with DNA or RNA, or as chiral precursors for the stereoselective synthesis of a range of indole alkaloids. The interesting and distinguishable *cis* and *trans* stereochemistry of the novel compounds were determined on the basis of ^{13}C NMR spectroscopic analysis, which supports well-documented compression effects.[10]

In our endeavor to synthesize important heterocyclic intermediates for the synthesis of indolo[2,3-*a*]quinolizine alkaloids,[11] tryptamine (**1a**), or L- or D-tryptophan methyl ester (**1b** and **1c**) was reacted with di(1,2-*O*-cyclohexylidene-α-D-xylopentodialdofuranose-5-hydrate)-5,5′:3′,5-dianhydride (**2a**)[12] (the dimeric form of 1,2-*O*-cyclohexylidene-3-hydroxy-α-D-xylofuranose-5-carbaldehyde) in dichloromethane with a catalytic amount of trifluoroacetic acid (TFA),[13] which resulted in the formation of β-carboline glycoside diastereomers **3a** and **3b** (dr 14:5), **4a** and **4b** (dr 25:7), or **5a** and **5b** (dr 7:2), quantitatively. The diastereomeric ratio was calculated on the basis of their isolated yield. When the same Pictet–Spengler reaction was conducted between **1a** and 1,2-*O*-cyclohexylidene-3-allyloxy-α-D-xylofuranose-5-carbaldehyde (**2b**), or between **1c** and 1,2-*O*-cyclohexylidene-3-propyloxy-α-D-xylofuranose-5-carbaldehyde (**2c**), the corresponding two



Scheme 1 The Pictet–Spengler reaction used to prepare *cis* and *trans* diastereomeric 1,2,3,4-tetrahydro-β-carboline glycosides

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diastereomers **6a** and **6b** (dr 17:7) or **7a** and **7b** (dr 9:1),[14] were obtained in quantitative yield (Scheme 1). Due to the presence of allyl group the diastereomeric **6a** shows some improved stereocontrol over **6b**.

The interesting stereochemical aspects of the above 1,3-disubstituted β-carboline glycosides were investigated by Cook and co-workers,[10] who analyzed the ^{13}C NMR spectral data and showed that C-1 and C-3 carbon signals appeared relatively downfield in all the *cis* isomers in comparison to the *trans* isomers. They reported that for the β-carboline derivatives obtained when L-tryptophan methyl ester reacted with benzaldehyde, the *cis* isomer exhibited signals for C-1 and C-3 at δ = 58.7 and 56.9 ppm, respectively, whereas the corresponding signals of the *trans* isomer appeared at δ = 54.9 and 52.3 ppm. Hence, the hydrogen atoms attached at C-1 and C-3 are on the same face for *cis* diastereoisomers whereas they are on opposite faces for the *trans* diastereoisomers. The chemical shifts of C-1 and C-3 carbon atoms of diastereoisomers **4a**, **5b** and **7b**, in our case, appeared at higher shifts in the ^{13}C NMR spectra, and were thus assigned as *cis* isomers, whereas those of the other diastereomers **4b**, **5a** and **7a** with lower δ values, were assigned as the *trans* isomers. The ^{13}C NMR chemical shift for C-1 and C-3 of all diastereoisomers are shown in Table 1. The spatial connectivity were revealed by NOE effects and NOESY correlations between 1-H and 3-H for the diastereoisomer **4a**, which confirmed its *cis* stereochemistry, whereas for **4b** there was no such connectivity found, which indicates its *trans* stereochemistry.

Unusually, 1,2-*O*-cyclohexylidene-3-allyloxy-α-D-xylofuranose-5-carbaldehyde derivatives **2b** and **2d**[15] react with **1b** under the same conditions to form only their respective *cis* diastereomer **8** and **10** (Scheme 2). Alternatively, they can react with **1c** to produce their respective *trans* diastereomers **9** and **11**, exclusively, with more than 98% isolated yield.

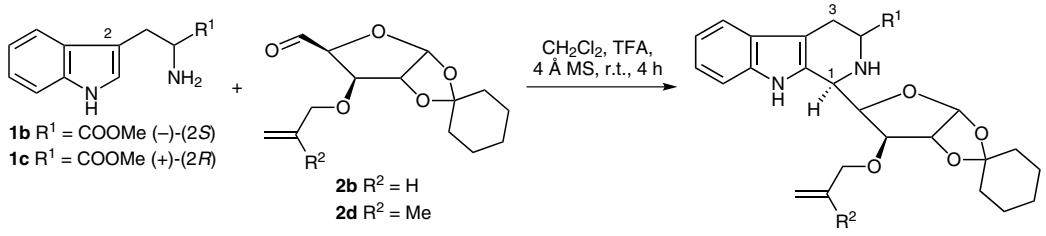
In the mechanism of Pictet–Spengler reaction, the product tetrahydro-β-carboline derivative is obtained through imine formation followed by nucleophilic attack from the 2-position of the indole ring, which is easy because of protonation of the imine in the acidic media. The reason for the observed stereoselectivity using allyl-substituted sugar aldehydes is not yet clear but it is possible that π-stacking interactions between the allyl and the imine intermediate allows cyclization by electrophilic attack on the 2-position of indole through a particular facial orientation. The involvement of a remote allyl group in the mechanism of the reaction that increases the diastereoselectivity of the process is a particularly unusual aspect of this methodology. For propyloxy aldehyde, which is a saturated form of the allyloxy aldehyde that lacks allylic π-electrons, the observed formation of two diastereoisomers supports the above conclusions.

Table 1 Chemical Shifts of C-1 and C-3 for Diastereoisomers

Diastereoisomer	^{13}C NMR (δ, ppm)		Stereochemistry
	C-1	C-3	
3a	52.95	42.91	
3b	52.70	41.91	
4a	56.27	52.80	*cis*
4b	52.97	51.02	*trans*
5a	53.87	49.80	*trans*
5b	56.52	52.78	*cis*
6a	52.97	41.71	
6b	51.64	43.62	
7a	53.87	48.39	*trans*
7b[a]	56.20	53.91	*cis*
8	56.53	52.36	*cis*
9	54.25	48.65	*trans*
10	57.95	52.33	*cis*
11	54.55	50.55	*trans*

[a] Determined from ^{13}C NMR spectroscopic analysis of the crude reaction mixture.

On reduction by Pd/C (H_2), diastereoisomer **9** gave only diastereomer **7a**, confirming that no interconversion between diastereoisomers took place. We also observed that all the major products have the same stereochemistry at C-1, which means that nucleophilic attack during the imine



8 R^1 = COOMe (*S*); R^2 = H; 100% *cis*
9 R^1 = COOMe (*R*); R^2 = H; 100% *trans*
10 R^1 = COOMe (*S*); R^2 = Me; 100% *cis*
11 R^1 = COOMe (*R*); R^2 = Me; 100% *trans*

Scheme 2 The unusual kinetic approach leading to stereoselectivity in the Pictet–Spengler reaction

stage favors a particular orientation. For isomers **8**–**11**, the presence of an allyl group and its participation in the π-stacking with the imine occur in that orientation. Molecular model studies of the probable energy-minimized imine intermediate[6a,16] suggest it may adopt the conformation shown in Figure 1, in which the double-headed arrow indicates possible π-stacking above the plane, and the attack (single-headed bent arrow) takes place from the below the plane.

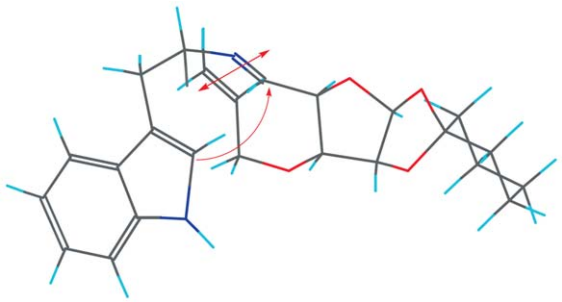


Figure 1 Possible π-stacking interaction (indicated by double-headed arrow) in the allyl imine intermediate and the favorable face of electrophilic attack on the 2-position of indole.

In summary, we have developed a straightforward and effective acid-catalyzed synthetic route to tetrahydro-β-carboline glycosides. This process is regioselective and also allows complete control over the stereochemistry at the C-1 and C-3 positions, depending on the substituents present on the 4′-position of the sugar moiety. We believe that π-stacking interactions direct the stereochemistry of the reaction and determines the conformation of the products. The high stereoselectivity exhibited by this methodology will be important for the preparation of a range of indole alkaloid intermediates. Further work on this methodology with other substrates and its application to a broader range of alkaloids towards new drug development is in progress.

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(13) **Preparation of Compounds 3–28; General Procedure:** To a stirred solution of free tryptamine (**1a**; 2 mmol) or L-tryptophan methyl ester (**1b**; 2 mmol) or D-tryptophan methyl ester (**1c**; 2 mmol), sugar aldehyde **2a**–**d** (2 mmol) and activated 4 Å molecular sieves (10 mg/mmol) in CH_2Cl_2 (20 mL), TFA (0.2 mL) was added. The reaction mixture was stirred at room temperature for 4–6 h and the progress was monitored by TLC ($CHCl_3$–MeOH, 9:1). Upon completion of the reaction, solvent was removed and the crude material was either directly used for column purification or diluted with H_2O, extracted with CH_2Cl_2 (3 × 25 mL), washed with very dilute aq HCl (10 mL), sat. $NaHCO_3$ (10 mL), H_2O (20 mL), and brine (20 mL) and dried over anhydrous Na_2SO_4 and the solvent was evaporated. The residue was purified by silica-gel column chromatography (petroleum ether–$CHCl_3$–MeOH).
10,11-*O*-Cyclohexylidene-12β-hydroxy-(1-tetrahydro-β-carbonlinyl)tetrahydrofuran (3a) and its conformer (3b): The residue was purified by chromatography over silica gel using $CHCl_3$ to afford **3a** (518 mg, 70%) and $CHCl_3$–MeOH (99:1) to afford **3b** (188.2 mg, 25%).
Compound 3a: mp 200–202 °C; $[\alpha]_D$ –54.0 (*c* 0.48, $CHCl_3$). IR (KBr): 3454, 3088, 1034, 735 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 8.50 (br s, 1 H, NH), 7.49 (d, *J* = 7.6 Hz, 1 H), 7.34 (d, *J* = 7.9 Hz, 1 H), 7.07–7.21 (m, 2 H), 6.08 (d, *J* = 3.6 Hz, 1 H), 4.53–4.60 (m, 2 H), 4.37–4.41 (m, 1 H), 4.26 (br s, 1 H), 3.33–3.38 (m, 1 H), 2.96–2.99 (m, 2 H), 2.77–2.85 (m, 2 H), 1.40–1.75 (m, 11 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 136.0, 131.6, 127.0, 121.8, 119.4, 118.1, 112.5, 111.0, 109.5, 104.9, 85.0, 81.5, 75.6, 52.9, 42.9, 36.4, 35.5, 24.8, 23.9, 23.5, 22.1. MS (ESI): *m*/*z* = 371 $[M + H]^+$. Anal. Calcd for $C_{21}H_{26}N_2O_4$: C, 68.09; H, 7.07; N, 7.56. Found: C, 67.81; H, 7.37; N, 7.91.
Compound 3b: mp 235–237 °C; $[\alpha]_D$ –19.7 (*c* 0.58, $CHCl_3$). IR (KBr): 3454, 2936, 1448, 1120, 1016, 734 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 8.20 (br s, 1 H, NH), 7.47 (d, *J* = 7.3 Hz, 1 H), 7.07–7.26 (m, 3 H), 5.98 (d, *J* = 3.5 Hz, 1 H), 4.49–4.54 (m, 2 H), 4.38 (d, *J* = 2.5 Hz, 2 H), 3.34–3.43 (m, 1 H), 3.00–3.10 (m, 1 H), 2.64–2.81 (m, 2 H), 1.41–1.74 (m,

11 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 136.3, 131.8, 127.7, 122.3, 119.8, 118.5, 112.7, 111.4, 110.6, 105.0, 85.5, 79.3, 77.8, 52.7, 41.9, 37.0, 35.9, 25.2, 24.3, 23.9, 22.3. MS (ESI): *m*/*z* = 371 $[M + H]^+$. Anal. Calcd for $C_{21}H_{26}N_2O_4$: C, 68.09; H, 7.07; N, 7.56. Found: C, 67.78; H, 7.27; N, 7.51.

10,11-*O*-Cyclohexylidene-12β-hydroxy(1-tetrahydro-3β-carbomethoxycarbolinyl)tetrahydrofuran (4a) and its isomer (4b): The residue was purified by chromatography over silica gel using $CHCl_3$–petroleum ether (95:5) to afford **4a** (643 mg, 75%) and the $CHCl_3$ eluent to afford **4b** (180 mg, 21%).

Compound 4a: mp 90–92 °C; $[\alpha]_D$ –50.90 (*c* 0.5, $CHCl_3$). IR (KBr): 3328, 2937, 1740, 1448, 1072, 753 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.43 (s, 1 H, NH), 7.52 (d, *J* = 7.7 Hz, 1 H), 7.39 (d, *J* = 7.9 Hz, 1 H), 7.22 (t, *J* = 7.9 Hz, 1 H), 7.14 (t, *J* = 7.5 Hz, 1 H), 6.13 (d, *J* = 3.4 Hz, 1 H), 4.67 (d, *J* = 6.4 Hz, 1 H), 4.58 (d, *J* = 3.4 Hz, 1 H), 4.39 (d, *J* = 3.4 Hz, 2 H), 3.85 (s, 3 H), 3.78 (t, *J* = 15.1 Hz, 1 H), 3.22 (dd, *J* = 15.3, 2.9 Hz, 1 H), 2.89 (t, *J* = 13.3 Hz, 1 H), 1.27–1.70 (m, 10 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 173.2, 136.7, 131.9, 127.1, 122.5, 120.0, 118.5, 113.1, 111.6, 108.7, 105.3, 85.3, 82.1, 75.7, 56.2, 53.0, 52.8, 36.8, 35.9, 25.7, 25.2, 24.2, 23.9. MS (ESI): *m*/*z* = 429 $[M + H]^+$. Anal. Calcd for $C_{23}H_{28}N_2O_6$: C, 64.47; H, 6.59; N, 6.54. Found: C, 64.51; H, 6.97; N, 6.71.

Compound 4b: mp 96–98 °C; $[\alpha]_D$ –16.90 (*c* 0.5, $CHCl_3$). IR (KBr): 3336, 2937, 1737, 1450, 1076, 754 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.56 (s, 1 H, NH), 7.45 (d, *J* = 7.62 Hz, 1 H), 7.28 (d, *J* = 7.8 Hz, 1 H), 7.15 (t, *J* = 7.1 Hz, 1 H), 7.07 (t, *J* = 7.45 Hz, 1 H), 5.97 (d, *J* = 3.6 Hz, 1 H), 4.59–4.64 (m, 1 H), 4.53 (d, *J* = 3.6 Hz, 1 H), 4.34 (t, *J* = 2.7 Hz, 1 H), 4.28 (t, *J* = 2.7 Hz, 1 H), 4.16–4.23 (m, 1 H), 3.76 (s, 3 H), 3.13–3.20 (m, 3 H), 2.78–2.81 (m, 1 H), 1.25–1.64 (m, 10 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 173.9, 136.5, 130.5, 127.1, 122.6, 119.9, 118.4, 112.8, 111.5, 109.1, 104.7, 85.5, 80.4, 76.9, 52.9, 52.6, 51.0, 36.8, 35.9, 25.4, 25.2, 24.2, 23.9. MS (ESI): *m*/*z* = 429 $[M + H]^+$. Anal. Calcd for $C_{23}H_{28}N_2O_6$: C, 64.47; H, 6.59; N, 6.54. Found: C, 64.31; H, 7.87; N, 7.01.

10,11-*O*-Cyclohexylidene-12β-hydroxy(1-tetrahydro-3α-carbomethoxy-β-carboli-nyl)tetrahydrofuran (5a) and its isomer (5b): The residue obtained was purified by chromatography over silica gel using $CHCl_3$–petroleum-ether (90:10) eluent to afford **5a** (630 mg, 73.5%) and $CHCl_3$ eluent to afford **5b** (180 mg, 21%).

Compound 5a: mp 142–144 °C; $[\alpha]_D$ –44.13 (*c* 0.5, $CHCl_3$). IR (KBr): 3447, 2934, 1712, 1448, 1022, 739 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.67 (s, 1 H, NH), 7.53 (d, *J* = 7.4 Hz, 1 H), 7.35 (d, *J* = 7.9 Hz, 1 H), 7.19 (t, *J* = 8.8 Hz, 1 H), 7.13 (t, *J* = 7.6 Hz, 1 H), 6.12 (d, *J* = 3.3 Hz, 1 H), 4.86 (d, *J* = 6.6 Hz, 1 H), 4.56 (d, *J* = 3.3 Hz, 1 H), 4.42 (t, *J* = 4.5 Hz, 1 H), 4.32 (d, *J* = 1.6 Hz, 1 H), 4.01 (t, *J* = 4.8 Hz, 1 H), 3.70 (s, 3 H), 3.12–3.24 (m, 2 H), 1.40–1.71 (m, 10 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 174.2, 136.6, 131.7, 127.1, 122.4, 119.8, 118.5, 113.0, 111.5, 107.5, 105.3, 85.3, 82.1, 75.7, 53.8, 52.7, 49.8, 36.7, 35.9, 25.2, 24.5, 24.3, 23.9. MS (ESI): *m*/*z* = 429 $[M + H]^+$. Anal. Calcd for $C_{23}H_{28}N_2O_6$: C, 64.47; H, 6.59; N, 6.54. Found: C, 64.44; H, 7.17; N, 6.82.

Compound 5b: mp 120–122 °C; $[\alpha]_D$ –10.54 (*c* 0.2, $CHCl_3$). IR (KBr): 2931, 1728, 1451, 1015, 744 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.33 (s, 1 H, NH), 7.48 (d, *J* = 7.2 Hz, 1 H), 7.37 (d, *J* = 8.1 Hz, 1 H), 7.20 (t, *J* = 8.2 Hz, 1 H), 7.14 (t, *J* = 8.2 Hz, 1 H), 6.05 (s, 1 H), 4.71 (s, 1 H), 4.55–4.66 (m, 2 H), 4.53 (s, 1 H), 3.84 (s, 3 H), 3.64 (dd, *J* = 11.2, 2.9 Hz, 1 H), 2.99 (t, *J* = 12.6 Hz, 1 H), 2.93 (t, *J* = 11.4 Hz, 1 H), 1.45–1.85 (m, 10 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 173.0, 136.6, 131.6, 127.3, 122.7, 120.2, 118.4, 112.9, 111.6, 109.2, 105.1, 85.2, 80.0, 76.9, 56.5, 53.3, 52.7, 37.0, 35.9, 25.8, 25.2, 24.3, 23.9. MS (ESI): *m*/*z* = 429 $[M + H]^+$. Anal. Calcd for $C_{23}H_{28}N_2O_6$: C, 64.47; H, 6.59; N, 6.54. Found: C, 64.31; H, 7.07; N, 6.61.

10,11-*O*-Cyclohexylidene-12β-allyloxy(1-tetrahydro-β-carbolinyl)tetrahydrofuran (6a) and its isomer (6b): The residue was purified by chromatography over silica gel using $CHCl_3$ to afford **6a** (558 mg, 68%) and $CHCl_3$–MeOH (99:1) eluent to afford **6b** (229.8 mg, 28%).

Compound 6a: mp 56–58 °C; $[\alpha]_D$ –107.72 (*c* 0.1, $CHCl_3$). IR (KBr): 3449, 2935, 1449, 1163, 1022, 741 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.75 (s, 1 H, NH), 7.53 (d, *J* = 7.4 Hz, 1 H), 7.39 (d, *J* = 7.8 Hz, 1 H), 7.18 (t, *J* = 7.1 Hz, 1 H), 7.14 (t, *J* = 6.3 Hz, 1 H), 6.11 (d, *J* = 3.6 Hz, 1 H), 5.96 (m, 1 H), 5.20–5.36 (m, 2 H), 4.70–4.72 (d, *J* = 3.6 Hz, 1 H), 4.32–4.37 (m, 2 H), 4.06–4.18 (m, 3 H), 3.12–3.26 (m, 2 H), 2.71–2.84 (m, 2 H), 2.62 (br s, 1 H, NH), 1.25–1.75 (m, 10 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 136.2, 133.2, 134.4, 127.0, 122.0, 119.3, 118.4, 117.9, 113.6, 111.5, 109.2, 106.3, 88.0, 84.4, 84.3, 71.9, 52.9, 41.7, 36.6, 35.3, 25.2, 24.2, 23.8, 22.7. MS (ESI): *m*/*z* = 433 $[M + Na]^+$. Anal. Calcd for $C_{24}H_{30}N_2O_4$: C, 70.22; H, 7.37; N, 6.82. Found: C, 70.12; H, 7.27; N, 6.92.

Compound 6b: mp 58–60 °C; $[\alpha]_D$ –111.28 (*c* 0.1, $CHCl_3$). IR (KBr): 3443, 2935, 1449, 1113, 1018, 744 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.78 (s, 1 H, NH), 7.53 (d, *J* = 7.4 Hz, 1 H), 7.34 (d, *J* = 7.7 Hz, 1 H), 7.12 (t, *J* = 7.0 Hz, 1 H), 6.17 (t, *J* = 6.8 Hz, 1 H), 5.96–6.03 (m, 2 H), 5.12–5.42 (m, 3 H), 4.63 (d, *J* = 3.7 Hz, 1 H), 4.15–4.39 (m, 4 H), 2.50–3.42 (m, 5 H including NH), 1.25–1.85 (m, 10 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 136.1, 134.4, 134.1, 127.4, 119.4, 118.6, 118.3, 113.2, 112.8, 111.5, 109.0, 105.3, 83.8, 82.1, 81.7, 71.3, 51.6, 43.6, 36.7, 36.3, 25.2, 24.2, 24.0, 22.6. MS (ESI): *m*/*z* = 433 $[M + Na]^+$. Anal. Calcd for $C_{24}H_{30}N_2O_4$: C, 70.22; H, 7.37; N, 6.82. Found: C, 69.72; H, 7.47; N, 7.02.

10,11-*O*-Cyclohexylidene-12β-propyloxy(1-tetrahydro-3α-carbomethoxy-β-carbolinyl)tetrahydrofuran (7a) and its isomer (7b): The residue was purified by chromatography over silica gel using $CHCl_3$–petroleum-ether (90:10) eluent to afford **7a** (757.5 mg, 80.5%) first and then **7b** (108.2 mg, 11.5%).

Compound 7a: mp 170–174 °C; $[\alpha]_D$ –175.04 (*c* 0.1, CHCl3). IR (neat): 3449, 2936, 1737, 1451, 1115, 746 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.60 (s, 1 H, NH), 7.52 (d, *J* = 7.7 Hz, 1 H), 7.36 (d, *J* = 7.8 Hz, 1 H), 7.19 (t, *J* = 7.8 Hz, 1 H), 7.12 (t, *J* = 7.5 Hz, 1 H), 6.08 (d, *J* = 3.4 Hz, 1 H), 4.66 (m, 2 H), 4.27 (m, 1 H), 4.11 (m, 1 H), 4.03 (m, 1 H), 3.72 (m, 4 H), 3.59 (m, 1 H), 3.18 (m, 2 H), 1.24–1.77 (m, 12 H), 1.06–1.02 (m, 3 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 173.8, 135.9, 133.0, 126.6, 121.5, 118.9, 117.9, 112.6, 111.0, 106.5, 105.0, 83.4, 82.4, 81.2, 72.0, 53.8, 52.0, 48.3, 36.3, 35.8, 24.7, 24.0, 23.7, 23.5, 23.0, 10.5. MS (ESI): *m*/*z* = 493 $[M + Na]^+$. Anal. Calcd for $C_{26}H_{34}N_2O_6$: C, 66.36; H, 7.28; N, 5.95. Found: C, 66.46; H, 7.37; N, 6.08.

Compound 7b: ^{13}C NMR (75 MHz, $CDCl_3$; obtained from a mixture with **7a**): δ = 173.1, 136.1, 132.2, 127.1, 121.7, 119.4, 117.7, 112.5, 110.8, 109.0, 104.2, 83.6, 83.1, 81.4, 72.4, 56.2, 53.9, 52.5, 36.5, 35.7, 25.2, 24.2, 23.9, 23.4, 23.1, 10.5.

10,11-*O*-Cyclohexylidene-12β-allyloxy(1-tetrahydro-3β-carbomethoxy-β-carboli-nyl)tetrahydrofuran (8) and 10,11-O-Cyclohexylidene-12β-allyloxy(1-tetrahydro-3α-carbomethoxy-β-carbolinyl)tetrahydrofuran (9): The residue obtained was purified by chromatography over silica gel using $CHCl_3$–petroleum-ether (90:10) eluent to afford **8** (915 mg, 97.5%) or **9** (919 mg, 98%), respectively.

Compound 8: mp 62–64 °C; $[\alpha]_D$ –142.36 (*c* 0.1, $CHCl_3$).

IR (KBr): 3448, 2935, 1738, 1448, 1165, 1023, 742 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 8.80 (s, 1 H, NH), 7.55 (d, *J* = 7.51 Hz, 1 H), 7.41 (d, *J* = 7.82 Hz, 1 H), 7.20 (t, *J* = 14.1 Hz, 1 H), 7.14 (t, *J* = 14.2 Hz, 1 H), 6.13–6.15 (m, 2 H), 5.36–5.48 (m, 2 H), 4.69 (d, *J* = 3.66 Hz, 1 H), 4.52 (d, *J* = 8.61 Hz, 2 H), 4.35 (dd, *J* = 5.22, 13.13 Hz, 2 H), 4.25 (d, *J* = 2.90 Hz, 1 H), 4.13 (dd, *J* = 12.6, 6.5 Hz, 1 H), 3.87 (s, 3 H), 3.25 (dd, *J* = 14.9, 2.9 Hz, 1 H), 2.95 (t, *J* = 15.8 Hz, 1 H), 2.60 (br s, 1 H, NH), 1.32–1.73 (m, 10 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 173.5, 136.5, 134.3, 133.8, 127.1, 122.0, 119.6, 119.4, 118.3, 113.3, 111.6, 107.9, 105.5, 83.9, 81.9, 81.7, 71.3, 56.5, 52.5, 52.3, 36.8, 36.4, 25.5, 25.2, 24.2, 24.0. MS (ESI): *m*/*z* = 491 $[M + Na]^+$. Anal. Calcd for $C_{26}H_{32}N_2O_6$: C, 66.65; H, 6.88; N, 5.98. Found: C, 66.72; H, 7.07; N, 5.91.

Compound 9: mp 60–62 °C; $[\alpha]_D$ –147.16 (*c* 0.1, $CHCl_3$). IR (KBr): 3446, 2934, 1736, 1451, 1164, 1021, 746 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 8.60 (s, 1 H, NH), 7.53 (d, *J* = 7.30 Hz, 1 H), 7.37 (d, *J* = 7.72 Hz, 1 H), 7.18 (t, *J* = 7.40 Hz, 1 H), 7.11 (t, *J* = 7.34 Hz, 1 H), 6.01–6.09 (m, 2 H), 5.46 (d, *J* = 17.20 Hz, 1 H), 5.32 (d, *J* = 10.46 Hz, 1 H), 4.67 (t, *J* = 19.8 Hz, 2 H), 4.25–4.36 (m, 2 H), 4.08–4.17 (m, 2 H), 4.01 (s, 1 H), 3.73 (s, 3 H), 3.17 (d, *J* = 3.61 Hz, 2 H), 2.56 (br s, 1 H, NH), 1.29–1.60 (m, 10 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 174.3, 136.4, 134.1, 133.6, 127.1, 122.0, 119.4, 118.6, 118.3, 113.1, 111.5, 107.1, 105.4, 83.8, 82.1, 81.7, 71.4, 54.2, 52.4, 48.6, 36.7, 36.2, 25.2, 24.6, 24.2, 24.0. MS (ESI): *m*/*z* = 491 $[M + Na]^+$. Anal. Calcd for $C_{26}H_{32}N_2O_6$: C, 66.65; H, 6.88; N, 5.98. Found: C, 65.92; H, 7.27; N, 6.01.

4,5-*O*-cyclohexyl-3-(2-methylallyloxy)tetrahydrofuran-2-carbaldehyde (2c): Colorless syrup; $[\alpha]_D^{18.9}$ –54.614 (*c* 1 mM, $CHCl_3$). IR (neat): 1737, 1672, 1168, 1022, 738 cm^{-1}. ^1H NMR (600 MHz, $CDCl_3$): δ = 9.62 (d, *J* = 2.1 Hz, 1 H), 6.07 (d, *J* = 3.42 Hz, 1 H), 4.86 (d, *J* = 8.94 Hz, 2 H), 4.55 (d, *J* = 3.42 Hz, 1 H), 4.49 (d, *J* = 3.42 Hz, 1 H), 4.22 (d, *J* = 4.14 Hz, 1 H), 3.91 (d, *J* = 12.36 Hz, 1 H), 3.79 (d, *J* = 12.42 Hz, 1 H), 1.61 (s, 3 H), 1.40–1.60 (m, 10 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 200.2, 140.8, 113.5, 113.3, 105.9, 84.6, 84.0, 81.7, 72.0, 36.7, 35.9, 24.8, 23.8, 23.6, 19.3. MS (ESI): *m*/*z* = 305 $[M + Na]^+$. Anal. Calcd for $C_{15}H_{22}O_5$: C, 63.81; H, 7.85. Found: C, 63.77; H, 7.91.

10,11-*O*-Cyclohexylidene-12β-(2-methylallyloxy)-(1-tetrahydro-3β-carbomethoxy-β-carboli-nyl)tetrahydrofuran (10) and 10,11-*O*-Cyclohexylidene-12β-(2-methylallyloxy)-(1-tetrahydro-3α-carbomethoxy-β-carbolinyl)-tetrahydrofuran (10): The residue obtained was purified by chromatography over silica gel using $CHCl_3$–MeOH (99:1) eluent to afford **10** (950 mg, 98.4%) or **11** (948 mg, 98.2%), respectively.

Compound 10: mp 174–176 °C; $[\alpha]_D^{20.5}$ –41.29 (*c* 1 mM, $CHCl_3$). IR (KBr): 3452, 2933, 1739, 1448, 1165, 1025, 741 cm^{-1}. ^1H NMR (600 MHz, $CDCl_3$): δ = 8.75 (br s, 1 H, NH), 7.21–7.45 (m, 2 H), 7.05 (t, *J* = 9.8 Hz, 1 H), 6.97 (t, *J* = 9.6 Hz, 1 H), 5.82 (s, 1 H), 4.85–5.25 (m, 2 H), 4.67 (s, 2 H), 4.25–4.55 (m, 3 H), 3.80–4.15 (m, 2 H), 3.70 (m, 1 H), 3.55 (s, 3 H), 3.23 (m, 1 H), 2.84 (br s, 1 H), 1.10–1.70 (m, 13 H). ^{13}C NMR (600 MHz, $CDCl_3$): δ = 172.5, 140.2, 137.0, 136.9, 125.9, 122.3, 119.4, 117.9, 114.1, 113.3, 111.9, 107.1, 104.6, 83.2, 81.1, 80.9, 74.2, 57.9, 56.7, 52.3, 36.1, 35.7, 24.7, 23.6, 23.5, 23.4, 19.3. MS (ESI): *m*/*z* = 506 $[M + Na]^+$. Anal. Calcd for $C_{27}H_{34}N_2O_6$: C, 67.20; H, 7.10; N, 5.81. Found: C, 67.31; H, 7.11; N, 5.79.

Compound 11: mp 166–168 °C; $[\alpha]_D^{19.5}$ –37.35 (*c* 1 mM, $CHCl_3$). IR (KBr): 3445, 2932, 1739, 1450, 1167, 1021, 747 cm^{-1}. ^1H NMR (600 MHz, $CDCl_3$): δ = 8.73 (br s, 1 H, NH), 7.40 (t, *J* = 8.94 Hz, 1 H), 7.20 (t, *J* = 4.8 Hz, 1 H), 7.09 (t, *J* = 7.56 Hz, 1 H), 7.02 (dd, *J* = 7.56 Hz, 1 H), 5.81 (s, 1 H), 4.80–5.10 (m, 2 H), 4.45–4.65 (m, 3 H), 4.00–4.20 (m, 2 H), 3.75–3.90 (m, 2 H), 3.45 (s, 3 H), 3.10 (s, 2 H), 2.98 (s, 1 H, NH), 1.63 (s, 3 H), 1.10–1.60 (m, 10 H). ^{13}C NMR (600 MHz, $CDCl_3$): δ = 172.1, 141.0, 136.9, 136.4, 126.1, 122.5, 119.7, 118.4, 113.5, 113.2, 111.6, 104.7, 104.4, 83.4, 81.3, 81.1, 73.8, 54.5, 53.0, 50.5, 36.2, 35.8, 24.7, 23.8, 23.6 (2), 19.7. MS (ESI): *m*/*z* = 506 $[M + Na]^+$. Anal. Calcd for $C_{27}H_{34}N_2O_6$: C, 67.20; H, 7.10; N, 5.81. Found: C, 67.21; H, 7.13; N, 5.75

(14) It was not possible to isolate the minor diastereoisomer, which was formed as an inseparable mixture with the major diastereoisomer. Hence, the diastereomeric ratio (dr) was determined from LCMS retention time and peak area of the diastereoisomers in crude reaction mixture

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