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-cyclohexyldiene-3-allyloxy-α-D-xylofuranose, yielding exclusively the cis or trans diastereomer of tetrahydro-β-carbol ine 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 tetrahydroisquinolines. 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-carbol ine 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 13C-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-cyclohexyldiene-α-D-xylopentodialdofuranose-5-hydrate)-5,5′,3′,5′-dianhydride (2a) 12 (the dimeric form of 1,2-O-cyclohexyldiene-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-carbol ine 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-cyclohexyldiene-3-allyloxy-α-D-xylofuranose-5-carbaldehyde (2b), or between 1c and 1,2-O-cyclohexyldiene-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-carbol ine glycosides

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The interesting stereochemical aspects of the above 1,3-disubstituted β-carboline glycosides were investigated by Cook and co-workers, who analyzed the 13C 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 13C NMR spectra, and were thus assigned as cis isomers, whereas those of the other diastereoisomers 4b, 5a and 7a with lower δ values, were assigned as the trans isomers. The 13C NMR chemical shift for C-1 and C-3 of all diastereomers is 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-cyclohexylidine-3-allyloxy-α-D-xylofuranose-5-carbaldehyde derivatives 2b and 2d 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 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-stack-}

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

<table>
<thead>
<tr>
<th>Diastereoisomer</th>
<th>13C NMR (δ, ppm)</th>
<th>Stereochemistry</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>C-1</td>
<td>C-3</td>
</tr>
<tr>
<td>3a</td>
<td>52.95</td>
<td>42.91</td>
</tr>
<tr>
<td>3b</td>
<td>52.70</td>
<td>41.91</td>
</tr>
<tr>
<td>4a</td>
<td>56.27</td>
<td>52.80 cis</td>
</tr>
<tr>
<td>4b</td>
<td>52.97</td>
<td>51.02 trans</td>
</tr>
<tr>
<td>5a</td>
<td>53.87</td>
<td>49.80 trans</td>
</tr>
<tr>
<td>5b</td>
<td>56.52</td>
<td>52.78 cis</td>
</tr>
<tr>
<td>6a</td>
<td>52.97</td>
<td>41.71</td>
</tr>
<tr>
<td>6b</td>
<td>51.64</td>
<td>43.62</td>
</tr>
<tr>
<td>7a</td>
<td>53.87</td>
<td>48.39 trans</td>
</tr>
<tr>
<td>7b</td>
<td>56.20</td>
<td>53.91 cis</td>
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<tr>
<td>8</td>
<td>56.53</td>
<td>52.36 cis</td>
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<tr>
<td>9</td>
<td>54.25</td>
<td>48.65 trans</td>
</tr>
<tr>
<td>10</td>
<td>57.95</td>
<td>52.33 cis</td>
</tr>
<tr>
<td>11</td>
<td>54.55</td>
<td>50.55 trans</td>
</tr>
</tbody>
</table>

* Determined from 13C NMR spectroscopic analysis of the crude reaction mixture.

On reduction by Pd/C (H2), 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 reduction by Pd/C (H2), 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
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 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](image_url) 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.

Acknowledgment

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References and Notes

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(3) 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 CH2Cl2 (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 (CHCl3–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 H2O, extracted with CH2Cl2 (3–25 mL), washed with very dilute aq HCl (10 mL), sat. NaHCO3 (10 mL), H2O (20 mL), and brine (20 mL) and dried over anhydrous Na2SO4 and the solvent was evaporated. The residue was purified by silica-gel column chromatography (petroleum ether–CHCl3–MeOH, 10,11-O-Cyclohexyldiene-12β-hydroxy-(1-tetrahydro-β-carbolinyl)tetrhydrofuran (3a) and its conformer (3b): The residue was purified by column chromatography over silica gel using CHCl3 to afford 3a (518 mg, 70%) and CHCl3–MeOH (99:1) to afford 3b (182.2 mg, 25%).

 Compound 3a: mp 200–202 °C; [α]D0 = 54.0 (c 0.48, CHCl3). IR (KBr): 3454, 3088, 1034, 735 cm⁻¹. 1H NMR (300 MHz, CDCl3): 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, 21 H). 13C NMR (75 MHz, CDCl3): δ = 136.0, 131.6, 127.0, 121.8, 119.4, 118.1, 112.5, 111.0, 109.4, 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. Caled for C21H26N2O4: C, 68.09; H, 7.07; N, 7.56. Found: C, 68.11; H, 7.37; N, 7.91.

 Compound 3b: mp 225–237 °C; [α]D0 = 19.7 (c 0.58, CHCl3). IR (KBr): 3454, 2926, 1448, 1120, 1016, 734 cm⁻¹. 1H NMR (300 MHz, CDCl3): 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), 3.34–3.33 (m, 1 H), 3.00–3.10 (m, 1 H), 2.64–2.81 (m, 2 H), 1.41–1.74 (m, 20 H), 1.30–1.00 (m, 12 H), 0.83–0.90 (m, 18 H). Anal. Caled for C42H54N2O4: C, 78.56; H, 7.54. Found: C, 78.61; H, 7.37; N, 7.91.

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1H, 13C NMR (75 MHz, CDCl3): δ = 136.3, 131.8, 127.7, 122.3, 119.8, 118.5, 112.7, 111.4, 106.0, 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 C23H28N2O6: C, 67.78; H, 7.27; N, 7.51.

10.11-O-Cyclohexylenidene-12β-hydroxy(1-tetrahydro-3β-carbomethoxy-β-carboline)tetrahydrofuran (4a) and its isomer (4b): The residue was purified by chromatography over silica gel using CHCl3–petroleum ether (90:10) eluent to afford 4a (558 mg, 68%) and CHCl3–MeOH (99:1) eluent to afford 4b (229 mg, 28%).

Compound 4a: mp 56–58 °C; [α]D = 107.2 (c 0.1, CHCl3). IR (KBr): 3443, 2935, 1449, 1113, 1018, 744 cm–1. 1H NMR (300 MHz, CDCl3): δ = 8.67 (s, 1 H, NH), 7.53 (d, J = 7.7 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). 13C NMR (75 MHz, CDCl3): δ = 136.1, 134.4, 134.1, 127.4, 119.4, 118.6, 118.3, 112.2, 112.8, 111.5, 109.0, 103.5, 83.8, 82.1, 81.7, 81.3, 56.3, 56.3, 56.2, 56.2, 55.3, 25.2, 24.2, 23.8, 22.7. MS (ESI): m/z = 433 [M + Na]+. Anal. Calcd for C26H34N2O6: C, 69.72; H, 7.47; N, 7.02.

10.11-O-Cyclohexylenidene-12β-propoxyxymethyl(1-tetrahydro-3α-carbomethoxy-β-carboline)tetrahydrofuran (7a) and its isomer (7b): The residue was purified by chromatography over silica gel using CHCl3–petroleum ether (90:10) eluent to afford 7a (757.5 mg, 80.5%) first and then 7b (105 mg, 11.5%).

Compound 7a: mp 170–174 °C; [α]D = −175.04 (c 0.1, CHCl3). IR (neat): 3449, 2936, 1737, 1451, 1115, 714 cm–1. 1H NMR (300 MHz, CDCl3): δ = 8.61 (s, 1 H, NH), 7.53 (d, J = 7.7 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). 13C NMR (75 MHz, CDCl3): δ = 136.1, 134.4, 134.1, 127.4, 119.4, 118.6, 118.3, 112.2, 112.8, 111.5, 109.0, 103.5, 83.8, 82.1, 81.7, 81.3, 56.3, 56.3, 56.2, 56.2, 55.3, 25.2, 24.2, 23.8, 22.7. MS (ESI): m/z = 433 [M + Na]+. Anal. Calcd for C26H34N2O6: C, 66.36; H, 7.28; N, 5.95. Found: C, 66.46; H, 7.37; N, 6.08.

Compound 7b: 13C NMR (75 MHz, CDCl3; obtained from a mixture with 7a): 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, 82.1, 81.2, 72.0, 53.8, 50.2, 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 C26H34N2O6: C, 66.36; H, 7.28; N, 5.95. Found: C, 66.46; H, 7.37; N, 6.08.

10.11-O-Cyclohexylenidene-12β-benzyl(1-tetrahydro-3β-carbomethoxy-β-carboline)tetrahydrofuran (9): The residue obtained was purified by chromatography over silica gel using CHCl3–petroleum ether (90:10) eluent to afford 9 (915 mg, 97.5%) or 9 (919 mg, 98%), respectively.

Compound 8: mp 62–64 °C; [α]D = −142.36 (c 0.1, CHCl3).
LETTER

Synthesis of Tetrahydro-β-Carboline Glycosides

1H NMR (300 MHz, CDCl3): 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). 13C NMR (75 MHz, CDCl3): 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 (EI): m/z = 941 [M + Na]+. Anal. Calcd for C26H31NO5: C, 67.20; H, 7.10; N, 5.91.

Compound 9: mp 60–62 °C; [α]D = –147.16 (c 0.1, CHCl3).

IR (KBr): 3452, 2933, 1739, 1448, 1167, 1025, 746 cm−1. 1H NMR (300 MHz, CDCl3): 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). 13C NMR (75 MHz, CDCl3): δ = 174.3, 136.4, 134.1, 133.6, 127.1, 122.0, 119.4, 118.6, 113.8, 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 (EI): m/z = 941 [M + Na]+. Anal. Calcd for C26H31NO5: C, 67.20; H, 7.10; N, 5.91.

Compound 10: mp 174–176 °C; [α]D = 41.29 (c 1 mM, CHCl3).

IR (KBr): 3445, 2932, 1739, 1448, 1165, 1025, 741 cm−1. 1H NMR (600 MHz, CDCl3), 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 (t, 2 H), 4.25–4.35 (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). 1C NMR (600 MHz, CDCl3): δ = 172.5, 140.2, 137.0, 136.9, 125.9, 123.9, 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 (EI): m/z = 506 [M + Na]+. Anal. Calcd for C32H35NO5: 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; [α]D = –37.35 (c 1 mM, CHCl3).

IR (KBr): 3445, 2932, 1739, 1450, 1167, 1021, 747 cm−1. 1H NMR (600 MHz, CDCl3), 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). 13C NMR (600 MHz, CDCl3): 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 (EI): m/z = 506 [M + Na]+. Anal. Calcd for C32H35NO5: C, 67.20; H, 7.10; N, 5.81. Found: C, 67.21; H, 7.13; N, 5.75.

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

