

0957-4166(95)00380-0

Pictet-Spengler Reaction of Biogenic Amines with (2*R*)-*N*-Glyoxyloylbornane-10,2-sultam. Enantioselective Synthesis of (*S*)-(+)-*N*-Methylcalycotomine

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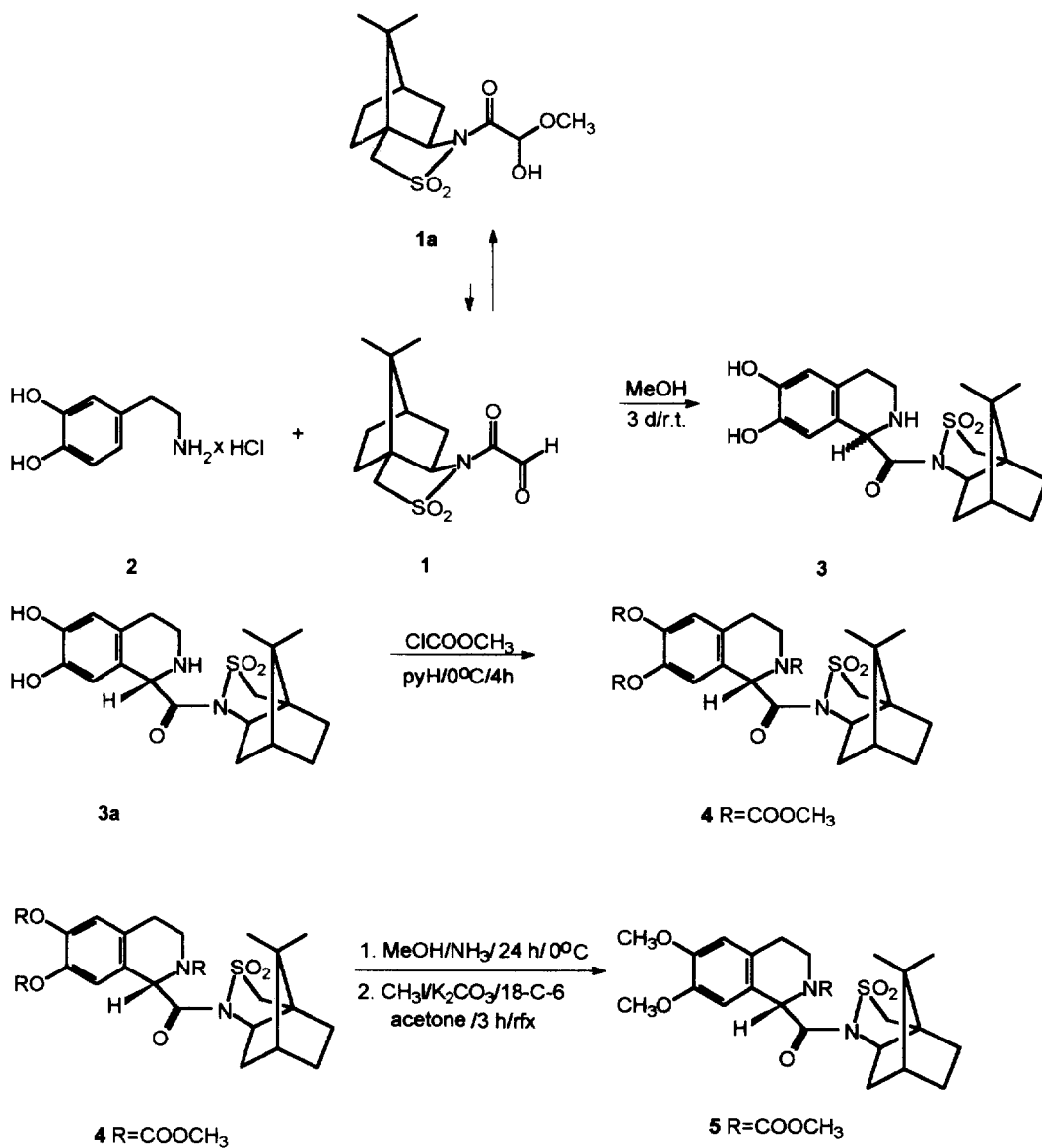
Abstract : (2*R*)-*N*-Glyoxyloylbornane-10,2-sultam reacted with dopamine hydrochloride, forming the Pictet-Spengler condensation product, which was further converted into (*S*)-(+)-*N*-methylcalycotomine of high enantiomeric purity. The same kind of reaction with tryptamine hydrochloride gave the condensation product with 100% d.e.

The Pictet-Spengler reaction has proven to be a tool of importance in the synthesis of isoquinolines and related heterocyclic systems^{1,3}. In the past years, the method has also been extended to an enantioselective and diastereoselective preparation of this type of compounds, using carbohydrates⁴, (*R*)- and (*S*)-glyceraldehyde⁵ or (-)-8-phenylmenthyl carbamates⁶ as sources of chirality. In some cases the method was the crucial part of a synthetic sequence that led to natural products of high enantiomeric purity⁵. Diastereoselectivity of the key step was, however, rarely exceeding 85% d.e.

In a search for still more effective chiral auxiliaries for the Pictet-Spengler condensation, we turned our attention to a *N*-glyoxyloyl derivative **1**⁶ of bornane-10,2-sultam⁷, which as a stable hemiacetal **1a** was widely employed in a variety of stereocontrolled *Diels-Alder* type reactions⁶.

Thus, treatment of **1a** with dopamine hydrochloride **2** at room temperature in methanol for 3 days caused the complete conversion of the substrates and formation of a condensation product **3**. Analysis of ¹H NMR spectrum at 500 MHz showed that **3** consisted of two diastereomers in the ratio 89:11. This value was further confirmed by HPLC analysis of the peracetyl derivative of **3**. The major diastereomer, **3a**⁸, was isolated in 57% chemical yield by column chromatography but appeared to be quite unstable and sensitive to air oxidation and the temperature above 25°C. We therefore converted **3a** into a stable amide-ester **4**⁹ which upon mild ammonolysis and di-*O*-methylation, afforded compound **5**¹⁰ in 87% overall chemical yield. Subsequent treatment with lithium-aluminum hydride (THF, reflux, 3h) brought about the reduction of the carbamate group along with the reductive cleavage of the CO-sultam bond. As the result, (*S*)-(+)-*N*-methylcalycotomine **6**¹¹ of

known absolute configuration¹² was isolated in 91% yield. The enantiomeric composition of **6** was additionally confirmed by ¹H-NMR experiment with 0.1 eq of Eu(hfc)₃. The integration of differentiated aromatic signals gave the ratio 96:4, which corresponds to 92% e.e. During a work up of the reaction mixture we were also able to recover the sultam in 96% yield, without any loss of the enantiomeric purity.



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8. Compound **3a** was isolated as a brown amorphous solid. $^1\text{H-NMR}$ (CDCl_3 , 500 MHz) δ : 6.91 (1H, s), 6.83 (1H, s), 4.82 (1H, br. t, $J=10.9$ Hz), 4.06 (1H, br. t, $J=5.4$ Hz), 4.00 - 3.83 (2H, m), 3.51 - 3.40 (2H, m), 2.98 - 2.92 (2H, dt, $J_1=17.5$ Hz, $J_2=5.4$ Hz), 1.91 - 1.75 (5H, m), 1.51 - 1.45 (1H, m), 1.31 - 1.25 (1H, m), 1.16 (3H, s), 1.00 (3H, s).
9. Compound **4** was isolated as a colourless foam, $[\alpha]_D^{23}$ -1.2 (c 1.11, CHCl_3), $^1\text{H-NMR}$ (CDCl_3 , 500 MHz) δ : 7.13 (1H, s), 7.10 (1H, s), 6.14 (1H, s), 4.23 - 4.16 (1H, m), 3.91 - 3.86 (2H, m), 3.87 and 3.89 (two s, 3H each), 3.73 (3H, s), 3.57 - 3.43 (2H, ABq, $J=10.1$ Hz), 3.24 - 3.17 (1H, m), 2.79 (1H, br. t, $J=15.6$ Hz), 1.95 - 1.81 (3H, m), 1.76 - 1.61 (2H, m), 1.49 - 1.39 (1H, m), 1.36 - 1.26 (1H, m), 0.91 (3H, s), 0.88 (3H, s). LSIMS (+) NBA 8 kV m/z (%): 280 (8.8), 294 (6.5), 338 (100), 366 (8.2), 581 ($\text{M} + \text{H}$) $^+$ (13.5), 603 ($\text{M} + \text{Na}$) $^+$, 1183 ($2\text{M} + \text{Na}$) $^+$. LSIMS HR: calculated for $\text{C}_{26}\text{H}_{33}\text{N}_2\text{O}_{11}\text{S}$ ($\text{M} + \text{H}$) $^+$: 581.1805, found: 581.1800.
10. Compound **5** was isolated as an amorphous white solid, $[\alpha]_D^{23}$ - 3.8 (c 1.26, CHCl_3), $^1\text{H-NMR}$ (CDCl_3 , 500 MHz) δ : 7.28 (1H, s), 6.65 (1H, s), 5.99 (1H, s), 4.23 - 4.19 (1H, m), 3.88 - 3.81 (2H, m), 3.82 and 3.84 (two s, 3H each), 3.73 (3H, s), 3.53 (2H, ABq, $J=13.3$ Hz), 3.39 - 3.31 (1H, m), 3.19 (1H, t, $J=15.4$ Hz), 1.93 - 1.71 (5H, m), 1.57 - 1.42 (2H, m), 1.26 (3H, s), 0.93 (3H, s). LSIMS (+) NBA 8 kV m/z (%): 250 (100), 493 ($\text{M} + \text{H}$) $^+$ (17.6), 515 ($\text{M} + \text{Na}$) $^+$ (26.5). LSIMS HR: calculated for $\text{C}_{24}\text{H}_{32}\text{N}_2\text{O}_7\text{SNa}$ ($\text{M} + \text{Na}$) $^+$ 515.1828, found 515.1828.
11. Compound **6** was isolated as an oil, $[\alpha]_D^{23}$ +50.4 (c 0.67, CHCl_3), lit.¹² $[\alpha]_D^{23}$ +55 (c 0.4, CHCl_3), CI MS m/z (%): 238 (32, $\text{M}^+ + 1$), 206 (100, $\text{M}^+ - \text{CH}_2\text{OH}$), $^1\text{H-NMR}$ (CDCl_3 , 200 MHz) δ : 6.61 (1H, s), 6.57 (1H, s), 3.82 and 3.83 (2x3H, two s), 3.75 (1H, m), 3.52 (2H, m), 3.13 (2H, m), 2.81 (2H, m), 2.54 (3H, s). Upon addition of 0.1 eq of $\text{Eu}(\text{hfc})_3$ signals at 6.61 and 6.57 ppm gave two pairs of signals: 6.70 and 6.68 ppm (major), and 6.61 and 6.60 ppm (minor).
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13. Compound **8** was isolated as a yellow foam, $[\alpha]_D^{23}$ -126.7 (c 1.15, CHCl_3), $^1\text{H-NMR}$ (CDCl_3 , 500 MHz) δ : 8.84 (1H, s), 7.49 (1H, d, $J=7.8$ Hz), 7.23 (1H, d, $J=8.1$ Hz), 7.16 - 7.07 (2H, m), 5.43 (1H, s), 3.95 (1H, dd, $J_1=4.5$ Hz, $J_2=7.6$ Hz), 3.71 - 3.57 (4H, m), 3.14 - 3.09 (2H, m), 2.35 - 2.15 (1H, m), 2.01 - 1.81 (5H, m), 1.46 - 1.30 (2H, m), 1.27 (3H, s), 1.01 (3H, s). LSIMS (+) NBA 8 kV m/z (%): 136 (16.5), 149 (18.2), 156 (24.7), 171 (100), 385 (22.3), 414 ($\text{M} + \text{H}$) $^+$ (20.6), 436 ($\text{M} + \text{Na}$) $^+$ (1.8), 827 ($2\text{M} + \text{H}$) $^+$ (4.7). LSIMS HR: calculated for $\text{C}_{22}\text{H}_{28}\text{N}_3\text{O}_3\text{S}$ ($\text{M} + \text{H}$) $^+$ 414.1851, found 414.1852.