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

Zbigniew Czarnocki*, Józef B. Mieczkowski, Jarosław Kiegiel, and Zbigniew Araźny

Department of Chemistry, University of Warsaw, Pasteura 1, 02-093, Warsaw, Poland

Abstract : (2R)-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 systems¹⁻³. 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 1⁶ 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° 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 6¹¹ of

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known absolute configuration¹² was isolated in 91% yield. The enantiomeric composition of 6 was additionally confirmed by ¹H-NMR experiment with 0.1eq 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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Different conditions were needed for the condensation of 1a with tryptamine hydrochloride. It was found that only at strictly controlled pH (phosphate buffer, pH 6.2) the reaction occured and compound 8^{13} could be isolated in 59% yield.



Analysis of ¹H NMR spectrum of 8 revealed the presence of only one diastereomer with the stereostructure probably resembling 3a, anticipating the same reaction mechanism as for the formation of 3a. This problem will be, however, subjected for a separate study.

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References and Notes.

- Shamma, M. and Moniot, J.L. In *Isoquinoline Alkaloids Research*. 1972-1977. Plenum Press, New York. 1978. Chapter 1.
- 2. Whaley, W.M. and Govindachari, T.R. Org. React. 1951, 6, 151.

- 3. Bates, H.A. J. Org. Chem. 1981, 46, 4931.
- 4. Piper, I.M.; MacLean, D.B.; Kvarnström, I. and Szarek, W.A. Can. J. Chem. 1983, 61, 2721.
- 5. Czarnocki, Z.; MacLean, D.B. and Szarek, W.A. Can. J. Chem. 1986, 64, 2205.
- 6. Bauer, T.; Chapuis, C.; Kozak, J. and Jurczak, J. Helv. Chim. Acta 1989, 72, 482.
- 7. Oppolzer, W. Pure Appl. Chem. 1990, 43, 1969 and references cited therein.
- Compound 3a was isolated as a brown amorphous solid. ¹H-NMR (CDCl₃, 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, J₁=17.5 Hz, J₂=5.4 Hz), 1.91 -1.75 (5H, m), 1.51 145 (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, $[\alpha]_{D}^{23} 1.2 (c \ 1.11, CHCl_3)$, ¹H-NMR (CDCl₃, 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 (M + H)⁺ (13.5), 603 (M + Na)⁺, 1183 (2M + Na)⁺. LSIMS HR : calculated for C₂₆H₃₃N₂O₁₁S (M + H)⁺: 581.1805, found : 581.1800.
- 10. Compound 5 was isolated as an amorphous white solid, [α]²³_D 3.8 (c 1.26, CHCl₃), ¹H-NMR (CDCl₃, 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 (M + H)⁺ (17.6), 515 (M + Na)⁺ (26.5). LSIMS HR : calculated for C₂₄H₃₂N₂O₇SNa (M + Na)⁺ 515.1828, found 515.1828.
- 11. Compound 6 was isolated as an oil, [α]²³_D+50.4 (c 0.67, CHCl₃), lit.¹² [α]²³_D+55 (c 0.4, CHCl₃), CI MS m/z (%):238 (32, M⁺+1), 206 (100, M⁺-CH₂OH), ¹H-NMR (CDCl₃, 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 0.1eq of Eu(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).
- 12. Kerekes, P.; Padam Sharma, N.; Brossi, A. and McLaughlin, J.L. J. Nat. Prod. 1985, 48, 142.
- 13. Compound 8 was isolated as a yellow foam, [α]²³_D-126.7 (c 1.15, CHCl₃), ¹H-NMR (CDCl₃, 500 MHz) δ : 8.84 (1H, s) 7.49 (1H, d, J=7.8 Hz), 7.23 (1H, d, J=8.1Hz), 7.16 7.07 (2H, m), 5.43 (1H, s), 3.95 (1H, dd, J₁=4.5 Hz, J₂=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 (M+H)⁺ (20.6), 436 (M + Na)⁺ (1.8), 827 (2M + H)⁺ (4.7). LSIMS HR : calculated for C₂₂H₂₈N₃O₃S (M + H)⁺ 414.1851, found 414.1852.