ENANTIOSELECTIVE SYNTHESIS OF NATURALLY OCCURRING (-)-TYLOPHORINE BY WAY OF AN ASYMMETRIC INTRAMOLECULAR DOUBLE MICHAEL REACTION[a]

Masataka Ihara, Yoshinobu Takino, and Keiichiro Fukumoto*
Pharmaceutical Institute, Tohoku University, Aobayama, Sendai 980, Japan
Tetsuji Kametani[†]
Institute of Medicinal Chemistry, Hoshi University, Ebara 2-4-41, Shinagawa-ku, Tokyo 142, Japan

Abstract —— Treatment of the 8-phenylmenthyl α,β-unsaturated amide ester (**3**) with tert.-butyldimethylsilyl trifluoromethanesulfonate and triethylamine produced, with a complete diastereofacial selection, the indolizidines (**4**), which were converted into (-)-(R)-tylophorine (**1**).

Recently a novel synthetic methodology for polyheterocyclic compounds possessing a nitrogen atom at the angular position by way of an intramolecular double Michael reaction was developed by us.[1] Since the annulation was carried out at low temperature on treatment of α,β-unsaturated amide esters with tert.-butyldimethylsilyl trifluoromethanesulfonate in the presence of a tertiary amine[1b], an efficient, enantioselective construction of the bicyclic system was expected.[2] Presented herein is a total synthesis of the naturally occurring (-)-(R)-enantiomer (**1**) of tylophorine, isolated from Tylophora asthmatica[3], by an exploitation of the asymmetric intramolecular double Michael reaction.

Condensation of the aldehyde (**2**)[1b] with the (-)-phenylmenthyl (triphenylphosphoranylidene)acetate[4] in refluxing MeCN gave the (E)-α,β-unsaturated ester (**3**)[†], $[\alpha]_D^{25}$+0.26° (c=1.48, $CHCl_3$), in 79 % yield. Treatment of (**3**) with tert.-butyldimethylsilyl trifluoromethanesulfonate in the presence of excess Et_3N in CH_2Cl_2 at 20°C for 5 min or at -78°C for 2 h gave rise smoothly to the intramolecular double Michael reaction. The 500 MHz nmr spectrum indicated that the product (**4**)[†], obtained in 74-89 % yield, was composed of two stereoisomers in a ratio of about 4:1. It was observed that the minor isomer was readily converted into the major one by the reaction with NaH in refluxing tetrahydrofuran. It was therefore assumed that these two compounds would be stereoisomers at the C-6 position on the indolizidine ring.[5] The complete diastereofacial selectivity was made clear in the stage of the pentacyclic compound (**5**). Thus oxidation of the above product

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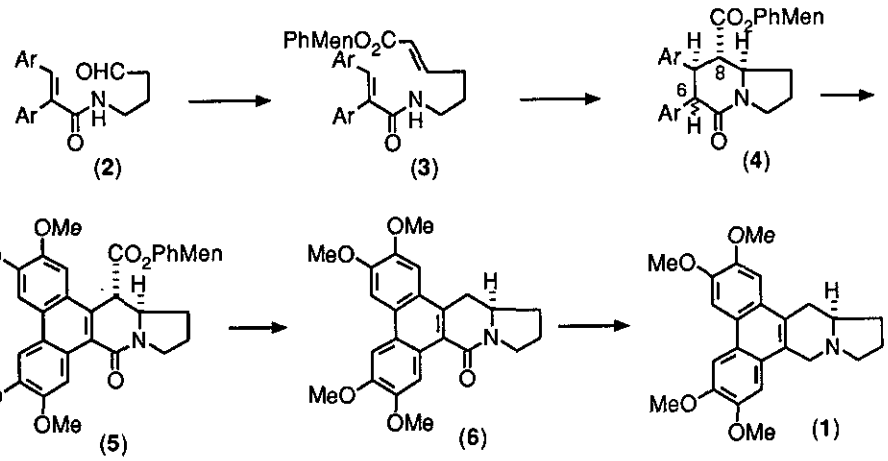
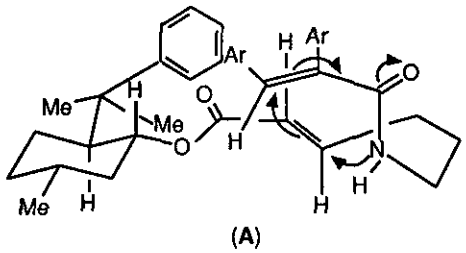
[a]Dedicated to Professor D. H. R. Barton on the occasion of his 70th birthday.
[†]Deceased October 11, 1988.





(4) as the stereoisomeric mixture using excess thallium(III) trifluoroacetate and $BF_3 \cdot Et_2O$ in a mixture of CH_2Cl_2 and CF_3CO_2H[6] furnished in 55 % yield the phenanthroindolizidine (5)†, $[\alpha]_D^{24}$-115.36° (c=1.32, $CHCl_3$) as a single stereoisomer, whose 500 MHz nmr spectroscopy established that the lactam (5) had >99 % d.e. It is noteworthy that the diastereoselectivity was not influenced by the reaction temperature between -78° and 20°C. Hydrolysis of (5) with KOH in refluxing EtOH for 24 h produced in 83 % yield the corresponding carboxylic acid, mp 194-198°C (decomp.), $[\alpha]_D^{26}$-247° (c=1.50, MeOH), which was transformed into (-)-tylophorine (1), mp 274-276°C (lit.,[7] mp 275°C), $[\alpha]_D^{25}$-76.5° (c=0.04, $CHCl_3$) [lit.,[3] $[\alpha]_D^{27}$-11.6° (c=1.07, $CHCl_3$)][8], cd $[\theta]^{25}$-8,235° (275nm) (c=1.7 x 10^{-5} M, EtOH) via (-)-9-oxotylophorine (6)[2], according to the method for the synthesis of the racemate.[1b]

The predominant formation of the (R)-isomer was expected from the consideration

about the conformation[4,9] of the intermediate during the intramolecular double Michael reaction. The endo type transient would be a disfavored one due to the nonbonding interaction between the aromatic substituent at the α position of the α,β-unsaturated amide and the phenylmenthyl ester. Therefore the cyclisation would proceed via the transition state geometry resembling (**A**) leading to (**4**).

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† Ir ($CHCl_3$) and nmr ($CDCl_3$) data: (**3**) ir 3410 (NH), 1700 and 1650 cm^{-1} (C=O); nmr (90 MHz) δ4.80(1H, dt, J 4.0 and 11.0 Hz, >CH-O-), 5.20(1H, d, J 16.0 Hz, =$CHCO_2$), and 7.73(1H, s, ArCH=CAr-); (**4**) ir 1720 and 1635 cm^{-1} (C=O); (**5**) ir 1710 and 1630 cm^{-1} (C=O); nmr (500 MHz) δ 0.72(3H, d, J 7.1 Hz, Me), 1.02 and 1.18(each 3H, each s, 2 x Me), 3.97, 4.13, 4.14 and 4.18(each 3H, each s, 4 x OMe), 4.70(1H, dt, J 4.7 and 11.7 Hz, >CH-O-), 7.21, 7.79, and 8.90(1H, 2H, and 1H, each s, 4 x ArH).

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