TOTAL SYNTHESIS OF KUKOAMINE A USING 2-METHYL-5,6-DIHYDRO-4H-1,3-OXAZINE AS A CARBOXAMIDE BUILDING BLOCK

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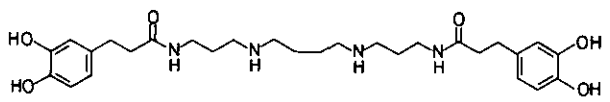
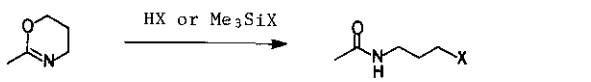
Abstract ——— Kukoamine A, the active constituent of Oriental medicine "Jikoppi" for hypertension, has been synthesized employing a new methodology for non-spermine-based polyamine construction.

The useful chemical reactivity that lurks in familiar 2-methyl-5,6-dihydro-4H-1,3-oxazine (2) has been revealed recently (Scheme 1).[1] Among the products accessible through this transformation, N-3-azidopropylacetamide seems to serve as a potent building block for polyamines. In order to put such strategy to test in making natural products which belong to a family of spermine and spermidine alkaloids, kukoamine A (1) was taken up as a target. This alkaloid was isolated from root barks of Lycium chinese by Hikino and coworkers who have disclosed as well that kukoamine A is responsible for antihypertensive activity,[2] one of remarkable physiological activities being exhibited by the above Oriental medicine of clinical interest.[3]



kukoamine A 1

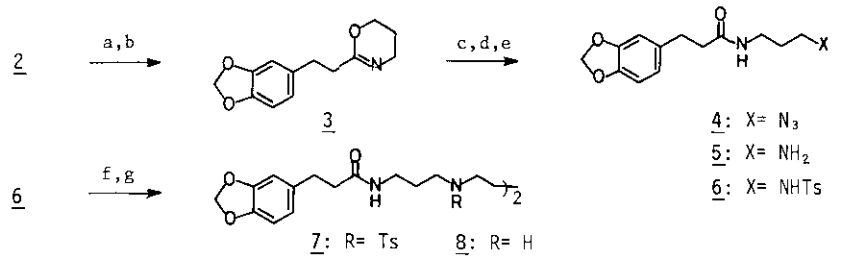


2 X= N_3, Cl, SPh, SePh

Scheme 1.

The first total synthesis of kukoamine A has been described by Chantraproma and Ganem,[4] developing a selective acylating methodology for the terminal amino groups of spermine.[5] Unlike this approach, we will present here a new approach to the polyamine derivative relying on the above-mentioned strategy which involves essentially three transformations as follows: alkylation of azaenolate of 2, nucleophilic ring opening of the oxazine moiety by hydrogen azide and subsequent reduction of the azide group to amino group, and coupling reaction of thus-obtained aminopropyl-

amide with 1,4-dibromobutane (Scheme 2).



a) LDA (1 eq)/THF/-78 °C, 1 h; b) piperonyl chloride (1 eq)/THF/-78 °C → rt; c) Me_3SiN_3 (1.05 eq)/MeOH (1.06 eq)/DMF/60 °C, 4 h; d) H_2/Pd-$CaCO_3$/EtOH/rt, 0.5 h; e) TsCl (1 eq)/Et_3N (1.01 eq)/CH_2Cl_2/0 °C, 0.5 h; f) $Br(CH_2)_4Br$ (0.5 mol eq)/K_2CO_3 (5.9 eq)/CH_3CN/reflux 24 h; g) + 4e$^-$/MeOH-CH_3CN(9:1)-Me_4NCl-(Pt-Hg)/rt (see reference 15)

Scheme 2.

Thus, azaenolate derived from 2[6] (LDA/THF/-78 °C) was alkylated efficiently with piperonyl chloride[7] (-78 °C, 0.5 h → rt) to give 2-(3,4-methylenedioxyphenylethyl)-5,6-dihydro-4H-1,3-oxazine (3)[8], which, without any purification, was dissolved in dry DMF and to this solution were added chlorotrimethylsilane and methanol, successively, at 0 °C. The resulting mixture was heated at 60 °C for 4 h to furnish an expected azidoamide (4) in 75% yield from 2 after recrystallization (ether, -78 °C).[9] The azido-group was, then, reduced to amino-group by the aid of Lindlar catalyst (H_2/EtOH/rt, 0.5 h)[10], giving rise to N-(3-aminopropyl)amide derivative (5) in 97% yield.[11] At this stage 5 was reacted with 1,4-dibromobutane in a two-to-one mole ratio. Although a variety of combinations for both solvent and base were searched, no desired coupling reaction was effected, only giving pyrolidine derivative in every case. Therefore, 5 was tosylated in a usual manner (TsCl/Et_3N/CH_2Cl_2/0 °C, 0.5 h) to afford tosylamide derivative (6) in 82% yield after purification by recrystallization of chromatographically pure 6 (benzene-ethyl acetate-ether).[12] Obviously 6 seems to allow alkylation of the terminal nitrogen atom with a usual alkyl halide. Thus, coupling reaction of 6 with 1,4-dibromobutane in a two-to-one fashion was successfully performed by the use of weak base (K_2CO_3) suspended in acetonitrile (reflux, 24 h) to give solely the desired product (7) in 97% yield after purification by silicagel chromatography.[13] A carbon-13 nmr spectrum of this symmetrical molecule exhibited twenty signals refecting the structure as such.

An attempted detosylation from 7 using a conventional recipe (Na/liq NH_3) resulted in the formation of complex mixture. However, an electroreductive protocol gave a satisfactory solution to this problem.[14] Thus, a solution of 7 in CH_3OH-CH_3CN (9 : 1) containing tetramethylammonium chloride as an electrolyte was electrolyzed using Pt-Hg electrodes in a divided cell.[15] Four-faraday

electricity was enough to effect the desired transformation, giving a precursor of kukoamine A (8) in 90% yield. A carbon-13 nmr spectrum of 8 showed fifteen signals whose chemical shifts are fully consistent with those reported.[16]

As a conversion of 8 to kukoamine A has been already known,[4] a formal total synthesis of 1 has been established based on non-condensative, non-spermine-based *polyamine construction methodology* which features 2 as amide building block. In view of the structural characteristics of the key intermediate 6 present strategy would be applicable to the total synthesis of other alkaloids of this family and make easy access to these possible which is now in progress.

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2) S. Funayama, K. Yoshida, C. Konno, and H. Hikino, Tetrahedron Lett., 1980, 21, 1355.

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4) K. Chantraproma and B. Ganem, Tetrahedron Lett., 1981, 22, 23.

5) Professor Ganem and his coworkers have extended methodology for selectively alkylating *spermidine to spermine*; see also J. S. McManis and B. Ganem, J. Org. Chem., 1980, 45, 2401, K. Chantraproma, J. S. McManis, and B. Ganem, Tetrahedron Lett., 1980, 21, 2475, and K. Chantraproma and B. Ganem, Tetrahedron Lett., 1980, 21, 2605.

6) Prepared as reported: H. Witte and W. Seeliger, Liebigs Ann. Chem., 1974, 996.

7) Prepared by the reaction of corresponding alcohol with conc. HCl: Org. Syn., Coll. Vol. IV, 1963, 576.

8) 3: ^{1}H nmr ($CDCl_3$) 1.79 (2H, quint, J=6 Hz), 2.1-3.0 (4H, m), 3.29 (2H, t, J=6 Hz), 4.06 (2H, t, J=6 Hz), 5.80 (2H, s), and 6.59 (3H, s) ppm; an attempted purification by silicagel chromatography resulted in significant decomposition of the oxazine moiety.

9) 4: mp 55-56 °C; ^{1}H nmr ($CDCl_3$) 1.72 (2H, quint, J=6.8 Hz), 2.41 (2H, m), 2.89 (2H, m), 3.30 (4H, m), 5.47 (1H, bs), 5.92 (2H, s), and 6.78 (3H, m) ppm; ir ($CHCl_3$) 3740, 2110, 1675, 1510, 1495, 1450, 1245, 1042, 940, and 815 cm^{-1}.

10) E. J. Corey, K. C. Nicolaou, R. D. Balanson, and Y. Machida, Synthesis, 1975, 590.

11) 5: *mp 66-68 °C; ^{1}H nmr ($CDCl_3$) 1.56 (4H, m), 2.25-3.01 (6H, m), 3.29 (2H, m), 5.86 (2H, s),*

and 6.64 (4H, m) ppm; ir ($CHCl_3$) 3460, 3340, 1662, 1502, 1490, 1440, 1240, 1035, 930, and 805 cm^{-1}.

12) 6: mp 89-90 °C; ^1H nmr ($CDCl_3$) 1.56 (2H, m), 2.28-2.43 (2H, m), 2.39 (3H, s), 2.71-2.91 (4H, m), 3.15-3.34 (2H, m), 5.82 (1H, TsNH, t, J=6.6 Hz), 5.87 (2H, s), 6.08 (1H, CONH, t, J=5.8 Hz), 6.49-6.71 (3H, m), 7.27 (2H, m), and 7.72 (2H, m) ppm; ir ($CHCl_3$) 3450, 3400, 3200, 1660, 1505, 1490, 1440, 1328, 1240, 1160, 1092, 1039, 932, and 810 cm^{-1}; ^{13}C nmr ($CDCl_3$) 21.44 (q), 29.34 (t), 31.44 (t), 35.87 (t), 38.36 (t), 39.82 (t), 100.79 (t), 108.15 (d), 108.73 (d), 121.06 (d), 126.96 (d), 129.69 (d), 134.52 (s), 137.10 (s), 143.29 (s), 145.82 (s), 147.58 (s), and 173.21 (s) ppm; before subjecting to the coupling reaction with 1,4-dibromobutane, 6 should be highly purified by recrystallization even after column chromatography because, otherwise, the reaction gave considerable amount of one-to-one type coupling product.

13) 7: mp 130-133 °C; ^1H nmr ($CDCl_3$) 1.36-1.90 (4H, m), 2.26-2.55 (2H, m), 2.43 (3H, s), 2.75-3.14 (6H, m), 3.14-3.40 (2H, m), 5.88 (2H, s), 6.26 (1H, t, J=6 Hz), 6.57-6.82 (3H, m), 7.30 (2H, m), and 7.62 (2H, m) ppm; ir ($CHCl_3$) 3450, 1670, 1510, 1495, 1445, 1335, 1248, 1160, 1092, 1042, 938, and 815 cm^{-1}; ^{13}C nmr ($CDCl_3$) 21.44 (q), 25.98 (t), 28.66 (t), 31.48 (t), 36.11 (t), 38.55 (t), 46.40 (t), 48.54 (t), 100.74 (t), 108.15 (d), 108.83 (d), 121.16 (d), 126.96 (d), 129.84 (d), 134.76 (s), 136.03 (s), 143.53 (s), 145.77 (s), 147.53 (s), and 172.29 (s) ppm.

14) L. Horner and H. Neumann, Chem. Ber., 1965, 98, 3462.

15) An H-shaped cell divided by a sintered glass filter (5G) was used. In a cathodic part was placed mercury (5 ml) into which a platinum wire was immersed and electrolytic solution [0.116 g of 7 in CH_3OH-CH_3CN (9 : 1) (13 ml) containing Me_4NCl (0.2 g)] was introduced to it. An anodic part was charged with CH_3OH (13 ml) containing the electrolyte (0.2 g) as well. While argon was bubbled into the cathodic room through a ball-like sintered glass, 50 mA of electricity was applied during 17 min. A tlc monitoring indicated that no starting 7 remained and a usual workup gave crystalline 8 (0.068 g, 90% yield) as a sole product.

16) 8: mp 119-121 °C; ^1H nmr ($CDCl_3$) 1.25-1.75 (5H, -NH- and $-CH_2-$, m), 2.22-2.72 (6H, CH_2-N-CH_2, and $COCH_2$, m), 2.72-3.00 (2H, Ar-CH_2, m), 3.13-3.44 (2H, CON-CH_2, m), 5.90 (2H, O-CH_2-O, s), and 6.45-6.79 (4H, Ar-H and CONH, m) ppm; ir ($CHCl_3$) 3480, 3300, 1662, 1525, 1510, 1495, 1365, 1250, 1122, 1100, 1042, 940, and 812 cm^{-1}; ^{13}C nmr ($CDCl_3$) 27.93 (t), 28.90 (t), 31.53 (t), 38.70 (t), 38.75 (t), 48.15 (t), 49.71 (t), 100.74 (t), 108.15 (d), 108.78 (d), 121.11 (d), 134.86 (s), 145.81 (s), 147.58 (s), and 171.95 (s) ppm [^{13}C nmr chemical shift reported for 8; 27.50, 28.54, 31.24, 38.15, 38.38, 47.56, 49.27, 100.47, 107.86, 108.47, 120.80, 134.52, 145.48, 147.23, and 171.7 (see reference 4)].

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