STEREOSELECTIVE TOTAL SYNTHESIS OF NECINE BASES, (±)-RETRONECINE AND (±)-TURNEFORCIDINE

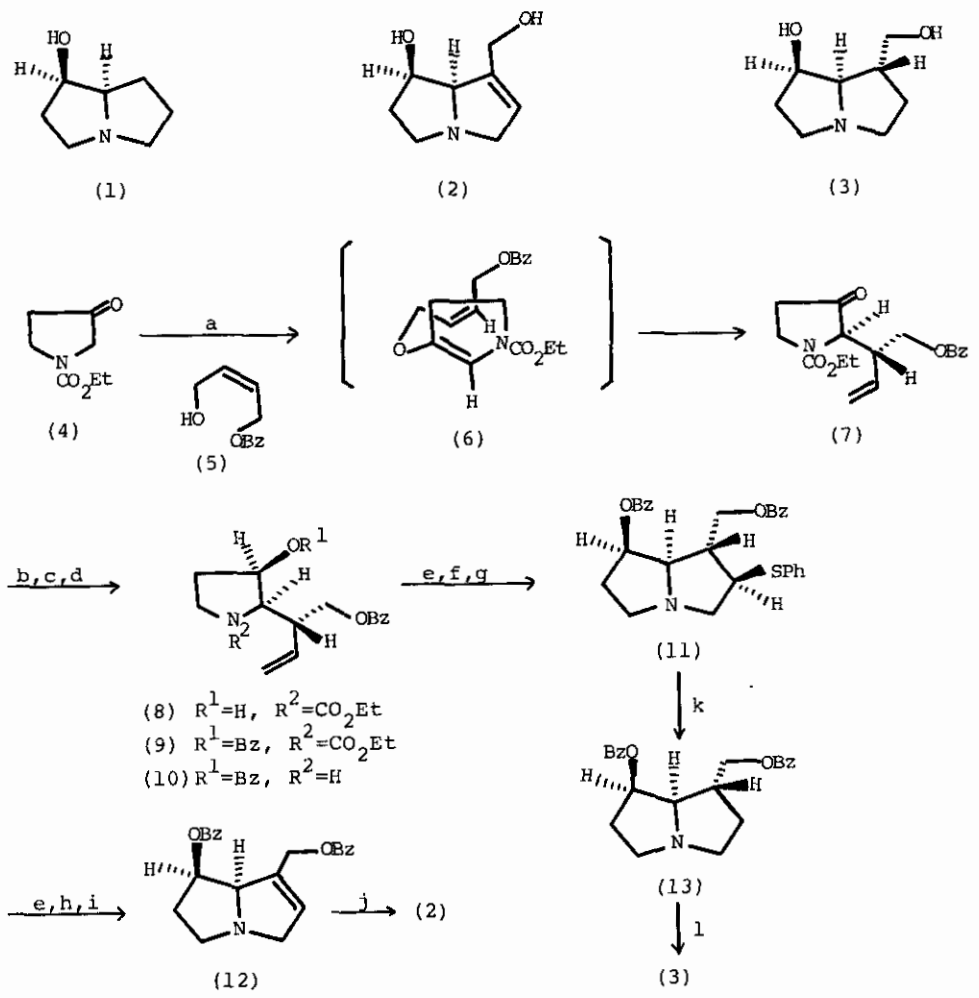
Tatsushi Ohsawa, Masataka Ihara, and Keiichiro Fukumoto
Pharmaceutical Institute, Tohoku University, Aobayama, Sendai 980, Japan
Tetsuji Kametani*
Institute of Medicinal Chemistry, Hoshi University, Ebara 2-4-41, Shinagawa-ku, Tokyo 142, Japan

Abstract —— (±)-Retronecine (2) was synthesised by a coupling of a regioselective [3,3]sigmatropic rearrangement with a sulpheno-cycloamination as key steps and the first stereoselective total synthesis of (±)-turneforcidine (3) was also accomplished.

Recently we reported an efficient and stereoselective synthesis of (±)-cis-1,8-H-1-hydroxypyrrolizidine (1)[1] by a regioselective [3,3]sigmatropic rearrangement and sulpheno-cycloamination with an addition of benzenesulphenyl chloride to olefinic amines followed by a base induced ring closure[2]. As an extension of this work, we have applied this methodology to a synthesis of pharmacologically interesting necine bases[3]. In this communication we describe a stereoselective total synthesis of (±)-retronecine (2)[4] and the first total synthesis of (±)-turneforcidine (3), a necine base of turneforcine[5].

A readily available 3-pyrrolidinone (4) was treated with the cis-butene (5)[6] in the presence of a catalytic amount of p-toluenesulphonic acid[7] and sodium sulphate with azeotropic removal of water to give the compound (7)[8] with a yield of 77 % (based on the 3-pyrrolidinone consumed) in a regioselective manner via the chair-like transition state (6). The stereochemical relationship between C_2 and C_1, of (7) was confirmed as shown by its conversion to (±)-turneforcidine (3).

Reduction of (7) with sodium borohydride afforded the alcohol (8)[8] in 76.8 % yield with its epimer (9.6 % yield). This reduction would occur from the less hindered side and the stereochemistry of the major carbinol (8) was ascertained by the



a) TsOH (cat.), Na_2SO_4, xylene, reflux b) $NaBH_4$, MeOH, 0°C c) NaH, BzBr, THF, reflux d) KOH, diethylene glycol, reflux e) HCl, Et_2O, MeOH f) PhSCl, CH_2Cl_2, 0°C g) K_2CO_3, NaI, MeCN, reflux h) m-CPBA, CH_2Cl_2, - 20°C i) xylene, reflux j) Li, liq. NH_3, THF, - 33°C k) Raney nickel, EtOH, reflux l) H_2, $PdCl_2$, MeOH-$CHCl_3$, room temp.

following transformation to (2) and (3). The alcohol (8) was benzylated in 81.2 % yield with benzyl bromide and sodium hydride in refluxing tetrahydrofuran (THF). After hydrolysis of the carbamate (9)[8] with potassium hydroxide in diethylene glycol, the resulting amine (10) (92.5 % yield) was applied to the sulpheno-cycloamination[1,2]. Namely, treatment of the hydrochloride of the amine (10) with benzenesulphenyl chloride in methylene chloride at 0°C followed by the ring closure

with potassium carbonate in acetonitrile in the presence of sodium iodide produced the sulphide (11)[8] as a single stereo-isomer in 71.9 % yield from (10). The stereochemistry of the adduct was assumed from a kinetic consideration and supported by the ease of a syn-elimination of the corresponding sulphoxide. Thus, the hydrochloride of (11) was oxidised with m-chloroperbenzoic acid in methylene chloride at - 20°C to afford the sulphoxide, which was then subjected to the syn-elimination reaction by refluxing in xylene giving the olefin (12)[8] in 44 % yield (based on the unrecovered sulphoxide). Subsequently, the olefin (12) was debenzylated with lithium in liquied ammonia and THF[4d] at - 33°C to furnish (±)-retronecine (2), m.p. 131 ∿ 132°C (lit.,[4a] m.p. 130 ∿ 131°C), whose i.r. and n.m.r. spectra were identical with those of natural retronecine donated from Prof. H. Furuya (Kitasato Univ.), to whom we thank.

Desulphurisation of (11) with Raney nickel followed by debenzylation of the resulting ether (13)[8] by a catalytic hydrogenolysis gave, in 91.8 % yield from (11), (±)-turneforcidine (3), whose n.m.r. spectrum was superimposable on that of the authentic compound[9]. Thus, the stereoselective total synthesis of (±)-retronecine and (±)-turneforcidine was achieved.

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