STEREOSELECTIVE SYNTHESIS OF
TRANS-3a-ARYLOCTAHYDOINDOLES USING CYCLIZATION OF
N-VINYLC α-(METHYLTHIO)ACETAMIDES

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Abstract — Treatment of N-(2-arylcyclohex-1-enyl)-α-(methylthio)acetamide with NCS underwent cyclization to give 3a-arylhexahydroindol-2-one, which was stereoselectively converted into trans-3a-aryloctahydroindole.

Lewis acid promoted inter- and intramolecular carbon-carbon bond forming reactions of α-chlorosulfides with alkenic bonds have emerged as valuable tool in organic synthesis.1 We previously reported that N-vinyl α-chloro-α-(methylthio)acetamide (1) underwent cyclization at 100 °C in the absence of Lewis acid to give product (3) in 30% yield (Scheme 1).2 This cyclization can be explained in terms of a high nucleophilic nature of the C=C bond of enamide and a high electrophilic nature of α-chlorosulfide, giving the acyliminium ion intermediate (2).

Scheme 1

PMB = p-methoxybenzyl

[Diagram]

□ This paper is dedicated to Prof. Dr. Satoshi Ōmura (The Kitasato Institute) with respect and admiration on the occasion of his 70th birthday.
We have now found that treatment of N-(2-arylcyclohex-1-enyl)-α-(methylthio)acetamide (6) with NCS at room temperature gives no α-chlorosulfide (8) but affords cyclization product, 3a-aryhexahydroindol-2-one (10) in good yield (Scheme 2). Subsequent reductions of 10 give no mesembrane (16) but afford stereoselectively trans-mesembrane (15). Herein, we report the preliminary result of the works in this area.

Scheme 2

Condensation of 2-(3,4-dimethoxyphenyl)cyclohexanone and (R)-1-(1-naphyl)ethylamine followed by acylation of the resulting imine (4) with (methylthio)acetyl chloride (5) at room temperature in the presence of N,N-dimethylaniline and 4-dimethylaminopyridine (DMAP) gave α-(methylthio)acetamide (6) having a chiral auxiliary on the nitrogen atom in 45% yield. When compound (6) was treated with N-chlorosuccinimide (NCS) in CCl₄ at room temperature, cyclization occurred smoothly within 30 min to give two stereoisomers (10) over possible four diastereoisomers in a ratio of 74:26 (determined by NMR) and in 59% yield: no α-chlorosulfide (8) was obtained. Easy access of 10 from 6 without the formation of α-chlorosulfide can be explained by an attack of an electron rich olefinic bond of enamide (7) on its thionium ion, which is an intermediate for the formation of α-chlorosulfide (8) from 6 and NCS, followed by deprotonation of the resulting iminium ion (9). An alternative mechanism for the formation of 10 may involve an intramolecular S_N2 type nucleophilic substitution of α-chlorosulfide (8). Although the cyclization of 1 needed high reaction temperature (100 °C, see Scheme 1), the cyclization of 7 or 8 proceeded even at room temperature, probably due to a more electron rich tetrasubstituted olefinic bond of enamide (7 or 8) than the
disubstituted olefinic bond of enamide (1).

Desulfurization of compound (10) with Raney Ni gave an inseparable 73:27 diastereoisomeric mixture of compound (11) in 94% yield. This result indicated that the chiral induction by a 1-(1-naphtyl)ethyl group was estimated to be 73:27.

The catalytic hydrogenation of the mixture of two diastereomers (11) in the presence of PtO$_2$ in acetic acid gave two separable stereoisomers (12a) and (12b) bearing 1-(5,6,7,8-tetrahydro-1-naphtyl)ethyl group on the nitrogen atom in 69 and 13% isolated yields, respectively, together with compound (13) (8%) (Scheme 3). Stereochemistry of the ring juncture of 12a was found to be trans by transforming 12a into trans-mesembrane (15) (vide infra) (the relative trans-stereochemistry of the ring juncture of 12a is depicted in Scheme 3).

Reduction of the major stereoisomer (12a) with LiAlH$_4$ followed by hydrogenolysis of the resulting amine in the presence of Pd(OH)$_2$/C gave compound (14) in 60% yield from 12a. N-Methylation of amine (14) with HCHO/NaBH$_3$(CN) gave trans-mesembrane (15)$^4$ in 88% yield (Scheme 4). Therefore, mesembrane (16) was not obtained by reduction of 11 with PtO$_2$/H$_2$, followed by hydrogenolysis and N-methylation.
Hydrogenation of 11 to trans-fused compounds (12) was in sharp contrast to that of enamide (17) which gave exclusively cis-fused compound (18) (Scheme 5).\(^5\)

Elucidation of the absolute configuration of trans-mesembrane (15) and mechanistic problems for the stereochemistry of the hydrogenation of enamides of the type (11) are currently underway

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**REFERENCES**