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# STEREOSELECTIVE SYNTHESIS OF *TRANS*-3a-ARYLOCTAHYDROINDOLES USING CYCLIZATION OF *N*-VINYLIC α-(METHYLTHIO)ACETAMIDES†

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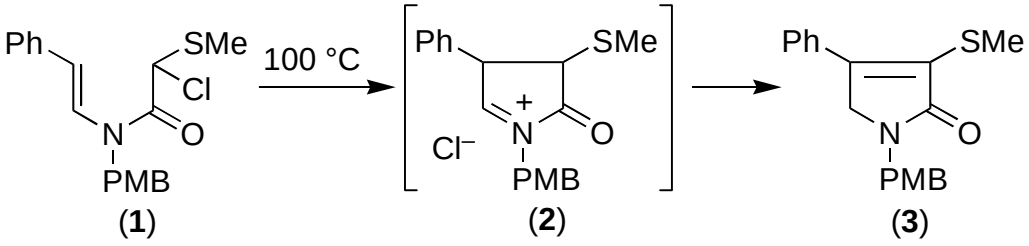
**Abstract** – Treatment of *N*-(2-arylcyclohex-1-enyl)-α-(methylthio)acetamide with NCS underwent cyclization to give 3a-arylhexahydroindol-2-one, which was stereoselectively converted into *trans*-3a-aryloctahydroindole.

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*-vinylic 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**



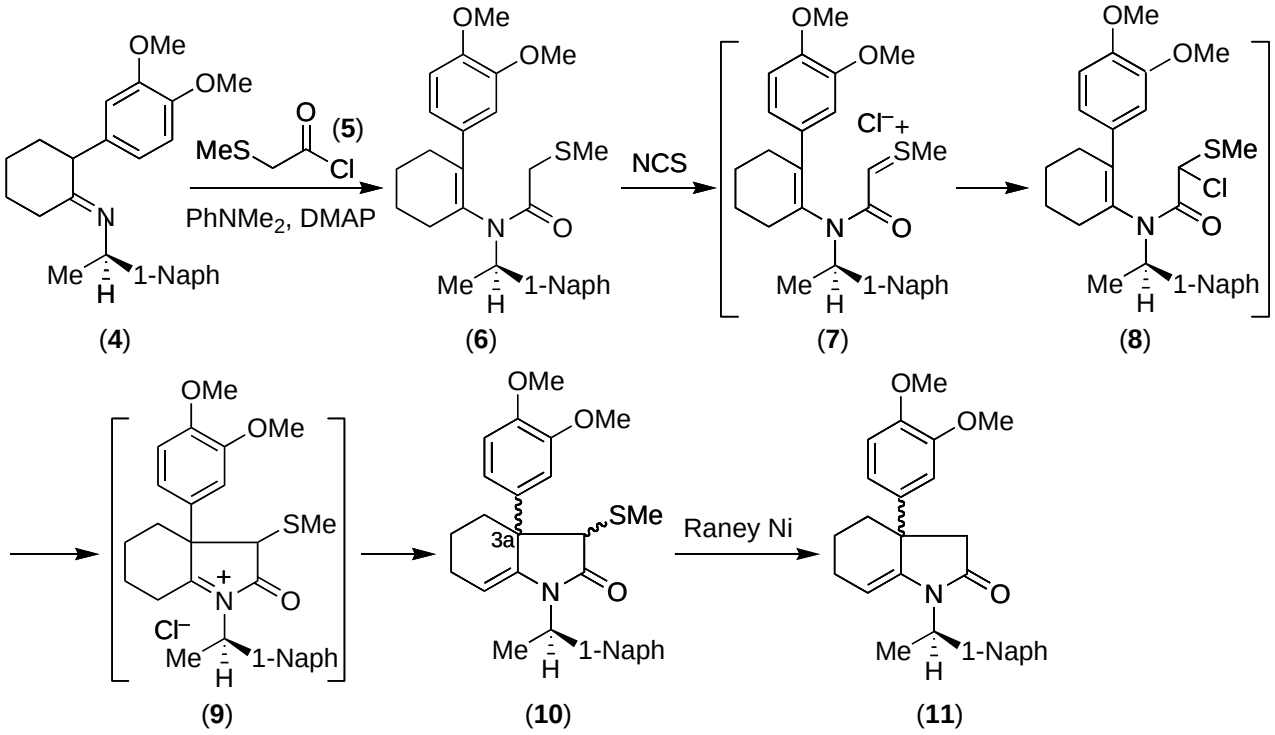

(**1**) (**2**) (**3**)

PMB = *p*-methoxybenzyl

† 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**)[3] 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.

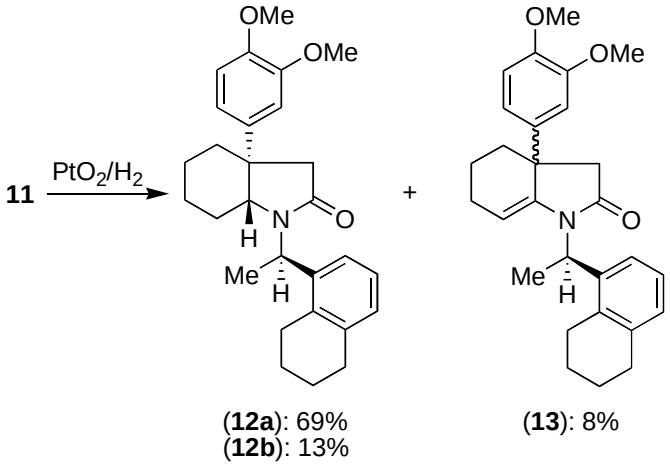
When compound (**6**) was treated with *N*-chlorosuccinimide (NCS) in $CCl_4$ at room temperature, cyclization occurred smoothly within 30 min to give two stereoisomers (**10**) over possible four diastereoisomers in a ratio of 74:26 (determined by NMR) and in 59% yield: no α-chlorosulfide (**8**) was 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

disubsituted 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.

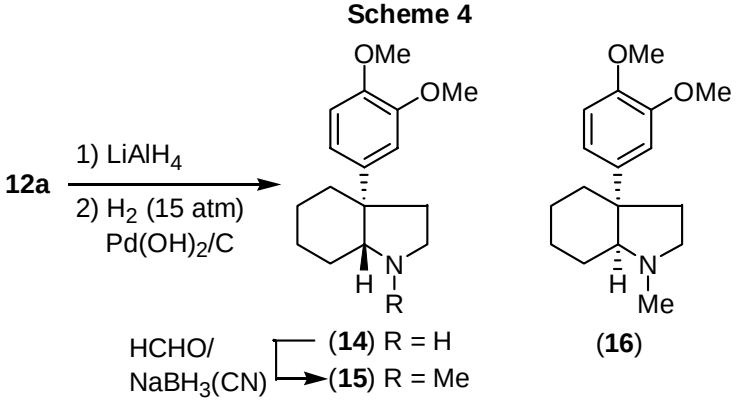
The catalytic hydrogenation of the mixture of two diastereomers (**11**) in the presence of $PtO_2$ in acetic acid gave two separable stereoisomers (**12a**) and (**12b**) bearing 1-(5,6,7,8-tetrahydro-1-naphtyl)ethyl group on the nitrogen atom in 69 and 13% isolated yields, respectively, together with 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).

**Scheme 3**



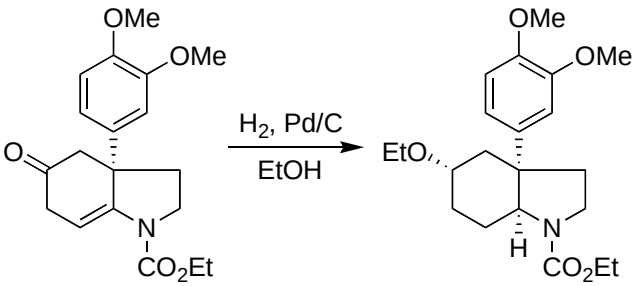

Reduction of the major stereoisomer (**12a**) with $LiAlH_4$ followed by hydrogenolysis of the resulting amine in the presence of $Pd(OH)_2/C$ gave compound (**14**) in 60% yield from **12a**. *N*-Methylation of amine (**14**) with $HCHO/NaBH_3(CN)$ gave *trans*-mesembrane (**15**)[4] in 88% yield (Scheme 4). Therefore, mesembrane (**16**) was not obtained by reduction of **11** with $PtO_2/H_2$, followed by hydrogenolysis and *N*-methylation.

**Scheme 4**



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]

**Scheme 5**




**17** **18**

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

## ACKNOWLEDGEMENTS

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