A NEW SYNTHETIC ROUTE TO THE CORYNANTHE TYPE INDOLE ALKALOIDS USING (±)-NORCAMPHOR

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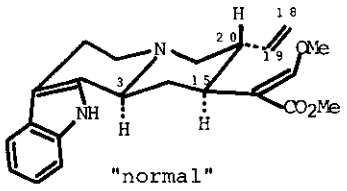
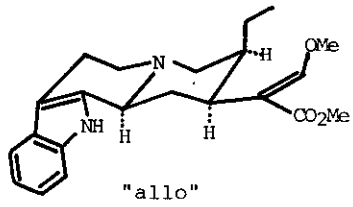
Abstract-----Conversion of (±)-norcamphor(5) into a number of the corynanthe alkaloids in racemic forms has been achieved. The conversion allows a formation of the 18,19-saturated alkaloids with all four possible configurations and the $\Delta^{18,19}$-unsaturated alkaloids with three of four possible configurations.

The corynanthe type indole alkaloids with all of four possible diastereomeric indoloquinolizidine skeleta have been found in nature as represented by the typical examples, corynantheine[1](1)("normal" configuration), corynantheidine[2](2)("allo" configuration), hirsuteine[3](3)("pseudo" configuration), and speciociliatine[4](4)("epiallo" configuration)(Scheme 1). With the intention of developing enantioselective synthesis of these four types of alkaloids from a common chiral starting material (-)-norcamphor[5]((-)-5), we carried out the present synthesis using the known acid[6](8) prepared diastereoselectively from (±)-norcamphor[7~11]((±)-5) through the cleavage reaction of α-diketone monothioketal bond[12](Scheme 2). In order to make formation of the alkaloids with all four configurations possible, we employed the strategy involved initial conversion of the amide[6](9), obtained from (8), into the thermodynamically less stable cis 15/20 lactams(10)("allo" or "epiallo" forms) with appropriate functionality allowing subsequent transformation into the corresponding diastereomers(11) with thermodynamically more stable trans 15/20 configurations("normal" or "pseudo") without accompanying epimerization of the pivotal chiral center(C-15)(Scheme 3). Although not all the reactions proceeded as initially intented, we have achieved the synthesis of the 18,19-saturated alkaloids with all four possible configurations and the $\Delta^{18,19}$-unsaturated alkaloids with three of four possible configurations.



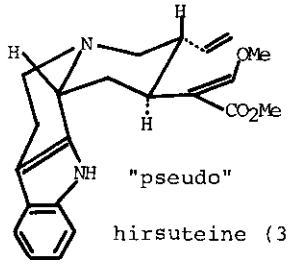
"normal"

corynantheine (1)



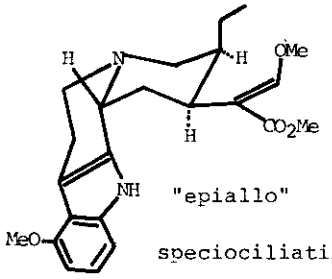
"allo"

corynantheidine (2)



"pseudo"

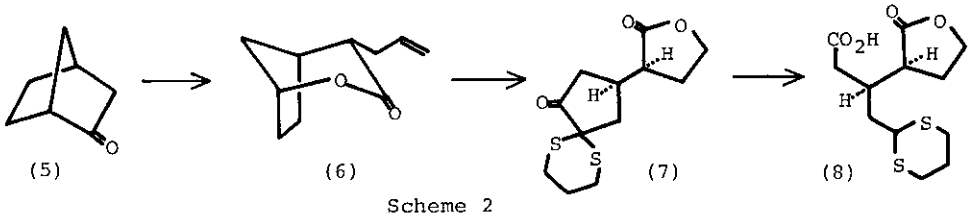
hirsuteine (3)



"epiallo"

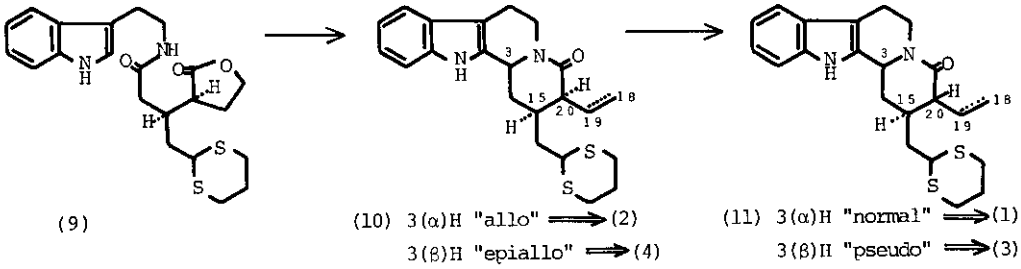
speciociliatine (4)

Scheme 1



(5) (6) (7) (8)

Scheme 2



(9)

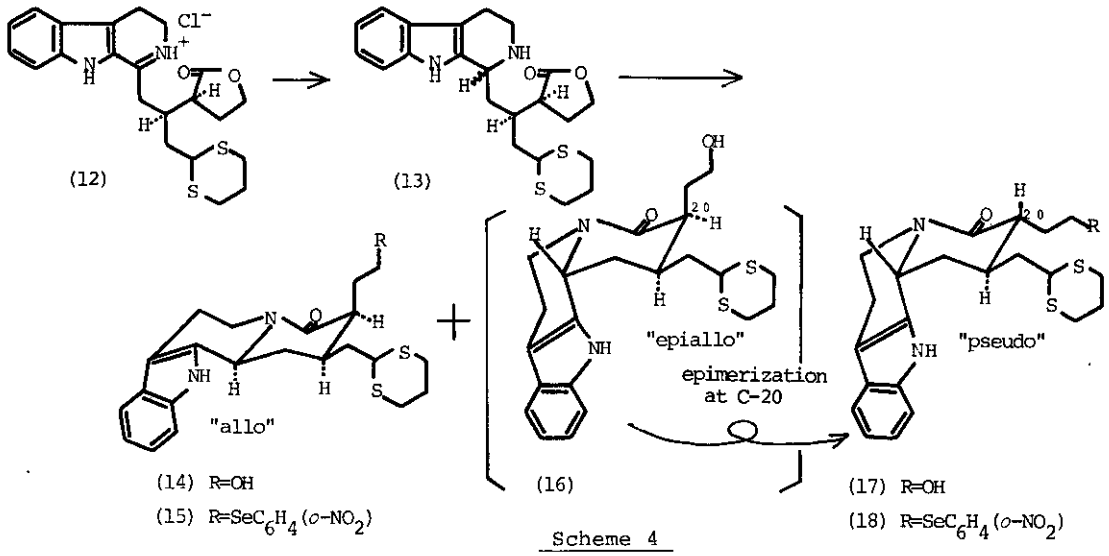
(10) 3(α)H "allo" ⟹ (2)
3(β)H "epiallo" ⟹ (4)

(11) 3(α)H "normal" ⟹ (1)
3(β)H "pseudo" ⟹ (3)

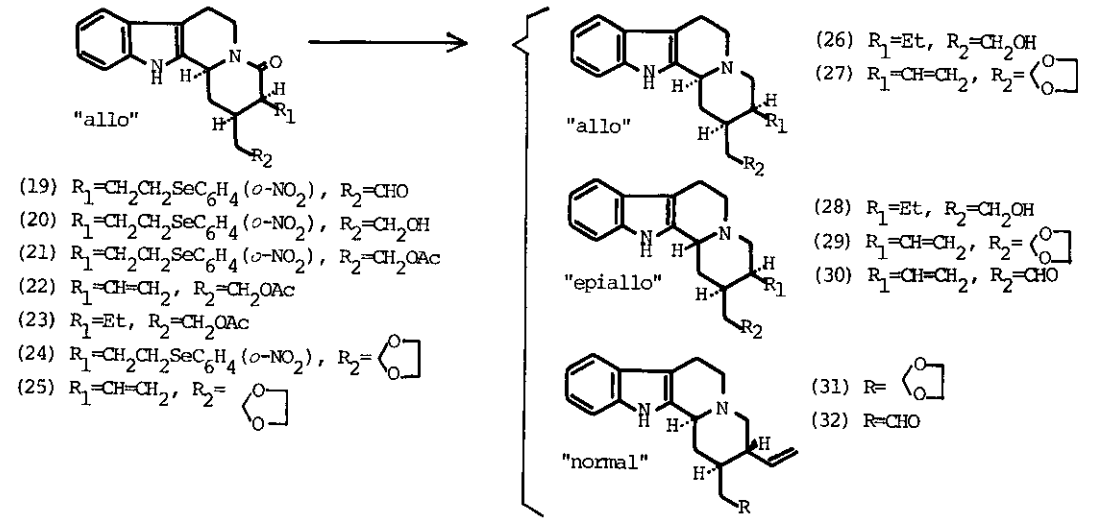
Scheme 3

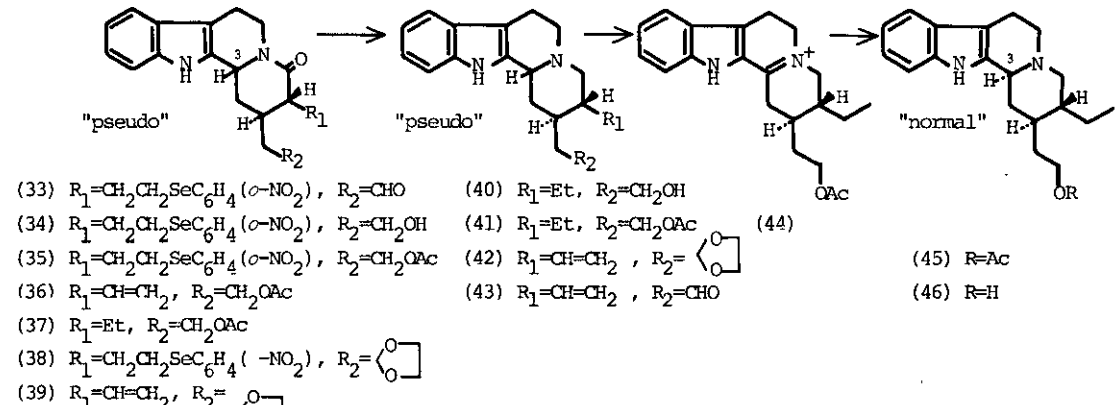
Bischler-Napieralski cyclization($POCl_3$, CH_2Cl_2, reflux) of the amide(9), prepared in 72 % yield from (8) through the mixed anhydride method[13], gave the imine hydrochloride(12) which on reduction($NaBH_4$, MeOH, 0 °C) afforded the tetracyclic lactam in 51 % overall yield as an inseparable mixture of epimers,(14)[14] and (17)[14], through a spontaneous lactam formation. Treatment of the diastereomeric mixture with o-nitrophenylselenocyanate in the presence of tri-n-butylphosphine[15](THF, room temperature) gave the "allo" selenide[16](15) and the "pseudo" selenide(18) in yields of 25 and 25 % after chromatographical separation(silica gel). In these conversions the less stable "epiallo" lactam(16) produced initially with the "allo" isomer(14) was presumed to be inverted at epimerizable C-20 center to take the thermodynamically more favorable "pseudo" configuration(17). Stereochemistry of the each isomer was rigorously deduced by converting the each into the known alkaloids. Namely, both isomeric lactams, (15) and (18), upon treatment with methyl iodide in aqueous acetonitrile[17](room temperature, 24 h) gave the corresponding aldehydes, (19) and (33), which were then converted into the corresponding acetates, (21) and (35), in overall yields of 51[18] and 86.5 % via the alcohols, (20) and (34), by reduction($NaBH_4$, MeOH, 0 °C), followed by acetylation(Ac_2O, AcONa). Oxidation of these acetates with m-chloroperbenzoic acid(CH_2Cl_2, -20 °C ∿ room temperature) afforded the corresponding $\Delta^{18,19}$-lactams, (22) and (36), in yields of 61[18] and 81 % via a spontaneous *syn* elimination reaction[19]. These were converted into the 18,19-saturated compounds, (23) and (37), in yields of 71 and 81 % on catalytic hydrogenation(H_2, PtO_2).

The "allo" acetate(23) upon reduction with lithium aluminum hydride(THF, room temperature) furnished two compounds, in 35 and 41 % yield, which were determined to be (±)-corynantheidol(26)("allo") and (±)-3-epicorynantheidol(28)("epiallo") by direct comparison with authentic materials obtained through the established route[11]. An apparent isomerization of "allo" configuration into "epiallo" configuration by inversion at C-3 center during the reduction with lithium aluminum hydride well corresponded to the reported observations encountered in the related systems under the same treatments[20,21]. The "pseudo" acetate(37), on the other hand, furnished (±)-hirsutinol(40)("pseudo") as a single product in 71 % yield without accompanying epimerization on the same reduction conditions. Sequential acetylation(Ac_2O, AcONa), dehydrogenation[21]($Hg(OAc)_2$, AcOH), reduction($NaBH_4$, MeOH), and alkaline hydrolysis (NaOH, MeOH) converted (±)-hirsutinol(40) obtained into (±)-dihydrocorynantheol[23] (46)("normal") with inversion at C-3 center via (41), (44), and (45).



Scheme 4





Scheme 5

Having established the stereochemistry of the two selenides, (15) and (18), rigorously, we next carried out the conversion of the both into the $\Delta^{18,19}$-alkaloids. The "allo" aldehyde(19) obtained from (15) was converted into the corresponding vinylacetal(25) in 42 % overall yield[18] by sequential acetalization(ethylene glycol, p-TsOH, benzene, reflux) and oxidative elimination(m-chloroperbenzoic acid, CH_2Cl_2, -20 °C ∿ room temperature) via (24). Similarly, the "pseudo" aldehyde(33) from (18) was converted into the corresponding vinylacetal(39) in 77 % yield via (38). In contrast to the saturated counterparts, the both $\Delta^{18,19}$-acetals did not yield the corresponding amines under the same reduction conditions using lithium aluminum hydride alone, however it was overcome by using a 1:1 complex of the hydride and aluminum chloride[24]. Namely, the "allo" lactam(25) on reduction with the complex (THF, -20 °C ∿ 0 °C) furnished two aminoacetals, one(29) with "epiallo" configuration through epimerization at C-3 center and the other(31) with "normal" configuration through epimerization at C-20 center, in 32.5 and 60 % yield. Different from the reduction of the saturated counterpart, a formation of the "allo" isomer(27) could not be detected. On the similar treatments the "pseudo" lactam(39) afforded the corresponding "pseudo" aminoacetal(42) as a sole product in 48.5 % yield. Each acetal upon hydrolysis(60 % acetic acid, reflux) furnished the corresponding aldehyde respectively: (±)-$\Delta^{18,19}$-aldehyde(30)("epiallo"), 70 % yield, from (29), (±)-corynantheal[25](32)("normal"), 86 % yield, from (31), and $\Delta^{18,19}$-dehydrohirsuteal[25](43) ("pseudo"), 69 % yield, from (42). These three compounds were further transformed into the corresponding saturated counterparts, (±)-3-epicorynantheidol(28), (±)-dihydrocorynantheol(46), and (±)-hirsutinol(40), for structure confirmation via a two-step sequence((i)$NaBH_4$, MeOH), (ii) H_2-PtO_2).

Since (-)-corynantheal(32) from natural origin has been transformed[26] into (-)-corynantheine(1), present synthesis of (±)-(32) consists a formal synthesis of (±)-(1). Although there have been no reports other than corynantheine(1) so far, the other two isomeric aldehydes, (30) and (43), would be convertible to their parent alkaloids, (±)-desmethoxyspeciociliatine(4) and (±)-hirsuteine(3), employing the same methodology used in the synthesis of corynantheine[26](1).

ACKNOWLEDGMENTS

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by different routes. We also thank Mr. K. Kawamura, Misses Y. Enomoto, C. Koyanagi, and K. Mushiake, for spectral and analytical measurements.

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