SYNTHETIC STUDIES ON OXYGENATED ASPIDOSPERMA ALKALOIDS: FACILE SYNTHESES OF 1-ACETYLASPIDOALBIDINE AND DEOXYASPIDODISPERMINE

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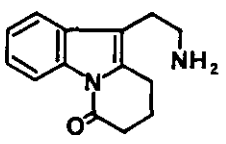
(Dedicated to Professor Gilbert Stork on the occasion of his 65th birthday.)

Abstract - The electrophilic displacements of the reactive anion of tetracyclic lactam 3 were investigated. Facile syntheses of 1-acetylaspidoalbidine (5) and deoxyaspidodispermine (6) were achieved by the partial reduction of a lactam carbonyl, followed by the stereoselective transannular cyclization.

It has been so far reported from this laboratory that the nine-membered lactam 2, efficiently prepared by photoisomerization of the 1-acylindole 1, could be a versatile precursor for syntheses of a variety of indole alkaloids, [1] and



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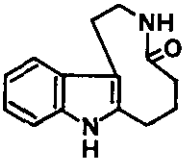

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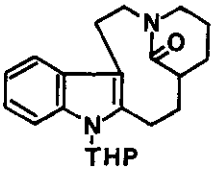

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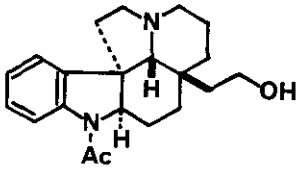

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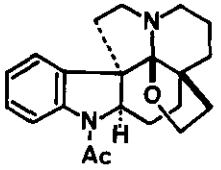

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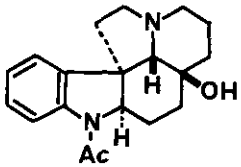

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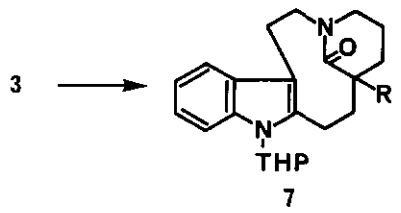
particularly, 2 was readily derived to 3, which was proved to be valuable as a direct precursor for syntheses of aspidosperma alkaloids. It is an important knowledge that the bridgehead proton of 3 is easily abstracted by LDA and the resultant quaternary anion can be reacted with ethyl bromide and allyl bromide[1b] even at -78°C. In the present paper, we demonstrate the further electrophilic displacements of 3 and the successful application to syntheses of the titled alkaloids.



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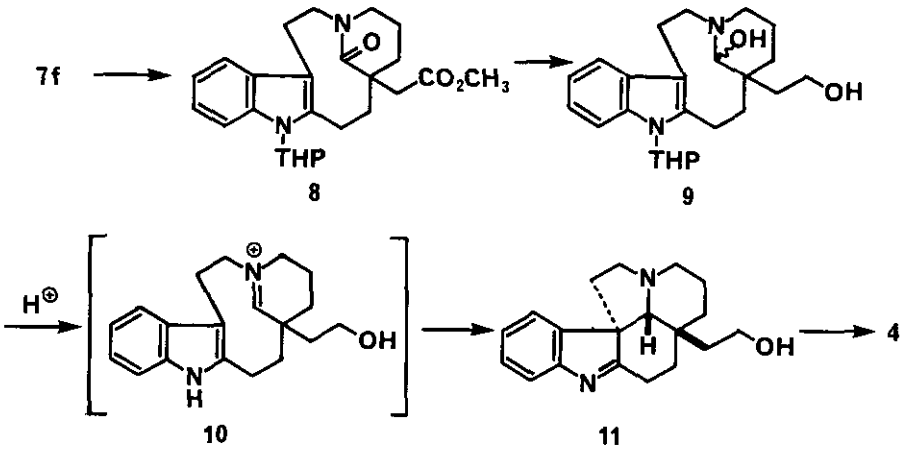
a: $-C_2H_5$
b: $-CH_2CH=CH_2$
c: $-I$
d: $-Br$
e: $-COCH_2Cl$
f: $-COCOOCH_3$
g: $-CH_2CH(SOCH_3)(SCH_3)$

Table 1. Electrophilic displacements of 3

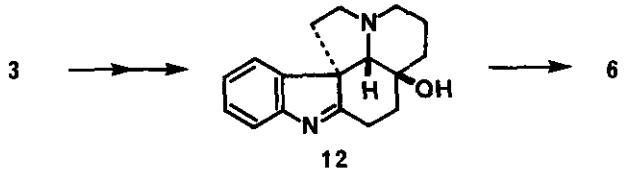
Entry	Electrophiles	Time[a]	Products 7	Yield (%)[b]
1	$I-C_2H_5$	45 min	7a	84%[1b]
2	$Br-CH_2HC=CH_2$	0.5 h	7b	71%[1b]
3	$I-CH_2COOCH_3$	0.5 h	7c	42%
4	$Br-CH_2COOCH_3$	0.5 h	7d	34%
5	$Cl-CH_2COOCH_3$	0.5 h	7e	66%
6	$(COOCH_3)_2$	45 min	7f	90%
7	$CH_2=C(SOCH_3)(SCH_3)$	20 h	7g	71%

a. All of the reactions were carried out in THF at -78°C.
b. Products were isolated as a mixture of the diastereoisomers.

For the synthesis of 5, the anion of 3 [mp 196-198°C; an equal amount of a mixture of diastereoisomers] was reacted with various two-carbon electrophiles as shown in Table 1. In the cases of methyl iodoacetate and methyl bromoacetate, halogenated compounds 7c and 7d were obtained, in moderate yields, respectively. Methyl chloroacetate, however, reacted with the above anion to give chloroacetylated compound 7e in 66% yield. On the other hand, acylation with methyl oxalate afforded the oxo ester 7f in 90% yield. Michael addition of



ketene thioacetal monosulfoxide[2] also took place smoothly to give adduct 7g in 71% yield as a mixture of four stereoisomers. Reduction of 7f (NH_2NH_2, KOH, diethylene glycol, 100-200°C, 2 h), followed by esterification (CH_2N_2, ether) of the crude acids afforded 8 in 52% yield accompanied by 20% of 3. $LiAlH_4$ reduction of 8 (THF, rt, 0.5 h), afforded the amino alcohol 9, which was subjected to transannular cyclization under acidic conditions (THF-10%HCl, 0°C, 0.5 h) to give indolenine 11[3] in 70% yield as a sole product. It is an interesting result that the lactam carbonyl of 8 could not be reduced to the saturated amine under these conditions, giving the partially reduced amino alcohol 9, which was eventually useful for the syntheses of aspidosperma alkaloids, because the stereoselective cyclization of 9 to 11 took place through a plausible iminium cation 10 under conventional conditions. Compound 11 was reduced by $LiAlH_4$ and acetylated to give deoxylimapodine (4), which was identical with an authentic sample. Thus, a formal synthesis of 1-acetylaspidoalbidine (5) was accomplished, since 4 had been already converted into 5 in this laboratory.[4]



The anion of 3 was treated with O_2 (-78°C,17 h) to provide an unstable peroxide, which was reduced immediately with $LiAlH_4$ (THF, rt, 0.5 h), followed by acidification (THF-10%HCl, rt, 0.5 h) afforded indolenine 12[5] as a single compound in 76% yield. Finally, reduction of 12 ($LiAlH_4$, THF, rt, 0.5 h),followed by acetylation furnished deoxyaspidodispermine (6) in 77% yield, which was identical with an authentic sample.[6]

Thus, the electrophilic substitution of the versatile intermediate 3 provided the useful compounds for syntheses of oxygenated aspidosperma alkaloids. The studies on syntheses of other alkaloids of this family are now in progress.

ACKNOWLEDGEMENTS

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3. 11: unstable oil; IR ($CHCl_3$) 3300, 2780, 2720, 1580 cm^{-1}, m/z 268 (M^+), 211; UV λ_{max}(EtOH) 257 nm, λ_{min} 237 nm; NMR ($CDCl_3$) δ0.90 (t, J=7.0 Hz, 3H), 1.0-2.0 (m, 6H), 2.0-3.9 (m, 9H), 2.63 (s, 1H), 6.90-7.55 (m, 4H), 7.80 7.80 (br, 1H).
4. Y. Ban, T. Ohnuma, K. Seki, and T. Oishi, Tetrahedron Lett., 727 (1975).
5. 12: unstable oil; IR ($CHCl_3$) 3300, 2780, 2720, 1580 cm^{-1}; m/z 268 (M^+), 211; UV λ_{max}(EtOH) 220, 259 nm, λ_{min} 239 nm; NMR ($CDCl_3$) δ1.0-2.45 (m, 10H), 2.55 (s, 1H), 2.60-2.99 (m, 3H), 3.00-3.34 (m, 2H), 7.0-7.6 (m, 4H).
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