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FORMAL SYNTHESIS OF (±)-IPALBIDINE

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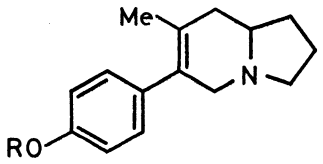
1-Aza-3-(4-methoxyphenyl)bicyclo[4,3,0]nonan-4-one, key intermediate to (±)-ipalbidine, was conveniently synthesized by intramolecular cyclization of the N-formylketone which was obtained via [3 + 2] cycloaddition reaction of the cyclic nitrone.

Ipalbidine 1, the aglycone of ipalbine 2 and ipomine 3 isolated from seeds of *Ipomoea alba* L.[1] and *Ipomoea muricata* Jacq.,[2,3] respectively, is the only instance of an indolizidine alkaloid with methyl substitution on the indolizidine nucleous occurring in nature.[4] Among reported syntheses of ipalbidine,[5-9] three syntheses have been concerned with the synthetic sequence utilizing the bicyclic ketone 12 as the key intermediate, which have been prepared by Dieckmann condensation[5] and intramolecular cyclization of an enamine[7] and vinylogous urethane.[9] In this report we describe a new, convenient procedure for the preparation of this intermediate. The key feature of the synthetic method involves highly selective 1,3-dipolar cycloaddition[10] in the synthesis of the β-amino alcohol 7, which was converted in subsequent steps with final intramolecular ring closure into the bicyclic ketone intermediate 12.

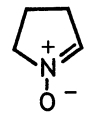


1: R = H
2: R = β-D-glucopyranosyl
3: R = 6-O-*p*-coumaroyl-β-D-glucopyranosyl

The reaction of 1-pyrroline 1-oxide 4 with *p*-allylanisole 5 in refluxing toluene produced the isoxazolidine 6 (oil) in 70% yield as the sole product. The high regioselectivity in the desired sense observed in this reaction is most explicable on the basis of the preference of dipole LUMO control[11,12] with nonconjugated electron-rich dipolarophile.[13] Subsequent N–O bond cleavage of 6 by hydrogenation (10% Pd/C) gave the β-amino alcohol 7 (mp 97 °C) in 82% yield. Thus functionalization required for the target was simply achieved at this early stage.

The amino alcohol 7 thus obtained was heated with formic acid in toluene to furnish the O,N-diformate 8 together with the N-formylcarbinol 9. For selective hydrolysis of the O-formate group, this mixture was subsequently exposed to ammonia in methanol to give the desired N-formylcarbinol 9 (oil) in 69% yield from 7. Collins oxidation (CH_2Cl_2, room temp) of 9 yielded the N-formylketone 10 (oil) in 72% yield. The cyclization of 10 to 11 by aldol reaction is unusual since the amide C=O is normally unreactive partner as the electrophile in this

reaction. After several unsuccessful attemts, however, cyclization was attained when heated with aluminum *t*-butoxide[14] in xylene, providing the bicyclic enaminone 11 (mp 121-122 °C) in 36% yield. Eventually selective reduction of the olefinic double bond of 11 was achieved by using lithium in liquid ammonia to afford the bicyclic ketone 12 (mp 109-110 °C) in 54% yield which had mp and spectral data identical to those reported in the literature.[9] Since the compound 12 has already been converted into (±)-ipalbidine 1 by two steps,[5,7] our preparation of this compound constitutes a formal total synthesis of racemic 1.



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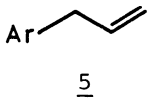

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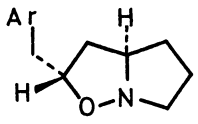

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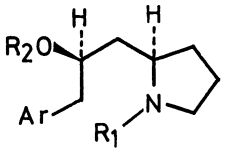
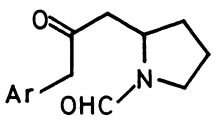


7: $R_1 = R_2 = H$
8: $R_1 = R_2 = CHO$
9: $R_1 = CHO$, $R_2 = H$



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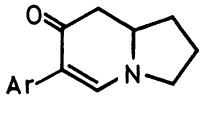

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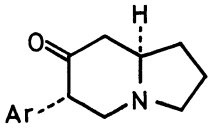

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Ar = *p*-MeO·C_6H_4

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