

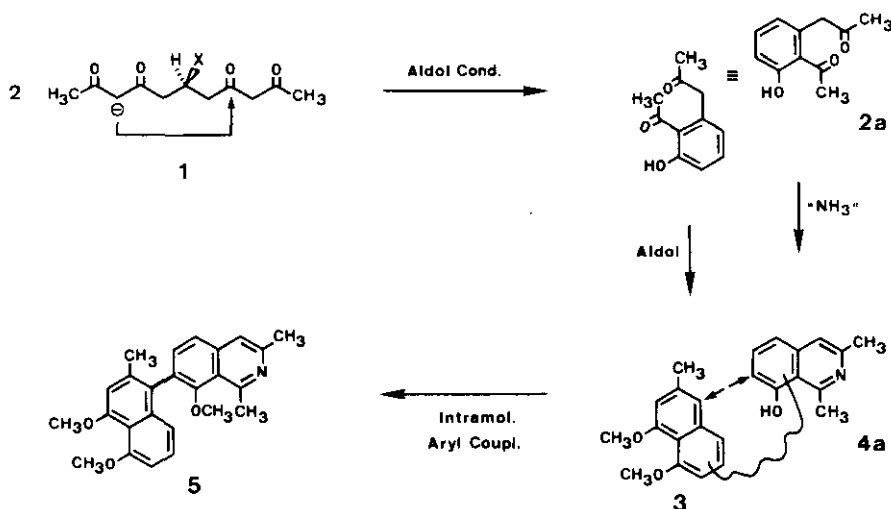
ONE POT PREPARATION OF 1,3-DIMETHYLTETRAHYDROISOQUINOLINES
FROM THEIR BIOSYNTHETIC DIKETO PRECURSORS¹

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Abstract - Biomimetic reactions modelling the nitrogen incorporation into the monocyclic precursors 2 of naphthylisoquinoline alkaloids, using pyridoxamine (9b) are described. The condensation of 2b with 9b, or, more simply, with benzylamine, though not giving a dihydroisoquinoline 7, provides an efficient one pot synthesis of already protected 1,3-dimethyltetrahydroisoquinolines 14, by *in situ* reduction of the resulting isoquinolinium salts 12.

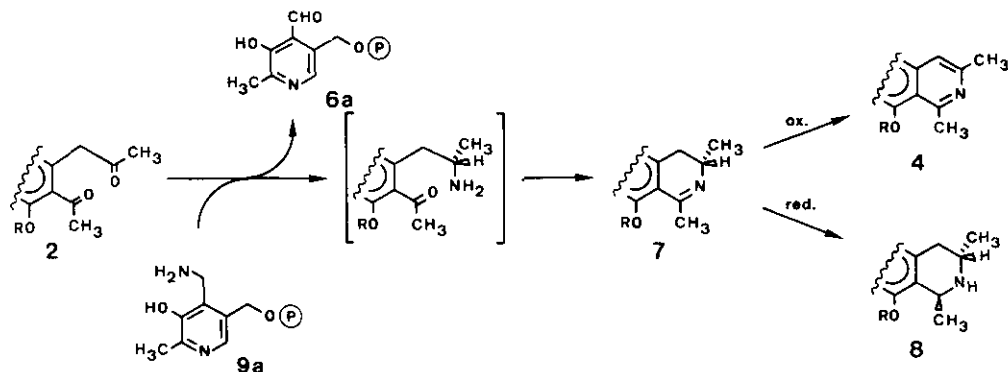
In the vast family of natural products bearing an isoquinoline system², the naphthylisoquinoline alkaloids³ like 5, isolated from tropical lianas, structurally, and thus biogenetically, occupy an outstanding position. We have recently reported the first total synthesis of a naphthylisoquinoline alkaloid (Scheme 1) by successive cyclization of labile β -polycarbonyl chains 1, via 2, optionally to naphthalene 3 and isoquinoline 4⁴⁻⁷, subsequent pre-fixation of these molecular moieties by an auxiliary bridge, and intramolecular coupling⁸ to 5:



Scheme 1

This biomimetic type synthesis leads to aromatic isoquinolines like 4, exclusively, which can be reduced with efforts to the corresponding tetrahydroisoquinolines (e.g. with Zn/HCl)⁸ - especially

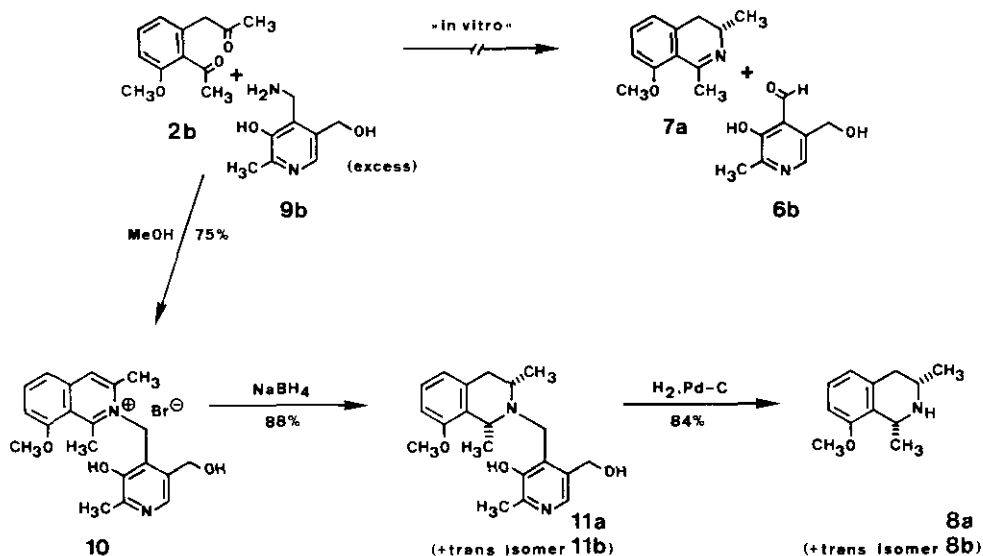
tedious when working on a large scale. Also for the biosynthetic formation, a reduction of the stable isoquinoline 4 to the corresponding di- and tetrahydroisoquinolines (which occur in the plants predominantly) seems quite improbable. Biochemically more plausible than the use of the toxin ammonia to build up 4, would be a directly reducing nitrogen incorporation into 2 in the sense of a reductive amination, e.g. with pyridoxamine phosphate (9a)^{3b}.



Scheme 2

The dihydroisoquinoline 7 thus primarily formed⁹ would then also chemically be a reasonable basis for subsequent oxidative or reductive transformations - a biosynthetic conception worth imitating in vitro.

Our condensation of 2b with pyridoxamine (9b) at different pH-values, however, does not even give traces of the desired product pair dihydroisoquinoline 7a / pyridoxal (6b) (see Scheme 3). Instead, the

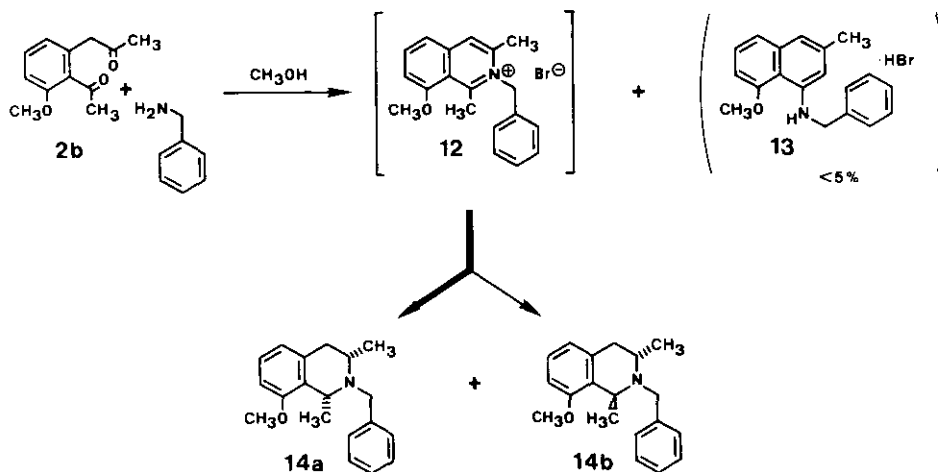


Scheme 3

isoquinolinium salt 10¹⁰ is found to be formed in a good yield (75 %; mp 220° C, dec. M⁺ not registered by EI or FD-MS; analyzes for C₂₀H₂₄N₂O₃Cl · H₂O). It is interesting to note that not even the less bulky N-benzyl substituent can be introduced alternatively by N-alkylation of the preformed isoquinoline 4¹¹, apparently due to the steric shielding of the nitrogen by the two coplanar methyl groups at C-1 and C-3.

Activated by its positive charge, this isoquinolinium salt 10 now very easily can be reduced, using e.g. NaBH₄ (*cis* / *trans* ratio of racemic diastereomers¹² = 85 : 15). This very mild overall incorporation of the "B₆-nitrogen" into the heterocyclic molecular moieties of *Triphyophyllum* alkaloids is then completed by the hydrogenolytic cleavage of crude 11 to the free tetrahydroisoquinolines 8a¹⁰ (mp of hydrobromide, 235° C) and 8b¹⁰ (mp of hydrobromide, 275-278° C). These two diastereomers (separation on silica gel, ether / methanol = 95 : 5), which are both needed for naphthylisoquinoline alkaloid syntheses¹³ prove to be identical in all respects with material previously⁸ synthesized by tedious Zn/HCl reduction of the corresponding isoquinoline 4.

The pyridoxyl residue, which here anyhow does not biomimetically display its expected tautomerizing activity, can consequently be replaced by the chromatographically and chemically less demanding benzyl group itself (see Scheme 4):



Scheme 4

Thus, reaction of 2b, now with benzylamine as a cheaper nitrogen source, followed by *in situ* reduction with NaBH₄ of the resulting isoquinolinium salt 12 (which does not need to be isolated), gives directly the tetrahydroisoquinolines 14a¹⁰ (mp of hydroperchlorate, 199-200° C) and 14b¹⁰ (mp of hydroperchlorate, 192-193° C), identical with material obtained by N-benylation of 8a, resp. 8b, (PhCH₂Br, K₂CO₃, n-propanol, reflux). The formation of the aminonaphthalene 13¹⁰ (mp of hydrobromide, 216-218° C) by an undesired carbocyclic ring closure - the main reaction (75 %) with benzylamine itself - is largely suppressed (yield 3.5 %) when using its hydrobromide. The *cis*-diastereoselectivity, obtained with NaBH₄ (14a / 14b = 78 : 22), is enhanced by reduction of 12 with NaCNBH₃ (14a / 14b = 82 : 18).

As the benzyl residue has been shown to be an appropriate protective group for the mixed aryl coupling to naphthyl isoquinolines⁸, 14 can directly be used as such for alkaloid syntheses, thus furthermore saving the two reaction steps of hydrogenation and N-protection.

Combined with the good availability of the diketo precursors 2 (biomimetically in most cases only one step!⁴⁻⁶), this short and efficient access to 1,3-dimethyltetrahydroisoquinolines 8 allows the preparation of a high scale substance base for rational, biosynthetically orientated total syntheses of acetogenin isoquinoline alkaloids.

ACKNOWLEDGEMENTS

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9. A similar reductive amination of an aliphatic diketo precursor to the monocyclic imine γ -coniine has been proposed in the biosynthesis of the hemlock toxin coniine: E. Leete, Accounts Chem. Res., 4, 100 (1971); M.F. Roberts, Phytochemistry, 10, 3057 (1971); ibid., 16, 1381 (1977).
10. All new compounds have been fully characterized by spectroscopic and analytic methods. Details will be reported in a full paper.
11. Thus, reaction of 8-methoxy-1,3-dimethylisoquinoline (4a, but OCH₃ instead of OH), with benzyl bromide (K₂CO₃ in acetone, n-propanol, or N,N-dimethylformamide) yields an isoquinolinium salt 12 in trace amounts (< 5 %), only.
12. All synthetic compounds are racemic. The drawn configuration denotes the relative stereochemistry.
13. The selective conversion of cis to trans configured tetrahydroisoquinolines is under investigation: G. Bringmann and J.R. Jansen, unpublished results.

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