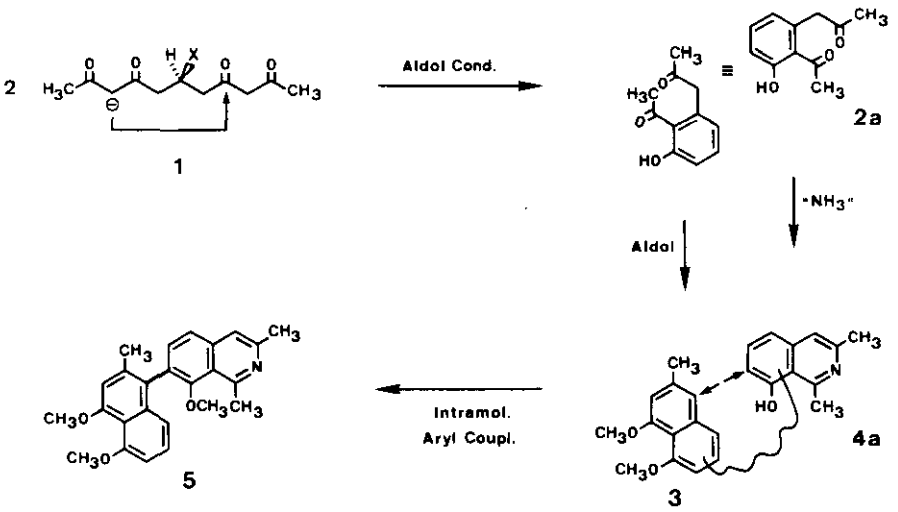
ONE POT PREPARATION OF 1,3-DIMETHYLTETRAHYDROISOQUINOLINES FROM THEIR BIOSYNTHETIC DIKETO PRECURSORS[1]

Gerhard Bringmann* and Johannes R. Jansen

Organisch-Chemisches Institut der Universität Münster,
Orléansring 23, D-4400 Münster, West Germany

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.

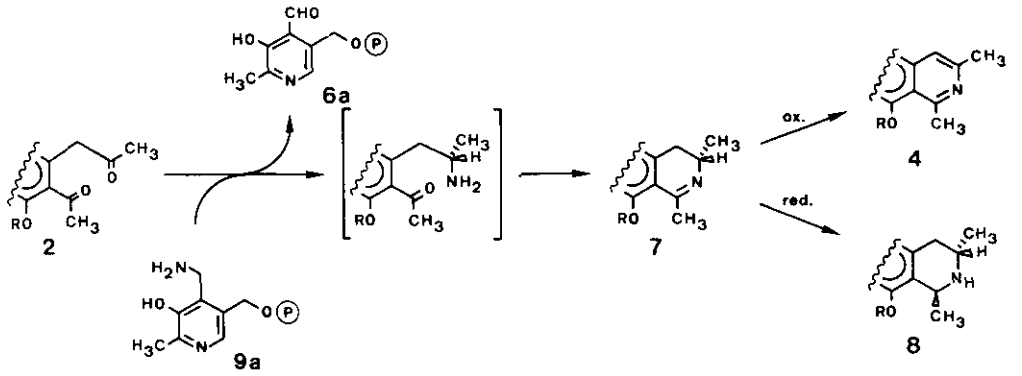
In the vast family of natural products bearing an isoquinoline system[2], the naphthylisoquinoline alkaloids[3] like 5, isolated from tropical lianas, structurally, and thus biogenetically, occupy an outstanding position. We have recently reported the first total synthesis of a naphthylisoquinoline alkaloid (Scheme 1) by successive cyclization of labile ß-polycarbonyl chains 1, via 2, optionally to naphthalene 3 and isoquinoline 4[4-7], subsequent pre-fixation of these molecular moieties by an auxiliary bridge, and intramolecular coupling[8] 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

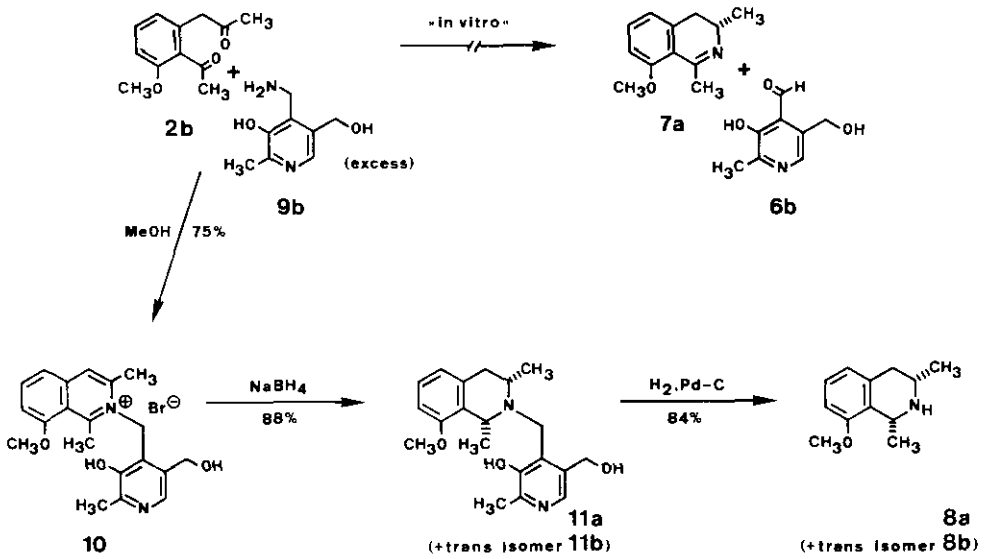
tedious when working on a large scale. Also for the biosynthetic formation, a reduction of the stable isoquinoline 4 to the corresponding di- and tetrahydroisoquinolines (which occur in the plants predominantly) seems quite improbable. Biochemically more plausible than the use of the toxin ammonia to 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 formed[9] 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

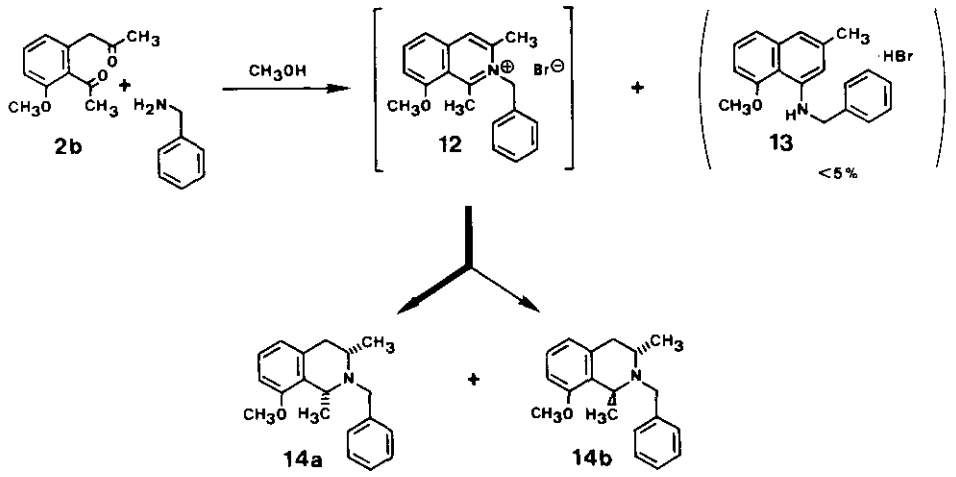


Scheme 3

isoquinolinium salt *10*[10] is found to be formed in a good yield (75 %; mp 220° C, dec. $M^{\oplus}$ not registrated by EI or FD-MS; analyzes for $C_{20}H_{24}N_2O_3Cl \cdot H_2O$). 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 *4*[11], 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. $NaBH_4$ (cis / trans ratio of racemic diastereomers[12] = 85 : 15). This very mild overall incorporation of the "B_6-nitrogen" into the heterocyclic molecular moieties of Triphyophyllum alkaloids is then completed by the hydrogenolytic cleavage of crude *11* to the free tetrahydroisoquinolines *8a*[10] (mp of hydrobromide, 235° C) and *8b*[10] (mp of hydrobromide, 276-278° C). These two diastereomers (separation on silica gel, ether / methanol = 95 : 5), which are both needed for naphthylisoquinoline alkaloid syntheses[13] prove to be *identical in all respects with material previously*[8] *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 $NaBH_4$ of the resulting isoquinolinium salt *12* (which does not need to be isolated), gives directly the tetrahydroisoquinolines *14a*[10] (mp of hydroperchlorate, 199-200° C) and *14b*[10] (mp of hydroperchlorate, 192-193° C), identical with material obtained by N-benzylation of *8a*, resp. *8b*, ($PhCH_2Br$, K_2CO_3, n-propanol, reflux). The formation of the aminonaphthalene *13*[10] (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 $NaBH_4$ (*14a* / *14b* = 78 : 22), is enhanced by reduction of *12* with $NaCNBH_3$ (*14a* / *14b* = 82 : 18).

As the benzyl residue has been shown to be an appropriate protective group for the mixed aryl coupling to naphthyl isoquinolines[8], *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 6 allows the preparation of a high scale substance base for rational, biosynthetically orientated total syntheses of acetogenin isoquinoline alkaloids.

ACKNOWLEDGEMENTS

We are grateful to the Deutsche Forschungsgemeinschaft (DFG) for the financial support of this work, and to Mrs. M. Hülsbusch for technical assistance.

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9. A similar reductive amination of an aliphatic diketo precursor to the monocyclic imine γ-coniceine 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 OCH_3 instead of OH), with benzyl bromide (K_2CO_3 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 configurated tetrahydroisoquinolines is under investigation: G. Bringmann and J.R. Jansen, unpublished results.

Received, 13th May, 1986