FIRST TOTAL SYNTHESIS OF KORUPENSAMINES A AND B[1]

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Dedicated to Professor Arnold Brossi, on the occasion of his 70th birthday

Abstract - The first total synthesis of korupensamines A (**1a**) and B (**1b**), highly polar naphthylisoquinoline alkaloids and, simultaneously, 'monomeric building blocks' of the michellamines, is described. Key step is the Pd[II] catalyzed intermolecular biaryl coupling of the two appropriately protected naphthalene and isoquinoline moieties (**10**) and (**11**), with the coupling positions activated by bromine and trialkylstannane substituents respectively.

Korupensamines A (**1a**) and B (**1b**) constitute interesting novel naphthylisoquinoline alkaloids from the rare tropical liana *Ancistrocladus korupensis*.[2] These naturally occurring biaryls are remarkable with respect to their high polarity, due to the presence of three phenolic hydroxyl groups and the secondary amino function, and the unusual 5,8'-coupling type,[3] which has heretofore very rarely been found, *e.g.* in ancistrobrevine B[4] (**2**). The korupensamines represent the monomeric 'halves' of dimeric naphthylisoquinoline alkaloids, such as michellamine B (**3**), unique naturally occurring quateraryls with promising anticytopathic properties against HIV-1 and 2.[5-8] Although the monomeric *naphthylisoquinolines (1) do not exhibit antiviral activities, they show promising antimalarial* properties against *Plasmodium falciparum*.[2] Because of this interesting biological activity and as a possible starting material for a first, hitherto not yet achieved total synthesis of the challenging structures of the michellamines, the elaboration of a synthetic access to **1** is a rewarding goal. In this paper, we report

the convergent first total synthesis of korupensamines A and B by intermolecular aryl coupling of the corresponding iso- and heterocyclic precursors.
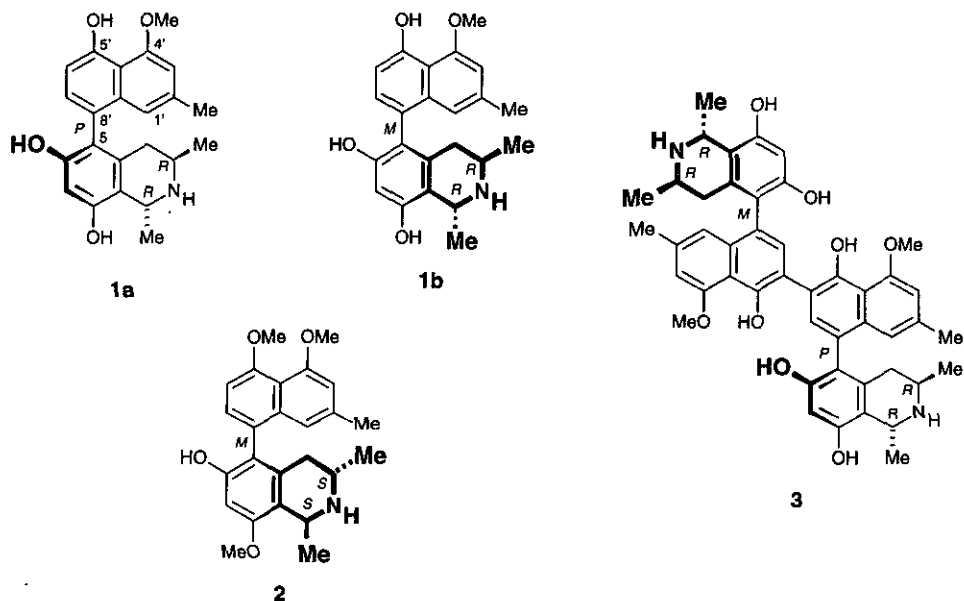
Characteristic structural demands for the synthesis of the korupensamines are not only the high degree of free OH and NH functions and thus the need for appropriate protective groups, but also the unusual position of the biaryl axis: in contrast to the various related alkaloids previously prepared in our laboratory,[9-11] the monomeric naphthylisoquinoline (1) with its 5,8'-coupling type does not have a C_1 sidechain in an *ortho*-position next to the axis. Consequently, our efficient 'lactone methodology'[9] was not applicable to this target biaryl, so that we envisaged an *inter*molecular coupling strategy for the construction of the axis. As a precursor to the isocyclic moiety of the korupensamines, with the free hydroxy function specifically only at C-5' and the methyl ether at C-4', we chose the naphthalene building block (7), with an *O*-isopropyl substituent as a protective group and the bromo substituent at the scheduled coupling position. Its synthesis, which is closely related to the preparation of related dimethoxy analogs,[12] is outlined in Scheme 1.

The synthesis starts with 4 (pale yellow oil),[14] prepared by *O*-isopropylation (*i*PrBr, acetone, 88 %) and subsequent bromination (Br$_2$, NaOAc, CH$_2$Cl$_2$, 62 %) of 3-hydroxybenzaldehyde. For the annulation of the second ring, the introduction of the missing C_4-unit by a Wittig reaction proved to give higher yields than the Stobbe approach frequently used in the literature.[12] With the known[15] building block (5) we obtained, after selective cleavage of the *tert*-butyl ester group with CF$_3$CO$_2$H, the α,β-unsaturated monoester (6) (mp 86 °C),[14] which was cyclized, *O*-deacetylated, and

O-methylated. Transformation of the ester functionality into the required methyl substituent was brought about by LAH-reduction and subsequent deoxygenation of the primary hydroxyl group by hydroxy/halogen exchange[9,13] and further reduction to give **7** (mp 78 °C).[14]
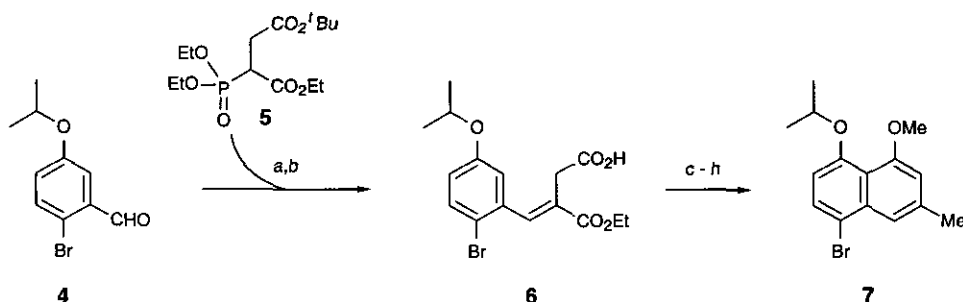
Scheme 1: Preparation of the naphthalene building block **7**. Reaction conditions: a) NaH, THF, 24 h, 0 °C to room temperature, 61 %; b) CF_3CO_2H/H_2O, 10 h, room temperature, 94 %; c) Ac_2O, 14 h, reflux; d) EtOH/EtONa, THF, 4 h, 89 % from **6**; e) Me_2SO_4, acetone, K_2CO_3, reflux, 15 h, 97 %; f) $LiAlH_4$, THF, 1 h, 0 °C, 93 %; g) $(BrCCl_2)_2/PPh_3$,[13] CH_2Cl_2, 30 min, room temperature, 93 %; h) $LiAlH_4$, THF, 2 h, 0 °C, 95 %.

As a precursor for the heterocyclic moiety of our target molecules, we chose the tetrahydroisoquinoline (**10**), *i.e.* with benzyl groups for the protection of both *N*- and *O*-functionalities, and again a bromine substituent at the site of the scheduled biaryl coupling. For its preparation, we could start from the correctly 1*R*,3*R*-configurated tetrahydroisoquinoline (**9**), the directed synthesis of which from the arylpropanone (**8**) had already been described.[16] Thus, whereas *O*-demethylation of **9** and subsequent double benzylation turned out to be very tedious, better results could be obtained by a stepwise *O*-benzylation / *O*-demethylation / *O*-benzylation sequence, followed by a regioselective bromination in the 5-position of the tetrahydroisoquinoline, to give **10** (characterized as its HCl salt: mp 130°C, $[\alpha]_D^{20}$ +36°, c = 0.49 in ethanol).[14]
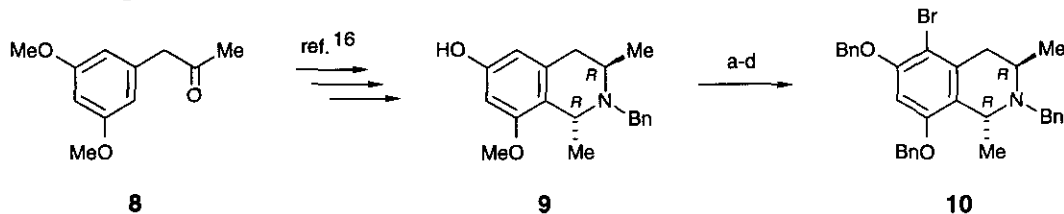
Scheme 2: Preparation of the isoquinoline building block (**10**). Reaction conditions: a) BnBr, 2N NaOH, CH_2Cl_2, $^nBu_3NBnCl$, 5 h, room temperature; b) ^iPrSNa, DMF, 150 °C, 5 h, 44 % from **9**; c) BnBr, 2N NaOH, CH_2Cl_2, $^nBu_3NBnCl$, 2 h, room temperature, 91 %; d) Br_2, DMF, 3 d, room temperature, 94 %.

For the activation of the coupling sites such as halogen or *O*-triflate leaving groups on the electrophilic partner and boronic acid or trialkylstannyl groups on the nucleophilic partner, the use of a

brominated isoquinoline (**10**) and a stannylated naphthalene (**11**) turned out to be the combination of choice. Initially tested with 4-bromoorcinol dimethyl ether (62 %) as a model for the isoquinoline part, also the bis-*O*-methylated analog of **10** (61 %), the respective dibenzyl derivative (**10**) itself (15 %) could likewise be coupled in satisfactory yields, giving the two atropodiastereomers (**12a/12b**),[14] the first synthetic 5,8'-coupled naphthylisoquinolines, in a 1.4:1 ratio. As both diastereomeric target molecules (**1a**) and (**1b**) occur in nature and will both be needed with respect to a later directed synthesis of michellamine B (**3**), this initial poor stereoselectivity was not further optimized at this point. Because of the very similar chromatographic properties of **12a** and **12b**, and the facile diastereomeric separation of **1a** and **1b** described in the literature,[2] **12a** and **12b** were not resolved, but immediately deprotected by treatment with BCl_3 to cleave the ether functions, and subsequent catalytic hydrogenation to set free the amino group, giving a mixture of **1a** and **1b**. Final atropodiastereomer separation was performed by hplc on an amino-bonded phase column, as published earlier.[2]
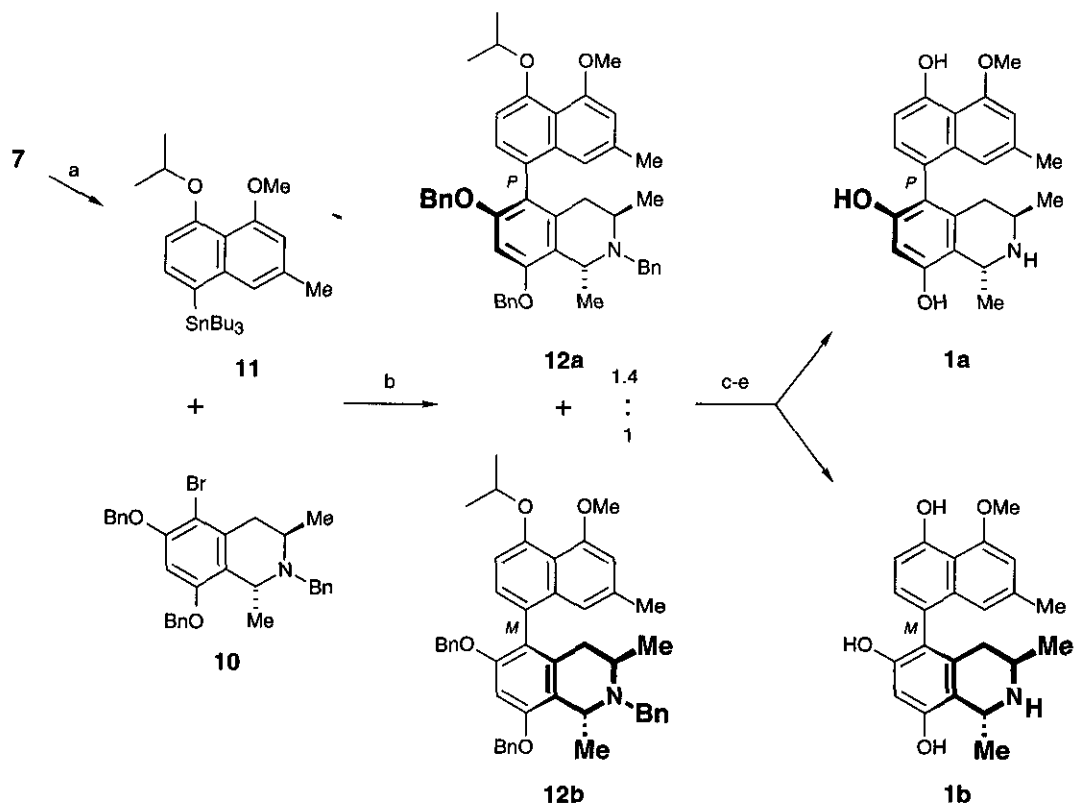
Scheme 3: Convergent construction of the alkaloids. Reaction conditions: a) ^{t}BuLi, Bu_3SnCl, THF, 2 h, -78 °C to room temperature, 89 % b) $PdCl_2$ $(PPh_3)_2$, PPh_3, LiCl, Cu(I)Br, DMF, 40 h, 135 °C, 15 %; c) BCl_3, CH_2Cl_2, 10 min, room temperature; d) H_2, Pd/C, MeOH; e) atropodiastereomer separation according to ref.[2]

By this way, the two atropodiastereomeric natural products (1a) and (1b) could be obtained in pure form. They proved to be fully identical with authentic samples kindly provided by Dr. M. Boyd, National Cancer Institute, Frederick, Maryland, USA, with respect to physical, chiroptical, spectroscopic, and chromatographic data, thus also unambiguously confirming the structure of these alkaloids as established recently.[2]

This first total synthesis of korupensamines A and B is of great importance not only because it constitutes the first preparative access to 5,8'-coupled naphthylisoquinolines and, at the same time, to the most polar representatives of this class of natural products ever synthesized, but also with respect to a scheduled first total synthesis of their dimeric analogs, the michellamines, which is in progress.

ACKNOWLEDGEMENTS

REFERENCES AND NOTES

1. "Acetogenic Isoquinoline Alkaloids", part 66; for part 65, see ref.[2]
2. Y.F. Hallock, K.P. Manfredi, J.W. Blunt, J.H. Cardellina, II, M. Schäffer, K.-P. Gulden, G. Bringmann, A.Y. Lee, J. Clardy, G. François, and M. Boyd, *J. Org. Chem.*, 1994, in press.
3. For an easier comparison of naphthylisoquinoline alkaloids of different coupling types, the naphthalene part is (contrary to the IUPAC rules) numbered such that it is always attributed a 2-methyl-4,5-dioxy substitution pattern, independent of the site of the axis.
4. G. Bringmann, R. Zagst, H. Reuscher, and L. Aké Assi, *Phytochemistry*, 1992, **31**, 4011.
5. K.P. Manfredi, J.W. Blunt, J.H. Cardellina, II, J.B. McMahon, L.L. Pannell, G.M. Cragg, and M.R. Boyd, *J. Med. Chem.*, 1991, **34**, 3402.
6. G. Bringmann, R. Zagst, M. Schäffer, Y.F. Hallock, J.H. Cardellina II, and M.R. Boyd, *Angew. Chem.*, 1993, **105**, 1242; *Angew. Chem. Int. Ed. Engl.*, 1993, **32**, 1190.
7. G. Bringmann, K.-P. Gulden, Y.F. Hallock, K.P. Manfredi, J.H. Cardellina II, M.R. Boyd, J. Fleischhauer, and B. Kramer, *Tetrahedron*, 1994, **50**, 7087.
8. M.R. Boyd, Y.F. Hallock, J.H. Cardellina, II, K.P. Manfredi, J.W. Blunt, J.B. McMahon, R.W. Buckheit, Jr, G. Bringmann, M. Schäffer, G.M. Cragg, D.W. Thomas, and J.G. Jato, *J. Med. Chem.*, 1994, **37**, 1740.

9. G. Bringmann, J.R. Jansen, and H.-P. Rink, *Angew. Chem.*, 1986, **98**, 917; *Angew. Chem. Int. Ed. Engl.*, 1986, **25**, 913.

10. G. Bringmann and H. Reuscher, *Angew. Chem.*, 1989, **101**, 1725; *Angew. Chem. Int. Ed. Engl.*, 1989, **28**, 1672.

11. G. Bringmann and J.R. Jansen, *Synthesis*, 1991, 825.

12. B.O. Handford and W. B. Whalley, *J. Chem. Soc.*, 1963, 3896.

13. G. Bringmann and S. Schneider, *Synthesis*, 1983, 139.

14. All new compounds gave satisfactory spectroscopic and analytic data.

15. W.M. Owton, P.T. Gallagher, and A. Juan-Montesinos, *Synthetic Commun.*, 1993, **23**, 2119, and lit. cited therein.

16. G. Bringmann, R. Weirich, H. Reuscher, J.R. Jansen, L. Kinzinger, and T. Ortmann, *Liebigs Ann. Chem.*, 1993, 877.