Tetrahedron Letters Vol.30,No.39,pp 5249-5252,1989 0040-4039/89 $3.00 + .00
Printed in Great Britain Pergamon Press plc

ARYL-COUPLING *VIA* "AXIALLY PROSTEREOGENIC" LACTONES: FIRST TOTAL SYNTHESIS OF (+)-ANCISTROCLADISINE AND (OPTIONALLY) ITS ATROPISOMER[1]

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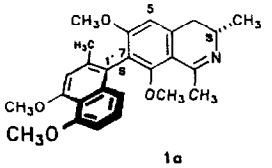
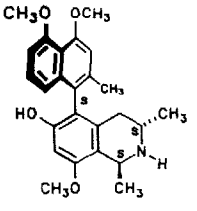
Abstract: The first total synthesis of the liana alkaloid ancistrocladisine (**1a**) and of its novel atropisomer **1b** is reported. The required mixed aryl coupling is brought about, regiospecifically, by prefixation of the two molecular moieties by an ester-type auxiliary bridge. A methodology is described for the recycling of the undesired, configurationally stable atropisomer **9b**, *via* the "axially prostereogenic" lactone **8** - chiral economy with respect to rotational isomerism.

(+)-Ancistrocladisine (**1a**), isolated from the roots of the Indian liana *Ancistrocladus heyneanus*[2], belongs to the increasing group of the structurally remarkable naphthyl isoquinoline alkaloids[3-5]. Its substitution pattern, as well as in *vitro* model reactions[6], suggest a biosynthetic origin from acetate units, rather than from the amino acid pool. Nothing, however, is known about its biological activities. For a thorough pharmacological investigation, the chemical preparation of stereochemically homogeneous ancistrocladisine (**1a**) - independent from delicate plant material - would be desirable. In this paper, we describe the first[7,8] total synthesis of (+)-ancistrocladisine (**1a**), and, optionally, its atropoisomer **1b**.



1a



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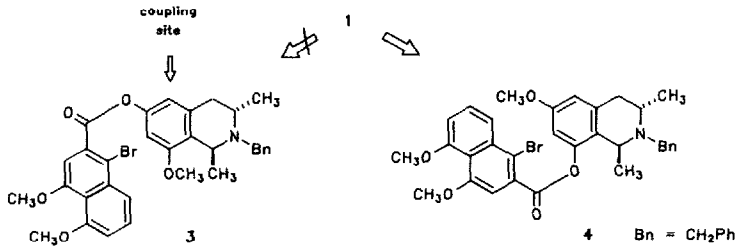
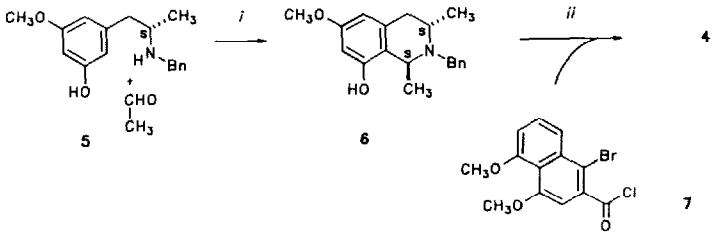
The most conspicuous structural feature of **1a** is the configurationally stable 7-1'-biphenyl axis between the isoquinoline moiety and the naphthalene part. We have recently reported a novel aryl coupling methodology, by pre-fixation of the two aromatic halves *via* an ether- or an ester-type bridge, followed by *intra*molecular coupling, and subsequent reductive ring opening. This procedure allowed a first synthetic access to naphthyl isoquinoline alkaloids, *e.g.* to ancistrocladine (**2**), its atropisomer hamatine, and others[4,5,9-11].

The isoquinoline-6-naphthoate **3**, however, was found not to be an appropriate precursor to **1a**, since it couples in the 5-position of the isoquinoline, practically exclusively - a reaction that could be exploited in the regioselective synthesis of ancistrocladine (**2**)[11]. Consequently, to achieve regiocontrol in favour of a 7-coupling, as required for a synthesis of **1a**, the naphthalene moiety had to be prefixed *via* the 8-oxygen function of the isoquinoline, as in **4**.

Scheme 1.



A synthesis of **4**, as presented in Scheme 2, necessitates the preparation of the tetrahydroisoquinoline **6**, with the free phenolic 8-oxygen function. This could be achieved by a regio- and stereocontrolled *Pictet-Spengler* condensation of **5**[12] with acetaldehyde at pH 4, giving **6**[13] (mp 156-158°C; $[\alpha]_D^{25}$ -79.3, c = 1.19, MeOH) as the main product[14], which is esterified with the naphthoyl chloride **7**[11], to give the ester **4**[13] (amorphous; $[\alpha]_D^{25}$ -19.3, c = 0.54, $CHCl_3$), with the desired prefixation of the two aromatic moieties.

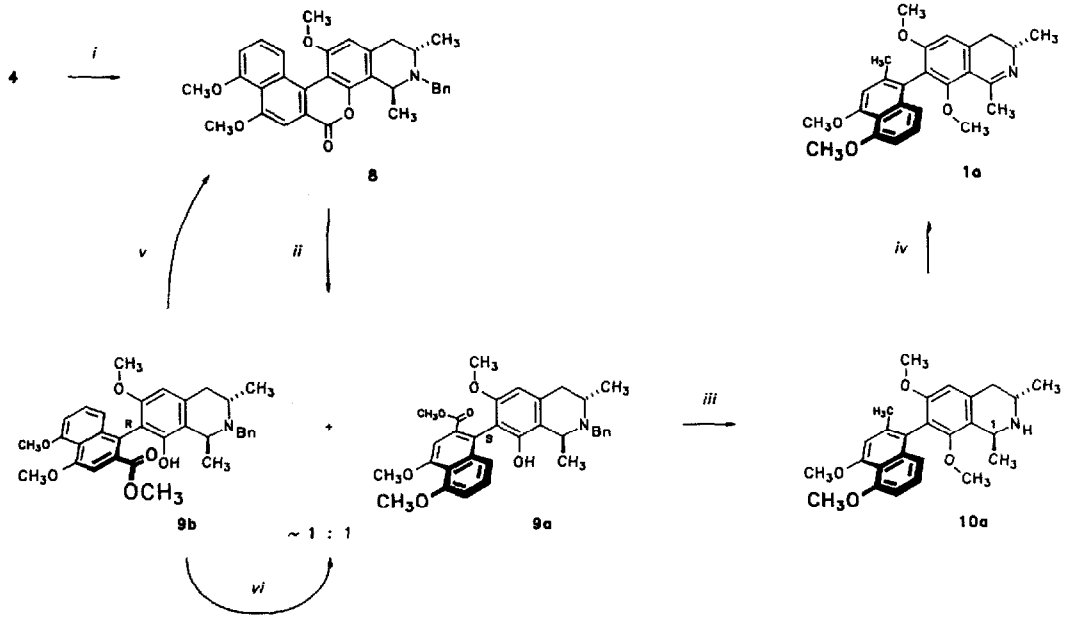


Scheme 2. Reagents and conditions: (*i*) CH_3CHO, *i*-C_3H_7OH/H_2O 1:2.5, pH 4; 45 %. (*ii*) NEt_3, DMAP, CH_2Cl_2; 96 %.

The intramolecular aryl coupling of **4** could be brought about by Pd-catalysis, to give the required lactone **8**[13] in a high yield (mp 131-135°C; $[\alpha]_D^{25}$ -51.1, c = 0.16, $CHCl_3$). With respect to stereochemistry, this cyclic biaryl **8** significantly differs from the corresponding ancistrocladine-type precursor (the coupling product from **3**), as obtained earlier[11]. In both cases, the auxiliary bridge dramatically lowers the rotational barrier at the axis, compared with the ring opened target biaryl. Whereas, however, the ancistrocladine precursor is still split up into helicene-like distorted stereoisomers[11], the less hindered ancistrocladisine precursor **8** presents itself, chromatographically and spectroscopically (*e.g.* by NMR) as but *one single species*, due to the fast fluctuating torsion around the flattened biphenyl linkage. It is thus not (yet) split up into detectable atropisomers, it is, as we proposed[5], "*axially prochiral*", or better "*axially prostereogenic*".

Assisted by the ring strain, **8** can, however, smoothly be ring opened, *e.g.* with methanol, to give the configurationally stable, *axially stereogenic* methylesters **9a**[13] (amorphous; $[\alpha]_D^{25}$ -18.9, c = 0.34, $CHCl_3$) and **9b**[13] (amorphous; $[\alpha]_D^{25}$ -49.4, c = 0.33, $CHCl_3$), with a slight excess in favour of the required stereoisomer **9a**. Unlike the final target molecule **1a**, the precursor **9a** can be separated quite conveniently from its atropoisomer **9b** (silica gel, modified with 10% conc. ammonia; elution with CH_2Cl_2/Et_2O = 99.8:0.2 ➔ 95:5).

For the subsequent transformation into ancistrocladisine (**1a**) (see below), the undesired ester **9b**, with the "wrong" configuration at the biaryl linkage, is not at all lost. It can be reutilized, by re-cyclization to the planarized, axially prostereogenic lactone **8** (Scheme 3a, *v*), and renewed, subsequent ring opening. Still more rationally, without isolation of a lactone-type intermediate, **9b** can be epimerized *directly* in MeOH/NaOMe (Scheme 3a, *vi*), to provide the thermodynamically controlled equilibrium mixture **9a/b**, again. Thus, in



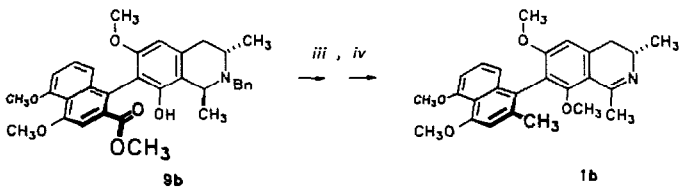
Scheme 3a. Reagents and conditions: (*i*) $Pd(PPh_3)_2Cl_2$, NaOAc, DMA, 130°C; 87 %. (*ii*) MeOH/NaOMe, 5 min; 85 %. (*iii*) 1) LAH, THF; 2) $(CH_3)_2SO_4$, PTC, CH_2Cl_2, 2N NaOH; 3) $C_2Br_2Cl_4$, PPh_3, CH_2Cl_2[15]; 4) LAH, THF; 5) H_2/Pd-C (10%), MeOH; 68 %. (*iv*) $KMnO_4$, THF; 14 % (46 % of **10a** reisolated). (*v*) 1) 2N NaOH, dioxan; 2) $(COCl)_2$, DMF, CH_2Cl_2, NEt_3; (71%). (*vi*) MeOH/NaOMe; 86%.

principle, the whole precious synthetic material can be converted into the desired rotational isomer **9a** (or, optionally, into **9b**) - chiral economy with respect to rotational isomerism[10].

9a can then be transformed, with complete retention of its configuration at the biphenyl axis, into the 1,2-dihydro-*ancistrocladisine* **10a**[13] (*mp 263-266°C, dec.*; $[\alpha]_D^{25}$ +49.7, *c* = 1.44, $CHCl_3$), using a reaction sequence established earlier[4,5,11].

The final step, the simple oxidation of **10a** to give **1a**, proved to be unexpectedly difficult with practically all standard procedures, problems obviously arising from the required, stereoelectronically most unfavourable abstraction of the equatorial[16] hydrogen at C-1. Nonetheless, the reaction finally succeeded by permanganate oxidation in THF, to yield optically active ancistrocladisine (**1a**) (mp 178°C; Lit.[2a] mp 178-180°C; $[\alpha]_D^{25}$ +7.8, c = 0.53, $CHCl_3$; **1a**·HCl: $[\alpha]_D^{25}$ -20.5, c = 0.50, $CHCl_3$; Lit.[2a] -16.13). Its identity was furthermore confirmed by comparison with authentic material from *A. heyneanus*[17].

Optionally, again starting from lactone **8**, also the novel 7-*epi*-ancistrocladisine (**1b**)[13] (mp 221-224°C; $[\alpha]_D^{25}$



Scheme 3b. Reagents and conditions as in Scheme 3a.

-36.8, c = 0.36, $CHCl_3$) can be prepared, by applying the same strategy to the atropisomeric ester **9b** (see Scheme 3b).

In summary, benzocoumarin-type lactones have proved to be most useful intermediates in the directed synthesis of stereochemically homogeneous biaryls. Besides favourable assistance in the intramolecular aryl coupling step (reliable *ortho*-regioselectivity and good coupling yields), the ester-type bridge allows the application of recycling techniques for undesired atropoisomers - by re-cyclization to flattened, "axially prostereogenic" biaryls like **8**, and renewed ring opening.

ACKNOWLEDGEMENTS

Financial support of this work by the Deutsche Forschungsgemeinschaft (DFG) and by the Fonds der Chemischen Industrie is gratefully acknowledged. We are indebted to Ms. L. Kinzinger for her skillful assistance in the laboratory, and to J.R. Jansen, M. Rübenacker and A. Hille for fruitful discussions.

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7. This synthesis was reported on International Conferences, *e.g.* in Heidelberg/FRG (IUPAC Conference on Heterocyclic Chemistry, August 1987), in Bürgenstock/Switzerland (Euchem Conference on Stereochemistry, May 1988), and in Angers/France (Conference on Medicinal Plants, June 1988), and additionally published as a symposia-in-print, see ref. 5.
8. Very recently, M. Rizzacasa and M.V. Sargent (*J. Chem. Soc., Chem. Commun.*, **1989**, 301) published an essentially linear synthesis of a *mixture of all 4 possible stereoisomers of ancistrocladisine*, which, since it evidently could not be resolved, was characterized by dehydrogenation to the (non-natural) fully aromatic, racemic didehydro-ancistrocladisine.
9. G. Bringmann, J.R. Jansen, *Tetrahedron Lett.*, 1984, **25**, 2537.
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11. G. Bringmann, J.R. Jansen, H.-P. Rink, *Angew. Chem.*, 1986, **98**, 917; *Angew. Chem. Int. Ed. Engl.*, 1986, **25**, 913.
12. Obtained from 1-(3,5-dimethoxyphenyl)-propan-2-one, by reductive amination with (*S*)-1-phenylethylamine (see ref. 11), thiolate-induced selective *mono-O*-demethylation, hydrogenolytic cleavage, benzoylation, and subsequent LAH-reduction. Details will be reported in a full paper.
13. All new compounds were fully characterized by spectroscopic and analytic methods.
14. Details about the regio- and stereocontrol in this *Pictet-Spengler* reaction will be reported in a full paper.
15. G. Bringmann, S. Schneider, *Synthesis*, **1983**, 139.
16. Apparently, this conformational situation not only originates from the *peri*-type 8-methoxy substituent, which strictly urges the 1-methyl group into an axial position (thus leaving only the equatorial 1-position for the hydrogen), but also from an additional buttdressing assistance by the naphthalene substituent: the molecular moiety (**10a**, but H instead of the naphthalene residue) is oxidized far more easily than **10a**, itself. Work to overcome this stereoelectronic problem, by developping other oxidative procedures, and starting from sterically more favourable precursors, is in progress.
17. We are grateful to Profs. M.R. Almeida (Thane), T.R. Govindachari (Madras), and S.M. Ketkar (Pune), for providing us with authentic plant material of *A. heyneanus*.

(Received in Germany 7 July 1989)