CHIRAL ECONOMY WITH RESPECT TO ROTATIONAL ISOMERISM: RATIONAL SYNTHESIS OF HAMATINE AND (OPTIONALLY) ANCISTROCLADINE FROM JOINT HELICAL PRECURSORS[1,2]

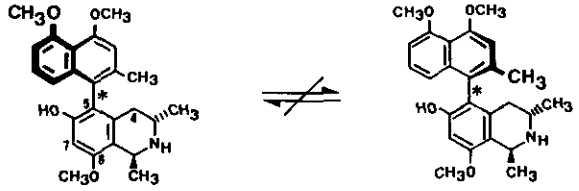
Gerhard Bringmann[a]* and Johannes R. Jansen[b]

a) Institut für Organische Chemie der Universität Würzburg
Am Hubland, D-8700 Würzburg, West Germany
b) Organisch-Chemisches Institut der Universität Münster
Orléansring 23, D-4400 Münster, West Germany

Dedicated to Professor Sir Derek H.R. Barton, on the occasion of his 70th birthday

Abstract - Unlike the target alkaloids **1a** and **1b**, which are configurationally stable at the biaryl linkage, the helicene-like distorted cyclic precursors **2** and **7** show dramatically lowered rotational thresholds: they equilibrate at room temperature, already. In contrast to the lactones **2a/b**, however, the cyclic ethers **7a** and **7b** interconvert slowly enough to be separated conveniently, on a preparative scale. Ring opening of the desired helimer (e.g. **7b**) and re-equilibration/re-separation of the rest allows the transformation of practically the whole synthetic material, optionally into **1b** or **1a** - practising "axially chiral economy".

Ancistrocladine[3] (**1a**) is the most widespread representative of the naphthylisoquinoline alkaloids - a remarkable group of meanwhile nearly 30 related, structurally intriguing compounds[4]. These interesting natural products are found in tropical lianas belonging to the plant families of the Ancistrocladaceae and the Dioncophyllaceae. Biomimetic syntheses of both molecular parts - the naphthalene *and* the isoquinoline moieties - from identical ß-polycarbonyl precursors strongly suggest an unprecedented biosynthesis from acetate units[5].



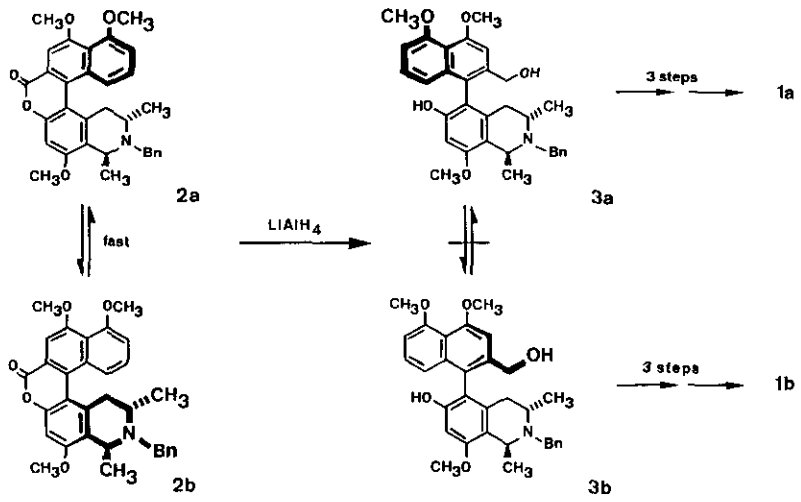
(-)-Ancistrocladine
1a

(+)-Hamatine
1b

Besides these biosynthetic aspects, the most evident structural feature of **1a** is its highly hindered biaryl linkage, which gives rise to rotational isomers that are configurationally

stable up to 200° C. Hamatine (**1b**), its natural[6] atropisomer, occurs, together with **1a**, *e.g.* in *Ancistrocladus tectorius* (Lour.) Merr.[7]. Though extracts of this South-East Asian medicinal plant are used to treat dysentery and malaria[8], and the crude alkaloid mixtures have been found to show inhibiting properties against Walker 256 tumor in rats[7], too little is known about the biological activities of the isolated pure alkaloids. For a thorough pharmacological investigation of these challenging natural products, independent from delicate and capricious plant material, our aim is to develop novel strategies for the rational synthesis of any desired atropisomer of such axially chiral natural products.

We have recently reported the first total synthesis of (-)-ancistrocladine (**1a**) and (+)-hamatine (**1b**)[9]. For the required regio- and stereoselective coupling to these four-fold *ortho*-substituted, constitutionally unsymmetrical biaryls **1**, we had to develop a novel strategy, namely the pre-fixation of the two aromatic moieties by the aid of an ester bridge, and subsequent *intra*-molecular aryl coupling to helicene-like[10] distorted lactones **2a** and **2b**:



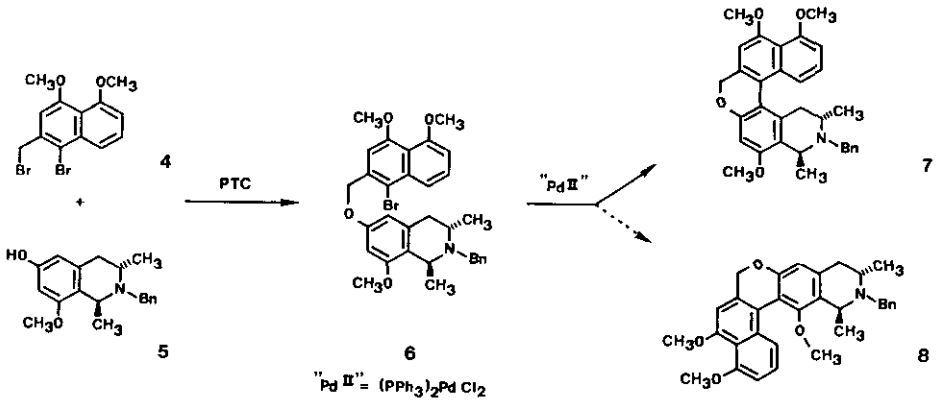
Scheme 1.

The atropisomer excess that can be obtained in this synthesis is dictated by the *thermodynamically controlled ratio of the two helimers* **2a** *and* **2b**, as they can be ring opened, with a "snapshot-like" retention of this ratio, leading to the alcohols **3a** (major) and **3b** (minor). As **3a** and **3b** are configurationally stable, this ratio can *not* be further upgraded in favour of the ancistrocladine precursor **3a**, and for a synthesis of hamatine (**1b**), this approach is not acceptable at all. Separation of the lactones **2a** and **2b**, already, is quite difficult and tedious, all the more as they helimerize very fast at room temperature ("half-life times" < 1 min, as estimated by 2-dimensional tlc)[11].

We hoped that an *ether-type* intermediate (like **7**) might epimerize more slowly - due to a longer C-O bond, and due to the expected less planarizing character of such an sp^3-type bridge.

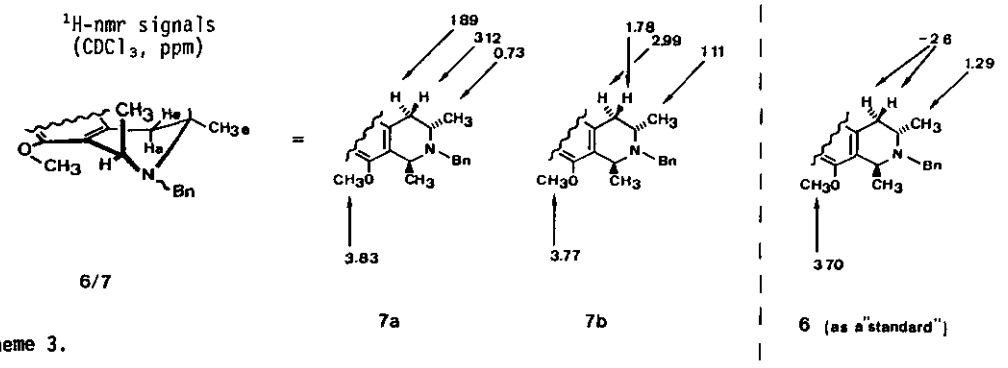
From **5** and **4**, which have previously been prepared in our laboratory[9,12], such an ether bridge is very effectively built up by phase transfer catalysis to give **6**[13] ("100 %"; mp of **6**·$2H_2O$

113-117° C; $[\alpha]_D^{20}$ -73.4°, c = 0.92, CH_2Cl_2). Palladium-catalyzed reaction (0.2 eq $Pd(PPh_3)_2Cl_2$, 5 eq NaOAc, N,N-dimethylacetamide [DMA][14], 130° C) gives essentially two[15] products (yield of pure isolated products, 61%), which slowly interconvert at room temperature (*e.g.* on 2-dimensional tlc), and consequently must be stereo- and not regioisomers.



Scheme 2.

Both products are described by the structure **7**, in its two helical forms, as the ^{1}H-nmr signal of the 8-methoxyl group shows "normal" values (see **Scheme 3**), and not a typical upfield shift that would have been expected for a 7-coupled product (such as **8**), thus demonstrating that the aryl coupling of the ether **6** is strikingly regioselective in favour of the 5-position of the isoquinoline nucleus, giving the ancistrocladine/hamatine-type regioisomer **7a/b**.

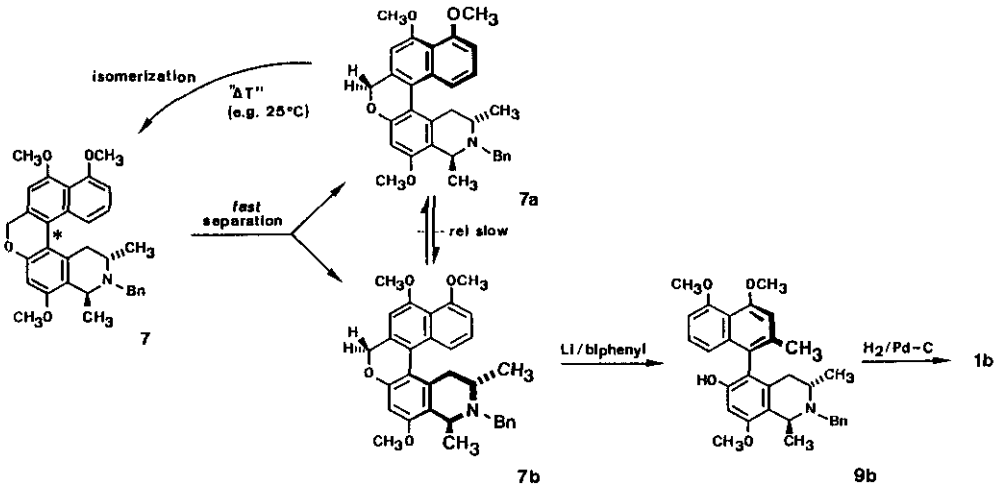


Scheme 3.

In contrast to the 8-methoxyl group, especially the protons at C-4 are strongly influenced by the anisotropic ring current effect that is exerted by the naphthalene substituent. The significant crosswise up- and downfield shifts of these diastereotopic axial and equatorial protons (see **Scheme 3**) allow to localize the relative position of the naphthalene, which is pressed vigorously against the chiral isoquinoline subunit. The major product (1.5 : 1.0) is found to be **7a**, with M-helicity (ancistrocladine type, see **Scheme 4**), and the minor stereoisomer is the P-helimer **7b** (hamatine type). This structural assignment is further confirmed unambiguously by the transformation of **7a** and **7b** into the known alkaloids **1a** and **1b** (see below).

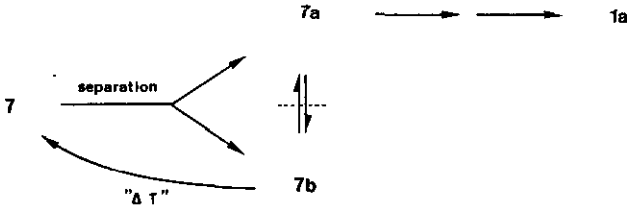
As anticipated, 7 isomerizes far more slowly (with "half-life times" of nearly 10 h) than the lactone 2. Moreover, 7 is also chemically more resistant than 2, which shows an enormous, strain-enhanced reactivity towards nucleophiles. Because of its sufficient chemical and conformational stability, 7 *can conveniently be resolved (silica gel, modified with 8 % conc.* ammonia; gradient elution with CH_2Cl_2/MeOH 500 : 0.1 → 500 : 1.0; crystallization from MeOH), to yield pure **7a**[13] (mp 160° C; $[\alpha]_D^{20}$ -307°, c = 0.46, CH_2Cl_2), and **7b**[13] (mp 125° C with subsequent crystal metamorphosis; final mp 160° C; $[\alpha]_D^{20}$ -40.8°, c = 0.46, CH_2Cl_2).

The reductive cleavage of dibenzopyrane-type ethers like **7a/b** is best achieved, following a procedure published by us earlier[12]. Thus, for a rational synthesis of hamatine (**1b**), pure **7b** is ring-opened with "dilithio biphenyl"[16] (THF, -35° C), with retention of its axial configuration, leading to N-benzylhamatine (**9b**)[13] (55 %, mp 109-110° C; $[\alpha]_D^{20}$ -134°, c = 1.01, CH_2Cl_2), which is easily debenzylated by catalytic hydrogenation, as described before[9], to give hamatine (**1b**), *identical in all respects with authentic material. The other, ancistro*cladine-type helimer **7a**, can be re-utilized, by equilibration in solution (*e.g.* at room temperature), and subsequent renewed resolution of the resulting mixture **7a/b** (see **Scheme 4**).



Scheme 4.

Vice versa, optionally also ancistrocladine (**1a**) can be prepared rationally, following this strategy, by ring opening of **7a** and subsequent re-epimerization of **7b**, as schematically sketched below (see **Scheme 5**):



Scheme 5.

In summary, ether- and ester-type auxiliary bridges accomplish manifold useful functions in the mixed aryl aryl coupling:

- due to the intramolecular character of the coupling, they allow good yields, also for severely hindered aromatics;
- they guarantee reliable *ortho*-type regioselectivity, sometimes even efficiently discriminating between two possible *ortho*-positions (*e.g.* **7** *vs.* **8**);
- and finally, they dramatically lower the isomerization threshold at the biphenyl axis, which can be exploited for rational, atropisomer-directed syntheses.

On the basis of this promising concept, the regio- and stereocontrolled total synthesis of further related natural products is in progress.

ACKNOWLEDGEMENTS

Financial support of this work by the Deutsche Forschungsgemeinschaft (DFG) and by the Fonds der Chemischen Industrie is gratefully acknowledged.

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Received, 25th August, 1988