CHIRAL ECONOMY WITH RESPECT TO ROTATIONAL ISOMERISM:
RATIONAL SYNTHESIS OF HAMETINE AND (OPTIONALLY) ANCISTROCLADINE FROM JOINT HELICAL PRECURSORS\textsuperscript{1, 2}

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

\textbf{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\textsuperscript{3} (1a) is the most widespread representative of the naphthylisoquinoline alkaloids - a remarkable group of meanwhile nearly 30 related, structurally intriguing compounds\textsuperscript{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 \( \text{D}-\text{polycarbonyl precursors} \) strongly suggest an unprecedented biosynthesis from acetate units\textsuperscript{5}.

\begin{align*}
\text{Ancistrocladine} & \quad \text{7b} \\
\text{Hametine} & 
\end{align*}

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 atropisomer, occurs, together with 1a, e.g. in Ancistrocladus tectorius (Lour.) Merr. Though extracts of this South-East Asian medicinal plant are used to treat dysentery and malaria, and the crude alkaloid mixtures have been found to show inhibiting properties against Walker 256 tumor in rats, 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). 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 distorted lactones 2a and 2b:

![Scheme 1](image)

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).

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 sp³-type bridge.

From 5 and 4, which have previously been prepared in our laboratory, such an ether bridge is very effectively built up by phase transfer catalysis to give 6 ("100 %"; mp of 6·2H₂O)
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113-117° C; [α]D²⁰ -73.4°, c = 0.92, CH₂Cl₂. Palladium-catalyzed reaction (0.2 eq Pd(PPh₃)₂Cl₂, 5 eq NaOAc, N,N-dimethylacetamide [DMA]¹⁴, 130° C) gives essentially two¹⁵ 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 ¹H-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 favor of the 5-position of the isoquinoline nucleus, giving the ancistrocladine/hamatine-type regioisomer 7α/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 7α, with M-helicity (ancistrocladine type, see Scheme 4), and the minor stereo-isomer is the P-helimer 7β (hamatine type). This structural assignment is further confirmed unambiguously by the transformation of 7α and 7β into the known alkaloids 1α and 1β (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 CH₂Cl₂/MeOH 500 : 0.1 → 500 : 1.0; crystallization from MeOH), to yield pure 7a\(^{19}\) (mp 160°C; [\(\alpha\)]\(_{D}\)\(^{20}\) = -30.7°, c = 0.46, CH₂Cl₂), and 7b\(^{13}\) (mp 125°C with subsequent crystal metamorphosis; final mp 160°C; [\(\alpha\)]\(_{D}\)\(^{20}\) = -40.8°, c = 0.46, CH₂Cl₂).

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)\(^{13}\) (mp 109-110°C; [\(\alpha\)]\(_{D}\)\(^{20}\) = -134°, c = 1.01, CH₂Cl₂), which is easily debenzylated by catalytic hydrogenation, as described before\(^{9}\), to give hamatine (1b), identical in all respects with authentic material. The other, ancistrocladine-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](image)

**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](image)

**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

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REFERENCES AND NOTES

2. This work was presented, in part, at the EUCEM Stereochemistry Conference, May 1988, Bürgenstock, Switzerland.
4. Reviews:


11. Strategies for the chemical preparations of stereochemically pure helimers 2a and 2b are under investigation and will be reported later.


13. All new compounds have been fully characterized by spectroscopic and analytic methods. Details will be reported in a full paper.


15. The formation of a third product (the hydro-dehalogenated, non-coupled ether, 6-Br+H, m/z = 497 can be prevented by rigorous drying of the solvent DMA and of the substrate 6, which has to be heated up, in vacuo, beyond its melting point.


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