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First Synthesis of Mastigophorenes A and B, by Biomimetic Oxidative Coupling of Herbertenediol[1]

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Abstract: The first synthesis of mastigophorenes A and B by oxidative phenolic coupling of partially protected derivatives of their joint natural monomeric half, herbertenediol, is described. The synthesis starts from this diol itself or from the corresponding aldehyde, both available by isolation from the liverwort, *Herbertus aduncus*. After transformation of herbertenediol to a chemically appropriate monophenolic coupling precursor, the oxidative dehydrodimerization was brought about using (*tert*-BuO)$_2$, followed by deprotection to give mastigophorenes A and B in their 'natural' atropisomeric ratio, as isolated from the liverwort.

Mastigophorenes A (*P*-**1**) and B (*M*-**1**) from the liverwort *Mastigophora diclados*[2] and aquaticenol (**2**) from the liverwort *Lejeunea aquatica*[3] are novel sesquiterpenoid biaryls, co-occurring with their monomeric phenolic precursors, herbertenediol (**3**) and 1,2-cuparenediol (**4**) respectively. Both mastigophorenes A (*P*-**1**) and B (*M*-**1**) exhibit nerve growth and network formation acceleration activities.[2] Because of these interesting properties and due to the difficulty of preparing sufficient quantities of these natural products for extended biological tests,[4] mastigophorenes A (*P*-**1**) and B (*M*-**1**) constitute attractive synthetic target molecules. Using a model system in which the chiral cyclopentyl residue is replaced by a *tert*-butyl group,

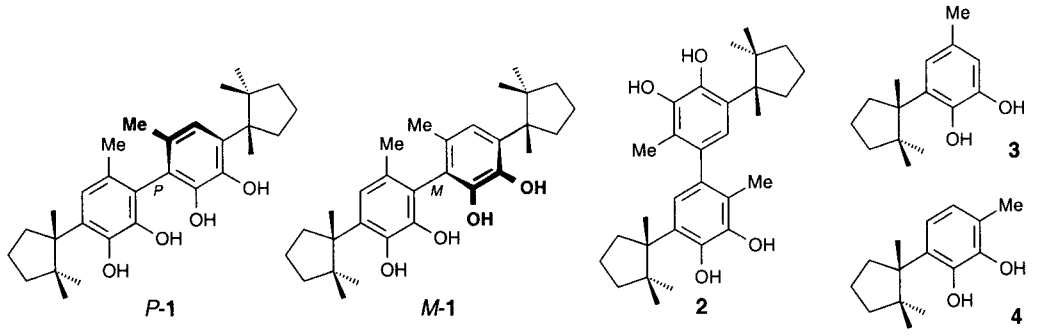

Fig. 1. Natural mono- and dimeric phenolic terpenoids.

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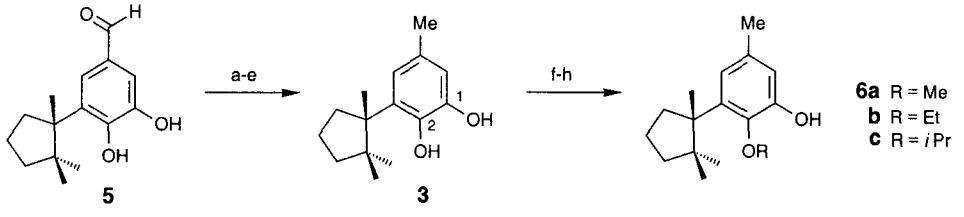
we have recently reported[5] two different strategies for the directed construction of the biaryl axis of mastigophorenes (**1**), firstly, by a biomimetic oxidative dimerization[6] of an appropriately protected monomeric precursor and, secondly by atropo-enantioselective synthesis *via* the 'lactone methodology'.[7,8,9] Very recently, Asakawa *et al.* reported the partial synthesis of a related, but sterically distinctly less hindered mastigophorene-related natural product, aquaticenol (**2**), which, in contrast to mastigophorenes A (*P*-**1**) and B (*M*-**1**), does not form stable or separable atropoisomers.[3] In this paper, we report on the application of our biomimetic dimerization strategy to the authentic molecular half **3** of **1** as prepared from natural material, leading to the first synthesis of mastigophorenes A (*P*-**1**) and B (*M*-**1**).

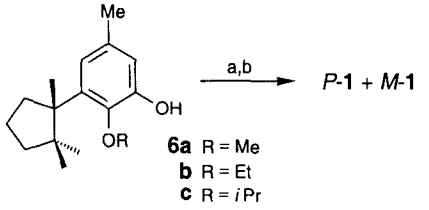
As the natural starting material, we chose **3** and the corresponding aldehyde **5**, both co-occurring in the liverwort *Herbertus aduncus*; their isolation followed standard procedures described previously.[10] Transformation[11] of **5** into **3** was achieved smoothly by *O*-methylation, LAH-reduction, and reductive deoxygenation *via* the corresponding bromide according to procedures elaborated earlier.[5,9,12] This partial synthesis of herbertenediol (**3**) confirms the absolute configuration of the natural aldehyde **5**, which had as yet been deduced only from its negative optical rotation.[10]

Conversion of **3** to the required monophenolic coupling precursor **6a** was achieved as elaborated previously for our model system,[5] by first specifically protecting the less hindered oxygen at C-1 with benzyl bromide, followed by *O*-methylation of the remaining phenolic oxygen at C-2 and ultimate hydrogenolytic cleavage of the benzyl group to give **6a**.



Scheme 1. Synthesis of the monophenolic coupling precursors **6a-c**. Reaction conditions: a) Me_2SO_4, K_2CO_3, acetone, rt, 73%; b) $LiAlH_4$, THF, 95%; c) $C_2Br_2Cl_4$, Ph_3P, CH_2Cl_2; d) $LiAlH_4$, Et_2O, 72%; e) BBr_3, CH_2Cl_2, 0 °C, 93%; f) BzlBr, K_2CO_3, acetone, rt, 90%; g) RI, Cs_2CO_3, Bzl(*n*-Bu)$_3$NBr, acetone, **a**, 97%; **b**, 85%; **c**, 65%; h) H_2, Pd/C (10%), EtOH/AcOEt, 1 atm, rt, 89% (resp. 80%, 75%).

Oxidative coupling of this monophenolic building block **6a** using (*tert*-BuO)$_2$ in refluxing chlorobenzene[13] (see Scheme 2) gave, after *O*-deprotection with BBr_3 in CH_2Cl_2, the two mastigophorenes A (*P*-**1**) and B (*M*-**1**) as an atropo-diastereomeric mixture. ^{1}H NMR analysis revealed a d.r. of 60:40 in favor of the *M*-configured diastereomer *M*-**1** , nearly identical to the 63:37 ratio of mastigophorenes B (*M*-**1**) and A (*P*-**1**) obtained by isolation from natural material by Fukuyama *et al.*[2] This virtually identical atropisomeric ratio of mastigophorenes A (*P*-**1**) and B (*M*-**1**) might suggest that mastigophorenes (**1**) are biosynthetically formed either by a non-enzymatic reaction or with the enzyme not exerting any additional stereoselectivity besides the internal asymmetric induction exerted by the chiral cyclopentyl residue. Subsequent chromatographic resolution by preparative TLC smoothly yielded *P*-**1** and *M*-**1** as stereochemically pure compounds, spectroscopically and chromatographically identical with authentic samples from *Mastigophora diclados* kindly provided by Prof. L.J. Harrison, Singapore.



6	d.r.	yield (%)
a	40:60	28[a]
b	50:50	18[b]
c	---	0

Scheme 2. Oxidative dehydrodimerization of various phenolic precursors **6** to give mastigophorenes A (*P*-**1**) and B (*M*-**1**). Reaction conditions: a) (*tert*-BuO)$_2$, C_6H_5Cl, reflux; b) BBr_3, CH_2Cl_2, 0 °C. [a] 42% of **3** recovered; [b] 34% of **6b** recovered.

Given the slight but significant asymmetric induction by the chiral cyclopentyl residue, we hoped that an increase of steric hindrance on the *O*-protective group might result in a more efficient chirality transfer from the quaternary stereogenic center to the coupling site. Using a 2-*O*-alkylation → 1-*O*-debenzylation strategy as for **6a**, the *O*-ethyl- and *O*-*iso*-propyl derivatives **6b** and **6c** were prepared in a similar way (see Scheme 1). Application of the coupling conditions to **6c** as above, however, led to a complete decomposition of the substrate, no dimerization being observed, the apparent reason being steric overload. By contrast, **6b** did give the required dimer, although in a reduced coupling yield (18%) and without any diastereoselectivity (see Scheme 2).

The reduced coupling yield of **6a** and **6b** in comparison to our *tert*-butyl substituted model (80%)[5] should likewise be due to the high steric demand of the cyclopentyl residue. The postulated sandwich-type geometry of the two phenoxyl radicals in the coupling step[13] should be severely hampered by the large chiral cyclopentyl residue.

This synthesis of mastigophorenes A (*P*-**1**) and B (*M*-**1**) constitutes a very effective and even slightly stereoselective first pathway to these natural products. Given the fact that herbertenediol (**3**) has previously been obtained by total synthesis (although in an as yet racemic form, but formally with the option of preparing optically active material)[14], the work presented in this paper likewise constitutes the formal first total synthesis of these dimeric sesquiterpenoid natural products. The directed atropo-divergent synthesis of both mastigophorene A (*P*-**1**) and mastigophorene B (*M*-**1**), using our 'lactone methodology',[7,8,9] is in progress.

ACKNOWLEDGEMENTS

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