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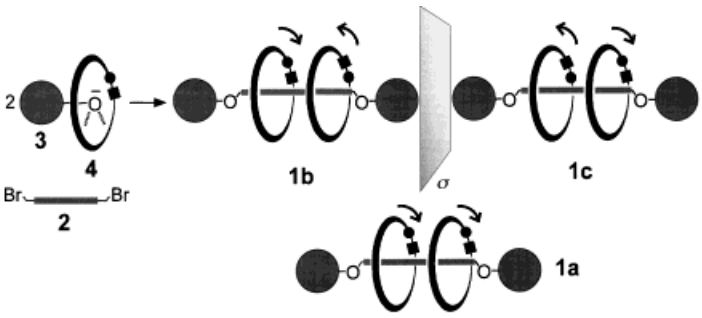


The First Cyclodiasteromeric [3]Rotaxane**

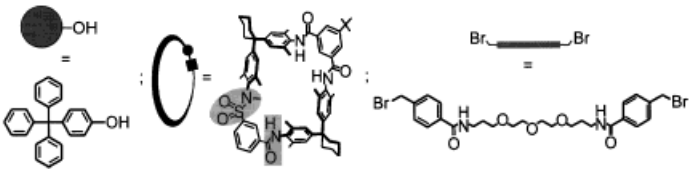
Roland Schmieder, Gosia Hübner, Christian Seel, and Fritz Vögtle*

Cycloenantiomerism in mechanically bonded molecules was first predicted by Frisch and Wassermann in 1961,[1] and the first catenanes and molecular knots displaying this property were synthesized by Sauvage et al. almost three decades later.[2, 3] As early as 1971, Schill proposed stereoisomeric [2]rotaxanes,[4] whose chiral information can be put down to a directed segment sequence in the macrocycle as well as in the axle. The axle and wheel are not chiral themselves; the mechanical connection, however, would yield a cycloenantiomeric rotaxane.

During the last decade several chiral [2]rotaxanes have been synthesized whose stereoisomerism is based on the central chirality.[5, 6] In 1997 we prepared the first cycloenantiomeric [2]rotaxanes and [1]rotaxanes as well as topologically chiral pretzelanes, which were separated into their enantiomers by means of chiral HPLC and chiroptically characterized.[6e] Recently several achiral [3]rotaxanes have been reported.[7] To our knowledge stereoisomeric [3]rotaxanes, however, have not been described yet.

We now succeeded in preparing a chiral [3]rotaxane containing two achiral wheels, which are mechanically bonded onto an achiral axle that is not directed. Analogous to the covalently linked tartaric acid, we obtained a cyclodiastereomeric compound.[8] Applying our new efficent trapping synthesis (chemical threading) for rotaxanes with diether axles,[9] we allowed the dibromide **2** to react with the stopper **3** in presence of the wheel **4**. Besides small amounts of the free axle and the [2]rotaxane (10%), the [3]rotaxane **1** was obtained in 29% yield (Scheme 1).[10]

If there is only one achiral wheel on a symmetrical axle, a [2]rotaxane with no stereoisomerism results. Rotaxanes like **1** bearing two wheels, the atomic sequences of which can be arranged clockwise or counterclockwise, should occur in a



Scheme 1. Schematic representation of the synthesis of the cylodiastereomeric [3]rotaxane as a pair of enantiomers (**1b**, **1c**) and as the *meso* form (**1a**).

meso form (**1a**) and a pair of enantiomers (**1b**, **1c**). The orientation of the macrocycles on the axle is caused by a different sequence of the three amide groups and the sulfonamide group. The two wheels **4** can have the same or opposite direction. In the case of the same orientation the *meso* compound **1a** is obtained, and the opposite direction of the wheels leads to **1b** and **1c**.

The high conformational flexibility of the molecule—in the sense of the extended translational and rotational movement of the wheels on the axle—raises the questions of whether the stereoisomers can be separated and whether chiroptical properties show significant differences. The results obtained hitherto on our separated chiral [2]- and [1]rotaxanes and catenanes indeed fueled our hopes for success. The enantiomers were successfully separated employing chiral HPLC (Chiralpak AD; Figure 1).[11, 12] First of all the (+) enantiomer was eluted in base line separation, followed by the (−) enantiomer. The retention time of the latter, however, differed only slightly from that of the *meso* form **1a** (Figure 1). Whereas the separation factor $\alpha_{(-),(+)}$ of the enan-

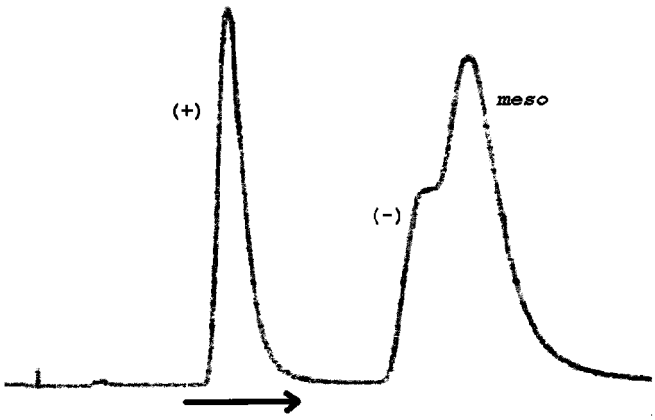


Figure 1. Chromatogram for the enantiomeric separation. Retention times: (+) enantiomer: 10.5 min, (−) enantiomer: 21.5 min, *meso* form: 23.5 min.[12]

[*] Prof. Dr. F. Vögtle, R. Schmieder, G. M. Hübner, Dr. C. Seel
Kekulé-Institut für Organische Chemie und
Biochemie der Universität
Gerhard-Domagk-Strasse 1, D-53121 Bonn (Germany)
Fax: (+49) 228-735-662
E-mail: voegtle@uni-bonn.de

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tiomers is 2.57, leading to a complete separation, $\alpha_{(-),meso}$ is only 1.11. Nevertheless, we were able to separate **1a** and the (−) enantiomer.

The pure enantiomer **1b** and the enriched **1c** (ca. 90%) show significant circular dichroism activity (Figure 2) as well as optical rotation at different wavelengths (Table 1).[13] In analogy to tartaric acid, the *meso* form **1a** is not optically active.

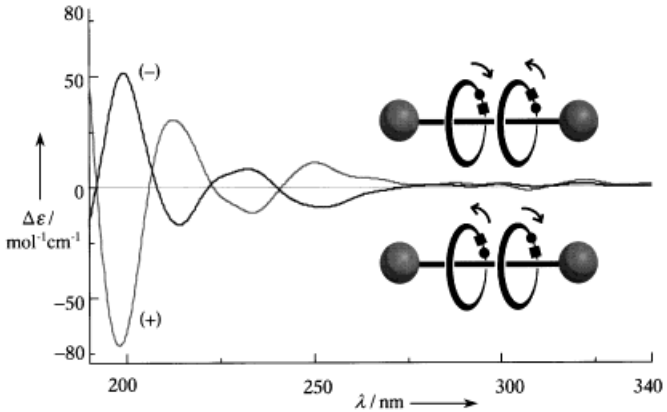

Figure 2. Circular dichroism spectra of the cycloenantiomers **1b** and **1c** in trifluoroethanol; concentration of (+) enantiomer 1.24×10^{-5} M, concentration of (−) enantiomer 3.22×10^{-5} M.

Table 1. Optical rotation ($[\alpha]^{26}$ in $CHCl_3$) of the cycloenantiomers **1b** and **1c** at different wavelengths; concentration of (+) enantiomer 5.82×10^{-4} M, concentration of (−) enantiomer 5.03×10^{-4} M.

λ[nm]	α(**1b**)[°][a]	α(**1c**)[°][a]
577	+8	−8
546	+5	−7
435	+10	−11
405	+16	−14
365	+26	−24

[a] A deviation of ±1° results from the precision of the polarimeter.

The remarkable property of this [3]rotaxane is the mechanical bonding of its achiral components, axle and wheels, which leads to a cyclodiastereomeric species. The stereoisomers are formed in statistical ratios (*meso*-**1**:(+)-**1**:(−)-**1** = 2:1:1), and can easily be separated by chromatographic methods. In this way it should be possible to form a [3]rotaxane with two different wheels, one unorientated and one orientated, as well as [*n*]rotaxanes that also show cyclostereoisomerism.[14] Thus, chiral rotaxanes will become more and more interesting in the future.[15]

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[10] The workup was carried out chromatographically (SiO_2, 40–60 μ; dichloromethane/*tert*-butyl methyl ether 12/1). The mixture of the isomers of rotaxane **1** showed the expected mass spectrum: *m/z* 3148.6 $[M+H]^+$ (FAB, 9-nitroanthracene (9-NA)) *m/z* 3167.4 $[M+Na]^+$ (MALDI-TOF; calcd for $C_{204}H_{220}N_{10}O_{17}S_2$: 3148.12). The compound has been characterized by ^1H and ^{13}C NMR spectroscopy. M.p. 278 °C; elemental analysis calcd for $C_{204}H_{220}N_{10}O_{17}S_2 \cdot 3CH_2Cl_2$: C 73.06, H 6.69, N 4.12, S 1.88; found: C 72.98, H 6.77, N 4.13, S 2.31; the dichloromethane is detected by NMR spectroscopy.

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[12] Each fraction was analyzed by mass spectroscopy (MALDI-TOF-MS). Every stereoisomer had the same mass peak. Conditions of the separation: Column Chiralpak AD (25 × 0.46 cm inner diameter), amylose tris[3,5-(dimethylphenyl)carbamate], eluent *n*-hexane/ethanol 81/19; flow rate 1.3 mL min^{-1}; pressure 23 bar; detector UV (Millipore Waters, Lambda Max, Model 481, LC Spectrophotometer); sample 10 mg mL^{-1} in chloroform/*n*-hexane (1/1).

[13] Optical rotation: JASCO Polarimeter P-1020, cell 100 × 3.5 mm inner diameter ($CHCl_3$); circular dichroism spectra: JASCO Spectropolarimeter J-720, cell 0.1 mm (trifluoroethanol).

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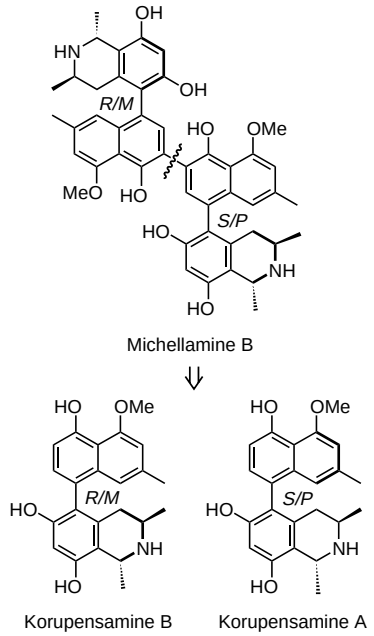

Scheme 1. Retrosynthesis of michellamine B to its components korupensamines A and B.

A Stereospecific, Intermolecular Biaryl-Coupling Approach to Korupensamine A En Route to the Michellamines**

Bruce H. Lipshutz* and John M. Keith

The michellamines make up a rather unusual group of highly active antiviral natural products, with michellamine B receiving most of the attention as a potent anti-HIV-1 and -2 agent.[1] The components of this alkaloid, korupensamines A and B, are related as diastereomers with respect to their axial chirality (Scheme 1).[2] All attempts to effect a *direct*, highly stereocontrolled biaryl coupling between the naphthyl and tetrahydroisoquinoline portions have thus far met with limited success,[3] which has encouraged a number of groups to devise clever, albeit indirect, alternatives.[4] We now describe a novel solution to this problem that allows for *exclusive* entry to the korpensamine A series through a Pd^0-mediated intermolecular biaryl cross-coupling reaction.

[*] Prof. B. H. Lipshutz, Dr. J. M. Keith
Department of Chemistry
University of California
Santa Barbara, CA 93106 (USA)
Fax: (+001) 805-893-8265
E-mail: lipshutz@chem.ucsb.edu

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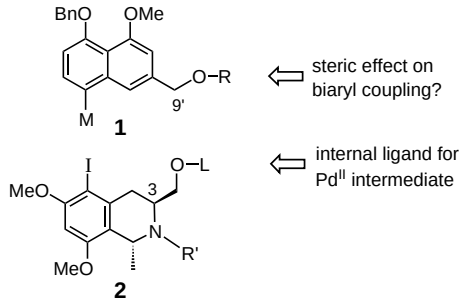
The guiding principles upon which our route was developed (Scheme 2) focus on the presence of a hydroxyl "handle" in each of the components. These were anticipated to afford considerable flexibility in fine-tuning the selectivity in the



Scheme 2. Possible influence of substituents on the hydroxymethyl "handles".

biaryl-forming step. Such a residue at C-9′ in **1** might facilitate the introduction of a potentially influential steric component, while an OH function on the methyl group at C-3 in **2** would provide an opportunity for intramolecular chelation, thereby directing biaryl formation from one face of a transient polycyclic array.

Our route to nonracemic, protected hydroxymethyliodotetrahydroisoquinoline **9** began with aryl chloride **3** (Scheme 3).[5] A copper-catalyzed opening of commercially available (*S*)-TBS-glycidol (TBS = *tert*-butyldimethylsilyl) with the Grignard reagent derived from **3** leads to alcohol **4**, which is suitable for a Mitsunobu inversion[6] with phthalimide followed by hydrazinolysis to give nonracemic amine **5**. Acetamide formation sets the stage for a temperature-sensitive[7] Bischler–Napieralski cyclization to imine **6**. Careful reduction with a 1:7 mixture of Me_3Al (in heptane) and

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