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Atropo-Enantioselective Biaryl Synthesis by Stereocontrolled Cleavage of Configuratively Labile Lactone-Bridged Precursors using Chiral *H*-Nucleophiles[1]

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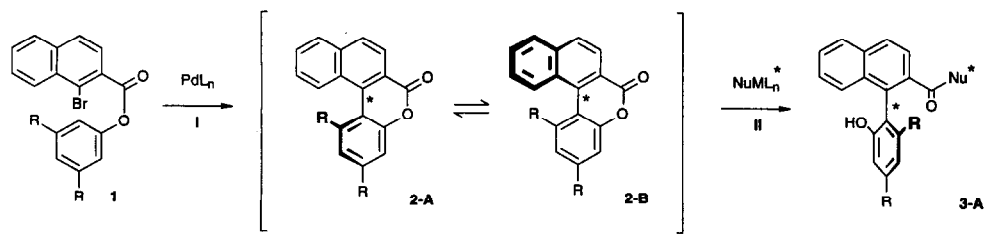
Dedicated to Prof. Sir Derek H.R. Barton, on the occasion of his 75th birthday.

Abstract: The atropo-enantioselective synthesis of axially stereogenic, sterically shielded biaryl systems is described, by stereocontrolled ring opening of the corresponding lactone-bridged, still configurationally labile precursors. The atropenantiomer excesses range up to 97% ee.

INTRODUCTION

The directed, *i.e.* regio- and stereoselective construction of even highly hindered, moreover unsymmetrical biaryl systems[2,3] constitutes a challenging task of increasing importance in organic synthesis, due to the rapidly growing number of naturally occurring biaryl compounds from natural sources. Moreover, during the past years, synthetic chemists have recognized the value of the strong stereodifferentiating capacity of biaryl-based reagents in organic synthesis[4]. We have recently developed a conceptionally novel approach to the regio- and stereoselective synthesis of axially chiral biaryls (Scheme 1): The first step (**I**) is the actual *C,C*-bond formation, by intramolecular aryl coupling of ester-type prefixed aromatics **1**, and subsequently, in a

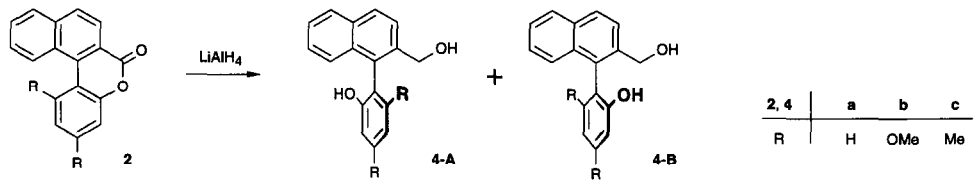


Scheme 1. Synthesis and atrop-selective ring opening of conformationally labile bridged biaryls **2**[5-8].

separate step (**II**), the resulting lactone **2** is ring opened with asymmetric induction at the preformed, yet still configurationally instable biaryl axis. For pyranones **2** that dispose of additional elements of chirality (*i.e.* stereogenic centers), this can be attained by a diastereoselective ring opening reaction using achiral *O*- or *H*-nucleophiles, a strategy exploited in several efficient total syntheses of naturally occurring naphthylisoquinoline alkaloids[5,6]. On substrates **2** devoid of stereocenters, which, due to rapid enantiomerization at the axis, appear as achiral macroscopically, an atropo-diastereoselective ring cleavage can be achieved with chiral metallated *O*- or *N*-nucleophiles[7]. For an (overall) enantioselective biaryl synthesis, however, a subsequent, sometimes tedious removal of the chiral auxiliary, by cleavage of the *C,O*- or *C,N*-bond, becomes necessary. In this paper, we describe direct atropo-enantioselective ring opening reactions using chirally modified aluminum hydrides and boranes as *H*-nucleophiles[9].

RESULTS AND DISCUSSION

As substrates for the planned atropo-enantioselective reactions, we chose the lactones **2a** - **c**, which can efficiently be prepared by intramolecular coupling of the corresponding esters **1**[10]. A racemic standard mixture of the ring opened alcohol **4** was obtained by reductive cleavage of **2** *e.g.* with lithium aluminum hydride, as described earlier[11].



Scheme 2. Preparation of the racemic alcohols **4a** - **c**[11].

1. Enantiomer Analysis of the Ring Opened Products 4

A crucial precondition for the evaluation of the quality of the planned enantioselective reactions was the availability of an analytical procedure for the rapid, exact, and reliable identification and quantification of the enantiomeric products **4**. For this purpose, we chose "direct methods"[12], by chromatography on chiral stationary phases, rather than "indirect" ones[13]. For the alcohols **4**, the best analytic results were obtained with the commercially available chiral adsorbents "Chiralcel OD" and "Chiralcel OF" (Daicel Chem. Ind.). After optimization of the mobile phases, all the alcohols **4a** - **c** could very efficiently be resolved into their atrop-enantiomers (see Table 1).

Thus, an efficient and rapid method for the investigation of the attained asymmetric inductions in the planned reduction experiments, was available.

2. Configurational Assignment of the Chiral Alcohols 4

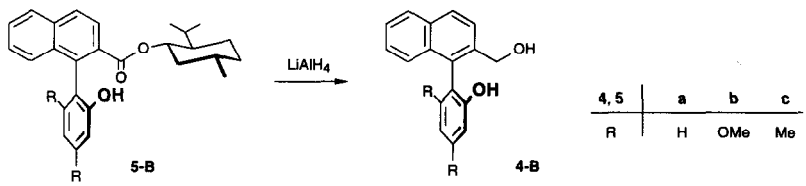
An important further requirement was the attribution of the absolute stereostructures of the alcohols **4**. A first tentative assignment of the axial configurations was possible by comparison of the chiroptical properties of **4a-B** - **4c-B** with those of the related esters **5a-B** - **5c-B**, as obtained by ring opening reactions with

Table 1. Results of the enantiomer resolution of **4a - c**.

Phase	Alcohol	Configuration[a]	t_1[b]	t_2[b]	α[c]	R_S[d]	eluent ratio[e]
OF	**4a**	*S*	30.9	34.5	1.15	1.69	90 : 10
OF	**4b**	*R*	40.2	48.4	1.25	2.34	85 : 15[f]
OD	**4c**	*R*	25.6	30.1	1.22	1.25	90 : 10

[a] Absolute configuration of the more rapidly eluting atropisomer. - [b] retention time [min]. - [c] separation factor α [= k'_2/k'_1]; capacity factors $k'_1 = (t_1 - t_0/t_0)$, resp. $k'_2 = (t_2 - t_0/t_0)$[14,15]. - [d] resolution factor R_S [= 1.198 $(t_1 - t_2)/(1/2W_1 - 1/2W_2)$][14]. - [e] eluent: petroleum ether (bp 56 - 64°C) / 2-propanol; 0.5 ml/min. - [f] addition of 0.05% formic acid.

mentholates as achiral *O*-nucleophiles[16]. For these esters the relative stereochemistry at axes *vs.* stereocenters and, given the known absolute configuration of the (+)-menthol part, also the *absolute* axial configuration had been established by X-ray structure analyses. An unambiguous confirmation of this stereochemical attribution was achieved by transformation of the esters **5** into the authentic enantiomerically pure alcohols **4**, by cautious reduction with lithium aluminum hydride, now allowing to clearly assign (see Table 1) the chromatographic peaks to the respective enantiomers.



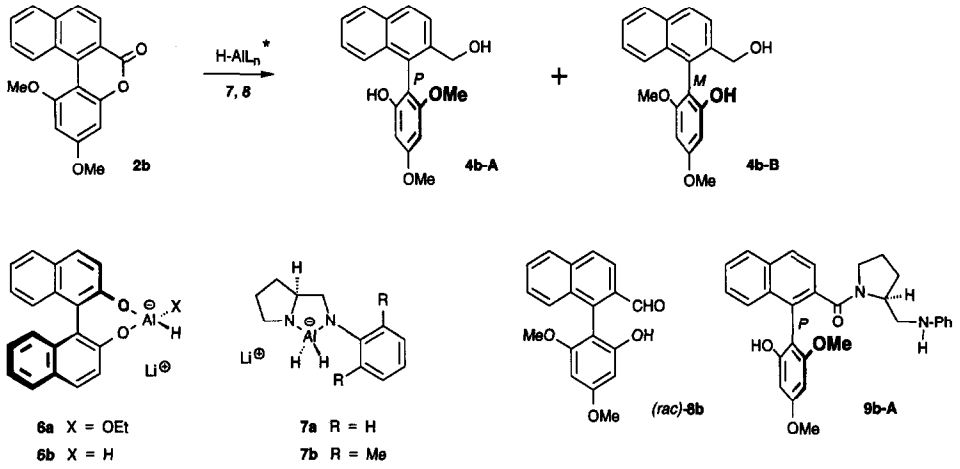
Scheme 3. Stereochemical correlation of the alcohols **4a-B - 4c-B** with the menthyl esters **5a-B - 5c-B**.

3. Enantioselective Ring Opening Reactions with Chiral Aluminum Hydrides

The first ring opening experiments were performed with the lactone **2b**, because it resembles more closely the substrates of previous successful atropo-diastereoselective ring opening reactions leading to naturally occurring biaryl-alkaloids[5,6]. As by the HPLC analysis on chiral stationary phases (see above) an efficient and sensitive method for the determination of the enantiomeric ratios of the alcohols **4** had been elaborated, initial reduction experiments could, first of all, be performed and optimized on an analytical scale (0.02 - 0.03 mmol), the best results then being repeated preparatively.

These experiments on the atropo-enantioselective cleavage of axially prostereogenic biaryl lactones with chiral *H*-nucleophiles showed a great *general* problem straightaway: the lacking reactivity of those reagents that originally had been designed for the enantioselective reduction of ketones. Thus, *Noyori's* "BINAL-H" (**6a**)[17], which had been described as most effective in the literature[18], proved to be completely unreactive towards the lactones **2b.** By contrast, using *Mukaiyama*'s otherwise very successful proline-derived *H*-nucleophile **7a**[19], a reduction of **2b** could indeed be achieved, yet, requiring very large excesses of this precious chiral reagent. But even in this case, the reaction was incomplete, since also the corresponding aldehyde **8b** was formed. HPLC-analysis of the desired alcohols **4b** revealed an only mediocre enantiomeric

ratio of 62 : 38. A repetition of the reaction on a preparative scale showed the isolated aldehyde **8b** (yield 8%) to be fully racemic - a first interesting hint at the expected[2] configurational instability of such aldehyde or lactolate intermediates (see below). Furthermore, two unexpected *Dragendorff*-active compounds were isolated, the atropo-diastereomeric amides **9b** (yield 12%), showing that, unprecedentedly, **7a** can, by "ligand transfer", also act as a chiral *N*-nucleophile, even with a distinct asymmetric induction at the axis (d.r. 80 : 20). The structure of the main atropo-diastereomer was tentatively assigned as **9b-A**, *i.e.* with *P*-configuration, by comparison of its CD spectrum *e.g.* with that of the alcohol **4b-A**.



Scheme 4. Atropo-enantioselective reductions with chirally modified aluminum hydrides.

Also the sterically more demanding reagent **7b**[20] proved to be completely unselective, so that further experiments again concentrated on more reactive representatives of the binaphthyl-modified aluminum hydrides. For this reason, also the dihydride "*(R)*-BINAL-H_2" (**6b**) was tested, although it had been reported to give practically no asymmetric inductions in the enantioselective reduction of ketones (*e.g.* 2% ee for acetophenone)[17].

For the atropo-enantioselective opening of axially prostereogenic lactones, however, this hydride transfer reagent **6b** proved to be, by far, superior to all the other reagents tested: A thorough optimization gave atropisomeric ratios of up to 88 : 12. In the course of these investigations, a remarkable dependence of the asymmetric inductions from the reaction temperature was observed (see Fig. 1): The enantiomeric ratios

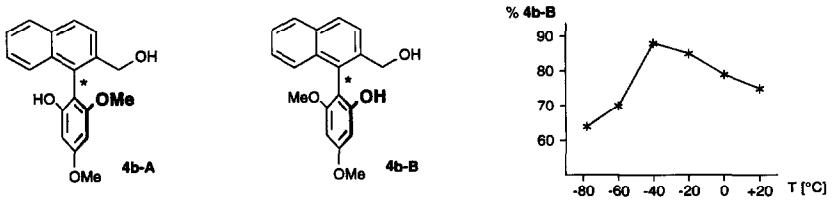


Fig. 1. Temperature dependence of the ratio of the alcohols **4b-A / 4b-B** using *(R)*-BINAL-H_2 (**6b**)

initially increased with decreasing temperature, reaching a maximum at about -40°C, below which, characteristically, they rapidly dropped with further decreasing reaction temperature - a significant finding with respect to our mechanistic considerations (see below).

Unexpectedly, the attempt to extend these results to the atropo-enantioselective cleavage of the related lactone **2c**, with a methyl instead of a methoxy group next to the biaryl axis, failed nearly completely, either giving no reaction or leading to racemic alcohols **4c** (see Table 2), and the relatively best results (42 : 58) could still be obtained with "*(R)*-BINAL-H_2" (**6b**), in the proximity of the temperature optimum (-40°C, see above) found for substrate **2b**. Initial speculations that the far better enantiomeric ratios for the alkoxylated lactone **2b** might be due to the presence of the oxygen functions, could be excluded since also the unsubstituted benzopyranone **2a** delivered quite acceptable asymmetric inductions (though not as good as **2b**), so that, in agreement with our mechanistic model (see below), the failure of the sterically more hindered biaryl system **2c** might be due to a completely frozen atrop-enantiomerization of this substrate at the denoted reaction temperatures, whereas, at higher temperatures, the selectivity of the reagent is not good enough.

Table 2. Extension of the aluminum hydride reductions to the lactones **2a** and **2c**.

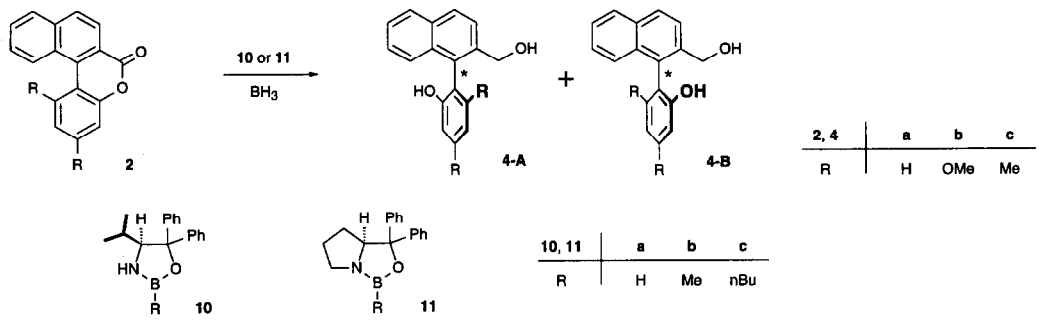
Lactone	H-ML_n*	Solvent	Temperature [°C]	Ratio **A** : **B**
2c	**6a**	THF	+20	no reaction
2c	**6b**	THF	-78	48 : 52
2c	**6b**	THF	-40	42 : 58
2c	**6b**	THF	+20	49 : 51
2c	**7a**	ether	-40	50 : 50
2c	**7b**	ether	-40	51 : 49
2a	**6b**	THF	-40	31 : 69
2a	**7a**	ether	-40	80 : 20

In summary, some quite remarkable atropisomer excesses could indeed be obtained with chirally modified aluminum hydrides, but not all the tested reagents were equally good for all the model lactones. Some of them, especially for the lactone **2c**, even proved to be completely ineffective. For this reason, other promising hydride transfer reagents were tested in the following.

4. Oxazaborolidine Assisted Borane Reductions

The main disadvantages of the above mentioned aluminum hydride reagents for the atropo-enantioselective ring opening were, as mentioned, the lacking chemical reactivity, the low asymmetric inductions, as well as the tendency also to transfer the chiral ligands. Hence, more reactive and, if possible, simultaneously still more selective chiral hydride transfer systems were required, for which purpose we chose the oxazaborolidines of the types **10**·BH_3 and **11**·BH_3. These reagents, developed by *Itsuno*[21] and *Corey*[22], had most successfully been applied to the enantioselective reduction of ketones, giving excellent optical and chemical yields, with very short reaction times, and even reactions with catalytic amounts of the chiral auxiliaries were possible. The oxazaborolidines **10a** and **11a** - **c** were already known[21-23], whereas the new heterocycles **10b** and

10c have recently been prepared for the first time[24], so that for the ring opening reaction a broad comparability of the two oxazaborolidine systems with identical *B*-substituents was possible.



Scheme 5. Atropo-enantioselective reductions with the chiral oxazaborolidines **10** and **11**.

First orientating experiments were performed with the *B*-unsubstituted reagent **11a**·BH_3 and the dimethyl lactone **2c**, *i.e.* the substrate for which nearly all the chiral aluminum hydrides had failed before (see above). First of all, exemplarily for this pair of reaction partners, the optimum molar ratios were investigated (see Table 3), showing that the use of catalytic amounts of **11a** (Entry A) delivered a quite considerable enantiomeric ratio of 80 : 20, straightaway, yet at a very slow reaction rate. Enhancement of the BH_3-quantities (Entry B) gave distinctly lower asymmetric inductions. Presumably, under these conditions, non-selective reduction processes by non-activated borane played an increasing role. By contrast, the use of over-stoichiometric amounts of the chiral auxiliary (Entry C) resulted in a rapid and highly stereoselective reduction of **2c** to give **4c-A** (88 : 12). Further experiments (entries D - H) showed that for a satisfying outcome of the reac-

Table 3. Optimization of the molar ratios for reductions of **2c** with **11a** / BH_3.

Entry[a]	Molar Ratios **2c** : **11a** : BH_3·THF	Ratio **4c-A** : **4c-B**	Remaining Lactone **2c**[c]
A	1 : 0.15 : 1.2	80 : 20	++
B	1 : 0.15 : 2.5	62 : 38	++
C	1 : 2 : 2.5	88 : 12	(+)
D	1 : 2 : 5	78 : 22	(-)
E	1 : 4 : 5	90 : 10	-
F	1 : 3 : 2	88 : 12	(+)
G	1 : 3 : 4	90 : 10	-
H[b]	1 : 3 : 4	83 : 17	-

[a] If not otherwise denoted, all experiments were run for 60 min at 30°C. - [b] Reaction temperature 0°C. - [c] According to TLC control.

tion, the borane / oxazaborolidine ratio must not be too high, the best results being obtained with an at least threefold excess of the reducing system **11a**·BH_3 (Entry G), with a reaction temperature of 30°C. Lower temperatures led to decreasing selectivities (Entry H), compared with the "ideal molar ratios" as in Entry G.

Applying these optimum reaction conditions, the subsequent analytical reactions were performed with a ratio lactone / oxazaborolidine / borane = 1 : 3 : 4, by addition of the corresponding lactone to the chiral heterocycle and borane in THF at 30°C. The results of the reductions of the benzonaphthopyranones **2a** - **c** with the oxazaborolidines **10** and **11** are represented in Table 4. Thus, the valinol-derived reagents **10a** - **c** deliver, throughout, good atropisomeric ratios (≥ 80 : 20), the variations in the selectivity being relatively small for the different lactones. The best results were obtained with the *B*-unsubstituted and *B*-methylated compounds **10a** and **10b,** whereas worse asymmetric inductions were attainable with the *B*-*n*-butyl-derivative **10c** (Table 4).

The distinct efficiency of these chiral borane-derived hydride transfer reagents, as already manifest from the reductions with **10a** - **c**, was still exceeded by the partially excellent asymmetric inductions using the *bicyclic* compounds **11a** - **c**, which (in a nearly quantitative reaction) gave enantiomeric ratios of at least 90 : 10 for the lactones **2b** and **2c**, and still at least 80 : 20 for the less hindered pyranone **2a**. A possible reason for these high selectivities might be the greater conformative rigidity of the bicycle **11**, compared with the more flexible monocycle **10.** The by far highest asymmetric inductions, independent from the lactone used, were obtained with the *B*-methyl and *B*-*n*-butyl derivatives **11b** and **11c**, the top values being achieved with **11b** (up to 98.5 : 1.5!).

Table 4. Results of the atropo-enantioselective borane reductions of the lactones **2a** - **c** in the presence of the oxazaborolidines **10** and **11** (30°C).

			Ratio						Ratio		
Reagent	Lactone	Alcohol	**A**	:	**B**	Reagent	Lactone	Alcohol	**A**	:	**B**
10a	**2a**	**4a**	86	:	14	**11a**	**2a**	**4a**	80	:	20
10a	**2b**	**4b**	93	:	7	**11a**	**2b**	**4b**	91	:	9
10a	**2c**	**4c**	84	:	16	**11a**	**2c**	**4c**	90	:	10
10b	**2a**	**4a**	84	:	16	**11b**	**2a**	**4a**	88	:	12
10b	**2b**	**4b**	89	:	11	**11b**	**2b**	**4b**	97	:	3
10b	**2c**	**4c**	88	:	12	**11b**	**2c**	**4c**	98.5	:	1.5
10c	**2a**	**4a**	80	:	20	**11c**	**2a**	**4a**	85	:	15
10c	**2b**	**4b**	85	:	15	**11c**	**2b**	**4b**	95	:	5
10c	**2c**	**4c**	84	:	16	**11c**	**2c**	**4c**	97	:	3

The specific advantage of the borane reagents employed apparently is their high efficiency even (and especially) at "elevated" temperatures (30°C), which are required for a rapid enantiomerization of **2c**, so that under these conditions, even this stereochemically most hindered lactone is really conformationally labile - a requirement for our concept. Running the reaction at lower temperatures (see Table 5) leads to a decrease in stereoselectivity, also in agreement with the temperature optimum for other reduction reactions with this reagent at 0 - 30°C[18].

Table 5. Temperature dependence of the atropisomeric ratios in the borane reduction of **2b** and **2c** with **11b**.

Lactone	Temperature [°C]	A : B	Lactone	Temperature [°C]	A : B
2b	+30	97 : 3	**2c**	+30	98.5 : 1.5
2b	+20	97 : 3	**2c**	+20	98 : 2
2b	0	94 : 6	**2c**	0	94 : 6
2b	-15	90 : 10	**2c**	-15	88 : 12

In final experiments, these very efficient oxazaborolidine-assisted ring opening reactions, which hitherto had been performed only on an analytical scale, were adopted to preparative conditions (60 - 80 mg) in order to investigate whether comparable asymmetric inductions could be attained. For this purpose, the lactones **2a - c** were reacted with the most selective reagent **11b**, giving practically identical enantioselectivities for the isolated alcohols as in the previous analytical reactions. The most important and remarkable result however, was that a simple recrystallization step did not only lead to enhanced atropisomeric ratios (as for **4a**), but even gave *enantiomerically pure* material for **4b** and **4c** (Table 6).

Table 6. Results of the preparative ring opening reactions of the lactones **2a - c**, using **11b** / BH_3.

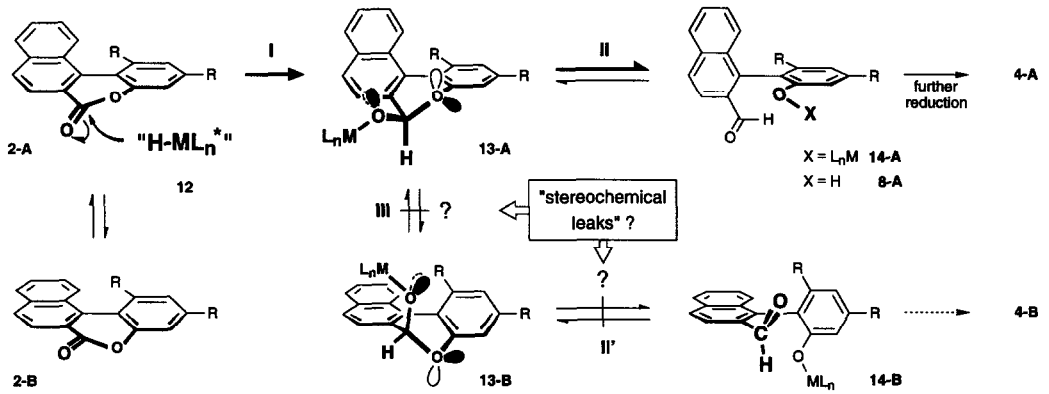
		4-A : 4-B	
Lactone	Alcohol	Initial Ratio	after Recrystallization
2a	**4a**	91 : 9	93 : 7
2a	**4b**	97 : 3	>99.95 : 0.05
2c	**4c**	98.5 : 1.5	>99.95 : 0.05

5. Mechanistic Aspects

The key step in this novel approach to the stereoselective synthesis of axially stereogenic biaryls is, "macroscopically", the stereocontrolled "twisting" of a bridged, stereochemically not yet differentiated biaryl system. An intensive investigation of the control principles upon which this novel procedure is based, are not only of fundamental stereochemical interest, but should also give hints how to improve this procedure in a directed and efficient way.

Our mechanistic working hypothesis, which is based upon numerous experimental observations, but also on extended theoretical work concerning the structure and dynamics of the postulated intermediates, is shown, in a simplified form, in Scheme 6.

According to this concept, the ring opening process is performed in high stereocontrol if several preconditions are fulfilled simultaneously: The chiral nucleophile **12** has to attack the prostereogenic carbonyl group from only one side of the lactone **2-A** and in only one mode (*e.g.* only axially), thus leading only to one of the four possible stereoisomeric forms of the intermediate lactolate, *e.g.* only to **13-A**, which should then ring open only out of this conformer, to give the opened biaryl **14-A** (or, alternatively, only out of another conformation).



Scheme 6. A mechanistic concept for the atropisomer-selective cleavage of biaryl lactones **2**.

Stereochemical "leaks" may result from the possibility of an additional pathway from **13-A** over to the enantiomeric alcohol **4-B**, by helimerization (step **III**) from **13-A** to **13-B**, and analogous ring opening to give **14-B**. This has to be taken into account especially for aldehyde-type intermediates **14-A**, if they are not rapidly enough further reduced to the configurationally stable alcohols **4**. These aldehydes may, by renewed cyclization to give **13-A**, subsequent helimerization to give **13-B**, followed by a non-selective ring opening from either of the two helimeric lactolates **13-A/B**, undergo a more or less complete loss of the stereochemical information at the biaryl axis.

This is underlined by the weak stereoselectivity in all those cases where larger amounts of the corresponding aldehyde (*e.g. rac*-**8b**, see above) are formed, combined with the fact that isolated aldehyde itself is always racemic. Work to investigate the conformational instability of such intermediates as "stereochemical *Achilles* heels" of the process, by computational methods and by the directed preparation of an *enantiomerically pure* free (*i.e.* not OH-protected) aldehyde **8**, which, in contrast *e.g.* to the corresponding alcohol **4** should undergo a rapid enantiomerization at room temperature, is in progress.

A further problem may arise from a too slow interconversion of the two helimeric enantiomers **2-A** and **2-B**, which is critical for the more hindered lactones (*e.g.* for **2c**), especially at lower temperatures (see above).

6. Outlook

The work described in this paper is based on a novel principle of stereoselective biaryl synthesis - the directed, atropo-enantioselective transformation of a configurationally labile bridged biaryl system into an axially chiral "ring opened" biaryl, by a stereoselective attack on a prostereogenic carbonyl group, followed by highly controlled conformational processes. Moreover, the reaction sequence is of great preparative value, since it gives access to even highly stereochemically hindered biologically relevant or preparatively useful biaryls of any desired configuration and in very high optical purities. The extension of this principle to other nucleophiles as well as to catalytic-type reactions, and, finally, the application of this principle to the stereoselective total synthesis of selected axially stereogenic natural and unnatural target molecules, are in progress.

ACKNOWLEDGEMENTS

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EXPERIMENTAL

Melting points were measured with a Kofler hot-stage apparatus and are corrected. Optical rotations were measured on a Perkin-Elmer 241 polarimeter. Microanalyses were performed by the microanalytical laboratory of the Inorganic Institute of the University of Würzburg. IR spectra were taken on a Perkin-Elmer 1420 infrared spectrophotometer. ^{1}H NMR spectra were obtained on a Bruker AC 200 spectrometer using $CDCl_3$ (δ = 7.26 ppm) as internal reference. Mass spectra were recorded on a Finnigan MAT 8200 spectrometer. HPLC analyses were carried out with a Knauer-364 pump, Chiralcel OF/OD columns (Daicel Chem. Ind., 25 x 0.46 cm) and an ERC-7215 UV detector; THF was freshly distilled from potassium using benzophenone ketyl as indicator. Ether and toluene were distilled from sodium wire and stored over 4 Å molecular sieves under argon. Optically pure (*R*)-(+)-1,1'-bi-2-naphthol[25], (*S*)-(+)-2-(anilinomethyl)pyrrolidine[19], (*S*)-(+)-2-(2,6-xylidinomethyl)pyrrolidine[20], (*S*)-(-)-α,α-diphenylprolinol[22], and (*S*)-(-)-α,α-diphenylvalinol[21] were prepared according to literature procedures. All asymmetric reactions were performed by the Schlenk-tube technique with dry glassware under an argon atmosphere.

*Conditions for the enantiomer analysis of the alcohols **4a** - **c** on chiral stationary phases:* Flow rate 0.5 ml/min; UV-Detection at 280 nm; the dead time t_0 was determined with 1,3,5-tri-*tert*-butylbenzene as standard[15]; sample concentration 1 µmol/ml; injection volume 5-10 µl.

*General procedure for the reduction of the menthyl esters **5**:* To a solution of 1 equivalent of the ester in THF (50 ml per mmol), 2 equivalents of $LiAlH_4$ were added at 0°C and stirring was continued for 2 h at room temp. The reaction mixture was hydrolyzed with 2 N HCl and extracted with ether. The combined organic layers were dried ($MgSO_4$), and after evaporation of the solvent under reduced pressure, the residue was purified chromatographically on silica gel (CH_2Cl_2) to yield the enantiomerically pure alcohols, which were analyzed by HPLC. Spectroscopic data, see below.

*General procedure for asymmetric reductions of **2** with diamine-derived reagents **7**:* To a suspension of 10 equivalents of $LiAlH_4$ in ether (5 ml per mmol), a solution of 12 equivalents of (*S*)-(+)-2-(anilinomethyl)-pyrrolidine, resp. (*S*)-(+)-2-(2,6-xylidinomethyl)pyrrolidine in ether (4 ml per mmol) was added dropwise over a period of 15 min under an argon atmosphere and the resulting reducing agent **7** was stirred for 1 h at room temp. After cooling to the required temperature, a solution of 1 equivalent of the lactone **2** in ether (60 ml per mmol) was added dropwise during 15 min and stirring was continued for 1 h. The reaction mixture was then hydrolyzed with water and adjusted to pH 4 - 5 with 1 N HCl. The organic layer was separated and the aqueous phase was extracted with ether. The combined organic extracts were washed with brine, dried ($MgSO_4$), filtered and evaporated to dryness under reduced pressure. Chromatographic purification of the residue on silica gel (Et_2O / petroleum ether, 1 : 1 to 2 : 1) afforded the alcohols **4**, which were analyzed by HPLC.

*(P)-1-(2'-Hydroxy-4',6'-dimethoxyphenyl)naphthalene-2-carboxylicacid-(S)-2''-(anilinomethyl)-1''-pyrrolidineamide (**9b-A**):* In the course of a preparative ring opening reaction with **7a**, besides the racemic aldehyde **8b** and the alcohol **4b**[26], also 12% of the corresponding amides **9b** (dr = 80 : 20) could be isolated and com-

plete characterization succeeded for the main *(P)*-configurated atropo-diastereomer **9b-A**; mp 106-108°C; $[\alpha]_D^{22}$ = + 118.1 (*c* = 0.505 in $CHCl_3$); CD: $\Delta\varepsilon_{205}$ +151.3, $\Delta\varepsilon_{225}$ -283.8, $\Delta\varepsilon_{250}$ +94.5, $\Delta\varepsilon_{283}$ -51.6; IR (KBr): ν 3380-3180 (br), 3025 (w), 2940 (w), 1590 (s), 1495 (m), 1460 (m), 1430 (m), 1195 (m), 1140 (m), 1095 (m), 810 (m), 745 (m); ^{1}H NMR: δ = 1.55-2.17 (m, 4 H), 3.31 (m_c, 5 H), 3.53, 3.85 (2 s, 3 H each), 4.42 (m_c, 1 H), 6.18-6.78 (m, 5 H), 7.16-7.97 (m, 8 H), 9.02 (s, 1 H); MS (70 eV): *m/z* (%) = 482 (29), 377 (18), 346 (15), 308 (34), 307 (100), 306 (74), 292 (15), 291 (12), 176 (12); Anal. Calcd for $C_{30}H_{30}N_2O_4$ (482.6): C, 74.67; H, 6.27; N, 5.80. Found: C, 74.37; H, 6.44; N, 5.67.

General procedure for the asymmetric reductions of lactones **2** *with binaphthol-derived reagents* ***6b****:* To a suspension of 10 equivalents of $LiAlH_4$ in THF (5 ml per mmol) at 0°C, a solution of 12 equivalents of *(R)*-(+)-1,1'-bi-2-naphthol in THF (6 ml per mmol) was added dropwise over a period of 15 min under an argon atmosphere. The resulting **6b** was stirred for 1 h at room temp., cooled to the required temperature, then a solution of **2** in THF (5 ml per mmol) was added dropwise during 15 min. After stirring for 1 h, the reaction mixture was hydrolyzed with water, acidified with 1 N HCl and extracted with ether. The combined organic layer was washed with brine, dried ($MgSO_4$), filtered and evaporated to dryness under reduced pressure. After purification of the residue on silica gel (Et_2O / petroleum ether, 1:2 to 2:1) the alcohols **2** could be analyzed by HPLC.

General procedure for the oxazaborolidine-assisted borane-reduction of the lactones **2***:* To a solution of 4 equivalents of borane-THF (0.2 M), a solution of 3 equivalents of **10** or **11** in THF (0.2 M) was added at 0°C under an argon atmosphere. After complete addition, the reaction mixture was warmed to 30°C, then a solution of 1 equivalent of **2** in THF (40 ml per mmol) was added dropwise during 10 min, and stirring was continued for 30 min. The reaction mixture was hydrolyzed with 1 M HCl, extracted with ether and the combined organic layers were dried ($MgSO_4$). After evaporation of the solvent under reduced pressure, the residue was filtered on silica gel (CH_2Cl_2) to yield the alcohols **4**.

In the course of preparative ring opening reactions with **11b**·BH_3, the isolated alcohols were recrystallized from CH_2Cl_2 / petroleum ether:

*(R)-2-Hydroxymethyl-1-(2-hydroxyphenyl)naphthalene (****4a-A****):* According to the general procedure, reduction of 49.3 mg (200 µmol) **2a** furnished 47.2 mg (188 µmol, 94%) of **4a** (**4a-A** : **4a-B** = 90.9 : 9.1) as a colorless solid. Recrystallization yielded 40.7 mg (163 µmol, 81%) of needle-shaped crystals; mp 185-187°C, 86% e.e., $[\alpha]_D^{25}$ = +3.36 (*c* = 0.160 in methanol). CD: $\Delta\varepsilon_{204}$ -130.9, $\Delta\varepsilon_{208}$ -127.1, $\Delta\varepsilon_{218}$ -197.3, $\Delta\varepsilon_{230}$ +100.1, $\Delta\varepsilon_{242}$ +21.9, $\Delta\varepsilon_{277}$ +38.9. **4a-A** is fully identical spectroscopically and chromatographically with racemic material obtained previously[11].

*(S)-2-Hydroxymethyl-1-(2-hydroxy-4,6-dimethoxyphenyl)naphthalene (****4b-A****):* According to the general procedure, reduction of 61.3 mg (200 µmol) **4b** yielded 58.5 mg (189 µmol, 95%) **4b-A** (**4b-A** : **4b-B** = 96.8 : 3.2). Recrystallization gave 48.3 mg (156 µmol, 78%) of enantiomerically pure material; mp 139°C, > 99.9% e.e., $[\alpha]_D^{25}$ = -15.7 (*c* = 0.130 in methanol). CD: $\Delta\varepsilon_{211}$ -93.8, $\Delta\varepsilon_{227}$ +31.5, $\Delta\varepsilon_{244}$ -22.9, $\Delta\varepsilon_{283}$ +2.4. **4b-A** is fully identical spectroscopically and chromatographically with racemic material previously obtained[11].

*(R)-2-Hydroxymethyl-1-(2-hydroxy-4,6-dimethylphenyl)naphthalene (****4c-A****):* According to the general procedure, reduction of 55.0 mg (200 µmol) **4c** gave 52.5 mg (188 µmol, 94%) **4c-A** (**4c-A** : **4c-B** = 98.5 : 1.5). Recrystallization furnished 44.9 mg (161 µmol, 81%) of enantiomerically pure material; mp 142°C, > 99.9% e.e., $[\alpha]_D^{25}$ = -34.9 (*c* = 0.134 in methanol). CD: $\Delta\varepsilon_{210}$ -244.5, $\Delta\varepsilon_{216}$ -210.7, $\Delta\varepsilon_{222}$ -262.0, $\Delta\varepsilon_{235}$ +59.8, $\Delta\varepsilon_{280}$ +48.0. **4c-A** is fully identical spectroscopically and chromatographically with racemic material obtained previously[11].

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