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Efficient kinetic resolution of a racemic 7-membered biaryl lactone: enantioselective synthesis of 2,2′-dihydroxymethyl-1,1′-binaphthyl †,‡

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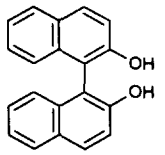
Abstract: A novel pathway to enantiomerically pure 2,2′-dihydroxymethyl-1,1′-binaphthyl is described, through kinetic resolution of its racemic 7-membered biaryl lactone precursor. Oxazaborolidine-assisted borane reduction of this lactone proceeds with very high enantioselectivity (k_{rel}=50). For optimum results on a preparative scale, a 'three fractions strategy' is suggested, which combines kinetic resolution and fractional crystallization and leads to both atropisomers in high enantiomeric excess. © 1997 Elsevier Science Ltd. All rights reserved.

Enantiomerically pure 2,2′-dihydroxy-1,1′-binaphthyl **1** and other C_2-symmetric biaryls have found widespread use as chiral building blocks for crown ethers,[2] chiral stationary phases,[3] as chiral shift reagents[4] and as chiral auxiliaries[5] for asymmetric reductions[6] and alkylations,[7] as well as stereoselective Ullmann coupling reactions.[8] Although several methods have been reported for the resolution of racemic **1** and related biaryls (*i.a.* fractional crystallization of diastereomeric compounds,[9,10] liquid chromatography on chiral stationary phases,[11] and enzymic hydrolysis of ester derivatives[12]), there is continued interest in further new methods for the preparation of such axially chiral compounds. Recently, homochiral **1** was prepared by fractional crystallization using L-proline[13] or *N*-benzylcinchonidinium chloride[14,15] or via a cyclic borate ester.[16] In this paper, we report on the enantioselective preparation of 2,2′-dihydroxymethyl-1,1-binaphthyl **2** by kinetic resolution of its racemic lactone precursor **3**, through highly efficient enantiomer-differentiating reduction by the oxazaborolidine–borane system. Stereochemically homogeneous **2** has previously been prepared by synthesis from other chiral compounds[17,18] and by asymmetric biaryl coupling reactions.[8,19,20]



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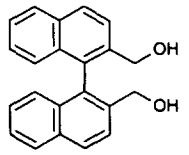

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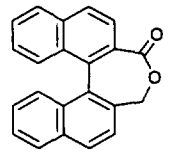

3

Results and discussion

Helically distorted lactone-biaryls such as **4** constitute valuable and easily available synthetic precursors to stereochemically homogeneous biaryls: as part of the 6-membered ring lactone, the biaryl axis of **4** is configurationally unstable, giving rise to rapidly interconverting helicene-like distorted atropo-enantiomers, *P*-**4** and *M*-**4**. Out of this helimeric mixture, **4** can be opened atropisomer-selectively, using *O*-, *N*- or *H*-nucleophiles.[21–23] Thus, atropo-enantioselective oxazaborolidine-assisted borane reduction leads to the configurationally stable diol **6** (Scheme 1) with high asymmetric inductions of up to 97% ee.[24,25]

† This paper is dedicated to Prof. Dieter Seebach, on the occasion of his 60th birthday.
‡ Part 64 of the series 'Novel Concepts in Directed Biaryl Synthesis'.[1]
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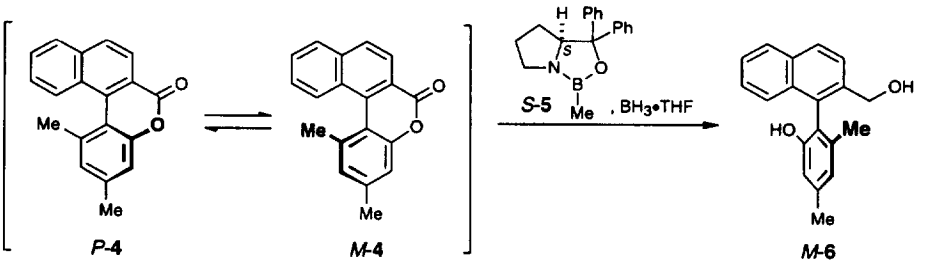
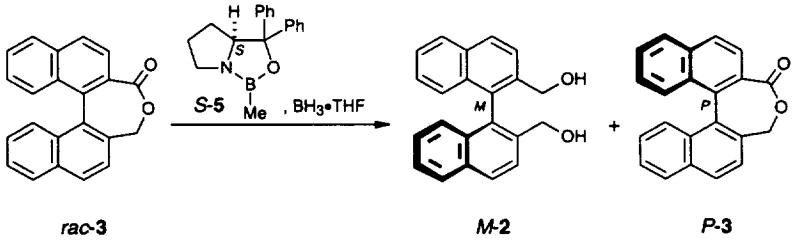


Scheme 1. Atropo-enantioselective ring opening of the configuratively labile lactone **4**.[24,25]

Mechanistic studies,[26] including extensive AM1 calculations,[27] suggest this unusual atropo-selective ring cleavage to be based on the enantiomer-differentiating reduction of **4**, here only in its *M*-atropisomeric form, with the rapid equilibrium *P*-**4** ⇌ *M*-**4** allowing a continuous supply of the more rapidly reacting helimer. Thus, virtually the entire racemic material is transformed into *M*-**6**, in the sense of a *dynamic* kinetic resolution. An extension of this methodology to the stereoselective reduction of structurally related 7-membered ring lactones like **3**, would be rewarding both for mechanistic reasons (ultimate proof of the kinetic resolution, in this case evident through the configurative stability of **3** at room temperature[28]), and because of the above-mentioned importance of enantiomerically pure diol **2** and the possible applicability of the method to the synthesis of natural products containing two C_1 units next to the biaryl axis.

For the rapid and exact quantification of the two enantiomers of lactone **3** and of the product alcohol **2**, chromatography on 'Chiralcel OF' (Daicel), a commercially available chiral stationary phase, proved to be the method of choice: With hexane:isopropanol (80:20; 0.8 ml/min) as the eluent, both compounds were efficiently resolved into their atropo-enantiomers in a single chromatographic run [for typical chromatograms, see Figure 1(A)]. Given the known absolute configurations of the lactone **3** enantiomers,[28] the absolute stereostructures of the resulting alcohols *P*- and *M*-**2** were easily deduced from the chromatogram.

Reduction of racemic lactone **3** with *S*-**5**/BH_3·THF (see Scheme 2) leads to an efficient kinetic resolution of the racemate: until nearly 50% conversion, *M*-**2** is produced with very high enantiomeric excesses of up to 96% ee, leaving unchanged *P*-**3** in virtually enantiopure form (ee >99%). The preferential formation of *M*-configured **2** supports the assumption of a dynamic kinetic resolution of **4** to follow the same selectivity principle.



Scheme 2. Kinetic resolution of racemic **3** by reduction with oxazaborolidine *S*-**5** and BH_3·THF.

Reaction parameters were optimized for different solvents and temperatures, initially on an analytical scale: in toluene the reaction is faster, but proceeds with a slightly lower degree of stereoselectivity. The best results were obtained in THF at −20°C with a calculated[29–31] relative rate k_{rel}=50 (compare Table 1).

The remaining homochiral lactone *P*-**3** can either be reduced with $LiAlH_4$ to give enantiopure *P*-**2**, or, if only *M*-configured material is required, *P*-**3** can be recycled by racemization in boiling decaline

for 13 h under Ar, followed by renewed stereoselective reduction of the *M*-enantiomer. This marks the mechanistic and thus preparative difference to the dynamic *in situ* recycling during the ring opening of the configuratively labile lactone **4**. Alternatively, *P*-configured material is accessible by reduction with the likewise available enantiomeric reagent, *R*-**5**.

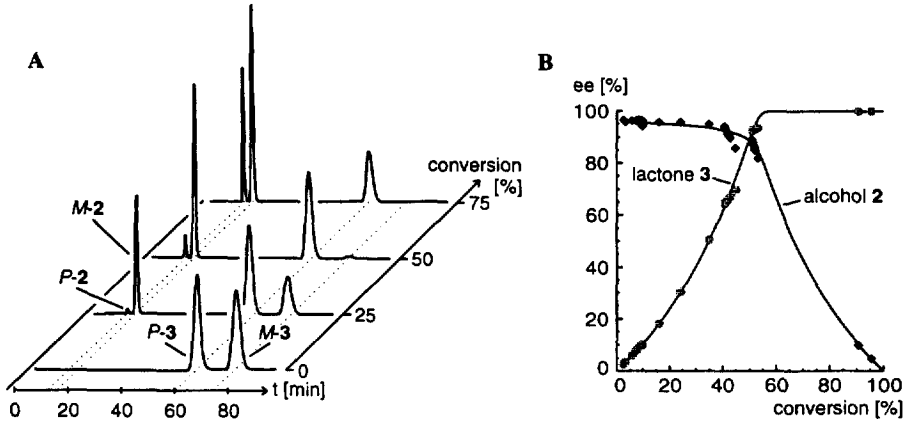


Figure 1. Oxazaborolidine-assisted borane reduction of *rac*-**3**: (A) the course of the kinetic resolution shown by chromatograms at various degrees of conversion and (B) enantiomeric excess of the remaining substrate *P*-**3** and the product *M*-**2** as a function of the conversion (THF, −20°C).

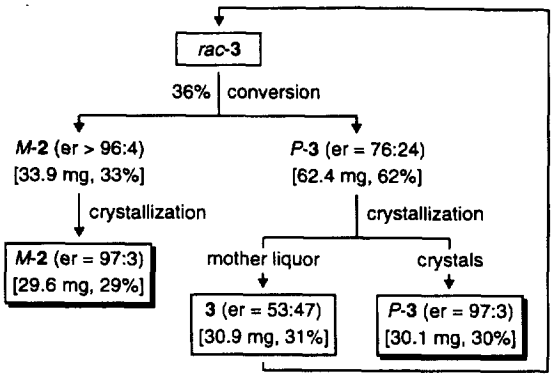
Table 1. Calculated relative rates k_{rel} for different reaction parameters

solvent	temp.	$k_{rel} = k_M / k_P$
THF	20°C	15
THF	0°C	30
THF	**-20°C**	**50**
toluene	20°C	17
toluene	-20°C	47

Without loss of enantioselectivity, the reaction can be performed preparatively (e.g. on a 100 mg scale), a 50% conversion leading to 46.4 mg (46%, i.e. 92% based on *M*-enantiomer present in **3**) of *M*-**2** (89% ee) and 46.0 mg (46%, i.e. 92%, see above) of *P*-**3** (87% ee), or alternatively, 40.6 mg (41%) of enantiopure *P*-**3** (>99% ee), at 58% conversion. By a single crystallization step, the enantiomeric purity can be further upgraded for both *M*-**2** and *P*-**3**, see Experimental.

Figure 1(B) suggests that even better preparative results might be obtained by interrupting the reaction at about 33% conversion to get *M*-2,2′-dihydroxymethyl-1,1′-binaphthyl *M*-**2** with high enantiomeric purity, to crystallize the less reactive *P*-enantiomer of the unreacted starting material, and to re-introduce the expected racemic mother liquor material to a renewed enantioselective reduction. This rational 'three fractions strategy' (see Scheme 3) was investigated on a preparative scale: the reaction was quenched after 36% conversion, to give ca a third of the material as *M*-2,2′-dihydroxymethyl-1,1′-binaphthyl *M*-**2**, still with a very high enantiomeric excess (93% ee, 33% yield; 94% ee after crystallization); from the enantiomerically enriched (ee 53%) unreacted lactone **3**, *P*-**3** (30%) was crystallized out in nearly enantiomerically pure form[28] (95% ee), while the remaining third fraction of essentially racemic lactone **3** in the mother liquor can be re-introduced back into the kinetic resolution process.

The presented work constitutes a conceptionally new approach to enantiomerically pure 2,2′-dihydroxymethyl-1,1′-binaphthyl **2** of predefined enantiomeric excess and any desired absolute



Scheme 3. The 'three fractions strategy' for the preparation of both *M*-**2** and *P*-**3** in highly enantiopure form.

configuration at the axis. The use of related 7-membered ring lactones for the preparation of naturally occurring biaryl target molecules is in progress.

Experimental

Melting points were determined with a Kofler hot-stage apparatus and are uncorrected. Optical rotations were measured on a Perkin–Elmer 241 MC polarimeter. HPLC analyses were carried out with a combination of a Waters HPLC pump 510, a 20 µl injection loop and a Chiralcel OF column (25×0.46 cm) with UV detection at 280 nm. The retention times are: *P*-**2**, 13 min; *M*-**2**, 16 min; *P*-**3**, 60 min; and *M*-**3**, 75 min. THF was freshly distilled from potassium, toluene was distilled from sodium wire. All reactions were carried out with dry glassware under an argon atmosphere. Compounds **2**[18] and **3**[28] were identical to material previously obtained.

Typical procedure (analytical scale)

To a solution of 26.8 mg (96.6 µmol) oxazaborolidine *S*-**5** in 1.5 ml solvent, 129 µl (129 µmol) of $BH_3 \cdot THF$ (1.0 M solution in THF) were added at 0°C. After stirring for 30 min at room temperature, the solution was added dropwise during 5 min to a solution of 10.0 mg (32.2 µmol) lactone **3** in 1.5 ml solvent at the given temperature. For HPLC analysis, 100 µl of the reaction mixture were quenched with 2 N HCl and extracted with diethyl ether. The organic solution was purified by TLC and then examined by HPLC.

M-*2,2′-Dihydroxymethyl-1,1′-binaphthyl* (M-*2*) *and* P-*dinaphth[2,1-c:1′,2′-e]oxepin-3-(5H)-one* P-*3*

On a preparative scale, the cooled (−20°C) reagent mixture analogously prepared from 1.29 ml (1.29 mmol) of $BH_3 \cdot THF$ and 268 mg (966 µmol) oxazaborolidine *S*-**5** in 8 ml THF, was added dropwise during 5 min to a solution of 100 mg (322 µmol) lactone **3** in 8 ml THF at −20°C. At 50% conversion, the reaction mixture was hydrolyzed by addition of 5 ml H_2O and acidified with 2 ml 2 N HCl. After removal of the solvent *in vacuo*, 10 ml H_2O were added and the mixture was extracted with CH_2Cl_2. The organic phase was dried over Na_2SO_4, the solvent was removed *in vacuo* and the residue was chromatographed on silica gel (diethyl ether:petroleum ether=3:1), leading to 46.4 mg (148 µmol, 46%) of *M*-**2** (89% ee) and 46.0 mg (148 µmol, 46%) of *P*-**3** (87% ee). Recrystallization from diethyl ether:CH_2Cl_2:petroleum ether yielded 39.7 mg (126 µmol, 39%) of *M*-**2** (99% ee) as colorless crystals; mp 168–170°C (lit.[17]: 167–168°C); $[\alpha]_D^{23}$ +67.9 (*c* 1.06, acetone) [lit.[17]: $[\alpha]_{546}^{21}$ +83.1, $[\alpha]_{579}^{21}$ +72.2 (*c* 1.15, acetone)] and 36.2 mg (117 µmol, 36%) of *P*-**3** (97% ee) as colorless needles; mp 230–231°C (lit.[28]: 229–230°C); $[\alpha]_D^{23}$ +493.6 (*c* 0.92, CH_2Cl_2) [lit.[28]: $[\alpha]_D^{25}$ +121 (*c* 0.035, CH_2Cl_2)].

In another experiment, the reaction was stopped after 58% conversion, yielding 55.2 mg (176 µmol, 54%) of *M*-**2** (73% ee) and 40.6 mg (131 µmol, 41%) of *P*-**3** (99.4% ee).

Kinetic resolution of rac-3 utilizing the 'three fractions strategy'

Under the same conditions, the reaction was interrupted after 36% conversion. Chromatography on silica gel as above gave 33.9 mg (108 μmol, 33%) of *M*-**2** (93% ee) and 62.4 mg (201 μmol, 62%) of *P*-**3** (53% ee), which were carefully crystallized from diethyl ether:CH_2Cl_2:petroleum ether to give 29.6 mg (94.2 μmol, 29%) of *M*-**2** (94% ee), 30.1 mg (97.0 μmol, 30%) of *P*-**3** (95% ee) and almost racemic (6% ee) mother liquor of lactone **3**, 30.9 mg (99.6 μmol, 31%).

Acknowledgements

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