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Enzymatic Resolution of 7,7′-Dihydroxy-8,8′-biquinolyl Dipentanoate and Its Conversion to 2,2′-Di-*tert*-butyl-7,7′-dihydroxy-8,8′-biquinolyl

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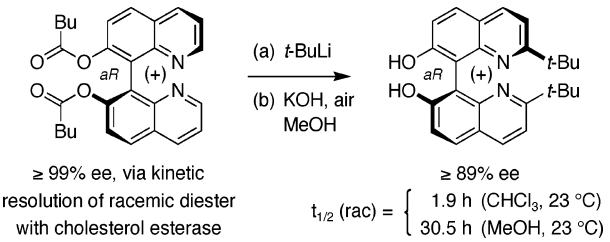

Incubation of (±)-7,7′-di(pentanoyloxy)-8,8′-biquinolyl (**4**) with a crude cholesterol esterase preparation (from bovine pancreas) yielded highly enantioenriched unreacted dextrorotatory material, (+)-(*aR*)-**4** (46%, ≥99% ee), accompanied by the expected diol product, (−)-(*aS*)-7,7′-dihydroxy-8,8′-biquinolyl (**1**), in modest enantiomeric excess (≥37%, ≥77% ee). Treatment of scalemic diesters **4** with *t*-BuLi, followed by saponification in the presence of air, gave 2,2′-di-*tert*-butyl-7,7′-dihydroxy-8,8′-biquinolyl (**2**) in enantio enriched form. Biquinolyl **2** is less configurationally stable than **1**, racemizing rapidly in $CHCl_3$ ($t_{1/2}$(rac) = 1.9 h, rt), and with a moderate rate in MeOH ($t_{1/2}$(rac) = 30.5 h, rt).

Axially chiral nitrogenous biaryl molecules present many tantalizing possibilities for the discovery of new asymmetric methods;[1,2] however, to date, relatively few enantioselective transformations utilizing these types of ligands have emerged.[3] By contrast, the proliferation of synthetic methodology based on analogous and less functionally diverse carbacyclic biaryl systems, particularly ligands of the 2,2′-disubstituted 1,1′-binaphthyl class (e.g., BINOL and BINAP),[4] continues apace.[5] The wider exploration of heterocyclic biaryl ligand families in asymmetric synthesis is hindered by a paucity of relevant data concerning atropisomer configurational stability and by the dearth of effective general methods for resolution of dinuclear heterocycles. Nevertheless, in search of novel ambifunctional chiral templates for stereoinduction, we identified the unusual 8,8′-biquinolyl scaffold[6] as a promising platform for study and sought an efficient enantioselective entry to 7,7′-dihydroxy-8,8′-biquinolyl (**1**) (Figure 1).[7] The synthesis of (±)-**1** was readily accomplished;[7a] however, we later struggled to realize a resolution of this intriguing molecule and ultimately resorted to an arduous procedure based on chromatographic separation of diastereomeric bismenthylcarbonate derivatives to achieve the desired goal.[7b] Our classical resolution of (±)-**1** served to provide small quantities of scalemic material for the determination of enantiomerization and chiroptical properties, but was recognized to be of limited practical value for the further development of the 8,8′-biquinolyl ligand family. To address this issue, we now report a superior method to resolve (±)-**1** into its enantiomorphic atropisomers by utilization of an efficient enzymatic hydrolytic kinetic resolution scheme, and also describe the attempted extension of this protocol to a 2,2′-disubstituted 8,8′-biquinolyl derivative (**2**).[8]

7,7′-Dihydroxy-8,8′-biquinolyl (**1**) is an aza-analogue of 1,1′-bi-2-naphthol (BINOL, **3**) in which peri C−H bonds have been formally replaced by N-atom lone pairs. Given the structural similarity between these two biaryl molecules, it is not an unreasonable proposition to suggest that tactics previously demonstrated for the resolution of BINOL may also be successfully applied to the comparable "azaBINOL" **1**. Among the many known methods for resolution of (±)-BINOL (**3**),[4a] a cholesterol esterase based protocol introduced by Kazlauskas was especially attractive.[9] Previously, bovine pancreas acetone

(1) Reviews: (a) Chelucci, G.; Thummel, R. P. *Chem. Rev.* **2002**, *102*, 3129. (b) Fletcher, N. C. *J. Chem. Soc., Perkin Trans. 1* **2002**, 1831.

(2) Significant new azacyclic biaryl molecules: (a) Mudadu, M. S.; Thummel, R. P. *J. Org. Chem.* **2006**, *71*, 7611. (b) Garciá-Cuadrado, D.; Cuadro, A. M.; Alvarez-Builla, J.; Sancho, U.; Castaño, O.; Vaquero, J. J. *Org. Lett.* **2006**, *8*, 5955. (c) Knoepfel, T. F.; Aschwanden, P.; Ichikawa, T.; Watanabe, T.; Carreira, E. M. *Angew. Chem., Int. Ed.* **2004**, *43*, 5971.

(3) A majority of such methods employ either 2,2′-bipyridyl or QUINAP related ligands. For selected examples, see: (a) Bouet, A.; Heller, B.; Papamicaël, C.; Dupas, G.; Oudeyer, S.; Marsais, F.; Levacher, V. *Org. Biomol. Chem.* **2007**, *5*, 1397. (b) Lyle, M. P. A.; Draper, N. D.; Wilson, P. D. *Org. Biomol. Chem.* **2006**, *4*, 877. (c) Taylor, A. M.; Schreiber, S. L. *Org. Lett.* **2006**, *8*, 143. (d) Kloetzing, R. J.; Knochel, P. *Tetrahedron: Asymmetry* **2006**, *17*, 116. (e) Aschwanden, P.; Stephenson, C. R. J.; Carreira, E. M. *Org. Lett.* **2006**, *8*, 2437. (f) Denmark, S. E.; Fan, Y.; Eastgate, M. D. *J. Org. Chem.* **2005**, *70*, 5235.

(4) Reviews: BINOL: (a) Brunel, J. M. *Chem. Rev.* **2005**, *105*, 857. (b) Chen, Y.; Yekta, S.; Yudin, A. K. *Chem. Rev.* **2003**, *103*, 3155. BINAP: (c) Berthod, M.; Mignani, G.; Woodward, G.; Lemaire, M. *Chem. Rev.* **2005**, *105*, 1801. (d) Noyori, R.; Takaya, H. *Acc. Chem. Res.* **1990**, *23*, 345.

(5) Selected recent highlights: (a) Tanaka, K.; Sagae, H.; Toyoda, K.; Noguchi, K.; Hirano, M. *J. Am. Chem. Soc.* **2007**, *129*, 1522. (b) Sakakura, A.; Ukai, A.; Ishihara, K. *Nature* **2007**, *445*, 900. (c) Hoen, R.; Tiemersma-Wegman, T.; Procuranti, B.; Lefort, L.; de Vries, J. G.; Minnaard, A. J.; Feringa, B. L. *Org. Biomol. Chem.* **2007**, *5*, 267. (d) Tosaki, S.-y.; Hara, K.; Gnanadesikan, V.; Morimoto, H.; Harada, S.; Sugita, M.; Yamagiwa, N.; Matsunaga, S.; Shibasaki, M. *J. Am. Chem. Soc.* **2006**, *128*, 11776. (e) Ooi, T.; Uematsu, Y.; Maruoka, K. *J. Am. Chem. Soc.* **2006**, *128*, 2548.

(6) 8,8′-Biquinolyls are little known in the literature. For a selection of examples not found within ref 7, see: (a) Ward, H. P.; Waring, M. G. *J. Am. Chem. Soc.* **1932**, *54*, 1697. (b) Lenner, M.; Lindgren, O. *Acta Crystallogr.* **1976**, *B32*, 1903. (c) Vaughan, L. G. *J. Organomet. Chem.* **1980**, *190*, C56. (d) Benito, Y.; Canoira, L.; Rodriguez, J. G. *Appl. Organomet. Chem.* **1987**, *1*, 535. (e) Staab, H. A.; Zirnstein, M. A.; Krieger, C. *Angew. Chem.* **1989**, *101*, 73. (f) Kitamura, C.; Yamamoto, S.; Ouchi, M.; Yoneda, A. *J. Chem. Res., Synop.* **2000**, 46.

(7) (a) Blakemore, P. R.; Kilner, C.; Milicevic, S. D. *J. Org. Chem.* **2005**, *70*, 373. (b) Blakemore, P. R.; Kilner, C.; Milicevic, S. D. *J. Org. Chem.* **2006**, *71*, 8212.

(8) Enzymatic kinetic resolution (via lipase catalyzed acetylation) has previously been applied to the heterocyclic biaryl molecule (±)-3,3′-bis-(hydroxymethyl)-2,2′-bipyridyl N,*N*′-dioxide, see: Sanfilippo, C.; D'Antona, N.; Nicolosi, G. *Tetrahedron: Asymmetry* **2006**, *17*, 12.

(9) (a) Kazlauskas, R. J. *J. Am. Chem. Soc.* **1989**, *111*, 4953. (b) Kazlauskas, R. J. *Org. Synth.* **1992**, *70*, 60.

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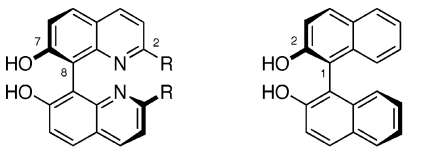
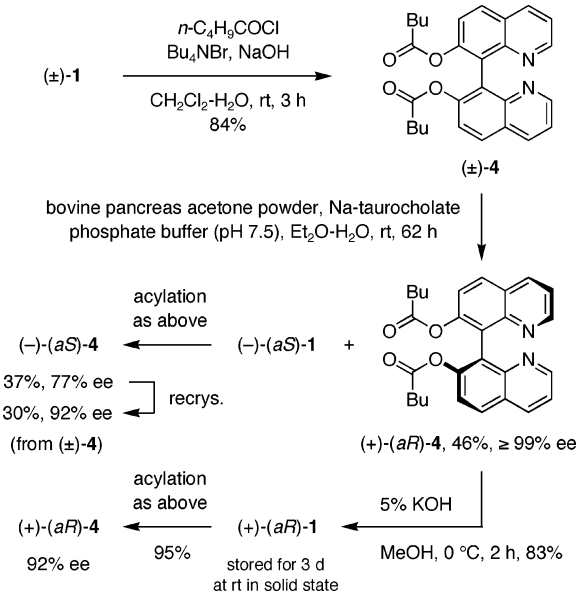


FIGURE 1. 7,7′-Dihydroxy-8,8′-biquinoyl (**1**) and 2,2′-di-*tert*-butyl-7,7′-dihydroxy-8,8′-biquinolyl (**2**), two sterically differentiated aza-analogues of 1,1′-bi-2-naphthol (BINOL, **3**).

SCHEME 1. Resolution of 7,7′-Dihydroxy-8,8′-biquinolyl (1)



powder, an inexpensive organ preparation with cholesterol esterase activity,[10,11] was shown to catalyze the hydrolysis of BINOL diesters in a bile salt emulsified H_2O-Et_2O mixture with excellent enantiodiscrimination favoring conversion of the (*aS*)-configurated atropisomer. In this manner, racemic BINOL dipentanoate was efficiently resolved on a 200 g scale to afford (−)-(*aS*)-**3** (33%/50%, >99% ee) and residual (*aR*)-configurated diester, which yielded (+)-(*aR*)-**3** (32%/50%, 99% ee) after saponification.[9a]

Eager to evaluate the Kazlauskas method against our chosen substrate, the dipentanoate derivative of (±)-**1** was prepared in a straightforward fashion under Schotten−Baumann conditions (Scheme 1). Unlike **1**,[7b] the optical isomers of **4** were readily distinguished by HPLC analysis on a standard chiral stationary phase,[12] therefore a means to directly assess the outcome of the projected resolution process was available. In the event, (±)-**4** was effectively resolved by the crude bovine cholesterol esterase. As with BINOL diesters, the enzyme preferentially hydrolyzed the (*aS*)-configurated atropisomer of **4** and left its antipode, (+)-(*aR*)-**4**, largely untransformed with essentially perfect enantiopurity (yield 46%/50%, ≥99% ee).[13] Conversion of the enzymatically generated (−)-(*aS*)-**1** back into its diester derivative, (−)-(*aS*)-**4**, for ease of isolation and stereochemical analysis, indicated that the diol had emerged from the kinetic resolution with submaximal enantiomeric excess (≥77% ee), due in part to the moderate configurational stability of **1**.[7b,14] Fortunately, recrystallization of the scalemic diester (−)-(*aS*)-**4** resulted in selective deposition of a highly crystalline racemate with an associated enhancement in the enantiopurity of the mother liquor to 92% ee. According to the above, both antipodes of diester **4** are now available in high enantiomeric excess from (±)-**4** via the agency of bovine cholesterol esterase. Significantly, it was discovered that these useful materials are not susceptible to unwanted racemization. Thus, an enantiopure sample of (+)-(*aR*)-**4** exhibited no errosion in percent ee after storage for 3 months in concentrated form at rt. Furthermore, no chemical nor stereochemical degradation was observed for a similar sample after protracted heating in toluene (110 °C, 7 d). Diesters (−)-(*aS*)-**4** and (+)-(*aR*)-**4** may therefore be regarded as shelf-stable precursors to scalemic samples of biquinolyl **1** and related enantioenriched 8,8′-biquinolyl-based materials (vide infra). A closed cycle of base-induced ester hydrolysis from **4** followed by re-acylation established the viability of this scheme: thus, saponification of (+)-(*aR*)-**4** (≥99% ee) with methanolic potassium hydroxide gave an enantioenriched sample of (+)-(*aR*)-**1** which, after a short period of storage in a pure state (3 d, rt), returned diester (+)-(*aR*)-**4** exhibiting 92% ee following pentanoylation.

Our interests in 8,8′-biquinolyl molecules extend beyond **1** to a variety of functionalized congeners,[7a] and at this juncture we sought 2,2′-disubstituted variants of the parent azaBINOL. Specifically, 2,2′-di-*tert*-butyl-7,7′-dihydroxy-8,8′-biquinolyl (**2**) was targeted as an axially chiral analogue of the useful 2,6-di-*tert*-butylpyridine class of sterically hindered Brønsted bases.[15,16] Introduction of substituents to the C2 position of quinoline compounds is most easily achieved by nucleophilic addition of an organolithium reagent followed by oxidative re-aromatization of the resulting dihydroquinoline. Accordingly, *t*-BuLi was added to carbamate (±)-**5**, the synthetic progenitor of (±)-**1**,[7a] to afford di-*tert*-butylated biquinolyl (±)-**6** in good but variable yields following spontaneous aerial oxidation during the course

(10) Reviews: (a) Hui, D. Y. *Biochim. Biophys. Acta* **1996**, *1303*, 1. (b) Rudd, E. A.; Brockman, H. L. In *Lipases*; Borgstrom, B., Brockman, H. L., Eds.; Elservier: Amsterdam, The Netherlands, 1984; pp 185−204.

(11) The structure for bovine pancreatic cholesterol esterase has been determined at 1.6 Å resolution, see: Chen, J. C.-H.; Miercke, L. J. W.; Krucinski, J.; Starr, J. R.; Saenz, G.; Wang, X.; Spilburg, C. A.; Lange, L. G.; Ellsworth, J. L.; Stroud, R. M. *Biochemistry* **1998**, *37*, 5107.

(12) A Daicel OD analytical HPLC column readily resolved enantiomers of **4** and was used to determine percent ee. See the Supporting Information for details.

(13) The absolute configurations for optical isomers of **1**, as (−)-(*aS*)-**1** and (+)-(*aR*)-**1** (for polarimeter readings in aq 1 M NaOH), were previously established unequivocally by an X-ray crystallographic analysis of a bismenthyl carbonate adduct derived from (−)-**1** and (+)-menthyl chloroformate, see ref 7b. From the chemical correlation experiments indicated in Scheme 1, it follows that the optical isomers of the diesters are likewise assigned as (−)-(*aS*)-**4** and (+)-(*aR*)-**4** (for polarimeter readings in $CHCl_3$).

(14) The isolation of homochiral (+)-(*aR*)-**4** in 46% yield admits the possibility of conversion of 4% of this material to (+)-(*aR*)-**1**, setting an upper limit of 85% ee for isolated (−)-(*aS*)-**1**. Further errosion in the enantiopurity of (−)-(*aS*)-**1** is accounted for by its background racemization during the resolution procedure (and subsequent processing of the material to (−)-(*aS*)-**4** for analysis).

(15) For an introduction to the chemistry of 2,6-disubstituted pyridines, see: (a) Andreeva, D. V.; Ip, B.; Gurinov, A. A.; Tolstoy, P. M.; Denisov, G. S.; Shenderovich, I. G.; Limbach, H.-H. *J. Chem. Phys. A* **2006**, *110*, 10872. (b) Spitzner, D. *Sci. Synth.* **2005**, *15*, 11. (c) Chardin, A.; Laurence, C.; Berthelot, M. *J. Chem. Res., Synop.* **1996**, 332. (d) Kanner, B. *Heterocycles* **1982**, *18*, 411.

(16) For selected applications of hindered pyridines and related bases, see: (a) Grundi, M. A.; Kaster, A.; Beaulieu, E. D.; Trauner, D. *Org. Lett.* **2006**, *8*, 5429. (b) Crich, D.; Smith, M.; Yao, Q.; Picione, J. *Synthesis* **2001**, *323*. (c) Carpino, L. A.; Ionescu, D.; El-Faham, A. *J. Org. Chem.* **1996**, *61*, 2460.

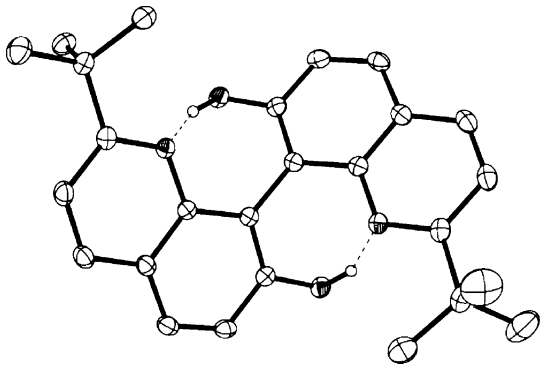
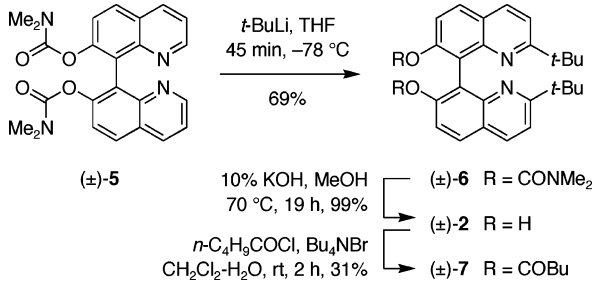


FIGURE 2. ORTEP diagram for biquinolyl (±)-**2** showing one of the two independent molecules present within the unit cell. The angle between least-squares fitted quinoline ring planes is 123.5°; N−HO contact distances for intramolecular hydrogen bonds are 1.70 and 1.83 Å. 50% Probability ellipsoids are plotted for non-hydrogen atoms.

SCHEME 2. Synthesis of (±)-2,2′-Di-*tert*-butyl-7,7′-dihydroxy-8,8′-biquinolyl (2)



of a normal workup (Scheme 2).[17] Basic hydrolysis of the carbamoyl residues from (±)-**6** released the desired azaBINOL derivative (±)-**2** as a crystalline material manifesting significantly different physical and chemical attributes to its parent biquinol **1**. For example, and as may be expected, compound **2** was observed to be less polar than **1** and as a consequence showed an excellent solubility profile in a wide range of common organic solvents, including MeOH, CH_2Cl_2, and THF (cf., solubility of **1** is limited to very polar media such as DMSO and H_2O). X-ray diffraction analysis of a good quality single crystal of (±)-**2** deposited from a MeOH solution established proof of structure for the biquinolyl and revealed a particularly obtuse interannular dihedral angle of 123.5° (Figure 2). This transoid conformational preference allowed for (or was promoted by) the formation of a pair of unusual intramolecular ring-to-ring N−H−O hydrogen bonds. Analogous solid state behavior was not observed for (±)-**1**, which preferentially crystallized from MeOH/H_2O as a solvate exhibiting intermolecular hydrogen bonds to MeOH with least-squares ring planes defining a less obtuse angle of 104.5°.[7a]

With an efficient synthesis of (±)-**2** established, its resolution was next explored. Ingenuously believing that (±)-**2** could be resolved in a like manner to (±)-**1**, the dipentanoate (±)-**7** was duly prepared and kinetic hydrolytic resolution with bovine cholesterol esterase attempted as before. Evidently, the promiscuity of the chosen enzyme did not extend to include recognition of a biaryl motif with bulky *t*-Bu appendages because neither enantiomorphic atropisomer of diester (±)-**7** was hydrolyzed to any detectable extent by the esterase. An alternate solution to the resolution problem presented itself when it was discovered that diester **4** could be converted to **2** by an analogous reaction sequence to that previously applied to dicarbamate **5**. Thus, addition of *t*-BuLi to diester **4** gave a complex diastereomeric mixture of dihydroquinolines **8** which converged on 2,2′-di-*tert*-butyl biquinolyl **2** in excellent overall yield following saponification in a stream of air.[18] When applied to an enantiopure sample of (+)-(*aR*)-**4**, this two-step transformation sequence produced dextrorotatory 2,2′-di-*tert*-butylated biquinolyl **2**, necessarily also (*aR*)-configurated, initially of at least 89% ee.[19]

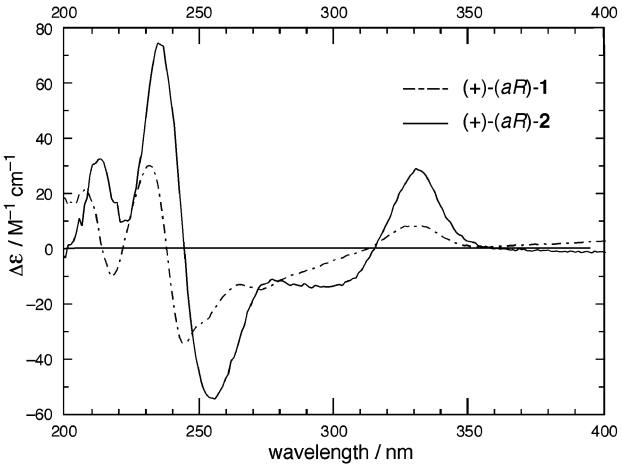
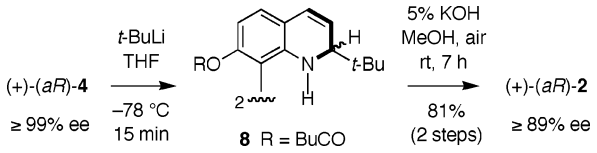


FIGURE 3. Comparison of electronic circular dichroism (CD) spectra for (+)-(*aR*)-7,7′-dihydroxy-8,8′-biquinolyl (**1**) and (+)-(*aR*)-2,2′-di-*tert*-butyl-7,7′-dihydroxy-8,8′-biquinolyl (**2**). CD spectrum for (+)-(*aR*)-**1** collected from H_2O solution (2.4 mM) at 50% ee; CD spectrum for (+)-(*aR*)-**2** collected from MeOH soluion (1.9 mM) at 40% ee. Both spectra are displayed as corrected to 100% ee.



The procurement of scalemic samples of **2** enabled study of chiroptical properties and configurational stability for this new biquinolyl molecule. Absolute configurations for the optical isomers of **2** were readily assigned as (+)-(*aR*)-**2** and (−)-(*aS*)-**2** (for polarimeter readings in MeOH or $CHCl_3$) by chemical correlation with appropriate stereodefined precursors **4**. The electronic circular dichroism spectrum of (+)-(*aR*)-**2** showed similar features to those previously observed for (+)-(*aR*)-**1**, but of 2-fold greater intensity (Figure 3).[7b] Specifically, the

(17) For representative examples of *t*-BuLi addition to quinolines, see: (a) Wolf, C.; Lerebours, R. *J. Org. Chem.* **2003**, *68*, 7077. (b) Klein Gebbink, R. J. M.; Watanabe, M.; Pratt, R. C.; Stack, T. D. P. *Chem. Commun.* **2003**, 630. (c) Delapierre, G.; Brunel, J. M.; Constantieux, T.; Buono, G. *Tetrahedron*: *Asymmetry* **2001**, *12*, 1345. (d) Stadlwieser, J.; Barbier, P.; Taylor, S. F. *Helv. Chim. Acta* **1998**, *81*, 1088.

(18) The survival of phenolic ester groups during the addition of *t*-BuLi to **4** is strongly suggestive that this transformation occurs via rapid single electron transfer from *t*-BuLi into a low-lying quinolyl orbital followed by radical−radical recombination. Aerial oxidation of **8** to **7** was achievable but sluggish; sparging air through the reaction mixture during saponification of **8** provided the most convenient and reliable way to oxidatively re-aromatize the quinoline nuclei en route to **2**. Use of CAN gave inferior results.

(19) Enantiomeric excess for **2** determined indirectly by HPLC analysis of its di-*p*-anisoyl derivative. See the Supporting Information for details.

dextrorotatory enantiomorph of **2** displayed a bisignate exciton couplet of negative chirality with positive maximum at 235 nm and negative minimum at 255 nm with an associated band intensity of $\Delta\Delta\epsilon = -130$ M^{-1} cm^{-1} (cf., $\Delta\Delta\epsilon = -65$ M^{-1} cm^{-1} for (+)-(*aR*)-**1**, values corrected to 100% ee in both cases).[20] Time addressed polarimeter readings for enantioenriched samples of **2** revealed an unexpectedly high configurational lability. Thus, dilute solutions (ca. 2.5 mM) of optically active material showed comparatively fast first-order exponential decay in their rotatory power with rate constants strongly dependent on solvent polarity. The racemization half-life of **2** in MeOH at ambient temperature (23 °C) was experimentally determined as 30.5 h; remarkably, racemization in $CHCl_3$ under otherwise identical conditions was observed to be over 16 times faster, with a half-life of just 1.9 h![21] By contrast, the racemization half-life for **1** was previously determined to be ca. 20 days at 43 °C in H_2O.[7b,22] The origin of the lower configurational stabililty for **2** vs **1** is not intuitively obvious; however, given that the racemization rate for **2** is strongly solvent dependent, we attribute the ability of this compound to form intramolecular hydrogen bonds to be linked to its ease of enantiomerization.[23]

In conclusion, a practical enzyme mediated method for the resolution of 7,7′-dihydroxy-8,8′-biquinolyl dipentanoate (**4**) has been demonstrated. Resolved diesters **4** may be regarded as convenient shelf-stable precursors to scalemic samples of "azaBINOL" **1** and other 8,8′-biquinolyls of interest, e.g., **2**. It is anticipated that this work will provoke the development of applications for 8,8′-biquinolyls in asymmetric synthesis.

Experimental Section

(±)-7,7′-Di(pentanoyloxy)-8,8′-biquinolyl (4). A solution of diol (±)-**1** (509 mg, 1.77 mmol)[7a] in 1.5 M aq NaOH (22 mL) was treated with Bu_4NBr (261 mg, 0.81 mmol) in CH_2Cl_2 (22 mL), followed by pentanoyl chloride (1.07 g, 8.87 mmol). The resulting biphasic mixture was stirred vigorously for 3 h at rt. H_2O (20 mL) and CH_2Cl_2 (20 mL) were then added and the layers shaken and separated. The aqueous phase was extracted with CH_2Cl_2 (2 × 40 mL) and the combined organic phases dried (Na_2SO_4) and concentrated in vacuo. The residue was recrystallized from EtOAc to give 403 mg of pure **4** as colorless prisms. The mother liquor residue was subjected to column chromatography (SiO_2, eluting with 20−100% EtOAc in hexanes) to afford a further 272 mg of pure solid **4**. Total yield = 676 mg (1.48 mmol, 84%): mp 145−146 °C (EtOAc); IR (KBr) 2923, 1752, 1494, 1460, 1154, 832 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.77 (2H, dd, J = 4.2, 1.7 Hz), 8.22 (2H, dd, J = 8.2, 1.7 Hz), 7.95 (2H, d, J = 8.9 Hz), 7.55 (2H, d, J = 8.9 Hz), 7.36 (2H, d, J = 8.3, 4.2 Hz), 2.08 (2H, dt, J = 15.6, 7.1 Hz), 2.00 (2H, dt, J = 15.6, 7.4 Hz), 1.17−1.04 (4H, m), 0.99 (4H, sextet, J = 7.1 Hz), 0.66 (6H, t, J = 7.3 Hz) ppm; ^{13}C NMR (75 MHz, $CDCl_3$, all 2C) δ 171.7 (0), 150.9 (1), 149.7 (0), 148.1 (0), 136.1 (1), 128.8 (1), 126.5 (0), 125.7 (0), 123.1 (1), 120.8 (1), 34.0 (2), 26.6 (2), 22.0 (2), 13.8 (3) ppm; MS (ES) *m*/*z* 479 $(M + Na)^+$, 457 $(M + H)^+$, 373, 271; HRMS (CI) *m*/*z* 457.2124 (calcd for $C_{28}H_{29}N_2O_4$ 457.2127).

Enzymatic Resolution of (±)-4 (Adapted from the method of Kazlauskas).[9] A 500 mL RB-flask equipped with a magnetic stir bar was charged with (±)-**4** (1.33 g, 2.91 mmol), Et_2O (125 mL), aq pH 7.5 phosphate buffer (125 mL, 0.1 M),[24] and then sodium taurocholate emulsifier (265 mg). Bovine pancreas acetone powder (320 mg, Sigma) was added and the contents of the then sealed flask stirred vigorously for 62 h at rt. The resulting yellow mixture was de-emulsified with EtOH (15 mL), Et_2O (125 mL) was added, and the layers were well shaken and separated. The aqueous phase was extracted with Et_2O (2 × 125 mL) and the combined organic extracts washed with brine (2 × 65 mL), dried (Na_2SO_4), and concentrated in vacuo. The residue was purified by column chromatograpy (eluting with 20−100% EtOAc in hexanes) to give (+)-(*aR*)-**4** (612 mg, 1.34 mmol, 46%) as a colorless oil with ≥99% ee (determined by HPLC analysis):[12] $[\alpha]^{20}_D$ +171 (*c* 1.28, $CHCl_3$). Hydrolysis product (−)-(*aS*)-**1** remained in the original aqueous phase and was converted without delay to (−)-(*aS*)-**4**. Thus, the aqueous phase was filtered through a glass wool plug and concentrated in vacuo. The residual crude diol (−)-(*aS*)-**1** (421 mg) was then esterified as described above for (±)-**1**, to yield (−)-(*aS*)-**4** (487 mg, 1.07 mmol, 37%, 77% ee) as an oily solid/gel following chromatography. Dissolution of the material in a minimum of hot EtOAc, thence cooling, resulted in deposition of racemic crystalline **4** (89 mg, 7%). The mother liquor was concentrated in vacuo to afford (−)-(*aS*)-**4** (397 mg, 0.870 mmol, 30%, 92% ee) as a colorless oil: $[\alpha]^{20}_D$ −147 (*c* 1.22, $CHCl_3$).

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Supporting Information Available: General experimental conditions, all other experimental procedures, ^1H and ^{13}C NMR spectra for all compounds, HPLC chromatograms, and a CIF file for (±)-**2**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(20) For introduction to the circular dichroism of biaryl compounds, see: (a) Mason, S. F.; Seal, R. H.; Roberts, D. R. *Tetrahedron* **1974**, *30*, 1671. (b) *Circular Dichroism and Linear Dichroism*; Rodger, A., Nordén, B., Eds.; Oxford University Press: New York, 1997. (c) Berova, N.; Nakanishi, K. In *Circular Dichroism*: *Principles and Applications*, 2nd ed.; Berova, N., Nakanishi, K., Woody, R. W., Eds.; Wiley-VCH: New York, 2000.

(21) First-order enantiomerization (k) rate constants for **2**: $k = 3.15 \times 10^{-6}$ s^{-1} (2.7 mM in MeOH, 23 °C); $k = 51.6 \times 10^{-6}$ s^{-1} (2.6 mM in $CHCl_3$, 23 °C). See the Supporting Information for details. Racemization half-life equals (ln 2)/2k, see: Ashweek, N. J.; Brandt, P.; Coldham, I.; Dufour, S.; Gawley, R. E.; Haeffner, F.; Klein, R.; Sanchez-Jimenez, G. *J. Am. Chem. Soc.* **2005**, *127*, 449.

(22) Interestingly, both **1** and **2** are configurationally stable in 5% KOH/MeOH solution at rt. Thus, polarimeter readings for enantioenriched materials in this medium (at 4−6 mM) were observed to be invariant during 7 d at rt. Good configurational stability for **1** in aq NaOH was noted previously, see ref 7b.

(23) Intramolecular N−H−O hydrogen bonds of the type observed in the X-ray crystal structure for **2** (Figure 2) may conceivably promote equilibration of the biquinolyl to a vinylogous amide (keto) tautomer with lower configurational stability than the phenolic form (this effect being most significant in a non-hydrogen-bonding solvent such as $CHCl_3$). In the case of BINOL (**3**), acid- or base-catalyzed generation of the keto-form dramatically reduces the energy barrier to interannular bond rotation, see: (a) Kyba, E. P.; Gokel, G. W.; de Jong, F.; Koga, K.; Sousa, L. R.; Siegel, M. G.; Kaplan, L.; Sogah, G. D. Y.; Cram, D. J. *J. Org. Chem.* **1977**, *42*, 4173. (b) Yudin, A. K.; Martyn, L. P. J.; Pandiaraju, S.; Zheng, J.; Lough, A. *Org. Lett.* **2000**, *2*, 41.

(24) Preparation of pH 7.5 phosphate buffer (0.1 M): aqueous stock solutions of 0.2 M NaH_2PO_4 (48 mL) and 0.2 M Na_2HPO_4 (252 mL) were mixed and then diluted with H_2O up to a total volume of 600 mL.