Natural Products

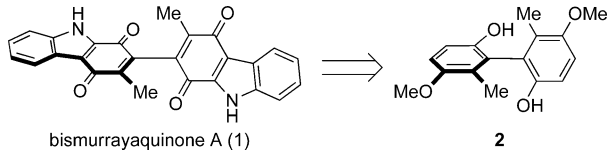
DOI: 10.1002/anie.201104726

Enantioselective Total Synthesis and Studies into the Configurational Stability of Bismurrayaquinone A**

*Leah C. Konkol, Fenghai Guo, Amy A. Sarjeant, and Regan J. Thomson**

The carbazole alkaloids represent a large and structurally rich family of natural products that are produced by a variety of terrestrial plants.[1] In particular, plants within the Rutaceae family are notable producers of these compounds, with the genus Murraya providing the greatest number of unique structures. Commonly found in the outer Himalayas and on the Indian peninsula, the leaves of *M. koenigii* (L.) Spreng are, among other things, extensively utilized as a spice flavoring by the people of these areas giving it the name "curry-leaf tree". Extracts of the plant are also used in local medicine owing to their antimicrobial activity.[2]

Within this large family of alkaloids, we were particularly interested in the axially chiral dimeric carbazoles,[3] and most specifically bismurrayaquinone A (**1**, Scheme 1). This unique dimeric carbazolequinone was isolated from the roots of *M. koenigii* (L.) Spreng by Furukawa and co-workers in 1993[4] and has been the subject of nonstereoselective total syntheses by the groups of both Bringmann and Murphy.[5] Somewhat surprisingly, there has never been an enantioselective synthesis of **1**. Bringmann and co-workers did, however, prepare racemic **1** and separated the two enantiomers using preparative HPLC,[5a] and in 2001 reported an approach towards a stereoselective synthesis.[6]

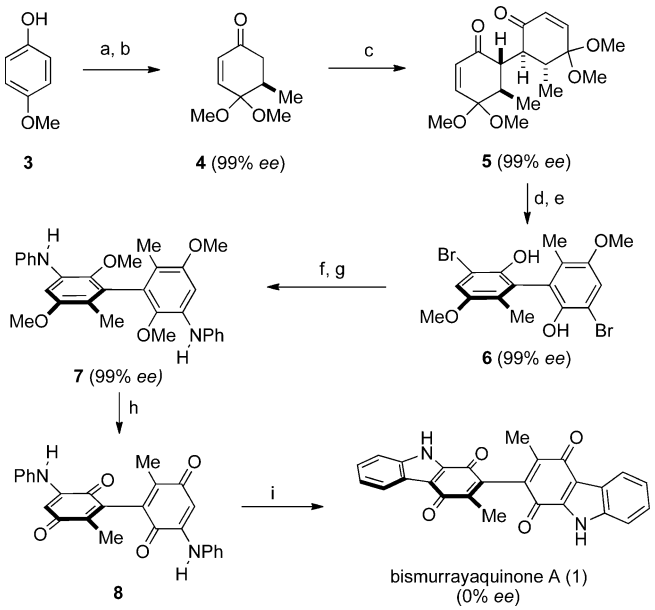


Scheme 1. Bismurrayaquinone A (**1**) and key biphenol **2**.

Because no enantioselective synthesis of bismurrayaquinone A (**1**) had been reported, and because there is very little literature data on axially chiral biquinones,[7] we were compelled to explore strategies for the enantioselective synthesis of these molecules. Recently, we reported the development of a new method for synthesizing enantiomerically pure axially chiral biphenols by a method we termed "traceless stereochemical exchange".[8] This method allows ready access to biphenols of the type represented by structure **2** (Scheme 1), and herein we report the use of this method to conduct the first enantioselective synthesis of bismurrayaquinone A (**1**). These studies have also revealed a fascinating phenomenon related to the configurational stability of chiral biquinones.

Our synthesis of bismurrayaquinone A (**1**) commenced from commercially available 4-methoxyphenol (**3**), which was converted into enone **4** by oxidation to the corresponding dimethylketal quinone[9] and subsequent enantioselective conjugate addition of dimethylzinc using Feringa's method (Scheme 2).[10]

The efficiency of the Feringa conjugate addition in terms of yield dropped from 52% on a 5 gram scale to 45% yield when conducted on 10 grams, but the enantioselectivity was



Scheme 2. a) $PhI(OAc)_2$ (1.2 equiv), MeOH, 91%; b) Me_2Zn (0.9 equiv), (*S*,*R*,*R*)-phosphoramidite ligand (4.5 mol%), $Cu(OTf)_2$ (2 mol%), 45–52%; c) LDA (1.1 equiv); $CuCl_2$ (1.1 equiv), 63%; d) $BF_3{\cdot}OEt_2$ (10 equiv), toluene, reflux, 87%; e) Br_2 (2.0 equiv), 90%; f) MeI (10 equiv), KOH (3.0 equiv), 84%; g) aniline (3.0 equiv), $Pd(OAc)_2$ (8 mol%), $[HPtBu_3][BF_4]$ (11 mol%), NaO*t*Bu (11 equiv), toluene, reflux, 93%; h) BBr_3 (20 equiv); SiO_2/air, 62%; i) $Pd(OAc)_2$ (0.5 equiv), $Cu(OAc)_2$ (5.0 equiv), AcOH, reflux, 33%. LDA = lithium diisopropylamide, (*S*,*R*,*R*)-phosphoramidite ligand = (*S*,*R*,*R*)-(−)-(3,5-Dioxa-4-phosphacyclohepta[2,1-a:3,4-a′]dinaphthalen-4-yl)bis(1-phenylethyl)amine, Tf = trifluoromethanesulfonyl.

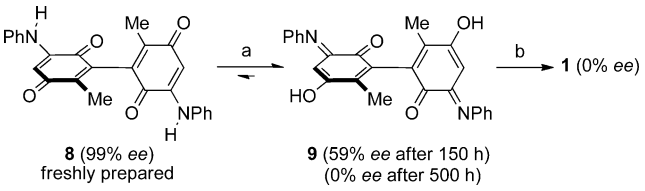
[*] L. C. Konkol, Dr. F. Guo, Dr. A. A. Sarjeant, Prof. R. J. Thomson
Department of Chemistry, Northwestern University
2145 Sheridan Rd, Evanston, IL 60208 (USA)
E-mail: r-thomson@northwestern.edu

[**] This work was supported by the National Institutes of Health (1R01GM085322), Northwestern University (NU), and Amgen. We thank Reed Larson (NU) for assistance with X-ray crystallographic analysis. We gratefully thank Prof. Dr. Gerhard Bringmann and Dr. Torsten Bruhn (University of Würzburg) for CD spectra calculations.

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/anie.201104726.

maintained at 99% *ee*. Gram-scale oxidative dimerization of **4** was conducted under our reported reaction conditions[8] to provide dione **5** in 63% yield (99% *ee*).[11] Conversion of dione **5** into bromophenol **6** proceeded smoothly after aromatization to **2** (not shown) and regioselective bromination. Our plan at this juncture was to utilize methods for palladium-catalyzed carbazolequinone synthesis to complete the synthesis.[12] Accordingly, we converted bromide **6** into bisaniline **7** through O-methylation followed by an efficient Buchwald–Hartwig amination with aniline (93%), using reaction conditions reported by Bedford and Betham.[13] Conversion of **7** into the open biquinone **8** was carried out as a prelude to carbazole formation. This transformation was best achieved by global demethylation of **7** with BBr_3 to produce the free dihydroquinone, which spontaneously oxidized to biquinone **8** upon stirring the reaction mixture with silica gel in the presence of air (62%). Exposure of biquinone **8** to the reaction conditions of Knölker et al. for $Pd(OAc)_2$-catalyzed carbon–carbon bond formation[12a] generated bismurrayaquinone A (**1**) in a modest 33% yield. The spectroscopic data (^1H and ^{13}C NMR) were identical to those reported in the literature,[4,5a] but analysis of the synthetic material revealed it to be racemic.[14]

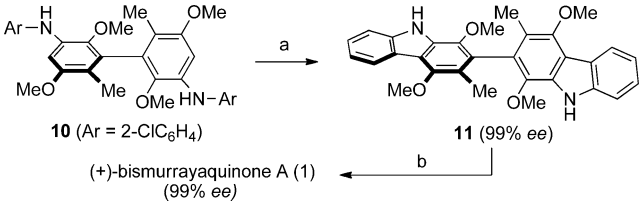
To determine the point at which racemization had occurred we first established that dihydroquinone **7** was optically pure (99% *ee*). Analysis of biquinone **8** shortly after it was isolated indicated that it maintained its optical purity initially, but underwent an interesting N–O tautomerization to form enol **9** after purification (Scheme 3). This tautomerization complicated the analysis of the optical purity. We could, however, resolve the enantiomeric tautomers of **9** by HPLC and after 150 hours at room temperature noted the sample was 59% *ee*. The sample was fully racemic after 500 hours at room temperature. Given the elevated temperatures required for carbazole formation, the 59% *ee* sample of **9** provided racemic bismurrayaquinone A (**1**) in 65% yield using the reaction conditions of Knölker et al. for carbazole formation.[12a]



Scheme 3. a) Room temperature, 150 h, 100% conversion; b) $Pd(OAc)_2$ (0.5 equiv), $Cu(OAc)_2$ (5.0 equiv), AcOH, reflux, 65%.

These findings raised questions regarding the configurational stability of the natural product itself. In their report on the isolation, Furukawa and co-workers did not record an optical rotation or CD-spectrum of natural bismurrayaquinone A (**1**),[4] and so it is not known whether **1** exists as a single enantiomer or as a racemate in nature. As mentioned in the introduction, Bringmann and co-workers were able to separate racemic **1** using HPLC. Despite recording CD spectra of their pure enantiomers they did not, however, mention anything regarding the configurational stability of **1**. In light of our findings regarding the stability of biquinone **8**, we anticipated that enantiomerically pure bismurrayaquinone A (**1**) would most likely undergo rapid racemization, and we next sought to generate optically pure bismurrayaquinone A (**1**) to test this assumption.

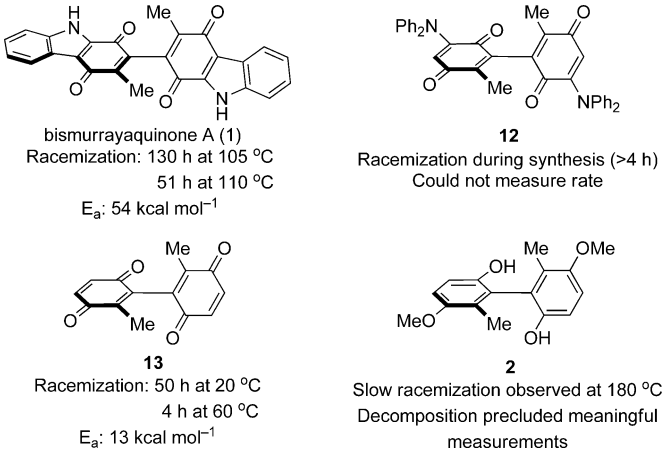
Given that dimethylhydroquinone **7** was configurationally stable, we expected the corresponding carbazole (i.e., **11**) to be similarly stable (Scheme 4). Mild oxidative conversion of



Scheme 4. a) $Pd(OAc)_2$ (20 mol%), $[HPtBu_3][BF_4]$ (28 mol%), NaO*t*Bu (7.0 equiv), 160°C, microwave, 73% b) CAN (10 equiv), $MeCN/H_2O$, 95%. CAN = ceric ammonium nitrate.

11 into **1** would then allow us to follow the racemization of the natural product and provide fundamental insight into these structures. Dihydroquinone **7** proved resistant to palladium-catalyzed carbazole formation under a wide variety of reaction conditions. However, conversion of bromide **6** into chloroaniline **10** by a Buchwald–Hartwig amination with 2-chloroaniline enabled the desired carbazole **11** to be formed in good yield (65%, 2 steps from **6**).[13,15] Conversion into bismurrayaquinone A (**1**) was achieved through a rapid and high yielding oxidation with ceric ammonium nitrate (95% yield).

Much to our surprise, synthetic bismurrayaquinone A (**1**) was configurationally stable at room temperature and did not tautomerize. We therefore decided to experimentally determine the activation barriers of atropisomerization for a number of biquinones, including the natural product (Scheme 5). While bismurrayaquinone A (**1**) was configurationally stable at room temperature, it racemized within



Scheme 5. Racemization studies of biquinones.

130 hours when heated at 105 °C and within 51 hours at 110 °C. The activation energy (E_a) of atropisomerization of **1** was determined to be 54 kcal mol^{-1} by monitoring the change in enantiomeric excess over time at two different temperatures (see the Supporting Information). Unfortunately, the open biquinone **8** proved difficult to study owing to tautomerization (see Scheme 3), and the diphenyl homologue **12** underwent rapid racemization during its synthesis from the corresponding dihydroquinone. The simplified quinone **13** was more stable than **12**, but significantly less so than bismurrayaquinone A (**1**); racemization was complete after 50 hours at room temperature. The E_a of atropisomerization of **13** was determined to be 13 kcal mol^{-1}, significantly lower than for bismurrayaquinone A (**1**). The corresponding biphenol **2** required heating to 180 °C for racemization to be observed, but competing decomposition afforded data that was unacceptable for calculating the activation barrier of atropisomerization.

Rationalization of the relative stability of bismurrayaquinone A (**1**) compared to the other biquinones studied was challenging. We initially speculated that racemization might be induced photochemically as related phenomena have been reported for several axially chiral biaryls.[16] Racemization of biquinone **8** proceeded just as rapidly in the dark as it did in sunlight, however. Lumb and Trauner showed in their elegant biomimetic synthesis of microphyllaquinone that binaphthoquinones will undergo a tautomerization/6π-electrocyclization cascade.[17] If such a process was reversible this may promote racemization, but under our neutral reaction conditions we never observed the formation of a pyran species that would indicate such a process was operative for **1** or **13**.[18] We next turned to the molecular modeling of the atropisomerization of **1** and **13**; this process was carried out by calculating an energy profile with a changing dihedral angle about the central C–C bond (Spartan, B3LYP 6-31G* level).[19] Unfortunately, at this level of theory both compounds gave activation barriers of approximately 23–25 kcal mol^{-1}, which are values significantly different than the experimentally determined values. We could not make any firm conclusions from these calculations.

Insight came when we succeeded in growing single crystals of bismurrayaquinone A (**1**) and biquinone **13** that were suitable for X-ray crystallographic analysis.[20] As anticipated each of the biquinones possessed shorter C–O bonds than the corresponding biphenol **2**[8] (1.22 Å for **1** and **13** versus 1.37 Å for **2**), thus establishing a rationale for the lower activation barriers of atropisomerization of biquinones compared to biphenols. In general, bond lengths for **1** and **13** were similar, but we noted greater out-of-plane distortion for biquinone **13** in comparison to bismurrayaquinone A (**1**). A view of the X-ray structures of each molecule, with an arrow highlighting the effect of the distortion, clearly shows this interesting phenomenon (Figure 1).

Out-of-plane distortion of the type exhibited by biquinone **13** has been proposed by Ling and Harris to explain observed trends in the activation parameters for the racemization of 2,2′-diiodobiphenyls.[21] These deformations lead to significant ground-state destabilization and allow the substituents on either side of the central carbon–carbon bond to pass one another sequentially during atropisomerization. Consequently, more easily accommodated out-of-plane distortion should lead to lower activation barriers of atropisomerization, an outcome consistent with our experimental observations in the current study. Related distortions are seen in the X-ray structure of gossypolone,[22] a 2,2′-binaphthoquinone that racemizes at room temperature.[7a,b]

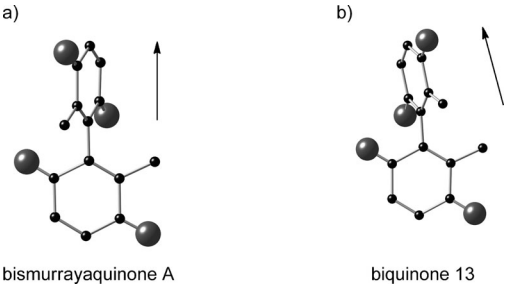


Figure 1. X-ray structures of a) bismurrayaquinone A (**1**) and b) biquinone **13**, with non-crucial atoms removed for clarity.

Lastly, our X-ray structure of bismurrayaquinone A (**1**) enabled us to confirm its absolute configuration though Bijvoet-pair analysis.[23] Thus, the sequences outlined herein provided (*R*)- or *M*-(+)-bismurrayaquinone A. We also prepared (*S*)- or *P*-(−)-bismurrayaquinone A through an analogous sequence, employing *ent*-**4**. Curiously, however, the CD spectrum we recorded for *M*-**1** and *P*-**1** displayed the opposite shape to that predicted by the calculations reported by Bringmann and co-workers in 1995.[5a] Bringmann and co-workers noted that application of the standard exciton chirality method[24] was not possible, and so made recourse to an alternative method involving semiempirical AM1 and CNDO calculations to predict the CD spectrum of each enantiomer. Advances in computational techniques, however, have now allowed a recalculation of the CD spectrum using the TDCAM-B3LYP/TZVP method.[25] These new results support our X-ray crystallographic analysis that (+)-bismurrayaquinone A possesses the (*R*)- or *M*-configuration. Despite the fact that any definitive statement as to the naturally occurring configuration of bismurrayaquinone A (**1**) will require reisolation from the curry-leaf tree, our work and that of Bringmann and co-workers serves to highlight the impact synthetic chemistry can have on fundamental questions of structure and stereochemistry.

In conclusion, we have completed the first enantioselective synthesis of bismurrayaquinone A (**1**) through a concise strategy that employs traceless stereochemical transfer. The approach utilized axially chiral bromide **6** as a late-stage precursor, thus enabling a bidirectional palladium-catalyzed carbazole synthesis. Future elaboration of this useful biphenyl core will enable the synthesis and biological evaluation of numerous bismurrayaquinone A analogues. The activation parameter for atropisomerisation of bismurrayaquinone A (**1**) was experimentally determined and a rationale based upon X-ray data analysis has been proposed to account for the observed differences in activation barriers of atropisomerization between related compounds. Further details of our

studies into the atropisomerism of biquinones will be reported in due course.

Received: July 7, 2011
Published online: September 7, 2011

Keywords: alkaloids · axial chirality · biquinones · natural products · total synthesis

[1] For relevant reviews on the isolation, biological activity, and synthesis of carbazole alkaloids, see: a) H.-J. Knölker, K. R. Reddy, *Chem. Rev.* **2002**, *102*, 4303 – 4427; b) H.-J. Knölker, *Top. Curr. Chem.* **2005**, *244*, 115 – 148.

[2] R. S. Ramsewak, M. G. Nair, G. M. Strasburg, D. L. DeWitt, J. L. Nitiss, *J. Agric. Food Chem.* **1999**, *47*, 444 – 447.

[3] For a review of biarylic biscarbazole alkaloids, see: a) S. Tasler, G. Bringmann, *Chem. Rec.* **2002**, *2*, 113 – 127; the following reviews on axially chiral biaryl compounds also contain a wealth of interesting information, see; b) G. Bringmann, A. J. P. Mortimer, P. A. Keller, M. J. Gresser, J. Garner, M. Breuning, *Angew. Chem.* **2005**, *117*, 5518 – 5563; *Angew. Chem. Int. Ed.* **2005**, *44*, 5384 – 5427; c) G. Bringmann, T. Gulder, T. A. M. Gulder, M. Breuning, *Chem. Rev.* **2011**, *111*, 563 – 639.

[4] C. Ito, Y. Thoyama, M. Omura, I. Kajiura, H. Furukawa, *Chem. Pharm. Bull.* **1993**, *41*, 296 – 2100.

[5] a) G. Bringmann, A. Ledermann, M. Stahl, K.-P. Gulden, *Tetrahedron* **1995**, *51*, 9353 – 9360; b) W. S. Murphy, M. Bertrand, *J. Chem. Soc. Perkin Trans. 1* **1998**, 4115 – 4119; c) G. Bringmann, S. Tasler, *Tetrahedron* **2001**, *57*, 331 – 343; Harrity and coworkers reported the synthesis of racemic *N*-methylbismurrayaquinone, see: d) M. W. Davies, C. N. Johnson, J. P. A. Harrity, *J. Org. Chem.* **2001**, *66*, 3525 – 3532.

[6] G. Bringmann, S. Tasler, H. Endress, J. Mühlbacher, *Chem. Commun.* **2001**, 761 – 762.

[7] The structurally related biquinone, gossypolone, has been shown to racemize at room temperature, see: a) V.-T. Dao, M. K. Dowd, M.-T. Martin, C. Gaspard, M. Mayer, R. J. Michelot, *Eur. J. Med. Chem.* **2004**, *39*, 619 – 624; b) L. Zhang, H. Jiang, X. Cao, H. Zhao, F. Wang, Y. Cui, B. Jiang, *Eur. J. Med. Chem.* **2009**, *44*, 3961 – 3972; for related phenomena observed for arylquinones, see: c) U. S. M. Maharoof, G. A. Sulikowski, *Tetrahedron Lett.* **2003**, *44*, 9021 – 9023.

[8] F. Guo, L. C. Konkol, R. J. Thomson, *J. Am. Chem. Soc.* **2011**, *133*, 18 – 20.

[9] Prepared according to the method of Pelter and Elgendy, see: A. Pelter, S. Elgendy, *Tetrahedron Lett.* **1988**, *29*, 677 – 680.

[10] R. Imbos, M. H. G. Brilman, M. Pineschi, B. L. Feringa, *Org. Lett.* **1999**, *1*, 623 – 625.

[11] The enantiomeric excess for all chiral molecules was determined by HPLC analysis. See the Supporting Information for details.

[12] a) H.-J. Knölker, K. R. Reddy, A. Wagner, *Tetrahedron Lett.* **1998**, *39*, 8267 – 8270; b) B. Liégault, D. Lee, M. P. Huestis, D. R. Stuart, K. Fagnou, *J. Org. Chem.* **2008**, *73*, 5022 – 5028.

[13] R. B. Bedford, M. Betham, *J. Org. Chem.* **2006**, *71*, 9403 – 9410.

[14] This was initially concluded based upon a flat CD spectrum, but later confirmed by HPLC analysis. See the Supporting Information for details.

[15] a) R. B. Bedford, M. Betham, J. P. H. Charmant, A. L. Weeks, *Tetrahedron* **2008**, *64*, 6038 – 6050; b) L.-C. Campeau, M. Parisien, A. Jean, K. Fagnou, *J. Am. Chem. Soc.* **2006**, *128*, 581 – 590; for the successful implementation of a similar carbazole formation in natural product synthesis, see: c) S. Bouclé, J. Guillard, *Synthesis* **2011**, 1616 – 1620; d) J. D. Sánchez, C. Avendaño, J. C. Menéndez, *Synlett* **2008**, 1371 – 1375.

[16] For some key examples, see: a) K. Mislow, A. J. Gordon, *J. Am. Chem. Soc.* **1963**, *85*, 3521 – 3521; b) H. E. Zimmerman, D. S. Crumrine, *J. Am. Chem. Soc.* **1972**, *94*, 498 – 506; c) M. Zhang, G. B. Schuster, *J. Phys. Chem.* **1992**, *96*, 3063 – 3067; d) T. Hattori, Y. Shimazumi, H. Goto, O. Yamabe, N. Morohashi, W. Kawai, S. Miyano, *J. Org. Chem.* **2003**, *68*, 2099 – 2108.

[17] J. P. Lumb, D. Trauner, *Org. Lett.* **2005**, *7*, 5865 – 5868.

[18] A 3,3′-diphenyl substituted biquinone that cannot tautomerize also racemized at room temperature, providing further evidence against such a mechanism.

[19] Details are provided in the Supporting Information.

[20] CCDC 829781 (**1**), 829782 (**2**), 829783 (**5**), 829784 (**13**), and 835897 (**S2**; see the Supporting Information) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif. Supporting Information for this manuscript contains additional details on the assignment of absolute strereochemistry through X-ray crystallographic analysis.

[21] C. C. K. Ling, M. M. Harris, *J. Chem. Soc.* **1964**, 1825 – 1835.

[22] X-ray structure: a) S. A. Talipov, B. T. Ibragimov, K. M. Beketov, Sh. Yu. Islambekov, R. G. Mardanov, A. I. Ismailov, *Khim. Prir. Soedin.* **1995**, 814 – 819; computations: b) C. L. Beisel, M. K. Dowd, P. J. Reilly, *J. Mol. Struct.: THEOCHEM* **2005**, *730*, 51 – 58; the related structure of 6,6′-dimethoxygossypolone displays similar deformations, see: c) C. A. Zelaya, E. D. Stevens, M. K. Dowd, *Acta Crystallogr. Sect. C* **2010**, *66*, 517 – 520.

[23] R. W. W. Hooft, L. H. Straver, A. L. Spek, *J. Appl. Crystallogr.* **2008**, *41*, 96 – 103. This assignment is consistent with the configuration established for biphenol **2** and bromide **S2** (see the Supporting Information for additional details).

[24] N. Harada, K. Nakanishi, *Circular Dichroic Spectroscopy—Exciton Coupling in Organic Stereochemistry*, University Science Books: Mill Valley, CA, and Oxford University Press: Oxford, **1983**.

[25] Details are contained within the Supporting Information.

