Organic LETTERS

Letter

pubs.acs.org/OrgLett

Remote Control of Helical Chirality: Thermodynamic Resolution of a Racemic Mixture of CTV Units by Remote Stereogenic Centers

Bastien Chatelet,[†] Lionel Joucla,[†] Daniele Padula,[§] Lorenzo Di Bari,[∥] Guillaume Pilet,[⊥] Vincent Robert,[#] Véronique Dufaud,[$] Jean-Pierre Dutasta,[†] and Alexandre Martinez*[,†,‡]

[†]Laboratoire de Chimie, École Normale Supérieure de Lyon, CNRS, UCBL, 46, Allée d'Italie, F-69364 Lyon, France

[‡]Equipe Chirosciences, Aix Marseille Université, Centrale Marseille, CNRS, iSm2 UMR 7313, 13397 Marseille, France

[§]Institute of Organic Chemistry and Biochemistry, Academy of Sciences, Flemingovo náměstí 2, 16610 Prague, Czech Republic

[∥]Dipartimento di Chimica e Chimica Industriale, Università di Pisa, Via Risorgimento 35, I-56126 Pisa, Italy

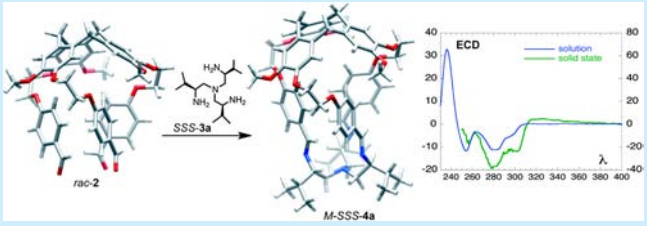
[⊥]Laboratoire des Multimatériaux et Interfaces, CNRS, Université Claude Bernard Lyon 1, 2 Avenue Grignard, F-69622 Villeurbanne, France

[#]Laboratoire de Chimie Quantique Institut de Chimie, UMR CNRS 7177, Université de Strasbourg, 4, rue Blaise Pascal, F-67070 Strasbourg, France

[$]Université de Lyon, Laboratoire de Chimie, Catalyse, Polymère, Procédés (C2P2), CNRS, Université Claude Bernard Lyon1, CPE Lyon, 43 Bd du 11 novembre 1918, F-69616 Villeurbanne Cedex, France

Supporting Information

ABSTRACT: Enantiopure hemicryptophanes designed from the cyclotriveratrylene (CTV) unit display remarkable properties in selective host−guest recognition or as supramolecular catalysts. The unprecedented control of the helical chirality of the CTV unit by remote stereogenic centers of a tren moiety is reported, providing an original access to this highly promising class of host molecules. Although the chiral centers and the CTV unit are separated by more than 10 Å, one single diastereomer is formed; the nature of the diastereoselective process is discussed and the procedure is exemplified using different enantiopure tren derivatives. This work also highlights the influence of the chirality of the CTV unit on the whole cage structure.



The design of molecular cages is of great interest because they can mimic biological systems like enzymes and can be used as artificial receptors or molecular vessels to perform catalytic reactions in the confined space of the active site.[1−19] Chirality plays a crucial role in most of the biological events and chiral synthetic bioinspired supramolecular systems have been designed to mimic and understand these processes.[20] However, the fast and easy synthesis of enantiopure molecular cages is a difficult challenge because of the high complexity of such molecules. Two main approaches have been followed to make chiral cages: the use of chiral units that introduce dissymmetry in the molecular structure or the inherent chirality of the host arising from the bowl shape of the molecular scaffold. Among the chiral molecular containers presenting an inherent chirality, cryptophanes and hemicryptophanes, both based on cyclotriveratrylene (CTV) units, display remarkable properties.[21,22] Convenient methods have been developed to produce sizable amounts of enantiopure cryptophanes with ee >98%.[23] They can be used in the stereoselective recognition of small chiral molecules such as chiral halogenomethanes[24] or epoxides.[25] The related hemicryptophane host molecules introduce more functionality at the molecular cavity level. They turned out to be efficient supramolecular catalysts and molecular receptors.[26,27]

Two main strategies have been followed to prepare enantiopure hemicryptophanes: (i) the resolution of racemic mixtures using chiral semipreparative HPLC with the major drawback of not being able to provide sizable amounts of compound[28] and (ii) the introduction of additional stereogenic centers to form diastereomers.[27a,d,29] However, their separation has proved tedious and difficult in most cases. For instance, following the latter strategy, enantiomerically and diastereomerically pure hemicryptophanes *M-SSS*-**1** and *P-SSS*-**1**, containing three asymmetric carbons at the benzylic positions with a controlled stereochemistry, were synthesized (Figure 1). Although they display remarkable properties for the enantioselective recognition of carbohydrates, their synthesis is time-consuming and their separation is harsh because it can be achieved only by column chromatography followed by alumina preparative TLC.[27d]

Warmuth et al.have previously reported an elegant dynamic thermodynamic resolution of a racemic mixture of CTV derivatives: the reaction of a racemic trialdehyde CTV

Received: December 5, 2014
Published: January 28, 2015

DOI: 10.1021/ol5035194
Org. Lett. 2015, 17, 500−503

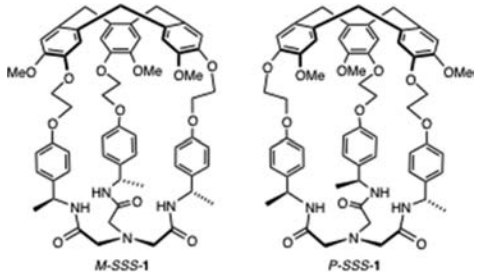


Figure 1. Structures of hemicryptophanes *M-SSS*-**1** and *P-SSS*-**1**.

compound with a chiral diamine leads to the formation of only one cryptophane stereoisomer.[30] The vicinity of the chiral centers and the CTV unit in the final cryptophane compound can account for the high efficiency of this process. As the separation of diasteromeric mixtures of hemicryptophanes derivatives revealed to be tedious and difficult in most cases, we decided to investigate if such a kinetic or thermodynamic resolution could be applied to a racemic mixture of a CTV cap to afford enantiomerically pure hemicryptophanes and thus avoiding the separation of the two diastereomers. Moreover, we were wondering whether the control of chirality of the CTV unit could be achieved although the chiral centers and the helical CTV cap are remote from each other. Herein we report on an easy synthesis of enantiopure hemicryptophanes via a thermodynamic resolution of a racemic CTV, leading to enantiomerically pure compounds. Assignment of the absolute configuration of the cage compounds was performed thanks to X-ray diffraction and ECD spectroscopy. The thermodynamic control of the resolution was further evidenced by DFT calculations and cross experiments. This remote control of the chirality of a CTV unit via stereogenic centers is unprecedented and demonstrates the ability of a CTV unit to transfer its stereochemical information through ten bonds (10 Å), therefore providing an easy access to enantiomerically pure hemicryptophane derivatives.

We have previously reported a very convenient and efficient modular approach for the synthesis of tren-hemicryptophane compounds, where the size, shape, and functionalities in the aromatic walls of the cavity could be easily modified.[31] Following this approach and using enantiopure tren derivatives should provide an easy way to obtain enantiopure hemicryptophanes. The reaction of the hemicryptophane precursor *rac*-**2** bearing three aldehyde moieties with the enantiopure tren *SSS*-**3a** in a $CHCl_3/CH_3OH$ mixture afforded the tris-imino-hemicryptophane **4a**. The chiral tren derivative *SSS*-**3a** containing isopropyl groups was synthesized according to a known procedure that relies on the reductive amination of N-protected nonracemic α-amino aldehydes in the presence of ammonium acetate.[32] The reduction of the imine functions of **4a** with sodium borohydride gave rise to the tren-hemicryptophane **5a** in 15% yield (Scheme 1). During the cyclization step, we expected the formation of both diastereomers due to the *P* or *M* configuration of the CTV moiety as observed in previous syntheses of enantiopure hemicryptophane derivatives.[27,29] Surprisingly, the ^{1}H NMR spectrum of the crude reaction mixture exhibited a single set of sharp signals and several broad resonances, suggesting that only one diastereomer was formed together with higher molecular weight species. The silica gel column chromatographic purification of the reaction mixture afforded only one diastereomer. No other compounds could be identified by mass spectrometry or ^{1}H NMR in the different collected fractions, suggesting that the reaction is highly diastereoselective. This experiment was repeated three times, leading to similar results (average yield: 15%).

The isolated diastereomers **5a** were characterized by X-ray diffraction of a single crystal grown by slow evaporation from a dichloromethane solution. The molecular structure of **5a** shows the cage molecule with a well-defined molecular cavity, the three stereogenic carbons of the tren moiety with the *S* configuration, and the *M* configuration for the CTV unit, proving the exclusive formation of the *M-SSS*-**5a** hemicryptophane (Figure 2, Flack parameter = 0.00(1)).

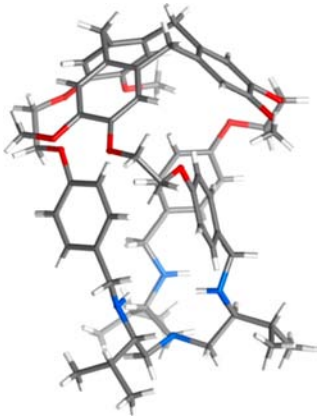
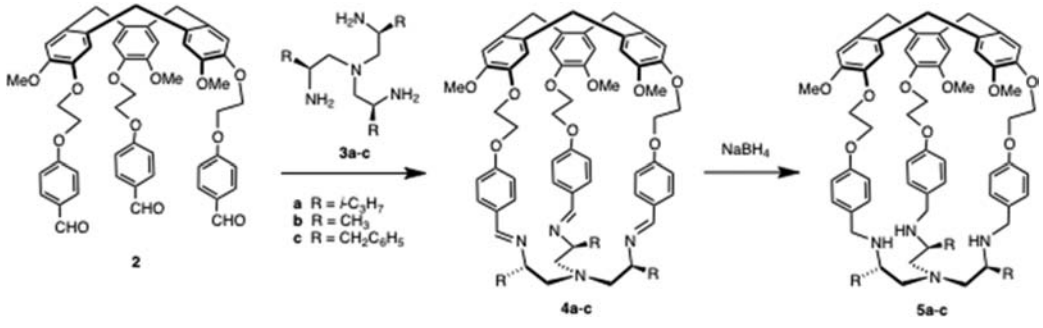


Figure 2. X-ray molecular structure of host *M-SSS*-**5a**.

The ECD spectra of this compound both in the solid state and in dichloromethane solution were recorded (Figure 3a). Each spectrum presents the classical behavior for hemicryptophane molecules, which consists of two exciton patterns roughly centered on the isotropic absorption of the ^1L_B (290 nm) and ^1L_A

Scheme 1. Synthesis of Hemicryptophanes 4a−c and 5a−c



DOI: 10.1021/ol5035194
Org. Lett. 2015, 17, 500−503

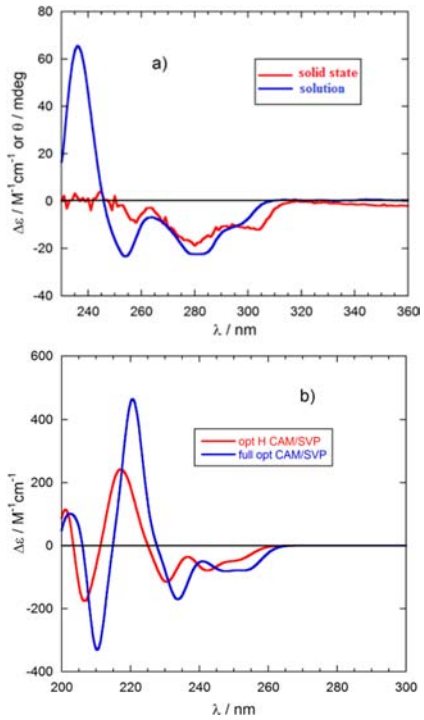


Figure 3. (a) Experimental CD spectra of *M-SSS*-**5a** in CH_2Cl_2 solution (298 K) and in the solid state; (b) TD-DFT calculated CD spectra of *M-SSS*-**5a** on fully optimized and partially optimized (only H atoms) geometries.

(240 nm) transitions. The absolute configuration of hemicryptophanes is usually determined by comparing the sign of the bands of the experimental ECD spectrum around the ^1L_A transition with the calculated spectrum. As shown by Collet et al., these signs are poorly sensitive to the nature of the substituents,[33] and *M* configuration can be assigned for molecules which present in their ECD spectra a sequence of signs positive−negative from high to low energy in the ^1L_A region. In the present case (Figure 3a), we thus observe the exclusive formation of the *M-SSS*-**5a** diastereomer and the *P*-**2** CTV enantiomer provides only uncharacterized (probably oligomeric) species.

This attribution was further confirmed by TD-DFT calculation of the ECD spectra of *M-SSS*-**5a** and *M-RRR*-**5a** using three hybrid functionals (B3LYP, BH&HLYP, and CAM-B3LYP) with the SVP basis set. The similarity of solution- and solid-state experimental ECD spectra demonstrates that there is no major conformational rearrangement between the two aggregation states and simplifies the spectral analysis. We considered only two structures, in both cases at DFT/B3LYP/6-31G* level: one derived from the XRD geometry (see below), where we optimized only the H atoms; alternatively, we took the XRD geometry and we fully relaxed it (Figure 3b and Figure S11, Supporting Information). The functionals CAM and BH&HLYP agree very well with the experimental spectra, while B3LYP underestimates the rotational strengths of the transitions and redshifts them by about 20 nm. Nevertheless, the signs sequence is the same for all of them and matches those of the experimental CD spectra, which confirms the configurational assignment.

Further insight into the diastereoselective reaction was obtained through the study of the nature of the control, kinetic or thermodynamic, of the resolution. A cross experiment was performed (Scheme S-3, Supporting Information). The precursor *rac*-**2** was first mixed with the enantiopure tren **3a**, leading to the formation of imine **4a** observed by mass spectrometry and ^{1}H NMR. After 24 h, no signal corresponding to the aldehyde function was detected by ^{1}H NMR, indicating the complete conversion of *rac*-**2** to give either polymeric materials or hemicryptophane compound **4a**. Then, 1 equiv of tris(2-aminoethyl)amine was added to the mixture. After 5 h, a new peak at *m*/*z* 945 was detected by mass spectrometry, evidencing the formation of the new imine **6**. This demonstrates that, under these conditions, the formation of the imine bonds is reversible, in agreement with previous work, which showed that the formation of imines is generally under thermodynamic control, resulting from the reversible covalent bond formation and the dissociation between an aldehyde and an amine.[34]

Thus, the resolution of the racemic mixture of the precursor *rac*-**2** turned out to be under thermodynamic control. Accordingly the *M-SSS* hemicryptophane imine should be more stable than the *P-SSS* counterpart: the precursor *M*-**2** provides the stable cage compound *M-SSS*-**4**, whereas the *P*-**2** enantiomer gives only oligomers or polymers because of the low stability of the related cage compound. We thus investigated further the relative stability of the *M-SSS*-**4a** and *P-SSS*-**4a** imines and addressed this issue by means of density functional theory (DFT) calculations. Full geometry optimizations of both diastereomers were carried out within a BP86/DFT framework. The gas-phase calculations show that the *M-SSS*-**4a** diastereomer is favored over the *P-SSS*-**4a** one by 17 kJ mol^{-1}, giving an equilibrium constant of 1000 (Figure S-13, Supporting Information). This is consistent with our experimental results and confirms that the resolution of the racemic CTV derivative is under thermodynamic control. In his previous work,[30] Warmuth described the dynamic thermodynamic resolution of the racemic CTV incorporating three aldehyde functions. Heating the compound in the presence of two equivalents of (*R,R*)-diaminocyclohexane led to the enantiomerically pure *P,P*-cryptophane. We carried out a similar reaction under the Warmuth's conditions (at 80 °C for 12 h, in the presence of a catalytic amount of TFA) with compounds **2** and **3a**. However, no improvement of the yield was observed. This result was attributed to the comparable stability of the *M-SSS*-**4a** hemicryptophane and the (polymeric) compound containing the *P*-CTV unit. Thus, under our standard conditions (room temperature, no TFA), there is probably no equilibrium between the enantiomer *P* and *M* of CTV **2** (the energy barrier for CTV derivatives is around 115 kJ mol^{-1} at room temperature),[21b] but both CTV react in a reversible way, giving either a polymer or an enantiopure cage.

To investigate further the scope of this diastereoselective process, two other enantiopure tren reactants **3b** and **3c** were tested, presenting, respectively, a less hindered methyl group or a benzyl substituent on the stereogenic centers (Scheme 1). In both cases, only one diastereomer was strongly favored. Each experiment was repeated twice, leading to similar results. The difference in the yields observed between **5a**, **5b**, and **5c** (15%, 20%, and 22%, respectively) probably arose from the relative stability of the polymeric species and the expected cage product, although such differences appear difficult to explain and to fully rationalize.[31] The ECD spectra were ontained and showed that the configuration of the CTV unit is *M* in both cases (Figures S-8 and S-9, Supporting Information). Thus, this thermodynamic resolution seems to be independent of the nature of the substituent on the stereogenic centers of the tren unit,

DOI: 10.1021/ol5035194
Org. Lett. 2015, 17, 500−503

highlighting the broad scope of this highly diastereoselective process.

In summary, we have described a convenient way to synthesize enantiopure hemicryptophane hosts involving a reductive amination between a chiral enantiopure tren moiety and a racemic CTV derivative. A thermodynamic resolution was observed: only the *M-SSS* diasteromeric cage compound was obtained allowing for an easy purification of the product. We can also notice that this corresponds to a remarkable remote stereocontrol of the chirality of the CTV unit by the stereogenic centers of the tren moiety because it was achieved through 10 covalent bonds (10 Å) whatever the nature of the substituents on the tren's asymmetric carbons. This constitutes an important step in the development of enantiopure hemicryptophane derivatives as chiral sensors or catalysts.

■ ASSOCIATED CONTENT

Supporting Information

Synthetic procedures; NMR spectra; experimental and calculated ECD spectra; computational methods; X-ray data for *MSSS*-**5a**. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: alexandre.martinez@ens-lyon.fr.

Notes

The authors declare no competing financial interest.

■ REFERENCES

(1) Kirby, A. J. *Angew. Chem., Int. Ed.* **1996**, *35*, 707.
(2) Sanders, J. K. M. *Chem.—Eur. J.* **1998**, *4*, 1378.
(3) Lehn, J.-M. *Rep. Prog. Phys.* **2004**, *67*, 245.
(4) Steed, J. W.; Atwood, J. L. In *Supramolecular Chemistry*, 2nd ed.; Wiley-VCH: Weinheim, 2009.
(5) Raynal, M.; Ballester, P.; Visal-Ferran, A.; Van Leeuwen, P. W. N. M. *Chem. Rev.* **2014**, *43*, 1660.
(6) Raynal, M.; Ballester, P.; Visal-Ferran, A.; Van Leeuwen, P. W. N. M. *Chem. Rev.* **2014**, *43*, 173.
(7) Oshovky, G. V.; Reinhoudt, D. N.; Verboom, W. *Angew. Chem., Int. Ed.* **2007**, *46*, 2366.
(8) Rebek, J., Jr. *Acc. Chem. Res.* **2009**, *42*, 1660.
(9) Yoshizawa, M.; Klosterman, J. K.; Fujita, M. *Angew. Chem., Int. Ed.* **2009**, *48*, 3418.
(10) Koblenz, T. S.; Wassenaar, J.; Reek, J. N. H. *Chem. Soc. Rev.* **2008**, *37*, 247.
(11) Feiters, M. C.; Rowan, A. E.; Nolte, R. J. M. *Chem. Soc. Rev.* **2000**, *29*, 375.
(12) Fiedler, D.; Leung, D. H.; Bergman, R. G.; Raymond, K. N. *Acc. Chem. Res.* **2005**, *38*, 349.
(13) Wiester, M. J.; Ulmann, P. A.; Mirkin, C. A. *Angew. Chem., Int. Ed.* **2010**, *50*, 114.
(14) Pluth, M. D.; Bergman, R. G.; Raymond, K. N. *J. Am. Chem. Soc.* **2007**, *129*, 11459.
(15) Chambron, J.-C.; Meyer, M. *Chem. Soc. Rev.* **2009**, *38*, 1663.
(16) Lyle, I. *Acc. Chem. Res.* **2014**, *47*, 2052.
(17) Ghale, G.; Nau, W. M. *Acc. Chem. Res.* **2014**, *47*, 2150.
(18) Hargrove, A. E.; Nieto, S.; Zhang, T.; Sessler, J. L.; Anslyn, E. V. *Chem. Rev.* **2011**, *111*, 6603.
(19) Breiner, B.; Clegg, J. K.; Nitschke, J. R. *Chem. Sci.* **2011**, *2*, 51.
(20) Brotin, T.; Guy, L.; Martinez, A.; Dutasta, J.-P. *Top. Curr. Chem.* **2013**, *341*, 177.
(21) (a) Brotin, T.; Dutasta, J.-P. *Chem. Rev.* **2009**, *109*, 88. (b) Collet, A.; Dutasta, J.-P.; Lozach, B.; Canceill, J. *Top. Curr. Chem.* **1993**, *165*, 103.
(22) Canceill, J.; Collet, A.; Gabard, J.; Kotzyba-Hibert, F.; Lehn, J.-M. *Helv. Chim. Acta* **1982**, *65*, 1894.
(23) (a) Canceill, J.; Lacombe, L.; Collet, A. *J. Am. Chem. Soc.* **1985**, *107*, 6993. (b) Brotin, T.; Barbe, R.; Darzac, M.; Dutasta, J.-P. *Chem.—Eur. J.* **2003**, *9*, 5784. (c) Cavagnat, D.; Buffeteau, T.; Brotin, T. *J. Org. Chem.* **2008**, *73*, 66. (d) Taratula, O.; Kim, M. P.; Bai, Y.; Philbin, J. P.; Riggle, B. A.; Haase, D. N.; Dmochowski, I. J. *Org. Lett.* **2012**, *14*, 3580. (e) Taratula, O.; Bai, Y.; D'Antonio, E. L.; Dmochowski, I. J. *Supramol. Chem.* **2014**, *27*, 65.
(24) Soulard, P.; Asselin, P.; Cuisset, A.; Aviles Moreno, J. R.; Huet, T. R.; Petitprez, D.; Demaison, J.; Freedman, T. B.; Cao, X.; Nafie, L. A.; Crassous, J. *Phys. Chem. Chem. Phys.* **2006**, *8*, 79.
(25) Bouchet, A.; Brotin, T.; Linares, M.; Ågren, H.; Cavagnat, D.; Buffeteau, T. *J. Org. Chem.* **2011**, *76*, 4178.
(26) (a) Martinez, A.; Dutasta, J.-P. *J. Catal.* **2009**, *267*, 188. (b) Makita, Y.; Sugimoto, K.; Furuyosho, K.; Ikeda, K.; Jujiwara, S. I.; Shin-ike, T.; Ogawa, A. *Inorg. Chem.* **2010**, *49*, 7220. (c) Makita, Y.; Ikeda, K.; Sugimoto, K.; Fujita, T.; Danno, T.; Bobuatong, K.; Ehara, M.; Jujiwara, S. I.; Ogawa, A. *J. Organomet. Chem.* **2012**, *706*, 26. (d) Perraud, O.; Sorokin, A. B.; Dutasta, J.-P.; Martinez, A. *Chem. Commun.* **2013**, *49*, 1288.
(27) (a) Cochrane, J. R.; Schmitt, A.; Wille, U.; Hutton, C. A. *Chem. Commun.* **2013**, *49*, 8504. (b) Schmitt, A.; Chatelet, B.; Collin, S.; Dutasta, J. P.; Martinez, A. *Chirality* **2013**, *25*, 475. (c) Perraud, O.; Martinez, A.; Dutasta, J. P. *Chem. Commun.* **2011**, *47*, 5861. (d) Schmitt, A.; Perraud, O.; Payet, E.; Chatelet, B.; Bousquet, B.; Valls, M.; Padula, D.; Di Bari, L.; Dutasta, J. P.; Martinez, A. *Org. Biomol. Chem.* **2014**, *12*, 4211.
(28) (a) Perraud, O.; Dimitrov-Raytchev, P.; Martinez, A.; Dutasta, J.-P. *Chirality* **2010**, *22*, 885. (b) Payet, E.; Dimitrov-Raytchev, P.; Chatelet, B.; Guy, L.; Grass, S.; Lacour, J.; Martinez, A.; Dutasta, J.-P. *Chiralty* **2012**, *24*, 1077.
(29) (a) Brégier, F.; Lavalle, J.; Chambron, J.-C. *Eur. J. Org. Chem.* **2013**, *13*, 2666. (b) Gautier, A.; Mulatier, J.-C.; Crassous, J.; Dutasta, J.-P. *Org. lett.* **2005**, *7*, 1207.
(30) Xu, D.; Warmuth, R. *J. Am. Chem. Soc.* **2008**, *130*, 7520.
(31) Chatelet, B.; Payet, E.; Perraud, O.; Dimitrov-Raytchev, P.; Chapellet, L.-L.; Dufaud, V.; Martinez, A.; Dutasta, J.-P. *Org. Lett.* **2011**, *13*, 3706.
(32) Liu, X.; Ilankumaran, P.; Guzei, I. A.; Verkade, J. G. *J. Org. Chem.* **2000**, *65*, 701.
(33) (a) Canceill, J.; Collet, A.; Gabard, J.; Gottarelli, G.; Spada, G. P. *J. Am. Chem. Soc.* **1985**, *107*, 1299. (b) Andraud, C.; Garcia, C.; Collet, A. In *Circular Dichroism, Principles and Applications,2nd ed., S-Substituted Aromatics and Exciton Chirality*; Berova, N., Nakanishi, K., Woody, R.W., Eds.; Wiley-VCH: Weinheim, 2000; pp 383−395. (c) Canceill, J.; Collet, A.; Gottarelli, G.; Palmieri, P. *J. Am. Chem. Soc.* **1987**, *109*, 6454.
(34) (a) Kovarlek, P.; Lehn, J.-M. *J. Am. Chem. Soc.* **2012**, *134*, 9446. (b) Ziach, K.; Kulesza, A.; Jurczak, J. *Org. Biomol. Chem.* **2014**, *12*, 3827. (c) Ciaccia, M.; Pilati, S.; Cacciapaglia, R.; Mandolini, L.; Di Stefano, S. *Org. Biomol. Chem.* **2014**, *12*, 3282.

DOI: 10.1021/ol5035194
Org. Lett. 2015, 17, 500−503