Total Syntheses of (−)-Herbertenediol, (−)-Mastigophorene A, and (−)-Mastigophorene B. Combined Utility of Chiral Bicyclic Lactams and Chiral Aryl Oxazolines

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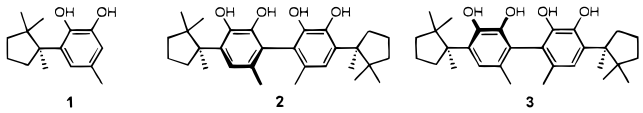
Abstract: A nonracemic bicyclic lactam has been used to construct a chiral cyclopentane containing vicinal quaternary carbon centers in optically pure form, which is common to all of the title compounds. An oxazoline-mediated asymmetric Ullmann coupling was then utilized to establish chirality about the biaryl axis of mastigophorenes A and B. Through the course of this synthesis, it was clearly demonstrated that smaller chiral auxiliaries lead to higher levels of atroposelection, a previously unknown phenomenon of the asymmetric Ullmann coupling.

(−)-Herbertenediol (**1**)[1,2] was isolated from the liverwort *Herberta adunca* and was found to possess potent anti-lipid peroxidation activity.[3] Mastigophorenes A (**2**) and B (**3**) were later isolated from the liverwort *Mastigophora diclados* and were shown to stimulate nerve growth.[4,5] It has been proposed that both are biosynthesized via an oxidative phenolic coupling of **1** that coexists in these liverwort extracts. Mastigophorenes A and B were targeted for synthesis as they presented the unique opportunity to extend the bicyclic lactam methodology[6] to the construction of a chiral cyclopentane containing vicinal quaternary carbon centers, as well as to further the understanding of the oxazoline-mediated asymmetric Ullmann coupling[7,8,9] developed in this laboratory.

Fukuyama[3a] has prepared herbertenediol (**1**) as its racemate and intercepted one of the intermediates in his synthesis of (±)-**1** in an enantioselective fashion, completing a formal synthesis of optically enriched (−)-**1**. To date, the only synthetic efforts



1 **2** **3**

toward mastigophorenes A or B were carried out with simpler analogues by Bringmann et al.[10,11] In their studies, analogues of **2** and **3** were prepared wherein the chiral cyclopentane units were replaced by *tert*-butyl groups, thus omitting the more difficult chiral centers. Herein, we describe the total synthesis of (−)-herbertenediol (**1**), (−)-mastigophorene A (**2**), and (−)-mastigophorene B (**3**), using a bicyclic lactam to construct the chiral cyclopentane and an oxazoline-mediated asymmetric Ullmann coupling to establish chirality about the biaryl axis of **2** and **3**.

Our original focus was the synthesis of mastigophorene A (Scheme 1), which we envisioned as arising from the reductive removal of bisoxazoline **4**. This, in turn, would be created via an oxazoline-mediated asymmetric Ullmann coupling of monomeric arylbromide **5**. The latter could be elaborated from simplified arene **6** by means of standard chemical manipulations. The cyclopentane unit of **6** would be derived from chiral cyclopentenone **7** via dialkylation and subsequent reduction. The cyclopentenone would arise from chiral, nonracemic bicyclic lactam **8,** which would be prepared via diastereoselective alkylation of the bicyclic lactam derived from ketoacid **9**. It was anticipated that ketoacid **9** could be elaborated from commercially available phenol **10**.[12]

To begin (Scheme 2), phenol **10** was subjected to Mannich conditions[13] to afford benzylamine **11** in quantitative yield. It

(1) (a) Matsuo, A.; Yuki, S.; Nakayama, M. *Chem. Lett.* **1983**, 1041. (b) Matsuo, A.; Yuki, S.; Nakayama, M. *J. Chem. Soc., Perkin Trans. 1* **1986**, 701.

(2) The absolute configuration of **1** was firmly established by correlation to (−)-camphonanic acid.[1b]

(3) (a) Fukuyama, Y.; Kiriyama, Y.; Kodama, M. *Tetrahedron Lett.* **1996**, *37*, 1261. (b) Harrowven, D. C.; Hannam, J. C. *Tetrahedron Lett.* **1998**, *39*, 9573. (c) Eicher, T.; Servet, F.; Speicher, A. *Synthesis* **1996**, 863.

(4) Fukuyama, Y.; Asakawa, Y. *J. Chem. Soc., Perkin Trans. 1* **1991**, 2737.

(5) The absolute configurations of **2** and **3** were assigned on the basis of the CD exciton chirality rule.[4] These syntheses further support this stereochemical assignment.

(6) For reviews on the use of chiral bicyclic lactams in synthesis, see: (a) Romo, D.; Meyers, A. I. *Tetrahedron* **1991**, *47*, 9503. (b) Brengel, G. P.; Meyers, A. I. *J. Chem. Soc., Chem. Comm.* **1997**, 1.

(7) For applications of the asymmetric oxazoline-mediated Ullmann coupling, see: (a) Meyers, A. I.; Willemsen, J. J. *Tetrahedron* **1998**, *54*, 10493. (b) Meyers, A. I.; Willemsen, J. J. *J. Chem. Soc., Chem. Commun.* **1997**, 1573. (c) Meyers, A. I.; Price, A. *J. Org. Chem.* **1998**, *63*, 412. (d) Meyers, A. I.; McKennon, M. J. *Tetrahedron Lett.* **1995**, *36*, 5869. (e) Nelson, T. D.; Meyers, A. I. *Tetrahedron Lett.* **1994**, *35*, 3259. (f) Nelson, T. D.; Meyers, A. I. *J. Org. Chem.* **1994**, *59*, 2655. (g) Nelson, T. D.; Meyers, A. I. *Tetrahedron Lett.* **1993**, *34*, 3061.

(8) For a review of the use of chiral oxazolines in synthesis, see: Meyers, A. I. *J. Heterocycl. Chem.* **1998**, *35*, 991 and references therein.

(9) For general reviews on the Ullmann reaction, see: (a) Fanta, P. E. *Synthesis* **1974**, 9. (b) Fanta, P. E. *Chem. Rev.* **1964**, *64*, 613. (c) Fanta, P. E. *Chem. Rev.* **1946**, *38*, 139.

(10) (a) Bringmann, G.; Pabst, T.; Busemann, S.; Peters, K.; Peters, E.-M. *Tetrahedron* **1998**, *54*, 1425. (b) Bringmann, G.; Pabst, T.; Rycroft, D. S.; Connolly, J. D. *Tetrahedron Lett.* **1999**, *40*, 483.

(11) After this paper had been accepted for publication, a synthesis of **2** and **3** was published, commencing with naturally occurring **1**. Mastigophorenes A and B were prepared by an oxidative dehydrodimerization of phenolic precursors in poor yields and with little selectivity.[10b]

(12) Aldrich Chemicals, 1998−1999.

(13) (a) Blicke, F. F. *Org. React.* **1942**, *1*, 303. (b) Bruson, H. A.; Macmullen, C. W. *J. Am. Chem. Soc.* **1941**, *63*, 270. (c) Mannich, C.; Ritsert, K. *Arch. Pharm. (Weinheim, Ger.)* **1926**, *264*, 164. (d) Mannich, C.; Ball, G. *Arch. Pharm. (Weinheim, Ger.)* **1926**, *264*, 65.

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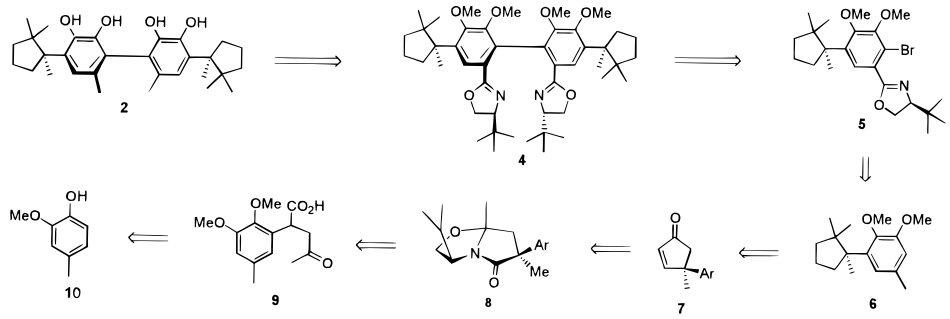
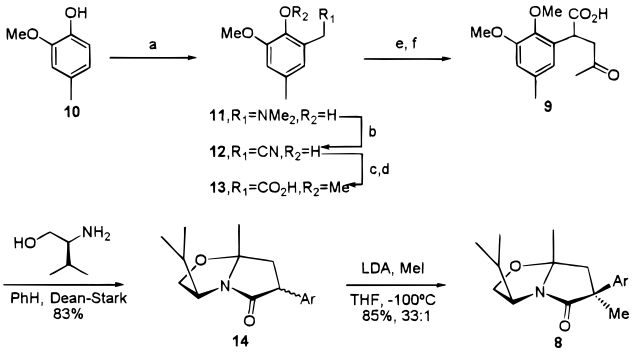
Scheme 1

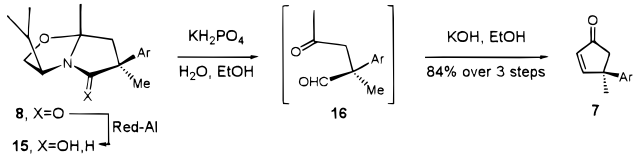


Scheme 2

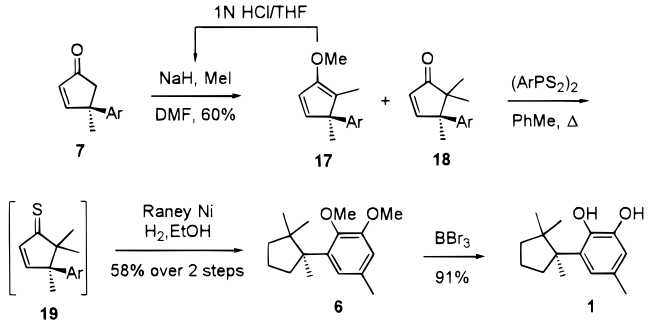


Legend: (a) H_2CO, Me_2NH, 100%; (b) i. MeI; ii. KCN, 90%; (c) Me_2SO_4, PTC, 100%; (d) NaOH, MeOH/H_2O, 97%; (e) 2eq. LDA then (±)-propylene oxide; (f) Swern, 80% (2 steps)

Scheme 3



Scheme 4



was hoped that quaternization of the benzylic amine could be performed in tandem with methylation of the phenol. However, all attempts to realize this outcome, including formation of the sodium alkoxide prior to addition of methyl iodide, failed to alkylate the phenol. Therefore, the reactions were performed in a stepwise manner, first forming the quaternary ammonium salt and displacing it with potassium cyanide to afford substituted phenylacetonitrile **12** in 90% yield. Protection of the phenol as its methyl ether under phase transfer conditions[14] then proceeded in quantitative yield. Basic hydrolysis of the nitrile gave phenylacetic acid **13** in 97% yield. The dianion of **13** was quenched with propylene oxide to give the γ-hydroxyacid as a 3:2 mixture of diastereomers, which was oxidized directly to afford the requisite racemic ketoacid **9** (80% over two steps). Condensation of **9** with (*S*)-valinol gave bicyclic lactam **14** as a 3:2 mixture of epimers. However, this mixture was inconsequential as deprotonation of either epimer gives rise to the same enolate. Alkylation of the latter with methyl iodide gave a 33:1 mixture of *endo-exo* diastereomers.[15] Recrystallization from heptane afforded the *endo*-alkylated product **8** as a single diastereomer. This process has been termed a "deracemizing alkylation" because all of the racemic ketoacid is completely utilized in the synthesis.[16]

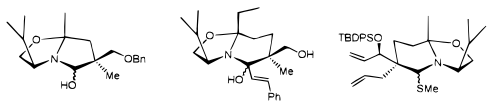
Reduction of bicyclic lactam **8** with Red-Al (Scheme 3) gave carbinolamine **15**, which upon hydrolysis with $Bu_4NH_2PO_4$ (20 equiv) afforded keto aldehyde **16**. Because of the expense of the ammonium phosphate buffer ($209/mol),[12] coupled with the need to hydrolyze sufficient quantities of carbinolamine **15** to allow completion of the synthesis, we screened a number of other buffer solutions in search of a more practical alternative. It was found that similar results could be obtained via replacement of $Bu_4NH_2PO_4$ with KH_2PO_4 ($2.11/mol).[12] Unpublished results in this laboratory suggest that this buffer system is widely applicable to other [5.5.0] and [5.6.0] bicyclic lactams,[17] yielding the corresponding keto aldehydes in yields consistent with those observed using $Bu_4NH_2PO_4$. Base-induced cyclization of keto aldehyde **16** afforded chiral cyclopentenone **7** in 84% from lactam **8**.

Attempts to introduce the *gem*-dimethyl group into **7** via formation of the lithium enolate were unsuccessful,[18] presumably as a result of steric crowding of the adjacent quaternary carbon center. However, deprotonation with NaH in DMF followed by treatment with MeI allowed formation of the vicinal quaternary carbon center in a 60% yield (Scheme 4). The remainder of material was found to be the methyl enol ether **17**, arising from C-alkylation followed by O-alkylation. This material was conveniently recycled via acid-catalyzed hydrolysis and resubjection to the previous reaction conditions, thus improving the yield to 82% over two recycles.

Attempts to reduce the olefin (Pd/C, H_2) of **18** followed by a Wolff−Kishner reduction[19] were unsuccessful; this is believed to be a result of the well-documented steric restraints of

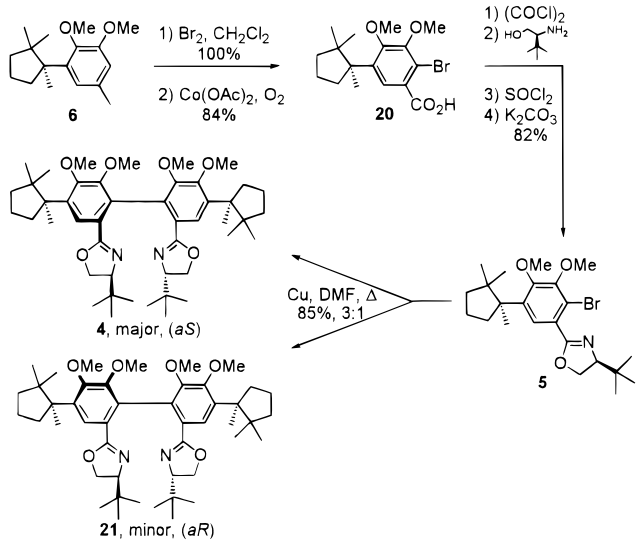
(14) McKillop, A.; Fiaud, J.-C.; Hug, R. P. *Tetrahedron* **1974**, *30*, 1379.
(15) The ratio of isomers was assigned by ^{1}H NMR integration.
(16) Pfau, M.; Revial, G.; Guingant, A.; d'Angelo, J. *J. Am. Chem. Soc.* **1985**, *107*, 273.

(17) The following substrates have been hydrolyzed using KH_2PO_3, providing results similar to those observed using $Bu_4NH_2PO_3$.



(18) (a) Meyers, A. I.; Lefker, B. A. *J. Org. Chem.* **1986**, *51*, 1541. (b) Wenkert, E.; Buckwater, B. L.; Craviero, A. A.; Sanchez, E. L.; Sathe, S. S. *J. Am. Chem. Soc.* **1978**, *100*, 1267.
(19) (a) Todd, D. *Org. React.* **1948**, *4*, 378. (b) Wolff, L. *Liebigs Ann. Chem.* **1912**, *394*, 86. (c) Kishner, N. *J. Russ. Phys. Chem. Soc.* **1911**, *43*, 582.

Scheme 5



hydrazone formation.[20] Furthermore, attempts to make the sterically demanding ethylene dithioketal were also fruitless. It was thought that we might bypass this obstacle by replacement of oxygen with a group smaller in size than the hydrazones and dithioketals mentioned above. Therefore, the oxygen was replaced with sulfur, using Belleau's reagent.[21] In view of the instability of thioenones,[22] **19** was utilized immediately in the next step. Reduction with Raney Ni and H_2 allowed removal of sulfur and hydrogenation of the olefin to afford dimethylherbertenediol (**6**) in 58% yield over two steps. Finally, removal of the methyl groups with BBr_3 provided (−)-herbertenediol in 91% yield. The synthetic product agreed in all respects with the natural material and exhibited a rotation of −54 (*c* 1.0, $CHCl_3$), whereas the reported[1] rotation for natural herbertenediol is −47 (*c* 1.4, $CHCl_3$). The structure and optical purity is further established through the subsequent synthesis of mastigophorenes A and B (vide supra).

It was now necessary to effect the dimerization of **6** and the establishment of stereochemistry about the newly formed biaryl axis (Scheme 5). Arene **6** was brominated (100%), followed by oxidation[23] to substituted benzoic acid **20** (84%), utilizing conditions similar to those used by Bringmann.[10a] The acid was subsequently transformed into the (*S*)-*tert*-leucinol derived oxazoline, **5**, in 82% yield under previously described conditions.[24]

The appropriate aromatic precursor was now in hand for the key asymmetric Ullmann coupling. Consistent with previous studies,[7e] the early stages of coupling proceeded with little atroposelectivity. However, heating the reaction mixture at reflux was accompanied by conversion of **4** to **21** until finally a steady state containing an equilibrium mixture of 3:1 (Figure 1) was reached.[15,25]

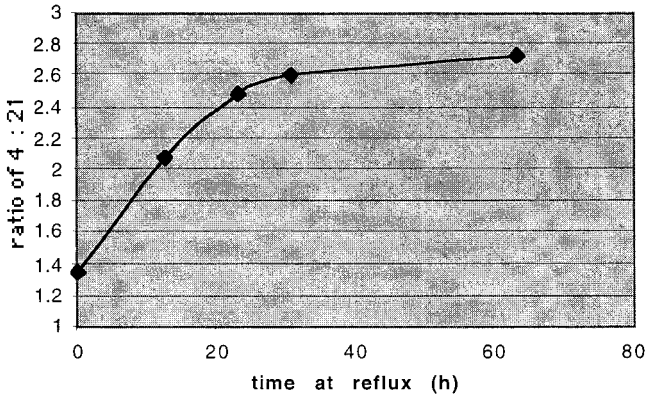
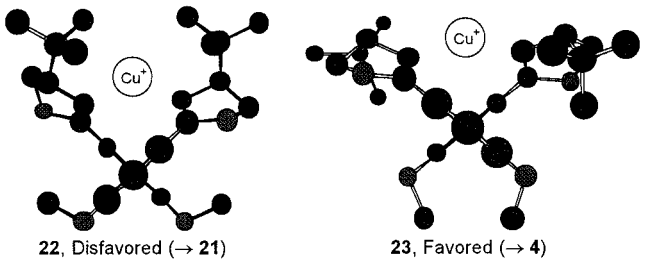


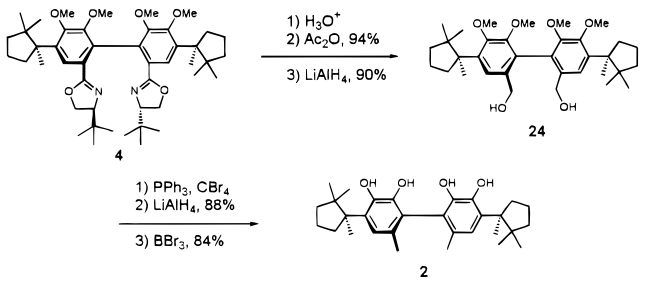
Figure 1. Equilibration of atropisomers.



All substituents not *ortho* to the biaryl axis have been omitted for clarity

Figure 2.

Scheme 6



This reaction profile can only be rationalized as a thermodynamic distribution of products. One can draw two diastereomeric complexes wherein both of the nitrogens are chelating to copper, each leading to a different atropisomer. The selectivity observed corresponds to the relative stability of initially formed copper complexes **22** and **23** (Figure 2.) In complex **22**, the *tert*-butyl groups are facing inward, toward one another and the coordinated copper ion. In **23**, the alkyl groups are situated on opposite faces of the molecule, decreasing their steric interaction. Heating the mixture at reflux allows the interconversion of **22** and **23** until an equilibrium is reached.

Although **4** and **21** are diastereomers, all attempts to separate them were unsuccessful. However, the propensity for only one of the bisoxazolines to coordinate to copper again became advantageous. If the crude Ullmann coupling was not washed with NH_4OH (to remove coordinated Cu) column chromatography gave **21** (uncomplexed) and **4** as its copper complex, which could then be washed with NH_4OH to release the diastereomerically pure bisoxazoline **4**.

It was now necessary to remove the chiral oxazoline moieties. Acidic hydrolysis to their aminoesters, protection as the bisacetamide (94% over two steps), and $LiAlH_4$ reduction (90%) afforded diol **24** (Scheme 6). Conversion to the bromide, followed by displacement with $LiAlH_4$, furnished tetramethylmastigophorene A in 88% over two steps. Treatment with BBr_3 allowed clean removal of all methyl groups, providing (−)-

(20) (a) Barton, D. H. R.; Ives, D. A. J.; Thomas, B. R. *J. Chem. Soc.* **1955**, 2056. (b) Barton, D. H. R.; Ives, D. A. J.; Thomas, B. R. *J. Chem. Soc.* **1954**, 903. (c) Huang-Minlon. *J. Am. Chem. Soc.* **1949**, *71*, 3301.

(21) Lajoie, G.; Lépine, F.; Maziak, L.; Belleau, B. *Tetrahedron Lett.* **1983**, *24*, 3815.

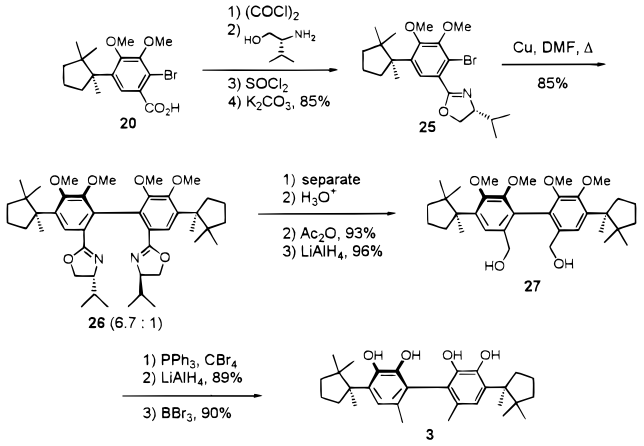
(22) (a) Scheibye, S.; Shabana, R.; Lawesson, S.-O.; Romming, C. *Tetrahedron* **1982**, *38*, 993. (b) Karakasa, T.; Motoki, S. *J. Org. Chem.* **1978**, *63*, 4147 and references therein.

(23) Onopchenko, A.; Schulz, J. G. D.; Seekircher, R. *J. Org. Chem.* **1972**, *37*, 1414.

(24) Frump, J. A. *Chem. Rev.* **1971**, *71*, 483.

(25) The stereochemistry about the biaryl axis was assigned by comparison to previous studies of the oxazoline-mediated asymmetric Ullmann coupling.[7] It was not until completion of the syntheses of **2** and **3** that the assignment was verified.

Scheme 7



mastigophorene A (**2**), consistent in all respects to the natural product (observed rotation = −68 (*c* 0.4, $CHCl_3$); literature[4] value = −65 (*c* 0.4, $CHCl_3$)).

Although mastigophorene B could have been prepared from the minor atropisomer produced above (**21**), it was deemed favorable to construct it from an Ullmann coupling wherein (*S*)-*tert*-leucinol has been replaced by another chiral auxiliary. As (*R*)-*tert*-leucinol is expensive, (*R*)-valinol was chosen despite the fear that this may be accompanied by even lower levels of diastereoselection in the Ullmann coupling. Construction of oxazoline **25** under the same conditions afforded the monomer, ready for coupling (Scheme 7). In this case, the Ullmann reaction gave a 6.7:1 ratio of atropisomers[15]—greater than double the selectivity seen in the *tert*-leucinol derived coupling! These were also separable, with **26** isolated as its copper complex. Subjection of **26** to the sequence described above gave epimeric mastigophorene B (**3**), identical to the natural product in all respects (observed rotation = −38 (*c* 0.35, $CHCl_3$); literature[4] value = −39 (*c* 0.35, $CHCl_3$)).

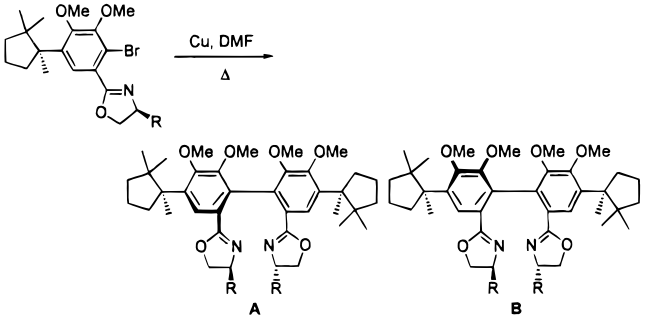
The observation that (*R*)-valinol gave higher diastereoselection than its larger (*S*)-*tert*-leucinol counterpart suggested the possibility that the chirality of the cyclopentane rings predisposed the biaryl axis to the (*aR*) configuration. This, however, was believed to be unlikely because of distance of the cyclopentanes from the biaryl axis. Alternately, it may be possible that *tert*-leucinol is simply too large to give good diastereoselectivity. Referring again to Figure 2, it may be that as the chiral auxiliary gets very large, its interaction with the arene becomes significant, favoring the "disfavored" atropisomer (**22**).

To identify the cause of this anomaly, a number of other chiral auxiliaries were screened (Table 1). It was found that as the size of the chiral auxiliary decreased (*A* values) the atroposelectivity increased, reaching a maximum of 7.2:1 for the (*S*)-alaninol derived oxazoline (**31**). This suggests that even very small alkyl groups in the 4-position of the oxazoline prevent the formation of complex **22**, and that the *level* of diastereoselection is primarily dependent on minimization of the interaction of the alkyl substituent with the arene in **23**.

Subjection of **32** to the conditions developed above afforded diol **24** (Scheme 8), identical in all respects to that synthesized previously, formally improving the synthesis of mastigophorene A.

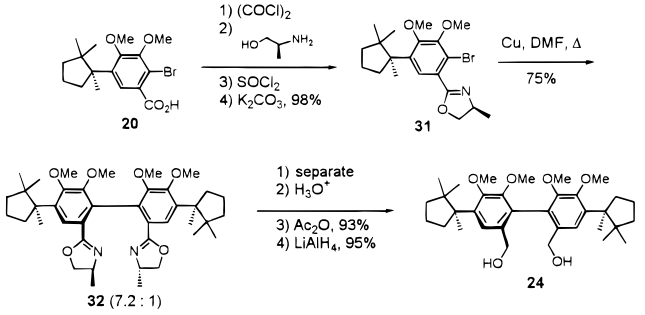
In summary, (−)-herbertenediol, (−)-mastigophorene A, and (−)-mastigophorene B have been synthesized in optically pure form. A nonracemic bicyclic lactam was used to construct a chiral cyclopentane containing vicinal quaternary carbon centers, which is common to all of the title compounds. During these

Table 1



compound	R	*A*-value	ratio of A:B[15]
5	*tert*-butyl	>4.5 (ref 26a)	3:1
28	phenyl	2.9 (ref 26b)	4:1
29	*i*sopropyl	2.1 (ref 26c)	6.4:1
30	ethyl	1.8 (ref 26c)	7.1:1
31	methyl	1.8 (ref 26c)	7.2:1

Scheme 8



studies, a more practical method of carbinolamine hydrolysis was developed (KH_2PO_4 vs $Bu_4NH_2PO_4$), reducing the cost to ∼1% of the previously employed conditions. An oxazoline-mediated asymmetric Ullmann coupling was then utilized to generate chirality about the biaryl axis of **2** and **3**. An attractive feature of this sequence is the inclusion of the chiral auxiliary into the oxazoline just prior to the key Ullmann coupling. The benefits bestowed by this aspect of the synthesis are twofold. First, advanced intermediate **20** could be coupled to favor either **2** or **3**. Second, it allowed the screening of multiple chiral auxiliaries and the realization that smaller directing groups give higher levels of atroposelection.

Experimental Section

Thin-layer chromatography (TLC) and flash chromatography were performed with E. Merck silica gel (230−400 mesh). All reagents were purchased from Aldrich. All nonaqueous reactions were conducted under an argon atmosphere in oven- or flame-dried apparatus. Microanalyses were performed by Atlantic Microlab, Inc., Norcross, Georgia.

***N,N*-Dimethyl-2-hydroxy-3-methoxy-5-methylbenzylamine, 11.** To a cooled (0 °C) flask charged with **10** (94 g, 725 mmol) was added dimethylamine (40% in H_2O, 102 g, 966 mmol) with stirring. Formaldehyde (37% in H_2O, 64.5 g, 850 mmol) was slowly added, with the temperature maintained below 40 °C. After the addition was complete, the ice bath was removed and the mixture was allowed to stir for 1.5 h. The mixture was poured into water (500 mL) and made slightly acidic with 1 N HCl. The aqueous phase was extracted with CH_2Cl_2 (3×), dried over Na_2SO_4, and concentrated to give 133 g (100%) of a light oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.22 (s, 3H), 2.29 (s, 6H), 3.57 (s, 2H), 3.83 (s, 3H), 6.36 (d, J = 1.5, 1H), 6.59 (d, J = 1.5, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 20.5, 44.0, 55.4, 62.2, 111.6, 120.3, 121.3, 127.3, 144.4, 147.1.

2-Hydroxy-3-methoxy-5-methylphenylacetonitrile, 12. To a stirred solution of **11** (0.20 g, 1 mmol) in DMF (2 mL, 0 °C) was added MeI

(140 μL, 2 mmol) in one portion. The mixture was stirred for 5 min at 0 °C and 30 min at room temperature and then recooled to 0 °C. To the crude methiodide was added freshly ground KCN (0.33 g, 5 mmol). The mixture was stirred at 0 °C for 10 min and then at room temperature for 1 h. The solution was poured into water (10 mL) and extracted into ether (2×). The aqueous phase was acidified and extracted with ether (2×). The organics were combined, washed with brine, dried over Na_2SO_4, and concentrated. Flash chromatography gave 0.16 g (90%) as a white solid: mp 45.0−46.9 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.28 (s, 3H), 3.67 (s, 2H), 3.86 (s, 3H), 5.61 (s, 1H), 6.63 (d, J = 1.5, 1H), 6.74 (d, J = 1.5, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 18.0, 21.2, 56.2, 111.6, 115.7, 118.2, 121.3, 129.8, 141.1, 146.3; IR (thin film) 3428(br), 2251 cm^{-1}. Anal. Calcd for $C_{10}H_{11}NO_2$: C 67.78, H 6.26. Found: C 67.70, H 6.30.

2,3-Dimethoxy-5-methylphenylacetic Acid, 13. A 1 L flask was charged with **12** (49.5 g, 283 mmol), $LiOH\cdot H_2O$ (17.8 g, 424 mmol), and benzyltributylammonium chloride (17.6 g, 56 mmol). To this was added water (400 mL), and the solution was allowed to stir for 1 min. CH_2Cl_2 (400 mL) was added, and the heterogeneous mixture was stirred for 1 min. To this was added Me_2SO_4 (40 mL, 424 mmol), and the mixture was vigorously stirred for 5 min. The layers were separated, and the aqueous layer was washed with CH_2Cl_2 (2×). The organics were washed with brine, dried over Na_2SO_4, and concentrated. The oil was taken up in EtOAc and filtered through a large pad of silica gel, eluting with EtOAc to yield 54 g (100%) of 2,3-dimethoxy-5-methylphenylacetonitrile as a light oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.29 (s, 3H), 3.66 (s, 2H), 3.83 (s, 3H), 3.84, (s, 3H), 6.69 (s, 1H), 6.74 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 18.2, 21.0, 55.5, 60.4, 113.2, 118.2, 121.0, 123.4, 134.1, 144.2, 152.1; IR (thin film) 2251 cm^{-1}.

To a stirred solution of 2,3-dimethoxy-5-methylphenylacetonitrile (53.7 g, 281 mmol) in methanol (450 mL) was added aqueous 25% NaOH (125 mL). The mixture was heated at reflux for 24 h; upon cooling, the solution was concentrated, redissolved in water, and extracted with ether (2×), and the ethereal layers were discarded. The aqueous phase was acidified with cold concentrated HCl and extracted into ether (3×), which was washed with brine, dried over Na_2SO_4, and concentrated to give 57.1 g (97%) of the acid as a white solid: mp 101−102 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.29 (s, 3H), 3.64 (s, 2H), 3.81 (s, 3H), 3.83 (s, 3H), 6.63 (d, J = 1.5, 1H), 6.67 (d, J = 1.5, 1H), 10.43 (bs, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.2, 35.5, 55.6, 60.5, 112.8, 123.0, 127.1, 133.7, 145.0, 152.2, 178.2; IR (thin film) 3000(br), 1698 cm^{-1}. Anal. Calcd for $C_{11}H_{14}O_4$: C 62.85, H 6.71. Found: C 63.05, H 6.65.

2-(2,3-Dimethoxy-5-methylphenyl)-4-oxopentanoic Acid, 9. A stirred solution of diisopropylamine (22 mL, 156 mmol) in THF (350 mL, 0 °C) was treated with *n*-BuLi (2.19 M in hexanes, 68 mL, 148 mmol), stirred for 30 min, and cooled to −78 °C. To this was added **13** (15 g, 71 mmol) in THF (100 mL) via cannula. The flask was placed in a 0 °C bath and stirred for 45 min before recooling to −78 °C. (±)-Propyleneoxide (13.7 mL, 195 mmol) was then added. The flask was placed in a 0 °C bath and stirred overnight while allowed to reach room temperature. The mixture was quenched with water and concentrated by rotary evaporation. The crude alcohol was taken up in water and extracted with ether (2×), and the ethereal layers were discarded. The aqueous layer was acidified with concentrated HCl and extracted with ether (3×). These organic layers were washed with brine, dried over Na_2SO_4, and concentrated to give a viscous oil. This crude γ-hydroxyacid was taken on directly below.

To a stirred solution of oxalyl chloride (6.8 mL, 79 mmol) in CH_2Cl_2 (350 mL, −78 °C) was added DMSO (10 mL, 143 mmol), and the mixture was allowed to stir for 15 min before addition of the crude hydroxyacid in CH_2Cl_2 (100 mL). The solution was allowed to stir for 1 h. To this was added Et_3N (40 mL, 288 mmol), and the mixture was stirred for 5 min. The cold bath was removed, and the mixture was allowed to reach room temperature. It was quenched by addition to water (200 mL) containing NaOH (9 g, 225 mmol), and the layers were separated. The organic layer was washed with 5% NaOH (2×); the aqueous extracts were combined and washed with ether (2×), and the ethereal solutions were discarded. The aqueous layer was acidified with cold concentrated HCl and extracted into CH_2Cl_2 (3×). These were washed with brine, dried over Na_2SO_4, and concentrated to give 15.3 g (80%) of the ketoacid as a very viscous oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.01 (s, 3H), 2.15 (s, 3H), 2.44 (dd, J = 18.0, 3.9, 1H), 3.18 (dd, J = 18.0, 9.9, 1H), 3.69 (s, 3H), 3.70 (s, 3H), 4.32 (dd, J = 9.9, 3.9, 1H), 6.46 (d, J = 1.5, 1H), 6.52 (d, J = 1.5, 1H), 10.5 (bs, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.4, 30.0, 40.3, 45.9, 55.7, 60.7, 112.8, 120.6, 131.4, 134.1, 144.3, 152.5, 179.2, 206.5; IR (thin film) 3150(br), 1713 cm^{-1}; HRMS (FAB+) for $C_{14}H_{18}O_5$ $(M)^+$ calcd 266.1154, found 266.1154.

***exo-endo*-(2,3-Dimethoxy-5-methylphenyl)bicyclic Lactam, 14.** A stirred solution of ketoacid **9** (15.3 g, 57 mmol) and (*S*)-valinol (6.2 g, 60 mmol) in benzene (250 mL) was heated under azeotropic removal of water with a Dean−Stark trap for 16 h. The solution was cooled and concentrated; the residue was taken up in ether; washed with saturated NH_4Cl, saturated Na_2CO_3, and brine; and then dried over $MgSO_4$. The solution was concentrated and filtered through a large pad of silica gel using 40% EtOAc/Hex to yield 15.9 g (84%) of a viscous oil, which was a 3:2 mixture of *exo-endo* epimers. The epimers could be separated by careful chromatography of the mixture. **Major**: $[\alpha]^{25}_D$ +3.56 (*c* 2.5, CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.87 (d, J = 6.6, 3H), 1.11 (d, J = 6.6, 3H), 1.44 (s, 3H), 1.70 (m, 1H), 2.09 (dd, J = 14.4, 6.3, 1H), 2.24 (s, 3H), 2.66 (dd, J = 13.8, 10.8, 1H), 3.68 (m, 1H), 3.76 (s, 3H), 3.78 (m, 1H), 3.80 (s, 3H), 3.89 (dd, J = 11.1, 6.3, 1H), 4.18 (t, J = 8.1, 1H), 6.50 (d, J = 1.5, 1H), 6.61 (d, J = 1.5, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.6, 16.5, 16.9, 20.4, 29.6, 36.0, 41.4, 51.1, 55.9, 59.0, 65.8, 94.5, 108.0, 116.8, 129.0, 129.2, 140.0, 147.9, 177.6; IR (thin film) 1712 cm^{-1}; HRMS (EI+) for $C_{19}H_{27}NO_4$ $(M)^+$ calcd 333.1940, found 333.1935.

Minor: $[\alpha]^{25}_D$ +35.9 (*c* 2.0, CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.87 (d, J = 6.2, 3H), 1.00 (d, J = 6.5, 3H), 1.51 (s, 3H), 1.69 (m, 1H), 2.22 (s, 3H), 2.32 (t, J = 11.1, 1H), 2.48 (dd, J = 12.9, 8.7, 1H), 3.69 (m, 1H), 3.76 (s, 3H), 3.78 (s, 3H), 3.89 (dd, J = 8.7, 5.4, 1H), 4.19 (m, 2H), 6.49 (s, 1H), 6.60 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.7, 15.9, 16.8, 20.9, 28.5, 39.3, 41.4, 51.2, 56.2, 57.4, 66.2, 92.6, 108.1, 117.4, 127.1, 129.0, 140.6, 147.7, 173.8; IR (thin film) 1713 cm^{-1}.

***endo*-Methyl-(2,3-Dimethoxy-5-methylphenyl)bicyclic Lactam, 8.** To a stirred solution of diisopropylamine (12.6 mL, 90 mmol) in THF (350 mL, 0 °C) was added *n*-BuLi (2.62 M in hexanes, 33 mL, 86.3 mmol). The solution was stirred for 30 min and cooled to −78 °C. To this was added **14** (23 g, 69 mmol) in THF (100 mL) via cannula, and the mixture was allowed to stir for 1 h. The solution was cooled to −100 °C, and MeI (11 mL, 180 mmol) was added dropwise. The mixture was stirred for 2 h, quenched by addition of water, and concentrated. The residue, a 33:1 ratio of alkylation epimers, was taken up in 20% EtOAc/Hex and filtered through a large pad of silica gel to give a white solid. This was recrystallized from *n*-heptane to yield 19.7 g (82%) of a white solid as a single diastereomer. The minor diastereomer was isolated by successive recrystallizations of the mother liquor to afford a 1:1 mixture of diastereomers. Careful chromatography of the enriched material then afforded the minor diastereomer. **Major** (**8**): mp 109−110 °C; $[\alpha]^{25}_D$ −46.7 (*c* 0.9, CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.87 (d, J = 6.6, 3H), 1.12 (d, J = 6.6, 3H), 1.28 (s, 3H), 1.49 (s, 3H), 1.70 (m, 1H), 2.19 (d, J = 13.5, 1H), 2.25 (s, 3H), 2.60 (d, J = 13.5, 1H), 3.67 (m, 1H), 3.79 (s, 3H), 3.81 (s, 3H), 4.18 (dd, J = 8.7, 7.5, 1H), 6.64 (s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 18.8, 20.6, 21.2, 24.1, 25.4, 33.8, 48.1, 50.3, 55.2, 59.5, 63.1, 69.9, 97.3, 112.0, 119.6, 132.4, 136.6, 144.0, 152.1, 184.1; IR (thin film) 1711 cm^{-1}. Anal. Calcd for $C_{20}H_{29}NO_4$: C 69.14, H 8.41 N 4.03. Found: C 69.08, H 8.41, N 3.99.

Minor: oil, $[\alpha]^{25}_D$ +64.1 (*c* 2.4, CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.90 (d, J = 6.6, 3H), 1.05 (d, J = 6.6, 3H), 1.55 (s, 3H), 1.67 (s, 3H), 1.70 (m, 1H), 2.07 (d, J = 13.2, 1H), 2.28 (s, 3H), 2.62 (d, J = 13.2, 1H), 3.76 (s, 3H), 3.78 (s, 3H), 3.82 (m, 1H), 4.29 (dd, J = 8.4, 7.8, 1H), 6.65 (s, 1H), 6.74 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.6, 16.1, 17.0, 20.4, 22.6, 29.6, 45.5, 46.5, 51.2, 55.2, 57.4, 66.2, 92.3, 108.6, 115.0, 127.6, 132.1, 139.8, 147.8, 178.2; IR (thin film) 1714 cm^{-1}.

(*S*)-4-(2,3-Dimethoxy-5-methylphenyl)-4-methylcyclopentenone, 7. To a stirred solution of **8** (10 g, 29 mmol) in THF (300 mL, −78 °C) was added Red-Al (65+ wt %, 10 mL, 33 mmol). The mixture

was allowed to reach room temperature, stirred for 24 h, quenched by addition of MeOH, and concentrated. The residue was taken up in water, extracted with ether (2×), made strongly basic with 20% KOH, and extracted with ether (2×). The combined extracts were washed with brine, dried over Na_2SO_4, and concentrated to give the crude carbinolamine. This was dissolved in 95% EtOH (460 mL) and added to a stirred solution of KH_2PO_4 (78.4 g, 576 mmol) in water (690 mL), and the mixture was stirred 12 h. The suspension was concentrated, dissolved in water, and extracted with ether (3×). The organics were washed with brine, dried over Na_2SO_4, and concentrated to give the crude keto aldehyde as a viscous oil. This was dissolved in absolute EtOH (500 mL), treated with 1 M KOH in EtOH (1.5 mL), and heated at reflux for 2 h. The solution was cooled, treated with silica gel, and concentrated to adsorb the crude cyclopentenone. Column chromatography (20% EtOAc/Hex) gave 5.95 g (84%) as a colorless oil: $[\alpha]^{25}_D$ +38.3 (*c* 1.5, CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.53 (s, 3H), 2.27 (s, 3H), 2.57 (d, J = 18.6, 1H), 2.69 (d, J = 18.6, 1H), 3.73 (s, 3H), 3.81 (s, 3H), 6.12 (d, J = 6.0, 1H), 6.54 (d, J = 1.5, 1H), 6.64 (d, J = 1.5, 1H), 7.82 (d, J = 5.4, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.5, 28.3, 47.3, 51.1, 55.7, 60.5, 112.5, 119.2, 130.6, 133.0, 138.0, 145.1, 153.0, 171.4, 209.8; IR (thin film) 1715 cm^{-1}. Anal. Calcd for $C_{15}H_{18}O_3$: C 73.15, H 7.37. Found: C 72.94, H 7.39.

(*S*)-4,5,5-Trimethyl-4-(2,3,dimethoxy-5-methylphenyl)cyclopentenone, 18. To a stirred suspension of NaH (1.78 g, 74 mmol) in DMF (30 mL) was added a solution of cyclopentenone **7** (6.6 g, 26.9 mmol) in DMF (20 mL) via cannula. The mixture was placed in a 10 °C bath, and MeI (4.4 mL, 70 mmol) was added. The bath was removed, and the mixture was stirred at room temperature. The bath was replaced as necessary to maintain a temperature below 40 °C. After the exotherm ceased, the bath was removed and the solution was allowed to stir overnight. The mixture was poured into water (250 mL), extracted into ether (4×), washed with water and brine, dried over Na_2SO_4, and concentrated to give an oil. The residue was recrystallized from heptane to give 3.96 g (54%) of **18** as a white solid. The mother liquor (**17**) was concentrated and redissolved in 3:1 THF/1 N HCl. After 10 min, the mixture was quenched by addition of $NaHCO_3$ and concentrated. The residue was taken up in water, extracted into ether (3×), washed with brine, dried over Na_2SO_4, and concentrated. This was resubjected to the conditions above, using 1.5 equiv NaH and 1.25 equiv MeI. Two recycles gave an additional 2.0 g (28%): mp 84.0−85.9 °C; $[\alpha]^{25}_D$ −79.4 (*c* 1.0, CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.64 (s, 3H), 1.22 (s, 3H), 1.46 (s, 3H), 2.27 (s, 3H), 3.78 (s, 3H), 3.82 (s, 3H), 6.05 (d, J = 6.0, 1H), 6.46 (s, 1H), 6.63 (d, J = 1.5, 1H), 7.91 (d, J = 5.7, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 19.7, 21.4, 26.1, 50.9, 54.7, 55.6, 60.3, 112.1, 120.6, 125.8, 132.8, 136.0, 145.3, 152.8, 171.4, 214.6; IR (thin film) 1705 cm^{-1}. Anal. Calcd for $C_{17}H_{22}O_3$: C 74.42, H 8.08. Found: C 74.30, H 8.10.

(*S*)-*O,O′*-Dimethylherbertenediol, 6. A flask was charged with cyclopentenone **18** (1.93 g, 7.0 mmol), Belleau's reagent (2.23 g, 4.23 mmol), and toluene (65 mL). The solution was heated to reflux and held there for 30 min. The solution was cooled, filtered through Fluorosil, washed with CH_2Cl_2, and concentrated to yield a bright pink oil, which was subjected to flash chromatography (5% EtOAc/Hex), taking all pink fractions. The residue was dissolved in EtOH (75 mL), and Raney Ni was added in portions with stirring until the solution was colorless. A hydrogen balloon was affixed, and stirring was continued overnight. The solution was filtered to give the crude cyclopentane. Flash chromatography (4% EtOAc/Hex) gave 1.05 g (58%) as a colorless oil: $[\alpha]^{25}_D$ −27.0 (*c* 1.3, CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.67 (s, 3H), 1.10 (s, 3H), 1.33 (s, 3H), 1.70 (m, 5H), 2.27 (s, 3H), 2.61 (m, 1H), 3.74 (s, 3H), 3.80 (s, 3H), 6.58 (d, J = 1.8, 1H), 6.73 (d, J = 1.5, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 20.5, 21.8, 24.3, 25.4, 27.0, 39.1, 41.1, 45.1, 51.7, 55.7, 60.5, 111.2, 121.8, 131.7, 140.2, 146.8, 153.2.

(−)-Herbertenediol, 1. To a stirred solution of dimethylherbertenediol (100 mg, 0.38 mmol) in CH_2Cl_2 (2 mL) at 0 °C was added BBr_3 (1 M in CH_2Cl_2, 1.5 mL, 1.5 mmol). The ice bath was removed, and after 40 min the solution was poured into 2% $NaHCO_3$, extracted into CH_2Cl_2 (3×), washed with brine, dried over Na_2SO_4, and concentrated. Column chromatography (20% EtOAc/Hex) gave 81 mg (91%) as a white crystalline solid: mp 89.9−90.5 °C; $[\alpha]^{25}_D$ −53.8 (*c* 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.77 (s, 3H), 1.20 (s, 3H), 1.42 (s, 3H), 1.50−1.80 (m, 5H), 2.23 (s, 3H), 2.61 (m, 1H), 5.32 (s, 1H), 5.41 (s, 1H), 6.55 (d, J = 1.5, 1H), 6.69 (d, J = 1.5, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 20.5, 21.3, 23.0, 25.6, 27.0, 39.4, 41.1, 45.0, 51.3, 113.6, 122.1, 128.8, 133.7, 141.1, 143.5; IR (thin film) 3507, 2959, 1300 cm^{-1}. Anal. Calcd for $C_{15}H_{22}O_2$: C 76.88, H 9.46. Found: C 77.08, H 9.60.

(*S*)-2-Bromo-3,4-dimethoxy-5-(1,2,2-trimethylcyclopentyl)benzoic Acid, 20. To a stirred solution of **6** (2.08 g, 7.95 mmol) in CH_2Cl_2 (42 mL, −10 °C) was added bromine (412 μL, 8.0 mmol) dropwise. After 5 min, the solution was poured into saturated $NaHCO_3$, extracted into CH_2Cl_2 (2×), washed with brine, dried over Na_2SO_4, and concentrated. Trace impurities were removed via flash chromatography (2% EtOAc/Hex) to give 2.71 g (100%) of (*S*)-1,2,2-trimethyl-1-(2,3-dimethoxy-4-bromo-5-methylphenyl)cyclopentane as a colorless oil: $[\alpha]^{25}_D$ −14.5 (*c* 1.3, CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.66 (s, 3H), 1.09 (s, 3H), 1.31 (s, 3H), 1.71 (m, 5H), 2.32 (s, 3H), 2.52 (m, 1H), 3.78 (s, 3H), 3.79 (s, 3H), 6.95 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 20.6, 23.2, 24.2, 25.4, 27.0, 39.3, 41.1, 45.0, 51.7, 59.9, 60.5, 117.7, 125.8, 132.2, 139.9, 150.9, 152.0; HRMS (EI+) for $C_{17}H_{25}NO_2Br$ $(M)^+$ calcd 340.1038, found 340.1029; HRMS (EI+) for $C_{23}H_{35}NO_381Br$ $(M)^+$ calcd 342.1017, found 342.1016.

A pressure tube was charged with (*S*)-1,2,2-trimethyl-1-(2,3-dimethoxy-4-bromo-5-methylphenyl)-cyclopentane (2.70 g, 7.9 mmol), $Co(OAc)_2 \cdot 4H_2O$ (0.66 g, 2.64 mmol), methyl ethyl ketone (2.84 mL, 32 mmol), and glacial acetic acid (25 mL). The tube was sealed, pressurized with oxygen (10 psi), and heated to 110 °C. The pressure was raised to 80 psi, and the mixture was allowed to stir for 4 h. The tube was depressurized and poured onto 3 volumes of ice to give a white precipitate. This was filtered to give 2.46 g (84%) of the acid as crystalline solid: mp 163−165 °C; $[\alpha]^{25}_D$ −37.3 (*c* 1.1, CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.68 (s, 3H), 1.12 (s, 3H), 1.34 (s, 3H), 1.75 (m, 5H), 2.52 (m, 1H), 3.80 (s, 3H), 3.89 (s, 3H), 7.84 (s, 1H), 12.35 (bs, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 15.8, 19.2, 20.7, 22.3, 34.8, 36.5, 40.3, 47.2, 55.4, 56.0, 112.6, 120.1, 124.2, 136.0, 147.2, 153.3, 167.3; IR (thin film) 3150(br), 1695 cm^{-1}. Anal. Calcd for $C_{17}H_{23}O_4Br$: C 55.00, H 6.24. Found: C 54.99, H 6.17.

(*S*)-*tert*-Leucinol-*o*-bromoaryloxazoline, 5. To a stirred solution of **20** (1.0 g, 2.7 mmol) in CH_2Cl_2 (10 mL) was added oxalyl chloride (0.35 mL, 4.0 mmol), followed by 1 drop of DMF. After 1 h, the solution was concentrated, redissolved in CH_2Cl_2 (10 mL), and cooled to 0 °C. To this was added a solution of (*S*)-*tert*-leucinol (0.38 g, 3.2 mmol) and Et_3N (0.49 mL, 3.5 mmol) in CH_2Cl_2 (5 mL). The ice bath was removed, and the mixture was stirred for 6 h. The solution was poured into 2% $NaHCO_3$, and the layers were separated and extracted twice more with CH_2Cl_2. The organics were combined, washed with brine, dried over $MgSO_4$, filtered, and concentrated. The residue was dissolved in CH_2Cl_2 (10 mL), treated with $SOCl_2$ (394 μL, 5.4 mmol), and stirred for 2 h at room temperature. The solvent was removed, and the residue was dissolved in CH_3CN (10 mL), treated with 20% K_2CO_3, and heated to reflux. After 5 h, the heterogeneous mixture was concentrated to remove the CH_3CN and extracted with ether (3×). The extracts were washed with brine, dried over Na_2SO_4, and concentrated. Flash chromatography gave 1.0 g (82%) as a viscous oil: $[\alpha]^{25}_D$ −79.4 (*c* 1.0, CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.66 (s, 3H), 0.97 (s, 9H), 1.09 (s, 3H), 1.31 (s, 3H), 1.68 (m, 5H), 2.49 (m, 1H), 3.77 (s, 3H), 3.83 (s, 3H), 4.05 (dd, J = 10.2, 7.8, 1H), 4.21 (dd, J = 8.1, 8.1, 1H), 4.33 (dd, J = 10.5, 9.0, 1H), 7.38 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 20.4, 23.7, 25.4, 26.1, 27.0, 34.1, 39.4, 41.2, 44.8, 51.7, 59.9, 60.5, 68.9, 76.7, 115.7, 124.8, 126.6, 140.6, 151.4, 155.7, 163.0; IR (thin film) 1660 cm^{-1}; HRMS (FAB+) for $C_{23}H_{35}NO_3Br$ $(M+H)^+$ calcd 452.1800, found 452.1786; HRMS (FAB+) for $C_{23}H_{35}NO_381Br$ $(M+H)^+$ calcd 454.1780, found 454.1775.

(*S*)-Phenylglycinol-*o*-bromoaryloxazoline, 28. Prepared from **20** by the same procedure as **5**, using (*S*)-phenylglycinol in place of (*S*)-*tert*-leucinol, in 83% yield as a colorless oil: $[\alpha]^{25}_D$ −35.3 (*c* 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.70 (s, 3H), 1.13 (s, 3H), 1.35 (s, 3H), 1.45−1.85 (m, 5H), 2.54 (m, 1H), 3.81 (s, 3H), 3.88 (s, 3H), 4.24 (dd, J = 8.4, 8.4, 1H), 4.79 (dd, J = 10.2, 8.4, 1H), 5.42 (dd, J = 9.9, 8.4, 1H), 7.23−7.38 (m, 5H), 7.55 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 20.6, 23.8, 25.5, 27.2, 39.5, 41.3, 45.0, 51.9, 60.1,

60.6, 70.7, 75.1, 116.0, 124.3, 126.9, 127.0, 127.7, 128.9, 140.9, 142.4, 151.5, 156.1, 164.6; IR (thin film) 1651 cm^{-1}.

(*S*)-Valinol-*o*-bromoaryloxazoline, 29. Prepared from **20** by the same procedure as **5**, using (*S*)-valinol in place of (*S*)-*tert*-leucinol, in 85% yield as a colorless oil: $[\alpha]^{25}_D$ −46.6 (*c* 1.3, CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.66 (s, 3H), 0.96 (d, J = 7.0, 3H), 1.03 (d, J = 6.6, 3H), 1.10 (s, 3H), 1.32 (s, 3H), 1.40−2.00 (m, 6H), 2.48 (m, 1H), 3.78 (s, 3H), 3.84 (s, 3H), 4.13 (m, 2H), 4.39 (dd, J = 12.9, 11.4, 1H), 7.40 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 18.2, 18.9, 20.4, 23.6, 25.4, 27.0, 32.7, 39.3, 41.2, 44.8, 51.7, 59.9, 60.4, 70.2, 72.9, 115.7, 124.7, 126.6, 140.6, 151.3, 155.7, 163.0; IR (thin film) 1655 cm^{-1}.

(*S*)-2-Aminobutanol-*o*-bromoaryloxazoline, 30. Prepared from **20** by the same procedure as **5**, using (*S*)-2-aminobutanol in place of (*S*)-*tert*-leucinol, in 77% yield as a colorless oil: $[\alpha]^{25}_D$ +1.86 (*c* 0.7, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.66 (s, 3H), 1.00 (t, J = 7.2, 3H), 1.10 (s, 3H), 1.31 (s, 3H), 1.40−1.85 (m, 6H), 2.48 (m, 1H), 3.77 (s, 3H), 3.84 (s, 3H), 4.05 (dd, J = 7.8, 7.8, 1H), 4.26 (m, 1H), 4.45 (dd, J = 8.4, 8.4, 1H), 7.39 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 9.9, 20.4, 23.7, 25.4, 27.0, 28.6, 39.3, 41.2, 44.8, 51.7, 59.9, 60.4, 68.3, 72.1, 115.7, 124.6, 126.5, 140.6, 151.3, 155.7, 163.1; IR (thin film) 1653 cm^{-1}.

(*S*)-Alaninol-*o*-bromoarylozazoline, 31. Prepared from **20** by the same procedure as **5**, using (*S*)-alaninol in place of (*S*)-*tert*-leucinol, in 98% yield as a colorless oil: $[\alpha]^{25}_D$ −15.1 (*c* 1.1, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.62 (s, 3H), 1.07 (s, 3H), 1.29 (s, 3H), 1.32 (d, J = 6.3, 3H), 1.50−1.80 (m, 5H), 2.48 (m, 1H), 3.75 (s, 3H), 3.81 (s, 3H), 3.91 (dd, J = 7.2, 7.2, 1H), 4.38 (m, 1H), 4.45 (dd, J = 9.6, 7.8, 1H), 7.39 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 20.5, 21.6, 23.7, 25.5, 27.1, 39.4, 41.3, 44.8, 51.7, 60.0, 60.5, 62.5, 74.2, 115.8, 124.5, 126.7, 140.7, 151.4, 155.8, 163.1; IR (thin film) 1651 cm^{-1}.

(*R*)-Valinol-*o*-bromoaryloxazoline, 25. Prepared from **20** by the same procedure as **5**, using (*R*)-valinol in place of (*S*)-*tert*-leucinol, in 85% yield as a colorless oil: $[\alpha]^{25}_D$ +7.53 (*c* 1.5, CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.66 (s, 3H), 0.95 (d, J = 7.0, 3H), 1.03 (d, J = 6.9, 3H), 1.10 (s, 3H), 1.31 (s, 3H), 1.40−1.95 (m, 6H), 2.48 (m, 1H), 3.77 (s, 3H), 3.84 (s, 3H), 4.13 (m, 2H), 4.38 (dd, J = 12.9, 11.4, 1H), 7.39 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 18.2, 18.9, 20.4, 23.7, 25.4, 27.0, 32.7, 39.3, 41.2, 44.8, 51.7, 59.9, 60.4, 70.1, 72.9, 115.7, 124.7, 126.5, 140.6, 151.3, 155.7, 162.9; IR (thin film) 1658 cm^{-1}.

(*S*)-*tert*-Leucinol-bisoxazoline, 4. A 10 mL flask with stirbar was charged with **5** (300 mg, 0.66 mmol), freshly activated[27] Cu (150 mg, 2.3 mmol), and DMF (1 mL). The mixture was heated to 95 °C for 8 h and then diluted with DMF (5 mL). A condenser was affixed, and the mixture was heated to reflux. After 3 d, the mixture was filtered through cotton to remove excess Cu, poured into water, and extracted into ether (3×). The organics were washed with water (2×) and then brine, dried over Na_2SO_4, and concentrated. Flash chromatography (5−50% EtOAc/Hex) gave the biaryl as its copper complex. This was taken up in ether, washed with NH_4OH (2×) and brine, and dried over Na_2SO_4 to yield the 0.158 g (64%) as a single atropisomer. **Major (4)**: $[\alpha]^{25}_D$ −50.6 (*c* 1.1, CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.70 (s, 18H), 0.75 (s, 6H), 1.15 (s, 6H), 1.37 (s, 6H), 1.50−1.90 (m, 10H), 2.68 (m, 2H), 3.55 (s, 6H), 3.71 (m, 4H), 3.79 (s, 6H), 3.92 (dd, J = 9.6, 8.1, 2H), 7.76 (s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 20.6, 24.4, 25.3, 26.1, 27.3, 33.8, 38.9, 41.3, 45.1, 51.7, 59.6, 60.0, 68.1, 76.3, 123.0, 125.2, 131.0, 139.3, 151.3, 154.7, 163.4; IR (thin film) 1655 cm^{-1}. Anal. Calcd for $C_{46}H_{68}N_2O_6$: C 74.16, H 9.20. Found: C 73.92, H 9.31.

Minor (21): $[\alpha]^{25}_D$ −13.0 (*c* 1.2, CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.62 (s, 18H), 0.77 (s, 6H), 1.15 (s, 6H), 1.36 (s, 6H), 1.50−1.90 (m, 10H), 2.69 (m, 2H), 3.59 (s, 6H), 3.73 (m, 10H), 3.81 (s, 6H), 3.95 (dd, J = 9.6, 7.8, 2H), 7.59 (s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 20.6, 24.5, 25.5, 26.1, 27.2, 33.8, 39.2, 41.2, 45.1, 51.8, 59.5, 60.1, 67.8, 76.7, 122.1, 125.2, 131.4, 139.3, 151.8, 154.9, 163.0; IR (thin film) 1654 cm^{-1}.

(*S*)-Alaninol-bisoxazoline, 32. Prepared from **31** by the same procedure as **4** in 66% yield as an amorphous solid. **Major**: $[\alpha]^{25}_D$ −87.9 (*c* 1.1, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.69 (s, 6H), 1.12 (d, 6H), 1.13 (s, 6H), 1.38 (s, 6H), 1.50−1.90 (m, 10H), 2.71 (m, 2H), 3.50 (m, 2H), 3.52 (s, 6H), 3.79 (s, 6H), 4.07 (m, 4H), 7.62 (s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 20.6, 21.4, 24.1, 25.6, 27.3, 39.0, 41.3, 45.2, 51.8, 59.5, 60.1, 62.0, 73.9, 122.8, 125.2, 130.4, 139.7, 151.5, 154.9, 164.3; IR (thin film) 1651 cm^{-1}.

(*R*)-Valinol-bisoxazoline, 26. Prepared from **25** by the same procedure as **4** in 74% yield as an amorphous solid. **Major**: $[\alpha]^{25}_D$ +43.9 (*c* 1.3, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.70 (d, J = 6.6, 6H), 0.72 (s, 6H), 0.79 (d, J = 6.6, 6H), 1.15 (s, 6H), 1.41 (s, 6H), 1.45−1.85 (m, 12H), 2.62 (m, 2H), 3.58 (s, 6H), 3.63 (m, 4H), 3.83 (s, 6H), 3.95 (dd, J = 8.7, 7.2, 2H), 7.57 (s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 18.3, 19.1, 20.4, 23.5, 25.4, 27.1, 32.8, 39.4, 41.2, 44.7, 51.5, 59.2, 59.9, 69.6, 72.7, 122.3, 124.6, 131.0, 139.1, 151.2, 154.7, 163.4; IR (thin film) 1652 cm^{-1}. Anal. Calcd for $C_{44}H_{64}N_2O_6$: C 73.71, H 9.00, N 3.91. Found: C 73.53, H 9.01, N 3.73.

Biaryldiol, 24. Bisoxazoline **4** (95 mg, 0.13 mmol) was dissolved in THF (2 mL) and 1 N HCl (2 mL). The solution was stirred at room temperature for 3 d. It was poured into saturated $NaHCO_3$, extracted into ether (3×), washed with brine, dried over Na_2SO_4, and concentrated to give the crude intermediate bisaminoester. The residue was dissolved in CH_2Cl_2 (5 mL) and treated with Ac_2O (30 μL, 0.31 mmol), Et_3N (50 μL, 0.35 mmol), and a crystal of DMAP. After 2 h of stirring, the solution was poured into saturated $NaHCO_3$, extracted into CH_2Cl_2 (3×), dried over Na_2SO_4, and concentrated. Flash chromatography (50% EtOAc/Hex) gave 0.103 g (94%) of the (*S*)-*tert*-leucinol derived bisacetamide as an amorphous solid: $[\alpha]^{25}_D$ −68.5 (*c* 1.0, CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.66 (s, 6H), 0.82 (s, 18H), 1.10 (s, 6H), 1.40 (s, 6H), 1.45−1.85 (m, 10H), 1.87 (s, 6H), 2.58 (m, 2H), 3.33 (s, 6H), 3.80 (s, 6H), 3.94 (m, 4H), 4.27 (m, 2H), 5.75 (d, J = 9.6, 2H), 7.75 (s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 20.6, 23.5, 23.7, 25.5, 27.0, 27.0, 34.1, 39.4, 41.2, 45.1, 51.9, 55.8, 59.3, 60.2, 63.9, 124.6, 126.2, 131.0, 139.8, 151.0, 156.5, 167.4, 170.0; IR (thin film) 3305(br), 1727, 1660 cm^{-1}.

To a stirred suspension of $LiAlH_4$ (46 mg, 1.2 mmol) in THF (5 mL, 0 °C) was added the (*S*)-*tert*-leucinol derived bisacetamide (200 mg, 0.23 mmol). The solution was warmed to room temperature and stirred for 2 h. The solution was quenched by addition of MeOH, followed by 20% aqueous KOH. The solid was filtered, and the eluent was concentrated. Column chromatography (20% EtOAc/Hex) gave 115 mg (90%) of the diol as an amorphous solid: $[\alpha]^{25}_D$ +71.5 (*c* 1.2, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.68 (s, 6H), 1.14 (s, 6H), 1.43 (s, 6H), 1.45−1.75 (m, 10H), 2.60 (m, 2H), 3.09 (bs, 2H), 3.54 (s, 6H), 3.79 (s, 6H), 4.14 (d, J = 11.7, 2H),4.20 (d, J = 11.1, 2H), 7.26 (s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 20.6, 23.7, 25.6, 27.2, 39.4, 41.3, 45.2, 51.9, 60.0, 60.3, 64.4, 126.2, 127.9, 134.4, 141.2, 150.7, 152.8; IR (thin film) 3362(br) cm^{-1}. Anal. Calcd for $C_{34}H_{50}O_6$: C 73.61, H 9.08. Found: C 73.77, H 9.19.

Biaryldiol, 27. The (*R*)-valinol derived bisacetamide was prepared from **26**, by the same procedure used to prepare the (*S*)-*tert*-leucinol derived bisacetamide (en route to **24**), in 93% yield as an amorphous solid: $[\alpha]^{25}_D$ +23.5 (*c* 1.2, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.76 (m, 18H), 1.10 (s, 6H), 1.25−1.90 (m, 12H), 1.35 (s, 6H), 1.88 (s, 6H), 2.69 (m, 2H), 3.41 (s, 6H), 3.75 (m, 2H), 3.78 (s, 6H), 3.95 (dd, J = 11.7, 3.6, 2H), 4.07 (dd, J = 11.4, 5.7, 2H), 5.78 (d, J = 9.0, 2H), 7.82 (s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 19.1, 19.3, 20.4, 23.3, 24.5, 25.0, 26.9, 29.2, 38.4, 40.8, 45.3, 51.7, 53.5, 59.6, 60.1, 65.2, 123.9, 126.8, 131.2, 140.2, 151.3, 156.7, 167.9, 169.9; IR (thin film) 3305(br), 1726, 1652 cm^{-1}.

Diol **27** was prepared from the (*R*)-valinol derived bisacetamide, by the same procedure used to prepare **24**, in 96% yield as an amorphous solid: $[\alpha]^{25}_D$ −70.2 (*c* 1.1, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.71 (s, 6H), 1.13 (s, 6H), 1.40 (s, 6H), 1.50−1.90 (m, 12H), 2.53 (bs, 2H), 2.80 (m, 2H), 3.55 (s, 6H), 3.78 (s, 6H), 4.22 (bs, 4H), 7.26 (s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 20.6, 24.5, 25.2, 27.1, 38.6, 40.8, 45.2, 51.9, 59.9, 60.4, 63.7, 126.1, 128.2, 133.8, 140.7, 150.9, 152.8; IR (thin film) 3289(br) cm^{-1}. Anal. Calcd for $C_{34}H_{50}O_6$: C 73.61, H 9.08. Found: C 73.62, H 9.23.

(26) (a) Hirsch, J. A. *Top. Stereochem.* **1967**, *1*, 199. (b) Eliel, E. L.; Manoharan, M. *J. Org. Chem.* **1981**, *46*, 1959. (c) Allinger, N.; Freiberg, L. *J. Org. Chem.* **1966**, *31*, 804.

(27) Fuson, R. C.; Cleveland, E. A. *Organic Syntheses*; Wiley: New York, 1955; Vol. III, p 339.

(−)-Mastigophorene A, 2. To a stirred solution of diol **24** (40 mg, 0.072 mmol) in THF (1.5 mL) were added PPh_3 (45 mg, 0.17 mmol) and CBr_4 (60 mg, 0.18 mmol) in one portion. After 30 min, TLC still showed additional starting material, so additional PPh_3 (38 mg, 0.14 mmol) and CBr_4 (48 mg, 0.14 mmol) were added in one portion. After 10 min, the solution was quenched by addition of MeOH, concentrated, and filtered through silica, eluting with CH_2Cl_2. The crude dibromide was dissolved in ether (1.5 mL) and treated with $LiAlH_4$ (1 M in ether, 0.5 mL, 0.5 mmol). The solution was stirred for 2 h and quenched by cautious addition of MeOH and then 20% aqueous KOH. The white precipitate was filtered. Column chromatography (2% EtOAc/Hex) of the eluent gave 33 mg (88%) of tetramethylmastigophorene A as a crystalline solid: mp 154−156 °C; $[\alpha]^{25}_D$ +8.68 (*c* 1.5, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.70 (s, 6H), 1.13 (s, 6H), 1.41 (s, 6H), 1.45−1.85 (m, 10H), 1.94 (s, 6H), 2.68 (m, 2H), 3.56 (s, 6H), 3.76 (s, 6H), 6.95 (s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 20.1, 20.7, 24.2, 25.5, 27.1, 39.0, 41.1, 45.2, 51.7, 59.7, 60.2, 125.1, 129.8, 130.7, 139.2, 151.1, 151.3.

Next, **2** was prepared from tetramethylmastigophorene A by the action of BBr_3 (10 equiv), utilizing the same procedure used to prepare **1**, in 84% yield: $[\alpha]^{25}_D$ −67.6 (*c* 0.4, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.78 (s, 6H), 1.19 (s, 6H), 1.44 (s, 6H), 1.45−1.85 (m, 10H), 1.92 (s, 6H), 2.67 (m, 2H), 4.69 (s, 2H), 5.56 (s, 2H), 6.84 (s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 19.3, 20.5, 22.8, 25.6, 27.2, 38.9, 41.2, 45.0, 51.4, 116.9, 122.8, 126.7, 133.9, 140.5, 141.6; IR (thin film) 3526, 2958, 1222 cm^{-1}. Anal. Calcd for $C_{30}H_{42}O_4 \cdot {}^2/_3H_2O$:[4] C 75.27, H 9.12. Found: C 75.60, H 9.08.

(−)-Mastigophorene B, 3. Tetramethylmastigophorene B was prepared from **27** by the same procedure used to prepare tetramethylmastigophorene A (en route to **2**) in 89% yield as a crystalline solid: $[\alpha]^{25}_D$ −26.2 (*c* 1.1, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.70 (s, 6H), 1.12 (s, 6H), 1.40 (s, 6H), 1.50−1.85 (m, 10H), 1.90 (s, 6H), 2.70 (m, 2H), 3.56 (s, 6H), 3.76 (s, 6H), 6.95 (s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 19.9, 20.7, 24.4, 25.5, 27.1, 39.0, 41.1, 45.2, 51.7, 59.7, 60.3, 125.3, 130.0, 130.3, 139.1, 151.1, 151.3.

Next, **3** was prepared from tetramethylmastigophorene B by the action of BBr_3 (10 equiv), utilizing the same procedure used to prepare **1**, in 90% yield: $[\alpha]^{25}_D$ +38.0 (*c* 0.35, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.79 (s, 6H), 1.21 (s, 6H), 1.47 (s, 6H), 1.50−1.80 (m, 10H), 1.92 (s, 6H), 2.62 (m, 2H), 4.76 (s, 2H), 5.58 (s, 2H), 6.85 (s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 19.2, 20.6, 22.6, 25.7, 27.2, 39.2, 41.3, 45.0, 51.4, 117.1, 122.7, 126.8, 133.9, 140.7, 141.6; IR (thin film) 3531, 2961, 1226 cm^{-1}.

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Supporting Information Available: Spectral data (^{1}H and ^{13}C NMR) of all key intermediates and final products (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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