Tetrahedron 66 (2010) 4796–4804

Contents lists available at ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

A two-step mimic for direct, asymmetric bromonium- and chloronium-induced polyene cyclizations

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ARTICLE INFO

Article history:
Received 28 January 2010
Received in revised form 8 March 2010
Accepted 9 March 2010
Available online 15 March 2010

Dedicated to Professor Brian M. Stoltz on the occasion of his receipt of the Tetrahedron Young Investigator Award

Keywords:
Total synthesis
Halogenation
Polyene Cyclization

ABSTRACT

Although direct, asymmetric, halonium-induced cyclizations have proven difficult to achieve in the absence of enzymes, this report provides a two-step alternative based on reacting polyenes with chiral mercury(II) complexes to afford a number of polycyclic organomercurials that can be subsequently converted, with retention, into their corresponding chlorine, bromine, and iodine derivatives in good yield and enantioselectivity. A five-step asymmetric total synthesis of the natural product 4-iso-cymobarbatol is also described.

1. Introduction

In the fifty years since Stork and Eschenmoser first delineated the cation-π cyclization hypothesis to account for the formation of various polycyclic scaffolds in Nature,[1] many investigators have developed useful laboratory protocols to effect such reactions in laboratory flasks, several of which are enantioselective.[2] One major area of synthetic deficiency, however, is the field of bromonium- and chloronium-induced polyene cyclizations, examples of which would include the conversion of napyradiomycin A1 (**1**, Scheme 1) into either napyradiomycin B4 (**2**) or B3 (**3**).[3,4] In Nature, these reactions are known to be accomplished enantiospecifically through the use of vanadium-based haloperoxidases;[5,6] in the laboratory, however, these transformations have proven difficult to achieve racemically, let alone enantioselectively. For example, most simple chemical initiators like Br_2, Cl_2, *N*-bromosuccinimide (NBS), or *N*-chlorosuccinimide (NCS) convert polyene starting materials into compounds such as **8** and **9** via the intermolecular attack of an external nucleophile or proton elimination in advance of intramolecular cyclization to **10**, especially if the proximal olefin is electron deficient.[7] As part of a research program seeking to tackle this overall challenge, we recently described the development of a reagent ($Et_2SBr \cdot SbBrCl_5$, BDSB)[8] that can smoothly effect direct, racemic, bromonium-induced cyclizations for a variety of substrates derived from geraniol, farnesol, and nerol, leading to the ability to fashion ring systems pertinent to several hundred natural products, potentially including **3**–**5**.[9,10] This manuscript details some of our recent studies to synthesize such products enantioselectively.

2. Results and discussion

2.1. Logic of approach pursued

To date, only asymmetric iodonium-based polyene cyclizations have been achieved successfully as described by Ishihara and co-workers[11] through complexation of *N*-iodosuccinimide (NIS) by a stoichiometric amount of a phosphorous-based chiral ligand. This approach has enabled access to 3 aryl-containing products, including **12** (Scheme 2), in high enantioselectivity and reasonable yield following 24 h of controlled reaction at −40 °C. As of yet, however, application of the same strategy to bromonium- and chloronium-based cyclizations has not met with success in terms of asymmetry. This result likely reflects the profound differences in reactivity between iodine and its halogen cousins,[12] where the rapid transfer of bromonium to unreacted alkenes in solution prior to intramolecular cyclization provides a pathway to degrade any enantioselectivity initially imparted by a chiral electrophilic halogen reagent, and chloronium species behave more like carbocations prone to eliminations and rearrangements.[13] Given this knowledge, we felt that an indirect (i.e., two-step) solution might be an effective way to solve this longstanding problem. Indeed,

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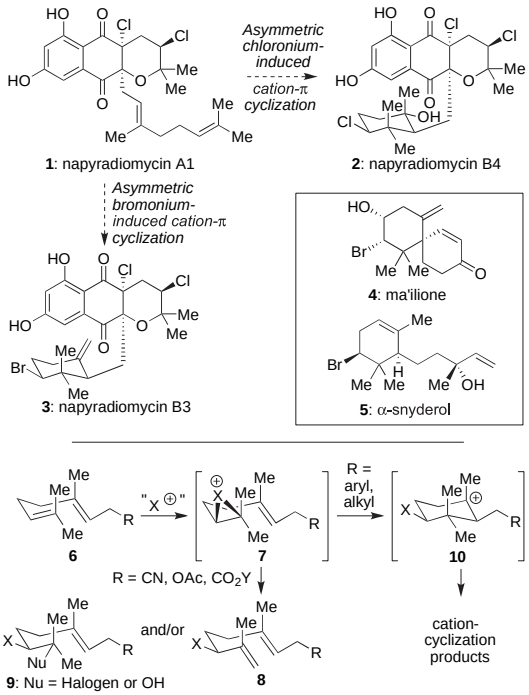
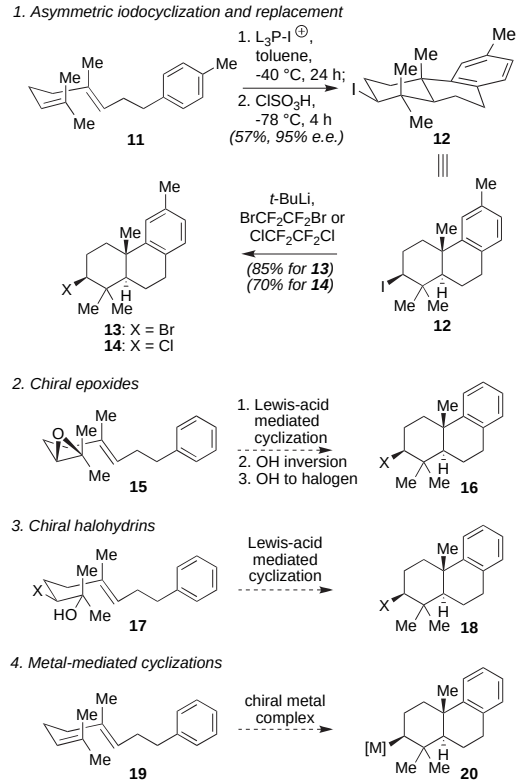
0040-4020/$ – see front matter © 2010 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2010.03.037



Scheme 1. Selected natural products, which likely result from asymmetric halonium-induced cation-π cyclizations and challenges in achieving these reactions, even in racemic format.

Ishihara and co-workers were able to develop one such approach by converting their chiral iodides (such as **12**) into the corresponding bromides and chlorides through lithiation and stereoretentive halide capture (to give **13** and **14**).[11] Other solutions for this problem, however, should exist, particularly ones with greater substrate generality.



Scheme 2. Possible multi-step alternatives for forming the effective products of direct, asymmetric halonium-induced cation-π cyclization.

Scheme 2 provides three possible alternatives. Two of these, the use of a chiral epoxide (#2)[14] or a halohydrin (#3)[15] starting material followed by a Lewis-acid mediated cyclization (**15**→**16** and **17**→**18**), were both anticipated to be difficult to reduce to practice. For instance, the chiral epoxide case requires two likely low-yielding inversion reactions following cyclization, while the other approach requires methodology to access halohydrins enantioselectively. The final alternative, one inspired by recent work from the Gagné group to form alkene products,[16] would be the use of a chiral metal-based complex to effect asymmetric cyclization (**19**→**20**), followed by a second step to replace that metal within **20** with retention to afford all halogen derivatives with high enantiocontrol. This option appeared the most attractive.

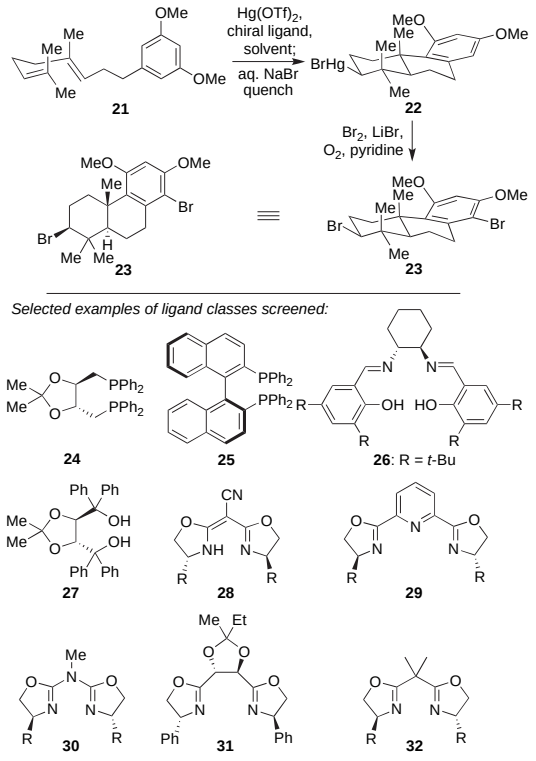
Cognizant of the unique power of Hg(II) salts to initiate a number of racemic cation-π cyclizations[17] and the capability to convert the resultant organomercurials into the corresponding iodides[18] and bromides[19] with the potential for retention,[20] we wondered if the cyclization step could be rendered asymmetric and thus provide a realization of this indirect alternative. However, while simply stated, precedent in support of such a notion was not encouraging. Indeed, even though many chiral forms of Hg(II) are known, such reagents have enabled only one reaction, an intramolecular mercurioetherification, to proceed with high levels of enantiocontrol;[21] most other attempts, including efforts to accomplish asymmetric oxymercuration with isoprenes,[22] have afforded little selectivity thus far.[23] Moreover, our desired application, a carbocyclization reaction, could not benefit from the ability of reactive groups to directly bind to the metal center prior to reaction, thereby rendering the reaction process arguably more difficult than those reported to date. Nevertheless, we hoped that with the right chiral ligand complex and an appropriately activated Hg(II) center, an asymmetric version of this reaction could be developed.

2.2. Chiral ligand selection and optimization

Based on several studies by Nishizawa, which revealed that simple amine complexes of $Hg(OTf)_2$ possess good solubility and electrophilic reactivity profiles,[24] we decided to begin our studies by screening a variety of chiral heteroatom-based ligands to determine if they could enable an asymmetric, Hg(II)-induced cation-π cyclization to be achieved. As shown in Scheme 3, our initial model substrate was the geraniol-derived polyene **21**, a molecule which we expected to cyclize to organomercurial **22** following its exposure to a complex formed by admixing 1.1 equiv of $Hg(OTf)_2$ with 1.2 equiv of a chiral ligand. Subsequent treatment with Br_2 (3.0 equiv) in oxygenated pyridine, according to the procedure of Hoye and Kurth,[19c] was anticipated to then complete the synthesis of **23** as a single diastereomer (with aryl bromination).

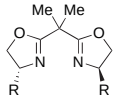
In the absence of any chiral ligand, these operations proceeded smoothly in 83% yield. However, once the $Hg(OTf)_2$ was complexed, only a few of the added ligands out of over 30 screened (including **24**–**32**)[25] led to any enantioselectivity (ee) in the opening step, with bis-oxazolines linked by a single carbon bridge being the only class that gave more than 25% ee with any of the commercially available structural variants screened (entries 1–4, Table 1) at −78 °C in a 1:1 mixture of CH_2Cl_2 and acetonitrile (MeCN) followed by warming. Though a modest start, the general ease of synthesis for members of this ligand class[26] led us to attempt optimization of this result.

Given the ease of altering aromatic rings versus aliphatic systems like *tert*-butyl or adamantyl, and considering the 2-naphthyl case within Table 1 (entry 6) as a potentially improved derivative of the phenyl reagent in entry 3, we began our initial screening by keeping phenyl constant and altering the bis-oxazoline structure in other locations. As indicated in Table 2, any additional substituent at R_2 afforded no improvement in enantioselection, while a modest increase (to 40% ee) was



Scheme 3. Preliminary studies to effect a mercury(II)-induced asymmetric carbocyclization reaction.

Table 1
Preliminary studies with bis-oxazoline ligands

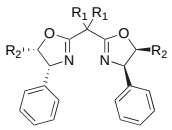


Entry	R	% ee **23** in 1:1 CH_2Cl_2/MeCN
1	Benzyl	0
2	$CH(CH_3)_2$	4
3	Ph	28
4	$C(CH_3)_3$	30
5	Adamantyl	33
6	2-Naphthyl	35

observed by altering the alkyl backbone substituents from the original methyl-based lead (entry 2) to ethyl groups (entry 3). Unfortunately, intensive efforts to improve upon this result through a number of other substantive changes to both backbone and linker structure (not shown) led either to no improvement or, more commonly, inferior enantioselection.[27,28] The same absence of improvement was observed when the reaction solvent was switched to one typically employed for Hg(II)-based cation-π cyclizations, such as pure MeCN or nitromethane.

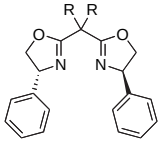
However, when the reaction was performed in pure CH_2Cl_2, a solvent that is not typically associated with cation-π cyclizations, substantial improvements in ee for compound **23** were obtained for several bis-oxazoline ligands, particularly those possessing longer backbone substituents (entries 3 and 6) than that of the original lead structure (entry 2). By exploring this lead further as shown in Table 3, enantioselection was maximized to 72% ee when pentyl chains were attached to the ligand backbone (entry 3), with decreasing control observed upon the addition of extra carbon atoms (entries 4–6) or additional branching (entry 7). With an optimized backbone in hand, exploration of a number of additional versions of the original C_2-symmetric aromatic rings revealed that adding electron donating groups (Table 4, entry 3) or bulk (entry 5) afforded no improvement in enantiocontrol, while strongly electron-withdrawing substitutents were deleterious; as an internal check that extra substitution at R_2 was not tolerated, we prepared the ligand in entry 2 and obtained the expected decrease in enantiocontrol. Thus, the optimized ligand (that of entry 1 in Table 4, named hereafter as **32a**) allowed for the synthesis of **23** in a total of 79% yield and an enantiomeric ratio of 6.4:1 (72% ee). Pleasingly, if the intermediate organomercurial (**22**) so produced was recrystallized prior to its conversion into **23**, the resultant solid was nearly racemic, providing a means to remove the minor enantiomer through filtration. Concentration of the mother liquor, followed by conversion of the resultant material into its bromide counterpart, accomplished a synthesis of **23** from **21** in 53% overall yield and 99% ee, a result commensurate to the Ishihara precedent.[11] We note that the absolute configuration of **22** was confirmed via X-ray crystallographic analysis to be that as drawn within Scheme 3.

Table 2
Initial optimization efforts with bis-oxazoline ligands



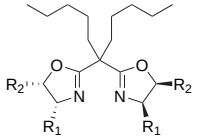
Entry	R_1	R_2	% ee **23** in 1:1 CH_2Cl_2/MeCN	% ee **23** in CH_2Cl_2
1	H	H	0	9
2	CH_3	H	28	30
3	CH_2CH_3	H	40	59
4	$-(CH_2)_3-$	H	18	—
5	$-(CH_2)_4-$	H	20	—
6	Benzyl	H	25	52
7	H	Ph	8	—
8	CH_3	Ph	29	—
9	CH_2CH_3	Ph	33	—

Table 3
Further optimization efforts with bis-oxazoline ligands



Entry	R	% ee **23** in CH_2Cl_2
1	CH_2CH_3	59
2	$(CH_2)_3CH_3$	70
3	$(CH_2)_4CH_3$	72
4	$(CH_2)_5CH_3$	70
5	$(CH_2)_7CH_3$	64
6	$(CH_2)_9CH_3$	64
7	$(CH_2)_2CH(CH_3)_2$	69

Table 4
Final optimization efforts with bis-oxazoline ligands

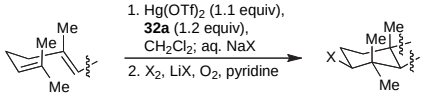


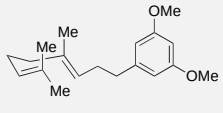
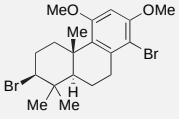
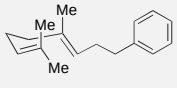
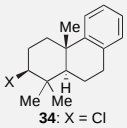
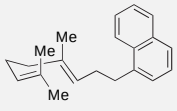
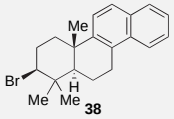
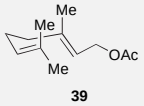
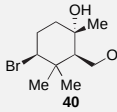
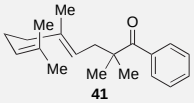
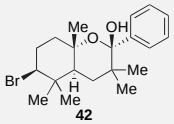
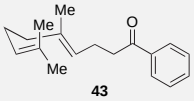
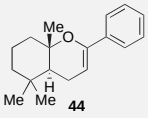
Entry	R_1	R_2	% ee **23** in CH_2Cl_2
1	Ph	H	72
2	Ph	Ph	52
3	*p*-OMePh	H	72
4	*p*-CF_3Ph	H	41
5	2-Naphthyl	H	68

2.3. Exploration of substrate scope

With this promising result in hand, we next tested the ability of the same optimized ligand (**32a**) to effect asymmetric cation-π cyclizations with a variety of other substrates as shown in Table 5, including those possessing smaller (entries 2–4) and larger aromatic systems (entry 5), as well as a series of non-aromatic terminating groups (entries 6–8) with differing degrees of electron-deficiency in the intervening chain. In all cases but one, cyclization yields and enantioselectivities were good. The one poor substrate (**41**, entry 7), at least in terms of enantioselection, was a model compound for a napyradiomycin B3 or B4 (**2** and **3**, cf. Scheme 1) total synthesis, likely failing due to the steric bulk imparted by the two methyl groups adjacent to the ketone, especially in light of the good enantioselectivity observed in the cyclization of compound **43** (entry 8).[29] Nevertheless, in all other cases, the reaction worked well in terms of chiral selection, and the optimized chiral ligand (**32a**) could be recovered at the end of each transformation and reused with no subsequent loss in enantiocontrol. We have also exchanged the intermediate organomercurial produced from the cyclization of **33** for chlorine, bromine, and iodine with equal efficiency to serve as proof-of-principle for broad halide generation, though some erosion in diastereoselectivity was observed for the iodine exchange in line with literature precedent[18] for this particular halogen. In addition, it is worth noting that every intermediate organomercurial we have produced thus far is crystalline; thus, enhancements in optical activity by recrystallization should be facile whenever needed.

Table 5
Exploration of the generality of mercury-induced cation-π cyclization with optimized chiral ligand **32a**

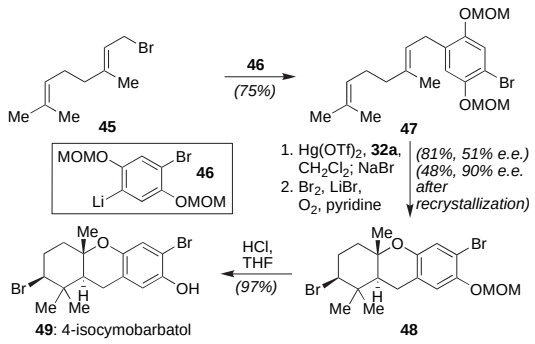


Entry	Starting material	Product	Yield (%)	ee (%)
1	 **21**	 **23**	79 53[a]	72 99[a]
2	 **33**	 **34**: X = Cl **35**: X = Br **36**: X = I	67 66 72	81[b] 81[b] 81[b,c]
3				
4				
5	 **37**	 **38**	77	64
6	 **39**	 **40**	65	62
7	 **41**	 **42**	80	28
8	 **43**	 **44**	74	69[d]

[a] After recrystallization.
[b] TfOH added at end of first step to promote final closure.
[c] Generated as a 3.4:1 mixture of diastereomers in final conversion to alkyl iodide, with the ee the same for both diastereomers.
[d] The intermediate organomercurial was reduced upon reaction with $NaBH_4$.
OTf=trifluoromethanesulfonate.

2.4. Total synthesis of 4-isocymobarbatol

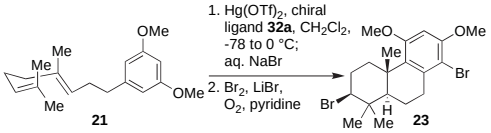
In a final exploration of the power of the developed chemistry, we decided to test a slightly more complex intermediate, namely polyene **47** (Scheme 4), in hopes of accomplishing an asymmetric total synthesis of the natural product 4-isocymobarbatol (**49**).[30,31] Pleasingly, this material, prepared readily via addition of lithium species **46** (derived from protection and lithiation of commercially available 2,5-dibromohydroquinone) to commercially available geranyl bromide (**45**), smoothly underwent cyclization (with concomitant cleavage of one of the methoxymethyl ethers) and bromination to afford **48** in 81% yield and 51% ee using optimized ligand **32a**; recrystallization of the bromide product afforded access to **48** in 48% yield and 90% ee (19:1 er). As a point of comparison for this key step, direct bromonium-induced cyclization of **47** with 2,4,4,6-tetrabromocyclohexa-2,5-dienone (TBCO) provided racemic **48** in only 35% yield.[31] A final, acid-induced deprotection of the remaining methoxymethyl ether then completed the synthesis of the target molecule (**49**).



Scheme 4. Enantioselective total synthesis of 4-isocymobarbatol (**49**) via an asymmetric cation-π cyclization.

Finally, we note that while all the above studies were conducted with stoichiometric amounts of chiral ligand, the reaction can also be performed with sub-stoichiometric quantities as well, since $Hg(OTf)_2$ itself is only barely soluble in CH_2Cl_2 while its ligand-complexed form is completely soluble. As indicated in Table 6, ligand loadings as low as 0.33 equiv still allowed for a productive

Table 6
Explorations into the ability to use sub-stoichiometric amounts of **32a** in the asymmetric mercury(II)-induced cation-π cyclization of **21**



Entry	Ligand **32a** (equiv)	Yield (%)	ee (%)
1	1.20	79	72
2	1.00	78	68
3	0.50[a]	80	59
4	0.33[a]	70	56
5	0.20[a]	65	31
6	0.10[a]	47	13

[a] K_2CO_3 (5 equiv) added.

cyclization of **21** without significant erosion in either the yield or enantioselectivity of **23**, with the addition of 5.0 equiv of K_2CO_3 performed to ensure that the ligand was not protonated (and thus turnover was possible).

3. Conclusions

We have developed a procedure capable of mimicking the direct, asymmetric, halonium-induced cation-π cyclizations commonly used in Nature to fashion complex architectures. Although it requires two steps and a stoichiometric amount of an activated metal, the process proceeds in good yield and enantioselectivity with a range of aryl- and non-aryl-containing geraniol derivatives with an easily prepared, and recoverable, chiral ligand. And, while it must be conceded that other, less potentially toxic, initiators would ultimately be more advantageous for this overall process,[32] mercury does provide some advantages that would be difficult to otherwise replicate, including: (1) the intermediate organomercurials are not only air stable but also readily recrystallized to provide near optically-pure products, and (2) the incorporated mercury can be replaced with many atoms other than halides (C, H, and OH, for example)[33] to afford a multiplicity of additional enantioenriched compounds. For now, however, this work provides a foundation for future studies, which hopefully will enable the enantioselective synthesis of materials as complex as the napyradiomycins to be achieved in a reaction flask without enzymatic intervention.

4. Experimental section

4.1. General

All reactions were carried out under an argon atmosphere with dry solvents under anhydrous conditions, unless otherwise noted. Dry methylene chloride (CH_2Cl_2) and tetrahydrofuran (THF) were obtained by passing commercially available pre-dried, oxygen-free formulations through activated alumina columns; acetonitrile (MeCN) was dried over 3 Å molecular sieves, distilled, and stored over 3 Å molecular sieves; pyridine was distilled from CaH_2 and stored over 3 Å molecular sieves; triethylamine (Et_3N) was distilled from KOH and stored over 3 Å molecular sieves. Yields refer to chromatographically and spectroscopically (^1H and ^{13}C NMR) homogeneous materials, unless otherwise stated. Reagents were purchased at the highest commercial quality and used without further purification, unless otherwise stated. Reactions were magnetically stirred and monitored by thin-layer chromatography (TLC) carried out on 0.25 mm E. Merck silica gel plates (60F-254) using UV light as visualizing agent and an aqueous solution of phosphomolybdic acid and cerium sulfate, and heat as developing agents. Preparative thin-layer chromatography was carried out on 0.50 mm E. Merck silica gel plates (60F-254). SiliCycle silica gel (60, academic grade, particle size 0.040–0.063 mm) was used for flash column chromatography. NMR spectra were recorded on Bruker DRX-300 and DRX-400 instruments and calibrated using residual undeuterated solvent as an internal reference. The following abbreviations were used to explain the multiplicities: s=singlet, d=doublet, t=triplet, q=quartet, m=multiplet, br=broad, app=apparent. IR spectra were recorded on a Nicolet Avatar 370 DTGS series FT-IR spectrometer. Melting points were taken on an Electrothermal MEL-TEMP® Model 1201D instrument, and are uncorrected. High-resolution mass spectra (HRMS) were recorded in the Columbia University Mass Spectral Core facility on a JOEL HX110 mass spectrometer using FAB (Fast Atom Bombardment) and EI (Electron Ionization) techniques. All enantiomeric excess (ee) values were obtained by HPLC using a Daicel CHIRALCEL OD column. Compounds **39**, **45**, **46**, and **47** were prepared according to the procedures defined in Ref. 8.

4.2. Synthesis of optimized ligand 32a

Diethyl malonate (3.00 mL, 19.8 mmol, 1.0 equiv) was added dropwise under a constant flow of argon to a suspension of NaH (1.03 g, 60% in mineral oil, 25.7 mmol, 1.3 equiv) in THF (20 mL) at 0 °C. 1-Iodopentane (3.88 mL, 29.7 mmol, 1.5 equiv) was then added and the solution was refluxed at 75 °C for 12 h. Upon completion, the reaction mixture was cooled to 0 °C and quenched slowly with 1 M HCl (40 mL) and brine (20 mL). The crude product was extracted into EtOAc (3×20 mL) and the combined organic layers were washed with saturated aqueous $NaHCO_3$ (20 mL) and brine (20 mL), dried ($MgSO_4$), and concentrated. This crude mixture of mono- (~80%) and bis-alkylated (~19%) material was resubjected to the identical alkylation procedure outlined above. The resultant crude product was purified by flash column chromatography (silica gel, hexanes/EtOAc, 19:1) to afford diethyl dipentylmalonate (4.78 g, 80% yield) as a light yellow oil.

A solution of NaOH (9.50 g, 239 mmol, 15 equiv) in deionized water (40 mL) was added to diethyl dipentylmalonate (4.78 g, 15.9 mmol, 1.0 equiv) in 1-propanol (20 mL). The resultant mixture was refluxed with vigorous stirring at 110 °C for 14 h, during which time it became homogeneous. Upon completion, the reaction contents were cooled to 0 °C and the resultant upper layer was isolated, concentrated, and then returned to the reaction mixture, which was subsequently acidified by the slow addition of concentrated HCl. The crude product was then extracted into Et_2O (5×100 mL) and the combined organic layers were concentrated to give dipentylmalonic acid (3.90 g, quantitative) as a light yellow solid. Although approximately 98% pure based on ^1H NMR analysis, the crude diacid could be purified further by recrystallization from boiling hexanes (~0.2 g/mL; first crop=3.45 g of large white needles, 89% yield; second crop=0.355 g of off-white needles, 98% combined yield).

Dipentylmalonic acid (1.00 g, 4.09 mmol, 1.0 equiv) and *N*,*N*-dimethylformamide (0.064 mL, 0.82 mmol, 0.2 equiv) were dissolved in dry CH_2Cl_2 (25 mL). Oxalyl chloride (1.73 mL, 20.5 mmol, 5.0 equiv) was added dropwise at 25 °C under a constant flow of argon. The reaction mixture was heated to 40 °C for 1 h, then cooled and concentrated by rotary evaporation in a fume hood to remove excess oxalyl chloride. The crude diacid chloride was redissolved in CH_2Cl_2 (20 mL) and added via addition funnel (over approximately 30 min) to a suspension of (*R*)-phenylglycinol (1.23 g, 9.00 mmol, 2.2 equiv) in CH_2Cl_2 (75 mL) containing Et_3N (2.84 mL, 20.5 mmol, 5.0 equiv) at −78 °C. Once the addition was complete, the reaction mixture was allowed to warm slowly to 0 °C over the course of 2 h, then quenched by the addition of 1 M HCl (50 mL) and extracted into CH_2Cl_2 (3×150 mL). The combined organic layers were washed with a mixture of saturated aqueous $NaHCO_3$/brine (1:1, 100 mL), which was back-extracted with CH_2Cl_2 (100 mL). The combined organic layers were then dried ($MgSO_4$), concentrated, and recrystallized from boiling EtOAc (~40 mL, then 10 mL) to yield the desired diamide product (first crop=1.54 g, 78% yield; second crop=0.250 g, 91% combined yield) as a white crystalline solid.

Methanesulfonyl chloride (1.24 mL, 16.0 mmol, 5.0 equiv) was added dropwise to a solution of the diamide obtained above (1.54 g, 3.19 mmol, 1.0 equiv) in Et_3N (4.4 mL, 31.9 mmol, 10 equiv) and CH_2Cl_2 (60 mL) at −78 °C. After 10 min of stirring at −78 °C, the reaction contents were allowed to warm to 25 °C, and 4 M KOH (20 mL) and $(n\text{-}Bu)_4NCl$ (0.20 g, 0.80 mmol, 0.25 equiv) were added sequentially. After 3 h of vigorous stirring, the organic layer was separated and the aqueous layer was washed with CH_2Cl_2 (2×15 mL). The combined organic layers were dried ($MgSO_4$) and concentrated to yield a dark yellow amorphous solid, which was purified by flash column chromatography (silica gel, hexanes/EtOAc, 4:1) to afford ligand **32a** (1.36 g, 95% yield) as a colorless amorphous solid. The total yield for **32a** over four steps was 68%. Compound **32a**: R_f=0.55 (silica gel, hexanes/EtOAc, 3:2); IR (film) ν_{max} 2952, 2922,

2865, 1652, 1491, 1448, 698 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.37–7.24 (m, 10H), 5.24 (dd, J=10.0, 8.0 Hz, 2H), 4.65 (dd, J=10.0, 8.4 Hz, 2H), 4.12 (t, J=8.0 Hz, 2H), 2.11 (m, 4H), 1.33 (br s, 12H), 0.88 (t, J=6.4 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.3 (2C), 142.6 (2C), 128.8 (4C), 127.6 (2C), 126.9 (4C), 75.1 (2C), 69.7 (2C), 46.4, 32.7 (2C), 32.1 (2C), 27.8 (2C), 22.6 (2C), 14.1 (2C); HRMS (FAB) calcd for $C_{29}H_{39}N_2O_2^+$ $[M+H]^+$ 447.3012, found 447.2991.

4.3. Typical procedure for enantioselective mercury-induced cation-π cyclization

$Hg(OTf)_2$ (0.055 g, 0.110 mmol, 1.1 equiv) and **32a** (0.054 g, 0.120 mmol, 1.2 equiv) were suspended in dry CH_2Cl_2 (9 mL) under an argon atmosphere and stirred vigorously at 25 °C for 10 min, at which time no precipitate remained; the resultant solution was then cooled to −78 °C. A solution of substrate **21** (0.029 g, 0.100 mmol, 1.0 equiv) in CH_2Cl_2 (1 mL) was added dropwise and the reaction mixture was stirred at −78 °C for 1 h. The reaction contents were then allowed to warm slowly to 0 °C over the course of 2 h. Upon completion, a mixture of saturated aqueous NaBr (1 mL), saturated $NaHCO_3$ (2 mL), and water (2 mL) was added to the reaction, and the resultant slurry was stirred vigorously at 25 °C for 15 min. The reaction contents were then extracted with CH_2Cl_2 (3×10 mL), and the combined organic layers were then dried ($MgSO_4$) and concentrated. Purification of the resultant crude amorphous solid by flash column chromatography (silica gel, hexanes/EtOAc, 1:0→1:1) afforded organomercurial **22** (0.052 g, 92% yield) as a white crystalline solid along with recovered ligand **32a** (0.052 g, 97% recovery). Enhancement of ee by recrystallization was achieved by dissolving the solid organomercury bromide **22** in warm EtOAc (5 mL), diluting with warm hexanes (50 mL), and storing at −20 °C for 24 h. Subsequently, the small white crystals (0.017 g, 30% yield) of nearly racemic **22** were isolated by filtration; concentration of the mother liquor afforded enantiopure **22** (0.035 g, 62% yield) as a white solid. Note: following bromination, ee values were determined to be 12% for the crystals and 99% for the filtrate. Compound **22**: mp=200 °C (with decomposition); R_f=0.40 (silica gel, hexanes:EtOAc, 4:1); IR (film) ν_{max} 2979, 2924, 2848, 2831, 1607, 1577, 1460, 1292, 1157, 1087 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.27 (d, J=2.4 Hz, 1H), 6.18 (d, J=2.4 Hz, 1H), 3.75 (s, 6H), 3.18 (dt, J=3.6, 13.6 Hz, 1H), 2.92–2.81 (m, 3H), 2.27 (dq, J=3.6, 13.6 Hz, 1H), 1.97 (dq, J=14.0, 3.6 Hz, 1H), 1.81 (m, 1H), 1.62 (m, 1H), 1.38 (d, J=11.2 Hz, 1H), 1.31 (s, 3H), 1.21 (dt, J=3.6, 13.6 Hz, 1H), 1.15 (s, 3H), 1.13 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.6, 158.2, 138.7, 129.3, 104.9, 97.8, 77.4, 56.6, 55.3, 55.2, 40.3, 39.9, 38.9, 37.2, 33.6, 27.7, 26.5, 20.9, 19.9; HRMS (FAB) calcd for $C_{19}H_{28}{}^{81}Br^{198}HgO_2^+$ $[M+H]^+$ 567.0881, found 567.0903.

4.4. Procedure for the replacement of mercury by bromine

Pure organomercurial **22** (0.035 g, 0.062 mmol, 1.0 equiv) and anhydrous LiBr (0.027 g, 0.308 mmol, 5.0 equiv) were sealed under an O_2 atmosphere. Anhydrous pyridine (0.6 mL) was then added and the resultant mixture was stirred for 10 min at 25 °C. The reaction flask was then covered with aluminum foil, and a solution of Br_2 in pyridine (0.284 mL, 104 mg of Br_2/mL, 0.185 mmol, 3.0 equiv) was added dropwise via syringe. The resultant mixture was stirred at 25 °C for 2 h in the dark. Upon completion, the reaction contents were quenched with freshly prepared 0.5 M aqueous Na_2SO_3 (5 mL) and extracted with CH_2Cl_2 (3×5 mL). The combined organic layers were then dried ($MgSO_4$) and concentrated. Purification of the resultant crude solid by flash column chromatography (silica gel, hexanes/EtOAc, 9:1) afforded pure **23** (0.024 g, 86% yield) as a white solid. Compound **23**: R_f=0.40 (silica gel, hexanes/EtOAc, 7:3); IR (film) ν_{max} 2943, 2871, 2838, 1589, 1456, 1434, 1344, 1312, 1201, 1179, 1073, 1022, 696 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.38 (s, 1H), 4.04 (dd, J=12.8, 4.4 Hz, 1H), 3.87 (s, 3H), 3.81 (s, 3H), 3.09 (dt, J=3.6, 14.0 Hz, 1H), 2.96 (dd, J=17.6, 3.6 Hz, 1H), 2.67 (ddd, J=19.2, 12.4, 6.8 Hz, 1H), 2.30 (dq, J=3.6, 13.2 Hz, 1H), 2.13 (dq, J=13.6, 4.0 Hz, 1H), 1.96 (dd, J=13.2, 6.8 Hz, 1H), 1.62 (dq, J=5.6, 12.4 Hz, 1H), 1.32 (s, 3H), 1.28 (m, 2H), 1.16 (s, 3H), 1.05 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 158.3, 154.4, 138.0, 131.0, 106.1, 95.6, 69.4, 56.4, 55.5, 53.8, 40.4, 39.6, 38.4, 35.2, 32.0, 31.0, 20.6, 19.6, 19.0; HRMS (FAB) calcd for $C_{19}H_{26}Br_2O_2^+$ $[M]^+$ 444.0300, found 444.0304; HPLC (OD column, 1.5% 2-propanol in hexanes, 1.0 mL/min, 30 °C, 288 nm) t_R (major)=6.21 min, t_R (minor)=6.94 min.

*4.4.1. Tricyclic bromide **35**.* White solid; R_f=0.45 (silica gel, hexanes/EtOAc, 19:1); IR (film) ν_{max} 3058, 2968, 2947, 1488, 1476, 1448, 1377, 764, 724 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.21 (m, 1H), 7.16–7.02 (m, 3H), 4.05 (dd, J=12.8, 4.4 Hz, 1H), 3.00–2.83 (m, 2H), 2.42–2.22 (m, 3H), 1.98 (m, 1H), 1.81 (m, 1H), 1.60 (dt, J=3.2, 13.2 Hz, 1H), 1.48 (dd, J=12.0, 2.0 Hz, 1H), 1.25 (s, 3H), 1.16 (s, 3H), 1.07 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 148.8, 134.9, 129.2, 126.0, 125.7, 124.6, 69.0, 51.4, 40.2, 40.0, 38.0, 31.7, 30.9, 30.7, 25.0, 20.7, 18.4; HRMS (EI) calcd for $C_{17}H_{23}Br^+$ $[M]^+$ 306.0983, found 306.0981; HPLC (OD column, 2.0% 2-propanol in hexanes, 1.0 mL/min, 30 °C, 265 nm) t_R (minor)=6.92 min, t_R (major)=9.43 min.

*4.4.2. Tetracyclic bromide **38**.* White solid; R_f=0.80 (silica gel, hexanes/EtOAc, 9:1); IR (film) ν_{max} 3058, 2969, 2949, 1509, 1453, 1376, 1038, 976, 811, 744 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.97 (d, J=8.0 Hz, 1H), 7.78 (d, J=8.0 Hz, 1H), 7.68 (d, J=8.2 Hz, 1H), 7.54–7.37 (m, 3H), 4.07 (dd, J=12.4, 4.0 Hz, 1H), 3.38 (dd, J=17.6, 6.0 Hz, 1H), 3.21–3.09 (m, 1H), 2.46–2.37 (m, 2H), 2.30 (m, 1H), 2.19 (m, 1H), 1.92 (m, 1H), 1.65–1.52 (m, 2H), 1.35 (s, 3H), 1.22 (s, 3H), 1.12 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 145.5, 132.3, 131.7, 129.5, 128.3, 126.7, 126.2, 125.3, 123.3 (2C), 68.9, 51.5, 40.4, 40.0, 38.4, 31.7, 30.7, 28.2, 24.4, 20.6, 18.4; HRMS (EI) calcd for $C_{21}H_{25}Br^+$ $[M]^+$ 356.1140, found 356.1146; HPLC (OD column, 1.0% 2-propanol in hexanes, 1.0 mL/min, 30 °C, 233 nm) t_R (minor)=7.53 min, t_R (major)=9.83 min.

*4.4.3. Cyclic acetate **40**.* Colorless amorphous solid; R_f=0.28 (silica gel, hexanes/EtOAc, 1:1); IR (film) ν_{max} 3456 (br), 2973, 2948, 2875, 1736, 1367, 1243, 1155, 1030 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.43 (dd, J=12.0, 5.2 Hz, 1H), 4.33 (dd, J=12.0, 5.2 Hz, 1H), 3.98 (dd, J=12.4, 4.0 Hz, 1H), 2.50 (s, 1H), 2.19 (dq, J=14.0, 4.0 Hz, 1H), 2.07 (s, 3H), 2.02 (dq, J=3.6, 13.6 Hz, 1H), 1.81 (dt, J=13.6, 3.6 Hz, 1H), 1.72 (t, J=5.2 Hz, 1H), 1.59 (dt, J=4.0, 14.0 Hz, 1H), 1.24 (s, 3H), 1.18 (s, 3H), 1.00 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.2, 71.9, 66.0, 63.6, 55.7, 43.1, 39.9, 32.2, 30.4, 24.0, 21.3, 17.8; HRMS (FAB) calcd for $C_{12}H_{22}BrO_3^+$ $[M+H]^+$ 293.0752, found 293.0742; HPLC (OD column, 8.0% 2-propanol in hexanes, 1.0 mL/min, 30 °C, 209 nm) t_R (minor)=7.84 min, t_R (major)=8.55 min.

*4.4.4. Cyclic hemiketal **42**.* White solid; R_f=0.71 (silica gel, hexanes/EtOAc, 8:2); IR (film) ν_{max} 3522 (br), 2968, 2948, 2870, 1478, 1447, 1379, 1149, 1043, 1020, 994, 708 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.51 (dd, J=8.4, 1.6 Hz, 2H), 7.34–7.24 (m, 3H), 4.05 (dd, J=12.4, 4.8 Hz, 1H), 2.30–2.10 (m, 3H), 2.06 (t, J=12.8 Hz, 1H), 1.82–1.68 (m, 3H), 1.51 (s, 3H), 1.32 (dd, J=12.8, 1.6 Hz, 1H), 1.08 (s, 3H), 1.05 (s, 3H), 0.96 (s, 3H), 0.65 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 144.1, 127.8, 127.4 (4C), 101.9, 75.8, 67.2, 48.8, 42.1, 39.2, 38.7, 32.8, 32.1, 29.7, 26.2, 26.1, 24.3, 17.9; HRMS (FAB) calcd for $C_{20}H_{28}BrO_2^+$ $[M-H]^+$ 379.1273, found 379.1272; HPLC (OD column, 2.0% 2-propanol in hexanes, 1.0 mL/min, 30 °C, 257 nm) t_R (major)=4.60 min, t_R (minor)=5.74 min.

4.5. Procedure for the replacement of mercury by chlorine

Cl_2 gas (7.4 mg, 0.104 mmol, 2.0 equiv) was syringed incrementally into a solution of anhydrous LiCl (6.6 mg, 0.155 mmol, 3.0 equiv) and the tricyclic organomercury chloride obtained from

starting material **33** (0.024 g, 0.052 mmol, 1.0 equiv) in anhydrous pyridine (1 mL) at −40 °C. After 20 min of stirring at −40 °C, the reaction contents were quenched with freshly prepared 0.5 M aqueous Na_2SO_3 (5 mL) and extracted with CH_2Cl_2 (3×5 mL). The combined organic layers were then dried ($MgSO_4$) and concentrated. Purification of the resultant crude solid by preparative TLC (silica gel, hexanes) afforded **34** (0.012 g, 87% yield) as a white solid. Compound **34**: R_f=0.48 (silica gel, hexanes/EtOAc, 19:1); IR (film) ν_{max} 3059, 2969, 2947, 1489, 1448, 1378, 878, 770, 758, 722 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.23–7.02 (m, 4H), 3.81 (dd, J=12.0, 4.8 Hz, 1H), 3.01–2.82 (m, 2H), 2.36 (m, 1H), 2.25–2.05 (m, 2H), 1.94 (m, 1H), 1.80 (m, 1H), 1.58 (dt, J=12.8, 4.4 Hz, 1H), 1.42 (dd, J=12.0, 2.4 Hz, 1H), 1.23 (s, 3H), 1.15 (s, 3H), 1.02 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 148.9, 134.9, 129.2, 126.0, 125.7, 124.6, 72.8, 51.4, 40.1, 38.9, 37.9, 30.8, 30.4, 29.4, 25.0, 20.1, 16.9; HRMS (EI) calcd for $C_{17}H_{23}Cl^+$ $[M]^+$ 262.1488, found 262.1493; HPLC (OD column, 2.0% 2-propanol in hexanes, 1.0 mL/min, 30 °C, 265 nm) t_R (minor)=6.83 min, t_R (major)=9.33 min.

4.6. Procedure for the replacement of mercury by iodine

A solution of the organomercurial iodide obtained from starting material **33** (0.032 g, 0.058 mmol, 1.0 equiv) in pyridine (3 mL) at 25 °C was stirred for 1 h under an oxygen atmosphere in a reaction flask covered in aluminum foil. Next, a solution of I_2 (0.073 g, 0.288 mmol, 5.0 equiv) in pyridine (1 mL), also covered in foil, was added very slowly by syringe pump over the course of 5 h. Once the addition was complete, the reaction contents were stirred for an additional 24 h at 25 °C in the dark and then quenched with freshly prepared 0.5 M aqueous Na_2SO_3 (10 mL) and extracted with CH_2Cl_2 (3×10 mL). The combined organic layers were then dried ($MgSO_4$) and concentrated. Purification of the resultant crude solid by flash column chromatography (silica gel, hexanes/CH_2Cl_2, 4:1) afforded **36** (3.4:1 dr favoring the equatorial iodide, 0.019 g, 93% yield) as a colorless amorphous solid. Compound **36**: R_f=0.43 (silica gel, hexanes/EtOAc, 19:1); IR (film) ν_{max} 3058, 2963, 2943, 2853, 1488, 1448, 1376, 1191, 737, 722 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, equatorial isomer) δ 7.20–7.02 (m, 4H), 4.28 (dd, J=12.8, 4.0 Hz, 1H), 2.95–2.87 (m, 2H), 2.54 (dq, J=3.6, 13.6 Hz, 1H), 2.45 (dq, J=14.0, 4.0 Hz, 1H), 2.18 (m, 1H), 2.00 (m, 1H), 1.81 (m, 1H), 1.63–1.54 (m, 2H), 1.25 (s, 3H), 1.14 (s, 3H), 1.09 (s, 3H); ^1H NMR (400 MHz, $CDCl_3$, axial isomer) δ 7.27 (m, 1H), 7.18–7.01 (m, 3H), 4.69 (br s, 1H), 2.97–2.89 (m, 2H), 2.25–2.10 (m, 4H), 1.86–1.70 (m, 3H), 1.23 (s, 3H), 1.18 (s, 3H), 1.14 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$, equatorial isomer) δ 148.9, 134.8, 129.2, 126.0, 125.7, 124.6, 53.6, 50.0, 42.0, 39.7, 38.3, 34.5, 33.2, 31.0, 25.0, 21.8, 21.3; ^{13}C NMR (75 MHz, $CDCl_3$, axial isomer) δ 149.3, 135.0, 129.2, 126.0, 125.5, 124.4, 55.4, 44.8, 38.1, 38.0, 37.9, 35.2, 31.0, 30.0, 26.4, 20.1, 18.6; HRMS (EI) calcd for $C_{17}H_{23}I^+$ $[M]^+$ 354.0845, found 354.0855; HPLC (OD column, 1.0% 2-propanol in hexanes, 1.0 mL/min, 30 °C, 265 nm) axial iodine: t_R (minor)=4.39 min, t_R (major)=4.71 min; equatorial iodine: t_R (minor)=7.54 min, t_R (major)=10.99 min.

4.7. Procedure for the replacement of mercury by hydrogen

A solution of the cyclic organomercury bromide obtained from starting material **43** (0.042 g, 0.078 mmol, 1.0 equiv) in a mixture of CH_2Cl_2/EtOH (1:1, 4 mL) was sparged with argon and then covered with aluminum foil. A solution of $NaBH_4$ (7.4 mg, 0.196 mmol, 2.5 equiv) in 4 M aqueous NaOH (0.1 mL) was then added dropwise and the resultant reaction contents were stirred at 25 °C for 15 min. Upon completion, solid $MgSO_4$ (~0.5 g) was added to the reaction mixture, and the resultant contents were filtered. The filtrate was concentrated, added to saturated aqueous NH_4Cl (10 mL), and extracted into hexanes (3×10 mL). The combined organic layers were then dried ($MgSO_4$), concentrated, and purified by flash column chromatography (silica gel, hexanes/CH_2Cl_2, 4:1) to afford **44** (0.019 g, 96% yield) as a colorless amorphous solid. Compound **44**: R_f=0.49 (silica gel, hexanes/CH_2Cl_2, 2:1); IR (film) ν_{max} 2926, 2865, 1651, 1447, 1376, 1326, 1098, 1061, 1051, 753 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.55 (app d, J=8.0 Hz, 2H), 7.32–7.21 (m, 3H), 5.30 (dd, J=5.6, 2.4 Hz, 1H), 2.17 (dt, J=17.6, 5.2 Hz, 1H), 2.06–1.93 (m, 2H), 1.69–1.51 (m, 4H), 1.47 (app d, J=11.6 Hz, 1H), 1.32 (app t, J=12.0 Hz, 1H), 1.27 (s, 3H), 0.97 (s, 3H), 0.88 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 149.2, 137.0, 128.2 (2C), 127.7, 124.8 (2C), 97.0, 77.0, 48.6, 41.8, 40.1, 33.5, 32.4, 20.9, 20.0 (2C), 19.2; HRMS (FAB) calcd for $C_{18}H_{24}O^+$ $[M^+]$ 256.1827, found 256.1812; HPLC (OD column, 0.2% 2-propanol in hexanes, 1.0 mL/min, 30 °C, 261 nm) t_R (minor)=5.81 min, t_R (major)=6.88 min.

4.8. Acid-catalyzed Friedel–Crafts step in the synthesis of 34, 35, and 36

TfOH (0.026 mL, 0.298 mmol, 3.0 equiv) was syringed dropwise into a solution of the mixture of chromatographically purified monocyclic and tricyclic organomercury chloride products (0.046 g, 0.099 mmol, 1.0 equiv) derived from the cyclization of **33** in dry CH_2Cl_2 (10 mL) at −78 °C. After stirring for 2 h at −78 °C, the reaction contents were quenched with saturated aqueous $NaHCO_3$ and extracted with CH_2Cl_2 (3×10 mL). The combined organic layers were then dried ($MgSO_4$), concentrated, and purified by flash column chromatography (silica gel, hexanes/EtOAC, 19:1) to afford the fully cyclized organomercurials as single diastereomers (0.042 g, 91% yield).

4.9. Synthesis of cyclization precursors

*4.9.1. Homogeranyl-3,5-dimethoxybenzene (**21**).* Approximately 0.5 mL of a solution of 3,5-dimethoxybenzyl chloride (0.373 g, 2.00 mmol, 2.0 equiv) in THF (5 mL) was added to magnesium turnings (activated with an acidic rinse and thoroughly flame dried; 0.097 g, 4.0 mmol, 4.0 equiv) under argon at 25 °C. Following initiation (~2 min), the reaction mixture was cooled to 0 °C and the remainder of the 3,5-dimethoxybenzyl chloride solution was added dropwise. After stirring for 1 h at 0 °C, the resultant Grignard solution was cooled to −40 °C and syringed quickly into a solution of geranyl diethyl phosphate (0.290 g, 1.00 mmol, 1.0 equiv) in THF (1 mL) at −40 °C. The reaction mixture was then warmed slowly to 25 °C over the course of 4 h and stirred for an additional 12 h at 25 °C. Upon completion, the reaction contents were quenched with saturated aqueous NH_4Cl (10 mL) and water (10 mL) and extracted with hexanes/EtOAc (2:1, 3×20 mL). The combined organic layers were then washed with saturated aqueous $NaHCO_3$ (20 mL) and brine (20 mL), dried ($MgSO_4$), and concentrated. The resultant crude yellow oil was purified by removal of 3,5-dimethoxytoluene via distillation (100 °C at 2 mmHg) followed by flash column chromatography (silica gel, hexanes/CH_2Cl_2, 1:1) to afford **21** (0.274 g, 95% yield) as a light yellow oil. Compound **21**: R_f=0.41 (silica gel, hexanes/EtOAc, 9:1); IR (film) ν_{max} 2928, 2855, 2837, 1596, 1462, 1428, 1205, 1155, 1068, 829 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.37 (d, J=2.0 Hz, 2H), 6.30 (t, J=2.0 Hz, 1H), 5.19 (dt, J=1.2, 7.2 Hz, 1H), 5.10 (tt, J=6.8, 1.2 Hz, 1H), 3.78 (s, 6H), 2.59 (app t, J=8.0 Hz, 2H), 2.30 (q, J=7.6 Hz, 2H), 2.12–1.96 (m, 4H), 1.69 (s, 3H), 1.61 (s, 3H), 1.59 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 160.8 (2C), 145.0, 135.9, 131.5, 124.5, 123.7, 106.7 (2C), 97.8, 55.4 (2C), 39.9, 36.6, 29.9, 26.9, 25.8, 17.8, 16.2; HRMS (FAB) calcd for $C_{19}H_{28}O_2^+$ $[M]^+$ 288.2089, found 288.2086.

*4.9.2. Homogeranylbenzene (**33**).* Prepared as in Section 4.9.1 in 92% yield, substituting benzyl chloride for 3,5-dimethoxybenzyl chloride and omitting the distillation portion of the purification. Compound **33**: colorless oil; R_f=0.58 (silica gel, hexanes/CH_2Cl_2, 4:1); IR (film) ν_{max} 3027, 2966, 2922, 2855, 1496, 1453, 1376, 746, 698 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.29 (m, 2H), 7.20 (m, 3H), 5.21 (dt, J=1.2,

7.2 Hz, 1H), 5.11 (tt, J=6.8, 1.2 Hz, 1H), 2.66 (app t, J=8.0 Hz, 2H), 2.32 (q, J=7.6 Hz, 2H), 2.12–1.97 (m, 4H), 1.71 (s, 3H), 1.62 (s, 3H), 1.57 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 142.6, 135.9, 131.5, 128.6 (2C), 128.3 (2C), 125.8, 124.5, 123.8, 39.9, 36.3, 30.1, 26.9, 25.8, 17.8, 16.1; HRMS (EI) calcd for $C_{17}H_{24}^{+}$ $[M]^+$ 228.1878, found 228.1891.

*4.9.3. 1-(Homogeranyl)naphthalene (**37**).* Prepared as in Section 4.9.1 in 71% yield, substituting 1-(chloromethyl)-naphthalene for 3,5-dimethoxybenzyl chloride and omitting the distillation portion of the purification. Compound **37**: colorless oil; R_f=0.8 (silica gel, hexanes/EtOAc, 1:9); IR (film) ν_{max} 3047, 2965, 2924, 2855, 1597, 1510, 1445, 1377, 777; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.08 (d, J=8.0 Hz, 1H), 7.86 (d, J=8.0 Hz, 1H), 7.72 (d, J=8.0 Hz, 1H), 7.55–7.31 (m, 4H), 5.30 (t, J=7.2 Hz, 1H), 5.12 (t, J=6.8 Hz, 1H), 3.11 (app t, J=7.6 Hz, 2H), 2.46 (q, J=7.6 Hz, 2H), 2.12–1.96 (m, 4H), 1.71 (s, 3H), 1.62 (s, 3H), 1.55 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 138.6, 136.0, 134.0, 132.1, 131.5, 128.9, 126.6, 126.1 125.8, 125.7, 125.5, 124.5, 124.0 (2C), 39.9, 33.3, 29.4, 26.9, 25.9, 17.8, 16.2; HRMS (EI) calcd for $C_{21}H_{26}^{+}$ $[M]^+$ 278.2035, found 278.2025.

*4.9.4. Geranylisobutyrophenone (**41**).* A solution of lithium diisopropyl amide was prepared by the slow addition of an *n*-BuLi solution (1.41 mL, 1.42 M in hexanes, 2.00 mmol, 2.0 equiv) to *i*-Pr_2NH (0.42 mL, 3.00 mmol, 3.0 equiv) in THF (5 mL) at −78 °C. After stirring for 10 min at −78 °C, the solution was stirred at 25 °C for 15 min, and then re-cooled to −78 °C. Isobutyrophenone (0.301 mL, 2.00 mmol, 2.0 equiv) was then added dropwise, and the solution was stirred for 30 min at −78 °C and then warmed to −40 °C. The resulting enolate solution was added via cannula into a solution of geranyl bromide (0.217 g, 1.00 mmol, 1.0 equiv) in THF (1 mL) at −40 °C. The reaction contents were then warmed slowly to 25 °C over the course of 4 h and stirred an additional 12 h at 25 °C. Upon completion, the reaction contents were quenched with saturated aqueous NH_4Cl (10 mL) and water (10 mL), and extracted with hexanes/EtOAc (2:1, 3×20 mL). The combined organic layers were then washed with saturated aqueous $NaHCO_3$ (20 mL) and brine (20 mL), dried ($MgSO_4$), and concentrated. The resultant crude yellow oil was purified by flash column chromatography (silica gel, hexanes/CH_2Cl_2, 1:0→2:1) and the remaining isobutyrophenone was distilled off (100 °C at 2 mmHg) to afford pure **41** (0.203 g, 71% yield) as a colorless oil. Compound **41**: R_f=0.30 (silica gel, hexanes:CH_2Cl_2, 1:1); IR (film) ν_{max} 2966, 2915, 2855, 1687, 1448, 690 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.63 (m, 2H), 7.47–7.35 (m, 3H), 5.11–5.01 (m, 2H), 2.43 (d, J=7.2 Hz, 2H), 2.08–1.94 (m, 4H), 1.66 (s, 3H), 1.58 (s, 3H), 1.54 (s, 3H), 1.30 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 209.6, 139.6, 138.0, 131.5, 130.7, 128.1 (2C), 127.6 (2C), 124.3, 119.9, 48.5, 40.1, 38.9, 26.7, 25.8 (3C), 17.8, 16.3; HRMS (FAB) calcd for $C_{20}H_{28}O^+$ $[M]^+$ 284.2140, found 284.2142.

*4.9.5. Geranylacetophenone (**43**).* Prepared as in Section 4.9.4 in 41% yield, substituting acetophenone for isobutyrophenone and omitting the distillation step of the purification. Compound **43**: light yellow oil; R_f=0.25 (silica gel, hexanes/CH_2Cl_2, 1:1); IR (film) ν_{max} 2968, 2926, 1675, 1468, 1445, 1386, 1178, 961, 716, 699 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.96 (app d, 2H), 7.55 (app t, 1H), 7.46 (app t, 2H), 5.19 (dt, J=1.2, 7.2 Hz, 1H), 5.08 (tt, J=6.8, 1.2 Hz, 1H), 3.00 (app t, J=7.6 Hz, 2H), 2.43 (q, J=7.2 Hz, 2H), 2.11–1.96 (m, 4H), 1.67 (s, 3H), 1.63 (s, 3H), 1.59 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 200.2, 137.2, 136.6, 133.0, 131.5, 128.7 (2C), 128.2 (2C), 124.4, 122.9, 39.8, 38.9, 26.8, 25.8, 23.0, 17.8, 16.2; HRMS (FAB) calcd for $C_{18}H_{25}O^+$ $[M+H]^+$ 257.1905, found 257.1918.

4.10. Asymmetric total synthesis of 4-isocymobarbatol

$Hg(OTf)_2$ (0.044 g, 0.088 mmol, 1.1 equiv) and **32a** (0.043 g, 0.096 mmol, 1.2 equiv) were suspended in dry CH_2Cl_2 (4 mL) under an argon atmosphere and stirred vigorously at 25 °C for 10 min, at which time no precipitate remained; the resultant solution was then cooled to −78 °C. A solution of substrate **47** (0.033 g, 0.080 mmol, 1.0 equiv) in CH_2Cl_2 (1 mL) was then added dropwise at −78 °C. The reaction contents were allowed to warm slowly to −40 °C and stirred at that temperature for an additional 6 h. Upon completion, a mixture of saturated aqueous NaBr (1 mL), saturated $NaHCO_3$ (4 mL), and water (4 mL) was added to the reaction, and the resultant slurry was stirred vigorously at 25 °C for 15 min. The reaction contents were then extracted with CH_2Cl_2 (3×10 mL), and the combined organic layers were dried ($MgSO_4$) and concentrated. Purification of the resultant crude solid by flash column chromatography (silica gel, hexanes/EtOAc, 9:1) gave the desired organomercury bromide intermediate (0.043 g, 83% yield) as a white crystalline solid. Next, this newly prepared organomercurial (0.043 g, 0.066 mmol, 1.0 equiv) and anhydrous LiBr (0.029 g, 0.332 mmol, 5.0 equiv) were sealed under an O_2 atmosphere. Anhydrous pyridine (0.7 mL) was then added and the resultant mixture was stirred for 10 min at 25 °C. The reaction flask was then covered with aluminum foil, and a solution of Br_2 in pyridine (0.267 mL, 119 mg of Br_2/mL, 0.199 mmol, 3.0 equiv) was added dropwise via syringe. The resultant mixture was stirred at 25 °C for 6 h in the dark. Upon completion, the reaction contents were quenched with freshly prepared 0.5 M aqueous Na_2SO_3 (5 mL) and extracted with CH_2Cl_2 (3×5 mL). The combined organic layers were then dried ($MgSO_4$) and concentrated. Purification of the resultant crude solid by flash column chromatography (silica gel, hexanes/EtOAc, 1:0→4:1) afforded pure **48** (0.029 g, 97% yield, 51% ee) as a white solid. Two consecutive recrystallizations from 2 mL boiling hexanes afforded enantioenriched **48** (0.017 g, 58% yield, 90% ee). HPLC conditions for **48**: (OD column, 2.0% 2-propanol in hexanes, 1.0 mL/min, 30 °C, 295 nm) t_R (minor)=5.97 min, t_R (major)=6.90 min. Finally, 12 M HCl (0.21 mL, 2.57 mmol, 40 equiv) was added dropwise to a solution of **48** (0.029 g, 0.064 mmol, 1 equiv) in THF (2 mL) at 25 °C. After stirring for 6 h at 25 °C, the reaction contents were diluted with water (5 mL) and extracted with EtOAc (3×10 mL). The combined organic layers were then dried ($MgSO_4$), concentrated, and purified by flash column chromatography (silica gel, hexanes/EtOAc, 9:1) to afford 4-isocymobarbatol (**49**, 0.025 g, 97% yield) as a light yellow solid. Compound **49**: mp=140.0–144.0 °C; R_f=0.51 (silica gel, hexanes/EtOAc, 7:3); $[\alpha]_D^{23}$ −44.8 ((c 0.61, $CHCl_3$) 90% ee; lit. −51.4° for enantiopure natural material[30]); IR (film) ν_{max} 3518 (br), 2999, 2975, 2868, 1487, 1476, 1219, 1148, 913, 868, 783 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.88 (s, 1H), 6.74 (s, 1H), 5.03 (s, 1H), 4.03 (dd, J=12.8, 4.0 Hz, 1H), 2.77–2.60 (m, 2H), 2.27 (dq, J=14.0, 4.0 Hz, 1H), 2.11 (dq, J=3.6, 14.0 Hz, 1H), 1.96 (dt, J=13.2, 3.6 Hz, 1H), 1.81–1.69 (m, 2H), 1.20 (s, 3H), 1.16 (s, 3H), 1.02 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 147.1, 145.8, 123.1, 119.8, 115.8, 108.1, 76.0, 65.8, 48.1, 40.7, 39.3, 31.6, 29.7, 24.7, 19.8, 17.0; HRMS (FAB) calcd for $C_{16}H_{20}Br_2O_2^+$ $[M]^+$ 401.9830, found 401.9840. All spectral data for this natural product matched those originally reported by Wall and co-workers as reported in Ref. 30.

Acknowledgements

We thank the NSF (CHE-0619638) for an X-ray diffractometer and Prof. Gerard Parkin and Mr. Aaron Sattler for analyzing **22**. We also acknowledge the generous gift of several aza-BOX ligands from Prof. Oliver Reiser at Regensburg University. Financial support was provided by Columbia University, an NSF CAREER Award (CHE-0844593), the ACS Petroleum Research Fund (47481-G), an Eli Lilly Grantee Award, the National Science Foundation (Predoctoral Fellowship to D.S.T.), the Deutscher Akademischer Austausch Dienst (Postdoctoral Fellowship to A.S.), New Faculty Awards from the

Camille and Henry Dreyfus Foundation, Amgen, and Eli Lilly, and a Sloan Research Fellowship (all to S.A.S.).

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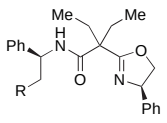

Entry	R	% *e.e. ent*-**22** in CH_2Cl_2
1	OH	13
2	Cl	28
3	Br	46

28. In all these studies, a reaction temperature of −78 °C was utilized; lower temperatures did not lead to improved enantioselectivity, though erosion was observed above −50 °C.
29. At present, we do not have an appropriately refined model to account for the observed stereoselection. We have attempted to secure a crystal structure of an $Hg(OTf)_2$/bis-oxazoline complex to assist in our transition state model, but have been unsuccessful thus far in our efforts. For two simpler Hg(II)-based crystal structures, see: (a) Halfpenny, J.; Small, R. W. H. *Acta Crystallogr.* **1997**, *C53*, 438–443; (b) Grdenic, D.; Popvic, Z.; Bruvo, M.; Korpar-Colig, B. *Inorg. Chim. Acta* **1991**, *190*, 169–172.
30. For the isolation of this natural product, see: (a) Wall, M. E.; Wani, M. C.; Manikumar, G.; Taylor, H.; Hughes, T. J.; Gaetano, K.; Gerwick, W. H.; McPhail, A. T.; McPhail, D. R. *J. Nat. Prod.* **1989**, *52*, 1092–1099; (b) Wall, M. E. *J. Nat. Prod.* **1992**, *55*, 1561–1568.
31. For a previous total synthesis of this compound, see: Tanaka, A.; Oritani, T. *Biosci. Biotechnol. Biochem.* **1995**, *59*, 516–517. Ref. 8 provides an improved synthesis.
32. Although certain compounds like MeHgCl and Me_2Hg are quite dangerous, higher molecular weight organomercurials are not anywhere near as toxic, and in fact are used in agrochemicals and medicine: Imagawa, H.; Iyenaga, T.; Nishizawa, M. *Org. Lett.* **2005**, *7*, 451–453 See also Ref. 20.
33. For selected examples of carbon replacement, see: (a) Kocovsky, P. *J. Organomet. Chem.* **2003**, *687*, 256–268; (b) Tökés, A. L.; Litkei, G.; Gulácsi, K.; Antus, S.; Baits-Gács, E.; Szántay, C.; Darkó, L. L. *Tetrahedron* **1999**, *55*, 9283–9296.