Asymmetric Total Synthesis of Chaetoglobin A

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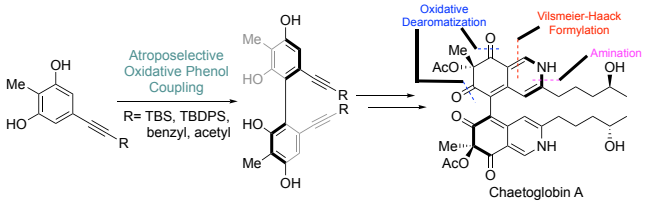
Supporting Information Placeholder

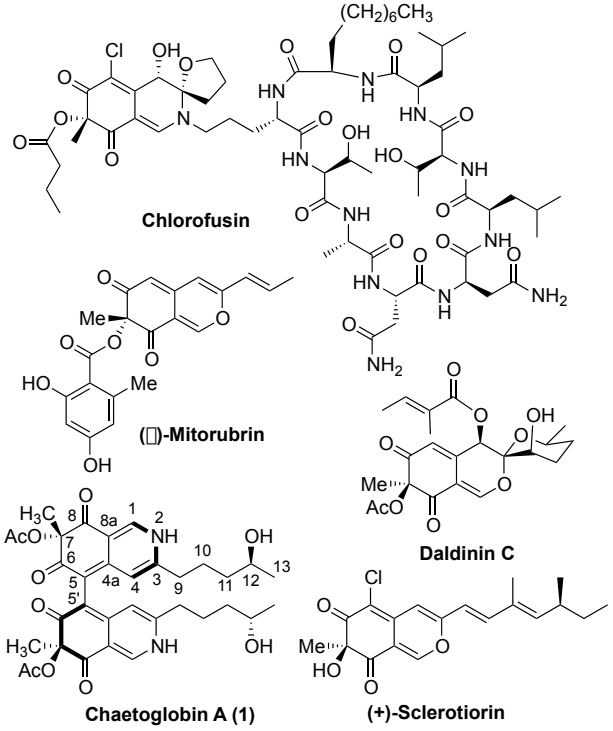


ABSTRACT: An asymmetric total synthesis of chaetoglobin A was achieved. Atroposelective oxidative coupling of a phenol incorporating all but one carbon of the final product was used as a key step to generate axial chirality. The stereochemical outcome of the catalytic oxidative phenolic with the highly substituted phenol used herein was found to be opposite that of the simpler congeners reported previously, providing a cautionary tale about extrapolating asymmetric processes from simple to more complex substrates. Optimization of the post-phenolic coupling steps including formylation, oxidative dearomatization, and selective deprotection steps are outlined. The tertiary acetates of chaetoglobin A were exceptionally labile due to activation by the adjacent keto groups, which complicated each of these steps. In contrast, the final oxygen to nitrogen exchange proceeded readily and the spectroscopic data from the synthetic material matches that of the isolated natural product in all respects.

Introduction

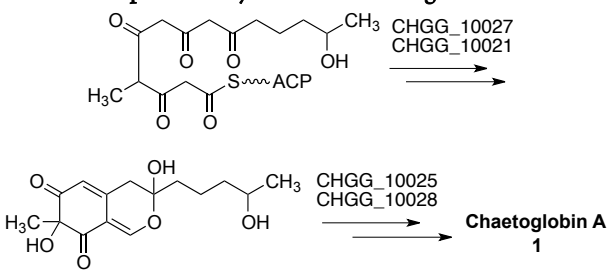
Myriad azaphilone alkaloids have been reported encompassing broad structural diversity and biological effects including antiviral,

Scheme 1. Azaphilone Natural Products



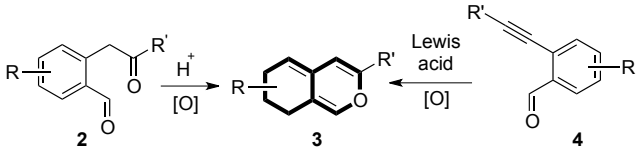
cytotoxic, anticancer, and antimicrobial activities.[1] The highly oxygenated bicyclic core combined with different substitution patterns not only distinguishes various classes of the azaphilones, but has also garnered attention owing to their structural complexity (**Scheme 1**). Chaetoglobin A (**1**), which is a unique dimeric azaphilone alkaloid, has a chiral axis connecting two identical azaphilone systems. It has been found to inhibit growth in human breast and colon cancer cell lines targeting the tumor-related genes that are common in human and animal cancers including *bcl-2, c-myc*, and *β-catenin*.[2] The gene cluster involved in the production of azaphilones in *chaetomium globosum*, including chaetoglobins A and B, has been identified.[3] On this basis a biosynthetic pathway was proposed (**Scheme 2**) wherein proteins CHGG_10027 and CHGG_10021 from C. *globosum* cyclize a linear precursor. The resultant aldol condensation, aromatization, oxidative dearomatization, and enol cyclization provide the corresponding monomeric unit including the quaternary carbon center. An acetyl transferase, CHGG_10028, installs an ester moiety on the tertiary alcohol group and dimerization can be achieved by CHGG_10025 enzyme. Non-enzymatic amination with NH_3 allows access the azaphilone dimer.

Scheme 2. Proposed Biosynthesis of Chaetoglobin A



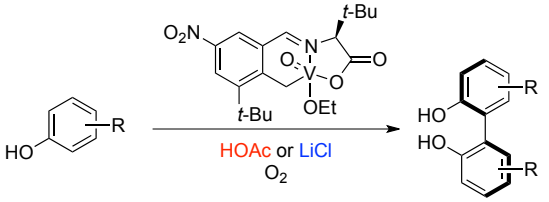
The main feature of the azaphilone natural products is the bicyclic ring system containing a chiral quaternary center and a highly oxygenated conjugated system. Over the last several decades, methods have been reported to construct the bicyclic core unit **3** via either acid-catalyzed cyclization followed by oxidation from formyl ketone **2** or via transition metal-catalyzed cycloisomerization/oxidation from alkyne **4** (**Scheme 3**). Early azaphilone syntheses utilize the former method employing combinations of P_2O_5[1a] or *p*-TsOH[1c,e,g] as the acid and $Pb(OAc)_4$ or IBX as the oxidant. Porco *et al.* successfully introduced the core backbone via the latter approach using Au(III)[1e,h] or Cu(II)[1b,d,f] to affect the cycloisomerization and oxidation in one-pot protocols.

Scheme 3. Prior Approaches to Build Bicyclic Core



The most prominent feature of chaetoglobin A is a chiral axis between C5-C5'. The difficulty in constructing this feature likely accounts for the lack of reports prior to our preliminary communication.[4] We leveraged an atroposelective oxidative phenol coupling that we developed previously using a vanadium catalyst with molecular oxygen (**Scheme 4**).[5] Herein, we detail a full report of our synthetic efforts to generate chaetoglobin A.[6]

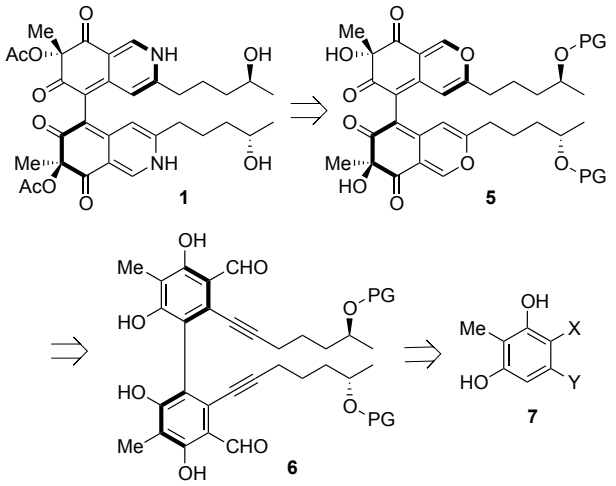
Scheme 4. Vanadium-Catalyzed Asymmetric Oxidative Phenol Coupling



Results and Discussion

Retrosynthesis: Our retrosynthetic analysis of chaetoglobin A is outlined in **Scheme 5**. The final azaphilone dimer **1** could be obtained by amination of the corresponding oxygenated analog **5** The tertiary alcohols of **5** would be derived from bisformylated **6** via an oxidative dearomatization reaction. Ideally, oxidative phenol coupling would afford dimer **6** from monomer **7**, but the exact nature of **7** that could be accommodated in the oxidative coupling was unclear at the outset.

Scheme 5. Retrosynthesis of Chaetoglobin A



Enantioselective Phenol Coupling: The first task was to determine any restrictions that the oxidative coupling would impose on the choice of monomer (i.e. **7**). The goal was to incorporate as much of the functionality needed for the azaphilone ring system keeping in mind that an unprotected phenol adjacent to the C-C coupling site is essential and that electron-withdrawing substituents raise the oxidation potential rendering the oxidative coupling inaccessible. In line with these restrictions, early efforts incorporating aldehyde groups met with failure, so protected analogs of the aldehydic moiety of **6** were surveyed as well as analogs lacking an aldehyde surrogate (**Figure 1**).

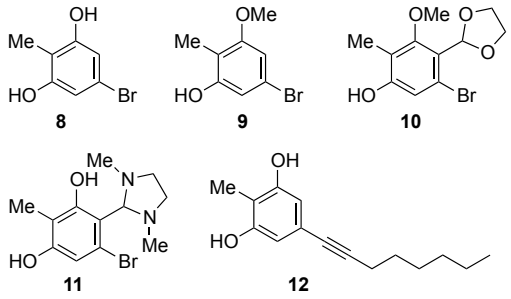
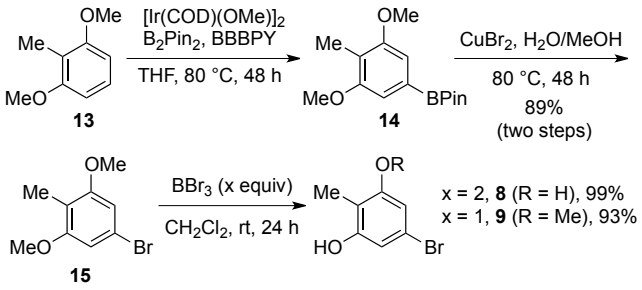


Figure 1. Asymmetric phenol coupling candidates.

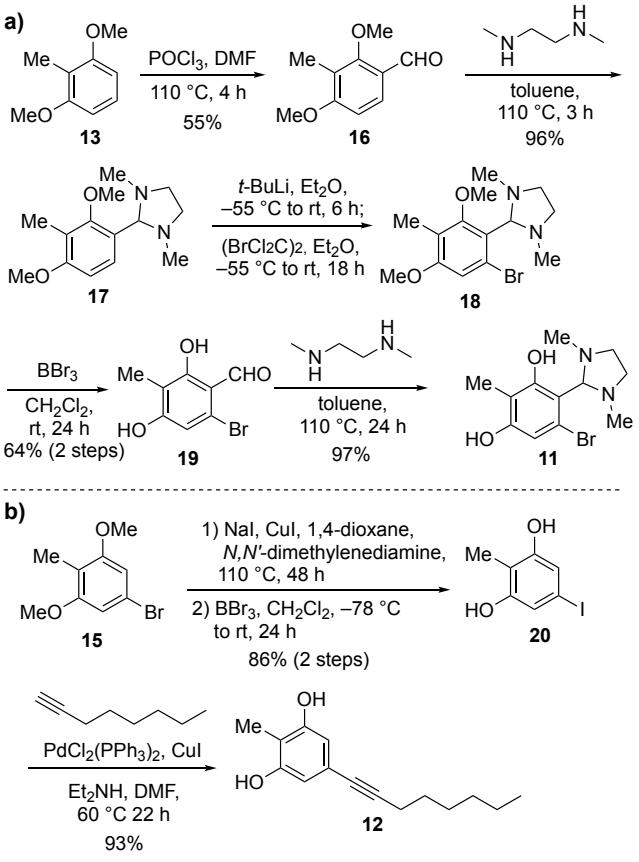
Phenols were synthesized from commercial source **13** via an iridium-catalyzed borylation to introduce the boronate at the least hindered position generating **14**. [7] Subsequent bromination[7] furnished the corresponding bromoarene **15**. Demethylation with excess BBr_3 provided bisphenol **8** while one equivalent BBr_3 gave mono-methoxy phenol **9** (**Scheme 6**).

Scheme 6. Synthesis of Bromophenols



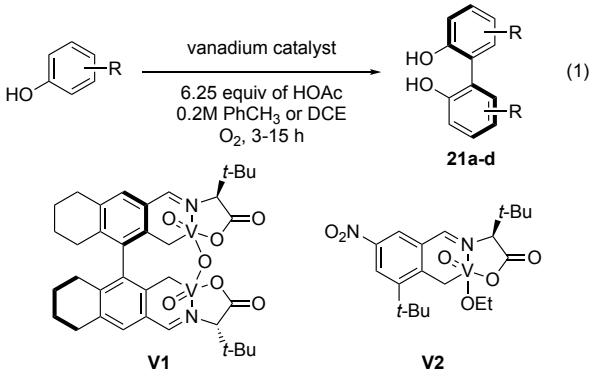
Phenol **10**, featuring a masked aldehyde, was proposed as further candidates for the oxidative coupling reaction. Due to several unsuccessful attempts to make ketal **10**, aminal **11** was prepared instead (**Scheme 7a**). Vilsmeier-Haack formylation[8] of **13** provided benzaldehyde **16** and formyl protection was achieved to obtain **17**. Next, selective bromination was accomplished by directed *ortho*-lithiation to afford aryl bromide **18**. [9] Excess BBr_3 caused dealkylation along with aminal deprotection to afford **19** in 64% yield over two steps. Reprotection afforded aminal substrate **11**. To obtain alkynylphenol **12**, halogen exchange [10] was undertaken followed by BBr_3 demethylation of bromoarene **15** to afford iodophenol **20** (**Scheme 7b**). The alkyne moiety of **12** was then introduced via Sonogashira coupling (see below for optimization).

Scheme 7. Synthesis of Aminal and Alkynylphenols



With four different phenols in hand, the oxidative phenol coupling was examined with a dimeric vanadium catalyst **V1**[11] and a monomeric catalyst **V2** (eq 1).[5] Bisphenol **8** showed promising enantioselectivity, 71% ee, with **V1** (Table 1, entry 1); however, it suffered from low reactivity even with higher catalyst loading (entry 2). The mono-protected phenol **9**, unfortunately, did result in improved reactivity or selectivity (entries 3, 4). The phenol coupling of aminal **11** was attempted in the presence of a stoichiometric amount of $VO(acac)_2$ to obtain racemic standards but the aminal group hydrolyzed during the reaction generating the aldehyde, which was unreactive due to its electron-withdrawing nature (entry 5). Exchanging the halide for the alkyne substituent of **12** offered significant improvements both in reactivity and selectivity (entries 6, 7). Monomeric catalyst (**V2**) provided up to 86% ee and further optimization with additives allowed access to the desired biaryl motif in 89% ee in the presence of LiCl (entry 8). This study revealed several important findings: 1) the alkyne, even though a nucleophilic π-system, was compatible with the oxidative coupling process allowing incorporation of virtually the entire carbon framework prior to dimerization, 2) protection of 3-OH is not needed and, indeed, better reactivity is observed with the unprotected bisphenolic variant, and 3) the aldehyde or protected equivalent could not be preinstalled, which necessitates a formylation post-oxidative coupling.

Table 1. Vanadium-catalyzed Oxidative Phenol Coupling (eq 1)

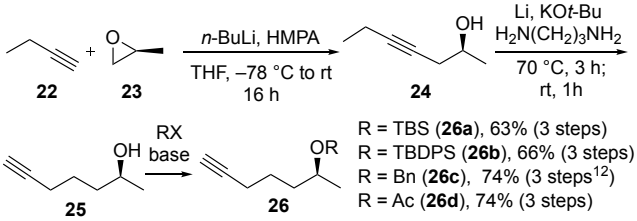


Entry	Phenol	Catalyst	Product	T (°C)	Conv. (%)[a]	*ee* (%)
1	**8**	**V1**	**21a**	rt	(28)[b]	71
2c	**8**	**V2**	**21a**	0	(24)[b]	20
3	**9**	**V1**	**21b**	rt	trace	38
4d	**9**	**V2**	**21b**	0	12	47
5[c]	**11**	$VO(acac)_2$	**21c**	25–40	0	-
6	**12**	**V1**	**21d**	rt	59	58
7[c]	**12**	**V2**	**21d**	0	67	86
8[e]	**12**	**V2**	**21d**	0	89(66)[b]	89

[a]Determined by ^{1}H NMR. [b]Isolated yield in parentheses [c]40 mol% of catalyst. [d]100 mol% of catalyst. [e]Using LiCl (6.25 equiv) as an additive instead of HOAc.

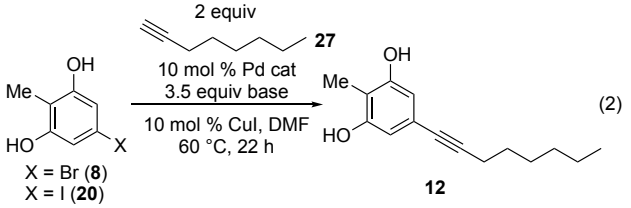
Incorporation of Chiral Alkynyl Substituent: To generate the monomer for the oxidative coupling with as much functionality corresponding to the natural product **1** intact, iodophenol **20** was synthesized as shown in **Scheme 7b** and terminal alkyne **26** was generated in three steps (**Scheme 8**). The stereocenter of **26** arises from commercially available (*S*)-propylene oxide **23** via ring opening with 1-butyne **22** to produce internal alkyne **24**. A zipper isomerization then affords terminal alkyne **25**.[12] The hydroxyl group was protected with TBSCl generating desired alkyne **26a** in 63% over three steps. In a similar fashion, the TBDPS (**26b**), Bn (**26c**),[12] and Ac (**26d**) analogs were generated (see Experimental).

Scheme 8. Generation of Chiral Alkyne Fragment



With the Songashira coupling partners in hand, the optimal conditions to prepare the alkynylphenol monomer were explored. Since bromophenol **8** could be prepared in fewer steps than the iodide **20**, this compound was assessed with 1-octyne and a variety of Pd sources. Pd(II) sources with phosphine ligands gave more promising results (**Table 2**, entry 1–5). To tackle the low conversion issue, higher catalyst loading and different base combinations were tested. *i*-Pr$_2$NEt or pyrrolidine showed improved yields relative to Et$_3$N, but still suffered from low reactivity (entry 6–7). The combination of PdCl$_2$(PPh$_3$)$_2$ and Et$_2$NH gave 77% conversion and 66% isolated yield (entry 8). Hypothesizing that slow oxidative addition of bromophenol **8** caused the incomplete conversion, iodophenol **20** was assessed. Notably, the facile oxidative addition with iodophenol resulted in full conversion with 93% isolated yield (entry 9). This improved yield offset the liability of introducing the additional synthetic step of converting bromophenol **8** to iodophenol **20**. This route was also higher yielding than a sequence incorporating direct conversion of boronate **14** (Scheme 6) to the corresponding iodide.[7]

Table 2. Sonogashira Coupling Optimization (eq 2)

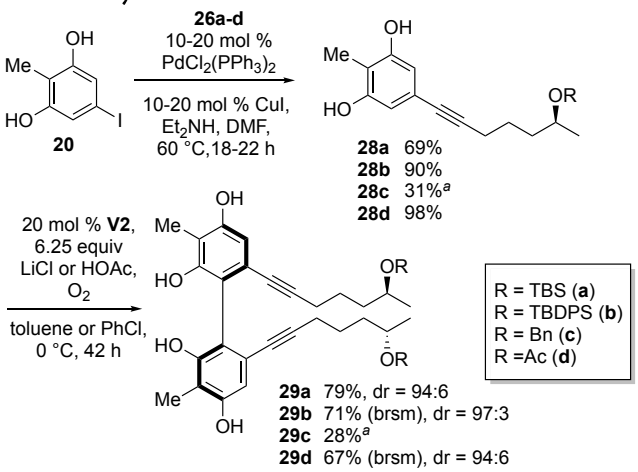


Entry	Phenol	Catalyst	Base	Conversion (%)[a]	Yield (%)[a]
1	**8**	Pd(OAc)$_2$	Et$_3$N	0	–
2	**8**	Pd(dba)$_2$	Et$_3$N	0	–
3	**8**	Pd(PPh$_3$)$_4$	Et$_3$N	47	–
4	**8**	PdCl$_2$(dppf)	Et$_3$N	47	–
5	**8**	PdCl$_2$(PPh$_3$)$_2$	Et$_3$N	55	27
6[b]	**8**	PdCl$_2$(PPh$_3$)$_2$	*i*-Pr$_2$NEt	52	36
7[b]	**8**	PdCl$_2$(PPh$_3$)$_2$	pyrrolidine	58	52
8[b]	**8**	PdCl$_2$(PPh$_3$)$_2$	Et$_2$NH	77	66
9	**20**	PdCl$_2$(PPh$_3$)$_2$	Et$_2$NH	100	93[c]

[a]Determined by ^{1}H NMR. [b]20 mol% of catalyst. [c]Isolated yield.

With the optimal Sonogashira coupling conditions, monomers **28a-d** were prepared readily prepared (**Scheme 9**). In addition, oxidative phenol coupling in the presence of **V2** and LiCl as an additive gave dimers **29a-d** in good yield and good diastereoselectivity (**Scheme 9**).

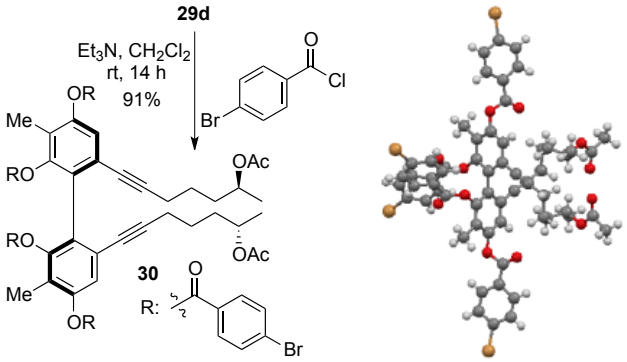
Scheme 9. Synthesis of Dimer 29



[a]Unoptimized.

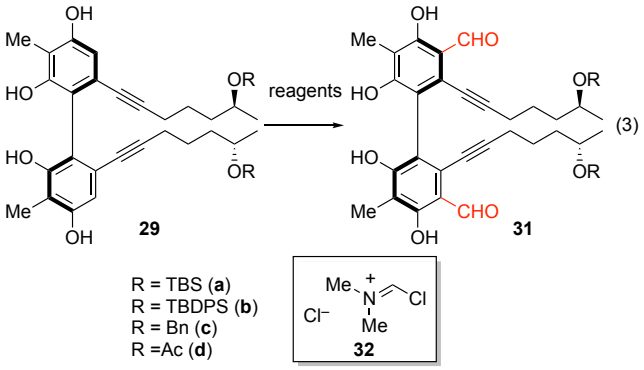
To confirm the axial stereochemistry, phenol **29d** was derivatized with *p*-bromobenzoyl chloride to increase crystallinity. Single crystal analysis of the adduct indicated *M*-helicity[4] (**Scheme 10**). Interestingly, the same **V2** catalyst provided a different atropoisomer in this case relative to simpler analogs. For example, the congener with a methyl group in place of the alkynyl group gives *P*-helicity as secured by X-ray crystallographic analysis.[5] It appears that the long alkynyl substituents creates a different steric profile relative to the methyl substituent and profoundly alters the outcome.

Scheme 10. Derivatization of Phenol Dimer 29d to Confirm its Axial Stereochemistry



Formylation of the Chiral Bisphenol: It was expected that the bisphenolic moiety **29a** would to lend itself to a double electrophilic aromatic substitution at the remaining unsubstituted aromatic sites, but conditions needed to be identified that would be compatible with the alkyne, which is also subject to electrophilic attack, as well as the alkoxy protecting groups. After several trials with monomer **12** lacking the alkyoxy substituent using an array of different conditions,[13] Vilsmeier–Haack formylation was found to be the most promising protocol. Importantly, the alkyne was compatible with these electrophilic conditions. With dimer **21d** lacking the alkoxy groups on the side chains, the Vilsmeier-Haack reaction introduced the formyl groups into in good yield at low temperature to provide **31e** (**Table 3**, entries 1 and 2).

Table 3. Vilsmeier–Haack Formylation with Dimer (eq 3)[a]



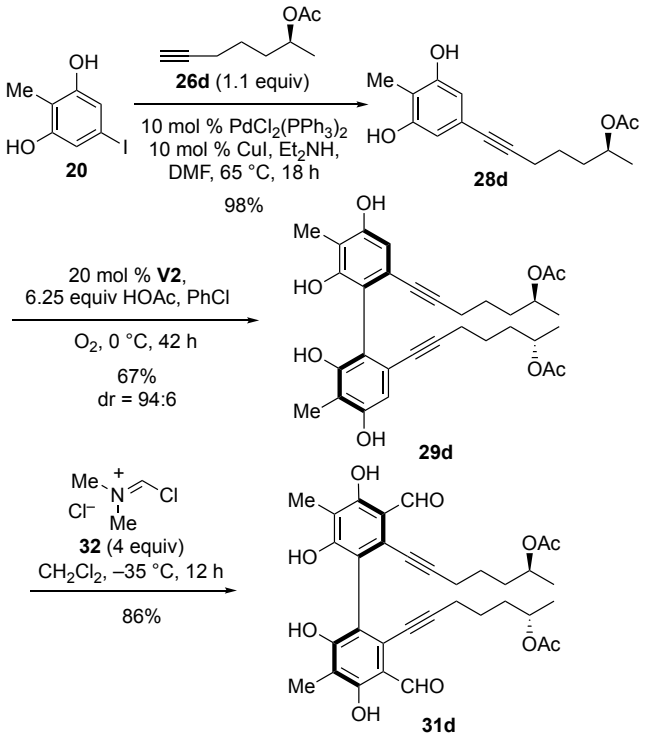
Entry	R	conditions	Temp. (°C)	Yield (%)[b]
1	**21d**	$POCl_3$, DMF	25	58 (**31e**)
2	**21d**	$POCl_3$, DMF	0	80 (**31e**)
3	TBS	$POCl_3$, DMF	0	0 (43)[c]
4	TBDPS	$POCl_3$, DMF	25	16
5	TBDPS	$POCl_3$, DMF	0	27
6	TBDPS	$POCl_3$, DMF	–50	–[d]
7	TBDPS	**32**	25	36
8	TBDPS	**32**, Na_2SO_4	25	14
9	TBDPS	**32**	0	42
10	Bn	**32**	25	25
11	Ac	**32**	25	23
12	Ac	**32**	0	43
13	Ac	**32**	–35	75 (86)[e]

[a]2.2 equiv of formylating agent except for **32** (4 equiv), CH_2Cl_2 or DCE, 1-10 h. [b]Isolated yield. [c]Silyl deprotected product (**31**) yield. [d]Deprotection was observed. [e]Isolated yield based on recovery of substrate in parentheses.

The next task was to identify an appropriate protecting group for the alkoxy group, which was unexpectedly problematic. With TBS protected dimer **29a**, deprotection issue arose during the Vilsmeier–Haack from innate generation of an acidic byproduct (entry 3). To avoid this problem, a more robust silyl protection group (TBDPS) was employed. It gave the desired bis-formylated product but with low yields (entries 4 and 5). Moreover, deprotection of the TBDPS was found to be faster than formylation (entry 6). To mitigate the amount of acid byproduct, a preformed Vilsmeier reagent (**32**) was employed which improved the yield to 36% (entry 7). Unfortunately, deprotection remained an issue and buffer conditions were not able to prevent removal of TBDPS (entry 8). Lower temperature afforded slightly higher yield but no substantial difference in yield (entry 9). Deprotection was also observed with a benzyl protecting group give rise to low yields (entry 10). Finally, an acetyl group, which was immune to deprotection, appeared promising although it still afforded low yield at ambient temperature (entry 11). After screening reaction temperatures, the bis-formylated product **31d** was ultimately obtained in 86% yield were used (entry 13).

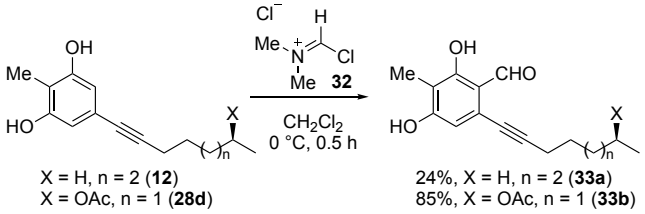
Based on the findings related to the optimal oxidative coupling precursor and the optimal hydroxyl protecting group, the revised synthetic route is shown in **Scheme 11**. The Sonogashira coupling between **20** and acetyl protected alkyne **26d** gave phenol coupling precursor **28d** in very high yield. The modified atroposelective oxidative phenol coupling formed dimeric compound **29d** in 67% yield and a 94:6 diastereomeric ratio. Dimer **31d** was synthesized by a double formylation using a preformed Vilsmeier reagent **32** in 86% yield, which represents 93% yield for each formylation.

Scheme 11. Summary of the Synthesis of Bisformylated Dimer 31d



Oxidative Dearomatization: Next, the oxidative dearomatization via Lewis acid–assisted cycloisomerization followed by oxidation needed to be implemented. Initial attempts were made on model substrates **33a** and **33b** (Scheme 12) that were obtained by unoptimized formylation of **12** and **28d**, respectively.

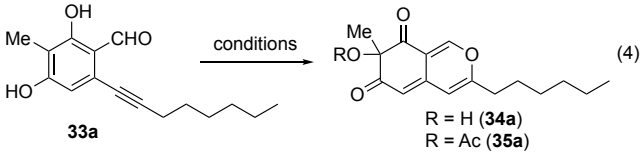
Scheme 12. Generation of Monomer Models for Oxidative Dearomatization



A variety of different oxidative dearomatization conditions, were tested with **33a** (**Table 4**, eq 4). Brønsted acid-catalyzed cyclization followed by oxidation in the presence of $Pb(OAc)_4$ only caused decomposition (entry 1). Using the protocol described by Porco and co-workers,[14] $Au(OAc)_3$ was found to be highly effective. When followed by $Pb(OAc)_4$ oxidation, this protocol provided the acylated product (entry 2). The yields could be improved by increasing the

reaction temperature (entry 3) and adding excess oxidant (entry 4) to ultimately provide acetate **35a** in 55% yield. The use of IBX as the oxidant provided a similar trend (entries 5-7). While the efficiency was high (95% yield) the tertiary alcohol **34a** was the product rather than targeted acetate **35a**.

Table 4. Oxidative Dearomatization Reaction with Monomer 33a (eq 4)



condition A: 1) *p*-TsOH, AcOH, DCE, rt 1 h; 2) $Pb(OAc)_4$, DCE, rt, 1 h

condition B: 1) $Au(OAc)_3$, TFA, DCE, rt, 1 min; 2) $Pb(OAc)_4$, DCE, rt, 1 h

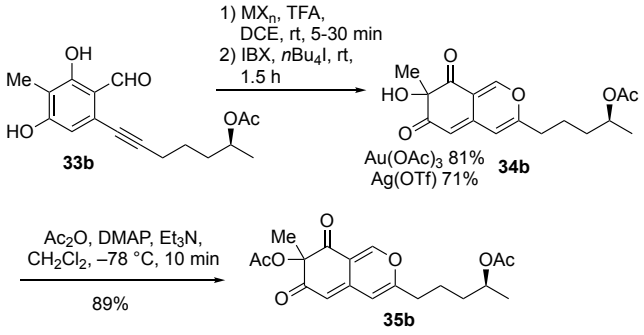
condition C: 1) $Au(OAc)_3$, TFA, DCE, rt, 1 min; 2) IBX, nBu_4I, DCE, rt, 1 h

entry	conditions	product	T (°C)	Conv (%)[a]	Yield (%)b
1	**A**	**35a**	100	Decomp.	–
2	**B**	**35a**	0	94	16
3	**B**	**35a**	25	100	26[c]
4	**B**	**35a**	25	100	55[c,d]
5	**C**	**34a**	0	54	15
6	**C**	**34a**	25	67	23[c]
7	**C**	**34a**	25	100	95[c,d]

[a]Determined by ^{1}H NMR based on recovered the substrate. [b]Determined by ^{1}H NMR. [c]Isolated yield. [d]Added 2 equiv of oxidant.

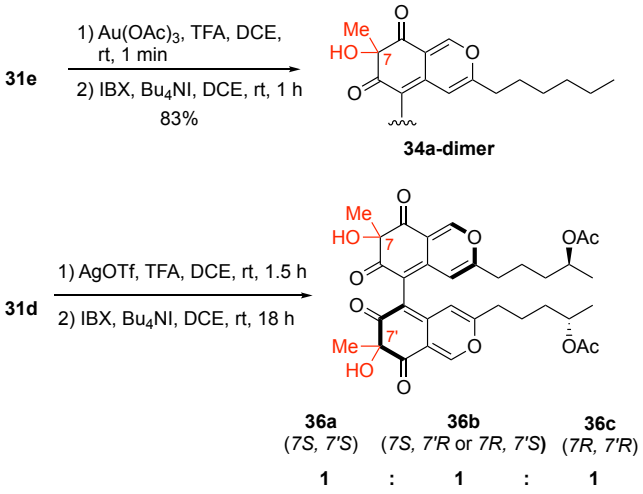
With more complex monomer **33b**, the latter protocol proved more effective vs the direct $Pb(OAc)_4$ approach. After the same two-step oxidative aromatization, subsequent acetylation with Ac_2O provided the target compound **35b** in 72% yield across two steps (**Scheme 13**).

Scheme 13. Two-Step Dearomatization/Acetylation



In the context of the dimer, this transformation was expected to be more difficult as two independent cascades need to occur. Indeed, the $Au(OAc)_3$ protocol from above was ineffective with the dimeric system **31d** although the oxygenated bicyclic backbone was produced in good yield with simple dimer **31e** (**Scheme 14**). The report from Porco *et al.* also intimated that Ag(I) salts were effective in the oxidative dearomatization. Screening of various Ag(I) salts revealed that AgOTf smoothly affected cyclization with the monomer albeit in a slightly lower 71% yield (**Scheme 13**).

Scheme 14. Stereochemical Outcome in the Formation of Tertiary Hydroxyl Group

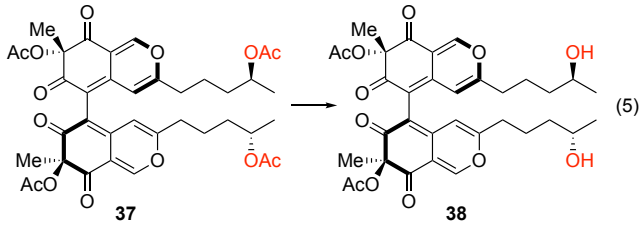


When deployed with dimer **31d**, the corresponding bicyclic core **36** was obtained with good efficiency (**Scheme 14**). We had anticipated that the sterically congested environment around axial chiral bond would shield one face of the aromatic system during the IBX oxidation; however, the process proved non-diastereoselective producing the three possible stereoisomers in near statistical 1:1:1 ratio. This result brings into question how these stereocenters are established biosynthetically. Based on the results observed, it appears that there is not a strong inherent facial bias directing oxidation. To move forward, the three isomers of **36** were separated by HPLC. The *C*$_2$-symmetric isomers **36a** and **36c** were readily distinguished from the non-*C*$_2$-symmetric isomer **36b** using ^{1}H NMR spectroscopy. The configurations of **36a** and **36c** were established by generation of the natural product and comparison of CD spectra (see below).

Selective Acetylation: At this point, the secondary acetates needed to be removed and the tertiary alcohols selectively acetylated. Reasoning that selective deprotection of the less hindered secondary acetates should be feasible, acetylation of the hindered tertiary hydroxyl groups was undertaken to afford **37**. However, the selective hydrolysis was unexpectedly difficult (eq 5). Apparently, the keto groups adjacent to the tertiary ester activate it toward cleavage.[15] Under acidic conditions,[16] promising amounts of the product from hydrolysis of both secondary esters (**38**) was observed (**Table 5**, entry 1), but could not be increased further upon additional trials. Mild inorganic base, K_2CO_3, [17] initially gave promising results (44% isolated yield), but proved irreproducible (entry 2). Attempts to control particle size or water content provide ineffective. Samarium diiodide[18] and lipase AS[19] were ineffective (entries 3, 4). The use of Bu_4NOH over 2.5 h result in only a slight

improvement (entry 5). After surveying a range of other methods,[20] freshly distilled Ti(O*i*-Pr)$_4$[21] was found to selectively cleave the secondary esters providing **38** in a reproducible 52% yield (entry 6).

Table 5. Selective Acetyl Deprotection (eq 5)



Entry	conditions	Yield (%)[a]
1	AcCl, MeOH, rt, 48 h	18
2	K_2CO_3, MeOH, rt, 12 h	8–44[b]
3	Sm, I_2, MeOH, rt, 3.5 h	19
4	Lipase PS, toluene, *n*-BuOH, 100 °C, 5 d	NR[c]
5	Bu_4NOH, MeOH, rt, 2.5 h	30
6	Ti(O*i*-Pr)$_4$, THF, 50 °C, 24 h	52

[a]Isolated yield. [b]Not reproducible. [c]Substrate decomposition occurred.

Final Sequence: The final oxidative dearomatization/protection/deprotection sequence is outlined in (**Scheme 15**). After cyclization and dearomatization of **31d**, the adduct **36** subjected to acylation to afford tetraacetate **37**. Cleavage of the secondary acetates afforded **38** which underwent by highly efficient amination (96%) using NH_4OAc as the amine source to produce chaetoglobin A (**1**).

Scheme 15. Final Steps to Chaetoglobin A

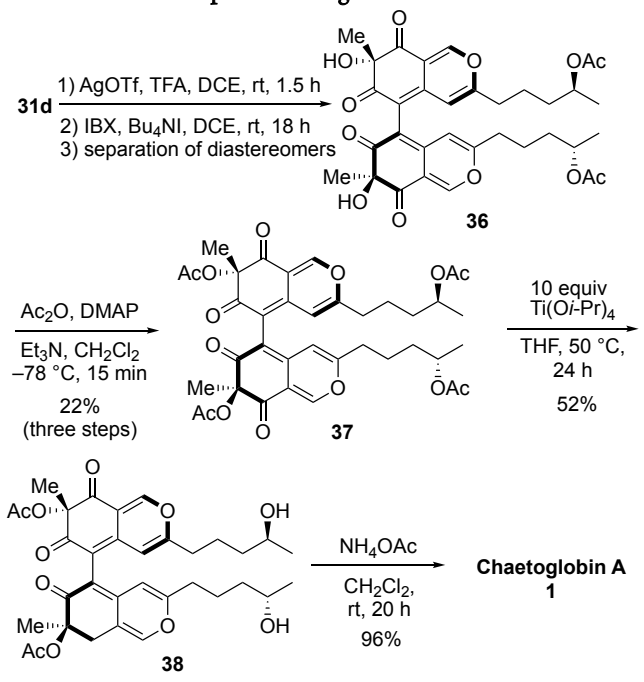


Table 6 shows that the NMR spectral data from the reported natural product[2] match that of the synthetic material generated herein. Furthermore, the Cotton effects characteristic of the tertiary alcohol centers and the chiral axis in the circular dichroism spectra of the synthesized compound match those of the natural product,[5] securing that the synthesized and natural product configurations are the same.

Table 6. Spectral Data of Natural Product vs Synthetic Product

Natural Product		Synthetic Product	
^{1}H NMR (ppm)	^{13}C NMR (ppm)	^{1}H NMR (ppm)	^{13}C NMR (ppm)
1.16 (d)	20.4	1.12 (d)	20.6
1.45 (m)	23.3	1.39–1.45 (m)	23.4
1.64 (s)	23.4	1.60 (s)	23.6
1.72 (m)	25.3	1.63–1.72 (m)	25.5
2.19 (s)	33.9	2.15 (s)	34.1
2.49 (t)	39.0	2.45 (t)	39.2
3.73 (m)	67.8	3.67–3.73 (m)	68.1
6.42 (s)	85.7	6.37 (s)	86.0
8.05 (s)	103.7	8.00 (s)	104.0
	116.0		116.1
	116.7		116.9
	139.6		139.7
	151.2		151.3
	153.2		153.2
	171.8		172.0
	189.6		189.9
	197.8		198.0

Conclusions

In summary, we report the total synthesis of axial chiral azaphilone dimer, chaetoglobin A (**1**), starting from 2,6-dimethoxytoluene, (*S*)-propylene oxide, and 1-butyne. A diastereoselective oxidative coupling of a chiral phenol by means of a chiral vanadium catalyst was used as a key step to generate the chiral axis that unites the two monomeric azaphilone units of the natural product. Notably, the coupling of the more complex phenol described herein generated the opposite stereoisomer relative to couplings with similar substrates, even though the same catalyst enantiomer was used in both cases. Clearly, caution needs to be exercised when extrapolating the outcomes of asymmetric processes from simple to more complex substrates.

With the chiral bisphenol nucleus established in this way, the two azaphilone moieties were built up by sequential Vilsmeier-Haack formylation, cyclization, oxidative dearomatization, selective deprotection, and amination. With the exception of the amination protocol, which proceeded unexpectedly well give that four bonds to oxygens are broken and then remade to nitrogens, each of the key steps exhibited very different profiles on the dimeric compound relative to the monomeric analogs and required considerable reoptimization. Ultimately, the absolute and relative stereochemistry of isolated chaetoglobin A were confirmed to match that of the synthesized material through X-ray crystallographic and circular dichroism analysis.

EXPERIMENTAL SECTION

*5-Bromo-1,3-dimethoxy-2-methylbenzene (**15**).*[4] In a glove box, $[Ir(COD)(OMe)]_2$ (54 mg, 0.08 mmol), 4,4'-di-*tert*-butyl-2,2'-dipyridyl (44 mg, 0.16 mmol), B_2Pin_2 (7.09 g, 27.9 mmol), and 2,6-dimethoxytoluene (5.00g, 32.9 mmol) were added to a Schlenk flask, which was then sealed with septum. The reactants were dissolved in distilled THF (41 mL) under an argon atmosphere and the resultant mixture was heated at 80 °C for 44 h in an oil bath. The mixture was cooled to ambient temperature and concentrated. After standing under vacuum for 3 h, the ester was subjected to MeOH (230 mL) and $CuBr_2$ (22.0 g, 98.6 mmol) in distilled H_2O (230 mL). The resultant mixture was heated at 80 °C for 48 h in an oil bath and then, cooled to ambient temperature. The mixture was extracted with EtOAc (150 mL × 3) and the combined organic layer were washed with brine, dried over Na_2SO_4, filtered, and concentrated. Column chromatography (hexanes:EtOAc = 99:1) afforded a white amorphous powder (6.78 g) in 89% overall yield: ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.67 (s, 2H), 3.80 (s, 6H), 2.02 (s, 3H); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 158.9, 119.3, 113.7, 107.4, 56.0, 8.2; IR (neat) 2938, 2834, 1586, 1464, 1402, 1310, 1283, 1253, 1227, 1181, 1139, 1126, 1041, 843 cm^{-1}; HRMS (EI-TOF) *m/z*: $[M]^+$ Calcd for $C_9H_{11}BrO_2$ 229.9942; found 229.9927.

*5-Bromo-2-methylbenzene-1,3-diol (**8**).* A solution of BBr_3 (1 M in CH_2Cl_2, 8.7 mL) was added dropwise to a solution of **17** (1.00 g, 4.34 mmol) in CH_2Cl_2 (8.7 mL) at −78 °C. The resultant mixture was allowed to warm to ambient temperature and stirred until completion as judged by TLC (24 h). The reaction mixture was quenched with water at 0 °C and the aqueous layer was extracted with CH_2Cl_2. (15 mL × 3). The combined organic layers were dried over Na_2SO_4 and filtered. Removal of solvent followed by chromatography (100% CH_2Cl_2) afforded a white amorphous solid (872 mg) in 99% yield: ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.58 (s, 2H), 4.77 (s, 2H), 2.08 (s, 3H); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 155.4, 118.9, 111.4, 109.8, 7.9; IR (film) 3390, 2985, 1705, 1599, 1376, 1089, 864, 567 cm^{-1}; HRMS (ESI-TOF) *m/z*: $[M]^+$ Calcd for $C_7H_7BrO_2$ 201.9629; found 201.9634.

*5-Bromo-3-methoxy-2-methylphenol (**9**).* Following the above procedure with 1 equiv of BBr_3, the product was obtained as a brown oil (84 mg) in 93% yield by chromatography (hexanes:EtOAc = 9:1): ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.82 (s, 1H), 6.81 (s, 1H), 5.85 (br, 1H), 3.80 (s, 3H), 2.05 (s, 3H); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 159.2, 155.1, 119.1, 111.8, 107.1, 56.1, 8.1; IR (film) 3429, 3002, 2934, 1587, 1299, 1111, 851, 567 cm^{-1}; HRMS (EI-TOF) *m/z*: $[M]^+$ Calcd for $C_8H_9BrO_2$ 215.9786; found 215.9786.

*2,4-Dimethoxy-3-methylbenzaldehyde (**16**).* $POCl_3$ (220 mL, 0.20 mol) was added dropwise to sealed flask with dry DMF (39 mL) at 0 °C. The resulting complex was stirred at room temperature for 30 min and added to a solution of 2,6-dimethoxytoluene (30 g, 0.20 mol) in DMF (39 mL) at 100 °C in an oil bath. The reaction mixture heated to 110 °C for 4 h. The mixture was quenched by pouring into cold water. The aqueous layer was extracted with EtOAc (200 mL × 3). The organic layers were washed with brine, dried over Na_2SO_4, filtered, and the solvent was evaporated under reduced pressure. Chromatography (hexanes:EtOAc = 9:1) afforded **16** as a yellow amorphous solid (19.5 g) in 55% yield: Spectral data were in agreement with those reported.[8] ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.17 (s, 1H), 7.68 (d, *J* = 9.0 Hz, 1H), 6.69 (t, *J* = 8.7 Hz, 1H), 3.83 (s, 3H), 3.80 (s, 3H), 2.10 (s, 3H)

*2-(2,4-Dimethoxy-3-methylphenyl)-1,3-dimethylimidazolidine (**17**).* Following the reported procedure,[1e] the product **17** was obtained as a crystalline (13.3 g) in 96% yield: Spectral data were in agreement with those reported.[1e]

*6-Bromo-2,4-dihydroxy-3-methylbenzaldehyde (**19**).* *t*-BuLi (1.65 M in pentane, 0.57 mL) was added dropwise at −55 °C under inert atmosphere, to a solution of aminal **17** (250 mg, 1.00 mmol) in distilled Et_2O (1.9 mL). The solution was stirred for 6 h at room temperature. The mixture was cooled again to −55 °C and a solution of 1,2-dibromotetrachloroethane (299 mg, 0.92 mmol) in Et_2O (0.57 mL) was added over 1 h. The reaction mixture was stirred for 18 h at room temperature. The reaction mixture was washed with water and Et_2O. The combined organic layers were dried over Na_2SO_4 and filtered. Removal of solvent afforded the product **18** as a brown-red gummy oil (259 mg). No further purification was necessary.

A solution of BBr_3 (1.0 M in CH_2Cl_2, 0.35 mL) was added dropwise to a solution of **18** (58 mg, 0.18 mmol) at −78 °C and stirred at room temperature for 24 h. the mixture was cooled to 0 °C and quenched with water. The aqueous layer was extracted with CH_2Cl_2 (5 mL × 3). The organic layer was washed with brine, dried over Na_2SO_4, filtered, and concentrated. Column chromatography (hexanes:EtOAc = 9:1) gave **19** as a white amorphous solid (26 mg) in 64% yield. Spectral data were in agreement with those reported.[1e]

*5-Bromo-4-(1,3-dimethylimidazolidin-2-yl)-2-methylbenzene-1,3-diol (**11**). N,N'*-Dimethylethylenediamine (0.02 mL, 0.22 mol) and 3 Å molecular sieves (50 mg) were added to a solution of **19** (50 mg, 0.22 mmol) in distilled toluene (0.36 mL). The mixture was heated at reflux in a sealed microwave vial. After 24 h, the mixture was cooled to room temperature, dried over Na_2SO_4, and filtered. Removal of solvent afforded the product **11** (58 mg) as white amorphous powder in 97% yield: ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.52 (s, 1H), 4.24 (s, 1H), 3.38 (s, 2H), 3.36 (s, 2H), 2.64 (s, 2H), 2.33 (s, 6H), 2.05 (s, 3H); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 159.1, 156.9, 122.1, 112.4, 110.4, 110.1, 88.8, 52.1, 50.4, 39.0, 36.1, 8.2; IR (film) 3251, 2947, 1602, 1454, 1109, 885 cm^{-1}; HRMS (ESI-TOF) *m/z*: $[M+H]^+$ Calcd for $C_{12}H_{18}BrN_2O_2$ 301.0552; found 301.0551.

*5-Iodo-2-methylbenzene-1,3-diol (**20**).*[4] A Schlenk flask was charged with CuI (279 mg, 1.47 mmol), NaI (8.80 g, 58.7 mmol), and **15** (6.78 g, 29.3 mmol). The reactants were dissolved in 1,4-dioxane (29 mL) and *N,N'*-dimethylethylenediamine (0.32 mL, 2.93 mmol) under an argon atmosphere. The resultant mixture was stirred at 110 °C for 48 h in an oil bath. The resulting suspension was allowed to cool to ambient temperature, diluted with satd NH_4Cl, poured into water, and extracted with CH_2Cl_2 (15 mL × 3). The combined organic phases were dried over Na_2SO_4 and filtered. Removal of solvent and chromatography (hexanes:EtOAc = 99:1) afforded 5-iodo-1,3-dimethoxy-2-methylbenzene as a white amorphous powder (7.75 g) in 95% yield: R_f = 0.61 (hexanes:EtOAc = 40:1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.85 (s, 2H), 3.80 (s, 6H), 2.03 (s, 3H); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 158.9, 114.8, 113.4, 89.7, 56.1, 8.2; IR (neat) 2996, 2911, 2852, 1575, 1485, 1448, 1435, 1396, 1304, 1279, 1234, 1180, 1132, 841

cm^{-1}; HRMS (EI-TOF) *m/z*: $[M]^+$ Calcd for $C_9H_{11}IO_2$ 277.9804; found 277.9804 (calcd and found were identical).

5-Iodo-1,3-dimethoxy-2-methylbenzene (6.94 g, 25.0 mmol) was dissolved in CH_2Cl_2 (50 mL). After cooling to –78 °C, a solution of BBr_3 (1 M in dichloromethane, 62 mL) was added dropwise. The resultant mixture was allowed to warm to ambient temperature and stirred until completion as judged by TLC (24 h). The mixture was subsequently quenched with water (15 mL) in an ice bath. The solution was extracted with CH_2Cl_2 (20 mL × 3). The combined organic phases were washed with brine and dried over Na_2SO_4. Removal of solvent followed by chromatography (100% CH_2Cl_2) afforded **20** as a white powder (5.62 g) in 90% yield: R_f = 0.22 (100 % CH_2Cl_2); ^1H NMR (500 MHz, $(CD_3)_2CO$) δ 8.37 (br s, 2H), 6.78 (s, 2H), 2.02 (s, 3H); $^{13}C\{^1H\}$ NMR (125 MHz, CD_3CN) δ 157.6, 116.8, 112.1, 89.6, 8.4; IR (neat) 3367, 2918, 2496, 1580, 1494, 1442, 1396, 1324, 1274, 1229, 1055, 952, 845 cm^{-1}; HRMS (EI-TOF) *m/z*: $[M]^+$ Calcd for $C_7H_7IO_2$ 249.9491; found 249.9475.

2-Methyl-5-(oct-1-yn-1-yl)benzene-1,3-diol ***(12)****.*[5] $Pd(PPh_3)_2Cl_2$ (561 mg, 0.80 mmol), CuI (152 mg, 0.80 mmol), and 1-octyne (1.2 mL, 8.0 mmol) were added to a flame-dried flask. A solution of **20** (1.0 g, 4.0 mmol) in DMF (13 mL) was transferred into the flask, followed by Et_2NH (1.5 mL, 14.0 mmol) under Ar. The resultant mixture was stirred at 60°C for 22 h in an oil bath. After cooling to ambient temperature, the reaction mixture was treated with satd NH_4Cl (10 mL). The mixture was extracted with EtOAc (15 mL × 3) and washed with brine. The organic layer was dried over Na_2SO_4 and filtered. Removal of the solvent followed by chromatography (hexanes:EtOAc = 6:1) gave the desired product **12** as a pale yellow amorphous solid (867 mg) in 93% yield: ^1H NMR (500 MHz, acetone-d_6) δ 8.20 (s, 2H), 6.44 (s, 2H), 2.86 (s, 3H), 2.35 (t, *J* = 7.0 Hz, 2H), 1.55 (m, 2H), 1.44 (m, 2H), 1.30 (m, 4H), 0.89 (t, *J* = 2.0 Hz, 3H); $^{13}C\{^1H\}$ NMR (125 MHz, acetone-d_6) δ 157.0, 122.4, 112.3, 110.5, 89.0, 81.7, 32.1, 28.6, 28.5, 22.5, 19.6, 14.3, 8.5; IR (film) 3435, 3053, 2931, 2857, 2232, 1772, 1735, 1618, 1583, 1322, 1080, 737 cm^{-1}; HRMS (ESI-TOF) *m/z*: $[M]^+$ Calcd for $C_{15}H_{20}O_2$ 232.1463; found 232.1457.

(R)-6,6'-Dibromo-3,3'-dimethyl-[1,1'-biphenyl]-2,2',4,4'-tetraol ***(21a)****.* Phenol, vanadium catalyst (20-40 mol%) and the additive are placed in an oven-dried microwave vial and sealed. The flask is purged with oxygen three times. The solids are dissolved in toluene or dichloroethane (0.2 M). The mixture is stirred at 0 °C for 3-15 h. The reaction mixture was purified via chromatography (SiO_2, CH_2Cl_2). Using **8** (0.10 mmol), **V1** (14 mg, 0.02 mmol), and dichloroethane (0.20 mL) as solvent, the product was isolated as an off-white amorphous solid (28%, 5.6 mg, 0.056 mmol, 71% ee): $[\alpha]_D^{22}$ +30.66 (*c* 0.36, 71% ee, CH_2Cl_2); ^1H NMR (500 MHz, $CDCl_3$) δ 6.83 (s, 2H), 5.52 (s, 2H), 4.95 (s, 2H), 2.13 (s, 6H); IR (film) 3691, 3055, 2987, 1639, 1612, 1477, 1422, 1330, 1266, 896 cm^{-1}; $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 156.2, 154.2, 122.2, 114.2, 112.1, 110.7, 8.6; HRMS (ESI) *m/z*: $[M+H]^+$Calcd for $C_{14}H_{13}Br_2O_4$ 402.9181; found 402.8989; HPLC (Chiralpak IA, *i*-PrOH/*n*-hexane = 20/80, flow rate = 1.0 mL/min, 1 = 254 nm): tR = 6.03 min (major, *S*), 9.27 min (minor, *R*)

(R)-6,6'-Dibromo-4,4'-dimethoxy-3,3'-dimethyl-[1,1'-biphenyl]-2,2'-diol ***(21b)****.* Phenol, vanadium catalyst (20-40 mol%) and the additive are placed in an oven-dried microwave dial and sealed. The flask is purged with oxygen three times. The solids are dissolved in toluene or dichloroethane (0.2 M). The mixture is stirred at 0 °C for 3-15 h. The reaction mixture was purified via chromatography (SiO_2, CH_2Cl_2). Using **9** (32 mg, 0.15 mmol), catalyst **V1** (21 mg, 0.03 mmol), and dichloroethane (0.30 mL) as solvent, the product was isolated as an off white solid (<5 mg, <15%, 38% ee): ^1H NMR (500 MHz, $CDCl_3$) δ 6.85 (s, 2H), 4.83 (s, 2H), 3.87 (s, 6H), 2.11 (s, 6H); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 159.9, 153.7, 122.5, 114.8, 112.7, 107.8, 56.0, 8.8; IR (film) 3472, 2938, 1601, 1572, 1394, 1305, 1104, 854, 738 cm^{-1}; HRMS (EI) *m/z*: $[M]^+$ Calcd for $C_{16}H_{16}Br_2O_4$ 429.9415; found 429.9428; HPLC (Chiralpak IA, *i*-PrOH/*n*-hexane = 20/80, flow rate = 1.0 mL/min, 1 = 254 nm): tR = 13.38 min (major, *S*), 19.34 min (minor, *R*)

(S)-3,3'-Dimethyl-6,6'-di(oct-1-yn-1-yl)-[1,1'-biphenyl]-2,2',4,4'-tetraol ***(21d)****.*[5] Using **12** (20 mg, 0.043 mmol) in toluene (0.21 mL) with 20 mol% **V2**, the product was isolated as an ivory sticky-solid (13.2 mg, 66%, 89% ee): $[\alpha]_D^{22}$ +56.65 (*c* 1.59, CH_2Cl_2); ^1H NMR (500 MHz, $CDCl_3$) δ 6.57 (s, 2H), 5.83 (s, 2H), 5.03 (s, 2H), 2.15 (s, 6H), 1.26-1.12 (m, 20H), 0.84 (t, 6H); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 154.8, 153.7, 123.2, 115.4, 111.3, 111.0, 93.2, 78.4, 31.5, 28.5, 28.3, 22.6, 19.4, 14.3, 8.7; IR (film) 3443, 3304, 3054, 2930, 2306, 1606, 1584, 1395, 1265, 1077, 739 cm^{-1}; HRMS (ESI) *m/z*: $[M+H]^+$ Calcd for $C_{30}H_{39}O_4$ 463.2848; found 463.2838; HPLC (Chiralpak IA, , *i*-PrOH/*n*-hexane = 20/80, flow rate = 1.0 mL/min, 1 = 254 nm): tR = 6.76 min (major, *S*), 15.98 min (minor, *R*)

(S)-tert-Butyl(hept-6-yn-2-yloxy)dimethylsilane ***(26a)****.* To a solution of **25** (250 mg, 2.23 mmol), which was prepared by the reported procedure[12] over two steps without chromatography, and imidazole (470 mg, 6.92 mmol) in DMF (7.4 mL) was added TBSCl (470 mg, 3.12 mmol). After 12 h, the mixture was diluted in Et_2O (80 mL) and washed with water four times followed by brine. The organic layer was dried over $MgSO_4$, filtered ,and concentrated to give **26a** as yellow oil (11.6 g) in 63% overall yield. No further purification was necessary. Spectral data were in agreement with those reported.[22] ^1H NMR (500 MHz, $CDCl_3$) δ 3.83-3.79 (m, 1H), 2.22 (m, 2H), 1.94 (m, 1H), 1.61-1.50 (m, 4H), 1.21 (d, *J* = 7.0 Hz, 3H), 0.91 (s, 6H), 0.88 (s, 9H); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 84.6, 68.3, 38.7, 25.8, 24.9, 23.9, 18.6, 18.2, -2.8, -4.3, -4.5

(S)-tert-Butyl(hept-6-yn-2-yloxy)diphenylsilane ***(26b)****.* The procedure for compound **26a** above was used substituting TBDPSCl to generate the product as light yellow oil (2.137g, 6.10 mmol) 66% overall yield: $[\alpha]_D^{22}$ –77.44 (*c* 3.96, 99% ee, CH_2Cl_2); ^1H NMR (500 MHz, $CDCl_3$) δ 7.73-7.67 (m, 5H), 7.42-7.37 (m, 5H), 3.89-3.85 (m, 1H), 2.13 (m, 2H), 1.91 (m, 1H), 1.57-1.53 (m, 4H), 1.07 (m, 12H); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 136.1, 134.6, 129.7, 127.7, 84.7, 69.2, 68.5, 38.6, 27.2, 24.4, 23.4, 19.5, 18.6; IR (film) 3071, 2930, 2118, 1472, 1428, 1391, 1259, 823, 740, 607 cm^{-1}; HRMS (ESI) *m/z*: $[M+H]^+$ Calcd for $C_{23}H_{31}OSi$ 351.2144; found 351.2141.

(S)-Hept-6-yn-2-yl acetate ***(26d)****.*[4] To a stirred solution of **25** (35.7 mmol), which was prepared by the reported procedure[12] over two steps without chromatography, in CH_2Cl_2 (71 mL) was added pyridine (5.8 mL, 71.4 mmol) at 0 °C, followed by 4-(dimethylamino)pyridine (1.09 g, 8.93 mmol) and Ac_2O (3.7 mL, 39.3 mmol). The resultant mixture was stirred for 30 min and then was quenched with 1*N* HCl (95 mL) in an ice bath. The resulting mixture was extracted with CH_2Cl_2 (20 mL × 3) and the combined

organic phases were sequentially washed with H_2O (50 mL) and satd $NaHCO_3$ (50 mL). The organic layer was dried over Na_2SO_4 and filtered. Removal of the solvent followed by chromatography (hexanes:EtOAc = 10:1) gave the desired product as clear liquid (4.09 g) in 74% over three steps: R_f = 0.75 (hexanes:EtOAc = 4:1); $[\alpha]_D^{22}$ = +4.1 (c 1.4, CH_3OH); ^1H NMR (500 MHz, $CDCl_3$) δ 4.88-4.94 (m, 1H), 2.20 (td, *J* = 7.0, 2.5 Hz, 2H), 2.02 (s, 3H), 1.95 (t, *J* = 2.5 Hz, 1H), 1.49-1.71 (m, 4H), 1.22 (d, *J* = 6.5 Hz, 3H); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 170.9, 84.1, 70.6, 68.8, 35.1, 24.5, 21.5, 20.1, 18.4; IR (neat) 3295, 2978, 2937, 2870, 1731, 1436, 1371, 1241, 1133, 1073, 1049, 1018, 976 cm^{-1}; HRMS (EI-TOF) *m/z*: $[M]^+$ Calcd for $C_9H_{14}O_2$ 154.0994; found 154.0982.

*(S)-5-(6-((tert-Butyldimethylsilyl)oxy)hept-1-yn-1-yl)-2-methylbenzene-1,3-diol (**28a**).* Following the same procedure as for **12**, the product was obtained via column chromatography (100% CH_2Cl_2) as a yellow oil (917 mg) in 69% yield: $[\alpha]_D^{22}$ +34.22 (*c* 0.82, 99% ee, CH_2Cl_2); ^1H NMR (500 MHz, $CDCl_3$) δ 6.44 (s, 2H), 4.95 (br, 2H), 3.86-3.83 (m, 1H), 2.37 (m, 2H), 2.11 (s, 3H), 1.58-1.55 (m, 4H), 1.15 (d, J = 7.0 Hz, 3H), 0.90 (s, 9H), 0.07 (s, 6H); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 154.4, 122.0, 117.1, 111.0, 89.6, 81.0, 68.3, 38.8, 25.9, 25.0, 23.8, 19.4, 18.2, 8.0, –4.4, –4.7; IR (film) 3584, 3400, 3054, 2930, 2305, 2237, 1619, 1583, 1322, 1080, 836 cm^{-1}; HRMS (EI-TOF) *m/z*: $[M]^+$ Calcd for $C_{20}H_{32}SiO_3$ 348.2121; found 348.2106.

*(S)-5-(6-((tert-Butyldiphenylsilyl)oxy)hept-1-yn-1-yl)-2-methylbenzene-1,3-diol (**28b**).* Conducted with aryl halide **20** (527 mg, 2.11 mmol). Following the same procedure as for **12**, the product was obtained via column chromatography (100% CH_2Cl_2) to yield 2-methyl-5-(oct-1-yn-1-yl)benzene-1,3-diol in a 90% yield (897 mg, 1.90 mmol) as brown oil: $[\alpha]_D^{22}$ +3.28 (*c* 0.84, 99% ee, CH_2Cl_2); ^1H NMR (500 MHz, $CDCl_3$) δ 7.78-7.67 (m, 4H), 7.48-7.32 (m, 6H), 6.41 (s, 2H), 5.08 (br s, 2H), 3.98-3.89 (m, 1H), 2.30 (t, *J* = 6.5 Hz, 2H), 2.13 (s, 3H), 1.74-1.55 (m, 4H), 1.12 (d, *J* = 6.0 Hz, 3H), 1.10 (s, 9H); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 154.5, 136.03, 136.00, 134.9, 134.8, 134.7, 129.6, 127.7, 127.6, 121.9, 111.2, 111.1, 89.7, 80.4, 69.3, 38.6, 27.2, 24.5, 23.3, 19.5, 19.4, 8.1; IR (film) 3434, 3070, 2957, 1341, 1110, 1042, 820 cm^{-1}; HRMS (EI) *m/z*: $[M\text{-}t\text{Bu}]^+$ Calcd for $C_{26}H_{27}O_3Si$ 415.1729; found 415.1732.

*(S)-7-(3,5-Dihydroxy-4-methylphenyl)hept-6-yn-2-yl acetate (**28d**).*[4] To an oven-dried Schlenk flask was added **20** (2.67 g, 10.7 mmol), $Pd(PPh_3)_2Cl_2$ (750 mg, 1.07 mmol), CuI (203 mg, 1.07 mmol) and **26d** (1.81 g, 11.7 mmol). The flask was sealed with a septum and purged with argon. The resultant mixture was dissolved in DMF (36 mL) and Et_2NH (3.9 mL, 37.4 mmol). The mixture was stirred at 65 °C for 18 h in an oil bath. After cooling to ambient temperature, the reaction mixture was treated with satd NH_4Cl (15 mL). The resultant mixture was poured into water and extracted with Et_2O (40 mL × 3). The combined organic layers were washed thoroughly with satd LiCl (3 mL × 3) and brine. The organic layer was dried over Na_2SO_4 and filtered. Removal of the solvent followed by chromatography (hexanes:EtOAc = 4:1) afforded a brown oil (2.88 g) in 98% yield: R_f = 0.36 (hexanes:EtOAc = 2:1); $[\alpha]_D^{22}$ = –4.5 (c 0.24, CH_3OH); ^1H NMR (500 MHz, $CDCl_3$) δ 6.46 (s, 2H), 5.99 (br s, 2H), 4.96-5.02 (m, 1H), 2.38 (t, *J* = 7.0 Hz, 2H), 2.11 (s, 3H), 2.06 (s, 3H), 1.53-1.77 (m, 4H), 1.24 (d, *J* = 6.5 Hz, 3H); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 172.1, 154.8, 121.5, 111.6, 110.9, 88.7, 80.9, 71.4, 35.0, 24.5, 21.5, 19.9, 19.2, 8.2; IR (neat) 3386, 2935, 1699, 1616, 1583, 1413, 1375, 1341, 1323, 1265, 1165, 1133, 1078, 1023, 950 cm^{-1}; HRMS (ESI-TOF) *m/z*: $[M+Na]^+$ Calcd for $C_{16}H_{20}O_4Na$ 299.1259; found 299.1273.

*(R)-6,6′-Bis((S)-6-((tert-butyldimethylsilyl)oxy)hept-1-yn-1-yl)-3,3′-dimethyl-[1,1′-biphenyl]-2,2′,4,4′-tetraol (**29a**).* To a microwave vial was added phenol **28a** (25 mg, 0.072 mmol), vanadium catalyst **V2** (6.4 mg, 0.014 mmol), and LiCl (19 mg, 0.45 mmol). The vial was sealed and toluene (0.36 mL) was added. Oxygen was added via an active purge. The deep blue solution was stirred for 42 h at 0 °C. The reaction mixture was directly chromatographed (hexanes:EtOAc = 4:1) to afford the coupled products as a yellow oil (19.8 mg) in 79% yield with 94:6 dr: $[\alpha]_D^{22}$ +31.99 (*c* 3.83, dr = 94:6, CH_2Cl_2); ^1H NMR (500 MHz, $CDCl_3$) δ 6.58 (s, 2H), 5.01 (br, 4H), 3.71 (s, 2H), 2.17 (s, 6H), 1.35 (m, 4H), 1.28-1.26 (m, 8H), 1.07 (d, J = 6.0 Hz, 6H), 0.87 (s, 18H), 0.04 (s, 6H), 0.03 (s, 6H); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 154.8, 153.6, 123.0, 115.4, 111.8, 111.5, 92.8, 78.6, 68.5, 38.3, 26.1, 24.8, 23.8, 19.5, 18.3, 8.8, -4.2, -4.6; IR (film) 3526, 3053, 2930, 2305, 2228, 1609, 1582, 1398, 1086, 730 cm^{-1}; HRMS (ESI-TOF) *m/z*: $[M+H]^+$ Calcd for $C_{40}H_{63}O_6Si_2$ 695.4163;, found 695.4161; Chiral HPLC (Chiralpak IA, *i*-PrOH/*n*-hexane = 20/80, flow rate = 1 mL/min, 1 = 254 nm): tR = 4.91 min (major, *R*), 12.09 min (minor, *S*)

*(R)-6,6′-Bis((S)-6-((tert-butyldiphenylsilyl)oxy)hept-1-yn-1-yl)-3,3′-dimethyl-[1,1′-biphenyl]-2,2′,4,4′-tetraol (**29b**).* Using **28b** (350 mg, 0.74 mmol) in toluene (0.74 mL) with 20 mol% **V2**, the product was isolated as a yellow oil (180 mg, 71% brsm, dr = 97:3): Major diasteroisomer: $[\alpha]_D^{22}$ +7.27 (*c* 2.24, dr = 82:18, CH_2Cl_2); ^1H NMR (500 MHz, $CDCl_3$) δ 7.67 (m, 10H), 7.38-7.36 (m, 10H), 6.42 (s, 2H), 4.93 (s, 2H), 4.52 (s, 2H), 3.73 (m, 2H), 2.10 (s, 6H), 2.04 (m, 4H), 1.33-1.30 (m, 8H), 1.04 (s, 18H), 0.98 (d, *J* = 6.0 Hz, 6H); $^{13}C\{^1H\}$ NMR (500 MHz, $CDCl_3$) δ 154.7, 153.5, 136.1, 135.0, 134.8, 129.7, 129.6, 127.7, 127.6, 123.2, 115.3, 111.5, 111.2, 92.9, 78.7, 69.3, 38.3, 29.9, 27.2, 24.3, 23.3, 19.5, 19.4, 8.7; IR (film) 3528, 3070, 2928, 2233, 1609, 1580, 1321, 1135, 1085, 822, cm^{-1}; HRMS (ESI) *m/z*: $[M+H]^+$ Calcd for $C_{60}H_{71}O_6Si_2$ 943.4789; found 943.4794; HPLC (Chiralpak IA, *i*-PrOH/*n*-hexane = 20/80, flow rate = 1.0 mL/min, 1 = 254 nm): tR = 4.97 min (major, *R*), 16.25 min (minor, *S*).

*(R)-2′(2S,8′)-((R)-4,4′,6,6′-Tetrahydroxy-5,5′-dimethyl-[1,1′-biphenyl]-2,2′-diyl)bis(hept-6-yne-7,2-diyl) diacetate (**29d**).*[4] To a microwave vial was added phenol **28d** (320 mg, 1.15 mmol), vanadium catalyst **V2** (103 mg, 0.23 mmol), and HOAc (13 mL, 0.23 mmol). The vial was sealed and chlorobenzene (2.3 mL) was added. Oxygen was added via an active purge. The deep blue solution was stirred for 42 h at 0 °C. The reaction mixture was directly chromatographed (hexanes:EtOAc = 4:1) to afford a mixture of coupled products (214 mg) in 67% yield with 94:6 dr (the diastereoselectivity varies depending on batch of the catalyst from 4:1 to >15:1). The combined mixture of products (1.497 g) was dissolved in methanol (10 mL). This solution was used as feeding solution (150 mg/mL) for Supercritical Fluid Chromatographic separation (SFC). The separation of the two isomers was performed using a Lux Celluiose-4 column (21 x 250 mm) with 30% MeOH / 70% CO_2 at 35 °C (flow rate 60 mL/min, BP 100 bar, detector 210 nm). Feeding solution was injected in 500 μL portions and two

fractions (2.2-2.5 min, and 3.1-3.7 min) were collected for each run. Concentration of the two fractions afforded 180 mg of the (*P*)-**29d** as light yellow amorphous powder and 1.05 g of **29d** as light yellow amorphous powder: R_f = 0.23 (hexanes:EtOAc = 2:1): $[\alpha]_D^{22}$ = –33.5 (c 0.30, CH_3OH); ^1H NMR (500 MHz, $CDCl_3$) δ 6.53 (s, 2H), 5.76 (br s, 2H), 5.03 (br s, 2H), 4.76-4.83 (m, 2H), 2.16-2.19 (m, 4H), 2.17 (s, 6H), 2.06 (s, 6H), 1.20-1.43 (m, 8H), 1.15 (d, *J* = 6.5 Hz, 6H); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 171.7, 155.1, 153.6, 123.1, 115.3, 112.0, 111.3, 92.1, 79.2, 71.1, 34.7, 24.6, 21.6, 20.0, 19.3, 8.8; IR (neat) 3540, 3375, 2950, 1708, 1683, 1604, 1585, 1431, 1404, 1377, 1345, 1323, 1288, 1277, 1239, 1163, 1136, 1076, 1047, 1020, 839 cm^{-1}; HRMS (ESI-TOF) *m/z*: $[M+H]^+$ Calcd for $C_{32}H_{39}O_8$ 551.2645; found 551.2650; Chiral HPLC (Chiralpak IA, *i*-PrOH/*n*-hexane = 20/80, flow rate = 1 mL/min, 1 = 254 nm), tR = 10.5 min (major, ***29d***), 28.7 min (minor, (*P*)-***29d***)

*(R)-6,6′-Bis((S)-6-acetoxyhept-1-yn-1-yl)-3,3′-dimethyl-[1,1′-biphenyl]-2,2′,4,4′-tetrayl tetrakis(4-bromobenzoate) (**30**).*[4] To a stirred solution of **29d** (50 mg, 0.09 mmol) in CH_2Cl_2 (0.91 mL) was added 4-bromobenzoyl chloride (90 mg, 0.41 mmol) and Et_3N (40 mL, 0.27 mmol) at room temperature. The mixture was stirred for 14 h and the resultant solution was washed with 1 *N* HCl (2 mL × 2) and brine. The organic layer was dried over Na_2SO_4 and filtered. Removal of the solvent and chromatography (hexanes:EtOAc = 10:1) afforded a light yellow amorphous powder (105 mg) in 91% yield. Crystallization from EtOAc and pentane via vapor diffusion gave white crystals. The absolute axial configuration was determined as *M* from the X-Ray crystal structure: R_f = 0.44 (hexanes:EtOAc = 4:1); $[\alpha]_D^{22}$ = –13.1 (*c* 2.30, CH_2Cl_2); ^1H NMR (500 MHz, $CDCl_3$) δ 8.07 (d, *J* = 8.5 Hz, 4H), 7.75 (d, *J* = 8.5 Hz, 4H), 7.67 (d, *J* = 8.5 Hz, 4H), 7.58 (d, *J* = 8.5 Hz, 4H), 7.20 (s, 2H), 4.81-4.88 (m, 2H), 2.25 (t, *J* = 6.0 Hz, 4H), 1.98 (s, 12H), 1.33-1.53 (m, 8H), 1.17 (d, *J* = 6.5 Hz, 6H); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 170.8, 163.6, 162.9, 149.4, 148.4, 132.3, 132.1, 131.8, 131.7, 130.1, 129.2, 128.8, 128.2, 128.1, 124.9, 123.8, 123.1, 94.6, 78.2, 70.8, 34.8, 24.3, 21.5, 20.0, 19.4, 11.2; IR (neat) 2940, 1737, 1588, 1484, 1398, 1371, 1246, 1173, 1154, 1132, 1110, 1084, 1068, 1009, 954 cm^{-1}; HRMS (ESI-TOF) *m/z*: $[M+H]^+$ Calcd for $C_{60}H_{51}Br_4O_{12}$ 1279.0114; found 1279.0121.

*(R)-4,4′,6,6′-Tetrahydroxy-2,2′-bis((S)-6-hydroxyhept-1-yn-1-yl)-5,5′-dimethyl-[1,1′-biphenyl]-3,3′-dicarbaldehyde (**31**, R = H).* To a solution of dry *N,N*-dimethylformamide (0.02 mL) at 0 °C, phosphoryl chloride (0.01 mL, 0.119 mmol) was added and the mixture was stirred for 30 min. The resulting Vilsmeier complex was then added to a solution of alkynyl arene (0.054 mmol) in dichloroethane or CH_2Cl_2 (0.067 M). The mixture was stirred at room temperature for 1-10 h. The reaction mixture was quenched with water and extracted with ethyl acetate. The organic layers were combined, washed with brine, dried over sodium sulfate, and concentrated. The product was purified by column chromatography (SiO_2, CH_2Cl_2). Using **29a** (28 mg, 0.05 mmol), in dichloromethane (0.75 mL), the product was isolated as a yellow oil (7.4 mg, 43%): $[\alpha]_D^{22}$ –17.94 (*c* 0.67, dr = 94:6, CH_2Cl_2); ^1H NMR (500 MHz, $CDCl_3$) δ 12.34 (s, 2H), 10.21 (s, 2H), 8.01 (s, 2H), 5.82 (br, 2H), 4.93 (m, 2H), 2.29 (m, 4H), 2.17 (s, 6H), 1.37-1.34 (m, 8H), 1.17 (d, *J* = 6.0 Hz, 6H); $^{13}C\{^1H\}$ NMR (500 MHz, $CDCl_3$) δ 195.5, 163.5, 160.9, 159.7, 128.4, 115.4, 113.0, 101.2, 74.3, 70.2, 34.6, 24.1, 20.0, 19.4, 7.9; IR (film) 3414, 3058, 2933, 2223, 1717, 1622, 1325, 1104, 738 cm^{-1}. HRMS (ESI-TOF) *m/z*: $[M+H]^+$ Calcd for $C_{30}H_{35}O_8$ 523.2332; found 523.2339.

*(R)-2,2′-Bis((S)-6-((tert-butyldiphenylsilyl)oxy)hept-1-yn-1-yl)-4,4′,6,6′-tetrahydroxy-5,5′-dimethyl-[1,1′-biphenyl]-3,3′-dicarbaldehyde (**31b**).* To a solution of dry *N,N*-dimethylformamide (0.02 mL) at 0 °C, phosphoryl chloride (0.01 mL, 0.119 mmol) was added and the mixture was stirred for 30 min. The resulting Vilsmeier complex was then added to a solution of alkynyl arene (0.054 mmol) in dichloroethane or CH_2Cl_2 (0.067 M). The mixture was stirred at 0 °C for 1-10 h. The reaction mixture was quenched with water and extracted with ethyl acetate. The organic layers were combined, washed with brine, dried over sodium sulfate, and concentrated. The product was purified by column chromatography (SiO_2, CH_2Cl_2). Using **29b** (235 mg, 0.25 mmol) in dichloromethane (3.6 mL), the product was isolated as a yellow oil (67 mg, 27%): $[\alpha]_D^{22}$ –45.84 (*c* 2.26, dr = 97:3, CH_2Cl_2); ^1H NMR (500 MHz, $CDCl_3$) δ 12.29 (s, 2H), 10.15 (s, 2H), 7.75-7.66 (m, 10H), 7.42-7.38 (m, 10H), 6.14 (s, 2H), 3.77 (m, 2H), 2.17 (s, 6H), 2.10 (m, 4H), 1.36-1.26 (m, 8H), 1.10 (s, 9H), 1.06 (s, 9H), 0.99 (d, *J* = 6.0 Hz, 6H); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 195.3, 163.2, 159.8, 135.9, 135.8, 134.6, 134.3, 129.53, 129.48, 128.4, 127.5, 127.4, 115.4, 114.5, 112.7, 102.0, 73.7, 68.8, 38.2, 27.0, 23.9, 23.2, 19.5, 19.3, 7.8; IR (film) 3508, 3052, 2928, 2222, 1623, 1111, 704 cm^{-1}; HRMS (ESI) *m/z*: $[M]^+$ Calcd for $C_{62}H_{70}O_8Si_2$ 998.4609; found 998.4597.

*(R)-(2S,2′S)-(3,3′-Diformyl-4,4′,6,6′-tetrahydroxy-5,5′-dimethyl-[1,1′-biphenyl]-2,2′-diyl)bis(hept-6-yne-7,2-diyl) diacetate (**31d**).*[4] The bisphenol **29d** (457 mg, 0.83 mmol) was dissolved in CH_2Cl_2 (41 mL). After cooling to –35 °C, five portions of commercial **32** (424 mg, 3.31 mmol) were added every 20 min. The reaction mixture was stirred for 12 h and the mixture was subsequently quenched with satd $NaHCO_3$ (20 mL) in an ice bath. The solution was extracted with EtOAc (40 mL × 3), washed thoroughly with satd LiOH solution (2 mL × 5), and brine. The combined organic layers were dried over Na_2SO_4. Removal of the solvent followed by chromatography (hexanes:EtOAc = 4:1) provided a yellow oil (433 mg) in 86% yield: R_f = 0.32 (hexanes:EtOAc = 2:1); $[\alpha]_D^{22}$ = –138.1 (*c* 0.43, CH_3OH); ^1H NMR (500 MHz, $CDCl_3$) δ 12.32 (s, 2H), 10.21 (s, 2H), 5.92 (s, 2H), 4.76-4.82 (m, 2H), 2.27 (t, *J* = 6.5 Hz, 4H), 2.17 (s, 6H), 2.01 (s, 6H), 1.28-1.44 (m, 8H), 1.12 (d, *J* = 6.5 Hz, 6H); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 195.5, 170.9, 163.5, 159.8, 128.4, 115.5, 114.8, 112.9, 101.4, 74.2, 70.2, 34.7, 24.2, 21.5, 20.0, 19.4, 7.9; IR (neat) 3350, 2936, 1734, 1622, 1417, 1368, 1324, 1292, 1248, 1177, 1142, 1104, 1021, 952 cm^{-1}; HRMS (ESI-TOF) *m/z*: $[M+H]^+$ Calcd for $C_{34}H_{39}O_{10}$ 607.2543; found 607.2546.

*4,4′,6,6′-Tetrahydroxy-5,5′-dimethyl-2,2′-di(oct-1-yn-1-yl)-[1,1′-biphenyl]-3,3′-dicarbaldehyde (**31e**).* To a solution of dry *N,N*-dimethylformamide (0.02 mL) at 0 °C, phosphoryl chloride (0.01 mL, 0.12 mmol) was added and the mixture was stirred for 30 min. The resulting Vilsmeier complex was then added to a solution of bisphenol **21d** (25 mg, 0.05 mmol) in CH_2Cl_2 (1.0 mL) and stirred for 1 h. The mixture was subsequently quenched with water and extracted with EtOAc (3 mL × 3). The combined organic layers were dried over Na_2SO_4. Removal of the solvent followed by chromatography (hexanes:EtOAc = 4:1) provided a yellow oil (9.4

mg) in 58% yield; ^{1}H NMR (500 MHz, $CDCl_3$) δ 12.38 (s, 2H), 10.25 (s, 2H), 5.64 (s, 2H), 2.23 (td, *J* = 6.9, 2.3 Hz, 4H), 2.17 (s, 6H), 1.32-1.10 (m, 16H), 0.86 (t, *J* = 7.2 Hz, 6H); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 195.4, 163.4, 160.3, 129.0, 116.0, 114.6, 113.0, 102.3, 73.9, 31.3, 28.35, 28.29, 22.6, 19.6, 14.1, 7.9; IR (neat) 3492, 3055, 2931, 2306, 2222, 1739, 1421, 1265, 739 cm^{-1}; HRMS (ESI-TOF) *m/z*: [M+H]$^+$ Calcd for $C_{32}H_{39}O_6$ 519.2747; found 519.2748.

2,4-Dihydroxy-3-methyl-6-(oct-1-yn-1-yl)benzaldehyde ***(33a)****.* Following the same procedure as **31e** for 30 min using **12** (50 mg, 0.22 mmol), the product was obtained as a white solid (14 mg, 0.053 mmol) in 24% yield after chromatography (hexanes:EtOAc = 4:1): ^{1}H NMR (300 MHz, $CDCl_3$) δ 12.31 (s, 1H), 10.20 (s, 1H), 6.49 (s, 1H), 4.85 (s, 1H), 2.44 (t, *J* = 7.0 Hz, 2H), 2.10 (s, 3H), 1.62-1.57 (m, 2H), 1.44-1.41 (m, 2H), 1.37-1.31 (m, 4H), 0.92-0.88 (m, 3H); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 195.6, 163.2, 160.9, 127.7, 114.6, 112.5, 111.7, 97.7, 76.0, 31.4, 28.8, 28.6, 22.7, 19.7, 14.2, 7.3; IR (neat) 3565, 3055, 2930, 2305, 1620, 740 cm^{-1}; HRMS (ESI-TOF) *m/z*: [M−H]$^+$ Calcd for $C_{16}H_{19}O_3$ 259.1340; found 259.1344

(S)-7-(2-Formyl-3,5-dihydroxy-4-methylphenyl)hept-6-yn-2-yl acetate ***(33b)****.*[4] Following the same procedure as **31d** for 30 min using **28d**, the product was obtained as yellow oil (601 mg) in 85% yield after chromatography (CH_2Cl_2:EtOAc = 20:1): R_f = 0.68 (CH_2Cl_2:EtOAc = 10:1); $[\alpha]_D^{22}$ = +9.3 (c 1.85, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 12.25 (s, 1H), 10.15 (s, 1H), 6.50 (s, 1H), 5.83 (s, 1H), 4.95-4.98 (m, 1H), 2.45 (t, *J* = 7.0 Hz, 2H), 2.09 (s, 3H), 2.06 (s, 3H), 1.57-1.78 (m, 4H), 1.24 (d, *J* = 6.0 Hz, 3H); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 195.1, 171.9, 163.1, 161.5, 127.0, 114.2, 112.5, 112.1, 96.2, 76.5, 71.0, 35.1, 24.4, 21.5, 19.9, 19.4, 7.3; IR (neat) 3250, 2933, 1732, 1703, 1614, 1487, 1432, 1368, 1305, 1248, 1174, 1139, 1107, 1080, 1046, 1023, 848 cm^{-1}; HRMS (ESI-TOF) *m/z*: [M+Na]$^+$ Calcd for $C_{17}H_{20}O_5Na$ 327.1208; found 327.1202

3-Hexyl-7-hydroxy-7-methyl-6H-isochromene-6,8(7H)-dione ***(34a)****.* An oven-dried round bottom flask was charged with **33a** (25 mg, 0.096 mmol) and $Au(OAc)_3$ (2.0 mg, 0.0048 mmol). The mixture was dissolved in 1,2-dichloroethane (0.70 mL), followed by trifluoroacetic acid (50 μL). The resulting mixture was stirred for 1 min at rt and then, 2-iodoxybenzoic acid (60 mg, 0.22 mmol) and tetrabutylammonium iodide (1.8 mg, 4.9 μmol) were added. The mixture was stirred for 1 h and quenched with satd NaS_2O_3 (10 mL). The resultant mixture was extracted with EtOAc (10 mL x 3) and the combined organic layers were washed with brine. The solution was dried over Na_2SO_4 and filtered. Chromatography (hexanes:EtOAc = 1:1) afforded a brown oil (27 mg) in 95% yield: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.87 (s, 1H), 6.90 (s, 1H), 5.49 (s, 1H), 3.95 (br s, 1H), 2.40 (t, *J* = 11.5 Hz, 2H), 1.52 (s, 3H), 1.33-1.22 (m, 8H), 0.87 (t, *J* = 6.7 Hz, 3H); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 196.5, 196.0, 163.3, 153.2, 144.4, 115.9, 108.5, 105.1, 83.6, 33.3, 31.5, 28.7, 28.6, 26.8, 22.6, 14.1; IR (neat) 3432, 3073, 2929, 1718, 1630, 1453, 1137, 858 cm^{-1}; HRMS (ESI-TOF) *m/z*: [M+H]$^+$ Calcd for $C_{16}H_{21}O_4$ [M+H]$^+$ 277.1440; found 277.1443

(2S)-5-(7-Hydroxy-7-methyl-6,8-dioxo-7,8-dihydro-6H-isochromen-3-yl)pentan-2-yl acetate ***(34b)****.*[4] An oven-dried round bottom flask was charged with **33b** (445 mg, 1.46 mmol) and $Au(OAc)_3$ (27 mg, 0.07 mmol) or AgOTf (38 mg, 0.15 mmol). The mixture was dissolved in 1,2-dichloroethane (7.3 mL), followed by trifluoroacetic acid (0.73 mL). The resulting mixture was stirred for 15 min at rt and then, 2-iodoxybenzoic acid (1.23 g, 4.39 mmol) and tetrabutylammonium iodide (27 mg, 0.07 mmol) were added. The mixture was stirred for 1.5 h and quenched with satd NaS_2O_3 (10 mL). The resultant mixture was extracted with EtOAc (10 mL X 3) and the combined organic layers were washed with brine. The solution was dried over Na_2SO_4 and filtered. Removal of the solvent was followed by chromatography (Hex:EtOAc = 1:2) afforded a red brown oil (379 mg) in 81% yield from the $Au(OAc)_3$ reaction (AgOTf gave 71%): R_f = 0.44 (100 % EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.85 (s, 1H), 6.10 (s, 1H), 5.49 (s, 1H), 4.89-4.92 (m, 1H), 3.93 (br s, 1H), 2.39-2.43 (m, 2H), 2.01 (s, 3H), 1.54-1.68 (m, 4H), 1.52 (s, 3H), 1.21 (d, *J* = 6.5 Hz, 3H); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 196.3, 195.8, 170.7, 162.2, 152.9, 143.9, 115.9, 108.6, 105.3, 83.5, 70.1, 35.1, 32.9, 28.5, 22.5, 21.3, 20.0; IR (neat) 3441, 2977, 2934, 1718, 1665, 1621, 1548, 1443, 1371, 1346, 1242, 1214, 1169, 1133, 1077, 1047, 1020, 963, 907 cm^{-1}; HRMS (ESI-TOF) *m/z*: [M+H]$^+$ Calcd for $C_{17}H_{21}O_6$ 321.1338; found 321.1333

3-Hexyl-7-methyl-6,8-dioxo-7,8-dihydro-6H-isochromen-7-yl acetate ***(35a)****.* An oven-dried round bottom flask was charged with **33a** (25 mg, 0.096 mmol) and $Au(OAc)_3$ (2.0 mg, 0.0048 mmol). The mixture was dissolved in 1,2-dichloroethane (0.70 mL), followed by trifluoroacetic acid (50 μL). The resulting mixture was stirred for 1 min at rt and then, the mixture was diluted in 1,2-dichloroethane (5.3 mL) under an argon atmosphere. $Pb(OAc)_4$ (55 mg, 0.125 mmol) was added in three portion over 15 min. The mixture was stirred for 1 h and quenched with cold water (5 mL). The resultant mixture was extracted with CH_2Cl_2 (5 mL x 3). The combined organic layers were dried over $MgSO_4$. Chromatography (100% CH_2Cl_2) afforded a brown oil (17 mg) in 55% yield: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.87 (s, 1H), 6.08 (s, 1H), 5.50 (s, 1H), 2.39 (m, 2H), 2.16 (s, 3H), 1.60 (m, 2H), 1.52 (s, 3H), 1.36-1.25 (m, 6H), 0.90 (t, *J* = 6.7 Hz, 3H); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 193.5, 192.8, 170.2, 162.6, 154.1, 142.0, 115.3, 108.7, 106.9, 84.5, 33.2, 31.5, 28.7, 26.6, 22.6, 22.4, 20.3, 14.1; HRMS (ESI-TOF) *m/z*: [M+H]$^+$ Calcd for $C_{18}H_{23}O_5$ 319.1545; found 319.1546.

(2S)-5-(7-Acetoxy-7-methyl-6,8-dioxo-7,8-dihydro-6H-isochromen-3-yl)pentan-2-yl acetate ***(35b)****.*[4] Alcohol **34b** was subject to the same procedure used for **26d** at –78 °C for 10 min with Et_3N as the base. The product was obtained as a red brown oil (379 mg) in 89% yield after chromatography (hexanes:EtOAc = 1:1): R_f = 0.43 (hexanex:EtOAc = 1:2): ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.82 (d, *J* = 1.0 Hz, 1H), 6.06 (s, 1H), 5.46 (d, *J* = 1.0 Hz, 1H), 4.86-4.89 (m, 1H), 2.36-2.39 (m, 2H), 2.10 (s, 3H), 1.99 (s, 3H), 1.49-1.63 (m, 4H), 1.47 (s, 3H), 1.18 (d, *J* = 6.5 Hz, 3H); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 193.2, 192.6, 170.6, 169.9, 161.6, 153.8, 142.5, 115.2, 108.9, 106.9, 84.4, 70.0, 35.0, 32.7, 22.4, 22.2, 21.3, 20.1, 19.9; IR (neat) 2940, 1716, 1669, 1634, 1592, 1553, 1446, 1370, 1343, 1308, 1243, 1181, 1132, 1088, 1045, 1019, 975, 939 cm^{-1}; HRMS (ESI-TOF) *m/z*: [M+H]$^+$ Calcd for $C_{19}H_{23}O_7$ 363.1444; found 363.1463

3,3'-Dihexyl-7,7'-dihydroxy-7,7'-dimethyl-6H,6'H-[5,5'-biisochromene]-6,6',8,8'(7H,7'H)-tetraone ***(34a-dimer)****.* Following the same procedure as **34a** with **31e** (75 mg, 0.145 mmol), the product was obtained as an orange oil (67 mg, dr = 1:1) in 83% yield after chromatography (hexanes:EtOAc = 1:2): ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.94 (s, 2H), 5.68 (s, 2H), 3.92 (s, 2H), 2.37 (m, 4H), 1.72 (s, 6H), 1.28-1.25 (m, 16H), 0.88 (t, *J* = 6.5 Hz,

6H); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 195.7, 195.0, 163.8, 152.6, 141.4, 116.4, 109.5, 106.7, 84.2, 33.7, 31.5, 29.8, 28.8, 27.0, 22.6, 14.1; IR (neat) 3375, 3060, 2927, 1716, 1624, 1263, 1136, 738 cm^{-1}; HRMS (ESI-TOF) *m/z*: $[M+H]^+$ Calcd for $C_{32}H_{39}O_8$ 551.2646; found 551.2625.

*(7S,7'S)-3,3'-Bis((S)-4-acetoxypentyl)-7,7'-dimethyl-6,6',8,8'-tetraoxo-7,7',8,8'-tetrahydro-6H,6'H-[5,5'-biisochromene]-7,7'-diyl diacetate (**37**).*[4] To **31d** (244 mg, 0.40 mmol) and AgOTf (10 mg, 0.04 mmol) were added 1,2-dichloroethane (4 mL) and trifluoroacetic acid (0.2 mL) addition. The resulting mixture was stirred for 1.5 h at rt and then, 2-iodoxybenzoic acid (676 mg, 2.41 mmol) and tetrabutylammonium iodide (7.4 mg, 0.02 mmol) were added. The mixture was stirred for an additional 18 h, followed by quenching with satd NaS_2O_3 (8 mL). The resultant mixture was extracted with EtOAc (10 mL × 3). The combined organic layers were washed with brine and dried over Na_2SO_4. Chromatography (hexanes:EtOAc = 1:2 to 1:5) afforded one separable isomer **36a** and mixture of two isomers **36b/36c** (1:1). Both fractions were contaminated with IBX byproducts.

Without further purification, the pure isomer **36a** (0.13 mmol) was dissolved in CH_2Cl_2 (7 mL) and the mixture was cooled to –78 °C. To the solution was added Ac_2O (76 mL, 0.80 mmol), 4-(dimethylamino)pyridine (33 mg, 0.27 mmol), and Et_3N (75 mL, 0.54 mmol). After stirring 15 min, the solution was quenched with 1*N* HCl (2 mL) in an ice bath. The resulting mixture was extracted with CH_2Cl_2 (10 mL × 3). The combined organic layers were washed with brine and dried over Na_2SO_4. Chromatography (hexanes:EtOAc = 1:1) gave the product as orange oil (64 mg) in 22% yield over three steps: R_f = 0.52 (hexanes:EtOAc = 1:2); $[\alpha]_D^{22}$ = –11.5 (*c* 0.24, CH_2Cl_2); ^1H NMR (500 MHz, $CDCl_3$) δ 7.92 (s, 2H), 5.95 (s, 2H), 4.84-4.90 (m, 2H), 2.35 (t, *J* = 7.0 Hz, 4H), 2.16 (s, 6H), 2.01 (s, 6H), 1.48-1.66 (m, 14H), 1.20 (d, *J* = 6.5 Hz, 6H); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 193.5, 190.7, 170.8, 170.5, 162.4, 153.7, 141.9, 115.6, 110.6, 107.8, 84.9, 70.4, 35.2, 33.2, 22.4, 22.3, 21.5, 20.4, 20.0; IR (neat) 2936, 1730, 1715, 1631, 1582, 1528, 1431, 1371, 1335, 1244, 1131, 1087, 1022, 985, 936 cm^{-1}; HRMS (ESI-TOF) *m/z*: $[M+H]^+$ Calcd for $C_{38}H_{43}O_{14}$ 723.2653; found 723.2661.

*(7S,7'S)-3,3'-bis((S)-4-hydroxypentyl)-7,7'-dimethyl-6,6',8,8'-tetraoxo-7,7',8,8'-tetrahydro-6H,6'H-[5,5'-biisochromene]-7,7'-diyl diacetate (**38**).*[4] Compound **37** (24 mg, 0.03 mmol) was dissolved in THF (0.66 mL) in a microwave vial under an argon atmosphere. Freshly distilled $Ti(O\textit{i}\text{-}Pr)_4$ (0.10 mL, 0.33 mmol) added to the mixture and the vial was sealed. The resultant mixture was stirred at 50 °C for 24 h in an oil bath. After cooling to ambient temperature, the reaction mixture was diluted with EtOAc (50 mL) and washed with satd Na_2SO_4 until the organic phase became clear. The combined aqueous layers were back-extracted with EtOAc (5 mL). The combined organic layers were washed with brine and dried over $MgSO_4$. Chromatography (hexanes:EtOAc = 1:5 to 100 % EtOAc) afforded yellow oil (11 mg) in 52% yield: R_f = 0.13 (hexanes:EtOAc = 1:2); $[\alpha]_D^{22}$ = +14.3 (*c* 0.22, CH_3OH); ^1H NMR (500 MHz, $CDCl_3$) δ 7.93 (s, 2H), 5.97 (s, 2H), 3.75-3.81 (m, 2H), 2.39 (t, *J* = 7.5 Hz, 4H), 2.17 (s, 6H), 1.68-1.77 (m, 2H), 1.54-1.62 (m, 10H), 1.42-1.47 (m, 4H), 1.17 (d, *J* = 6.2 Hz, 6H); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 193.4, 190.6, 170.9, 162.9, 153.9, 142.1, 115.6, 110.4, 107.7, 85.2, 67.6, 38.2, 33.0, 23.5, 22.49, 22.47, 20.5; IR (neat) 3463, 2924, 1713, 1663, 1629, 1582, 1525, 1432, 1372, 1247, 1183, 1132, 1086, 986, 937, 875 cm^{-1}; HRMS (ESI-TOF) *m/z*: $[M+H]^+$ Calcd for $C_{34}H_{39}O_{12}$ 639.2442; found 639.2450.

*Chaetoglobin A (**1**).*[4] Compound **38** (9.0 mg, 0.01 mmol) in CH_2Cl_2 (0.28 mL) was treated with NH_4OAc (22 mg, 0.28 mmol) and stirred for 20 h at room temperature. Removal of the solvent followed by chromatography (CH_2Cl_2:MeOH = 9:1) afforded an orange red gum (8.6 mg) in 96% yield: R_f = 0.10 (CH_2Cl_2:CH_3OH = 10:1); $[\alpha]_D^{22}$ = +478.4 (*c* 0.10, CH_3OH); ^1H NMR (500 MHz, CD_3OD) δ 8.00 (s, 2H), 6.37 (s, 2H), 3.67-3.73 (m, 2H), 2.45 (t, *J* = 7.5 Hz, 4H), 2.15 (s, 6H), 1.63-1.72 (m, 4H), 1.60 (s, 6H), 1.39-1.45 (m, 4H), 1.12 (d, *J* = 6.2 Hz, 6H); $^{13}C\{^1H\}$ NMR (125 MHz, CD_3OD) δ 198.0, 189.9, 172.0, 153.2, 151.3, 139.7, 116.9, 116.1, 104.0, 86.0, 68.1, 39.2, 34.1, 25.5, 23.6, 23.4, 20.6; IR (neat) 3383, 2928, 1732, 1692, 1643, 1547, 1465, 1373, 1248, 1206, 1130, 1081, 994 cm^{-1}; HRMS (ESI-TOF) *m/z*: $[M+H]^+$ Calcd for $C_{34}H_{41}N_2O_{10}$ 637.2761; found 637.2775.

ASSOCIATED CONTENT

Data Availability Statement.

The data underlying this study are available in the published article and its Supporting Information.

Supporting Information.

General experimental and copies of NMR spectra (pdf)

This material is available free of charge via the Internet at http://pubs.acs.org.

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ACKNOWLEDGMENT

We are grateful to the NSF (CHE2102626) and the NIH (R35 GM131902, RO1 GM112684) for financial support of this research. Partial instrumentation support was provided by the NIH and NSF (1S10RR023444, 1S10RR022442, CHE-0840438, CHE-0848460, 1S10OD011980, CHE-1827457). Drs. Rakesh Kohli and Charles W. Ross III (UPenn) are acknowledged for obtaining HRMS data. We thank Prof. Virgil Percec and Benjamin Partridge (UPenn) for assistance with CD measurements. We are grateful to Dr. Patrick Carroll for assistance with crystallographic structures. We are grateful to Hanna Roenfanz and Cameron Berlin (UPenn) for assistance in rescanning NMR spectra and resubmitting accurate mass samples.

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