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A Common C_2-Symmetric 2,2′-Biphenol Building Block and its Application in the Synthesis of (+)-di-*epi*-Gonytolide A

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Abstract: A variety of biaryl polyketides exhibit remarkable bioactivities. However, their synthetic accessibility is often challenging. Herein, the enantioselective preparation and synthetic application of an axially chiral 2,2′-biphenol building block is outlined that represents a common motif of these intriguing natural products. Based on the highly regioselective and scalable bromination of a phenol precursor, a coupling process by Lipshutz cuprate oxidation was developed. A copper-mediated deracemization strategy proved to be superior to derivatization or kinetic resolution approaches. Key steps in the overall building block synthesis were rationalized through DFT studies. Utilizing the 2,2′-biphenol, a highly diastereoselective five step synthesis of formerly unknown (+)-di-*epi*-gonytolide A was developed, thus showcasing the building block's general potential for the synthesis of natural products and their derivatives. En route, the first enantioselective construction of a chromone dimer intermediate was established.

Introduction

Aromatic polyketides represent a structurally highly diverse class of natural products produced by fungi, bacteria, and plants.[1] Among the variety of late-stage tailoring transformations that nature uses to expand their chemical space, dimerization reactions have received increasing attention over the last two decades.[2] Along with non-biaryl representatives, these oxidative coupling processes form structurally intriguing biaryl compounds that exhibit a remarkable range of clinically relevant bioactivities and are often more potent than their monomeric counterparts.[3] The binaphtho-α-pyranone[4] viriditoxin for instance shows antibacterial activity against drug-resistant bacterial pathogens[5] as well as potent antitumor activities, which were also found for a variety of binaphtho-γ-pyranones[6] such as ustilaginoidin A (Figure 1A).[7] Further examples include the antifeedant bicoumarin isokotanin A[8] or the more complex tetrahydroxanthone dimer[9] rugulotrosin A[10] and chromanone lactone dimer[11] gonytolide A[3b] that

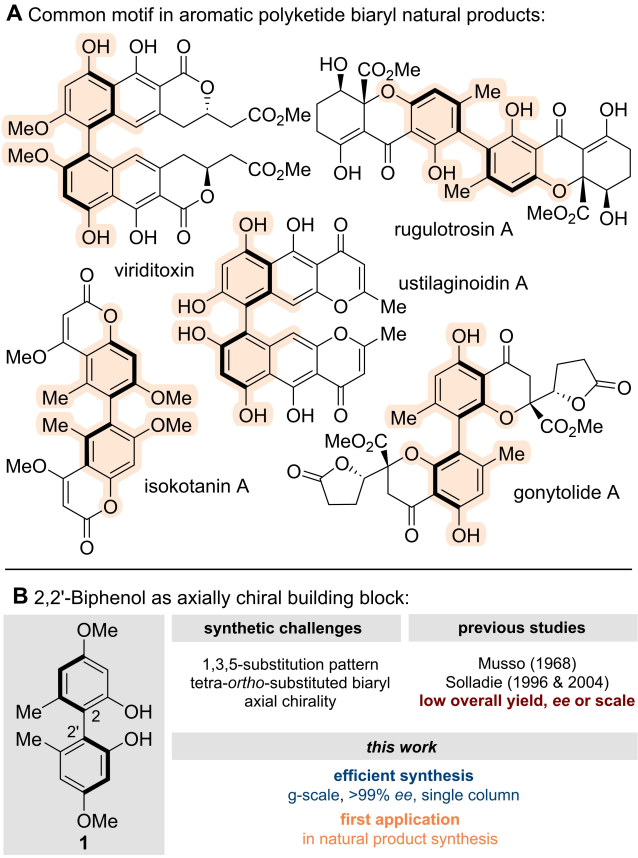

Figure 1. A 2,2′-biphenol as common motif building block for the synthesis of aromatic polyketide dimer natural products and their derivatives.

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feature antibacterial and immuno-stimulating activities, respectively. In many of these dimeric polyketides, rotation around the biaryl axis is hindered, which causes the corresponding molecules to be axially chiral. This phenomenon of atropisomerism[12] has found growing interest among medicinal chemists in recent times[13] highlighting the impact of natural product structures on drug development.[14] However, from a synthetic point of view,[15] the construction of the stereogenic axis is a major challenge due to its inherently crowded nature, which is exemplified by the lack of well-established atropselective coupling[16] or resolution[17] methods that are broadly applicable. Hence, there is no general solution for the construction of bioactive molecules featuring a stereogenic axis. Still, for certain targets tailor-made and remarkable solutions have been developed. Often, the stereogenic axis is introduced by a late-stage biaryl coupling.[18] The atropselectivity of these methods, however, commonly relies on specific carbon scaffolds, substitution patterns or coordinating groups. In other cases, the atropselectivity of the coupling step depends on a stereoinduction by chiral monomeric precursors, which is difficult to anticipate. To avoid these uncertainties, alternative strategies seek to establish the axial configuration early on by using hindered biaryl intermediates in the initial stages of the synthesis.[19] While these strategies eliminate atropselectivity concerns, the intermediates used are often highly specialized and require lengthy auxiliary chemistry or tedious chromatographic separations and functional group interconversions. This can limit their scalable preparation and general applicability. Therefore, a readily accessible axially chiral biaryl with a common substitution pattern would be a valuable building block. It would not only provide control over the axial configuration, but also enable more modular synthetic approaches. This, in turn, should allow for an efficient synthesis of biaryl polyketides and their analogues.

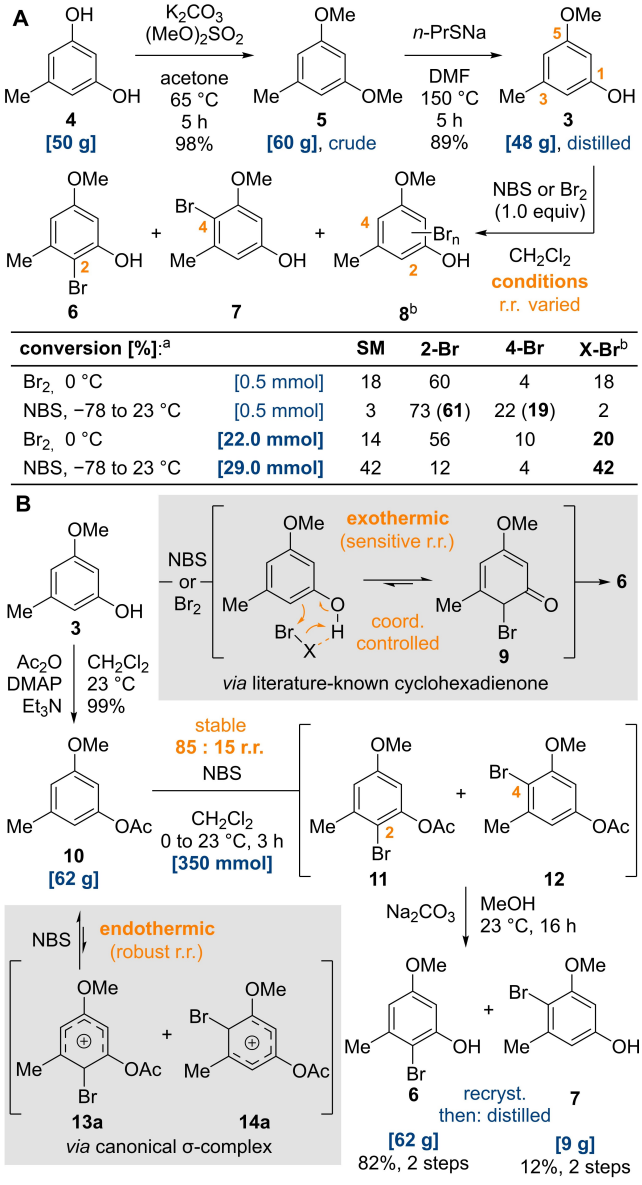
The specific biaryl suggested is 2,2′-biphenol **1** (Figure 1B), which represents a common 1,1′,5,5′-tetraoxy-3,3′-dicarbo-2,2′-biaryl motif that can be found in a variety of aromatic polyketide dimers (Figure 1A). Indeed, biphenol **1** is known by seminal work of Musso since the late 1960 s[20] and later syntheses by Solladie.[21] However, considering our intended use, the reported synthetic routes suffer from insufficient overall yield, scalability or enantiomeric excess. In consequence, no application of 2,2′-biphenol **1** in the field of natural product synthesis is known to date.

Results and Discussion

Three structural features of 2,2′-biphenol **1** have been identified as key challenges for an efficient synthesis: (a) the 1,3,5-substitution pattern, (b) the tetra-*ortho*-substituted biaryl bond, and (c) the axial configuration. The substitution pattern was established early in the synthesis. This should avoid lengthy, and potentially harsh functional group interconversions that could potentially deteriorate the overall yield or enantiomeric excess of biphenol **1** at a late stage. The atropselective construction of the stereogenic axis was divided into a coupling and resolution step. This division aimed to overcome challenges related to steric crowding and enantioselectivity in an independent manner. Herein, our optimized route to 2,2′-biphenol **1** is outlined and its first application as dimeric polyketide building block is showcased in the selective and efficient preparation of (+)-2′,11-di-*epi*-gonytolide A (**2**).

Bromophenol synthesis

The monomeric unit of 2,2′-biphenol **1**, 3-methyl-5-methoxy phenol (**3**) was synthesized starting from low-cost orcinol (**4**) in two steps (Scheme 1A). First, dimethyl orcinol **5** was obtained in



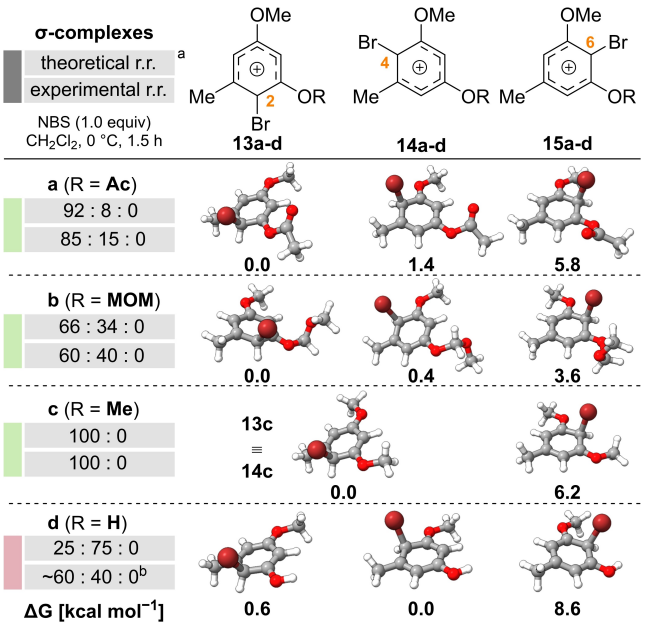
Scheme 1. Synthesis and bromination of unprotected phenol **3** (**A**); robust and scalable preparation of 2-bromophenol **6** enabled by a transient acetyl protection likely leading to a change in mechanism (**B**). [a] Ratios determined by ^{1}H-NMR analysis; used to derive regioisomeric ratios (r.r.). [b] Most prominently 2,4-dibromophenol.

98% yield through permethylation using dimethyl sulfate. Subsequently, the arene was efficiently desymmetrized by selective monodemethylation with sodium *n*-propyl thiolate, possibly facilitated by the intermediate sodium phenolate's reduced electrophilicity. Distillation afforded phenol **3** in 89% yield on a 50 g-scale.[22]

To enable a regioselective coupling of the monomeric unit **3**, typical bromination conditions were investigated. When treated with elemental bromine or *N*-bromosuccinimide (NBS) on small scales of 0.5 mmol, phenol **3** was predominately brominated in the 2-position and 2-bromophenol **6** could be isolated in up to 61% yield.[23] In addition, 4-bromophenol **7** and other brominated arenes **8** were formed as side products. However, upon scaling (up to 29 mmol phenol **3**), the observed regioisomeric ratios (r.r.) generally varied and a marked increase in the formation of side products **8** was observed (most prominently 2,4-dibromination, up to 42%, see Table SI-2). Separation of these side products was challenging, thereby impeding the reproducible isolation of desired 2-bromophenol **6** in larger amounts.

The bromination of free phenols proceeds via cyclohexadienone intermediates **9**.[24] These intermediates are thought to be formed in a concerted and exothermic manner after electrophile coordination by the phenolic alcohol (Scheme 1B, upper gray box). This results in a kinetically controlled *ortho*-selectivity, which is in accordance with the predominant 2-bromination of phenol **3**. Hence, the lack of robustness and selectivity observed during scaling may be attributed to the concentration dependency of the initial coordination, along with the exothermic nature of the selectivity-determining bromination step. Consequently, the protection of the hydroxy group was reasoned to enhance the overall robustness, chemo- and regioselectivity. After simple ester formation using acetic anhydride, phenol acetate **10** was selectively monobrominated to 2-bromo- (**11**) and 4-bromoacetate **12** with a highly reproducible and improved r.r. of 85:15 (Scheme 1B). Methanolysis yielded a mixture of regioisomers **6** and **7** which were easily separated and purified due to the absence of any side products **8**. Repetitive recrystallization and distillation of the concentrated mother liquor provided desired 2-bromophenol **6** on a 60 g-scale in an useful overall yield of 82%.

The improved control in regioselectivity was attributed to a change in mechanism towards a canonical S_EAr pathway. This likely involved the initial endothermic formation of the 2-bromo and 4-bromo σ-complex intermediates **13a** and **14a** (Scheme 1B, lower gray box).[25] To validate this hypothesis and explain the protecting group's influence on the selectivity, DFT studies[26] on the theoretical regioisomeric σ-complexes **13**, **14** and **15** were conducted that carry different protecting groups (Scheme 2 and Figures S7–S11).[25,27] Following the Hammond postulate, these should resemble the late transition states of a canonical bromination process. As a result, their energetic difference should match the observed regioselectivities. Indeed, it was found that there is a good correlation between the relative free energies of *O*-acetyl- (**a**), *O*-methoxymethyl (MOM)- (**b**) or *O*-methyl- (**c**) protected σ-complexes and experimental r.r. data. As the protecting group's acceptor ability increases

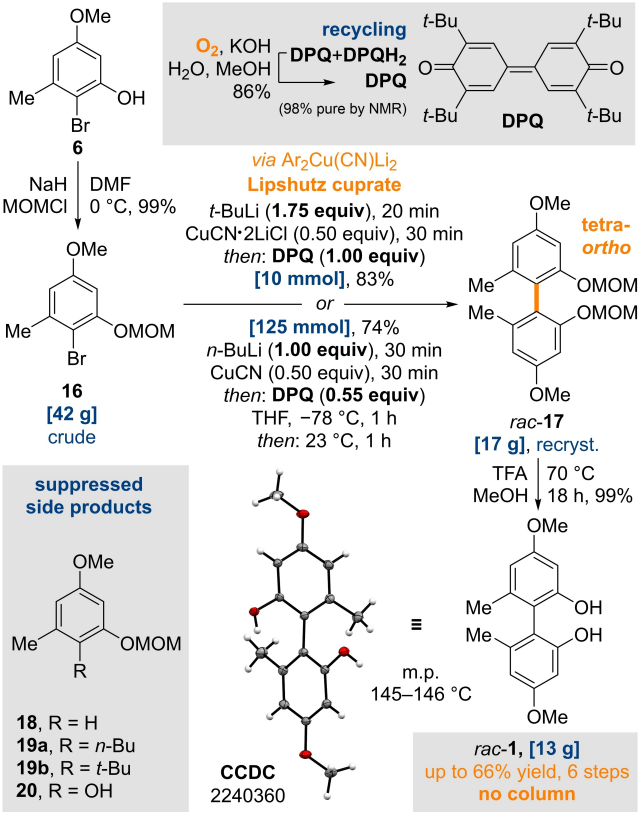


Scheme 2. DFT studies on theoretical regioisomeric σ-complexes validated the hypothesized change in mechanism. [a] Experimental data for the bromination of (protected) phenols at the indicated conditions; calculations were performed at the M06-2X/def2-TZVPP/C-PCM(CH_2Cl_2)//r^{2}SCAN-3c/C-PCM(CH_2Cl_2) level of theory.[26] [b] Regioisomeric ratios (r.r.) varied and the formation of over-brominated products was observed.

(from methyl to MOM to acetyl), a more pronounced energetic differentiation of the 2- and 4-position was predicted which was in perfect agreement with the observed regioselectivities. The corresponding 6-bromo intermediates **15a–c** were significantly disfavored and generally not observed experimentally. In contrast, for the free phenol intermediates **13d**, **14d** and **15d** the theoretical ratios deviate qualitatively from the experimental results, which is in line with the suggested change in mechanism.

Homocoupling

With 2-bromophenol **6** in hand, we turned towards the development of an efficient protocol for the challenging formation of the tetra-*ortho*-substituted biaryl axis. After protection, *O*-MOM-bromophenol **16** was subjected to various homocoupling conditions. While simple Ullmann coupling as well as halogen-metal exchange of the electron-rich arene using Grignard reagents[28] failed, treatment with *n*-butyllithium followed by oxidation with iron(III) chloride[19i] led to an initial formation of *O*-MOM-diprotected 2,2′-biphenol **17** in 9% yield (Table S4, Figure S22 for X-ray structure, CCDC 2240361). However, predominant formation of protodehalogenated side product **18** and minor amounts of butylated side product **19a** were observed. Ultimately, oxidation of a higher order biaryl Lipshutz cuprate[29] turned out to be particularly suited for the construction of the crowded biaryl bond (Scheme 3).



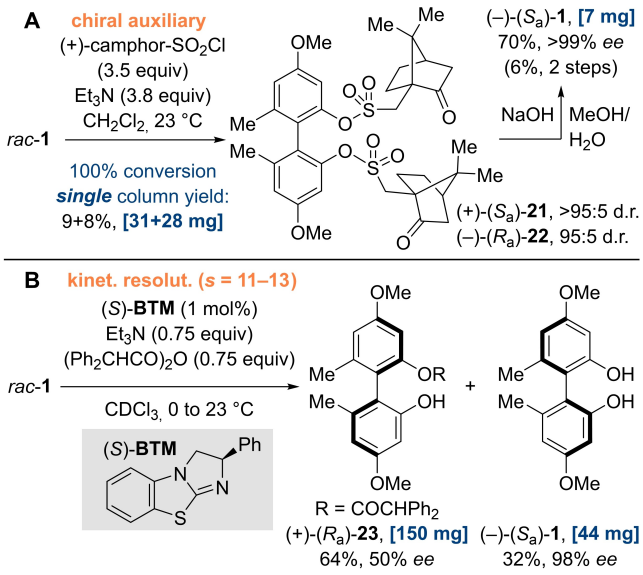
Scheme 3. Optimized homocoupling for the column-free synthesis of tetra-*ortho*-substituted 2,2′-biphenol **1** on a decagram scale. The use of recovered **DPQ** resulted in an identical reaction outcome; the X-ray structure (CCDC 2240360) is shown as ORTEP at 50% probability.

The di-lithium cyano cuprate $Ar_2Cu(CN)Li_2$ was formed by a halogen-metal exchange of bromide **16** with *tert*-butyllithium followed by the addition of 0.5 equivalents of a copper(I) cyanide di-lithium chloride solution. While the literature-described direct treatment of this cuprate with molecular oxygen[29] produced phenol **20** as major side product, the use of readily available tetra-*tert*-butyldiphenoquinone (**DPQ**) as alternative oxidant yielded biaryl **17** in 83% yield. Though quinones are known oxidants for such copper-mediated homocouplings,[30] the particular combination of a Lipshutz cuprate with **DPQ**[28] is, to the best of our knowledge, a new reagent combination and might be generally useful for the construction of sterically demanding biaryl bonds. Scaled reaction conditions employing up to 125 mmol starting material used *n*-butyl- instead of *tert*-butyllithium due to safety considerations and showed only slightly diminished yields of 74%. Additional modifications of the scaled conditions included the use of crude starting material, solid copper cyanide as well as reduced amounts of organolithium reagent and diquinone oxidant. Furthermore, the biaryl product was isolated by recrystallization and reoxidation of the hydrodiquinone by-product $\mathbf{DPQH_2}$ under alkaline conditions could be used to regenerate **DPQ** in 86% yield. Subsequent deprotection of **17** with trifluoracetic acid in methanol yielded the desired tetra-*ortho*-substituted 2,2′-biphenol **1** on a decagram scale. In total, starting from monophenol **3**,[22] yields of up to 66% over six steps were obtained without the need for column chromatographic purification or precious transition metals.

Resolution and deracemization

For the resolution of racemic **1**, we strategically utilized its 2,2′-diol motif. In search for an efficient process, various methods have been evaluated.

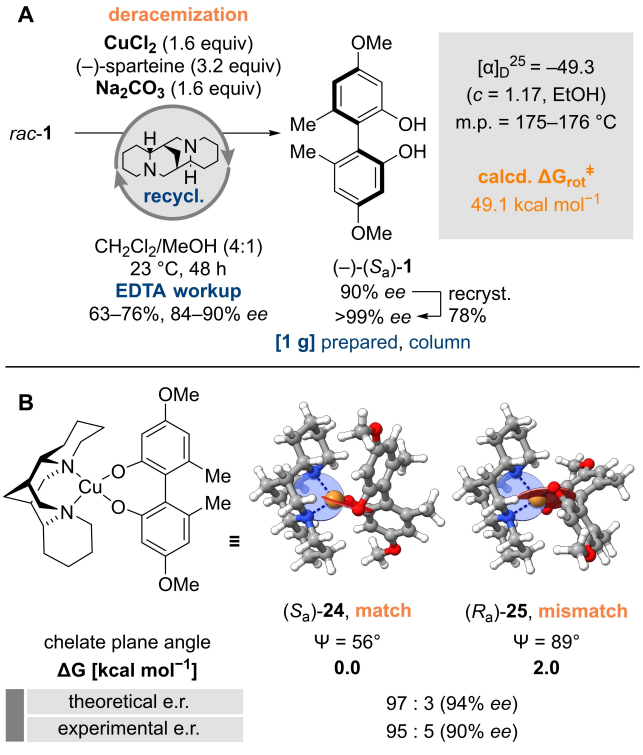
Initially, a classic derivatization approach was investigated using (+)-camphorsulfonyl chloride as chiral auxiliary (Scheme 4A).[31] After clean diester formation, the resulting pair of diastereomeric sulfonates (S_a)-**21** and (R_a)-**22** was subjected to a single column chromatographic isolation, resulting in an incomplete separation and yields of 9% and 8%, respectively. While the subsequent hydrolysis of **21** proceeded cleanly and enantiomerically pure (S_a)-biphenol **1** was obtained successfully, the overall practicality was limited by the inefficient and laborious chromatographic separation. Subsequently, a recently established kinetic resolution method for biaryl-2,2′-diols was examined.[32] Birman's (*S*)-benzotetramisole (**BTM**) catalyst was used in an enantioselective monoacylation of racemic **1** using diphenylacetic anhydride as acyl donor (Scheme 4B). The reaction yielded (S_a)-biphenol **1** and (R_a)-monoester **23** in 32% and 64% with 98% *ee* and 50% *ee*, respectively. The moderate selectivity factor[33] *s* of 11–13 for biphenyl **1** may not be unexpected, as the applied as well as other known resolution methods for atropisomers are optimized for arguably less challenging binaphthyl systems.[17b,32,34] While the overall scale and efficacy could be increased relative to the derivatization approach, the methodology still lacked sufficient practicality for a building block synthesis.



Scheme 4. Atropenantiomer resolution by 'chiral derivatization'-chromatographic separation (**A**) or kinetic resolution (**B**); the methods yielded highly enantioenriched (−)-(S_a)-2,2′-biphenol **1** but showed limited efficacy.

Consequently, we turned towards a copper-mediated deracemization approach that should have the advantage of inherently higher yields and was originally developed for the enantioselective synthesis of BINOL-type ligand scaffolds[35] as well as more recently applied in total synthesis.[36] The method involves formation of diastereomeric sparteine copper(II) complexes with chiral biaryl-2,2′-diols. These complexes enable an epimerization of the biaryl axis and result in an accumulation of one atropenantiomer by favoring the thermodynamically more stable complex with a matching axial configuration relative to the rigid chiral diamine ligand. The deracemization method was successfully transferred to 2,2′-biphenol **1** (Scheme 5A).

Reproducibility and stable yields were ensured by formation of the diastereomeric (−)-sparteine copper(II) biphenol complexes (S_a)-**24** and (R_a)-**25** from copper(II) chloride[35a] rather than *in-situ* oxidized copper(I) chloride.[35c] Addition of sodium carbonate as auxiliary base was needed to keep enantiomeric excesses stable and is thought to prevent protonation of the chiral amine ligand by the additionally released equivalent of hydrogen chloride.[35d] Complex hydrolysis after 48 h at 23 °C yielded (S_a)-**1** in up to 76% yield and 90% *ee*. As electron-rich and bidentate 2,2′-biphenol **1** was found to be sensitive to oxidation in the presence of residual copper during the quenching process, a workup using hexadentate ethylenediaminetetraacetic acid (EDTA) was developed, that prevented post-reaction product degradation. Additionally, it allowed an effortless acid-base extraction of sparteine that could be reisolated in 93% yield after column chromatography. Alternatively, crude sparteine could be used directly in another deracemization reaction with only slight effects on the final enantiomeric excess of biphenol **1** (84% *ee* after second reuse). Recycling (−)-sparteine in this batch-wise manner resulted in the preparation of (−)-(S_a)-2,2′-biphenol **1** on a gram scale and with >99% *ee* after additional recrystallization (78% mass recovery). Besides HPLC analyses, the excellent enantiomeric excess of **1** was highlighted by its high specific rotation and an elevated melting point of 175–176 °C relative to the racemate (145–146 °C).[20]



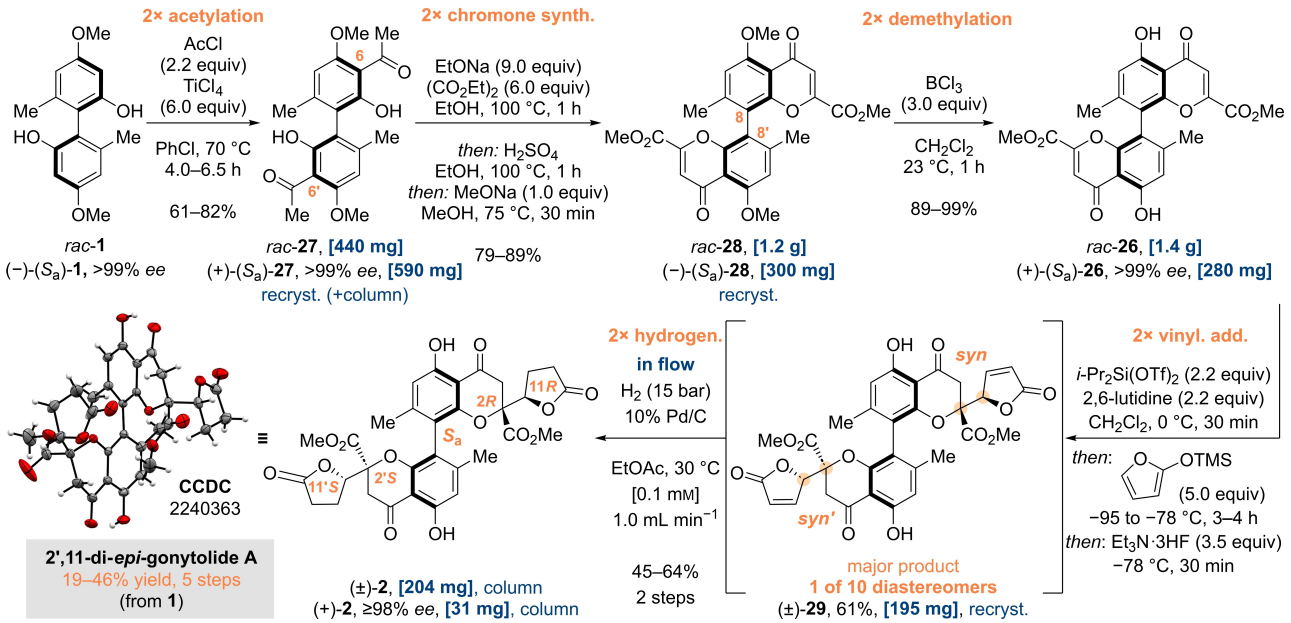
Scheme 5. Single-step preparation of (−)-(S_a)-2,2′-biphenol **1** by a (−)-sparteine/copper(II) mediated deracemization featuring ligand recycling and EDTA workup (**A**); DFT studies on the theoretical diastereomeric complexes (S_a)-**24** and (R_a)-**25** (**B**); Ψ refers to the angle between the two chelate planes (N–Cu–N and O–Cu–O, indicated as blue and red disks); calculations were performed at the M06/def2-QZVP//r^{2}SCAN-3c level of theory.[26]

To understand the thermodynamic factors, which led to the observed stereochemical outcome, corresponding DFT studies[26] were performed (Scheme 5B). Geometries and relative free energies of the theoretical diastereomeric complexes (S_a)-**24** and (R_a)-**25** were calculated. The resulting energetic difference of 2.0 kcal mol^{-1} in favor of the (S_a)-complex with the matched configuration correlated well with the observed equilibrium ratio of 95:5 e.r. after complex hydrolysis. While a more detailed analysis is provided in the Supporting Information, it can be briefly summarized that the cause of the energetic enantio-discrimination likely originates from an increased distortion of the copper(II) ligand sphere from a preferred square planar geometry and a strained biphenol ligand scaffold within mismatched complex (R_a)-**24** relative to (S_a)-**25** (chelate plane angle Ψ indicated in Scheme 5B and Figure S15–S17).[35b,c,36d] Kinetically, the deracemization reaction is believed to be enabled by a single electron transfer from one of the phenol moieties to copper(II), resulting in a copper(I) phenoxyl radical with increased sp^3-character in the 1-position and a thereby reduced rotational barrier of the biphenol ligand.[12b,35d,37] By contrast, the isolated (S_a)-2,2′-biphenol **1** is configurationally stable. Additional DFT studies[26,38] indicated a high thermal rotational barrier of $\Delta G^{\ddagger}_{rot} = 49.1$ kcal mol^{-1} (Figure S4) ensuring stereochemical integrity in subsequent transformations. In combination with the straightforward preparation of racemic material, the single-step resolution process allowed for efficient access to large quantities of enantiopure 2,2′-biphenol **1** in sufficient yields to be of use as a building block.

Application

To exemplify its applicability in the preparation of complex polyketide dimer structures and their derivatives, a synthetic showcase is presented. Starting from biphenol **1**, a concise approach towards a diastereomer of natural chromanone lactone dimer gonytolide A[3b,18e,f,39] via an axially chiral chromone-8,8′-dimer **26** was developed (Scheme 6). It was envisioned that the presence of a stereogenic axis within intermediate **26** could be utilized for a diastereoselective construction of the stereochemical dyads within the chromanone lactone moieties.

Synthesis of chromone dimer **26** commenced with a bidirectional Friedel–Crafts acylation of biphenol **1**. A regioselective



Scheme 6. Application of racemic and enantiopure 2,2′-biphenol building block **1** in the selective synthesis of complex chromanone lactone dimer (+)-2′,11-di-*epi*-goytolide A (**2**). Racemic (±)-**29** could be isolated by recrystallization and reprecipitation; crude (S_a)-**29** was submitted to hydrogenation directly; the X-ray structure (CCDC 2240363) is shown as ORTEP at 50% probability.

functionalization in 6,6′-position was enabled by the 2,2′-diol motif. After kinetic *O*-acylation with acetyl chloride, a titanium chloride-mediated *ortho*-selective Fries rearrangement yielded acetophenone dimer **27** in up to 82% yield.[19f]

Enantiomeric excesses were observed to be unaffected, which agreed with the predicted high rotational barrier of **1** and **27** ($\Delta G^{\ddagger}_{rot} = 39.2$ kcal mol^{-1}, Figure S5).[38] Reaction of acetophenone dimer **27** with diethyl oxalate and sodium ethoxide in ethanol, followed by acidic condensation and transesterification in methanol were found to be ideal conditions and resulted in the clean formation of 5,5′-methoxy chromone dimer **28** (Schemes S9, S10).[40] Notably, a distinct increase in solubility for enantiopure (S_a)-**28** relative to racemic material was observed (Figure S31) that was also reflected in the corresponding melting points [212–214 °C ((S_a)-**28**), decomps. >300 °C (*rac*-**28**)].[41] Demethylation of **28** was performed using boron trichloride in dichloromethane. With an excess of Lewis acid, the double demethylation proceeded quickly, likely promoted by boron trichloride coordination through the ketones in direct proximity to the 5,5′-methoxy substituents. The resulting 5,5′-dihydroxy chromone dimer **26** could be isolated in 89–99% yield (Figure S33 for X-ray structure, CCDC 2240362). Again, the enantiomeric excess of (S_a)-**26** was found to be unaffected by the employed reaction conditions in line with a calculated $\Delta G^{\ddagger}_{rot}$ of 42.3 kcal mol^{-1} (Figure S6).[12b,38] Chromanone lactones can be synthesized from 5-hydroxy chromones through a vinylogous Michael addition of siloxyfuran to a silyl triflate-generated benzopyrylium followed by deprotection and hydrogenation of the formed chromanone butenolides.[42] The method was successfully reproduced in the synthesis of monomeric (±)-*epi*- and (±)-gonytolide C and showed literature consistent yields as well as kinetic *syn*- and thermodynamic *anti*-selectivity (20:1 d.r., reaction at −78 °C vs 1:3 d.r. after epimerization at 0 °C, Figure S11). Subsequently, the reaction conditions were transferred to dimeric hydroxychromone **26**. After presumed formation of a benzopyrylium triflate dimer with di-*iso*-propylsilyl bistriflate, addition of trimethylsiloxyfuran followed by global silyl deprotection after 3–4 h at −95–(−78) °C yielded a major non-C_2-symmetrical chromanone butenolide dimer **29** (~85% by crude NMR) as one out of ten possible diastereomers. Note that, due to the symmetrical constitution, there are less than the theoretical maximum of sixteen diastereomers (Scheme S18). After catalytic hydrogenation in flow, the corresponding chromanone lactone dimer **2** could be isolated in up to 64% yield and ≥98% *ee* on scales of 30–200 mg. An X-ray crystallographic analysis of the final product **2** revealed the highly diastereoselective formation of (*syn*,*syn*′)-configured (+)-2′,11-di-*epi*-gonytolide A (for details see Figures S18–S21, Scheme S13, S14; CCDC 2240363).

In summary, an effective and highly enantio- as well as diastereoselective five step synthesis of the complex chromanone lactone dimer **2** in up to 46% yield has been developed. This synthesis started from an axially chiral 2,2′-biphenol building block **1** that has been designed based on biphenol motifs found ubiquitously in nature and has been made accessible on a gram scale.

Conclusion

A scalable and efficient synthesis was developed for the 2,2′-biphenol building block **1** that represents a common substitution pattern of dimeric aromatic polyketides. After establishing the 3-methyl-5-methoxy substitution pattern on the monomeric

subunit, a robust and selective 2-bromination of monomeric phenol **3** on a 60 g scale was enabled by a temporary *O*-acetylation. DFT studies confirmed that a modulation of the phenol's electronics by the protection likely results in a change in mechanism alongside a significantly improved regioselectivity. High-yielding construction of the challenging tetra-*ortho*-substituted biaryl bond was achieved via oxidation of a homomeric biaryl Lipshutz cuprate using the diquinone **DPQ** as oxidant that could be recycled using molecular oxygen. Starting from phenol **3**,[22] racemic 2,2′-biphenol **1** was obtained in up to 66% overall yield on a decagram scale and in only six steps without the need for column chromatography. Different resolution strategies were established and evaluated. While derivatization-chromatographic separation and organocatalytic kinetic resolution approaches proved to be viable routes, a copper(II)/sparteine-mediated deracemization was found to be the superior and more efficient strategy. Enantiopure (S_a)-biphenol **1** was prepared in useful quantities of more than one gram and copper scavenging using EDTA enabled recycling of the chiral diamine ligand. Note that even though the availability and price of sparteine varied in recent years,[43] both natural alkaloid enantiomers are readily available by O'Brien's concise gram scale synthesis[44] granting access to either biaryl antipodes. Complementary DFT studies on the molecular basis of the central-to-axial chirality transfer during deracemization identified an increased distortion of the ligand-sphere and a strained biphenol scaffold within the mismatched theoretical sparteine copper biphenol complex (R_a)-**25**. The scalable access to biphenol (S_a)-**1** enables application towards complex natural product synthesis. In a bidirectional manner, the biphenol building block was advanced to 5,5′-dimethoxy- and 5,5′-dihydroxy-chromonecarboxylate-8,8′-dimers **28** and **26**. While these axially chiral natural product fragments and simplified derivatives thereof have been known since the 1960 s[45] and gained interest more recently,[46] the outlined work represents their first enantioselective synthesis. Starting from **26**, the so far unknown unsymmetrical chromanone lactone dimer (+)-2′,11-di-*epi*-gonytolide A **2** was synthesized. In a highly diastereoselective double siloxyfuran addition followed by in-flow hydrogenation, **2** was obtained as the major product being one out of ten possible diastereomers and implying a marked stereoinduction by the biaryl axis. Overall, yields of up to 46% in only five steps starting from biphenol **1** were obtained, underlining the strength of the presented building block strategy for the construction of highly complex natural products, their fragments, or derivatives. While remarkable progress has been seen in the direct construction of axially chiral biphenyls over the recent years,[18g,47] the presented synthetic route will serve as a blueprint for the construction of other homodimeric biphenols as building blocks or axially chiral ligands. Additionally, and due to its common polyketide substitution pattern, 2,2′-biphenol **1** should provide a privileged platform for the chemical space exploration around chromanone lactones and related aromatic polyketide dimers, supporting the evaluation of their rich bioactivity profiles in future diversity-oriented or targeted endeavors.

Supporting Information

Deposition Numbers 2240360 (for **1**), 2240361 (for **17**), 2240362 (for **26**), 2240363 (for **2**) contain the supplementary crystallographic data for this paper. These data are provided free of charge by the joint Cambridge Crystallographic Data Centre and Fachinformationszentrum Karlsruhe Access Structures service.

Additional references cited within the Supporting Information.[48]

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Conflict of Interests

The authors declare no conflict of interest.

Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Keywords: natural products · atropisomerism · total synthesis · building block · density functional calculations

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