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Asymmetric Synthesis of Gonytolide A: Strategic Use of an Aryl Halide Blocking Group for Oxidative Coupling

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Abstract

The first synthesis of the chromanone lactone dimer gonytolide A has been achieved employing vanadium(V)-mediated oxidative coupling of the monomer gonytolide C. An *ortho*-bromine blocking group strategy was employed to favor *para-para* coupling and to enable kinetic resolution of ($\pm$)-gonytolide C. Asymmetric conjugate reduction enabled practical kinetic resolution of a chiral, racemic precursor and the asymmetric synthesis of (+)-gonytolide A and its atropisomer.

Graphical Abstract

1. INTRODUCTION

Gonytolide A (**1**) is a dimeric chromanone natural product isolated by the Kikuchi group in 2011.^{1a} In an effort to search for regulators of innate immunity from natural sources, an *ex vivo* culture system based on the *Drosophila* immune deficiency (IMD) signaling pathway² identified gonytolide A as a potent innate immune promoter from the fungus *Gonytrichum* sp. Several related, non-active derivatives (gonytolides B–G, Figure 1) were co-isolated from the same fungal extract^{1b} including the monomers gonytolide C (**3**) and gonytolide G (**7**). Gonytolide A (**1**) possesses four chiral centers and a chiral biaryl axis. The dimers gonytolide A (**1**), D (**4**) and F (**6**) share the same *para-para* linkage, whereas gonytolide B (**2**) and E (**5**) are connected by an *ortho-para* biaryl bond. The congeners gonytolides D (**4**) and E (**5**) are heterodimers in which one chromanone lactone is replaced by a

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Notes

The authors declare no competing financial interests.

Supporting Information

Experimental and computational details, and CIF files for **6** and **13**. This material is available free of charge via the Internet at <http://pubs.acs.org>.

tetrahydroxanthone moiety. It was shown that gonytolide A increases TNF- α -stimulated production of IL-8 in human umbilical vein endothelial cells (HUVECs).^{1a} In later studies, the Kikuchi group prepared simplified bischromone and bisflavone analogues³ lacking the lactone moiety which also promoted the mammalian TNF- α signaling pathway. One key structural element observed for immune-promoting activity from their SAR studies is the requirement for bischromanone/bischromone moieties possessing a *para-para* linkage, which in the case of gonytolide A is a crowded chiral biaryl axis which presents a formidable synthetic challenge.

We have previously developed methodology involving copper-mediated biaryl coupling of aryl stannanes to synthesize the related natural products secalonic acids A (**8**) and D (**9**) (Figure 1).^{4b} However, in initial studies⁵ we were not successful in using this methodology to forge the crowded biaryl bond of gonytolide A, largely due to difficulty in accessing the requisite hindered aryl stannane reaction partner. Accordingly, we explored alternative oxidative coupling methods to construct this biologically active and synthetically challenging molecule in an atom- and step-economical fashion.⁶ The Kozlowski group has demonstrated the power of metal-catalyzed, oxidative coupling employing chiral copper/1,5-diaza-*cis*-decalin catalysts⁷ to synthesize a number of perylenequinone natural products including cercosporin and hypocrellin.⁸ The Pappo group has showcased use of iron-catalyzed, consecutive oxidative cross-couplings to prepare phlorotannin natural products.⁹ In oxidative coupling of phenols, control of chemo-, regio-, and stereoselectivity are significant challenges. Such issues have been recently studied in a number of different contexts.⁶ For example, the Waldvogel group has developed highly efficient, anodic cross-couplings to selectively access non-symmetric biphenols.¹⁰ The Pappo group has utilized chiral iron-phosphate catalysts for enantioselective homo- and cross-coupling of 2-naphthols.¹¹ In a recent study, Pappo and coworkers reported oxidative coupling of halophenols with β -keto esters in which the halogenation site influenced C-O vs. C-C coupling.¹² The Kozlowski group has also pioneered work on selective *ortho-ortho*, *ortho-para*, *para-para* oxidative homo-couplings of phenols using metal-salen complexes.¹³

Although *para-para* selective oxidative couplings have been documented using catalyst control by Kozlowski¹³ and others,¹⁴ substrates thus far have been limited to relatively simple phenols. In the current study, we wished to solve the regioselectivity issue for oxidative coupling of a complex phenolic substrate using a blocking group strategy. Our retrosynthetic analysis for gonytolide A is shown in Scheme 1. Dimeric chromanone **1** may be derived from *para-para* oxidative coupling of the monomer **3** in which the *ortho* position of the phenol is blocked with a halogen substituent such as bromine. It was anticipated that the installed halogen may also potentially stabilize developing metal phenoxyl radicals¹⁵ during the coupling process. We considered that the oxidative coupling substrate **10** may be obtained from ($\pm$)-gonytolide C (**3**) by an asymmetric bromination/kinetic resolution process. Recent reports have shown significant interest in stereoselective halogenation in natural product synthesis¹⁶ including examples involving dynamic kinetic resolution (DKR) *via* asymmetric bromination.¹⁷ Compound **3** may be accessed using vinylogous addition of siloxyfuran (**12**) to chromone (**11**)^{4a} which we have previously used to access tetrahydroxanthone dimers including secalonic acids **8** and **9** and rugulotrosin A.^{4b-d}

2. RESULTS AND DISCUSSION

We first optimized the vinylogous addition by varying both solvent and temperature (Table 1). Chromone **11** was activated to a siloxybenzopyrylium species by treatment with diisopropylsilyl triflate and 2,6-lutidine which was followed by addition of siloxyfuran **12** under various reaction conditions. The corresponding chromanone-butenolides **13** and **14** (found to be unstable to silica gel chromatography) were produced as a mixture of diastereomers and were directly subjected to conjugate reduction without purification to afford gonytolide C (**3**)¹⁸ and its diastereomer **15**, compounds known from our previous study^{4a} to be the thermodynamic and kinetic products, respectively. Vinylogous addition in CH₂Cl₂ (0 °C) gave the best results to afford **3/15** in 66 % yield and in a 3:1 diastomeric ratio (dr) (entry 1). Further raising the reaction temperature or use of other solvents resulted in diminished yield or negatively impacted the dr (entries 2-8).

With (±)-gonytolide C (**3**) in hand, we next prepared (±)-bromo-gonytolide C (**10**) by bromination with *N*-bromosuccinimide in CH₂Cl₂ at room temperature (Table 2). We subsequently carried out the key oxidative coupling using (±)-**10**. After evaluation of an array of commonly used metal catalysts and oxidants (Table 2), including FeCl₃ (entry 1),¹⁹ Cr-Salen (entry 3),^{13,20} Cu(OH)Cl-TMEDA (entry 4),²¹ Mn(OAc)₃ (entry 5),²² PhI(OH) (OTs) (entry 6),²³ MoCl₅ (entry 7)²⁴ and a number of vanadium oxidants,²⁵ and electrochemical methods (entry 12),²⁶ we were pleased to discover that the silica gel-supported ferric chloride (FeCl₃/SiO₂) (entry 2)^{19a} and oxyvanadium trifluoride (VOF₃) (entry 11) in TFA/TFAA²⁷ both led to clean oxidative coupling to afford brominated dimers as indicated by UPLC-MS analysis.⁵ The crude dimers were subsequently dehalogenated with Pd/C under a hydrogen atmosphere to afford (±)-gonytolide A and its isomers. Theoretically, two homodimers (**1** and **16**) with C₂-symmetry and two heterodimers (**17** and **18**) with C_s-symmetry derived from oxidative coupling of different enantiomers may be produced. The FeCl₃/SiO₂ conditions (entry 2) afforded only trace amounts of the desired dimer gonytolide A, and the reaction required considerable time to reach completion (6 days). Other conditions either gave no reaction or led to undesired byproducts.⁵ It should be noted that the VOF₃-oxidative coupling of (±)-gonytolide C (**3**) largely afforded decomposition⁵ thereby demonstrating the importance of the halide blocking group. Attempts to install alternative blocking groups (*e.g.* benzyl, triisopropylsilyl, and *tert*-butyldiphenylsilyl ethers) on the phenol of **3** failed to give the desired dimers using VOF₃/TFA/TFAA conditions. Instead, the blocking groups were cleaved during the reaction and afforded complex mixtures of dimers, trimers, and tetramers derived from gonytolide C.⁵

Using the VOF₃/TFA/TFAA oxidative coupling conditions, (±)-gonytolide A **1** was produced in an 11% yield along with its atropisomer (**16**) in 23% yield after reductive debromination. In addition, the heterodimer C_s-gonytolide A (**17**) was produced in 23% yield; the corresponding C_s-atropisomer (**18**) was not observed. The structure of C_s-gonytolide A (**17**) was confirmed by X-ray crystallographic analysis (Figure 2). Interestingly, the crystal structure of **17** shows out-of-plane distortion (9.4°) of the biaryl axis. This distortion observed in the solid state appears to occur based on minimization of

steric interactions (*e.g.* CH₃ – CH₃ and CH₃ – CO₂Me) between monomer units. Similar distortions have been observed in other strained biaryl systems.²⁸

In order to eliminate the formation of a *Cs*-dimer during the oxidative coupling and achieve asymmetric synthesis of gonytolide A, access to enantiopure monomer **3** was required.^{4c} Based on reported examples of asymmetric halogenation of alkenes and phenols,^{16,17} we evaluated cinchona alkaloid catalysts²⁹ for asymmetric bromination of (±)-**3**. After considerable experimentation, we found that the dimeric catalyst (DHQD)₂Pyr could achieve bromination of (±)-gonytolide C to effect kinetic resolution (Scheme 2). Under optimized conditions,⁵ the desired *ortho*-bromo gonytolide C **10** was obtained in 88:12 e.r. (16% yield) which after crystallization from iso-propanol slowly formed a single crystal which was characterized by X-ray crystallography to determine absolute stereochemistry. Given that the bromination site is far from point chirality, the asymmetric bromination represents an interesting example of remote asymmetric induction. Monomer (–)-**10** bearing the incorrect absolute stereochemistry to access natural gonytolide was produced in an overall low yield due to formation of the *para*- and *di*-bromination byproducts **19** and **20**.⁵

As shown in reported examples of asymmetric fluorination with cinchona alkaloid catalysts, *N*-fluorinated-cinchona derivatives have been characterized and identified as catalytic species.³⁰ We reasoned that NBS should first brominate the tertiary nitrogen^{29b} of the cinchona catalyst and that the resulting *N*-Br species may have a preference to recognize substrate enantiomers and deliver bromine to the *ortho*-position of **3**. Accordingly, we conducted DFT calculations of the complex of [(DHQD)₂PyrBr]⁺ and both enantiomers of **3** (Figure 3). Geometry optimizations of the pre-transition state (pre-TS) at the B3LYP/LAV3P level showed that both enantiomers can be anchored to the *N*-brominated-cinchona catalyst through hydrogen-bonding interactions. The unnatural (–)-enantiomer of gonytolide C appears to be preferred in the catalyst pocket with an energy 3.2 kcal/mol lower in comparison to the natural (+)-enantiomer which is consistent with the observed reaction outcome. The difference in energy may be attributed in part to a OH- π interaction³¹ between the pyrimidine spacer and the phenol of (–)-**3**. For (+)-**3**, a weaker hydrogen bonding interaction is observed between the phenol and the methoxy group on the cinchona sidearm.

Although the asymmetric bromination of gonytolide C (**3**) provided access to an enantiopure, monomeric coupling substrate and enabled determination of absolute stereochemistry, the presence of *para*- and *di*-bromination byproducts made product purification somewhat tedious and lowered the isolated yield of *ortho*-bromide **10**. Extensive screening of additives, solvents, bromine sources, temperature, and catalysts did not improve results.⁵ Accordingly, we considered asymmetric reduction of butenolide **13** for kinetic resolution, as asymmetric conjugate reductions of butenolides have been well documented by both the Lipshutz³² and Buchwald³³ laboratories using copper hydride.³⁴ In exploring these reductions, (Scheme 3) we found that butenolide **13** was very sensitive to silica gel chromatography and decomposed to afford an elimination product.⁵ Chiral HPLC analysis of (±)-butenolide **13** also showed partial decomposition. Further studies revealed that **13**, **14**, and the elimination product are interconvertible under basic conditions. Subsequent recrystallization was used to obtain pure samples of butenolides **13** and **14** and the elimination product from crude mixtures.⁵ After examination of various chiral ligands, we

found that the Josiphos ligand was effective at promoting CuH reduction with useful levels of e.r. Under optimized conditions using Josiphos SL-J001-2, (+)-gonytolide **3** was produced in 49% yield and in 89:11 e.r. from ($\pm$)-butenolide **13**. This material was further enriched to 97:3 e.r. by recrystallization and was carried forward to the bromination/oxidative coupling/hydrogenation sequence. As expected, *Cs*-gonytolide **A** was not observed in the reaction, and gonytolide **A** was produced in 12% yield along with *atrop*-gonytolide **A** (35% yield).

In order to gain mechanistic insight into the VOF₃-induced oxidative coupling and to understand the role of the halide blocking group, we carried out several mechanistic experiments. *O*-Methylation of monomer **10** afforded methyl ether substrate **21** (Scheme 3) which was subjected to standard oxidative coupling conditions to afford dimeric products, albeit in a much lower conversion than substrate **10**.⁵ In line with literature precedents³⁵ and based on the need for a blocking group and also the reactivity observed with the *O*-methylated substrate **21**, we propose that the oxidative dimerization may proceed through nucleophilic addition of **10** to an electrophilic radical cation^{19b} (Figure 4). We propose that the *ortho*-bromide **10** may be oxidized by VOF₃/TFA/TFAA to form a phenoxyl radical cation **22**, likely through a charge transfer complex.³⁶ The *ortho*-bromine may potentially stabilize the radical cation through electronic effects. Moreover, calculations^{5,37} support such stabilization effects by showing that the spin density can reside on the bromine atom of **22**. Unoxidized **10** may then add to the stabilized radical cation **22** to form radical cation intermediate **23** to initiate the coupling reaction. Intermediate **23** may undergo further oxidation to pre-biaryl structures **24** and **25**.

We further considered that atropdiastereoselection for production of either **26** or **27** may be thermodynamically controlled by the relative energies of cyclohexadienone intermediates **24** and **25**. We reasoned that, during the rearomatization process, chiral information should be maintained. For example, conformers **24A** and **25A** should lead to **26** and **24B** and **25B** should afford **27**, similar to the traceless chirality exchange involving rearomatization of dimeric 1,4-diketones reported by the Thomson group.³⁸ In order to probe this hypothesis, we computed DFT energies⁵ for both conformers of **24/25** at the B3LYP/LACV3P level which showed that the precursors for bromo-*atrop*-gonytolide **A** (**27**) have lower relative energy, regardless of the C-8 configuration (Figure 4).

In addition, no interconversion of **1** and **16** was observed after thermolysis of either compound in refluxing toluene for 24 h. The rotational barrier for interconversion of atropisomers was calculated to be 47.5 kcal/mol using the B3LYP/6-31G(d) level of theory.⁵ Although the rotational barrier is high, the Pappo group^{11a} and others³⁹ have demonstrated that BINOL can undergo racemization under oxidative conditions. This prompted us to examine single electron transfer (SET) conditions with either *atrop*-gonytolide **A** (**16**) or its brominated precursor bromo-*atrop*-gonytolide **A** (**27**) (Table 3). Conditions reported by Pappo and coworkers^{11a} (entries 1 and 2) did not reveal any reactivity. Use of an acridinium photocatalyst⁴⁰ under visible light conditions was found to decompose substrate **16** (entry 3) and led to no reaction with substrate **27** (entry 4). Use of (NH₄)₂Ce(NO₃)₆ as single electron oxidant did not lead to conversion of **27** to **26** (entry 5). Finally, resubjection of dimer **27** to

VOF₃/TFA/TFAA conditions also led to decomposition (entry 6). These results are highly interesting given that the unnatural atropisomers **16/27** were favored during the oxidative coupling, but could not be isomerized to the natural atropisomers **1/26**.

Finally, we evaluated various halogen blocking groups on the monomer gonytolide C (+)-**3** for examination in the VOF₃-oxidative coupling in an effort to tune atropselectivity (Table 4). Various halogen blocking groups were introduced using conventional methods, resulting in nearly equal amounts of *para/ortho* halogenation with the exception of BnMe₃NiCl₂ which preferentially afforded the *ortho*-iodide. Interestingly, a trend for atropselectivity was observed. Use of an *ortho*-iodo blocking group afforded exclusively *atrop*-gonytolide A (entry 1), while a 1:3 ratio of atropisomers in favor of *atrop*-gonytolide A was observed using a bromine blocking group (entry 2). The ratio of atropisomers increased to nearly 1:1 employing an *ortho*-chlorine blocking group (entry 3). In addition, we found that use of an *ortho*-fluorine blocking group completely inhibited reactivity (entry 4). These results showed the critical role of halogen blocking group in the oxidative coupling, and the possibility to tune atropselectivity by choice of halogen. Moreover, DFT computations⁵ provided insight on how the halogen blocking group may influence atropselectivity to produce either **1** or **16**. Figure 5 shows the disfavored model of **24A** showing close proximity of the aryl bromide and the appended lactone moiety as well as the favored model of **24B** where the bromine is proximal to a methyl ester. This steric analysis is also consistent with the atropselectivity trend observed from I → Br → Cl blocking groups in which greater amounts of gonytolide A are observed. Unfortunately, attempts to use chiral ligands⁴¹ or a chiral oxovanadium complexes⁴² in oxidative coupling of **10** to further tune the atropselectivity failed to yield dimers.⁵ These results are not surprising as the mechanism suggests an outer-sphere oxidation process.⁴³

3. CONCLUSION

In conclusion, we have synthesized the natural product (+)-gonytolide A and its unnatural atropisomer (-)-*atrop*-gonytolide A in five steps from a chromone ester monomer. The synthesis features vinylogous addition to rapidly construct a chromanone butenolide substrate, asymmetric conjugate reduction/asymmetric bromination to resolve a chiral, racemic butenolide monomer, and oxidative coupling using a halide blocking group to construct the crowded biaryl linkage of the dimer gonytolide A and its atropisomer. The halogen blocking group appears to have several different roles in the oxidative coupling: 1) stabilization of radical cation intermediates, 2) control of *para-para* coupling selectivity, and 3) steric tuning of atropdiastereoselection providing access to both natural and unnatural atropisomers in varying ratios depending on the halogen blocking group. Further studies on the syntheses and biology of dimeric chromanones and derivatives are currently ongoing in our lab and will be reported in due course.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1.
Gonytolide A and Related Natural Products

Figure 2.
X-ray Crystal Structure of Cs-gonytolide A (17)

Figure 3.
Models for Asymmetric Bromination of 3

Figure 4.
Proposed Mechanism for Oxidative Coupling

Figure 5.
Space Filling Models for Biaryl Precursors

Scheme 1.
Initial Retrosynthetic Analysis for 1

Scheme 2.
Attempted Asymmetric Bromination

Scheme 3.

Asymmetric Conjugate Reduction and Synthesis of (+)-Gonytolide A

Table 1

Evaluation of the Vinylogous Addition

entry	temperature	solvent	overall yield (3+15)	dr(3 : 15)
1	0°C	CH_2Cl_2	66%	3 : 1
2	rt	CH_2Cl_2	57%	3 : 1
3	reflux	CH_2Cl_2	54%	3 : 1
4	0°C	THF	60%	1 : 5
5	0°C	$\text{Et}_2\text{O}/\text{CH}_2\text{Cl}_2$ (2 : 1)	39%	2 : 1
6	0°C	toluene	47%	1 : 4
7	rt	benzene	52%	1 : 1
8	rt	MeCN	24%	3 : 1

Table 2

Oxidative Coupling of (±)-gonytolide C (3)

entry	conditions ^a	results
1	0.1 equiv. FeCl ₃ , 2.5 equiv. t-BuOOt-Bu, HFIP, rt	No reaction
2	FeCl ₃ /SiO ₂ , 70 °C, no solvent, 6 days	<5% 1 , 19% 17 , 28% 16
3	1.0 equiv. Cr-salen, DCE, O ₂ , 70 °C	No reaction
4	1.0 equiv. Cu(OH)Cl-TMEDA, DCE, O ₂ , 70 °C	Decomposition
5	1.0 equiv. Mn(OAc) ₃ , AcOH, rt	No reaction
6	0.5 equiv. PhI(OH)(OTs), HFIP, rt	Complex mixture
7	4.0 equiv. MoCl ₅ , CH ₂ Cl ₂ , rt	<i>Para</i> -chlorination of 10
8	2.0 equiv. VOCl ₃ , THF, rt	<i>Para</i> -chlorination of 10
9	2.0 equiv. VOSO ₄ , CH ₂ Cl ₂ , O ₂ , rt	No reaction
10	2.0 equiv. VOF ₃ , HFIP, rt	No reaction
11	2.5 equiv. VOF ₃ , TFA/TFAA, rt	11% 1 , 23% 17 , 23% 16
12	Divided cell, graphite anode, TFE/H ₂ O 4:1, 0.2 M LiClO ₄ , 1.0 mA, 3.0~4.0 V	Decomposition

^aReaction conducted for 12 h unless specified otherwise.

Table 3

Attempted Atropisomerism of Gonytolide Dimers

entry	X	conditions ^a	results
1	H	0.1 equiv. FeCl ₃ , DCE/HFIP 1:1, rt	No reaction
2	Br	0.1 equiv. FeCl ₃ , 1.5 equiv. t-BuOOt-Bu, DCE/HFIP 1:1, rt	No reaction
3	H	0.1 equiv. 9-mesityl-10-methylacridinium tetra-fluoroborate, CH ₃ CN, 427 nm, rt	Complete decomposition
4	Br	0.1 equiv. 9-mesityl-10-methylacridinium tetra-fluoroborate, CH ₃ CN, 427 nm, rt	No reaction
5	Br	0.5 equiv. (NH ₄) ₂ Ce(NO ₃) ₆ , CH ₃ CN/H ₂ O 1:1, rt	Decomposition
6	Br	0.5 equiv. VOF ₃ , TFA/TFAA 20:1, rt	Complete decomposition

^aReaction conducted for 12 h unless specified otherwise.

Table 4

Oxidative Coupling Using Various Halogen Blocking Groups

Entry	Conditions ^a	Halogenation results	Coupling results
1	BnMe ₃ NiCl ₂ , CaCO ₃ , CH ₂ Cl ₂ /CH ₃ OH, rt	70%, X= I	0% 1 , 25% 16
2	NBS, CH ₂ Cl ₂ , rt	53%, X= Br	11% 1 , 35% 16
3	NCS, DMF, 60 °C 4 h	44%, X= Cl	23% 1 , 27% 16
4	Selectfluor [®] , CH ₃ CN, rt	31%, X= F	No reaction

^aReaction conducted for 12 h unless specified otherwise.