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Asymmetric Syntheses of the Flavonoid Diels–Alder Natural Products Sanggenons C and O

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Supporting Information

ABSTRACT: Metal-catalyzed, double Claisen rearrangement of a bis-allyloxyflavone has been utilized to enable a concise synthesis of the hydrobenzofuro[3,2-*b*]chromenone core structure of the natural products sanggenon A and sanggenol F. In addition, catalytic, enantioselective [4+2] cycloadditions of 2′-hydroxychalcones have been accomplished using $B(OPh)_3$/BINOL complexes. Asymmetric syntheses of the flavonoid Diels–Alder natural products sanggenons C and O have been achieved employing a stereodivergent reaction of a racemic mixture (stereodivergent RRM) involving [4+2] cycloaddition.

Sanggenon-type natural products (Figure 1) are intriguing synthetic targets due to their complex chemical structures and potent biological activities.[1] In particular, the congener sanggenon C[2] has antitumor, antiviral, and anti-inflammatory properties[1c,d,3] which makes it an attractive synthetic target. Although chemical syntheses of related Diels–Alder (DA)-type natural products, including sorocenol B[4] and brosimones A and B,[5] have been achieved, there are no reported catalytic, enantioselective [4+2] cycloadditions of 2′-hydroxychalcones, nor are there published reports of DA cycloadditions of complex flavonoid dienes. Here we report the first total syntheses of sanggenon A (**1**) and sanggenol F (**2**), both featuring complex benzofuro[3,2-*b*]chromenone structures. Further structural complexity was obtained employing enantioselective [4+2] cycloaddition to construct sanggenon C (**3**) and sanggenon O (**4**)[6] using a unique stereodivergent RRM.[7]

Sanggenons C (**3**), D (**5**),[8] and O (**4**) are apparent DA cycloadducts between a flavonoid diene (**7**) and a 2′-hydroxychalcone (**6**) (Scheme 1). Among these compounds, sanggenons C and O were shown to be *endo* cycloadducts and epimers at C-2 and C-3. We considered stereodivergent RRM of chiral, racemic diene **7** as a promising strategy, assuming that issues of *endo*/*exo* selectivity, face selectivity, and enantioselectivity could be addressed. Compound **7** may be derived from dehydrogenation of the prenyl group of sanggenol F or its protected derivative (**9**).[5a,9] Alternatively, **7** may be derived from isomerization of the chromene ring in sanggenon A or protected substrate (**8**).[10] Sanggenol F core structure **9** may arise from olefin cross-metathesis of precursor **10**. We envisioned that **10** may be derived from metal-catalyzed double Claisen rearrangement[11] of bis-allyloxyflavone ether **11**, followed by hemiketalization.

Synthesis of **11** commenced with tetra-MOM group protection of the commercially available compound morin (**12**) and

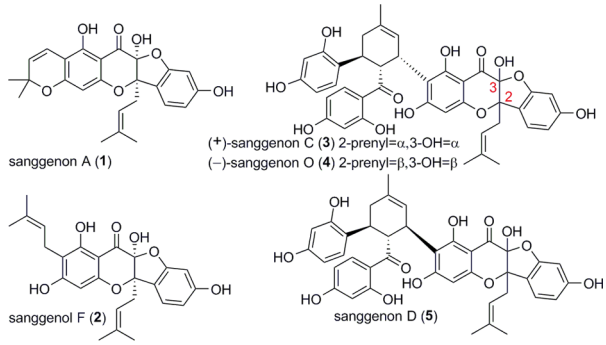
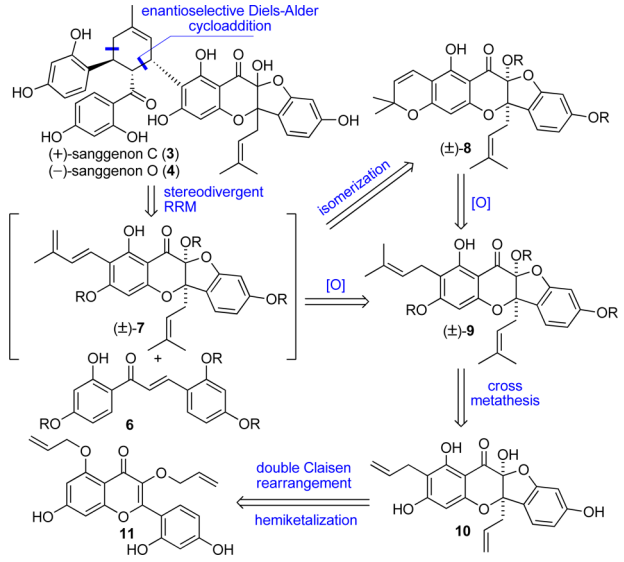


Figure 1. Structures of sanggenon-type natural products.

Scheme 1. Retrosynthetic Analyses for Sanggenons C and O



subsequent 5-allylation to afford the protected intermediate **13** (Scheme 2). Selective 3-MOM deprotection was accomplished using NaI and a catalytic amount of aqueous HCl.[12] In this transformation, protonation of the 4-carbonyl and O-3 of **13** appears to activate the 3-MOM group for chemoselective deprotection. Finally, 3-allylation and global MOM deprotection afforded the desired substrate **11** in 33% overall yield (5 steps).

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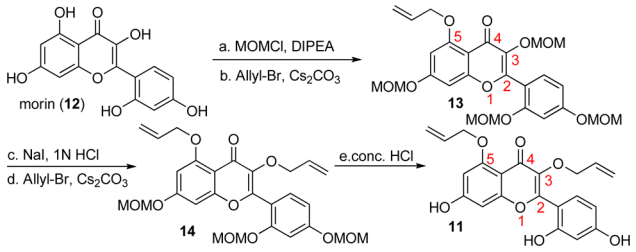
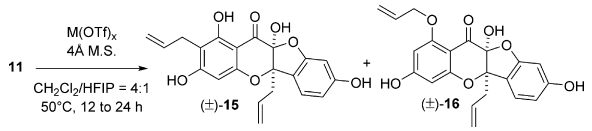
Scheme 2. Synthesis of Morin Di-allyl Ether[a]



[a]Reagents and conditions: (a) MOMCl (5 equiv), DIPEA (5 equiv), CH_2Cl_2, 0 °C to rt, 55%; (b) allyl-Br (1.2 equiv), Cs_2CO_3 (1.2 equiv), DMF, 65 °C, 12h, 93%; (c) NaI (0.8 equiv), 1 N HCl (0.1 equiv), 40 °C, 12h, 73%; (d) allyl-Br (2.0 equiv), Cs_2CO_3 (2.0 equiv), DMF, 65 °C, 12h, 96%; (e) conc. HCl, MeOH, 40 °C, 93%.

Table 1. Lewis Acid-mediated Double Rearrangement[a]



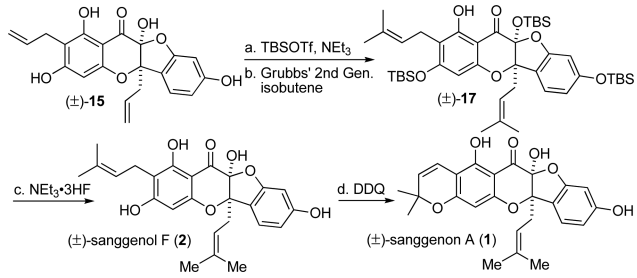
entry[b]	$M(OTf)_x$	ionic radii (pm)[c]	yields of **15**, **16** (%)
1	$Yb(OTf)_3$	86.8	72, 0
2	$Y(OTf)_3$	90.0	60, 36
3	$Gd(OTf)_3$	93.8	48, 40
4	$Nd(OTf)_3$	98.3	38, 62
5	$La(OTf)_3$	103.2	0, 70

[a]See SI for experimental details. [b]All reactions were carried out with substrate **11** (0.13 mmol) and $M(OTf)_3$ (15 mol%) at 0.1 M in CH_2Cl_2/HFIP (4:1) at 50 °C. [c]For effective ionic radius, see ref 15.

A number of rare earth (RE) metal triflates were evaluated for double rearrangement of **11** (Table 1).[13] Among the metal triflates, $Yb(OTf)_3$ was found to produce the double rearrangement product **15** in 72% yield. In this reaction, hexafluoro-2-propanol (HFIP) was used as a polar, non-coordinating[14] cosolvent to solubilize the polar rearrangement substrate. Other RE triflates were found to produce **15** along with the single rearrangement product **16** in varying ratios. Based on examination of a DFT molecular model[13] for **11**, there are two possible chelation sites between O-3, O-4 (2.85 Å) and O-5, O-4 (2.72 Å) through either five- or six-membered arrangements. Selective binding to either or both chelation pockets may occur depending on the ionic radius[15] of the Lewis acid to enable 3-allyl rearrangement and/or 5-allyl rearrangement.[16] Different modes of chelation by RE metal triflates may explain the product distributions observed in Table 1. For example, $La(OTf)_3$ with a larger ionic radius (1.03 Å) may preferentially chelate between O-3 and O-4 with a larger binding pocket to afford the 3-allyl rearrangement product **16** as the major product.

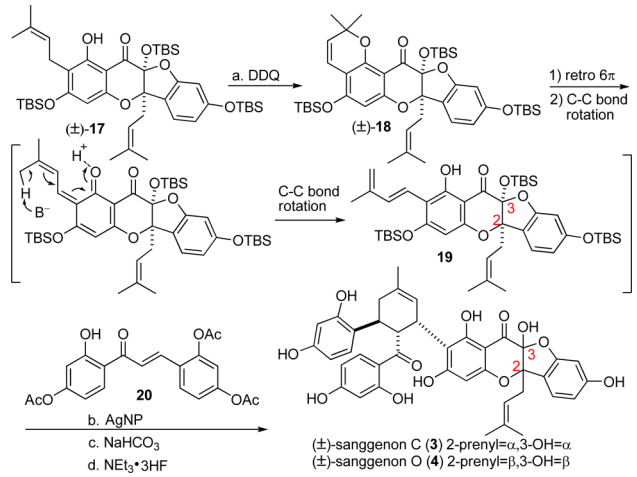
After obtaining the desired hydrobenzofuro[3,2-*b*]chromenone core structure (±)-**15** via double rearrangement, we investigated syntheses of the derived natural products **1** and **2**. Although the prenyl group could be installed by cross-metathesis[17] of hemiacetal (±)-**15** to directly access (±)-sanggenol F (**2**), we found that silylation of (±)-**15** followed by cross-metathesis produced the tri-silyl-protected (±)-sanggenol F (±)-**17** in excellent yield (Scheme 3). This sequence enabled purification of the final product from residual ruthenium byproducts. Desilylation of (±)-**17** afforded (±)-**2**, which was

Scheme 3. Syntheses of Sanggenol F and Sanggenon A[a]



[a]Reagents and conditions: (a) TBSOTf (3.2 equiv), NEt_3 (3.0 equiv), CH_2Cl_2, rt, 6h; (b) Grubbs second generation catalyst (10 mol%), isobutene, 40 °C, 24h, 92%, 2 steps; (c) NEt_3·3HF (8.0 equiv), CH_3CN, 0 °C, 3h, 91%; (d) DDQ (1.2 equiv), THF, 60 °C, 12h, 78%.

Scheme 4. Syntheses of (±)-Sanggenons C and O[a]



[a]Reagents and conditions: (a) DDQ (1.5 equiv), THF, 60 °C, 73%; (b) **20** (1.2 equiv), AgNP (0.25 mol%), AcOH (2 equiv), DCE, 65 °C, 3d; (c) sat. $NaHCO_3$, MeOH, rt, 12h; (d) NEt_3·3HF (8.0 equiv), CH_3CN, rt, 12h, 36% (3 steps), sanggenon C (**3**):sanggenon O (**4**) = 4:1.

dehydrogenated with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ)[10,18] to afford (±)-sanggenon A (**1**) in 78% yield.

We next evaluated **1** as a diene precursor for [4+2] cycloaddition. Treatment of **1** under Brønsted acidic, thermal, or photochemical conditions in the presence of silica-supported silver nanoparticles (AgNPs)[19] and 2′-hydroxychalcone (cf. **20**) as dienophile did not lead to the desired [4+2] cycloaddition; only decomposition of (±)-sanggenon A was observed. Accordingly, we elected to prepare a protected variant of sanggenon A to serve as a diene equivalent. Specifically, transformation of the prenyl flavonoid (±)-**17** to chromene (±)-**18** was investigated. Treatment of (±)-**17** with DDQ in tetrahydrofuran (THF) cleanly afforded (±)-**18** (73%) (Scheme 4). However, severe decomposition of **17** was observed when halogenated solvents (e.g. CH_2Cl_2, $CHCl_3$, or PhCl) were employed. As DDQ is a strong electron-acceptor,[20] a charge-transfer complex may be produced when an electron-donating solvent such as THF is employed.[21] Formation of such a complex may modulate the reactivity of DDQ,[22] which appears to largely suppress decomposition observed using oxidative conditions with halogenated solvents. We anticipated that the TBS-protected chromene **18** could generate the desired diene **19** *in situ* through retro 6π-electrocyclization followed by deprotonation/protonation (for-

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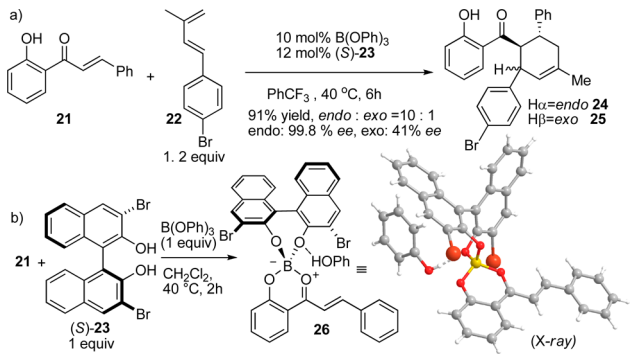
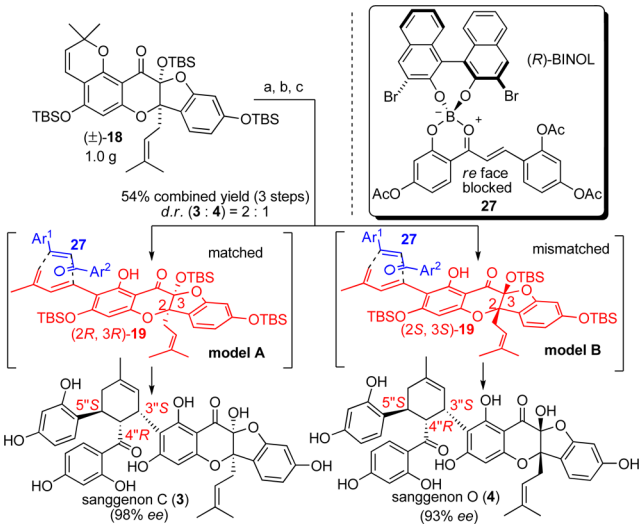
mal [1,7] hydrogen shift).[23] Accordingly, (±)-**18** was employed in cycloadditions with acetylated 2′-hydroxychalcone **20** in the presence of AgNPs to yield a mixture of two *endo* cycloadducts and minimal production of *exo* diastereomers. The mixture of *endo* cycloadducts was sequentially treated with aqueous $NaHCO_3$ and $NEt_3{\cdot}3HF$[24] to yield a mixture of (±)-sanggenons C (**3**) and O (**4**) in 36% yield (3 steps, 4:1 d.r.).

Unfortunately, our previously developed conditions for asymmetric Claisen rearrangement[11] failed to give useful levels of enantioselectivity employing bis-allyloxyflavone substrate **11**. We considered that sanggenons C and O are both *endo* cycloadducts with the same absolute configurations for the chiral cyclohexene moiety and epimers at both C-2 and C-3. Accordingly, we proposed that enantioselective [4+2] cycloaddition of chiral, racemic substrate **18** and dienophile **20** should efficiently deliver two natural products simultaneously utilizing a stereodivergent process. In our initial studies,[25] we found that borate complexes derived from chiral 1,1′-bi-2-naphthol (BINOL)[5b,26] could be used in catalytic, enantioselective [4+2] cycloadditions of 2′-hydroxychalcones. A two-dimensional screen was conducted using a number of borates ($B(OPh)_3$, tris(*p*-chlorophenyl), tris(pentafluorophenyl), and tris(hexafluoroisopropyl) borate) and BINOL ligands. We found that asymmetric [4+2] cycloaddition of the model dienophile 2′-hydroxychalcone **21** and diene **22**[27] using a catalytic amount of (*S*)-3,3′-dibromoBINOL **23** and triphenylborate afforded the [4+2] cycloadducts **24** and **25** in 91% combined yield, 10:1 *endo*/*exo* ratio, with >99% and 41% ee, respectively (Scheme 5a). By mixing **21**, **23**, and $B(OPh)_3$ in CH_2Cl_2, we obtained borate complex **26**, the structure of which was confirmed by single-crystal X-ray structure analysis.[13] The predicted absolute stereochemistry of the corresponding *endo* cycloadduct **24** based on the expected face selectivity of **26** was also confirmed by X-ray crystallography.[13] We found that 1 equiv of phenol was also bound to the borate complex as shown in the X-ray crystal structure (Scheme 5b). The bound phenol could serve to further activate the chalcone for cycloaddition and may also protonate the cycloadduct to turnover the boron/BINOL catalyst for additional catalytic cycles. Wulff and coworkers have reported a hydrogen-bonded complex of a boroxinate catalyst and a protonated iminium substrate.[26b] We also found that treatment of crystalline **26** with diene **22** led to similar results, producing **24** in high enantioselectivity.[13] The latter result reinforces the involvement of borate complex **26** in the catalytic asymmetric DA cycloaddition, which is also supported by literature precedent.[28]

Scheme 5. Model Reaction and Proposed Active Complex for [4+2] Cycloaddition



Scheme 6. Asymmetric Syntheses of Sanggenons C and O[a]



[a]Reagents and conditions: (a) $B(OPh)_3$ (20 mol%), **23** (22 mol%), **20** (1 equiv), $PhCF_3$, 80 °C, 48h; (b) sat. $NaHCO_3$, MeOH, rt, 12h; (c) $NEt_3{\cdot}3HF$ (8.0 equiv), CH_3CN, rt, 12h.

We next applied this catalytic system to a stereodivergent RRM strategy to synthesize enantioenriched sanggenons C and O. Based on the model reaction (cf. Scheme 5), a catalytic amount of $B(OPh)_3$ and (*R*)-BINOL **23** were used to mediate asymmetric [4+2] cycloaddition of diene precursor (±)-**18** and dienophile **20** (Scheme 6). After sequential deprotection of both acetate and silyl protecting groups, promising enantioselectivities were observed. A number of BINOL ligands were evaluated; best results were obtained when $B(OPh)_3$ and **23** were employed. A mixture of cycloadducts was observed, which was followed by consecutive deprotections ($NaHCO_3$; $NEt_3{\cdot}3HF$) to afford sanggenon C (**3**) and sanggenon O (**4**) in 2:1 ratio with 98% and 93% ee, respectively. The high *endo*/*exo* selectivity (cf. Scheme 5) suggested that minimal amounts of *exo* diasteromers were generated which we were not able to isolate and characterize. In this transformation, we expected four different stereoisomers: sanggenon C (**3**) and *ent*-sanggenon O (**4**) from (2*R*,3*R*)-**18**, and *ent*-sanggenon C (**3**) and sanggenon O (**4**) from (2*S*,3*S*)-**18** (Scheme 6). As shown in the (*R*)-BINOL/$B(OPh)_3$/chalcone complex **27**, the *re* face of the chalcone dienophile is blocked by the bulky bromo substituent. As a result, the derived dienes (2*R*,3*R*)-**19** and (2*S*,3*S*)-**19** approach from the *si* face of the chalcone **20** to afford **3** and **4**. Using (*S*)-BINOL **23**/$B(OPh)_3$ as catalyst, *ent*-sanggenon C (**3**) and *ent*-sanggenon O (**4**) were isolated in 2:1 ratio with 99% and 93% ee, respectively.[13] We also noticed that, in the stereodivergent RRM, sanggenon C is produced in both high enantiomeric excess and diastereomeric ratio relative to sanggenon O. This result suggests that matched/mismatched cycloadditions may also be operative based on differential interactions of the chiral borate catalyst with both enantiomers of diene **19**.

To understand the greater preference for formation of sanggenon C vs O (cf. Scheme 4), and the higher enantioselectivity observed for sanggenon C, we conducted computational studies of dienophile **27** using both enantiomers of a simplified variant of the diene (**19′**, TMS instead of TBS) to analyze the interacting complex of reagents engaging in DA cycloaddition.[13,29] Cycloaddition models A and B are shown in Scheme 6, with the lowest energy conformer of diene **19**. It

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appears that cycloaddition through model A is favored in comparison to the corresponding model B using (*R*)-BINOL, which results in greater amounts of sanggenon C derivatives and therefore favored production of (2*R*,3*R*) stereoisomers in the product mixture. Our preliminary reaction assembly calculations[13] show that there are significant steric interactions between the prenyl and phenyl groups on the chalcone dienophile which are likely responsible for the significantly increased energy in assemblies related to model B. Based on the X-ray structure of the chiral borate complex (cf. Scheme 5), we predicted that the use of (*R*)-BINOL as catalyst should yield (3″*S*,4″*R*,5″*S*) for both sanggenons C and O. This prediction is in agreement with absolute stereochemistry determinations reported by Nomura and coworkers.[2b]

In summary, we have achieved the first asymmetric syntheses of the flavonoid Diels–Alder natural products sanggenons C and O. The syntheses employ a Lewis acid-promoted double Claisen rearrangement to construct the hydrobenzofuro[3,2-*b*]chromenone core of sanggenon A and sanggenol F. The first catalytic enantioselective [4+2] cycloadditions of 2′-hydroxychalcones have been developed using BINOL-boron catalysis. The high enantio- and diastereoselectivity of this catalytic system enabled a stereodivergent reaction of a chiral, racemic flavonoid diene precursor to afford enantioenriched sanggenons C and O. Preliminary calculations of the interactions of diene–dienophile complexes support the stereochemical outcomes observed in stereodivergent cycloadditions. Further studies on the chemistry and biology of DA natural products are ongoing and will be reported in due course.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.5b12778.

Experimental details and characterization data (PDF)
X-ray crystallographic data for **24** (CIF)
X-ray crystallographic data for **26** (CIF)

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‡C.Q. and Y.X. contributed equally to this paper.

Notes

The authors declare no competing financial interest.

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