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Communication

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

Chao Qi, ‡ Yuan Xiong, ‡ Vincent Eschenbrenner-Lux, Huan Cong, and John A. Porco, Jr. *

Department of Chemistry and Center for Molecular Discovery (BU-CMD), Boston University, Boston, Massachusetts 02215

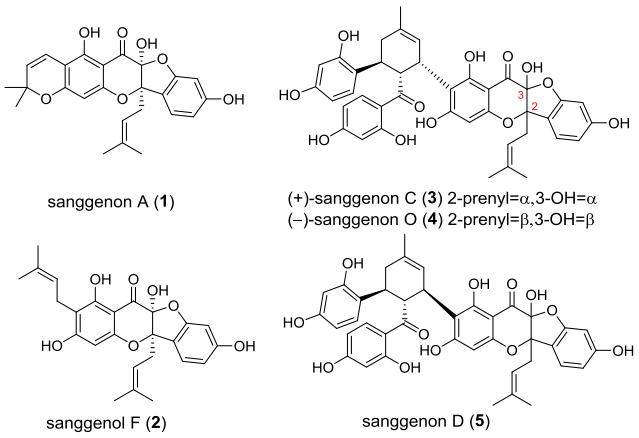
Supporting Information Placeholder

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.

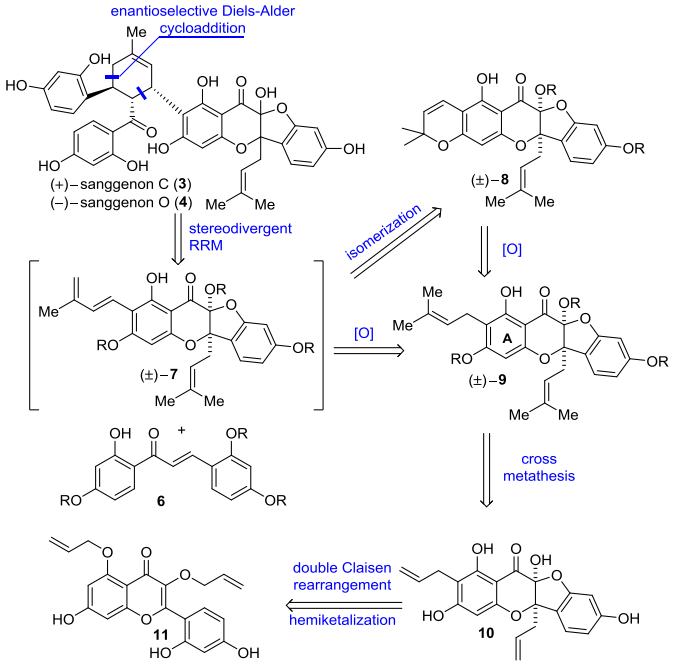
Sanggenon-type natural products (**Figure 1**) are intriguing synthetic targets due to their complex chemical structures and potent biological activities.[1] In particular, the congener sanggenon C[2] has antitumor, antiviral, and anti-inflammatory properties[3] which underscores the compound as an attractive synthetic target. Although chemical syntheses of related Diels-Alder 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 Diels-Alder cycloadditions of complex flavonoid dienes. Herein, 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 sanggenons C (**3**) and O (**4**).[6] In particular, a unique stereodivergent reaction on a racemic mixture (stereodivergent RRM)[7] was employed to obtain enantioenriched sanggenons C (**3**) and O (**4**) in an efficient manner.

Sanggenons C (**3**), D (**5**),[8] and O (**4**) are apparent Diels-Alder 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

Figure 1. Structures of Sanggenon-Type Natural Products



Scheme 1. Retrosynthetic Analyses for Sanggenons C and O

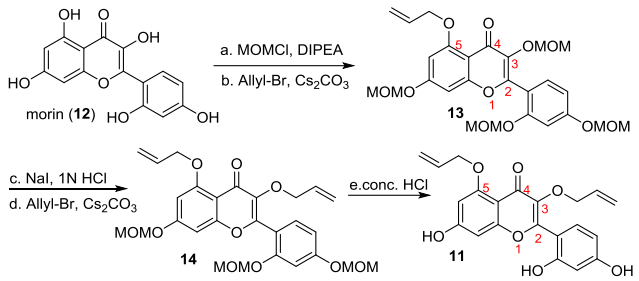


the chiral, racemic diene **7** as a promising strategy to synthesize these two targets assuming that issues of *endo/exo*, face-, and enantio-selectivity could be addressed. The requisite flavonoid diene (**7**) may be derived from dehydrogenation of the prenyl group of sanggenol F or its protected derivative (**9**).[5a, 9] Alternatively, the flavonoid diene may be derived from isomerization of the chromene ring in sanggenon A or the corresponding 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 the requisite *bis*-allyloxyflavone substrate **11** commenced with *tetra*-MOM group protection of the commercially available compound morin (**12**) and 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 substrate **13** appears to activate the 3-MOM group for chemoselective deprotection. Finally, 3-allylation and global MOM deprotection afforded the desired *bis*-allyloxyflavone ether substrate **11** in 33% overall yield (five steps).

A number of rare earth metal triflates were evaluated for double rearrangement of *bis*-allyloxyflavone substrate **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,

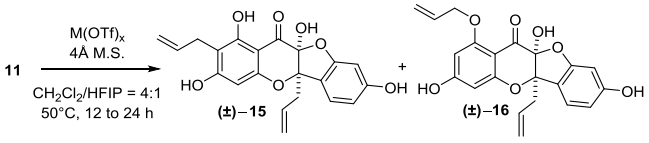
Scheme 2. Synthesis of Morin *Di*-allyl Ether



Conditions: (a) MOMCl (5 equiv.), DIPEA (5 equiv.), CH_2Cl_2, 0 °C to r.t., 55%; (b) allyl-Br (1.2 equiv.), Cs_2CO_3 (1.2 equiv.), DMF, 65°C, 12h, 93%; (c) NaI (0.8 equiv.), 1N 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%.

hexafluoro-2-propanol (HFIP) was used as a polar, non-coordinating[14] cosolvent to solubilize the polar rearrangement substrate. Other rare earth triflates were found to produce the double rearrangement product **15** along with the single rearrangement product **16** in varying ratios. Based on examination of a DFT molecular model[13] for substrate **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 rare earth metal triflates may explain the product distributions observed in **Table 1**. For example, $La(OTf)_3$ with a larger ionic radius (103.2 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. The product of mono-aromatic Claisen rearrangement (*not shown*) was not observed during the screening.

Table 1. Evaluation of Lewis Acids for Double Rearrangement of 11[a]

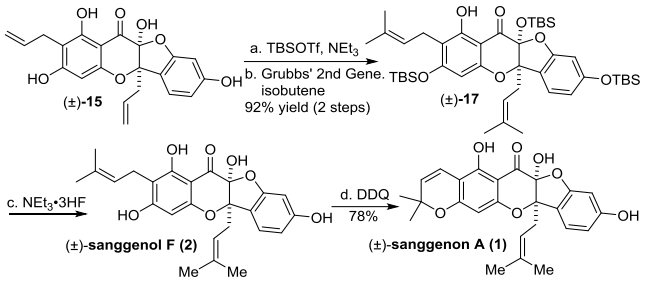


entry[b]	$M(OTf)_x$	ionic radii (pm)[c]	yield% (**15**, **16**)[d]
1	$Yb(OTf)_3$	86.8	72%, 0%
2	$Y(OTf)_3$	90.0	60%, 36%
3	$Gd(OTf)_3$	93.8	48%, 40%
4	$Nd(OTf)_3$	98.3	38%, 62%
5	$La(OTf)_3$	103.2	0%, 70%

[a] Please see the Supporting Information for complete 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. [d] Isolated yield determined using purified **15** and **16**.

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. This sequence enabled purification of the final product from residual ruthenium byproducts. Desilylation of (±)-**17** afforded (±)-**2** which was dehydrogenated with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) [10,18] to afford (±)-sanggenon A (**1**) in 78% yield.

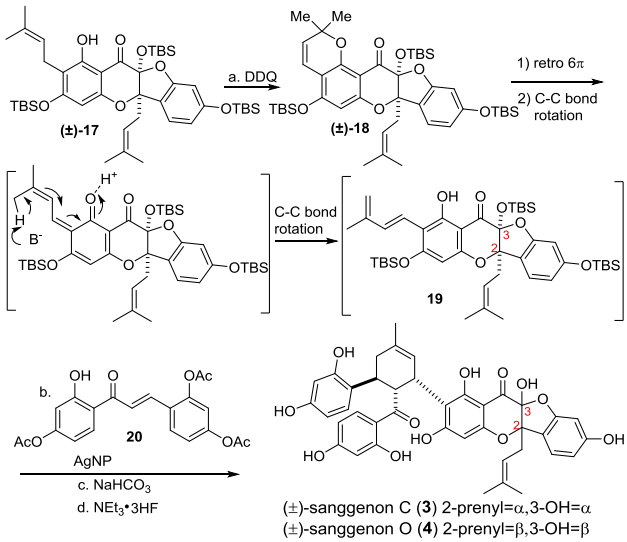
Scheme 3. Syntheses of Sanggenol F and Sanggenon A



Conditions: (a) TBSOTf (3.2 equiv.), NEt_3 (3.0 equiv.), CH_2Cl_2, r.t., 6h; (b) Grubbs' 2nd gen. cat. (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%.

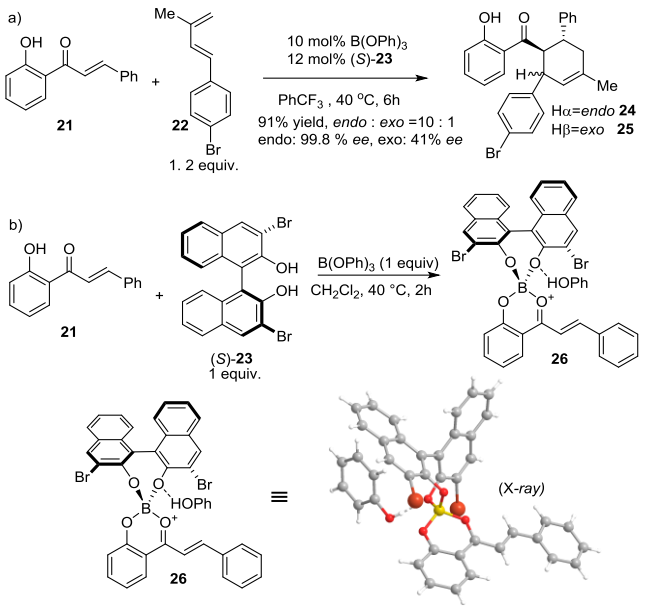
We next evaluated (±)-sanggenon A (**1**) as a diene precursor for [4+2] cycloaddition. Treatment of **1** under Brønsted acidic, thermal, or photochemical conditions in the presence of silica-supported silver nanoparticles (AgNP's) [19] and 2′-hydroxychalcone (*cf.* **20**) as dienophile did not lead to the desired [4+2] cycloaddition; only severe 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 THF cleanly afforded chromene (±)-**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] The 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 TBS-protected chromene **18** could generate the desired diene **19** *in situ* through retro 6π-electrocyclization followed by deprotonation/protonation (formal 1,7 hydrogen shift).[23] Accordingly, (±)-chromene **18** was employed in cycloadditions with acetylated 2′-hydroxychalcone

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



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, r.t., 12h; (d) NEt_3•3HF (8.0 equiv.), CH_3CN, r.t., 12h, 36% (3 steps), sanggenon C (**3**): sanggenon O (**4**) = 4:1.

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

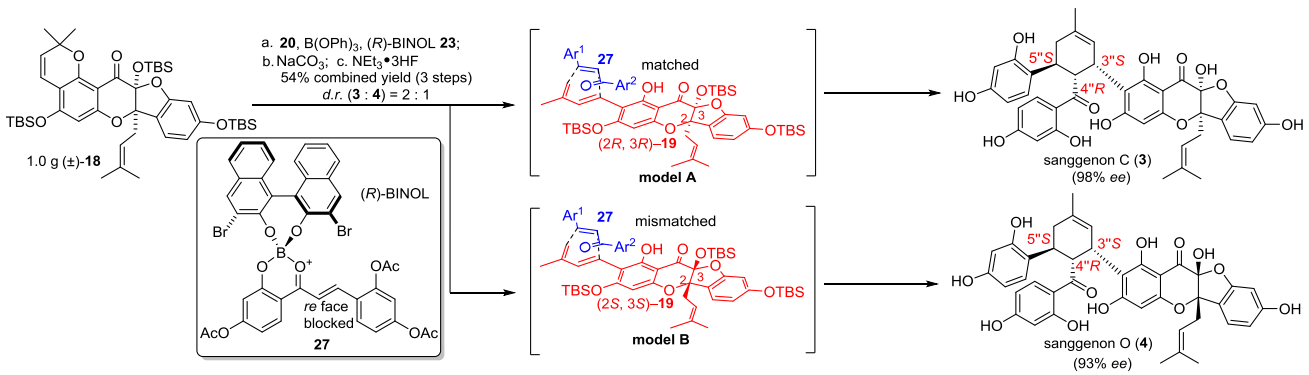


20 in the presence of AgNP's to yield a mixture of two *endo* cycloadducts and minimal production of *exo* diastereomers. The mixture of *endo* cycloadducts was sequentially treated with aqueous $NaHCO_3$ and NEt_3•3HF [24] to yield a mixture of (±)-sanggenons C (**3**) and O (**4**) in 36% yield over 3 steps in a 4 : 1 diastereomeric ratio.

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, and in >99% and 41% *ee*, respectively (**Scheme 5a**). A bright orange color change was observed when the borate catalyst and 2′-hydroxychalcone were combined, leading us to hypothesize that a borate-substrate complex (*cf.* **26**) may be generated as an active species for [4+2] cycloaddition. By mixing 2′-hydroxychalcone **21**, (*S*)-BINOL **23**, and $B(OPh)_3$ in CH_2Cl_2, we obtained borate complex **26**, the structure of which was confirmed by single X-ray crystal structure analysis.[13] The predicted absolute stereochemistry of the corresponding *endo* cycloadduct **24** based on the expected face selectivity of complex **26** was also confirmed by X-ray crystallography.[13] We found that 1 equivalent 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 to produce **24** in high enantioselectivity.[13] The latter result reinforces the involvement of borate complex **26** in the catalytic asymmetric Diels-Alder cycloaddition which is also supported by literature precedent.[28]

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 (*R*)-BINOL **23** were employed. A mixture of cycloadducts were observed which was followed by consecutive deprotections ($NaHCO_3$; NEt3•3HF) to afford sanggenon C (**3**) and sanggenon O (**4**) in 2: 1 ratio and 98%, 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**; *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 sanggenon C (**3**) and sanggenon O (**4**). Using (*S*)-BINOL **23** as catalyst, *ent*-sanggenon C (**3**) and *ent*-sanggenon O (**4**) were isolated in a 2 : 1 ratio and in 99%, 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

Scheme 6. Asymmetric Syntheses of Sanggenons C and O



Conditions: (a) $B(OPh)_3$ (20 mol%), **23** (22 mol%), 80 °C, 48h; (b) *sat.* $NaHCO_3$, MeOH, r.t.,12h; (c) NEt_3•3HF (8.0 equiv.), CH_3CN, r.t., 12h.

matched/mismatched cycloadditions may also be operative based on differential interactions of the chiral borate catalyst with both enantiomers of diene **19**.

In order 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 complex **27** using and both enantiomers of a simplified variant of the diene (**19'**, TMS instead of TBS groups) to analyze the interacting complex of reagents engaging in Diels-Alder cycloaddition.[13, 29] Simplified cycloaddition models **A** and **B** are shown in **Scheme 6** with the lowest energy conformer of diene **19**. It 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[30] (See Supporting Information) show that there are significant steric interactions between the prenyl and phenyl group 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 for the natural products.[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 scaffold 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 enantioselectivity 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 Diels-Alder natural products, as well as a complete energetic profiling of the key stereodivergent RRM, are ongoing and will be reported in due course.

ASSOCIATED CONTENT

Supporting Information. Experimental procedures and characterization data for all new compounds described herein, including CIF files for compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

AUTHOR INFORMATION

Corresponding Author

porco@bu.edu

Author Contributions

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

Notes

The authors declare no competing financial interests.

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