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Total syntheses of hyperaspidinols A and B enabled by a bioinspired diastereoselective cascade sequence

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ABSTRACT

A bioinspired acid-triggered hemiacetalization/dehydration/[3 + 3]-type cycloaddition cascade process was disclosed, diastereoselectively furnishing furo[2,3-*b*]chromene skeleton under mild conditions. The viability of this approach was demonstrated by syntheses of a series of furo[2,3-*b*]chromene and pyrano[2,3-*b*]chromene derivatives. The successful total syntheses of two lignan-phloroglucinol hybrids, hyperaspidinols A and B, exemplified the synthetic utility of our biomimetic methodology.

Benzopyran-fused polycyclic ketals are prevalent in diverse natural products with significant biological properties such as potent L-calcium channel blocking activity, inhibitory activity against acetylcholine esterase, antioxidative property, and protective effect on mitochondria [1–5]. Their unique structural characteristics and potential biological activities have made them privileged pharmacophores for the development of industrially significant pharmaceuticals and agrochemicals. Moreover, their fascinating and complex scaffolds with potential usefulness, which were responsive for various serious diseases or pharmacological applications, have served as popular synthetic targets and sparked a wide range of notable synthetic efforts in recent years [6–22]. However, their access with high stereoselectivity under mild conditions remains to be desired. Herein, we report a bioinspired hemiacetalization/dehydration/[3 + 3]-type cycloaddition cascade to construct benzopyran-fused polycyclic ketals with generally good diastereoselectivities under mild conditions and the first bioinspired total syntheses of hyperaspidinols A (**1**) and B (**2**) *via* this strategy.

Hyperaspidinols A and B were isolated from *Hypericum chinense* L. (Hypericaceae) [23], which served as highly active traditional herb agents for the treatment of sepsis, acute laryngopharyngitis, conjunctivitis, hepatitis, and snake bite [24–28]. Structurally, hyperaspidinols A and B feature a novel furo[2,3-*b*]chromene framework (Fig. 1, highlighted in bold) and represent an intriguing and ubiquitous family of lignan derivatives with fascinating hybrid skeletons (Fig. 1) [23]. The remarkable potential biological activities and novel structural features of the two molecules make them appealing targets for the synthetic community [29–31]. Moreover, the successful syntheses of hyperaspidinols A and B will pave the way to efficiently access a series of biologically interesting natural products with hybrid structures such as melipatulinones A–C [32], patulignans (Fig. 1) [33] and divergent syntheses of their analogues towards drug development.

Inspired by these characteristic scaffolds in pharmaceutically active natural products, we speculated that hyperaspidinols A and B could evolve from substantially less complex natural products hyperione **9** or **10** by hybridization with the corresponding aspidinols C (**4**) and D (**5**), which were isolated together with hyperaspidinols A and B from the same herb [23]. Our continued interest in biomimetic construction of polycyclic ketal skeletons [34–38] guided us to speculate that hyperaspidinols A and B might arise from the methyleneoxonium intermediate **6** *via* a formal [3 + 3]-type cycloaddition cascade process (Scheme 1), similar to our previous strategies utilized in biomimetic total syntheses of

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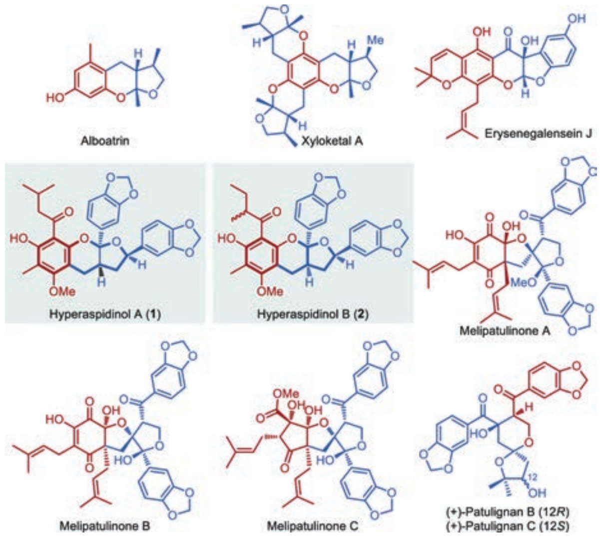
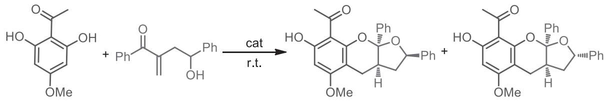


Fig. 1. Representative natural products bearing furo[2,3-*b*]chromene or hybrid skeletons.

myrtucommuacetalone [35], sanctis [37], and tomentosones [38]. **6** might generate from hyperione A (**9**) or B (**10**) *via* a retro-Michael addition/hemiacetalization/dehydration cascade sequence. In this regard, from the biogenetic perspective, if a one-pot acid-catalyzed cascade sequence merging the fascinating multistep transformations was established, it would render straightforward syntheses of hyperaspidinols A and B (**1** and **2**) with high efficiency.

With the biomimetic scenario in mind, we first explored the construction of the benzopyran ketal skeleton. Optimization studies commenced with an evaluation of solvent, time, and catalyst by using the readily accessible phloroglucinol **11a** [39,40] and hydroxyl vinyl ketone **12a** [41] as model substrates (Table 1). When the two substrates were treated with TFA in methanol, only complex mixtures were observed (entry 1). Gratifyingly, switching the solvent to THF delivered the desired cascade reaction smoothly, furnishing the corresponding furo[2,3-*b*]chromene products **13a** and **14a** in 74% isolated yield with 8:1 diastereomeric ratio (entry 2).

Table 1
Optimization of reaction conditions.[a]

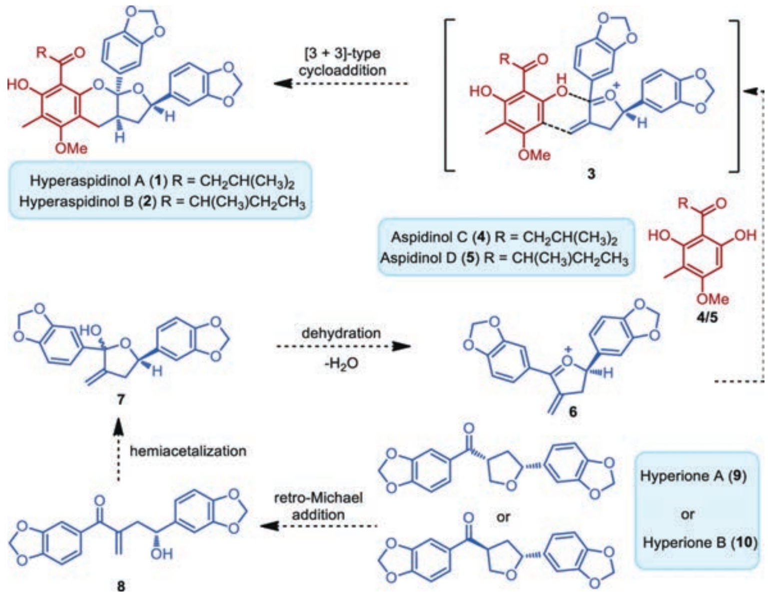


12a 13a 14a

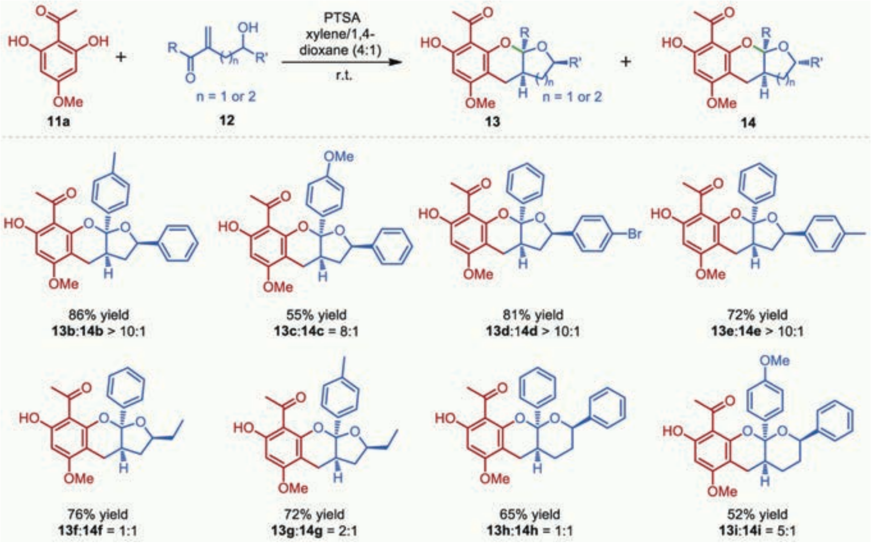
Entry	Solvent	Catalyst (equiv.)	Time (min)	Yield (%)[b]	Ratio (**13a**:**14a**)[c]
1	MeOH	TFA (2.0)	45	-	-
2	THF	TFA (2.0)	90	74	8:1
3	xylene	TFA (2.0)	45	62	5:1
4	DCM	TFA (2.0)	60	58	5:1
5	DCM/xylene (1:1)	TFA (2.0)	60	65	8:1
6	DCM/THF (1:1)	TFA (2.0)	60	25	5:1
7	1,4-dioxane	TFA (2.0)	90	65	8:1
8	THF/xylene (1:2)	TFA (2.0)	60	72	8:1
9	THF/xylene (1:2)	PPTS (0.1)	60	NR	-
10	THF/xylene (1:2)	PTSA (0.1)	45	80	10:1
11	THF/xylene (1:2)	AcOH (0.1)	60	NR	-
12	xylene/1,4-dioxane (4:1)	PTSA (0.1)	35	83	>10:1
13	xylene/1,4-dioxane (1:1)	PTSA (0.1)	45	75	10:1
14	xylene/1,4-dioxane (10:1)	PTSA (0.1)	30	78	10:1

[a] Standard conditions: **11a** (0.11 mmol), **12a** (0.1 mmol), catalyst in solvent (10 mL) stirred at room temperature under N_2 unless noted otherwise;
[b] Combined yield of the isolated mixture of **13a** and **14a**;
[c] Determined by ^1H NMR analysis.

A systematic screening of solvents disclosed that nonpolar solvents such as xylene, dichloromethane, tetrahydrofuran, and their mixtures worsened the reaction in both yields and diastereoselectivities except for faster reaction rate (entries 2–6). The solvent screening showed that 1,4-dioxane and xylene/THF mixture solvents could provide almost identical yield and diastereomeric ratio as those of THF (entries 7 and 8). Attempting to further improve the yield and selectivity, we then screened several protonic acids as catalysts. Catalytic amount of pyridinium *p*-toluenesulfonate (PPTS) and stoichiometric AcOH were proven to be non-effective, whereas *p*-toluenesulfonic acid (PTSA) could trigger the desired transformation (entries 9–11). Notably, when we occasionally changed the solvent mixture to xylene/1,4-dioxane, both the yield and diastereoselectivity were obviously increased (entry 12). However, changing the ratio of the mixture solvents failed to further improve the



Scheme 1. Proposed biogenesis of hyperaspidinols A and B.



Scheme 2. Substrate scope with respect to hydroxyl vinyl ketones. Reaction conditions: **11a** (0.22 mmol), **12** (0.2 mmol), PTSA (0.02 mmol) in xylene/1,4-dioxane (4:1, 10 mL) stirred at room temperature for 0.5–3 h; combined yields of the isolated mixture of **13** and **14**; ratio (**13**:**14**) determined by ^{1}H NMR unless noted otherwise.

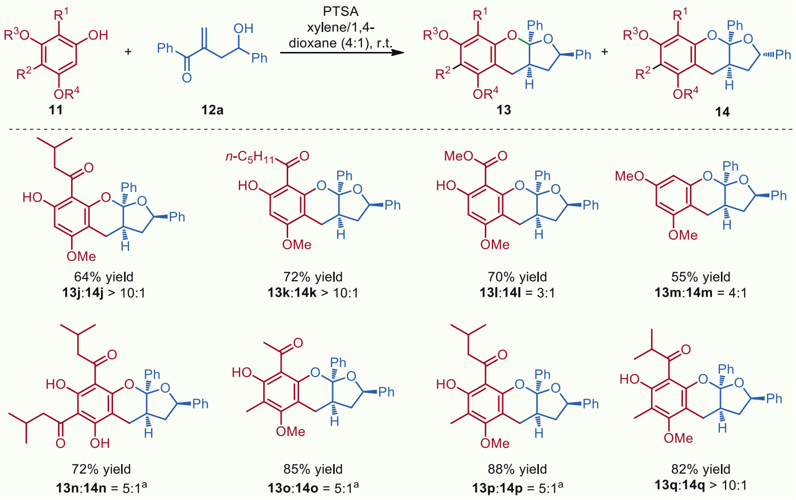
reaction efficiency (entries 13 and 14). Finally, 0.1 equiv. of PTSA as catalyst in xylene/1,4-dioxane (4:1) were selected as the optimal reaction condition (83% yield, >10:1 dr, Table 1, entry 12), thereby laying a solid foundation for the efficient syntheses of the benzopyran-fused polycyclic ketals.

With the optimized reaction conditions established, the scope of the biomimetic cascade reaction with respect to both reaction partners was evaluated. A series of hydroxyl vinyl ketones (**12**) could be converted to the corresponding furo[2,3-*b*]chromene products **13** and **14** in moderate to high yields with different diastereoselectivities as summarized in Scheme 2. Hydroxyl vinyl ketones bearing different aryl groups such as 4-methylphenyl (**12b** or **12e**), 4-methoxylphenyl (**12c**), and 4-bromophenyl (**12d**) were suitable reaction candidates, delivering the corresponding products **13b-e** in 55%–86% yields with good diastereoselectivities. Notably, hydroxyl vinyl ketones with an alkyl group attached on the α-carbon gave good yields but with poor diastereoselectivities (**13f**-**g** and **14f**-**g**), probably due to steric effects. Furthermore, hydroxyl vinyl ketones bearing an extended chain could also undergo this transformation smoothly albeit with imperfect stereoselectivity, allowing the efficient construction of benzopyran-fused polycyclic ketals **13h**-**i** and **14h**-**i**.

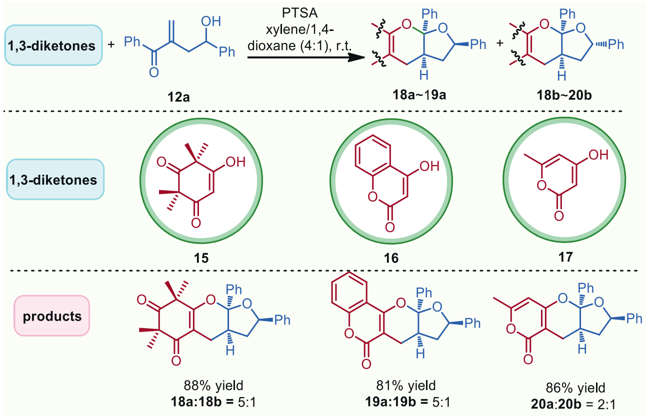
Encouraged by the aforementioned excellent results, further efforts towards verifying the substrate scope and versatility of the phenolic reaction partner **11** were also conducted. As shown in Scheme 3, the phenol substrates with different acyl substituents such as *iso*-valeryl (**11j**) and *n*-hexanoyl (**11k**) were well tolerated under the standard reaction conditions, which could give rise to the desired products in good yields and diastereomeric ratios, thus clarifying excellent tolerance of the developed cascade sequence. Similarly, the ester substituted phloroglucinol (**11l**) could also smoothly react with hydroxyl vinyl ketone **12a** to afford the polycyclic ketals **13l** and **14l** in 70% overall yield with a ratio about 3:1. 3,5-Dimethoxyphenol **11m** was also suitable reaction partner, allowing the synthesis of **13m** and **14m** in reasonable yield with acceptable diastereoselectivity. Moreover, diacylphloroglucinol **11n** delivered the corresponding products **13n** and **14n** with comparable yield and diastereoselectivity to those of the monoacylphloroglucinol **11j**. Much to our delight, the methyl substituted phloroglucinols (**11o**-**q**) could undergo this transformation and afford the corresponding furo[2,3-*b*]chromene products in yields more than 80% with good to excellent diastereoselectivities, generating a series of structurally diverse and closely similar analogues of melipatulinones A-C, which marked an advantage of this method and strongly indicated the promising utility of this cascade methodology to efficiently synthesize such lignin-phloroglucinol hybrid natural products and pharmacological compounds.

The synthetic possibility of this fascinating bioinspired hemiacetalization/dehydration/[3 + 3]-type cycloaddition cascade reaction was further reflected by intelligent orchestrations with straightforward structural combinations for the critical fragments of the pharmaceutically meaningful natural products. As delineated in Scheme 4, the potential bioactive fragment syncarpic acid **15**, which shared an intriguing tetramethylcyclohexenedione skeleton responsive for the most characteristic unit of natural polycyclic polymethylated phloroglucinols mainly encountered in the Myrtaceae plants [42], was treated with hydroxyl vinyl ketone **12a**, and the desired cascade reaction proceeded smoothly, delivering polycyclic ketals **18a** and **18b** in 88% yield with good diastereoselectivity. Moreover, 4-hydroxy-2*H*-chromen-2-one (**16**), answering for the biologically meaningful pharmaceutical core scaffold in numerous natural products [43,44] underwent the established reaction, also providing the desired products **19a** and **19b** in good combined yield as expected. Remarkably, the common naturally occurring 4-hydroxy-6-methyl-2-pyrone (**17**) [45] was also successfully converted to the targeted polycyclic ketals **20a** and **20b** in satisfactory yield. Collectively, the aforementioned representative structural combinations of the critical natural product fragments chemologically clarified its promising potential to efficiently access a focused library of natural products-modified analogues bearing diverse biologically functional units and might open up new vistas in structural optimizations of related natural products for broad scientific interest.

Building on the above initial success of the bioinspired methodology of hemiacetalization/dehydration/[3 + 3]-type cycloaddition cascade, the concise total syntheses of hyperaspidinols A and B were then performed to verify its potent synthetic utility. We initiated the preparation of the corresponding phloroglucinols **4** and **5** as depicted in Scheme 5. Selective protection of the free phenolic hydroxyl groups with allyl bromide followed by methylation of 2,4,6-trihydroxybenzaldehyde efficiently afforded aldehyde **24** in 65% yield over 2 steps. Further treatment of aldehyde **24** with $NaBH_3CN$ under acidic condition generated **25** in 94% yield effi-



Scheme 3. Substrate scope with respect to phenolic reaction partner. Reaction conditions: **11** (0.22 mmol), **12a** (0.2 mmol), PTSA (0.02 mmol) in xylene/1,4-dioxane (4:1, 10 mL) stirred at room temperature for 0.5–3 h; combined yield of the isolated mixture of **13** and **14**; ratio (**13**:**14**) determined by ^{1}H NMR unless noted otherwise. [a]Ratio of isolated products of **13** and **14**.

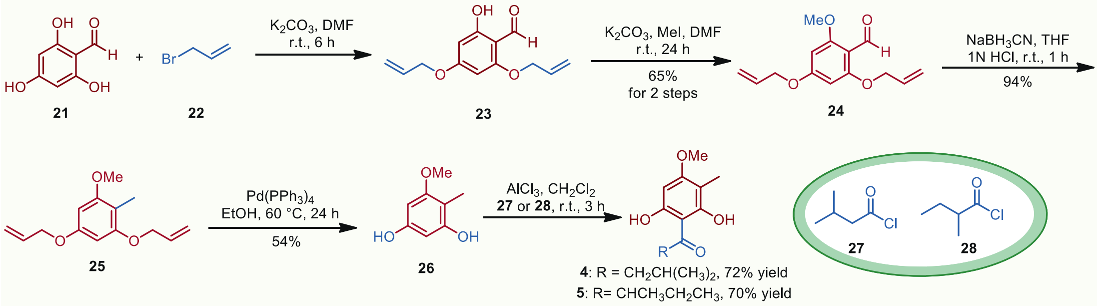


Scheme 4. Substrate scope with respect to 1,3-diketones. Reaction conditions: 1,3-Diketone (0.22 mmol), **12a** (0.2 mmol), PTSA (0.02 mmol) in xylene/1,4-dioxane (4:1, 10 mL) stirred at room temperature for 0.5–3 h; combined yield of diastereomers; ratio of the diastereomers.

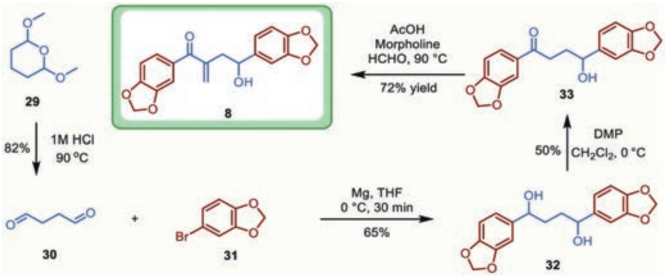
ciently. Deprotection of the allyl functionalities with Pd(PPh_3)$_4$ expectedly freed the two phenolic hydroxyl groups in moderate yield. Next, the critical phloroglucinol precursors **4** and **5** (asipidinols C and D) were delivered propitiously *via* Friedel-Crafts acylation of phenol **26** with acyl chlorides **27** and **28** in about 72% and 70% yield, respectively. Notably, asipidinols C (**4**) and D (**5**) were also biologically active natural products with various pharmaceutical activities [46,47] and they were completely synthesized for the first time in this study.

At this stage, efforts were further made to synthesize the other critical precursor **8**. As shown in Scheme 6, **8** was readily prepared from commercially available acetal **29**, which underwent hydrolysis under an acidic condition to afford butanedial **30** referring to previously established procedure [48]. Exposure of butanedial **30** to the Grignard reagent generated *in situ* from 4-bromo-1,2-(methylenedioxy)benzene **31** and magnesium under nitrogen atmosphere smoothly delivered the symmetrical diol **32** in 65% yield. Selective mono-oxidation of benzyl diol **32** with Dess-Martin periodinane (DMP) furnished the targeted aryl ketone **33** in moderate yield. The morpholine catalyzed aldol condensation followed by dehydration afforded the critical precursor **8** in 72% yield.

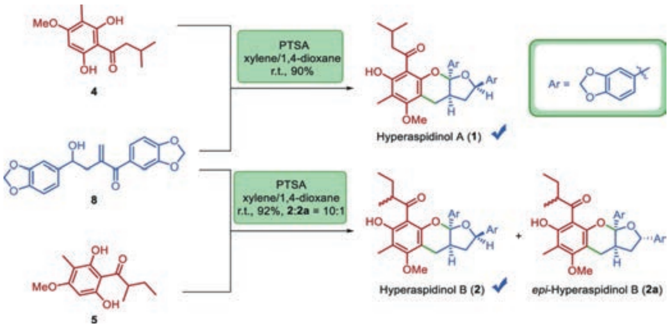
Acquisition of the critical precursors asipidinols C and D (**4**, **5**) and hydroxyl vinyl ketone **8** set the stage for the biomimetic total syntheses of hyperaspidinols A and B *via* the key biosynthetic hemiacetalization/dehydration/[3 + 3]-type cycloaddition cascade. Gratifyingly, aspidinol **4** reacted with hydroxyl vinyl ketone **8** smoothly to generate hyperaspidinol A in excellent yield with the diastereoslectivity more than 10:1, and the treatment of **8** with racemic aspidinol **5** gave the desired product in 92% yield as a 10:1 mixture of diastereoisomers favoring hyperaspidinol B (**2**) (Scheme 7). The NMR and HR-ESIMS spectra of the synthetic hyperaspidinol A are in full agreement with literature reports [23], and the synthetic hyperaspidinol B displayed NMR spectral properties in agreement with the reported ones except the different diastereomeric ratios (about 1:1) in regard to the acyl



Scheme 5. Syntheses of critical precursors asipidinols C and D (**4, 5**).



Scheme 6. Synthesis of critical precursor **8**.



Scheme 7. Biomimetic total syntheses of hyperaspidinols A and B (**1, 2**).

group on the phloroglucinol motif [23]. In this regard, the first total syntheses of hyperaspidinols A and B were accomplished, which strongly suggested that the aforementioned hemiacetalization/dehydration/[3 + 3]-type cycloaddition cascade sequence might probably proceed by mimicking their biosynthetic pathway.

In summary, a biomimetic hemiacetalization/dehydration/[3 + 3]-type cycloaddition cascade methodology for the efficient establishment of furo[2,3-*b*]chromene was defined, and it was attested by the efficient total syntheses of hyperaspidinols A and B. The effectiveness of our strategy is borne out by the fact that a broad spectrum of novel furo[2,3-*b*]chromene derivatives could be constructed in moderate to good yields with different diastereoselectivities. Further applications of this strategy in the total syntheses of other natural products with similar skeletons are currently ongoing in our laboratory and will be reported in due course.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgments

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.cclet.2021.08.035.

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