Facile and Divergent Synthesis and Antifungal Evaluation of Drimane Meroterpenoids by Merging Decarboxylative Borylation and Suzuki Coupling

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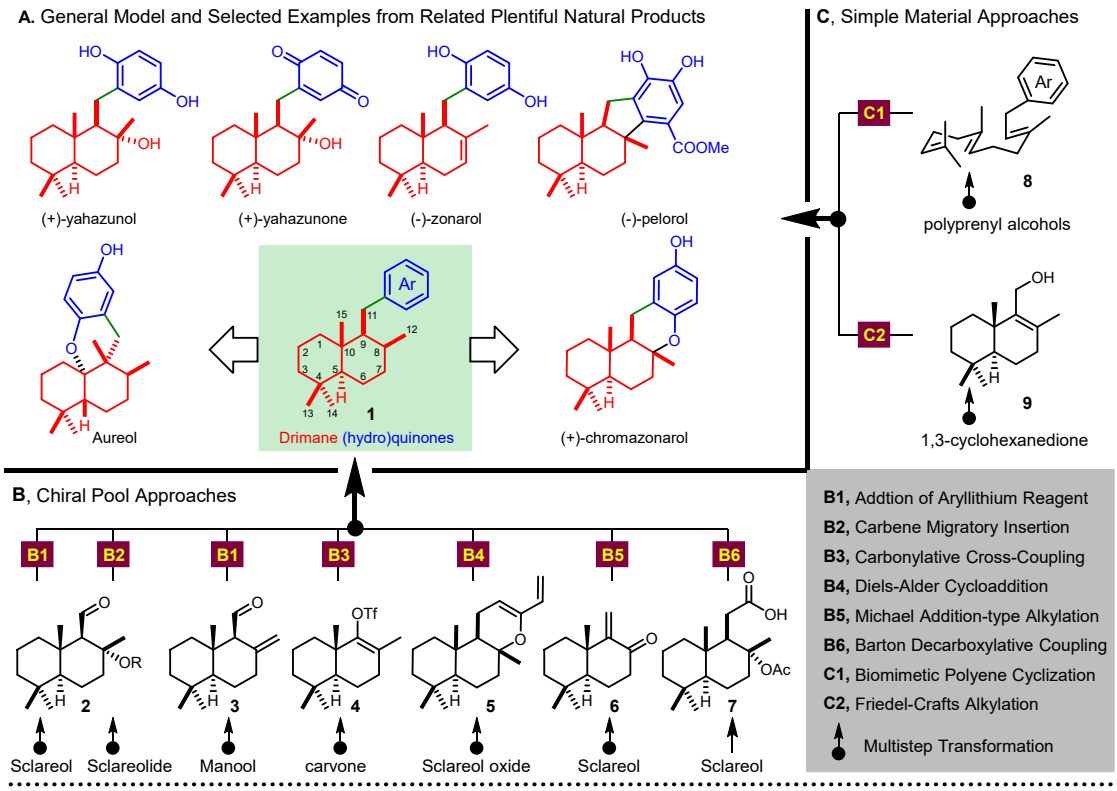
Abstract Drimane meroterpenoids have attracted increasing attention in the discovery of therapeutically important probes, while the laggard synthetic accessibility and variety is a conspicuous challenge. A new paradigm merging decarboxylative borylation and Suzuki coupling was developed as a powerful platform to access a large variety of drimane meroterpenoids. Key features of this tactic include mild conditions, operational facility, broad scope, scalability, and good chemofidelity as well as easy availability of the coupling partners. This modular strategy enables the expedient formal synthesis of a large number of natural products and the rapid generation of analogs. The high degree of practicality bodes well for the discovery of pharmaceutically important entities and allowed the first evaluation of some non-natural mimics as antifungal agents.

Introduction

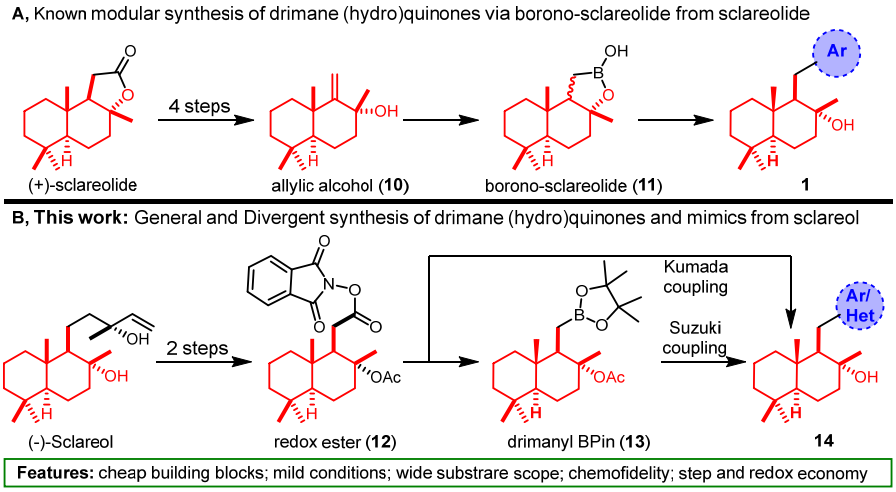
Natural products occupied an irreplaceable role in the discovery of therapeutically important entities due to their unique biological profiles or uncharted chemotypes.[1] An analysis of medicinal compounds synthesized over the past 50 years demonstrates the importance of the combination between sp^2 and sp^3 hybridized carbons for drug discovery.[2] Though assimilation of the sp^3-rich scaffolds into drug leads often results in favorable pharmacological properties, the average fraction of sp^3 hybridized carbon atoms is declining.[3] Drimane (hydro)quinones (Scheme 1A) are a large family of secondary metabolites from mixed biogenesis of polyketide-terpenoids origins.[4] Decoration or tiny modification on either the aromatic ring or drimane segment of the common scaffold **1**, will lead to vast swaths of natural products (Scheme 1A) possessing a wealth of bioactivities,[5] ranging from anti-inflammatory, anti-HIV, antitumor, antiviral, antimalarial to antifungal potentials. This kind of natural products showed a tremendous advantage as an ideal model in drug discovery in the view of a structural standpoint by assembling the preinstalled stereospecific sp^3 hybridized skeleton with sp^2 hybridized aromatic equivalents. Considerable attentions have been devoted to identifying the potential targets, including cholesteryl ester transport protein[6], PI3kinase[7], sphingosine kinase[8] and succinate dehydrogenase.[9]



Scheme 1, Previous approaches to drimane (hydro)quinones

The biological importance and distinctive structure have promoted some synthetic efforts to this kind of natural products (Scheme 1B and Scheme 1C). The majority of contributions have focused on the chiral pool approaches through the degradation of sclareol,[10] sclareolide[11], or (+)-manool[12] to afford *β*-hydroxyl/acetoxy aldehyde **2** or the homoallylic aldehyde **3**. Subsequent nucleophilic attack by the aryl lithium reagents and deoxidation at the C_{11} position will lead to the product **1**. The palladium-catalyzed tandem carbene migratory insertion of an aryl iodide and a drimanal hydrazine of the intermediate **2** was also developed.[13] The trifluoromethane sulfonate **4** synthesized from *R*-carvone was successfully used to construct the central framework *via* Stille carbonylative cross-coupling reaction and Michael cyclization.[14] Sclareol oxide was converted to the diene **5** in the Diels-Alder cycloaddition approach.[15] A cationic-resin-promoted Michael-type Friedel-Crafts alkylation[16] was conducted based on the *α,β*-unsaturated ketone **6**. Barton decarboxylative coupling was realized for the efficient

synthesis of (+)-yahazunol and related natural products with the homodrimanic acid **7** as a key synthon.[17] Lewis acids catalyzed cyclization of the corresponding farnesyl derivatives **8** were also realized recapitulating the biosynthetic logic.[18] Total synthesis with Weiland Miesher ketone synthesis and Friedel-Crafts alkylation as key steps was attempted starting from 1,3-cyclohexanedione (*via* allylic alcohol **9**).[19] While such tactics can generate certain natural products and analogues, the harsh conditions (*e.g.* sensitive organometallic reagents, toxic reagents, cryogenic environment), multistep, limited scope, poor chemo-fidelity and selectivity impeded the suitability for scale applications and the diversity for detailed chemicobiology.



Scheme 2, Modular synthesis of drimane (hydro)quinones and our work

Since synthetic efforts in the discovery of functional molecules place emphasis on modular disconnections, a general strategy to access these natural products and mimics in a concise and divergent fashion is highly desirable. Practical and simple methods to forge linkages between sp^2 and sp^3 hybridized carbons are of extreme importance for this kind of natural products, elegant demonstrations of the convenience and practicality of such a philosophy was reported by Baran group harnessing "borono-sclareolide" **11** (Scheme 2A).[20] This fruitful radical coupling led us to hypothesize that the catalytic and direct suture of drimane with the aromatic ring is feasible through the sp^2-sp^3 coupling. Inspired by the significant advances in the decarboxylative

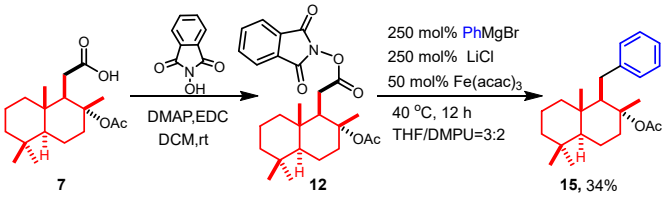
functionalization,[21] we envisage that the bench stable and easily accessible homodrimanic acid **7** can be transformed to a synthetic hub for the modular and divergent synthesis of drimane (hydro)quinones. Realization of this hypothesis will facilitate the acquirement of manifold drimane meroterpenoids without the previously encountered inconvenience including cryogenic temperatures, unstable intermediate, (super)stoichiometric metals, and undesired epimerization. Herein, we would like to disclose the discovery of the cross-talk of decarboxylative borylation and Suzuki coupling as an operationally facile tool for the modular and divergent synthesis of drimane (hydro)quinones and mimics **14** (Scheme 2B).

Results and Discussion

In the pursuit of a practical route or a platform to drimane meroterpenoids of wide substituent variability, our work commenced with seeking potential "synthetic hubs" based on the easily accessible homodrimanic acid **7**, which can be directly synthesized from the cheap and bulky natural product sclareol.[17]

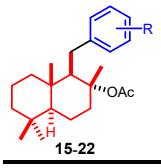
Kumada Coupling Approach. Inspired by the established elegant coupling of redox-active esters with organomagnesium reagents (Kumada coupling),[21f] the homodrimanic acid **7** was converted to the redox-active homodrimanyl-*N*-hydroxyphthalimide (NHPI) ester **12** and tested directly in the Fe catalyzed Kumada coupling with the commercially available Grignard reagent PhMgBr for the construction of drimane meroterpenoid **15**. The optimized reaction conditions reported by Baran and coworkers were transferred directly to the current model reaction. Though full conversion of the redox-active ester **12** was observed, the desired drimane meroterpenoid **15** can only be prepared in modest yield, and always be contaminated by the acid **7** and biphenyls from hydrolysis of compound **12** and the homocoupling the Grignard reagent, respectively.

Table 1, Synthesis of drimane meroterpenoids via Kumada Coupling



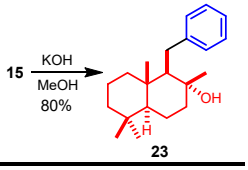
Entry	Devition in the Kumada Coupling	Isolated yield of **15** (%)
1	30 °C	26%
2	30 °C, THF in stead of THF/DMPU	26%
3	50 °C	14%
4	125 mol% PhMgBr	7%
5	20 mol% $Fe(acac)_3$	19%
6	$FeCl_3$ in stead of $Fe(acac)_3$	31%
7	TCNHPI in stead of NHPI	10%
8	Without LiCl	15%

Different Grignard Reagents in Kumada Coupling



15, R = H 34%
16, R = *ortho*-MeO 37%
17, R = *meta*-MeO 48%
18, R = *para*-MeO 40%
19, R = *para*-Me 32%
20, R = *para*-F 28%
21, R = *meta*-F 31%
22, R = *para*-Ph 15%

Hydrolysis of compound **15**

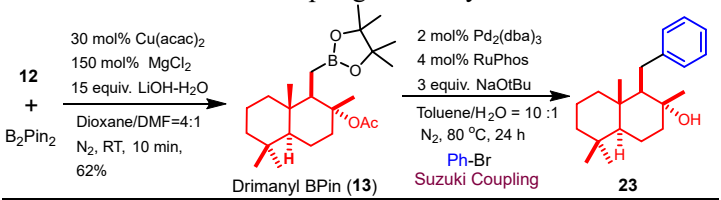


To make the mixture simpler, single ether solvents were tested and THF gave a comparative isolated yield (Table 1, entries 1 and 2), *albeit* in low conversion. Elevating the reaction temperature, diminution of the loading of the Grignard reagent or Fe catalyst (Table 1, entries 3-5) showed a detrimental effect on the production of drimane meroterpenoid **15**. To our delight, other iron species were also productive (e.g. $FeCl_3$, Table 1, entry 6). Replacement of the NHPI by the more electron-deficient tetrachloro counterpart TCNHPI ester didn't lead to any improvement of compound **15** (Table 1, entry 7). The turbo-Grignard reagent (PhMgBr/LiCl) demonstrated a significant advantage over that with the standard Grignard reagent (PhMgBr) (Table 1, entry 8). Though no obvious improvements were achieved after extensive optimization of all the factors for this transformation (see Supporting Information for more details), the tolerance of the acetate group is noteworthy and open a new window for the further modification without the intentional introduction of the protective groups. A portfolio of drimane hydroquinone mimics can be prepared accordingly (**15**-**22**). Both electron-rich and electron-poor Grignard reagents were compatible in this transformation, with the former ones affording much higher yields of the drimane meroterpenoids (**18** *vs* **20**,

17 *vs* **21**). It is worthy to note that simple treatment of these products under basic conditions will furnish a few yahazunol analogues in good yields, exemplified by the acquirement of compound **23** from the precursor **15**. The modest yields, tedious separation caused by the homocoupling of the Grignard reagents, the concomitant hydrolysis of the redox-active ester **12**, and the limited substrate scope (dependence on the Grignard reagents) remained the glaring limitations of for this system.

Combination of Decarboxylative Borylation and Suzuki Coupling. Though certain drimane meroterpenoids can be prepared through the aforementioned method, the programmability and practicality were hampered by the dependence on the organometallic Grignard reagents and the inevitable side reactions. Therefore, we deprioritized the above tactic and shifted our attention to merging the decarboxylative borylation[21a] and the well-known Suzuki coupling.[22] An alternative detour leveraging these two powerful tactics together to the desired drimane meroterpenoids was conceived and executed.

Table 2, Optimization of the Suzuki coupling for the synthesis of drimane meroterpenoids



Entry	Devition in the Suzuki Coupling	Isolated yield of **23** (%)
1	None	46%
2	$Pd(OAc)_2$ or $PdCl_2$ or $Pd(TFA)_2$ instead of $Pd_2(dba)_3$	<5%
3	$Pd(dba)_2$ instead of $Pd_2(dba)_3$	36%
4	$Pd(dppf)Cl_2$ instead of $Pd_2(dba)_3$-RuPhos	30%
5	XPhos or DavePhos or PPh_3 or XantPhos instead of RuPhos	<5%
6	MePhos or Brettphos instead of RuPhos	26%
7	KOtBu instead of NaOtBu	37%
8	K_3PO_4 or K_2CO_3 or Cs_2CO_3 instead of NaOtBu	<5%
9	*t*-Butanol instead of Toluene	78%
10	DMF instead of Toluene	34%
11	2-MeTHF instead of Toluene	61%
12	$(CH_2Cl)_2$ instead of Toluene	6%
13	*t*-Butanol instead of Toluene, 4 equiv. NaOtBu	81%
14	*t*-Butanol instead of Toluene, 4 equiv. NaOtBu; 18 h, 100 °C	89%
15	*t*-Butanol instead of Toluene, 4 equiv. NaOtBu; 36 h, 80 °C	76%
16	*t*-Butanol instead of Toluene, 4 equiv. NaOtBu; 18 h, 110 °C	80%

The drimanyl Bpin (**13**) was envisioned as an advanced intermediate and was smoothly synthesized from the redox-active ester **12** with good chemofidelity and stereo fidelity.

This bench stable intermediate was confirmed unambiguously with X-ray single-crystal diffraction (CCDC 2006960). This synthetic hub was employed in the optimization of Suzuki coupling with PhBr for efficiently forging the Csp^2-Csp^3linkage. To our delight, a much simpler reaction mixture compared with the Kumada coupling (*vide supra*) was achieved with the catalytic combination of $Pd_2(dba)_3$/RuPhos. Noteworthily, the deprotection of the acetyl group underwent synchronously and the desired meroterpenoid **23** with free tertiary alcohol can be easily isolated (46%, Table 2, entry 1, standard conditions) without any additional manipulation. A strong synergistic effect between the palladium species and the selected ligated ligands were observed. The reaction became sluggish when $Pd_2(dba)_3$ was replaced by other Pd(II) salts including $Pd(OAc)_2$, $PdCl_2$, and $Pd(TFA)_2$ (Table 2, entry 2). $Pd_2(dba)_3$ catalytic systems from other monodentate Buchwald ligands diminished (Table 2, entry 6, MePhos or Brettphos) or even inhibited (Table 2, entry 5, XPhos or DavePhos) the production of the meroterpenoid **23**. It was an alternative to utilize $Pd(dppf)_2Cl_2$ as a catalytic system, which afforded a serviceable amount of the desired product (Table 2, entry 4).

No obvious products were detected in the catalytic systems with the monodentate triphenylphosphine or the bidentate Xantphos (Table 2, entry 5). Strong bases were necessary to this transformation (Table 2, entries 7 and 8), and the effect of the cationic metals is inscrutable but significant, in which Na^+ demonstrated an advantageous characteristic. Enrichment of the target meroterpenoid **23** benefited from the solvent screening. *t*-Butanol was introduced to replace the nonpolar toluene and identified to be a superior component compared with others, such as DMF, 2-MeTHF, and $ClCH_2CH_2Cl$, etc. Other factors were regulated routinely, including the ratio of the solvent mixture, substrates and base loading, reaction time and temperature, etc., which were fully summarized in the supporting information. The optimal conditions (Table 2,

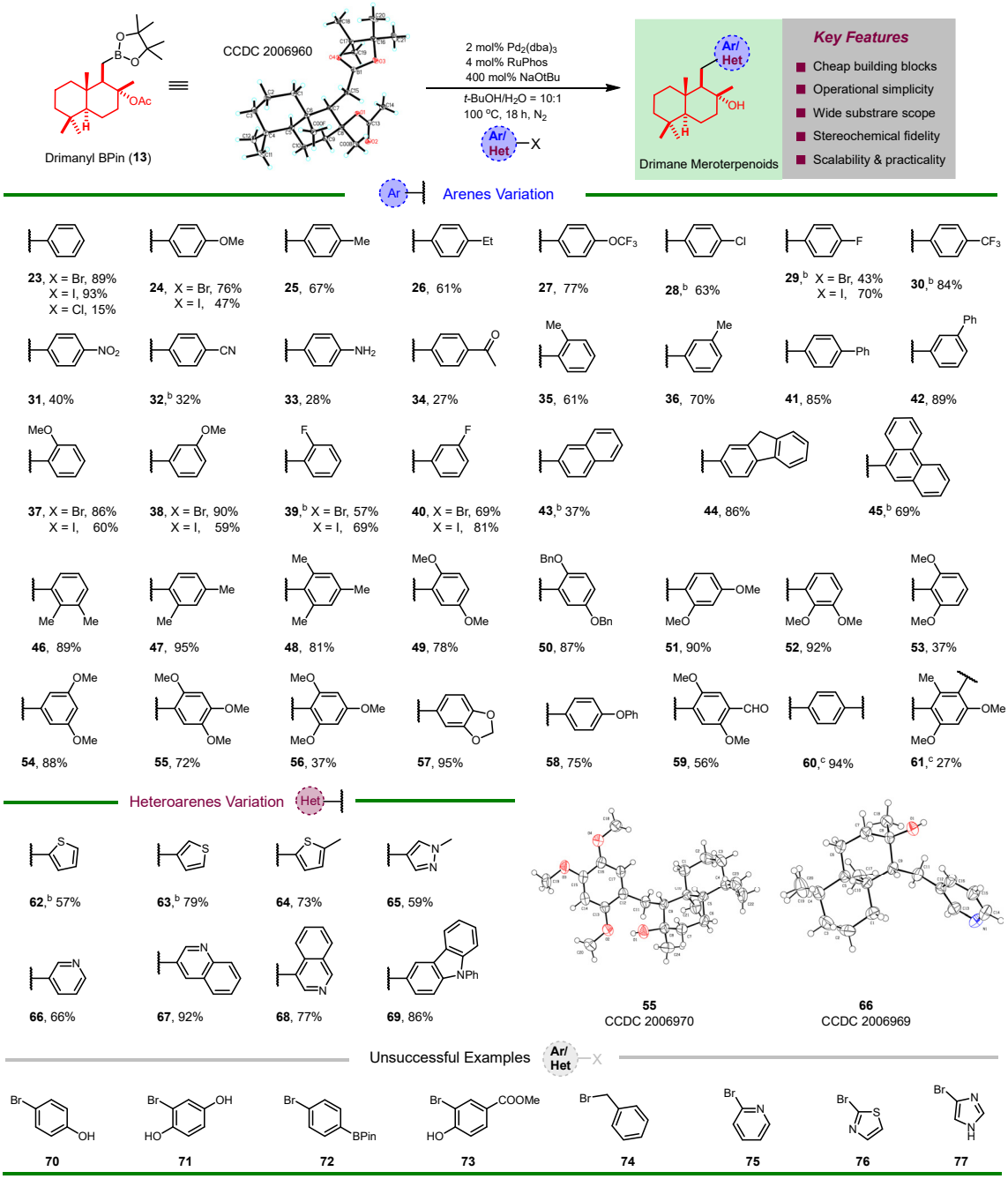
entry 14) emerged after an extensive investigation, furnishing the desired product **23** in 89% yield from the coupling of drimanyl BPin **13** with phenyl bromide.

The established methodology proved to be general and powerful across a range of substrates as shown in Table 3 (>45 examples). The scope with regards to the functional group tolerance and the electronic effect was first evaluated based on the coupling with *para*-substituted halobenzenes, to produce drimane hydroquinones **23**-**34**. Either electron-rich or electron-poor substituted arenes are employed successfully as viable coupling partners. The modest yield from the *para*-F-phenyl bromide can be enhanced significantly by the employment of iodide counterpart (**29**). A small amount of the natural product (+)-drim-9(11)-en-8α-ol[23] is detectable from deboronylative dehydrogenation of drimanyl BPin **13** in the coupling procedure with the electron-withdrawing aromatic halides, and sometimes contaminate the desired product. Remarkable amongst these examples is the tolerance of a variety of functional groups, including ether (**24** and **27**), halides (**28** and **29**), nitro group (**31**), cyano group (**32**), and ketone (**34**). The compatibility of these functional groups will provide enormous opportunities for further derivatization and elaboration of meroterpenoids analogues for pharmaceutical purposes, some of which are otherwise not so easy in Kumada coupling (*vide supra*).

Switching the substituents to the *meta* or *ortho* positions was well tolerated (**35**-**40**). Interestingly, the advantageous effect of the aromatic iodides on the coupling outcomes (**39** and **40**) is reversed when the substitution was changed from fluoro to electron-donating methoxyl group (**37** and **38**). Reaction with biphenyl bromides (**41** and **42**) underwent smoothly with good coupling yields. Fused aromatic counterparts, including 2-bromonaphthalene, 2-bromofluorene, and 9-bromophenanthrene are also feasible, delivering the meroterpenoids **43**-**45** with the yields varying from 39% to 86%. A more

sterically hindered aromatic 2,4,6-trimethyliodobenzene can be coupled smoothly to give compound **48** in good yield (81%).

Table 3, Modular synthesis of drimane (hydro)quinones via Suzuki Coupling



a, Unless otherwise mentioned, reactions were carried out with 0.25 mmol of Ar-Br or Het-Br, 0.3 mmol of drimanyl BPin (13), yields of isolated products are presented in each case. b, The yield was calculated based on ^{1}HNMR of the isolated inseparable mixture of the desired product and (+)-drim-9(11)-en-8α-ol after chromatography. c, 0.25 mmol of Ar-Br, 0.6 mmol of drimanyl BPin **13**, 4 mol% $Pd_2(dba)_3$, 8 mol% RuPhos, 800 mol% NaOtBu.

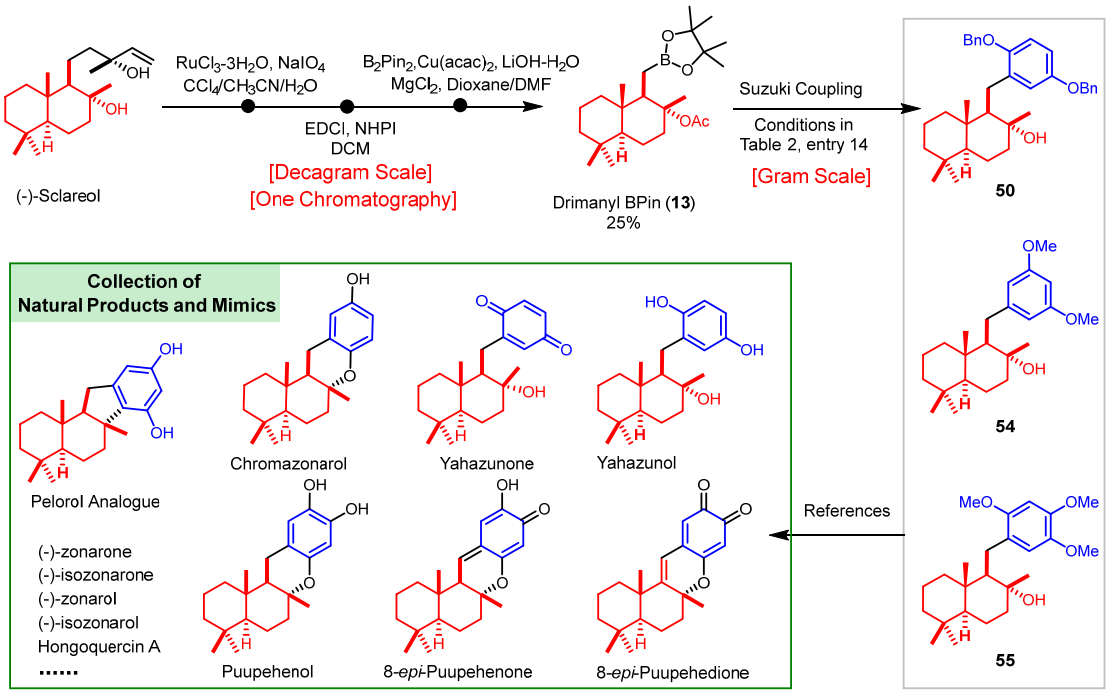
We next mainly focused on the multi substituted aromatic halides with alkoxyl groups, which were prevalent in the natural drimane hydroquinones.[4-5] The resulting coupled

products can serve as versatile precursors for the expedite construction of natural products themselves or mimics. To our delight, the coupling paradigm went smoothly under the optimized conditions providing a number of yahazunol analogues or the precursors of the related drimane meroterpenoids in good to excellent yields (**48**-**59**). Interestingly, the double coupling is amenable by introducing appropriate aromatic bromides as "bridges" to access the dimeric natural products mimics (**60** and **61**).

The ever-present heterocyclic motifs found in medicinally important structures could also be applied in this transformation. Based on our previous design and progress in the acquirement of antifungal drimane meroterpenoids,[24] a range of heterocycles are intentionally tested and enlisted aiming at synthesizing unnatural products with improved drug-like properties. Besides the good tolerance for the electron-rich thiophene (**62**-**64**), the electron-poor pyridine (**66**), quinoline (**67**), as well as isoquinoline (**68**) could also be coupled with compound **13** in good yields. The *N*-phenyl carbazole bromide could also be recruited successfully in this transformation (**69**). Though with a wide scope of coupling partners, a glaring limitation was also detected in this transformation. The tolerance of simple phenolic hydroxyl group (**70** and **71**), boronate (**72**), ester (**73**), thiazole (**76**), and imidazole (**77**) are still not yet realized. Attempts with aliphatic bromide (**74**) and the o-*Bromo*-heterocycles (**75**-**77**) didn't provide serviceable quantities of product.

Improvement and Formal Synthesis of Natural Products. The scalability and practicality of this process leveraging decarboxylative borylation and Suzuki coupling were further enhanced by the improved synthesis of the homodrimanic acid **7** (Scheme 3). $RuCl_3$ catalyzed the cascade oxidative degradation of sclareol can be accomplished in a short time (3~5 hrs) and give a rather simple reaction mixture, wherein the precursor **7** can be purified easily in a satisfactory yield. Direct and facile utilization of

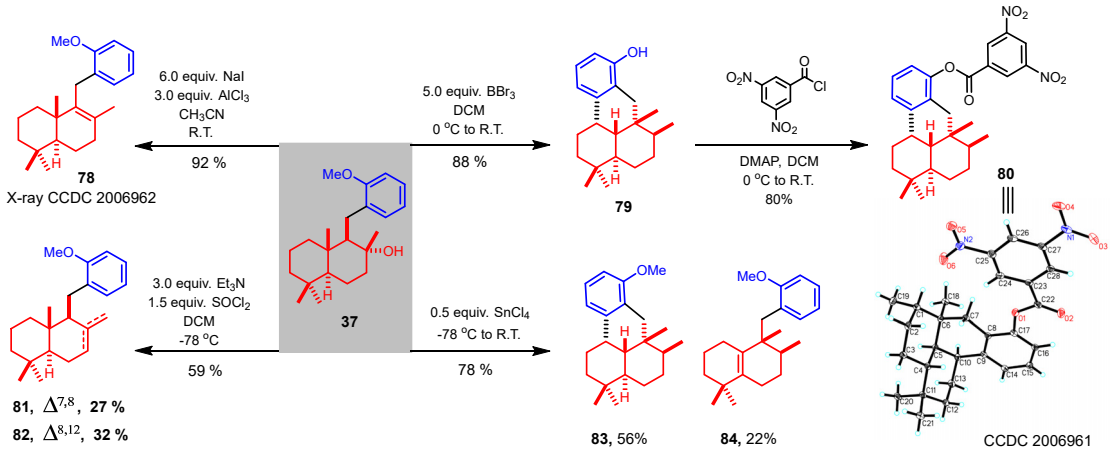
the crude product from scale-up transformation (10 g scale) was demonstrated to be doable through solvent partitioning/aqueous wash for the subsequent Steglich-type condensation. Synthesis of the drimanyl Bpin **13** can be performed efficiently (< 20 min) in grams scale. The Suzuki coupling with the 2-Bromo-1,4-dimethoxybenzene or its benzyl protecting congener proceeded in good yields under the unmodified optimal conditions shown in Table 2, entry 14. The resultant coupled products, exemplified by **50**, **54**, and **55**, could serve as key intermediates for the efficient transformations to a wealth of natural drimane meroterpenoids (Scheme 3)[7, 17, 25]. This may open a new window to efficiently deliver many natural products and their mimics, without recourse on the application of instable and air/water sensitive organometallics.



Scheme 3, Improved scalable synthesis of Drimanyl Bpin **13** and formal synthesis of natural drimane meroterpenoids

Versatile Transformations to other Scaffolds. The promising potential to other core skeletons of meroterpenoids is also remarkable as exemplified by the translational diversity of **37** (Scheme 4). Treatment of compound **37** with excess BBr_3 n DCM will lead to the coincidence of demethylation and rearrangement in one pot, affording the

structurally interesting and biologically important 6-6-6-6 ring fused scaffold **79** enantioselectively in good yield, which was unambiguously determined by the X-ray diffraction of its ester **80** (CCDC 2006961). The similar Lewis acids initiated H and methyl group shifts were detected in the treatment with the Lewis acid $SnCl_4$ at -78 °C, delivering a mixture of scaffold-rearranged products **83** and **84** (analogues and precursors of Aureol[26]) in a combined 78% yield. The tetrasubstituted olefin **78** and the trisubstituted congeners **81** and **82** (analogues of zonarol and isozonarol[27]) can be prepared and isolated through regioselective dehydration. Besides the synthetic potentials confirmed by the translational diversities and formal synthesis of complex natural products, it is noteworthy that the synthesized products themselves delineated in Table 3 can be deemed as unnatural mimics of drimane meroterpenoids. The listed examples may be only a drop in the bucket since aromatic halides are among the most widespread building blocks. This may forebode an almost limitless variety of arene flanked drimane meroterpenoids, with demonstrable values to the researchers in either chemistry or biology.



Scheme 4, Translational diversities of the synthesized drimane hydroquinone **37**

Initial Antifungal Evaluation. In our continuing interest in the exploitation of drimane meroterpenoids and analogues as potential antifungal leads,[17, 24] we sought to explore the inhibitory effect of the synthesized mimics against a series of agriculturally

important plant pathogens (Table 4). To our delight, the antifungal effects were enhanced by either the introduction of polar substitutions (**33** and **34**) or heterocyclic segments (**62**-**68**) compared with the original models **15** and **23**. This represents the first evaluation of the analogues of dysideanones[28] as antifungal candidates and the fortuitous results gave us reasons to expand this kind of non-natural compounds for further structure and activity relationships. The effect of the aromatic substituents or the different skeleton on the antimicrobial activity suggests there may be distinct targets or pathways involved in the observed phenomenon, and necessitate an additional study to enable a more in-depth evaluation and insights in the future.

Table 4, Antifungal activities of the synthesized drimane meroterpenoids and mimics

Fungi. \ Compd.	15	23	24	25	26	27	28	29	30	31	32	33	34	35	36	37	38	39	40	41	42	43	44	45
S. sclerotiorum	28	71	63	59	42	53	55	63	55	68	56	89	68	67	69	67	69	76	73	37	35	36	45	49
R. solani	25	41	41	36	18	26	36	47	42	39	63	63	48	44	47	50	42	51	47	7	4	9	0	30
F. graminearum	26	48	42	37	22	24	32	54	32	67	64	61	61	34	29	38	34	56	49	5	18	5	8	25
B. cinerea	23	31	44	32	15	10	24	44	17	33	62	65	45	33	26	30	46	37	33	13	11	20	15	21
G. graminsis	53	44	57	56	56	57	63	35	45	55	46	75	61	32	44	44	51	43	54	26	30	25	30	62
M. grisea	37	19	38	25	32	10	26	41	20	37	46	34	54	13	24	40	37	37	34	0	8	0	3	20
Fungi. \ Compd.	**46**	**47**	**48**	**49**	**50**	**51**	**52**	**53**	**54**	**55**	**56**	**57**	**58**	**59**	**60**	**61**	**62**	**63**	**64**	**65**	**66**	**67**	**68**	**69**
S. sclerotiorum	34	35	37	54	36	42	58	58	69	75	61	67	60	62	51	49	77	74	73	77	65	89	96	29
R. solani	37	25	22	35	19	32	43	36	44	7	32	43	12	44	2	11	53	45	53	49	45	51	59	0
F. graminearum	28	23	25	35	6	32	36	35	51	7	46	50	12	48	7	8	56	51	59	59	50	55	56	9
B. cinerea	26	20	25	25	23	30	35	34	38	48	54	43	25	68	21	31	53	48	42	80	56	47	57	15
G. graminsis	78	79	52	55	45	55	52	33	64	31	49	72	39	54	33	46	55	81	63	41	53	63	60	23
M. grisea	20	17	17	28	4	27	35	28	33	19	19	31	4	43	9	13	36	26	45	49	36	71	58	8

NOTE: at 20 mM, *S. sclerotiorum*: Sclerotinia sclerotiorum; *R. solani*: Rhizoctonia solani; *B. cinerea*: Botrytis cinerea; *F. graminearum*: Fusarium graminearum; *G. graminsis*: Gaeumanomyces graminis; *M. grisea*: Magnaporthe grisea.

Inhibitory Effect

Conclusion

In summary, the tactic delineated herein permits simple, modular, and scalable access to drimane meroterpenoids and mimics. With the invention of the bench stable and easily accessible drimanyl Bpin from the inexpensive natural diterpene sclareol, a new paradigm merging decarboxylative borylation and Suzuki coupling was developed as a powerful platform for a large variety of precursors, non-natural mimics and ring-distorted motifs of drimane meroterpenoids. Expedient formal synthesis of a large number of natural products or mimics is feasible *via* the current chemistry. The high degree of practicality bodes well for the discovery sciences towards pharmaceutically important meroterpenoids through detailed SAR study. The facile accessibility to this

kind of chemical entities allowed the unprecedented evaluation of these scaffolds as antifungal agents. The promising activity of the non-natural mimics may open a new window for structural optimization and the identification of new targets. Future efforts are devoted to an expanded library of meroterpenoids and mimics through this tactic for the discovery of new therapeutically important agents.

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Author contributions

S. Li conceived this work. X. Wang and S. Zhang conducted all experimental work and analyzed the results. P. Cui helped to prepare some intermediates. X. Wang and S. Li analyzed the data and wrote the manuscript.

ADDITIONAL INFORMATION

Supporting Information

The Supporting Information is available free of charge on the website.

Experimental procedures and characteristic data (PDF).

X-ray crystallographic data for **13**, **55**, **66**, **78,** and **80**.

Competing Financial Interests:

The authors declare no competing financial interest.

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