Article

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A Tandem Decarboxylative Cyclization/Alkenylation Strategy for the Total Syntheses of (+)-Longirabdiol, (–)-Longirabdolactone, and (–)-Effusin

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Radical cascade reaction, Total synthesis, ent-Kaurane diterpenoids, Lactone formation, Anti-cancer activity

ABSTRACT: Structurally complex and bioactive *ent*-kaurane diterpenoids have well-characterized biological functions and have drawn widespread attention from chemists for many decades. However, the construction of highly oxidized forms of such diterpenoids still presents considerable challenges to synthetic chemists. Herein, we report the first total syntheses of C19 oxygenated spiro-lactone *ent*-kauranoids, including longirabdiol, longirabdolactone, and effusin. A concise synthesis of the common intermediate used for all three syntheses was enabled via three free-radical-based reactions: 1) a newly devised tandem decarboxylative cyclization/alkenylation sequence that forges the *cis*-19, 6-lactone concomitantly with vicinal alkenylation; 2) a Ni-catalyzed decarboxylative Giese reaction that constructs C10 quaternary center stereoselectively; and 3) a vinyl radical cyclization that generates a rigid bicyclo[3.2.1]octane. A series of late-stage oxidations from the common intermediate then provided each of the natural products in turn. Further biological evaluation of these synthetic natural products reveal broad anti-cancer activities.

INTRODUCTION

Ent-kauranes, a family of structurally diverse diterpenoids isolated from the *Isodon* genus, possess a broad spectrum of biological activities—they have demonstrated potential utility as antibacterial, anti-inflammatory, and antineoplastic agents.[1] In particularly, spiro-lactone type *ent*-kauranoids have attracted extensive interest in the chemistry community owing to their intriguing structures and potent biological activities, culminating in a number of elegant total syntheses.[2] For example, both the Reisman and Liang groups have completed the syntheses of trichorabdal A (**1**) and maoecrystal Z;[3] and both the Zhai and

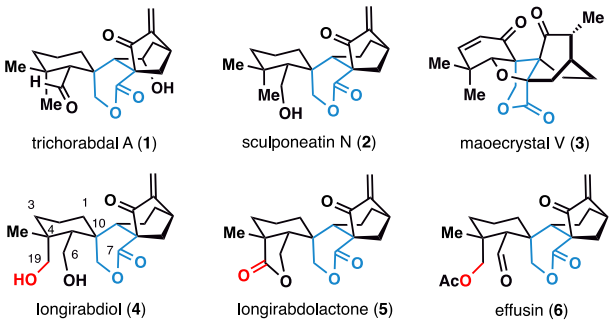
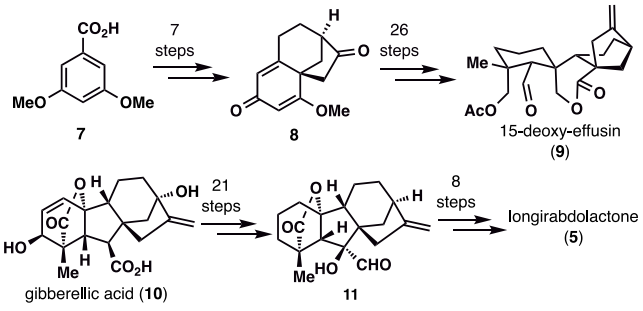


Figure 1. Spiro-lactone type *ent*-Kauranes.

Thomson groups have reported the total synthesis of sculponeatin N (**2**).[4] Maoecrystal V (**3**), a highly congested *ent*-kaurenoid, has been the subject of numerous synthetic studies over the past decade (Figure 1).[5] The most recent synthesis, from the Baran group, furnishes this natural product in gram quantities over merely 11 steps.[5f] Despite these seminal achievements, few syntheses of C19 oxygenated spiro-lactone type *ent*-kauranoids—possessing an intriguing quaternary stereocenter at C4—have been demonstrated to date. In 1986, Mander and co-workers reported the synthesis of 15-deoxy effusin (**9**) in 33 steps from 3,5-dimethoxybenzoic acid (**7**) (Scheme 1).[6] In 2003, the same group reported a 29-step preparation of longirabdolactone (**5**) from gibberellic acid (**10**).[7] Here, we report the first asymmetric total syntheses of longirabdiol (**4**), longirabdolactone (**5**), and effusin (**6**) via three free-radical-based reactions.[8]

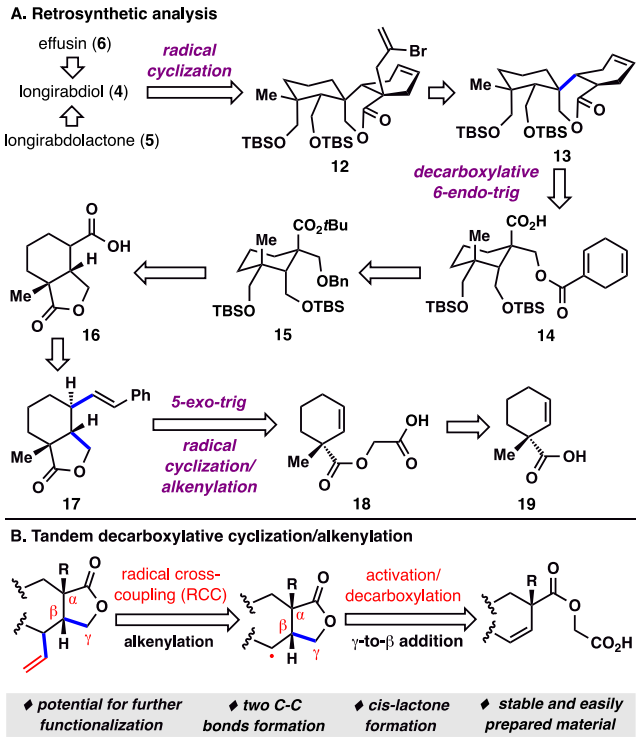
Scheme 1. Previous Synthetic Studies toward Effusin and Longirabdolactone (Mander 1986 and 2003)



Retrosynthetically, we envisaged that longirabdolactone (**5**) and effusin (**6**) could be accessed from longirabdiol (**4**) divergently via oxidations (Scheme 2, A). The bicyclo[3.2.1]octane ring of **4** could be obtained from **12**

through a classical vinyl radical cyclization.[9] The vinyl side chain in **12** may be installed via allylation on **13**. Compound **13** which contains a γ-disubstituted δ-valerolactone could be obtained through a decarboxyaltive 6-*endo*-trig radical cyclization (intramolecular Giese reaction) from carboxylic acid **14**.[10] Compound **14** could be easily synthesized from benzyl ether **15**. The tertiary carboxylic ester of **15** could be further disconnected to acid **16**, and the carboxylic acid of **16** could be derived through the oxidative cleavage of the alkene moiety in **17**. Our plan to synthesize the key intermediate **17** drew inspiration from recent progress in decarboxylative radical cross-coupling (RCC):[11] a sequential radical cyclization/alkenylation cascade was envisioned to stereoselectively furnish γ-lactone **17** from carboxylic acid **18**.[12]

Scheme 2. Current Retrosynthetic Analysis and Key Considerations of the Synthesis Plan

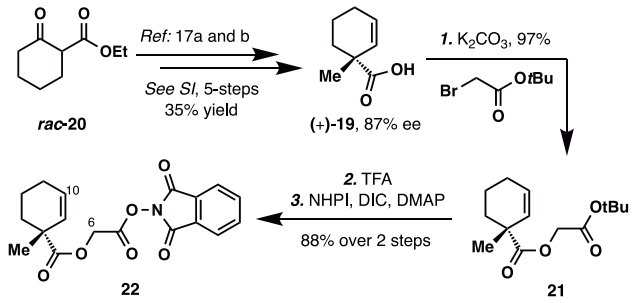


γ-lactone ring systems are found in a wide variety of biologically active natural products, and functionalization of such γ-lactones is a common strategy for the synthesis of stereo-defined cyclic or acyclic compounds and natural products.[13] Although many synthetic methods have been developed for the construction of such versatile scaffolds, including intriguing radical cyclization,[14] it is noteworthy that practical assembly of γ-lactones via a C_γ-to-C_β radical addition are rare,[15] as the corresponding α-oxy halides or seleniums do not exist or are toxic. Recently, α-oxycarboxylic acids, easily prepared and stable building blocks, have been demonstrated—via decarboxylative reactions—as excellent radical precursors for radical cross-coupling (RCC).[12a-b, 16] In this context, we envision that α-oxycarboxylic acids might be suitable radical precursors for C_γ-to-C_β addition in the synthesis of γ-lactone ring systems (Scheme 2B), and the sequentially formed carbon radical could potentially be engaged for following vicinal alkenylation; such products could then serve as a versatile "handle" for further modification based on the richly developed olefin chemistry. Notably, our exploration of this new strategy for the construction of highly functionalized and versatile γ-lactone ring systems also motivated an investigation into tandem decarboxylative cyclization/alkenylation.

RESULTS AND DISCUSSION

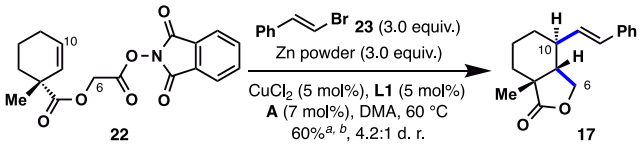
Preparation of the Cyclization/alkenylation Precursor. The total synthesis of **4-6** commenced with the acid (+)-(**19**) (Scheme 3), which could be prepared in 5-steps on decagram scale in 87% *ee* and 35% overall yield from commercially available ethyl 2-cyclohexanonecarboxylate (*rac*-**20**, see SI for details).[17] The coupling of **19** with *t*-butyl bromoacetate followed by the exposure of the ensuing ester to TFA provided a carboxylic acid which could be conveniently activated with *N*-hydroxyphthalimide (NHPI) to afford the redox-active ester (RAE) **22** in excellent yields.

Scheme 3. Synthesis of Redox-Active Ester 22

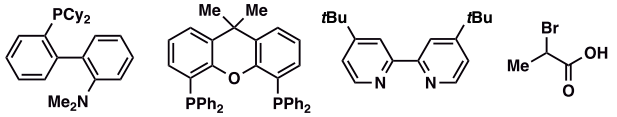


Cu-Catalyzed Tandem Decarboxylative Cyclization/Alkenylation. It was envisaged that **22** could undergo single-electron reductive decarboxylation, providing an alkyl radical that could engage in 5-*exo-trig* cyclization. The resulting secondary radical may participate in the sequential alkenylation. A vinyl zinc reagent was employed in the initial study, which is much akin to Baran's seminal study in decarboxylative alkenylation.[12a] However, the reaction of **22** with vinyl zinc reagents using a variety of nickel or iron ligand complexes led to the direct alkenylation of the C6 position. This may be ascribed to the rapid reaction rates of iron- or nickel-catalyzed decarboxylative reactions. This result prompted us to survey reductive cross-coupling between RAE and sp^2-halide, as developed by the Reisman and Weix groups.[12b, 18] Gratifyingly, exposure of **22** and β-bromostyrene to (dtbbpy)$NiBr_2$ and Zn powder provided the desired product **17** in 34% yield as a 3.2:1 mixture of diastereomers (Table 1, entry 6). An extensive investigation of alternative catalysts and ligands revealed the combination of 5 mol% $CuCl_2$ and 5 mol% Davephos as the optimal choice—this catalyst system furnished the desired products in 45% yield (entry 10). The addition of 2-bromopropanoic acid (7 mol%) was found to bolster the yield further, as **17** was afforded in 60% yield.[19] Systematic evaluation of other reaction parameters indicated that the choice of Cu(II) salt (entries 1-5), ligand (entries 7-9), additive (entry 11) and reductant (entries 12) each exerted tangible effects on reaction outcomes (see SI for further details), while omission of Zn led to no desired products (entries 13). Notably, although the pendant vicinal alkene was delivered as a 4.2:1 mixture of diastereomers, both of them could be used in the following synthesis (*via infra*). Additionally, the scalability of this process was demonstrated through the *decagram scale* synthesis of compound **17**, which was prepared in 55% yield.[19]

Table 1. Optimization of the Radical Cyclization/Alkenylation Reaction



entry[a]	deviation from above	yield (%)[b]	entry[a]	deviation from above	yield (%)[b]
1	w/o $CuCl_2$	18	8	**L2** instead of **L1**	35
2	3 mol% $CuCl_2$/3 mol% **L1**	47	9	**L3** instead of **L1**	37
3	7 mol% $CuCl_2$/7 mol% **L1**	60	10	w/o **A**	45
4	$CuBr_2$ instead of $CuCl_2$	57	11	AcOH instead of **A**	40
5	CuCl instead of $CuCl_2$	19	12	Mn instead of Zn	10
6	5 mol% (dtbbpy)$NiBr_2$	34[c]	13	w/o Zn	0
7	w/o **L1**	25	14	RT	44

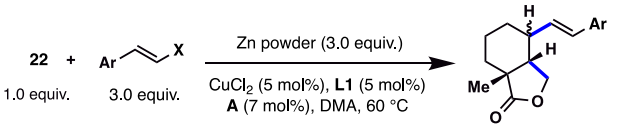


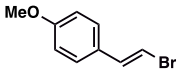
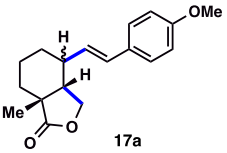
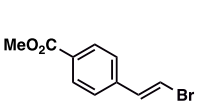
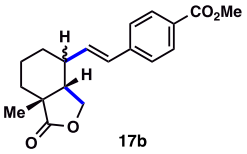
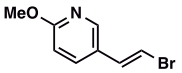
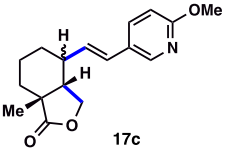
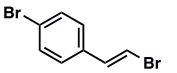
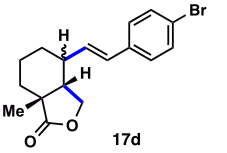
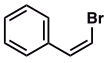
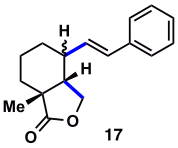
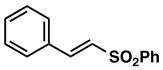
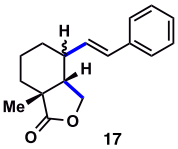
DavePhos (**L1**) XantPhos (**L2**) dtbbpy (**L3**) **A**

[a]1.0 mmol. [b]Yield determined by ^{1}H NMR with CH_2Br_2 as an internal standard. [c]w/o **A**, d. r. = 3.2:1.

With an optimized set of conditions in hand, and encouraged by the potential utility of this tandem cyclization/alkenylation process, we next explored its use with a range of representative β-substituted styrenes aiming to further understand the underlying reaction mechanism. As outlined in Table 2, both electron-rich and electron-deficient styrenes (entries 1 and 2) afforded useful yields. Heterocyclic styrene (entry 3) was a viable coupling partner as well. Interestingly, bromide substituted β-bromostyrene was also tolerated (entry 4), and the desired product **17d** was provided in a 43% yield. Further attempts for the decarboxylative cyclization/arylation using aryl halides in place of β-bromostyrene were unsuccessful in these reaction conditions (see SI for further details). Notably, when (*Z*)-vinyl bromide **23e** was used (entry 5), alkene **17** was provided in 30% yield as an exclusive (*E*)-isomer, which mechanistically indicated that this process is a reductive radical cyclization/addition-fragmentation reaction.[10c, 20] Using this mechanism, vinyl sulfone **23f** (entry 6) was further examined. However, the desired alkene **17** was furnished in only a relatively low yield (22%). These low yields, provided by **23e** and **23f**, cautioned us that a copper-catalyzed cross-coupling mechanism (oxidative addition/reductive elimination) could not be ruled out completely.[21] Several lines of evidence from these reactions supported the existence of such a cross-coupling mechanism: i) if this is a pure radical addition-fragmentation mechanism, both (*E*)-vinyl bromide **23** and (*Z*)-vinyl bromide **23e** should provide the desired alkene **17** in similar yield; however, recall that (*Z*)-vinyl bromide **23e** only gave a 30% yield. ii) **23f**, which is a competent coupling partner of (*E*)-**23** but cannot be employed in the cross-coupling mechanism (oxidative addition), providing the desired product **17** in only 22% yield. iii) **34** (*via infra*, Table 3), a more suitable substrate for the radical addition-fragmentation mechanism rather than cross-coupling (owing to its stable and sterically hindered tertiary radical intermediate), was provided in low yield (30%). iv) (*Z*)-vinyl bromide **23e** has been reported as a very inefficient partner in radical cross-coupling reactions, while (*E*)-vinyl bromide is known to be good partner.[22] Thus, we presumed that the high yield of sp^2-sp^3 bond formation that we observed for the alkenylation step of the tandem cyclization/alkenylation between (*E*)-vinyl bromide **23** and RAE **22** actually resulted from a combination of a radical addition-fragmentation process and a copper-catalyzed radical cross-coupling reaction. Moreover, we speculate that the low yields generated from (*Z*)-vinyl bromide **23e** and vinyl sulfone **23f** could be a result of the sole addition-fragmentation pathway.

Table 2. Scope of β-Substituted Styrenes



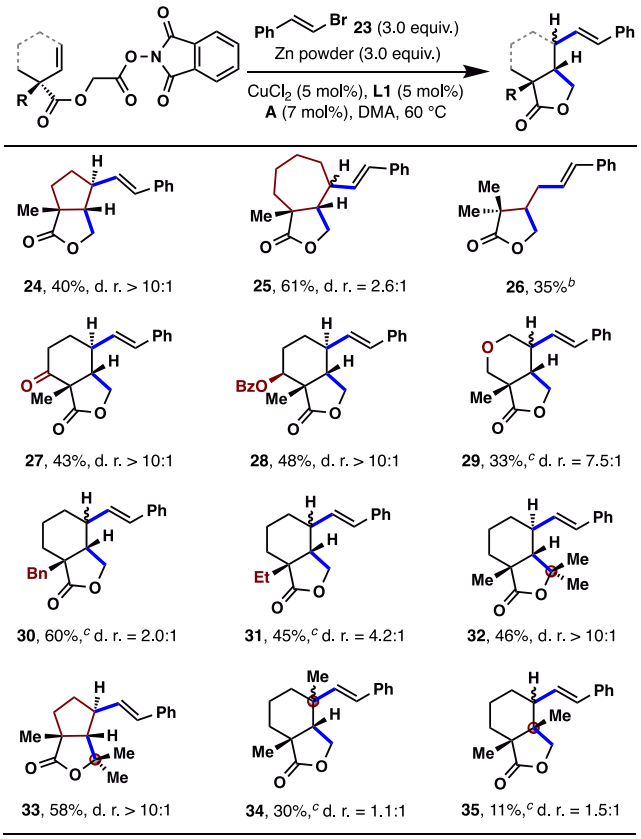
entry[a]	β-substituted styrenes	products	yield (%)[b]
1	 **23a**	 **17a**	57% d. r. = 3.5:1
2	 **23b**	 **17b**	42% d. r. = 3.6:1
3	 **23c**	 **17c**	55% d. r. = 3.0:1
4	 **23d**	 **17d**	43% d. r. = 3.0:1
5	 **23e**	 **17**	30%[c] d. r. = 3.7:1
6	 **23f**	 **17**	22%[c] d. r. = 3.8:1

[a]0.5 mmol. [b]Isolated yield; d. r. determined by ^{1}H NMR. [c]Yield determined by ^{1}H NMR with CH_2Br_2 as an internal standard.

Next, we explored the capacity of this tandem cyclization/alkenylation for construction of structurally diverse lactone systems (Table 3). First, substrates with different cyclic and acyclic systems were studied; in each case, the desired products (**24**-**26**) were isolated in synthetically useful yields. Substrates **27** and **28**, both of which were provided as single diastereomers, are particularly striking because they might open a unique synthetic route to other highly oxidized *ent*-kauranoids such as trichorabdals C and E.[23] Notably, a 3,4-dihydro-2*H*-pyran ring (**29**) also tolerated these reaction conditions. Displacing the methyl group on the existing

quaternary carbon to a benzyl (**30**) or ethyl group (**31**) did not erode the yield. Construction of quaternary centers remains a challenging task in organic synthesis, so we examined our tandem cyclization/alkenylation strategy for the formation of quaternary centers. Gratifyingly, quaternary centers could be made successfully at the site of the initial cyclization, and the desired products **32** and **33** were afforded as single diastereomers. Moreover, quaternary centers could also be forged at the position of alkenylation, although vinyl alkene **34** was afforded in a relatively low yield (30%); potential reasons for this low yield have been considered above. However, quaternary center formation at the initial cyclization acceptor position (**35**) was unsatisfactory.

Table 3. Scope of Cyclization Partners[a]

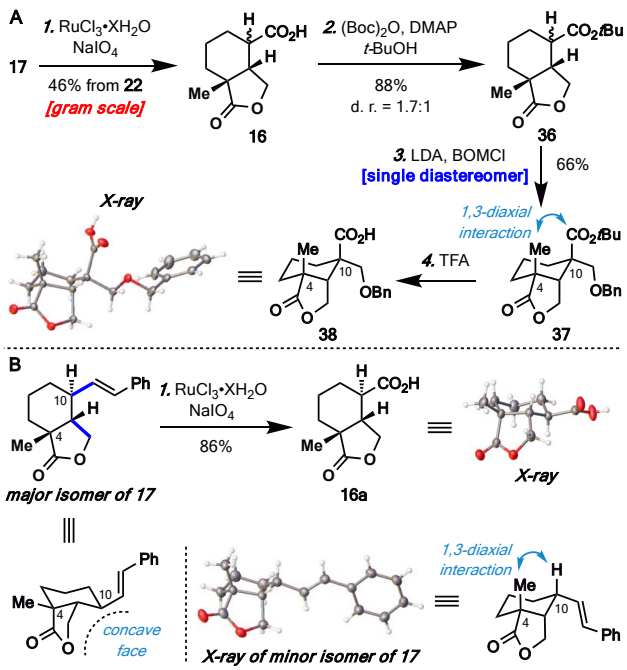


[a]0.5 mmol; isolated yields; d. r. determined by ^{1}H NMR. [b]$CuCl_2$ (10 mol%)/**L1** (10 mol%) was used. [c]Yield determined by ^{1}H NMR with CH_2Br_2 as an internal standard.

Insights into the Stereochemical Outcomes of the C10 Quaternary Center and Tandem Cyclization/Alkenylation. With scalable synthesis of **17** in hand, we set out to construct the quaternary stereocenter at C10 (Scheme 4A). Oxidative cleavage of styrene **17** by $RuCl_3$ and $NaIO_4$ delivered carboxylic acid **16** in 46% yield over 2 steps from the redox-active ester (RAE) **22**. Esterification of **16** with Boc_2O using Takeda's procedure afforded ester **36** in 88% yield as a 1.7:1 mixture of diastereomers.[24] Interestingly, Treatment of mixed diastereomers of **36** with LDA followed by the addition of BOMCl gave rise to **37** as a single diastereomer. We presumed that the observed high stereoselectivity at the newly formed quaternary center should be attributable to a 1,3-diaxial interaction generated from the axial methyl group at C4. Consequently, the benzyl methyl ether moiety was installed at the less sterically hindered face. The proposed configuration of **37** was further confirmed by X-ray crystallographic analysis of **38**, which was provided by the *t*Bu ester deprotection of **37** in the presence of TFA.

Our speculation and experimentation focused on the effects of this 1,3-diaxial interaction on the formation of the C10 quaternary stereocenter also focused our attention on questions about the steric outcomes of the alkenylation step in our tandem cyclization/alkenylation process. Specifically, it was intriguing that, for the major product, the stereochemistry of the vicinal alkene group at C10 of **17** was at the same side as the methyl group at C4 (Scheme 4B). To pursue this, the major isomer of **17** was treated with $RuCl_3$ and $NaIO_4$, and the structure of the resulting acid **16a** was elucidated by X-ray crystallographic analysis. This clearly demonstrated that the configuration of the newly formed carboxylic acid was positioned opposite to the lactone moiety, and the methyl group at C4 occupied an equatorial position. Based on this result, we can deduce that the stereochemistry of the major isomer of alkenylation was here determined by the crowded concave face effect of the bicyclic lactone. Note that we also confirmed the configuration of the minor isomer of **17** by X-ray crystallographic analysis (Scheme 4B), which revealed the interesting finding that the configuration of the alkene group of the minor isomer was determined by the 1,3-diaxial interaction.

Scheme 4. Construction of the C10 Quaternary Stereocenter and Insights into Its Stereochemical Outcomes

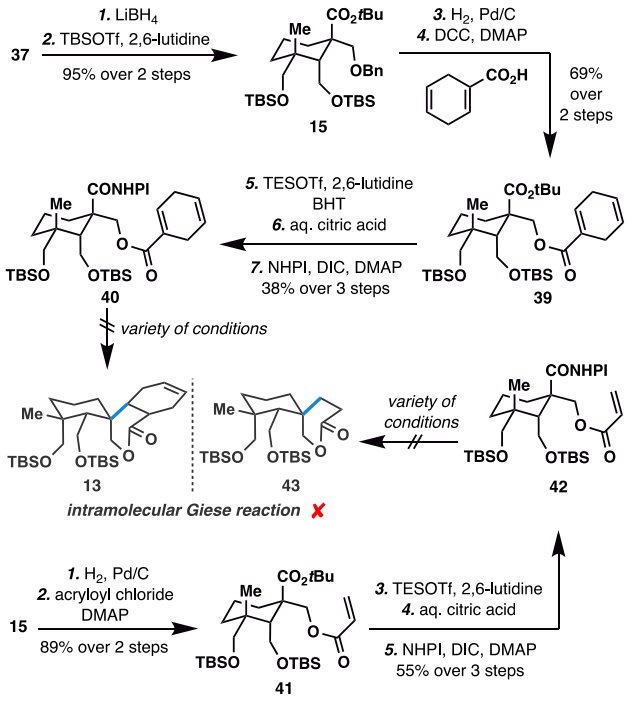


Intramolecular Giese Reaction: A Challenging Proposition. Logically, based on the decisive effect of the 1,3-diaxial interaction on the stereochemical outcome of C10 quaternary center, the direct decarboxylative Giese reaction on acid **38** would likely produce an undesired stereoisomer. To overpower the 1,3-diaxial interaction from the aforementioned concave face effect, the lactone moiety in **37** was reduced by $LiBH_4$, and the resulting diol was protected with two bulky TBS groups (Scheme 5). Hydrogenation of benzyl ether **15** followed by esterification of the newly formed alcohol with cyclohexa-1,4-diene-1-carboxylic acid afforded ester **39** in 69% yield.

Removal of the *t*Bu ester group of **39** without disturbing the two TBS groups or the labile 1,4-cyclohexadiene moiety was demanding. Happily, after extensive screening of reaction conditions, we found that treatment of **39** with TESOTf and 2,6-lutidine in the presence of BHT followed by hydrolysis of the resulting TES ester with aq. citric acid gave rise to the desired carboxylic acid,[25] which was sequentially activated with *N*-hydroxyphthalimide (NHPI) to afford the RAE **40** in moderate yields. Unfortunately, the proposed intramolecular decarboxylative Giese reaction proved problematic. Subjection of RAE **40** to Baran's reductive decarboxylation conditions or Overman's visible-light photocatalysis conditions led only to a complex mixture.[10c-e] These failures were mainly ascribed to direct decarboxylation, alkene migration, and other unknown side reactions based on crude NMR analysis. Direct treatment of the acid precursor of RAE **40** with Macmillan's photocatalysis conditions proved fruitless as well.[10b]

To avoid the lability of the 1,4-cyclohexadiene moiety, we next employed a simple acrylic ester to study the proposed 6-*endo*-trig cyclization. Using the same synthetic strategy as above, acrylate **42** was prepared smoothly from compound **15** over 5 steps in good yields (Scheme 5). However, exposure of RAE **42** to Baran's reductive decarboxylation conditions resulted in direct decarboxylation and hydrolysis of RAE: no desired lactone **43** was observed. Increasing the reaction temperature only led to decomposition. Exposure of RAE **42** or its precursor acid to a variety of photocatalysis conditions was similarly unsuccessful.[10b-d] We speculated that the high strained spiro δ-lactone transition state and left-handed congested cyclohexane ring likely prevented the desired cyclization process.

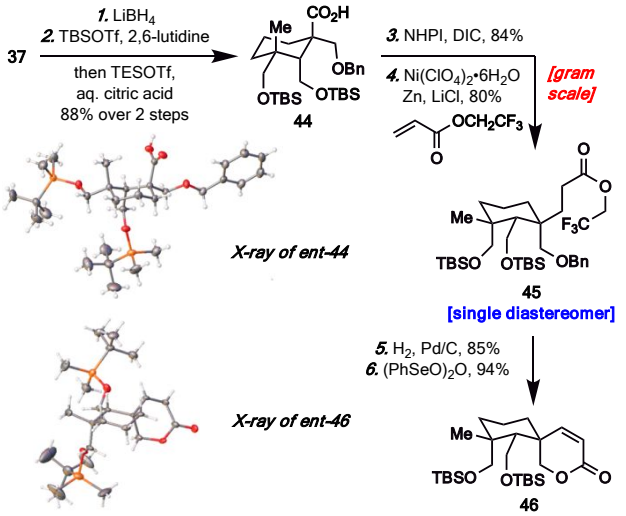
Scheme 5. Initial Studies toward the Intramolecular Giese Reaction.



Intermolecular Giese Reaction: A New Plan Forward. The failures in 6-*endo*-trig cyclization led us to an alternative strategy—construction of the C10 quaternary center using an intermolecular decarboxylative Giese reaction first, followed by a intramolecular esterification. For this tactic, 2,2,2-trifluoroethylacrylate was examined directly instead of cyclohexa-1,4-diene-1-carboxylate,[3a-c] because: i) the steric effect between the β-substituted Michael acceptor (cyclohexa-1,4-diene-1-carboxylate) and the congested left-hand cyclohexane would likely only provide the coupled product in low yield; ii) even if the radical addition worked, the following deprotection of the benzyl group in the presence of a cyclohexene and two TBS groups would almost certainly be problematic.

As outlined in Scheme 6, reduction of the lactone moiety of **37** by $LiBH_4$ followed by a one-pot reaction for protection of the resulting diol with TBS groups and deprotection of the *t*-butyl ester with TESOTf provided acid **44** in 88% yield. The structure of acid **44** was confirmed by X-ray crystallographic analysis, which showed that the bottom face of cyclohexane was blocked by a bulky TBS group, thereby leaving a suitable approach for the subsequent decarboxylative Giese reaction from the top face. Toward this end, direct activation of **44** using *N*-hydroxyphthalimide (NHPI) and DIC in THF furnished the corresponding RAE in 84% yield; the use of DMAP or CH_2Cl_2 led to lower yields. Exposure of the resulting RAE to 2,2,2-trifluoroethylacrylate with $Ni(ClO_4)_2$ and Zn successfully afforded the desired **45** as a single diastereomer in 80% yield.[10e] Removal of the benzyl group under hydrogenation conditions followed by a spontaneous lactonization generated the key spiro-lactone, which was oxidized with benzeneselenic acid anhydride to afford unsaturated lactone **46** in high yields.[26] The structure of **46** was also verified by X-ray crystallographic analysis.

Scheme 6. Intermolecular Giese Reaction Enabled Synthesis of the Spiro-lactone

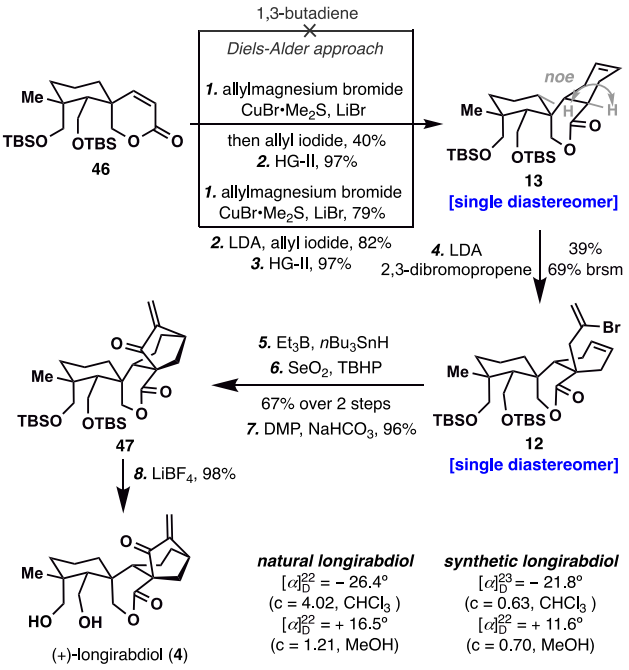


Completion of the Syntheses of Longirabdiol, Longirabdolactone, and Effusin. Having secured access to the spiro-lactone **46**, we next explored elaboration of bridged ring systems en route to the completion of our total syntheses. The seemingly simple synthesis of **13** through Diels-Alder reaction between dienophile **46** and 1,3-butadiene proved challenging. A variety of parameters were examined (temperature, pressure, with or without Lewis acid additives) to no avail. In most cases, the starting material **46** was recovered. Thus, we adopted a two-step process: the stereoselective conjugate addition of allyl cuprate species to **46** followed by treatment with allyl iodide

gave a diene in moderate yield as a single diastereomer. Subsequent RCM reaction of this diene delivered the desired **13** in 97% yield.[27] The configuration of **13** was elucidated by NMR. A stepwise protocol for the formation of the diene for the RCM reaction was also investigated, and the desired diene was provided in 65% overall yield.

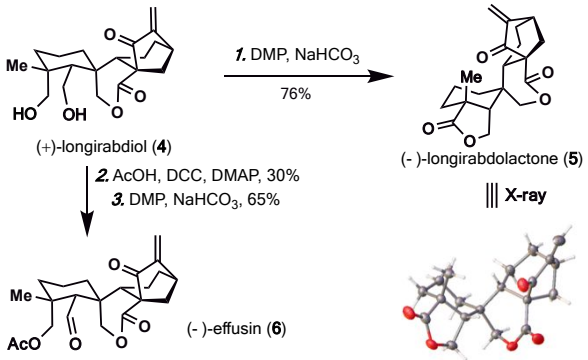
Deprotonation of **13** with LDA followed by allylation with 2,3-dibromopropene gave **12** in 39% yield as the only diastereomer (along with 51% recovery of **13**). Attempts to improve the conversion were unfruitful. Exposure of **12** to nBu$_3$SnH and Et$_3$B triggered 5-*exo* radical annulation, and the resulting bicyclo[3.2.1]octane underwent allylic oxidation to produce an alcohol in 67% yield over two steps.[4a,9] Dess-Martin oxidation of the newly formed alcohol followed by global deprotection using $LiBF_4$ smoothly furnished longirabdiol (**4**),[28] which displayed spectral and chiroptic properties in agreement with authentic reference standards for this natural product.

Scheme 7. Completion of the Synthesis of Longirabdiol (4)



Using (+)-longirabdiol (**4**) as the starting material, expedient syntheses of longirabdolactone (**5**) and effusin (**6**) were achieved. Briefly, oxidation of diol **4** by Dess-Martin periodinane gave lactone **5** in 76% yield, wherein the high chemoselectivity is likely attributable to the steric hindrance around the spironolactone. Next, the left-hand alcohol was acetylated using Steglich esterification in a regioselective fashion (*r.r.* = 2.1:1) (25% of **4** was recovered along with 10% diacetate). A Dess-Martin oxidation of the remaining alcohol then led to the first total synthesis of (−)-effusin.

Scheme 8. Total Syntheses of Longirabdolactone (5) and Effusin (6)



Anti-cancer Activity Evaluation of the Synthesized Natural Products. Crude extracts of plants from the genus *Isodon* have been shown to exert anti-tumor effects, with known cytotoxic contributions from isolated *ent*-kauranoids. However, the specific bioactivities of longirabdiol (**4**), longirabdolactone (**5**), and effusin (**6**) have not been disclosed to date. Having achieved the synthesis of these three natural products, we investigated their effects on the cell viability of ten cancer cell lines derived from seven different human tissues. As shown in Table 4, these synthetic compounds displayed broad and considerable anti-cancer activity (in the μM range); of particular note, longirabdolactone (**5**) was generally more potent than other two, with an IC_{50} in A673 cells below 1 μM. Moreover, as the IC_{50} values for these three compounds were highly correlated among the ten tested cancer cell lines, it is reasonable to speculate that they may share the same cellular target(s). Further studies directed toward the identification of their target(s) are underway and will be reported in due course.

Table 4. IC_{50} Values (μM) of Synthetic Natural Products against Ten Different Cancer Cell Lines

Cell Lines	Cancer Type	4	5	6
A549	Non-small cell lung cancer	9.23	5.84	7.00
A673	Rhabdomyosarcoma	1.94	0.86	1.62
HCT116	Colorectal cacer	3.59	1.50	3.03
Huh7	Hepatocellular carcinoma	3.11	2.00	3.79
eHAP	Chronic myeloid leukemia	2.31	1.13	2.04
DLD1	Colorectal cacer	2.26	1.01	1.50
Hela	Cervical cancer	14.29	5.33	6.75
H460	Non-small cell lung cancer	11.25	6.19	8.40
RKO	Colorectal cacer	4.89	3.92	4.82
U2OS	Osteosarcoma	4.30	2.27	2.74

CONCLUSION

In summary, the first asymmetric total syntheses of three C19 oxygenated *ent*-kauranoids, logirabdiol (**4**), longirabdolactone (**5**), and effusin(**6**), were achieved via a sequence of 20, 21, and 22 steps, respectively, from known carboxylic acid **19**. Highlights of the successful synthetic route include three free-radical-based reactions. Of particular note is an in-house-developed copper-catalyzed decarboxylative tandem cyclization/alkenylation sequence which installed a *cis*-lactone and an adjacent olefin. This robust process can deliver a variety of structurally diverse lactone ring systems in useful yield, including those possessing quaternary centers. Combined with oxidative olefin cleavage, decarboxylative cross-coupling reactions (e.g., decarboxylative Giese reaction), and the functionalization of lactone rings, this synthetic strategy offers a streamlined approach to access sterically congested terpenoid

systems. Further biological activity examination revealed that these synthetic natural products possess notable anti-cancer activities.

ASSOCIATED CONTENT

Supporting Information

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

Experimental details, spectroscopic data for all new compounds (PDF)

X-ray crystallographic data for *rac*-**17β** (CIF)
X-ray crystallographic data for *rac*-**16a** (CIF)
X-ray crystallographic data for *rac*-**36b** (CIF)
X-ray crystallographic data for *rac*-**38** (CIF)
X-ray crystallographic data for *rac*-**44** (CIF)
X-ray crystallographic data for *rac*-**46** (CIF)
X-ray crystallographic data for (−)-**5** (CIF)

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Notes

The authors declare no competing financial interest.

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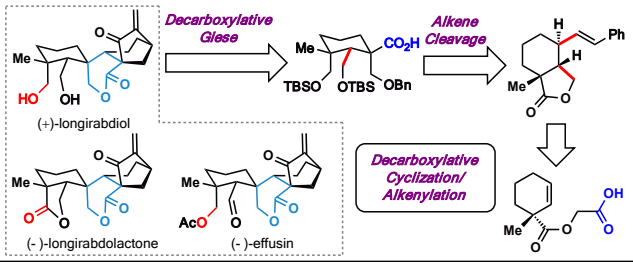
Decarboxylative Giese
Alkene Cleavage
Decarboxylative Cyclization/ Alkenylation
(+)-longirabdiol
(-)-longirabdolactone
(-)-effusin