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Synthesis of (−)-cotylenol, a 14-3-3 molecular glue component

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Abstract

Small molecules that modulate the 14-3-3 protein-protein interaction (PPI) network represent valuable therapeutics and tool compounds. However, access has been lost to 14-3-3 PPI molecular glues of the cotylenin class, leading to investigations into practical chemical syntheses of congeners and analogues. Here we report a concise synthesis of (−)-cotylenol via a 10-step asymmetric entry into a diversifiable 5-8-5 core. This route features a mild Liebeskind-Srogl fragment coupling that tolerates unprecedented steric hindrance to produce a highly congested ketone, and a tandem Claisen-ene cascade that establishes the 8-membered ring. Late-stage control of stereochemistry and functionality leads to (−)-cotylenol and sets the stage for focused library synthesis.

Graphical Abstract

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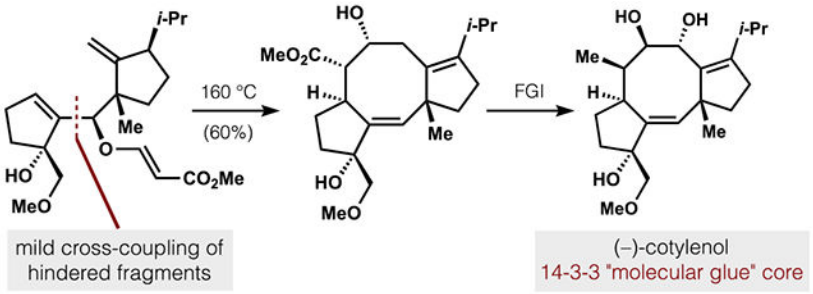

INTRODUCTION

Cotylenin A (**1**) is a member of the fusicoccanes, a family of 5-8-5 tricyclic diterpenoids produced by phytopathogenic fungi (Figure 1).[1,2] Initially isolated as a plant growth regulator, **1** has since been shown to induce differentiation of human acute myeloid leukemia (AML) in primary culture,[3] sensitize human cancer types to existing drugs,[4a,5] and significantly decrease levels of the tumorigenic transcription factor c-Myc.[6,7] Its aglycon cotylenol[8] (**3**) is also bioactive, inducing differentiation in murine leukemia cells at a modestly lower (~10×) potency than **1**.[9] The activity of these compounds is believed to result from their function as “molecular glues” that can selectively stabilize (or disrupt[10]) complexes between the 14-3-3 signaling hub and its numerous client proteins.[11] This property has attracted attention in both academia and industry,[12] since 14-3-3 clients include cancer-relevant proteins such as C-RAF, p53, and BAD,[4a,13] and 14-3-3 PPIs have been proposed to underlie resistance to standard-of-care drugs (e.g., cisplatin, etoposide, doxorubicin).[14] As such, researchers have sought to broadly understand how **1** and **3** modulate different PPIs within the 14-3-3 interactome, as well as determine structure-activity relationships (SAR) to optimize potency and selectivity.[4,9,15,16] Despite important progress, realization of these objectives has been hampered for at least 12 years because the producer organism of **1** and **3**, a *Cladosporium* species, has lost the ability to proliferate in culture.[17] Both the supply and diversification of the cotylenol scaffold are thus critical to advance the cotylenin chemotype towards therapeutic applications, analogous to immunomodulatory imide drug (IMiD) molecular glues.[18]

Currently, access to material requires use of mimics prepared through multistep semisynthesis (e.g., **2** in 14 steps from fusicoccin A)[19] or total synthesis. One total synthesis of cotylenin A has been reported to date (25 steps, 0.15%),[20] along with two syntheses of its aglycon, cotylenol (**3**) (21–32 steps, <1–3.9% yield).[20,21] Here we report an alternative synthesis of **3** that provides expedient access to material and rapidly reaches a scaffold amenable to diversification.

RESULTS AND DISCUSSION

Prior syntheses by Takeshita and Nakada revealed that assembly of the $\Delta^{1,2}$-alkene with an *E*-configuration enabled efficient cyclooctene closure via ene or α-alkenylation reactions (Figure 2).[20,21] However, synthesis of the cyclization precursors required 28 and 17 steps, respectively, due to the extreme steric congestion that flanked the alkene. As an

important step towards broad studies of the cotylenin chemotype, we aimed to access **3** via expedient synthesis of substrate **4**, which incorporated the *E*-$\Delta^{1,2}$-alkene with all native A- and C-ring functionality. As shown by X-ray crystallography, these rings form extensive contacts with 14-3-3 and its client in a deep cleft,[22] whereas the C7–9 bridge and sugar motif point towards solvent-exposed regions. To forge the encumbered $\Delta^{1,2}$-alkene, we reasoned that the severe steric demands would be most readily accommodated in an *intra*-molecular rearrangement coupled to a strong driving force. A Claisen rearrangement appeared well-suited due to 1) exothermicity of C=O bond formation to offset steric repulsion, 2) established models to understand and control product stereochemistry,[23] and 3) chemoselectivity.[24] Analysis of Claisen transition states and experimental feedback (see SI and Scheme 7) eventually suggested allyl vinyl ether **5** as the required starting material, which could arrive in convergent fashion from prefunctionalized A- and C-rings.[25]

First-generation synthesis of A- and C-ring fragments and their cross-coupling.

Our first-generation synthesis aimed to couple the A- and C-ring fragments through an addition of an A-ring vinyllithium to a C-ring electrophile. We therefore targeted an A-ring hydrazone and a C-ring aldehyde, which could be united under Shapiro reaction conditions.

Preparation of the A-ring began with acyloin cyclization of dimethyl glutarate,[26] followed by a $Zn(OTf)_2$-catalyzed Mukaiyama aldol reaction with dimethoxymethane (Scheme 1a). The trimethylsilyl ether was cleanly deprotected with Montmorillonite K10 in MeOH to afford ketone *rac*-**6**. Chiral preparative supercritical fluid chromatography (SFC) provided access to pure enantiomers ((*R*)- and (*S*)-**6**), where the absolute configuration was assigned by derivatization and X-ray crystallography (see SI). Condensation of (*S*)-**6** with $TrisNHNH_2$ produced hydrazone **7**, and the tertiary alcohol was silylated to produce **8**.

Synthesis of the C-ring began with known alcohol **9**, prepared in 50 mmol quantities from (−)-limonene in 4 steps and 56% yield (Scheme 1b).[27] Alkylation with sodium chloroacetate formed **10** in quantitative yield. To generate the C11 quaternary center, **10** was treated with LiTMP to effect a [2,3]-Wittig rearrangement. Oxidative cleavage of the resulting α-hydroxyacid **11** afforded aldehyde **12** in 66% yield over two steps.

With sulfonylhydrazone **8** and aldehyde **12** in hand, we pursued their union via a Shapiro reaction that would convert **8** to its corresponding alkenyllithium. However, subjection of silyl-protected hydrazone **8** to standard Shapiro conditions (2 equiv. *n*-BuLi, THF, −78 °C) consistently resulted in retro-[1,4]-Brook rearrangement to generate a vinyl silane (protonated form of **13**, Scheme 2a). Productive reaction with aldehyde **12** required an excess of *n*-BuLi (3 equiv) to generate either a nucleophilic silicate anion or organolithium (**14**). Under such conditions, allylic alcohol **15** was produced with high diastereoselectivity, possibly from Felkin-Anh control or coordination of the C-ring aldehyde to the A-ring lithium alkoxide. Unfortunately, this diastereomer proved unproductive in the synthesis according to classic Claisen rearrangement models combined with experimental validation (*vide infra*, also see SI). Use of free alcohol-containing substrate **7** averted the retro-[1,4]-Brook rearrangement, but still resulted in addition to **12** with the incorrect facial

selectivity (Scheme 2b). Attempts to reverse stereoselectivity with additives or alternative organometallics proved unsuccessful.

Because addition to the C-ring aldehyde afforded the undesired alcohol epimer, we sought a higher oxidation state electrophile to enable formation of a ketone that could be stereoselectively reduced. We thus targeted a C-ring thioester as both an electrophile and a gateway to alternative carboxylic acid derivatives (Scheme 3a).

Alcohol **9** was converted to thioether **16** through BF_3•OEt_2-promoted substitution with 4-chlorothiophenol. This thioether was then reacted with dichlorocarbene to form sulfonium ylide **17**, which underwent facile [2,3]-Wittig rearrangement to deliver intermediate **18**.[28] Chromatography on hydrated silica gel converted this dichlorothioether to thioester **19** as a single diastereomer in 83% yield from **16**. The use of NaO*t*-Bu in place of KO*t*-Bu enabled higher conversions and yields, due to either a lower rate of alkoxide addition to :CCl_2 or slower α-elimination that limits :CCl_2 concentration and thus homodimerization.[29,30] This preparation of thioester **19** scaled easily to produce >10 grams in a single pass.

To merge the A- and C-rings while avoiding the retro-Brook rearrangement encountered with **8**, we returned to free alcohol **7** (Scheme 3b). Treatment of **7** with *n*-BuLi (>3 equiv) and KO*t*-Bu at 0 °C, however, did not result in coupling with numerous acyl electrophiles, including acid chlorides. Given that reactivity with aldehyde **12** was achieved (*vide supra*), it was evident that the A-ring could be converted to a competent nucleophile, but that the steric hindrance of poorly electrophilic carboxylic acid derivatives prevented reaction. This challenge was ultimately overcome with a Cu(I)-mediated coupling.[31] In this protocol, **7** was treated with *n*-BuLi and KO*t*-Bu, followed by the (2-thienyl)CuCNLi complex developed by the Lipshutz group,[32] and lastly **19** to yield 63% of product **20**. 4-Chloro substitution on the thioester was necessary to achieve good yield, whereas the parent phenyl thioester led to a low yield and low conversion of the C-ring electrophile. Whereas Cu(I)-mediated couplings of thioesters with hard organometallic nucleophiles have seen significant development, their use in the convergent coupling of highly functionalized or hindered fragments is scarce.[33]

The success of this Cu(I)-promoted reaction likely resulted from its mechanistic deviation from typical acyl substitution reactions via carbonyl addition-elimination (Scheme 3c). For the reaction of interest (**7** + **19** to **20**), an addition-elimination mechanism would require formation of an hindered tetrahedral intermediate with vicinal, fully substituted carbons. In contrast to 1,2-addition, the Cu(I)-mediated process has been proposed to involve C–S oxidative addition to form a considerably less hindered metal acyl complex, which then undergoes C–C reductive elimination.[34] An analogous consideration of mechanism and steric effects would later guide reaction selection in our second-generation route (*vide infra*).

With access to **20** secured, an alcohol-directed Luche reduction ($NaBH_4$, $CeCl_3$•$7H_2O$, −78 °C) advanced the material towards a Claisen rearrangement substrate (Scheme 4). The unstable diol **21** was obtained with the desired C1 stereochemistry as a single desired diastereomer in *ca.* 80% yield.[35] The high reactivity and stereochemical outcome are consistent with transition state **TS1**, in which the C3 tertiary alcohol directs reduction and the C-ring occupies a pseudo-equatorial position. Alternative scenarios of ketone-cerium

coordination or chelation are disfavored by the following data: C3 silyl ether **22** did not undergo any reduction under identical Luche conditions, and the C3 epimer of **20** delivered the C1-epimeric alcohol (20:1 dr).

Whereas this route established convergent access to targeted intermediate **21**, several issues noted by the Referees significantly limited its practicality and use in medicinal chemistry. First, the use of preparative chiral SFC constrained material throughput due to instrument time (13 h per gram of (*S*)-**6**), cost ($90/h), and reliance on specialized facilities (Waters 150 AP). Second, the convergent coupling proved difficult to scale and was most reliably carried out with 40 mg **7**. Operationally, it required tedious and carefully timed preparation of four discrete organometallic species ((2-thienyl)Li, (2-thienyl)CuCNLi, A-ring vinyllithium, A-ring cuprate). Moreover, yields were difficult to reproduce because of the reaction's extreme sensitivity to adventitious water and oxygen.[36] With the objective to broadly enable studies of the cotylenin chemotype, we sought improved material throughput via an asymmetric synthesis of the A-ring and a more practical convergent coupling.

Enantioselective synthesis of A-ring fragment and second-generation cross-coupling with C-ring.

Our initial efforts towards an asymmetric A-ring synthesis targeted ketone **6** in enantiomerically enriched form. Despite its structural simplicity, its enantioselective synthesis was repeatedly thwarted by poor enantioselectivity or an inability to productively elaborate synthetic intermediates. Consequently, we explored the synthesis of a cyclic vinylboron coupling partner, encouraged by precedent for the formation of cyclic vinylboronic esters by ring-closing metathesis[37] and the versatility of the C–B bond as a precursor to C–X or C–[M] species. This sequence commenced with ketone **23**, which is known in one step from methoxyacetonitrile[38] or accessible from methoxyacetic acid in a highly scalable 2-step protocol (Scheme 5).[39] To establish the chiral C3 tertiary alcohol, **23** was subjected to addition of trimethylsilylacetylene in the presence of Et_2Zn and a chiral amino alcohol ligand, inspired by foundational work by Noyori.[40]

The use of 20 mol% (−)-MIB[41] (**L1**), derived from (+)-camphor in 3 steps, was found to give the desired product in 81:19 er at room temperature (90% over 2 steps, following desilylation). Cooling to 0 °C improved enantioselectivity (95:5 er), but at the expense of yield (66%). An intermediate temperature (12 °C, dioxane/dry ice) provided both high yields and enantioselectivity, and **L1** was found to be superior to other chiral amino alcohols used for asymmetric alkynylation of ketones with proximal coordinating groups.[42] Using the optimized conditions, alkynylation and subsequent desilylation produced propargyl alcohol **25** (92:8 er) in 86% yield over two steps. This protocol delivered >7 grams of **25** in a single pass, and **L1** could be recovered in >90% yield through extractive workup.

Scalemic propargyl alcohol **25** was subjected to an efficient α-selective hydroboration based on a protocol from the Carretero group, introducing a handle for subsequent cross-coupling while setting the stage for A-ring closure (Scheme 6).[43] Cyclization of **26** was accomplished through ring-closing metathesis with the Hoveyda-Grubbs II catalyst (5 mol %), which provided the boronic ester coupling partner **27** in 74% yield. This material was used

without chromatography to avoid substantial losses on silica gel (74% vs. 53%). This robust sequence enabled straightforward access to >2 grams of **27** in a single pass and 5.2 grams over 3 runs.

Access to gram amounts of pinacolboronic ester **27** allowed us to explore cross-coupling methods more practical than the cuprate-thioester coupling (Scheme 3). In keeping with lessons from the first-generation cuprate coupling, we first investigated transition metal-catalyzed cross-couplings that proceeded through metal acyl complexes to avoid hindered tetrahedral intermediates. We considered a Liebeskind-Srogl coupling (Figure 3) to be ideal, as no change to either substrate would be necessary.[44] However, no literature precedent supported use of a hindered, cyclic boronic ester nucleophile and model studies were discouraging. For example, PhBpin failed to couple with **19**. $PhB(OH)_2$ showed improved reactivity (12%, Figure 3F) but **27** could not be cleanly converted to its boronic acid due to facile 1,3-transposition of the allylic alcohol. In light of these unfavorable results, we were surprised to find that boronic ester **27** engaged thioester **19** in a Liebeskind-Srogl coupling under typical conditions ($Pd_2(dba)_3$, $P(2\text{-furyl})_3$, CuTC, THF), albeit in only 30% yield at 50 °C. Whereas variation of phosphine ligands, Pd pre-catalysts, and Cu reagents failed to improve reaction efficiency, boric acid ($B(OH)_3$) exhibited positive effects, possibly as a Lewis acid, pinacol scavenger,[45] hydroxide donor to Pd,[46] or precursor to borate esters involving the C3 tertiary alcohol.[47] Its inclusion nearly doubled the yield to 54% (1.4 g of **20** in one pass, Figure 3a) and allowed efficient coupling to occur without heating. This represents a remarkably facile synthesis of a hindered ketone *under neutral conditions at room temperature*. The successful coupling of a hindered vinylboronic ester contrasts with the current state-of-the-art, which requires the use of vinylstannanes[48] to form challenging C–C bonds. Vinylborons, on the other hand, have been restricted to unhindered cases (*trans*-1-alkenyl) and almost always require the use of boronic acids.[49]

Intrigued by the mild formation of hindered ketone **20** from a nontraditional Liebeskind-Srogl partner, we sought a better understanding of this reaction and the determinants of its success. The generally restricted scope of vinylborons in hindered Liebeskind-Srogl couplings suggested transmetallation to be a limiting factor (see below and Figure 3F). In the canonical coupling of boronic acids, Liebeskind proposed simultaneous thiolate abstraction and transmetallation, both mediated by CuTC (**28**, Figure 3b).[50] A computational study subsequently proposed stepwise transfer of the organoboron to an acyl-Pd^{2+}-thiolate, followed by thiolate departure (**29**).[51] A third possibility involved thiolate abstraction by CuTC to form an acylpalladium carboxylate intermediate (**30**), followed by transmetallation. Although such an intermediate has not been invoked in the Liebeskind-Srogl coupling, it is a proposed intermediate in Pd-catalyzed couplings of arylcarboxylic acid anhydrides with boronic acids.[52]

In the course of improving the cross-coupling, we evaluated the reaction dependence on the *S*-aryl group, which would directly participate in the pathways **28** and **29** but not **30**. Electronically differentiated *S*-aryl groups led to similar yields, suggesting that **28** and **29** (Figure 3c) may not be major contributors to productive transmetallation of the boronic ester onto Pd^{2+}. Although **28** and **29** could not be rigorously excluded, they did not account for all observed reactivity, as revealed by analysis of unpurified reaction mixtures. Identifiable

side products included 3-*epi*-**20** (4%, from the minor enantiomer of **27**) and mixed anhydride **31** (8%), derived from **19** and CuTC (Figure 3d). The symmetrical anhydride **32** was also observed (4%), possibly resulting from hydrolysis of **31** under the reaction conditions, followed by acylation by a second molecule of **31**. The structure of both anhydrides was confirmed by independent synthesis, and their stability to chromatographic purification testifies to the exceedingly encumbered environment of the C-ring. When subjected to the cross-coupling conditions, both **31** and **32** failed to yield product (**20**), establishing that anhydride formation is nonproductive.

These findings are most consistent with the intermediacy of an acylpalladium carboxylate complex (e.g. **30**), which has been shown through prior stoichiometric studies to account for all observed reactivity (Figure 3e). Yamamoto, Ogiwara and Sakai demonstrated that C–C coupling occurs in good yield upon treatment of related acylpalladium carboxylate complexes with arylboronic acids.[52b,53] Alper has shown that a complex with the less donating PPh_3 ligand spontaneously undergoes C–O reductive elimination to generate anhydrides.[54] This process occurs following dissociation of a phosphine ligand, and is of relevance since our experiments employ $P(2\text{-furyl})_3$, which is both thermodynamically and kinetically more labile than PPh_3.[55] Notably, numerous studies have provided evidence against C–O bond formation via outer-sphere nucleophilic attack on the acyl group, which would not require complex **30**.[56] Interestingly, in the coupling of less hindered systems, Liebeskind and Srogl have only observed decarbonylation as a side reaction, suggesting that the steric demands of the substrate may alter relevant reaction pathways.[44]

The likely involvement of intermediate **30** suggested that extremely hindered Liebeskind-Srogl couplings require efficient transmetallation to a congested acylpalladium carboxylate complex in order to outcompete C–O reductive elimination. Consistent with this mechanistic picture, the use of excess boronic ester **27** (3 equiv) improved the yield of **20** (62% vs. 54% under identical conditions, Figure 3f), and not because the reaction was limited by protodeboronation.[57] To investigate whether proximal functional groups influenced the transmetallating ability of **27**, closely related boronic esters were reacted with thioester **19**. Unsubstituted boronic ester **33** and C3-deoxy boronic ester **34** failed to couple with **19**, whereas hydroxyl-substituted substrate **35** proved competent (36%). These observations were mirrored in arylboronic esters and acids, where the presence of a 2-hydroxy group significantly enhanced reactivity relative to the parent compound (**36a**–**c**, **37a**–**b**). The pendant hydroxy group may serve to lower the barrier to transmetallation via coordination to Pd^{2+} as a directing group (as has been demonstrated for alkylboronic esters[58]), or hydrogen bonding with a Pd-bound acyl group or carboxylate; the coordination of boric acid may strengthen these interactions. While the experiments above demonstrated the beneficial effect of the proximal alcohol, it was not found to be broadly sufficient to enable cross-coupling with hindered thioester **19** (see SI). These data emphasize the general difficulty of hindered Liebeskind-Srogl reactions and the unique efficiency of the coupling to form **20**.

These insights into the reactivity of boronic ester **27** led us to evaluate the extent to which hindered Liebeskind-Srogl couplings depended on the thioester partner. In contrast to the boronic ester, numerous sterically encumbered thioesters coupled successfully (**38a**–**h**, Figure 4). These experiments revealed several insights. First, the transformation did not rely

on the exocyclic alkene in **19** to stabilize acylpalladium species.[59] Second, the reaction yield increased for less encumbered thioesters, possibly due to faster transmetallation of less-hindered acylpalladium carboxylates relative to C–O reductive elimination. Finally, under no circumstances did we observe decarbonylation, possibly since decarbonylation to form *tert*-alkylpalladium complexes incurs prohibitive steric penalties. Overall, this investigation has shown that the Liebeskind-Srogl coupling can enable facile synthesis of hindered ketones if transmetallation is accelerated, and we have outlined key considerations for the success of this demanding transformation.

More importantly, this second-generation route to **20** accomplished the two goals outlined during its conception. The first goal of developing an asymmetric A-ring synthesis was made possible by an enantioselective ketone alkynylation, which enabled rapid elaboration to a vinylboronic ester. The second goal of developing a robust, operationally simple and scalable cross-coupling was achieved through a $B(OH)_3$-enhanced Liebeskind-Srogl coupling. This transformation produced hindered ketone **20** under mild conditions and obviated the laborious and sensitive organocuprate coupling from the first-generation synthesis. The coupling has been scaled to produce >1 gram of **20** per run, intercepting the end of the first-generation route with far greater material throughput.

Claisen rearrangement and completion of cotylenol.

Access to the 5-8-5 scaffold and completion of cotylenol (**3**) required identification of a suitable enol ether substrate for Claisen rearrangement to construct the highly congested $\Delta^{1,2}$-alkene (Scheme 7a). A successful substrate would need to: (1) be accessible from the hindered C1 alcohol, (2) undergo Claisen rearrangement faster than decomposition (especially elimination of the C3 tertiary allylic alcohol), (3) afford the correct *E*-geometry at the formed $\Delta^{1,2}$-alkene, and (4) afford the correct *R* configuration at C6.

With these criteria in mind, we initially attempted to surmount these challenges from allylic alcohol **15**, which was more readily accessed than its epimer **21** during initial route development (Scheme 2). The first task of forging the enol ether was met with resistance. Steric hinderance prevented synthesis of vinyl ether **40a** using alkenyl electrophiles with Pd^{2+} or Hg^{2+} catalysis, while extensive decomposition thwarted access to silyl ketene acetal/hemiaminal **40b** and **40c** under forcing Johnson- or Eschenmoser-Claisen conditions (Scheme 7b). Enol ether synthesis was eventually accomplished to form ynol ether **40d** (from Waser's reagent[60]) and enol ethers **40e**,**f** (from esterification/silylation or *oxa*-Michael addition). However, these compounds failed to undergo productive Claisen rearrangements, likely due to barriers exceeding those of decomposition pathways.

Further experimentation revealed that vinylogous ester **40g** was accessible from *oxa*-Michael addition (see SI) and reactive in the Claisen rearrangement (Scheme 7c). Upon heating in PhMe at 130 °C, **40g** converted into **41g** in 56% yield, furnishing the hindered $\Delta^{1,2}$-alkene with the necessary *E*-geometry for elaboration to **3**. The alkene geometry was rationalized as shown in **TS2**: the C3 substitution on the A-ring caused $A^{1,2}$-strain to dominate over 1,3-diaxial strain, forcing the C-ring to occupy a pseudoaxial position in the chair-like transition state (Scheme 7e).[23] The importance of C3-substitution was verified with model

substrate **42** (Scheme 7d).[61] This compound also underwent Claisen rearrangement, but the absence of C3-substitution rendered $A^{1,2}$-strain insufficient to overcome 1,3-diaxial strain. Thus, the C-ring instead occupied a pseudoequatorial position in **TS3**, producing **43** with the undesired alkene geometry.

Although enol ether **40g** satisfied 3 out of 4 requirements, its Claisen rearrangement yielded the incorrect C6 stereochemistry, a result of the 1*S*-configuration. Our collective findings led us to posit that all four requirements could be met with the C1-epimer of **40g**.

Realization of a successful stereoselective Claisen rearrangement (Scheme 8) began with C1-epimeric alcohol **21**, which was accessed via Liebeskind-Srogl coupling and reduction (Scheme 4). *Oxa*-Michael addition of the hindered C1 alcohol to methyl propiolate was mediated by *N*-methylmorpholine (NMM) at 0 °C with exceptional ease, likely through an alkoxide/enammonium caged pair.[62] The resulting vinyl ether **44** was heated in silylated glass to provide 5-8-5 tricycle **45** via a stereoselective Claisen rearrangement/ene reaction cascade.[21,63] In accordance with the insights gained from Scheme 7, the A-ring substitution at C3 and the *R*-configuration at C1 translated cleanly to the requisite hindered *E*-alkene and the 6*R*-configuration, respectively (**TS4**). The *E*-alkene placed the C8 aldehyde proximal to the $\Delta^{9,10}$-alkene, such that the thermal conditions also effected an ene reaction (**TS5**) analogous to that developed by Takeshita.[21b,c] This protocol readily afforded 750 mg of the advanced tricycle **45** in a single pass.

A simple sequence then converted **45** to cotylenol (**3**). First, β-hydroxyketone **46** was obtained following uneventful oxidation of the β-hydroxyester and decarboxylative aldol reaction with formaldehyde (Scheme 9a). Elimination of the β-hydroxyl group yielded enone **47**, which was subjected to a series of stereoselective transformations to establish the C7–9 stereotriad. α-Hydroxylation of **47** at C9 proved efficient (94%) and highly stereoselective (>20:1 dr), contrasting prior syntheses wherein oxidations of related intermediates delivered mixtures of C9 epimers (2.7–1.5:1).[20,21] The rigid conformation enforced by the all-sp^2 C7–9 bridge of **50** (the potassium enolate of **47**) may allow reagents to avoid the *i*-Pr substituent but not the C18 methyl on the opposite face (Scheme 9b).[64] Late-stage intermediates of prior syntheses possessed pseudo-equatorial methyl groups at C7, which likely twisted the enolate (relative to **50**) to expose the internal face. α-Hydroxyketone **48** was then subjected to a diimide reduction, which also occurred from the exterior face with high dr (7:1). Finally, Nakada's protocol for directed reduction furnished **3** in 83% yield and >20:1 dr without recourse to C3 alcohol protection/deprotection as used previously.[20]

CONCLUSION

In summary, we have developed a short synthesis of (−)-cotylenol (16 linear steps, 9 steps from convergence of A and C-rings) via mild Liebeskind-Srogl coupling of hindered and fully functionalized A- and C-rings, and a Claisen-ene cascade reaction (Scheme 10). The synthetic sequence scales well, expediently affording 750 mg of 5-8-5 scaffold **45** in 10 linear steps (3.8%, 1st generation *versus* 4.2–6.8%, 2nd generation route, depending on preparation of A-ring starting material). Furthermore, the route is highly amenable to

diversification at numerous positions: the A and C rings through cross-coupling, and the B-ring through manipulation of the Claisen-ene product **45**. We plan to leverage this synthesis to prepare a focused library of analogues and explore the selective engagement of 14-3-3 protein/client complexes.[65] These efforts will benefit from available crystal structures for 14-3-3 protein/client/cotylenin A complexes and existing SAR data for cotylenin congeners and semisynthetic fusicoccin analogues. We aim to identify novel natural product-based lead compounds for future development, and efforts toward this goal are underway.[66]

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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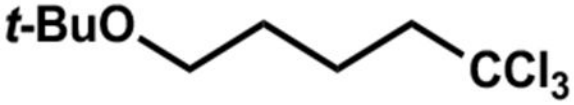

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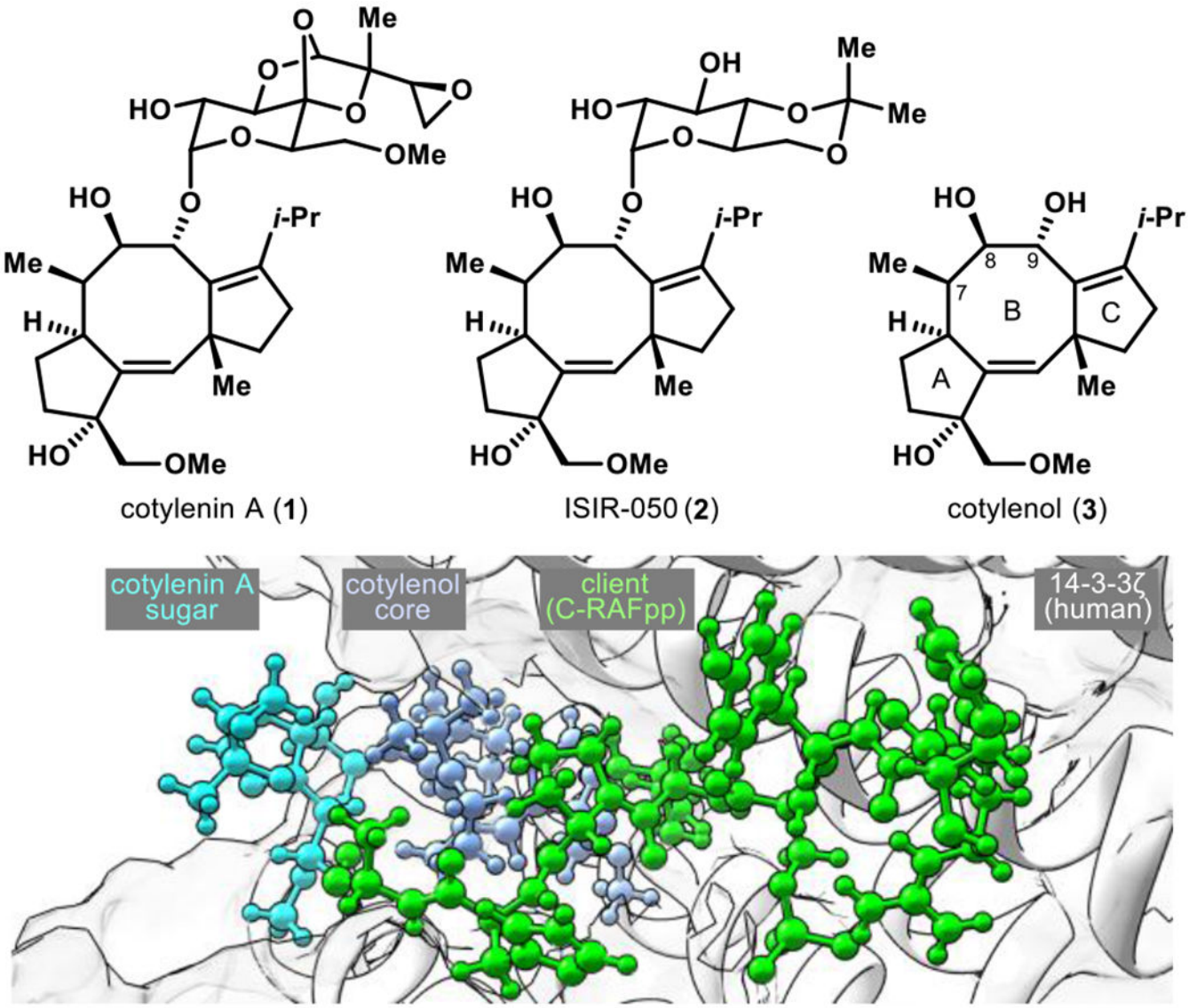


Figure 1.

Fusicoccanes such as cotylenin A function as molecular glues between 14-3-3 proteins and phosphoprotein clients (from PDB: 4IHL, ref. 4a). C-RAFpp = diphosphorylated C-RAF peptide.

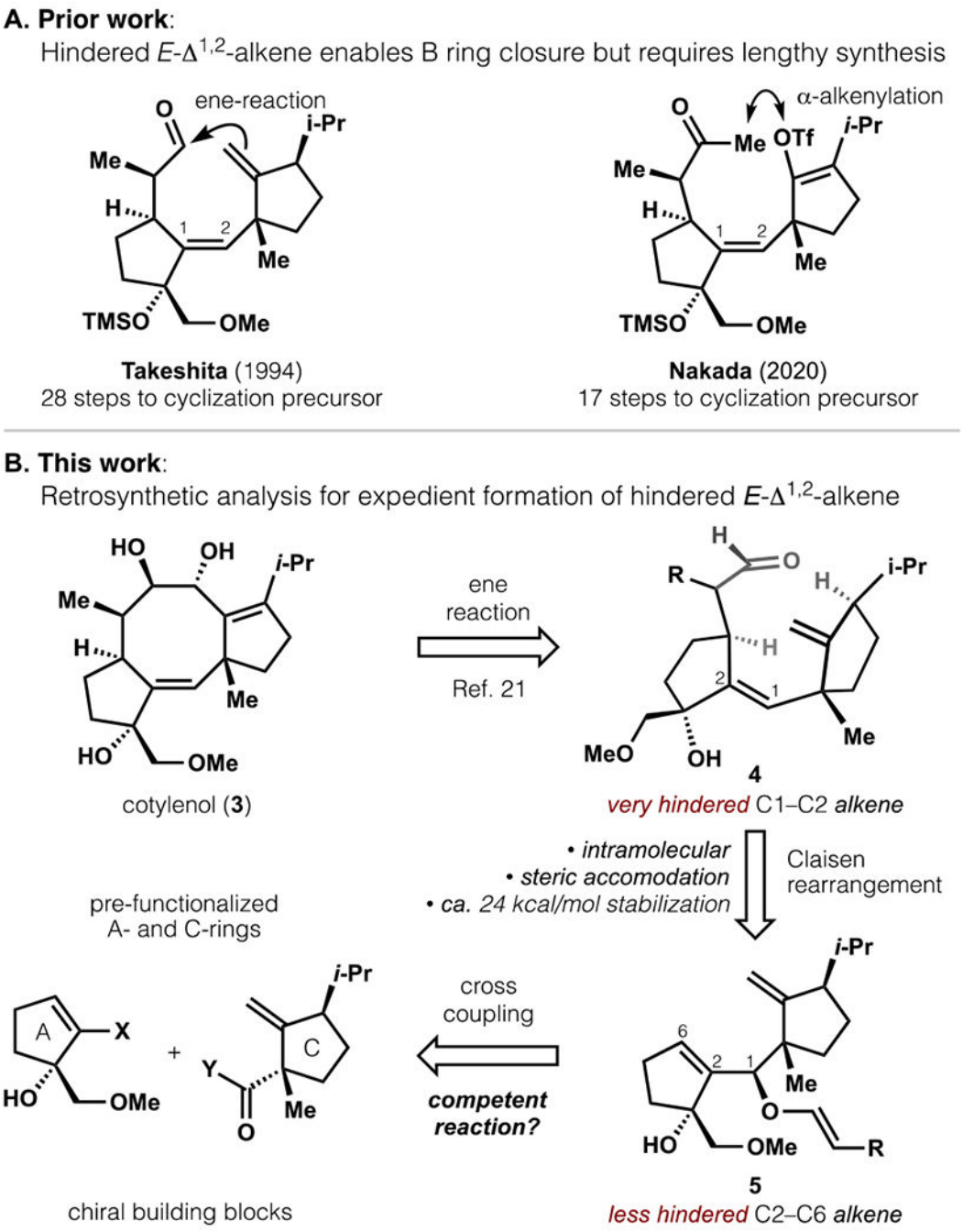


Figure 2.
Synthetic strategies to access cotylenol.

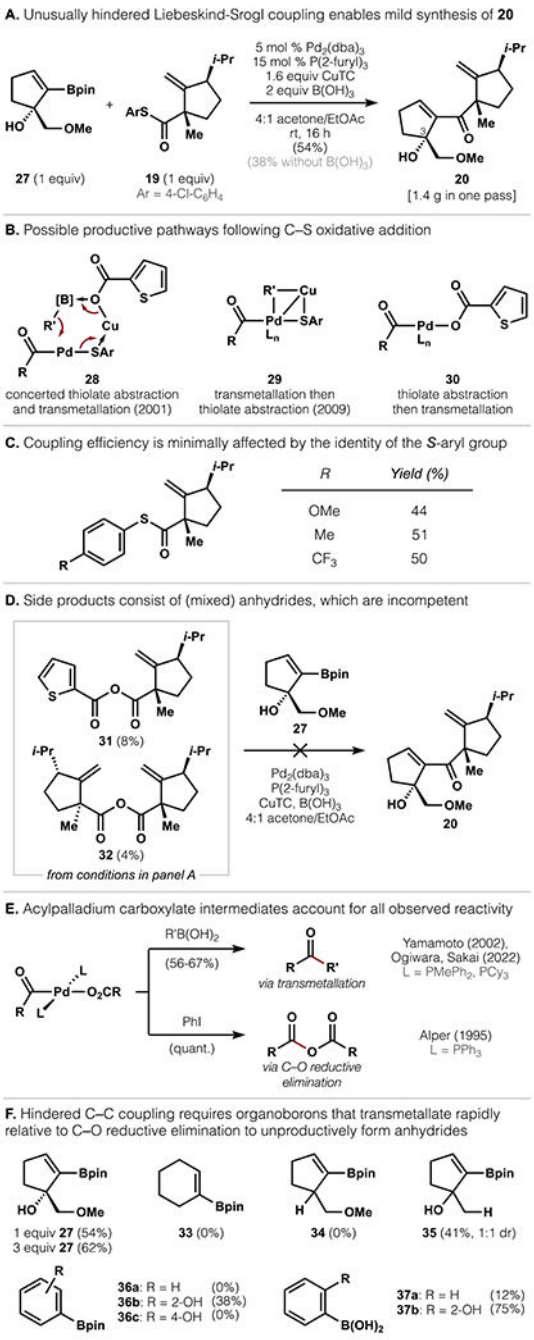


Figure 3.

Discovery and investigation of an unusually hindered Liebeskind-Srogl fragment coupling.

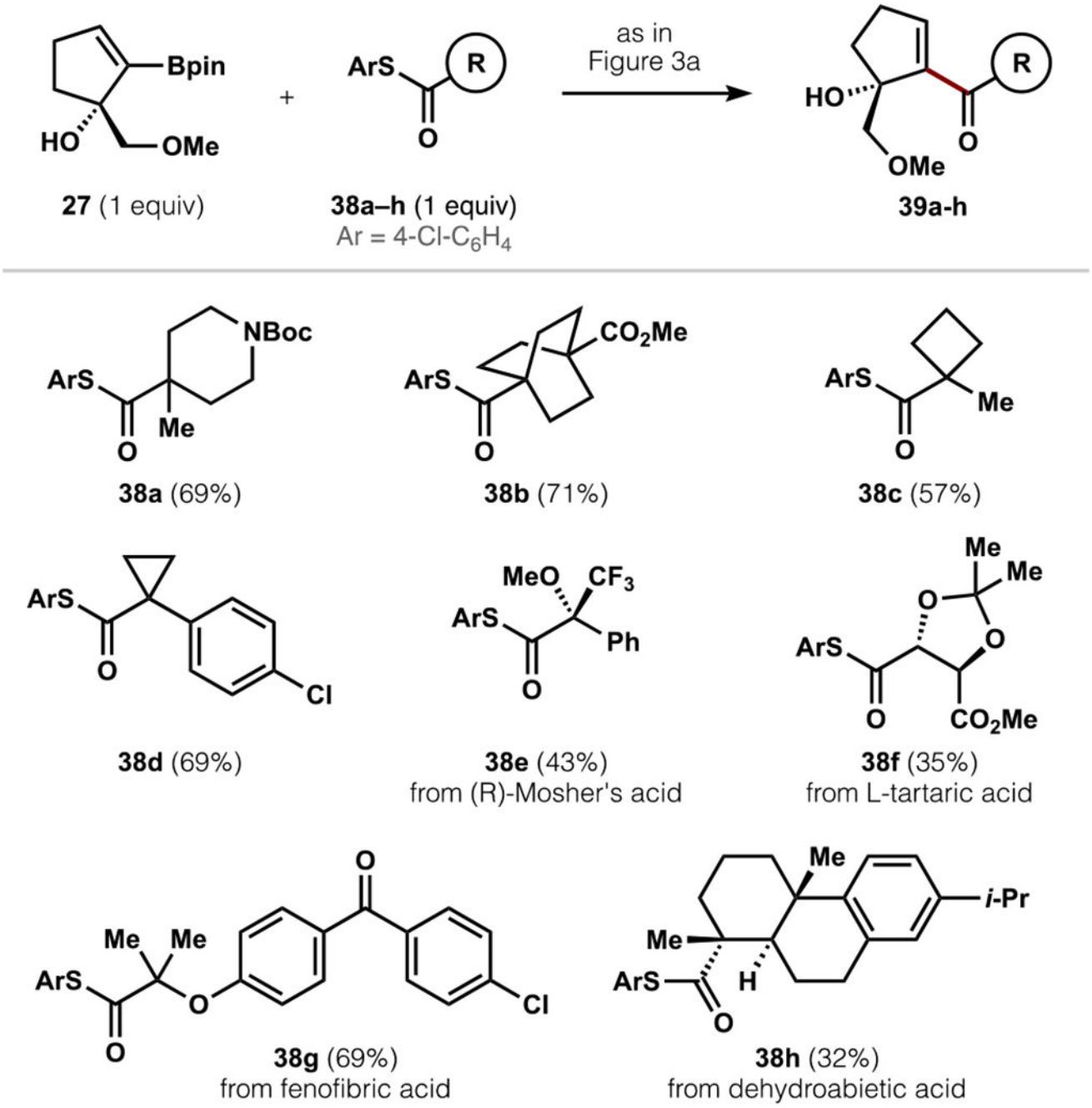
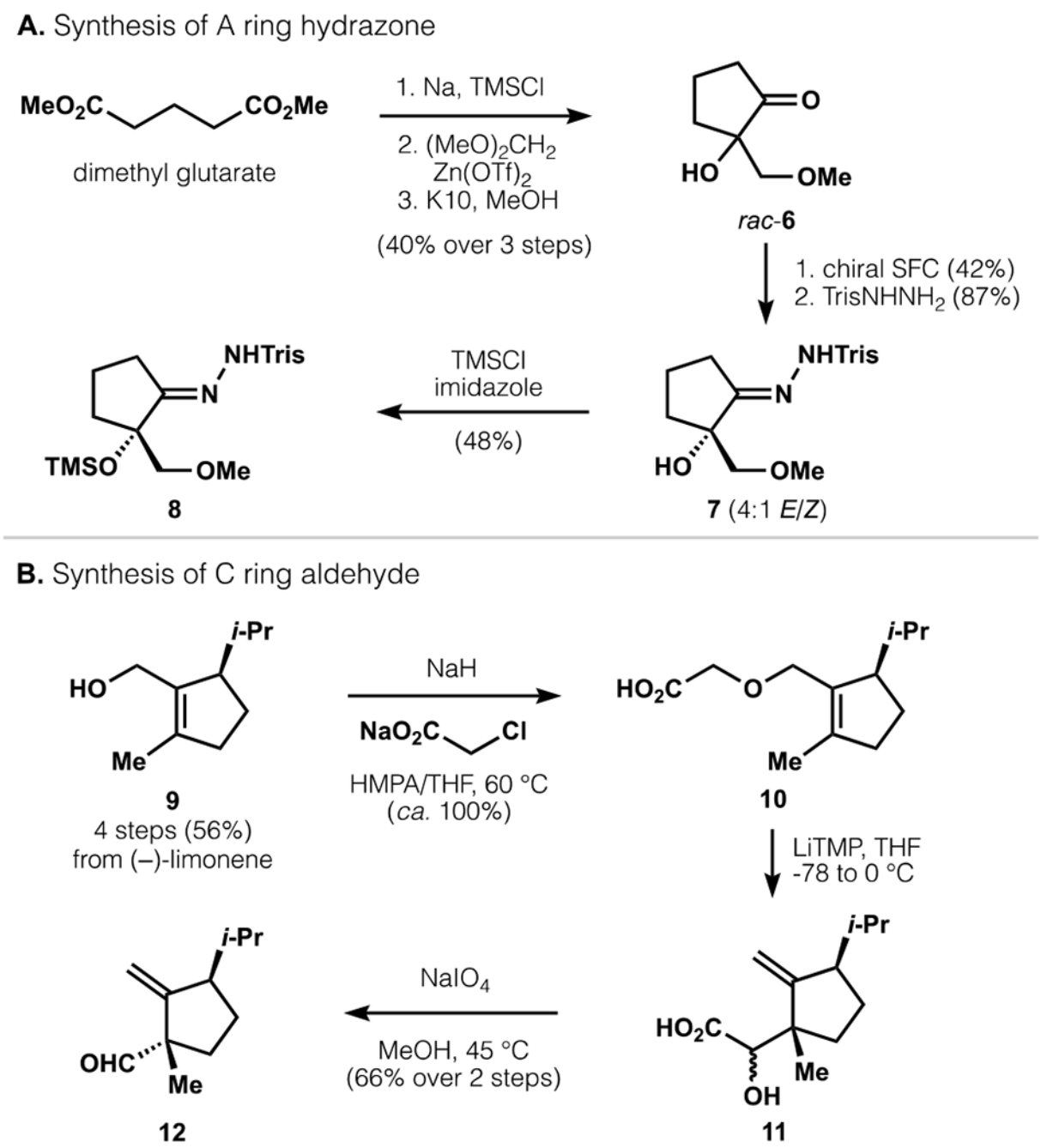
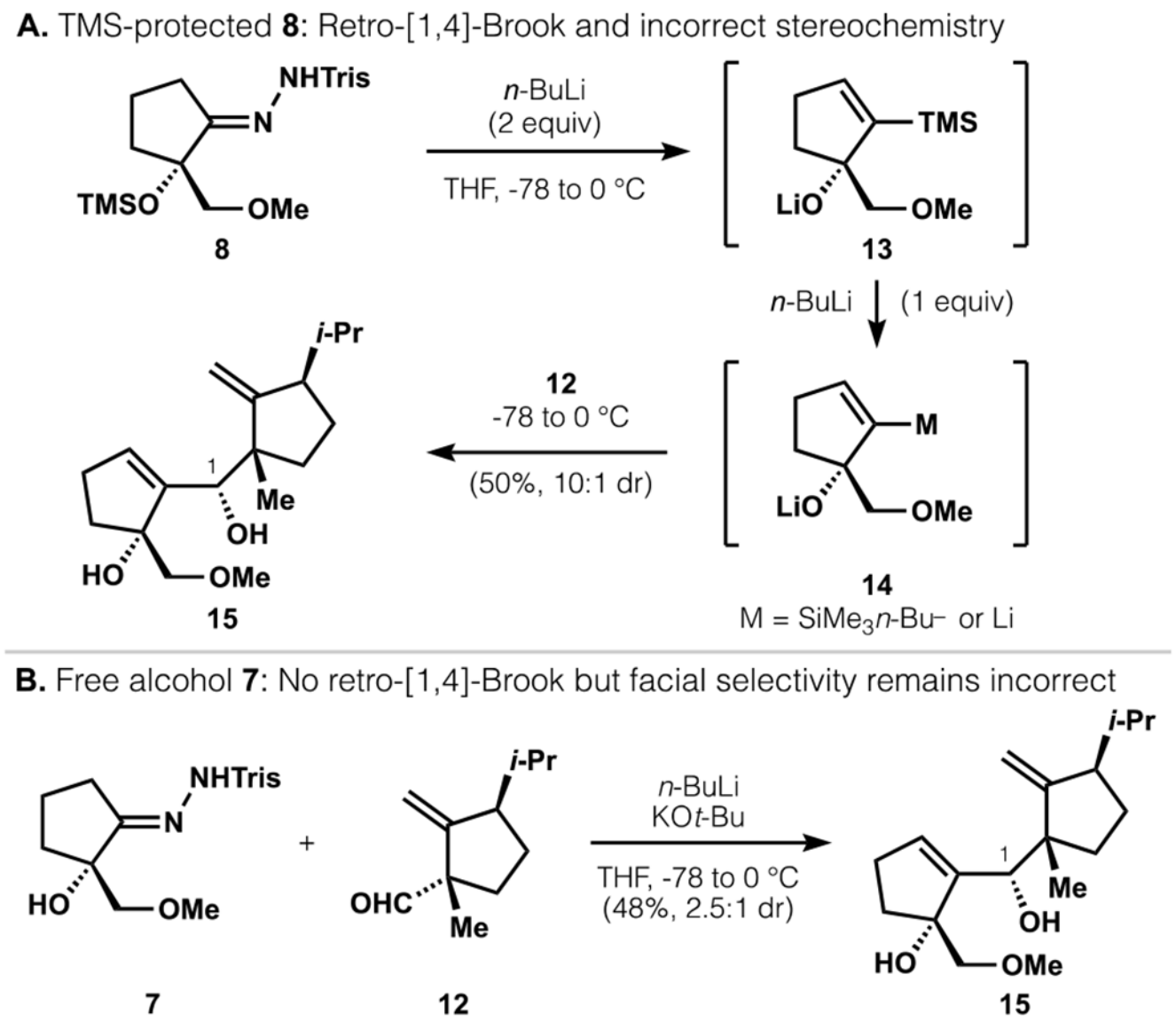


Figure 4.

Scope of hindered ketones. Reaction conditions: **27** (0.12 mmol), **38a–h** (1 equiv), $Pd_2(dba)_3$•$CHCl_3$ (5 mol %), P(2-furyl)**3** (15 mol %), CuTC (1.6 equiv), $B(OH)_3$ (2 equiv), 4:1 acetone/EtOAc, rt, 16 h.

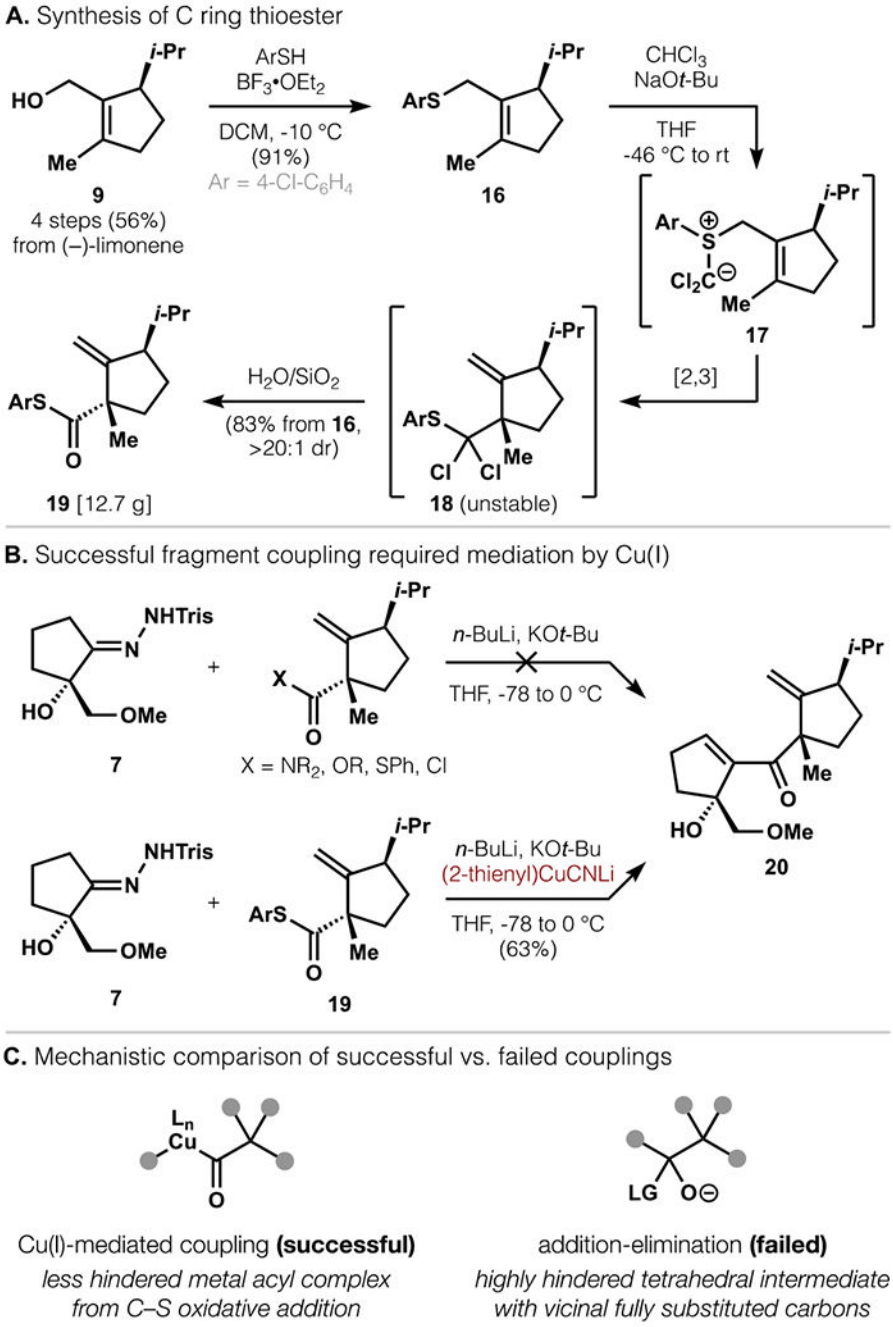


Scheme 1.
Initial synthesis of A- and C-ring fragments, revised in Schemes 3, 5 and 6.



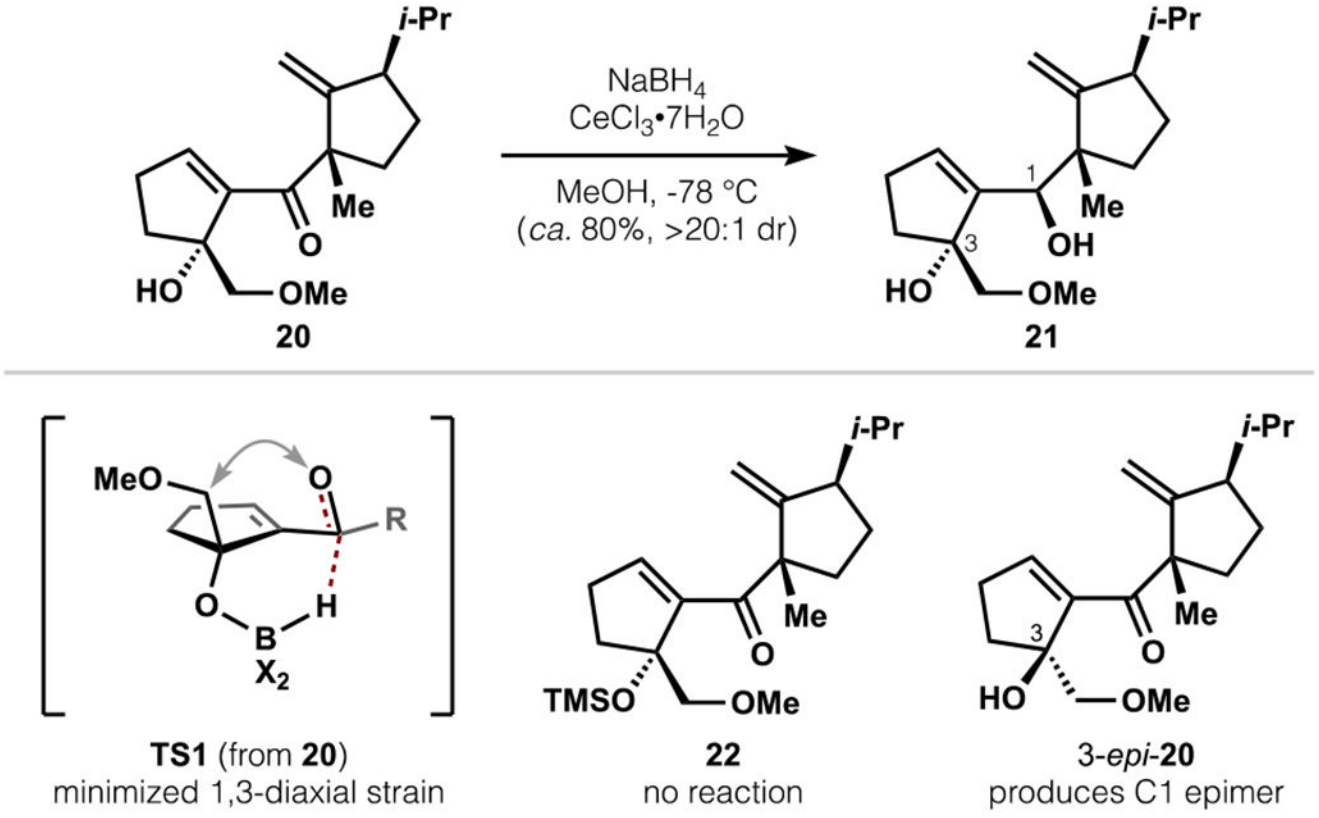
Scheme 2.

Addition to C-ring aldehyde yields incorrect diastereomer **15**.

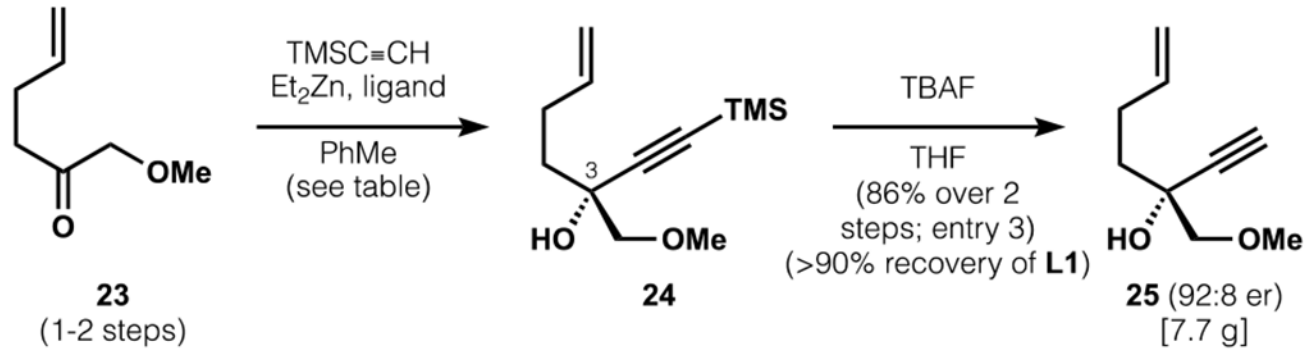


Scheme 3.

Realization of fragment coupling with a higher oxidation state C-ring electrophile.

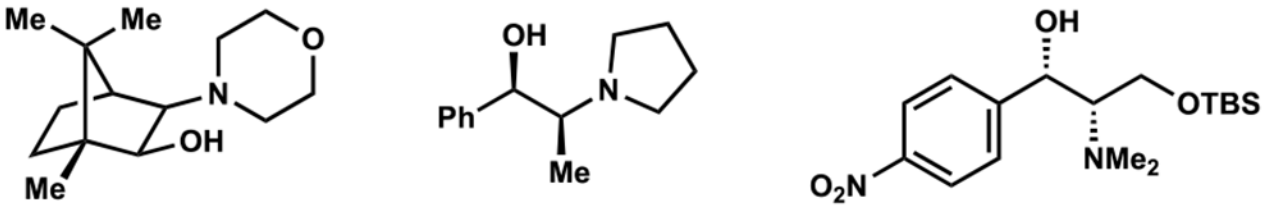


Scheme 4.
Stereoselective Luche reduction to establish desired C1 configuration.

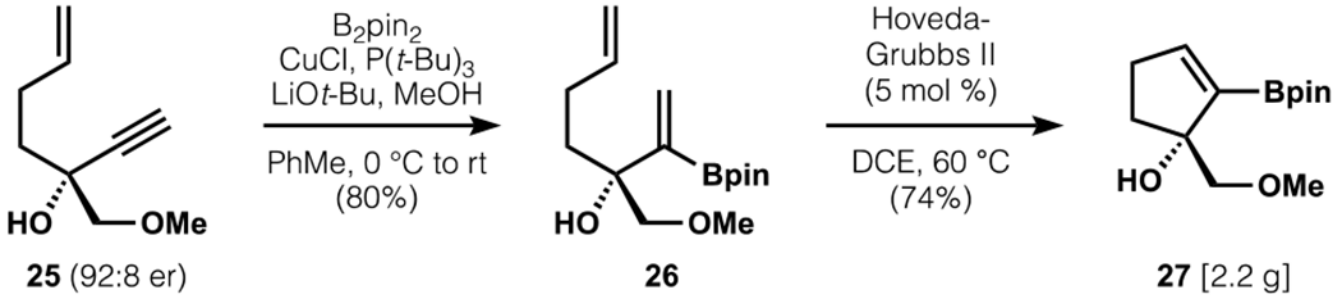


Entry	*Ligand (20 mol %)*	*Temperature* (°C)	*Yield (%)*	*er*
1	**L1**	22	90[a]	81:19
2	**L1**	0	66	95:5
3	**L1**	12	86[a]	92:8
4	**L2**	12	70	7:93
5	**L3**	12	68	74:26

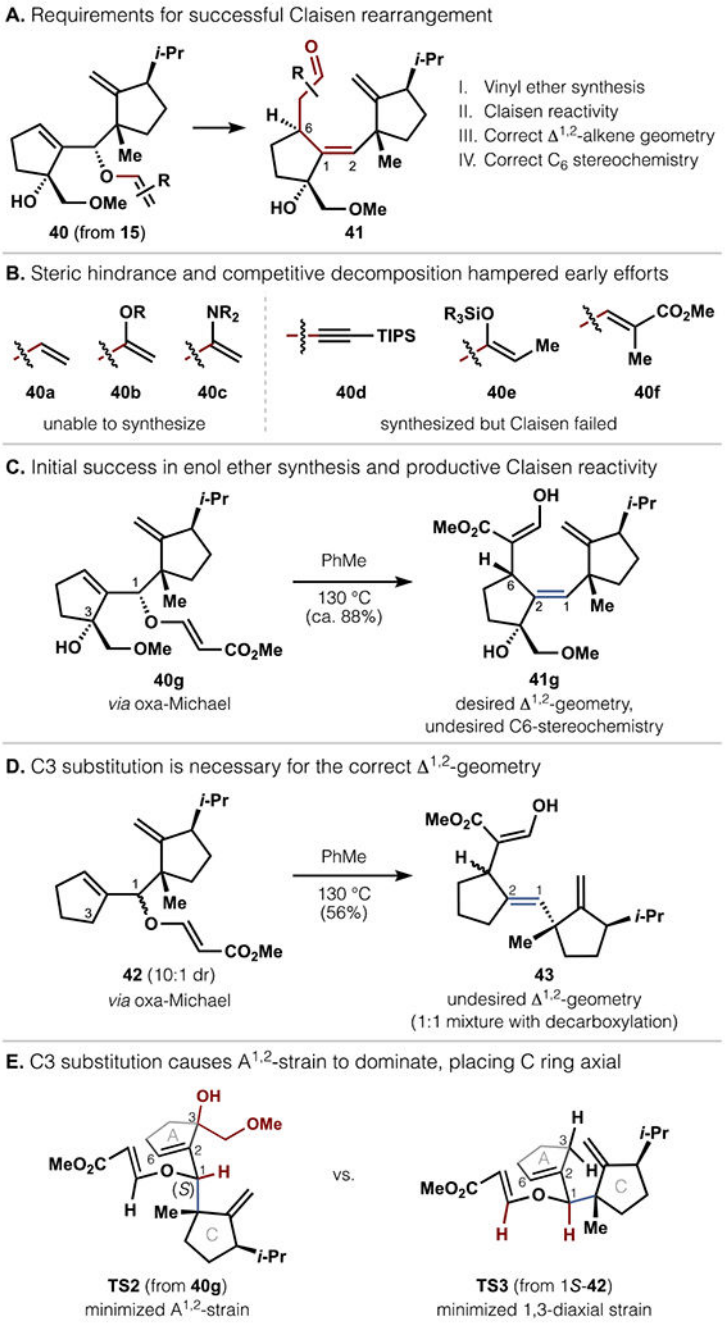
[a]Following desilylation.



Scheme 5.
Asymmetric synthesis of C3 tertiary alcohol for second-generation A-ring synthesis.

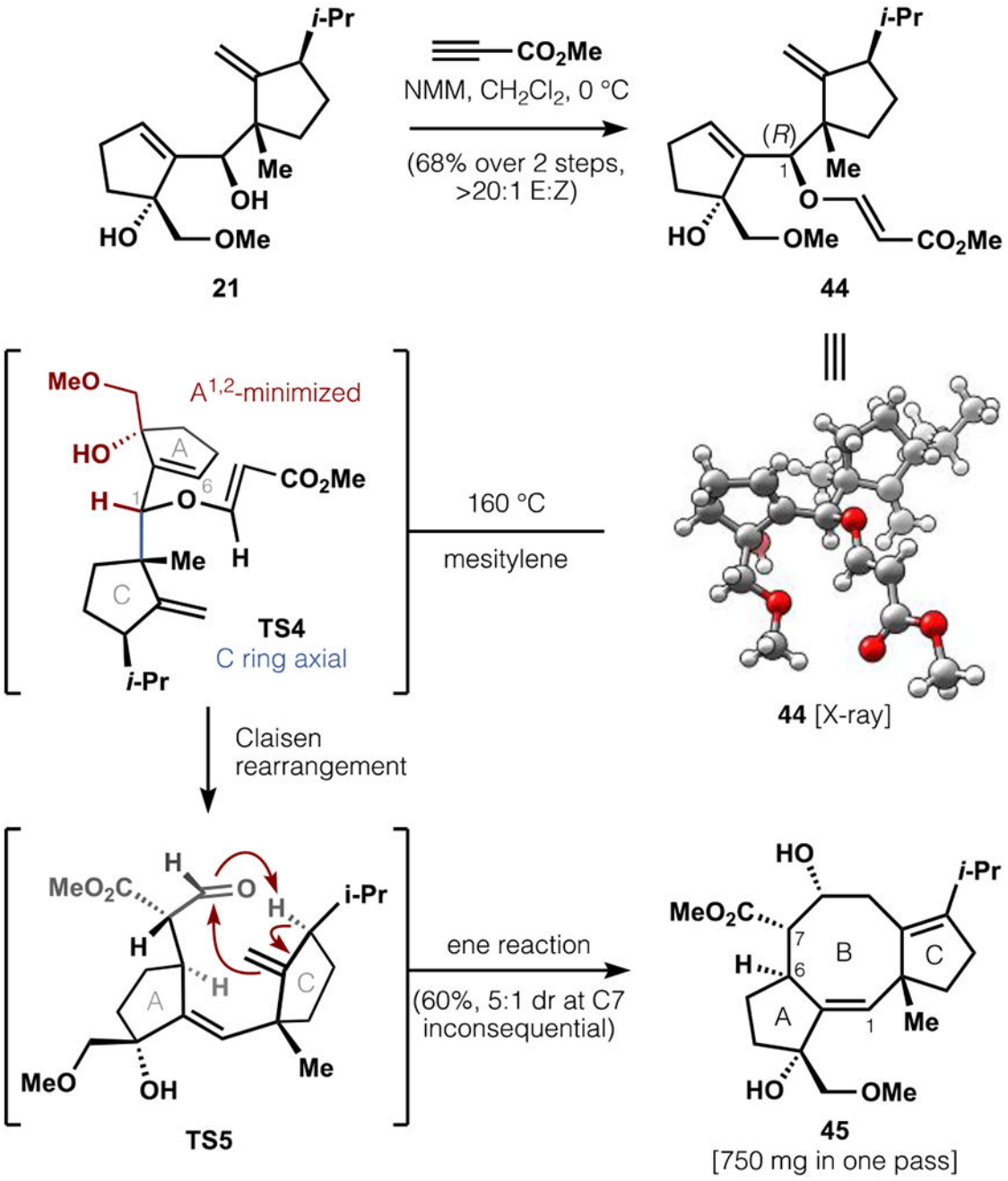


Scheme 6.
Elaboration to an A-ring cyclic vinylboronic ester.

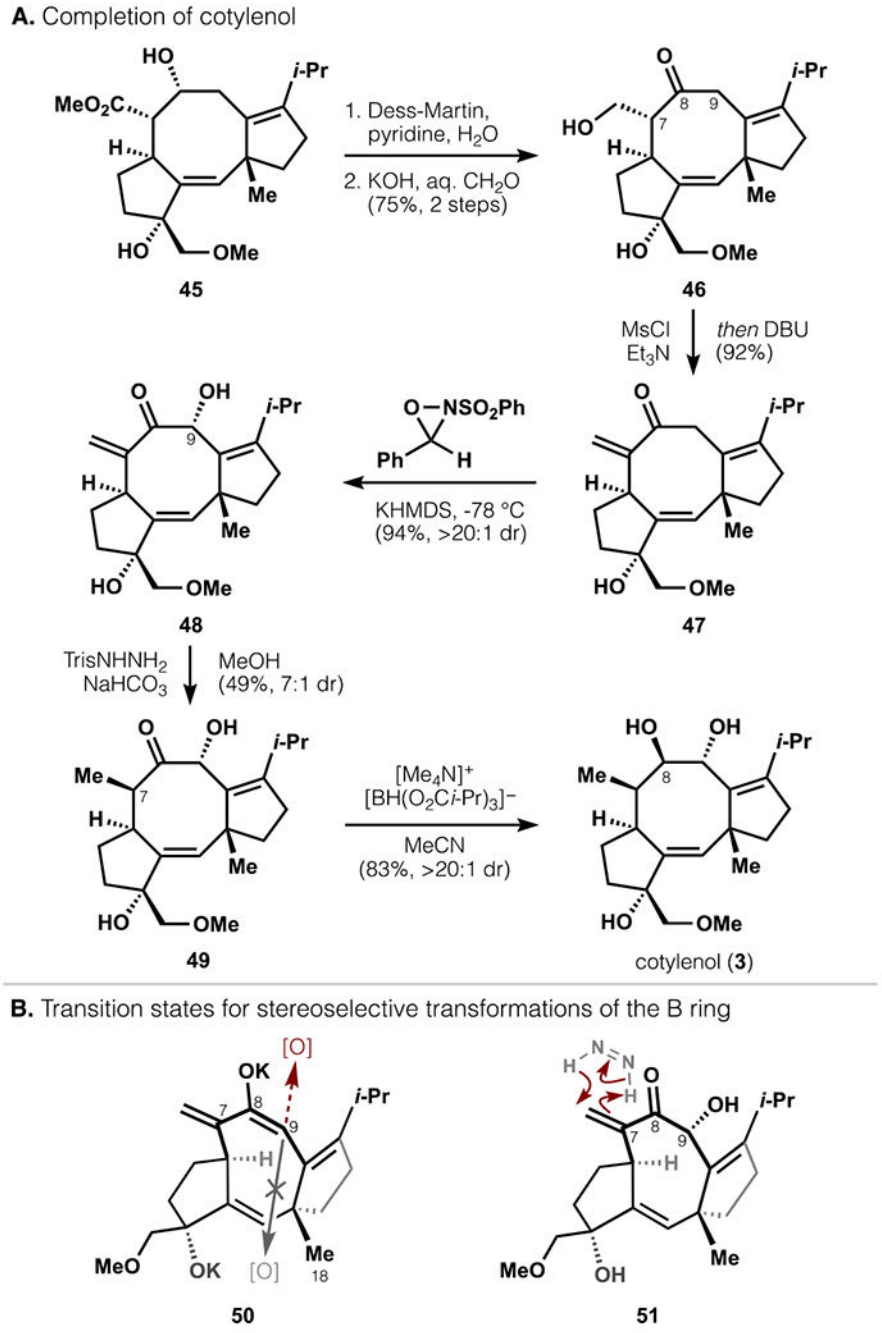


Scheme 7.

Incremental progress towards identification of a suitable Claisen rearrangement substrate.

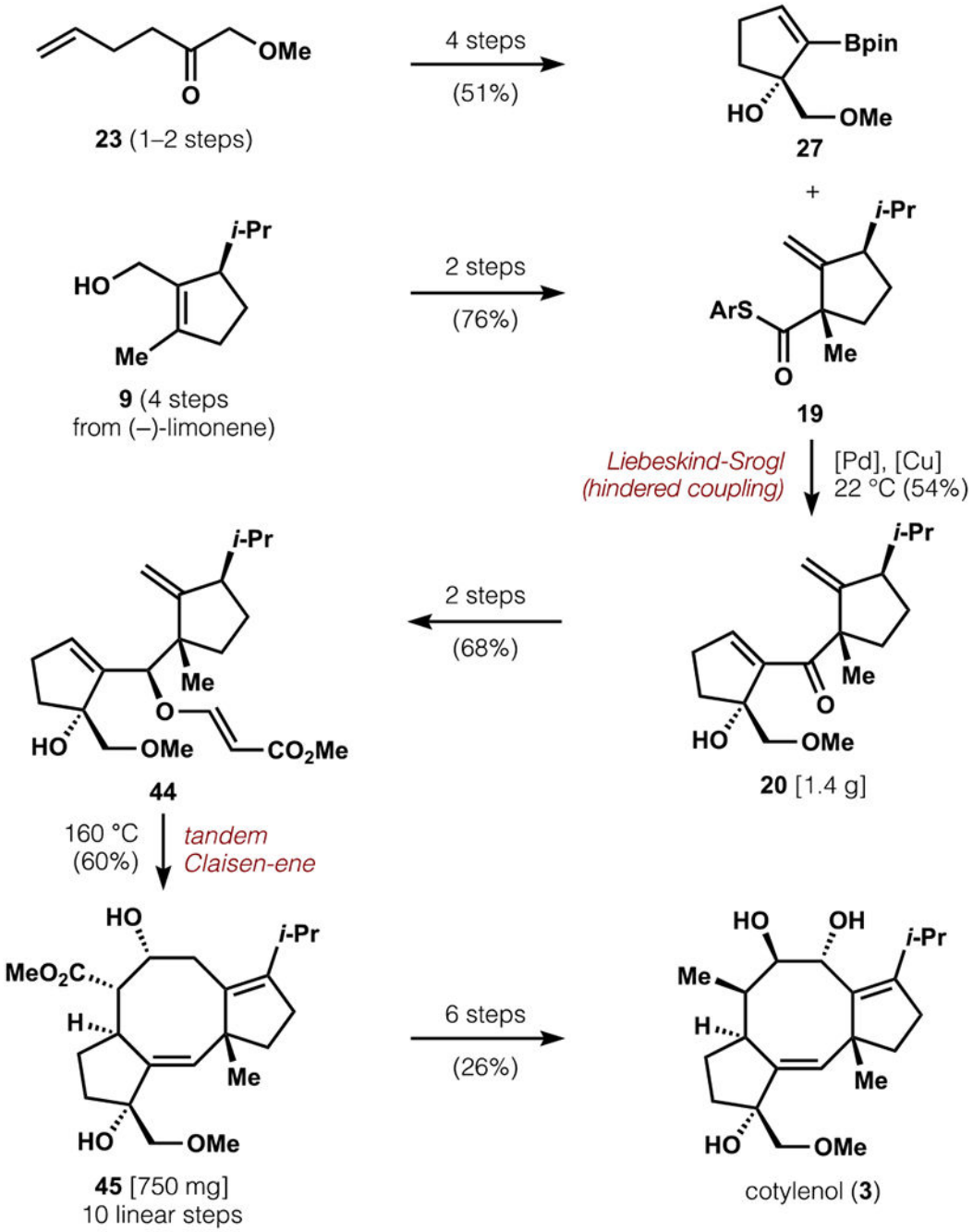


Scheme 8.
Tandem Claisen-ene cascade.



Scheme 9.

Completion of cotylenol via stereoselective B-ring manipulations.



Scheme 10.
Summary of completed synthesis.