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Development of a modular synthetic route to (+)-pleuromutilin, (+)-12-*epi*-mutilins, and related structures

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ABSTRACT: We describe the development of an enantioselective synthetic route to (+)-pleuromutilin (**1**), (+)-12-*epi*-mutilin, and related derivatives. A key hydrindanone was prepared in three steps and 48% overall yield from cyclohex-2-en-1-one. 1,4-Hydrocyanation provided a nitrile (53%, or 85% based on recovered starting material) that was converted to the eneimide **57** in 80% yield by the 1,2-addition of methyllithium to the nitrile function, cyclization, and *in situ* acylation with di-*tert*-butyldicarbonate. The eneimide **57** was employed in a two-fold neopentylic coupling reaction with an organolithium reagent derived from the alkyl iodides (*R*)- or (*S*)-**30**, which contain the C11–C13 atoms of the target, to provide diastereomeric diketones in 60% or 48% yield (for coupling with (*R*)- or (*S*)-**30**, respectively). The diketone derived from (*S*)-**30** contains the (*S*)-C12 stereochemistry found in pleuromutilin, and was elaborated to an alkynylaldehyde. Nickel-catalyzed reductive cyclization of this alkynylaldehyde, to construct the eight-membered ring of the target, unexpectedly provided a cyclopentene (67%), which arises from participation of the C12-α-olefin in the transformation. The diketone derived from the enantiomeric C12-fragment (*R*)-**30** underwent reductive cyclization to provide the desired cyclization product in 60% yield. This was elaborated to 12-*epi*-mutilin by a four-step sequence (39% overall). Installation of the glycolic acid residue, followed by C12 epimerization (Berner et. al *Monatsh. Chem.* **1986**, *117*, 1073) generated (+)-pleuromutilin (**1**). (+)-12-*Epi*-pleuromutilin and (+)-11,12-di-*epi*-pleuromutilin were prepared by related sequences. This work establishes a convergent entry to the pleuromutilins and provides a foundation for the production of novel antibiotics to treat drug-resistant and Gram-negative infections.

Introduction

(+)-Pleuromutilin (**1**) was isolated in 1951 by Kavanagh, Hervey, and Robbins from *Pleurotus mutilus* and *Pleurotus passeckerianus* and shown to inhibit the growth of Gram-positive bacteria (Figure 1).[1] Anchel,[2] Arigoni,[3] and Birch[4] established the structure of **1**, which was confirmed by X-ray crystallographic analysis.[5] (+)-Pleuromutilin (**1**) is comprised of a densely-functionalized eight-membered carbocycle fused to a *cis*-hydrindanone core and contains eight contiguous stereocenters, three of which are quaternary. The biosynthesis of (+)-pleuromutilin (**1**), from geranylgeranyl pyrophosphate, has been elucidated.[4,6]

The antibacterial properties of pleuromutilins derive from the inhibition of bacterial protein synthesis. The tricyclic core and the C14 glycolic acid residue bind the A- and P-sites, respectively, of the peptidyl transferase center.[7] The C14[8] glycolic acid residue is essential for antibacterial activity; by comparison, the deacylated derivative (+)-mutilin (**2**) is not active against Gram-positive bacteria.[9] Thousands of C14 analogs have been prepared from natural (+)-pleuromutilin (**1**).[10] Tiamulin (**3**) and valnemulin (not shown) are C14 analogs used in veterinary applications since the 1980s. Retapamulin (**4**) was approved in 2007 for the treatment of impetigo in humans.[11] Most pleuromutilins tested to date elicit very low mutational frequencies,[12] and as of 2014 clinical resistance to retapamulin (**4**) therapy has not been recorded.[13] Lefamulin (**5**) recently passed a Phase III clinical trial for the treatment of community-acquired bacterial pneumonia (IV-to-oral administration).[14]

The derivatives **3**–**5** (and other C14 analogs) are active against primarily Gram-positive pathogens. Functionalization of the cyclooctane ring has the potential to significantly improve the spectrum of activity. For example, epimerization of the C12 position (by an unusual retroallylation–allylation reaction discovered by Berner, *vide infra*),[15] followed by functionalization of the transposed alkene provides 12-*epi*-pleuromutilin derivatives such as **6**, which possess activity against Gram-negative pathogens.[16] This improved activity is due in part to decreased AcrAB-TolC efflux,[16b] a common resistance mechanism in Gram-negative strains. Pleuromutilins inhibit the three bacterial strains recently classified as urgent threats by the Centers for Disease Control and Prevention:[17] *Clostridium difficile*,[18] carbapenem-resistant *Enterobacteriaceae* (CRE),[16h] and drug-resistant *Neisseria gonorrhoeae*.[16a]

As outlined, semisynthesis has primarily enabled modification of C14 and, to a lesser extent, C12. Although a limited number of changes to other positions have been made,[10] much of the chemical space surrounding the carbon skeleton remains unexplored. A fully synthetic route to pleuromutilins would enable access to a greater diversity of antibiotics with potentially expanded activity spectra and improved pharmacological properties. Herein we describe in full detail our synthetic studies toward (+)-pleuromutilin (**1**), culminating in the development of a convergent, enantioselective, 16-step route to the (+)-12-*epi*-mutilin scaffold as well as a 19-step route to (+)-pleuromutilin (**1**) itself.[19,20,21] We believe this work provides a

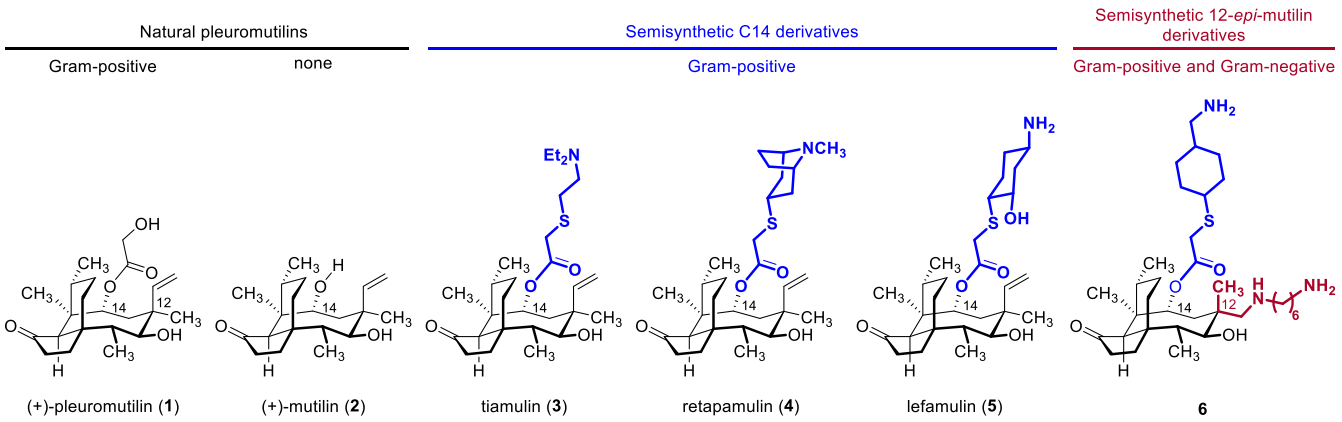


Figure 1. Structures of natural (+)-pleuromutilin (**1**) and the deacylated derivative (+)-mutilin (**2**), structures of the semisynthetic C14 derivatives tiamulin (**3**), retapamulin (**4**), and lefamulin (**5**), and the structure of a representative 12-*epi*-mutilin derivative **6**. Natural (+)-pleuromutilin (**1**) and the semisynthetic C14 derivatives **3**–**5** are active primarily against Gram-positive pathogens. 12-*Epi*-mutilin derivatives possess extended spectrum activity against Gram-negative and drug-resistant pathogens.

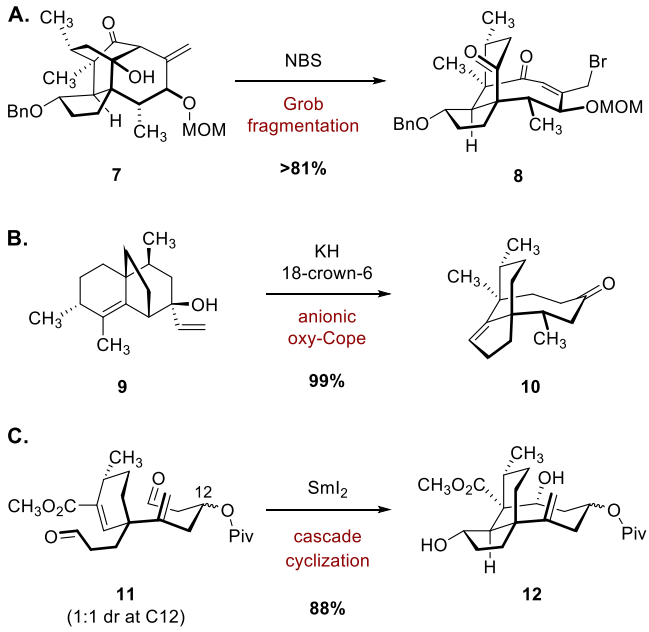
foundation to leverage the wealth of existing target binding and structure–activity data toward the production of improved fully synthetic analogs. Successes in the development of fully synthetic routes to other clinical classes of antibiotics, such as β-lactams,[22] vancomycins,[23] tetracyclines,[24] and macrolides,[25] underscore the potential for antibiotic development through chemical synthesis.[26]

Results

Three syntheses of pleuromutilin (**1**) have been reported, and the key transformations used to construct the eight-membered ring in each are summarized in Scheme 1. Gibbons, working in the laboratory of the late R. B. Woodward, introduced this ring by a bromonium ion-induced Grob fragmentation (**7**→**8**, Scheme 1A, step 13 of 31 linear steps).[27] This transformation was discovered while attempting to form an epoxide from **7** via a bromohydrin intermediate. Boeckman and co-workers employed an anionic oxy-Cope rearrangement to construct the eight-membered ring (**9**→**10**, Scheme 1B, step 7 of 27 linear steps).[28] Finally, Procter and co-workers utilized a samarium diiodide-mediated cyclization cascade to construct the five- and eight-membered rings simultaneously (**11**→**12**, Scheme 1C, step 9 of 34 linear steps).[29] This last work constitutes the first enantioselective route to (+)-pleuromutilin (**1**). These syntheses are timeless achievements in their own right that feature important strategic and methodological advances, and have been reviewed.[10] Several synthetic studies toward (+)-pleuromutilin (**1**) have also been reported.[30]

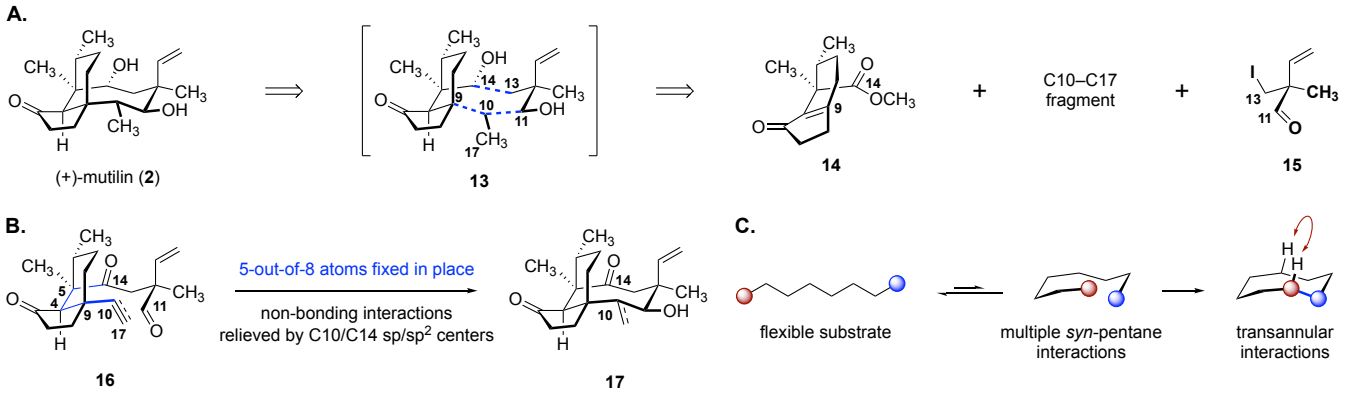
Our strategy-based design was informed by the challenges encountered by Gibbons, Boeckman, and Procter in the steps of their syntheses following formation of the 8-membered carbocycle. Each synthesis constructs the core relatively early (steps 7, 9, or 13) and follows with 18–25 further transformations. We sought to limit the number of reactions after formation of the 8-membered ring to achieve a more step-economic[31] and convergent synthesis. Working within these constraints, we aimed to close the 8-membered ring towards the end of our synthesis using only the innate functionality of the pleuromutilins and with all quaternary centers and functional groups in place. This goal forced us to target powerful transformations for the construction of carbon–carbon bonds in sterically-congested settings.

Scheme 1. Key steps in the Gibbons (A),[27] Boeckman (B),[28] and Procter (C)[29] syntheses of pleuromutilin (1).



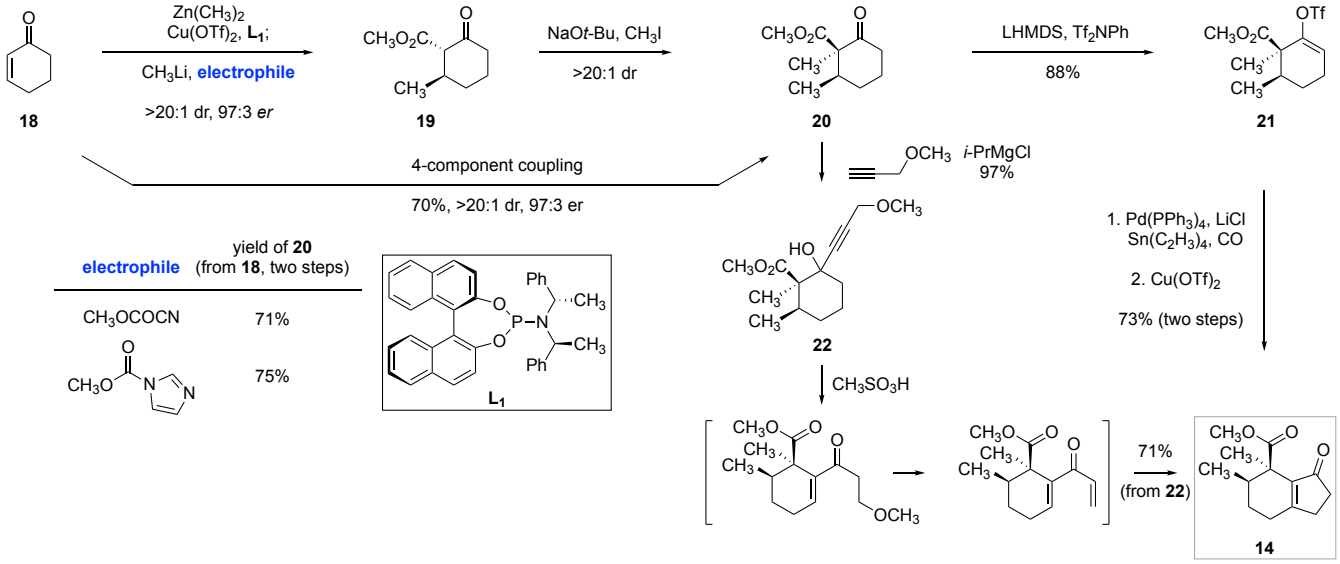
Scheme 2A depicts the key elements of our retrosynthetic analysis. As with all routes to pleuromutilin, the glycolic acid residue was installed in the final steps of the synthesis.[29] The eight-membered ring was deconstructed via the hypothetical bond disconnections (shown in structure **13**) to the hydrindanone **14**, a two-carbon (C10–C17) fragment, and the bridging synthon **15**. In the forward sense, construction of the C9–C10 and C13–C14 bonds would afford the aldehyde **16** (Scheme 2B). We envisioned many possible modes of C10–C11 bond formation from **16** including a Nozaki–Hiyama–Kishi[32] cyclization through a C10–C17 vinyl triflate or a reductive cyclization of an enal[33] or ynal[34] via a C10–C17 alkene or alkyne, respectively. The design of this cyclization strategy was informed by well-known physical organic properties of medium-sized rings (Scheme 2C).[35] When using flexible, fully saturated cyclization precursors, entropic and enthalpic penalties arising from substrate reorganization and *syn*-pentane

Scheme 2. A. The outlines of our strategy to access (+)-mutilin (2). B. The cyclization substrate 16 targeted. C. Destabilizing *syn*-pentane and transannular interactions arising from a more flexible and saturated cyclization precursor.



Key design criteria and challenges: maximize convergency, minimize post-macrocyclization reactions, utilize innate functionality, develop neopentylic bond constructions

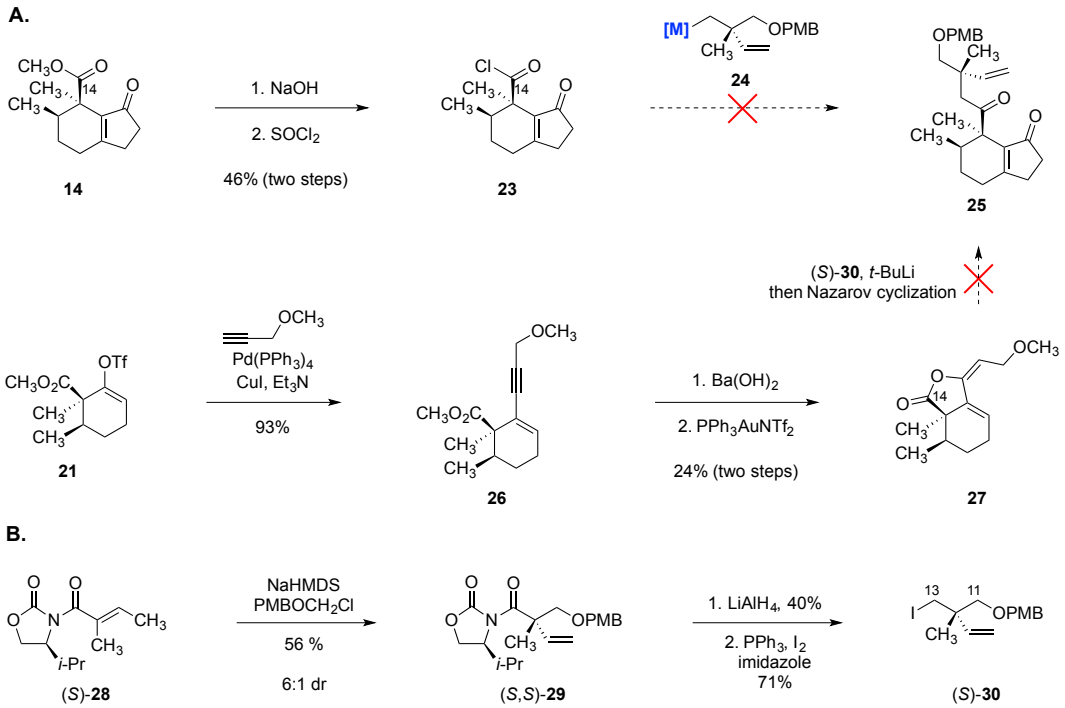
Scheme 3. Stereoselective synthesis of the hydrindanone 14.



interactions, respectively, result in a high kinetic barrier to ring formation. For example, C–O bond forming ring closures to make 8-membered cyclic ethers are ~10^5 times slower than for 5-membered cyclic ethers.[36] Repulsive non-bonded interactions in the cyclization transition state manifest transannular interactions in the eight-membered ring product. By comparison, the cyclization strategy we designed breaks the 8-membered ring into two shorter fragments (C10–C17 and C11–C14) thereby more effectively exploiting the preorganization afforded by the rigid *cis*-hydrindanone. This strategy locks 5-out-of-8 atoms (C4, C5, C9, C10, C14) in the developing ring in place. Furthermore, utilizing sp- or sp^2-hybridized carbons at C10 and C14 alleviates transannular interactions in the cyclization product **17**. Overall, we anticipated that the 8-membered ring formation (C10–C11 bond construction) and the fragment coupling (C13–C14 bond construction) steps, both of which are two-fold neopentylic couplings, would be the most challenging transformations of this synthesis.

Initially, we prepared the hydrindanone **14** from cyclohex-2-en-1-one (**18**) by a five-step sequence (Scheme 3). The route began with a stereoselective conjugate addition–acylation reaction[19] that comprises copper-catalyzed enantioselective 1,4-addition of dimethyzinc to cyclohex-2-en-1-one (**18**), *in situ* activation of the resulting alkyl zinc enolate with methyllithium,[37] and *C*-acylation with methyl cyanoformate (Mander's reagent).[38] Diastereoselective methylation of the resulting β-ketoester **19** provided the α-methyl-β-ketoester **20** in 71% overall yield, >20:1 dr, and 97:3 er. Due to the high cost and safety concerns associated with the use of Mander's reagent, we sought a safe and inexpensive alternative. Methyl 1*H*-imidazole-1-carboxylate[39] was identified as a superior reagent that afforded the product **20** in comparable yield (75% overall, two steps). Ultimately, the conjugate addition–acylation and alkylation steps were carried out in one flask to access the α-methyl-β-ketoester **20** in one step (70%).[21] Deprotonation of the α-methyl-β-ketoester **20** and trapping of the resulting enolate with *N*-phenyltriflimide afforded the vinyl triflate **21** (88%). The triflate **21** was subjected to a carbonylative Stille coupling[40] with tetravinyl tin; the resulting dienone (not shown) underwent selective Nazarov cyclization on treatment with copper triflate[41] to provide the hydrindanone **14** in 73%

Scheme 4. A. Attempted synthesis of the diketone 25 via the acid chloride 23 or the lactone 27. B. Synthesis of the alkyl iodide (*S*)-30.



yield from **21** (five steps, 48% overall yield from **18**). Although the Nazarov cyclization was in some instances efficient, tin-based impurities carried over from the Stille coupling led to variable yields of **14**. To address this and to avoid using toxic alkenylstannane reagents, an alternative cyclopentannulation was developed.[21] 1,2-Addition of the magnesium acetylide derived from methyl propargyl ether[30b,42] provided the alcohol **22** in 97% yield and 10:1 dr (stereoselectivity of addition not determined). Treatment with methanesulfonic acid induced a Rupe rearrangement–Nazarov cyclization cascade[30b,42] to generate the hydrindanone **14** directly in 71% yield (from **22**; three steps, 48% overall yield from **18**).

We then focused on developing conditions to functionalize the C14 carbonyl group (Scheme 4). Saponification of the ester (sodium hydroxide) followed by treatment of the resulting carboxylic acid with thionyl chloride afforded the acid chloride **23** in 46% yield (two steps, Scheme 4A). The acid chloride **23** was surprisingly resistant to hydrolysis and could be purified by flash-column chromatography. This stability may be due to the pseudoaxial disposition of the C14 carbonyl and the presence of an α-quaternary center. These factors, and the observation that the enone function of **23** was readily enolizable, presaged the difficulties we would encounter in the fragment coupling.

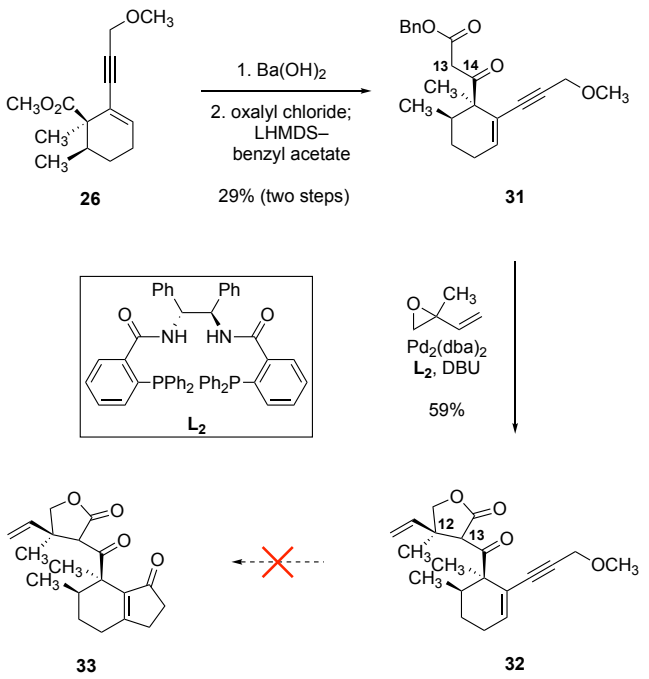
The alkyl iodide fragment (*S*)-**30** contains the C11–C13 atoms of the target and was prepared in three steps from the chiral tigloyl derivative (*S*)-**28** (Scheme 4B). Site- and stereoselective *α*-alkylation of the imide (*S*)-**28** with *para*-methoxybenzyl chloromethyl ether afforded the imide (*S*,*S*)-**29** in 56% yield (6:1 *dr*).[43] Reduction of the imide and deoxyiodination generated the alkyl iodide (*S*)-**30** in 28% yield (two steps).

We envisioned accessing the diketone **25** by coupling the alkyl iodide (*S*)-**30** with the acid chloride **23**. However, despite extensive efforts including cross-coupling with an organozinc reagent **24** ([M] = ZnI)[44] derived from (*S*)-**30** or cross-electrophile coupling with (*S*)-**30** directly,[45] the addition product **25** was never detected. Strongly basic or nucleophilic reagents appeared to enolize or add to the enone, while attempts to activate the acid chloride using many transition metals resulted in rapid decarbonylation, presumably due to the stability of the resulting allylic metal intermediate.

We then targeted the enelactone **27** as a fragment coupling partner (Scheme 4A). This species possesses a fused bicyclic skeleton which was expected to facilitate C14-addition by releasing ring strain on opening, and the cyclopentanone functionality is masked as an acyl enol ether, thereby removing any complications arising from deprotonation or 1,2-addition. The enelactone **27** was obtained in three steps and 22% yield from the vinyl triflate **21**. Sonogashira coupling of **21** with methyl propargyl ether[46] afforded the enyne **26** (93%). Saponification of the methyl ester (barium hydroxide) followed by gold-catalyzed 5-*exo*-dig cyclization[47] generated the enelactone **27** (24%, two steps). Unfortunately, addition of the alkyllithium reagent derived from (*S*)-**30** (formed by lithium–halogen exchange) did not proceed, and unreacted **27** was recovered. The addition of methyllithium to **27** successfully opened the lactone to afford the desired dienone (not shown), suggesting the combined steric hindrance of the two neopentyl reagents **27** and **30** as the likely cause of failure.

We also pursued an entirely distinct fragment coupling that relied on a Claisen condensation to install the C14 ketone early in the route and a Tsuji–Trost reaction[48] to forge the C12–C13 bond (Scheme 5). Claisen condensation of benzylacetate with the acid chloride derived from the enyne **26** (not shown) provided the β-ketoester **31** in 29% yield (two steps), thereby providing the key C13–C14 bond. Palladium-catalyzed allylic alkylation of the β-ketoester **31** using *rac*-2-methyl-2-vinyloxirane afforded the lactone **32** (59%).[48] Unfortunately, we were not able to obtain the hydrindanone **33** from the

Scheme 5. Attempted synthesis of the hydrindanone 33.



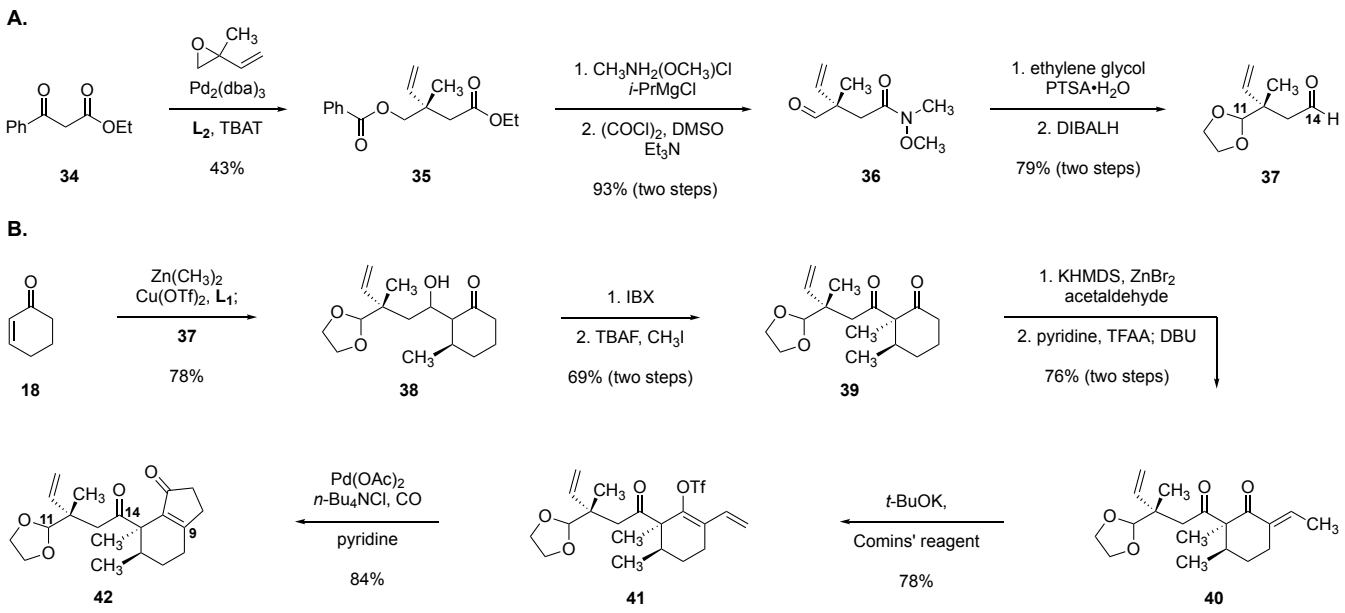
enyne **32**. Extensive attempts to hydrate the alkyne within **32** (by inter- or intramolecular addition) were unsuccessful.

Given these difficulties, we temporarily set aside our goal of a convergent synthesis and focused on appending the C11–C14 fragment at the outset. Strategically, this allowed us to advance material to the cyclization reaction and elucidate key aspects of that transformation that would be necessary in the final route. To enable this, we prepared the aldehyde **37**, which contains the C11–C14 atoms of the target (Scheme 6A). Allylic alkylation of ethyl benzoylacetate (**34**), followed by *in situ* benzoyl migration,[48] generated the diester **35** (43%, 99:1 er). Cleavage of both esters was effected by treatment with excess *N,O*-dimethylhydroxylamine hydrogen chloride and *iso*-propylmagnesium chloride.[49] Swern oxidation of the resulting primary alcohol (not shown) generated the amido aldehyde **36** (93%, two steps). Protection of the aldehyde function and reduction of the Weinreb amide (di-*iso*-butylaluminum hydride, DIBALH) provided **37** (79%, two steps).

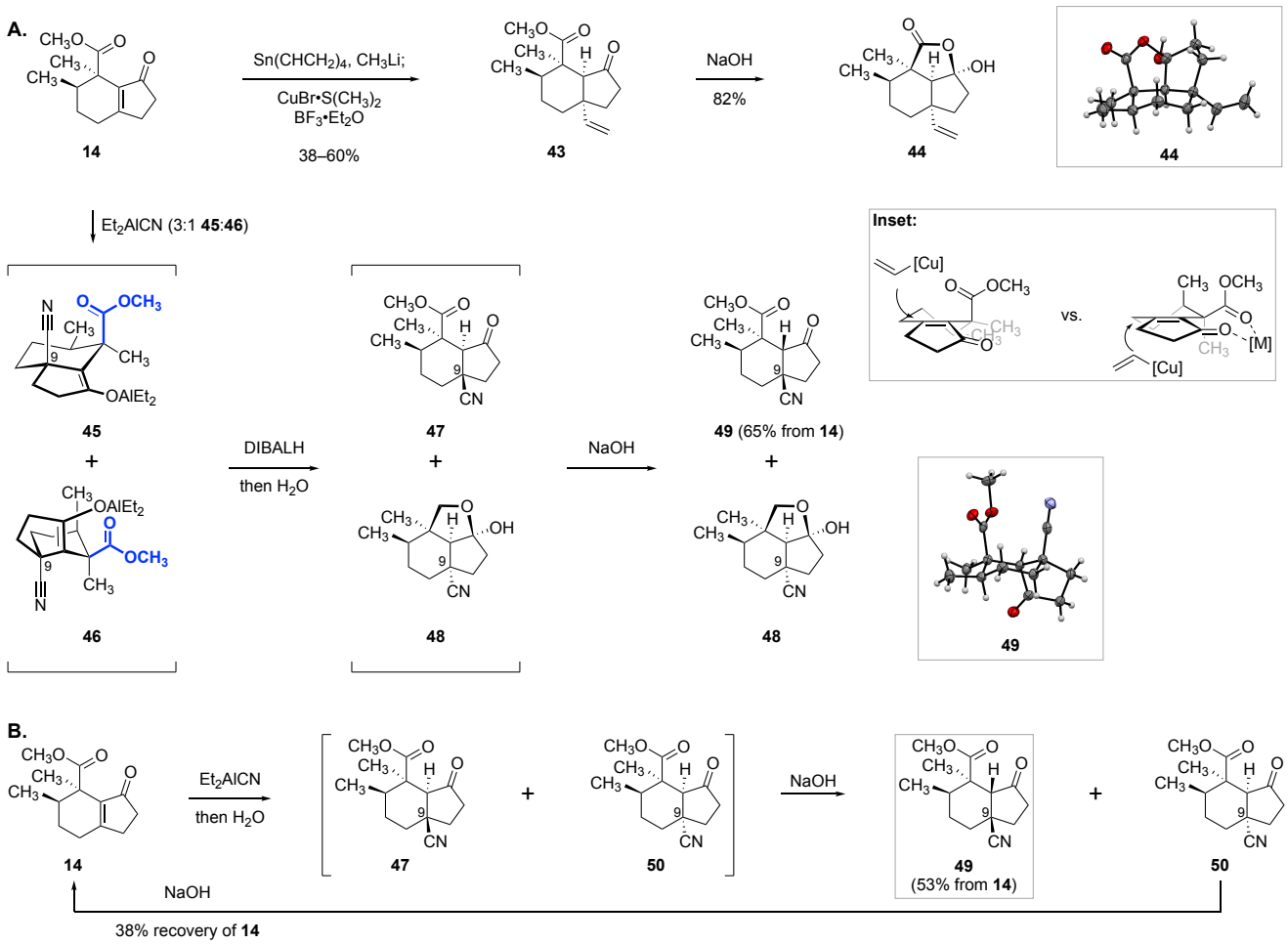
Copper-catalyzed stereoselective 1,4-addition of dimethylzinc to cyclohex-2-en-1-one (**18**), followed by addition of the aldehyde **37**, afforded the β-hydroxyketone **38** in 78% yield and as a mixture of diastereomers (Scheme 6B).[50] The β-hydroxyketone **38** was oxidized with 2-iodoxybenzoic acid (IBX) and the resulting β-diketone (not shown) was treated with iodomethane and tetra-*n*-butylammonium fluoride (TBAF), to provide the α-methyl-β-diketone **39** (69%, two steps, >20:1 dr). Advancement of this material via the usual route involving Nazarov cyclization was not possible due to the acid-sensitivity of the acetal group. Instead, we implemented a strategy involving site-selective deprotonation of the α-methyl-β-diketone **39** (potassium hexamethyldisilazide, KHMDS) and treatment of the resulting enolate with acetaldehyde to afford a *β*-hydroxyketone (not shown). Activation of the hydroxyl group with trifluoroacetic anhydride (TFAA) and elimination of the resulting trifluoroacetate ester (1,8-diazabicyclo[5.4.0]undec-7-ene, DBU)[51] provided the enone **40** (76%, two steps). Extended enolate formation and trapping with *N*-(5-chloro-2-pyridyl)triflimide (Comins' reagent)[52] afforded the dienyl triflate **41** in 78% yield. The dienyl triflate **41** was transformed to the hydrindanone **42** in 84% yield by a palladium-catalyzed carbonylative cyclization.[53]

Our attention then turned toward functionalization of the C9 position to install C10–C17 fragment required for eight-membered ring construction. The hydrindanone **14** (Scheme 3) was employed as a model substrate since it was more accessible than **42**. In line with Paquette's attempted intramolecular additions to the C9 position,[30b] 1,4-addition to the tetrasubstituted enone functionality within **14** proved challenging (Scheme 7).

Scheme 6. A. Synthesis of the C11–C14 aldehyde 37. B. Synthesis of the hydrindanone 42.



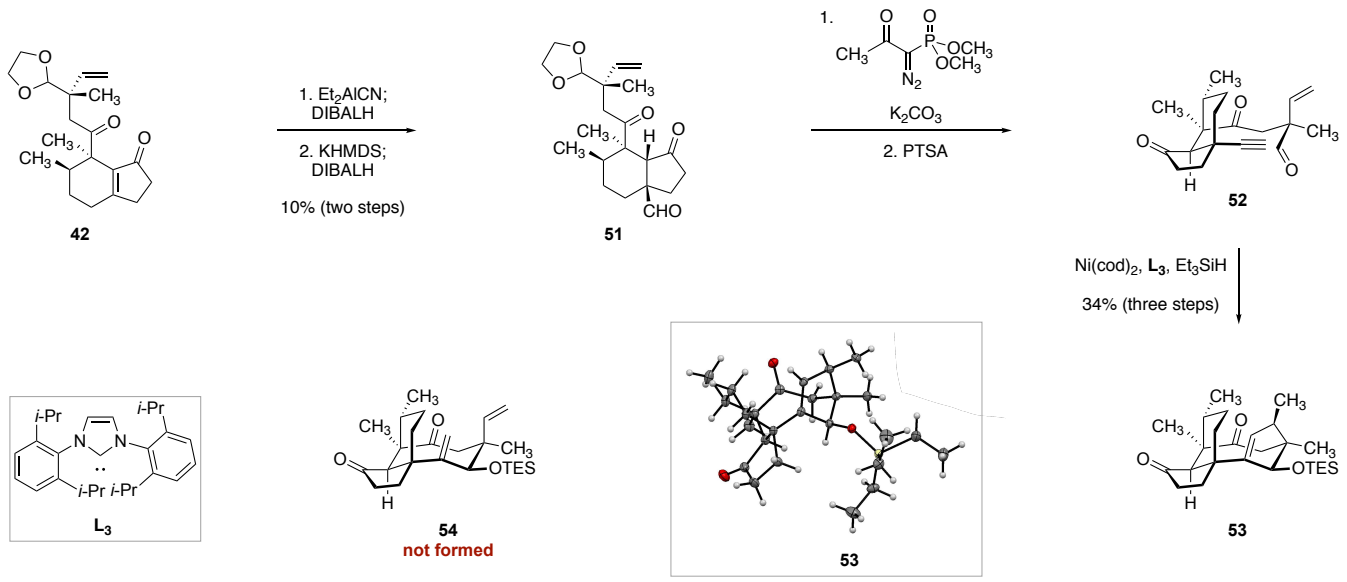
Scheme 7. A. 1,4-Addition of lithium divinylcuprate and hydrogen cyanide to the hydrindanone 14. B. Improved procedure for the 1,4-hydrocyanation of 14 involving recycling of the undesired diastereomer 50.



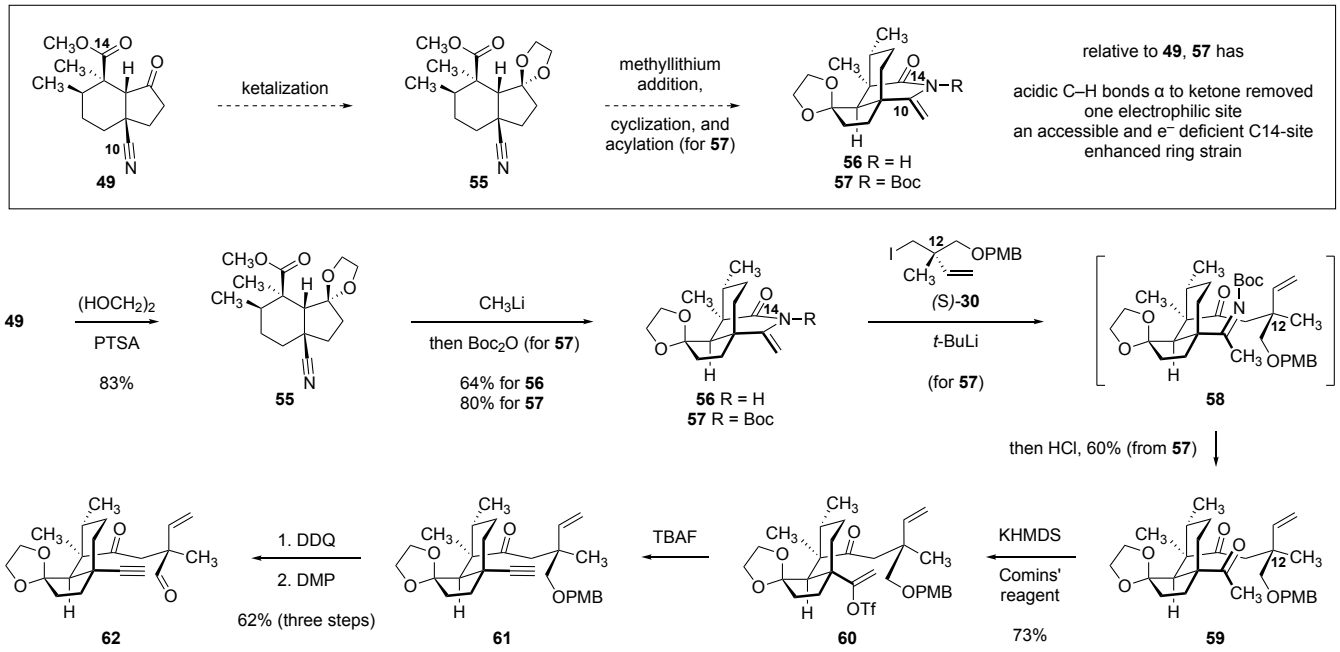
Attempted addition of acetylide-[54]or alkenyl-based[55] nucleophiles generally resulted in recovery of unreacted **14** or the production of 1,2-addition products. Boron trifluoride–diethyl etherate-promoted addition of lithium divinylcuprate[56] was successful and provided the addition product **43** in variable yields (38–60%) as a single detectable diastereomer (Scheme 7A). Unfortunately, X-ray crystallographic analysis of the hemiketal **44**, obtained by saponification of **43**, revealed that the addition proceeded with the undesired facial selectivity. Based on NOE analysis, we believe the ester substituent occupies the pseudoaxial orientation. Therefore, we expected nitrile addition *syn* to the ester substituent, which would correspond to pseudoaxial attack, in accord with the Fürst–Plattner rule. We hypothesize that metal chelation by the 1,4-ketoester may drive the ester into the pseudoequatorial position (as shown in the inset), thereby making addition *anti* to the ester substituent now the pseudoaxial, and more favorable, mode of approach.

Fortunately, we found that 1,4-hydrocyanation[57] of **14** proceeded with 3:1 selectivity in favor of the desired C9 diastereomer. Careful analysis of the product mixture revealed that the desired C9-addition product underwent kinetic protonation to the *trans* diastereomer **47**, and that this slowly converted to the desired *cis* isomer **49** upon concentration and purification. By comparison, the C9 adduct arising from addition to the *Si*-face was formed exclusively as the *cis*-diastereomer and was configurationally-stable (see **50**, Scheme 7B). Unfortunately, separation of the three diastereomers **47**, **49**, and **50** was difficult on preparative scales. Accordingly, we investigated methods to resolve them *in situ*. We found that the undesired C9 addition intermediate **46** could be selectively reduced (at the ester function) by introduction of DIBALH directly. The desired addition intermediate **45** was unreactive, presumably due to the reduced accessibility of the axial ester substituent. The reduction of **46** proceeded to the alcohol oxidation state; upon neutralization this species cyclized to the hemiketal **48**, which facilitated its separation from **47**. After additional experimentation, we found that **47** could be quantitatively epimerized to **49** by treatment with dilute sodium hydroxide (65% yield of **49** from **14**). The relative stereochemistry of **49** was confirmed by X- ray analysis (see inset, Scheme 7A). Alternatively, subjecting the mixture of *trans*-hydrindanone **47** and the undesired addition product **50** to epimerization using aqueous sodium hydroxide provided the *cis*-diastereomers **49** and **50**, which could be separated by flash-column chromatography (Scheme 7B). Although the yield of the desired product **49** is somewhat lower in this approach (53%) the undesired isomer could be

Scheme 8. Synthesis of the cyclopentene 53 from the enone 42.



Scheme 9. Synthesis of the alkynylaldehyde 62 from the hydrocyanation product 49.

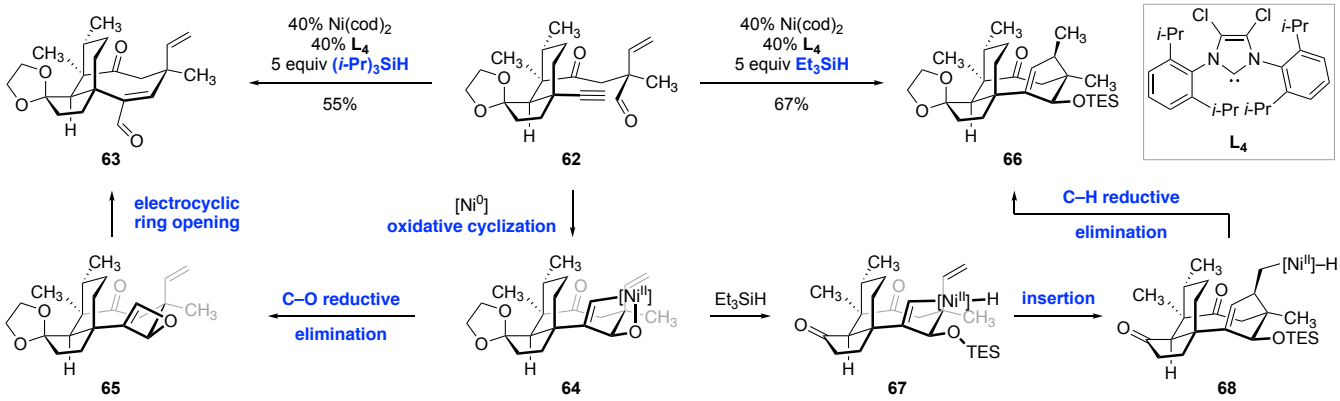


efficiently recycled by elimination of hydrogen cyanide using concentrated sodium hydroxide to regenerate **14** (38% recovery based on **14**), ultimately allowing higher material throughput (85% yield of **49** based on recovered **14**).

1,4-Hydrocyanation of the fully-elaborated hydrindanone **42** and reduction (DIBALH) of the resulting nitrile (with *in situ* protection of the ketone as its corresponding enolate)[58] provided the aldehyde **51** in 10% yield over two steps (Scheme 8). Homologation with the Ohira–Bestmann reagent[59] followed by aldehyde deprotection generated the cyclization precursor **52**. With the alkynyl aldehyde **52** in hand, conditions to effect the *exo*-selective reductive cyclization were examined.[34,60] In the presence of bis(1,5-cyclooctadiene)nickel ($Ni(cod)_2$), 1,3-bis(2,6-di-*iso*-propylphenyl)-1,3-dihydro-*2H*-imidazol-2-ylidene (**L_3**), and triethylsilane, conditions slightly modified from those developed by Montgomery and co-workers to promote the *exo*-selective reductive cyclization of ynals,[60] a single product was obtained from the aldehyde **52** (34% over three steps). Although limitations in sample size impeded full characterization of this product at this time, the expected ^{1}H NMR resonances for the vinyl group in the desired product **54** were conspicuously absent. Subsequently, the structure of this product was identified as the tetracycle **53** by comparison to a related cyclization product (see **66**, Scheme 10) and, ultimately, single crystal X-ray analysis (see inset).

The poor yields and linear nature of our route to the ynal **52** motivated us to explore other pathways to cyclization precursors. Recognizing that access to nitrile **49** provided new avenues for fragment coupling, we applied lessons learned from our prior studies to transform **49** into a viable coupling

Scheme 10. Divergent cyclization pathways of the alkynyl aldehyde 62.



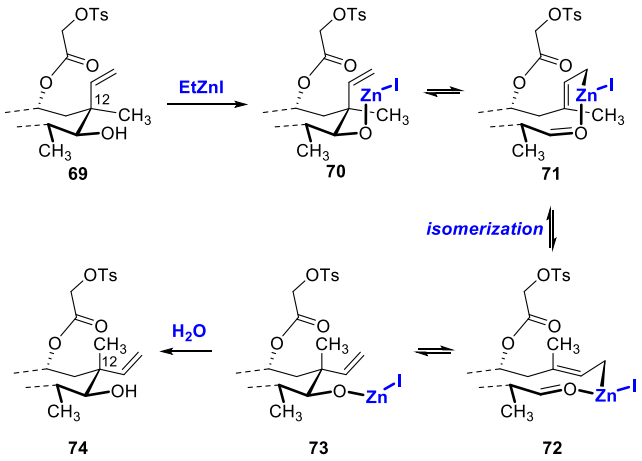
partner (see top, Scheme 9). First, we planned to address the acidity of the ketone function of **49** by protection as a ketal (**55**). Second, we needed strategies to enhance the electrophilicity of the C14 carbonyl group while mitigating the additional steric hindrance imparted by the axial nitrile group. Conversion to an eneamide **56** or eneimide **57** was an attractive strategy as it was expected to alleviate C10–C14 diaxial interactions and make C14 more accessible to nucleophiles. Use of this strategy also introduced ring strain and electronic activation of C14 for fragment coupling. These modifications were envisioned to work together to make the key bis(neopentylic) fragment coupling more favorable. In addition, we anticipated production of a methyl ketone function following eneamine (amide) hydrolysis after ring opening. This would help us to realize our strategy (Scheme 2B, C) to break the 8-membered ring into two short fragments (C10–C17 and C11–C14) and effectively exploit the preorganization afforded by the rigid *cis*-hydrindanone.

In practice, protection of the ketone [ethylene glycol, *p*-toluenesulfonic acid (PTSA)] proceeded smoothly to afford the ketal **55** (81%, Scheme 9). Treatment of **55** with methyllithium provided the eneamide **56** (64%), resulting from 1,2-addition to the nitrile and *in situ* cyclization. In order to protect the acidic amide functionality and enhance the electrophilicity of C14, we synthesized the eneimide **57** by introducing di-*tert*-butyldicarbonate (Boc_2O) directly to the reaction mixture following the cyclization step (80% yield). Generation of the organolithium reagent derived from (*S*)-**30** (*tert*-butyllithium) followed by introduction of the eneimide **57** resulted in 1,2-addition to provide an intermediate acylimine (**58**) that was hydrolyzed (hydrochloric acid) to the methyl ketone **59** (60%). This key fragment coupling served to forge one of the bis(neopentylic) carbon–carbon bonds in the target. The methyl ketone **59** was dehydrated to the alkyne **61** via the vinyl triflate **60**. Removal of the *p*-methoxybenzyl ether (2,3-dichloro-5,6-dicyano-1,4-benzoquinone, DDQ) followed by oxidation (Dess–Martin periodinane, DMP)[61] generated the alkynyl aldehyde **62** (45%, four steps).

With an efficient route to the alkynyl aldehyde **62**, we were positioned to fully investigate the key Ni-catalyzed reductive cyclization step. Using tri-*iso*-propylsilane as a reductant and 4,5-dichloro-1,3-bis(2,6-di-*iso*-propylphenyl)-1,3-dihydro-*2H*-imidazol-2-ylidene (**L_4**) as the ligand, as recommended by Montgomery and co-workers,[60b] the enal **63** was obtained unexpectedly (55%, Scheme 10). We speculate that **63** is formed by oxidative cyclization to the metallacyclopentene **64**, C–O bond reductive elimination (**64**→**65**), and electrocyclic ring opening (**65**→**63**). Although **63** was not the desired product, this result demonstrated the feasibility of the oxidative cyclization step, and suggested that tri-*iso*-propylsilane was too bulky to engage the metalacycle **64**. Consistent with this, when triethylsilane was used as reductant, the pentacycle **66** was obtained in 67% yield. This compound was prepared in sufficient quantities for complete characterization, and provided a basis for elucidating the structure of **53** (Scheme 8). A logical mechanism for the generation of **66** involves σ-bond metathesis of triethylsilane and the metallacyclopentene **64** to generate **67**, 1,2-insertion of the α-olefin into the nickel–carbon bond to generate **68**, and carbon–hydrogen bond reductive elimination.

As discussed above, Berner had reported[15] that the C12 position of pleuromutilin could be epimerized by a retroallylation–allylation reaction on heating with ethylzinc iodide (Scheme 11). The mechanism of this transformation is believed to comprise formation of the zinc alkoxide **70**, retroallylation to generate the allylzinc species **71**, isomerization to **72**, allylation to **73**, and protonolysis. An approximately equimolar mixture of **69** and the 12-*epi*-derivative **74** was obtained, suggesting they are nearly equal in energy. With this in mind, we recognized that the undesired alkene insertion (responsible for the formation of **66**) could be avoided by placing the alkene in the pseudoequatorial position; following ring closure, the C12 position could be epimerized by the reverse of the pathway shown in Scheme 11. From the standpoint of

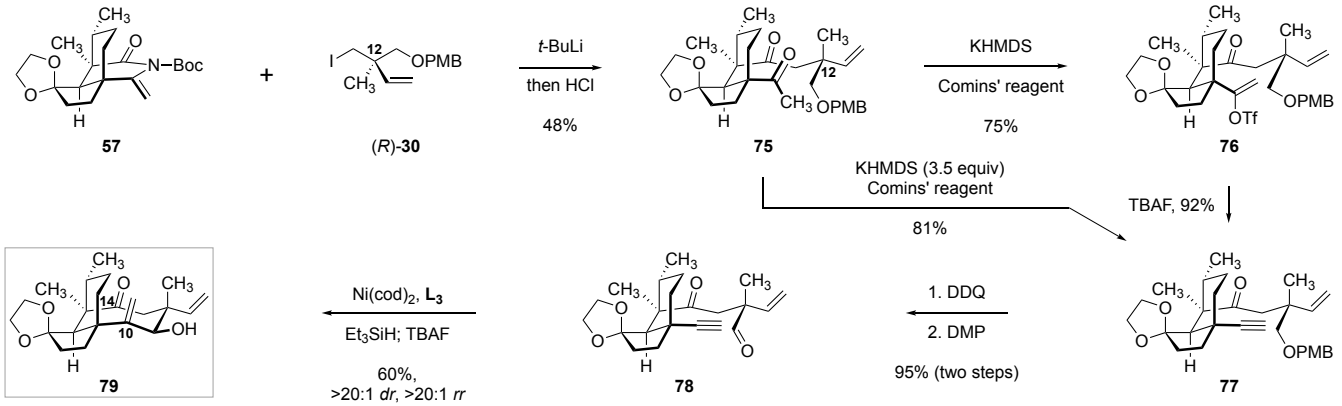
Scheme 11. C12 epimerization of pleuromutilin 22-*O*-tosylate (69) reported by Berner.[15]



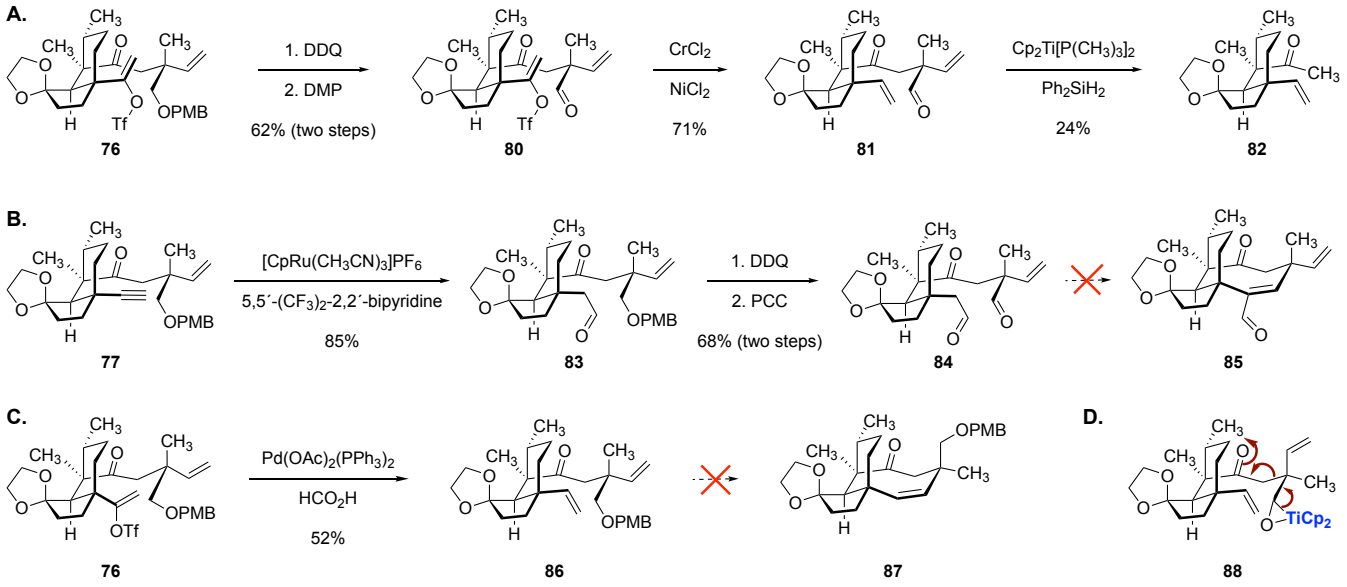
antibiotic development, this approach could be more useful. As discussed in the introduction, 12-*epi*-mutilin derivatives bearing polar functionality in the pseudoequatorial C12 position (such as **6**, Figure 1) possess extended spectrum activity, including activity against drug-resistant and Gram-negative pathogens. Synthesis of pleuromutilins with a pseudoequatorial alkene substituent (as in 12-*epi*-mutilins) would allow for direct functionalization at this position and could capitalize on these known improvements in activity.

Our approach to the alkyl iodide (*S*)-**30** relied on the stereoselective alkylation of the Evans imide (*S*)-**28** (Scheme 4B). Because both enantiomers of the Evans auxiliary are commercially-available, this approach to the C11–C13 fragment allowed us to easily obtain the alternate enantiomer (*R*)-**30** by an identical pathway (see Supporting Information). The eneimide **57** successfully underwent ring opening upon addition of the alkyllithium derived from (*R*)-**30** to provide the diketone **75** in 48% yield after hydrolysis of the acylimine intermediate (Scheme 12). The methyl ketone **75** was converted to the alkyne **77** by conversion to the vinyl triflate **76**, followed by elimination with TBAF[62] (69%, two steps), or more conveniently in one step by vinyl triflate formation in the presence of excess base (81%). Removal of the *p*-methoxylbenzyl ether with DDQ afforded a primary alcohol (not shown) that was oxidized to the aldehyde **78** (95%, two steps). When the ynal **78** was subjected to the nickel-catalyzed reductive cyclization using $\mathbf{L_3}$ (the chlorinated ligand $\mathbf{L_4}$ was not essential to the success of this transformation),[34,60] participation of the α-olefin was not observed, and the allylic alcohol **79** was obtained in 60% yield after removal of the silyl ether. As discussed in the introduction and shown in Schemes 2B and 2C, preorganization by the *cis*-hydrindanone skeleton, as well as the presence of sp^2 centers at C10 and C14 in the product **79** (which alleviate transannular interactions) may facilitate this transformation. Substrate organization by formation of a nickel η^2-carbonyl-η^2-alkyne complex may be another contributing factor.

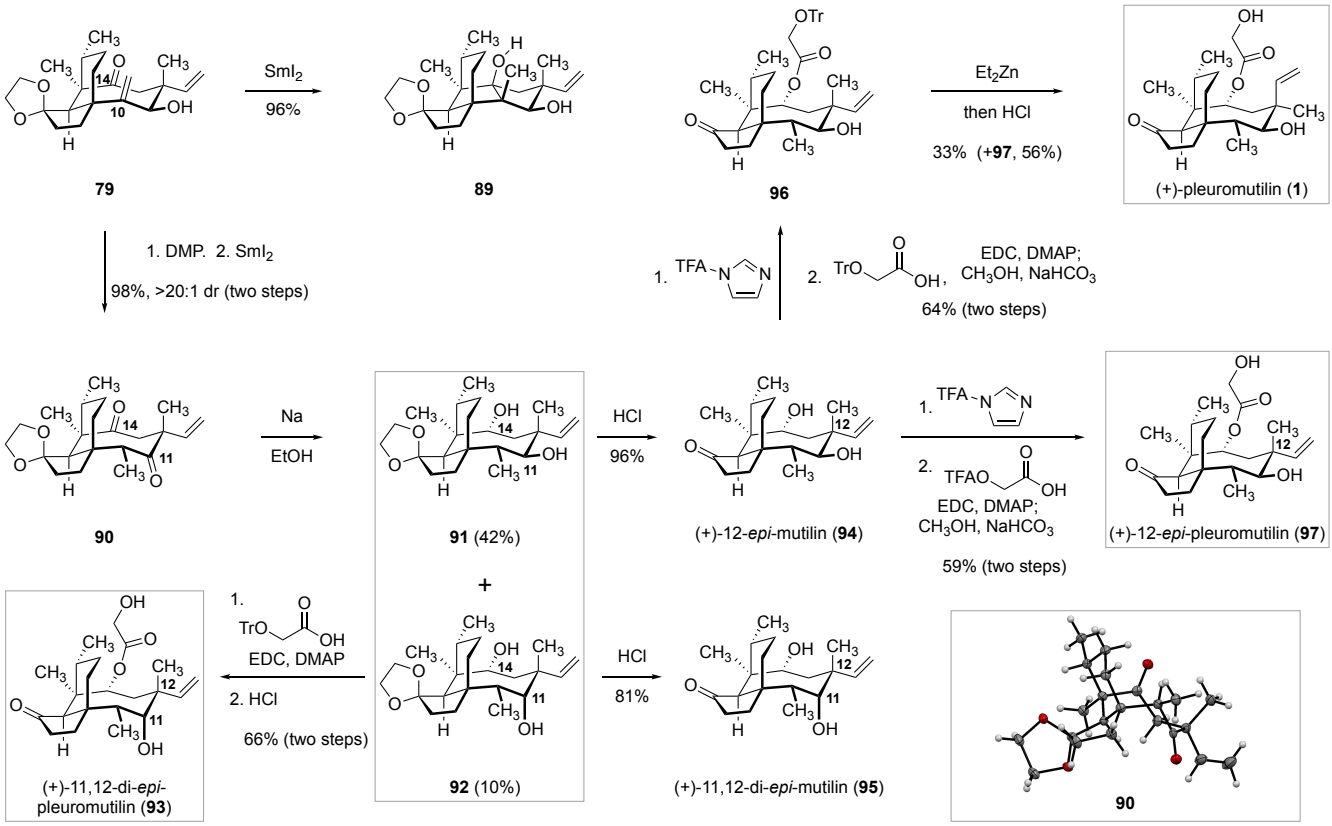
Scheme 12. Synthesis of the tetracycle 79.



Scheme 13. A. Attempted Nozaki–Hiyama–Kishi cyclization of the vinyl triflate 80 and attempted reductive cyclization of the alkenyl aldehyde 81. B. Attempted aldol–dehydration ring closure of the dialdehyde 84. C. Attempted ring-closing metathesis of the diene 86. D. Proposed mechanism for the reductive cleavage of 81.



Scheme 14. Synthesis of (+)-pleuromutilin (1), (+)-12-*epi*-pleuromutilin (97), and (+)-11,12-di-*epi*-pleuromutilin (93).



We also investigated other ring closure strategies. The vinyl triflate **80**, obtained from **76** in two steps (*p*-methoxybenzylether cleavage and oxidation of the resulting alcohol, 62%, Scheme 13A), could conceivably undergo a Nozaki–Hiyama–Kishi[32] cyclization, but under a variety of conditions only the reduction product **81** was obtained. The alkene **81** could undergo a titanium(II)-mediated reductive cyclization;[33] however, only the methyl ketone **82** was obtained (24%) when **81** was treated with bis(cyclopentadienyl)-bis(trimethylphosphine)titanium(II). We speculate that **82** is formed by reductive cleavage of the 1,4-dicarbonyl functional group to afford the corresponding enolates (see **88**, Scheme 13D). Alternatively, radical cleavage (to generate the α-keto radical corresponding to **82**), followed by reduction to a titanium enolate, may be the operative pathway. In a separate strategy, anti-Markovnikov hydration[63] of the terminal alkyne **77** provided the aldehyde **83** (85%, Scheme 13B). The dialdehyde **84** was obtained after *p*-methoxybenzylether cleavage and oxidation of the resulting alcohol (68%, two steps). Unfortunately, the dialdehyde **84** did not undergo aldol condensation[64] to **85**. The terminal alkene **86**, obtained in 52% yield by reduction of the vinyl triflate **76**,[65] was subjected to ring-closing metathesis using the Grubbs second-generation catalyst,[66] but did not provide the desired product **87** (Scheme 13C).

To complete the synthesis, the C14 and C10 positions of the cyclization product **79** needed to be reduced with stereocontrol (Scheme 14). Given the boat–chair conformation of the substrate, hydridic reagents were expected to approach from the exterior of the 8-membered ring, which would provide the undesired pseudoaxial stereochemical outcome. Accordingly, we focused on single-electron reductions that may proceed by pseudoaxial hydrogen atom abstraction to deliver the desired C10 and C14 pseudoequatorial diastereomers. Attempted samarium diiodide-mediated reduction of the C14 carbonyl of **79** provided the pentacycle **89** (96%), presumably by 5-*exo*-trig cyclization of a C14 ketyl radical. To prevent this, we investigated reduction of the C10 alkene first in the presence of the C12 olefin. Attempts to effect a net redox-neutral one-step isomerizationof the C10–C11 allylic alcohol were unsuccessful. Accordingly, the allylic alcohol within **79** was oxidized to an enone (not shown) that was treated with samarium diiodide[67] to afford the diketone **90** with the expected pseudoequatorial stereochemistry at C10. The relative stereochemistry of **90** was confirmed by X-ray analysis (see inset). The diketone **90** was reduced with sodium in ethanol[27] to provide the diol **91** (42%) and the C11 diastereomer **92** (10%). Each product could be separately deprotected (hydrochloric acid) to access 12-*epi*-mutilin (**94**, 96%) or 11,12-di-*epi*-mutilin (**95**, 81%). (+)-11,12-Di-*epi*-pleuromutilin (**93**) was obtained by site-selective acylation of 11,12-di-*epi*-mutilin (**95**), followed by deprotection (66%, two steps). To access (+)-pleuromutilin (**1**), 12-*epi*-mutilin (**94**) was treated with trifluoroacetylimidazole[29] and the resulting C11 ester (not shown) was coupled with *O*-tritylglycolic acid to afford **96** (64%, two steps). Epimerization of the C12 position, followed by acidification, provided (+)-pleuromutilin (**1**, 33%). Finally, (+)-12-*epi*-pleuromutilin (**97**) was obtained by stepwise acylation of the C11 and C14 alcohols with trifluoroacetylimidazole and *O*-trifluoroacetylglycolic acid, respectively, followed by methanolysis of the trifluoroacetyl esters (59%, two steps).

Conclusion

We have described the development of modular and efficient enantioselective synthetic routes to (+)-pleuromutilin (**1**), (+)-12-*epi*-pleuromutilin (**97**), (+)-11,12-di-*epi*-pleuromutilin (**93**), 12-*epi*-mutilin (**94**) and 11,12-di-*epi*-mutilin (**95**). Obstacles we faced during the study were overcome with several notable breakthroughs. Nagata hydrocyanation of the tetrasubstituted hydrindanone **14** established a handle for installation of a variety of C10–C17 fragments to develop a method for construction of the ehtig-membered ring. The identification of the eneimide **57** was essential to realize the key fragment coupling involving two neopentylic reagents. Finally, nickel-catalyzed reductive cyclization provided the desired eight-membered ring, and unusual reaction pathways, such as rearrangement to the enal **63** and double cyclization to the cyclopentenes **53** and **66**, were discovered.

The work herein provides a blueprint for the preparation of novel pleuromutilins by total synthesis. In order to maximally capitalize on this work, methods to shorten the annulation strategy, incorporate heteroatoms into the eight-membered, and modulate the structure of the hydrindanone residue are being pursued. These studies will be guided by the well-characterized interaction of pleuromutilins with the bacterial ribosome[7] and are envisioned to allow access to positions of the molecule that have previously been inaccessible by semisynthetic or fully synthetic approaches.

ASSOCIATED CONTENT

Supporting Information

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

Detailed experimental procedures and NMR spectroscopic data for all new compounds are included in the Supporting Information (PDF).

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The manuscript was written through contributions of all authors. All authors have given approval to the final version of the manuscript.

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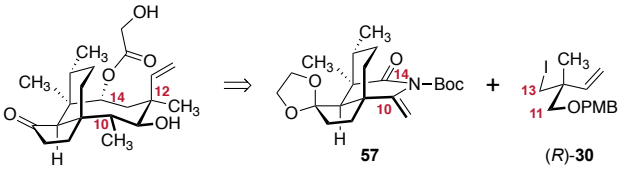

(+)-pleuromutilin (**1**) **57** (*R*)-**30**

(late-stage C12-stereoinversion)