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Enantioselective Total Synthesis of (−)-Acylfulvene and (−)-Irofulven

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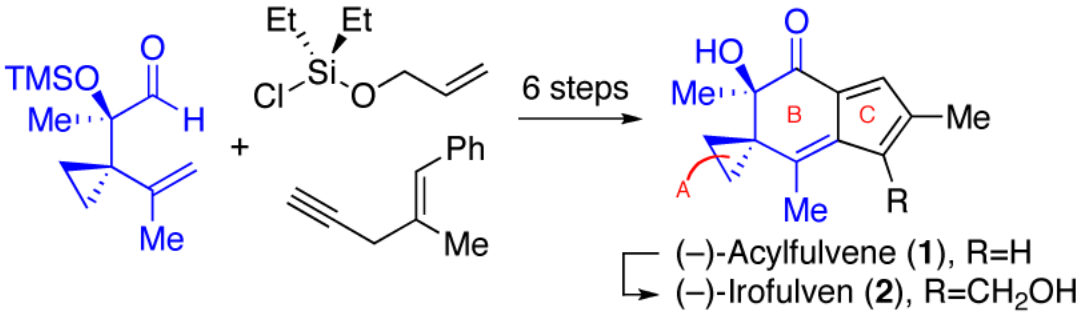
Abstract



We report our full account of the enantioselective total synthesis of (−)-acylfulvene (**1**) and (−)-irofulven (**2**), which features metathesis reactions for the rapid assembly of the molecular framework of these antitumor agents. We discuss (1) the application of an Evans' Cu-catalyzed aldol addition reaction using a strained cyclopropyl ketenethioacetal, (2) an efficient enyne ring-closing metathesis (EYRCM) cascade reaction in a challenging setting, (3) the reagent IPNBSH for a late stage reductive allylic transposition reaction, and (4) the final RCM/dehydrogenation sequence for the formation of (−)-acylfulvene (**1**) and (−)-irofulven (**2**).

Introduction

The illudins are a family of highly cytotoxic sesquiterpenes isolated from the bioluminescent mushroom *Omphalotus illudens* (Jack O'Lantern mushroom) and other related fungi.[1] Illudin M (**3**) and illudin S (**4**) (Figure 1) are among the most cytotoxic members of this family, and have been studied extensively for their promising antitumor activity.[2] Despite their high cytotoxicity, these illudins exhibit low therapeutic indices in solid-tumor systems.[3] Consequently, several analogs of the natural illudins have been prepared and evaluated for the treatment of various cancers.[4] One such semi-synthetic derivative, irofulven (**2**), was prepared from illudin S through treatment with excess acid and formaldehyde, and has demonstrated greatly enhanced therapeutic potential against several solid tumor systems.[5] The superior pharmacological properties of irofulven (**2**) are accompanied by a markedly lower cytotoxicity than that of illudin S (**4**).[6] Several studies have been directed toward elucidating the mechanism of biological activity of the illudins, acylfulvene (**1**), and irofulven (**2**) in order to understand the nature of this selective toxicity.[7] The mechanism is believed to involve an initial activation

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Supporting Information Available: Experimental procedures and spectroscopic data for new products. This material is available free of charge via the Internet at http://pubs.acs.org.

step by conjugate addition of a hydride (NADPH) or thiol (glutathione, or cysteine) nucleophile into the enone moiety followed by nucleophilic addition of DNA to the strained cyclopropane ring to generate a stable aromatic DNA adduct **18** (Scheme 1). The observed onset of apoptosis is believed to be a result of DNA alkylation followed by strand cleavage through this general mechanism. Irofulven (**2**) is currently undergoing clinical trials for the treatment of various cancers as both a monotherapy and in combination with other chemotherapeutics.[8]

The promising antitumor properties and the highly reactive molecular framework of (−)-irofulven (**2**) and other illudins have rendered them interesting synthetic targets.[9] Our laboratory has disclosed concise enantioselective syntheses of (−)-acylfulvene (**1**) and (−)-irofulven (**2**).[10] Key features of our approach include a stereoselective aldol addition of a strained ketenehemithioacetal **26**, which secures the C2 stereocenter and enables ready access to aldehyde (+)-**22** (Scheme 2). A key enyne ring-closing metathesis (EYRCM)[11] cascade reaction of trienyne **21** generates the AB-ring system **20**. A reductive allylic transposition then sets the stage for the final ring-closing olefin metathesis (RCM) to build the C-ring and complete the syntheses of (−)-acylfulvene (**1**) and (−)-irofulven (**2**). Herein we describe the development of our general synthetic strategy to these fascinating molecules.

Results and Discussion

Synthesis of the key aldehyde 22

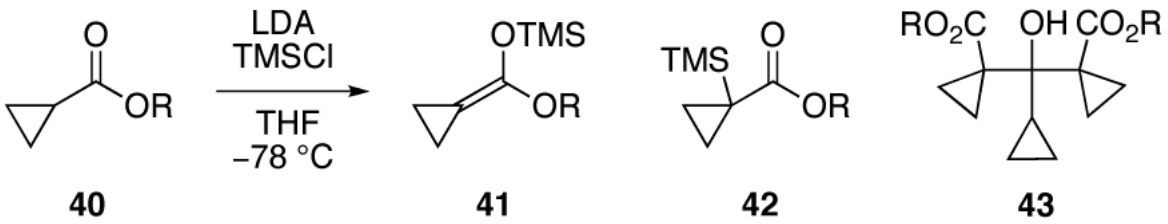
Since aldehyde **22** contains the reactive cyclopropane and tertiary alcohol substructure common to acylfulvene (**1**), irofulven (**2**), and most members of the illudin family, its efficient synthesis was of critical importance. Initially, we developed a synthetic route that enabled us to rapidly generate large quantities of the racemic aldehyde **22** for evaluation of our synthetic strategy (Scheme 3).[12] This route involved treatment of pentane-2,4-dione (**27**) with 1,2-dibromoethane and potassium carbonate in dimethylsulfoxide (DMSO) to afford cyclopropyl diketone **28** in 61% yield (Scheme 3). Mono olefination using the Wittig reaction afforded intermediate **29** in 56% yield. Silylcyanation with stoichiometric TMSCN in the presence of catalytic $InBr_3$ then afforded cyanohydrin **30** in 81% yield, and DIBAL-H reduction afforded the racemic aldehyde **22** in multi-gram quantities.

The enantioselective total synthesis of the target compounds required an enantioselective synthesis of aldehyde **22**. Initially, we considered an asymmetric silylcyanation strategy to generate the tertiary alcohol stereocenter (Scheme 4), based on the route to the racemic aldehyde **22**. Examination of Jacobsen's thiourea catalyst **31**[13] provided the desired optically enriched cyanohydrin **30**; however, the conversion and level of stereoselection with ketone **29** was non-ideal (50 h, 13%, 53% ee). Furthermore, the selectivity was detrimentally affected by the long reaction times that were required for full conversion of the starting material (8 d, 71%, 34% ee). The use of ketone **29** as substrate with Hoveyda's catalyst **32**[14] in the presence of $Al(O^iPr)_3$ and Ph_3PO afforded the desired compound in good yields (79%), but unfortunately without enantioselection. Likewise, the use of Deng's silylcyanation reaction[15] conditions employing a cinchona alkaloid based catalyst ($(DHQD)_2AQN$) also proved problematic, highlighting the challenge in developing a solution strictly based on the proven route to racemic **30**.[16]

We investigated several asymmetric oxidation reactions as a means of accessing the tertiary alcohol stereocenter including a Sharpless dihydroxylation, a Sharpless epoxidation, and a substrate directed epoxidation relying on a stereocenter set by a Carreira alkynylation reaction (Scheme 5). Double olefination of diketone **28** afforded the volatile diene **33**, which was subjected to Sharpless' dihydroxylation conditions.[17] While the desired diol **34** was generated in 50% yield, the diene 33 proved to be a poor substrate for enantioselective dihydroxylation. We proceeded to explore the Sharpless asymmetric epoxidation[18] reaction with alcohol **35**,

which was prepared from ketone **29** through a Shapiro reaction with dimethylformamide (DMF) followed by a Luche reduction. Unfortunately, the Sharpless epoxidation of diene **35** provided a complex mixture of products likely resulting from the oxidation of the undesired olefin. Also, alternative synthesis of racemic **36** highlighted its undesired propensity to undergo a Lewis acid catalyzed rearrangement to aldehyde **37**. An approach based on asymmetric alkynylation of aldehyde **37** followed by substrate directed epoxidation also did not provide the desired C2-stereocenter.[19] While Carreira's alkynylation reaction provided the desired product **38** with excellent stereoselectivity (99% ee) using superstoichiometric $Zn(OTf)_2$ and *N*-methylephedrine (NME), the subsequent epoxidation of the allylic alcohol **38** using *meta*-chloroperbenzoic acid (*m*CPBA) resulted in the formation of a complex mixture of products. Since oxidation reactions[20] aimed at forming the stereocenter adjacent to the cyclopropane proved to be problematic, we pursued an alternative route.

We sought to use Evans' copper catalyzed aldol reaction for the formation of the desired tertiary alcohol stereocenter,[21] in which we needed to generate a highly strained cyclopropyl silylketenehemithioacetal nucleophile **26** (Scheme 2). Initial studies by Ainsworth and coworkers aimed at generating the *O*-silylated cyclopropyl keteneacetal **41**, revealed that formation of this strained exocyclic double bond was problematic. They reported that the product **41** was generated in at most 10% yield (R = Me, Equation 1).[22] Instead, the *C*-silylated product **42** was formed as the major product (40%, R = Me, Equation 1). Following this report, Pinnick and coworkers observed the formation of the trimer **43** in addition to the *C*- and *O*-silylated products **41** and **42** (R = Et, Equation 1).[23] These cyclopropyl ester enolate anions are generally regarded as pyramidalized carbanion centers rather than the *O*-lithiated planar methylene cyclopropane species.[24]



40 **41** **42** **43**

(1)

Our studies revealed that enolization of 1-cyclopropylethanone (**44**) at the cyclopropyl carbon is problematic if competing enolization pathways are accessible. Both hard and soft enolization conditions afforded the undesired silyl enol ether **45** exclusively (Scheme 6).[25]

Interestingly, Seebach and coworkers were able to generate a lithium cyclopropanecarbothioate anion from the corresponding thiol ester and characterize it through X-Ray crystallographic analysis.[26] This structure exhibited features characteristic of a normal planar *O*-lithiated enolate, as opposed to a pyramidal *C*-lithiated center. Guided by this observation, we reasoned that the enolate of cyclopropylthiol esters might prefer the formation of the *O*-silylated ketenehemithioacetal rather than the *C*-silylated product. To our delight, the *O*-silylated ketenehemithioacetals **26a** and **26b** were generated as the major products through treatment of the cyclopropylthiol esters **46a** and **46b** with lithium diisopropylamide (LDA) and trimethylsilyl chloride (TMSCl) in THF at −78 °C (Scheme 7). This reaction afforded an inseparable mixture of the *O*- and *C*-silylated products **26** and **47**. The highest selectivity was achieved with the ethylthiol ester **26b** to generate a 9:1 mixture of **26b** and **47b** in 70% yield; whereas, the *tert*-butylthiol ester **46a** led to a 3:2 mixture of **26b** and **47b** in 67% yield. Fortunately, the undesired *C*-silylated products **47a** and **47b** did not interfere with the planned aldol reaction. The mixture of compounds **26b**/**47b** (9:1) could be generated on multi-gram

scale and could be stored under an argon atmosphere at −10 °C for greater than a month without any decomposition or *O*- to *C*-silyl transfer. To the best of our knowledge, this is the first example of the formation of a cyclopropyl silylketenehemithioacetal that can be applied in a Mukaiyama aldol reaction.[27]

Due to the strain associated with the exocyclic double bond, the cyclopropyl ketenehemithioacetals **26a** and **26b** are highly reactive and are excellent substrates for Evans' copper catalyzed aldol reaction[21] (Table 1). Under optimal conditions, treatment of silylketenehemithioacetal **26b** (1.1 equiv, mixture of **26b**:**47b** = 9:1) with methylpyruvate (**25**) in the presence of 10 mol% of (*R,R*)-CuBox provided the enantiomerically enriched thiol ester (+)-**48b** (R^2 = TMS) in 95% yield and 92% ee (entry 10, Table 1).[28] This reaction was performed on large scale to generate a 20-gram batch of the desired product (+)-**48b**, and the (*R,R*)-Box ligand was recovered in approximately 85 % yield from the reaction mixture. As a part of these studies, we also evaluated the (*R,R*)-CuPybox catalyst, but it proved to be inferior to the CuBox system for this transformation (entries 2 and 3, Table 1). While the *t*-butylketenehemithioacetal substrate, **26a**, was competent for this transformation under the optimized conditions (entry 6, Table 1), attempts to derivatize the resulting *t*-butylthiol ester **48a** proved to be ineffective *(vide infra*, Scheme 8).

With the bisesters **48a** and (+)-**48b** in hand, we proceeded to derivatize the thiol ester selectively. Initially, we investigated methylcuprate addition into the C4 thiolester.[29] Attempts to functionalize the *tert*-butylthiol ester **48a** proved to be inefficient (Scheme 8). Surprisingly, using a large excess of methylcuprate (10 equiv), methyl addition occurred exclusively at the C1 methyl ester to afford the lactone **49** in 45% yield. In contrast, addition of 1 equivalent methylcuprate to the more reactive ethylthiol ester (+)-**48b** afforded the desired product (+)-**50** in 25% yield. However, this reaction was complicated by significant decomposition of the sensitive cyclopropylketone (+)-**50** under the reaction conditions.

We found that the ethanethiol ester (+)-**48b** could be selectively derivatized through a modified Fukuyama cross-coupling protocol.30 Using the reported reaction conditions,[30a] we obtained the desired product (+)-**50** in 42% yield (entry 1, Table 2). Under these conditions, the reaction suffered from incomplete conversion of the starting material (27% recovered (+)-**48b**) and the instability of the catalyst, which was evident from the precipitation of palladium black over the course of the reaction. We developed the optimal conditions for the substrates of interest by evaluating various ligands, reaction temperatures, and solvents (Table 2). Using the optimal conditions, multi-gram quantities of the methyl ketone (+)-**50** were efficiently prepared in 83% yield via the cross-coupling of thiol ester (+)-**48b** with iodomethylzinc using 2-dicyclohexylphosphino-2′,6′-dimethoxy-1,1′-biphenyl (SPhos)[30b] as a supporting ligand in a 1:1.5 THF:NMP30c solvent mixture (entry 7, Table 2). SPhos proved to be the ideal ligand for this difficult transformation providing improved stability for the palladium metal center and increased reaction rates.

Methylenation of the sensitive and sterically hindered ketone (+)-**50** was achieved through a Takai olefination (Scheme 9).[31] Treatment of ketone (+)-**50** with CH_2I_2, Zn dust, $TiCl_4$, and catalytic $PbCl_2$ afforded olefin (+)-**51** in 89% yield.[32] The ester (+)-**51** was then treated with DIBAL-H to afford a mixture of the desired aldehyde (+)-**22** and the corresponding fully reduced primary alcohol (1:2.5 respectively). Without purification, this mixture was immediately oxidized with Dess-Martin periodinane (DMP) to give aldehyde (+)-**22** exclusively in 91% yield over the two steps.

The configuration of C2 in aldehyde (+)-**22** was verified through X-ray crystallographic analysis of a corresponding derivative with (−)-brucine (Scheme 10).10,[33] This efficient aldol-based approach for securing the C2 stereochemistry enabled us to generate multi-gram

quantities of the key aldehyde (+)-**22**. Notably, aldehyde (+)-**22** possesses a substructure that can be mapped on to most of the illudin sesquiterpenes.

Preparation of the substrates for evaluation in the EYRCM cascade

With the routes to the racemic and optically enriched aldehyde **22** established, we developed a two-step sequence to generate several substrates for the evaluation of the EYRCM reaction.[12] Addition of a series of alkynes **53a–m** to aldehyde **22** followed by desilylation provided the diols **54a–m** as a mixture of C3 diastereomers (3*S*:3*R*, 4–9:1) favoring the Felkin-Ahn mode of carbonyl addition (Scheme 11).[34] We then added the allylsilane tether[12] for the planned enyne metathesis cascade. Thus, monosilylation of diols **54a–j** with allyldimethylsilyl chloride afforded the enynes **55a–j** (Scheme 11).

Evaluation of the EYRCM cascade

The EYRCM sequence described in Scheme 12 represented our planned approach toward the synthesis of the functional AB-ring system common to the illudins. The enyne metathesis between the tethered olefin and the alkyne of **56** could generate a ruthenium alkylidene **58**, that would undergo a ring-closing olefin metathesis to afford a tetrasubstituted alkene on a highly substituted B-ring **59**.[35] We envisioned that elaboration of the functionalized side chain of **59** would potentially allow rapid access to various members of the illudin family.

The initial studies of the key EYRCM step were carried out on the enynes **55a–d** containing a functional side chain potentially en route to our targets. These trienynes **55a–d** were treated with the first- or second-generation Grubbs' ruthenium catalyst (**G1**36 and **G2**[37] respectively), and the reactions were monitored by ^{1}H NMR spectroscopy (Scheme 13).[12] However, none of the trienynes **55a–d** afforded the desired EYRCM products **60a–d**. The lack of reactivity of these substrates indicated that the efficiency of the EYRCM is highly sensitive to steric congestion around the alkyne. A similar lack of reactivity was observed with the trienyne **55n**,[38] which suggested that unhindered terminal olefins competitively reacted with and reduced the activity of the metathesis catalyst toward the desired EYRCM cascade.

Accordingly, we selected trienyne **55f** bearing a side chain with a less reactive trisubstituted olefin, and monitored the EYRCM reaction of this substrate using ^{1}H NMR (Scheme 14). We were delighted to find that treatment of trienyne **55f** with **G2** for 1 h at 65 °C generated the desired cyclic silane **60f** with good conversion (90%, ^{1}H NMR). Interestingly, when the **G1** catalyst was used, the enyne **55f** was converted to the cyclopentenyl product, **61**. Extensive 2D-NMR analysis and X-ray crystallographic analysis of a related product[39] allowed for the assignment of the structure of the cyclopentene **61**.[40]

A plausible mechanism for the formation of the two metathesis products **60f** and **61** is described in Scheme 15. In the presence of the **G2** catalyst, the initial metathesis occurs at the terminal olefin **62** to give, after the EYRCM, the desired cyclic silane **60f**. Conversely, it is plausible that the less reactive **G1** allows reversible formation of ruthenium alkylidene **64**, which undergoes a more facile enyne metathesis reaction to produce cyclopentene **61**.[41]

The encouraging result obtained with enyne **55f** using **G2** prompted us to evaluate the efficiency of the key metathesis reaction on other substrates. Thus, enynes **55f–p** were subjected to **G2** (10 mol%) in PhH at 65 °C for 1 h to afford the desired tricyclic dienes **60f–p** in modest to good yields (Scheme 16).[10] *In situ* ^{1}H NMR monitoring of these reactions revealed clean conversion in all cases. Thus, the moderate yields are attributed to the sensitivity of these silanes towards silica gel chromatography. Notably, the enyne metathesis conditions proved to tolerate sensitive functional groups such as the aldehyde of **55o**[42] and the primary iodide of **55p**.[43]

Relay ring-closing metathesis strategy for the C-ring formation

Encouraged by these results, we focused our efforts on building the C-ring of the illudins. Our initial strategy was inspired by the work of Hoye and coworkers on the relay ring-closing metathesis reaction (Scheme 17).[44] Initial metathesis of the allyl group of a tetraene **68**, obtained from the cyclic silyl ether **59**, would generate the ruthenium alkylidene **69**. This would set the stage for an intramolecular olefin metathesis providing compound **70** with the ruthenium at the site required for the final cyclization to generate **71**.[45]

Thus, we prepared the substrates **73** and **74** for the relay ring-closing metathesis (Scheme 18). Wittig olefination of **60o** afforded **60n** in a low 30% yield, complicated due to the sensitivity of the allylic silane. The triol, **72**, was then prepared in 30% yield through a Tamao oxidation.[46] The allyl silane tether was then selectively appended to the terminal allylic alcohol to afford **73** in 47% yield. Alternatively, the cyclic ether **60n** could be treated with allylmagnesium bromide to afford the allylsilane **74** directly in 45% yield. Unfortunately, when we evaluated the relay RCM with the tetraenes **73** and **74** using **G1** or **G2** catalysts, we only observed dimerization or decomposition of the substrates.[47] These findings prompted us to consider a different approach for assembling the C-ring of the target illudins that would involve a more reactive olefin.

First generation synthesis of (−)-acylfulvene (1) via a reductive allylic transposition strategy

Accordingly, we revised our synthesis to incorporate a reductive allylic transposition reaction (Scheme 19). Through this strategy, alcohol **76** could be elaborated to the terminal olefin **77**, which could then be converted to tricycle **78** via a RCM reaction. Oxidative dehydrogenation would then provide the fulvene **79**.

Due to the difficulty of forming the triol **76** from the allylsilane through oxidative methods (**60n**→**72**, Scheme 18), we investigated alternative olefin tethers for the EYRCM cascade.[12] In the midst of these studies, we made a tactical change to use allyloxydialkylsilyl tethers in the EYRCM (Scheme 20). These tethers obviated the problematic oxidation step and allowed direct access to the stable triol product from the EYRCM reaction via *in situ* removal of the tether. During the preliminary screening of several tethers using a model substrate,[12] allyloxydiethylsilyl tether **80** demonstrated an optimal combination of stability and reactivity. Selective monosilylation of diol **54k–m** with allyloxydiethylsilyl chloride **80**[48] gave the enyne metathesis substrates **81k–m** in good yields (83–95%).

Our first generation synthesis of the tricyclic system began with the OPMB substrate **81m** and featured a Stille cross coupling reaction to append the appropriate isopropenyl side chain for the final RCM step (Scheme 21). EYRCM of the *p*-methoxybenzyl ether substrate **81m** followed by *in situ* TBAF cleavage of the oxysilane tether furnished the desired cyclohexenyl product **82m** directly in 64% yield.[12] In contrast to the allyldimethylsilyl tether (Scheme 16), the allyloxysilane tethered substrate **81m** required a higher temperature (110 °C) to achieve complete conversion in the EYRCM reaction. Selective TBS protection of the triol **82m** at the primary allylic alcohol followed by protection of the diol as a carbonate with triphosgene afforded compound **83**. Removal of the PMB group by the action of 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) followed by bromination of the pendant alcohol then afforded intermediate **84**, poised for a Stille cross-coupling. Isopropenyltributylstannane was coupled to the allylic bromide to generate substrate **85** in 35% yield to set up the olefinic side chain for the final RCM reaction. Desilylation of ether **85** gave the allylic alcohol **86**, which was primed for a reductive allylic transposition reaction.

Exposure of allylic alcohol **86** to 2-nitrobenezenesulfonyl hydrazide (NBSH)[49] under Mitsunobu conditions furnished the terminal olefin **87** (30%, 6*S*:6*R*, 3:1)[34] via Myers'

reductive allylic transposition chemistry (Scheme 22). Gratifyingly, the planned RCM reaction employing **G2** in benzene at 65 °C generated the C-ring to afford cyclopentene **88** in 45% yield (6*S*:6*R*, 3:1). Dehydrogenation with DDQ furnished the fulvene **89** in 93% yield, and hydrolytic cleavage of the carbonate afforded the diol **90** in 99% yield. *o*-Iodoxybenzoic acid (IBX) oxidation[9g] then provided acylfulvene (**1**) in 83% yield.[50] In the course of these studies, we found a more efficient route that would circumvent derivatization of the side chain (Scheme 20). Thus, we used the optimal acetylides **53k** and **53l** (Scheme 11) that could be directly applied in the C-ring RCM step for the synthesis of acylfulvene (**1**).

Optimization of the EYRCM

We first evaluated the tandem EYRCM-desilylation sequence with the phenethyl derivative **81k** (Table 3). As with intermediate **81m** (Scheme 21), the EYRCM of **81k** required high temperature (110 °C) and high catalyst loading of **G2** (30 mol%) to achieve complete conversion. We reasoned that at this high temperature, the lifetime of the catalyst might be reduced. Using the optimal concentration (0.01M) and catalyst loading of **G2** (30 mol%), the desired triol **82k** was isolated in 52% yield, after removal of the silyl moiety with TBAF (entry 4, Table 3). Decreasing the concentration and raising the catalyst loading did not improve the yield of the final triol **82k** (entries 5 and 6). Moreover, the use of milder desilylation condition or use of ruthenium scavengers[51] during isolation afforded similar yields of the triol **82k**. We speculated that at high temperature, partial loss of the allyloxydiethylsilyl tether, promoted by the vicinal hydroxyl group, was responsible for the low efficiency of the reaction.

In order to increase the stability of the enyne metathesis substrate and improve the yield of desired triol, the C2 tertiary hydroxyl group was converted to the corresponding trimethylsilyl ether. The reactivity of the silyl ether substrates **91k** and **91l** were significantly enhanced under the EYRCM conditions and required only 15 mol% catalyst loading of **G2** at 90 °C (Scheme 23).[10] After *in situ* desilylation of the EYRCM product, a mixture of the desired triol **82k** and byproduct **92** were isolated in 52% and 20% yield, respectively. Conversely, the styrenyl derivative **91l**[10] containing a C7–C8 trisubstitued styrenyl alkene underwent the EYRCM cascade and desilylation reaction smoothly to afford the desired triol **82l** exclusively in 79% yield (Scheme 23). The undesired product **92** was not observed for substrate **91l**, which is consistent with the lower reactivity of styrenyl olefins under the EYRCM conditions.

The formation of the unexpected triol **92** was investigated in detail. *In situ* ^{1}H NMR studies revealed that some trienyne **91k** diverges from the desired EYRCM pathway (**91k**→**82k**, Scheme 24) to undergo a competing olefin metathesis with the C7–C8 alkene affording a ten-membered ring intermediate **95** (Scheme 24). Subsequent enyne metathesis and olefin isomerization[52] of cyclic alkyne **95** produced the tricyclic disiloxane **96**. *In situ* nOe analysis of intermediate **96** confirmed the *E* geometry for the C7–C8 olefin, which was opposite to the triol derived from desilylation of alkyne **95**. Interestingly, lower reaction temperatures (80 °C) led to an increase in the yield of the olefin metathesis product **95**, which is attributed to the higher energy barrier generally required for an EYRCM as compared to a RCM. The sensitive cyclic alkyne **95** was isolated and resubmitted to the optimal enyne metathesis conditions at higher temperature (90 °C) to give the triol **92** after silyl cleavage.

With the key triols **82k** and **82l** in hand, we evaluated the reductive allylic transposition reaction and RCM reaction for the completion of the synthesis of (−)-acylfulvene (**1**) and (−)-irofulven (**2**). We found it necessary to mask the tertiary and secondary alcohols, and developed a tandem process to generate the carbonates **97k** and **97l** (Scheme 25). Monosilylation of the allylic alcohols **82k** and **82l** with ^{t}butyldimethylsilyl trifluoromethanesulfonate (TBSOTf, 1 equiv) selectively protected the primary alcohol. Sequential treatment with triphosgene and treatment with TBAF afforded the desired carbonates **97k** and **97l** in good overall yields in a single flask.

Optimization of the reductive allylic transposition reaction

Substrates **97k** and **97l** were subjected to Myers' reductive allylic transposition reaction to give desired trienes (Table 4).[49] Low temperature Mitsunobu displacement with NBSH generates the allylic hydrazide derivatives, which upon warming, spontaneously lose 2-nitrobenzene sulfinic acid followed by dinitrogen to afford the desired terminal olefins **99k–l**.

When treated with diethylazodicarboxylate (DEAD), triphenylphosphine (PPh_3), and NBSH at 0.02M concentration in *N*-methyl morpholine (NMM), the allylic alcohol **97k** provided the desired product **99k** (6*S*:6*R*, 3:1) along with a significant amount of unreacted starting material (entry 1, Table 4). By increasing the concentration of the reaction mixture[49a] we observed full consumption of the alcohol **97k**; however, the yield was still unsatisfactory (43%, entry 2, Table 4). Careful examination of this reaction revealed that thermal decomposition of the unreacted NBSH generated diimide in the reaction mixture, which reduced a significant amount (19%) of the product **99k** at the C7–C8 terminal olefin. Gratifyingly, addition of allylbenzene as a scavenger for the diimide and further increasing the reaction concentration afforded the desired product **99k** in 75% yield (entry 3). Unfortunately, when we tried to apply these conditions to the reductive allylic transposition of substrate **97l**, the yield of the isolated product **99l** was modest (54%, entry 4) as a result of the poor solubility of this substrate.[10] To address the lack of reactivity of alcohol **97l**, we added neopentyl alcohol to improve the efficiency of the Mitsunobu displacement.[53] Unfortunately, neopentyl alcohol further decreased the solubility of the substrate resulting in poor yield of olefin **99l** (35%, entry 5). The use of THF in place of NMM improved the homogeneity of the reaction mixture, but also increased the formation of undesired byproducts (entry 6). Furthermore, a mixture of THF and NMM as solvent did not improve the efficiency of allylic transposition (entries 7–8). Due to the insolubility of the substrate in the reaction media at low temperature and at high concentration, variable yields of the desired product were obtained.

In order to address the complications associated with substrate **97l**, we considered the use of a more stable derivative of NBSH that would allow us to carry out the challenging Mitsunobu displacement at higher temperatures and lower solvent concentrations. Thus, the acetone hydrazone derivative, *N*-isopropylidene-*N*'-2-nitrobenzenesulfonyl hydrazine (IPNBSH),[54] was prepared and used for the reductive allylic transposition of alcohol **97l** (Table 5). We were pleased to find that the Mitsunobu displacement of alcohol **97l** with IPNBSH proceeded smoothly at temperatures between 5–23 °C and at lower concentrations to give the stable hydrazone intermediate **100l**. Exposure of intermediate **100l** to hydrolytic conditions then afforded transposition product **99l**. Water alone was insufficient for the hydrolysis of the hydrazone (entry 1, Table 5); however, the addition of alcoholic co-solvent greatly enhanced the yield and rate of formation of the product **99l** (entries 2–5). Interestingly, the solvolysis of hydrazone **100l** using 2,2,2-trifluoroethanol (TFE) at 0 °C occurred with the greatest efficiency to afford the desired olefin **99l** in 71% yield (entry 5).

Completion of the synthesis of (−)-acylfulvene (1) and (−)-irofulven (2)

Preliminary studies on the final steps of the synthesis were carried out using triene **99k**. Treatment of triene **99k** with 15 mol% of **G2** at 65 °C resulted in clean conversion to the desired diene **88** (82%, 6*S*:6*R*, 7.6:1, Scheme 26), which was accessed in our first generation synthesis (Scheme 22). Isolation of the carbonate from this reaction mixture was found to be problematic. The (6*R*)-diastereomer of carbonate **88** was particularly sensitive to silica gel chromatography. Furthermore, oxidation of the minor isomer (6*R*)-**88** proved to be very slow. Therefore, we carried forward only the major diastereomer 6*S*-**88** through the remaining steps of the sequence shown in Scheme 26.

We were pleased to find that oxidation of the cyclopentene (6*S*)-**88** with DDQ afforded the desired fulvene carbonate **89** in 93% yield (Scheme 26) in a manner similar to the first generation route described above (Scheme 22). Subsequent hydrolysis of the carbonate **89** gave the diol fulvene **90** as reported by Brummond and coworkers.[9f] The synthesis of acylfulvene (**1**)[55] was then completed by oxidation of the secondary alcohol with IBX.[9g]

With the final steps of the synthesis of acylfulvene (**1**) in place, we focused on streamlining the final stages of syntheses of (−)-acylfulvene (**1**) and (−)-irofulven (**2**). These final optimizations were performed on enantiomerically enriched samples of triene **99l** prepared from the key aldehyde (+)-**22**. In order to efficiently convert both diastereomers of triene **99l** to the final diol fulvene **90** we bypassed the isolation of the sensitive carbonate **88** (Scheme 27) via an *in situ* hydrolysis of the carbonate. Thus, after the RCM of triene **99l**, the mixture was sequentially diluted with dimethylformamide (DMF) and treated with aqueous lithium hydroxide. The resulting diol **101** was quickly subjected to aqueous work up, filtered through silica gel, and immediately oxidized to the desired diol fulvene **90** using chloranil in 70% yield over the three steps.

We then established a tandem process to include the RCM, hydrolysis, and dehydrogenation in a single flask. Thus, the triene **99l** was subjected to a three step sequence involving the RCM, carbonate hydrolysis, and sequential chloranil oxidation to afford the desired diol fulvene **90** directly in 70% yield (Scheme 28). Interestingly, by replacing chloranil with DDQ, a more potent oxidant, the triene **99l** could be converted directly to the target (−)-acylfulvene (**1**) in 30% yield without isolation of any intermediates (Scheme 28). Finally, (−)-acylfulvene (**1**) was converted to (−)-irofulven (**2**) in 63% yield using the protocol described by McMorris and coworkers.5,[10] All spectroscopic data for (−)-acylfulvene (**1**) and (−)-irofulven (**2**) matched those reported in the literature.

Conclusion

We have described the development of our synthesis of two potent antitumor agents (−)-acylfulvene (**1**) and (−)-irofulven (**2**). The optimal sequence is summarized in Scheme 29. The asymmetric copper catalyzed Evans aldol addition reaction with the strained ketene acetal **26** secured the C2 stereocenter of the target compounds. The powerful EYRCM cascade reaction with the allyloxysilane tether was successfully employed for the B-ring construction. The successful implementation of this strategy required the identification of optimal derivatives for rapid post-EYRCM derivatization. The reagent IPNBSH efficiently provided the necessary reductive transposition of an advanced allylic alcohol. Finally, a tandem RCM/dehydrogenation process was employed for the C-ring construction to complete the synthesis of (−)-acylfulvene (**1**) and (−)-irofulven (**2**).

Experimental Section

(+)-(*R*)-methyl-2-(1-((ethylthio)carbonyl)cyclopropyl)-2-((trimethylsilyl)oxy)propanoate (48b)

A flame-dried flask was charged with (*R*,*R*)-2,2′-isopropylidene-bis(4-*tert*-butyl-2-oxazoline) (2.03 g, 6.90 mmol, 0.10 equiv)[56] and copper (II) trifluoromethanesulfonate (2.50 g, 6.90 mmol, 0.10 equiv) in a glove-box under a dinitrogen atmosphere. The flask was sealed with a rubber septum and removed from the glove-box. The flask containing the solids was charged with THF (304 mL) at 23 °C and was flushed with argon. After 1h, the resulting bright green solution was cooled to −78 °C, and methyl pyruvate (**25**, 7.80 g, 76.0 mmol, 1.10 equiv) was added via syringe followed by (cyclopropylidene-ethylsulfanyl-methoxy)-trimethyl-silane (**26b** [mixture of **26b**:**47b** = 9:1], 15.5 g, 69.0 mmol, 1 equiv **26b**) via syringe. After 19 h, the reaction mixture was diluted with diethyl ether (300 mL), and filtered through a plug of silica gel (6 × 6 cm, eluent: 1% triethyamine in diethyl ether). The filtrate was concentrated under

reduced pressure and the residue was purified by flash column chromatrography (silica gel: diam. 9 cm, ht. 15 cm; eluent: 1% triethylamine in [2% ethyl acetate in hexanes] to 1% triethylamine in [20% ethyl acetate in hexanes]) to afford the desired (2*R*)-2-(1-ethylsulfanylcarbonyl-cyclopropyl)-2-(trimethyl-silanyloxy)-propionic acid methyl ester (**48b**, 19.8 g, 95%, $[\alpha]^{20}_{D}$ = +30.2 (*c* 2.22, $CHCl_3$)) as a colorless liquid. Protodesilylation of the C2-trimethylsilyloxy group of **48b** afforded samples of the corresponding C2-alcohol that were found to be of 92% ee by chiral HPLC analysis [Chirapak AD-H; 1.5 mL/min; 10% ^{i}PrOH in hexanes; t_R(minor) = 4.65 min, t_R(major) = 5.17 min]. The (*R*,*R*)-2,2′-isopropylidene-bis(4-*tert*-butyl-2-oxazoline) ligand was recovered from the reaction mixture (~85%) and purified by flash column chromatography (silica gel: diam. 2.5 cm, ht. 10 cm; eluent: 20% ethyl acetate in dichloromethane). TLC (10% ethyl acetate in hexanes), R*f*: 0.4 (UV, CAM). ^{1}H NMR (500 MHz, $CDCl_3$): δ 3.72 (s, 3H), 2.79 (q, *J* = 7.3 Hz, 2H), 1.58–1.54 (m, 1H), 1.53 (s, 3H), 1.27–1.19 (m, 2H), 1.19 (t, *J* = 7.3 Hz, 3H), 1.12–1.08 (m, 1H), 0.07 (s, 9H). ^{13}C NMR (125.8 MHz, $CDCl_3$): δ 200.9, 173.4, 75.4, 52.1, 41.8, 24.2, 23.0, 15.3, 14.8, 11.6, 1.5. FTIR (neat) cm^{-1}: 2954, 1747, 1666, 1456, 1413, 1372, 1289, 1263. HRMS (ESI): calc'd for $C_{13}H_{24}NaO_4SSi$ $[M+Na]^+$: 327.1057, found: 327.1066.

Representative procedure for the synthesis of diols 54a–54m. Synthesis of (2*R*,3*S*)-6-(*tert*-butyldimethyl-silyloxy)-7,7-dimethyl-2-(1-(prop-1-en-2-yl)cyclopropyl)non-8-en-4-yne-2,3-diol (54c)

n-Butyllithium (2.50 M in hexanes, 100 μL, 250 μmol, 1.30 equiv) was added dropwise via syringe to a solution of diisopropylamine (37.0 μL, 270 μmol, 1.40 equiv) in THF (300 μL) at 0 °C. After 30 min, the mixture was cooled to −78 °C and a solution of alkyne **53c** (55.0 mg, 230 μmol, 1.20 equiv) in THF (0.9 mL) was added dropwise via cannula. After 35 min, a solution of the aldehyde **22** (43.0 mg, 190 μmol, 1 equiv) in THF (0.6 mL) was added dropwise via cannula. After 2 h, saturated aqueous ammonium chloride solution (0.5 mL) was added. The resulting mixture was allowed to warm to 23 °C, was diluted with diethyl ether (40 mL) and was washed with water (10 mL). The aqueous layer was extracted with diethyl ether (2 × 40 mL), and the combined organic layers were dried over anhydrous magnesium sulfate and were concentrated under reduced pressure. The crude silyl ether residue was dissolved in THF (3 mL) and to this solution was added hydrogen fluoride-triethylamine complex (20.0 μL, 190 μmol, 1.00 equiv) at 0 °C. After 2 h, saturated aqueous sodium bicarbonate solution (3 mL) was added, and the resulting mixture was warmed to 23 °C and was diluted with diethyl ether (100 mL) and water (10 mL). The aqueous layer was extracted with diethyl ether (2 × 40 mL), and the combined organic layers were dried over anhydrous sodium sulfate and were concentrated under reduced pressure. The resulting crude oil was purified by flash column chromatography (silica gel: diam. 2 cm, ht. 16 cm; eluent: 75% diethyl ether in *n*-pentane) to afford the desired diol **54c** (46 mg, 63%, (3*S*:3*R*, 4:1), 2:1 mixture of C6 diastereomers). TLC (15% diethyl ether in *n*-pentane) R*f*: 0.15 (Anis). ^{1}H NMR (400 MHz, C_6D_6, 4:1 mixture of (3*S*)- and (3*R*)-diastereomers; major (3*S*)-diastereomer reported): δ 6.06 (ddd, *J* = 17.2, 10.8, 6.3 Hz 1H), 5.11–5.03 (m, 3H), 4.90 (br-s, 1H), 4.43 (d, *J* = 5.6 Hz, 1H), 4.09 (br-s, 1H), 1.89 (br-s, 1H), 1.76 (br-s, 3H), 1.64 (br-s, 1H), 1.27 (s, 3H), 1.27–1.17 (m, 1H), 1.15 (s, 3H), 1.14 (s, 3H), 0.99 (s, 9H), 0.95–0.84 (m, 1H), 0.60–0.52 (m, 1H), 0.46–0.40 (m, 1H), 0.25 (s, 3H), 0.10 (s, 3H). ^{13}C NMR (100.6 MHz, C_6D_6): δ 147.9, 145.2, 118.1, 113.0, 87.6, 85.3, 75.0, 71.3, 69.7, 43.1, 33.2, 26.2, 23.6, 23.2, 23.0, 22.9, 18.6, 10.9, 9.5, −3.9, −4.9. FTIR (neat) cm^{-1}: 3457, 3082, 2958, 1637, 1472, 1252, 1082. HRMS (ESI): calc'd for $C_{23}H_{40}NaO_3Si$ $[M+Na]^+$: 415.2639, found: 415.2631.

Representative procedure for the synthesis of 55a–55j. Synthesis of (2*R*,3*S*)-3-(allyldimethyl-silyloxy)-7-methyl-2-(1-(prop-1-en-2-yl)cyclopropyl)-oct-4-yn-2-ol (55j)

To a solution of the diol **54j** (100 mg, 420 μmol, 1 equiv, (3*S*:3*R*, 6.7:1)) in dichloromethane (2 mL) at 23 °C was added triethylamine (175 μL, 1.26 mmol, 3.00 equiv) followed by

allylchlorodimethylsilane (79.0 μL, 510 μmol, 1.20 equiv) via syringe. After 40 min, the resulting mixture was purified directly by flash chromatography (silica gel: diam. 3.0 cm, ht. 15 cm; eluent: 9% diethyl ether in *n*-pentane) to afford dienyne **55j** (127 mg, 83%, (3*S*:3*R*, 8:1)) as a clear colorless oil. TLC (25% diethyl ether in hexanes) R*f*: 0.50 (UV, Anis). ^{1}H NMR (400 MHz, C_6D_6, 8:1 mixture of (3*S*)- and (3*R*)-diastereomers; major (3*S*)-diastereomer reported): δ 5.93–5.78 (m, 1H), 5.28 (d, *J* = 2.5 Hz), 5.02–4.91 (m, 3H), 4.64 (t, 1H, *J* = 1.7 Hz), 2.14 (br-s, 1H), 1.91–1.89 (m, 5H), 1.78–1.60 (m, 3H), 1.54–1.46 (m, 1H), 1.36 (br-s, 3H), 1.17–1.10 (m, 1H), 0.86 (d, *J* = 6.7 Hz, 6H), 0.69–0.63 (m, 1H), 0.56–0.50 (m, 1H), 0.22 (s, 3H), 0.20 (s, 3H). ^{13}C NMR (100.6 MHz, C_6D_6, 8:1 mixture of (3*S*)- and (3*R*)-diastereomers; major (3*S*)-diastereomer reported): δ 147.7, 134.2, 117.7, 114.0, 86.7, 81.0, 74.6, 70.3, 32.6, 28.1, 28.0, 25.2, 23.8, 23.5, 22.0, 11.0, 9.2, −1.5, −1.9. FTIR (neat) cm^{-1}: 3570, 3078, 2959, 2925, 2230, 1632, 1374, 1253, 1062, 859. HRMS (ESI): calc'd for $C_{20}H_{34}NaO_2Si$ $[M+Na]^+$: 357.2220, found: 357.2235.

Representative procedure for the EYRCM of the allyldimethylsilyl ethers 60f–60p. Synthesis of 3-((8*R*,8a*S*)-8-hydroxy-2,2,6,8-tetramethyl-2,3,8,8a-tetrahydrospiro[benzo[*e*][1,2] oxasiline-7,1′-cyclopropane]-5-yl)propanal (60o)

Silyl ether **55o** (176 mg, 530 μmol, 1 equiv) was dissolved in benzene (35.0 mL) in a Schlenk vessel. The resulting solution was degassed thoroughly by passage of a stream of argon and **G2** (44 mg, 53 μmol, 0.10 equiv) was added as a solid. After 5 min, the light pink reaction mixture was heated to 65 °C by placement in a pre-heated oil bath. After 1 h, the catalyst was quenched by addition of ethylvinyl ether (0.5 mL). After 5 min, the reaction mixture was cooled to 23 °C and the solvent volume was reduced to ~50% under reduced pressure. The resulting mixture was immediately purified by flash chromatography (silica gel: diam. 4 cm, ht 15 cm; eluent: 10% ethyl acetate in hexanes) to afford the desired diene **60o** (96 mg, 59%) as a clear colorless oil. TLC (10% ethyl acetate in hexanes), *Rf*: 0.3 (UV, Anis). ^{1}H NMR (500 MHz, C_6D_6): δ 9.32 (t, *J* = 1.5 Hz, 1H), 5.80–5.75 (m, 1H), 4.19 (s, 1H), 2.60 (br-s, 1H), 2.43–2.38 (m, 2H), 2.08–1.96 (m, 2H), 1.30 (dd, *J* = 13.0, 7.5 Hz, 1H), 1.20 (dd, 1H, *J* = 13.0, 7.5 Hz), 1.14 (s, 3H), 1.12 (s, 3H), 1.00–0.94 (m, 1H), 0.78–0.72 (m, 1H), 0.56–0.50 (m, 1H), 0.49–0.44 (m, 1H), 0.05 (s, 3H), 0.02 (s, 3H). ^{13}C NMR (125.8 MHz, C_6D_6): δ 200.3, 137.9, 132.2, 128.9, 120.8, 76.4, 71.8, 43.0, 28.9, 22.3, 21.2, 14.6, 13.9, 8.1, 7.6, −0.6, −1.0. FTIR (neat) cm^{-1}: 3535, 2927, 1720, 1377, 1253, 1102. HRMS (ESI) calc'd for $C_{17}H_{26}NaO_3Si$ $[M+Na]^+$: 329.1543, found: 329.1548.

Supplementary Material

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Acknowledgments

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(27). For an approach using C-silyl cyclopropyl esters as nucleophiles in the aldol reaction, see:Paquette LA, Blankenship C, Wells GJ. J. Am. Chem. Soc 1984;106:6442.

(28). The enantiomeric excess of the desilylated C2 alcohol (+)-**48b** (R^2 = H) was established by chiral HPLC analysis and the absolute stereochemistry of this reaction was verified through X-ray crystallographic analysis (Scheme 10).

(29). Anderson RJ, Henrick CA, Rosenblum LD. J. Am. Chem. Soc 1974;96:3654.

(30). (a) Tokuyama H, Yokoshima S, Yamashita T, Fukuyama T. Tetrahedron Lett 1998;39:3189. (b) Milne JE, Buchwald SL. J. Am. Chem. Soc 2004;126:13028. [PubMed: 15469301] (c) Zhou J, Fu GC. J. Am. Chem. Soc 2003;125:12527. [PubMed: 14531697] Synthesis of MeZnI in NMP: (d) Huo S. Org. Lett 2003;5:423. [PubMed: 12583734]

(31). Takai K, Kakiuchi T, Kataoka Y, Utimoto K. J. Org. Chem 1994;59:2668.

(32). Alternative olefination protocols including the Wittig, Petasis, Tebbe, Peterson, and standard Takai reactions were ineffective at carrying out this transformation. For references, see:(a) Petasis NA, Lu S-P. J. Am. Chem. Soc 1995;117:6394. (b) Tebbe FN, Parshall GW, Reddy GS. J. Am. Chem. Soc 1978;100:3611. (c) Peterson DJ. J. Org. Chem 1968;33:780. (d) Okazoe T, Takai K, Utimoto k. J. Am. Chem. Soc 1987;109:951.

(33). Structural parameters for the carboxylic acid **52** salt with (−)-brucine are freely available from the Cambridge Crystallographic Data Center under CCDC-622286. Also see Supporting Information of Ref. [10].

(34). For clarity, only the major diastereomer is shown throughout the text.

(35). For examples of synthesis of cyclohexenes containing tetrasubstituted olefin via enyne metathesis see:(a) Kitamura T, Sato Y, Mori M. Chem. Comm 2001;14:1258. (b) Kitamura T, Sato Y, Mori M. Adv. Synth. Catal 2002;344:678.

(36). Miller SJ, Blackwell HE, Grubbs RH. J. Am. Chem. Soc 1996;118:9606.

(37). Scholl M, Ding S, Lee CW, Grubbs RH. Org. Lett 1999;1:953. [PubMed: 10823227]

(38). The enyne **55n** was prepared from the dienyne **55i** by sequential cleavage of the pivaloate ester (DIBAL-H, CH_2Cl_2, −78 °C, 93%) followed by hydroxyl displacement (I_2, PPh_3, imid., CH_2Cl_2, 75%) and base-promoted elimination (^{t}BuOK, THF, 66%).

(39). See Ref. [12]. The X-ray crystal structure of the related cyclopentenyl structure has been deposited at the Cambridge Crystallographic Data Center, please see: CCDC# 735275.

(40). **63** could be isolated in 15% yield (**G1** (10 mol%), CH_2Cl_2 (0.02M), 23 °C, 16 h). For the preparation of tetraene **63** and its spectroscopic data see the Supporting Information.

(41). It may also be plausible that the formation of product **63** occurs through initial complexation of the metathesis catalyst ($L_nRu{=}CH_2$) with the alkyne followed by EYRCM.

(42). The enyne substrate **55o** was prepared from the dienyne **55h** by sequential cleavage of the pivaloate ester (DIBAL-H, CH_2Cl_2, −78 °C, 93%) followed by Dess-Martin periodinane oxidation (55%) of the resulting alcohol.

(43). The iodide **55p** was prepared from the dienyne **55i** by sequential cleavage of the pivaloate ester (DIBAL-H, CH_2Cl_2, −78 °C, 93%) followed by hydroxyl displacement (I_2, PPh_3, imid., CH_2Cl_2, 75%).

(44). Hoye TR, Jeffrey CS, Tennakoon MA, Wang J, Zhao H. J. Am. Chem. Soc 2004;126:10210. [PubMed: 15315410]

(45). For applications of the Relay-RCM strategy see:(a) Wang X, Bowman EJ, Bowman BJ, Porco JA Jr. Angew. Chem. Int. Ed 2004;43:3601. (b) Wallace DJ. Angew. Chem. Int. Ed 2005;44:1912.

(46). (a) Tamao K, Ishida N, Kumada M. Org. Synth 1990;69:96.For examples of Tamao oxidation of silicon tethered metathesis products, see: (b) Chang S, Grubbs RH. Tetrahedron Lett 1997;38:4757. (c) Yao Q. Org. Lett 2001;3:2069. [PubMed: 11418051]

(47). We did not observe any evidence of the formation of the relay RCM intermediate **70** (Scheme 18) in these reactions, which highlighted the difficulty of carrying out an RCM with a conjugated trisubstituted olefin.

(48). **80** was prepared according to the procedure ofKrolevets AA, Antipova VV, Popov AG, Adamov AV. Zh. Obsch. Khim 1988;58:2274.

(49). (a) Myers AG, Zheng B. Tetrahedron Lett 1996;37:4841. (b) Myers AG, Zheng B, Movassaghi M. J. Org. Chem 1997;62:7507. [PubMed: 11671877]

(50). These initial studies for the synthesis of acylfulvene via the Stille coupling of the OPMB side chain were carried out on racemic material.

(51). Maynard H, Grubbs RH. Tetrahedron Lett 1999;40:4137.

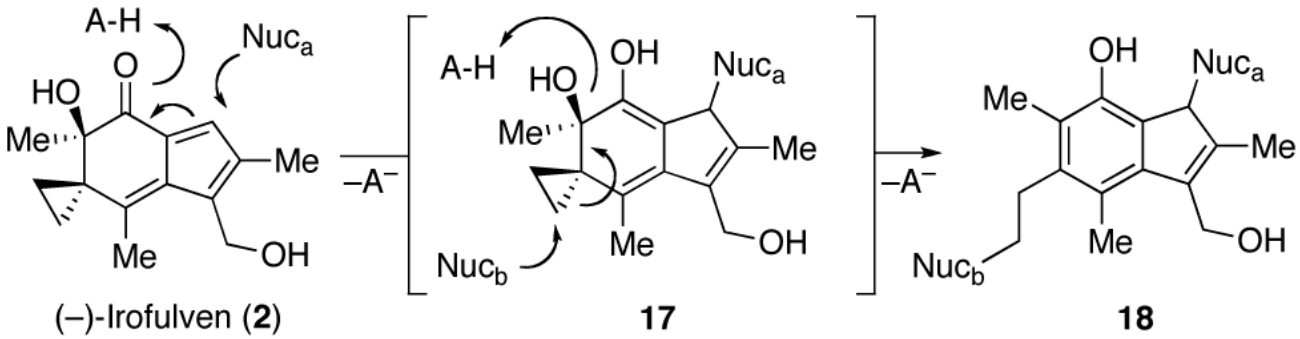
(52). For examples of olefin isomerization catalyzed by ruthenium complexes, see:(a) Sutton AE, Seigal BA, Finnegan DF, Snapper ML. J. Am. Chem. Soc 2002;124:13390. [PubMed: 12418884] (b) Hong SH, Day MW, Grubbs RH. J. Am. Chem. Soc 2004;126:7414. [PubMed: 15198568] (c) Hong SH, Sanders DP, Lee CW, Grubbs RH. J. Am. Chem. Soc 2005;127:17160. [PubMed: 16332044]

(53). (a) Walker MA. J. Org. Chem 1985;60:5352. (b) Myers AG, Movassaghi M, Zheng B. J. Am. Chem. Soc 1997;119:8572.

(54). For an evaluation of the scope of IPNBSH, see:(a) Movassaghi M, Ahmad OK. J. Org. Chem 2007;72:1838. [PubMed: 17274659] For use of IPNBSH in a stereospecific palladium-catalyzed route to monoalkyl diazenes, see: (b) Movassaghi M, Ahmad OK. Angew. Chem. Int. Ed 2008;47:8909.

(55). These initial studies for the synthesis of acylfulvene with **99k** were performed using racemic material.

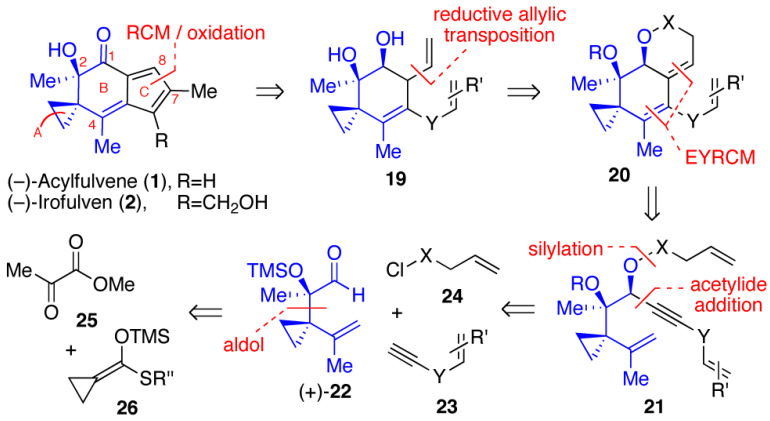
(56). For the preparation of (*R*,*R*)-2,2′-isopropylidene-bis(4-^{t}butyl-2-oxazoline) see:Evans DA, Peterson GS, Johnson JS, Barnes DM, Campos KR, Woerpel KA. J. Org. Chem 1998;63:4541–4544.



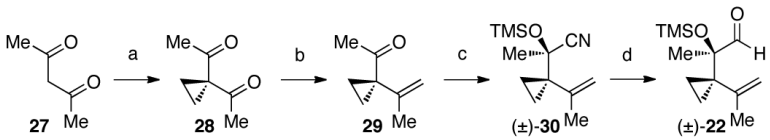
SCHEME 1.

Proposed mechanism of biological activity of (−)-irofulven (**2**).[a]

[a] Nuc_a = glutathione, cysteine, or hydride (NADPH). Nuc_b = DNA.



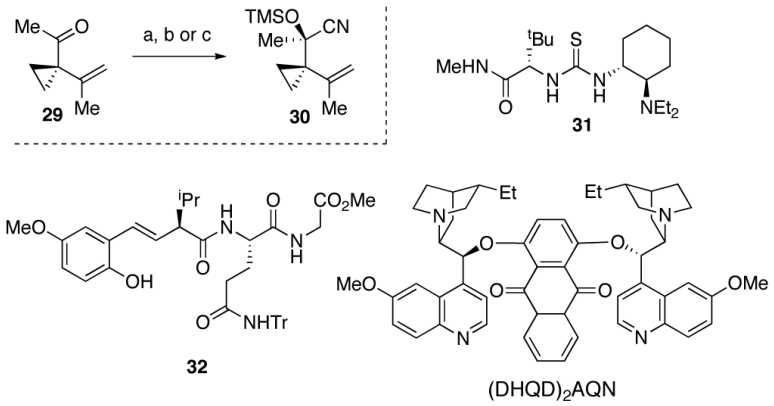
SCHEME 2.
Retrosynthetic analysis.



SCHEME 3.

Synthesis of the aldehyde (±)-**22**.[a]

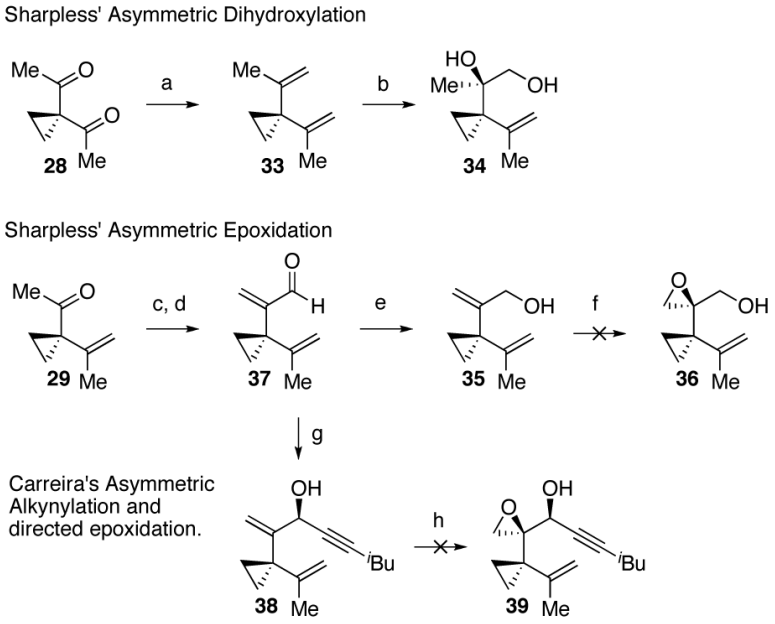
[a] Conditions: a) $(CH_2Br)_2$, K_2CO_3, DMSO, 61%. b) $MePh_3PBr$, ^tBuOK, Et_2O, 56%. c) TMSCN, $InBr_3$ (5 mol%), CH_2Cl_2, 81%. d) DIBAL-H, Et_2O, −78 °C, 69%.



SCHEME 4.

Asymmetric silylcyanation reactions with ketone **29**.[a]

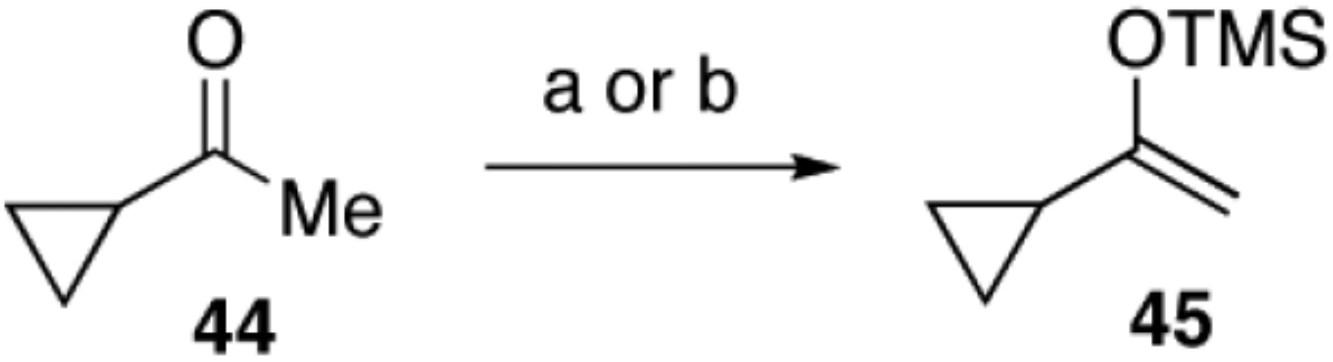
[a] Conditions: a) TMSCN, **31**, TFE, CH_2Cl_2, 50 h, 13%, 53% ee; 8 d, 71%, 34% ee. b) TMSCN, $Al(O^iPr)_3$, **32**, MeOH, PhMe, 3Å MS, 79%, 0% ee. c) TMSCN, $(DHQD)_2AQN$, CH_2Cl_2, 7 d, 11%, 0% ee.



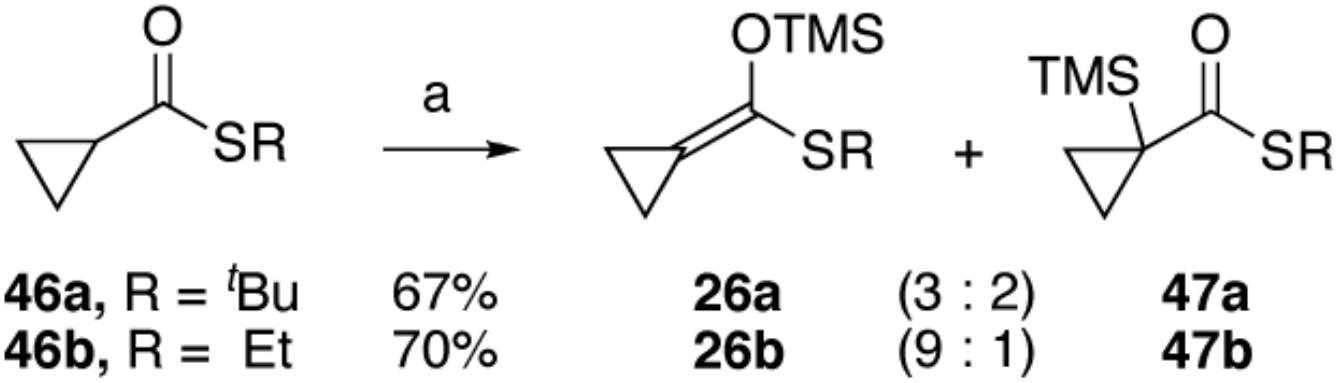
SCHEME 5.

Asymmetric oxidation approaches to secure the tertiary alcohol stereocenter.[a]

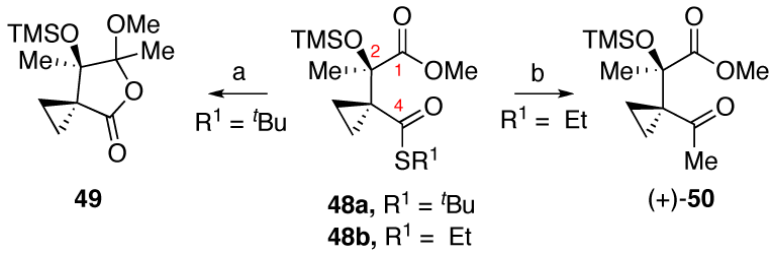
[a] Conditions: a) $MePh_3PBr$, ^tBuOK, Et_2O, 8%. b) AD-mix α, $MeSO_2NH_2$, ^tBuOH, H_2O, 50%, 0% ee. c) $TrisNHNH_2$, cat. TsOH, MeCN, 73%. d) ^sBuLi, TMEDA, hexanes; DMF, 86%. e) $NaBH_4$ $CeCl_3$, CH_2Cl_2, MeOH, 75%. f) $Ti(O^iPr)_4$, (−)-DET, ^tBuOOH, CH_2Cl_2. g) HCC^iBu, $Zn(OTf)_2$, (−)-NME, Et_3N, PhMe, 25%, 99% ee. h) *m*CPBA, CH_2Cl_2.



SCHEME 6.
Enolization of 1-cyclopropylethanone (**44**).[a]
[a] Conditions: a) LDA, TMSCl, THF, −78 °C, 84%. b) TMSOTf, Et_3N, CH_2Cl_2, −78 °C, 87%.



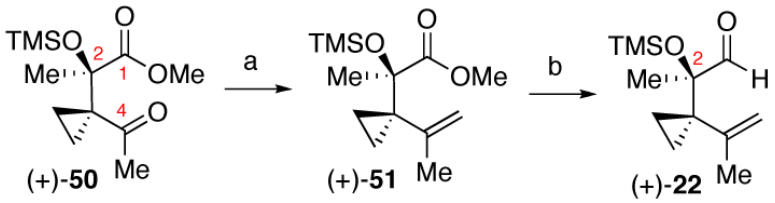
SCHEME 7.
Synthesis of ketenehemithioacetals **26a** and **26b**.[a]
[a] Conditions: a) LDA, TMSCl, THF, −78 °C.



SCHEME 8.

Cuprate addition to the thiol esters **48a** and **48b**.[a]

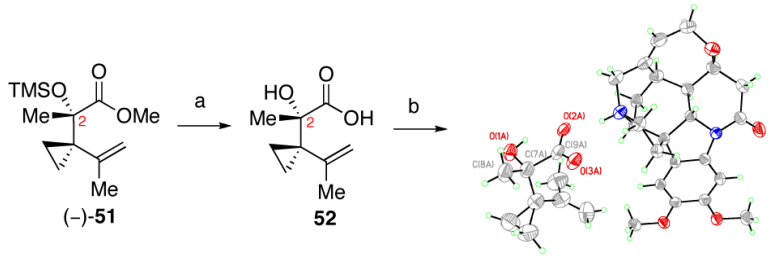
[a] Conditions: a) **48a**, Me_2CuLi (10 equiv), Et_2O, 0 °C, 2 h, 45%. b) (+)-**48b** Me_2CuLi (1 equiv), Et_2O, 23 °C, 30 min, 25%.



SCHEME 9.

Synthesis of aldehyde (+)-**22**.[a]

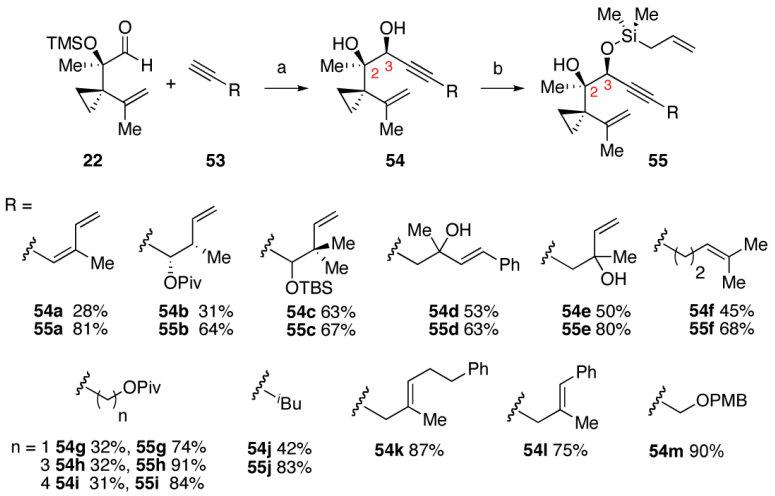
[a] Conditions: a) CH_2I_2, Zn, $TiCl_4$, $PbCl_2$, THF, 89%. b) DIBAL-H, Et_2O; DMP, CH_2Cl_2, 91%.



SCHEME 10.

Thermal ellipsoid representation of the carboxylic acid **52** salt with (−)-brucine.[a]

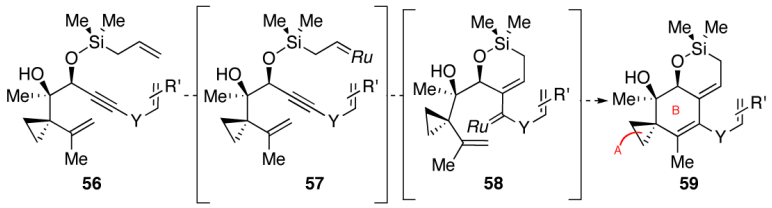
[a] Conditions: a) LiOH, THF, 82% b) (−)-brucine.



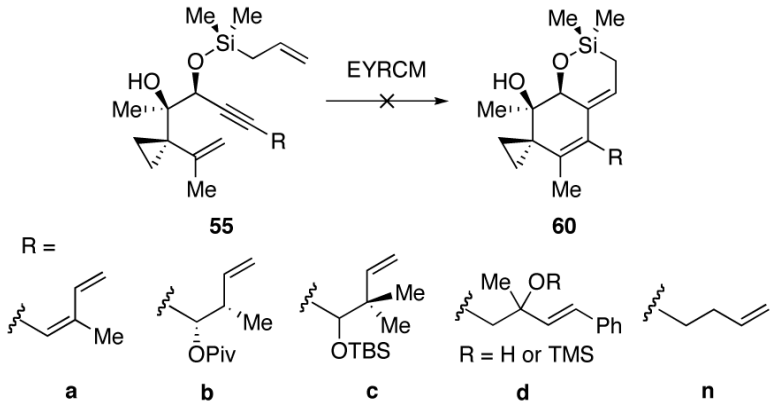
SCHEME 11.

Acetylide addition to aldehyde **22** and allyldimethylsilyl tethers formation.[a]

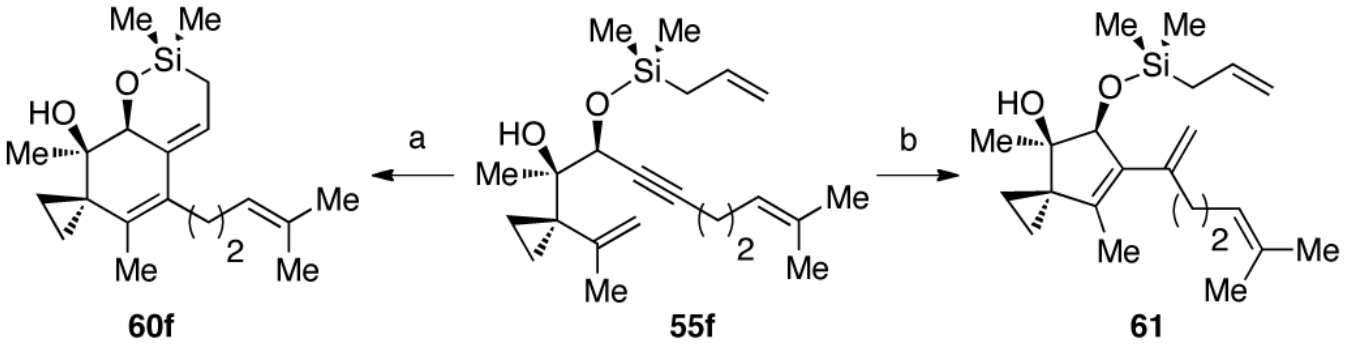
[a] Conditions: a) LDA or LiHMDS, THF, −78 °C; TBAF or $Et_3N{\cdot}(HF)_3$. b) allyldimethylsilyl chloride, Et_3N, CH_2Cl_2.



SCHEME 12.
Our initial EYRCM approach.



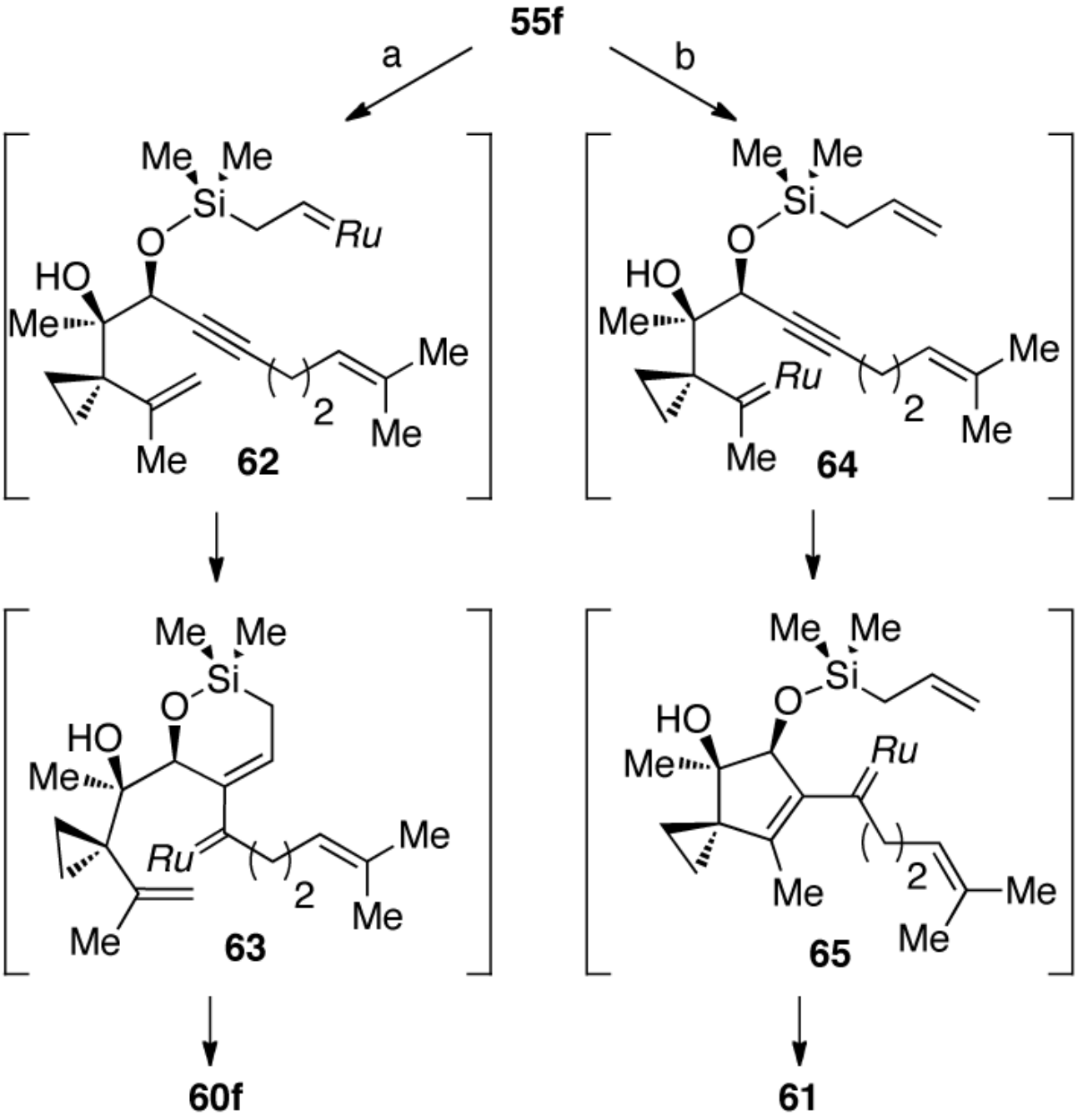
Scheme 13.
Initial studies of the EYRCM.[a]
[a] Conditions: **G1** or **G2**, C_6D_6 (0.02M), 80 °C, 12–36 h.



SCHEME 14.

^{1}H NMR analysis of the EYRCM with trienyne **55f**.[a]

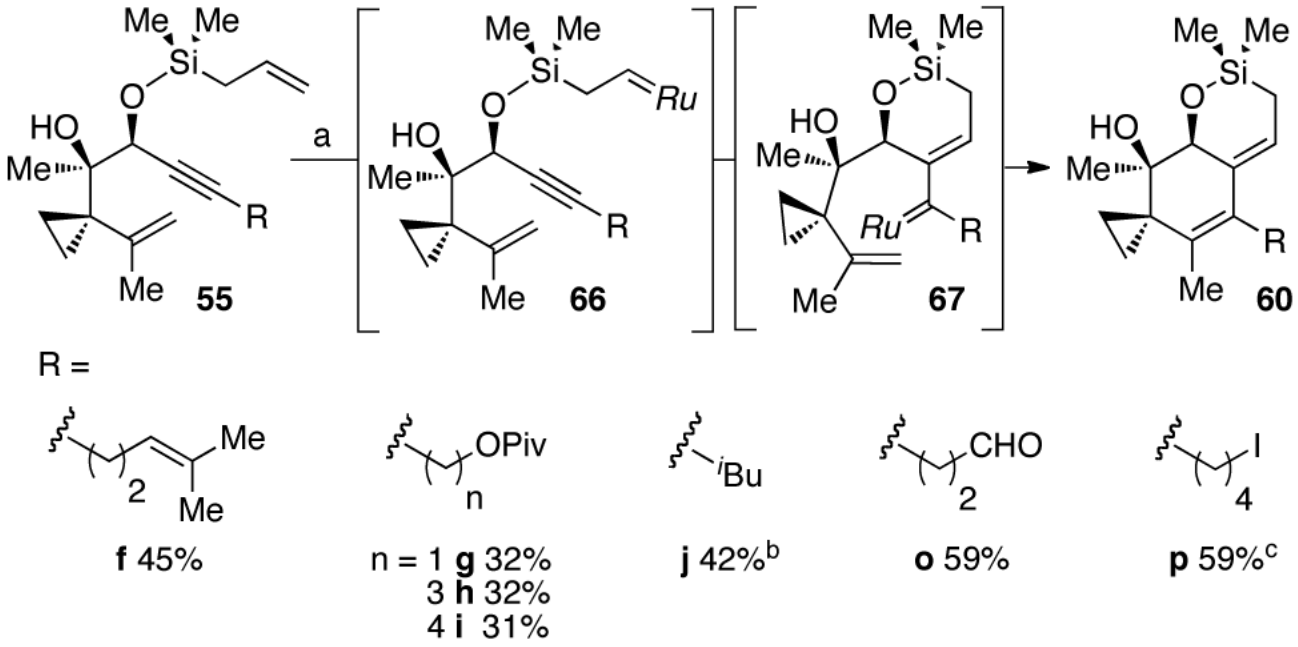
[a] Conditions: a) **G2** (10 mol%), C_6D_6 (0.02M), 65 °C, 1 h, 90% (^{1}H NMR). b) **G1** (10 mol%), C_6D_6 (0.02M), 65 °C, 1 h, 25% (H NMR).



SCHEME 15.

Plausible mechanism for the formation of **60f** and **61**.

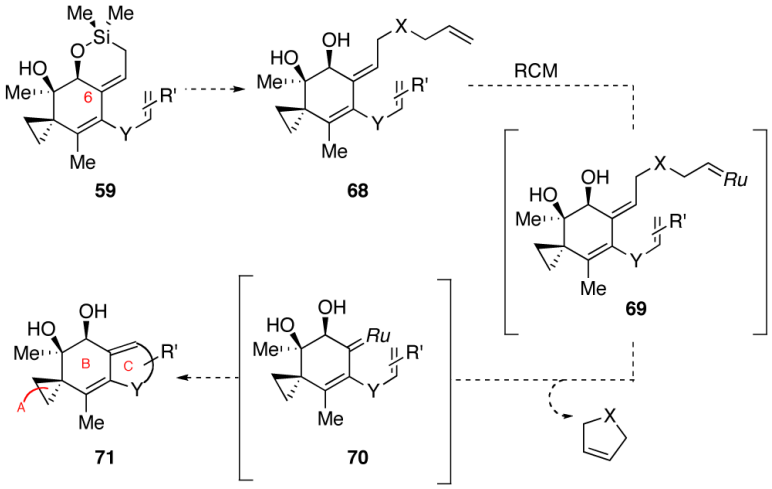
Conditions: a) **G2** (10 mol%), C_6D_6 (0.02M), 65 °C, 1 h, 90% (^{1}H NMR). b) **G1** (10 mol%), C_6D_6 (0.02M), 65 °C, 1 h, 25% (^{1}H NMR).



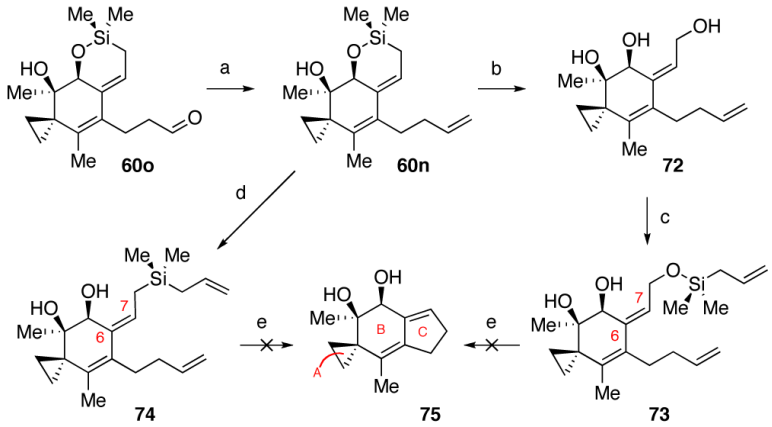
SCHEME 16.

EYRCM of enynes **55f–p**.[a]

[a] Conditions: a) **G2** (10 mol%), PhH, (0.02M), 65 °C, 1 h. [b] Reaction was run in toluene at 80 °C for 40 min. [c] Reaction was run for 6 h.



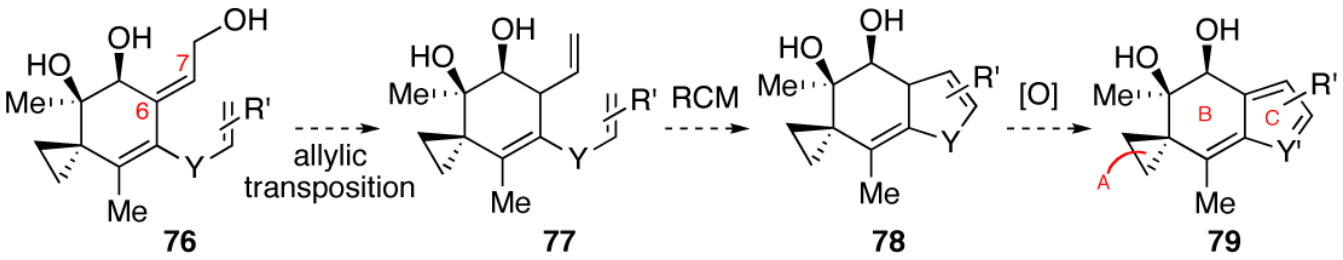
SCHEME 17.
Relay ring-closing metathesis strategy.



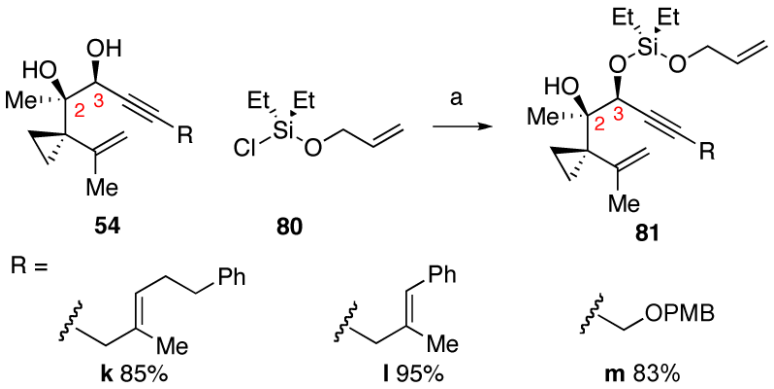
SCHEME 18.

Synthesis of intermediates for the relay ring-closing metathesis.[a]

[a] Conditions: a) Ph_3PMeBr, ^tBuLi, THF, 30%. b) H_2O_2, KF, $NaHCO_3$, MeOH, THF, 23 °C, 30%. c) allylchlorodimethylsilane, Et_3N, CH_2Cl_2, 23 °C, 47%. d) AllylMgCl, THF, 0 °C, 45%. e) **G1** or **G2**, various conditions.



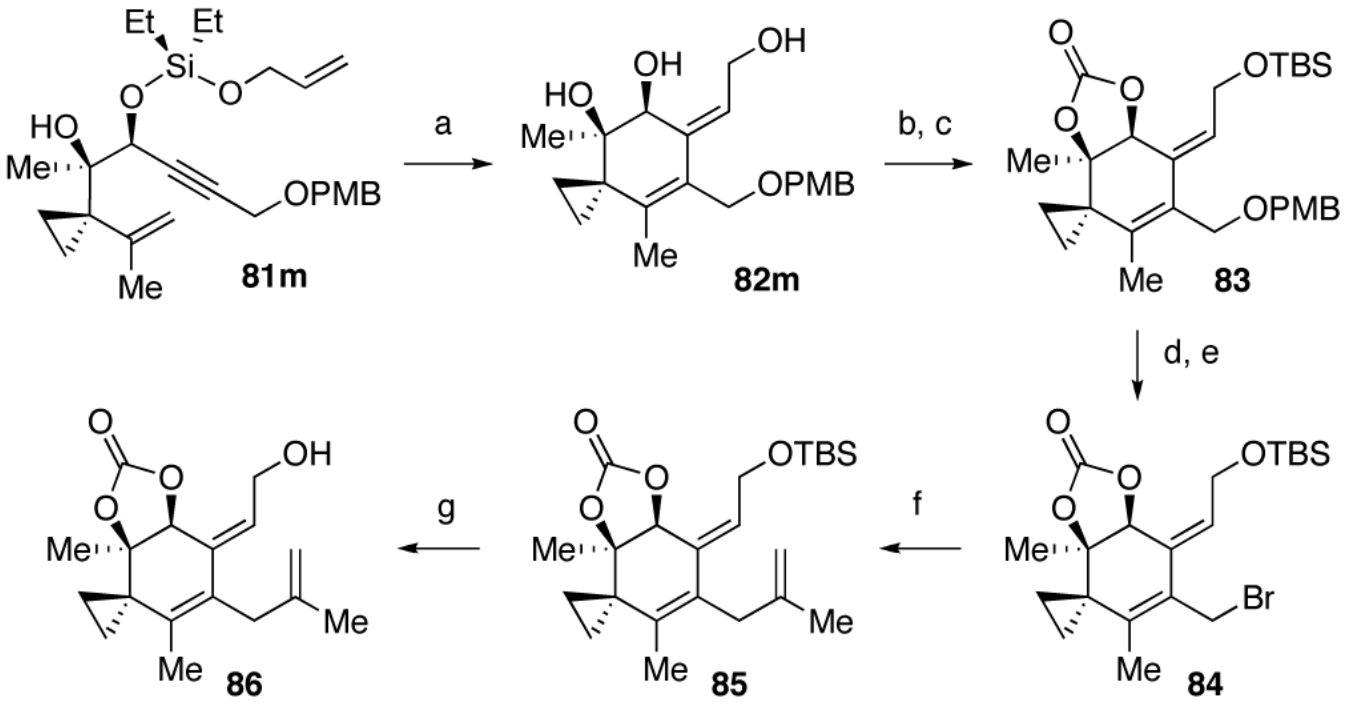
SCHEME 19.
Reductive allylic transposition strategy.



SCHEME 20.

Introduction of the diethylallyloxysilyl tether.

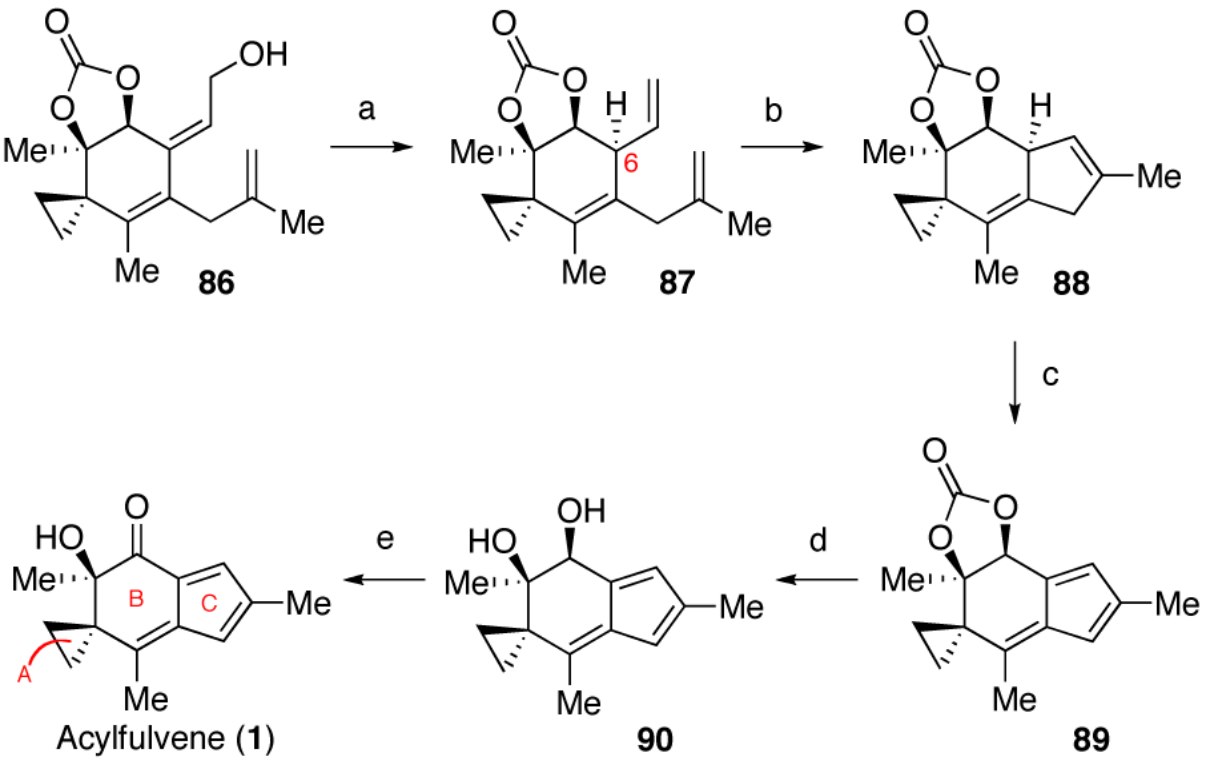
[a] Conditions: a) Et_3N, CH_2Cl_2, 23 °C.



SCHEME 21.

Synthesis of the trieneol **86** via a Stille coupling.[a]

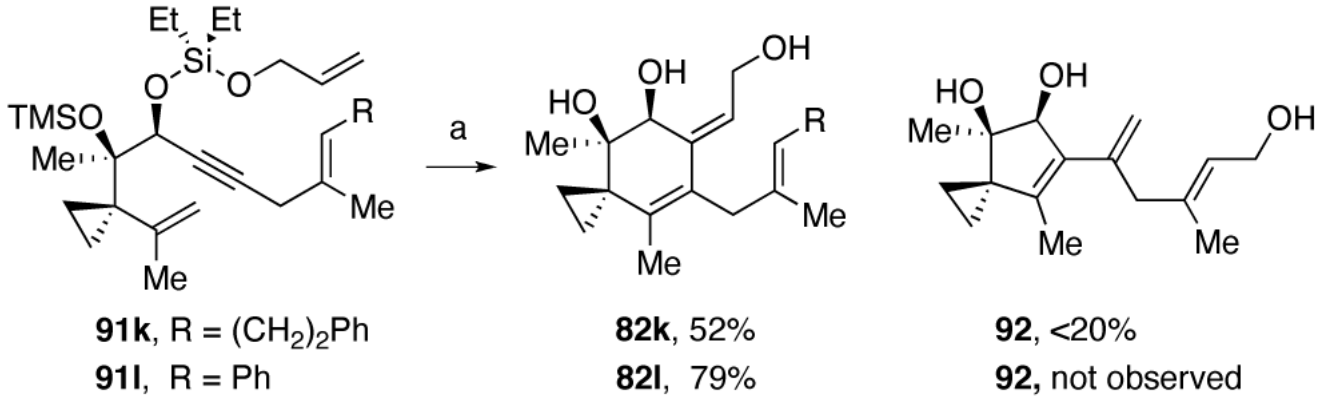
[a] Conditions: a) **G2**, PhMe, 110 °C; TBAF, 64%. b) TBSCl, imid., DMF, 23 °C, 36 h, 83%. c) triphosgene, pyr., 23 °C, 1 h, 93%. d) DDQ, H_2O, CH_2Cl_2, 0 °C, 5.5 h, 80%. e) DDQ, PPh_3, TBABr, 23 °C, 5 min, 86%. f) $PdCl_2$(MeCN) (10 mol%), isopropenyl-tributylstannane, NMP, 23 °C, 1 h, 35%. g) TBAF, THF, 0 °C, 45 min, 79%.



SCHEME 22.

First generation synthesis of acylfulvene (**1**) via a reductive allylic transposition reaction.[a]

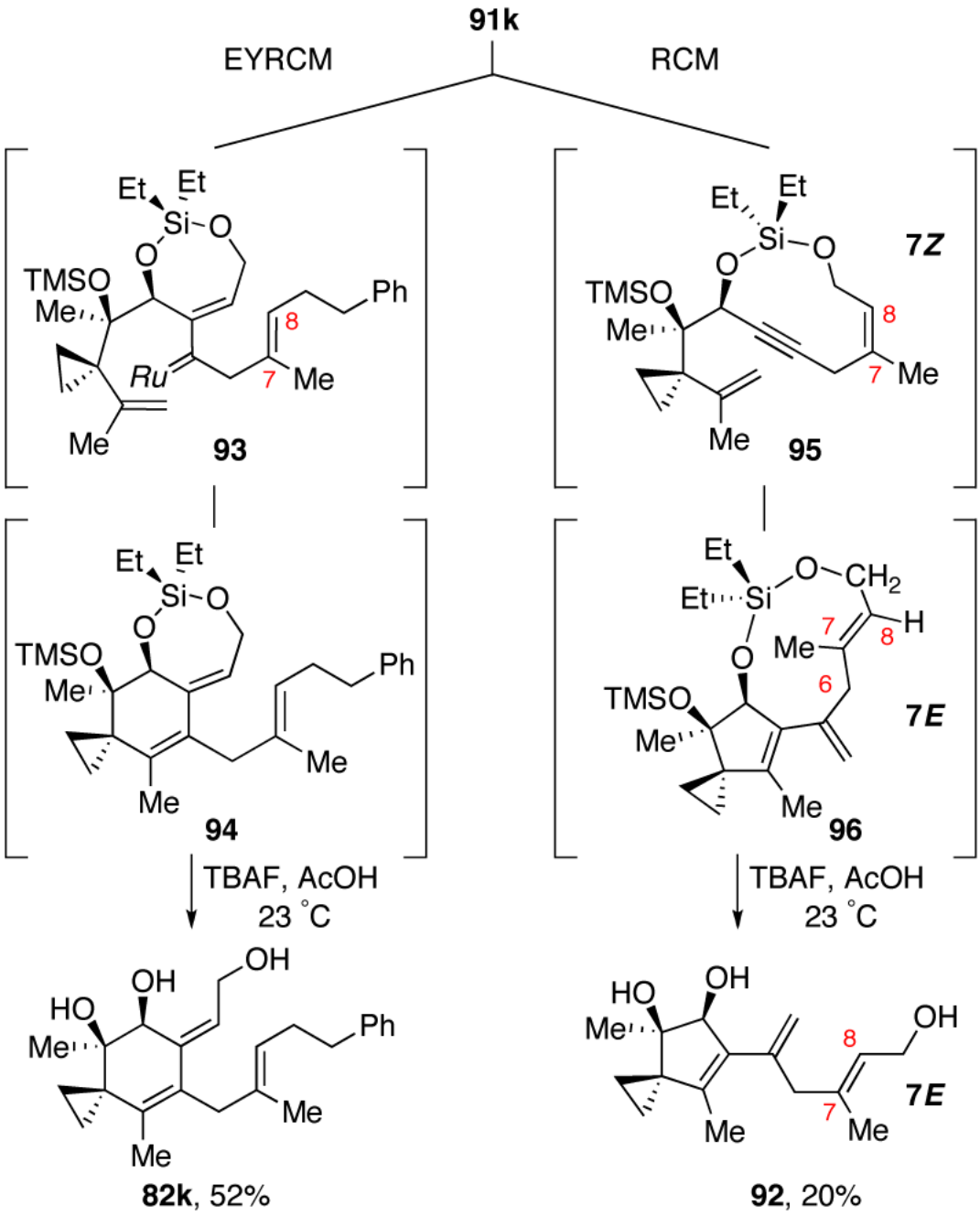
[a] Conditions: a) NBSH, DEAD, PPh_3, NMM, −30 °C to 23 °C, 30% (6*S*:6*R*, 3:1). b) **G2** (10 mol%), C_6D_6, 65 °C, 45 min, 45% (6*S*:6*R*, 3:1). c) DDQ, C_6H_6, 23 °C, 12 h, 93%. d) NaOH, dioxane, 1 h, 23 °C, 99%. e) IBX, DMSO, 83%.



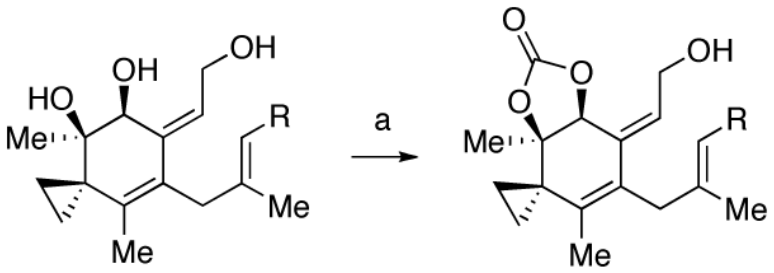
SCHEME 23.

EYRCM cascade with **91k** and **91l**.[a]

[a] Conditions: a) **G2** (15 mol%), PhMe (0.01M), 90 °C, 30 min; TBAF, AcOH, THF, 23 °C, 10 min.



SCHEME 24.
Proposed mechanism for the formation triols **82k** and **92**.



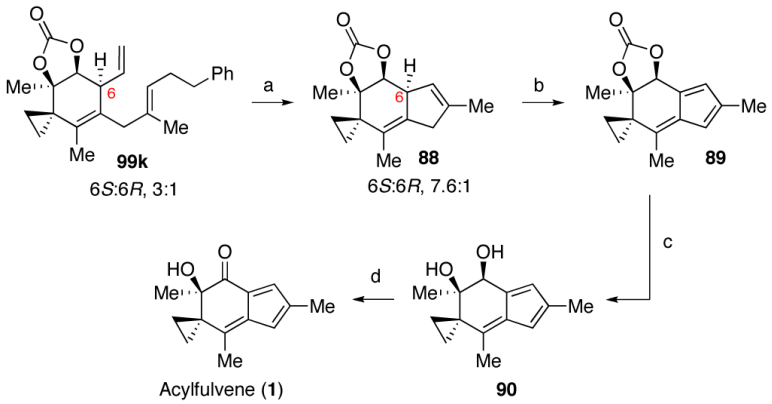
82k, R = $(CH_2)_2Ph$ **97k**, 60%

82l, R = Ph **97l**, 67%

SCHEME 25.

One-pot synthesis of carbonates **97k–l**.[a]

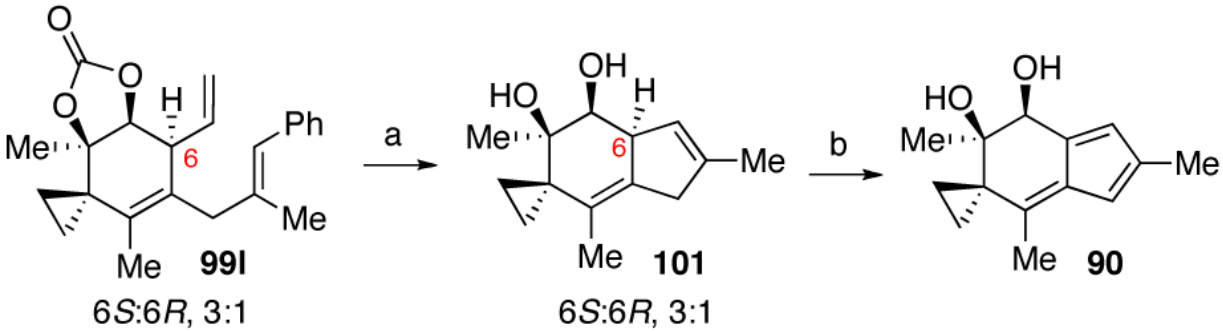
[a] Conditions: a) TBSOTf, 2,6-lutidine, CH_2Cl_2, −78 °C; triphosgene, 23 °C; TBAF.



SCHEME 26.

RCM of triene **99k** and synthesis of acylfulvene (**1**).[a]

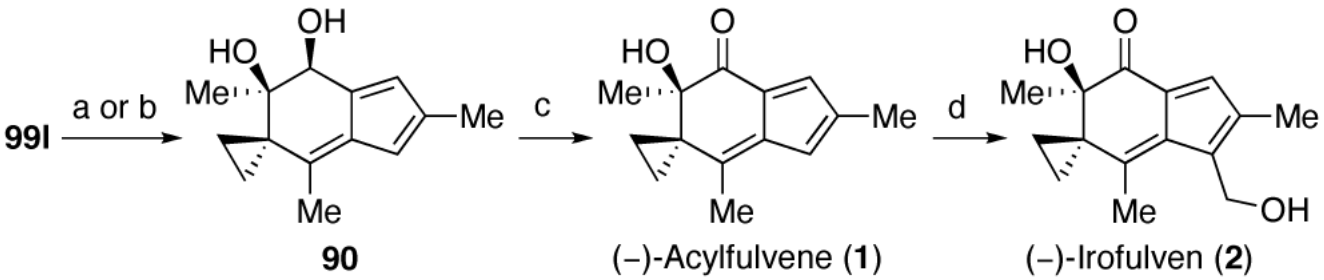
[a] Conditions: a) **G2** (15 mol%), C_6D_6, 65 °C, 82% (6*S*:6*R*, 7.6:1). b) DDQ, PhH, 93%. c) aq NaOH, Dioxane, 99%. d) IBX, DMSO, 83%.



SCHEME 27.

Conversion of triene **99l** to the fulvene diol **90**.

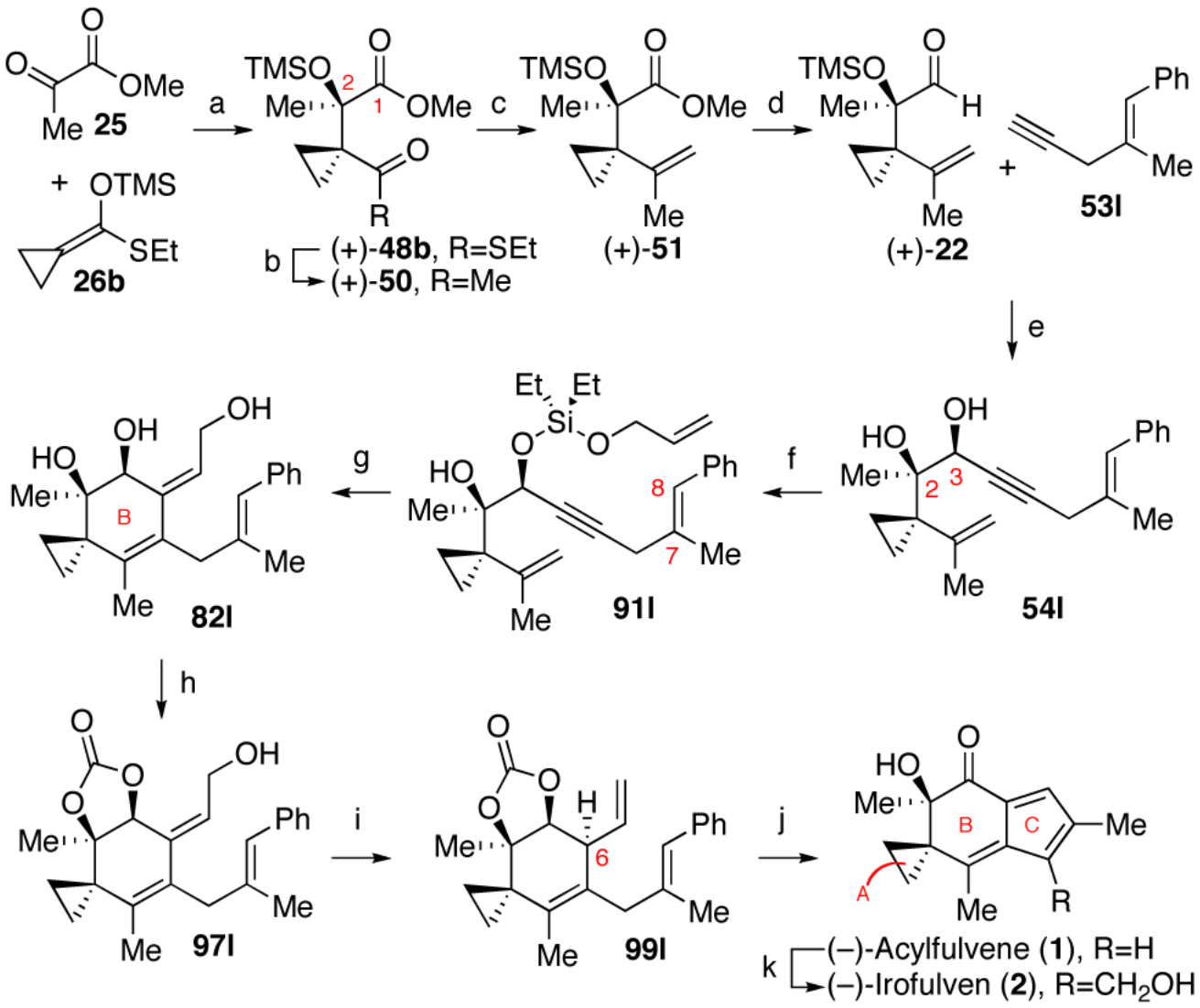
[a] Conditions: a) **G2** (15mol%), PhH, 80 °C; aq LiOH, DMF, 23 °C, 12h. b) chloranil, PhH, 70% (3 steps).



SCHEME 28.

Synthesis of (−)-acylfulvene (**1**) and (−)-irofulven (**2**).

[a] Conditions: a) **99l**→(−)-(**1**): **G2** (15mol%), PhH, 80 °C, 50 min; NaOMe, MeOH, 23 °C, 18 h; AcOH; DDQ, MeCN, 14 h, 30%. b) **99l**→**90**: **G2** (15mol%), PhH, 80 °C, 50 min; NaOMe, MeOH, 23 °C, 18 h; AcOH; chloranil, MeCN, 13 h, 70%. c) IBX, DMSO, 83%. d) H_2SO_4, CH_2O aq., Me_2CO, 63%.



SCHEME 29.

Summary of the enantioselective total synthesis of (−)-acylfulvene (**1**) and (−)-irofulven (**2**).[a]

[a] For clarity, only the major diastereomer of the intermediates **54l–99l** is shown. Conditions: a) (*R*,*R*)-2,2′-isopropylidene-bis(4-*t*butyl-2-oxazoline), $Cu(OTf)_2$, THF, −78 °C, 12 h, 95%, 92% ee. (b) MeZnI, $Pd_2(dba)_3$, SPhos, THF, NMP, 65 °C, 2 h, 83%. (c) CH_2I_2, $TiCl_4$, Zn, $PbCl_4$, CH_2Cl_2, THF, 23 °C, 4 h, 89%. (d) DIBAL-H, Et_2O, −78 °C; Dess-Martin periodinane, CH_2Cl_2, 23 °C, 91%. e) **53l**, LHMDS, THF, −78→−40 °C; TBAF, AcOH, 75%. f) $(Et)_2Si(Cl)OCH_2CH{=}CH_2$, 2,6-lutidine, CH_2Cl_2; TMSOTf, −78 °C, 83%. g) **G2** (15 mol%), PhMe, 90 °C, 30 min; TBAF, AcOH, 79%. h) TBSOTf, 2,6-lutidine, CH_2Cl_2, −78 °C; triphosgene; TBAF, 67%. i) IPNBSH, DEAD, Ph_3P, THF, 0–23 °C; TFE, H_2O, 71%. j) **G2** (15 mol%), PhH, 80 °C; NaOMe; AcOH; DDQ (**99l**→**1**, 30%) - or use chloranil to isolate **90** (70%), then IBX, DMSO, 83%. k) H_2SO_4, CH_2O_{aq}, 63%.

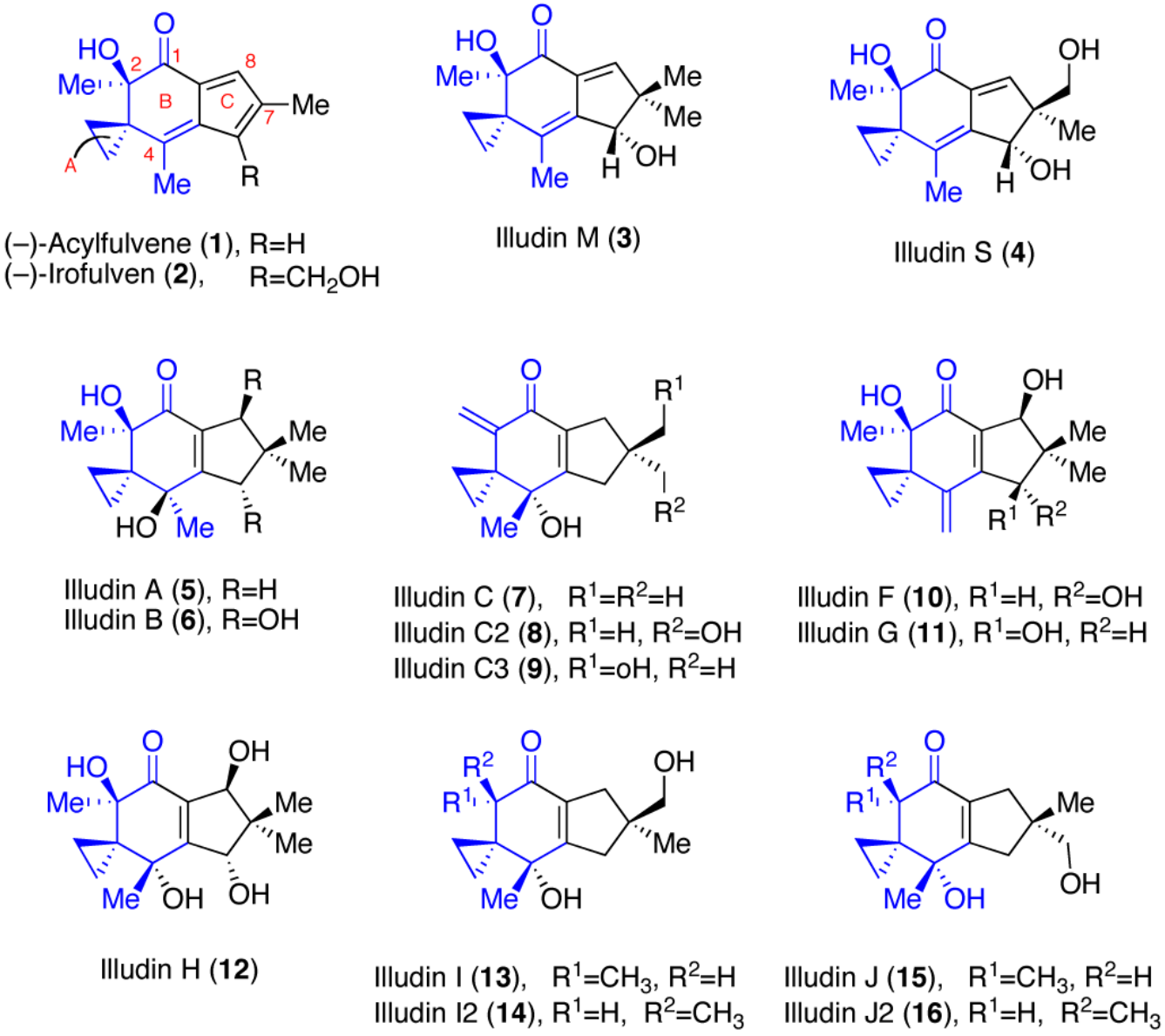


FIGURE 1.
The illudin family of sesquiterpenes.

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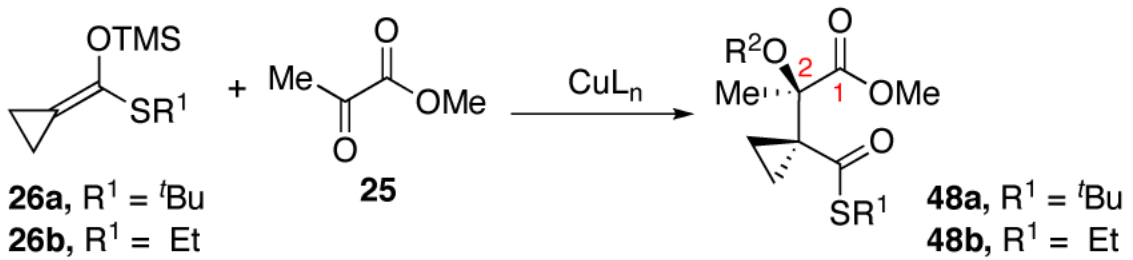
TABLE 1

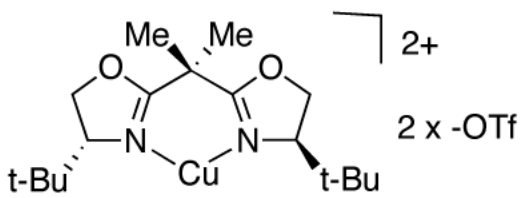
The use of cyclopropyl ketenehemithioacetal in Evans' asymmetric aldol addition reaction.[a]



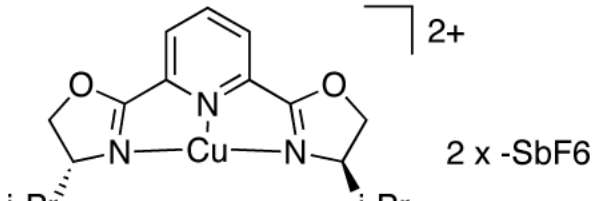
26a, R^1 = ^{t}Bu
26b, R^1 = Et

25

48a, R^1 = ^{t}Bu
48b, R^1 = Et



(*R,R*)-CuBox



(*R,R*)-CuPybox

Entry	Substrat	Catalyst	Solvent	Temp (°C)	Time (h)	Yield (%) R^2 = TMS : H	% ee
1	**26a**	$Cu(OTf)_2$	CH_2Cl_2	−78	2	- : 51	-
2	**26a**	*R,R*-CuPybox	CH_2Cl_2	−78	48	- : 20	0
3[b]	**26a**	*R,R*-CuPybox	CH_2Cl_2	−78	18	- : 19	0
4	**26a**	*S,S*-CuBox	CH_2Cl_2	−78	6.5	- : 73	−90
5	**26a**	*S,S*-CuBox	CH_2Cl_2	23	2	- : 77	−85
6	**26a**	*S,S*-CuBox	THF	−78	2	- : 92	−95
7[c]	**26b**	*S,S*-CuBox	THF	−78	8	71 : 8	−99
8[b,c]	**26b**	*S,S*-CuBox	THF	−78	1	76 : 19	−95
9	**26b**	*R,R*-CuBox	THF	−78	12	- : 93	93
10[c]	**26b**	***R,R*-CuBox**	**THF**	**−78**	**12**	**95 : 0**	**92**

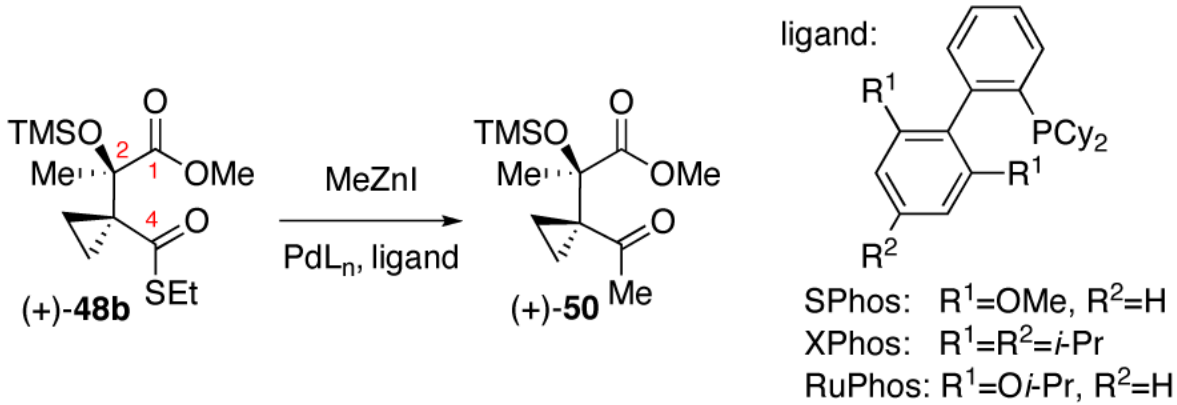
[a] Reactions were run at [**25**] = 0.25M, with 10 mol% catalyst loading, and were quenched with TBAF followed by filtration through a plug of silica gel. Enantiomeric excess (ee) determined by HPLC using a chiralcel AD-H column with the corresponding free alcohol **48** (R^2 = H) after desilylation.

[b] Reactions were run in the presence of TMSOTf (1 equiv).

[c] Reactions were directly filtered through a plug of silica gel without TBAF treatment.

TABLE 2

Thiolester cross coupling.[a]



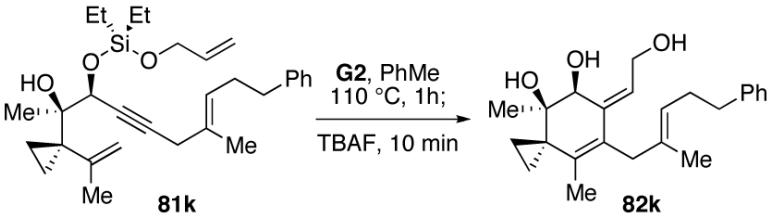
Entry	Catalyst	Ligand	Solvent[b]	Temp (°C)	Time (h)	Yield (%)
1	$pdCl_2(PPh_3)_2$	-	PhMe	23	11	42
2	$PdCl_2(PPh_3)_2$	-	THF, NMP	65	15	66
3	$Pd_2(dba)_3$	SPhos	PhMe	23	11	0
4	$Pd_2(dba)_3$	SPhos	THF	23	11	0
5	$Pd_2(dba)_3$	SPhos	PhMe	65	11	19
6	$Pd_2(dba)_3$	SPhos	THF	65	11	42
7	**$Pd_2(dba)_3$**	**SPhos**	**THF, NMP**	**65**	**2**	**83**
8	$Pd_2(dba)_3$	XPhos	THF, NMP	65	2	70
9	$Pd_2(dba)_3$	RuPhos	THF, NMP	65	2	66

[a] Reactions were run with PdL_n (5 mol%), ligand (20 mol%), MeZnI (5 equiv), [(+)-**48b**] = 0.3M.

[b] THF, NMP (1:1.5).

TABLE 3

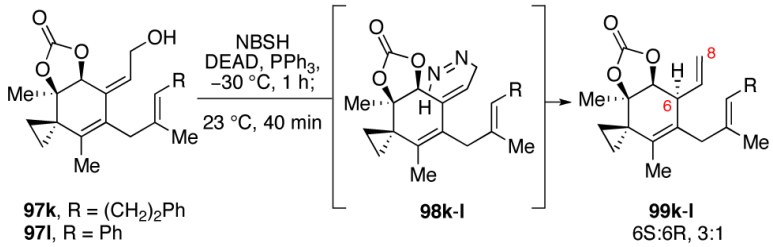
EYRCM with **81k**.



Entry	cat. (mol%)	Conc.	Yield
1	10	0.02M	18%
2	10	0.04M	21%
3	20	0.01M	25%
4	**30**	**0.01M**	**52%**
5	30	0.003M	45%
6	100	0.001M	29%

TABLE 4

Reductive allylic transposition using NBSH.[a]



Entry	Substrate	Solvent	Additive (equiv)[b]	Conc.	Yield (%)
1	**97k**	NMM	-	0.20M	27%
2	**97k**	NMM	-	0.25M	43%[c]
3	**97k**	NMM	**A** (15)	0.30M	75%
4	**97l**	NMM	**A** (10)	0.30M	54%
5	**97l**	NMM	**A** (10), **B** (2)	0.30M	35%
6	**97l**	THF	**A** (10), **B** (2)	0.20M	27%
7	**97l**	NMM:THF[a]	**A** (10), **B** (2)	0.30M	54%
8	**97l**	NMM:THF[a]	**A** (10), **B** (1)	0.20M	67%

[a] NBSH (3.0 equiv), DEAD (3.0 equiv), and PPh_3 (3.1 equiv) were used.

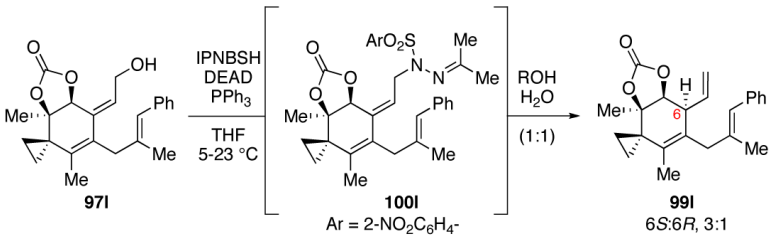
[b] Additive **A** = allylbenzene, **B** = neopentyl alcohol.

[c] The C7–C8 reduction product of **99k** was also isolated (19%).

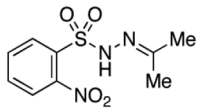
[d] NMM:THF (1:1).

TABLE 5

IPNBSH mediated transposition reactions.[a]



Entry	Conc.	ROH	Yield
1	0.20M	none	33%
2	0.25M	MeOH	57%
3	0.10M	^{i}PrOH	58%
4	0.10M	EtOH	57%
5	**0.10M**	**TTE**	**71%**



[a]The reactions were performed with 2 equiv of IPNBSH, DEAD, and PPh3.