Asymmetric Synthesis

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Enantioselective Total Synthesis of (−)-Acylfulvene and (−)-Irofulven[**]

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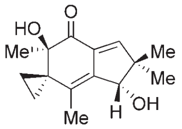
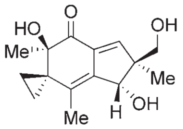
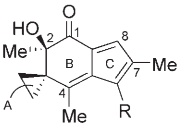
While sesquiterpene illudins M and S (**1** and **2**, respectively) are highly cytotoxic compounds isolated from *Omphalotus illudens*, a semisynthetic derivative, (−)-irofulven (**4**; hydroxymethyl acylfulvene (HMAF)), has recently demonstrated far superior efficacy as an antitumor agent.[1,2] (−)-Irofulven (**4**) is currently in phase II clinical trials for the treatment of ovarian, prostate, and thyroid cancers both as monotherapy and combination therapy.[2] Significantly, it has demonstrated activity against a variety of solid tumors. Prior syntheses of irofulven using the Padwa carbonyl ylide 1,3-dipolar cycloaddition reaction and the Pauson–Khand reaction have been reported.[3] Herein, we describe a convergent enantioselective total synthesis of (−)-acylfulvene (**3**) and (−)-irofulven (**4**).



Illudin M (**1**)



Illudin S (**2**)



(−)-Acylfulvene (**3**), R=H
(−)-Irofulven (**4**), R=CH_2OH

The inhibition of DNA synthesis and S-phase arrest in cells treated with these compounds stems from sequential nucleophilic addition at C8 and cyclopropyl ring opening, thus

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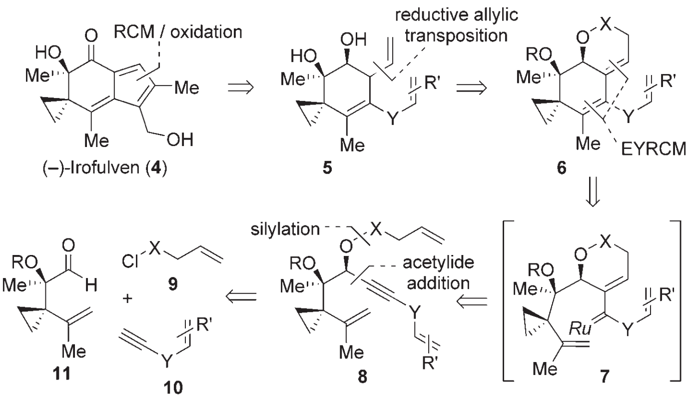
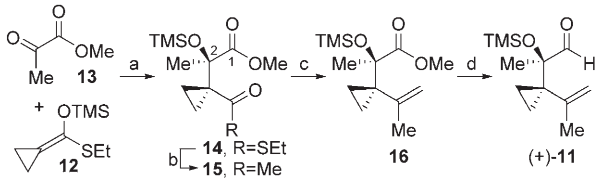
leading to B-ring aromatization.[3a] In light of their potent antitumor activity, we sought to develop a general solution to the synthesis of the fully functional spirocyclic AB-ring system common to these antitumor agents by employing a versatile enyne ring-closing metathesis reaction (EYRCM; Scheme 1).[4] A convergent assembly of trienyne **8** by addition of a lithium acetylide to a suitable α-alkoxy aldehyde **11** followed by temporary introduction of an allyl group was envisioned. The planned EYRCM cascade of trienyne **8** would provide rapid access to the fully functional tricycle **6**, which contains the core structure of compounds **1**–**4**, via the ruthenium alkylidene **7**. Deconjugation of the newly formed diene **6** would set the stage for the final ring-closing metathesis (RCM)/oxidation sequence to complete the synthesis of the target compounds.[4,5]



Scheme 1. Retrosynthetic analysis of (−)-irofulven (**4**). *Ru* = 1,3-dimesityl-4,5-dihydroimidazol-2-ylidene ruthenium dichloride, X = $\mathrm{SiR_2}$ or $\mathrm{Si(O)R_2}$.

An enantioselective route to aldehyde **11** (R = TMS) was developed based on the Evans copper-catalyzed aldol addition reaction (Scheme 2).[6] The addition of the strained ketene hemithioacetal **12**[7] to a solution of methyl pyruvate **13** and (*R*,*R*)-2,2′-isopropylidene-bis(4-*tert*-butyl-2-oxazoline)-copper(II) triflate (10 mol%) in THF at −78 °C gave the desired *O*-trimethylsilyl diester **14** (95%, 92% *ee*; Scheme 2). The stereochemistry at C2 of **14** was secured by X-ray analysis (a related salt with (−)-brucine)[7] and was found to be consistent with the predicted sense of carbonyl addition.[6a]

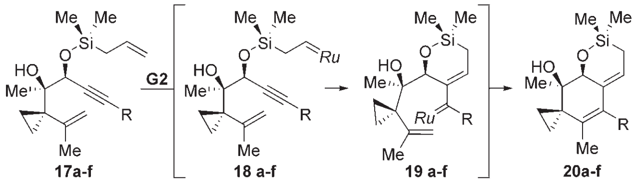


Scheme 2. Enantioselective synthesis of (+)-aldehyde **11**. Reagents and conditions: a) (*R*,*R*)-2,2′-isopropylidene-bis(4-*tert*-butyl-2-oxazoline), $\mathrm{Cu(OTf)_2}$, THF, −78 °C, 12 h (95%, 92% *ee*); b) MeZnI, $[\mathrm{Pd_2dba_3}]$, SPhos, THF, NMP, 65 °C, 2 h (83%); c) $\mathrm{CH_2I_2}$, $\mathrm{TiCl_4}$, Zn, $\mathrm{PbCl_4}$, $\mathrm{CH_2Cl_2}$, THF, 23 °C, 4 h (89%); d) DIBAl-H, $\mathrm{Et_2O}$, −78 °C; Dess–Martin periodinane, $\mathrm{CH_2Cl_2}$, 23 °C (91%). dba = dibenzylideneacetone, Dess–Martin periodinane = 1,1,1-triacetoxy-1,1-dihydro-1,2-benziodoxol-3-(1*H*)-one, DIBAl-H = diisobutylaluminumhydride, NMP = *N*-methylpyrrolidinone, OTf = trifluoromethane sulfonate, SPhos = 2-dicyclohexylphosphino-2′,6′-dimethoxy-1,1′-biphenyl, TMS = trimethylsilyl.

Under optimal conditions, the methyl ketone **15** was efficiently prepared by the cross-coupling of thiol ester **14** with methylzinc iodide using SPhos as a supporting ligand.[8] Methods employing more nucleophilic reagents were plagued by significant decomposition of the reactive cyclopropyl ketone **15**. Methylenation of the sensitive and sterically hindered ketone **15** was achieved using $\mathrm{CH_2I_2/Zn/TiCl_4}$ in the presence of catalytic $\mathrm{PbCl_4}$[9] to provide multigram batches of the methyl ester **16**. The conversion of ester **16** into the corresponding aldehyde (+)-**11** afforded the key building block for the synthesis of the spirocyclic AB-ring system of **1**–**4**. Given the presence of this substructure in a number of natural illudins, the efficiency of this aldol-based approach in securing the 2*R* stereochemistry of the intermediates in large quantities is noteworthy.[10]

The proposed EYRCM cascade (**8**→**6**; Scheme 1) would require the formation of a tetrasubstituted alkene on a sterically congested and fully substituted B ring.[11] We examined the EYRCM of dienynes **17a**–**f** (Table 1) to quickly probe the potential generality of this approach in the synthesis of the B ring. The dienyne substrates **17** were prepared by allyldimethylsilylation of the corresponding diol obtained by addition of the lithium acetylide of an appropriate alkyne to the key aldehyde **11**.[12] Gratifyingly, treatment of the dienynes **17** with the Grubbs second generation catalyst (**G2**)[13] afforded the desired corresponding tricyclic dienes **20** (Table 1).[14]

Table 1: Evaluation of the EYRCM strategy.[a]

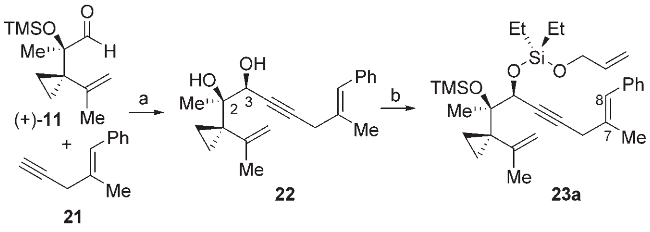


Entry	Substrate	R	Yield [%][b]
1	**a**	$\mathrm{CH_2CHMe_2}$	76[c]
2	**b**	$\mathrm{(CH_2)_2CH{=}CMe_2}$	64
3	**c**	$\mathrm{CH_2OPiv}$	66
4	**d**	$\mathrm{(CH_2)_4OPiv}$	66
5	**e**	$\mathrm{(CH_2)_2CHO}$	59
6	**f**	$\mathrm{(CH_2)_4I}$	52[d]

[a] Uniform reaction conditions (unless noted): **G2** (10 mol%), benzene, 65 °C, [**17**] = 0.02 M, 1 h. [b] Yield of the isolated product **20** after purification. [c] Toluene, 80 °C, 40 min. [d] *t* = 6 h.

Interestingly, this strategy not only provides the fully functional and substituted AB-ring system of many illudins,[15] but it also tolerates sensitive functional groups, such as an aldehyde or a primary iodide (Table 1, entries 5 and 6, respectively). Monitoring these reactions by ^{1}H NMR spectroscopic analysis in situ ([D$_6$]benzene) revealed excellent conversion of the starting dienynes into the EYRCM products. The yield of the isolated dienes **20** (Table 1) is diminished as a result of their sensitivity to chromatography on silica and alumina gel. Attempted protodesilylative transposition of the dienes **20** (namely, **6**→**5** in Scheme 1) to provide the vinyl group necessary for the final RCM was plagued by extensive decomposition. Additionally, tricycles **20** were found to be sensitive toward oxidative breakdown; for example, Tamao oxidation of product **20a** (Table 1, entry 1) gave the corresponding triol in poor yield (27%).[16] We reasoned that the use of an allyloxydialkylsilyl tether in the EYRCM cascade (**8**→**6**; Scheme 1) would not only obviate the need for the isolation of dienes **20**, but also permit alternative methods for the synthesis of the key triene **5** (Scheme 1).[17,18]

The successful synthesis of (−)-acylfulven and (−)-irofulven by using the above EYRCM strategy began with the rapid assembly of the key trienyne **23a** through the multigram scale coupling of the readily available aldehyde (+)-**11**, enyne **21**, and allyloxydiethylchlorosilane (Scheme 3).



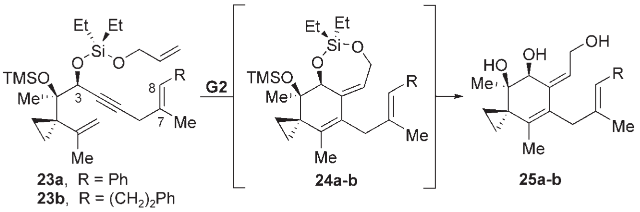
(+)-**11** + **21** → **22** → **23a**

Scheme 3. Synthesis of the trienyne **23a**. For clarity, the major diastereomer of the intermediates is shown. Reagents and conditions: a) **21**, LHMDS, THF, −78→−40°C; (+)-**11**; TBAF, AcOH (75%); b) $(Et)_2Si(Cl)OCH_2CH{=}CH_2$, 2,6-lutidine, CH_2Cl_2; TMSOTf, −78°C (83%). LHMDS = lithium hexamethyldisilazide, TBAF = tetrabutylammonium fluoride, TMSOTf = trimethylsilyltrifluoromethane sulfonate.

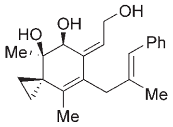
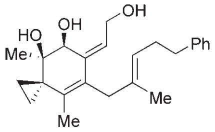
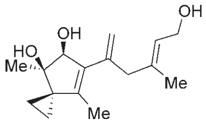
Addition of the corresponding lithium acetylide of enyne **21** (two steps from α-methylcinnamyl alcohol)[7] to (+)-**11** provided the diol **22** in 75% yield after desilylation of the immediate product from silyl migration (C2→C3) as a mixture of C3 diastereomers (3*S*/3*R* ≈ 6:1), thus favoring the Felkin–Ahn mode of carbonyl addition (Scheme 3). Given the final stage oxidation of the hydroxy group at C3 to the corresponding carbonyl group of the target compounds, both diastereomers were moved forward in the optimized synthetic sequence without chromatographic separation. The diastereomeric mixture of diol **22** was subjected to sequential secondary alcohol allyloxydiethylsilylation followed by trimethylsilylation of the tertiary alcohol at C2 to give trienyne **23a** (3*S*/3*R* = 6:1) in 83% yield in a single step (Scheme 3).[7] Protection of the tertiary hydroxy group of **22** was found to increase the stability of these trienynes during purification.

We were delighted to find that the treatment of **23a** with the Grubbs **G2** catalyst (15 mol%) in toluene (0.01 M) at 90°C afforded the desired dihydrodioxasilepine **24a** (≥90%; Table 2, entry 1) in 30 min, which was directly converted into the key triol **25a** (3*S*/3*R* = 6:1) in 74–79% yield of the isolated product. Thus, use of the allyloxysilyl tether in the key EYRCM cascade not only removed the need for the isolation of sensitive intermediates, but also led to a marked increase in the overall efficiency of the process.[19] The key triol **25a** contained all the necessary functional groups and the carbon skeleton needed for completion of the synthesis.

Table 2: Implementation of the EYRCM cascade.[a]



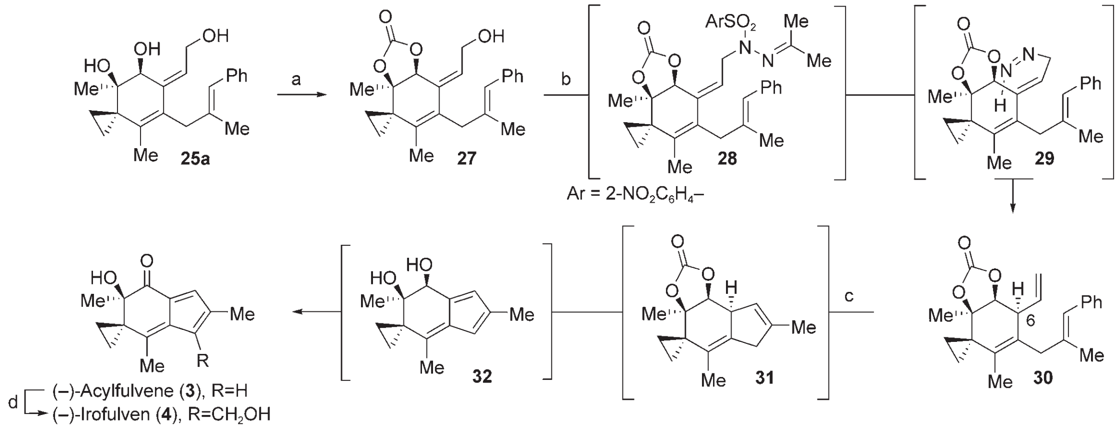
23a, R = Ph
23b, R = $(CH_2)_2Ph$
24a-b
25a-b

Entry	Substrate	Product		Yield [%]
1	**23a**		**25a**	74–79
2	**23b**		**25b**	52
			**26**	<20

[a] Reaction conditions: **G2** (15 mol%), toluene, 90°C, [**23**] = 0.01 M, 30 min, then TBAF, AcOH, THF, 23°C, 10 min.

Importantly, both C3 diastereomers of **23a** were equally effective substrates for this key EYRCM cascade. While this EYRCM cascade provided the desired triol with a range of dienyne substrates, a minor EYRCM by-product (**26**, Table 2, entry 2) was observed when employing trienyne **23b**.[20] Careful inspection of this transformation revealed that triol **26** was formed by sequential RCM involving the C7 alkene of **23b**, EYRCM, and C7 olefin isomerization.[7] Significantly, the by-product **26** is not observed when the C7–C8 segment is appropriately masked as in trienyne **23a** (also see Table 1, entry 2). Guided by this insight and using **23a**, multigram quantities of the desired triol **25a** (Table 2, entry 1) were prepared.

Sequential exposure of the key triol **25a** to TBSOTf (1 equiv) followed by triphosgene (1.5 equiv) and tetrabutylammonium fluoride (TBAF) afforded the desired alcohol **27** (Scheme 4), thus setting the stage for the planned reductive allylic transposition and RCM steps. The Mitsunobu displacement of alcohol **27** with 2-nitrobenzene-sulfonylhydrazide (NBSH) in *N*-methylmorpholine (−30→23°C) gave the triene **30** (6*S*/6*R* = 3:1) through a sigmatropic loss of dinitrogen from the intermediate monoalkyldiazene **29**.[21] The poor solubility of **27** in optimal solvents for this transformation and the required high concentration of reagents (≈0.3 M) led to variable yields of product **30** (35–54%). We found that use of the more stable acetone hydrazone of NBSH gave the (isolable) hydrazone **28** through an efficient Mitsunobu reaction at a more dilute concentration (≈0.1 M in



Scheme 4. Synthesis of **3** and **4**. For clarity, the major diastereomer of the compounds **25a**–**32** is shown. Reagents and conditions: a) TBSOTf, 2,6-lutidine, CH$_2$Cl$_2$, −78 °C; triphosgene; TBAF (67%); b) 2-NO$_2$C$_6$H$_4$SO$_2$NHN=CMe$_2$, DEAD, Ph$_3$P, THF, 0→23 °C; TFE, H$_2$O (71%); c) Grubbs **G2** catalyst (15 mol%), PhH, 78 °C; NaOMe; AcOH; DDQ (**30**→**3**, 30%)—or use chloranil to isolate **32** (70% from **30**) then IBX, DMSO (83%); d) H$_2$SO$_4$, CH$_2$O$_{aq}$ (63%). DDQ = 2,3-dichloro-5,6-dicyano-1,4-benzoquinone, DEAD = diethylazadicarboxylate, DMSO = dimethyl sulfoxide, IBX = *ortho*-iodoxybenzoic acid, TBSOTf = *tert*-butyldimethysilyltrifluormethane sulfonate, TFE = 2,2,2-trifluoroethanol.

THF) and without requiring sub-zero reaction temperatures or additives. Importantly, the addition of trifluoroethanol and water following the Mitsunobu displacement step led to in situ hydrolysis and fragmentation of **28** to give the desired triene **30** in 71 % yield of the isolated product (6*S*/6*R* = 3:1) from **27** (Scheme 4).

The **G2**-catalyzed RCM reaction of triene **30** afforded the sensitive tricyclic diene carbonate **31** (70 %, 6*S*/6*R* = 3:1). Initially, **31** was isolated and converted into the stable diol fulvene **32** by sequential dehydrogenation with DDQ followed by hydrolysis of the cyclic carbonate. We later discovered that addition of sodium methoxide upon completion of the RCM reaction, followed by treatment with chloranil gave the desired diol **32** with greater overall efficiency (70 %). Treatment of **32** with IBX in DMSO provided the target compound (−)-acylfulvene (**3**) in 83 % yield.[3a] Importantly, simple exchange of chloranil with DDQ provided **3** from **30** without isolation of the intermediates in 30 % yield in a sequence that involved RCM, methanolysis, and two consecutive dehydrogenation reactions. (−)-Acylfulvene (**3**) was converted into (−)-irofulven (**4**) based on conditions described by McMorris and co-workers.[3a] Spectroscopic data of our synthetic (−)-**3** and (−)-**4** matched those in the literature.[7]

The powerful EYRCM and RCM reactions play key roles in our enantioselective total synthesis of **3** and **4**. Only five intermediates (**22**, **23a**, **25a**, **27**, and **30**) need to be isolated in the conversion of the readily available aldehyde (+)-**11** and alkyne **21** to (−)-acylfulvene (**3**), the direct precursor to the potent anticancer agent (−)-irofulven (**4**). Noteworthy features of this chemistry include an aldol addition strategy that uses new reagent **12** to secure the stereochemistry at C2, a general EYRCM cascade to introduce the AB-ring system of these compounds, and the development of new conditions for the generation of a transient monoalkyldiazene species for reductive allylic transposition. The application of this chemistry to the synthesis of other cytotoxic illudins is underway. This synthetic route is expected to provide ready access to derivatives of **3** and **4** not available through semisynthesis.

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[18] Initial EYRCM reactions to test the new allyloxydiethylsilyl tether were successfully carried out on dienynes related to those described in Table 1.

[19] The EYRCM reaction of the C2 hydroxy variants of trienynes **23a–b** exclusively gave the desired triols **25a–b**, respectively, in approximately 50% yield of the isolated product, but required a longer reaction time and higher catalyst loadings.

[20] The trienyne **23b** was prepared according to the procedure described for the trienyne **23a**.

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