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Diastereoselective syntheses of substituted cis-hydrindanones featuring sequential inter- and intramolecular Michael reactions

Junjia Liu[#§], **Maurice A. Marsini**[#‡], **T. Aaron Bedell**, **Paul J. Reider**, and **Erik J. Sorensen**[*]

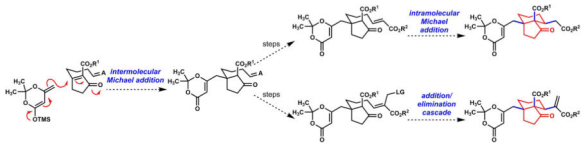
Department of Chemistry, Princeton University, Frick Chemical Laboratory, Princeton, NJ 08544, USA

[#] These authors contributed equally to this work.

Abstract

The hydrindane (bicyclo[4.3.0]nonane) structural motif (**1**) and related *cis*-1-hydrindanone skeleton (**2**) are common substructures in many natural products. Herein, we describe efficient access to substituted *cis*-1-hydrindanones enabled by a sequence of Michael reactions. A copper-catalyzed intermolecular Michael addition of a cyclic silyl ketene acetal to a β-substituted-α-alkoxycarbonyl-cyclopentenone enables construction of a quaternary center and is followed, after incorporation of an additional Michael acceptor, by a second, intramolecular addition of a nucleophilic β-ketoester. This strategy affords stereoselective access to substituted bicyclic *cis*-hydrindanone ring systems containing up to three contiguous stereocenters.

Graphical Abstract



Keywords

hydrindanone; Michael reaction; conjugate addition; 1,4-addition; olefin cross metathesis; linchpin

[*] Corresponding authors. Tel.: +1-609-258-8135; fax: +1-609-258-1980; ejs@princeton.edu.
[§]Present address: Eastman Chemical Company, P.O. Box 1972, Kingsport, TN 37662, USA.
[‡]Present address: Boehringer Ingelheim Pharmaceuticals, 900 Ridgebury Rd, Ridgefield, CT 06877, USA.

Supplementary data

Supplementary data associated with this article (experimental procedures, characterization of new compounds and spectra) can be found in the online version. X-ray crystallographic data for compounds **35** and **54** have been deposited at the Cambridge Crystallographic Data Centre under the numbers CCDC 847896 and 847897. These data can be obtained free of charge from The Director, CCDC, 12 Union Road, Cambridge CB2 1RZ, England, or *via* www.ccdc.cam.ac.uk/data_request/cif.

1. Introduction

The hydrindane skeleton (**1**) is a ubiquitous structural element in diverse families of biologically active natural products.[1] Within this family, substituted *cis*-1-hydrinanone (**2**) and its structural derivatives are found in numerous polycyclic natural products, such as pinguisone (**3**),[2] pleuromutilin (**4**),[3] exiguaquinol (**5**),[4] aplykurodinone-1 (**6**),[5] bromotetrasphaerol (**7**)[6] and thiersindole B (**8**) (Figure 1).[7] Our laboratory has a long-standing interest in the rapid generation of molecular complexity, particularly in the context of biologically active secondary metabolites,[8a] and we became interested in applying this concept to the general construction of *cis*-1-hydrindanones, *en route* to pleuromutilin (**4**) and pleuromutilin-like scaffolds.[8b,c] We report herein the development of a strategy for synthesizing substituted *cis*-hydrindanones that is founded on sequential inter- and intramolecular Michael reactions.[9]

Our strategy was designed around the powerful carbon–carbon bond-forming Michael reaction (Scheme 1). We envisioned that silyl ketene acetal **9**[10] could readily engage a β-substituted-αcarboalkoxy-cyclopentenone (**10)** in a 1,4-conjugate addition, generating β-ketoester **11,** and a quaternary center in the process.[11] After unveiling a latent Michael acceptor, we would be poised for a second, intramolecular Michael addition of the β-ketoester domain. This Michael addition would presumably proceed *via* a chair-like transition state and give rise to the desired *cis*-hydrindanone framework (**13**). Alternatively, incorporation of an internal Lawton-style reagent[12] would act as a Michael acceptor and bifunctional “linchpin” motif to regenerate a reactive α,β-unsaturated carbonyl (**15**) for use at a later stage.

2. Results and Discussion

To test our proposed strategy, we began by pursuing the construction of a suitable cyclopentenone precursor **10** utilizing technology developed by Crimmins involving a formal [3 + 2] cycloaddition of a zinc homoenolate to an acetylenic ester.[13a] To this end, commercially available hexyn-1-ol (**16**) was protected as its benzyl ether (Scheme 2).

Deprotonation of the alkyne with *n*-butyllithium and subsequent quenching with methyl chloroformate provided the desired alkynoate **17** in 86% yield over two steps. When **17** was treated with zinc homoenolate **18** in the presence of 1,3-dimethyl-3,4,5,6-tetrahydro-2(1H)-pyrimidinone (DMPU),[13b] trimethylsilyl chloride (TMSCl), and catalytic copper(I) bromide-dimethyl sulfide complex, the desired cyclopentenone **19** was generated in 65% yield. Pleasingly, treatment of **19** with silyl ketene acetal **9** and a catalytic amount of copper(II) triflate gave rise to **20** in 80% yield. Of particular note is the fact that reagent **9** proved to be a dependable candidate for conjugate addition to doubly activated enones[14] to build quaternary stereocenters, while also serving as a protected β-ketoester and latent source of acylketene.

After hydrogenolysis of benzyl ether **20**, the resultant alcohol **21** was subjected to several different oxidation conditions. However, the resulting intermediate aldehyde **22** was found to be unstable, undergoing a facile and irreversible ring-forming aldol reaction with the

pendant β-ketoester. To prevent this undesired ring formation, the β-ketoester domain of **20** was protected *via* the corresponding triisopropylsilyl (TIPS) and methoxymethyl (MOM) enol ethers (**23** and **24**, respectively) to suppress its nucleophilicity (Scheme 3). Subsequent debenzylation afforded alcohols **25** and **26** in good yield. With the nucleophilic domain masked, alcohol **25** could be converted to aldehyde **27** in high yield. Unfortunately, subsequent investigations with aldehyde **27** illustrated its lack of stability in the presence of a relatively strong base (e.g. DBU) and silyl group cleavage was followed by the previously observed, undesired ring-forming aldol. The MOM-protected derivative **28** was found to be much more stable and was used for the remainder of our studies.

A Knoevenagel[15] condensation between aldehyde **28** and dimethyl malonate could be achieved in moderate yields under the conditions shown in Scheme 4. The use of powered 4Å molecular sieves was found to be critical for the outcome of this reaction; attempts to use molecular sieves in other forms were unsuccessful (Scheme 4). Upon exposure to dry HCl, the MOM-ether of **31** was cleaved to reveal the corresponding unprotected β-ketoester and the desired intramolecular Michael reaction occurred instantaneously. This process generated *cis*-hydrindanone **35** with three contiguous stereocenters, of which two are quaternary, in good yield and with high diastereoselectivity (>10:1). The relative stereochemistry of the major diastereomer was confirmed by X-ray crystallographic analysis. An analogous sequence of reactions transformed the related bis-allyl ester **32** into *cis*-hydrindanone **36**.

We next wished to probe how electron-deficient the pendant Michael acceptor needed to be for efficient cyclization to occur (Scheme 5). Aldehyde **28** was easily converted to ester **38** *via* a Horner–Wadsworth–Emmons olefination.[16] While the acid-catalyzed hydrolyses of the MOM ethers in compounds **31** and **32** was attended by spontaneous intramolecular Michael reactions, the cleavage of the MOM ether in **38** simply afforded the corresponding β-ketoester **39**. Nevertheless, a diastereoselective, ring-forming Michael reaction could be induced by warming a solution of compound **39** and the amidine base DBU in dichloromethane to 40 °C; this bond construction gave compound **40** in 94% yield.

Having constructed contiguous, quaternary stereocenters via sequential Michael reactions, we sought an effective synthesis of a *cis*-hydrindanone of the type **15** (Scheme 1); our intent was to utilize this type of compound in a third Michael reaction to give the molecular architecture of the pleuromutilin class of antibiotics. Our approach to the functional group-rich hydrindanone **15** would retain the logic of the sequential Michael reactions, although we wanted to reduce the high step count (e.g. the path from **16** to **40** required 10 steps with an overall yield of 12%) and our previous reliance on functional group manipulations. To achieve these aims, we would pursue an approach featuring an olefin cross metathesis (CM) given its proven capacity to directly transform simple, terminal olefins into functionalized, substituted olefins.[17] Our path to structural type **15** would pass through a multifunctional intermediate of the type **14** (Scheme 1), and we hoped that a late-stage CM would produce the bifunctional and potentially delicate trisubstituted alkene for a final, pivotal Michael cyclization/elimination sequence.

To our delight, compound **46** is readily available from commercially available 2,3-dihydrofuran (**41**) and 5-iodo-1-pentene (**42**) by a known, three-step sequence of reactions involving intermediates **43-45** (Scheme 6).[18] When an ethereal solution of compound **46** was treated with aqueous sodium hydroxide, a Knoevenagel cyclocondensation[15] occurred and gave rise to cyclopentenone **47** in 61% yield. Under reaction conditionsanalogous to those shown in Scheme 2, a copper(II) triflate-catalyzed addition of silyl ketene acetal **9** to the doubly-activated alkene in **47** gave rise to a somewhat unstable β-ketoester, which was converted directly to the vinylogous MOM carbonate **48**.

After a preliminary investigation of CM on related substrates, we were delighted to observe that treatment of alkene **48** with commercially available bromo ester **49** in the presence of Grubbs's 2nd-generation metathesis catalyst[17] could generate the desired cyclization precursor **50** in modest yield (Scheme 7). Although the desired intramolecular Michael reaction did not spontaneously occur during the acid-catalyzed hydrolysis of the MOM group in **50**, the addition of DBU to a solution of β-ketoester **51** in dichloromethane induced efficient cyclization to afford α,βunsaturated ester **53**. While the yield for incorporating the bromomethyl enoate structural element by CM was modest, our diastereoselective synthesis of the functionalized *cis*-hydrindanone **53** from compound **47** was only five steps.

From the vantage point of compound **53**, it was not possible to replace the ring junction ester or its derived carboxyl group with hydrogen, presumably due to the strained nature of the transition state for decarboxylation.[19] Nevertheless, we could achieve this aim by cleaving the *tert*-butyl ester function earlier in the sequence and executing the decarboxylation either just before or in the course of the base-mediated annulation of the six-membered ring (Scheme 8). Exposure of compound **50** to trifluoroacetic acid (TFA) in dichloromethane at 0 °C → rt caused the successive cleavages of the MOM and *tert*-butyl ester groups and afforded the putative β-ketoacid **55** (confirmed by IR of the crude reaction mixture). Without isolation, the reaction mixture was concentrated *in vacuo* and taken up in dichloromethane. A subsequent addition of DBU then accomplished a smooth decarboxylative Michael addition/cyclization with concomitant bromide elimination to afford *cis*-hydrindanone **54** in 52% yield and >10:1 dr for the one-pot process. After several attempts, crystals of **54** were obtained and analyzed by X-ray crystallography; the ORTEP figure shown in Scheme 8 unambiguously confirmed our stereochemical assignment. Overall, this design comprising an intermolecular Michael reaction, an olefin cross metathesis, and a final Michael cyclization/E1cB-elimination sequence has permitted a rather direct and diastereoselective synthesis of the potential pleuromutilin building block **54**.

3. Conclusion

The studies described herein provide further demonstrations of the relative insensitivity of the Michael reaction toward alkene substitution and its considerable power for forming somewhat crowded carbon-carbon bonds.[9] This venerable reaction is superbly suited for effective syntheses of highly substituted and multifunctional *cis*-hydrindanones, and our efforts to feature it in stereocontrolled syntheses of biologically active natural products are ongoing.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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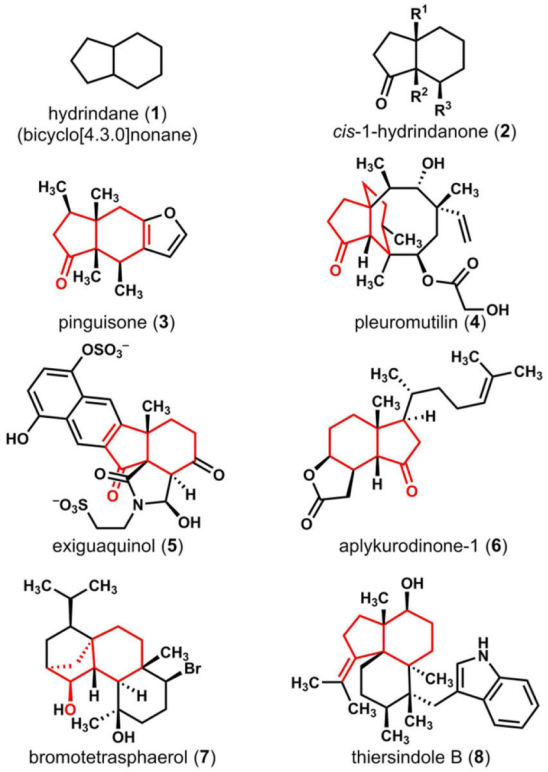
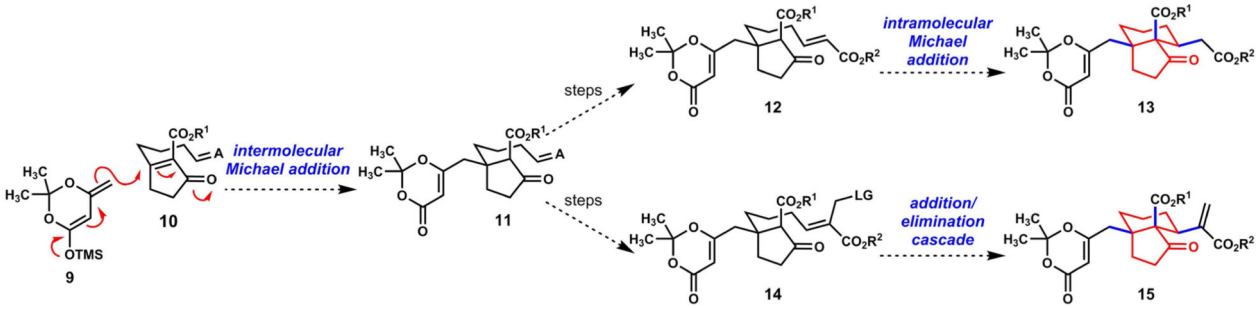
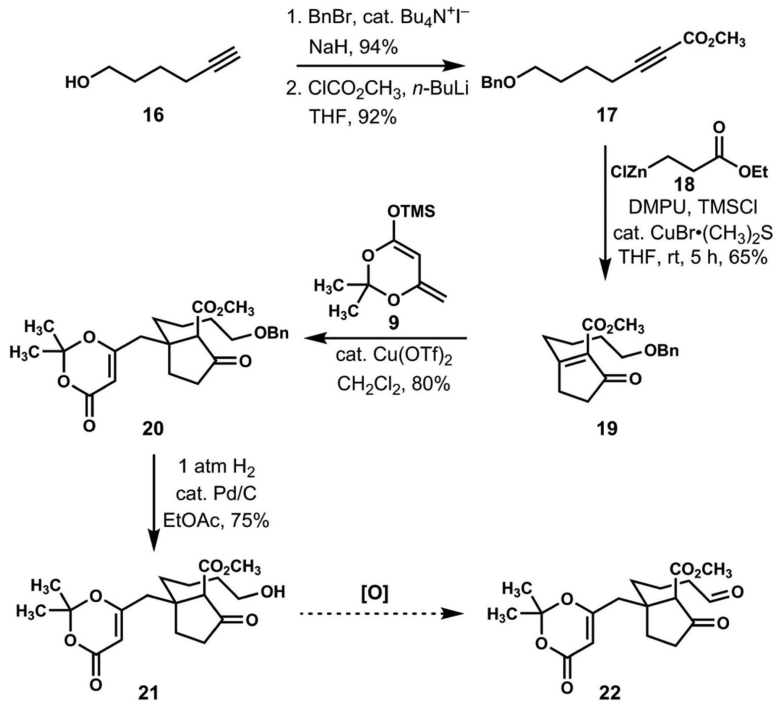


Figure 1.
Natural products containing the *cis*-hydrindane motif.



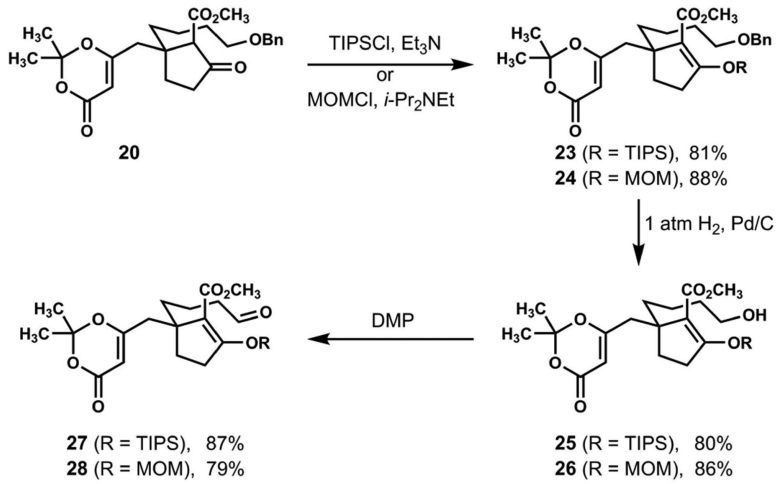
Scheme 1.

A general strategy for *cis*-1-hydrindanone synthesis utilizing sequential Michael additions. A = CH_2 or O; LG = leaving group.



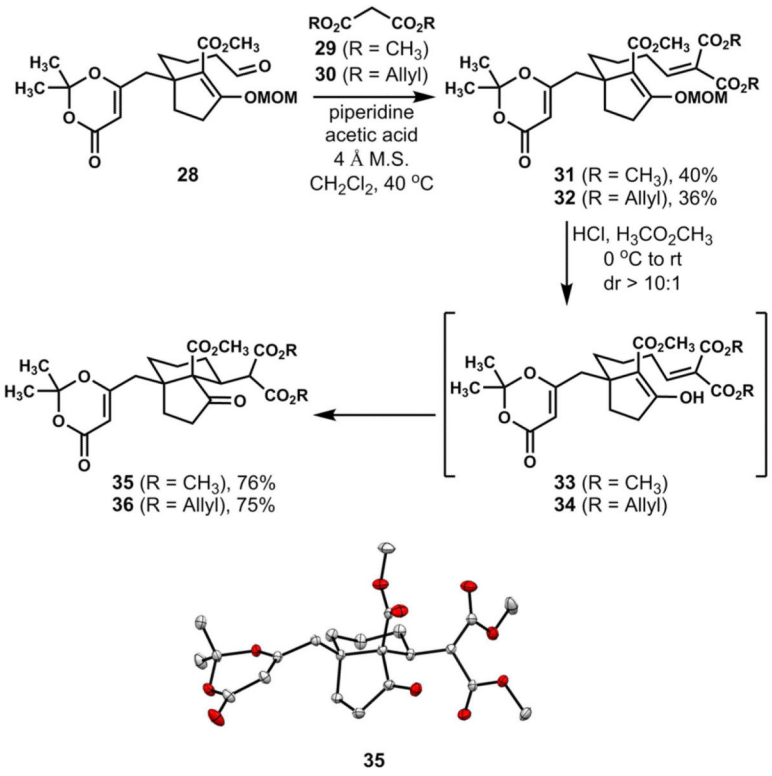
Scheme 2.

Quaternary stereocenter formation *via* intermolecular Michael addition of silyl ketene acetal **9** to cyclopentenone **19**. DMPU = 1,3-dimethyl-3,4,5,6-tetrahydro-2(1H)-pyrimidinone; TMSCl = trimethylsilyl chloride; THF = tetrahydrofuran.



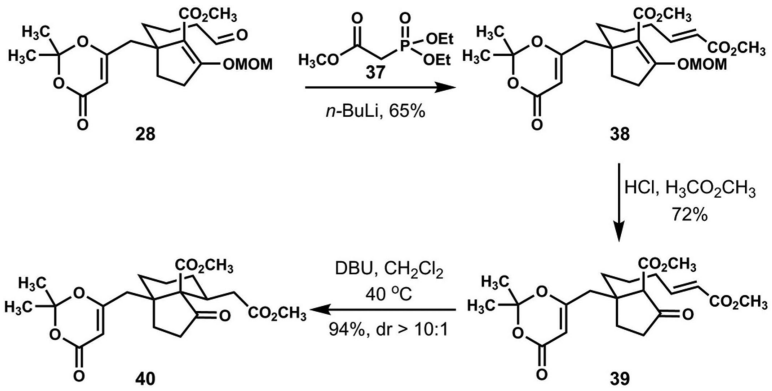
Scheme 3.

Protection of the β-ketoester domain. TIPS = triisopropylsilyl; MOM = methoxymethyl; DMP = Dess–Martin periodinane.



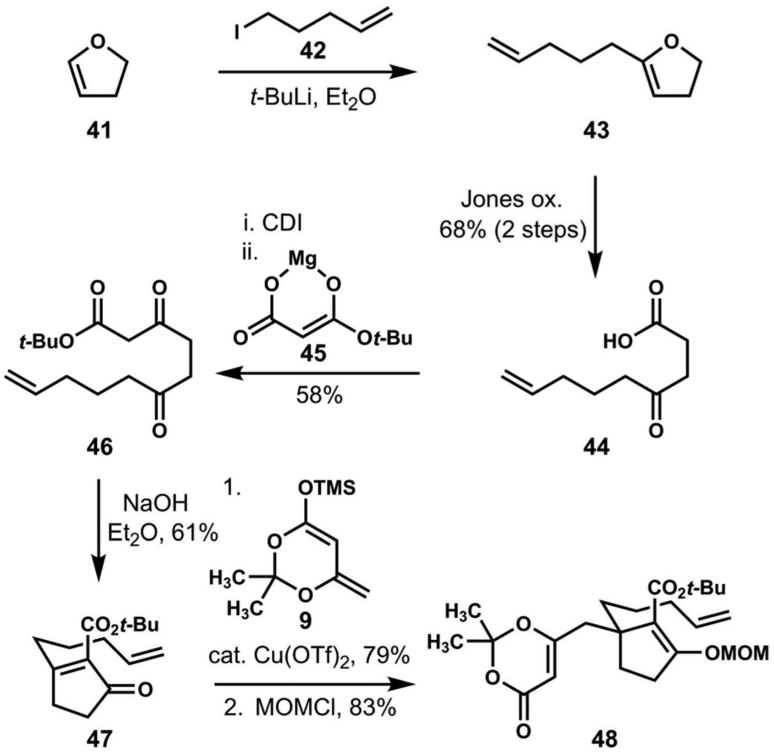
Scheme 4.

Diastereoselective synthesis of *cis*-hydrindanes **35** and **36**. M.S. = molecular sieves.



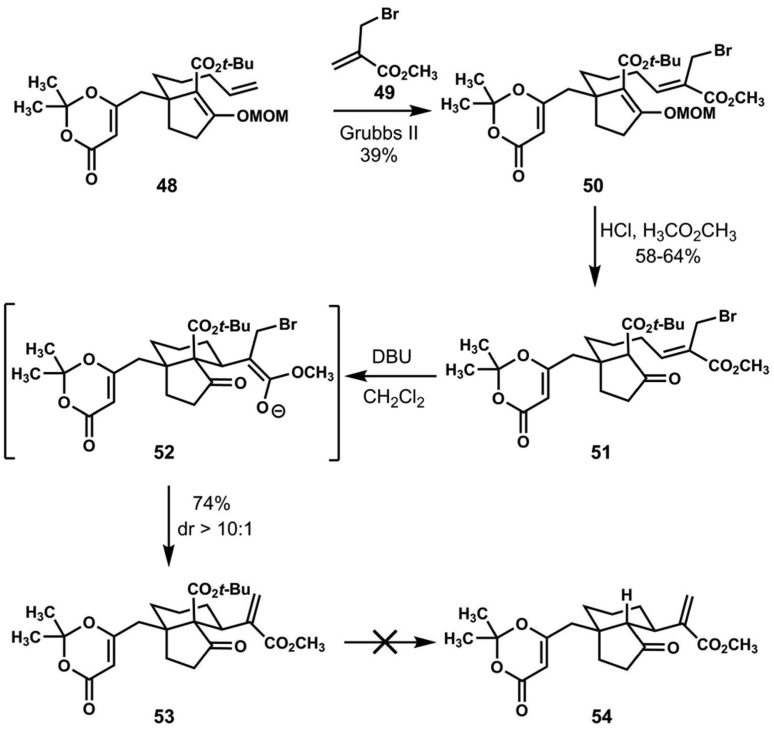
Scheme 5.

Synthesis of *cis*-hydrindane **40**. DBU= 1,8-diazabicyclo[5.4.0]undec-7-ene.



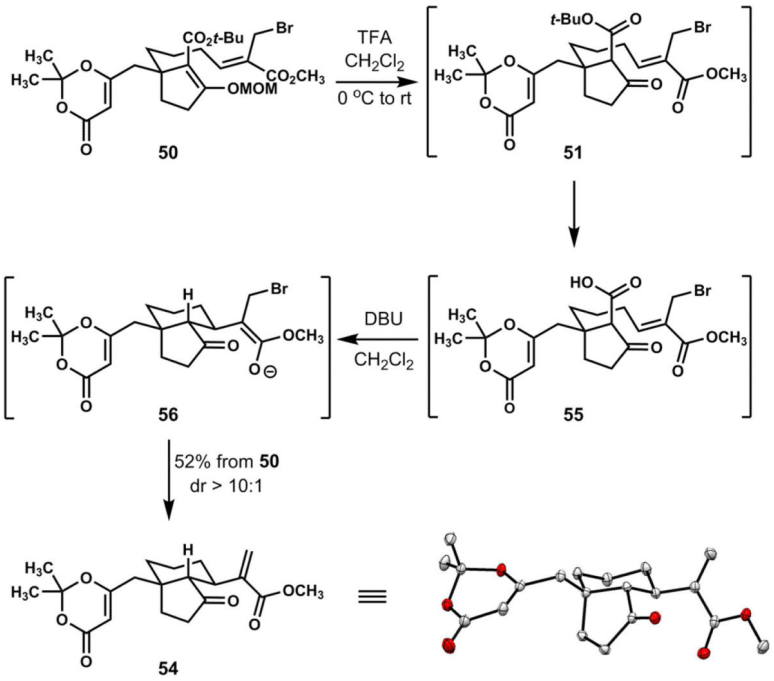
Scheme 6.

Efficient cyclopentenone synthesis. CDI = carbonyl diimidazole.



Scheme 7.

Synthesis of *cis*-hydrindane **53**. Grubbs II = Grubbs's 2nd-generation olefin metathesis catalyst.



Scheme 8.

Synthesis of *cis*-hydrindane **54** by a one-pot decarboxylative cyclization/elimination sequence. TFA = trifluoroacetic acid.