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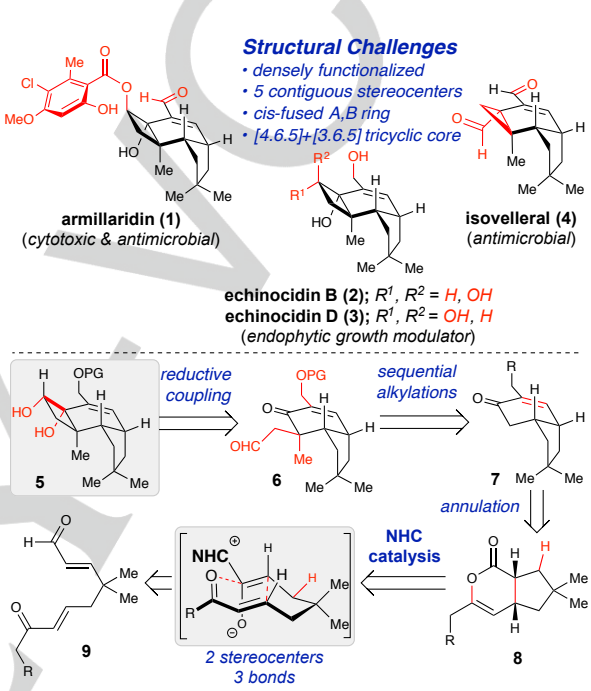
A Carbene Catalysis Strategy for the Synthesis of Protoilludane Natural Products**

M. Todd Hovey,[a] Daniel T. Cohen,[a] Daniel M. Walden,[b] Paul H-Y. Cheong,[b] and Karl A. Scheidt*[a]

Dedicated to Prof. Dr. W. Robert Scheidt on the occasion of his 75th birthday

Abstract: The *Armillaria* and *Lactarius* genera of fungi produce antimicrobial and cytotoxic mellolide, protoilludane, and marasmane sesquiterpenoids. Herein, we report a unified synthetic strategy to access the protoilludane, mellolide, and marasmane families of natural products. The significance of these syntheses lies in a) the organocatalytic, enantioselective construction of key chiral intermediates from a simple achiral precursor, b) the utility of a key 1,2-butanediol intermediate to serve as a progenitor to each natural product class, and c) a direct chemical conversion of a protoilludane to a marasmane via serendipitous ring contraction, providing experimental support for their proposed biosynthetic relationships.

The rise in bacterial resistance to current treatments is a critical threat to society.[1] Since the discovery of penicillin, global research activity has taken inspiration from natural products to drive the development of new antimicrobial therapeutics.[2] The antimicrobial protoilludane and marasmane sesquiterpenoids were isolated in the 1960s from the *Armillaria mellea* and *Lactarius vellereus* species of parasitic basidiomycetes fungi (Scheme 1, **1**-**4**).[3] These compounds gained attention for their structurally unique and densely functionalized perhydrocyclobuta[*e*]indene and related frameworks.[4] Recently, the mellolide armillaridin (**1**) has gained considerable attention for possessing apoptotic and radiosensitizing activity towards several cancer cell lines.[3a-c, 3e] The biosynthetically related marasmanes (including isovelleral, **4**), exhibit broad-spectrum antimicrobial and anti-feedant activity.[3g, 5] These tricyclic sesquiterpenoids have five contiguous stereocenters, a *cis*-fused cyclohexyl/cyclopentyl ring system, at least one quaternary carbon, a vicinal cyclobutane-diol, as well as an α,β-unsaturated aldehyde. An asymmetric catalytic strategy that could efficiently address these architectural challenges would add to the body of work dedicated to synthesizing complex natural products through catalysis. Notably, Banwell has reported a chemoenzymatic route to access members of the mellolide family as single antipodes.[6] However, abiotic asymmetric catalysis has not been successfully utilized to generate either the mellolides or protoilludanes.[4]



Scheme 1. Overall Synthesis Plan.

Biological systems frequently employ linear substrates to quickly prepare complex molecules. In this regard, we sought to utilize our previously developed *N*-heterocyclic carbene (NHC)-catalyzed asymmetric annulation reaction to construct the difficult *cis*-fused octahydro-1*H*-indene ring systems found in the mellolides and protoilludanes from a linear precursor (i.e., **9**).[7] In contrast, the *trans*-fused [5.6] carbocyclic system can be prepared by enolate annulations, compelling us to examine our methodology in the context of these specific targets.[8] Moreover, developing a unified approach to this core would provide opportunities to prepare several members of each family and analogs to further translational/chemical biology investigations.

Two major disconnections anchor our retrosynthetic approach. We initially identified the late stage intermediate triol **5** as the key divergence point (Scheme 1). We envisioned the vicinal cyclobutane-diol functional group arising from a pinacol-type reductive coupling.[9] To the best of our knowledge, this approach toward cyclobutane-diols has not been utilized in complex total synthesis.

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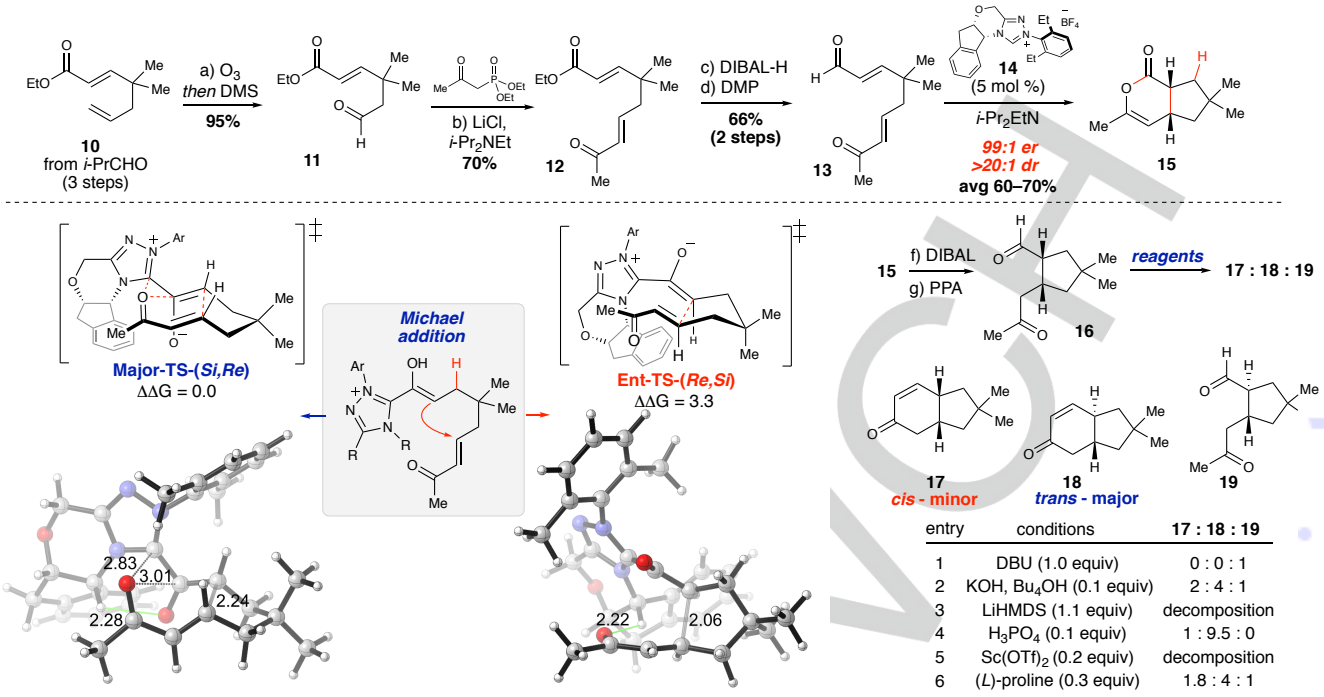

entry	conditions	17 : 18 : 19
1	DBU (1.0 equiv)	0 : 0 : 1
2	KOH, Bu_4OH (0.1 equiv)	2 : 4 : 1
3	LiHMDS (1.1 equiv)	decomposition
4	H_3PO_4 (0.1 equiv)	1 : 9.5 : 0
5	$Sc(OTf)_2$ (0.2 equiv)	decomposition
6	(*L*)-proline (0.3 equiv)	1.8 : 4 : 1

Scheme 2. Exploration of NHC-catalyzed annulation strategy. See Supporting Information for more details.

The pinacol-coupling substrate, enone **6**, would be prepared from *cis*-fused carbocycle **7**. This intermediate could arise from bicyclic lactone **8** leading back to the second key strategic disconnection, affording annulation linear precursor **9**. In the forward sense, we anticipated that an asymmetric intramolecular NHC annulation we previously developed could yield the desired lactone **8**, serving as the key enantioselective step by selectively installing the two key *cis*-stereocenters.[10] Our synthesis commenced with 1,5-dienoate **10**, prepared in large quantities (>100 g) over three steps from isobutyraldehyde (Scheme 2).[11] A large-scale (>60 g) ozonolysis of enoate **10** furnished aldehyde **11** in excellent yield. A Masamune-Roush modified Horner-Wadsworth-Emmons (HWE) olefination afforded enone **12** in good yield.[12] A careful diisobutylalumnium hydride (DIBAL-H) reduction followed by Dess-Martin oxidation yielded the desired enal substrate **13** in gram quantity. The exposure of acyclic enals to NHC pre-catalyst **14** in the presence of amine bases affords vinyl lactone products.[10a] The conversion of enal **13** to lactone **15** was achieved in 61% isolated yield and 99:1 *er* with low catalyst loading (5 mol %). To gain insight on the stereoselection aspects of this annulation, we employed Gaussian calculations to probe the transition state energies. These efforts revealed a unique mode of stabilization in which the formal step-wise [4+2] annulation more closely resembles a [4+3] type process (see SI, Fig. S1). The electron deficient nature of the NHC carbon (**Major-TS)** appears to interact favorably with the forming alkoxide of the enone oxygen through electrostatic attraction, which affords improved stability of the transition state leading to the *cis*-fused product **15**. The annulation was followed by reduction of lactone **15** to a lactol, which upon treatment with acid yielded keto-aldehyde **16**. Unfortunately, further elaboration of this key intermediate to the desired bicyclic *cis*-enone **17** was complicated by the generation of the isomeric *trans*-enone **18** and the epimeric keto-aldehyde **19**, prompting revision of our synthetic strategy (Scheme 2, *entries 1–6*). Calculations of the ground state energies of **16** and **19** identified a 1.7 kcal preference for *trans*-epimer **19**, which explains the appearance of *trans*-enone **18** as the major annulation product (see SI, Fig. S2). We surmised that an intramolecular Horner-Wadsworth-Emmons olefination strategy utilizing α–ketophosphonate **20** as an acylic substrate (Scheme 3) could circumvent the need for epimerically labile intermediates like keto-aldehyde **16**.

Consequently, ketophosphonate **20** was prepared by α–iodination of ketone **12**,[13] an Arbuzov reaction to yield the corresponding α–ketophosophonate, followed by global DIBAL-H reduction and subsequent manganese dioxide double oxidation to afford enal **20**, carried out on a large scale (> 10 g). Employing our NHC annulation yielded lactone **21** on decagram scale, exhibiting superlative enantioselectivity and diastereoselectivity. Of particular note, an NHC annulation on this scale is rare, underscoring the robust nature of the highly selective process.

Our attention turned toward investigating lactone **21** as the precursor to the required *cis*-fused enone **7**. Our initial studies on the reduction of lactone **21** to intermediary lactol **IV** unexpectedly yielded small quantities of phosphonate-enone **22**. An evaluation of hydride reagents identified the sterically hindered lithium tri-*tert*-butoxyaluminium hydride as optimal for yielding enone **22**. The required hydroxy-methylene functional group was installed through hydrogenation, olefination, and regioselective hydrobromination to yield bromohydrin **23**. Silylation of the primary alcohol of **23** followed by addition of lithium carbonate promoted elimination of the bromide to yield enone **24** in good yield on gram scale. Attempts to alkylate or allylate the a'-position of enone **24** using common enolization conditions initially yielded only recovered starting material, *O*-alkylation products, or oxidation to the phenol (not shown). We determined that formation of the desired α-ketoester **25**

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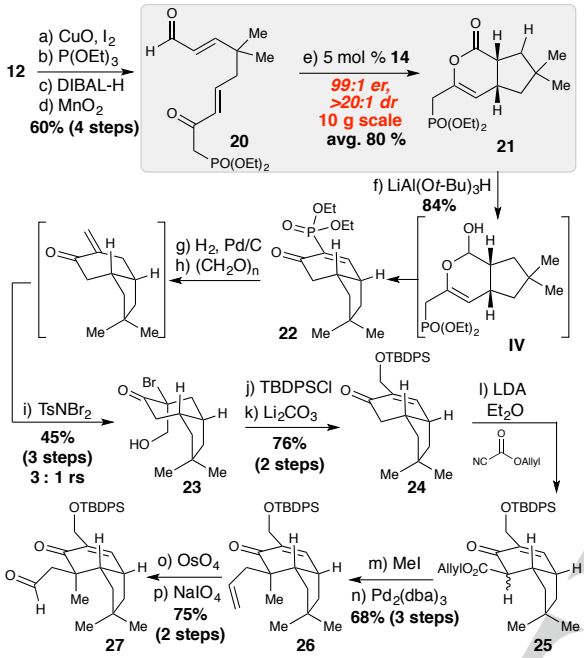
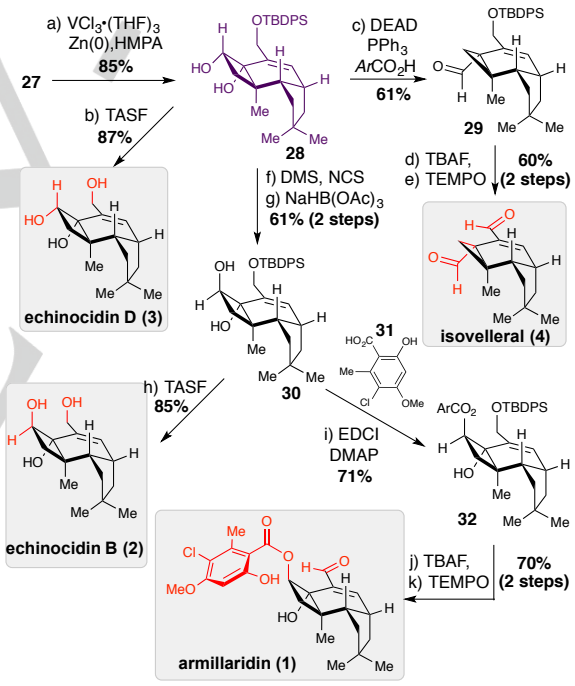
depended on a precise temperature profile during preparation of the lithium enolate. Methylation of α-ketoester **25** (>10:1 dr) followed by palladium-catalyzed diastereoselective Tsuji-Trost-Stoltz decarboxylative allylation (>20:1 dr) afforded the desired diastereomer of alkylated enone **26**.[14] Oxidative cleavage of the olefin delivered the desired aldehyde **27** with the necessary aldehyde functional group installed.



Scheme 3. Synthesis of reductive coupling susbstrate. See Supporting Information for more details.

Our attention turned toward synthesizing key intermediate *cis*-cyclobutane-diol **28** using an intramolecular pinacol reductive coupling strategy (Scheme 4). A report by Pedersen in 1991 highlighted a single example of a cyclobutane-diol (*cis* or *trans)* being prepared from 4-oxo-butanals using an *in situ* prepared vanadium(II)/ zinc(II) bimetallic complex.[9b] In contrast, a majority of intramolecular pinacol-type reductive couplings utilize titanium(III) species.[9a] Fortunately, the desired *cis*-cyclobutane-diol **28** was generated under modified Pedersen conditions (pH 7 buffer quench), which avoided decomposition under standard work up conditions (Scheme 4). To the best of our knowledge, this step serves as the first example of producing a cyclobutane diol from an enone/aldehyde in complex total synthesis.[15] Intermediate **28** serves as the key divergence point in order to complete the unified total synthesis of the protoilludane, mellolide and marasmane natural products.

The final phase of our synthetic route commenced with the desilylation of *cis*-diol **28** by exposure to anhydrous TAS-F, affording the protoilludane echinocidin D (**3**) cleanly and in high yield, constituting the first total synthesis of this protoilludane triol (Scheme 4).[3i, 16] Spectroscopic characterization of synthetic echinocidin D (^{1}H and ^{13}C NMR, IR, $[\alpha]^D$, HRMS) matched all data reported for the natural compound, while simultaneously confirming the absolute stereochemistry established in our enantioselective NHC annulation and the correct diastereomer of cylcobutane-diol **28** had been synthesized.[3i] Our attempts to convert the *cis*-diol **28** directly to orsellinate **32** using orsellinic acid derivative **31** under Mitsunobu reaction conditions yielded no desired product. Interestingly, when using *para*-nitrobenzoic acid we observed an unexpected semi-pinacol ring contraction to yield cyclopropane **29**. While the general idea that protoilludanes and marasmanes are biogenetically related through carbon skeleton rearrangement was advanced by Nozoe[17], this particular transformationhas not been explored or experimentally validated until our serendipitous discovery of **28** undergoing conversion to **29**, albeit under non-biological conditions.[18] From cyclopropane **29**, a deprotection using tetrabutylammonium fluoride (TBAF) buffered with acetic acid followed by oxidation using 4-NHAc-TEMPO under acidic conditions produced isovelleral (**4**) in good yield.[6] The spectral data (1H and 13C NMR, IR, α[D]) of synthetic isovelleral (**4**) matched the reported spectral data, which confirms our structural assignment of the unusual ring-contraction cyclopropane product **29**.



Scheme 4. Synthesis of armillaridin (**1**), echinocidin B&D (**2**&**3**), and isovelleral (**4**). See Supporting Information for more details.

To access mellolide armillaridin (**1**), the inversion of the secondary alcohol of *cis*-diol **28** to the *trans* configuration was compulsory and an oxidation/directed reduction sequence was explored. A Corey-Kim oxidation afforded the desired intermediate ketone.[19] A directed reduction with sodium triacetoxyborohydride yielded the desired *trans*-diol **30** (12:1 dr) and subsequent desilylation with TAS-F yielded protoilludane echinocidin B (**2**), which possessed spectroscopic data in agreement with published data.[3h] The synthesis of echinocidin B (**2**) confirms the *trans*-diol stereochemistry of the penultimate intermediate **30** as well as represents the first total synthesis of this protoilludane triol. The esterification of *trans*-diol **30** with

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orsellinic acid derivative **31** using EDCI afforded orsellinate ester **32**.[20] The exposure of orsellinate **32** to TBAF buffered with acetic acid gave facile (<15 min) deprotection to the allylic alcohol, which was then oxidized using a 4-NHAc-TEMPO/*para*-toluensulfonic acid combination to yield armillaridin (**1**). The spectral data of synthetic armillaridin (**1**) matched all reported data on the natural material, thus completing the first total synthesis of this natural product.[3a, 3d]

In total, the unified total syntheses of the protoilludanes, mellolides, and marasmane have been achieved through a key organocatalytic enantioselective annulation. The elaboration of key bicyclic lactone **21** is the molecular springboard from which the first enantioselective total syntheses of protoilludanes echinocidin B (**2**), echinocidin D (**3**) and mellolide armillaridin (**1**) as well as the synthesis of the marasmane isovelleral (**4**) are accomplished. The vanadium(II)/zinc(II) reductive coupling yielded the final ring of the densely functionalized *cis*-fused carbocyclic core. Lastly, the unexpected semi-Pinacol-type ring contraction to establish cyclopropyl aldehyde **29** from the cyclobutane-diol **28** is potentially biomimetic in origin. With a succinct and unified route to these classes of biologically active compounds further investigations into their biology and therapeutic potential are now ongoing.

Keywords: Total Synthesis • NHC • Armillaridin • Protoilludane • Marasmane

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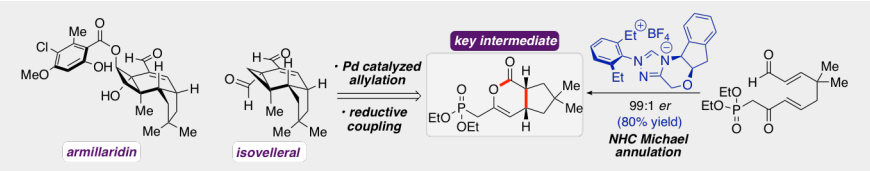

The first total syntheses of the protoilludanes armillaridin and echinochidins B/D are reported. Notable features of the unified synthesis include: i. A large-scale enantioselective NHC-catalyzed annulation to establish the critical *cis*-cyclopentane core of the products' [5.6] fused backbones; ii. A late-stage vanadium(II)/zinc(II)-promoted reductive pinacol coupling to give an advanced *cis*-cyclobutane-diol intermediate; iii. A serendipitous and potentially biomimetic ring-contraction of the protoilludane skeleton to give the marasmane core, which was verified by total synthesis of the related marasmane natural product isovelleral.

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