A New Organocatalytic Desymmetrization Reaction Enables the Enantioselective Total Synthesis of Madangamine E

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Abstract:

The enantioselective total synthesis of madangamine E has been completed in 30 steps, enabled by a new catalytic and highly enantioselective desymmetrizing intramolecular Michael addition reaction of a prochiral ketone to a tethered *β,β'*-disubstituted nitroolefin. This key carbon–carbon bond forming reaction efficiently constructed a chiral bicyclic core in near-perfect enantio- and diastereo-selectivity, concurrently established three stereogenic centers, including a quaternary carbon stereocenter, and proved highly scalable. Furthermore, the pathway and origins of enantioselectivity in this catalytic cyclisation were probed using density functional theory (DFT) calculations, which revealed the crucial substrate/catalyst interactions in the enantio-determining step. Following construction of the bicyclic core, the total synthesis of madangamine E could be completed, with key steps including a mild one-pot oxidation-lactamisation, a two-step *Z*-selective olefination of a sterically hindered ketone, and ring-closing metatheses to install the two macrocyclic rings.

Main Text:

New methods for the efficient elaboration of complex enantioenriched sp^3-rich three-dimensional molecular scaffolds are of great value to synthetic chemistry and are highly coveted reactions. Enantioselective desymmetrization represents a powerful strategic

framework within which to develop such reactions and enables the conversion of relatively simple achiral starting materials to high-value stereochemically-rich products.[1–4] Furthermore, given the prominent role that natural products are forecast to play in the future of medicinal chemistry,[5–7] efficient routes that enable rapid generation of structural and stereochemical complexity are of particularly high importance. We therefore envisioned that the development of highly enantio- and diastereoselective organocatalytic desymmetrization reactions and their application in natural product synthesis would elegantly demonstrate the enabling power and scope of such a synthetic strategy.

The madangamine natural product family, isolated from marine sea sponges of the *Xestospongia* genus,[8–10] are characterized by an architecturally complex pentacyclic fused-ring system possessing two nitrogen atoms (Figure 1A). Three of the rings constitute a diazatricyclic core (ABC rings) that is common to all family members (madangamines A-F), as is the macrocyclic E ring (with the exception of madangamine F), while the D ring differs in each and every madangamine. We were attracted to this structurally unique family and reasoned that, via judicious application of an enantioselective desymmetrization reaction, we would be able to install all the ensuing stereochemical information from this single chirality inducing step.

Since their isolation, the madangamines have attracted significant attention from the synthetic community with numerous reported strategies to polycyclic core fragments.[11–22] However, there exist only two reports of total syntheses of members of the family and a single formal synthesis of madangamine A (Figure 1B).[23–26] In 2014, Amat reported the first asymmetric total synthesis of madangamine D, employing a stereoselective cyclocondensation of phenylglycinol to establish an enantio-enriched bicyclic (rings BC) scaffold. In 2017, Chida and Sato's unified total synthesis of madangamine's A, C and E demonstrated the divergent application of a late-stage tetracyclic intermediate. This intermediate was constructed via a key *N*-acyl-iminium cyclization of an enantioenriched octahydronaphthyridine (rings AB) derivative, and its elaboration hinged upon a highly stereoselective allene hydroboration to install the *Z*-configured double bond observed in the macrocyclic E ring.

In contrast to the previous synthetic strategies, we recognized that the AC bicyclic motif would be well-suited to construction from a catalytic enantioselective desymmetrization reaction while also providing a rigid scaffold onto which the remaining madangamine structural features could be elaborated with high stereochemical fidelity. Towards this end, we wish to report our findings, including the discovery of a novel, highly enantioselective and

efficient organocatalytic desymmetrization reaction of tri-substituted nitroolefin-linked cyclohexanones and its application to the total synthesis of madangamine E.

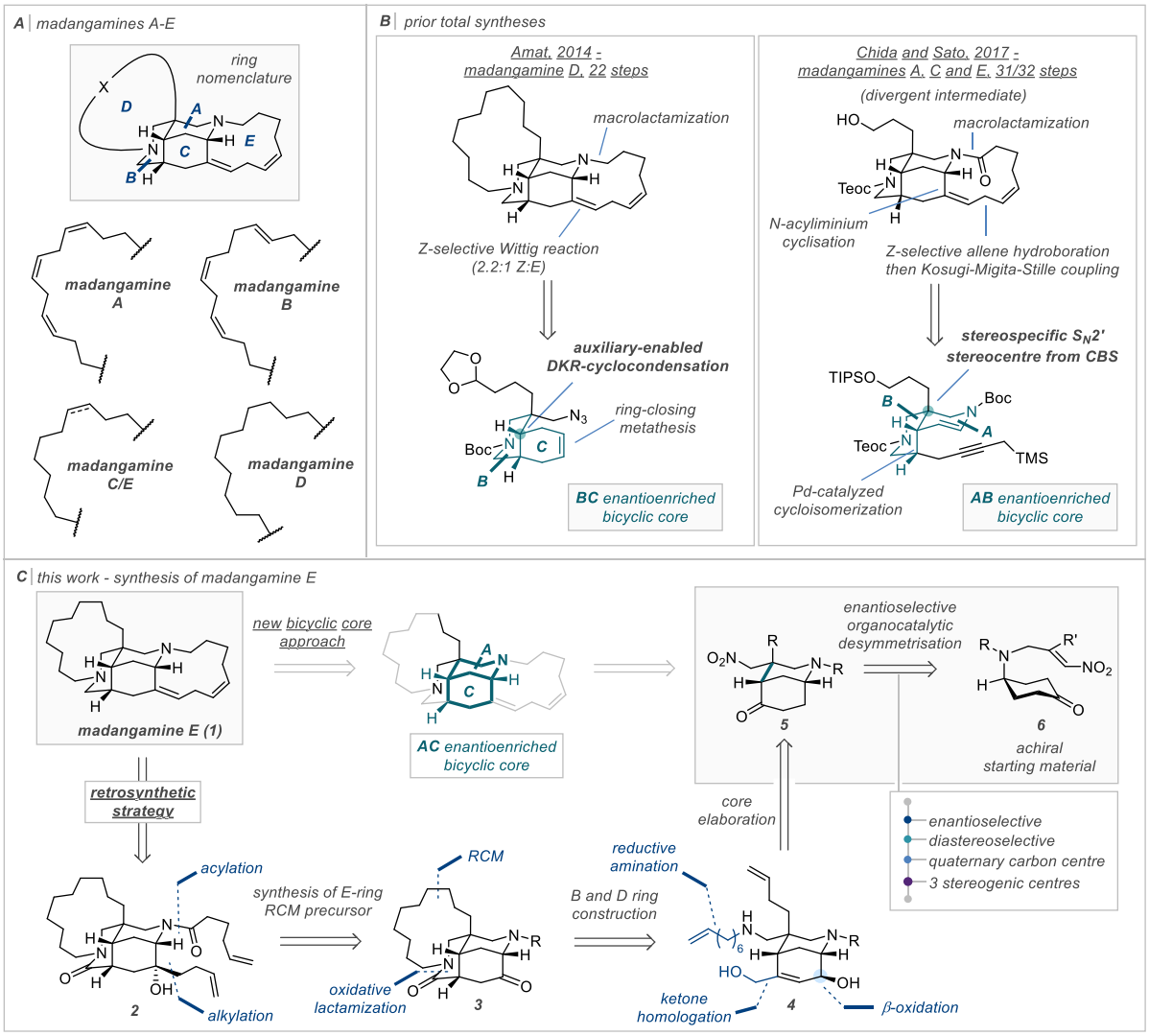

Figure 1. A. The madangamine family and divergence in the D rings of members A-E; **B.** Prior total syntheses of madangamine natural products with key strategic events highlighted; **C.** Retrosynthetic strategy to madangamine E culminating in an enantioselective desymmetrization of a prochiral cyclohexanone-linked nitroolefin.

Results and discussion:

Tackling the pentacyclic skeleton retrosynthetically (Figure 1C), the end-game to madangamine E (**1**) would rely on the functionalisation of tetracyclic ketone **3**. Two promising strategies for this macrocycle construction included: mirroring Amat's stereoselective Wittig approach using a *cis*-configured octenoate phosphonium ylide; or alternatively, introducing two alkyl chains bearing terminal alkenes that could be connected via a ring-closing metathesis (RCM) reaction. Our aim was to access ketone **5** in isomerically pure form from prochiral cyclohexanone **6** using a highly enantio- and diastereo-selective desymmetrization reaction.

Functional group manipulation, an oxidative lactamization, and ring-closing metathesis would complete the B and D rings (**5** to **3**, via **4**). Pivotal to our synthetic strategy was the development and deployment of an unprecedented enantioselective desymmetrising Michael addition of a 4-aminocyclohexanone derivative possessing a tethered *β,β'*-disubstituted nitroolefin **6**.

As inspiration for this key disconnection we took the enantioselective desymmetrising intramolecular Michael addition to *α,β*-unsaturated esters previously reported by our group using bifunctional primary amine thiourea organocatalysts (Figure 2A).[27] However, this work focused exclusively on unsaturated ester Michael acceptors and many potential synthetic challenges remained in expanding this transformation to challenging *β,β'*-disubstituted nitroolefins, while maintaining the high enantio- and diastereo-selectivity previously observed. Furthermore, while enantioselective intermolecular Michael addition reactions with nitroolefins has been well-established,[28–32] intramolecular desymmetrising variants that concurrently establish a quaternary carbon centre are unreported.[33–34]

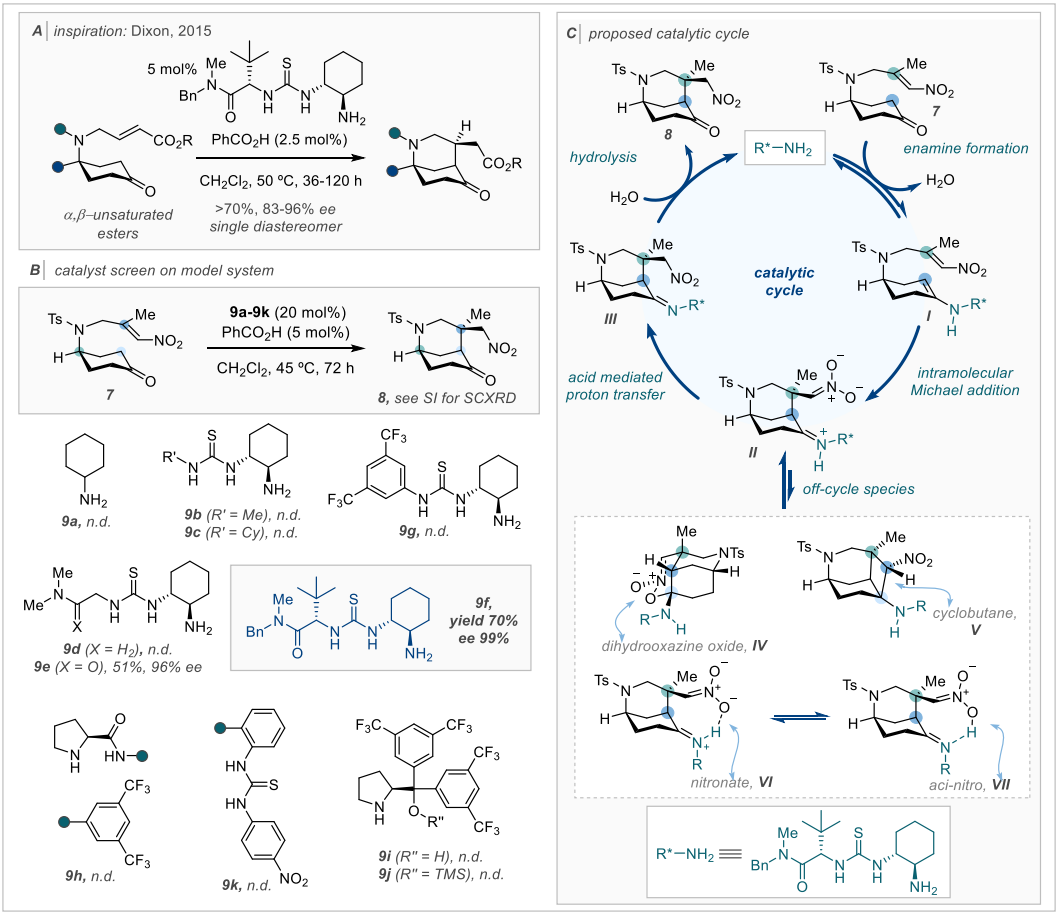

Figure 2. A. Prior work on related enantioselective desymmetrisation of cyclohexanones; **B.** catalyst screen for the desymmetrizing intramolecular Michael addition of nitroolefin **7**; n.d. = not detected, SCXRD = single crystal X-ray diffraction **C.** proposed catalytic cycle of the enantioselective desymmetrization of nitro-olefin-tethered

cyclohexanones catalyzed by a primary-amine thiourea organocatalyst, including off-cycle species investigated computationally.

Methyl-substituted nitroolefin **7** was selected as an ideal model substrate to develop the enantioselective intramolecular Michael addition reaction. An oxidative radical nitration was employed to efficiently construct **7** in 3 steps from commercially available 1,4-cyclohexanedione monoethylene acetal (See SI, Scheme S1).[35] With **7** in hand, the performance of a range of chiral single enantiomer primary and secondary amine organocatalysts was investigated, including *trans*-cyclohexanediamine and proline-derived scaffolds (Figure 2B), in dichloromethane, at 20 mol% loading, in the presence of benzoic acid as a co-catalyst. Most of tested catalysts (**9a**-**9d**, **9g**-**9k**) did not provide cyclised product **8** but gave rise instead to complex product mixtures.

Despite this unfavourable and challenging reactivity, Jacobsen's thiourea catalyst **9f**, which previously gave one of the best results for the organocatalytic desymmetrization of *α,β*-unsaturated esters, provided an almost uniquely efficient reaction profile and gave the desired bicyclic Michael adduct **8** in 70% yield as a single diastereomer in 99% ee. The relative, and absolute stereochemical configuration of **8** was established by single-crystal X-ray diffraction analysis (see SI).[36] Furthermore, a simplified bifunctional primary amine catalyst **9e** also yielded **8** in 51% yield as a single diastereoisomer in 96% ee.

To further understand the nature of this reaction, including such a narrow catalyst structure allowance, the intramolecular Michael addition of nitroolefin **7** was investigated computationally as a model substrate using DFT calculations (Figure 2C, Figure 3). The computed reaction pathway begins with an addition reaction of the primary amine of the catalyst to the ketone substrate to form a hemiaminal intermediate **Int1**, which, after elimination of water then forms imine **Int2**.[37] Despite formation of this imine being endergonic, it is likely that the thiourea activates the ketone and promotes collapse of the hemiaminal. Enamine **Int3** is then formed by tautomerization from the imine **Int2**. A conformational search for the transition structure of the key stereoselectivity-determining C–C bond forming intramolecular Michael addition identified 16 possible structures. **TS1** emerged as the most energetically favorable transition structure by $\Delta\Delta G^{\ddagger}$ = 3.0 kcal mol^{-1} compared to the second-lowest-energy transition structure, amounting to a computed 99% ee that is in excellent agreement with the experimental enantioselectivity (99% ee). This Michael addition is highly exergonic (ΔG_{rxn} = –19.4 kcal mol^{-1}) and furnishes an iminium-nitronate species **Int4**, which has been proposed as a reaction intermediate by several other groups in related, but distinct

reactions.[38–42] Therefore, this C–C bond formation through **TS1** is an irreversible and stereoselectivity-determining step, and the kinetically preferred TS is stabilized, compared to other possible TSs, because it adopts a conformation that benefits from several hydrogen bonding interactions with the thiourea, nitro group, and enamine moieties, consistent with a cooperative push/pull-type mechanism.[43]

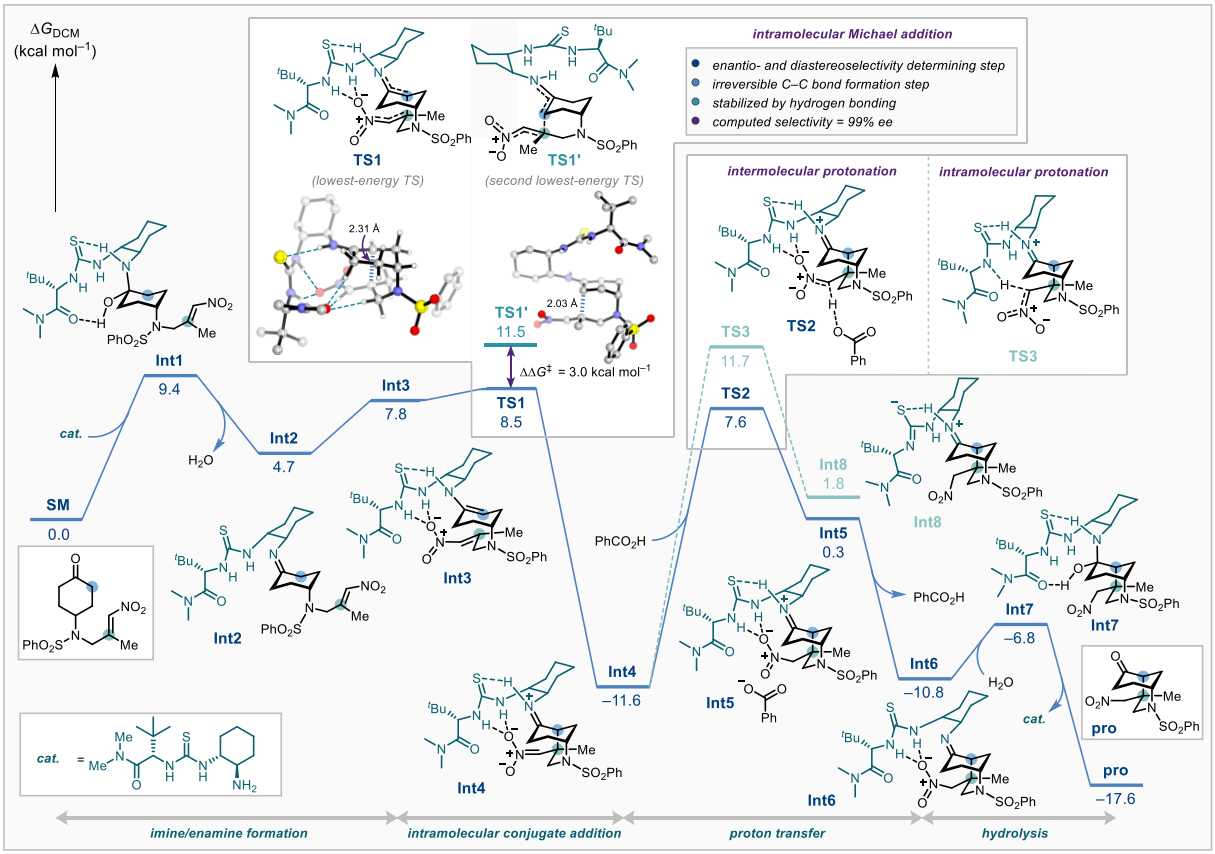

Figure 3. Computed reaction energy profile (Δ*G* in kcal mol^{-1}) for the pathway through the lowest-energy intramolecular Michael addition transition structure leading to the morphan core computed at COSMO(DCM)-ZORA-M06-2X/TZ2P//COSMO(DCM)-ZORA-BLYP-D3(BJ)/DZP.

Following the C–C bond formation event, we considered several pathways from the iminium-nitronate species **Int4** to obtain the cyclized product. The energy barrier for intermolecular protonation of **Int4** by benzoic acid through **TS2** is lower than the one for intramolecular protonation by the thiourea, and this process is faster than the reverse C–C bond cleavage reaction, indicating that the enantio- and diastereoselectivities are, indeed, determined by the kinetically controlled intramolecular Michael addition (see SI for more details). Interestingly, when the nitro group is computationally replaced with an *α,β*-unsaturated ester, calculations indicate that the intramolecular protonation reaction is preferred over the intermolecular protonation.[27] It is expected that this difference in mechanism is the result of

the *p*Ka difference between the nitronate and enolate [*p*Ka = 17 (nitro) < 20 (thiourea) < 30 (ester)]. In other words, the deprotonation of the thiourea by the enolate is favorable, whereas the deprotonation by the nitronate is unfavorable. The formation of dihydrooxazine oxide intermediate ***IV*** (Figure 2C) and its reactivity was also studied, but this pathway is unfavorable and goes with a higher energy barrier than **TS2** (see SI, Figure S4). The cyclobutane intermediate ***V*** can be formed from **Int4** prior to the intermolecular protonation process; however, the highly strained species is energetically unstable and can easily reopen with a low energy barrier. Lastly, *O*-protonation of the nitronate ***VI*** by the proton transfer process from the iminium is also facile, however the formed aci-nitro species ***VII*** is less electronegative at the α-position, therefore the protonation process from this species does not occur. After the protonation step, the resulting complex **Int6** is hydrolyzed through the hemiaminal species **Int7** to furnish the product with the experimentally observed stereochemical configuration as confirmed by single crystal X-ray diffraction studies. This energetically most favorable pathway constitutes a catalytic cycle summarized in Figure 2B.

Following the discovery of this highly efficient, enantio- and diastereo-selective, organocatalytic desymmetrization reaction on the model nitroolefin, its application in the total synthesis of the madangamine natural products, in particular madangamine E, was investigated. To introduce the requisite functional handles, nitroolefin **17**, possessing a β-butenyl substituent, was required; however, translation of the previously successful nitration chemistry failed and, accordingly, a new, high yielding and scalable route to access **17** was sought.

Our restructured route to access nitroolefin **17** (Figure 4A) began with a reductive amination of 1,4-cyclohexanedione monoethylene acetal (**10**) with allylamine and subsequent *N*-tosylation, to give tosyl amide **11** over 2 steps. Oxidative cleavage of the terminal alkene, Henry reaction, and then dehydration, mediated by mesyl chloride and base, gave β-substituted nitroolefin **13** (72% yield over 3 steps). Installation of the butenyl chain was achieved by Michael addition reaction of an organo-zinc-copper complex, as reported by Denmark,[44] to give the branched nitroalkane **14** in 90% yield and proved highly scalable (17 g scale). Selenoxide elimination chemistry proved most effective for the installation of the nitroolefin and proceeded in 52% yield over 3 steps (*E:Z* = 3.8:1, see SI for confirmation of stereochemical configuration), followed by a final deprotection of the ketal, to reveal desymmetrization precursor **17E/Z**. It was observed that the efficiency of the selenoxide elimination demonstrated strong dependence on the solvent mixture employed in the reaction, with Et_2O:CH_2Cl_2 (2:1, 0.033M) proving optimal.

The newly developed route provided both scalable and efficient access to multigram quantities of the desired *β,β′*-disubstituted nitroolefin, enabling investigation of the key organocatalytic enantioselective desymmetrization (Figure 4B). Pleasingly, treatment of **17E** with 20 mol% catalyst **9f** in the presence of 20 mol% benzoic acid provided the desired bicyclic nitroalkane **18** in excellent yield (95%) and near-perfect enantio- and diastereoselectivity (>99% ee, single diastereomer, >5g scale). The relative and absolute stereochemical configuration of **18** was determined through single crystal X-ray diffraction analysis of the oxidised enone **S10** (oxidation conditions, see SI).[36]

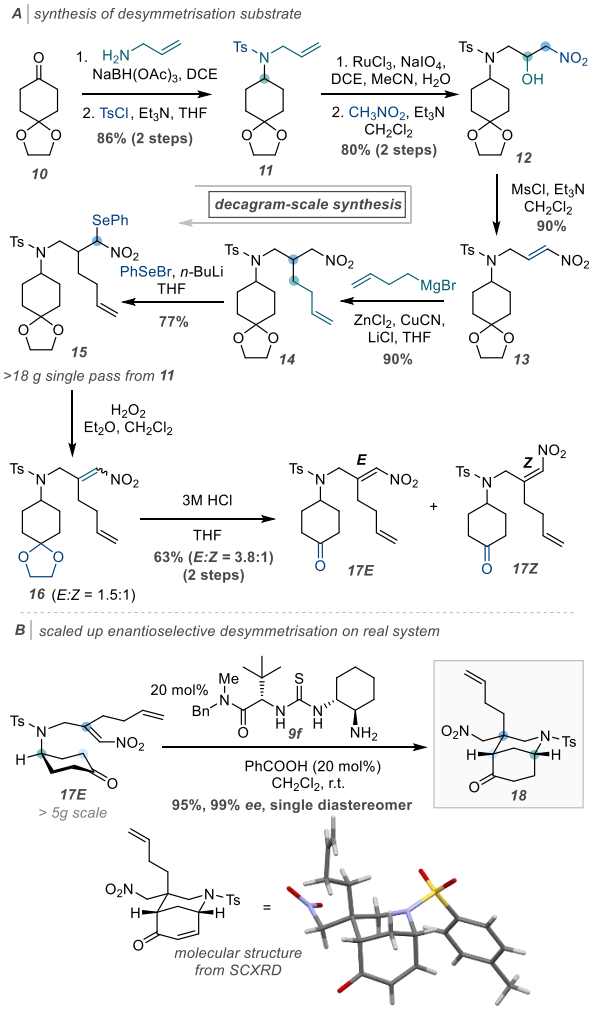

Figure 4. Scalable preparation of nitroolefin **17** and key enantioselective desymmetrization reaction

With the successful realisation of a catalytic, expedient and highly enantioselective synthesis of the bicyclic core, synthetic efforts could focus on advancing the synthesis towards madangamine E (Figure 5). Elaboration of bicyclic ketone **18** towards the key intermediate **4** required reduction of the nitro group, and β-hydroxylation, with a subsequent one carbon homologation, at the ketone moiety. Attempts to reduce the nitro group to an amine in the presence of the unprotected ketone led to an undesired pyrrolidine-containing product.

Therefore, we investigated ketone protection and observed that upon treatment with catalytic *p*-toluenesulfonic acid in methanol, methyl enol ether **19** was observed in good yield. Given the unexpected stability of the enol ether – attributed to the sterically hindered bicyclic skeleton – the synthesis was advanced from **19**. Reduction of the nitro group, with $LiAlH_4$, provided a primary amine which could be protected as the Boc-PMB-amine and then trivially converted to ketone **20**, with a total yield of 70% yield over 4 steps – notably, employing the methyl enol ether as a convenient protecting group for such a bicyclic ketone.

The challenge of both homologating the ketone in **20** while introducing oxygenation at the β position was succinctly achieved by adapting Garg's three-step strategy developed in the synthesis of the akuammiline natural products.[45] The dehydrogenation of ketone **20** was rigorously investigated, with Nicolaou's IBX-NMO-mediated oxidation reaction proving optimal and affording enone **21** in moderate yield.[46] Epoxidation of **21**, with hydrogen peroxide and aqueous NaOH in MeOH, introduced the requisite oxygenation at C3 and proceeded in high yield. The Wittig homologation, using (methoxymethyl)triphenylphosphonium chloride and NaHMDS as base, was investigated to effect the simultaneous ketone homologation and epoxide ring opening. Under standard reaction conditions, complete consumption of the substrate was observed however the yield of aldehyde **23** was low (26%). By incorporating a rigorous reaction mixture quench using saturated aqueous NH_4Cl, at 60 ºC for 3 hours, following treatment of **22** with the phosphonium ylide, the yield of desired aldehyde **23** could be improved to 86% (b.r.s.m 99%, see SI). Sequential aldehyde reduction, and partial amine deprotection steps were successfully carried out with sodium borohydride and ceric ammonium nitrate (CAN), giving diol **24** in 77% yield over 2 steps. Following Boc-deprotection with trifluoroacetic acid, a reductive amination with oct-7-en-1-al, in the presence of sodium triacetoxyborohydride and acetic acid, was employed to install the remaining carbon atoms of ring D and thus provide aminodiol **4** in 79% yield over 2 steps. Closure of the B ring was efficiently enabled by an oxidative lactamization employing Iwabuchi's oxidation conditions, accompanied by the desired concurrent oxidation of the secondary alcohol.[47] In this way, treatment of **4** with catalytic quantities of AZADO, copper chloride, 2,2'-bipyridine, and DMAP, open to air, smoothly facilitated construction of the B ring system to afford the desired tricyclic enone **25** in good yield. This elegantly establishes the utility of such mild oxidative lactamization reactions in the synthesis of complex alkaloid skeletons. A RCM reaction of **25** was carried out with Grubbs 1st generation catalyst in CH_2Cl_2, under high dilution conditions, at 40 ºC to close the D ring efficiently, giving tetracyclic enone **26** in 82% yield.[23] Subsequent treatment of **26** with palladium on carbon under a ~1 bar hydrogen atmosphere gave saturated

ketone **3**. Overreduction product S**6** accounted for the rest of the material and could be converted back to ketone **3**, employing catalytic AZADO and PIDA as the oxidant, in high yield.

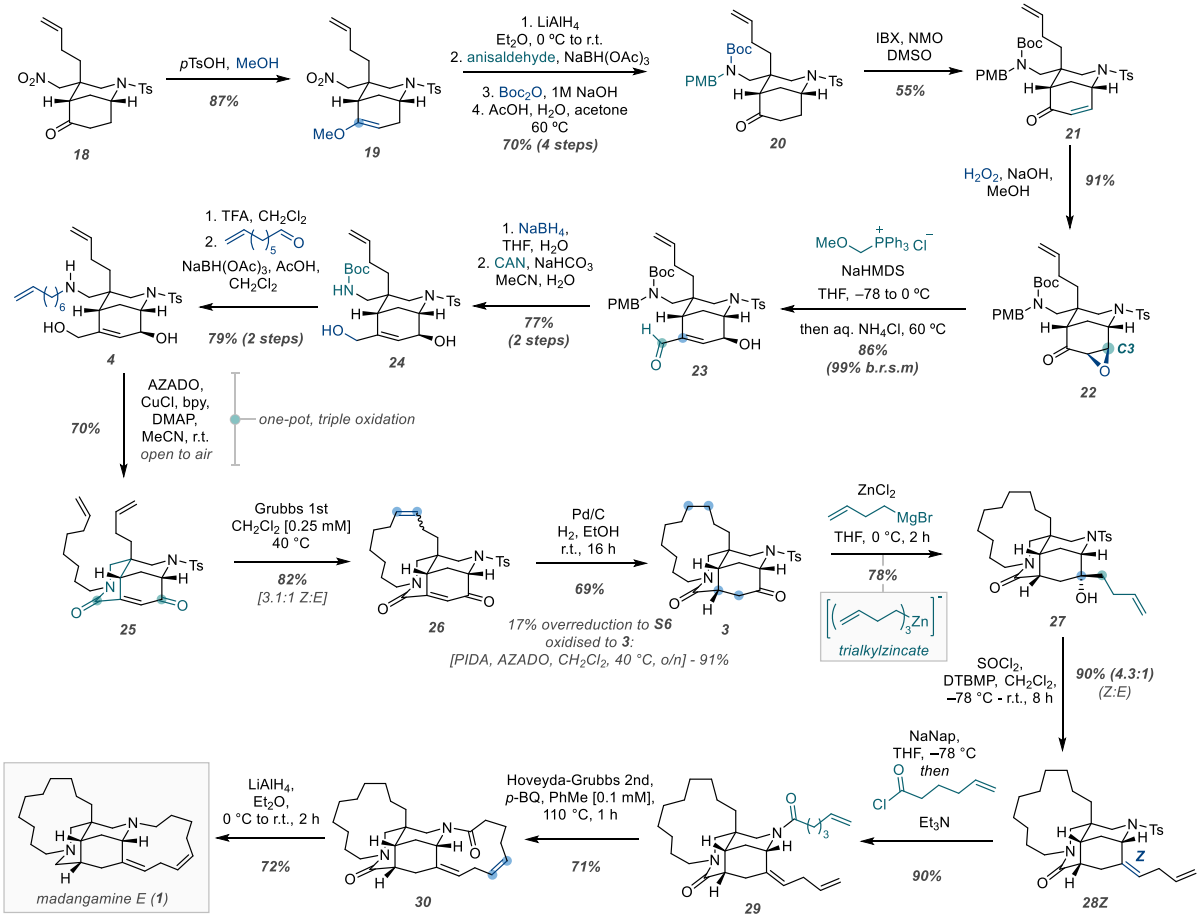

Figure 5. Total synthesis of madangamine E

Elaboration of ketone **3** proved highly challenging, with it resisting almost all trialled conditions and deprotonation consistently out-competing the desired functionalisation attempts. Notably, attempted application of Amat's Wittig reaction of an octenoate phosphonium salt was largely unsuccessful despite extensive experimentation and invaluable advice from the original authors. We concluded that the subtly different bond geometries and flexibility of ketone **3**, as compared to Amat's related substrate, render it significantly more sensitive to a competing deleterious deprotonation pathway. Ultimately, following rigorous investigation, ketone **3** was found to react with non-basic, yet highly nucleophilic organocerium reagents.[48] Incorporation of a butenyl chain was possible in high yield, employing the butenyl cerium reagent derived from the corresponding Grignard reagent, however the reaction proved highly capricious and was particularly sensitive to the quality of the organocerium reagent. Seeking a more reproducible and operationally straightforward

transformation, Ishihara's triorganozincate reagents were investigated.[49] To our delight, following minor modification to Ishihara's procedure, tertiary alcohol **27** could be afforded in high yields (70-78%) in a highly reproducible manner.

In a single operation, the tosyl protecting group could be exchanged for a hexenoate side chain in good yield to afford RCM precursor **S8**. All attempts to form the macrocyclic E ring via RCM resulted in no desired cyclisation – a result attributed to the distant spatial arrangement of the terminal alkenes. Changing the proposed order of events, early elimination of tertiary alcohol **27**, proceeded to give the desired *Z*-configured skipped diene **28** in excellent yield and good *Z*-selectivity (90%, 4.3:1), when using $SOCl_2$ with 2,6-di-*tert*-butyl-4-methylpyridine (DTBMP). RCM precursor **29** could be efficiently reached in a single step and treatment of **29** with Hoveyda-Grubbs 2nd generation catalyst, in PhMe at 110 °C, employing co-catalytic *p*-benzoquinone (*p*-BQ) to minimise undesirable isomerisation and at very high dilution to minimise dimerization, afforded diamide **30** in 71% yield.[50] The profound effect that the spatial organisation of reacting alkenes had on the outcome of the RCM reaction is noteworthy and should guide future macrocyclization campaigns employing this strategy.

A final double amide reduction was successfully carried out in 72% yield using excess $LiAlH_4$ in Et_2O to afford synthetic madangamine E (**1**). All analytical data were highly consistent with that reported by Chida and Sato and by the isolation team of Andersen.[9,25]

Conclusion:

A 30-step enantioselective total synthesis of madangamine E has been achieved. Most notably, the early application of an organocatalytic enantioselective desymmetrization reaction enabled the construction of the bicyclic madangamine core with exquisite enantio- and diastereo-selectivity and introduces a new method for the construction of stereogenic quaternary carbon centres from β,β'-dialkylsubstituted nitroolefins. This powerful transformation has been further probed computationally and its near-perfect selectivity profile has been rationalized by means of state-of-the-art density functional theory. Both the relative and absolute stereochemical configuration of the three newly formed stereogenic centers are set by the irreversible intramolecular Michael addition of an enamine to a thiourea-activated nitroolefin, and the lowest-energy conformation of the transition structure for this step benefits from stabilization from several hydrogen bonding interactions involving the thiourea, nitro group, and the enamine moieties. The subsequent construction of madangamine E hinged upon this early introduction of stereochemical information and featured a one-pot oxidative

lactamization, a two-step *Z*-selective olefination of a sterically hindered ketone, and two complementary RCM reactions to close the two macrocyclic rings. These results demonstrate the utility of catalytic enantioselective desymmetrization reactions in the synthesis of high-value saturated molecular scaffolds and highlight their potential for the rapid and atom-economical generation of stereochemical complexity in target molecule synthesis.

Methods:

See Supporting Information for detailed synthetic procedures and computational methods.

Data Availability: Crystallographic data are available free of charge from the Cambridge Crystallographic Data Centre under references CCDC 2113247 (**8**) and CCDC 2113248 (**S10**). Additional optimization data, full synthetic methods, and characterization data are available in the supplementary materials.

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Author contributions

†S.S. and B.D.A.S performed the synthetic work to complete the total synthesis and contributed equally to this work.

K.Y. performed the computations. T.A.H. designed and directed the computational study. D.V. and A.L.F.A. designed and performed experiments on the model system to discover the desymmetrization reaction. A.L.F.A. conducted single crystal X-Ray diffraction experiments. B.D.A.S, K.Y., S.S., T.A.H. and D.J.D. wrote the manuscript. D.J.D. conceived and directed the project.

Competing interests

Authors declare no competing interests.

Additional information

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