

A Unified Approach to Polycyclic Alkaloids of the Ingenamine Estate: Total Syntheses of Keramaphidin B, Ingenamine, and Nominal Njaoamine I

Zhanchao Meng,[†] Simon M. Spohr,[†] Sandra Tobegen, Christophe Farès, and Alois Fürstner*



Cite This: *J. Am. Chem. Soc.* 2021, 143, 14402–14414



Read Online

ACCESS |



Metrics & More

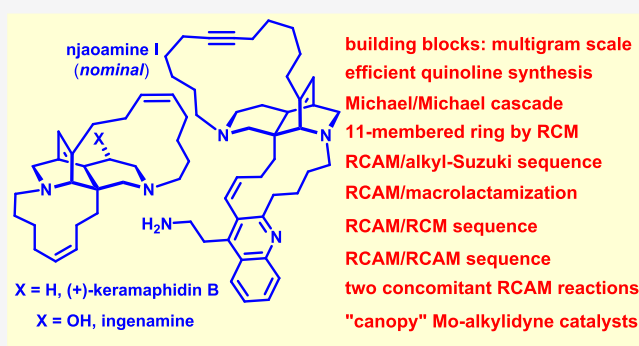


Article Recommendations



Supporting Information

ABSTRACT: Many polycyclic marine alkaloids are thought to derive from partly reduced macrocyclic alkyldipyrindine derivatives via a transannular Diels–Alder reaction that forms their common etheno-bridged diaza-decaline core (“Baldwin–Whitehead hypothesis”). Rather than trying to emulate this biosynthesis pathway, a route to these natural products following purely chemical logic was pursued. Specifically, a Michael/Michael addition cascade provided rapid access to this conspicuous tricyclic scaffold and allowed different handles to be introduced at the bridgehead quaternary center. This flexibility opened opportunities for the formation of the enveloping medium-sized and macrocyclic rings. Ring closing alkyne metathesis (RCAM) proved most reliable and became a recurrent theme en route to keramaphidin B, ingenamine, xestocyclamine A, and nominal njaoamine I (the structure of which had to be corrected in the aftermath of the synthesis). Best results were obtained with molybdenum alkyldiyne catalysts endowed with (tripodal) silanolate ligands, which proved fully operative in the presence of tertiary amines, quinoline, and other Lewis basic sites. RCAM was successfully interlinked with macrolactamization, an intricate hydroboration/protonation/alkyl–Suzuki coupling sequence, or ring closing olefin metathesis (RCM) for the closure of the second lateral ring; the use of RCM for the formation of an 11-membered cycle is particularly noteworthy. Equally rare are RCM reactions that leave a pre-existing triple bond untouched, as the standard ruthenium catalysts are usually indiscriminative vis-à-vis the different π -bonds. Of arguably highest significance, however, is the use of two consecutive or even concurrent RCAM reactions en route to nominal njaoamine I as the arguably most complex of the chosen targets.



INTRODUCTION

In a recent Communication we reported the first total syntheses of ingenamine and nominal xestocyclamine A.¹ These polycyclic alkaloids had originally been proposed to be “pseudoenantiomeric” to each other, differing in the exact positioning of the double bond embedded into the 11-membered ring (Scheme 1).^{2–4} Our data, however, provided compelling evidence that the originally assigned structure of xestocyclamine A needs to be corrected in exactly this detail: natural xestocyclamine A ((–)-2) and ingenamine ((+)-2) are in fact almost certainly true enantiomers.¹

At the meta-level, this conclusion is not all that surprising in view of the proposed biosynthesis of these and related alkaloids. It has long been speculated that the gambit of the famous “Baldwin–Whitehead pathway” might not be enzyme-dependent.^{5,6} It consists of a transannular Diels–Alder reaction of a partly reduced macrocyclic dipyrindine derivative of type A, which affords the enantiomeric iminium ions B and *ent*-B in the first place; reduction leads to keramaphidin B (1), which indeed occurs in nature in both enantiomeric forms.^{4,7–9} Although this observation strongly suggests that the initial [4 +

2] cycloaddition proceeds without intervention of a biocatalyst, attempts at emulating this step in the laboratory met with limited success in that the yield of (\pm)-1 was minute (0.2–0.3%), despite considerable experimentation.¹⁰ Even a more conventional approach based on an *intermolecular* Diels–Alder reaction followed by two concurrent macrocyclizations via ring closing olefin metathesis (RCM) was very low yielding (1–2%).¹¹

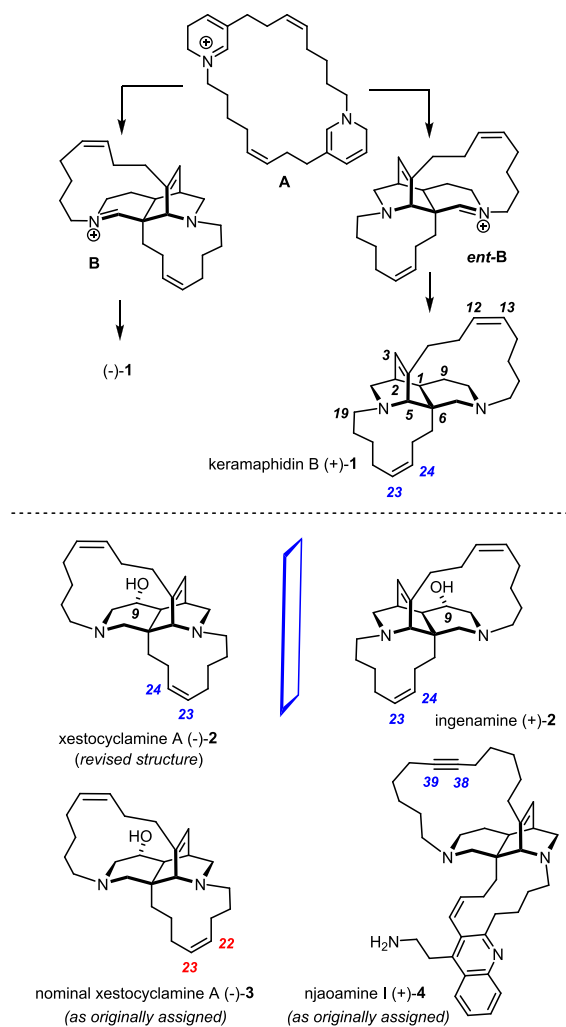
Studies toward keramaphidin B^{12–15} as well as (nominal) xestocyclamine A^{16,17} that were not intending to emulate the proposed biosynthesis have also been reported.^{18–20} The different strategies notwithstanding, none of the approaches reached these targets in the end. This is also why the originally

Received: July 30, 2021

Published: August 27, 2021



Scheme 1. Key Step of the Proposed Biosynthesis of Keramaphidin B; Representative Alkaloids Thought To Originate from Similar Pathways

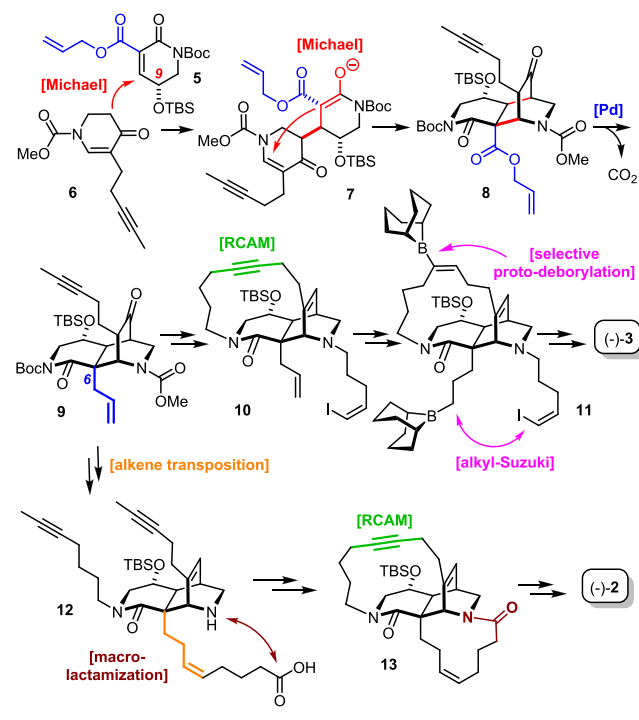


mis-assigned structure of xestocyclamine A² went unrecognized for over 25 years.

Our successful foray differed from this literature precedent in that the 1,4-etheno-bridged 2,7-diazadecaline core was formed by two consecutive Michael addition reactions, which we had hoped would proceed in one pot but ultimately had to be carried out in a stepwise manner.^{1,21,22} For the closure of the enveloping medium-sized and macrocyclic rings, we opted for methods that are strictly orthogonal in chemical terms (Scheme 2). This decision paid valuable dividends, as it ultimately allowed compound **9** to be used as a common intermediate for the total synthesis of nominal xestocyclamine A ((-)-3) and *ent*-ingenamine (that is, natural xestocyclamine A ((-)-2)) alike. Specifically, ring closing alkyne metathesis (RCAM)^{23–25} allowed the 13-membered cycle to be forged before an involved maneuver merging hydroboration/protonation with an alkyl-Suzuki coupling^{26,27} was used to close the yet missing 11-membered ring of (-)-3. In the case of (-)-2, an inverse order was successful in that macrolactamization with formation of the medium-sized ring preceded macrocyclization via RCAM.¹

With the first total syntheses of nominal xestocyclamine A ((-)-3) and (-)-ingenamine ((-)-2) completed and the

Scheme 2. Executive Summary of the “First-Generation” Approach



likely misassignment of the former corrected,¹ we revisited this project altogether with the intention of rendering the individual syntheses even more productive and the underlying blueprint more comprehensive. To this end, the following chemical, tactical, and strategic issues had to be addressed: (i) although the building blocks **5** and **6** serving as Michael acceptor and donor for the preparation of the central core could be made on decagram scale, the yields were moderate; (ii) an upgrade of the stepwise Michael/Michael addition sequence to a true reaction cascade should be aimed for;^{28,29} (iii) an extension to members of the opposite enantiomeric series is desirable to provide material for future biological testing; (iv) the original route allowed only an allyl substituent to be placed at the bridgehead C6-position of the 2,7-diazadecaline core by means of a palladium catalyzed decarboxylative allylation (**8** → **9**);^{30,31} the ability to install other handles would increase the flexibility during the subsequent macrocyclization phase and hence expand the reach and scope of the chosen approach;³² (v) the same is true if a larger panel of chemically orthogonal macrocyclization reactions could be utilized; (vi) in parallel work, a new class of alkyne metathesis catalysts was developed in our laboratory that hold the promise of working well in the presence of amines and basic heterocyclic motifs;^{33–37} the ingenamine estate of alkaloids provides an arguably stringent testing ground.^{38–46}

All of these aspects have been successfully addressed as manifested in a second-generation synthesis of natural (+)-ingenamine (as the enantiomer of xestocyclamine A), the first highly efficient conquest of keramaphidin B after the only low-yielding biomimetic approaches cited above,^{10,11} and the first total synthesis of a member of the njoamine family, even though a subtle misassignment of the originally proposed structure was noticed and corrected.^{47–49} This class of marine alkaloids, though obviously related to ingenamine/xestocyl-

amine **A**, is considerably more challenging in synthetic terms for it contains an additional side chain terminating in a primary amine as well as a quinoline moiety annulated to the macrocyclic ring.

RESULTS AND DISCUSSION

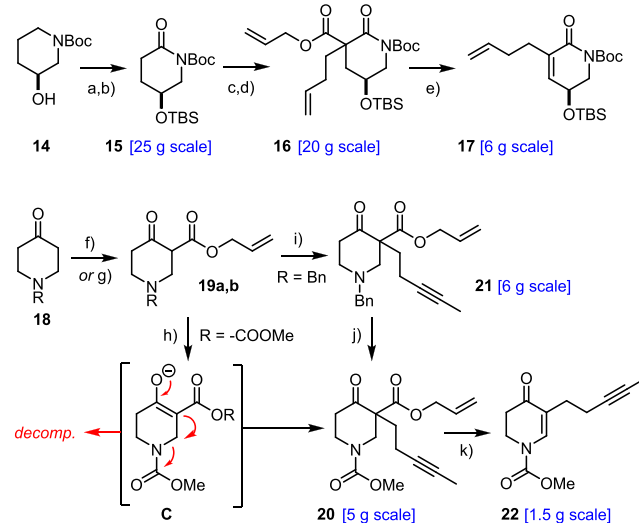
Building Blocks and the Michael/Michael Cascade Revisited. Our initial design had tried to match the reactivity of the Michael acceptor and donor in the best possible way (Scheme 2).¹ To this end, the highly electrophilic alkylidene β -ketoester **5** was deemed optimal, as it was expected to render the first Michael addition particularly facile,⁵⁰ at the same time, the malonate-type anion **7** primarily formed should expedite the subsequent intramolecular Michael addition that closes the diaza-tricyclic core of **8**.⁵¹ An allyl ester was chosen as the exocyclic activating group in **5**, as it lends itself to decarboxylative allylation with formation of the required quaternary C6-bridgehead position.^{30,31,52,53}

Although successfully reduced to practice on gram scale, we ultimately found this setting suboptimal. The fact that the formation of the 2,7-diazadecaline core had to be carried out in a stepwise manner was tentatively attributed to the fact that enolate **7** derived from a 1,3-dicarbonyl derivative is actually too stabilized. Although it likely engages in the second Michael addition, it also seems to be too good a leaving group; as such, it renders this step reversible, thus preventing an efficient cyclization cascade from occurring.¹ Moreover, one might want to revisit the choice of the allyl ester: although the palladium-catalyzed decarboxylative allylation worked perfectly well in terms of yield and selectivity, this reaction is limiting in conceptual terms, as it does not allow other substituents to be attached to the bridgehead position. This handicap had already surfaced in our original campaign: while the allyl handle was ideal for the synthesis of nominal xestocyclamine A ((-)-**3**) via hydroboration/cross coupling, a stepwise transposition of the double bond by hydroboration/oxidation and subsequent Wittig olefination with formation of **12** was necessary on the way to actual xestocyclamine A ((-)-**2**).¹

In an attempt to remedy these issues, to save steps in the longest linear sequence, and gain higher flexibility at the same time, it was decided to include the appropriate handle for macrocyclization in the Michael acceptor from the very beginning. For proof-of-concept, compound **17** carrying a butenyl substituent was prepared by O-silylation of commercial **14** followed by regioselective C–H oxidation with RuO₂ cat./NaIO₄ (Scheme 3).^{1,54} The elaboration of **15** thus formed into **16** was also high yielding. A particularly noteworthy improvement concerns the use of a modified Saegusa-type decarboxylative dehydrogenation catalyzed by Pd₂(dba)₃ to set the internal double bond of the Michael acceptor **17**;⁵⁵ the formation of the original building block **5**, which is much more electrophilic and hence more sensitive, had mandated stoichiometric selenation/selenoxide elimination for this purpose.¹

The preparation of the required Michael donor was also much improved in practical terms. Direct alkylation of **19a** (R = –COOMe), as previously described, does work on scale but is rather inefficient (36% yield);¹ this poor outcome is attributed to the good leaving group properties of the carbamate adjacent to the enolate **C** formed upon deprotonation. To circumvent this problem, the alkylation was carried out with the N-Bn protected derivative **19b**, which, indeed, led to a much more favorable outcome. To prevent the basic

Scheme 3. Building Blocks (Ingenamine Series)^{4a}

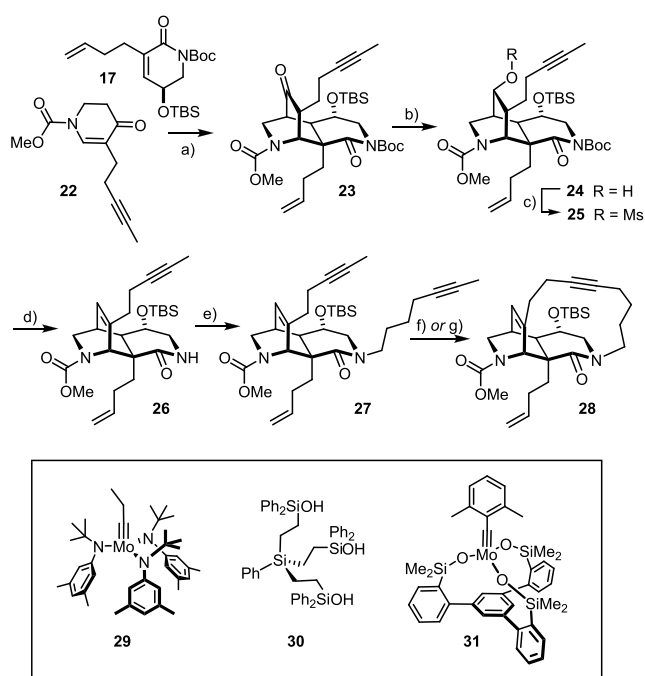


^{4a}Reagents and conditions: (a) TBSCl, Et₃N, CH₂Cl₂, quant.; (b) RuO₂ (6 mol %), NaIO₄, EtOAc/H₂O, 55%; (c) LiHMDS, allyl chloroformate, THF, –78 °C, 94%; (d) 4-bromo-1-butene, Cs₂CO₃, DMF, 94%; (e) Pd₂(dba)₃·CHCl₃ (5 mol %), MeCN, reflux, 83%; (f) LiHMDS, allyl chloroformate, toluene, –78 °C → 0 °C, 50% (R = COOMe); (g) NaH, diallyl carbonate, THF, 45% (R = Bn); (h) 1-iodo-3-pentyne, K₂CO₃, acetone, reflux, 36%; (i) 1-iodo-3-pentyne, Cs₂CO₃, DMF, 91%; (j) ClCOOMe, toluene, reflux, quant.; (k) Pd₂(dba)₃·CHCl₃ (5 mol %), MeCN, reflux, 96%

amine site from interfering with any downstream process, most notably the palladium catalyzed Saegusa oxidation, **21** was reacted with ClC(=O)OMe in refluxing toluene: under these conditions, the benzyl group is cleanly swapped for the carbamate and the stage set for yet another palladium-catalyzed decarboxylative dehydrogenation.⁵⁵ This sequence to the desired fragment **22** is considerably more efficient than the original route. In addition, it is flexible with regard to the side chain; this aspect is best illustrated by the total synthesis of nominal njaoamine I outlined below, which would not have been successful otherwise.

Gratifyingly, the redesigned building blocks could be coaxed to participate in a true Michael/Michael cascade (Scheme 4).^{28,29} After some experimentation, it was found that the reaction is best performed with LiOtBu as the base; although the N-Boc group was also cleaved, the desired diaza-tricyclic product **23** was the only discrete isomer detected in the crude material (after reprotection); reduction with NaBH₄ furnished alcohol **24** as a single isomer, which is more polar than **23** and hence easier to purify by flash chromatography. This key compound was isolated in analytically pure form in 53% yield over two steps (740 mg scale, single largest batch), which marks yet another significant improvement over our original foray.¹ The base-induced elimination of the derived mesylate **25** required harsh conditions but proceeded cleanly; as the –NBoc group was concomitantly cleaved, the stage was nicely set for subsequent N-alkylation of **26** with formation of **27**.

As expected, this substrate readily succumbed to RCAM when treated with a catalyst generated by mixing complex **29** and trisilanol **30**, which had also served our original study in this field.^{56–58} Although the true nature of the active species generated in situ is unknown, all evidence suggests that the chosen silanolate ligand partly cross-links the active metal fragments; the resulting mixture of (cyclo)oligomeric alkyl-

Scheme 4. Michael/Michael Cascade and Further Elaboration^a

^aReagents and conditions: (a) (i) *t*BuOLi, THF, $-50\text{ }^{\circ}\text{C} \rightarrow \text{RT}$; (ii) Boc_2O , DMAP; (b) NaBH_4 , MeOH, $0\text{ }^{\circ}\text{C}$, 53% (over two steps); (c) MsCl, Et_3N , DMAP, CH_2Cl_2 , $0\text{ }^{\circ}\text{C} \rightarrow \text{RT}$, 91%; (d) (i) 2,6-lutidine, $170\text{ }^{\circ}\text{C}$; (ii) TBSOTf, CH_2Cl_2 , 73%; (e) 1-iodo-5-heptyne, NaH, DMF, $0\text{ }^{\circ}\text{C}$, 95%; (f) **29** (25 mol %), **30** (30 mol %), toluene, MS 5 Å, $100\text{ }^{\circ}\text{C}$, 79%; (g) **31** (20 mol %), toluene, MS 5 Å, reflux, 83% (1.3 g scale).

dynes effects the desired transformation. Gratifyingly, we found that the newly developed and molecularly well-defined molybdenum alkydine complex **31** distinguished by a tripodal silanolate ligand sphere is at least equipotent.^{33–35} Although a fairly high loading and rather forcing conditions proved necessary to overcome the strain of the incipient tetracyclic scaffold, cycloalkyne **28** was obtained in 83% yield on a 1.3 g scale (for reaction optimization, see the Supporting Information (SI)); its constitution and stereostructure were unambiguously established by 2D NMR spectroscopy and X-ray diffraction (Figure 1).

Second Generation Synthesis of (+)-Ingenamine. With a short, efficient, and scalable route to **28** secured, we

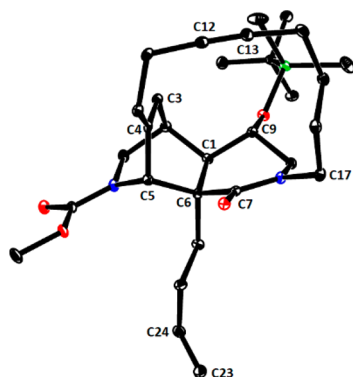


Figure 1. Structure of cycloalkyne **28** in the solid state.

were in the favorable position to explore new ways of forging the yet missing medium-sized ring en route to the ingenamine estate of alkaloids. Most notably, alternatives to the alkyl-Suzuki coupling used in the original synthesis of (–)-**3** or the more conventional macrolactamization en route to (–)-**2** seemed worth investigating.^{1,32}

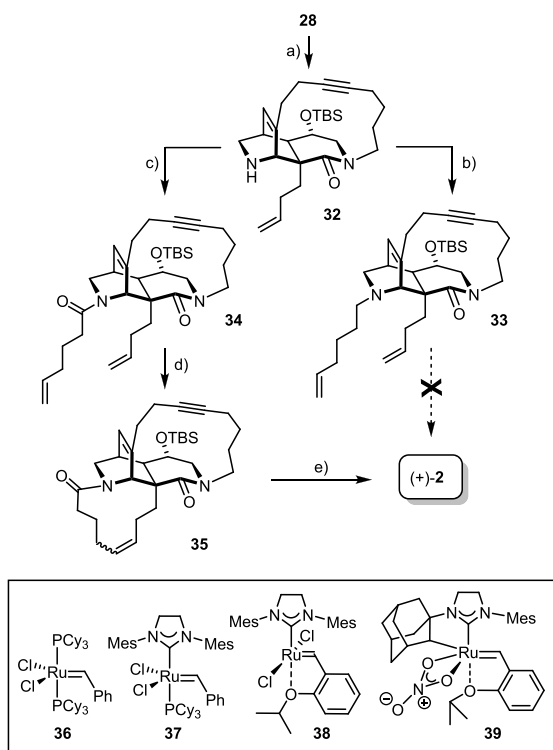
The unsaturated handle branching off the bridgehead in **28** invited the use of ring closing olefin metathesis (RCM),^{59–61} even though the number of successful applications to 11-membered carbo- and heterocycles is comparatively small and the yields were rather moderate in many cases.^{62–78} Since RCM is largely driven by the gain in entropy when a given diene substrate is converted into a cyclic olefin plus ethylene (which desolvates upon evaporation), the reaction does not allow large enthalpic barriers to be overcome. 11-Membered rings, however, largely draw their chemical and physical attributes from transannular as well as angle strain; in the transition state, these factors represent formidable kinetic handicaps for ring closure.⁷⁹

In addition to this fundamental aspect, serious chemoselectivity issues needed to be considered. All modern alkyne metathesis catalysts leave alkenes untouched,^{23–25} whereas the standard olefin metathesis catalysts are largely indiscriminate: in fact, productive enyne metathesis is only possible because metal carbenes react with both types of π -systems similarly well.^{59,80} In the projected case, any ene/yne crossover would be detrimental. However, we conjectured that conformational preorganization by the rigid tricyclic backbone of the substrates in question might mitigate the risk and make the successive use of RCAM and RCM possible.⁸¹

To test this enticing scenario, **28** was elaborated by selective cleavage of the methyl carbamate group with *L*-selectride in THF (Scheme 5).⁸² The resulting free amine **32** was converted into amide **34** as well as into *tert*-amine **33**. All attempts at subjecting the latter to ring closure met with failure; the outcome was independent of whether the free base was first protonated with CSA or not^{83–89} and of whether Grubbs-type ruthenium carbenes of the first or second generation were used. When seen against this backdrop, the success of the RCAM reactions in the presence of two different *tert*-amines and a quinoline, as pursued en route to nominal njoamine I (**4**), will be fully appreciated (see below).

Amide **34** was more compliant. Interestingly, however, only the classical first-generation Grubbs carbene **36**⁹⁰ allowed the ring to be closed under high dilution conditions in toluene at elevated temperatures. Since the rate of decomposition of this complex under such forcing conditions is on the same order as productive RCM,⁹¹ the catalyst had to be slowly added to the mixture; this provision notwithstanding, a very high loading (50 mol %) was necessary to reach full conversion. The reaction furnished **35** as an isomer mixture, in which the undesired *E*-alkene slightly prevailed (*E/Z* \approx 60:40). All attempts at improving this outcome by recourse to the more reactive second-generation catalysts (**37**, **38**; decomposition)^{92–94} or the (*Z*)-selective cyclometalated variant **39** (unreactive)⁹⁵ were to no avail.

The isolation of the required (*Z*)-**35** was only possible by HPLC. This compound intercepts our previous route to ingenamine/xestocyclamine A (except that the original foray had been carried out in the enantiomeric series).¹ The way from **35** to (+)-**2** commences with a semihydrogenation of the triple bond over nickel boride,^{96,97} followed by reduction of the two remaining amide groups with excess AlH_3 generated in

Scheme 5^a

^aReagents and conditions: (a) L-Selectride, THF, 40 °C, 91%; (b) hex-5-enal, NaBH(OAc)₃, CH₂Cl₂, 96%; (c) hex-5-enoyl chloride, Et₃N, CH₂Cl₂, 0 °C → RT, 71%; (d) **36** (50 mol %), toluene, 100 °C, 97% (*E/Z* = 60:40); (e) see ref 1.

situ; under these conditions, the silyl ether is concomitantly cleaved. The constitutional and stereochemical integrity of ingenamine thus formed has previously been proven by X-ray diffraction.¹

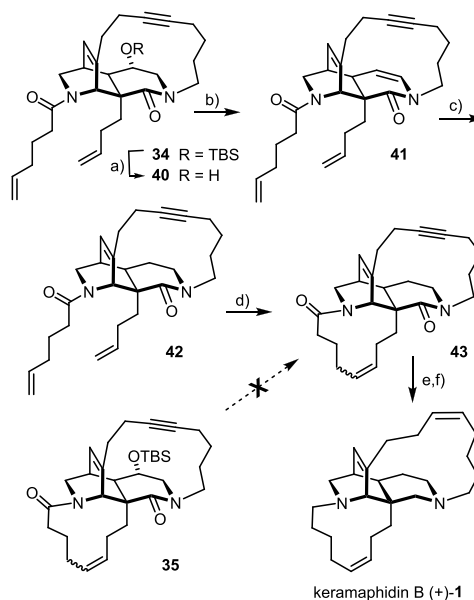
In chemical terms, this “second generation” synthesis of ingenamine based on RCAM/RCM is shorter than the original route¹ relying on macrolactamization/RCAM (16 versus 19 steps, longest linear sequence; see the SI). With ~2%, however, the overall yields of the two approaches are virtually identical because the advantage of the shorter sequence is outweighed by the lack of stereocontrol in the RCM reaction.

Total Synthesis of (+)-Keramaphidin B. As mentioned in the Introduction, keramaphidin B (**1**) is the first distinct product on the Baldwin–Whitehead pathway;^{5,10,11} it is thought to derive from the initial Diels–Alder product **B** by reduction of the imine functionality (Scheme 1); interestingly, **1** was isolated in scalemic form from an Okinawan marine sponge of the genus *Amphimedon* sp. only after this intriguing biosynthetic prediction had been made.^{4,7,9,98}

(+)-**1** and (–)-**1** differ from ingenamine ((+)-**2**) and xestocyclamine A ((–)-**2**), respectively, in that the –OH group at C-9 is missing. In the context of our synthesis, however, this particular substituent plays a quintessential role: placed in the initial Michael acceptor in –OTBS protected form, it enforces the *trans*-attack of the incoming Michael donor as necessary for proper closure of the caged diazatri-cyclic scaffold (Scheme 2). In this way, the stereochemical information encoded in the C9–OH is relayed to all other chiral centers of the core. Only after it has exerted this critically

important function, the directing –OR group can be removed in an attempt to gain access to keramaphidin B.

We had originally planned to perform the deoxygenation at the very end of the synthesis, after both enveloping macrocyclic rings have been set. Although no exhaustive screening exercise was carried out, attempted elimination of the –OH group of **35** under various conditions was not encouraging (Scheme 6). The effort was discontinued when we

Scheme 6^a

^aReagents and conditions: (a) TBAF, THF, 0 °C, quant.; (b) Martin’s sulfurane, toluene, 100 °C, 97%; (c) NaBH₃CN, TFA, CH₂Cl₂, 0 °C → RT, 73%; (d) **36** (50 mol %), 1,2-dichloroethane, 83% (*E/Z* = 1:1); (e) Ni(OAc)₂·4H₂O, NaBH₄, ethylenediamine, H₂ (1 bar), EtOH, 37% (over two steps, pure isomer); (f) Dibal-H, Et₂O/hexane, 38%.

learned that Martin’s sulfurane⁹⁹ effected the analogous reaction in almost quantitative yield at the stage of **40**, prior to the RCM reaction. Enamide **41** thus formed was then swiftly reduced on treatment with NaBH₃CN and trifluoroacetic acid.

Figure 2 shows the structure of the resulting amide **42** in the solid state. Of particular interest is the conformation adopted by the tangling 5-hexenamide group that has to participate in

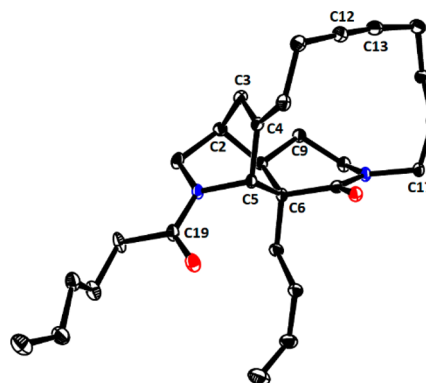


Figure 2. Structure of compound **42** in the solid state.

the projected RCM reaction with the butenyl group at the C6-bridgehead position: both substituents point “downwards”, away from the triple bond (C12–C13). Although the static picture of the X-ray structure must not be overinterpreted, it might explain why the closure of the 11-membered ring worked without any competing ene/yne crossover. In the event, treatment of **42** with Grubbs catalyst **36** (50 mol %) ⁹⁰ in 1,2-dichloroethane at reflux temperature was necessary to enforce the reaction; under these conditions, product **43** was obtained as a 1:1 mixture of the olefin isomers in high yield, which were separable by conventional flash chromatography after the subsequent Z-selective semihydrogenation of the triple bond with the aid of nickel-boride. ^{96,100} Reduction of both amide groups then completed the total synthesis of (+)-**1**. The analytical and spectral data of the synthetic samples matched those of authentic keramaphidin B ^{7,9} very well and hence leave no doubt about structural integrity and identity (for details, see the SI).

Total Synthesis of Nominal Njaoamine I: Background and Strategic Considerations. The polycyclic alkaloids of the njaoamine family were isolated from marine sponges of the genera *Reniera* and *Neopetrosia* sp. collected off the Tanzania coast line. ^{47–49} They differ from each other mainly in the size and degree of unsaturation of one of the macrocyclic rings as well as in the oxidation pattern of the quinoline nucleus (Figure 3). Although no comprehensive biological profiling of

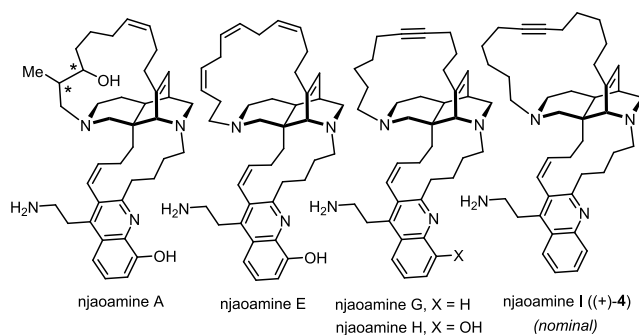


Figure 3. Representative members of the njaoamine family (* stereocenters of unknown configuration).

these compounds was reported, they exhibit moderate to high cytotoxicity against three human cancer cell lines as well as potent activity in a brine shrimp assay. ^{47–49} The structural relationship with keramaphidin B/ingenamine is obvious; in terms of biosynthesis, it was proposed that a hetero-Diels–Alder reaction between an ingenamine-type precursor and an oxidized tryptophane derivative entails annulation of the quinoline. ⁴⁷ As one might infer from the isolation reports, the absolute configuration of these enticing natural products was tacitly assumed to be that of (+)-keramaphidin B/ingenamine, even though a rigorous proof was missing.

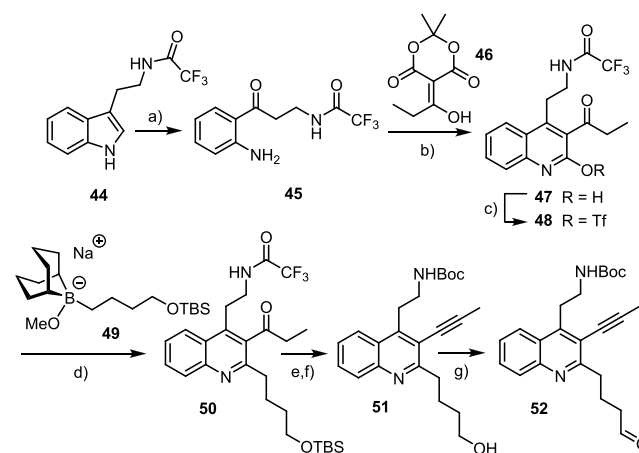
An extension of our program to compounds of this level of complexity, which have never been targeted in the past, was tempting. For the excellent record of RCAM in the current campaign, (nominal) njaoamine I ((+)-**4**) incorporating an intact triple bond in one of the peripheral rings was chosen as our prime target. The answer to the question as to how the second unsaturated macrocycle annulated to the distinguishing quinoline moiety should be forged was less compelling. In view of the failed attempts to effect RCM of an amine or the derived ammonium salt en route to keramaphidin B (see above), this

method was unlikely to work in the present context for the additional basic sites in **4** and was therefore ruled out from the very beginning.

Cross-coupling, as pursued in the original synthesis of nominal xestocyclamine A, ¹ should be viable; yet, we conjectured that a second RCAM reaction might actually be a better option. Neither tertiary alkylamines nor substituted pyridine derivatives seem to interfere with the activity of the latest generation of catalysts such as **31**, despite the high-valent Mo(+6) center in the operative alkylidyne unit. ^{33,36,101,102} Therefore it was tempting to make use of RCAM twice en route to **4**, even though—or because—such a maneuver was without precedent at the outset of this project.

Quinoline Building Block. Tryptamine was N-trifluoroacetylated before the heterocyclic ring was oxidatively cleaved with NaIO₄ and the resulting formamide hydrolyzed off with aqueous HCl (Scheme 7). A Die-

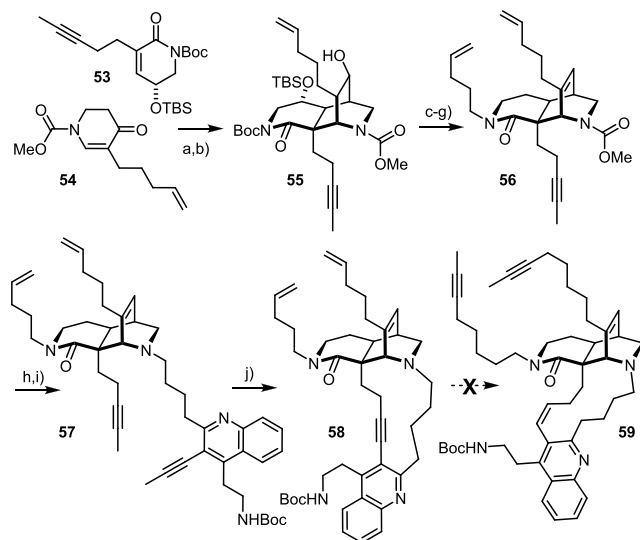
Scheme 7^a



^aReagents and conditions: (a) (i) NaIO₄, MeOH/H₂O; (ii) aq. HCl, MeOH, 81%; (b) toluene, reflux, then SiO₂, 94%; (c) Tf₂O, pyridine, 0 °C → RT, 88%; (d) **49**, Pd(PPh₃)₄ (5 mol %), THF, reflux, 73%; (e) (i) PhNTf₂, KHMDS (excess), THF, –78 °C; (ii) Boc₂O, DMAP, MeCN; (f) TBAF, THF, 0 °C → RT, 72% (over three steps); (g) pyridine·SO₃, DMSO, Et₃N, 0 °C → RT, 77%.

ckmann-type condensation of **45** thus formed with **46** furnished hydroxyquinoline **47** on scale. ¹⁰³ The derived triflate **48** was cross-coupled with borate **49** formed by hydroboration of TBS-protected 3-butene-1-ol with 9-H-9-BBN followed by addition of 1 equiv of NaOMe; no further base is necessary under these conditions for the alkyl-Suzuki reaction to proceed. ^{27,104} The ketone group of **50** was then transformed into the required triple bond via the corresponding enol triflate, which succumbed to spontaneous elimination when excess KHMDS was present in the mixture. ¹⁰⁵ Treatment of the resulting product with Boc₂O followed by a workup with NH₄Cl swapped the protecting group at the amine terminus. Cleavage of the silyl ether followed by oxidation gave aldehyde **52** to be incorporated into the RCAM precursor via reductive amination.

First Foray. The improved syntheses of the required building blocks and the ability to forge the nitrogenous core by a true Michael/Michael cascade proved enabling at this stage of the project. Simple adaptation opened access to **53** and **54** and the derived double-Michael adduct **55** comprising a pentynyl group branching off the bridgehead (Scheme 8; for

Scheme 8. Failed First Foray^a

^aReagents and conditions: (a) (i) Bn_2NLi , DMPU, $-50\text{ }^\circ\text{C} \rightarrow 0\text{ }^\circ\text{C}$; (ii) Boc_2O , DMPU; (b) NaBH_4 , MeOH, $0\text{ }^\circ\text{C}$, 42% (over two steps); (c) MsCl , Et_3N , DMAP, CH_2Cl_2 , 85%; (d) 2,6-lutidine, $170\text{ }^\circ\text{C}$, 81%; (e) (i) NaH , 1-iodo-4-pentene, DMF; (ii) TBAF, 98%; (f) (i) $\text{ClCH}_2\text{SO}_2\text{Cl}$, Et_3N , DMAP, CH_2Cl_2 ; (ii) DBU, 77% (over two steps); (g) NaBH_3CN , TFA, CH_2Cl_2 , $0\text{ }^\circ\text{C} \rightarrow \text{RT}$, 60%; (h) *L*-Selectride, THF, $40\text{ }^\circ\text{C}$; (i) **52**, $\text{NaBH}(\text{OAc})_3$, CH_2Cl_2 , 73% (over two steps); (j) **29** (30 mol %), **30** (30 mol %), MS 5 Å, toluene, reflux, 77%.

details, see the SI). Note that the stereochemistry matches that of natural xestocyclamine A rather than ingenamine; this choice reflected nothing but the material supply at this point of the project. Elaboration of **55** into **56** echoed the route outlined above without need for major adaptation.¹⁰⁶ Cleavage of the methyl carbamate followed by reductive amination¹⁰⁷ with aldehyde **52** furnished **57** in readiness for RCAM. Gratifyingly, this transformation proceeded smoothly, despite the presence of a *tert*-amine and a quinoline functionality.

We had planned to elaborate cycloalkyne **58** in a single operation into diyne **59**, as required for the second macrocyclization, by exhaustive hydroboration, selective proto-deborylation of the alkenylborane originating from the triple bond,¹⁰⁸ and cross-coupling of the remaining alkenylborane functionalities derived from the terminal alkenes with 1-halo-1-propyne (or a synthetic equivalent thereof).¹⁰⁹ Very much to our dismay, this plan could not be reduced to practice, despite considerable experimentation. Various alternative and more conventional stepwise approaches also failed. Although the complexity of the resulting mixtures prevented full analyses, the reluctance of the triple bond of **58** to undergo hydrometalation (or semihydrogenation) and the unexpected resilience of the alkenylmetal species, once formed, to protodemetalation were identified as major obstacles.

Tactical Change and Completion of the Total Synthesis. As the projected late-stage introduction of the alkynes needed for the second RCAM reaction was unsuccessful, we had no choice but to carry these handles through the synthesis in masked format. Surrogates of or protecting groups for triple bonds are not commonplace; in the present case, they have to withstand (strongly) basic, acidic, oxidative, and various reductive conditions and must not be cleaved by fluoride either. Actually, none of the established

alkyne surrogates seemed to meet these boundary conditions;¹¹⁰ after careful consideration of the possible pitfalls, we finally opted for *vic*-dibromoalkenes,^{111,112} despite the danger that the halide atoms could jeopardize the success of the palladium-catalyzed Saegusa-type oxidations and/or the necessary alkyne semireduction over a (noble) metal catalyst.

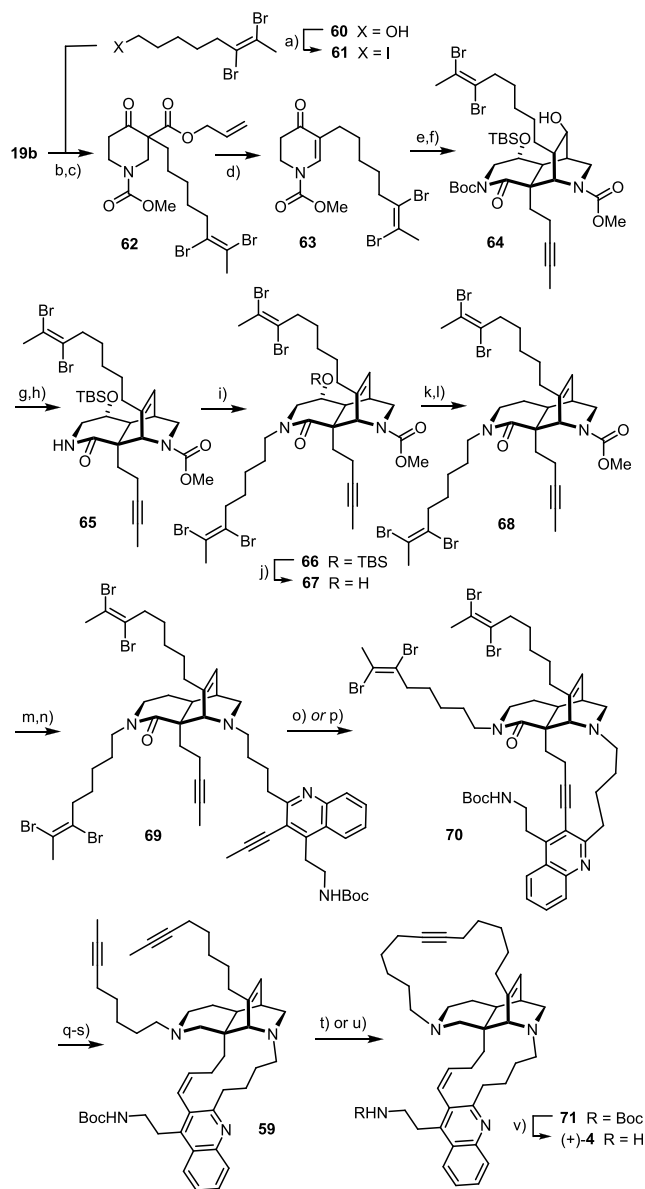
The first of these concerns was quickly found to be unjustified (Scheme 9). By following the now established route, **19b** was alkylated with iodide **61** comprising such a *vic*-dibromoalkene moiety (readily available from 6-octyne-1-ol). Gratifyingly, this group did not interfere at all in the subsequent Saegusa oxidation: this favorable result is tentatively attributed to the fact that the reaction works with $\text{Pd}_2(\text{dba})_3$ as the catalyst without need for an external ligand;⁵⁵ while this “bare” palladium species is capable of activating the allyl ester, it is not sufficiently electron-rich to engage in competitive oxidative insertion into the alkenyl bromide bonds, which would be detrimental in the present case.

The base-induced Michael/Michael cascade and subsequent elaboration of the core fragment **64** proceeded uneventfully; the only minor concern was the reduction of enamide formed upon elimination of the 9-OH group of **67** with Martin’s sulfurane:⁹⁹ as the reaction requires treatment with excess $\text{NaBH}_3\text{CN}/\text{TFA}$, it proved mandatory to quench the reaction as soon as full conversion of the substrate was reached; under this proviso, the results were well reproducible (66%, 660 mg scale, single largest batch).

An unexpected problem was encountered in the seemingly trivial cleavage of the methyl carbamate. *L*-Selectride had served this purpose well before (see above) but was found inadequate for **68**, as it led to extensive reduction of the *vic*-dibromoalkenes present in this substrate (see below). The problem was ultimately circumvented by recourse to TMSI.¹¹³ Subsequent attachment of the quinoline-containing side chain via reductive amination furnished diyne **69** as necessary for the first macrocyclization event.

This exigent transformation worked again very nicely, independent of whether the in situ catalyst mixture (**29/30**)⁵⁶ or the structurally defined canopy catalyst **31**^{33–35} was used. The need for fairly high loadings is again tentatively ascribed to the forcing conditions necessary to override the incipient ring strain of the polycyclic product **70**, which certainly also accelerate catalyst decomposition (for reaction optimization, see the SI); this notion is supported by recent results from our laboratory.¹¹⁴ As expected, the *vic*-dibromoalkenes neither compromise the activity of the catalyst nor become damaged. This result adds another important entry to the list of functional groups that are compatible with these versatile molybdenum alkylidyne.

The difficulties encountered in the first foray to subject cycloalkyne **58** to any kind of stereoselective semireduction foreshadowed the challenge to engage the closely related but even more highly functionalized analogue **70**; in fact, hydrometalation was not viable. With regard to more classical hydrogenations, it is pointed out that this substrate incorporates a quinoline which likely acts as an internal catalyst poison. Though tentative, this may explain why many standard reagents and catalysts either failed to react altogether or resulted in intractable mixtures.¹⁰⁰ After many failed attempts, it was found that *unpoisoned* Pd/CaCO_3 was appropriate, provided the reaction was carried out in THF as the solvent and the “catalyst” was used in excess (2 equiv). Under these conditions, the required (*Z*)-alkene was isolated

Scheme 9^a

^aReagents and conditions: (a) I_2 , PPh_3 , imidazole, CH_2Cl_2 , 0 °C, 99%; (b) **61**, Cs_2CO_3 , DMF, 67%; (c) $ClCOOMe$, toluene, 100 °C, 97%; (d) $Pd_2(dba)_3$ (5 mol %), MeCN, reflux, 92%; (e) (i) **53**, $tBuOLi$, THF, -50 °C → RT; (ii) Boc_2O , DMAP; (f) $NaBH_4$, MeOH, 0 °C, 55% (over two steps); (g) $MsCl$, Et_3N , DMAP, CH_2Cl_2 , 0 °C → RT, 94%; (h) (i) 2,6-lutidine, 170 °C; (ii) $TBSOTf$, CH_2Cl_2 , 78%; (i) **61**, NaH , DMF/THF, 0 °C → RT; (j) TBAF, THF, 92% (over two steps); (k) Martin's sulfurane, toluene, 100 °C, quant.; (l) $NaBH_3CN$, TFA, CH_2Cl_2 , 0 °C → RT, 66%; (m) TMSI, CH_2Cl_2 ; (n) **52**, $NaBH(OAc)_3$, CH_2Cl_2 , 67% (over two steps); (o) **29** (30 mol %), **30** (30 mol %), MS 5 Å, toluene, reflux, 77%; (p) **31** (30 mol %), MS 5 Å, toluene, reflux, 77%; (q) H_2 (1 bar), $Pd/CaCO_3$, THF, 52%; (r) Dibal-H, Et_2O , 0 °C → RT; (s) Zn , THF, HOAc, 44% (over two steps); (t) **29** (30 mol %), **30** (30 mol %), MS 5 Å, toluene, reflux, 73%; (u) **31** (30 mol %), MS 5 Å, toluene, reflux, 98%; (v) HCl in 1,4-dioxane, EtOAc, quant.

as the only isomer in 52% yield with the lateral four alkenyl bromide moieties intact.

The subsequent selective reduction of the amide turned out to be no less demanding: it required considerable experimentation to find that Dibal-H in Et_2O shows the proper

selectivity profile. The choice of solvent is critical, and the conversion must be carefully monitored: once the substrate is consumed, the reaction has to be immediately quenched to prevent reduction of the C–Br bonds.

Compared with these two rather taxing chemoselective reduction steps, the completion of the total synthesis was straightforward. Thus, treatment with zinc dust in acidic medium swiftly unmasked the triple bonds.^{111,115} In line with our expectations, the subsequent RCAM reaction of **59** proceeded cleanly. Once again, the in situ catalyst mixture **29/30**⁵⁶ and the well-defined canopy catalyst **31**^{33–35} were both operative, with the latter affording the desired cycloalkyne **71** in essentially quantitative yield. This result is deemed very rewarding, since the effectiveness of the high-valent molybdenum alkylidyne endowed with the silanolate ligand sphere is not compromised by the presence of two different tertiary amines, a quinoline, and a Lewis basic carbamate group in the substrate. To properly assess this result, one has to recall that RCM of **33** comprising a single *tert*-amine could not be enforced at all with the aid of Grubbs-type ruthenium carbene complexes, even after protonation. Therefore, this example—together with a number of other advanced applications^{39–44,57,116–126}—may help correct the misperception that high-valent early transition metal catalysts provide (too) few opportunities when working with densely decorated compounds; in any case, it is fair to claim that the newly developed molybdenum alkylidynes with (tripodal) silanolate ligands are distinguished by a remarkable and enabling functional group tolerance.

Final cleavage of the –NBoc group with HCl in 1,4-dioxane/ $EtOAc$ ¹²⁷ completed the total synthesis of what had been proposed to be njaoamine I ((+)-**4**). Yet, the analytical and spectral properties of the synthetic samples showed small deviations from the tabulated NMR data.⁴⁹ A comparison with an authentic sample confirmed that the differences are beyond the error bar even though they are extremely subtle and the compounds were not distinguishable by HPLC either (see the SI). The fact, however, that the mismatch was clustered in the macrocycle comprising the triple bond suggested that the issue might have to do with the exact location of the alkyne within this ring.

Structure Revision of Njaoamine I. With the tiny amount (<1 mg) of the isolated natural product made available to us by the generosity of the isolation team, we were able to confirm this supposition.

To this end, a complete and unambiguous reassignment of the entire 12-carbon chain from C33 to C44 was mandatory; this task proved challenging because the dilute sample in $[D_5]$ -pyridine rendered heteronuclear long-range coupling experiments (in particular HMBC) impractical. Moreover, the limited resolution impeded assignment, especially between 1.1 and 1.7 ppm where 20 methylene protons (14 of them from the chain in question) and one methine proton resonate; likewise, there are two very similar methylene ^{13}C signals at 27.7 and 27.8 ppm, the correlations of which can only be separated by very high-resolution multidimensional experiments.

The challenges were ultimately met by a series of CLIP-COSY,¹²⁸ high-resolution HSQC, and high-resolution HSQC-TOCSY experiments (see the SI); the latter proved particularly informative: they provided compelling evidence that the triple bond is located at $C37\equiv C38$ (rather than $C38\equiv C39$, as had originally been proposed by the isolation team).⁴⁹ Njaoamine I

is hence a regioisomer of the originally assigned structure in which the triple bond is shifted by one C atom (Figure 4).

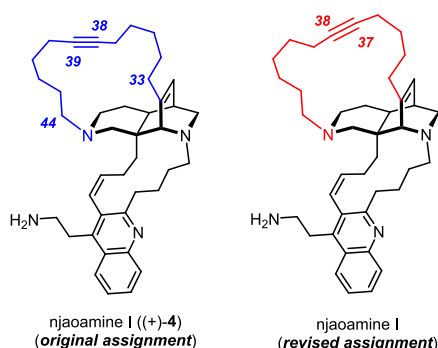


Figure 4. Originally assigned and revised structure of njaoamine I.

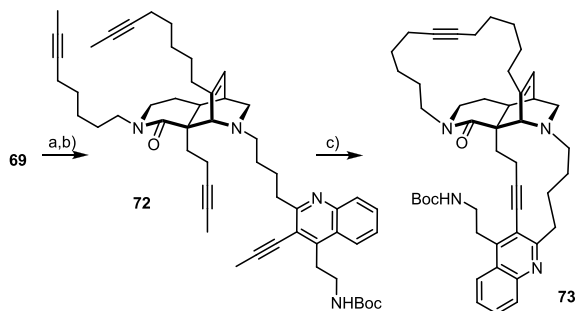
A brief comment on the absolute configuration is also warranted. In contrast to what the drawing in the isolation paper might insinuate,⁴⁹ it seems probable that the absolute configuration of the natural product is *opposite* to that of natural ingenamine: though isomeric to each other, synthetic nominal njaoamine I ((+)-4) and authentic njaoamine I are both dextrorotatory. Since (+)-4 derives from *ent*-14 (via 53), it is likely that njaoamine I is a sister compound of xestocyclamine A rather than ingenamine (for details, see the SI).

Coda: Concurrent Formation of Both Macrocycles.

The poor results obtained in the biomimetic studies directed toward keramaphidin B mentioned in the Introduction, in which concurrent formation of both macrocycles had been attempted,^{10,11} had prompted us to pursue a stepwise approach toward nominal njaoamine I in the first place as outlined above. Yet, the ability to effect an RCAM/RCM sequence en route to 35 without competing ene/yne crossover implies that the orientation of the tangling side chains on a rigid tricyclic core is favorable. Therefore, *simultaneous closure of both enveloping rings* by RCAM of a tetra-yne derivative seemed possible.

To test this tantalizing concept, 69 was treated with *L*-selectride as a nonoptimized shortcut for the preparation of the required tetra-yne derivative 72 (Scheme 10). Both catalyst systems used herein did an excellent job in converting this compound into 73 and small amounts of a second as yet

Scheme 10. Two Concurrent RCAM Reactions



^aReagents and conditions: (a) *L*-Selectride, THF, 40 °C; (b) 52, NaBH(OAc)₃, CH₂Cl₂, HOAc, 67% (over two steps); (c) 29 (60 mol %), 30 (60 mol %), MS 5 Å, toluene, reflux, 35% (73 + 17% (isomer), see text).

unidentified isomer formed by improper concatenation of the ends. The (almost) copolarity of the silanolate ligand hydrolyzed off the catalysts during workup turned out to be a technical issue; for these separation problems, the isolated yield of analytically pure 73 was only 35%, even though the reaction itself is clean. No further attempt was made to optimize the result (ligand variation, catalyst loading, etc.) because the subsequent site-selective reduction of the very hindered C31–C32 alkyne without touching the more accessible C36–C37 triple bond has so far not worked out. Yet, the successful double ring closure opens new perspectives for the use of RCAM in target-oriented synthesis at large; opportunities along these lines are currently under investigation in this laboratory.

CONCLUSIONS

The triumph of olefin metathesis is not only rooted in the abundance of olefins but also in the availability of catalysts that activate double bonds while leaving almost all other functional groups intact.^{129–131} This virtue allows retrosynthetic disconnections to be realized that are largely orthogonal to the conventional logic.^{59–61,132,133} Although (internal) alkynes in general are chemically more “expensive” than olefins and their use therefore only justified when specific and purposeful advantage is taken of their rich reactivity,^{23–25} it is of note that the latest generation of alkyne metathesis catalysts work in the presence of certain functional groups that even some of the most accomplished olefin metathesis catalysts cannot handle. The conquests of the polycyclic alkaloids keramaphidin B, ingenamine, xestocyclamine A, and, not least, nominal njaoamine I bear witness of the notion that alkyne metathesis has reached strategy level. This aspect notwithstanding, further improvements of the catalysts are necessary and perhaps likely in the near future.^{134,135}

At the same time, the present study illustrates that the implementation of alkyne metathesis can be limited by the lack of appropriate triple bond surrogates and/or the inability to address and manipulate a given alkyne in the presence of other functionality: the difficulties in subjecting compounds 58 and 70 to seemingly trivial chemoselective hydrometalation or semihydrogenation illustrate this aspect. In the future, the significance of alkyne metathesis will also be defined by the upstream and/or downstream alkyne chemistry. Therefore, our laboratory is committed to explore opportunities along these lines¹³⁶ in parallel to our ongoing work on fundamental and applied aspects of alkyne metathesis proper.^{35,36,114,137,138}

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at <https://pubs.acs.org/doi/10.1021/jacs.1c07955>.

Experimental section including supporting crystallographic information, experimental procedures, and characterization data; copies of NMR spectra of new compounds (PDF)

Accession Codes

CCDC 2081189–2081190 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

■ AUTHOR INFORMATION

Corresponding Author


Alois Fürstner – Max-Planck-Institut für Kohlenforschung,
45470 Mülheim/Ruhr, Germany;  orcid.org/0000-0003-0098-3417; Email: fuerstner@kofo.mpg.de

Authors

Zhanchao Meng – Max-Planck-Institut für Kohlenforschung,
45470 Mülheim/Ruhr, Germany

Simon M. Spohr – Max-Planck-Institut für Kohlenforschung,
45470 Mülheim/Ruhr, Germany

Sandra Tobegen – Max-Planck-Institut für Kohlenforschung,
45470 Mülheim/Ruhr, Germany

Christophe Farès – Max-Planck-Institut für Kohlenforschung,
45470 Mülheim/Ruhr, Germany;  orcid.org/0000-0001-6709-5057

Complete contact information is available at:

<https://pubs.acs.org/10.1021/jacs.1c07955>

Author Contributions

[†]Z.M. and S.M.S. contributed equally.

Funding

Open access funded by Max Planck Society.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

Generous financial support by the MPG is gratefully acknowledged. We thank PharmaMar, Madrid, most notably Dr. M. Pérez, for making a sample of authentic njaoamine I available to us; we also acknowledge the assistance of Prof. C. Jiménez, A. Coruña, in this matter. We thank J. Rust and Prof. C. W. Lehmann for solving the X-ray structures, S. Kestermann for help with the HPLC separations, and all analytical departments of our Institute for excellent support throughout our program.

■ REFERENCES

- Meng, Z.; Fürstner, A. Total Synthesis Provides Strong Evidence: Xestocyclamine A is the Enantiomer of Ingenamine. *J. Am. Chem. Soc.* **2020**, *142* (27), 11703–11708.
- Rodriguez, J.; Crews, P. Revised Structure of Xestocyclamine A and Description of a New Analogue. *Tetrahedron Lett.* **1994**, *35*, 4719–4722.
- Kong, F.; Andersen, R. J.; Allen, T. M. Ingenamine, A Novel Pentacyclic Alkaloid From the Marine Sponge *Xestospongia ingens*. *Tetrahedron Lett.* **1994**, *35*, 1643–1646.
- Kong, F.; Andersen, R. J. Ingenamine Alkaloids Isolated from the Sponge *Xestospongia ingens*: Structure and Absolute Configurations. *Tetrahedron* **1995**, *51*, 2895–2906.
- Baldwin, J. E.; Whitehead, R. C. On the Biosynthesis of Manzamines. *Tetrahedron Lett.* **1992**, *33*, 2059–2062.
- For different biosynthetic considerations, see: Kaiser, A.; Billot, X.; Gateau-Olesker, A.; Marazano, C.; Das, B. C. Selective Entry to the Dimeric or Oligomeric Pyridinium Sponge Macrocycles via Aminopentadienal Derivatives. Possible Biogenetic Relevance with Manzamine Alkaloids. *J. Am. Chem. Soc.* **1998**, *120* (32), 8026–8034.
- Kobayashi, J.; Tsuda, M.; Kawasaki, N.; Matsumoto, K.; Adachi, T. Keramaphidin B, a Novel Pentacyclic Alkaloid from a Marine Sponge *Amphimedon* sp.: A Plausible Biosynthetic Precursor of Manzamine Alkaloids. *Tetrahedron Lett.* **1994**, *35*, 4383–4386.
- Kobayashi, J. i.; Kawasaki, N.; Tsuda, M. Absolute stereochemistry of keramaphidin B. *Tetrahedron Lett.* **1996**, *37* (45), 8203–8204.

(9) Tsuda, M.; Inaba, K.; Kawasaki, N.; Honma, K.; Kobayashi, J. Chiral Resolution of (±)-Keramaphidin B and Isolation of Manzamine L, a New β -Carboline Alkaloid from a Sponge *Amphimedon* sp. *Tetrahedron* **1996**, *52*, 2319–2323.

(10) Baldwin, J. E.; Claridge, T. D. W.; Culshaw, A. J.; Heupel, F. A.; Lee, V.; Spring, D. R.; Whitehead, R. C.; Boughtflower, R. J.; Mutton, I. M.; Upton, R. J. Investigations into the Manzamine Alkaloid Biosynthetic Hypothesis. *Angew. Chem., Int. Ed.* **1998**, *37*, 2661–2663.

(11) Baldwin, J. E.; Claridge, T. D. W.; Culshaw, A. J.; Heupel, F. A.; Lee, V.; Spring, D. R.; Whitehead, R. C. Studies on the Biomimetic Synthesis of the Manzamine Alkaloids. *Chem. - Eur. J.* **1999**, *5*, 3154–3161.

(12) Gil, L.; Baucherel, X.; Martin, M. T.; Marazano, C.; Das, B. C. Model Studies towards a Biomimetic Synthesis of Keramaphidin B and Halicyclamine A. *Tetrahedron Lett.* **1995**, *36*, 6231–6234.

(13) Gomez, J. M.; Gil, L.; Ferroud, C.; Gateau-Olesker, A.; Martin, M. T.; Marazano, C. Selective Oxidation of a Keramaphidin B Model. *J. Org. Chem.* **2001**, *66*, 4898–4903.

(14) Jakubec, P.; Farley, A. J. M.; Dixon, D. J. Towards the Total Synthesis of Keramaphidin B. *Beilstein J. Org. Chem.* **2016**, *12*, 1096–1100.

(15) Shimoda, H.; Shibata, T.; Sekine, D.; Nakada, M. Synthetic Studies on Keramaphidin B: Formation of a Macrocyclic Ring by Intramolecular Diels-Alder Reaction. *Heterocycles* **2020**, *100*, 3–11.

(16) Gagnon, A.; Danishefsky, S. J. Evaluation of Diene Hierarchies for Diels-Alder Reactions en route to Xestocyclamine A: Elaboration of an Ansa Bridge by B-Alkyl Suzuki Macrocyclization. *Angew. Chem., Int. Ed.* **2002**, *41*, 1581–1584.

(17) Yun, H.; Gagnon, A.; Danishefsky, S. J. Towards the Synthesis of Xestocyclamine A: Investigation of Double Michael Reaction and Aza Diels-Alder Reaction. *Tetrahedron Lett.* **2006**, *47*, 5311–5315.

(18) Cheng, B.; Reyes, J. Recent Progress on the Total Syntheses of Macrocyclic Diamine Alkaloids. *Nat. Prod. Rep.* **2020**, *37*, 322–337.

(19) Zhou, X.; Xu, T.; Yang, X. W.; Huang, R.; Yang, B.; Tang, L.; Liu, Y. Chemical and Biological Aspects of Marine Sponges of the Genus *Xestospongia*. *Chem. Biodiversity* **2010**, *7*, 2201–2227.

(20) Nishida, A.; Nagata, T.; Nakagawa, M. Strategies for the Synthesis of Manzamine Alkaloids. *Top. Heterocycl. Chem.* **2006**, *5*, 255–280.

(21) Ihara, M.; Fukumoto, K. Synthesis of Polycyclic Natural Products Employing the Intramolecular Double Michael Reaction. *Angew. Chem., Int. Ed. Engl.* **1993**, *32*, 1010–1022.

(22) Faisal, M.; Shahzad, D.; Saeed, A.; Lal, B.; Saeed, S.; Larik, F. A.; Channar, P. A.; Mahesar, P. A.; Mahar, J. Review on Asymmetric Synthetic Methodologies for Chiral Isoquinuclidines; 2008 to Date. *Tetrahedron: Asymmetry* **2017**, *28*, 1445–1461.

(23) Fürstner, A. Alkyne Metathesis on the Rise. *Angew. Chem., Int. Ed.* **2013**, *52* (10), 2794–2819.

(24) Fürstner, A. Teaching Metathesis “Simple” Stereochemistry. *Science* **2013**, *341* (6152), 1229713.

(25) Ehrhorn, H.; Tamm, M. Well-Defined Alkyne Metathesis Catalysts: Developments and Recent Applications. *Chem. - Eur. J.* **2018**, *25*, 3190–3208.

(26) Chemler, S. R.; Trauner, D.; Danishefsky, S. J. The B-Alkyl Suzuki-Miyaura Cross-Coupling Reaction: Development, Mechanistic Studies, and Applications in Natural Product Synthesis. *Angew. Chem., Int. Ed.* **2001**, *40*, 4544–4568.

(27) Seidel, G.; Fürstner, A. Suzuki reactions of extended scope: the ‘9-MeO-9-BBN variant’ as a complementary format for cross-coupling. *Chem. Commun.* **2012**, *48* (15), 2055–2070.

(28) Nicolaou, K. C.; Edmonds, D. J.; Bulger, P. G. Cascade Reactions in Total Synthesis. *Angew. Chem., Int. Ed.* **2006**, *45*, 7134–7186.

(29) Tietze, L. F.; Brasche, G.; Gericke, K. *Domino Reactions in Organic Synthesis*; Wiley-VCH: Weinheim, 2006.

(30) Behenna, D. C.; Liu, Y.; Yurino, T.; Kim, J.; White, D. E.; Virgil, S. C.; Stoltz, B. M. Enantioselective Construction of Quaternary N-

Heterocycles by Palladium-Catalyzed Decarboxylative Allylic Alkylation of Lactams. *Nat. Chem.* **2012**, *4*, 130–133.

(31) Weaver, J. D.; Recio, A.; Grenning, A. J.; Tunge, J. A. Transition Metal-Catalyzed Decarboxylative Allylation and Benzylolation Reactions. *Chem. Rev.* **2011**, *111* (3), 1846–1913.

(32) Fürstner, A. Lessons from Natural Product Total Synthesis: Macrocyclization and Postcyclization Strategies. *Acc. Chem. Res.* **2021**, *54* (4), 861–874.

(33) Hillenbrand, J.; Leutzsch, M.; Yiannakas, E.; Gordon, C. P.; Wille, C.; Nöthling, N.; Copéret, C.; Fürstner, A. Canopy Catalysts for Alkyne Metathesis: Molybdenum Alkylidyne Complexes with a Tripodal Ligand Framework. *J. Am. Chem. Soc.* **2020**, *142* (25), 11279–11294.

(34) Hillenbrand, J.; Leutzsch, M.; Fürstner, A. Molybdenum Alkylidyne Complexes with Tripodal Silanolate Ligands. The Next Generation of Alkyne Metathesis Catalysts. *Angew. Chem., Int. Ed.* **2019**, *58*, 15690–15696.

(35) Haack, A.; Hillenbrand, J.; Leutzsch, M.; van Gastel, M.; Neese, F.; Fürstner, A. Productive Alkyne Metathesis with “Canopy Catalysts” Mandates Pseudorotation. *J. Am. Chem. Soc.* **2021**, *143* (15), 5643–5648.

(36) Hillenbrand, J.; Leutzsch, M.; Gordon, C. P.; Copéret, C.; Fürstner, A. ¹⁸³W NMR Spectroscopy Guides the Search for Tungsten Alkylidyne Catalysts for Alkyne Metathesis. *Angew. Chem., Int. Ed.* **2020**, *59*, 21758–21768.

(37) Thompson, R. R.; Rotella, M. E.; Du, P.; Zhou, X.; Fronczek, F. R.; Kumar, R.; Gutierrez, O.; Lee, S. Siloxide Podand Ligand Scaffold for Molybdenum-Catalyzed Alkyne Metathesis and Isolation of a Dynamic Metallatetrahedrane Intermediate. *Organometallics* **2019**, *38*, 4054–4059.

(38) For applications of RCAM in alkaloid synthesis using earlier generations of catalysts, see refs 39–46 and the following: Guo, L. D.; Huang, X. Z.; Luo, S. P.; Cao, W. S.; Ruan, Y. P.; Ye, J. L.; Huang, P. Q. Organocatalytic, Asymmetric Total Synthesis of (–)-Halicionin A. *Angew. Chem., Int. Ed.* **2016**, *55*, 4064.

(39) Luo, S.-P.; Huang, X.-Z.; Guo, L.-D.; Huang, P.-Q. Catalytic Asymmetric Total Synthesis of Macrocyclic Marine Natural Product (–)-Halicionin A. *Chin. J. Chem.* **2020**, *38* (12), 1723–1736.

(40) Boeckman, R. K.; Wang, H.; Rugg, K. W.; Genung, N. E.; Chen, K.; Ryder, T. R. A Scalable Total Synthesis of (–)-Nakadomarin A. *Org. Lett.* **2016**, *18*, 6136–6139.

(41) Gebauer, K.; Fürstner, A. Total Synthesis of the Biphenyl Alkaloid (–)-Lythranidine. *Angew. Chem., Int. Ed.* **2014**, *53*, 6393–6396.

(42) Kyle, A. F.; Jakubec, P.; Cockfield, D. M.; Cleator, E.; Skidmore, J.; Dixon, D. J. Total Synthesis of (–)-Nakadomarin A. *Chem. Commun.* **2011**, *47*, 10037–10039.

(43) Nilson, M. G.; Funk, R. L. Total Synthesis of (–)-Nakadomarin A. *Org. Lett.* **2010**, *12*, 4912–4915.

(44) Smith, B. J.; Sulikowski, G. A. Total Synthesis of (±)-Halicionacyclamine C. *Angew. Chem., Int. Ed.* **2010**, *49*, 1599–1602.

(45) Fürstner, A.; Rumbo, A. Ring-Closing Alkyne Metathesis. Stereoselective Synthesis of the Cytotoxic Marine Alkaloid Matuporamine C. *J. Org. Chem.* **2000**, *65*, 2608–2611.

(46) Fürstner, A.; Guth, O.; Rumbo, A.; Seidel, G. Ring Closing Alkyne Metathesis. Comparative Investigation of Two Different Catalyst Systems and Applications to the Stereoselective Synthesis of Olfactory Lactones, Azamacrolides and the Macrocyclic Perimeter of the Marine Alkaloid Nakadomarin A. *J. Am. Chem. Soc.* **1999**, *121*, 11108–11113.

(47) Reyes, F.; Fernández, R.; Urda, C.; Francesch, A.; Bueno, S.; de Eguilior, C.; Cuevas, C. Njaoamines A-F, new cytotoxic polycyclic alkaloids from the haplosclerid sponge Reniera sp. *Tetrahedron* **2007**, *63* (11), 2432–2438.

(48) Sorek, H.; Rudi, A.; Benayahu, Y.; Kashman, Y. Njaoamines G and H, two new cytotoxic polycyclic alkaloids and a tetrahydroquinolone from the marine sponge Neopetrosia sp. *Tetrahedron Lett.* **2007**, *48* (43), 7691–7694.

(49) Urda, C.; Pérez, M.; Rodríguez, J.; Fernández, R.; Jiménez, C.; Cuevas, C. Njaoamine I, a cytotoxic polycyclic alkaloid from the Haplosclerida sponge Haliclona (Reniera) sp. *Tetrahedron Lett.* **2018**, *59* (26), 2577–2580.

(50) Casamitjana, N.; López, V.; Jorge, A.; Bosch, J.; Molins, E.; Roig, A. Diels-Alder Reactions of 5,6-Dihydro-2(1H)-pyridones. *Tetrahedron* **2000**, *56*, 4027–4042.

(51) Giardini, A.; Lesma, G.; Passarella, D.; Perez, M.; Silvani, A. Double Michael Reaction of N-Carboethoxy-2,3-dihydropyridin-4-one. *Synlett* **2001**, *2001*, 132–134.

(52) For other recent applications in alkaloid synthesis, see ref 53 and the following: Hartrampf, N.; Winter, N.; Pupo, G.; Stoltz, B. M.; Trauner, D. Total Synthesis of the Norhasubanan Alkaloid Stephidamine. *J. Am. Chem. Soc.* **2018**, *140*, 8675.

(53) Pritchett, B. P.; Stoltz, B. M. Enantioselective Palladium-Catalyzed Allylic Alkylation Reactions in the Synthesis of Aspidosperma and Structurally Related Monoterpene indole Alkaloids. *Nat. Prod. Rep.* **2018**, *35*, 559–574.

(54) Kaname, M.; Yoshifuji, S.; Sashida, H. An Efficient Transformation of Cyclic Ene-carbamates into m-(N-Formylamino)-carboxylic Acids by Ruthenium Tetroxide Oxidation. *Chem. Pharm. Bull.* **2008**, *56*, 1310–1313.

(55) Tsuji, J.; Minami, I.; Shimizu, I.; Kataoka, H. Enone Formation from Allyl 2-Keto Esters, Alkenyl Allyl Carbonates, Silyl Enol Ethers, and Enol Acetates by the Phosphine-Free Palladium Catalyst. *Chem. Lett.* **1984**, *13*, 1133.

(56) Schaubach, S.; Gebauer, K.; Ungeheuer, F.; Hoffmeister, L.; Ilg, M. K.; Wirtz, C.; Fürstner, A. A Two-Component Alkyne Metathesis Catalyst System with an Improved Substrate Scope and Functional Group Tolerance: Development and Applications to Natural Product Synthesis. *Chem. - Eur. J.* **2016**, *22* (25), 8494–8507.

(57) For applications of this two-component catalyst system to natural product synthesis, see ref 58 and the following: Meng, Z.; Fürstner, A. Total Synthesis of (–)-Sinulariadiolide. A Transannular Approach. *J. Am. Chem. Soc.* **2019**, *141*, 805.

(58) Schulthoff, S.; Hamilton, J. Y.; Heinrich, M.; Kwon, Y.; Wirtz, C.; Fürstner, A. The Formosalides: Structure Determination by Total Synthesis. *Angew. Chem., Int. Ed.* **2021**, *60* (1), 446–454.

(59) Grubbs, R. H.; O’Leary, D. J. *Handbook of Metathesis*; Wiley-VCH: Weinheim, 2015.

(60) Nicolaou, K. C.; Bulger, P. G.; Sarlah, D. Metathesis Reactions in Total Synthesis. *Angew. Chem., Int. Ed.* **2005**, *44* (29), 4490–4527.

(61) Fürstner, A. Olefin Metathesis and Beyond. *Angew. Chem., Int. Ed.* **2000**, *39* (17), 3012–3043.

(62) Winkler, J. D.; Holland, J. M.; Kasparec, J.; Axelsen, P. H. Design and synthesis of constrained ephothilone analogs: The efficient synthesis of eleven-membered rings by olefin metathesis. *Tetrahedron* **1999**, *55* (27), 8199–8214.

(63) Arisawa, M.; Kato, C.; Kaneko, H.; Nishida, A.; Nakagawa, M. Concise synthesis of azacycloundecenes using ring-closing metathesis (RCMC). *J. Chem. Soc. Perkin Trans. 1* **2000**, No. 12, 1873–1876.

(64) Nicolaou, K. C.; Vassilikogiannakis, G.; Montagnon, T. The Total Synthesis of Coleophomones B and C. *Angew. Chem., Int. Ed.* **2002**, *41* (17), 3276–3281.

(65) Denmark, S. E.; Yang, S.-M. Intramolecular Silicon-Assisted Cross-Coupling Reactions: General Synthesis of Medium-Sized Rings Containing a 1,3-cis-cis Diene Unit. *J. Am. Chem. Soc.* **2002**, *124* (10), 2102–2103.

(66) Kim, Y. J.; Lee, D. Use of N-N Bond Stereodynamics in Ring-Closing Metathesis to Form Medium-Sized Rings and Macrocycles. *Org. Lett.* **2004**, *6* (23), 4351–4353.

(67) Fürstner, A.; Müller, C. Total synthesis of aspercyclide C. *Chem. Commun.* **2005**, No. 44, 5583–5585.

(68) Dougherty, J. M.; Jiménez, M.; Hanson, P. R. Synthesis of cyclic sulfamoyl carbamates and ureas via ring-closing metathesis. *Tetrahedron* **2005**, *61* (26), 6218–6230.

(69) Lejkowski, M.; Gais, H.-J.; Banerjee, P.; Vermeeren, C. Asymmetric Modular Synthesis of Highly Functionalized Medium-Sized Carbocycles and Lactones via Ring-Closing Metathesis of

Sulfoximine-Substituted Trienes. *J. Am. Chem. Soc.* **2006**, *128* (48), 15378–15379.

(70) Matsumura, T.; Akiba, M.; Arai, S.; Nakagawa, M.; Nishida, A. Synthetic study of manzamine B: synthesis of the tricyclic central core by an asymmetric Diels-Alder and RCM strategy. *Tetrahedron Lett.* **2007**, *48* (7), 1265–1268.

(71) Cluzeau, J.; Oishi, S.; Ohno, H.; Wang, Z.; Evans, B.; Peiper, S. C.; Fujii, N. Design and synthesis of all diastereomers of cyclic pseudo-dipeptides as mimics of cyclic CXCR4 pentapeptide antagonists. *Org. Biomol. Chem.* **2007**, *5* (12), 1915–1923.

(72) Brown, M. K.; Hoveyda, A. H. Enantioselective Total Synthesis of Clavirolide C. Applications of Cu-Catalyzed Asymmetric Conjugate Additions and Ru-Catalyzed Ring-Closing Metathesis. *J. Am. Chem. Soc.* **2008**, *130* (39), 12904–12906.

(73) Kaewpet, M.; Odell, B.; King, M. A.; Banerji, B.; Schofield, C. J.; Claridge, T. D. W. Synthesis and conformational analysis of cyclic analogues of inverse γ -turns. *Org. Biomol. Chem.* **2008**, *6* (19), 3476–3485.

(74) Braddock, D. C.; Millan, D. S.; Pérez-Fuertes, Y.; Pouwer, R. H.; Sheppard, R. N.; Solanki, S.; White, A. J. P. Bromonium Ion Induced Transannular Oxonium Ion Formation-Fragmentation in Model Obtusallene Systems and Structural Reassignment of Obtusallenes V-VII. *J. Org. Chem.* **2009**, *74* (5), 1835–1841.

(75) Cai, Z.; Yongpruksa, N.; Harmata, M. Total Synthesis of the Terpenoid Buddledone A: 11-Membered Ring-Closing Metathesis. *Org. Lett.* **2012**, *14* (7), 1661–1663.

(76) Pospíšil, J.; Müller, C.; Fürstner, A. Total Synthesis of the Aspercyclides. *Chem. - Eur. J.* **2009**, *15* (24), 5956–5968.

(77) Mao, S.; Jia, Y. Construction of the A ring of halichomycin via a RCM strategy. *Tetrahedron Lett.* **2013**, *54* (32), 4343–4345.

(78) Fernandes, R. A.; Chavan, V. P. A 12-membered to a strained 11-membered ring: first stereoselective total synthesis of (–)-asteriscunolide C. *Chem. Commun.* **2013**, *49* (32), 3354–3356.

(79) Prelog, V. Conformation and reactivity of medium-sized ring compounds. *Pure Appl. Chem.* **1963**, *6* (4), 545–560.

(80) Diver, S. T.; Giessert, A. J. Enyne Metathesis (Enyne Bond Reorganization). *Chem. Rev.* **2004**, *104*, 1317–1382.

(81) A total synthesis of manzamine A provides important precedent for a macrocyclization by RCM in the presence of a macrocyclic cycloalkyne and tertiary amines; however, the reaction required large amounts of Grubbs catalyst (1 equiv). See: Toma, T.; Kita, Y.; Fukuyama, T. Total Synthesis of (+)-Manzamine A. *J. Am. Chem. Soc.* **2010**, *132*, 10233–10235.

(82) Coop, A.; Rice, K. C. L-Selectride as a Convenient Reagent for the Selective Cleavage of Carbamates. *Tetrahedron Lett.* **1998**, *39*, 8933–8934.

(83) Several total syntheses of polycyclic diamine alkaloids provide an important precedent for the closure of medium-sized or macrocyclic rings in the presence of caged tertiary amines or the derived ammonium salts; see refs 84–88 and the following: Garg, N. K.; Hiebert, S.; Overman, L. E. Total Synthesis of (–)-Sarain A. *Angew. Chem., Int. Ed.* **2006**, *45*, 2912–2915.

(84) Becker, M. H.; Chua, P.; Downham, R.; Douglas, C. J.; Garg, N. K.; Hiebert, S.; Jaroch, S.; Matsuoka, R. T.; Middleton, J. A.; Ng, F. W.; Overman, L. E. Total Synthesis of (–)-Sarain A. *J. Am. Chem. Soc.* **2007**, *129* (39), 11987–12002.

(85) Jakubec, P.; Cockfield, D. M.; Dixon, D. J. Total Synthesis of (–)-Nakadomarin A. *J. Am. Chem. Soc.* **2009**, *131* (46), 16632–16633.

(86) Wang, C.; Yu, M.; Kyle, A. F.; Jakubec, P.; Dixon, D. J.; Schrock, R. R.; Hoveyda, A. H. Efficient and Selective Formation of Macrocyclic Disubstituted Z Alkenes by Ring-Closing Metathesis (RCM) Reactions Catalyzed by Mo- or W-Based Monoaryloxide Pyrrolide (MAP) Complexes: Applications to Total Syntheses of Epilachnane, Yuzu Lactone, Ambrettolide, Epothilone C, and Nakadomarin A. *Chem. - Eur. J.* **2013**, *19* (8), 2726–2740.

(87) Cheng, B.; Wu, F.; Yang, X.; Zhou, Y.; Wan, X.; Zhai, H. Efficient Total Synthesis of Marine Alkaloid (–)-Nakadomarin A. *Chem. - Eur. J.* **2011**, *17* (45), 12569–12572.

(88) Clark, J. S.; Xu, C. Total Synthesis of (–)-Nakadomarin A. *Angew. Chem., Int. Ed.* **2016**, *55* (13), 4332–4335.

(89) For an early precedent from this group in which macrocyclization by RCM failed in the presence of an amine or the derived ammonium salt, see: Fürstner, A.; Langemann, K. Macrocycles by Ring-Closing Metathesis. *Synthesis* **1997**, 792–803.

(90) Schwab, P.; Grubbs, R. H.; Ziller, J. W. Synthesis and Applications of $\text{RuCl}_2(\text{CHR}')(\text{PR}_3)_2$: The Influence of the Alkylidene Moiety on Metathesis Activity. *J. Am. Chem. Soc.* **1996**, *118* (1), 100–110.

(91) Schrodi, Y., Mechanisms of Olefin Metathesis Catalyst Decomposition and Methods of Catalyst Reactivation. In *Handbook of Metathesis*; Grubbs, R. H., Wenzel, A. G., O'Leary, D. J., Khosravi, E., Eds.; Wiley-VCH: Weinheim, 2015; Vol. 1, pp 323–342.

(92) Vougioukalakis, G. C.; Grubbs, R. H. Ruthenium-Based Heterocyclic Carbene-Coordinated Olefin Metathesis Catalysts. *Chem. Rev.* **2010**, *110* (3), 1746–1787.

(93) Hoveyda, A. H.; Gillingham, D. G.; Van Veldhuizen, J. J.; Kataoka, O.; Garber, S. B.; Kingsbury, J. S.; Harrity, J. P. A. Ru complexes bearing bidentate carbenes: from innocent curiosity to uniquely effective catalysts for olefin metathesis. *Org. Biomol. Chem.* **2004**, *2* (1), 8–23.

(94) For a study which showed how the E/Z-geometry can be controlled by proper choice of catalyst, see: Fürstner, A.; Radkowski, K.; Wirtz, C.; Goddard, R.; Lehmann, C. W.; Mynott, R. Total Syntheses of the Phytotoxic Lactones Herbarumin I and II and a Synthesis-Based Solution of the Pinolidoxin Puzzle. *J. Am. Chem. Soc.* **2002**, *124* (24), 7061–7069.

(95) Keitz, B. K.; Endo, K.; Patel, P. R.; Herbert, M. B.; Grubbs, R. H. Improved Ruthenium Catalysts for Z-Selective Olefin Metathesis. *J. Am. Chem. Soc.* **2012**, *134* (1), 693–699.

(96) Brown, C. A.; Ahuja, V. K. Catalytic Hydrogenation. VI. The Reaction of Sodium Borohydride with Nickel Salts in Ethanol Solution. P-2 Nickel, A Highly Convenient, New, Selective Hydrogenation Catalyst with Great Sensitivity to Substrate Structure. *J. Org. Chem.* **1973**, *38*, 2226–2230.

(97) For applications in combination with RCAM, see the following reference and literature cited therein: Wölfl, B.; Mata, G.; Fürstner, A. Total Synthesis of Callyspongiolide, Part 2: The Ynoate Metathesis/cis-Reduction Strategy. *Chem. - Eur. J.* **2019**, *25* (1), 255–259.

(98) The crystals used by the isolation team for X-ray diffraction were racemic. The mother liquor from which they were grown contained (+)-1 as well as (–)-1 in a 20:1 ratio; cf. ref 9.

(99) Arhart, R. J.; Martin, J. C. Sulfuranes. VI. Reactions involving the alkoxy ligands of dialkoxydiarylsulfuranes. Formation of olefins and ethers. *J. Am. Chem. Soc.* **1972**, *94* (14), 5003–5010.

(100) Oger, C.; Balas, L.; Durand, T.; Galano, J.-M. Are Alkyne Reductions Chemo-, Regio-, and Stereoselective Enough To Provide Pure (Z)-Olefins in Polyfunctionalized Bioactive Molecules? *Chem. Rev.* **2013**, *113* (3), 1313–1350.

(101) Heppkeausen, J.; Stade, R.; Goddard, R.; Fürstner, A. Practical New Silyloxy-Based Alkyne Metathesis Catalysts with Optimized Activity and Selectivity Profiles. *J. Am. Chem. Soc.* **2010**, *132*, 11045.

(102) Heppkeausen, J.; Stade, R.; Kondoh, A.; Seidel, G.; Goddard, R.; Fürstner, A. Optimized Synthesis, Structural Investigations, Ligand Tuning and Synthetic Evaluation of Silyloxy-Based Alkyne Metathesis Catalysts. *Chem. - Eur. J.* **2012**, *18*, 10281–10299.

(103) Sasakura, K.; Sugawara, T. Simple Synthesis of Pyrrolo[3,4-c]-Quinoline-3-Ones and Pyrrolo[3,4-c]Quinoline-3,4-Diones. *Synth. Commun.* **1987**, *17* (6), 741–753.

(104) Fürstner, A.; Seidel, G. Palladium-catalyzed arylation of polar organometallics mediated by 9-methoxy-9-borabicyclo[3.3.1]nonane: Suzuki reactions of extended scope. *Tetrahedron* **1995**, *51* (41), 11165–11176.

(105) Brummond, K. M.; Gesenberg, K. D.; Kent, J. L.; Kerekes, A. D. A new method for the preparation of alkynes from vinyl triflates. *Tetrahedron Lett.* **1998**, *39* (47), 8613–8616.

(106) A minor change concerned the elimination of the C9-OH group which was performed via the derived chloromethylsulfonate

ester rather than with Martin's sulfurane; for this reagent, see: Shimizu, T.; Ohzeki, T.; Hiramoto, K.; Hori, N.; Nakata, T. Chloromethanesulfonate as an Efficient Leaving Group: Rearrangement of the Carbon-Carbon Bond and Conversion of Alcohols into Azides and Nitriles. *Synthesis* **1999**, *1999*, 1373–1385.

(107) Abdel-Magid, A. F.; Carson, K. G.; Harris, B. D.; Maryanoff, C. A.; Shah, R. D. Reductive Amination of Aldehydes and Ketones with Sodium Triacetoxyborohydride. Studies on Direct and Indirect Reductive Amination Procedures. *J. Org. Chem.* **1996**, *61*, 3849–3862.

(108) Fürstner, A.; Seidel, G. Shortcut Syntheses of Naturally Occurring 5-Alkylresorcinols with DNA-Cleaving Properties. *J. Org. Chem.* **1997**, *62*, 2332–2336.

(109) Soderquist, J. A.; Santiago, B.; Rivera, I. Allyl, benzyl, and propargyl silanes via the Suzuki reaction. *Tetrahedron Lett.* **1990**, *31* (35), 4981–4984.

(110) Orita, A.; Otera, J. Elimination Strategy for Aromatic Acetylenes. *Chem. Rev.* **2006**, *106* (12), 5387–5412.

(111) Karabiyikoglu, S.; Iafe, R. G.; Merlic, C. A. Ring-Closing Metathesis with Vicinal Dibromoalkenes as Protected Alkynes: A Synthetic Approach to Macrocyclic Enynes. *Org. Lett.* **2015**, *17* (21), 5248–5251.

(112) Charlton, J. L.; Chee, G. Synthesis of chiral esters of acetylenedicarboxylic acid. *Tetrahedron Lett.* **1994**, *35* (34), 6243–6246.

(113) Arakawa, Y.; Tajima, M.; Arakawa, Y.; Yoshifuji, S. Stereospecific Synthesis of New 4-Amino-1,2,3-cyclohexanetricarboxylic Acids and 4-Amino-1,3-cyclohexanedicarboxylic Acids. *Chem. Pharm. Bull.* **2005**, *53* (1), 81–85.

(114) Hillenbrand, J.; Korber, J. N.; Leutzsch, M.; Nöthling, N.; Fürstner, A. Canopy Catalysts for Alkyne Metathesis: Investigations into a Bimolecular Decomposition Pathway and the Stability of the Podand Cap. *Chem. - Eur. J.* **2021**. DOI: 10.1002/chem.202102080.

(115) Adjé, N.; Breuilles, P.; Uguen, D. Desymmetrisation of meso propargylic diols. *Tetrahedron Lett.* **1993**, *34* (29), 4631–4634.

(116) Ralston, K. J.; Ramstadius, H. C.; Brewster, R. C.; Niblock, H. S.; Hulme, A. N. Self-Assembly of Disorazole C1 through a One-Pot Alkyne Metathesis Homodimerization Strategy. *Angew. Chem., Int. Ed.* **2015**, *54* (24), 7086–7090.

(117) Neuhaus, C. M.; Liniger, M.; Stieger, M.; Altmann, K. H. Total Synthesis of the Tubulin Inhibitor WF-1360F Based on Macrocyclic Formation through Ring-Closing Alkyne Metathesis. *Angew. Chem., Int. Ed.* **2013**, *52* (22), 5866–5870.

(118) Hickmann, V.; Kondoh, A.; Gabor, B.; Alcarazo, M.; Fürstner, A. Catalysis-based and Protecting-Group-free Total Syntheses of the Marine Oxylipins Hybridolactone and the Ecklonialactones A, B, and C. *J. Am. Chem. Soc.* **2011**, *133*, 13471–13480.

(119) Chaladaj, W.; Corbet, M.; Fürstner, A. Total Synthesis of Neurymenolide A Based on a Gold-Catalyzed Synthesis of 4-Hydroxy-2-pyrones. *Angew. Chem., Int. Ed.* **2012**, *51*, 6929–6933.

(120) Benson, S.; Collin, M.-P.; Arlt, A.; Gabor, B.; Goddard, R.; Fürstner, A. Second-Generation Total Synthesis of Spirastrellolide F Methyl Ester: The Alkyne Route. *Angew. Chem., Int. Ed.* **2011**, *50* (37), 8739–8744.

(121) Valot, G.; Regens, C. S.; O'Malley, D. P.; Godineau, E.; Takikawa, H.; Fürstner, A. Total Synthesis of Amphidinolide F. *Angew. Chem., Int. Ed.* **2013**, *52*, 9534–9538.

(122) Willwacher, J.; Kausch-Busies, N.; Fürstner, A. Divergent Total Synthesis of the Antimitotic Agent Leiodermatolide. *Angew. Chem., Int. Ed.* **2012**, *51* (48), 12041–12046.

(123) Willwacher, J.; Fürstner, A. Catalysis-Based Total Synthesis of Putative Mandelalide A. *Angew. Chem., Int. Ed.* **2014**, *53* (16), 4217–4221.

(124) Kwon, Y.; Schulthoff, S.; Dao, Q. M.; Wirtz, C.; Fürstner, A. Total Synthesis of Disciformycin A and B: Unusually Exigent Targets of Biological Significance. *Chem. - Eur. J.* **2018**, *24* (1), 109–114.

(125) Karier, P.; Ungeheuer, F.; Ahlers, A.; Anderl, F.; Wille, C.; Fürstner, A. Metathesis at an Implausible Site: A Formal Total Synthesis of Rhizoxin D. *Angew. Chem., Int. Ed.* **2019**, *58* (1), 248–253.

(126) Löffler, L. E.; Wirtz, C.; Fürstner, A. Collective Total Synthesis of Casbane Diterpenes: One Strategy, Multiple Targets. *Angew. Chem., Int. Ed.* **2021**, *60* (10), 5316–5322.

(127) Zhuo, C.-X.; Fürstner, A. Catalysis-Based Total Syntheses of Pateamine A and DMDA-Pat A. *J. Am. Chem. Soc.* **2018**, *140* (33), 10514–10523.

(128) Koos, M. R. M.; Kummerlöwe, G.; Kaltschnee, L.; Thiele, C. M.; Luy, B. CLIP-COSY: A Clean In-Phase Experiment for the Rapid Acquisition of COSY-type Correlations. *Angew. Chem., Int. Ed.* **2016**, *55* (27), 7655–7659.

(129) Trnka, T. M.; Grubbs, R. H. The Development of $L_2X_2Ru = CHR$ Olefin Metathesis Catalysts: An Organometallic Success Story. *Acc. Chem. Res.* **2001**, *34*, 18–29.

(130) Grubbs, R. H. Olefin-Metathesis Catalysts for the Preparation of Molecules and Materials. *Angew. Chem., Int. Ed.* **2006**, *45* (23), 3760–3765.

(131) Schrock, R. R. Multiple Metal-Carbon Bonds for Catalytic Metathesis Reactions. *Angew. Chem., Int. Ed.* **2006**, *45*, 3748–3759.

(132) Fürstner, A. Metathesis in Total Synthesis. *Chem. Commun.* **2011**, *47* (23), 6505–6511.

(133) Hoveyda, A. H. Evolution of Catalytic Stereoselective Olefin Metathesis: From Ancillary Transformation to Purveyor of Stereochemical Identity. *J. Org. Chem.* **2014**, *79* (11), 4763–4792.

(134) Cui, M.; Bai, W.; Sung, H. H. Y.; Williams, I. D.; Jia, G. Robust Alkyne Metathesis Catalyzed by Air Stable $d^2 Re(V)$ Alkylidyne Complexes. *J. Am. Chem. Soc.* **2020**, *142*, 13339–13344.

(135) Groos, J.; Hauser, P. M.; Koy, M.; Frey, W.; Buchmeiser, M. R. Highly Reactive Cationic Molybdenum Alkylidyne N-Heterocyclic Carbene Catalysts for Alkyne Metathesis. *Organometallics* **2021**, *40*, 1178–1184.

(136) Fürstner, A. *trans*-Hydrogenation, *gem*-Hydrogenation, and *trans*-Hydrometalation of Alkynes: An Interim Report on an Unorthodox Reactivity Paradigm. *J. Am. Chem. Soc.* **2019**, *141* (1), 11–24.

(137) Hillenbrand, J.; van Gastel, M.; Bill, E.; Neese, F.; Fürstner, A. Isolation of a Homoleptic Non-oxo $Mo(V)$ Alkoxide Complex: Synthesis, Structure, and Electronic Properties of Penta-*tert*-Butoxymolybdenum. *J. Am. Chem. Soc.* **2020**, *142* (38), 16392–16402.

(138) Haack, A.; Hillenbrand, J.; van Gastel, M.; Fürstner, A.; Neese, F. Spectroscopic and Theoretical Study on Siloxy-Based Molybdenum and Tungsten Alkylidyne Catalysts for Alkyne Metathesis. *ACS Catal.* **2021**, *11*, 9086–9101.