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Communication

Total Synthesis Provides Strong Evidence: Xestocyclamine A is the Enantiomer of Ingenamine

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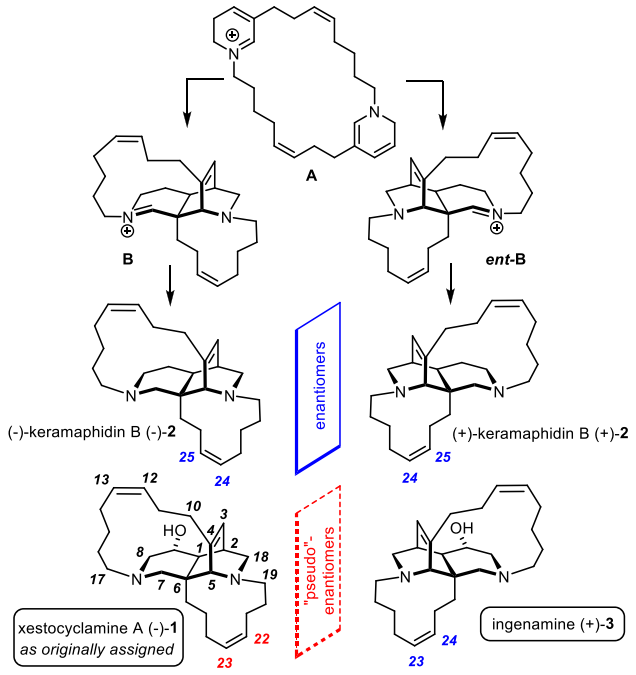
ABSTRACT: Xestocyclamine A ((−)-**1**) is featured prominently in a biosynthesis pathway leading to a large family of polycyclic alkaloids. The first total synthesis now proves that the structure of this compound had originally been misassigned. The route to (−)-**1** is based on a double Michael addition for the formation of the bridged diazadecalin core and a palladium-catalyzed decarboxylative allylation to install the quaternary bridgehead center. Ring-closing alkyne metathesis allowed a 13-membered cycloalkyne to be forged, which was selectively reduced during an involved sequence of hydroboration/selective protodeborylation/alkyl-Suzuki coupling used to close the 11-membered ring. Crystallographic data prove the identity of synthetic (−)-**1** with nominal xestocyclamine, but the spectra differ from those of the authentic alkaloid. To clarify the point, the synthesis was redirected toward ingenamine (**3**), which is supposedly a positional isomer of **1**. The recorded data confirm the assignment of this particular natural product and strongly suggest that xestocyclamine A is in fact the enantiomer of ingenamine (+)-**3**.

A large family of polycyclic alkaloids is thought to derive from macrocyclic dimers such as **A** as the biosynthetic precursors, which are composed of partly reduced 3-alkylpyridine units (Scheme 1).[1] The key step of this "Baldwin−Whitehead postulate" set forth in 1992 consists of a transannular Diels−Alder reaction leading to **B** in the first place;[2] keramaphidin B (**2**) is the reduced form of this iminium salt, a natural product that was isolated only after this intriguing biosynthetic proposition had been made.[3] The fact that both enantiomers of **2** occur in nature might imply that the critical cycloaddition is not enzyme-dependent; however, emulation of this biomimetic route in vitro gave only minute amounts of (±)-**2** (0.2−0.3%) despite considerable optimization.[4,5] A second approach to (±)-**2**, in which the Diels−Alder reaction was performed intermolecularly and the macrocycles were then forged by two concurrent ring-closing metathesis (RCM) reactions, was also very low-yielding (1−2%).[5,6]

Scheme 1. Biosynthetic Reasoning and Structures of Some Alkylpyridine-Derived Alkaloids



The closest analogues of **2** are nominal xestocyclamine A ((−)-**1**)[7] and ingenamine ((+)-**3**)[8] as the parent compounds of two subsets of alkaloids endowed with remarkable biological properties.[1] These compounds are supposedly pseudoenantiomeric in that they differ in the exact positioning of the double bond within the 11-membered ring. Their central rank on the Baldwin−Whitehead pathway notwithstanding,[2] no total syntheses of these prominent targets have been reported in over 25 years since their discovery. The challenges posed by the pentacyclic framework, which comprises a 1,4-etheno-bridged 2,7-diazadecalin core enveloped by two ansa bridges forming the signature macrocycles, were highlighted by in-depth studies directed toward **1** by the Danishefsky group (Scheme 2).[9] Those authors reached the core by a sophisticated Diels−Alder/"stitching" annulation strategy; they were also able to show that an alkyl-Suzuki coupling[10,11] allows the strained 11-membered ring to be closed. However,

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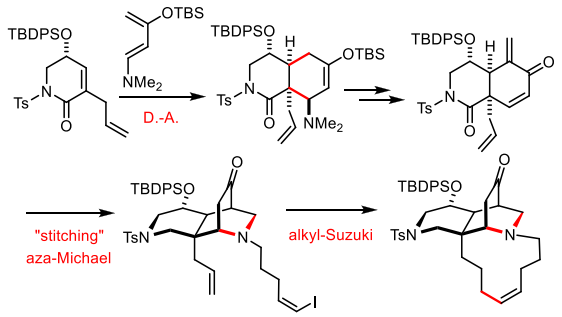
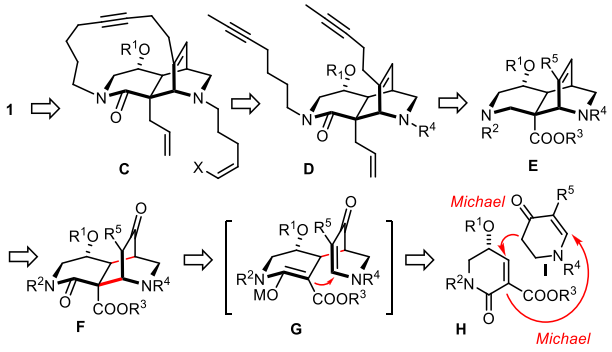
Scheme 2. Major Literature Precedent: The Danishefsky Model Study[9a]



appropriate handles for the formation of the second macrocycle could not be incorporated at the very beginning, and their late-stage attachment had not been described either.[9]

While contemplating various alternative blueprints for the synthesis of (−)-**1** as our first target, we were guided by the following considerations: (i) The poor outcome of the double-RCM route toward (±)-**2**[5] suggested that consecutive closure of the two macrocycles by chemically orthogonal methodologies is preferable. (ii) If the successful alkyl-Suzuki reaction was to be retained in some format (Scheme 3),[9] it would be

Scheme 3. Retrosynthetic Analysis

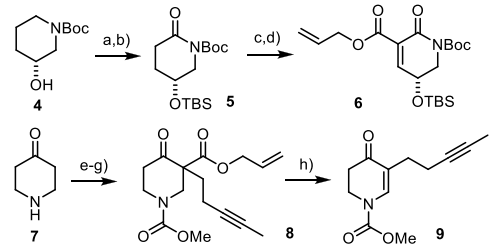


better allied with ring-closing alkyne metathesis (RCAM)[12−14] than with olefin RCM; while modern RCAM catalysts leave all kinds of double bonds untouched, RCM might fail to discriminate the two (*Z*)-alkenes in the target and hence result in scrambling.[15] (iii) Ideally, the chosen building blocks should already carry handles for the macrocyclization events; this boundary condition is difficult to meet with an approach based on a [4 + 2] cycloaddition for the formation of the diazadecalin core, as clearly documented in the prior art.[9,16] (iv) Whatever alternative method was chosen, it had to provide control over the stereocenters on the rim, including the quaternary bridgehead position. (v) A transannular strategy, though intellectually appealing,[4,5] would be handicapped on entropic and steric grounds (see above) and therefore likely inadequate.

With these caveats in mind, a Michael/Michael cascade using synthons of type **H** and **I** was deemed to be promising (Scheme 3).[17,18] These partners exhibit matching reactivity profiles that should result in proper orchestration: Specifically, the high electrophilicity of **H** is expected to power the first C−C bond formation under stereochemical control by the adjacent stereogenic center. This first critically important step in turn generates an excellent Michael donor **G**, which should engage with the less electrophilic partner and forge a suitably functionalized bridged diazadecalin segment **F**.

Access to **6** as an adequate incarnation of **H** requires nine steps if one commences by a literature-known route;[19] therefore, a considerably shorter entry was developed (Scheme 4). O-Silylation of **4** and subsequent regioselective C−H

Scheme 4[a]



[a]Reagents and conditions: (a) TBSCl, imidazole, DMF; (b) RuO_2 (6 mol %), $NaIO_4$, EtOAc/H_2O, 55% (over two steps); (c) LiHMDS, allyl chloroformate, THF, then PhSeCl, −78 °C → RT; (d) aqueous H_2O_2 (35% w/w), CH_2Cl_2, 0 °C, 76%; (e) ClCOOMe, K_2CO_3, THF/H_2O, quant.; (f) LiHMDS, allyl chloroformate, toluene, −78 °C → 0 °C, 50%; (g) 1-iodo-3-pentyne, K_2CO_3, acetone, reflux, 36%; (h) $Pd_2(dba)_3$·$CHCl_3$ (10 mol %), MeCN, reflux, quant.

oxidation with RuO_2 cat./$NaIO_4$ furnished lactam **5** in 55% yield (>99% ee) over the two steps on a >18 g scale.[20] Deprotonation with excess LiHMDS was followed by sequential addition of allyl chloroformate and PhSeCl; the resulting product was treated with H_2O_2 under strictly neutral conditions to give product **6** in high yield, again on a multigram scale. The fact that the mild selenation/oxidation chemistry[21] worked better than conceivable alternative methods is tentatively attributed to the pronounced electrophilicity of this sensitive product.

A suitable partner **9** was prepared by acylation/alkylation of **7**. Product **8** thus formed underwent decarboxylative dehydrogenation upon treatment with $Pd_2(dba)_3$·$CHCl_3$ as the catalyst.[22] Only this phosphine-free procedure proved to be selective and scalable (>2 g, single largest batch), whereas alternative Pd sources furnished mixtures of little preparative utility.

In contrast to what had been anticipated, the double Michael reaction did not proceed as a cascade[23] because the second step turned out to be reversible in the presence of a strong base such as LiHMDS; this result suggests that the enolate derived from the 1,3-dicarbonyl unit is too good a leaving group. Gratifyingly, however, a change of the base allowed product **11** to be reached in a very practical manner (Scheme 5). Specifically, **9** was deprotonated with LiHMDS, and the resulting enolate reacted with acceptor **6**. Spectral evidence suggested that product **10** was formed as mixture of isomers at C2, but with excellent stereocontrol of the critically important C1 position (xestocyclamine numbering). When this crude mixture was exposed to K_2CO_3 in refluxing MeCN, the second, now intramolecular Michael addition took place: the desired caged compound **11** was easily separated from the C2-isomeric product at this stage, thus opening entry into the diazadecalin core of xestocyclamine A on a gram scale. The subsequent Pd-catalyzed decarboxylative allylation[24−26] allowed the challenging quaternary center C6 in **12** to be set and an appropriate

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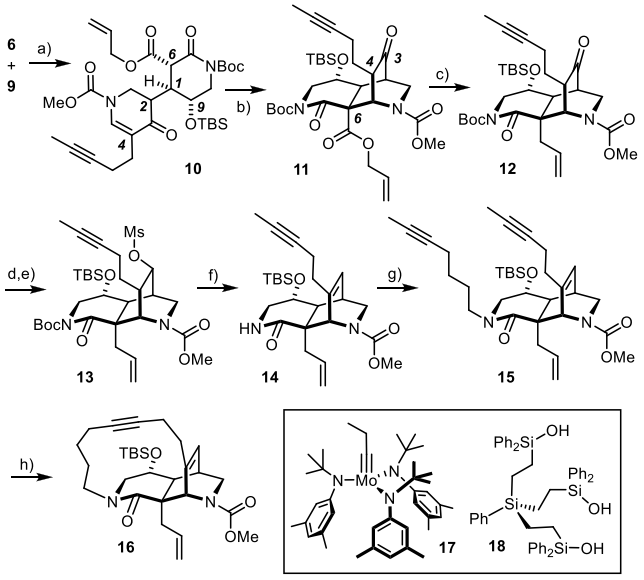
Scheme 5[a]



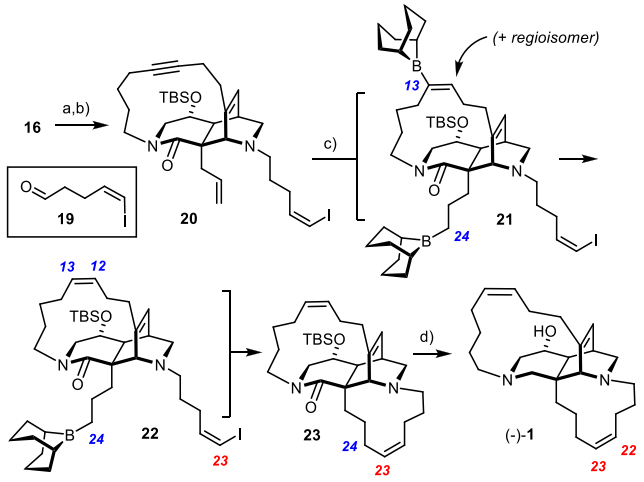
[a]Reagents and conditions: (a) LiHMDS, THF, −78 °C; (b) K_2CO_3, MeCN, reflux, 43% (over two steps); (c) $Pd(PPh_3)_4$ (10 mol %), toluene, 50 °C, quant.; (d) $NaBH_4$, MeOH, 0 °C; (e) MsCl, Et_3N, DMAP, CH_2Cl_2, 81% (over two steps); (f) 2,6-lutidine, 170 °C, then TBSOTf, CH_2Cl_2, RT, 72%; (g) NaH, 7-iodo-2-heptyne, DMF, 0 °C, 91%; (h) **17** (25 mol %), **18** (25 mol %), toluene, 110 °C, 85%.

handle for the projected ring closure to be installed in essentially quantitative yield. This rewarding outcome reflects the rigorous stereocontrol imposed by the rigid tricyclic scaffold. Reduction of the ketone with $NaBH_4$ gave the corresponding alcohol as a single diastereomer.[27] The subsequent elimination proved to be surprisingly difficult and failed under a variety of conditions.[28] Finally, it was found that treatment of the derived mesylate **13** with lutidine at 170 °C furnished alkene **14** in good yield; the concomitant cleavage of the N-Boc protecting group was a favorable side effect of these harsh conditions.

Compound **14** was N-alkylated with 7-iodo-2-heptyne, and the resulting diyne was subjected to RCAM. Use of the two-component catalyst system comprising complex **17** and trisilanol ligand **18** cleanly furnished the 13-membered ring in a reaction time of <10 min.[29,30] The structure of the resulting cycloalkyne **16** was confirmed by X-ray diffraction (see the Supporting Information (SI)). Cleavage of the methyl carbamate with excess L-Selectride[31] followed by reductive N-alkylation[32,33] set the stage for the formation of the 11-membered ring.

The successful implementation of an alkyl-Suzuki coupling into the model study by the Danishefsky group[9] inspired us to pursue a more involved scenario (Scheme 6). Specifically, treatment of compound **20** with excess 9H-9-BBN led to hydroboration of the terminal alkene and non-regioselective hydroboration of the internal alkyne but left the trisubstituted olefin and the iodoalkene untouched. Since a C_{sp^2}−BBN moiety is substantially more labile than a C_{sp^3}−BBN group, addition of dilute HOAc resulted in selective protonolysis of the alkenylborane site of **21**; this maneuver unveiled the signature $\Delta^{12,13}$ (*Z*)-alkene moiety of the target while keeping the donor at C-24 intact for the projected cross-coupling.[34] Excess acid was then quenched with $NaHCO_3$, and the mixture

Scheme 6[a]



[a]Reagents and conditions: (a) L-Selectride, THF; (b) **19**, CH_2Cl_2, $NaBH(OAc)_3$, 89% (over two steps); (c) (i) 9H-9-BBN, THF; (ii) H_2O, HOAc, THF; (iii) THF, $NaHCO_3$; (iv) [(dppf)$PdCl_2$] cat., $AsPh_3$ cat., and Tl_2CO_3, THF/DMF/H_2O (6:3:1), 48%; (d) Dibal-H, THF, then MeOH, 57%.

was diluted with THF. The resulting solution of **22** was slowly added to a solution of [(dppf)$PdCl_2$] cat., $AsPh_3$ cat., and Tl_2CO_3 in THF/DMF/H_2O to close the yet missing 11-membered ring. This intricate but convenient tactic merged stereoselective alkyne semireduction with macrocycle formation and gave **23** in very reproducible 48% overall yield. Final lactam reduction and deprotection was achieved in one step with Dibal-H followed by a MeOH quench.

The constitution and stereostructure of our samples, including the correct positions and *Z* configurations of the two olefins embedded in the macrocycles, were rigorously proven by spectroscopic means and X-ray diffraction: synthetic (−)-**1** is definitely nominal xestocyclamine A (Figure 1).

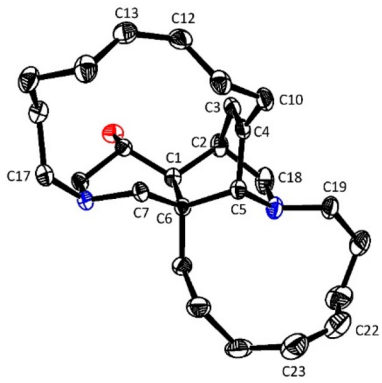


Figure 1. Structure of nominal xestocyclamine A ((−)-**1**) in the solid state. H atoms have been omitted for clarity.

However, the NMR spectra of the free base and the derived salt (−)-**1**·2HCl (and any stage in between) slightly differ from the literature data.[7] In consideration of the proposed biosynthesis (Scheme 1), the misalignment of the $\Delta^{22,23}$ olefin by the isolation team was deemed the most likely reason for the mismatch: xestocyclamine A might either be identical with or enantiomeric to ingenamine (+)-**3** (just as keramaphidin occurs in both forms in nature).

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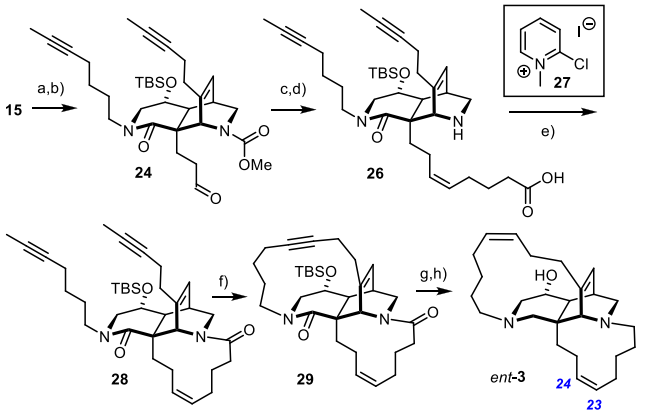
Since the spectra of the natural products were recorded in different solvents and authentic samples of neither alkaloid were available any longer for reinspection, a total synthesis of ingenamine was necessary to obtain material for comparison. As the most pragmatic approach toward this end, the route to xestocyclamine A was diverted at the stage of compound **15** (Scheme 7). Selective hydroboration/oxidation of the terminal

Scheme 7[a]



[a]Reagents and conditions: (a) 9H-9-BBN, THF, then $NaBO_3 \cdot H_2O$; (b) PDC, 4 Å MS, CH_2Cl_2, 74% (over two steps); (c) $[Ph_3P(CH_2)_4COOH]Br$ (**25**), NaHMDS, THF, 0 °C, then **24**, −90 °C → 0 °C; (d) L-Selectride, THF, 40 °C; (e) **27**, $(iPr)_2NEt$, CH_2Cl_2, 39% (over three steps); (f) **17** (30 mol %), **18** (30 mol %), toluene, 100 °C, 82%; (g) $Ni(OAc)_2 \cdot 4H_2O$, $NaBH_4$, ethylenediamine, EtOH, then H_2 (1 atm), 86%; (h) $LiAlH_4$, $AlCl_3$, THF, 58%.

alkene[35] opened access to aldehyde **24**, which was subjected to Wittig reaction with the nonstabilized ylide derived from the commercial salt $[Ph_3P(CH_2)_4COOH]Br$ (**25**). Cleavage of the carbamate with L-Selectride furnished amino acid **26** in readiness for macrolactamization with Mukaiyama's reagent (**27**).[36] For polarity reasons, this sequence was carried out without rigorous characterization of the intermediates; it furnished **28** in 39% yield over three steps. The subsequent RCAM reaction under the conditions described above proceeded smoothly to give cycloalkyne **29** (the structure in the solid state is contained in the SI). Semireduction of this compound with nickel boride[37] was followed by concomitant reduction of the two amides and cleavage of the silyl ether with excess AlH_3. The X-ray structure shown in Figure 2 confirms the structural integrity of synthetic *ent*-ingenamine ((−)-**3**).

Gratifyingly, the NMR spectra of (−)-**3** thus formed in MeOH-d_4 matched those of rigorously acid-free natural ingenamine in the same solvent.[38] Because the spectra in $CDCl_3$/DMSO-d_6 were found to be very sensitive to the exact solvent ratio and even trace acid in the medium, any direct comparison is difficult.[39] However, in the presence of 0.4 equiv of trifluoroacetic acid, the ^1H and ^{13}C NMR spectra of synthetic (−)-**3** reproduce well those of xestocyclamine A reported in the literature. Therefore, and in consideration of the sign of the optical rotation of the samples, we firmly conclude that xestocyclamine A had originally been misassigned: in all likelihood it is the enantiomer rather than a pseudoenantiomer of ingenamine, even though only authentic material from the natural source can provide ultimate proof.[40] Since these compounds are featured prominently on the Baldwin−Whitehead biosynthesis pathway, the total syntheses reported above provide an essential clarification.

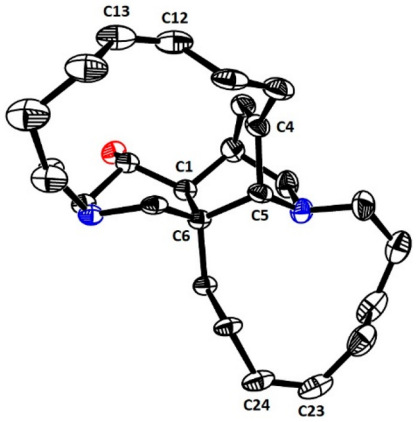


Figure 2. Structure of *ent*-ingenamine ((−)-**3**) in the solid state. H atoms have been omitted for clarity.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/jacs.0c05347.

Experimental section including characterization data, HPLC traces, NMR spectra of new compounds, and supporting X-ray crystallographic data for compounds (PDF)

X-ray crystallographic data for **16** (CIF)

X-ray crystallographic data for **29** (CIF)

X-ray crystallographic data for (−)-**1** (CIF)

X-ray crystallographic data for (−)-**3** (CIF)

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Notes

The authors declare no competing financial interest.

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