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Oxamidation of Unsaturated *O*-Alkyl Hydroxamates: Synthesis of the Madangamine Diazatricylic (ABC Rings) Skeleton

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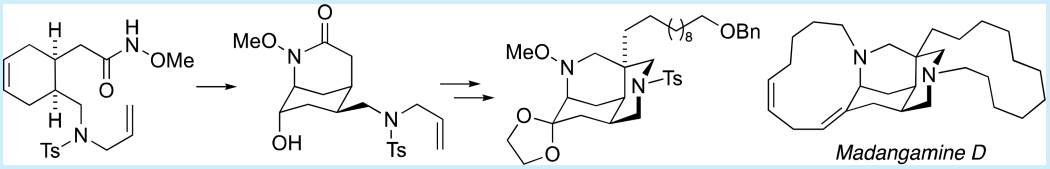
Supporting Information



ABSTRACT: A novel approach to the diazatricyclic madangamine ABC ring system and the synthesis of an advanced, differentially protected intermediate for the synthesis of madangamine D is reported. Central to the success of this approach is the iodine(III)-mediated intramolecular oxamidation of an unsaturated *O*-methyl hydroxamate, a π−N$^+$-type cyclization which proceeds in high yield and with complete regioselectivity to generate the 2-azabicyclo[3.3.1]nonane (morphan) system encompassing rings A and C.

Isolated from marine sponges of the order *Haplosclerida*, the madangamines are a small family of cytotoxic 3-alkylpiperidine alkaloids (Figure 1).[1] Since the initial discovery of madangamine A (**1**) in 1994 by Andersen,[2] five other members of this group (B−F, **2**−**6**) have been found.[3] The structure of these natural products was initially determined by an extensive combination of spectroscopic techniques, but it was not until 2014 that the absolute configuration of the family was firmly established through enantioselective total synthesis of madangamine D (**4**).[4] Although madangamines A (**1**), D (**4**), and F (**6**) display differential cytotoxicity toward a range of tumor cell lines,[5] investigation of their mode of action or identification of other biological activities has been hampered by their paucity in nature.

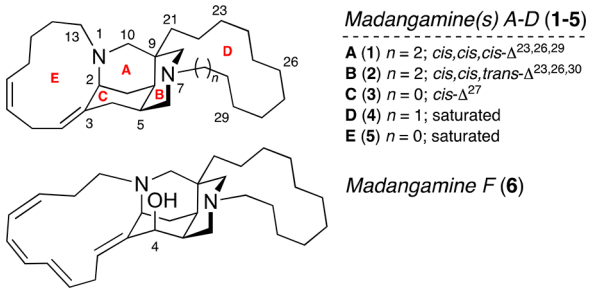


Figure 1. Members of the madangamine alkaloid family.

Structurally, the madangamines are characterized by a pentacyclic skeleton with variations of the size and degree of unsaturation in macrocyclic rings E and D. With the exception of madangamine F (**6**), which differs only in being oxidized at the C-4 position, all members of this family share the same diazatricyclic skeleton (rings ABC), encompassing the 2-azabicyclo[3.3.1]nonane ring system. Despite sustained interest, only two total syntheses of this group have been reported to date: Amat and Bosch completed the first asymmetric synthesis of (+)-madangamine D (**4**) in 2014,[4] while Chida has more recently reported a unified route to madangamines A (**1**), C (**3**), and E (**5**).[5] In addition to these pioneering accomplishments, several studies directed toward construction of the pendant macrocycles and the tricyclic core have been reported.[1,6] Routes to the latter system, including the one reported here, can be broadly categorized as following one of the strategies outlined in Figure 2.

The most widely employed approach to the core ABC ring system has been the *N*-cyclization of *cis*-perhydroisoquinolines, such as **7** and **8**, which encompass rings B and C (**A**, Figure 2). While Weinreb,[7] and later Amat and Bosch,[8a] have employed alkene aminomercuration to establish ring A, ring opening of epoxides of type **8** has been successfully employed by Amat and Bosch to the same end.[4,8,9] Kibayashi's route to the tricyclic core also features N-1/C-2 (madangamine numbering) bond formation but, in this case, ring A closure was accomplished through generation and reduction of bridgehead iminium ion **9**.[10]

An alternative approach to ring A formation has been developed by Diaba and Bonjoch, who employed the 6-*exo*-*trig* cyclization of 3-aza-6-heptenyl radical **10** to form the C-9/C-11 bond (**B**, Figure 2).[11] Routes to the ABC nucleus involving ring C formation been reported by Chida,[5,12] who used the *N*-acyliminium cyclization of propargyl silane **11**, and Marazano, who has reported the biomimetic condensation of dihydropyridinium ion **12** and the sodium salt of diethylacetonedicarbox-

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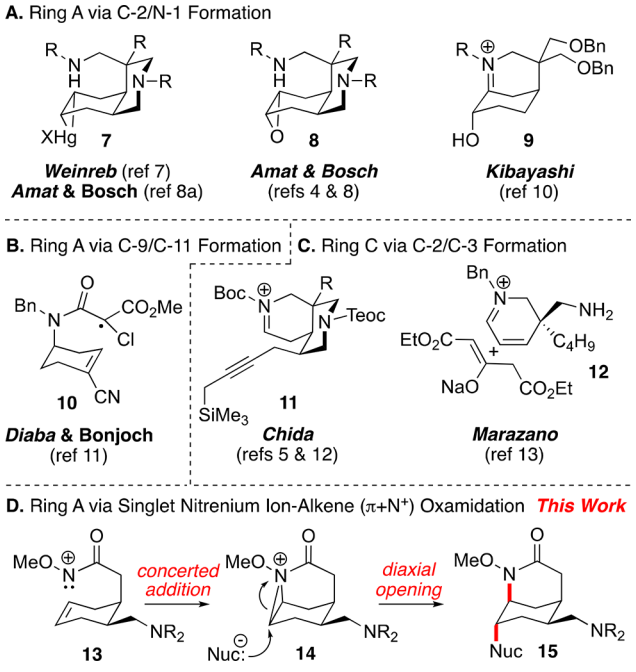


Figure 2. Prior and current synthetic approaches to the madangamine diazatricyclic skeleton.

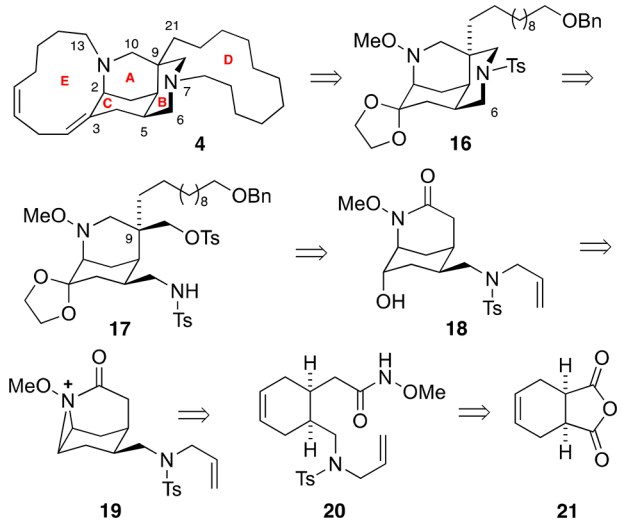
ylate to simultaneously establish the C-2/C-3, C-5/C-11 and C-6/N-7 bonds (**C**, Figure 2).[13]

Herein, we report a novel approach to the madangamine ABC ring system and the synthesis of an advanced, differentially protected intermediate for the synthesis of madangamine D (**4**) (**D**, Figure 2). The central transformation of this work involves the cyclization of unsaturated singlet nitrenium ion **13** to generate aziridinium ion **14**. Ion pair collapse of this highly reactive intermediate proceeds with complete regioselectivity to simultaneously establish the 2-azabicyclo[3.3.1]nonane madangamine core and introduce functionality at C-3 necessary for later-stage introduction of ring E. Use of this π+N$^+$-type alkene oxamidation represents an extension of our ongoing study of nitrenium ions and the application of these reactive intermediates to the synthesis of alkaloid natural products and azacyclic systems, in general.[14,15]

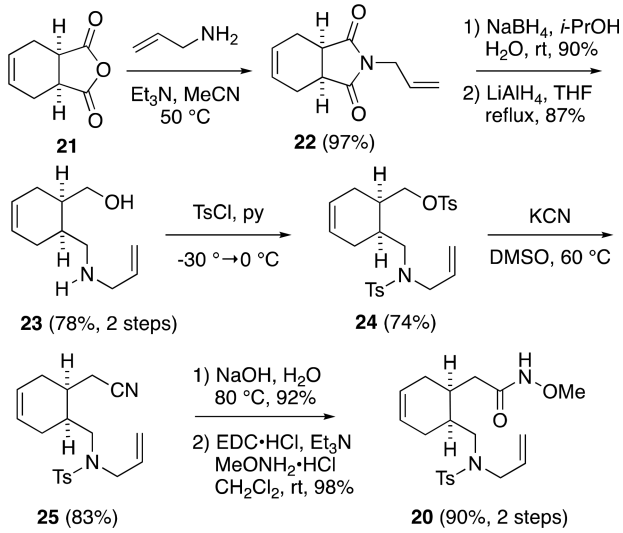
When planning our route to the madangamine skeleton and madangamine D (**4**) itself, we envisioned that late-stage, macrocycle installation could be accomplished with most flexibility, viz-à-viz order of D/E ring formation, from fully functionalized, orthogonally protected diamine **16**, which encompasses rings ABC (Scheme 1). Disconnection of the N-7/C-8 bond, leading to **17**, revealed two challenges: (a) installment of the pivotal quaternary stereocenter at C-9 and (b) construction of the 2-azabicyclo[3.3.1]nonane system itself. Morphan **18** was anticipated to rise from the ring opening of intermediate **19**, which would be generated during the iodine(III)-mediated oxamidation of **20**.[15a] One-carbon homologation of *meso* anhydride **21** would then provide ready access to this unsaturated *O*-methyl hydroxamate.

Our route to the madangamine core commenced from imide **22**, prepared in high yield by condensation of *cis*-tetrahydrophthalic anhydride (**21**) with allylamine (Scheme 2). Treatment of **22** with sodium borohydride in a mixture of *i*-PrOH−H_2O (6:1),[16] and reduction of the resulting γ-hydroxy-*N*-allylamide with $LiAlH_4$ provided amino alcohol **23** as a single diastereomer in 78% overall yield.[17] Taking advantage of the *p*-tolylsulfonyl

Scheme 1. Retrosynthetic Analysis



Scheme 2. Preparation of Oxamidation Substrate 20



moiety's duality as *N*-protecting group and alcohol activator, **23** was treated with excess (3 equiv) *p*-toluenesulfonyl chloride at low temperature (−30 °C) to generate bis-*N*,*O*-tosylate **24** (74% yield).[18] One-carbon homologation of this material was accomplished by treatment with KCN in DMSO to provide **25** in 83% yield. Nitrile hydrolysis under basic conditions and then carbodiimide-mediated coupling of the resulting carboxylic acid with *O*-methoxylamine gave hydroxamate ester **20** in 90% yield over two steps.

Employing our previously reported conditions for the oxamidation of unsaturated *O*-alkyl hydroxamates,[15a] sequential treatment of **20** with trifluoroacetic acid (1.0 equiv) and phenyliodine(III) bis(trifluoroacetate) (PIFA) (1.2 equiv) in CH_2Cl_2, provided **18** in high yield after in situ cleavage of trifluoroacetate ester **26** with methanolic ammonia (Scheme 3). Compound **18** was isolated as a single diastereomer, which arises from regioselective ring opening at C-3;[19] no trace of the 2-azabicyclo[3.2.2]nonan-7-ol arising from distal opening was detected. Importantly, this process is amenable to scale up and has been conducted on multigram scales without decrease in efficiency.

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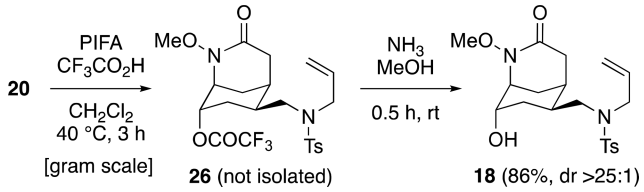
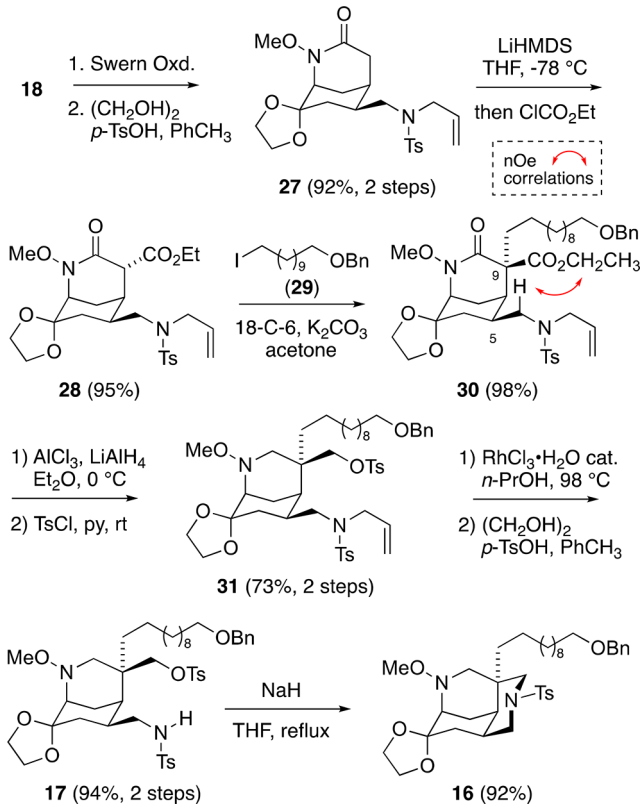
Scheme 3. Generation of 2-Azabicyclo[3.3.1]nonane Ring System



In preparation for generation of the key quaternary stereocenter at C-9, secondary alcohol **18** was oxidized under Swern conditions to provide the corresponding ketone which was condensed with ethylene glycol to provide acetal **27** in excellent overall yield (Scheme 4). Generation of the enolate of

Scheme 4. Madangamine ABC Core Skeleton



morphan **27** using LiHMDS and addition of ethyl chloroformate provided **28** as a single diastereomer. Now employing anhydrous K_2CO_3 in conjunction with 18-crown-6[20] to minimize competitive enolate *O*-alkylation, **28** underwent exclusive *exo*-face *C*-alkylation with 11-iodoundecan-1-yl benzyl ether (**29**)[21] to provide **30** in near-quantitative yield. As indicated in Scheme 4, the configuration of the quaternary stereocenter was confirmed by a NOESY NMR experiment, which revealed a cross peak between the methylene group of the C-9 ethyl ester and one of the protons of the C-5 *endo* aminomethyl substituent.[22]

Rather than cleaving the *N*-methoxyl group of lactam **30**, we now took advantage of this substituent as an *N*-protecting group.[23] Thus, treatment of **30** with excess alane (AlH_3) (2.7 equiv) reduced the lactam and ethyl ester groups but did not cleave the N−O bond, leaving this *N*-center effectively blocked. While, *O*-tosylation of the C-9 hydroxymethyl substituent proceeded without incident to provide **31**, removal of the *N*-allyl group from this sulfonamide proved to be unexpectedly challenging. In this regard, a number of two-step deallylation methods, involving alkene isomerization and hydrolysis, failed to afford the desired product and led to substrate decomposition. Fortunately, this transformation was accomplished using catalytic quantities of $RhCl_3 \cdot H_2O$ (5 mol %) in anhydrous *n*-propanol at reflux, as reported by Zacuto and Xu.[24] These conditions also mediated acetal solvolysis, which may result from the presence of HCl liberated upon the reaction of $RhCl_3$ with *n*-PrOH. Reacetalization of the C ring ketone, under the conditions employed before, gave **17** in excellent overall yield from compound **31**. With the stage now set for closure to form ring B, exposure of **31** to sodium hydride in THF at reflux effected intramolecular *N*-alkylation to provide **16** in high yield, thereby establishing the ABC madangamine core.

In conclusion, we have developed a general strategy for the preparation of diazatricyclic (ABC) skeleton common to the madangamine alkaloids. The synthesis of advanced intermediate **16**, which is differentially protected and fully functionalized for installation of rings D and E, was accomplished in 17 steps, with an overall yield of 17%. The key transformation in this approach involves formation of the core azabicyclo[3.3.1]-nonane (morphan) framework through the intramolecular oxamidation of an unsaturated *O*-methyl hydroxamate. Extension of the chemistry reported here to the total synthesis of madangamine D and other morphan-based natural products is underway.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.7b03283.

Experimental details and characterization data for all reported compounds (PDF)

^1H and ^{13}C NMR spectra NMR spectra (PDF)

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Notes

The authors declare no competing financial interest.

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