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Natural Product Synthesis

Total Synthesis of (±)-Haliclonacyclamine C**

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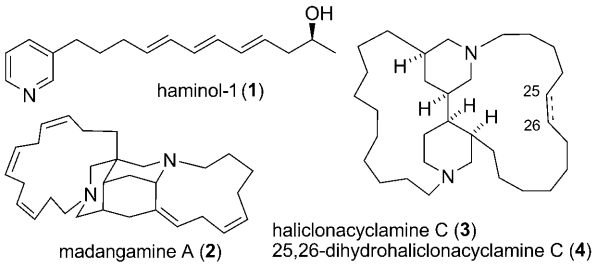
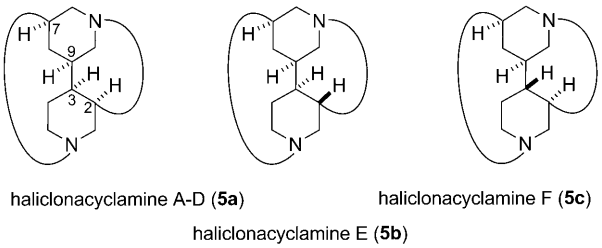
The alkylpiperidine alkaloids are a group of natural products that are hypothetically derived from nicotinic acid and isolated from various marine organisms.[1,2] The simplest family members are 3-alkylpyridines with molecular complexity increasing with the incorporation of tricyclic, tetracyclic and pentacyclic structural motifs (Scheme 1). A number



Scheme 1. Alkylpiperidine alkaloids. Haliclonacyclamine C contains a C=C double bond between C25 and C26.

of alkylpiperidine alkaloids have been the subject of intense synthetic investigation owing to their novel structures and biological activity. To date, the majority of this synthetic effort has been focused on a pentacyclic subgroup that includes manzamines,[3] sarains[4] and madangamines.[5] Little progress has been reported toward the synthesis of the intermediate tetracyclic class of alkylpiperidines that feature a central 3,4-linked bis(piperidine) core that is appended to two aliphatic macrocycles.[6] Members of this subgroup include the halicyclamines,[7] haliclonacyclamines[8] and arenosclerins.[9] Over sixteen tetracyclic alkaloids have been isolated from a variety of marine sponges, with haliclonacyclamines A–F constituting the largest subgroup of those isolated (Scheme 2).[8,9a] Haliclonacyclamines have been reported to display cytotoxic, antibiotic and antifungal properties.[8a]

Haliclonacyclamines A–F differ structurally in the number and location of *cis* olefins in the alkyl side chain



Scheme 2. Variation in the bis(piperidine) stereochemistry of haliclonacyclamines.

and in the relative stereochemistry within the bis(piperidine) core (Scheme 2). As an entry point to developing a synthetic route to members of the tetracyclic alkylpiperidine alkaloid family, we chose haliclonacyclamine C (**3**) and dihydrohaliclonacyclamine C (**4**) as targets for total synthesis. Dihydrohaliclonacyclamine C (**4**) is the hydrogenation product of haliclonacyclamines A–C; the structural assignments of haliclonacyclamines A–B have been firmly supported by single-crystal X-ray analyses.[8]

A major challenge associated with developing a synthetic strategy toward tetracyclic alkylpiperidines is the introduction of the four stereocenters incorporated within the bis(piperidine) core (Scheme 2). The selection of dihydrohaliclonacyclamine C (**4**) as our initial synthetic target was partially because the anticipated stereoselective hydrogenation of diene **6** to bis(piperidine) **7**, which leads to the relative stereochemistry pattern for haliclonacyclamines A–D (Scheme 3). Our stereochemical analysis of the hydrogenation of **6** was based on the incorporation of the central 1,3-diene of tricycle **6** into a 17-membered macrocycle that would favor the peripheral hydrogenation of the C9–C10 alkene to afford a product with the desired *cis* relationship between the C7 and C9 stereocenters.[10] Less certain was the diastereofacial selectivity of the hydrogenation of the C2–C3 double bond (**6**), as this carbon–carbon double bond is situated in a piperidine ring that possesses a stereochemically dynamic nitrogen atom (see **6a** and **6b**). Assuming that the latter hydrogenation proceeds with modest facial selectivity, we predicted the delivery of two diastereomers: the desired *cis-syn-cis* isomer (**7b**) and the corresponding *cis-anti-cis* isomer (**7a**) (Scheme 3). Assembly of the key intermediate (**6**) required a combination of cross-coupling and ring-closing metathesis reactions as described below. A ring-closing metathesis (RCM) reaction, alkene hydrogenation and

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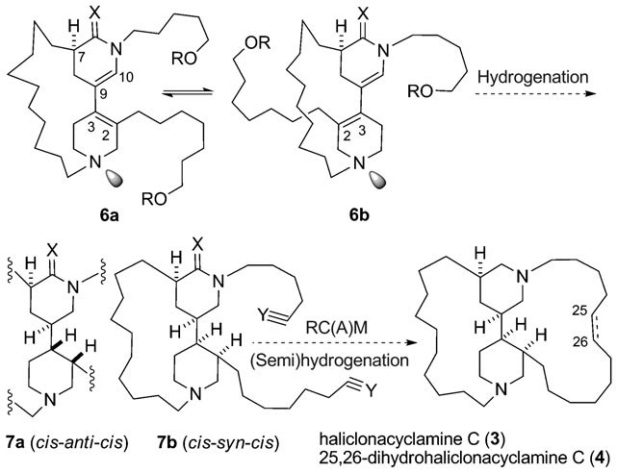
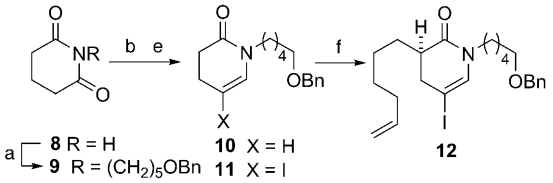


Scheme 3. Synthetic strategy toward haliclonacyclamine C (**3**) and dihydrohaliclonacyclamine C (**4**). Haliclonacyclamine C contains a C=C double bond between C25 and C26.

lactam reduction would advance diene **7b** (Y = H, CH_2) to dihydrohaliclonacyclamine C (**4**), whilst the total synthesis of haliclonacyclamine C (**3**) would require a ring-closing alkyne metathesis (RCAM) starting from the corresponding diyne (**7b**, Y = CCH_3), followed by semihydrogenation to introduce the C25–C26 *cis* alkene.[11]

Our synthesis started with a six-step preparation of 3-iodoenamide **12** from glutarimide (**8**; Scheme 4). Iodoenamide **12** served as one of two piperidine units for a cross-coupling reaction that led to the formation of the central C3–C9 bond of **6** (Scheme 3). The reaction sequence started with a Mitsunobu condensation of **8** with 5-benzyloxypentanol to provide glutarimide **9**. Sodium borohydride reduction of **9** followed by a trifluoroacetic anhydride-mediated dehydration afforded enamide **10** in 79% overall yield.[12] Reaction of **10** with iodine monochloride in methanol resulted in a regioselective iodomethoxylation to afford an intermediate δ-methoxylactam that was briefly subjected to catalytic trifluoroacetic acid in refluxing toluene (15 min) to provide iodoenamide **11** from **10** in 66% yield.[13] Deprotonation of amide **11** with LHMDS in THF at −78 °C followed by the addition of 6-iodo-1-hexene completed the assembly of iodoenamide **12**.



Scheme 4. Synthesis of fragment **12**: a) 5-Benzyloxypentanol, PPh_3, DIAD, THF, 23 °C, 91%; b) $NaBH_4$, HCl/EtOH, −20 °C; c) TFAA, THF, 23 °C, 79% from **9**; d) ICl, MeOH, −78 °C; e) TFA, Toluene, 145 °C, 66% from **10**; f) LHMDS, 6-iodo-1-hexene, THF, −78 °C, 84%. DIAD = diisopropylazodicarboxylate, TFAA = trifluoroacetic anhydride, TFA = trifluoroacetic acid, LHMDS = lithium hexamethyldisilazide.

Stannane **16** (Scheme 5) was derived from β-keto ester **13**,[14] starting with the formation of an intermediate enol triflate that afforded allyl alcohol **14** upon reduction with diisobutylaluminum hydride. Silylation of **14** (TBSCl, imidazole, DMAP) preceded Stille coupling with hexamethyldistannane to afford stannane **16**.[15] The optimal conditions for the cross-coupling reaction between **12** and **16** employed copper(I) chloride as an accelerant and furnished bis(piperidine) **17** in 75% yield.[16] Exchange of TBS ether **17** for allylic acetate **18** set the stage for a second Stille coupling between **18** and (*E*)-6-(tributylstannyl)hex-5-en-1-ol to provide **19** in 80% yield.[17] With all carbons now in place, we turned our attention to the first of two ring-closing metathesis reactions. To this end, hydrochloride salt **19**·HCl was treated with Fürstner's ruthenium indenylidene catalyst in refluxing dichloromethane to provide tricyclic amine **20** (> 90% *trans*).[18–20] Exhaustive hydrogenation of **20**·TFA at 500 psi in ethanol over Pearlman's catalyst at 70 °C for 8 days led to an inseparable 1.3:1 mixture of two isomers that were tentatively assigned to **21a** and **21b**, respectively. The mixture of diols (**21**) was oxidized with Dess–Martin periodinane to give the moderately stable bis(aldehyde) **22**. Without purification, **22** was treated with 10 equivalents of methylenetriphenylphosphorane to provide bis(alkene) **23**. The tetracyclic ring system was completed upon treatment of the TFA salt, derived from **23**, with Grubb's first generation catalyst to provide the resolved isomers, **24a** and **24b**, in a combined yield of 80%. Amines **24a** and **24b** were separated by flash chromatography and each were determined to contain a *trans* double bond [6:1 (**24a**) and > 95:5 (**24b**)]. Hydrogenation of **24a** (100 psi, $Pd(OH)_2$, EtOH) provided lactam **25**, the single-crystal X-ray analysis of which confirmed the *cis-syn-cis* stereochemistry of the bis(piperidine) core (Figure 1).[21,23]

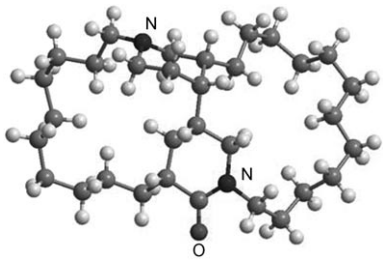
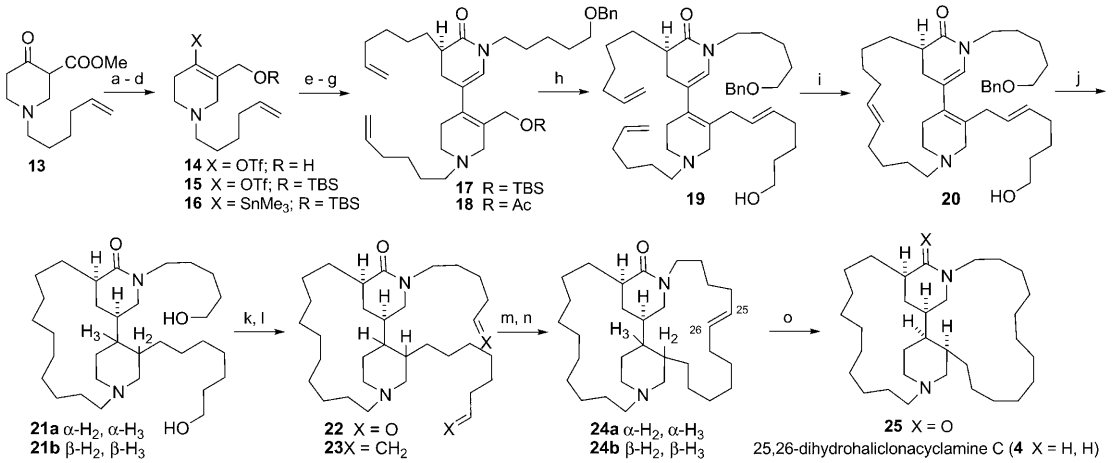
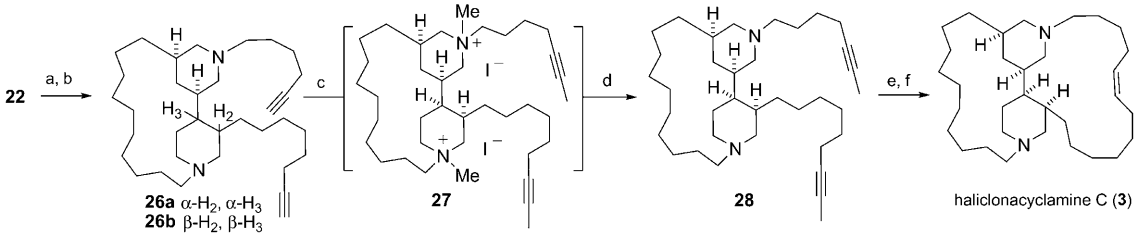


Figure 1. X-ray crystal structure of lactam **25**.[23]

The X-ray analysis was significant since the reduction of **25** with Red–Al led to the formation of dihydrohaliclonacyclamine C (**4**) whose ^1H and ^{13}C NMR spectra did not match the NMR data of the dihydrohaliclonacyclamine C that had been derived from the hydrogenation of haliclonacyclamine A.[22] After passing both samples of synthetic and semi-synthetic dihydrohaliclonacyclamine C through a strong cation exchange (SCX) column, the spectral properties of both samples were identical.



Scheme 5. Final stages of the synthesis of **4**: a) KHMDS, *N*,*N*-bis(trifluoromethylsulfonyl)-5-chloro-2-pyridylamine, THF, −78 °C, 94%; b) DIBAL–H, CH_2Cl_2, −50 °C→0 °C, 92%; c) TBSCl, imidazole, DMAP, THF, 0→23 °C, 88%; d) Me_6Sn_2, LiCl, $[Pd(PPh_3)_4]$, THF, 80 °C, 75%; e) **12**, CuCl, LiCl, $[Pd(PPh_3)_4]$, DMSO, 60 °C, 67%; f) TBAF, THF, 0 °C; g) Ac_2O, NEt_3, DMAP, CH_2Cl_2, 23 °C, 96% from **17**. h) (*E*)-6-(tributylstannyl)hex-5-en-1-ol, LiCl, $[Pd(dba)_2]$, DMF, 65 °C, 80%. i) HCl/Et_2O, then bis(tricyclohexylphosphine)-3-phenyl-1H-inden-1-ylidene ruthenium(II) dichloride (10 mol%), CH_2Cl_2, 40 °C, 64%; j) TFA, H_2 (500 psi), $Pd(OH)_2$, EtOH, 70 °C, 79% (1.3:1, **21a**/**21b**); k) Dess–Martin periodinane, CH_2Cl_2, 0→23 °C; l) KHMDS, Methyltriphenylphosphonium bromide, THF, 0 °C, 51% from **21**; m) TFA then bis(tricyclohexylphosphine) benzylidine ruthenium(IV) chloride (10 mol%), CH_2Cl_2, 40 °C, 80%; n) TFA then H_2 (100 psi), Pd/C, MeOH, 60 °C, 62%; o) Red–Al, PhMe, reflux, 90%. KHMDS = potassium hexamethyldisilazide, DIBAL = diisobutylaluminum, TBSCl = *tert*-butyldimethylsilylchloride, DMAP = *N*,*N*-dimethyl-4-aminopyridine, DMSO = dimethyl sulfoxide, TBAF = tetra-n-butylammonium fluoride, dba = 1,5-diphenyl 1,4-pentadiene-3-one, DMF = *N*,*N*-dimethylformamide, Red–Al = sodium bis(2-methoxyethoxy)aluminumhydride.



Scheme 6. Synthesis of **3**: a) $(MeO)_2P(O)C(N_2)C(O)Me$, K_2CO_3, MeOH, 54% from **21**; b) Red–Al, toluene, reflux, 51% (**26a**) and 39% (**26b**); c) *n*BuLi (8 equiv), THF, −78 °C to 23 °C then MeI (excess), −78→23 °C; d) NaSPh (10 equiv), DMF, 130 °C, 41% from **26a**; e) Ph_3SiOH (3 equiv), $[(Me_3SiO)_2\{(Me_3Si)_2N\}MoN]$, toluene, 80 °C then **28**, 23 to 130 °C, 63%; (f) H_2, Lindlar catalyst, EtOAc, 23 °C, 88%.

The total synthesis of haliclonacyclamine C (**3**), which was completed using the RCAM followed by semihydrogenation strategy introduced by Fürstner, required prior-conversion of bis(aldehyde) **22** into diyne **28** (Scheme 6). To this end, **22** was reacted with an excess of the Bestman–Ohira reagent[24] to give the corresponding diyne. Reduction of the lactam carbonyl group with Red-Al afforded a separable mixture of amines **26a** (51%) and **26b** (39%). Bis(methylation) of terminal alkyne **26a** was invariably accompanied by N-methylation to give quaternary salt **27**. Amine **28** was generated directly from ammonium salt **27** upon treatment with an excess of sodium thiophenoxide in dimethylformamide. The RCAM cyclization of **28** was examined using a variety of catalysts and reaction conditions. Only the catalyst system derived from the in situ combination of $[(Me_3SiO)_2\{(Me_3Si)_2N\}MoN]$ and Ph_3SiOH (3 equiv), as recently described by Fürstner and co-workers, led to the desired RCAM reaction.[25] Under these conditions free amine **28** underwent the RCAM reaction in 63% yield. Semihydrogenation of the resulting cycloalkyne with the Lindlar catalyst afforded haliclonacyclamine C, which was identical in all respects to the natural product apart from optical rotation.[8b]

In summary, we have completed the synthesis haliclonacyclamine C (**3**) and dihydrohaliclonacyclamine C (**4**). The synthetic strategy should be easily modifiable to provide access to other haliclonacyclamines and their related tetracyclic alkylpiperidine alkaloids. Evaluation of the biological activity of the structurally unique haliclonacyclamine C is under investigation and will be reported in due course.

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[21] The stereochemistry of **24b** (*cis-anti-cis*) was assigned following extensive NMR analysis. See the Supporting Information for details.

[22] We are very grateful to Professor Mary Garson (University of Queensland) for providing an authentic sample of dihydrohaliclonacyclamine C.

[23] CCDC 744717 (**25**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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