Natural Product Synthesis

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Total Synthesis of (+)-Madangamine D**

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Abstract: *Madangamines are a group of bioactive marine sponge alkaloids, embodying an unprecedented diazapentacyclic skeletal type. The enantioselective total synthesis of madangamine D has been accomplished, and represents the first total synthesis of an alkaloid of the madangamine group. It involves the stereoselective construction of the diazatricyclic ABC core using a phenylglycinol-derived lactam as the starting enantiomeric scaffold and the subsequent assembly of the peripheral macrocyclic rings. The synthesis provides, for the first time, a pure sample of madangamine D and confirms the absolute configuration of this alkaloid family.*

Sponges of the order Haplosclerida have proven to be a rich source of structurally diverse but biogenetically related alkaloids,[1] most of which display significant biological activities. These marine alkaloids comprise a great variety of unusual skeletal types, including an array of complex polycyclic diamine structures bearing macrocyclic rings, such as saraines, ingenamines, manzamines, nakadomarin A, and madangamines.[2] Madangamines are one of the least studied of these alkaloids from a synthetic standpoint,[3] and no total synthesis on this series has been reported so far.[4] The first isolation of an alkaloid of this group was madangamine A, which was reported by Andersen and co-workers in 1994[5] to have been found in the marine sponge *Xestospongia ingens*, collected in Papua New Guinea. A few years later the same team described[6] four new related alkaloids, madangamines B–E,[7] from the same organism, and more recently, Berlinck and co-workers reported the isolation of madangamine F from the Brazilian sponge *Pachychalina alcaloidifera*.[8] Madangamines A and F have shown significant in vitro cytotoxicity against a number of tumor cell lines. However, no bioactivity data have been reported for madangamines B–E, and further pharmacological research on this alkaloid group has been thwarted by the minute amounts of alkaloid samples available from natural sources.

Structurally, madangamines are pentacyclic alkaloids with an unprecedented skeletal type, characterized by a diazatricyclic core (ABC rings) bearing three contiguous stereogenic centers, one of them quaternary, and two linear carbon bridges which connect N7 to C9 (D ring) and N1 to C3 (E ring). The peripheral macrocyclic ring D is different in each madangamine, in size as well as in degree and position of unsaturation, whereas ring E is identical in madangamines A–E but different in madangamine F, which also incorporates a C4 hydroxy group (Figure 1).

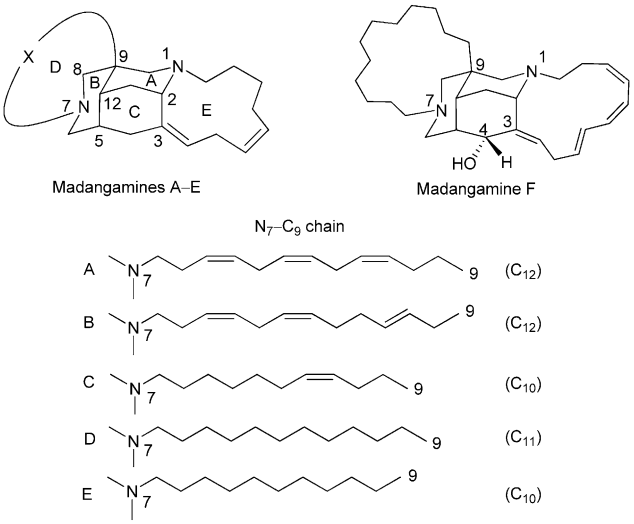

Figure 1. Alkaloids of the madangamine group.

We present herein the enantioselective synthesis of (+)-madangamine D, and it provides, for the first time, a pure sample[7] of this natural product and constitutes the first total synthesis of an alkaloid of the madangamine group. By using a phenylglycinol-derived bicyclic lactam[9] as the starting enantiomeric scaffold,[10] our approach involves the initial construction of the bridged diazatricyclic ABC core common to all madangamines,[11] and the subsequent building of the macrocyclic D and E rings (Figure 2).

The starting enantiopure lactam **2** was easily accessible[12] by cyclocondensation of the oxoester **1** with (*R*)-phenylglycinol, a process which installs the first stereocenter (C5 in the madangamine numbering)[13] by dynamic kinetic resolution of the racemic substrate. The key functionalized diazatricyclic intermediates would be prepared from an unsaturated lactam, derived from **2**, by successive construction of the carbocyclic C and piperidine A rings. Crucial stereochemical issues are the generation of the required B/C *cis* ring junction, by a stereoselective conjugate addition reaction followed by a ring-closing metathesis process, and the control of the C9

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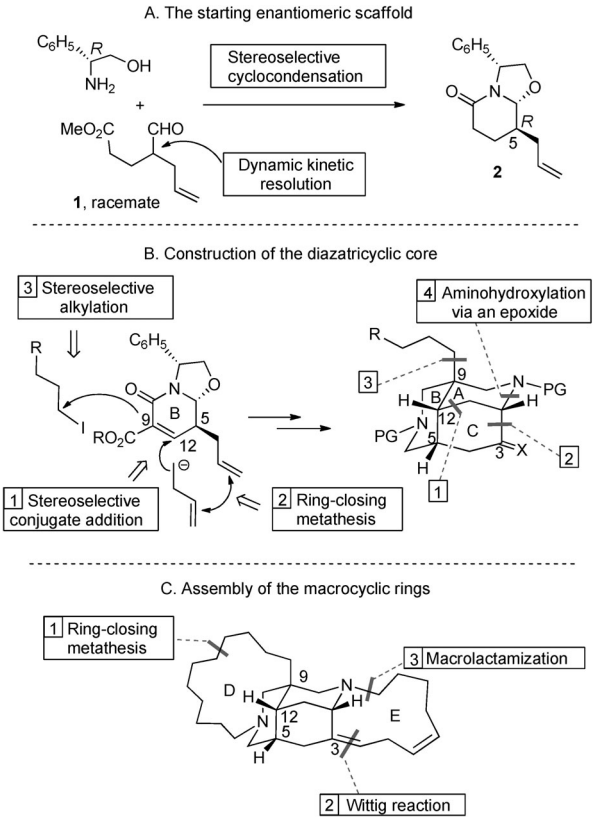

Figure 2. Synthetic strategy.

stereochemistry in the alkylation step. Finally, the assembly of the macrocyclic rings would be accomplished by a ring-closing metathesis reaction (ring D) and a Wittig olefination followed by macrolactamization (ring E).

The overall synthetic sequence is shown in Scheme 1. The lactam **2** was converted in excellent overall yield to the unsaturated lactam **3**, through an epimeric mixture of intermediate seleno derivatives. A stereoselective, stereoelectronically controlled,[14] conjugate addition of an allyl residue led to the *cis*-diallyl-substituted lactam **4**, from which the carbocyclic C ring was constructed by a ring-closing metathesis reaction to give the *cis*-octahydroisoquinolone derivative **5**. A stereoselective alkylation from the most accessible face of the β-ketoester moiety of **5** generated the quaternary C9 stereocenter in **6** and installed a C9 functionalized carbon chain. At this point, the removal of the phenylethanol moiety from the chiral auxiliary was achieved by successive treatment of **6** with Na in liquid NH_3, which caused the cleavage of the benzylic C–N bond, and $LiAlH_4$, which brought about the reduction of the resulting unstable α-oxylactam. Under the latter conditions, the lactam and ester carbonyl functions were also reduced to give an N-unsubstituted piperidine-3-methanol derivative, which was immediately protected as the N-Boc piperidine **7**. In this way, the *tert*-butoxycarbonyl group not only provided activation towards the conjugate addition step and allowed the stereoselective alkylation of the 1,3-dicarbonyl intermediate **5**, but also serves as the precursor of the aminomethyl chain required for the closure of the piperidine A ring. The latter was accomplished by a stereocontrolled cascade aminohydroxylation. To this end, once **7** was converted into the azide **8** via a mesylate, and the cyclohexene double bond was epoxidized, a Staudinger reduction of **9** led to an intermediate amino epoxide, which underwent a smooth in situ cyclization. A subsequent protection of the resulting diazatricyclic alcohol led to the N-tosyl derivative **10**.

With the functionalized diazatricyclic derivative **10** in hand, the next phase of the synthesis was the construction of the western 14-membered D ring.[15] After benzylation of the C3 hydroxy group, selective deprotection of N7 in the resulting orthogonally protected diamino derivative, followed by acylation with 7-octenoyl chloride, led to the tricyclic amide **11**. Hydrolysis of the acetal function and Wittig methylenation of the resulting aldehyde gave the required dialkene derivative **12**. A ring-closing metathesis reaction of **12** under dilute conditions using the first-generation Grubbs catalyst provided the expected tetracyclic alkene **13** (2:1 mixture of *Z*/*E* isomers). A subsequent catalytic hydrogenation, which led to both the reduction of the carbon–carbon double bond and the removal of the benzyl ether protecting group, followed by Dess–Martin periodinane oxidation of the resulting alcohol led to the ketone **14**, which served as a platform to construct the eastern 11-membered E ring.

The (*Z*,*Z*)-unsaturated eight-carbon fragment required to complete the synthesis of madangamine D was incorporated in a straightforward manner by a Wittig reaction using the ylide generated from the phosphonium salt **15**[16] under strictly anhydrous conditions. Removal of the tosyl substituent in the resulting diastereoisomeric mixture of alkenes **16** (2.2:1 *Z*/*E* ratio),[17] followed by hydrolysis of the ester function and macrolactamization, led to the pentacyclic dilactam **17**. A final $LiAlH_4$ reduction provided madangamine D. The ^1H and ^{13}C NMR data of our synthetic madangamine were coincident with those reported[6] for the natural product (see Tables in the Supporting Information).

To date, the absolute configuration of madangamines has only been inferred by correlation with that of their presumed[1,2b,d,3a,b] biosynthetic precursors, ingenamines.[18] Given that our synthetic madangamine D, having unambiguous 2*S*, 5*S*, 9*R*, 12*R* absolute configuration, has a specific rotation $\{[\alpha] = +101.3\ (c = 0.29, CHCl_3)\}$ with the same sign as in the closely related madangamines A–C,[19] our synthesis confirms the absolute configuration of this alkaloid family.

Madangamine D showed significant in vitro cytotoxic activity against human colon HT29 (GI_{50} 4.4 $\mu g\,mL^{-1}$) and pancreas PSN1 (GI_{50} 7.4 $\mu g\,mL^{-1}$) cancer cell lines, but was inactive against lung NSCLC A549 and breast MDA-MB-231 cancer cell lines at the highest assayed concentration (10 $\mu g\,mL^{-1}$).

By using appropriately C9-substituted diazatricyclic derivatives, the strategy we have developed could be applied to the synthesis of other members of the madangamine group.[20]

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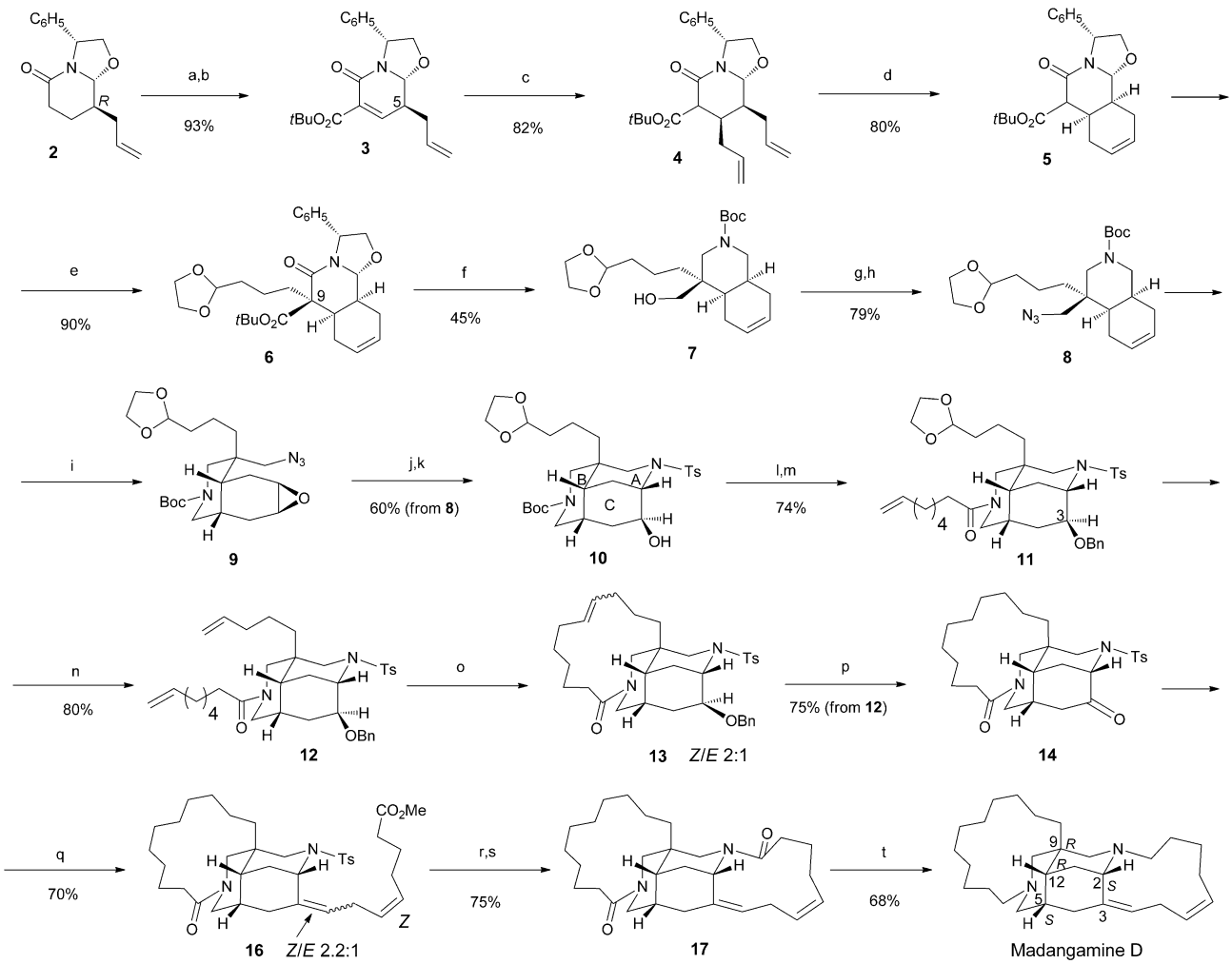

Scheme 1. Enantioselective synthesis of madangamine D. Reagents and conditions: a) LiHMDS, $(Boc)_2O$; then C_6H_5SeCl, THF, −78 °C, 93 %; b) H_2O_2, CH_2Cl_2, RT, 2 h; c) $CH_2{=}CHCH_2MgBr$, CuI, LiCl, TMSCl, THF, −78 °C, 20 h, 82 % (from the seleno derivative); d) Grubbs second generation catalyst, CH_2Cl_2, RT, 18 h, 80 %; e) NaH, $(CH_2O)_2CH(CH_2)_3Br$, TBAI, DMF, RT, 18 h, 90 %; f) Na/liq. NH_3, −33 °C, 2 min; then $LiAlH_4$, 1,4-dioxane, reflux, 20 h; then $(Boc)_2O$, CH_2Cl_2, RT, 4 h, 45 %; g) Et_3N, MsCl, CH_2Cl_2, RT, 4 h; h) NaN_3, DMF, 90 °C, 48 h, 79 % (from **7**); i) *m*-CPBA, CH_2Cl_2, RT, 5 h; j) Me_3P, THF, 1 h; then H_2O, RT, 20 h; k) *p*-TsCl, Et_3N, CH_2Cl_2, 0 °C, 2.5 h, 60 % (from **8**); l) NaH, BnBr, TBAI, DMF, 0.05 M, RT, 20 h, 80 %; m) TFA, CH_2Cl_2, RT, 30 min; then $ClCO(CH_2)_5CH{=}CH_2$, Et_3N, CH_2Cl_2, 0 °C, 3 h; then RT, 18 h, 92 %; n) HCl, THF, RT, 2 h; then KO*t*Bu, Br^- $Ph_3P^+CH_3$, THF, RT, 20 h, 80 %; o) Grubbs first generation catalyst, CH_2Cl_2, 0.2 mM, reflux, 12 h; p) H_2, Pd/C, EtOH, RT, 24 h; then Dess–Martin, CH_2Cl_2, RT, 4 h, 75 % (from **12**); q) NaHMDS, Br^- (*Z*)-$Ph_3P^+CH_2CH_2CH{=}CH(CH_2)_3CO_2Me$ (**15**), THF, 0 to 60 °C, 70 %; r) Na, naphthalene, THF, −78 °C; s) aq. LiOH, THF; then EDCI, HOBt, DMF/CH_2Cl_2 (1:9), 0.02 M, RT, syringe pump, 75 % (from **16**); t) $LiAlH_4$, THF, RT, 3 h, 68 %. Boc = *tert*-butoxycarbonyl, DMF = *N*,*N*-dimethylformamide, EDCI = 1-(3-dimethylaminopropyl)-3-ethyl-carbodiimide hydrochloride, HMDS = hexamethyldisilazide, HOBt = 1-hydroxybenzotriazole, Ms = methanesulfonyl, TBAI = tetra-*n*-butylammonium iodide, TFA = trifluoroacetic acid, THF = tetrahydrofuan, TMS = trimethylsilyl, Ts = 4-toluenesulfonyl.

Keywords: alkaloids · asymmetric synthesis · macrocycles · nitrogen heterocycles · total synthesis

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[20] For model studies on the construction of the western D ring of other madangamines see Ref. [17].

