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Total synthesis of the marine cytotoxic caulibugulones A–D

David Alagille,[a] Ronald M. Baldwin[a] and Gilles D. Tamagnan[a,b,*]

[a]*Department of Psychiatry, Yale University and VAHCS, 950 Campbell Avenue, West Haven, CT 06516, USA*
[b]*Institute for Neurodegenerative Disorders, 60 Temple Street, Suite 8B, New Haven, CT 06510, USA*

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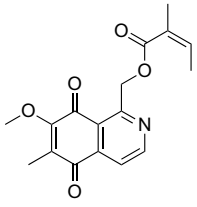
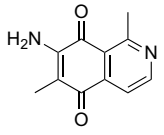
Abstract—We report the first total synthesis of the cytotoxic marine alkaloids caulibugulone A–D. This synthesis confirmed the assigned structures and provided sufficient material for further biological testing.

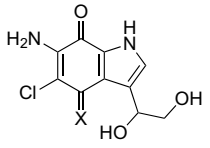
Marine organisms such as sponges, tunicates, coelenterates, and phytoplankton have proven to be a valuable source of biologically active secondary metabolites.[1] Very recently, Milanowski et al.[2] identified four new isoquinoline quinone derivatives and two iminoquinones, termed caulibugulones A–F (Fig. 1) from the marine bryozoan *Caulibugula intermis* Harmer (Bugulidae) and reported interesting cytotoxic activity. A number of isoquinoline quinones, including the renierones[3,4] and cribrostatins[5,6] have been isolated and reported to exhibit antimicrobial and antitumor activity. Quinoneimines are well represented in marine alkaloids, such as isobatzellines,[7] makaluvamines,[8,9] and secobatzellines A–B,[10] and exhibit interesting cytotoxic and antimicrobial profiles. The structural characteristic of caulibugulones is an isoquinoline-5,8-dione carrying a substituted amino group in position-7 and substituted at position-6 by hydrogen, bromine or



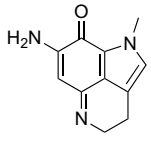
Renierone



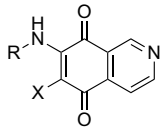
Cribostatin 1

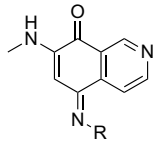


Secobatzelinline A X = NH
Secobatzelinline B X = O



Makaluvamine A





(**1**) **Caulibugulone A**: R = CH_3 X = H IC_{50}= 0.34[a]
(**2**) **Caulibugulone B**: R = CH_3 X = Br IC_{50}= 0.22[a]
(**3**) **Caulibugulone C**: R = CH_3 X = Cl IC_{50}= 0.28[a]
(**4**) **Caulibugulone D**: R = CH_2CH_2OH X = H IC_{50}= 1.67[a]

Caulibugulone E: R = H IC_{50}= 0.03[a]
Caulibugulone F: R = CH_2CH_2OH IC_{50}= 0.1[a]

Figure 1. [a]IC_{50} are expressed in μg/mL against the murine IC-2^{WT} cell line in an in vitro antiproliferative assay.[2]

Keywords: Caulibugulones A–D; Isoquinoline-5,8-diones; Cytotoxicity.
* Corresponding author. Tel.: +1-2034014309; fax: +1-2037892119; e-mail: gtamagnan@indd.org

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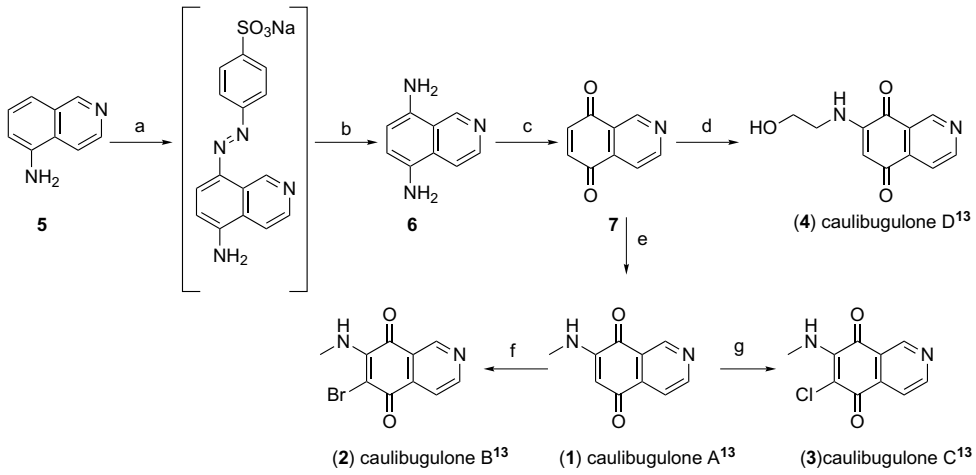

Scheme 1. Reagents and conditions: (a) sulfanilic acid, $NaNO_2$, H_2SO_4, AcOH, AcONa; (b) NaOH, $Na_2S_2O_4$; (c) $K_2Cr_2O_7$, H_2SO_4;[11] (d) $NH_2CH_2CH_2OH$, $CeCl_3$, EtOH, rt; (e) $MeNH_2$, $CeCl_3$, EtOH, rt; (f) NBS, MeOH, rt; (g) NCS, MeOH, rt.

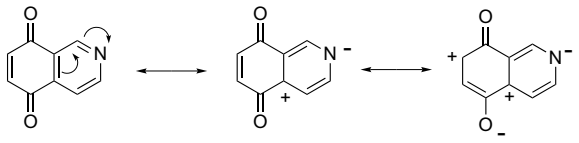

Figure 2.

chlorine (caulibugulones A–D, **1**–**4**). Caulibugulones E and F are analogues of caulibugulone A (**1**) carrying an imine group at position-5. As part of an ongoing effort on synthesis of new bioactive heterocycles, the present paper describes the first de novo synthesis of caulibugulones A–D.

The key intermediate 5,8-isoquinolinedione (**7**) was prepared in three steps (30% overall yield) according to the methodology described by Joseph and Joullie [11,12] starting from the commercially available 5-aminoisoquinoline (**5**) as outlined in Scheme 1. Compound **7** was converted regioselectively to **1**[13] (74%) and **4**[13] (50%) by oxidative amination with methylamine or 2-aminoethanol in ethanol in the presence of $CeCl_3$ (Scheme 1). The regioselectivity of this reaction can be explained by resonance stabilization of the 1,4-adduct at C-7 via the pyrinoid nitrogen (Fig. 2), which favors substitution at C-7. Subsequent treatment of **1** with *N*-bromosuccinimide or *N*-chlorosuccinimide in methanol provided the desired compound **2**[13] and **3**[13] in 97% and 94% yield, respectively (Scheme 1).

In conclusion, the synthesis of the naturally occurring caulibugulones A–D confirmed the assigned structures and provided sufficient material for further biological testing.

Acknowledgements

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13. Spectral data of selected compounds: The ^{1}H and ^{13}C spectrum for caulibugulones A–D (**1**–**4**) were identical to those described.[2] Compound **1**: purification (SiO_2, CH_2Cl_2/MeOH, 95:5), red solid, mp = 208–210 °C (dec), HRMS calcd for $C_{10}H_8N_2O_2$ (M+): 188.0585, found 188.0587. Compound **2**: purification (SiO_2, CH_2Cl_2/MeOH 95/5), red solid, mp = 183–185 °C (dec), HRMS calcd for $C_{10}H_7BrN_2O_2$ (M+): 265.9690, found 265.9694. Compound **3**: purification (SiO_2, CH_2Cl_2/MeOH, 95:5), red solid, mp = 151–153 °C (dec), HRMS calcd for $C_{10}H_7ClN_2O_2$ (M+): 222.0196, found 222.0198. Compound **4**: purification (SiO_2, CH_2Cl_2/MeOH, 90:10), red solid, mp = 173–175 °C, HRMS calcd for $C_{11}H_{10}N_2O_3$ (M+): 218.0691, found 218.0684.