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Total synthesis of the marine alkaloids Caulibugulones A and D

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ABSTRACT

Total synthesis of the marine cytotoxic alkaloids Caulibugulones A and D is accomplished in three steps with an overall yield of 60–62% from easily accessible starting materials. The key features include isoquinoline-5,8-diol core construction by ammonia mediated iminoannulation of 2-ethynyl-3,6-dihydroxybenzaldehyde, and subsequent in situ oxidation followed by oxidative amination.

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1. Introduction

Caulibugulones A–F (Fig. 1, **1**–**6**) are isoquinoline quinone alkaloids,[1] isolated from an extract of the marine bryozoan *Caulibugula intermis* collected in the Indo-Pacific off Palau, by Milanowski and co-workers in 2004.[2] Compounds **1**–**6** were found to have interesting cytotoxic activity (IC_{50} of 0.03–1.67 μg/mL) against murine tumour cells.[2] Valderrama et al. reported the synthesis of 4-methoxycarbonyl-3-methylisoquinoline-5,8-quinone (which contains the Caulibugulone core) and their analogues, which expressed valuable in vitro cytotoxic activity against MRC-5 (healthy lung fibroblasts) and human cancer cell lines: AGS (gastric), SK-MES-1 (lung), J82 (bladder) and HL-60 (leukaemia).[3] The Brission group reported that Caulibugulones are selective in vitro inhibitor of the Cdc25 family of cell cycle-controlling protein phosphatases.[4]

However, to the best of our knowledge, there are only three reports on the synthesis of Caulibugulones.[5–7] In 2004, Tamagnan et al. reported the first total synthesis of Caulibugulones from 5,8-isoquinolinedione, which was prepared 30% overall yield from 5-aminoisoquinoline.[5] In the same year, Wipf and co-workers reported the synthesis of **1**–**6** from oxidation of 5-hydroxyisoquinoline by iodobenzene bis(trifluoroacetate) PIFA in a H_2O/EtOH and the subsequent in situ addition of methylamine, and they reported that compounds **1**–**6** are potent and selective inhibitors of the dual specificity phosphatase Cdc25B.[6] Most recently, Caulibugulones A–D were synthesized in six steps starting from 2,5-dimethoxybenzaldehyde. The key intermediate 5,8-dimethoxyisoquinoline was prepared from Pomeranz–Fritsch reaction of *N*-(2,5-dimethoxybenzyl)-*N*-(2,2-dimethoxyethyl)-2-nitrobenzenesulfonamide.[7] We planned a different efficient and simple route for the synthesis of key intermediate 5,8-dihydroxyisoquinoline by utilizing ammonia-mediated iminoannulation of the corresponding 1,2-alkynylaldehyde.

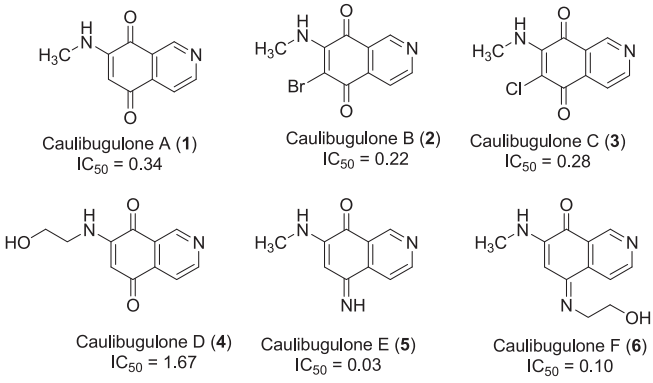

Fig. 1. Structure of Caulibugulones A–F (IC_{50} are expressed in μg/mL against the murine tumour cell line).[2]

2. Results and discussion

The significant biological activity and very few methods for the synthesis of Caulibugulones[5–7] prompted us to find a new approach

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towards the synthesis of these marine alkaloids. We recently reported the first total synthesis of the marine alkaloid Mansouramycin D via iminoannulation.[8] We herein report a simple and concise total synthesis of Caulibugulones A and D via iminoannulation with an overall yield of 62% and 60% over three steps from an easily accessible known starting material. Fig. 2 shows the retrosynthetic analysis for the synthesis of **1** and **4**. Caulibugulone A and D (**1** and **4**) are the direct products of aminolysis of isoquinoline-5,8-dione (**5**) with methylamine and 2-aminoethanol, respectively. In addition, Caulibugulone A (**1**) would be extended to Caulibugulone B (**2**) C (**3**) and E (**5**) by halogenation using NBS or NCS or imination.[6] The dione **7** could easily be synthesized from the 5,8-dihydroxyisoquinoline **8**. The formation of protected 5,8-dihydroxyisoquinoline from corresponding alkynylaldehyde **9** would be the key step in this report. The alkynylaldehyde **9** would be accessed from Sonogashira cross coupling[9] of bromoaldehyde **10** with trimethylsilylacetylene followed by removal of trimethylsilyl group.

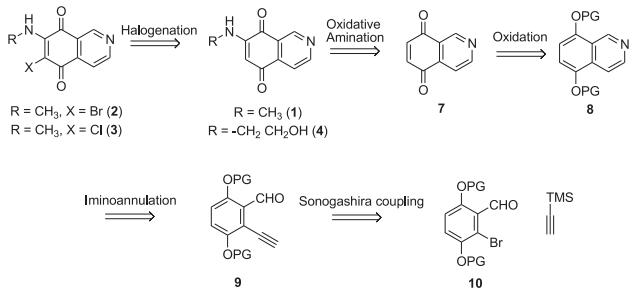
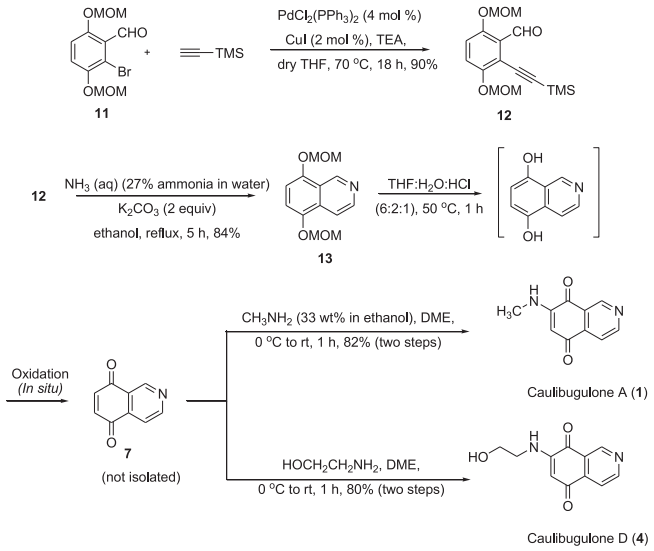


Fig. 2. Retrosynthetic analysis of Caulibugulones A–D.

2-Bromo-3,6-bis(methoxymethoxy)benzaldehyde (**11**) was readily prepared by bromination, followed by MOM protection of 2,5-dihydroxybenzaldehyde in 82% yield over two steps.[10] The selection of the MOM group was designed to be easily tailored to provide isoquinoline-5,8-diol. Then, Sonogashira coupling of **11** with trimethylsilylacetylene in the presence of 4 mol % of $PdCl_2(PPh_3)_2$, 2 mol % of CuI provided the coupled product **12** as pale yellow oil in 90% yield. With compound **12** in hand, the reaction was proceeded with the trimethylsilyl (TMS) group, because we anticipated its removal after cyclization under K_2CO_3 in ethanol reaction condition. The cyclization underwent smoothly with an excess of aqueous ammonia (27% ammonia in water), 2 equiv of K_2CO_3, in ethanol under reflux conditions and gave the expected product 5,8-bis(methoxymethoxy)isoquinoline (**13**) in 84% yield. In a parallel study, we attempted the synthesis of **13** by Larock iminoannulation[11] via preparation of *tert*-butyl imine of **12**, followed by copper catalyzed cyclization, but this was unsuccessful.

The completion of total synthesis of Caulibugulones A (**1**) and D (**4**) is shown in Scheme 1. Compound **13** is further subjected to removal of the MOM group by treating with THF/H_2O/concd HCl (6:2:1 ratio) with heating at 50 °C to afford the required isoquinoline-5,8-diol, which was further converted into isoquinoline-5,8-dione (**7**) by in situ oxidation. Unfortunately, the dione **7** has insufficient stability, the next step was proceeded after a water work up and sodium bicarbonate wash without further purification and isolation of **7**. This observation is consistent with the previous literature reports on difficulties of isolating and characterizing of **14**.[6,7] Therefore, crude compound **7** is directly subjected to aminolysis[12] using 3 equiv of methylamine (33 wt % in ethanol). After complete conversion as monitored by TLC (1 h), the product was purified by column chromatography using silica gel to afford Caulibugulone A (**1**) in a yield of 82% over the two steps (Scheme 1). Caulibugulone D (**4**) was also synthesized with 80% yield from dione **7** by aminolysis with ethanolamine (2 equiv) in DME. The structure of Caulibugulone D (**4**) was unambiguously confirmed by single-crystal X-ray diffraction analysis,[13] the ORTEP of **4** is shown in Fig. 3.



Scheme 1. Total synthesis of Caulibugulones A and D.

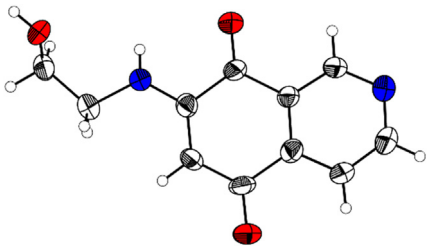


Fig. 3. ORTEP diagram of Caulibugulone D (**4**).

The regioselective oxidative amination of **7** and formation of the major isomer is explained by the resonance stabilization of compound **7**.[5] C-7 position of isoquinoline-5,8-dione is more favourable for oxidative amination than C-6 and so that the required regioisomer was formed as a sole product. With Caulibugulone A in hand, it would be converted into Caulibugulones B (**2**), C (**3**) and E (**5**) potentially by following the previously reported studies by Wipf and co-workers[6] (Fig. 4).

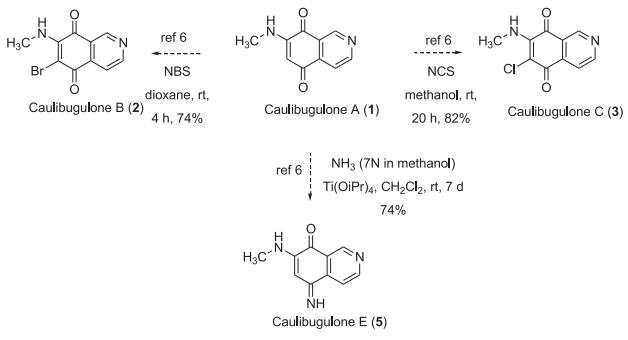


Fig. 4. Formal synthesis of Caulibugulones B, C and E.

Thus, we have completed the total synthesis of Caulibugulones A and D with overall yields of 62% and 60%, respectively, the highest overall yields so far. NMR and high-resolution mass data of the synthesized compounds (**1** and **4**) are in full accordance with natural Caulibugulones A (**1**) and D (**4**). Spectroscopic data comparison is given in Tables S1 and S2 (see Supplementary data).

3. Conclusion

In summary, we have disclosed a concise synthesis of Caulibugulones A (**1**) and D (**4**) via three steps with overall yields of 62% and 60%, respectively. Noteworthy features of this synthesis include; (a) the effective preparation of isoquinoline-5,8-diol core via ammonia mediated iminoannulation, (b) in situ oxidation and regioselective oxidative amination, (c) generally excellent yield, (d) overall operational simplicity, (e) Caulibugulones B, C and E (**2**, **3** and **5**) can easily be synthesized from Caulibugulone A (**1**) by following the literature procedure. (f) The protocol presented herein potentially allows the preparation of biologically active Caulibugulones for further biological screening and evaluation.

4. Experimental section

4.1. General information

^{1}H and ^{13}C NMR spectra were recorded at 400 and 100 MHz, respectively, or at 500 and 125 MHz, respectively. Chemical shifts are calculated in parts per million (ppm) downfield from TMS (δ=0) for ^{1}H NMR, and relative to the central $CDCl_3$ resonance (δ=77.00) and CD_3CN (δ=118.20) for ^{13}C NMR. Data are presented as follows: chemical shift, multiplicity (br s=broad singlet, s=singlet, d=doublet, t=triplet, dt=doublet of triplet), coupling constant in hertz (Hz) and integration. IR spectra were recorded on FT/IR-5700 instrument. TOF and quadrupole mass analyzer types are used for the HRMS measurements. Melting points were measured in open capillary tubes and are uncorrected. All the obtained products were purified by column chromatography using silica gel (100–200 mesh). All reaction solvents used were of GR grade and used without drying unless mentioned. All other commercial reagents were used as received.

The starting material 2-bromo-3,6-bis(methoxymethoxy)benzaldehyde (**11**) was prepared as reported.[8]

4.2. General procedure

*4.2.1. 3,6-Bis(methoxymethoxy)-2-(2-(trimethylsilyl)ethynyl)benzaldehyde (**12**).* An oven-dried 50 mL Schlenk tube equipped with a Teflon-coated magnetic stirring bar is charged with 2-bromo-3,6-bis(methoxymethoxy)benzaldehyde (**11**) (1 g, 3.2 mmol), CuI (12 mg, 2 mol %) and $PdCl_2(PPh_3)_2$ (91 mg, 4 mol %), freshly distilled triethylamine (0.5 mL), dry THF (4 mL) and trimethylsilylacetylene (1.8 mL, 12.8 mmol) was added under nitrogen atmosphere and the resulting mixture was heated at 70 °C. After 18 h, the complete conversion of starting material was observed by TLC. The reaction mixture was cooled to room temperature, it was diluted with 50 mL of $CHCl_3$ and filtered through Celite bed. Then, water (10 mL) was added to the diluted solution, which was then extracted with $CHCl_3$ (2×50 mL). The combined organic layer was dried with anhydrous Na_2SO_4 and concentrated under vacuum and purified by column chromatography on silica gel (eluent: 5% ethyl acetate in hexanes) to afford the 3,6-bis(methoxymethoxy)-2-(2-(trimethylsilyl)ethynyl) benzaldehyde (**12**) as a viscous oil (0.95 g) in 90% yield. R_f=0.41 (20% ethyl acetate in hexanes). IR (neat): 2925, 2853, 2154, 1698, 1576, 1468, 1441, 1393, 1000, 922, 752 cm^{-1}; ^{1}H NMR (400 MHz, TMS, $CDCl_3$) δ: 10.59 (s, 1H), 7.25 (d, J=9.2 Hz, 1H), 7.15 (d, J=9.2 Hz, 1H), 5.22 (s, 2H), 5.21 (s, 2H), 3.56 (s, 3H), 3.51 (s, 3H), 0.29 (s, 9H); ^{13}C NMR (100 MHz, TMS, $CDCl_3$) δ: 190.4, 153.8, 152.9, 127.2, 122.6, 117.6, 117.3, 107.1 (aromatic C), 96.9, 96.0, 95.6, 56.4, 0.2 (aliphatic C) HRMS (ESI-MS) calcd for $C_{16}H_{22}O_5Si$: 345.1134 (M+Na), found: 345.1131.

*4.2.2. 5,8-Bis(methoxymethoxy)isoquinoline (**13**).* An oven-dried 10 mL round-bottomed flask equipped with a Teflon-coated magnetic stirring bar was charged with 3,6-bis(methoxymethoxy)-2-(2-(trimethylsilyl)ethynyl)benzaldehyde (**12**) (100 mg, 0.31 mmol) and K_2CO_3 (128 mg, 0.93 mmol), 2 mL of ethanol and excess of aqueous ammonia (0.5 mL) (27% ammonia in water). The reaction mixture was allowed to stir under reflux for 2 h. The complete conversion of starting material was observed (TLC). Then, the reaction mixture was allowed to cool to room temperature and extracted with $CHCl_3$ (2×10 mL). The organic layer was washed with 10 mL of water and 5 mL of brine, dried over anhydrous sodium sulfate and solvent was removed under reduced pressure. The crude product was purified by column chromatography on silica gel (eluent: 10% ethyl acetate in hexanes). The product was eluted in 10% eluent as a thick pale yellow liquid (65 mg) in 84% yield. R_f=0.20 (20% ethyl acetate in hexanes). IR (neat): 2954, 2827, 1625, 1575, 1491, 1453, 1375, 1273, 1110, 1024, 920, 821, 716 cm^{-1}; ^{1}H NMR (400 MHz, TMS, $CDCl_3$) δ: 9.63 (s, 1H), 8.59 (d, J=5.6 Hz, 1H), 7.97 (d, J=6.0 Hz, 1H), 7.22 (d, J=8.4 Hz, 1H), 7.09 (d, J=8.4 Hz, 1H), 5.38 (s, 2H), 5.34 (s, 2H), 3.56 (s, 3H), 3.55 (s, 3H); ^{13}C NMR (100 MHz, TMS, $CDCl_3$) δ: 148.3, 147.2, 146.5, 143.3, 129.5, 114.5, 112.6, 109.1 (aromatic C), 95.3, 95.1, 56.3, 56.2 (aliphatic C); HRMS (ESI-MS) calcd for $C_{13}H_{15}NO_4$: 250.1079 (M+H), found: 250.1075.

*4.2.3. Caulibugulone A (**1**).* An oven-dried 10 mL round-bottomed flask equipped with a Teflon-coated magnetic stirring bar was charged with 5,8-bis(methoxymethoxy)isoquinoline (**13**) (50 mg, 0.20 mmol) in 1 mL THF. Solution of THF, H_2O and concd HCl (6:4:1 ratio) (1 mL) was added dropwisely to the reaction mixture. Then reaction mixture was allowed to stir at 50 °C for 2 h. The reaction mass turned in dark yellow colour after 30 min. The complete conversion observed by TLC. The solvent THF was removed under reduced pressure. The resultant residue was extracted with ethyl acetate (2×10 mL), washed with saturated sodium bicarbonate solution, water, brine and concentrated under reduced pressure. This crude material (red colour residue) was then taken for next step without further purification. The residue was diluted with 2 mL of 1,2-dimethoxymethane (1,2-DME). The reaction mixture was then cooled to 0 °C and 33 wt % absolute ethanolic solution of methylamine (0.6 mL, 0.06 mmol) was added dropwise. Then it was allowed to stir at room temperature. After 2 h complete conversion was observed in TLC. After removing the solvent under reduced pressure, the reaction mixture was poured in 10 mL of water and extracted with ethyl acetate (2×20 mL). The organic layer was washed with water (10 mL) and brine (5 mL), dried over anhydrous sodium sulfate and the solvent was removed under reduced pressure. The crude product was purified by column chromatography (eluent: 20% ethyl acetate in hexanes). The product was eluted in 20% eluent as a red solid (31 mg) in 82% yield. R_f=0.37 (20% ethyl acetate in hexanes). Mp 218–220 °C; IR (neat): 3371, 2958, 2922, 2852, 2362, 1733, 1683, 1603, 1585, 1362, 1261, 1078, 797 cm^{-1}; ^{1}H NMR (500 MHz, TMS, $CDCl_3$) δ: 9.19 (s, 1H), 8.94 (d, J=5.0 Hz, 1H), 7.84 (d, J=5.0 Hz, 1H), 6.02 (br s, 1H), 5.75 (s, 1H), 2.89 (d, J=5.0 Hz, 3H); ^{13}C NMR (125 MHz, TMS, $CDCl_3$) δ: 181.2, 180.9, 156.3, 148.8, 147.9, 139.3, 124.2, 119.0, 101.2 (aromatic C), 29.2 (aliphatic C); HRMS (ESI-MS) calcd for $C_{10}H_8N_2O_2$: 189.0664 (M+H), found: 189.0661. R_f value and other spectroscopic properties were found to be identical with the Caulibugulone A reported earlier.[5–7]

*4.2.4. Caulibugulone D (**4**).* Same experimental protocol as adopted in the synthesis of Caulibugulone A (1) was followed. To a solution of THF, H_2O and concd HCl (6:4:1 ratio) (1 mL),

5,8-bis(methoxymethoxy)isoquinoline (**13**) (50 mg, 0.20 mmol) in 1 mL THF was added dropwise. Resulting residue was diluted with 2 mL of 1,2-dimethoxymethane. The reaction mixture was then cooled to 0 °C and 2-aminoethanol (36 mg, 0.60 mmol) in 1 mL of 1,2-DME was added dropwise. Then it was allowed to stir at room temperature. After 2 h, complete conversion was observed in TLC. After removing the solvent in reduced pressure, the reaction mixture was poured in 10 mL of water and extracted with ethyl acetate (2×20 mL). The organic layer was washed with water (10 mL) and brine (5 mL), dried over anhydrous sodium sulfate and the solvent was removed under reduced pressure. The crude product was purified by column chromatography (eluent: 40% ethyl acetate in hexanes). The product was eluted in 40% eluent as an orange solid (35 mg) in 80% yield. R_f=0.42 (95:5 ethyl acetate/methanol). Mp 180–182 °C; IR (neat): 3312, 3193, 3015, 2973, 1689, 1633, 1594, 1561, 1524, 1354, 1327, 1101, 991, 753 cm^{-1}; ^1H NMR (500 MHz, TMS, CD_3CN) δ: 9.16 (s, 1H), 8.97 (d, J=5.0 Hz, 1H), 7.81 (d, J=5.0 Hz, 1H), 6.57 (br s, 1H), 5.83 (s, 1H), 3.71 (t, J=5.5 Hz, 2H), 3.31 (dt, J=5.0, 5.5 Hz, 2H); ^{13}C NMR (125 MHz, TMS, CD_3CN) δ: 182.3, 181.5, 156.9, 149.6, 148.2, 140.0, 125.5, 119.2, 101.4 (aromatic C), 59.7, 45.3 (aliphatic C); HRMS (ESI-MS) calcd for $C_{11}H_{10}N_2O_3$: 219.0769 (M+H), found: 219.0768.

R_f value and other spectroscopic properties were found to be identical with the Caulibugulone D reported earlier.[5–7]

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Supplementary data

Supplementary data associated with this article can be found in the online version, at http://dx.doi.org/10.1016/j.tet.2014.12.059.

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13. The CCDC deposition number for Caulibugulone D (4) is 1026827. Formula: $C_{11}H_{10}N_2O_3$. Unit cell parameters: a=4.054(4); b=10.691(10); c=23.15(2), space group: P-1.