Tetrahedron 71 (2015) 801–804

Contents lists available at ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

Total synthesis of the marine alkaloids Caulibugulones A and D

K.S. Prakash, Rajagopal Nagarajan *

School of Chemistry, University of Hyderabad, Hyderabad 500 046, India

ARTICLE INFO

Article history:
Received 25 November 2014
Received in revised form 13 December 2014
Accepted 15 December 2014
Available online 19 December 2014

Keywords:
Marine alkaloids
Total synthesis
Iminoannulation
Caulibugulones
Oxidative amination

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.

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.

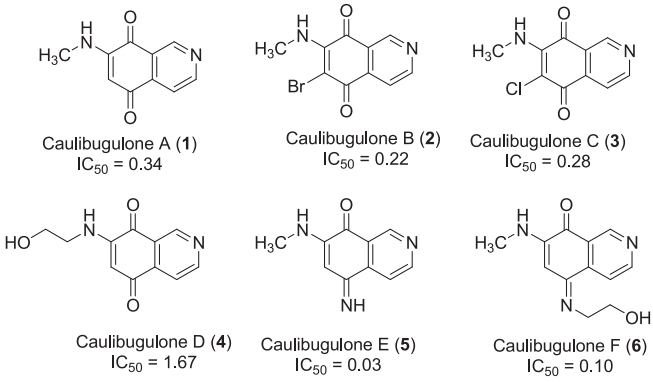


Fig. 1. Structure of Caulibugulones A–F (IC_{50} are expressed in μg/mL against the murine tumour cell line).[2]

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

* Corresponding author. Tel.: +91 40 23134831; fax: +91 40 23012460; e-mail addresses: rnsc@uohyd.ernet.in, naga_indole@yahoo.co.in (R. Nagarajan).

http://dx.doi.org/10.1016/j.tet.2014.12.059
0040-4020/

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.

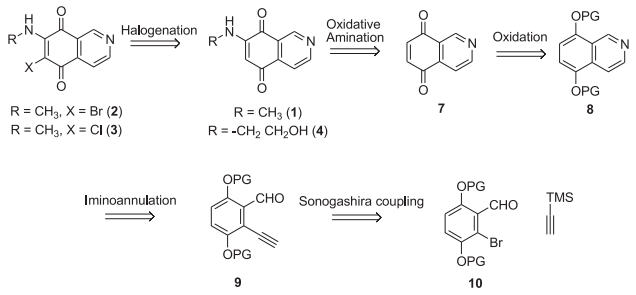
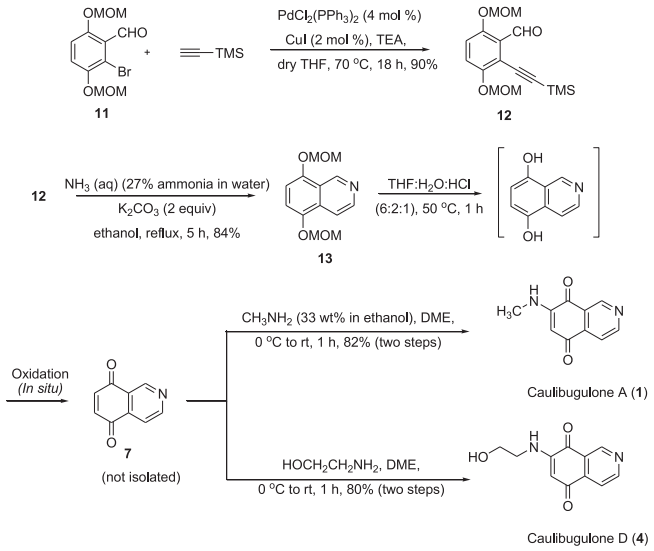


Fig. 2. Retrosynthetic analysis of Caulibugulones A–D.

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.

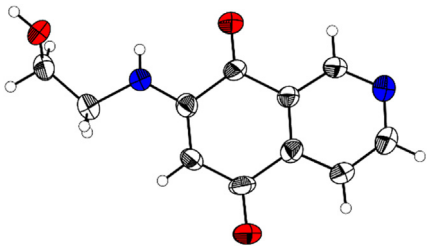


Fig. 3. ORTEP diagram of Caulibugulone D (**4**).

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).

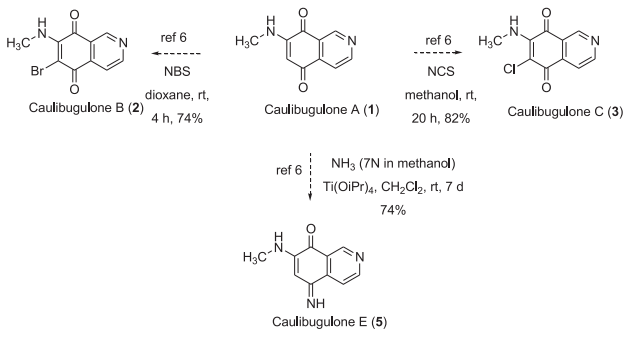


Fig. 4. Formal synthesis of Caulibugulones B, C and E.