Total synthesis of caulibugulone B

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INTRODUCTION

Caulibugulones (Figure 1) are marine isoquinoline alkaloids with anticancer activity isolated from bryoan Caulibugula intermis. Among caulibugulones A-D, compound B is the most active against CDC25 phosphatases. There are only two syntheses of this class of compounds and both of them were done at the same year of isolation. Both strategies use the oxidation of a preexistent isoquinoline nucleus as the key-step, and a sequence of amination/oxidation/halogenation reactions to achieve these compounds. In our work we describe the synthesis of caulibugulone B using Pomeranz-Fritsch cyclization to build the isoquinoline nucleus and a oxidative ether cleavage of the alkoxy groups to give the desired compound.

RESULTS AND DISCUSSION

Reductive amination of 2,5-dimethoxybenzaldehyde (2) with 2,2-dimethoxyethanamine (3) and sodium borohydride furnished the benzylamine 5 which generated 5,8-dimethoxyisoquinoline (6) after Pomeranz-Fritsch based cyclization with heating in trifluoacetic acid (Figure 2). Oxidative ether cleavage of alkoxy groups in 6 with N-bromosuccinimide in water/tetrahyrufuran gave dibromoisoquinoline-5,8-dione (7) which reacted promptly with methylamine in ethanol yielding caulibugulone B (1) (Figure 2).

CONCLUSION

We developed a new synthesis of caulibugulone B using simple and commercially available starting materials. Our sequence allowed concurrent oxidative ether deprotection and bromination of the isoquinoline nucleus, which suffered aminolysis with methylamine regioselectively.

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