

Total synthesis of sulfur-containing pyrroloiminoquinone marine product, (\pm)-makaluvamine F using hypervalent iodine(III)-induced reactions

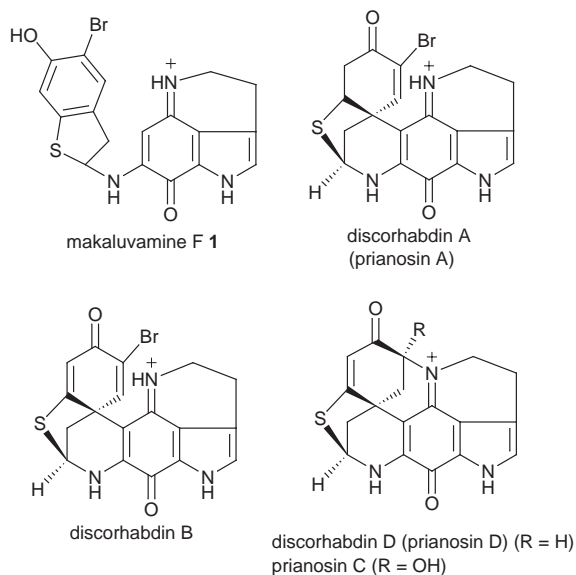
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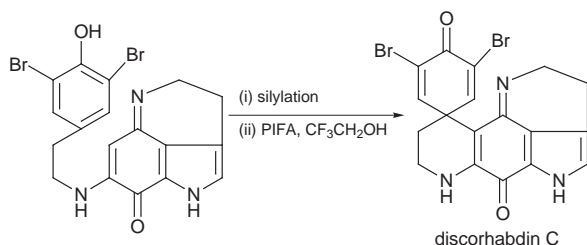
Received (in Cambridge, UK) 9th November 1998, Accepted 20th November 1998

The first total synthesis of potent cytotoxic makaluvamine F **1**, a sulfur-containing pyrroloiminoquinone marine product, has been accomplished using hypervalent iodine(III)-induced reactions.

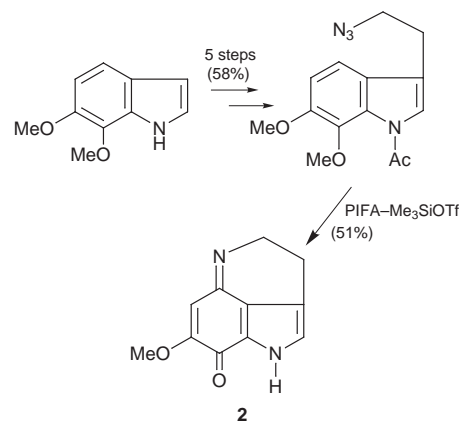
The makaluvamines,¹ a new family of marine alkaloids, were isolated from the Fijian sponge *Zyzya cf. marsailis* (A–F) and the Indonesian sponge *Histodermella* sp. (G). Among them,



makaluvamine F **1** exhibits the most potent biological activity [*e.g.* cytotoxicity towards the human colon tumor cell-line HCT-116 ($IC_{50} = 0.17 \mu M$) and inhibition of topoisomerase II]^{1,2} and has an α -aminodihydrobenzothiophene skeleton which is a labile *N,S*-acetal structure present in all sulfur-containing discorhabdins.³ Synthetic studies towards makaluvamines and discorhabdins have been carried out by several groups.⁴ We have also reported the total synthesis of discorhabdin C (Scheme 1)⁵ and a facile and efficient synthesis of pyrroloiminoquinone derivatives **2** using the hypervalent iodine(III) reagent, phenyliodine bis(trifluoroacetate) (PIFA) (Scheme 2).⁶ However, in most cases these efforts have been



Scheme 1



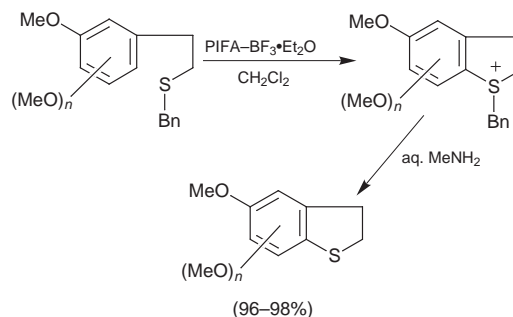
Scheme 2

devoted only towards the preparation of the pyrroloiminoquinone and spirodienone units.

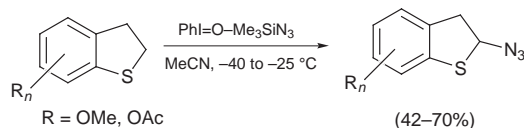
To the best of our knowledge, the total syntheses of sulfur-containing discorhabdins and **1** have not yet been reported, in spite of their potent cytotoxicity and their unique structure. This is probably due to the difficulty of construction of the labile and highly strained *N,S*-acetal skeletons. We report herein the first total synthesis of potent cytotoxic makaluvamine F **1** using hypervalent iodine(III)-induced reactions. Our synthetic strategy for the total synthesis of **1** involves a final coupling reaction between **2** and 2-aminodihydrobenzothiophene derivative **3**.

In order to construct **3** bearing the *N,S*-acetal skeleton, it was first essential to develop an efficient route for the synthesis of the starting dihydrobenzothiophene bearing a hydroxy group. In our previous report, various dihydrobenzothiophenes were prepared from phenol ethers bearing an alkyl sulfide sidechain *via* intramolecular cyclization using PIFA- $BF_3 \cdot Et_2O$ followed by treatment with aq. $MeNH_2$ without yielding any sulfoxides (Scheme 3).⁷ Using this method, 6-benzyloxy-5-bromodihydrobenzothiophene **4** was synthesized effectively.

Next, we attempted to introduce the azido group at the 2-position of **4**. Subsequent to the first report by Böhme and Morf,⁸ acyclic α -azido sulfides have generally been synthesized stepwise, *via* halogenation followed by azidation of sulfides,⁹ or *via* thioketals.¹⁰ On the other hand, α -azidation of dihy-



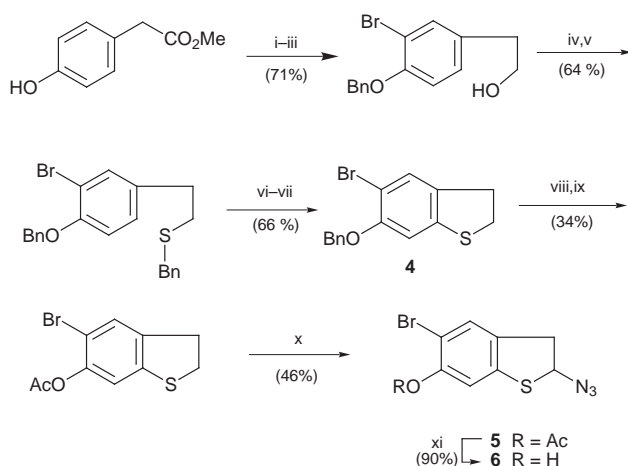
Scheme 3



Scheme 4

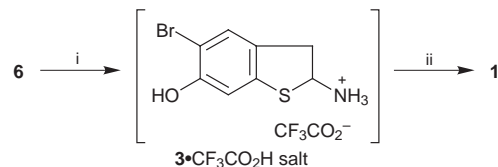
dibenzothiophenes has never been reported, probably due to readily occurring side reactions such as aromatization, sulfoxide formation, benzylic oxidation and α -oxidation of the sulfur atom under oxidative conditions. We examined the known stepwise methods to obtain α -azidodihydrobenzothiophene. However, the aromatization occurred exclusively to give benzothiophene derivatives in the initial halogenation step.

Very recently, we developed a novel and direct α -azidation of dihydrobenzothiophenes using a combination of PhI=O and Me₃SiN₃ (Scheme 4).¹¹ However, the azidation of **4** gave only a trace amount of the expected α -azido compound. This is because there appears to be a large number of reactive sites on phenol ether **4** toward the hypervalent iodine-induced azidation. Hence, we then performed the azidation after debenzoylation followed by acetylation of **4** to give the corresponding α -azido compound **5** in 46% yield. After hydrolytic deprotection of the 6-acetoxy group, 2-azido-5-bromo-6-hydroxy-dihydrobenzothiophene **6** was finally obtained. The route to **6** from commercially available methyl (4-hydroxyphenyl)acetate is outlined in Scheme 5.



Scheme 5 Reagents and conditions: i, Br₂, AcOH; ii, BnBr, K₂CO₃, EtOH; iii, LiAlH₄, THF; iv, I₂, PPh₃, imidazole, PhMe; v, AcSBn, NaOH, MeOH; vi, PIFA-BF₃·OEt₂; vii, aq. MeNH₂; viii, BF₃·OEt₂, EtSH; ix, Ac₂O, NaOAc, aq. NaOH; x, PhI=O-Me₃SiN₃, MeCN, -40 to -25 °C; xi, 5% NaOH, MeOH.

Sequential attempts to transform the azido group to the amino group by catalytic hydrogenation or other reductive methods under non-acidic conditions proved unsatisfactory (*i.e.* 2-amino-5-bromo-6-hydroxydihydrobenzothiophene **3** was found to be quite labile under basic conditions). Furthermore, Wittig-type reactions between the phosphine imine prepared from **6** and several quinones were also unsuccessful. Finally, we found that the catalytic hydrogenation of **6** using 10% Pd-C in the presence of 4 equiv. of TFA resulted in complete reduction to give **3** as a TFA salt in quantitative yield without any side reactions. The final coupling reaction in MeOH between both synthetic precursors, **3** (TFA salt) and **2**, proceeded in 86% yield



Scheme 6 Reagents and conditions: i, H₂, 10% Pd-C, EtOH-TFA; ii, **2**, MeOH, room temp.

to give the TFA salt of **1**, whose spectral data were identical to those previously reported¹ (Scheme 6).

In conclusion, the first total synthesis of (\pm)-makaluvamine F has been achieved *via* a facile construction of the labile *N,S*-acetal skeleton by a combination of hypervalent iodine oxidation reactions. Synthetic studies towards more complicated sulfur-containing discorhabdins and their analogs are now underway.

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Communication 8/08715F