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

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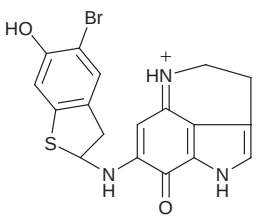
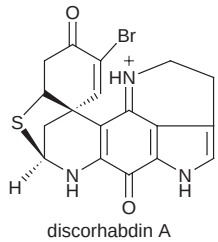
The first total synthesis of potent cytotoxic makaluvamine F 1, a sulfur-containing pyrroloiminoquinone marine product, has been accomplished using hypervalent iodine(III)-induced reactions.

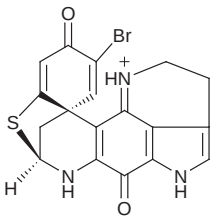
The makaluvamines,[1] a new family of marine alkaloids, were isolated from the Fijian sponge *Zyzzya cf. marsailis* (A–F) and the Indonesian sponge *Histodermella* sp. (G). Among them,



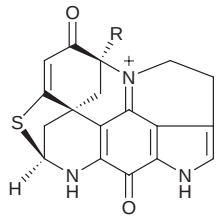
makaluvamine F **1**



discorhabdin A (prianosin A)

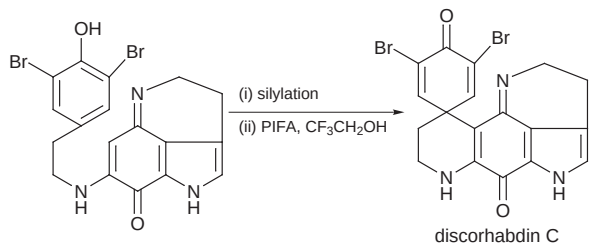


discorhabdin B

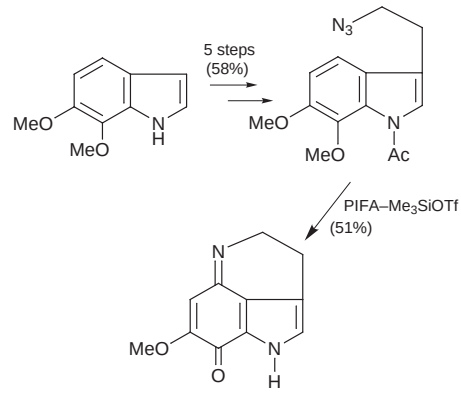


discorhabdin D (prianosin D) (R = H)
prianosin C (R = OH)

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 μM) 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(III) bis(trifluoroacetate) (PIFA) (Scheme 2).[6] However, in most cases these efforts have been



Scheme 1



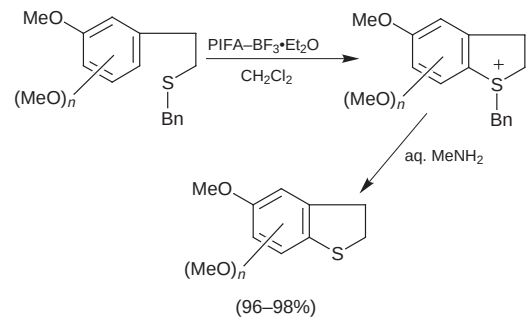
Scheme 2

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

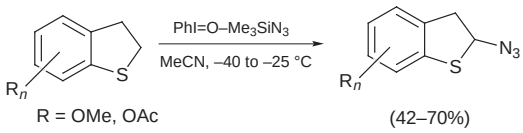
To the best of our knowledge, the total syntheses of sulfur-containing discorhabdins and **1** have not yet been reported, in spite of their potent cytotoxicity and their unique structure. This is probably due to the difficulty of construction of the labile and highly strained *N*,*S*-acetal skeletons. 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·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-



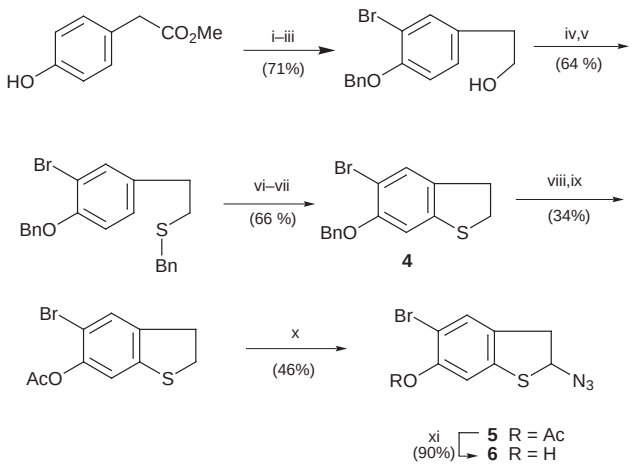
Scheme 3



Scheme 4

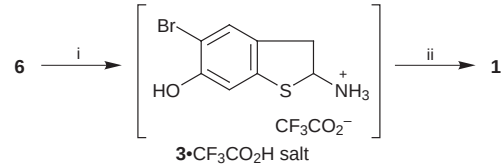
drobenzothiophenes has never been reported, probably due to readily occurring side reactions such as aromatization, sulfoxide formation, benzylic oxidation and α-oxidation of the sulfur atom under oxidative conditions. We examined the known stepwise methods to obtain α-azidodihydrobenzothiophene. However, 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 Me_3SiN_3 (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 debenzylation 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, Br_2, AcOH; ii, BnBr, K_2CO_3, EtOH; iii, $LiAlH_4$, THF; iv, I_2, PPh_3, imidazole, PhMe; v, AcSBn, NaOH, MeOH; vi, PIFA–BF_3·OEt_2; vii, aq. $MeNH_2$; viii, BF_3·OEt_2, EtSH; ix, Ac_2O, NaOAc, aq. NaOH; x, PhI=O–Me_3SiN_3, 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, H_2, 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 reported[1] (Scheme 6).

In conclusion, the first total synthesis of (±)–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.

Notes and references

1 D. C. Radisky, E. S. Radisky, L. R. Barrows, B. R. Copp, R. A. Kramer and C. M. Ireland, *J. Am. Chem. Soc*., 1993, **115**, 1632.

2 L. R. Barrows, D. C. Radisky, B. R. Copp, D. S. Swaffar, R. A. Kramer, R. L. Warters and C. M. Ireland, *Anti-Cancer Drug Des*., 1993, **8**, 333.

3 J.-F. Cheng, Y. Ohizumi, M. R. Wälchli, H. Nakamura, Y. Hirata, T. Sasaki and J. Kobayashi, *J. Org. Chem*., 1988, **53**, 4621; H. H. Sun, S. Sakemi, N. Burres and P. McCarthy, *J. Org. Chem*., 1990, **55**, 4964; J. W. Blunt, M. H. G. Munro, C. N. Battershill, B. R. Copp, J. D. McCombs, N. B. Perry, M. R. Prinsep and A. M. Thompson, *New J. Chem*., 1990, **14**, 761; J. Kobayashi, J.-F. Cheng, S. Yamamura and M. Ishibashi, *Tetrahedron Lett*., 1991, **32**, 1227 and references cited therein; T. F. Molinski, *Chem. Rev*., 1993, **93**, 1825; B. R. Copp, K. F. Fulton, N. B. Perry, J. W. Blunt and M. H. G. Munro, *J. Org. Chem*., 1994, **59**, 8233; A. Yang, B. J. Baker, J. Grimwade, A. Leonard and J. B. McClintock, *J. Nat. Prod*., 1995, **58**, 1596.

4 Y. Kita, T. Yakura, H. Tohma, K. Kikuchi and Y. Tamura, *Tetrahedron Lett*., 1989, **30**, 1119; H. J. Knölker and K. Hartmann, *Synlett*, 1991, 428; S. Hamabuchi, H. Hamada and M. Somei, *Heterocycles*, 1991, **32**, 443; S. Nishiyama, J.-F. Cheng, X. L. Tao and S. Yamamura, *Tetrahedron Lett*., 1991, **32**, 4151; T. Izawa, S. Nishiyama and S. Yamamura, *Tetrahedron*, 1994, **50**, 13593; J. D. White, K. M. Yager and T. Yakura, *J. Am. Chem. Soc*., 1994, **116**, 1831; E. V. Sadanandan, S. K. Pillai, M. V. Lakshmikantham, A. D. Billimoria, J. S. Culpepper and M. P. Cava, *J. Org. Chem*., 1995, **60**, 1800; D. Roberts, M. Alvarez and J. A. Joule, *Tetrahedron Lett*., 1996, **37**, 1509; R. Zhao and J. W. Lown, *Synth. Commun*., 1997, **27**, 2103; D. Roberts, J. A. Joule, M. A. Bros and M. Alvarez, *J. Org. Chem*., 1997, **62**, 568; M. Makosza, J. Stalewski and O. S. Maslennikova, *Synthesis*, 1997, 1131; M. Iwao, O. Motoi, T. Fukuda and F. Ishibashi, *Tetrahedron*, 1998, **54**, 8999; G. A. Kraus and N. Selvakumar, *Synlett*, 1998, 845.

5 Y. Kita, H. Tohma, M. Inagaki, K. Hatanaka and T. Yakura, *J. Am. Chem. Soc*., 1992, **114**, 2175.

6 Y. Kita, M. Egi, A. Okajima, M. Ohtsubo, T. Takada and H. Tohma, *Chem. Commun*., 1996, 1491; Y. Kita, H. Watanabe, M. Egi, T. Saiki, Y. Fukuoka and H. Tohma, *J. Chem. Soc*., *Perkin Trans. 1*, 1998, 635.

7 Y. Kita, M. Egi, M. Ohtsubo, T. Saiki, T. Takada and H. Tohma, *Chem. Commun*., 1996, 2225.

8 H. Böhme and D. Morf, *Chem. Ber*., 1957, **90**, 446.

9 H. Böhme and F. Ziegler, *Liebigs Ann. Chem*., 1974, 734; I. W. J. Still, W. L. Brown, R. J. Colville and G. W. Kutney, *Can. J. Chem*., 1984, **62**, 586.

10 B. M. Trost, M. Vaultier and M. L. Santiago, *J. Am. Chem. Soc*., 1980, **102**, 7929.

11 H. Tohma, M. Egi, M. Ohtsubo, H. Watanabe, S. Takizawa and Y. Kita, *Chem. Commun*., 1998, 173.

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