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Total Synthesis of Flustramine C via Dimethylallyl Rearrangement

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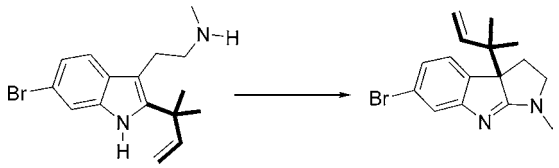
ABSTRACT



The marine natural product flustramine C from the bryozoan *Flustra foliacea* was synthesized in five steps and 38% yield starting from N_b-methyltryptamine. The key step is the biomimetic oxidation of the natural product deformylflustrabromine causing selective 1,2-rearrangement of the inverse prenyl group. By $^1H,^{15}N$ HMBC experiments, it is unambiguously shown that the reaction with *t*-BuOCl commences with chlorination of the side chain nitrogen. Deformylflustrabromine itself was synthesized via Danishefsky inverse prenylation.

The bryozoan *Flustra foliacea* has been a rich source of brominated indole alkaloids bearing isoprenyl substituents at various positions.[1] The discovery of deformylflustrabromine (**1**, Figure 1) as a major metabolite of *F. foliacea*

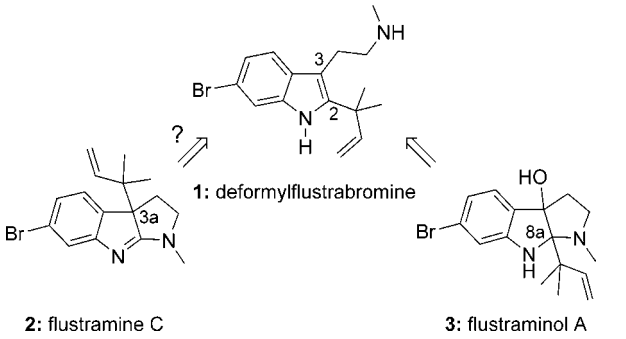


Figure 1. Inversely prenylated bromoindole alkaloids from the bryozoan *Flustra foliacea*.

collected near the North Sea island of Helgoland[2,3] prompted us to investigate the chemical link between **1** and the pyrrolo-[2,3-*b*]indole flustramine C (**2**).

Flustramine C (**2**) is functionalized by a 1,1-dimethylallyl ("inverse prenyl") group at the bridgehead C3a and co-occurred with hydroxylated flustraminol A (**3**) in the same specimen of *F. foliacea*.[4] The biosynthesis of **2** and **3** could involve oxidation of deformylflustrabromine (**1**). Whereas flustraminol A (**3**) appears to be formed via epoxidation of the indole C2−C3 double bond of **1**, the biogenesis of flustramine C (**2**) requires oxidation and rearrangement of the prenyl group. It is unclear whether the prenyl shift is enzyme assisted. Christophersen et al. did not report optical activity for flustramine C (**2**) or flustraminol A (**3**),[4] and König et al. isolated (−)-**2**.[3a] The optical purity of (−)-**2** ($[\alpha]_D^{22} = -10.1$) has not been determined.

(1) (a) Carlé, J. S.; Christophersen, C. *J. Am. Chem. Soc.* **1979**, *101*, 4012−4013. (b) Carlé, J. S.; Christophersen, C. *J. Org. Chem.* **1980**, *45*, 1586−1589. (c) Wright, J. L. C. *J. Nat. Prod.* **1984**, *47*, 893−895. (d) Laycock, M. V.; Wright, J. L. C.; Findlay, J. A.; Patil, A. D. *Can. J. Chem.* **1985**, *64*, 1312−1316. (e) Keil, P.; Nielsen, E. G.; Anthoni, U.; Christophersen, C. *Acta Chem. Scand. B* **1986**, *40*, 555−558. (f) Holst, P. B.; Anthoni, U.; Christophersen, C.; Nielsen, P. H. *J. Nat. Prod.* **1994**, *57*, 997−1000.

(2) Lysek, N.; Rachor, E.; Lindel, T. *Z. Naturforsch. C: Biosci.* **2002**, *57c*, 1056−1061.

(3) (a) Peters, L.; König, G. M.; Terlau, H.; Wright, A. D. *J. Nat. Prod.* **2002**, *65*, 1633−1637. (b) Peters, L.; Wright, A. D.; Krick, A.; König, G. M. *J. Chem. Ecol.* **2004**, *30*, 1165−1181.

(4) Carlé, J. S.; Christophersen, C. *J. Org. Chem.* **1981**, *46*, 3440−3443.

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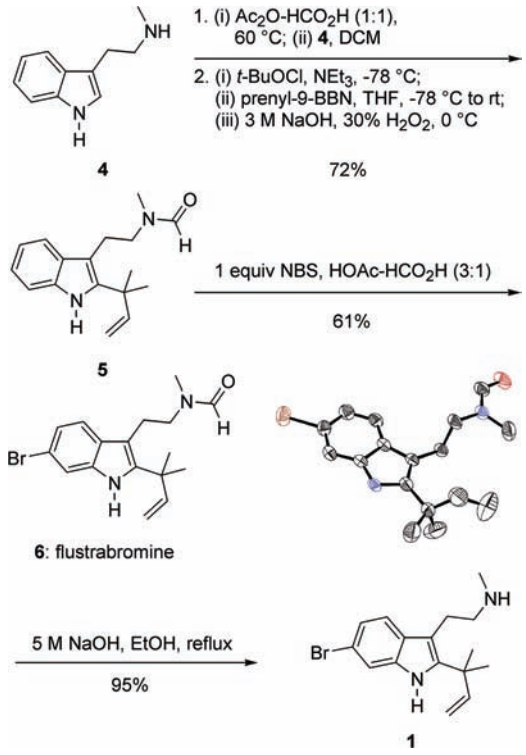
Deformylflustrabromine (**1**) affects the nicotinic acetylcholine receptor (nAChR).[5] Flustramine C (**2**) shows elevated concentrations in exposed parts of *F. foliacea*, and it is secreted into the surrounding water and could play an important role in ecological interactions.[3] It has also been suggested that the *Flustra* alkaloids are important for the bryozoan by controlling bacterial growth on its surface.[6]

There are two total syntheses of flustramine C by the Sakamoto[7] and Funk[8] groups, both utilizing intermediates oxygenated at the indole 2-position. Our approach presented here employs deformylflustrabromine (**1**) as an immediate precursor. For the synthesis of deformylflustrabromine, N_b-methyltryptamine (**4**) was converted to N_b-formyl-N_b-methyltryptamine[9] which cleanly underwent Danishefsky inverse prenylation[10−12] upon treatment with *t*-BuOCl and freshly prepared prenyl-9-BBN,[13] affording 1,1-dimethylallyl indole **5** in 80% yield (Scheme 1). It proved to be beneficial if 1,1-

Scheme 1. Synthesis of Deformylflustrabromine (**1**)

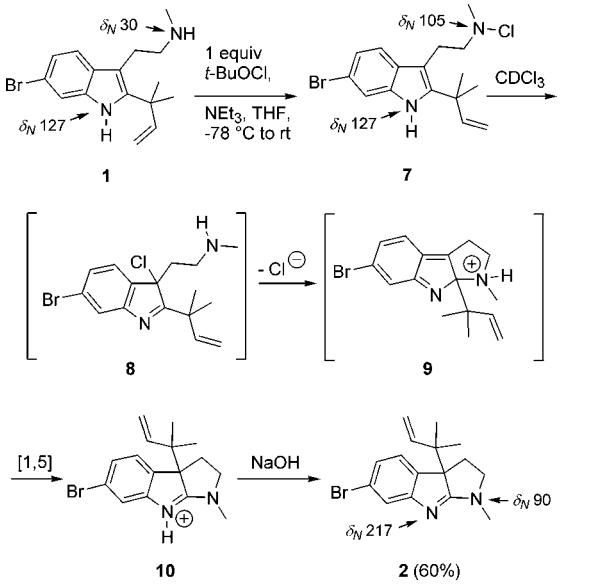


dimethylallene[14] and 9-BBN−H were allowed to react for 18 h at room temperature before use.

Monobromination of **5** proceeded on treatment with 1 equiv of *N*-bromosuccinimide (NBS) in HOAc/HCO_2H (3:1) affording the natural product flustrabromine (**6**, X-ray analysis)[15] in 61% yield.[16] As a side product, minor amounts (15%) of the 4-brominated analogue were obtained.[17] Alkaline hydrolysis of flustrabromine (**6**) afforded deformylflustrabromine (**1**).

With gram quantities of deformylflustrabromine (**1**) in hand, we were now able to investigate our key question. For oxidative conversion of **1** to **2**, we first investigated *t*-BuOCl. On treatment of deformylflustrabromine (**1**) with 1 equiv of *t*-BuOCl in the presence of NEt_3 in THF at −78 °C, an isolable, yet unstable, intermediate was formed (Scheme 2).

Scheme 2. Conversion of Deformylflustrabromine (**1**) to Flustramine C (**2**)[a]



[a] Compounds were characterized by ^1H,^{15}N HMBC experiments.

The ESI(−)FTMS spectrum indicated replacement of a hydrogen by a chlorine atom. In the NMR spectrum, chemical shifts of the side chain had shifted downfield and the signals of the indole moiety remained almost unchanged. We concluded that the side chain nitrogen had been

(5) Sala, F.; Mulet, J.; Reddy, K. P.; Bernal, J. A.; Wikman, P.; Valor, L. M.; Peters, L.; König, G. M.; Criado, M.; Sala, S. *Neurosci. Lett.* **2005**, *373*, 144−149.

(6) Peters, L.; König, G. M.; Wright, A. D.; Pukall, R.; Stackebrandt, E.; Eberl, L.; Riedel, K. *Appl. Environ. Microbiol.* **2003**, *69*, 3469−3475.

(7) Kawasaki, T.; Terashima, R.; Sakaguchi, K.; Sekiguchi, H.; Sakamoto, M. *Tetrahedron Lett.* **1996**, *37*, 7525−7528.

(8) Fuchs, J. R.; Funk, R. L. *Org. Lett.* **2005**, *7*, 677−680.

(9) (a) Nakagawa, M.; Yoshikawa, K.; Hino, T. *J. Am. Chem. Soc.* **1975**, *97*, 6496−6501. (b) Bosch, J.; Roca, T.; Armengol, M.; Fernández-Forner, D. *Tetrahedron* **2001**, *57*, 1041−1048.

(10) (a) Schkeryantz, J. M.; Woo, J. C. G.; Danishefsky, S. J. *J. Am. Chem. Soc.* **1995**, *117*, 7025−7026. (b) Schkeryantz, J. M.; Woo, J. C. G.; Siliphaivanh, P.; Depew, K. M.; Danishefsky, S. J. *J. Am. Chem. Soc.* **1999**, *121*, 11964−11975.

(11) Liu, K.; Wood, H. B.; Jones, A. B. *Tetrahedron Lett.* **1999**, *40*, 5119−5122.

(12) (a) Roe, J. M.; Webster, R. A. B.; Ganesan, A. *Org. Lett.* **2003**, *5*, 2825−2827. (b) Hewitt, P. R.; Cleator, E.; Ley, S. V. *Org. Biomol. Chem.* **2004**, *2*, 2415−2417.

(13) Kramer, G. W.; Brown, H. C. *J. Organomet. Chem.* **1977**, *132*, 9−27.

(14) (a) Mayr, H.; Halberstadt-Kausch, I. K. *Chem. Ber.* **1982**, *115*, 3479−3515. (b) Crandall, J. K.; Keyton, D. J.; Kohne, J. *J. Org. Chem.* **1968**, *33*, 3655−3657.

(15) (a) Wulff, P.; Carlé, J. S.; Christophersen, C. *Comp. Biochem. Physiol.* **1982**, *71b*, 523−524. (b) For a recent synthesis of debrominated flustrabromine, see: Zhun, I. V.; Ignatenko, A. V. *Russ. Chem. Bull.* **2004**, *53*, 2221−2223.

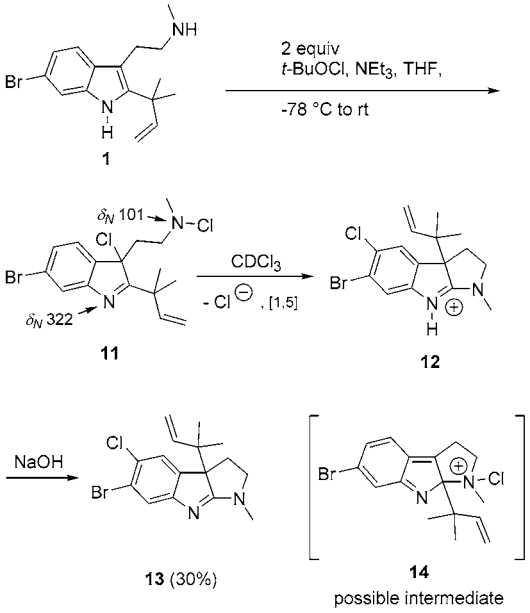
(16) The solvent mixture had been used for the dibromination of tryptamine affording a mixture of three regioisomers: Miyake, F. Y.; Yakushijin, K.; Horne, D. A. *Org. Lett.* **2004**, *6*, 711−713.

chlorinated, as shown in structure **7**. This was supported by a $^{1}H,^{15}N$ HMBC experiment revealing δ_N 105 ppm for the side chain and 127 ppm for the indole nitrogen ($CDCl_3$, referenced to $\delta(NH_3)$ 0 ppm). In comparison to compound **1**, the signal of the indole nitrogen had shifted by only 0.1 ppm, and the chlorinated side chain nitrogen exhibited a downfield shift of about 75 ppm.

On standing in $CDCl_3$, we observed cyclization and rearrangement of **7** to protonated compound **10** which was also characterized by 2D NMR. Deprotonation of **10** on treatment with 2 N NaOH afforded flustramine C (**2**) in 60% overall yield. Mechanistically, the reaction of **7** could commence with intra- or intermolecular chlorination of the indole 3-position affording chloroindolenine **8** which loses chloride-forming cation **9**.[1,5] Sigmatropic rearrangement would then yield protonated flustramine C (**2**).

N-Chlorinated intermediate **7** was always accompanied by a minor side product (1:4) which was formed exclusively when 2 equiv of *t*-BuOCl was employed. On the basis of ESI(+)HRMS and NMR spectra, we found that dichlorinated compound **11** (Scheme 3) was generated. Whereas the ^{15}N NMR chemical shift of the side chain nitrogen is close to the case of N-chlorinated compound **7** (δ 101 ppm compared to δ 105 ppm), the indole nitrogen experienced a pronounced downfield shift (δ 322 ppm compared to δ 127 ppm). This is due to the formation of a 3-chloroindolenine partial structure with an imine nitrogen.

Scheme 3. Conversion of Deformylflustrabromine (**1**) to 5-Chloroflustramine C (**13**) by Treatment with 2 equiv of *t*-BuOCl/NEt_3[a]

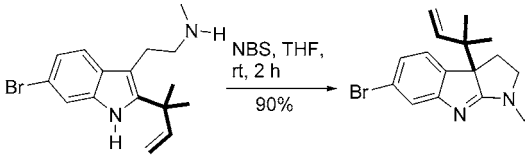


[a] Intermediate **11** was characterized by $^{1}H,^{15}N$ HMBC.

Over days in $CDCl_3$ at room temperature, chloroindolenine **11** reacted to give a mixture of compounds among which the protonated forms of 5-chloroflustramine C (**12**) and flustramine C were the major components. After treatment with 2 N NaOH, 5-chloroflustramine C (**13**, 30%) and flustramine C (**2**, 25%) were isolated. As an intermediate, *N*-chlorotrialkylammonium cation **14** is possible. It is known that *N*-chlorotrialkylammonium salts are selective agents for the chlorination of aromates.[18]

The synthesis of flustramine C was substantially improved by replacing *t*-BuOCl with 1 equiv of NBS, providing **2** in an isolated yield of 90% (Scheme 4). No brominated side product was formed. In this case, we were not able to isolate any intermediate of the reaction pathway. Thus, initial formation of a 3-bromoindolenine without side chain bromination may also be possible.

Scheme 4. Most Efficient Conversion of Deformylflustrabromine (**1**) to Flustramine C (**2**)



The biosynthesis of flustramine C and dihydroflustramine C (**17**) in *Flustra foliacea* has never been investigated. However, biosynthesis of prenylated indole alkaloids in general has been the subject of intense investigation.[19] It is discussed (a) where and how inverse or direct prenyl groups are initially introduced and (b) if and how migrations of inverse or direct prenyl groups may proceed. In this paper, we give an example of possible biomimetic chemistry regarding the latter part.

Starting from the natural product **15**,[15a] Scheme 5 outlines three possible pathways. Following a classical proposal, aza-Claisen rearrangement of an N-prenylated precursor (**16**, path A) could occur. Alternatively, direct introduction of an inverse prenyl group by S_N2' reaction at C3 may occur (path B), without the involvement of inverse prenylation at C2, as proposed by Harrison for the biosynthesis of roquefortine.[20] Inverse prenyl groups at C3 may also arise via a 1,2-shift from C2 (path C), as proposed by Barrow[21] and by

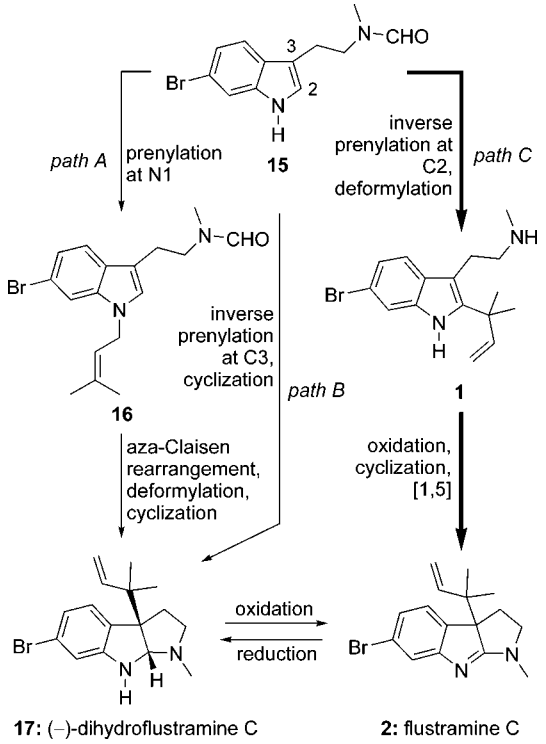
(17) In the crystal, the *E*-rotamer of **6** occurs, and in solution, both rotamers are present in almost equal percentages. CCDC-270034 (**6**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam. ac.uk/conts/retrieving.html (or from the Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge CB21EZ, UK; fax (+44) 1223-336-033 or deposit@ ccdc.cam.ac.uk).

(18) (a) Smith, J. R. L.; McKeer, L. C.; Taylor, J. M. *J. Chem. Soc., Perkin Trans. 2* **1987**, 1533−1537. (b) Smith, J. R. L.; McKeer, L. C.; Taylor, J. M. *J. Chem. Soc., Perkin Trans. 2* **1988**, 385−391.

(19) For a review on the biosynthesis of tryptophan-derived prenylated alkaloids, see: Williams, R. M.; Sanz-Cervera, J. F.; Stocking, E. In *Top. Curr. Chem.*; Leeper, F., Vederas, J.C., Eds.; Springer-Verlag: Berlin, 2000; Vol. 209, pp 97−173.

(20) (a) Bhat, B.; Harrison, D. M.; Lamont, H. M. *J. Chem. Soc., Chem. Commun.* **1990**, 1518−1519. (b) Bhat, B.; Harrison, D. M.; Lamont, H. M. *Tetrahedron* **1993**, *49*, 10663−10668.

Scheme 5. Possible Biogenetic Pathways toward Dihydroflustramine C (**17**) and Flustramine C (**2**), Starting from the Natural Product **15**



Gorst−Allman[22] for the biosynthesis of roquefortine and by Williams for paraherquamide A.[23]

Our investigation shows that, from a chemical perspective, the biogenesis of flustramine C (**2**) may indeed proceed via inverse prenylation of the indole 2-position (path C) in an oxidative process.

Beyond ring contractions of carbazole derivatives,[24] the conversion of **1** to **2** is the first chemically achieved 1,2-shift of a nonfunctionalized inverse prenyl group from the indole 2-position to the 3-position. Surprisingly, few 1,2-prenyl shifts have been exploited for the total syntheses of indole alkaloids. Successful reactions include acid-induced rearrangements of N-prenylated indoles to varying mixtures of 2-inversely and 2-directly prenylated indoles,[25] of a 3-prenylated pyrrolo[2,3-b]indole to a 2-prenylated indole under ring opening,[26] and of a 3-prenylated indole to a 1:9 mixture of inversely and directly 2-prenylated indoles.[27] In the absence of the C2−C3 double bond, acid-catalyzed aza-Claisen rearrangement of inversely N-prenylated indoles resulted in 7-prenylation.[28]

Our novel approach to flustramine C (**2**) is quite efficient (five steps, 38% yield starting from N_b-methyltryptamine (**4**)).

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Supporting Information Available: Detailed experimental procedures and characterization data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(21) Barrow, K. D.; Colley, P. W.; Tribe, D. E. *J. Chem. Soc., Chem. Commun.* **1979**, 225−226.

(22) Gorst-Allman, C. P.; Steyn, P. S.; Vleggaar, R. *J. Chem. Soc., Chem. Commun.* **1982**, 652−653.

(23) (a) Stocking, E. M.; Sanz-Cervera, J. F.; Williams, R. M. *Angew. Chem., Int. Ed.* **1999**, *38*, 786−789. (b) Stocking, E. M.; Williams, R. M.; Sanz-Cervera, J. F. *J. Am. Chem. Soc.* **2000**, *122*, 9089−9098.

(24) For examples, see: (a) Williams, R. M.; Cao, J.; Tsujushima, H.; Cox, R. J. *J. Am. Chem. Soc.* **2003**, *125*, 12172−12178. (b) Cushing, T. D.; Sanz-Cervera, J. F.; Williams, R. M. *J. Am. Chem. Soc.* **1996**, *118*, 557−579. (c) Stoermer, D.; Heathcock, C. H. *J. Org. Chem.* **1993**, *58*, 564−568.

(25) (a) Casnati, G.; Marchelli, R.; Pochini, A. *J. Chem. Soc., Perkin Trans. 1* **1970**, 754−757. (b) Cardoso, A. S.; Lobo, A. M.; Prabhakar, S. *Tetrahedron Lett.* **2000**, *41*, 3611−3613.

(26) Muthusubramanian, P.; Carlé, J. S.; Christophersen, C. *Acta Chem. Scand. B* **1983**, *37*, 803−807.

(27) Plate, R.; Ottenheijm, H. C. J. *Tetrahedron Lett.* **1986**, *27*, 3755−3758.

(28) Roe, J. M.; Webster, R. A. B.; Ganesan, A. *Org. Lett.* **2003**, *5*, 2825−2827.