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Concise syntheses of 5,6-dibromotryptamine and 5,6-dibromo-*N*,*N*-dimethyltryptamine en route to the antibiotic alternatamide D

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ABSTRACT

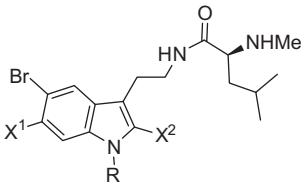
Concise syntheses of the natural products 5,6-dibromotryptamine, 5,6-dibromo-*N*,*N*-dimethyltryptamine and the bromotryptamine antibiotic alternatamide D have been accomplished starting from the common intermediate, 5,6-dibromoindole-3-carbaldehyde.

Alternatamides A–D (**1**–**4**) are four bromotryptamine peptide antibiotics isolated from the Atlantic bryozoan *Amathia alternata* in 1997 by Fenical and co-workers[1] (Fig. 1). The indole nuclei present in alternatamides A–D are decorated with varying degrees of bromination, and of particular interest to our laboratory is alternatamide D (**4**), the member of the family that possesses a rare 5,6-dibromoindole moiety that has only been observed in a very small number of natural products to date.[2] Furthermore, there is a total absence of synthetic work directed towards the alternatamides. Due to our ongoing interest in the synthesis of natural products possessing rare bromination patterns[3] and for reasons outlined above, we initiated a synthesis of alternatamide D (**4**).

A retrosynthetic consideration of alternatamide D (**4**) suggests disconnection of the amide bond is the most straightforward option, leaving 5,6-dibromotryptamine (**5**) and *N*-methyl-L-leucine (**6**)[4] (Scheme 1). 5,6-Dibromotryptamine (**5**) is itself a natural product isolated from a variety of marine sources[5] and our initial thoughts were aimed at the synthesis of **5**. Although 5,6-dibromotryptamine has been reported as a starting material for the preparation of several β-carboline compounds as potential CNS drugs, no details were disclosed regarding its synthesis.[6]

Recently, we disclosed the efficient, large scale synthesis of 5,6-dibromoindole-3-carbaldehyde (**7**) by the validation of an historic dibromination of an indole-3-carboxylate.[3] This intermediate was subsequently used in the first synthesis and structural validation of the nNOS inhibitor, 5,6-dibromo-2′-demethylaplysinopsin.[3] Prior to our report, aldehyde **7** was only available as a side product (5%) from the bromination of indole-3-carbaldehyde[7] or in seven steps from 6-nitroindoline.[8] Herein we report the further utility of **7**, describing its use in an efficient synthetic route to 5,6-dibromotryptamines that has ultimately led to the synthesis of three natural products (Scheme 2). In a recent noteworthy development, Mollica et al. reported the first asymmetric route to a 5,6-dibromotryptophan derivative that relied on the selective monobromination of 6-bromoisatin followed by reduction to 5,6-dibromoindole,[9] thus providing a valuable addition to current methods available for the synthesis of this heterocyclic moiety.

With multigram quantities of 5,6-dibromoindole-3-carbaldehyde (**7**) readily available,[3] the synthesis of 5,6-dibromotrypta-



1 Alternatamide A. R = Me, $X^1 = X^2 = Br$
2 Alternatamide B. R = H, $X^1 = X^2 = Br$
3 Alternatamide C. R = H, $X^1 = H$, $X^2 = Br$
4 Alternatamide D. R = H, $X^1 = Br$, $X^2 = H$

Figure 1. Alternatamides A–D.

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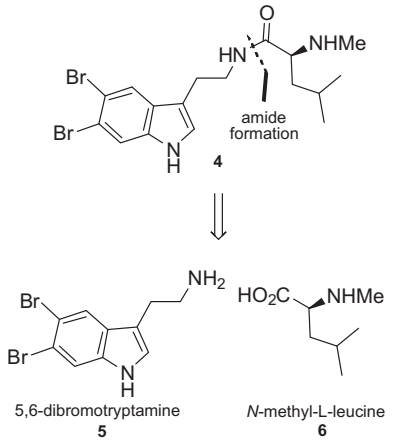
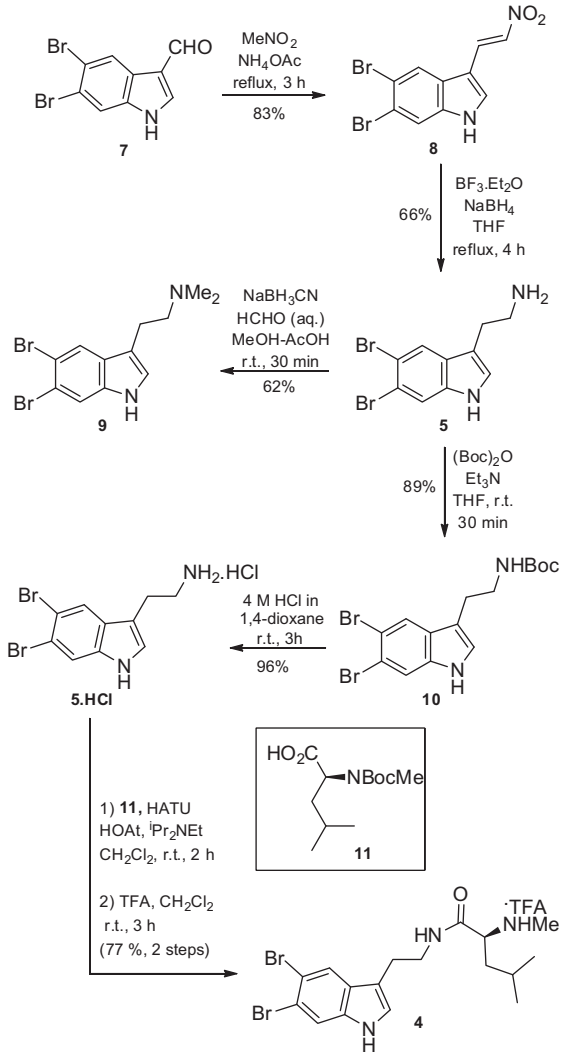


Scheme 1. Retrosynthetic analysis of alternatamide D (**4**).



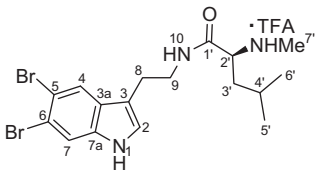
Scheme 2. Synthesis of naturally occurring 5,6-dibromotryptamines.

mine (**5**) was undertaken. The Henry reaction of **7** in nitromethane at reflux in the presence of ammonium acetate proceeded smoothly, furnishing the novel nitroalkene **8**. Initially, the key reduction of **8** to the desired 5,6-dibromotryptamine (**5**) gave disappointing results, with lithium aluminium hydride[10] and various hydrogenation conditions[11] resulting in extensive debromination of the indole ring. However, employing in situ generated BH_3·THF[12] gratifyingly effected nitroalkene reduction with no detriment to the dibrominated indole, affording 5,6-dibromotryptamine (**5**) in good yield. The spectroscopic data of **5** were in good agreement with the literature values.[5a,13] As an aside, 5,6-dibromotryptamine (**5**) was subjected to reductive dialkylation affording 5,6-dibromo-*N*,*N*-dimethyltryptamine (**9**), a natural product with significant antidepressant properties.[14] The spectroscopic data of **9** matched those of the natural product.[13,14a]

Due to the small amount of impurities present and its tendency to undergo degradation after an extended period, 5,6-dibromotryptamine (**5**) was converted into its *tert*-butyloxycarbonyl (Boc) derivative **10** and subjected to purification by flash chromatography. The Boc group was then removed from **10** with anhydrous HCl in 1,4-dioxane, giving the hydrochloride salt of 5,6-dibromotryptamine (**5**·**HCl**) that is stable for months at room temperature (Scheme 2).

With **5**·**HCl** in hand, the final steps towards the synthesis of alternatamide D (**4**) could now be completed. Unfortunately, **5**·**HCl** failed to undergo amide coupling with *N*-methyl-L-leucine (**6**) despite attempting a plethora of peptide coupling agents. This result was not surprising as there is a dearth of examples reporting *N*-methylleucine as a willing participant in amide couplings,[15,16] presumably due to the unprotected secondary amine present in **6**. This problem was solved by subjecting **5**·**HCl** and Boc-*N*-

Table 1
NMR data of synthetic and natural alternatamide D (**4**)



Atom no.	Natural alternatamide D[1]		Synthetic alternatamide D[13]	
	^{1}H (δ) (300 MHz, $CDCl_3$)	^{13}C (δ) (50 MHz, $CDCl_3$)	^{1}H (δ) (400 MHz, $CDCl_3$)	^{13}C (δ) (100 MHz, $CDCl_3$)
N1	8.53 (1H, s)		8.27 (1H, br s)	
C2	7.08 (1H, s)	124.2	7.05 (1H, d, *J* 2.2 Hz)	124.0
C3		112.6		113.2
C3a		128.4		128.7
C4	7.85 (1H, s)	123.0	7.87 (1H, s)	123.3
C5		117.0		117.4
C6		114.5		114.9
C7	7.66 (1H, s)	115.9	7.67 (1H, s)	116.0
C7a		135.9		136.1
C8	2.92 (2H, dd, *J* 6.4 and 6.8 Hz)	25.0	2.93 (2H, m)	25.3
C9	3.58 (2H, m)	39.3	3.60 (2H, m)	39.3
N10	7.58 (1H, s)		7.32 (1H, br s)	
C1′		171.4		171.4
C2′	3.63 (1H, m)[a]	62.5	2.93 (1H, m)	63.6
C3′	1.25 (1H, m) 1.56 (1H, m)	41.4	1.27 (1H, m) 1.57 (1H, m)	42.7
C4′	1.56 (1H, m)	25.0	1.57 (1H, m)	25.4
C5′	0.84 (3H, d, *J* 6.4 Hz)	22.3	0.87 (3H, d, *J* 6.3 Hz)	22.0
C6′	0.92 (3H, d, *J* 6.4 Hz)	22.7	0.94 (3H, d, *J* 6.3 Hz)	23.3
C7′	2.31 (3H, s)	33.9	2.29 (3H, s)	35.4

[a] The chemical shift of the proton at C2′ was incorrectly reported in the original isolation paper and should read ~2.91 ppm.

methyl-L-leucine (**11**) to HATU and HOAt in the presence of Hünig's base,[17] giving Boc-alternatamide D[13] that was immediately deprotected with trifluoroacetic acid (TFA) in dichloromethane, gratifyingly affording alternatamide D (**4**)[13] (Scheme 2). The NMR data of natural and synthetic **4** is shown in Table 1. The amide coupling was presumed to proceed without racemisation as a uronium-based coupling agent was employed.[17]

The ^{1}H NMR spectroscopic data of natural and synthetic **4** were in good agreement, apart from the chemical shift of the proton at C2′ (δ 3.63 vs δ 2.93, Table 1). After some initial confusion, communication with the authors of the isolation paper confirmed that the chemical shift of C2′ was incorrectly quoted in the isolation report and should in fact read δ 2.91 and not δ 3.63 as quoted originally.[1] The ^{1}H NMR data of synthetic and natural alternatamide D were now in good agreement. The ^{13}C NMR spectroscopic data were also in good agreement with the literature values (Table 1).[1,13] Sadly, due to the length of time elapsed since its isolation from the natural source, it was not possible to obtain an authentic sample of alternatamide D (**4**) for direct comparison with our synthetic material.

In conclusion, we have disclosed an efficient synthetic route to 5,6-dibromotryptamines which has been subsequently applied to the synthesis of the three natural products alternatamide D (**4**), 5,6-dibromotryptamine (**5**) and 5,6-dibromo-*N*,*N*-dimethyltryptamine (**9**). Further work towards the synthesis of natural products possessing rare halogenation patterns is in progress.

Acknowledgements

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Supplementary data

Supplementary data (full experimental procedures for the preparation of the natural products **4**, **5** and **9**, along with relevant spectra) associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2011.05.126.

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