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Synthesis of marine sponge alkaloid hachijodine B and a comment on the structure of ikimine B and on the absolute configuration of niphatesine D

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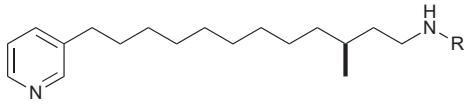
Abstract—The syntheses of the proposed structures of hachijodine B **1**, ikimine B **2** and niphatesine D **3** from *S*-citronellol are described. Our results suggest that the gross structures of hachijodine B and niphatesine D are correct, but that ikimine B was incorrectly assigned. We have also established that the previous absolute stereochemical assignment for niphatesine D is unreliable.

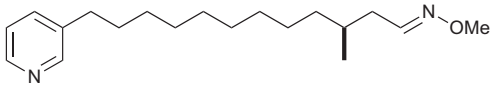
Marine sponges have continued to fascinate chemists due to the rich and diverse natural products they produce.[1] 3-Alkylpyridine alkaloids are a class of natural products that occurs widely in marine sponges.[2] Hachijodine B was recently isolated by Fusetani and co-workers from a marine sponge of the genus *Xestospongia* collected off Hachijo-jima Island in Japan, and found to show cytotoxic activity towards P388 murine leukaemia cells.[3] The structure of hachijodine B was proposed as **1** based on a combination of NMR spectroscopy and mass spectrometry. The presence of an α-amino terminus with γ-methyl substitution distinguishes hachijodine B from the majority of the monomeric 3-alkylpyridine alkaloids. Interestingly this structural motif is also shared by two other marine sponge alkaloids ikimine B and niphatesine D although the oxidation state of the terminal nitrogen function differs in the three alkaloids.

Ikimine B was isolated from an unidentified sponge collected off Ant Atoll, Micronesia by Carroll and Scheuer and showed cytotoxicity against KB cells.[4] They proposed that the structure of ikimine B was **2** based on NMR and electron impact mass spectrometry studies. The natural product was isolated as the *E*-oxime, but the authors observed that it readily isomerised to an *E*/*Z*-mixture in chloroform. The absolute stereochemistry of ikimine B was not determined and its specific rotation was not recorded.[5]

Niphatesine D was isolated by Kobayashi et al. from an Okinawan sponge of the genus *Niphates* and it was shown to be antineoplastic.[6] The gross structure of niphatesine D was established as **3** by NMR and electron impact mass spectrometry, and the specific rotation of niphatesine D was reported to be $[\alpha]_D^{25}$ +4.4 (*c* 0.045, MeOH). Subsequently Rao and Reddy completed the



hachijodine B 1, R = OMe, stereochemistry unknown
niphatesine D 3, R = H, stereochemistry assigned as *S*



ikimine B 2, stereochemistry unknown

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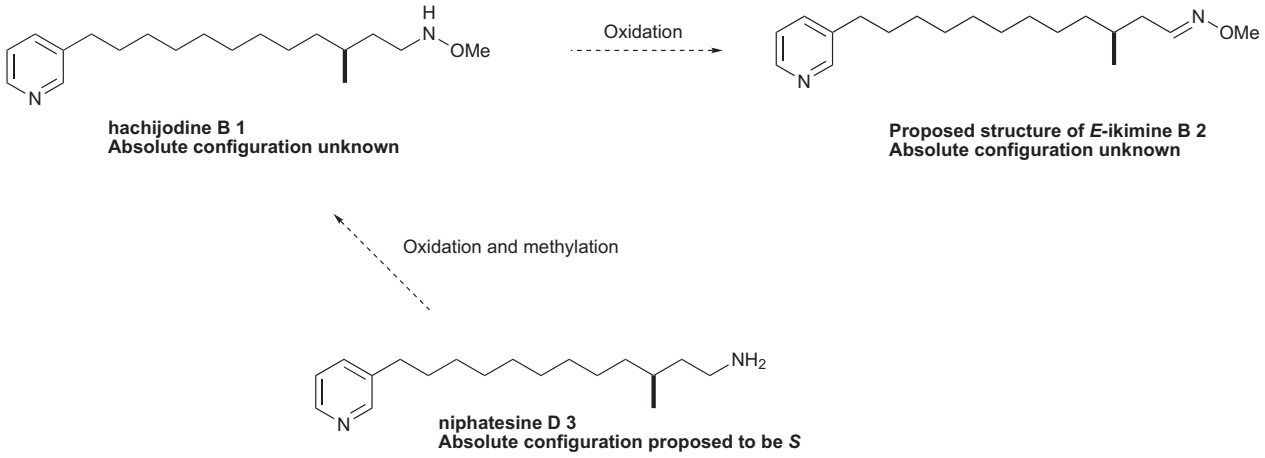
synthesis of niphatesine D and proposed that the absolute configuration of natural product is *S* by comparison of specific rotations.[7]

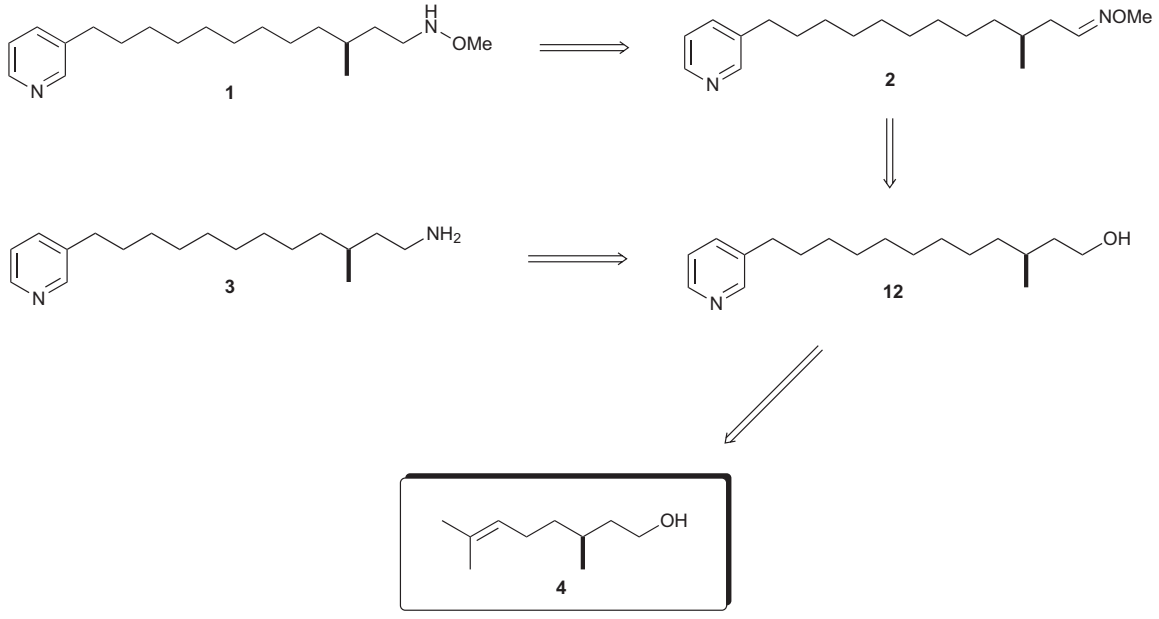
Although the specific rotations of hachijodine B **1** and ikimine B **2** were not determined, it is likely that both compounds are nonracemic. As the three alkaloids were isolated from marine sponges it is possible that they might be biosynthetically related. Thus, **2** could be formed by the oxidation of **1**, which in turn could be produced from **3** by oxidation and methylation (Scheme 1). Hence we speculate that the configurations of the methyl-bearing carbons of **1**, **2** and **3** are identical. No syntheses of **1** and **2** have been reported, and our continued interest in 3-alkylpyridine alkaloids[8,9] prompted us to develop an efficient and flexible synthetic route that would provide access to all three alkaloids.

Retrosynthetically **1**, **2** and **3** could be derived from **12**, which in turn was prepared from *S*-citronellol **4** (Scheme 2).

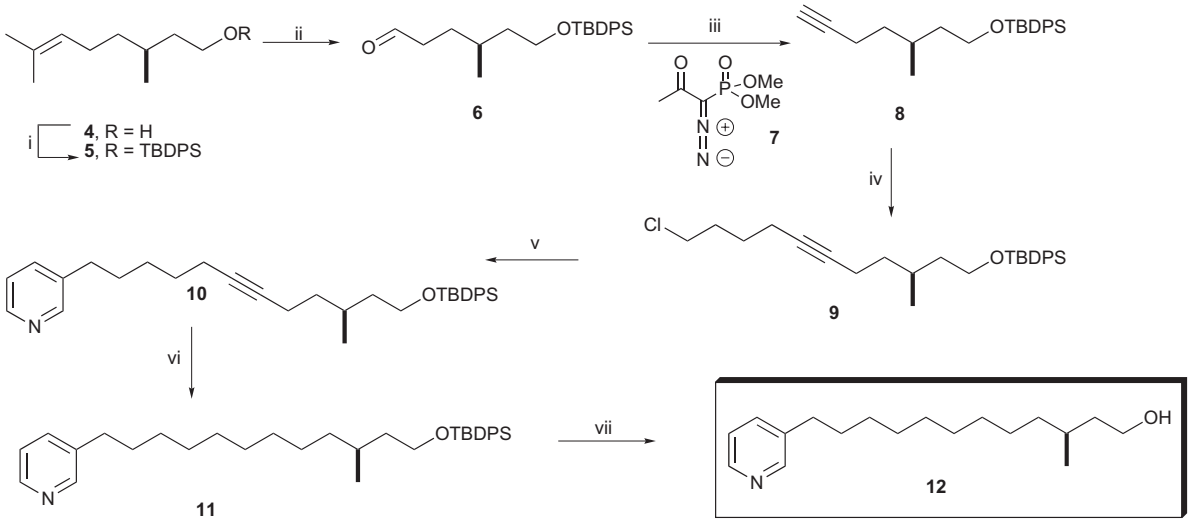
S-Citronellol **4** was converted into its *tert*-butyldiphenylsilyl ether **5** in 93% yield using TBDPSCl and imidazole in THF.[10] Silyl ether **5** was subjected to ozonolysis followed by treatment with triphenylphosphine to give aldehyde **6** in 91% yield,[11] which was subsequently converted into alkyne **8** in 96% yield using dimethyl (1-diazo-2-oxopropyl)phosphonate **7** and potassium carbonate in methanol.[12] Alkyne **8** was deprotonated by *n*-butyllithium followed by addition of 1-iodo-4-chlorobutane in the presence of DMPU to deliver **9** in 86% yield (based on recovered starting material).[13] The primary chloride of **9** was displaced with lithiated 3-picoline in a mixture of DMPU and THF to deliver **10** in



Scheme 1. Possible biogenetic relationship between **1**, **2** and **3**.



Scheme 2.



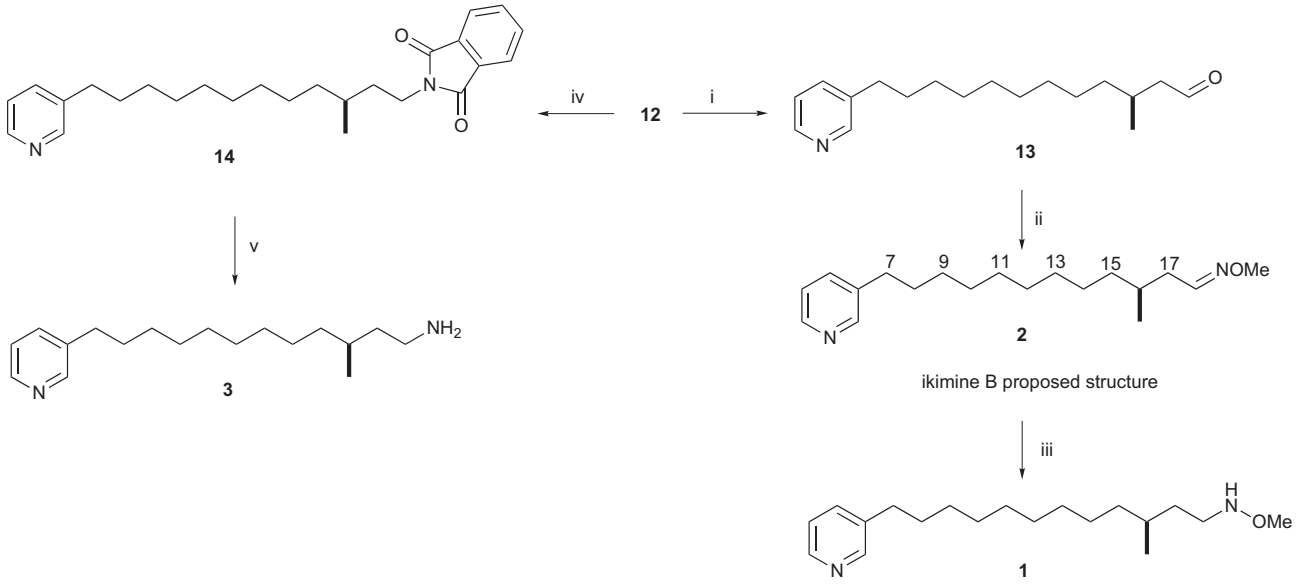
Scheme 3. Reagents and conditions: (i) TBDPSCl, imidazole, THF, 3 h, 93%; (ii) O_3, CH_2Cl_2, −78 °C, 30 min, then PPh_3, 91%; (iii) **7**, K_2CO_3, MeOH, 5 h, 96%; (iv) ^{n}BuLi, DMPU, $Cl(CH_2)_4I$, −78 °C to rt, 6 h, 86%; (v) 3-picoline, LDA, DMPU, THF, −78 °C to rt, 22 h, 85%; (vi) $Pd(OH)_2$, H_2, MeOH, 24 h, 95%; (vii) NH_4F, MeOH, 70 °C, 10 h, 98%.

85% yield.[14] Saturation of the triple bond in **10** by hydrogenation with Pearlman's catalyst in methanol[15] gave **11** in 95% yield, which was deprotected with ammonium fluoride in methanol to afford the key alcohol **12** in 98% yield[16] (Scheme 3).

o-Iodoxybenzoic acid (IBX) oxidation[17] of **12** afforded aldehyde **13** in 83% yield and condensation with methoxylamine hydrochloride in the presence of sodium acetate in methanol gave the putative structure of ikimine B *S*-**2** in 78% yield as a mixture of *E*/*Z* isomers.[18] Reduction of **2** with sodium cyanoborohydride at pH 3 in methanol gave *S*-hachijodine B *S*–**1** in 92% yield.[19] A Mitsunobu reaction of **12** with phthalimide delivered **14** in 99% yield, which was deprotected using hydrazine hydrate in ethanol to afford *S*-niphatesine D *S*-**3** in 83% yield[20] (Scheme 4).

The ^{1}H NMR spectroscopic data of **1** (in $CDCl_3$ with 4 equiv of trifluoroacetic acid added) was in good agreement with the spectra of natural hachijodine B hence the gross structure of hachijodine B is confirmed.

The spectra of synthetic **2** showed some discrepancies with the published data for ikimine B. In the ^{13}C NMR spectrum of natural ikimine B, Carroll and Scheuer assigned the signals between 26 and 33 ppm as the resonances of C-7 to C-17. They also specifically indicated



Scheme 4. Reagents and conditions: (i) IBX, THF, DMSO, 6 h, 83%; (ii) $MeONH_2$·HCl, NaOAc, MeOH, 4 h, 78%; (iii) $NaCNBH_3$, MeOH, pH 3, 0 °C, 4 h, 92%; (iv) phthalimide, PPh_3, DIAD, THF, 18 h, 99%; (v) N_2H_4·H_2O, MeOH, 60 °C, 2 h, 83%.

Table 1. ^{13}C Data of *E*-ikimine B and *S*-**2** in $CDCl_3$

E-ikimine B[4] 75 MHz	*S*-**2** (*E*/*Z* mixture) 125.8 MHz
155.31	150.9
149.41	150.1
146.85	149.8
138.31	147.0
136.17	137.8
124.73	135.6
61.11	123.1
32.95	61.3
30.75	61.0
29.73	**36.6**[c]
29.48[a]	**36.5**[c]
29.35	**36.3**[c]
29.10	32.9
29.02	32.5
26.89[b]	31.3
19.55	31.0
	30.8
	29.6
	29.5
	29.4
	29.3
	29.2
	29.0
	26.8
	19.7
	19.4

[a] Reported as overlapping signals of four carbons.
[b] Assigned as C-17.
[c] Assigned as C-15 of *E*/*Z*-oximes and C-17 of *E*-oxime.

C-17 resonated at 26.89 ppm. In contrast, the ^{13}C NMR spectrum of synthetic **2** (as a mixture of *E*/*Z* isomers) showed three peaks at ca. 36 ppm (two of these are assigned as C-15 of the *E* and *Z* oximes, and the other as C-17 of the *E*-oxime based on COSY and HMQC analysis), which are absent from the tabulated data of *E*-ikimine B[21] (Table 1). Close examination of the ^1H NMR spectrum of synthetic *S*-**2** revealed that one of the diastereomeric pair of protons at H-15 resonates outside the methylene envelope at 1.11–1.20 ppm as a distinct peak, which is absent from the tabulated ^1H NMR data for ikimine B. Based on these differences, we conclude that the structure proposed by Carroll and Scheuer is incorrect.[22]

The ^1H NMR spectrum of **3** under acidic conditions (4 equiv of TFA were added to the NMR sample) matched the literature values for niphatesine D, suggesting that the alkaloid had been isolated as its bis-trifluoroacetate salt rather than as the free base. This observation was not explicitly indicated in either of the previous syntheses of niphatesine D.[7,23]

Our specific rotation measurements of *S*-**3** {$[\alpha]_D^{25}$ −1.3 (*c* 1.0, MeOH) of *S*-**3** as free base and $[\alpha]_D^{25}$ −1.0 (*c* 1.0, MeOH) of *S*-**3** as its bis-trifluoroacetate salt} were different from the previously reported values. Rao and Reddy published the first synthesis of *S*-niphatesine D and reported the specific rotation of their synthetic sample as $[\alpha]_D$ +4.4 (*c* 0.5, MeOH), hence they concluded that the absolute configuration of the natural product was *S*.[7] Bracher and Papke prepared both enantiomers of the alkaloid and noted that their specific rotations were $[\alpha]_D^{20}$ −1.9 (*c* 0.8, MeOH) for *R*-**3** and $[\alpha]_D^{20}$ +1.7 (*c* 0.5, MeOH) for *S*-**3**.[23] Although their specific rotation values differed in magnitude to Kobayashi's, Bracher and Papke did not raise any query about this discrepancy. The three different specific rotations observed by the three groups for synthetic *S*-niphatesine D imply that in this case the sign of specific rotation is not a reliable means to determine the absolute stereochemistry and the original measurement may be incorrect.

It should be noted that the optical rotation of natural niphatesine D was recorded at a very low concentration and its absolute value was small. Assuming the optical rotation measurement of a solution sample is performed at a concentration of 0.045 g/100 mL using a 1 dm cell in a polarimeter with a measurement accuracy of ±0.002° (angular reading),[24] the inherent experimental error in the specific rotation of this sample (assuming there is no error in the sample weight) will be ±4.4, that is, 100% of Kobayashi's observed value. This is further illustrated by our observation that the specific rotation of our synthetic *S*-**3** switched from negative to positive {$[\alpha]_D^{25}$ +1.4 (*c* 0.05, MeOH)} when measured at high dilution. These results are summarised in Table 2.

In conclusion, we have achieved the synthesis of **1**, **2** and **3** using a highly efficient strategy. The synthesis of **2** has cast doubt upon the structure of natural ikimine B. The gross structures of hachijodine B and niphatesine D have been correctly assigned, however we have demonstrated that the assignment of the absolute stereochemistry of niphatesine D based on optical rotation comparison is not reliable, and may be incorrect.

Table 2. Various recorded specific rotations of niphatesine D

Entry	Group	Sample	$[\alpha]_D$	Concentration	Temperature (°C)
1	Kobayashi	**3**	+4.4	0.045	25
2	Rama Rao and Reddy	*S*-**3**	+4.4	0.5	—
3	Bracher and Papke	*S*-**3**	+1.7	0.5	20
4	Bracher and Papke	*R*-**3**	−1.9	0.8	20
5	This work	*S*-**3**	−1.3	1	25
6	This work	*S*-**3**	+1.4	0.05	25
7	This work	*S*-**3** + TFA	−1.0	1	25

Acknowledgements

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