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Synthesis of (−)-(3*S*)-1-(3-aminopropyl)-3-methylazacyclodecane, the structure proposed for the marine alkaloid haliclorensin

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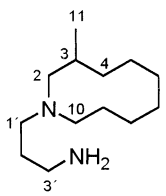
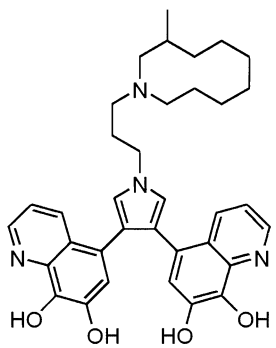
Abstract—The total synthesis of both enantiomers of the title compound has been achieved in seven steps with 19% overall yield. The synthetic diamine differs in its NMR data and optical rotation from haliclorensin, a marine alkaloid for which the same structure had been proposed. © 2001 Published by Elsevier Science Ltd.

Haliclorensin (**1**), a diamino alkaloid with an azacyclodecane ring, was isolated from the South African marine sponge *Haliclona tulearensis* by Kashman et al.[1] in 1998. The structure of the alkaloid was determined from its spectroscopic data and the synthesis of various model compounds. Haliclorensin forms part of the structure of halitulin (**2**), a more complex bisquinolylpyrrole alkaloid from the same organism that exhibits strong cytotoxic activity against mouse leukemia cells.[2]



1



2

In order to apply our biomimetic strategy[3] for the synthesis of 3,4-diarylpyrrole alkaloids to halitulin (**2**) we have prepared both enantiomers of haliclorensin (**1**) and determined the stereochemistry of the (−)-form as 3*S*.

The synthetic steps leading to **1** are depicted in Scheme 1. Condensation of 4-pentenylamine (**3**)[4] with *o*-nitrobenzenesulfonyl chloride furnished sulfonamide **4**,[5,6] which was converted to the protected secondary amine **6** by reaction with the optically pure alcohol **5** under Mitsunobu conditions.[7] (2*S*)-2-Methyl-5-hexen-1-ol (**5**) was obtained in optically pure form in five steps from commercially available methyl (2*R*)-3-hydroxy-2-methylpropanoate with 73% overall yield.[8]

The ring-closing metathesis of diene **6** to the azacycloalkene **7**[9] was carried out under standard conditions using the Grubbs catalyst in dry dichloromethane.[10] We observed that the formation of dimers and oligomers is the predominant reaction, which can, however, be minimized by using concentrations lower than 0.5 mmol/L. The removal of the protecting group from **7** with PhSH and K_2CO_3 according to Fukuyama[6] furnished the free amine **8** that was converted to the β-aminonitrile **9**[11] by treatment with acrylonitrile. Hydrogenation of **9** over Raney-Ni in MeOH saturated with NH_3 yielded the primary amine, and catalytic hydrogenation over Pd/C in dry MeOH removed the double bond and yielded (−)-(3*S*)-1-(3-aminopropyl)-3-methylazacyclodecane (**1**).[12] (−)-**1** was obtained from the known compounds **3** and **5** in seven steps with 19% overall yield. In the same manner (+)-**1**, was prepared from (2*R*)-2-methyl-5-hexen-1-ol (**5**). Compound **1** was completely characterized by its spectroscopic data and the structure was confirmed by NMR experiments (Table 1).

Unfortunately, the ^{13}C NMR shifts of the synthetic compound (Table 1) differ considerably from the values given for haliclorensin[1] which makes the proof of identity ambiguous.[13] Furthermore, the optical rotation

Keywords: haliclorensin; alkaloids; marine metabolites; sponges; synthesis; metathesis.

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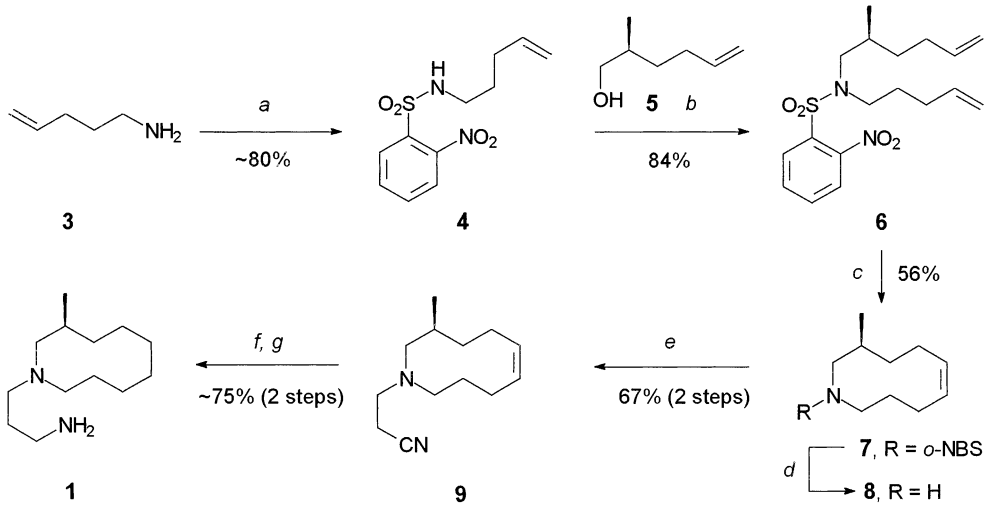

Scheme 1. *Reagents and conditions*: (a) *o*-nitrobenzenesulfonyl chloride (1 equiv.), K_2CO_3 (1 equiv.), CH_2Cl_2, rt, 2.5 h. (b) (2*S*)-2-Methyl-5-hexen-1-ol (1.2 equiv.), PPh_3 (1 equiv.), DEAD (1 equiv.), dry THF, rt, 24 h. (c) Grubbs catalyst (0.1 equiv.), CH_2Cl_2, reflux, 18 h. (d) PhSH (1.2 equiv.), K_2CO_3 (3 equiv.), dry DMF, rt, 1.5 h. (e) Acrylonitrile (1.1 equiv.), dry MeOH, 0°C→rt, 12 h. (f) Raney-Ni, 20 bar (290 psi) H_2, NH_3 satd MeOH, rt, 5 h. (g) Pd/C (10% Pd), 10 bar (145 psi) H_2, dry MeOH, rt, 12 h.

Table 1. ^{13}C and ^{1}H NMR data of synthetic **1** (600 MHz, DMSO-d_6)

C	δ_c	H	δ_H (mult, *J* in Hz)	COSY	HMBC (H→C)
2	60.5	2a	2.31 (dd, *J*=12.5, 12.1)	2b, 3	3, 4, 10, 11, 1′
		2b	2.06 (m)	2a, 3	3, 4, 10, 11, 1′
3	29.6	3	1.87 (m)	2a, 2b, 4a, 11	2, 4, 5, 11
4	31.8	4a	1.53 (m)	3, 4b, 5b	2, 3, 5, 6, 11
		4b	1.30 (m)	4a	5, 6
5	21.9	5a	1.81 (m)		
		5b	1.35 (m)		
6	26.3	6	1.36 (m)		
7	24.4	7a	1.74 (m)		
		7b	1.36 (m)		
8	24.1	8a	1.53 (m)		
		8b	1.44 (m)		6
9	25.6	9a	1.63 (m)	9b, 10a, 10b	7
		9b	1.35 (m)	9a, 10a, 10b	
10	53.0	10a	2.68 (ddd, *J*=13.2, 10.6, 4.0)	9a, 9b, 10b	2, 8, 9, 1′
		10b	2.15 (ddd, *J*=13.2, 4.7, 4.4)	9a, 9b, 10a	2, 8, 9, 1′
11	19.5	11	0.77 (d, *J*=6.8)	3	2, 3, 4
1′	52.6	1′a	2.50 (m)	1′b, 2′	2, 10, 2′, 3′
		1′b	2.07 (m)	1′a, 2′	2, 10, 2′, 3′
2′	31.0	2′	1.50 (quin, *J*=7.2)	1′a, 1′b, 3′	1′, 3′
3′	40.5	3′	2.54 (m)	2′	1′, 2′

given for the natural product $\{[\alpha]_D^{20}$ −2.2 (*c* 1.3, MeOH)} is much lower than that of synthetic (−)-**1** $\{[\alpha]_D$ −70 (*c* 0.9, MeOH)}.

Acknowledgements

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9. Compound **7**: pale yellow solid, mp 101–103°C. ^{1}H NMR (600 MHz, $CDCl_3$): δ 0.82 (d, 3H, $J=6.7$ Hz), 1.43–1.49 (m, 1H), 1.54–1.58 (m, 2H), 1.88–1.95 (m, 2H), 1.97–2.03 (m, 1H), 2.14–2.20 (m, 1H), 2.53 (dd, 1H, $J=3.6$ and 13.0 Hz), 2.73–2.80 (m, 1H), 2.95–2.99 (m, 2H), 3.02 (dd, 1H, $J=4.7$ and 13.0 Hz), 3.11 (ddd, 1H, $J=1.7$, 5.0 and 14.4 Hz), 3.42 (dd, 1H, $J=9.7$ and 13.1 Hz), 5.44–5.46 (m, 2H), 7.54 (dd, 1H, $J=1.9$ and 7.2 Hz), 7.67–7.72 (m, 2H), 7.89 (dd, 1H, $J=1.9$ and 7.2 Hz). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 20.7, 23.2, 24.7, 26.7, 27.2, 35.0, 45.5, 57.9, 123.8, 128.5, 129.9, 131.0, 131.1, 131.9, 133.5, 149.0. HRMS calcd for $C_{16}H_{22}N_2O_4S$ (M^+) 338.1300. Found 338.1300. Anal. calcd C, 56.78; H, 6.55; N, 8.28; S, 9.48. Found C, 56.73; H, 6.51; N, 8.01; S, 9.02. $[\alpha]_D$ −88 (*c* 0.9, MeOH).
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12. Compound **1**: colorless oil. (−)-**1**, $[\alpha]_D$ −70 (*c* 0.9, MeOH); (+)-**1**, $[\alpha]_D^{20}$ +71 (*c* 0.6, MeOH). NMR data (see Table 1). HRMS calcd for $C_{13}H_{28}N_2$ (M^+) 212.2253. Found 212.2247. GC–MS *m*/*z* (rel. int.): 212 (7, M^+), 182 (6, $M^+-CH_2NH_2$), 168 (100, $M^+-C_2H_4NH_2$), 154 (28), 140 (8), 126 (38).
13. Professor Yoel Kashman, Tel Aviv, kindly informed us about a current re-isolation of haliclorensin which will allow a direct comparison.