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Absolute configuration of marine diterpenoid kalihinol A

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Abstract

The absolute configuration of marine diterpenoid kalihinol A (**1**) was determined by applying the CD exciton chirality method to bis-*p*-bromobenzamide **5**, which was converted from kalihinol A (**1**). This is the first determination of the absolute configuration of a kalihinane-type diterpenoid.

Keywords: marine metabolites; natural products; terpenes; terpenoids; antimalarial compounds.

Kalihinol A (**1**), isolated from the Guamanian marine sponge, *Acanthella* sp., by Scheuer and coworkers in 1984, is a richly functionalized tricyclic diterpenoid having isocyano, hydroxyl, tetrahydropyranyl and chlorine functions.[1] Succeeding to the isolation of kalihinol A (**1**), more than forty kalihinane-type diterpenoids, each with isocyano, isothiocyanato and/or formamido functionalities, have been obtained from marine sponges.[2–14] The relative stereochemistry of these diterpenoids has been determined by X-ray and/or spectroscopic analysis, but to date, there has been no determination of the absolute configuration of any of these compounds. Biological activity, including antimicrobial,[1–3] antifungal,[1–3,5,7] cytotoxic,[5] anthelmintic[4–6] and antifouling,[10–13] have been reported. The authors recently isolated new kalihinane-type diterpenoids along with previously obtained kalihinane-type diterpenoids, such as kalihinol A (**1**) from the Okinawan sponge, *Acanthella* sp. and the compounds were found to express antimalarial activity (Fig. 1).[15] Kalihinol A (**1**) was noted to strongly inhibit proliferation of the malaria parasite, *Plasmodium falciparum* (EC_{50} 1.2×10^{-9} M) and express a remarkable selective index (SI 317), defined as the ratio of FM3A cell cytotoxity to *P. falciparum*. This paper describes the determination of the absolute configuration of kalihinol A (**1**) by applying the CD exciton chirality method to bis-*p*-bromobenzamide **5** converted from kalihinol A (**1**).

Kalihinol A (**1**) has two isocyano groups. If these groups are converted to benzamido groups via amino groups, the absolute configuration of kalihinol A (**1**) may be determined by application of the CD exciton chirality method to this derivative.[16,17]

The two isocyano groups of kalihinol A (**1**)[1,15] were hydrolyzed with acetic acid to give 5,10-bisformamidokalihinol A (**2**) in 99% yield (Scheme 1). Bisformamide **2** was converted to diamine dihydrochloride **3** by hydrolysis of two formamido groups with 10% HCl in 48% yield. Diamine dihydrochloride **3** was converted to diamine **4**[18] by treatment with NaOH for chemical characterization

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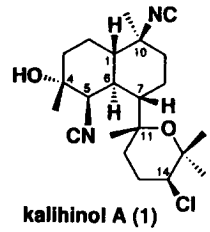
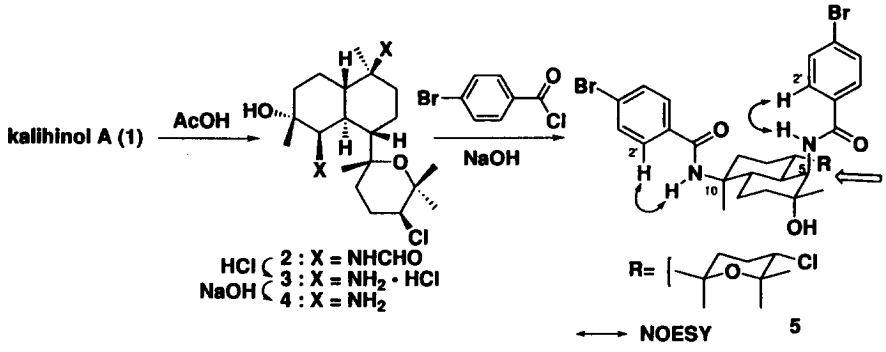


Figure 1.

of **3**. Diamine dihydrochloride **3** was treated with *p*-bromobenzoyl chloride in the presence of NaOH aqueous solution to afford bis-*p*-bromobenzamide **5**[19] as the sole product in 67% yield. The conformation of each of the two *p*-bromobenzamido groups in **5** was confirmed to be *s-trans* based on a NOESY correlation between the amide proton and H-2′ proton. The *s-cis* conformation of **5** could not be detected at all by ^{1}H NMR spectroscopy. The CD exciton chirality method was thus applicable to bis-*p*-bromobenzamide **5**.[16a]



Scheme 1.

The CD spectrum of **5** showed a negative Cotton effect at 252 nm ($\Delta\varepsilon$ −27.6) and positive Cotton effect at 229 nm ($\Delta\varepsilon$ +9.36), indicating negative chirality between the two chromophores (two *p*-bromobenzamide groups) of **5** (Fig. 2). The CD data indicated 5*R* and 10*S* configuration in **5** and the

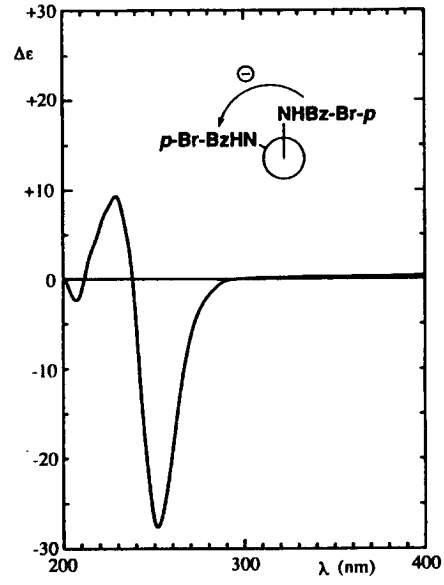


Figure 2. CD spectrum of bis-*p*-bromobenzamide **5**

absolute configuration of eight chiral centers in kalihinol A (**1**) is concluded to be 1*S*, 4*R*, 5*R*, 6*S*, 7*S*, 10*S*, 11*R*, and 14*S*. This is the first determination of the absolute configuration of a kalihinane-type diterpenoid.

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18. Compound **4**: colorless oil: $[\alpha]_D^{27}$ −2.6 (*c* 0.31, $CHCl_3$); FABMS *m/z*: 373 (M^++H); HRFABMS calcd for $C_{20}H_{38}{}^{35}ClN_2O_2$ (M^++H) 373.2622: found 373.2628; IR (neat) ν_{max} 3358, 3281 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.98 (3H, s), 1.19 (1H, m), 1.2–1.7 (10H, m), 1.24 (3H, s), 1.29 (3H, s), 1.29 (3H, s), 1.36 (3H, s), 1.90 (1H, dt, *J*=3.0, 11.3 Hz), 1.95–2.15 (3H, m), 3.22 (1H, d, *J*=1.5 Hz), 3.72 (1H, dd, *J*=12.3, 4.4 Hz).
19. Compound **5**: colorless powder: mp 121–122°C; $[\alpha]_D^{27}$ −73.6 (*c* 0.26, EtOH); FABMS *m/z*: 737 (M^++H); HRFABMS calcd for $C_{34}H_{44}{}^{79}Br_2{}^{35}ClN_2O_4$ (M^++H) 737.1356: found 737.1342; IR (KBr) ν_{max} 3438, 1658 cm^{-1}; CD (EtOH) λ_{ext} (Δε) 252 nm (−27.6), 238 (0), 229 (+9.36); UV (EtOH) λ_{max} 239 nm (ε 35310); ^1H NMR (400 MHz, $CDCl_3$) δ 1.20 (1H, m), 1.24 (3H, s), 1.28 (3H, s), 1.30 (3H, s), 1.31 (3H, s), 1.37 (3H, s), 1.5–1.7 (7H, m), 1.78 (2H, m), 1.98 (1H, m), 2.09 (1H, m), 2.47 (2H, t, *J*=11.7 Hz), 2.57 (1H, m), 3.64 (1H, dd, *J*=12.4, 4.4 Hz), 4.65 (1H, br d, *J*=8.0 Hz), 5.77 (1H, s), 6.28 (1H, br d, *J*=8.4 Hz), 7.57 (4H, s), 7.61 (2H, d, *J*=8.5 Hz), 7.70 (2H, d, *J*=8.5 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 20.7 (CH_3), 21.1 (CH_3), 22.4 (CH_2), 23.0 (CH_3), 23.1 (CH_2), 27.7 (CH_2), 29.9 (CH_3), 30.7 (CH_3), 34.1 (CH_2), 35.4 (CH_2), 36.7 (CH), 37.6 (CH), 37.7 (CH_2), 47.0 (CH), 57.4 (C), 57.5 (CH), 65.4 (CH), 73.5 (C), 76.2 (C), 77.0 (C), 125.9 (C), 126.0 (C), 128.3 (CH), 128.6 (CH), 131.9 (CH), 131.9 (CH), 134.4 (C), 134.8 (C), 165.7 (C), 166.1 (C).