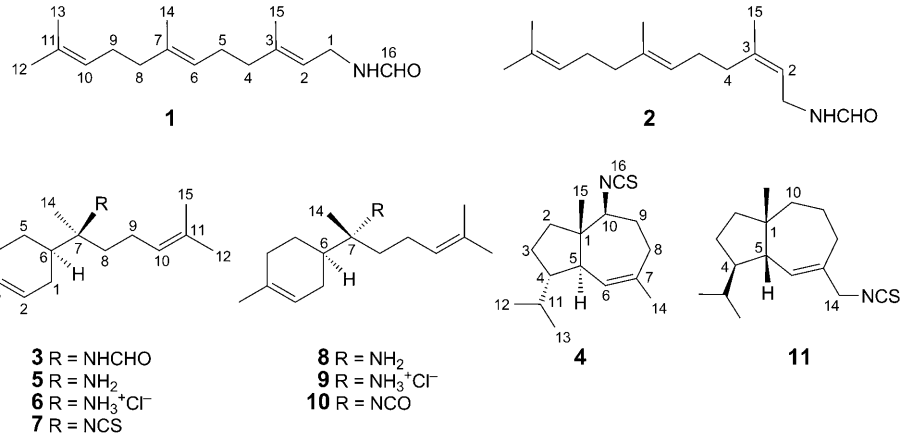
New N-Containing Sesquiterpenes from Hainan Marine Sponge *Axinyssa* sp.

by **Zhen-Yu Li**, **Zhi-Guo Yu**, and **Yue-Wei Guo***

State Key Laboratory of Drug Research, Shanghai Institute of Materia Medica, Chinese Academy of Science, Zu Chong Zhi Rd. 555, Shanghai 201203, P. R. China (phone: 86-21-50805813; e-mail: ywguo@mail.shcnc.ac.cn)

Three new N-containing sesquiterpenes, isofarnesyl formamide (**2**), 7-formamido-7,8-dihydro-α-bisabolane (**3**), 4,5-epi-10-isothiocyanatoisodauc-6-ene (**4**), and a known sesquiterpene, farnesyl formamide (**1**), were isolated from the Hainan marine sponge *Axinyssa* sp. The structures of the new compounds were elucidated by detailed analyses of their spectroscopic data and by comparison of their NMR data with those of structurally related compounds.

Introduction. – Marine sponges of the genus *Axinyssa* (order Halichondrida, family Halichodriidae) have attracted considerable research interest due to the presence of sesquiterpenes containing unusual N-containing functional groups, such as isothiocyanate, formamide, isonitrile, and thiocyanate [1–7]. Interestingly, most of these N-containing compounds have exhibited various biological activities such as antithelmintic [2], antimicrobial [4], antimalarial [6] activity, and lethality for brine shrimp [7]. As part of our ongoing research on the discovery of biologically active substances from Chinese marine invertebrates [8–11], we made a collection of the sponge *Axinyssa* sp. off Sanya, Hainan Province, P. R. China. Chemical investigation of the Et_2O-soluble fraction of an acetone extract of this sponge led to the isolation of three new N-containing sesquiterpenes, isofarnesyl formamide (**2**), 7-formamido-7,8-dihydro-α-bisabolane (**3**), 4,5-epi-10-isothiocyanatoisodauc-6-ene (**4**), and a known related



sesquiterpene, farnesyl formamide (**1**) [12]. This report deals with the isolation and structure elucidation of the new compounds.

Results and Discussion. – Freshly collected animals were immediately put at $-20°$ and kept frozen prior to extraction. Frozen material was extracted exhaustively with acetone. The acetone extract was then partitioned between Et_2O and H_2O. The Et_2O-soluble extract was subjected to repeated silica gel and *Sephadex LH-20* column chromatography to afford the pure compounds **1**–**4**.

Compounds **1**–**3** showed IR absorptions indicative of the amide group (3280 and 1685 cm^{-1}). The typical ^{1}H-NMR signals at δ(H) 8.10–8.20 implied the presence of a –NHCHO group, in agreement with the doubling of most of the ^{13}C-NMR signals, due to the existence of two rotational isomers of the formamide group.

Compound **1** was readily determined as farnesyl formamide by careful analysis of its the ^{1}H- and ^{13}C-NMR data, and by comparison with those of the [^{14}C] labeled farnesyl formamide, which was synthesized in a biosynthesis study of dichloroimines [12]. However, this is the first time that **1** was isolated from a natural source.

Compound **2**, isofarnesyl formamide, was isolated as a colorless oil. Its molecular formula was determined as $C_{16}H_{27}NO$ on the basis of HR-EI-MS (*m*/*z* 249.2097, $C_{16}H_{27}NO^+$), identical with that of compound **1**. The ^{1}H- and ^{13}C-NMR data of **2** showed great similarities to those of **1**. In fact, the ^{13}C-NMR data of **2** and **1** (*Table*) were almost identical except for those of C(4) and C(15). These differences could be easily explained by the different geometry of the C=C bond at $\Delta^{2(3)}$ ((*Z*) for **2** and (*E*) for **1**). The $\Delta^{2(3)}$ (*Z*) configuration in **2** was confirmed by the strong NOE correlations of H–C(2)/Me(15) and CH_2(1)/CH_2(4), and further supported by the upfield shifted ^{13}C-NMR resonances of C(4) (δ(C) 39.4 in **1** and 31.9 in **2**), and by the downfield

Table. *^{13}C-NMR Data*[a]) *of Compounds* **1**–**5**. Measured at 100 MHz; δ are given in ppm.

Position	**1**	**2**	**3**	**4**	**5** [13]
1	36.0, 39.4 (*t*)	35.8, 39.3 (*t*)	26.3, 26.4 (*t*)	48.0 (*s*)	25.8 (*t*)
2	119.2, 120.0 (*d*)	120.1, 120.9 (*d*)	119.9, 120.4 (*d*)	41.4 (*t*)	120.1 (*d*)
3	140.6, 140.3 (*s*)	140.8, 140.4 (*s*)	134.0, 134.2 (*s*)	24.0 (*t*)	133.4 (*s*)
4	39.4 (*t*)	31.9, 32.2 (*t*)	30.9, 31.1 (*t*)	50.9 (*d*)	30.8 (*t*)
5	26.2 (*t*)	26.2 (*t*)	21.9, 22.3 (*t*)	51.5 (*d*)	23.5 (*t*)
6	123.6, 123.4 (*d*)	123.5, 123.2 (*d*)	40.7, 43.5 (*d*)	128.5 (*d*)	41.6 (*d*)
7	135.4, 135.6 (*s*)	135.9, 136.1 (*s*)	57.6, 59.3 (*s*)	138.0 (*s*)	55.6 (*s*)
8	39.6 (*t*)	39.7 (*t*)	36.2, 39.9 (*t*)	32.9 (*t*)	38.4 (*t*)
9	26.7 (*t*)	26.7 (*t*)	23.3, 23.9 (*t*)	29.3 (*t*)	23.3 (*t*)
10	124.2 (*d*)	124.2 (*d*)	123.3, 124.1 (*d*)	66.3 (*d*)	123.8 (*d*)
11	131.4 (*s*)	131.5 (*s*)	131.7, 132.5 (*s*)	31.3 (*d*)	131.3 (*s*)
12	25.7 (*q*)	25.7 (*q*)	25.7 (*q*)	21.7 (*q*)	25.3 (*q*)
13	17.7 (*q*)	17.7 (*q*)	23.2, 23.3 (*q*)	18.6 (*q*)	22.9 (*q*)
14	16.0 (*q*)	16.0 (*q*)	20.7, 21.1 (*q*)	25.1 (*q*)	21.9 (*q*)
15	16.3 (*q*)	23.3 (*q*)	17.7 (*q*)	14.8 (*q*)	17.3 (*q*)
16	160.9, 164.5 (*d*)	160.8, 164.8 (*q*)	160.3, 163.1 (*d*)	[b])	–

[a]) In $CDCl_3$, referred to the signal of $CDCl_3$ (δ(C) 77.0 ppm). [b]) Not observed.

shifted δ values of C(15) (δ(C) 16.3 in **1** and 23.3 in **2**). All this spectroscopic evidence led to structure proposal **2** for this isolate.

Compound **3** was obtained as a colorless, optically active oil ($[\alpha]_D^{23} = +7$ ($c = 0.2$, $CHCl_3$)). Its molecular formula, $C_{16}H_{27}NO$, was established by a HR-EI-MS molecular ion peak at m/z 249.2086 (M^+), indicating four degrees of unsaturation. The ^{1}H-NMR spectrum of **3** displayed four Me signals at δ(H) 1.24 and 1.28 (2*s*, each 3/2 H, Me(14)), 1.60 (*s*, Me(15)), 1.64 (*s*, Me(13)), and 1.68 (*s*, Me(12)), and two olefinic H-atoms at δ(H) 5.05 (br. *t*, $J = 7.5$, H–C(10)) and 5.35 (br. *s*, H–C(2)). The ^{13}C-NMR and DEPT spectra provided evidence for two trisubstituted C=C bonds, one formamide group, four Me groups, five sp^3-CH_2 groups, one sp^3-CH group, and one heteroatom-bearing quaternary sp^3-C-atom implying, from the required degrees of unsaturation, a monocyclic sesquiterpene with a formamide group. The NMR data of **3** were strongly reminiscent of the structurally related sesquiterpene, (6*R*,7*S*)-7-amino-7,8-dihydro-α-bisabolane (**5**) [13]. A comparison of the overall ^{13}C-NMR data of **3** and **5** (*Table*) revealed that **3** differs from **5** only by the substituent at C(7) (–NHCHO in **3**, $-NH_2$ in **5**). The formamide group at C(7) was confirmed by a strong HMBC correlation between H–C(16) (δ(H) 8.10 (br. *s*)) and C(7) (δ(C) 59.3). This spectroscopic evidence suggested that compound **3** is an α-bisabolene-type sesquiterpene with a formamide moiety at C(7). The relative configuration at C(6) and C(7) was tentatively assigned to be (*R**) and (*S**), respectively, mainly based on biogenetic considerations [13–15]. Thus, the structure of compound **3** was determined as (6*R**,7*S**)-7-formamido-7,8-dihydro-α-bisabolene.

Compound **4** was also obtained as a colorless oil. The EI-MS spectrum displayed a molecular ion peak at m/z 263, along with a diagnostic peak at m/z 205 due to the loss of a –NCS group from the molecular ion. The HR-EI-MS, ^{13}C-NMR and DEPT spectra established the molecular formula as $C_{16}H_{25}NS$, indicating five degrees of unsaturation. The IR absorption at 2130 cm^{-1} indicated the presence of an isothiocyanate group. The ^{1}H-NMR spectrum showed two Me *doublet*s at δ(H) 0.77 and 0.79 (*d*, $J = 7.4$, Me(12), Me(13)), and two Me *singlet*s at δ(H) 0.74 (*s*, Me(15)) and 1.70 (*s*, Me(14)), one CH *double doublet* at δ(H) 3.28 (*dd*, $J = 12.2, 3.5$, H–C(10)), and one broad *singlet* at δ(H) 5.15 (*s*, H–C(6)). The ^{13}C-NMR and DEPT spectra revealed 15 C-atom signals due to one trisubstituted C=C bond, one sp^3 quaternary C-atom, four sp^3 CH groups, four sp^3 CH_2 groups, and four Me groups. Among them, the CH group (δ(H) 3.28; δ(C) 66.3) was ascribed to bear the isothiocyanate group, of which the C-atom signal (C(16)) was not detected in the ^{13}C-NMR spectrum. The –NCS and C=C groups accounted for three degrees of unsaturation; thus, the remaining two degrees of unsaturation were attributed to a bicyclic ring system. A literature survey revealed that the NMR data of **4** was reminiscent of those of 14-isothiocyanatoisodauc-6-ene (**11**) [16]. Comparison of the NMR data of **4** with those of **11** suggested that **4** was also an isothiocyanate-bearing isodaucane-type sesquiterpene. In fact, the only difference between **4** and **11** lies in the position of the isothiocyanate group (in the former at C(10), and in the latter at C(14)). A significant HMBC correlation (*Figure*) between Me(15) (δ(H) 0.74) and C(10) (δ(C) 66.3), and the strong downfield-shift of C(10) (+20.9 ppm) confirmed the location of the –NCS group at C(10). Due to the electron-withdrawing effect of the –NCS group at C(10), C(1) and C(9) were deshielded (+6.0 and +8.4 ppm, respectively), while C(15) (δ(C) 19.1 in **11** and 14.8 in **4**) was shifted upfield due to a γ-

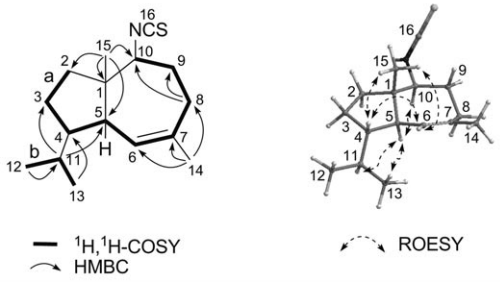


Figure. *Selected two-dimensional NMR correlations for compound* **4**

gauche effect. All these spectroscopic evidence established the constitutional formula of **4**.

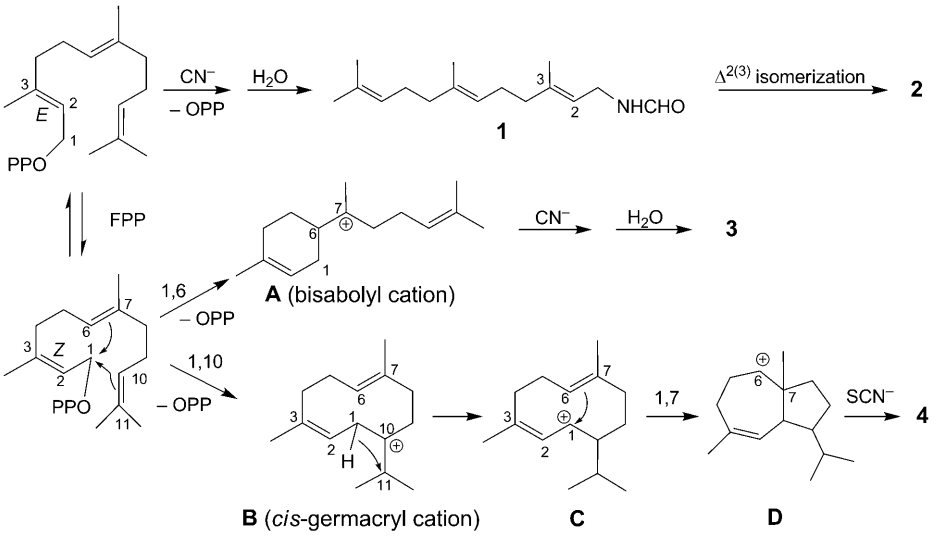
The relative configuration of **4** was established by analysis of the ROESY spectrum (*Figure*). ROESY cross-peaks of Me(15)/H–C(4) and H–C(6), H–C(5)/H–C(10), H–C(11), and Me(12), and no correlation between H–C(5) and Me(15) implied a *trans*-junction for the rings *A*/*B*, α-orientation of the isopropyl group at C(4) and the β-orientation of isothiocyanate group at C(10). Thus, compound **4**, possessing a different configuration at C(4) and C(5) compared to **11**, was elucidated as 4,5-epi-10-isothiocyanatoisodauc-6-ene.

Although sesquiterpenes **1**–**4** are formally quite different, featuring three different carbon skeletons, they are actually closely related to each other from a biogenetic point of view. The proposed biogenetic relationship of compounds **1**–**4** is shown in the *Scheme*. Previous biosynthetic studies have shown that isocyanides, isothiocyanates, and formamide functions of the sponge metabolites are derived from inorganic cyanide or thiocyanate, respectively [17]. Sesquiterpenes **1**–**4** have a common precursor, namely farnesyl pyrophosphate (FPP), which, after nucleophilic attack by inorganic cyanide and hydrolysis yields **1**. Successively, isomerization of the $\Delta^{2(3)}$ olefin of **1** leads to **2**. For compound **3**, formation of a C(1)–C(6) bond within FPP affords an intermediate **A**, and the formamide group is introduced similarly as for **1**. Alternatively, formation of a C(1)–C(10) bond within FPP yields the *cis*-germacryl cation **B**, which, after a series of reactions such as a 1,3-hydrogen shift, cyclization and incorporation of inorganic thiocyanate ion, finally can generate **4**.

Recently, we have isolated a series of N-containing sesquiterpenes, that are structurally related to compounds **1**–**4**, from Hainan nudibranches *Hexabranchus sangueneus* [8] and *Phyllidiella pustulosa* [18], and these compounds were presumed to be sequestered from their dietary sponges serving possibly as defensive substances to protect themselves against predation. The discovery of **1**–**4** from the title sponge strongly suggests the prey and predator relationship between the title sponge and the above mentioned nudibranches, since they were collected from the same environment.

Compounds **1**–**4** have been evaluated for cytotoxity against tumor cell lines A-549, HL-60, and P-388, but they were all inactive at a concentration of 10 μg/ml. Other bioassay studies such as anti-inflammatory and antimicrobial activities are currently underway.

Scheme. *Plausible Biogenetic Relationship of Compounds* **1**–**4**



Experimental Part

General. Column chromatography: commercial silica gel (SiO_2; *Qing Dao Hai Yang Chemical Group Co.*; 200–300 mesh), and *Sephadex LH-20* (*Amersham Biosciences*). TLC: precoated SiO_2 plates (*Yan Tai Zi Fu Chemical Group Co.*; *G60*, *F-254*). Optical rotation: *Perkin-Elmer 341* polarimeter. IR Spectra: *Nicolet Magna FT-IR 750* spectrophotometer; ν_{max} in cm^{-1}. ^1H- and ^{13}C-NMR Spectra: *Varian Mercury 400* spectrometer (400 MHz for ^1H, and 100 MHz for ^{13}C); chemical shifts δ in ppm, with residual $CHCl_3$ (δ(H) 7.26, δ(C) 77.0) as internal standard, coupling constants *J* in Hz. EI-MS and HR-EI-MS: *Finnigan-MAT-95* mass spectrometer; in *m*/*z*.

Biological Material. Specimens of *Axinyssa* sp., identified by Prof. *J.-H. Li* of Institute of Oceanology, CAS, were collected off Sanya, Hainan Province, P. R. China, in 2001, at a depth of −10 m, and were frozen immediately after collection. A voucher specimen (No. 01SS-20) is available for inspection at the Shanghai Institute of Materia Medica, CAS.

Extraction and Isolation. The frozen animals (300 g, dry weight) were cut into small pieces and exhaustively extracted with acetone (3 × 0.5 l) at r.t. The extract was concentrated, and the resulting residue was partitioned between Et_2O and H_2O. The Et_2O-soluble fraction (2.1 g) was fractionated by SiO_2 CC using light petroleum ether (PE) with increasing amounts of Et_2O as eluent to afford nine fractions. *Fr. 1* was further purified over SiO_2 column (PE/Et_2O system) to afford **4** (2.1 mg). *Fr. 3* was further chromatographed on SiO_2 column (PE/AcOEt system) and *Sephadex LH-20* column ($CHCl_3$ as eluent) to afford **1** (3.5 mg), **2** (3.1 mg), and **3** (2.3 mg), respectively.

Farnesyl Formamide (= N-*[(2*E*,6*E*)-3,7,11-Trimethyldodeca-2,6,10-trien-1-yl]formamide*; **1**). Colorless oil. IR (KBr): 3280, 2940, 1685, 870. ^1H-NMR (400 MHz, $CDCl_3$): 1.59 (*s*, Me(13), Me(14)); 1.67 (*s*, Me(12), Me(15)); 1.94–2.12 (*m*, CH_2(4), CH_2(5), CH_2(8), CH_2(9)); 3.89 (*t*, *J* = 6.3, CH_2(1)); 5.04–5.10 (*m*, H–C(6), H–C(10)); 5.20 (*dt*, *J* = 7.0, 1.2, H–C(3)); 5.49 (br. *s*, N*H*CHO); 8.07 (*d*, *J* = 12.0, NHC*H*O); 8.15 (*s*, NHC*H*O). ^{13}C-NMR: see *Table*. EI-MS: 249 (M^+), 204, 136, 93, 69. HR-EI-MS: 249.2098 ($C_{16}H_{27}NO^+$, calc. 249.2093).

Isofarnesyl Formamide (= N-*[(2*Z*,6*E*)-3,7,11-Trimethyldodeca-2,6,10-trien-1-yl]formamide*; **2**): Colorless oil. IR (KBr): 3278, 2942, 1683, 870. ^1H-NMR (400 MHz, $CDCl_3$): 1.60 (*s*, Me(13), Me(14)); 1.67 (*s*, Me(12)); 1.73 (*s*, Me(15)); 1.98–2.10 (*m*, CH_2(4), CH_2(5), CH_2(8), CH_2(9)); 3.87 (*t*, *J* = 6.3, CH_2(1)); 5.06–5.12 (*m*, H–C(6), H–C(10); 5.20 (*dt*, *J* = 7.2, 1.4, H–C(3)); 5.40 (br. *s*, N*H*CHO); 8.06 (*d*, *J* = 12.1,

NHC*H*O); 8.14 (*s*, NHC*H*O). ^{13}C-NMR: see *Table*. EI-MS: 249 (M^+), 204, 135, 93, 69. HR-EI-MS: 249.2097 ($C_{16}H_{27}NO^+$, calc. 249.2093).

7-Formamido-7,8-dihydro-α-bisabolane (= N-*{(2*S*)-6-Methyl-2-[(1*R*)-4-methylcyclohex-3-en-1-yl]-hept-5-en-2-yl}formamide*; **3**): Colorless oil. $[\alpha]_D^{23} = +7$ ($c = 0.20$, $CHCl_3$). IR (KBr): 3275, 1680, 1440, 1325. ^{1}H-NMR (400 MHz, $CDCl_3$): 1.24, 1.28 (2*s*, Me(14)); 1.43–1.47 (*m*, H_β–C(5)); 1.50–1.54 (*m*, H–C(6)); 1.51–1.57 (*m*, H_β–C(4)); 1.52–1.56 (*m*, H_a–C(8)); 1.60 (*s*, Me(15)); 1.63–1.67 (*m*, H_a–C(9)); 1.64 (*s*, Me(13)); 1.68 (*s*, Me(12)); 1.74–1.78 (*m*, H_α–C(1)); 1.93–1.98 (*m*, H_b–C(8)); 1.95–1.99 (*m*, H_α–C(4)); 1.98–2.03 (*m*, H_β–C(1), H_α–C(5)); 2.01–2.05 (*m*, H_b–C(9)); 5.05 (br. *t*, $J = 7.5$, H–C(10)); 5.10 (br. *s*, 0.33 H, N*H*CHO); 5.35 (br. *s*, H–C(2)); 5.50 (br. *d*, $J = 10.8$, 0.67 H, N*H*CHO); 8.10 (br. *s*, 0.33 H, NHC*H*O); 8.18 (*d*, $J = 12.3$, 0.67 H, NHC*H*O). ^{13}C-NMR: see *Table*. EI-MS: 249 (M^+), 204, 189, 166, 154, 121, 119. HR-EI-MS: 249.2086 ($C_{16}H_{27}NO^+$, calc. 249.2093).

4,5-Epi-10-isothiocyanatoisodauc-6-ene (= *(1*S*,3a*S*,4*S*,8a*R*)-4-Isothiocyanato-3a,7-dimethyl-1,2,3,3a,4,5,6,8a-octahydro-1-(prop-2-yl)azulene*; **4**). Colorless oil. $[\alpha]_D^{23} = +2$ ($c = 0.12$, $CHCl_3$). IR (KBr): 2950, 2130, 1448, 1381. ^{1}H-NMR (400 MHz, $CDCl_3$): 0.74 (*s*, Me(15)); 0.77, 0.79 (2*s*, Me(12), Me(13)); 1.33–1.36 (*m*, H_α–C(3)); 1.35–1.39 (*m*, H_α–C(2)); 1.51–1.55 (*m*, H–C(11)); 1.65–1.70 (*m*, H_β–C(3)); 1.70 (*s*, Me(14)); 1.70–1.74 (*m*, H_β–C(9)); 1.70–1.75 (*m*, H_β–C(2)); 1.77–1.82 (*m*, H–C(4)); 1.92–1.97 (*m*, H_β–C(8)); 1.98–2.03 (*m*, H–C(5)); 2.01–2.07 (*m*, H_α–C(9)); 2.25 (*t*, $J = 11.5$, H_α–C(8)); 3.28 (*dd*, $J = 12.2$, 3.5, H–C(10)); 5.15 (br. *s*, H–C(6)). ^{13}C-NMR: see *Table*. EI-MS: 263 (M^+), 205 ([M – NCS]$^+$), 161, 149, 121, 81. HR-EI-MS: 263.1701 ($C_{16}H_{25}NS^+$; calc. 263.1708).

This research work was financially supported by the *National Marine '863' Projects* (Nos. 2006AA09Z447, 2006AA09Z412, and 2007AA09Z447), *Natural Science Foundation of China* (Nos. 30730108, 20721003, 20772136), *STCSM Projects* (Nos. 07XD14036 and 06DZ22028), and *CAS Key Project* (grant KSCX2-YW-R-18).

REFERENCES

[1] A. H. Marcus, T. F. Molinski, E. Fahy, D. J. Faulkner, C. Xu, J. Clardy, *J. Org. Chem.* **1989**, *54*, 5184.
[2] K. A. Alvi, L. Tenenbaum, P. Crews, *J. Nat. Prod.* **1991**, *54*, 71.
[3] H. Y. He, J. Salva, R. F. Catalos, D. J. Faulkner, *J. Org. Chem.* **1992**, *57*, 3191.
[4] R. S. Compagnone, D. J. Faulkner, *J. Nat. Prod.* **1995**, *58*, 145.
[5] A. D. Patil, A. J. Freyer, R. Reichwein, M. F. Bean, L. Faucette, R. K. Johnson, R. C. Haltiwanger, D. S. Eggleston, *J. Nat. Prod.* **1997**, *60*, 507.
[6] J. S. Simpson, M. J. Garson, J. N. A. Hooper, E. I. Cline, C. K. Angerhofer, *Aust. J. Chem.* **1997**, *50*, 1123.
[7] M. Iwashima, I. Terada, K. Iguchi, T. Yamori, *Chem. Pharm. Bull.* **2002**, *50*, 1286.
[8] W. Zhang, M. Gavagnin, Y.-W. Guo, E. Mollo, M. T. Ghiselin, G. Cimino, *Tetradedron* **2007**, *63*, 4725.
[9] S.-C. Mao, E. Manzo, Y.-W. Guo, M. Gavagnin, E. Mollo, M. L. Ciavatta, R. van Soest, G. Cimino, *Tetradedron* **2007**, *63*, 11108.
[10] X.-H. Yan, M. Gavagnin, G. Cimino, Y.-W. Guo, *Tetradedron Lett.* **2007**, *48*, 5313.
[11] R. Jia, Y.-W. Guo, P. Chen, Y.-M. Yang, E. Mollo, M. Gavagnin, G. Cimino, *J. Nat. Prod.* **2007**, *70*, 1158.
[12] J. S. Simpson, A. Brust, M. J. Garson, *Org. Biomol. Chem.* **2004**, *2*, 949.
[13] I. Kitagawa, N. Yoshioka, C. Kamba, M. Yoshikawa, Y. Hamatoto, *Chem. Pharm. Bull.* **1987**, *35*, 928.
[14] B. W. Sullivan, D. J. Faulkner, K. T. Okamoto, M. H. M. Chen, J. Clardy, *J. Org. Chem.* **1986**, *51*, 5134.
[15] N. K. Gulavita, E. D. De Silva, M. R. Hagadone, P. Karuso, P. J. Scheuer, G. D. Van Duyne, J. Clardy, *J. Org. Chem.* **1986**, *51*, 5136.
[16] L. Mayol, V. Piccialli, D. Sica, *Tetrahedron* **1987**, *43*, 5381.
[17] M. J. Garson, J. S. Simpson, *Nat. Prod. Rep.* **2004**, *21*, 164.
[18] E. Manzo, M. L. Ciavatta, M. Gavagnin, E. Mollo, Y.-W. Guo, G. Cimino, *J. Nat. Prod.* **2004**, *67*, 1701.

Received March 11, 2008