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SIX NEW DITERPENE ISONITRILES FROM THE SPONGE *ACANTHELLA CAVERNOSA*

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ABSTRACT.—Six new diterpene isonitriles, 10-*epi*-isokalihinol F [**1**], 10-*epi*-isokalihinol H [**2**], 1-*epi*-kalihinene [**4**], 15-isothiocyanato-1-*epi*-kalihinene [**5**], 1,10-*diepi*-kalihinene [**6**], and kalihipyran [**7**] were isolated, together with the known compound isokalihinol B [**3**], from *Acanthella cavernosa* collected in the Seychelles. The structures of the new diterpenes were elucidated by interpretation of spectral data. The ring system of kalihipyran [**7**] differs from that of the kalihinols and kalihinenes.

The kalihinols and related compounds are diterpenoids from sponges of the genus *Acanthella* that contain two, and often three, isonitrile functionalities (1–6). Members of this series of compounds have been reported to have antimicrobial (1–3), antifungal (1–3), cytotoxic (5), and anthelmintic (4,6) properties. We wish to report the isolation of seven diterpene isonitriles [**1–7**] from a specimen of *Acanthella cavernosa* Dendy, 1922 (Axinellida, Dictyonellidae), collected in the Seychelles.[1] One of these diterpene isonitriles, isokalihinol B [**3**], was previously isolated from *A. klethra* (5).

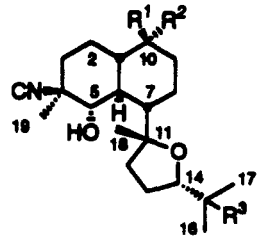
RESULTS AND DISCUSSION

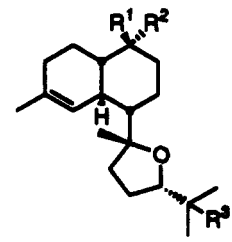
The EtOAc-soluble material from a MeOH extract of a small sample of the sponge *A. cavernosa* was fractionated by chromatography on Si gel to obtain fractions rich in terpenoids. Further separation of these fractions by hplc led to the isolation of 10-*epi*-isokalihinol F [**1**] (0.055% dry wt), 10-*epi*-isokalihinol H [**2**] (0.02% dry wt), isokalihinol B [**3**] (0.006% dry wt), 1-*epi*-kalihinene [**4**] (0.087% dry wt), 15-isothiocyanato-1-*epi*-kalihinene [**5**] (0.016% dry wt), 1,10-*diepi*-kalihinene [**6**] (0.031% dry wt), and kalihipyran [**7**] (0.019% dry wt).

10-*epi*-Isokalihinol F [**1**] was isolated as a white microcrystalline solid, mp 117°. High-resolution mass spectrometry established a molecular formula of $C_{23}H_{33}N_3O_2$, isomeric with the known compounds kalihinol F [**8**] and isokalihinol F [**9**]. The ir spectrum contained bands at 3280 and 2135 cm^{-1} that were indicative of hydroxyl and isonitrile groups. Comparison of the ^{13}C-nmr spectrum of **1**, which was assigned with the aid of the HMBC experiment, with those of the known kalihinols revealed a very close similarity with that of isokalihinol F [**9**] but not with that of kalihinol F [**8**]. In particular, the signal at δ 76.7 (d) in the ^{13}C-nmr spectrum required the presence of a secondary alcohol at C-5 while the chemical shifts of signals assigned to the C-11 to C-18 portion of the molecule were almost identical to those of other kalihinols. Clearly, the only difference between 10-*epi*-isokalihinol F [**1**] and isokalihinol F [**9**] involved the stereochemistry about the bicyclic ring system. The ^1H-nmr spectrum[2] was assigned by interpretation of the COSY experiment that revealed two contiguous spin systems, one of which corresponded to the H-12 to H-14 moiety. The coupling constants for the H-6 signal at δ 1.71 (q, 1H, J=10 Hz) required that H-1, H-5, H-6, and H-7 all be axial in a *trans*-decalin ring system. The stereochemistry at C-4 and C-10 was defined by the ^{13}C-nmr chemical shifts of the C-19 and C-20 methyl signals at δ 19.7 (q) and 27.7 (q)

[1]A preliminary report (7) that this sponge [90–075] contained bromophakellin was incorrect.

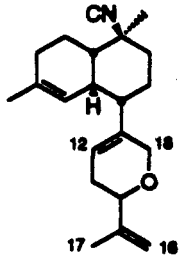
[2]Many of the nmr spectra were recorded in C_6D_6 solution because the signals were better resolved in that solvent.





1 R^1=Me, R^2=R^3=NC
2 R^1=Me, R^2=NCS, R^3=NC
3 R^1=NC, R^2=Me, R^3=Cl
9 R^1=R^3=NC, R^2=Me

4 R^1=R^3=NC, R^2=Me
5 R^1=NC, R^2=Me, R^3=NCS
6 R^1=Me, R^2=R^3=NC



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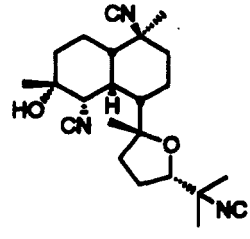

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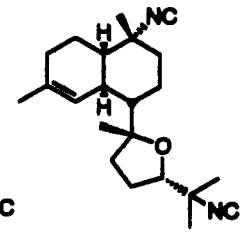

10

(cf., δ 19.9 and 20.3 in [**9**]), which requires axial and equatorial methyl groups, respectively. The stereochemistry about the tetrahydrofuran ring was defined by the observation of a strong nOe of the H-14 signal on irradiation of the CH_3-18 signal. It has normally been assumed that the relative stereochemistry at the C-7, C-11 junction is the same as determined by X-ray analysis for other members of this series; support for this assumption was provided in the case of compound **1** by the observation of enhancements of the H-6 and 5-OH signals on irradiation of the CH_3-18 signal, which were predicted by examination of a molecular model generated by the PC Model program.[3]

10-*epi*-Isokalihinol H [**2**] was isolated as a colorless oil of molecular formula $C_{23}H_{33}N_3O_2S$. The molecular formula suggested the presence of an isothiocyanate in place of one of the isonitrile groups in [**1**] and the ir spectrum contained bands at 3280, 2135, and 2085 cm^{-1} that were assigned to hydroxyl, isonitrile, and isothiocyanate groups, respectively. Comparison of the ^1H and ^{13}C-nmr spectra of compounds **1** and **2** revealed considerable similarity and suggested that one of the isonitrile groups in **1** was replaced by an isothiocyanate group in **2**. The isothiocyanate group was placed at C-10 because, when compared with the ^1H-nmr spectrum of **1**, the H-1 and CH_3-20 signals in the ^1H-nmr spectrum did not show broadening due to coupling to the nitrogen in an isonitrile group. The stereochemistry at C-10 was determined by observation of nOes of the H-1 (8%) and H-2_{eq} (7.5%) signals on irradiation of the CH_3-20 signal.

Isokalihinol B [**3**] was isolated as a very minor constituent of molecular formula $C_{23}H_{33}ClN_2O_2$. Although it was difficult to compare our nmr spectral data recorded in C_6D_6 solution (9) with those reported for a $CDCl_3$ solution (5), interpretation of our

[3]The PC Model program (Serena Software) predicts a high barrier to rotation about the C-7, C-11 bond and a conformation of **1** that places CH_3-18 close to H-6 and 5-OH.

spectral data suggested that the compounds were the same. In particular, the chlorine must be at C-15 because the ^{1}H-nmr signals for both the 16- and 17-methyl groups were sharpened, and the chemical shifts of the ^{13}C-nmr signals for both the 19- and 20-methyl groups are in the correct range for axial methyl groups. It is interesting to note that our sample of isokalihinol B [**3**] has a relatively strong optical rotation, $[\alpha]_D$ +56.7°, while the literature sample was racemic.

1-*epi*-Kalihinene [**4**] was isolated as a colorless oil of molecular formula $C_{22}H_{32}N_2O$, isomeric with kalihinene [**10**], the structure of which was determined by X-ray analysis (5). The ir spectrum contained a band at 2130 cm^{-1} due to the isonitrile functionality but there was no hydroxyl band present. The ^{1}H-nmr spectrum (in C_6D_6), which was assigned by interpretation of the COSY experiment, contained an olefinic proton signal at δ 6.22 (br s, 1 H) that was assigned to H-5. The H-5 signal was not coupled to the H-6 signal at δ 1.76 (br t, 1 H, J=11 Hz) because, according to models, the dihedral angle between H-5 and H-6 is about 90°. The H-6 signal must therefore be coupled to two other axial proton signals (H-1 and H-7) in a *trans*-decalin ring system. The methyl group at C-10 must be axial because irradiation of the H-8$_{ax}$ signal at δ 0.58 caused enhancement of both the H-6 and Me-20 signals. The stereochemistry about the tetrahydrofuran ring was assigned by observing an enhancement of the H-14 signal at δ 3.43 on irradiation of the Me-18 signal at δ 0.73. It must be assumed that the relative stereochemistry at C-7 and C-11 is the same as in all other members of this series.

15-Isothiocyanato-1-*epi*-kalihinene [**5**] was isolated as a colorless oil of molecular formula $C_{22}H_{32}N_2OS$. The ir spectrum contains bands at 2125 (-N≡C) and 2095 (-NCS) cm^{-1}, indicating that the sulfur atom was incorporated in an isothiocyanate group. The ^{1}H- and ^{13}C-nmr spectra were almost identical to those of **4** except in the region of C-15, where the isothiocyanate group replaces an isonitrile. The ^{1}H-nmr signals assigned to Me-16 and Me-17 at δ 1.04 and 0.79 are sharp, indicating isothiocyanate substitution at C-15, while the Me-20 signal at δ 0.90 is broad due to coupling with the C-10 isonitrile nitrogen.

1,10-*diepi*-Kalihinene [**6**] was isolated as a colorless oil of molecular formula $C_{22}H_{32}N_2O$, isomeric with kalihinene and 1-*epi*-kalihinene [**4**]. The ir spectrum again contained an isonitrile band at 2130 cm^{-1}. The ^{1}H-nmr spectrum of **6** was similar in many respects to that of **4** except that the H-6 signal at δ 2.34 (br t, 1 H, J=12 Hz) was shifted 0.67 ppm downfield from its position in **4** while keeping the same coupling constants. This indicated that the substitution pattern at C-1, C-6, and C-7 in the *trans*-decalin ring system remained the same but that epimerization had occurred at C-10. This was supported by the downfield shift of the Me-20 signal in the ^{13}C-nmr spectrum from δ 20.0 in **4** to 27.5 in **6** and an nOe experiment in which irradiation of the Me-20 signal caused enhancements of the H-1 and H-2$_{eq}$ signals.

Kalihipyran [**7**] was isolated as a colorless oil. The molecular formula, $C_{21}H_{29}NO$, suggested a diterpene with only one isonitrile group and two more unsaturation equivalents than the kalihinenes. The presence of the isonitrile group was confirmed by the observation of an ir band at 2130 cm^{-1}. The ^{13}C-nmr spectrum revealed the presence of six olefinic signals, of which two were trisubstituted and the third was a disubstituted methylene. Kalihipyran [**7**] is therefore tricyclic. Examination of the ^{1}H- and ^{13}C-nmr spectra strongly suggested that the *trans*-decalin ring system found in 1-*epi*-kalihinene [**4**] was present but that there was a very different monocyclic eight-carbon unit attached at C-7. The COSY experiment revealed strong coupling between the olefinic signal at δ 5.34 (br dd, 1 H, J=5.5 and 3.5 Hz, H-12) and methylene proton signals at δ 2.17 (br ddd, 1 H, J=17, 10.5, and 3.5 Hz, H-13) and 1.88 (br ddd, J=17, 5.5, and 3.5 Hz, H-13), that were in turn coupled to an oxymethine signal at δ 3.84 (br dd, 1 H, J=10.5

and 3.5 Hz, H-14). Weaker allylic couplings were observed between the olefinic proton signal at δ 5.34 and two oxymethine proton signals at δ 4.06 (br d, 1H, J=16 Hz, H-18) and 3.99 (br d, 1H, J=16 Hz, H-18), between the oxymethine proton signal at δ 3.84 and the olefinic methylene signals at δ 5.17 (br s, 1H, H-16) and 4.89 (br s, 1 H, H-16) and between the methyl signal at δ 1.74 (s, 3H) and the same olefinic methylene signals. Weak homoallylic coupling between the H-13 and H-18 signals was also noted. Two nOeds experiments provided support for this structure: irradiation of the H-14 signal caused enhancements of the H-16 (δ 4.98), Me-17, and H-12 (δ 4.06) signals and irradiation of the H-12 signal at δ 4.06 caused enhancement of the H-14 and H-5 signals. It was not possible to determine the relative stereochemistry at C-14.

The oxidation pattern observed in kalihipyran [**7**] is different from that observed in other kalihinols and kalihinenes. The crude extract showed very modest inhibition of *Staphylococcus aureus, Bacillus subtilis,* and *Candida albicans* but, although the activity was sufficient to follow during fractionation, the pure compounds showed only minimal zones of inhibition at 100 μg/disk.

EXPERIMENTAL

ANIMAL MATERIAL, EXTRACTION AND CHROMATOGRAPHY.—The orange sponge *Acanthella cavernosa* Dendy, 1922 (SIO invertebrate Collection no. P1136) was collected by hand (−10 m) at Beau Vallon Beach, Mahé, Seychelles, and kept frozen until extraction. The sponge (7.5 g dry weight) was extracted twice with MeOH, the solvent was evaporated, and the residue was partitioned between H_2O and EtOAc. The EtOAc extract (86 mg) was subjected to flash chromatography on Si gel using a solvent gradient from hexane to EtOAc to yield a number of fractions that appeared by ^{1}H-nmr spectroscopy to contain diterpenes. Fractions eluted with hexane to 10% EtOAc in hexane were combined and separated by hplc on Partisil 10 using 20% EtOAc in hexane as eluent to obtain 1-*epi*-kalihinene [**4**] (2.3 mg), 15-isothiocyanatokalihinene [**5**] (1.2 mg), 1,10-*diepi*-kalihinene [**6**] (3.8 mg), and kalihipyran [**7**] (1.4 mg). The fraction eluting with 20% EtOAc in hexane was separated under identical hplc conditions to obtain 1-*epi*-kalihinene [**4**] (4.2 mg, 6.7 mg total) and 1,10-*diepi*-kalihinene [**6**] (1.1 mg, 4.9 mg total). Fractions eluting with 50–60% EtOAc in hexane were separated by hplc on Si gel using 30% EtOAc in hexane as eluent to obtain 10-*epi*-isokalihinol F [**1**] (4.1 mg), 10-*epi*-isokalihinol H [**2**] (1.5 mg) and isokalihinol B [**3**] (0.45 mg).

10-*EPI*-ISOKALIHINOL F [**1**].—Mp 117° (CH_2Cl_2); [α]D −21.2° (c=0.41, CH_2Cl_2); ir (KBr) ν max 3280, 2975, 2940, 2135, 1685, 1450, 1380, 1030 cm^{-1}; ^{1}H-nmr ($CDCl_3$) δ 6.41 (1H, d, J=3.5 Hz, OH-5), 3.89 (1H, br m, H-14), 3.63 (1H, br d, J=10 Hz, H-5), 2.17 (1H, m, H-13), 2.10 (1H, dt, J=9 and 3 Hz, H-3$_{eq}$), 2.04 (1H, m, H-13), 1.96 (1H, br d, J=13 Hz, H-8$_{eq}$), 1.91 (2H, m, H-12), 1.81 (1H, m, H-3$_{ax}$), 1.80 (1H, dq, J=10 and 3.5 Hz, H-2$_{eq}$), 1.71 (1H, q, J=10 Hz, H-6), 1.66 (1H, m, H-9$_{eq}$), 1.61 (1H, dddd, J=13, 12, 10, and 3 Hz, H-8$_{ax}$), 1.54 (1H, td, J=10 and 3 Hz, H-7), 1.48 (3H, br s, H-19), 1.47 (3H, br t, J=1.5 Hz, H-16), 1.44 (1H, m, H-2$_{ax}$), 1.41 (3H, br s, H-20), 1.36 (3H, br s, H-17), 1.34 (3H, s, H-18), 1.20 (1H, br t, J=10 Hz, H-1); ^{13}C nmr, see Table 1; ms, m/z 384 $[MH]^+$, 356 $[M-HCN]^+$, 327 $[M-2HCN]^+$, 302 $[M-3HCN]^+$, 285 $[M-3HCN-OH]^+$; hrms, m/z 383.2545 ($C_{23}H_{33}N_3O_2$ requires 383.2572).

10-*EPI*-ISOKALIHINOL H [**2**].—Colorless oil; [α]D −32.1° (c=0.17, CH_2Cl_2); uv (MeOH) λ max 244 nm (ε 1265); ir (neat) ν max 3360, 2940, 2870, 2135, 2085 (br), 1455, 1380, 1180, 885 cm^{-1}; ^{1}H nmr (C_6D_6) δ 6.22 (1H, d, J=4 Hz, OH-5), 3.51 (1H, dd, J=11 and 3.5 Hz, H-5), 2.94 (1H, br m, H-14), 1.65 (1H, dt, J=13.5 and 3.5 Hz, H-3$_{eq}$), 1.56 (1H, q, J=11 Hz, H-6), 1.46 (3H, br s, H-19), 1.22 (1H, br t, J=11.5 Hz, H-7), 1.08 (3H, br s, H-16), 1.01 (3H, s, H-18), 0.91 (1H, qd, J=12 and 3 Hz, H-2$_{ax}$), 0.79 (1H, qd, J=12 and 3 Hz, H-8$_{ax}$), 0.71 (3H, s, H-20), 0.63 (3H, br s, H-17), 0.37 (1H, td, J=11 and 4.5 Hz, H-1); ^{13}C nmr, see Table 1; hrfabms, m/z 548.1348 $[M+Cs]^+$ ($C_{23}H_{33}N_3O_2SCs$ requires 548.1348).

ISOKALIHINOL B [**3**].—Colorless oil; [α]D +56.7° (c=0.03, CH_2Cl_2); ir (neat) ν max 3350, 2960, 2145, 1380, 1130, 895 cm^{-1}; ^{1}H nmr (C_6D_6) δ 6.31 (1H, d, J=4 Hz, OH-5), 3.41 (1H, dd, J=9.5 and 4.5 Hz, H-14), 3.40 (1H, dd, J=9.5 and 4 Hz, H-5), 1.65 (1H, m, H-13), 1.64 (1H, dt, J=13.5 and 3.5 Hz, H-9$_{eq}$), 1.58 (1H, dq, J=13.5 and 3.5 Hz, H-8$_{eq}$), 1.50 (1H, dt, J=13 and 3.5 Hz, H-3$_{eq}$), 1.46 (1H, m, H-13), 1.40 (1H, br t, J=13 Hz, H-9$_{ax}$), 1.39 (1H, br t, J=14 Hz, H-3$_{ax}$), 1.37 (1H, m, H-12), 1.35 (3H, s, H-16), 1.25 (1H, m, H-12), 1.23 (3H, br t, J=1.5 Hz, H-19), 1.15 (3H, s, H-18), 1.07 (1H, ddd, J=12.5, 9.5, and 3.5 Hz, H-1), 0.94 (1H, m, H-2$_{eq}$), 0.92 (1H, dt, J=11 and 9.5 Hz, H-6), 0.85 (3H, s, H-17), 0.84 (1H, td, J=11.5 and 3 Hz, H-7), 0.75 (3H, br t, J=1.5 Hz, H-20), 0.64 (1H, tdd, J=14, 12, and

TABLE 1. ^{13}C-Nmr Data [50 MHz, δ (mult.)] for Diterpenes **1–7**.

Carbon	Compound						
	1[a]	**2**[a]	**3**[a]	**4**[b]	**5**[a]	**6**[b]	**7**[b]
1	47.0 (d)	48.7 (d)	46.9 (d)	47.3 (d)	47.5 (d)	46.6 (d)	47.2 (d)
2	21.0 (t)	21.3 (t)	21.1 (t)	23.6 (t)	24.1 (t)	23.2 (t)	23.4 (t)
3	36.8 (t)	36.9 (t)	36.7 (t)	30.3 (t)	30.4 (t)	30.1 (t)	30.8 (t)
4	61.6[c]	—[h]	61.5 [c]	133.2 (s)	133.1 (s)	132.3 (s)	135.4 (s)
5	76.7 (d)	76.8 (d)	76.7 (d)	124.2 (d)	124.6 (d)	124.8 (d)	121.9 (d)
6	43.4 (d)	43.6 (d)	42.7 (d)	38.3 (d)	38.6 (d)	38.5 (d)	38.3 (d)
7	53.9 (d)	53.8 (d)	53.6 (d)	51.3 (d)	51.4 (d)	51.3 (d)	47.9 (d)
8	26.5 (t)	26.9 (t)	25.4[d] (t)	25.1[d] (t)	25.2[d] (t)	25.2[d] (t)	28.9[d] (t)
9	39.0 (t)	39.8[d] (t)	40.3[e] (t)	37.9 (t)	37.8 (t)	38.0 (t)	40.5 (t)
10	60.8[c]	64.2 (s)	59.5[c]	60.4[c]	60.2[c]	60.5[c]	60.3[c]
11	88.2 (s)	87.9 (s)	87.2 (s)	87.1 (s)	87.3 (s)	87.5 (s)	145.2 (s)
12	39.2 (t)	38.9[d] (t)	38.9[e] (t)	40.5 (t)	40.7 (t)	39.7 (t)	120.0 (d)
13	25.0 (t)	25.0 (t)	25.4[d] (t)	25.5[d] (t)	25.6[d] (t)	25.4[d] (t)	29.6[d] (t)
14	82.4 (d)	82.3 (d)	83.9 (d)	82.6 (d)	83.5 (d)	82.7 (d)	75.8 (d)
15	60.1[c]	—	71.0 (s)	60.3[c]	63.7 (s)	60.5[c]	138.4 (s)
16	25.4 (q)	25.5[e] (q)	28.9[f] (q)	25.0[e] (q)	25.4[e] (q)	25.4[d] (q)	110.6 (t)
17	25.7 (q)	25.8[e] (q)	27.7[f] (q)	26.2[e] (q)	25.0[e] (q)	26.2[d] (q)	19.9 (q)
18	18.4 (q)	18.3 (q)	17.8 (q)	18.4 (q)	19.9 (q)	18.4 (q)	66.9 (t)
19	19.6 (q)	19.7 (q)	19.5[g] (q)	23.8 (q)	23.9 (q)	23.7 (q)	23.3 (q)
20	27.7 (q)	27.3 (q)	19.9[g] (q)	20.0 (q)	18.3 (q)	27.5 (q)	18.8 (q)
NC	151.9[c]	—[h]	—[h]	152.1[c]	154.8[c]	—[h]	152.4[c]
NC	154.9[c]	—[h]	—[h]	153.9[c]	—[h]	—[h]	—[h]
NC	155.5[c]	—[h]		—[h]	—[h]	—[h]	

[a]C_6D_6 solution.
[b]$CDCl_3$ solution.
[c]Signal appears as a broad 1:1:1 triplet due to coupling with the isonitrile nitrogen.
[d–g]Signals may be interchanged.
[h]Signal not observed.

3.5 Hz, H-8_{ax}), 0.47 (1H, tdd, J=14, 12.5, and 3.5 Hz, H-2_{ax}); ^{13}C nmr, see Table 1; ms, *m/z* 392/394 $[M]^+$, 366/368 $[M-CN]^+$, 357 $[M-Cl]^+$, 339/341 $[M-CN-HCN]^+$, 330 $[M-Cl-HCN]^+$, 303 $[M-Cl-CN-HCN]^+$; hrfabms, *m/z* 525.1264 $[M+Cs]^+$ ($C_{22}H_{33}N_2O^{35}Cl$ requires 525.1285).

1-*EPI*-KALIHINENE [**4**].—Colorless oil; $[\alpha]_D$ −171.5° (c=0.431, CH_2Cl_2); ir (neat) ν max 2965, 2875, 2130, 1670, 1450, 1380, 1085, 1040, 820 cm^{-1}; ^{1}H nmr (C_6D_6) δ 6.22 (1H, br s, H-5), 3.43 (1H, br m, H-14), 2.05 (1H, ddt, J=12, 6, and 2 Hz, H-2_{eq}), 1.85 (1H, br t, J=17 Hz, H-3_{ax}), 1.74 (1H, dd, J=17 and 5 Hz, H-3_{eq}), 1.67 (1H, br t, J=11 Hz, H-6), 1.65 (3H, s, H-19), 1.62 (1H, dt, J=13 and 3.5 Hz, H-9_{eq}), 1.55 (1H, m, H-9_{ax}), 1.53 (2H, m, H-13), 1.39 (1H, q, J=11 Hz, H-12), 1.35 (1H, br t, J=11 Hz, H-2_{eq}), 1.21 (1H, ddd, J=12.5, 11, and 3.5 Hz, H-7_{ax}), 1.17 (1H, ddd, J=11.5, 8, and 4 Hz, H-12), 1.12 (3H, br s, H-16), 1.06 (1H, dq, J=14 and 3.5 Hz, H-8_{eq}), 1.05 (1H, m, H-2_{ax}), 0.93 (3H, br s, H-17), 0.91 (3H, br t, J=1.5 Hz, H-20), 0.73 (3H, s, H-18), 0.58 (1H, dddd, J=14, 13, 12, and 4 Hz, H-8_{ax}); ^{13}C nmr, see Table 1; ms *m/z* 340 $[M]^+$, 325 $[M-CH_3]^+$, 313 $[M-HCN]^+$, 298 $[M-CH_3-HCN]^+$ 286 $[M-2HCN]^+$; hrms, *m/z* 340.2500 ($C_{22}H_{32}N_2O$ requires 340.2515).

15-ISOTHIOCYANATO-1-*EPI*-KALIHINENE [**5**].—Colorless oil; $[\alpha]_D$ −149° (c=0.132, CH_2Cl_2); uv (MeOH) λ max 245 nm (ε 1206); ir (neat) ν max (neat) 2965, 2935, 2875, 2125, 2095 (br), 1450, 1380, 1085, 1037 cm^{-1}; ^{1}H nmr (C_6D_6) δ 6.17 (1H, br s, H-5), 3.38 (1H, dd, J=8 and 4 Hz, H-14), 2.03 (1H, ddt, J=12, 6, and 2 Hz, H-2_{eq}), 1.81 (1H, br t, J=17 Hz, H-3_{ax}), 1.70 (1H, dd, J=17 and 5 Hz, H-3_{eq}), 1.67–1.63 (2H, m), 1.62 (3H, br s, H-19), 1.45–1.32 (4H, m), 1.26 (1H, ddd, J=14, 10, and 3.5 Hz, H-9_{ax}), 1.16–1.00 (3H, *m*), 1.04 (3H, *s*, H-16), 0.90 (3H, br t, J=1.5 Hz, H-20), 0.79 (3H, s, H-17), 0.71 (3H, s, H-18); ^{13}C nmr, see Table 1; hrfabms *m/z* 505.1315 $[M+Cs]^+$ ($C_{22}H_{32}N_2OSCs$ requires 505.1290).

1,10-*DIEPI*-KALIHINENE [**6**].—Colorless oil, $[\alpha]_D$ −66.2° (c=0.47, CH_2Cl_2); ir (neat) ν max 2925, 2835, 2130, 1455, 1380, 1085, 1040, 890 cm^{-1}; ^{1}H nmr (C_6D_6) δ 6.38 (1H, br s, H-5), 3.35 (1H, br m, H-14), 2.34 (1H, br t, J=12 Hz, H-6), 1.84–1.74 (2H, m), 1.71 (3H, br s, H-19), 1.65 (1H, dq, J=12 and 3 Hz, H-2_{eq}), 1.58–1.44 (6H, m), 1.41 (1H, qd, J=12 and 3.5 Hz, H-8_{ax}), 1.30 (1H, td, J=11 and 3.5 Hz, H-7_{ax}), 1.24 (1H, dq, J=12 and 3.5 Hz, H-8_{eq}), 1.16 (3H, br s, H-16), 0.97 (3H, br s, H-20), 0.91 (3H, s, H-18), 0.87 (3H, br s, H-17), 0.72 (1H, br td, J=12 and 3 Hz, H-1); ^{13}C nmr, see Table 1; ms, *m/z* 340

$[M]^+$, 314 $[M-CN]^+$, 288 $[M-2CN]^+$, 287 $[M-CN-HCN]^+$; hrms *m/z* 340.2528 ($C_{22}H_{32}N_2O$ requires 340.2515).

KALIHIPYRAN [7].—Colorless oil; $[\alpha]_D$ +104.1° (*c*=0.29, CH_2Cl_2); ir (neat) ν max 2935, 2870, 2130, 1655, 1450, 1380, 1090, 900 cm^{-1}; ^1H nmr ($CDCl_3$) δ 5.34 (1H, br dd, *J*=5.5 and 3.5 Hz, H-12), 5.30 (1H, s, H-5), 5.17 (1H, br s, H-16), 4.89 (1H, br s, H-16), 4.06 (1H, br d, *J*=16 Hz, H-18), 3.99 (1H, br d, *J*=16 Hz, H-18), 3.84 (1H, br dd, *J*=10.5 and 3.5 Hz, H-14), 2.17 (1H, br ddd, *J*=17, 10.5, and 3.5 Hz, H-13), 1.98 (1H, ddt, *J*=13, 6.5, and 2 Hz, H-2), 1.88 (1H, br ddd, *J*=17, 5.5, and 3.5 Hz, H-13), 1.75 (2H, m, H-3), 1.74 (3H, s, H-17), 1.63 (1H, m, H-8), 1.58 (1H, m, H-9), 1.52 (3H, s, H-19), 1.50 (1H, m, H-6), 1.27 (1H, m, H-7), 1.26 (1H, m, H-1), 1.22 (1H, m, H-9), 1.01 (1H, m, H-2), 0.99 (1H, m, H-8), 0.87 (3H, br t, *J*=1.5 Hz, H-20); ^{13}C nmr, see Table 1; ms, *m/z* 311 $[M]^+$, 284 $[M-HCN]^+$; hrfabms *m/z* 334.2157 $[M+Na]^+$ ($C_{21}H_{29}NONa$ requires 334.2147).

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