times of the scans. The structures were solved by direct methods and refined by full-matrix least-squares analysis based on F, using the SDP software package.[8] No crystal decomposition was observed during the data collection.

For 9: Crystals of **9** for X-ray analysis were prepared by recrystallization from EtOAc/hexane. The relative stereochemical configurations were readily assigned since all non-hydrogen atoms were evident in Fourier maps. Least-squares refinements of all coordinates and isotropic temperature factors indicate relatively large rotational motion or packing disorder of the phenyl ring and methyl atoms of the silyl and ester groups. By contrast, the intermolecularly hydrogen-bonded amide (N--O distance = 2.92 Å) and backbone atoms are relatively well defined.

For 8c: This salt crystallizes as a monohydrate (thin plates) from moist EtOAc/hexane solvent mixtures. All non-hydrogen atoms were located and refined assuming individual isotropid motions. Fixed hydrogens were introduced at idealized positions consistent with peaks on difference maps. A final difference map contained only some small peaks attributable to anisotropic motion; however, since the number of "observed" intensities was limited, no attempt was made to refine an anisotropic model (only 9% of the intensities measured beyond $2\theta = 100°$ had $I > 3\sigma$). The observed S configuration at the carbinol center (relative to the known S configuration of the phenethylamine moiety) is consistent with the observed crystal structure of **9**. Intermolecular amide hydrogen bonding is similar to that in **9**; the water molecule is hydrogen bonded to the carbinol and carboxyl oxygen atoms.

Supplementary Material Available: Tables of unit cell data, atomic coordinates, and thermal parameters (13 pages). Ordering information is given on any current masthead page.

(8) Structure Determination Package, A. Frenz and associates, College Station, TX 77804.

New Nitrogenous Sesquiterpenes from Two Philippine Nudibranchs, *Phyllidia pustulosa* and *P. varicosa*, and from a Palauan Sponge, *Halichondria* cf. *lendenfeldi*

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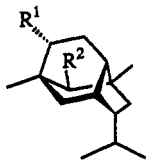
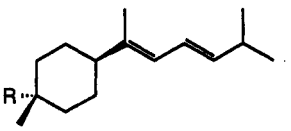
Dorid nudibranchs are shell-less marine molluscs that often contain high concentrations of defensive allomones, which they normally acquire from their sponge diet.[1,2] Nudibranchs of the genus *Phyllidia* are particularly renowned for their toxicity.[3] Hawaiian specimans of *Phyllidia varicosa* contained 9-isocyanopupukeanane (**1**) and 2-isocyanopupukeanane (**2**) (Chart I), both of which were determined to be metabolites of the sponge *Ciocalypta* sp. [ex. *Hymeniacidon* sp.].[4-6] A different isonitrile, 3-isocyanotheonellin (**3**), was isolated from specimens of the same nudibranch from Sri Lanka.[6] Both 9-isocyanopupukeanane (**1**) and its C-9 epimer were obtained from

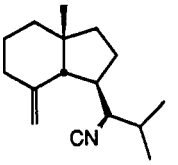
Chart I



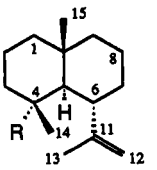
1 R^1 = NC R^2 = H
2 R^1 = H R^2 = NC



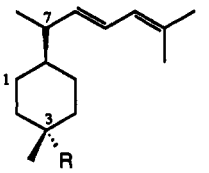
3 R = NC
12 R = NHCHO



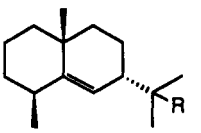
4



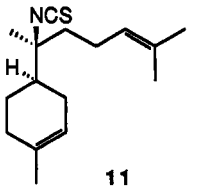
5 R = NC
6 R = NHCHO
7 R = NCS



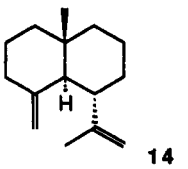
8 R = NC
13 R = NHCHO



9 R = NC
10 R = NCS



11



14

the Japanese nudibranch *P. bourguini*.[7] The Mediterranean nudibranch *P. pulitzeri* contained axisonitrile-1 (**4**),[8] which had previously been reported as a metabolite of the sponge *Axinella cannabina*.[9] This paper reports a study of the chemical constituents of Philippine specimens of the nudibranchs *P. varicosa* and *P. pustulosa* and ascribes the origin of some of these metabolites to sponges of the order Halichondrida.

Specimens of both *P. varicosa* and *P. pustulosa* were collected by hand in the channel between Negros Island and Cebu Island and from shallow waters off San Sebastian, Cebu. Despite their abundance in these habitats, they were never encountered on sponges but were always found "swimming" in the water column or crawling over the sand bottom. Each species of nudibranch was stored separately in acetone. The acetone extracts were subjected to a standard separation procedure that involved flash chromatography on silica gel followed by HPLC to obtain pure compounds. Four specimens of *P. varicosa* yielded the novel compounds, 4α-isocyanogorgon-11-ene (**5**, 0.85 mg/animal) and 4α-formamidogorgon-11-ene (**6**, 0.28 mg/animal). Extraction of 19 specimens of *P. pustulosa* gave the novel metabolites, 4α-isocyanogorgon-11-ene (**5**, 2.33 mg/animal), 4α-formamidogorgon-11-ene (**6**, 0.57

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mg/animal), 4α-isothiocyanatogorgon-11-ene (7, 0.28 mg/animal), and 3-isocyanobisabolane-8,10-diene (8, 0.05 mg/animal) together with 11-isocyano-7β-H-eudesm-5-ene (9, 0.8 mg/animal) and 11-isothiocyanato-7β-H-eudesm-5-ene (10, 0.1 mg/animal), both of which had previously been isolated from the sponge *Axinella cannabina*,[10] and (6R,7S)-7-isothiocyanato-7,8-dihydro-α-bisabolene (11, 0.005 mg/animal, which is a known metabolite of a Palauan *Halichondria* species.[11] The known metabolites were identified by comparison of spectral data with those published in the literature. The minor metabolite 3-isocyanobisabolane-8,10-diene (8) has also been found in the Palauan sponge *Halichondria* cf. *lendenfeldi*, which provided sufficient material to complete the structural elucidation. This sponge also contained 3-isocyanotheonellin (3),[6] 3-formamidotheonellin (12),[12] and 3-formamidobisabolane-8,10-diene (13), which decomposed before it could be completely characterized.

4α-Isocyanogorgon-11-ene (5) is a colorless oil that must be handled with care due to its high volatility. The molecular formula, $C_{16}H_{25}N$, was established by HREIMS (m/z = 231.1985). The characteristic band at 2135 cm^{-1} in the IR spectrum was assigned to the isonitrile functionality.[13] The ^1H and ^{13}C NMR spectra of the compound were not compatible with any of the known sesquiterpenoid isonitriles from nudibranchs or sponges.[14] The ^1H NMR spectrum contained two olefinic signals at δ 4.92 (br s, 1 H) and 4.78 (br s, 1 H) that were coupled to each other (J = 2.2 Hz) and to an allylic methine signal at 2.50 (ddd, 1 H, J = 11.2, 9.1, 3.3 Hz). The olefinic signal at δ 4.78 was also coupled to the methyl signal at 1.82 (br s, 3 H), suggesting the presence of an isopropylidene moiety. The ^{13}C NMR spectrum contained the expected 16 carbon signals that included the olefinic signals at δ 147.9 (s) and 113.5 (t). The signals at δ 154.6 and 60.1 each consist of three lines of equal intensity that are unaffected by broad band decoupling: these signals are characteristic of an isonitrile carbon and the quaternary carbon atom to which the isonitrile nitrogen is attached. The ^1H NMR signal at δ 1.46 (br s, 3 H) is due to a methyl group attached at the carbon bearing the isonitrile group. The structure must be bicyclic to account for the five unsaturations required by the molecular formula. The ^1H NMR signal at δ 0.97 (s, 3 H) and the ^{13}C NMR signal at 34.9 (s) must be assigned to a methyl group at the bicyclic ring junction. A decalin ring system was proposed because W couplings were observed in the COSY spectrum between the H-3_{eq} and H-1_{eq} signals and between the Me-15 signal and the H-1_{ax} and H-9_{ax} signals; these assignments were confirmed by decoupling. Irradiation of the methine proton signal at δ 2.50 resulted in the collapse of a doublet at 1.64 (d, 1 H, J = 11.2 Hz) to a singlet; since there are only two methine signals in the ^{13}C NMR spectrum, the decoupling experiment suggests that isonitrile 5 must have a rare sesquiterpene carbon skeleton, which is similar to the eudesmane skeleton except that the isopropyl side chain is at C-6 instead of C-7. β-Gorgonene (14), which was isolated from the gorgonian *Psuedopterogorgia americana*,[15] has the same carbon skeleton, now defined as the "gorgonane" skeleton.[16] The HMQC experiment, which records one-bond carbon–hydrogen correlations,[17] confirmed the assignments of all signals in the ^1H and ^{13}C NMR spectra of 4α-isocyanogorgon-11-ene (5).

The stereochemistry of the compound was determined by NOEDS experiments. Irradiation of Me-15 signal at δ 0.97 caused enhancements of the signals of H-1_{eq} (0.5%), H-9_{eq} (0.5%), H-6 (5.6%), and Me-14 (2.3%); irradiation of the Me-14 signal at 1.46 led to enhancement of the signals due to H-3_{eq} (3.7%), H-12 (3.1%), H-6 (5.8%), H-6 (5.8%), and Me-15 (2.1%), thereby establishing a *cis* relationship between H-6, Me-14, and Me-15. The only structure compatable with these data is a *trans*-decalin with axial configurations for H-6, Me-14, and Me-15. Thus the structure of 4-isocyanogorgon-11-ene (5) was defined as 4β,10β-dimethyl-4α-isocyano-6α-isopropenyl-*trans*-decalin.

4α-Formamidogorgon-11-ene (6) had a molecular formula of $C_{16}H_{27}NO$ that gave rise to a molecular ion at m/z = 249.2093 and a prominent amide band at 1665 cm^{-1} in the IR spectrum. Two sets of signals were observed in the ^1H and ^{13}C NMR spectra due to restricted rotation around the NH–CO bond, with the major isomer being the E isomer.

4α-Isothiocyanatogorgon-11-ene (7) gave the expected molecular ion at m/z = 263.1708 for $C_{16}H_{25}NS$. The isocyanate group gave rise to a broad absorption at 2110 cm^{-1} in the IR spectrum. Both the ^1H and ^{13}C NMR spectra were very similar to those of 5 with the signal of the isothiocyanate carbon being too weak to be observed.

3-Isocyanobisabolane-8,10-diene (8) was obtained as a colorless oil. Its spectral characteristics were very similar to those of 3-isocyanotheonellin (3).[6] The molecular formula, $C_{16}H_{25}N$, was established by high resolution mass measurement. The characteristic band at 2140 cm^{-1} in the IR spectrum was assigned to an isonitrile functionality. The UV absorption at 237 nm (ε 15 300) was typical of a conjugated diene. The ^1H NMR spectrum contained four methyl signals at δ 1.73 (s, 3 H), 1.71 (s, 3 H), 1.40 (s, 3 H), and 0.97 (d, 3 H, J = 6.7 Hz). A signal at δ 2.02 (m, 1 H, H-7) was coupled to the methyl signal at 0.97 and to the terminal olefinic proton signal of the conjugated diene at 5.33 (dd, 1 H, J = 14.9, 8.8 Hz). An olefinic signal at δ 6.14 (dd, 1 H, J = 14.9, 10.8 Hz) was coupled (J = 14.9 Hz, E stereochemistry) to the signal at 5.33 and to a signal at 5.75 (br d, 1 H, J = 10.8 Hz) that was broadened by allylic coupling to the methyl signals at 1.73 and 1.71. The ^{13}C NMR spectrum was assigned by comparison of the data with those of known compounds, including 3-isocyanotheonellin (3). The nearly identical chemical shifts of the signals assigned to the isonitrile carbon (δ 151.9 in 3 and 8), C-3 (56.8 in 3, 57.0 in 8) and Me-13 (25.1 in 3 and 25.7 or 25.9 in 8) indicate that the stereochemistry about the six-membered ring is the same in both compounds.

3-Formamidobisabolane-8,10-diene (13) was tentatively identified by comparison of its ^1H NMR data with those of 3-formamidotheonellin (12),[17] but the sample decomposed during or after the acquisiton of a ^{13}C NMR spectrum of poor quality.

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Experimental Section

Extraction of *Phyllidia pustulosa*. Nineteen specimens (length: 0.3–2.5 cm) were collected by hand using SCUBA (–6 to –9 m) off San Sebastian, Cebu, The Phillipines, in April, 1990, and were stored in acetone (50 mL). After 3 months at 4 °C, the acetone was decanted and the animals were washed with fresh acetone. The combined acetone extracts were evaporated in vacuo to give an aqueous suspension (ca. 15 mL), which was diluted with an equal amount of water and extracted with dichloromethane (3 × 30 mL). The organic extract was dried over $MgSO_4$ and the solvent evaporated. The resulting oil was subjected to flash chromatography on silica using an elution gradient from hexane to ethyl acetate. The fraction containing isothiocyanates and isonitriles was eluted with 9:1 hexane–ethyl acetate and was rechromatographed using HPLC on silica (95:5 hexane–ethyl acetate) followed by HPLC on C18 silica (3% H_2O in MeOH), if necessary, to obtain 4α-isothiocyanatogorgon-11-ene (**7**, 5.4 mg, 0.2% dry wt), 11-isothiocyanato-7β-*H*-eudesm-5-ene (**10**, 1.8 mg 0.07% dry wt), (6*R*,7*S*)-7-isothiocyanato-7,8-dihydro-α-bisabolene (**11**, 0.1 mg, 0.004% dry wt), 4α-isocyanogorgon-11-ene (**5**, 44.3 mg, 1.68% dry wt), 11-isocyano-7β-*H*-eudesm-5-ene (**9**, 15.1 mg, 0.57% dry wt), and 3-isocyanobisabolane-8,10-diene (**8**, 5.2 mg, 0.20% dry wt). The material eluting with ethyl acetate was purified by reversed-phase HPLC (C18 silica) using 8:1:1 methanol–acetone–water as eluent to obtain 4α-formamidogorgon-11-ene (**6**, 10.9 mg, 0.41% dry wt).

Extraction of *P. varicosa*. Four specimens (length: 5 cm each) were collected by hand using SCUBA (–6 to –9 m) off San Sebastian, Cebu, The Philippines, in April, 1990, and were stored in acetone (25 mL). The specimens were extracted exactly as described above to obtain a crude dichloromethane extract. The extract was subjected to flash chromatography on silica using an elution gradient from hexane to ethyl acetate. The fraction eluted with 9:1 hexane–ethyl acetate was rechromatographed by using HPLC on silica (95:5 hexane–ethyl acetate) to obtain 4α-isocyanogorgon-11-ene (**5**, 3.4 mg, 0.22% dry wt). The material eluting with ethyl acetate was purified by reversed-phase HPLC (C18 silica) using 8:1:1 methanol–acetone–water as eluent to obtain 4α-formamidogorgon-11-ene (**6**, 1.1 mg, 0.07% dry wt).

Extraction of *Halichondria* cf. *lendenfeldi*. A specimen of *H.* cf. *lendenfeldi* (29 g, collection no 88-604), which is a dark grey-green hispid rope sponge, was collected by hand using SCUBA from a marine lake in Palau (–2 m) in January, 1988, and was stored frozen (–18 °C) for 7 months. It was then thawed and soaked in methanol (2 × 300 mL). The methanol was evaporated under reduced pressure, and the resulting aqueous suspension was consecutively extracted with hexane, dichloromethane, and ethyl acetate. The organic extracts, which appeared very similar by TLC and had similar ^1H NMR spectra, were recombined, dried over Na_2SO_4 and evaporated to yield an oil, which was chromatographed on sephadex LH-20 (2:1:1 hexane–dichloromethane–methanol), following the separation by monitoring the UV absorbance at 254 nm. The UV-absorbing fractions were combined to give a nonpolar and a polar fraction. The nonpolar fraction was chromatographed on biobeads S-X8 (1:1 dichloromethane–acetonitrile) followed by flash chromatography and HPLC on silica (35:65 hexane–ethyl acetate) to obtain 3-isocyanotheonellin (**3**, 15.8 mg, 0.054% dry wt) and 3-isocyanobisabolane-8,10-diene (**8**, 4.5 mg, 0.016% dry wt). The polar fraction was chromatographed on biobeads S-X8 (1:1 dichloromethane–acetonitrile) followed by chromatography on Sephadex LH-20 (1:1 methanol–dichloromethane) and HPLC on silica (35:65 hexane–ethyl acetate) to yield 3-formamidotheonellin (**12**, 7.2 mg, 0.025% dry wt) and 3-formamidobisabolane-8,10-diene (**13**, 2.8 mg, 0.01% dry wt).

4α-Isocyanogorgon-11-ene (5): colorless oil; $[\alpha]_D$ –66.9° (*c* 1.6, $CHCl_3$); IR ($CHCl_3$) 3075, 2935, 2870, 2135, 1640, 1460, 1445, cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.97 (s, 3 H, Me-15), 1.20 (m, 1 H, H-1_{ax}), 1.22 (m, 1 H, H-9_{ax}), 1.34 (m, 1 H, H-9_{eq}), 1.38 (ddd, 1 H, *J* = 13.3, 3.2, 2.1 Hz, H-1_{eq}), 1.46 (br s, 3 H, Me-14), 1.49 (m, 2 H, H-8), 1.52 (m, 1 H, H-2_{ax}), 1.55 (m, 1 H, H-2_{eq}), 1.60 (m, 2 H, H-7), 1.64 (d, 1 H, *J* = 11.2 Hz, H-5), 1.82 (br s, 3 H, Me-13), 1.84 (dd, 1 H, *J* = 12.8, 5.6 Hz, H-3_{ax}), 2.04 (ddd, 1 H, *J* = 12.8, 2.3, 2.1 Hz, H-3_{eq}), 2.50 (ddd, 1 H, *J* = 11.2, 9.1, 3.3 Hz, H-6), 4.78 (dd, 1 H, *J* = 2.2, 1.0 Hz, H-12), 4.92 (d, 1 H, *J* = 2.2 Hz, H-12); ^{13}C NMR ($CDCl_3$) δ 154.6 (1:1:1 t, C-16), 147.9 (s, C-11), 113.5 (t, C- 12), 60.1 (1:1:1 t, C-4), 51.5 (d, C-5), 45.1 (2t, C-3, C-9), 44.3 (d, C-6), 41.41 (t, C-1), 34.9 (s, C-10), 33.6 (t, C-7), 21.6 (q, C-14), 20.9 (t, C-8), 20.2 (q, C-15), 19.4 (q, C-13), 18.2 (t, C-2); GCMS (20 eV) *m/z* (rel intensity) 231 (5), 216 (12), 204 (7), 189 (91), 135 (12), 109 (100); HREIMS, obsd *m/z* = 231.1985, $C_{16}H_{25}N$ requires *m/z* = 231.1987.

4α-Formamidogorgon-11-ene (6): white crystals, mp > 300 °C dec; $[\alpha]_D$ –61.8° (*c* 0.11, $CHCl_3$); IR ($CHCl_3$) 3005, 2935, 2875, 2855, 1655 cm^{-1}; ^1H NMR ($CDCl_3$, major isomer (δ 1.04 (s, 3 H, Me-15), 1.33 (s, 3 H, Me-14), 1.64 (s, 3 H, Me-13), 2.50 (ddd, 1 H, *J* = 11.5, 2.8 Hz, H-6), 4.74 (br s, 1 H, H-12), 4.87 (br s, 1 H, H-12), 5.74 (br s, 1 H, NH), 8.12 (d, 1 H, J = 12.3 Hz, H-16); ^{13}C NMR ($CDCl_3$, a major isomer) δ 161.8 (d), 150.4 (s), 112.4 (t), 57.1 (s), 55.7 (d), 45.4 (t), 44.5 (d), 42.8 (t), 41.5 (t), 35.7 (s), 33.9 (t), 21.1 (t), 20.7 (q), 20.3 (q), 18.6 (t), 18.0 (q); EIMS (70 eV) *m/z* (rel intensity) 249 (12), 234 (12), 204 (62), 189 (100), 163 (28), 109 (44), 98 (67); HREIMS, obsd *m/z* = 249.2093, $C_{16}H_{25}NS$ requires *m/z* = 249.2093.

4α-Isothiocyanatogorgon-11-ene (7): colorless oil; $[\alpha]_D$ –101.6° (*c* 0.5, $CHCl_3$); IR ($CHCl_3$) 3065, 2970, 2930, 2855, 2110, 1640, 1455, 1445 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.97 (s, 3 H, Me-15), 1.16 (m, 1 H, *J* = 12.7, 3.5 Hz, H-1_{ax}), 1.18 (m, 1 H, H-9_{ax}), 1.29 (m, 1 H, H-9_{eq}), 1.33 (m, 1 H, H-1_{eq}), 1.39 (s, 3 H, Me-14), 1.46–1.62 (m, 7 H), 1.65 (m, 1 H, H-3_{ax}), 1.75 (br s, 3 H, Me-13), 1.85 (m, 1 H, H-3_{eq}), 2.45 (ddd, 1 H, *J* = 11.2, 9.1, 3.5 Hz, H-6), 4.74 (dd, 1 H, *J* = 2.4, 1.2 Hz, H-12), 4.78 (d, 1 H, *J* = 2.4 Hz, H-12); ^{13}C NMR ($CDCl_3$) δ 149.8 (s), 111.1 (t), 60.8 (s), 54.1 (d), 45.3 (2t), 44.6 (d), 41.4 (t), 35.2 (s), 33.9 (t), 23.3 (q), 21.1 (t), 20.2 (q), 18.9 (t), 18.1 (q); EIMS (70 eV) *m/z* (rel intensity) 263 (8), 204 (17), 189 (30), 163 (60), 109 (80), 93 (50), 81 (100); HREIMS, obsd *m/z* = 263.1708, $C_{16}H_{25}NS$ requires *m/z* = 263.1708.

3-Isocyanobisabolane-8,10-diene (8): colorless oil; $[\alpha]_D$ –5.6° (*c* 0.2, $CHCl_3$); UV 246 nm (ε 11 100, sh), 237 (15 300), 230 (14 000, sh); IR ($CHCl_3$) 2990, 2965, 2945, 2860, 2140, 1660, 1615, 1460 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.97 (d, 3 H, *J* = 7.0 Hz, Me-14), 1.10–1.35 (m, 8 H), 1.40 (br s, 3 H, Me-13), 1.66 (m, 1 H), 1.71 (br s, 3 H, Me-12/15), 1.73 (br s, 3 H, Me-12/15), 2.02 (m, 1 H, *J* = 6.7 Hz, H-7), 5.33 (dd, 1 H, *J* = 14.8, 8.8 Hz, H-8), 5.75 (d, 1 H, *J* = 10.8 Hz, H-10), 6.14 (dd, 1 H, *J* = 14.9, 10.8 Hz, H-9); ^{13}C NMR ($CDCl_3$) δ 151.9 (br s, C-16), 135.8 (d, C-8), 133.4 (s, C-11), 126.1 (d, C-9/10), 124.9 (d, C-9/10), 57.0 (1:1:1 t, C-3), 40.8 (d, C-6/7), 40.6 (d, C-6/7), 37.5 (2t, C-2, C-4), 25.9 (q, C-12/13), 25.7 (q, C-13/12), 25.3 (t, C-1/15), 25.1 (t, C-1/5), 18.4 (q, C-14/15), 18.2 (q, C-14/15); EIMS (70 eV) *m/z* (rel intensity) 231 (18), 216 (8), 204 (12), 189 (12), 109 (100), 81 (66), 67 (83); HREIMS, obsd *m/z* = 231.1995, $C_{16}H_{25}N$ requires *m/z* = 231.1987.

3-Formamidobisabolane-8,10-diene (13): ^1H NMR ($CDCl_3$, 200 MHz) δ 1.02 (d, 1 H, *J* = 7 Hz), 1.33 (s, 1.5 H), 1.40 (s, 1.5 H), 1.65 (br s, 3 H), 1.79 (br s, 3 H), 5.2 (br, 0.5 H, NH), 5.40 (dd, 1 H, *J* = 15, 9 Hz), 5.7 (br, 0.5 H, NH), 5.80 (br d, 1 H, *J* = 11 Hz), 6.14 (dd, 1 H, *J* = 15, 11 Hz), 8.04 (br s, 0.5 H), 8.29 (d, 0.5 H, *J* = 12 Hz). [Compound decomposed before any other data could be recorded.]

Hydrolysis of Isonitrile 5. Glacial acetic acid (0.5 mL) was added dropwise over a period of 2 days to a solution of the isonitrile **5** (23 mg, 0.1 mmol) in ether (1 mL) until no more starting material was detected by TLC. The reaction mixture was diluted with ethyl acetate (10 mL), washed with saturated Na_2CO_3 solution (10 mL), and dried over $MgSO_4$, and the solvent was evaporated. The crude product was chromatographed by using HPLC (8:1:1 MeOH–H_2O–acetone) to yield the formamide **6** (8.6 mg, 35% theoretical), which was identical with the natural product in all respects.

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Supplementary Material Available: ^1H NMR spectra of 5-8 and 13 and ^{13}C NMR spectra of 5-8 (9 pages). Ordering information is given on any current masthead page.

Synthesis of 2-Aminobenzophenones via Rapid Halogen-Lithium Exchange in the Presence of a 2-Amino-*N*-methoxy-*N*-methylbenzamide

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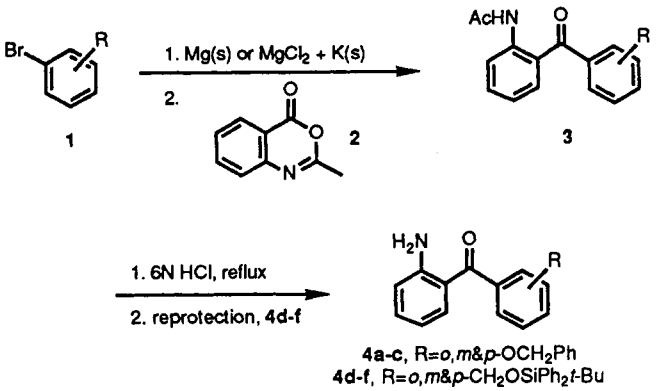
2-Aminobenzophenones are important precursors to 1,4-benzodiazepines.[1] The continued discovery of novel 1,4-benzodiazepines with new biological activities[2] makes versatile routes for the synthesis of 2-aminobenzophenones essential to further investigations of the structure-activity relationships of these seemingly ubiquitous receptor ligands.[3]

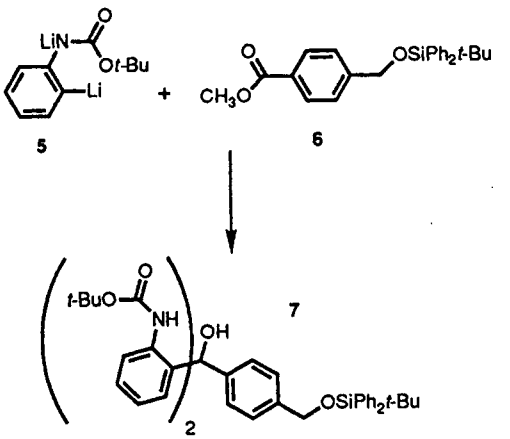
We were interested in preparing 2-aminobenzophenones of general structure **4** (Scheme I) as precursors to a novel series of 1,4-benzodiazepines. The initial approach to these compounds was based upon the route depicted in Scheme I.[4] There were two major drawbacks to this approach: (1) the formation of the requisite Grignard reagents in some cases were low yielding and highly irreproducible (even under the conditions described by Rieke[5]), giving at best a 50% yield of the desired adduct; (2) the silicon protecting groups that were desirable for protection of the benzyl alcohol functionality of **4d-f** were unstable toward the acidic hydrolysis required to deprotect the aniline nitrogen. In an attempt to combine a more reproducible anion-forming reaction and a facile nitrogen deprotection, the condensation of the anion of *N*-(*tert*-butoxycarbonyl)-aniline **5**[6] with methyl ester **6** was examined (Scheme II). However, overaddition of the aryllithium gave **7** as the major product. This result contrasts with the success of monoaddition of lithiopivaloylanilines to methyl benzoate.[4]

The problems encountered with the routes mentioned above, as well as considerations of availability of starting materials, led to the synthetic approach outlined in Scheme III. Reaction of isatoic anhydride (**8**) with *N,O*-dimethylhydroxylamine[7] followed by silica gel chromatography and distillation gave **9** in 75% yield.[8] When a 1:1 mixture of **9** and an aryl bromide (**1a-q**) is treated with 2 equiv of *n*-butyllithium at -78 to -100 °C, many of the desired 2-aminobenzophenones are produced directly in moderate to good yield in a matter of minutes (Table I). The reaction of **9** with **1a-c** has been carried out on up to a 0.1 mol scale with no dimunition in yield and, as anticipated, no products of overaddition are detected.[8] Advantages of this synthetic approach include (1) its brevity; (2) the ability to carry out the reaction without protection of the aniline nitrogen; (3) the ready availability of a large variety of aryl bromides; (4) the mild conditions and ease of workup relative to previous routes often involving high-temperature Friedal-Crafts reactions.[4] As noted in Table I the reaction fails in cases where there is an electrophilic substituent ortho to the incipient anion in the aryl bromides, in bromides containing an acidic hydrogen (even though 3 equiv of *n*-butyllithium was used), and for *o*-chloro- and *o*- and *p*-nitrobromobenzene. The diminished effectiveness of these substrates in this reaction may be due to the attenuation of the nucleophilicity of the derived anion since formation of the anions is expected to be facile.[9] If 1 equiv of *n*-butyllithium is used, very little product formation is detected by TLC. The reaction

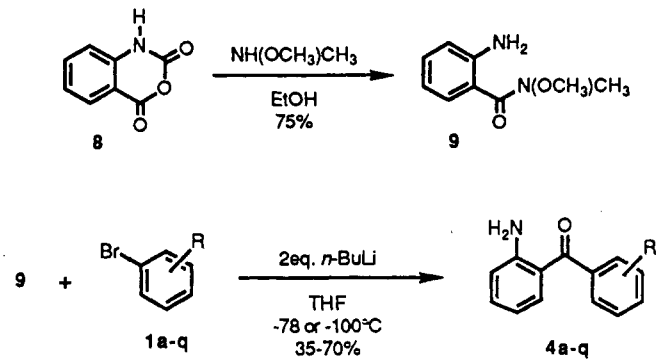
Scheme I



Scheme II



Scheme III



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