Sesquiterpene Thiocyanates and Isothiocyanates from *Axinyssa aplysinoides*

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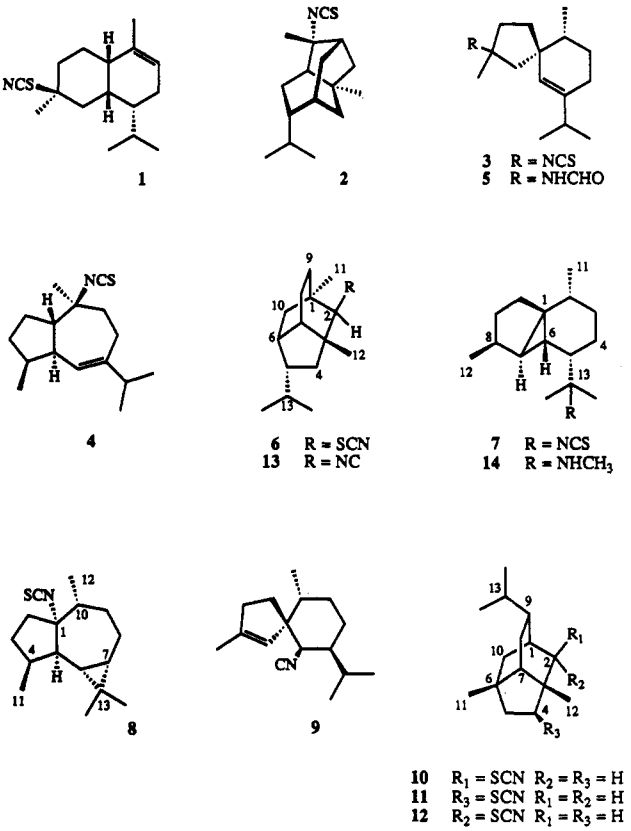
A speciment of *Axinyssa* (= *Trachyopsis*) *aplysinoides* from Palau contains (1*R**,2*R**,3*R**,5*R**,6*S**,7*S**)-2-thiocyanatopupukeanane (**6**) in addition to the metabolites previously reported. A specimen of *A. aplysinoides* from Pohnpei yielded two new isothiocyanates, (1*S**,2*R**,5*S**,6*S**,7*R**,8*S**)-13-isothiocyanatocubebane (**7**) and (1*R**,4*S**,5*R**,6*S**,7*S**,10*R**)-1-isothiocyanatoaromadendrane (**8**). A second specimen of *A. aplysinoides* from Pohnpei contained axisonitrile-3 (**9**) and (1*S**,2*S**,3*R**,6*R**,7*S**,9*R**)-2-thiocyanato*neo*pupukaenane (**12**), which has a different stereochemistry at C-2 to that assigned previously.

Although many marine sponges of the order Halichondrida produce sesquiterpene isonitriles, isothiocyanates, and formamides, the corresponding thiocyanates have rarely been encountered.[1] In 1989, we reported the first example of a sesquiterpene thiocyanate, (1*S**,4*S**,6*S**,7*R**)-4-thiocyanato-9-cadinene (**1**), from a Palauan specimen of *Axinyssa* (= *Trachyopsis*)[2] *aplysinoides*.[3] The same sponge also contained three sesquiterpene isothiocyanates, **2**–**4**, and a sesquiterpene formamide, **5**. Reinvestigation of the same sponge has yielded a second thiocyanate, (1*R**,2*R**,3*R**,5*R**,6*S**,7*S**)-2-thiocyanatopupukeanane (**6**), as a minor metabolite. A specimen of *A. aplysinoides* from Pohnpei yielded two new isothiocyanates, (1*S**,2*R**,5*S**,6*S**,7*R**,8*S**)-13-isothiocyanatocubebane (**7**) and (1*R**,4*S**,5*R**,6*S**,7*S**,10*R**)-1-isothiocyanatoaromadendrane (**8**). Recently, Pham et al. reported the isolation of axisonitrile-3 (**9**) and 2-thiocyanato*neo*pupukaenane (**10**) from an unidentified sponge from Pohnpei, and 4-thiocyanato*neo*pupukaenane (**11**) and 2-thiocyanato*neo*pupukaenane (**10**) from *Phycopsis terpnis* from Okinawa.[4] We have examined a second specimen of *A. aplysinoides* from Pohnpei and have isolated axisonitrile-3 (**9**) and a thiocyanate to which we have assigned the structure (1*S**,2*S**,3*R**,6*R**,7*S**,9*R**)-2-thiocyanato*neo*pupukaenane (**12**).

(1*R**,2*R**,3*R**,5*R**,6*S**,7*S**)-2-Thiocyanatopupukeanane (**6**) was isolated as a colorless oil of molecular formula $C_{16}H_{25}NS$. The sharp IR band of medium intensity at 2150 cm^{-1} and a ^{13}C NMR signal at δ 115.4 (s)[5] were characteristic of a thiocyanate rather than an isothiocyanate functionality. Since the ^{13}C NMR spectrum did not contain any olefinic signals, the hydrocarbon skeleton attached to the thiocyanate must be tricyclic. The NMR data for the hydrocarbon portion of the molecule were similar to those of 2-isocyanopupukeanane (**13**).[6] A detailed analysis of the COSY spectra in both $CDCl_3$ and acetone-d_6 confirmed this assignment. The H-4 and H-4′ methylene signals at δ 1.76 (dd, 1 H, J = 14, 9.7 Hz) and 0.87 (dd, 1 H, J = 14, 8.6 Hz) were coupled to the H-5 signal at 1.14 (m, 1 H), that was in turn coupled to the H-6 signal at 1.71 (m, 1 H) and the H-13 signal at 1.24 (m, 1 H). The H-13 signal was coupled to two methyl signals at δ 0.76 (d, 3 H, J = 6.5 Hz) and 0.75 (d, 3 H, J = 6.5 Hz), and these signals were assigned to a terminal isopropyl group. The H-6 signal was coupled to the H-7 signal at δ 0.95 (br d, 1 H, J = 5 Hz) and to the H-10 and H-10′ methylene signals at 1.06 (m, 1 H) and 0.97 (m, 1 H). The >C(7)C(8)H_2C(9)H_2– moiety was clearly observed in the COSY spectra. The remaining signals in the ^1H NMR spectrum are two quaternary methyl signals at δ 1.18 (s, 3 H) and 0.86 (s, 3 H), and a signal at 2.99 (d, 1 H, J = 2 Hz), that was assigned to the proton adjacent to the thiocyanate group (H-2). The H-2 signal was *W*-coupled to the H-9′ signal at 0.81, and the H-9 signal was *W*-coupled to the H-10′ signal; these *W*-couplings are typical of a bicyclo[2.2.2]-octane ring system. A series of NOEDS experiments provided confirmation of the pupukaenane ring system and defined the stereochemistry at C-2 and C-5. Irradiation of the H-2 signal resulted in enhancement of the H-4′ signal, irradiation of the Me-12 signal caused enhancement of the H-4 signal, and irradiation of the H-4 signal produced an enhancement of the H-5 signal.



(**1**S*,2R*,5S*,6S*,7R*,8S*)-13-Isothiocyanatocubebane (**7**) is an isomer of thiocyanate **6**. The strong, broad IR band at 2120 cm^{-1} and the weak ^{13}C NMR signal at δ 128.8 were typical of an isothiocyanate group, the presence of

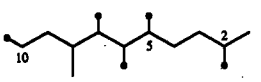
(1) Faulkner, D. J. *Nat. Prod. Rep.* **1991**, *8*, 97 and previous reviews.
(2) *Trachyopsis aplysinoides* has recently been reclassified as *Axinyssa aplysinoides* (Dendy, 1922). Van Soest, R. W. M.; Diaz, M. C.; Pomponi, S. A. *Beaufortia* **1990**, *40*, 27.
(3) He, H.; Faulkner, D. J.; Shumsky, J. S.; Hong, K.; Clardy, J. *J. Org. Chem.* **1989**, *54*, 2511.
(4) Pham, A. T.; Ichiba, T.; Yoshida, W. Y.; Scheuer, P. J.; Uchida, T.; Tanaka, J.; Higa, T. *Tetrahedron Lett.* **1991**, *32*, 4843.
(5) Pretsch, E.; Seibl, J.; Simon, W.; Clerc, T. *Tables of Spectral Data for Structure Determination of Organic Compounds*; Springer-Verlag: Berlin, 1983; p c200.
(6) Hagadone, M. R.; Burreson, B. J.; Scheuer, P. J.; Finer, J. S.; Clardy, J. *Helv. Chim. Acta* **1979**, *62*, 2484.

0022-3263/92/1957-3191$03.00/0

Table I. ^{1}H NMR Data (360 MHz) for Thiocyanate 6 (4:1 C_6D_6–$CDCl_3$), Isothiocyanate 7 ($CDCl_3$), and Isothiocyanate 8 ($CDCl_3$)

H No.	6 [δ(mult, J in Hz)]	7 [δ(mult, J in Hz)]	8 [δ(mult, J in Hz)]
2	2.99 (d, 2.2)	2.05 (br dq, 7.2, 6.8)	1.92 (m)
			2.08 (m)
3		1.28 (br d, 15)	1.36 (m)
		1.40 (m)	1.94 (m)
4	0.87 (dd, 14, 8.6)	0.91 (m)	2.47 (m)
	1.76 (dd, 14, 9.7)	1.40 (m)	
5	1.14 (m)	1.85 (dt, 12, 4)	1.90 (m)
6	1.71 (m)	0.88 (t, 4)	0.22 (dd, 11.9, 8.6)
7	0.95 (br d, 5)	1.12 (t, 4)	0.61 (ddd, 12.3, 8.6, 5.4)
8	1.34 (m)	2.25 (m)	1.25 (m)
	1.38 (m)		1.75 (m)
9	0.81 (m)	0.75 (m)	1.57 (m, 2 H)
	1.16 (m)	1.54 (m)	
10	0.97 (m)	1.68 (m, 2 H)	2.23 (dqd, 11, 7, 5)
	1.06 (m)		
11	0.86 (s, 3 H)	0.86 (d, 3 H, 6.8)	0.97 (d, 3 H, 6.8)
12	1.18 (s, 3 H)	1.03 (d, 3 H, 6.5)	1.00 (d, 3 H, 6.8)
13	1.24 (m)		
14	0.76 (d, 3 H, 6.5)	1.44 (s, 3 H)	1.03 (s, 3 H)
15	0.75 (d, 3 H, 6.5)	1.45 (s, 3 H)	0.99 (s, 3 H)

which was confirmed by lithium aluminum hydride reduction of 7 to the corresponding methylamino derivative 14. The presence of two methyl signals in the ^{1}H NMR spectrum at δ 1.44 (s, 3 H) and 1.43 (s, 3 H) and a strong fragment peak in the mass spectrum at m/z 163 [M^+ – $C(CH_3)_2NCS$, 100] indicated that the isothiocyanate was attached to an isopropyl group. With the exception of the two isopropyl methyl signals, all of the remaining signals in the ^{1}H NMR spectrum could be assigned to a single fragment a on the basis of the COSY and XHCORR experiments (see Table I). A COLOC experiment revealed long-range correlations between the H-5 and both the C-14 and C-15 signals, indicating that the isopropyl group was attached at C-5. The bonds from C-2, C-6, C-7, and C-10 must all therefore be joined to the remaining quaternary carbon atom forming the cubebane carbon skeleton.



fragment a

The stereochemistry about the tricyclic ring system was defined by a series of NOEDS experiments. In the most important of these, the H-7 signal was significantly enhanced by irradiation of either the Me-11 or H-8 signals. The methyl group must be axial to the six-membered ring and H-7 must be cis to the six-membered ring. The axial stereochemistry of H-5 was apparent from the large coupling constant (J = 12 Hz) to H-4_{ax}. These data define the structure of (1*S**,2*R**,5*S**,6*S**,7*R**,8*S**)-13-isothiocyanatocubebane (7).

(1*R**,4*S**,5*R**,6*S**,7*S**,10*R**)-1-Isothiocyanatoaromadendrane (8) was isolated as a colorless oil of molecular formula $C_{16}H_{25}NS$, isomeric with thiocyanate 6 and isothiocyanate 7. The strong IR band at 2110 cm^{-1} was again indicative of an isothiocyanate group, but the isothiocyanate signal in the ^{13}C NMR spectrum was too weak to observe. However, the presence of a signal at δ 74.5 (s) indicated that the isothiocyanate group was attached to a quaternary carbon. The ^{1}H NMR spectrum contained two mutually coupled signals at δ 0.22 (dd, 1 H, J = 11.9, 8.6 Hz) and 0.61 (ddd, 1 H, J = 12.3, 8.6, 5.4 Hz) that were due to cis-oriented cyclopropyl protons. Interpretation of the COSY spectrum showed that all signals except two methyl singlets at δ 0.99 (s, 3 H) and 1.03 (s, 3 H) were located in a single fragment that was assigned to an aromadendrane carbon skeleton with the isothiocyanate group at C-1. The large coupling (J = 11.9 Hz) between H-5 and H-6 indicated a trans-diaxial stereochemistry. Irradiation of the H-10 signal at δ 2.23 (dqd, 1 H, J = 11, 7, 5 Hz) caused small but significant enhancements of the H-6 (2.6%), H-7 (2.4%), and H-2 (3.1%) signals, indicating that H-10 must be on the same side of the seven-membered ring as H-6 and H-7 and that the ring junction must be cis with both the isothiocyanate group and H-5 being on the opposite side of the ring. The stereochemistry of C-4 was defined by the observation of an enhancement of H-5 on irradiation of the H-4 signal.

(1*S**,2*S**,3*R**,6*R**,7*S**,9*R**)-2-Thiocyanato*neo*pupukaenane (12) has the molecular formula $C_{16}H_{25}NS$, which requires five unsaturation equivalents. The sharp IR band of medium intensity at 2150 cm^{-1}, and a ^{13}C NMR signal at δ 112.9 (s) indicated the presence of a thiocyanate group. In addition to the thiocyanate signal, the ^{13}C NMR spectrum contained four methyl, four methylene, five methine, and two quaternary carbon signals, all of which are in the aliphatic region of the spectrum. The thiocyanate must therefore be tricyclic. The ^{1}H NMR spectrum in benzene-d_6 contained four methyl signals at δ 0.85 (s, 3 H, H-12), 0.78 (s, 3 H, H-11), 0.75 (d, 3 H, J = 6.5 Hz, H-15), and 0.67 (d, 3 H, J = 6.5 Hz, H-14); the latter two signals were both coupled to a signal at 1.13 (m, 1 H, H-13) and were assigned to an isopropyl group. The presence of a ^{1}H NMR signal at δ 3.06 (br s, 1 H, H-2) and a ^{13}C NMR signal at 64.3 (d, C-2) indicated the presence of a secondary thiocyanate. The HMQC experiment showed that the methylene proton signals were at δ 1.51 (ddd, 1 H, J = 14, 8.2, 5 Hz, H-4) and 0.99 (m, 1 H, H-4′), 1.37 (ddd, 1 H, J = 14.5, 11.5, 1.5 Hz, H-8) and 0.92 (ddd, 1 H, J = 14.5, 5.5, 3 Hz, H-8′), 1.20 (ddd, 1 H, J = 14, 4, 1.5 Hz, H-10) and 1.14 (m, 1 H, H-10′), and 1.13 (m, 2 H, H-5).

The tricyclic ring system was established as follows. In the COSY spectrum, the H-2 signal at δ 3.06 (br s, 1 H) was coupled to a signal at 1.81 (br dt, 1 H, J = 3.6, 2.5 Hz, H-1); this must be a vicinal coupling (as opposed to a long-range coupling) because irradiation of the signal at 3.06 caused a strong nuclear Overhauser enhancement of the signal at 1.81. A similar rationale indicated a vicinal coupling between the H-1 and H-9 signals. The COSY spectrum indicated that the H-8 and H-8′ methylene signals at δ 1.37 and 0.92 were both coupled to two methine proton signals at 0.55 (m, 1 H, H-7) and 0.53 (t, 1 H, J = 7 Hz, H-9). In the HMBC experiment (J = 8 Hz), the H-12 methyl signal at δ 0.85 showed long-range couplings to the C-2, C-3, C-4, and C-7 carbon signals, allowing a six-membered ring to be defined. The H-4 signals at δ 1.51 and 0.99 were coupled to the H-5 signals at 1.13. In the HMBC spectrum, the H-11 methyl signal at δ 0.78 showed long-range couplings to the C-5, C-6, C-7, and C-10 carbon signals, which defined a second five-membered ring. The H-10 signals at δ 1.20 and 1.14 were coupled to the H-1 signal at 1.81 and the C-10 signal showed a 3-bond coupling to the H-2 signal at 3.06. These data defined the third, six-membered ring. A weak coupling between H-9 and H-13 in the COSY spectrum indicated the position of the isopropyl group. These data established the *neo*pupukaenane ring system.[7]

The stereochemistry of the thiocyanate group was es-

(7) Karuso, P.; Poiner, A.; Scheuer, P. J. *J. Org. Chem.* **1989**, *54*, 2095.

tablished by the observation of *W*-couplings and by nuclear Overhauser effect difference spectroscopy. The COSY spectrum contained a cross-peak for a *W*-coupling (J = 1.5 Hz) between the H-2 signal and the H-10 signal at δ 1.20. Irradiation of the H-2 signal caused enhancements of the H-1, H-9, and Me-12 signals; the corresponding interatomic distances calculated using PCModel are 2.54, 2.15, and ca. 2.41 Å. The stereochemistry at C-2 is opposite to that determined by Pham et al.[4] Comparison of the ^{13}C NMR spectrum and the ^1H NMR spectrum of **12** in $CDCl_3$ with an authentic spectrum of 2-thiocyanato*neo*pupukaenane (**10**) showed that the two compounds are identical.[8] We therefore suggest that the stereochemistry reported by Pham et al. be revised on the basis of interpretation of the spectral data recorded in benzene-d_6, in which the signals are better dispersed.[9]

Although all three sponges were identified taxonomically as *A. aplysinoides*, they were separated in the field because of slight differences in morphology and color. It is significant that two of the three specimens contained sesquiterpene thiocyanates, which are rare in comparison with isothiocyanates or isonitriles, and it is also comforting to find more examples of this group. The biosynthesis of sesquiterpene thiocyanates cannot be accommodated by the mechanisms proposed for the similar isonitriles and isothiocyanates,[10] and it therefore seems reasonable to propose that the C_1 unit in these molecules might be derived from an immediate precursor containing both sulfur and nitrogen.

Experimental Section

Extraction and Isolation. The first specimen of *A. aplysinoides* (85-065) was collected in Palau (−20 m) and immediately frozen. The freeze-dried sponge tissue (19.8 g) was exhaustively extracted with hexane/EtOAc (7:3). The extract was filtered, and the solvent removed under reduced pressure. The residual brown oil (0.6 g) was chromatographed on silica gel, eluting with a solvent gradient from hexane to ethyl acetate. The hexane fraction gave a mixture of isothiocyanates. Repeated separation by HPLC (hexane/Et_2O, 98:2) afforded isothiocyanates **2** (15 mg), **3** (6 mg), and **4** (13 mg). The hexane/EtOAc (98:2) fraction contained a mixture of thiocyanates that was further separated by HPLC (hexane/Et_2O, 98:2) to obtain thiocyanate **2** (25 mg) and (1*R**,2*R**,3*R**,5*R**,6*S**,7*S**)-2-thiocyanatopupukeanane (**6**, 5 mg, 0.025% dry wt). The hexane/EtOAc (7:3) fraction gave formamide **5** (35 mg), after purification by HPLC (hexane/EtOAc, 4:6).

The second specimen of *A. aplysinoides* (89–026) was collected at Ant Atoll, Pohnpei (−20 m). The frozen sponge tissue (25 g dry wt) was extracted exhaustively with methanol. The combined extract was evaporated to obtain an aqueous suspension that was partitioned between water and ethyl ether. The organic layer was separated, dried over Na_2SO_4, and evaporated to yield a light brown oil (2.4 g). A portion of the oil (1.5 g) was chromatographed on silica gel using a mixed solvent gradient from hexane to ethyl acetate as eluent. The hexane/EtOAc (99:1) fraction gave a mixture of isothiocyanates after purification by HPLC (hexane/EtOAc, 99:1). Repeated fractionation of the mixture by reversed-phase HPLC on a Dynamax C_{18} column (MeOH/H_2O, 99:1) yielded the known compounds, epipolasin-A (8 mg, 0.051% dry wt) and epipolasin-B[11] (6 mg, 0.038% dry wt), and (1*S**,2*R**,5*S**,6*S**,7*R**,8*S**)-13-isothiocyanatocubebane (**7**, 31 mg, 0.20% dry wt) and (1*R**,4*S**,5*R**,6*S**,7*S**,10*R**)-1-isothiocyanatoaromadendrane (**8**, 2.5 mg, 0.016% dry wt).

The third specimen of *A. aplysinoides* (89–095, 101 g dry wt) was collected in Mutok Harbor, Pohnpei, and immediately frozen. The frozen sponge was sliced and extracted with methanol. The methanolic extract was filtered and the solvent removed under reduced pressure. The residue was partitioned between water and, successively, hexane, dichloromethane, and ethyl acetate. The hexane-soluble (328 mg) and dichloromethane-soluble (250 mg) materials (578 mg) were chromatographed on silica gel columns using mixtures of hexane and ethyl acetate in increasing polarity as eluants. Selected fractions were combined, and after successive HPLC separations on Partisil (hexane/EtOAc, 95:5) and Dynamax C_{18} (MeOH/H_2O, 97:3), axisonitrile-3 (**9**, 28 mg, 0.028% dry wt) was isolated. Further fractionation on a Dynamax C_{18} column (MeOH/CH_3CN/H_2O, 47:47:6) afforded (1*S**,2*S**,3*R**,6*R**,7*S**,9*R**)-2-thiocyanato*neo*pupukaenane (**12**, 14 mg, 0.014% dry wt).

(1*R,2*R**,3*R**,5*R**,6*S**,7*S**)-2-Thiocyanatopupukeanane (6)**: colorless oil; $[\alpha]_D$ +5.8° (c = 0.5, $CHCl_3$); IR ($CHCl_3$) 2150 cm^{-1} (sharp, medium intensity); ^1H NMR, see Table I; ^{13}C NMR (50 MHz, $CDCl_3$) δ 115.4 (s), 74.2 (d), 50.1 (t), 49.5 (d), 44.7 (d), 44.3 (s), 38.2 (d), 34.8 (t), 33.1 (s), 29.3 (d), 28.2 (t), 27.2 (q), 25.1 (q), 21.7 (q), 21.6 (q), 17.4 (t); EIMS obsd m/z 263.1691 ($C_{16}H_{25}NS$ requires m/z 263.1708), 205 (M − SCN, 100).

(1*S,2*R**,5*S**,6*S**,7*R**,8*S**)-13-Isothiocyanatocubebane (7)**: colorless oil; $[\alpha]_D$ −19.9° (c = 1.1, $CHCl_3$); UV (MeOH) 242 nm (ϵ 1277); IR ($CHCl_3$) 2120 cm^{-1} (broad, strong); ^1H NMR see Table I; ^{13}C NMR (50 MHz, $CDCl_3$) δ 128.8 (br s), 65.0 (s), 45.6 (d), 35.7 (d), 34.0 (t), 32.9 (s), 30.4 (t), 29.1 (t), 27.8 (q), 27.5 (d), 27.1 (d), 26.9 (q), 18.6 (q), 17.9 (q), 17.1 (d), 16.2 (t); EIMS obsd m/z 263.1724, $C_{16}H_{25}NS$ requires m/z 263.1708.

(1*R,4*S**,5*R**,6*S**,7*S**,10*R**)-1-Isothiocyanatoaromadendrane (8)**: colorless oil; $[\alpha]_D$ +128.0° (c = 0.24, $CHCl_3$); UV (MeOH) 242 nm (ϵ 1226); IR ($CHCl_3$) 2110 cm^{-1} (broad, strong); ^1H NMR see Table I; ^{13}C NMR (50 MHz, $CDCl_3$) δ 74.5 (s), 51.2 (d), 39.3 (d), 38.9 (d), 35.8 (d), 30.5 (t), 30.3 (t), 28.6 (q), 23.5 (d), 22.9 (d), 20.0 (t), 18.6 (s), 17.5 (q), 15.8 (q), 15.4 (q); EIMS obsd m/z = 263.1713, $C_{16}H_{25}NS$ requires m/z 263.1708.

(1*S,2*S**,3*R**,6*R**,7*S**,9*R**)-2-Thiocyanato*neo*-pupukaenane (12)**: oil; $[\alpha]_D$ −71.5° (c = 0.5, $CHCl_3$); IR ($CHCl_3$) 2150 cm^{-1} (sharp, medium intensity); ^1H NMR (500 MHz, benzene-d_6) see Table II; ^{13}C NMR (50 MHz, $CDCl_3$) see Table II; HRFABMS obsd m/z 262.1619 ($C_{16}H_{24}NS$ (M^+ − 1) requires 262.1629), 205 (M − SCN, 100).

13-(Methylamino)cubebane (14). LAH (8 mg) was added to a solution of isothiocyanate **7** (6.7 mg) in dry THF (0.5 mL) and the solution was stirred for 8 h. Water (ca. 1 mL) was added to destroy excess reagent, and the reaction product was extracted with EtOAc (2 × 1 mL). The organic layer was dried over an-

Table II. ^{13}C (50 MHz, Benzene-d_6), ^1H NMR (500 MHz, Benzene-d_6), and HMBC (J = 8 Hz) Data for (1*S,2*S**,3*R**,6*R**,7*S**,9*R**)-2-Thiocyanato*neo*pupukaenane (12)**

C No.	^{13}C [δ(mult)]	^1H [δ(mult, J in Hz)]	long-range correlations
1	35.6 (d)	1.81 (br s)	
2	64.3 (d)	3.06 (br s)	C-1, C-4, C-9, C-10, C-12, C-16
3	44.7 (s)		
4	33.6 (t)	0.99 (m)	C-2, C-5, C-12
		1.51 (ddd, 14, 8, 5)	C-2, C-3, C-6, C-7
5	40.6 (t)	1.13 (m, 2 H)	C-4, C-7, C-10
6	39.2 (s)		
7	50.9 (d)	0.53 (t, 3)	
8	21.9 (t)	0.92 (ddd, 14.5, 5, 3)	C-3, C-13
		1.37 (ddd, 14.5, 11, 3)	
9	44.6 (d)	0.55 (m)	
10	32.5 (t)	1.14 (m)	C-5, CH11
		1.20 (ddd, 14, 4, 1.5)	C-2, C-11
11	26.1 (q)	0.78 (s, 3 H)	C-5, C-6, C-7, C-10
12	26.3 (q)	0.85 (s, 3 H)	C-2, C-3, C-4, C-7
13	32.4 (d)	1.13 (m)	
14	20.1 (q)	0.67 (d, 3 H, 6.5)	C-9, C-13, C-15
15	20.7 (q)	0.76 (d, 3 H, 6.5)	C-9, C-13, C-14
16	112.9 (s)		

(8) We thank Professor Paul Scheuer for providing the ^1H and ^{13}C NMR spectra of 2-thiocyanatopupukaenane.

(9) We were unable to differentiate several of the overlapping signals in the ^1H NMR spectrum run in $CDCl_3$ solution and therefore chose to examine the benzene-d_6 solution data.

(10) Hagadone, M. R.; Scheuer, P. J.; Holm, A. *J. Am. Chem. Soc.* **1984**, *106*, 2447. Garson, M. J. *J. Chem. Soc., Chem. Commun.* **1986**, 35. Garson, M. J. *Nat. Prod. Rep.* **1989**, *6*, 143.

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hydrous Na_2SO_4 and the solvent evaporated to obtain a white residue that was passed through a small silica gel column in hexane/EtOAc (1:1) to obtain the amine **14** (5.6 mg): ^1H NMR (360 MHz, $CDCl_3$) δ 2.31 (s, 3 H), 2.23 (m), 2.03 (br dq, J = 6.5, 6.5 Hz), 1.77 (dq, J = 12.2, 3.6 Hz), 1.66 (m, 2 H), 1.56 (m), 1.40 (m), 1.26 (m), 1.24 (m), 1.09 (s, 3 H), 1.03 (s, 3 H), 1.02 (m), 1.00 (d, 3 H, J = 6.5 Hz), 0.83 (d, 3 H, J = 6.8 Hz), 0.81 (m), 0.77 (m, 2 H); EIMS m/z 235 (M^+, 7).

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Supplementary Material Available: IR and NMR spectra of **6-8**, **12**, and **14** (16 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

Stereocontrolled Total Synthesis of the Unnatural Enantiomers of Castanospermine and 1-*epi*-Castanospermine

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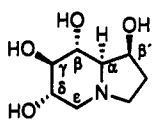
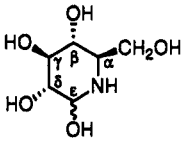
A concise practical synthesis (13 steps, ca. 10-12% overall yield) of the unnatural enantiomer of castanospermine ((-)-1) and its 1-epimer **2** from 2,3,4-tri-*O*-benzyl-D-xylose (**3**) is described. Key steps in the synthesis are two organometal aldehyde additions, vinylation of **3** to **4** and allylation of **6a** to **11**, both of which proceed with a considerably high degree of stereocontrol. The fused ring system is generated from the acyclic amino polyol derivative **16a** by two successive S_N2-type cyclizations. Notably, the annulation of the six-membered ring makes use of tetravalent phosphonium reagents (Appel or Mitsunobu type) which cyclize the amino alcohol **22a/b** directly to **23a/b** without need for N-deprotection and O-activation manipulations.

Introduction

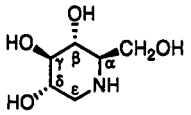
Castanospermine (+)-1, a tetrahydroxylated indolizidine alkaloid, can be isolated in appreciable amounts from the tropical trees Castanospermum australe[1] and Alexa Leiopetale,[2] respectively. The compound has attracted considerable interest due to its high anticancer,[3] antiviral,[4] and antiretroviral[5] activities. (+)-1 is a potent inhibitor for various α- and β-glucosidases[6] (including those involved in the processing of glycoproteins) similar to nojirimycin and 1-deoxynojirimycin,[7] whereas it is ineffective toward α- and β-galactosidases and α-mannosidases. Possibly this specifity is connected with the substitution pattern of the α-δ-region, which is quite similar to that in nojirimycin, 1-deoxynojirymicin, and D-glucose itself and may serve as a recognition pattern in the substrate-enzyme interaction. In this connection a change of these crucial configurations



Castanospermine (+)-1



Nojirimycin



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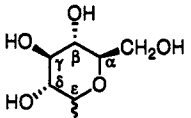
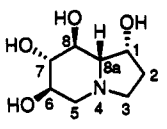
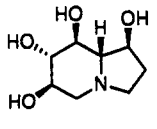


D-Glucose



(-)-1



2

† Preparative work.

‡ Crystal structure analysis of compound **23b**.

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