The Absolute Configuration of Axinellamine A, a Pyrrole Alkaloid of the Marine Sponge *Axinella* sp., was Determined as *R* by Synthesizing Its (*S*)-Isomer

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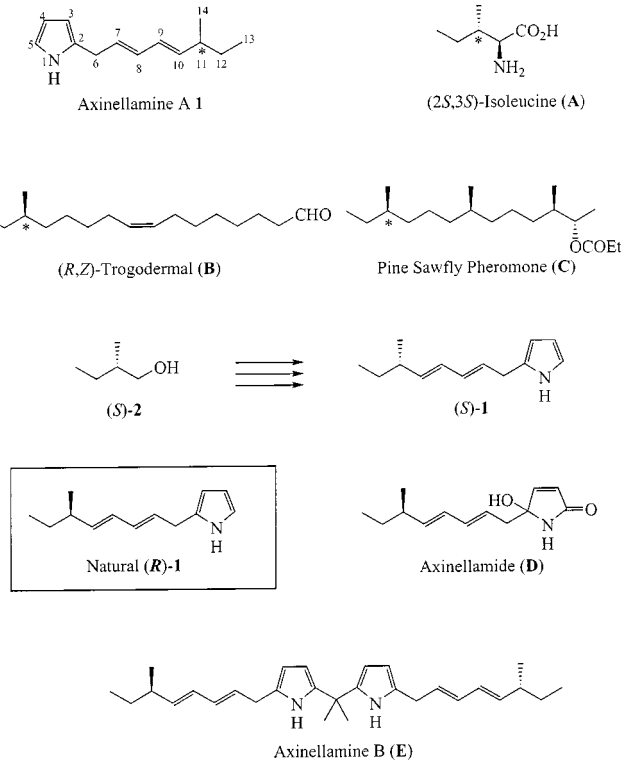
(*S*)-(+)-Axinellamine A [(2*E*,4*E*,6*S*)-2-(6-methyl-2,4-octadienyl)pyrrole, **1**] was synthesized by starting from (*S*)-(−)-2-methylbutan-1-ol and pyrrole. The absolute configuration of the naturally occurring (−)-axinellamine A, a metabolite of the marine sponge *Axinella* sp., was therefore determined as *R*.

Introduction

In 1998, Tinto, Reynolds and their respective co-workers isolated (−)-axinellamine A from the Caribbean marine sponge *Axinella* sp., and assigned its structure as **1** mainly on the basis of its NMR analysis, although its absolute configuration remained unknown.[1] We became interested in clarifying it, because we have been engaged in the determination of the absolute configuration of various natural products with a *sec*-butyl group since 1973.[2] (+)-Isoleucine (**A**) as well as optically active (−)-amyl alcohol (2-methylbutan-1-ol, **2**) in fusel oil are known to possess an *S* configuration. On the other hand, insect pheromones such as trogodermal (**B**),[2,3] the dermestid beetle pheromone, and the pine sawfly pheromone (**C**)[4] possess an *R* configuration at the asterisked stereogenic center. This paper reports the synthesis of (*S*)-(+)-axinellamine A (**1**) starting from (*S*)-(−)-2-methylbutan-1-ol (**2**). Our result implies that the levorotatory marine natural product must be (*R*)-axinellamine A (**1**). The two congeners of **1**, which were also isolated from the same sponge *Axinella* sp., may possess the same *R* absolute configuration. It is thus highly probable that both axinellamide (**D**)[5] and axinellamine B (**E**)[1] possess the *R* configuration, as shown in Scheme 1.



Scheme 1. Structure of axinellamine A and related compounds

Results and Discussion

Our synthesis of (*S*)-axinellamine A (**1**) started from pyrrole, as summarized in Schemes 2 and 3. Pyrrole was converted into the *N*-*tert*-butoxycarbonyl (Boc)-protected ester **3**[6] by homolytic substitution with a radical generated from ethyl iodoacetate in the presence of iron(II) sulfate and hydrogen peroxide in DMSO,[7] followed by *N*-protection with Boc_2O.[8] Reduction of **3** with diisobutylaluminum hydride (DIBAL) in dichloromethane afforded the unstable aldehyde **4**, whose chain-elongation under standard Horner−Wadsworth−Emmons conditions[9] gave the α,β-unsaturated ester **5** in 63% yield based on **3**. DIBAL reduction of **5** furnished the allylic alcohol **6**, which was oxidized with manganese(IV) oxide to furnish the α,β-unsaturated aldehyde **7**. It should be added that the use of the *p*-methoxybenzyl (PMB) protective group instead of the Boc group failed due to the difficulty in removing the PMB group without damaging the product.

As for the olefin formation reaction to give **1**, we employed Kocieński's *E*-selective olefination based on the condensation of aldehyde **7** with metallated 1-phenyl-1*H*-tetrazol-5-yl sulfone.[10,11] Accordingly, as shown in Scheme 3, (*S*)-2-methylbutan-1-ol (**2**) was coupled with 1-phenyl-1*H*-tetrazole-5-thiol (**8**) in the presence of triphenylphosphane and diisopropyl azodicarboxylate (DIAD) to give sulfide (*S*)-**9**. Oxidation of (*S*)-**9** with hydrogen peroxide in the presence of ammonium molybdate[12] furnished sulfone (*S*)-

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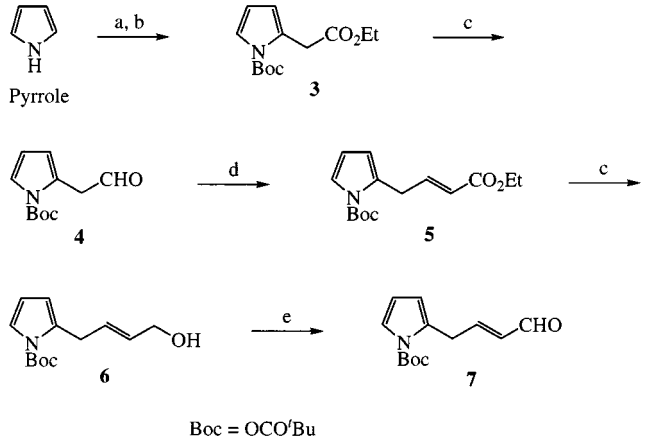
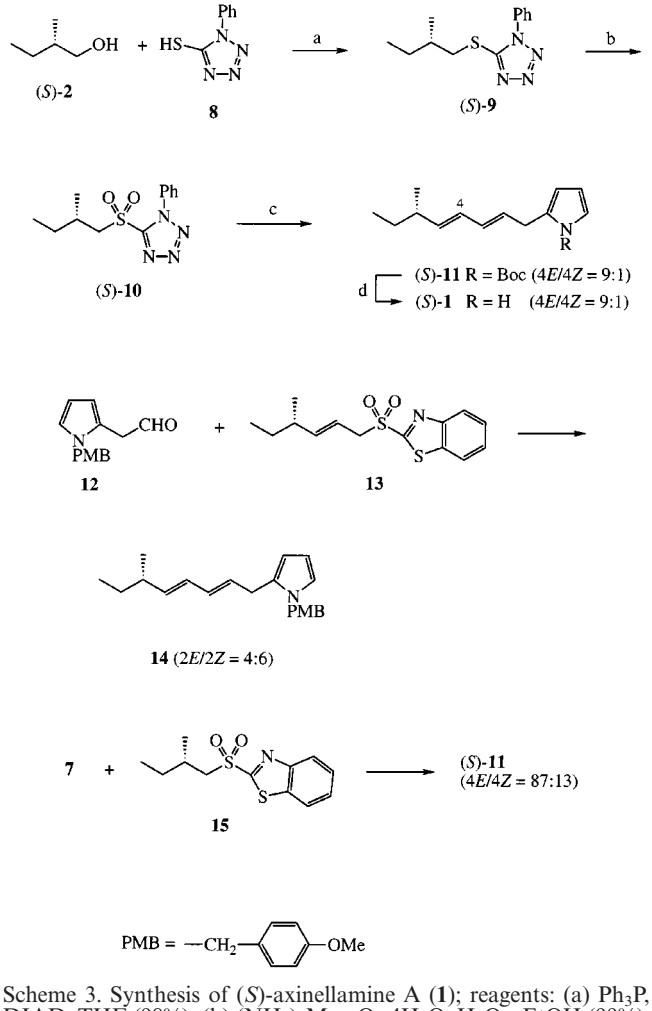


Scheme 2. Synthesis of the achiral building block **7**; reagents: (a) ICH_2CO_2Et, $FeSO_4 \cdot 7H_2O$, H_2O_2, DMSO (72%); (b) $(Boc)_2O$, DMAP, MeCN (93%); (c) DIBAL, CH_2Cl_2; (d) $(EtO)_2P(O)CH_2CO_2Et$, NaH, THF (63% based on **3**); (e) MnO_2, $CHCl_3$



Scheme 3. Synthesis of (*S*)-axinellamine A (**1**); reagents: (a) Ph_3P, DIAD, THF (98%); (b) $(NH_4)_6Mo_{24}O_7 \cdot 4H_2O$, H_2O_2, EtOH (99%); (c) LDA, THF, then **7** (58% based on **5**); (d) NaOMe, MeOH/THF (90%)

10. The anion generated from (*S*)-**10** by treatment with lithium diisopropylamide (LDA) was allowed to react with aldehyde **7** to give, in 58% yield based on **5**, the *N*-Boc-protected (*S*)-axinellamine A (**11**). This was shown to be a 9:1 mixture of **11** and its 4*Z*-isomer as revealed by its ^1H NMR analysis. Use of 3-benzothiazolyl sulfones[13] such as **13** and **15** to effect the olefination reaction (**12** + **13** → **14** and **7** + **15** → **11**) resulted in a less selective outcome (2*E*/2*Z* = 4:6 and 4*E*/4*Z* = 87:13, respectively).

Removal of the Boc protective group of **11** was successful under basic conditions employing sodium methoxide in methanol and THF.[14] More conventional acid conditions with trifluoroacetic acid led to decomposition of **1**. The resulting (*S*)-axinellamine A (**1**) was contaminated with ca. 10% of its 4*Z*-isomer as estimated by its ^1H NMR analysis. The ^1H and ^{13}C NMR spectra of (*S*)-**1** were identical with those reported for the natural **1** except for the presence of minor signals due to the 4*Z*-isomer of **1** (see Experimental Section). The overall yield of (*S*)-**1** was 33% based on **3** (6 steps). Since there was no synthetic step to cause severe racemization, the product (*S*)-**1** was supposed to be of high enantiomeric purity (99.9% *ee*) reflecting that of the starting (*S*)-**2**.[15] (*S*)-Axinellamine A was dextrorotatory: $[\alpha]_D^{23} = +40.1$ ($CHCl_3$), while the natural product was reported to be levorotatory: $[\alpha]_D^{23} = -45.4$ ($CHCl_3$). The absolute configuration of the natural axinellamine A was therefore determined as *R*.

In summary, the (*S*)-enantiomer of the marine pyrrole alkaloid axinellamine A was synthesized, and the Caribbean marine sponge *Axinella* sp. was found to produce (*R*)-axinellamine A. Accordingly, this sponge belongs to the producers of (*R*)-configured *sec*-butyl branching, as do such insects as the dermestid beetle and the pine sawfly.

Experimental Section

General: IR: Jasco A-102 and Perkin−Elmer 1640. − ^1H NMR: Jeol JNM-EX 90A (90 Hz), Jeol JNM-AL300 (300 MHz) and Jeol JNM-LA500 (500 MHz) (TMS at δ = 0.00 or $CHCl_3$ at δ = 7.26 as an internal standard). − ^{13}C NMR: Jeol JNM-LA500 (125 MHz) ($CHCl_3$ at δ = 77.00 as an internal standard). − Optical rotation: Jasco DIP-1000. − MS: Jeol JMS-SX102A. − Column chromatography: Merck Kieselgel 60 Art 1.07734. − TLC: 0.25 mm Merck silica gel plates (60F−254).

***N*-*tert*-Butoxycarbonyl-2-(formylmethyl)pyrrole (4):** To a stirred and cooled (−78 °C) solution of **3** (322 mg, 1.27 mmol) in dry CH_2Cl_2 (5 mL) was added dropwise at −78 °C under argon a solution of diisobutylaluminum hydride (0.9 M in hexane, 1.7 mL, 1.5 mmol). This mixture was stirred at −78 °C for 2 h and then quenched with MeOH. After stirring for 30 min, the mixture was filtered through a pad of Celite. The filtrate was concentrated in vacuo to give 260 mg (quant.) of crude **4**. This was employed in the next step without further purification. − IR(film): $\tilde{\nu}$ = 2720 cm^{-1} (w, OC−H), 1740 (s, C=O), 1320 (s), 1130 (s). − ^1H NMR (90 MHz, $CDCl_3$): δ = 1.57 [s, 9 H, $C(Me)_3$], 3.90 (d, *J* = 1.5 Hz, 2 H, 6-H), 6.10−6.15 (m, 2 H, 3,4-H), 7.23−7.28 (m, 1 H, 5-H), 9.72 (t, *J* = 1.5 Hz, 1 H, CHO).

Ethyl (*E*)-4-[2-(*N*-*tert*-Butoxycarbonyl)pyrrolyl]-2-butenoate (5): A solution of triethyl phosphonoacetate (370 mg, 1.65 mmol) in dry THF (4 mL) was added to a stirred and ice-cooled suspension of NaH (60% oil suspension, 91 mg, 1.52 mmol) in dry THF (3 mL), and stirring was continued for 30 min at 0 °C. To the resulting

mixture was added a solution of **4** (260 mg, 1.27 mmol) in dry THF (3 mL) at 0 °C. It was allowed to warm to room temperature while stirring for 1 h, then quenched with water, and extracted with diethyl ether. The ethereal extract was washed with water and brine, dried with $MgSO_4$, and concentrated in vacuo. The residue was chromatographed on silica gel (15 g, hexane/ethyl acetate, 60:1) to give 224 mg (63% from **3**) of **5** as a colorless oil. $n_D^{22} = 1.4898$. − IR(film): $\tilde{\nu} = 1740\ cm^{-1}$ (vs, C=O), 1720 (vs, C=O), 1660 (w), 1330 (s), 1160 (s), 1120 (s), 840 (s), 720 (s). − ^1H NMR (300 MHz, $CDCl_3$): δ = 1.28 (t, *J* = 7.2 Hz, 3 H, CH_2CH_3), 1.58 [s, 9 H, $C(Me)_3$], 3.76 (d, *J* = 6.2 Hz, 2 H, 6-H), 4.18 (q, *J* = 7.2 Hz, 2 H, CH_2CH_3), 5.78 (dt, *J* = 16.0, 1.5 Hz, 1 H, 8-H), 5.98−6.05 (m, 1 H, 3-H), 6.08−6.11 (m, 1 H, 4-H), 7.11 (dt, *J* = 16.0, 6.2 Hz, 1 H, 7-H), 7.21−7.23 (m, 1 H, 5-H). − $C_{15}H_{21}NO_4$ (279.3): calcd. C 64.50, H 7.58, N 5.01; found C 64.26, H 7.69, N 4.73.

(*E*)-4-[2-(*N*-*tert*-Butoxycarbonyl)pyrrolyl]-2-buten-1-ol (6): A solution of diisobutylaluminum hydride (0.9 M in hexane, 1.2 mL, 1.1 mmol) was added dropwise to a solution of **5** (98 mg, 0.35 mmol) in dry CH_2Cl_2 (5 mL) at −78 °C under argon. This mixture was stirred at −78 °C for 2 h and then quenched with MeOH. After stirring for 30 min, the mixture was filtered through a pad of Celite and the filter cake was washed with diethyl ether. The combined filtrate and washings were concentrated in vacuo to give 80 mg (96%) of crude **6** as a pale yellow oil, which was used immediately in the next reaction. IR(film): $\tilde{\nu} = 3400\ cm^{-1}$ (br. s, O−H), 1740 (s, C=O), 1330 (s), 1160 (s), 1120 (s). − ^1H NMR (300 MHz, $CDCl_3$): δ = 1.58 [s, 9 H, $C(Me)_3$], 3.61 (d, *J* = 6.5 Hz, 2 H, 6-H), 4.12 (dd, *J* = 5.7, 1.5 Hz, 2 H, 9-H), 5.68 (ddt, *J* = 15.0, 5.7, 1.5 Hz, 1 H, 8-H), 5.88 (ddt, *J* = 15.0, 6.5, 1.5 Hz, 1 H, 7-H), 5.95−5.98 (m, 1 H, 3-H), 6.07−6.09 (m, 1 H, 4-H), 7.20 (dd, *J* = 3.5, 1.8 Hz, 1 H, 5-H).

(*E*)-4-[2-(*N*-*tert*-Butoxycarbonyl)pyrrolyl]-2-butenal (7): A solution of **6** (80 mg, 0.43 mmol) in $CHCl_3$ (1.5 mL) was added to a suspension of MnO_2 (1.00 g) in $CHCl_3$ (5 mL), and stirring was then continued for 12 h at room temperature. This mixture was filtered through a pad of Celite. The filtrate was concentrated in vacuo to give 79 mg (quant.) of crude **7**. This was employed in the next step without further purification. IR(film): $\tilde{\nu} = 1740\ cm^{-1}$ (s, C=O), 1700 (s, C=O), 1660 (m), 1620 (m), 1330 (s), 1180 (s), 1130 (s). − ^1H NMR (90 MHz, $CDCl_3$): δ = 1.58 [s, 9 H, $C(Me)_3$], 3. 90 (d, *J* = 6.2 Hz, 2 H, 6-H), 5.99−6.20 (m, 3 H, 3,4,8-H), 7.00 (dt, *J* = 15.8, 6.2 Hz, 1 H, 7-H), 7.20−7.25 (m, 1 H, 5-H), 9.55 (d, *J* = 7.9 Hz, 1 H, CHO).

(*S*)-5-(2-Methylbutyl)thio-1-phenyl-1*H*-tetrazole (9): To a stirred solution of (*S*)-**2** (1.06 g, 12.0 mmol) in dry THF (50 mL) at room temperature under argon was added **8** (2.59 g, 14.5 mmol) and triphenylphosphane (3.78 g, 14.4 mmol). The resulting solution was cooled to 0 °C and diisopropyl azodicarboxylate (DIAD, 3.18 g, 15.7 mmol) was added dropwise. The mixture was warmed to room temperature and stirred for 2 h. The solvent was then removed in vacuo. The residue was chromatographed on silica gel (70 g, hexane/ethyl acetate, 100:1) to give 2.91 g (98%) of **9** as a colorless oil. $n_D^{24} = 1.5592$. − $[\alpha]_D^{26} = +13.1$ (*c* = 1.00, $CHCl_3$). − IR(film): $\tilde{\nu} = 3070\ cm^{-1}$ (w), 2870 (w), 1600 (m), 1500 (s), 1460 (m), 1410 (m), 760 (s), 690 (s). − ^1H NMR (500 MHz, $CDCl_3$): δ = 0.94 (t, *J* = 7.3 Hz, 3 H, 10-Me), 1.03 (d, *J* = 6.7 Hz, 3 H, 11-Me), 1.26−1.34 (m, 1 H, 9-H), 1.50−1.57 (m, 1 H, 9-H), 1.82−1.92 (m, 1 H, 8-H), 3.27 (dd, *J* = 12.8, 7.6 Hz, 1 H, 7-H), 3.46 (dd, *J* = 12.8, 5.8 Hz, 1 H, 7-H), 7.55−7.61 (m, 5 H, aromatic). − $C_{12}H_{16}N_4S$ (248.4): calcd. C 58.04, H 6.49, N 22.56; found C 58.21, H 6.74, N 22.52.

(*S*)-5-(2-Methylbutyl)sulfonyl-1-phenyl-1*H*-tetrazole (10): To a stirred solution of **9** (2.64 g, 10.6 mmol) in EtOH (50 mL) at room temperature was added dropwise a solution of ammonium molybdate tetrahydrate (1.31 g, 0.11 mmol) in aqueous hydrogen peroxide (34.5 wt%, 10.3 g, 106 mmol). The resulting mixture was stirred vigorously for 14 h and then partitioned between diethyl ether (60 mL) and water (50 mL). The layers were separated and the aqueous phase was extracted with diethyl ether. The combined organic phases were washed with water and brine, dried with $MgSO_4$, and concentrated in vacuo. The residue was chromatographed on silica gel (70 g, hexane/ethyl acetate, 5:1) to give 2.94 g (99%) of **10** as a colorless oil. $n_D^{24} = 1.5354$. − $[\alpha]_D^{24} = +7.87$ (*c* = 1.03, $CHCl_3$). − IR(film): $\tilde{\nu}_{max} = 3070\ cm^{-1}$ (w), 1600 (m), 1500 (s), 1340 (vs), 1150 (vs), 760 (s), 690 (s), 630 (s). − ^1H NMR (500 MHz, $CDCl_3$): δ = 0.95 (t, *J* =7.6 Hz, 3 H, 10-Me), 1.15 (d, *J* = 7.0 Hz, 3 H, 11-Me), 1.39−1.48 (m, 1 H, 9-H), 1.58−1.65 (m, 1 H, 9-H), 2.24−2.33 (m, 1 H, 8-H), 3.58 (dd, *J* = 14.5, 7.6 Hz, 1 H, 7-H), 3.81 (dd, *J* = 14.5, 5.0 Hz, 1 H, 7-H), 7.58−7.66 (m, 3 H, aromatic), 7.68−7.70 (m, 2 H, aromatic). − $C_{12}H_{16}N_4O_2S$ (280.4): calcd. C 51.41, H 5.75, N 19.99; found C 51.57, H 5.88, N 19.98.

(2*E*,4*E*,6*S*)-*N*-*tert*-Butoxycarbonyl-2-(6-methyl-2,4-octadienyl)-pyrrole (11): To a stirred solution of diisopropylamine (0.06 mL, 0.43 mmol) in dry THF (2 mL) at 0 °C under argon was added dropwise a solution of *n*-butyllithium (1.60 M in hexane, 0.27 mL, 0.43 mmol). The resulting solution of lithium diisopropylamide was stirred for 10 min and then cooled to −78 °C. A solution of **10** (145 mg, 0.52 mmol) in dry THF (2 mL) was added dropwise. The reaction mixture was stirred for 30 min and then treated dropwise with a solution of **7** (79 mg, 0.34 mmol) in dry THF (1 mL). It was allowed to warm to room temperature while stirring for 5 h, then poured into saturated aqueous NH_4Cl, and extracted with diethyl ether. The ethereal extract was washed with water and brine, dried with $MgSO_4$, and concentrated in vacuo. The residue was chromatographed on silica gel (1 g, hexane/ethyl acetate, 150:1) to give 58 mg (58% from **7**) of **11** (4*E*/4*Z* = 9:1 as judged by ^1H NMR analysis) as a pale yellow oil. $n_D^{22} = 1.5062$. − $[\alpha]_D^{22} = +23.5$ (*c* = 0.48, $CHCl_3$). − IR(film): $\tilde{\nu} = 1740\ cm^{-1}$ (s, C=O), 1330 (s), 1120 (s), 990 (s), 720 (s). − ^1H NMR (500 MHz, $CDCl_3$): **4*E*** δ = 0.85 (t, *J* = 7.3 Hz, 3 H, 13-Me), 0.98 (d, *J* = 6.7 Hz, 3 H, 14-Me), 1.28−1.34 (m, 2 H, 12-H), 1.58 [s, 9 H, $C(Me)_3$] , 2.02−2.07 (m, 1 H, 11-H), 3.61 (d, *J* = 6.7 Hz, 2 H, 6-H), 5.47 (dd, *J* = 14.3, 7.3 Hz, 1 H, 10-H), 5.74 (dd, *J* = 14.3, 6.7 Hz, 1 H, 7-H), 5.95−5.97 (m, 1 H, 3-H), 5.98−6.06 (m, 2 H, 8,9-H), 6.08 (dd, *J* = 3.3, 3.3 Hz, 1 H, 4-H), 7.21 (dd, *J* = 3.3, 1.8 Hz, 1 H, 5-H). **4*Z*** δ = 0.83 (t, *J* = 7.3 Hz, 3 H, 13-Me), 0.95 (d, *J* = 6.7 Hz, 3 H, 14-Me), 1.20−1.27 (m, 2 H, 12-H), 1.58 [s, 9 H, $C(Me)_3$], 2.43−2.50 (m, 1 H, 11-H), 3.65 (d, *J* = 6.7 Hz, 2 H, 6-H), 5.11 (dd, *J* = 10.5, 10.5 Hz, 1 H, 10-H), 5.79−5.82 (m, 1 H, 7-H), 5.95−5.97 (m, 1 H, 3-H), 6.00−6.06 (m, 1 H, 9-H), 6.08 (dd, *J* = 3.3, 3.3 Hz, 1 H, 4-H), 6.31−6.33 (m, 1 H, 8-H), 7.21 (dd, *J* = 3.3, 1.8 Hz, 1 H, 5-H). − $C_{18}H_{27}NO_2$ (289.4): calcd. C 74.70, H 9.40, N 4.84; found C 74.61, H 9.42, N 4.71.

(*S*)-Axinellamine A [(2*E*,4*E*,6*S*)-2-(6-Methyl-2,4-octadienyl)pyrrole] (1): A stirred solution of **11** (79 mg, 0.27 mmol) in THF (0.7 mL) and MeOH (0.2 mL) at room temperature under argon was treated with sodium methoxide (44 mg, 0.81 mmol). After stirring for 40 min the mixture was partitioned between diethyl ether and water and the layers were separated. The aqueous phase was extracted with diethyl ether. The combined organic extracts were washed with brine, dried with $MgSO_4$, and concentrated in vacuo. The residue was chromatographed on silica gel (1 g, hexane/ethyl acetate, 80:1) to give 46 mg (90%) of (*S*)-**1** (4*E*/4*Z* = 9:1) as a yellow oil. $n_D^{23} = 1.5172$. − $[\alpha]_D^{23} = +40.1$ (*c* = 0.38, $CHCl_3$). {ref.[1] $[\alpha]_D^{23} = -45.4$ (*c* = 0.24, $CHCl_3$)}. − IR(film): $\tilde{\nu} = 3400\ cm^{-1}$ (m, N−H), 3000

(s), 1580 (m) 1460 (m), 1420 (m), 1380 (w), 1320 (w), 1120 (m), 1100 (m), 1030 (m), 1000 (s), 960 (m), 890 (m), 790 (m), 720 (s). – ^{1}H NMR (500 MHz, $CDCl_3$): **4*E*** δ = 0.87 (t, *J* = 7.3 Hz, 3 H, 13-Me), 0.99 (d, *J* = 6.7 Hz, 3 H, 14-Me), 1.29–1.35 (m, 2 H, 12-H), 2.02–2.11 (m, 1 H, 11-H), 3.40 (d, *J* = 7.0 Hz, 2 H, 6-H), 5.53 (dd, *J* = 15.0, 7.5 Hz, 1 H, 10-H), 5.69 (dt, *J* = 15.0, 7.0 Hz, 1 H, 7-H), 5.94–5.96 (m, 1 H, 4-H), 6.00 (dd, *J* = 15.0, 10.4 Hz, 1 H, 9-H), 6.10 (dd, *J* = 15.0, 10.4 Hz, 1 H, 8-H), 6.13–6.15 (m, 1 H, 4-H), 6.69 (d, *J* = 1.6 Hz, 1 H, 5-H), 7.95 (br. s, 1 H, N–H). These ^{1}H NMR spectroscopic data are in good agreement with those reported for the natural **1**.[1] **4*Z*** δ = 0.85 (t, *J* = 7.3 Hz, 3 H, 13-Me), 0.97 (d, *J* = 6.7 Hz, 3 H, 14-Me), 1.26–1.32 (m, 2 H, 12-H), 2.47–2.53 (m, 1 H, 11-H), 3.44 (d, *J* = 7.0 Hz, 2 H, 6-H), 5.16 (dd, *J* = 10.4, 10.4 Hz, 1 H, 10-H), 5.76 (dt, *J* = 15.3, 7.1 Hz, 1 H, 7-H), 5.94–5.98 (m, 2 H, 3, 9-H), 6.13–6.15 (m, 1 H, 4-H), 6.39–6.45 (m, 1 H, 8-H), 6.69 (d, *J* = 1.6 Hz, 1 H, 5-H), 7.95 (br. s, 1 H, N–H). – ^{13}C NMR (125 MHz, $CDCl_3$): δ = 11.7 (13-C), 20.0 (14-C), 29.7 (12-C), 31.1 (6-C), 38.3 (11-C), 105.6 (3-C), 108.4 (4-C), 116.7 (5-C), 128.0 (9-C), 128.3 (7-C), 130.1 (2-C), 132.4 (8-C), 139.8 (10-C). These ^{13}C NMR spectroscopic data are in good agreement with those reported for the natural **1**.[1] – HR-MS [$C_{13}H_{19}N$]: calcd. 189.1519; found 189.1507.

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