Axiphenylalaninium and Axityrosinium, Modified Amino Acids from the Mediterranean Marine Sponge *Axinella polypoides*

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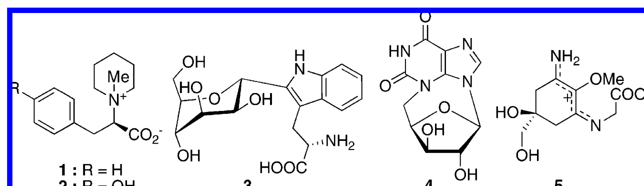
Two new modified amino acids, axiphenylalaninium (**1**) and axityrosinium (**2**), along with four known metabolites, C^2-α-D-mannosylpyranosyl-L-tryptophan (**3**), N^3,5′-cycloxanthosine (**4**), palythine (**5**), and taurine, were isolated from the marine sponge *Axinella polypoides* collected in the Mediterranean Sea. The structures were determined by spectroscopic studies and confirmed by X-ray analysis and chemical modifications.

As part of our continuing efforts to discover new metabolites in sponges belonging to Axinellidae and Agelasidae families and their biological activities, we further examined *Axinella polypoides*, Schmidt, 1862 (Demospongiae, Halichondrida, Axinellidae). This sponge, which is widely distributed in the Mediterranean Sea, is of rather great importance for chemical ecology investigations. Thus, exhaustive chemical studies to determine the chemical fingerprint of various *Axinella* sponges collected in different ecosystems became extremely important for chemotaxonomic reasons. In this context, the structural characterization of the purified compounds is the first goal to be achieved. We have investigated the methanolic extract of *A. polypoides*. To our knowledge, the previous investigations that have been reported on the chemistry of this sponge relate to sterols and lectin families only.[1−3] Herein we describe the isolation of two new modified amino acids, axiphenylalaninium (**1**) and axityrosinium (**2**), along with the known metabolites C^2-α-D-mannosylpyranosyl-L-tryptophan (**3**), N^3,5′-cycloxanthosine (**4**), palythine (**5**), and taurine.

The MeOH extract (303.7 g) of freeze-dried *A. polypoides* collected in April 2006 in the Mediterranean Sea accounted for 29% of the total dry weight of the sponge. The MeOH-soluble fraction was purified on silica gel chromatography columns. Further intensive reversed-phase HPLC resulted in the isolation of axiphenyalaninium (**1**, 8.4 mg, 0.009%) and axityrosinium (**2**, 3 mg, 0.001%) along with C^2-α-D-mannosylpyranosyl-L-tryptophan, N^3,5′-cycloxanthosine, palythine, and taurine.



HRESIMS of **1** supported the molecular formula $C_{15}H_{21}NO_2Na$ from the pseudomolecular ion *m/z* 270.1479 $[M + Na]^+$. The ^1H and ^{13}C NMR spectra (Table 1) implied the presence of an *N*-methyl group (δ_H 3.28, H-7′), a monosubstituted benzene ring (δ_H 7.19−7.27, H5−9), one benzylic methylene (δ_H 3.20/3.17, H-3) flanking the deshielded methine at δ_H 3.89, (H-2), two deshielded methylenes at δ_H 3.66/3.36 (H2′) and 3.56/3.52 (H6′), and three lower field methylenes at δ_H 1.68/1.75 (H4′, 2H) and 1.86−1.99 (H3′/5′, 4H). Furthermore, the appearance of a ^{13}C NMR resonance at δ_C 170.9 ppm was consistent with a carboxylic acid. The IR spectrum displayed a strong absorption band at 1728 cm^{-1}, indicating the presence of an acid function. Protons H-5 and H-9 showed HMBC correlations with the carbon at δ_C 33.8 (C-3), to which the diastereotopic protons at δ_H 3.20 (H-3a) and 3.17 (H-3b) were attached. Both H-3a and H-3b showed HMBC correlations with the carbons at δ_C 137.1 (C-4) and 130.7 (C-5/9). These findings confirmed that C-3 was a benzylic carbon attached to C-4. The $^1H-^1H$ COSY spectrum revealed that the diastereotopic protons H-3a and H-3b were positioned next to the aliphatic methine proton H-2 (δ_H 3.89), which was attached to the carbon at δ_C 79.9 (C-2). These characteristic data suggested that **1** was a derivative of the α-amino acid phenylalanine. Strong HMBC correlations from H-3a, H-3b, and H-2 to a carboxylic acid carbonyl at δ_C 170.9 (C-1) provided further proof for this assignment. The connections of the methylene at δ_H 3.66 (H-2′a) with the methylene protons at δ_H 3.52 and 3.56 (H-6′) via three consecutive methylenes (H-3′, -4′, and -5′) were readily deduced from the COSY spectrum. The HMBC correlation between H-6′ and C-2′ suggested that C-6′ and C-2′ were joined by a nitrogen atom to form a piperidine unit (Figure 1).

Further HMBC correlations between the methyl (H-7′) at δ_H 3.28 and both carbons C-2′ at δ_C 62.3 and C-6′ at δ_C 61.9 indicated the presence of the N1-Me group. Linkage of this *N*-methylpiperidinium to the amino acid portion was achieved via HMBC correlations from the methyl protons (H-7′) to the carbonyl at δ_C 170.9 (C-1) and to both carbons at δ_C 79.9 (C-2) and δ_C 33.8 (C-3). Given the deshielded character of the nitrogenous methylene carbons and the co-occurrence of quaternary ammonium and carboxylic acid functions, the structure for this *N*-methylpiperidinium was elucidated to be **1**, which was named axiphenylalaninium (**1**). The structure was then supported by treatment of **1** with potassium *tert*-butoxide/CH_2Cl_2, which gave *trans*-cinnamic acid (**6**), identified by comparison of the ^1H NMR spectrum with that of a commercial sample (Scheme 1).

The absolute configuration of axiphenylalaninium was suggested by comparison of it circular dichroism (CD) curve to that reported for phenylalanine betaine.[4] Positive CD bands are indicated at 212 and 216 nm for (*S*)-phenylalanine betaine in an acidic solution, while negative bands at 208.4 and 211 nm were observed for **1**. The CD of the (*R*)-phenylalanine in acidic solution showed a negative maxima at 218 nm. Although not an ideal comparison, this suggests the *R* configuration for the betaine **1**.

Compound **2** showed the molecular formula $C_{15}H_{22}NO_3$ by HRESIMS. The IR spectrum revealed the presence of a phenolic OH (3217 cm^{-1}) and a carbonyl group (1728 cm^{-1}). The ^1H and

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Table 1. NMR Spectroscopic Data for Axiphenylalaninium (**1**) and Axityrosinium (**2**)

	axiphenylalaninium (1)				axityrosinium (2)	
position	δ_C[a]	δ_H (J in Hz)[a]	δ_H (J in Hz)[b]	HMBC[b,c]	δ_C[a]	δ_H (J in Hz)[a]
1	170.9, qC				171.1 qC	
2	79.9, CH	3.89, m	4.11, dd (5.6, 8.0)	3, 7′, 2′, 6′, 4, 1	80.0 CH	3.87, dd (4.0, 10.6)
3a	33.8, CH_2	3.20, m	3.57, dd (8.0, 13.8)	1, 2, 4, 5, 9	33.0 CH_2	3.17, dd (4.0, 12.6)
3b		3.17, m	3.13, dd (5.6, 13.8)	1, 2, 4, 5, 9		3.13, dd (10.6, 12.6)
4	137.1, qC				127.4 qC	
5	130.7, CH	7.27, m	7.31−7.35, m	3, 7	131.7 CH	7.12, d (7.3)
6	129.9, CH	7.27, m	7.31−7.35, m		116.6 CH	6.72, d (7.3)
7	128.4, CH	7.19, m	7.25, m	5, 9	157.8 qC	
8	129.9, CH	7.27, m	7.31−7.35, m		116.6 CH	6.72, d (7.3)
9	130.7, CH	7.27, m	7.31−7.35, m	3, 7	131.7 CH	7.12, d (7.3)
2′a	62.3, CH_2	3.66, m	4.00, ddd (3.2, 9.2, 13.6)	3′, 6′, 7′	62.3 CH_2	3.68, ddd (3.9, 9.0, 12.7)
2′b		3.36, m	3.37, m	3′, 6′, 7′		3.37, m
3′a	21.4, CH_2	1.86−1.99, m	2.10, m	2′, 4′	21.3 CH_2	1.88−2.00, m
3′b			1.84, m	2′, 4′		
4′a	22.3, CH_2	1.75, m	1.69, m	2′, 3′, 5′, 6′	22.3 CH_2	1.74, m
4′b		1.68, m	1.66, m			1.67, m
5′a	21.3, CH_2	1.86−1.99, m	1.86, m	4′, 6′	21.3 CH_2	1.88−2.00, m
5′b			1.78, m	4′, 6′		
6′a	61.9, CH_2	3.56, m	3.30, m	2, 2′, 4′, 5′, 7′	61.8 CH_2	3.56, m
6′b		3.52, m				3.52, m
7′	45.3, CH_3	3.28, s	3.35, s	2, 2′, 6′	45.3 CH_3	3.29, s

[a] 500 MHz, MeOD-d_4. [b] 600 MHz, $CDCl_3$. [c] HMBC correlations are from proton(s) stated to the indicated carbon.

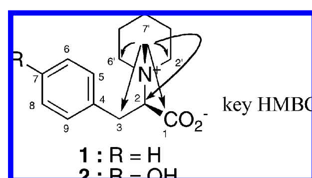
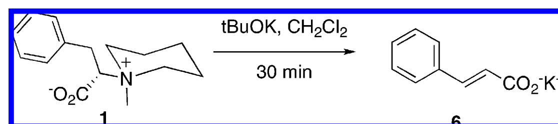


Figure 1. Selected HMBC correlations for **1** and **2**.

Scheme 1. Elimination Transforming **1** into **6**



^{13}C NMR spectra of **2** are similar to those of **1**, except for the presence of a 1,4-disubstituted benzene ring (δ_H 7.12/6.72) instead of a monosubstituted benzene ring in **1**. This system was oxygenated at C-7 on the basis of $^3J_{CH}$ HMBC correlations from both H-5/9 (δ_H 7.12) to a carbon at δ_C 157.8. Chemical shift arguments and HMQC and $^1H-^1H$ COSY correlations allowed us to assign all of the signals in the ^{13}C and ^1H NMR spectra of **2** (Table 1). These characteristic data suggested that **2** was a derivative of the α-amino acid tyrosine with the *N*-methylpiperidinium moiety (Figure 1). The linkage of the *N*-methylpiperidine to the amino acid was achieved via HMBC correlations from the methyl protons (H-7′) to the carbonyl at δ_C 171.1 (C-1) and to both carbons at δ_C 80.0 (C-2) and 33.0 (C-3). On the basis of all these data the structure of axityrosinium (**2**) has been established as *N*-methyl-*N*-tyrosinylpiperidinium.

The absolute configuration for **2** is undetermined. A CD spectrum for **2** was obtained, and interestingly, positive maxima were observed at 219.4 and 219 nm, unlike the negative maxima observed for **1**. Unfortunately, no CD data for tyrosine betaine are available in the literature for comparison. The opposite signs observed for the CD spectra of **1** and **2**, while their $[\alpha]^{28.3}_D$ values are +38.7 and +48.4, respectively, require confirmation of the absolute configurations by stereoselective synthesis.

X-ray analysis was successfully conducted on **2**, which was crystallized from a mixture of EtOAc and heptane. An ORTEP plot of the crystal structure of **2** is shown in Figure 2. Crystal structure data indicated that the piperidinium salt adopts the chair conformation in which the methyl group is axial. Water is an integral part of the crystal structure, acting as an H-bond donor to the phenol and carboxylic functions. The phenol group is bound to the carboxylic acid of the adjacent molecule via H_2O.

Compounds **3**−**5** and taurine were readily identified as the known metabolites by comparison of their spectroscopic properties with those reported in the literature. C^2-α-D-mannosylpyranosyl-L-tryptophan (**3**) is an unusual *C*-glycosylated tryptophan also isolated from the sponge *Erylus* sp. in 2005.[5−7] The presence of **3** in the Mediterranean sponge *A. polypoides* suggests that tryptophan *C*-glycosylation as a biosynthetic event may be more widespread than previously documented.[6] The occurrence of the modified tryptophan **3** in humans,[7] ascidians,[8] and sponges[4] is of great importance from the biosynthetic point of view. N^3,5′-cycloxanthosine (**4**) is a cyclic nucleoside first isolated from *Erylus* sp. in 2005.[6] The synthesis of **4** was described by Chern and co-workers in 2004 before its isolation.[9] Interestingly, the known cyclonucleoside **4** was also isolated from the sponge *Erylus* sp. (Demospongiae, Astrophorida, Geodidae) together with **3**.[6] The co-occurrence of the two compounds in two different sponges probably points out their biochemical or ecological relationship. Palythine **5** is a mycosporine first isolated from the red alga *Chondrus yendoi* and the zoanthid *Palythoa tuberculosa* in 1978.[10] The very common taurine was also isolated as the major product. Taurine is very often present in sponges and alga in high quantities.[11] The relative HPLC profile of the fraction containing the above isolated metabolites **1**−**5** is presented below (Figure 3).

In summary, we have isolated two new piperidiniums, axiphenylalaninium (**1**) and axityrosinium (**2**), and four known compounds, C^2-α-D-mannosylpyranosyl-L-tryptophan (**3**), N^3,5′-cycloxanthosine (**4**), palythine (**5**), and taurine. The metabolites **1** and **2** are interesting for their new natural methylpiperidinium amino acid skeleton. Although trimethylammonium amino acid betaines have been reported from natural sources including plants[12] and sponges,[13] our new amino acid betaines **1** and **2** appear particularly remarkable since they represent the first methylpiperidinium compounds from a natural source. The biosynthetic pathway leading to this type of compounds derived from the amino acids is an interesting question. Related synthetic piperidine derivatives have been described for their curarimimetic activity.[14,15] Further exhaustive chemical studies related to the minor modified amino acids present in *A. polypoides* collected at different sites of the Mediterranean Sea are in progress.

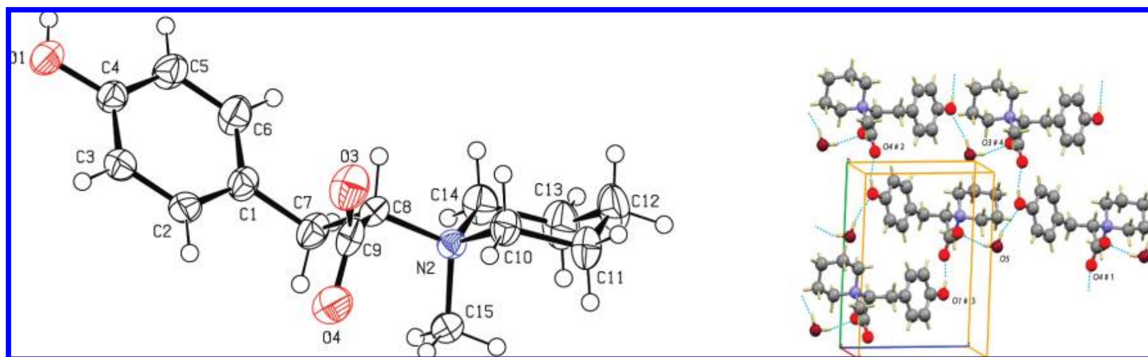


Figure 2. ORTEP plot derived from a single-crystal X-ray analysis and the crystal structure of **2** with waters (dark red) and dashed lines to indicate hydrogen bond network [symmetry codes: (#1) $x + 1$, y, z + 1(#2) $-x$, $y + 1/2$, $-z + 1$, (#3) $-x - 1$, $-1/2 + y$, $1 - z$, (#4) $1 - x$, $1/2 + y$, $2 - z$].

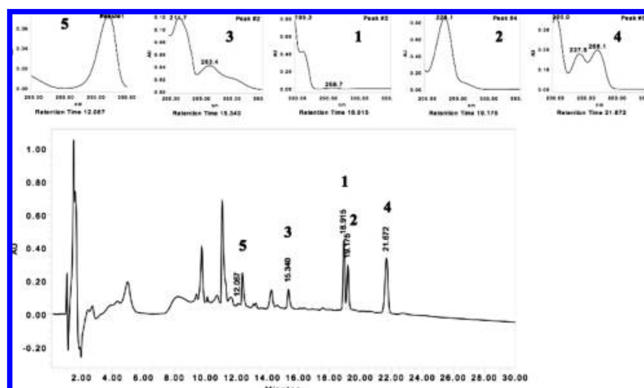


Figure 3. HPLC chromatogram of the fraction containing compounds **1**−**5** (Hypercarb, Thermo, Φ 4.6 × 100 mm, 5 μ; $d = 1$ mL/min; A: H_2O + 0.1% HCO_2H; B: MeCN + 0.1% HCO_2H; gradient: A/B 99/1 for 5 min to 0/100 over 40 min).

Experimental Section

General Experimental Procedures. Optical rotations were determined in MeOH with a Jasco P1010 polarimeter (cell capacity: 350 μL). The UV spectra were recorded on a Waters 996 photodiode array detector with the HPLC mobile phase as the solvent. Circular dichroism (CD) spectra were recorded on a JASCO J-810 spectropolarimeter. The IR spectra were conducted (neat) on a Perkin-Elmer BX-FT-IR spectrometer. NMR experiments were conducted with Bruker Avance 600 MHz and DRX 500 MHz spectrometers using MeOH-d_4 (δ_H 3.31 ppm, δ_C 49.15 ppm) and $CDCl_3$ (δ_H 7.27 ppm, δ_C 77.0 ppm). HRMS data were obtained with an electrospray source (Lockspray) coupled with a time-of-flight analyzer (LCT, Micromass). Samples were prepared in MeOH and injected in the MS system using a Waters 2795 system. The mobile phase was MeOH/H_2O (50/50, v/v) with a 0.2 mL/min flow. Preparative HPLC was performed on an autoprep system (Waters 600 controller and Waters 600 pump with a Waters 996 photodiode array detector). Samples were injected by the Waters 2700 Sample Manager.

Collection and Identification of the Sponge. *Axinella polypoides* samples were collected in March 2006 by scuba diving off the city of Marseille, on Riou Island at 35 m depth. A voucher specimen is available at the Station Marine d'Endoume (Marseille, France) under the accession number 060330-Ma6-01.

Extraction and Isolation. The sponge was frozen after collection, freeze-dried and ground, and finally stored at −20 °C until workup. The dry, powdered sponge (303.7 g) was extracted four times by maceration with MeOH (3, 2, and 2 × 1.5 L) at room temperature. After removal of the solvent under reduced pressure, the resulting crude extract (88.1 g) was triturated in MeOH. The major insolubles contained almost pure taurin (49.9 g). The MeOH-soluble extract (38.2 g) was purified by chromatography on silica gel (1.35 kg, 35−70 μm) using a CH_2Cl_2/MeOH (100/0 to 0/100) gradient as eluent and monitored by TLC. The fraction that eluted with the mixture CH_2Cl_2/MeOH (20/80) (4.74 g) was flash chromatographed on a silica gel column using a mixture of solvents (EtOAc/MeCN/H_2O/HCO_2H, 5/3/0.1/0.1 to 5/3/1/1) to give 12 fractions. After LC-MS analysis, the main fraction (F6: 1.69 g) was purified directly by semipreparative reversed-phase HPLC (Hypercarb, Thermo Hypersil, 5 μm, 10 × 150 mm column, 4.7 mL/min) using a gradient of H_2O/CH_3CN/HCO_2H (95/5/0.5 to 92/8/0.5 over 5 min, to 87/13/0.5 over 10 min, to 83/17/0.5 over 50 min), affording axiphenylalaninium (**1**) (8.4 mg, 0.0027% of the freeze-dried sponge) and axityrosinium (**2**) (3.3 mg, 0.001%). Another fraction (F3) was treated by semipreparative reversed-phase HPLC (Hypercarb, Thermo Hypersil, 5 μm, 10 × 150 mm column, 4.7 mL/min) using a gradient of H_2O/MeCN/HCO_2H (95/5/0.5 for 3 min to 50/50/0.5 over 37 min) and yielded compounds **3** (1.2 mg, 0.0004%) and **4** (8.3 mg, 0.0027%). Finally, palythine (**5**) (1.7 mg, 0.0006%) was obtained by purification of the fifth fraction (F5) on semipreparative reversed-phase HPLC (Hypercarb, Thermo Hypersil, 5 μm, 10 × 150 mm column, 4.7 mL/min) using a gradient of H_2O/MeCN/HCO_2H (97/3/0.5 for 3 min to 90/10/0.5 over 25 min, to 75/25/0.5 over 10 min).

Axiphenylalaninium (1): white solid; $[\alpha]^{28.3}_D$ +38.7 (c 0.68, MeOH); UV (HPLC, mobile phase) λ_{max} 209, 259 nm; CD (c 0.1 mg/mL, 1 N HCl) λ 208.4 nm ($\Delta\epsilon$ −0.875), 211 nm ($\Delta\epsilon$ −0.805); IR (neat) ν_{max} 3362, 3026, 2918, 2850, 1728, 1656, 1606, 1455 cm^{-1}; ^1H and ^{13}C NMR see Table 1; HRESIMS m/z 270.1479 $[M + Na]^+$ (calcd for $C_{15}H_{21}NO_2Na$, 270.1470).

Axityrosinium (2): white solid; $[\alpha]^{25.4}_D$ +48.4 (c 0.86, MeOH); UV (mobile phase) λ_{max} 199, 225, 274 nm; CD (c 0.1 mg/mL, 1 N HCl) λ 219.4 nm ($\Delta\epsilon$ 1.787), 219 nm ($\Delta\epsilon$ 1.761); IR (neat) ν_{max} 3391, 3217, 2930, 2880, 1728, 1623, 1516, 1451, 1375, 1251 cm^{-1}; ^1H and ^{13}C NMR see Table 1; HRESIMS m/z 264.1588 $[M + H]^+$ (calcd for $C_{15}H_{22}NO_3$, 264.1600).

X-ray Crystal Structure Analysis of Axityrosinium (2).[16] The data were collected on an Enraf-Nonius kappaCCD diffractometer at 293(2) K using graphite-monochromated Mo Kα radiation (λ = 0.7107 Å). The structure was solved by direct methods using SHELXS-97 ii a,c and refined by full-matrix least-squares on F^2 using SHELXL-97.[17] All H atoms were located by difference Fourier synthesis and then treated as riding atoms, with C−H = 0.93 Å for aromatic, 0.97 Å for methylene, 0.98 Å for methine, 0.96 Å for methyl groups (AFIX 137 in SHELXL), 0.82 Å for the hydroxy H, 0.86 Å for the hydrogen attached to nitrogen atoms, and $U_{iso}(H) = kU_{eq}$(atom carrier), with k = 1.2 or 1.5 for methyl and hydroxy H atoms. DFIX and DANG restraints were used for the water H atoms before using AFIX 3 during the final refinement round. The structure was displayed using the ORTEP module as implemented in PLATON.[18] Colorless prism (0.50 × 0.26 × 0.18 mm), $C_{15}H_{21}NO_3$, H_2O, M_r = 281.34, monoclinic system, space group $P2_1$, $Z = 2$, a = 7.179(4) Å, b = 11.121(5) Å, c = 9.854(4) Å, β = 110.661(5)°, V = 736.1(6) Å^3, D_{calcd} = 1.269 g/cm^3, $F(000)$ = 304, μ = 0.091 mm^{-1}, 8475 collected reflections (2.87° ≤ θ ≤ 30.02°, $-10 \le h \le 10$, $-15 \le k \le 15$, $-13 \le l \le 13$), 2231 independent reflections (R_{int} = 0.0217), goodness-of-fit on F^2 S = 1.042, R1 = 0.0538 and wR2 = 0.1108 for all reflections, R1 = 0.0397 and wR2 = 0.1008 for 1834 observed reflections [$I > 2\sigma(I)$], refining 182 parameters and 1 restraint, semiempirical absorption correction from multi ϕ- and ω-scans (T_{min} = 0.869, T_{max} = 0.988), final electron density between −0.160 and 0.145 e Å^{-3}.

***C*²-α-D-Mannosylpyranosyltryptophan (3)** was identified by comparison of its spectroscopic properties with those reported in the literature.[6,13]

***N*³,5′-Cycloxanthosine (4)** was identified by comparison of its spectroscopic properties with those reported in the literature.[5,8]

Palythine (5) was identified by comparison of its spectroscopic properties with those reported in the literature.[9]

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Supporting Information Available: ^{1}H and ^{13}C NMR spectra for compounds **1**−**5** and X-ray and CD data. This material is available free of charge via the Internet at http://pubs.acs.org.

References and Notes

(1) Crist, V.; Djerassi, C. *Steroids* **1983**, *42*, 331–343.
(2) Minale, L.; Sodano, G. J. C. S. *J. Chem. Soc., Perkin Trans. 1* **1974**, 1888.
(3) Buck, F.; Schulze, C.; Breloer, M.; Strupat, K.; Bretting, H. *Comp. Biochem. Phys. Part B: Biochem. Mol. Biol.* **1998**, *121*, 153–160.
(4) Gacek, M.; Undhein, K. *Tetrahedron* **1973**, *29*, 863–866.
(5) Hofsteenge, J.; Mueller, D. R.; de Beer, T.; Loeffler, A.; Richter, W. J.; Vliegenthart, J. F. G. *Biochemistry* **1994**, *33*, 13524–13530.
(6) Capon, R. J.; Trotter, N. S. *J. Nat. Prod.* **2005**, *68*, 1689–1691.
(7) Gutsche, B.; Grun, C.; Scheutzow, D.; Herderich, M. *Biochem. J.* **1999**, *343*, 11–19.
(8) Garcia, A.; Lenis, L. A.; Jimenez, C.; Debitus, C.; Quinoa, E.; Riguera, R. *Org. Lett.* **2000**, *2*, 2765–2767.
(9) Chen, G. S.; Chen, C. S.; Chien, T. C.; Yeh, J. Y.; Kuo, C. C.; Talekar, R. S.; Chern, J. W. *Nucleosides, Nucleotides Nucleic Acids* **2004**, *23*, 347–359.
(10) (a) Tsujino, I.; Yabe, K.; Sekikawa, I.; Hamanaka, N. *Tetrahedron Lett.* **1978**, *16*, 1401–1402. (b) Takano, S.; Uemura, D.; Hirata, Y. *Tetrahedron Lett.* **1978**, *26*, 2299–2300.
(11) Broberg, A.; Kenne, L.; Pedersén, M. *Planta* **1998**, *206*, 300–307.
(12) Stanikunaite, R.; Mohamed, M.; Radwan, M. M.; Trappe, J. M.; Fronczek, F.; A.Ross, S. A. *J. Nat. Prod.* **2008**, *71*, 2077–2079.
(13) (a) Segraves, N., L.; Crews, P. *J. Nat. Prod.* **2005**, *68*, 1484–1488. (b) Aillo, A.; Borelli, F.; Capasso, R.; Fattorusso, E.; Luciano, P.; Menna, M. *Bioorg. Med. Chem. Lett.* **2003**, *13*, 4481–4483. (c) Campanuelo, C.; Fattorusso, E.; Taglialatela-Scafati, O. *Eur. J. Org. Chem.* **2003**, 284–287.
(14) Najer, H.; Chabrier, P.; Giudicelli, R.; Duchemin, J. *Ann. Pharm. Fr.* **1960**, *18*, 126–132.
(15) Cheymol, J.; Giudicelli, R.; Chabrier, P.; Najer, H. *Arch. Int. Pharmacodyn.* **1960**, *125*, 121–131.
(16) Crystallographic data for the structure of axityrosinium (**2**) reported in this paper have been deposited with the Cambridge Crystallographic Data Centre (CCDC 720550). Copies of the data can be obtained, free of charge, on application to the Director, CCDC, 12 Union Road, Cambridge CB21EZ, UK (fax: +44-(0)1223-336033 or e-mail: deposit@ccdc.cam.ac.uk).
(17) (a) Sheldrick, G. M. *SHELXS-97, Program for the Solution of Crystal Structures*; University of Göttingen: Germany, 1997. (b) Sheldrick, G. M. *SHELXL-97, Program for the Refinement of Crystal Structures*; University of Göttingen: Germany, 1997. Review: (c) Sheldrick, G. M. *Acta Crystallogr., Sect. A* **2008**, *64*, 112–122.
(18) Spek, A. L. *J. Appl. Crystallogr.* **2003**, *36*, 7–13.

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