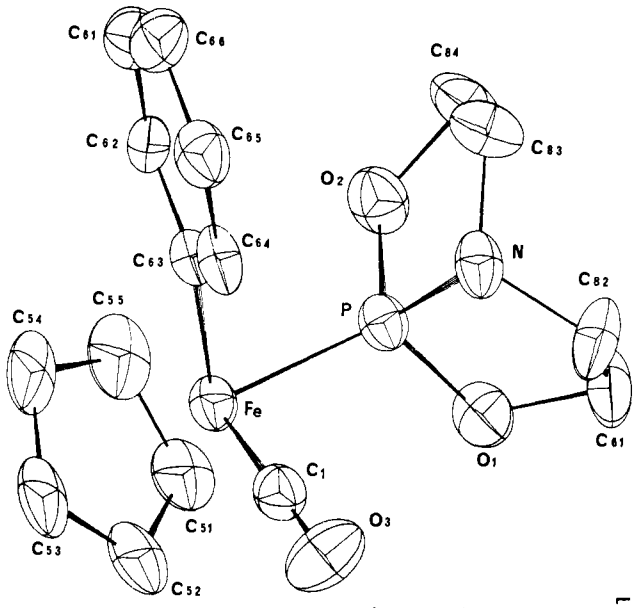

Figure 1. Molecular structure of $(\eta^5\text{-}C_5H_5)(\eta^1\text{-}C_6H_5)(CO)Fe[P(OCH_2CH_2)_2N]$. Selected bond lengths: Fe-P 2.105 (2), Fe-C1 1.715 (5), Fe-C63 2.037 (5), Fe-Cp(mean) 2.102 (5), P-N 1.692 (4), P-O1 1.620 (3), P-O3 1.602 (4) Å. Angles: P-Fe-C1 90.6(2), C63-Fe-C1 94.5 (2), C63-Fe-P 83.9 (2), Fe-P-N 123.3 (2), Fe-P-O1 114.5 (2), Fe-P-O2 115.5 (2), P-N-C82 108.6 (3), P-N-C83 107.4 (3), C82-N-C83 117.6 (4)°.

An ORTEP picture of the structure is shown in Figure 1. Its most unexpected feature is that the phenyl group is no longer bound to phosporus, but to iron, while the ligand has undergone a rearrangement into a bicyclic entity, as a result of the formation of a P-N bond. The iron atom lies in the plane of the phenyl group, and the Fe-C(phenyl) σ bond is short (2.04 Å) when compared to that found in $(\eta^5\text{-Cp})Fe(CO)(PPh_3)(\eta^1\text{-}C_6H_5)$ (2.14 Å).[6] The P-Fe bond distance of 2.105 Å is also much shorter than that (2.23 Å) of the PPh_3 derivative **6**; it appears to be the shortest P-Fe bond found so far in an iron(II) compound.[7] This may originate both from a lessening of steric hindrance when triphenylphosphane is replaced by the much more compact bicyclic ligand and from the expected increase in σ character of the phosphorus hybrid orbital binding iron, due to the greater electronegativity of the phosphorus substituents in the bicyclic ligand.[8] The P-N bond is also remarkably short (1.69 Å) and is comparable with bond distances found in aminophosphanes for which it is customary to invoke a p_π-d_π contribution[9,10] (Me_2N-PCl_2 : 1.69 Å),[11] in spite of the fact that here the nitrogen atom is markedly pyramidal (sum of the angles around nitrogen: 333.6 ± 1.0°).. This bond length is also shorter than the 1.75 Å found when N is coordinated to a BH_3 group in the bis(borane)-bicyclophosphane adduct $H_3B{\cdot}P[OC(CH_3)_2CH_2]_2N{\cdot}BH_3$.[9] The free bicyclic ligand has lately been synthesized;[12] in its uncoordinated form it is, however, unstable at room temperature with respect to polymerization.

Another very surprising observation is that the migration of the phenyl group is *reversible*: when gaseous HCl is bubbled through a THF solution of **5** at room temperature, the color changes from orange to deep red. The conversion is quantitative, as shown by the IR spectrum of the solution. The addition of $NH_4^+PF_6^-$ allows the recovery, in 60% yield, of compound **2**.

This new behavior of the cyclic P/N ligand appears to have no precedent in the literature. The rearrangement cannot be compared, for example, to the observation that PPh_3 can undergo oxidative addition to zero-valent metals, as observed, for example, by Fahey and Mahan,[13] since there is neither a change of oxidation state and coordination number for the metal nor a change of the phosphane into a phosphide ligand. It cannot be compared, either, to the irreversible transfer of a phenyl group from a phosphonium ion to iron, as observed by Ellis[14] or from a phosphorus ylide to nickel, as reported by Keim et al.[15] This original behavior clearly entails the assistance of the NH group. We suggest that it is the action of an acid or a base on that group that triggers a redistribution of bonds about phosporus and iron, probably in a synchronous pair of 1,2 shifts at the P-Fe bond, that is perhaps uniquely attributable to the transannular relationship of N and P in this flexible ligand.

Supplementary Material Available: A table of atomic positions and thermal parameters and a table of bond lengths and angles (2 pages). Ordering information is given on any current masthead page.

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Acanthifolicin, a New Episulfide-Containing Polyether Carboxylic Acid from Extracts of the Marine Sponge *Pandaros acanthifolium*

Francis J. Schmitz,* Ravi S. Prasad,
Yalamanchili Gopichand, M. Bilayet Hossain, and
Dick van der Helm*

*Department of Chemistry, University of Oklahoma
Norman, Oklahoma 73019*

Paul Schmidt

*Oklahoma Medical Research Foundation
Oklahoma City, Oklahoma 73104*

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Bacteria and other microorganisms present in marine sponges as endosymbionts or as a result of filter feeding by the sponges are suspected of being the source of some of the metabolites isolated from the entire sponge assemblages.[1] While unambiguous determination of the ultimate source of specific metabolites from sponge assemblages is obviously difficult, a reasonable assignment might be made in cases where metabolites known to be unique to certain microorganisms are isolated. In our bioassay-guided search for antitumor agents in marine organisms, we now have isolated a highly cytotoxic compound, acanthifolicin (**1**),[2] from extracts of the sponge *Pandaros acanthifolium*, and have established by X-ray analysis that it is a novel episulfide-containing member of the polyether antibiotic class of compounds[3] isolated heretofore only from bacteria. Acanthifolicin is the first polyether carboxylic acid reported from marine sources. Its episulfide functionality, rare in any natural product, is an unprecedented feature among the known polyether antibiotics that have attracted much attention during the last decade.[3] The isolation of this

(1) See, for example, L. Minale, *Pure Applied Chem.*, **48**, 7 (1976); C. Charles, J. C. Braekman, D. Daloze, B. Tursch, and R. Karlsson, *Tetrahedron Lett.*, 1519 (1978); C. Delseth, L. Tolela, P. J. Scheuer, R. J. Wells, and C. Djerassi, *Helv. Chim. Acta.*, **62**, 101 (1979), and references cited therein.
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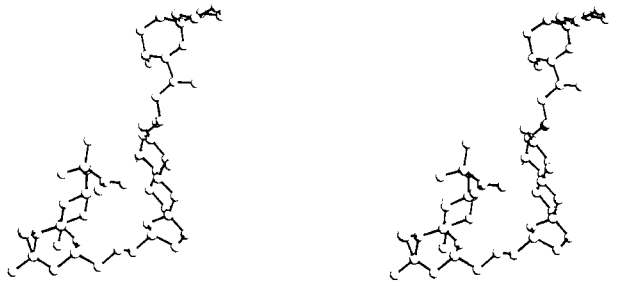


Figure 1. Stereoview of acanthifolicin.

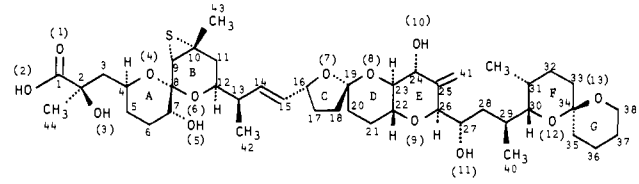
typical bacterial metabolite from a sponge extract strengthens the assumption that bacteria are the sources of some of the products isolated from sponges.

Specimens of *P. acanthifolium* collected around the U.S. Virgin Islands were extracted with isopropyl alcohol, and the dichloromethane solubles of the concentrated extracts were partitioned according to the procedure of Kupchan.[4] The cytotoxic carbon tetrachloride and chloroform fractions therefrom were passed over Sephadex LH-20 [$CHCl_3$–MeOH (1:1)] and the most active fraction was resolved further by repeated chromatography on silica gel [benzene–ethyl acetate (1:1) with increasing amounts of methanol] to give acanthifolicin (**1**), mp 167–169 °C, $[\alpha]_D$ +25.3° (0.018, $CHCl_3$), after several recrystallizations from a chloroform–benzene mixture; $C_{44}H_{68}O_{13}S$ (by X-ray analysis). The IR spectrum possessed broad absorptions at 3400, 1720, and 1080 cm^{-1}, indicative of hydroxyl, carboxyl, and ether groups. The 360-MHz spectrum of **1**[5] showed signals for two strongly deshielded quaternary methyl groups (1.38, 1.72 ppm), three secondary methyl groups (0.93, 0.97, 1.05 ppm), and a variety of downfield signals indicative of double bonds and hydroxyl and/or ether substituents. These spectral data were suggestive of a polyether structure.

X-ray analysis was carried out on crystals of the free acid obtained from chloroform–benzene: thin, prismatic needles belonging to the orthorhombic space group $P2_12_12$ with a = 10.580 (3), b = 34.594 (8), c = 14.007 (5) Å; V = 5126.6 Å^3 at −135 °C; Z = 4. Intensities of 5881 unique reflections with $2\theta \leq 150°$ were measured at −135 (2) °C on a Nonius CAD-4 automatic diffractometer, using Ni-filtered Cu K$\bar{\alpha}$ radiation and employing θ–2θ scan techniques.[6] Out of the total, 4593 (78%) reflections were stronger than 1.5 times the standard deviations of their intensities.

The structure was determined by direct methods coupled with successive difference Fourier syntheses. As the chemical composition of the compound was unknown, each difference map was carefully scrutinized and atom identifications were made on the basis of both their peak heights and isotropic thermal parameters. The heavy atom was initially refined as oxygen with double occupancy and later confirmed as sulfur by comparing with the known geometry of an episulfide function.[7] All refinements were carried out by using a block-diagonal least-squares program. The difference Fourier calculated at the later stage of the refinements indicated the presence of two disordered benzene molecules per asymmetric unit. One of these was included in the refinements, while a badly disordered one was left out. Forty-six hydrogen atoms were placed in their ideal positions, and their contributions were included in structure factor calculations. The final R factor for the 4340 observed reflections included in the least squares is 0.087.

The absolute configuration of the molecule was determined by the Bijvoet method, using anomalous dispersion of Cu K$\bar{\alpha}$ radiation by the sulfur atom. Twenty Friedel pairs with highest Bijvoet difference were used. The absolute configuration and the numbering scheme are shown in Formula **1** and Figure 1 (2*R*,4*S*,7*R*,8*S*,9*S*,10*R*,12*S*,13*R*,16*R*,19*S*,22*R*,23*S*,24*R*,26*S*,-27*S*,29*S*,30*S*,31*R*,34*S*). The molecular backbone consists of a



1

2R,4S,7R,8S,9S,10R,12S,13R,16R,19S,22R,23S,24R,26S,27S,29S,30S,31R,34S

C_{38} chain which spans six tetrahydropyran rings and one tetrahydrofuran ring. One end of the molecule assumes a cyclic conformation forming the familiar cavity observed in most natural polyether antibiotic structures.[3,8] The cavity has a diameter of 5–7 Å and is held together by an intramolecular hydrogen bond between the carboxyl group attached to ring A and the hydroxyl on ring E. Out of the 13 oxygen atoms in the molecule, 10 cluster around this cavity, with 7 oxygen atoms within 4.0 Å from its central point, a situation quite suitable for complexation of a cation. Rings F and G are separated from the cavity region by an extended alkyl chain giving the overall molecule a length of about 15 Å.

The bond distances and bond angles are normal and comparable to those observed in other related structures.[8] The C–O distances within the cyclic ether rings range from 1.406 to 1.478 Å with an average value of 1.437 Å. The episulfide bond lengths are S–C(9), 1.825 Å; S–C(10), 1.809 Å, C(9)–C(10), 1.444 Å; episulfide bond angles are C(9)–S–C(10), 46.9°; S–C(9)–C(10), 65.9°; S–C(10–C(9), 67.2°. The double bond lengths C(14)–C(15) and C(25)–C(41) are 1.316 and 1.332 Å, respectively. The bond angles at the three spiro centers vary significantly from tetrahedral values: 106.7–113.4° at atom C(8), 104.3–118.9° at atom C(19), and 104.1–114.6° at atom C(34).

There are four short O···O distances: O(1)···O(10) of 2.92 Å, O(3)···O(4) of 2.79 Å, O(5)···O(11) [$-^1/_2 + x$, $^1/_2 - y$, $2 - z$] of 2.78 Å, and O(2)···O(10) [$-^1/_2 + x$, $^1/_2 - y$, $1 - z$] of 2.90 Å. They suggest the possibility of hydrogen bonding involving all the hydroxyl groups present in the molecule.

Acanthifolicin differs from known polyether antibiotics in a number of ways, most notably in the presence of the episulfide group. It also has the longest carbon backbone (C_{38}) of any reported polyether antibiotic but has less alkyl branching than is found in many others (6 methyl groups in a C_{38} backbone compared to an average of 10–12 methyl/ethyl groups in carboxylic acid ionophores with C_{25-30} backbones). Acanthifolicin does not have a hydroxyl group near the tail end of the carbon backbone as is common in most other polyether antibiotics, and

(4) See, for example, S. M. Kupchan, R. W. Britton, M. F. Ziegler, and C. W. Sigel, *J. Org. Chem.*, **38**, 178 (1973).

(5) ^1H NMR ($CDCl_3$) [Chemical shift (multiplet, J in Hz, tentative proton assignments)] 0.93 (d, 6.75), 0.97 (d, 6.75, H-42), 1.05 (d, 6.75), 1.38 (s, H-44), 1.72 (s, H-43), 2.34 (dd, 14.6, 2.25, H-11$_{eq}$), 3.17 (s, H-9), 3.28 (dd, 11.25, 2.25, H-7), 3.33 (br t, 9, H-12), 3.36 (t, 9, H-23), 3.48–3.70 (m, 3 protons), 3.94 (d, 9, H-26), 4.04 (m, 1 proton), 4.12 (d, 9, H-24), 4.55 (q, 6.75, H-16), 5.06 (br s, H-41), 5.39 (dd, 14.6, 8.55, H-15), 5.45 (br s, H-41), 5.60 (dd, 14.6, 9, H-14) ppm. Besides these absorptions, the spectrum contained complex overlapping multiplets in the range 0.8–2.25 ppm.

(6) Details of experimental techniques are described in an earlier report: F. J. Schmitz, K. H. Hollenbeak, D. C. Carter, M. B. Hossain, and D. van der Helm, *J. Org. Chem.*, **44**, 2445 (1979).

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(8) See, for example, E. N. Duesler and I. C. Paul, "The Polyether Antibiotics: Carboxylic Acid Ionophores", J. W. Westley, Ed., Marcel Dekker, New York, in press; G. D. Smith, P. D. String, and W. L. Duax, *Acta Crystallogr., Sect. B* **B34**, 3436 (1978); D. L. Ward, K. T. Wei, T. G. Hoogerheided, and A. I. Popov, *ibid.*, **B34**, 110 (1978).

(9) R. I. Gueran, N. H. Greenberg, M. M. MacDonald, A. M. Schumacher, and B. J. Abbott, *Cancer Chemother. Rep., Part 3*, **3** (2), 1–103 (1972). Effective doses (ED_{50}) in the tissue culture tests are expressed as concentrations in mcg/mL of test material in the growth medium that cause 50% inhibition of cell growth. "Active" materials display an $ED_{50} \leq 20$ mcg/mL. KB refers to a cell culture of a human carcinoma of the nasopharynx. PS refers to in vitro lymphocytic leukemia. LE refers to L1210 lymphoid leukemia.

it has two spirofused six-membered ketal ring systems in place of the more commonly encountered spiroketal involving six- and fixe-membered rings. The presence of two fused tetrahydropyran rings (D, E) is also unique.

Acanthifolicin exhibits ED_{50}'s of 2.8×10^{-4}, 2.1×10^{-3}, and 3.9×10^{-3} mcg/mL, respectively, against P388, KB, and L1210 cell lines. In vivo antitumor tests and other biological activity evaluation are in progress.

Efforts are under way to isolate microorganisms associated with *P. acanthifolium* that may produce acanthifolicin. In this connection it may be noted that a macrolide polyether antibiotic, aplasmomycin, has been isolated from a marine bacterium.[10]

Acknowledgment. This investigation was supported by Grant CA-17256, CA-17562, and Contract N01-CM-67108 awarded by the National Cancer Institute, DHEW. We thank Ms. Lin Craft for sponge identification and assistance in sample collection. 360-MHz ^1H NMR spectra were obtained at the Purdue Biochemical Magnetic Resonance Laboratory supported by NIH Grant RR 01077.

Supplementary Material Available: A listing of the final parameters, bond angles, torsion angles, structure factors, bond lengths, and Bijvoet differences is available (40 pages). Ordering information is given on any current masthead page.

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Okadaic Acid, a Cytotoxic Polyether from Two Marine Sponges of the Genus *Halichondria*

Kazuo Tachibana† and Paul J. Scheuer*

Department of Chemistry, University of Hawaii at Manoa Honolulu, Hawaii 96822

Yasumasa Tsukitani and Hiroyuki Kikuchi

Fujisawa Pharmaceutical Co., Ltd. Tokyo, Japan

Donna Van Engen and Jon Clardy*

Department of Chemistry-Baker Laboratory Cornell University, Ithaca, New York 14853

Yalamanchili Gopichand and Francis J. Schmitz*

Department of Chemistry, University of Oklahoma Norman, Oklahoma 73019

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A new polyether derivative of a C_{38} fatty acid, okadaic acid (**1**), has been isolated independently from two sponges, *Halichondria* (syn *Reniera*) *okadai* Kadota, a black sponge, commonly found along the Pacific coast of Japan,[1] and *H. melanodocia*, a Caribbean sponge collected in the Florida Keys.

Mammalian toxicity of a crude extract of *H. okadai* guided the isolation of a colorless crystalline solid ($\sim 10^{-4}$% from wet animal). The methanolic homogenate was further extracted at room temperature thrice with methanol and once with acetone. After partial solvent evaporation, the 70% aqueous residue was washed with *n*-hexane. The aqueous residue after complete organic solvent removal was finally extracted with ethyl acetate. Repeated chromatography of the organic residue [polystyrene gel (Hitachi 3019), MeOH; Sephadex LH-20, MeOH; silicic acid, *n*-hexane/acetone 5:1], followed by crystallization from MeOH and recrystallization from dichloromethane/hexane, furnished the acid, mp 171–175 °C, $[\alpha]^{20}_D$ +21° (*c* 0.33, $CHCl_3$). Okadaic acid was toxic (LC_{50} 192 μg/kg; ip mice) and inhibited growth of KB cells by more than 30% at 2.5 ng/mL and more than 80% at 5 ng/mL.

From *H. melanodocia* the Oklahoma group isolated okadaic acid by a procedure similar to that used for acanthifolicin.[2] A concentrated 2-propanol extract of the sponge collected near Summerland Key, FL, was diluted with water and extracted continuously with CH_2Cl_2. The CH_2Cl_2 solubles were suspended in 10% aqueous MeOH and extracted successively with hexane, CCl_4, and $CHCl_3$, as the water content of the aqueous MeOH phase was increased after the hexane and CCl_4 washes to 20 and 30%, respectively. The $CHCl_3$ solubles were chromatographed over Sephadex LH-20 (MeOH–$CHCl_3$, 1:1), and fractions exhibiting mouse toxicity were chromatographed over deactivated[3] silica gel ($CHCl_3 \rightarrow CHCl_3$–5% MeOH) to give the toxic component as a brown powder. One crystallization from benzene, followed by several recrystallizations from benzene–$CHCl_3$, afforded a white crystalline solid, mp 164–166 °C, $[\alpha]^{25}_D$ +25.4° (*c* 0.24, $CHCl_3$); approximate yield, 1×10^{-4}% of wet sponge weight.[4] The pure compound exhibited ED_{50} values[5] of 1.7×10^{-3} and 1.7×10^{-2}, respectively, against P388 and L 1210 cell lines. Okadaic acid was toxic at doses of ≥0.12 mg/kg (ip) and showed no tumor inhibition at subtoxic doses when tested in vivo against P388 lymphocytic leukemia.

^1H NMR spectra (360, 270 MHz) of the two samples of okadaic acid were identical. Nearly complete assignments are shown in Chart I.[6] UV (end absorption) and IR (3450, 1740, 1080, 880 cm^{-1}) spectra were rather uninformative. An electron impact mass spectrum exhibited its highest mass peak at *m/z* 786 for a composition of $C_{44}H_{66}O_{12}$. Only a trivial fragmentation peak at *m/z* 771 was readily interpretable.[7] ^{13}C NMR spectra in $CDCl_3$ and pyridine-d_5 revealed 44 peaks: 1 carboxyl singlet at 179.3 ppm, 6 olefinic carbons [exo-methylene at 147.9, 111.5 ppm; trisubstituted olefin (137.7, 126.8 ppm); trans disubstituted olefin, 135.5, 131.6 ppm], 3 ketal or hemiketal singlets near 100 ppm, 12 carbons bearing oxygen between 85.9 and 60.4 ppm (one quaternary carbon at 75.2, one CH_2 at 60.4 ppm, all other methines); the remaining 22 highfield signals (46.0–11.0 ppm) included 5 methyls and 3 methines.[8] The carbon data and preparation of a tetraacetate (vide infra) showed that okadaic acid possesses 13 (1 C=O, 12 C—O) rather than 12 oxygens, as had been indicated by EI mass spectrometry. A field desorption mass spectrum of *p*-bromophenacyl okadaate, mp 134–135 °C, subsequently confirmed a molecular formula of $C_{44}H_{68}O_{13}$.

Treatment of **1** with diazomethane furnished methyl okadaate, mp 127–133 °C (hexane–benzene); $[\alpha]^{25}_D$ +28° (*c* 0.38, $CHCl_3$); IR ($CHCl_3$) 3600, 3500 (brd), 1745, 1725 cm^{-1}; ^1H NMR signals in ref 9.

Preparation of an amorphous tetracetate (Ac_2O, pyridine, 20 h, room temperature), $[\alpha]^{20}_D$ +53° (*c* 1.4, $CDCl_3$), unambiguously proved presence of four hydroxyls by four acetate singlets at δ

† Suntory Institute for Bioorganic Research, Osaka, 618, Japan.

(1) A preliminary account of this work was presented at the Third International Symposium on Marine Natural Products in Brussels, Belgium, Sept 16–19, 1980. In part from the Ph.D. Dissertation of K.T., University of Hawaii, 1980.

(2) Schmitz, F. J.; Prasad, R. S.; Gopichand, Y.; Houssain, M. B.; van der Helm, D.; Schmidt, P. *J. Am. Chem. Soc.*, preceding paper in this issue.

(3) Silica gel was slurried in methanol containing 5% water, packed, and then flushed with $CHCl_3$ before initiating the chromatography.

(4) Initially designated melanodocin in U.S. Patent Application SN 170 927.

(5) See ref 2.

(6) Measured in $CDCl_3$ on an NT-360 instrument at the Suntory Institute for Bioorganic Research, Osaka, Japan.

(7) After the structure **1** was known, the following major peaks were interpretable from a FDMS of the *p*-bromophenacyl ester: *m/z* 519, fission of C-12,13; *m/z* 241, fission of C-26,27; and *m/z* 101, fission shown in diagram.

(8) The crowded high field region did not permit unambiguous distinction between singlet and triplet signals among the remaining 14 carbons.

(9) Methyl okadaate: ^1H NMR (270 MHz, $CDCl_3$) [chemical shift-(multiplet, *J*. (Hz), partial assignments)] 0.93 (d, 6.75), 1.04 (d, 6.75, H-42), 1.07 (d, 6.75), 1.37 (s, H-44), 1.73 (s, H-43), 3.25–3.75 (7 H, m), 3.81 (s, OCH_3), 3.90–4.20 (4 H, m), 4.48 (q, 8, H-16), 5.06 (s, H-41), 5.48 (dd, 15.5, 8, H–15), 5.58 (dd, 15.5, 8, H-14) ppm; exchangeable absorptions at 2.52, 2.89, and 4.94 ppm. Besides these absorptions the spectrum contained complex overlapping multiplets in the range 1.20–2.35 ppm.

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