structure **19** contains the intact, completely functionalized, stereochemically elaborated C6–C13 bicyclic ring system of the azinomycins, including the C7–C8 tetrasubstituted *E*-double bond[21] and C12–C13 selectively acylated *trans*-1,2-diol characteristic of this family of antitumor agents. Spectral characterization of **19**[21,22] was in accord with literature precedent.[2,6a,b]

(21) The *E*-geometry of the double bond of **19** was confirmed by the observation of a strong positive nuclear Overhauser enhancement of C13-H in the NOE difference spectrum of **19** when the NH was irradiated (500 MHz, $CDCl_3$). No enhancement was seen in similar experiments with the isomeric aziridino[1,2-*a*]pyrrolidine.

(22) Compound **19** was characterized: ^1H NMR (500 MHz, $CDCl_3$) δ 7.50 (br s, 1 H, NH), 5.25 (br s, 1 H, C13-H), 4.51 (br d, J = 4.4 Hz, 1 H, C12-H), 3.81 (s, 3 H, CO_2CH_3), 3.68 (s, 3 H, CO_2CH_3), 3.16 (apparent q, J = 4.5 Hz, 1 H, C11–H), 2.62 (br m, 1 H, C10–H_{exo}), 2.56 (d, J = 3.7 Hz, 1 H, C10-H_{endo}), 2.10 (s, 3 H, CH_3CO), 0.85 (s, 9 H, $SiC(CH_3)_3$), 0.06 (s, 6 H, $Si(CH_3)_2$); IR (neat) ν_{max} 3324, 1734, 1251, 838, 779 cm^{-1}; HRMS *m/e* calcd for $C_{18}H_{30}N_2O_7Si$ 414.1822, found 414.1819.

Acknowledgment. We thank the American Cancer Society (JFRA-319) and the Camille and Henry Dreyfus Foundation (NF-89-18) for their generous support of this work. We thank Molecular Design Ltd. for the use of their synthetic database. NMR spectra were obtained on instruments purchased with funds from the National Science Foundation (CHE-8411172 and CHE-8904942) and the National Institutes of Health (S10-RR02425).

Supplementary Material Available: Detailed experimental procedures and full spectral characterization for **10–14** and **16–19** (9 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.

Allium Chemistry: Simple Syntheses of Antithrombotic Cepaenes from Onion and Deoxycepaenes from Oil of Shallot by Reaction of 1-Propenethiolate with Sulfonyl Halides

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Received July 27, 1992

Summary: Stereoisomers of MeCH=CHSLi from Li/NH_3 reduction of MeCH=CHSPr react with varying proportions of MsCl giving the respective stereoisomers of either bis(1-propenyl) disulfide (**1**), *S*-1-propenyl methanesulfonothiate (**2a**), or 6-ethyl-4,5,7-trithiadeca-2,8-diene (**3**); oxidation of **3**, a shallot oil component, gives 6-ethyl-4,5,7-trithiadeca-2,8-diene 7-oxide (cepaene, **4**), an antithrombotic compound from onion.

Oil of shallot (*Allium ascalonicum*) contains α,β-unsaturated organosulfur compounds such as bis(1-propenyl) disulfide (**1**), *S*-1-propenyl methane- and propanesulfonothioate (MeCH=CHSSO$_2$R, **2a/2b**, R = Me/Pr), and (*E,E*)-6-ethyl-4,5,7-trithiadeca-2,8-diene ((*E,E*)-**3**, a "deoxycepaene").[1] The 7-oxide of (*E,E*)-**3** ((*E,E*)-**4**), termed a "capaene," has been isolated from extracts of onion (*Allium cepa*) and shows significant biological activity.[2] We describe here simple stereospecific syntheses of **1–4**, notable in involving 1-propenethiolate and sulfonyl halides, RSO_2Cl, in the first step of each synthesis! Our work demonstrates the unusual reactions that can occur with enethiols.

We required pure samples of (*E,Z*)-**1** as well as (*E,E*)- and (*Z,Z*)-**1** for our continuing study of *Allium* chemistry.[3] While (*E,E*)- and (*Z,Z*)-**1** could be prepared by oxidation of lithium (*E*)- and (*Z*)-1-propenethiolate ((*E*)-**5** and (*Z*)-**5**), respectively, synthesis of (*E,Z*)-**1** required a more indirect route, e.g, reaction of (*E*)-**5**, or the corresponding potassium salt, with (*Z*)-**2** (eq 1). While (*Z*)-**2** should be available

(1)

by regiospecific S,S-dioxidation of (*Z*)-MeCH=CHSSR, this approach suffers from difficulty in controlling the regiochemistry of oxidation, unexpected side products and C=C isomerization.[4] In the course of exploring synthesis of **2** by reaction of **5** with RSO_2Cl, we discovered remarkable one-step syntheses of **1–3**, described herein.

Slow addition of (*E*)-**5** (Li/NH_3 cleavage of (*E*)-1-propenyl propyl sulfide ((*E*)-**6**)[5]) to 20 equiv of MsCl in THF at −78 °C gives (*E*)-**2a**, in 22% yield, along with (*E,E*)-**1** (Table I).[6] Similarly, MsCl and $PrSO_2Cl$ give (*Z*)-**2a** and (*Z*)-**2b** in 34% and 30% yield, respectively, from (*Z*)-**5**.[5,6] Addition of 0.8 equiv of MsCl in THF to (*E*)- or (*Z*)-**5** at −65 °C affords (*E,E*)- or (*Z,Z*)-6-ethyl-4,5,7-trithiadeca-2,8-diene ((*E,E*)- or (*Z,Z*)-**3**; 27% and 20% yield) and (*E,E*)- or (*Z,Z*)-5,8-diethyl-4,6,7,9-tetrathiadodeca-2,10-diene, as pairs of diastereomers ((*E,E*)- or (*Z,Z*)-**7a,b**; 15% and 10% yield, respectively),[7] and 2,4,6-triethyl-1,3,5-trithiane isomers (**8**, trace).[6] Addition of 2 equiv of MsCl in ether to (*E*)- or (*Z*)-**5** at −78 °C, followed after 5 min by quenching with water and rapid warming to 5 °C, gives (*E,E*)- and (*Z,Z*)-**1** (>95% isomeric purity;

(1) (a) Kuo, M.-C.; Chien, M.; Ho, C. T. *J. Agric. Food Chem.* **1990**, *38*, 1378. (b) Kuo, M.-C.; Ho, C. T. *J. Agric. Food Chem.* **1992**, *40*, 111. (c) Kuo, M.-C. Ph.D. Thesis, Rutgers, The State University of New Jersey, 1991.

(2) Dorsch, W.; Schneider, E.; Bayer, T.; Breu, W.; Wagner, H. *Int. Arch. Allergy Immunol.* **1990**, *92*, 39. Bayer, T.; Breu, W.; Seligmann, O.; Wray, V.; Wagner, H. *Phytochemistry* **1989**, *29*, 2373. Bayer, T.; Wagner, H.; Wray, V.; Dorsch, W. *Lancet* **1988**, *8616*/I, 906.

(3) (a) Bayer, T.; Wagner, H.; Block, E.; Grisoni, S.; Zaho, S. H.; Neszmelyi, A. *J. Am. Chem. Soc.* **1989**, *111*, 3085. (b) Block, E.; Bayer, T. *J. Am. Chem. Soc.* **1990**, *112*, 4584. (c) Block, E.; Zhao, S.-H. *Tetrahedron Lett.* **1990**, *31*, 4999. (d) Block, E. *Phosphorus, Sulfur, Silicon Relat. Elem.* **1991**, *58*, 3. (e) Block, E. *Angew. Chem., Int. Ed. Engl.* **1992**, *31*, 1135. (f) Block, E.; Naganathan, S.; Putman, D.; Zhao, S.-H. *J. Agric. Food Chem.*, in press. (g) Block, E.; Putman, D.; Zhao, S.-H. *J. Agric. Food Chem.*, in press. (h) Block, E.; Naganathan, S.; Putman, D.; Zhao, S.-H. *Pure Appl. Chem.*, in press and references cited therein.

(4) Naganathan, S. Ph.D. Thesis, SUNY-Albany, 1992.

(5) Preparation of (*Z*)- and (*E*)-**6**: base-induced isomerization of propyl 2-propynyl sulfide (from propanethiol and propargyl bromide or chloride) to propyl 1-propynyl sulfide (95% yield) followed by $LiAl(OMe)_3H$ reduction giving (*Z*)-**6** (75%) or by $LiAlH_4$ reduction giving (*E*)-**6** (60%).[4]

(6) New compounds have been fully characterized by spectroscopic means; mass spectra of compounds **1–3** matched the spectra of the shallot oil components.[1]

(7) Oxidation of MeCH=CHSCHEtSLi (**11**) prepared from MeCH=CHSCHEtSAc/MeLi gives a product identical by GC–MS to **7a,b**, supporting the structure proposed for **7a,b**.

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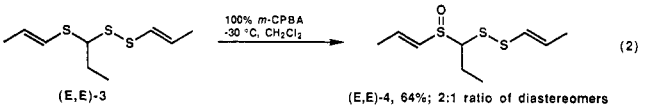
Table I. 1-Propenethiolate/Sulfonyl Chloride Reaction Products

	reagents		ratio/mode[d]	products (isolated yield)[e]
1	(*E*)-MeCH=CHSLi[a]	MsCl	20/I, −78 °C	(*E*)-**2a** (22%), (*E,E*)-**1** (++)
2	(*E*)-MeCH=CHSLi[a]	MsCl	2/D, −78 °C	(*E,E*)-**1** (82%)
3	(*E*)-MeCH=CHSLi[a]	MsCl	0.8/D, −65 °C[g]	(*E,E*)-**3** (27%),[f] (*E,E*)-**7a,b** (18%), (*E,E*)-**1** (++)
4	(*E,Z*)-MeCH=CHSLi[b]	MsCl	0.3/D, −65 °C[g]	**1** (++), **3** (tr), **7** (tr)[c]
5	(*E,Z*)-MeCH=CHSLi[a]	TsCl	0.8/D, −65 °C[g]	**1** (++), **3** (++), **7** (+)[c]
6	(*Z*)-MeCH=CHSLi[a]	MsCl	20/I, −78 °C	(*Z*)-**2a** (34%), (*Z,Z*)-**1** (++)
7	(*Z*)-MeCH=CHSLi[a]	$PrSO_2Cl$	20/I, −78 °C	(*Z*)-**2b** (30%), (*Z,Z*)-**1** (++)
8	(*Z*)-MeCH=CHSLi[a]	MsCl	2/D, −78 °C	(*Z,Z*)-**1** (72%)
9	(*Z*)-MeCH=CHSLi[a]	MsCl	0.8/D, −65 °C[g]	(*Z,Z*)-**3** (23%),[f] (*Z,Z*)-**7a,b** (13%), (*Z,Z*)-**1** (++)
10	10/(*E*)-MeCH=CHLi	(*E,E*)-**1**	−65 °C	(*E,E*)-**3** (31%), (*E,E*)-**7a,b** (16%)

[a] From Li/NH_3 reduction of (*E*)-, (*Z*)- or (*E,Z*)-MeCH=CHSPr (**6**). [b] From reaction of (*E,Z*)-MeCH=CHSAc with MeLi. [c] GC experiment. [d] RSO_2Cl–thiolate mol ratio; I (inverse) indicates addition of thiolate to RSO_2Cl, D (direct) indicates addition of RSO_2Cl to thiolate. [e] tr, +, and ++ indicate trace, moderate and significant amounts, respectively. [f] Trace 2,4,6-triethyl-1,3,5-trithiane (**8**) detected by GC–MS. [g] Rapidly warmed to 5 °C.

82% and 72% yield, respectively).[8] Finally, reaction of *potassium* (*E*)-1-propenethiolate (from (*E*)-MeCH=CHSC(O)Ph/K_2CO_3/MeOH)[9] with (*Z*)-**2a** affords stereochemically pure (*E,Z*)-**1** in 60% yield (eq 1). Despite the modest yields, the simplicity and stereospecificity of these reactions, coupled with ease of product isolation, makes them the method of choice for preparation of these novel α,β-unsaturated disulfide derivatives. Furthermore, since oxidation of 1-propenethiolate isomers to the corresponding disulfides with iodine results in considerable *E*/*Z* isomerization as well as substantially lower yields (ca. 45%), the utility of mesyl chloride for disulfide synthesis is demonstrated.[10]

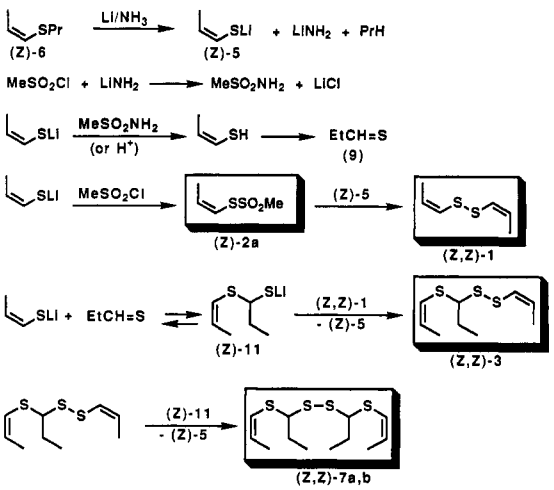
Oxidation of (*E,E*)- or (*Z,Z*)-**3** at −30 °C with 1.06 equiv of 100% *m*-CPBA gave the cepaenes (*E,E*)- or (*Z,Z*)-6-ethyl-4,5,7-trithiadeca-2,8-diene 7-oxide ((*E,E*)-**4a,b** or (*Z,Z*)-**4a,b**), 2:1 mixtures of diastereoisomers, each in 64% isolated yield (eq 2).[6] (*E,E*)-**4a,b** is spectroscopically



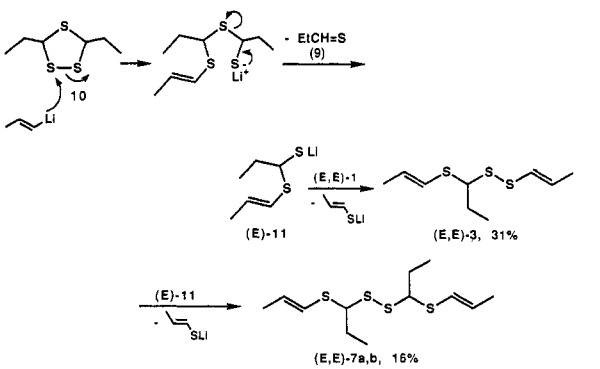
(2)

identical to the diastereomers isolated from onion.[2,11] Cepaenes (*E,E*)-**4a**, (*E,E*)-**4b**, and (*Z,Z*)-**4a,b** inhibit human platelet aggregation with ID_{50} (μM)[12] of 26, 22, and 19 (collagen; 2 μg/mL PRP) and 125, 173, and 104 (10 μM ADP), respectively. Sensory evaluation shows (*Z,Z*)-**1**, (*E,E*)-**3**, and (*E,E*)-**4a,b** to, respectively, have a green, slight onion-like, rubbery sulfur flavor with a taste threshold of 0.01–10 ppb, a green onion, tropical fruit, slightly rubbery sulfur flavor with a taste threshold of 5 ppb, and a slight fresh onion and fruity-melon-like flavor with a taste threshold of 10 ppb.

Scheme I



Scheme I explains product formation in the reaction of (*Z*)-MeCH=CHSLi with MsCl. This scheme, in which propanethial (**9**) is suggested to play a key role, takes into consideration the facts that (1) TsCl gives similar results, excluding involvement of sulfene as an intermediate, (2) treatment of (*E*)-MeCH=CHSLi ((*E*)-**5**) prepared from (*E*)-MeCH=CHSAc/MeLi with MsCl gave only (*E,E*)-**1**, suggesting that the Li/NH_3 reduction is necessary for formation of **3** and **7a,b**; (3) propanethial trimer,[13] 2,4,6-triethyl-1,3,5-trithiane (**8**), is detected by GC–MS; (4) reaction of (*E*)-1-propenyllithium with 3,5-diethyl-1,2,4-trithiolane (**10**) followed by treatment with (*E,E*)-**1** gave (*E,E*)-**3** (31%) and (*E,E*)-**7a,b** (16%) (eq 3), suggesting that



(3)

(8) Prior syntheses of **1**: Hiramitsu, T. Jpn. Kokai Tokkyo Koho JP 01,117,856 [89,117,856] (cl. C07C149/00) 10 May 1989 (*Chem. Abstr.* **1989**, *111*, 194106t). Brandsma, L.; Schuijl, P. J. W. *Recl. Trav. Chim.* **1969**, *88*, 519.

(9) If (*E*)-**5** is instead prepared by Li/NH_3 reduction of (*E*)-**6**, (*E,Z*)-**1** is diastereomerically less pure.

(10) Field previously recommended 1,2-dithiane 1,1,2,2-tetraoxide for mild oxidation of disulfides: Field, L.; Barbee, R. B. *J. Org. Chem.* **1969**, *34*, 1792.

(11) (a) We describe elsewhere[3e,11b] the synthesis of fully saturated and singly unsaturated cepaenes such as 1-(methylsulfinyl)propyl methyl disulfide and 1-(methylsulfinyl)propyl (*E,Z*)-1-propenyl disulfide, isolated by Kawakishi and Morimitsu[11c], and 1-((*E*)-1-propenylsulfinyl)propyl propyl disulfide isolated by Wagner and co-workers.[2] Kawakishi has also synthesized several fully saturated deoxycepaenes and cepaenes.[11d] (b) Gulati, H. M.S. Thesis, SUNY-Albany, 1992; Putman, D. Ph.D. Thesis, SUNY-Albany, 1992. Block, E.; Gulati, H.; Putman, D. Manuscript in preparation. (c) Kawakishi, S.; Morimitsu, Y. *Lancet* **1988**, 330. Morimitsu, Y.; Kawakishi, S. *Phytochemistry* **1990**, *29*, 3435. Morimitsu, Y.; Kawakishi, S. *Agric. Biol. Chem.* **1991**, *55*, 889. Morimitsu, Y.; Morioka, Y.; Kawakishi, S. *J. Agric. Food Chem.* **1992**, *40*, 368. (d) Kawakishi, S., personal communication.

(12) (a) For collagen, the average response of two different blood donors is given. (b) For procedure, see: Block E.; Ahmad, S.; Catalfamo, J. L.; Jain, M. K.; Apitz-Castro, R. *J. Am. Chem. Soc.* **1986**, *108*, 7045.

(13) For triethylamine-catalyzed tautomerization of 1-propenethiol with trithiane formation, see: Brandsma, L. *Rec. Trav. Chim.* **1970**, *89*, 593.

thiolate addition to 9 is reversible. The success of our synthesis depends on forming just enough 9 to form 3 without getting a lot of 7 or trimer 8 while at the same time avoiding (*E,Z*)-isomerization of 5 or MeCH=CHSH.

Acknowledgment. We thank Dr. J. Catalfamo for platelet data and gratefully acknowledge support for this work by the donors of the Petroleum Research Fund, administered by the American Chemical Society, the Herman Frasch Foundation, the National Science Foundation, Société Nationale Elf Aquitaine, and McCormick and Company.

Supplementary Material Available: Experimental procedures for preparation of stereoisomers of 1-4, 6 and 7 (6 pages). This material is contained in many libraries on microfiche, immediately following this article in the microfilm version of the journal and can be ordered from the ACS; see any current masthead page for ordering information.

Sch 47918: A Novel PAF Antagonist from the Fungus *Phoma* sp.

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Received August 4, 1992

Summary: A novel platelet activating factor (PAF) antagonist, Sch 47918, was isolated from the fermentation broth of the fungus, *Phoma* sp. The structure of this compound was elucidated by spectroscopic methods. The proposed structure and stereochemistry of Sch 47918 were confirmed by single-crystal X-ray diffraction analysis. Sch 47918 was found to be active at IC_{50} = 6.96 μM in the in vitro PAF-induced human platelet aggregation assay.

Platelet activating factor (PAF, 1-*O*-alkyl-*sn*-glycerol-3-phosphocholine) is a potential mediator of allergic[1,2] and nonallergic inflammatory[3] diseases. This substance is a very attractive target for developing a new type of antiallergic and antiinflammatory drug. In the course of our screening program for new PAF antagonists, a novel macrocyclic compound, Sch 47918, has been discovered from the fermentation of a fungal culture, SCF-0592, *Phoma* sp.[4] (ATCC 74077). The microorganism, *Phoma* sp., was isolated from a leaf litter sample of mixed *Quercus* species, which was collected in a second growth mixed hardwood lot in Baton Rouge, Louisiana. In this paper, we describe the structure elucidation and biological properties of Sch 47918.

The purification of Sch 47918 was accomplished by EtOAc extraction and gel permeation chromatography followed by precipitation and recrystallization.[5] Its molecular formula, $C_{20}H_{28}O_3$, was determined by HREIMS (*m/z* calcd 316.2038, found 316.2034) in combination with carbon and proton NMR data.[6] IR absorptions at 1705 and 1689 cm^{-1} indicated the presence of aldehyde and conjugated ketone functional groups, and their existence was supported by signals at δ 193.7 and 203.0, respectively, in the ^{13}C NMR spectrum. APT and DEPT experiments revealed that two vinyl carbon signals overlapped at δ 137.9, and thus a total of four olefinic carbons were involved in two C=CH bonds. Two oxygenated carbon resonances at δ 63.3 and 64.2 were ascribed to a trisubstituted epoxide. ^1H NMR spectral data were consistent with the analysis of the ^{13}C NMR spectrum. A doublet of an aldehyde proton at δ 9.90 (*J* = 1.2 Hz) was split by an adjacent methine proton at δ 3.80. Two vinyl protons at δ 5.23 and 6.96 displayed two trisubstituted double bonds. A singlet of oxygenated proton at δ 3.47 suggested an epoxide which is conjugated with a carbonyl group. One doublet and three singlets at δ 0.88, 1.11, 1.32, and 1.60 were assigned as four methyl groups in connection with a methine, an oxygenated carbon, a quarternary carbon, and a double bond, respectively. Analysis of the results of 2D-COSY, HETCOR, and SINEPT experiments (Figure 1) suggested a partial structure (1) containing an aldehyde-attached cyclohexene ring conjugated with a carbonyl group, as well as a subunit (2) that possessed a seven-carbon chain with a trisubstituted double bond and an epoxide ring. As shown in Figure 1, SINEPT long-range ^1H–^{13}C correlation experiments further suggested that the

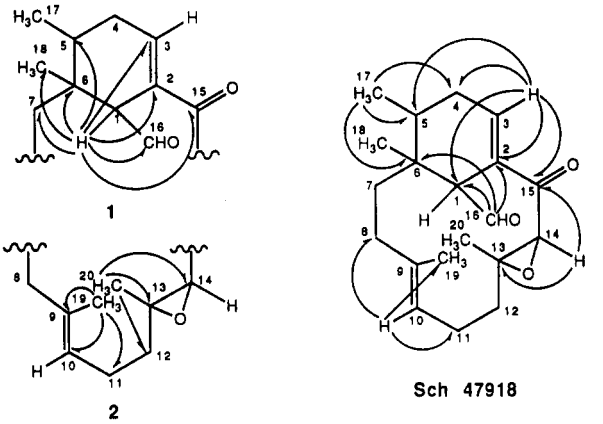

Figure 1. Structure of Sch 47918 as revealed by SINEPT experiments. Arrows indicate ^1H–^{13}C long-range couplings.

(1) Henson, P. M.; Pinckarol, R. N. *J. Immunol.* **1977**, *119*, 2179.
(2) Knover, K. A.; Lightenstein, L. N.; Adikinson, N. F., Jr.; Fish, L. E. *N. Engl. J. Med.* **1981**, *304*, 1404.
(3) Weiss, H. J. *N. Engl. J. Med.* **1975**, *293*, 580.
(4) The fungus was supplied by Dr. B. Katz from MYCOsearch.
(5) A paper describing details of the taxonomy, fermentation, and isolation will be submitted to *J. Antibiot.*
(6) Sch 47918: mp 204–205 °C, $[\alpha]_D^{22}$ +22.4° (*c* 0.3, $CHCl_3$); CI-MS *m/z* 317 $(M + H)^+$; λ_{max} (MeOH) end, 244 (6, 352); ^1H NMR (300 MHz, $CDCl_3$) δ 0.88 (d, *J* = 7.1 Hz, 3H-17), 1.11 (s, 3H-20, 1.12–2.10 (m, 2H-12), 1.32 (s, 3H-18), 1.50–1.65 (m, 1H-5), 1.60 (s, 3H-19), 1.75 (dd, *J* = 7.8, 14.3 Hz, 2H-7), 1.86–2.68 (m, 2H-4), 1.88–2.35 (m, 2H-8), 1.90–2.44 (m, 2H-11), 3.47 (s, 1H-14), 3.80 (br. s, 1H-1), 5.23 (br. d, *J* = 12.1 Hz, 1H-10), 6.96 (br. s, 1H-3) 9.90 (d, *J* = 1.2 Hz, 1H-16); ^{13}C NMR (75 MHz, $CDCl_3$) δ 53.0 (C_1) 133.3 (C_2), 137.9 (C_3), 31.0 (C_4), 36.0 (C_5), 40.2 (C_6), 34.4 (C_7), 24.7 (C_8) 137.9 (C_9), 125.0 (C_{10}), 35.0 (C_{11}), 38.1 (C_{12}), 63.3 (C_{13}), 64.2 (C_{14}), 203.0 (C_{15}), 193.7 (C_{16}), 17.4 (C_{17}), 21.8 (C_{18}), 16.0 (C_{19}), 14.4 (C_{20}).

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