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# First total synthesis of the mastigophorenes C and D and of simplified unnatural analogs

Gerhard Bringmann,* Thomas Pabst, Petra Henschel and Manuela Michel

*Institut für Organische Chemie, Universität Würzburg, Am Hubland, D-97074 Würzburg, Germany*

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**Abstract**—The first total synthesis of the mastigophorenes C (**2**) and D (**3**), natural 'dimeric' sesquiterpenes isolated from the liverwort *Mastigophora diclados* with interesting biological activities, is described. As previously for mastigophorenes A (**1**) and B, the divergent synthetic approach was first optimized on a simplified model system with a *tert*-butyl group instead of the chiral cyclopentyl residue, also in order to find more easily available compounds with similar or even improved biological activity. © 2001 Elsevier Science Ltd. All rights reserved.

## 1. Introduction

The mastigophorenes are novel 'dimeric' sesquiterpenes from the liverwort *Mastigophora diclados* (Mastigophoraceae).[1–4] Besides the core–core coupled, axially chiral natural biaryl product mastigophorene A (**1**) and its atropodiastereomer mastigophorene B (not shown), the constitutionally asymmetric core–sidechain linked isomer mastigophorene C (**2**) was isolated, as well as the again $C_2$-symmetric sidechain–sidechain coupled analog mastigophorene D (**3**). All mastigophorenes are biosynthetically formed from a joint monomeric precursor, herbertenediol (**4**), by oxidative phenolic coupling.[2,3,5] The mastigophorenes A (**1**), B, and D (**3**) exhibit neurotrophic activity and are therefore interesting structures for new therapeutic agents against neurodegenerative diseases.[2,6,7] Mastigophorene C (**2**) and herbertenediol (**4**), by contrast, have negative effects on the growth of nerve cells.[2] Stimulated

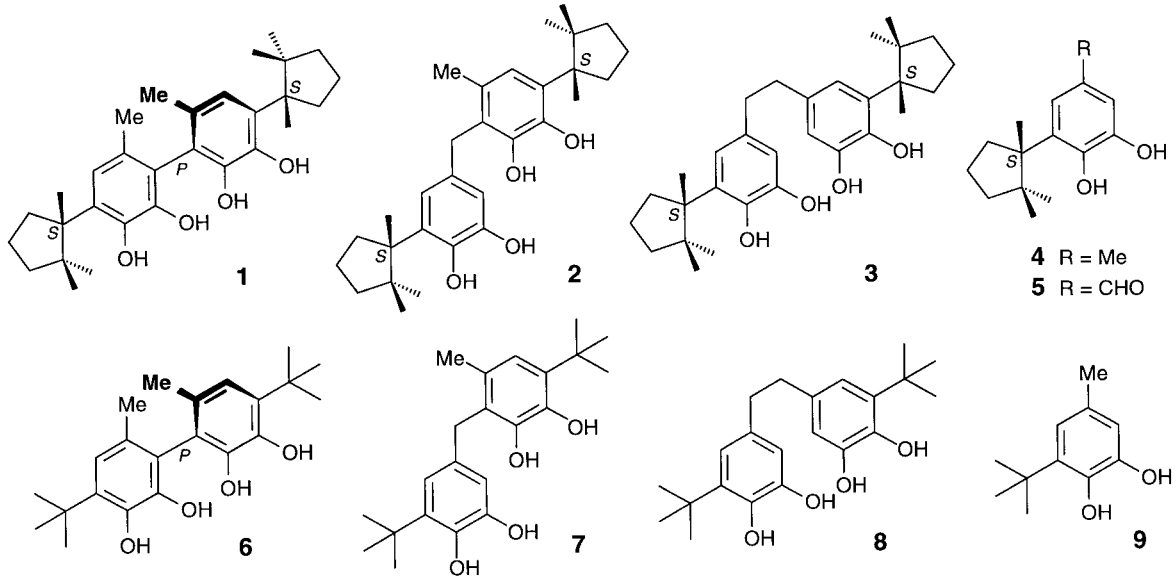


**Figure 1.** Natural sesquiterpenes **1**–**5** from liverworts and simplified unnatural analogs thereof.

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* Corresponding author. Tel.: +49-931-888-5323; fax: +49-931-888-4755; e-mail: bringman@chemie.uni-wuerzburg.de


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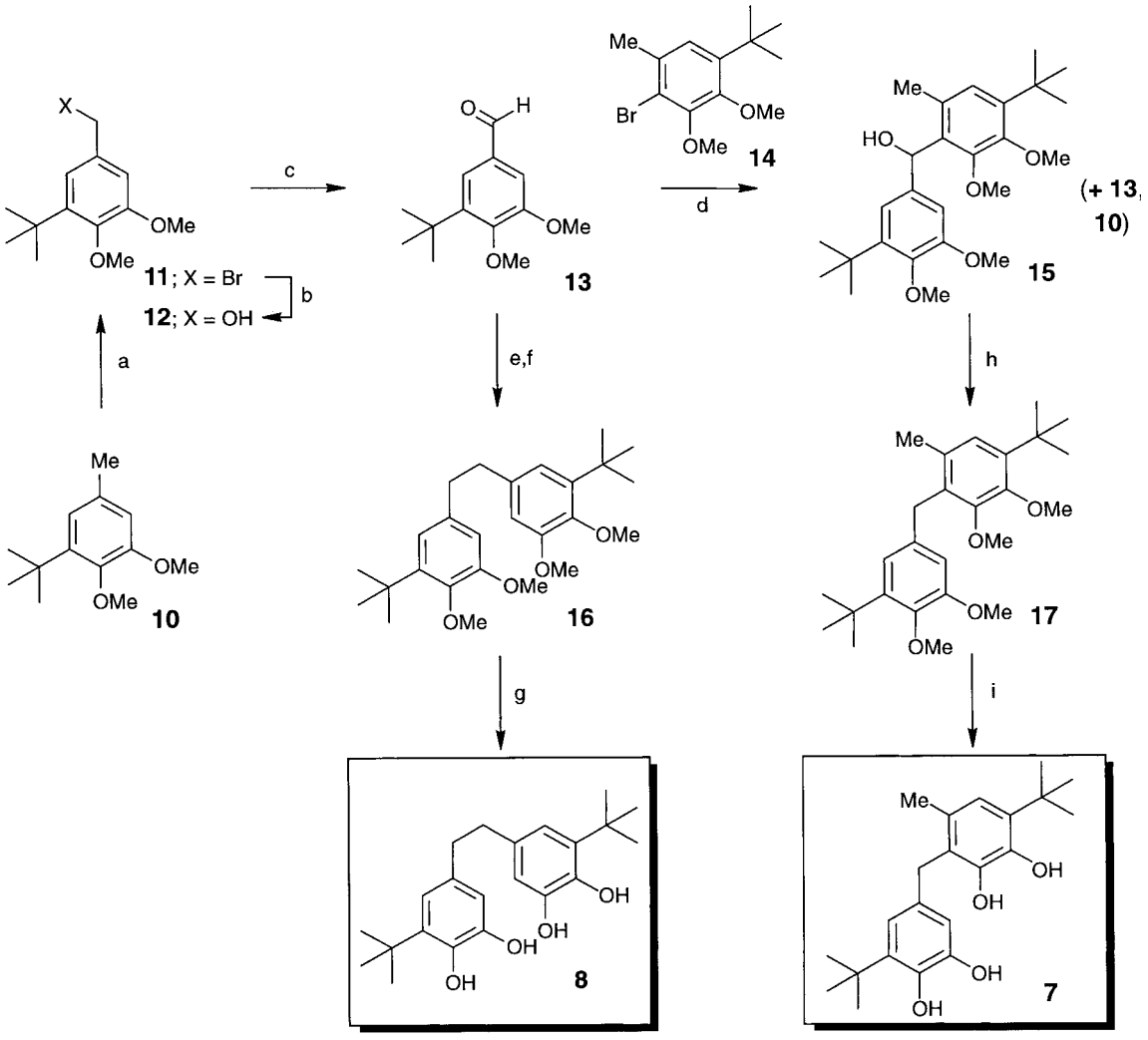



**Scheme 1.** Synthesis of **7** and **8**, as analogs of mastigophorenes C (**2**) and D (**3**). *Reaction conditions*: (a) NBS, $CHCl_3$, 83%; (b) $CaCO_3$, $H_2O$/dioxan; (c) $MnO_2$, $CH_2Cl_2$, 94% from **11**; (d) *n*-BuLi, THF, 60%; (e) $TiCl_4$, Zn, THF, 58%; (f) $H_2$, Pd/C, 95%; (g) $BBr_3$, $CH_2Cl_2$, 91%; (h) $NaBH_4$, $CF_3COOH$, 89%; (i) $BBr_3$, $CH_2Cl_2$, 73%.

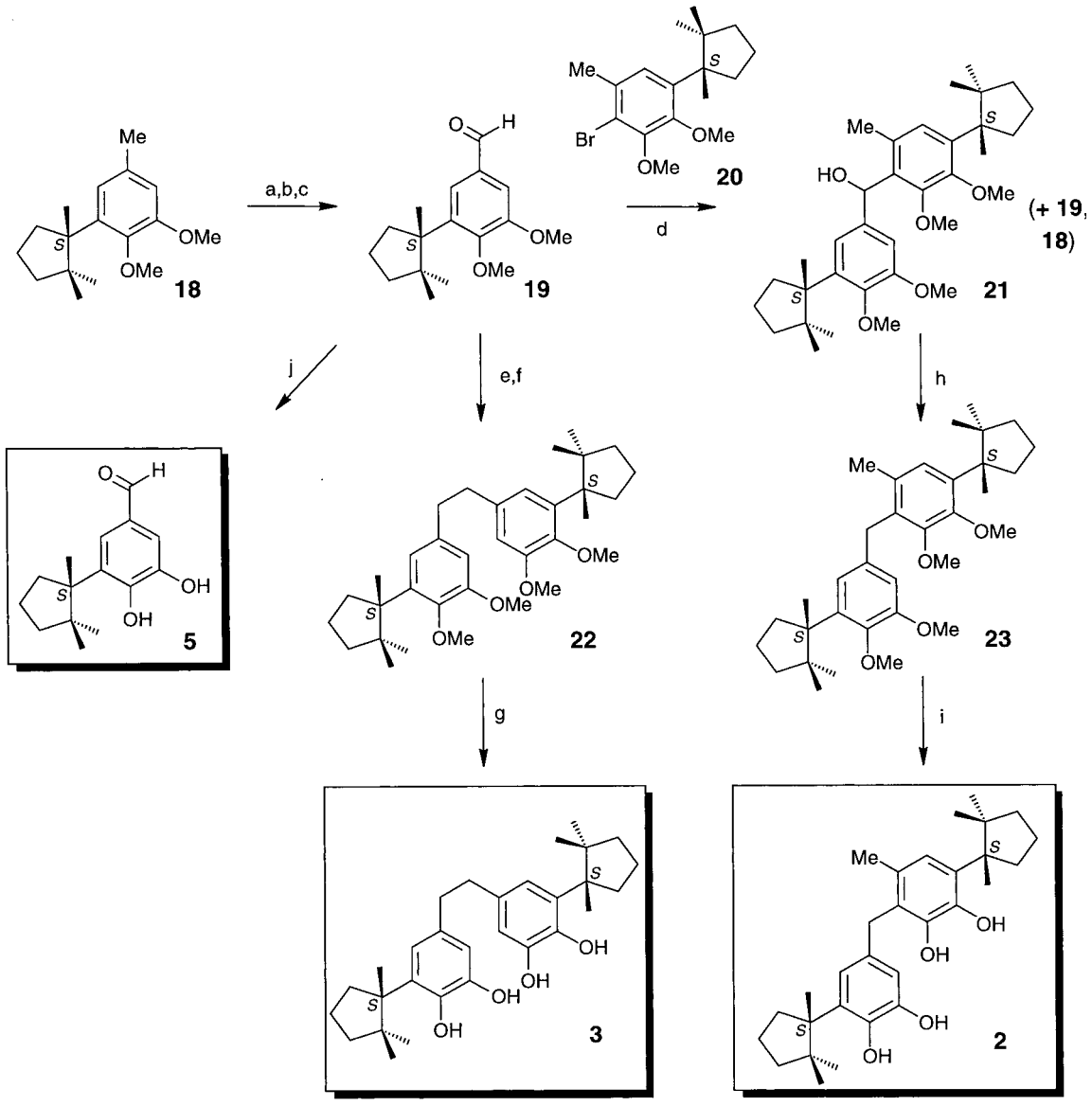
by these bioactivities, we have recently developed methods for the stereoselective total synthesis of herbertenediol (**4**)[8] and for the atropisomer-selective synthesis of mastigophorenes A (**1**) and B.[8,9] In order to find simplified and more easily available structures with similar or even better activities, we have, starting from the achiral herbertenediol analog **9**, prepared the novel model mastigophorene **6** and some derivatives,[10] which were found to be active, too.[11] In these simplified compounds, the chiral cyclopentyl residue is replaced by a *tert*-butyl group. Here we present a short synthesis of the achiral simplified analogs **7** and **8** of the mastigophorenes C (**2**) and D (**3**) and the first total synthesis of the natural products **2** and **3** themselves. In this context, the naturally occurring[12] aldehyde **5** has been prepared for the first time, too (Fig. 1).

## 2. Results and discussion

Suitable synthetic strategies for the preparation of **2** and **3** were first developed on the model system, thus saving the more precious authentic chiral material for the ultimate synthesis and, simultaneously, getting simplified analogs with perhaps even better bioactivities. For a short and rational synthesis of both target molecules, **7** and **8**, from a joint synthetic precursor, aldehyde **13** was chosen as the starting material.

Compound **13** was synthesized in three smooth reaction steps from the *O*,*O*-dimethylated herbertenediol analog **10**,[8] by sidechain bromination with NBS, hydrolysis and subsequent oxidation with $MnO_2$. Transformation of the known[10] building block **14** to the corresponding aryl lithium reagent and reaction with **13** gave the (racemic) diarylcarbinol **15** as the main product, despite the high steric hindrance in **14**. As side products, **13** (unreacted starting material) and **10** (formed from **14** by hydrodehalogenation) were isolated and could be recycled, thus increasing the overall yield. Reductive deoxygenation of **15** with $NaBH_4$/$CF_3COOH$[13] smoothly led to the still tetra-*O*-methylated analog **17**. Ultimate deprotection with $BBr_3$ gave the simplified analog **7** of mastigophorene C (**2**).

'Dimerization' of the same aldehyde **13** under the conditions




**Scheme 2.** First total synthesis of mastigophorenes C (**2**) and D (**3**) and of the aldehyde **5**. *Reaction conditions*: (a) NBS, $CHCl_3$; (b) $CaCO_3$, $H_2O$/dioxan; (c) $MnO_2$, $CH_2Cl_2$, 55% from **18**; (d) *n*-BuLi, THF, 58%; (e) $TiCl_4$, Zn, THF; (f) $H_2$, Pd/C, 67% from **19**; (g) $BBr_3$, $CH_2Cl_2$, 95%; (h) $NaBH_4$, $CF_3COOH$, 83%; (i) $BBr_3$, $CH_2Cl_2$, 94%; (j) $BBr_3$, $CH_2Cl_2$, 92%.

of a McMurry coupling,[14] with subsequent catalytic hydrogenation of the resulting stilbene, led to the sidechain–sidechain coupled product **16** in an overall 55% yield. Subsequent O-demethylation with $BBr_3$ gave the mastigophorene D analog **8** (Scheme 1).

The application of this synthetic strategy to the preparation of the authentic natural target molecules, **2** and **3**, is shown in Scheme 2. In full analogy to the model system above, the joint synthetic precursor to both natural products, compound **19**, was prepared from herbertenediol dimethylether (**18**), which was available from previous total syntheses.[8,15] Arylation of **19** with lithiated **20**[8] gave **21** as a diastereomeric mixture, which, in analogy to the reaction sequence described above, was deoxygenated to **23** and O-demethylated to mastigophorene C (**2**). The product obtained was found to be in full agreement with the data published for the natural product.[1,2] Likewise according to the protocol worked out for the simplified analog **8**, McMurry coupling of **19** and hydrogenation led to **22**, whose O-demethylation completed the straightforward synthesis of mastigophorene D (**3**). The spectroscopic data of **3** were again in full accordance with those reported in the literature.[1,2]

From the key aldehyde **19** even a third synthetically as yet unattained natural product could be prepared (Scheme 2): simple deprotection of **19** with $BBr_3$ gave **5**, a natural 'monomeric' sesquiterpene from the liverwort *Herbertus aduncus*.[12]

The presented total synthesis of mastigophorenes C (**2**) and D (**3**) and the preparation of their simplified analogs **7** and **8** provides sufficient quantities for extended biological tests, which are now under investigation. In addition, the syntheses rigorously confirm the structures and absolute configurations of the natural products.

## 3. Experimental

### 3.1. General

Melting points were measured on a Reichert-Jung Thermovar hot-plate and are uncorrected. IR spectra were taken on a Perkin–Elmer 1420 infrared spectrophotometer and are reported in wave numbers ($cm^{-1}$). NMR spectra were recorded with a Bruker AC 200, AC 250, or AMX 400 spectrometer. The chemical shifts $\delta$ are given in parts per million (ppm) with the proton signals in the deuterated solvent as the internal reference for $^1H$ and $^{13}C$ NMR. Coupling constants, *J*, are reported in Hertz. The mass spectra were obtained on Finnigan MAT 8200 and MAT 90 mass spectrometers at 70 eV in the EI mode.

**3.1.1. 5-Bromomethyl-3-*tert*-butyl-1,2-dimethoxybenzene (11).** To a solution of 1.00 g (4.80 mmol) **10** in 50 ml $CCl_4$, 850 mg (4.80 mmol) NBS and 250 mg (1.03 mmol) $(PhCOO)_2$ were added. After refluxing overnight the reaction mixture was cooled, filtered, and washed with water. The extract was dried ($Na_2SO_4$) and the residue obtained after evaporation of the solvent was purified by column chromatography on silica gel (petroleum ether/$Et_2O$ 10:1), to give 1.15 g (83%) of **11** as an oil: IR (film): $\tilde{\nu}$ 2970, 2920, 2840, 2800 (C–H), 1300, 1130, 1050, 1000; $^1H$ NMR (250 MHz, $CDCl_3$): $\delta$=1.38 [s, 9H, $C(CH_3)_3$], 3.87 (s, 3H, $OCH_3$), 3.88 (s, 3H, $OCH_3$), 4.49 (s, 2H, $CH_2Br$), 6.87 (d, *J*=2.1 Hz, 1H, Ar–H), 6.93 (d, *J*=2.1 Hz, 1H, Ar–H); $^{13}C$ NMR (63 MHz, $CDCl_3$): $\delta$=30.39 [$C(CH_3)_3$], 34.76 ($CH_2Br$) 35.05 [$C(CH_3)_3$], 55.71, 60.34 ($OCH_3$), 111.3, 119.7, 132.0, 143.4, 148.7, 153.2 (Ar–C); MS: *m/z* (%)=288/286 (3/3) [$M^+$], 207 (100) [$M^+-Br$], 193 (70) [$207-CH_2$], 178 (46) [$193-CH_3$]; Anal. calcd for $C_{13}H_{19}BrO_2$ (287.2): C, 54.37; H, 6.67. Found: C, 54.73; H 6.78.

**3.1.2. 5-*tert*-Butyl-3,4-dimethoxybenzaldehyde (13).** To a solution of 1.00 g (3.48 mmol) **11** in a mixture of 25 ml water and 25 ml dioxan, 1.74 g (17.4 mmol) $CaCO_3$ were added. The solution was refluxed overnight, then acidified with 2N HCl and extracted with $CH_2Cl_2$. The dried ($Na_2SO_4$) extract was concentrated to ca. 150 ml and, after addition of 3.10 g (35.7 mmol) $MnO_2$, the reaction mixture was warmed to 30°C with ultrasonic irradiations. After complete reaction the mixture was filtered and purified by column chromatography on silica gel (petroleum ether/$Et_2O$ 4:3) to yield **13** (726 mg, 97%) as colorless oil. IR (KBr): $\tilde{\nu}$ 3050, 2940, 2850 (C–H), 1680 (C=O), 1375, 1302, 1225, 1000; $^1H$ NMR (250 MHz, $CDCl_3$): $\delta$=1.41 [s, 9H, $C(CH_3)_3$], 3.92 (s, 3H, $OCH_3$), 3.95 (s, 3H, $OCH_3$), 7.35 (d, *J*=1.8 Hz, 1H, 2-H or 6-H), 7.46 (d, *J*=1.8 Hz, 1H, 2-H or 6-H), 9.88 (s, 1H, CHO); $^{13}C$ NMR (63 MHz, $CDCl_3$): $\delta$=30.23 [$C(CH_3)_3$], 35.27 [$C(CH_3)_3$], 55.84, 60.60 ($OCH_3$), 109.1, 123.8, 131.3, 143.2, 153.8, 154.3 (Ar–C), 191.7 (C=O); MS: *m/z* (%)=222 (54) [$M^+$], 207 (100) [$M^+-CH_3$], 192 (23) [$207-CH_3$], 179 (36) [207−CO]; Anal. calcd for $C_{13}H_{18}O_3$ (222.3): C, 70.24; H, 8.16. Found: C, 69.96; H, 7.93.

Optional workup after hydrolysis and column chromatography on silica gel (petroleum ether/$Et_2O$ 1:1) and subsequent crystallization from petroleum ether gave 5-*tert*-butyl-3,4-dimethoxybenzyl alcohol (**12**): mp 73°C; IR (film): $\tilde{\nu}$ 3300, 3260 (OH), 2960, 2940, 2820 (C–H), 1140, 1070, 1010; $^1H$ NMR (250 MHz, $CDCl_3$): $\delta$=1.38 [s, 9H, $C(CH_3)_3$], 3.87 (s, 6H, $OCH_3$), 4.62 (s, 2H, $CH_2OH$), 6.87–6.89 (m, 2H, Ar–H); $^{13}C$ NMR (63 MHz, $CDCl_3$): $\delta$=30.49 [$C(CH_3)_3$], 35.07 [$C(CH_3)_3$], 55.70, 60.36 ($OCH_3$), 65.74 ($CH_2OH$), 109.5, 117.5, 135.33, 143.3, 148.0, 153.3 (Ar–C); MS: *m/z* (%)=224 (49) [$M^+$], 209 (100) [$M^+-CH_3$], 194 (37) [$209-CH_3$]; Anal. calcd for $C_{13}H_{20}O_3$ (224.3): C, 69.61; H, 8.99. Found C, 69.25; H, 8.88.

**3.1.3. (*rac*)-4,5′-Di-*tert*-butyl-6-methyl-2,3,3′,4′-tetramethoxy-diphenylmethanol (15).** To a cooled (0°C) solution of 116 mg (403 μmol) **14** and 73 μl (806 μmol) TMEDA (*N*,*N*,*N*′,*N*′-tetramethylethylenediamine) in dry THF (3 ml), 177 μl (443 μmol) of *n*-BuLi (2.5 M in *n*-hexane) were added. After 20 min of stirring a solution of 98.5 mg (443 μmol) **13** in 3 ml dry THF was added dropwise. The obtained solution was stirred for 1 h at 0°C and then at room temperature overnight. The reaction mixture was quenched with water and 2N HCl and extracted with $Et_2O$. The extract was dried ($Na_2SO_4$), the solvent was evaporated, and the obtained residue was fractionated by column chromatography on silica gel (petroleum ether/$Et_2O$ 10:1→1:1) to yield 104 mg (60% relative to **14**) of **15** as an oil, besides 29.2 mg (30%) of **13** and 26.0 mg (31% relative to **14**) of **10**. IR (film): $\tilde{\nu}$ 3420 (OH), 2920, 2840, 2800 (C–H), 1560, 1440, 1290, 1220, 1060; $^1H$ NMR (250 MHz, $CDCl_3$): $\delta$=1.29 [s, 9H, $C(CH_3)_3$], 1.37 [s, 9H, $C(CH_3)_3$], 2.32 (s, 3H, $CH_3$), 3.34 (s, 3H, $OCH_3$), 3.81 (s, 3H, $OCH_3$), 3.82 (s, 3H, $OCH_3$), 3.85 (s, 3H, $OCH_3$), 4.20 (d, *J*=10.7 Hz, 1H, C*H*OH), 6.72 (dd, *J*=2.1 Hz, *J*=0.9 Hz, 1H, 2′-H or 6′-H), 6.87 (d, *J*=0.6 Hz, 1H, 5-H), 6.90 (dd, *J*=2.0 Hz, *J*=0.8 Hz, 1H, 2′-H or 6′-H); $^{13}C$ NMR (63 MHz, $CDCl_3$): $\delta$=19.61 ($ArCH_3$), 30.48, 30.49 [$C(CH_3)_3$], 34.88, 35.06 [$C(CH_3)_3$], 55.73, 59.35, 59.51, 60.33 ($OCH_3$), 71.65 (CHOH), 108.3, 116.0, 123.6 (Ar–CH), 130.0, 134.0,139.3, 142.5, 143.0, 147.2, 151.0, 151.8, 153.0 (Ar–C); MS: *m/z* (%)=430 (38) [$M^+$], 373 (17) [$M^+-C_3H_9$], 235 (100) [$CH_3C_6H(C_4H_9)(OCH_3)_2CO^+$], 207 (19) [$CH_3C_6H(C_4H_9)(OCH_3)_2^+$], 57 (19) [$C_3H_9^+$]; Anal. calcd for $C_{26}H_{38}O_5$ (430.6): C, 72.53; H, 8.90. Found: C, 72.25; H, 9.00.

**3.1.4. 4,5′-Di-*tert*-butyl-6-methyl-2,3,3′,4′-tetramethoxy-diphenylmethane (17).** A suspension of 22.0 mg (576 μmol) $NaBH_4$ in 1 ml trifluoroacetic acid was stirred for 15 min. Then a solution of 62.0 mg (144 μmol) **15** in trifluoroacetic acid (5 ml) was added dropwise at room temperature. After stirring for 2 h the mixture was cooled, diluted with water, and NaOH was added. The mixture was extracted with $Et_2O$, the extract was washed with brine, dried over $Na_2SO_4$, and the solvent was removed under reduced pressure. Column chromatography on silica gel (petroleum ether/$Et_2O$ 5:1) gave **17** (53.2 mg, 89%) as colorless oil. IR (KBr): $\tilde{\nu}$ 2930, 2840, 2810 (C–H), 1560, 1440, 1290, 1230, 1060, 1040; $^1H$ NMR (250 MHz, $CDCl_3$): $\delta$=1.32 [s, 9H, $C(CH_3)_3$], 1.38 [s, 9H, $C(CH_3)_3$], 2.22 (s, 3H, $CH_3$), 3.71 (s, 3H, $OCH_3$), 3.76 (s, 3H, $OCH_3$), 3.82 (s, 3H, $OCH_3$), 3.88 (s, 3H, $OCH_3$), 3.93 (s, 2H, $CH_2$), 6.63 (d, *J*=2.0 Hz, 1H, 2′-H or 6′-H), 6.72 (d, *J*=2.0 Hz, 1H, 2′-H or 6′-H), 6.85 (s, 1H, 5-H); $^{13}C$ NMR (50 MHz, $CDCl_3$):

$\delta$=19.75 ($ArCH_3$), 30.60, 30.63 [$C(CH_3)_3$], 32.45 ($CH_2$), 34.82, 34.98 [$C(CH_3)_3$], 55.66, 59.79, 59.91, 60.39 ($OCH_3$), 110.9, 118.9, 123.4 (Ar–CH), 131.3, 131.5,135.5, 141.3, 142.7, 146.2, 150.7, 151.9, 153.0 (Ar–C); MS: *m/z* (%)=414 (100) [$M^+$], 399 (14) [$M^+-CH_3$], 353 (14) [$M^+-C_4H_9$], 221 (42) [$CH_3C_6H(C_4H_9)(OCH_3)_2CH_2^+$], 207 (40) [$CH_3C_6H(C_4H_9)(OCH_3)_2^+$], 57 (48) [$C_4H_9^+$]; Anal. calcd for $C_{26}H_{38}O_4$ (414.6): C, 75.32; H, 9.24. Found: C, 74.68; H, 8.95.

**3.1.5. 4,5′-Di-*tert*-butyl-6-methyl-2,3,3′,4-tetrahydroxydiphenylmethane (7).** To a cooled (0°C) solution of 35.0 mg (84.5 μmol) **17** in 10 ml dry $CH_2Cl_2$, 370 μl (370 μmol) of a $BBr_3$ solution (1 M in $CH_2Cl_2$) was added. After complete reaction (TLC), the solution was quenched with MeOH, the solvent was removed under reduced pressure, and the residue was purified by column chromatography on silica gel (petroleum ether/$Et_2O$ 4:3). Crystallization from *n*-hexane gave 22.2 mg (73%) of **7**: mp 162°C; IR (KBr): $\tilde{\nu}$ 3460 (OH), 3010, 2940, 2880, 2840 (C–H), 1580, 1420, 1300, 1220, 1190, 970; $^1$H NMR (200 MHz, $CDCl_3$): $\delta$=1.40 [s, 9H, $C(CH_3)_3$], 1.41 [s, 9H, $C(CH_3)_3$], 2.26 (s, 3H, $CH_3$), 3.87 (s, 2H, $CH_2$), 6.34 (d, *J*=2.2 Hz, 1H, 2′-H or 6′-H), 6.72 (s, 1H, 5-H), 6.72 (d, *J*=2.1 Hz, 1H, 2′-H or 6′-H); $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$=19.73 ($ArCH_3$), 29.52, 29.63 [$C(CH_3)_3$], 32.29 ($CH_2$), 34.36, 34.68 [$C(CH_3)_3$], 112.3, 119.3, 120.2 (Ar–CH), 123.5, 126.9, 129.4, 134.1, 137.0, 141.8, 141.9, 142.0, 143.3 (Ar–C); MS: *m/z* (%)=358 (60) [$M^+$], 193 (83) [$CH_3C_6H(C_4H_9)(OH)_2CH_2^+$], 192 (100) [$CH_3C_6H(C_4H_9)(OH)_2CH^+$], 177 (52) [$CH_3C_6H_2(C_4H_9)(OH)_2^+$]; exact mass calcd for $C_{22}H_{30}O_4$: 358.2144. Found: 358.2145.

**3.1.6. (*E*)-1,2-Bis-(5′-*tert*-butyl-3′,4′-dimethoxyphenyl)-ethene.** To a stirred suspension of 1.10 g (16.9 mmol) zinc powder in 11 ml dry THF, 780 μl (7.19 mmol) $TiCl_4$ were added dropwise at −10°C. Then this mixture was heated to reflux and a solution of 576 mg (2.59 mmol) **13** in 23 ml dry THF was added slowly. After 24 h of refluxing the reaction was quenched with saturated aqueous $NaHCO_3$ solution, the organic solvent was removed under reduced pressure and the remaining layer was extracted with $Et_2O$. The extract was dried ($MgSO_4$), concentrated in vacuo, and the obtained residue was purified by column chromatography on silica gel (petroleum ether/$Et_2O$ 5:1). Crystallization from petroleum ether gave 310 mg (58%) of (*E*)-1,2-bis-(5′-*tert*-butyl-3′,4′-dimethoxyphenyl)ethene as colorless crystals: mp 157–160°C; IR (KBr): $\tilde{\nu}$ 2980, 2925, 2840, 2800 (C–H), 1560, 1315, 1245, 1060, 1000; $^1$H NMR (250 MHz, $CDCl_3$): $\delta$=1.41 [s, 18H, $C(CH_3)_3$], 3.89 (s, 6H, $OCH_3$), 3.92 (s, 6H, $OCH_3$), 6.94 (s, 2H, C=CH), 7.00 (d, *J*=2.1 Hz, 2H, 2′-H or 6′-H), 7.03 (d, *J*=2.1 Hz, 2H, 2′-H or 6′-H); $^{13}$C NMR (63 MHz, $CDCl_3$): $\delta$=30.54 [$C(CH_3)_3$], 35.13 [$C(CH_3)_3$], 55.77, 60.48 ($OCH_3$), 107.8 (C=C), 118.0, 127.7 (Ar–CH), 132.3, 143.3, 148.3, 153.4 (Ar–C); MS: *m/z* (%)=412 (100) [$M^+$], 397 (29) [$M^+-CH_3$], 57 (35) [$C_4H_9^+$]; Anal. calcd for $C_{26}H_{36}O_4$ (412.6): C, 75.69; H, 8.80. Found: C, 75.72; H, 8.56.

**3.1.7. 1,2-Bis-(5′-*tert*-butyl-3′,4′-dimethoxyphenyl)ethane (16).** To a solution of 310 mg (751 μmol) (*E*)-1,2-bis-(5′-*tert*-butyl-3′,4′-dimethoxyphenyl)ethene in 10 ml EtOH and 10 ml ethyl acetate, 50 mg Pd/C (10%) were added and the mixture was hydrogenated with $H_2$ at atmospheric pressure. After complete reaction (TLC) the solvent was removed in vacuo and the obtained residue was submitted to column chromatography on silica gel (petroleum ether/$Et_2O$ 5:1) and to crystallization from *n*-hexane, to yield pure **16** (296 mg, 95%): mp 118°C; IR (KBr): $\tilde{\nu}$ 3040, 2980, 2920, 2840, 2800 (C–H), 1560, 1400, 1310, 1240, 1055, 1000; $^1$H NMR (250 MHz, $CDCl_3$): $\delta$=1.35 [s, 18H, $C(CH_3)_3$], 2.84 (s, 4H, $CH_2$), 3.82 (s, 6H, $OCH_3$), 3.85 (s, 6H, $OCH_3$), 6.59 (d, *J*=1.8 Hz, 2H, 2′-H or 6′-H), 6.67 (d, *J*=2.1 Hz, 2H, 2′-H or 6′-H); $^{13}$C NMR (63 MHz, $CDCl_3$): $\delta$=30.61 [$C(CH_3)_3$], 35.01 [$C(CH_3)_3$], 38.16 ($CH_2$), 55.68, 60.35 ($OCH_3$), 110.9, 118.8 (Ar–CH), 136.3, 142.8, 146.5, 152.9 (Ar–C); MS: *m/z* (%)=414 (16) [$M^+$], 207 (100) [$(C_6H_2(OCH_3)_2C(CH_3)_3CH_2^+$]; Anal. calcd for $C_{26}H_{38}O_4$ (414.6): C, 75.32; H, 9.24. Found: C, 75.07; H, 8.96.

**3.1.8. 1,2-Bis-(5′-*tert*-butyl-3′,4′-dihydroxyphenyl)ethane (8).** To a cooled (0°C) solution of 100 mg (241 μmol) **16** in 15 ml dry $CH_2Cl_2$, 92.0 μl (968 μmol) $BBr_3$ were added. After 3 h of stirring the reaction was quenched with MeOH, the solvent was removed in vacuo and the obtained residue was purified by column chromatography on silica gel ($Et_2O$). Crystallization from *n*-hexane gave 79.0 mg (91%) **8** as a colorless solid: mp 194–196°C; IR (KBr): $\tilde{\nu}$ 3460, 3410 (OH), 2930, 2880, 2840 (C–H), 1575, 1420, 1290; $^1$H NMR [250 MHz, $(CD_3)_2CO$]: $\delta$=1.37 [s, 18H, $C(CH_3)_3$], 2.67 (s, 4H, $CH_2$), 6.56 (d, *J*=1.5 Hz, 2H, 2′-H or 6′-H), 6.60 (d, *J*=1.8 Hz, 2H, 2′-H or 6′-H); $^{13}$C NMR [63 MHz, $(CD_3)_2CO$]: $\delta$=29.76 [$C(CH_3)_3$], 34.94 [$C(CH_3)_3$], 38.55 ($CH_2$), 113.6, 118.5 (Ar–CH), 132.7, 135.9, 142.7, 144.7 (Ar–C); MS: *m/z* (%)=358 (10) [$M^+$], 179 (100) [$C_6H_2(OH)_2C(CH_3)_3CH_2^+$]; Anal. calcd for $C_{22}H_{30}O_4$ (358.5): C, 73.71; H, 8.44. Found: C, 73.18; H, 8.34.

**3.1.9. (1′*S*)-3,4-Dimethoxy-5-(1,2,2-trimethylcyclopentyl)-benzaldehyde (19).** To a solution of 400 mg (1.52 mmol) **18** in 20 ml $CCl_4$, 271 mg (1.52 mmol) NBS and 73.9 mg (305 μmol) $(PhCOO)_2$ were added. After refluxing for 3 h the reaction mixture was cooled, filtered, and washed with water. The extract was dried ($MgSO_4$) and, after evaporation of the solvent, the obtained residue was purified by column chromatography on silica gel (petroleum ether/$Et_2O$ 10:1), to give a light yellow oil of 5-bromomethyl-1,2-dimethoxy-3-(1,2,2-trimethylcyclopentyl)benzene, which was directly dissolved in 13 ml dioxan. To this solution, 13 ml water and 763 mg (7.62 mmol) $CaCO_3$ were added and the mixture was heated to reflux overnight. The reaction mixture was acidified with 2N HCl and extracted with $CH_2Cl_2$. The dried ($Na_2SO_4$) extract was concentrated to about 60 ml and, after addition of 1.32 g (15.2 mmol) $MnO_2$, the reaction mixture was warmed to 40°C with ultrasonic irradiation. After completion of the reaction (TLC) the mixture was filtered and purified by column chromatography on silica gel (petroleum ether/$Et_2O$ 4:3) to yield **19** (230 mg, 55%) as a colorless oil: $[\alpha]_D^{23}$=−62.7 (*c*=0.91 in $CHCl_3$); IR (KBr): $\tilde{\nu}$ 3040, 2930, 2850, 2800, 2700 (C–H), 1675 (C=O), 1130; $^1$H NMR (200 MHz, $CDCl_3$): $\delta$=0.68 (s, 3H, $CH_3$), 1.14 (s, 3H, $CH_3$), 1.36 (s, 3H, $CH_3$), 1.39–1.91 (m, 5H, 3′-, 4′-H,

5′-C*H*H), 2.53–2.67 (m, 1H, 5′-CH*H*), 3.87 (s, 3H, $OCH_3$), 3.90 (s, 3H, $OCH_3$), 7.31 (d, $J$=1.8 Hz, 1H, Ar–H), 7.49 (d, $J$=1.9 Hz, 1H, Ar–H), 9.85 (s, 1H, CHO); $^{13}$C NMR (50 MHz, $CDCl_3$): $\delta$=20.28 ($CH_2$), 23.79, 25.22, 26.86 ($CH_3$), 39.23, 41.02 ($CH_2$), 44.90, 51.69 (C-1′ and C-2′), 55.75, 60.48 ($OCH_3$), 108.5, 126.3, 130.9, 141.2, 153.9, 154.7 (Ar–C), 191.6 (C=O); MS: $m/z$ (%)=276 (86) [$M^+$], 245 (87) [$M^+-OCH_3$], 206 (57) [$M^+-C_5H_{10}$], 194 (96) [$M^+-C_6H_{10}$], 193 (73) [$M^+-C_6H_{11}$], 191 (100) [$M^+-C_6H_{13}$], 165 (54) [194−CHO], 163 (69) [191−CO]; Anal. calcd for $C_{17}H_{24}O_3$ (276.4): C, 72.88; H, 8.75. Found: C, 73.53; H, 8.48.

**3.1.10. (1″,1‴*S*)-4,5′-Bis-(1,2,2-trimethylcyclopentyl)-6-methyl-2,3,3′,4′-tetramethoxy-diphenylmethane (23).** To a solution of 89.7 mg (263 μmol) **20** and 48 μl (532 μmol) TMEDA in dry THF (3 ml), 116 μl (289 μmol) of an *n*-BuLi solution (2.5 M in *n*-hexane) were added at 0°C. After stirring for 20 min, 80.0 mg (289 μmol) of the aldehyde **19**, dissolved in 2 ml of dry THF, were added dropwise. The reaction mixture was stirred for 1 h at 0°C and overnight at room temperature, then quenched with water and 2N HCl, and extracted with $Et_2O$. The solvent was evaporated and the obtained residue was fractionated by column chromatography on silica gel (petroleum ether/$Et_2O$ 10:1) to yield 82.0 mg (58% relative to **20**) of the expected product **21** as an oil, besides 26.7 mg (33%) of **19** and 29.8 mg (42% relative to **20**) of **18**. The obtained oil was dissolved in $CF_3COOH$ (2 ml) and added dropwise to a solution of 22.5 mg (595 μmol) $NaBH_4$ in 2 ml $CF_3COOH$. After stirring for 3 h, the reaction mixture was diluted with water, and 2.9 g of solid NaOH were added. Extraction with $Et_2O$, drying with $MgSO_4$, and purification by column chromatography on silica gel (petroleum ether/$Et_2O$ 5:1) gave **23** (64.8 mg, 83%) as a colorless oil. $[\alpha]^{23}_D$=−28.6 ($c$=0.89 in $CHCl_3$); IR (film): $\tilde{\nu}$ 2940, 2840 (C–H), 1560, 1440, 1400, 1380, 1050, 1000; $^1$H NMR (400 MHz, $CDCl_3$): $\delta$=0.63 (s, 3H, $CH_3$), 0.72 (s, 3H, $CH_3$), 0.97 (s, 3H, $CH_3$), 1.15 (s, 3H, $CH_3$), 1.30 1.39 (s, 3H, $CH_3$), 1.47–1.84 (m, 10H, 3″-, 3‴-, 4″-, 4‴-H, 5″-, 5‴-C*H*H), 2.39–2.49 (m, 1H, 5″-CH*H* or 5‴-CH*H*), 2.57–2.70 (m, 1H, 5″-CH*H* or 5‴-CH*H*), 3.63 (s, 3H, $OCH_3$), 3.76 (s, 3H, $OCH_3$), 3.80 (s, 3H, $OCH_3$), 3.81 (s, 3H, $OCH_3$), 3.93–4.02 (m, 2H, α-$CH_2$) 6.54 (d, $J$=1.8 Hz, 1H, 2′- or 6′-H), 6.67 (d, $J$=1.8 Hz, 1H, 2′- or 6′-H), 6.92 (s, 1H, 5-H); $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$=19.67 ($ArCH_3$), 20.23, 20.44 ($CH_2$), 24.07, 24.40, 24.94, 25.24, 26.25, 26.84 ($CH_3$), 32.08 (α-$CH_2$), 38.86, 38.95, 40.59, 40.87 ($CH_2$), 44.88, 45.06, 51.43, 51.60 ($C_q$), 55.52, 59.76, 59.89, 60.40 ($OCH_3$), 110.3, 120.6, 125.5, 131.0, 134.6, 138.5, 140.0, 146.7, 151.1, 152.1, 153.2 (Ar–C); MS: $m/z$ (%)=522 (100) [$M^+$], 440 (11) [$M^+-C_6H_{10}$], 275 (21) [$C_6H(OCH_3)_2(C_8H_{13})CH_3CH_2^+$], 261 (11) [$C_6H(OCH_3)_2(C_8H_{13})CH_3^+$]; Exact mass calcd for $C_{34}H_{50}O_4$: 522.3709. Found: 522.3704.

**3.1.11. Mastigophorene C (2).** To a cooled (0°C) solution of 26.0 mg (49.8 μmol) of tetramethylether **23** in dry $CH_2Cl_2$ (3 ml), 200 μl of $BBr_3$ (1 M in $CH_2Cl_2$) were added. After 3 h of stirring the reaction was quenched with MeOH, the solvent was removed under reduced pressure, and the residue was purified by filtration through silica gel (petroleum ether/$Et_2O$ 1:1), giving 21.8 mg (94%) of **2** as a colorless foam. $[\alpha]^{23}_D$=−47.3 ($c$=0.69 in $CHCl_3$) {Lit.[2] $[\alpha]^{23}_D$=−46.7 ($c$=0.4 in $CHCl_3$)}.

**3.1.12. (1‴,1‴‴*S*)-1,2-Bis-[5′-(1,2,2-trimethylcyclopentyl)-3′,4′-dimethoxyphenyl]ethane (22).** To a cooled (−10°C) suspension of 155 mg (2.37 mmol) zinc powder in 1.6 ml of dry THF, 110 μl (1.01 mmol) $TiCl_4$ were added slowly. The reaction mixture was heated to reflux and a solution of 100 mg (362 μmol) **19** in 3 ml dry THF was added dropwise. After refluxing for 2 h the mixture was cooled and quenched with saturated aqueous $NaHCO_3$ solution, the organic solvent was removed under reduced pressure and the remaining layer was extracted with $Et_2O$. The dried ($MgSO_4$) extract was purified by column chromatography on silica gel (petroleum ether/$Et_2O$ 5:1) to yield a colorless solid. This was directly dissolved in a mixture of 2 ml EtOH and 2 ml ethyl acetate and hydrogenated with $H_2$ and with Pd/C (10%) as the catalyst under atmospheric pressure. After complete reaction (TLC) the mixture was purified by filtration through silica gel (petroleum ether/$Et_2O$ 5:1) to yield **22** as a colorless solid (63.0 mg, 67%): mp 101°C (*n*-hexane); $[\alpha]^{23}_D$= −22.3 ($c$=1.0 in $CHCl_3$); IR (KBr): $\tilde{\nu}$ 2920, 2840 (C–H), 1560, 1450, 1400, 1050, 1000, 830; $^1$H NMR (250 MHz, $CDCl_3$): $\delta$=0.67 (s, 6H, $CH_3$), 1.09 (s, 6H, $CH_3$), 1.34 (s, 6H, $CH_3$), 1.39–1.83 (m, 10H, 3′-, 4′-H, 5′-C*H*H), 2.64–2.49 (m, 2H, 5′-CH*H*), 2.84 (s, 4H, $CH_2$) 3.76 (s, 6H, $OCH_3$), 3.78 (s, 6H, $OCH_3$), 6.51 (d, $J$=2.0 Hz, 2H, Ar–H), 6.71 (d, $J$=2.0 Hz, 2H, Ar–H); $^{13}$C NMR (63 MHz, $CDCl_3$): $\delta$=20.38 ($CH_2$), 24.21, 25.19, 26.75 ($CH_3$), 38.00 ($ArCH_2$), 38.92, 40.80 ($CH_2$), 44.99, 51.59 (C-1′ and C-2′), 55.62, 60.35 ($OCH_3$), 110.6, 121.2, 135.4, 140.1, 147.0, 153.0 (Ar–C); MS: $m/z$ (%)=522 (65) [$M^+$], 440 (13) [$M^+-C_6H_{10}$], 261 (100) [$C_6H_2(OCH_3)_2(C_8H_{13})CH_2^+$], 179 (60) [261−$C_6H_{10}$]; Exact mass calcd for $C_{34}H_{50}O_4$: 522.3709. Found: 522.3714.

**3.1.13. Mastigophorene D (3).** To a cooled (0°C) solution of 31.0 mg (59.4 μmol) **22** in 3 ml dry $CH_2Cl_2$, 238 μl (238 μmol) of a $BBr_3$ solution (1 M in $CH_2Cl_2$) were added. After 1 h of stirring at 0°C and 1 h at room temperature the reaction was quenched with MeOH, the solvent was removed in vacuo, and the obtained residue was purified by filtration through silica gel ($Et_2O$/petroleum ether 1:1). Crystallization from *n*-hexane gave 26.2 mg (95%) **3** as a colorless solid: mp 213–216°C (Lit.[2] 201–203°C); $[\alpha]^{23}_D$=−48.2 ($c$=0.50 in $CHCl_3$) {Lit.[2] $[\alpha]^{23}_D$=−46.1 ($c$=0.5 in $CHCl_3$)}.

**3.1.14. (1′*S*)-3,4-Dihydroxy-5-(1,2,2-trimethylcyclopentyl)benzaldehyde (5).** To a cooled (0°C) solution of 24.7 mg (89.4 μmol) **19** in dry $CH_2Cl_2$ (2 ml), 300 μl of a $BBr_3$ solution (1 M in $CH_2Cl_2$) were added. The stirred solution was allowed to warm up to RT and stirring was continued overnight. Then MeOH was added, the solvent was evaporated, and the residue was purified by column chromatography on silica gel (petroleum ether/$Et_2O$ 1:1). The obtained solid was crystallized from $CH_2Cl_2$ to yield 20.3 mg (92%) of **5** as colorless needles: mp 154°C (Lit.[12] 153–155°C); $[\alpha]^{23}_D$=−76.6 ($c$=0.56 in $CHCl_3$) {Lit.[12] $[\alpha]^{23}_D$=−11 ($c$=1.5 in $CHCl_3$)}; authentic sample of **5** from *Herbertus aduncus*[12,17] $[\alpha]^{23}_D$=−76.1 ($c$=0.50 in $CHCl_3$).

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