ISSN 1984-6428
ONLINE
www.orbital.ufms.br

| Vol 4 | | No. 4 | | October-December 2012 |

Full Paper

Total synthesis of aripuanin, a megastigmane from *Ficus aripuanensis*

*Aline F. Nascimento, Mauricio G. Constantino, and Paulo M. Donate**

Departamento de Química, Faculdade de Filosofia, Ciências e Letras da Universidade de São Paulo, Avenida Bandeirantes nº 3900, 14040-901, Ribeirão Preto, SP, Brazil.

Received: 29 August 2012; revised: 10 October 2012; accepted: 06 December 2012. Available online: 30 December 2012.

ABSTRACT: *The first total synthesis of the natural product aripuanin, a megastigmane recently isolated, was achieved with moderate yields starting from isophorone.*

Keywords: *aripuanin; synthesis; megastigmane; Ficus aripuanensis*

Introduction

A large number of megastigmanes, which are considered to be substances derived from carotenoids by oxidative cleavage of conjugated double bonds, have been isolated from different species of plants [1]. In 1999, a new natural product denominated aripuanin **1**, the norsesquiterpene (*3S,5R,6R,7E,9ξ*)-megastigmane-7-ene-3,5,6,9-tetrol, was isolated from the leaves of *Ficus aripuanensis* C. C. Berg (Moraceae), which belongs to one of the main families of the Amazonian forest [2]. In spite that no use in traditional medicine has been described particularly for *Ficus Aripuanensis*, some species of the *Ficus* genus are used in folk medicine for their antihelmintic, antirheumatic, antifungal, antimicrobial, antibacterial, antiulcer and anti-inflammatory properties, in leucorrhoea and leprosy [2, 3].

Compound **1** can be considered an aglycone of the natural products kiwiinoside **2** and actinidioionoside **3**, whose structures were already elucidated [4] (Figure 1). To the best of our knowledge, no reports describing the synthesis of aripuanin **1** have yet been reported. In this paper, we describe the first total synthesis of **1** starting from readily available isophorone **4**, as outlined in Scheme 1.

* Corresponding author. E-mail: pmdonate@usp.br

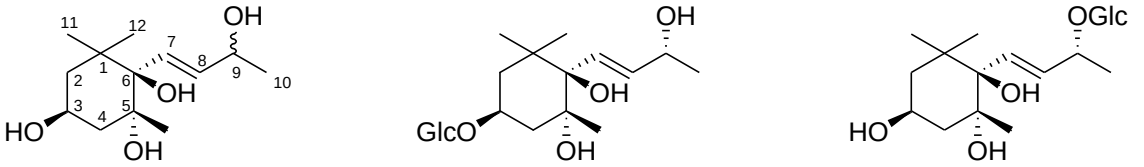


Figure 1. Aripuanin and analogues compounds.

Material and Methods

The common reagents and solvents are commercially available. Column chromatography separation was performed with silica gel 60 (70-230 mesh, Merck). NMR spectra were recorded using a Bruker DRX-400 instrument; chemical shifts are in ppm downfield from a tetramethylsilane internal standard. Infrared spectra were measured with a Perkin Elmer Spectrum RX IFTIR System, and only the most intense or representative bands are reported. HPLC separations were performed on a Shimadzu system with a Shim-pack CLC-CN(M) column. GC-MS analyses were performed by EI ionization at 70 eV on a Shimadzu GC/MS QP-2010 spectrometer. HRMS were recorded on a VG AutoSpec instrument. Elemental analyses were performed with a Carlo Erba instrument EA-1110.

Synthesis of 3,5,5-trimethylcyclohex-3-enol (6)

A solution of compound **5** (5.6911 g, 41.2 mmol), obtained by by the method of Kharasch and Tawney [5], in anhydrous ethyl ether (15 mL), was added to a suspension of $LiAlH_4$ (1.4094 g, 37.1 mmol) in anhydrous ethyl ether (75 mL) at 0 °C. The mixture was heated again to reflux for 4 h, and after the reaction was quenched with cold water (1.5 mL), NaOH 15% (1.5 mL) and finally water (4.5 mL). The solution was filtered through Celite, the filtrate was evaporate and the residue was purified by Kugelrohr distillation under reduced pressure (bp 50 °C, 2 mmHg) to give **6** (5.5375 g, 39.55 mmol, 96%) as a colorless oil.

Analytical data for compound 6: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 5.10 (br s, 1H), 3.95 (dddd, *J* 11.9, 9.3, 5.6 and 3.5 Hz, 1H), 2.21 (dd, *J* 16.4 and 5.6 Hz, 1H), 1.87 (ddq, *J* 16.4, 9.3 and 1.3 Hz, 1H), 1.72 (ddt, *J* 11.9, 3.5 and 1.3 Hz, 1H), 1.65 (s, 3H), 1.52 (br s, 1H), 1.32 (t, *J* 11.9 Hz, 1H), 0.99 (s, 3H), 0.97 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 131.5 (CH), 128.5 (C), 65.5 (CHOH), 45.9 (CH_2), 39.6 (CH_2), 33.9 (C), 31.4 (CH_3), 29.5 (CH_3), 23.2 (CH_3). IR ν_{max}/cm^{-1} 3338, 1742, 1669, 1394, 1360, 1050, 1014, 835. MS: *m/z* (relative intensity) 140 (12, M^+), 125 (100), 122 (7), 107 (36), 91 (23), 84 (47), 69 (42), 55 (30), 41 (35), 39 (27).

Synthesis of 3,5,5-trimethylcyclohex-3-enyl acetate (7)

To a solution of compound **6** (1.0015 g, 7.15 mmol) in anhydrous CH_2Cl_2 (2 mL), were added Et_3N (0.8640 g, 8.54 mmol), Ac_2O (0.8640 g, 8.46 mmol) and DMAP (0.0872 g, 0.71 mmol). The reaction mixture was stirred at room temperature for 3 h and then extracted with ethyl ether. The combined ethereal extracts were washed with HCl (2*M*), saturated solution of $NaHCO_3$ and dried over anhydrous $MgSO_4$. The solvent was removed under reduced pressure and the residue was purified by column chromatography through silica gel using as an eluent a mixture of *n*-hexane and ethyl acetate (9:1) to give **7** (1.1773 g, 6.47 mmol, 90%) as a colorless oil.

Analytical data for compound 7: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 5.12 (1H, s), 5.07 (1H, dddd, *J* 11.9, 9.1, 5.8 and 3.8 Hz), 2.28 (1H, dd, *J* 16.4 and 5.8 Hz), 2.04 (3H, s), 1.93 (1H, ddq, *J* 16.4, 9.1 and 1.3 Hz), 1.72 (1H, ddt, *J* 11.9, 3.8 and 1.3 Hz), 1.64 (3H, s), 1.44 (1H, t, *J* 11.9 Hz), 1.01 (6H, s). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 170.8 (C=O), 131.7 (=CH), 128.2 (=C), 69.4 (CH-O), 41.8 (CH_2), 35.8 (CH_2), 33.7 (CH_3), 31.1 (CH_3), 29.4 (C), 23.2 (CH_3), 21.4 (CH_3). IR ν_{max}/cm^{-1} 1733, 1240, 1034.

Synthesis of 3-hydroxy-3,5,5-trimethyl-4-oxocyclohexyl acetate (8)

To a well-stirred mixture of compound **7** (0.2146 g, 1.17 mmol), water (110 mL), and $MgSO_4$ (0.5275 g, 4.38 mmol), previously cooled to 4 °C, was added dropwise a solution of $KMnO_4$ (0.2242 g, 1.42 mmol) in water (70 mL), maintaining the temperature of the reaction mixture below 6 °C. After the mixture was stirred at room temperature for 15 h, enough sodium sulfite was added to decolorize the solution, and the reaction mixture was filtered through Celite. The clear solution was extracted with ethyl ether in a liquid-liquid extractor. The resultant ethereal solution was dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. The residue was purified by preparative HPLC eluting with a mixture of *n*-hexane and 2-propanol (95:5) to give **8** (0.2096 g, 0.98 mmol, 83%) as a 1:1 mixture of diastereomers *(3R)*-**8a** (white cristalline solid, mp 52-53 °C) and *(3S)*-**8b** (colorless oil).

***Analytical data for compound (3R)-8a*:** ^{1}H NMR ($CDCl_3$, 400 MHz) δ 5.26 (1H, ddt, *J* 7.8, 6.6 and 4.8 Hz), 2.22 (1H, ddd, *J* 14.4, 4.8 and 1.5 Hz), 2.11-2.05 (2H, m), 2.01 (3H, s), 1.86 (1H, dd, *J* 13.9 and 7.8 Hz), 1.38 (3H, s), 1.21 (3H, s), 1.17 (3H, s). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 215.8 (C=O), 170.3 (C=O), 74.5 (C-OH), 66.7 (CH-O), 43.1 (CH_2), 43.1 (CH_2), 43.1 (C), 27.6 (CH_3), 27.5 (CH_3), 27.4 (CH_3), 21.3 (CH_3). IR ν_{max}/cm^{-1} 3447, 1745,1718, 1368, 1247, 1167, 1030.

Analytical data for compound (3S)-8b: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 5.27 (1H, tt, *J* 11.6 and 4.2 Hz), 2.43 (1H, ddd, *J* 12.3, 4.2 and 3.3 Hz), 2.12 (1H, ddd, *J* 13.1, 4.2 and 3.3 Hz), 2.07 (3H, s), 1.89 (1H, dd, *J* 12.3 and 11.6 Hz), 1.74 (1H, dd, *J* 13.1 and 11.6 Hz), 1.47 (3H, s), 1.29 (3H, s), 1.19 (3H, s). ^{13}C-RMN ($CDCl_3$, 100 MHz) δ 217.2 (C=O), 170.8 (C=O), 75.1 (C-OH), 66.5 (CH-O), 45.0 (CH_2), 44.9 (CH_2), 43.3 (C), 28.7 (CH_3),

27.8 (CH_3), 26.8 (CH_3), 21.6 (CH_3). IR ν_{max}/cm^{-1} 3488, 1740,1703, 1368, 1250, 1163, 1031.

Synthesis of 2,4-dihydroxy-2,6,6-trimethylcyclohexanone (9)

A mixture of the diastereomers **8a**/**8b** (0.6046 g, 2.83 mmol), methanol (4 mL), and an aqueous solution of K_2CO_3 10% (4 mL), was stirred at room temperature for 30 min. The methanol was removed under reduced pressure and the residue was extracted with ethyl ether. The organic layer was washed with water, saturated brine, dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. The residue was purified by column chromatography through silica gel using as an eluent a mixture of *n*-hexane and ethyl acetate (1:1) to give **9** (0.4373 g, 2.54 mmol, 90%) as a 1:1 mixture of diastereomers *(3R)*-**9a** (white cristalline solid, mp 86-87 °C) and *(3S)*-**9b** (white cristalline solid, mp 63-64 °C).

***Analytical data for compound (2R)-9a*:** ^{1}H NMR ($CDCl_3$, 400 MHz) δ 4.38 (1H, ddt, *J* 9.1, 7.8 and 4.7 Hz), 2.28 (1H, ddd, *J* 14.0, 4.7 and 2.3 Hz), 2.01 (1H, ddd, *J* 13.6, 4.7 and 2.3 Hz), 1.96 (1H, dd, *J* 14.0 and 7.8 Hz), 1.84 (1H, dd, *J* 13.6 and 9.1 Hz), 1.64 (br s, 1H), 1.44 (3H, s), 1.27 (3H, s), 1.24 (3H, s). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 216.5 (C=O), 75.1 (C-OH), 63.8 (CH-OH), 47.5 (CH_2), 47.4 (CH_2), 43.6 (C), 28.2 (CH_3), 28.1 (CH_3), 27.8 (CH_3). IR ν_{max}/cm^{-1} 3393, 1708, 1374, 1044. Anal. Calcd. for $C_9H_{16}O_3$: C, 62.77; H, 9.36; O, 27.87. Found: C, 63.01; H, 9.52.

***Analytical data for compound (2S)-9b*:** ^{1}H NMR ($CDCl_3$, 400 MHz) δ 4.26 (1H, tt, *J* 10.6 and 4.0 Hz), 2.62 (br s, 1H), 2.40 (1H, ddd, *J* 12.6, 4.0 and 3.3 Hz), 2.08 (1H, ddd, *J* 13.1, 4.0 and 3.3 Hz), 1.87 (1H, dd, *J* 12.6 and 10.6 Hz), 1.72 (1H, dd, *J* 13.1 and 10.6 Hz), 1.42 (3H, s), 1.25 (3H, s), 1.20 (3H, s). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 217.3 (C=O), 74.8 (C-OH), 63.9 (CH-OH), 48.6 (CH_2), 48.1 (CH_2), 42.9 (C), 28.3 (CH_3), 27.6 (CH_3), 26.8 (CH_3). IR ν_{max}/cm^{-1} 3391, 1705, 1367, 1049. Anal. Calcd. for $C_9H_{16}O_3$: C, 62.77; H, 9.36; O, 27.87. Found: C, 62.59; H, 9.13.

Synthesis of (2R,4S)-2,4-bis(methoxymethoxy)-2,6,6-trimethylcyclohexanone (10a)

To a solution of pure compound **9a** (0.1247 g, 0.72 mmol) in anhydrous CH_2Cl_2 (2 mL), were added DPEA (0.2792 g, 2.16 mmol) and methoxymethyl chloride (0.2318 g, 2.88 mmol). The reaction mixture was stirred at room temperature for 4 h and then a saturated solution of $NaHCO_3$ was added. The product was extracted with CH_2Cl_2 and the organic layer was washed with water, saturated brine, dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. The residue was purified by column chromatography through silica gel using as an eluent a mixture of *n*-hexane and ethyl acetate (8:2) to give **10a** (0.1414 g, 0.54 mmol, 75%) as a colorless oil.

***Analytical data for compound 10a*:** ^{1}H NMR ($CDCl_3$, 400 MHz) δ 4.72 (1H, d, *J* 7.1 Hz), 4.70 (1H, d, *J* 7.1 Hz), 4.59 (1H, d, *J* 7.1 Hz), 4.45 (1H, d, *J* 7.1 Hz), 4.33 (1H, tt, *J* 11,1 and 4.3 Hz), 3.40 (3H, s), 3.36 (3H, s), 2.55 (1H, ddd, *J* 13.9, 4.3 Hz and 3.5 Hz), 2.10 (1H, ddd, *J* 13.1, 4.3 and 3.5 Hz), 1.63 (1H, dd, *J* 13.1 and 11.1 Hz), 1.62 (1H, dd, *J* 13.9 and 11.1 Hz), 1.31 (3H, s), 1.29 (3H, s), 1.11 (3H, s). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 211.4 (C=O), 95.2 (CH_2-O), 92.0 (CH_2-O), 79.6 (C-O), 68,3 (CH-O), 55.7 (CH_3-O), 55.3 (CH_3-O), 46.1 (CH_2), 46.0 (CH_2), 44.0 (C), 27.5 (CH_3), 27.2 (CH_3), 21.6 (CH_3). IR ν_{max}/cm^{-1} 1708, 1149, 1102, 1044.

Synthesis of tert-butyl(but-3-yn-2-yloxy)dimethylsilane (11)

To a solution of commercial racemic 3-butyn-2-ol (0.4254 g, 6.0 mmol) in anhydrous THF (7 mL), were added a solution of imidazole (0.4085 g, 6.0 mmol) in anhydrous THF (7 mL). The reaction mixture was stirred at room temperature for 30 min, cooled to 0 °C and then a solution of TBDMSCl (1.0551 g, 7.0 mmol) in anhydrous THF (7 mL) was added. The reaction mixture was stirred overnight at room temperature and then water was added and the product was extracted with ethyl ether. The organic layer was washed with water, saturated brine, dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. The residue was purified by Kugelrohr distillation (bp 50 °C, 30 mm Hg) to yield **11** (1.0212 g, 5.5 mmol, 92%) as a colorless oil.

***Analytical data for compound 11*:** ^{1}H NMR ($CDCl_3$, 400 MHz) δ 4.50 (1H, qd, *J* 6.6 and 2.0 Hz), 2.36 (1H, d, *J* 2.0 Hz), 1.41 (3H, d, *J* 6.6 Hz), 0.89 (9H, s), 0.12 (3H, s), 0.10 (3H, s). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 86.4 (C≡), 71.1 (≡C-H), 58.7 (CH-O), 25.7 (3 CH_3), 25.3 (CH_3), 18.2 (C), -5.0 (CH_3-Si), -4.7 (CH_3-Si). IR ν_{max}/cm^{-1} 3313, 1258, 1104, 1052, 778.

Synthesis of (2R,4S)-1-[3-(tert-butyldimethylsilanoxy)-but-1-ynyl]-2,4-bis-(methoxymethoxy)-2,6,6-trimethylcyclohexanol (12)

To a solution of compound **11** (0.3864 g, 2.10 mmol) in THF (4 mL) at -78 °C was added a solution of *n*-butyllithium in hexane (1.8 mL, 2.34 mmol) and stirred for 40 min. A solution of compound **10a** (0.2188 g, 0.84 mmol) in THF (1 mL) was added and stirred at -78 °C for 5 h. The reaction mixture was quenched by addition of a saturated aqueous solution of ammonium chloride and the product was extracted with ethyl ether. The ethereal layer was washed with water, saturated brine, dried over anhydrous $MgSO_4$ and evaporated. The residue was purified by column chromatography through silica gel using as an eluent a mixture of *n*-hexane and ethyl acetate (8:2) to give compound **12** (0.3183 g, 0.72 mmol, 85%) as a mixture of diastereomers that were used in the next step without further separation.

***Analytical data for compound 12*:** ^{1}H NMR ($CDCl_3$, 400 MHz) δ 4,81 (2H, d, *J* 7.3 Hz),

4.69 (2H, d, *J* 7.3 Hz), 4.65 (2H, d, *J* 6.8 Hz), 4.62 (2H, d, *J* 6.8 Hz), 4.54 (1H, q, *J* 6.6 Hz), 4.53 (1H, q, *J* 6.6 Hz), 3.91 (2H, tt, *J* 11.1 and 4.3 Hz), 3.39 (6H, s), 3.34 (6H, s), 2.20 (2H, ddd, *J* 13.9, 4.3 and 2.3 Hz), 1.82-1.63 (6H, m), 1.47 (6H, s), 1.40 (3H, d, *J* 6.5 Hz), 1.39 (3H, d, *J* 6,5 Hz), 1.14 (6H, s), 1.12 (6H, s), 0.86 (18H, s), 0.08 (6H, s), 0.07 (6H, s). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 94.9 (2 CH_2), 91.6 (2 CH_2), 89.3 (2 C-OH), 83.7 (2 C≡), 82.9 (2 C≡), 77.8 (2 C-O), 69.6 (2 CH-O), 58.9 (2 CH-OSi), 56.3 (2 CH_3), 55.1 (2 CH_3), 43.7 (CH_2), 43.6 (CH_2), 41.2 (CH_2), 41.1 (CH_2), 40.3 (2 C), 29.3 (2 CH_3), 25.7 (6 CH_3), 25.3 (CH_3), 25.2 (CH_3), 23.1 (2 CH_3), 21.7 (2 CH_3), 18.1 (2 C), -5.1 (2 CH_3-Si), -4.7 (2 CH_3-Si). IR ν_{max}/cm^{-1} 3442, 1252, 1145, 1101, 1048, 778.

Synthesis of (2R,4S)-1-[(E)-3-(tert-butyldimethylsilanoxy)-but-1-enyl]-2,4-bis(methoxy-methoxy)-2,6,6-trimethylcyclohexanol (13)

To a solution of compound **12** (0.0411 g, 0.092 mmol) in THF (2 mL), maintained at 0 °C under an nitrogen atmosphere, was added dropwise a solution of Red-Al® 70% in toluene (0.15 mL, 0.54 mmol). The reaction mixture was stirred at room temperature for 6 h. Cold water was added, and the produced white solid was filtered and washed several times with ethyl ether. The organic layer was dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. The residue was purified by column chromatography through silica gel using as an eluent a mixture of *n*-hexane and ethyl acetate (8:2) to yield compound **13** (0.0301 g, 0.067 mmol, 73%) as a mixture of diastereomers that could not be separated.

***Analytical data for compound 13*:** ^{1}H NMR ($CDCl_3$, 400 MHz) δ 5.83 (1H, dd, *J* 15.2 and 4.5 Hz), 5.82 (1H, dd, *J* 15,2 and 4.5 Hz), 5.71 (1H, dd, *J* 15.2 and 3.0 Hz), 5.70 (1H, dd, *J* 15.2 and 3.0 Hz), 4.80 (2H, d, *J* 7.3 Hz), 4.73 (2H, d, *J* 7.3 Hz), 4.68 (2H, d, *J* 6.8 Hz), 4.65 (2H, d, *J* 6.8 Hz), 4.30 (1H, qdd, *J* 6.5, 4.5 and 3.0 Hz), 4.29 (1H, qdd, *J* 6.5, 4.5 and 3.0 Hz), 3.99 (2H, tt, *J* 11.6 and 4.5 Hz), 3.42 (6H, s), 3.36 (6H, s), 2,26 (2H, ddd, *J* 13.9, 4.5 and 2.8 Hz), 1.77 (1H, ddd, *J* 13.4, 4.5 and 2.8 Hz),1.76 (1H, ddd, *J* 13.4, 4.5 and 2.8 Hz), 1.49-1.37 (4H, m), 1.16 (6H, s), 1.14 (6H, d, *J* 6.5 Hz), 1.10 (3H, s), 1.05 (3H, s), 0.89 (18H, s), 0.83 (3H, s), 0.79 (3H, s), 0.05 (6H, s), 0.04 (3H, s), 0,03 (3H, s). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 133.4 (2 HC=), 126.8 (=CH), 126.6 (=CH), 94.3 (2 CH_2), 90.6 (2 CH_2), 82.1 (2 C-OH), 77.8 (2 C-O), 69.2 (2 C-O), 68.2 (CH-OSi), 68.1 (CH-OSi), 55.8 (2 CH_3), 54.5 (2 CH_3), 43.7 (2 CH_2), 40.7 (CH_2), 40.6 (CH_2), 38.8 (2 C), 28.3 (2 CH_3), 28.2 (CH_3), 25.7 (6 CH_3), 24.2 (2 CH_3), 24.0 (2 CH_3), 20.8 (CH_3), 20.7 (CH_3), 17.6 (2 C), -5.4 (2 CH_3-Si), -5.3 (2 CH_3-Si). IR ν_{max}/cm^{-1} 3561, 1250, 1147, 1099, 1051, 835, 775.

Synthesis of (3S,5R,6R/6S,7E,9R/9S)-megastigmane-7-ene-3,5,6,9-tetrol (1a and 1b)

Compound **13** (0.0241 g, 0.054 mmol) was dissolved in 2-propanol (1 mL) and

treated with PPTS (0.0272 g, 0.11 mmol). The reaction mixture was stirred at 50 °C for 48 h and then the solvent was removed under reduced pressure. The residue was purified by column chromatography through silica gel using as an eluent a mixture of *n*-hexane and ethyl acetate (1:1) to give **1a** and **1b** (0.0069 g, 0.028 mmol, 53%) in a 1:1 ratio, together another compound (0.0042 g, 0.015 mmol, 27%) still containing only one protective methoxymethoxy group. For analytical purposes, the diastereomers **1a** and **1b** were separated as colorless oils by column chromatography through silica gel using as an eluent a mixture of *n*-hexane and ethyl acetate (2:8).

Spectral data of isomer 1a (3S,5R,6S,9R/9S): ^{1}H NMR (400 MHz, CD_3OD) δ 5.75 (1H, d, *J* 15.5 Hz, H-7), 5.68 (1H, dd, *J* 15.5 and 6.5 Hz, H-8), 4.20 (1H, m, *J* 6.5 Hz, H-9), 4.02 (1H, tt, *J* 11.6 and 4.6 Hz, H-3), 1.88 (1H, ddd, *J* 13.5, 4.6 and 2.6 Hz, H-4eq), 1.55 (1H, ddd, *J* 12.5, 4.6 and 2.6 Hz, H-2eq), 1.43 (1H, dd, *J* 13.5 and 11.6 Hz, H-4ax), 1.39 (1H, dd, *J* 12.5 and 11.6 Hz, H-2ax), 1.19 (OH, br s), 1.14 (3H, s, H-13), 1.12 (3H, d, *J* 6.5 Hz, H-10), 0.94 (3H, s, H-11 or H-12), 0.72 (3H, s, H-12 or H-11). ^{13}C NMR (100 MHz, CD_3OD) δ 134.1 (C-8), 131.4 (C-7), 79.9 (C-6), 77.1 (C-5), 69.3 (C-9), 65.1 (C-3), 48.1 (C-2), 46.9 (C-4), 40.3 (C-1), 29.4 (C-11), 27.6 (C-12), 25.4 (C-13), 24.0 (C-10).

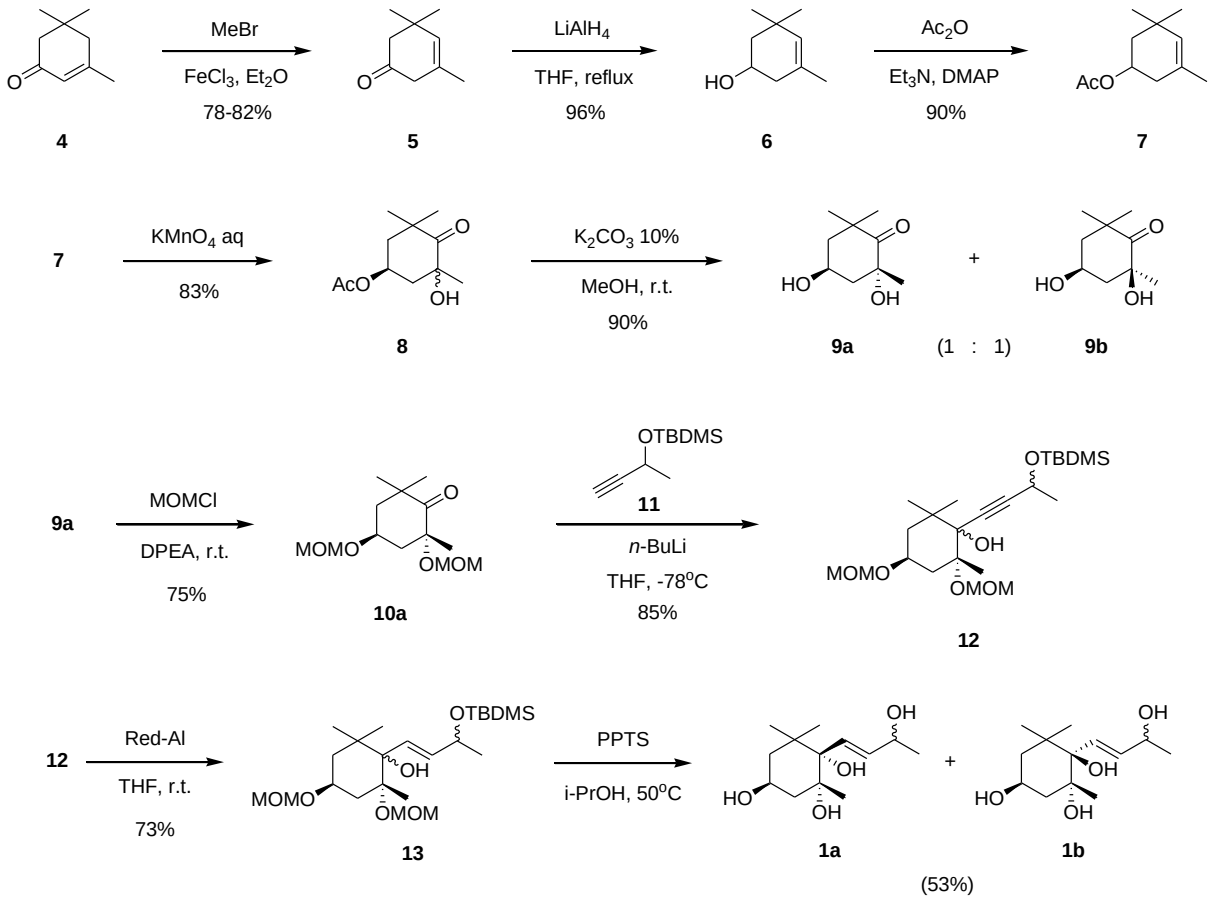
Spectral data of isomer 1b (3S,5R,6R,9R/9S): ^{1}H NMR (400 MHz, CD_3OD) δ 5.75 (1H, d, *J* 15.5 Hz, H-7), 5.67 (1H, dd, *J* 15.5 and 6.5 Hz, H-8), 4.20 (1H, m, *J* 6.5 Hz, H-9), 4.01 (1H, tt, *J* 11.4 and 4.5 Hz, H-3), 1.88 (1H, ddd, *J* 13.4, 4.5 and 2.7 Hz, H-4eq), 1.56 (1H, ddd, *J* 12.5, 4.4 and 2.7 Hz, H-2eq), 1.44 (1H, dd, *J* 13.4 and 11.6 Hz, H-4ax), 1.37 (1H, dd, *J* 12.5 and 11.6 Hz, H-2ax), 1.14 (3H, s, H-13), 1.12 (3H, d, *J* 6.5 Hz, H-10), 0.98 (3H, s, H-11 or H-12), 0.69 (3H, s, H-12 or H-11). ^{13}C NMR (100 MHz, CD_3OD) δ 134.9 (C-8), 129.9 (C-7), 79.9 (C-6), 77.7 (C-5), 68.3 (C-9), 65.0 (C-3), 45.0 (C-2), 44.6 (C-4), 39.5 (C-1), 26.5 (C-11), 26.3 (C-12), 25.3 (C-13), 23.5 (C-10).

Espectral data for mixture of 1a and 1b: IR ν_{max}/cm^{-1} 3395, 1699, 1368, 1229, 981. HRMS *m/z* Calcd for $C_{13}H_{24}O_4$: 244,1675. Found: 244,1642.

Results and Discussion

Several synthetic methods for the megastigmane skeleton have been reported [1, 6]. Our synthesis started from isophorone **4**, that by application of the classic method of Kharasch and Tawney [5] afforded the 3-cyclohexenone **5** in 78-82% yield after purification (Scheme 1). Racemic alcohol **6** was obtained by reduction of **5** with $LiAlH_4$ in 96% yield [7]. Treatment of alcohol **6** with acetic anhydride in triethylamine and 4-*N,N*-dimethylaminopyridine (DMAP) afforded the acetate **7** in 90% yield [8]. Oxidation of **7** with potassium permanganate in neutral aqueous medium gave the keto-alcohol **8** in 83% yield, as a mixture of diastereomers that were separated by preparative HPLC for

analytical purposes. Hydrolysis of the acetate group of **8** was accomplished with a K_2CO_3 solution (10%) in methanol [9] to afford a 1:1 mixture of the diastereomeric keto-diols **9a/9b** in 90% yield, which were separated by column chromatography through silica gel using a 1:1 mixture of *n*-hexane and ethyl acetate as eluent. The protection of the two hydroxyl groups of **9a** by reaction with methoxymethyl chloride and *N,N*-diisopropylethylamine (DPEA) [10] furnished compound **10a** in 75% yield. Reaction of the lithium derivative of compound **11** (obtained by protection of the commercial 3-butyn-2-ol with *tert*-butyldimethylsilyl chloride) [11] with ketone **10a** at -78°C afforded the alkyne **12** in 85% yield, as a 1:1 mixture of diastereomers that could not be separated. Subsequent reduction of **12** with Red-Al® furnished the *7-E* isomer of compound **13** in 73% yield [12]. Treatment of **13** under acidic conditions (HCl/MeOH) cleave the protective groups [10,13] and resulte in a complex mixture of products. On the other hand, the reaction of **13** with 2 equivalents of pyridinium *p*-toluenesulfonate (PPTS) [14] in 2-propanol at 50 °C for 48 h afforded a mixture of compounds **1a**/**1b** (53% yield) in a 1:1 ratio, together another compound (27%) still containing only one protective methoxymethoxy group.



Scheme 1. Synthesis of aripuanin **1** from isophorone **4**.

For analytical purposes, the four diastereomers of **1** were separated in two pairs

of epimers (**1a** and **1b**) by column chromatography through silica gel. The synthetic material **1b** exhibited spectral data in agreement with those reported earlier in literature for aripuanin [2], particularly with regard to the relative stereochemistry at carbons *3S*, *5R* and *6R* that actually corresponds to that of the natural product. However, the absolute configuration of the 9-position remained to be determined.

Conclusion

We have thus accomplished the first total synthesis of the natural product aripuanin **1**, in nine steps starting from commercial isophorone, in an overall yield of 6.5%.

Acknowledgments

The authors thank the Fundação de Amparo à Pesquisa do Estado de São Paulo (FAPESP), the Coordenadoria de Aperfeiçoamento de Pessoal do Ensino Superior (CAPES), and the Conselho Nacional de Desenvolvimento Científico e Tecnológico (CNPq) for financial support. Useful discussions with Dr Gil Valdo José da Silva (FFCLRP-USP) are also acknowledged.

References and Notes

[1] (a) Naves, Y. R. *Perfum. Essent. Oil Rec.* **1964**, *55*, 658-667. (b) Enzell, C. R. *Pure Appl. Chem.* **1969**, *20*, 497. [CrossRef] (c) Ohloff, G. in *Progress in the Chemistry of Organic Natural Products*, Herz, W.; Grisebach, H.; Kirby, G. W. Eds. Wien-Springer-Verlag: New York, 1978, vol. 35, pp. 431. (d) Fraga, B. M. *Nat. Prod. Rep.* **1998**, *15*, 73. [CrossRef] (e) Fraga, B. M. *Nat. Prod. Rep.* **2000**, *17*, 483. [CrossRef] (f) Skouroumounis, G. K.; Gunata, Y. Z.; Baumes, R. L. *J. Essent. Oil Res.* **2000**, *12*, 653. [CrossRef] (g) Wirth, J.; Guo, W. F.; Baumes, R. L.; Gunata, Y. Z. *J. Agric. Food Chem.* **2001**, *49*, 2917. [CrossRef] (h) Fraga, B. M. *Nat. Prod. Rep.* **2001**, *18*, 650. [CrossRef] (i) Fraga, B. M. *Nat. Prod. Rep.* **2002**, *19*, 650. [CrossRef] (j) Fraga, B. M. *Nat. Prod. Rep.* **2003**, *20*, 392. [CrossRef] (k) Kanchanapoom, T.; Chumsri, P.; Kasai, R.; Otsuka, H.; Yamasaki, K. *Phytochemistry* **2003**, *63*, 985. [CrossRef] (l) Takeda, Y.; Shimizu, H.; Masuda, T.; Hirata, E.; Shinzato, T.; Bando, M.; Otsuka, H. *Phytochemistry* **2004**, *65*, 485. [CrossRef]

[2] Nascimento, M; Arruda, A. C.; Arruda, M. S. P.; Müler, A. H.; Yoshioka, C. Y. *Fitoterapia* **1999**, *70*, 628. [CrossRef]

[3] (a) Carauta, J. P. P. *Albertoa* **1989**, *2*, 6. (b) Lopes, D.; Villela, C. T.; Kaplan, M. A. C.; Carauta, J. P. P. *Phytochemistry* **1993**, *34*, 279. [CrossRef] (c) Baungartner, B.; Erdelmeier, C. A. J.; Wright, A. D.; Rali, T.; Sticher, O. *Phytochemistry* **1990**, *29*, 3327. [CrossRef] (d) Jain, N.; Yadava, R. N. *Fitoterapia* **1994**, *65*, 94.

[4] Otsuka, H.; Hirata, E.; Shinzato, T.; Takeda, Y. *Phytochemistry* **2003**, *62*, 763.

[CrossRef]
[5] Kharasch, M. S.; Tawney, P. O. *J. Am. Chem. Soc.* **1941**, *63*, 2308. [CrossRef]
[6] (a) Takazawa, O.; Tamura, H.; Kogami, K.; Hayashi, K. *Bull. Chem Soc. Jpn.* **1982**, 1907. (b) Constantino, M. G.; Donate, P. M.; Petragnani, N. *Tetrahedron Lett*. **1982,** *23*, 1051. [CrossRef] (c) Constantino, M. G.; Donate, P. M.; Petragnani, N. *J. Org. Chem.* **1986**, *51*, 253. [CrossRef] (d) Constantino, M. G.; Donate, P. M.; Petragnani, N. *J. Org. Chem.* **1986**, *51*, 387. [CrossRef] (e) Quirin, M. J.; Taran, M.; Delmond, B. *Synth. Commun.* **1995**, *25*, 3339. [CrossRef] (f) Boulin, B.; Arreguy-San Miguel, B.; Delmond, B. *Tetrahedron* **2000,** *56*, 3927. [CrossRef] (g) Boulin, B.; Arreguy-San Miguel, B.; Delmond, B. *Synth. Commun.* **2003**, *33*, 1047. [CrossRef]
[7] Constantino, M. G.; Donate, P. M.; Frederico, D.; Carvalho, T. V. C.; Cardoso, L. E.; Zuckerman-Schpector J. *Synth. Commun.* **2000**, *30*, 3327. [CrossRef]
[8] Höfle, G.; Steglich, W.; Vorbrüggen, H. *Angew. Chem. Int. Ed. Engl.* **1978**, *17*, 569. [CrossRef]
[9] Plattner, J. J.; Gless, R.D.; Rapoport, H. *J. Am. Chem. Soc.* **1972**, *94*, 8613. [CrossRef]
[10] (a) Greene, T. W.; Wuts, P. G. M. *Protective Groups in Organic Synthesis*, John Wiley & Sons: New York, 3rd ed. 1999. (b) Stork, G.; Takahashi, T. *J. Am. Chem. Soc.* **1977**, *99*, 1275. [CrossRef]
[11] Brandsma, L. *Preparative Acetylenic Chemistry*, Elsevier: Amsterdam, 2nd ed. 1988.
[12] Mayer, H. J.; Rigassi, N.; Schwieter, U.; Weedon, B. C. L. *Helv. Chim. Acta* **1976**, *59*, 1424. [CrossRef]
[13] Wetter, H.; Oertle, K. *Tetrahedron Lett.* **1985**, *26*, 5515. [CrossRef]
[14] Miyashita, M.; Yoshikoshi, A.; Grieco, P. A. *J. Org. Chem.* **1977**, *42*, 3772. [CrossRef]