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An Expeditious Synthesis of Ostopanic Acid, a Plant Anticancer Agent

Dominique Castet-Caillabet, Yvan Ramondenc, Gérard Plé and Lucette Duhamel*

Université de Rouen, IRCOF, UPRES A 6014, F-76821 Mont Saint Aignan Cedex, France.

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Abstract : A new and stereoselective synthesis is described as an easy route to ostopanic acid using a versatile reagent : (2E,4E)-5-bromopentadienal.

Keywords: Antitumour compounds; polyenes; polyenals; polyenones.

The conjugated polyene structure is found in many natural products[1,2] and it has been shown that the double bond geometry is essential to their biological activity. Fatty acids possessing such a conjugated polyene structure occur in plants. One of them, ostopanic acid **1**[3] isolated from stems and fruits of *Ostodes Paniculata Blume* (Euphorbiaceae) inhibits the growth of P-388 lymphocytic leukemia test system in vitro.

To our knowledge, three total syntheses[4-6] have been reported so far in the literature. They feature from *n*-hexyl furane (12% yield),[4] from (1E,3E)-1,4-bis(trimethylsilyl)-1,3-butadiene (53% yield)[5] or from 4-pentynal (47% yield).[6] In addition, two syntheses of ethyl ostopanate from furfural (16% yield)[7] and from diethyl pimelate (57% yield)[8] have also been described.

e-mail : Lucette.Duhamel@univ-rouen.fr; Fax : 33 02 35 52 29 71

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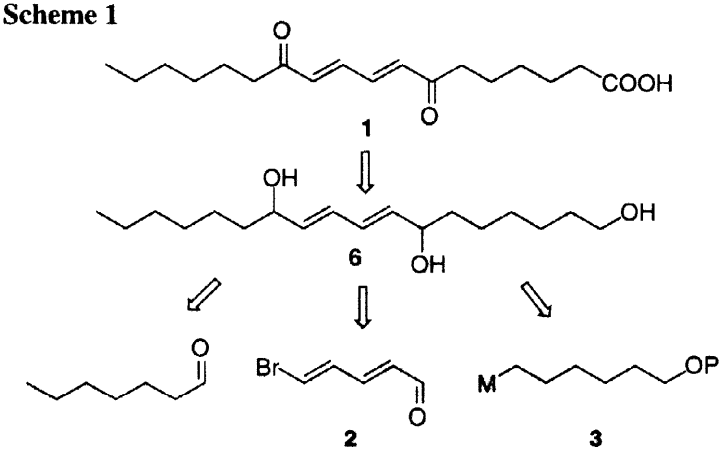
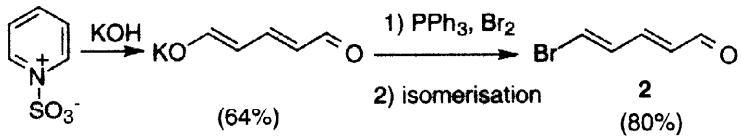
The E,E-dienyl diketone skeleton structure of ostopanic acid **1**, as well as its biological activity, prompted us to develop a synthetic pathway relying on (2E,4E)-5-bromopentadienal **2**[9-11] to introduce the central polyenic pattern with the right configuration in one step (scheme 1).

Scheme 1



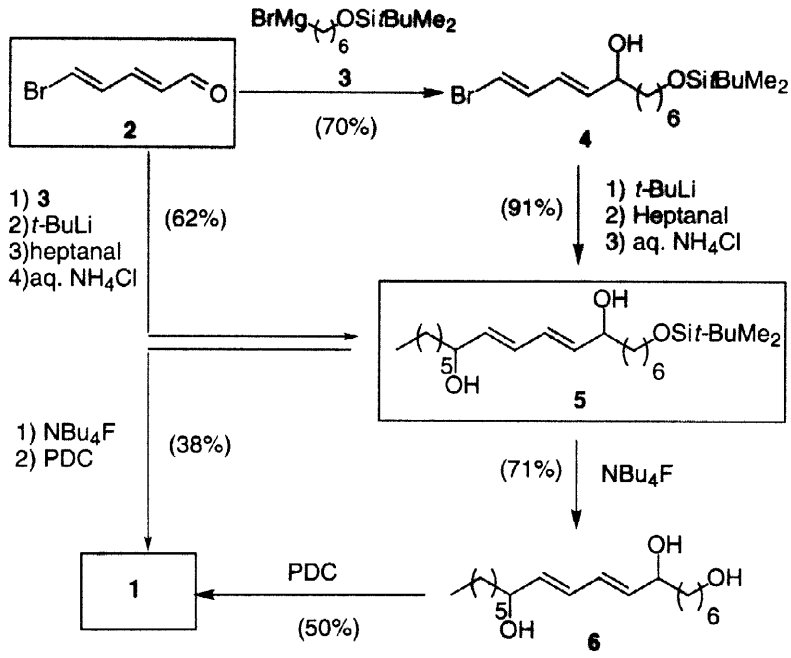
All trans 5-bromopentadienal **2** is obtained by bromination of the potassium salt of glutaconaldehyde with the bromine-triphenylphosphine complex (scheme 2). The two stereoisomers formed (2E,4E/2E,4Z : 75/25) can be easily separated by fractional crystallization (**2** crystallizes in Et_2O at 0°C), or by flash chromatography.[9,10] Moreover, we have recently improved the access to all trans **2** by isomerizing its (2E,4Z) isomer in quantitative yield.[11]

Scheme 2



The first step of the synthesis is the condensation of the organometallic compound **3**[12] on the aldehyde **2** to give the bromohydroxydiene **4** with an all trans configuration. Bromine lithium exchange reaction, followed by condensation with heptaldehyde led to the eighteen carbon atom skeleton of ostopanic acid (*viz.* the monoprotected triol **5**). Deprotection of the primary alcohol of **5** was carried out using tetrabutylammonium fluoride in THF. Then pyridinium dichromate (PDC) oxidation of the resulting trienol **6** led directly to ostopanic acid **1** (scheme 3).

Scheme 3



To improve this procedure we developed a one pot synthesis of **5** from **2**. Furthermore after deprotection of **5**, PDC oxidation can be performed with the crude product **6** without purification. Accordingly, monoprotected triol **5** was obtained in 62% yield, similar to the overall yield of the two step procedure. The transformation of **5** into ostopanic acid **1** performed in the same pot occurred in 38% yield against 36% for the two-step procedure (scheme 3).

In short, we have developed an expeditious two-step stereocontrolled synthesis of ostopanic acid **1** from (2E,4E)-5-bromopentadienal **2** with an overall 23% yield.

EXPERIMENTAL SECTION

230-400 Mesh silica gel was used for flash column chromatography. ^{1}H NMR data were recorded at 200 MHz or 400 MHz and ^{13}C NMR data at 50 MHz or 100 MHz. Mass spectra were recorded by electronic impact at 70 eV. Transmission IR spectra were recorded on FT-IR instrument.

6-Bromo-1-*tert*-butyldimethylsilyloxyhexane

Under argon, TBDMSCl (3.25 g, 21.55 mmol) was added to 6-bromohexan-1-ol (3.00 g, 16.58 mmol) and imidazole (2.60 g, 38.13 mmol) in dry DMF (100 ml). After stirring at room temperature for 2 h the reaction mixture was washed with saturated Na_2CO_3 (50 ml), extracted with light petroleum ether and dried over $MgSO_4$. After removal of the solvent, the residue was chromatographed (eluted with petroleum ether/Et_2O : 90/10) to give a colorless oil (4.63 g, 15.69 mmol, 96 %). GC and MS analyses indicated a partial bromine chlorine exchange:

6-bromo-1-*tert*-butyldimethylsilyloxyhexane / 6-chloro-1-*tert*-butylsilyloxyhexane : 88/12.^{1}H NMR (C_6D_6) (200 MHz) δ : 3.46 (t, 2H, J=6.0), 3.09 (t, 0.24H, J=6.7, CH_2Cl), 2.93 (t, 1.76H, J=6.9, CH_2Br), 1.47 (m, 4H), 1.15 (m, 4H), 0.97 (s, 9H), 0.05 (s, 6H) ppm, ^{13}C NMR (C_6D_6) (50 MHz) δ : 62.96, 33.52, 32.94, 32.85, 28.06, 26.12, 25.24, 18.45 ppm ; IR (cm^{-1}), 2932, 2858, 1472, 1462, 1256, 1104.

1-Bromo-5-hydroxy-11-*tert*-butyldimethylsilyloxyundeca-1,3-diene (4)

A solution of 6-bromo-1-*tert*-butyldimethylsilyloxyhexane (1.03 g, 3.49 mmol) in dry THF (3.4 mL) was added slowly to Mg (0.13 g, 5.35 mmol). After stirring at 45°C for about 3 h, the solution was titrated (I_2 / $Na_2S_2O_3$, C=0.65 M). Then, a solution of all trans 5-bromopentadienal **2** (0.35 g, 2.17 mmol) in dry THF (1 mL) was added at -10°C and stirred for 2h at 0°C. The mixture was quenched with aqueous 10% NH_4Cl (4 mL), extracted with Et_2O ; the organic layer was dried over $MgSO_4$, filtered and reduced in vacuo. Purification of the residue by flash chromatography (eluted with light petroleum ether / Et_2O : 70/30) gave **4** as a yellow syrup (0.57 g, 70 %).^{1}H NMR ($CDCl_3$) (200 MHz) δ : 6,52 (dd, 1H, J=10.8, J=13.4), 5.91 (d, 1H, J=13.5), 5.79 (dd, 1H, J=10.8, J=15.2), 5.34 (dd, 1H, J=6.0, J=15.2), 3.75 (m, 1H), 3.56 (t, 2H, J=6.2), 1.35 (m, 10H + OH), 1.00 (s, 9H), 0.08 (s, 6H) ppm ; ^{13}C NMR ($CDCl_3$) (50 MHz) δ : 137.52, 136.77, 127.10, 108.58, 71.89, 63.10, 36.97, 32.64, 29.22, 25.89, 25.213, 18.24, 5.34 ppm; IR (cm^{-1}), 3368, 2930, 2856, 1584, 1472, 1462, 1256, 1100 ; MS (EI 70eV) m/z (rel. int) 378 (M^++2, 4), 376 (M^+, 4) 321 (16), 303 (59), 279 (9), 239 (33), 205 (17), 173 (45), 145 (100), 119 (81), 93 (91), 65 (90). Anal. Calcd for $C_{17}H_{33}O_2BrSi$: C, 54.10 ; H, 8.81. Found : C, 54.02 ; H, 8.44.

7,12-Dihydroxy-1-*tert*-butyldimethylsilyloxyoctadeca-8,10-diene (5)

a) From **4**

A solution of freshly titrated[13] *t*-BuLi (0.7 mL, 1.77 M in pentane, 1.24 mmol) was added under argon to a solution of bromohydroxydiene **4** (0.13 g, 0.34 mmol) in dry Et_2O (4.0 mL) at -76°C and stirred for 1.5 h. Heptaldehyde (0.09 g , 0.79 mmol) in dry Et_2O (1.0 mL) was added at the same temperature, the mixture was stirred at 0°C for 4 h then quenched with aqueous 10% NH_4Cl (3.0 mL) and extracted with Et_2O. The combined organic layers were dried ($MgSO_4$), filtered and reduced in vacuo. The residue purified by flash silica gel chromatography (eluted with light petroleum ether / Et_2O : 30/70) afforded the dihydroxydiene **5** as a yellow syrup (0.13 g, 91 %). ^{1}H NMR ($CDCl_3$) (200 MHz) δ : 6.18 (m, 2H), 5.69 (m, 2H), 4.11 (m, 2H), 3.57 (t, 2H, J=6.2), 1.41 (m, 20H + 2OH), 0.88 (s, 12H), 0.03 (s, 6H) ppm; ^{13}C NMR ($CDCl_3$) (50 MHz) δ : 136.35, 129.48, 72.27, 63.12, 37.18, 32.67, 31.70, 29.26, 29.16, 25.85, 25.64, 25.30, 22.50, 18.22, 13.97 ppm; IR (cm^{-1}), 3354, 2928, 2856, 1464, MS (EI, 70eV), m/z (rel. int), 394 (16), 338 (100), 309 (16), 245 (47), 223 (21), 185 (81), 161 (59), 135 (93), 113 (95), 91 (87), 59 (81). Anal. Calcd for $C_{24}H_{48}SiO_3$ C, 69.84 ; H, 11.72. Found : C, 69.84 ; H, 11.52.

b) One pot procedure from **2**

A solution of 6-bromo-1-*tert*-butyldimethylsilyloxyhexane (bromoether / chloroether : 88/12) (1.40 g, 4.74 mmol) in dry THF (1.5 mL) was added to Mg (0.25 g, 10.30 mmol) in dry THF (0.5 mL), the mixture was refluxed for 2 h under argon. The solution was titrated (I_2 / $Na_2S_2O_3$, C=1.24 M). A solution of all trans 5-

bromopentadienal **2** (0.40 g, 2.48 mmol) in dry THF (1.5 mL) was added at -10°C and stirred for 2 h. Dry THF (4.0 mL) and a solution of *t*-BuLi (4.1 mL, 1.7 M in pentane, 7.0 mmol) were successively added at -76°C stirred for 1.5 h. Heptaldehyde (0.51 g, 4.47 mmol) in dry THF (2.0 mL) was added at the same temperature, the mixture was stirred at 0°C for 1.5 h. After quenching with aqueous 10% NH_4Cl solution (10 mL), the reaction mixture was extracted with Et_2O, dried ($MgSO_4$), filtered and reduced in vacuo. Flash silica gel chromatography (eluted with petroleum ether / Et_2O : 50 / 50) yielded 0.63 g (62 %) of dihydroxydiene **5**.

(8E,10E)-Octadeca-8,10-dien-1,7,12-triol (6)

A solution of NBu_4F (0.57 mL, 1M in THF, 0.57 mmol) was added under argon to a solution of **5** (0.21 g, 0.51 mmol) in dry THF (0.5 mL) and stirred at room temperature for 6h. Saturated aqueous $NaHCO_3$ (1 mL) was then added. The mixture was extracted with Et_2O, dried ($MgSO_4$) and evaporated in vacuo. Crystallization at 0°C from Et_2O gave triol **6** (0.11 g, 72 %). ^1H NMR ($CDCl_3$) (200 MHz) δ : 6.17 (m, 2H), 5.67 (m, 2H), 4.08 (dd, 2H, J=6.3, J=7.1), 3.60 (t, 2H, J=6.5), 1.10-1.65 (m, 23H), 0.85 (t distorted, 3H) ppm.

Ostopanic acid (1)

a) From **6**

Under argon, PDC (2.20 g, 5.88 mmol) was added to a solution of triol **6** (0.25 g, 0.84 mmol) in DMF (6.5 mL) at 0°C. After stirring for 5 h at 0°C then 15 h at room temperature, water (80 mL) was added, extracted with Et_2O. The solution was dried ($MgSO_4$) and reduced to give a white solid which was crystallized at 0°C from Et_2O to give ostopanic acid **1** (0.13 g, 50 %). ^1H NMR ($CDCl_3$) (400 MHz) δ : 7.19 (m, 1H), 7.13 (m, 1H), 6.49 (m, 1H), 6.45 (m, 1H), 2.60 (t, 2H, J=7.5), 2.57 (t, 2H, J=7.5), 2.35 (t, 2H, J=7.4), 1.63 (m, 6H), 1.26 (m, 8H), 0.87 (t distorted, 3H) ppm; MS (EI, 70eV), m/z (rel. int), 308 (M^+, 50), 290 ($M^+ - H_2O$, 10), 223 ($M^+ - C_6H_{13}$, 27), 210 (40), 195 (55),165 (100), 138 ($C_9H_{14}O$+, 88), 123 (95), 95 (85), 81 (80), 55 (60). m.p. : 133°C, (lit.:[4] 132-133°C).

b) Direct procedure from **5**

A solution of NBu_4F (2.7 mL, 1M in THF, 2.70 mmol) was added under argon to a solution of silyloxy ether **5** (0.57 g, 1.38 mmol) in dry THF (1.5 mL) and stirred at room temperature for 12 h. Saturated aqueous $NaHCO_3$ (5 mL) was added. The reaction mixture was extracted with Et_2O, dried ($MgSO_4$) and reduced in vacuo. The residue was diluted in DMF (7 mL) and PDC (3.45 g) was added at 0°C under argon, stirred for 12 h at this temperature and then for 10 h at room temperature. Water (90 mL) was added. The mixture was extracted with Et_2O, dried ($MgSO_4$), filtered and reduced in vacuo. Crystallization at 0°C from Et_2O gave ostopanic acid **1** (0.16 g, 38 %).

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