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Simple Synthesis of Climacostol, a Defensive Secretion by the Ciliate Climacostomum virens

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Note

Simple Synthesis of Climacostol, a Defensive Secretion by the Ciliate *Climacostomum virens*

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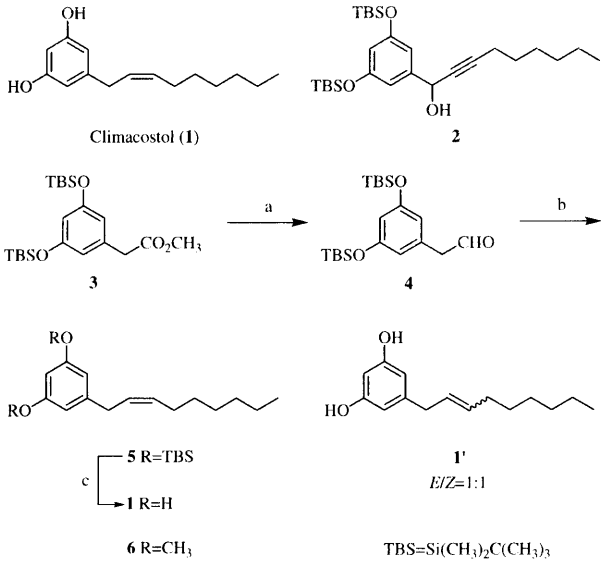
Climacostol {1,3-dihydroxy-5-[(*Z*)-2′-nonenyl] benzene, 1}, a defensive secretion by the protozoan ciliate *Climacostomum virens* against predators, was synthesized in a 43% overall yield in three steps by starting from methyl 1,3-bis(*tert*-butyldimethylsilyloxy) phenylacetate (3).

Key words: alkenyl resorcinol; ciliate; *Climacostomum virens*; defensive toxin; resorcinolic lipid

There are many resorcinolic lipids among natural products, and some of them are ecologically important bioregulators.[1)] In continuation of our work on the synthesis of bioactive alkenylphenols,[2)] we report herein a simple and short synthesis of climacostol (**1**), a defensive secretion produced by the protozoan ciliate, *Climacostomum virens* when it is attacked by the predatory ciliate, *Dileptus margaritifer*.[3)] Iio and his co-workers have verified their proposed structure **1** of climacostol by its synthesis.[3)] Their synthetic route, however, was rather lengthy (six steps starting from 3,5-dihydroxybenzaldehyde) and involved **2** as an intermediate, whose hydroxy group must be reductively removed, and the triple bond had to be reduced to a double bond.[3)]

It occurred to us that climacostol (**1**) might be synthesized simply by employing *Z*-selective Wittig olefination according to Bestmann.[4)] Scheme 1 summarizes our synthesis of **1**. Reduction of known ester **3**,[5)] whose phenolic hydroxy groups were protected as *tert*-butyldimethylsilyl (TBS) ethers, with diisobutylaluminum hydride in toluene at −78°C yielded aldehyde **4**. Treatment of **4** with the Wittig reagent prepared from heptyltriphenylphosphonium bromide and sodium hexamethyldisilazide in tetrahydrofuran (THF) afforded alkene **5**. Fortunately, in this case, the reaction proceeded with high selectivity to give (*Z*)-**5** exhibiting two signals at $\delta = 127.7$ and 131.0 in its ^{13}C-NMR spectrum. An HPLC analysis of **5** revealed it to be 95% pure with 5% of its (*E*)-isomer. Tetrabutylammonium fluoride in THF removed the TBS protective groups of **5** to give climacostol (**1**) in a 43% overall yield based on **3** (three steps). Our synthetic **1** showed ^{1}H- and ^{13}C-NMR spectral data identical with those reported by Iio and his co-workers.[3)] Especially in its ^{13}C-NMR spectrum, only two signals at $\delta = 127.2$ and 131.5 could be observed, revealing it to be a (*Z*)-alkene. A direct HPLC analysis of **1** could not be achieved. Our synthetic **1**, however, was thought to be of 95% purity (*E*/*Z* = 5:95), reflecting the purity of its precursor **5**, because tetrabutylammonium fluoride could hardly cause isomerization of the double bond geometry of **5**. It should be added that demethylation of **6** with boron tribromide in dichloromethane furnished an *E*/*Z* mixture **1′** (*E*/*Z* = 1:1 as estimated by an HPLC analysis of its bisTBS ether), which showed its ^{13}C-NMR signals at $\delta =$



Scheme 1. Synthesis of Climacostol (**1**).
Reagents: (a) $[(CH_3)_2CHCH_2]_2AlH$, toluene. (b) $CH_3(CH_2)_6P(C_6H_5)_3Br$, $NaN[Si(CH_3)_3]_2$, THF (46%, 2 steps). (c) $[CH_3(CH_2)_3]_4NF$, THF (93%).

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127.3, 128.0, 131.4 and 132.5, indicating it to be a mixture of climacostol **1** and its (*E*)-isomer.

In conclusion, a simple synthesis of climacostol was achieved in only three steps of conventional reactions by employing a known starting material.

Experimental

EI-MS: Jeol JMS-AX505HA. IR: Jasco A-102. ^{1}H-NMR: Jeol JNM-LA400 (400 MHz), Jeol JNM-LA500 (500 MHz) (TMS at $\delta=0.00$, $CHCl_3$ $\delta=7.26$ as internal standards). ^{13}C-NMR: Jeol JNM-LA400 (100 MHz), Jeol JNM-LA500 (125 MHz) (TMS at $\delta=0.00$, $CDCl_3$ $\delta=77.0$ as internal standards).

3,5-Bis(tert-butyldimethylsilyloxyphenyl)acetaldehyde (4). A solution of diisobutylaluminum hydride in toluene (1.0 M, 0.60 ml, 0.60 mmol) was added to a stirred and cooled solution of methyl 1,3-bis (*t*-butyldimethylsilyloxy)phenylacetate (206 mg, 0.502 mmol) in dry toluene (2.0 ml) at −78°C under argon. The reaction mixture was allowed to warm to −65°C while stirring for 2.5 h, cooled to −78°C again, and then quenched with MeOH. The mixture was filtered through Celite, and the resulting solid was washed with ether. The filtrate and washings were successively washed with water and brine, dried over anhydrous $MgSO_4$, and concentrated under reduced pressure. The residue was chromatographed on silica gel (4 g; hexane/ethyl acetate, 80:1) to give crude **4** as an oil. Obtained **4** was used for the next step without further purification. IR ν_{max} (film) cm^{-1}: 2955 (s, Ar), 2930 (s, Ar), 2820 (w, CHO), 1730 (s, C=O), 1590 (s, Ar), 1450 (s, Ar), 1260 (s, Si-Me), 1165 (s, C-O), 1040 (m, Si-O). ^{1}H-NMR δ_H (300 MHz, $CDCl_3$): 0.20 (12H, s, Si-CH_3), 0.98 (18H, s, Si-C(CH_3)$_3$), 3.52 (2H, d, $J=2.1$ Hz, 1′-H), 6.28 (1H, t, $J=2.1$ Hz, 4-H), 6.33 (2H, d, $J=2.1$ Hz, 2-H, 6-H), 9.67 (1-H, t, $J=2.4$ Hz, CHO).

1,3-Bis(tert-butyldimethylsilyloxy)-5-[(Z)-2′-nonenyl]benzene (5). A phosphonium salt (11.1 g, 90%) was prepared from 1-bromoheptane (5.00 g, 27.9 mmol) and triphenylphosphine (11.0 g, 41.9 mmol) in dry toluene (100 ml). Sodium bis(trimethylsilyl)amide (1.0 M, 1.0 ml, 1.0 mmol) was added dropwise to a suspension of this phosphonium salt (413 mg, 0.935 mmol) in dry hexane (3.5 ml) at 80°C for 3 h under argon. After having been cooled to −20°C, dry THF (3.0 ml) was added to the reaction mixture, and the mixture was left to stand for 1 h. Then supernatant ylid solution was transferred to a flask for the Wittig reacton. A solution of **4** in dry THF (3.0 ml) was added dropwise to the ylid solution at −78°C under argon. The reaction mixture was allowed to warm to room temperature while stirring for 2 h. It was then concentrated under reduced pressure and diluted with hexane. The insoluble solid was removed by filtration through Celite, and the solid was washed with hexane. The filtrate and washings were successively washed with water and brine, dried over anhydrous $MgSO_4$, and cooled again to −20°C to precipitate the remaining triphenylphosphine oxide. The solid was removed by filtration, and the filtrate was concentrated under reduced pressure. The residue was chromatographed on silica gel (4 g; hexane) to give 106 mg (46%, 2 steps) of **5** as an oil. $n_D^{25}=1.4805$. IR ν_{max} (film) cm^{-1}: 2955 (m, Ar), 2930 (s, Ar), 1590 (s, Ar), 1450 (m, C=C), 1250 (m, Si-Me), 1160 (s, C-O), 1030 (s, Si-O). ^{1}H-NMR δ_H (400 MHz, $CDCl_3$): 0.18 (12H, s, Si-CH_3), 0.89 (3H, t, $J=6.8$ Hz, 9′-H), 0.97 (18H, s, Si-C(CH_3)$_3$), 1.30–1.43 (8H, m, 5′-H, 6′-H, 7′-H, 8′-H), 2.10–2.14 (2H, m, 4′-H), 3.26 (2H, d, $J=5.4$ Hz, 1′-H), 5.50 (2H, m, 2′-H, 3′-H), 6.16 (1H, t, $J=2.2$ Hz, 2-H), 6.29 (2H, d, $J=2.2$ Hz, 4-H, 6-H). ^{13}C-NMR δ_C (100 MHz, $CDCl_3$): 14.1, 18.2, 22.6, 25.7, 27.2, 29.0, 29.7, 31.8, 33.3, 109.5, 113.5, 127.7, 131.0, 143.2, 156.3. *Anal.* Found: C, 70.04; H, 11.14%. Calcd. for $C_{27}H_{50}O_2Si_2$: C, 70.06; H, 10.89%. HPLC [Pegasil silica 60-5 column (4.6 mm × 25 cm), hexane eluent at 1 ml/min] $t_R=$ 83.7 min [(*E*)-isomer, 5%], 100.7 min [(*Z*)-**5**, 95%].

1,3-Dihydroxy-5-[(Z)-2′-nonenyl]benzene (climacostol, 1). A solution of tetra-*n*-butylammonium fluoride (TBAF) in THF (1.0 M, 0.34 ml, 0.34 mmol) was added to a solution of **5** (63.4 mg, 0.137 mmol) in dry THF (0.70 ml) at 0°C. After stirring for 2 h at room temperature, the reaction mixture was diluted with water and extracted with ether. The extract was successively washed with dil. HCl aq., water and brine, dried over anhydrous $MgSO_4$, and concentrated under reduced pressure. The residue was chromatographed on silica gel (1 g; hexane/ethyl acetate, 10:1) to give 29.9 mg (91%) of **1** as an oil. $n_D^{25}=1.5223$. IR ν_{max} (film) cm^{-1}: 3335 (s, O-H), 3010 (m, C-H), 2950 (s, Ar), 2925 (s, Ar), 2855 (s, C-H), 1700 (w), 1600 (s, Ar), 1510 (m, Ar), 1465 (s, C=C), 1370 (w), 1335 (s), 1305 (s), 1260 (m, C-O), 1205 (m), 1155 (s), 1000 (s), 915 (m), 835 (s), 725 (m), 685 (m). ^{1}H-NMR δ_H (500 MHz, $CDCl_3$): 0.89 (3H, t, $J=7.0$ Hz, 9′-H), 1.26–1.35 (6H, m, 6′-H, 7′-H, 8′-H), 1.35–1.40 (2H, m, 5′-H), 2.10 (2H, m, 4′-H), 3.28 (2H, d, $J=5.8$ Hz, 1′-H), 4.70 (2H, s, O-H), 5.51 (2H, m, 2′-H, 3′-H), 6.18 (1H, t, $J=2.1$ Hz, 2-H), 6.25 (2H, d, $J=2.1$ Hz, 4-H, 6-H). ^{13}C-NMR δ_C (125 MHz, $CDCl_3$): 14.1 (C-9′), 22.6 (C-8′), 27.2 (C-4′), 29.0 (C-5′), 29.6 (C-6′), 31.7 (C-7′), 33.2 (C-1′), 100.3 (C-2), 108.0 (C-4, C-6), 127.2 (C-3′), 131.5 (C-2′), 144.4 (C-5), 156.6 (C-1, C-3). HRMS *m/z* (M^+): calcd. for $C_{15}H_{22}O_2$, 234.1620; found, 234.1623. *Anal.* Found: C, 76.88; H, 9.46%. Calcd. for $C_{15}H_{22}O_2$: C, 76.51; H, 9.39%.

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