Extremely simple and practical synthesis of (±)-vertinolide *via* the Michael addition

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(±)-Vertinolide (**1**) was synthesized from the readily available tetronic acid derivative **5** in 3 steps. The Michael reaction of the anion derived from **6** with (*E*)-5-ethoxyocta-1,6-dien-3-one (**12**) gave the vertinolide precursor **9** in high yield, which was then easily converted to (±)-vertinolide (**1**).

Introduction

Several attractive tetronic acid analogues, with quaternary stereogenic centres, were isolated, for example, (*S*)-vertinolide (**1**),[1,2] (*R*)-aspertetronin A (**2a**),[3] (*S*)-gregatin A (**2b**),[4] (*R*)-thiolactomycin (**3a**),[5] and (*R*)-thiotetromycin (**3b**)[6] (Fig. 1). These

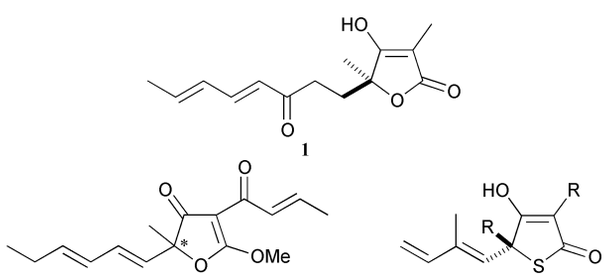

Fig. 1 Several tetronic acid derivatives including a quaternary stereogenic center.

analogues are expected to possess high bioactivity, however, this is a matter for future research because of a lack of material. The practical and simple synthesis of these analogues will open the way to their research. We report herein the extremely simple synthesis of vertinolide (**1**). The key step in our synthesis is the introduction of a quaternary carbon *via* the Michael addition of readily available tetronic acid derivatives.

Results and discussion

3,5-Dimethyltetronic acid (**5**) was prepared from ethyl 2-methyl-3-oxopentanoate (**4**)[7] by the reported procedure.[8] The hydroxy group was protected with chloromethyl methyl ether (MOMCl) to give 4-methoxymethoxy-3,5-dimethylfuran-2(5*H*)-one (**6**) in 99% yield. This was treated with LDA at −78 °C and the resulting anion was reacted with methyl vinyl ketone to give the ketone **7**.The aldol reaction of the anion from **7** with crotonaldehyde furnished the alcohol **8** in 63% yield, which was readily dehydrated to **9** in the presence of basic alumina. Finally, removal of the MOM group gave (±)-vertinolide (**1**) in 94% yield (Scheme 1).

We have shown that (±)-vertinolide (**1**) can be prepared from 3,5-dimethyltetronic acid (**5**) in four steps. We have also investigated a single step introduction of the side chain by use of (*E*)-5-ethoxyocta-1,6-dien-3-one (**12**) as a Michael acceptor. The enone **12** was prepared by the reaction of crotonaldehyde diethyl acetal (**10**)[9] and 2-trimethylsilyloxybuta-1,3-diene (**11**)[10] in the presence of titanium tetrachloride in 71% yield, which readily underwent elimination to give the conjugated enone **13**[11] (Scheme 2). Treatment of **6** with enone **12** and LDA at −78 °C successfully gave the MOM protected vertinolide **9** in 97% yield, which was deprotected to afford (±)-vertinolide (**1**) in 94% yield (Scheme 3).

Previously, (±)-vertinolide (**1**) was prepared from 2-methyl-5-oxotetrahydrofuran-2-carboxylic acid in 8 steps using acid-catalyzed lactonization.[2e] Our approach is accomplished by the Michael reaction of the readily available tetronic acid derivative **6** and the enone **12**. We hope that this extremely simple synthesis of **1** will be helpful in identifying bioactive properties in the future.

Experimental

Registry Number **1**: 79950-84-8, **2a**: 21494-09-7, **2b**: 65794-79-8, **3a**: 82079-32-1, **3b**: 85263-97-4, **4**: 759-66-0, **5**: 22621-29-0, **9**: 91852-00-5, **10**: 63511-92-2, **11**: 38053-91-7.

THF was distilled before use from a deep-blue solution resulting from benzophenone and sodium. CH_2Cl_2 was distilled from calcium hydride. All reactions were monitored by thin-layer chromatography (TLC) on 0.25 mm Merck silica gel (60F–254) precoated glass plates. TLC plates were visualized with UV light and 7% phosphomolybdic acid or *p*-anisaldehyde in ethanol. Column chromatography was carried out on a column packed with Fuji Silysia silica gel BW-820H. Melting points were measured on a Yanaco micro-melting point apparatus and are uncorrected. ^{1}H NMR spectra in $CDCl_3$ were recorded on a JEOL JNM-MY60 instrument, chemical shifts (δ) are expressed in ppm downfield from the internal tetramethylsilane, and *J* values are given in Hz. Infrared spectra were recorded on a SHIMADZU FTIR-8200A spectrometer. Mass spectra (eV) were recorded on a SHIMADZU GCMS-QP5050 spectrometer. Microanalyses were performed with a Perkin Elmer-240.

4-Hydroxy-3,5-dimethylfuran-2(5*H*)-one (5)

The starting tetronic acid **5** was prepared from ethyl 2-methyl-3-oxopentanoate (**4**)[7] according to the procedure reported in the literature.[8] R_f = 0.32 (ethyl acetate); ^{1}H NMR δ 1.54 (d, *J* = 7.8, 3H, -CH_3), 1.77 (s, 3H, -CH_3), 4.98 (q, *J* = 7.8, 1H, -CH_3), 9.4 (s,

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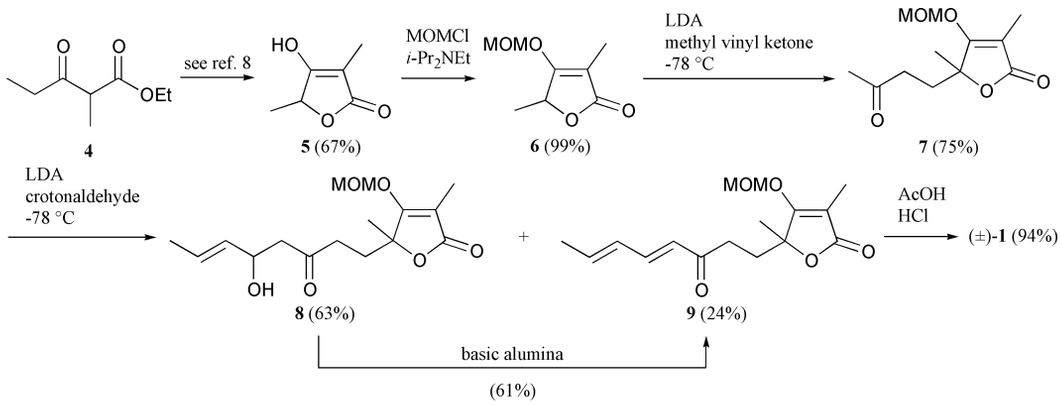
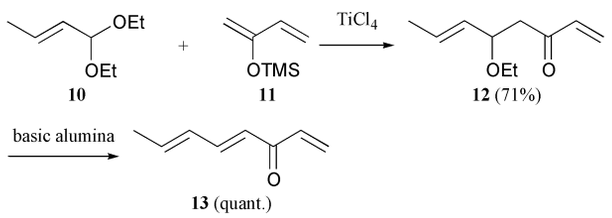
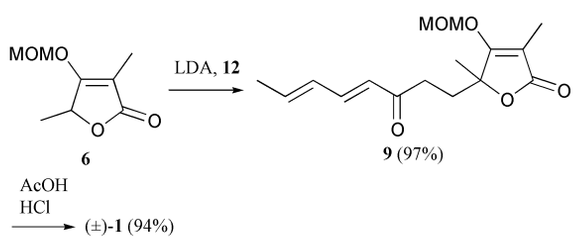


Scheme 1 Synthesis of (±)-vertinolide (**1**) from 2-methyl-3-oxopentanoate (**4**).



Scheme 2 Synthesis of (*E*)-5-ethoxyocta-1,6-dien-3-one (**12**).



Scheme 3 Synthesis of (±)-vertinolide (**1**) from the tetronic acid **6** in two steps.

1H, -OH); IR (KBr) 3870, 1724, 1662, 1452, 1406, 1365, 1116, 1008 cm^{-1}.

4-Methoxymethoxy-3,5-dimethylfuran-2(5*H*)-one (6)

To a solution of **5** (304 mg, 2.37 mmol) in CH_2Cl_2 (3 mL) was added dropwise diisopropylethylamine (346 mg, 2.68 mmol), and the mixture was stirred for 10 min at room temperature. To the mixture chloromethyl methyl ether (0.25 mL, 3.29 mmol) was added dropwise at 0 °C, and the reaction mixture was stirred for 3 h at room temperature. CH_2Cl_2 was removed under reduced pressure, and water (3 mL) was added to the residue. The aqueous layer was extracted with AcOEt (2 × 10 mL). The organic extracts were washed with brine (5 mL), dried over Na_2SO_4, and concentrated to give the crude oil, which was purified by column chromatography (silica gel, hexane–ethyl acetate = 50 : 50) to give the tetronic acid **6** (404 mg, 99% yield): R_f = 0.58 (hexane–ethyl acetate = 50 : 50); ^{1}H NMR δ 1.41 (d, J = 7.8, 3H, -CH_3), 1.87 (s, 3H, -CH_3), 3.48 (s, 3H, -OCH_3), 4.70 (q, J = 7.8, 1H, -CH-), 5.2 (s, 2H, -OCH_2-); IR (neat) 2985, 1755, 1668, 1454, 1415, 1307, 1105 cm^{-1}; MS (EI) *m*/*z* 172 (M^+, 1), 157 (1), 142 (1), 45 (100). Anal. Calcd for $C_8H_{12}O_4$: C, 55.81; H, 7.02. Found, C, 55.54; H, 7.03%.

4-Methoxymethoxy-3,5-dimethyl-5-(3-oxobutyl)furan-2(5*H*)-one (7)

To a solution of LDA (1.10 mmol) in THF (1 mL) was added dropwise a solution of the tetronic acid **6** (170 mg, 0.99 mmol) in THF (3 mL) over a period of 3 min at −78 °C, and the mixture was stirred for 1 h. To this mixture was added a solution of methyl vinyl ketone (88 μL, 1.08 mmol) in THF (1 mL), and the reaction mixture was stirred for 3 h. The mixture was quenched with saturated NH_4Cl (1 mL) and concentrated under reduced pressure. The aqueous mixture was extracted with AcOEt (3 × 10 mL). The combined organic extracts were washed with brine (5 mL), dried over Na_2SO_4, and concentrated to give a crude oil, which was purified by column chromatography (silica gel, hexane–ethyl acetate = 60 : 40) to give the ketone **7** (179 mg, 75% yield): R_f = 0.430 (hexane–ethyl acetate = 50 : 50); ^{1}H NMR δ 1.42 (s, 3H, -CH_3), 1.60–2.72 (m, 4H, -CH_2CH_2-), 1.90 (s, 3H, -CH_3), 2.09 (s, 3H, -CH_3), 3.48 (s, 3H, -OCH_3), 5.22 (s, 2H, -CH_2O-); IR (KBr) 1733, 1660, 1313, 1163, 947 cm^{-1}; MS (EI) *m*/*z* 242 (M^+, 0.5), 172 (3), 142 (2), 45 (100). Anal. Calcd for $C_{12}H_{18}O_5$: C, 59.08; H; 7.54. Found, C, 59.26; H, 7.54%.

5-(5-Hydroxy-3-oxoocta-6-enyl)-4-methoxymethoxy-3,5-dimethylfuran-2(5*H*)-one (8)

To a solution of LDA (0.63 mmol) in THF (1 mL) was added dropwise a solution of ketone **7** (101 mg, 0.42 mmol) in THF (3 mL) over a period of 3 min at −78 °C, and the mixture was stirred for 5 min. To this mixture was added crotonaldehyde (190 μL, 2.22 mmol), and the reaction mixture was stirred for 1 h. The reaction mixture was quenched with saturated NH_4Cl (1 mL) and concentrated under reduced pressure. The aqueous mixture was extracted with AcOEt (3 × 10 mL). The combined organic extracts were washed with brine (5 mL), dried over Na_2SO_4, and concentrated to give a crude oil, which was purified by column chromatography (silica gel, hexane–ethyl acetate = 60 : 40) to give the alcohol **8** (82 mg, 63% yield) and the conjugate enone **9** (29 mg, 24% yield). Alcohol **8** was easily converted to the conjugate enone **9** (61% yield) by stirring in the presence of basic alumina in a CH_2Cl_2 suspension.

Compound 8. R_f = 0.332 (ethyl acetate); ^{1}H NMR δ 1.43 (s, 3H, -CH_3), 1.68 (d, J = 7.8, 3H, -CH_3), 1.92 (s, 3H, -CH_3), 1.02–2.78 (m, 7H, -CH_2CH_2-, -CH_2CO-, -OH), 3.48 (s, 3H, -OCH_3), 4.21–4.60 (m, 1H, -C*H*OH), 5.23 (s, 2H, -OCH_2O-), 5.35–5.90 (m, 2H, -CH=CH-); IR (neat) 3467, 2935, 1749, 1712, 1666, 1454, 1315, 1163 cm^{-1}; MS (EI) *m*/*z* 313 (M^+, 0.3), 295 (15), 250 (9), 99 (100).

Compound 9.[2e] R_f = 0.571 (hexane–ethyl acetate = 50 : 50); ^{1}H NMR δ 1.45 (s, 3H, -CH_3), 1.80–2.70 (m, 4H), 1.90 (d, J = 6.0, 3H, -CH_3), 2.15 (s, 3H, -CH_3), 3.48 (s, 3H, -OCH_3), 5.12 (s, 2H, -OCH_2O-), 5.8–6.3 (m, 3H), 6.8–7.4 (m, 1H); IR (KBr) 1760, 1670, 1650, 1600 cm^{-1}.

(*E*)-5-Ethoxyocta-1,6-dien-3-one (12)

To a solution of the acetal **10**[9] (2.36 g, 16.5 mmol) in THF (20 mL) was added dropwise titanium tetrachloride (2.15 mL, 20.2 mmol) at −78 °C. To the mixture was added dropwise a solution of the buta-1,3-diene **11**[10] (2.21 g, 15.5 mmol) in THF (15 mL), and the mixture stirred for 14 h. The reaction mixture

was quenched with 25% K_2CO_3 aq. (15 mL) and filtered under reduced pressure. The filtrate was extracted with Et_2O (3 × 10 mL). The organic extracts were washed with water (5 mL), dried over Na_2SO_4, and concentrated to give a crude oil, which was purified by column chromatography (silica gel, hexane–ethyl acetate = 80 : 20) to give the enone **12** (1.86 g, 71% yield), which was easily converted to the conjugated enone **13**[11] by stirring in the presence of basic alumina in a CH_2Cl_2 suspension: R_f = 0.419 (hexane–ethyl acetate = 90 : 10); ^{1}H NMR δ 1.10 (t, J = 6.6, 3H, -CH_3), 1.66 (d, J = 6.6, 3H, -CH_3), 2.10–3.84 (m, 4H), 3.85–4.20 (m, 1H), 5.05–6.50 (m, 5H); IR (KBr) 2974, 1687, 1614, 1400, 1082, 968 cm^{-1}.

(*E*,*E*)-4-Methoxymethoxy-3,5-dimethyl-5-(3-oxoocta-4,6-dienyl)furan-2(5*H*)-one (9)[2e]

To a solution of LDA (8.06 mmol) in THF (3 mL) was added dropwise a solution of the tetronic acid **6** (703 mg, 4.08 mmol) in THF (5 mL) over a period of 3 min at −78 °C, and the mixture was stirred for 60 min. To this mixture was added a solution of the enone **12** (573 mg, 3.40 mmol) in THF (4 mL), and the reaction mixture was stirred for 3 h. The reaction mixture was quenched with saturated NH_4Cl (2 mL) and concentrated under reduced pressure. The aqueous mixture was extracted with AcOEt (3 × 10 mL). The combined organic extracts were washed with brine (5 mL), dried over Na_2SO_4, and concentrated to give a crude oil, which was purified by column chromatography (silica gel, hexane–ethyl acetate = 70 : 30) to the conjugate enone **9** (972 mg, 97% yield).

4-Hydroxy-3,5-dimethyl-5-((*E*)-3-oxoocta-4,6-dienyl)furan-2(5*H*)-one ((±)-vertinolide, 1)[1,2]

To a solution of the conjugate enone **9** (1.15 g, 3.40 mmol) in AcOH (3 mL) were added 3 drops of concentrated hydrochloric acid at room temperature, and the mixture was stirred for 4 h. The reaction mixture was diluted with AcOEt (5 mL), and washed with brine (10 mL). The aqueous solution was neutralized with saturated $NaHCO_3$, and extracted with AcOEt (3 × 10 mL). The combined organic extracts were washed with brine (5 mL), dried over Na_2SO_4, and concentrated to give a crude oil, which was purified by column chromatography (silica gel, hexane–ethyl acetate–acetic acid = 50 : 50 : 0.1) to give the (±)-vertinolide **1** (798 mg, 94% yield): R_f = 0.43 (ethyl acetate–acetic acid = 98 : 2); ^{1}H NMR δ 1.49 (s, 3H, -CH_3), 1.72 (s, 3H, -CH_3), 1.85 (d, J = 6.0 Hz, 3H, -CH_3), 2.1–2.4 (m, 2H), 2.4–2.8 (m, 2H), 5.8–6.4 (m, 3H), 6.9–7.4 (m, 1H); IR (KBr) 3500, 1720, 1700, 1650, 1610 cm^{-1}; MS (EI) *m*/*z* 250 (M^+, 0.2), 235 (1), 95 (100).

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