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Synthesis of polyacetylenic montiporic acids by means of organosilicon compounds

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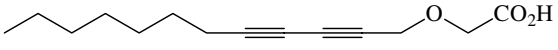
Abstract

A straightforward synthesis of polyacetylenic montiporic acids A and B has been developed, based upon the selective and sequential substitution of the two trimethylsilyl groups of the readily available 1,4-bis(trimethylsilyl)-1,3-butadiyne.

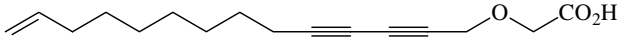
Keywords: Silicon compounds; Polyacetylenes; Coupling reactions; Antifungal agents

1. Introduction

In recent years, stony corals have been objects of investigation by organic chemists as sources of interesting bioactive natural products. In particular, the stony coral *Montipora* sp. is especially rich in acetylenic compounds that have been shown to possess antifungal, antibacterial, ichthyotoxic, and cytotoxic properties [1]. Recently, two new diacetylenic carboxylic acids, montiporic acids A **1** and B **2**, have been isolated [1a,1c] from the eggs of the scleractinian hermaphroditic coral *Montipora digitata* and exhibited interesting biological activities, such as antimicrobial activity against *Escherichia coli* and cytotoxicity against P-388 murine leukemia cells.



1 ***Montiporic Acid A***



2 ***Montiporic Acid B***

So far, in spite of the interesting properties of these compounds, only one report [2] has described the total synthesis of montiporic acids A and B, employing two different synthetic strategies for the two products.

In connection with our previous studies dealing with the synthesis of stereodefined conjugated polyunsaturated systems [3] and of a series of natural compounds [4], we have recently reported [5] a straightforward and general route to a variety of unsymmetrically substituted conjugated diynes, based upon the selective and sequential substitution of the trimethylsilyl groups of the readily available 1,4-bis(trimethylsilyl)-1,3-butadiyne with alkyl, aryl and vinyl groups. Now, we wish to report a straightforward and expeditious procedure for the total synthesis of both montiporic acids A **1** and B **2** starting from a common intermediate and following the same reaction sequence.

2. Results and discussion

Our overall retrosynthesis is summarized in Scheme 1.

Montiporic acids A and B differ in the aliphatic chain linked to the diyne moiety, a *n*-heptyl group for montiporic acid A (**1**, $n = 3$) and a 8-nonenyl group

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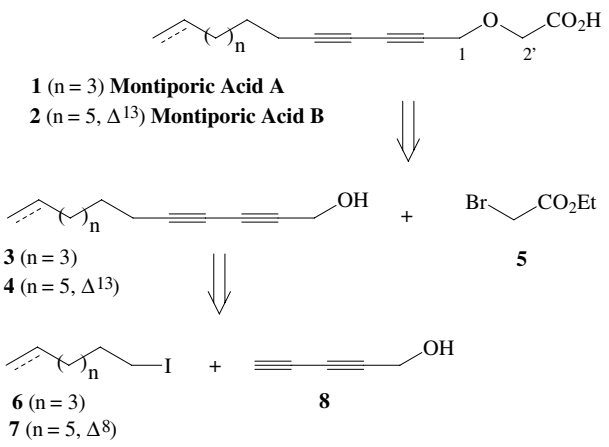


Scheme 1.

for montiporic acid B (**2**, $n = 5$, Δ^{13}). Thus, the disconnection of the O–$C_{2'}$ bond leads to the polyunsaturated alcohols **3**, **4** and to the bromoester **5**. A further disconnection of the C_5–C_6 bond leads to the appropriate halides **6**, **7** and to the key intermediate **8**.

Accordingly, the synthesis of both the montiporic acids **1** and **2** can be realized employing the same methodology, starting with a coupling reaction between the diynol **8** [6] and the readily available halides **6** or **7** which leads to the polyunsaturated alcohols **3** [1a,2,7] or **4** [1a,1d,2]. The subsequent functionalization with the halide **5** can directly give both the montiporic acids **1** and **2**.

The synthesis of the diynol **8** was performed as depicted in Scheme 2, in accordance with our recently published procedure for the synthesis of conjugated diynes [5], starting from the same intermediate, the commercially available 1,4-bis(trimethylsilyl)-1,3-butadiyne **9**.

The diyne **9** was selectively desilylated with MeLi–LiBr complex affording the lithium salt of the mono-silylated terminal diyne which was coupled with paraformaldheyde to give the mono-silylated diynol **11** [6b,8] in 86% yield. A further desilylation reaction of **11** with K_2CO_3 in MeOH led to compound **8** in 80% yield.

Therefore, the synthesis of montiporic acids A and B was performed as depicted in Scheme 3.

Both montiporic acids A and B were synthesized starting from the same compound **8**. In the case of montiporic acid A, the coupling reaction of the lithium salt of **8** with 1-iodoheptane **6** led to compound **3** in 62% yield.

The subsequent reaction of compound **3** with ethyl 2-bromoacetate **5** under phase transfer catalysis conditions [9] gave montiporic acid A in 80% yield.

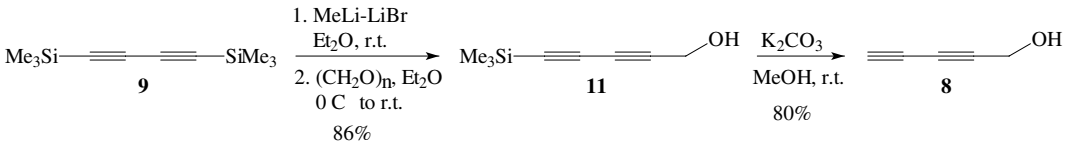
For the synthesis of montiporic acid B, that was obtained in 82% yield, the same reaction sequence was followed employing in the first step a different halide, 9-iodonon-1-ene **7**.

It is noteworthy that also the diacetylene alcohols **3** and **4** are marine metabolites isolated from the stony coral *Montipora* sp. and other species of hermatypic corals [1a,1d]. These compounds possess antifungal, antibacterial, ichthyotoxic properties and exhibited significant cytotoxicity against a small panel of human solid tumor cell lines.

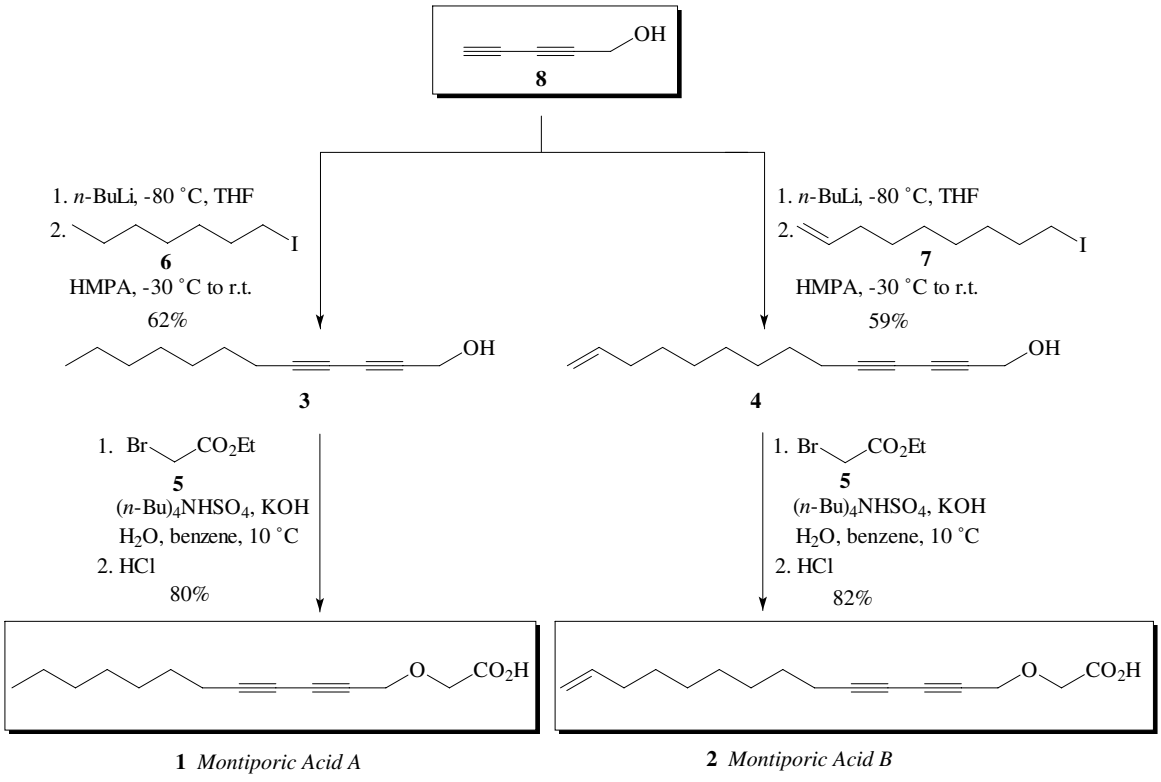
In conclusion, the procedure described here appears to be a useful route to polyacetylenic montiporic acids. A special advantage of our strategy is represented by the possibility of synthesizing both the montiporic acids starting from a common intermediate and employing the same reaction sequence. Moreover, the simplicity of the operations involved, the mild reactions conditions and the ready availability of the silyl derivative employed are additional features making the procedure very promising.

3. Experimental section

THF and Et_2O were dried before use by distillation from Na/benzophenone ketyl under nitrogen. All other solvents were used as obtained. All reactions were carried out under nitrogen in dried glassware. Macherey–Nagel silica gel (60, particle size 0.040–0.063 mm) for column chromatography and Macherey–Nagel aluminum sheets with silica gel 60 F_{254} for TLC were used. GC analysis were performed on a Varian 3900 gas chromatograph equipped with a J&W capillary column (DB-1301, 30 m × 0.25 mm i.d.). GC/mass-spectrometry analysis were performed on a Shimadzu GCMS-QP5000 gas chromatograph-mass spectrometer equipped with a Zebron capillary column (methyl polysiloxane, 30 m × 0.25 mm i.d.). ^{1}H NMR spectra were recorded in deuterochloroform on a Bruker AM 500 spectrometer at 500 MHz. ^{13}C NMR spectra were recorded in deuterochloroform on a Bruker AM 500 spectrometer at 125.7 MHz. IR spectra were measured



Scheme 2.



Scheme 3.

on a Perkin–Elmer FT-IR 1710 spectrometer. Melting points (uncorrected) were determined on a Reichert Microscope. The halide 9-iodonon-1-ene **7** was synthesizing from commercial 1,9-nonandiol using literature procedures [10,11].

3.1. 5-Trimethylsilyl-2,4-pentadiyn-1-ol (*11*) [6b]

MeLi–LiBr complex (1.5 M) in ether (20.6 mL, 30.9 mmol) was added to an ether solution (50 mL) of 1,4-bis(trimethylsilyl)-1,3-butadiyne **9** (5.0 g, 25.7 mmol) at room temperature under nitrogen. After complete desilylation (8 h), the reaction mixture was cooled to 0 °C, a suspension of paraformaldheyde (0.773 g, 25.7 mmol) in Et_2O (10 mL) was added, then the mixture was brought to room temperature. After reaction completion (7 h), the mixture was quenched with a saturated aqueous solution of NH_4Cl (80 mL), and extracted with ethyl acetate (3×80 mL). The organic extracts were dried over anhydrous Na_2SO_4 and concentrated under vacuum. Purification by column chromatography of the residue with petroleum ether/EtOAc (8:2) as eluent led to compound **11** as a pale yellow oil; yield: 3.37 g (86%). ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 4.29$ (s, 2H), 2.34 (br s, 1H), 0.16 (s, 9H). ^{13}C NMR (125.7 MHz, $CDCl_3$): $\delta = 87.4, 87.2, 75.8, 70.3, 51.0, -0.6$. IR (neat): $\nu = 3367, 2961, 2901, 2862, 2224, 2108, 1423, 1384, 1252, 1020, 862, 845, 761$ cm^{-1}. GC–MS: *m/z* (%) = 152 (M^+, 7), 137 (76), 109 (30), 85 (25), 83 (22), 77 (37), 75 (100), 55 (15), 53 (36), 45 (97), 43 (59).

3.2. 2,4-Pentadiyn-1-ol (*8*) [6a]

K_2CO_3(1.64 g, 11.87 mmol) was added to a MeOH solution (15 mL) of compound **11** (1.5 g, 9.85 mmol). The reaction mixture was stirred for 1 h at room temperature, then quenched with a saturated aqueous solution of NH_4Cl (40 mL), and extracted with ethyl ether (3×50 mL). The organic extracts were washed with a saturated aqueous solution of NaCl (50 mL), dried over Na_2SO_4 and concentrated at atmospheric pressure. Purification of the residue by percolation on florisil column with petroleum ether/Et_2O (7:3) as eluent led to compound **8** as a yellow-orange oil; yield: 0.635 g (80%). ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 4.28$ (br s, 2H), 2.77 (br s, 1H), 2.18 (t, $J = 1.1$ Hz, 1H). ^{13}C NMR (125.7 MHz, $CDCl_3$): $\delta = 74.5, 69.6, 68.3, 67.3, 50.9$. IR (neat): $\nu = 3300, 3290, 2918, 2862, 2220, 2065, 1445, 1385, 1358, 1138, 1015, 631$ cm^{-1}. GC–MS: *m/z* (%) = 80 (M^+, 8), 79 (20), 63 (28), 62 (25), 61 (19), 52 (100), 51 (54), 50 (51), 49 (23).

3.3. 2,4-Dodecadiyn-1-ol (*3*) [1a,7c]

A solution of *n*-BuLi 1.6 M in hexane (5.2 mL, 8.32 mmol) was slowly dropped, at −80 °C, under

nitrogen, to a solution of 2,4-pentadiyn-1-ol **8** (0.30 g, 3.75 mmol) in anhydrous THF (10 mL). The resulting reaction mixture was maintained for 30 min at −80 °C, then the reaction temperature was raised to −30 °C. After HMPA addition (1.3 mL, 7.50 mmol), a solution of 1-iodoheptane **6** (0.848 g, 3.75 mmol) in anhydrous THF (10 mL) was added dropwise, then the reaction temperature was slowly raised to room temperature. After reaction completion (15 h), the mixture was quenched with a saturated aqueous solution of NH_4Cl (30 mL) and extracted with ethyl acetate (3 × 30 mL). The organic extracts were washed with a saturated aqueous solution of NaCl (3 × 30 mL), dried over anhydrous Na_2SO_4 and concentrated under vacuum. The residue was purified by column chromatography with petroleum ether/EtOAc (8:2) as eluent leading to compound **3** as a pale yellow solid; yield: 0.414 g (62%), m.p. 36–38 °C (lit. [7c] 34–36 °C). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 4.27 (s, 2H), 2.24 (t, J = 7.2 Hz, 2H), 1.93 (br s, 1H), 1.50 (quint, J = 7.2 Hz, 2H), 1.39–1.31 (m, 2H), 1.30–1.19 (m, 6H), 0.85 (t, J = 6.9 Hz, 3H). ^{13}C NMR (125.7 MHz, $CDCl_3$): δ = 81.9, 73.5, 70.9, 64.3, 51.5, 31.6, 28.8, 28.7, 28.1, 22.6, 19.2, 14.0. IR (neat): ν = 3313, 2955, 2929, 2857, 2256, 1466, 1383, 1233, 1026 cm^{-1}. GC–MS: *m/z* (%) = 149 (2), 145 (2), 135 (7), 117 (8), 107 (14), 105 (10), 91 (39), 79 (58), 77 (41), 67 (26), 65 (27), 55 (45), 51 (25), 43 (60), 41 (100).

3.4. (Dodeca-2,4-diynyloxy)acetic acid (Montiporic acid A) (1) [1c]

Ethyl 2-bromoacetate **5** (0.19 mL, 1.70 mmol) was added at 10 °C to a vigorously stirred mixture of compound **3** (0.20 g, 1.12 mmol) in benzene (6 mL), 50% aqueous solution of KOH (3 mL) and $(n\text{-Bu})_4NHSO_4$ (0.19 g, 0.56 mmol). The stirring was continued for 3 h, then the mixture was quenched with diluted HCl (30 mL) and extracted with ethyl acetate (4 × 30 mL). The organic extracts were washed whit water (3 × 30 mL), dried over anhydrous Na_2SO_4 and concentrated under vacuum. The residue was purified by column chromatography (petroleum ether/EtOAc 8:2 to EtOAc/MeOH 9:1 as eluents) leading to montiporic acid A **1** as a colorless oil; yield: 0.212 g (80%). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 9.25 (br s, 1H), 4.33 (s, 2H), 4.21 (s, 2H), 2.24 (t, J = 7.2 Hz, 2H), 1.49 (quint, J = 7.2 Hz, 2H), 1.34 (quint, J = 7.2 Hz, 2H), 1.29–1.19 (m, 6H), 0.84 (t, J = 6.9 Hz, 3H). ^{13}C NMR (125.7 MHz, $CDCl_3$): δ = 175.1, 82.1, 72.8, 69.8, 65.7, 64.1, 58.9, 31.6, 28.7, 28.6, 28.0, 22.5, 19.2, 14.0. IR (neat): ν = 2955, 2929, 2857, 2255, 1734, 1119 cm^{-1}. GC–MS: *m/z* (%) = 235 ($M^+ - 1$, <1), 207 (2), 177 (2), 152 (7), 131 (15), 117 (25), 105 (18), 91 (47), 79 (36), 77 (36), 76 (29), 67 (28), 65 (24), 55 (49), 51 (33), 50 (23), 43 (70), 41 (100).

3.5. Tetradec-13-en-2,4-diyn-1-ol (4) [1a,1d]

A solution of *n*-BuLi 1.6 M in hexane (3.1 mL, 4.96 mmol) was added dropwise, at −80 °C, under nitrogen, to a solution of compound **8** (0.178 g, 2.23 mmol) in anhydrous THF (8 mL). The resulting reaction mixture was maintained for 30 min at −80 °C, then the reaction temperature was raised to −30 °C. After HMPA addition (0.78 mL, 4.48 mmol), a solution of 9-iodonon-1-ene **7** (0.562 g, 2.23 mmol) in anhydrous THF (8 mL) was added dropwise, then the reaction temperature was slowly raised to room temperature. After reaction completion (15 h), the mixture was quenched with a saturated aqueous solution of NH_4Cl (30 mL) and extracted with ethyl acetate (3 × 30 mL). The organic extracts were washed with a saturated aqueous solution of NaCl (3 × 30 mL), dried over anhydrous Na_2SO_4 and concentrated under vacuum. The residue was purified by column chromatography with petroleum ether/EtOAc (8:2) as eluent leading to compound **4** as a yellow-orange oil; yield: 0.268 g (59%). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 5.79 (ddt, J = 17.1, 10.2, 6.7 Hz, 1H), 4.97 (ddt, J = 17.1, 2.2, 1.5 Hz, 1H), 4.91 (ddt, J = 10.2, 2.2, 1.2 Hz, 1H), 4.30 (br s, 2H), 2.26 (tt, J = 7.2, 1.0 Hz, 2H), 2.05–1.99 (m, 2H), 1.63 (br s, 1H), 1.51 (quint, J = 7.2 Hz, 2H), 1.40–1.32 (m, 4H), 1.31–1.24 (m, 4H). ^{13}C NMR (125.7 MHz, $CDCl_3$): δ = 139.0, 114.1, 81.7, 73.6, 70.7, 64.4, 51.3, 33.7, 28.9, 28.8, 28.8, 28.7, 28.0, 19.2. IR (neat): ν = 3349, 3076, 2928, 2856, 2256, 1640, 1461, 1384, 1232, 1025, 910 cm^{-1}. GC–MS: *m/z* (%) = 161 (2), 147 (3), 145 (2), 143 (4), 133 (5), 131 (7), 129 (6), 105 (14), 91 (38), 81 (14), 79 (34), 77 (25), 67 (32), 65 (21), 55 (50), 53 (22), 51 (18), 41 (100).

3.6. (Tetradec-13-en-2,4-diynyloxy)acetic acid (Montiporic acid B) (2) [1c]

Ethyl 2-bromoacetate **5** (0.15 mL, 1.35 mmol) was added at 10 °C to a vigorously stirred mixture of compound **4** (0.176 g, 0.86 mmol) in benzene (5 mL), 50% aqueous solution of KOH (2 mL) and $(n\text{-Bu})_4NHSO_4$ (0.147 g, 0.43 mmol). The stirring was continued for 4 h, then the mixture was quenched with diluted HCl (30 mL) and extracted with ethyl acetate (4 × 30 mL). The organic extracts were washed whit water (3 × 30 mL), dried over anhydrous Na_2SO_4 and concentrated under vacuum. The residue was purified by column chromatography (petroleum ether/EtOAc 8:2 to EtOAc/MeOH 9:1as eluents) leading to montiporic acid B **2** as a yellow-orange oil; yield: 0.185 g (82%). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.90 (br s, 1H), 5.79 (ddt, J = 17.1, 10.2, 6.7 Hz, 1H), 4.97 (ddt, J = 17.1, 2.2, 1.6 Hz, 1H), 4.91 (ddt, J = 10.2, 2.2, 1.2 Hz, 1H), 4.35 (s, 2H), 4.23 (s, 2H), 2.26 (t, J = 7.2 Hz, 2H), 2.05–1.99 (m, 2H), 1.51 (quint, J = 7.2 Hz, 2H), 1.40–1.32 (m, 4H), 1.31–1.23 (m, 4H). ^{13}C NMR

(125.7 MHz, $CDCl_3$): δ = 175.0, 139.0, 114.2, 82.0, 72.8, 69.8, 65.6, 64.2, 58.9, 33.7, 28.9, 28.8, 28.8, 28.7, 28.0, 19.2. IR (neat): ν = 3077, 2928, 2855, 2255, 1733, 1640, 1117, 910 cm^{-1}. GC–MS: *m/z* (%) = 203 (1), 173 (1), 171 (1), 161 (2), 159 (2), 157 (3), 152 (3), 145 (5), 143 (8), 131 (11), 129 (13), 117 (17), 115 (11), 105 (17), 91 (43), 79 (26), 77 (25), 67 (26), 55 (43), 51 (23), 41 (100).

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