The First Total Synthesis of the Proposed Structure of Montiporyne E

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Abstract: Montiporyne E, a novel diacetylenic lactam isolated from the stony coral *Montipora sp.*, was shown to exhibit cytotoxicity against certain solid tumor cells. Construction of a suitably functionalized α,β-unsaturated lactam for palladium-catalyzed couplings was realized via a Beckmann rearrangement. Subsequent Sonagoshira coupling with a known alkyne chain efficiently afforded the alleged structure of the natural product.

Key words: synthesis, Beckmann, lactams, coupling reactions, alkynes

Soft corals have been extensively studied since the 1960s. In contrast, stony corals (hard coral, scleractinian) have historically been dismissed by chemists partly based on the belief that a hard coral would barely produce enough organic extract since it consists mainly of a calcarious skeleton.[1] Recently, however, hard corals have resurfaced as sources of interesting biologically active natural products.[2] Among the marine metabolites often found are a number of diacetylenic compounds, mostly isolated from hermaphroditic scleractinian corals such as *Montipora digitata*.[1,3] Several new diacetylenic compounds found in the hard coral *Montipora sp.* were reported,[4] two of which were recently synthesized.[5]

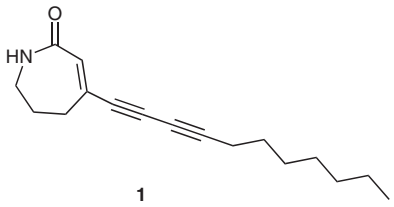
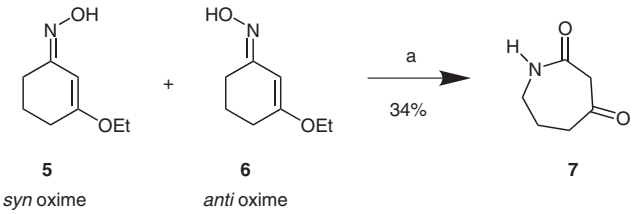


Figure 1 Supposed structure of montiporyne E

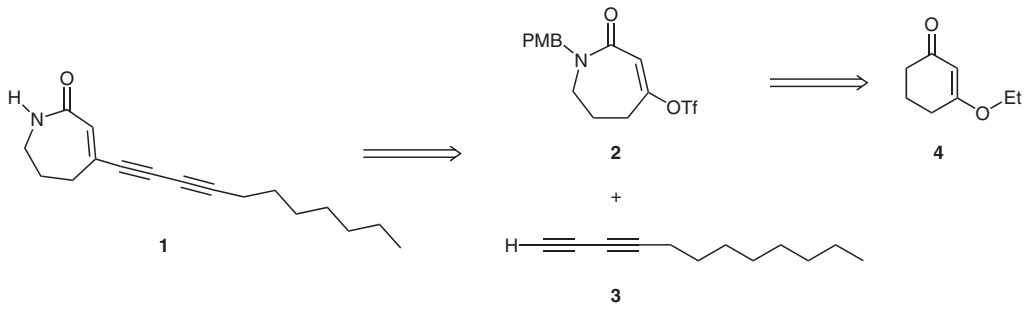
The genus *Montipora* is especially rich in acetylenic compounds that have been shown to possess antifungal, antibacterial, ichthyotoxic, and cytotoxic properties. Biological evaluation of these acetylenic compounds showed that montiporyne E (**1**) has moderate cytotoxicity against a small panel of human solid tumor cell lines.[4]

Based on the analysis of its structure, our retrosynthetic strategy involved a Sonogashira coupling of a lactam enol triflate **2** with the known diyne side chain **3**[6] (Scheme 1). The lactam **2** was envisioned as coming from a Beckmann rearrangement of the commercially available 3-ethoxy-2-cyclohexen-1-one (**4**). Beckmann rearrangements with vinylic halides were often met with poor yields.[7] As such, we needed to investigate a method that was compatible with a vinyl functional group so that coupling via oxidative addition with a palladium catalyst could follow.



Scheme 2 *Reagents and conditions*: a) PPA, 110–120 °C.

Initially, Beckmann rearrangement of *syn*- and *anti*-oximes **5** and **6** was attempted with polyphosphoric acid at 110–120 °C for one hour since it had been reported that isomerization occurs under these conditions to afford exclusively one desired product, **7** (Scheme 2).[7] The resulting reaction mixture was extracted with dichloromethane to give the crude product **7** in 34% yield.



Scheme 1 Retrosynthetic analysis of montiporyne E

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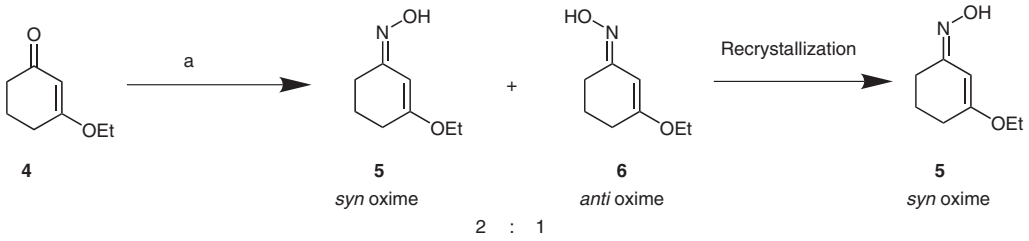
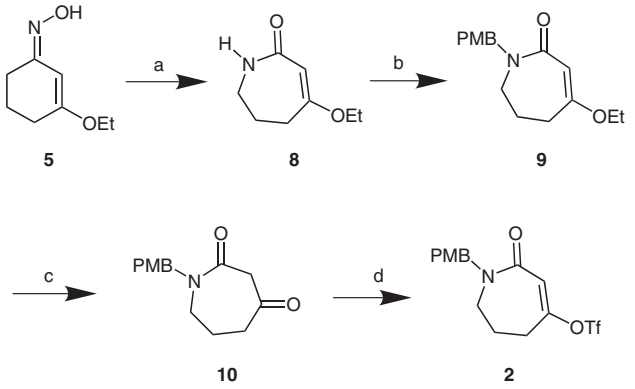


Scheme 3 *Reagents and conditions*: a) $NH_2OH{\cdot}HCl$, NaOAc, EtOH, 55–60 °C, 12 h.

Since β-keto lactam **7** was difficult to extract from water, and required exorbitant amounts of dichloromethane for extraction, this method was not practical. In addition, premature formation of the β-keto lactam complicated our efforts to enolize and trap the intermediate since the lactam nitrogen was not yet protected.

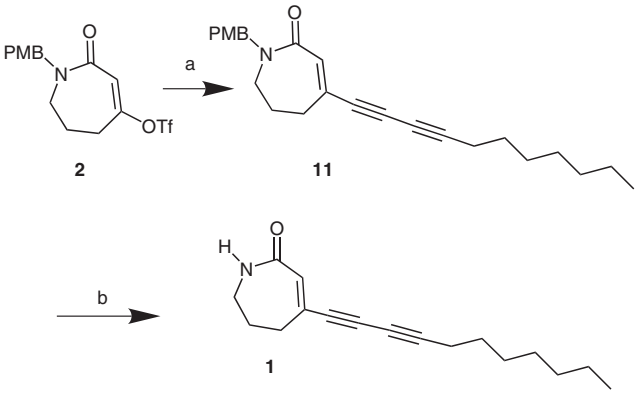
Therefore our approach was modified to facilitate protection of the nitrogen. Commercially available ethoxy-2-cyclohexen-1-one (**4**) was treated with hydroxylamine hydrochloride and sodium acetate in absolute ethanol. The solution was heated to 55 °C for two hours to give the desired oxime product.[8,9] The solid white product obtained was a 2:1 mixture of *syn*/*anti*-oximes (Scheme 3.)[10] The two isomers could be readily distinguished by their distinctive olefinic protons: a larger olefinic shift was observed for the *syn*-oxime relative to the *anti*-oxime.[11]



Scheme 4 *Reagents and conditions*: a) *p*-TsCl/Et_3N, THF, then 10% K_2CO_3 (80%); b) PMBCl, NaH, DMF 63%; c) Concd HCl, EtOH–H_2O (87%); d) Tf_2O, NaOH (3 N), CH_2Cl_2 (60%).

Beckmann rearrangement was facilitated by *p*-toluenesulfonyl chloride instead of polyphosphoric acid. Since these conditions were milder, only the *syn*-oxime could undergo rearrangement. We treated the recrystallized *syn*-oxime **5** with *p*-toluenesulfonyl chloride and triethylamine to give the lactam **8** in 80% yield (Scheme 4).[7] In addition to spectroscopic techniques, the structure of lactam **8** was characterized by X-ray crystallographic analysis to verify the correct direction of Beckmann rearrangement.

With the lactam **8** in hand, the nitrogen was then protected as a *p*-methoxybenzyl group (PMB). Lactam **8** was treated with PMBCl to afford PMB-protected lactam **9** in 63% yield. Next, acidic hydrolysis of **9** gave the corresponding β-keto lactam **10** in 87% yield. Finally, β-keto lactam **10** was converted to the desired enol triflate **2** in 60% yield via treatment with trifluoromethane sulfonic anhydride and a sodium hydroxide solution (3 N) in a two-phase system.



Scheme 5 *Reagents and conditions*: a) **3**, $Pd(PPh_3)_2Cl_2$, CuI, DMF (90%); b) CAN, MeCN–H_2O (88%).

The Sonogashira coupling[12] of the enol triflate **2** with diyne **3** ensued, when treated with bis(triphenylphosphine)palladium(II) dichloride and copper(I) iodide in DMF, to give the desired coupled product **11** in 90% yield (Scheme 5).[13] Removal of PMB in **11** was achieved via treatment with CAN in acetonitrile and water at room temperature[14] to afford the presumed structure of montiporyne E (**1**) in 88% yield after purification by column chromatography.

Comparison of the ^1H and ^{13}C NMR spectral data of the synthetic sample with those of the natural product suggests they are not identical (Table 1). Despite the spectral differences, we are confident that we have synthesized the reported structure of montiporyne E. However, largely due to the many impurities present in the spectral data of the isolated natural product, it remains difficult to explain the observed significant shift discrepancies.[15]

In summary, an efficient synthetic approach to the proposed structure of the natural product montiporyne E has been explored. Our synthesis has resulted in a convergent strategy using a Sonogashira coupling for the connection of a monosubstituted diacetylenic side chain with a novel seven-membered lactam enol triflate. All spectral data for our synthesized compound **1** are in agreement with its chemical structure.

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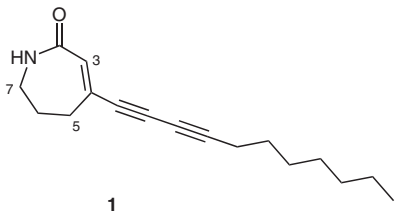
Table 1 Comparisons of the ^{1}H and ^{13}C NMR Data for the Synthetic and Natural Sample of **1**



1

Position	^{1}H **1** (ppm)	^{1}H Natural (ppm)	^{13}C **1** (ppm)	^{13}C Natural (ppm)
3	6.22	6.60	131.2	115.7
5	2.58	2.75	32.9	28.2
6	2.03	1.86	28.2	23.4
7	3.27	3.35	39.7	42.9

All solvents were freshly distilled before use and anhyd THF and Et_2O were distilled under argon from Na/benzophenone. Chemical shifts in ^{1}H and ^{13}C NMR spectra are reported relative to residual solvents. Progress of the reactions were monitored by TLC using Kodak silica gel 60 F254 pre-coated plates and visualized using UV lamps or staining with a mixture of *p*-anisaldehyde/H_2SO_4/EtOH or $KMnO_4$/NaOH/K_2CO_3/H_2O. The products were purified by column chromatography (SiO_2). Analytical data of all known compounds were compared with the literature, and new compounds that were stable were fully characterized.

4-Ethoxy-1,5,6,7-tetrahydroazepin-2-one (8)

To a solution of *syn*-3-ethoxy-2-cyclohexen-1-one (**5**; 1.0g, 6.5 mmol) in anhyd THF (25 mL) was added Et_3N (1.8 mL) at 0–5 °C, followed by addition of *p*-TsCl (1.5 g, 7.8 mmol). After stirring for an additional 1 h at this temperature, the reaction was quenched with a 10% solution of K_2CO_3 (20 mL). After removal of the ice water bath, the reaction mixture was allowed to warm to r.t. for 1 h. The solvent was removed under reduced pressure, the residue was neutralized with 1 N HCl and extracted with CH_2Cl_2 (2 × 15 mL). The combined organic layers were washed with H_2O (30 mL), brine (25 mL), dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by flash chromatography to give the pure product **8** as colorless needles (795 mg, 80%);[7,11] mp 117–118 °C.

IR (film): 3260, 1680,1580 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.08 (br s, 1 H), 5.11 (s, 1 H), 3.82 (q, *J* = 7.0 Hz, 2 H), 3.29–3.25 (m, 2 H), 2.52 (t, *J* = 7.0 Hz, 2 H), 2.0–1.96 (m, 2 H), 1.35 (t, *J* = 7.0 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 172.9, 168.4, 97.0, 63.9, 41.4, 33.1, 27.4, 14.6.

LC-MS (APCI+): *m*/*z* = 156.1 (M + H), 311.0 (2 M + H).

4-Ethoxy-*N*-(*p*-methoxybenzyl)-1,5,6,7-tetrahydroazepin-2-one (9)

To a solution of **8** (50 mg, 0.3 mmol) in anhyd DMF (1 mL), was added NaH (60%; 15.4 mg, 0.4 mmol) at r.t., followed by the addition of PMBCl (65 μL, 0.5 mmol). The reaction mixture was stirred at r.t. for 6 h and then quenched with H_2O (5 mL). The mixture was extracted with EtOAc (2 × 8 mL), the combined organic phases were washed with brine (10 mL), dried over $MgSO_4$, filtered, and concentrated. The residue was purified by column chromatography to give the pure product **9** as a yellow oil (55 mg, 63%).

IR (film): 1680, 1520, 1260 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.25 (d *J* = 8.7 Hz, 2 H), 6.86 (d, *J* = 8.7 Hz, 2 H), 5.15 (s, 1 H), 4.61 (s, 2 H), 3.81 (s, 3 H), 3.80 (q, *J* = 7.0 Hz, 2 H), 3.31 (dd, *J* = 7.4, 6.0 Hz, 2 H), 2.36 (t, *J* = 7.3 Hz, 2 H), 1.81–1.75 (m, 2 H), 1.34 (t, *J* = 7.0 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 166.2, 159.3, 130.8, 129.9, 116.5, 114.3, 96.8, 63.9, 55.6, 50.4, 46.8, 31.1, 27.8, 14.7.

LC/MS (APCI+): *m*/*z* = 276.0 (M + H).

HRMS (ESI): *m*/*z* calcd for $C_{16}H_{21}O_3N$ [M$^+$]: 275.1516; found: 275.15201.

***N*-(*p*-Methoxybenzyl)azepane-2,4-dione (10)**

To a solution of **9** (231 mg, 0.8 mmol) in EtOH (3 mL), was added H_2O (3 mL) and concd HCl (1 mL). The mixture was heated to 50 °C for 2–3 h, then cooled to r.t. The mixture was poured into an ice bath, neutralized with a 10% solution of K_2CO_3 (10 mL), and then extracted with EtOAc (2 × 10 mL). The resulting organic layers were dried over $MgSO_4$, filtered, and concentrated to give **10** as a pure yellow oil (180 mg, 87%).

IR (film): 1700, 1650, 1520, 1250 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.24 (d, *J* = 8.7 Hz, 2 H), 6.87 (d, *J* = 8.7 Hz, 2 H), 4.59 (s, 2 H), 3.81 (s, 3 H), 3.61 (s, 2 H), 3.52 (t, *J* = 6.0 Hz, 2 H), 2.54 (t, *J* = 7.1 Hz, 2 H), 1.79 (m, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 203.5, 167.0, 159.2, 129.6 (2 C), 129.2, 114.1 (2 C), 55.2, 52.2, 50.1, 46.2, 41.6, 25.5.

HRMS (ESI): *m*/*z* calcd for $C_{14}H_{17}O_3NNa$ [M + Na]: 270.1101; found: 270.1093.

Trifluoromethanesulfonic Acid *N*-(*p*-Methoxybenzyl)-2-oxoazepan-4-yl Ester (2)

To a solution of **10** (146 mg, 0.6 mmol) in CH_2Cl_2 (4 mL) was added an aq solution of NaOH (3 N, 4 mL), followed by the dropwise addition of Tf_2O (0.2 mL, 1.2 mmol) at 0 °C. The resulting mixture was slowly warmed to r.t. over 12 h. The mixture was diluted with CH_2Cl_2 (10 mL) and the phases separated. The organic phase was washed with H_2O (15 mL) and brine (15 mL), dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by column chromatography to give **2** as a colorless oil (133 mg, 60%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.23 (d, *J* = 8.6 Hz, 2 H), 6.90 (d, *J* = 8.6 Hz, 2 H), 6.19 (s, 1 H), 4.61 (s, 2 H), 3.82 (s, 3 H), 3.39 (m, 2 H), 2.65 (t, *J* = 7.1 Hz, 2 H), 1.89 (m, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 164.0, 159.2, 156.9, 129.6 (2 C), 128.8, 118.8, 113.9 (2 C), 55.2, 50.7, 45.8, 43.4, 31.7, 26.3.

LC-MS (APCI+): *m*/*z* = 380.0 (M + H).

***N*-(*p*-Methoxybenzyl)-4-undeca-1,3-diynyl-1,5,6,7-tetrahydroazepin-2-one (11)**

To a solution of enol triflate **2** (29 mg, 0.08 mmol) and diacetylene **3** (13.6 mg, 0.09 mmol) in DMF (2 mL) was added CuI (2.9 mg, 0.2 mmol) and $Pd(PPh_3)_2Cl_2$ (5.4 mg, 0.1 mmol), followed by the addition of Et_3N (21.5 μL, 0.15 mmol) at r.t. The solution was stirred for 12 h and then diluted with Et_2O (8 mL). The organic phase was washed with a sat. solution of $NaHCO_3$, a sat. solution of NH_4Cl (10 mL), H_2O (10 mL), and brine (15 mL), dried over $MgSO_4$, filtered, and concentrated in vacuo. The crude product was purified by column chromatography to afford **11** as a brown oil (26 mg, 90%).

IR (film): 2920, 2240, 1640, 1510, 1460, 1210 cm^{-1}.

^{1}H NMR (400 MHz, CD_3OD): δ = 7.25 (d, *J* = 8.6 Hz, 2 H), 6.89 (d, *J* = 8.6 Hz, 2 H), 6.30 (s, 1 H), 4.58 (s, 2 H), 3.78 (s, 3 H), 3.36 (t, *J* = 6.20 Hz, 2 H), 2.37 (t, *J* = 7.1 Hz, 2 H), 2.35 (t, *J* = 7.5 Hz, 2 H), 1.79 (m, 2 H), 1.55 (m, 2 H), 1.42–1.40 (m, 2 H), 1.34–1.31 (m, 6 H), 0.91 (t, *J* = 6.6 Hz, 3 H).

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^{13}C NMR (100 MHz, CD_3OD): δ = 168.3, 159.4, 131.7, 130.6, 129.4, 129.2 (2 C), 113.6 (2 C), 87.1, 77.8, 74.1, 64.0, 54.2, 49.4, 45.5, 31.4, 30.6, 28.4, 28.3, 28.0, 27.8, 22.2, 18.6, 12.9.

HRMS (ESI): *m/z* calcd for $C_{25}H_{33}O_2N$ $[M + H]^+$: 378.2428; found: 378.2413.

4-Undeca-1,3-diynyl-1,5,6,7-tetrahydroazepin-2-one (1)

To a solution of **11** (5 mg, 13.3 mol) in H_2O (0.2 mL) and MeCN (0.8 mL), CAN (36 mg, 0.07 mmol) was added at r.t. The mixture was stirred for 2–5 h, then poured into H_2O (5 mL), and extracted with EtOAc (3 × 5 mL). The combined organic layers were washed with a sat. solution of $NaHCO_3$ (5 mL), H_2O (5 mL), brine (10 mL), dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by column chromatography to give **1** as a white foam (3 mg, 88%).

IR (film): 3320–3180, 2220, 1660 cm^{-1}.

^{1}H NMR (400 MHz, CD_3OD): δ = 6.22 (s, 1 H), 3.27 (t, *J* = 4.4 Hz, 2 H), 2.58 (t, *J* = 6.9 Hz, 2 H), 2.42 (t, *J* = 6.9 Hz, 2 H), 2.03 (quin, *J* = 6.7 Hz, 2 H), 1.60 (quin, *J* = 7.2 Hz, 2 H), 1.48–1.44 (m, 2 H), 1.38–1.31 (m, 6 H), 0.95 (t, *J* = 6.8 Hz, 3 H).

^{13}C NMR (100 MHz, CD_3OD): δ = 170.1, 133.5, 131.0, 87.2, 77.7, 74.4, 64.0, 39.7, 32.9, 31.5, 28.5 (2C), 28.2, 27.8, 22.2, 18.6, 12.9.

HRMS (ESI): *m/z* calcd for $C_{17}H_{25}ON$ $[M + H]^+$: 258.1852; found: 258.1857.

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(15) The ^{1}H and ^{13}C NMR spectra of natural montiporyne E were provided by Dr. Jee H. Jung, College of Pharmacy, Pusan National University, Korea.

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