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A practical total synthesis of gelastatins☆

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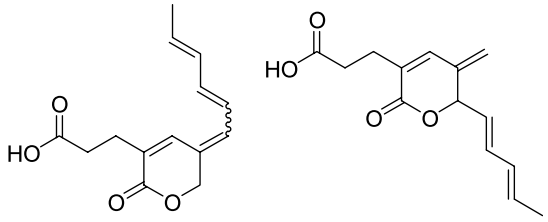
Abstract—The first and practical total synthesis of gelastatins **1**, a novel matrix metalloproteinase inhibitor possessing antitumor activity, was accomplished in nine steps starting from Meldrum's acid.



Gelastatins, 1 Dykellic acid

Gelastatins (**1**) were isolated as a mixture of two olefinic stereoisomers from the culture broth of *Westerdykella multispora* F50733 found in soil sample in Korea in 1997[1] and later found to be attainable from more abundant and related natural product dykellic acid[2] through acid catalyzed rearrangement during isolation. Stereoisomers of gelastatins (gelastatin A and gelastatin B) were separable by LC but readily isomerized back to the same mixture of isomers and slowly decomposed in the air at room temperature. Gelastatins were found to exhibit impressive biological activities, including inhibition of gelatinase A (MMP-2) and inhibition of tumor necrosis factor-α converting enzyme (TACE) that play important roles in a number of inflammatory and degenerative diseases including rheumatoid arthritis, stroke, multiple sclerosis, tumour invasion, and metastasis.[3]

As a part of our ongoing research program to develop potent and selective MMP-2 inhibitors for treatment of cancer[3b] preparation of a large quantity of gelastatins was required for in vivo biological study as well as for preparation of various analogs of gelastatins. Since gelastatins could not be obtained in large quantities from natural sources, we decided to devise a synthetic route that would not only accomplish the total synthesis of gelastatins but also provide an access to a large quantity of gelastatins. Synthetic analysis for total synthesis of gelastatin quickly revealed few obvious synthetic routes starting from glutaric acid derivatives (Scheme 1).[4]

However, none of the strategies was executed successfully to a practical synthesis of gelastatins. Ring closing olefin metathesis reaction[5] of **3** only produced a dimer of **3** instead of the desired lactone ring. Intramolecular Wittig reaction of **4** and aldol type condensation reactions of related compounds did not produce any cyclized products. Lastly, intermolecular Wittig reaction followed by lactonization reaction of **2** produced the esters of gelastatins (Scheme 2). However, the lactonization was so sluggish that the product, *t*-butyl ester of **1** decomposed before the completion of the lactonizaiton reaction to yield less than 20% of the desired product.

Since several seemingly obvious synthetic routes turned out to be unsatisfactory because the formation of unsaturated lactone rings directly from acyclic precursors was not amenable,[6] the basic synthetic plan was modified as the introduction of the unsaturation in the lactone ring would be deferred until the final stage of the synthesis.

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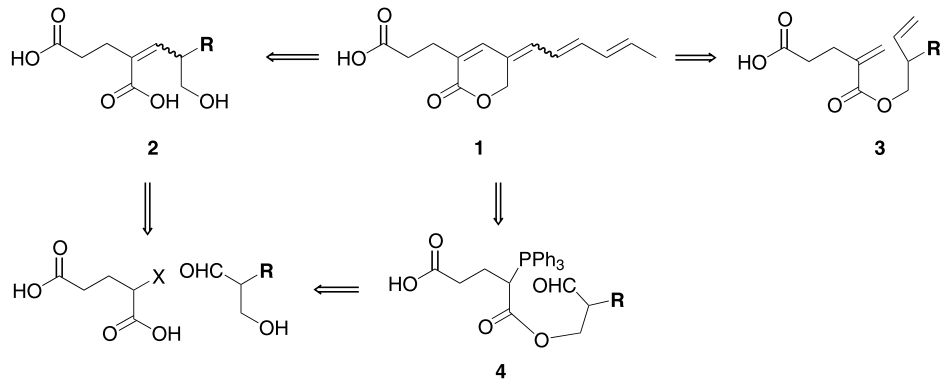
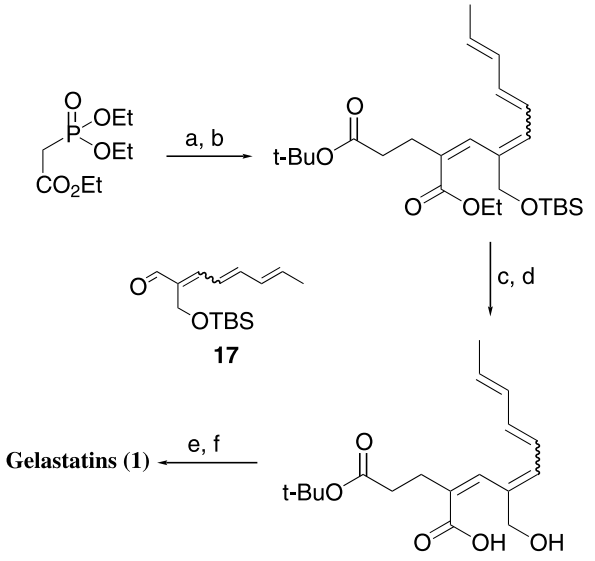
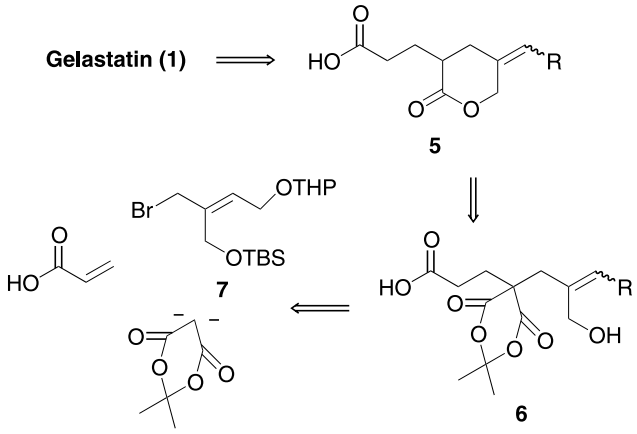


Scheme 1.



Scheme 2. *Reagents and conditions*: (a) *t*-butyl acrylate, NaH, THF, 0°C to rt, 48%; (b) **17**, NaH, THF, rt, 83%; (c) TBAF, THF, 0°C, 85%; (d) 1N LiOH, MeOH–H_2O, rt, 88%; (e) EDCI, HOBT, DIPEA, DMF, rt, 10–20%; (f) TFA, Et_3SiH, CH_2Cl_2.



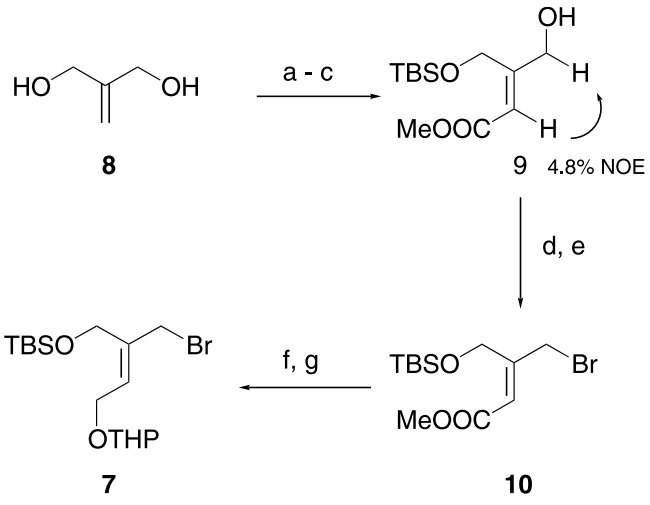
Scheme 3.

A new synthetic analysis suggested that Meldrum's acid would be a good starting point since the propionyl and polyene appendages could be introduced to Meldrum's acid and the properly substituted Meldrum's acid could be transformed into the lactone ring (Scheme 3).

The total synthesis of gelastatins started with the preparation of the first crucial intermediate **6**. One of the starting material, **7** was prepared from commercially available 2-methylene 1,3-propanediol **8** (Scheme 4).

First, the terminal olefin of the mono-protected **8** was replaced with a conjugated ester through ozonolysis followed by Wittig olefination reaction with methyl (triphenylphosphoranylidene) acetate to produce **9** stereoselectively ($E/Z=1/20$).[7] The stereochemistry of **9** was determined through NOE experiment. After the alcohol was converted to the bromide, the ester of **10** was reduced to the corresponding alcohol and the resulting alcohol was protected as THP ether to yield **7**.[8]

With all the starting materials in hand, the synthesis of **5** proceeded with Michael addition reaction of Meldrum's acid with acrylate to afford exclusively the mono substituted Meldrum's acid **11**[9] (Scheme 5). Alkylation of **11** with allylic bromide **7** gave **12**. As anticipated, exposure of **12** to Bu_4NF at room temperature not only caused cleavage of the silyl ether but also facilitated simultaneous lactonization and decarboxylation[10] to give the desired saturated lactone **13**. Since the lactone ring of **13** appeared to be unstable under prolonged exposure to the air or acidic environment, unsaturation was introduced to **13** at this point to stabilize the lactone ring. Saegusa oxidation[11] of corresponding silyl enol ether of the lactone **13** introduced unsaturation regioselectively to form the dihydropyranone **14** as an inseparable mixture of *E*, *Z* isomers. The remaining task was to transform the allylic alcohol into the conjugated alkyl group of gelastatins. This final stage of the synthesis was to be accomplished through Wittig type olefination of the corresponding aldehyde or phosphorous ylide of **14**. However, all the attempts to convert the alcohol of **14** to the corresponding aldehyde were not successful. While the conjugated allylic alcohol of **14** was inert to various conventional oxidation conditions (MnO_2, PCC, Swern's oxidation etc.), substitution reaction of



Scheme 4. *Reagents and conditions*: (a) TBDMSCl, NaH, THF, 91%; (b) O_3; PPh_3, CH_2Cl_2, −78°C to rt; (c) Ph_3PCHCO_2Me, benzene, reflux, 54% for two steps; (d) MsCl, Et_3N, CH_2Cl_2, 0°C; (e) LiBr, acetone, rt, 92% for two steps; (f) DIBAL-H, CH_2Cl_2, −78°C; (g) DHP, PPTS, CH_2Cl_2, rt, 54% for two steps.

the activated alcohol was successful to afford the bromide **15**. Though the formation of the anticipated Wittig reagent from **15** was not fruitful, substitution reaction of the bromide with the anion of 2-butenylphenylsulfone[12] underwent smoothly to the phenylsulfonyl analog of gelastatin. Base treatment of the sulfone produced methyl esters of gelastatins **16**. Finally, hydrolysis of the methyl ester of **16** using barium hydroxide produced gelastatins without noticeable decomposition. The synthetic gelastatins showed the same spectroscopic properties of natural gelastatins with 1:3 ratio of isomers A and B.[13] Thus, we were able to complete the total synthesis of gelastatins in 9 steps from Meldrum's acid. Since all the synthetic steps were straightforward and reproducible in a preparatory scale synthesis, we were able to provide gram quantities of gelastatins through current synthetic route for preparation of analogs of gelastatins and for various biological tests.

In summary, we have achieved the first and practical total synthesis of gelastatins. Currently, we are pursuing the synthesis of various analogs of gelastatins through this synthetic route and study of the structure activity relationship of gelastatin analogs with MMP's and in vivo activity.

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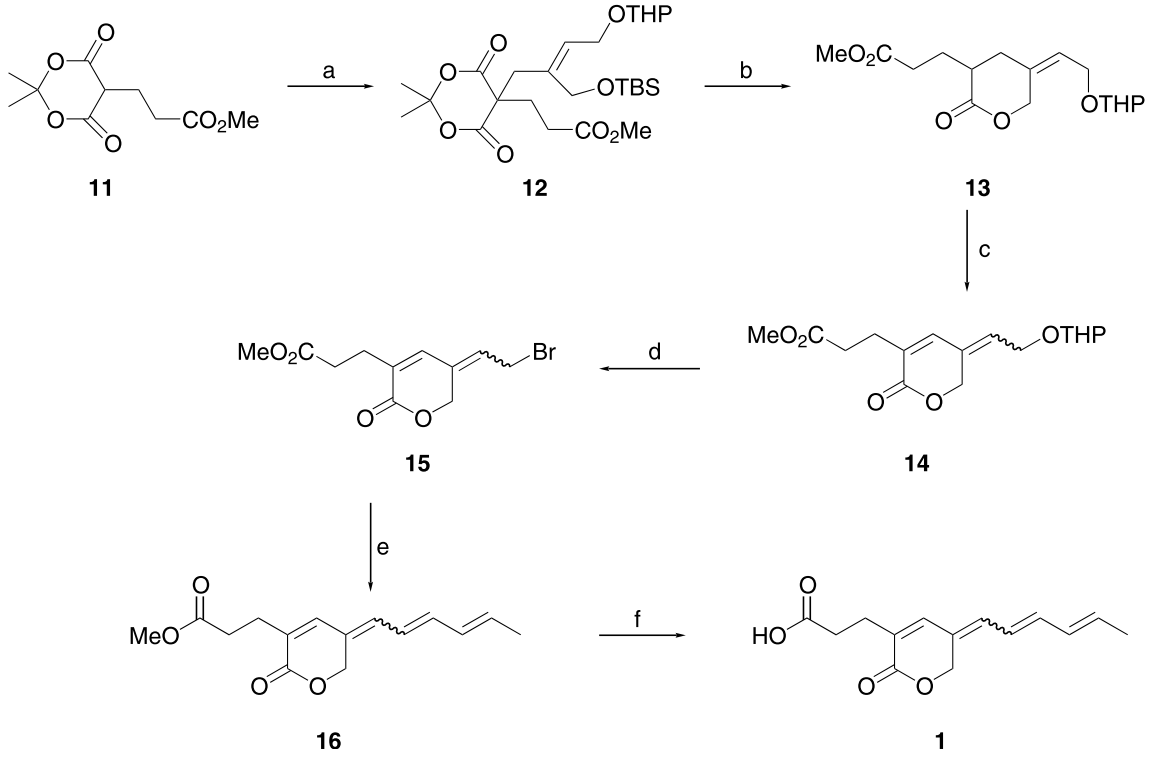

Scheme 5. *Reagents and conditions*: (a) **7**, K_2CO_3, DMF, 87%; (b) TBAF, THF, rt, 67%; (c) i. LHMDS, TMSCl, THF, −78°C; ii. $Pd(OAc)_2$, CH_3CN, rt, 65%; (d) i. *p*-TsOH, EtOH, rt, 85%; ii. MsCl, Et_3N, CH_2Cl_2, 0°C; iii. LiBr, acetone, rt, 86%; (e) i. 2-butenyl phenyl sulfone, LHMDS, THF, −78°C; ii. DBU, CH_2Cl_2, rt, 49%; (f) $Ba(OH)_2$, H_2O, MeOH, rt, 85%.

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8. Spectral data of **7**: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 5.81 (t, $J=6.8$ Hz, 1H), 4.59 (t, $J=2.8$ Hz, 1H), 4.30 (s, 2H), 4.24 (dd, $J=13.2$, 5.9 Hz, 1H), 4.08 (s, 2H), 4.06 (dd, $J=13.9$, 5.9 Hz, 1H), 3.85–3.79 (m, 1H), 3.51–3.47 (m, 1H), 1.78–1.48 (m, 6H), 0.89 (s, 9H), 0.08 (s, 6H).
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13. Spectral data of **12**, **15**, **1**. **12** ^{1}H NMR ($CDCl_3$, 400 MHz) δ 5.59 (t, $J=6.3$ Hz, 1H), 4.56 (t, $J=3.0$ Hz, 1H), 4.24 (dd, $J=13.0$, 6.0 Hz, 1H), 4.07 (s, 2H), 3.99 (dd, $J=13.0$, 6.7 Hz, 1H), 3.80–3.75 (m, 1H), 3.63 (s, 3H), 3.48–3.45 (m, 1H), 2.84 (s, 2H), 2.34 (s, 4H), 1.68 (s, 3H), 1.66 (s, 3H), 1.70–1.64 (m, 2H), 1.54–1.46 (m, 4H), 0.86 (s, 9H), 0.03 (s, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 171.9, 168.3, 168.3, 136.0, 130.4, 105.8, 97.9, 62.7, 61.9, 60.8, 53.9, 51.9, 41.5, 33.6, 30.4, 29.8, 29.7, 29.5, 25.8, 19.2, 18.3, −5.5; **15** isomer A: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 6.82 (s, 1H), 5.96 (t, $J=8.8$ Hz, 1H), 5.10 (d, $J=2.1$ Hz, 2H), 3.96 (d, $J=8.8$ Hz, 2H), 3.65 (s, 3H), 2.73–2.64 (m, 2H), 2.61–2.54 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 172.9, 163.3, 139.8, 132.0, 131.9, 127.6, 70.4, 65.7, 51.6, 32.4, 26.5; isomer B: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.19 (s, 1H), 5.86 (t, $J=7.1$ Hz, 1H), 4.85 (s, 2H), 4.05 (d, $J=8.6$ Hz, 2H), 3.66 (s, 3H), 2.70–2.66 (m, 2H), 2.59–2.55 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 172.9, 163.3, 139.8, 132.9, 130.2, 126.1, 70.4, 51.6, 32.5, 27.1, 24.6; **1**. IR (CH_2Cl_2, cm^{-1}): 2931, 1714, 1600, 1417, 1204, 1109, 1040, 991; HR-MS (ESI) m/z: calcd for $M+H^+$: 249.1127, obs. 249.1121; NMR spectra for isomer A: ^{1}H NMR (CD_3OD, 400 MHz) δ 7.54 (s, 1H), 6.60 (dd, $J=11.6$, 14.4 Hz, 1H), 6.43 (dd, $J=11.2$, 15 Hz, 1H), 6.33–6.15 (m, 2H), 5.97–5.88 (m, 1H), 4.90 (s, 2H), 2.67–2.53 (m, 4H), 1.81 (br d, $J=6.8$ Hz, 3H); ^{13}C NMR (CD_3OD, 100 MHz) δ 176.3, 167.2, 139.7, 137.1, 134.5, 133.0, 132.5, 129.5, 126.9, 125.1, 72.2, 33.8, 27.9, 18.6; for isomer B: ^{1}H NMR (CD_3OD, 400 MHz) δ 7.00 (s, 1H), 6.46 (dd, $J=11.8$, 22.6 Hz, 1H), 6.33–6.15 (m, 3H), 5.97–5.86 (m, 1H), 5.20 (s, 2H), 2.65–2.50 (m, 4H), 1.81 (br d, $J=6.8$ Hz, 3H); ^{13}C NMR (CD_3OD, 100 MHz) δ 176.3, 167.0, 143.4, 140.7, 135.0, 134.1, 133.1, 128.1, 127.7, 125.4, 68.0, 33.7, 27.5, 18.6.