

α -Carbonyl radical cyclization approach toward spiro[4.4]nonene: total synthesis of dimethyl gloiosiphone A

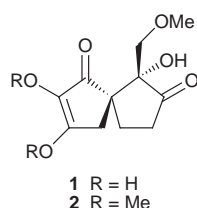
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The total synthesis of dimethyl gloiosiphone A **2** was achieved via an α -carbonyl radical spirocyclization.

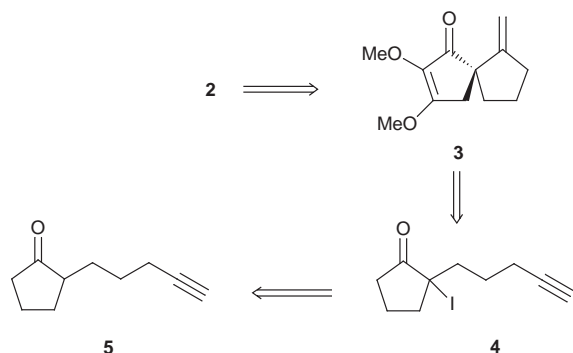
Gloiosiphone A **1** and its dimethyl derivative **2** were isolated from red marine algae *Gloiosiphonia verticillaris*.¹ Crude lipid collections of *Gloiosiphonia verticillaris* were found to exhibit profound antimicrobial activity against several *Staphylococcus*,



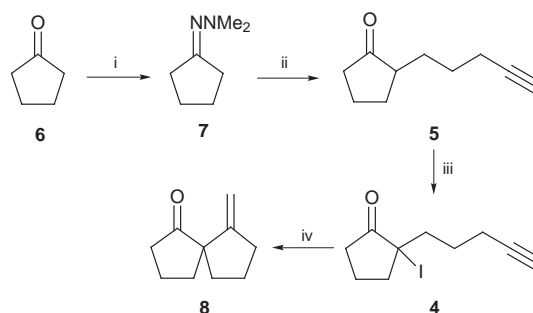
Bacillus and *Salmonella* species. Since the causative agent **1** was not stable enough for isolation, the crude collections were treated with CH_2N_2 to furnish the more stable dimethyl derivative **2**.

Compounds **1** and **2** comprise a new structural class featuring a highly oxygenated spiro[4.4]nonene system. Due to their potential antimicrobial activity and novel molecular skeleton, these compounds are challenging synthetic targets. The first total synthesis of dimethyl gloiosiphone A **2** has been achieved recently by Paquette's group.² As an extension of our work on the α -carbonyl radical cyclization reaction,³ we report herein the total synthesis of **2** using an α -carbonyl radical cyclization as the key step. The retrosynthetic analysis is outlined in Scheme 1. The spirononene structure in **2** could be produced by an α -carbonyl radical cyclization followed by appropriate oxidation (**4**→**3**). The radical precursor iodo ketone **4** would be generated according to our method⁴ from **5**, which in turn could be prepared from cyclopentanone **6** according to Yamashita's procedure.⁵

Treatment of cyclopentanone **6** with *N,N*-dimethylhydrazine in the presence of TFA as catalyst furnished hydrazone **7** (Scheme 2). Deprotonation of **7** with Bu^nLi at 0 °C followed by alkylation with 5-iodopent-1-yne and hydrolysis yielded the required ketone **5**. Ketone **5** was sequentially treated with HMDS/TMSI and NaI/MCPBA in THF to afford iodo ketone **4**.



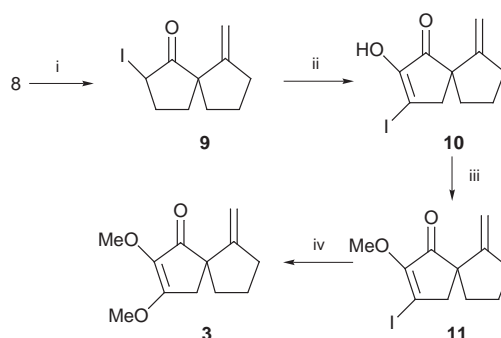
Scheme 1



Scheme 2 Reagents and conditions: i, H_2NNMe_2 , 90%; ii, Bu^nLi , 0 °C, 5-iodopent-1-yne, then 10% HCl, 1 h, 80%; iii, HMDS, TMSI, CH_2Cl_2 , then NaI, MCPBA, THF, 82%; iv, $(\text{Bu}_3\text{Sn})_2$ (0.1 equiv.), sun lamp, C_6H_6 , 1.5 h, then Bu_3SnH (1.05 equiv.), AIBN, C_6H_6 , 87%.

Treatment of **4** with Bu_3SnH under standard conditions furnished the required spirocyclic compound **8** in 50% yield. To improve the yield, an atom transfer radical reaction was adopted.⁶ Thus, irradiation of a benzene solution of ketone **4** at reflux with a sun lamp in the presence of $(\text{Bu}_3\text{Sn})_2$ (0.1 equiv.) followed by reduction of the resulting vinyl iodide with Bu_3SnH (1.05 equiv.) using AIBN as initiator furnished spiro compound **8** in 87% overall yield.

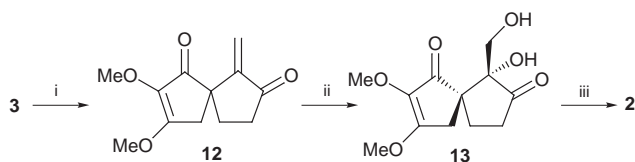
We then focused our attention on the introduction of enol ether moieties into **8**. First, iodo ketone **9** was generated from **8** by the same method used for the transformation of **5**→**4** (Scheme 3).³ The iodo ketone **9** was then converted into unsaturated ketone **10** via a modified version of Sato's method.⁷ Accordingly, **9** was oxidized with DMSO at 70 °C followed by addition of I_2 (1 equiv.) to provide **10**.



Scheme 3 Reagents and conditions: i, HMDS, TMSI, CH_2Cl_2 , then NaI, MCPBA, THF, 82%; ii, DMSO, I_2 , 86%; iii, NaH, MeI, DMF, 95%; iv, NaOMe (10 equiv.), MeOH, 92%.

Compound **10** was subsequently methylated with NaH and MeI to give methoxy iodo enone **11**. Nucleophilic displacement of iodide in **11** with NaOMe then furnished dimethoxy enone **3**.

Allylic oxidation of **3** with SeO_2 gave diketone **12** (60%) (Scheme 4). Treatment of **12** with a catalytic amount of OsO_4 with NMO as the co-oxidant gave dihydroxy ketone **13**. Finally, selective methylation of the primary alcohol with dimethyl sulfate in presence of excess K_2CO_3 (10 equiv.) afforded



Scheme 4 Reagents and conditions: i, SeO_2 , dioxane, reflux, 60%; ii, OsO_4 , NMO, Bu^tOH , THF, H_2O , 87%; iii, K_2CO_3 (10 equiv.), Me_2SO_4 , 75%.

dimethyl gloiosiphone A **2**. All spectral data for **2** are in good agreement with those reported in the literature.^{1,2}

In summary, a total synthesis of dimethyl gloiosiphone A **2** has been accomplished in a stereoselective manner in which an α -carbonyl radical cyclization reaction was employed to facilitate the construction of the key spiro[4.4]nonene skeleton. Application of this versatile α -carbonyl radical cyclization methodology toward the total synthesis of more complex natural products is under current investigation.

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Notes and references

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