

A STEREOSPECIFIC SYNTHESIS OF (±)-PERFORENONE[†]George Majetich* and Clay Ringold¹

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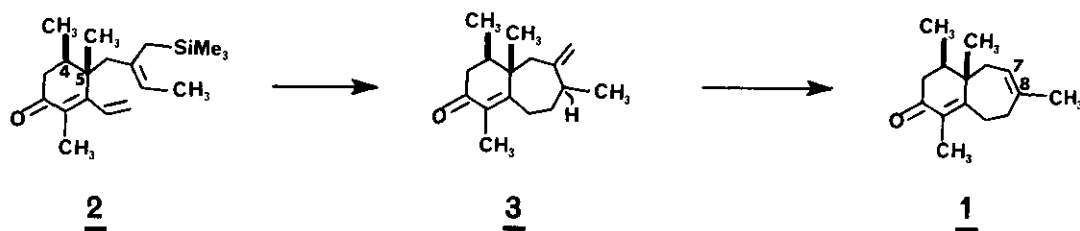
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Abstract — The total synthesis of (±)-perforenone is reported featuring an intramolecular Sakurai reaction to construct the bicyclic skeleton.

[†]Dedicated with appreciation and best wishes to Professor Gilbert Stork on the occasion of his sixty-fifth birthday.

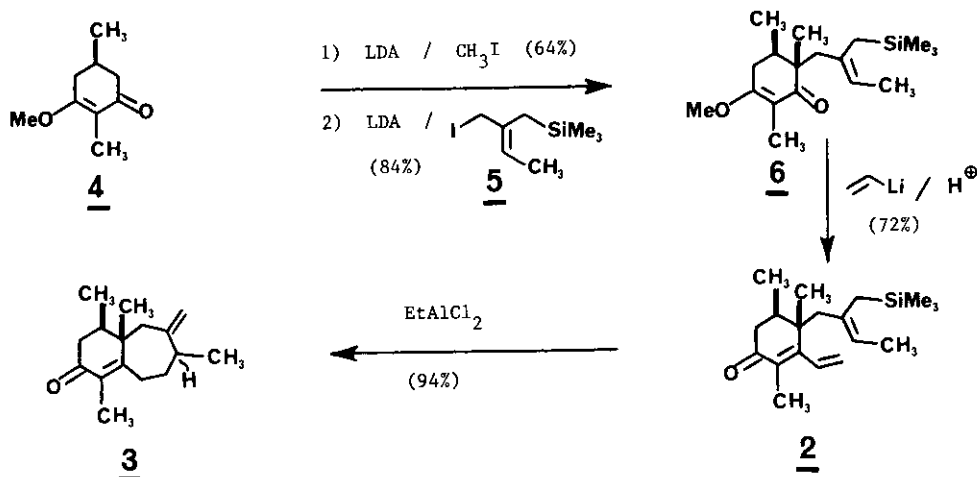
Lewis acid-catalyzed additions of allylsilanes to conjugated dienones efficiently produce seven-membered rings.^{2,3} Here we report the application of this new annulation procedure to the total synthesis of (±)-perforenone (**1**), a metabolite isolated from the marine alga *Laurencia perforata*.⁴

The key transformation in our synthetic scheme (shown below) is the ring closure of trienone **2** to bicyclic enone **3**. Accordingly, we undertook a stereocontrolled synthesis of this precursor.



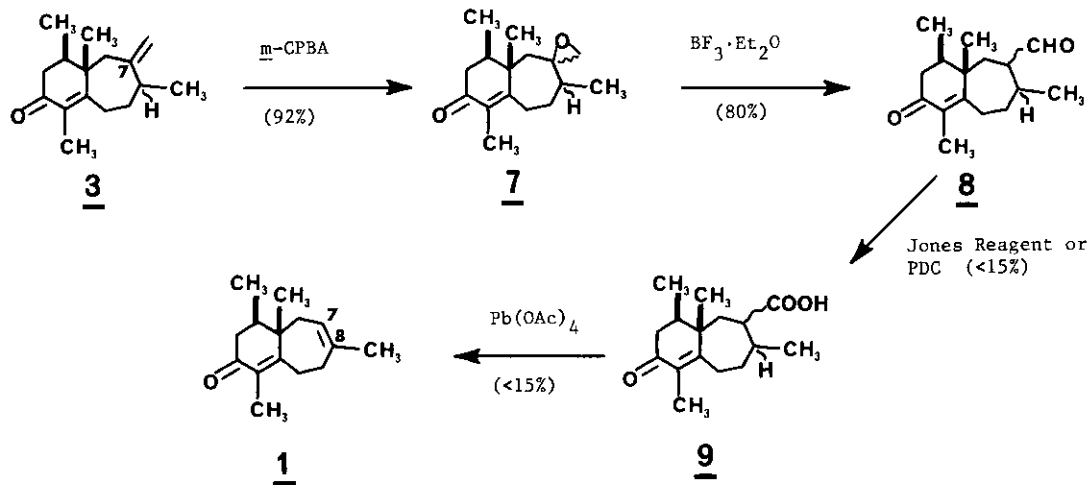
The starting material for this synthesis was the methylated enol ether **4**.^{5,6} Previously, we reported that the *cis*-C(4),C(5)-dimethyl relationship found in trienone **2** could be established by the order of alkylation of a similar enol ether.^{7,8} Thus alkylation of **4** first with methyl iodide and then with allylsilane-iodide **5**⁹ provided a 5:1 mixture of diastereomers of which **6** is the major isomer (Scheme II). Treatment of **6** with vinylolithium in THF at 0°C, followed by mild acid hydrolysis, provided dienone **2**. Cyclization of trienone **2** with ethylaluminum dichloride at room temperature gave a 94% yield of bicyclic enone **3** as a 2:1 mixture of C(8) epimers.¹⁰

SCHEME II



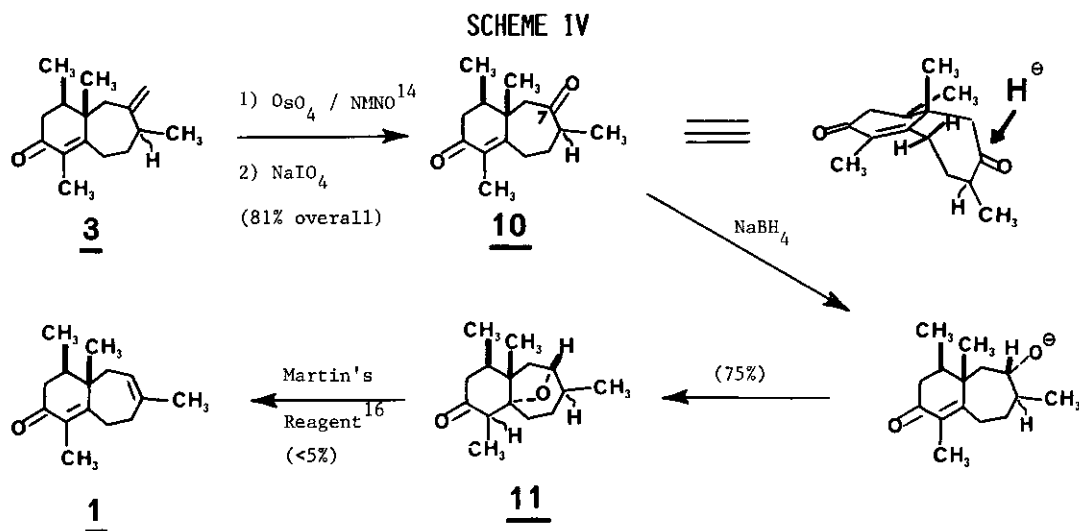
The assumption that the remaining conversion of exo-cyclic olefin **3** to perforenone would pose few problems proved to be incorrect. Our original plan was to convert **3** to carboxylic acid **9**, which would furnish perforenone upon oxidative decarboxylation (Scheme III). Although the Lewis acid-catalyzed rearrangement of epoxide **7** proceeded smoothly,¹¹ oxidation of **8** to **9** occurred in low yield. Furthermore, the oxidative degradation of **9** using lead tetraacetate was found to be inefficient.¹²

SCHEME III



After our initial strategy for introducing the C(7),C(8) olefin failed, we sought to achieve this transformation by the following sequence: (1) selective oxidation of the C(7) olefin

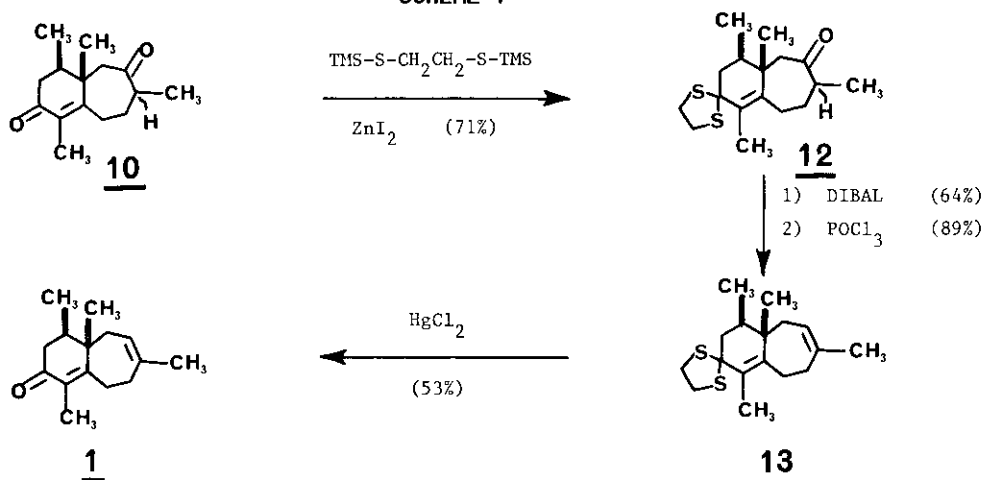
followed by glycol cleavage; (2) selective reduction of the resulting ketone; and (3) dehydration (Scheme IV). Regiospecific cleavage of the exocyclic olefin of 3 with OsO_4 - NaIO_4 afforded diketone 10 in 30% yield.¹³ However, isolation of the intermediate diol, followed by glycol cleavage, resulted in a 81% yield of diketone 10.¹⁴



We anticipated the regioselective and stereospecific reduction of the C(7) carbonyl, via hydride approach from the less-hindered β -surface, based on conformational analysis and choice of reducing agent.¹⁵ This prediction was experimentally confirmed when reduction of diketone 10 with sodium borohydride gave exclusively a single secondary alcohol; other common hydride reagents [LAH, DIBAL, lithium tri-*tert*-butoxyaluminumhydride] produced significant amounts of diol. Our conclusion that this reduction was stereospecific rests upon the exclusive isolation of tricyclic tetrahydrofuran 11 upon workup. The formation of this intramolecular Michael condensation product could not be suppressed. Tetrahydrofuran 11 could be dehydrated to perforenone using bis[α , α -(trifluoromethyl)benzenemethanolato]diphenylsulfur,¹⁶ albeit in low yield.

Masking the cyclohexenone unit prior to the elaboration of the cycloheptane ring ultimately permitted the preparation of perforenone. Treatment of diketone 10 with (ethylenedithio)bis(trimethylsilane) and zinc iodide selectively ketalized the C(2) carbonyl,¹⁷ without migration of the C(1),C(10) olefin. DIBAL reduction of the C(7) carbonyl, followed by dehydration using POCl_3 in pyridine, provided dienone 13. Deprotection of the C(2) carbonyl provided crystalline racemic perforenone, mp 76 - 77°C , whose spectral properties were identical with those of the natural product.

SCHEME V



ACKNOWLEDGEMENTS

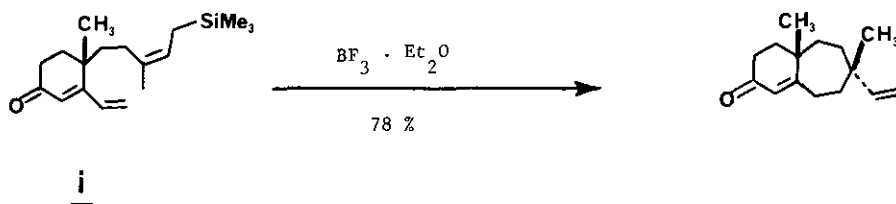
Special thanks are extended to Professor J. D. Martin of the Universidad de la Laguna for an authentic sample of perforenone. Thanks are also due to Dr. Philip Bowen for conducting the MM_2 studies. Acknowledgement is made to the donors of the Petroleum Research Fund, administered by the American Chemical Society, for support of this work.

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