

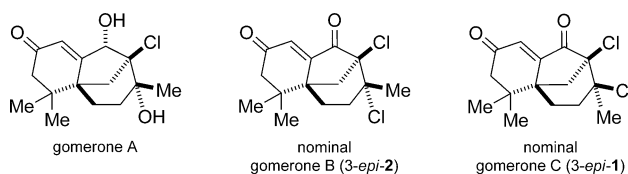
Total Synthesis and Stereochemical Revision of the Chlorinated Sesquiterpene ($\pm$)-Gomerone C**

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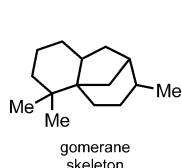
Red algae from the genus *Laurencia* (Ceramiales) are the source of over 500 halogenated terpenes, cyclic ethers, and acetogenides, which in some cases have been suggested to serve as chemical defence agents because of their activity against pathogenic marine bacteria and herbivores.^[1,2] In 2008 a Spanish research group reported the isolation and structural elucidation of three novel chlorinated sesquiterpenes, gomerones A–C, from samples of *Laurencia majuscula* collected at the southern coast of La Gomera, Canary Islands (Scheme 1).^[3] The structurally interesting and unprecedented

The synthetic challenges encountered in the gomerones include the angular, tricyclic carbon skeleton, two contiguous quaternary centers at C6 and C11, as well as two chloride-substituted tertiary carbon centers, one of which is positioned at the bridgehead of a bicyclo[3.2.1]octane. Consideration of Bredt's rule thus suggests that the bridgehead chloride would be precluded from being introduced by enolate chemistry once both rings have been formed. With this limitation in mind, we became intrigued by the possibility of forging the bicyclic scaffold by a late-stage Conia-ene reaction involving an α -chlorinated silyl enol ether and an alkyne. Such a transformation, if successful, would install the required 6-membered ring and also concomitantly generate an exocyclic olefin that could be employed as a flexible handle for further elaboration toward the natural products (Scheme 2).^[5] Structure 3, the necessary precursor for the ene reaction, could be further simplified retrosynthetically, as indicated, to arrive at intermediate 4, which could arise from a [4+2] cycloaddition reaction.

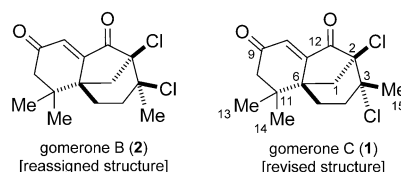
A) Originally Assigned Structures:



B)

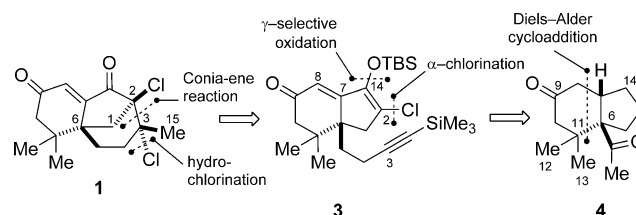


C) This Work:



Scheme 1. A) Proposed structures of gomerones A–C; B) gomerane skeleton; C) structural revision and reassignment.

gomerane skeleton in combination with their unexplored biological activity as well as the halogenated nature of these natural products rendered them noteworthy targets for synthesis.^[4] Herein, we report a total synthesis of gomerone C (1), which not only represents the first synthesis of a member of this novel class of chlorinated sesquiterpenes, but also resulted in the revision of the relative stereochemistry of gomerone C (1) and hence to a stereochemical reassignment of gomerone B (2).



Scheme 2. Retrosynthetic analysis of gomerone C.

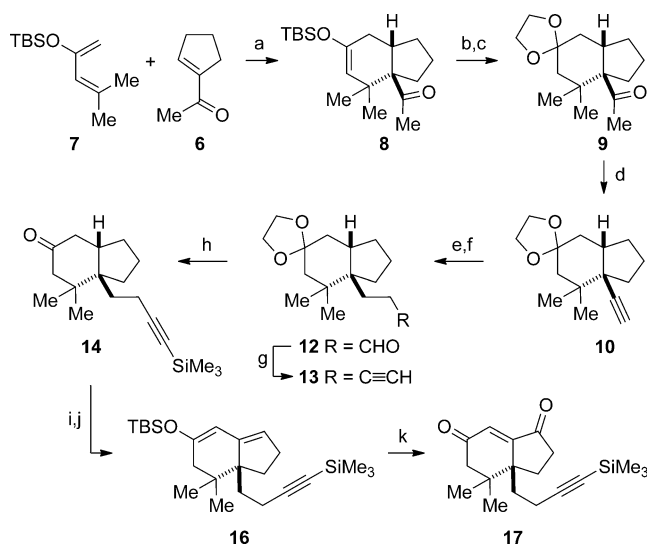
The synthesis commenced with a Diels–Alder reaction between silyloxydiene 7 and commercially available 1-acetyl-1-cyclopentene (6), thereby allowing for the rapid formation of the fused 5,6-membered ring system and the concomitant installation of the two adjacent quaternary centers at the very beginning of the synthetic route (Scheme 3). Despite the hindered character of the diene and the sometimes limited reactivity of cyclopentene dieneophiles in cycloaddition reactions, the reaction was found to proceed well, delivering the desired product in 69 % yield.^[6] The structure and relative configuration of the Diels–Alder adduct obtained was confirmed by X-ray crystallography (see the Supporting Information). Subsequent cleavage of the TBS enol ether under acidic conditions followed by regioselective mono-acetalization of the obtained diketone 4 delivered methyl ketone 9 in 58 % overall yield (three steps).^[7]

Next, we turned our attention to the introduction of the but-3-ynyl side chain. Preliminary experiments revealed that the sterically hindered carbonyl carbon atom of the methyl

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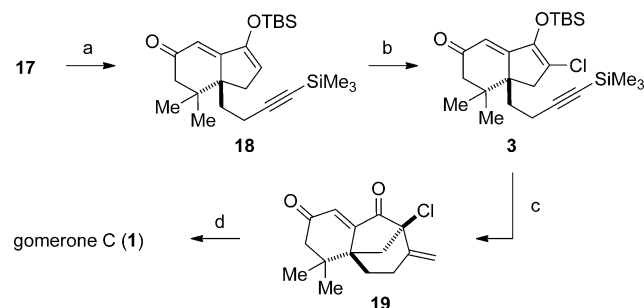
Scheme 3. Reagents and conditions: a) Me_2AlCl (20 mol %), toluene/ CH_2Cl_2 (2:1), -15°C , 24 h; then 0°C , 24 h, 69%; b) $\text{F}_3\text{CCO}_2\text{H}$, CH_2Cl_2 , RT, 2 h, 89%; c) 2-methyl-2-ethyl-1,3-dioxolane, $\text{TsOH}\cdot\text{H}_2\text{O}$ (25 mol %), ethylene glycol (12 mol %), RT, 45 min, 95%; d) phosphazene base P_2tBu (3.0 equiv), $\text{F}_3\text{C}_3\text{SO}_2\text{F}$ (1.3 equiv), DMF, -10°C to RT, 2 h; then RT for 24 h, 92%; e) $n\text{BuLi}$, THF, -78°C to RT, 40 min; then $\text{BF}_3\cdot\text{OEt}_2$, -78°C , 10 min; then DMF (3.3 equiv), 60 min, 78%; f) Pd/C (10 mol %), H_2 (1 atm), EtOAc , RT, 2 h, 84%; g) dimethyl-1-diazo-2-oxopropylphosphonate, K_2CO_3 , MeOH, 2.5 h, 88%; h) $n\text{BuLi}$, Me_3SiCl , THF, -78°C to RT, 20 h; then 0.1 M aq. HCl, THF, reflux, 4 h, 92%; i) $\text{LiN}(\text{SiMe}_3)_2$, THF, -78°C ; then $\text{PhS}(=\text{N}-t\text{Bu})\text{Cl}$, 2 h, 94%; j) TBSOTf , 2,6-lutidine, CH_2Cl_2 , 0°C , 1.5 h; k) CrO_3 (15 equiv), 3,5-dimethylpyrazole (15 equiv), CH_2Cl_2 , -20°C , 20 min, 66% for 2 steps. Ts = toluene-4-sulfonyl, DMF = *N,N*-dimethylformamide, TBS = *tert*-butyldimethylsilyl.

ketone in **9** was relatively inert towards attack by nucleophiles. Consequently, we opted to transform the methyl ketone into the corresponding terminal acetylene via an elimination reaction. To this end, two well-established procedures were attempted in which the ketone is first converted into its enol phosphate or enol triflate, before it is treated, in a second step, with amide base to effect elimination.^[8] However, after some unsuccessful experimentation with the above protocols, a novel one-step procedure was examined that had been reported to allow for the direct conversion of methyl ketones into simple, terminal alkynes. Treatment of methyl ketone **9** with phosphazene base P_2tBu (Schwesinger's base) and nonafluorobutanesulfonyl fluoride (NfF) in dry DMF cleanly afforded terminal alkyne **10** in 92% yield in a single step.^[9] Lewis acid promoted formylation of the corresponding lithium acetylide with DMF followed by the reduction of the intermediate propiolaldehyde with catalytic Pd/C under an atmosphere of hydrogen then furnished aliphatic aldehyde **12**.^[10] Transformation of the aldehyde into the terminal acetylene **13** could subsequently be brought about by means of the Ohira–Bestmann procedure.^[11] Finally, the sequence was completed by a one-pot reaction, which included the protection of the terminal acetylene with trimethylsilyl chloride and subsequent cleavage of the 1,3-dioxolane by using aqueous HCl. The sequence described above reliably allowed for the introduction of the

desired but-3-ynyl side chain and efficiently delivered ketone **14** in 28% overall yield from the starting materials.

With a viable route for the synthesis of ketone **14** in hand, the remaining challenge toward the preparation of the key Conia-ene precursor **3** was the introduction of the proper oxidation pattern in the northern quadrant of the molecule. To address this task, ketone **14** was first transformed into the corresponding enone by means of the Mukaiyama-dehydrogenation procedure, furnishing the targeted compound in 94% yield.^[12] Subsequent treatment with TBSOTf and 2,6-lutidine in dichloromethane then selectively delivered silyloxydiene **16**. Inspired by a single preliminary report involving an 1-acetoxy diene, we found that subjection of dienol silane **16** to an excess of CrO_3 –3,5-dimethylpyrazole complex in dichloromethane directly led to the formation of the enedione **17** in a single step (66% overall yield for steps j and k).^[13]

The chlorination of enedione **17** at the α -position of the 5-membered ring ketone turned out to be surprisingly difficult. Selective formation of the lithium enolate at the sterically less hindered C2-position of the molecule and subsequent treatment with TsCl preferentially gave the corresponding tosyl enol ether in 60% yield, instead of the chlorinated product, which is usually observed under these conditions.^[14] Treatment with TfCl , on the other hand, led to complex mixtures of products. After quite some experimentation with many other chlorinating agents, we eventually found that silyl enol ether **18**, upon exposure to Bu_4NCl_3 (Mioskowski's reagent), was directly transformed into α -chlorinated silyl enol ether **3**, without loss of the silyl group.^[15] This welcome result renders unnecessary steps that would otherwise be required to regenerate the silyl enol ether (Scheme 4).



Scheme 4. Reagents and conditions: a) $\text{KN}(\text{SiMe}_3)_2$ (1.3 equiv), TBSOTf (2.0 equiv), THF, -78°C to RT, 3 h; b) Bu_4NCl_3 (2.4 equiv), CH_2Cl_2 , -78°C to RT, 5 h, 51% for 2 steps; c) $(\text{MeCN})[(2\text{-biphenyl})\text{di-}t\text{-butylphosphine}]\text{gold(I) hexafluoroantimonate}$ (0.5 equiv), acetone, 45°C , 6 h, 65%; d) HCl (gas), SnCl_4 (30 equiv), CH_2Cl_2 , sealed tube, -78°C to RT, 5 h, 67%.

We then turned our attention to the crucial Conia-ene reaction. After a few preliminary experiments with related precursors (e.g. **18**) and some minor optimization, we were pleased to observe that treatment of **3** with acetonitrile[(2-biphenyl)di-*tert*-butylphosphine]gold(I) hexafluoroantimonate (Echavarren's catalyst) in dry acetone at 45°C effected both the desired cyclization as well as the concomitant removal of the silyl protecting group on the alkyne.^[16] It is worth noting that although haloalkynes have been studied in gold-medi-

ated Conia-ene cyclizations by Toste and co-workers, to our knowledge, chlorinated silyl enol ethers have not been examined.^[17,18] Tricyclic product **19** was obtained in good yield, and the stage was set to address the final hydrochlorination reaction. The exocyclic olefin in **19** was found to be unreactive towards addition of hydrogen chloride under mild conditions (e.g. treatment of **19** with AcCl/EtOH), which is most likely due to the proximal electron-withdrawing functional groups.^[19] We thus had to resort to vigorous conditions for the installation of the chloride substituent. In the experiment, saturation of a dichloromethane solution of substrate **19** at -78°C with gaseous hydrogen chloride in the presence of an excess of SnCl_4 followed by slow warm-up to ambient temperature, brought about the desired transformation.^[20]

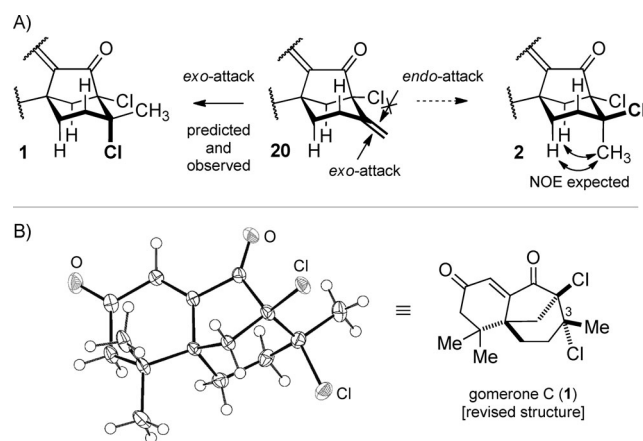
The ^1H and ^{13}C NMR spectra of the product obtained from the hydrochlorination reaction were in very good agreement with those assigned to nominal gomerone C. This, however, was rather puzzling, because it suggested that the double bond in **19** had undergone selective hydrochlorination from the *endo*-face of the bicyclo[3.2.1]octane substructure; which molecular modeling indicated is the more hindered face (Scheme 5). Consistent with our hesitation, no

ical revision of the structure of the natural product and hence also led to reassignment of the related gomerone B (**2**). The synthesis relies on a key, late-stage Conia-ene reaction of a chlorinated enol silane and an alkyne, which efficiently provides access to the novel gomerane skeleton with the attendant bridgehead chloride. The formed bicyclo[3.2.1]octane core is set up for the subsequent introduction of the second tertiary chloride. Additional salient features of the synthesis include a Diels–Alder reaction, which introduces two contiguous quaternary centers with concomitant construction of the fused perhydroindene core. Moreover, in the context of the total synthesis we showcase in a complex setting the use of Schwesinger's base/NfF for the convenient one-step conversion of a ketone into an alkyne as well as the selective oxygenation of a 1-silyloxydiene mediated by CrO_3 -3,5-dimethylpyrazole. Efforts to expand the strategy to the synthesis of the other two members of the family as well as preliminary biological testing of the obtained gomerone C (**1**) are currently ongoing and will be reported in due course.

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Scheme 5. Crystal structure^[22] and structural revision of gomerone C (**1**). Thermal ellipsoids are set at 50% probability.

nuclear Overhauser effect (NOE) was observed between the supposedly axial C15 methyl group and the two protons in the 1,3-diaxial position at C1 and C5, even though a chair conformation was clearly indicated by all the ^1H , ^1H -coupling constants for the 6-membered ring. Definitive evidence was obtained when we were able to grow single crystals suitable for X-ray diffractometry. The diffraction data clearly showed that in gomerone C (**1**) the chloro substituent, and not the methyl group, occupies the axial position (see the Supporting Information). Consequently, the structure of gomerone C (**1**) necessitated revision, which we propose corresponds to nominal gomerone B. It would therefore appear that in the original isolation and characterization work the structures of gomerone B and C had been interchanged.^[21]

In conclusion, we have documented the first total synthesis of gomerone C (**1**), which resulted in the stereochem-

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