Total Synthesis

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Total Synthesis of Gracilioether F: Development and Application of Lewis Acid Promoted Ketene–Alkene [2+2] Cycloadditions and Late-Stage C–H Oxidation[**]

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Abstract: *The first synthesis of gracilioether F, a polyketide natural product with an unusual tricyclic core and five contiguous stereocenters, is described. Key steps of the synthesis include a Lewis acid promoted ketene–alkene [2+2] cycloaddition and a late-stage carboxylic acid directed C(sp^3)–H oxidation. The synthesis requires only eight steps from norbornadiene.*

The gracilioethers (e.g., **1**–**4**, Figure 1) are a class of recently isolated polyketides from several families of marine sponge.[1] Common to this class of molecules is the presence of an unusual tricyclic core and at least five contiguous stereogenic centers (two of which are quaternary). Several members of the family also exhibit considerable biological activity.[1c,d] Our interest in these molecules stems primarily from the perspective that the structural uniqueness of the tricyclic core and the dense array of stereogenic centers would provide a unique challenge to state-of-the-art chemical synthesis. No studies towards the synthesis of any member of the tricyclic gracilioether family have been reported to date.[2]

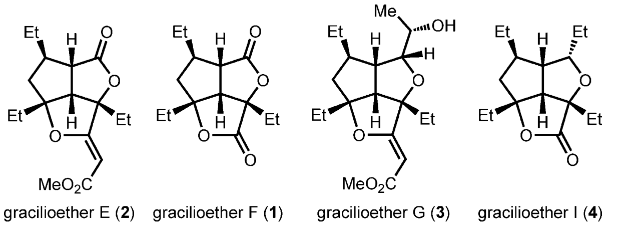
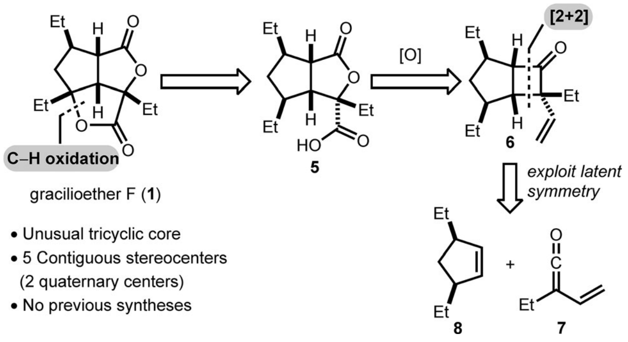


Figure 1. Several members of the gracilioether family.

Herein, we disclose an eight-step synthesis of gracilioether F (**1**) from norbornadiene. In the context of these studies, two key features of our synthesis have emerged. The first is the development of a new method for Lewis acid promoted [2+2] cycloadditions between alkenes and monosubstituted ketenes, and the second is the strategic use of a late-stage carboxylic acid directed C(sp^3)–H oxidation. Finally, the synthesis of gracilioether F (**1**) was pursued because we envisioned that it could be a potential intermediate to access other, more functionalized members of the natural product family (e.g., **2**–**4**).

Our retrosynthetic analysis for gracilioether F (**1**) is illustrated in Scheme 1. Two points were central to our design: 1) Cyclobutanone **6** as a key intermediate. Our laboratory has taken an interest in the development of Lewis acid promoted ketene–alkene [2+2] cycloadditions.[3] These promoters permit efficient reactions between components that do not undergo traditional thermally induced cycloadditions.[3,4] We envisioned that preparation of cyclobutanone **6** from alkenyl ethyl ketene **7** and alkene **8** would be an ideal testing ground for our newly developed method. 2) Strategic disconnection of the C–O bond by C–H oxidation. Implementation of this non-traditional strategy has allowed for great simplification of the target structure by ultimately exploiting latent symmetry.[5] It should be noted that strategic late-stage C–H oxidations have rarely been employed in total synthesis settings.[6,7]



Scheme 1. Retrosynthetic analysis of gracilioether F.

As mentioned above, our laboratory has recently developed the first method for Lewis acid promoted ketene–alkene [2+2] cycloadditions.[3] The method offers several advantages over more traditional thermally induced variants, such as increased reactivity and selectivity, which has consequently allowed for the synthesis of highly congested cyclobutanones. The [2+2] cycloaddition needed for the synthesis of gracilioether F requires the use of an alkenyl ketene. This

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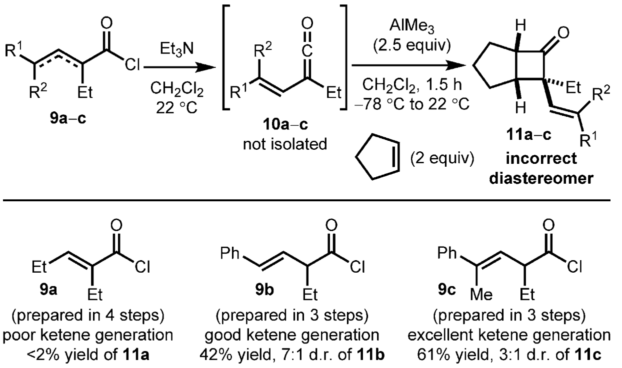
substrate, however, was not investigated in our original study,[3] and therefore, studies were initiated on model systems to probe for reactivity.

One of the key challenges with reactions of alkenyl ketenes is that they tend to be more reactive than their alkyl or aryl counterparts.[8] As such, alkenyl ketenes are always generated in situ in the presence of the reacting partner (e.g., alkene or imine).[8] Furthermore, owing to the propensity of alkenyl ketenes to undergo dimerization through a [4+2] cycloaddition, [2+2] cycloadditions with alkenes under thermally induced conditions are rare and typically require forcing conditions and a large excess of the alkene.[8]

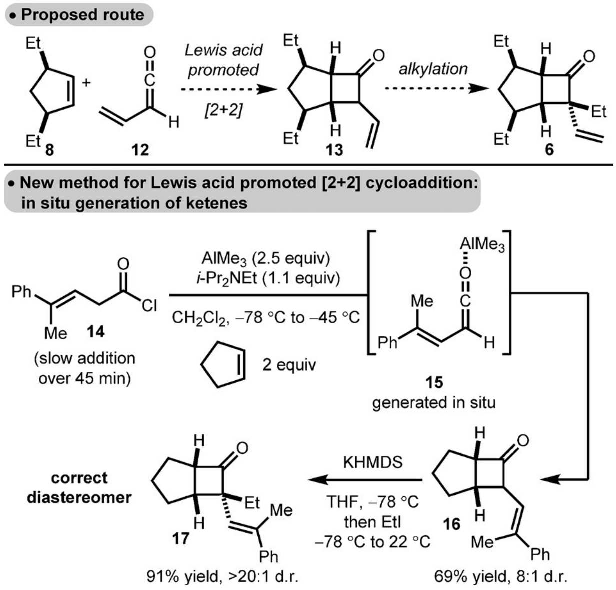
For Lewis acid promoted ketene–alkene [2+2] cycloadditions, the original method required that the ketene be generated prior to use (isolation of the ketene not required).[3] Therefore, we initiated our studies by searching for a suitable set of conditions and a ketene precursor (i.e., unsaturated acid chloride) that would allow for clean generation of an alkenyl ketene.

As illustrated in Scheme 2, attempts to generate an alkenyl ketene from α,β-unsaturated acid chloride **9a** and Et_3N did not lead to formation of the desired alkenyl ketene owing to a slow dehydrohalogenation process. The slow rate of ketene generation from acid chloride **9a** is likely due to the poorly acidic γ-protons. To increase the acidity of the γ-protons and hence the rate of ketene generation a phenyl group was installed at the γ-position. It should be noted that additional substitution at the γ-position is inconsequential to the total synthesis, as the alkene will ultimately be cleaved under oxidative conditions (see below). For ease of synthesis, the β,γ-unsaturated acid chlorides **9b–c** were prepared (as opposed to the analogous α,β-unsaturated acid chlorides).[9] Treatment of acid chloride **9b** with Et_3N led to rapid formation of the ketene at 22 °C. Lewis acid promoted ketene–alkene cycloaddition with $AlMe_3$ and a model alkene, namely cyclopentene (2.0 equiv), was then carried out and led to the formation of cyclobutanone **11b** in 42 % yield and 7:1 d.r. Further studies revealed that acid chloride **9c**, which incorporates an additional methyl substituent, led to very clean generation of the alkenyl ketene and consequently to a higher yield of cycloadduct **11c** (61 %). The increase in yield is likely due to the increase in steric bulk imposed by the methyl group, which presumably reduces the rates of ketene dimerization/polymerization. Upon confirmation of the stereochemical identities of cyclobutanones **11b** and **11c**, however, it was discovered that a diastereomer of the one necessary for the synthesis of gracilioether F (**1**) had been generated. This diastereomer is likely formed by approach of the alkene *syn* to the alkenyl group, which is consistent with related cycloadditions involving aryl substituents.[3]



Scheme 2. Original strategy for the [2+2] cycloaddition.

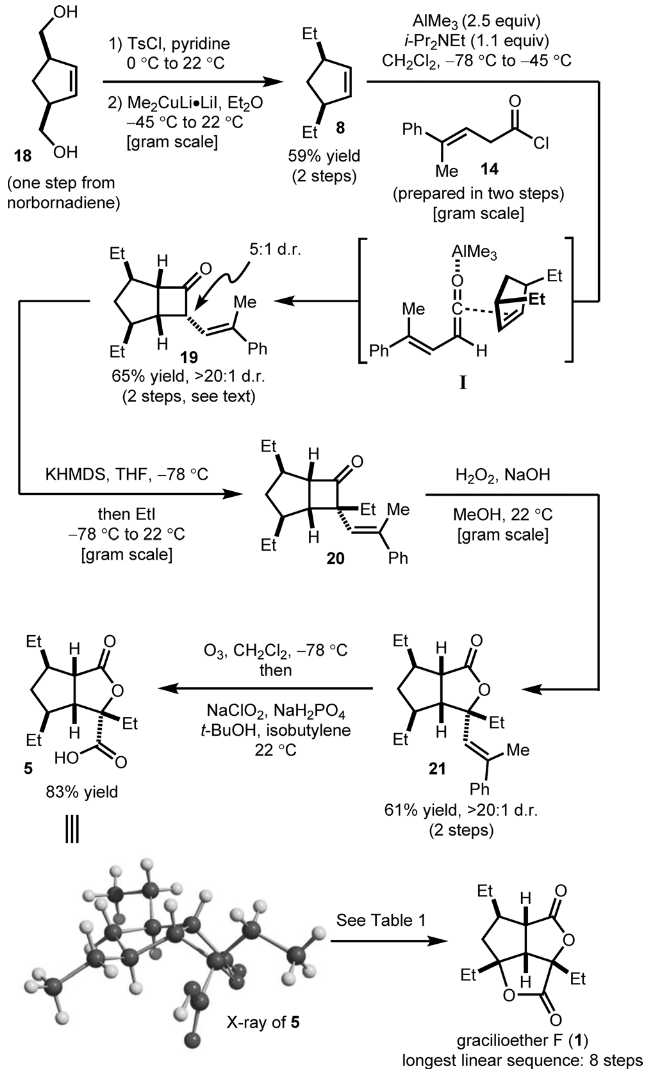
A revised route to key cyclobutanone intermediate **6** was then devised (Scheme 3). It was reasoned that if cyclobutanone **13** could be prepared from a [2+2] cycloaddition employing a monosubstituted alkenyl ketene (e.g., **12**), subsequent diastereoselective α-alkylation with EtI would lead to formation of the desired diastereomer. Pre-generation of the requisite monosubstituted alkenyl ketene (like most monosubstituted ketenes), however, was not possible.[10] Thus, it was necessary to establish a new method for Lewis acid promoted ketene–alkene [2+2] cycloadditions with monosubstituted ketenes.



Scheme 3. Revised strategy for the Lewis acid promoted [2+2] cycloaddition. KHMDS = potassium hexamethyldisilazide.

After considerable experimentation we found that through slow addition of acid chloride **14** to a solution of $AlMe_3$, $i$$Pr_2NEt$, and cyclopentene, cyclobutanone **16** could be generated in 69 % yield (8:1 d.r., inconsequential to the total synthesis; Scheme 3). These conditions function well because the ketene, when generated in the presence of the Lewis acid,[11] is consumed through cycloaddition at a rate that is similar to its formation; therefore, side reactions resulting from polymerization of the ketene are minimized. Similar to previous studies outlined in Scheme 2, the presence of γ-Ph,Me-substituted acid chloride **14** was necessary for rapid generation of the corresponding ketene at low temperatures. To complete the model studies, cyclobutanone **16** was deprotonated with KHMDS and the resulting enolate trapped with EtI to provide cyclobutanone **17** in 91% yield and > 20:1 d.r. (Scheme 3).

With a method for the synthesis of the desired diastereomer of the key cyclobutanone in a model system, our attention then focused on the total synthesis of gracilioether F (**1**; Scheme 4). The synthesis of the requisite diethylcyclopentene **8** was accomplished in two steps from known diol **18**[12] by tosylation and subsequent displacement with $Me_2CuLi{\cdot}LiI$. Lewis acid promoted cycloaddition between cyclopentene **8** (2 equiv) and acid chloride **14** led to cyclobutanone **19** in 65% yield and > 20:1 d.r. (5:1 d.r. at the α-carbon atom, inconsequential to the synthesis) over two steps from the carboxylic acid precursor to **14**. The diastereoselectivity is easily rationalized by inspection of the pre-transition state assembly **I**.



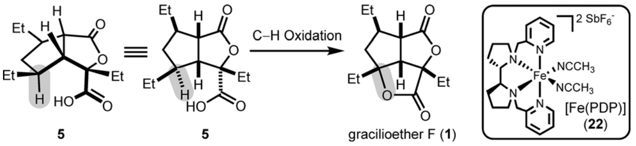
Scheme 4. Synthesis of gracilioether F. Ts = *para*-toluenesulfonyl.

Cycloadduct **19** was converted into carboxylic acid **5** through a straightforward sequence, starting with α-alkylation of cyclobutanone **19** with KHMDS and EtI to provide **20** in > 20:1 d.r. (Scheme 4). The high selectivity of the alkylation reaction is likely the result of the EtI approaching on the convex face of the enolate. Regioselective Baeyer–Villiger oxidation provided lactone **21** in 61% yield over two steps. One-pot ozonolysis and quenching under Pinnick oxidation conditions led to the formation of carboxylic acid **5** in 83% yield. The entire sequence to carboxylic acid **5** required only seven steps from norbornadiene and, with the exception of the conversion of **21** into **5**, was carried out on gram scale.

To complete the synthesis of gracilioether F, a selective C–H oxidation was necessary. Analysis of the desired C–H oxidation reveals two key points: 1) Based on electronic considerations, oxidation is likely to occur at the desired C–H bond because it is the tertiary $C(sp^3)$–H bond that is most distant from the electron-withdrawing groups.[6] 2) The desired C–H bond is located on the concave face of the bicyclic scaffold. Thus its accessibility to external oxidants is likely to be hindered.[6]

Considering primarily the former point, we investigated common methods that typically oxidize the most electron-rich $C(sp^3)$–H bond, barring consideration of any steric effects.[6] However, treatment of carboxylic acid **5** with RuO_4 (generated form $RuCl_3$ and $KBrO_3$)[13] or TFDO[14] led to either mostly consumption or complete recovery of the carboxylic acid **5**, respectively, with < 2% product formation (Table 1, entries 1 and 2). The lack of selectivity observed in the reaction with RuO_4 is likely due to the vastly different steric environments of the C–H bond that should be oxidized and the C–H bonds whose oxidation is undesired. Thus efforts were directed towards utilizing the neighboring carboxylic acid substituent to perhaps direct C–H oxidation to occur at the desired site.[15,16] To the best of our knowledge, only one report details the carboxylic acid directed C–H oxidation of tertiary $C(sp^3)$–H bonds. The White group has demonstrated

Table 1: Late-stage $C(sp^3)$–H oxidation.



Entry	Conditions[a]	Yield[b] [%]	RSM[b] [%]
1	$RuCl_3$ (10 mol%), $KBrO_3$, pyridine, $MeCN/H_2O$	< 2	–[c]
2	TFDO, CH_2Cl_2, −45 °C to 22 °C	< 2	> 90
3	[Fe(PDP)] (20 mol%), H_2O_2, MeCN, 22 °C	9	48
4	$Fe(OAc)_2$ (1 equiv), H_2O_2, MeCN, 22 °C	< 2	ca. 80
5	$Mn(OAc)_2$ (1 equiv), H_2O_2, MeCN, 22 °C	< 2	ca. 80
6	$Cu(OAc)_2$ (1 equiv), H_2O_2, MeCN, 22 °C	15 (15)	51
7	$Cu(OAc)_2$ (1 equiv), H_2O_2, MeCN, 0 °C	10	88
8[d]	$Cu(OAc)_2$ (1 equiv), H_2O_2, MeCN, 22 °C	< 2	> 90

[a] See the Supporting Information for experimental details. [b] Determined by NMR analysis using 1,3,5-trimethoxybenzene as the internal standard. Yield of isolated product given in parentheses. [c] Conversion of starting material > 80%. [d] The methyl ester of **5** was used as the starting material. RSM = recovered starting material, TFDO = trifluoromethyldioxarane.

that [Fe(PDP)] (**22**) is effective for carboxylic acid directed C−H oxidation.[17] When carboxylic acid **5** was treated with [Fe(PDP)] ((*S,S*) or racemate) under the reported conditions, 9 % of gracilioether F (**1**) was generated with 48 % recovered starting material (entry 3). The loss in mass balance may be due to undesired decarboxylation. The formation of undesired oxidation products was limited to < 5 %.

In the context of our efforts to identify alternative conditions that might improve the yield of the C−H oxidation, we reasoned that perhaps if metals without ancillary ligands were used, the desired C-H-oxidation might be favored owing to fewer adverse steric interactions. Therefore, we evaluated several first-row transition metals (e.g., Fe^{II}, Mn^{II}, Cu^{II}) for their ability to promote C−H oxidation (entries 4–6).[18,19] Among these metal salts, the use of $Cu(OAc)_2$ in combination with H_2O_2 led to the formation of the desired product in 15 % yield with 51 % recovered starting material (entry 6, 84 mg scale). The iron- and copper-promoted hydroxylations are significant for several reasons: 1) Their strategic implementation has enabled the synthesis of gracilioether F through unconventional means in only eight steps. 2) A large amount of starting material can be recovered thus counterbalancing the low yield of isolated product (this is a common scenario for many C−H oxidation reactions).[6] Furthermore, when the copper-promoted oxidation was carried out at 0 °C, 10 % of gracilioether F was formed with 88 % recovered starting material (entry 7). 3) To the best of our knowledge, the use of copper salts and H_2O_2 to promote selective $C(sp^3)$−H oxidation reactions is unknown.[18–20]

The mechanism of the copper-promoted C−H oxidation is not clear at this time, but is likely related to Fenton-type reactions.[18,19] Several additional key points are noteworthy: 1) The carboxylic acid moiety is necessary for C−H oxidation. When the corresponding methyl ester of **5** was used, < 2 % of **1** was observed with > 90 % recovery of starting material (entry 8). 2) The use of catalytic quantities of copper led to inferior yields. 3) The portion-wise addition of $Cu(OAc)_2$ and H_2O_2 was necessary to obtain optimal yields. 4) The formation of undesired oxidation products was observed only in minimal quantities (< 5 %). Similar to the iron-catalyzed reactions, the loss in mass balance may be due to decarboxylation and subsequent decomposition.[21]

In summary, we have prepared gracilioether F (**1**) with a longest linear sequence of eight steps from norbornadiene without the use of protecting groups. The synthesis was enabled through the development of a new variant of a Lewis acid promoted ketene–alkene [2+2] cycloaddition and the development of a carboxylic acid directed $C(sp^3)$−H oxidation. This synthesis also highlights the state of the art in $C(sp^3)$−H oxidation as a powerful transformation and underscores the need for the development of new methods.

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