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Synthesis of an A–E Gambieric Acid Subunit with Use of a *C*-Glycoside Centered Strategy

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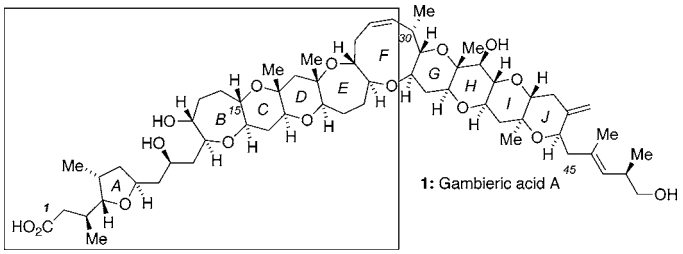
ABSTRACT



This paper describes our synthesis of the A–E subunit of gambieric acid (GA) in addition to the synthesis of the A-ring and the C–E tricycle. The use of an enol ether-olefin RCM strategy to couple the A and C–E subunits and, in the process, generate the B-ring is noteworthy.

The gambieric acids A−D (GA's) are members of the marine ladder toxin family of natural products whose isolation from the marine dinoflagellate *Gambierdiscus toxicus* was first reported in 1992 by Yasumoto and co-workers.[1] As part of their initial studies, the Yasumoto group determined the relative structure of the GA's; they subsequently elucidated their absolute structure.[2] The polycyclic ether architecture of the GA's consists of one 9-membered ring, two 7-membered rings, six 6-membered rings, and one 5-membered ring along with 27 stereocenters. The members of this family differ from one another at the J-ring side chain (free alcohol vs ester) and the B-ring alcohol (2° vs 3°).

Equally interesting to their structures is the biological profile of the GA's. Most of the preliminary data that have been published have come from work with GA-A. Although GA-A lacks toxicity in mice,[3] it has been shown to be capable of inhibiting the binding of brevetoxin B (PbTx-3) to site 5 of voltage gated sodium channels.[4,5] Interestingly, GA-A is a potent antifungal agent, has been shown to promote the growth of *Gambierdiscus toxicus*, and is the only member of this family that is excreted into the aqueous medium.[6,7] As with the other members of the marine ladder toxin family, a thorough understanding of the biological activity of the GA's awaits their chemical synthesis as they are not generated in any significant quantity by the producing organism.[8]

Not surprisingly, the polycyclic ether architecture and intriguing biological activity of the GA's has attracted the attention of chemists interested in their synthesis, including us.[9] Central to our approach to these and other structurally related targets have been three reactions: the generation of carbon (*C*)-glycosides from the single flask coupling of glycal

(1) (a) Nagai, H.; Torigoe, K.; Satake, M.; Murata, M.; Yasumoto, T.; Hirota, H. *J. Am. Chem. Soc.* **1992**, *114*, 1102. (b) Nagai, H.; Murata, M.; Torigoe, K.; Satake, M.; Yasumoto, T. *J. Org. Chem.* **1992**, *57*, 5448.

(2) Morohashi, A.; Satake, M.; Nagai, H.; Oshima, Y.; Yasumoto, T. *Tetrahedron* **2000**, *56*, 8995.

(3) Because of a limited supply, the highest concentration that the GA's were tested at was 1 mg/kg. In comparison, the LD_{50} for ciguatoxin (CTX) in mice is 0.35 μg/kg. See refs 4 and 6.

(4) Inoue, M.; Hirama, M.; Satake, M.; Sugiyama, K.; Yasumoto, T. *Toxicon* **2003**, *41*, 469.

(5) Brevenal and gambierol are two other members of this family that inhibit PbTx-3 binding. See: LePage, K. T.; Rainier, J. D.; Johnson, H. W. B.; Baden, D. G.; Murray, T. F. Submitted for publication.

(6) Sakamoto, B.; Nagai, H.; Hokama, Y. *Phycologia* **1996**, *35*, 350.

(7) Nagai, H.; Makami, Y.; Yazawa, K.; Gonoi, T.; Yasumoto, T. *J. Antibiot.* **1993**, *46*, 520.

(8) A 5000 L fermentation broth yielded 14.9 mg of GA's A−D.

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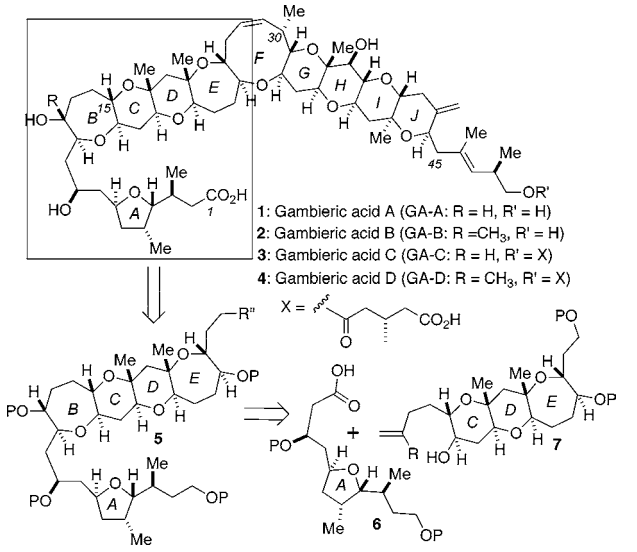
Scheme 1

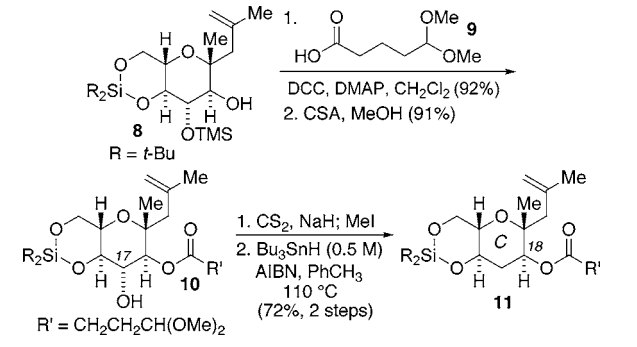


anhydrides with nucleophiles, the synthesis of cyclic enol ethers with ring-closing metathesis (RCM), and the synthesis of cyclic enol ethers with acid-catalyzed cyclizations.[10]

With these reactions in mind, the GA's would arise from the sequential coupling of appropriately substituted A-ring (i.e., **6**) and C−E (i.e., **7**) subunits followed by the pairing of the resulting pentacycle with an appropriately substituted tricyclic H−J precursor. As envisioned, key to both building and combining each of these subunits would be enol ether-olefin RCM chemistry. Described in this paper are our preliminary results in this area and the assembly of the A and C−E rings along with their coupling to generate a GA A−E pentacycle.

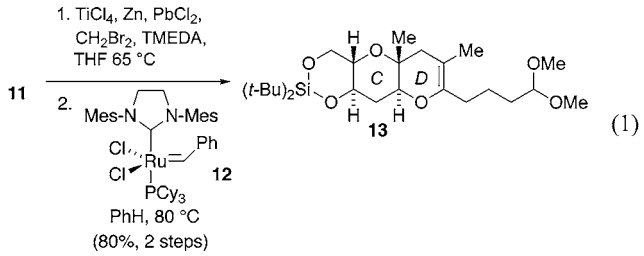
After having explored several *C*-glycoside centered approaches to the C−E tricycle we settled upon the sequence of reactions outlined in Schemes 2 and 3 and eqs 1−3.

Scheme 2



Central to our synthesis of this subunit was a 3-step sequence to the D- and E-rings from the fully functionalized C-ring **11**.[11] Starting from L-glucal derived *C*-ketoside[8,12,13] **8**, esterification with 5,5-dimethoxypentanoic acid (**9**) and TMS ether hydrolysis gave **10**.[14] Deoxygenation of the C(17) alcohol via the intermediacy of the methyl xanthate gave olefinic ester cyclization precursor **11**.[15]

Acyclic enol ether formation with the Takai Utimoto conditions and enol ether-olefin RCM delivered **13** in 80% overall yield.[16] As we had observed during our gambierol efforts,[10] this reaction required the use of the Grubbs second generation Ru alkylidene **12** as a consequence of the ability of **12** to withstand the elevated temperatures required for tetrasubstituted enol ether formation.[17,18]



(1)

From **13**, the conversion to tricycle **15** was accomplished in two flasks. Oxidation of the D-ring enol ether with DMDO and reduction of the intermediate anhydride with DIBAL-H gave alcohol **14** in 95% yield as the only detectable isomer. Subjecting **14** to PPTS, pyridine, and heat effected cyclization to the corresponding mixed acetal and elimination to give the GA E-ring oxepene as **15**.[19] To incorporate the requisite atoms needed for a subsequent pairing with a precursor to the H−J tricycle, we subjected **15** to DMDO and propenyl magnesium chloride to give **16** as a 2:1 mixture of diastereomers. The mixture of diastereomers resulted from a lack of selectivity in the oxidation reaction as determined by ^{1}H NMR.[20] Interestingly, the anhydride from the DMDO oxidation of **15** was unusually robust; its coupling with propenyl

(9) (a) Evans, P. A.; Roseman, J. D.; Garber, L. T. *J. Org. Chem.* **1996**, *61*, 4880. (b) Kadota, I.; Oguro, N.; Yamamoto, Y. *Tetrahedron Lett.* **2001**, *42*, 3645. (c) Kadota, I.; Takamura, H.; Yamamoto, Y. *Tetrahedron Lett.* **2001**, *42*, 3649. (d) Clark, J. S.; Fessard, T. C.; Wilson, C. *Org. Lett.* **2004**, *6*, 1773. (e) Sato, K.; Sasaki, M. *Org. Lett.* **2005**, *7*, 2441. (f) Clark, J. S.; Kimber, M. C.; Robertson, J.; McErlean, C. S. P.; Wilson, C. *Angew. Chem., Int. Ed.* **2005**, *44*, 6157. (g) Sato, K.; Sasaki, M. *Angew. Chem., Int. Ed.* **2007**, *46*, 2518.

(10) For an example of the use of this approach in the generation of ladder toxins see: (a) Majumder, U.; Cox, J. M.; Johnson, H. W. B.; Rainier, J. D. *Chem. Eur. J.* **2006**, *12*, 1736. (b) Johnson, H. W. B.; Majumder, U.; Rainier, J. D. *Chem. Eur. J.* **2006**, *12*, 1747.

(11) We employed a similar sequence in our formal total synthesis of hemibrevetoxin B. See: (a) Rainier, J. D.; Allwein, S. P.; Cox, J. M. *Org. Lett.* **2000**, *2*, 231. (b) Rainier, J. D.; Allwein, S. P.; Cox, J. M. *J. Org. Chem.* **2001**, *66*, 1380.

(12) Available in 11 steps from L-glucose. See the Supporting Information and: (a) Boulineau, F. P.; Wei, A. *J. Org. Chem.* **2004**, *69*, 3391. (b) Boulineau, F. P.; Wei, A. *Org. Lett.* **2004**, *6*, 119.

(13) Roberts, S. W.; Rainier, J. D. *Org. Lett.* **2005**, *7*, 1141.

(14) Majumder, U.; Cox, J. M.; Rainier, J. D. *Org. Lett.* **2003**, *5*, 913.

(15) Paquette, L. A.; Oplinger, J. A. *J. Org. Chem.* **1988**, *53*, 2953.

(16) Takai, K.; Kakiuchi, T.; Kataoka, Y.; Utimoto, K. *J. Org. Chem.* **1994**, *59*, 2668.

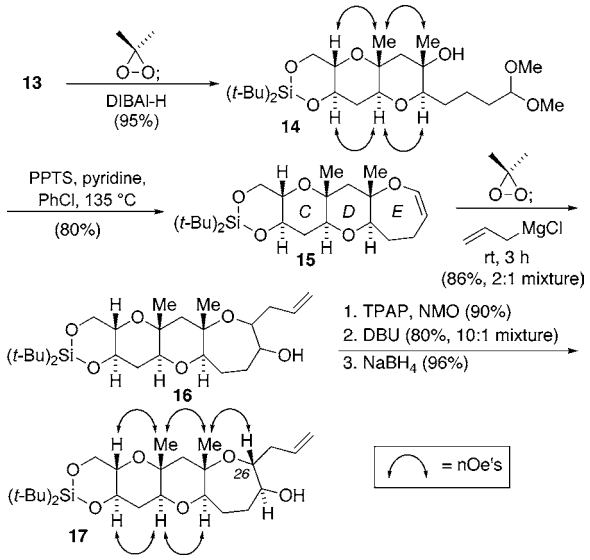
(17) Scholl, M.; Ding, S.; Lee, C. W.; Grubbs, R. H. *Org. Lett.* **1999**, *1*, 953.

(18) Sanford, M. S.; Love, J. A.; Grubbs, R. H. *J. Am. Chem. Soc.* **2001**, *123*, 6543.

(19) (a) Allwein, S. P.; Cox, J. M.; Howard, B. E.; Johnson, H. W. B.; Rainier, J. D. *Tetrahedron* **2002**, *58*, 1997. (b) Rainier, J. D.; Allwein, S. P. *Tetrahedron Lett.* **1998**, *39*, 9601.

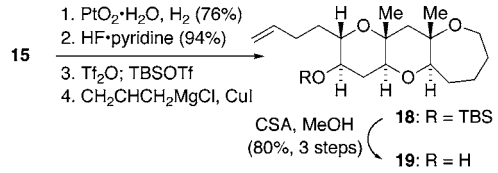
(20) For a theoretical discussion of the effect of substitution on anhydride formation see: Orendt, A. M.; Roberts, S. W.; Rainier, J. D. *J. Org. Chem.* **2006**, *71*, 5565.

Scheme 3



magnesium chloride required 3 h at room temperature.[21] Although the lack of selectivity in the formation of **16** was obviously an undesired outcome, it turned out to be of little consequence as the mixture could be converted to the desired stereoisomer (i.e., **17**) through the illustrated three-step equilibration sequence.

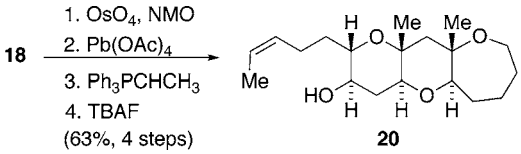
In addition to examining the incorporation of the appropriate E-ring functionality, we also utilized **15** to model the coupling of a C−E tricycle (i.e., **19** and **20**) with the A-ring precursor (i.e., **26**). The conversion of **15** into **18** and **19** is illustrated in eq 2 and involved the reduction of the oxepene,



(2)

removal of the silylene, generation of the 1° triflate and 2° TBS ether, and displacement of the triflate with allyl cuprate. Hydrolysis of the TBS ether gave terminal olefin coupling precursor **19**.

Internal olefin coupling precursor **20** was generated from **18** with use of standard conditions (eq 3).

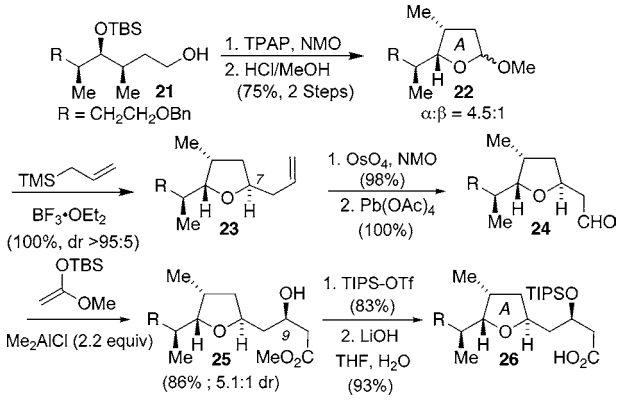


(3)

Having successfully uncovered an approach to the GA C−E ring precursors, we next pursued the GA A-ring

(21) We observed a similar result in our hemibrevetoxin B work. See ref 11.

Scheme 4



(Scheme 4). Our efforts to this subunit began with **21** (available in six steps from the alkylation of Myer's pseudoephedrine auxiliary).[9b,22] Oxidation of **21** and treatment of the resulting aldehyde with HCl and MeOH resulted in hydrolysis of the TBS ether and cyclization to give tetrahydrofuran **22** in 75% yield. The addition of allylsilane to **22** in the presence of BF_3•Et_2O resulted in the formation of **23** in quantitative yield as a single diastereomer as evidenced by ^{1}H NMR of the crude reaction mixture.[23,24] Conversion of **23** into the corresponding C(9) aldehyde **24** and the coupling of **24** with the TBS ketene acetal of methyl acetate gave the chelated 1,3-induction product **25** as the major diastereomer.[25] The completion of the A-ring coupling precursor **26** was accomplished by protection of the 2° alcohol as the corresponding TIPS ether and hydrolysis of the ester.

With precursors **19**, **20**, and **26** in hand, we were prepared to examine their combination and, in the process, the generation of the GA B-ring. As mentioned above, central to our approach to solving problems like this has been the use of an enol ether-olefin RCM coupling sequence.[26] The union of **19** and **26** by using the Yamaguchi protol gave ester **27** in an unoptimized 69% yield (Scheme 5).[27] Although ester **27** underwent quantitative conversion to acyclic enol ether **28** the subsequent RCM reaction gave a multitude of products regardless of the conditions and catalyst used. Our best results involved the use of the Schrock Mo catalyst **29**[28] and gave <50% yield of a mixture that contained a significant quantity of cyclic enol ether **30** but that also contained other unknown substances that we have tentatively assigned as oligomers of **28**.

(22) (a) Myers, A. G.; Yang, B. H.; Chen, H.; McKinstry, L.; Kopecky, D. J.; Gleason, J. L. *J. Am. Chem. Soc.* **1997**, *119*, 6496. (b) White, J. D.; Xu, Q.; Lee, C.-S.; Valeriote, F. A. *Org. Biomol. Chem.* **2004**, *2*, 2092.

(23) We also examined the coupling of **24** with enol silanes without any success.

(24) Larsen, C. H.; Ridgway, B. H.; Shaw, J. T.; Smith, D. M.; Woerpel, K. A. *J. Am. Chem. Soc.* **2005**, *127*, 10879.

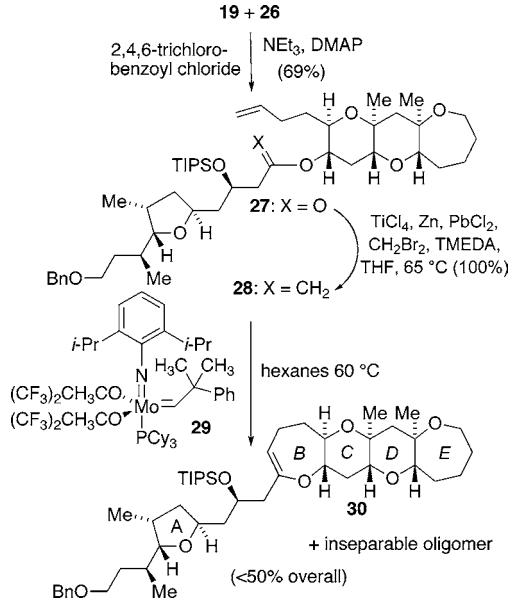
(25) (a) Evans, D. A.; Allison, B. D.; Yang, M. G.; Masse, C. E. *J. Am. Chem. Soc.* **2001**, *123*, 10840. (b) Evans, D. A.; Allison, B. D.; Yang, M. G. *Tetrahedron Lett.* **1999**, *40*, 4457.

(26) See ref 10 and: Johnson, H. W. B.; Majumder, U.; Rainier, J. D. *J. Am. Chem. Soc.* **2005**, *127*, 848.

(27) Inanaga, J.; Hirata, K.; Saeki, H.; Katsuki, T.; Yamaguchi, M. *Bull. Chem. Soc. Jpn.* **1979**, *52*, 1989.

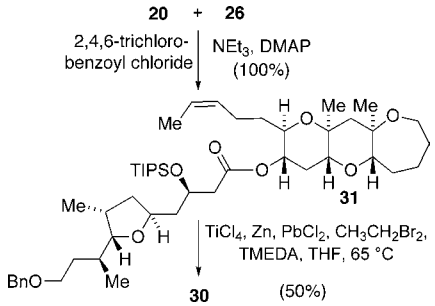
(28) Schrock, R. R.; Murdzek, J. S.; Bazan, G. C.; Robbins, J.; DiMare, M.; O'Regan, M. B. *J. Am. Chem. Soc.* **1990**, *112*, 3875.

Scheme 5



In our total synthesis of gambierol we had overcome problems associated with oligomer formation by utilizing an internal rather than a terminal olefin as a cyclization precursor and decided to adopt this tactic in our GA B-ring efforts. To this goal, we coupled **20** with **26** to give **31** in quantitative yield (Scheme 6). In the acyclic enol ether forming reaction

Scheme 6



we decided to employ a titanium ethylidene rather than a methylidene to avoid complications resulting from olefin cross-metathesis. Much to our surprise and delight, when dibromoethane rather than dibromomethane was used to generate the Takai−Utimoto reagent we did not observe any acyclic enol ether but instead only cyclized product **30**.[29,30] Presumably, **30** comes from an olefin metathesis, carbonyl olefination mechanism implying that the more sterically hindered titanium ethylidene reagent preferentially undergoes reaction with the olefin in **31**.[31] That the product distribution from olefinic ester cyclizations can be effected by simple changes in the alkylidene reagent is a potentially powerful discovery. We are currently examining this phenomenon with other substrates.

In summary, we have synthesized the A−E subunit of the marine ladder toxin gambieric acid A utilizing a *C*-glycoside and enol ether olefin RCM centered strategy. In addition to the generation of the C−E subunit from L-glucal, of note in these studies is the efficient generation of the A-ring, the convergent coupling of the A- and C−E subunits, and the generation of the B-ring using an in situ prepared titanium ethylidene reagent. Future efforts include the generation of the H−J ring system, the completion of the synthesis of GA, and the examination of GA's fascinating biological profile.

Acknowledgment. We are grateful to the National Institutes of Health, General Medical Sciences (GM56677) for support of this work. We would like to thank the support staff at the University of Utah and especially Dr. Charles Mayne (NMR), and Mr. Elliot M. Rachlin and Dr. Jim Muller (mass spectrometry) for help in obtaining data.

Supporting Information Available: Experimental procedures and spectroscopic data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(29) As **30** decomposed upon standing at −40 °C for 12 h in neutralized chloroform, we believe that the moderate yield for this transformation is a result of the relative instability of **30**. We plan to address this problem when we turn to the real GA precursor.

(30) Related reactions have been reported. See refs 10, 26, 31 and: (a) Stille, J. R.; Grubbs, R. H. *J. Am. Chem. Soc.* **1986**, *108*, 855. (b) Stille, J. R.; Santarsiero, B. D.; Grubbs, R. H. *J. Org. Chem.* **1990**, *55*, 843. (c) Nicolaou, K. C.; Postema, M. H. D.; Claiborne, C. F. *J. Am. Chem. Soc.* **1996**, *118*, 1565. (d) Nicolaou, K. C.; Postema, M. H. D.; Yue, E. W.; Nadin, A. *J. Am. Chem. Soc.* **1996**, *118*, 10335.

(31) (a) Allwein, S. P.; Cox, J. M.; Howard, B. E.; Johnson, H. W. B.; Rainier, J. D. *Tetrahedron* **2002**, *58*, 1997. (b) Majumder, U.; Rainier, J. D. *Tetrahedron Lett.* **2005**, *46*, 7209.