Organic LETTERS

Letter

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Synthesis of the A–D Ring System of the Gambieric Acids

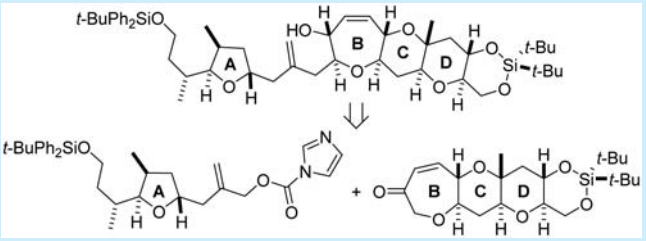
J. Stephen Clark,*[,†] Filippo Romiti,[†] Bora Sieng,[†] Laura C. Paterson,[†] Alister Stewart,[‡] Subhabrata Chaudhury,[†] and Lynne H. Thomas[†]

[†]WestCHEM, School of Chemistry, Joseph Black Building, University of Glasgow, University Avenue, Glasgow G12 8QQ, United Kingdom

[‡]School of Chemistry, University of Nottingham, University Park, Nottingham NG7 2RD, United Kingdom

Supporting Information

ABSTRACT: The A–D fragment of gambieric acids A and C has been synthesized using an asymmetric Tsuji–Trost allylation reaction to couple the two key segments. The A ring fragment has been prepared by a short and highly efficient route involving diastereoselective Lewis acid mediated alkylation of an acetal. Iterative ring-closing metathesis reactions have been used to construct cyclic ethers and assemble the tricyclic B–D fragment.



The gambieric acids (Figure 1) are polycyclic ethers that were first isolated by Yasumoto and co-workers from a culture of the marine dinoflagellate *Gambierdiscus toxicus* (GII1 strain), the organism responsible for ciguatera poisoning in humans.[1] The gambieric acids possess potent activity against a variety of filamentous fungi[1c] and display 2000-fold greater antifungal activity than amphotericin B in some assays.[2] Interestingly, although gambieric acid A inhibits binding of the brevetoxin B derivative PbTx-3 to site 5 of voltage-gated sodium channels in excitable membranes, the gambieric acids lack the potent neurotoxicity that is associated with many other large fused polyether natural products of marine origin.[2] The significant antifungal activity of the gambieric acids combined with their moderate toxicity toward mammalian cells makes them potential lead compounds for the discovery of novel antifungal agents.[1]

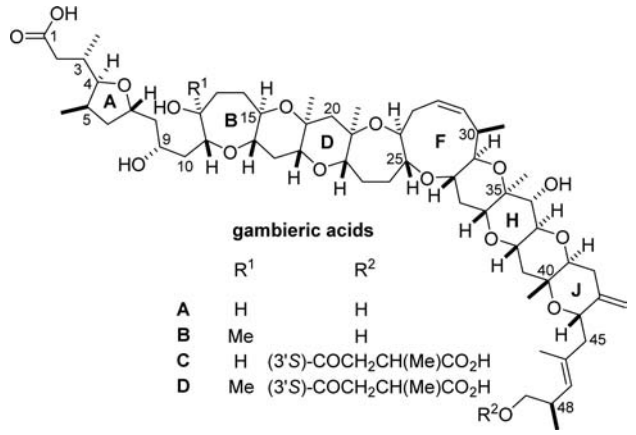


Figure 1. Confirmed structures of gambieric acids A–D.

Yasumoto and co-workers established the relative stereochemical relationships in the B–J polyether array of the gambieric acids using two-dimensional NMR methods.[1] The absolute configurations at positions C-3, C-4, and C-48 and in the side chain ester R^2 (C3′) were determined using Mosher's method, with or without prior degradation and fragment functionalization with a chiral anisotropic reagent.[1d] However, assignment of the relative stereochemical relationship between stereogenic centers in the A ring and those in the B–J polyether array remained tentative until completion of the first total synthesis of gambieric acid A by Sasaki and co-workers in 2012,[3] which permitted unambiguous stereochemical assignments to be made (Figure 1).[1]

The gambieric acids possess an array of nine *trans*-fused cyclic ethers with 6-, 7-, and 9-membered rings forming the typical laddered structure found in this class of marine natural product. These natural products also possess an isolated trisubstituted tetrahydrofuran (the A ring) and a side chain on the J ring (attached to C-44).

The immense synthetic challenges presented by the gambieric acids coupled with their potent bioactivity make them highly attractive synthetic targets. We have already reported the syntheses of both the A ring and the F–J fragment of gambieric acids.[4] Herein, we describe a concise synthesis of the A–D fragment of (−)-gambieric acids A and C that includes a novel, more efficient, and robust second-generation synthesis of the A ring system.

At the outset, the stereochemical relationship between the stereogenic centers in the A ring and those in the B–J fragment had not been established firmly, and so choice of enantiomer of the chiral pool starting material for the B–J array was arbitrary. Sasaki's synthesis of (+)-gambieric acid A and revision of

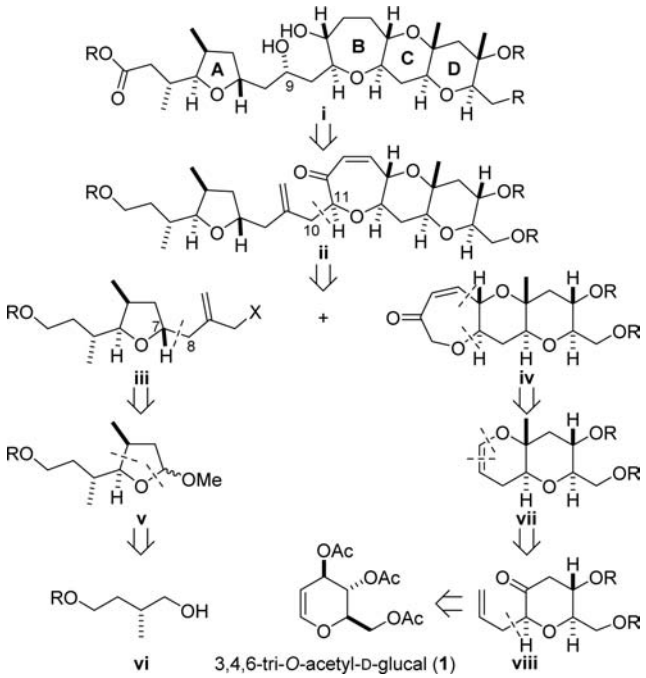
Received: July 21, 2015
Published: September 14, 2015

DOI: 10.1021/acs.orglett.5b02093
Org. Lett. 2015, 17, 4694–4697

stereochemical assignments was published at a point where our synthesis of the A−D fragment was well advanced, and at this stage it became clear that we were preparing the antipode.

Our intention is to construct the full polyether system of the gambieric acids by union of a tetracyclic A−D fragment with a pentacyclic F−J fragment followed by closure of the E ring. The retrosynthetic analysis of the A−D fragment (**i**) of (−)-gambieric acids A and C is shown in Scheme 1. Replacement of the C-9

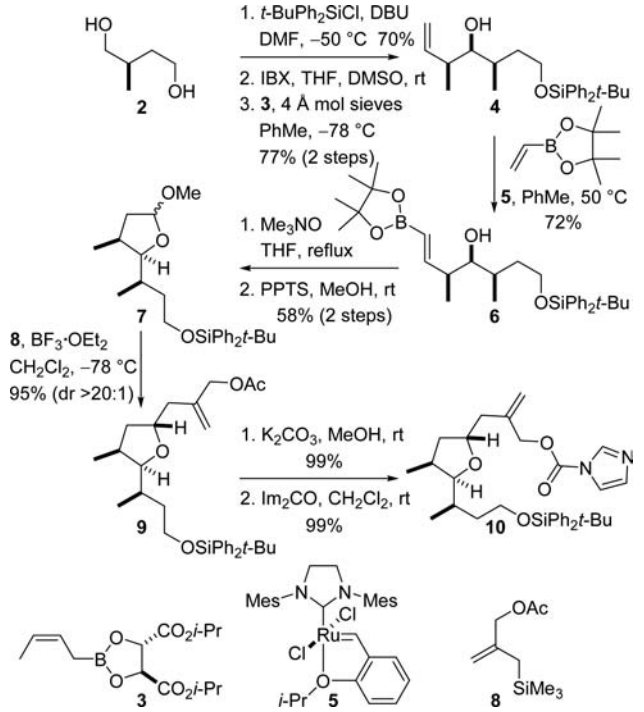
Scheme 1. Retrosynthetic Analysis of the A−D Fragment



hydroxyl group with a methylene group and the B-ring hydroxyl group with an enone reveals the tetracyclic array **ii**. This system can now undergo disconnection of the A ring segment **iii** from the B−D tricyclic polyether **iv** at the C-10−C-11 bond, a process that suggests a Tsuji−Trost allylation reaction in the forward direction.[5,6] Disconnection (C-7−C-8) of tetrahydrofuran **iii** reveals the acetal **v**, and further simplification gives the chiral pool alcohol **vi**. Disconnection of the seven-membered ring of the tricyclic enone **iv** reveals bicyclic ether **vii**. Scission of the enol ether reveals the pyranone **viii**, which can be prepared from commercially available tri-*O*-acetyl-D-glucal (**1**).

Synthesis of the A ring fragment commenced with regioselective monosilylation of the commercially available diol **2** (Scheme 2).[7] Sequential oxidation of the alcohol and asymmetric crotylation of the intermediate aldehyde, using the *Z*-crotylboronate **3**,[8] afforded the alcohol **4** with a good level of diastereocontrol (dr = 4:1−9:1). It should be noted that the crotylation reaction was completely stereoselective, but the intermediate aldehyde underwent partial racemization prior to reaction. The alkene **4** was subjected to cross-metathesis with vinyl pinacol boronate, mediated by the Hoveyda−Grubbs second-generation catalyst **5** (10 mol %), to afford the coupled *E*-alkene **6** as a single isomer in good yield. Oxidation of the vinylic boronate by treatment with trimethylamine *N*-oxide resulted in aldehyde formation and spontaneous cyclization to produce a hemiacetal, which was converted into the acetal **7**. Stereoselective installation of the side chain was accomplished by Lewis acid promoted allylation of the acetal **7** using the commercially

Scheme 2. Synthesis of the A-Ring Fragment 10



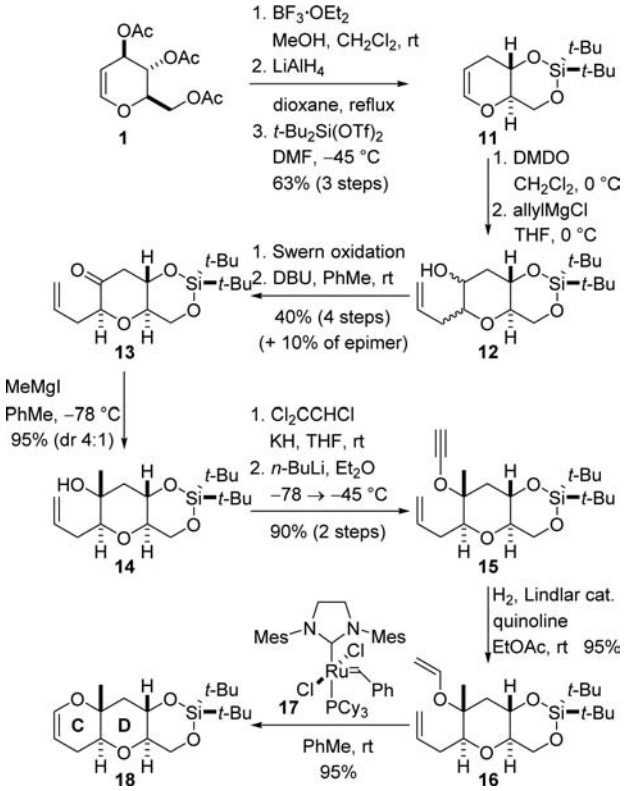
available allylic silane **8**. The trisubstituted tetrahydrofuran **9** was obtained in excellent yield and with high diastereoselectivity, mirroring the levels of stereocontrol observed by the groups of Woerpel and Rainier for Lewis acid mediated reactions of allylic silanes with closely related acetals.[9] Cleavage of the acetate group was accomplished by treatment of the ester **9** with potassium carbonate in methanol. The resulting alcohol was converted into the carbamate **10** by reaction with carbonyl diimidazole. Thus, the carbamate **10** required for the impending coupling sequence was prepared from the alcohol **2** in just nine steps and with excellent overall yield (21%).

Completion of the A ring meant that efforts could be focused on the preparation of the fused tricyclic B−D fragment (Scheme 3). We had already demonstrated that it is possible to construct fused polycyclic ethers possessing a variety of ring sizes by performing highly efficient ring-closing metathesis (RCM) reactions.[4b,9c,10,11] We decided to apply this robust strategy to the synthesis of the B−D fragment commencing from tri-*O*-acetyl-D-glucal (**1**) (Scheme 3). Treatment of the triacetate **1** with methanol in the presence of boron trifluoride diethyl etherate resulted in elimination of the allylic acetate group and concomitant acetal formation.[12] Reduction of the acetal with lithium aluminum hydride[12] and protection of the resulting 1,3-diol as the di-*tert*-butylsiloxane delivered the enol ether **11** in 63% yield over three steps. Epoxidation of the enol ether **11** using dimethyldioxirane followed by addition of allylmagnesium chloride delivered the alcohol **12** as a diastereomeric mixture. Swern oxidation and subsequent epimerization delivered the ketone **13** in 40% yield over four steps.

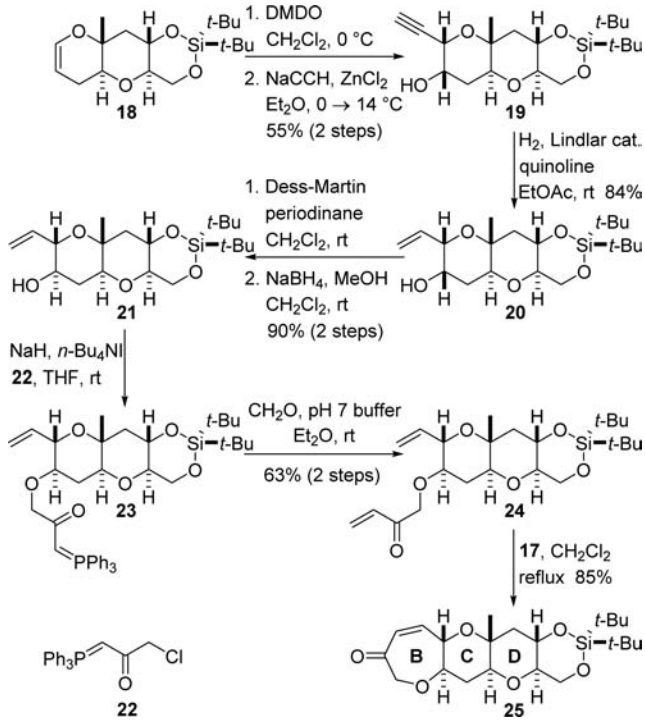
Stereoselective introduction of the ring-junction methyl group was achieved by treatment of ketone **13** with methylmagnesium iodide.[4b] A separable mixture of the tertiary alcohols (dr 4:1) was obtained in a combined yield of 95% with the required alcohol **14** predominating. Subsequent alkynyl ether formation using Greene's procedure[13] afforded the enyne **15** in excellent yield. Partial hydrogenation using Lindlar catalyst produced vinyl ether

DOI: 10.1021/acs.orglett.5b02093
Org. Lett. 2015, 17, 4694−4697

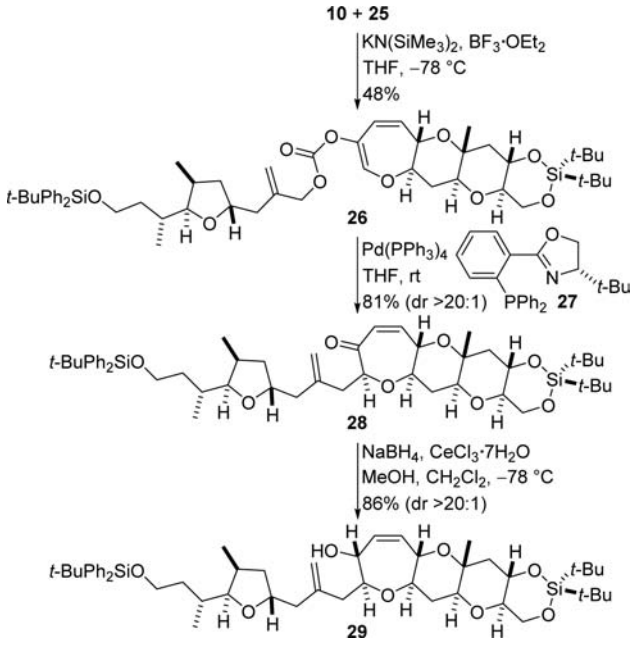
Scheme 3. Synthesis of the Bicyclic CD Fragment 18



Scheme 4. Synthesis of the Tricyclic B−D Fragment 25



Scheme 5. Stereoselective Palladium-Catalyzed Coupling of the A and B−D Fragments To Give the A−D Ring System



Construction of the B ring commenced with stereoselective epoxidation (dr >9:1) of the cyclic enol ether **18** using dimethyldioxirane (Scheme 4). Zinc(II) chloride promoted opening of the epoxide with sodium acetylide[15] afforded the alcohol **19** in 55% yield over two steps. Partial hydrogenation of the alkyne in the presence of Lindlar catalyst gave the alkene **20** in high yield.

Inversion of configuration at the hydroxyl-bearing stereogenic center of the alcohol **20** was necessary at this stage and was accomplished by sequential Dess−Martin oxidation and ketone reduction with sodium borohydride. The resulting alcohol **21** was converted into the RCM precursor **24** by etherification with 3-chloro-2-oxopropylidene triphenylphosphorane (**22**) and reaction of the resulting phosphonium ylide **23** with formaldehyde under buffered conditions.[16] The RCM reaction of the diene **24** was performed using the Grubbs second-generation catalyst **17** (5 mol %) to provide the crystalline enone **25** in 85% yield. The structure of this tricyclic enone and the stereochemical assignments were confirmed by X-ray crystallography.[17]

Both key fragments were available in sufficient quantities, and so the stage was set for attempted stereoselective fragment coupling of the A ring **10** to the tricyclic B−D segment **25** using the asymmetric Tsuji−Trost allylation reaction[5] developed by Stoltz and co-workers (Scheme 5).[6] Formation of the required enol carbonate **26** proved to be extremely challenging, but under optimized conditions the required compound was obtained in 48% yield (Scheme 5). Furthermore, the enol carbonate was found to be prone to decomposition and had to be used immediately in the subsequent asymmetric palladium-catalyzed rearrangement reaction. Pleasingly, asymmetric allylation using $Pd(PPh_3)_4$ (10 mol %) in the presence of the chiral ligand (*S*)-*t*-BuPHOX (**27**, 12.5 mol %) afforded substituted enone **28** as a single diastereomer in 81% yield.[18] Subsequent Luche reduction of the ketone **28**[19] delivered the alcohol **29** in excellent yield and with high diastereoselectivity.

In summary, the tetracyclic alcohol **29** corresponding to the A−D fragment of the gambieric acids A and C was prepared from commercially available tri-*O*-acetyl-D-glucal (**1**) in 23 steps (longest linear sequence) and 1.45% overall yield. The tetrahydrofuran in the A ring segment was prepared by

DOI: 10.1021/acs.orglett.5b02093
Org. Lett. 2015, 17, 4694−4697

diastereoselective Lewis acid mediated alkylation of an acetal. The iterative ring-closing metathesis strategy developed by our group was successfully applied to the construction of the tricyclic B–D fragment. Coupling of the A-ring fragment **10** to the tricyclic B–D fragment **25** was accomplished using a highly stereoselective Tsuji–Trost allylation reaction. The synthesis of the natural enantiomer of the A–D fragment and its attachment to the F–J fragment is currently in progress, and results of these synthetic studies will be reported in due course.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b02093.

X-ray data for enone **25** (CIF)

Experimental details plus spectroscopic and other data for compounds **2**, **4**–**7**, **9**–**16**, **18**–**21**, **23**–**25**, **28**, and **29** (PDF)

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: stephen.clark@glasgow.ac.uk.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

The authors gratefully acknowledge EPSRC (grant EP/F031505/1) and the University of Glasgow for funding.

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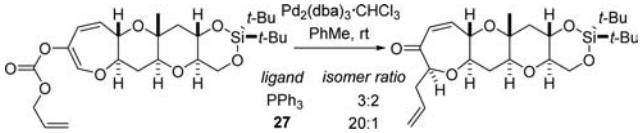
(17) X-ray data (CIF files) for the enone **25** can be found in the Supporting Information. Data have been deposited with the Cambridge Crystallographic Data Centre (CCDC 1413202) and can be obtained free of charge from CCDC via www.ccdc.cam.ac.uk.

(18) The presence of ligand **27** was essential for high levels of diastereocontrol. In model studies performed using the simple allyl carbonate analogue of carbonate **26**, a low level of diastereocontrol was obtained in the absence of a chiral ligand.



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DOI: 10.1021/acs.orglett.5b02093
Org. Lett. 2015, 17, 4694–4697