Synthetic Methods

DOI: 10.1002/ange.200501925

Rapid Two-Directional Synthesis of the F–J Fragment of the Gambieric Acids by Iterative Double Ring-Closing Metathesis**

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The gambieric acids A–D are potent antifungal agents, first isolated by Yasumoto and co-workers from a culture of the marine dinoflagellate *Gambierdiscus toxicus* (GII1 strain) collected near the Gambier Islands in French Polynesia (Scheme 1).[1] The structures of these complex fused polyether natural products and the relative stereochemistry of the

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[**] This work was funded by the Engineering and Physical Sciences Research Council, UK (grant numbers GR/M30654/01 and GR/S15761/01).

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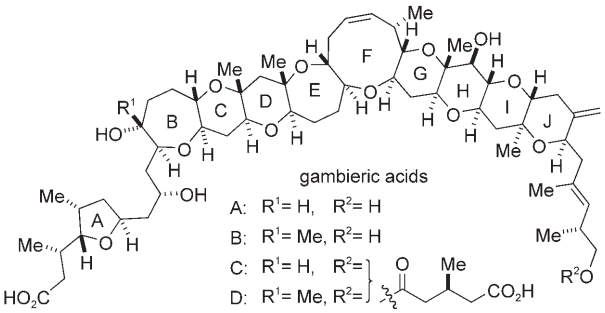


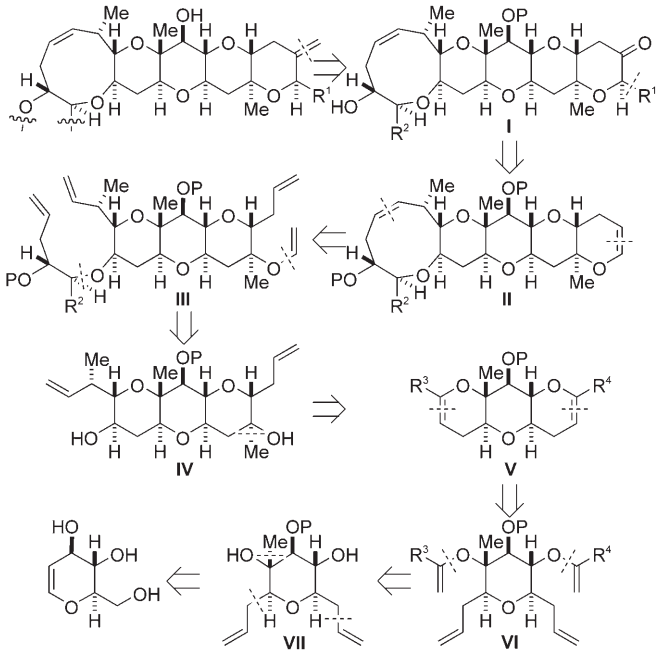
Scheme 1. The structures of the gambieric acids A–D.

trans-fused ring system (rings B–J) were determined by using NMR spectroscopic analysis in conjunction with mass-spectrometric analysis.[1b] Absolute stereochemical assignments were later established by NMR spectroscopic analysis of compounds obtained by derivatization as the Mosher ester followed by oxidative cleavage of the side chain attached to the J ring, and by functionalization of the carboxylic acid functionality by using a chiral anisotropic reagent.[1c]

The gambieric acids are potent and selective antifungal agents—they display significant activity against filamentous fungi but are inactive against yeasts—that exhibit up to 2000-fold higher activity against some fungi than amphotericin B in certain assays.[2] The gambieric acids are also cytotoxic, but they do not possess the significant neurotoxicity associated with most other large marine fused-polyether natural products, such as the brevetoxins, ciguatoxins, yessotoxins, and maitotoxins.[2] Interestingly, although the gambieric acids do not function as potent neurotoxins, gambieric acid A does inhibit binding of the brevetoxin B derivative PbTx-3 to site 5 of voltage-gated sodium channels of excitable membranes.[3]

The obvious synthetic challenges presented by the gambieric acids, coupled with their potent antifungal activity, make them alluring targets for total synthesis. Recently, elegant total syntheses of the related marine polyether natural products brevetoxin A,[4] brevetoxin B,[5] ciguatoxin CTX-3,[6] gambierol,[7] and gymnocin[8] have been reported. In contrast, there is a paucity of published work that concerns the synthesis of the polycyclic ether framework of the gambieric acids or even small subunits of these natural products.[9]

We recently initiated a program to synthesize the gambieric acids based on the ring-closing metathesis (RCM) methodology that we had developed to address the general problem of fused-polyether construction[10] and have recently described a concise synthesis of the A ring fragment of the gambieric acids by using copper-carbenoid chemistry.[11] To construct the full ten-ring polyether system of the gambieric acids, we intend to pursue a highly convergent synthetic strategy in which the target will be constructed by the union of a tetracyclic A–D fragment and a pentacyclic F–J fragment followed by final closure of the E ring. Retrosynthetic disconnection of the F–J fragment **I** by removal of the side chain (R^1) and functional group interconversion suggests the enol ether **II** as an advanced precursor (Scheme 2). Scission of the F and J rings then leads to the tricyclic intermediate **III**, and removal of the acyclic ether substituents leads to the diol

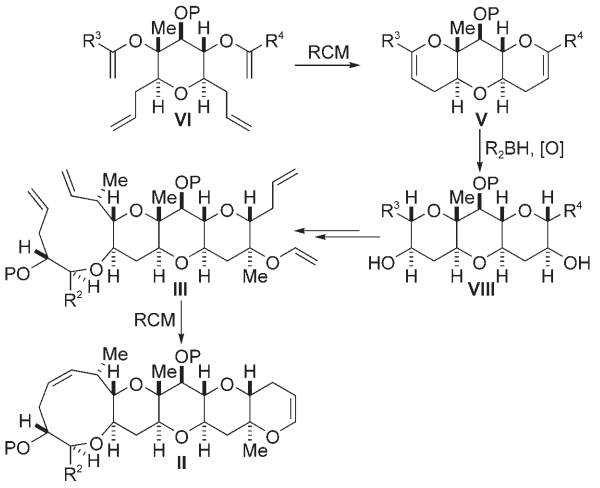


Scheme 2. Retrosynthetic analysis of the F–J fragment of the gambieric acids.

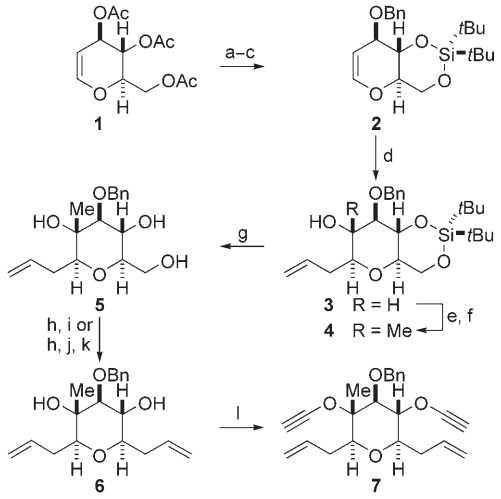
IV. Removal of the methyl group and retrosynthetic dehydration then reveals the bis(enol ether) **V**, and scission of the G and I rings leads to the monocyclic intermediate **VI**, which corresponds to the H ring. The tetrahydropyran unit can then be straightforwardly disconnected through the diol **VII** to reveal D-glucal as the chiral-pool starting material.

The use of a two-directional double-RCM reaction twice in the synthetic sequence to construct the tetrahydropyran G and I rings simultaneously and then the nine-membered F ring and the six-membered F ring and the six-membered J ring simultaneously is intrinsic to the retrosynthetic analysis shown in Scheme 2. In the forward direction, this approach would involve double RCM of a bis(enol ether) **VI** and then hydroboration of the tricyclic product **V** to give the diol **VIII** after oxidative work-up (Scheme 3).[10a,e,12] The diol **VIII** would then be converted into the triene enol ether **III**; a second double two-directional RCM reaction would then deliver the pentacyclic F–J fragment to which the requisite side chain could be attached.

The anticipated strategy involves two-directional synthesis by iterative double simultaneous (as opposed to sequential) ring closure. Although there have been some early examples of two-directional synthesis, the potential of simultaneous two-directional homologation has only been fully appreciated within last decade.[13] Some of the most elegant examples of this approach have been reported by Schreiber and co-workers in connection with their syntheses of the polyol-containing natural products mycotycins and hizikimycin.[14] The implementation of a synthetic strategy that involves simultaneous two-directional homologation is attractive because such a reflexive approach can, in principle, improve the efficiency of both linear and convergent syntheses.[15] However, unless the target molecule is entirely symmetrical, it must be possible to perform reactions simulta-



Scheme 3. The use of iterative double-RCM reactions to construct the F–J fragment of the gambieric acids.



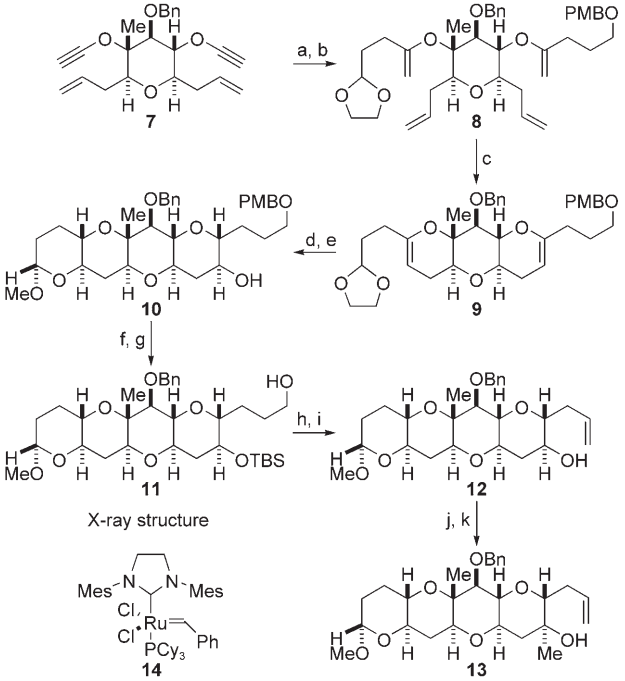
Scheme 4. Synthesis of the armed H-ring fragment **7**. a) NaOMe, MeOH, RT; b) tBu$_2$Si(OTf)$_2$, DMF, pyridine, −40 °C; c) NaH, BnBr, THF/DMF, 0 °C→RT (85 %, 3 steps); d) DMDO, CH_2Cl_2, 0 °C, then CH_2CHCH_2MgCl, THF, 0 °C (82 %); e) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, −78 °C→RT; f) MeLi, PhMe, −78 °C (76 %, 2 steps); g) $(HF)_3{\cdot}NEt_3$, THF, 0 °C (98 %); h) Tf_2O then Et_3SiOTf, 2,6-lutidine, CH_2Cl_2, −78 °C (88 %); i) nBu$_3$SnCHCH$_2$, nBuLi, CuCN, THF, −78 °C then TBAF, THF, 0 °C (78 %); j) HCCSiMe$_3$, nBuLi, DMPU, THF, 0 °C, then TBAF, THF, 0 °C (96 %); k) H_2, the Lindlar catalyst, quinoline, EtOAc, RT (82 %); l) KH, Cl_2CCHCl, THF, 0 °C then nBuLi, Et_2O, −78→−40 °C (88 %). DMF = dimethylformamide, DMDO = dimethyldioxirane, DMSO = dimethyl sulfoxide, TBAF = tetrabutylammonium fluoride, DMPU = *N*,*N*′-dimethyl-*N*,*N*′-propyleneurea.

neously at both ends of the molecule while being able to differentiate the termini at various stages along the synthetic route.

We have recently demonstrated that it is possible to construct tricyclic polyether fragments that possess a variety of ring sizes in good-to-excellent yield by performing simultaneous double ring construction by using RCM.[16] Substrates bearing enol ethers, allylic ethers, and alkynyl ethers or mixtures of these functional groups were employed as substrates for the double-RCM reactions. The objective of the investigation described herein was to demonstrate that the F–J fragment of the gambieric acids could be assembled by a two-directional approach, in which simultaneous double-RCM reactions are used twice, and that many of the other reactions used to assemble the pentacyclic unit could be performed in a simultaneous or sequential two-directional fashion.

The two-directional synthesis of the F–J fragment of the gambieric acids commenced with deacetylation of the commercially available triacetate **1** (Scheme 4). Conversion of the resulting D-glucal into ether **2** was accomplished by protection of the primary and proximal secondary hydroxy groups with a di-*tert*-butylsilylene group and benzylation of the remaining hydroxy group.[16,17] The enol ether **2** was then subjected to highly diastereoselective oxidation with dimethyldioxirane[18] and the resulting anomeric epoxide underwent ring opening with allylmagnesium chloride to give the alcohol **3** in good yield.[19] Swern oxidation followed by treatment of the resulting ketone with methyllithium at low temperature afforded the tertiary alcohol **4** in good yield and with a reasonable level of diastereocontrol (d.r. = 6:1). Subsequent removal of the di-*tert*-butylsilylene protecting group afforded the corresponding triol **5** in high yield, and sequential treatment of this triol with trifluoromethanesulfonic anhydride and triethylsilyl trifluoromethanesulfonate in the presence of 2,6-lutidine in a one-pot procedure gave the primary triflate with concomitant protection of the secondary hydroxy group. Introduction of the alkene side chain was then accomplished in a single operation by displacement of the triflate group with the higher-order cyanocuprate, generated from vinyllithium (formed in situ by transmetalation from tri-*n*-butylvinylstannane) and copper(I) cyanide at low temperature,[20] and the diol **6** was obtained in good yield thereafter by desilylation of the secondary hydroxy site. The alkenyl side chain was also constructed by displacement of the triflate with lithium trimethylsilylacetylide followed by treatment of the alkyne product with fluoride and partial hydrogenation using the Lindlar catalyst in the presence of quinoline. The overall yield of the diol **6** obtained by using the less-direct route was similar to that obtained by using the higher-order cyanocuprate to displace the triflate directly. Diol **6** was then converted into the bis(alkynyl ether) **7** by using the one-pot alkynylation procedure developed by Greene and co-workers.[21] The alkynylation reaction was the first two-directional reaction in our synthetic sequence, and it is noteworthy that both alkynyl ethers were generated simultaneously in excellent yield and that the highly hindered tertiary alcohol underwent reaction cleanly.

The bis(enol ether) required for the first double-RCM reaction was prepared from the bis(alkynyl ether) **7** by using sequential carbocupration reactions (Scheme 5).[22] The first side chain was introduced by a completely regioselective addition of a homocuprate reagent at the less sterically encumbered alkynyl ether. An acetal-containing side chain was then installed by reaction of the remaining hindered alkynyl ether with an excess of the cyanocuprate generated from equimolar amounts of the Grignard reagent 1,3-dioxolan-2-ylethylmagnesium bromide and copper(I) cya-



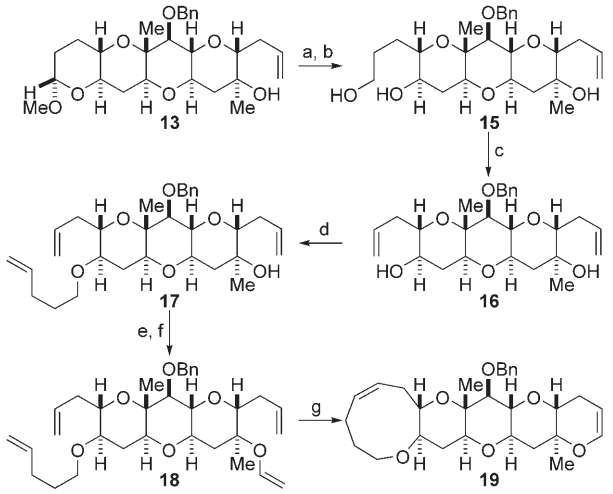
Scheme 5. Synthesis of the tricyclic G–I fragment **13**. a) PMBO-$(CH_2)_3MgBr$, CuBr, LiBr, THF, −95→−78 °C (85 %); b) $(OCH_2CH_2O)CH(CH_2)_2MgBr$, CuCN, LiCl, THF, −78 °C (84 %); c) catalyst **14** (10 mol %), PhMe, 70 °C (89 %); d) thexyl borane, THF, 0 °C→RT then $NaBO_3 \cdot 4H_2O$, pH 7 buffer (62 %); e) TsOH, MeOH, RT (71 %); f) *t*$BuMe_2SiCl$, DMAP, Et_3N, CH_2Cl_2, RT; g) CAN, MeCN, H_2O, RT (56 %, 2 steps); h) *o*-$O_2NC_6H_4SeCN$, *n*Bu_3P, THF, RT then H_2O_2, $NaHCO_3$ aq., 40 °C; i) TBAF, THF, RT (83 %, 2 steps); j) Dess–Martin periodinane, CH_2Cl_2, 0 °C; k) MeMgI, PhMe, −78 °C (83 %, 2 steps). PMB = pentamethylbenzyl, Cy = cyclohexyl, Mes = mesityl, Bn = benzyl, TBS = *tert*-butyldimethylsilyl, Ts = *para*-toluenesulfonyl, DMAP = 4-dimethylaminopyridine , CAN = cerium(IV) ammonium nitrate.

nide.[23] The yields for both carbocupration reactions were excellent and the exceptionally high level of regiocontrol obtained during the first carbocupration reaction of the sequence is remarkable.

The bis(enol ether) **8** was subjected to double RCM by treatment with ruthenium catalyst **14**,[24] and the tricyclic product **9** was obtained in excellent yield from this two-directional ring-closure reaction (Scheme 5).[16] Double hydroboration of the metathesis product **9** was accomplished by using an excess of thexylborane, and mild oxidation of the intermediate organoborane with sodium perborate delivered the required diol in 62 % yield.[25] Treatment of the diol with *para*-toluenesulfonic acid in methanol yielded the tetracyclic acetal **10** in excellent yield and resulted in differentiation of the two secondary hydroxy groups. The free secondary alcohol was then protected as its *tert*-butyldimethylsilyl ether and the *para*-methoxybenzyl ether side chain was cleaved with CAN. The resulting alcohol **11** was a crystalline solid, and both the structure and relative stereochemistry of this tetracyclic intermediate were confirmed by X-ray crystallographic analysis.[26]

The alkene required for the second double-RCM reaction was installed by dehydration of the side chain (Scheme 5). Thus, the primary alcohol **11** was treated with *ortho*-nitrophenyl selenocyanate and tri-*n*-butylphosphine followed by oxidation of the intermediate selenide with buffered hydrogen peroxide and thermal elimination of selenoxide in situ.[27] Removal of the silicon protecting group afforded the alcohol **12**, and subsequent oxidation and stereoselective addition of methylmagnesium iodide to the intermediate ketone delivered the tertiary alcohol **13** in a highly diastereoselective manner.

Acetal **13** was then elaborated to give the F–J ring fragment of the gambieric acids by using the sequence shown in Scheme 6. Acetal **13** was converted into the corresponding



Scheme 6. Completion of the pentacyclic F–J fragment **19**. a) HCl aq., THF, 60 °C; b) $NaBH_4$, MeOH, 0 °C (84 %, 2 steps); c) *o*-$O_2NC_6H_4SeCN$, *n*Bu_3P, THF, RT then H_2O_2, $NaHCO_3$ aq., 40 °C (96 %); d) $CH_2CH(CH_2)_3Br$, *n*Bu_4NI, THF/DMF, reflux (66 % (81 % brsm)); e) KH, Cl_2CCHCl, THF, 0 °C then *n*BuLi, Et_2O, −78→−40 °C; f) H_2, Lindlar catalyst, quinoline, EtOAc, RT (49 %, 2 steps); g) catalyst **14** (10 mol %), PhMe, 80 °C (60 %).

cyclic hemiacetal by treatment with aqueous acid, and subsequent reduction with sodium borohydride gave diol **15**. Dehydration of the side chain was effected by formation of selenide, oxidation, and elimination of selenoxide (cf. **11**→**12**, Scheme 5), but protection of the secondary alcohol was not required in this case. Selective monoalkylation of the secondary hydroxy group of diene **16** was accomplished by sequential treatment with sodium hydride and 5-bromo-1-pentene in the presence of tetra-*n*-butylammonium iodide. The remaining hydroxy group of triene **17** was then converted into the requisite vinyl ether by sequential alkynyl ether formation and Lindlar reduction,[16] thus giving the second double-RCM precursor **18** in reasonable yield. The final crucial double-RCM reaction to give the required nine- and six-membered cyclic ethers was then effected by treatment of the tricyclic compound **18** with the ruthenium complex **14**.[24] The pentacyclic array **19**, which corresponds to the F–J ring fragment of the gambieric acids, was obtained from the reaction in 60 % yield. Analysis of partially cyclized material isolated from the reaction suggested that ring closure of the enol ether proceeds at a much faster rate than formation of the nine-membered ring.

In summary, we have demonstrated that the F–J fragment of the gambieric acids can be assembled by a rapid and efficient two-directional approach in which simultaneous double-RCM reactions are employed in an iterative manner. The formation of alkynyl ethers and carbocupration have also been performed in a two-directional manner, and it should be noted that by reordering some of the steps in the synthetic sequence, other reactions (e.g., the formation of selenide, oxidation, and elimination of selenoxide) could also be performed simultaneously, thus leading to an even more efficient route. The synthesis of the F–J fragment with the appropriate functionalities for the attachment of the A–D fragment is currently in progress, and results of these synthetic studies will be reported in due course.

Received: June 2, 2005
Published online: August 31, 2005

Keywords: cyclization · metathesis · natural products · polyethers

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[26] Crystal data for the acetal **11**: $C_{32}H_{52}O_8Si$, $M_r = 592.85$, colorless block cut from lath, crystal dimensions $0.52 \times 0.48 \times 0.32$ mm^3,

orthorhombic, space group $P2_12_12_1$, $a = 9.287(4)$, $b = 24.984(11)$, $c = 43.067(19)$ Å, $V = 9993(8)$ Å^3, $Z = 12$, $\rho_{calcd} = 1.182$ Mg m^{-3}, $\mu(Mo_{K\alpha})$ 0.117 mm^{-1}, $T = 150(2)$ K; 28321 reflections collected of which 15595 independent, $2\theta_{max} = 50°$, absorption correction made using multi-scan method (SADABS), $T_{min/max} = 0.562/1.00$. Structure solved by direct methods (SHELXS-97) and refined by full-matrix least squares against F^2 (SHELXTL), $R_1 = 0.106$, $wR_2 = 0.248$, 1101 parameters. One tBuMe$_2$Si group showed disorder and was modeled over two sites with occupancies 0.577(7) and 0.423(7) and isotropic atomic displacement parameters. All hydrogen atoms were placed in geometrically calculated positions, except those of OH groups which were located from difference Fourier syntheses and refined as rigid rotors. Maximum and minimum residual electron density = 0.66 and −0.50 e Å^{-3}. CCDC-273286 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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