Natural Products Synthesis

DOI: 10.1002/anie.200604625

Studies toward the Total Synthesis of Gambieric Acids A and C: Convergent Assembly of the Nonacyclic Polyether Skeleton**

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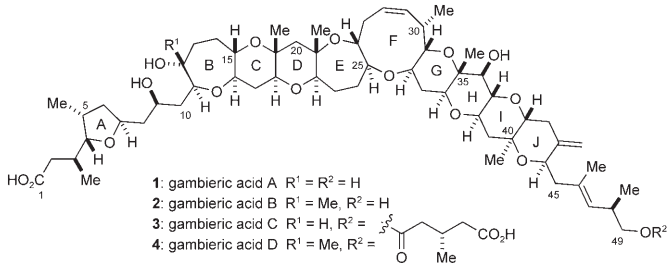
A number of polycyclic-ether natural products with potent and diverse biological activities have been isolated from marine sources.[1] Gambieric acids A–D (**1**–**4**, Scheme 1) were



Scheme 1. Structures of gambieric acids A–D.

isolated by Nagai, Yasumoto, and co-workers from the culture media of the marine dinoflagellate *Gambierdiscus toxicus*, which is the causative organism of ciguatera seafood poisoning.[2] These polycyclic ethers exhibited extremely potent antifungal activity against *Aspergillus niger* (their potency is 2000 times greater than that of amphotericin B), whereas they show only moderate toxicity toward mice or cultured mammalian cells. These useful biological aspects make polycyclic ethers potential lead compounds for the discovery of antifungal agents. Moreover, Inoue et al. reported recently that gambieric acid A (**1**) inhibits the binding of [^{3}H]dihydrobrevetoxin B ([^{3}H]PbTx-3) to voltage-sensitive sodium channels, although its binding affinity is significantly lower than those of the brevetoxins and ciguatoxins.[3] These intriguing biological properties and the molecular complexity of the gambieric acids have generated considerable interest within the synthetic community, and several synthetic approaches toward the total synthesis of these potentially useful polycyclic ethers have been reported to date.[4–6] Herein, we describe a convergent synthesis of the nonacyclic polyether skeleton **5** of gambieric acids A and C.

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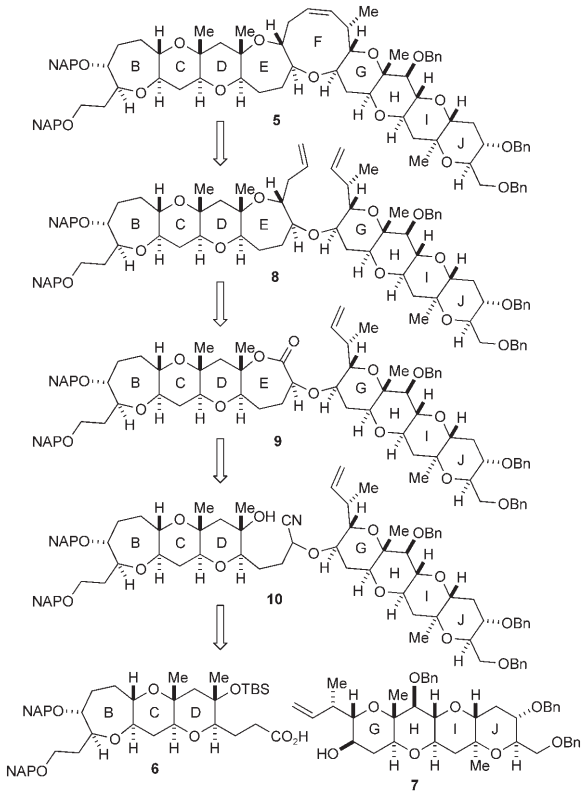
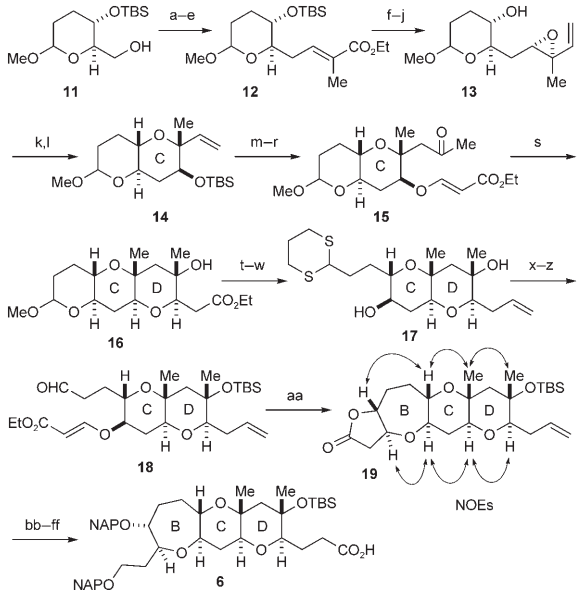
[**] This research was supported financially in part by the Sumitomo Foundation and Grants-in-Aid for Scientific Research from the Japan Society for Promotion of Science (JSPS) and the Ministry of Education, Culture, Sports, Science and Technology, Japan (Scientific Research (B) 16310145 and Priority Area 16073202). A research fellowship to K.S. from the JSPS is acknowledged.

We reported previously a convergent synthesis of the central CDEFG ring system of the gambieric acids.[4] The synthetic approach involved the convergent union of the CD- and G-ring fragments through esterification, followed by construction of the E and F rings. We envisaged the application of this strategy to the construction of the nonacyclic BCDEFGHIJ polyether skeleton **5** of gambieric acids A and C from the two complex fragments **6** and **7**, as illustrated in Scheme 2. The nine-membered F ring of **5** would be accessible by ring-closing metathesis (RCM) from the precursor diene **8**, which we planned to obtain from lactone **9** through reductive acylation[7] followed by stereoselective allylation. Lactone **9**, in turn, could be derived from the α-cyano ether **10**, which could be obtained from two complex fragments, the BCD-ring carboxylic acid **6** and the GHIJ-ring alcohol **7**, according to previously described chemistry.[4]

The synthesis of the BCD-ring fragment **6** (Scheme 3) started with the known alcohol **11**, which is available in four steps from tri-*O*-acetyl-D-glucal.[8] Parikh–Doering oxidation[9] and Wittig olefination, followed by hydroboration



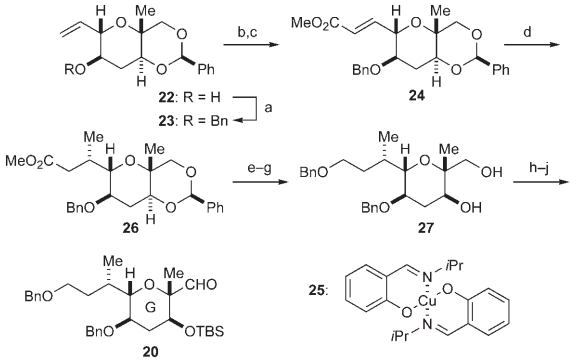
Scheme 2. Retrosynthesis of the nonacyclic BCDEFGHIJ ring system **5** of gambieric acid A and C. Bn = benzyl, NAP = 2-naphthylmethyl.



Scheme 3. Reagents and conditions: a) SO_3·pyridine, Et_3N, DMSO/CH_2Cl_2, 0 °C→RT; b) Ph_3PCH_3Br, NaN(TMS)$_2$, THF, 0 °C→RT, 95% (2 steps); c) 9-BBN, THF; aq NaOH, H_2O_2, 0 °C→RT, 79%; d) SO_3·pyridine, Et_3N, DMSO/CH_2Cl_2, 0 °C→RT; e) $Ph_3P{=}C(Me)CO_2Et$, toluene, 100 °C, 90% (2 steps); f) DIBAL-H, CH_2Cl_2, −78 °C, 99%; g) *t*BuOOH, (+)-DET, Ti(O*i*Pr)$_4$, 4-Å MS, CH_2Cl_2, −20 °C; h) SO_3·pyridine, Et_3N, DMSO/CH_2Cl_2, 0 °C→RT; i) Ph_3PCH_3Br, NaN(TMS)$_2$, THF, 0 °C→RT, 89% (3 steps); j) TBAF, THF, 0 °C→RT, 93%; k) PPTS, CH_2Cl_2, 0 °C→RT, 96%; l) TBSOTf, 2,6-lutidine, CH_2Cl_2, 0 °C→RT, 97%; m) $BH_3{\cdot}SMe_2$, 2-methyl-2-butene, THF; aq NaOH, H_2O_2, 0 °C→RT, 98%; n) SO_3·pyridine, Et_3N, DMSO/CH_2Cl_2, 0 °C; o) MeMgBr, THF, 0 °C→RT, 89% (2 steps); p) TPAP, NMO, 4-Å MS, CH_2Cl_2, 0 °C→RT, 92%; q) TBAF, THF, 0 °C→RT, 99%; r) ethyl propiolate, NMM, CH_2Cl_2, 0 °C→RT; s) SmI_2, MeOH, THF, 0 °C→RT, 81% (2 steps); t) TMSOTf, 2,6-lutidine, CH_2Cl_2, 0 °C, 92%; u) DIBAL-H, toluene, −78 °C; v) Ph_3PCH_3Br, NaN(TMS)$_2$, THF, 0 °C→RT, 93% (2 steps); w) 1,3-propanedithiol, TMSOTf, MeCN, 0 °C, 93%; x) ethyl propiolate, NMM, CH_2Cl_2, 0 °C→RT, 94%; y) TBSOTf, 2,6-lutidine, CH_2Cl_2, 0 °C→RT, 97%; z) MeI, $NaHCO_3$, MeCN/H_2O, RT, 96%; aa) SmI_2, MeOH, THF, RT; bb) $LiAlH_4$, THF, 0 °C, 89% (2 steps); cc) NaH, NAPBr, TBAI, DMF, 0 °C→RT, 96%; dd) 9-BBN, THF; aq NaOH, H_2O_2, 0 °C→RT, 99%; ee) SO_3·pyridine, Et_3N, DMSO/CH_2Cl_2, 0 °C→RT; ff) $NaClO_2$, 2-methyl-2-butene, KH_2PO_4, *t*BuOH/H_2O, 0 °C→RT, 87% (2 steps). 9-BBN = 9-borabicyclo[3.3.1]nonane, DET = diethyl tartrate, DIBAL-H = diisobutylaluminum hydride, DMF = *N*,*N*-dimethylformamide, DMSO = dimethyl sulfoxide, MS = molecular sieves, NMM = 4-methylmorpholine, NMO = 4-methylmorpholine *N*-oxide, PPTS = pyridinium *p*-toluenesulfonate, TBAF = tetrabutylammonium fluoride, TBAI = tetrabutylammonium iodide, TBS = *tert*-butyldimethylsilyl, Tf = trifluoromethanesulfonyl, TMS = trimethylsilyl, TPAP = tetra-*n*-propylammonium perruthenate.

with 9-BBN, produced an alcohol in 75% overall yield. This primary alcohol was subjected to a second oxidation/Wittig reaction sequence to afford the α,β-unsaturated ester **12** in 90% yield. Ester **12** was reduced with DIBAL-H, and the resulting allylic alcohol was subjected to Sharpless asymmetric epoxidation. The oxidation of the epoxy alcohol thus formed and a Wittig reaction, followed by desilylation, gave the hydroxy epoxide **13** in 82% overall yield. The treatment of **13** with PPTS effected 6-*endo* cyclization[10] to afford the C-ring tetrahydropyran **14** after TBS protection (93%, two steps). The terminal olefinic unit of **14** was converted into a methyl ketone by a standard four-step sequence, and the TBS ether was replaced with a β-alkoxy *E* acrylate group to give **15**. The treatment of **15** with SmI_2 in the presence of MeOH induced reductive cyclization[11] to afford the CD ring system **16** as a single diastereomer. After TMS protection of the hydroxy group, the ethyl ester was reduced with DIBAL-H, and the resulting aldehyde underwent a Wittig reaction to give a terminal alkene in 86% overall yield. Subsequent treatment with 1,3-propanedithiol in the presence of TMSOTf provided the dithiane diol **17** in 93% yield. A selective hetero-Michael reaction of the secondary hydroxy group in **17** with ethyl propiolate, followed by TBS protection of the remaining tertiary hydroxy group and hydrolysis of the thioacetal, delivered aldehyde **18** in 89% yield. The reductive cyclization of **18** with SmI_2 again proceeded smoothly to form the seven-membered B ring. The sole product formed was γ-lactone **19**, the stereostructure of which was confirmed by the observed NOEs indicated. After reduction with $LiAlH_4$, the resulting diol was protected as the corresponding NAP ethers (85% from **18**).[12,13] Hydroboration of the terminal olefinic unit with 9-BBN provided a primary alcohol (99%), which was subjected to a two-step oxidation to furnish the desired BCD-ring carboxylic acid **6** in 87% yield for the two steps.

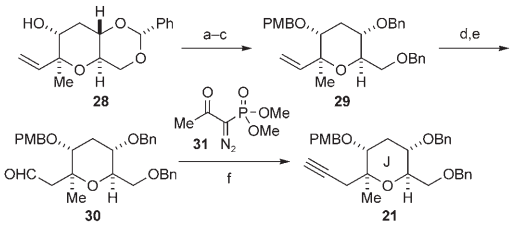
The GHIJ-ring fragment **7** was synthesized by connecting the G and J rings (**20** and **21**) followed by formation of the H and I rings according to the strategy developed by the Nakata research group (Scheme 6).[14] The synthesis of the G-ring aldehyde **20** began with the known alcohol **22**,[15] which was protected as the benzyl ether **23** (Scheme 4). Oxidative cleavage of the double bond followed by a Wittig reaction gave the α,β-unsaturated ester **24** in 80% yield. Subsequent treatment with MeMgBr and TMSCl in the presence of the Cu^{II} salt **25**[16] gave the desired 1,4-adduct **26** in 96% yield.[4,8] DIBAL-H reduction, benzyl protection, and hydrolysis of the benzylidene acetal provided diol **27** in 90% yield for the three steps. The secondary hydroxy group of **27** was protected selectively as the TBS ether by double TBS protection



Scheme 4. Reagents and conditions: a) NaH, BnBr, TBAI, DMF, 0 °C→RT, 99%; b) OsO_4, NMO, THF/H_2O_2, RT; $NaIO_4$; c) $Ph_3P{=}CHCO_2Me$, THF, RT, 80% (2 steps); d) MeMgBr, TMSCl, **25**, THF, −45 °C, 96%; e) DIBAL-H, CH_2Cl_2, −78 °C, 99%; f) NaH, BnBr, TBAI, DMF, 0 °C→RT; g) TsOH, MeOH, 40→70 °C, 91% (2 steps); h) TBSOTf, 2,6-lutidine, CH_2Cl_2, 0 °C→RT; i) CSA, MeOH/CH_2Cl_2, 0 °C, 95% (2 steps); j) SO_3·pyridine, Et_3N, DMSO/CH_2Cl_2, 0 °C→RT, 96%. CSA = camphorsulfonic acid, TsOH = *p*-toluenesulfonic acid.

followed by selective deprotection of the primary hydroxy group (95%, two steps). The resulting primary alcohol was oxidized under Parikh–Doering conditions[9] to furnish the G-ring aldehyde **20** in 96% yield.

The synthesis of the J-ring alkyne **21** commenced with the known alcohol **28** (Scheme 5).[17] Its protection as the PMB

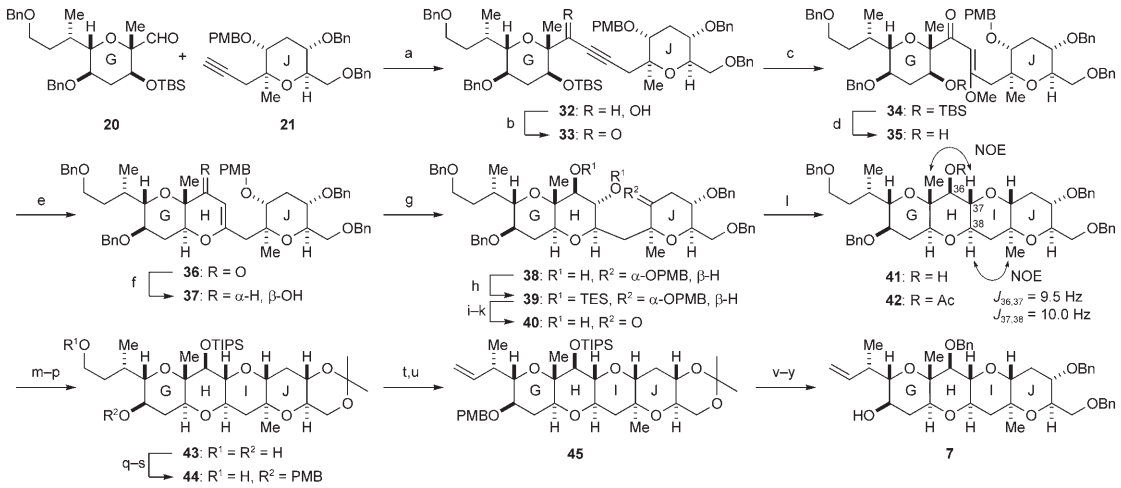


Scheme 5. Reagents and conditions: a) NaH, PMBCl, TBAI, DMF, 0°C→RT; b) CSA, MeOH, 0°C→RT, 86% (2 steps); c) NaH, BnBr, TBAI, DMF, 0°C→RT, 94%; d) 9-BBN, THF, 0°C→RT; aq NaOH, H_2O_2, 0°C→RT, 71%; e) TPAP, NMO, 4-Å MS, CH_2Cl_2, 0°C→RT, 77%; f) Cs_2CO_3, *i*PrOH, 0°C→RT, 93%. PMB = *p*-methoxybenzyl.

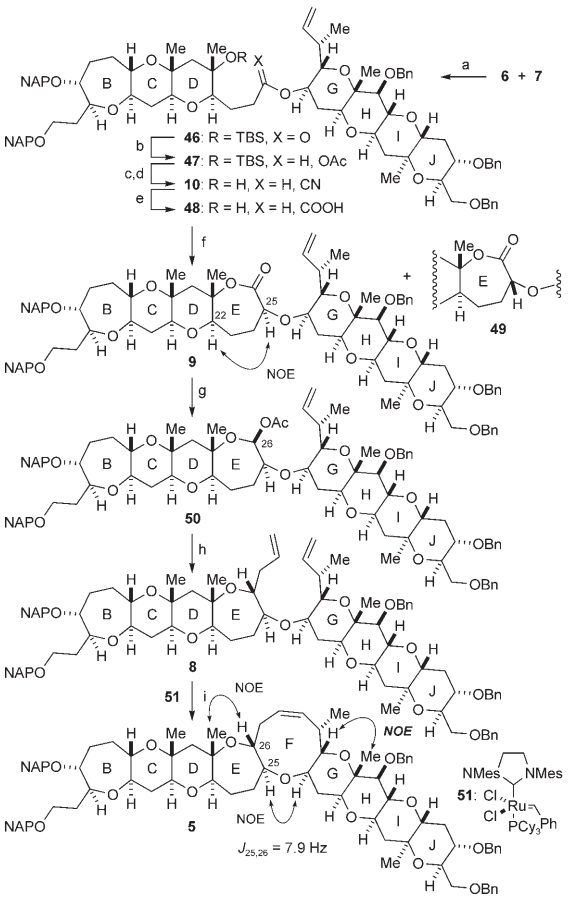
ether, followed by removal of the benzylidene acetal and benzylation of the resulting diol, provided **29** in 81% yield. Hydroboration of the terminal alkene unit with 9-BBN and oxidation of the resulting alcohol with TPAP/NMO[18] afforded aldehyde **30** (55%). The treatment of aldehyde **30** with the Ohira–Bestmann reagent **31**[19] completed the synthesis of the J-ring alkyne **21** in 93% yield.

The lithium acetylide derived from alkyne **21** was treated with aldehyde **20** to provide the propargylic alcohol **32** in 95% yield as a mixture of diastereomers (Scheme 6). Swern oxidation of **32** afforded the corresponding ketone **33**, which was then treated with sodium methoxide to give the β-methoxyenone **34** in 91% overall yield. After removal of the TBS group, the resulting alcohol **35** was treated with PPTS to induce an intramolecular hetero-Michael reaction, which led to dihydropyranone **36** in 87% yield. DIBAL-H reduction of **36** proceeded stereoselectively to afford alcohol **37**, with the hydroxy group in the β orientation, as the sole product in 93% yield. Hydroboration of the enol ether led exclusively to diol **38** (91%), which was then protected as the bis(TES) ether **39** in 99% yield. Removal of the PMB group in **39**, followed by oxidation of the resulting alcohol with TPAP/NMO[18] and removal of the TES groups, afforded dihydroxyketone **40** in 81% yield (three steps). The treatment of **40** with Et_3SiH and TMSOTf delivered the tetracyclic ether **41** in 83% yield. The stereostructure of **41** was established on the basis of ^1H NMR spectroscopic analysis of the corresponding acetate **42**. A further four-step sequence of protecting-group manipulations yielded **43** from **41** in 65% overall yield. Diol **43** was converted in a further three steps into the primary alcohol **44**, which was in turn converted into the terminal alkene **45** by the method developed by Grieco, Gilman, and Nishizawa.[20] The TIPS and acetonide groups in **45** were exchanged for benzyl protecting groups, and the PMB group was removed selectively[21] to complete the synthesis of the desired GHIJ-ring fragment **7**.

With the requisite key fragments **6** and **7** in hand, the stage was now set for the union of these fragments and subsequent formation of the E and F rings. Acid **6** and alcohol **7** were joined by esterification under Yamaguchi conditions[22] to afford ester **46** in 92% yield (Scheme 7). Ester **46** was then subjected to reductive acetylation according to the protocol of Rychnovsky and co-workers[7] to give the α-acetoxy ether **47**



Scheme 6. Reagents and conditions: a) *t*BuLi, THF/HMPA, −78°C; then **20**, −78°C, 95%; b) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, −78°C→RT, 93%; c) NaOMe, MeOH/THF, RT, 98%; d) HF·pyridine/pyridine/THF (2:1:4), 0°C→RT, 91%; e) PPTS, toluene, 100°C, 87%; f) DIBAL-H, toluene, −78°C, 93%; g) BH_3·THF, THF; aq NaOH, H_2O_2, THF, 0°C→RT, 91%; h) TESOTf, 2,6-lutidine, CH_2Cl_2, 0°C→RT, 99%; i) DDQ, CH_2Cl_2/pH 7 buffer, 0°C; j) TPAP, NMO, 4-Å MS, CH_2Cl_2, 0°C→RT; k) TBAF, AcOH, THF, RT, 81% (3 steps); l) TMSOTf, Et_3SiH/MeCN (1:4), −10°C, 83%; m) TIPSOTf, 2,6-lutidine, CH_2Cl_2, 0°C→RT; n) H_2, Pd/C, MeOH, RT; o) 2,2-dimethoxypropane, CSA, DMF, 30°C; p) PPTS, MeOH, CH_2Cl_2, 0°C, 65% (4 steps); q) PivCl, pyridine, 0°C, 82%; r) NaH, PMBCl, TBAI, DMF, 0°C→RT, 78%; s) DIBAL-H, CH_2Cl_2, −78°C, 72%; t) *o*-nitrophenylselenocyanate, nBu_3P, THF, RT; u) MCPBA, Et_3N, CH_2Cl_2, 0→35°C, 94% (2 steps); v) TBAF, THF, 0°C→RT, 92%; w) TsOH, MeOH, 0°C; x) NaH, BnBr, TBAI, DMF, 0°C→RT, 89% (2 steps); y) BF_3·OEt_2, Et_3SiH, MeCN, 0°C, 99%. DDQ = 2,3-dichloro-5,6-dicyano-1,4-benzoquinone, HMPA = hexamethylphosphoramide, MCPBA = *m*-chloroperbenzoic acid, Piv = pivaloyl, TES = triethylsilyl, TIPS = triisopropylsilyl.



Scheme 7. Reagents and conditions: a) 2,4,6-trichlorobenzoyl chloride, Et_3N, THF, 0→40 °C; DMAP, toluene, 40 °C, 92%; b) DIBAL-H, CH_2Cl_2, −78 °C; Ac_2O, DMAP, pyridine, CH_2Cl_2, −78→0 °C, 54%; c) TMSCN, TMSOTf, DTBMP, CH_2Cl_2, −78→0 °C; d) TBAF, MeCN, 70 °C, 89% (2 steps); e) KOH, ethylene glycol, 150 °C; f) 2,4,6-trichlorobenzoyl chloride, Et_3N, THF/toluene; DMAP, reflux, 37% for **9**, 33% for **49** (2 steps); g) DIBAL-H, CH_2Cl_2, −78 °C; Ac_2O, DMAP, pyridine, CH_2Cl_2, −78→0 °C, 68%; h) $CH_2{=}CHCH_2TMS$, $BF_3{\cdot}OEt_2$, 4-Å MS, MeCN, −40→−30 °C, 58%; i) **51**, CH_2Cl_2, 40 °C, 67%. Cy = cyclohexyl, DMAP = 4-dimethylaminopyridine, DTBMP = 2,6-di-*tert*-butyl-4-methylpyridine.

in 54% yield as an approximately 1:1 mixture of diastereomers. The treatment of **47** with TMSCN afforded the corresponding α-cyano ether, which was desilylated to give alcohol **10** in 89% yield (two steps). The cyano group was hydrolyzed subsequently under alkaline conditions to provide carboxylic acid **48** as a 1:1 mixture of diastereomers. Yamaguchi lactonization[22] of **48** provided a mixture of seven-membered lactones, which was separated by flash column chromatography to give **9** and **49** in 37 and 33% yield, respectively (two steps).[23] An NOE observed between C22−H and C25−H in **9** established the configuration at C25 unambiguously.

The reductive acetylation of lactone **9** produced acetate **50** in 68% yield with d.r. ≈ 10:1. The configuration at C26 of **50** was assigned tentatively on the basis of our previous model studies.[4] Upon treatment of **50** with allyltrimethylsilane in the presence of $BF_3{\cdot}OEt_2$, a stereoselective allylation occurred from the less hindered α side of the molecule to give diene **8** in 58% yield. Finally, a RCM reaction of **8** with the second-generation Grubbs catalyst **51**[24,25] resulted in the formation of the nine-membered F ring to furnish the targeted nonacyclic BCDEFGHIJ ring system **5** in 67% yield (Table 1). The stereostructure of **5** was established unequivocally by extensive NMR experiments to be that shown in Scheme 7.

Table 1: Selected physical properties of compound **5**.

$[\alpha]_D^{28} = -2.5$ ($c = 0.28$, $CHCl_3$); IR (film): $\tilde{\nu} = 2925, 2872, 1632, 1454, 1384, 1069, 739, 698\ cm^{-1}$; ^1H NMR (500 MHz, C_6D_6): $\delta = 7.69–7.56$ (m, 14H), 7.45–7.41 (m, 3H), 7.33–7.07 (m, 12H), 6.12 (ddd, $J = 11.0, 11.0, 5.0$ Hz, 1H), 5.63 (dd, $J = 10.5, 10.5$ Hz, 1H), 5.12 (d, $J = 12.5$ Hz, 1H), 4.92 (d, $J = 12.5$ Hz, 1H), 4.53–4.41 (m, 6H), 4.29 (d, $J = 12.0$ Hz, 1H), 4.24 (d, $J = 11.5$ Hz, 1H), 4.16–4.10 (m, 1H), 3.82–3.81 (m, 1H), 3.78–3.70 (m, 2H), 3.67–3.66 (m, 2H), 3.62–3.59 (m, 2H), 3.51–3.46 (m, 4H), 3.32–3.20 (m, 5H), 3.22 (dd, $J = 12.0, 3.0$ Hz, 1H), 3.00–2.98 (m, 1H), 2.92–2.89 (m, 2H), 2.34–2.12 (m, 8H), 1.94–1.53 (m, 15H), 1.32 (s, 3H), 1.28 (s, 3H), 1.22 (s, 3H), 1.20 (d, $J = 7.0$ Hz, 3H), 1.09 ppm (s, 3H); ^{13}C NMR (125 MHz, C_6D_6): $\delta = 140.2, 139.4, 139.0, 136.8, 136.5, 134.4, 133.9$ (×2), 133.5 (×2), 128.54 (×3), 128.46 (×2), 128.43 (×2), 128.3, 128.2 (×2), 128.1 (×2), 127.9 (×2), 127.80 (×3), 127.75, 127.54 (×2), 127.48, 126.43 (×2), 126.31, 126.27, 126.0 (×3), 125.9 (×2), 85.1, 85.0, 84.9, 84.7, 83.7, 83.6, 82.0, 81.4, 81.2, 79.9, 79.7, 79.2, 78.6, 77.4, 75.7, 74.6, 74.2, 74.1, 73.53 (×2), 73.48, 73.36, 73.2, 72.8, 70.9, 70.8, 70.4, 67.3, 54.5, 44.1, 35.9, 33.0, 32.9, 32.6, 32.3, 31.2, 30.7, 27.3, 24.0, 23.4, 18.3, 16.7, 16.3, 16.0, 11.2 ppm; HRMS (ESI): *m/z* calcd for $C_{85}H_{100}O_{14}Na$ $[M+Na]^+$: 1367.7113; found: 1367.7224.

In summary, we have synthesized the nonacyclic BCDEFGHIJ ring skeleton **5** of gambieric acids A and C in a convergent fashion. Our synthesis features 1) the convergent union of the BCD-and GHIJ-ring fragments through esterification; 2) the construction of the seven-membered E ring in the form of a lactone through reductive acetylation; 3) a stereoselective allylation to establish the C26 stereocenter; and 4) cyclization to form the nine-membered F ring by ring-closing metathesis. Further studies along these lines toward the total synthesis of gambieric acids A and C are in progress, the results of which will be reported in due course.

Received: November 14, 2006
Published online: February 27, 2007

Keywords: cyclization · metathesis · natural products · polyethers · total synthesis

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