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Synthesis of the J ring segment of gambieric acid

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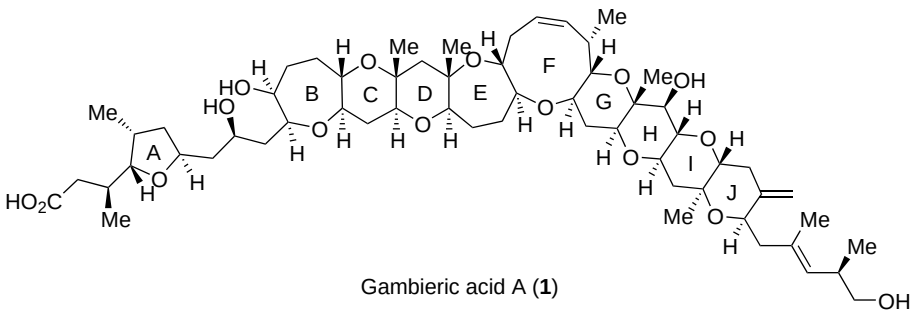
Abstract—The J ring segment **2** of gambieric acid was synthesized stereoselectively by the coupling between the cyclic ether component **3** and the alkenyl iodide **4**. The tetrahydropyran **3** was stereoselectively synthesized by the 6-*endo*-cyclization of a hydroxyepoxide prepared from deoxy-D-ribose. The side chain moiety **4** was prepared by the stereoselective hydrostannation of an internal alkyne.

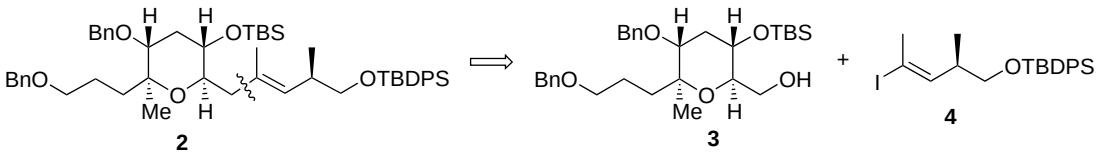
In the preceding paper,[1] we described the stereoselective synthesis of the A ring segment of gambieric acid (**1**). We now report the synthesis of the J ring segment of **1**.



Gambieric acid A (**1**)

Scheme 1 describes our synthetic strategy. The target molecule **2** is broken down to the alcohol **3** and the vinylic iodide **4**. The tetrahydropyran ring of **3** can be constructed by the stereoselective 6-*endo* cyclization of a hydroxyepoxide. The olefin **4** can be prepared by the stereoselective hydrostannation of an internal alkyne.

A Wittig reaction of the aldehyde **5**, prepared from deoxy-D-ribose by the known procedure,[2] gave the α,β-unsaturated ester **6** in 89% yield (Scheme 2). Deprotection of the TBS protective group of **6** (97%) followed by the acid catalyzed 6-*endo*-cyclization of the resulting hydroxyepoxide **7** afforded the tetrahydropyran **8** as the sole product in 78% yield.[3] Hydrogenation of the unsaturated ester **8** gave **9** in 95% yield. The ester **9** was reduced with $LiAlH_4$ to give the diol **10** in 91% yield. Protection of **10** using BnBr/KH gave the bis-benzyl ether **11** in 90% yield. The benzylidene acetal of **11** was cleaved by acidic treatment to give the diol **12** in 91% yield. Protection of **12** with TBSCl gave the bis-silyl ether **13** in 96% yield. Selective deprotection of the primary silyloxy group of **13** was carried out using a catalytic amount of CSA in CH_2Cl_2–MeOH to give the alcohol **3** in 92% yield.



Scheme 1. Retrosynthesis of the J ring segment **2**.

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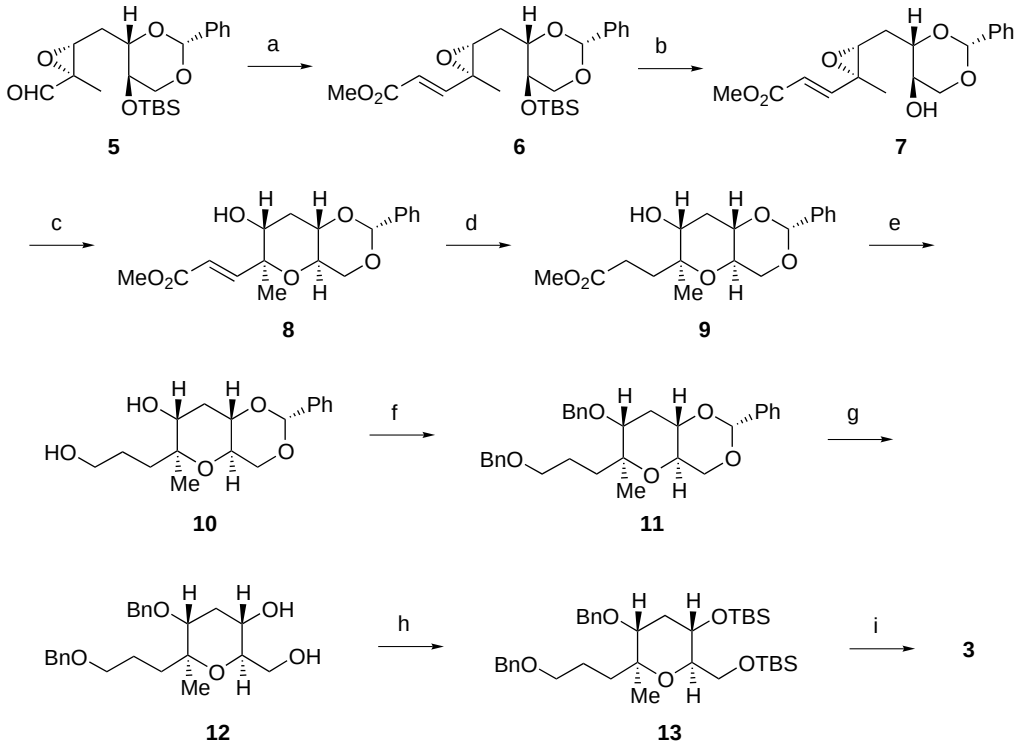
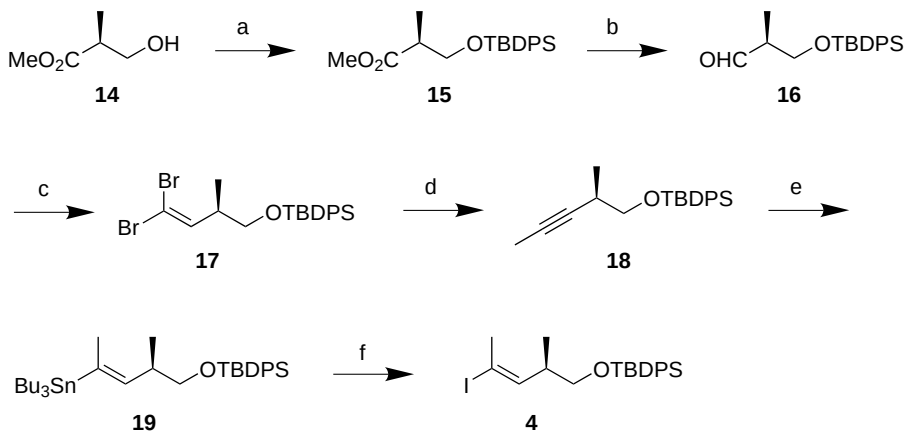


Scheme 2. (a) $Ph_3P{=}CHCO_2Me$, cat. $PhCO_2H$, benzene, rt, 89%; (b) TBAF, THF, rt, 97%; (c) cat. PPTS, CH_2Cl_2, rt, 78%; (d) H_2, cat. 5% Pd–C, MeOH, rt, 95%; (e) $LiAlH_4$, ether, 0°C, 91%; (f) BnBr, KH, THF, 0°C, 90%; (g) cat. CSA, CH_2Cl_2–MeOH, rt, 91%; (h) TBSCl, imidazole, DMF, 70°C, 96%; (i) cat. CSA, CH_2Cl_2–MeOH, 0°C, 92%.

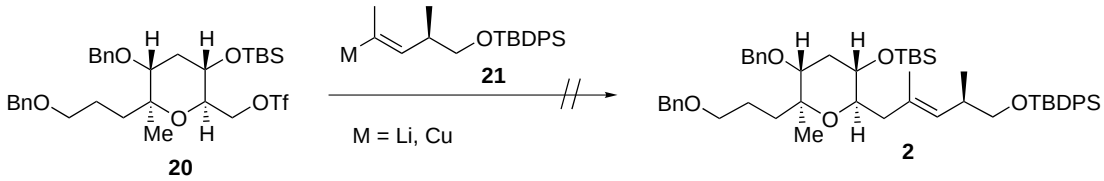
Scheme 3 summarizes the preparation of the side chain moiety **4**. Protection of the chiral alcohol **14** with TBDPSCl gave **15** in quantitative yield. Reduction of the ester **15** with DIBALH gave the aldehyde **16** in 96% yield. Dibromomethylenation of **16** was carried out with CBr_4/PPh_3 to give **17** in 90% yield. Treatment of **17** with *n*-BuLi followed by trapping with MeI gave the internal alkyne **18** in 84% yield.[4] Regio- and stereoselective hydrostannation of **18** was performed by using palladium catalyst to give the vinylsyannane **19**,[5] which was treated with iodine to give the vinyliodide **4** in 56% yield.

Next, we examined the S_N2 alkylation of the triflate **20** prepared from **3** with the vinylmetals derived from **4** according to the reported procedure (Scheme 4).[6] However, the desired coupling product **2** was not obtained from these reactions. The less nucleophilic reagents **21** acted as a base to decompose the reactive triflate **20**.

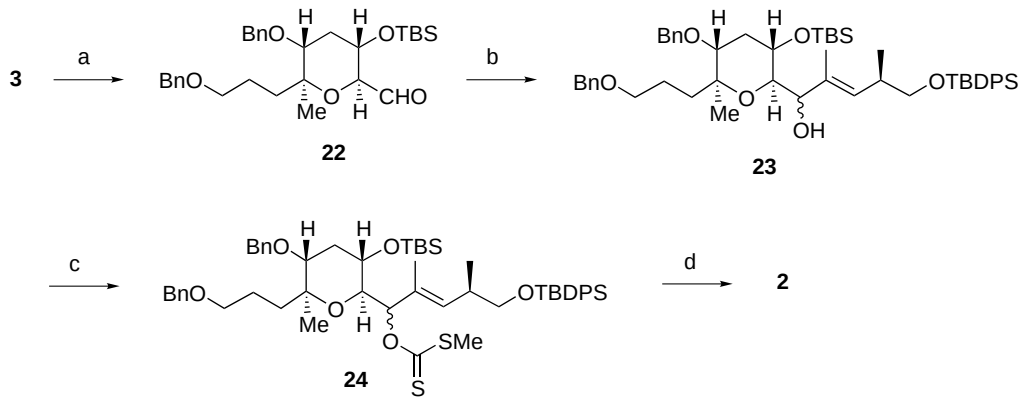
An alternative synthetic route to **2**, based on the addition of **21** to an aldehyde followed by Barton reduction,[7] is described in Scheme 5. The alcohol **3** was converted to the aldehyde **22** by Swern oxidation. Reaction of **22** with the vinyllithium reagent **21** afforded the



Scheme 3. (a) TBDPSCl, imidazole, DMF, rt, 100%.; (b) DIBALH, CH_2Cl_2, –90°C, 96%.; (c) CBr_4, PPh_3, CH_2Cl_2, 0°C, 90%; (d) *n*-BuLi, THF, –78°C; MeI, –78°C to rt, 84%; (e) Bu_3SnH, cat. $PdCl_2(PPh_3)_2$, CH_2Cl_2, rt; (f) I_2, benzene, rt, 56% from **18**.



Scheme 4.



Scheme 5. (a) $(COCl)_2$, DMSO, CH_2Cl_2, −78°C; Et_3N, −78°C to rt, 89%; (b) **4**, *t*-BuLi, ether, −78°C, 76%; (c) CS_2, KH, ether, rt; MeI, rt, 98%; (d) Bu_3SnH, cat. AIBN, benzene, reflux, 25%.

addition product **23** as a mixture of diastereoisomers in 76% yield. Treatment of **23** with CS_2/KH, followed by the reaction with MeI gave the xanthate **24** in 98% yield. Hydrogenolysis of **24** was carried out with Bu_3SnH and a catalytic amount of AIBN in refluxing benzene to give **2** in 25% yield.[8]

In conclusion, we have reported the synthesis of the A and J ring segments of gambieric acid in this and the preceding paper. Further studies toward the total synthesis of gambieric acid are in progress in our laboratories.

Acknowledgements

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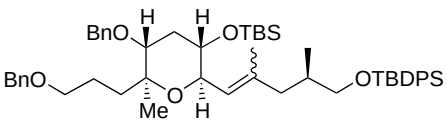
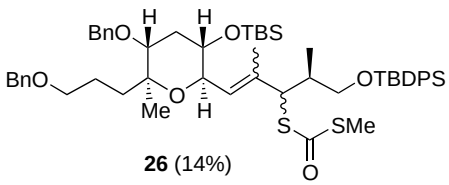
8. The reaction gave the olefinic isomers **25** (22%) and the dithiocarbonates **26** (14%) as by-products. Similar rearrangement in the hydrogenolysis of allylic xanthates has been reported, see Ref. 7.



25 (22%)



26 (14%)