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# A Concise and Stereoselective Synthesis of the A-Ring Fragment of the Gambieric Acids

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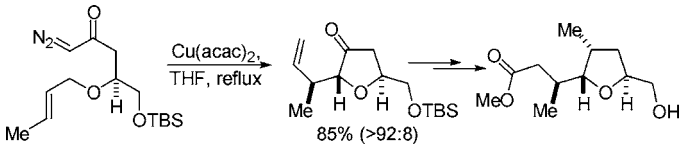
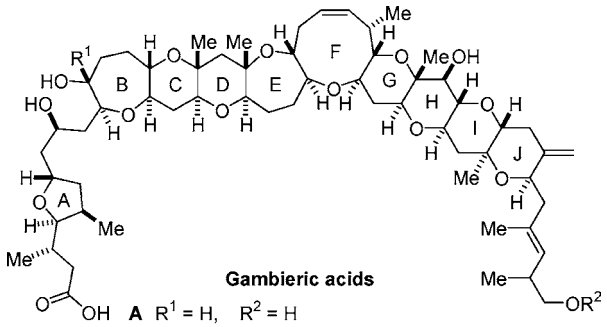
## ABSTRACT




**The A-ring fragment of the gambieric acids has been prepared by a short and efficient route. The key 3(2*H*)-furanone intermediate has been obtained by [2,3] rearrangement of an allylic oxonium ylide generated from intramolecular reaction of a crotyl ether with a copper carbenoid. A single stereogenic center has been set by using a chiral pool starting material and the other three have been established by using highly diastereoselective substrate-controlled transformations.**

The gambieric acids A−D were isolated from a culture broth of the marine dinoflagellate *Gambierdiscus toxicus*, the organism responsible for ciguatera poisoning in humans, by Yasumoto and co-workers in 1992.[1] The gambieric acids have aroused considerable interest because of their unusual polyether structure and their significant antifungal activity against a variety of filamentous fungi.[1c] The gambieric acids display considerably greater antifungal activity than amphotericin B in many assays and only moderate toxicity toward mammalian cells, making them potential lead compounds for the discovery of new antifungal agents.[1]

The gambieric acids possess an array of nine trans-fused 6-, 7-, and 9-membered cyclic ethers and a side chain bearing an isolated trisubstituted tetrahydrofuran (the A-ring unit). As part of our research program directed toward the discovery of efficient routes to the gambieric acids and related polyether natural products, we have developed a short and highly diastereoselective synthesis of the tetrahydrofuran A-ring fragment that is described herein.[2]




The retrosynthetic analysis of the key A-ring fragment **i** is shown in Scheme 1. Functional group interconversion of the methyl group and hydroxyl protection leads to the methylene tetrahydrofuran **ii** as a late synthetic intermediate. Conversion of the methylene group into a ketone and the ester group into a hydroxyl group then leads to the 3(2*H*)-furanone **iii**. Retrosynthetic dehydration of the alcohol leads

(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. (c) Nagai, H.; Mikami, Y.; Yazawa, K.; Gonoi, T.; Yasumoto, T. *J. Antibiot.* **1993**, *46*, 520. (d) Morohashi, A.; Satake, M.; Nagai, H.; Oshima, Y.; Yasumoto, T. *Tetrahedron* **2000**, *56*, 8995.

(2) For a previous synthesis of the A-ring fragment of the gambieric acids, see: Kadota, I.; Oguro, N.; Yamamoto, Y. *Tetrahedron Lett.* **2001**, *42*, 3645.

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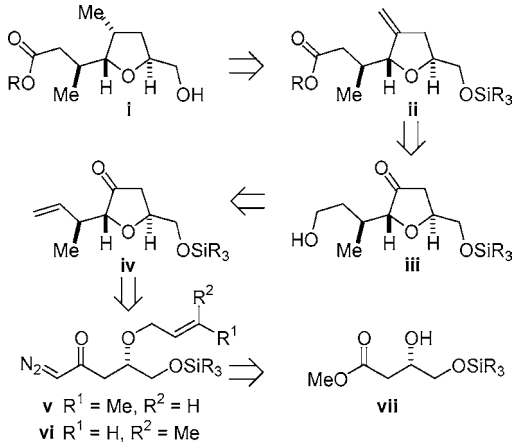
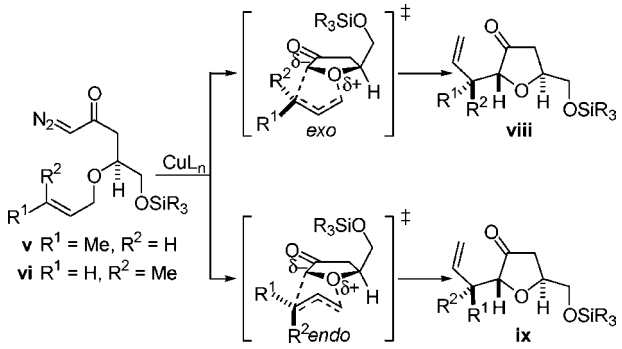
**Scheme 1**




to the alkene **iv**, the key intermediate in our route. The intermediate **iv** is then disconnected to give the diazo ketones **v**/**vi** (*vide infra*) and further functional group interconversion and cleavage of the crotyl ether gives the methyl ester **vii**, which can be obtained from (*S*)-malic acid.[3]

The key reaction in our route was to be the generation of a copper carbenoid from the diazo ketone **v**/**vi** followed by oxonium ylide formation and rearrangement, resulting in C−O and C−C bond formation with concomitant ring closure and the creation of two stereogenic centers (Scheme 2).[4,5] If the rearrangement of the ylide proceeded through

**Scheme 2**

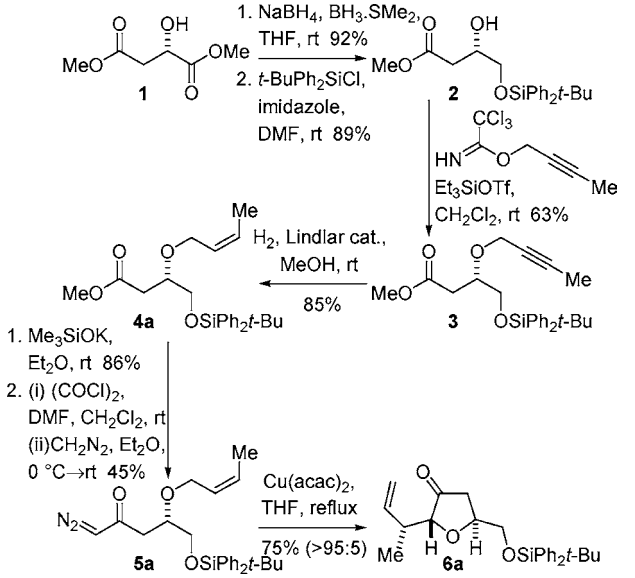



the *exo* transition state, the 3(2*H*)furanone **viii** would be obtained, whereas rearrangement through the *endo* transition state would deliver the isomeric product **ix**. Thus, to obtain the required diastereoisomer **iv**, it would be necessary for the oxonium ylide generated from the *Z*-crotyl ether to rearrange via the *exo* transition state (**vi** → **viii**) or the ylide generated from the *E*-crotyl ether to rearrange via the *endo* transition state (**v** → **ix**).

It was not possible to predict whether rearrangement of the oxonium ylide would proceed via an *exo* or *endo* transition state based on literature data.[5b,6] Consequently, we prepared both the *E*- and *Z*-crotyl ether precursors and treated each of them with copper(II) acetylacetonate to determine the stereochemical outcome of the oxonium ylide formation and [2,3] rearrangement process.

The *Z*-crotyl ether precursor was prepared from dimethyl malate (**1**), using the route shown in Scheme 3. Regioselec-

**Scheme 3**




tive directed ester reduction, using conditions first described by Moriwake and co-workers,[3] followed by selective *tert*-butyldiphenylsilyl protection of the resulting primary hydroxyl group afforded the alcohol **2**. The alcohol was then converted into the propargylic ether **3** by triethylsilyl trifluoromethanesulfonate or trifluoromethanesulfonic acid mediated reaction with butynyl 2,2,2-trichloroacetimidate,[7] and subsequent Lindlar reduction produced the *Z*-crotyl ether **4a** in a highly stereoselective manner. The *Z*-crotyl ether **4a** was transformed into the cyclization precursor **5a** by mild

(3) Saito, S.; Hasegawa, M.; Inaba, M.; Nishida, R.; Fujii, T.; Nomizu, S.; Moriwake, T. *Chem. Lett.* **1984**, 1389.

(4) (a) Clark, J. S. *Tetrahedron Lett.* **1992**, *33*, 6193. (b) Clark, J. S.; Krowiak, S. A.; Street, L. J. *Tetrahedron Lett.* **1993**, *34*, 4385. (c) Clark, J. S.; Whitlock, G. A. *Tetrahedron Lett.* **1994**, *35*, 6381. (d) Clark, J. S.; Dossetter, A. G.; Whittingham, W. G. *Tetrahedron Lett.* **1996**, *37*, 5605. (e) Clark, J. S.; Dossetter, A. G.; Blake, A. J.; Li, W.-S.; Whittingham, W. G. *Chem. Commun.* **1999**, 749. (f) Clark, J. S.; Bate, A. L.; Grinter, T. *Chem. Commun.* **2001**, 459. (g) Clark, J. S.; Whitlock, G. A.; Jiang, S.; Onyia, N. *Chem. Commun.* **2003**, 2578.

(5) (a) Pirrung, M. C.; Werner, J. A. *J. Am. Chem. Soc.* **1986**, *108*, 6060. (b) Roskamp, E. J.; Johnson, C. R. *J. Am. Chem. Soc.* **1986**, *108*, 6062. (c) Eberlein, T. H.; West, F. G.; Tester, R. W. *J. Org. Chem.* **1992**, *57*, 3479. (d) West, F. G.; Eberlein, T. H.; Tester, R. W. *J. Chem. Soc., Perkin Trans. 1* **1993**, 2857. (e) West, F. G.; Naidu, B. N.; Tester, R. W. *J. Org. Chem.* **1994**, *59*, 6892. (f) Tester, R. W.; West, F. G. *Tetrahedron Lett.* **1998**, *39*, 4631. (g) Marmsater, F. P.; West, F. G. *J. Am. Chem. Soc.* **2001**, *123*, 5144. (h) Marmsater, F. P.; Vanecko, J. A.; West, F. G. *Tetrahedron* **2002**, *58*, 2027.

(6) Doyle, M. P.; McKervey, M.; Ye, T. *Modern Catalytic Methods with Diazo Compounds*; Wiley: New York, 1998; Chapter 7, pp 355−432.

(7) (a) Overman, L. E.; Clizbe, L. A. *J. Am. Chem. Soc.* **1976**, *98*, 2352. (b) Wei, S.-Y.; Tomooka, K.; Nakai, T. *J. Org. Chem.* **1991**, *56*, 5973. (c) Wei, S.-Y.; Tomooka, K.; Nakai, T. *Tetrahedron* **1993**, *49*, 1025.

ester cleavage using potassium trimethylsilanolate,[8] conversion of the resulting carboxylic acid into the corresponding acid chloride, and then reaction with diazomethane. Treatment of the diazo ketone **5a** with copper(II) acetylacetonate in THF at reflux afforded the required 3(2*H*)-furanone **6a** in 75% yield and with an excellent level of diastereocontrol (>95:5). Only two of the four possible diastereoisomers were obtained, and neither of the *cis*-3(2*H*)-furanone diastereoisomers was produced.

The 3(2*H*)-furanone **6a** was a solid compound and crystals suitable for X-ray analysis were obtained (Figure 1).[9,10] The X-ray data revealed that the relative stereochemistry of the major isomer is that shown in Scheme 3 (i.e., the product with incorrect configuration at the methyl-bearing carbon had been obtained) and established that [2,3] rearrangement had occurred via the *endo* transition state.

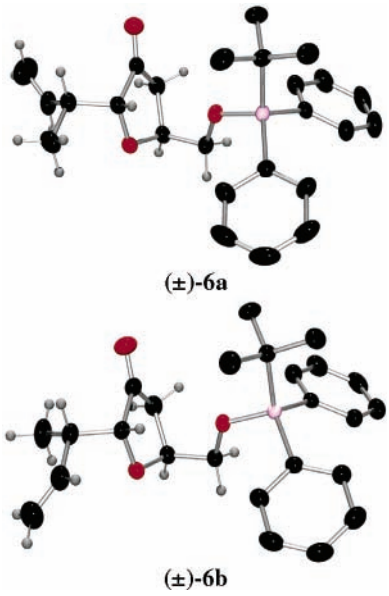
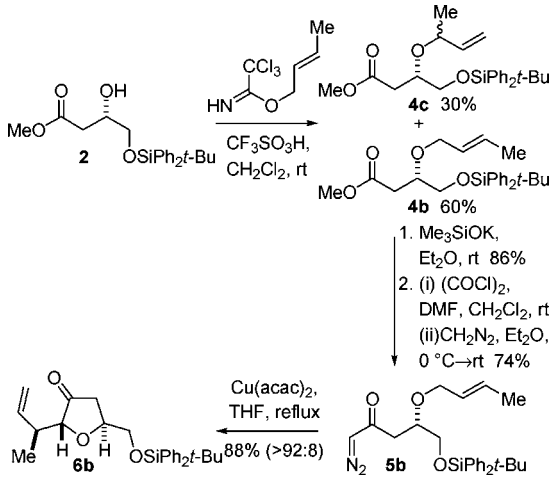



**Figure 1.** X-ray structures (displacement elipsoid plot drawn at the 50% probability level) of 3(2*H*)-furanones **(**±**)-6a** and **(**±**)-6b** (H atoms on the *tert*-butyldiphenylsilyl group removed for clarity).

The synthesis of the corresponding *E*-crotyl ether cyclization precursor was also undertaken. The alcohol **2** was treated with *E*-crotyl 2,2,2-trichloroacetimidate[11] in the presence of trifluoromethanesulfonic acid to give a separable mixture of the required ether **4b** and the isomeric ether **4c** (the $S_N2'$ displacement product) with the former predominating. The ester **4b** was converted into the cyclization precursor **5b** by using the same ester cleavage and diazo ketone formation procedure that was employed to obtain the isomeric compound **5a**. Treatment of the diazo ketone **5b** with copper(II) acetylacetonate in THF at reflux afforded the required 3(2*H*)-furanone **6a** in 88% yield and with excellent diastereoselectivity (>92:8).[12] Once again, two of the four possible diastereomeric products were isolated and neither of the possible *cis*-3(2*H*)-furanone diastereoisomers was obtained from the reaction. The 3(2*H*)-furanone **6b** was a solid and X-ray analysis[9] (Figure 1) revealed the relative stereochemistry of the major isomer to be that shown in Scheme 4 (i.e., the required configuration at the methyl-bearing carbon had been obtained), confirming that [2,3] rearrangement had occurred via the *endo* transition state.

**Scheme 4**




The synthesis of the A-ring fragment was then completed by the sequence shown in Scheme 5. Regioselective hydroboration of the alkene was accomplished by using excess dicyclohexylborane, a reaction that proceeded with concomitant ketone reduction. Subsequent oxidation with excess PDC then delivered the keto acid **7** in reasonable yield. Esterification to give either the methyl or *tert*-butyl ester followed by ketone methylenation with the Nysted reagent[13] and titanium(IV) chloride then afforded the methylene tetrahydrofurans **8** and **9**. Attempted hydrogenation of the alkene with use of palladium on carbon resulted in a complex mixture of isomeric products. Further investigation of the reaction suggested that competitive isomerization of the allylic ether was occurring to give the corresponding dihydrofuran and this compound then underwent hydrogenation to give a mixture of products.[14]

(8) Laganis, E. D.; Chenard, B. L. *Tetrahedron Lett.* **1984**, *51*, 5831.

(9) The crystals used for X-ray analysis were obtained by recrystallization of racemic material.

(10) The crystallographic data (excluding structure factors) for the compounds (±)-**6a** and (±)-**6b** have been deposited (**6a** CCDC 226336; **6b** CCDC 226337) with the Cambridge Crystallographic Data Centre. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge, CB2 1EZ, UK [fax +44(0) 1223 336033; e-mail deposit@ccdc.cam.ac.uk].

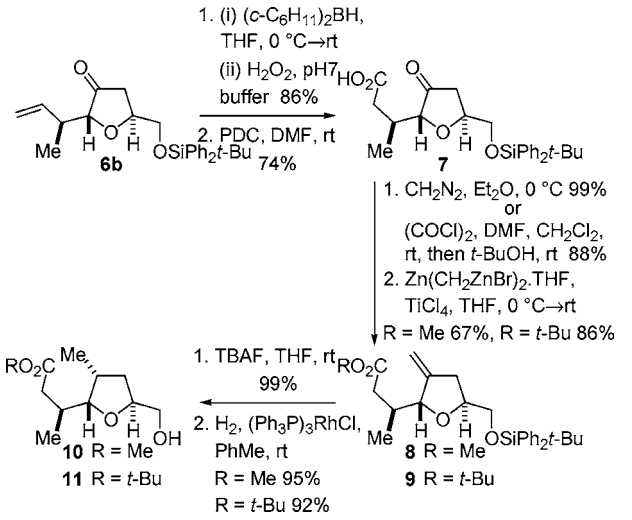
(11) (a) Overman, L. E. *J. Am. Chem. Soc.* **1976**, *98*, 2901. (b) Patil, V. J. *Tetrahedron Lett.* **1996**, *37*, 1481. (c) Maleczka, R. E., Jr.; Geng, F. *Org. Lett.* **1999**, *1*, 1111.

(12) The *E*-crotyl alcohol used to prepare the *E*-crotyl 2,2,2-trichloroacetimidate contained a small amount (5−8%) of *Z*-crotyl alcohol, and so the level of stereocontrol during rearrangement of the oxonium ylide is actually greater than that reflected by the isomer ratio in this case.

(13) Matsubara, S.; Sugihara, M.; Utimoto, K. *Synlett* **1998**, 313.

(14) Bueno, J. M.; Coterón, J. M.; Chiara, J. L.; Fernández-Mayoralas, A.; Fiandor, J. M.; Valle, N. *Tetrahedron Lett.* **2000**, *41*, 4379.

**Scheme 5**




To circumvent the isomerization problem, we removed the silicon protecting group from the esters **8** and **9** and then performed hydroxyl-directed hydrogenation using Wilkinson's catalyst. In both cases, the reaction delivered the gambieric acid A-ring fragment **10**/**11** as a single isomer in good yield.[15]

In summary, we have constructed the A-ring fragment of the gambieric acids by a novel and efficient 12-step route from (*S*)-dimethylmalate. In this sequence, one stereogenic center has been obtained from the chiral pool and the other three centers have been introduced by using highly diastereoselective substrate-controlled reactions. Stereoselective ring formation has been accomplished by tandem catalytic carbenoid generation, ylide formation, and [2,3] rearrangement.

Coupling of the A-ring fragment and further synthetic endeavors toward the gambieric acids are in progress and will be reported in due course.

**Acknowledgment.** We thank the EPSRC and University of Nottingham for financial support.

**Supporting Information Available:** Experimental procedures along with spectroscopic and other data for compounds **6a**, **6b**, and **7**−**11**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(15) The stereochemical outcome of the hydrogenation reaction was confirmed by comparison of $^1$H NMR chemical shift and coupling constant data for the alcohols **10** and **11** with that of the natural product (ref 1).