ORGANIC LETTERS

2001
Vol. 3, No. 18
2919−2922

C-Glycosides to Fused Polycyclic Ethers. An Efficient Entry into the A–D Ring System of Gambierol

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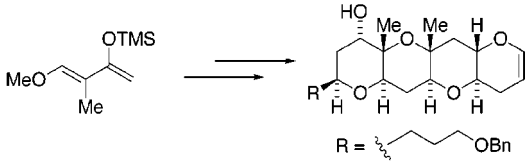
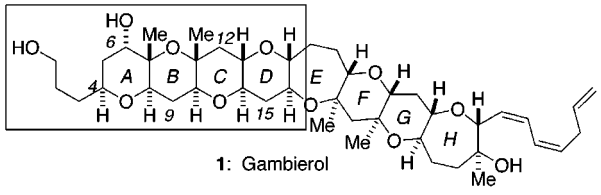
Received July 13, 2001

ABSTRACT



This Letter describes our use of C-glycosides to synthesize the A–D ring system of the marine ladder toxin gambierol in 20 steps.

Gambierol was isolated in 1993 by Yasumoto and co-workers as part of a screening study to determine the causative agent of ciguatera poisoning from the marine dinoflagellate *Gambierdiscus toxicus*.[1] As part of this initial study, the Yasumoto group determined gambierol's relative configuration; in subsequent experiments, they elucidated its absolute structure.[2]



1: Gambierol

Not surprisingly, gambierol's polycyclic ether architecture and its intriguing biological activity has attracted the interest of a number of synthetic chemists. Thus far, this attention has led to the generation of the A−B, C−G, and E−H ring systems by Yamamoto[3] and the synthesis of the F−H ring system by Sasaki.[4]

As part of our program utilizing C-glycosides in the synthesis of polycyclic ether containing natural products, we have also become interested in the synthesis of gambierol. Retrosynthetically, we envisioned that gambierol's octacyclic framework could be constructed from the coupling of a tetracyclic A−D subunit with a tricyclic F−H subunit. In turn, we were confident that each of these fragments could be constructed in a linear fashion using a strategy that would be similar to the one that we had employed in our formal synthesis of (±)-hemibrevetoxin B.[5] Outlined herein is the partial achievement of these goals through the synthesis of the gambierol A−D ring system.

From our perspective, the A−D subunit presented several challenging stereochemical problems, of which the most noteworthy involved the selective incorporation of the C-7 and C-11 stereocenters where the angular methyl groups were in a 1,3-diaxial orientation to one another.[6] We were hopeful that our ability to generate C-glycosides having either cis or trans stereochemistry relative to the adjacent alcohol would enable us to overcome these challenges.[7]

(1) Satake, M.; Murata, M.; Yasumoto, T. *J. Am. Chem. Soc.* **1993**, *115*, 361.

(2) Morohashi, A.; Satake, M.; Yasumoto, T. *Tetrahedron Lett.* **1999**, *40*, 97.

(3) Kadota, I.; Park, C.-H.; Ohtaka, M.; Oguro, N.; Yamamoto, Y. *Tetrahedron Lett.* **1998**, *39*, 6365. (b) Kadota, I.; Kadowaki, C.; Yoshida, N.; Yamamoto, Y. *Tetrahedron Lett.* **1998**, *39*, 6369. (c) Kadota, I.; Ohno, A.; Matsukawa, Y.; Yamamoto, Y. *Tetrahedron Lett.* **1998**, *39*, 6373. (d) Kadowaki, C.; Chan, P. W. H.; Kadota, I.; Yamamoto, Y. *Tetrahedron Lett.* **2000**, *41*, 5769. (e) Kadota, I.; Ohno, A.; Matsuda, K.; Yamamoto, Y. *J. Am. Chem. Soc.* **2001**, *123*, 6702.

(4) Fuwa, H.; Sasaki, M.; Tachibana, K. *Tetrahedron Lett.* **2000**, *41*, 8371. (b) Fuwa, H.; Sasaki, M.; Tachibana, K. *Tetrahedron* **2000**, *57*, 3019.

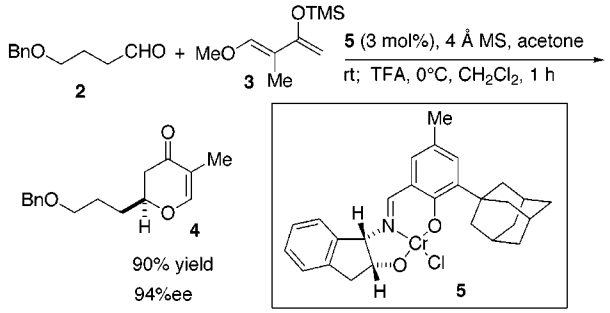
(5) Rainier, J. D.; Allwein, S. P.; Cox, J. M. *J. Org. Chem.* **2001**, *66*, 1380.

(6) Sasaki and Yamamoto have employed somewhat circuitous routes to the similarly substituted gambierol F,G-ring system. See refs 3d and 4.

10.1021/ol016434w CCC: $20.00
Published on Web 08/08/2001

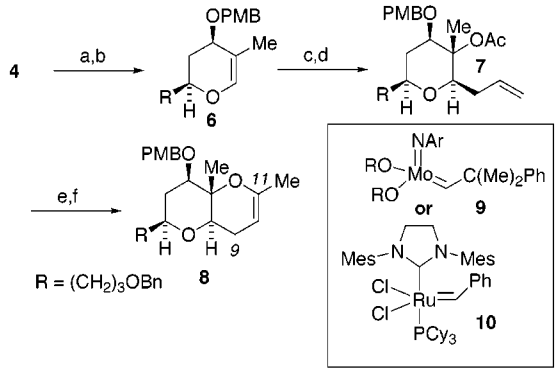
Our efforts toward the gambierol A−D subunit began with the synthesis of the dihydropyran A-ring using a hetero-Diels−Alder cycloaddition reaction between aldehyde **2**[8] and diene **3**.[9] Because of its success in catalyzing the analogous reaction between Danishefsky's diene and **2**,[8] our initial experiments examined Keck's titanium BINOL protocol.[10] Surprisingly, when diene **3** was subjected to **2**, BINOL, and Ti(O*i*-Pr)$_4$, no reaction was observed.[11] Although other Lewis acid/BINOL complexes gave moderate yields of cycloadduct, the cycloadduct was formed racemically or in low enantiomeric excess.[12]

With the failure of the BINOL complexes to catalyze the asymmetric reaction between **2** and **3**, we turned to Jacobsen's tridentate Cr(III) catalyst **5**.[13] Although **5** had not been subjected to **3** prior to our work, this catalyst had performed remarkably well with other substituted dienes. To our delight, **5** catalyzed the reaction between **2** and **3** to give cycloadduct **4** in both high yield and high enantiomeric excess (eq 1).[14,15]



With an efficient entry into pyrone **4**, we set out to convert it into the gambierol A,B-dihydropyran **8** (Scheme 1). 1,2-

Scheme 1[a]



[a] (a) $NaBH_4$, $CeCl_3 \cdot 7H_2O$, EtOH, −60 °C to rt; (b) PMBCl, NaH, DMF, 0 °C to rt (95%, 2 steps); (c) DMDO, CH_2Cl_2, −60 °C to rt; CH_2CHCH_2MgCl, THF (65%); (d) Ac_2O, *i*-Pr_2NEt, DMAP, CH_2Cl_2 (78%); (e) $TiCl_4$, Zn, $PbCl_2$, TMEDA, CH_2Br_2, TMEDA, THF; (f) **10** (20 mol %), rt, 16 h (65%, 2 steps).

Reduction of the carbonyl in **4** using Luche's conditions[16] gave **6** after PMB ether formation. Although **6** is epimeric at C-6 relative to gambierol, we were confident that a subsequent Mitsunobu inversion would enable us to access the correct C-6 diastereomer. Moreover, we were hopeful that the C-6 stereocenter could be used to control the facial selectivity in the subsequent reaction of **6** with dimethyl dioxirane.[17]

Fortunately, we had the opportunity to test this latter notion immediately. Exposure of **6** to dimethyldioxirane[18] followed by propenylmagnesium chloride[19] resulted in the generation of **7** after acylation of the newly formed 3° hydroxyl group. As we had hoped-for, the C-3 alkoxy substituent had controlled the facial selectivity in the oxidation reaction; anti addition to the glycal anhydride had resulted in the desired stereochemistry at C-8.

Having established the gambierol A-ring, we investigated the synthesis of the B-ring using an enol ether-olefin ring closing metathesis (RCM) protocol.[20] As in our previous work, Takai's procedure was utilized to generate the acyclic enol ether from **7**.[21] Both the Schrock Mo alkylidene **9**[22] and the 2nd generation Grubbs Ru alkylidene **10**[23] catalyzed the conversion of the acyclic enol ether into the cyclic enol ether **8**.

With ready access to **8**, we were in a position to examine the use of our C-glycoside forming technology in the formation of the critical C-11 stereocenter. Unfortunately, the addition of allyl nucleophiles to the epoxide from **8** resulted in either the exclusive formation of the undesired C-11 diastereomer or in the formation of mixtures at C-11.[24]

Our inability to selectively generate the gambierol C-11 stereocenter forced us to consider other methods for its preparation. It occurred to us that a solution to our problem might come from the use of a Claisen rearrangement from a C-10 allyl enol ether. This strategy was appealing not only because of the likelihood that the C-7 angular methyl would direct the stereoselectivity in the rearrangement in the desired sense but also because of the possibility that we could generate the rearrangement precursor by simply subjecting a bicyclic ketal precursor to an acid-catalyzed elimination reaction.[25]

To generate the precursor to the Claisen rearrangement, we subjected glycal **8** to *m*-CPBA in MeOH. This resulted in the formation of the corresponding hydroxy ketal as an inconsequential 2:1 mixture of anomers in a 92% overall yield. Allyl ether formation then provided rearrangement

(7) Rainier, J. D.; Cox, J. M. *Org. Lett.* **2000**, *2*, 2707.

(8) McDonald, F. E.; Vadapally, P. *Tetrahedron Lett.* **1999**, *40*, 2235.

(9) Miyashita, M.; Yamasaki, T.; Shiratani, T.; Hatakeyama, S.; Miyazawa, M.; Irie, H. *Chem. Commun.* **1997**, 1787. (b) Barrett, A. G. M.; Carr, R. A. E.; Attwood, S. V.; Richardson, G.; Walshe, N. D. A. *J. Org. Chem.* **1986**, *51*, 4840.

(10) Keck, G. E.; Li, X.-Y.; Krishnamurthy, D. *J. Org. Chem.* **1995**, *60*, 5998.

(11) The analogous cycloaddition reaction between Danishefsky's diene and **2** proceeds in 95% ee and 65% yield. See ref 8.

(12) We examined the use of BINOL with $AlMe_3$ and $B(OPh)_3$.

(13) Dossetter, A. G.; Jamison, T. F.; Jacobsen, E. N. *Angew. Chem., Int. Ed.* **1999**, *38*, 2398.

(14) Compound **4** is enantiomeric to that expected on the basis of Jacobsen's results. See ref 13.

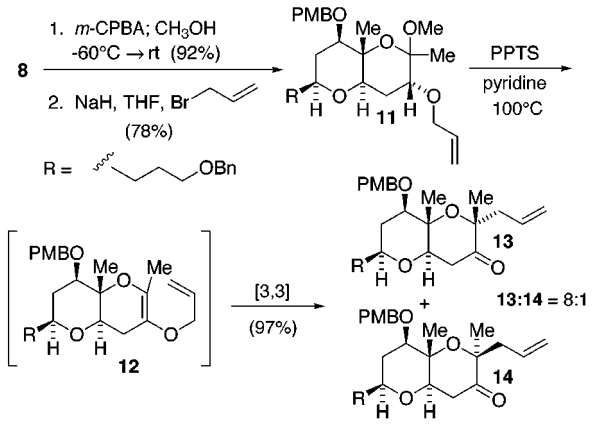
(15) The enantiomeric excess of **4** was determined using a chiracel OD HPLC column.

(16) Gemal, A. L.; Luche, J.-L. *J. Am. Chem. Soc.* **1981**, *103*, 5454.

(17) Halcomb, R. L.; Danishefsky, S. J. *J. Am. Chem. Soc.* **1989**, *111*, 6661.

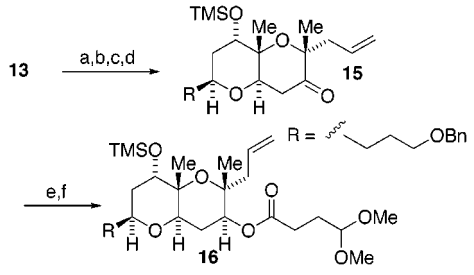
precursor **11**. When **11** was exposed to PPTS and pyridine in $PhCH_3$ we isolated an 8:1 mixture of C-glycosides **13** and **14** in 97% yield. As predicted, the major isomer from the rearrangement (i.e., **13**) had the desired C-11 stereochemistry.[26] Although it was not isolated, we presume that the reaction proceeded through allyl enol ether intermediate **12** and a subsequent Claisen rearrangement.[27]

Scheme 2



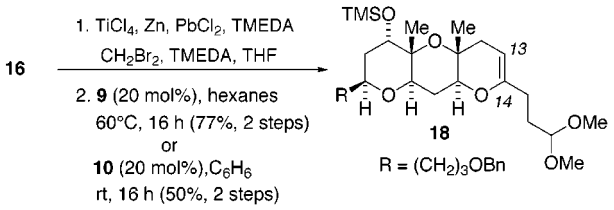
With an efficient approach to **13**, we were prepared to examine the inversion of the C-6 stereocenter. Oxidative hydrolysis of the PMB ether and inversion of the resulting 2° alcohol using Martin's Mitsunobu protocol[28] gave **15** having the desired gambierol stereochemistry at C-6 after TMS ether formation.[29] Reduction of the C-10 ketone to the desired equatorial alcohol[30] was followed by esterification with **17** to give RCM precursor **16**.

Scheme 3[a]

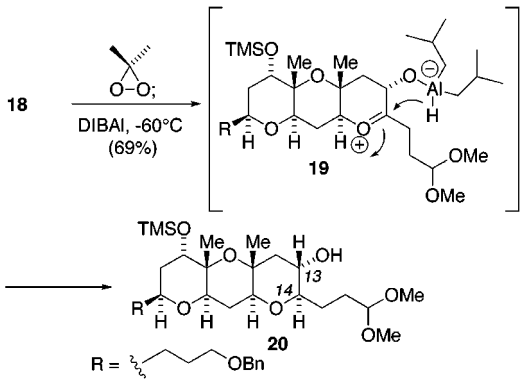


[a] (a) DDQ, CH_2Cl_2, H_2O (93%); (b) DEAD, PPh_3, *p*-$NO_2C_6H_4$-CO_2H $PhCH_3$, 110 °C; (c) NaOH, H_2O, THF, MeOH (70%, 2 steps); (d) TMSOTf, *i*-Pr_2NEt, CH_2Cl_2 (87%); (e) $NaBH_4$, EtOH; (f) DCC, DMAP, $(MeO)_2CH(CH_2)_2CO_2H$ (**17**), CH_2Cl_2 (91%, 2 steps).

As in the conversion of **7** into **8**, acyclic enol ether formation using the Takai protocol was followed by enol ether−olefin RCM to give tricyclic enol ether **18**. While both the Schrock Mo catalyst **9** and the Grubbs Ru catalyst **10** could be used to generate **18**, the Schrock catalyst provided a significantly higher yield.

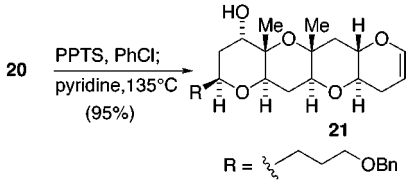


Our next challenge was to establish the C-13 and C-14 stereochemistry. Assuming that the epoxidation of **18** with dimethyl dioxirane would occur from the face opposite the C-11 angular methyl group, our plan was to establish the C-13 stereocenter through the use of a subsequent reduction reaction. In this context, we were hopeful that the epoxide oxygen could be used to deliver hydride to an oxocarbenium ion at C-14.[31] In the event, exposure of tricyclic glycal **18** to dimethyl dioxirane followed by DIBAl resulted in the formation of the desired alcohol **20** in 69% yield. As illustrated (eq 3), we presume that the **18** → **20** transformation occurs through the intermediacy of oxocarbenium ion **19** and the intramolecular delivery of hydride.



To complete our synthesis of the A−D subunit of gambierol, it remained to convert **20** into **21**. Exposure of **20** to PPTS, pyridine, and heat resulted in the formation of **21** in 95% yield.[25]

Of note is the fact that the conversion of the functionalized A,B ring system (i.e., **16**) into the A−D tetracycle **21** required only four transformations. From our perspective, this demonstrates the efficiency with which C-glycosides can be used in the synthesis of fused polycyclic ethers.



To conclude, this Letter has described the use of C-glycosides in the formation of the A−D tetracyclic subunit

(18) Adam, W.; Bialas, J.; Hadjiarapoglou, L. *Chem. Ber.* **1991**, *124*, 2377.

of the marine ladder toxin gambierol in 20 synthetic transformations from diene **3**. In addition to the successful application of our previously reported strategies to fused polycyclic ethers, we have also found a unique Claisen rearrangement approach to C-glycosides. We are continuing our efforts in each of these areas.

Acknowledgment. We gratefully acknowledge the National Institutes of Health (GM56677), Research Corporation, and Gencorp for support of this work. We would like to thank Professor Michael P. Doyle for the use of his HPLC and Professor Doyle and Professor Dominic McGrath for the use of their polarimeters. The authors would also like to thank Dr. Arpad Somagyi and Dr. Neil Jacobsen for help with mass spectra and NMR experiments, respectively.

Supporting Information Available: Experimental procedures and spectroscopic data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(19) For the addition of propenylmagnesium chloride to glycal epoxides, see: (a) Best, W. M.; Ferro, V.; Harle, J.; Stick, R. V.; Tilbrook, D. M. G. *Aust. J. Chem.* **1997**, *50*, 463. (b) Evans, D. A.; Trotter, B. W.; Côté, B. *Tetrahedron Lett.* **1998**, *39*, 1709. (c) Rainier, J. D.; Allwein, S. P. *J. Org. Chem.* **1998**, *63*, 5310.

(20) For recent reviews on RCM, see: (a) Fürstner, A. *Angew. Chem., Int. Ed.* **2000**, *39*, 3012. (b) Grubbs, R. H.; Chang, S. *Tetrahedron* **1998**, *54*, 4413.

(21) Takai, K.; Kakiuchi, T.; Kataoka, Y.; Utimoto, K. *J. Org. Chem.* **1994**, *59*, 2668.

(22) Schrock, R. R.; Murdzek, J. S.; Bazan, G. C.; Robbins, J.; DiMare, M.; O'Regan, M. B. *J. Am. Chem. Soc.* **1990**, *112*, 3875. (b) Fujimura, O.; Fu, G. C.; Grubbs, R. H. *J. Org. Chem.* **1994**, *59*, 4029.

(23) Scholl, M.; Ding, S.; Lee, C. W.; Grubbs, R. H. *Org. Lett.* **1999**, *1*, 953. (b) Chatterjee, A. K.; Morgan, J. P.; Scholl, M.; Grubbs, R. H. *J. Am. Chem. Soc.* **2000**, *122*, 3783. (c) Rainier, J. D.; Cox, J. M.; Allwein, S. P. *Tetrahedron Lett.* **2001**, *42*, 179.

(24) The use of propenylmagnesium chloride resulted in the selective formation of the undesired β-C-allyl glycoside, whereas the use of triallyl aluminum and triallyl borane resulted in the formation of 1.5:1 and 1:1.5 mixtures of α- and β-C-allyl glycosides, respectively.

(25) Rainier, J. D.; Allwein, S. P. *Tetrahedron Lett.* **1998**, *39*, 9601.

(26) Determined from NOE experiments. See Supporting Information

(27) To the best of our knowledge, this is the first example of this reaction. For related Claisen rearrangements to C-glycosides, see: (a) Vidal, T.; Haudrechy, A.; Langlois, Y. *Tetrahedron Lett.* **1999**, *40*, 5677. (b) Wallace, G. A.; Scott, R. W.; Heathcock, C. H. *J. Org. Chem.* **2000**, *65*, 4145 and references therein.

(28) Martin, S. F.; Dodge, J. A. *Tetrahedron Lett.* **1991**, *32*, 3017.

(29) The relative stereochemistry was established through the use of extensive NOE experiments. The absolute stereochemistry was established through the conversion of **13** into the corresponding C-6 Mosher's esters and using the Kakisawa method for determining the absolute stereochemistry. See ref 2 and Ohtani, I.; Kusumi, T.; Kashman, Y.; Kakisawa, H. *J. Am. Chem. Soc.* **1991**, *113*, 4092.

(30) The selectivity in the $NaBH_4$ reduction of the C-10 ketone is expected on the basis of axial attack on the ketone and from the side opposite the C-7 angular methyl group. For a discussion of related reductions in cyclohexanones, see: Eliel, E. L.; Wilen, S. H.; Mander, L. N. *Stereochemistry of Organic Compounds*; Wiley: New York, 1994; pp 734−735.

(31) Murai has carried out a related reaction. See: Fujiwara, K.; Awakura, D.; Tsunashima, M.; Nakamura, A.; Honma, T.; Murai, A. *J. Org. Chem.* **1999**, *64*, 2616.