Concise Synthesis of Cyclic Ethers via the Palladium-Catalyzed Coupling of Ketene Acetal Triflates and Organozinc Reagents. Application to the Iterative Synthesis of Polycyclic Ethers

Isao Kadota,† Hiroyoshi Takamura, Kumi Sato, and Yoshinori Yamamoto*

Research Center for Sustainable Materials Engineering, Institute of Multidisciplinary Research for Advanced Materials, and Department of Chemistry, Graduate School of Science, Tohoku University, Sendai 980-8578, Japan

yoshi@yamamoto1.chem.tohoku.ac.jp

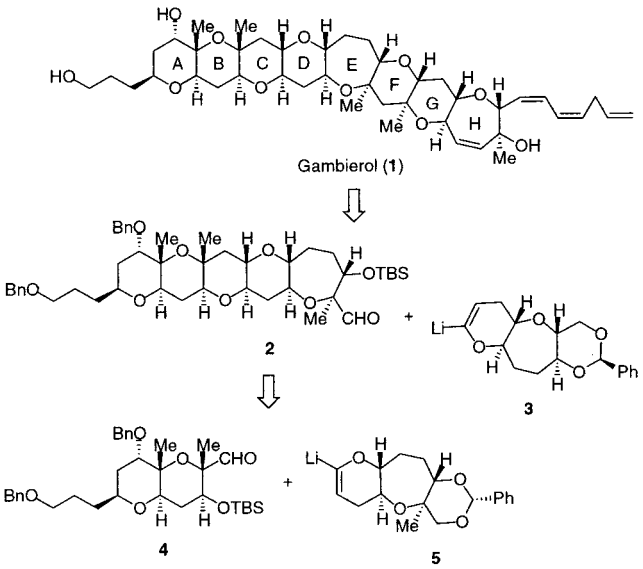
Received January 30, 2002

The reaction of the ketene acetal triflates **9a**−**e** and a zinc homoenolate **10** in the presence of a catalytic amount of $Pd(PPh_3)_4$ gave the enol ethers **11a**−**e** in good yields. The products were converted to the corresponding cyclic ethers **14a** and **14b** by hydroboration and lactonization. The present methodology allowed us to synthesize the DE and GH ring segment of gambierol in a concise manner. Iterative syntheses of the polycyclic ethers **26** and **32** are also described.

Introduction

In recent years there has been an explosion of interest in biologically active natural products of marine origin.[1] Because of their structural novelty and toxicity, polycyclic ethers are particularly attractive targets for synthetic chemists.[2] Gambierol (**1**), a potent neurotoxin isolated from the cultured cells of *Gambierdiscus toxicus*, has 8 ether rings and 18 stereogenic centers.[3] The compound shows toxicity against mice (LD_{50} 50 μg/kg), and the symptoms resemble those caused by ciguatoxins, inferring the possibility that it is also implicated in ciguatera poisoning.[1] The unique structural features have attracted the attention of synthetic chemists, and a number of strategies have been investigated.[4] Scheme 1 illustrates our initial synthetic approach toward **1**. Retrosynthetic disassembly of the target molecule **1** based on the vinyllithium−aldehyde condensation followed by Barton deoxygenation afforded **2** and **3**.[5] The ABCDE ring segment **2** would be synthesized from **4** and **5** by the same methodology. On the basis of this analysis, we synthesized the GH ring segment **8**, precursor of **3**, as shown in Scheme 2. The intramolecular reaction of **6**, prepared from 2-deoxy-D-ribose in 12 steps, mediated by $BF_3{\cdot}OEt_2$ gave **7** as the sole product in quantitative yield.[4c] The product **7** was converted to **8** by a four-step sequence including ozonolysis, Wittig reaction, hydrogenation, and lactonization.[4l] Although the GH ring segment **8** was obtained in a highly stereoselective manner, the synthesis was not particularly efficient because of the relatively long synthetic schemes (total 17 steps). This problem prompted us to develop a new synthetic route. Here we report an efficient and concise synthesis of medium sized cyclic ethers via the palladium-catalyzed coupling of ketene acetal triflates and organozinc reagents.[6,7]

Scheme 1. Retrosynthetic Analysis of Gambierol (1)



† Institute of Multidisciplinary Research for Advanced Materials.

(1) For recent reviews, see: (a) Shimizu, Y. *Chem. Rev.* **1993**, *93*, 1685−1698. (b) Yasumoto, T.; Murata, M. *Chem. Rev.* **1993**, *93*, 1897−1909.

(2) For recent reviews, see: (a) Alvarez, E.; Candenas, M.-L.; Pérez, R.; Ravelo, J. L.; Martín, J. D. *Chem. Rev.* **1995**, *95*, 1953−1980. (b) Nicolaou, K. C. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 589−607. (c) Mori, Y. *Chem. Eur. J.* **1997**, *3*, 849−852. Also see: (d) Hoberg, J. O. *Tetrahedron* **1998**, *54*, 12630−12670.

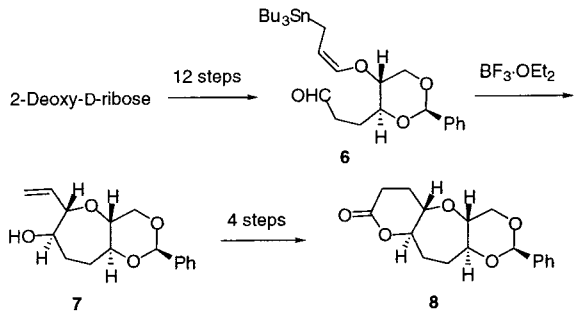
(3) (a) Satake, M.; Murata, M.; Yasumoto, T. *J. Am. Chem. Soc.* **1993**, *115*, 361−362. (b) Morohashi, A.; Satake, M.; Yasumoto, T. *Tetrahedron Lett.* **1999**, *39*, 97−100.

(4) (a) Kadota, I.; Park, C.-H.; Ohtaka, M.; Oguro, N. Yamamoto, Y. *Tetrahedron Lett.* **1998**, *39*, 6365−6368. (b) Kadota, I.; Kadowaki, C.; Yoshida, N. Yamamoto, Y. *Tetrahedron Lett.* **1998**, *39*, 6369−6372. (c) Kadota, I.; Ohno, A.; Matsukawa, Y.; Yamamoto, Y. *Tetrahedron Lett.* **1998**, *39*, 6373−6376. (d) Kadowaki, C.; Philip, W. H. C.; Kadota, I.; Yamamoto, Y. *Tetrahedron Lett.* **2000**, *41*, 5769−5772. (e) Fuwa, H.; Sasaki, M.; Tachibana, K. *Tetrahedron Lett.* **2000**, *41*, 8371−8375. (f) Kadota, I.; Takamura, H.; Sato, K.; Yamamoto, Y. *Tetrahedron Lett.* **2001**, *42*, 4729−4731. (g) Kadota, I.; Ohno, A.; Matsuda, K.; Yamamoto, Y. *J. Am. Chem. Soc.* **2001**, *123*, 6702−6703. (h) Sakamoto, Y.; Matsuo, G.; Matukura, H.; Nakata, T. *Org. Lett.* **2001**, *3*, 2749−2752. (i) Cox, J. M.; Rainier, J. D. *Org. Lett.* **2001**, *3*, 2919−2922. (j) Fuwa, H.; Sasaki, M.; Tachibana, K. *Tetrahedron* **2001**, *57*, 3019−3033. (k) Fuwa, H.; Sasaki, M.; Tachibana, K. *Org. Lett.* **2001**, *3*, 3549−3552. (l) Kadota, I.; Kadowaki, C.; Park, C.-H.; Takamura, H.; Sato, K.; ChanP. W. H.; Thorand, S.; Yamamoto, Y. *Tetrahedron*, **2002**, *58*, 1799−1816.

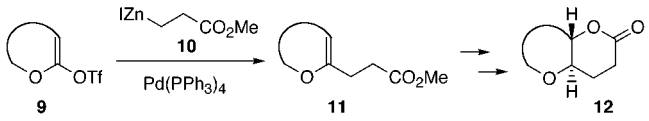
(5) Nicolaou, K. C.; Theodorakis, E. A.; Rutjes, F. P. J. T.; Sato, M.; Tiebes, J.; Xiao, X.-Y.; Hwang, C.-K.; Duggan, M. E.; Yang, Z.; Couladouros, E. A.; Sato, F.; Shin, J.; He, H.-M.; Bleckman, T. *J. Am. Chem. Soc.* **1995**, *117*, 10239−10251.

10.1021/jo025566f CCC: $22.00
Published on Web 04/25/2002

Scheme 2



Scheme 3

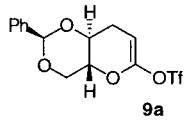
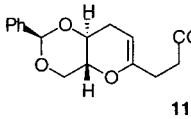
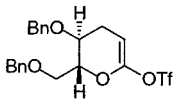
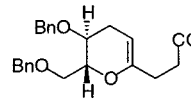
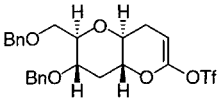
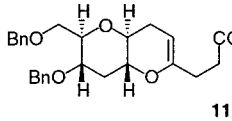
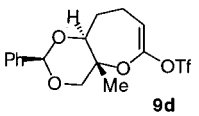
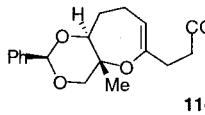
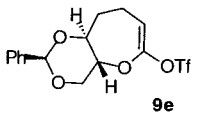
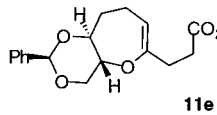


Results and Discussion

Our new synthetic strategy is illustrated in Scheme 3. Since the palladium-catalyzed coupling of alkylzinc reagents and aryl halides was reported by Negishi in 1977,[8] a number of modified reactions have been developed.[9] In 1986, Tamaru reported the palladium-catalyzed coupling of alkenyl triflates, derived from ketones, and zinc homoenolates.[10] It was thought that the coupling of the ketene acetal triflate **9**, derived from lactones, and the zinc homoenolate **10**[11] would give the cyclic enol ether **11**, and the subsequent hydroboration of the double bond of **11** followed by lactonization would provide the desired cyclic ether **12**.

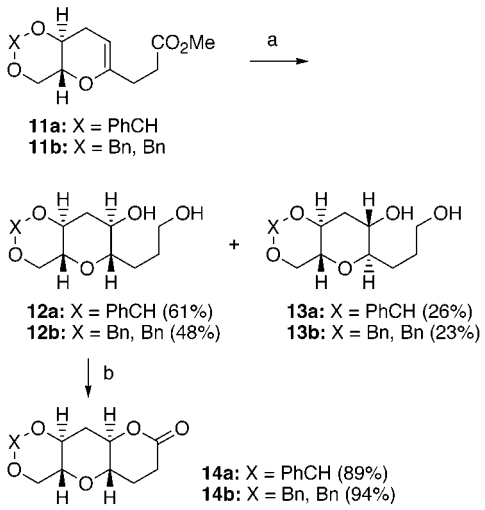
The results of the coupling of **9** and **10** are summarized in Table 1. Treatment of **9a**, prepared from the corresponding lactone by the standard procedure,[7e] with 2 equiv of the zinc homoenolate **10** in the presence of $Pd(PPh_3)_4$ at room temperature gave the enol ether **11a** in 74% yield (entry 1). Similarly, the reaction of the six-membered ketene acetal triflates **9b** and **9c** with **10** under the same reaction conditions gave the corresponding cyclic enol ethers **11b** and **11c**, respectively, in good yields (entries 2 and 3). To synthesize the DE and GH rings of gambierol, it was necessary to know whether the palladium-catalyzed coupling methodology is applicable to seven-membered ketene acetal triflates. The reaction of **9d** with **10** under the same reaction conditions afforded the desired cyclic enol ether **11d** in 82% yield (entry 4). Also, **9e** gave **11e** in 76% yield (entry 5).

Table 1. Palladium-Catalyzed Coupling of Ketene Acetal Triflates 9 and Zinc Homoenolate 10[a]

entry	enol triflate[b]	product	yield[c]
1	 **9a**	 **11a**	74%
2	 **9b**	 **11b**	78%
3	 **9c**	 **11c**	74%
4	 **9d**	 **11d**	82%
5	 **9e**	 **11e**	76%

[a] Reactions were carried out with **10** (2 equiv) in the presence of $Pd(PPh_3)_4$ (5 mol %) in benzene at room temperature. [b] Ketene acetal triflates were prepared from the corresponding lactones by the standard procedure and used without purification. [c] Isolated yields.

Scheme 4[a]



[a] Reagents and conditions: (a) $BH_3{\cdot}SMe_2$. THF, 0 °C to rt, then 30% H_2O_2, 3 N NaOH, rt; (b) TEMPO, NaClO, KBr, CH_2CH_2/H_2O, 0 °C.

Scheme 4 describes the conversion of the enol ethers obtained to the corresponding bicyclic ethers. Hydroboration of **11a** with $BH_3{\cdot}SMe_2$ followed by oxidative workup gave a 7:3 mixture of the diols **12a** and **13a** in 87% combined yield.[12] Although attempts to effect

(6) For a preliminary communication, see ref 4f.

(7) For the synthesis of cyclic ethers via the coupling of ketene acetal triflates derived from lactones, see: (a) Tsushima, K.; Araki, K.; Murai, A. *Chem. Lett.* **1989**, 1313−1316. (b) Tsushima, K.; Murai, A. *Chem. Lett.* **1990**, 761−764. (c) Feng, F.; Murai, A. *Chem. Lett.* **1992**, 1587−1590. (d) Feng, F.; Murai, A. *Synlett* **1995**, 863−865. (e) Fujiwara, K.; Tsunashima, M.; Awakura, D.; Murai, A. *Tetrahedron Lett.* **1995**, *36*, 8263−8266. (f) Nicolaou, K. C.; Theodorakis, E. A.; Rutjes, F. P. J. T.; Tiebes, J.; Sato, M.; Untersteller, E.; Xiao, X.-Y. *J. Am. Chem. Soc.* **1995**, *117*, 1171−1172. (g) Nicolaou, K. C.; Theodorakis, E. A.; Rutjes, F. P. J. T.; Sato, M.; Tiebes, J.; Xiao, X.-Y.; Hwang, C.-K.; Duggan, M. E.; Yang, Z.; Couladouros, E. A.; Sato, F.; Shin, J.; He, H.-M.; Bleckman, T. *J. Am. Chem. Soc.* **1995**, *117*, 10239−10251. (h) Nicolaou, K. C.; Sato, M.; Miller, N. D.; Gunzner, J. L.; Renaud, J.; Untersteller, E. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 889−891. (i) Sasaki, M.; Fuwa, H.; Inoue, M.; Tachibana, K. *Tetrahedron Lett.* **1998**, *39*, 9027−9030.

(8) Negishi, E.; King, A. O.; Okukado, N. *J. Org. Chem.* **1977**, *42*, 1821−1823.

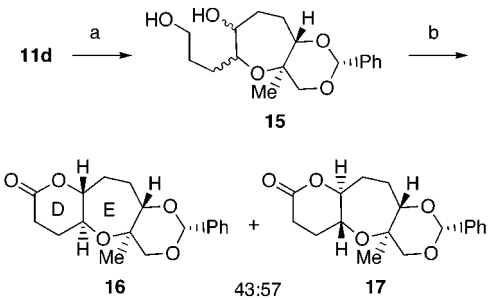
(9) For recent reviews, see: (a) Erdik, E. *Tetrahedron* **1992**, *48*, 9577−9648. (b) Knochel, P.; Singer, R. D. *Chem. Rev.* **1993**, *93*, 2117−2188. (c) Knochel, P.; Perea, J. J. A.; Jones, P. *Tetrahedron* **1998**, *54*, 8275−8391.

(10) Tamaru, Y.; Ochiai, H.; Nakamura, T.; Yoshida, Z. *Tetrahedron Lett.* **1986**, *27*, 955−958.

(11) Tamaru, Y.; Ochiai, H.; Nakamura, T.; Tsubaki, K.; Yoshida, Z. *Tetrahedron Lett.* **1985**, *26*, 5559−5562.

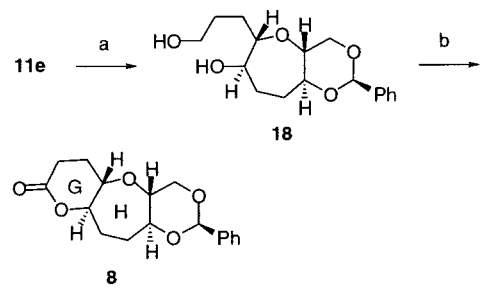
(12) The similar hydroboration−reduction of unsaturated esters with diborane giving the corresponding diols has been reported; see: Brown, H. C.; Keblys, K. A. *J. Am. Chem. Soc.* **1964**, *86*, 1795−1801.

Scheme 5[a]



[a] Reagents and conditions: (a) BH_3·SMe_2. THF, 0 °C to rt, then 30% H_2O_2, 3 N NaOH, rt; (b) TEMPO, NaClO, KBr, CH_2CH_2/H_2O, 0 °C, 79% (2 steps).

Scheme 6[a]



[a] Reagents and conditions: (a) (i) thexylborane, THF, 0 °C to rt, then 30% H_2O_2, 3 N NaOH, rt; (ii) $LiAlH_4$, ether, 0 °C; (b) TEMPO, NaClO, KBr, CH_2CH_2/H_2O, 0 °C, 68% (3 steps).

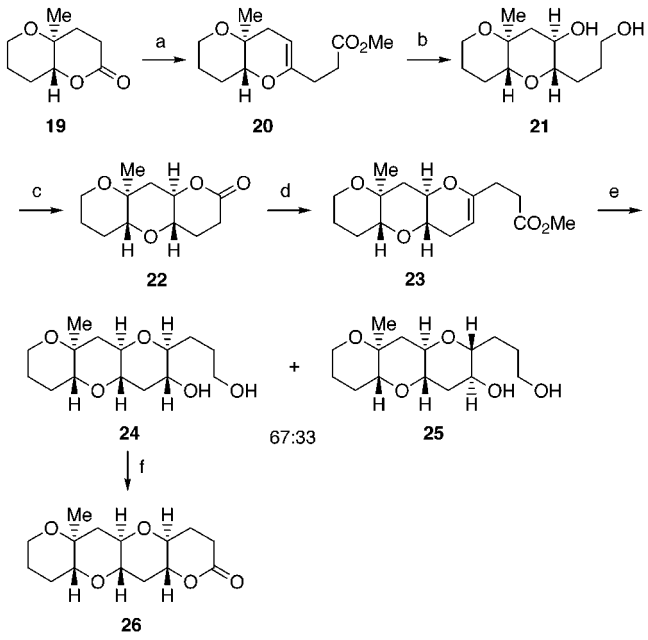
chemoselective hydroboration of the double bond in the presence of an ester group giving the corresponding δ-hydroxy ester resulted in failure, the diol **12a** could be converted directly to the desired lactone **14a** by TEMPO oxidation. The treatment of **12a** with aqueous NaClO in the presence of catalytic amounts of TEMPO and KBr afforded **14a** in 89% yield.[13] Similarly, the bicyclic lactone **14b** was obtained from **11b** in reasonable yield (45% in two steps).

On the basis of these results, we next investigated the synthesis of the DE and GH ring segment of **1**. Treatment of **11d** with BH_3·SMe_2 followed by oxidative work up gave the diol **15** as a mixture of diastereomers (Scheme 5). TEMPO oxidation of **15** gave a 43:57 mixture of the DE ring segment **16** and its stereoisomer **17** in 79% yield from **11d**. Although several attempts such as the use of bulky borane reagents were made to improve the stereoselectivity, the diastereomer ratio remained about 1:1.

Scheme 6 describes the synthesis of the GH ring segment. Hydroboration of **11e** with thexylborane gave a mixture of the diol **18** and unidentified compounds having ester and aldehyde groups. Treatment of this mixture with $LiAlH_4$ gave pure **18** as a single stereoisomer. Oxidation of **18** gave the GH ring segment **8** in 68% yield in three steps from **11e**.

Encouraged by the performance of the present methodology described above, we attempted to carry out the iterative synthesis of polycyclic ethers.[14,15] Treatment of the lactone **19** with KHMDS and $PhNTf_2$ gave the corresponding ketene acetal triflate, which was directly subjected to the palladium-catalyzed coupling with **10** to give the cyclic enol ether **20** in 73% yield (Scheme 7).

Scheme 7[a]



[a] Reagents and conditions: (a) (i) $PhNTf_2$, KHMDS, DMPU, THF, −78 °C; (ii) **10**, $Pd(PPh_3)_4$, benzene, rt, 73% (2 steps); (b) BH_3·SMe_2, THF, 0 °C to rt, then 30% H_2O_2, 3 N NaOH, rt, 92%; (c) TEMPO, NaClO, KBr, CH_2CH_2/H_2O, 0 °C, 87 %; (d) same as a, 80%; (e) same as b, 81%; (f) same as c, 82%.

Hydroboration of **20** with BH_3·SMe_2 followed by oxidative workup afforded the diol **21** as the sole product in 92% yield. TEMPO oxidation of **21** provided **22** in 87% yield. The similar transformation as above produced the tetracyclic compound **26** in an allowable yield (36% in four steps), although the stereoselectivity in the hydroboration of **23** was moderate.

Scheme 8 demonstrates the synthesis of the polyoxepane **32**. Triflation of **27** followed by palladium-catalyzed coupling with zinc bishomoenolate **28** gave the seven-membered cyclic enol ether **29** in 78% yield. Hydroboration of **29** with thexylborane afforded the corresponding β-hydroxy cyclic ether having an unreacted ester group, which was then saponified and subjected to Yamaguchi lactonization to give **30** as a sigle stereoisomer in 71% overall yield.[16] Iteration of this five-step sequnce starting from **30** provided the 7,7,7-tricyclic lactone **32** in 34% overall yield.

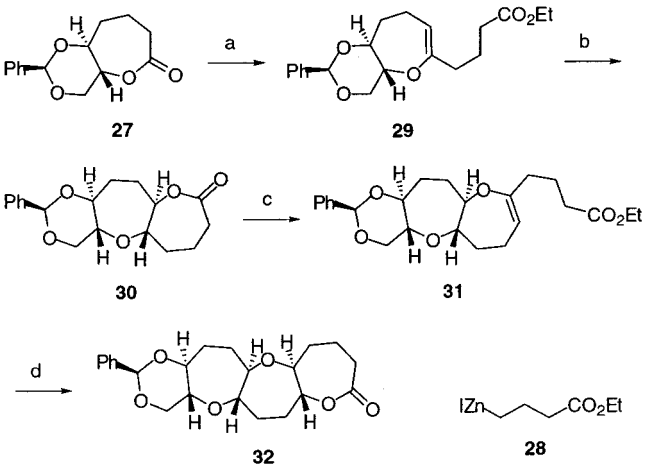
(13) Anelli, P. L.; Banfi, S.; Montanari, F.; Quici, S. *J. Org. Chem.* **1989**, *54*, 2970−2972.

(14) For examples of the iterative synthesis of polycyclic ethers, see: (a) Kozikowski, A. P.; Ghosh, A. K. *J. Org. Chem.* **1985**, *50*, 3017−3019. (b) Nicolaou, K. C.; Prasad, C. V. C.; Somers, P. K.; Hwang, C.-K. *J. Am. Chem. Soc.* **1989**, *111*, 5330−5334. (c) Yamamoto, Y.; Yamada, J.; Kadota, I. *Tetrahedron Lett.* **1991**, *32*, 7069−7072. (d) Palazón, J. M.; Soler, M. A.; Ramírez, M. A.; Martín, V. S. *Tetrahedron Lett.* **1993**, *34*, 5467−5470. (e) Lee. E.; Tae, J. S.; Chong, Y. H.; Park, Y. C.; Yun, M.; Kim, S. *Tetrahedron Lett.* **1994**, *35*, 129−132. (f) Hoffmann, R. W.; Münster, I. *Tetrahedron Lett.* **1995**, *36*, 1431−1434. (g) Evans, P. A.; Roseman, J. D.; Garber, L. T. *J. Org. Chem.* **1996**, *61*, 4880−4881. (h) Hayashi, N.; Fujiwara, K.; Murai, A. *Tetrahedron Lett.* **1996**, *37*, 6173−6176. (i) Mori, Y.; Yaegashi, K.; Furukawa, H. *J. Am. Chem. Soc.* **1996**, *118*, 8158−8159. (j) Bowman, J. L.; McDonald, F. E. *J. Org. Chem.* **1998**, *63*, 3680−3682. (k) Rainier, J. D.; Allwein, S. P. *Tetrahedron Lett.* **1998**, *39*, 9601−9604. (l) Hori, N.; Matsukura, H.; Matsuo, G.; Nakata, T. *Tetrahedron Lett.* **1999**, *40*, 2811−2814. (m) Marmsäter, F. P.; West, F. G. *J. Am. Chem. Soc.* **2001**, *123*, 5144−5145.

(15) For examples of biomimetic synthesis of polycyclic ethers by the cascade reaction of polyepoxides, see: (a) Tokiwano, T.; Fujiwara, K.; Murai, A. *Synlett* **2000**, 335−338. (b) McDonald, F. E.; Wang, X.; Do, B.; Hardcastle, K. I. *Org. Lett.* **2000**, *2*, 2917−2919.

(16) Inanaga, J.; Hirata, K.; Saeki, H.; Katsuki, T.; Yamaguchi, M. *Bull. Chem. Soc. Jpn.* **1979**, *52*, 1989−1993.

Scheme 8[a]



[a] Reagents and conditions: (a) (i) $PhNTf_2$, KHMDS, DMPU, THF, −78 °C; (ii) **28**, $Pd(PPh_3)_4$, benzene, rt, 78% (2 steps); (b) (i) thexylborane, THF, 0 °C to rt, then H_2O_2, 3 N NaOH, 0 °C; (ii) LiOH, THF−H_2O, 40 °C; (iii) 2,4,6-trichlorobenzoyl chloride, Et_3N, THF, 0 °C to rt, the DMAP, benzene, rt, 71% (3 steps); (c) same as a, 71%; (d) same as b, 48%.

Conclusion

We have developed a novel method for the concise synthesis of *trans*-fused cyclic ethers via the palladium-catalyzed coupling of ketene acetal triflates and organozinc reagents. We are now in a position to synthesize the DE and GH ring segments of gambierol efficiently with a shorter number of steps (11 and 10 steps from 2-deoxy-D-ribose, respectively) in comparison with the previous methods.[4c,l] Furthermore, the present methodology was successfully applied to the iterative synthesis of polycyclic ethers.

Experimental Section

General Methods. All reactions involving air- and/or moisture-sensitive materials were carried out under argon with dry solvents. On workup, extracts were dried over $MgSO_4$. Reactions were monitored by thin-layer chromatography carried out on 0.25 mm silica gel plates (60F-254). Column chromatography was performed with silicagel (60N, spherical, neutral, particle size 0.100−0.210 mm). Yields refer to chromatographically and spectroscopically homogeneous materials.

Typical Procedure for the Palladium-Catalyzed Coupling of Ketene Acetal Triflates 9 and Zinc Homoenolate 10. Synthesis of 11a. To a suspension of Zn−Cu couple (367 mg, 5.5 mmol) in benzene (4 mL) and DMA (0.5 mL) was added methyl 3-iodopropionate (330 μL, 2.8 mmol). The mixture was refluxed for 2 h and then cooled to room temperature. A solution of **9a** (510 mg, 1.4 mmol) in benzene (5 mL) and a solution of $Pd(PPh_3)_4$ (80 mg, 0.07 mmol) in benzene (5 mL) were added to the resulting mixture, successively. After stirring for 3 h, the mixture was quenched with Et_3N, filtered through a silica gel pad, and concentrated. The residue was purified by silica gel chromatography (hexane/EtOAc, 4:1 containing 0.5% Et_3N) to give **11a** (313 mg, 73%): colorless needle; mp 122 °C (hexane/CH_2Cl_2); R_f = 0.31 (hexane/EtOAc, 4:1); $[\alpha]^{23}_D$ +58.2° (*c* 1.00, $CHCl_3$); IR (KBr) 1726, 1674 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.52−7.36 (m, 5H), 5.61 (s, 1 H), 4.56 (dd, *J* = 5.0, 2.3 Hz, 1 H), 4.39 (dd, *J* = 8.4, 2.9 Hz, 1 H), 3.88−3.82 (m, 1 H), 3.79−3.75 (m, 2 H), 3.69 (s, 3 H), 2.51−2.46 (m, 2 H), 2.38−2.24 (m, 4 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.2, 152.2, 137.4, 129.0, 128.2, 126.1, 101.5, 94.0, 74.9, 69.8, 68.9, 51.5, 31.7, 28.8, 26.6. Anal. Calcd for $C_{17}H_{20}O_5$: C, 67.09; H, 6.62. Found: C, 66.84; H, 6.59.

Hydroboration of 11a. To a mixture of **11a** (101 mg, 0.33 mmol) in THF (3 mL) at 0 °C was added BH_3·SMe_2 (130 μL, 1.33 mmol), and the mixture was allowed to warm to room temperature with stirring. After 2 h, 1 N NaOH (2 mL) and 30% H_2O_2 (1 mL) were added at 0 °C, and the resulting mixture was vigorously stirred for 0.5 h at room temperature. The mixture was diluted with EtAOc, then washed with saturated Na_2SO_3 and brine. Concentration and chromatography gave **12a** (60 mg, 61%) and **13a** (25 mg, 26%).

12a: colorless needle; mp 173 °C (EtOAc); R_f = 0.35 (EtOAc); $[\alpha]^{20}_D$ −28.8° (*c* 1.00, MeOH); IR (KBr) 3600−3200 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.51−7.35 (m, 5 H), 5.52 (s, 1 H), 4.31 (dd, *J* = 10.5, 4.8 Hz, 1 H), 3.71−3.64 (m, 3 H), 3.59−3.49 (m, 2 H), 3.41−3.33 (m, 1 H), 3.24 (ddd, *J* = 8.8, 8.8, 2.6 Hz, 1 H), 2.48 (ddd, *J* = 11.4, 4.4, 4.4 Hz, 1 H), 2.05−1.98 (m, 2 H), 1.79−1.53 (m, 4 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 137.3, 129.1, 128.3, 126.2, 101.7, 82.4, 76.6, 73.1, 69.5, 69.2, 62.8, 38.3, 28.4, 28.2. Anal. Calcd for $C_{16}H_{22}O_5$: C, 65.29; H, 7.53. Found: C, 65.09; H, 7.71.

13a: colorless needle; mp 157−158 °C (EtOAc); R_f = 0.21 (EtOAc); $[\alpha]^{21}_D$ +20.6° (*c* 1.00, MeOH); IR (KBr) 3500−3000 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.50−7.35 (m, 5 H), 5.59 (s, 1 H), 4.22 (dd, *J* = 10.1, 4.6 Hz, 1 H), 4.07−3.98 (m, 2 H), 3.87 (dd, *J* = 10.5, 4.6 Hz, 1 H), 3.80−3.60 (m, 4 H), 2.19 (ddd, *J* = 13.2, 3.8, 3.8 Hz, 1 H), 2.02−1.93 (m, 3 H), 1.77−1.54 (m, 4 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 129.1, 128.3, 126.1, 102.1, 79.2, 74.5, 69.9, 69.6, 66.1, 62.3, 46.8, 32.2, 28.8, 25.3. Anal. Calcd for $C_{16}H_{22}O_5$: C, 65.29; H, 7.53. Found: C, 65.10; H, 7.71.

TEMPO Oxidation of 12a. To a solution of **12a** (30 mg, 0.1 mmol) in 3 mL of CH_2Cl_2 at 0 °C were added aqueous KBr (1.0 M, 10 μL) and a catalytic amount of TEMPO. While vigorously stirring, a freshly prepared NaClO solution (ca. 0.3 M, 1:1 mixture of comercial bleach solution and saturated $NaHCO_3$, 1.2 mL, 0.37 mmol) was added dropwise. After 1 h, the mixture was quenched with Na_2SO_3 and extracted with EtOAc. The organic layer was washed with brine and concentrated. The residue was purified by chromatography (hexane/EtOAc, 1:1) to give **14a** (26 mg, 89%): colorless needle; mp 317 °C (hexane/CH_2Cl_2); R_f = 0.38 (hexane/EtOAc, 1:1); $[\alpha]^{21}_D$ +63.1° (*c* 0.75, $CHCl_3$); IR (KBr) 1742 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.49−7.36 (m, 5 H), 5.55 (s, 1 H), 4.33 (dd, *J* = 10.5, 4.8 Hz, 1 H), 4.16−4.08 (m, 1 H), 3.75−3.46 (m, 4 H), 2.83 (ddd, *J* = 18.1, 9.1, 4.7 Hz, 1 H), 2.72−2.60 (m, 2 H), 2.27−2.16 (m, 1 H), 1.96−1.81 (m, 2 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.8, 136.9, 129.2, 128.4, 126.1, 101.9, 76.1, 75.8, 74.9, 73.6, 68.9, 34.8, 27.8, 24.3. Anal. Calcd for $C_{16}H_{18}O_5$: C, 66.19; H, 6.25. Found: C, 65.89; H, 6.12.

Synthesis of 8. To a solution of 2,3-dimethyl-2-butene (29 μL, 0.24 mmol) in THF (1 mL) at 0 °C was added BH_3·SMe_2 (23 μL, 0.24 mmol). The mixture was stirred at 0 °C for 1 h. To the resulting thexylborane solution at 0 °C was added a solution of **11e** (65 mg, 0.20 mmol) in THF (1 mL), and the mixture was stirred at room temperature. After 2 h, 1 N NaOH (0.4 mL) and 30% H_2O_2 (0.2 mL) were added at 0 °C, and the mixture was vigorously stirred at room temperature for 0.5 h. The mixture was quenched with saturated Na_2SO_3 at 0 °C and extracted with EtOAc. The organic layer was washed with brine, concentrated, and dissolved in ether (2 mL). To the mixture at 0 °C was added $LiAlH_4$ (16 mg, 0.41 mmol). After 1 h, the reaction was quenched with brine, and the resulting white precipitate was removed by filteration through a Celite pad. The filtrate was concentrated to give the crude diol **18**, which was subjected directly to TEMPO oxidation to give **8** (42 mg, 68%): colorless prism; mp 189 °C (hexane/CH_2Cl_2); R_f = 0.18 (hexane/EtOAc, 1:1); $[\alpha]^{23}_D$ +62.2° (*c* 1.00, $CHCl_3$); IR (KBr) 1740 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.46−7.33 (m, 5 H), 5.42 (s, 1 H), 4.32−4.23 (m, 1 H), 4.16−4.09 (m, 1 H), 3.70−3.55 (m, 4 H), 2.70 (ddd, *J* = 16.3, 8.2, 8.2 Hz, 1 H), 2.55 (ddd, *J* = 17.2, 7.0, 7.0 Hz, 1 H), 2.21−1.97 (m, 5 H), 1.94−1.81 (m, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.3, 137.3, 129.0, 128.3, 126.0, 101.1, 81.0, 80.8, 77.4, 75.2, 69.3, 28.5, 28.2, 27.6, 26.0. Anal. Calcd for $C_{17}H_{20}O_5$: C, 67.09; H, 6.62. Found: C, 66.90; H, 6.60.

Synthesis of 30. Hydroboration of **29** (53 mg, 0.15 mmol) with thexylborane followed by the usual oxidative workup gave

the corresponding hydroxy ester, which was used directly for the next reaction. To a mixture of the ester in THF (0.4 mL) and H_2O (0.2 mL) was added $LiOH \cdot H_2O$ (10 mg, 0.23 mmol), and the mixture was stirred at 40 °C for 3.5 h. The mixture was acidified carefully by 1 N HCl to pH 3−4 at 0 °C and extracted with EtOAc. The organic layer was washed with brine and concentrated. The residure was dissolved in THF (1 mL) and then treated with Et_3N (32 μL, 0.23 mmol) and 2,4,6-trichlorobenzoyl chloride (40 μL, 0.24 mmol) at 0 °C. After stirring for 3 h at room temperature, the mixture was diluted with benzene (7 mL) and introduced to a mixture of DMAP (37 mg, 0.30 mmol) in benzene (3 mL). After stirring at room temperature for 11 h, the mixture was diluted with EtOAc, and the insoluble material was filtered off. The filtrate was concentrated and purified by chromatography (hexane/EtOAc, 1:1) to give **30** (24 mg, 71%): colorless prism; mp 208 °C (hexane/CH_2Cl_2); $R_f = 0.29$ (hexane/EtOAc, 1:1); $[\alpha]^{23}_D$ +24.4° (*c* 1.00, $CHCl_3$); IR (KBr) 1724 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.47−7.32 (m, 5 H), 5.43 (s, 1 H), 4.42−4.40 (m, 1 H), 4.23 (dd, $J = 10.6$, 3.6 Hz, 1 H), 3.61 (t, $J = 9.9$ Hz, 1 H), 3.50−3.38 (m, 3 H), 2.65−2.57 (m, 2 H), 2.19−1.97 (m, 6 H), 1.77−1.62 (m, 2 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.4, 137.4, 129.0, 128.3, 126.1, 101.4, 84.0, 83.1, 82.1, 80.6, 69.7, 35.7, 33.5, 29.1, 27.4, 21.1. Anal. Calcd for $C_{18}H_{22}O_5$: C, 67.91; H, 6.97. Found: C, 67.41; H, 7.13.

Acknowledgment. This work was financially supported by a Grant-in-Aid for Scientific Research from the Ministry of Education, Science and Culture of Japan.

Supporting Information Available: Characterization data for **11b**−**e**, **12b**, **13b**, **14b**, **16**, **17**, **20**−**26**, **29**, **31**, and **32** and copies of ^1H and ^{13}C NMR spectra of all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

JO025566F