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Synthesis of the E Ring of Gambierol

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Abstract: The synthesis of the E ring of gambierol was achieved from D-ribose *via* the intramolecular reaction of allylstannane with an aldehyde as a key step. The undesired stereoisomer formed in this reaction was converted to the desired product by using DBU isomerization. © 1998 Elsevier Science Ltd. All rights reserved.

In the preceding paper, the construction of the AB ring system of gambierol was described.[1] We next examined the synthesis of the E ring. We have already developed an efficient method for the stereocontrolled synthesis of 7-membered cyclic ethers *via* the intramolecular allylic tin-aldehyde condensation.[2] The methodology was applied to the present synthesis as shown below.

The starting material **1**[3] derived from D-ribose was converted to the α,β-unsaturated ester **2** with $Ph_3P{=}CHCO_2Me$ in 70% yield. Hydrogenation of the double bond of **2** produced **3** in 83% yield. The primary hydroxy group of **3** was protected as a TBS ether using TBSCl/imidazole to give **4** in 99% yield. Reduction with $LiAlH_4$ produced **5** in 96% yield. Protection of the resulting alcohol with TBDPS group gave **6** in 98% yield. Selective removal of the acetonide and the TBS protective group was performed using $PdCl_2(CH_3CN)_2$ to give the triol **7** in 73% yield.[4] Selective protection of the 1,3-diol with $PhCH(OMe)_2$/CSA gave **8** in 85% yield. Oxidation followed by treatment with MeMgI in toluene afforded the tertiary alcohol **9** as a single stereoisomer.[5] Williamson type allylation produced the allylic ether **10** in quantitative yield. Generation of the corresponding oxo-substituted allylic anion by using *sec*-BuLi/TMEDA, followed by the trapping with n-Bu_3SnCl gave the allylic tin compound **11** in 85% yield. The TBDPS group of **11** was removed by the treatment with TBAF to give **12** in quantitative yield. Oxidation of the alcohol **12** produced the aldehyde **13** in 97% yield. The cyclization of **13** was a key step for the synthesis of the E ring. The treatment of **13** with $BF_3{\cdot}OEt_2$ gave a 30:70 mixture of the 7-membered cyclic ethers **14** and **15** in 92% yield. Unfortunately, the desired stereoisomer **14** was obtained as the minor product. The stereochemistries of **14** and **15** were determined by ^1H NMR analysis and NOE experiments of the corresponding acetate derivatives **16** and **17**, respectively, as shown in Figure 1.[6] Irradiation of the methyl group (1.55 ppm) of **16** gave enhancements of the resonances at the H_a proton (4.28 ppm, 8.2%) and the acetyl group (2.09 ppm, 0.7%) indicating the *cis* relationship of these substituents. On the other hand, NOEs were observed between H_a (4.22 ppm) and H_b (3.96 ppm) of **17** and between the methyl group (1.49 ppm) and H_c (4.95 ppm), indicating the *cis*-stereochemistry of these substituents (see Figure 1).

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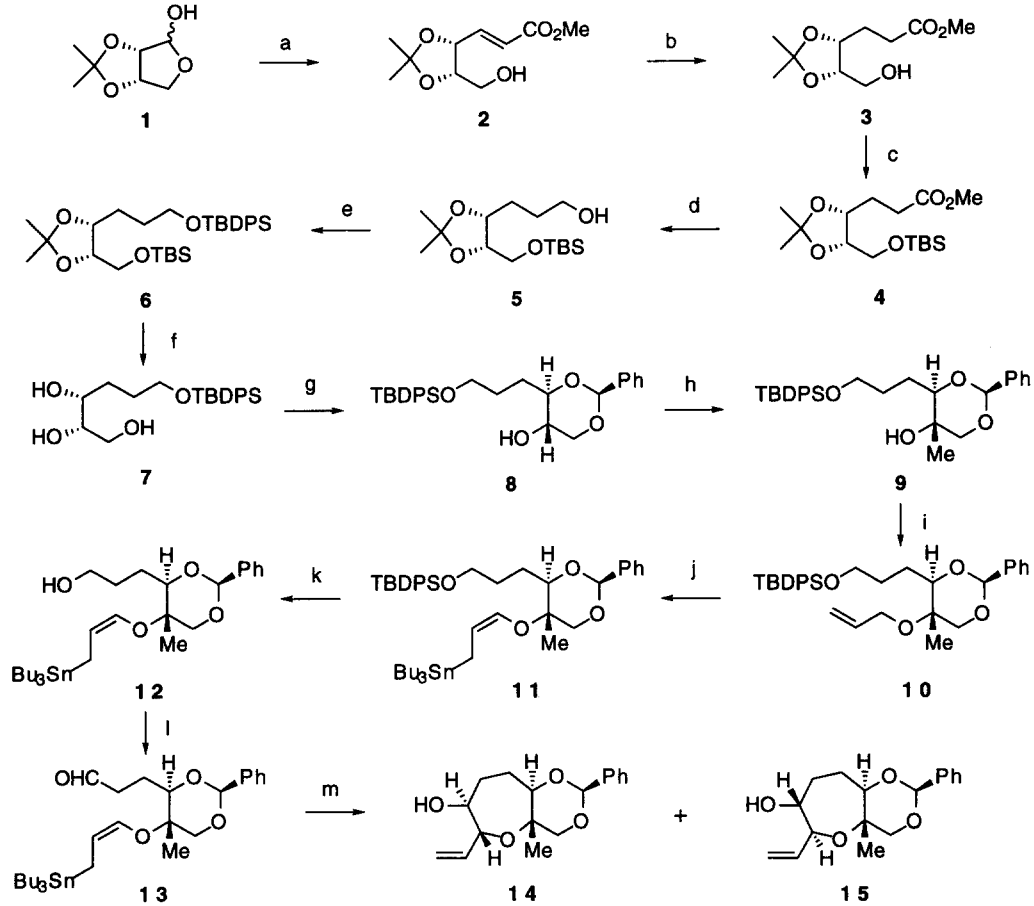
Scheme 1[a]



[a](a) $Ph_3P{=}CHCO_2Me$, THF, reflux, overall 70% from D-ribose by 3 steps; (b) H_2, 10% Pd-C, MeOH, rt, 83%; (c) TBSCl, imidazole, DMF, 0 °C to rt, 99%; (d) $LiAlH_4$, THF, 0 °C, 96%; (e) TBDPSCl, imidazole, DMF, 0 °C to rt, 98%; (f) $PdCl_2(CH_3CN)_2$, wet CH_3CN, rt, 73%; (g) $PhCH(OMe)_2$, CSA, CH_2Cl_2, rt, 85%; (h) (i) $(COCl)_2$, DMSO, CH_2Cl_2, -78 °C, then Et_3N, -78 °C to rt; (ii) MeMgI, toluene, -78 °C, 65%; (i) KH, THF, 0 °C, then allyl bromide, 0 °C to rt, 100%; (j) *sec*-BuLi, TMEDA, THF, -78 °C, then *n*-Bu_3SnCl, -78 °C to rt, 85%; (k) TBAF, THF, rt, 100%; (l) SO_3·py, DMSO, Et_3N, CH_2Cl_2, 0 °C to rt, 97%; (m) $BF_3{\cdot}OEt_2$, CH_2Cl_2, -78 °C, 92% (**14**:**15** = 30:70).

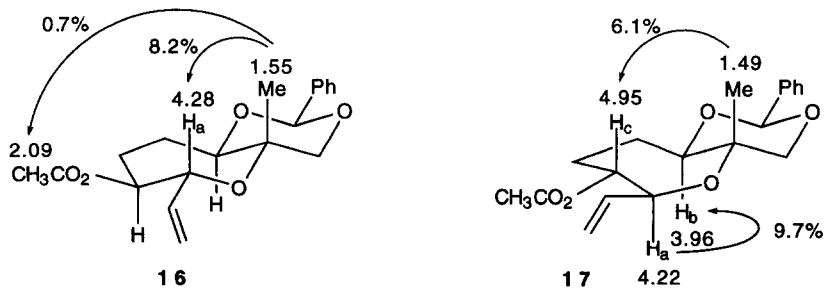


Figure 1. NOE experiments on the acetate derivatives **16** and **17**.

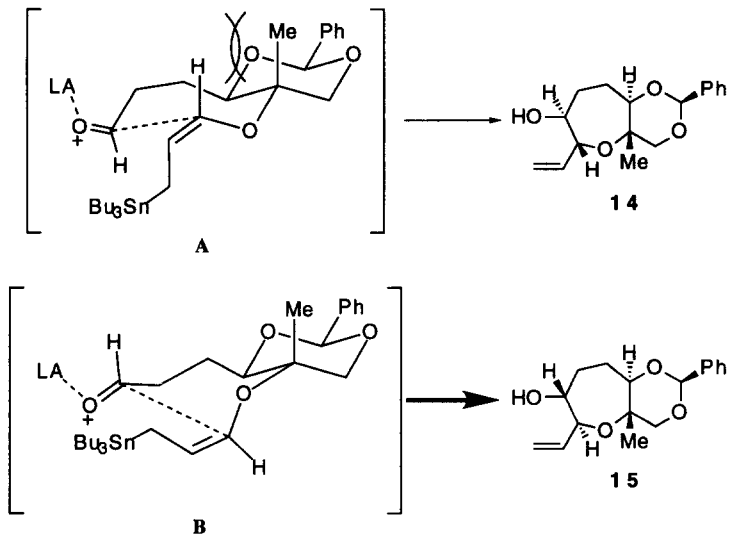
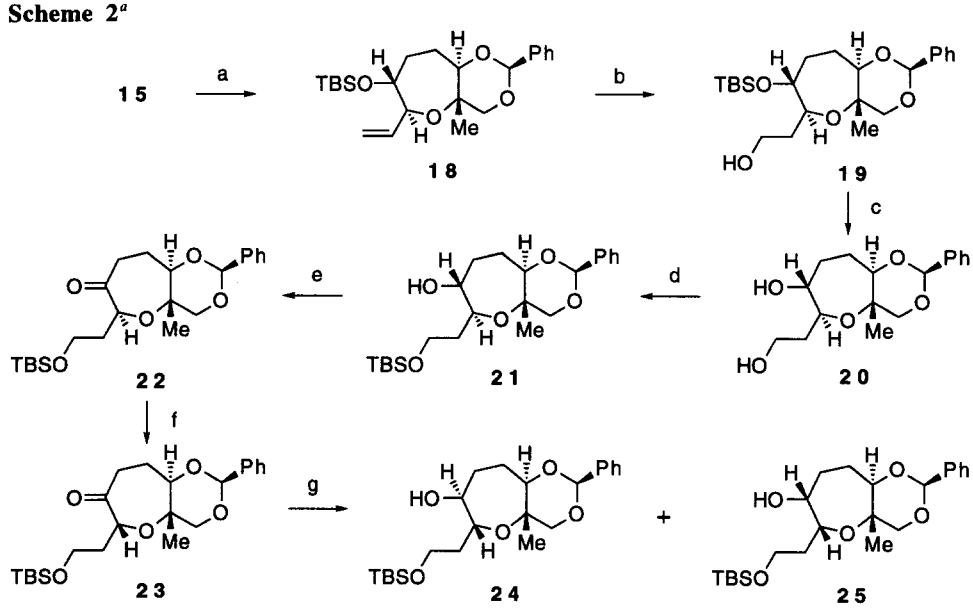


Figure 2. Transition state structures **A** and **B**.

Scheme 2[a]



[a](a) TBSOTf, 2,6-lutidine, CH_2Cl_2, 0 °C, 100%; (b) (*cyc*-Hex)$_2$BH, THF, 0 °C, then 3N NaOH, H_2O_2, 0 °C to rt, 99%; (c) TBAF, THF, rt, 100%; (d) TBSCl, imidazole, DMF, 0 °C to rt, 94%; (e) $(COCl)_2$, DMSO, CH_2Cl_2, -78 °C, then Et_3N, -78 °C to rt, 92%; (f) DBU, toluene, reflux, 98% (**23**:**22** = 97:3); (g) DIBAL-H, methylaluminum bis(2,6-di-*t*-butyl-4-methylphenoxide) (MAD), toluene, -78 °C, 89% (**24**:**25** = 67:33).

The observed stereoselectivity can be explained by the transition state model as depicted in Figure 2. To avoid the steric repulsion between methyl group and the olefinic proton in the transition state **A**, the cyclization of **13** would proceed *via* the transition state **B** to give **15** predominantly.

Since several attempts for improving the stereoselectivity resulted in failure, we next examined the stereoisomerization of the undesired product **15** as shown in Scheme 2. The hydroxy group of **15** was protected as a TBS ether using TBSOTf/2,6-lutidine to give **18** in quantitative yield. Hydroboration of **18** gave the alcohol **19** in 99% yield. Removal of the TBS protective group using TBAF afforded the diol **20** in quantitative yield. Selective protection of the primary alcohol of **20** afforded **21** in 94% yield. The secondary alcohol **21** was oxidized to yield the ketone **22** in 92% yield. Epimerization of **22** was achieved by using DBU in refluxing toluene to give the thermodynamically stable **23** in 95% yield. Finally, stereoselective reduction of **23** was performed using DIBAL-H in the presence of bulky Lewis acid, methylaluminum bis(2,6-di-*t*-butyl-4-methylphenoxide), gave a mixture of **24** and **25** in the ratio of 67:33 in 89% yield.[7] Although the allyltin-aldehyde cyclization method gave unexpectedly the undesired stereoisomer **15** as the major product, the epimerization method enabled us to obtain the desired stereoisomer **24**, corresponded to the E ring.

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(6) **16**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.50-7.48 (m, 2H), 7.37-7.34 (m, 3H), 5.89 (ddd, *J* = 16.0, 10.5, 5.5 Hz, 1H), 5.51 (s, 1H), 5.31 (ddd, *J* = 17.0, 1.5, 1.5 Hz, 1H), 5.13 (ddd, *J* = 10.5, 1.5, 1.5 Hz, 1H), 5.00 (ddd, *J* = 5.0, 2.6, 2.6 Hz, 1H), 4.28 (dddd, *J* = 13.5, 2.0, 2.0, 2.0 Hz, 1H), 3.88 (d, *J* = 10.0 Hz, 1H), 3.67 (dd, *J* = 11.6, 1.0 Hz, 1H), 3.62 (dd, *J* = 11.3, 4.0 Hz, 1H), 2.09 (s, 3H), 1.98-1.92 (m, 2H), 1.85-1.79 (m, 2H), 1.55 (s, 3H).
17: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.50-7.46 (m, 2H), 7.40-7.34 (m, 3H), 5.84 (ddd, *J* = 17.1, 10.6, 6.3 Hz, 1H), 5.51 (s, 1H), 5.24 (ddd, *J* = 17.1, 1.4, 1.4 Hz, 1H), 5.15 (ddd, *J* = 10.6, 1.4, 1.4 Hz, 1H), 4.95 (ddd, *J* = 9.3, 9.3, 3.2 Hz, 1H), 4.22 (dddd, *J* = 8.1, 6.5, 1.0, 1.0 Hz, 1H), 3.96 (dd, *J* = 9.6, 5.1 Hz, 1H), 3.83 (d, *J* = 10.5 Hz, 1H), 3.72 (dd, *J* = 10.5, 1.0 Hz, 1H), 2.04 (s, 3H), 2.01-1.73 (m, 4H), 1.49 (s, 3H).

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