

Synthesis of the H Ring of Gambierol

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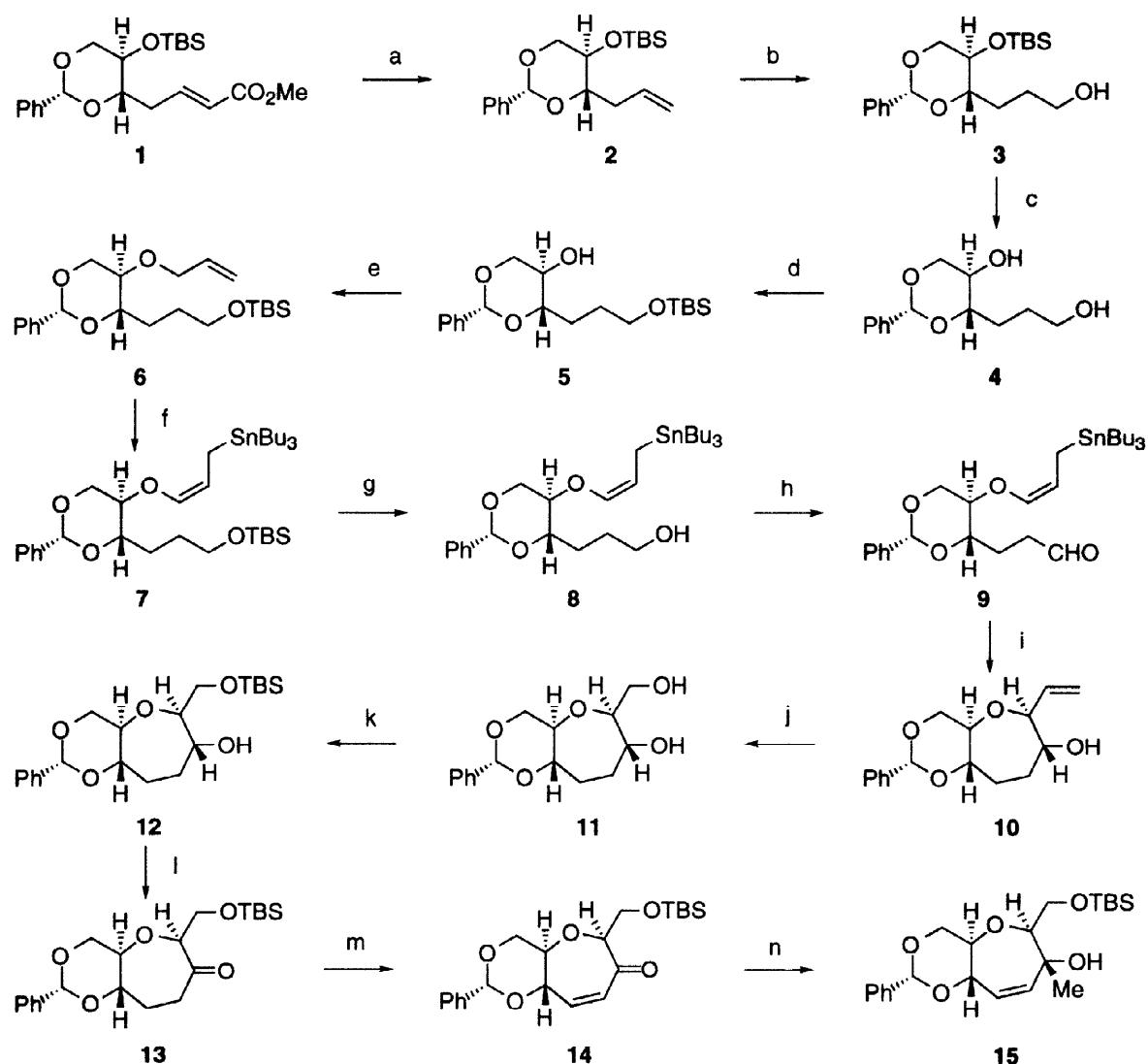
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Abstract: Stereoselective synthesis of the H ring of gambierol was achieved from 2-deoxy-D-ribose by using the intramolecular reaction of allylstannane with aldehyde as a key step. Modified Stille coupling was successfully applied for the construction of the triene side chain. © 1998 Elsevier Science Ltd. All rights reserved.

In the preceding two papers,^{1,2} the construction of the AB and E ring systems of gambierol was described. We now report the stereoselective synthesis of the H ring. Construction of the seven-membered cyclic ether skeleton of the H ring was performed *via* the intramolecular reaction of an allylstannane with an aldehyde³ as shown in Scheme 1. Ozonolysis of **1**, prepared from 2-deoxy-D-ribose by the known procedure,⁴ followed by Wittig reaction with $\text{Ph}_3\text{P}=\text{CH}_2$ gave the olefin **2** in 80% yield. Hydroboration of **2** with 9-BBN afforded the primary alcohol **3** in 94% yield. The TBS protective group of **3** was removed using TBAF to give the diol **4** in 97% yield. Selective protection of the primary hydroxy group was performed with TBSCl/ Et_3N /DMAP to give **5** in 96% yield. Alkylation of the secondary alcohol of **5** with allyl bromide/KH gave allyl ether **6** in 98% yield. Generation of the corresponding allylic anion by using *sec*-BuLi/IMEDA followed by trapping with *n*-Bu₃SnCl afforded **7** in 93% yield. Treatment of **7** with TBAF gave **8** in 96% yield. Oxidation of the primary alcohol with $\text{SO}_3 \cdot \text{py}/\text{DMSO}/\text{Et}_3\text{N}$ produced the cyclization precursor **9** in 91% yield. The aldehyde obtained was then subjected to the cyclization. Treatment of **9** with $\text{BF}_3 \cdot \text{OEt}_2$ at -78°C gave the desired oxepane derivative **10** as the sole product in 98% yield. No other stereoisomer was detected, and the benzyldene acetal moiety was not affected under the reaction conditions.

We next examined the introduction of the double bond and the methyl group on the H ring (Scheme 1). Ozonolysis of the double bond of **10** followed by the treatment with NaBH_4 gave the diol **11** in 84% yield. The primary hydroxy group was protected with TBSCl/imidazole to give **12** in 95% yield. Swern oxidation of the secondary alcohol gave the ketone **13** in 98% yield. Generation of the lithium enolate of **13** with LiHMDS followed by the trapping with PhSeCl gave the corresponding selenide, which was treated with H_2O_2 to afford the α,β -unsaturated ketone **14** in 70% yield.⁵ The reaction of **14** with MeMgI in toluene⁶ proceeded in a highly stereoselective manner to give **15** as the sole product in 83% yield.

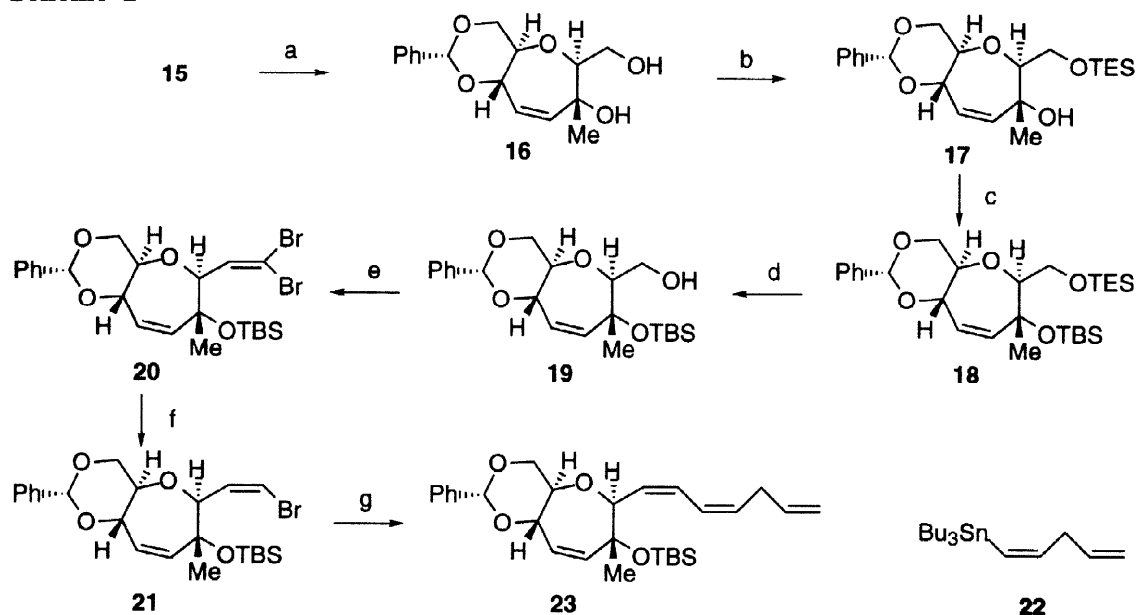
Scheme 1^a

^a(a) (i) O₃, CH₂Cl₂, -78 °C, then PPh₃, -78 °C to rt; (ii) Ph₃P⁺CH₃Br⁻, NaHMDS, THF, -78 °C, 80%; (b) 9-BBN, THF, rt, then 3N NaOH, H₂O₂, rt, 94%; (c) TBAF, THF, rt, 97%; (d) TBSCl, Et₃N, DMAP, CH₂Cl₂, rt, 96% (e) allyl bromide, KH, THF, 0 °C to rt, 98%; (f) *sec*-BuLi, TMEDA, THF, -78 °C, then *n*-Bu₃SnCl, -78 °C to rt, 93%; (g) TBAF, THF, rt, 96%; (h) SO₃·py, DMSO, Et₃N, CH₂Cl₂, 0 °C to rt, 91%; (i) BF₃·OEt₂, CH₂Cl₂, -78 °C, 98%; (j) O₃, CH₂Cl₂-MeOH (1:1), -78 °C, then NaBH₄, -78 °C to rt; 92%; (k) TBSCl, imidazole, DMF, 0 °C, 95%; (l) (COCl)₂, DMSO, CH₂Cl₂, -78 °C, then Et₃N, -78 °C to rt; 98%; (m) (i) LiHMDS, THF, -78 °C, then PhSeCl, -78 °C to rt; (ii) H₂O₂, THF-H₂O, rt, 70%; (n) MeMgI, toluene, -78 °C, 83%.

Construction of the triene side chain is shown in Scheme 2. The TBS group of **15** was removed by TBAF to give the diol **16** in 99% yield. Selective protection of the primary alcohol with TESCl/Et₃N gave **17** in 99% yield. The tertiary alcohol was protected with TBSOTf/2,6-lutidine to give the bis-silyl ether **18** in 99% yield. Selective removal of the TES group was performed by using Amberlyst-15 to give the primary alcohol **19** in 99% yield. Oxidation of **19** followed by the treatment with CBr₄/PPh₃ gave the dibromoalkene **20** in 86% yield.⁷ Stereoselective hydrogenolysis of **20** was performed by using *n*-Bu₃SnH in the presence of Pd(PPh₃)₄ to give the (*Z*)-bromoalkene **21** in 82% yield.⁸ Finally, palladium catalyzed coupling of **21** with

(*Z*)-1,4-pentadienylstannane **22**⁹ afforded the H ring fragment **23** in 63% yield.¹⁰ The stereochemistry was determined by ¹H NMR analysis and NOE experiments on the corresponding alcohol **24**,¹¹ prepared from **23** by the treatment with TBAF, as shown in Figure 1. Irradiation of the methyl group (1.26 ppm) gave enhancements of the resonance at the H_a (5.49 ppm, 8.7%) and H_b proton (4.40 ppm, 7.3%). Similarly, the *cis* relationship of the H_c (4.47 ppm), H_d (3.60 ppm), and the hydroxylic proton (2.74 ppm) was determined by the observed NOEs depicted in Figure 1. The coupling constants of the olefinic protons on the triene moiety were identical with those of gambierol.

Scheme 2^a



^a(a) TBAF, THF, rt, 99%; (b) TESCl, Et₃N, CH₂Cl₂, rt, 99%; (c) TBSOTf, 2,6-lutidine, CH₂Cl₂, rt, 99%; (d) Amberlyst-15, MeOH, 0 °C, 99%; (e) (i) (COCl)₂, DMSO, CH₂Cl₂, -78 °C, then Et₃N, -78 °C to rt; (ii) CBr₄, PPh₃, CH₂Cl₂, 0 °C, 86%; (f) *n*-Bu₃SnH, Pd(PPh₃)₄, benzene, rt, 82%; (g) **22**, Pd₂(dba)₃, CHCl₃, P(furyl)₃, CuI, DMSO, rt, 63%.

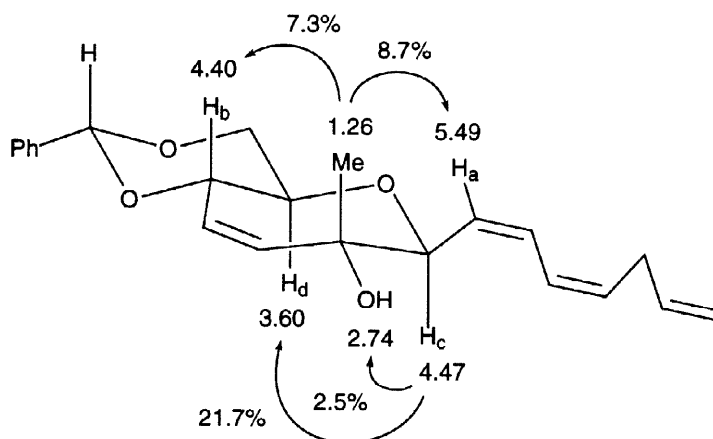


Figure 1. NOE experiments on **24**.

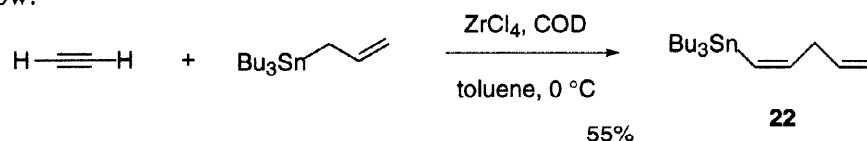
In conclusion, we have reported the syntheses of the AB, E, and H ring system of gambierol in the preceding and this papers. Further studies toward the total synthesis of gambierol are in progress in our laboratories.

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- (9) (*Z*)-1,4-Pentadienylstannane **22** was prepared by the ZrCl_4 mediated *cis*-allylstannylation of acetylene as shown below.



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- (11) **24**: ^1H NMR (500 MHz, CD_3CN) δ 7.46-7.42 (m, 2H), 7.40-7.35 (m, 3H), 6.52-6.47 (m, 1H), 6.44-6.38 (m, 1H), 5.85 (dddd, $J = 17.2, 10.2, 6.3, 6.3$ Hz, 1H), 5.80 (dd, $J = 12.8, 2.9$ Hz, 1H), 5.61-5.55 (m, 1H), 5.55 (dd, $J = 12.8, 2.0$ Hz, 1H), 5.51-5.46 (m, 1H), 5.50 (s, 1H), 5.06 (dddd, $J = 17.2, 1.9, 1.7, 1.7$ Hz, 1H), 4.99 (dddd, $J = 10.2, 1.9, 1.7, 1.7$ Hz, 1H), 4.47 (brd, $J = 7.6$ Hz, 1H), 4.42-4.38 (m, 1H), 4.12 (ddd, $J = 8.2, 8.2, 5.0$ Hz, 1H), 3.64-3.56 (m, 2H), 2.98-2.94 (m, 2H), 2.74 (s, 1H), 1.26 (s, 3H).