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Synthetic studies towards gambierol. Part 2: Synthesis of the EFGH ring segment

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Abstract—The EFGH ring segment of gambierol was synthesized from 2-deoxy-D-ribose in 40 steps. The present synthesis includes a SmI_2 -mediated reductive cyclization and a Pd-catalyzed coupling of enol triflate with a zinc bis-homoenolate as key steps. © 2001 Elsevier Science Ltd. All rights reserved.

In the preceding paper, we described the synthesis of the AB ring segment of gambierol.¹ We next examined the synthesis of the EFGH ring segment.²

Scheme 1 describes the synthesis of the EF ring segment. The starting material 1,3 derived from 2-deoxy-Dribose, was converted into 2 in 67% yield by hydrogenation, Swern oxidation, methylation, hydrolysis, and Yamaguchi lactonization.⁴ The lactone 2 was treated with PhNTf₂ and KHMDS to give the corresponding enol triflate,⁵ which was subjected to the palladium-catalyzed carbonylation to give 3 in 90% yield.⁶ DIBALH reduction of the ester 3 followed by MPM protection gave 4 in 99% yield. Hydroboration of the enol ether 4 with BH₃·SMe₂ gave a 3:2 mixture of the desired alcohol 5 and its stereoisomer 6 in 89% yield. Protection of 5 with MPMCl, hydrolysis of the benzylidene acetal, protection of the resulting diol as a bis-TBS ether, and selective removal of the primary TBS group afforded 7 in 57% yield. One carbon elongation of the hydroxymethyl group of 7 was achieved by Swern oxidation and subsequent Wittig reaction of the resulting aldehyde followed by hydroboration to give alcohol 8 in 77% yield. Swern oxidation followed by the addition of MeMgBr to the resulting aldehyde gave the corresponding methyl carbinol, which was oxidized under Swern conditions, giving the methyl ketone 9 upon desilylation, in 66% yield. Construction of the F ring including 1,3-diaxial methyl groups was carried out

Construction of the EFGH ring system is illustrated in Scheme 2. Protection of the hydroxy group of 11 with TMS-imidazole followed by reduction of the ester with LiAlH₄ gave the alcohol **12** in quantitative yield. Swern oxidation of 12 followed by Wittig reaction gave the enol ether 13 in 64% yield. After hydrolysis, the resulting aldehyde was oxidized to the corresponding hydroxy carboxylic acid, which was allowed to cyclize under Yamaguchi conditions to give 14 in 74% yield.8 Treatment of the lactone 14 with PhNTf₂ and KHMDS gave the corresponding ketene acetal triflate,⁹ which was allowed to react with IZn(CH₂)₃CO₂Et in the presence of Pd(PPh₃)₄ to afford 15 in 87% yield.¹⁰⁻¹² Unfortunately, hydroboration of the enol ether 15 gave the undesired stereoisomer 16 as the sole product, although the yield was quantitative. Stereoisomerization of 16 was performed by the following steps; Dess-Martin oxidation¹³ of **16** followed by treatment with DBU gave 17 in 64% yield, and then reduction of the ketone 17 with NaBH₄ gave the desired alcohol 18 as a single stereoisomer in 98% yield. Hydrolysis of the ester followed by Yamaguchi lactonization gave the EFGH ring segment 19 in 76% yield.¹⁴ The stereochemistry of 19 was unambiguously confirmed by ¹H NMR analysis and NOE experiments as illustrated in Fig. 1.

by the Nakata protocol.⁷ Thus, treatment of the alcohol **9** with ethyl propiolate and 4-methylmorphorine gave the acrylate **10**, which was then subjected to the SmI₂-mediated reductive cyclization to give the bicycle **11** as a single stereoisomer in 97% yield.

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Scheme 1. (a) (i) H_2 , 5% Pd–C, EtOAc, 98%; (ii) (COCl)₂, DMSO, CH_2Cl_2 , -78°C, then Et_3N , -78°C to rt; (iii) Me₃Al, CH_2Cl_2 , -20°C, 70% (two steps); (iv) LiOH, THF/H₂O, rt, 100%; (v) 2,4,6-trichlorobenzoyl chloride, Et_3N , THF, rt, then DMAP, benzene, rt, 98%; (b) (i) PhNTf₂, KHMDS, HMPA, THF, -78°C; (ii) CO, Et_3N , Pd(PPh₃)₄, MeOH, rt, 90% (two steps); (c) (i) DIBALH, CH₂Cl₂, -78°C, 99%; (ii) MPMCl, KH, THF, 0°C to rt, 100%; (d) BH₃·SMe₂, THF, 0°C to rt, then 30% H₂O₂, 3N NaOH, 0°C, 53% for **5**, 36% for **6**; (e) (i) MPMCl, KH, THF, 0°C to rt, 77%; (ii) CSA, CH₂Cl₂/MeOH, rt, 84%; (iii) TBSOTf, 2,6-lutidine, CH₂Cl₂, 0°C to rt, 96%; (iv) CSA, CH₂Cl₂/MeOH, 0°C, 91%; (f) (i) (COCl)₂, DMSO, CH₂Cl₂, -78°C, then Et_3N , -78°C to rt, 95%; (ii) Ph₃P⁺CH₃Br⁻, NaHMDS, THF, 0 to rt, 96%; (iii) (*c*-Hex)₂BH, 0°C, then H₂O₂, 3N NaOH, 0°C, 84%; (g) (i) (COCl)₂, DMSO, CH₂Cl₂, -78°C, then Et_3N , -78°C to rt, 86%; (ii) MeMgI, ether, 0°C; (iii) (COCl)₂, DMSO, CH₂Cl₂, rt, 100%; (i) SmI₂, MeOH, THF, 0°C, 97%.

We should mention the difficulties we encountered on introducing the two bridgehead methyl groups of the EFGH ring segment. We attempted to install a methyl group by the reaction of an acetal with organometals such as Me_2Zn^{15} and Me_3Al^{16} in the presence of a variety of Lewis acids, but all attempts resulted in failure. Finally, the SmI₂ and palladium methods enabled us to synthesize the EFGH ring segment, relatively easily.



Figure 1. Observed NOEs are shown by arrows.

In conclusion, the synthesis of the EFGH ring segment of gambierol was achieved in 40 steps from 2-deoxy-D-ribose in 1.9% total yield. The SmI₂-mediated reductive cyclization was successfully applied to the construction of the EF ring bearing two 1,3-diaxial methyl groups. The palladium-catalyzed coupling of enol triflate and zinc bis-homoenolate was very effective and efficient for synthesizing the GH ring moiety. Further studies toward the total synthesis of gambierol are now in progress in our laboratories.

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Scheme 2. (a) (i) TMS-imidazole, CH_2Cl_2 , rt; (ii) LiAlH₄, ether, 0°C, 100% (two steps). (b) (i) SO₃·py, DMSO, Et₃N, CH_2Cl_2 , rt, 87%; (ii) Ph₃P+CH₂OMeCl⁻, NaHMDS, THF, -78°C to rt, 74%; (c) (i) CSA, CH_3CN/H_2O , rt, 83%; (ii) NaClO₂, 2-methyl-2-butene, NaH₂PO₄, *t*-BuOH/H₂O, rt; (iii) 2,4,6-trichlorobenzoyl chloride, Et₃N, THF, rt, then DMAP, benzene, rt, 89% (two steps); (d) (i) PhNTf₂, KHMDS, HMPA, THF, -78°C; (ii) IZn(CH₂)₃CO₂Et, Pd(PPh₃)₄, benzene, rt, 87% (two steps); (e) BH₃·SMe₂, THF, 0°C, then 30% H₂O₂, satd NaHCO₃, 94%; (f) (i) Dess–Martin periodinane, NaHCO₃, CH₂Cl₂, rt; (ii) DBU, toluene, rt, 64% (two steps); (g) NaBH₄, CH₂Cl₂/MeOH, -78°C, 98%; (h) (i) LiOH, THF/H₂O, 40°C; (ii) 2,4,6-trichlorobenzoyl chloride, Et₃N, THF, rt, then DMAP, benzene, rt, 76% (two steps).

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- 14. Compound 19: colorless needles; mp 155°C (hexane/CH₂Cl₂, 2:1); R_f=0.26 (hexane/EtOAc, 1:1); [α]_D²⁵=-31.2 (c 0.99, CHCl₃); IR (KBr) 2941, 1755, 1514, 1109 cm⁻¹; ¹H NMR (300 MHz, CDCl₃): δ 7.22 (d, J=8.6 Hz, 2H), 7.19 (d, J=8.6 Hz, 2H), 6.86 (d, J=8.6 Hz, 2H), 6.83 (d, J=8.6 Hz, 2H), 4.47 (s, 2H), 4.43 (d, J=11.8 Hz, 1H), 4.36 (d, J=11.8 Hz, 1H), 4.13 (ddd, J=10.4, 10.4, 5.1 Hz, 1H), 4.00 (bs, 1H), 3.80 (s, 3H), 3.79 (s, 3H), 3.68 (bs, 1H), 3.61 (ddd, J=9.3, 9.3, 3.3 Hz, 1H), 3.42 (dd, J=9.8, 5.0 Hz, 1H), 3.29 (dd, J=

9.7, 6.3 Hz, 1H), 3.19 (dd, J=11.8, 3.3 Hz, 1H), 3.13 (dd, J=13.2, 3.5 Hz, 1H), 2.68 (dd, J=13.5, 7.0 Hz, 1H), 2.55 (dd, J=13.6, 13.6 Hz, 1H), 2.32–1.45 (m, 12H), 1.47 (s, 3H), 1.29 (s, 3H); ¹³C NMR (75 MHz, CDCl₃): δ 174.4, 159.1, 159.0, 130.6, 130.5, 129.2, 128.9, 113.7, 113.7, 88.8, 79.7, 78.2, 77.8, 76.4, 75.8, 73.0, 72.4, 71.9, 70.4, 70.1, 55.2, 53.4, 36.0,

34.4, 30.7, 25.4, 23.3, 20.6, 17.0, 16.6; HRMS (EI) calcd for $C_{27}H_{37}O_8~(M-C_8H_9O)$ 489.2488, found 489.2499.

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