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Total Synthesis of an Anticancer Agent, Mucocin. 2. A Novel Approach to a γ-Hydroxy Butenolide Derivative and Completion of Total Synthesis

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Abstract: Total synthesis of mucocin (1) was accomplished through a palladium-catalyzed cross coupling reaction of the C₁₀-C₃₄ fragment of 1 and a newly designed γ -hydroxy butenolide subunit, which was synthesized by taking advantage of radical cyclization of an acyclic olefin having a selenocarbonate group derived from L-rhamnose. © 1999 Elsevier Science Ltd. All rights reserved.

Having completed the stereoselective synthesis of the left-half segment 2 of mucocin (1),¹ we next turned our attention to the synthesis of the right-half segment including a γ -hydroxy butenolide. Although several methods for preparation of such γ -lactone subunit of annonaceous acetogenins have been devised, the synthetic examples reported so far have mainly relied on aldol addition of γ -alkyloxy esters with a chiral aldehyde or alkylation with an optical active terminal epoxide or a chiral γ -lactone.² In this paper, we describe a novel synthesis of a γ -hydroxy butenolide derivative 3 and the total synthesis of 1 therefrom.³



The synthesis of fragment 3 began with L-rhamnose and involved construction of a γ -lactone moiety utilizing a radical cyclization as a key step. Phenyl 5-O-acetyl-2,3-O-isopropylidene-1-thio-L-rhamnofuranoside 4⁴ was subjected to methanolysis, and then the liberated hydroxy group was protected as a methoxyphenylmethyl (MPM) ether (Scheme 1). This was treated with N-bromosuccinimide in aqueous tetrahydrofuran to afford a hemiacetal 5⁵ in 85% yield from 4. For stereoselective introduction of the C4-side chain into 5, coupling reaction of 5 with a butyn derivative 6 was examined. Reaction with the Grignard reagent obtained from 6 in ether gave a separable mixture of acetylene alcohols (7⁵ and 8⁵) in good yield

Scheme 1^a



^aReagents and conditions: (a) NaOMe, MeOH, rt. (b) MPMCl, NaH, Bu4NI, DMF, 0 °C. (c) *N*-Bromosuccinimide, aq. THF, 0 °C. (d) *n*-BuLi, hexane-Et2O (3 : 1), -78 °C to rt. (e) MOMCl, *i*-Pr2NEt, CH2Cl2, 0 °C. (f) 5% Rh/Al2O3, H2, EtOAc, rt. (g) aq. AcOH, rt. (h) HC(OMe)3, PPTS, CH2Cl2, rt. (i) Ac2O, 135 °C. (j) DDQ, aq. CH2Cl2, 0 °C. (k) triphosgene, pyridine, CH2Cl2, 0 °C, and then PhSeH, Et3N. (l) Bu3SnH, AIBN, toluene, 100 °C. (m) TBAF, AcOH, THF, rt. (n) DBU, CH3CN, 0 °C. (o) Swern oxidation, -75 °C. (p) CH13, CrCl2, THF, 0 °C to rt. (q) **2**, (Ph3P)2PdCl2, CuI, Et3N, rt. (r) (Ph3P)3RhCl, H2, benzene-EtOH (6 : 1), rt. (s) BF3·Et2O, Me2S, 0 °C.

(79%). The major isomer obtained in 64% yield, however, was revealed to be an undesired β -alcohol 7 by the modified Mosher's method.⁶ On the other hand, the reversed diastereofacial selectivity was observed when the corresponding lithium derivative was employed (Table 1). In particular, the use of a mixed solvent system (hexane-ether = 3:1) was effective; 67% yield of 8 was attained along with 7 (11%). The difference in these stereoselectivities would be explained by two types of chelation as shown below.

Entry	Conditions	Ratio (8/7)	Yield (%)	ц
1	EtMgBr, Et ₂ O, -78 °C \rightarrow rt	19/81	79	
2	<i>n</i> -BuLi, MgBr ₂ , Et ₂ O, −78 °C \rightarrow rt	55/45	21	TOR' I
3	<i>n</i> -BuLi, Lil, Et₂O, -78 °C → rt	71/29	79	R' H
4	<i>n</i> -BuLi, Et ₂ O, -78 °C → rt	80/20	73	o to t
5	<i>n</i> -BuLi, hexane-Et ₂ O (3 : 1), -78 °C \rightarrow rt	86/14	78	10.0

The two hydroxy groups in 8 were simultaneously protected as a methoxymethyl (MOM) ether, and the triple bond of the resulting compound was hydrogenated over rhodium on alumina to give a di-MOM ether 9^5 in 85% yield. Exposure of 9 to mild acidic conditions led to selective removal of the acetonide group, giving a diol 10 in 75% yield. This was deoxygenated⁷ via the corresponding orthoester to afford a Z-olefin 11^5 in 85% yield. After deprotection⁸ of the MPM group (81%), the homoallyl alcohol 12 obtained was treated successively with triphosgen⁹ in the presence of pyridine, and then benzeneselenol¹⁰ and triethylamine, giving a selenocarbonate derivative 13^5 in 78% yield. Radical cyclization of 13 with Bu₃SnH in toluene at 100 °C proceeded nicely to give a 3,4-*trans*- γ -lactone 14^5 in 86% yield. In addition, a trace amount of 3,4-*cis*-isomer 15^5 (3%) was also obtained. These relative stereochemistries were established by the NMR analyses together with the difference NOE experiments.¹¹ Although both isomers could be a key intermediate for preparation of 3, the major isomer 14 was employed to the next step. The TBDPS group in 14 was removed by tetrabutylammonium fluoride in the presence of acetic acid, and then the resulting alcohol was treated briefly with DBU in acetonitrile at 0 °C, affording a hydroxy butenolide 16 in 54% yield from 14.¹² Swern oxidation and a vinyl iodide formation¹³ of 16 afforded the right-half segment 3^5 as a 4.5:1 mixture of *E*/Z isomers in 74% yield.

The complete carbon skeleton of 1 was assembled by joining 2 and 3 under Hoye's conditions¹⁴ to give a labile enyne 17 in 79% yield. This underwent regioselective reduction with Wilkinson's catalyst in benzeneethanol to give a fully protected mucocin 18 in 61% yield. Finally, all of the MOM groups in 18 were cleaved by $BF_3 \cdot Et_2O$ in methyl sulfide¹⁵ to give 76% yield of mucocin (1),⁵ whose spectral properties were indistinguishable from those of the natural product.¹⁶

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- All stable new compounds gave satisfactory results of elemental analyses. Values of $[\alpha]_D$ and δ_H , δ_C 5. were measured for the solution in CHCl₃ and CDCl₃, respectively, at $24\pm2^{\circ}$. 7: [α]_D +8.0° (c 0.20); $\delta_{\rm H}$ 3.52 (1H, dq, J = 7.8, 5.8 Hz), 4.02 (1H, brt, J = 7.8, 7.8, 1.5 Hz), 4.12 (1H, dd, J = 6.8, 5.4 Hz). **8**: $[\alpha]_D$ +12.9° (c 0.16); δ_H 3.49 (1H, dq, J = 7.8, 5.8 Hz), 3.72 (1H, dt, J = 8.3, 8.3, 1.4 Hz), 4.15 (1H, dd, J = 7.3, 5.9 Hz). 9: [α]_D -11.0° (c 2.29); δ _H 3.39 (3H, s), 3.43 (3H, s), 3.49 (1H, qd, J =6.4, 6.4 Hz), 3.61 (2H, t, J = 6.4 Hz), 3.69 (1H, brq, J = 6.4, 4.3 Hz), 3.72 (3H, s), 3.86 (1H, t, J = 6.1 Hz), 4.00 (1H, dd, J = 6.1, 4.3 Hz), 4.11 (1H, t, J = 6.4 Hz). 11: [α]_D +0.4° (c 1.19); δ _H 3.47 (1H, dq, J = 6.4, 4.2 Hz), 4.40 (1H, ddd, J = 6.2, 4.2, 2.0 Hz), 5.50 (2H, m). 13: $[\alpha]_D - 12.5^{\circ} (c = 1.2 + 1.2)$ 0.69; $\delta_{\rm H}$ 4.45 (1H, dd, J = 9.3, 4.4 Hz), 5.02 (1H, m), 5.39 (1H, t, J = 10 Hz), 5.59 (1H, t, J = 10Hz); $\delta_{\rm C}$ 166.2. 14: [α]_D -28.3° (c 1.42); $v_{\rm max}$ 1778 cm⁻¹; $\delta_{\rm H}$ 2.84 (1H, ddd, J = 6.4, 4.6, 3.4 Hz), 3.77 (1H, m), 3.82 (1H, dd, J = 7.3, 6.1 Hz), 4.34 (1H, dd, J = 6.4, 6.1 Hz); δ_C 63.5, 75.1, 79.4, 85.2, 175.8. 15: $[\alpha]_D$ -12.0° (c 0.44); v_{max} 1775 cm⁻¹; δ_H 2.91 (1H, ddd, J = 6.8, 6.3, 5.9 Hz), 3.82 (1H, m), 4.02 (1H, d, J = 5.9 Hz), 4.60 (1H, brq, J = 6.9 Hz); δ_{C} 63.7, 76.2, 80.0, 80.2, 177.4. 3: v_{max} 1753 cm⁻¹; δ_H 5.99 (0.82H, td, J = 14.7, 1.5, 1.5 Hz), 6.15 (0.18H, ddd, J = 7.3, 7.3, 7.3 Hz), 6.21 (0.18H, dd, J = 7.3, 1.0 Hz), 6.49 (0.82H, ddd, J = 14.7, 7.3, 7.3 Hz); δ_C 173.8; HRMS calcd for C14H21O4NaI [M+Na]⁺ 403.0382, found 403.0375. 1: mp 59-60 °C (lit.¹ 57-58 °C); $[\alpha]_D - 13.9^\circ$ (c 0.11, CH₂Cl₂) { lit.^{1b} - 10.8° (CH₂Cl₂)}; δ_C 14.1, 19.1, 22.7, 25.5, 26.2, 26.9, 28.3, 28.7, 28.8, 29.3, 29.4, 29.5, 29.6, 29.7, 31.9, 32.0, 32.4, 32.6, 33.3, 35.6, 37.4, 69.9, 70.6, 73.5, 73.8, 78.0, 79.3, 80.1, 81.9, 82.0, 131.2, 151.8, 174.6; HRMS calcd for C₃₇H₆₇O₈ [M+H]⁺ 639.4836, found 639.4833.
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