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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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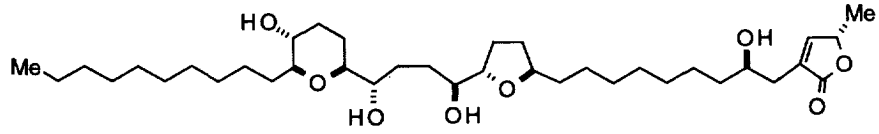
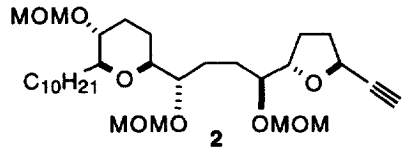
Abstract: *Total synthesis of mucocin (1) was accomplished through a palladium-catalyzed cross coupling reaction of the C_{10}-C_{34} fragment of 1 and a newly designed γ-hydroxy butenolide subunit, which was synthesized by taking advantage of radical cyclization of an acyclic olefin having a selenocarbonate group derived from L-rhamnose.*

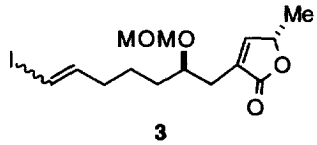
Having completed the stereoselective synthesis of the left-half segment **2** of mucocin (**1**),[1] we next turned our attention to the synthesis of the right-half segment including a γ-hydroxy butenolide. Although several methods for preparation of such γ-lactone subunit of annonaceous acetogenins 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]



Mucocin (1)



2



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 **4**[4] 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 **5**[5] 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 (**7**[5] and **8**[5]) in good yield

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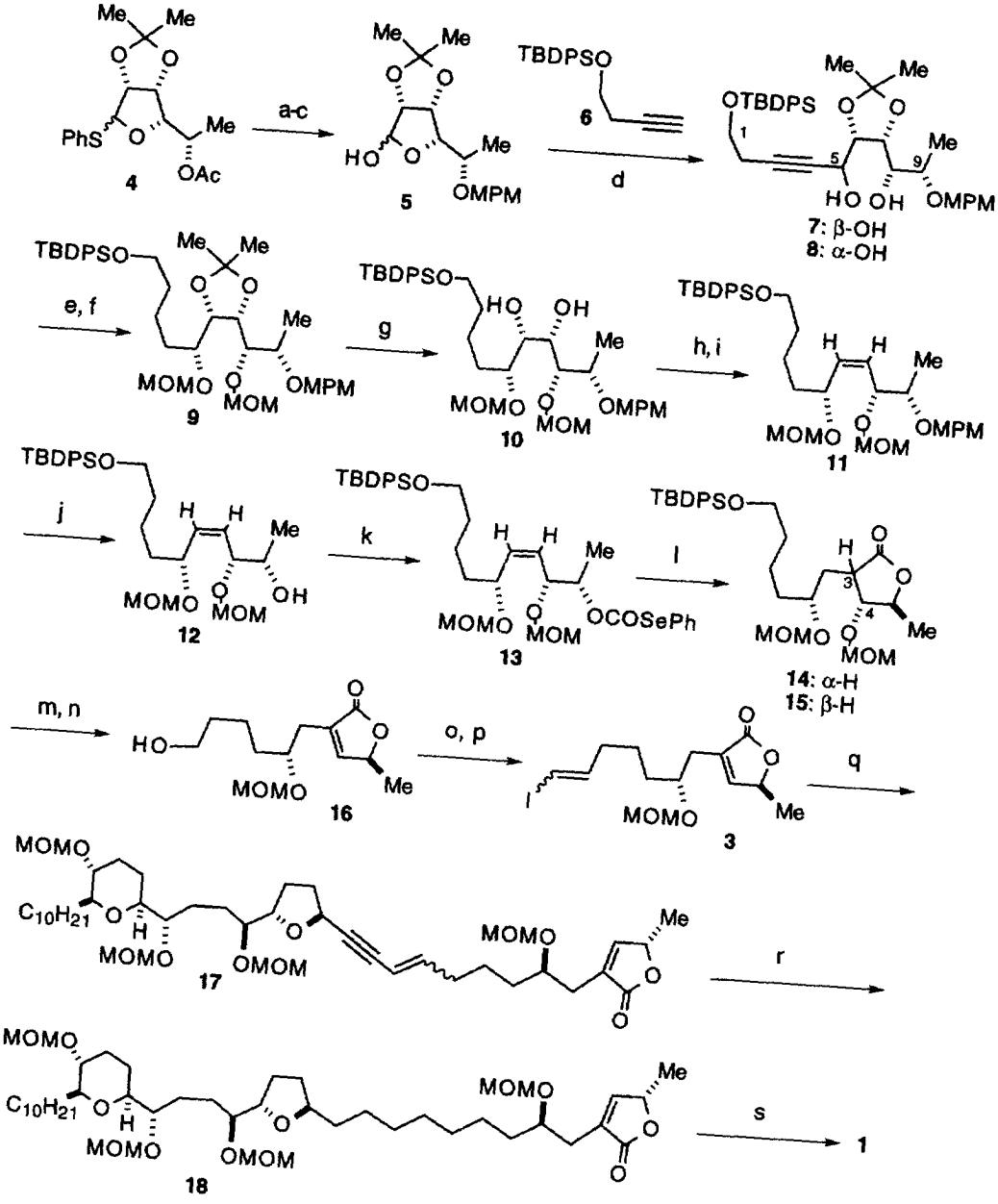
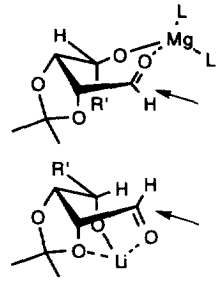
Scheme 1[a]



[a]Reagents and conditions: (a) NaOMe, MeOH, rt. (b) MPMCl, NaH, Bu_4NI, DMF, 0 °C. (c) *N*-Bromosuccinimide, aq. THF, 0 °C. (d) *n*-BuLi, hexane-Et_2O (3 : 1), -78 °C to rt. (e) MOMCl, *i*-Pr_2NEt, CH_2Cl_2, 0 °C. (f) 5% Rh/Al_2O_3, H_2, EtOAc, rt. (g) aq. AcOH, rt. (h) $HC(OMe)_3$, PPTS, CH_2Cl_2, rt. (i) Ac_2O, 135 °C. (j) DDQ, aq. CH_2Cl_2, 0 °C. (k) triphosgene, pyridine, CH_2Cl_2, 0 °C, and then PhSeH, Et_3N. (l) Bu_3SnH, AIBN, toluene, 100 °C. (m) TBAF, AcOH, THF, rt. (n) DBU, CH_3CN, 0 °C. (o) Swern oxidation, -75 °C. (p) CHI_3, $CrCl_2$, THF, 0 °C to rt. (q) **2**, $(Ph_3P)_2PdCl_2$, CuI, Et_3N, rt. (r) $(Ph_3P)_3RhCl$, H_2, benzene-EtOH (6 : 1), rt. (s) $BF_3{\cdot}Et_2O$, Me_2S, 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 (%)
1	EtMgBr, Et_2O, -78 °C → rt	19/81	79
2	*n*-BuLi, $MgBr_2$, Et_2O, -78 °C → rt	55/45	21
3	*n*-BuLi, LiI, Et_2O, -78 °C → rt	71/29	79
4	*n*-BuLi, Et_2O, -78 °C → rt	80/20	73
5	*n*-BuLi, hexane-Et_2O (3 : 1), -78 °C → rt	86/14	78



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 deoxygenated[7] *via* the corresponding orthoester to afford a *Z*-olefin **11**[5] in 85% yield. After deprotection[8] of the MPM group (81%), the homoallyl alcohol **12** obtained was treated successively with triphosgen[9] in the presence of pyridine, and then benzeneselenol[10] and triethylamine, giving a selenocarbonate derivative **13**[5] in 78% yield. Radical cyclization of **13** with Bu_3SnH 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 formation[13] 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 conditions[14] to give a labile enyne **17** in 79% yield. This underwent regioselective reduction with Wilkinson's catalyst in benzene-ethanol 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 sulfide[15] to give 76% yield of mucocin (**1**),[5] whose spectral properties were indistinguishable from those of the natural product.[16]

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References and notes

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5. All stable new compounds gave satisfactory results of elemental analyses. Values of $[\alpha]_D$ and δ_H, δC were measured for the solution in $CHCl_3$ and $CDCl_3$, respectively, at 24±2°. **7**: $[\alpha]_D$ +8.0° (*c* 0.20); δ_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**: $[\alpha]_D$ -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**: $[\alpha]_D$ +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° (*c* 0.69); δ_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* = 10 Hz); δ_C 166.2. **14**: $[\alpha]_D$ -28.3° (*c* 1.42); ν_{max} 1778 cm^{-1}; δ_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); ν_{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**: ν_{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 $C_{14}H_{21}O_4NaI$ $[M+Na]^+$ 403.0382, found 403.0375. **1**: mp 59-60 °C (lit.[1] 57-58 °C); $[\alpha]_D$ -13.9° (*c* 0.11, CH_2Cl_2) {lit.[1b] -10.8° (CH_2Cl_2)}; 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 $C_{37}H_{67}O_8$ $[M+H]^+$ 639.4836, found 639.4833.
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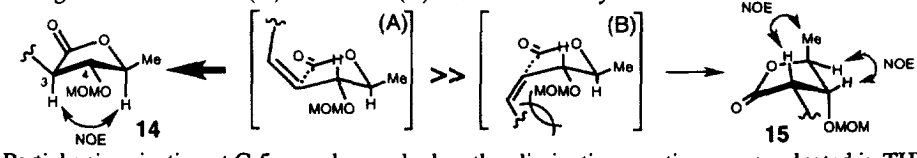
11. The 3,4-*trans* stereoselection in the radical cyclization would result from reaction of the acyl radical through a transition state (A) rather than (B) because of an allylic strain.



12. Partial epimerization at C-5 was observed when the elimination reaction was conducted in THF at rt.
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16. After this paper was submitted, we knew that Neogi and co-workers reported a total synthesis of mucocin with Articles ASAP (Web release date, October 27, 1998) in ACS Web Editions.