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Total Synthesis of an Anticancer Agent, Mucocin. 1. Stereoselective Synthesis of the Left-Half Segment

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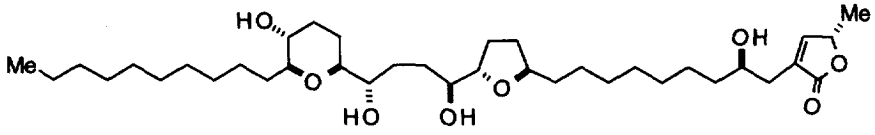
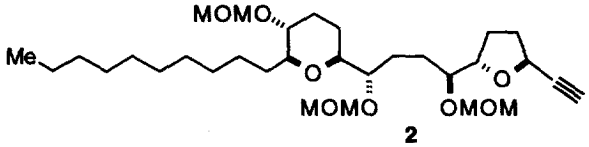
Abstract: *The left-half segment of mucocin (1) was stereoselectively synthesized through a coupling reaction of a tetrahydropyranyl aldehyde and a tetrahydrofuran derivative having an ethynyl group, which were prepared from 2,3,4,6-tetra-O-benzyl-D-galactono-1,5-lactone and 2,5-anhydro-D-mannitol, respectively.*

The rapidly expanding family of annonaceous acetogenins has attracted much attention owing to the wide spectrum of their biological activities such as cytotoxic, insecticidal, fungicidal, anthelmintic, and cancerostatic effects.[1] Mucocin (**1**), which was recently isolated from the leaves of *Rollinia mucosa* (Jacq.) Baill. (Annonaceae) by McLaughlin et al.,[2] is the first annonaceous acetogenin to be reported that bears a tetrahydropyran ring along with a tetrahydrofuran ring.[2] This compound shows remarkable inhibitory activities against A-549 (lung cancer) and PACA-2 (pancreatic cancer) solid tumor lines with a potency of more than 10^4 times that of adriamycin. The powerful antitumor activity and the unique structure of **1** have consequently stimulated synthetic efforts toward **1**.[3] We describe the stereocontrolled synthesis of the left-half segment **2** of **1** in this communication, and the synthesis of the right-half segment and total synthesis of **1** in the following paper.[4]



Mucocin (1)



2

Our synthetic strategy directed toward **2** was based on a convergent process involving (a) a facile preparation of a 2,6-disubstituted tetrahydropyran-3-ol derivative **8** by taking advantage of Kishi's C-glycosidation method,[5] (b) stereoselective synthesis of a highly functionalized tetrahydrofuran derivative **15**, and (c) construction of the left-half segment **2** through a condensation reaction of **8** and **15**.

The tetrahydropyran **8** was prepared from 2,3,4,6-tetra-*O*-benzyl-D-galactono-1,5-lactone (**3**)[5] as follows (Scheme 1). Reaction of **3** with decylmagnesium bromide in ether at -78 °C afforded a hemiacetal, which was

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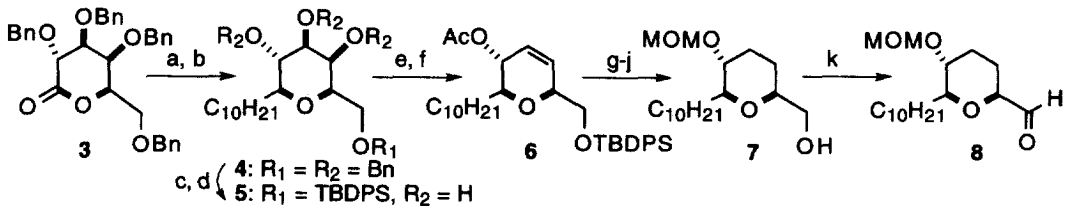
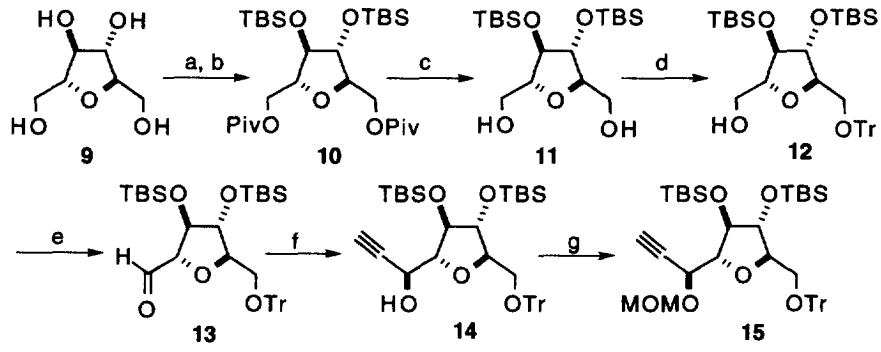
Scheme 1[a]



[a]Reagents and conditions: (a) Decylmagnesium bromide, Et_2O, -78 °C. (b) Et_3SiH, BF_3·Et_2O, CH_2Cl_2, -40 °C. (c) 10% Pd/C, H_2, EtOAc-MeOH, rt. (d) TBDPSCl, Imidazole, DMF, rt. (e) $HC(OMe)_3$, CSA, CH_2Cl_2, rt. (f) Ac_2O, 135 °C. (g) 10% Pd/C, H_2, EtOAc, rt. (h) NaOMe, MeOH, rt. (i) MOMCl, *i*-Pr_2NEt, CH_2Cl_2, 0 °C to rt. (j) TBAF, THF, rt. (k) Swern oxidation, -75 °C.

treated with triethylsilane in the presence of BF_3·Et_2O at -40 °C to give a β-glycoside **4**[6] in 80% yield.[7] Subsequent debenzylation and mono-silylation of **4** afforded a triol **5** in 78% yield. Deoxygenation[8] of **5** was accomplished through an orthoester (66%) to provide an olefin **6**[6] in 78% yield. This was converted into a primary alcohol **7**[6] by the following sequence: (1) hydrogenation of a double bond, (2) deacetylation, (3) formation of a methoxymethyl (MOM) ether, (4) desilylation (93% overall yield). Swern oxidation of **7** gave the building block **8**[6] in almost quantitative yield.

Scheme 2[a]

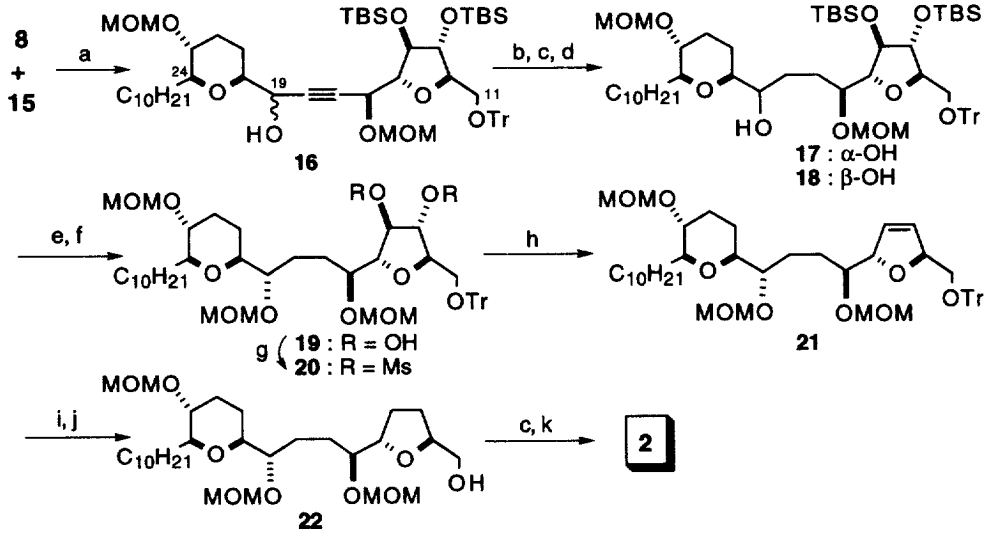


[a]Reagents and conditions: (a) PivCl, pyridine, 0 °C to rt. (b) TBDMSCl, imidazole, DMF, rt. (c) LAH, Et_2O, 0 °C. (d) TrCl (1.1eq.), 2,6-di-t-bu-4-methylpyridine, CH_2Cl_2, rt. (e) Swern oxidation, -75 °C. (f) ethynyl magnesium chloride, $ZnCl_2$, CH_2Cl_2-Et_2O-THF, -78 °C. (g) MOMCl, *i*-Pr_2NEt, CH_2Cl_2, 0 °C to rt.

On the other hand, the synthesis of the tetrahydrofuran **15**[6] started with 2,5-anhydro-D-mannitol (**9**) (Scheme 2). Differential protection of the primary and secondary alcohols in **9** with pivaloyl chloride and *t*-$BuMe_2SiCl$ (TBDMSCl), respectively, gave a fully protected compound **10** (69%), whose pivaloyl groups were effectively removed with LAH, producing **11** in 70% yield. Partially tritylation of **11** was achieved with trityl chloride (1.1 molar equiv) in the presence of 2,6-di-*t*-butyl-4-methylpyridine to furnish a monotrityl alcohol **12**[6] (68%, based upon **11** consumed). Swern oxidation of **12** gave an aldehyde **13** which was allowed to react with ethynylmagnesium chloride in the presence of $ZnCl_2$ in dichloromethane-ether-THF[9] to give a 93 : 7 mixture of the desired β-alcohol **14**[6] and its epimer in 70% yield.[10] For this α-chelation

controlled addition of the ethynyl group, the presence of a TBSO-group was essential.[11] The major isomer **14** was then converted into a MOM ether **15**[6] in 83% yield, and the condensation reaction with **8** was examined.

Scheme 3[a]



[a]Reagents and conditions: (a) *n*-BuLi, $CeCl_3$, THF, -78 ℃. (b) 5% PtO_2, H_2, EtOAc, rt. (c) Swern oxidation, -75 ℃. (d) L-Selectride, THF, -78 ℃. (e) MOMCl, *i*-Pr_2NEt, CH_2Cl_2, 0 ℃ to rt. (f) TBAF, THF, rt. (g) MsCl, Et_3N, CH_2Cl_2, 0 ℃ to rt. (h) Zn, NaI, DMF, 140 ℃. (i) 10% Pd/C, H_2, EtOAc, rt. (j) aq. AcOH, 50 ℃. (k) dimethyl-1-diazo-2-oxopropylphosphonate, K_2CO_3, MeOH, 0 ℃ to rt.

Initial attempts[12] to react **8** with a lithium or magnesium compound derived from **15** resulted in a low yield of the coupled product **16** as an inseparable mixture (Scheme 3). In contrast, addition of anhydrous $CeCl_3$[13] to the solution of the lithium acetylide prior to addition of **8** gave a mixture of alcohols **16** in good yield (78% yield). ^{1}H-NMR analyses,[10] however, revealed the major isomer was an undesired β-alcohol (86% d. e.).[14, 15] After several experimentations, the corresponding saturated isomers (**17**[6] and **18**[6]) were found to be readily separated by column chromatography on silica gel. Conveniently, a simple two-step oxidation-reduction sequence: (1) Swern oxidation, (2) L-Selectride reduction, of the mixture gave the desired α-alcohol **17** in high yield (88% from **16**) and its isomer **18** (3%). As the requisite stereochemistry at C(19) was thus efficiently installed, our attention was next turned to deoxygenation on the tetrahydrofuran ring. After protection of the 19-hydroxy group as the MOM ether and deprotection of the TBS group in **17**, the resultant diol **19** was converted into a dimesylate **20** in 87% yield. Treatment[16] of **20** with zinc-sodium iodide in DMF afforded an olefin **21**. This underwent hydrogenation and de-tritylation, giving a primary alcohol **22** in 77% yield from **20**. Swern oxidation of **22** gave an aldehyde, which was transformed into the left-half segment **2**[6] by Bestmann's procedure.[17]

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H. Koshino (RIKEN) for measurement of 2D-NMR spectra, Ms. K. Harata (RIKEN) for mass spectral measurements, and Dr. T. Chihara and his collaborators in RIKEN for the elemental analyses.

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6. 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°. **4**: $[\alpha]_D$ -5.9° (*c* 0.36); δ_H 3.23 (1H, ddd, *J* = 8.8, 8.8, 2.4 Hz). **6**: $[\alpha]_D$ -90.2° (*c* 0.26); δ_H 2.08 (3H, s), 5.74 (1H, ddd, *J* = 10, 10, 2.0 Hz), 5.94 (1H, ddd, *J* = 10, 10, 1.5 Hz). **7**: $[\alpha]_D$ -42.3° (*c* 2.23); δ_H 3.17 (1H, ddd, *J* = 8.8, 8.8, 2.3 Hz), 3.22 (1H, ddd, *J* = 9.3, 9.3, 3.9 Hz). **8**: δ_H 9.63 (1H, brs); δ_C 201.7. **12**: $[\alpha]_D$ +13.1° (*c* 1.10); δ_H 3.11 (1H, dd, *J* = 9.7, 6.0 Hz), 3.37 (1H, dd, *J* = 9.7, 7.0 Hz). **14**: $[\alpha]_D$ +2.9° (*c* 1.34); δ_H 2.47 (1H, d, *J* = 2.0 Hz), 4.54 (1H, ddd, *J* = 7.3, 3.4, 2.0 Hz). **15**: $[\alpha]_D$ +28.6° (*c* 1.01); δ_H 4.58 (1H, dd, *J* = 9.3, 2.0 Hz). **17**: $[\alpha]_D$ -31.5° (*c* 0.18); δ_H 3.40 (1H, m), 3.76 (1H, ddd, *J* = 7.4, 7.4, 3.9 Hz); δ_C 76.6, 80.2, 80.5. **18**: $[\alpha]_D$ -23.4° (*c* 1.13); δ_H 3.31 (1H, dd, *J* = 9.3, 6.3 Hz), 3.59 (1H, m), 3.79 (1H, m); δ_C 79.6, 80.6, 80.7. **2**: $[\alpha]_D$ -67.8° (*c* 0.46); δ_H 2.40 (1H, d, *J* = 2.0 Hz), 3.09 (1H, ddd, *J* = 9.3, 8.8, 2.4 Hz), 3.19 (1H, ddd, *J* = 9.8, 8.8, 3.9 Hz), 3.36 (3H, s), 3.37 (3H, s), 3.38 (3H, s), 4.16 (1H, brq, *J* = 7.0 Hz); δ_C 68.1, 72.6, 75.8, 79.1, 79.3, 79.4, 80.9, 81.0, 83.8; HRMS calcd for $C_{31}H_{56}O_8Na$ $[M+Na]^+$ 579.3873, found 579.3846.
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11. Use of other protecting groups such as TBDPS and Bn was not effective. Reaction of the corresponding 3,4-dideoxygenated aldehyde with a metalated acetylene under a variety of conditions also gave unsatisfactory results.
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14. This high selectivity can be explained by the Felkin-Anh transition state model.
15. Differences in the chemical shifts (Δ_{S-R} values in δ) between (*R*)- and (*S*)-MTPA esters of **16** (86% d. e.) are as follows; H_2-11 (+0.01, +0.02), H-12 (+0.00), H-13 (+0.02), H-14 (+0.02), H-15 (+0.03), H-16 (+0.01), H-19 (+0.01), H-20 (-0.06), H_2-21 (-0.15, -0.09), H_2-22 (-0.02, -0.06), H-23 (-0.09), H-24 (-0.09), H-25 (-0.26, -0.05).
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