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# Enantioselective Total Synthesis of the Potent Antitumor Agent (−)-Mucocin Using a Temporary Silicon-Tethered Ring-Closing Metathesis Cross-Coupling Reaction

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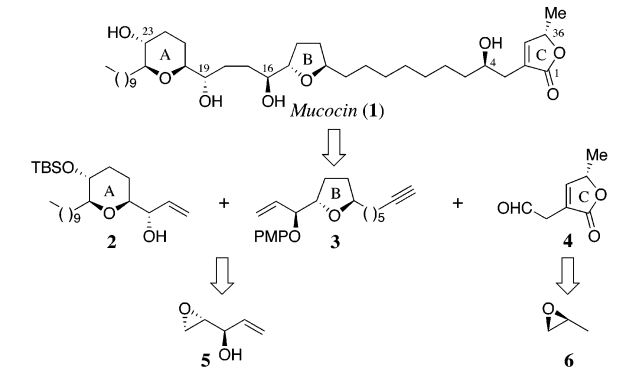
The potent antitumor agent mucocin (**1**) was isolated from the leaves of *Rollinia mucosa* (jacq.) Baill. (Annonaceae) by McLaughlin and co-workers in 1995.[1−3] This agent has exquisite selectivity for the inhibition of A-549 (lung cancer) and PACA-2 (pancreatic cancer) solid tumor cell lines with potency 10,000 times that of adriamycin (doxorubicin). Annonaceous acetogenins selectively inhibit cancerous cells through the blockage of the mitochondrial complex I (NADH-ubiquinone oxidoreductase), and the inhibition of the plasma membrane NADH oxidase, which depletes ATP and induces apoptosis (programmed cell death) in malignant cells.[4]

In a program directed toward the construction of nonadjacent tetrahydrofuran containing acetogenins, we have developed a new approach to the construction of $C_2$-symmetrical 1,4-diols, using a temporary silicon-tethered (*TST*) ring-closing metathesis (*RCM*) homo-coupling reaction.[5] Herein, we now describe a novel and expeditious synthesis of mucocin (**1**), which utilizes the *TST-RCM* cross-coupling reaction (Scheme 1).[6,7] This approach capitalizes on the localized $C_2$-symmetry and thereby permits the construction of **2** and **3** from a common synthetic intermediate, the known homoallylic epoxide **5**.[8] We further envisioned that the C4−C5 bond could be formed by enantioselective addition of the alkyne **3** to the aldehyde **4**, thereby providing a new strategic disconnection for this class of biologically important molecules.[9] The key feature of this approach is the utilization of a triply convergent strategy, that can be adapted to facilitate the synthesis of related annonaceous acetogenins, resulting in one of the most expeditious syntheses of a complex acetogenin developed to date.

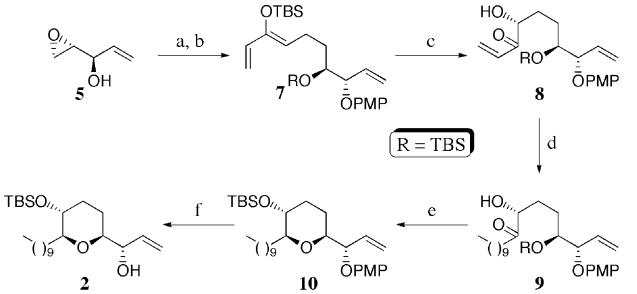
The synthesis of the 3-hydroxy-2,6-disubstituted tetrahydropyran **2** was accomplished using the novel six-step strategy outlined in Scheme 2. Mitsunobu inversion of the allylic alcohol **5** using *p*-methoxyphenol afforded the requisite aryl ether.[10] Regiospecific ring opening of the epoxide with the homoenolate equivalent[11] derived from *tert*-butyldimethylsilyl protected divinyl carbinol, followed by an *in situ* protection of the resultant secondary alcohol, afforded the differentially protected triene **7** in 96% overall yield. Chemoselective Sharpless asymmetric dihydroxylation of the triene **7** using AD-mix-$\beta$ furnished the hydroxy ketone **8** in 70% yield (*ds* ≥99:1 by HPLC), after recycling the recovered triene **7** (2×).[12] The alkyl side chain was then introduced *via* the conjugate addition of the cuprate derived from octylmagnesium bromide and copper cyanide to furnish the ketone **9** and thereby set the stage for the reductive etherification. Treatment of **9** with bismuth tribromide and *tert*-butyldimethylsilane in acetonitrile, followed by *in situ* protection of the secondary alcohol, furnished the *tert*-butyldimethylsilyl ether **10** in 93% yield (*ds* ≥19:1 by NMR).[13] Finally, the *p*-methoxyphenyl ether was oxidatively cleaved with ceric ammonium nitrate (CAN) to complete the construction of **2**.[10]

The construction of the tetrahydrofuran **3** was also initiated from the homoallylic epoxide **5**, as outlined in Scheme 3. Mitsunobu inversion of **5** followed by regiospecific ring opening of the epoxide

***Scheme 1***

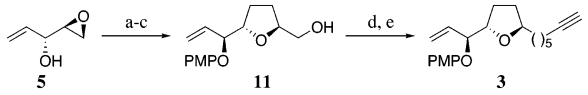



***Scheme 2*** [a]




[a] (a) *p*-MeOC$_6$H$_4$OH, DIAD, PPh$_3$, THF, 0 °C, 80%; (b) (CH$_2$═CH)$_2$CHOTBS, $^s$BuLi, THF, −78 °C, then TBSOTf, 2,6-lutidine, −78 to 0 °C, 96%; (c) AD-mix-$\beta$, $^t$BuOH/H$_2$O, MeSO$_2$NH$_2$, 0 °C (3×), 70%; (d) $^n$octylMgBr, CuCN, THF, −78 °C, 65%; (e) BiBr$_3$, $^t$BuMe$_2$SiH, MeCN, 0 °C, then 2,6-lutidine, TBSOTf, 0 °C, 93%; (f) (NH$_4$)$_2$Ce(NO$_3$)$_6$, MeCN/H$_2$O, −5 °C, 91%.

***Scheme 3*** [a]




[a] (a) *p*-MeOC$_6$H$_4$OH, DIAD, PPh$_3$, THF, 0 °C, 80%; (b) CH$_2$═CHCH$_2$MgBr, CuCN, Et$_2$O, −78 °C, 90%; (c) Co(modp)$_2$, O$_2$, $^t$BuOOH, $^i$PrOH, 60 °C, 83%; (d) Tf$_2$O, Et$_3$N, CH$_2$Cl$_2$, −78 °C, 86%; (e) TMSC≡C(CH$_2$)$_4$MgBr, CuI, THF, −20 to −10 °C; then MeOH, TBAF, −20 °C to room temperature, 73%.

(*cf.* Scheme 2) with the cuprate derived from allylmagnesium bromide and catalytic copper cyanide afforded the secondary alcohol, which was subjected to a cobalt(II) catalyzed oxidative cyclization to afford the *trans*-2,5-tetrahydrofuran **11** in 75% overall yield (*ds* ≥19:1).[2d,14] Conversion of the primary alcohol **11** to triflate, followed by cuprate displacement and *in situ* deprotection of trimethylsilyl group, furnished the B-ring fragment **3**.

The synthesis of butenolide fragment **4** commenced with the regioselective ring opening of commercially available (*S*)-propylene oxide **6** (Scheme 4). Treatment of **6** with the carbanion derived from the alkyne **12** afforded the secondary alcohol, which was



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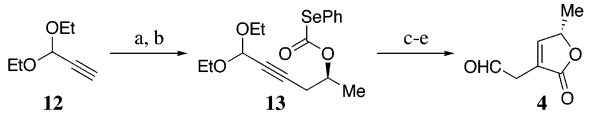
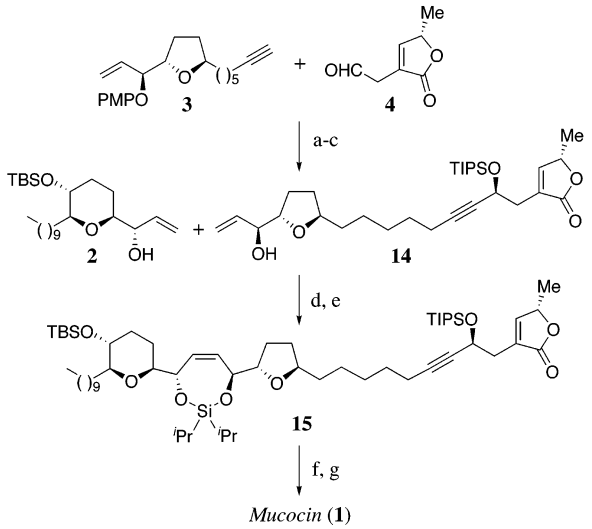
converted to the selenocarbonate **13** using phosgene and phenylselenol.[15] The selenocarbonate **13** was subjected to standard free radical conditions, to afford the $\gamma$-butyrolactone in 80% yield. Metal-catalyzed isomerization of the *exo*-cyclic olefin and subsequent hydrolysis of the diethyl acetal furnished the requisite aldehyde **4** in good overall yield.

***Scheme 4*** [a]




[a] (a) *S*-Propylene oxide **6**, $^n$BuLi, HMPA, THF, −30 °C; (b) $COCl_2$, $Et_3N$, $C_6H_6$, 0 °C to room temperature, then PhSeH, pyridine, THF/$C_6H_6$, 0 °C to room temperature, 60% overall yield from **12**; (c) $^n Bu_3SnH$, AIBN, $C_6H_6$, Δ, 80%; (d) $RhH(CO)(PPh_3)_3$, $C_6H_6$, 85 °C, 84%; (e) HCOOH, pentane, 0 °C, 90%.

***Scheme 5*** [a]




[a] (a) **3**, $Et_2Zn$, PhMe, Δ, then (*R*)-BINOL, $Ti(O^iPr)_4$, THF, **4**, 0 °C, 81%; (b) TIPSOTf, pyridine, DMAP, THF, 0 °C, 96%; (c) $(NH_4)_2Ce(NO_3)_6$, MeCN/$H_2O$, −10 °C, 91%; (d) **2**, $^iPr_2SiCl_2$ (xs), $CH_2Cl_2$, imidazole, 0 °C to room temperature, then **14**, imidazole, 0 °C to room temperature, 74%; (e) Grubbs' catalyst (1.8 equiv), 1,2-DCE, Δ, 83%; (f) HF/MeCN, $CH_2Cl_2$, room temperature, 91%; (g) $TsNHNH_2$, NaOAc, 1,2-DME/$H_2O$, Δ, 95%.

Scheme 5 outlines the manner in which the three fragments were assembled to complete the synthesis of mucocin (**1**). The enantioselective addition of the alkynyl zinc reagent derived from **3** to the aldehyde **4** furnished the propargylic alcohol in 81% yield with excellent selectivity (*ds* = 20:1 by HPLC).[9,16] Protection of the alcohol as the triisopropylsilyl ether followed by deprotection of the *p*-methoxyphenyl ether afforded the allylic alcohol **14**[10] and thereby set the stage for the *TST-RCM* cross-coupling reaction. The construction of the mixed *bis*-alkoxy silane was achieved from the allylic alcohol **2** through the treatment with excess diisopropyldichlorosilane to afford the *mono*-alkoxychlorosilane, followed by the removal of the excess silylating agent and addition of the second allylic alcohol **14**. Ring-closing metathesis of the silicon-tethered diene using stoichiometric Grubbs' catalyst furnished **15** in 83% yield and completed the construction of the carbon skeleton of mucocin (**1**) (Scheme 5).[17] The synthesis was concluded with the fluoride-mediated deprotection of **15**, followed by chemoselective reduction with diimide.[18] The spectroscopic data and optical rotation of synthetic mucocin (**1**) were identical in all respects to the values reported for the natural substance [$^1H/^{13}C$ NMR, IR, $[\alpha]^{26}_D$ −16.0 ($c$ = 0.25, $CH_2Cl_2$)].

In conclusion, we have accomplished an enantioselective total synthesis of the annonaceous acetogenin (−)-mucocin (**1**) using a triply convergent 12-step sequence (longest linear sequence) in 13.6% overall yield. This approach represents the first application of the temporary silicon-tethered (*TST*) ring-closing metathesis (*RCM*) cross-coupling reaction and the enantioselective alkyne/aldehyde addition in the synthesis of a complex annonaceous acetogenin. Finally, the synthesis highlights the utility of the bismuth tribromide-mediated reductive etherification for the construction of 3-hydroxy-2,6-disubstituted tetrahydropyrans.

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**Note Added after ASAP.** In the version posted 11/5/03, in Scheme 2 the absolute configuration for the secondary *tert*-butyldimethylsilyl ether in **7**, **8**, and **9** was incorrect. The version posted 11/11/03 and the print version are correct.

**Supporting Information Available:** Spectral data and detailed experimental procedures for all of the synthetic intermediates (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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