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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 equivalent¹¹ 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- β furnished the hydroxy ketone **8** in 70% yield (*ds* \geq 99:1 by HPLC), after recycling the recovered triene **7** (2 \times).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* \geq 19:1 by NMR).¹³ Finally, the *p*-methoxyphenyl

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>.

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 (*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 converted to the selenocarbonate **13** using phosgene and phenylselenol.¹⁵ The selenocarbonate **13** was subjected to standard free radical conditions, to afford the γ -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 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 diisopropylchlorosilane 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/¹³C NMR, IR, [α]_D²⁶ -16.0 (*c* = 0.25, CH₂Cl₂)].

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.

Supplementary Material

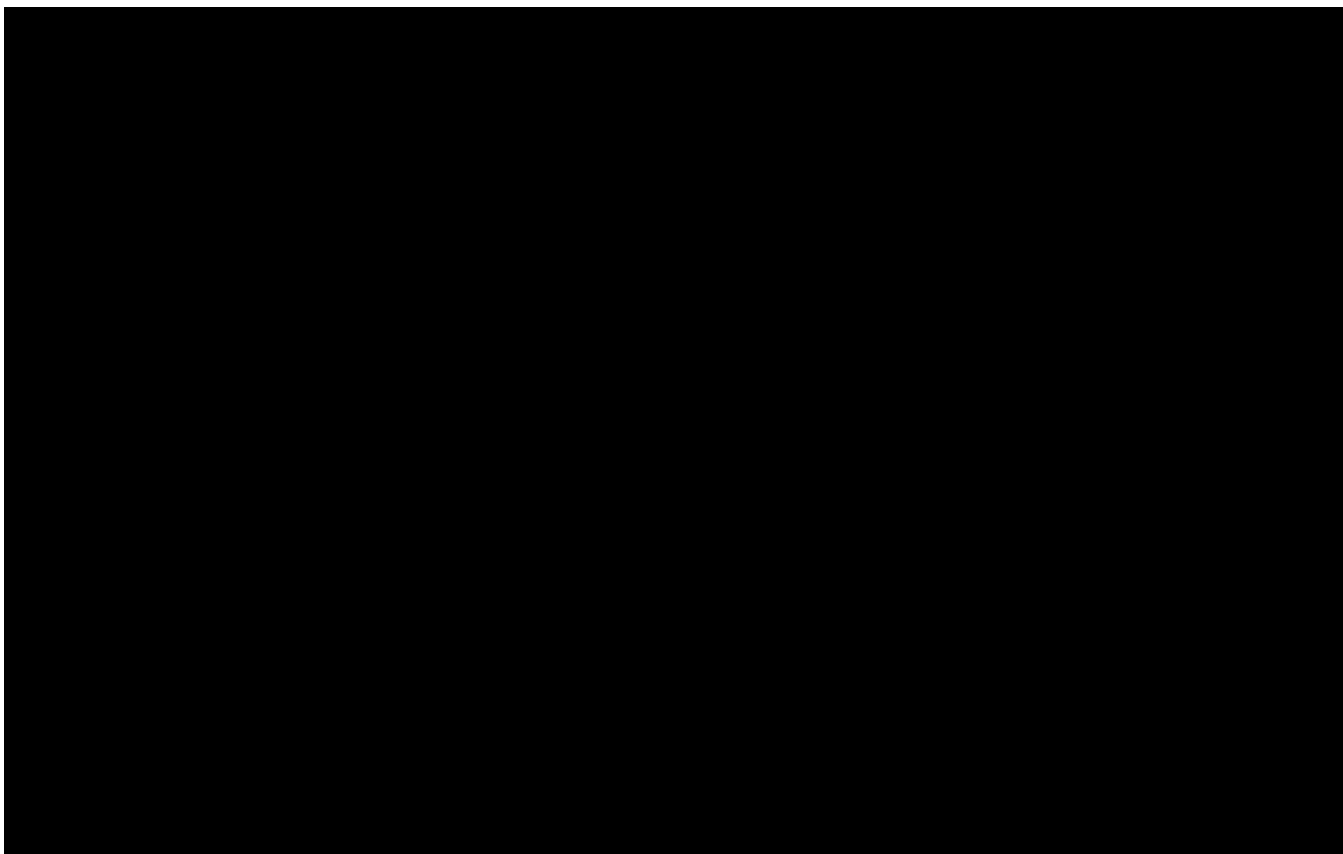
Refer to Web version on PubMed Central for supplementary material.

Acknowledgment.

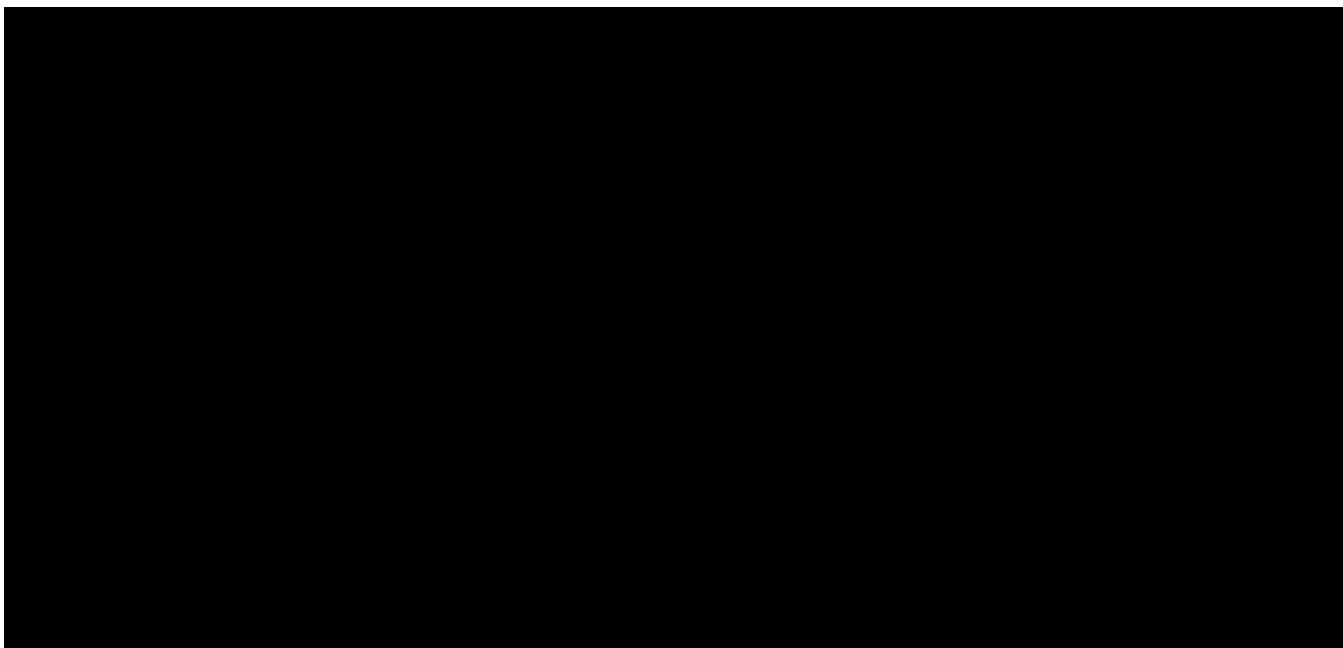
This work is dedicated to Professor Philip D. Magnus on the occasion of his 60th birthday. We sincerely thank the National Institutes of Health (GM58877) for generous financial support. We also thank Johnson and Johnson for a *Focused Giving Award* and Pfizer Pharmaceuticals for the *Creativity in Organic Chemistry Award*. The Camille and Henry Dreyfus Foundation is thanked for a *Camille Dreyfus Teacher-Scholar Award* (P.A.E.).

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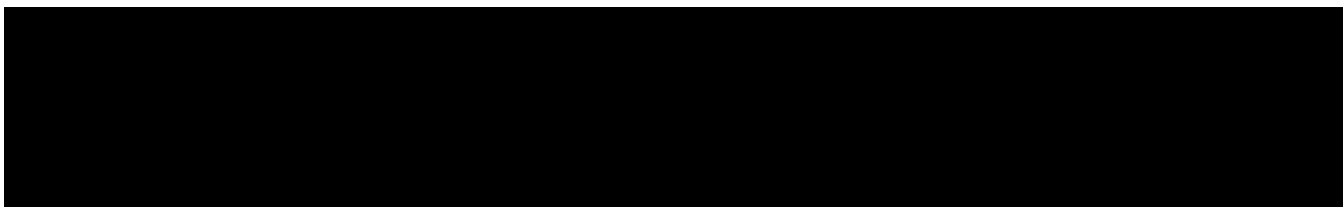
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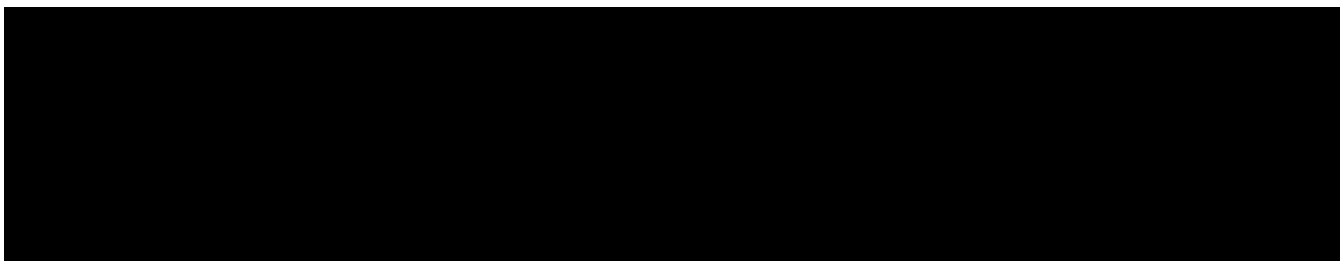
Scheme 1.

**Scheme 2a.**

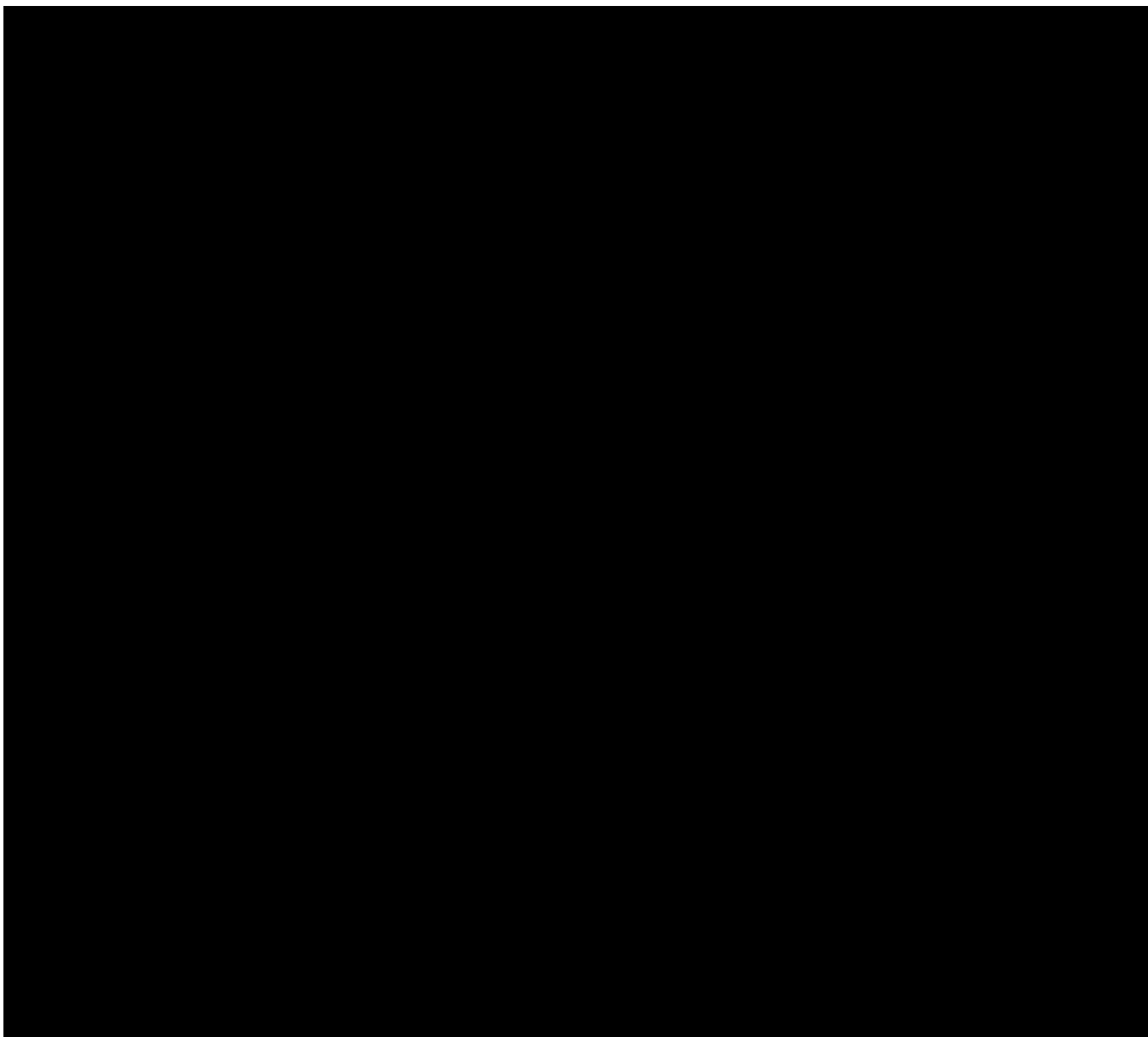
(a) *p*-MeOC₆H₄OH, DIAD, PPh₃, THF, 0 °C, 80%; (b) (CH₂=CH)₂CHOTBS, ^sBuLi, THF, -78 °C, then TBSOTf, 2,6-lutidine, -78 to 0 °C, 96%; (c) AD-mix-β, ^tBuOH/H₂O, MeSO₂NH₂, 0 °C (3×), 70%; (d) ⁿoctylMgBr, CuCN, THF, -78 °C, 65%; (e) BiBr₃, ^tBuMe₂SiH, MeCN, 0 °C, then 2,6-lutidine, TBSOTf, 0 °C, 93%; (f) (NH₄)₂Ce(NO₃)₆, MeCN/H₂O, -5 °C, 91%.

**Scheme 3a.**

(a) *p*-MeOC₆H₄OH, DIAD, PPh₃, THF, 0°C, 80%; (b) CH₂=CHCH₂MgBr, CuCN, Et₂O, -78°C, 90%; (c) Co(modp)₂, O₂, ^tBuOOH, ^tPrOH, 60°C, 83%; (d) Tf₂O, Et₃N, CH₂Cl₂, -78°C, 86%; (e) TMS-C≡C(CH₂)₄MgBr, CuI, THF, -20 to -10°C; then MeOH, TBAF, -20°C to room temperature, 73%.

**Scheme 4a.**

(a) *S*-Propylene oxide **6**, $n\text{BuLi}$, HMPA, THF, $-30\text{ }^\circ\text{C}$; (b) COCl_2 , Et_3N , C_6H_6 , $0\text{ }^\circ\text{C}$ to room temperature, then PhSeH , pyridine, THF/ C_6H_6 , $0\text{ }^\circ\text{C}$ to room temperature, 60% overall yield from **12**; (c) $n\text{Bu}_3\text{SnH}$, AIBN, C_6H_6 , Δ , 80%; (d) $\text{RhH}(\text{CO})(\text{PPh}_3)_3$, C_6H_6 , $85\text{ }^\circ\text{C}$, 84%; (e) HCOOH , pentane, $0\text{ }^\circ\text{C}$, 90%.

**Scheme 5a.**

(a) **3**, Et₂Zn, PhMe, Δ, then (*R*)-BINOL, Ti(O^{*i*}Pr)₄, THF, 4, 0 °C, 81%; (b) TIPSOTf, pyridine, DMAP, THF, 0 °C, 96%; (c) (NH₄)₂Ce(NO₃)₆, MeCN/H₂O, -10 °C, 91%; (d) **2**, ^{*i*}Pr₂SiCl₂ (xs), CH₂Cl₂, 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, CH₂Cl₂, room temperature, 91%; (g) TsNHNH₂, NaOAc, 1,2-DME/H₂O, Δ, 95%.