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# Asymmetric Total Synthesis of Rollicosin

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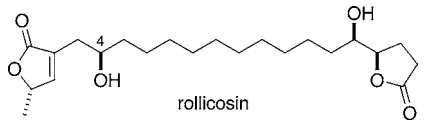
## ABSTRACT

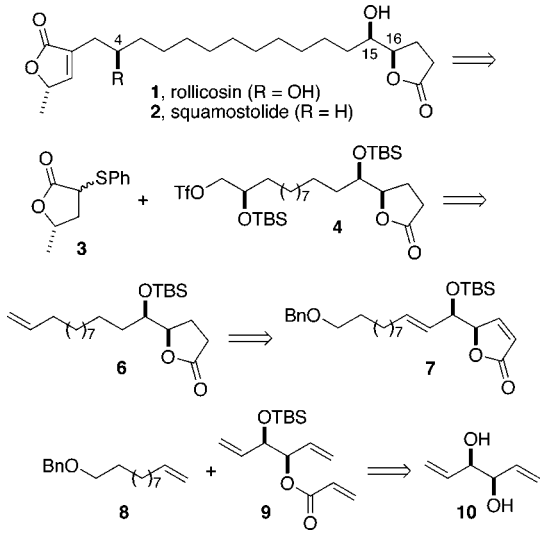



**The first total synthesis of rollicosin, a member of a rare subgroup of Annonaceous acetogenins containing two terminal γ-lactones, is reported. The approach features a highly regio- and stereoselective tandem ring-closing/cross-metathesis reaction for construction of the east-wing lactone and incorporation of the alkyl spacer. Establishment of the C4 stereocenter and addition of the west-wing lactone were achieved by Sharpless asymmetric dihydroxylation and enolate alkylation.**

The Annonaceous acetogenins are a class of polyketide natural products with wide-ranging biological profiles, including activity as antitumor, antiparasitic, insecticidal, and immunosuppressive agents.[1] Structural features common to acetogenins are a terminal γ-lactone and a terminal aliphatic side chain connected by a linker containing variously located oxygenated functional groups and/or rings. Members of this family are classified into several subtypes based on structural features present in the linker and the nature of the terminal γ-lactone.[2]

Rollicosin (**1**, Scheme 1), isolated in low yield from *Rollinia mucosa* in 2003, is one of two compounds in a new subclass of acetogenins containing two terminal γ-lactones.[3] Squamostolide (**2**), the other member, differs from **1** by only the absence of the C4 hydroxyl,[4] and both are likely derived from oxidative cleavage of classical THF-containing acetogenins. In cytotoxicity assays, both **1** and **2** exhibited significant in vitro inhibitory activity against human tumor cell lines, suggesting potential of truncated acetogenins as prototype anticancer agents and utility as SAR probes. Their biological activities and limited availabilities make **1** and **2** excellent candidates for synthesis. To date, however, only one approach has been reported, which culminated in the synthesis of *ent*-**2**.[5]

**Scheme 1.** Retrosynthetic Analysis




(1) For reviews, see: (a) Alali, F. Q.; Liu, X. X.; McLaughlin, J. L. *J. Nat. Prod.* **1999**, *62*, 504. (b) Cavé, A.; Figadére, B.; Laurens, A.; Cortes, D. In *Progress in the Chemistry of Natural Products*; Herz, W., Kirby, G. W., Moore, R. E., Steglich, W., Tamm, C., Eds.; Springer-Verlag: New York, 1997; Vol. 70, pp 81−288.

(2) Figadére, B. *Acc. Chem. Res.* **1995**, *28*, 359.

(3) Liaw, C. C.; Chang, F. R.; Wu, M. J.; Wu, Y. C. *J. Nat. Prod.* **2003**, *66*, 279.

(4) Xie, H. H.; Wei, X. Y.; Wang, J. D.; Liu, M. F.; Yang, R. Z. *Chin. Chem. Lett.* **2003**, *14*, 588.

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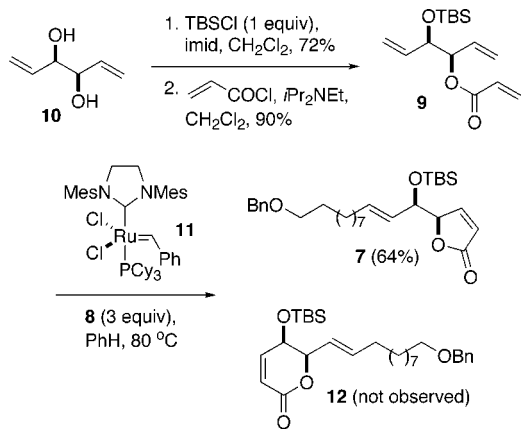
We describe herein the asymmetric total synthesis of **1** highlighting our recently reported tandem ring-closing/cross-metathesis (RCM/CM) strategy for allyl butenolide preparation.[6] Our approach is outlined retrosynthetically in Scheme 1. We envisioned installation of the west-wing lactone by alkylation of the enolate of (5*S*)-methyl-3-phenylsulfanyldihydrofuran-2-one **3**[7] with triflate **4**, which would arise from **6** via Sharpless asymmetric dihydroxylation[8] (SAD) and subsequent selective diol activation/protection. Terminal alkene **6** would, in turn, be available by straightforward functionalization of **7**. Butenolide **7** would be produced by tandem RCM/CM with initial RCM[9] of acrylate **9** preceding CM[10] with the benzyl ether of 10-undecen-1-ol (**8**). Hexa-1,5-diene-3,4-diol **10**,[11] with the requisite (3*R*,4*R*) absolute stereochemistry corresponding to C15 and C16 of rollicosin, would serve as our starting material.

Metathesis substrate **9** could be prepared readily in multigram quantities by mono-TBS protection of **10** and subsequent acylation with acryloyl chloride (Scheme 2). We

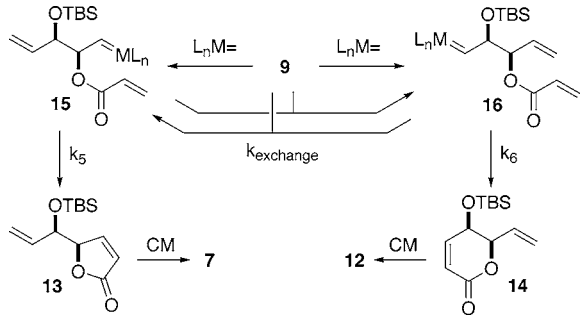
**Scheme 2.** Preparation and RCM/CM of **9**




were pleased to find that treatment of a solution of **9** and coupling partner **8** with 10 mol % of second generation Grubbs' catalyst **11**[12] gave desired extended butenolide **7** as the only isolable product in 64% yield. Assignment of the tandem product as **7** rather than regioisomeric **12** was based on the relatively large downfield chemical shifts of the $\beta$-proton (7.44 ppm) and the carbonyl carbon (172.9 ppm) in the $^1$H and $^{13}$C NMR spectra. The (*E*)-stereochemistry of the acyclic olefin was inferred from the $^1$H NMR spectrum ($J$ = 15.4 Hz). Optimal yields were achieved by slow addition of **11** to a 0.01 M solution of **9** and 3 equiv of **8** in refluxing PhH via syringe pump. Despite the clear synthetic utility of this process, surprisingly few examples of simple triene RCM/CM reactions exist.[13]

It is notable that none of the dihydropyranone **12** was isolated from the metathesis reaction, as it implies that **9** underwent initial RCM with complete regioselectivity for generation of butenolide **13** (Scheme 3). The observed

**Scheme 3.** Regioselective RCM of **9**




regioselectivity can be rationalized by consideration of two mechanistic pathways. The first is site-selective initiation by the catalyst ($L_nM$=) to produce intermediate **15** exclusively.[14] The second is establishment of a pre-equilibrium between intermediates **15** and **16** followed by fast formation of **13** (relative to **14**) in an irreversible ring-closing step ($k_{exchange} > k_5 > k_6$).[15] In the case of **9**, the likely steric preference for formation of **15** and the kinetic preference for five-membered ring formation reinforce one another; thus, the observed regiochemistry would be the predicted outcome of either mechanistic scenario. RCM of the benzyl analogue of **9**, in which the nonacrylate olefins are not as clearly differentiated by their steric environments, also proceeds with complete regioselectivity for five-membered ring formation, however, suggesting the second mechanistic pathway.[6] Examples of regioselective CM[16] and *chemoselective* RCM[17] of 1,5-hexadien-3-ol derivatives have been reported. To our knowledge, however, only two other examples of *regioselective* RCM of 1,5-hexadien-3-yl acrylates such as **9** exist.[6,13b] Studies to determine factors influencing (and thus, potential means for manipulating) the regiochemical outcomes of such reactions are currently underway.

With reliable access to **7** using our tandem RCM/CM approach, we turned our attention to its functionalization to

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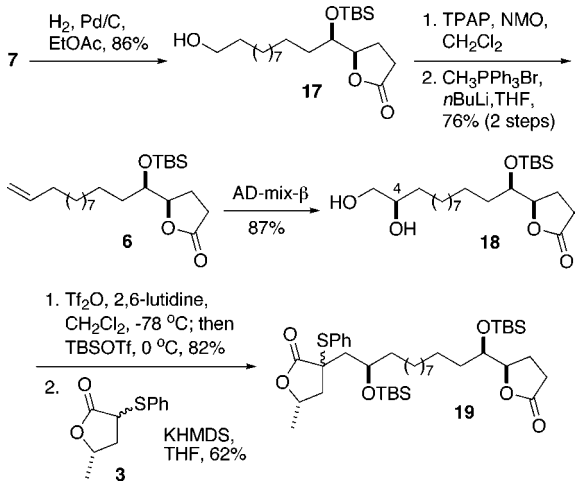
(9) For a recent review on the use of RCM for synthesis of heterocycles, see: Dieters, A.; Martin, S. F. *Chem. Rev.* **2004**, *104*, 2199.
(10) For a recent review of CM, see: Connon, S. J.; Blechert, S. *Angew. Chem., Int. Ed.* **2000**, *42*, 1900.
(11) (a) Burke, S. D.; Sametz, G. M. *Org. Lett.* **1999**, *1*, 72. (b) Crombez-Robert, C.; Benazza, M.; Frechou, C.; Demailly, G. *Carbohydr. Res.* **1997**, *303*, 359.
(12) Scholl, M.; Ding, S.; Lee, C. W.; Grubbs, R. H. *Org. Lett.* **1999**, *1*, 953.
(13) (a) Virolleaud, M. A.; Bressy, C.; Piva, O. *Tetrahedron Lett.* **2003**, *44*, 8081. (b) Virolleaud, M. A.; Piva, O. *Synlett* **2004**, 2087.
(14) Initiation of the acrylate olefin of **9** is not considered because of its substantially reduced reactivity relative to the nonacrylate olefins.
(15) For a similar analysis of regioselective enyne RCM, see: Maifield, S. V.; Miller, R. L.; Lee, D. *J. Am. Chem. Soc.* **2004**, *126*, 12228.
(16) BouzBouz, S.; Simmons, R.; Cossy, J. *Org. Lett.* **2004**, *6*, 3465.
(17) Numerous reports of chemoselective RCM of 1,5-hexadien-3-yl acrylates for synthesis of dihydropyranones have been made. For a leading reference, see: Falomir, E.; Murga, J.; Ruiz, P.; Carda, M.; Marco, J. A. *J. Org. Chem.* **2003**, *68*, 5672.

allow for incorporation of the west-wing lactone. To this end, **7** was exposed to $H_2$ in the presence of Pd/C to effect removal of the benzyl ether and concomitant alkene reduction to provide alcohol **17** in 86% yield (Scheme 4). TPAP

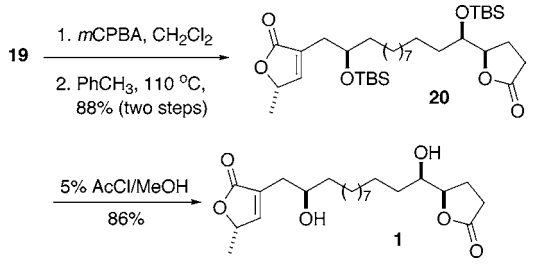
**Scheme 4.** Functionalization of **7**




oxidation to the corresponding aldehyde and one-carbon Wittig homologation then gave terminal alkene **6** in 76% over two steps and set up SAD. Treatment of **6** with AD-mix-$\beta$ provided diol **18** in 87% yield and proceeded with excellent selectivity for establishment of the (*R*)-configured C4 stereocenter. Only trace formation of the C4 epimer was observed in the dihydroxylation, and the diastereomers could be separated by column chromatography without difficulty. Selective activation of the primary alcohol as a triflate and subsequent silylation of the remaining secondary alcohol were achieved in a one-pot process.[18] Coupling of the triflate with the enolate of **3** then provided **19** as an inseparable 12:1 mixture of diastereomers in 62% overall yield.[19] As a result of the low reactivity of the triflate as an alkylating agent, extended reaction times were required, during which the yield of **19** was somewhat diminished because of decomposition of the triflate. The proper choice of enolate counterion proved critical to the outcome of the reaction with lithium and sodium enolates (formed with LDA, LHMDS, or NaHMDS) providing only minimal yields of **19** even in the presence of HMPA or DMPU. Attempts to alkylate the enolate of **3** with the epoxide of **6** met with failure due to formation of mixtures of translactonization products.

The synthesis was completed as outlined in Scheme 5.

**Scheme 5.** Completion of the Synthesis




Oxidation of sulfide **19** to the sulfoxide and thermal elimination gave **20**, and TBS deprotection by treatment with in situ generated HCl in MeOH provided rollicosin (**1**) in 76% over three steps. Synthetic **1** was isolated as a white solid (mp = 102−104 °C) and displayed spectral data (IR, $^1$H and $^{13}$C NMR) and optical rotation consistent with that of naturally occurring rollicosin.[3]

In conclusion, the first total synthesis of rollicosin (**1**) was accomplished in 9% yield over 12 steps from $C_2$-symmetric dienediol **10**. Key to the overall efficiency of the route was use of a highly regio- and stereoselective tandem RCM/CM reaction for construction of the east-wing lactone and incorporation of alkyl spacer. The synthesis provides confirmation of the structural assignment of **1**, and the inherent flexibility of this approach will make it useful for analogue preparation.

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**Supporting Information Available:** Experimental procedures, characterization data, and $^1$H and $^{13}$C NMR spectra for **1**, **6**, **7**, **9**, **17**−**20**, and the mono-TBS ether of **10**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(19) For alkylation of the enolate of **3** in the synthesis of other 4-hydroxylated acetogenins, see: (a) Schaus, S. E.; Brånalt, J.; Jacobsen, E. N. *J. Am. Chem. Soc.* **1941**, *63*, 4876. (b) Marshall, J. A.; Piettre, A.; Paige, M. A.; Valeriote, F. *J. Org. Chem.* **2003**, *68*, 1771. (c) Maezaki, N.; Kojima, N.; Sakamota, A.; Tominaga, H.; Iwata, C.; Tanaka, T.; Monden, M.; Damdensuren, B.; Nakamor, S. *Chem. Eur. J.* **2003**, *9*, 389.