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Total Synthesis of (–)-Mucocin

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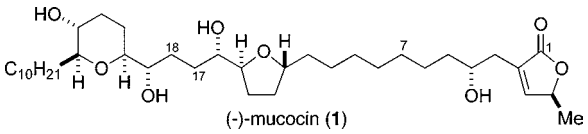
ABSTRACT



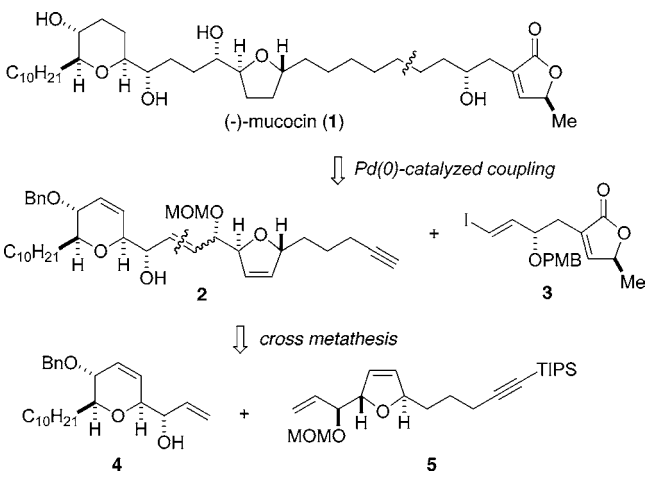
(-)-mucocin (**1**)

An enantioselective total synthesis of (–)-mucocin has been completed. A combination of asymmetric glycolate aldol additions and ring closing metathesis reactions were exploited to construct the C18–C34 and C7–C17 fragments. A selective cross-metathesis reaction was employed as the key step to couple two complex fragments.

In 1995 mucocin (**1**), a novel member of the anonnaceous acetogenin family, was isolated from the leaves of *Rollinia mucosa* by McLaughlin and co-workers.[1] The annonaceous acetogenins are a series of polyethers with antimitotic and cytotoxic properties, containing either adjacent or nonadjacent tetrahydrofuran (THF) rings. Mucocin was the first member of this family reported to bear a tetrahydropyran (THP) ring along with a THF ring.[2] Mucocin is quite active in the brine shrimp toxicity (BST) assay (IC_{50} 1.3 μg/mL), and shows remarkably selective inhibitory effects against A-549 (lung cancer) and PACA-2 (pancreatic cancer) tumor cell lines with potency 10 000 times that of the known antitumor agent adriamycin.[3] Mucocin's mode of action is believed to result from inhibition of both the mitochondrial complex I (NADH-ubiquinone oxidoreductase) and the plasma membrane NADH oxidase. Consequently, the ATP level of the tumor cells decreases and apoptosis is induced.[4] The potent antitumor activity and the unique structure of mucocin have stimulated numerous synthetic endeavors; five previous total syntheses of mucocin have been published.[5]

Herein we describe an enantioselective total synthesis of (−)-mucocin. Mucocin was envisioned to derive from the coupling of advanced acetylene **2** and known butenolide **3**[6] via a Pd(0) catalyzed Sonogashira reaction (Scheme 1). The bis cyclic ether **2** would be generated by coupling fragments **4** and **5** through a cross-metathesis reaction, wherein both fragments would be prepared via an asymmetric glycolate aldol-ring closing metathesis (RCM) sequence.

Scheme 1



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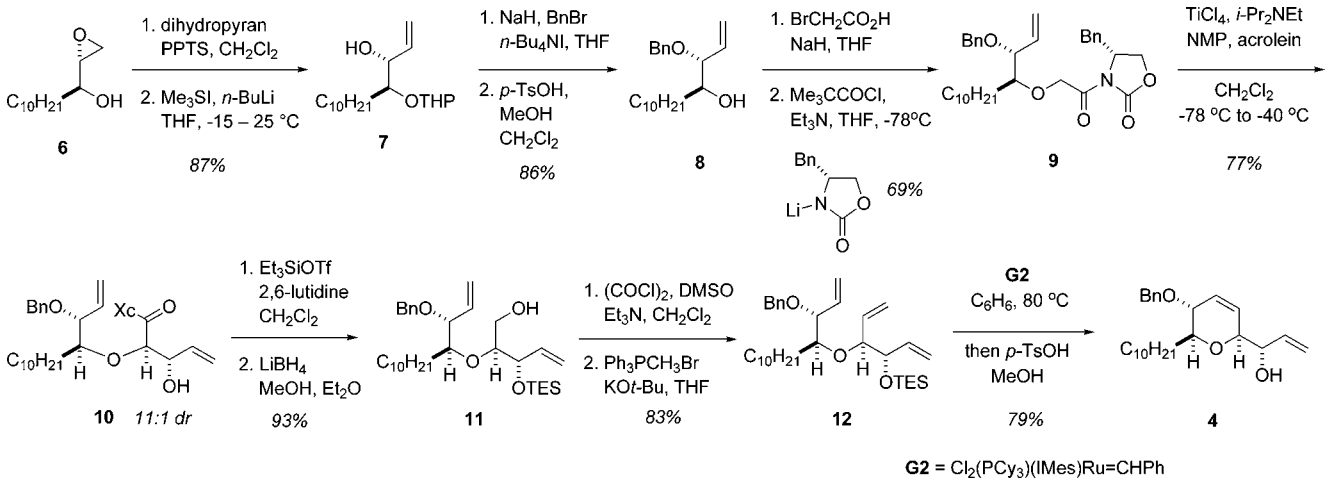
Scheme 2



The synthesis of the C18−C34 fragment **4** started with the protection of the known compound (2*R*,3*R*)-1-oxiranyl-undecan-1-ol (**6**)[7] as its THP ether, followed by epoxide opening[8] to afford the homologated allylic alcohol **7** in 87% yield (Scheme 2). The resulting secondary alcohol was protected as a benzyl ether, and the THP group was removed under acidic conditions to deliver alcohol **8** in 86% yield over the two steps. Alkylation of the sodium alkoxide of alcohol **8** with sodium bromoacetate gave a glycolic acid, which was converted to its mixed pivalic anhydride and treated with (*R*)-3-lithio-4-benzyl-2-oxazolidinone to generate the *N*-glycolyloxazolidinone **9** in 69% yield (2 steps). Our recently developed aldol reaction protocol[9] was then exploited, where the chlorotitanium enolate of glycolate **9** was formed by treatment with $TiCl_4$ (1.0 equiv), *i*-Pr_2NEt (2.5 equiv), and *N*-methyl-2-pyrrolidinone (1.0 equiv). Addition of acrolein to the enolate solution gave the desired syn aldol adduct **10** in good yield and diastereoselectivity (77%, 11:1 dr). Other aldol protocols gave significantly lower yields and diastereoselectivity. Protection of the resulting alcohol **10** as its TES ether and reductive removal of the chiral auxiliary afforded primary alcohol **11** in 93% yield. The subsequent Swern oxidation[10]−Wittig reaction sequence delivered triene **12** in 83% yield. Triene **12** was exposed to the Grubbs second generation catalyst[11] [$Cl_2(PCy_3)$(IMes)Ru═CHPh], followed by acidic workup to remove the TES protecting group in the same pot, regioselectively generating dihydropyran **4** in good yield.[12] The use of the triethylsilyl ether as the alcohol protecting group in triene **12** resulted in less than 5% of the corresponding seven-membered-ring metathesis product.

Preparation of the C7−C17 fragment **5** began by protecting the terminal alkyne of 5-hexyn-1-ol (**13**) with a TIPS group (Scheme 4).[13] Swern oxidation of the resultant primary alcohol and a subsequent Grignard reaction with vinylmagnesium bromide delivered allylic alcohol **14** in 66% yield over three steps. Allylic alcohol **14** was then exposed to the standard Sharpless kinetic resolution conditions[14] [(+)-dicyclohexyl tartrate (DCHT), Ti(*i*-PrO)$_4$, *t*-BuOOH, 4 Å molecular sieves]. The reaction was quenched at 52% conversion to provide alcohol **15** in 92% ee.[15] Alkylation of the secondary alcohol with sodium bromoacetate and coupling of the resultant acid to (*R*)-3-lithio-4-benzyl-2-oxazolidinone gave glycolate **16** in 77% yield. Once again, the NMP-promoted asymmetric aldol reaction was utilized. Exposure of glycolate **16** to these conditions with acrolein provided the aldol adducts in 82% yield (93% based on recovered starting material), with a 4:1 dr favoring the desired syn adduct **17**. Silylation of the mixture of diastereomers as TES ethers and reductive removal of the auxiliary afforded the primary alcohol **18** in 89% yield.

With the desired stereocenters established, efforts focused on the regioselective formation of the five-membered ring. Previous studies from our laboratory showed that the RCM reaction of simple triene **19** with the ruthenium alkylidene catalysts gave a poor regioselectivity of five-membered and six-membered cyclic ethers (Scheme 3).[16] We rationalized that the unexpected result was due to indiscriminate insertion of the ruthenium carbene into all three alkenes of triene **19**, followed by fast ring closure to generate both regioisomers. To circumvent this problem, Hoye's "activation" strategy was utilized, where the RCM substrate **20** was modified to contain an allyloxymethyl side chain.[17] In this case, the ruthenium carbene complex preferentially inserts in the

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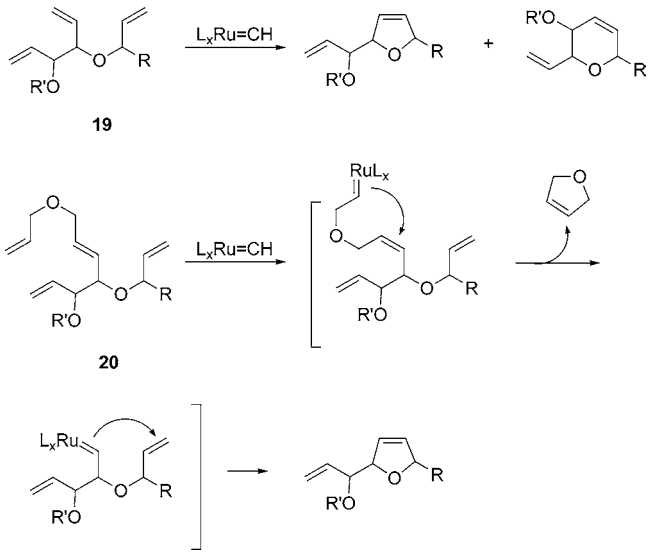
(11) Morgan, J. P.; Grubbs, R. H. *Org. Lett.* **1999**, *1*, 953.
(12) When the secondary allylic alcohol of triene **12** was protected as its MOM ether rather than the TES ether, a 2:1 mixture of six-membered and seven-membered cyclic ethers was produced under the same RCM conditions.
(13) Layton, M. E.; Morales, C. A.; Shair, M. D. *J. Am. Chem. Soc.* **2002**, *124*, 773.
(14) Gao, Y.; Hanson, R. M.; Klunder, J. M.; Ko, S. Y.; Masamune, H.; Sharpless, K. B. *J. Am. Chem. Soc.* **1987**, *109*, 5765.
(15) The ee was determined by first converting alcohol **15** to UV active glycolate **16**, followed by HPLC of **16**.

Scheme 3

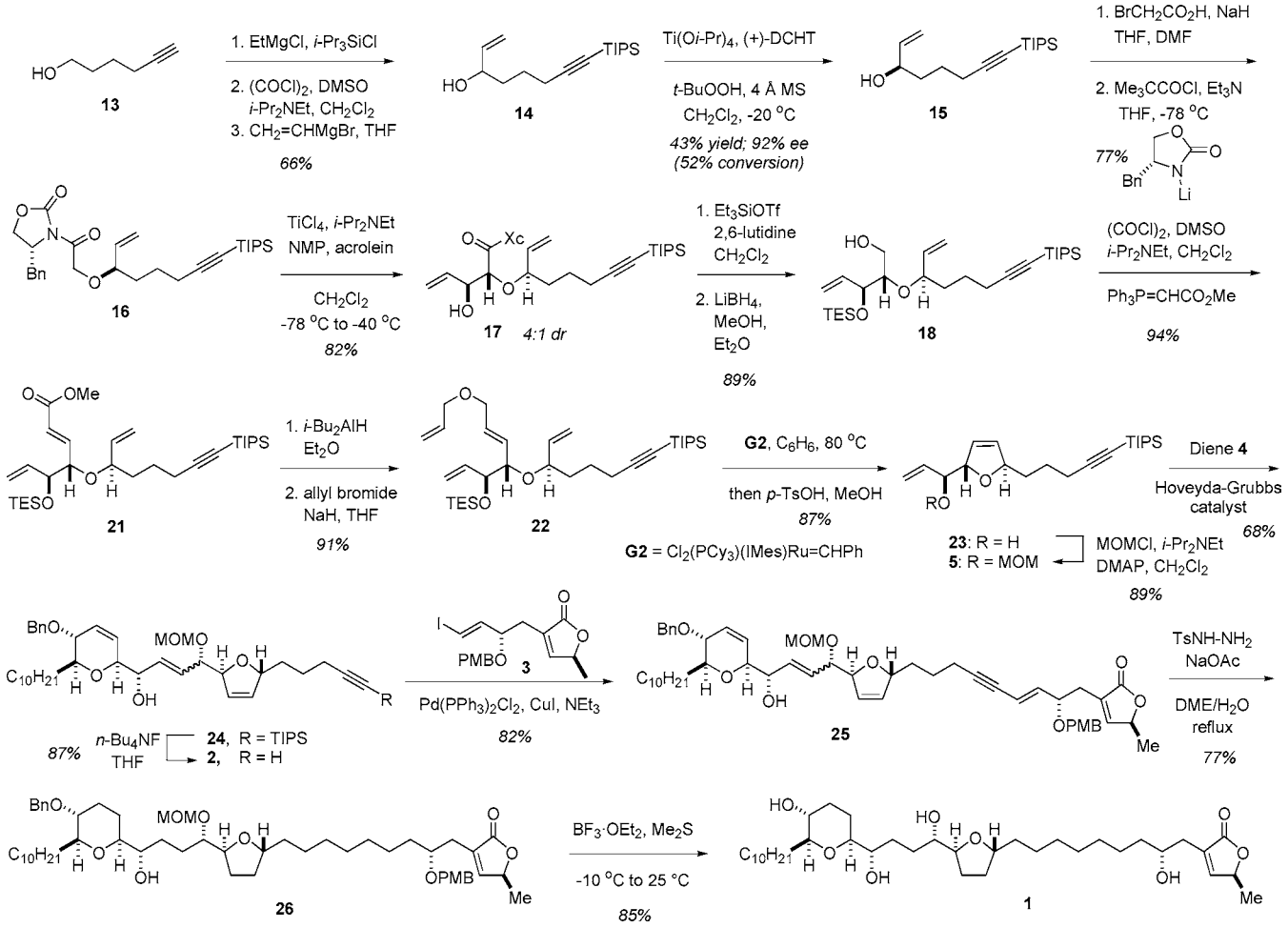


terminal alkene of the allyloxymethyl group for both steric and electronic reasons, generating 2,5-dihydrofuran as a byproduct and leaving the metal carbene in the desired position to construct the five-membered cyclic ether selectively.

This successful strategy was applied to the synthesis of fragment **5** (Scheme 4). Alcohol **18** was subjected to Swern oxidation, followed by Wittig olefination with $Ph_3P{=}CHCO_2Me$ in the same pot (no evidence of epimerization of the aldehyde was detected). The resultant α,β-unsaturated ester **21** underwent selective 1,2-reduction with *i*-Bu_2AlH, whereupon the primary alcohol was *O*-alkylated with allyl bromide to deliver tetraene **22** in excellent yield. Exposure of tetraene **22** to the Grubbs second generation catalyst provided excellent regioselectivity, giving a 7:1 ratio of the five- and six-membered rings. After removal of the TES group with acidic workup of the RCM reaction, cyclic ether **23** was isolated in 87% yield. No byproduct from any metathesis reaction of the acetylene was identified. The alcohol **23** was then converted to its MOM ether **5** in 89% yield.

With fragments **4** and **5** in hand, the key cross-metathesis reaction was undertaken (Scheme 4). The disubstituted internal olefin of each fragment was expected to be unreactive under cross-metathesis conditions, allowing for chemoselective reactions between the remaining two terminal

Scheme 4



vinyl groups of these compounds. The MOM protecting group on fragment **5** was anticipated to modify the steric accessibility of the nearby allylic olefin, making it less reactive than the structrually similar unprotected allylic olefin on fragment **4**. The difference in reactivities of the two alkenes would lead to a selective cross-metathesis reaction.[18] Exposure of a 1:1 mixture of alkenes **4** and **5** to the Hoveyda−Grubbs second generation catalyst [Cl_2(IMes)Ru═CH-*o*-O*i*-PrC_6H_4][19] yielded the desired cross-coupling product **24** in 68% yield (6:1 *E*:*Z* by HPLC), along with 13% of alkene **5** recovered and 23% of the homodimer of **4**.[20] Using the Grubbs second generation catalyst gave a lower yield of 53% under similar reaction conditions. Mootoo recently reported a similar cross-metathesis approach to mucocin[5e] as well as other acetogenins,[21] but utilizing different allylic alcohol protecting groups. The terminal TIPS group was then readily removed. The resultant alkyne **2** was coupled with known vinyl iodide **3**[6] under Sonogashira coupling conditions [Pd(PPh_3)$_2Cl_2$, CuI, NEt_3][22] to provide polyenyne **25**. The use of Pd(PPh_3)$_2Cl_2$ as a precatalyst proved superior to Pd(PPh_3)$_4$ (82% vs 50% yield). Selective hydrogenation of the pentaenyne moiety with diimide generated in situ from tosylhydrazide[23] afforded butenolide **26** in 77% yield. The total synthesis of (−)-mucocin was completed by removal of the protecting groups with BF_3·OEt_2 and Me_2S.[6] Synthetic **1** was identical in all aspects (^{1}H, ^{13}C, MS, $[\alpha]^{24}_D$) to the natural product.[5]

In summary, the enantioselective total synthesis of (−)-mucocin has been accomplished in 19 linear steps from commerically available 5-hexyn-1-ol. This approach highlights a combination of asymmetric glycolate aldol additions and RCM metatheses to construct the cyclic ethers. In addition, Hoye's "activation" strategy was applied to the regioselective formation of a dihydrofuran. The synthesis also employed a selective cross-metathesis reaction for the coupling of two complex alkene fragments.

Acknowledgment. Financial support of this work by the National Institute of General Medical Sciences (GM60567) is acknowledged with thanks.

Supporting Information Available: Experimental procedures as well as ^{1}H and ^{13}C spectra for all new compounds and synthetic (−)-mucocin. This material is available free of charge via the Internet at http://pubs.acs.org.

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(20) No cross-metathesis product was obtained under the same reaction conditions when the allylic alcohol of fragment **5** was protected as the TES ether, and only the homodimer of **4** was identified as a product.

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