Total Synthesis of (-)-Mucocin

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ABSTRACT

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 annonaceous acetogenin family, was isolated from the leaves of Rollinia mucosa by McLaughlin and co-workers. 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. Mucocin is quite active in the brine shrimp toxicity (BST) assay (IC50 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. 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. The potent antitumor activity and the unique structure of mucocin have stimulated numerous synthetic endeavors; five previous total syntheses of mucocin have been published.

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 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.

The synthesis of the C18–C34 fragment 4 started with the protection of the known compound (2R,3R)-1-oxiranyl-undecan-1-ol (6) as its THP ether, followed by epoxide opening 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 was then exploited, where the chlorotitanium enolate of glycolate 9 was formed by treatment with TiCl$_4$ (1.0 equiv), i-Pr$_2$NEt (2.5 equiv), and N-methyl-2-pyrrolidinolinone (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 over three steps. Allylic alcohol 14 was then exposed to the standard Sharpless kinetic resolution conditions [$($-)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. Alkylation of the secondary alcohol with sodium bromoacetate and coupling of the resultant acid to ($($)-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 aldol 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). 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 allyloxyethyl side chain. In this case, the ruthenium carbene complex preferentially inserts in the

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). 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 reacted with the standard Sharpless kinetic resolution conditions [$($+)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. Alkylation of the secondary alcohol with sodium bromoacetate and coupling of the resultant acid to ($($)-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 aldol 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.

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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 Ph₃P=CHCO₂Me 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-Bu₂AlH, whereupon the primary alcohol was O-alkylated with allyl bromide to deliver tetaene 22 in excellent yield. Exposure of tetaene 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
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 structurally 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 [Cl2(IMes)Ru=CH-α-Oi-PrC6H4]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 muco5c 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 36 under Sonogashira coupling conditions [Pd(PPh3)2Cl2, Cul, NEt3]22 to provide polyenyne 25. The use of Pd(PPh3)2Cl2 as a precatalyst proved superior to Pd-

(PPh3)4 (82% vs 50% yield). Selective hydrogenation of the pentaenyne moiety with diimide generated in situ from tosylhydrazide23 afforded butenolide 26 in 77% yield. The total synthesis of (−)-mucocin was completed by removal of the protecting groups with BF3·OEt2 and Me2S.6 Synthetic 1 was identical in all aspects (1H, 13C, MS, [α]D24) to the natural product.5

In summary, the enantioselective total synthesis of (−)-mucocin has been accomplished in 19 linear steps from commercially 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.

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Supporting Information Available: Experimental procedures as well as 1H and 13C 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.