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Stereoselective Synthesis of the 2,6-Disubstituted Tetrahydropyran-3-ol of the Potent Antitumor Agent Mucocin *via* an Acyl Radical Cyclization

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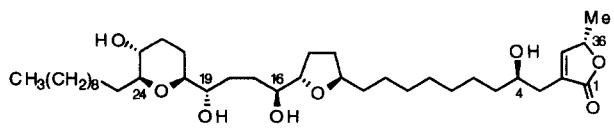
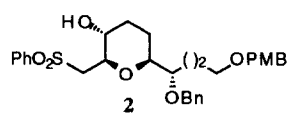
Abstract: *The intramolecular acyl radical cyclization of the acyl selenide* ***8****, using a Z-vinylogous sulfonate to control rotamer population, affords the* cis*-2,6-disubstituted tetrahydropyran-4-one* ***9****, applicable to the potent antitumor agent mucocin* ***1****, in 81% yield.* © 1997 Elsevier Science Ltd.

The potent antitumor agent mucocin **1** was recently isolated by McLaughlin and coworkers from the leaves of *Rollinia mucosa* (jacq.) Baill. (Annonaceae).[1] Mucocin is the first annonaceous acetogenin to be reported that contains a hydroxylated *tetrahydropyran* ring and thus represents a new skeleton type for this family.[2] This agent demonstrated selective inhibitory effects against A-549 (lung cancer) and PACA-2 (pancreatic cancer) solid tumor lines with a potency of more than 10,000 times that of adriamycin, making it of significant therapeutic interest. The annonaceous acetogenins selectively inhibit cancerous cells by the blockage of mitochondrial complex I (NADH-ubiquinone oxidoreductase) and through the inhibition of the plasma membrane NADH oxidase. This depletes ATP and thus induces apoptosis (programmed cell death) in the malignant cells. Further studies demonstrated that mucocin inhibits oxygen uptake by rat liver mitochondria, indicating that the tetrahydropyran ring had not altered this well established mode of action.



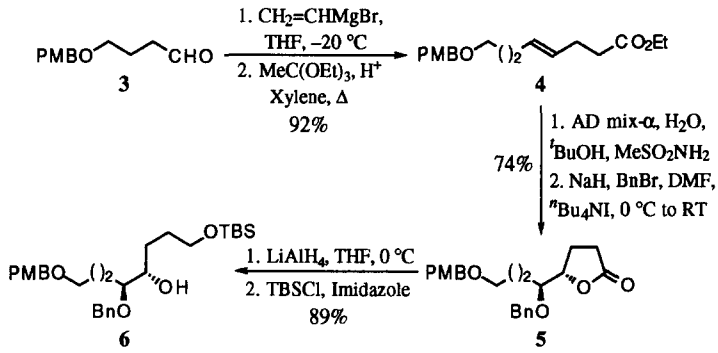
Mucocin **1**



2

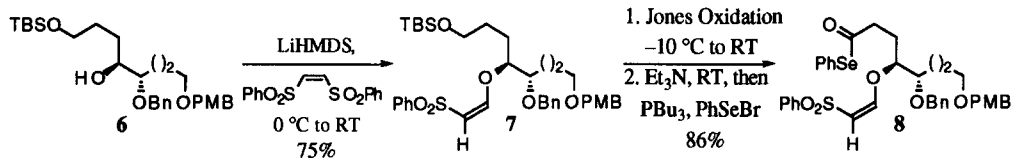
Although the tetrahydrofuran based analogs have been well studied, relatively little attention has been focused on the *tetrahydropyran* series.[2] Therefore, a viable synthetic route to mucocin is required for further biological evaluation and structure activity studies.[1] In this paper, we describe an enantioselective route to the C-16 to C-26 fragment that contains the novel 2,6-disubstituted tetrahydropyran-3-ol derivative applicable to mucocin **1**, *via* a stereoselective intramolecular acyl radical cyclization.[3,4]

Treatment of the aldehyde **3** with vinyl magnesium bromide gave the allylic alcohol,[5] which upon treatment with triethyl orthoacetate and a catalytic amount of propionic acid in refluxing xylene undergoes a Claisen rearrangement to furnish ester **4**[6] in 92% overall yield (**Scheme 1**). Sharpless asymmetric dihydroxylation of the alkene **4** gave a diol which underwent *in situ* lactonization to afford the γ-lactone. The secondary alcohol was then protected as a benzyl ether to furnish **5**[6] in 74% overall yield from the alkene **4**.[7] Lithium aluminum hydride reduction of the lactone **5**, followed by the selective protection of the primary alcohol furnished the *tert*-butyldimethylsilyl ether **6**[6] in 89% overall yield.



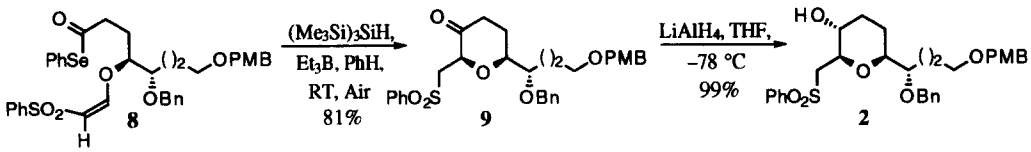
Scheme 1

Scheme 2 outlines the sequence for the synthesis of the acyl selenide **8**.[6] Treatment of the secondary alcohol **6** with LiHMDS at 0 °C followed by *Z*-bis(phenylsulfonyl)-1,2-ethylene furnished the *Z*-vinylogous sulfonate **7**[6] in 75% yield.[9] Although the vinylogous sulfonates are geometrically stable, the addition is not completely stereospecific since a minor amount (≤5%) of the *E*-isomer was isolated, which is presumably the result of competitive addition/elimination of the alkoxide derived from **6** to **7**. The primary *tert*-butyldimethylsilyl ether **7** was then oxidized with Jones reagent to the corresponding carboxylic acid,[10] which was converted to the acyl selenide **8** using the Crich protocol.[11]



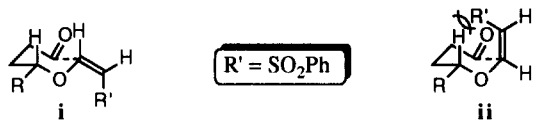
Scheme 2

Treatment of the acyl selenide **8** with tris(trimethylsilyl)silane and triethylborane at room temperature, in the presence of air, furnished the cyclic ether **9**[6] in 81% yield as a single diastereoisomer (**Scheme 3**). The stereochemical assignment was confirmed by NOE studies. The *cis*-2,6-disubstituted tetrahydropyran-3-one **9** was then reduced using lithium aluminum hydride at –78 °C to the secondary alcohol **2**[6] (15 : 1 diastereoselectivity) in near quantitative yield to complete the synthesis of the C-16 to C-26 fragment of mucocin **1**.



Scheme 3

The high degree of stereocontrol in this cyclization is presumably the result of the favored transition state **i** having the alkyl substituent pseudo-equatorial with the vinylogous sulfonate *s-trans*, to alleviate $A^{1,3}$ strain (**Figure 1**). The vinylogous sulfonate was chosen specifically from our preliminary investigations,[12] in which we also demonstrated that the *Z- vs E*-vinylogous sulfonates can dramatically improve the rotamer population and thus the degree of stereocontrol in the intramolecular 6-exo trigonal acyl radical cyclization.[4b] This phenomenon has been utilized widely to improve poor diastereoselectivity in cyclization reactions.[13] The excellent regiochemical control in the cyclization may be rationalized from the intramolecular addition of a nucleophilic acyl radical to the LUMO of the vinylogous sulfonate in a manner similar to the vinylogous carbonates.[14]



Favored TS *Disfavored TS*

Figure 1

In conclusion, we have achieved the enantioselective synthesis of the C-16 to C-26 fragment that contains the novel 2,6-disubstituted tetrahydropyran-3-ol of the antitumor agent mucocin, *via* a stereoselective intramolecular 6-exo trigonal acyl radical cyclization. The ability to utilize geometrically stable *Z*-vinylogous sulfonates to overcome poor diastereoselectivity is likely to have significant synthetic utility for target directed synthesis, and complements the related chemistry of vinylogous carbonates.[4] Further synthetic studies are currently underway to complete the total synthesis of mucocin.

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References and Footnotes

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2. For an alternative approach to the tetrahydropyran ring of mucocin **1**, see: Crimmins, M. T.; Rafferty, S. W. *Tetrahedron Lett.* **1996**, *37*, 5649.

3. For examples of acyl radicals from acyl selenides, see: (a) Pfenninger, J.; Graf, W. *Helv. Chim. Acta* **1980**, *63*, 1562. (b) Boger, D. L.; Mathvink, R. J. *J. Org. Chem.* **1992**, *57*, 1429. (c) Batty, D.; Crich, D. *J. Chem. Soc. Perkin Trans. 1* **1992**, 3193. (d) Hayes, C. J.; Pattenden, G. *Tetrahedron Lett.* **1996**, *37*, 271 and pertinent references cited therein.

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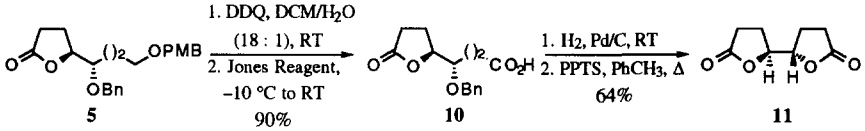
6. All new compounds exhibited spectroscopic (IR, ^{1}H and ^{13}C-NMR) and analytical (HRMS) data in accord with the assigned structure.

7. The absolute configuration and enantiomeric purity of the γ-lactone **5** was established by the conversion to the known *bis*-lactone **11**. Treatment of the γ-lactone **5** with DDQ removed the *p*-methoxybenzyl group to afford the primary alcohol, which was then oxidized with Jones reagent to the corresponding carboxylic acid **10**[6] in 90% overall yield. Hydrogenolysis of the benzyl ether **10** furnished the hydroxy acid, which was lactonized with pyridinium *p*-toluenesulfonate in refluxing toluene to furnish the *bis*-lactone **11** {$[\alpha]_D^{20}$ = +75 (c = 1.23, $CHCl_3$), Lit.[8] $[\alpha]_D^{20}$ = -83.3 (c = 1.2, $CHCl_3$) for the enantiomer} in 64% overall yield from **10**.



5 **10** **11**

The sign and magnitude of the rotation was consistent with the Sharpless asymmetric dihydroxylation having given the *S,S*-enantiomer in ≥90% enantiomeric excess.

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11. Batty, D.; Crich, D. *Synthesis* **1990**, 273.

12. Evans, P. A.; Manangan, T. *J. Org. Chem.* Submitted

13. Curran, D. P.; Porter, N. D.; Giese, B. In *Stereochemistry of Radical Reactions: Concepts, Guidelines and Synthetic Applications*; VCH Publishers: New York, 1995, pp 77-81.

14. The LUMO of a vinyl sulfone and a vinyl ether are known to have larger coefficients at the β- and α-carbons respectively, thus reinforcing each other in a β-alkoxy vinyl sulfone. See: (a) Sims, J.; Houk, K. N. *J. Am. Chem. Soc.* **1973**, *95*, 5798. (b) Fleming, I. *Frontier Orbitals and Organic Chemical Reactions*, John Wiley and Sons: New York, **1977**, p 186.

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