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Enantioselective Construction of the Tetrahydropyran and Tetrahydrofuran Fragments of the Antitumor Agent Mucocin from a Common Intermediate†

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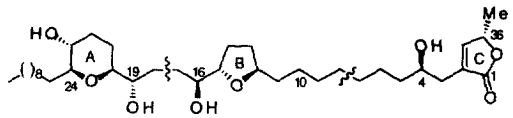
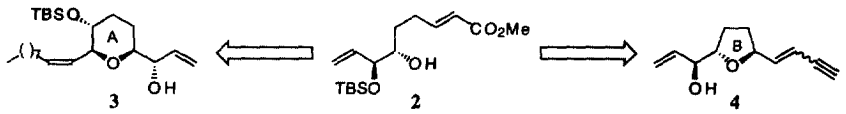
Abstract: *The* cis-*2,6-disubstituted tetrahydropyran* **3** *and* trans-*2,5-disubstituted tetrahydrofuran* **4** *required for the total synthesis of the potent antitumor agent mucocin* **1** *were prepared from the α,β-unsaturated ester* **2** *using a complementary Sharpless asymmetric epoxidation/cyclization protocol.*

The potent antitumor agent mucocin **1**, recently isolated by McLaughlin and coworkers from the leaves of *Rollinia mucosa* (jacq.) Baill. (Annonaceae), is the first annonaceous acetogenin to be reported that contains a hydroxylated *tetrahydropyran* ring.[1] Furthermore, this agent demonstrates 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.



Mucocin **1**



The mode of action of the annonaceous acetogenins is now fairly well established as being the selective inhibition of cancerous cells by the blockage of mitochondrial complex I (NADH-ubiquinone oxidoreductase) and the inhibition of the plasma membrane NADH oxidase. This depletes ATP and thus induces apoptosis (programmed cell death) in the malignant cells. Preliminary studies indicate that mucocin **1** has an analogous mode of action, which serves as another pertinent example of the degree of tolerance exhibited by this class of molecules to structural modifications without dramatically altering the mode of action.[1] Hence, detailed *Structure Activity Studies* are necessary to elucidate the key pharmacophore for biological activity, and thus expedite the synthesis of analogs of this important antitumor agent.

†This paper precedes the paper entitled "Enantioselective Synthesis of the 4-Hydroxy Buteneolide Terminus of Mucocin and Related Annonaceous Acetogenins" published in Volume 39, Number 52, pp 9627–9628. Also an erratum appears on p 1423.

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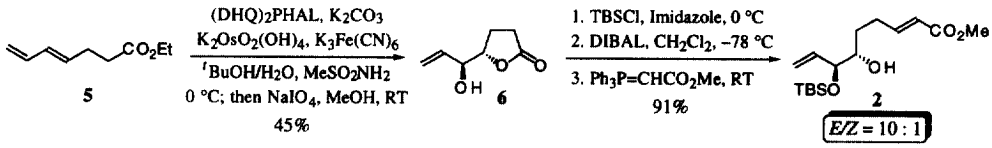
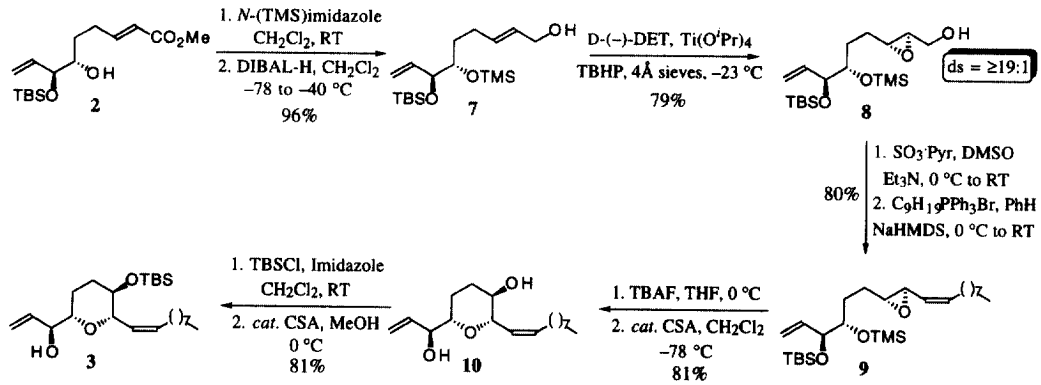
In this paper, we describe an enantioselective route to the *cis*-2,6-disubstituted tetrahydropyran-3-ol **3**[2] and the *trans*-2,5-disubstituted tetrahydrofuran **4** required for the total synthesis of the potent antitumor agent mucocin **1**, using the α,β-unsaturated ester **2** as a common synthon. The allylic alcohol containing fragments **3** and **4** will then be coupled using the newly developed temporary silicon-tethered/ring-closing metathesis strategy.[3]



Scheme 1

The α,β-unsaturated ester **2** was prepared from the diene **5**[4] using the 4 step synthetic sequence outlined in **Scheme 1**. Sharpless asymmetric dihydroxylation[5] of the diene **5** gave a diol, which underwent *in situ* lactonization to furnish the γ-lactone **6**[6,7] in 45% yield. The regioisomeric diol also obtained, was oxidatively cleaved to the aldehyde and recycled to the diene **5** using a Wittig methylenation. Protection of the secondary alcohol **6** as a *tert*-butyldimethylsilyl ether, followed by diisobutylaluminum hydride reduction of the lactone gave the lactol. Wittig homologation of the aldehyde derived from the lactol with the stabilized ylide methyl (triphenylphosphoranylidene)acetate, furnished the α,β-unsaturated ester **2**[6] in 91% overall yield from **6**, as a 10:1 ratio of *E*/*Z*-isomers that were readily separable by column chromatography.

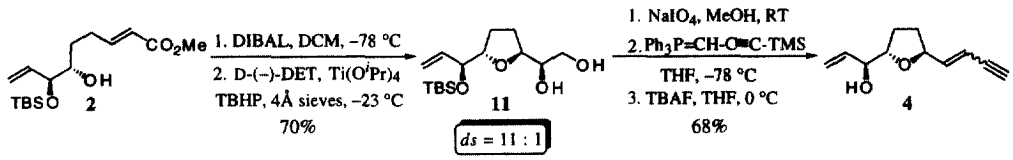


Scheme 2

Scheme 2 delineates the synthetic sequence required for the preparation of the *cis*-2,6-disubstituted tetrahydropyran-3-ol **3**. Protection of the secondary alcohol **2** as a trimethylsilyl ether, followed by the reduction of the α,β-unsaturated ester with diisobutylaluminum hydride reduction, afforded the allylic alcohol **7**[6] in 96% overall yield. Sharpless asymmetric epoxidation[9] of the allylic alcohol **7** then furnished the epoxide **8**[6] in 79% yield, with ≥19:1 diastereoselectivity. Oxidation of the primary alcohol **8**

with sulfur trioxide pyridine complex gave the aldehyde, which upon Wittig homologation afforded the allylic epoxide **9**[6] in 80% overall yield, favoring the *Z*-isomer (≥19:1).

The preparation of the *cis*-disubstituted tetrahydropyran-3-ol **10** required the following two step sequence, owing to the failure of the attempted one-pot selective desilylation of the trimethylsilyl ether and concomitant intramolecular cyclization. Treatment of the *bis*-silyl ether **9** with tetra-*N*-butylammonium fluoride furnished the diol, which was then treated with a catalytic amount of camphorsulfonic acid at –78 °C to afford the cyclic ether **10**[6] in 81% overall yield, as a single diastereoisomer (≥19:1).[10] The assigned stereochemistry was confirmed using a series of NOE and proton decoupling experiments. The differentially protected *cis*-2,6-disubstituted tetrahydropyran-3-ol fragment **3** was then completed in the following manner. Protection of the diol **10** as the bis-*tert*-butyldimethylsilyl ether, followed by the selective deprotection of the allylic silyl ether furnished after recycling (2x) through this two-step sequence, the allylic alcohol **3**[6] in 81% overall yield.



Scheme 3

The *trans*-2,5-disubstituted tetrahydrofuran fragment **4** was prepared by a complementary *exo*-epoxide ring opening (**Scheme 3**). Diisobutylaluminum hydride reduction of the α,β-unsaturated ester **2** afforded the allylic alcohol. Sharpless asymmetric epoxidation[9] of the allylic alcohol gave the epoxide which underwent rapid *in situ* Lewis acid catalyzed ring-opening to furnish the diol **11**[6] in 70% yield, as a 11:1 mixture of diastereoisomers.[9c] Oxidative cleavage of the diol **11** with sodium periodate in methanol furnished the aldehyde which then underwent smooth Wittig homologation[11] to afford the enyne (*E*/*Z* = ~1:1). Desilylation of the silyl groups with tetra-*N*-butylammonium fluoride gave the required *trans*-2,5-disubstituted tetrahydrofuran fragment **4**[6,12] in 68% overall yield from **11**.

In conclusion, we have completed the enantioselective synthesis of the *cis*-2,6-disubstituted tetrahydropyran **3** and *trans*-2,5-disubstituted tetrahydrofuran **4** fragments of the potent antitumor agent mucocin, *via* complementary intramolecular 6-*endo*- and 5-*exo*-tet ring openings of the epoxides derived from the α,β-unsaturated ester **2**. Synthetic studies are currently underway to couple the fragments using the temporary silicon-tethered ring-closing metathesis protocol,[3] and thus complete the total synthesis of this important molecule.

Acknowledgments

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References and Footnotes

1. Shi, G.; Alfonso, D.; Fatope, M. O.; Zeng, L.; Gu, Z. -m.; Zhao, G. -x.; He, K.; MacDougal, J. M.; McLaughlin, J. L. *J. Am. Chem. Soc.* **1995**, *117*, 10409.

2. For an alternative approach to the tetrahydropyran ring of mucocin **1**, see: (a) Crimmins, M. T.; Rafferty, S. W. *Tetrahedron Lett.* **1996**, *37*, 5649. (b) Evans, P. A.; Roseman, J. D. *Tetrahedron Lett.* **1997**, *38*, 5249.

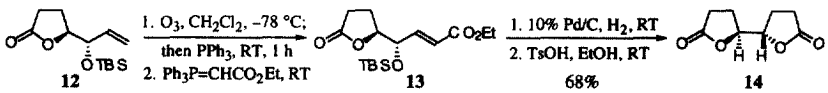
3. Evans, P. A.; Murthy, V. S. *J. Org. Chem.* **1998**, *63*, 6768.

4. Weinreb, S. M.; Khatri, N. A.; Shringarpure, J. *J. Am. Chem. Soc.* **1979**, *101*, 5073.

5. Xu, D.; Crispino, G. A.; Sharpless, K. B. *J. Am. Chem. Soc.* **1992**, *114*, 7570.

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 **6** was established by the conversion to the known *bis*-lactone **14**. Ozonolysis of the alkene **6** furnished the aldehyde, which was homologated to the α,β-unsaturated ester **13**[6] in 90% overall yield. Hydrogenation of the alkene **13** furnished the ester, which was desilylated and lactonized *in situ* with *p*-toluenesulfonic acid to afford the *bis*-lactone **14** {$[\alpha]_D^{24}$ = +78.6 (c = 1.23, $CHCl_3$), Lit.[8] $[\alpha]_D^{20}$ = –83.3 (c = 1.2, $CHCl_3$) for the enantiomer} in 68% overall yield from **13**.



The sign and magnitude of the rotation are consistent with the Sharpless asymmetric dihydroxylation having given the *S,S*-enantiomer in 94% enantiomeric excess.

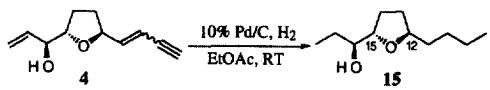
8. Maier, M. E.; Reuter, S. *Synlett* **1995**, 1029.

9. (a) Johnson, R. A.; Sharpless K. B. in *Catalytic Asymmetric Synthesis*; Ojima, I. Ed; VCH Publishers: New York, 1993, p 103. (b) Katsuki, T.; Sharpless, K. B. *J. Am. Chem. Soc.* **1980**, *102*, 5974. (c) Doherty, A. M.; Ley, S. V. *Tetrahedron Lett.* **1986**, *27*, 105.

10. Nicolaou, K. C.; Duggan, M. E. Hwang, C. -K. *J. Am. Chem. Soc.* **1989**, *111*, 6666.

11. Corey, E. J.; Ruden, R. A. *Tetrahedron Lett.* **1973**, 1495.

12. The stereochemical assignment of the *trans*-2,5-tetrahydrofuran **4** was confirmed by analogy of the ^{13}C NMR shifts of C-12 and C-15 portion of mucocin **1** with the reduced tetrahydrofuran derivative **15**[6] (using mucocin numbering). This was also supported by the characteristic δ value at H-15 and the relatively large difference between the two geminal protons at C-13 and C-14.[1]



		C-12	C-15
Mucocin	**1**	79.3	81.9
	15	79.3	81.6