Pergamon

Tetrahedron Letters 39 (1998) 9627–9628

TETRAHEDRON LETTERS

Enantioselective Synthesis of the 4-Hydroxy Buteneolide Terminus of Mucocin and Related Annonaceous Acetogenins

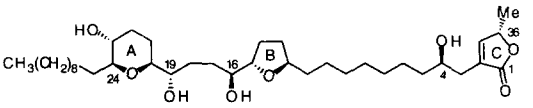
P. Andrew Evans* and V. Srinivasa Murthy

Brown Laboratory, Department of Chemistry and Biochemistry,
University of Delaware, Newark, DE 19716.

Received 24 September 1998; accepted 7 October 1998

Abstract:. *The 4-hydroxy buteneolide terminus* **3**, *applicable to mucocin* **1** *and related annonaceous acetogenins, was prepared in an expeditious manner from the selenocarbonate* **2** via *an intramolecular acyl radical cyclization followed by an enantioselective Lewis-acid catalyzed Keck-allylation reaction.*

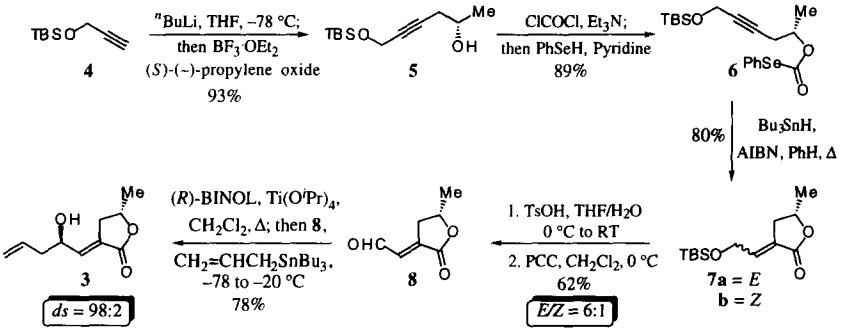
The linear annonaceous acetogenins represent an important and growing class of natural products that continue to attract attention.[1] This is due, at least in part, to their broad and impressive biological profile, which includes antitumor, pesticidal, antimicrobial and immunosuppresent activity. Examination of this family of polyketide derivatives revealed that although buteneolide moiety is ubiquitous, the most potent agents contain the C-4 hydroxyl group. Although a number of attractive syntheses of the C-4 hydroxyl containing fragment have been forthcoming,[2] we decided to examine an alternative approach. In a program directed towards the total synthesis of the antitumor agent mucocin **1**[3,4] we anticipated that the selenocarbonate **2** could be converted to the 4-hydroxy buteneolide terminus **3** in an expeditious manner and thus provide a versatile route to this key pharmacophore. Suzuki cross-coupling of the alkylborane derived from **3** with the corresponding alkynyl bromide would then complete the union of the fragments.



Mucocin **1**

Regioselective ring-opening of commercially available (*S*)-(-)-propylene oxide with the carbanion derived from the protected propargylic alcohol **4**, furnished the secondary alcohol **5** in 93% yield (**Scheme 1**). The selenocarbonate **6**[5] was then prepared from **5** in 89% yield, using phosgene followed by freshly prepared phenylselenol. Treatment of **6** under standard radical cyclization conditions (syringe pump addition of tributyltin hydride) afforded the γ-lactones **7a/b**[5] in 80% yield, as a 6:1 mixture of *E/Z*-isomers.[6] The geometrical isomers, although inconsequential, were separated by column chromatography, and relative geometry confirmed by NOE experiments. Removal of the *tert*-butyldimethylsilyl ether of **7a** with *p*-toluenesulfonic acid furnished the primary alcohol, which was oxidized using pyridinium chlorochromate to afford the aldehyde **8**[5] in 62% overall yield. Enantioselective Keck-allylation[7] of the aldehyde **8**, afforded the secondary alcohol **3**[5] in 78% yield as a 98:2 mixture of diastereoisomers, and thus completed the synthesis of the 4-hydroxy buteneolide fragment.[8]

0040-4039/98/$ - see front matter
PII: S0040-4039(98)02206-0



Scheme 1

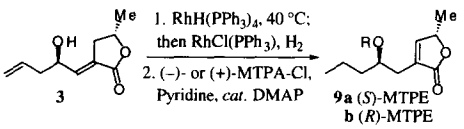
Therefore, we have achieved a 6 step enantioselective synthesis of the 4-hydroxy buteneolide terminus **3** of the antitumor agent mucocin and related annonaceous acetogenins, *via* an intramolecular 5-exo digonal acyl radical cyclization followed by an enantioselective Keck-allylation. This represents both an expeditious and stereochemically versatile synthesis of this important fragment.

Acknowledgments

We would like to thank the National Institutes of Health (GM54623) for generous financial support.

References and Footnotes

1. Marshall, J. A.; Hinkle, K. W.; Hagedorn, C. E. *Israel J. Chem.* **1997**, *37*, 97 and pertinent references therein.
2. For alternative approaches to the 4-hydroxy buteneolide terminus, see: (a) Koert, U. *Tetrahedron Lett.* **1994**, *35*, 2517. (b) Hoye, T. R.; Hanson, P. R.; Hasenwinkel, L. E.; Ramirez, E. A.; Zhuang, Z. *Tetrahedron Lett.* **1994**, *35*, 8529. (c) Hoye, T. R.; Tan, L. *Tetrahedron Lett.* **1995**, *36*, 1981. (d) Trost, B. M.; Calkins, T. L. *Tetrahedron Lett.* **1995**, *36*, 6021. (e) Wang, T. -L.; Hu, E.; Cassady, J. M. *Tetrahedron Lett.* **1995**, *36*, 9301. (f) Schaus, S. E.; Brånalt, J.; Jacobsen, E. N. *J. Org. Chem.* **1998**, *63*, 4876 and pertinent references therein.
3. 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.
4. For our synthetic approach to mucocin **1**, see Evans, P. A.; Murthy, V. S. *Tetrahedron Lett.* preceding paper.
5. All new compounds exhibited spectroscopic (IR, ^{1}H and ^{13}C-NMR) and analytical (HRMS) data in accord with the assigned structure.
6. Bachi, M. D.; Bosch, E. *J. Org. Chem.* **1992**, *57*, 4696.
7. Keck, G. E.; Tarbet, K. H.; Geraci, L. S. *J. Am. Chem. Soc.* **1993**, *115*, 8467.
8. The absolute configuration at the C-4 hydroxyl in **3** was confirmed by comparing the Mosher's esters **9a/b** with the C-4 Mosher's esters of mucocin **1**, using the method of Hoye and coworkers.[2b]



	H-3	H-35	H-36	H-37	C-4-config./ Mosher Ester config.
4-(*S*)-MTPE-**1**	2.58	6.72	4.86	1.28	R/S
4-(R)-MTPE-**1**	2.64	6.98	4.90	1.31	R/R
9a	2.58	6.70	4.85	1.27	R/S
9b	2.64	6.96	4.90	1.30	R/R