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An Outside-In Approach to Adjacent Bistetrahydrofuran Annonaceous Acetogenins with C_2 Core Symmetry. Total Synthesis of Asimicin and a C32 Analogue

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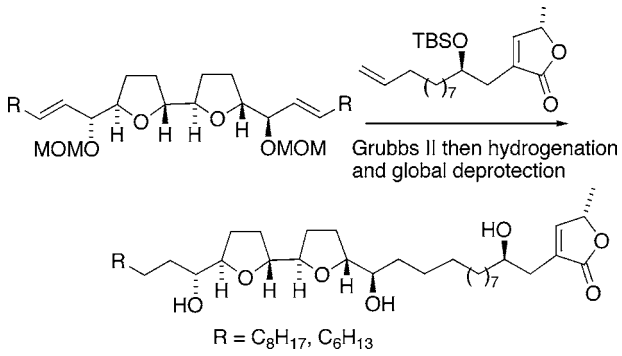
ABSTRACT



A synthesis of the Annonaceous acetogenin asimicin and a side-chain analogue has been achieved by a highly convergent route in which Grubbs cross-metathesis plays a key role.

Since their initial isolation in 1982, Annonaceous acetogenins have increasingly gained the attention of synthetic and medicinal chemists. Now numbering over 350 members, this family exhibits a broad range of bioactivities as potential pesticides, antifeedants, and immunosuppressive and antitumor agents.[1] As the name implies, acetogenins are derived biogenetically from acetate. Typical structures consist of an unbranched chain of 30−32 carbon atoms with a central core unit of one, two, or three adjacent tetrahydrofuran rings near the midpoint. One end of the chain is attached to the 2-position of a (*S*)-4-methylbutenolide, which is thought to be the biological pharmacophore (Figure 1). Compounds containing two adjacent tetrahydrofuran rings flanked on each side by hydroxyl substituents and containing one additional hydroxyl group on either of the attached chains exhibit the highest cytotoxicity toward tumor cells, including those exhibiting multiple drug resistance.[2]

The core unit of the adjacent bistetrahydrofuran acetogenins contains six oxygenated stereocenters, and much of

(1) For recent reviews of Annonaceous acetogenins, see: (a) Alali, F. Q.; Liu, X.-X.; McLaughlin, J. L. *J. Nat. Prod.* **1999**, *62*, 504. (b) Zafra-Polo, M. C.; Figadere, B.; Gallardo, T.; Tormo, J. R.; Cortes, D. *Phytochemistry* **1998**, *48*, 1087. (c) Cave, A.; Figadere, B.; Laurens, A.; Cortes D. In *Progress in the Chemistry of Organic Natural Products*: *Acetogenins from Annonaceae*; Hertz, W., Ed.; Springer-Verlag: New York, 1997; Vol. 70, pp 81−288. (d) Zeng, L.; Ye, Q.; Oberlies, N. H.; Shi, G.; Gu, Z.-M.; He, K.; McLaughlin, J. L. *Nat. Prod. Rep.* **1996**, *13*, 275. (e) Gu, Z.; Zhao, G.; Oberlies, N. H.; Zeng, L.; McLaughlin, J. L. Phytochemistry of Medicinal Plants. In *Recent Advances in Phytochemistry;* Arnason, J. T., Mata, R., Romeo, J. T., Eds.; Plenum Press: New York, London, 1995; Vol. 29, pp 249−310.

(2) Oberlies, N. H.; Chang, C.; McLaughlin, J. L. *J. Med. Chem.* **1997**, *40*, 2102.

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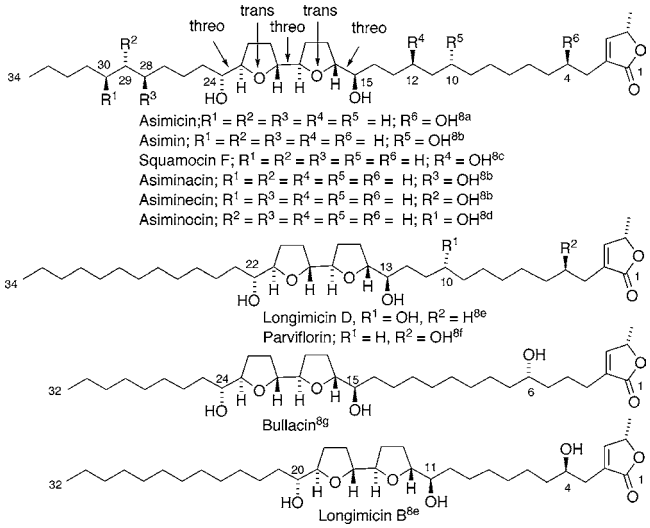

Figure 1. Structures for bioactive bistetrahydrofuran Annonaceous acetogenins with *threo,trans,threo,trans,threo* core stereochemistry.

the synthetic work on the family has been focused in that direction. The first successful approach was recorded in 1991 by Hoye and co-workers who employed a two-directional inside-out epoxide cascade sequence to prepare a core enantiomer of uvaricin.[3] This synthesis was important in establishing the absolute stereostructure of the natural product. Subsequently, numerous synthetic approaches to related core tetrahydrofuran arrays have been reported including a remarkably efficient improvement on their bidirectional epoxide cascade by Hoye and Ye.[4]

Other more recent noteworthy achievements include a bidirectional oxidative cyclization of bishomoallylic alcohols leading to 36 stereoisomeric bistetrahydrofuran core units with appendages suitable for further elaboration to a complete library of core isomers.[5,6] A recent report by Tanaka and co-workers outlines a stereodivergent approach to multiple core stereoisomers of bistetrahydrofuran core segments.[7]

The goal of the present study was to develop a convergent route to a single-core segment of the *threo,trans,threo,trans,threo* stereochemistry, present in asimicin and a number of other highly cytotoxic natural acetogenins (Figure 1),[8] with a view to prepare various analogues differing in the length and nature of the pendant side chains. We were motivated to pursue this line of investigation by a report of Miyoshi and co-workers who concluded from molecular modeling and SAR studies that the length and flexibility of the spacer moiety that links the THF core unit to the butenolide terminus is the most important factor affecting the activity of these compounds as inhibitors of tumor cell growth.[9] The stereochemistry of the core units was judged relatively unimportant. Related followup NOE studies by McLaughlin and coworkers on asimicin, parviflorin, and longimicin B bound to small unilamellar vesicles verified and extended those conclusions.[10] In the aforementioned three acetogenins, the spacer chain between the butenolide end group and the tetrahydrofuran core contains, respectively, 13, 11, and 9 carbons. The length of the spacer chain was shown to influence the conformation of the membrane-bound acetogenin with the shorter 9-carbon chain favoring a U-shaped conformation and the longer 9- and 11-carbon spacers favoring a sickle-shaped conformer. This conformational change results in the repositioning of the active butenolide pharmacophore within the lipid bilayer. The longer chain acetogenins were 100 times more active than parviflorin in the brine shrimp lethality screen.

In the present report, we detail a bidirectional outside-in hydroxy mesylate cascade cyclization route to a *threo,trans, threo,trans,threo*-bistetrahydrofuran core unit which can be further elaborated by Grubbs cross-metathesis[11] to a number of natural Annonaceous acetogenins and analogues. To illustrate the approach, we selected asimicin[8a] and a C32 analogue that differ in the length of the alkyl chain attached to C24 of the bistetrahydrofuran. The route is highly convergent and should be well suited to the preparation of additional side-chain analogues.

The first key intermediate in our synthetic sequence, triene diester **3**, had previously been prepared by Hoye and Ye from all-*trans*-1,5,9-cyclododecatriene in three steps (45% yield).[4] We prepared this diester from 4-penten-1-ol (**1**) by sequential Grubbs dimerization and subsequent Swern−Wittig homologation in 61% yield as a 5:1 mixture of (*E*)- and (*Z*)-isomers.[12] Selective asymmetric dihydroxylation with AD-mix α[13] afforded the crystalline diol **4** in 73% yield along with recovered triene **3**. Bisdihydroxylation of the derived mesylate **5** with AD-mix β led to a tetrol which, without

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(9) Miyoshi, H.; Ohshima, M.; Shimada, H.; Akagi, T.; Iwamura, H.; McLaughlin, J. L. *Biochimica Biophys. Acta* **1998**, 443.

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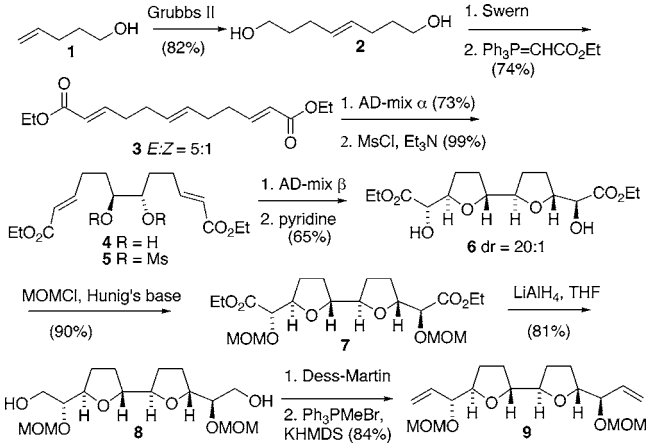
(11) Chatterjee, A. K.; Choi, T.-L.; Sanders, D. P.; Grubbs, R. H. *J. Am. Chem. Soc.* **2003**, *125*, 11360.

(12) In a preliminary report of this methodology, metathesis of ethyl (*E*)-2,6-heptadienoate with the Grubbs I ruthenium catalyst was used to prepare the triene ester **3** as a ca. 2:1 mixture of (*E*) and (*Z*) isomers which was ultimately converted to the *threo,cis,threo,cis,threo*-isomer of the bistetrahydrofuran diene **9**. Marshall, J. A.; Sabatini, J. J. *Org. Lett.* **2005**, *7*, 4819.

(13) Kolb, H. C.; VanNieuwenhze, M. S.; Sharpless, K. B. *Chem. Rev.* **1994**, *94*, 2483.

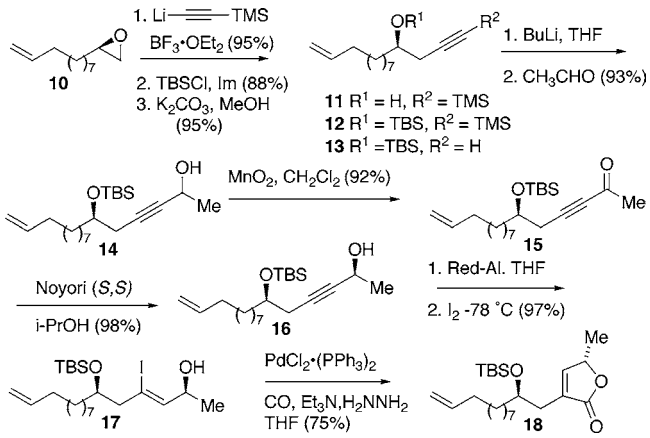
purification, was converted to the bistetrahydrofuran diol diester **6** in refluxing pyridine[5] with an overall yield of 64% for the three steps. This intermediate was judged to contain less than 5% of isomeric impurities on the basis of analysis of the ^{1}H NMR spectrum. Protection of the diol **6** as the MOM ether **7**, reduction of the diester with $LiAlH_4$ followed by sequential Dess−Martin oxidation,[14] and Wittig homologation afforded the *threo,trans,threo,trans,threo* core diene unit **9** in 61% overall yield (Scheme 1).

Scheme 1



An appropriate 4-hydroxy butenolide side-chain precursor for our planned synthesis of asimicin and the C32 analogue was constructed as outlined in Scheme 2 starting from

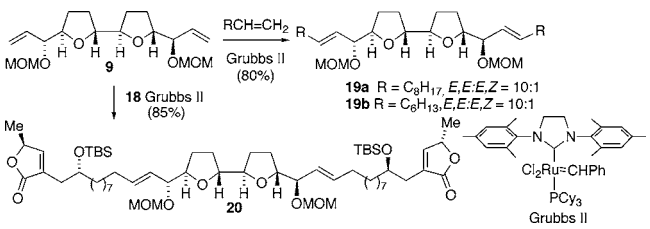
Scheme 2



epoxide **10** prepared by Jacobsen resolution[15] of the racemate. Addition of lithio TMS acetylene led to the alcohol **11** with >95% enantiomeric purity as measured by ^{19}F NMR analysis of the Mosher ester.[16] Protection of the alcohol as the silyl ether **12** and removal of the alkynyl TMS substituent afforded the alkyne **13** which, after lithiation and addition to acetaldehyde, yielded the propargylic alcohol **14**. Oxidation followed by Noyori asymmetric transfer hydrogenation with the (*S,S*) catalyst[17] gave the propargylic alcohol **16** with greater than 95% diastereomeric purity. Attempts to effect a more convergent synthesis of alcohol **16** through addition of the lithiated TBS or TES ether derivative of (*S*)-3-butyn-2-ol to epoxide **10**, with or without BF_3 promotion, caused decomposition of the epoxide.[18] The conversion of alcohol **16** to the butenolide **18** was conducted along the lines reported by Hoye for an analogous intermediate.[4]

We were now in a position to address desymmetrization strategies for further elaboration of the diene core unit **9** to the acetogenin targets asimicin and its C32 analogue. As diene **9** is a "type II" olefin, we felt that oligomerization would defeat attempts at selective mono cross-metathesis with the butenolide segment **18** or a terminal alkene such as 1-decene.[11] Accordingly, we prepared the symmetrical cross-metathesis products, dienes **19a** and **19b**, by reaction of diene **9** with 1-decene and 1-octene. The alkenes were employed in excess to minimize oligomerization of the bis-THF diene **9**. The bisbutenolide analogue **20** was likewise prepared from diene **9** and the butenolide segment **18** (Scheme 3).

Scheme 3



Oligomerization of the internal "type III" dienes **19a**, **19b**, and **20** was expected to be much slower than a metathesis exchange with the terminal olefin side-chain precursor **9**. In principle, each of these three internal symmetrical dienes could provide one of the targeted acetogenins, although the former two represent the more accessible precursors. The next stage of our studies was aimed at evaluating the relative efficiency of the two alternative cross-metathesis strategies.

Reaction of the bisbutenolide **20** with 1 equiv of 1-decene catalyzed by 5 mol % of Grubbs II catalyst led, after 12 h, to the asimicin precursor **21a** (24%) and recovered bislactone **20** (30%) along with an analyzable but inseparable mixture of bislactone **23** (21%) and bis-THF diene **19a** (6%) and the monobutenolide **22a** (13%) accounting for 94% of the starting material. With the exception of **23** and **19a**, these products could be easily separated by column chromatography on silica gel (Scheme 4).

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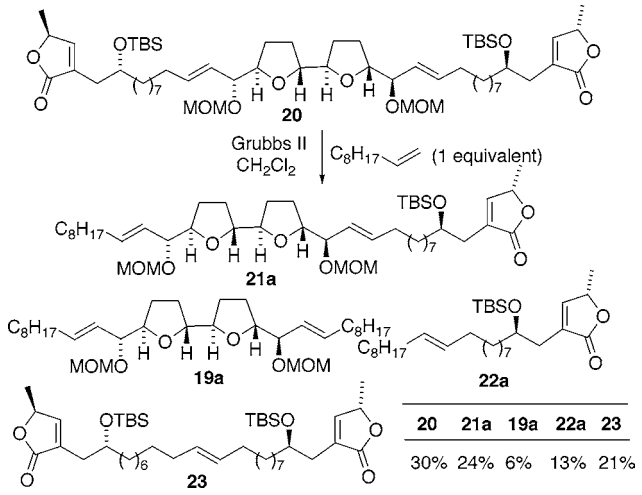
(16) Dale, J. A.; Mosher, H. S. *J. Am. Chem. Soc.* **1973**, *95*, 512.
(17) Matsumura, K.; Hashiguchi, S.; Ikariya, T.; Noyori, R. *J. Am. Chem. Soc.* **1997**, *119*, 8738.
(18) Hoye, T. R.; Humpal, P. E.; Jimenez, J. I.; Mayer, M. J.; Tan, L.; Ye, Z. *Tetrahedron Lett.* **1994**, *35*, 7517.

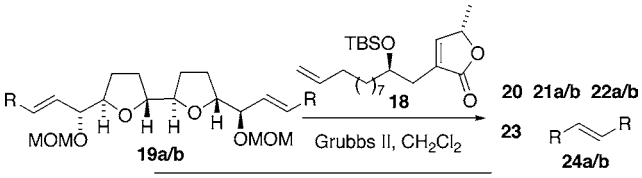
Scheme 4



20	21a	19a	22a	23
30%	24%	6%	13%	21%

Cross-metathesis of the bis-THF dienes **19a** and **19b** with the butenolide segment **18** proved somewhat more efficient, affording 38% and 40% of the acetogenin precursors **21a** and **21b** and 28% and 19% of recovered starting dienes **19a** and **19b** (Scheme 5). The inseparable mixtures of **19a/b** and

Scheme 5



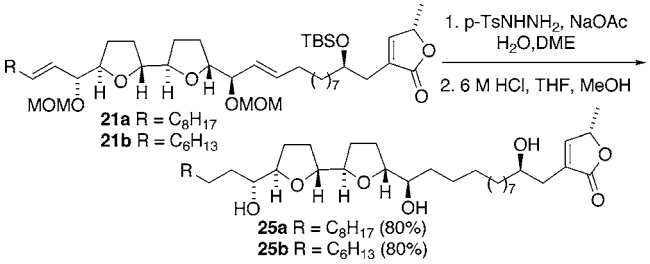
R[a]	20	21	19	22	23	24
C_8H_{17}	9	38	28	9	7	5
C_6H_{13}	10	40	19	11	5	14

[a] **a** series R = C_8H_{17}, **b** series R = C_6H_{13}

23 could be resubjected to the metathesis procedure leading to additional quantities of the acetogenin products **21a** and **21b**.[19] The cross products **22a/b** could also be recycled with **19a/b** to afford the additional asimicin precursor **21a** and its analogue.

To complete the synthesis, the side-chain double bonds of the principle cross-metathesis products **21a** and **21b** were selectively hydrogenated and the resulting tetrahydro products were subjected to global deprotection with 6 N HCl in THF−methanol to afford asimicin (**22a**) and the analogue **22b** in high yield (Scheme 6). The spectral properties and

Scheme 6



rotations of the former were in close agreement with the reported value. Not surprisingly, the ^1H and ^{13}C NMR spectra of the two were virtually indistinguishable. However, the high-resolution mass spectra were clearly different and in full accord with the perceived structures.

The foregoing highly convergent route to Annonaceous acetogenins with a *threo,trans,threo,trans,threo* core unit is straightforward and should be amenable to "mix and match" variations to access a range of analogues with desirable medicinal applications. Although the yield of the desired acetogenin products is less than 50%, the net efficiency of the process is high because all byproducts can be resubjected to the metathesis conditions to generate additional quantities of the final product.[19] It should be noted that nearly 100% of the material is recovered in these reactions.

Note Added in Proof. Two papers on acetogenin synthesis appeared after submission of the present manuscript. Both involve ingenious applications of cross metathesis reactions. Mucocin: Crimmins, M. T.; Zhang, Y.; Diaz, F. A. *Org. Lett.* **2006**, *8*, 2368. Gigantecin: Hoye, T. R.; Eklov, B. M.; Jeon, J.; Khoroosi, M. *Org. Lett.* **2006**, *8*, 3383.

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Supporting Information Available: Experimental procedures and ^1H NMR spectra for all key compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(19) A single recycle of the byproducts afforded the asimicin precursor **21a** in 25−30% yield.