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ABC synthesis and antitumor activity of a series of Annonaceous acetogenin analogs with a *threo*, *trans*, *threo*, *trans*, *threo*-bis-tetrahydrofuran core unit

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Abstract—Side-chain analogs of Annonaceous acetogenins with a *threo*, *trans*, *threo*, *trans*, *threo*-bis-tetrahydrofuran core unit have been prepared and tested for cytotoxicity against HCT-116 human colon cancer cells.

First described in 1982[1], the class of natural products known as Annonaceous acetogenins now number more than 350 members.[2] All are isolated from members of the plant family Annonaceae, and many show potent antitumor, antimicrobial, antimalarial, pesticidal, and antifeedant activities. Biogenetically derived from polyoxygenated C32 or C34 fatty acids and a branched propionate moiety at C2 as part of a butenolide terminus, the most active compounds generally possess one or two tetrahydrofuran rings flanked by hydroxyl substituents near the center of the fatty acid chain (Fig. 1).

The biological activity of these compounds stems from their inhibition of the terminal electron transfer step of cell membrane mitochondrial Complex I. It is postulated that the oxygenated central segment of the bis-tetrahydrofuran acetogenins acts as a hydrophilic anchor to the glycerol backbone region of liposomal membranes with the appended aliphatic arms extending into the lipid bilayer.[3] These arms are thought to control the positioning of the butenolide terminus within the bilayer and its proximity to the active site of Complex I.[4] Since the requisite hairpin conformation of the membrane-bound acetogenin can be realized with a variety of core stereoisomers it is further postulated that the length of the butenolide spacer chain has a greater influence on biological activity than the stereochemistry of the bis-tetrahydrofuran core.[3] However, this postulate has not been much explored because few examples of natural Annonaceous acetogenins differing only in spacer chain length are known. Furthermore, most synthetic studies have focused on relatively few of the natural acetogenins or core stereoisomers of natural acetogenins.[5]

We recently reported a highly convergent bidirectional route to acetogenins with a *threo*, *trans*, *threo*, *trans*, *threo* core unit by a modular approach involving Grubbs cross-metathesis methodology for attachment of the aliphatic side chains to a readily prepared core unit.[6] This route seemed ideally suited for a preliminary examination of the influence of side chains on bioactivity in acetogenin analogs with a common core stereochemistry.

Our overall plan, as summarized in Figure 2, consisted of three stages starting with a synthesis of the aforementioned

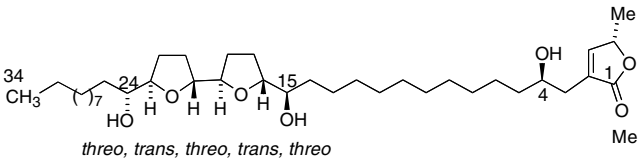

Figure 1. Asimicin. A typical *threo*, *trans*, *threo*, *trans*, *threo* bis-tetrahydrofuran Annonaceous acetogenin derived from a C34 fatty acid.

Keywords: Acetogenins; Cross-metathesis; Antitumor activity; Cytotoxicity.
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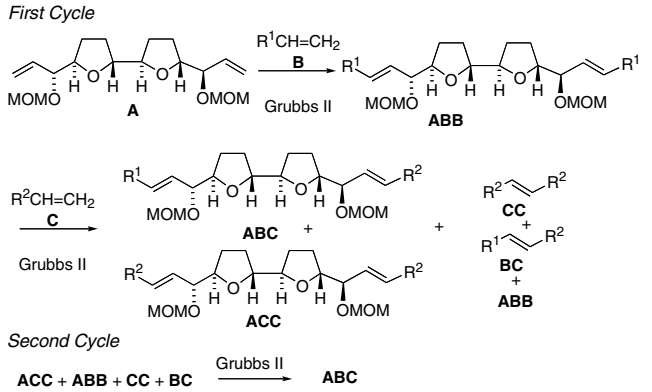
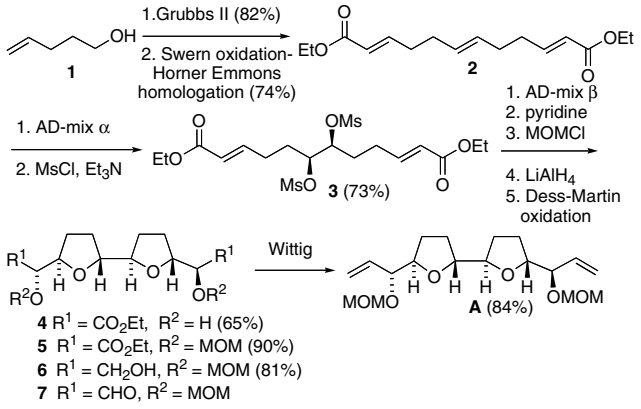


Figure 2. ABC plan for the synthesis of Annonaceous acetogenin analogs with C_2 core symmetry.



Scheme 1.

core unit **A** which would then be elaborated by a Grubbs cross-metathesis reaction with a terminal alkene precursor **B** of one of the side chains to form the symmetric diene **ABB**.[7] This 'type III' diene would then be subjected to a second cross metathesis with a terminal alkene precursor **C** of the second side chain to yield the unsymmetrical diene **ABC**. Final elaboration of this intermediate to the targeted acetogenin analog would then require only hydrogenation and global deprotection. An excess of the initial terminal alkene **B** would be employed to minimize the potentially competing oligomerization of the diene **A**. The expected byproducts of the second cross metathesis, an equilibrium mixture of **ACC**, **BC**, **CC**, and recovered **ABB**, can be resubjected to cross metathesis thereby generating additional quantities of **ABC**. For our initial studies we focused on functional variations in the nonbutenolide side chain to evaluate the flexibility of the approach. Additional studies on systematic chain length variations of the butenolide chain are planned for a future date.

As the **B** components of the present analog synthesis, we chose readily available alkenes as these would be employed in excess for the initial cross metathesis (Fig. 3). For the **C** components we mainly used the hydroxy butenolide $\mathbf{C}^1$ because 4-hydroxy substituted acetogenins show some of the highest reported activity against tumor cells. In these initial studies we were more interested in exploring the versatility of the synthetic methodology than devising a series of closely related (R = Me, Et, Pr, Bu, etc.) series of analogs. We were particularly interested in the previously unknown terminal alcohol analogs derived from $\mathbf{B}^3$ and $\mathbf{B}^4$ as these compounds and possible derivatives might have higher water solubility than their alkyl counterparts.

The core tetrahydrofuran segment **A** was prepared as previously described starting from 4-penten-1-ol (**1** Scheme 1).[6] Dimerization with the Grubbs II catalyst[7] followed by in situ Swern oxidation and Horner–Emmons phosphonate homologation afforded the triene diester **2** which was selectively dihydroxylated with the Sharpless AD-mix α reagent. Conversion to the dimesylate **3** then dihydroxylation of the conjugated double bonds with AD-mix β led to a tetraol, which was heated in pyridine to effect conversion to the bis-tetrahydrofuran diester **4**. Protection of the diol with MOMCl followed by reduction of the diester **5** with lithium aluminum hydride afforded the diol **6**. Oxidation to dialdehyde **7** and Wittig homologation of dialdehyde **7**completed the sequence to diene **A** in an overall yield of 18%.

The terminal alkene precursors to side chain $\mathbf{B}^1$(1-decene) and $\mathbf{B}^2$ (1-octene) are commercially available and those of $\mathbf{B}^3$ and $\mathbf{B}^4$ are the TBS ethers of commercially available 5-hexen-1-ol and 10-undecen-1-ol.

Our synthesis of the 4-hydroxy butenolide side-chain precursor **17**, outlined in Scheme 2, is an improved version of our previous sequence. Asymmetric dihydroxylation of 1,11-dodecadiene (**9**), easily prepared from 10-undecenal (**8**) by Wittig homologation, afforded the diol **10** of 92% enantiomeric purity in 60% yield.[8] Selective tosylation then TBS protection and treatment with NaI then led to the iodide **13**. Alkylation of White's

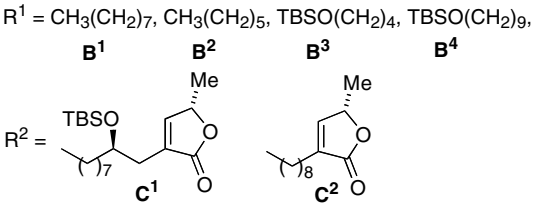
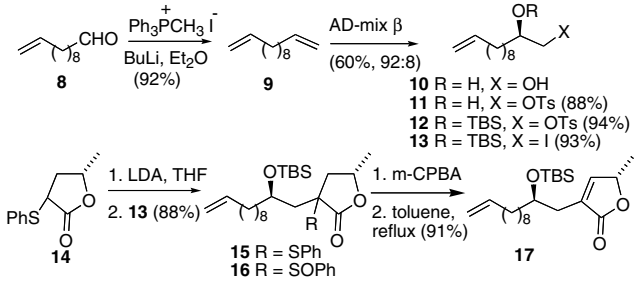
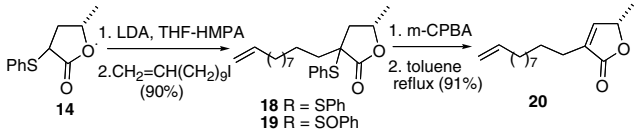


Figure 3. Terminal alkenes $R^1CH{=}CH_2$ and $R^2CH{=}CH_2$ employed in cross metathesis.



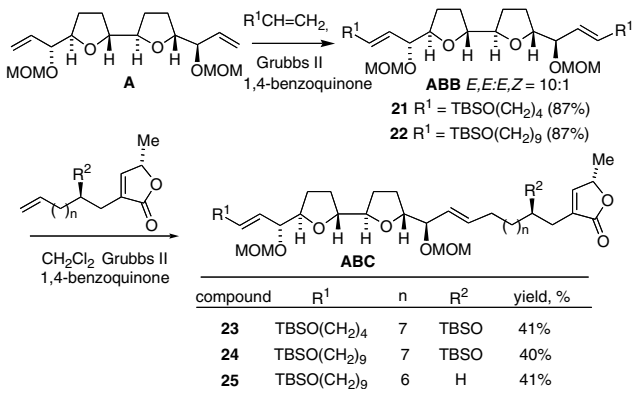
Scheme 2.



Scheme 3.

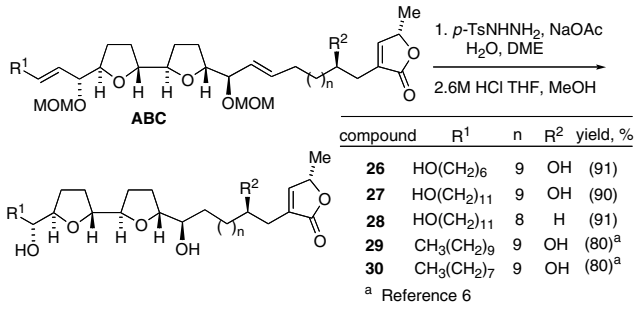
lactone **14**[9] with this iodide proceeded in 88% yield. The homologated lactone **15** was converted to the sulfoxide **16** which underwent elimination in refluxing toluene to the butenolide **17** in 91% yield.[5b] The butenolide precursor **20** of side chain **C**[2] was prepared analogously (Scheme 3).

We next addressed coupling of the core unit **A** with the various **B** and **C** side chain alkenes by cross metathesis (Scheme 4). In our preliminary report of this methodology, in which the unfunctionalized alkenes 1-decene and 1-octene were employed in the initial cross metathesis, we found that the reaction proceeded smoothly with 5 mol% of the Grubbs II catalyst. However, with the oxygenated alkenes related to **B**[3] and **B**[4] of the current study, this protocol was not successful owing to extensive migration of the terminal double bonds and catalyst deactivation. Fortunately, this side reaction could be shut down through use of added *p*-benzoquinone to intercept the responsible RuH intermediate.[10] However, it was necessary to increase catalyst loading to 35 mol%. These same conditions were successfully employed for the cross-metathesis reactions as summarized in Scheme 5. In each case we obtained the **ABC** products in about



compound	R^1	n	R^2	yield, %
23	$TBSO(CH_2)_4$	7	TBSO	41%
24	$TBSO(CH_2)_9$	7	TBSO	40%
25	$TBSO(CH_2)_9$	6	H	41%

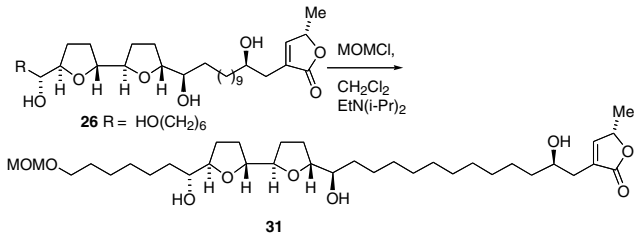
Scheme 4.



compound	R^1	n	R^2	yield, %
26	$HO(CH_2)_6$	9	OH	(91)
27	$HO(CH_2)_{11}$	9	OH	(90)
28	$HO(CH_2)_{11}$	8	H	(91)
29	$CH_3(CH_2)_9$	9	OH	(80)[a]
30	$CH_3(CH_2)_7$	9	OH	(80)[a]

[a] Reference 6

Scheme 5.



Scheme 6.

40% yield and recovered approximately 20% of the **ABB** starting material, 20% of the **ABB** double exchange product, and 10% each of the dimeric **CC** and cross **BC** products. Typically, more than 90% of the total material could be accounted for. We have previously shown that recycling of the recovered materials results in additional quantities of the **ABC** product along with the others in a comparable ratio.[6] This option was not examined in the present cases.

Reduction of the disubstituted alkenes and global deprotection of the **ABC** intermediates was smoothly effected by sequential treatment with diimide and methanolic HCl (Scheme 5).[6] The terminal OH derivative **26** was chain-extended by selective reaction with MOMCl leading to the MOM derivative **31** (Scheme 6). We had hoped that replacing two of the methylene groups of the side chain with oxygen would increase water solubility, but this was not the case. Ether **31** exhibited no measurable solubility in water.

Table 1 summarizes cytotoxicity data for the acetogenin analogs **26**–**31** against HCT-116 colon cancer cells.[5b] Notably all analogs show IC_{50}values in the nanomolar range. Of the terminal hydroxy analogs **26**, **27**, and **28** the latter, lacking a C4 OH, is the least active in keeping with expectation based on reported activities of natural acetogenins. Interestingly, the truncated analog **30** of asimicin (**29**) is some 20 times more active than its natural counterpart. Although an exact comparison is not possible owing to differing chain lengths, the comparable activity exhibited by the terminal hydroxy compounds **26** and **27** and the related alkyl compounds **30** and **29** suggests that the added terminal OH group does not markedly affect cytotoxicity. While enhanced water solubility was not observed with the hydroxylated compounds, it may be possible to realize that goal through conversion of the OH to a water soluble derivative that could be cleaved in vivo.

Table 1. Cytotoxicity against HCT-116 colon cancer cells

Compound	IC_{50} (ng/mL)	IC_{50} (nM)
26	2.2	3.8
27	0.39	0.60
28	22	35
29[a]	5.5	8.8
30[a]	0.30	0.50
31	9.9	16

[a] Ref. 6.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.bmcl.2007.02.033.

References and notes

1. Jolad, S. D.; Hoffmann, J. J.; Schram, K. H.; Cole, J. R. *J. Org. Chem.* **1982**, *47*, 3151.
2. Reviews (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.
3. Miyoshi, H.; Ohshima, M.; Shimada, H.; Akagi, T.; Iwamura, H.; McLaughlin, J. L. *Biochim. Biophys. Acta* **1998**, 443.
4. Shimada, H.; Grutzner, J. B.; Kozlowski, J. F.; McLaughlin, J. L. *Biochemistry* **1998**, *37*, 854.
5. Recent examples (a) Takahashi, S.; Nakata, T. *J. Org. Chem* **2002**, *67*, 5739; (b) Marshall, J. A.; Pietttre, A.; Paige, M. A.; Valeriote, F. *J. Org. Chem.* **2003**, *68*, 1771; (c) Nattrass, G. L.; Diez, E.; McLachlan, M. M.; Dixon, D. J.; Ley, S. V. *Angew. Chem., Int. Ed.* **2005**, *44*, 580; (d) Tinsley, J. M.; Roush, W. R. *J. Am. Chem. Soc.* **2005**, *127*, 10818; (e) Keum, G.; Hwang, C. H.; Kang, S. B.; Kim, Y.; Lee, E. *J. Am. Chem. Soc.* **2005**, *127*, 10396; (f) Das, S.; Li, L.-S.; Abraham, S.; Chen, Z.; Sinha, S. C. *J. Org. Chem.* **2005**, *70*, 5922; (g) Crimmins, M. T.; Zhang, Y.; Diaz, F. A. *Org. Lett.* **2006**, *8*, 2369; (h) Bandur, N. G.; Brückner, D.; Hoffmann, R. W.; Koert, U. *Org. Lett.* **2006**, *8*, 3829; (i) Zhao, H.; Gorman, S. T.; Pagenkopf, B. L. *Org. Lett.* **2006**, *8*, 4379; (j) Wysocki, L. M.; Dodge, M. W.; Voight, E. A.; Burke, S. D. *Org. Lett.* **2006**, *8*, 5637.
6. Marshall, J. A.; Sabatini, J. J. *Org. Lett.* **2006**, *8*, 3557.
7. (a) Grubbs, R. H. *Tetrahedron* **2004**, *60*, 7117; (b) Chatterjee, A. K.; Choi, T.-L.; Sanders, D. P.; Grubbs, R. H. *J. Am. Chem. Soc.* **2003**, *125*, 11360.
8. Curran, D. P.; Zhang, Q.; Richard, C.; Lu, H.; Gudipati, V.; Wilcox, C. S. *J. Am. Chem. Soc.* **2006**, *71*, 3559.
9. White, J. D.; Somers, T. C.; Reddy, G. N. *J. Org. Chem.* **1992**, *57*, 4991.
10. Hong, S. H.; Sanders, D. P.; Lee, C. W.; Grubbs, R. H. *J. Am. Chem. Soc.* **2007**, *127*, 17160.