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Total Synthesis and Structure Confirmation of the Annonaceous Acetogenins 30(*S*)-Hydroxybullatacin, Uvarigrandin A, and 5(*R*)-Uvarigrandin A (Narumicin I?)

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Received October 27, 2002

A synthesis of the bistetrahydrofuran Annonaceous acetogenins 30(*S*)-hydroxybullatacin, uvarigrandin A, and 5(*R*)-uvarigrandin A through application of a previously disclosed four-component modular approach is described in which extended core segments are coupled to a C4- or C5-hydroxy butenolide terminus. The butenolide termini segments were prepared from (*S*)- or (*R*)-malic acid. Spectral properties of synthetic 30(*S*)-hydroxybullatacin and uvarigrandin A, as well as their Mosher ester derivatives, were in close agreement to the reported values for the natural substances. The synthetic 5(*R*)-uvarigrandin A is possibly identical to narumicin I, but subtle differences in the reported NMR spectra prevented an unambiguous assessment of this point.

Acetogenins of the Annonaceae have proven to be a rich source of natural products with a wide range of bioactivities.[1] In particular, a bistetrahydrofuran subgroup of this family has been found to inhibit the growth of human tumor cells at submicromolar levels. A number of these compounds are also cytotoxic to tumor cells that have developed resistance to typical chemotherapeutic agents.[2]

Despite the abundance of their plant sources the Annonaceous acetogenins remain scarce because they are present in minute amounts as complex mixtures of isomers that can be separated only with great difficulty.[3] Important structural features of the most active antitumor compounds are depicted in Figure 1. The structures feature an unbranched chain of 32 carbons attached to the α-position of a γ-methyl butenolide. Embedded in the central portion of this chain is a hydrophilic bistetrahydrofuran core moiety with two flanking hydroxyl groups. Of the 64 possible stereoisomers of this core unit only 7 have been found in Nature.[4] All of these have the (*R*) configuration at C23 and the (*S*) configuration at C36. A third hydroxyl group is also present in those compounds with the highest activity. This group is typically located at C4, C10, or C30 and less commonly at C5, C28, or C29.

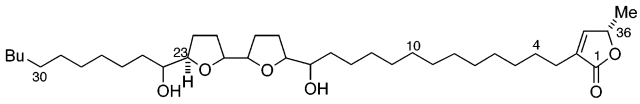

FIGURE 1. Generic root structure of cytotoxic bistetrahydrofuran Annonaceous acetogenins.

Not surprisingly, considerable effort has been devoted to the synthesis of Annonaceous acetogenins.[5−8] As few of these lipophilic compounds are crystalline, structure analysis has relied mainly upon spectroscopic methods with occasional confirmation through total synthesis. We recently disclosed a modular synthetic approach to the structure types shown in Figure 1.[9] This approach featured highly selective additions of chiral α-oxygenated allylic stannane and indium reagents such as **B** and **D** (M = $SnBu_3$ or $InBr_2$) to an acylic core aldehyde precursor (**A** then **C**) followed by core ring closure (**E** → **F**) and

† University of Virginia.

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(1) (a) Gu, Z.-M.; Zhao, G.-X.; Oberlies, N. H.; Zeng, L.; McLaughlin, J. L. In *Recent Advances in Phytochemistry*; Arnason, J. T., Mata, R., Romeo, J. T., Eds.; Plenum Press: New York, 1995; Vol. 29, pp 249−310. (b) Zeng, L.; Ye, Q.; Oberlies, N. H.; Shi, G.; Gu, Z.-M.; He, K.; McLaughlin, J. L. *Nat. Prod. Rep.* **1996**, 275. (c) Cavé, A.; Figadére, B.; Laurens, A.; Cortes, D. In *Progress in the Chemistry of Natural Products*; Herz, W., Kirby, G. W., Moore, R. E., Steglish, W., Tamm, C., Eds.; Springer-Verlag Chemistry: New York, 1997; pp 81−287.

(2) (a) Oberlies, N. H.; Croy, V. L.; Harrison, M. L.; McLaughlin, J. L. *Cancer Lett.* **1997**, *115*, 73. (b) Oberlies, N. H.; Chang, C.-J.; McLaughlin, J. L. *J. Med. Chem.* **1997**, *40*, 2102.

(3) Zhao, G.-X.; Miesbauer, L. R.; Smith, D. L.; McLaughlin, J. L. *J. Med. Chem.* **1994**, *37*, 1971.

(4) (a) Rupprecht, J. K.; Hui, Y. H.; Mclaughlin, J. L. *J. Nat. Prod.* **1990**, *53*, 237. (b) Alzli, F. Q.; Liu, X.-X.; McLaughlin, J. L. *J. Nat. Prod.* **1999**, *62*, 504.

(5) (a) Marshall, J. A.; Hinkle, K. W. *J. Org. Chem.* **1996**, *61*, 4247. (b) Marshall, J. A.; Hinkle, K. W. *J. Org. Chem.* **1997**, *62*, 5989. (c) Marshall, J. A.; Chen, M. *J. Org. Chem.* **1997**, *62*, 5996.

(6) (a) Marshall, J. A.; Hinkle, K. W. *Tetrahedron Lett.* **1998**, *39*, 1303. (b) Marshall, J. A.; Jiang, H. *Tetrahedron Lett.* **1998**, *39*, 1493. (c) Marshall, J. A.; Jiang, H. *J. Org. Chem.* **1998**, *63*, 7066. (d) Marshall, J. A.; Jiang, H. *J. Org. Chem.* **1999**, *64*, 971. (e) Marshall, J. A.; Jiang, H. *J. Nat. Prod.* **1999**, *62*, 1123.

(7) Reviews: (a) Figadére, B. *Acc. Chem. Res.* **1995**, *28*, 359. (b) Hoppe R.; Scharf, H.-D. *Synthesis* **1995**, 1447. (c) Marshall, J. A.; Hinkle, K. W.; Hagedorn, C. E. *Isr. J. Chem.* **1997**, *37*, 97. (d) Casiraghi, G.; Zanardi, F.; Battistina, L.; Rassu, G.; Appendino, G. *Chemtracts: Org. Chem.* **1998**, *11*, 803.

(8) (a) Hoye, T. R.; Hanson, P. R.; Kovelesky, A. C.; Ocain, T. D.; Zhuang, Z. *J. Am. Chem. Soc.* **1991**, *113*, 9369. (b) Naito, H.; Kawahara, E.; Maruta, K.; Naeda, M.; Sasaki, S. *J. Org. Chem.* **1995**, *60*, 4419. (c). Sinha, S.; Sinha, A.; Yazbak, A.; Keinan, E. *J. Org. Chem.* **1996**, *61*, 7640. (d) Hoye, T. R.; Ye, Z. *J. Am. Chem. Soc.* **1996**, *118*, 1801. (e) Sinha, S. C.; Sinha, A.; Keinan, E. *J. Am. Chem. Soc.* **1997**, *119*, 12014 and references therein. (f) Emde, U.; Koert, U. *Tetrahedron Lett.* **1999**, *40*, 5979. (g) Avedission, H.; Sinha, S. C.; Yazbek, A.; Sinha, A.; Neogi, P.; Sinha, S. C.; Keinan, E. *J. Org. Chem.* **2000**, *65*, 6035.

(9) Marshall, J. A.; Piettre, A.; Paige, M. A.; Valeriote, F. *J. Org. Chem.* **2003**, *68*, 1771.

10.1021/jo0266137 CCC: $25.00 © 2003 American Chemical Society
Published on Web 02/08/2003

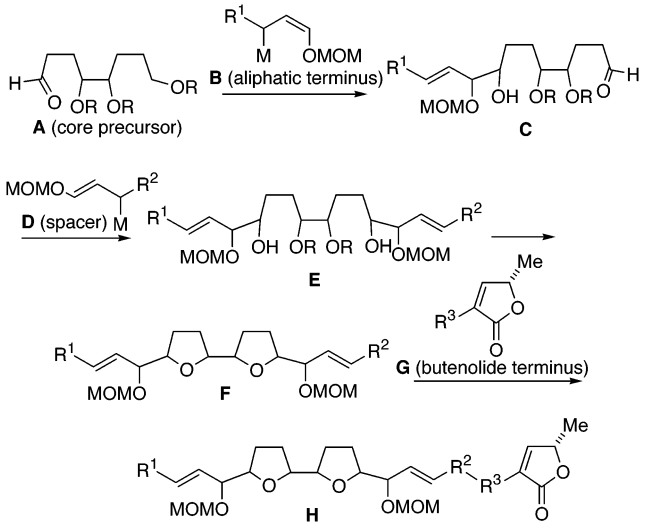


FIGURE 2. Modular synthetic approach to bistetrahydrofuran Annonaceous acetogenins.

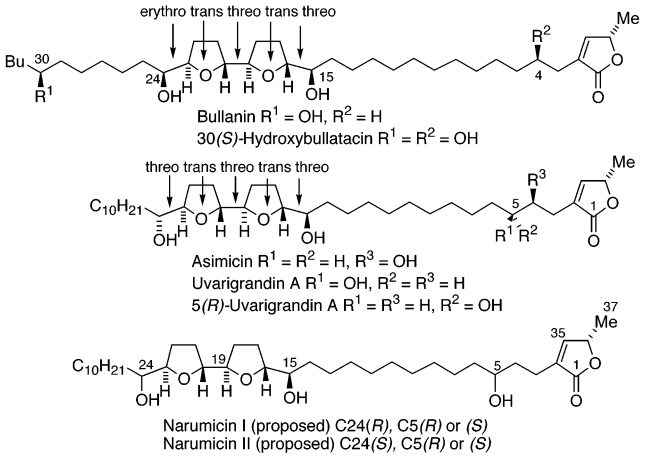


FIGURE 3. Structures of C4, C5, and C30 hydroxylated bistetrahydrofuran Annonaceous acetogenins.

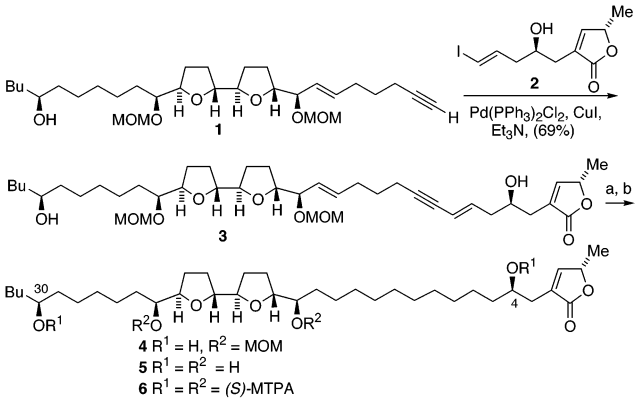
ensuing Sonogashira coupling (**F** + **G** → **H**) to append the butenolide segment (Figure 2). This straightforward strategy permits the efficient assemblage of the acetogenin structure from four basic subunits. By interchanging these subunits a variety of natural acetogenins and their isomers should be accessible in relatively few steps.

Our initial application of this strategy resulted in syntheses of the C10 and C4 hydroxylated acetogenins asimin and asimicin and the two C30 hydroxylated core isomers asiminocin and bullanin (Figure 3). We now describe an application of this strategy to the novel C5 hydroxylated acetogenins uvarigrandin A and 5(*R*)-uvarigrandin A (narumicin I?) and a C4, C30 tetrahydroxy acetogenin, 30(*S*)-hydroxybullatacin.

McLaughlin and co-workers isolated the novel tetrahydroxy threo, trans, threo, trans, erythro (C15 → C24) bistetrahydrofuran acetogenins 32-hydroxybullatacin, 31-hydroxybullatacin, and 30-hydroxybullatacin from ethanolic extracts of bark from *Annona bullata* Rich.[10] The

(10) Gu, Z.-M.; Zeng, L.; Schwedler, J. T.; Wood, K. V.; McLaughlin, J. L. *Phytochemistry* **1995**, *40*, 467.

SCHEME 1[a]



[a] (a) *p*-TsNHNH$_2$, NaOAc (66%); (b) $BF_3{\cdot}OEt_2$, Me_2S (74%).

former two were identified as the 32(*S*) and 31(*S*) isomers, respectively, whereas the latter was isolated as an inseparable 4:1 mixture of (*S*) and (*R*) isomers at C30 (see Figure 3). The assignment of the 30(*S*) configuration to the major component of this mixture was based on differences in the chemical shifts of the terminal CH_3 signals of the tetra MTPA Mosher ester mixtures ($\Delta\,\delta_H = 0.06$ ppm).[10,11]

In our initial application of the aforementioned four-component modular approach to Annonaceous acetogenins, we prepared a 30(*S*)-hydroxylated bistetrahydrofuran, bullanin (Figure 3), from the enyne **1**, corresponding to **F** in our general approach (Figure 2). The 4(*R*)-hydroxylated butenolide segment **2**, corresponding to **G**, was also prepared and utilized in a synthesis of asimicin (Figure 3). These two intermediates represent the essential structural features assigned to 30(*S*)-hydroxybullatacin (Figure 3). Accordingly a total synthesis of this acetogenin would only require coupling of the two segments followed by hydrogenation and deprotection. In fact, the union of enyne **1** with the butenolide terminus **2** proceeded efficiently under standard Sonogashira conditions to afford the dienyne **3** in 69% yield (Scheme 1). As in our previous applications,[6] selective hydrogenation of the dienyne function was achieved with diimide to afford the octahydro product **4**. Hydrolysis of the MOM ethers was effected with Me_2S and BF_3 etherate. The ^1H and ^{13}C NMR spectra of the tetraol product **5** were in complete accord with the reported spectra. As an additional confirmation of structure and stereochemistry, the tetra (*S*)-MTPA ester **6** was prepared.[11] The ^1H NMR spectrum of this derivative closely matched the reported spectrum of the 30(*S*) isomer. The foregoing synthesis therefore confirms the assigned structure and stereochemistry of the natural material.

In 1991, Hisham et. al reported studies on the isolation and structure assignment of two C5 hydroxylated bistetrahydrofuran acetogenins, narumicin I and narumicin II (Figure 3).[12] Though inseparable, the two were postulated as threo, trans, threo, trans, threo and threo, trans, threo, trans, erythro core stereoisomers on the basis of differ-

(11) Dale, J. A.; Mosher, H. S. *J. Am. Chem. Soc.* **1973**, *95*, 512.
(12) Hisham, A.; Pieters, L. A. C.; Claeys, M.; Van Den Heuvel, H.; Esmons, E.; Domisse, R.; Vlietinck, A. J. *Phytochemistry* **1991**, *30*, 2373.

ences in the ^{1}H and ^{13}C NMR spectra in comparison to related known acetogenins such as asimicin and bullanin. Subsequently Raynaud and co-workers isolated the same mixture from a different plant source and were able to separate the two isomeric narumicins by preparative HPLC.[13] They confirmed the assigned core stereochemistry, but the relative stereochemistry at C5 and C36 remained undefined along with the absolute stereochemistry.

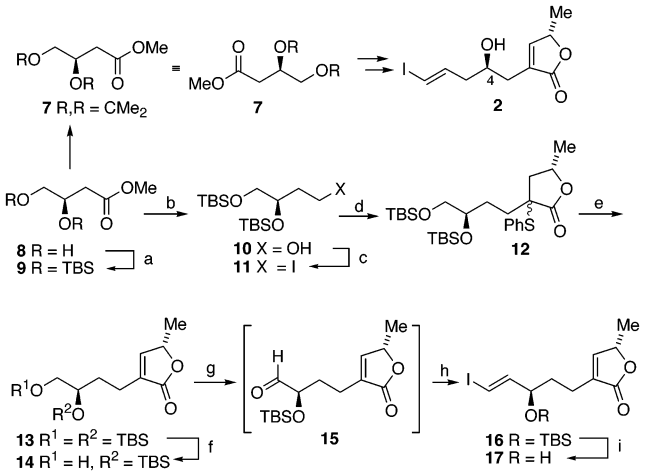
A third C5 hydroxylated bistetrahydrofuran acetogenin, uvarigrandin A, was described in 1997 by Pan and Yu.[14] Through application of Mosher MTPA ^{1}H NMR analysis, these investigators were able to assign the relative and absolute stereochemistry as 5(*S*), 24(*S*) threo, trans, threo, trans, threo (Figure 3).

To date C5 hydroxylated acetogenins have received scant attention. No synthesis has been reported and no studies on the cytotoxicity of these bistetrahydrofuran compounds have appeared. For these reasons we decided to extend our four-component strategy to uvarigrandin A and its C5(*R*) epimer. This latter substance could conceivably be identical to narumicin I. We were also interested in evaluating the activity of these compounds against human tumor cells. The antitumor activity of C5 hydroxylated acetogenins has not previously been reported.

As part of our earlier studies we prepared the threo, trans, threo, trans, threo core unit **18**. This was coupled to the C4 hydroxylated butenolide segment **2** to yield a precursor of asimicin (Figure 3).[9] An application of this strategy to the aforementioned C5 hydroxylated isomers would require the previously unknown C5 hydroxylated butenolide segments corresponding to **17** and the C5 diastereoisomer. These were prepared from the two enantiomers of ester diol **8**, which are easily obtained through selective reduction of (*R*)- or (*S*)-dimethyl malate (Scheme 2).[15] The use of these starting materials was particularly appropriate as we had previously employed acetonide derivative **7** of diol **8** in our synthesis of the butenolide segment **2** of asimicin. For the present application the bis-TBS ether **9** was reduced to the alcohol **10** and converted to iodide **11**, which reacted with the enolate of "White's lactone" to afford lactone **12**.[16] Oxidation to the sulfoxide derivative and thermal elimination led to butenolide **13**, which was selectively desilylated to the primary alcohol **14**. Takai olefination[17] of aldehyde **15** afforded the vinyl iodide **16**, which was desilylated to the C5 hydroxy segment **17**.

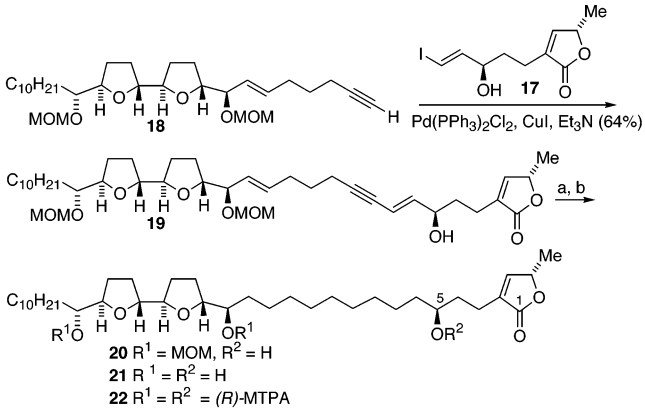
Coupling of the bistetrahydrofuran segment **18**[9] and the hydroxy butenolide **17** by the Sonogashira protocol proceeded uneventfully to afford the dienyne **19**. Selective reduction with diimide, as previously described, afforded the bis-MOM-protected acetogenin **20**. Hydrolysis of the MOM ethers was effected with aqueous HCl in methanolic THF to complete the synthesis. The ^{1}H NMR spectrum of our synthetic triol **21** was in close agreement

SCHEME 2[a]



[a] (a) TBSCl, DMF, Im (93%); (b) DIBAL-H, hexanes, −78 °C (85%); (c) I_2, PPh_3, Im, Et_2O−MeCN (90%); (d) White's lactone, LDA, then iodide **11**, THF−HMPA (79%); (e) *m*-CPBA, then toluene, reflux (84%); (f) HF·pyr, THF, 0 °C (75%); (g) Dess−Martin periodinane, CH_2Cl_2; (h) $CrCl_2$, CHI_3,THF−dioxane (40%, 2-steps); (i) HF·pyr, THF (92%).

SCHEME 3[a]



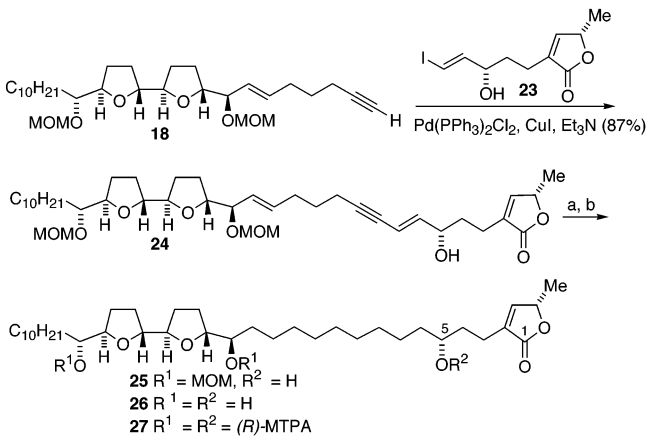
[a] (a) $TsNHNH_2$, NaOAc, DME (94%); (b) HCl, THF−MeOH (86%).

with the reported spectrum of uvarigrandin A. Of equal importance, the ^{1}H NMR spectrum of the tri-(*R*) Mosher ester derivative **22** compared favorably with the reported spectrum. The most notable comparison features of this spectrum were diagnostic signals for hydrogens at C3, C35, C36, and C37 (see Supporting Information).

The C5 epimer, 5(*R*)-uvarigrandin A (**26**), of uvarigrandin A was prepared by a parallel sequence starting from the bistetrahydrofuran core unit **18** and the butenolide segment **23** (Scheme 4). The latter compound was synthesized as outlined in Scheme 2 by employing the enantiomer of diol **8**. As expected the ^{1}H NMR spectrum of triol **26** and the (*R*)-Mosher triester derivative **27** were clearly different from those of uvarigrandin A. As noted above, Raynaud and co-workers suggested that narumicin I is a C5 hydroxylated C_{37} threo, trans, threo, trans, threo bistetrahydrofuran acetogenin of unknown configuration at C5. Our synthesis confirms the identity of the 5(*S*) isomer as uvarigrandin A. It can therefore be concluded than narumicin I must be the 5(*R*) isomer. We

(13) Raynaud, S.; Fourneau, C.; Hocquemiller, R.; Sévenet, T.; Hadi, H. A.; Cavé, A. *Phytochemistry* **1997**, *46*, 321.
(14) Pan, X. P.; Yu, D. Q. *Acta Pharm. Sin.* **1997**, *32*, 286.
(15) Saito, S.; Hasegawa, T.; Inaba, M.; Nishida, R.; Fujii, T.; Nomizu, S.; Moriwake, T. *Chem. Lett.* **1984**, 1389.
(16) White, J. D.; Somers, T. C.; Reddy, G. N. *J. Org. Chem.* **1992**, *57*, 4991.
(17) Takai, K.; Nitta, K.; Utimoto, K. *J. Am. Chem. Soc.* **1986**, *108*, 7408.

SCHEME 4[a]



[a] (a) $TsNHNH_2$, NaOAc, DME; (b) HCl, THF−MeOH (57%, 2 steps).

TABLE 1. Cytotoxicity of Annonaceous Acetogenins toward H-116 Colon Cancer Cells

compound	IC_{50} (g/mL)	IC_{90} (g/mL)
(30*S*)-hydroxybullatacin[a]	2×10^{-4}	2×10^{-1}
uvarigrandin A[a]	2×10^{-4}	1.5×10^{-2}
(5*R*)-uvarigrandin A[a]	2.5×10^{-4}	3×10^{-1}
5-fluorouracil[b]	1.5×10^{-1}	1.5

[a] 1 g/mL ≈ 1.5 M. [b] 1 g/mL ≈ 7 M.

were unable to obtain spectra of narumicin I or the MTPA derivative for comparison with our synthetic **26**. While the tabulated ^{13}C NMR data of the two are quite similar, slight chemical shift differences at 14.0 vs 14.1, 22.6 vs 22.7, 29.3 vs 29.5, 31.9 vs 31.8, 37.5 vs 37.4, 70.8 vs 70.7, 81.8, vs 81.7, 133.9 vs 134.0, 149.5 vs 149.4, and 176.7 vs 174.1 prevents an unequivocal opinion regarding their identity. An additional 13 peaks showed exact correspondence between the two samples (less than 37 peaks are observed owing to overlap of two or more signals; see Supporting Information for a tabulation). Lacking copies of the actual ^1H and ^{13}C spectra of narumicin I for peak height and pattern comparison, we are unable to render a valid opinion regarding its identity with our 5(*R*)-uvarigrandin A (**26**).

Samples of the three synthesized bistetrahydrofuran acetogenins were evaluated for cytotoxicity against H-116 human colon cancer cells (Table 1). 5-Fluorouracil, a current colon cancer drug was also tested against these tumor cells for comparison.[18] The IC_{50} and IC_{90} values for the three acetogenins were comparable to those previously found for asimicin and asimin and were considerably lower than those of 5-fluorouracil.

The present investigations extend the scope of our modular four-component synthesis of Annonaceous acetogenins to C4,C30-dihydroxylated and C5-hydroxylated bistetrahydrofurans. As illustrated, the approach makes possible the construction of a variety of stereo and "remote" hydroxyl isomers in only a few steps through use of a few common, well-defined segments. Although not specifically addressed in the present work, combinations of existing or easily prepared segments can be made that will lead to acetogenin structures with no natural counterparts for systematic structure−activity correlations. Applications along these lines will be reported in due course.

(18) Blumberg, D.; Ramananthan, R. K. *J. Clin. Gastroenterol.* **2002**, *34*, 15.

Experimental Section

Methyl (*R*)-3,4-Bis(*tert*-butyldimethylsilyloxy)butanoate (9). A solution of diol **8** (4.11 g, 30.6 mmol), TBSCl (13.8 g, 91.5 mmol), and imidazole (12.5 g, 184 mmol) in DMF (60 mL) was stirred for 15 h and then diluted with ether. The organic layer was then washed with saturated aqueous $NaHCO_3$, water, and brine, dried over Na_2SO_4, filtered, concentrated under reduced pressure, and chromatographed (ether−petroleum ether 1:19) to afford bis-silyl ether **9** (10.4 g, 93%). $[\alpha]_D$ 27.3 (*c* 0.84, $CHCl_3$); IR (film) 1747 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 4.15 (1H, m), 3.67 (3H, s), 3.60 (1H, ddd, J = 9.9, 5.1, 1.2 Hz), 3.44−3.37 (1H, m), 2.65 (1H, ddd, J = 14.7, 4.5, 1.5 Hz), 2.37 (1H, ddd, J = 14.8, 8.4, 1.2 Hz), 0.92−0.85 (18H, m), 0.08−0.05 (12H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.3, 70.3, 66.9, 51.4, 40.0, 25.9, 25.7, 18.3, 18.0, −4.5, −5.1, −5.4, −5.4. Anal. Calcd for $C_{17}H_{38}O_4Si_2$: C, 56.30; H, 10.56. Found: C, 56.58; H, 10.64.

(*R*)-3,4-Bis(*tert*-butyldimethylsilyloxy)butan-1-ol (10). To a stirred solution of ester **9** (10.4 g, 28.7 mmol) in 68 mL of hexanes, cooled to −78 °C, was added DIBAL-H (72 mL, 1 M solution in hexanes) over a 40-min period by means of a syringe pump. Stirring was continued for 30 min, and then the reaction mixture was poured into 290 mL of saturated aqueous Rochelle's salt solution and vigorously stirred at room temperature overnight. The two layers were separated. The aqueous layer was extracted with ether, and the combined organic extracts were washed with brine, dried over Na_2SO_4, filtered, concentrated under reduced pressure, and chromatographed (ether−petroleum ether 1:19, 1:9 then 1:5) to afford alcohol **10** (8.14 g, 85%). $[\alpha]_D$ 16.8 (*c* 0.88, $CHCl_3$); IR (film) 3381 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 3.90 (1H, m), 3.83−3.69 (2H, m), 3.62 (1H, ddd, J = 9.9, 4.8, 1.5 Hz), 3.52 (1H, ddd, J = 9.8, 7.5, 1.2 Hz), 2.70 (1H, t, J = 5.7 Hz), 1.96−1.83 (1H, m), 1.82−1.69 (1H, m), 0.90 (18H, m), 0.12−0.05 (12H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 72.2, 66.9, 59.7, 36.8, 25.9, 25.8, 18.3, 18.0, −4.5, −5.0, −5.5.

(*R*)-1,2-Bis(*tert*-butyldimethylsilyloxy)-4-iodobutane (11). To a solution of alcohol **10** (3.63 g, 10.8 mmol) in 56 mL of a 3:1 mixture of ether−CH_3CN, cooled to 0 °C, was successively added PPh_3 (3.13 g, 11.9 mmol), imidazole (809 mg, 11.9 mmol), and iodine (3.01 g, 11.9 mmol) by portions. The reaction mixture was stirred for 1 h 15 min, quenched by addition of 50 mL of saturated aqueous $NaHCO_3$, and extracted with ether. The combined organic extracts were washed with 10% $Na_2S_2O_3$ and water, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude product was triturated with hexanes and filtered to remove $Ph_3P(O)$. After removal of the solvent under reduced pressure, the resulting product was purified by column chromatography with a gradient of hexanes to 97:3 hexanes−Et_2O to afford iodide **11** (4.30 g, 90%). $[\alpha]_D$ 30.8 (*c* 0.77, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 3.73 (1H, m), 3.58 (1H, ddd, J = 9.9, 5.1, 1.2 Hz), 3.42 (1H, ddd, J = 9.9, 6.6, 1.2 Hz), 3.35−3.17 (2H, m), 2.23−2.08 (1H, m), 1.94 (1H, m), 0.90 (18H, m), 0.12 (3H, s), 0.09 (3H, s), 0.06 (6H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 72.9, 66.8, 38.7, 25.9, 25.9, 18.3, 18.1, 3.0, −4.2, −4.6, −5.3, −5.4. Anal. Calcd for $C_{16}H_{37}IO_2Si_2$: C, 43.23; H, 8.39. Found: C, 43.61; H, 8.45.

Lactone 12. To a stirred solution of diisopropylamine (1.2 mL, 8.56 mmol) in anhydrous THF (14 mL), cooled to −78°C, was added dropwise BuLi (3.65 mL, 8.03 mmol). After 20 min, a solution of "White's lactone" (1.67 g, 8.03 mmol) in 8.6 mL of THF was added dropwise. The dry ice−acetone bath was replaced by an ice bath. After 15 min, a solution of iodide **11** (4.27 g, 9.62 mmol) in 8.6 mL of a 5:1 mixture of THF−HMPA was added. The reaction mixture was slowly allowed to warm

to room temperature, stirred for 16 h, diluted with ether, washed with saturated aqueous NH_4Cl, 10% $Na_2S_2O_3$, water, and brine, dried over Na_2SO_4, filtered, concentrated under reduced pressure, and chromatographed (ether−petroleum ether 1:19 then 1:9) to afford lactone **12** (3.35 g, 79%) as a 95:5 mixture of diastereoisomers. Major isomer: IR (film) 1771 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.60−7.51 (2H, m), 7.43−7.29 (3H, m), 4.56−4.42 (1H, m), 3.62 (1H, m), 3.56−3.48 (1H, m), 3.40−3.31 (1H, m), 2.49 (1H, ddd, J = 23.2, 12.5, 3.0 Hz), 2.03−1.91 (2H, m), 1.91−1.84 (1H, m), 1.84−1.72 (1H, m), 1.53−1.41 (1H, m), 1.23 (3H, dd, J = 10.5, 3.5 Hz), 0.93−0.82 (18H, m), 0.07−0.00 (12H, m). Anal. Calcd for $C_{27}H_{48}O_4SSi_2$: C, 61.78; H, 9.22. Found: C, 61.70; H, 9.32.

Butenolide 13. To sulfide **12** (3.34 g, 6.36 mmol) in 32 mL of anhydrous CH_2Cl_2 at 0 °C was added portionwise *m*-CPBA (1.10 g, 6.37 mmol). After 50 min, an additional amount of *m*-CPBA (198 mg, 1.15 mmol) was added. Stirring was continued for 15 min, and then the reaction mixture was quenched by addition of 56 mL of a 1:1 mixture of saturated aqueous $NaHCO_3$ and saturated aqueous $Na_2S_2O_3$, slowly allowed to warm to room temperature, stirred for 1 h 45 min, and extracted with CH_2Cl_2. The combined organic extracts were washed with brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give 3.50 g of crude sulfoxide as a thick colorless foam. The crude sulfoxide was then refluxed in 80 mL of toluene for 1 h. After removal of the solvent under reduced pressure, the crude product was chromatographed (ether−petroleum ether 1:19, 1:9 then 1:5) to afford butenolide **13** (2.23 g, 84%) contaminated with a small amount of PhSOH. $[\alpha]_D$ 30.5 (*c* 0.72, $CHCl_3$); IR (film) 1766, 1656 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 6.99 (1H, q, J = 1.5 Hz), 4.99 (1H, m), 3.71 (1H, m), 3.56 (1H, dd, J = 10.0, 5.5 Hz), 3.42 (1H, dd, J = 10.2, 6.5 Hz), 2.46−2.23 (2H, m), 1.89−1.81 (1H, m), 1.68−1.60 (1H, m), 1.41 (3H, d, J = 6.5 Hz), 0.89 (9H, s), 0.89 (9H, s), 0.06 (6H, s), 0.05 (3H, s), 0.05 (3H, s); ^{13}C NMR (125 MHz, $CDCl_3$) δ 173.5, 148.6, 134.2, 77.3, 72.2, 66.9, 31.7, 25.8, 25.7, 25.6, 20.7, 19.0, 18.2, 17.9, −4.4, −4.9, −5.5, −5.5.

Alcohol 14. To a solution of bis-silyl ether **13** (157 mg, 0.379 mmol) in 3.8 mL of anhydrous THF at 0 °C in a Nalgene reaction vessel was added 40 μL of HF−pyridine solution. The reaction mixture was stirred for 7 h, quenched by addition of 4 mL of saturated aqueous $NaHCO_3$, diluted with EtOAc, washed with water, saturated aqueous $CuSO_4$, and brine, dried over Na_2SO_4, filtered, concentrated under reduced pressure, and chromatographed (ether−petroleum ether 1:9 then 3:1) to afford 71 mg of alcohol **14** (62% yield, 75% based on recovered starting material). $[\alpha]_D$ 16.8 (*c* 0.88, $CHCl_3$); IR (film) 3457, 1748, 1650 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.01 (1H, q, J = 1.5 Hz), 5.00 (1H, m), 3.79 (1H, m), 3.63−3.56 (1H, m), 3.54−3.46 (1H, m), 2.42−2.20 (2H, m), 1.90 (1H, bs), 1.82−1.73 (2H, m), 1.40 (3H, d, J = 6.6 Hz), 0.90 (9H, s), 0.09 (6H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.6, 149.0, 133.8, 77.5, 72.0, 65.9, 31.4, 25.7, 21.1, 19.1, 18.0, −4.6, −4.6. Anal. Calcd for $C_{15}H_{28}O_4Si$: C, 59.96; H, 9.39. Found: C, 59.81; H, 9.53.

Aldehyde 15. To a solution of alcohol **14** (376 mg, 1.25 mmol) in 20 mL of anhydrous CH_2Cl_2 at 0 °C was added Dess−Martin periodinane (586 mg, 1.38 mmol), and the reaction mixture was allowed to warm to room temperature. After stirring for 3, 3.5, and 4 h, 300, 618, and 308 mg of Dess−Martin periodinane were added, respectively, until the reaction was judged complete by TLC. The reaction mixture was then quenched by addition of saturated aqueous $Na_2S_2O_3$, stirred until a clear solution was obtained, and extracted with CH_2Cl_2. The combined organic extracts were washed with brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give 412 mg of crude aldehyde **15,** which was used without further purification. IR (film) 3086, 2717, 1759, 1653 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 9.63 (1H, d, J = 1.5 Hz), 7.03 (1H, q, J = 1.5 Hz), 5.01 (1H, qd, J = 7.8, 1.5 Hz), 4.04 (1H, m), 2.39 (2H, td, J = 8.4, 1.2 Hz), 2.03−1.83 (2H, m), 1.41 (3H, d, J = 6.9 Hz), 0.98−0.85 (9H, m), 0.14−0.04 (6H, m).

Vinyl Iodide 16. To a suspension of $CrCl_2$ (1.09 g, 8.87 mmol) in 4 mL of anhydrous THF was added a solution of the preceding aldehyde **15** and recrystallized iodoform (986 mg, 2.50 mmol) in 22 mL of dioxane, over a 1-h period by means of a syringe pump. The reaction mixture was stirred for 16 h and then quenched by successive addition of 10 mL of Et_2O and 20 mL of water. The two layers were separated. The aqueous layer was saturated with solid NaCl and extracted with Et_2O. The combined organic extracts were washed with brine, dried over Na_2SO_4, filtered, concentrated under reduced pressure, and chromatographed (ether−petroleum ether 1:19 then 1:3) to afford 211 mg of vinyl iodide **16** (40% for the last two steps). $[\alpha]_D$ 41.8 (*c* 0.95, $CHCl_3$); IR (film) 1754 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 6.98 (1H, d, J = 1.8 Hz), 6.51 (1H, ddd, J = 14.4, 6.0, 2.1 Hz), 6.26 (1H, ddd, J = 14.5, 2.1, 1.2 Hz), 5.05−4.93 (1H, m), 4.15 (1H, m), 2.41−2.20 (2H, m), 1.79−1.68 (2H, m), 1.40 (3H, dd, J = 6.6, 1.8 Hz), 0.88 (9H, s), 0.07−0.01 (6H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.5, 149.0, 148.3, 133.8, 77.4, 76.5, 74.4, 34.9, 25.8, 20.7, 19.1, 18.1, −4.6, −4.9.

Alcohol 17. To a solution of silyl ether **16** (94 mg, 0.224 mmol) in 8.7 mL of anhydrous THF in a Nalgene reaction vessel was added 0.81 mL of HF−pyridine solution. The reaction mixture was stirred for 19 h, carefully poured into 80 mL of saturated aqueous $NaHCO_3$, and extracted with EtOAc. The combined organic extracts were washed with saturated aqueous $CuSO_4$, water, and brine, dried over Na_2SO_4, filtered, concentrated under reduced pressure, and chromatographed (ether−petroleum ether 3:1) to afford alcohol **17** (63 mg, 92%). $[\alpha]_D$ 31.6 (c 0.64, $CHCl_3$); IR (film) 3418, 1740 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.06 (1H, d, J = 1.2 Hz), 6.57 (1H, dd, J = 14.5, 6.0 Hz), 6.39 (1H, dd, J = 14.7, 1.2 Hz), 5.07−4.97 (1H, m), 4.13 (1H, m), 2.62 (1H, d, J = 4.2 Hz), 2.49−2.29 (2H, m), 1.78 (2H, m), 1.41 (3H, d, J = 6.9 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.0, 150.0, 147.8, 133.3, 77.7, 73.4, 34.2, 20.9, 19.0.

Enyne 24. To a solution of vinyl iodide **23** (41 mg, 0.135 mmol), $Pd(PPh_3)_2Cl_2$ (9.9 mg, 0.014 mmol), and CuI (7.9 mg, 0.041 mmol) in 2.6 mL of Et_3N, stirred at room temperature for 30 min, was added dropwise a solution of alkyne **18** (78 mg, 0.149 mmol) in 2.0 mL of Et_3N. After 3.5 h, the reaction mixture was concentrated under reduced pressure, and the resultant brown residue was purified by column chromatography (silica gel treated with 2.5% of Et_3N, ether−petroleum ether 1:5, 1:2, 4:1 then ether) to afford enyne **24** (83 mg, 87%). $[\alpha]_D$ −1.2 (*c* 0.80, $CHCl_3$); IR (film) 3456, 1758 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.03 (1H, d, J = 1.5 Hz), 6.03 (1H, dd, J = 16.0, 6.0 Hz), 5.73−5.64 (2H, m), 5.38 (1H, dd, J = 16.0, 8.0 Hz), 5.01 (1H, m), 4.81 (1H, d, J = 6.5 Hz), 4.69 (1H, d, J = 6.0 Hz), 4.66 (1H, d, J = 6.5 Hz), 4.58 (1H, d, J = 6.5 Hz), 4.16 (1H, m), 4.02 (1H, m), 4.01−3.96 (1H, m), 3.93 (3H, m), 3.46 (1H, m), 3.38 (3H, s), 3.37 (3H, s), 2.46−2.33 (2H, m), 2.29 (2H, td, J = 7.0, 2.0 Hz), 2.16 (2H, q, J = 7.0 Hz), 2.11 (1H, d, J = 4.0 Hz), 1.92 (4H, m), 1.84−1.57 (9H, m), 1.53−1.38 (6H, m), 1.40 (3H, d, J = 6.5 Hz), 1.38−1.21 (16H, m), 0.87 (3H, t, J = 7.0 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.8, 149.5, 143.4, 134.3, 133.5, 127.5, 110.8, 96.6, 93.6, 90.9, 81.6, 81.4, 81.3, 81.1, 79.5, 78.5, 77.5, 71.1, 55.6, 55.1, 34.6, 31.8, 31.3, 31.1, 29.7, 29.5, 29.2, 28.2, 28.1, 28.0, 27.0, 25.5, 22.6, 21.1, 19.0, 18.7, 14.0. Anal. Calcd for $C_{41}H_{66}O_9$: C, 70.05; H, 9.46. Found: C, 69.96; H, 9.53.

5*(R)*-Uvarigrandin A (26). To a refluxing solution of enyne **24** (75 mg, 0.107 mmol) and *p*-toluenesulfonylhydrazide (1.34 g, 7.19 mmol) in 16 mL of DME was added a solution of sodium acetate (729 mg, 8.87 mmol) in 20 mL of water over a 4-h period via a syringe pump. After cooling to room temperature, the reaction mixture was poured into water and extracted with EtOAc. The combined organic extracts were washed with water and brine, dried over Na_2SO_4, filtered, concentrated under reduced pressure, and purified by column chromatography (ether−petroleum ether 1:1, 4:1 then ether) to afford 59 mg of 5(*R*)-uvarigrandin A MOM ether **(25)** contaminated by some residual tosyl hydrazide.

The preceding bis-MOM ether **25** was stirred at room temperature for 12 h in 10.5 mL of a mixture of 6 M HCl−THF−MeOH (1:2:2), poured into 60 mL of water, and extracted with EtOAc. The combined organic extracts were washed with brine, dried over Na_2SO_4, filtered, concentrated under reduced pressure, and purified by column chromatography (EtOAc−petroleum ether 70:30 with 1% then 2% MeOH) to give 28 mg of 5(*R*)-uvarigrandin A **(26)** (57% yield for the last two steps). $[\alpha]_D$ 11.5 (*c* 0.54, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.03 (1H, m), 5.00 (1H, m), 3.86 (2H, m), 3.82 (2H, m), 3.58 (1H, m), 3.38 (2H, m), 2.55 (2H, d, J = 4.0 Hz), 2.49−2.33 (2H, m), 2.13 (1H, m), 2.02−1.92 (4H, m), 1.88 (1H, bs), 1.75−1.67 (6H, m), 1.54−1.20 (40H, m), 1.40 (3H, d, J = 7.0 Hz), 0.87 (3H, t, J = 7.0 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 174.1, 149.4, 134.0, 83.1, 81.7, 77.5, 74.0, 70.7, 37.4, 35.3, 33.4, 31.8, 29.7, 29.6, 29.5, 29.3, 28.9, 28.3, 25.6, 22.6, 21.4, 19.1, 14.0.

Tri-(*R*)-Mosher Ester of 5*(R)*-Uvarigrandin A 27. The reported procedure was employed.[18] ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.63 (3H, m), 7.57−7.53 (2H, m), 7.43−7.39 (3H, m), 7.39−7.35 (5H, m), 7.03 (1H, d, J = 1.5 Hz), 5.10 (1H, m), 5.06−4.97 (3H, m), 4.00 (2H, q, J = 7.0 Hz), 3.93 (2H, m), 3.61 (6H, s), 3.55 (3H, s), 2.38−2.25 (2H, m), 2.01−1.98 (6H, m), 1.98−1.79 (2H, m), 1.65−1.53 (11H, m), 1.48 (4H, m), 1.41 (3H, d, J = 7.0 Hz), 1.33−1.09 (30H, m), 0.89 (3H, t, J = 7.0 Hz).

Acknowledgment. Funding was provided by research grant R01GM CA56769 from the National Institutes of General Medical Sciences.

Supporting Information Available: Additional experimental procedures, ^{1}H NMR spectra of key intermediates, and selected ^{13}C NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

JO0266137