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The First Total Synthesis of Annonacin, the Most Typical Monotetrahydrofuran Annonaceous Acetogenins

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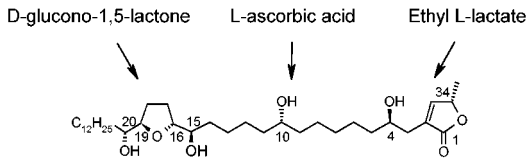
ABSTRACT



The first total synthesis of annonacin (1) was achieved by a highly convergent synthetic strategy. All the stereogenic centers were derived from three natural hydroxy acids respectively, except that those at C19 and C20 were produced from a Sharpless AD reaction.

Annonacin (**1**), the first monotetrahydrofuran acetogenin discovered, was isolated by Cassady and co-workers from the stembark of *Annona densicoma* in 1987[1] and subsequently was also found in more than 10 other species of Annonaceae.[2] This compound demonstrated 9ASK (astrocytoma reversal) activity and high cytotoxicity against KB cells (human nasopharyngeal carcinoma) and P388 cells (mouse leukemia).[1,2a] Although to some extent the structure of annonacin seems to be simple, the construction of the seven chiral centers, especially the two isolated at C4 and C10, still presents a challenge. To date there is no report on the synthesis of annonacin, although the synthesis[3] of a diastereomer of annonacin A, the C-20 epimer of annonacin, has recently been achieved. In this Letter, we describe the first total synthesis of annonacin **1**.

Our retrosythetic analysis of **1** is illustrated in Figure 1. Thus, the key precursor **2** was dissected into two major building blocks, the THF unit **3** and the epoxide **4**. The THF fragment **3** could be prepared from D-glucono-δ-lactone via

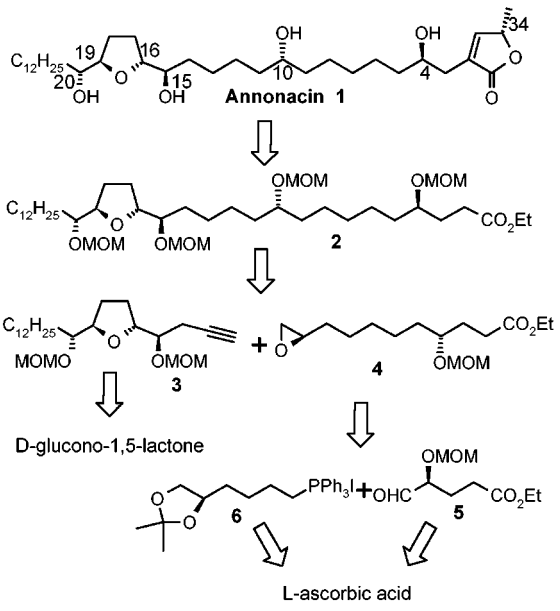


Figure 1.

(1) McCloud, D. J.; Smith, D. L.; Chang, C.-J.; Cassady, J. M. *Experientia* **1987**, *59*, 947.

(2) For other isolations, see: (a) Alkofahi, A.; Rupprecht, J. K.; Smith, D. L.; Chang, C.-J.; Maclaughlin, J. L. *Experientia* **1988**, *44*, 83. (b) Chen, W.-S.; Yao, Z.-J.; Wu, Y.-L. *Youji Huaxue* **1995**, *15*, 85. (c) Jossang, A.; Dubaele, A.; Cave, A.; Bartoli, M.-H.; Beriel, H. *Tetrahedron Lett.* **1990**, *31*, 1861. (d) Ye, Q.; Zeng, L.; Zhang, Y.; Zhao, G.-X.; Maclaughlin, J. L.; Woo, M. H. and Evert, D. R. *J. Nat. Prod.* **1995**, *58*, 1398. (e) Zhang, L.-L.; Yang, R.-Z.,; Wu, S.-J. *Acta Botanica Sinica (Zhiwu Xuebao)* **1993**, *35*, 390.

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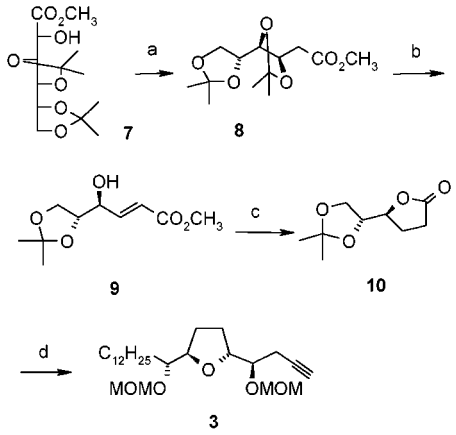
Scheme 1[a]



[a] Reagents and conditions: (a) PPh_3, I_2, imidazole, toluene, reflux, 69%; (b) LiHMDS, THF, −78 °C, 95%; (c) (i) H_2/Pd−C, MeOH; (ii) acetone, p-TsOH (cat.) 86%; (d) ref 6.

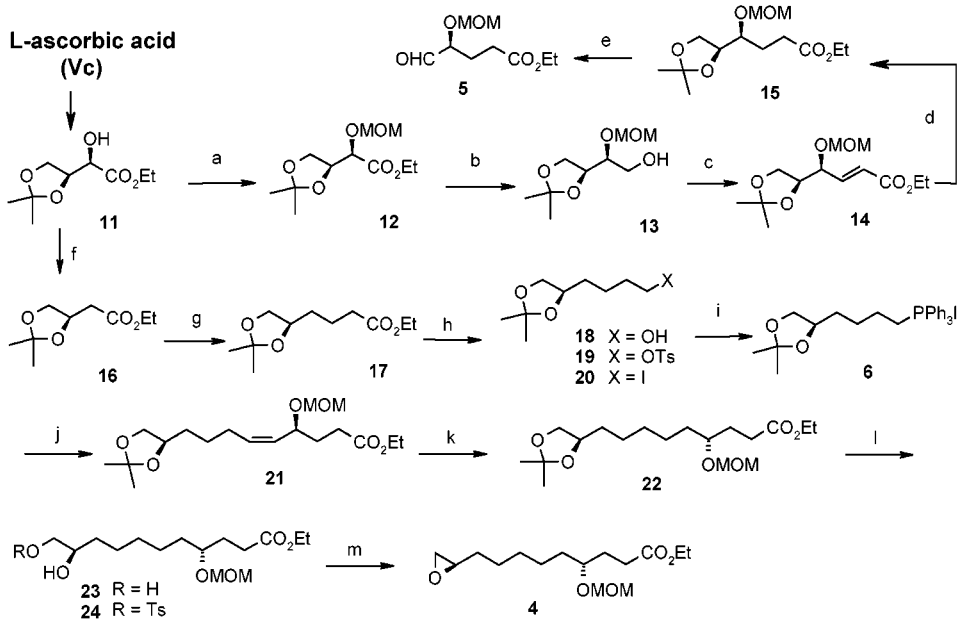
a multiple-step sequence, while epoxide **4** could be synthesized from L-ascorbic acid via phosphonium salt **6** and aldehyde **5**.

The THF fragment **3** was prepared as shown in Scheme 1. The D-glucono-δ-lactone-derived α-hydroxyl ester[4] **7** was deoxygenated using the PPh_3/I_2/imidazole system[5] to give 2-deoxy ester **8**, which was treated with LiHMDS to produce α,β-unsaturated ester **9**. Catalytic hydrogenation followed by an acid-catalyzed ring closure reaction gave lactone **10**. A subsequent multistep transformation with the Sharpless asymmetric dihydroxylation reaction as a key step to introduce the C19 and C20 chiral centers, reported by us earlier,[6] was adapted to furnish the THF acetylene **3**.

The synthesis of epoxide **4** is summarized in Scheme 2. The α-hydroxy ester[7] **11** obtained from L-ascorbic acid was protected as the MOM ether before the chain was elongated by two carbons to give ester **15** using a four-step sequence. The reduction of **12** with LAH gave alcohol **13**. Swern oxidation of **13** followed by a Wittig reaction with carbethoxymethylenetriphenyphosphorane led to α,β-unsaturated ester **14**. Subsequent hydrogenation afforded the corresponding saturated ester **15**, which was then treated with H_5IO_6[8] to give the chiral aldehyde **5**.

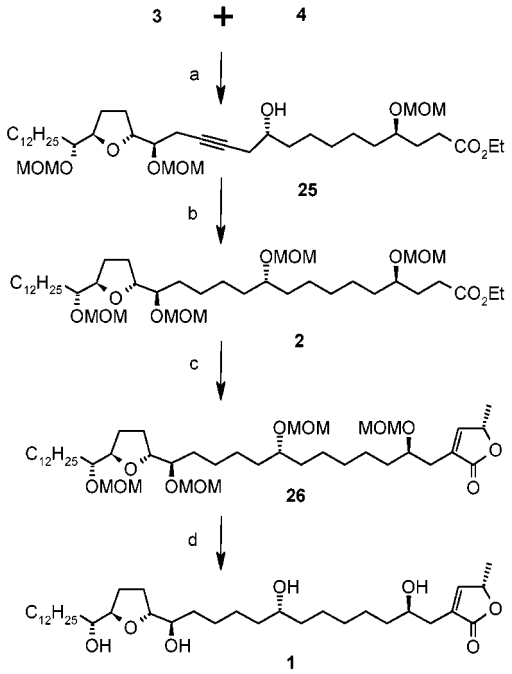
On the other hand, **11** was converted to 2-deoxy ester **16** according to a known procedure.[9] Reduction with LAH of **16** followed by Swern oxidation, a Wittig reaction, and hydrogenation gave ester **17** as mentioned above for the preparation of **15**. After reduction with LAH, the resultant alcohol **18** was converted to iodide **20** by tosylation, followed by substitution with iodide. The latter, upon reaction with PPh_3, afforded phosphonium salt **6**. Treatment of **6** with NaHMDS generated the corresponding ylide, which reacted with aldehyde **5** to give olefin **21**. Hydrogenation and cleavage of the isopropylidene group in **22** with aqueous HOAc led to 1,2-diol **23**, which was transformed selectively to primary tosylate **24** by Bu_2SnO-catalyzed tosylation.[10]

Scheme 2[a]



[a] Reagents and conditions: (a) MOMCl, $^i Pr_2NEt$, CH_2Cl_2, 0 °C → rt, 88%; (b) LAH, THF, 0 °C → rt, 96%; (c) (i) oxalyl chloride, DMSO, $^i Pr_2NEt$; (ii) $PPh_3{=}CHCO_2Et$, CH_2Cl_2, reflux, 81%; (d) H_2/Pd−C, EtOH, rt, 97%; (e) H_5IO_6, Et_2O, rt, 71%; (f) ref 9; (g) (i) LAH, THF, 0 °C → rt; (ii) oxalyl chloride, DMSO, Et_3N; (iii) $PPh_3{=}CHCO_2Et$, CH_2Cl_2, reflux, 73% for three steps; (iv) H_2/Pd−C, EtOH, rt, 95%; (h) (i) LAH, THF, 0 °C → rt, 95%; (ii) p-TsCl, Et_3N, CH_2Cl_2, 0 °C → rt, 94%; (iii) NaI, acetone, rt, 98%; (i) PPh_3, Na_2CO_3, CH_3CN, quantitative; (j) NaHMDS, THF, 0 → −78 °C, then **5**, 81%; (k) H_2/Pd−C, $NaHCO_3$, EtOH, rt, 97%; (l) (i) 60% aqueous HOAc, 97%; (ii) p-TsCl, Et_3N, Bu_2SnO (cat.), CH_2Cl_2, 81%; (m) DBU, CH_2Cl_2, rt, 97%.

Scheme 3[a]



[a] Reagent and conditions: (a) BuLi, THF, −78 °C, 1 h, then BF_3·Et_2O, 30 min, then **4,** 77%; (b) (i) PtO_2, EtOH, rt, 93%; (ii) MOMCl, $^iPr_2NEt$, CH_2Cl_2, 0 °C → rt, 95%; (c) (i) LDA, THF, −78 °C, then *O*-THP lactaldehyde; (ii) HOAc/THF/H_2O (4:2:1); (iii) $(CF_3CO)_2O$, Et_3N, 0 °C → rt, 41% for three steps; (d) BF_3·Et_2O, Me_2S, 0 °C → rt, 85%.

Then the momotosylate was treated with DBU to afford the epoxide **4** in excellent yield.

With the two major fragments **4** and **3** in hand, we proceeded to complete the carbon skeleton of **1** (Scheme 3). Thus, the lithiated derivative of THF alkyne **3** was reacted with epoxide **4** in the presence of BF_3·Et_2O to afford alkynol **25**. Catalytic hydrogenation of **25** with PtO_2 in ethanol gave the corresponding alcohol, which was then protected as the MOM ether **2**. It is noteworthy that hydrogenation of **25** over Pd/C led to ca. a 1:1 ratio of the desired alcohol and the 10-deoxygenated byproduct. Subsequent construction of the butenolide segment of **1** was furnished using the method developed by us.[11] Accordingly, the enolate derived from **2** was condensed with (*S*)-*O*-THP lactal prepared from (+)-ethyl lactate to give the aldol product, which was subjected to acidic cleavage of the THP group and dehydration with trifluoroacetic anhydride and triethylamine[12] to give the α,β-unsaturated lactone **26**. The final removal of all of the MOM protecting groups with boron trifloride etherate in the presence of dimethyl sulfide afforded annonacin **1**,[13] whose R_f value and spectroscopic data are identical to those reported for the natural product.

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(13) Physical data for synthetic annonacin: white solid; mp 69−71 °C; $[\alpha]_D = +21$ (*c* 0.51, $CHCl_3$) {lit.[2e] $[\alpha]_D = 20.78$ (*c* 5.05 $CHCl_3$)}; $[\alpha]_D = +19$ (*c* 0.40, CH_3OH) {lit.[2b] $[\alpha]_D = 11.4$ (*c* 0.04 CH_3OH)}; ^1H NMR (600 MHz $CDCl_3$) δ 7.18 (s, 1H), 5.06 (q, *J* = 6.6 Hz 1H), 3.85 (m, 1H), 3.81 (dt, *J* = 11.7, 6.6 Hz, 2H), 3.59 (m, 1H), 3.41 (dt, *J* = 11.7, 6.0 Hz, 2H), 2.52 (d, *J* = 14.7 Hz, 1H), 2.40 (dd, *J* = 14.7, 7.8 Hz, 1H), 2.04 (br. 4 OH), 1.99 (m, 2H), 1.68 (m, 2H), 1.60−1.20 (m, 40H), 1.43 (d, *J* = 7.2 Hz, 3H), 0.88 (t, 6.8 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 174.58, 151.80, 131.18, 82.67, 82.60, 77.95, 74.05, 73.95, 71.74, 69.90, 37.36, 37.27, 33.48, 33.37, 29.70−29.57 signal overlap, 29.47, 29.32, 28.72, 25.64, 25.58, 25.48, 22.66, 19.09, 14.08.