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Total Synthesis of a New Cytotoxic Acetogenin, Jimenezin, and the Revised Structure

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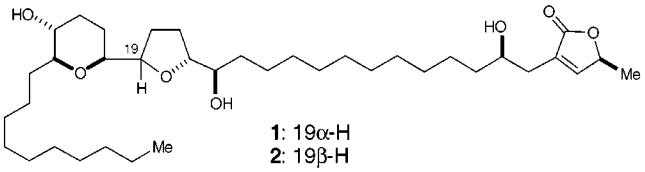
ABSTRACT



1: 19α-H
2: 19β-H

The first total synthesis of jimenezin was achieved by using carbohydrates as chiral building blocks, thus revising the proposed structure 1 to 2. The key steps in this synthesis include an efficient construction of the THP–THF fragments 3 and 16 through a stereoselective condensation between the pyranyl aldehyde 5 and the acetylene derivative 6, and a palladium-catalyzed coupling reaction of 3 or 16 with a terminal butenolide 4.

In 1998, Mata et al. isolated a new annonaceous acetogenin[1] from the seeds of *Rollinia mucosa* (Jacquin) Bail. (Annonaceae) and named it jimenezin.[2] The structure was elucidated by chemical and spectral means to be **1**, possessing a tetrahydropyran (THP) ring[3] along with an adjacent tetrahydrofuran (THF) ring. Jimenezin is structurally related to the antitumor acetogenin muconin,[4] differing remarkably in the stereorelationship of the THP and THF rings (erythro vs threo) and bearing a hydroxyl group on the THP ring. This natural product was quite active in the BST assay[5] (IC_{50} 5.7 × 10^{-3} μg/mL), and exhibited potent cytotoxic activity against six human solid tumor cell lines. As part of our continuing efforts toward synthesis of aniticancer acetogenins,[6] we describe here the first total synthesis of jimenezin that dictates revision of the formula to **2**.

Our synthetic strategy directed toward **1** was based on a convergent process which involves a Pd-catalyzed cross-coupling reaction of the THP−THF segment **3** and a vinyl iodide **4**,[6b] as illustrated in Scheme 1. The central core **3** can be further disconnected to a pyranyl aldehyde **5**[6a] and a terminal acetylene **6**. The latter might be readily prepared from L-arabinose, while segments **4** and **5** were already synthesized from L-rhamnose and D-galactose, respectively.[6] In addition, these synthetic processes would make feasible the preparation of epimer **2** (vide infra).

Our synthesis started with the preparation of acetylene derivative **6** (Scheme 2). Wittig reaction of **7**[7] and subsequent hydrogenation gave isopropylidene alcohol **8** in 84% yield.[8] After Dess−Martin oxidation,[9] the resulting aldehyde was

(1) For recent review on Annonaceous acetogenins, see: Zeng, L.; Ye, Q.; Oberlies, H. N.; Shi, G.; Gu, Z. M.; He, K.; McLaughlin, J. L. *Nat. Prod. Rep.* **1996**, *13*, 275. Allali, F. Q.; Liu, X.-X.; McLaughlin, J. L. *J. Nat. Prod.* **1999**, *62*, 504.

(2) Chavez, D.; Acevedo, L. A.; Mata, R. *J. Nat. Prod.* **1998**, *61*, 419.

(3) For other acetogenins as having a THP ring, see the following. (a) Mucocin: 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. (b) Pyranicin and pyragonicin: Alali, F. Q.; Rogers, L.; Zhang, Y.; McLaughlin, J. L. *Tetrahedron* **1998**, *54*, 5833.

(4) Shi, G.; Kozlowski, J. F.; Schwedler, J. T.; Wood, K. V.; MacDougal, J. M.; McLaughlin, J. L. *J. Org. Chem.* **1996**, *61*, 7988.

(5) McLaughlin, J. L. In *Methods in Plant Biochemistry*; Hostettmann, K., Ed.; Academic Press: London, 1991; Vol. 6, p 1. Meyer, B. N.; Ferrigni, N. R.; Putnam, J. E.; Jacobsen, L. B.; Nichola, D. E.; McLaughlin, J. L. *Planta Med.* **1982**, *45*, 31

(6) (a) Takahashi, S.; Nakata, T. *Tetrahedron Lett.* **1999**, *40*, 723. (b) Takahashi, S.; Nakata, T. *Tetrahedron Lett.* **1999**, *40*, 727.

(7) Thompson, D. K.; Hubert, C. N.; Wightman, R. H. *Tetrahedron* **1993**, *49*, 3827.

(8) All new compounds were fully chracterized by IR, NMR, high-resolution mass spectra, and/or combustion analyses.

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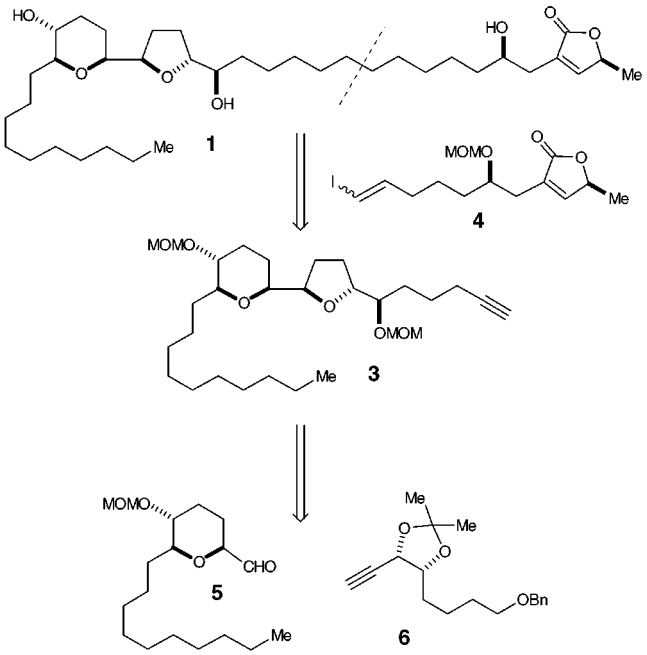
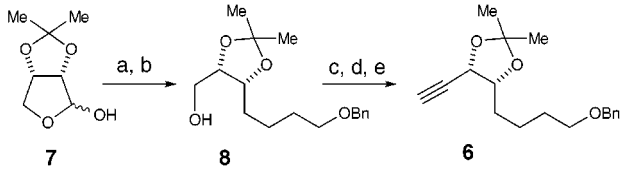
Scheme 1



converted into **6** via a dibromoolefin[10] in 88% overall yield from **8**.

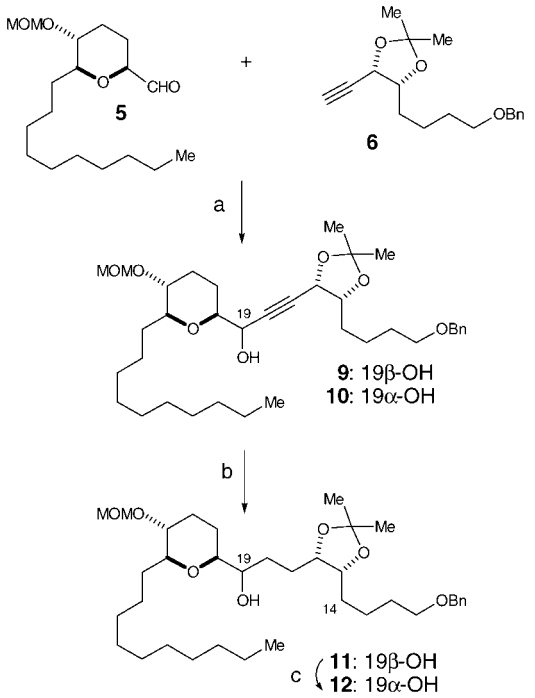
For the synthesis of **1**, we needed alcohol **11** with the *R* configuration at the C-19 position (jimenezin numbering) as a key intermediate (Scheme 3). An efficient diastereofacially selective addition of **6** to the carbonyl group of **5** under Cram mode would make it theoretically possible to obtain the alcohol **11**. After model experimentations using several acetylene compounds, we found that reaction of the corresponding lithium derivative with **5** gave predominantly the Cram-type product. On the basis of these results, we examined the coupling reaction between **5** and **6**. The best result was obtained by using THF−HMPA (6:1) as the solvent at −78 °C, giving a 92:8 mixture of the desired carbinol **9** and its diastereomer **10** in 72% yield.[11] These isomers could be separated by chromatography on silica gel. From a practical point of view, separation of the mixture after the following hydrogenation reaction was found to be more efficient. Hence, hydrogenation of the mixture using

Scheme 2[a]



[a] Reagents and conditions: (a) $Ph_3PBrC_3H_6OBn$, *n*-BuLi, THF, −78 °C to room temperature, 89%; (b) 10% Pd/C, H_2, EtOAc, room temperature, 94%; (c) (i) Dess−Martin periodinane, CH_2Cl_2, room temperature; (ii) Ph_3P, CBr_4, CH_2Cl_2, −78 °C, 97%; (e) EtMgBr, THF, 0 °C, 91%.

Scheme 3[a]



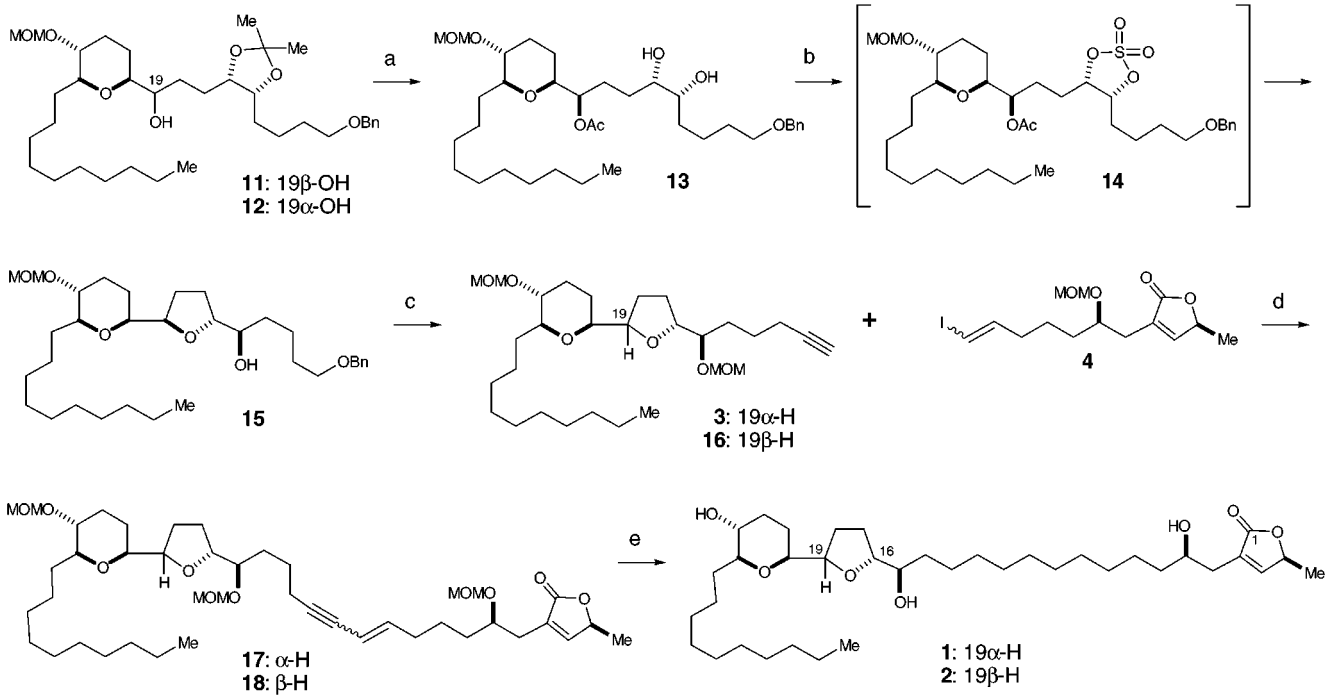
[a] Reagents and conditions: (a) *n*-BuLi, THF−HMPA, −78 °C, 72%; (b) 10% PtO_2, H_2, EtOAc, room temperature, 88%; (c) (i) Dess−Martin periodinane, CH_2Cl_2, room temperature; (ii) L-Selectride, THF, −78 °C, 97%.

PtO_2 gave the desired 19*β*-alcohol **11**[12] in 82% yield along with its 19-epimer **12** (6%) after chromatography on silica gel. On the other hand, Dess−Martin oxidation of the mixture (**11** and **12**), and subsequent reduction with L-Selectride in THF at −78 °C produced the 19α-alcohol **12** (94% de) in 97% overall yield.

The 19*β*-alcohol **11** was acetylated, and then hydrolysis under acidic conditions afforded a diol **13** (mp 77.5−78 °C) in 95% yield (Scheme 4). The THF ring formation as a key step proceeded nicely as follows. Compound **13** was treated with thionyl chloride and triethylamine, and then the resulting sulfite was oxidized with $NaIO_4$−$RuCl_3$,[13] giving a cyclic sulfate **14**. Upon treatment with a base,[14] **14** afforded the THF alcohol **15** in 83% overall yield from **13**. The bis-cyclic ether **15** was converted into the central core **3** in 61% overall yield via a four-step sequence: (1) protection of the hydroxy

(9) Dess, D. B.; Martin, J. C. *J. Org. Chem.* **1983**, *48*, 4156.
(10) Corey, E. J.; Fuchs, P. L. *Tetrahedron Lett.* **1972**, 3769.
(11) The stereochemistry was determined by the modified Mosher's method: (a) Ohtani, I.; Kusumi, T.; Kashman, Y.; Kakisawa, H. *J. Org. Chem.* **1991**, *56*, 1296. (b) Ohtani, I.; Kusumi, T.; Kashman, Y.; Kakisawa, H. *J. Am. Chem. Soc.* **1991**, *113*, 4092. See also, Dale, J. A.; Mosher, H. S. *J. Am. Chem. Soc.* **1973**, *95*, 512.
(12) Differences in the chemical shifts (Δ_{S-R} values in δ) between (*R*)- and (*S*)-MTPA esters of **11** are as follows: H_2-14 (+0.08, +0.08), H-15 (+0.06), H-16 (+0.08), H_2-17 (+0.11, +0.17), H_2-18 (+0.08, +0.10), H-19 (−0.03), H-20 (−0.09), H_2-21 (−0.10, −0.13), H_2-22 (−0.08, −0.09), H-23 (−0.08), H-24 (−0.09), H_2-25 (−0.05, −0.07).
(13) Gao, Y.; Sharpless, K. B. *J. Am. Chem. Soc.* **1988**, *110*, 7538.
(14) For a review of the use of cyclic sulfates and cyclic sulfites as epoxide-like synthons, see: Lohray, B. B. *Synthesis* **1992**, 1035.

Scheme 4[a]



[a] Reagents and conditions: (a) (i) Ac_2O, pyr, room temperature; (ii) aqueous AcOH, room temperature, 95%; (b) (i) $SOCl_2$, Et_3N, CH_2Cl_2, room temperature; (ii) cat. $RuCl_3$, $NaIO_4$, aqueous CH_3CN, room temperature; (iii) NaOMe, MeOH, room temperature; (iv) aqueous H_2SO_4-Et_2O, room temperature, 83%; (c) (i) MOMCl, *i*-Pr_2NEt, CH_2Cl_2, room temperature; (ii) 10% Pd/C, H_2, EtOH, room temperature; (iii) Dess−Martin periodinane, CH_2Cl_2, room temperature; (iv) dimethyl-1-diazo-2-oxopropylphosphonate, K_2CO_3, MeOH, room temperature; 61% for **3**, 35% for **16** (in 10 steps from **12**); (d) $(Ph_3P)_2PdCl_2$, CuI, Et_3N, room temperature; 79% for **17**, 84% for **18**; (e) (i) $(Ph_3P)_3RhCl$, H_2, benzene-EtOH (6:1), room temperature; (ii) $BF_3{\cdot}Et_2O$, Me_2S, 0 °C, 56% for **1**, 68% for **2**.

group as a methoxymethyl (MOM) ether; (2) hydrogenolysis of the benzyl group; (3) Dess−Martin oxidation; (4) installation of the terminal acetylene by using Bestmann's procedure.[15]

The complete carbon skeleton of **1** was assembled by joining **3** and **4** under Hoye's conditions,[16] to give enyne **17** in 79% yield. This underwent regioselective reduction with Wilkinson's catalyst to give a fully protected jimenezin, in which all of the MOM groups were subsequently cleaved by $BF_3{\cdot}Et_2O$ in methyl sulfide[17] to give **1**.[18] The spectroscopic and physical properties of the synthetic material **1** were found to differ from those of natural jimenezin. In particular, the coupling constant value between H-19 and H-20 of the synthetic product was clearly different from that of the natural one: $J = 6.3$ Hz (synthetic) vs $J = 2.3$ Hz (natural). In addition, the natural product contained two multiplets at δ 3.90 (H-16), and 3.94 (H-19), which were observed at 3.77, and 3.82 ppm, respectively, in the ^{1}H NMR spectrum of the synthetic product. The four signals for C-16 and C-19−21 of the synthetic material deviated by 0.4−1.0 ppm compared with the respective signals of the natural compound in the ^{13}C NMR spectrum. These results suggested a difference in the stereochemistry around the THF ring.

In reexamining the NMR data reported,[2] we estimated that the relationship between H-19 and H-20 of natural jimenezin should be threo, suggesting an epimer **2** bearing a *cis* THF ring. Disconnection of the structure **2** can revert it to two fragments **16** and **4**; hence the α-alcohol **12** was regarded as an ideal starting material (Scheme 4). According to the procedure described in the synthesis of **3**, the chromatographically pure 19α-alcohol **12** was transformed into the terminal acetylene derivative **16** in 35% overall yield. The coupling reaction of **16** with **4** gave the enyne **18** in 84% yield. Finally, reduction and deprotection of **18** afforded **2**,[19] whose physical and spectral data ($[\alpha]_D$,[20] ^{1}H and ^{13}C NMR) were identical with those of the natural jimenezin.

(15) Muller, S.; Liepold, B.; Roth, G. J.; Bestmann, H. J. *Synlett* **1996**, 521.

(16) (a) Hoye, T. R.; Hanson, P. R.; Kovelsky, A. C.; Ocain, T. D.; Zang, Z. *J. Am. Chem. Soc.* **1991**, *113*, 9369. (b) Hoye, T. R.; Hanson, P. R. *Tetrahedron Lett.* **1993**, *34*, 5043. (c) Hoye, T. R.; Tan, L. *Tetrahedron Lett.* **1995**, *36*, 1981. (d) Hoye, T. R.; Ye, Z. *J. Am. Chem. Soc.* **1996**, *118*, 1801.

(17) Naito, H.; Kawahara, E.; Maruta, K. Maeda, M.; Sasaki, S. *J. Org. Chem.* **1995**, *60*, 4419.

(18) Physical and spectroscopic data for **1**: $[\alpha]_D^{25}$ −0.8° (*c* 1.40, MeOH); IR (film) 3700−3100, 2925, 2854, 1744, 1655, 1466, 1320, 1204, 1068, 953 cm^{-1}; ^{1}H NMR (400 MHz) δ 7.18 (ddd, $J = 1.7, 1.5, 1.5$ Hz, 1H), 5.05 (dddq, $J = 6.8, 1.5, 1.5, 1.5$ Hz, 1H), 3.82 (m, 2H), 3.77 (ddd, $J = 6.8, 6.6, 6.3$ Hz, 1H), 3.37 (ddd, $J = 6.3, 6.1, 6.1$ Hz, 1H), 3.26 (ddd, $J = 9.3, 9.0, 4.9$ Hz, 1H), 3.16 (ddd, $J = 10.5, 6.3, 2.0$ Hz, 1H), 3.01 (ddd, $J = 9.0, 9.0, 2.2$ Hz, 1H), 2.53 (dddd, $J = 15.1, 3.4, 1.7, 1.5$ Hz, 1H), 2.39 (dddd, $J = 15.1, 8.3, 1.5, 1.5$ Hz, 1H), 2.10−1.25 (m, 49H), 1.43 (d, $J = 6.8$ Hz, 3H), 0.88 (t, $J = 6.8$ Hz, 3H); ^{13}C NMR (100 MHz) δ 174.6, 151.8, 131.2, 82.9, 82.2, 81.3, 79.7, 78.0, 74.1, 70.9, 70.0, 37.4, 33.5, 33.3, 32.7, 32.0, 31.9, 29.7, 29.6, 29.5, 29.4, 28.9, 28.1, 25.6, 25.5, 22.7, 19.1, 14.1; HR−MS (FAB) calcd for $C_{37}H_{67}O_7$ $[M + H]^+$ 623.4887, found 623.4890.

In summary, we have achieved the first total synthesis of jimenezin, thus leading to a revison of the structure **1** originally proposed for natural jimenezin to the corresponding epimer **2**.

(19) Physical and spectroscopic data for **2**: mp 57−59 °C; $[\alpha]_D^{26}$ −13.4° (*c* 0.25, MeOH); IR (film) 3700−3150, 2926, 2855, 1748, 1654, 1457, 1319, 1204, 1068, 953 cm^{-1}; ^1H NMR (400 MHz) δ 7.18 (ddd, J = 1.5, 1.5, 1.5 Hz, 1H), 5.05 (dddq, J = 6.8, 1.5, 1.5, 1.5 Hz, 1H), 3.93 (ddd, J = 6.4, 6.4, 2.3 Hz, 1H), 3.89 (ddd, J = 6.4, 5.9, 3.9 Hz, 1H), 3.83 (m, 1H), 3.34 (m, 1H), 3.27 (ddd, J = 10.3, 9.3, 4.4 Hz, 1H), 3.23 (ddd, J = 11.2 2.4, 2.4 Hz, 1H), 3.03 (ddd, J = 9.3, 9.3, 2.4 Hz, 1H), 2.52 (dddd, J = 15.1, 3.4, 1.7, 1.5 Hz, 1H), 2.39 (dddd, J = 15.1, 8.3, 1.5, 1.5 Hz, 1H), 2.10−1.20 (m, 49H), 1.42 (d, J = 6.8 Hz, 3H), 0.87 (t, J = 7.1 Hz, 3H); ^{13}C NMR (100 MHz) δ 174.6, 151.8, 131.2, 82.4, 82.3, 80.9, 79.0, 78.0, 73.9, 70.5, 70.0, 37.4, 34.9, 33.5, 33.3, 32.9, 32.0, 31.9, 29.7, 29.6, 29.5, 29.4, 28.3, 28.1, 27.9, 25.9, 25.6, 25.5, 22.7, 19.1, 14.1; HR−MS (FAB) calcd for $C_{37}H_{67}O_7$ $[M + H]^+$ 623.4887, found 623.4906.

(20) The reported specific rotation for jimenezin is $[\alpha]_D^{20}$ +8.3° (*c* 1.2 mg/mL, MeOH); see ref 2. However, we found that natural jimenezin kindly provided by Dr. Mata showed the opposite rotation {$[\alpha]_D^{26}$ −8.9° (*c* 0.05, MeOH)}.

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Supporting Information Available: Physical and spectroscopic data for compounds **3**, **6**, **9**−**13**, and **15-18**. This material is available free of charge via the Internet at http://pubs.acs.org.

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