

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

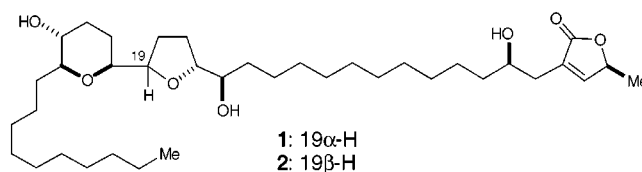
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ABSTRACT



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 pyranaldehyde 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 acetogenin¹ 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) ring³ 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 assay⁵ (IC_{50} 5.7×10^{-3} μ g/mL), and exhibited potent cytotoxic activity

against six human solid tumor cell lines. As part of our continuing efforts toward synthesis of anticancer 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 pyranaldehyde **5**^{6a} and a terminal acetylene **6**. The latter might be readily prepared from L-rhamnose, 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) Muconin: Shi, G.; Alfonso, D.; Fatope, M. O.; Zeng, L.; Gu, Z. M.; Zhao, G. X.; He, K.; MacDougall, J. M.; McLaughlin, J. L. *J. Am. Chem. Soc.* **1995**, *117*, 10409. (b) Pyranicin and pyragonin: 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.; MacDougall, J. M.; McLaughlin, J. L. *J. Org. Chem.* **1996**, *61*, 7988.

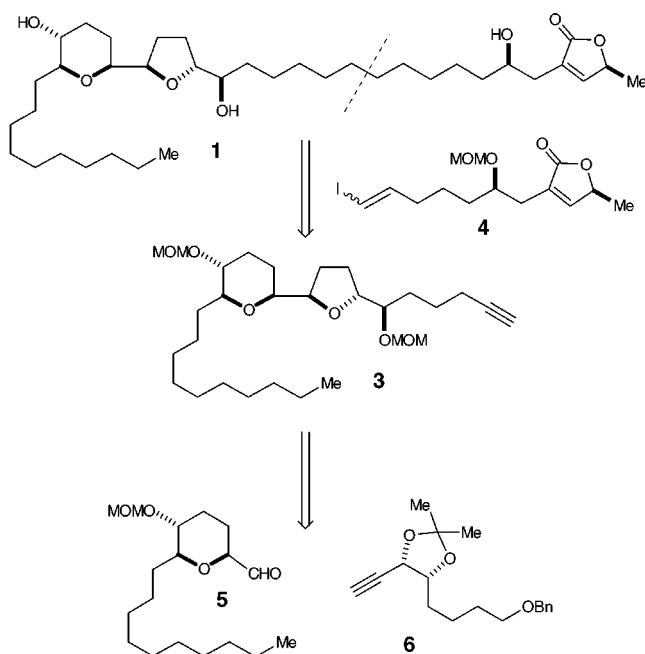
(5) McLaughlin, J. L. In *Methods in Plant Biochemistry*; Hostettmann, K., Ed.; Academic Press: London, 1991; Vol. 6, p 1. Meyer, B. N.; Ferrigni, N. R.; Putnam, J. E.; Jacobsen, L. B.; Nichola, D. E.; McLaughlin, J. L. *Planta Med.* **1982**, *45*, 31.

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

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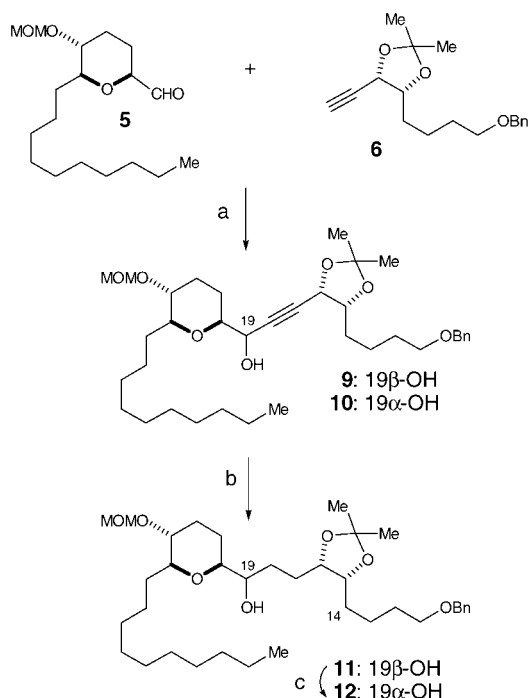
(8) All new compounds were fully characterized by IR, NMR, high-resolution mass spectra, and/or combustion analyses.

Scheme 1



converted into **6** via a dibromoolefin¹⁰ in 88% overall yield from **8**.

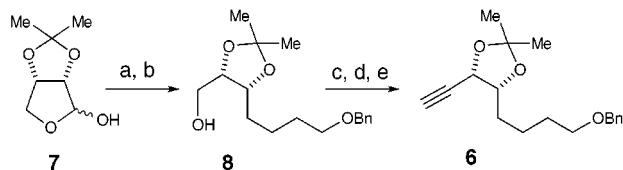
For the synthesis of **1**, we needed alcohol **11** with the *R* configuration at the C-19 position (jimenezin numbering) as a key intermediate (Scheme 3). An efficient diastereofacially selective addition of **6** to the carbonyl group of **5** under Cram mode would make it theoretically possible to 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 $-78\text{ }^{\circ}\text{C}$, 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 3^a

^a Reagents and conditions: (a) *n*-BuLi, THF–HMPA, $-78\text{ }^{\circ}\text{C}$, 72%; (b) 10% PtO₂, H₂, EtOAc, room temperature, 88%; (c) (i) Dess–Martin periodinane, CH₂Cl₂, room temperature; (ii) L-Selectride, THF, $-78\text{ }^{\circ}\text{C}$, 97%.

PtO₂ gave the desired 19β-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 $-78\text{ }^{\circ}\text{C}$ produced the 19α-alcohol **12** (94% de) in 97% overall yield.

The 19β-alcohol **11** was acetylated, and then hydrolysis under acidic conditions afforded a diol **13** (mp $77.5\text{--}78\text{ }^{\circ}\text{C}$) 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 NaIO₄–RuCl₃,¹³ 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

Scheme 2^a

^a Reagents and conditions: (a) Ph₃PBrC₃H₆OBn, *n*-BuLi, THF, $-78\text{ }^{\circ}\text{C}$ to room temperature, 89%; (b) 10% Pd/C, H₂, EtOAc, room temperature, 94%; (c) (i) Dess–Martin periodinane, CH₂Cl₂, room temperature; (ii) Ph₃P, CBr₄, CH₂Cl₂, $-78\text{ }^{\circ}\text{C}$, 97%; (e) EtMgBr, THF, $0\text{ }^{\circ}\text{C}$, 91%.

(9) Dess, D. B.; Martin, J. C. *J. Org. Chem.* **1983**, *48*, 4156.

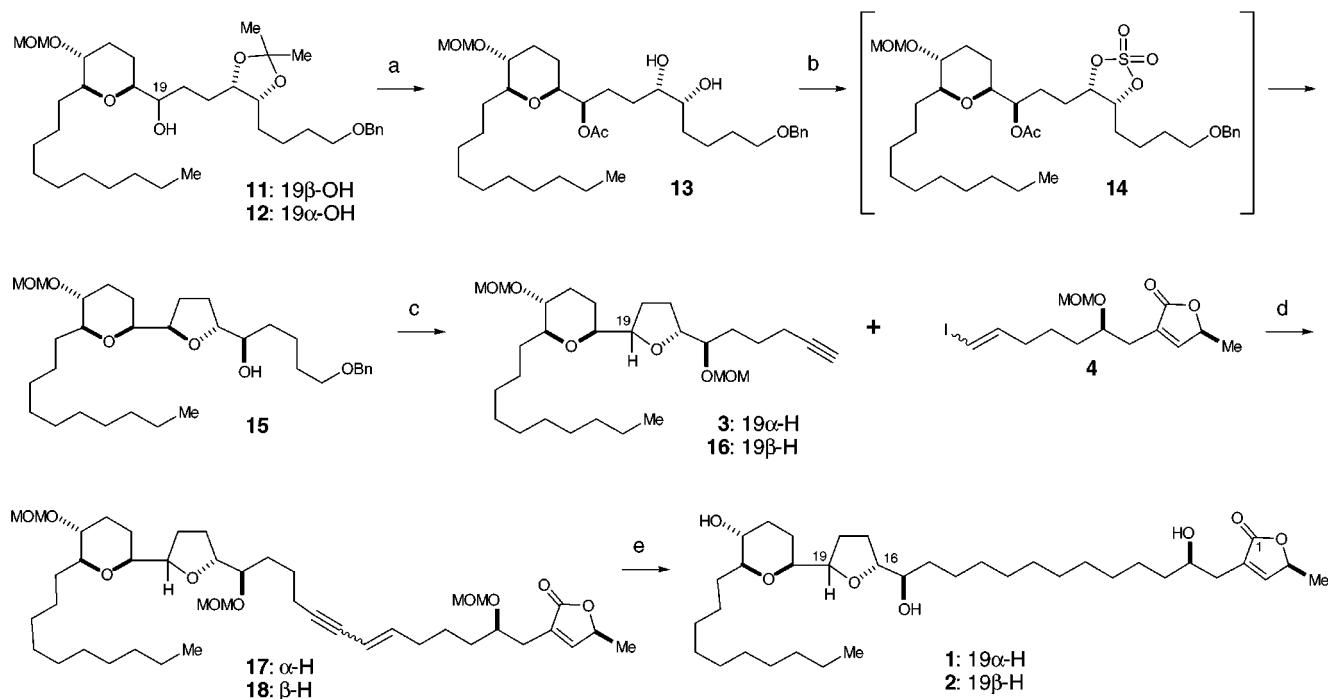
(10) Corey, E. J.; Fuchs, P. L. *Tetrahedron Lett.* **1972**, 3769.

(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 ($\Delta\delta_{S-R}$ values in δ) between (*R*)- and (*S*)-MTPA esters of **11** are as follows: H₂-14 (+0.08, +0.08), H-15 (+0.06), H-16 (+0.08), H₂-17 (+0.11, +0.17), H₂-18 (+0.08, +0.10), H-19 (−0.03), H-20 (−0.09), H₂-21 (−0.10, −0.13), H₂-22 (−0.08, −0.09), H-23 (−0.08), H-24 (−0.09), H₂-25 (−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) Ac₂O, pyr, room temperature; (ii) aqueous AcOH, room temperature, 95%; (b) (i) SOCl₂, Et₃N, CH₂Cl₂, room temperature; (ii) cat. RuCl₃, NaIO₄, aqueous CH₃CN, room temperature; (iii) NaOMe, MeOH, room temperature; (iv) aqueous H₂SO₄-Et₂O, room temperature, 83%; (c) (i) MOMCl, *i*-Pr₂NEt, CH₂Cl₂, room temperature; (ii) 10% Pd/C, H₂, EtOH, room temperature; (iii) Dess–Martin periodinane, CH₂Cl₂, room temperature; (iv) dimethyl-1-diazo-2-oxopropylphosphonate, K₂CO₃, MeOH, room temperature; 61% for **3**, 35% for **16** (in 10 steps from **12**); (d) (Ph₃P)₂PdCl₂, CuI, Et₃N, room temperature; 79% for **17**, 84% for **18**; (e) (i) (Ph₃P)₃RhCl, H₂, benzene-EtOH (6:1), room temperature; (ii) BF₃·Et₂O, Me₂S, 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 Hoyer'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 BF₃·Et₂O in methyl sulfide¹⁷ to give **1**.¹⁸ The spectro-

scopic 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 ¹H 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 ¹³C 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 19 α -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 ([α]_D,²⁰ ¹H and ¹³C 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) Hoyer, T. R.; Hanson, P. R.; Kovelsky, A. C.; Ocain, T. D.; Zang, Z. *J. Am. Chem. Soc.* **1991**, *113*, 9369. (b) Hoyer, T. R.; Hanson, P. R. *Tetrahedron Lett.* **1993**, *34*, 5043. (c) Hoyer, T. R.; Tan, L. *Tetrahedron Lett.* **1995**, *36*, 1981. (d) Hoyer, 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**: [α]_D²⁵ -0.8° (*c* 1.40, MeOH); IR (film) 3700–3100, 2925, 2854, 1744, 1655, 1466, 1320, 1204, 1068, 953 cm⁻¹; ¹H 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); ¹³C 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 C₃₇H₆₇O₇ [M + H]⁺ 623.4887, found 623.4890.

In summary, we have achieved the first total synthesis of jimenezin, thus leading to a revision 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; $[\alpha]_{\text{D}}^{26} -13.4^{\circ}$ (*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 $\text{C}_{37}\text{H}_{67}\text{O}_7$ [*M* + *H*] $^{+}$ 623.4887, found 623.4906.

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

Acknowledgment. We are grateful to Dr. R. Mata of Universidad Nacional Autonoma de Mexico for providing us with natural jimenezin and the spectra of jimenezin and its related compounds. We also express our thanks to Dr. H. Koshino for measurement of 2D-NMR spectra, Ms. K. Harata for mass spectral measurements, and Dr. T. Chihara and his staff in RIKEN for the elemental analyses. K.M. thanks Professor K. Oshima (Kyoto University) for his encouragement. This work was supported by a Special Grant for Promotion of Research from RIKEN.

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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