JOC Notes

Feigrisolide C: Structural Revision and Synthesis

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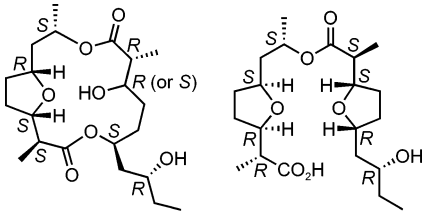


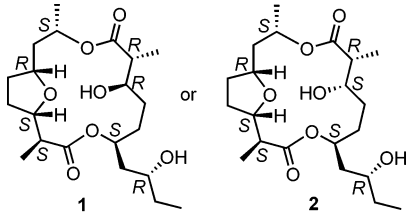
Feigrisolide C

The original macrodiolide structure proposed for feigrisolide C was incorrect. The true structure of feigrisolide C was identified as (2′*S*,3′*S*,6′*R*,8′*R*)-homononactoyl (2*R*,3*R*,6*S*,8*S*)-nonactic acid, which was confirmed by total synthesis.

Feigrisolide C was isolated from the culture broth of *Streptomyces griseus* (strain GT 051022)[1] and was also claimed to be a metabolite of *Streptomyces* sp. 6167 of marine origin.[2] The structure was proposed[1] to be a 15-membered macrodiolide **1** (originally intended to be **2**) incorporating 8-*epi*-nonactic acid (Figure 1). Both these compounds were synthesized in our laboratory and found to be different from feigrisolide C.[3]

A small sample of natural feigrisolide C was subjected to exhaustive reduction with excess amount of lithium aluminum hydride, and the crude products were acetylated[4] to furnish two products **A** and **B** (Scheme 1).

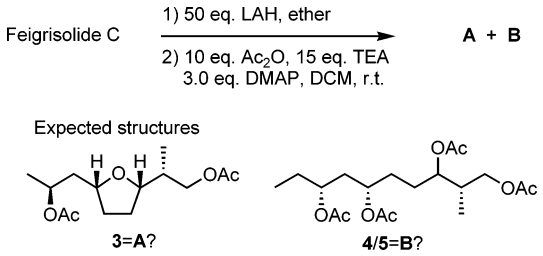
If one assumes that the true structure of feigrisolide C is epimeric to structure **1** or **2**, then diacetate **3** should represent **A**, and a tetraacetate epimeric to **4** or **5** should correspond to **B**. Surprisingly, examination of the NMR spectra of the major product[5] **B** clearly indicated that it was a diacetate originated from a *threo* homononactic acid with the characteristic ABX signals from C1 methylene group (δ 3.96 and 4.20, $\Delta\delta \geq 0.2$). Diacetates from *erythro* nonactic acids should exhibit ABX signals different from those of C1 methylene protons; $\Delta\delta$ 0.1.[4]



Incorrect structures of feigrisolide C

FIGURE 1. Structures proposed for feigrisolide C.

SCHEME 1. Chemical Transformation of Feigrisolide C



(+)-Methyl homononactate (**12**) was synthesized from methyl (*R*)-3-hydroxypentanoate (**6**)[6] following the scheme used for previous synthesis of (+)-methyl nonactate (**14**)[7] (Scheme 2). The diacetate **13** obtained from **12** after $LiBH_4$ reduction/acetylation exhibited NMR spectra identical to those of **B**.

Examination of the NMR spectra[8] of **A** indicated that it was also a diacetate from a *threo* nonactic acid. The diacetate **15**, prepared from (+)-methyl nonactate (**14**), furnished NMR spectra identical to those of **A**. For comparison, the alternative diacetate **3** was prepared from (+)-methyl 8-*epi*-nonactate (**16**),[3] and it was clearly different from **A**.

Four candidates for feigrisolide C then emerged: (2′*S*,3′*S*,6′*R*,8′*R*)-homononactoyl (2*S*,3*S*,6*R*,8*R*)-nonactic acid (**17**), ***ent*-17**, (2′*S*,3′*S*,6′*R*,8′*R*)-homononactoyl (2*R*,3*R*,6*S*,8*S*)-nonactic acid (**18**), or ***ent*-18** (Figure 2).

Spectroscopic differences between **17** and **18** were anticipated to be small, and it was decided to prepare both isomers for comparison. The benzyl ether **19** of (2′*S*,3′*S*,6′*R*,8′*R*)-homononactic acid was prepared from the methyl ester **11**. It was reacted with methyl (2*S*,3*S*,6*R*,8*R*)-nonactate (**14**) under Yamaguchi conditions to furnish the diester **20**, which was converted into **17** via **21**. Using **19** and ***ent*-14**, we also prepared the other

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(1) Tang, Y.-Q.; Sattler, I.; Thiericke, R.; Grabley, S.; Feng, X.-Z. *J. Antibiot*. **2000**, *53*, 934−943.

(2) Sobolevskaya, M. P.; Fotso, S.; Havash, U.; Denisenko, V. A.; Helmke, E.; Prokofeva, N. G.; Kuznetsova, T. A.; Laatsch, H.; Elyakov, G. B. *Chem. Nat. Compd*. **2004**, *40*, 282−285.

(3) Kim, W. H.; Jung, J. H.; Sung, L. T.; Lim, S. M.; Lee, E. *Org. Lett*. **2005**, *7*, 1085−1087.

(4) This strategy was used previously in our synthesis of pamamycin-607 to check epimerization problems at C2 and C2′ of *seco* acids: Jeong, E. J.; Kang, E. J.; Sung, L. T.; Hong, S. K.; Lee, E. *J. Am. Chem. Soc*. **2002**, *124*, 14655−14662.

(5) The yield of **A** was much lower than that of **B**, and **A** was initially overlooked as TLC separation was difficult.

(6) Noyori, R.; Ohkuma, T.; Kitamura, M.; Takaya, H.; Sayo, N.; Kumobayashi, H.; Akutagawa, S. *J. Am. Chem.* Soc. **1987**, *109*, 5856−5858.

(7) Lee, E.; Choi, S. J. *Org. Lett*. **1999**, *1*, 1127−1128.

(8) We failed to get clean NMR spectra of **A** due to the lack of material, but the characteristic features were easily recognized.

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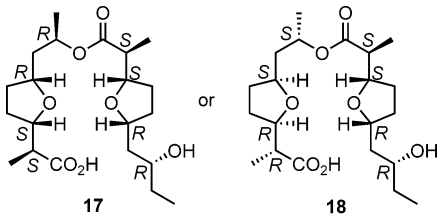
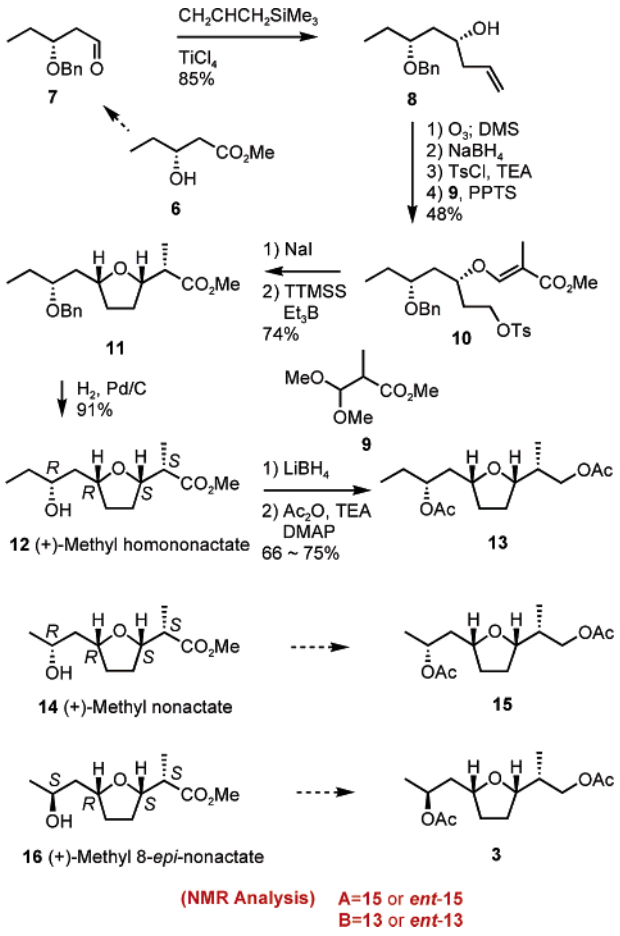


FIGURE 2. Possible structures of feigrisolide C.

SCHEME 2. Preparation of Diacetates 3, 13, and 15

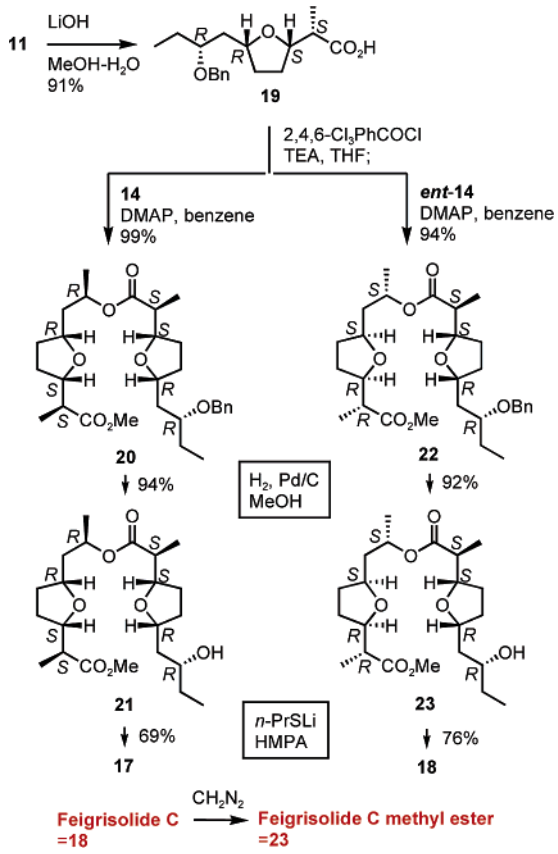


candidate **18** via **22** and **23**. Careful comparison studies revealed that **18** exhibited spectroscopic characteristics identical to those of feigrisolide C. The synthetic sample of **18** had the same optical rotation value ($[\alpha]^{25}_D$ +16.2 (*c* 0.2, MeOH)) as that reported for feigrisolide C ($[\alpha]^{20}_D$ +17.2 (*c* 0.4, MeOH)), and the true structure of feigrisolide C was finally identified as **18** (Scheme 3). A small sample of feigrisolide C was converted into the methyl ester via reaction with diazomethane, and it exhibited spectroscopic properties identical to those of **23**,[9] confirming the conclusion.

A literature search revealed that bonactin[10] (isolated from a *Streptomyces* sp. BD21-2 cultured from a shallow

(9) In ^{1}H NMR spectra, the features around δ 1.7 were diagnostic in differentiating between **17** and **18** and also their methyl esters **21** and **23**.

SCHEME 3. Synthesis of the Possible Structures of Feigrisolide C



water sediment sample, $[\alpha]^{25}_D$ 0 (*c* 0.84, CH_2Cl_2)), has the same gross structure as that of feigrisolide C, but it was claimed to consist of a racemic mixture of (±)-nonactic acid and (±)-homononactic acid.[11] A nonactoyl homononactic acid of unknown stereochemistry was also recently claimed to be isolated from a strain of *Streptomyces globisporus*.[12] Determination of the exact structure of each of these compounds is quite difficult, and the present studies suggest expedient ways of solving the problems.

Experimental Section

Ester 22. To a mixture of carboxylic acid **19** (63 mg, 0.21 mmol) and TEA (0.065 mL, 0.48 mmol) in THF (2.5 mL) was added 2,4,6-trichlorobenzoyl chloride (0.05 mL, 0.35 mmol). The reaction mixture was stirred for 2 h at room temperature. The white precipitate that formed was removed by filtration under N_2 via cannula transfer to a glass pipet equipped with a septum and a plug of glass wool. The THF filtrate was evaporated by a stream of N_2. The residue was diluted with benzene (5 mL), and DMAP (75 mg, 0.63 mmol) was added. To this mixture was added alcohol ***ent*-14** (65 mg, 0.30 mmol) in benzene (2.5 mL). The reaction mixture was stirred for 2 h at room temperature, and the reaction was quenched with saturated NH_4Cl solution (8 mL). The reaction mixture was extracted with DCM (20 mL × 3), and the organic extracts were dried over $MgSO_4$, filtered, and concentrated. Purification by flash column chromatography (hexane−EtOAc, 2:1) gave ester **22** (98 mg (oil), 94%). R_f 0.50

(10) Schumacher, R. W.; Talmage, S. C.; Miller, S. A.; Sarris, K. E.; Davidson, B. S.; Goldberg, A. *J. Nat. Prod.* **2003**, *66*, 1291−1293.

(11) This claim is probably erroneous if bonactin is a single compound.

(12) Řezanka, T.; Spížek, J.; Přikrylová, V.; Prell, A.; Dembitsky, V. M. *Tetrahedron* **2004**, *60*, 4781−4787.

(hexane−EtOAc, 2:1). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.36−7.27 (m, 5H), 5.04−4.93 (m, 1H), 4.54 and 4.48 (AB q, 2H, J = 11.3 Hz), 4.07−3.94 (m, 3H), 3.92−3.83 (m, 1H), 3.67 (s, 3H), 3.58−3.51 (m, 1H), 2.55−2.43 (m, 2H), 2.02−1.92 (m, 4H), 1.77−1.72 (m, 2H), 1.69−1.42 (m, 8H), 1.23 (d, 3H J = 6.3 Hz), 1.09 (d, 6H, J = 7.0 Hz), 0.92 (t, 3H, J = 7.4 Hz); ^{13}C NMR (75 MHz, $CDCl_3$): δ 175.2, 174.2, 139.0, 128.2, 127.7, 127.3, 80.3, 80.1, 78.1, 76.6, 76.5, 71.5, 69.2, 51.5, 45.7, 45.3, 42.5, 40.8, 31.5, 31.3, 28.4, 28.3, 27.1, 20.5, 13.2, 13.1, 9.2. IR (neat): ν_{max} = 3450, 2972, 2877, 1738, 1497, 1456, 1377, 1259, 1196, 1167, 1061 cm^{-1}. MS *m/z* (FAB, relative intensity): 505 (M^+ + 1, 49), 397 (10), 307 (24), 199 (100), 154 (64), 136 (46), 91 (79). HRMS (FAB) calcd for $C_{29}H_{45}O_7$ (M^+ + 1) 505.3165, found 505.3169. $[\alpha]^{25}_D$ −15.0 (*c* 2.75, $CHCl_3$).

Alcohol 23. Ester **22** (38 mg, 0.073 mmol) was dissolved in MeOH (3.2 mL), and palladium on activated carbon (10% w/w, 16 mg) was added. The mixture was stirred under hydrogen atmosphere for 30 min and then filtered through a filter paper. After solvent evaporation, flash column chromatography (hexane−EtOAc, 2:1) yielded alcohol **23** (28 mg (oil), 92%). R_f 0.41 (hexane−EtOAc, 1:3). ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.05−4.94 (m, 1H), 4.16−4.12 (m, 1H), 4.02−3.95 (m, 2H), 3.93−3.84 (m, 1H), 3.78−3.67 (m, 1H), 3.69 (s, 3H), 2.79 (d, 1H J = 4.8 Hz), 2.56−2.44 (m, 2H), 2.04−1.94 (m, 4H), 1.80−1.43 (m, 10H), 1.24 (d, 3H J = 6.2 Hz), 1.10 (d, 6H, J = 7.0 Hz), 0.93 (t, 3H, J = 7.4 Hz); ^{13}C NMR (75 MHz, $CDCl_3$): δ 175.3, 174.2, 80.8, 80.4, 76.6, 76.4, 70.3, 69.4, 51.6, 45.4, 45.3, 42.4, 40.7, 31.3, 30.6, 30.1, 28.6, 28.5, 20.5, 13.3, 13.2, 10.1. IR (neat): ν_{max} = 2974, 1732, 1462, 1379, 1263, 1198, 1063 cm^{-1}. MS *m/z* (FAB, relative intensity): 415 (M^+ + 1, 64), 391 (27), 307 (19), 282 (68), 199 (54), 154 (100), 136 (71), 107 (25). HRMS (FAB) calcd for $C_{22}H_{39}O_7$ (M^+ + 1) 415.2696, found 415.2706. $[\alpha]^{25}_D$ +6.0 (*c* 0.53, $CHCl_3$).

(2′*S*,3′*S*,6′*R*,8′*R*)-Homononactoyl (2*R*,3*R*,6*S*,8*S*)-Nonactic Acid (18). To a solution of alcohol **23** (28 mg, 0.067 mmol) in HMPA (0.27 mL) was added lithium *n*-propyl mercaptide (0.48 M in HMPA, 0.027 mL). The reaction mixture was stirred for 2 h at room temperature. The reaction was quenched by addition of saturated $NaHCO_3$ (0.15 mL) solution and water (0.11 mL). The reaction mixture was extracted with $CHCl_3$ (0.11 mL × 6). The aqueous phase was acidified to pH 1 with 2 N HCl and extracted with $CHCl_3$ (0.22 mL × 8). The organic extracts were dried over $MgSO_4$, filtered, and concentrated. Purification by flash column chromatography ($CHCl_3$−MeOH, 9:1) gave (2′*S*,3′*S*,6′*R*,8′*R*)-homononactoyl (2*R*,3*R*,6*S*,8*S*)-nonactic acid (**18**, 21 mg (oil), 76%). R_f 0.40 ($CHCl_3$−MeOH, 9:1). ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.09−5.03 (m, 1H), 4.17−4.11 (m, 1H), 4.05−3.91 (m, 3H), 3.80−3.72 (m, 1H), 2.52−2.46 (m, 2H), 2.04−1.97 (m, 4H), 1.83−1.46 (m, 11H), 1.25 (d, 3H J = 6.3 Hz), 1.17 (d, 3H, J = 7.0 Hz), 1.11 (d, 3H, J = 7.0 Hz), 0.93 (t, 3H, J = 7.4 Hz); ^{13}C NMR (75 MHz, $CDCl_3$): δ 176.8, 174.3, 81.1, 80.5, 77.2, 76.7, 70.4, 68.9, 45.4, 44.9, 42.2, 40.3, 31.0, 30.4, 29.8, 29.2, 28.8, 20.3, 13.7, 13.5, 10.1. IR (neat): ν_{max} = 3444, 2970, 2933, 2873, 1730, 1460, 1379, 1263, 1198, 1061 cm^{-1}. MS *m/z* (FAB, relative intensity): 401 (M^+ + 1, 47), 307 (20), 289 (10), 199 (25), 154 (100), 136 (76), 107 (33). HRMS (FAB) calcd for $C_{21}H_{37}O_7$ (M^+ + 1) 401.2539, found 401.2543. $[\alpha]^{25}_D$ +16.2 (*c* 0.24, $CHCl_3$).

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Supporting Information Available: Experimental procedures, ^{1}H NMR spectra of **A**, **B**, **3**, **13**, **15**, **21**, **23**, feigrisolide C, and feigrisolide C methyl ester, and ^{13}C NMR spectra of the intermediates. This material is available free of charge via the Internet at http://pubs.acs.org.

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