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Stereoselective synthesis of (−)-jimenezin

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Abstract—Total synthesis of jimenezin was achieved via radical cyclization of β-alkoxyacrylate and β-alkoxyvinyl sulfoxide intermediates and intramolecular olefin metathesis reaction.
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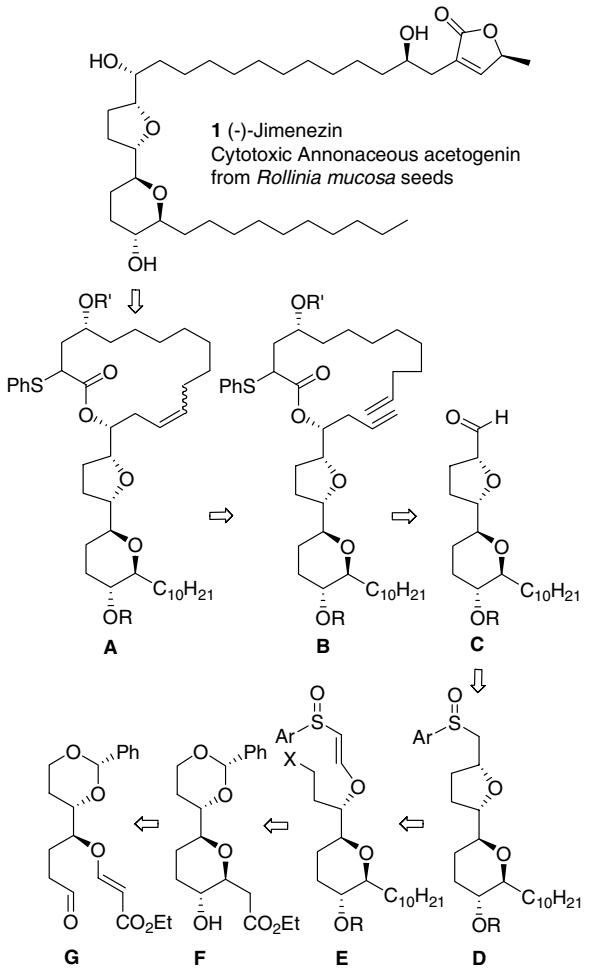
Jimenezin (**1**) is an Annonaceous acetogenin isolated from the seeds of *Rollinia mucosa* (Jacquin) Baillon.[1] It is quite active in the brine shrimp lethality test (IC_{50} 5.7 ng/mL) and exhibits potent cytotoxic activity against six human solid tumor lines. The original structure proposed was corrected by Takahashi and co-workers via total synthesis, which was achieved by using carbohydrates as chiral building blocks.[2] Jimenezin (**1**) is a rare example of acetogenins possessing a hydroxylated *cis*-2,6-disubstituted oxane ring along with an adjacent *cis*-2,5-disubstituted oxolane ring and one flanking hydroxyl group on the oxolane side (Scheme 1). Radical cyclization reactions of β-alkoxyacrylates and related vinyl ethers are now well known to produce *cis*-2,5-disubstituted oxolane and *cis*-2,6-disubstituted oxane rings,[3] and we intended to examine the efficacy of these reactions in a stereocontrolled synthesis of jimenezin (**1**).

In retrosynthetic analysis, hydroxy oxane **F** was to be prepared from a β-alkoxyacrylate aldehyde precursor **G** via samarium(II) iodide-mediated cyclization. Oxolane derivative **D** was envisaged to arise via radical cyclization of β-alkoxyvinyl sulfoxide **E**. The homoallylic alcohol prepared from aldehyde **C** was to be converted into carboxylate ester **B**, which may serve as a precursor for macrolactone **A** via ring-forming olefin metathesis. Incorporation of (*S*)-propylene oxide unit into **A** and further manipulations should generate jimenezin (**1**) (Scheme 1).



Scheme 1.

Keywords: Jimenezin; β-Alkoxyacrylate; β-Alkoxyvinyl sulfoxide; Radical cyclization; Intramolecular olefin metathesis.
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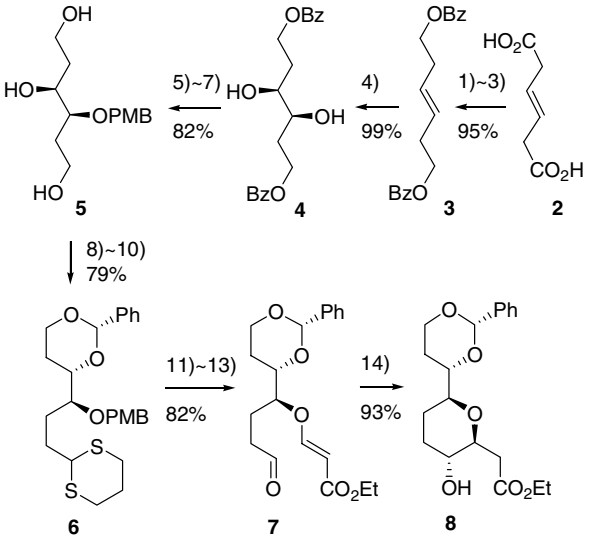
Dibenzoate **3** was prepared from *trans*-3-hexenedioic acid (**2**) and transformed into diol **4** (96% ee)[4] via Sharpless asymmetric dihydroxylation.[5] The PMB acetal prepared from **4** was reduced in the presence of titanium chloride and sodium cyanoborohydride[6] and triol **5** was prepared via subsequent removal of benzoate groups via LAH reduction.

Selective benzylidene acetal protection of the 1,3-diol moiety in **5**, iodide substitution of the primary hydroxyl group, and subsequent substitution with lithiated 1,3-dithiane produced the dithiane intermediate **6**. PMB ether deprotection of **6**, reaction with ethyl propiolate in the presence of NMM, and dithiane deprotection yielded β-alkoxyacrylate aldehyde **7**. Samarium iodide-mediated radical cyclization[7] of **7** proceeded smoothly, and the oxane derivative **8** was obtained in high yield (Scheme 2).

Conversion of **8** into olefin **9** required MOM protection of the hydroxyl group, and Wittig reaction of the corresponding aldehyde. DIBAL reduction of **9** produced a benzyl ether intermediate, from which (*E*)-β-alkoxyvinyl (*S*)-sulfoxide **10** was obtained via hydrogenation/hydrogenolysis, tosylation of the primary hydroxyl group, reaction with ethynyl *p*-tolyl (*S*)-sulfoxide, and iodide substitution. The key radical cyclization (matched case)[8] of **10** in the presence of tributylstannane and triethylborane at low temperature furnished a single oxolane product **11**, and aldehyde **12** was prepared via

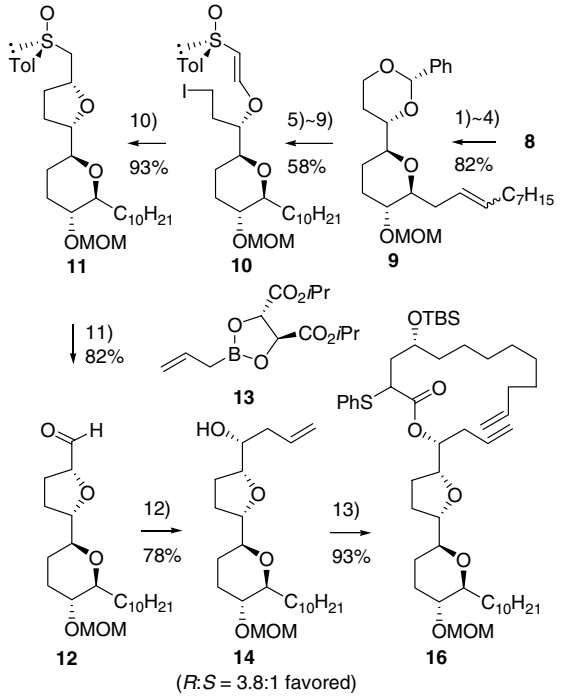


Scheme 2. Reagents and conditions: (1) EtOH, cat. H_2SO_4, benzene, reflux (–H_2O), 2 d; (2) 2.0 equiv LAH, ether, 0 °C–rt; (3) 2.2 equiv BzCl, 2.5 equiv pyridine, DCM, 0 °C–rt, 10 h; (4) 0.4 mol % OsO_4, 0.01 equiv DHQ_2(PHAL), 3.0 equiv K_3FeCN_6, 3.0 equiv $NaHCO_3$, 3.0 equiv K_2CO_3, 1.0 equiv $MeSO_2NH_2$, *t*-BuOH–H_2O (1:1) (0.1 M), 0 °C, 12 h; (5) 1.5 equiv (*p*-MeO)PhCH(OMe)$_2$, 0.02 equiv CSA, DCM, rt; (6) 1.2 equiv $TiCl_4$, 1.5 equiv $NaBH_3CN$, 2.0 equiv TEA, MeCN, 0 °C, 50 min; (7) 2.0 equiv LAH, ether, 0 °C–rt; (8) 2.2 equiv PhCH(OMe)$_2$, 0.01 equiv CSA, DCM, rt; (9) 1.5 equiv I_2, 1.5 equiv Ph_3P, 2.0 equiv imidazole, DCM, rt; (10) 2.2 equiv *n*-BuLi, 2.2 equiv 1,3-dithiane, 3.0 equiv HMPA, THF, −30 °C–rt; (11) 1.1 equiv DDQ, DCM–H_2O (20:1), rt; (12) 2.5 equiv $HCCCO_2Et$, 0.15 equiv NMM, MeCN–DCM (1:1), rt; (13) 5.0 equiv MeI, 7.0 equiv $NaHCO_3$, MeCN–H_2O (3:1), rt; (14) 3.0 equiv SmI_2, THF, 3.0 equiv MeOH, 0 °C, 10 min.

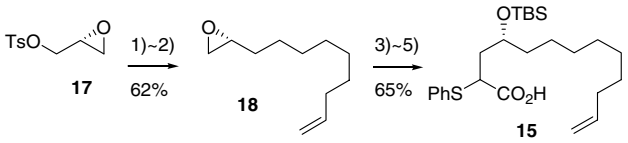
Pummerer rearrangement. Reaction of **12** with the Roush boronate **13**[9] provided a 3.8:1 mixture favoring (*R*)-homoallylic alcohol **14**.[10] Yamaguchi esterification of **14** with carboxylic acid **15** proceeded smoothly to yield the ester diene **16** (Scheme 3).

Epoxide **18** was obtained from (*R*)-glycidyl tosylate (**17**)[11] via reaction with octenyl Grignard reagent and DBU treatment, and a three-step sequence provided carboxylic acid **15** (Scheme 4).

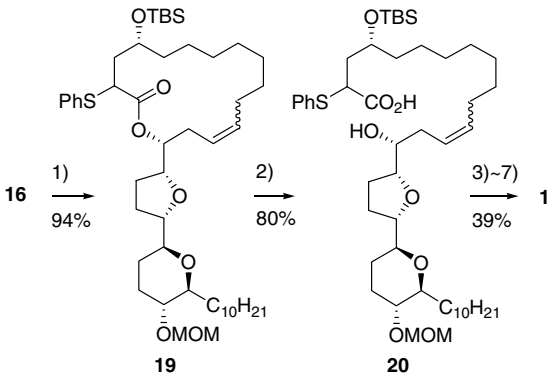
The crucial ring-closing olefin metathesis reaction of **16** proceeded efficiently to give the olefin mixture **19**.[12]



Scheme 3. Reagents and conditions: (1) 5.0 equiv MOMCl, 8.0 equiv DIPEA, DCM, 0 °C–rt; (2) 1.0 equiv LAH, ether, 0 °C–rt; (3) 2.0 equiv Dess–Martin periodinane, DCM, rt, 2 h; (4) 2.6 equiv *n*-BuLi, 2.6 equiv *n*-$C_8H_{17}PPh_3^+I^-$, THF, −78 °C–rt; (5) 2.2 equiv DIBAL, DCM, 0 °C; (6) H_2, Pd–C, MeOH, rt; (7) 1.0 equiv *p*-TsCl, 0.02 equiv *n*-Bu_2SnO, 1.0 equiv TEA, rt, 10 h; (8) 3.0 equiv (*S*)-*p*-TolS(O)CCH, 1.0 equiv NMM, DCM, 0 °C–rt, 1 d; (9) 4.0 equiv NaI, acetone, reflux, 16 h; (10) 1.5 equiv *n*-Bu_3SnH, 0.5 equiv Et_3B, toluene, −30 °C; (11) 2.0 equiv TFAA, 5.0 equiv 2,4,6-collidine, 0 °C, 10 min; 5.0 equiv K_2CO_3, 0.2 M NaH_2PO_4–Na_2HPO_4 buffer (pH 7.0), 0 °C, 30 min; (12) **13**, 4 Å MS, toluene, −78 °C, 3 h; (13) 1.5 equiv 2,4,6-$Cl_3PhCOCl$, 1.7 equiv TEA, 1.2 equiv **15**, THF; 2.0 equiv DMAP, benzene, **14**.



Scheme 4. Reagents and conditions: (1) 1.5 equiv $C_8H_{15}MgBr$, THF, −40 °C, 3 h; (2) 2.1 equiv DBU, DCM, rt, 2 h; (3) 3.0 equiv $PhSCH_2CO_2H$, 3.0 equiv LDA, THF, −78 °C–rt, 16 h; (4) 3.0 equiv TBSCl, 5.0 equiv DCM, rt, 12 h; (5) 3.0 equiv K_2CO_3, MeOH–H_2O (7:1), rt.



Scheme 5. Reagents and conditions: (1) 15 mol % $(Cy_3P)_2RuCl_2(CHPh)$, DCM, rt, 16 h; (2) 6 N LiOH, 12-crown-4, MeOH–THF (1:1), reflux; (3) 5.0 equiv TESCl, 6.0 equiv imidazole, DCM, rt; 3.0 equiv K_2CO_3, MeOH–H_2O (7:1), rt; (4) 3.0 equiv LDA, 5.0 equiv (*S*)-propylene oxide, THF; *p*-TsOH, benzene, rt; (5) 1.0 equiv *m*-CPBA, DCM, 0 °C; toluene, reflux, 1 h; (6) H_2, 10 mol % $(Ph_3P)_3RhCl$, benzene, rt; (7) 10% HCl–MeOH, DCM, rt.

Enolates derived from **19** failed to react with (*S*)-propylene oxide,[13] and it was instead converted into the corresponding hydroxy acid **20** under basic hydrolytic conditions. After selective TES-protection of the hydroxyl group, lithium enolate generated was reacted with (*S*)-propylene oxide to form an α-phenylthio γ-lactone, which provided a butenolide intermediate via oxidation–elimination protocol. (−)-Jimenezin (**1**)[14] was finally obtained via selective hydrogenation and acidic deprotection of protecting groups (Scheme 5).

In this synthesis, the oxane and oxolane moieties were introduced in high stereoselectivity via radical cyclization of β-alkoxyacrylate and β-alkoxyvinyl sulfoxide intermediates. Ring-closing olefin metathesis reaction was employed for butenolide side-chain elongation.

Acknowledgements

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Supplementary data

Supplementary Information available: experimental details for preparation of **8**, **11**, **19** and **1**, and ^1H and ^{13}C NMR spectra of **1**. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2005.07.148.

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14. The sample exhibited identical spectroscopic characteristics as those of the synthetic sample reported in Ref. 2: $[\alpha]_D^{[29]}$ −9.1 (*c* 0.34, MeOH). (Data for the natural sample: $[\alpha]_{26}^{D}$ −8.9 (*c* 0.05, MeOH).)[2]