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Total Synthesis of Jimenezin via an Intramolecular Allylboration

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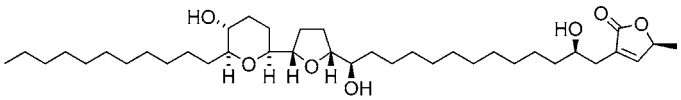
ABSTRACT

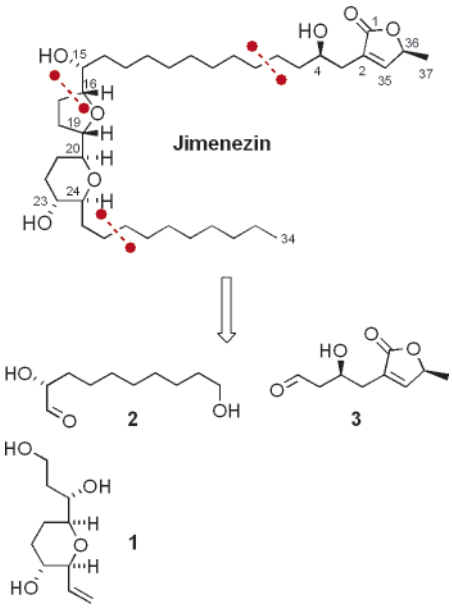


Jimenezin

An efficient total synthesis of the annonaceous acetogenin jimenezin was achieved. The key steps used were a highly stereoselective intramolecular allylboration to establish the tetrahydropyran ring and an intramolecular Williamson reaction to close the tetrahydrofuran ring.

The annonaceous acetogenins form a class of natural products with interesting antitumor properties.[1] Jimenezin was isolated from seeds of *Rollinia mucosa* in 1998.[2] Its structure consisting of a tetrahydropyran (THP) ring adjacent to a tetrahydrofuran (THF) ring was proposed using spectroscopic techniques[2] and revised after a total synthesis by Takahashi.[3] Although most annonaceous acetogenins contain one to three THF rings in the polyether part, jimenezin belongs to the small subgroup with an additional THP ring and is structurally related to mucocin.[4,6] The stereocontrolled synthesis of this THP ring represents one of the challenges of a total synthesis of jimenezin. Takahashi[3] used a chiral pool approach from galactono-1,5-lactone to solve the THP problem, whereas Lee[5] applied a Samarium iodide-mediated radical cyclization in his synthesis. Our synthetic plan is shown in Scheme 1. Three CC disconnections transformed the synthetic target into three building blocks, **1**, **2**, and **3**. The chiral pool was intended as a source for the stereocenters

Scheme 1. Retrosynthetic Analysis



(1) For recent reviews on annonaceous acetogenins: (a) Bermejo, A.; Figadère, B.; Zafra-Polo, M.-C.; Barrachina, I.; Estornell, E.; Cortes, D. *Nat. Prod. Rep.* **2005**, *22*, 269. (b) Allali, F. Q. 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) Takahashi, S.; Maeda, K.; Hirota, S.; Nakata, T. *Org. Lett.* **1999**, *1*, 2025.

(4) For mucocin syntheses, see: (a) Neogi, P.; Doundoulakis, T.; Yazbak, A.; Sinha, Sa. C.; Sinha, Su. C.; Keinan, E. *J. Am. Chem. Soc.* **1998**, *120*, 11279. (b) Bäurle, S.; Hoppen, S.; Koert, U. *Angew. Chem., Int. Ed.* **1999**, *38*, 1263. (c) Takahashi, S.; Nakata, T. *J. Org. Chem.* **2002**, *67*, 5739 and references therein. (d) Takahashi, S.; Kubota, A.; Nakata, T. *Angew. Chem., Int. Ed.* **2002**, *41*, 4751. (e) Evans, P. A.; Cui, J.; Gharpure, S. J.; Polosukhin, A.; Zhang, H. *J. Am. Chem. Soc.* **2003**, *125*, 14702. (f) Zhu, L.; Mootoo, D. R. *Org. Biomol. Chem.* **2005**, *3*, 2750. (g) Crimmins, M. T.; Zhang, Y.; Diaz, F. A. *Org. Lett.* **2006**, *8*, 2369.

(5) Hwang, C. H.; Keum, G.; Sohn, K. I.; Lee, D. H.; Lee, E. *Tetrahedron Lett.* **2005**, *46*, 6621.

(6) Hoppen, S.; Bäurle, S.; Koert, U. *Chem.−Eur. J.* **2000**, *6*, 2382.

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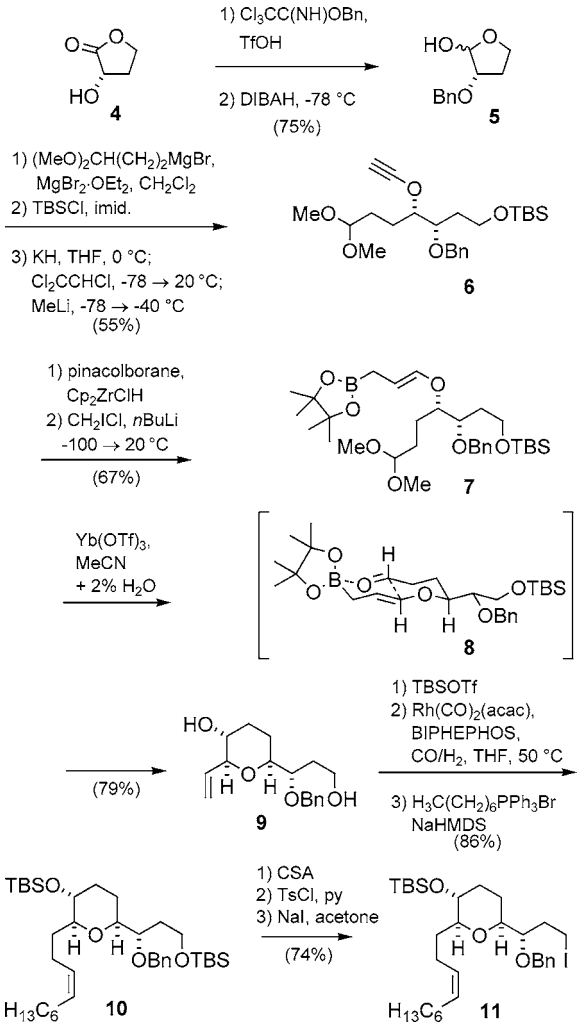
C19 (malic acid), C15 (glycidol), and C36 (propene oxide). The C4 stereocenter is accessible via known aldehyde **3** with 97% ee.[6] Stereocenters C16, C20, C23, and C24 remain as a task in stereoselective synthesis.

The generation of (*E*)-γ-alkoxyallylboronates and their intramolecular addition to aldehydes provide a highly stereocontrolled entry into substituted THP rings.[7,8] Here, we report on the successful use of this intramolecular allylboration in a total synthesis of jimenezin.

The synthesis of the THP ring is outlined in Scheme 2. The starting point was the α-hydroxy lactone **4**[9] which was

Scheme 2. Synthesis of the THP Ring



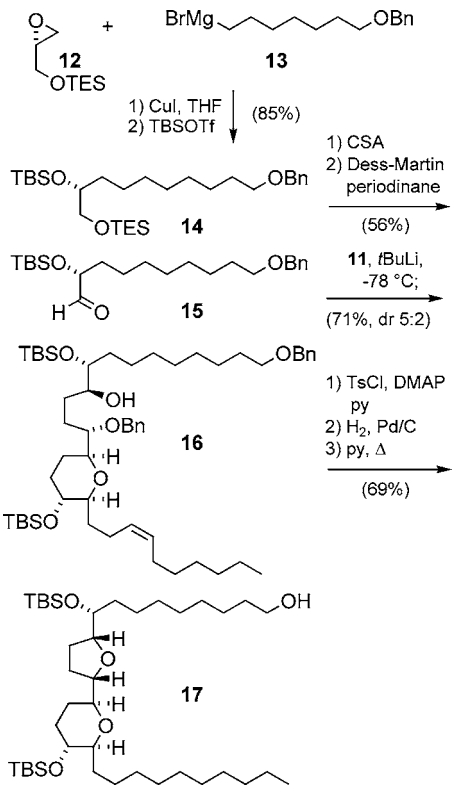
benzylated and subsequently reduced to the lactol **5**. Addition of 3 equiv of $(MeO)_2CH(CH_2)_2MgBr$ prepared in THF[10] to **5** dissolved in CH_2Cl_2 in the presence of 1.1 equiv of $MgBr_2$ gave the corresponding diol with a diastereoselectivity of 99:1. After TBS protection of the primary OH group, the remaining secondary hydroxy function was transformed into the ynol ether **6** following Greene's procedure.[11] The triple bond in **6** was converted by a zirconium-mediated hydroboration[12] into an *E*-vinyl boronate, which was homologized into the *E*-allyl boronate **7** by treatment with chloromethyllithium.[7,13]

With **7** in hand, the stage was set for the intramolecular allylboration provided that conditions were found to transform the acetal in **7** into an aldehyde function without side reactions at the sensitive allylboronate (**7** → **8** → **9**). A screening of several deprotection conditions revealed that $LiBF_4$[14] or $Yb(OTf)_3$[15] in acetonitrile with 2% water led to the desired allylboration product **9**. Unexpectedly, the reaction was associated with the desilylation of the primary TBS ether. A chairlike transition state of type **8** with all-equatorial substituents can explain the exclusive formation of the desired stereoisomer.

With the successful assembly of the THP ring, the C25−34 aliphatic side chain was addressed next. After TBS protection, the hydroformylation of the terminal alkene **9** with the reliable $Rh(CO)_2$acac/BIPHEPHOS catalyst[16] led to the corresponding aldehyde, which was subsequently transformed into the alkene **10** by a Wittig olefination. Cleavage of the primary TBS ether and conversion of the alcohol into an iodide led to compound **11**.

The attachment of the THF ring to the THP fragment required the preparation of the aldehyde **15** (Scheme 3). To this end, TES-protected (*S*)-glycidol **12**[17] was allowed to react with the Grignard reagent **13**[18] to produce the corresponding

Scheme 3. Synthesis of the THF Ring



(7) Hoffmann, R. W.; Hense, A.; Münster, I.; Krüger, J.; Brückner, D.; Gerusz, V. ACS Symposium Series 783; American Chemical Society: Washington, DC, 2001; p 160.

(8) Hoffmann, R. W.; Krüger, J.; Brückner, D. *New J. Chem.* **2001**, *25*, 102.

(9) Schinzer, D.; Bauer, A.; Schieber, J. *Chem.−Eur. J.* **1999**, *5*, 2492.

(10) Molander, G. A.; Losada, C. P. *Tetrahedron* **1998**, *54*, 5819.

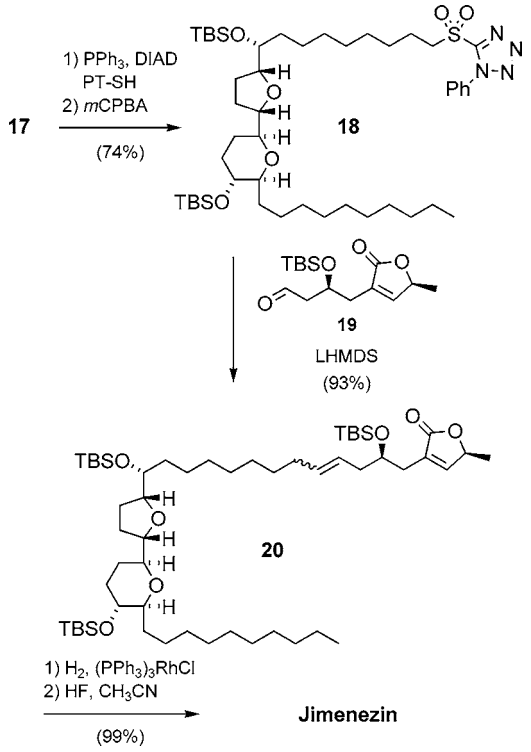
secondary alcohol which was TBS protected to yield compound **14**. After a selective TES deprotection, a Dess−Martin oxidation of the resulting alcohol gave the aldehyde **15**.

An iodine−lithium exchange reaction of **11** gave the corresponding organolithium compound which added to the aldehyde **15** with a modest Felkin−Anh selectivity of 5:2. The desired stereoisomer **16** was obtained in 53% yield after chromatographic separation. Tosylation of the secondary hydroxy group in **16** opened the THF ring-closure sequence. The following hydrogenation cleaved two benzyl ethers and hydrogenated the double bond in the C25−34 side chain. Refluxing the product of this sequence in pyridine initiated the intramolecular Williamson reaction to produce compound **17** in quantitative yield.

Having completed the synthesis of the THP−THF substructure, we turned our attention to the final part of the synthesis, the attachment of the butenolide fragment (Scheme 4). At first, the alcohol **17** was converted into the 1-phenyl-1*H*-tetrazol-5-yl (PT) sulfone **18**. A Julia−Kocienski olefination[19] of the sulfone **18** with the aldehyde **19**[6] gave the alkene **20** as an inseparable *E/Z*-mixture. A chemoselective hydrogenation of the isolated double bond in **20** using Wilkinson's catalyst[20] led to tris-TBS-protected jimenezin. Cleavage of all three silyl ethers with HF in acetonitrile provided (−)-jimenezin ($[\alpha]_D = -10.4$, $c = 0.75$ in MeOH) which was found to be identical to the natural product with respect to the spectroscopic data.

In summary, the enantioselective synthesis of (−)-jimenezin has been completed in 3.8% yield for the longest linear sequence of 24 steps starting from commercially available (*S*)-glycidol. Our strategy highlights the intramolecular allylboration as a highly stereocontrolled access to the THP part of jimenezin.

Scheme 4. Attachment of the Butenolide



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Supporting Information Available: Experimental procedures and analytical data for all new compounds and synthetic (−)-jimenezin. This material is available free of charge via the Internet at http://pubs.acs.org.

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(11) Moyano, A.; Charbonnier, F.; Greene, A. E. *J. Org. Chem.* **1987**, *52*, 2919.
(12) Pereira, S.; Srebnik, M. *Organometallics* **1995**, *14*, 3127.
(13) Sadhu, K. M.; Matteson, D. S. *Organometallics* **1985**, *4*, 1687.
(14) Lipshutz, B. H.; Harvey, D. F. *Synth. Commun.* **1982**, *12*, 267.
(15) Inanga, J.; Yokoyama, Y.; Hanamoto, T. *Tetrahedron Lett.* **1993**, *34*, 2791.
(16) Ojima, I.; Vidal, E. S. *J. Org. Chem.* **1998**, *63*, 7999.
(17) Mori, Y.; Asai, M.; Okumura, A.; Furukawa, H. *Tetrahedron* **1995**, *51*, 5299.
(18) The corresponding bromide is described in: Yang, L.-M.; Huang, L.-F.; Luh, T.-Y. *Org. Lett.* **2004**, *6*, 1461.
(19) Blakemore, P. R.; Cole, W. J.; Kocienski, P. J.; Morley, A. *Synlett* **1998**, 26.
(20) Avedissian, H.; Sinha, S. C.; Yazbak, A.; Sinha, A.; Neogi, P.; Sinha, S. C.; Keinan, E. *J. Org. Chem.* **2000**, *65*, 6035.