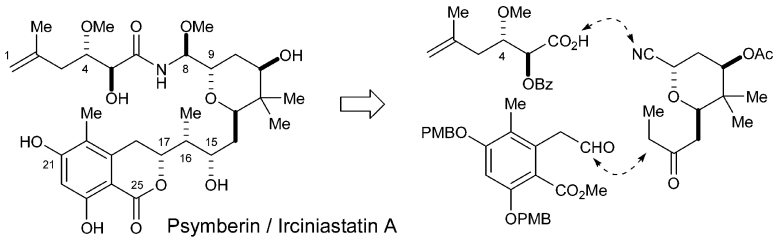
Communication

Synthesis and Complete Stereochemical Assignment of Psymberin/Irciniastatin A

Xin Jiang, Jorge Garca-Fortanet, and Jef K. De Brabander

J. Am. Chem. Soc., **2005**, 127 (32), 11254-11255• DOI: 10.1021/ja0537068 • Publication Date (Web): 21 July 2005



More About This Article

Additional resources and features associated with this article are available within the HTML version:

- Supporting Information
- Links to the 11 articles that cite this article, as of the time of this article download
- Access to high resolution figures
- Links to articles and content related to this article
- Copyright permission to reproduce figures and/or text from this article

View the Full Text HTML

J|A|C|S
COMMUNICATIONS

Published on Web 07/21/2005

Synthesis and Complete Stereochemical Assignment of Psymberin/Irciniastatin A

Xin Jiang, Jorge García-Fortanet, and Jef K. De Brabander*

Department of Biochemistry, The University of Texas Southwestern Medical Center at Dallas, 5323 Harry Hines Boulevard, Dallas, Texas 75390-9038

Received June 6, 2005; E-mail: jdebra@biochem.swmed.edu

In 2004, two groups led by Pettit and Crews independently disclosed the isolation of constitutionally identical cytotoxins, irciniastatin A[1] and psymberin[2] from the marine sponges *Ircinia ramose* and *Psammocinia* sp., respectively. NMR and chiroptical data substantiated the assigned relative and absolute configuration for psymberin shown in **1**, save for the undefined configuration at C_4.[2] The relative stereochemistry of irciniastatin A (**2**) was only resolved for the C_8-C_{13} aminal fragment.[1] Interestingly, the C_8-aminal configuration in irciniastatin A was opposite to the corresponding center assigned for psymberin.[3] Psymberin/irciniastatin most closely resemble the pederin family of natural products (e.g., **3** and **4**, see Figure 1).[4,5] However, a constellation of unique structural attributes (dihydroisocoumarin and acyclic left half)[6] and unprecedented tumor cell selectivity[1,2] indicate that **1**/**2** might be functionally distinct from the pederin family of protein synthesis inhibitors. Herein, we communicate a short, highly convergent synthesis of **1**/**2** that (1) resolves the stereochemical ambiguities and (2) provides material and synthetic avenues for future biochemical and preclinical investigation.

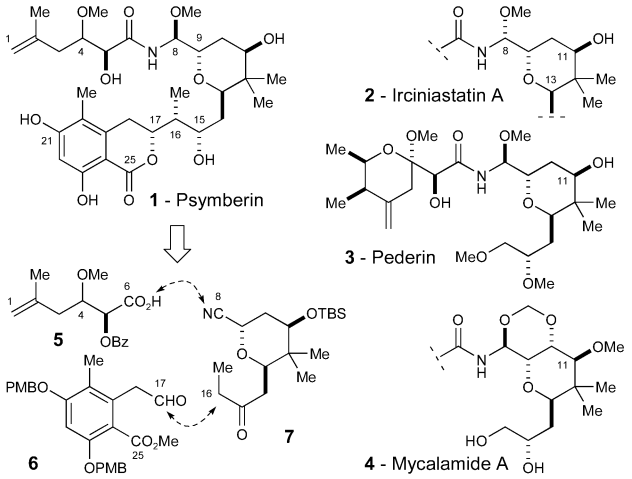
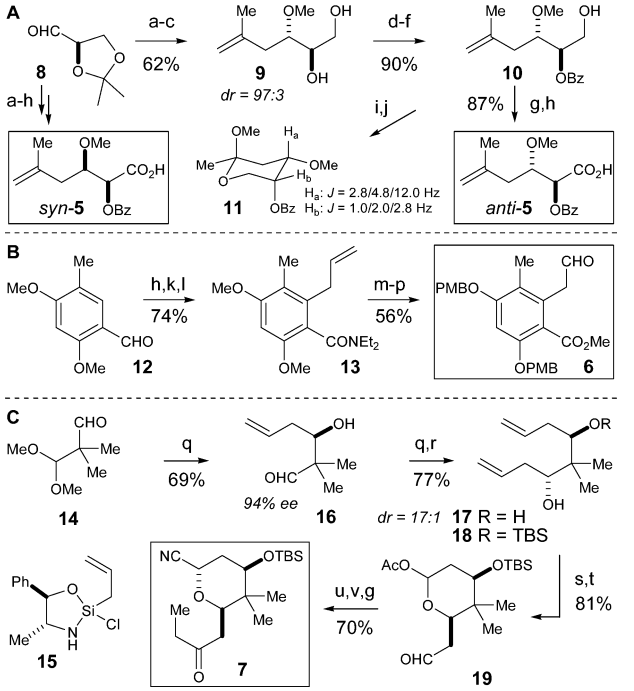


Figure 1. Psymberin, irciniastatins, and related natural products.

Our approach to **1**/**2** envisioned the coupling of fragments **6**−**7** via carbon-bond formation to control stereochemistry of the $C_{15}-C_{17}$ stereotriad, followed by appending carboxylic acid **5**. Given the unknown stereochemistry at C_4, we prepared both *anti*- and *syn*-**5** (Scheme 1A).[7] Asymmetric methallylation[8] of aldehyde **8** followed by methylation and acetonide hydrolysis provided diol **9**, to be converted to benzoate **10** via silylation, benzoylation, and desilylation. The relative stereochemistry was confirmed through ^{1}H NMR analysis of acetal **11**. Finally, a two-step oxidation of alcohol **10** yielded *anti*-**5** (8 steps, 49% from **8**). *Syn*-**5** was prepared from **8**, starting with antipodal methallyl borane reagent.

The aryl fragment **6** was obtained in 7 steps (41% overall yield, Scheme 1B) from known aldehyde **12**[9] via: (1) oxidation/amidation

Scheme 1. Synthesis of Fragments **5**−**7**[a]



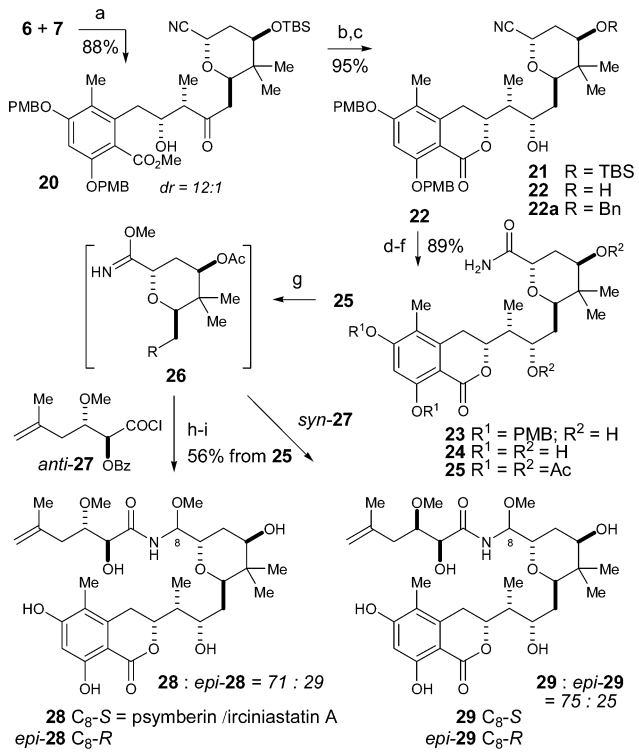
[a] Reagents and conditions: (a) (−)-(Ipc)$_2$BOMe for the *anti*-**5** series and (+)-(Ipc)$_2$BOMe for the *syn*-**5** series, CH_2CMeCH_2Li, Et_2O, −78 °C; (b) NaH, MeI, THF; (c) PPTS, MeOH/H_2O, 50 °C; (d) TBSCl, imid, CH_2Cl_2; (e) BzCl, py; (f) aq 3 N HCl; (g) Dess−Martin periodinane, CH_2Cl_2; (h) NaH_2PO_4, $NaClO_2$, 2-methyl-2-butene, *t*-BuOH/H_2O; (i) O_3, CH_2Cl_2; Me_2S; (j) TsOH, $CH(OMe)_3$, MeOH; (k) $SOCl_2$, benzene; Et_2NH; (l) *sec*-BuLi, CuBr·SMe_2, allylBr, THF, −78 °C; (m) BBr_3, CH_2Cl_2, −78→25 °C; (n) Me_3OBF_4, CH_2Cl_2; Na_2CO_3, MeOH; (o) PMBCl, Bu_4NI, K_2CO_3, DMF, 80 °C; (p) cat. OsO_4, NMO, THF/H_2O; $NaIO_4$, aq MeOH (q) **15**, PhMe, −15 °C; (r) TBSOTf, 2,6-lutidine, CH_2Cl_2, 0 °C; (s) O_3, CH_2Cl_2; Ph_3P; (t) Ac_2O, Et_3N, DMAP, CH_2Cl_2, 0 °C; (u) *N*,*N*′-(1*R*,2*R*-cyclohexane-1,2-diyl)bis(trifluoromethanesulfonamide), Ti(O^{i}Pr)$_4$, Et_2Zn, PhMe, −15 °C; (v) TMSCN, ZnI_2, MeCN, 0 °C; aq 1 N HCl.

(CHO → $CONEt_2$); (2) *ortho*-metalation/allylation (→ **13**);[10] (3) BBr_3-mediated methyl ether deprotection; (4) methyl ester formation using a protocol reported by Keck;[11] (5) phenol protection; and (6) oxidative double bond cleavage (→ **6**).

The synthesis of central fragment **7** commences with the preparation of C_2-symmetrical diol **17** via allylation of monoprotected dialdehyde **14**[12] using Leighton's silane reagent **15**,[13] followed by a second allylation of aldehyde **16**, which was unmasked during the workup (Scheme 1C). Monosilylation (**18**) and ozonolysis destroys the symmetry and provides a lactol (trapped as acetate **19**) that differentiates the chain termini. Addition of diethylzinc using conditions reported by Kobayashi[14] gave a secondary alcohol, which was oxidized to ketone **7** after acetate displacement with TMSCN (8 steps, 30% from **14**).[5f]

10.1021/ja0537068 CCC: $30.25

Scheme 2. Synthesis of 4 Psymberin/Irciniastatin Diastereomers[a]



[a] Reagents and conditions: (a) $PhBCl_2$, DIPEA, CH_2Cl_2, −78 °C; (b) catecholborane, THF, 0 °C; aq 2 N NaOH; (c) TBAF, THF; (d) cat. $[PtH(PMe_2OH)(PMe_2O)_2H]$, $EtOH/H_2O$, 80 °C; (e) 10% Pd/C, H_2, EtOH; (f) Ac_2O, py; (g) Me_3OBF_4, polyvinylpyridine, CH_2Cl_2; filter; (h) *anti*- or *syn*-**27**, $^iPr_2NEt$, PhMe, 40 °C; then add $NaBH_4$, EtOH, 0 °C; (i) LiOH, MeOH.

With the three fragments in hand, the foundation was laid to explore their union via a double convergent coupling strategy (Scheme 2). Treatment of the (*Z*)-chlorophenylboryl enolate derived from **7** with aldehyde **6** yielded one major *syn*-aldol product **20** predicted from enolate facial bias imposed by the β-alkoxy substituent.[15] Reduction of **20** with catecholborane provided lactone **21** directly after basic workup,[16,17] followed by silyl deprotection to alcohol **22**. Crystallographic analysis of crystals obtained from benzyl ether **22a** fully confirmed the assigned structure and relative stereochemistry.[18] Hydrolysis of the nitrile group in **22** with the platinum(II) catalyst of Ghaffar and Parkins[19] yielded amide **23** in >95% yield. Hydrogenolysis (**24**) and peracetylation furnished tetraacetate **25** (>90%, 2 steps).

We had planned to acylate imidate **26** and intercept the incipient acylimidate with a reducing agent but were unable to prepare and handle imidates related to and including **26** using Me_3OBF_4 as reported.[20] Extensive experimentation identified a uniquely beneficial effect of adding polyvinylpyridine during the imidate formation with Me_3OBF_4 (soluble pyridine or other amine bases could not substitute for immobilized pyridine). After TLC analysis indicated complete conversion, the reaction mixture was filtered and concentrated, followed by dissolving the crude imidate **26** in toluene and addition of Hunig's base and acid chloride **27** (from **5** with $(COCl)_2$). The mixture was heated to 40 °C for 2 h, cooled to 0 °C, and treated with an ethanolic sodium borohydride solution. After workup, the crude compounds were saponified to afford a separable mixture of **28** and *epi*-**28** (71:29 ratio) with acid chloride *anti*-**27** (56% from **25**), or an inseparable mixture of **29** and *epi*-**29** (75:25 ratio) with *syn*-**27** (50%). Of the four diastereomers, only spectral data (^1H, ^{13}C) recorded for **28** corresponded exactly with those of psymberin[2] (CD_3OD) and irciniastatin A[1] ($CDCl_3$). The rotation of synthetic **28** ($[\alpha]_D = +25.2$, *c* 0.11, MeOH) agreed with those reported for psymberin ($[\alpha]_D = +29$, *c* 0.02, MeOH)[2] and irciniastatin A ($[\alpha]_D = +24.4$, *c* 0.55, MeOH).[1]

In summary, we prepared compounds with structures relevant to those proposed for psymberin/irciniastatin, leading to a complete stereochemical assignment and the notion that psymberin and irciniastatin A are identical compounds represented by **28**. Starting from fragments **5**−**7** (7−8 steps each, 30−49% overall yield) the synthesis of **28** was completed in an additional 9 steps and 30% yield (17 steps, 8.9% overall from **14**).

Acknowledgment. This work was supported by the National Institutes of Health (CA 90349), the Robert A. Welch Foundation, and Merck Research Laboratories. We thank Dr. Radha Akella for crystallographic analysis of compound **22a**. J. G.-F. thanks the Spanish Ministry of Education and Science for a FPU fellowship. J. K. De Brabander is a fellow of the Alfred P. Sloan Foundation.

Supporting Information Available: Experimental procedures, characterization data, copies of NMR spectra, and X-ray crystal structure data for compound **22a** (PDF, CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

References

(1) Pettit, G. R.; Xu, J. P.; Chapuis, J. C.; Pettit, R. K.; Tackett, L. P.; Doubek, D. L.; Hooper, J. N. A.; Schmidt, J. M. *J. Med. Chem.* **2004**, *47*, 1149. A C_{11}-oxo analogue irciniastatin B was also isolated.

(2) Cichewicz, R. H.; Valeriote, F. A.; Crews, P. *Org. Lett.* **2004**, *6*, 1951.

(3) The published spectral data, acquired in different NMR solvents, were insufficient to decisively establish a homomeric or diastereomeric correspondence between the two natural products.

(4) (a) For a review, see: Narquizian, R.; Kocienski, P. J. In *The Role of Natural products in Drug Discovery*; Mulzer, J., Bohlmann, R., Eds.; Ernst Schering Research Foundation Workshop 32; Springer: New York, 2000; pp 25−56. (b) For a complete listing of structures of pederin related natural products including references, see the Supporting Information of ref 2.

(5) For selected examples of total syntheses, see ref 4a and: (a) Kocienski, P.; Narquizian, R.; Raubo, P.; Smith, C.; Farrugia, L. J.; Muir, K.; Boyle, F. T. *J. Chem. Soc., Perkin Trans. 1* **2000**, 2357. (b) Roush, W. R.; Pfeifer, L. A. *Org. Lett.* **2000**, *2*, 859. (c) Takemura, T.; Nishii, Y.; Takahashi, S.; Kobayashi, J.; Nakata, T. *Tetrahedron* **2002**, *58*, 6359. (d) Trost, B. M.; Yang, H.; Probst, G. D. *J. Am. Chem. Soc.* **2004**, *126*, 48. (e) Sohn, J.-H.; Waizumi, N.; Zhong, H. M.; Rawal, V. H. *J. Am. Chem. Soc.* **2005**, *127*, 7290. (f) Nakata, T.; Nagao, S.; Mori, N.; Oishi, T. *Tetrahedron Lett.* **1985**, *26*, 6461.

(6) Without exception, all ~35 members of the pederin family display an identical cyclic left half pederate side chain; none of them display a dihydroisocoumarin unit in the bottom half.

(7) During review of this manuscript, the synthesis and configuration of *syn* and *anti* models of the psymberin side chain was reported: Kiren, S.; Williams, L. J. *Org. Lett.* **2005**, *7*, 2905.

(8) Jadhav, P. K.; Bhat, K. S.; Perumal, P. T.; Brown, H. C. *J. Org. Chem.* **1986**, *51*, 432.

(9) Lambooy, J. P. *J. Am. Chem. Soc.* **1956**, *78*, 771.

(10) (a) Kamila, S.; Mukherjee, C.; Mondal, S. S.; De, A. *Tetrahedron* **2003**, *59*, 1339. (b) Casas, R.; Cavé, C.; d'Angelo, J. *Tetrahedron Lett.* **1995**, *36*, 1039.

(11) Keck, G. E.; McLaws, M. D.; Wager, T. T. *Tetrahedron* **2000**, *56*, 9875.

(12) Johnson, P. R.; White, J. D. *J. Org. Chem.* **1984**, *49*, 4424.

(13) Kubota, K.; Leighton, J. L. *Angew. Chem., Int. Ed.* **2003**, *42*, 946.

(14) Takahashi, H.; Kawakita, T.; Ohno, M.; Yoshioka, M.; Kobayashi, S. *Tetrahedron* **1992**, *48*, 5691.

(15) Evans, D. A.; Calter, M. A. *Tetrahedron Lett.* **1993**, *34*, 6871.

(16) Evans, D. A.; Hoveyda, A. H. *J. Org. Chem.* **1990**, *55*, 5190.

(17) Workup with aq Na,K-tartrate allowed the diol to be isolated for derivatization as an acetonide derivative, confirming the relative 1,2-*syn*, 2,3-*syn* stereochemistry at C_{15}−C_{17}.[18]

(18) See the Supporting Information.

(19) (a) Ghaffar, T.; Parkins, A. W. *Tetrahedron Lett.* **1995**, *36*, 8657. (b) Ghaffar, T.; Parkins, A. W. *J. Mol. Catal. A* **2000**, *160*, 249. (c) For a nice application, see: Herzon, S. B.; Myers, A. G. *J. Am. Chem. Soc.* **2005**, *127*, 5342.

(20) This approach has been used for the synthesis of pederin; see refs 4a and 5c and references therein.

(21) We thank Profs. Cherry Herald and George Pettit for kindly providing NMR spectra of irciniastatin A.

JA0537068