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From Silphinenes to Penifulvins: A Biomimetic Approach to Penifulvins B and C

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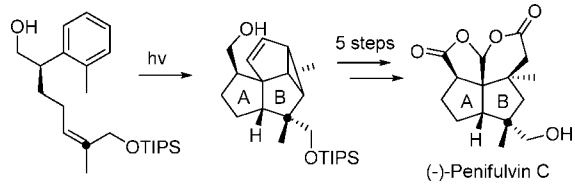
ABSTRACT



The biomimetic total synthesis of penifulvins B and C uses a *meta*-photocycloaddition as a key step which gives rapid access to the fenestrane-type carboskeleton with control of an onring quaternary stereocenter. The route is concise, stereocontrolled, scaleable, and flexibile and requires only one protecting group.

Recently, Gloer et al. described the isolation of novel sesquiterpenoids named penifulvin A, and B, C (**1**−**3**), as well as 12-hydroxy-silphinen-15-oic acid **4**[1] from the fungus *Penicillium griseofulvum* (syn. *P. patulum* Bain.; *P. urticae* bain.), which were obtained from white mycelia growth on dead hardwood branches collected in Hawaiian forests. Among these metabolites, **1** shows significant antiinsectan activity in assays against the fall armyworm *Spodoptera frugiperda*.[2] The overall structures of **1**−**3** and **4** were secured (except for the absolute configurations) by X-ray crystallographic analysis and revealed a highly complex dioxa[5.5.5.6]fenestrane structure in which four rings share a central quaternary carbon atom (Figure 1). **1** and **4** contain five stereocenters, whereas **2** and **3** have six of them, three of which are quaternary.

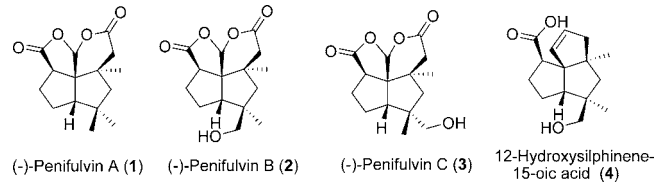


Figure 1. Structures of penifulvins A−C and 12-hydroxysilphinene-15-oic acid.

Due to this unusually dense array of stereogenic carbons, these compounds represent attractive targets for total synthesis. Recently, we disclosed the synthesis of penifulvin A (**1**).[3] Herein we wish to report two enantioselective total syntheses of penifulvins B (**2**) and C (**3**) by means of a *meta*-photocycloaddition[4,5] (Scheme 1).

Our synthesis was guided by two major interests. First we wanted to corroborate our biosynthetic hypothesis for

(1) (a) Penifulvin A: Shim, H. S.; Swenson, D. C.; Gloer, J. B; Dowd, P. F; Wicklow, D. T. *Org. Lett.* **2006**, *8*, 1225–1228. (b) Penifulvins B and C, 12-hydroxy-silphinen-15-oic acid: Shim, H. S.; Gloer, J. B.; Wicklow, D. T *J. Nat. Prod.* **2006**, *69*, 1601–1605. In this paper also, penifulvins D and E were described.

(2) See for instance: Capinera, J. L. Fall armyworm. Homepage of the University of Florida Institute of Agriculture and Consumer Services, Division of Plant Industry, and University of Florida Institute of Food and Agricultural Sciences, Department of Entymology and Nematology, July 1999.

(3) Gaich, T.; Mulzer, J. *J. Am. Chem. Soc.* **2009**, *131*, 452–453.

(4) (a) Bryce-Smith, D.; Gilbert, A.; Orger, B. H. *Chem. Commun.* **1966**, 512–514. (b) Wilzbach, K. E.; Kaplan, L. *J. Am. Chem. Soc.* **1966**, *88*, 2066–2067. (c) Morrison, H. A.; Ferree, W. I., Jr. *Chem. Commun.* **1969**, 268–269.

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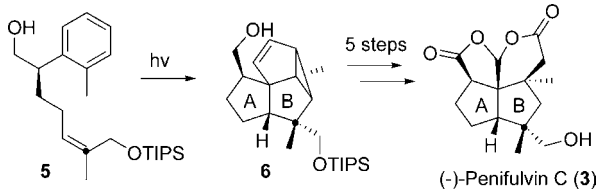
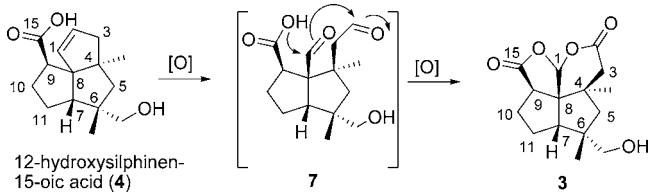
Scheme 1. *meta*-Photocycloaddition as a Key Step for the Formation of the Carbocyclic Core of the Penifulvins



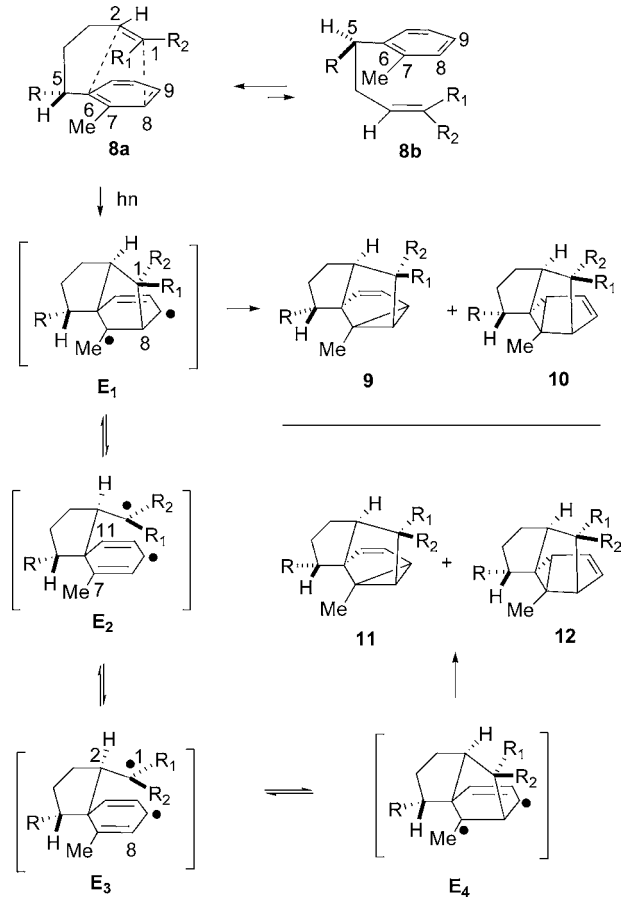
the oxidative formation of the dioxa[5.5.5.6]fenestrane structure type (e.g., **3**) from the well-known silphinene carbon skeleton (**4**) (Scheme 2).[6]

Scheme 2. Biomimetic Oxidative Cyclization Cascade



As penifulvins B and C are epimers regarding the C-6 quaternary carbon center, they provide us with a second interesting opportunity, the testing of the suprafacial selectivity of the *meta*-photocycloaddition, which is the key transformation in our synthesis (Scheme 3). If we postulate that the photoreaction forms two σ-bonds (C1−C8 and C2−C6) to generate an exciplex E_1 first, the C1−C8 bond might be reopened in the next step to form a highly stabilized cyclohexadienyl-*tert*-alkyl-diradical species E_2 which undergoes 1,2-rotation to E_3 and recloses the C1−C8 bond to E_4. It thus depends on the relative rates of C7−C9/C7−C11 ring closure (formation of a highly strained cyclopropyl system) vs C1−C8 ring opening (considerable strain release) whether regioisomers **9**/**10** alone or additionally **11**/**12** are obtained. Direct ring closures of E_2 and E_3 are unlikely due to high ring strain. Similarly, a C1−C7 or C1−C11 combination in E_2/E_3 would create a highly strained cyclobutane ring. Another issue is the equilibrium between the

Scheme 3. Stereochemical Implications of the *meta*-Photocycloaddition



two potentially reactive conformers **8a**/**8b**. The $A^{1,3}$-strain[7] between the 5-*R*-group and the 7-Me **8b** is strongly disfavored, so **8a** may be assumed as the preferred conformer, which directs the cycloaddition onto the top-face of the benzenoid ring.

We thus prepared the trisubstituted *E*/*Z*-isomers **15** (for **2**) and **5** (for **3**) via Myers alkylation[8] (Scheme 4) and submitted them to photocyclization. To our delight, the photoreaction proceeded exclusively with suprafacial stereochemistry (Scheme 5). Hence **19** and **6** were formed from the irradiation of *Z*-isomer **5**, and **17** and **18** were formed from *E*-isomer **15**. Both cyclizations proceeded via *exo* transition states.[9] The synthesis was completed by separation

(5) For pioneering applications in natural product synthesis, see: (a) Wender, P. A.; Dreyer, G. B *Tetrahedron* **1981**, *37*, 4445–4450. (b) Wender, P. A.; Dreyer, G. B. *J. Am. Chem. Soc.* **1982**, *104*, 5805–5807. (c) Wender, P. A.; Ternansky, R. J. *Tetrahedron Lett.* **1985**, *26*, 2625–2628. (d) Wender, P. A.; Fisher, K. *Tetrahedron Lett.* **1986**, *27*, 1857–1860. (e) Wender, P. A.; von Geldern, T. W.; Levine, B. H. *J. Am. Chem. Soc.* **1988**, *110*, 4858–4860. (f) Wender, P. A.; Singh, S. K. *Tetrahedron Lett.* **1990**, *31*, 2517–2520. (g) For a comprehensive review, see: Chappell, D.; Russell, A. T. *Org. Biomol. Chem.* **2006**, *4*, 4409–4430.

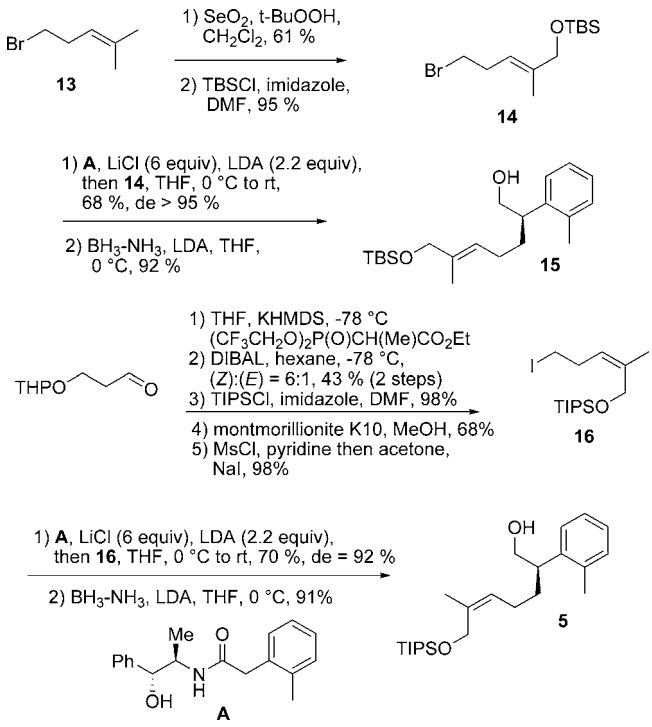
(6) For biooxidative C−C bond cleavages, see for instance: (a) Thibaut, D.; Debussche, L.; Blanche, F. *Proc. Natl. Acad. Sci. U.S.A.* **1990**, *87*, 8800–8804. (b) Sheng, D.; Ballou, D. P.; Massey, V. *Biochemistry* **2001**, *40*, 11156–11167. (c) Mihovilovic, M. D.; Müller, B.; Stanetty, P. *Eur. J. Org. Chem.* **2002**, 3711–3730.

(7) Hoffmann, R. W. *Chem. Rev.* **1989**, *89*, 1841–1860.

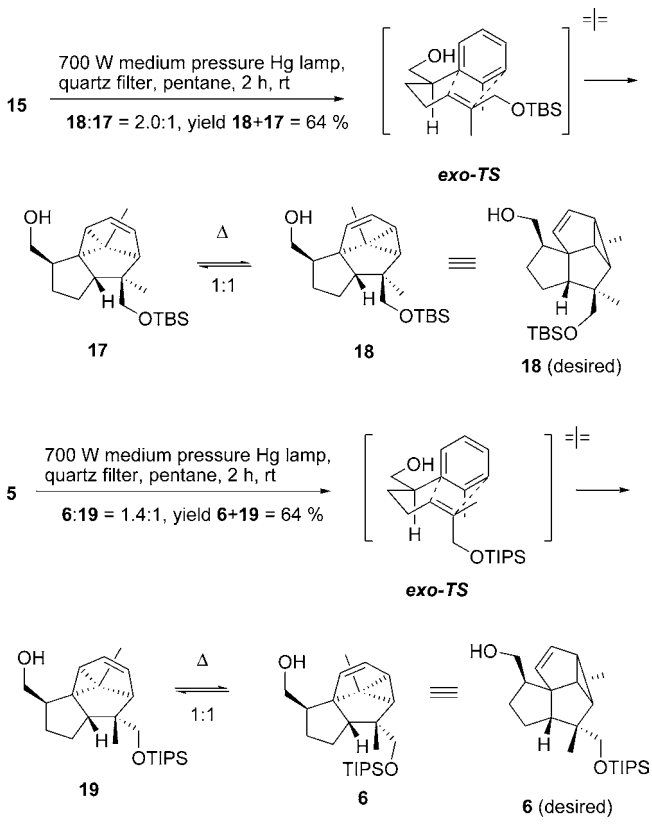
(8) Myers, A. G.; Yang, B. H.; Chen, H.; McKinstry, L.; Kopecky, D. J.; Gleason, J. L. *J. Am. Chem. Soc.* **1997**, *119*, 6496–6511.

(9) Intermolecular additions prefer *endo*-selectivity: (a) Srinivasan, R.; Merritt, V. Y.; Subrahmanyam, G. *Tetrahedron Lett.* **1974**, *32*, 2715–2718. (b) Srinivasan, R.; Ors, J. A. *Chem. Phys. Lett.* **1976**, *42*, 506–508. (c) Ors, J. A.; Srinivasan, R. *J. Org. Chem.* **1977**, *42*, 1321–1327. (d) Jans, A. W. H.; Van Dijk-Knepper, J. J.; Cornelisse, J. *Recl. Trav. Chim. Pays-Bas* **1982**, *101*, 275–276. (e) de Vaal, P.; Osselton, E. M.; Krijnen, E. S.; Lodder, G.; Cornelisse, J *Recl. Trav. Chim. Pays-Bas* **1988**, *107*, 407–411. For intramolecular reactions, both *endo*- and *exo*-selectivity have been observed: Ferree, W. I.; Grutzner, J. B.; Morrison, H. *J. Am. Chem. Soc.* **1971**, *93*, 5502–5512. See also a recent paper that reports high regioselectivity: Morales, R. C.; Lopez-Mosquera, A.; Roper, N.; Jenkins, P. R.; Fawcett, J.; Garcia, M. D. *Photochem. Photobiol. Sci.* **2006**, *5*, 649–652.

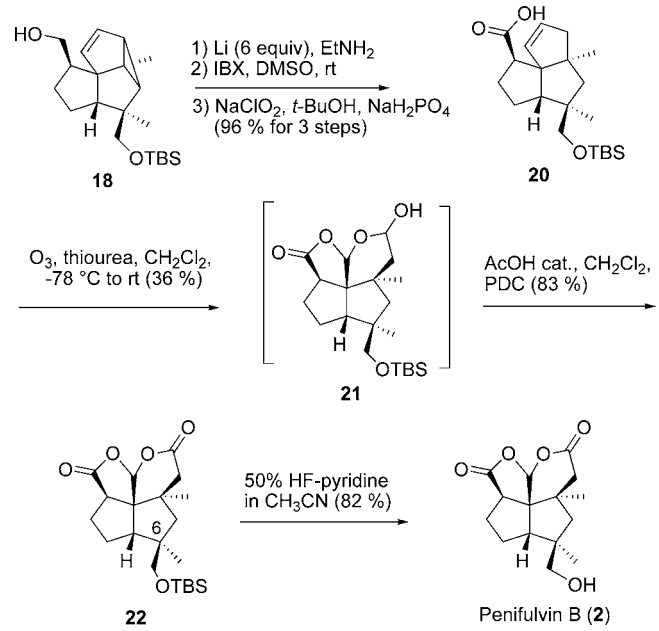
Scheme 4. Synthesis of the *meta*-Photocycloaddition Precursors **15** and **5** of Penifulvins B and C



Scheme 5. *meta*-Photocycloaddition of **15** and **5**

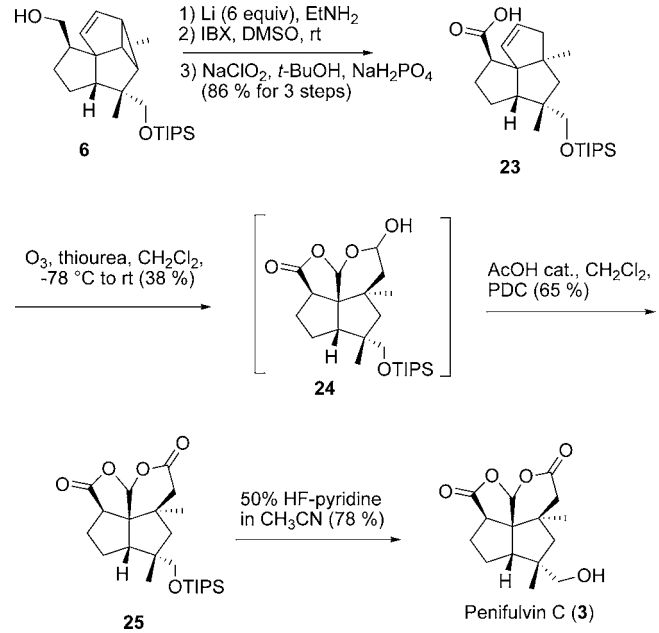


Scheme 6. Completion of the Synthesis of **2**



of the regioisomeric pairs (**17**/**18** and **19**/**6**), which could be re-equilibrated via a thermal vinylcyclopropane−cyclopentene rearrarrangement[10] so that no material was lost. Next the cyclopropane ring in **18** was opened regioselectively under Birch-type conditions, and the primary alcohol was oxidized to carboxylic acid **20** (Scheme 6). Ozonolytic cleavage of the double bond converted **20** via a nonisolable dialdehyde into the hemiacylal **21**. Further oxidation to lactone **22** and

Scheme 7. Completion of the Synthesis of **3**



removal of the protective group furnished penifulvin B (**2**). An analogous sequence was used to transform **6** into **3** (Scheme 7). All analytical data of our synthetic samples of **2** and **3** matched those reported by Gloer.[1b]

Although all intermediates could be isolated and characterized, their ultimate purification proved difficult and was thus postponed to **22**/**25**, which were shown to be diastereomerically pure with respect to the crucial quaternary center at C6.

In conclusion, we have developed the first enantioselective total syntheses of penifulvins B and C (**2** and **3**). Both syntheses, which confirm the absolute configurations tentatively assigned previously,[1b] use only one protecting group and are concise, requiring 10 steps for **2** and 13 steps for **3**, respectively. The endgame supports our biosynthetic hypothesis, in which the silphinene carbon skeleton is converted into the dioxa[5.5.5.6]fenestrane ring system in a cascade oxidation. Additionally our findings exponentiate the synthetic value of the *meta*-photocycloaddition, because due to its suprafacial stereochemistry with respect to the olefin component the challenging problem of synthesizing stereogenic on-ring quaternary carbon centers[11] is reduced to selectively generating trisubstituted *E*/*Z* double bonds.[12]

Acknowledgment. We thank Hanspeter Kählig, Susanne Felsinger, and Lothar Brecker, all at University of Vienna, for NMR analysis

Supporting Information Available: Experimental data and analytical characterization for all new compounds provided. This material is available free of charge via the Internet at http://pubs.acs.org.

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(10) See, for instance: (a) Doering, W. v. E.; Lambert, J. B. *Tetrahedron* **1963**, *19*, 1989–94. (b) Mazzocchi, P. H.; Tamburin, H. J. *J. Am. Chem. Soc.* **1970**, *92*, 7220–7221. (c) Schneider, M.; Merz, I. *Tetrahedron Lett.* **1974**, *23*, 1995–1998. (d) Hudlicky, T.; Kutchan, T. M.; Naqvi, S. M. *Org. React.* **1985**, *33*, 247–335. (e) Buchert, M.; Reissig, H. U. *Liebigs Ann.* **1996**, 2007–2013. (f) Houk, K. N.; Nendel, M.; Wiest, O.; Storer, J. W. *J. Am. Chem. Soc.* **1997**, *119*, 10545–10546. (g) Baldwin, J. E.; Dunmire, D. A. *J. Org. Chem.* **2000**, *65*, 6791–6794. (h) Doubleday, C. *J. Phys. Chem. A* **2001**, *105*, 6333–6341.

(11) Reviews: Corey, E. J.; Guzman-Perez, A. *Angew. Chem., Int. Ed.* **1998**, *37*, 388–401. Christoffers, J.; Barto, A. *Quaternary Stereocenters*; Wiley-VCH: Weinheim, 2005. For some recent syntheses of chiral quaternary centers, see: (a) Adhikari, S.; Caille, S.; Hanbauer, M.; Ngo, V. X.; Overman, L. E. *Org. Lett.* **2005**, *7*, 2795–2797. (b) Sklute, G.; Marek, I. *J. Am. Chem. Soc.* **2006**, *128*, 4642–4649. (c) Sibi, M. P.; He, L. *Synlett* **2006**, 689–692. (d) Lee, K. S.; Brown, M. K.; Hird, A. W.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2006**, *128*, 7182–7184. (e) Martin, D.; Kehrli, S.; d'Augustin, M.; Clavier, H.; Mauduit, M.; Alexakis, A. *J. Am. Chem. Soc.* **2006**, *128*, 8416–8417. (f) Soorukram, D.; Knochel, P. *Org. Lett.* **2007**, *9*, 1021–1023, and references cited therein. (g) Nibbs, A. E.; Baize, A. L.; Herter, R. M. ; Scheidt, K. A. *Org. Lett.* **2009**, *11*, 4010–4013.

(12) General reviews: (a) Wittig-type olefination: KellyS. E. in *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon: Oxford, 1991; Vol. 1 (ed. Schreiber, S. L.), p 729. (b) sp^2-sp^3-coupling: Tamao, K. *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon: Oxford, 1991; Vol. 3 (ed. Pattenden, G.), p 435. (c) Claisen rearrarrangement: Ziegler, F. E. *Chem. Rev.* **1988**, *88*, 1423–1452. *The Claisen Rearrangement*; Hiersemann, M., Nubbemeyer, U., Eds.; Wiley-VCH: Weinheim, Germany, 2007; p 571. (d) For a recent overview of available methodology: Prantz, K.; Mulzer, J. *Angew. Chem., Int. Ed.* **2009**, *48*, 5030–5033.