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A Diverted Total Syntheses of Potent Cell Adhesion Inhibitor Peribysin E Analogues

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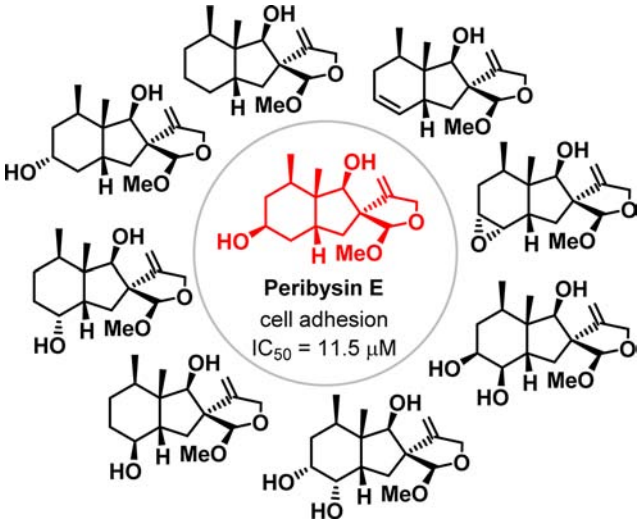
ABSTRACT



Preliminary results from a program aimed at the creation of a focused library of analogues around the natural product peribysin E, a potent biologically active and structurally fascinating molecule, are reported. The total synthesis of (±)-peribysin E was accomplished using a short route. Eight new analogues of the natural compound have been accomplished by means of "diverted total synthesis" in less than 10 steps. The present effort highlights protecting-group-free total syntheses and the shortest route to access these functionally embellished hydrindanes.

A group of natural products called peribysins (A−G) were isolated by Yamada's group from a strain of *Periconia byssoides* OUPS-N133 originally separated from the sea hare, *Aplysia kurodai*.[1] The structurally interesting natural products, especially peribysin E (**1**), attracted our attention toward developing anticancer and anti-inflammatory agents owing to its potent cell adhesion inhibitory activity (Figure 1).[2] It was claimed that the natural product (−)-peribysin E has shown more potent activity than the gold standard herbimycin **2** in the cell adhesion inhibition assay (Figure 1). Due to its attractive biological activity, coupled with intriguing structural features and scarcity of the material, compound **1** has already attracted the attention of groups such as Danishefsky and Sha. Danishefsky and co-workers achieved the first total synthesis of peribysin E which helped in reassigning the absolute configuration of the natural product. In their elegant synthesis, the Diels−Alder reaction followed by semipinacol-type ring contraction served to secure the stereochemistry of peribysin E (**1**).[3] In another interesting effort, Sha's group executed the synthesis of racemic peribysin E by using α-carbonyl radical cyclization as a key step.[4] Here, we disclose the synthesis of several novel analogues of peribysin E through "diverted total synthesis"[5] in less than 10 steps starting from readily accessible materials (Figure 1).

(1) Yamada, T.; Doi, M.; Miura, A.; Harada, W.; Hiramura, M.; Minoura, K.; Tanaka, R.; Numata, A. *J. Antibiot.* **2005**, *58*, 185.

(2) The cell adhesion inhibition was measured in leukemia HL-60 cells to human-umbilical-vein endothelial cells (HUVEC).

(3) Angeles, A. R.; Dorn, D. C.; Kou, C. A.; Morre, M. A. S.; Danishefsky, S. J. *Angew. Chem., Int. Ed.* **2007**, *46*, 1451. (b) Angeles, A. R.; Waters, S. P.; Danishefsky, S. J. *J. Am. Chem. Soc.* **2008**, *130*, 13765.

(4) Lee, H.-Y.; Sha, C.-K. *J. Org. Chem.* **2012**, *77*, 598.

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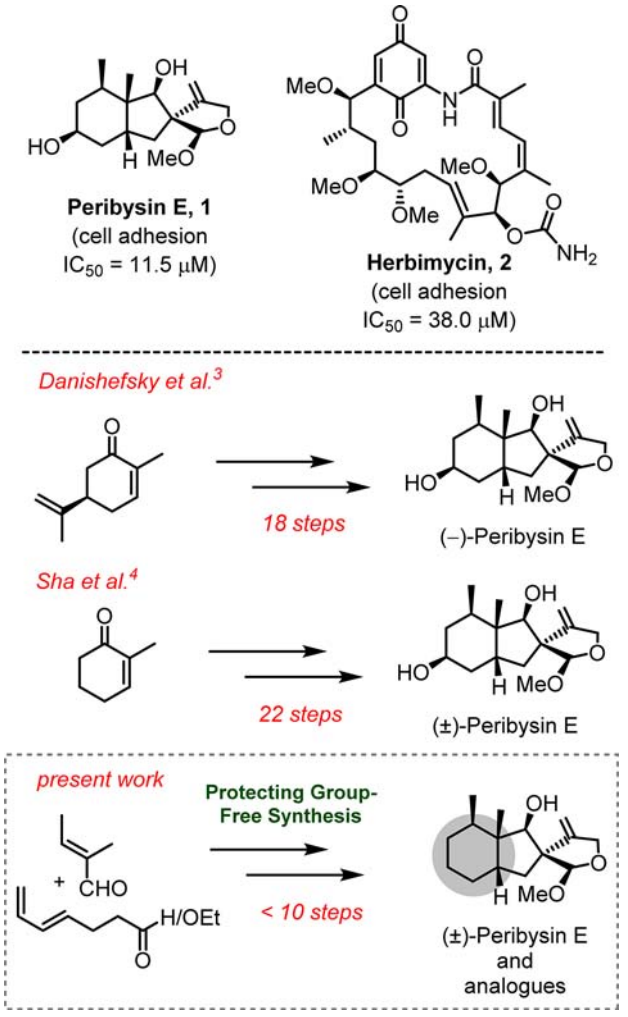
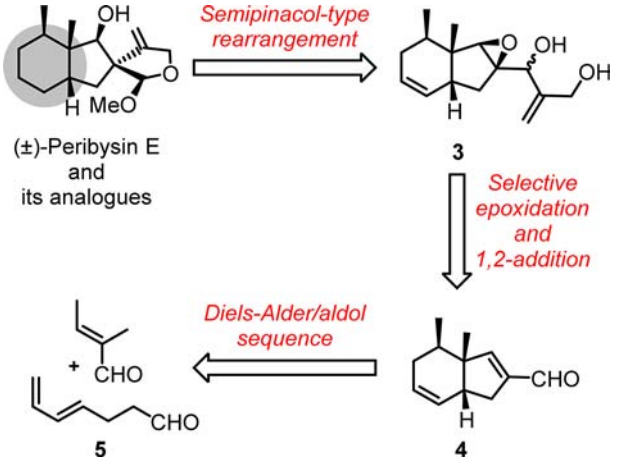


Figure 1. Structures of natural products and synthetic approaches.

Retrosynthetically, peribysin E and planned analogues could be prepared from appropriately functionalized six-membered hydrindane system **3**, which is ready for semipinacol-type rearrangement (Scheme 1). Chemoselective epoxidation followed by 1,2-addition would provide intermediate **3** from **4**. Synthesis of key *cis*-hydrindane building block **4**, with chemically differentiable double bonds, was planned starting from readily accessible diene **5** and tiglic aldehyde, using the Diels–Alder/aldol sequence previously developed by one of us.[6]

Accordingly, the reaction of tiglic aldehyde and diene **5**[7] in the presence of a Lewis acid such as Et_2AlCl or $BF_3{\bullet}Et_2O$, followed by base treatment, furnished the enal

Scheme 1. Retrosynthesis



4 in 15% and 10% yields, respectively (Scheme 2). Despite a few experimental variations, the yield has not improved further. However, the same transformation was achieved in 47% yield in a highly diastereoselective fashion, by replacing the diene **5** with more stable diene **6**[8] and by the addition of two more routine steps (reduction and oxidation). This transformation established the requisite stereochemistry of three contiguous chiral centers of the peribysin family of natural products. The Lewis acid mediated intermolecular Diels–Alder reaction produces the endo adduct having the aldol partners (i.e., aldehydes) in close proximity, allowing for subsequent intramolecular aldol reaction to give **4**.[9] The diastereo- and regioselectivity can be explained on the basis of secondary orbital interactions and atomic coefficient preferences, respectively.[10] The functionally embellished *cis*-hydrindane intermediate **4** is ideally suited for the construction of the target molecule peribysin and related compounds, as it possesses chemically differentiated olefins for the selective functionalization of either ring. The isolated double bond present in compound **4** was oxidized using Wacker conditions[11] to

(5) Inspired by the concept of the diverted total synthesis of bioactive natural products. Selected references: (a) Danishefsky, S. *Nat. Prod. Rep.* **2010**, *27*, 1114. (b) Wilson, R. M.; Danishefsky, S. J. *J. Org. Chem.* **2006**, *71*, 8329. (c) Wender, P. A.; Miller, B. J. *Nature* **2009**, *460*, 197. (d) Fürstner, D.; Kirk, M. D. B.; Fenster, C.; Aïssa, D.; De Souza, O.; Müller *Proc. Natl. Acad. Sci. U.S.A.* **2005**, *102*, 8103. (e) Szpilman, A. M.; Carreira, E. M. *Angew. Chem., Int. Ed.* **2010**, *49*, 9592. (f) Szpilman, A. M.; Carreira, E. M. *Angew. Chem., Int. Ed.* **2010**, *49*, 9592. (g) Wach, J.-Y.; Gademann, K. *Synlett* **2012**, 163. (h) Fürstner, A. *Isr. J. Chem.* **2011**, *51*, 329. (I) Hoffmann, R. W. *Angew. Chem., Int. Ed.* **2013**, *52*, 123 and references cited therein.

(6) Reddy, D. S. *Org. Lett.* **2004**, *6*, 3345.

(7) Reed, S. *J. Org. Chem.* **1964**, *30*, 1663.

(8) Spino, C.; Crawford, J.; Bishop, J. *J. Org. Chem.* **1995**, *60*, 844.

(9) For related Diels–Alder reactions, see selected refs: (a) Bonnesen, P. V.; Puckett, C. L.; Honeychuck, R. V.; Hersh, W. H. *J. Am. Chem. Soc.* **1989**, *111*, 6070. (b) Hashimoto, Y.; Nagashima, T.; Kobayashi, K.; Hasegawa, M.; Saigo, K. *Tetrahedron* **1993**, *49*, 6349. (c) Winkler, J. D.; Kim, H. S.; Kim, S.; Penkett, C. S.; Bhattacharya, S. K.; Ando, K.; Houk, K. N. *J. Org. Chem.* **1997**, *62*, 2957. (d) Baillie, L. C.; Batsanov, A.; Bearder, J. R.; Whiting, D. A. *J. Chem. Soc., Perkin Trans. 1* **1998**, 3471. (e) Ge, M.; Stoltz, B. M.; Corey, E. J. *Org. Lett.* **2000**, *2*, 1927. (f) Reddy, D. S.; Kozmin, S. A. *J. Org. Chem.* **2004**, *69*, 4860. (g) Kraus, G. A.; Kim, J. J. *Org. Lett.* **2004**, *6*, 3115. (h) Reddy, D. S.; Palani, K.; Balasubrahmanyam, D.; Vijju, K. V. B.; Iqbal, J. *Tetrahedron Lett.* **2005**, *46*, 5211. (i) Srinivas, P.; Reddy, D. S.; Shiva Kumar, K.; Dubey, P. K.; Iqbal, J.; Das, P. *Tetrahedron Lett.* **2008**, *49*, 6084. (j) Srinivas, P.; Reddy, D. S.; Iqbal, J.; Dubey, P. K.; Das, P. *Synthesis* **2009**, *22*, 3833.

(10) (a) Sauer, J. *Angew. Chem., Int. Ed. Engl.* **1967**, *6*, 16. (b) Houk, K. N.; Strozier, R. W. *J. Am. Chem. Soc.* **1973**, *95*, 4094–4096. (c) Houk, K. N. *Acc. Chem. Res.* **1975**, *8*, 361. (d) Eisenstein, O.; LeFour, J. M.; Anh, N. T.; Hudson, R. F. *Tetrahedron* **1977**, *33*, 523.

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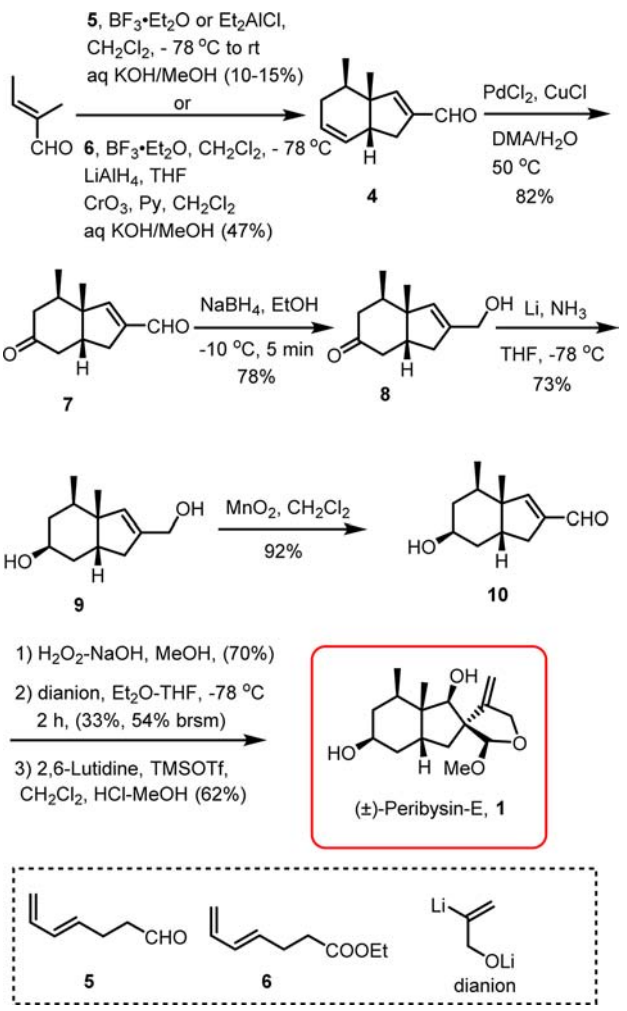
Scheme 2. Synthesis of (±)-Peribysin E



provide keto-aldehyde **7** in a highly regioselective manner. The regiochemistry was assigned on the basis of NMR spectra analysis. Selective reduction of aldehyde functionality using $NaBH_4$ at −10 °C furnished the alcohol **8** which was subjected to Li−NH_3 reaction, to give diol **9** with the requisite stereochemistry present in peribysin E in a selective fashion. The selective oxidation (MnO_2) of the primary alcohol produced an α,β-unsaturated aldehyde **10** in 92% yield. Epoxidation (H_2O_2−NaOH) of the conjugated double bond in compound **10** resulted in an epoxy aldehyde in good yield.[12] The reaction of the epoxy aldehyde with the dianion (generated from 2-iodopropen-1-ol using *n*-BuLi) resulted in an ∼1:1 mixture of epoxy-alcohols such as **3**, which set the stage for semipinacol-type rearrangement[13] identical to that of Sha's approach,[4] except that no protecting group was used in the present case. The poor diastereoselectivity at the newly generated stereocenter is not a concern, as it is going to be destroyed in the following step. The mixture of epoxy alcohols was treated with TMSOTf in the presence of 2,6-lutidine to afford the lactol intermediate (through a semipinacol-type rearrangement), which was subsequently treated with HCl/MeOH, to result in the target molecule peribysin E (**1**). The authenticity of the synthesized peribysin E (**1**) sample was confirmed by comparing the spectral data with the reported data.[1,3,4]

After the successful synthesis of peribysin E, we focused our attention on generating a focused library of molecules around the peribysin E skeleton. Toward this effort, the intermediate **4** in the present synthesis is suitable for the generation of diverse structures, as it possesses functionalities with orthogonal reactivities. The conjugated double bond in enal **4** was subjected to selective epoxidation (H_2O_2−NaOH) to produce **11** in 74% yield (Scheme 3). The reaction of the aldehyde in **11** with the dianion resulted in an ∼1:1 mixture of epoxy-alcohols (**3**), which on semipinacol-type rearrangement similar to the previous scheme resulted in a new peribysin E analogue **12** (108 mg, 64%). For the creation of more analogues, the double bond in the six-membered ring in compound **12** was chemoselectively epoxidized to give **13** (128 mg, 72%) in an ∼9:1 diastereoselective ratio. The stereochemistry was unambiguously established with the help of the single X-ray crystal structure of **13**. Although attack from the exo face is preferred, the steric effects of the two methyl groups seem to control the product formation to obtain the endo product as the major isomer. $LiAlH_4$ reduction in **13** produced the mixture of alcohols which were cleanly separated using a silica gel column (using Combiflash MPLC). All three isolated compounds **14** (45 mg, 36%), **15** (54 mg, 43%), and **16** (16 mg, 13%) were characterized with the help of 2D NMR experiments, and key NOE correlations are shown in the Supporting Information.[14] Surprisingly, we could not isolate the alcohol (out of four possible isomers) that corresponds to peribysin E (**1**). This is probably due to the minor epoxide, which was opened from one side only to give compound **16**. It is noteworthy to mention that the epoxide can be opened with various nucleophiles to generate more analogues. For the generation of a deoxyperibysin E analogue, the intermediate **11** was hydrogenated to give saturated hydrindane **17**. The three-step sequence, comprising dianion addition, TMSOTf treatment, and subsequent exposure to methanolic HCl, resulted in the desired analogue **18** (38 mg, 60%) of peribysin E. It is interesting to note that peribysin A and D lack the hydroxyl group on the six-membered ring and show more potency in the cell adhesion inhibition assay as compared to that of **1**.[15] To increase further diversity of the structures, compound **12** was subjected to OsO_4-catalyzed dihydroxylation to furnish a mixture of triols **19** and **20** (58 mg as a mixture of two compounds, 88%) in a highly chemoselective manner.[16]

(12) We could not isolate pure epoxyaldehyde, as we found it to be an unstable compound. The epoxyaldehyde was immediately used for the next step which may contain 5−10% of the undesired isomer.

(13) Snape, T. J. *Chem. Soc. Rev.* **2007**, *36*, 1823.

(14) Key NOE correlations and copies of 2D NMR spectra are available in the Supporting Information.

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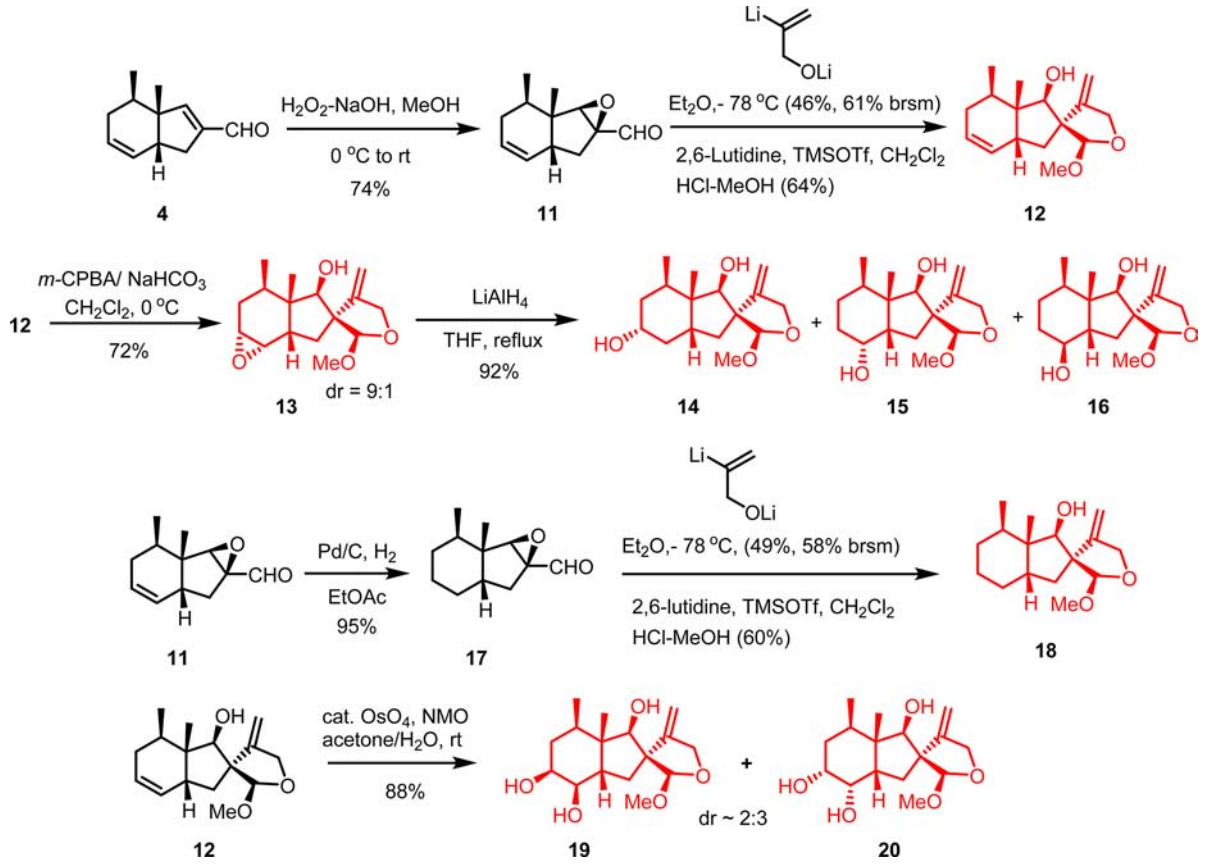
(16) The mixture was not separated to give pure triols, requiring further trials.

Scheme 3. Syntheses of Peribysin E Analogues



In summary, we have accomplished the synthesis of (±)-peribysin E in the shortest route. Synthesis of the eight novel analogues (**12**, **13**, **14**, **15**, **16**, **18**, **19**, and **20**) of peribysin E was also achieved using diverted total synthesis toward identifying potent cell adhesion inhibitors. No protecting group was used in the entire sequence. The present route is flexible, faster, and capable of producing several analogues of the natural product. We are now focusing on structure–activity relationship studies using cell adhesion inhibition assays, and access to promising compounds in enantiopure form.

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Supporting Information Available. Detailed experimental procedures, characterizations of new compounds, and NMR spectra of new compounds (PDF); X-ray single crystal data for **13** (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.