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Concise Total Synthesis of (±)-Dasyscyphin D

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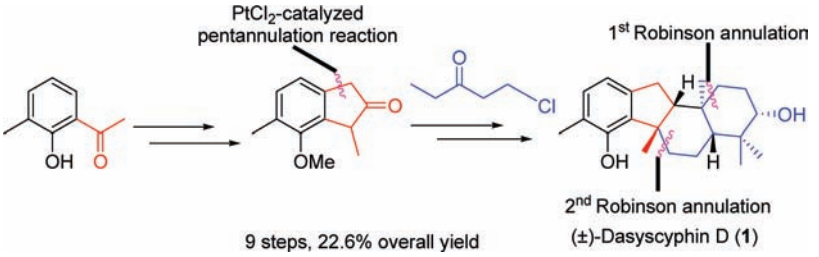
ABSTRACT



The first and efficient total synthesis of (±)-dasyscyphin D was achieved in 9 steps with 22.6% overall yield. The key steps involved a $PtCl_2$-catalyzed pentannulation reaction and acid-catalyzed double Robinson annulations.

Dasyscyphins (A−E) bear a unique [6−5−6−6] fused tetracyclic skeleton and are a family of tetracyclic terpenoid natural products possessing potent cytotoxic and moderate antimocrobial activities (Figure 1).[1] Among them, dasyscyphin D, isolated from *Dasyscyphus niveus* by Till Opatz and co-workers in 2008, inhibits the germination of conidia of Magnaporthe grisea at 20 μg/mL and imbeds five stereogenic centers, which contain two quaternary stereocenters.[2] These intriguing structural features, along with low availability from natural sources, have attracted our attention to define this compound as a synthetic target. Herein, we report a concise and efficient total synthesis of (±)-dasyscyphin D via a $PtCl_2$-catalyzed pentannulation reaction and acid-catalyzed Robinson annulation as key steps.

Our retrosynthetic analysis was outlined in Scheme 1. (±)-Dasyscyphin D (**1**) was envisioned to be obtained from tetracyclic precursor **2** through a simple functional group interconversion, which could be prepared from 2-indanone

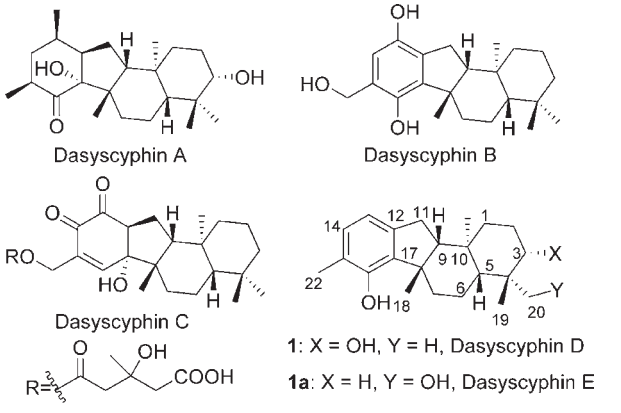


Figure 1. Structures of dasyscyphin A−E.

3 by acid-catalyzed Robinson annulations. In the case of **3**, it could be obtained from **4** by a $PtCl_2$-catalyzed pentannulation reaction developed by Ohe's group previously.[3,4] Toward this end, ester **4** could be readily prepared by acetophenone **5** by a simple transformation.

Our synthesis began with readily available acetophenone **5**, which was protected by MeI, followed by nucleophilic

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(1) (a) Rojas de la Parra, V.; Mierau, V.; Anke, T.; Sterner, O. *Tetrahedron* **2006**, *62*, 1828–1832. (b) Mierau, V.; Rojas de la Parra, V.; Sterner, O.; Anke, T. J. *Antibiot*. **2006**, *59*, 53–56.

(2) Liermann, J. C.; Kolshorn, H.; Anke, H.; Thines, E.; Opatz, T. *J. Nat. Prod*. **2008**, *71*, 1654–1656.

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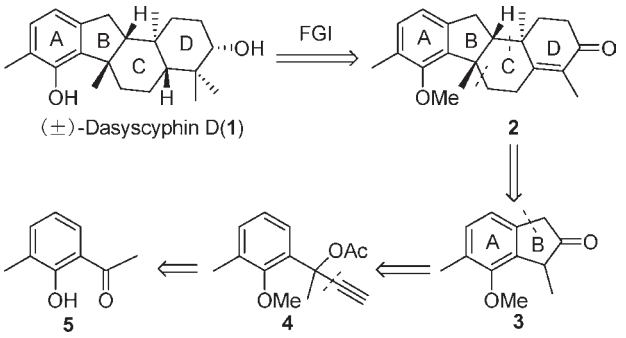
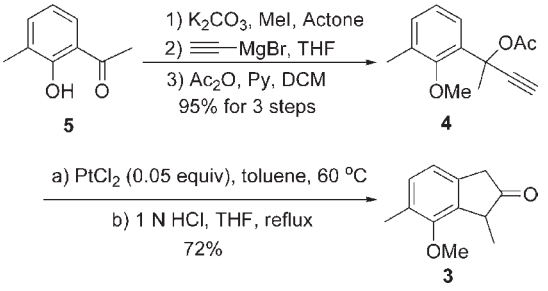
Scheme 1. Retrosynthetic Analysis of (±)-Dasyscyphin D



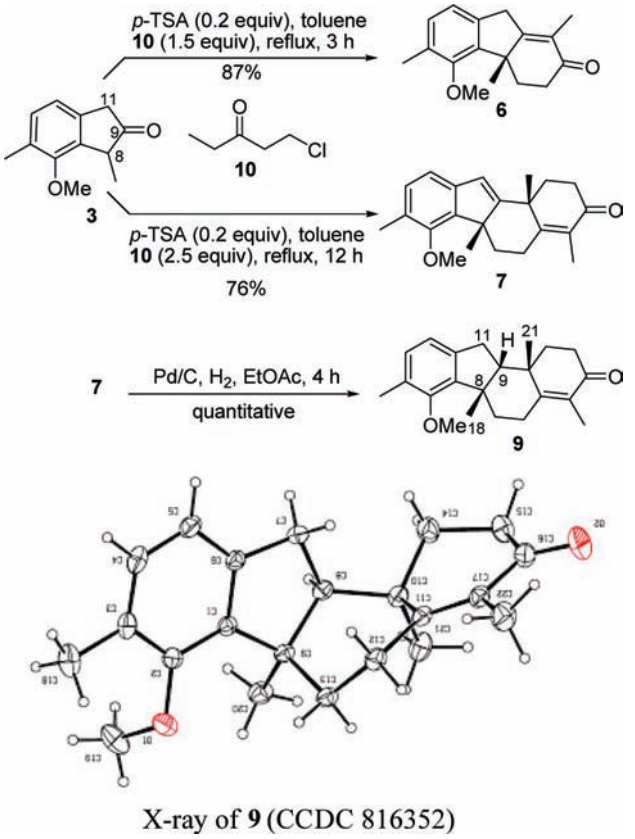
Scheme 2. Synthesis of Indanone **3**



addition of ethynylmagnesium bromide and afforded the corresponding alcohol, which was further protected by acetyl to obtain **4** in 95% yield (Scheme 2). Treatment of ester **4** with 5 mol % $PtCl_2$ in toluene underwent the desired $PtCl_2$-catalyzed pentannulation reaction and then acidic hydrolysis to give the desired 2-indanone **3** in 72% yield.

With the key intermediate **3** in hand, the C and D rings of **1** were then constructed via Robinson annulation, which was widely used in the synthesis of complex natural products.[5−7] However, to the best of our knowledge, Robinson annulation has not been utilized in the construction of the [6−5−6] skeleton, because of the similar acidity of the two benzylic positions of **3**. Initially, construction of the C ring was proceeded by treatment of **3** with ethyl vinyl ketone or **10** under base conditions (K_2CO_3/MeOH, NaH or EtONa, etc.); however, only a complex mixture was obtained, owing to the similar acidity of H-8 and H-11. After many trials, attention was then turned to acidic conditions. We were pleased to find that when exposing **3** and **10** (1.5 equiv) to *p*-toluenesulfonic acid in refluxing toluene, the desired tricycle **6** was obtained in 87% yield, together with a small amount (< 1%) of tetracycle **7**, which could be generated by the second Robinson annulation from compound **6**, and found that the percentage of tetracycle **7** increased with prolongation of the reaction time (Scheme 3).

Scheme 3. Robinson Annulation of **3**



Even **7** could be obtained as the major product in 76% yield by annulation of **3** with 2.5 equiv of **10** over 12 h in refluxing toluene. Hydrogenation of **7** readily provided **9** in quantitative yield. The structure of **9** was confirmed by single crystal X-ray analysis. This finding featured construction of the C and D ring in one step; although effective, the relative configuration of CH_3-18 and CH_3-21 of **9** was *cis*, which was not consistent with the natural Dasyscyphins' skeleton.

(3) (a) Ohe, K.; Nakanishi, Y.; Miki, K. *Tetrahedron* **2007**, *63*, 12138–12148. (b) Miki, K.; Ohe, K.; Uemura, S. *J. Org. Chem.* **2003**, *68*, 8505–8513 and reference cited therein.

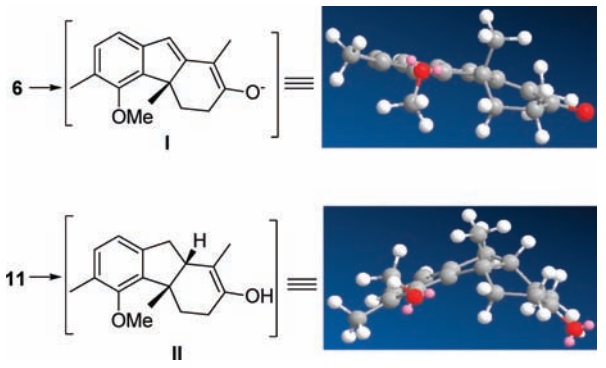
(4) For selected pentannulation examples, see: (a) Bhanu Prasad, B. A.; Yoshimoto, F. K.; Sarpong, R. *J. Am. Chem. Soc.* **2005**, *127*, 12468–12469. (b) Brian, G. P.; Bhanu Prasad, B. A.; Sarpong, R. *J. Am. Chem. Soc.* **2006**, *128*, 6786–6787. (c) Marco-Contelles, J.; Soriano, E. *Chem.—Eur. J.* **2007**, *13*, 1350–1357. (d) Piers, E.; Renaud, J. *J. Org. Chem.* **1993**, *58*, 11–13.

(5) (a) Kawanami, H.; Ikushima, Y. *Tetrahedron Lett.* **2004**, *45*, 5147–5150. (b) Frontier, A. J.; Raghavan, S.; Danishefsky, S. J. *J. Am. Chem. Soc.* **2000**, *122*, 6151–6159. (c) White, J. D.; Hrnciar, P.; Stappenbeck, F. *J. Org. Chem.* **1999**, *64*, 7871–7884. (d) Paquette, L. A.; Wang, T.-Z.; Sivik, M. R. *J. Am. Chem. Soc.* **1994**, *116*, 11323–11334. (e) Shi, B.; Hawryluk, N. A.; Snider, B. B. *J. Org. Chem.* **2003**, *68*, 1030–1042.

(6) For construction of [6.6.6] core, see: (a) Buckbinder, L.; Haugeto, A. I.; McNiff, P. A.; Millham, M. L.; Robinson, R. P. *J. Med. Chem.* **2009**, *52*, 1731–1743. (b) Gan, Y.; Spencer, T. A. *J. Org. Chem.* **2006**, *71*, 5870–5875. (c) Howell, F. H.; Taylor, D. A. H. *J. Chem. Soc.* **1958**, 1248–1254. (d) Howell, F. H.; Taylor, D. A. H. *J. Chem. Soc.* **1959**, 1607–1613. (e) Paquette, L. A.; Belmont, D. T.; Hsu, Y.-L. *J. Org. Chem.* **1985**, *50*, 4667–4672. (f) Banerjee, A. K.; Azocar, J. A. *Synth. Commun.* **1999**, *29*, 249–256. (g) Suryawanshi, S. N.; Fuchs, P. L. *J. Org. Chem.* **1986**, *51*, 902–921.

(7) (a) Heathcock, C. H.; Mahaim, C.; Schlecht, M. F.; Utawanit, T. *J. Org. Chem.* **1984**, *49*, 3264–3274. (b) Kerwin, S. M.; Paul, A. G.; Heathcock, C. H. *J. Org. Chem.* **1987**, *52*, 1686–1695. (c) Zoretic, P. A.; Branchaud, B.; Maestrone, T. *Tetrahedron Lett.* **1975**, *16*, 527–528.

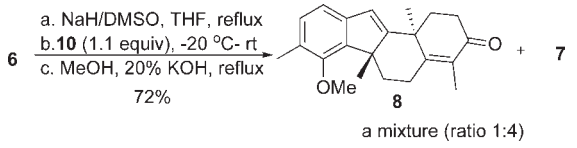
Scheme 4. Chem 3D of the Intermediate **I** and **II**



Constructing the D ring was the next task for completion of the total synthesis. Upon treatment of tricycle **6** with ketone **10** (1.1 equiv) under basic conditions, a mixture of **8** and **7** was obtained in 72% combined yield.[8] After analysis of the sterechemistry of dasyscyphin D, we think that it is favorable if the C=C bond of tricycle **6** was reduced to a saturated one. This was clearly illustrated in Scheme 4. Electrophilic **10** could be approached from the convex face of the intermediate **II** with higher selectivity than the intermediate **I**.

With this idea in mind, the stage was then set for the reduction of the α,β-enone of tricycle **6** (Scheme 5). Birch reduction of enone **6** was performed in $Li/NH_3(l)/t$-BuOH to provide tricycle ketone **11** (α:β = 1:6) in 88% yield. In a similar fashion to the first Robinson annulation, ketone **11** was treated with ketone **10** catalyzed by *p*-TSA in refluxing benzene. The second Robinson annulation took place, and the tetracycle **2** was obtained in 55% yield (~20% recovery of starting material, 69% BRSM).[9] The relative configration of tetracycle **2** was consistent with the skeleton of the natural product as expected. The sequential Birch reduction–alkylation reaction of **2** proceeded and was quenched by excessive CH_3I,[10] followed by removal of the methyl protecting group, and ketone **12** was obtained in 68% yield. Finally, with reduction of ketone **12** with $NaBH_4$ in MeOH, the total synthesis of (±)-dasyscyphin D (**1**) was accomplished. Our synthetic sample was in good agreement with the natural sample on the basis of ^1H NMR, ^{13}C NMR, HRMS, and IR.

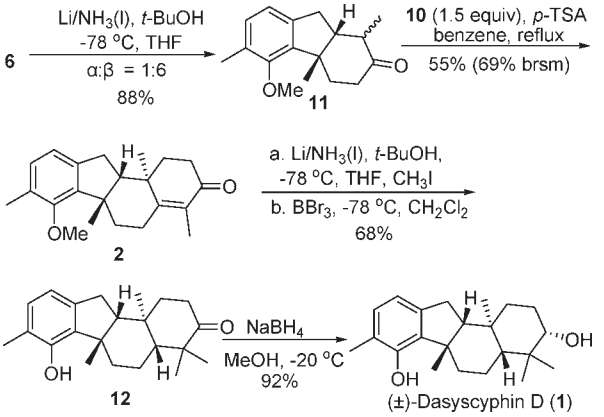
(8) Favaloro, F. G., Jr.; Honda, T.; Honda, Y .; Gribble, G. W.; Suh, N.; Risingsong, R.; Sporn, M. B.; Gribble, G. W. *Org. Biomol. Chem.* **2003**, *1*, 4384–4391.



(9) (a) Paquette, L. A.; Wang, T. Z.; Sivik, M. R. *J. Am. Chem. Soc.* **1994**, *116*, 2665–2666. (b) Paquette, L. A.; Wang, T. Z.; Sivik, M. R. *J. Am. Chem. Soc.* **1994**, *116*, 11323–11334.

(10) (a) Stork, G.; Rosen, P.; Goldman, N. L. *J. Am. Chem. Soc.* **1961**, *83*, 2965–2966. (b) Stork, G.; Rosen, P.; Goldman, N.; Coombs, R. V.; Tsuji, J. J. *Am. Chem. Soc.* **1965**, *87*, 275–286. (c) Hiroya, K.; Ichihashi, Y.; Furutono, A.; Inamoto, K.; Sakamoto, T.; Doi, T. *J. Org. Chem.* **2009**, *74*, 6623–6630 and references cited therein.

Scheme 5. Completion of Total Synthesis of (±)-Dasyscyphin D



In conclusion, a concise and efficient total synthesis of (±)-dasyscyphin D was acomplished in 9 steps with 22.6% overall yield. Our sythesis features two points: (1) preparing the 2-indanone **3** by a $PtCl_2$-catalyzed pentannulation reaction; (2) constructing the fused cyclic system by a double acid-catalytic Robinson annulation, which transformed 2-indanone into a tetracyclic [6–5–6–6] skeleton and installed C(8) and C(10), two all-carbon quaternary stereocenters. We believe that the synthetic efforts will pave the way for the syntheses of other members of the dasyscyphins family.

Acknowledgment. We are grateful for the generous financial support by the MOST (2010CB833200) and the NSFC (21072086, 20872054, 20732002) and Program 111.

Supporting Information Available. Detailed experimental procedures, characterizations, and copies of ^1H and ^{13}C NMR spectra of all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.