JACS
JOURNAL OF THE AMERICAN CHEMICAL SOCIETY
Communication
pubs.acs.org/JACS

Total Synthesis of (−)-Fusarisetin A and Reassignment of the Absolute Configuration of Its Natural Counterpart

Jun Deng,[†] Bo Zhu,[†] Zhaoyong Lu, Haixin Yu, and Ang Li*

State Key Laboratory of Bioorganic and Natural Products Chemistry, Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, 345 Lingling Road, Shanghai 200032, China

Supporting Information

ABSTRACT: The first total synthesis of (−)-fusarisetin A, the enantiomer of naturally occurring acinar morphogenesis inhibitor (+)-fusarisetin A, was accomplished in 13 steps, leading to the reassignment of the absolute configuration of the natural product. The synthesis featured a Lewis acid-promoted intramolecular Diels−Alder reaction, a Pd-catalyzed O→C allylic rearrangement, a chemoselective Wacker oxidation, and a Dieckmann condensation/hemiketalization cascade.

Natural products serve as an abundant source in the search for anticancer agents due to unparalleled structural diversity and accompanying molecular modes of action.[1] Recently, small molecules that inhibit cancer cell metastasis have received increasing interest in related drug discovery process,[2] because such action may complement that of existing anticancer drugs such as the tubulin stabilizers/destabilizers and topoisomerase inhibitors. In May 2011, Ahn et al. reported the isolation of a biologically intriguing natural product, fusarisetin A (**1**, Figure 1), from a soil fungus, *Fusarium* sp. FN080326,

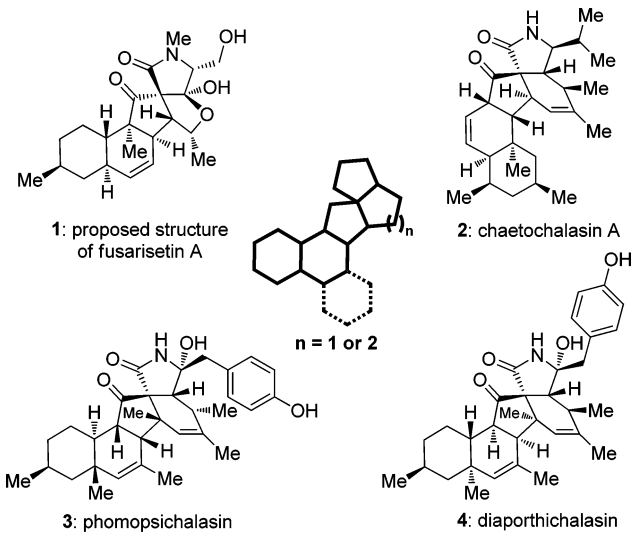


Figure 1. Fusarisetin A (**1**) and structurally related natural products **2**−**4**.

which displays significant inhibition of acinar morphogenesis as well as cell migration and invasion without apparent cytotoxicity.[3] The mechanism of action remains to be elucidated. The molecular structure of **1** was determined by employing X-ray crystallographic analysis (relative stereochemistry) and the exciton chirality circular dichroism method (absolute configuration).[3] From a structural perspective, **1** exhibits a 6,6,5,5,5-fused pentacyclic ring system (Figure 1) bearing 10 stereogenic centers. Of particular interest is the intricate 5,5,5-angular tricycle motif, reminiscent of the molecular scaffolds of certain other natural products, such as chaetochalasin A,[4a] phomopsichalasin,[4b] and diaporthichalasin[4c] (**2**−**4**, Figure 1). The interesting chemical structure as well as biological activity of fusarisetin A made it an attractive target for total synthesis. Herein, we report the first total synthesis of the proposed structure of this molecule.

From a strategic point of view, a successful synthesis of the 6,6,5,*n*,5-fused (*n* = 5 or 6) pentacyclic system shown in Figure 1 must solve the following problems: (1) construction of a decalin building block for the left-hand side of the molecule; (2) assembly of the 5,5-spirobicyclic structure, especially introduction of the quaternary stereogenic center on the angular position of the 5,*n*,5-fused tricyclic moiety; and (3) formation of the right-hand side *n*-membered ring (*n* = 5 or 6). Problem 2, the most severe synthetic challenge posed by the whole class of structurally related natural products, might ideally be solved together with problem 3 in one step or pot. Based on this general guideline, a retrosynthetic analysis of **1** was undertaken, as shown in Figure 2. We considered the initial disassembly of the 5-membered lactol and its neighboring spirobicycle through a retro hemiketalization/Dieckmann condensation sequence, to render tricyclic intermediate **5**. The next obvious disconnection at the amide bond of **5**, followed by dehydration of its secondary hydroxyl functionality, resulted in simplified tricyclic compound **6**, which could be further disconnected to a *trans*-decalin derivative **7** by cleavage of its allylic C−C bond. Thus, an intramolecular S_N2' or a transition-metal-catalyzed allylation reaction was expected to give **6** in the forward direction. Compound **7** was envisioned to derive from a linear precursor such as **8** through a diastereoselective intramolecular Diels−Alder (D-A) reaction. The desired D-A substrate could be assembled from known aldehyde **9** and phosphonates **10** and **11** through double Horner−Wadsworth−Emmons (H-W-E) olefinations.

Based on the above analysis, we first investigated the preparation of *trans*-decalin **7** employing an intramolecular D-A reaction as the key transformation,[5−7] as shown in Scheme 1.

Received: December 7, 2011
Published: December 26, 2011

   dx.doi.org/10.1021/ja211444m | *J. Am. Chem.Soc.* 2012, 134, 920−923

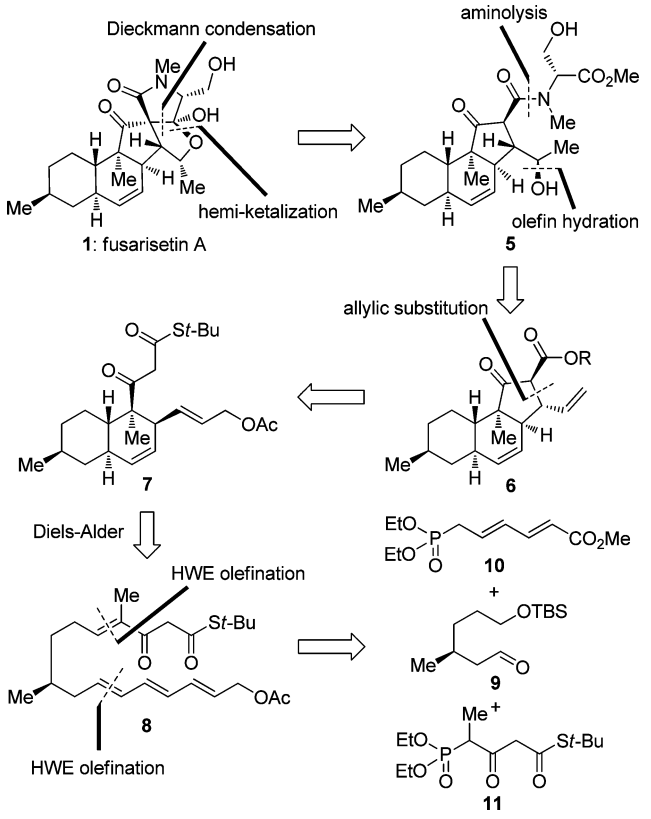
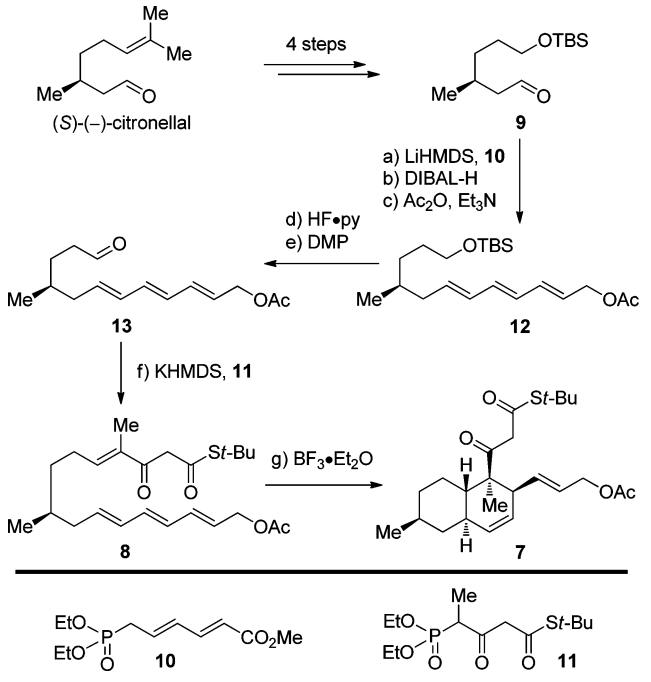


Figure 2. Retrosynthetic analysis of fusarisetin A (**1**).

Scheme 1. Preparation of Decalin Derivative 7[a]



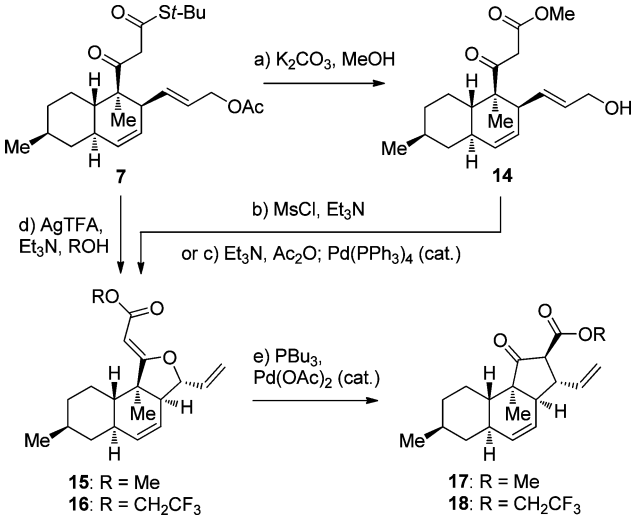
[a]Reagents and conditions: (a) **10** (1.1 equiv), LiHMDS (1.0 equiv), **9** (1.0 equiv), THF, −78 °C → 0 °C, 30 min; then 0 °C, 30 min, 71%; (b) DIBAL-H (2.2 equiv), THF, −78 °C, 30 min, 98%; (c) Ac_2O (1.4 equiv), Et_3N (1.6 equiv), CH_2Cl_2, 22 °C, 2 h, 96%; (d) HF·py/THF (1:4), 0 °C, 2 h, 93%; (e) DMP (1.2 equiv), CH_2Cl_2, 22 °C, 30 min, 85%; (f) **11** (1.1 equiv), KHMDS (2.1 equiv), **13** (1.0 equiv), THF, −78 °C, 1 h, 66%; (g) BF_3·OEt_2 (3.0 equiv), CH_2Cl_2, −78 °C, 10 min; then −40 °C, 40 min, 63%.

Starting with aldehyde **9**, which is readily prepared from (−)-citronellal[8] or (−)-citronellol,[6] we carried out H-W-E reaction with lithiated phosphonate **10**.[9] Reduction with DIBAL-H and acetylation of the resulting primary alcohol led to triene **12** with good overall efficiency (67%, 3 steps). Desilylation of **12** with HF·py and subsequent oxidation with Dess−Martin periodinane (79%, 2 steps) set the stage for a second H-W-E olefination. Aldehyde **13** was readily converted to ketothioester **8** as a single *E* isomer in 66% yield by treatment with phosphonate **11**[6,10] and KHMDS. With **8** in hand, we examined a variety of conditions for the intramolecular D-A reaction. To our delight, BF_3·OEt_2 was found to be an efficient promoter for this transformation, and *trans*-decalin **7** was obtained as a single isolable diastereomer in 63% yield.[6b] The structure of **7** was confirmed by X-ray crystallographic analysis of a later intermediate (*vide infra*). As we expected, a similar D-A reaction employing the methyl ester counterpart of **8** as substrate also proceeded smoothly to give the corresponding desired product, although the preparation of the methyl ester substrate from the corresponding phosphonate (counterpart of **11**) and aldehyde **13** was much less effective. Interestingly, analogous D-A precursors with monocarbonyl dienophile (aldehyde and ester) led to a mixture of diastereomers, the major components of which were two *endo* cycloadducts, under thermal or Lewis acidic (only effective for aldehyde substrate) conditions. The diastereochemical output of the above D-A processes indicated an unusual mode of interaction between the dicarbonyl substrate and commonly monocoordinate Lewis acid BF_3, which remains interesting for further investigations.[11]

With **7** in hand, we turned our attention to the synthesis of a 6,6,5-fused tricyclic intermediate such as **6** (Figure 2), according to our retrosynthetic analysis. The allylic hydroxyl functionality of **7** was released by treatment with K_2CO_3 in MeOH to afford alcohol **14**, which was subsequently activated under mesylation conditions. However, without observation of the corresponding mesylate, *O*-allylation compound **15** was immediately generated in 93% yield, as shown in Scheme 2. In an alternative attempt, the re-acetylated product from **14** was subjected to standard Pd-catalyzed allylic substitution conditions [$Pd(PPh_3)_4$, LiOAc] but also rapidly converted into hydrofuran **15**. Interestingly, under very mild transesterification conditions [Ag(TFA), Et_3N, MeOH, or trifluoroethanol],[12] cyclization product **15** or **16** was readily formed from **7** in one pot in high yield. The structure of **16** was unambiguously proven by X-ray crystallographic analysis (Figure 3),[13] which also confirmed the stereochemistry of D-A product **7**. At this point, it became obvious that the *O*-allylation product was kinetically more favored than the desired *C*-allylation product in this particular case. Thus, proper conditions to activate the allylic C−O bond are desired, since the spontaneous and irreversible reconstruction of an allylic C−C bond would drive the "equilibrium" to the *C*-allylation side.[14] Considering that the basicity and leaving ability of *β*-ketoester enolate are similar to those of phenoxide, we rationalized that a transition metal complex that promotes the substitution of a phenyl allyl ether[15] would fit the requirement. Much to our delight, treatment of **15** or **16** with $Pd(OAc)_2$ and electron-rich ligand PBu_3 cleanly rendered the expected *C*-allylation product **17** or **18**, respectively, in satisfactory yield. The vinyl group of these compounds was postulated to repose in the desired orientation based on the diastereoselectivity of the *O*-allylation reaction,

dx.doi.org/10.1021/ja211444m | J. Am. Chem.Soc. 2012, 134, 920−923

Scheme 2. Pd-Catalyzed O→C Allylic Rearrangement Approach to 6,6,5-Tricycles 17 and 18[a]



[a]Reagents and conditions: (a) K_2CO_3 (2.0 equiv), MeOH/CH_2Cl_2 (1:1), 22 °C, 3 h, 89%; (b) MsCl (3.0 equiv), Et_3N (5.0 equiv), CH_2Cl_2, 0 °C, 5 min, 93%; (c) (i) Ac_2O (1.5 equiv), Et_3N (2.0 equiv), CH_2Cl_2, 0 °C, 1 h, 96%; (ii) $Pd(PPh_3)_4$ (0.25 equiv), LiOAc (2.0 equiv), THF, 22 °C, 15 min, 80%; (d) Ag(TFA) (2.0 equiv), Et_3N (4.0 equiv), MeOH or CF_3CH_2OH, 0 °C, 15 min; then 22 °C, 3 h, 90% for **15**, 91% for **16**; (e) $Pd(OAc)_2$ (0.50 equiv), PBu_3 (1.25 equiv), 22 °C, 1 h, 70% for 17, 75% for **18**.

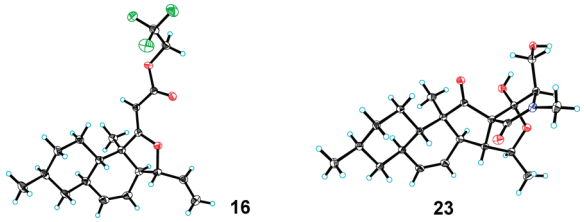
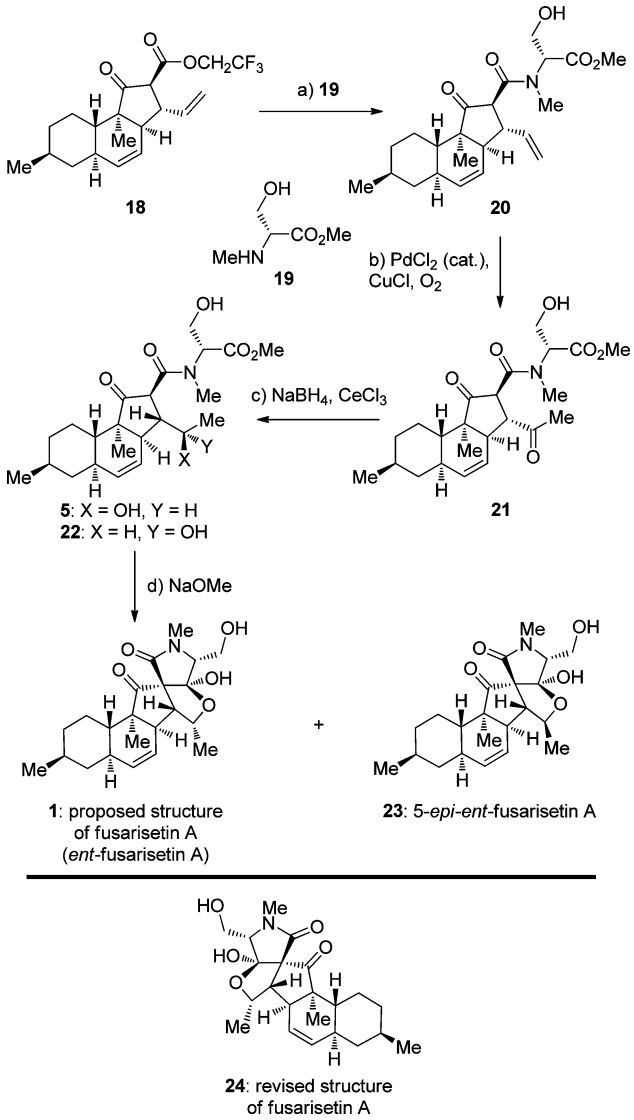


Figure 3. X-ray-derived ORTEPs of **16** and **23**. Non-hydrogen atoms are shown as 30% ellipsoids.

confirmed at a later stage by X-ray crystallographic analysis (*vide infra*).

Having successfully assembled the left half of **1**, we entered the last stage of our total synthesis journey: construction of the spirobicyclic moiety and the 5-membered lactol, as shown in Scheme 3. The amino acid side chain was introduced by aminolysis of trifluoroethyl ester **18** with methyl amine **19**[16] derived from D-serine at elevated temperature, furnishing **20** in 72% yield. The next challenge would be the chemo- and regioselective Markovnikov hydration of the terminal C=C bond of **20**. However, oxymercuration of **20** with a variety of Hg(II) species proved to be fruitless, while electrophilic activators such as cationic halogen and selenium reagents preferentially reacted with the more electron-rich and distorted endocyclic C=C bond. Although a similar example of selective dihydroxylation of the terminal C=C bond in the presence of endocyclic competitor using Sharpless AD-mix-β was reported,[17] **20** decomposed into an intractable mixture under such conditions. Despite the failure of this attempt, we were inspired that transition-metal-mediated reactions, which are often more sensitive to steric rather than electronic effects, may offer the solution to this selectivity problem. To our delight, Wacker oxidation of **20** furnished the desired ketone **21** in

Scheme 3. Completion of the Total Synthesis of (−)-Fusarisetin A and Reassignment of the Absolute Configuration of Natural Fusarisetin A[a]



[a]Reagents and conditions: (a) **19** (5.4 equiv), 4-DMAP (2.5 equiv), toluene, 90 °C, 2 h, 72%; (b) $PdCl_2$ (0.25 equiv), CuCl (1.5 equiv), O_2 (balloon), DMF/water (10:1), 22 °C, 12 h, 79%; (c) $CeCl_3 \bullet 7H_2O$ (1.3 equiv), $NaBH_4$ (1.1 equiv), MeOH, −20 °C, 20 min; (d) NaOMe (5.0 equiv), MeOH, 0 °C, 10 min; then 22 °C, 1 h, 41% (2 steps) for **1**, 8% (2 steps) for **23**.

good yield while sparing the endocyclic C=C bond. Unfortunately, the next move toward alcohol **5** through chemo- and diastereoselective reduction also proved to be problematic. Treatment of **21** with sterically hindered hydride sources such as L-Selectride, Red-Al, and $LiAlH(Ot\text{-}Bu)_3$ resulted in diol **22**, the undesired diastereomer of **5**, as the major product. **22** was further subjected to Dieckmann condensation conditions (NaOMe/MeOH) to render the 5-epimer of fusarisetin A (**23**) with good overall efficiency from **21**. The structure of **23** was unambiguously determined by X-ray crystallographic analysis (Figure 3),[13] which also confirmed the vinyl group direction of **18**. Commonly used asymmetric ketone reduction methods also proved to be unsuccessful: Corey−Bakshi−Shibata reduction conditions[18] led to complete

dx.doi.org/10.1021/ja211444m | J. Am. Chem.Soc. 2012, 134, 920−923

decomposition of the substrate, while Noyori reduction[19] gave a ca. 1:1 mixture of **5** and **22** in poor yield. Finally, we were pleased to find Luche reduction as a suitable mean for the selective reduction, affording a ca. 5:1 mixture of **5** and **22**. This mixture underwent Dieckmann condensation in the presence of NaOMe in MeOH, followed by a spontaneous hemiketalization, furnishing a synthetic sample of the proposed structure of fusarisetin A (**1**) in 41% yield over 2 steps, together with a small portion of its 5-epimer (**23**). The physical properties of synthetic **1** matched those reported for the natural material,[3] except for the sign of its optical rotation {synthetic: $[\alpha]_D^{27}$ = −88.0 (c = 0.15 in MeOH); natural: $[\alpha]_D^{25}$ = +84.6 (c = 0.2 in MeOH)}. Thus, the absolute configuration of naturally occurring **1** was reassigned as that of **24** based on our total synthesis.

In conclusion, we developed an efficient synthetic strategy for the total synthesis of the enantiomer of fusarisetin A, a newly discovered acinar morphogenesis inhibitor possessing an intricate structure, and reassigned the absolute configuration of the natural product through our synthesis. The synthesis featured an intramolecular Diels−Alder reaction, a Pd-mediated O→C allylic rearrangement, a chemoselective Wacker oxidation, and a Dieckmann condensation/hemiketalization cascade. The reported synthetic strategy and methods are expected to be applicable to the construction of other structurally or biosynthetically related natural products, as well as designed analogues of fusarisetin A, and thus to facilitate the exploration of its mechanism of action on a molecular level.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Experimental procedures and compound characterization. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

ali@sioc.ac.cn

Author Contributions

†These authors contributed equally.

■ ACKNOWLEDGMENTS

This paper is dedicated to Prof. K. C. Nicolaou. We thank Zhunzhun Yu and Shuhang Wu for technical contributions, Prof. Chunyang Cao for NMR assistance, and Dr. D. J. Edmonds and Prof. Dawei Ma for helpful discussions. Financial support was provided by State Key Laboratory of Bioorganic and Natural Products and Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences.

■ REFERENCES

(1) (a) Gordaliza, M. *Clin. Transl. Oncol.* **2007**, *9*, 767. (b) Newman, D. J.; Cragg, G. M. *J. Nat. Prod.* **2007**, *70*, 461.

(2) Hulkower, K. I.; Herber, R. L. *Pharmaceutics* **2011**, *3*, 107.

(3) Jang, J.-H.; Asami, Y.; Jang, J.-P.; Kim, S.-O.; Moon, D. O.; Shin, K.-S.; Hashizume, D.; Muroi, M.; Saito, T.; Oh, H.; Kim, B. Y.; Osada, H.; Ahn, J. S. *J. Am. Chem. Soc.* **2011**, *133*, 6865.

(4) Selected natural products that are structurally related to fusarisetin A: (a) Oh, H.; Swenson, D. C.; Gloer, J. B. *Tetrahedron Lett.* **1998**, *39*, 7633. (b) Horn, W. S.; Simmonds, M. S. J.; Schwartz, R. E.; Blaney, W. M. *Tetrahedron* **1995**, *51*, 3969. (c) Pornpakakul, S.; Roengsumran, S.; Deechangvipart, S.; Petsom, A.; Muangsin, N.; Ngamrojnavanich, N.; Sriubolmas, N.; Chaichit, N.; Ohta, T. *Tetrahedron Lett.* **2007**, *48*, 651.

(5) Systematic studies on intramolecular D-A reaction for synthesizing bicyclic systems: (a) Roush, W. R.; Hall, S. E. *J. Am. Chem. Soc.* **1981**, *103*, 5200. (b) Roush, W. R.; Peseckis, S. M. *J. Am. Chem. Soc.* **1981**, *103*, 6696. (c) Roush, W. R.; Gillis, H. R.; Ko, A. I. *J. Am. Chem. Soc.* **1982**, *104*, 2269. (d) Roush, W. R.; Gillis, H. R. *J. Org. Chem.* **1982**, *47*, 4825.

(6) Elegant syntheses of decalin natural product equisetin using D-A reaction: (a) Burke, L. T.; Dixon, D. J.; Ley, S. V.; Rodríguez, F. *Org. Lett.* **2000**, *2*, 3611. (b) Burke, L. T.; Dixon, D. J.; Ley, S. V.; Rodríguez, F. *Org. Biomol. Chem.* **2005**, *3*, 274.

(7) Excellent review ofD-A reaction in total synthesis: Nicolaou, K. C.; Snyder, S. A.; Montagnon, T.; Vassilikogiannakis, G. *Angew. Chem., Int. Ed.* **2002**, *41*, 1668.

(8) Inoue, A.; Kanematsu, M.; Yoshida, M.; Shishido, K. *Tetrahedron Lett.* **2010**, *51*, 3966.

(9) (a) Nicolaou, K. C.; Daines, R. A.; Chakraborty, T. K.; Ogawa, Y. *J. Am. Chem. Soc.* **1988**, *110*, 4685. (b) Amans, D.; Bellosta, V.; Cossy, J. *Angew. Chem., Int. Ed.* **2006**, *45*, 5870.

(10) Hayashi, Y.; Narasaka, K. *Chem. Lett.* **1998**, 313.

(11) Dicarbonyl/BF_2 complexcould possibly be generated *in situ* from BF_3·OEt_2 and dicarbonyl substrateand serve as an activated intermediate for D-A reaction. Preparationand characterization of such class of complex: Maeda, H.; Yohei, H.; Nakanishi, T. *J. Am. Chem. Soc.* **2007**, *129*, 13661.

(12) (a) Masamune, S.; Hayase, Y.; Schilling, W.; Chan, W. K.; Bates, G. S. *J. Am. Chem. Soc.* **1977**, *99*, 6756. (b) Booth, P. M.; Fox, C. M. J.; Ley, S. V. *Tetrahedron Lett.* **1983**, *24*, 5143.

(13) CCDC-854787 and CCDC-854788 contain the supplementary crystallographic data for **16** and **23**, respectively, and are available free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

(14) Mechanistically similarPd-catalyzed O→C allylic migration reactions: Mohr, J. T.; Stoltz, B. M. *Chem. Asian J.* **2007**, *2*, 1476 and referencestherein.

(15) Hosokawa, T.; Kono, T.; Uno, T.; Murahashi, S.-I. *Bull. Chem. Soc. Jpn.* **1986**, *59*, 2191.

(16) White, K. N.; Konopelski, J. P. *Org. Lett.* **2005**, *7*, 4111.

(17) Wipf, P.; Kim, Y.; Goldstein, D. M. *J. Am. Chem. Soc.* **1995**, *117*, 11106.

(18) Comprehensivereview: Corey, E. J.; Helal, C. J. *Angew. Chem., Int. Ed.* **1998**, *37*, 1986.

(19) Fujii, A.; Hashiguchi, S.; Uematsu, N.; Ikariya, T.; Noyori, R. *J. Am. Chem. Soc.* **1996**, *118*, 2521.