JOC The Journal of Organic Chemistry

Article

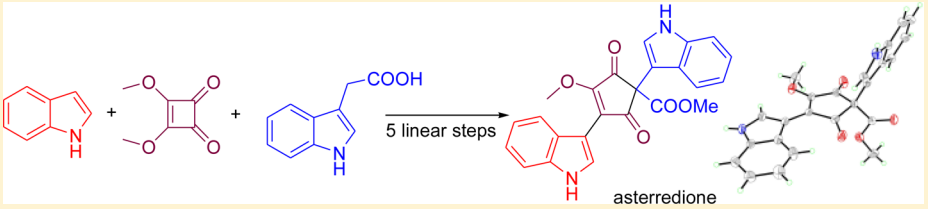
pubs.acs.org/joc

Total Synthesis of Asterredione

Sinan Gai, Qing Zhang, and Xiangdong Hu*

Department of Chemistry & Material Science, Key Laboratory of Synthetic and Natural Functional Molecule Chemistry of the Ministry of Education of China, Northwest University, Xi'an 710069, China

Supporting Information



ABSTRACT: The first total synthesis of asterredione was efficiently accomplished over five linear steps and in 21.5% overall yield. As the crucial step, the 2-quaternary 1,3-cyclopentenedione skeleton of asterredione was readily achieved using the Darzens/ring-expansion strategy developed in our laboratory. The structure of synthesized asterredione was fully confirmed by X-ray crystallography.

INTRODUCTION

Rhizosphere soil-derived microorganisms provide an important resource for the research of secondary metabolites possessing therapeutic potential.[1,2] In addition, rhizospheres of desert plants have also been considered to be a unique opportunity to discover unusual secondary metabolites.[3] Through extensive investigations on the rhizosphere microflora of Sonoran desert plants, asterredione (**1**; Scheme 1) was discovered from *Aspergillus terreus* existing in the rhizosphere of *Opuntia versicolor* by Gunatilaka in 2003.[4] The biological study showed that **1** exhibited moderate anticancer activity against three sentinel cancer cell lines: the NCI-H460 nonsmall cell lung cancer, MCF-7 breast cancer, and SF-268 CNS glioma cell lines.

Structurally, **1** is an unusual alkaloid characterized by a congested 2-quaternary 1,3-cyclopentenedione core and two indole motifs. Gunatilaka proposed a biosynthetic pathway to **1** through a hydroperoxy-mediated ring contraction of the homologous natural product asterriquinone D.[4] Although the biological activity and the congested structure make this compound an attractive target, there has been no report on the synthesis of **1** in the 10 years since its discovery. Herein, we describe the first total synthesis of **1**.

RESULTS AND DISCUSSION

In the synthesis, constructing the 2-quaternary 1,3-cyclopentenedione unit of **1** was the major challenge that we faced. The ring expansion of squaric acid derivatives and cyclobutenediones is an attractive research field to organic synthetic chemists in which Moore,[5,6] Liberskind,[7,8] Paquette,[9,10] Burnell,[11,12] and others have made great contributions. As a new development in this field, a Darzens/ring-expansion process was developed during our study on the total synthesis of linderaspirone A and bilinderone,[13] affording an efficient strategy for 1,3-cyclopentenedione units. However, the 1,3-cyclopentenedione obtained in our previous research has one hydrogen on C2, which enabled the formation of the expected product through enolization. In this article, we sought to achieve the quaternary carbon center in **1** through a new version of Darzens/ring-expansion process. From the retrosynthetic analysis shown in Scheme 1, the synthesis starts from three commercially available materials: indole **7**, dimethyl squarate **8**, and 3-indoleacetic acid **10**. Fragments **4** and **5** were designed for the Darzens/ring-expansion cascade, which would form the 2-quaternary-1,3-cyclopentenedione skeleton and generate key intermediate **2**. Lastly, **1** would be obtained through the removal of two protecting groups in **2**.

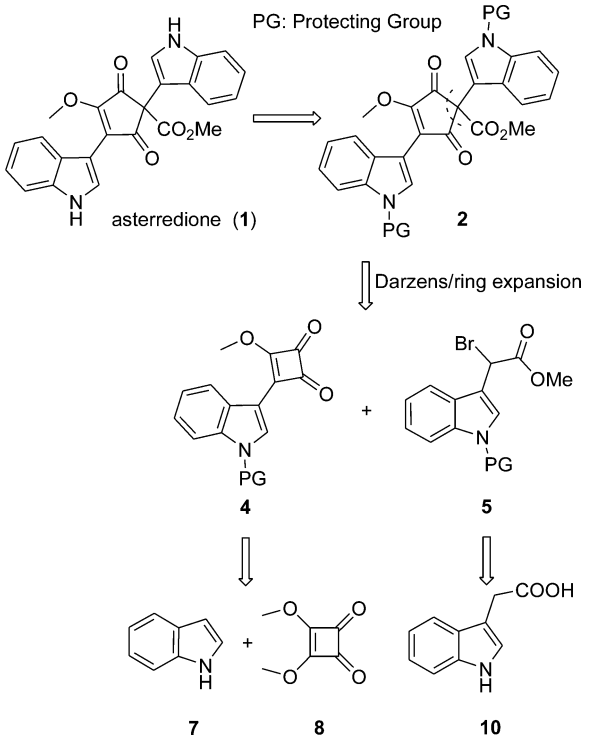
Our synthesis began with the preparation of fragments **4** and **5** (Scheme 2). Bromide **6** was prepared in 97% yield from indole **7** through bromination and protection treatments.[14] The in situ formed organlithium reagent from bromine−lithium exchange between *n*-butyllithium and **6** smoothly attacked dimethyl squarate **8** at −110 °C. After the following acid-promoted rearrangement, fragment **4** was generated with 76% yield in one pot. Starting from 3-indoleacetic acid **10**, ester **9** was obtained in 94% yield from the esterification and protection transformations.[15] Bromination of **9** was successfully achieved under the radical conditions of NBS and AIBN rather than through the employment of LiHMDS and NBS. Because of the instant decomposition,[16] fragment **5** was obtained in worse purity and yield after chromatography. Therefore, crude **5** was subjected to the next step directly.

With fragments **4** and **5** in hand, we next moved our attention to the construction of the 2-quaternary 1,3-cyclopentenedione skeleton of **1**, namely, the synthesis of

Received: December 23, 2013
Published: February 11, 2014

dx.doi.org/10.1021/jo4028177 | J. Org. Chem. 2014, 79, 2111−2114

Scheme 1. Retrosynthetic Pathway to Asterredione (1)



intermediate **2** (Scheme 3). Toward this end, the mixture of fragments **4** and **5** was treated with various bases to validate the Darzens/ring-expansion process. The countercation ion in the base has been proven to have an important effect on the reaction as commercially available hexamethyldislazides are applied. The best result came from the employment of NaHMDS, which afforded **2** in 40% yield over two steps from **9**. Yields of **2** of only 10 and 5% were obtained using LiHMDS and LDA as bases, respectively.

Regioselectivity is usually an important concern in the nucleophilic addition of cyclobutenediones because the addition to different carbonyl groups will lead to completely different products.[17−19] However, it is not the case in this event. Although there would be two intermediates, **3a** and **3b**, formed in the process, their ring expansions, through a semipinacol rearrangement of epoxides,[20−23] will furnish the same product **2** in the end.

The final target, asterredione (**1**), was eventually obtained in 81% yield through the deprotection treatment of **2** with TBSOTf in dichloromethane (Scheme 3). The identity of synthesized **1** was initially confirmed by the comparison of the ^{1}H NMR spectral data of the solution in deuterated chloroform with that of natural asterredione.[24] Fortunately, we secured the single crystal of synthesized **1** from its solution in a mixture of methanol, dichloromethane, and hexane. The structure of synthesized **1** was unambiguously confirmed by X-ray crystallographic analysis (see the ORTEP diagram in Scheme 4).

CONCLUSIONS

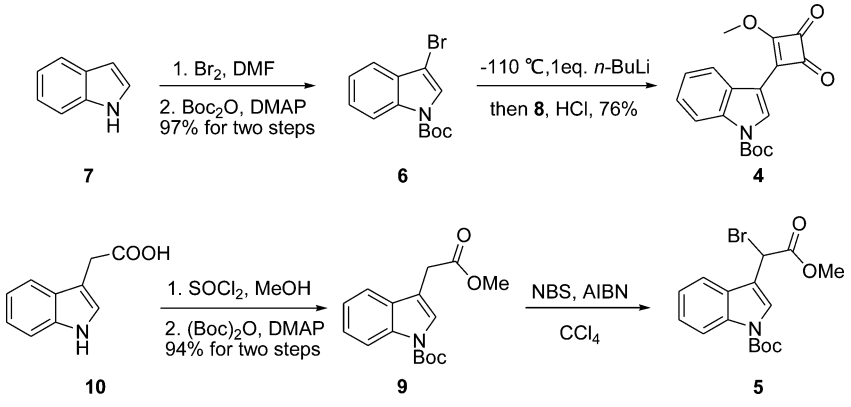
The total synthesis of asterredione was achieved for the first time. The entire approach requires only five linear steps, affording asterredione in 21.5% total yield. Meanwhile, the Darzens/ring-expansion strategy developed in our laboratory was confirmed to be an efficient approach to access 1,3-cyclopentenedione units containing quaternary carbon on C2.

EXPERIMENTAL SECTION

***tert*-Butyl-3-bromo-1*H*-indole-1-carboxylate (6).** A solution of Br_2 (2.3 mL, 45.7 mmol) in DMF (20 mL) was added dropwise to indole **7** (1.63g, 13.91 mmol) in DMF (80 mL) at 0 °C. After 30 min, the mixture was poured into the mixed solution of $NaHCO_3$ (3.6g, 44.68 mmol) and $NaHSO_3$ (4.6 g, 44.7 mmol) at 0 °C. After 24 h of stirring, the precipitate was isolated by filtration, washed with H_2O, and dried in vacuum to afford crude 3-bromo-1*H*-indole as a white solid powder. Then, Et_3N (0.15 mL, 0.1 mol), DMAP (250 mg, 2.0 mmol), and di-*tert*-butyl dicarbonate (3.9 mL, 16.7 mmol) was added to a solution of 3-bromo-1*H*-indole (2.73 g, 13.9 mmol) in DCM (20 mL) at room temperature. The mixture was stirred for 3 h at room temperature. The reaction mixture was quenched with a NH_4Cl saturated aqueous solution and extracted with DCM. The organic layer was washed with water and brine and dried over Na_2SO_4. The solvent was removed under reduced pressure. The product was purified by silica gel chromatography (PE/EtOAc, 10:1) to afford **6** (4.0 g, 97%) in two steps as yellow solid powder. mp 54−55 °C. IR (neat) ν_{max} 2981, 1730, 1450, 1380, 1248, 1157, 1060, 739 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.14 (br s, 1H), 7.64 (s, 1H), 7.52 (d, J = 8.0 Hz, 1H), 7.37 (t, J = 12.0 Hz, 1H), 7.30 (t, J = 16.0 Hz, 1H), 1.66 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 148.8, 134.5, 129.3, 125.3, 124.7, 123.2, 119.5, 115.1, 97.9, 84.2, 28.1. We failed to collect the mass spectra because of the ready decomposition of **6**.

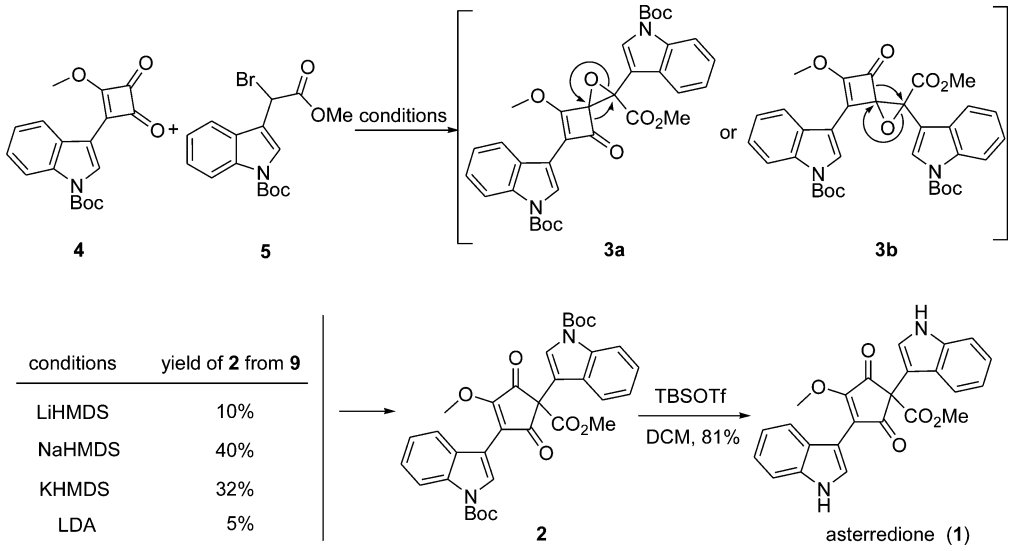
***tert*-Butyl-3-(2-methoxy-3,4-dioxocyclobut-1-enyl)-1*H*-indole-1-carboxylate (4).** To a solution of **6** (668 mg, 2.25 mmol) in THF (15 mL) was added *n*-butyllithium (2.40 M in hexanes, 1.10 mL, 2.6 mmol) slowly under an argon atmosphere at −110 °C. After 10 min, a solution of dimethyl squarate **8** in THF (2.0 mL) was added into the mixture. After 0.5 h of stirring at −110 °C, 12 N HCl in THF

Scheme 2. Synthesis of Fragments 4 and 5

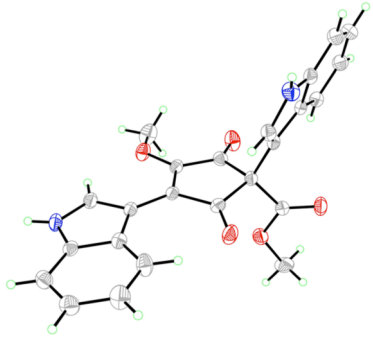


dx.doi.org/10.1021/jo4028177 | J. Org. Chem. 2014, 79, 2111−2114

Scheme 3. Synthesis of Asterredione (1)



Scheme 4. X-ray-Derived ORTEP of Asterredione (1)



was added slowly to the reaction mixture (adjusting the pH value to 3–4). After warming to room temperature, the reaction mixture was quenched with a $NaHCO_3$ saturated aqueous solution and extracted with EtOAc. The organic layer was washed with water and brine and dried over Na_2SO_4. The solvent was removed under reduced pressure. The product was purified by silica gel chromatography (PE/EtOAc, 7:1) to give **4** (562.7 mg, 76.3%) in two steps as yellow solid powder. mp 84–85 °C. IR (neat) ν_{max} 2985, 1593, 1741, 1396, 1315, 1159, 1041, 758 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 8.32 (s, 1H), 8.12 (d, J = 8.0 Hz, 1H), 8.07 (d, J = 8.0 Hz, 1H), 7.37 (t, J = 16.0 Hz, 1H), 7.30 (t, J = 8.0 Hz, 1H), 4.56 (s, 1H), 1.72 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 191.6, 190.4, 169.1, 148.5, 135.1, 128.7, 126.5, 125.6, 123.9, 122.1, 115.1, 109.5, 85.6, 61.4, 27.9. HRMS (ESI^+) m/z: $[M + K]^+$ calcd for $C_{18}H_{17}KNO_5$, 366.0738; found, 366.0755.

***tert*-Butyl-3-(2-methoxy-2-oxoethyl)-1*H*-indole-1-carboxylate (9).** To a solution of 3-indoleacetic acid **10** (5.1 g, 29.1 mmol) in dry MeOH (200 mL) precooled to 0 °C was added $SOCl_2$ (11.0 mL, 145.0 mmol) slowly. After being stirred for 4 h at room temperature, the reaction mixture was poured into an $NaHCO_3$ (200 mL) saturated aqueous solution precooled at 0 °C. The mixture was stirred for 10 min and extracted with EtOAc. The organic layer was washed with saturated $NaHCO_3$ aqueous solution and brine and dried over Na_2SO_4. The solvent was removed under reduced pressure to give crude methyl ester (5.28 g) as yellow oil. To the solution of crude methyl ester (5.28 g, 27.90 mmol) in DCM (50 mL) were added Et_3N (0.35 mL, 0.1 mmol), DMAP (0.67 g, 5.5 mmol), and di-*tert*-butyl dicarbonate (9.8 mL, 42.0 mmol) under an argon atmosphere at room temperature. After stirring for 5 h, the reaction mixture was quenched with a NH_4Cl saturated aqueous solution and extracted with DCM. The organic layer was washed with water and brine and dried over Na_2SO_4. The solvent was removed under reduced pressure. The product was purified by silica gel chromatography (PE/EtOAc, 20:1) to afford **9** (7.9 g, 94%) in two steps as yellow oil. IR (neat) ν_{max} 2979, 1737, 1692, 1455, 1373, 1259, 1157, 1014, 752 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 8.18–8.16 (br s, 1H), 7.60 (s, 1H), 7.56 (d, J = 8.0 Hz, 1H), 7.36 (t, J = 12.0 Hz, 1H), 7.29 (t, J = 12.0 Hz, 1H), 3.75 (s, 2H), 3.74 (s, 3H), 1.67 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.4, 149.5, 135.3, 130.0, 124.5, 124.4, 122.6, 118.9, 115.2, 113.0, 83.5, 52.1, 30.8, 28.1. HRMS (ESI^+) m/z: $[M + Na]^+$ calcd for $C_{16}H_{19}NNaO_4$, 312.1206; found, 312.1224.

Di-*tert*-butyl-3,3′-(4-methoxy-1-(methoxycarbonyl)-2,5-dioxocyclopent-3-ene-1,3-diyl)bis(1*H*-indole-1-carboxylate) (2). To a solution of **9** (290 mg, 1.01 mmol) in CCl_4 (15 mL) were added 2.20 equiv of NBS (400 mg, 2.27 mmol) and 0.05 equiv of AIBN (8.0 mg, 0.05 mmol). The mixture was heated under reflux in an argon atmosphere for 24 h. After cooling to room temperature, the reaction mixture was quenched with water and extracted with DCM. The organic layer was washed with water and brine and dried over Na_2SO_4. Crude **5** was obtained after the solvent was removed under reduced pressure. Because of its ready decomposition,[16] crude **5** was used for next step directly without purification. NMR data of crude **5**: ^1H NMR (400 MHz, $CDCl_3$) δ 8.17–8.15 (br s, 1H), 7.90 (s, 1H), 7.73 (d, J = 8.0 Hz, 1H), 7.36 (t, J = 16.0 Hz, 1H), 7.30 (t, J = 16.0 Hz, 1H), 5.69 (s, 1H), 3.83 (s, 3H), 1.66 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.2, 149.0, 135.5, 127.7, 125.7, 125.0, 122.9, 119.7, 115.3, 114.8, 84.3, 53.3, 38.8, 28.0.

Crude product **5** (400 mg, 1.1 mmol) and **4** (260 mg, 0.79 mmol) were dissolved in THF (7.0 mL) at −78 °C. In another roud-bottomed flask, sodium bis(trimethylsilyl) amide (2.0 M, in THF, 0.55 mL, 1.11 mmol) was dissolved in THF (7.0 mL) at −78 °C. Then, the two parts of the solution were added simultaneously to a third round-bottomed flask (25 mL) using two double-ended needles. After stirring for 5 min, the reaction mixture was quenched with water and extracted with EtOAc. The organic layer was washed with water and brine and dried over Na_2SO_4. The solvent was removed under reduced pressure. The product was purified by silica gel chromatography (PE/Et_2O, 7:1) to give **2** (194.72 mg, 40%) in two steps as yellow oil. IR (neat) ν_{max} 2979, 1737, 1616, 1454, 1373, 1257, 1155, 1083, 746 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 8.35 (s, 1H), 8.24 (d, J = 8.0 Hz, 1H), 8.16 (d, J = 4 Hz, 1H), 7.82 (d, J = 8.0 Hz, 1H), 7.76 (d, J = 8.0 Hz, 1H), 7.65 (s, 1H), 7.40–7.24 (m, 5H), 4.44 (s, 1H), 3.82 (s, 1H), 1.69 (s, 1H), 1.64 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 191.1, 190.7, 166.3, 162.8, 149.2, 149.1, 135.3, 130.6, 129.7, 128.5, 128.0, 125.5, 125.0, 124.8, 123.2, 122.9, 122.5, 121.4, 115.2, 112.5, 108.5, 84.8, 84.2, 63.8, 60.6, 53.7, 28.1. HRMS (ESI^+) m/z: $[M + Na]^+$ calcd for $C_{34}H_{34}N_2NaO_9$, 637.2157; found, 637.2153.

dx.doi.org/10.1021/jo4028177 | J. Org. Chem. 2014, 79, 2111–2114

Asterredione (1).[24] To a solution of **2** (110 mg, 0.18 mmol) in 10 mL of dry CH_2Cl_2 was added TBSOTf (0.1 mL, 0.45 mmol) slowly. After stirring for 2 h, the mixture was quenched with a $NaHCO_3$ saturated aqueous solution and extracted with DCM. The organic layer was washed with water and brine and dried over Na_2SO_4. The solvent was removed under reduced pressure. The product was purified by silica gel chromatography (PE/Et_2O, 1:2) to give asterredione (**1**) (60.4 mg, 81%) as yellow solid. The yellow rhombus crystal of **1** was obtained from the crystallization of the solution of **1** in a mixture of methanol, dichloromethane, and hexane (1:3:8). **1**: mp 113−115 °C. **1**: IR (neat) ν_{max} 3388, 1744, 1678, 1599, 1454, 1425, 1370, 1318, 1259, 1131, 1103, 744 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 8.69 (s, 1H), 8.25 (d, J = 2.4 Hz, 1H), 8.21 (s, 1H), 8.05 (d, J = 8.0 Hz, 1H), 7.81 (d, J = 8.0 Hz, 1H), 7.43 (d, J = 8.0 Hz, 1H), 7.36 (d, J = 8.0 Hz, 1H), 7.30 (d, J = 2.4 Hz, 1H), 7.28 (t, J = 8.0 Hz, 1H), 7.23 (t, J = 8.4 Hz, 1H), 7.19 (t, J = 8.0 Hz, 1H), 7.14 (t, J = 12.0 Hz, 1H), 4.47 (s, 1H), 3.81 (s, 1H). ^1H NMR (400 MHz, DMSO-d_6) δ 12.07 (s, 1H), 11.30 (s, 1H), 8.23 (s, 1H), 7.92 (d, J = 8.0 Hz, 1H), 7.57 (d, J = 8.0 Hz, 1H), 7.49 (d, J = 8.0 Hz, 1H), 7.39 (d, J = 8.0 Hz, 1H), 7.29 (s, 1H), 7.21 (t, J = 14.4 Hz, 1H), 7.15−7.08 (m, 2H), 7.00 (t, J = 14.4 Hz, 1H), 4.39 (s, 1H), 3.74 (s, 1H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 192.8, 190.6, 167.1, 159.9, 136.4, 132.5, 131.1, 125.7, 125.2, 125.0, 122.5, 122.4, 121.5, 120.5, 119.2, 112.2, 111.8, 106.8, 103.7, 64.2, 60.2, 55.0, 53.3. HRMS (ESI^+) m/z: $[M + Na]^+$ calcd for $C_{24}H_{18}N_2NaO_5$, 437.1108; found, 437.1125.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

^1H and ^{13}C NMR spectra of related compounds and X-ray crystallographic data for asterredione (**1**). This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

*xiangdonghu@nwu.edu.cn

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We are grateful for the financial support from the National Natural Science Foundation of China (NSF nos. 21002078 and 21372184), the State Education Ministry Scientific Research Foundation for the Returned Overseas Chinese Scholars, and the Shaanxi Province Technology Foundation for Selected Overseas Chinese. Qing Zhang was supported by a project for National Basic Science Personnel Training Funding (nos. J1103311 and J1210057).

■ REFERENCES

(1) Curl, E. A.; Truelove, B. *The Rhizosphere*; Springer-Verlag: New York, 1986.

(2) Martin, B. D. In *Soil Microbial Ecology*; Metting, F. B., Jr., Ed.; Marcel Dekker: New York, 1993.

(3) Garrity, G. M.; Heimbuch, B. K.; Gagliardi, M. *J. Ind. Microbiol. Biotechnol.* **1996**, *17*, 260−267.

(4) Wijeratne, E. M. K.; Turbyville, T. J.; Zhang, Z.; Bigelow, D.; Pierson, L. S., III; VanEtten, H. D.; Whitesell, L.; Canfield, L. M.; Gunatilaka, A. A. L. *J. Nat. Prod.* **2003**, *66*, 1567−1573.

(5) Moore, H. W.; Decker, O. H. W. *Chem. Rev.* **1986**, *86*, 821−830.

(6) Hergueta, A. R.; Moore, H. W. *J. Org. Chem.* **2002**, *67*, 1388−1391.

(7) Liebeskind, L. S.; Leeds, J. P.; Baysdon, S. L.; Iyer, S. *J. Am. Chem. Soc.* **1984**, *106*, 6451−6453.

(8) Shi, X.; Amin, S. R.; Liebeskind, L. S. *J. Org. Chem.* **2000**, *65*, 1650−1664.

(9) Negri, J.; Morwick, T.; Doyon, J.; Wilson, P. D.; Hickey, E. R.; Paquette, L. A. *J. Am. Chem. Soc.* **1993**, *115*, 12189−12190.

(10) Dong, S.; Parker, G. D.; Tei, T.; Paquette, L. A. *Org. Lett.* **2006**, *8*, 2429−2431.

(11) Crane, S. N.; Burnell, D. J. *J. Org. Chem.* **1998**, *63*, 5708−5710.

(12) Gao, F.; Burnell, D. J. *J. Org. Chem.* **2006**, *71*, 356−359.

(13) Xiao, F.; Liu, W.; Wang, Y.; Zhang, Q.; Li, X.; Hu, X. *Asian J. Org. Chem.* **2013**, *2*, 216−219.

(14) For a previous report on the preparation of **6**, see: James, C. A.; Coelho, A. L.; Gevaert, M.; Forgione, P.; Snieckus, V. *J. Org. Chem.* **2009**, *74*, 4094−4103.

(15) For a previous report on the preparation of **9**, see: Ghosh, N.; Nayak, S.; Sahoo, A. K. *J. Org. Chem.* **2011**, *76*, 500−511.

(16) For a previous report on the preparation and decomposition of **5**, see: Suárez-Castillo, O. R.; Meléndez-Rodríguez, M.; Cano-Escudero, I. C.; De Ita-Gutiérrez, S. L.; Sánchez-Zavala, M.; Morales-Ríos, M. S.; Joseph-Nathan, P. *Heterocycles* **2010**, *81*, 1169−1182.

(17) Packard, E.; Pascoe, D. D.; Maddaluno, J.; Gonçalves, T. P.; Harrowven, D. C. *Angew. Chem., Int. Ed.* **2013**, *52*, 13076−13079.

(18) Trost, B. M.; Thiel, O. R.; Tsui, H.-C. *J. Am. Chem. Soc.* **2003**, *125*, 13155−13164.

(19) Verma, S. K.; Fleischer, E. B.; Moore, H. W. *J. Org. Chem.* **2000**, *65*, 8564−8573.

(20) For reviews on semipinacol rearrangement of epoxides, please see refs 20−23 in: Parker, R. E.; Isaacs, N. S. *Chem. Rev.* **1959**, *59*, 737−799.

(21) Milstein, D.; Buchman, O.; Blum, J. *Tetrahedron Lett.* **1974**, *15*, 2257−2260.

(22) Rao, A. S.; Paknikar, S. K.; Kirtane, J. G. *Tetrahedron* **1983**, *39*, 2323−2367.

(23) Song, Z.-L.; Fan, C.-A.; Tu, Y.-Q. *Chem. Rev.* **2011**, *111*, 7523−7556.

(24) We failed to collect the ^{13}C NMR spectra of synthesized **1** because of its very poor solubility and instability in deuterated chloroform. NMR spectral data of **1** were obtained in good quality using deuterated dimethyl sulfoxide as the solvent. Please see the Supporting Information for details.