Available online at www.sciencedirect.com
SCIENCE DIRECT®
Tetrahedron 60 (2004) 3689–3694
Tetrahedron

Synthesis of (+)-zeylenone from shikimic acid

An Liu,[a] Zhan Zhu Liu,[b] Zhong Mei Zou,[a,*] Shi Zhi Chen,[b] Li Zhen Xu[a,*] and Shi Lin Yang[a]

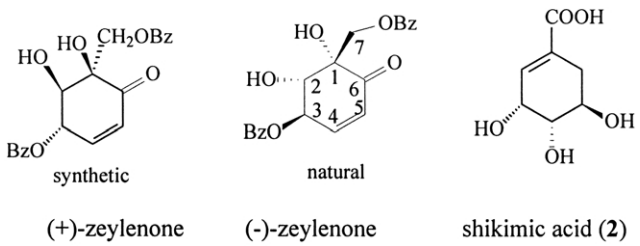
[a]*Institute of Medicinal Plant Development, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing 100094, People's Republic of China*
[b]*Institute of Materia Medica, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing 100050, People's Republic of China*

Received 19 November 2003; revised 16 February 2004; accepted 20 February 2004

Abstract—Starting from shikimic acid, the total synthesis of zeylenone was studied. The product was proved to be the (+)antipode of zeylenone through analysis and comparison of their respective spectra (including NMR, MS, IR and CD) and optical data. The absolute configuration of the natural product was thus determined to be (1*S*,2*S*,3*R*).

1. Introduction

A number of polyoxygenated cyclohexenes, which show anticancer, antiviral and antibiotic activities, have been isolated from the *Uvaria* genus.[1] As a part of our project of searching for the anticancer components from the plant source, zeylenone (Fig. 1) was isolated from *Uvaria grandiflora*, which showed remarkable inhibition of nucleoside transport in Ehrlich carcinoma cells and interesting cytotoxicity to cultured cancer cells.[2] The relative stereochemistry of zeylenone was assigned on the basis of the modern NMR techniques but the absolute configuration was not elucidated. Kunio Ogasawara and co-workers synthesized (−)tonkinenin A, which was isolated from *Uvaria tonkinensis*,[3] and corrected its structure to be the same as zeylenone.[4] As our continuous effort to confirm the structure and to study the structure–activity relationship of zeylenone, we report herein the enantioselective synthesis of the enantioisomer of zeylenone from shikimic acid (**2**).[5]



(+)-zeylenone (-)-zeylenone shikimic acid (**2**)

Figure 1. The structures of zeylenone and shikimic acid.

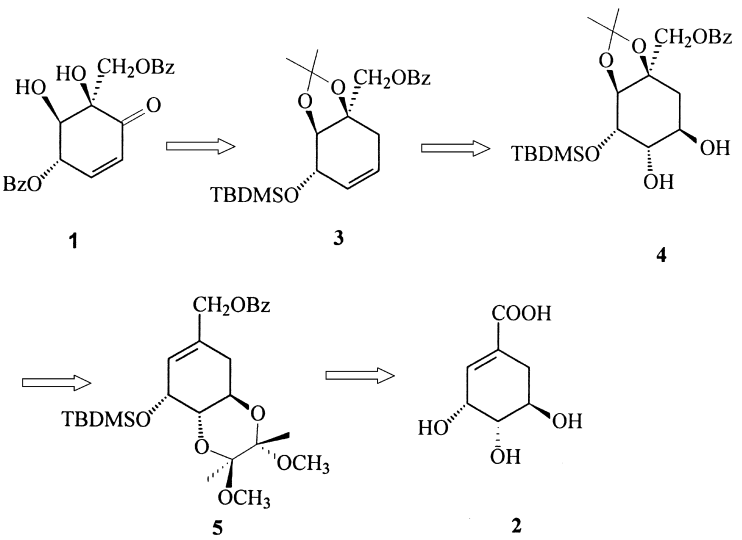
The retrosynthetic analysis for zeylenone is outlined in Scheme 1. Zeylenone could be obtained by oxidation of olefin **3** with SeO_2. The olefin **3** could be synthesized from the *trans* diol **4**, which could be derived from olefin **5** by oxidation with OsO_4. The olefin **5** could be obtained from shikimic acid (**2**) by reduction and selective protection.

2. Results and discussion

Our synthesis of **1** began with the methylation of shikimic acid (**2**), followed by regio-selective protection of *trans* vicinal diol **6** with 2,3-butanedione, (±)-camphorsulfonic acid (CSA, cat.) and trimethyl orthoformate in methanol at reflux to give compound **7** in 87% yield.[6] At the same time, we obtained the protected *cis* diol **8** in 10%. Fortunately, compound **8** could be converted into **7** with catalytic amount of (±)-CSA in refluxing methanol under Ar for 18 h in 92% yield, After introduction of *tert*-butyldimethylsilyl (TBDMS) group,[7] compound **9** was obtained in 97% yield from the protected diol **7**. After reduction of **9** with diisobutylaluminum hydride (DIBAL-H), alcohol **10** was obtained in 92% yield.[8] Benzoylation of **10** with benzoyl chloride afforded olefin **5** in 97% yield. The olefin **5** was dihydroxylated with OsO_4 and *N*-methylmorphorline-*N*-oxide (NMO) in THF/H_2O (1:1) under Ar to give stereoselectively the sole diol isomer **11** in 94% yield. The *cis* diol **11** was protected with 2,2-dimethylpropane to give acetonide **12** in 99% yield,[9] followed by selective deprotection with TFA/H_2O (1:1) to give the *trans* vicinal diol **4**(Scheme 2).[10]

Keywords: Zeylenone; Absolute configuration; Shikimic acid; Total synthesis; Enantiomer.
* Corresponding authors. Tel.: +86-10-62899705 (L.Z.X.); tel.: +86-10-63165253 (Z.Z.L.);
e-mail addresses: liuan62@yahoo.com.cn; liuzhanzhu@imm.ac.cn

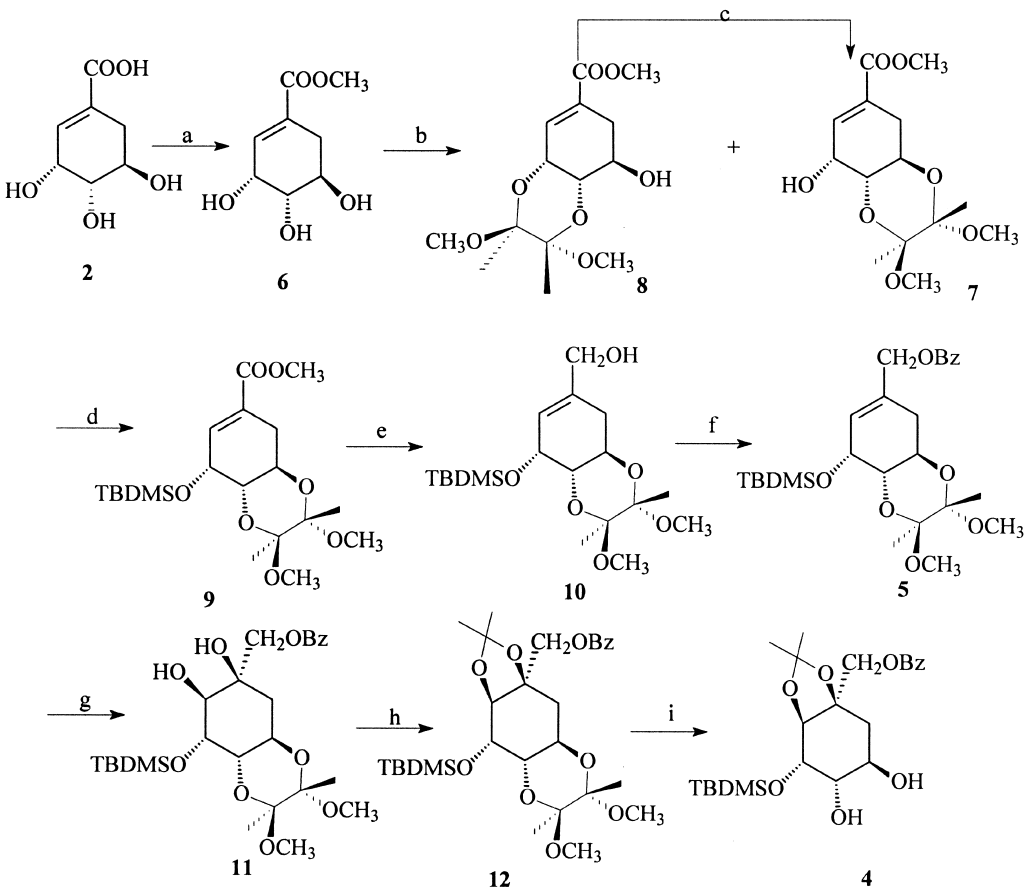
0040–4020/$ - see front matter © 2004 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2004.02.066



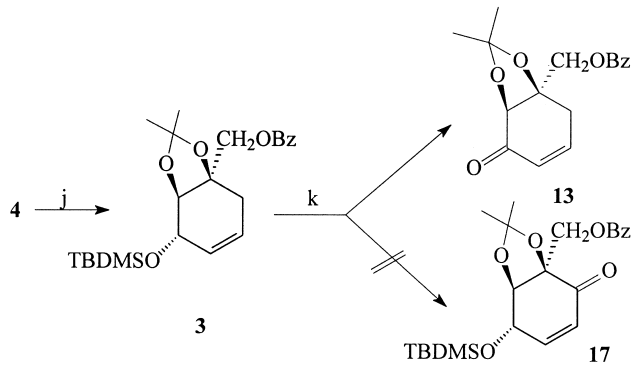
Scheme 1.

The treatment of *trans* vicinal diol **4** with Ph_3P, imidazole and iodine in toluene at reflux gave cyclohexene **3** in 87% yield.[10,11] We have tried to oxidize cyclohexene **3** by CrO_3/*t*-BuOOH, PCC, CuBr/*t*-BuOOH, or SeO_2 to synthesize enone. Unfortunately, we could not get the desired product **17**, only to obtain the TBDMS-deprotected enone **13** (Scheme 3).

So, the cyclohexene **3** was deprotected with *tetra*-butylammonium fluoride (TBAF) and benzoic acid in dry THF to



Scheme 2. (a) $SOCl_2$, MeOH, 10 °C, 93%; (b) $(CH_3CO)_2$, $CH(OMe)_3$, (±) CSA, MeOH, Ar, 48 h, 90 °C, 87%; (c) (±) CSA, MeOH, Ar, 18 h; (d) TBDMSCl, imidazole, DMAP, CH_2Cl_2, room temperature, 24 h, 97%; (e) DIBAL-H, toluene, −78 °C, 92%; (f) BzCl, DMAP, pyridine, room temperature 97%; (g) OsO_4, NMO, THF/H_2O (1:1), Ar, 94%; (h) $(CH_3)_2C(OCH_3)_2$, TsOH, CH_2Cl_2, Ar, room temperature, 99%; (i) TFA/H_2O (1:1), CH_2Cl_2, 79%.



Scheme 3. (j) Ph_3P, imidazole, I_2, reflux, 87%; (k) *t*-BuOOH, CrO_3, CH_2Cl_2, 36%.

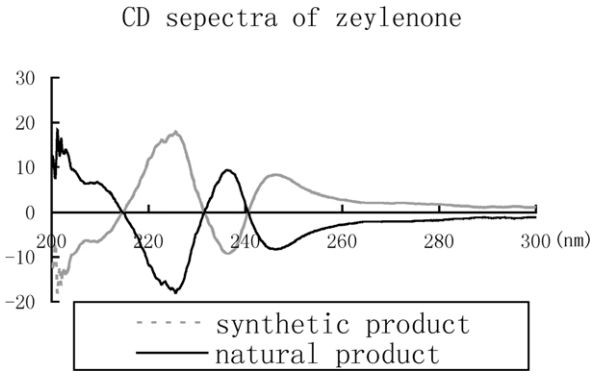


Figure 2. The CD spectra of zeylenone.

give alcohol **14**,[12] followed by the protection with benzoyl group to give olefin **15**. The enone **16** was obtained from **15** by oxidation with SeO_2 in dry THF at reflux for 24 h 40% yield.[13] Subsequent deprotection of **15** with TFA/H_2O (9:1) in CH_2Cl_2 at room temperature provided the target compound **1** in 85% yield (Scheme 4).

The spectral data (including NMR, MS and IR) of compound **1** were identical with those of natural zeyleone, which indicated that the relative stereochemistry of **1** was the same as that of the natural product. The positive Cotton effect[14] of the synthetic product **1** suggested the absolute stereochemistry of **1** to be of (1*R*,2*R*,3*S*). But the value and sign of the optical rotation of the compound **1** {$[\alpha]_D^{20}$=+118 (*c* 0.56, $CHCl_3$), $[\alpha]_D^{20}$=+26 (*c* 0.23, CH_3OH)} were opposite to those of the natural product {lit.[2] $[\alpha]_D^{20}$=−126.5 (*c* 0.747, $CHCl_3$); lit.[3] $[\alpha]_D^{20}$=−26.0 (*c* 0.89, MeOH); $[\alpha]_D^{20}$=−120 (*c* 0.60, $CHCl_3$), $[\alpha]_D^{20}$ −26 (*c* 0.26, CH_3OH)}. In addition, Cotton effects in CD spectra of the two compounds were opposite too (Fig. 2). All the data proved that compound **1** is the (+)-antipode of the natural product. So the absolute configuration of the natural product was determined to be (1*S*,2*S*,3*R*). This also proved that zeylenone and (−)-tonkinenin A were the same natural products.

3. Conclusion

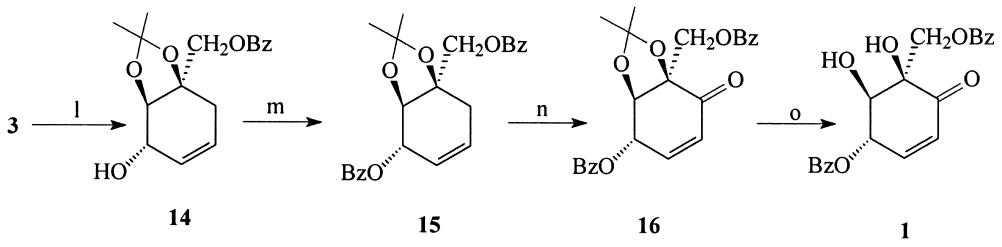
In summary, we have achieved the asymmetric total synthesis of (+)-antipode of zeylenone via a multi-step enantioselective route starting from shikimic acid. Our study shows the absolute configuration of the natural product zeylenone was proved to be (1*S*,2*S*,3*R*) and that zeylenone and (−)-tonkinenin A were the same natural products. Further work on the synthesis of the authentic natural product and its analogues is in progress.

4. Experimental

4.1. General

Melting points were obtained on a Yanaco apparatus and were uncorrected. Infrared spectra were measured on a Perkin–Elmer 683 spectrometer. ^1H and ^{13}C NMR spectra were recorded on a JEOL FX-90Q spectrometer. Chemical shifts were reported in ppm with tetramethylsilane as the internal standard and *J* values in Hz. Mass spectra and high-resolution mass data were obtained on a VGZAB-2F spectrometer. Silica gel was used for flash column chromatography. All solvents were purified and dried by standard techniques or used as supplied from commercial sources as appropriate.

4.1.1. (3*R*,4*S*,5*R*)-3,4,5-Trihydroxy-1-cyclohexene-1-carboxylate methyl ester (6). To a solution of shikimic acid (**2**) (20 g, 0.11 mol) in MeOH, $SOCl_2$ (15 mL, 0.21 mol) was added dropwise during 1 h at 0 °C. Then the reaction mixture was warmed to room temperature and stirred overnight. Removal of the solvent and recrystallization from EtOAc afforded **6** as white solid (19.9 g, 93%). Mp 112–113 °C, $[\alpha]_D^{20}$=−125 (*c* 1.8, EtOH), IR (KBr): 3330, 2900, 1716, 1658, 1435, 1244, 1095, 1068, 930, 746 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 6.71–6.73 (m, 1H, H-2), 4.83 (s, 3H, OCH_3), 4.31 (br s, 1H, H-3), 3.93 (dd, 1H, *J*=12.3, 5.1 Hz, H-5), 3.61–3.65 (m,1H, H-4), 3.25 (s, 1H, OH), 2.60–2.67 (m, 1H, H-6β), 2.17 (dd, 1H, *J*=18.0, 5.1 Hz, H-6α).



Scheme 4. (l) TBAF, benzoic acid, THF, room temperature, 94%; (m) BzCl, DMAP, pyridine, room temperature, 99%; (n) SeO_2, THF, reflux, 40%; (o) TFA/H_2O (9:1), CH_2Cl_2, 85%.

4.1.2. Methyl (3*R*,4*S*,5*R*)-3-hydroxy-4,5-(2,3-dimethoxybutan-2,3-dioxy)-cyclohex-1-ene-1-carboxylate (7) and methyl (3*R*,4*S*,5*R*)-5-hydroxy-3,4-(2,3-dimethoxybutan-2,3-dioxy)-cyclohex-1-ene-1-carboxylate (8). Trimethyl orthoformate (60 g, 0.57 mol) was added to a mixture of **6** (17.8 g, 0.095 mol), 2,3-butanedione (20 g, 0.23 mol) and catalytic amount of DMAP (0.12 g, 0.1 mmol) in MeOH (200 mL), and the whole mixture was refluxed under Ar for 48 h. After being cooled to room temperature, $NaHCO_3$ (20 g) was added to the mixture and stirred for 10 min. Removal of the solvent and purification of the residue by column chromatography (acetone/petroleum ether 1:5) afforded colorless oil **7** (24.9 g, 87%) and white solid **8** (3.7 g, 12%). Compound **7**: $[\alpha]_D^{20}=+23.1$ (*c* 0.89, $CHCl_3$), ^1H NMR ($CDCl_3$, 300 MHz) δ 6.90 (dd, 1H, *J*=5.1, 2.7 Hz, H-2), 4.39 (t, 1H, *J*=4.8 Hz, H-3), 4.06–4.15 (m, 1H, H-5), 3.76 (s, 3H, OCH_3), 3.62 (dd, 1H, *J*=10.8, 4.5 Hz, H-4), 3.28 (s, 3H, OCH_3), 3.26 (s, 3H, OCH_3), 2.84 (dd, 1H, *J*=17.7, 5.7 Hz, H-6a), 2.25 (ddd, 1H, *J*=17.7, 7.5, 2.7 Hz, H-6b), 1.34 (s, 3H, CH_3), 1.31 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 166.6, 135.0, 131.8, 100.0, 99.2, 70.5, 65.0, 62.4, 52.1, 48.0, 47.9, 30.0, 17.8, 17.7; EIMS *m*/*z*: 271, 213, 154, 139, 125, 101, 95, 75; FAB-HRMS: cacld for $C_{14}H_{22}O_7Na$ $[M+Na]^+$: 325.1263, found 325.1283. Compound **8**: mp 137–138 °C, $[\alpha]_D^{20}=-144.2$ (*c* 0.26, $CHCl_3$), ^1H NMR ($CDCl_3$, 300 MHz) δ 6.98 (s, 1H, H-2), 4.39 (d, 1H, *J*=1.2 Hz, H-3), 4.17 (br s, 1H, H-5), 4.11 (br s, 1H, H-4), 3.73 (s, 3H, $COOCH_3$), 3.27 (s, 3H, OCH_3), 3.26 (s, 3H, OCH_3), 2.64 (ddd, 1H, *J*=18.3, 6, 3 Hz, H-6β), 2.40 (d, H, *J*=18.3 Hz, H-6α), 1.27 (s, 3H, CH_3), 1.24 (s, 3H, CH_3). EIMS *m*/*z*: 271, 154, 139, 122, 101, 95, 75. FAB-HRMS: cacld for $C_{14}H_{22}O_7Na$ $[M+Na]^+$: 325.1263, found 325.1283.

A solution of **8** (1.0 g, 3.3 mmol) and catalytic amount of (±)-CSA was stirred in MeOH (20 mL) at reflux under Ar for 18 h. After being cooled to room temperature, $NaHCO_3$ (0.5 g) was added to the mixture and stirred for 5 min. Removal of the solvent and purification of the residue by column chromatography (acetone/petroleum ether 1:5) afforded colorless oil **7** (0.92 g, 92%).

4.1.3. Methyl (3*R*,4*S*,5*R*)-3-*O*-*tert*-butyldimethylsilyl-4,5-(2,3-dimethoxybutan-2,3-dioxy)- cyclohex-1-ene-1-carboxylate (9). To a solution of **7** (10.0 g, 33.1 mmol), imidazole (3.8 g, 55.4 mmol) and catalytic amount of dimethylaminopyridine (DMAP, 0.05 g, 0.4 mmol) in dry CH_2Cl_2 (300 mL), *tert*-butyldimethyl-silyl chloride (5.0 g, 33.2 mmol) was added, and the mixture was stirred at room temperature for 24 h. After quenching the reaction with saturated aqueous NH_4Cl (150 mL), the reaction mixture was extracted with CH_2Cl_2 (3×150 mL), washed with brine (50 mL), and dried ($MgSO_4$). The solvent was removed and the product was purified by column chromatography (acetone/petroleum ether 1:10), which yielded **9** as white solid (13.3 g, 97%). Mp 71–72 °C, $[\alpha]_D^{20}=-15.6$ (*c* 0.18, $CHCl_3$), ^1H NMR ($CDCl_3$, 300 MHz) δ 6.75 (dd, 1H, *J*=5.7, 2.7 Hz, H-2), 4.29 (t, 1H, *J*=4.5 Hz, H-3), 4.10 (dt, 1H, *J*=10.5, 6 Hz, H-5), 3.73 (s, 3H, OCH_3), 3.46 (dd, 1H, *J*=10.2, 4.5 Hz, H-4), 3.23 (s, 3H, OCH_3), 3.21 (s, 3H, OCH_3), 2.88 (dd, 1H, *J*=17.4, 6 Hz, H-6α), 2.20 (ddd, 1H, *J*=17.4, 10.2, 2.7 Hz, H-6β), 1.27 (s, 3H, CH_3), 1.26 (s, 3H, CH_3), 0.87 (s, 9H, CH_3×3), 0.11 (s, 3H, CH_3), 0.08 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 167.1, 136.8, 129.7, 99.5, 98.7, 70.8, 66.0, 62.4, 52.0, 47.8, 47.6, 30.4, 25.8 (C×3), 18.3, 17.9, 17.7, −4.70 (C×2); HRFABMS: cacld for $C_{20}H_{36}O_7SiNa$ $[M+Na]^+$: 439.2122, found 439.2127.

4.1.4. (3*R*,4*S*,5*R*)-3-*O*-*tert*-Butyldimethylsilyl-4,5-(2,3-dimethoxybutan-2,3-dioxy)-cyclohex-1-ene-1-methanol (10). A solution of diisobutylaluminium hydride (1 M, 58 mL) in toluene was added dropwise to the solution of **9** (12.1 g, 29 mmol) in dry toluene under Ar at −78 °C. After being stirred for 20 min, water (100 mL) was added to the reaction mixture to quench the reaction. The mixture was extracted with diethyl ether (3×100 mL), washed with brine (50 mL) and dried ($MgSO_4$). The solvent was removed in vacuo and purified by column chromatography (acetone/petroleum ether 1:6) to yield alcohol **10** (11.3 g, 92%) as white solid. Mp 90–91 °C, $[\alpha]_D^{20}=+8.6$ (*c* 0.11, $CHCl_3$), IR ν_{max}^{KBr} cm^{-1}:: 3244, 2971, 1685, 1255, 1124, 839, 775, 673 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 5.69 (d, 1H, *J*=4.5 Hz, H-2), 4.22 (t, 1H, *J*=4.5 Hz, H-3), 4.14 (td, 1H, *J*=10.5, 6.0 Hz, H-5), 4.02 (s, 2H, H-7), 3.48 (dd, 1H, *J*=10.8, 3.9 Hz, H-4), 3.24 (s, 3H, OCH_3), 3.22 (s, 3H, OCH_3), 2.34 (dd, 1H, *J*=16.8, 6.0 Hz, H-6α), 2.09 (dd, 1H, *J*=16.8, 10.5 Hz, H-6β), 1.27 (s, 6H, CH_3×2), 0.90 (s, 9H, CH_3×3), 0.09 (6H, s, CH_3×2); ^{13}C NMR ($CDCl_3$, 75 Hz) δ 138.2, 128.2, 99.4, 98.6, 71.3, 66.4, 65.9, 62.1, 48.2, 47.7, 31.5, 25.7 (C×3), 18.4, 17.9, 17.7, −4.6, −4.8.

4.1.5. (3*R*,4*S*,5*R*)-1-Benzoyloxymethyl-3-*O*-*tert*-butyldimethylsilyl-4,5-(2,3-dimethoxybutan-2,3-dioxy)-cyclohex-1-ene (5). Benzoyl chloride (5.3 mL, 43.5 mmol) was added dropwise to a solution of alcohol **10** (11.0 g, 28.4 mol) and catalytic amount of DMAP (0.05 g, 0.4 mmol) in dry pyridine (200 mL) at room temperature during a period 20 min. Stirring was continued for another 2 h and then saturated aqueous $NaHCO_3$ (100 mL) was added to the reaction mixture to quench the reaction. The mixture was extracted with CH_2Cl_2 (3×100 mL), washed with brine (30 mL) and dried ($MgSO_4$). The solvent was removed and the product purified by column chromatography (acetone/petroleum ether 1:10), which yielded protected alcohol **5** (13.8 g, 97%) as white solid. Mp 59–60 °C, $[\alpha]_D^{20}=+2.8$ (*c* 0.64, $CHCl_3$); IR ν_{max}^{KBr} cm^{-1}:: 2947, 2854, 1720, 1452, 1375, 1267, 1140, 1076, 1039, 987, 901, 860, 833, 781, 719 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 8.06 (d, 2H, *J*=7.5 Hz, H-2′ and 6′), 7.55 (d, 1H, *J*=7.5 Hz, H-4′), 7.45 (t, 2H, *J*=7.5 Hz, H-3′ and 5′), 5.80 (d, 1H, *J*=3.9 Hz, H-2), 4.75 (s, 2H, H-7), 4.22–4.27 (m, 1H, H-3), 4.19 (dd, 1H, *J*=10.5, 4.3 Hz, H-5), 3.53 (dd, 1H, *J*=10.8, 3.9 Hz, H-4), 3.25 (s, 6H, OCH_3×2), 2.44 (dd, 1H, *J*=17.5, 6.3 Hz, H-6α), 2.30 (ddd, 1H, *J*=17.5, 10.2, 1.8 Hz, H-6β), 1.28 (s, 6H, CH_3×2), 0.88 (s, 9H, CH_3×3), 0.10 (s, 3H, CH_3), 0.09 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 166.2, 133.8, 133.1, 130.0, 129.7 (C×2), 128.4 (C×2), 125.9, 99.4, 98.7, 71.0, 67.8, 66.3, 62.6, 47.8, 47.7, 32.1, 25.8 (C×3), 18.3, 17.9, 17.7, −4.6, −4.8.

4.1.6. (1*R*,2*R*,3*R*,4*S*,5*R*)-1-Benzoyloxymethyl-1,2-dihydroxy-3-*O*-*tert*-butyldimethylsilyl-4,5- (2,3-dimethoxybutan-2,3-dioxy)-cyclohexane (11). A suspension of olefin **5** (13 g, 26 mmol), *N*-methylmorpholine-*N*-oxide (NMO, 5.7 g, 42.0 mmol), and catalytic amount of OsO_4 (70.0 mg, 0.28 mmol) in THF/H_2O (250 mL, v/v 1:1) under

Ar was stirred violently at room temperature for 12 h. The solid $Na_2S_2O_3$ (25 g) and EtOAc (100 mL) were added to the reaction mixture and stirred for another 30 min. The mixture was loaded onto a flash chromatographic column and washed with EtOAc. Removal of the EtOAc and purification of the residue by column chromatography (acetone/petroleum ether 1:3) afforded white solid **11** (13.1 g, 94%). Mp 136–138 °C, $[\alpha]_D^{20}$=+73 (*c* 0.64, $CHCl_3$), ^{1}H NMR (300 MHz, $CDCl_3$, *J* in Hz) δ 4.85 (d, 1H, *J*=12 Hz, H-7a), 4.45 (d, 1H, *J*=12 Hz, H-7b), 4.16 (t, 1H, *J*=3.3 Hz, H-3), 3.90–3.96 (m, 1H, H-5), 3.83 (dd, 1H, *J*=10.5, 3.3 Hz, H-4), 3.81 (d, 1H, *J*=3.3 Hz, H-2), 2.42–2.50 (m, 1H, H-6a), 1.85–1.93 (m, 1H, H-6b), 3.25 (s, 3H, OCH3), 3.22 (s, 3H, OCH_3), 1.29 (s, 3H, CH_3), 1.27 (s, 3H, CH_3), 0.88 (s, 9H, CH_3×3), 0.15 (s, 3H, CH_3), 0.08 (s, 3H, CH_3), benzoyl groups: δ 8.04 (d, 2H, *J*=7.5 Hz), 7.59 (t, 1H, *J*=7.5 Hz), 7.46 (d, 2H, *J*=7.5 Hz); ^{13}C NMR (75 MHz, $CDCl_3$, *J* in Hz) δ 167.2, 133.4, 129.7, 129.5 (2C), 128.5 (2C), 99.7, 99.0, 77.4, 77.0, 76.6, 74.2, 73.5, 71.9, 69.5, 62.4 (C×2), 47.8, 47.6, 34.1, 25.7 (C×3), 18.2, 17.8, 17.6, −4.9, −5.3; TOFMS *m*/*z*: 405, 315, 297, 237, 199, 197, 181, 169, 122, 105, 75; HRTOFMS: cacld for $C_{26}H_{42}O_9SiNa$ $[M+Na]^+$: 549.2490, found 549.2479.

4.1.7. (1*R*,2*R*,3*R*,4*S*,5*R*)-1-Benzoyloxymethyl-1,2-*O*,*O*-isopropylidine-3-*O*-*tert*-butyldimethyl- silyl-4,5-(2,3-dimethoxybutan-2,3-dioxy)-cyclohexane (12). Dimethoxypropane (1.2 g, 11.4 mmol) was added to the solution of diol **11** (3.0 g, 5.7 mmol) and catalytic amount of *p*-toulenesulfonic acid (19 mg, 0.11 mmol) in dried CH_2Cl_2 (100 mL), and the mixture was stirred under Ar at room temperature for 3 h. After adding 10% aqueous $NaHCO_3$ (50 mL), the reaction mixture was stirred for 5 min and then extracted with CH_2Cl_2 (3×50 mL). The organic layers were combined, washed with brine, and dried ($MgSO_4$). The solvent was removed and the residue was purified by column chromatography (acetone/petroleum ether 1:10) to yield **12** as white solid (3.2 g, 99%). Mp 148–150 °C, $[\alpha]_D^{20}$=+19 (*c* 0.25, $CHCl_3$), ^{1}H NMR (300 MHz, CD_3Cl, *J* in Hz) δ 8.05 (d, 2H, *J*=7.8 Hz), 7.58 (t, 1H, *J*=7.8 Hz), 7.44 (t, 2H, *J*=7.8 Hz), 4.65–4.73 (m, 1H), 4.2–4.4 (m, 4H), 3.94–4.03 (m, 1H), 3.31 (s, 3H, OCH_3), 3.30 (s, 3H, OCH_3), 2.10–2.20 (m, 1H, H-6a), 1.85–1.94 (m, 1H, H-6b), 1.52 (s, 6H, CH_3), 1.36 (s, 3H, CH_3), 1.32 (s, 3H, CH_3), 0.84 (s, 9H, CH_3), 0.14 (s, 3H, CH_3), 0.17 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 166.1, 133.1, 130.0, 129.7 (C×2), 128.4 (C×2), 109.0, 99.9, 96.5, 80.6, 70.5, 69.8, 66.0, 62.6, 48.3, 48.4, 36.6, 28.1, 26.7, 25.6 (C×3), 23.6, 18.1, 18.0 (C×2), −4.5, −5.3.

4.1.8. (1*R*,2*R*,3*R*,4*S*,5*R*)-1-Benzoyloxymethyl-1,2-*O*,*O*-isopropylidine-3-*O*-*tert*-butyldimethyl- silyl-4,5-dihydroxy-cyclohexane (4). To a violently stirred solution of **12** (3.1 g, 5.6 mmol) in CH_2Cl_2 (150 mL), 50% aqueous TFA (v/v, 1:1, 10.0 mL) was added. After 6 h, 100 mL 5% aqueous $NaHCO_3$ was added to the reaction mixture. Stirring for 5 min, the mixture was extracted with CH_2Cl_2 (3×100 mL), washed with brine (50 mL) and dried ($MgSO_4$). Removal of the solvent and purification of the residue by column chromatography (acetone/ petroleum ether 1:5) gave diol **4** (2.0 g, 80%) as white solid. Mp 46–48 °C, $[\alpha]_D^{20}$=−40 (*c* 0.20, $CHCl_3$), IR ν_{max}^{KBr} cm^{-1}: 3465, 2931, 1726, 1275, 1097, 1066, 839, 712 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$, *J* in Hz) δ 8.05 (2H, d, *J*=7.5 Hz), 7.57 (1H, t, *J*=7.5 Hz), 7.44 (2H, t, *J*=7.5 Hz), 4.66 (1H, d, *J*=12.3 Hz, H-7a), 4.38 (1H, t, *J*=3 Hz, H-3), 4.18–4.25 (1H, m, H-2), 4.20 (1H, d, *J*=12.3 Hz, H-7b), 3.74–3.80 (1H, m, H-5), 3.69 (1H, dd, *J*=9.3, 3 Hz, H-4), 2.25 (1H, dd, *J*=13.5, 4.2 Hz, H-6a), 2.03 (1H, t, *J*=13.5 Hz, H-6b), 1.50 (3H, s, CH_3), 1.35 (3H, s, CH_3), 0.86 (9H, s, CH_3×3), 0.14 (3H, s, CH_3), 0.10 (3H, s, CH_3); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 166.1, 133.1, 129.9, 129.6 (C×2), 128.4 (C×2), 108.9, 80.4, 77.9, 73.9, 70.9, 67.2, 65.9, 38.1, 28.2, 26.7, 25.8 (C×3), 18.0, −4.8, −5.0; HRFABMS: cacld for $C_{23}H_{37}O_7Si$ $[M+H]^+$: 453.2303, found 453.2306.

4.1.9. (1*R*,2*R*,3*S*)-1-Benzoyloxymethyl-1,2-*O*,*O*-isopropylidine-3-*O*-*tert*-butyldimethylsilyl- cyclohex-4-ene (3). To a solution of diol **4** (2.0 g, 4.4 mmol) in toluene (100 mL) were added triphenylphosphine (4.6 g, 18.0 mmol), imidazole (1.2 g, 18.0 mmol) and iodine (3.4 g, 13.0 mmol). The mixture was heated under reflux for 4 h. After cooling, the reaction mixture was diluted with EtOAc and washed successively with 10% aqueous sodium thiosulfate solution, saturated $NaHCO_3$ solution, brine and dried ($MgSO_4$). Removal of the solvent and purification of the residue by column chromatography (EtOAc/petroleum ether 1:10) gave olefin **3** (1.6 g, 87%) as colorless oil: $[\alpha]_D^{20}$=+48 (*c* 0.19, $CHCl_3$), ^{1}H NMR (300 MHz, $CDCl_3$, *J* in Hz) δ 8.08 (2H, d, *J*=7.5 Hz), 7.57 (1H, t, *J*=7.5 Hz), 7.44 (2H, t, *J*=7.5 Hz), 5.80–5.90 (2H, m, H-3 and 4), 4.46 (1H, d, *J*=11.4 Hz, H-7a), 4.35–4.43 (1H, m, H-6), 4.27 (1H, d, *J*=11.4 Hz, H-7b), 4.20 (1H, d, *J*=3.3 Hz, H-5), 2.44 (1H, dd, *J*=15.9, 3.3 Hz, H-6a), 2.30 (1H, t, *J*=15.9 Hz, H-6b), 1.42 (3H, s, CH_3), 1.40 (3H, s, CH_3), 0.86 (9H, s, CH_3×3), 0.09 (3H, s, CH_3), 0.08 (3H, s, CH_3); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 166.2, 133.0, 130.0, 129.7 (C×2), 129.3, 128.3 (C×2), 126.5, 108.8, 80.8, 79.9, 68.1, 67.9, 32.3, 28.1, 27.1, 25.7 (C×3), 18.2, −4.7, −4.9; HRFABMS: cacld for $C_{23}H_{35}O_5Si$ $[M+H]^+$: 419.2248, found 419.2236.

4.1.10. (1*R*,2*S*)-1-Benzoyloxymethyl-1,2-*O*,*O*-isopropylidine-cyclohex-4-en-3-one (13). A solution of **3** (72.0 mg 0.17 mmol) in dried CH_2Cl_2 was added to a solution of 70% *t*-BuOOH (0.25 mL, 1.8 mmol) and catalytic amount of CrO_3 (1.7 mg, 0.017 mmol) in CH_2Cl_2 (2 mL) under Ar. The reaction mixture was stirred at room temperature for 24 h, and then poured into column chromatography washing with EtOAc. The solvent was removed and the residue was purified by column chromatography (acetone/petroleum ether 1:15), to give enone **13** as a white solid (30 mg, 56%). Mp 43–45 °C, ^{1}H NMR ($CDCl_3$, 300 MHz, *J* in Hz) δ 8.00 (d, 2H, *J*=7.2 Hz), 7.58 (t, 1H, *J*=7.2 Hz), 7.44 (t, 2H, *J*=7.2 Hz), 6.90–7.01 (m, 1H, H-5), 6.24 (td, 1H, *J*=10.5, 2.1 Hz, H-4), 4.40 (d, 1H, *J*=11.4 Hz, H-7a), 4.39 (s, 1H, H-2), 4.34 (d, 1H, H-7b), 2.79–2.87 (m, 2H, H-6), 1.50 (s, 3H, CH_3), 1.34 (s, 3H, CH_3); IR ν_{max}^{KBr} cm^{-1}: 3430, 1720, 1698, 1271, 1113, 714;

4.1.11. (1*R*,2*R*,3*S*)-1-Benzoyloxymethyl-1,2-*O*,*O*-isopropylidine-3-hydroxy-cyclohex-4-ene (14). Tetrabutylammonium fluoride (1.0 M in THF, 14.4 mL, 14.4 mmol) and benzoic acid (2.0 g, 14.4 mmol) were added to the solution of **3** (1.5 g, 3.6 mmol) in dry THF (60 mL). The solution was stirred at room temperature for 24 h, and then

was evaporated under reduced pressure to leave a residue, which was partitioned between water and EtOAc. The organic layer was dried ($MgSO_4$). Removal of the solvent and purification of the residue by column chromatography (acetone/petroleum ether 1:5) gave alcohol **14** (1.0 g, 94%) as colorless oil: $[\alpha]_D^{20}=-4.7$ (*c* 0.32, $CHCl_3$), ^1H NMR (300 MHz, $CDCl_3$, *J* in Hz) δ 8.06 (2H, d, *J*=7.5 Hz), 7.53 (1H, t, *J*=7.5 Hz), 7.40 (2H, t, *J*=7.5 Hz), 5.87 (2H, m, H-4 and 5), 4.37–4.43 (1H, m, H-2), 4.39 (1H, d, *J*=11.7 Hz, H-7a), 4.31 (1H, d, *J*=11.7 Hz, H-7b), 4.20 (1H, d, *J*=3.3 Hz, H-3), 2.52 (1H, dd, *J*=17.1, 5.4 Hz, H-6a), 2.29 (1H, d, *J*=17.1 Hz, H-6b), 1.45 (3H, s, CH_3), 1.42 (3H, s, CH_3); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 166.5, 147.7, 133.5, 129.7 (C×2), 129.0, 128.5 (C×2), 126.8, 109.2, 81.6, 79.7, 68.4, 67.9, 32.4, 28.3, 27.2; HRFABMS: cacld for $C_{17}H_{20}O_5Na$ $[M+Na]^+$: 327.1203, found 327.1221.

4.1.12. (1*R*,2*R*,3*S*)-1-Benzoyloxymethyl-1,2-*O*,*O*-isopropylidine-3-benzoyloxy-cyclohex-4-ene (15). Benzoyl chloride (0.38 mL, 3.3 mmol) was added dropwise to a solution of alcohol **14** (0.66 g, 2.2 mol) and catalytic amount of DMAP (5 mg, 0.04 mmol) in dry pyridine (20 mL) at room temperature during a period 5 min. Stirring was continued for another 2 h and then saturated aqueous $NaHCO_3$ (10 mL) was added to the reaction mixture to quench the reaction. The mixture was extracted with CH_2Cl_2 (3×10 mL), washed with brine (5 mL) and dried ($MgSO_4$). The solvent was removed and the product was purified by flash chromatography (acetone/petroleum ether 1:5), to yield alcohol **15** (0.88 g, 99%) as colorless oil: $[\alpha]_D^{20}=+114$ (*c* 0.24, $CHCl_3$), ^1H NMR ($CDCl_3$, 300 MHz) δ 8.03 (2H, d, *J*=7.5 Hz), 7.96 (2H, d, *J*=7.5 Hz), 7.50–7.57 (2H, m), 7.33–7.50 (4H, m), 6.00–6.07 (2H, m, H-4 and 5), 5.70 (1H, s, H-3), 4.55 (1H, d, *J*=11.7 Hz, H-7a), 4.48–4.52 (1H, m, H-2),4.38 (1H, d, *J*=11.7 Hz, H-7b), 2.43–2.58 (2H, m, H-6), 1.49 (3H, s, CH_3), 1.45 (3H, s, CH_3); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 166.2, 165.6, 133.2, 133.1 (C×2), 129.7 (C×4), 129.4 (C×2), 128.5 (C×4), 124.7, 109.4, 79.3, 77.9, 69.4, 67.4, 32.2, 28.0, 27.3; HRFABMS: cacld for $C_{24}H_{25}O_6$ $[M+H]^+$: 409.1646, found 409.1650.

4.1.13. (1*R*,2*R*,3*S*)-1-Benzoyloxymethyl-1,2-*O*,*O*-isopropylidine-3-benzoyloxy-cyclohex-4-en-one (16). A suspension of olefin **15** (0.20 g, 0.49 mmol) and SeO_2 (0.22 g, 2.0 mmol) in dried THF were stirred under reflux for 24 h. After cooling, the reaction mixture was poured into a flash chromatography and washed with EtOAc. The solvent was removed and the product purified by flash chromatography (acetone/petroleum ether 1:10), which yielded enone **16** (83 mg, 40%) as colorless oil: $[\alpha]_D^{20}=+132$ (*c* 0.12, $CHCl_3$); IR ν_{max}^{KBr} cm^{-1}: 2989, 1726, 1691, 1452, 1273, 1093, 860, 710; ^1H NMR ($CDCl_3$, 300 MHz, *J* in Hz) δ 7.94 (2H, d, *J*=7.5 Hz), 7.84 (2H, d, *J*=7.5 Hz), 7.42–7.54 (2H, m), 7.36–7.42 (2H, m), 7.24–7.34 (2H, m), 7.04 (1H, ddd, *J*=1.5, 4.8 Hz, 10.2, H-4), 6.38 (1H, d, *J*=10.2 Hz, H-5), 5.97 (1H, d, *J*=4.05 Hz, H-3), 4.70 (1H, d, *J*=11.4 Hz, H-7a), 4.67–4.69 (1H, m, H-2), 4.62 (1H, d, *J*=11.4 Hz, H-7b), 1.48 (3H, s, CH_3), 1.41 (3H, s, CH_3); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 195.5, 165.6, 165.2, 141.4, 133.6, 133.4 (C×2), 130.6 (C×2), 130.3 (C×4), 128.4 (C×4), 110.0, 80.0, 77.7, 66.0, 63.9, 27.4, 26.4; HRFABMS: cacld for $C_{24}H_{23}O_7$ $[M+H]^+$: 423.1438, found 423.1441.

4.1.14. (+)-Zeyleone (1). TFA/H_2O (9:1, v/v, 0.2 mL, 2.2 mmol) was added to the solution of **15** (70 mg, 0.18 mmol) in CH_2Cl_2 (5 mL). The reaction mixture was stirred violently for 6 h. Then, 5 mL 5% aqueous $NaHCO_3$ was added to the reaction mixture and stirred for 5 min. The mixture was extracted with CH_2Cl_2 (3×10 mL), washed with brine (3 mL) and dried ($MgSO_4$). Removal of the solvent and purification of the residue by column chromatography (acetone/petroleum ether 1:5) yielded **1** as white solid (54 mg, 85%). Mp 150–152 °C; $[\alpha]_D^{20}=+118$ (*c* 0.56, $CHCl_3$), $[\alpha]_D^{20}=+26$ (*c* 0.23, CH_3OH); ^1H NMR ($CDCl_3$, 300 MHz) δ 4.38 (dd, 1H, *J*=3.3, 1.5 Hz, H-2), 4.59 (d, 1H, *J*=11.4 Hz, H-7a), 4.86 (d, 1H, *J*=11.4 Hz, H-7b), 5.95 (td, 1H, *J*=4.2 Hz, 0.9, H-3), 6.35 (dd, 1H, *J*=10.2, 0.9 Hz, H-5), 6.96 (ddd, 1H, *J*=10.2, 4.2, 0.9 Hz, H-4), two benzoyl groups: δ 7.93–8.06 (m, 4H), 7.53–7.60 (m, 2H), 7.26–7.45 (m, 4H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 65.5 (C-7), 69.1 (C-3), 71.6 (C-2), 77.2 (C-1), 128.6 (C-5), 142.6 (C-4), 196.2 (C-6), two benzoyl groups: δ 128.4, 128.5, 128.7 (C×2), 129.7 (C×2), 129.8 (C×2), 133.4, 133.7, 165.3, 166.2; IR ν_{max}^{KBr} cm^{-1}: 3421, 1716, 1693, 1271, 1113, 714; EIMS *m/z*: 282, 260, 220, 136, 122, 105, 94; HRMS (TOF): cacld. for $C_{21}H_{19}O_7$ $[M+1]^+$ 383.1125, found 383.1126.

Acknowledgements

We are grateful to the National Natural Science Foundation of China (No. 39970084) and the Chinese Doctoral Grants of the Ministry of Science and Technology of China (No. 96-901-96-54) for financial support.

References and notes

1. For review, see: (a) Parmar, V. S.; Tyagi, O. D.; Malhotra, A.; Singh, S. K.; Jain, R. *Nat. Prod. Rep.* **1994**, *11*, 219–224. (b) Yu, D. Q. *Pure Appl. Chem.* **1999**, *71*, 1119–1122. (c) Thebtaranonth, C.; Thebtaranonth, Y. *Acc. Chem. Res.* **1986**, *19*, 84–90.
2. Liao, Y. H.; Xu, L. Z.; Yang, S. L.; Dai, J.; Zhen, Y. S.; Sun, N. J. *Phytochemistry* **1997**, *45*, 729–732.
3. Zhao, W.-M.; Qin, G.-W.; Yang, R.-Z.; Jiang, T.-Y.; Li, W.-X.; Scott, L.; Snyder, J. K. *Tetrahedeon* **1996**, *52*, 12373–12380.
4. Hiroya, K.; Ogasawara, K. *Chem. Commun.* **1999**, 2197–2198.
5. Ganem, B. *Tetrahedeon* **1978**, *34*, 3353–3383.
6. Armesto, N.; Ferrero, M.; Fernández, S.; Gotor, V. *Tetrahedron Lett.* **2000**, *41*, 8759–8762.
7. Shing, T. K. M.; Tam, E. K. W. *J. Org. Chem.* **1998**, *63*, 1547–1554.
8. Alves, C.; Barros, M. T.; Maycock, C. D.; Ventura, M. R. *Tetrahedron* **1999**, *55*, 8443–8456.
9. Song, C.; Jiang, S.; Singh, G. *Synlett* **2001**, 1983–1985.
10. Mereyala, H. B.; Pannala, M. *J. Chem. Soc., Perkin Trans. 1* **1997**, 1755–1758.
11. Garegg, P. J.; Samuelsson, B. *Synthesis* **1979**, 813–814.
12. Trost, B. M.; Caldwell, C. G.; Murayama, E.; Heissler, D. *J. Org. Chem.* **1983**, *48*, 3252–3265.
13. Bestmann, H. J.; Schobert, R. *Angew. Chem. Int. Ed. Engl.* **1985**, *24*, 791–792.
14. Chang, J. H.; Chen, R. F.; Wang, Q.; Liu, P.; Pan, X. P.; Yu, D. Q. *Acta Chim. Sin.* **2000**, *58*, 554–558.