Pergamon

Tetrahedron 58 (2002) 6799–6804

TETRAHEDRON

Enantioselective total synthesis of (+)-isoaltholactone

Xiaoshui Peng,[a] Anpai Li,[a] Jiangping Lu,[a] Qiaoling Wang,[a] Xinfu Pan[a,*] and Albert S. C. Chan[b]

[a]*National Laboratory of Applied Organic Chemistry, Department of Chemistry, Lanzhou University, Lanzhou 730000, People's Republic of China*

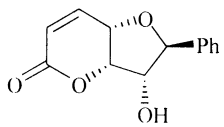
[b]*Department of Applied Biology and Chemical Technology, The Hong Kong Polytechnic University, Hong Kong, People's Republic of China*

Received 5 April 2002; revised 13 June 2002; accepted 4 July 2002

Abstract—A facile enantioselective route to highly functionalized α,β-unsaturated -δ-lactones has allowed for the synthesis of (+)-isoaltholactone in 6.4% overall yield from furylmethanol. This approach derived its asymmetry by applying Sharpless kinetic resolution on racemic 2-furylmethanol. The resulting pyranone was produced in high enantioexcess and was stereoselectively transformed into (+)-isoaltholactone via a highly diastereoselective epoxidation and a key PPTS catalyzed intramolecular cyclization.

1. Introduction

(+)-Isoaltholactone **1** (Fig. 1), a furanopyrone member of the styryllactone family, was isolated from the plants of *Goniothalamus malayanus*, *G. montanus* and *G. tapis*.[1] This class of compounds feature 6-substituted α,β-unsaturated-δ-lactones. This family from various plants and fungi share the common 5-oxygenated-5,6-dihydro-2*H*-pyran-2-one structural motifs.[2] These members include 5-acetoxy-goniothalamin, goniodiol, altholactone and others.[3] These natural products have interesting biological activities including anti-tumor, anti-fungal and anti-bacterial properties.[4] Due to the wide distribution of this class of natural product in the nature, many synthetic methodologies have been employed to synthesize their core structure.[5] Several research groups have reported the synthesis of altholactone.[6–9] These synthesis ranged from 13 steps from D-gluconolactone[7] to 16 steps from D-glyceraldehyde acetonide.[8] Many of them derived their asymmetry from carbohydrate derivatives,[6–8] diethyl L-tartrate,[10] a substituted benzaldehyde chromium(0) complex,[11] or the Sharpless asymmetric dihydroxylation.[9]



1 (+)-isoaltholactone

Figure 1.

As a part of our continuing to synthesize biologically active natural products[12] and to extend our research for the synthesis of α,β-unsaturated-δ-lactones from cheap and readily available 2-furylmethanol **2**, we designed a flexible route to synthesize the natural product (+)-isoaltholactone **1**. Retrosynthetically, our approach is shown in Scheme 1.

2. Results and discussion

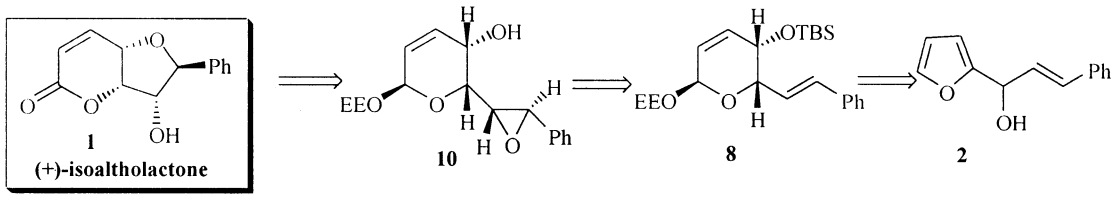
(+)-Isoaltholactone **1** could be obtained via an intramolecular cyclization from epoxide **10** and subsequent functional group transformations. Epoxide **10**, in turn, could be prepared from compound **8** via a diastereoselective epoxidation.[13] The stereochemistry in **8a** could then be established via a Sharpless kinetic resolution from readily available 2-furylmethanol **2**.[14]

The kinetic resolution of compound **2** was carried out with *t*-butyl hydroperoxide (TBHP) (0.6 mol equiv.) and a catalytic amount of L-(+)-diisopropyl tartrate (L-(+)-DIPT) (30 mol%) and titanium tetraisopropoxide [Ti(O-^{i}Pr)$_4$] (20 mol%) in anhydrous CH_2Cl_2 in the presence of molecular sieves 4 Å at −30 to −40°C under argon atmosphere for 24 h to afford the pyranone **3** in 38% yield.[14] Protection the free hydroxyl group in lactol **3** with ethyl vinyl ether gave α- and β-ethoxy ethyl ethers **4** and **5** in 74 and 10% yield and >76% ee, respectively. The α-anomer **4** was reduced with $NaBH_4$ and $CeCl_3{\cdot}7H_2O$ in methanol at −40°C to furnish the allyl alcohols **6** and **7** in 78 and 4% yield, respectively, and >90% de.[15] The stereochemistry of the hydroxy group in the compound **6** could not be determined at this stage; however, it was assumed to be 3*R* based on the results of similar works by Sammes et al.[16] and was unambiguously established by converting **6** into the natural product (+)-isoaltholactone **1** as follows. The

Keywords: total synthesis; (+)-isoaltholactone; enantioselective and stereoselective.

* Corresponding author. Tel.: +86-931-8912407; fax: +86-931-8912582; e-mail: panxf@lzu.edu.cn

0040–4020/02/$ - see front matter
PII: S0040-4020(02)00791-3



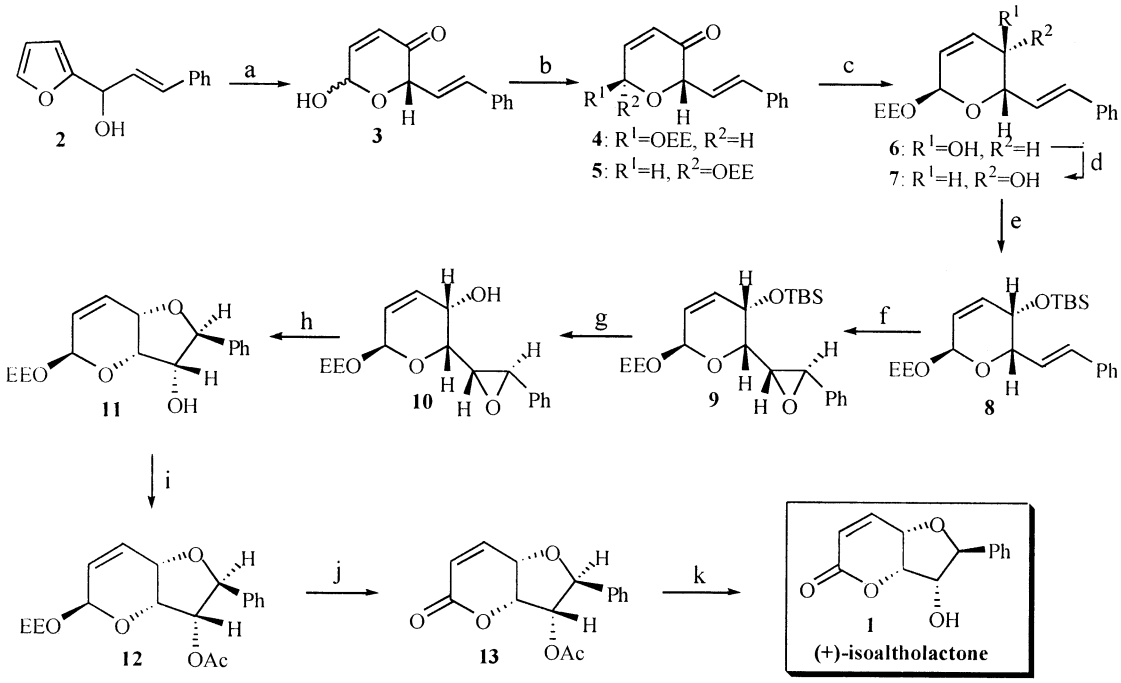
Scheme 1.

inversion of the *anti*-alcohol **6** into the *syn*-alcohol **7** was accomplished via the Mitsunobu reaction by using 1.5 equiv. of Ph_3P, DEAD and *p*-$NO_2C_6H_4COOH$ in anhydrous THF, followed by hydrolysis of the corresponding *p*-nitrobenzoate. **7** was thus obtained in 82% overall yield.[17] TBS protection of the hydroxy group in **7** (TBSCl, Et_3N, DMAP, CH_2Cl_2, 95%) followed by the treatment of the resulted silyl ether with *m*-CPBA and $NaHCO_3$ led to the regioselective (>20:1) and diastereoselective (α–β>9.6:1) formation of **9** in 82% yield. Deprotection of the TBS group was easily achieved with tetra-*n*-butylammonium fluoride in anhydrous THF, providing **10** in 80% yield. The stereochemistry of epoxide **10** was assigned to α-facial epoxide on the basis of the stereochemistry of the above reactions. Epoxide **10** is unstable and decomposes into alcohol or aldehyde in the presence of strong acids, such as CSA, $ZnBr_2$, $BF_3{\cdot}Et_2O$, $TiCl_4$, $ZnCl_2$ and $AlCl_3$ (Scheme 2).

For our synthesis of (+)-isoaltholactone, the *endo*-cyclization reaction of compound **10** is the key reaction. We carried out many experiments to establish the conditions for the *endo*-cyclization reaction of **10**, and found that excellent stereoselectivity could be achieved by using catalytic amount of PPTS in anhydrous CH_2Cl_2.[18] The desired bicyclic intermediate **11** was thus obtained in 90% yield. Protection of the free hydroxy in **11** was accomplished with Ac_2O, pyridine and DMAP in anhydrous CH_2Cl_2 affording **12** in 92% yield. Deprotection of the ethoxy ethyl group and oxidation the resulted allylic alcohol with CrO_3/HOAc yield in the same reactive flask provided **13** in 83% yield. Finally, deprotection of the acetyl group with K_2CO_3 in methanol afforded (+)-isoaltholactone **1** in 78% yield.[19] All physical data (MS, ^1H and ^{13}C NMR, optical rotation, mp) of the synthetic (+)-isoaltholactone **1** were in full agreement with those reported for the natural (+)-isoaltholactone **1**.[1]

3. Conclusion

We have successfully synthesized the natural (+)-isoaltholactone **1** in 6.4% overall yield from readily available racemic 2-furylmethanol **2**. The synthesis required only in 11 chemical operations and was highly enantio- and diastereoselective. Sharpless kinetic resolution on racemic 2-furylmethanol **2**, diastereoselective epoxidation of olefin **8** and PPTS catalyzed intramolecular cyclization of epoxide alcohol **10** are the key steps for our synthesis. Our strategy has provided a general and efficient access to α,β-unsaturated δ-lactones in their optically active form and is expected to find more applications in the synthesis of other related natural products such as altholactone, 3-acetylaltholactone, goniothalesdiol.



Scheme 2. (a) L-(+)-DIPT, Ti(O-^{i}Pr)$_4$, TBHP, 4 Å MS, CH_2Cl_2, −30 to −40°C, 24 h, 38%; (b) ethyl vinyl ether, PPTS, CH_2Cl_2, 25°C, 4 h, α (78%), β (10%); (c) $NaBH_4$, $CeCl_3{\cdot}7H_2O$, MeOH, −30 to −40°C; 5 h, **6** (78%), **7** (4%); (d) DEAD, PPh_3, *p*-$NO_2C_6H_5COOH$, THF; then K_2CO_3, MeOH, rt, 10 h, 82%; (e) TBSCl, Et_3N, DMAP, CH_2Cl_2, 0°C, 12 h, 95%; (f) *m*-CPBA, $NaHCO_3$, CH_2Cl_2, 25°C, 24 h, 82%, α–β>9.6:1; (g) TBAF, THF, 25°C, 6 h, 80%; (h) PPTS, CH_2Cl_2, 25°C, 4 h, 90%; (i) Ac_2O, Py, DMAP, 25°C, 3.5 h, 92%; (j) CrO_3/HOAc, 25°C, 3 h, 83%; (k) K_2CO_3, MeOH, 25°C, 5 h, 78%.

4. Experimental

4.1. General

The melting point was measured with a X-4 apparatus. IR spectra were recorded on a Nicolet 170 SXFT-IR spretrometer. The ^{1}H NMR data in $CDCl_3$ solution were recorded on a Brucker AM-400 MHz spectrometer. The chemical shifts are reported in ppm relative to TMS. Mass spectra were measured with a ZAB-HS mass spectrometer (EI) by direct inlet at 70 eV and signal are given in *m/z*. Optical rotation measurements were carried out on a TASCO 20C polarimeter. All solvents were freshly purified and dried by standard techniques prior to use. Purification of products was performed by flash column chromatography on silica gel (200–300 mesh) purchased from Qing Dao Marine Chemical Co. (Qingdao, China) and eluting with a solvent mixture (v/v) of petroleum spirit (60–90°C) (bp) and ethyl acetate (EA). TLC was performed on a glass plate (2×5 cm) coated with GF_{254} purchased from Qing Dao Marine Chemical Co. (Qingdao, China), and the compounds were extracted with CH_2Cl_2 or AcOEt.

4.1.1. (2*S*)-6-Hydroxy-2-[(*E*)-styryl]-6*H*-pyran-3(2*H*)-one (3). To a stirred solution of the furyl alcohol **2** (11 g, 0.055 mol) and L-(+)-DIPT (1.93 g, 8.25 mmol) in anhydrous CH_2Cl_2 (120 mL) was added activated molecular sieves 4 Å (1.84 g) at room temperature under argon. The stirred mixture was cooled to −30°C, treated with Ti(O-^{i}Pr)$_4$ (1.57 g, 5.5 mmol), and stirring was continued for 30 min at −30°C. The reaction mixture was treated with TBHP (5.0–6.0 M, in nonane solution, 5.5 mL, 27.5 mmol) and was then stirred for 24 h at the same temperature. A freshly prepared solution of $FeSO_4{\cdot}7H_2O$ (4.62 g, 16.6 mmol) and tartaric acid (16.6 g, 110 mmol) in deionized water (30 mL) was added to the reaction mixture at −30°C. The resulting mixture was stirred at room temperature until the mixture was clear. The phase were separated and the aqueous layer was extracted with CH_2Cl_2 (5×40 mL). The organic layer was combined and washed with brine and dried over anhydrous Na_2SO_4. Evaporation of the solvent gave a residue, which was purified by column chromatography on silica gel using petroleum ether–ethyl acetate (4:1, v/v) as eluent to afford the pyranone **3** (4.51 g, 38%) as a brown oil; $[\alpha]_D^{20}$=+126.3 (*c* 0.5, $CHCl_3$); ν_{max} (KBr)/cm^{-1} 3350, 1720, 1680, 1640; *m/z* (EI) 216 (6, M$^+$), 198 (8), 131 (16), 115 (29), 84 (84), 77 (19); δ_H (400 MHz, $CDCl_3$) 3.8–4.2 (1H, br s, O*H*), 4.80 (0.2H, d, *J*=5.9 Hz, OC*H*CH=CHPh), 5.26 (0.8H, dd, *J*=5.7 and 1.5 Hz, OC*H*CH=CHPh), 5.77 (1H, br s, C*H*OH), 6.18 (1H, dd, *J*=10.3 and 1.5 Hz, CHCH=C*H*CO), 6.39 (0.8H, dd, *J*=15.8 and 5.72 Hz, C*H*=CHPh), 6.48 (0.2H, dd, *J*=15.8 and 6.3 Hz, C*H*=CHPh), 6.75 (1H, dd, *J*=15.8 and 1.9 Hz, CH=C*H*Ph), 6.95 (0.8H, dd, *J*=10.3 and 3.3 Hz, CHC*H*=CHCO), 6.98 (0.2H, dd, *J*=10.3 and 1.9 Hz, CHC*H*=CHCO) and 7.25–7.45 (5H, m, C_6H_5); δ_C (100 MHz, $CDCl_3$) 86.3, 91.8, 125.8 (2), 126.5, 126.9, 127.4, 128.5 (2), 129.5, 131.2, 133.6, 190.2; Found: C, 72.4; H, 5.57. $C_{13}H_{12}O_3$ requires C, 72.2; H, 5.56%.

4.1.2. (2*S*,6*S*)- and (2*S*,6*R*)-6-(1-Ethoxyethoxy)-2-[(*E*)-styryl]-6*H*-pyran-3(2*H*)-one (4) and (5). To a stirred solution of the lactol **3** (3.56 g, 16.48 mmol) in CH_2Cl_2 (20 mL) were added ethyl vinyl ether (11.90 g, 164.8 mmol) and a catalytic amount of pyridium toluene-*p*-sulphonate at room temperature. The reaction mixture was stirred for 3 h at room temperature and poured into water (30 mL). The phase were separated and the aqueous layer was extracted with CH_2Cl_2 (5×30 mL). The organic layer was combined and washed with brine, dried over anhydrous Na_2SO_4. Evaporation of the solvent gave a residue, which was purified by column chromatography on silica gel using petroleum ether–ethyl acetate (12:1, v/v) as eluent. The first fraction gave the α-anomer **4** (3.51 g, 74%) as yellow oil. $[\alpha]_D^{20}$=+5.6 (*c* 0.15, $CHCl_3$); ν_{max} (KBr)/cm^{-1} 3040, 1720, 1680, 1640; *m/z* (EI) 243 (68, M$^+$−45), 216 (10), 198 (19), 131 (8), 115 (24), 103 (15), 84 (59), 77 (74); δ_H (400 MHz, $CDCl_3$) 1.22 and 1.25 (3H, each t, *J*=7.2 Hz, CH_2Me), 1.43 and 1.45 (3H, each d, *J*=4.8 Hz, CH*Me*), 3.55–3.75 (2H, m, CH_2Me), 5.01 and 5.11 (1H, each q, *J*=5.3 Hz, C*H*Me), 5.12 and 5.22 (1H, each dd, *J*=5.4 and 1.7 Hz, EEOCHOC*H*), 5.62 and 5.66 (1H, each d, *J*=3.5 Hz, EEOC*H*O), 6.15 and 6.18 (1H, each d, *J*=10.3 Hz, CHCH=C*H*CO), 6.40 and 6.45 (1H, each dd, *J*=15.6 and 5.6 Hz, C*H*=CHPh), 6.73 (1H, d, *J*=15.6 Hz, CH=C*H*Ph), 6.90 and 6.92 (1H, each dd, *J*=9.9 and 3.4 Hz, CHC*H*=CHCO) and 7.25–7.45 (5H, m, C_6H_5); δ_C (100 MHz, $CDCl_3$) 15.1, 21.7, 60.7, 85.8, 88.7, 97.6, 126.6, 126.7 (2), 127.2, 128.1, 128.8 (2), 129.6, 139.3, 143.8, 193.6; Found: C, 70.86; H, 6.92. $C_{17}H_{20}O_4$ requires C, 70.83; H, 6.94%.

The second fraction gave β-anomer **5** (0.47 g, 10%) as yellow oil. $[\alpha]_D^{20}$=+19.6 (*c* 0.15, $CHCl_3$); ν_{max} (KBr)/cm^{-1} 3040, 1720, 1680, 1640; *m/z* (EI) 243 (68, M$^+$−45), 216 (10), 198 (19), 131 (8), 115 (24), 103 (15), 84 (59), 77 (72); δ_H (400 MHz, $CDCl_3$) 1.19 and 1.25 (3H, each t, *J*=7.2 Hz, CH_2Me), 1.38 and 1.45 (3H, each d, *J*=5.0 Hz, CH*Me*), 3.35–3.75 (2H, m, CH_2Me), 4.82 and 4.98 (1H, each d, *J*=6.5 Hz, EEOCHOC*H*), 5.01 and 5.13 (1H, each q, *J*=6.3 Hz, C*H*Me), 5.64–5.76 (1H, m, EEOC*H*O), 6.13–6.28 (1H, m, CHCH=C*H*CO), 6.44 and 6.65 (1H, each dd, *J*=15.6 and 6.6 Hz, C*H*=CHPh), 6.70 and 6.73 (1H, each d, *J*=15.6 Hz, CH=C*H*Ph), 6.90 and 6.95 (1H, each dd, *J*=9.9 and 3.4 Hz, CHC*H*=CHCO) and 7.25–7.45 (5H, m, C_6H_5); δ_C (100 MHz, $CDCl_3$) 15.3, 21.2, 60.9, 85.6, 88.7, 97.3, 126.5, 126.7 (2), 127.4, 128.1, 128.8 (2), 129.6, 139.1, 143.6, 192.9; Found: C, 70.84; H, 6.96. $C_{17}H_{20}O_4$ requires C, 70.83; H, 6.94%.

4.1.3. (2*S*,3*R*,6*S*)- and (2*S*,3*S*,6*S*)-6-(1-Ethoxyethoxy)-2-[(*E*)-styryl]-3,6-dihydro-2*H*-pyran-3-ol (6) and (7). To a stirred solution of the enone **4** (3.5 g, 12.2 mmol) and $CeCl_3{\cdot}7H_2O$ (4.52 g, 12.2 mmol) in MeOH (40 mL) at −30 to −40°C was added powdered sodium borohydride (0.464 g, 12.2 mmol). The reaction mixture was stirred for 1 h at room temperature. After dilution with brine (30 mL) the mixture was extracted with ethyl acetate (5×30 mL). The organic layer was washed with brine and dried over anhydrous Na_2SO_4. Evaporation of the solvent gave a residue, which was purified by column chromatography on silica gel using petroleum ether–ethyl acetate (5:1, v/v) as eluent. The first fraction gave the compound **6** (2.75 g, 78%) as a green oil, $[\alpha]_D^{20}$=−31.2 (*c* 0.2, $CHCl_3$); ν_{max} (KBr)/cm^{-1} 3434, 1640, 1600; *m/z* (EI) 218 (26, M$^+$−72), 176 (49), 151 (26), 131 (79), 115 (12), 103 (35), 77 (23); δ_H (400 MHz, $CDCl_3$) 1.18 and 1.23 (3H, each

t, J=7.2 Hz, CH_2Me), 1.36 and 1.38 (3H, each d, J=5.7 Hz, $CHMe$), 1.86–1.92 (1H, br s, OH), 3.48–3.73 (2H, m, CH_2Me), 4.08–4.10 (1H, br s, C*H*OH), 4.27 and 4.33 (1H, each dd, J=9.2 and 6.7 Hz, OC*H*CH=CHPh), 4.93 and 5.0 (1H, each q, J=5.4 Hz, C*H*Me), 5.26 and 5.35 (1H, each br s, EEOC*H*O), 5.73 and 5.81 (1H, each dt, J=11.2 and 2.4 Hz, EEOCHC*H*=CH), 6.0 (1H, dd, J=11.2 and 1.2 Hz, EEOCHCH=C*H*), 6.32 (1H, ddd, J=16.1, 6.5 and 3.1 Hz, C*H*=CHPh), 6.74 (1H, d, J=16.1 Hz, CH=C*H*Ph) and 7.25–7.43 (5H, m, C_6H_5); δ_C (100 MHz, $CDCl_3$) 15.3, 21.5, 63.2, 71.5, 77.5, 91.5, 98.8, 125.5 (2), 126.3, 127.5, 127.9, 128.1 (2) 128.8, 129.5, 133.1; Found: C, 70.32; H, 7.60. $C_{17}H_{22}O_4$ requires C, 70.34; H, 7.59%.

The second fraction gave the compound **7** (0.14 g, 4%) as green oil. $[\alpha]_D^{20}=-14.7$ (c 0.2, $CHCl_3$); ν_{max} (KBr)/cm^{-1} 3434, 1640, 1600; m/z (EI) 218 (26, M^+-72), 176 (49), 151 (21), 131 (79), 115 (8), 103 (35), 77 (23); δ_H (400 MHz, $CDCl_3$) 1.16 and 1.23 (3H, each t, J=7.4 Hz, CH_2Me), 1.36 and 1.38 (3H, each d, J=5.8 Hz, $CHMe$), 1.90–2.10 (1H, br s, OH), 3.46–3.82 (2H, m, CH_2Me), 4.05–4.12 (1H, br s, C*H*OH), 4.25 and 4.31 (1H, m, OC*H*CH=CHPh), 4.92 and 5.0 (1H. each q, J=5.3 Hz, C*H*Me), 5.35 (1H, br s, EEOC*H*O), 5.82 and 5.85 (1H, each t, J=2.3 Hz, EEOCHC*H*=CH), 6.04 (1H, d, J=10.5 Hz, EEOCHCH=C*H*), 6.32 (1H, dd, J=16.2 and 6.7 Hz, C*H*=CHPh), 6.76 (1H, d, J=16.2 Hz, CH=C*H*Ph) and 7.25–7.45 (5H, m, C_6H_5); δ_C (100 MHz, $CDCl_3$) 15.2, 21.3, 63.2, 71.7, 77.3, 91.5, 98.7, 125.5 (2), 126.5, 127.8, 127.9, 128.2 (2) 128.7, 129.8, 133.1; Found: C, 70.33; H, 7.60. $C_{17}H_{22}O_4$ requires C, 70.34; H, 7.59%.

4.2. To invert the *anti*-alcohol (6) into the *syn*-alcohol (7)

To a stirred solution of the *anti*-alcohol **6** (2.1 g, 7.24 mmol) in anhydrous THF (40 mL) was added powered Ph_3P (2.85 g, 10.86 mmol) and p-$NO_2C_6H_4COOH$ (1.82 g, 10.86 mmol) at room temperature. After 20 min, the mixture was cooled to 0°C and added a solution of DEAD (1.87 g, 10.86 mmol) in anhydrous THF (10 mL) under argon. The reaction mixture was stirred for 10 h at room temperature. The solvent was removed under reduced pressure to give a residue. Ethyl ether (50 mL) was added and the white precipitate was filtered off. The filtrate was evaporated to dryness to give a crude product, which was purified by column chromatography on silica gel using petroleum–ethyl acetate (15:1, v/v) as eluent to afford 2.8 g (quant.) the p-nitrobenzoate of the compound **6** as yellow oil.

At room temperature to the stirred solution of the p-nitrobenzoate of compound **6** (2.8 g, 6.14 mmol) in MeOH (30 mL) was added K_2CO_3 (1.02 g, 7.37 mmol) and the reaction mixture was stirred for 10 h. After the addition of H_2O (20 mL) and dilution with CH_2Cl_2 (50 mL), the phase were separated and the aqueous layer was extracted with CH_2Cl_2 (5×30 mL). The organic layer was washed with brine and dried over anhydrous Na_2SO_4. Evaporation of the solvent gave a residue, which was purified by column chromatography on silica gel with petroleum ether–ethyl acetate (5:1) as eluent to afford the alcohol **7** (1.72 g, 82%).

4.2.1. (2*S*,3*S*,6*S*)-3-*tert*-Butyldimethylsilanyloxy-6-(1-ethoxyethoxy)-2-[(*E*)-styryl]-3,6-dihydro-2*H*-pyran (8). To a stirred solution of the compound **7** (1.72 g, 5.93 mmol) in anhydrous CH_2Cl_2 (30 mL) was added Et_3N (4.12 mL) in a round bottom flask and cooled to 0°C. A catalytic amount of DMAP was added and followed by addition of *tert*-butyldimethylsilyl chloride (1.07 g, 7.12 mmol). The solution was stirred for 8 h at 0°C. The reaction was quenched with Et_2O (50 mL) and saturated aqueous $NaHCO_3$ (20 mL). The phase were separated and the aqueous layer was extracted with Et_2O (5×20 mL). The organic fractions were combined, washed with saturated aqueous $NaHCO_3$ and dried over anhydrous Na_2SO_4. Evaporation of the solvent gave a residue, which was purified by column chromatography on silica gel using petroleum ether–ethyl acetate (35:1, v/v) as eluent to afford the compound **8** (2.28 g, 95%) as colorless oil. $[\alpha]_D^{20}=+64$ (c 2.8, $CHCl_3$); ν_{max} (KBr)/cm^{-1} 2932, 1384, 1099, 998; m/z (EI) 332 (7, M^+-72), 315 (41), 289 (6), 272 (16), 258 (6), 243 (4), 200 (67), 143 (23), 131 (25), 91 (49), 77 (51), 73 (100), 45 (13); δ_H (400 MHz, $CDCl_3$), 0.91 (9H, s, C(Me)$_3$), 0.10 (3H, s, SiCH_3), 0.06 (3H, s, SiCH_3), 1.14 and 1.24 (3H, each t, J=7.2 Hz, CH_2Me), 1.35 and 1.38 (3H, d, J=6.0 Hz, $CHMe$), 3.46–3.82 (2H, m, OCH_2Me), 4.66–4.69 (1H, m, C*H*CH=CHPh), 4.90 and 4.98 (1H, each q, J=5.4 Hz, OC*H*Me), 5.32 (1.5H, m, C*H*OTBS and EEOC*H*O), 5.43 (0.5H, br s, EEOC*H*O), 5.86–6.07 (2H, m, EEOCHC*H*=C*H*), 6.36 (1H, dd, J=16.2 and 7.2 Hz, C*H*=CHPh), 6.64 (1H, d, J=16.2 Hz, CH=C*H*Ph), 7.24–7.42 (5H, m, C_6H_5); δ_C (100 MHz, $CDCl_3$) −4.6 (2), 15.1, 15.3, 21.5, 25.9 (3), 64.7, 72.9, 77.2, 91.7, 99.8, 126.8 (2), 127.3, 127.8, 128.5, 129.8 (2), 130.1, 131.9, 136.8; Found: C, 68.34; H, 8.89. $C_{23}H_{36}SiO_4$ requires C, 68.32; H, 8.91%.

4.2.2. (2*S*,3*S*,6*S*)-3-*tert*-Butyldimethylsilanyloxy-6-(1-ethoxyethoxy)-2-[(3*R*)-3-phenyloxiranyl]-3, 6-dihydro-2*H*-pyran (9). To a stirred solution of compound **8** (2.10 g, 5.2 mmol) and $NaHCO_3$ (2.62 mg, 31.2 mmol) in CH_2Cl_2 (20 mL) was added the power of m-CPBA (1.79 g, 10.4 mmol). The reaction was stirred for 10 h at room temperature. The reaction was then quenched with Et_2O (40 mL) and saturated aqueous $NaHCO_3$ (20 mL). The phase were separated and the aqueous layer was extracted with Et_2O (5×30 mL). The organic fractions were combined and dried over anhydrous Na_2SO_4. Evaporation of the solvent gave a residue, which was purified by column chromatography on silica gel using petroleum ether–ethyl acetate (40:1–35:1, v/v) as eluent to afford the compound **9** (1.79 g, 82%) as a white solid. Mp 114–116°C; $[\alpha]_D^{20}=+28$ (c 2.4, $CHCl_3$); ν_{max} (KBr)/cm^{-1} 3390, 2928, 1384, 1068; m/z (EI) 348 (6, $M-72$), 331 (12), 273 (5), 261 (19), 245 (5), 235 (21), 200 (61), 131 (13), 91 (77), 77 (12), 73 (100), 45 (18); δ_H (400 MHz, $CDCl_3$), 0.90 (9H, s, C(CH_3)$_3$), 0.15 (3H, s, SiCH_3), 0.12 (3H, s, SiCH_3), 1.16 and 1.22 (3H, each t, J=7.2 Hz, CH_2Me), 1.36 and 1.38 (3H, d, J=6.0 Hz, $CHMe$), 3.44 (1H, dd, J=6.8 and 2.0 Hz, C*H*(O)CHPh), 3.46–3.80 (2H, m, CH_2Me), 3.95 (1H, d, J=2.0 Hz, CH(O)C*H*Ph), 4.28–4.35 (1H, m, C*H*CH(O)CHPh), 4.75 (1H, m, C*H*OTBS), 4.90 and 4.96 (1H, each q, J=5.4 Hz, C*H*Me), 5.34 (1H, br s, EEOC*H*O), 5.85–6.03 (2H, m, EEOCHC*H*=C*H*), 7.21–7.35 (5H, m, C_6H_5); δ_C (100 MHz, $CDCl_3$) −4.8 (2), 15.1, 18.2, 21.5, 25.7 (3), 57.6, 58.5, 61.1, 71.3, 77.3, 91.3, 99.6, 125.7, 127.6, 128.2 (2), 128.4 (2), 131.2, 134.6; Found: C, 65.69; H, 8.48. $C_{23}H_{36}SiO_5$ requires C, 65.71; H, 8.50%.

4.2.3. (2*S*,3*S*,6*S*)-6-(1-Ethoxyethoxy)-2-[(3*R*)-3-phenyloxiranyl]-3,6-dihydro-2*H*-pyran-3-ol (10). To a stirred solution of compound **9** (1.72 g, 4.1 mmol) and TBAF (2.68 g, 10.25 mmol) was dissolved in THF (30 mL) at room temperature. The reaction was stirred for 2 h at room temperature. The reaction was then quenched with Et_2O (40 mL) and saturated aqueous $NaHCO_3$ (20 mL). The phase were separated and the aqueous layer was extracted with Et_2O (5×20 mL). The organic fractions were combined and dried over anhydrous Na_2SO_4. Evaporation of the solvent gave a residue, which was purified by column chromatography on silica gel with petroleum ether–ethyl acetate (8:1, v/v) as eluent to afford the compound **10** (1.0 g, 80%) as colorless oil. $[\alpha]_D^{20}=+39$ (*c* 3.92, $CHCl_3$); ν_{max} (KBr)/cm^{-1} 3418, 2980, 1388, 1083, 1001; *m/z* (EI) 306 (8, M^+), 289 (21), 261 (2), 234 (20), 199 (15), 158 (9), 149 (14), 131 (18), 91 (94), 77 (41), 73 (100), 45 (70); δ_H (400 MHz, $CDCl_3$), 1.16 and 1.24 (3H, each t, *J*=7.0 Hz, CH_2*Me*), 1.36 and 1.38 (3H, d, *J*=5.8 Hz, CH*Me*), 2.62 (1H, br s, O*H*), 3.46–3.81 (2H, m, C*H*$_2$Me), 3.54 (1H, dd, *J*=5.8 and 1.8 Hz, C*H*(O)CHPh), 3.98 (1H, d, *J*=1.8 Hz, CH(O)C*H*Ph), 4.08 (1H, dd, *J*=5.8 and 3.0 Hz, C*H*OH), 4.22–4.24 (1H, m, C*H*CH(O)CHPh), 4.92 and 4.98 (1H, each q, *J*=5.5 Hz, C*H*Me), 5.37 (1H, br s, EEOC*H*O), 5.80 and 5.84 (1H, each t, *J*=2.6 Hz, EEOCHC*H*=CH), 6.15 (1H, d, *J*=10.4 Hz, EEOCHCH=C*H*), 7.23–7.37 (5H, m, C_6H_5); δ_C (100 MHz, $CDCl_3$) 15.2, 21.4, 56.8, 57.2, 61.8, 70.6, 77.3, 91.4, 99.6, 125.6, 126.1, 128.4 (2), 128.7 (2), 129.6, 136.8; Found: C, 66.65; H, 7.20. $C_{17}H_{22}O_5$ requires C, 66.67; H, 7.19%.

4.2.4. 6*S*-6-(1-Ethoxyethoxy)-isoaltholactone (11). The compound **10** (980 mg, 3.2 mmol) was dissolved in CH_2Cl_2 (15 mL) and a catalytic amount of PPTS was added to the solution at room temperature. The reaction was stirred for 4 h at room temperature. The reaction was quenched with Et_2O (30 mL) and saturated aqueous $NaHCO_3$ (10 mL). The phase were separated and the aqueous layer was extracted with Et_2O (5×20 mL). The organic fractions were combined and dried over anhydrous Na_2SO_4. Evaporation of the solvent gave a residue, which was purified by column chromatography on silica gel using petroleum ether–ethyl acetate (5:1, v/v) as eluent to afford the compound **11** (882 mg, 90%) as a white solid. Mp 138–141°C; $[\alpha]_D^{20}=+32$ (*c* 1.4, $CHCl_3$); ν_{max} (KBr)/cm^{-1} 3405, 3394, 2924, 1382, 1066; *m/z* (EI) 234 (6, $[M-72]^+$), 217 (11), 126 (8), 122 (20), 107 (43), 105 (9), 97 (83), 95 (13), 91 (17), 77 (65); δ_H (400 MHz, $CDCl_3$), 1.10 and 1.21 (3H, each t, *J*=7.2 Hz, CH_2*Me*), 1.27 and 1.34 (3H, each d, *J*=5.8 Hz, CH*Me*), 2.1 (1H, br s, O*H*), 3.38–3.92 (2H, m, OC*H*$_2$Me), 4.28 (1H, m, C*H*OH), 4.51 (1H, d, *J*=7.6 Hz, OC*H*Ph), 4.83 (1H, m, C*H*OCHPh), 4.93 and 4.99 (1H, each q, *J*=5.6 Hz, C*H*Me), 5.14 (1H, dd, *J*=6.2, 5.8 Hz, OC*H*CHOH), 5.37 (1H, br s, EEOC*H*O), 5.82 and 5.85 (1H, each t, *J*=2.8 Hz, EEOCHC*H*=CH), 6.11 (1H, dd, *J*=10.4, 4.0 Hz, EEOCHCH=C*H*), 7.22–7.45 (5H, m, C_6H_5); δ_C (100 MHz, $CDCl_3$) 142.8, 138.3, 128.6 (2), 128.5, 128.4 (2), 125.7, 87.9, 85.6, 78.9, 77.6, 67.4, 64.3, 21.2, 15.5, 14.2; Found: C, 66.68; H, 7.21. $C_{17}H_{22}O_5$ requires C, 66.67; H, 7.19%.

4.2.5. (3*S*,6*S*)-3-Acetyl-6-(1-ethoxyethoxy)-isoaltholactone (12). A stirred solution of the alcohol **11** (860 g, 2.81 mmol), a catalytic amount of 4-dimethylaminopyridine, acetic anhydride (860 mg, 8.43 mmol) and a drop wise pyridine in CH_2Cl_2 (15 mL) was stirred for 5 h at room temperature and then poured into water (10 mL). The crude product was extracted with CH_2Cl_2 (5×20 mL), and the organic layer was washed using brine and dried over anhydrous Na_2SO_4. Evaporation of the solvent gave a residue, which was purified by column chromatography on silica gel with petroleum ether–ethyl acetate (10:1, v/v) as eluent to afford the acetate **12** (978 mg, 92%) as a white solid. Mp 132–134°C; $[\alpha]_D^{20}=-6$ (*c* 0.8, $CHCl_3$); ν_{max} (KBr)/cm^{-1} 3412, 3382, 2975, 1742, 1378, 1082; *m/z* (EI) 276 (3, M^+-72), 261 (6), 216 (32), 198 (5), 191 (17), 169 (6), 107 (5), 91 (17), 77 (34), 73 (100), 45 (20); δ_H (400 MHz, $CDCl_3$), 1.13 and 1.20 (3H, each t, *J*=7.0 Hz, CH_2*Me*), 1.26 and 1.36 (3H, d, *J*=6.0 Hz, CH*Me*), 2.62 (3H, s, OCO*Me*), 3.42–3.90 (2H, m, C*H*$_2$Me), 4.82 (1H, m, C*H*OCHPh), 4.94 and 4.98 (1H, each q, *J*=5.7 Hz, C*H*Me), 4.96 (1H, d, *J*=5.3 Hz, C*H*OAc), 5.15 (1H, dd, *J*=5.3 and 2.4 Hz, OC*H*COAc), 5.35 (1H, dd, *J*=4.2 and 2.2 Hz, C*H*Ph), 5.38 (1H, br s, EEOC*H*O), 5.80 and 5.84 (1H, each t, *J*=3.0 Hz, EEOCHC*H*=CH), 6.11 (1H, d, *J*=10.4 and 4.2 Hz, EEOCHCH=C*H*), 7.25–7.37 (5H, m, C_6H_5); δ_C (100 MHz, $CDCl_3$) 15.5, 19.7, 21.1, 61.6, 72.7, 76.8, 80.3, 89.7, 98.5, 125.7, 125.9, 128.3, 128.5 (2), 128.7 (2), 130.7, 138.9, 170.7; Found: C, 65.49; H, 6.87. $C_{19}H_{24}O_6$ requires C, 65.52; H, 6.90%.

4.2.6. 3-Acetyl-isoaltholactone (13). To a stirred solution of the compound **12** (960 mg, 2.76 mmol) in HOAc (5 mL) was added the solution of CrO_3/HOAc (3.32 mmol). The reaction mixture was stirred for 5 h at room temperature. The mixture was poured into water (20 mL) and extracted with CH_2Cl_2 (5×20 mL). The organic layer was washed with brine and saturated aqueous $NaHCO_3$ and dried over anhydrous Na_2SO_4. Evaporation of the solvent gave a residue, which was purified by column chromatography on silica gel using petroleum ether–ethyl acetate (2:1, v/v) as eluent to afford the lactone **13** (627 mg, 83%) as a white solid. Mp 153–156°C; $[\alpha]_D^{20}=+66$ (*c* 1.1, EtOH); ν_{max} (KBr)/cm^{-1} 2924, 1736, 1228, 1032, 1070; *m/z* (EI) 215 (5, $[M+H-OHCOCH_3]^+$), 199 (8), 163 (5), 126 (52), 122 (6), 107 (10), 105 (17), 97 (27), 95 (12), 77 (21); δ_H (400 MHz, $CDCl_3$), 2.08 (3H, s, CO*Me*), 4.91 (1H, t, *J*=5.2 Hz, C*H*OCHPh), 4.96 (1H, d, *J*=4.2 Hz, C*H*OAc), 5.06 (1H, t, *J*=5.2 Hz, OC*H*CHOAc), 5.36 (1H, dd, *J*=4.2 and 2.2 Hz, C*H*Ph), 6.23 (1H, d, *J*=9.8 Hz, OCOC*H*=CH), 6.92 (1H, dd, *J*=9.8 and 5.2 Hz, OCOCH=C*H*), 7.21–7.42 (5H, m, C_6H_5); δ_C (100 MHz, $CDCl_3$) 170.4, 161.2, 141.8, 138.2, 128.8 (2), 128.6 (2), 125.6, 122.4, 81.8, 78.4, 76.4, 68.2, 20.8; Found: C, 65.65; H, 5.14. $C_{15}H_{14}O_5$ requires C, 65.67; H, 5.11%.

4.2.7. (+)-Isoaltholactone (1). To a stirred solution of the compound **13** (610 mg, 2.23 mmol) in MeOH (15 mL) was added K_2CO_3 (0.46 g, 3.34 mmol) at room temperature. The mixture was stirred for 6 h at room temperature. The reaction was quenched with Et_2O (30 mL) and water (10 mL). The phase were separated and the aqueous layer was extracted with Et_2O (5×20 mL). The organic phrase were combined, washed with water and dried over anhydrous Na_2SO_4. Evaporation of the solvent gave a residue, which was purified by column chromatography on

silica gel using petroleum ether–ethyl acetate (1:1, v/v) as eluent to afford the natural product **1** (403 mg, 78%) as a needle solid. Mp 101.5–103.2°C; $[\alpha]_D^{20}=+35$ (*c* 0.80, EtOH); ν_{max} (KBr)/cm^{-1} 3500, 3030, 1730, 1645; *m*/*z* (EI) 232 (8, M^+), 126 (8), 122 (13), 107 (28), 97 (100), 91 (14), 77 (25); δ_H (400 MHz, $CDCl_3$), 2.86 (1H, br s, O*H*), 4.28 (1H, m, C*H*OH), 4.80 (1H, d, *J*=7.5 Hz, C*H*Ph), 4.89 (1H, t, *J*=5.5 and 4.5 Hz, C*H*OCHPh), 5.07 (1H, t, *J*=5.5 Hz, OC*H*CHOH), 6.23 (1H, dd, *J*=10.2 and 1.1 Hz, OCOC*H*=CH), 6.89 (1H, dd, *J*=10.2 and 4.8 Hz, OCOCH=C*H*), 7.26–7.42 (5H, m, C_6H_5); δ_C (100 MHz, $CDCl_3$) 162, 142, 138, 129 (2), 128, 126 (2), 123, 84, 79, 78, 68; Found: C, 67.26; H, 5.14. $C_{13}H_{12}O_4$ requires C, 67.24; H, 5.17%. Its spectroscopic data are identical with those reported.[1]

Acknowledgments

We are grateful to the National Science Foundation of China (No. 20172023) for financial support. In addition, we thank Dr Yun He and Professor Teng-Kuei Yang for careful reading and helpful comment on the manuscript.

References

1. Goh, S. H.; Chung, V. C.; Sha, C. K.; Mak, T. C. W. *Phytochemistry* **1990**, *29*, 1704–1706.
2. (a) Argoudelis, A. D.; Zieserl, J. F. *Tetrahedron Lett.* **1966**, *18*, 1969. (b) Yasui, K.; Tamura, Y.; Nakatani, T.; Kawada, K.; Ohtani, M. *J. Org. Chem.* **1955**, *60*, 7567–7574. (c) Bermejo, A.; Blazqoz, M. A.; Rao, K. S.; Cortes, D. *Phytochem. Anal.* **1999**, *10*, 127–131.
3. (a) Ahmad, F. B.; Tuko, W. A.; Omar, S.; Sharif, A. M. *Phytochemistry* **1991**, *30*, 2430. (b) Fang, X. P.; Anderson, J. E.; Chung, C. J.; Mclanghlin, J. L.; Fanwick, P. E. *J. Nat. Prod.* **1991**, *54*, 1034.
4. For a review of 5,6-dihydro-2*H*-pyran-2-ones, see: Davies-Coleman, M. T. A.; Rivett, D. E. *Progress in the Chemistry of Organic Natural Products*; Herz, W., Grisebach, H., Kirby, G. W., Tamm, Ch., Eds.; Springer: New York, 1989; Vol. 55, pp 1–35.
5. (a) See Ref. 2. (b) Schlessing, R. H.; Gillman, K. W. *Tetrahedron Lett.* **1999**, *40*, 1257–1260. (c) Tsubuki, M.; Kanai, K.; Nagase, H.; Honda, T. *Tetrahedron* **1999**, *55*, 2493. (d) Gomez, A. M.; Lopez, U. B.; Valverde, S.; Lopez, J. C. *J. Chem. Soc., Chem. Commun.* **1997**, 1647. (e) Yang, Z. C.; Zhou, W. S. *Tetrahedron Lett.* **1995**, *36*, 5617–5618.
6. (a) Gesson, J. P.; Jacquesy, J. C.; Mondon, M. *Tetrahedron Lett.* **1987**, *28*, 3945–3948. (b) Gesson, J. P.; Jacquesy, J. C.; Mondon, M. *Tetrahedron* **1989**, *45*, 2627–2640.
7. Shing, T. K. M.; Tsui, H. C.; Zhou, Z. H. *J. Org. Chem.* **1995**, *60*, 3121–3130.
8. (a) Tsubuki, M.; Kanai, K.; Honda, T. *Synlett* **1993**, 653–655. (b) Tsubuki, M.; Kanai, K.; Nagase, H.; Honda, T. *Tetrahedron* **1999**, *55*, 2493–2514.
9. Joel, M. H.; O'Doherty, G. A. *Org. Lett.* **2000**, *2*, 2983–2986.
10. Somfa, P. *Tetrahedron* **1994**, *50*, 11315–11320.
11. Mukai, C.; Hirai, S.; Kim, I. J.; Hanaoka, M. *Tetrahedron Lett.* **1996**, *37*, 5389–5392.
12. (a) Peng, X. S.; Li, A. P.; Zhang, C. L.; Wang, H.; Pan, X. F. *J. Chem. Res.* **2002**. in press. (b) Peng, X. S.; Li, A. P.; Shen, H.; Wang, H.; Pan, X. F. *J. Chem. Res.* **2002**. in press.
13. Chaomin, L.; Emily, A. P.; Mei, C. L.; Emil, L.; Thomas, D. G.; John, A. P. J. *J. Am. Chem. Soc.* **2001**, *123*, 11308–11309.
14. (a) Kusakabe, M.; Kitano, Y.; Kobayaashi, Y.; Sato, F. *J. Org. Chem.* **1989**, *53*, 1586. (b) Woodard, S. S.; Finn, M. G.; Sharpless, K. B. *J. Am. Chem. Soc.* **1991**, *113*, 113–126.
15. Toshi, H.; Hironao, T.; Shigehiro, M.; Masayoshi, T. *Tetrahedron Lett.* **1993**, *34*, 8275.
16. Sammes, P. G.; Thetford, D. *J. Chem. Soc., Perkin Trans 1* **1988**, 111.
17. Mitsunobu, O. *Synthesis* **1981**, *1*.
18. Kim, K.; Okamoto, S.; Sato, F. *Org. Lett.* **2001**, *1*, 67–69.
19. Robert, M. H. *Chem. Rev.* **1991**, *91*, 437–475.