Pergamon

Tetrahedron: *Asymmetry* 13 (2002) 1799–1804

TETRAHEDRON: *ASYMMETRY*

First enantioselective synthesis of daphneticin and its regioisomer

Xinfeng Ren, Xiaochuan Chen, Kun Peng, Xingang Xie, Yamu Xia and Xinfu Pan*

Department of Chemistry, National Laboratory of Applied Organic Chemistry, Lanzhou University, Lanzhou 730000, PR China

Received 9 July 2002; accepted 15 August 2002

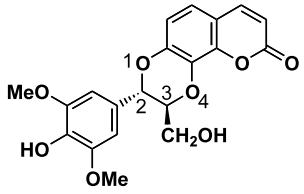
Abstract—An enantioselective total synthesis of chiral daphneticin and its regioisomer is reported for the first time. © 2002 Published by Elsevier Science Ltd.

1. Introduction

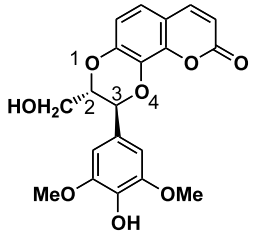
Coumarinolignoids are a relatively new and rare group of natural products consisting of C_6, C_3, C_6 units. In these molecules the coumarin moieties are linked with the phenyl propanoid units through a 1,4-dioxane bridge.[1] Because of their varied biological activities, especially their cytotoxicity and antihepatotoxic activities,[2] several efficient syntheses of natural coumarinolignoids have been reported.[3]

Daphneticin **1** has been isolated as a racemic compound[2] from the roots and stems of *Daphne tangutica*. As a coumarinolignoid, daphneticin showed[4] cytotoxic activity in vitro in the walker-256-carcinosarcomaascites system. Cordell and Lin[3a] reported the synthesis of daphneticin under oxidative reaction conditions (horseradish peroxidase and silver oxide). Later, Tanaka et al.[3g] described that daphneticin could also prepared using Ph_2SeO as the oxidizing agent. However, Cordell and Lin[5] recently revised the structure of daphneticin to have the formula **1** by using the selective INEPT pulse programme with daphneticin diacetate. Although Tanaka et al.[3c,d] synthesized daphneticin **1** and its regioisomer **2** in racemic form, we felt that it was a pity that a total asymmetric synthesis of daphneticin has not yet been reported, and this prompted the investigations which we report herein.

In our previous work,[6] we reported the first asymmetric and regioselective synthetic approach to 1,4-benzodioxane lignans. On the basis of this work, we now wish to report an enantioselective synthesis of daphneticin **1** and its regioisomer **2** from the readily available compound **10** and commercially available 7-hydroxycoumarin **3**.



1



2

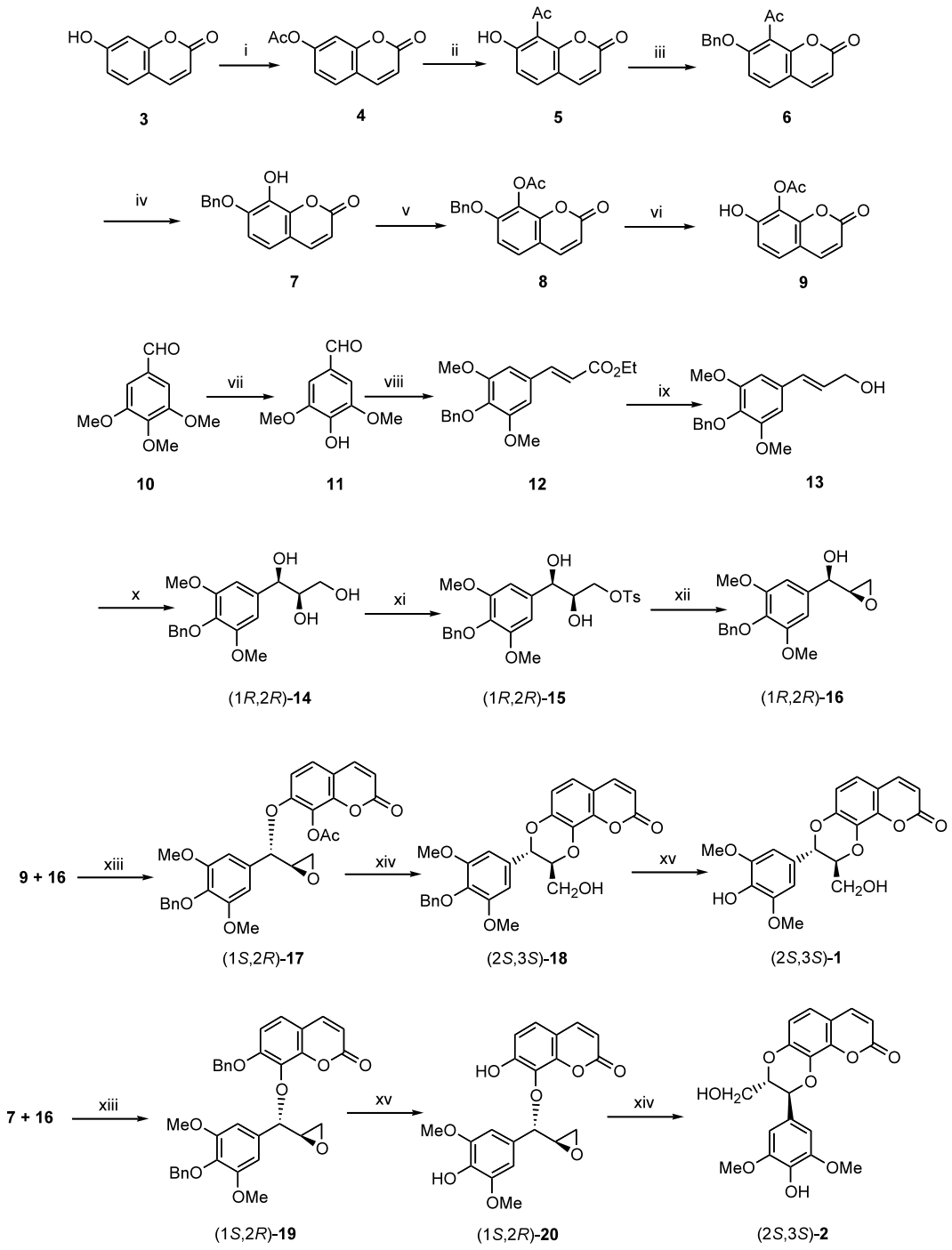
2. Results and discussion

As shown in Scheme 1, the first half of the convergent synthesis required preparation of the coumarin **9**. Initially, 7-hydroxycoumarin **3** was easily converted into 7-acetoxycoumarin **4** by acetylation. Treatment of **4** with $AlCl_3$ under 160°C gave 8-acetyl-7-hydroxycoumarin **5**.[7] Then, compound **7** was prepared by benzylation of compound **5** followed by Baeyer–Villiger oxidation with hydrogen peroxide in alkaline dioxane solution. On treatment with Ac_2O, compound **7** was converted to the acetate **8**, which was then subjected to catalytic hydrogenation yielding the debenzylation product **9**.

Synthesis of the functionalised aryl unit **16** began from 3,4,5-trimethoxybenzaldehyde **10**. Selective demethylation of **10** with piperidine gave 4-hydroxy-3,5-dimethoxybenzaldehyde **11**.[8] Aldehyde **11** was reacted with monoethyl malonate[9] in the presence of pyridine and piperidine to give an unsaturated ester.[10] Protection of the 4-hydroxyl group with benzyl bromide afforded the benzyl ether **12**, which was reduced with lithium aluminium hydride/$AlCl_3$ in THF to the corresponding alcohol **13**.[11] Asymmetric dihydroxylation of **13** with

* Corresponding author. E-mail: panxf@lzu.edu.cn

0957-4166/02/$ - see front matter © 2002 Published by Elsevier Science Ltd.
PII: S0957-4166(02)00482-2



Scheme 1. *Reagents and conditions*: (i) Ac_2O, pyridine, rt, 24 h, 97%; (ii) $AlCl_3$, 160°C, 2 h, 79%; (iii) BnBr, K_2CO_3, 24 h, 94%; (iv) H_2O_2, NaOH, 20 min, 94%; (v) Ac_2O, pyridine, rt, 24 h, 90%; (vi) Pd/C (5%), H_2, EtOAc, rt, 6 h, 92%; (vii) piperidine, H_2O, reflux, 48 h, 80%; (viii) (1) $CO_2HCH_2CO_2Et$, pyridine, piperidine, reflux, 6 h; (2) BnBr, K_2CO_3, 24 h, 80%; (ix) LAH, $AlCl_3$, THF, 0.5 h, 86%; (x) AD-mix-β, $MeSO_2NH_2$, *t*-BuOH, H_2O, 0°C, 20 h, 87%; (xi) TsCl, pyridine, 91%; (xii) K_2CO_3, MeOH, rt, 3 h, 80%; (xiii) DIAD, Ph_3P, THF, rt, 24 h, 65%; (xiv) K_2CO_3, MeOH, rt, 3 h, 90%; (xv) Pd/C (5%), H_2, EtOAc, rt, 6 h, 81%.

AD-mix-β afforded (1*R*,2*R*)-**14** in 93% e.e.[12] Reaction of (1*R*,2*R*)-**14** with TsCl in pyridine provided the primary tosylate (1*R*,2*R*)-**15**. Ring closure of (1*R*,2*R*)-**15** was promoted by potassium carbonate in methanol, generating the oxirane (1*R*,2*R*)-**16**.[13] Mitsunobu reaction[14] between (1*R*,2*R*)-**16** and compound **9** gave the characterized ether (1*S*,2*R*)-**17**, where the absolute configuration at the C-1 stereogenic centre was inverted completely from the S_N2-type nucleophilic displacement by 8-acetoxy-7-hydroxycoumarin. Removal of the acetyl group of (1*S*,2*R*)-**17** followed by intramolecular cyclization using potassium carbonate in methanol afforded (2*S*,3*S*)-**18**, where nucleophilic attack at C-2 of the oxirane by the phenol hydroxyl group in the presence of K_2CO_3 led to complete inversion of the absolute configuration at C-2 and the formation of the

1,4-benzodioxane ring.[15] The benzyl group was removed by hydrogenolysis under hydrogen (at atmospheric pressure) in the presence of 5% Pd/C in ethyl acetate to afford (2*S*,3*S*)-**1**. In the ^{1}H NMR spectrum of (2*S*,3*S*)-**1**, H-2 resonated as a doublet signal at δ 5.11 with a coupling constant ($J=7.9$ Hz) which is typical of a *trans*-isomer and indicates a *threo* configuration. The ^{13}C NMR spectrum showed signals at δ 61.4, 76.5, 78.6 indicating a six-membered 2-aryl-3-hydroxymethyl-1,4-benzodioxane skeleton.[16]

We also synthesized daphneticin's regioisomer **2**. Mitsunobu reaction[14] between compound **7** and compound **16** gave the ether (1*S*,2*R*)-**19**. The two benzyl groups of compound (1*S*,2*R*)-**19** were removed by catalytic hydrogenation, leaving the epoxide ring intact, to afford (1*S*,2*R*)-**20**.[17] Cyclization of (1*S*,2*R*)-**20** with potassium carbonate in methanol then afforded (2*S*,3*S*)-**2**.

In summary, we have carried out the enantioselective synthesis of daphneticin **1** and its regioisomer **2** in 17 and 14% yield, respectively. All spectral data were in agreement with those found in the literature.[2,3c,3d] This is the first enantioselective total synthesis of these coumarinolignoids.

3. Experimental

3.1. General

Melting points were measured on a Kofler apparatus and were uncorrected. The ^{1}H and ^{13}C NMR data were recorded with Bruker AM-80 and Avance-200 MHz spectrometers. The chemical shifts are reported in ppm relative to TMS. Mass spectra were recorded on a ZAB-HS spectrometer. Elemental analyses were performed on a Carlo–Erba 1106 instrument. Optical rotations were determined on a Perkin–Elmer 341 polarimeter. Chrial analysis was performed on Varian Dynamax SD-300 using chiralcel column CDMPC (150×4.6 mm D) with hexane/isopropyl alcohol as eluant (*n*-hexane:isopropyl alcohol, 20:1, 0.5 mL/min, 25°C). Flash column chromatography was generally performed on silica gel (200–300 mesh) eluting with petroleum ether:ethyl acetate and TLC inspections on silica gel GF_{254} plates with petroleum ether:ethyl acetate, if not noted especially below.

3.2. 7-Acetoxycoumarin, 4

To a stirred solution of 7-hydroxycoumarin **3** (3.1 g, 19.1 mmol) in CH_2Cl_2 (50 mL), Ac_2O (2 mL) and pyridine (one drop) were added. After the solution was stirred overnight at room temperature, it was evaporated in vacuo. The crude products were dissolved in water and then extracted with EtOAc (3×50 mL). The combined organic layer was washed with brine, and then dried with Na_2SO_4. The solvent was distilled off under reduced pressure and the residue was flash chromatographed using petroleum ether and ethyl acetate (3:1, v/v) as eluent to afford **4** as a white solid (3.84 g, yield 97%). Mp 143–145°C. MS (EI): 204 (M^+), 162, 134, 105, 43. ^{1}H NMR (80 MHz, $CDCl_3$): δ 2.36 (s, 3H), 6.42 (d, 1H, $J=9.6$ Hz), 7.08 (dd, 1H, $J=8.1$, 2.0 Hz), 7.13 (d, 1H, $J=2.1$ Hz), 7.52 (d, 1H, $J=8.1$ Hz), 7.72 (d, 1H, $J=9.6$ Hz).

3.3. 8-Acetyl-7-hydroxycoumarin, 5

Compound **4** (3.54 g, 17.3 mmol) and $AlCl_3$ (8.53 g, 63.9 mmol) were mixed together, and the mixture was heated at 160°C for 2 h. The reaction mixture was cooled and dilute aqueous hydrochloric acid was added. The solution was stirred for 1 h at room temperature and then heated under steam bath for 0.5 h. The solution was cooled and extracted with EtOAc (3×50 mL). The combined organic layer was washed with brine and dried with Na_2SO_4. The solvent was distilled off and the residue was flash chromatographed using petroleum ether and ethyl acetate (5:1, v/v) as eluent. A light yellow solid **5** (2.8 g) was obtained in 79% yield. Mp 165–167°C. MS (EI): 204 (M^+), 189, 161, 133, 105, 77, 43. ^{1}H NMR (80 MHz, $CDCl_3$): δ 2.98 (s, 3H), 6.29 (d, 1H, $J=9.4$ Hz), 6.91 (d, 1H, $J=8.3$ Hz), 7.54 (d, 1H, $J=8.5$ Hz), 7.66 (d, 1H, $J=9.6$ Hz), 13.65 (s, 1H).

3.4. 8-Acetyl-7-benzyloxycoumarin, 6

A mixture of compound **5** (1.8 g, 8.8 mmol), benzyl bromide (2 mL) and anhydrous potassium carbonate (1.9 g) in acetone (100 mL) was stirred overnight at room temperature. The reaction mixture was evaporated in vacuo. The crude products were dissolved in water and then extracted with ethyl acetate (3×50 mL). The combined organic layer was washed with brine and dried with Na_2SO_4. The solvent was distilled off and the residue was flash chromatographed using petroleum ether and ethyl acetate (4:1, v/v) as eluent. The product **6** was obtained as white solid (2.44 g, yield 94%). Mp 113–115°C. MS (EI): 294 (M^+), 276, 252, 189, 160, 91, 43. ^{1}H NMR (200 MHz, $CDCl_3$): δ 2.61 (s, 3H), 5.20 (s, 2H), 6.26 (d, 1H, $J=9.4$ Hz), 6.91 (d, 1H, $J=8.6$ Hz), 7.37 (m, 5H), 7.41 (d, 1H, $J=8.6$ Hz), 7.62 (d, 1H, $J=9.6$ Hz).

3.5. 7-Benzyloxy-8-hydroxycoumarin, 7

A solution of 30% aqueous H_2O_2 (30 mL) was added dropwise to a mixture of **6** (1 g, 3.4 mmol) in dioxane (30 mL) and 1N NaOH (20 mL) at 10°C, and stirred at the same temperature for more than 20 min. The reaction mixture was poured into ice-water and neutralized with 5% HCl, then extracted with ethyl acetate (3×30 mL). The combined organic layer was washed with brine, dried over Na_2SO_4 and evaporated. The crude product was flash chromatographed using petroleum ether and ethyl acetate (3:1, v/v) as eluent. The product, **7** was obtained as a white solid (0.8 g, 94%). Mp 163–164°C. MS (EI): 268 (M^+), 211, 177, 125, 91, 65. ^{1}H NMR (200 MHz, $CDCl_3$): δ 5.22 (s, 2H), 5.8 (s, 1H), 6.26 (d, 1H, $J=9.4$ Hz), 6.88 (d, 1H, $J=8.6$ Hz), 6.96 (d, 1H, $J=8.8$ Hz), 7.37 (m, 5H), 7.60 (d, 1H, $J=9.6$ Hz).

3.6. 8-Acetoxy-7-benzyloxycoumarin, 8

A mixture of **7** (0.85 g, 3.17 mmol), acetic anhydride (5 mL) and pyridine (0.5 mL) in CH_2Cl_2 was stirred overnight at room temperature. The reaction mixture was poured into water and extracted with ethyl acetate (3×30 mL). The combined organic layer was washed with brine, dried over Na_2SO_4 and evaporated to dryness. The residue was flash chromatographed using petroleum ether and ethyl acetate (3:1, v/v) as eluent to afford **8** as a white solid (0.88 g, 90%). Mp 127–128°C. MS (EI): 310 (M^+), 268, 177, 149, 121, 91, 43. ^{1}H NMR (200 MHz, $CDCl_3$): δ 2.39 (s, 3H), 5.19 (s, 2H), 6.26 (d, 1H, J=9.6 Hz), 6.92 (d, 1H, J=8.6 Hz), 7.27 (d, 1H, J=8.6 Hz), 7.37 (m, 5H), 7.62 (d, 1H, J=9.6 Hz).

3.7. 8-Acetoxy-7-hydroxycoumarin, 9

A suspension of **8** (137 mg, 0.44 mmol) and 5% Pd–C (13 mg) in ethyl acetate (10 mL) was stirred under a H_2 atmosphere. The reaction mixture was filtered and the filtrate was concentrated. The residue was flash chromatographed using petroleum ether and ethyl acetate (2:1, v/v) as eluent to afford **9** as a white solid (89 mg, 92%). Mp 160–162°C. MS (EI): 220 (M^+), 178, 150, 138, 81, 69. ^{1}H NMR (200 MHz, acetone-d_6): δ 2.36 (s, 3H), 6.21 (d, 1H, J=9.4 Hz), 6.95 (d, 1H, J=8.6 Hz), 7.43 (d, 1H, J=8.6 Hz), 7.91 (d, 1H, J=9.6 Hz), 9.38 (br s, 1H).

3.8. 4-Hydroxy-3,5-dimethoxybenzaldehyde, 11

A solution of 3,4,5-trimethoxybenzaldehyde **10** (3.48 g, 17.7 mmol) in piperidine (35 mL) and water (35 mL) was heated under reflux for 48 h and the cooled mixture was poured into 4N aqueous hydrochloric acid. The mixture was extracted with ethyl acetate (3×50 mL). The combined organic layer was washed with 2N hydrochloric acid, water, dried over Na_2SO_4. The solvent was distilled off and the residue was flash chromatographed using petroleum ether and ethyl acetate (4:1, v/v) as eluent to afford **11** as a white solid (2.58 g, 80%). Mp 113–114°C. MS (EI): 182 (M^+), 167, 139, 111, 96, 65. ^{1}H NMR (80 MHz, $CDCl_3$): δ 3.97 (s, 6H), 6.12 (br s, 1H), 7.17 (s, 2H), 9.83 (s, 1H).

3.9. Ethyl 4-benzyloxy-3,5-dimethoxycinnamate, 12

Monoethyl malonate (1.523 g, 11.54 mmol) was added to the solution of compound **11** (1.05 g, 5.77 mmol) in pyridine (15 mL) and piperidine (0.25 mL). The mixture was heated under reflux at 120°C for 6 h, then the pyridine was evaporated. The crude product was dissolved in ethyl acetate and the solution was washed with 5% sodium bicarbonate and water, dried over Na_2SO_4. The solvent was distilled off and the residue was flash chromatographed using petroleum ether and ethyl acetate (3:1, v/v) as eluent. Ethyl 4-hydroxy-3,5-dimethoxycinnamate was obtained as a white solid (1.3 g, 89%). Mp 59–61°C. MS (EI): 252 (M^+), 224, 207, 180, 140, 121, 65, 53. ^{1}H NMR (80 MHz, $CDCl_3$): δ 1.35 (t, 3H, J=7.1 Hz), 3.93 (s, 6H), 4.28 (q, 2H, J=7.1 Hz), 5.77 (br s, 1H), 6.31 (d, 1H, J=15.9 Hz), 6.79 (s, 2H), 7.62 (d, 1H, J=15.8 Hz). A mixture of ethyl 4-hydroxy-3,5-dimethoxy cinnamate (1.6 g, 6.35 mmol), benzyl bromide (1.8 mL) and anhydrous potassium carbonate (1.6 g) in acetone (100 mL) were stirred overnight at room temperature. The reaction mixture was evaporated in vacuo. The crude products were dissolved in water and then extracted with ethyl acetate (3×50 mL). The combined organic layer was washed with brine and dried with Na_2SO_4. The solvent was distilled off and the residue was flash chromatographed using petroleum ether and ethyl acetate (4:1, v/v) as eluent. The product **12** was obtained as a white solid (2.02 g, 93%). Mp 71–73°C. MS (EI): 342 (M^+), 297, 251, 177, 135, 91, 65. ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.34 (t, 3H, J=7.2 Hz), 3.85 (s, 6H), 4.27 (q, 2H, J=7.2 Hz), 5.05 (s, 2H), 6.35 (d, 1H, J=16.0 Hz), 6.74 (s, 2H), 7.31–7.50 (m, 5H), 7.60 (d, 1H, J=16.0 Hz).

3.10. 4-Benzyloxy-3,5-dimethoxycinnamyl alcohol, 13

To a suspension of $LiAlH_4$ (0.274 g, 7.2 mmol) in dry THF (50 mL), $AlCl_3$ (0.32 g, 2.4 mmol) was added portionwise at room temperature. After the suspension was stirred for 10 min, a solution of compound **12** (0.82 g, 2.4 mmol) in dry THF was added dropwise to the suspension. The reaction mixture was stirred at room temperature for 0.5 h. Then the reaction was quenched with ice-water, extracted with ethyl acetate and the combined organic layers were washed with brine, and then dried with Na_2SO_4. The solvent was distilled off and the residue was flash chromatographed using petroleum ether and ethyl acetate (2:1, v/v) as eluent. Compound **13** was obtained as a colorless oil (0.62 g, 86%). MS (EI): 300 (M^+), 209, 177, 149, 121, 91, 65. ^{1}H NMR (200 MHz, $CDCl_3$): δ 3.81 (s, 6H), 4.28 (d, 2H, J=5.4 Hz), 5.01 (s, 2H), 6.26 (dt, 1H, J=15.8 Hz, 5.6 Hz), 6.51 (d, 1H, J=15.8 Hz), 6.59 (s, 2H), 7.27–7.52 (m, 5H).

3.11. (1*R*,2*R*)-1-(4-Benzyloxy-3,5-dimethoxyphenyl)-2,3-dihydroxypropanol, (1*R*,2*R*)-14

To a stirred solution of *tert*-BuOH (25 mL) and H_2O (25 mL), AD-mix-β (7 g) and $MeSO_2NH_2$ (475 mg) was added, the mixture was stirred at room temperature until both phases were clear, and then cooled to 0°C, compound **13** (1.5 g, 5 mmol) was added immediately, the mixture was stirred vigorously at 0°C until TLC revealed the absence of **13**. The reaction was quenched at 0°C by addition of Na_2SO_3 (7.5 g), then warmed to room temperature and stirred for 0.5 h. The reaction mixture was extracted with ethyl acetate (3×50 mL). The combined organic layer was washed with a 2N KOH solution, water and dried over Na_2SO_4. The solvent was distilled off and the residue was flash chromatographed using petroleum ether and ethyl acetate (1:3, v/v) as eluent. A white powder of (1*R*,2*R*)-**14** (1.45 g, 87%) was obtained in 93% e.e. (retention times 18.5 min). Mp 77–79°C. $[\alpha]_D^{25}$ −18 (*c* 1.60, $CHCl_3$). MS (EI): 334 (M^+), 273, 183, 123, 91, 65. ^{1}H NMR (200 MHz, $CDCl_3$): δ 3.48 (m, 2H), 3.76 (m, 1H), 3.77 (s, 6H), 4.55 (d, 1H, J=6.6 Hz), 4.96 (s, 2H), 6.55 (s, 2H), 7.29–7.48 (m, 5H).

3.12. (1*R*,2*R*)-1-(4-Benzyloxy-3,5-dimethoxyphenyl)-2,3-dihydroxypropyl tosylate, (1*R*,2*R*)-15

Compound (1*R*,2*R*)-**14** (0.55 g, 1.65 mmol) in pyridine (15 mL) was cooled to 0°C under N_2, then TsCl (0.345 g, 1.8 mmol) was added. The reaction mixture was stirred at room temperature for 20 h, diluted with ethyl acetate (50 mL) and extracted with 1N HCl (3×20 mL). The organic phase was dried with Na_2SO_4, concentrated in vacuo, and the residue was flash chromatographed using petroleum ether and ethyl acetate (1:2, v/v) as eluent to yield (1*R*,2*R*)-**15** as a white powder (0.73 g, 91%) in 96% e.e. (retention times 13.7 min). Mp 121–122°C. $[\alpha]_D^{25}$ −10 (*c* 2.90, $CHCl_3$). MS (EI): 488 (M^+), 470, 424, 345, 334, 300, 172, 107, 91. ^{1}H NMR (200 MHz, $CDCl_3$): δ 2.44 (s, 3H), 3.79 (s, 6H), 3.88 (m, 1H), 3.97 (m, 2H), 4.61 (d, 1H, J=5.8 Hz), 4.97 (s, 2H), 6.54 (s, 2H), 7.29–7.77 (m, 9H).

3.13. (1*R*,2*R*)-2,3-Expoxy-1-(4-benzyloxy-3,5-dimethoxyphenyl)propanol, (1*R*,2*R*)-16

K_2CO_3 (0.146 g, 1.06 mmol) was added to a solution of (1*R*,2*R*)-**15** (0.47 g, 0.96 mmol) in MeOH (20 mL). The suspension was vigorously stirred at room temperature for 3 h under Ar and was poured into water (30 mL). The layers were separated and the aqueous layer was extracted with ethyl acetate (3×20 mL). The combined organic phase was dried over Na_2SO_4, concentrated in vacuo and purified by flash chromatography using petroleum ether and ethyl acetate (1:1, v/v) as eluent gave (1*R*,2*R*)-**16** as a white solid (0.35 g, 80%) with 90% e.e. (retention time 9.2 min). Mp 98–100°C. $[\alpha]_D^{25}$ −8 (*c* 1.60, $CHCl_3$). MS (EI): 316 (M^+), 225, 195, 153, 139, 91. ^{1}H NMR (200 MHz, $CDCl_3$): δ 2.86 (m, 2H), 3.23 (m, 1H), 3.81 (s, 6H), 4.43 (d, 1H, J=5.6 Hz), 5.00 (s, 2H), 6.64 (s, 2H), 7.31–7.51 (m, 5H).

3.14. (1*S*,2*R*)-8-Acetoxy-7-[2,3-epoxy-1-(4-benzyloxy-3,5-dimethoxyphenyl)propoxy]coumarin, (1*S*,2*R*)-17

A solution of PPh_3 (136 mg, 0.52 mmol) and (1*R*,2*R*)-**16** (150 mg, 0.47 mmol) in dry THF (10 mL) was added dropwise to a solution of 8-acetoxy-7-hydroxycoumarin (114 mg, 0.52 mmol) and DIAD (105 mg, 0.52 mmol) in dry THF at room temperature under nitrogen. After stirring the mixture overnight at room temperature, the mixture was evaporated in vacuo. The residue was flash chromatographed using petroleum ether and ethyl acetate (2:1, v/v) as eluent. A white solid of (1*S*,2*R*)-**17** (150 mg, 65%) was obtained in 92% e.e. (retention times 12.6 min). Mp 69–71°C. $[\alpha]_D^{25}$ −44 (*c* 3.2, $CHCl_3$). MS (EI): 518 (M^+), 476, 397, 385, 367, 355, 299, 91. ^{1}H NMR (200 MHz, $CDCl_3$): δ 2.43 (s, 3H), 2.84 (m, 2H), 3.33 (m, 1H), 3.82 (s, 6H), 4.99 (s, 2H), 5.09 (d, 1H, J=3.8 Hz), 6.27 (d, 1H, J=9.4 Hz), 6.58 (s, 2H), 6.69 (d, 1H, J=8.8 Hz), 7.15 (d, 1H, J=8.8 Hz), 7.30–7.49 (m, 5H), 7.59 (d, 1H, J=9.6 Hz).

3.15. (2*S*,3*S*)-18

K_2CO_3 (73 mg, 0.53 mmol) was added to a solution of (1*S*,2*R*)-**17** (110 mg, 0.21 mmol) in methanol (10 mL) and the solution was stirred vigorously for 2 h at room temperature. The methanol in the reaction mixture was evaporated in vacuo and 2N HCl (2 mL) was added. The mixture was extracted with ethyl acetate (3×20 mL) and the combined organic layer was washed with brine and dried over Na_2SO_4. The solvent was distilled off and the residue was flash chromatographed using petroleum ether and ethyl acetate (2:1, v/v) as eluent. A white solid of (2*S*,3*S*)-**18** (91 mg, 90%) was obtained in 93% e.e. (retention times 23.6 min). Mp 182–185°C. $[\alpha]_D^{25}$ +28 (*c* 0.7, $CHCl_3$). MS (EI): 476 (M^+), 385, 299, 277, 207, 91. ^{1}H NMR (200 MHz, $CDCl_3$): δ 3.65 (m, 2H), 3.82 (s, 6H), 4.28 (m, 1H), 5.01 (s, 2H), 5.15 (d, 1H, J=8.1 Hz), 6.31 (d, 1H, J=9.4 Hz), 6.62 (s, 2H), 6.73 (d, 1H, J=8.6 Hz), 7.17 (d, 1H, J=8.8 Hz), 7.28–7.46 (m, 5H), 7.61 (d, 1H, J=9.6 Hz).

3.16. Daphneticin, (2*S*,3*S*)-1

A solution of (2*S*,3*S*)-**18** (210 mg, 0.44 mmol) in ethyl acetate (10 mL) was hydrogenated over 5% Pd–C (20 mg) under a H_2 atmosphere. The reaction mixture was filtered and the filtrate was concentrated. The residue was flash chromatographed using petroleum ether and ethyl acetate (1:1, v/v) as eluent. A white solid of (2*S*,3*S*)-**1** (138 mg, 81%) was obtained with 92% e.e. Retention times: (2*S*,3*S*)-**1** 27.6 min, (2*R*,3*R*)-**1** 25.8 min. $[\alpha]_D^{25}$ +11 (*c* 1.40, $CHCl_3$). Mp 229–231°C. MS (EI): 386 (M^+), 368, 353, 277, 209, 177, 167, 149, 43. ^{1}H NMR (200 MHz, acetone-d_6): δ 3.74 (m, 2H), 3.88 (s, 6H), 4.25 (m, 1H), 5.11 (d, 1H, J=7.9 Hz), 6.27 (d, 1H, J=9.4 Hz), 6.67 (s, 2H), 7.14 (d, 1H, J=8.6 Hz), 7.35 (d, 1H, J=8.8 Hz), 7.68 (d, 1H, J=9.6 Hz). ^{13}C NMR (50 MHz, acetone-d_6): δ 56.6, 61.4, 76.5, 78.6, 106.1, 114.6, 121.5, 125.1, 130.7, 138.9, 144.6, 145.9, 148.9, 160.5. IR (KBr/cm^{-1}): 3449, 1713, 1609, 1456, 1334, 1271, 1130, 1063, 835. Found: C, 62.23; H, 4.68. $C_{20}H_{18}O_8$ requires C, 62.17; H, 4.66%.

3.17. (1*S*,2*R*)-7-Benzyloxy-8-[2,3-epoxy-1-(4-benzyloxy-3,5-dimethoxyphenyl)propoxy]coumarin, (1*S*,2*R*)-19

A solution of PPh_3 (292 mg, 1.11 mmol) and (1*R*,2*R*)-**17** (320 mg, 1.01 mmol) in dry THF (10 mL) was added dropwise to a solution of 7-benzyloxy-8-hydroxycoumarin (298 mg, 1.11 mmol) and DIAD (225 mg, 1.11 mmol) in dry THF at room temperature under nitrogen. After stirring of the mixture overnight at room temperature, the mixture was evaporated in vacuo. The residue was flash chromatographed using petroleum ether and ethyl acetate (2:1, v/v) as eluent. A white solid of (1*S*,2*R*)-**19** (344 mg) was obtained in 92% e.e. (retention times 15.1 min) and 60% yield. Mp 47–49°C. $[\alpha]_D^{25}$ +31 (*c* 2.0, $CHCl_3$). MS (EI): 566 (M^+), 475, 445, 385, 358, 322, 299, 91. ^{1}H NMR (200 MHz, $CDCl_3$): δ 2.83 (m, 2H), 3.45 (m, 1H), 3.74 (s, 6H), 4.95 (s, 2H), 5.16 (s, 2H), 5.27 (d, 1H, J=5.4 Hz), 6.23 (d, 1H, J=9.6 Hz), 6.73 (s, 2H), 6.85 (d, 1H, J=8.8 Hz), 7.09 (d, 1H, J=8.6 Hz), 7.28–7.46 (m, 5H), 7.56 (d, 1H, J=9.6 Hz).

3.18. (1*S*,2*R*)-7-Hydroxy-8-[2,3-epoxy-1-(4-hydroxy-3,5-dimethoxyphenyl)propoxy]coumarin, (1*S*,2*R*)-20

A solution of (1*S*,2*R*)-**19** (500 mg, 0.88 mmol) in ethyl acetate (10 mL) was hydrogenated over 5% Pd–C (50 mg) under a H_2 atmosphere. The reaction mixture was filtered and the filtrate was concentrated. The residue was flash chromatographed using petroleum ether and ethyl acetate (1:1, v/v) as eluent. A white solid (1*S*,2*R*)-**20** (255 mg, 75% yield, 92% e.e., retention times 21.3 min) was obtained. $[\alpha]_D^{25}$ +17 (*c* 1.40, $CHCl_3$). Mp 121–123°C. MS (EI): 386 (M^+), 355, 325, 277, 225, 207, 93, 65. ^1H NMR (200 MHz, $CDCl_3$): δ 2.80 (m, 2H), 3.42 (m, 1H), 3.78 (s, 6H), 5.23 (d, 1H, $J=5.6$ Hz), 6.24 (d, 1H, $J=9.4$ Hz), 6.58 (s, 2H), 6.76 (d, 1H, $J=8.6$ Hz), 7.13 (d, 1H, $J=8.6$ Hz), 7.59 (d, 1H, $J=9.6$ Hz).

3.19. Daphneticin's regioisomer, (2*S*,3*S*)-2

A mixture of (1*S*,2*R*)-**20** (120 mg, 0.31 mmol) and anhydrous K_2CO_3 (138 mg, 1.0 mmol) in MeOH (5 mL) was stirred at room temperature for 30 min. The solvent was evaporated and 2N HCl (2 mL) was added, then the mixture was extracted with EtOAc (3×20 mL). The combined organic layer was washed with brine and dried with Na_2SO_4. The solvent was removed under reduced pressure. The residue was flash chromatographed using petroleum ether and ethyl acetate (1:2, v/v) as eluent to afford (2*S*,3*S*)-**2** (106 mg, 89% yield, 92% e.e.) as a white solid. Retention times: (2*S*,3*S*)-**2** 30.7 min, (2*R*,3*R*)-**2** 27.4 min. $[\alpha]_D^{25}$ −8 (*c* 1.10, $CHCl_3$). Mp 242–244°C. MS (EI): 386 (M^+), 368, 328, 219, 210, 191, 167. ^1H NMR (200 MHz, $CDCl_3$): δ 3.58 (m, 2H), 3.93 (s, 6H), 4.07 (m, 1H), 5.07 (d, 1H, $J=8.4$ Hz), 6.31 (d, 1H, $J=9.4$ Hz), 6.66 (s, 2H), 6.94 (d, 1H, $J=8.8$ Hz), 7.03 (d, 1H, $J=8.6$ Hz), 7.67 (d, 1H, $J=9.6$ Hz). ^{13}C NMR (50 MHz, acetone-d_6): δ 56.7, 61.5, 77.9, 79.7, 106.3, 113.8, 114.1, 120.5, 127.3, 130.7, 138.1, 144.6, 145.1, 148.9, 160.6. IR (KBr/cm^{-1}): 3468, 3185, 1725, 1614, 1570, 1457, 1341, 1269, 1119, 1057, 836. Found: C, 62.25; H, 4.63. $C_{20}H_{18}O_8$ requires C, 62.17; H, 4.66%.

Acknowledgements

Support from the National Natural Science Foundation of China (No. 29972015; 20172023) is gratefully acknowledged.

References

1. Chatterjee, A.; Das, P. C.; Joshi, P. C.; Mandal, S. *J. Indian Chem. Soc.* **1994**, *71*, 475–482.
2. Zhuang, L. G.; Seligmann, O.; Wagner, H. *Phytochemistry* **1983**, *22*, 617.
3. (a) Lin, L. J.; Cordell, G. A. *J. Chem. Soc., Chem. Commun.* **1984**, 160; (b) Tanaka, H.; Kato, I.; Ito, K. *Chem. Pharm. Bull.* **1985**, *33*, 3218–3223; (c) Tanaka, H.; Kato, I.; Ito, K. *Chem. Pharm. Bull.* **1986**, *34*, 628–632; (d) Tanaka, H.; Ishihara, M.; Ichino, K.; Ito, K. *Heterocycles* **1987**, *26*, 3115–3122; (e) Tanaka, H.; Ishihara, M.; Ichino, K.; Ito, K. *Chem. Pharm. Bull.* **1988**, *36*, 1738–1743; (f) Tanaka, H.; Ishihara, M.; Ichino, K.; Ito, K. *Chem. Pharm. Bull.* **1988**, *36*, 3833–3837; (g) Tanaka, H.; Ishihara, M.; Ichino, K.; Ito, K. *Heterocycles* **1988**, *27*, 2651–2658.
4. Zhuang, L. G.; Seligmann, O.; Jurcic, K.; Wagner, H. *Planta Med.* **1982**, *45*, 172.
5. Lin, L. J.; Cordell, G. A. *J. Chem. Soc., Chem. Commun.* **1986**, 377.
6. Gu, W. X.; Chen, X. C.; Pan, X. F.; Albert, S. C. Chan, Yang Teng-Kuei, *Tetrahedron: Asymmetry* **2000**, *11*, 2801–2807.
7. Russell, A.; Frye, J. R. *Org. Synth.* **1955**, *III*, 281.
8. Quillinan, A. J.; Scheinmann, F. *J. Chem. Soc. (C)* **1973**, 1329.
9. Strube, R. E. *Org. Synth.* **1957**, *37*, 34.
10. Alexander, G. *J. Am. Chem. Soc.* **1946**, *68*, 376.
11. Ding, P. Y.; Yu, D. Q. *Chinese J. Med. Chem.* **1995**, *5*, 59–61.
12. Sharpless, K. B.; Amberg, W.; Bennani, Y. L.; Crispino, G. A.; Hartung, J.; Jeong, K. S.; Kwong, H. L.; Morikawa, K.; Wang, Z. M.; Xu, D.; Zhang, X. L. *J. Org. Chem.* **1992**, *57*, 2768–2771.
13. Bergeron, R. J.; Muiler, R.; Mcmanis, J. S.; Yao, G. W.; Huang, G. F. *Synthesis* **2001**, *7*, 1043–1048.
14. Mitsunobu, O. *Synthesis* **1981**, 1–26.
15. Ganesh, T.; Krupadanam, G. L. D. *Synth. Commun.* **1998**, *28*, 3121–3131.
16. Fukiyama, Y.; Hasegawa, T.; Toda, M.; Kodama, M. *Chem. Pharm. Bull.* **1992**, *40*, 252.
17. Taniguchi, E.; Yamauchi, S.; Nagata, S.; Ohnishi, T. *Biosci. Biotech. Biochem.* **1992**, *56*, 630–635.