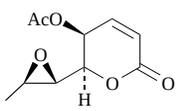
Total syntheses of (+)-asperlin, (+)-acetylphomalactone and (5*S*,6*S*,7*R*,8*S*)-asperlin based on the kinetic resolution of 2-furylmethanols

Zhi-Cai Yang, Xiao-Bin Jiang,† Zhi-Min Wang and Wei-Shan Zhou*

Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, 354 Fenglin Lu, Shanghai 200032, China

The total syntheses of (+)-asperlin 1, (+)-acetylphomalactone 2 and (5*S*,6*S*,7*R*,8*S*)-asperlin 3 have been achieved employing the kinetic resolution of unsymmetric divinylmethanol using modified Sharpless reagents, which produced two oxidation products, as a key step.

(+)-Asperlin **1**, as a crystalline metabolite isolated from *Aspergillus nidulans*[1] and *Aspergillus caespitosus*,[2] has been shown to exhibit antitumour and antibacterial activity, while (+)-acetylphomalactone **2** and (+)-(5*S*,6*S*,7*R*,8*S*)-asperlin **3**,



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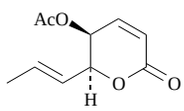

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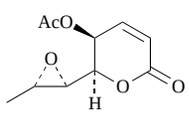
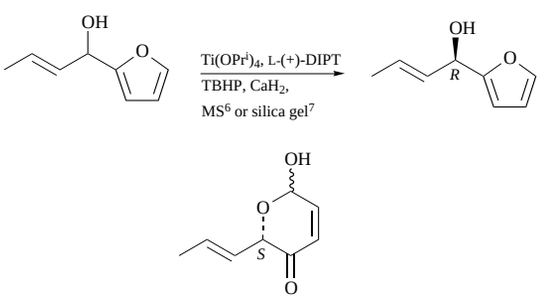


3

isolated from *Aspergillus caespitosus* together with (+)-asperlin **1**,[2] have exhibited antimicrobial activity. Because of their interesting bioactivity these compounds have been synthesized by several groups.[3–5] Recently, a convenient synthesis of natural compound **1** starting from 2-furylmethanol (divinylmethanol) has been reported by Honda[6] and by us.[7] Now, we report here the enantioselective syntheses of (+)-asperlin, (+)-acetylphomalactone and (+)-(5*S*,6*S*,7*R*,8*S*)-asperlin based on kinetic resolution of racemic unsymmetrical divinylmethanols employing modified Sharpless reagents.[8]

After the asymmetrical epoxidation of symmetrical divinylmethanols had been described by several groups,[9] kinetic resolution of racemic 2-furylmethanols was independently shown by Honda and by ourselves to produce two oxidation products (Scheme 1). Subsequently, we carried out systematic

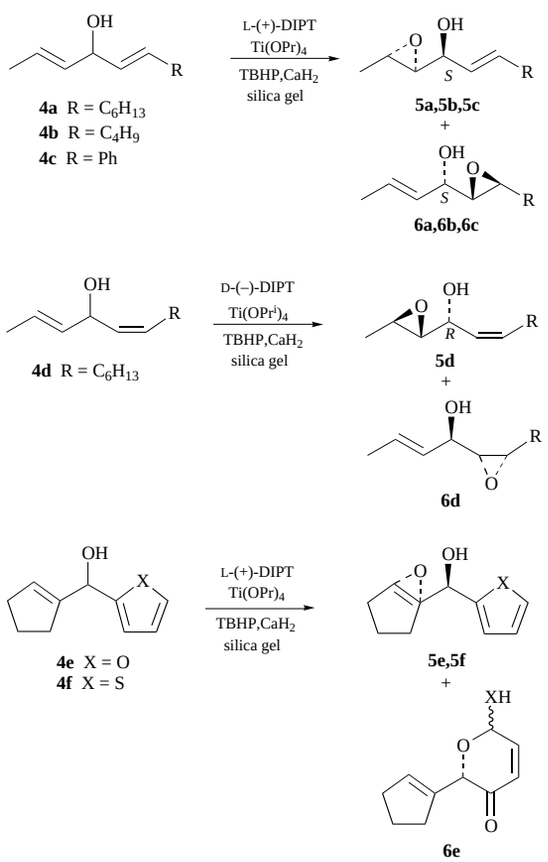


Scheme 1

studies on the kinetic resolution of unsymmetrical divinylmethanols.[10]

† On leave from Shanghai Medical University, Shanghai 200032.

The kinetic resolution of **4a–c** with *tert*-butyl hydroperoxide (TBHP; 0.5 equiv.) in the presence of Ti(OPr^i)$_4$ and L-(+) or D-(−)-diisopropyl tartrate (DIPT) (Scheme 2) gave products **5a–c** and **6a–c** both in good yield and with high ee values (Table



1). However, for **4d** the reaction produced **5d** both in high yield and with a high ee value, together with a trace of the oxidation product **6d**, in which a *cis*-double bond had been oxidized (Table 1). This result may be due to the lower reaction activity of the *cis*- double bond compared with the *trans*- double bond. We also found that the double bond in a five-membered ring, *e.g.* in **4e** and **4f**, was easily oxidized in good yields but with only low ee values (Table 1). It can also be seen from the kinetic resolution of **4g** that the furyl ring is more easily oxidized than a normal double bond.[5] The slow-reacting enantiomers in all these kinetic resolutions gave a complex mixture during work-up.

Table 1 Kinetic resolution of **4a–f** (0.5 equiv. of TBHP was used)[a]

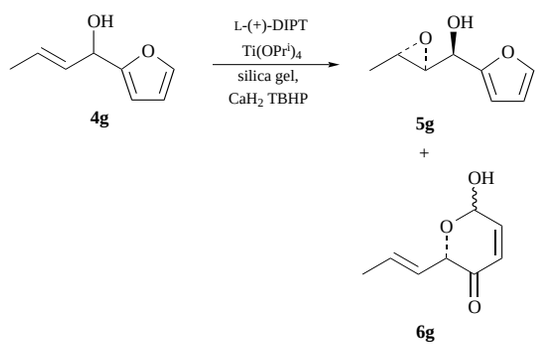
			5			**6**		
Substrate	DIPT	Time (h)	Yield (%)	ee[b] (%)	Conf'n[c]	Yield (%)	ee[b] (%)	Conf'n[c]
4a	L-(+)-	6	24.4	>95	*S*	22.1	>95	*S*
4b	L-(+)-	6	24	>95	*S*	21	>95	*S*
4c	D-(−)-	6	27.9	>95	*R*	19.1	>95	*R*
4d	L-(+)-	48	42.5	>95	*S*	2.5	82	*S*
4e	D-(−)-	6	21.4	65	—	24	—	—
4f	D-(−)-	6	35	50	—	—	—	—
4g	L-(+)-	6	4.5	>95	*R*	33	>95	*S*
1g	D-(−)-	6	4	>95	*S*	32	>95	*R*

[a] All reactions were carried out with 1.0 equiv. of $Ti(OPr^i)_4$, 1.2 equiv. of DIPT in the presence of CaH_2 and silica gel at −25 °C. [b] The ee values were determined by the Mosher ester method based on ^{1}H NMR (300 MHz) analyses. [c] Determined by ^{1}H NMR (300 MHz) analyses of (*R*)- and (*S*)-Mosher ester.

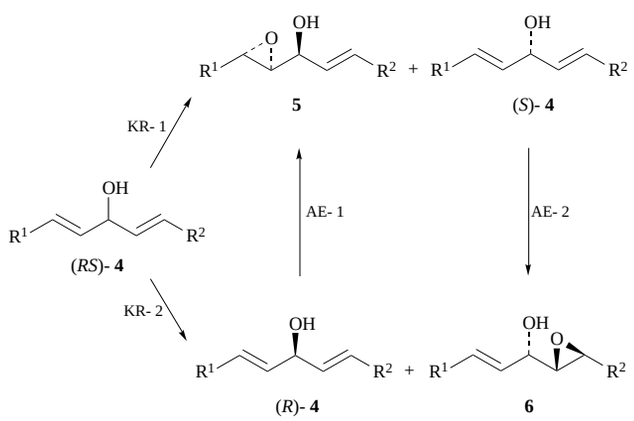
Table 2 Kinetic resolution of **4a–f** (1.0 equiv. of TBHP was used)[a]

			5			**6**		
Substrate	DIPT	Time (h)	Yield (%)	ee[b] (%)	$[\alpha]_D^{20}$[c]	Yield (%)	ee[b] (%)	$[\alpha]_D^{20}$[c]
4a	L-(+)-	6	41.2	>95	−20.4	41	>95	−25.2
	D-(−)-	6	40.9	>95	+21	40	>95	+24.7
4b	L-(+)-	6	42	>95	−24.8	40	>95	−25.3
	D-(−)-	6	46.2	>95	+25.7	44.1	>95	+24.5
4c	L-(+)-	6	41.6	>95	−46.5	32.2	>95	−29.7
	D-(−)-	6	39.7	>95	+46.4	30.4	>95	+27.4
4d	D-(−)-	48	45.5	>95	−20.9	23.5	80	+10.6
4e	L-(+)-	6	46	50	+5.1	42	—	—
4f	L-(+)-	6	55	46	−2.4	—	—	—
4g	L-(+)-	6	30.3	>95	−11	36.4	>95	—
	D-(−)-	6	34	>95	+11	33	>95	—

[a] All reactions were carried out with 1.0 equiv. of $Ti(OPr^i)_4$, 1.2 equiv. of DIPT in the presence of CaH_2 and silica gel at −25 °C. [b] The ee values were determined by the Mosher ester method based on ^{1}H NMR (300 MHz) analyses. [c] All optical rotations were measured in ethanol (*c* 1.0–2.0).



Scheme 2



Scheme 3

Use of 1.0 equiv. rather than 0.5 equiv. of TBHP gave higher product yields, especially for the oxidation of substrates with a double bond of relatively low activity, such as **6d** and **5g** (Table 2). It was noteworthy that the ee values were almost unchanged (Table 2).

Since there are two oxidized moieties in the racemic substrate **4**, a double kinetic resolution (KR-1 and KR-2) occurred (Scheme 3). When L-(+)-DIPT was used, the 'left-hand' double bond in substrate **4** could be oxidized by the chiral complex of $Ti(OPr^i)_4$ and L-(+)-DIPT to provide the epoxy alcohol **5** and a slow-reacting enantiomer (*S*)-**4** (KR-1). Similarly, the 'right-hand' double bond in **4** could also be oxidized by the reagents to give the oxidation product **6** and another slow-reacting enantiomer (*R*)-**4** (KR-2). The reaction rates of KR-1 and KR-2 depend on the reaction activities of the two double bonds. After the kinetic resolutions, further asymmetric epoxidations may also occur to convert (*R*)-**4** into **5** (AE-1) in which oxidation of the 'left-hand' double bond is matched with the chiral complex, while that of the 'right-hand' double bond is mismatched. In the same way, (*S*)-**4** may also be transformed into **6** (AE-2).

The absolute configurations of the α-carbon of the secondary alcohols were determined by ^{1}H NMR (300 MHz) analyses of the (*R*)- and (*S*)-Mosher esters (Fig. 1).[11]

Based on this strategy, we next describe two short synthetic routes to natural asperlin **1** from (+)-**5g** and acetylphomalactone **2** and (5*S*,6*S*,7*R*,8*S*)-asperlin **3** from (+)-**6g** (Scheme 4).

Oxidation of (+)-**5g** with TBHP in the presence of a catalytic amount of $VO(acac)_2$ afforded the pyranone **7** (74.5%) as a mixture of α- and β-anomers. This mixture was then oxidized with chromium(VI) oxide, followed by immediate reduction with sodium triacetoxyborohydride in one pot to provide the alcohol **8a** and **8b** (**8a**:**8b** ≈ 1:1). Finally, acetylation of **8a** and **8b** with acetic anhydride gave (+)-asperlin **1** (21% from **7**), mp 70–71 °C, $[\alpha]_D^{20}$ +330‡ (*c* 0.3, EtOH) {lit.,[3d,2] mp 71 °C, $[\alpha]_D^{20}$ +332 (EtOH)}, together with the 5-*epi*-asperlin **9** (19% from **7**), mp

‡ $[\alpha]_D$ Values given in units of 10^{-1} deg cm^2 g^{-1}.

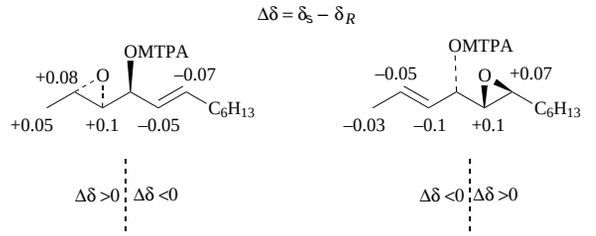
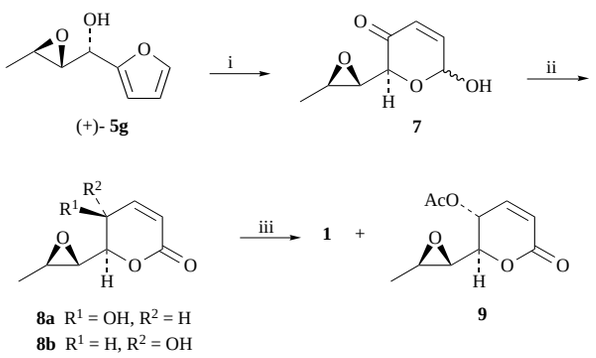
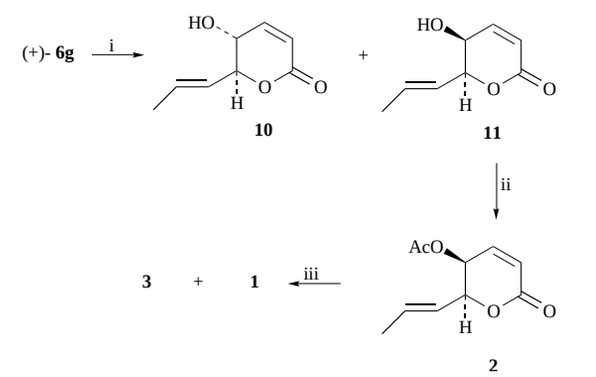


Fig. 1



Scheme 4 *Reagents and conditions:* i, TBHP, $VO(acac)_2$, CH_2Cl_2, 0 °C; ii, CrO_3, HOAc, 25 °C, 15 min; then $NaBH(OAc)_3$, HOAc, Pr^iOH, −5 °C, 1 h; iii, Ac_2O, py, DMAP, RT



Scheme 5 *Reagents and conditions:* i, CrO_3, HOAc, 25 °C, 15 min; then $NaBH(OAc)_3$, HOAc, Pr^iOH, −5 °C, 1 h; ii, Ac_2O, py, DMAP, RT; iii, *m*-CPBA, CH_2Cl_2, RT, 48 h

80–81 °C, $[\alpha]_D^{20}$ −186 (*c* 0.5, EtOH) {lit.,[3d] mp 81–81.5 °C, $[\alpha]_D^{20}$ −185 (*c* 0.5, EtOH)}.

Another synthetic route to natural compounds **2** and **3** from (+)-**6g** is shown in Scheme 5. Oxidation of the pyranone (+)-**6** by chromium(VI) oxide afforded **10** (29%), together with **11** (32%). Acetylation of **11** with acetic anhydride provided natural **2** (75%). Finally, oxidation of **2** with *m*-CPBA yielded **1** (35%) and **3** (19%).

In summary, a highly efficient double-kinetic resolution of unsymmetrical divinylmethanols has been developed utilizing a modified Sharpless reagent. This resolution can be used as a general method to provide two epoxy alcohols with three chiral centres and the utilization of both of them as good chiral building blocks for syntheses of natural products. This has been illustrated by the convenient syntheses of (+)-asperlin, (+)-acetylphomalactone and (5*S*,6*S*,7*R*,8*S*)-asperlin.

Experimental

All mps are uncorrected. ^{1}H NMR spectra were recorded on a Bruker AM300 instrument in $CDCl_3$ with TMS as the internal standard; chemical shifts are given in δ and *J* values are given in Hz. Mass spectra were obtained on HP5890A spectrometer. IR spectra were taken for solid samples in KBr pellets and for liquid samples in film, on a Shimadzu-440 spectrophotometer. Optical rotations were measured on a Perkin-Elmer 241MC polarimeter and $[\alpha]_D$ values are given in units of 10^{-1} deg cm^2 g^{-1}.

General process for kinetic resolutions

Into a mixture of $Ti(OPr^i)_4$ (0.58 cm^3, 2.0 mmol), CaH_2 (10 mg) and silica gel (20 mg) in dry dichloromethane (15 cm^3) under nitrogen at −25 °C was injected L-(+) or D-(−)-DIPT (0.51 cm^3, 2.4 mmol) *via* a syringe. After the mixture had been stirred for 10 min, the substrate **4** (2.0 mmol) in dichloromethane (5 cm^3) was added to it at once. The reaction mixture was stirred for a further 10 min after which anhydrous TBHP (0.5 equiv. or 1.0 equiv.) was injected into it at −25 °C. After the mixture had been stirred for 6 h at −25 °C, 10% aqueous tartaric acid (10 cm^3) was added to it at −25 °C. Stirring was then continued at room temperature until the aqueous layer had become clear. After separation and concentration of the mixture *in vacuo*, the residue was diluted with THF and water (10 cm^3, 3 : 1), and then treated with $LiOH\cdot H_2O$ (420 mg, 10 mmol) at 0 °C (**6e**, **6g** must be separated by chromatography before treatment with LiOH). The mixture was stirred at 0 °C for 1–2 h after which the organic layer was separated and the aqueous layer was extracted with ethyl acetate. The combined organic layers were washed with brine, dried ($MgSO_4$) and concentrated under reduced pressure. The residue was separated by flash chromatography [ethyl acetate–hexane (1 : 9)] to afford the oxidation products **5** and **6**, respectively.

Compounds 5a and 6a

Compound **4a** (366 mg, 2.0 mmol) was treated with $Ti(OPr^i)_4$, L-(+)-DIPT and TBHP as described in the general procedure to afford **5a** (158 mg, 41.2%) as an oil, $[\alpha]_D^{20}$ −20.4 (*c* 1.2, EtOH); ν_{max}(film)/cm^{-1} 3350 (OH); $\delta_H(CDCl_3)$ 0.88 (3 H, t, *J* 6.8, Me), 1.28–1.39 (8 H, m, 4 CH_2), 1.33 (3 H, d, *J* 5.3, Me), 1.99 (1 H, s, OH), 2.06 (2 H, m, CH=CHC*H*$_2$), 2.79 (1 H, dd, *J* 2.9, 2.6, epoxy), 3.07 (1 H, dd, *J* 5.3, 2.9 epoxy), 4.22 (1 H, dd, *J* 6.5, 2.6, HOC*H*), 5.43 (1 H, dd, *J* 15.4, 6.5, CH=CH) and 5.78 (1 H, dt, *J* 15.4, 5.4, CH=C*H*); *m*/*z* 198 (M^+) and 181 (M^+ − OH); [Found (HRMS): *m*/*z* 198.1611. Calc. for $C_{12}H_{22}O_2$ 198.1609]; and **6a** (157 mg, 41%) as an oil, $[\alpha]_D^{20}$ −25.2 (*c* 1.1, EtOH), ν_{max}(film)/cm^{-1} 3350 (OH); $\delta_H(CDCl_3)$ 0.89 (3 H, t, *J* 7.0, Me), 1.29–1.60 (10 H, m, 5 × CH_2), 1.73 (3 H, d, *J* 6.7, Me), 1.97 (1 H, s, OH), 2.81 (1 H, dd, *J* 3.1, 2.4, epoxy), 2.98 (1 H, dt, *J* 5.5, 2.4, epoxy), 4.22 (1 H, dd, *J* 5.0, 3.1, HOC*H*), 5.46 (1 H, dd, *J* 15.4, 5.0, CH=CH) and 5.82 (1 H, dq, *J* 15.4, 6.6, CH=CH); *m*/*z* 199 (M^+ + 1), 181 (M^+ − OH); [Found (HRMS): *m*/*z* 198.1606. Calc. for $C_{12}H_{22}O_2$ 198.1609].

Determination of the absolute configuration of 5a and 6a

MTPA-ester of 5a. To a solution of pyridine (0.2 cm^3), DMAP(1 mg) and **5a** (24 mg) in CH_2Cl_2 (2 cm^3) was added a solution of MTAP chloride (1.5 cm^3; 50 mg cm^{-3} in CH_2Cl_2). After 24 h at room temperature, the reaction mixture was poured into water (5 cm^3) and the organic layer was separated and washed successively with 5% aq. HCl, water and brine and then dried (Na_2SO_4) and evaporated under reduced pressure to give a crude oil. This was purified by chromatography on silica gel to afford the MTPA ester of **5a** (25 mg). (*R*)-(+)-MTPA-ester of **5a**: $\delta_H(CDCl_3)$ 5.94 (1 H, CH=C*H*), 5.44 (1 H, C*H*=CH), 2.89 (1 H, epoxy), 2.78 (1 H, epoxy), 1.26 (3 H, CH_3); (*S*)-(−)-MTPA-ester of **5a**: $\delta_H(CDCl_3)$ 5.87 (1 H, CH=C*H*), 5.39 (1 H, C*H*=CH), 2.97 (1 H, epoxy), 2.88 (1 H, epoxy) and 1.31 (3 H, CH_3).

MTPA-ester of 6a. The MTPA-ester of **6a** (20 mg) was prepared by the method as described above. (*R*)-(+)-MTPA-ester of **6a**: $\delta_H(CDCl_3)$ 5.94 (1 H, CH=C*H*), 5.51 (1 H, C*H*=CH), 2.78 (1 H, epoxy), 2.81 (1 H, epoxy), 1.75 (3 H, CH_3); (*S*)-(−)-MTPA-ester of **6a**: $\delta_H(CDCl_3)$ 5.89 (1 H, CH=C*H*), 5.41 (1 H, C*H*=CH), 2.88 (2 H, epoxy) and 1.72 (3 H, CH_3).

Compounds 5b and 6b

Compound **4b** (308 mg, 2.0 mmol) was treated with $Ti(OPr^i)_4$, L-(+)-DIPT and TBHP by the above described general procedure to afford **5b** (142 mg, 42%) as an oil, $[\alpha]_D^{20}$ −24.8 (*c* 1.2, EtOH); ν_{max}(film)/cm^{-1} 3350 (OH); $\delta_H(CDCl_3)$ 0.90 (3 H, d, *J* 7.2, Me), 1.26–1.40 (7 H, m, Me, 2 CH_2), 2.03 (1 H, br, OH), 2.07 (2 H, m, CH=CHCH_2), 2.79 (1 H, dd, *J* 3.0, 2.8, epoxy), 3.05 (1 H, dt, *J* 7.1, 2.8, epoxy), 4.21 (1 H, dd, *J* 7.1, 3.0, HOC*H*), 5.44 (1 H, dd, *J* 15.8, 7.1, CH=CH) and 5.79 (1 H, dt, *J* 15.8, 16.4, CH=CH); *m*/*z* 153 (M^+ − OH) [Found (HRMS): *m*/*z* 153.1238. Calc. for $C_{10}H_{17}O$ 153.1235]; and **6b** (136 mg, 40%) as an oil, $[\alpha]_D^{20}$ −25.3 (*c* 1.3, EtOH), ν_{max}(film)/cm^{-1} 3350 (OH); $\delta_H(CDCl_3)$ 0.91 (3 H, t, *J* 6.8, Me), 1.39 (4 H, m, 2 × CH_2), 1.55 (2 H, m, CH_2), 1.73 (3 H, d, *J* 6.4, Me), 1.99 (1 H, br, OH), 2.88 (1 H, dd, *J* 5.0, 2.6, epoxy), 2.99 (1 H, m, epoxy), 4.28 (1 H, dd, *J* 7.0, 2.6, HOC*H*), 5.45 (1 H, dq, *J* 15.4, 7.0, CH=CH) and 5.80 (1 H, dd, *J* 15.4, 6.4, CH=CH); *m*/*z* 170 (M^+) and 153 (M^+ − OH) [Found (HRMS): *m*/*z* 170.1312. Calc. for $C_{10}H_{18}O_2$ 170.1329].

Compounds 5c and 6c

Compound **4c** (185 mg, 1.1 mmol) was treated with $Ti(OPr^i)_4$, L-(+)-DIPT and TBHP by the above described general procedure to afford **5c** (84 mg, 41.6%) as an oil, $[\alpha]_D^{20}$ −46.5 (*c* 2.3, EtOH); $\delta_H(CDCl_3)$ 1.35 (3 H, d, *J* 5.3, Me), 2.90 (1 H, dd, *J* 3.2, 2.3, epoxy), 3.47 (1 H, dq, *J* 5.3, 2.3, epoxy), 4.46 (1 H, dd, *J* 6.8, 3.2, HOC*H*), 6.18 (1 H, dd, *J* 15.9, 6.8, CH=CH), 6.70 (1 H, m, *J* 15.9, CH=CH) and 7.25–7.42 (5 H, m, Ph); *m*/*z* 190 (M^+), 173 (M^+ − OH) and **6c** (65 mg, 32.2%) as an oil, $[\alpha]_D^{20}$ +46.4 (*c* 1.3, EtOH); $\delta_H(CDCl_3)$ 1.70 (3 H, d, *J* 6.3, Me), 2.68 (2 H, m, epoxy), 4.06 (1 H, dd, *J* 9.0, 4.0, HOC*H*), 5.50 (1 H, dd, *J* 15.4, 4.0, CH=CH), 5.64 (1 H, dq, *J* 15.4, 6.3, CH=CH) and 7.17–7.30 (5 H, m, Ph): *m*/*z* 189 (M^+ − 1).

Compounds 5d and 6d

Compound **4d** (364 mg, 2.0 mmol) was treated with $Ti(OPr^i)_4$, D-(−)-DIPT and TBHP by the above described general procedure to afford **5d** (180 mg, 45.5%) as an oil, $[\alpha]_D^{20}$ −20.9 (*c* 1.4, EtOH); $\delta_H(CDCl_3)$ 0.89 (3 H, t, *J* 6.7, Me), 1.28–1.41 (8 H, m, 4 × CH_2), 1.34 (3 H, d, *J* 5.2, CH_3), 1.95 (1 H, br, OH), 2.12 (2 H, m, CH=CHCH_2), 2.77 (1 H, dd, *J* 2.7, 5.4, epoxy), 3.09 (1 H, m, epoxy), 4.64 (1 H, dd, *J* 8.6, 5.4, HOC*H*), 5.33 (1 H, dd, *J* 8.4, 8.6, CH=CH) and 5.65 (1 H, dd, *J* 10.9, 8.4, CH=CH); *m*/*z* 181 (M^+ − OH) [Found (HRMS): *m*/*z* 181.1628. Calc. for $C_{12}H_{21}O$ 181.1622]; and **6d** (93 mg, 23.5%) as an oil, $[\alpha]_D^{20}$ +10.6 (*c* 1.4, EtOH); $\delta_H(CDCl_3)$ 0.89 (3 H, t, *J* 6.9, Me), 1.35–1.70 (10 H, m, 5 × CH_2), 1.75 (3 H, d, *J* 5.5, Me), 2.91 (1 H, dd, *J* 7.3, 4.1, epoxy), 3.05 (1 H, dd, *J* 5.4, 4.1, epoxy), 3.99 (1 H, dd, *J* 7.3, 7.0, HOC*H*), 5.65 (1 H, dd, *J* 15.3, 7.0, CH=CH) and 5.84 (1 H, dd, *J* 15.3, 5.5, CH=CH); *m*/*z* 198 (M^+) and 181 (M^+ − OH) [Found (HRMS): *m*/*z* 198.1605. Calc. for $C_{12}H_{22}O_2$ 198.1600].

Compounds 5e and 6e

Compound **4e** (328 mg, 2.0 mmol) was treated with $Ti(OPr^i)_4$, L-(+)-DIPT and TBHP by the above described general procedure to afford **5e** (166 mg, 46%) as an oil, $[\alpha]_D^{20}$ +5.1 (*c* 1.0, EtOH); $\delta_H(CDCl_3)$ 1.50–2.10 (6 H, m, 3 × CH_2), 2.71 (1 H, br OH), 3.68 (1 H, br, epoxy), 5.01 (1 H, s, HOC*H*), 6.35 (2 H, br, furyl) and 7.40 (1 H, br, furyl); *m*/*z* 180 (M^+) and 163 (M^+ − OH) [Found (HRMS): *m*/*z* 163.0749. Calc. for $C_{10}H_{11}O_2$: (M^+ − OH), 163.0718]; and **6e** (150 mg, 42%) as an oil, $\delta_H(CDCl_3)$ 1.95 (2 H, m, CH_2), 2.40 (4 H, m, 2 × CH_2), 5.17 (1 H, t, *J* 6.1, CH=C), 5.67 (1 H, br, OCH), 5.79 (1 H, br, HO−C*H*), 6.15 (1 H, d, *J* 10.5, CH=CH) and 6.91 (1 H, dd, *J* 10.5, 2.8, CH=CH); *m*/*z* 181 (M^+ + 1) and 163 (M^+ − OH); [Found (HRMS): *m*/*z* 180.0796. Calc. for $C_{10}H_{12}O_3$ (M^+) 180.0790].

Compound 5f

Compound **4f** (360 mg, 2.0 mmol) was treated with $Ti(OPr^i)_4$, L-(+)-DIPT and TBHP by the above described general procedure to afford **5f** (215 mg, 55%) as an oil, $[\alpha]_D^{20}$ −2.4 (*c* 1.9, EtOH); $\delta_H(CDCl_3)$ 1.40–2.10 (6 H, m, 3 × CH_2), 2.83 (1 H, br, OH), 3.70 (1 H, br, epoxy), 5.26 (1 H, s, HOC*H*), 6.98 (1 H, dd, *J* 5.9, 3.6, thiofuryl), 7.09 (1 H, d, *J* 3.6, thiofuryl) and 7.30 (1 H, d, 5.9, thiofuryl); *m*/*z* 196 (M^+) and 179 (M^+ − OH).

Compounds 5g and 6g

Compound **4g** (276 mg, 2.0 mmol) was treated with $Ti(OPr^i)_4$, L-(+)-DIPT and TBHP by the above described general procedure to afford **5g** (93 mg, 30%), mp 42.0–43.5 °C, $[\alpha]_D^{20}$ −11 (*c* 1.3, EtOH); ν_{max}(film)/cm^{-1} 3400 (OH); $\delta_H(CDCl_3)$ 1.38 (3 H, d, *J* 5.5, Me), 2.30 (1 H, br, OH), 3.06 (1 H, dd, *J* 3.4, 2.3, 2-H), 3.26 (1 H, dd, *J* 5.5, 2.3, 3-H), 4.89 (1 H, d, *J* 3.4, 1-H), 6.37 (2 H, m, furyl) and 7.43 (1 H, m, furyl); *m*/*z* 154 (M^+) and 137 (M^+ − OH) [Found (HRMS): *m*/*z* 154.0600. Calc. for $C_8H_{10}O_3$ (M^+) 154.0630]; and **6g** (112 mg, 36.4%), mp 68.0–70.0 °C, $[\alpha]_D^{20}$ +78.1 (*c* 1.2, CH_3CO_2Et); ν_{max}(film)/cm^{-1} 3400 (OH), 1690 (C=O) and 1630 (C=C); $\delta_H(CDCl_3)$ 1.79 (3 H, dt, *J* 6.5, 1.4, 1.0, Me), 3.09 (1 H, br, OH), 5.01 (1 H, d, *J* 6.6, 2-H), 5.58–5.67 (1 H, m, CH=CH), 5.70 (1 H, dd, *J* 4.5, 3.3, 6-H), 5.84–5.94 (1 H, m, CH=CH), 6.15 (1 H, d, *J* 10.3, 4-H) and 6.92 (1 H, dd, *J* 10.3, 3.3, 5-H); *m*/*z* 154 (M^+) and 136 (M^+ − H_2O).

(2*S*)-6-Hydroxy-2-[(1*R*,2*R*)-1,2-epoxypropyl]-2,6-dihydropyran-3-one 7

To a mixture of (+)-**5g** (225 mg, 1.474 mmol) and $VO(acac)_2$ in dichloromethane (20 cm^3), TBHP (7.01 mol dm^{-3}; 0.32 cm^3; 2.24 mmol) was added at 0 °C. After the reaction mixture had been stirred for 12 h at 0 °C, then dimethyl sulfide (0.3 cm^3) was added to it at 0 °C and stirring continued for 30 min. at 0 °C; 3% aqueous ammonium chloride (5 cm^3) was then added to the mixture. The organic layer was separated and the aqueous layer was extracted with dichloromethane. The combined organic layers were washed with brine, dried ($MgSO_4$) and concentrated under reduced pressure. The residue was purified by flash chromatography [ethyl acetate–hexane (1:4)] to afford **7** (185 mg, 74.5%); ν_{max}(film)/cm^{-1} 3350 (OH), 1730 (C=O) and 1630 (C=C); $\delta_H(CDCl_3)$ 1.33 (3 H, d, *J* 5.2, Me), 3.09–3.28 (2 H, m, 7-H, 8-H), 4.47 (0.4 H, d, *J* 2.1, 2-H), 4.75 (0.6 H, d, *J* 3.0, 2-H), 5.58 (0.4 H, d, *J* 2.0, 6-H), 5.69 (0.6 H, d, *J* 3.0, 6-H), 6.12 (1 H, d, *J* 10.5, 4-H) and 6.90–6.97 (1 H, m, 5-H); *m*/*z* 170 (M^+) and 152 (M^+ − H_2O) [Found (HRMS): *m*/*z* 170.0543. Calc. for $C_8H_{10}O_4$ (M^+) 170.0579].

(+)-Asperlin 1 and 5-*epi*-asperlin 9

To a stirred solution of compound **7** (170 mg, 1.0 mmol) in acetic acid (7 cm^3), was added chromium(VI) oxide (120 mg, 1.2 mmol) in acetic acid (8 cm^3) at 20 °C. After being stirred for 20 min at 20 °C, the reaction mixture was treated with isopropyl alcohol (15 cm^3) and stirring continued for a further 2 min. The resulting mixture was then cooled to −5 °C and treated with freshly prepared sodium triacetoxyborohydride [prepared from sodium borohydride (760 mg) and acetic acid (15 cm^3)]. The reaction mixture was then stirred at −5 °C for 30 min, after which it was poured into water (100 cm^3) and dichloromethane (20 cm^3). The organic layer was separated and the aqueous layer was extracted with dichloromethane. The combined organic layers were washed with saturated aqueous sodium hydrogen carbonate and brine, dried ($MgSO_4$) and concentrated under reduced pressure to provide a mixture of **8a** and **8b**. The mixture was used for next step without separation.

To a stirred mixture of above residue (**8a** and **8b**), pyridine (0.1 cm^3) and DMAP (2 mg) in dichloromethane (8 cm^3), was added acetic anhydride (0.075 cm^3) at room temperature. After the mixture had been stirred for 1 h at room temperature, saturated aqueous cupric sulfate (10 cm^3) was added to it. The organic layer was separated and the aqueous layer was extracted with dichloromethane. The combined organic layers were washed with saturated aqueous cupric sulfate, dried

($MgSO_4$) and concentrated under reduced pressure. The residue was separated by flash chromatography [ethyl acetate–hexane (1:4)] to afford the first fraction **9** (40 mg, 19% from **7**), mp 80–81 °C; $[\alpha]_D^{20}$ −186 (*c* 0.5, EtOH) {lit.,[9d] mp 81–81.5 °C, $[\alpha]_D^{20}$ −185 (*c* 0.5, EtOH)}; ν_{max}(film)/cm^{-1} 1730 (C=O); δ_H($CDCl_3$) 1.35 (3 H, d, *J* 5.2, Me), 2.14 (3 H, s, AcO), 2.84 (1 H, dd, *J* 6.6, 2.0, 7-H), 3.05 (1 H, m, 8-H), 4.21 (1 H, t, *J* 6.6, 6-H), 5.52 (1 H, ddd, *J* 5.1, 4.1, 1.0, 5-H), 6.18 (1 H, dd, *J* 9.8, 1.0, 3-H) and 6.88 (1 H, dd, *J* 9.8, 4.1, 4-H); *m*/*z* 213 (M^+ + 1) and 153 (M^++1−HOAc); and the second fraction **1** (44 mg, 21% from **7**), mp 69–70 °C; $[\alpha]_D^{20}$ +330 (*c* 0.3, EtOH) {lit.,[9d] mp 70.5–71 °C, $[\alpha]_D^{20}$ +332 (*c* 0.4, EtOH)}; ν_{max}(film)/cm^{-1} 1730 (C=O); δ_H($CDCl_3$) 1.38 (3 H, d, *J* 4.5, Me), 2.13 (3 H, s, AcO), 3.03–3.11 (2 H, m, 7-H, 8-H), 4.10 (1 H, dd, *J* 6.5, 3.0, 6-H), 5.32 (1 H, dd, *J* 5.5, 3.0, 5-H), 6.21 (1 H, d, *J* 9.8, 3-H) and 7.06 (1 H, dd, *J* 9.8, 5.5, 4-H); *m*/*z* 213 (M^+ + 1) and 153 (M^+ + 1 − HOAc).

(+)-Phomalactone 11 and 5-*epi*-phomalactone 10

To a stirred solution of compound (+)-**6g** (269 mg, 1.746 mmol) in acetic acid (10 cm^3), was added chromium(VI) oxide (210 mg, 2.1 mmol) in acetic acid (10 cm^3) at 20–30 °C. After the mixture had been stirred for 15 min at the same temperature, it was treated with isopropyl alcohol (15 cm^3) and stirred for a further 2 min. The resulting mixture was then cooled to −5 °C, and treated with freshly prepared sodium triacetoxyborohydride [prepared from sodium borohydride (760 mg) and acetic acid (15 cm^3)]. After the reaction mixture had been stirred for 1 h, the temperature being allowed to rise from −5 °C to room temperature, it was poured into water (100 cm^3) and dichloromethane (20 cm^3). The organic layer was separated and the aqueous layer was extracted with dichloromethane. The combined organic layers were washed with saturated aqueous sodium hydrogen carbonate and brine, dried ($MgSO_4$) and concentrated under reduced pressure. The residue was separated by flash chromatography [ethyl acetate–hexane (1:4)] to afford the first fraction **10** (78 mg, 29%), mp 76–77 °C, $[\alpha]_D^{20}$ −70 (*c* 0.8, EtOH) {lit.,[4b] mp 77 °C, $[\alpha]_D^{20}$ −68.6 (*c* 0.6, EtOH)}; ν_{max}(film)/cm^{-1} 3400 (OH), 1720 (C=O) and 1630 (C=C); δ_H($CDCl_3$) 1.80 (3 H, dd, *J* 6.5, 1.4, Me), 2.20 (1 H, br, OH), 4.33 (1 H, dt, *J* 8.7, 2.2, 5-H), 4.63 (1 H, dd, *J* 8.7, <1.0, 6-H), 5.57 (1 H, m, CH=CH), 5.96 (1 H, m, CH=CH), 6.0 (1 H, dd, *J* 9.9, 2.0, 3-H) and 6.87 (1 H, dd, *J* 9.9, 2.2, 4-H); *m*/*z* 155 (M^+ + 1) and 137 (M^+ + 1 − H_2O); and the second fraction **11** (86 mg, 32%), mp 56–57 °C; $[\alpha]_D^{20}$ +172 (*c* 0.6, EtOH) {lit.,[12] mp 57 °C, $[\alpha]_D^{20}$ +175 (EtOH)}; ν_{max}(film)/cm^{-1} 3400 (OH), 1720 (C=O) and 1630 (C=C); δ_H($CDCl_3$) 1.81 (3 H, dd, *J* 6.5, 1.2, Me), 2.20 (1 H, br, OH), 4.20 (1 H, dd, *J* 5.3, 3.1, 5-H), 4.83 (1 H, dd, *J* 7.0, 3.1, 6-H), 5.76 (1 H, m, CH=CH), 6.01 (1 H, m, CH=CH), 6.13 (1 H, d, *J* 9.7, 3-H) and 6.99 (1 H, dd, *J* 9.7, 5.3, 4-H); *m*/*z* 155 (M^+ + 1), 137 (M^+ + 1 − H_2O) and 122 (M^+ − Me − OH).

(+)-Acetylphomalactone 2

To a stirred mixture of **11** (40 mg, 0.26 mmol), pyridine (0.064 cm^3) and DMAP (1 mg) in dichloromethane (8 cm^3), was added acetic anhydride (0.05 cm^3) at room temperature. After the mixture had been stirred for 1 h at room temperature it was treated with saturated aqueous cupric sulfate (10 cm^3). The organic layer was separated and the aqueous layer was extracted with dichloromethane. The combined organic layers were washed with saturated aqueous cupric sulfate, dried ($MgSO_4$) and concentrated under reduced pressure. The residue was purified by flash chromatography [ethyl acetate–hexane (1:4)] to afford **2** (38 mg, 75%), mp 54–55 °C; $[\alpha]_D^{20}$ +305 (*c* 1.3, EtOH) {lit.,[4b] mp 54 °C, $[\alpha]_D^{20}$ +300 (*c* 0.4, EtOH)}; ν_{max}(film)/cm^{-1} 1730 (C=O) and 1630 (C=C); δ_H($CDCl_3$) 1.77 (3 H, dd, *J* 6.4, 1.2, Me), 2.10 (3 H, s, AcO), 4.94 (1 H, dd, *J* 7.2, 3.0, 6-H), 5.23 (1 H, dd, *J* 5.5, 3.0, 5-H), 5.61 (1 H, m, CH=CH), 5.94 (1 H, m, CH=CH), 6.22 (1 H, d, *J* 9.7, 3-H) and 6.98 (1 H, dd, *J* 9.7, 5.4, 4-H); *m*/*z* 197 (M^+ + 1) and 137 (M^+ + 1 − HOAc).

(+)-Asperlin 1 and (5*S*,6*S*,7*R*,8*S*)-asperlin 3

To a stirred solution of **2** (24 mg, 0.122 mmol) in dichloromethane (5 cm^3), *m*-CPBA (80%; 46 mg) was added at 30 °C. The reaction mixture was stirred for 60 h at 30 °C after which 3% aqueous sodium hydrogen carbonate (5 cm^3) was added to it. The organic layer was separated and the aqueous layer was extracted with dichloromethane. The combined organic layers were washed with saturated aqueous cupric sulfate, dried ($MgSO_4$) and concentrated under reduced pressure. The residue was separated by flash chromatography [ethyl acetate–hexane (1:4)] to afford the first fraction (+)-asperlin **1** (9 mg, 35%), and the second fraction (5*S*,6*S*,7*R*,8*S*)-asperlin **3** (5 mg, 19.3%), mp 63–64 °C, $[\alpha]_D^{20}$ +210 (*c* 0.2, EtOH) {lit.,[13] mp 64 °C, $[\alpha]_D^{20}$ +224 (MeOH);[4b] mp 63.5 °C, $[\alpha]_D^{20}$ +211 (*c* 0.3, EtOH)}; ν_{max}(film)/cm^{-1} 1730 (C=O); δ_H($CDCl_3$) 1.34 (3 H, d, *J* 4.7, Me), 2.15 (3 H, s, AcO), 2.99–3.07 (2 H, m, 7-H, 8-H), 4.36 (1 H, t, *J* 4.0, 6-H), 5.51 (1 H, dd, *J* 5.0, 3.6, 5-H), 6.21 (1 H, d, *J* 9.8, 3-H) and 6.85 (1 H, dd, *J* 9.8, 5.0, 4-H); *m*/*z* 213 (M^+ + 1) and 153 (M^+ + 1 − HOAc).

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