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Total synthesis of (+)-asperlin

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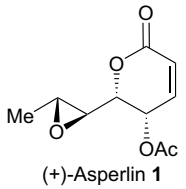
Abstract—Syntheses of (+)-asperlin **1** were achieved via two different synthetic routes. 1,2-Addition of α-furyl anion to (2*R*,3*S*)-2-^{t}butyldimethylsilyloxy-3-chlorobutanal **6** gave (1*S*,2*R*,3*S*)-1-(2-furyl)-2-^{t}butyldimethylsilyloxy-3-chlorobutanol **7**, which was converted to the chiral intermediate, (1*S*,2*R*,3*R*)-1-(2-furyl)-2,3-epoxybutanol **8** (37% overall yield from **6**) for the synthesis of (+)-**1**. The second synthesis of (+)-asperlin **1** from (2*R*,3*S*)-**6** was achieved in 8% overall yield, based on a combination of the indium-assisted stereoselective addition of 3-bromopropenyl acetate **9** to (2*R*,3*S*)-**6** and the ring closing metathesis (RCM) using Grubbs catalyst.

1. Introduction

(+)-Asperlin **1**, isolated from *Aspergillus nidulans* and *Aspergillus caespiyosus*, has been shown to exhibit antitumor and antibacterial activity. Its structure, including the absolute configuration, was determined by spectroscopic and chemical studies,[1–3] as shown in Figure 1. Due to its interesting bioactivity, the synthesis of the natural product **1** and the related compounds has already been reported by several groups.[4] Syntheses of (+)-**1** from natural products such as L-rhamnose,[5] (*S*,*S*)-tartaric acid,[6] and D-glucose[7] have been reported. Recently, the convenient synthesis of (+)-**1** based on the Sharpless asymmetric epoxidation of unsymmetrical divinylmethanol congeners has been reported.[8] On the other hand, we reported the lipase-assisted resolution of racemic α-acetoxy ester (±)-**2**, a key intermediate in the synthesis of (+)-asperlin, to give (2*R*,3*S*)-α-hydroxy ester **3** (40%, 89% ee) and (2*S*,3*R*)-α-acetoxy ester **2** (45%, 87% ee).[9] The *E*-value of this resolution was estimated to be 16.2. Repeated lipase-assisted resolution of both (2*R*,3*S*)-**3** (89% ee) and (2*S*,3*R*)-**2** (87% ee) gave enantiomerically pure (2*R*,3*S*)-**3** (>99% ee) and (2*S*,3*R*)-**2** (>99% ee), respectively, as shown in Scheme 1. Herein, we report two concise syntheses of (+)-asperlin **1** based on the stereoselective addition of carbon-nucleophile to the chiral α-silyloxy aldehyde, (2*R*,3*S*)-3-chloro-2-*tert*-butyldimethylsilyloxybutanal **6**, derived from (2*R*,3*S*)-**3** as shown in Schemes 2 and 4.



(+)-Asperlin **1**

Figure 1.

2. Results and discussion

2.1. Formal synthesis of (+)-asperlin 1

The formal synthesis of (+)-asperlin **1** from (2*R*,3*S*)-**3** is shown in Scheme 2. Silylation of (2*R*,3*S*)-**3** with ^{t}butyldimethylsilyl chloride (TBDMSCl) gave the corresponding silyl ether (2*R*,3*S*)-**4** (92%), which was reduced with diisobutylaluminum hydride (Dibal-H) to afford alcohol (2*R*,3*S*)-**5** in 88% yield. Pyridinium chlorochromate (PCC) oxidation of (2*R*,3*S*)-**5** gave the desired aldehyde (2*R*,3*S*)-**6** (69%), which was reacted with α-furyl anion to afford the (1*S*,2*R*,3*S*)-secondary alcohol **7** stereoselectively in 72% yield. To confirm the stereochemistry of (1*S*,2*R*,3*S*)-**7**, it was converted to the known chiral intermediate, epoxy-alcohol (−)-(1*S*,2*R*,3*S*)-**7**,[8a,b] for the synthesis of (+)-**1**. Protection of the secondary alcohol group of (1*S*,2*R*,3*S*)-**7** as a tetrahydropyranyl (THP) group, followed by consecutive desilylation and K_2CO_3 treatment gave an epoxide, which was subjected to deprotection of the THP group to provide the desired epoxy-alcohol **8** in

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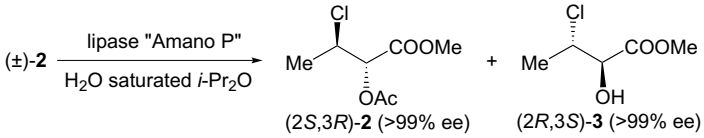
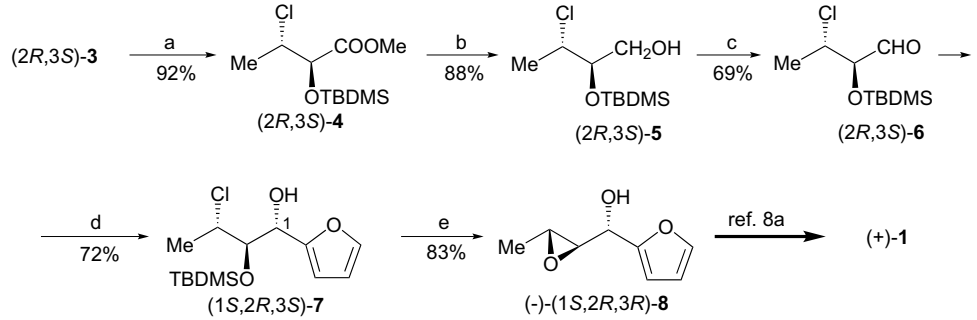


Scheme 1.



Scheme 2. Reagents: (a) TBDMSCl/imidazole/DMF; (b) Dibal-H; (c) PCC; (d) furan/*n*-BuLi; (e) (1) ethyl vinyl ether/PPTS; (2) TBAF; (3) K_2CO_3; (4) AcOH/H_2O/THF.

83% overall yield from **7**. Spectral data (^{1}H and ^{13}C NMR) of the synthetic **8** were identical with those of the reported (−)-(1*S*,2*R*,3*R*)-**8**.[8a] The specific rotation of the synthetic **8** {$[\alpha]_D^{24} = -42.2$ (*c* 0.67, $CHCl_3$)} was in accord with that of the reported (−)-(1*S*,2*R*,3*R*)-**8**[8a] {$[\alpha]_D = -43$ ($CHCl_3$)}, including the sign of the specific rotation. The synthesis of (+)-**1** from (−)-(1*S*,2*R*,3*R*)-**8** was already achieved by Honda et al.[8a]

The stereoselective formation of (−)-(1*S*,2*R*,3*S*)-**7** from (2*R*,3*S*)-**6** could be explained by a Felkin–Anh model as shown in Figure 2.

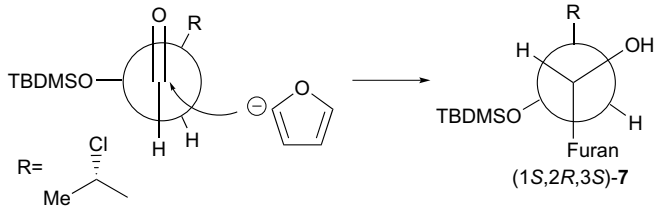
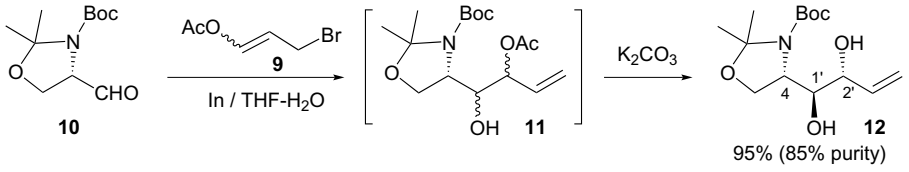


Figure 2. Felkin–Anh model for the preparation of *anti, anti*-**7**.

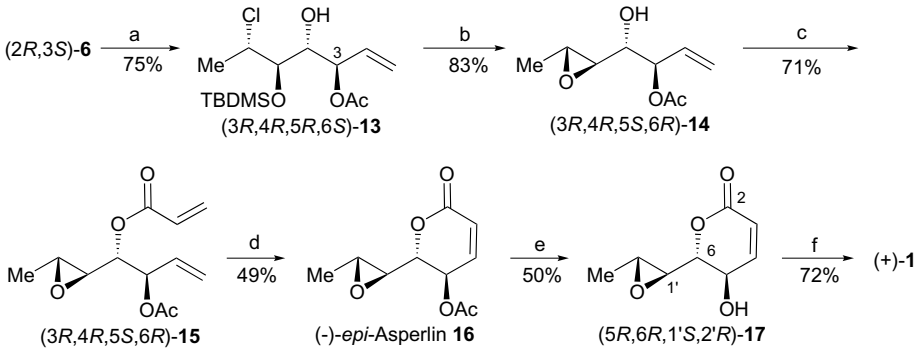
2.2. Concise synthesis of (+)-asperlin 1

A concise synthesis of (+)-asperlin **1** from (2*R*, 3*S*)-**6** based on a combination of the indium-assisted stereoselective addition of 3-bromopropenyl acetate **9**[10] to the α-silyloxy aldehyde, (2*R*,3*S*)-**6** and the ring closing metathesis (RCM) using Grubbs catalyst,[11] is shown in Scheme 4. Recently, Lombardo et al. reported that the α-hydroxyallylation reaction of Garner aldehyde **10** using **9** in the presence of indium gave predominantly a C(4)–C(1′)-*anti*-C(1′)–C(2′)-*anti*-diol **12** via **11** as shown in Scheme 3.[12] This strategy could be promising for the construction of the four contiguous stereogenic centers in asperlin **1**.

The reaction of (2*R*,3*S*)-**6** with 3-bromopropenyl acetate **9** in the presence of indium gave predominantly alcohol **13** in 75% yield, which was converted to epoxyalcohol **14**. Protection of the secondary alcohol group of **13** as a THP group followed by consecutive desilylation and K_2CO_3 treatment gave an epoxide, which was subjected to deprotection of the THP group to provide the desired epoxyalcohol **14** in 83% overall yield from **13**. Treatment of **14** and acryloyl chloride gave the corresponding acrylate **15** in 71% yield, which was subjected to the RCM reaction using Grubbs catalyst 2nd generation[13] to afford (−)-*epi*-asperlin **16** in 49% yield. Spectral data (^{1}H and ^{13}C NMR) of the synthetic (−)-**16** were identical with those of the reported (−)-**16**.[4b] The specific rotation of the synthetic (−)-**16** {$[\alpha]_D^{24} = -181.9$ (*c* 0.13, EtOH)} was in accord with the reported value for (−)-**16**[4b] {$[\alpha]_D^{20} = -185$ (*c* 0.50, EtOH)}, including the sign of the specific rotation. Based on the conversion of **13** to (−)-**16**, the stereochemistry of **13** was



Scheme 3.



Scheme 4. Reagents: (a) In/3-bromopropenyl acetate **9**/THF/H_2O (1:1); (b) (1) ethyl vinyl ether/PPPTS; (2) TBAF; (3) K_2CO_3; (4) AcOH/H_2O/THF; (c) acryloyl chloride/$(i\text{-Pr})_2$NEt; (d) Grubbs catalyst (2nd)/CH_2Cl_2; (e) lipase PL/H_2O saturated $(i\text{-Pr})_2O$; (f) Ph_3P/AcOH/DEAD/THF.

Table 1. Ring closing metathesis of (3*R*,4*R*,5*S*,6*R*)-**11**

Entry	Grubbs reagent	Condition	Time (h)	Concentration (mol/L)	Product
1	1st (0.08 equiv)	CH_2Cl_2 (40 °C)	10	0.013	No reaction
2	2nd (0.2 equiv)	Toluene (110 °C)	32	0.064	Complex mixture
3	2nd (0.08 equiv)	Toluene (110 °C)	31	0.009	Complex mixture
4	2nd (0.08 equiv)	Toluene (110 °C)	22.5	0.023	**16** (11%), S.M. (39%)
5	2nd (0.08 equiv)	CH_2Cl_2 (40 °C)	21	0.0079	**16** (38%), S.M. (49%)
6	2nd (0.1 equiv)	CH_2Cl_2 (40 °C)	5.5	0.0095	**16** (49%), S.M. (17%)

determined to be (3*R*,4*R*,5*R*,6*S*). The yield of (−)-**16** was found to be governed by the substrate concentration and the reaction temperature as shown in Table 1.

When the hydrolysis of the acetyl group in (−)-**16** was carried out using K_2CO_3 in MeOH, the desired product **17** was not obtained. The lipase PL (from *Alcaligenesis* sp.)-assisted hydrolysis of (−)-**16** in H_2O saturated $(i\text{-Pr})_2O$ gave the desired alcohol **17** (50%) along with the starting material (−)-**16** (32% recovery). Finally, alcohol **17** was treated with AcOH in the presence of triphenylphosphine (Ph_3P) and diethyl azodicarboxylate (DEAD) to provide (+)-asperlin **1** in 72% yield. Spectral data (^1H and ^{13}C NMR) of the synthetic (+)-**1** were identical with those of the reported (+)-**1**.[8a] The specific rotation of the synthetic (+)-**1** $\{[\alpha]_D^{25} = +328.0$ (*c* 0.54, EtOH)} was in accordance with that of the reported (+)-**1**[8d] $\{[\alpha]_D^{20} = +330$ (*c* 0.3, EtOH)}, including the sign of the specific rotation.

The stereoselective formation of **13** from (2*R*,3*S*)-**6** can be explained by insights reviewed by Lombardo et al.[14] Among the four possible twist-boat transition states (TSs), TS-**A**, -**B**, -**C**, and -**D** as shown in Figure 3, TS-**C** (or TS-**D**) might be more favored than TS-**A** (or TS-**B**) because steric repulsion between the aldehyde substituent (**R**) and the acetoxyl group appears to be small. This insight might imply the formation of C(3)–C(4)-*anti*-**13**. On the other hand, the C(4)–C(5)-*anti*-stereoselection of **13** could be explained by Paquette et al.[15] who showed that the 1,2-addition of the allylindium reagents to α-oxygenated aldehydes gave the non-chelation-controlled product, which corresponds to the 1,2-*anti* product by the Felkin–Anh model.

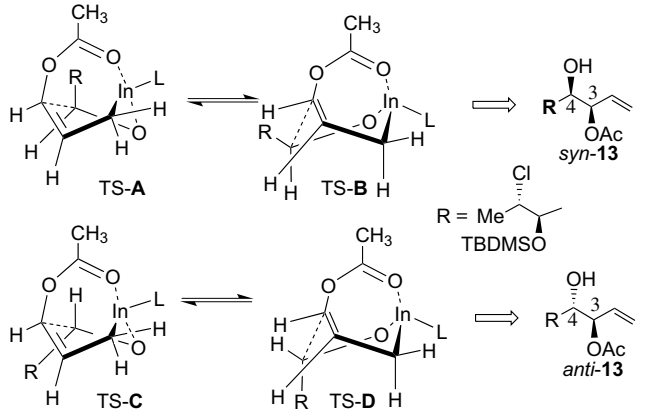


Figure 3. Chelation model for the preparation of *anti*-**13**.

3. Conclusion

The syntheses of (+)-asperlin **1** were achieved by two different routes. One is the formal synthesis of (+)-**1** based on the 1,2-addition of an α-furyl anion to 2-silyloxygenated aldehyde (2*R*,3*S*)-**6** giving the 1-(2-furyl)-2-silyloxybutanol congener **7** and the conversion of **7** to the chiral intermediate, 1-(2-furyl)-2,3-epoxybutanol **8** (37% overall yield from **6**) for the synthesis of (+)-**1**. The other is the concise synthesis of (+)-asperlin **1** from (2*R*,3*S*)-**6** in 8% overall yield, which was achieved based on a combination of the indium (In)-assisted stereoselective addition of 3-bromopropenyl acetate **9** to α-silyloxy aldehyde, (2*R*,3*S*)-**6** and the ring closing metathesis (RCM) using Grubbs catalyst. Indium-mediated α-hydroxyallylation reaction of (2*R*,3*S*)-**6** with

3-bromopropenyl acetate **9** gave selectively (3,4)-*anti*-(4,5)-*anti* product **13** (75%), which was subjected to consecutive epoxy formation and acrylation to provide epoxy-acrylate **16**. The RCM reaction of **16** afforded (−)-*epi*-asperlin **16**, which was subjected to consecutive hydrolysis and Mitsunobu inversion to give (+)-asperlin **1**.

4. Experimental

^{1}H and ^{13}C NMR spectra were recorded on JEOL AL 400 spectrometer in $CDCl_3$. Carbon substitution degrees were established by DEPT pulse sequence. The fast atom bombardment mass spectra (FAB MS) were obtained with JEOL JMS 600H spectrometer. IR spectra were recorded with a JASCO FT/IR-300 spectrometer. Optical rotations were measured with a JASCO DIP-370 digital polarimeter. All the evaporations were performed under reduced pressure. For column chromatography, silica gel (Kieselgel 60) was employed.

4.1. (2*R*,3*S*)-2-^{t}Butyldimethylsiloxy-3-chlorobutanal 6

(i) To a solution of (2*R*,3*S*)-**3** (3.13 g, 20.5 mmol) in DMF (50 mL) were added imidazole (2.79 g, 41 mmol) and *tert*-butyldimethylsilyl chloride (TBDMSCl; 5.57 g, 37 mmol) and the reaction mixture was stirred for 15 h at rt. The reaction mixture was diluted with brine and extracted with AcOEt. The organic layer was dried over $MgSO_4$ and evaporated to give a crude oil, which was chromatographed on silica gel (150 g, *n*-hexane/AcOEt = 20:1) to give (2*R*,3*S*)-**4** (5.03 g, 92%) as a colorless oil. (2*R*,3*S*)-**4**: $[\alpha]_D^{24} = -25.0$ (*c* 0.34, $CHCl_3$); IR (neat): 1758 cm^{-1}; ^{1}H NMR: δ 0.10 (3H, s), 0.11 (3H, s), 0.92 (9H, s), 1.47 (3H, d, $J = 6.6$ Hz), 3.75 (3H, s), 4.26–4.32 (2H, m). ^{13}C NMR: δ −5.3 (q), −5.1 (q), 18.2 (s), 19.5 (q), 25.6 (3C, q), 52.1 (q), 57.4 (d), 76.9 (d), 171.2 (s). HR-MS (FAB): calcd for $C_{11}H_{24}O_3ClSi$ (M^++1): 267.1183, found: 267.1194. (ii) To a solution of (2*R*,3*S*)-**4** (3.50 g, 13.5 mmol) in dry toluene (50 mL) were added 1 M solution of diisobutylaluminum hydride (Dibal-H) in toluene (31 mL, 31 mmol) under ice cooling and the reaction mixture was stirred for 1 h at the same temperature. The reaction mixture was diluted with H_2O and filtered off with the aid of Celite. The filtrate was extracted with AcOEt. The organic layer was dried over $MgSO_4$ and evaporated to give a crude oil, which was chromatographed on silica gel (90 g, *n*-hexane/AcOEt = 40:1) to give (2*R*,3*S*)-**5** (2.75 g, 88%) as a colorless oil. (2*R*,3*S*)-**5**: $[\alpha]_D^{24} = -5.2$ (*c* 0.6, $CHCl_3$); IR (neat): 3389 cm^{-1}; ^{1}H NMR: δ 0.12 (3H, s), 0.14 (3H, s), 0.92 (9H, s), 1.50 (3H, d, $J = 6.6$ Hz), 1.76 (1H, br s), 3.64 (1H, dd, $J = 3.8$, 11.4 Hz), 3.74 (1H, dd, $J = 3.8$, 6.6 Hz), 3.82 (1H, dd, $J = 3.8$, 11.4 Hz), 4.12 (1H, quintet, $J = 6.6$ Hz). ^{13}C NMR: δ −4.6 (q), −4.4 (q), 18.1 (s), 20.9 (q), 25.8 (3C, q), 57.0 (d), 63.8 (t), 76.8 (d). HR-MS (FAB): calcd for $C_{10}H_{24}O_2ClSi$ (M^++1): 239.1235, found: 239.1236. (iii) To a solution of (2*R*,3*S*)-**5** (2.02 g, 8.5 mmol) in CH_2Cl_2 (50 mL) was added pyridinium chlorochromate (PCC; 3.6 g, 16.7 mmol) at rt and the reaction mixture was stirred for 12 h at the same temperature. The reaction mixture was filtered off with the aid of Celite. The filtrate was concentrated to give a residue, which was chromatographed on silica gel (50 g, *n*-hexane/AcOEt = 50:1) to give (2*R*,3*S*)-**6** (1.38 g, 69%) as a colorless oil. (2*R*,3*S*)-**6**: $[\alpha]_D^{29} = -24.4$ (*c* 0.41, $CHCl_3$); IR (neat): 1738 cm^{-1}; ^{1}H NMR: δ 0.12 (3H, s), 0.15 (3H, s), 0.94 (9H, s), 1.49 (3H, d, $J = 6.8$ Hz), 4.05 (1H, dd, $J = 1.6$, 4.4 Hz), 4.20–4.28 (1H, m), 9.54 (1H, d, $J = 1.6$ Hz). ^{13}C NMR: δ −4.9 (q), −4.6 (q), 18.2 (s), 19.8 (3C, q), 25.7 (q), 56.7 (d), 81.0 (d), 201.1 (d). HR-MS (CI+): calcd for $C_{10}H_{22}O_2ClSi$ (M^++1): 237.1078, found: 237.1048.

4.2. (1*S*,2*R*,3*S*)-1-(2-Furyl)-2-^{t}butyldimethylsilyloxy-3-chlorobutanol 7

To a solution of furan (1.16 g, 17 mmol) in THF (10 mL) was added 1.5 M solution of *n*-butyllithium in pentane (5 mL, 12 mmol) under an argon atmosphere at −78 °C and the reaction mixture was stirred for 1.5 h at the same temperature. A solution of (2*R*,3*S*)-**6** (1.34 g, 5.7 mmol) in THF (5 mL) was added to the above mixture and the whole mixture was stirred for 40 min at rt. The reaction mixture was diluted with a saturated NH_4Cl solution and extracted with AcOEt. The organic layer was washed with brine and dried over $MgSO_4$. Evaporation of the organic solvent gave a residue, which was chromatographed on silica gel (30 g, *n*-hexane/AcOEt = 100:1) to give (1*S*,2*R*,3*S*)-**7** (1.24 g, 72%) as a colorless oil. (1*S*,2*R*,3*S*)-**7**: $[\alpha]_D^{26} = -3.51$ (*c* 0.94, $CHCl_3$); IR (neat): 3484 cm^{-1}; ^{1}H NMR: δ −0.09 (3H, s), 0.15 (3H, s), 0.15 (3H, s), 0.86 (9H, s), 1.51 (3H, d, $J = 5.9$ Hz), 4.20–4.26 (2H, m), 4.72 (1H, t, $J = 5.4$ Hz), 6.34–6.36 (2H, m), 7.39 (1H, t, $J = 0.8$, 1.2 Hz). ^{13}C NMR: δ −4.8 (q), −4.1 (q), 18.4 (s), 19.4 (q), 26.0 (3C, q), 58.4 (d), 69.8 (d), 78.2 (d), 108.3 (d), 110.4 (d), 142.0 (d), 153.1 (s). HR-MS (CI+): calcd for $C_{14}H_{24}O_3ClSi$ (M^+−1): 303.1183, found: 303.1170.

4.3. (1*S*,2*R*,3*R*)-1-(2-Furyl)-2,3-epoxybutanol 8

To a solution of (1*S*,2*R*,3*S*)-**7** (150 mg, 0.49 mmol) in CH_2Cl_2 (5 mL) were added ethyl vinyl ether (70 mg, 0.97 mmol) and a catalytic amount of pyridinum *p*-toluenesulfonate (PPTS) at rt and the reaction mixture was stirred for 1 h at the same temperature. The reaction mixture was diluted with H_2O and extracted with AcOEt. The organic layer was washed with brine and dried over $MgSO_4$. Evaporation of the organic solvent gave a crude THP ether. To a solution of THP ether in THF (4 mL) was added a 1 M solution of tetrabutylammonium fluoride (TBAF) in THF (2 mL, 2 mmol) at rt and the reaction mixture was stirred for 12 h at the same temperature. The reaction mixture was evaporated to give a residue. A mixture of the above residue in MeOH (5 mL) and K_2CO_3 (135 mg, 0.98 mmol) was stirred for 12 h at rt and the reaction mixture was diluted with H_2 O and extracted with AcOEt. The organic layer was washed with brine and dried over $MgSO_4$. Evaporation of the organic solvent gave a crude oil. A solution of the crude oil in THF (1 mL)/H_2O (1 mL) and AcOH (2 mL) was stirred for 2 h at rt and the reaction mixture was stirred for 2 h at the same temperature. The reaction mixture was diluted with a saturated $NaHCO_3$ solution and extracted with AcOEt. The organic layer was washed with brine and dried over $MgSO_4$. Evaporation of the organic solvent gave a residue, which was

chromatographed on silica gel (10 g, *n*-hexane/AcOEt = 6:1) to give (1*S*,2*R*,3*R*)-**8** (63 mg, 83%) as a colorless oil. (1*S*,2*R*,3*R*)-**8**: $[\alpha]_D^{24} = -42.2$ (*c* 0.67, $CHCl_3$); IR (neat): 3401 cm^{-1}; ^1H NMR: δ 1.38 (3H, d, $J = 5.2$ Hz), 2.34 (1H, br s), 3.05 (1H, dd, $J = 2.4$, 3.6 Hz), 3.25 (1H, dq, $J = 2.4$, 5.2 Hz), 4.87 (1H, d, $J = 3.6$ Hz), 6.35–6.38 (2H, m), 7.42 (1H, dd, $J = 0.8$, 1.8 Hz). ^{13}C NMR: δ 17.1 (q), 51.7 (d), 59.8 (d), 65.2 (d), 107.7 (d), 110.2 (d), 142.5 (d), 152.4 (s). HR-MS (FAB): calcd for $C_8H_{11}O_3$ (M^++1): 155.0708, found: 155.0706.

4.4. (3*R*,4*R*,5*R*,6*S*)-3-Acetoxy-5-*t*butyldimethylsilyloxy-6-chloro-4-hydroxy-1-heptene 13

To a mixture of (2*R*,3*S*)-**6** (843 mg, 3.56 mmol) in THF (5 mL)/H_2O (5 mL) were added In powder (1.23 g, 10.7 mmol) and 3-bromopropenyl acetate (1.91 g, 10.7 mmol) at 0 °C and the reaction mixture was stirred for 1.5 h at rt. The reaction mixture was diluted with H_2O and extracted with AcOEt. The organic layer was washed with brine and dried over $MgSO_4$. Evaporation of the organic solvent gave a residue, which was chromatographed on silica gel (40 g, *n*-hexane/AcOEt = 30:1) to give (3*R*,4*R*,5*R*,6*S*)-**9** (920 mg, 77%) as a colorless oil. (3*R*,4*R*,5*R*,6*S*)-**13**: $[\alpha]_D^{25} = +16.0$ (*c* 0.4, $CHCl_3$); IR (neat): 3481, 1744 cm^{-1}; ^1H NMR: δ 0.16 (3H, s), 0.20 (3H, s), 0.94 (9H, s), 1.49 (3H, d, $J = 6.8$ Hz), 2.09 (3H, s), 3.82 (1H, d, $J = 2.8$ Hz), 3.89 (1H, dd, $J = 2.8$, 6.4 Hz), 4.38 (1H, dq, $J = 3.2$, 6.8 Hz), 5.26–5.55 (2H, m), 5.53 (1H, t, $J = 5.2$ Hz), 5.89–5.97 (1H, m). ^{13}C NMR: δ −4.6 (q), −3.9 (q), 18.3 (s), 19.0 (q), 20.9 (q), 25.9 (3C, q), 58.2 (d), 74.0 (d), 74.1 (d), 76.7 (d), 119.8 (t), 131.5 (d), 169.4 (s). HR-MS (CI+): calcd for $C_{15}H_{30}O_4ClSi$ (M^++1): 337.1602, found: 337.1609.

4.5. (3*R*,4*R*,5*S*,6*R*)-3-Acetoxy-5,6-epoxy-4-hydroxy-1-heptene 14

To a solution of (3*R*,4*R*,5*R*,6*S*)-**13** (1.77 g, 5.3 mmol) in CH_2Cl_2 (20 mL) were added ethyl vinyl ether (1.13 g, 15.7 mmol) and a catalytic amount of pyridinum *p*-toluenesulfonate (PPTS) at rt and the reaction mixture was stirred for 3 h at the same temperature. The reaction mixture was diluted with a saturated $NaHCO_3$ solution and extracted with $CHCl_3$. The organic layer was washed with brine and dried over $MgSO_4$. Evaporation of the organic solvent gave a crude THP ether. To a solution of THP ether in THF (10 mL) was added 1 M solution of tetrabutylammonium fluoride (TBAF) in THF (11 mL, 11 mmol) at rt and the reaction mixture was stirred for 3 h at the same temperature. To the reaction mixture was added K_2CO_3 (2.18 g, 15.8 mmol) at rt and the whole mixture was stirred for 7 h at rt. The reaction mixture was diluted with H_2O and extracted with $CHCl_3$. The organic layer was washed with brine and dried over $MgSO_4$. Evaporation of the organic solvent gave a crude oil. A solution of the crude oil in THF (2 mL)/H_2O (2 mL) and AcOH (8 mL) was stirred for 20 h at rt. The reaction mixture was diluted with a saturated $NaHCO_3$ solution and extracted with $CHCl_3$. The organic layer was washed with brine and dried over $MgSO_4$. Evaporation of the organic solvent gave a residue, which was chromatographed on silica gel (10 g, *n*-hexane/AcOEt = 3:1) to give (3*R*,4*R*,5*S*,6*R*)-**14** (812 mg, 83%) as a pale yellow oil. (3*R*,4*R*,5*S*,6*R*)-**14**: $[\alpha]_D^{26} = +16.3$ (*c* 0.52, EtOH); IR (neat): 3448, 1739 cm^{-1}; ^1H NMR: δ 1.32 (3H, d, $J = 5.3$ Hz), 2.12 (3H, s), 2.8 (1H, dd, $J = 2.3$, 4.0 Hz), 3. 8 (1H, dd, $J = 2.3$, 5.3 Hz), 3.88 (1H, dd, $J = 4.0$, 6.0 Hz), 5.30–5.42 (3H, m), 5.89–5.97 (1H, m). ^{13}C NMR: δ 17.0 (q), 21.1 (q), 51.6 (d), 58.3 (d), 70.8 (d), 75.8 (d), 119.4 (t), 132.0 (d), 170.1 (s). HR-MS (CI+): calcd for $C_9H_{15}O_4$ (M^++1): 187.0970, found: 187.0983.

4.6. (3*R*,4*R*,5*S*,6*R*)-3-Acetoxy-4-acryloyloxy-5,6-epoxy-1-heptene 15

To a solution of (3*R*,4*R*,5*R*,6*R*)-**14** (812 mg, 4.3 mmol) in CH_2Cl_2 (10 mL) were added diisopropylethylamine (2.81 g, 27.6 mmol) and acryloyl chloride (680 mg, 7.5 mmol) under an argon atmosphere at −20°C and the reaction mixture was stirred for 3 h at the same temperature. The reaction mixture was diluted with H_2O and extracted with CH_2Cl_2. The organic layer was washed with brine and dried over $MgSO_4$. Evaporation of the organic solvent gave a residue, which was chromatographed on silica gel (50 g, *n*-hexane/AcOEt = 30:1) to give (3*R*,4*R*,5*R*,6*R*)-**15** (740 mg, 71%) as a pale yellow oil. (3*R*,4*R*,5*S*,6*R*)-**15**: $[\alpha]_D^{25} = +19.1$ (*c* 0.54, EtOH); IR (neat): 1730 cm^{-1}; ^1H NMR: δ 1.30 (3H, d, $J = 5.2$ Hz), 2.10 (3H, s), 2.83 (1H, dd, $J = 2.2$, 6.0 Hz), 3.04 (1H, dq, $J = 2.2$, 5.2 Hz), 4.92 (1H, dd, $J = 3.7$, 6.0 Hz), 5.35–5.45 (2H, m), 5.55–5.58 (1H, m), 5.87–5.97 (2H, m), 6.09–6.19 (1H, m), 6.40–6.47 (1H, m). ^{13}C NMR: δ 17.1 (q), 21.0 (q), 53.1 (d), 55.9 (d), 73.1 (d), 74.0 (d), 120.0 (t), 127.8 (t), 131.3 (d), 131.8 (d), 164.9 (s), 169.8 (s). HR-MS (CI+): calcd for $C_{12}H_{17}O_5$ (M^++1): 241.1076, found: 241.1097.

4.7. (−)-*epi*-Asperlin 16

To a solution of (3*R*,4*R*,5*R*,6*R*)-**15** (227 mg, 0.95 mmol) in CH_2Cl_2 (95 mL) was added a solution of Crubbs catalyst 2nd generation (80 mg, 0.095 mmol) in CH_2Cl_2 (5 mL) under an argon atmosphere at rt and the reaction mixture was stirred for 5.5 h at 40 °C. The reaction mixture was evaporated to give a residue, which was chromatographed on silica gel (20 g) to afford the starting (3*R*,4*R*,5*R*,6*R*)-**15** (46 mg, 20% recovery) from *n*-hexane/AcOEt = 30:1 elution and (−)-*epi*-Asperlin (**16**; 98 mg, 49%) as a pale yellow oil from *n*-hexane/AcOEt = 4:1 elution. (−)-**16**: $[\alpha]_D^{24} = -181.9$ (*c* 0.13, EtOH); IR (neat): 1731 cm^{-1}; ^1H NMR: δ 1.35 (3H, d, $J = 5.2$ Hz), 2.13 (3H, s), 2.85 (1H, dd, $J = 2.0$, 6.6 Hz), 3.05 (1H, dq, $J = 2.0$, 5.2 Hz), 4.21 (1H, t, $J = 6.0$ Hz), 5.51 (1H, ddd, $J = 1.1$, 3.8, 5.2 Hz), 6.18 (1H, dd, $J = 1.1$, 9.9 Hz), 6.87 (1H, dd, $J = 4.0$, 9.9 Hz). ^{13}C NMR: δ 17.0 (q), 20.7 (q), 53.9 (d), 57.0 (d), 64.0 (d), 80.1 (d), 123.4 (d), 141.9 (d), 160.9 (s), 169.8 (s). HR-MS (CI+): calcd for $C_{10}H_{13}O_5$ (M^++1): 213.0763, found: 213.0784.

4.8. (5*R*,6*R*,1′*S*,2′*R*)-5,6-Dihydro-5-hydroxy-6-(1′,2′-epoxypropyl)-2*H*-pyran-2-one 17

A mixture of (−)-**16** (47 mg, 0.22 mmol) and lipase PL (50 mg) in H_2O saturated (*i*-Pr)$_2O$ (8 mL) was incubated

for 5 h at 33 °C. The reaction mixture was dried over $MgSO_4$ and evaporated to give a residue, which was chromatographed on silica gel (5 g) to afford the starting (−)-**16** (15 mg, 32% recovery) from *n*-hexane/AcOEt = 8:1 elution and (5*R*,6*R*,1′*S*,2′*R*)-**17** (19 mg, 50%) as a colorless oil from *n*-hexane/AcOEt = 1:1 elution. (−)-(5*R*,6*R*,1′*S*,2′*R*)-**17**: $[\alpha]_D^{24} = -32.4$ (*c* 0.33, EtOH); IR (neat): 3410, 1710 cm^{-1}; ^1H NMR: δ 1.38 (3H, d, $J = 5.1$ Hz), 3.00 (1H, dd, $J = 2.0$, 6.5 Hz), 3.12 (1H, dq, $J = 2.0$, 5.1 Hz), 4.04–4.07 (1H, m), 4.62–4.64 (1H, m), 6.01 (1H, dd, $J = 1.7$, 10.0 Hz), 6.86 (1H, dd, $J = 5.2$, 10.0 Hz). ^{13}C NMR: δ 17.1 (q), 54.3 (d), 58.4 (d), 64.7 (d), 81.0 (d), 120.1 (d), 148.0 (d), 161.8 (s). HR-MS (FAB): calcd for $C_8H_{11}O_4$ (M^++1): 171.0657, found: 171.0671.

4.9. (+)-Asperlin 1

To a solution of (−)-(5*R*,6*R*,1′*S*,2′*R*)-**17** (40 mg, 0.24 mmol) in THF (2 mL) were added AcOH (72 mg, 1.2 mmol) and triphenylphosphine (Ph_3P; 105 mg, 0.4 mmol) at rt. To the above reaction mixture was added diethyl azodicarboxylate (DEAD; 40% in toluene, 0.19 mL, 0.4 mmol) under an argon atmosphere at −78 °C and the reaction mixture was stirred for 1 h at −78 °C. The reaction mixture was diluted with a saturated $NaHCO_3$ solution and extracted with AcOEt. The organic layer was dried over $MgSO_4$ and evaporated to give a residue, which was chromatographed on silica gel (8 g, *n*-hexane/AcOEt = 5:1) to afford (+)-**1** (37 mg, 73%) as a colorless oil. (+)-**1**: $[\alpha]_D^{25} = +328.0$ (*c* 0.54, EtOH); IR (neat): 1727 cm^{-1}; ^1H NMR: δ 1.38 (3H, d, $J = 5.2$ Hz), 2.14 (3H, s), 3.05–3.10 (2H, m), 4.11 (1H, dd, $J = 2.8$, 7.2 Hz), 5.32 (1H, dd, $J = 2.8$, 5.6 Hz), 6.22 (1H, d, $J = 9.6$ Hz), 7.07 (1H, dd, $J = 5.6$, 9.6 Hz). ^{13}C NMR: δ 17.0 (q), 20.5 (q), 54.6 (d), 54.9 (d), 62.1 (d), 78.9 (d), 124.9(d), 140.4 (d), 161.5 (s), 169.8 (s). HR-MS (EI): calcd for $C_{10}H_{12}O_5$ (M^+): 212.0685, found: 212.0678.

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