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Stereodivergent Syntheses of All Stereoisomers of (−)-Shikimic Acid: Development of a Chiral Pool for the Diverse Polyhydroxy-cyclohexenoid (or -cyclohexanoid) Bioactive Molecules

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Novel stereodivergent total syntheses of all the seven stereoisomers of (−)-shikimic acid [(−)-SA **1**] have been systematically performed. (+)-*ent*-SA *ent*-**1** was synthesized from (−)-SA **1** via 9 steps in 31% overall yield; (−)-3-*epi*-SA **2** was synthesized from (−)-SA **1** via 5 steps in 66% overall yield; (+)-3-*epi*-*ent*-SA *ent*-**2** was synthesized from (−)-SA **1** via 7 steps in 43% overall yield; (−)-4-*epi*-SA **3** was synthesized from (−)-SA **1** via 11 steps in 32% overall yield; (+)-4-*epi*-*ent*-SA *ent*-**3** was synthesized from (−)-SA **1** via 7 steps in 42% overall yield; (−)-5-*epi*-SA **4** was synthesized from (−)-SA **1** via 6 steps in 56% overall yield; and (+)-5-*epi*-*ent*-SA *ent*-**4** was synthesized from (−)-SA **1** via 12 steps in 29% overall yield. The stereochemistry of all the above seven stereoisomers of (−)-SA **1** were further studied by two dimensional (2D) ^{1}H NMR technique.

Introduction

(−)-Shikimic acid [(−)-SA **1**, in Figure 1] is a fascinating natural product featured with a structural motif of chiral polyhydroxyl-substituted cyclohexene. It has captured worldwide attentions in the recent decades[1] due to many uses in pharmaceutical industry. (−)-SA **1** could be obtained by means of extraction from plants,[2] fermentation based on microbial engineering[1f,h,3] and chemical syntheses.[1a,4] So far (−)-SA **1** has been found in a lot of plant species,[5] and it is noted to be extremely high abundant (up to 17% on dry basis[5h]) in Chinese star anise (the fruit of *Illicium verum* Hook. f.). Chinese star anise is a popular flavoring material for foods in China, it can be readily and annually planted in many areas, therefore, (−)-SA **1** can be manufactured in a large quantity by extraction from the Chinese star anise using new rapid and high-yielding extraction methods.[2b,6] (−)-SA **1** is very useful material for syntheses of drugs and pharmaceutically valuable natural products. For examples, it has been extensively used in the syntheses of oseltamivir phosphate (Tamiflu),[7] valiolamine,[8] valienamine,[8a,9] NOV,[10] NOEV,[10] pericosines (A, B, D and E),[11] zeylenones,[12] (−)-MK7607,[13] previtamin D_3,[14] quercitols,[15] and (−)-quinic acid.[16] (−)-SA **1** and its derivatives might also be very important in drug discovery, since they have shown a wide range of physiological activities[17] such as antiviral, anti-bacterial, anti-fungi, anti-osteoclastogenesis, anti-platelet, anti-thrombogenic, anti-inflammatory, anti-oxidant, and anti-tumor activities.

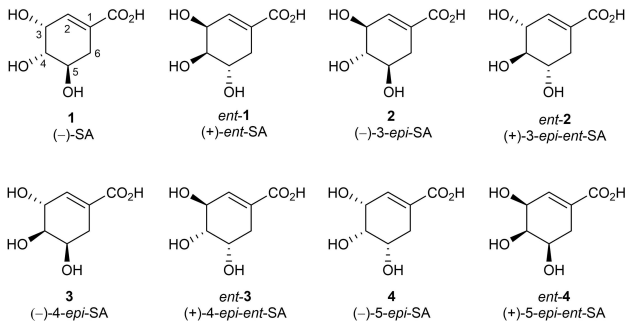

Figure 1. The structures of all stereoisomers of (−)-SA **1**.

As a molecule with three stereogenic centers, it should have totally eight stereoisomers as depicted in Figure 1. They are (−)-SA **1**, (+)-*ent*-SA *ent*-**1**, (−)-3-*epi*-SA **2**, (+)-3-*epi*-*ent*-SA *ent*-**2**, (−)-4-*epi*-SA **3**, (+)-4-*epi*-*ent*-SA *ent*-**3**, (−)-5-*epi*-SA **4** and (+)-5-*epi*-*ent*-SA *ent*-**4**, respectively. Although (−)-SA **1** itself has been extensively studied in synthetic chemistry and physiological chemistry, only few physiological or synthetic studies of the other stereoisomers have been reported. (−)-4-*epi*-SA **3** has been used as building block for the syntheses of glycomimetics[18] and sialytransferase inhibitors;[19] (−)-3-*epi*-SA **2**, (−)-4-*epi*-SA **3** and (−)-5-*epi*-SA **4** have also been used as building blocks in the syntheses of vitamin D_3 analogues.[20] (−)-SA **1** and all of its stereoisomers might constitute a versatile chiral pool for the syntheses of diverse polyhydroxy-cyclohexenoid (or polyhydroxy-cyclohexanoid) bioactive natural products and their analogues. However, all the seven stereoisomers of (−)-SA **1** can scarcely be obtained from natural resources, so it is very important to develop convenient and

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practical methods to synthesize all of these stereoisomers. In order to facilitate the studies on bioactivities and synthetic applications of all stereoisomers of (−)-SA **1**, we have performed and herein would like to report the stereodivergent syntheses of all the seven stereoisomers of (−)-SA **1** starting from the commercially available and inexpensive (−)-SA **1**.

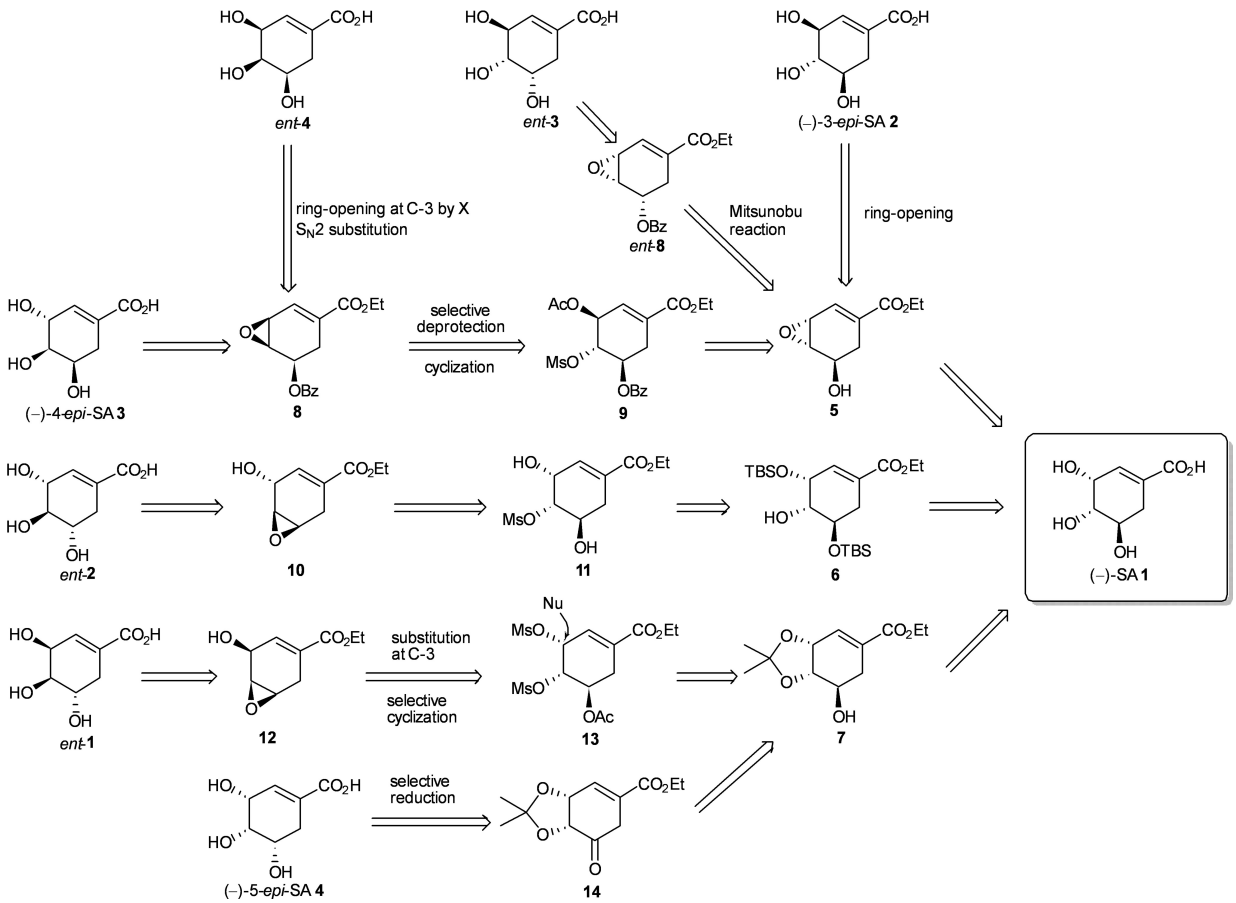
Results and Discussion

Our retrosynthetic analysis of all the seven stereoisomers of (−)-SA **1** was outlined in Scheme 1, which showed that all the target molecules can be synthesized starting from (−)-SA **1** via several common intermediates such as compounds **5**, **6** and **7**, which can be efficiently prepared from (−)-SA **1** by the known methods.[7e,8b] As the diagram depicted, (−)-3-*epi*-SA **2** can be prepared via ring-opening of the key epoxide **5**. (+)-4-*epi*-*ent*-SA *ent*-**3** can be prepared via ring-opening of epoxide *ent*-**8**, which can also be prepared from epoxide **5** by Mitsunobu reaction. Both of (+)-5-*epi*-*ent*-SA *ent*-**4** and (−)-4-*epi*-SA **3** can be prepared from a common epoxide **8**, which can be derived from intermediate **9**; compound **9** can also be prepared from the key epoxide **5**. (+)-3-*epi*-*ent*-SA *ent*-**2** can be prepared via ring-opening of epoxide **10**, which can be obtained from intermediate **11**, the compound **11** can be prepared from the bis-silylated ethyl shikimate **6**. (+)-*ent*-SA *ent*-**1** can be prepared via ring-opening of epoxide **12**, which can be obtained from compound **13** via the successive substitution at C-3 and intramolecular regioselective cyclization, compound **13** can be prepared from the key intermediate **7**. (−)-5-*epi*-SA **4** can be prepared via reduction of compound **14**, which can be obtained via oxidation of the key common compound **7**.

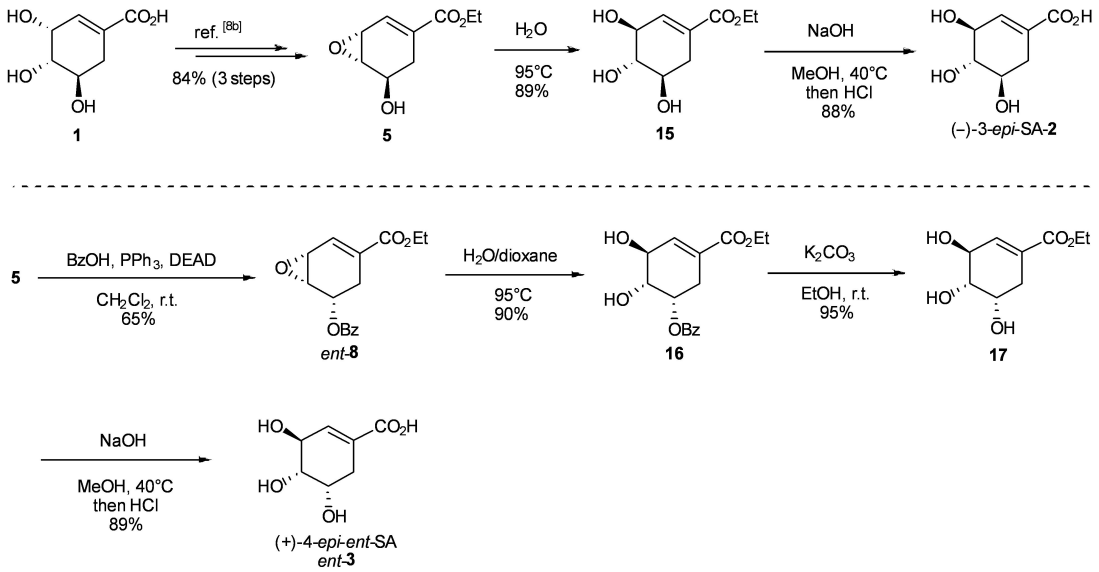
According to the above retrosynthetic analysis, our synthetic routes for all the seven stereoisomers of (−)-SA **1** are depicted in Schemes 2–6. These novel syntheses are discussed as below:

Synthesis of (−)-3-epi-SA 2 from (−)-SA 1

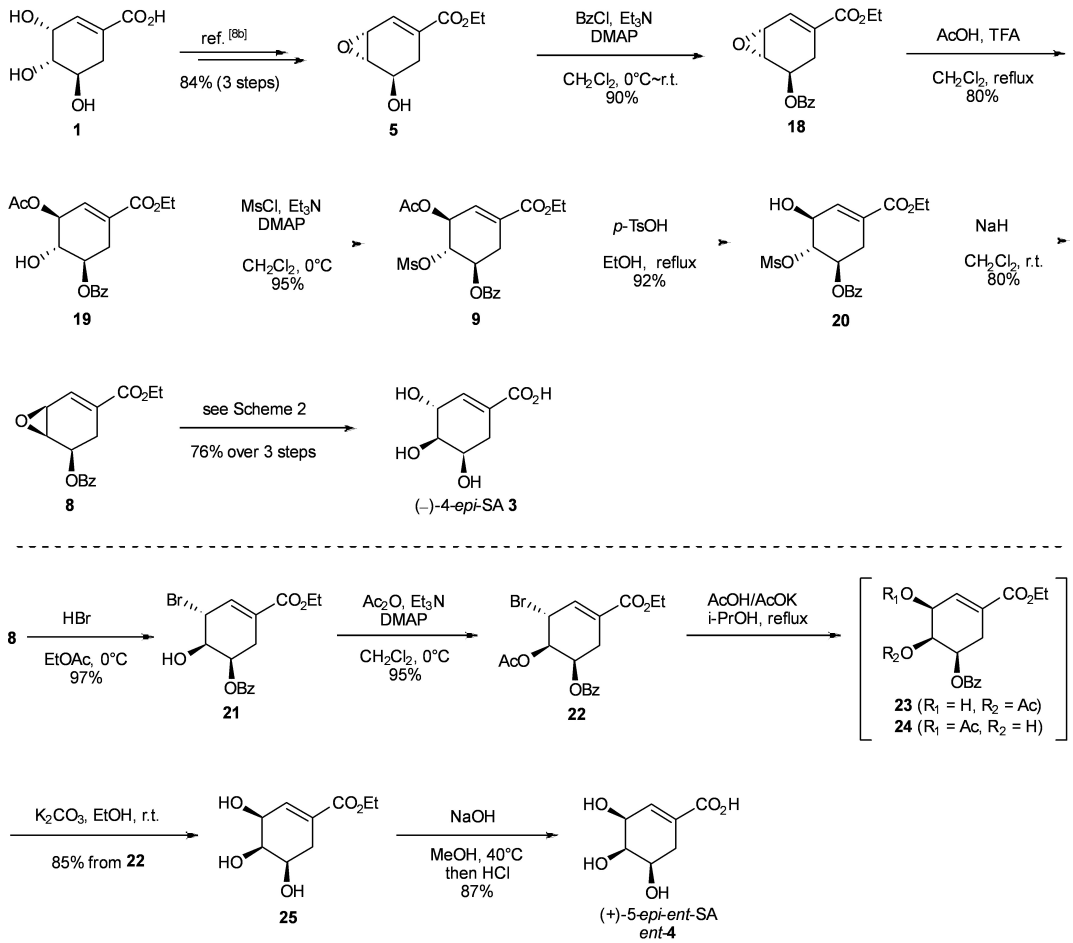
(−)-3-*epi*-SA **2** is a naturally occurring compound in some plants[21] and was first isolated from *Sequoiadendron giganteum* by Pluovier *et al.* in 1959.[21a] Frederickson *et al.* reported the first synthesis of (−)-3-*epi*-SA **2**.[22] Sugai *et al.* also reported a synthesis of (−)-3-*epi*-SA **2** via Diels-Alder reaction and enzyme-catalyzed resolution.[23] Herein, we disclose a short and more efficient synthesis of (−)-3-*epi*-SA **2** starting from (−)-SA **1**. Our synthetic route was depicted in Scheme 2. Firstly, epoxide **5** can be easily prepared from (−)-SA **1** in 84% yield via 3 steps by a known method.[8b] Epoxide **5** then underwent highly regio-



Scheme 1. Retrosynthetic analysis of all stereoisomers of (−)-SA **1**.

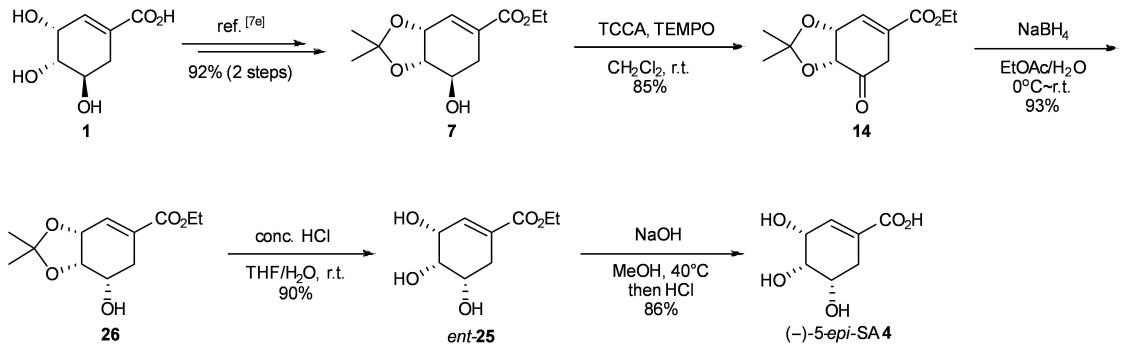


Scheme 2. Syntheses of (−)-3-*epi*-SA **2** and (+)-4-*epi*-*ent*-SA *ent*-**3** from (−)-SA **1**.

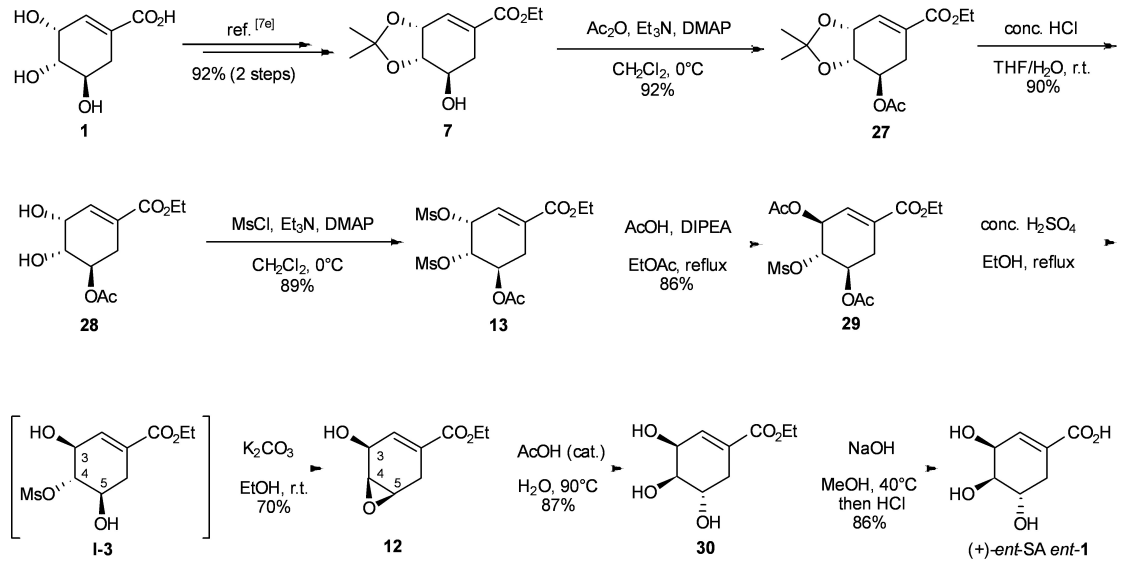


Scheme 3. Syntheses of (−)-4-*epi*-SA **3** and (+)-5-*epi*-*ent*-SA *ent*-**4** from (−)-SA **1**.

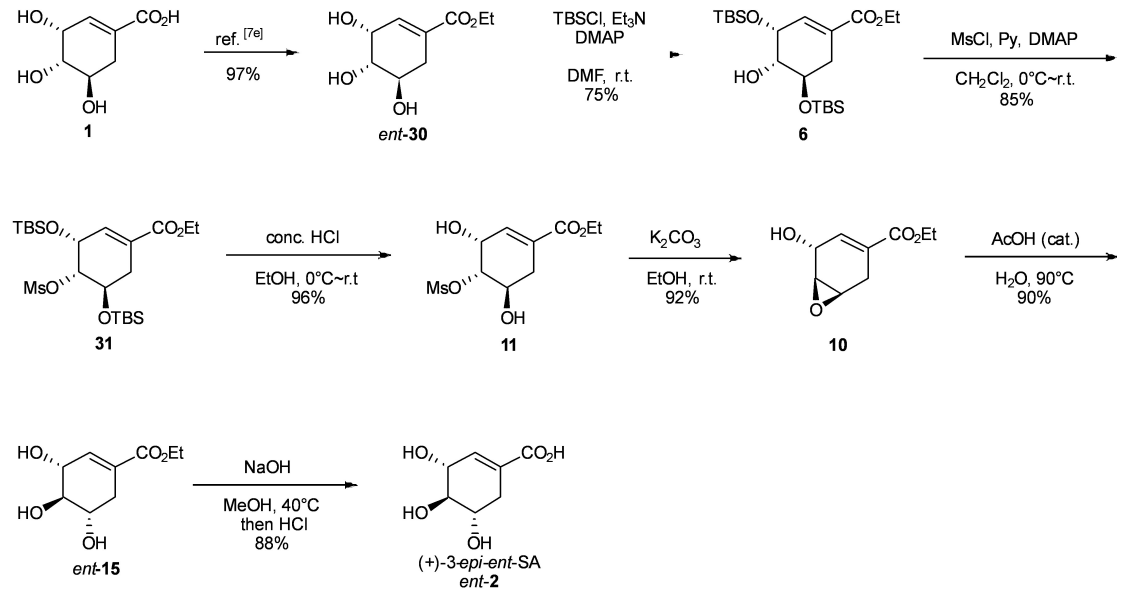
selective ring-opening at more reactive allylic C-3 position at 95 °C to afford compound **15** in 89% yield. In the ring-opening, water was both used as a nucleophile and the environment-friendly solvent. Subsequently, compound **15** was first treated



Scheme 4. Synthesis of (−)-5-*epi*-SA **4** from (−)-SA **1**.



Scheme 5. Synthesis of (+)-*ent*-SA *ent*-**1** from (−)-SA **1**.



Scheme 6. Synthesis of (+)-3-*epi*-SA *ent*-**2** from (−)-SA **1**.

with 2.0 equiv. of NaOH in methanol at 40 °C, and then treated with diluted aq. HCl, the (−)-3-*epi*-SA **2** could be thus obtained in 88% yield.

Synthesis of (+)-4-epi-ent-SA ent-3 from (−)-SA 1

Only one synthesis of (+)-4-*epi*-*ent*-SA *ent*-**3** from *L*-tartaric acid has been reported by Yan *et al.* in 2014.[24] Herein we disclose a new synthesis of (+)-4-*epi*-*ent*-SA *ent*-**3** from (−)-SA **1** according to the route depicted in Scheme 2. As can be seen from Scheme 2, epoxide **5** was treated with 1.5 equiv. of benzoic acid (BzOH), 1.5 equiv. of triphenylphosphine (PPh_3) and 1.5 equiv. of diethyl azodicarboxylate (DEAD) in CH_2Cl_2 at room temperature. The Mitsunobu reaction occurred to give epoxide *ent*-**8** in 65% yield, during this S_N2 substitution, the (*R*) configuration at C-5 was inversed to (*S*) configuration. Then epoxide *ent*-**8** then underwent highly regio-selective ring-opening at more reactive allylic C-3 position at 95 °C in a mixed solvent of H_2O and 1,4-dioxane (*v*:*v* = 2:3) to afford compound **16** in 90% yield. Subsequently, compound **16** was exposed to 1.5 equiv. of anhydrous K_2CO_3 in absolute ethanol at room temperature, debenzylation occurred smoothly to furnish compound **17** in 95% yield. Finally, compound **17** was first treated with 2.0 equiv. of NaOH in methanol at 40 °C, and then treated with diluted aq. HCl, (+)-4-*epi*-SA *ent*-**3** could be thus obtained in 89% yield.

Synthesis of (−)-4-epi-SA 3 from (−)-SA 1

Rapoport *et al.* reported the first synthesis of (−)-4-*epi*-SA **3** from (−)-quinic acid in 1973.[25] Berchtold *et al.* also reported a synthesis of (−)-4-*epi*-SA **3** from (−)-quinic acid in 1985.[26] Later, Yan *et al.* reported a synthesis of (−)-4-*epi*-SA **3** from *L*-tartaric acid in 2014.[24] Our novel and efficient synthesis of (−)-4-*epi*-SA **3** starting from (−)-SA **1** was depicted in Scheme 3. As can be seen from Scheme 3, epoxide **5** was treated with 1.5 equiv. of benzyl chloride, 2.0 equiv. of Et_3N and 0.1 equiv. of 4-*N*,*N*-dimethylaminopyridine (DMAP) in CH_2Cl_2 at 0 °C to room temperature to afford **18** in 90% yield. Compound **18** was exposed to 5.0 equiv. of AcOH and 0.5 equiv. of trifluoroacetic acid (TFA) in CH_2Cl_2 under refluxing to furnish compound **19** in 80% yield. In this reaction, the acetoxy anion regio-selectively attacked the allylic C-3 position, and the (*R*) configuration at C-3 was inversed to (*S*) configuration during the reaction. The compound **19** was treated with 1.2 equiv. of methanesulfonyl chloride (MsCl), 1.5 equiv. of Et_3N and 0.1 equiv. of DMAP in CH_2Cl_2 at 0 °C to give compound **9** in 95% yield. Then compound **9** was exposed to 2.0 equiv. of *p*-toluenesulfonic acid (*p*-TsOH) in ethanol under refluxing, the selective deacetylation occurred smoothly to afford compound **20** in 90% yield. Next, compound **20** was treated with 2.0 equiv. of NaH (w/w 60%) in CH_2Cl_2 at room temperature, an intramolecular S_N2 substitution occurred to give pivotal epoxide *ent*-**8** in 80% yield. Finally, (−)-4-*epi*-SA **3** was prepared from epoxide **8** in 76% yield over 3 steps according to the same procedures as described in Scheme 2 for synthesis of (+)-4-*epi*-*ent*-SA *ent*-**3** from epoxide *ent*-**8**.

Synthesis of (+)-5-epi-ent-SA ent-4 from (−)-SA 1

Only one synthesis of (+)-5-*epi*-*ent*-SA *ent*-**4** via asymmetric Diels-Alder reaction was reported by Carretero *et al.* in 1997.[27] Our novel synthetic route was depicted in Scheme 3. As can be seen from Scheme 3, epoxide **8** was treated with 2.0 equiv. of hydrobromic acid (HBr, w/w 40%) in ethyl acetate at 0 °C, exclusive regiospecific ring-opening at allylic C-3 position by bromide anion occurred to produce compound **21** in 97% yield. Compound **21** was then exposed to 1.3 equiv. of acetic anhydride (Ac_2O), 1.5 equiv. of Et_3N and 0.1 equiv. of DMAP in CH_2Cl_2 at 0 °C to afford compound **22** in 95% yield. Next, when compound **22** was treated with 8.0 equiv. of acetic acid (AcOH) and 2.0 equiv. of potassium acetate (AcOK) in isopropyl alcohol (*i*-PrOH) under refluxing, inseparable mixture of two isomers **23** and **24** formed via Woodward-Prevost reaction.[28] ^{1}H NMR analysis revealed that ratio of compounds **23** and **24** was approximate 1:1. Then the mixture of compounds **23** and **24** were exposed to 3.0 equiv. of anhydrous K_2CO_3 in ethanol at room temperature to furnish the desired (+)-ethyl 5-*epi*-*ent*-shikimate **25** in 85% yield over two steps (from compound **22**). Finally, compound **25** was first treated with 2.0 equiv. of NaOH in methanol at 40 °C, and then treated with diluted aq. HCl, (+)-5-*epi*-*ent*-SA *ent*-**4** could be thus obtained in 87% yield.

Synthesis of (−)-5-epi-SA 4 from (−)-SA 1

The first synthesis of (−)-5-*epi*-SA **4** from *D*-ribose was reported by Wightman *et al.* in 1994.[29] Then Vankar *et al.* also reported a synthesis of (−)-5-*epi*-SA **4** from *D*-ribose in 2009.[30] Gotor *et al.* also reported a synthetic route to methyl ester of (−)-5-*epi*-SA **4** from (−)-quinic acid.[31] Our novel synthetic route was depicted in Scheme 4. As can be seen from Scheme 4, to protect the *cis*-vicinal diols, compound **7** was prepared from (−)-SA **1** in 92% yield over two steps by a known method.[7e] Compound **7** was treated with 1.3 equiv. of trichloroisocyanuric acid (TCCA) and 0.05 equiv. of 2,2,6,6-tetramethyl-piperidine *N*-oxide (TEMPO) in CH_2Cl_2 at room temperature to afford a ketone **14** in 85% yield. Then compound **14** was exposed to 1.2 equiv. of sodium borohydride ($NaBH_4$) in a mixed solvent of EtOAc and H_2O (*v*/*v* = 7:1) at 0 °C to room temperature to furnish compound **26** in 93% yield with >98% de. During the reduction of ketone **14**, the high steric hindrance of the isopropylidene moiety forced the borohydride anion to attack the carbonyl group *via* upward side, and thus the desired (*S*) configuration of secondary alcohol at C-5 formed. Subsequently, compound **26** was treated with 5 equiv. of conc. HCl in a mixed solvent of tetrahydrofuran (THF) and water (*v*/*v* = 10:1) at room temperature to produce compound *ent*-**25** in 90% yield. Finally, compound *ent*-**25** was first treated with 2.0 equiv. of NaOH in methanol at 40 °C, and then treated with diluted aq. HCl to afford (−)-5-*epi*-SA **4** in 86% yield.

Synthesis of (+)-ent-SA ent-1 from (−)-SA 1

The synthesis of (+)-*ent*-SA *ent*-**1** via asymmetric Diels-Alder reaction was achieved by Evans *et al.* and Carretero *et al.* in 1997.[27,32] Then Vankar *et al.*[30] and Yan *et al.*[24] revealed the syntheses of (+)-*ent*-SA *ent*-**1** from *D*-ribose and *L*-tartaric, respectively. Our novel synthetic route for the synthesis of (+)-*ent*-SA *ent*-**1** was depicted in Scheme 5. As can be seen from Scheme 5, the common intermediate **7** was treated with 1.2 equiv. of Ac_2O, 1.5 equiv. of Et_3N and 0.1 equiv. of DMAP in CH_2Cl_2 at 0 °C to afford acetylated product **27** in 92% yield. Then compound **27** was exposed to 5 equiv. of conc. HCl in a mixed solvent of tetrahydrofuran and water ($v/v = 15:1$) at room temperature to provide the *cis*-vicinal diol **28** in 90% yield. Subsequently, compound **28** was treated with 3.0 equiv. of MsCl, 4.0 equiv. of Et_3N and 0.2 equiv. of DMAP to give bismesylate **13** in 89% yield. Next, according to our known method,[33] compound **13** was treated with 6.0 equiv. of acetic acid (AcOH) and 1.5 equiv. of diisopropylethylamine (DIPEA) in EtOAc under refluxing to produce compound **29** in 86% yield. In this reaction, the much more reactive methanesulfoxyl (OMs) leaving group at allylic C-3 position was replaced by acetoxy anion to give the product **29** with high regioselectivity. Compound **29** was first treated with a catalytic amount of conc. H_2SO_4 (20 mol%) in ethanol under refluxing to give intermediate **I-3**, which was then directly treated with 1.2 equiv. of potassium carbonate (K_2CO_3) at room temperature to afford epoxide **12** in 70% yield over 2 steps. It is worth noting that two epoxides (i.e. an epoxide between C-3 and C-4 as well as another epoxide between C-4 and C-5) might be formed, but the latter is much more favorable due to less repulsion between epoxy and π electrons of the double bond.[34] Epoxide **12** could spontaneously crystallize out from the generated mixture as white acicular crystals. Subsequently, epoxide **12** underwent epoxide-opening in water at 90 °C to afford compound **30** in 87% yield using 5 mol% of AcOH as the catalyst. Finally, compound **30** was first treated with 2.0 equiv. of NaOH in methanol at 40 °C, and then treated with diluted aq. HCl, the desired (+)-*ent*-SA *ent*-**1** could be thus obtained in 86% yield.

Synthesis of (+)-3-epi-ent-SA ent-2 from (−)-SA 1

Kiessling *et al.* revealed a synthesis of (+)-3-*epi*-*ent*-SA *ent*-**2** from *D*-arabinose in 2011.[18] Banwell *et al.* reported a synthesis of methyl ester of *ent*-**2** from (−)-quinic acid in 2003.[35] Gotor *et al.* also reported a synthesis of methyl ester of *ent*-**2** from (−)-quinic acid in 2006.[36] Our novel synthetic route for the synthesis of (+)-3-*epi*-*ent*-SA *ent*-**2** was depicted in Scheme 6. As can be seen from the Scheme 6, ethyl shikimate *ent*-**30** was treated with 2.5 equiv. of *tert*-butyldimethylsilyl chloride (TBSCl), 3.0 equiv. of Et_3N and 0.2 equiv. of DMAP in dimethylformide (DMF) at room temperature to give compound **6** in 75% yield. In this reaction, two less hindered hydroxyls at C-3 and C-5 positions of compound *ent*-**30** were selectively protected by two TBS groups. Compound **6** was then treated with 2.0 equiv. of MsCl and 5.0 equiv. of pyridine and 0.2 equiv. of DMAP in CH_2Cl_2 at room temperature to furnish compound **31** in 85% yield. Compound **31** was exposed to 4.8 equiv. of conc. HCl in ethanol at room temperature to afford diol **11** in 96% yield. Subsequently, compound **11** was treated with 1.5 equiv. of anhydrous K_2CO_3 in absolute ethanol at room temperature to afford epoxide **10** in 92% yield. Epoxide **10** was treated with 0.05 equiv. of AcOH in water at 90 °C to provide *ent*-**15** in 90% yield. In the epoxide-opening, water attacked the less hindered C-5 position with high regio-selectivity to afford the desired *trans*-vicinal hydroxyls. Finally, compound *ent*-**15** was first treated with 2.0 equiv. of NaOH in methanol at 40 °C, and then treated with diluted aq. HCl, the (+)-3-*epi*-*ent*-SA *ent*-**2** was thus obtained in 88% yield.

Two dimensional (2D) ^{1}H NMR study on the stereochemistry of all the seven stereoisomers of (−)-SA 1

Although stereochemical structures of all the above seven stereoisomers (i.e., *ent*-**1**, **2**, *ent*-**2**, **3**, *ent*-**3**, **4** and *ent*-**4**) obtained from (−)-SA **1** via above synthetic routes (Schemes 2–6) are quite certain, the stereochemistry of these stereoisomers of (−)-SA **1** were further studied by ^{1}H-^{1}H COSY and ^{1}H-^{1}H NOESY spectra. Discussions are detailed in the "Supporting Information".

Conclusion

In conclusion, we revealed the novel syntheses of all the seven stereoisomers (i.e., *ent*-**1**, **2**, *ent*-**2**, **3**, *ent*-**3**, **4** and *ent*-**4**) of (−)-SA **1** starting from the naturally abundant (−)-SA**1** itself. (+)-*ent*-SA *ent*-**1** was synthesized from (−)-SA **1** via 9 steps in 31% overall yield; (−)-3-*epi*-SA **2** was synthesized from (−)-SA **1** via 5 steps in 66% overall yield; (+)-3-*epi*-*ent*-SA *ent*-**2** was synthesized from (−)-SA **1** via 7 steps in 43% overall yield; (−)-4-*epi*-SA **3** was synthesized from (−)-SA **1** via 11 steps in 32% overall yield; (+)-4-*epi*-*ent*-SA *ent*-**3** was synthesized from (−)-SA **1** via 7 steps in 42% overall yield; (−)-5-*epi*-SA **4** was synthesized from (−)-SA **1** via 6 steps in 56% overall yield; (+)-5-*epi*-*ent*-SA *ent*-**4** was synthesized from (−)-SA **1** via 12 steps in 29% overall yield.

In comparison to the literature syntheses of the target molecules, our novel stereodivergent syntheses might be more efficient, benign and economical. In addition, all the target molecules and the synthetic intermediates (i.e., compounds **5**–**30**) as shown in the Schemes 2–6 are useful chiral compounds, they would constitute a versatile chiral pool for the syntheses of diverse stereodivergent polyhydroxy-cyclohexenoid (or-cyclohexanoid) natural products and their analogues, which have various bioactivities and might be very important in medicinal chemistry and pharmaceutical industry.

The shikimate pathway was present in many plants and microorganisms,[37] and (−)-SA **1** is an important metabolite in shikimate pathway. With all the seven stereoisomers of (−)-SA **1** in hands, it worth exploring how these seven compounds react with the enzymes in the shikimate pathway in future.

Experimental Section

General Method. Optical rotation was tested by a Rudolph Autopol I S2 polarimeter. ^{1}H NMR and ^{13}C NMR spectra were acquired on a Bruker AM-400 instrument; chemical shifts are given on the δ scale as parts per million (ppm) with tetramethylsilane (TMS) as the internal standard (zero point), positive values represent downfield from TMS, and negative values represent upfield from TMS. 2D NMR spectra were acquired on a Bruker Avance-III-500 instrument. Infrared (IR) spectra were recorded with a Nicolet Magna IR-550 instrument. Mass spectra were performed with an HP1100 LC-MS spectrometer. Melting points were determined on a Mel-TEMP II apparatus. Column chromatography was performed on silica gel (200–300 mesh, Qingdao Ocean Chemical Corp.), unless otherwise indicated. All chemicals were analytically pure. (−)-Shikimic acid **1** can be purchased from many chinese venders such as Guangxi Fenghui Biotechnology Co. Ltd., Xi-an Kono Chemical Co. Ltd., Shaanxi Sinote Biotechnology Co. Ltd., and Jia-xing Eisen Chemical Co. Ltd. Compounds **5** and **7** were prepared according to the known procedures.[8b,7e]

Synthesis of (−)-3-epi-SA 2

Ethyl (3*S*,4*S*,5*R*)-3,4,5-trihydroxy-cyclohex-1-ene-1-carboxylate 15. Epoxide **5** (8.002 g, 43.44 mmol) was put into a round-bottom flask, and water (150 mL) was then added. The mixture was heated to 95 °C, and was stirred with a magnetic stirrer bar for 2 h. After the reaction was complete (checked by TLC, EtOAc/hexane = 1 : 2), the mixture was cooled to room temperature and water was removed by vacuum distillation to afford pale yellow crude, which was purified by flash chromatography (eluent: EtOAc/hexane = 1 : 4–9 : 1) to afford pure compound **15** (7.817 g, 38.66 mmol) as white solid in 89% yield. M.p. 112–114 °C. $[\alpha]_D^{25} = -16.4$ (*c* 0.52, MeOH). ^{1}H NMR (400 MHz, DMSO-d_6) δ [ppm] = 6.52 (dd, $J_1 = 2.3$ Hz, $J_2 = 2.5$ Hz, 1H, H-2), 4.11 (q, $J = 7.2$ Hz, 2H, OCH_2CH$_3$), 4.01–3.94 (m, 1H, H-3), 3.52–3.41 (m, 1H, H-5), 3.19 (dd, $J_1 = 9.7$ Hz, $J_2 = 7.6$ Hz, 1H, H-4), 2.61–2.51 (m, 1H, H-6), 2.07–1.87 (m, 1H, another H-6), 1.19 (t, $J = 7.2$ Hz, 3H, OCH$_2$CH_3). ^{13}C NMR (100 MHz, DMSO-d_6) δ [ppm] = 165.73 (COOEt), 140.54 (C-2), 127.02 (C-1), 76.61, 71.23, 68.47, 60.20, 32.54, 14.03. HRMS (ESI) calcd. for $[C_9H_{14}O_5Na]^+$: 225.0739; found: 225.0736. IR (KBr film) 3424 (br.), 2994, 2916, 1715, 1646, 1275, 1254, 1074, 974, 890, 863, 738 cm^{-1}.

(−)-3-*epi*-SA 2. Compound **15** (4.002 g, 19.80 mmol) and methanol (80 mL) were added into a round-bottom flask with a magnetic stirrer bar, and then NaOH (1.584 g, 39.60 mmol) was added at room temperature. The mixture was heated to 40 °C and then stirred for approximate 10 h. After the reaction was complete (checked by TLC, eluent: EtOAc), methanol was removed by vacuum distillation. The residue was dissolved in water (20 mL), and a dilute aqueous solution of HCl (1 *N*) was added to adjust pH = 4.1–4.4. After water was removed by vacuum distillation, ethanol (50 mL) and activated carbon (1.00 g) were added. The mixture was stirred at room temperature for 10 h. The suspension was filtered by a Buchner funnel and rinsed twice with ethanol (2 × 10 mL). Filtrate was concentrated by vacuum distillation to afford crude product as a colorless oil. A column (2 × 20 cm) of Amberlite IR 120 resin (Na^+ form, particle size: 0.600–0.800 mm) was first washed successively with an aqueous solution of HCl (1 mol/L) and water prior to use, and then the crude product was purified by chromatography on the resin column (eluent: pure water) to afford (−)-3-*epi*-shikimic acid **2** (3.034 g, 17.42 mmol) as white solid in 88% yield. M.p. 188–190 °C. $[\alpha]_D^{25} =< M- > 30.1$ (*c* 1.20, H2O) {lit.22b $[\alpha]_D^{25} = -31.0$ (*c* 0.1, H_2O)}. ^{1}H NMR (400 MHz, D_2O) δ [ppm] = 6.55 (dd, $J_1 = 2.7$ Hz, $J_2 = 2.4$ Hz,1H, H-2), 4.18–4.10 (m, 1H, H-3), 3.65 (ddd, $J_1 = 10.2$ Hz, $J_2 = 6.0$ Hz, $J_3 = 4.2$ Hz, 1H, H-5), 3.35 (dd, $J_1 = 10.2$ Hz, $J_2 = 8.1$ Hz, 1H, H-4), 2.65 (dd, $J_1 = 17.2$ Hz, $J_2 = 6.0$ Hz, 1H, H-6), 2.14–2.01 (m, 1H, another H-6). ^{13}C NMR (100 MHz, D_2O) δ [ppm] = 169.68 (*C*=O), 139.16 (C-2), 128.15 (C-1), 76.18, 71.47, 68.60, 31.76. HRMS (ESI) calcd. for $C_7H_9O_5$: 173.0450. Found: 173.0449. IR (KBr film) 3472, 3326, 3147, 2921, 2876, 1680, 1650, 1430, 1415, 1281, 1257, 1075, 1067, 985 cm^{-1}.

Synthesis of (+)-4-epi-ent-SA ent-3

Ethyl (3*R*,4*S*,5*S*)-5-benzoyloxy-3,4-epoxy-cyclohex-1-ene-1-carb-oxylate *ent*-8. Compound **5** (15.04 g, 81.65 mmol), benzoic acid (14.96 g, 122.5 mmol) and triphenylphosphine (32.13 g, 122.5 mmol) were dissolved in dichloromethane (300 mL), and then diethyl azodicarboxylate (21.32 g, 122.4 mmol) was slowly added at room temperature over 10 min. The mixture was stirred for 5 h. After the reaction was complete (checked by TLC, EtOAc/hexane = 1 : 6), dichloromethane was removed by vacuum distillation and then ethyl acetate (100 mL) and hexane (50 mL) were added. The suspension was filtrated by Buchner funne and the filtrate was concentrated by vacuum distillation to give pale yellow oil, which was purified by chromatography (eluent: EtOAc/hexane = 1 : 8) to afford compound *ent*-**8** (15.29 g, 53.07 mmol) as a colorless oil in 65% yield. $[\alpha]_D^{25} = +49.0°$ (*c* 1.11, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ [ppm] = 8.15–8.08 (d, $J = 8.2$ Hz, 2H, two *ortho*-H in Bz), 7.59 (t, $J = 7.6$ Hz, 1H, *para*-H in Bz), 7.50–7.41 (dd, $J_1 = 8.2$ Hz, $J_2 = 7.6$ Hz, 2H, two *meta*-H in Bz), 7.08 (dd, $J_1 = 4.0$ Hz, $J_2 = 3.3$ Hz, 1H, H-2), 5.50–5.43 (m, 1H, H-5), 4.21 (q, $J = 7.1$ Hz, 2H, OCH_2CH$_3$), 3.81 (dd, $J_1 = 4.4$ Hz, $J_2 = 2.0$ Hz, 1H, H-3), 3.57 (dd, $J_1 = 4.4$ Hz, $J_2 = 4.3$ Hz, 1H, H-4), 3.09–2.99 (m, 1H, H-6), 2.46–2.34 (m, 1H, another H-6), 1.29 (t, $J = 7.1$ Hz, 3H, OCH$_2$CH_3). ^{13}C NMR ($CDCl_3$, 100 Hz) δ [ppm] = 166.10 (*C*=O), 165.22 (*C*=O), 133.41 (sp^2–C), 133.36 (sp^2–C), 132.65 (sp^2–C), 129.84 (two sp^2–C), 129.66 (sp^2–C), 128.45 (two sp^2–C), 70.53, 61.19, 56.21, 48.55, 25.88, 14.20. HRMS (ESI) calcd. for $[C_{16}H_{16}O_5Na]^+$: 311.0895, found: 311.0887. IR (neat) 3064, 2980, 2936, 2906, 1718, 1601, 1584, 1451, 1375, 1321, 1257, 1202, 1177, 1110, 1073, 1051, 1026, 990, 965, 924, 893, 881, 854, 833, 740, 713 cm^{-1}.

Ethyl (3*S*,4*R*,5*S*)-5-benzoyloxy-3,4-dihydroxy-cyclohex-1-ene-1-carboxylate 16. Compound *ent*-**8** (10.02 g, 34.78 mmol) was dissolved in a mixed solvent of water (60 mL) and 1,4-dioxane (90 mL) at room temperature and the mixture was stirred at 90 °C for 4 h. After the reaction was complete, the mixture was cooled to room temperature. Ethyl acetate (150 mL) was added, and the mixture was further stirred for 5 min., two phases were separated and the aqueous solution was extracted twice with ethyl acetate (80 mL × 2). The organic ectracts were combined and dried over anhydrous $MgSO_4$. Organic solvents were removed by vacuum distillation to give pale yellow oil, which was purified by flash chromatography (eluent: EtOAc/hexane = 1 : 2) to afford compound **16** (9.600 g, 31.34 mmol) as white crystals in 90% yield. M.p. 98–99 °C. $[\alpha]_D^{25} = +70.6°$ (*c* 1.03, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ [ppm] = 7.95 (d, $J = 7.0$ Hz, 2H, two *ortho*-H in Bz), 7.52 (t, $J = 7.4$ Hz, 1H, *para*-H in Bz), 7.38 (dd, $J_1 = 7.4$ Hz, $J_2 = 7.0$ Hz, 2H, two *meta*-H in Bz), 6.93–6.89 (m, 1H, H-2), 5.58–5.50 (m, 1H, H-5), 4.63–4.54 (m, 1H, H-3), 4.16 (q, $J = 7.1$ Hz, 2H, OCH_2CH$_3$), 3.94–3.78 (m, 3H, H-4 and two O*H*), 2.78–2.59 (m, 2H, two H-6), 1.27 (t, $J = 7.1$ Hz, 3H, OCH$_2$CH_3). ^{13}C NMR (100 MHz, $CDCl_3$) δ [ppm] = 166.54 (*C*=O), 166.29 (*C*=O), 138.23 (sp^2–C), 133.32 (sp^2–C), 129.72 (two sp^2–C), 129.70 (sp^2–C), 128.42 (two sp^2–C), 127.93 (sp^2–C), 72.81, 71.86, 69.29, 61.10, 29.82, 14.14. HRMS (ESI) calcd. for $[C_{16}H_{18}O_6Na]^+$: 329.1001; found: 329.1008.

Ethyl (3*S*,4*S*,5*S*)-3,4,5-trihydroxy-cyclohex-1-ene-1-carboxylate 17. Compound **16** (8.004 g, 26.13 mmol) was dissolved in absolute ethanol (150 mL) and powdered anhydrous K_2CO_3 (5.418 g, 39.20 mmol) was added. The mixture was stirred at room temperature for 24 h. After the reaction was complete (checked by TLC, EtOAc/hexane = 1 : 1), the suspension was filtered by a Buchner

funnel and rinsed twice with ethanol (2×10 mL). Filtrate was concentrated by vacuum distillation to give pale yellow oil, which was purified by flash chromatography (eluent: EtOAc) to afford oily compound **17** (5.019 g, 24.82 mmol) in 95% yield. $[\alpha]_D^{25} = +74.0°$ (*c* 1.62, MeOH). ^{1}H NMR (400 MHz, DMSO-d_6 with addition of D_2O) δ [ppm] = 6.63–6.57 (m, 1H, H-2), 5.19 (d, *J* = 5.6 Hz, 0.24H, O*H*, partially exchanged with D_2O), 4.78 (d, *J* = 4.6 Hz, 0.24H, O*H*, partially exchanged with D_2O), 4.73 (d, *J* = 4.4 Hz, 0.24H, O*H*, partially exchanged with D_2O), 4.11 (q, *J* = 7.1 Hz, 2H, OCH_2CH_3), 4.09–4.02 (m, 1H, H-3), 3.85–3.77 (m, 1H, H-5), 3.47–3.41 (dd, J_1 = 5.6 Hz, J_2 = 2.3 Hz, 1H, H-4), 2.41–2.29 (m, 1H, H-6), 2.28–2.17 (m, 1H, another H-6), 1.20 (t, *J* = 7.1 Hz, 3H, OCH_2CH_3). ^{13}C NMR (100 MHz, DMSO-d_6) δ [ppm] = 166.69 (CO_2Et), 139.13 (C-2), 128.58 (C-1), 73.59, 69.11, 67.05, 60.60, 31.02, 14.57. HRMS (ESI) calcd. for $[C_9H_{14}O_5Na]^+$: 225.0739; found: 225.0733.

(+)-4-*epi*-*ent*-SA *ent*-3. Compound **17** (3.810 g, 18.84 mmol) and methanol (80 mL) were added into a round-bottom flask with a magnetic stirrer bar, and then NaOH (1.508 g, 37.70 mmol) was added at room temperature. The mixture was heated to 40 °C and then stirred for approximate 10 h. After the reaction was complete (checked by TLC, eluent: EtOAc), methanol was removed by vacuum distillation. The residue was dissolved in water (20 mL), and a dilute aqueous solution of HCl (1 *N*) was added to adjust pH = 4.1–4.4. After water was removed by vacuum distillation, ethanol (50 mL) and activated carbon (1.00 g) were added. The mixture was stirred at room temperature for 10 h. The suspension was filtered by a Buchner funnel and filter cake was rinsed twice with ethanol (2× 10 mL). Filtrate was concentrated by vacuum distillation to afford crude product as a colorless oil. A column (2×20 cm) of Amberlite IR 120 resin (Na^+ form, particle size: 0.600–0.800 mm) was first washed successively with an aqueous solution of HCl (1 mol/L) and water prior to use, and then the crude product was purified by chromatography on the resin column (eluent: pure water) to afford (+)-4-*epi*-SA *ent*-**3** (2.918 g, 16.76 mmol) as white crystals in 89% yield. M.p. 110–112 °C. $[\alpha]_D^{25} = +79.8$ (*c* 0.64, H2O) {lit.26 $[\alpha]_D^{22} = -80.6$ (*c* 1.03, H_2O) for **3**}. ^{1}H NMR (400 MHz, D_2O) δ [ppm] = 6.77–6.72 (m, 1H, H-2), 4.37–4.30 (m, 1H, H-3), 4.10 (ddd, J_1 = 3.2 Hz, J_2 = 4.4 Hz, J_3 = 2.4 Hz, 1H, H-5), 3.68 (dd, J_1 = 7.2 Hz, J_2 = 2.4 Hz, 1H, H-4), 2.62–2.52 (m, 1H, H-6), 2.44–2.35 (dd, J_1 = 18.4 Hz, J_2 = 4.4 Hz, 1H, another H-6). ^{13}C NMR (100 MHz, D_2O) δ [ppm] = 170.12 (*C*=O), 137.94 (C-2), 128.65 (C-1), 72.98, 68.53, 67.79, 30.46. IR (KBr film) 3378, 3279, 2957, 2920, 2895, 1601, 1695, 1418, 1371, 1329, 1305, 1271, 1242, 1206, 1126, 1089, 1073, 1036, 1016, 951, 922, 901, 837, 763, 733 cm^{-1}.

Synthesis of (−)-4-epi-SA 3

Ethyl (3*R*,4*S*,5*R*)-5-benzoyloxy-3,4-epoxy-cyclohex-1-ene-1-carb-oxylate 18. Epoxide **5** (20.03 g, 108.7 mmol), triethylamine (22.04 g, 217.8 mmol) and 4-dimethylamino-pyridine (1.328 g, 10.87 mmol) were dissolved in dichloromethane (200 mL) in a round-bottom flask, which was equipped with a magnetic stirrer bar. The solution was cooled to 0 °C by an ice bath and then benzoyl chloride (22.93 g, 163.1 mmol) was added dropwise over 15 min. The ice bath was removed and the mixture was further stirred at room temperature for 2 h. After the reaction was complete (checked by TLC, EtOAc/hexane = 1:4), an aqueous solution of potassium carbonate (200 mL, 10% w/w) was added and the mixture was further stirred for 3 h. Then two phases were separated by a separatory funnel and the organic layer was successively washed with an aqueous solution of HCl (150 mL, 2 *N*) and water (50 mL). After organic layer was dried over anhydrous $MgSO_4$, the solution was concentrated by vacuum distillation to afford a pale yellow oil, which was purified by flash chromatography (eluent: EtOAc/hexane = 1:8) to afford compound **18** (28.20 g, 97.81 mmol) as a colorless oil in 90% yied. $[\alpha]_D^{25} = +253.2$ (*c* 1.16, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ [ppm] = 7.96 (d, *J* = 7.7 Hz, 2H, two *ortho*-H in Bz), 7.54 (t, *J* = 7.4 Hz, 1H, *para*-H in Bz), 7.40 (dd, J_1 = 7.7 Hz, J_2 = 7.4 Hz, 2H, two *meta*-H in Bz), 7.19 (dd, J_1 = 3.6 Hz, J_2 = 3.4 Hz, 1H, H-2), 5.90–5.84 (m, 1H, H-5), 4.21 (q, *J* = 7.1 Hz, 2H, OCH_2CH_3), 3.79–3.72 (m, 1H, H-3), 3.54 (dd, J_1 = 3.9 Hz, J_2 = 3.6 Hz, 1H, H-4), 2.96 (dd, J_1 = 18.1 Hz, J_2 = 2.0 Hz, 1H, H-6), 2.45 (dd, J_1 = 18.1 Hz, J_2 = 5.2 Hz, 1H, another H-6), 1.28 (t, *J* = 7.1 Hz, 3H, OCH_2CH_3). ^{13}C NMR (100 MHz, $CDCl_3$) δ [ppm] = 165.77 (*C*=O), 165.67 (*C*=O), 133.30 (sp^2–C), 132.83 (sp^2–C), 131.30 (sp^2–C), 129.74 (two sp^2–C), 129.65 (sp^2–C), 128.40 (two sp^2–C), 66.24, 61.05, 54.02, 46.61, 26.47, 14.17. HRMS (ESI) calcd. for $[C_{16}H_{16}O_5Na]^+$: 311.0895; found: 311.0894. IR (neat) 2939, 2841, 1715, 1451, 1382, 1340, 1258, 1240, 1094, 1024, 925, 810, 764, 711 cm^{-1}.

Ethyl (3*S*,4*S*,5*R*)-5-benzoyloxy-3-acetoxy-4-hydroxy-cyclohex-1-ene-1-carboxylate 19. Compound **18** (15.04 g, 52.17 mmol), acetic acid (15.67 g, 260.9 mmol) and trifluoroacetic acid (2.974 g, 26.09 mmol) were dissolved in dichloromethane (300 mL) in a round-bottom flask with a magnetic stirrer bar. The mixture was stirred at reflux for 30 h. After the reaction was complete (checked by TLC, EtOAc/hexane = 1:2), the mixture was cooled to room temperature and water (200 mL) was added. Powder potassium carbonate (25.00 g) was slowly added to neutralize the solution, which then transformed to a separatory funnel. Two phases were separated, and aqueous solution was twice extracted by dichloromethane (150 mL×2). Organic extracts were combined and dried over $MgSO_4$. The solution was then concentrated by vacuum distillation to give the crude product as a pale yellow oil, which was purified by flash chromatography (eluent: EtOAc/hexane = 1:4) to afford compound **19** (14.55 g, 41.77 mmol) as a colorless oil in 80% yield. $[\alpha]_D^{25} = -5.6$ (*c* 1.98, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ [ppm] = 8.04 (d, *J* = 7.9 Hz, 2H, two *ortho*-H in Bz), 7.56 (t, *J* = 7.2 Hz, 1H, *para*-H in Bz), 7.43 (dd, J_1 = 7.9 Hz, J_2 = 7.2 Hz, 2H, two *meta*-H in Bz), 6.72–6.67 (m, 1H, H-2), 5.54 (dd, J_1 = 3.0 Hz, J_2 = 2.9 Hz, 1H, H-3), 5.32 (m, 1H, H-5), 4.21 (q, *J* = 7.1 Hz, 2H, OCH_2CH_3), 4.09 (dd, J_1 = 7.4 Hz, J_2 = 4.8 Hz, 1H, H-4), 3.12–2.95 (m, 2H, H-6 and O*H*), 2.50 (dd, J_1 = 17.8 Hz, J_2 = 8.8 Hz, 1H, another H-6), 2.10 (s, 3H, CH_3 in Ac), 1.29 (t, *J* = 7.1 Hz, 3H, OCH_2CH_3). ^{13}C NMR (100 MHz, $CDCl_3$) δ [ppm] = 170.92 (*C*=O), 166.23 (*C*=O), 165.40 (*C*=O), 133.98 (sp^2–C), 133.37 (sp^2–C), 130.07 (sp^2–C), 129.79 (two sp^2–C), 129.65 (sp^2–C), 128.44 (two sp^2–C), 73.62, 71.62, 71.40, 61.28, 29.18, 20.97, 14.18. HRMS (ESI) calcd. for $[C_{18}H_{20}O_7Na]^+$: 371.1107; found: 371.1113. IR (neat) 3481, 2982, 2936, 1718, 1450, 1372, 1315, 1233, 1178, 1114, 1098, 1069, 1028, 959, 929, 894, 865, 806, 738, 714 cm^{-1}.

Ethyl (3*S*,4*S*,5*R*)-5-benzoyloxy-3-acetoxy-4-methanesulfonyloxy-cyclohex-1-ene-1-carboxylate 9. Compound **19** (15.00 g, 43.06 mmol), triethylamine (6.536 g, 64.59 mmol) and 4-dimethylamino-pyridine (526.5 mg, 4.306 mmol) were dissolved in dichloromethane (300 mL) in a round-bottom flask. The solution was cooled to 0 °C by an ice bath, and then methanesulfonyl chloride (6.130 g, 53.50 mmol) was added dropwise over 10 min. The mixture was further stirred at 0 °C for 2 h. After the reaction was complete (checked by TLC, EtOAc/hexane = 1:2), an aqueous solution of HCl (150 mL, 1 *N*) was added, mixture was further stirred for 5 min. Two phases were separated by a separatory funnel, and the organic layer was successively washed with an aqueous solution of K_2CO_3 (100 mL, 5% w/w) and water (50 mL). After organic layer was dried over anhydrous $MgSO_4$, the solution was concentrated by vacuum distillation to give an off-white crude, which was triturated in a mixed solution of ethyl acetate and hexane (EtOAc/hexane = 1:4). The mixture was filtered by suction and rinsed twice by the above mixed solvent to afford compound **9** (17.45 g, 40.92 mmol) as white crystals in 95% yield. M.p. 128–129 °C. $[\alpha]_D^{25} = -46.8$ (*c* 4.52, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ [ppm] = 8.10 (d, *J* = 7.8 Hz, 2H, two *ortho*-H in Bz), 7.60 (t, *J* = 7.4 Hz,

1H, *para*-H in Bz), 7.46 (dd, $J_1 = 7.8$ Hz, $J_2 = 7.4$ Hz, 2H, two *meta*-H in Bz), 6.72–6.67 (m, 1H, H-2), 5.82–5.75 (m, 1H, H-3), 5.53–5.43 (m, 1H, H-5), 5.13 (dd, $J_1 = 9.6$ Hz, $J_1 = 7.6$ Hz, 1H, H-4), 4.22 (q, $J = 7.1$ Hz, 2H, OCH_2CH_3), 3.20 (dd, $J_1 = 17.9$ Hz, $J_2 = 6.0$ Hz, 1H, H-6), 2.93 (s, 3H, CH_3 in Ms), 2.62–2.52 (m, 1H, another H-6), 2.12 (s, 3H, CH_3 in Ac), 1.29 (t, $J = 7.1$ Hz, 3H, OCH_2CH_3). ^{13}C NMR (100 MHz, $CDCl_3$) δ [ppm] = 170.06 (*C*=O), 165.36 (*C*=O), 164.76 (*C*=O), 133.63 (sp^2–C), 133.19 (sp^2–C), 130.02 (sp^2–C), 129.89 (two sp^2–C), 129.11 (sp^2–C), 128.59 (two sp^2–C), 78.15, 70.46, 68.27, 61.47, 38.78, 29.68, 20.82, 14.15. HRMS (ESI) calcd. for $[C_{19}H_{22}O_9SNa]^+$: 449.0882; found: 449.0872. IR (KBr film) 3088, 3057, 2938, 2939, 2921, 2850, 1750, 1346, 1271, 1218, 1166, 1112, 1034, 1009, 969, 923, 756, 734 cm^{-1}.

Ethyl (3*S*,4*R*,5*R*)-5-benzoyloxy-3-hydroxy-4-methanesulfonyl-oxy-cyclohex-1-ene-1-carboxylate 20. Compound **9** (20.03 g, 46.97 mmol), *p*-toluenesulfonic acid (17.87 g, 93.94 mmol) and absolute ethanol (300 mL) were added into a round-bottom flask. Then the mixture was heated to reflux, and was further stirred under refluxing for 7 h. After the reaction was complete (checked by TLC, EtOAc/hexane = 1:2), the solution was cooled to room temperature, and concentrated to dryness by vacuum distillation. Ethyl acetate (350 mL) and water (150 mL) were added into the flask, powdered K_2CO_3 (8.002 g) was added slowly to neutralize the solution. The mixture was warmed up to 50 ~ 60 °C, and further stirred for 15 min., and two phases were then separated under the warm temperature. The aqueous solution was twice extracted with ethyl acetate (150 mL × 2). The organic extracts were combined and dried over anhydrous $MgSO_4$. After filtration under the warm temperature, the solution was concentrated by vacuum distillation to give an off-white solid product, which was triturated in a mixed solution of ethyl acetated and hexane (eluent: EtOAc/hexane = 1:2). The mixture was filtered by suction and rinsed twice by the above mixed solvent to afford compound **20** (16.60 g, 43.18 mmol, 92%) as a white crystals in 92% yield. M.p. 159–161 °C. $[\alpha]_D^{25} = -101.8$ (*c* 1.20, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ [ppm] = 8.08 (d, $J = 7.9$ Hz, 2H, *ortho*-H in Bz), 7.58 (t, $J = 7.4$ Hz, 1H, *para*-H in Bz), 7.46 (dd, $J_1 = 7.9$ Hz, $J_2 = 7.4$ Hz, 2H, two *meta*-H in Bz), 6.82–6.78 (m,1H, H-2), 5.46–5.36 (m, 1H, H-5), 5.00–4.91 (m, 1H, H-4), 4.71–4.62 (m, 1H, H-3), 4.21 (q, $J = 7.0$ Hz, 2H, OCH_2CH_3), 3.19 (dd, $J_1 = 17.7$ Hz, $J_2 = 6.3$ Hz, 1H, H-6), 3.02 (s, 3H, CH_3 in Ms), 2.89 (s, 1H, O*H*), 2.51 (dd, $J_1 = 17.7$ Hz, $J_2 = 9.8$ Hz, 1H, another H-6), 1.28 (t, $J = 7.1$ Hz, 3H, OCH_2CH_3). ^{13}C NMR (100 MHz, $CDCl_3$) δ [ppm] = 165.61 (*C*=O), 165.07 (*C*=O), 136.53 (sp^2–C), 133.63 (sp^2–C), 129.87 (two sp^2–C), 129.20 (sp^2–C), 128.65 (two sp^2–C), 128.46 (sp^2–C), 82.85, 70.32, 68.35, 61.39, 38.68, 30.20, 14.17. HRMS (ESI) calcd. for $[C_{17}H_{20}O_8SNa]^+$: 407.0777; found: 407.0774. IR (KBr film) 3429, 3021, 2998, 2954, 1701, 1450, 1421, 1356, 1313, 1285, 1257, 1167, 1118, 1095, 980, 896, 863, 852, 784, 751 cm^{-1}.

Ethyl (3*S*,4*R*,5*R*)-5-benzoyloxy-3,4-epoxy-cyclohex-1-ene-1-carboxylate 8. Compound **20** (10.02 g, 26.07 mmol) was dissolved in dichloromethane (300 mL), and the resoluting solution was cooled to 0 °C by an ice bath. Sodium hydride (2.086 g, 52.14 mmol, 60% w/w) was slowly added in portions over 1 h. When addition was finished, the mixture was warmed to room temperature, and was further stirred for 6 h. After the reaction was complete (checked by TLC, EtOAc/hexane = 1:4), the reaction solution was quenched by slow addition of water (50 mL). Two phases were separated, and aqueous solution was twice washed with dichloromethane (50 mL × 2). Organic extracts were combined and dried over anhydrous $MgSO_4$. The solution was concentrated by vacuum distillation to afford crude product as a bright yellow oil, which was purified by flash chromatography (eluent: EtOAc/hexane = 1:8) to give compound **8** (6.014 g, 20.86 mmol, 80%) as a colorless oil. $[\alpha]_D^{25} = -48.3$ (*c* 2.69, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ [ppm] = 8.11 (d, $J = 8.0$ Hz, 2H, *ortho*-H in Bz), 7.59 (t, $J = 7.3$ Hz, 1H, *para*-H in Bz), 7.48 (dd, $J_1 = 8.0$ Hz, $J_2 = 7.3$ Hz, 2H, two *meta*-H in Bz), 7.12–7.08 (m, 1H, H-2), 5.52–5.42 (m, 1H, H-5), 4.22 (q, $J = 7.1$ Hz, 2H, OCH_2CH_3), 3.82 (d, $J = 3.7$ Hz, 1H, H-3), 3.58 (dd, $J_1 = 6.4$ Hz, $J_2 = 3.7$ Hz, 1H, H-4), 3.05 (dd, $J_1 = 16.4$ Hz, $J_2 = 6.6$ Hz, 1H, H-6), 2.45–2.35 (m, 1H, another H-6), 1.30 (t, $J = 7.1$ Hz, 3H, OCH_2CH_3). ^{13}C NMR (100 MHz, $CDCl_3$) δ [ppm] = 166.15 (*C*=O), 165.25 (*C*=O), 133.47 (sp^2–C), 133.38 (sp^2–C), 132.64 (sp^2–C), 129.87 (two sp^2–C), 129.68 (sp^2–C), 128.47 (two sp^2–C), 70.53, 61.21, 56.22, 48.57, 25.89, 14.20. HRMS (ESI) calcd. for $[C_{16}H_{16}O_5Na]^+$: 311.0895; found: 311.0901. IR (neat) 3063, 3031, 2981, 2931, 2870, 1718, 1450, 1374, 1320, 1257, 1201, 1177, 1110, 1072, 1025, 924, 739, 713 cm^{-1}.

(−)-4-*epi*-SA 3. It was prepared from compound **8** in 76% yield (3 steps) through the same sequence as that for the preparation of (+)-4-*epi*-SA *ent*-**3** from compound *ent*-**8**. Characterization data: M.p. 110–112 °C. $[\alpha]_D^{25} = -79.7$ (*c* 0.65, H2O) {lit.26 $[\alpha]_D^{22} = -80.6$ (*c* 1.03, H_2O)}. ^{1}H NMR (400 MHz, D_2O) δ [ppm] = 6.76–6.71 (m, 1H, H-2), 4.37–4.27 (m, 1H, H-3), 4.10 (ddd, $J_1 = 3.2$ Hz, $J_2 = 4.4$ Hz, $J_3 = 2.5$ Hz, 1H, H-5), 3.66 (dd, $J_1 = 7.2$ Hz, $J_2 = 2.5$ Hz, 1H, H-4), 2.61–2.51 (m, 1H, H-6), 2.46–2.32 (m, $J_1 = 18.3$ Hz, $J_2 = 4.4$ Hz, 1H, another H-6). ^{13}C NMR (101 MHz, D_2O) δ [ppm] = 170.07 (*C*=O), 137.97 (C-2), 128.62 (C-1), 72.98, 68.52, 67.79, 30.45. HRMS (ESI) calcd. for $[C_7H_9O_5]$: 173.0450; found: 173.0449.

Synthesis of (+)-5-epi-ent-SA ent-4

Ethyl (3*R*,4*R*,5*R*)-3-bromo-5-benzoyloxy-4-hydroxy-cyclohex-1-ene-1-carboxylate 21. Compound **8** (15.04 g, 52.17 mmol) was dissolved in ethyl acetate (300 mL). After the solution was cooled to 0 °C by an ice bath, hydrobromic acid (21.10 g, 104.3 mmol, 40% w/w) was added dropwise over 10 min. After the reaction was complete (checked by TLC, EtOAc/hexane = 1:2), an aqueous solution of K_2CO_3 (200 mL, 5% w/w) was added to quench the reaction. Two phases were separated and the aqueous solution was twice extracted with ethyl acetate (150 mL × 2). Organic extracts were combined and dried over anhydrous $MgSO_4$, and then the solution was concentrated by vacuum distillation to give a pale yellow oily crude product, which was purified by flash chromatography (eluent: EtOAc/hexane = 1:4) to afford compound **21** (18.68 g, 50.59 mmol) as a colorless oil in 97% yield. $[\alpha]_D^{25} = -122.8$ (*c* 0.68, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ [ppm] = 8.02 (d, 2H, $J = 8.4$ Hz, two *ortho*-H in Bz), 7.58 (t, 1H, $J = 8.4$ Hz, *para*-H in Bz), 7.44 (dd, $J_1 = 8.4$ Hz, $J_2 = 7.4$ Hz, 2H, two *meta*-H in Bz), 7.05–6.99 (m, 1H, H-2), 5.71–5.60 (m, 1H, H-5), 4.86–4.75 (m, 2H, H-3 and O*H*), 4.33 (dd, $J_1 = 5.7$ Hz, $J_2 = 2.2$ Hz, 1H, H-4), 4.22 (q, $J = 7.2$ Hz, 2H, OCH_2CH_3), 3.00–2.88 (m, 1H, H-6), 2.88–2.76 (m, 1H, another H-6), 1.30 (t, $J = 7.2$ Hz, 3H, OCH_2CH_3). ^{13}C NMR (100 MHz, $CDCl_3$) δ [ppm] = 165.98 (*C*=O), 165.51 (*C*=O), 135.18 (sp^2–C), 133.46 (sp^2–C), 129.75 (two sp^2–C), 129.58 (sp^2–C), 129.34 (sp^2–C), 128.51 (two sp^2–C), 72.53, 69.71, 61.33, 47.55, 27.68, 14.19. HRMS (ESI) calcd. for $[C_{16}H_{17}O_5BrNa]^+$: 391.0157; found: 391.0160. IR (neat) 3470, 3065, 2980, 2937, 1717, 1601, 1584, 1451, 1368, 1314, 1270, 1177, 1113, 1098, 1069, 1027, 963, 947, 905, 875, 844, 805, 787, 771, 751, 713 cm^{-1}.

Ethyl (3*R*,4*R*,5*R*)-4-acetoxy-3-bromo-5-benzoyloxy-cyclohex-1-ene-1-carboxylate 22. Compound **21** (12.01 g, 32.53 mmol), acetic anhydrate (4.320 g, 42.32 mmol) and DMAP (397.4 mg, 3.253 mmol) were dissolved in dichloromethane (200 mL). After the solution was cooled to 0 °C by an ice bath, triethylamine (4.938 g, 48.80 mmol) was dropwise added over 10 min., the mixture was further stirred for 2 h at 0 °C. After the reaction was complete (checked by TLC, EtOAc/hexane = 1:4), an aqueous solution of HCl (100 mL, 1 *N*) was added to quench the reaction. Two phases were separated, and the organic layer was successively washed with an aqueous solution of K_2CO_3 (50 mL, 5% w/w) and water (50 mL). The organic solution was dried over anhydrous $MgSO_4$ and then concentrated by vacuum distillation to give crude product as a pale yellow oil, which

was purified by flash chromatography (eluent: EtOAc/hexane = 1:6) to afford compound **22** (12.70 g, 30.88 mmol) as an off-white solid in 95% yield. M.p. 84–86 °C. $[\alpha]_D^{25} = -162.4$ (*c* 0.92, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$) δ [ppm] = 7.98 (d, $J = 8.4$ Hz, 2H, two *ortho*-H in Bz), 7.57 (t, $J = 7.4$ Hz, 1H, *para*-H in Bz), 7.45 (dd, $J_1 = 8.4$ Hz, $J_2 = 7.4$ Hz, 2H, two *meta*-H in Bz), 7.05–6.99 (m, 1H, H-2), 5.77–5.69 (m, 1H, H-5), 5.47 (dd, $J_1 = 5.5$ Hz, $J_2 = 2.3$ Hz, 1H, H-4), 4.86–4.78 (m, 1H, H-3), 4.24 (q, $J = 7.1$ Hz, 2H, OCH_2CH_3), 3.07–2.95 (m, 1H, H-6), 2.85–2.74 (m, 1H, another H-6), 2.11 (s, 3H, CH_3 in Ac), 1.31 (t, $J = 7.1$ Hz, 3H, OCH_2CH_3). ^{13}C NMR (100 MHz, $CDCl_3$) δ [ppm] = 169.91 (*C*=O), 165.47 (*C*=O), 165.32 (*C*=O), 134.70 (sp^2–C), 133.40 (sp^2–C), 129.72 (sp^2–C), 129.70 (two sp^2–C), 129.56 (sp^2–C), 128.50 (two sp^2–C), 72.86, 67.23, 61.39, 42.90, 27.69, 20.84, 14.20. HRMS (ESI) calcd. for $[C_{18}H_{19}O_6BrNa]^+$: 433.0263; found: 433.0258. IR (KBr film) 3072, 2994, 2974, 2898, 1746, 1719, 1602, 1583, 1493, 1448, 1373, 1343, 1301, 1317, 1281, 1249, 1222, 1201, 1135, 1121, 1101, 1084, 1069, 1042, 1015, 969, 938, 908, 889, 862, 767, 748, 717 cm^{-1}.

Ethyl (3*S*,4*R*,5*R*)-3,4,5-trihydroxy-cyclohex-1-ene-1-carboxylate 25. Compound **22** (14.03 g, 34.12 mmol) and acetic acid (16.39 g, 273.0 mmol) were dissolved in isopropanol (200 mL). Powdered anhydrous potassium acetate (6.697 g, 68.24 mmol) was added, and the mixture was heated to reflux, and was then stirred under refluxing for 30 h. After the reaction was complete (checked by TLC, EtOAc/hexane = 1:2), isopropanol was removed by vacuum distillation. Then ethyl acetate (350 mL) and an aqueous solution of K_2CO_3 (250 mL, 15% w/w) were added. After the mixture was vigorously stirred for 30 min., two phases were separated and the aqueous solution was twice extracted with ethyl acetate (150 mL × 2). Organic extracts were combined and dried over anhydrous $MgSO_4$. The solution was concentrated by vacuum distillation to give a pale yellow oil, which was purified by flash chromatography (eluent: EtOAc/hexane = 1:4) to afford a mixture of compounds **23** and **24**. It was then dissolved in absolute ethanol (250 mL) in a round-bottom flask. Then powdered anhydrous K_2CO_3 (14.14 g, 102.4 mmol) was added into the flask, and the mixture was then stirred at room temperature for 7 h. After the reaction was complete, the suspension was filtered by a Buchner funnel, and the filter cake was washed twice with ethanol (50 mL × 2). The filtrates were combined and concentrated by vacuum distillation to give a pale yellow oil, which was purified by flash chromatography (eluent: EtOAc) to afford compound **25** (5.860 g, 28.98 mmol) as white crystals in 85% yield. M.p. 134–135 °C. $[\alpha]_D^{25} = +55.1$ (*c* 0.55, MeOH). ^1H NMR (400 MHz, DMSO-d_6) δ [ppm] = 6.52–6.46 (m, 1H, H-2), 4.23–4.15 (m, 1H, H-3), 4.09 (q, $J = 7.1$ Hz, 2H, OCH_2CH_3), 3.80–3.73 (m, 1H, H-4), 3.68–3.60 (m, 1H, H-5), 2.36–2.25 (dd, $J_1 = 16.8$ Hz, $J_2 = 5.8$ Hz, 1H, H-6), 2.18–2.06 (m, 1H, another H-6), 1.17 (t, $J = 7.1$ Hz, 3H, OCH_2CH_3). ^{13}C NMR (100 MHz, DMSO-d_6) δ [ppm] = 166.27 (CO_2Et), 139.79 (C-2), 127.91 (C-1), 70.30, 67.85, 67.14, 60.50, 28.29, 13.90. HRMS (ESI) calcd. for $[C_9H_{14}O_5Na]^+$: 225.0739; found: 225.0730. IR (KBr film) 3371, 3204, 2987, 2959, 2931, 2848, 1714, 1478, 1434, 1411, 1376, 1247, 1155, 1085, 1062, 1033, 950, 923, 896, 878, 861, 801, 735 cm^{-1}.

(+)-5-*epi*-*ent*-SA *ent*-4. Compound **25** (3.902 g, 19.30 mmol) and methanol (80 mL) were added into a round-bottom flask with a magnetic stirrer bar, and then NaOH (1.545 g, 38.63 mmol) was added at room temperature. The mixture was heated to 40 °C and then stirred for approximate 10 h. After the reaction was complete (checked by TLC, eluent: EtOAc), methanol was removed by vacuum distillation. The residue was dissolved in water (20 mL), and a dilute aqueous HCl (1 *N*) was added to adjust pH = 4.1–4.4. After water was removed by vacuum distillation, ethanol (50 mL) and activated carbon (1.0 g) were added. The mixture was stirred at room temperature for 10 h. The suspension was filtered by a Buchner funnel and filter cake was rinsed twice with ethanol (2 × 10 mL). Filtrate was concentrated by vacuum distillation to afford crude product as a colorless oil. A column (2 × 20 cm) of Amberlite IR 120 resin (Na^+ form, particle size: 0.600–0.800 mm) was first washed successively with an aqueous solution of HCl (1 mol/L) and water prior to use, and then the crude product was purified by chromatography on the resin column (eluent: pure water) to afford (+)-5-*epi*-*ent*-SA *ent*-**4** (2.925 g, 16.80 mmol) as white crystals in 87% yield. M.p. 108–110 °C. $[\alpha]_D^{25} = +63.2$ (*c* 0.59, H_2O). ^1H NMR (400 MHz, D_2O) δ [ppm] = 6.68 (d, $J = 3.6$ Hz, 1H, H-2), 4.52–4.43 (m, 1H, H-3), 4.04 (dd, $J_1 = 3.6$ Hz, $J_2 = 2.8$ Hz, 1H, H-4), 3.97 (ddd, $J_1 = 4.0$ Hz, $J_2 = 6.2$ Hz, $J_3 = 2.8$ Hz, 1H, H-5), 2.58 (dd, $J_1 = 17.4$ Hz, $J_2 = 6.2$ Hz, 1H, H-6), 2.33–2.19 (m, 1H, another H-6). ^{13}C NMR (100 MHz, D_2O) δ [ppm] = 169.87 (*C*=O), 138.95 (C-2), 128.74 (C-1), 70.55, 68.13, 67.36, 27.56. IR (KBr film) 3377, 2963, 2922, 2905, 1697, 1442, 1415, 1377, 1347, 1299, 1274, 1251, 1236, 1152, 1107, 1089, 1059, 1042, 1025, 976, 923, 881, 787, 716 cm^{-1}.

Synthesis of (−)-5-epi-SA 4

Ethyl (3*R*,4*R*)-3,4-isopropylidenedioxy-5-oxo-cyclohex-1-ene-1-carboxylate 14. Compound **7** (12.03 g, 49.66 mmol) was dissolved in dichloromethane (240 mL), and then trichloroisocyanuric acid (15.00 g, 64.56 mmol) and 2,2,6,6-tetramethyl-1-piperidine *N*-oxide (388.0 mg, 2.483 mmol) were added. The mixture was stirred at room temperature for 4 h. After the reaction was complete (checked by TLC, EtOAc/hexane = 1:3), dichloromethane was removed by vacuum distillation. Then ethyl acetate (250 mL) and water (150 mL) were added and further stirred for 0.5 h. The suspension was filtrated by a Buchner funnel, and the filter cake was twice rinsed with ethyl acetate (20 mL × 2). Two phases were separated and the aqueous solution was twice extracted with ethyl acetate (100 mL × 2). The organic extracts were combined and dried over anhydrous $MgSO_4$. The solution was concentrated by vaccum distillation to give a bright yellow oil, which was purified by flash chromatography (eluent: EtOAc/hexane = 1:6) to afford compound **14** (10.15 g, 42.25 mmol) as a pale yellow oil in 85% yield. $[\alpha]_D^{25} = -20.6$ (*c* 1.34, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$) δ [ppm] = 7.00–6.96 (m, 1H, H-2), 5.10–5.02 (m, 1H, H-3), 4.50 (d, $J = 6.2$ Hz, 1H, H-4), 4.26 (q, $J = 7.1$ Hz, 2H, OCH_2CH_3), 3.42 (d, $J = 19.7$ Hz, 1H, H-6), 3.24 (d, $J = 19.7$ Hz, 1H, another H-6), 1.47 (s, 3H, CH_3 in isopropylidene), 1.42 (s, 3H, another CH_3 in isopropylidene), 1.32 (t, $J = 7.1$ Hz, 3H, OCH_2CH_3). ^{13}C NMR (100 MHz, $CDCl_3$) δ [ppm] = 203.41 (C-5), 165.07 (*C*=O), 133.17 (sp^2–C), 130.13 (sp^2–C), 111.54, 77.63, 75.96, 61.58, 37.05, 27.45, 26.08, 14.18. HRMS (ESI) calcd. for $[C_{12}H_{16}O_5Na]^+$: 263.0895; found: 263.0891. IR (neat) 3067, 2986, 2937, 2908, 1719, 1456, 1374, 1249, 1160, 1082, 1019, 978, 926, 911, 853, 785, 741 cm^{-1}.

Ethyl (3*R*,4*S*,5*S*)-3,4-isopropylidenedioxy-5-hydroxy-cyclohex-1-ene-1-carboxylate 26. Compound **14** (10.05 g, 41.83 mmol) was dissolved in ethyl acetate (175 mL) in a round-bottom flask, which was cooled to 0 °C by an ice bath. Then sodium borohydride (1.900 g, 50.22 mmol) was dissolved in water (25 mL), and then was added dropwise into the flask over 10 min. Then the ice bath was removed and the solution was stirred at room temperature for 2 h. After the reaction was complete (checked by TLC, EtOAc/hexane = 1:2), ethyl acetate (50 mL) and water (150 mL) were added. The solution was further stirred at room temperature for 0.5 h. Two phases were separated and the aqueous layer was twice extracted with ethyl acetate (100 mL × 2). The organic extracts were combined and then dried over anhydrous $MgSO_4$. The solution was concentrated by vacuum distillation to give a colorless oil, which was purified by flash chromatography (eluent: EtOAc/hexane = 1:2) to afford compound **26** (9.420 g, 38.88 mmol) as a colorless oil in 93% yield. $[\alpha]_D^{25} = +35.2$ (*c* 1.37, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$) δ [ppm] = 6.78–6.69 (m, 1H, H-2), 4.74–4.64 (m, 1H, H-3), 4.38 (dd, $J_1 = 5.8$ Hz, $J_2 = 2.6$ Hz, 1H, H-4), 4.17 (q, $J = 7.1$ Hz, 2H, OCH_2CH_3), 3.95–3.85 (m, 1H, H-5), 2.76–2.54 (m, 2H, H-6 and OH), 2.50–2.38 (m, 1H,

another H-6), 1.36 (s, 3H, CH_3 in isopropylidene), 1.34 (s, 3H, another CH_3 in isopropylidene), 1.26 (t, J = 7.1 Hz, 3H, OCH$_2$CH_3). ^{13}C NMR (100 MHz, $CDCl_3$) δ [ppm] = 166.31 (C=O), 134.52 (sp^2–C), 129.47 (sp^2–C), 109.98 (ketal *C* in isopropylidene), 75.54, 73.03, 66.96, 61.00, 27.61, 27.43, 26.05, 14.13. HRMS (ESI) calcd. for $[C_{12}H_{18}O_5K]^+$: 281.0791; found: 281.0791. IR (neat) 3462, 2985, 2934, 2911, 1713, 1445, 1376, 1297, 1239, 1163, 1141, 1095, 1059, 1032, 978, 950, 904, 859, 833, 786, 741, 724 cm^{-1}.

Ethyl (3*R*,4*S*,5*S*)-3,4,5-trihydroxy-cyclohex-1-ene-1-carboxylate *ent*-25. Compound **26** (8.001 g, 33.02 mmol) was dissolved in tetrahydrofuran (150 mL) in a round-bottom flask. Concentrated HCl aqueous solution (14 mL, 167.0 mmol, 36.5 % w/w) was diluted with water (10 mL) and then added dropwise at room temperature over 5 min. The solution was further stirred for 8 h. After the reaction was complete (checked by TLC, EtOAc/hexane = 1 : 1), THF was removed by vacuum distillation. The residue was dissolved in ethyl acetate (250 mL). Then powdered K_2CO_3 (11.45 g, 82.84 mmol) was added slowly to neutralize the solution. After the suspension was vigorously stirred for 2 h, the mixture was filtrated by a Buchner funnel and filter cake was twice rinsed with ethyl acetate (20 mL × 2). Then the filtrate was concentrated by vacuum distillation to give a colorless oil, which was purified by flash chromatography (eluent: EtOAc) to afford compound *ent*-**25** (6.010 g, 29.72 mmol) as white solid in 90 % yield. M.p. 135–136 °C. $[\alpha]_D^{25} = -54.2$ (*c* 0.97, MeOH). ^{1}H NMR (400 MHz, DMSO-d_6) δ [ppm] = 6.54–6.47 (m, 1H, H-2), 4.87 (d, J = 7.5 Hz, 1H, OH), 4.76 (d, J = 5.7 Hz, 1H, OH), 4.59 (d, J = 3.7 Hz, 1H, OH), 4.23–4.15 (m, 1H, H-3), 4.12 (q, J = 7.1 Hz, 2H, OCH_2CH$_3$), 3.79–3.73 (m, 1H, H-5), 3.63 (dd, J_1 = 10.0 Hz, J_2 = 5.9 Hz, 1H, H-4), 2.31 (dd, J_1 = 16.8 Hz, J_2 = 5.8 Hz, 1H, H-6), 2.22–2.11 (m, 1H, another H-6), 1.22 (t, J = 7.1 Hz, 3H, OCH$_2$CH_3). ^{13}C NMR (101 MHz, DMSO-d_6) δ [ppm] = 165.89 (*C*O$_2$Et), 140.30 (C-2), 127.82 (C-1), 70.72, 68.13, 67.45, 60.03, 28.79, 14.08. HRMS (ESI) calcd. for $[C_9H_{14}O_5Na]^+$: 225.0739; found: 225.0730. IR (KBr film) 3346, 3176, 2982, 2958, 2919, 2849, 1713, 1441, 1377, 1324, 1248, 1233, 1176, 1156, 1084, 1063, 1030, 949, 917, 896, 879, 799, 735 cm^{-1}.

(−)-5-*epi*-SA 4. Compound *ent*-**25** (3.501 g, 17.31 mmol) and methanol (70 mL) were added into a round-bottom flask with a magnetic stirrer bar, and then NaOH (1.386 g, 34.65 mmol) was added at room temperature. The mixture was heated to 40 °C and further stirred for approximate 10 h. After the reaction was complete(checked by TLC, eluent: EtOAc), methanol was removed by vacuum distillation. The residue was dissolved in water (20 mL), and a dilute aqueous solution of HCl (1 *N*) was added to adjust pH = 4.1–4.4. After water was removed by vacuum distillation, ethanol (50 mL) and activated carbon (1.0 g) were added. The mixture was stirred at room temperature for 10 h. The suspension was filtered by a Buchner funnel and filter cake was rinsed twice with ethanol (2 × 10 mL). Filtrate was concentrated by vacuum distillation to afford crude product as a colorless oil. A column (2 × 20 cm) of Amberlite IR 120 resin (Na^+ form, particle size: 0.600–0.800 mm) was first washed successively with an aqueous solution of HCl (1 mol/L) and water prior to use, and then the crude product was purified by chromatography on the resin column (eluent: pure water) to afford (−)-5-*epi*-SA **4** (2.580 g, 14.81 mmol) as white crystals in 86 % yield. M.p. 108–109 °C. $[\alpha]_D^{25} = -63.5$ (*c* 1.04, H2O). {lit.29 $[\alpha]_D^{20} = -57.6$ (*c* 0.8, MeOH)}. ^{1}H NMR (400 MHz, D_2O) δ [ppm] = 6.66 (d, J = 3.6 Hz, 1H, H-2), 4.48–4.41 (m, 1H, H-3), 4.02 (dd, J_1 = 3.6 Hz, J_2 = 2.8 Hz, 1H, H-4), 3.97 (ddd, J_1 = 4.0 Hz, J_2 = 6.2 Hz, J_3 = 2.8 Hz, 1H, H-5), 2.56 (dd, J_1 = 17.4 Hz, J_2 = 6.2 Hz, 1H, H-6), 2.30–2.18 (m, 1H, another H-6). ^{13}C NMR (100 MHz, D_2O) δ [ppm] = 169.81 (*C*=O), 138.97 (C-2), 128.70 (C-1), 70.53, 68.11, 67.35, 27.54. HRMS (ESI) calcd. for $[C_7H_9O_5]$: 173.0450; found: 173.0449.

Synthesis of (+)-ent-SA ent-1

Ethyl (3*R*,4*S*,5*R*)-5-acetoxy-3,4-isopropylidenedioxy-cyclohex-1-ene-1-carboxylate 27. Compound **7** (15.04 g, 62.08 mmol), triethylamine (9.420 g, 93.09 mmol) and DMAP (760.0 mg, 6.221 mmol) were dissolved in dichloromethane (300 mL). The solution was cooled to 0 °C by an ice bath and then acetic anhydrate (7.610 g, 74.54 mmol) was added dropwise over 10 min. The solution was further stirred at 0 °C for 0.5 h. After the reaction was complete (checked by TLC, EtOAc/hexane = 1 : 2), an aqueous solution of K_2CO_3 (200 mL, 10 % w/w) was added to quench the reaction. Two phases were separated and aqueous solution was extracted with dichloromethane (150 mL) again. The organic extracts were combined and was washed with water (150 mL). Then the solution was dried over anhydrous $MgSO_4$ and then concentrated by vacuum distillation to give crude product as a colorless oil. The crude was purified by flash chromatography (eluent: EtOAc/hexane = 1 : 6) to afford compound **27** (16.24 g, 57.12 mmol, 92 %) as a white solid in 92 % yield. $[\alpha]_D^{25} = -60.7$ (*c* 1.35, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ [ppm] = 6.91–6.85 (m, 1H, H-2), 5.16–5.07 (m, 1H, H-5), 4.71 (dd, J_1 = 5.8 Hz, J_2 = 3.8 Hz, 1H, H-3), 4.24–4.14 (m, 3H, H-4 and OCH_2CH$_3$), 2.76 (dd, J_1 = 17.7 Hz, J_2 = 4.5 Hz, 1H, H-6), 2.35–2.25 (m, 1H, another H-6), 2.05 (s, 3H, CH_3 in Ac), 1.39 (s, 3H, CH_3 in isopropylidene), 1.36 (s, 3H, another CH_3 in isopropylidene), 1.27 (t, J = 7.1 Hz, 3H, OCH$_2$CH_3). ^{13}C NMR (100 MHz, $CDCl_3$) δ [ppm] = 170.16 (*C*=O), 165.83 (*C*=O), 133.79 (sp^2–C), 129.88 (sp^2–C), 109.92 (ketal *C* in isopropylidene), 74.11, 71.90, 69.96, 61.03, 27.77, 26.52, 25.93, 21.08, 14.12. HRMS (ESI) calcd. for $[C_{14}H_{20}O_6Na]^+$: 307.1158; found: 307.1161. IR (neat) 2985, 2936, 1748, 1718, 1446, 1372, 1287, 1237, 1166, 1106, 1060, 1038, 940, 863, 753, 728 cm^{-1}.

Ethyl (3*R*,4*R*,5*R*)-5-acetoxy-3,4-dihydroxy-cyclohex-1-ene-1-carb-oxylate 28. Compound **27** (15.01 g, 52.79 mmol) was dissolved in tetrahydrofuran (300 mL) in a round-bottom flask at room temperature. Concentrated aqueous solution of hydrochloric acid (22 mL, 36.5 % w/w, 262.9 mmol) was diluted with water (20 mL), which was then added dropwise into the flask over 10 min. The solution was further stirred at room temperature for 8 h. After the reaction was complete (checked by TLC, EtOAc), powdered K_2CO_3 (18.17 g, 131.5 mmol) was added slowly to quench the reaction. After the mixture was vigorously stirred for 1 h, tetrahydrofuran was removed by vacuum distillation, ethyl acetate (300 mL) was added into the flask. The suspension was filtrated by a Buchner funnel and filter cake was twice rinsed with ethyl acetate (30 mL × 2). The filtrate was dried over anhydrous $MgSO_4$ and concentrated by vacuum distillation to give a colorless oil, which was purified by flash chromatography (eluent: EtOAc/hexane = 1 : 1) to afford compound **28** (11.60 g, 47.49 mmol) as white solid in 90 % yield. M.p. 92–94 °C. $[\alpha]_D^{25} = -140.1$ (*c* 0.78, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ [ppm] = 6.88–6.79 (m, 1H, H-2), 5.23–5.11 (m, 1H, H-5), 4.40 (m, 1H, H-3), 4.18 (q, J = 7.1 Hz, 2H, OCH_2CH$_3$), 3.93–3.78 (dd, J_1 = 5.8 Hz, J_2 = 4.8 Hz,1H, H-4), 3.52–3.20 (m, 2H, two OH), 2.84 (dd, J_1 = 18.4 Hz, J_2 = 5.0 Hz, 1H, H-6), 2.36–2.24 (m, 1H, another H-6), 2.06 (s, 3H, CH_3 in Ac), 1.27 (t, J = 7.1 Hz, 3H, OCH$_2$CH_3). ^{13}C NMR (101 MHz, $CDCl_3$) δ [ppm] = 171.16 (*C*=O), 166.17 (*C*=O), 136.30 (sp^2–C), 129.76 (sp^2–C), 69.93, 69.32, 66.07, 61.10, 28.21, 21.18, 14.15. HRMS (ESI) calcd. for $[C_{11}H_{16}O_6Na]^+$: 267.0845; found: 267.0841. IR (KBr film) 3281, 2984, 2938, 1718, 1477, 1434, 1373, 1316, 1279, 1235, 1099, 1055, 1037, 931, 830, 796, 752, 684 cm^{-1}.

Ethyl (3*R*,4*S*,5*R*)-5-acetoxy-3,4-bis(methanesulfonyloxy)-cyclo-hex-1-ene-1-carboxylate 13. Compound **28** (10.02 g, 41.03 mmol), triethylamine (16.53 g, 163.4 mmol) and DMAP (1.000 g, 8.206 mmol) were dissolved in dichloromethane (200 mL). The solution was cooled to 0 °C by an ice bath and then methanesulfonyl chloride (14.07 g, 122.8 mmol) was added dropwise over 30 min. Then the solution was further stirred at 0 °C for 2 h. After the reaction was complete (checked by TLC, EtOAc/hexane = 1 : 1), an

aqueous solution of HCl (160 mL, 1 *N*) was added to quench the reaction. Two phases were separated and the organic layer was washed with an aqueous solution of K_2CO_3 (100 mL, 5% w/w). The organic solution was dried over anhydrous $MgSO_4$ and concentrated by vacuum distillation to give crude oily product. The crude product was purified by flash chromatography (eluent: EtOAc/hexane = 1:2) to afford compound **13** (14.60 g, 36.46 mmol) as a colorless oil in 89% yield. $[\alpha]_D^{25} = -126.5$ (*c* 2.21, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ [ppm] = 6.82–6.73 (m, 1H, H-2), 5.50–5.44 (m, 1H, H-3), 5.38–5.29 (m, 1H, H-5), 4.93 (dd, $J_1 = 8.8$ Hz, $J_2 = 3.9$ Hz, 1H, H-4), 4.20 (q, $J = 7.1$ Hz, 2H, OCH_2CH_3), 3.13 (s, 3H, SO_2CH_3), 3.11 (s, 3H, SO_2CH_3), 3.02 (dd, $J_1 = 19.0$ Hz, $J_2 = 5.7$ Hz, 1H, H-6), 2.49–2.34 (dd, $J_1 = 19.0$ Hz, $J_2 = 6.8$ Hz, 1H, another H-6), 2.07 (s, 3H, CH_3 in Ac), 1.27 (t, $J = 7.1$ Hz, 3H, OCH_2CH_3). ^{13}C NMR (101 MHz, $CDCl_3$) δ [ppm] = 169.50 (*C*=O), 164.64 (*C*=O), 133.36 (sp^2–C), 130.04 (sp^2–C), 74.83, 72.70, 66.21, 61.61, 38.84, 38.66, 28.97, 20.91, 14.10. HRMS (ESI) calcd. for $[C_{13}H_{20}O_{10}S_2\ Na]^+$: 423.0396; found: 423.0392. IR (neat) 3029, 2982, 2941, 2878, 2737, 2663, 2529, 2346, 2312, 2108, 1749, 1717, 1467, 1416, 1361, 1254, 1231, 1177, 1139, 1103, 1076, 1047, 973, 905, 852, 769, 749 cm^{-1}.

Ethyl (3*S*,4*S*,5*R*)-3,5-diacetoxy-4-methanesulfonyloxy-cyclohex-1-ene-1-carboxylate 29. Compound **13** (13.20 g, 32.97 mmol) was dissolved in ethyl acetate (70 mL) in a round-bottom flask. AcOH (11.91 g, 198.3 mmol) was dissolved ethyl acetate (60 mL) in another flask, which was cooled to 0 °C by an ice bath, and then *N*,*N*-diisopropyl-ethylamine (6.381 g, 49.37 mmol) was added dropwise. The resulting solution of AcOH/DIPEA (4:1) was then added to the above solution of compound **13**. The reaction solution was heated to reflux and further stirred for 2 h. After the reaction was complete (checked by TLC, EtOAc/hexane = 1:2), the solution was cooled to room temperature. Ethyl acetate (100 mL) and an aqueous solution of K_2CO_3 (200 mL, 15% w/w) were added and the solution was stirred for 5 min. Two phases were separated and aqueous solution was twice extracted with ethyl acetate (100 mL × 2). The organic extracts were combined and dried over anhydrous $MgSO_4$. The solution was concentrated by vacuum distillation to give crude oily product, which was purified by flash chromatography (eluent: EtOAc/hexane = 1:4) to afford compound **29** (10.34 g, 28.38 mmol) as a colorless oil in 86% yield. $[\alpha]_D^{25} = +29.8$ (*c* 0.93, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ [ppm] = 6.63–6.58 (m, 1H, H-2), 5.73–5.66 (m, 1H, H-5), 5.24–5.16 (m, 1H, H-3), 4.91 (dd, $J_1 = 10.3$ Hz, $J_2 = 7.7$ Hz, 1H, H-4), 4.20 (q, $J = 7.1$ Hz, 2H, OCH_2CH_3), 3.09–2.98 (m, 4H, H-6 and SO_2CH_3), 2.47–2.35 (m, 1H, another H-6), 2.12 (s, 3H, CH_3 in Ac), 2.10 (s, 3H, CH_3 in another Ac), 1.27 (t, J = 7.1 Hz, 3H, OCH_2CH_3). ^{13}C NMR (100 MHz, $CDCl_3$) δ [ppm] = 169.96 (*C*=O), 169.87 (*C*=O), 164.68 (*C*=O), 133.19 (sp^2–C), 130.01 (sp^2–C), 78.86, 70.74, 67.61, 61.46, 38.83, 29.71, 20.93, 20.84, 14.14. HRMS (ESI) calcd. for $[C_{14}H_{20}O_9SNa]^+$: 387.0726; found: 387.0719. IR (neat) 3022, 2984, 2941, 2875, 2724, 2663, 2523, 2409, 2347, 2309, 2105, 1749, 1718, 1442, 1358, 1303, 1223, 1177, 1118, 1078, 1047, 1026, 967, 933, 892, 841, 781, 749 cm^{-1}.

Ethyl (3*S*,4*S*,5*R*)-4,5-epoxy-3-hydroxy-cyclohex-1-ene-1-carboxy-late 12. Compound **29** (8.001 g, 21.96 mmol) and concentrated sulfuric acid (440.5 mg, 4.401 mmol, 98% w/w) were dissolved in absolute ethanol (160 mL) at room temperature. Then the solution was heated to reflux and further stirred for 12 h. After the compound **29** disappeared (checked by TLC, EtOAc/hexane = 1:2), the solution was cooled to room temperature. Then powdered anhydrous K_2CO_3 (3.641 g, 26.35 mmol) was added. The mixture was heated to 50 °C and further stirred for 18 h. After the intermediate disappeared (checked by TLC, EtOAc/hexane = 1:1), the suspension was filtrated by a Buchner funnel and the filter cake was twice rinsed with ethanol (10 mL × 2). The filtrate was concentrated by vacuum distillation to give crude product as a pale yellow oil. The crude product was purified by flash chromatography (eluent: EtOAc/hexane = 1:2) to afford a colorless oil, which crystalized spontaneously after standing for several hours to give compound **12** (2.830 g, 15.36 mmol) as white crystals in 70% yield. M.p. 84–86 °C. $[\alpha]_D^{25} = +46.4$ (*c* 1.28, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ [ppm] = 6.71–6.62 (m, 1H, H-2), 4.58–4.47 (m, 1H, H-3), 4.16 (q, $J = 7.1$ Hz, 2H, OCH_2CH_3), 3.53–3.47 (m, 2H, H-4 and O*H*), 3.02–2.93 (m, 1H, H-5), 2.92 (d, $J = 10.3$ Hz, 1H, H-6), 2.48–2.37 (m, 1H, another H-6), 1.25 (t, $J = 7.1$ Hz, 3H, OCH_2CH_3). ^{13}C NMR (100 MHz, $CDCl_3$) δ [ppm] = 166.15 (*C*=O), 135.82 (sp^2–C), 126.61 (sp^2–C), 65.45, 60.94, 54.66, 52.14, 24.23, 14.15. HRMS (ESI) calcd. for $[C_9H_{12}O_4Na]^+$: 207.0633; found: 207.0634. IR (KBr film) 3284, 2993, 2983, 2960, 2926, 1712, 1656, 1476, 1422, 1386, 1367, 1298, 1258, 1204, 1115, 1087, 1027, 983, 927, 900, 872, 850, 745, 694 cm^{-1}

Ethyl (3*S*,4*R*,5*S*)-3,4,5-trihydroxy-cyclohex-1-ene-1-carboxylate 30. Compound **12** (6.000 g, 32.58 mmol) was dissoved in water (120 mL), and then AcOH (96.5 mg, 1.608 mmol) added. The solution was heated to 90 °C and further stirred for 2 h. After the reaction was complete (checked by TLC, EtOAc/hexane = 1:1), the solution was cooled to room temperature. Water was removed by vacuum distillation to give crude product as a white solid. The crude product was triturated with a mixed solvent of ethyl acetate and hexane (EtOAc/hexane = 1:3, v/v). The mixture was filtered by suction and rinsed twice with the above mixed solvent to afford compound **30** (5.731 g, 28.34 mmol) as white crystals in 87% yield. M.p. 74–76 °C. $[\alpha]_D^{25} = +128.6$ (*c* 0.50, MeOH). ^{1}H NMR (400 MHz, DMSO-d_6) δ [ppm] = 6.61 (dd, $J_1 = 3.6$ Hz, $J_2 = 1.6$ Hz, 1H, H-2), 4.88–4.80 (m, 2H, two O*H*), 4.64 (d, $J = 4.3$ Hz, 1H, O*H*), 4.26–4.18 (m, 1H, H-3), 4.11 (q, $J = 7.1$ Hz, 1H, OCH_2CH_3), 3.91–3.81 (m, 1H, H-5), 3.57 (dd, $J_1 = 10.1$ Hz, $J_2 = 4.4$ Hz,1H, H-4), 2.48–2.37 (m, 1H, H-6), 2.11–2.00 (m, 1H, another H-6), 1.21 (t, $J = 7.1$ Hz, 3H, OCH_2CH_3). ^{13}C NMR (101 MHz, DMSO-d_6) δ [ppm] = 166.20 (*C*=O), 139.52 (sp^2–C), 127.53 (sp^2–C), 70.01, 66.76, 65.38, 59.98, 29.58, 14.11. HRMS (ESI) calcd. for $[C_9H_{14}O_5Na]^+$: 225.0739; found: 225.0731. IR (KBr film) 3376, 2987, 2942, 2905, 2680, 2474, 1721, 1449, 1423, 1390, 1370, 1318, 1252, 1184, 1095, 1071, 1056, 1039, 998, 931, 845, 767, 747 cm^{-1}.

(+)-*ent*-SA *ent*-1. Compound **30** (3.800 g, 18.80 mmol) and methanol (75 mL) were added into a round-bottom flask with a magnetic stirrer bar, and then NaOH (1.505 g, 38.63 mmol) was added at room temperature. The mixture was heated to 40 °C and then stirred for approximate 10 h. After the reaction was complete (checked by TLC, eluent: EtOAc), methanol was removed by vacuum distillation. The residue was dissolved in water (20 mL), and a dilute aqueous solution of HCl (1 *N*) was added to adjust pH = 4.1–4.4. After water was removed by vacuum distillation, ethanol (50 mL) and activated carbon (1.0 g) were added. The mixture was stirred at room temperature for 10 h. The suspension was filtered by a Buchner funnel and filter cake was rinsed twice with ethanol (2 × 10 mL). Filtrate was concentrated by vacuum distillation to afford crude product as a colorless oil. A column (2 × 20 cm) of Amberlite IR 120 resin (Na^+ form, particle size: 0.600–0.800 mm) was first washed successively with an aqueous solution of HCl (1 mol/L) and water prior to use, and then the crude product was purified by chromatography on the resin column (eluent: pure water) to afford (+)-*ent*-SA *ent*-**1** (2.846 g, 16.34 mmol) as white crystals in 87% yield. M.p. 183–185 °C (lit.[38] m.p. 183–184 °C for compound **1**). $[\alpha]_D^{25} = +179.7$ (*c* 0.50, H2O). {lit.[38] $[\alpha]_D^{20} = -179.5$ (*c* 0.8, H_2O) for compound **1**}.^{1}H NMR (400 MHz, D_2O) δ [ppm] = 6.77 (d, J = 3.6 Hz, 1H, H-2), 4.42–4.36 (m, 1H, H-3), 3.97 (ddd, 1H, $J_1 = 5.4$ Hz, $J_2 = 4.8$ Hz, $J_3 = 6.3$ Hz, H-5), 3.71 (dd, $J_1 = 8.2$ Hz, $J_2 = 4.8$ Hz, 1H, H-4), 2.67 (dd, $J_1 = 16.5$ Hz, $J_2 = 5.4$ Hz, 1H, H-6), 2.22–2.08 (m, 1H, another H-6). ^{13}C NMR (100 MHz, D_2O) δ [ppm] = 169.97 (*C*=O), 137.22 (sp^2–C), 129.61 (sp^2–C), 71.00, 66.48, 65.69, 30.29. HRMS (ESI) calcd. for $[C_7H_9O_5]$: 173.0450; found: 173.0451. IR (KBr film) 3482, 3386, 3223, 2904, 2882, 2662, 2522, 1682, 1453, 1387, 1351, 1293, 1275, 1239, 1131, 1113, 1092, 1070, 1018, 930, 862, 751, 742 cm^{-1}.

Synthesis of (+)-3-epi-ent-SA ent-2

Ethyl (3*R*,4*S*,5*R*)-3,5-bis(*tert*-butyldimethylsilyloxy)-4-hydroxy-cyclohex-1-ene-1-carboxylate 6. Compound *ent*-**30** (20.05 g, 99.15 mmol), triethylamine (30.10 g, 297.5 mmol) and DMAP (2.423 g, 19.83 mmol) were dissolved in fresh DMF (100 mL), and then *tert*-butyldimethylsilyl chloride (37.35 g, 247.9 mmol) was added slowly. The mixture was further stirred at room temperature for 6 h. After the reaction was complete (checked by TLC, EtOAc/hexane = 1:8), hexane (250 mL) and water (150 mL) were added into the flask. After the solution was stirred for about 5 min, two phases were separated. The aqueous solution was extracted again with hexane (150 mL). The organic extracts were combined and then washed with water (150 mL). After dried over anhydrous $MgSO_4$, the organic solution was concentrated by vacuum distillation to give a colorless oil, which was purified by flash chromatography (eluent: EtOAc/hexane = 1:15) to afford compound **6** (32.04 g, 74.38 mmol) as a colorless oil in 75% yield. $[\alpha]_D^{25} = -65.3$ (*c* 1.30, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ [ppm] = 6.62–6.58 (m, 1H, H-2), 4.55–4.46 (m, 1H, H-3), 4.24–4.12 (m, 3H, H-5 and OCH_2CH_3), 3.72–3.64 (dd, J_1 = 6.8 Hz, J_2 = 5.2 Hz, 1H, H-4), 2.65–2.54 (m, 1H, H-6), 2.25–2.16 (m, 1H, another H-6), 1.28 (t, J = 7.1 Hz, 3H, OCH_2CH_3), 0.91 (s, 9H, *t*-C_4H_9 in TBS), 0.84 (s, 9H, *t*-C_4H_9 in another TBS), 0.13 (s, 3H, $SiCH_3$ in TBS), 0.12 (s, 3H, $SiCH_3$ in TBS), 0.06 (s, 3H, $SiCH_3$ in TBS), 0.05 (s, 3H, $SiCH_3$ in TBS). ^{13}C NMR (100 MHz, $CDCl_3$) δ [ppm] = 166.82 (C=O), 137.04 (sp^2–C), 128.82 (sp^2–C), 70.69, 68.27, 67.61, 60.70, 29.64, 25.85 (three CH_3 in *t*-Bu), 25.74 (three CH_3 in *t*-Bu), 18.20, 18.00, 14.27, −4.55 ($SiCH_3$ in TBS), −4.74 ($SiCH_3$ in TBS), −4.84 ($SiCH_3$ in TBS), −4.90 ($SiCH_3$ in TBS). HRMS (ESI) calcd. for $[C_{21}H_{42}O_5Si_2Na]^+$: 453.2469; found: 453.2462. IR (neat) 3419, 2955, 2931, 2890, 2851, 1718, 1469, 1253, 1094, 1047, 960, 907, 838, 809 cm^{-1}.

Ethyl (3*R*,4*S*,5*R*)-3,5-bis(*tert*-butyldimethylsilyloxy)-4-methane-sulfonyloxy-cyclohex-1-ene-1-carboxylate 31. Compound **6** (20.00 g, 46.43 mmol), pyridine (18.36 g, 232.2 mmol) and DMAP (2.837 g, 23.22 mmol) were dissolved in fresh dichloromethane (300 mL). After the solution was cooled to 0 °C by an ice bath, methanesulfonyl chloride (10.6 g, 93.0 mmol) was added dropwise over 30 min. Then the ice bath was removed and the solution was further stirred at room temperature for 6 h. After the reaction was complete (checked by TLC, EtOAc/hexane = 1:15), an aqueous solution of HCl (200 mL, 2 *N*) was added to quench the reaction. Two phases were separated and the organic layer was washed with an aqueous solution of K_2CO_3 (200 mL, 5% w/w). The organic solution was dried over anhydrous $MgSO_4$ and then concentrated by vacuum distillation to give a colorless oil, which was purified by flash chromatography (eluent: EtOAc/hexane = 1:15) to afford compound **31** (17.55 g, 34.49 mmol) as a colerless oil in 85% yield. $[\alpha]_D^{25} = -69.2$ (*c* 1.51, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ [ppm] = 6.70–6.64 (m, 1H, H-2), 4.80–4.71 (m, 1H, H-3), 4.62–4.53 (m, 1H, H-5), 4.31 (dd, J_1 = 10.2 Hz, J_2 = 4.0 Hz 1H, H-4), 4.20 (q, J = 7.1 Hz, 2H, OCH_2CH_3), 3.05 (s, 3H, CH_3 in Ms), 2.77–2.64 (m, 1H, H-6), 2.35–2.24 (m, 1H, another H-6), 1.29 (t, J = 7.1 Hz, 3H, OCH_2CH_3), 0.92 (s, 9H, *t*-C_4H_9 in TBS), 0.86 (s, 9H, *t*-C_4H_9 in another TBS), 0.15 (s, 3H, $SiCH_3$ in TBS), 0.14 (s, 3H, $SiCH_3$ in TBS), 0.10 (s, 3H, $SiCH_3$ in TBS), 0.09 (s, 3H, $SiCH_3$ in TBS). ^{13}C NMR (100 MHz, $CDCl_3$) δ [ppm] = 166.17 (C=O), 136.89 (sp^2–C), 128.86 (sp^2–C), 80.30, 66.68, 66.10, 60.89, 38.50, 30.79, 25.89, 25.85 (three CH_3 in *t*-Bu), 25.68 (three CH_3 in *t*-Bu), 18.33, 17.90, 14.21, −4.74 ($SiCH_3$ in TBS), −4.78 ($SiCH_3$ in TBS), −4.81 ($SiCH_3$ in TBS), −4.92 ($SiCH_3$ in TBS). IR (neat) 2954, 2931, 2896, 2858, 1718, 1470, 1364, 1250, 1178, 1123, 1101, 1084, 1056, 1003, 964, 918, 840, 779 cm^{-1}.

Ethyl (3*R*,4*S*,5*R*)-3,5-dihydroxy-4-methanesulfonyloxy-cyclohex-1-ene-1-carboxylate 11. Compound **31** (15.01 g, 29.53 mmol) was dissolved in absolute ethanol (100 mL), and then the solution was cooled to 0 °C by an ice bath. Concentrated aqueous solution of hydrochloric acid (12 mL, 143.4 mmol, 36.5% w/w) was diluted with absolute ethanol (50 mL) and then was added dropwise into the flask over 5 min. Then the ice bath was removed and the solution was further stirred at room temperature for 10 h. Atfer the reaction was complete (checked by TLC, EtOAc/hexane = 1:15), ethanol was removed by vacuum distillation. Then ethyl acetate (200 mL) and water (150 mL) were added, and the mixtuer was stirred for a few minutes. Two phases were separated and the aqueous solution was twice extracted with ethyl acetate (150 mL × 2). The organic extracts were combined and dried over anhydrous $MgSO_4$. The solution was concentrated by vacuum distillation to give a colorless oil, which was purified by flash chromatography (eluent: EtOAc/hexane = 1:1) to afford compound **11** (7.950 g, 28.36 mmol) as off-white crystals in 96% yield. M.p. 85–87 °C. $[\alpha]_D^{25} = -112.2$ (*c* 0.63, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ [ppm] = 6.80–6.72 (m, 1H, H-2), 4.67–4.61 (m, 1H, H-4), 4.58 (dd, J_1 = 8.3 Hz, J_2 = 3.9 Hz, 1H, H-3), 4.29–4.20 (m, 1H, H-5), 4.16 (q, J = 7.1 Hz, 2H, OCH_2CH_3), 3.13 (s, 3H, CH_3 in Ms), 2.82 (dd, J_1 = 18.4 Hz, J_2 = 5.3 Hz, 1H, H-6), 2.37–2.23 (m, 1H, another H-6), 1.25 (t, J = 7.1 Hz, 3H, OCH_2CH_3). ^{13}C NMR (100 MHz, $CDCl_3$) δ [ppm] = 166.27 (C=O), 135.20 (sp^2–C), 130.41 (sp^2–C), 82.06, 65.08, 64.51, 61.30, 38.21, 31.24, 14.05. IR (KBr film) 3471, 3049, 3028, 2978, 2959, 2921, 1702, 1345, 1329, 1273, 1254, 1174, 1106, 1066, 1042, 983, 969, 914, 866 cm^{-1}.

Ethyl (3*R*,4*S*,5*R*)-4,5-epoxy-3-hydroxy-cyclohex-1-ene-1-carboxy -late 10. Compound **11** (10.03 g, 35.78 mmol), anhydrous powdered K_2CO_3 (7.418 g, 53.67 mmol) and absolute ethanol (200 mL) were added into a round-bottom flask, the mixture was stirred at room temperature for 15 h. After the reaction was complete (checked by TLC, EtOAc/hexane = 1:1), the suspension was filtrated by a Buchner funnel and the filter cake was rinsed with ethyl acetate (20 mL × 2). The filtrate was concentrated by vacuum distillation to give crude oily product, which was purified by flash chromatography (eluent: EtOAc/hexane = 1:2) to afford compound **10** (6.067 g, 32.94 mmol) as a colorless oil in 92% yield. $[\alpha]_D^{25} = -30.4$ (*c* 0.71, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ [ppm] = 6.76–6.68 (m, 1H, H-2), 4.61–4.52 (m, 1H, H-3), 4.14 (q, J = 7.2 Hz, 2H, OCH_2CH_3), 3.38 (dd, J_1 = 3.9 Hz, J_2 = 2.8 Hz, 1H, H-4), 3.31 (d, J = 7.2 Hz, 1H, O*H*), 3.24–3.20 (m, 1H, H-5), 2.91–2.82 (m, 1H, H-6), 2.64–2.53 (m, 1H, another H-6), 1.24 (t, J = 7.2 Hz, 3H, OCH_2CH_3). ^{13}C NMR (100 MHz, $CDCl_3$) δ [ppm] = 166.71 (C=O), 133.78 (sp^2–C), 126.78 (sp^2–C), 62.78, 61.11, 52.84, 50.71, 24.23, 14.07. IR (neat) 3428, 2986, 2934, 2906, 1715, 1447, 1421, 1368, 1304, 1254, 1094, 1081, 1031, 946, 802, 775 cm^{-1}.

Ethyl (3*R*,4*R*,5*S*)-3,4,5-trihydroxy-cyclohex-1-ene-1-carboxylate *ent*-15. Compound **10** (6.004 g, 32.60 mmol) and AcOH (96.9 mg, 1.630 mmol) were dissolved in water (100 mL). The mixture was stirred at 90 °C for 2 h. After the reaction was complete (checked by TLC, EtOAc/hexane = 1 : 2), water was removed by vacuum distillation to give crude product as a white solid. The crude product was triturated with a mixed solvent of ethyl acetate and hexane (EtOAc/hexane = 1 : 2). The mixture was filtered by suction and rinsed twice by the above mixed solvent to afford compound *ent*-**15** (5.940 g, 29.38 mmol) in 90 % yield. M.p. 110–112 °C. $[\alpha]_D^{25} = +16.9$ (*c* 1.50, MeOH). ^{1}H NMR (400 MHz, DMSO-d_6) δ [ppm] = 6.53 (dd, $J_1 = 2.4$ Hz, $J_2 = 2.6$ Hz, 1H, H-2), 5.17 (d, $J = 6.1$ Hz, 1H, O*H*), 4.98 (d, $J = 4.2$ Hz, 1H, O*H*), 4.85 (d, $J = 4.5$ Hz, 1H, O*H*), 4.11 (q, $J = 7.1$ Hz, 2H, OCH_2CH$_3$), 4.02–3.93 (m, 1H, H-3), 3.52–3.41 (m, 1H, H-5), 3.20 (dd, $J_1 = 9.6$ Hz, $J_2 = 7.6$ Hz, 1H, H-4), 2.61–2.52 (m, 1H, H-6), 2.06–1.94 (m, 1H, another H-6), 1.21 (t, $J = 7.1$ Hz, 3H, OCH$_2$CH_3). ^{13}C NMR (100 MHz, DMSO-d_6) δ [ppm] = 165.75 (*C*=O), 140.58 (sp^2–C), 127.02 (sp^2–C), 76.62, 71.23, 68.46, 60.21, 32.56, 14.05. HRMS (ESI) calcd. for $[C_9H_{14}O_5Na]^+$: 225.0739; found: 225.0729.

(+)-3-*epi*-*ent*-SA *ent*-2. Compound *ent*-**1**5 (3.950 g, 19.53 mmol) and methanol (80 mL) were added into a round-bottom flask with a magnetic stirrer bar, and then NaOH (1.564 g, 39.10 mmol) was added at room temperature. The mixture was heated to 40 °C and then stirred for approximate 10 h. After the reaction was complete (checked by TLC, eluent: EtOAc), methanol was removed by vacuum distillation. The residue was dissolved in water (20 mL), and a dilute aqueous solution of HCl (1 *N*) was added to adjust pH = 4.1–4.4. After water was removed by vacuum distillation, ethanol (50 mL) and activated carbon (1.00 g) were added. The mixture was stirred at room temperature for 10 h. The suspension was filtered by a Buchner funnel and rinsed twice with ethanol (2 × 10 mL). Filtrate was concentrated by vacuum distillation to afford crude product as a colorless oil. A column (2 × 20 cm) of Amberlite IR 120 resin (Na^+ form, particle size: 0.600–0.800 mm) was first washed successively with an aqueous solution of HCl (1 mol/L) and water prior to use, and then the crude product was purified by chromatography on the resin column (eluent: pure water) to afford (+)-3-*epi*-SA *ent*-**2** (2.995 g, 17.20 mmol) as white solid in 88 % yield. M.p. 187–189 °C. $[\alpha]_D^{25} = +30.0$ (*c* 1.05, H_2O). ^{1}H NMR (400 MHz, D_2O) δ [ppm] = 6.57 (dd, $J_1 = 2.6$ Hz, $J_2 = 2.4$ Hz, 1H, H-2), 4.20–4.12 (m, 1H, H-3), 3.66 (ddd, $J_1 = 10.2$ Hz, $J_2 = 6.0$ Hz, $J_3 = 4.2$ Hz, 1H, 1H, H-5), 3.38 (dd, $J_1 = 10.2$ Hz, $J_2 = 8.1$ Hz, 1H, H-4), 2.67 (dd, $J_1 = 17.3$ Hz, $J_2 = 6.0$ Hz, 1H, H-6), 2.16–2.03 (m, 1H, another H-6). ^{13}C NMR (100 MHz, D_2O) δ [ppm] = 169.77 (*C*=O), 139.11 (C-2), 128.20 (C-1), 76.20, 71.49, 68.62, 31.78.

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Conflict of Interest

The authors declare no conflict of interest.

Keywords: Chiral pool · Cyclitol · Shikimic acid · Stereodivergent synthesis · Stereoisomers

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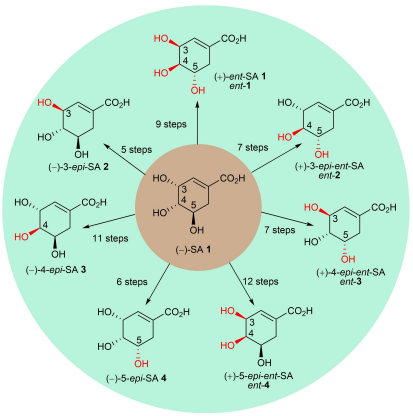
FULL PAPERS

(−)-Shikimic acid [(−)-SA **1**] is a naturally-abundant product from Chinese star anise. All of the seven stereoisomers [i.e. (+)-*ent*-SA *ent*-**1**, (−)-3-*epi*-SA **2**, (+)-3-*epi*-*ent*-SA *ent*-**2**, (−)-4-*epi*-SA **3**, (+)-4-*epi*-*ent*-SA *ent*-**3**, (−)-5-*epi*-SA **4** and (+)-5-*epi*-*ent*-SA *ent*-**4**] have been systematically synthesized from (−)-SA **1**.



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