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Novel Stereoselective Syntheses of (+)-Streptol and (−)-1-*epi*-Streptol Starting from Naturally Abundant (−)-Shikimic Acid

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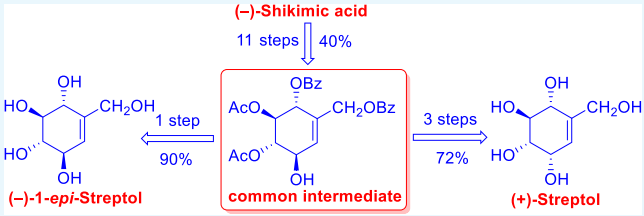
ABSTRACT: Novel highly stereoselective syntheses of (+)-streptol and (−)-1-*epi*-streptol starting from naturally abundant (−)-shikimic acid were described in this article. (−)-Shikimic acid was first converted to the common key intermediate by 11 steps in 40% yield. It was then converted to (+)-streptol by three steps in 72% yield, and it was also converted to (−)-1-*epi*-streptol by one step in 90% yield. In summary, (+)-streptol and (−)-1-*epi*-streptol were synthesized from (−)-shikimic acid by 14 and 12 steps in 29 and 36% overall yields, respectively.



1. INTRODUCTION

C_7-cyclitols are an important category of natural products possessing a broad spectrum of biological activities, so that a lot of natural C_7-cyclitols and their derivatives have become the targets of organic synthesis due to these attractive biological properties.[1] (+)-Streptol [also known as (+)-valienol, **1** in Figure 1] and (−)-1-*epi*-streptol [or (−)-1-*epi*-valienol, **2** in Figure 1] are two members of C_7-cyclitols. (+)-Streptol **1** has been isolated from some microbial organisms[2] such as *Streptomyces* sp. no. 1409,[2a] *Dacthylosporangium aurantiacum* SANK 61299,[2b] and *Streptomyces lincolnensis* DSM 40355.[2c] It has shown plant growth inhibitory activity[2a,b,3] and antitumor activity.[4] (−)-1-*epi*-Streptol **2** is an intermediate involved in the biosyntheses of acarbose and salbostatin (α-glucosidase inhibitors) in *Actinoplanes* and *Streptomyces*.[5] Several total syntheses of (+)-streptol **1** and (−)-1-*epi*-streptol **2** have been reported.[6] (+)-Streptol **1** has been synthesized from (*R*,*R*)-tartaric acid,[6a] D-glucose,[6b,c] D-gluconolactone,[6d,e] and some chiral building blocks.[6f−h] (−)-1-*epi*-Streptol **2** has also been synthesized from D-glucose[6b,i] and D-gluconolactone.[6e] Despite the above-mentioned syntheses, novel practical and efficient syntheses of cyclitols **1** and **2** might be highly desirable to further investigate the biological activities of these two particular C_7-cyclitols and their derivatives.

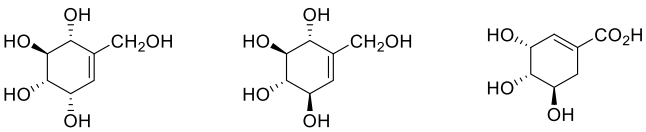


Figure 1. Three related compounds.

(−)-Shikimic acid (see Figure 1) has captured worldwide attention[7] in recent decades due to its wide use in the syntheses of drugs or pharmaceutically valuable molecules (Tamiflu, valiolamine, valienamine, and so on)[8] as well as some chiral building blocks.[9] Many researchers have tried to improve the production of (−)-shikimic acid by means of extraction from plants,[7a,10] fermentation based on microbial engineering,[7c,e,g,11] and chemical syntheses.[7a,12] (−)-Shikimic acid has been found in many plant species.[13] It is noted to be in extremely high abundance in Chinese star anise (*Illicium verum*)[14] and thus can be readily manufactured in a large quantity by extraction from the Chinese star anise due to the development of new methods for rapid and high-yielding extraction.[15] Recently, we have been engaged in developing novel stereoselective syntheses of various pharmaceutically valuable molecules from (−)-shikimic acid.[8a−j] Herein, we want to disclose highly stereoselective, efficient, and practical syntheses of (+)-streptol **1** and (−)-1-*epi*-streptol **2** by commercially available and inexpensive (−)-shikimic acid as the starting material.

2. RESULTS AND DISCUSSION

The novel total syntheses of (+)-streptol **1** and (−)-1-*epi*-streptol **2** starting from (−)-shikimic acid are depicted in Scheme 1. The total syntheses can be briefly described as follows: esterification of (−)-shikimic acid first produced

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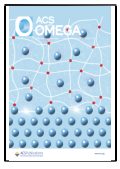

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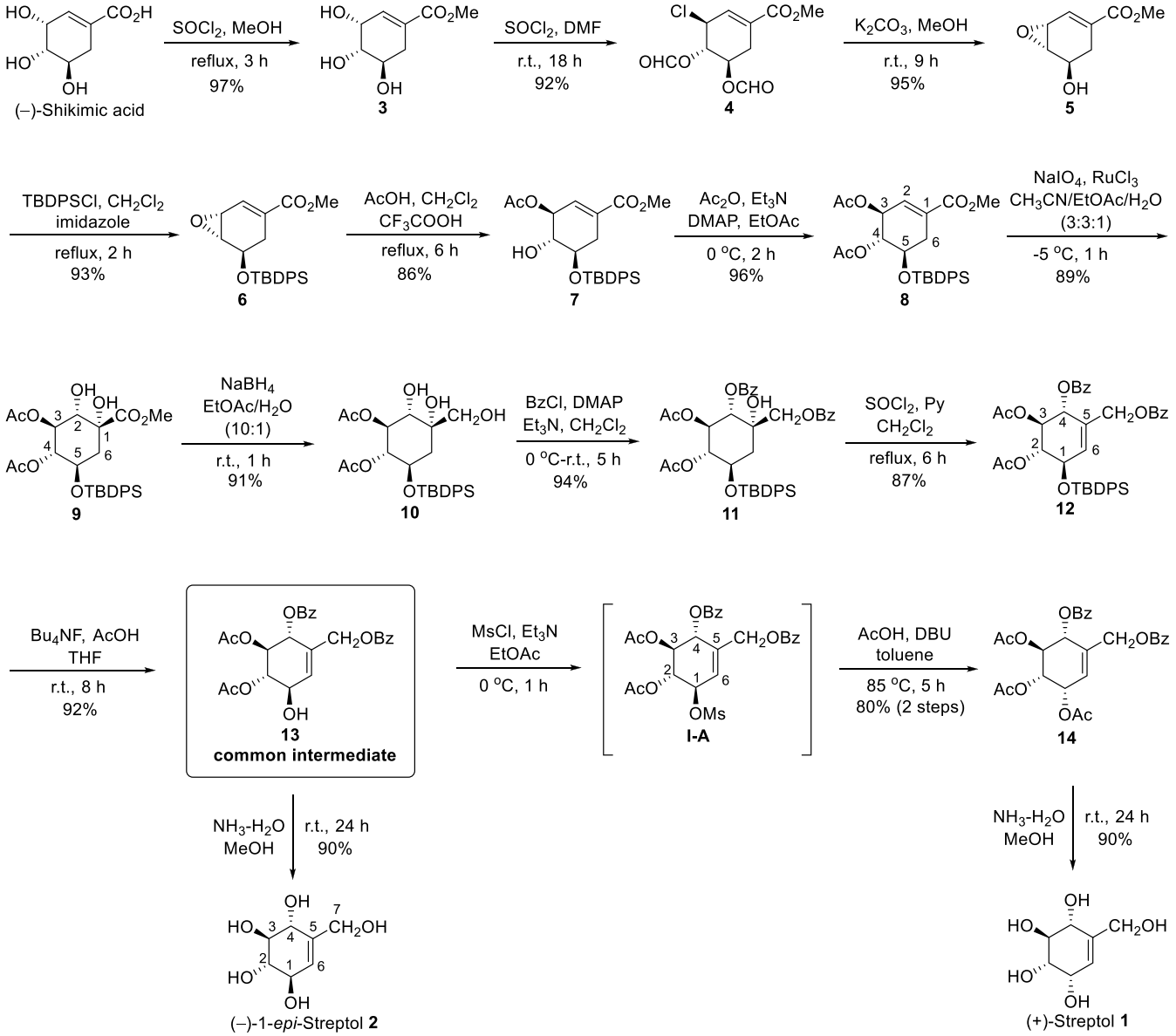
Scheme 1. Total Syntheses of (+)-Streptol 1 and (−)-1-*epi*-Streptol 2 Starting from (−)-Shikimic Acid



methyl (−)-shikimate **3** in 97% yield.[16] Next, when compound **3** was exposed to 5.0 equiv of $SOCl_2$ in anhydrous *N*,*N*-dimethylformamide (DMF) at room temperature (r.t.) for 18 h, compound **4** was thus obtained in 92% yield; the regioselectivity of this chlorination is very high just like a previous report.[8e] Reaction of compound **4** with 2.0 equiv of K_2CO_3 in absolute methanol at room temperature for 9 h furnished epoxide **5** in 95% yield. Protection of the hydroxyl at the C-5 position with the *tert*-butyldiphenylsilyl (TBDPS) group could be achieved by treatment of compound **5** with 1.5 equiv of *tert*-butyldiphenylsilyl chloride and 3.0 equiv of imidazole in CH_2Cl_2 under reflux for 2 h; compound **6** was thus obtained in 93% yield. When compound **6** was treated with 5.0 equiv of AcOH and 0.5 equiv of CF_3COOH in CH_2Cl_2 under reflux for 6 h, high regioselective ring openning of epoxide took place smoothly to give compound **7** in 86% yield, and during this epoxide opening, the nucleophile (AcOH) favorably attacked the more reactive allylic C-3 position rather than the C-4 position. When compound **7** was treated with 1.5 equiv of Ac_2O, 2.0 equiv of Et_3N, and 0.1 equiv of *N*,*N*-dimethylaminopyridine (DMAP) in anhydrous ethyl acetate at 0 °C for 2 h, acylation of the hydroxyl at the C-4 position occurred rapidly to afford compound **8** in 96% yield.

Subsequently, $RuCl_3$-catalyzed highly stereoselective dihydroxylation[17] of *α*,*β*-unsaturated ester **8** produced the desired pinacol **9**. When compound **8** was treated with 0.02 equiv of $RuCl_3$ and 1.5 equiv of $NaIO_4$ in a mixed solvent (CH_3CN/EtOAc/H_2O = 3:3:1) at −5 °C for 1 h, compound **9** could be obtained in 89% yield. During the stereoselective dihydroxylation of compound **8**, the ruthenium catalyst coordinated with the double bond in the opposite direction of the OAc (at C-3) and *o*-*tert*-butyldiphenylsilyl (OTBDPS) (at C-5) groups due to their high steric hindrance, so that two hydroxyls at C-1 and C-2 of compound **9** should have the desired downward orientation. Compound **9** was then exposed to 5.0 equiv of $NaBH_4$ at room temperature for 1 h in a mixed solvent (EtOAc/H_2O = 10:1), the ester group (CO_2Me) at C-1 was selectively reduced, and other two ester groups (two OAc at C-3 and C-4) remained intact during the reaction; compound **10** was thus obtained in 91% yield.

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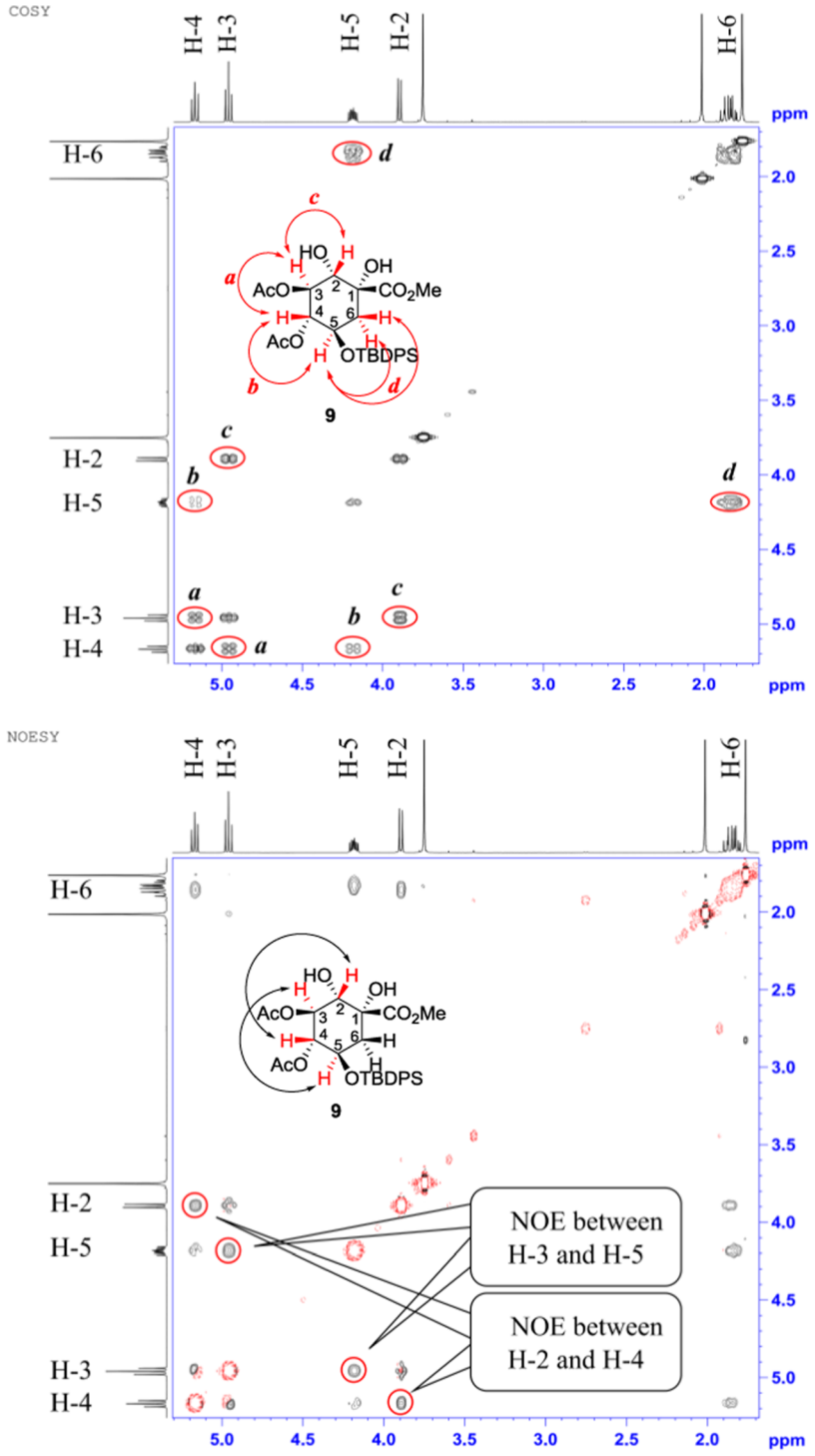

Figure 2. ^{1}H−^{1}H COSY and ^{1}H−^{1}H NOESY spectra of **9**.

Next, when compound **10** was treated with 3.0 equiv of benzoyl chloride, 4.0 equiv of Et_3N, and 0.1 equiv of *p*-dimethylaminopyridine (DMAP) in dichloromethane at 0 °C to room temperature for 5 h, selective benzoylation of primary and secondary hydroxyls occurred smoothly to afford compound **11** in 94% yield; in the meantime, the tertiary hydroxyl in compound **10** remained unchanged during the reaction probably due to its high steric hindrance. Exposure of compound **11** to 5.0 equiv of $SOCl_2$ and 3.0 equiv of pyridine in dichloromethane under reflux for 6 h led to the formation of olefinic compound **12** in 87% yield via regioselective *β*-elimination. The silyl protecting group (TBDPS) was then removed by treatment of compound **12** with 4.5 equiv of Bu_4NF and 4.5 equiv of AcOH in tetrahydrofuran for 8 h at room temperature; compound **13** could be thus obtained in 92% yield.

Compound **13** is a common intermediate for syntheses of targeted molecules **1** and **2**. When compound **13** was treated with a large excess of aqueous ammonia in methanol for 24 h at room temperature, all four acyl groups were removed in the one-pot reaction, and (−)-1-*epi*-streptol **2** was obtained in 90% yield. Next, when compound **13** was exposed to 2.0 equiv of

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methanesulfonyl chloride (MsCl) and 1.5 equiv of Et_3N in ethyl acetate at 0 °C for 1 h, olefinic methanesulfonate **I-A** was formed and was immediately used for the following step without purification due to its unstability. When crude intermediate **I-A** was treated with 6.0 equiv of acetic acid (AcOH) and 3.0 equiv of 1,8-diazabicyclo[5,4,0]undec-7-ene (DBU) in toluene at 85 °C for 5 h according to our previous report,[18] an S_N2-type substitution took place to furnish compound **14** in 80% yield over two steps. The (*R*) configuration of the chiral center at the C-1 position was inversed to an (*S*) configuration during the S_N2-type substitution. Finally, when compound **14** was treated with a large excess of aqueous ammonia in methanol for 24 h at room temperature, all five acyl groups were removed in the one-pot reaction, and (+)-streptol **1** was thus obtained in 90% yield.

In addition, some particular points in the above-described total syntheses (as shown in Scheme 1) are worthy to be further discussed in the following.

First, in the $RuCl_3$-catalyzed highly stereoselective dihydroxylation of *α,β*-unsaturated ester **8**, the stereochemistry of product **9** has been unequivocally confirmed by the two-dimensional (2D) NMR technique. $^1H-^1H$ correlation spectroscopy (COSY) and $^1H-^1H$ nuclear Overhauser effect (NOE) spectroscopy (NOESY) spectra of compound **9** are shown in Figure 2. As can be seen from the $^1H-^1H$ COSY spectrum of compound **9**, the dd peak at 5.18 ppm could be assigned to proton H-4, which has correlation spots (***a*** and ***b***) with protons H-3 and H-5; the dd peak at 4.96 ppm could be assigned to proton H-3, which has correlation spots (***c*** and ***a***) with protons H-2 and H-4; the m peak at 4.19 ppm could be assigned to proton H-5, which has correlation spots (***b*** and ***d***) with protons H-4 and H-6; the d peak at 3.94 ppm could be assigned to proton H-2, which only has a correlation spot (***c***) with proton H-3; and the m peak at 1.86 ppm could be assigned to proton H-6, which only has a correlation spot (***d***) with proton H-5. As can be seen from the $^1H-^1H$ NOESY spectrum of compound **9**, there are obvious NOE correction spots between H-3 and H-5, meaning that protons H-3 and H-5 have the cis relationship, there are obvious NOE correction spots between H-2 and H-4, and also there is no correction spot between H-2 and H-5, meaning that protons H-2 and H-4 have the cis relationship and that protons H-2 and H-5 have the trans relationship, so the chiral center at C-2 of compound **9** has an (*S*) configuration. According to the mechanism of Ru-catalyzed dihydroxylation of olefins,[17b] two hydroxyls at C-1 and C-2 positions in compound **9** should have the cis relationship, so the chiral center at C-1 of compound **9** has an (*R*) configuration.

Second, it is worth noting that chemoselectivity for the reduction of compound **9** with $NaBH_4$ was very high; a reasonable explanation for the high chemoselectivity of the reduction of compound **9** to compound **10** is proposed in Figure 3 according to the literature.[19] The *α*-hydroxy group of CO_2Me in compound **9** first reacted with $NaBH_4$ to produce intermediate complex **I-B,** and then, it underwent intramolecular reduction of the methyl ester group (CO_2Me) to lead to the desired compound **10**.

Third, as can be seen from Tables 1 and 2, ^1H and ^{13}C NMR data of the samples of (+)-streptol **1** and (−)-1-*epi*-streptol **2** from present syntheses shown in Scheme 1 are consistent with the literature data for authentic samples.[2a,6g] (Note that $^1H/^{13}C$ NMR data of the authentic sample of compound **1** were published by Sakuda et al. in 1987[2a] and $^1H/^{13}C$ data of the authentic sample of compound **2** were published by Leermann et al. in 2010.[6g])

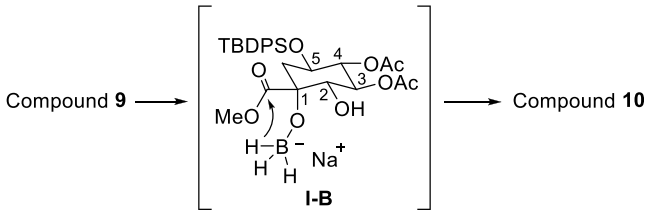

Figure 3. Chemoselective reduction of **9** with $NaBH_4$.

Table 1. Comparison between $^1H/^{13}C$ NMR Data (*δ* ppm) of the Synthetic and Authentic Samples of (+)-Streptol 1[a]

	synthetic sample		authentic sample	
positions	^1H NMR	^{13}C NMR	^1H NMR	^{13}C NMR
1	4.30	68.3	4.33	68.3
2	3.58	72.9	3.61	72.9
3	3.71	74.4	3.73	74.3
4	4.09	74.7	4.11	74.4
5		144.3		144.3
6	5.85	124.3	5.88	122.4
7	4.15 (**7a**)	63.4	4.17 (**7a**)	63.5
	4.24 (**7b**)		4.26 (**7b**)	

[a]D_2O was used as the solvent.

Table 2. Comparison between $^1H/^{13}C$ NMR Data (*δ* ppm) of the Synthetic and Authentic Samples of (−)-1-*epi*-Streptol 2[ab]

	synthetic sample		authentic sample	
positions	^1H NMR	^{13}C NMR	^1H NMR	^{13}C NMR
1	4.10 (m)	71.3	4.17 (m)	73.6
2	3.36	71.9	3.43	74.2
3	3.42	75.1	3.49	77.4
4	4.10 (m)	75.5	4.17 (m)	77.8
5		138.3		140.6
6	5.51	124.9	5.58	127.2
7	3.99 (**7a**)	61.0	4.06 (**7a**)	63.3
	4.10 (m) (**7b**)		4.17 (m) (**7b**)	

[a]D_2O was used as the solvent. [b]The same difference (0.07 ppm) of the *δ* value for each proton between ^1H NMR spectra of synthetic and authentic samples might result from a zero-point calibration error.

3. CONCLUSIONS

In conclusion, we have performed stereoselective total syntheses of (+)-streptol [(+)-valienol] **1** and (−)-1-*epi*-streptol [(−)-1-*epi*-valienol] **2** starting from the naturally abundant (−)-shikimic acid. (+)-Streptol **1** has been synthesized starting from the naturally abundant (−)-shikimic acid in 14 steps in 29% overall yield; (−)-1-*epi*-streptol **2** has also been synthesized starting from (−)-shikimic acid in 12 steps in 36% overall yield. Moreover, the stereochemistry of key intermediate compound **9** has been unequivocally confirmed by analyses of its $^1H-^1H$ COSY and $^1H-^1H$ NOESY spectra (see Figure 2).

Compared with the known syntheses of (+)-streptol **1** and (−)-1-*epi*-streptol **2**,[6] present total syntheses, albeit with moderate overall yields, are more economic and practical because none of the expensive reagents such as lithium diisopropylamide (LDA),[6e] diisobutylaluminum hydride

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(DIBAL-H),[6a,h] K-selectride[6b,e] LiHMDS,[6i] TBSOTf,[6f] and excessive $Ag(OAc)_2$[6g] were used and also none of the drastic reaction conditions such as Ph_2O/230 °C,[6f] LDA/−78 °C,[6c,e] $(COCl)_2$/dimethyl sulfoxide (DMSO)/−78 °C,[6d] trifluoroacetic anhydride (TFAA)/DMSO/−78 °C,[6c,i] and DIBAL-H/−78 °C[6a,h] were used in every step.

4. EXPERIMENTAL SECTION

4.1. General Method. ^{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. IR spectra were recorded with a Nicolet Magna IR-550 instrument. Mass spectra were acquired with an HP1100 LC-MS spectrometer. Optical rotations of chiral compounds were measured on a PerkinElmer polarimeter at room temperature. Melting points were determined on a Mel-TEMP II apparatus. Column chromatography was performed on silica gel (Qingdao Ocean Chemical Corp.). Methyl shikimate **3** was prepared in 97% yield according to a known procedure.[16]

4.2. Methyl (3*S*,4*S*,5*R*)-3-Chloro-4,5-bis(formyloxy)-cyclohex-1-ene-1-carboxylate 4. $SOCl_2$ (63.42 g, 533.1 mmol) was dropwise added to anhydrous DMF (120 mL) at room temperature for 15 min. The resulting solution was cooled to 5 °C by an ice bath, and then, the crushed methyl shikimate 3 (20.06 g, 106.6 mmol) was slowly added in portions. After the addition was finished, the ice bath was removed, and the solution was further stirred at room temperature for 18 h. The reaction solution was poured into stirred biphasic solvents of toluene (500 mL) and ice-water (600 mL). After the above well-stirred biphasic mixture was put into an ice bath, powered K_2CO_3 (148.0 g, 1.071 mol) was slowly added until the pH was adjusted to 8−9. The biphasic mixture was transferred into a separatory funnel, two phases were separated, and the aqueous phase was extracted again with toluene (200 mL). The extracts were combined and dried over anhydrous $MgSO_4$. Evaporation of toluene under vacuum gave an oily crude product that was purified by flash chromatography (eluent, EtOAc/hexane = 1:5) to furnish compound **4** (25.76 g, 98.08 mmol) as colorless oil in 92% yield. $[\alpha]_D^{25}$ = +28.3 (*c* 1.0, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.45−2.54 (m, 1H, H-6), 3.04 (dd, J_1 = 17.8 Hz, J_2 = 5.7 Hz, 1H, another H-6), 3.77 (s, 3H, OCH_3), 4.68 (dd, J_1 = 2.5 Hz, J_2 = 8.1 Hz, 1H, H-3), 5.16−5.24 (m, 1H, H-5), 5.47 (dd, J_1 = 9.5 Hz, J_2 = 8.1 Hz, 1H, H-4), 6.79 (d, J = 2.5 Hz, 1H, H-2), 8.03 (s, 1H, OCHO), 8.14 (s, 1H, another OCHO). ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.14, 159.65, 159.39, 135.17, 128.81, 73.25, 67.94, 55.53, 52.48, 29.13. High-resolution mass spectrometry (HRMS) (electrospray ionization (ESI)) calcd for $C_{10}H_{11}O_6NaCl$ $[M + Na]^+$: 285.0142, found: 285.0140. IR (neat) ν 2955, 1728, 1377, 1254, 1171, 1077, 752 cm^{-1}.

4.3. Methyl (3*R*,4*S*,5*R*)-3,4-Epoxy-5-hydroxy-cyclohex-1-ene-1-carboxylate 5. Compound **4** (10.05 g, 38.26 mmol) was dissolved in anhydrous methanol (100 mL), and powered K_2CO_3 (10.58 g, 76.55 mmol) was added. The reaction mixture was allowed to be stirred at room temperature for 9 h. When the reaction was finished (checked by thin-layer chromatography (TLC); eluent, EtOAc/hexane = 1:3), the potassium salt was filtered by suction, and the filtrate was concentrated under vacuum to give an oily residue, which was partitioned between ethyl acetate (200 mL) and water (30 mL). Two phases were separated, and the aqueous solution was extracted twice with ethyl acetate (50 × 2 mL). Organic extracts were combined and dried over anhydrous $MgSO_4$. Removal of the solvent by vacuum distillation gave an oily crude product that was purified by flash chromatography (eluent, EtOAc/hexane = 1:3) to furnish compound **5** (6.186 g, 36.35 mmol) as colorless oil in 95% yield. $[\alpha]_D^{25}$ = +227.8 (*c* 1.0, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.20 (ddd, J_1 = 17.5 Hz, J_2 = 5.2 Hz, J_3 = 3.3 Hz, 1H, H-6), 2.68 (dd, J_1 = 17.5 Hz, J_2 = 3.0 Hz, 1H, another H-6), 3.04 (d, J = 5.6 Hz, 1H, OH), 3.45−3.37 (m, 1H, H-5), 3.48 (dd, J_1 = 4.6 Hz, J_2 = 3.5 Hz, 1H, H-4), 3.68 (s, 3H, OCH_3), 4.44−4.48 (m, 1H, H-3), 7.04 (dd, J_1 = 3.7 Hz, J_2 = 3.3 Hz, 1H, H-2). ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.83, 133.59, 130.66, 63.04, 56.01, 52.16, 46.35, 29.11. HRMS (ESI) calcd for $C_8H_{10}O_4Na$ $[M + Na]^+$: 193.0477, found: 193.0475. IR (neat) ν 3421, 2954, 1715, 1645, 1439, 1268, 1096, 1005 cm^{-1}.

4.4. Methyl (3*R*,4*S*,5*R*)-5-(*tert*-Butyldiphenylsilyloxy)-3,4-epoxy-cyclohex-1-ene-1-carboxylate 6. Compound **5** (5.013 g, 29.46 mmol) was dissolved in CH_2Cl_2 (50 mL), TBDPSCl (12.15 g, 44.20 mmol) and imidazole (6.017 g, 88.38 mmol) were then added. The resulting solution was heated to reflux (41 °C) and further stirred for 2 h. After the reaction was complete (ckecked by TLC; eluent, EtOAc/hexane = 1:5), the solution was concentrated under vacuum to remove dichloromethane, and then ethyl acetate (60 mL) and an aqueous solution of potassium carbonate (15% w/w, 50 mL) were added. After the mixture was vigorously stirred for 15 min at room temperature, two phases were separated, and the aqueous solotion was extracted again with ethyl acetate (50 mL). Organic extracts were combined and dried over anhydrous $MgSO_4$. Removal of the solvent by vacuum distillation gave an oily crude product that was purified by flash chromatography (eluent, EtOAc/hexane = 1:7) to furnish compound **6** (11.20 g, 27.41 mmol) as colorless oil in 93% yield. $[\alpha]_D^{25}$ = +113.5 (*c* 1.0, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.03 (s, 9H, *t*-Bu), 2.09 (ddd, J_1 = 17.2 Hz, J_2 = 4.9 Hz, J_3 = 3.2 Hz, 1H, H-6), 2.73 (dd, J_1 = 17.2 Hz, J_2 = 2.0 Hz, 1H, another H-6), 3.35 (ddd, J_1 = 4.9 Hz, J_2 = 2.7 Hz, J_3 = 2.0 Hz, 1H, H-5), 3.44 (dd, J_1 = 4.5 Hz, J_2 = 2.7 Hz, 1H, H-4), 3.75 (s, 3H, OCH_3), 4.52 (dd, J_1 = 4.5 Hz, J_2 = 2.4 Hz, 1H, H-3), 7.16 (dd, J_1 = 4.5 Hz, J_2 = 3.2 Hz, 1H, H-2), 7.35−7.47 (m, 6H, Ph-H), 7.61−7.69 (m, 4H, Ph-H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.59, 135.77 (2C), 135.72 (2C), 133.65, 133.39, 133.15, 131.30, 129.95, 129.93, 127.81 (2C), 127.76 (2C), 64.98, 56.15, 51.98, 46.79, 29.14, 26.87 (3C), 19.24. HRMS (ESI) calcd for $C_{24}H_{28}O_4SiNa$ $[M + Na]^+$: 431.1655, found: 431.1652. IR (neat) ν 3071, 2955, 2931, 2858, 1719, 1647, 1429, 1263, 1109, 1094, 1008, 938, 823, 705, 611, 508 cm^{-1}.

4.5. Methyl (3*S*,4*R*,5*R*)-5-(*tert*-Butyldiphenylsilyloxy)-3-acetoxy-4-hydroxyl-cyclohex-1-ene-1-carboxylate 7. Compound **6** (10.15 g, 24.84 mmol) was first dissolved in dichloromethane (100 mL), and AcOH (7.458 g, 124.2 mmol) and CF_3COOH (1.416 g, 12.42 mmol) were then added. The resulting solution was heated to reflux (41 °C), and further stirred under reflux for 6 h. After the reaction was complete (checked by TLC; eluent, EtOAc/hexane = 1:4), dichloromethane was removed by vacuum distillation. Ethyl acetate (120 mL) and an aqueous solution of potassium carbonate (20% w/w, 100 mL) were added. After the mixture was vigorously stirred for 15 min at room temperature, two phases were separated, and the aqueous solution was extracted twice with ethyl acetate (2×100 mL). Organic extracts were combined and dried over anhydrous $MgSO_4$. Removal of the solvent by vacuum distillation gave an oily crude product that

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was purified by flash chromatography (eluent, EtOAc/hexane = 1:4) to give compound **7** (10.01 g, 21.36 mmol) as colorless oil in 86% yield. $[\alpha]_D^{25}$ = +28.2 (*c* 1.0, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.09 (s, 9H, *t*-Bu), 2.10 (s, 3H, CH_3 in Ac), 2.25−2.35 (m, 1H, H-6), 2.51−2.59 (m, 1H, another H-6), 3.67 (s, 3H, OCH_3), 3.80−3.89 (m, 2H, H-4 and H-5), 5.34 (dd, J_1 = 2.8 Hz, J_2 = 4.2 Hz, 1H, H-3), 6.53 (dd, J_1 = 2.8 Hz, J_2 = 2.6 Hz, 1H, H-2), 7.36−7.48 (m, 6H, Ph-H), 7.66−7.73 (m, 4H, Ph-H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.67, 166.02, 135.93 (2C), 135.67 (2C), 134.48, 133.12, 133.04, 130.09, 129.98, 127.99, 127.86 (2C), 127.84 (2C), 74.57, 73.54, 71.63, 52.05, 32.59, 27.00 (3C), 21.02, 19.32. HRMS (ESI) calcd for $C_{26}H_{32}O_6SiNa$ $[M + Na]^+$: 491.1866, found: 491.1860. IR (neat) ν 3500, 3071, 2954, 2933, 2858, 1723, 1659, 1430, 1373, 1235, 1112, 1088, 970, 823, 705, 612, 506 cm^{-1}.

4.6. Methyl (3*S*,4*R*,5*R*)-5-(*tert*-Butyldiphenylsilyloxy)-3,4-diacetoxy-cyclohex-1-ene-1-carboxylate 8. Compound **7** (9.986 g, 21.31 mmol), Et_3N (4.313 g, 42.62 mmol), and DMAP (260.5 mg, 2.132 mmol) were dissolved in anhydrous ethyl acetate (100 mL), and the solution was then cooled to 0 °C by an ice bath. Ac_2O (3.265 g, 31.98 mmol) was then dropwise added for 10 min. The mixture was further stirred at 0 °C for 2 h. After the reaction was complete (checked by TLC; eluent, EtOAc/hexane = 1:5), an aqueous solution of HCl (2 N, 50 mL) was added to quench the reaction. After the mixture was vigorously stirred for 5 min, the two phases were separated by a separatory funnel. The aqueous solution was extracted again with ethyl acetate (50 mL). Organic extracts were combined, washed with an aqueous solution of potassium carbonate (15% w/w, 50 mL), and then dried over anhydrous $MgSO_4$. Removal of the solvent by vacuum distillation gave an oily crude product that was purified by flash chromatography (eluent, EtOAc/hexane = 1:6) to furnish compound **8** (10.45 g, 20.46 mmol) as white crystals in 96% yield; mp 88−90 °C. $[\alpha]_D^{25}$ = +34.5 (*c* 1.0, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.05 (s, 9H, *t*-Bu), 1.79 (s, 3H, CH_3 in Ac), 2.04 (s, 3H, CH_3 in another Ac), 2.34−2.45 (m, 1H, H-6), 2.56 (dd, J_1 = 17.8 Hz, J_2 = 5.8 Hz, 1H, another H-6), 3.69 (s, 3H, OCH_3), 4.03 (dd, J_1 = 9.0 Hz, J_2 = 5.8 Hz, J_3 = 5.6 Hz, 1H, H-5), 5.27 (dd, J_1 = 9.0 Hz, J_2 = 7.2 Hz, 1H, H-4), 5.41 (dd, J_1 = 7.2 Hz, J_2 = 5.4 Hz, 1H, H-3), 6.55 (dd, J_1 = 2.2 Hz, J_2 = 5.4 Hz, 1H, H-2), 7.35−7.46 (m, 6H, Ph-H), 7.62−7.71 (m, 4H, Ph-H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.39, 170.22, 165.88, 136.00 (2C), 135.72 (2C), 133.76, 133.07, 130.20, 130.00, 129.78, 127.78 (2C), 127.66 (2C), 74.27, 71.50, 68.46, 52.12, 32.64, 26.78 (3C), 20.92, 20.89, 19.21. HRMS (ESI) calcd for $C_{28}H_{34}O_7SiNa$ $[M + Na]^+$: 533.1971, found: 533.1973. IR (KBr film) ν 3072, 2955, 2930, 2857, 1750, 1723, 1657, 1430, 1367, 1240, 1112, 1061, 974, 822, 705, 610, 506 cm^{-1}.

4.7. (1*R*,2*S*,3*S*,4*R*,5*R*)-5-(*tert*-Butyldiphenylsilyloxy)-3,4-diacetoxy-1,2-dihydroxy-1-methoxycarbonyl-cyclohexane 9. Sodium periodate (4.412 g, 20.63 mmol), ruthenium trichloride (57.0 mg, 0.275 mmol), and water (10 mL) were added into a round-bottomed flask that was equipped with a stirrer bar. The mixture was stirred at room temperature for 15 min, and the color changed to bright yellow. Compound **8** (7.022 g, 13.75 mmol) was dissolved in a mixed solvent of ethyl acetate (30 mL) and acetonitrile (30 mL), and the resulting solution was cooled to −5 °C by a salt ice bath. The above bright yellow aqueous viscous solution was added, and the mixture was further stirred at −5 °C for 1 h. After the reaction was complete (checked by TLC; eluent, EtOAc/hexane = 1:3), ethyl acetate (100 mL) and a saturated aqueous solution of $Na_2S_2O_3$ (80 mL) were added. The mixture was vigorously stirred for 15 min, and then, the two phases were separated by a separatory funnel. The aqueous solution was extracted twice with ethyl acetate (2 × 80 mL). Organic extracts were combined, washed with brine (20 mL), and then dried over anhydrous $MgSO_4$. The organic solution was concentrated under vacuum to give the crude product, which was then purified by flash chromatography (eluent, EtOAc/hexane = 1:2) to afford compound **9** (6.667 g, 12.24 mmol) as white crystals in 89% yield; mp 133−134 °C. $[\alpha]_D^{25}$ = −24.9 (*c* 1.0, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.01 (s, 9H, *t*-Bu), 1.77 (s, 3H, CH_3 in Ac), 1.79−1.88 (m, 2H, two H-6), 2.02 (s, 3H, CH_3 in another Ac), 2.51 (s, 1H, OH), 3.36 (s, 1H, another OH), 3.76 (s, 3H, OCH_3), 3.90 (d, J = 9.7 Hz, 1H, H-2), 4.14−4.23 (m, 1H, H-5), 4.96 (dd, J_1 = 9.9 Hz, J_2 = 9.8 Hz, 1H, H-4), 5.17 (dd, J_1 = 9.8 Hz, J_2 = 9.7 Hz, 1H, H-3), 7.34−7.46 (m, 6H, Ph-H), 7.58−7.67 (m, 4H, Ph-H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.73, 171.44, 170.20, 135.86 (2C), 135.71 (2C), 133.26, 133.21, 129.94, 129.81, 127.73 (2C), 127.65 (2C), 75.75, 75.38, 73.94, 73.78, 68.68, 53.55, 38.82, 26.75 (3C), 20.84, 20.79, 19.19. HRMS (ESI) calcd for $C_{28}H_{36}O_9SiNa$ $[M + Na]^+$: 567.2026, found: 567.2025. IR (KBr film) ν 3490, 3072, 2957, 2934, 2858, 1746, 1429, 1367, 1243, 1113, 1047, 826, 705, 608, 504 cm^{-1}.

4.8. (1*S*,2*S*,3*S*,4*R*,5*R*)-3,4-Diacetoxy-1,2-dihydroxy-1-hydroxymethyl-5-(*tert*-butyldiphenylsilyloxy)-cyclohexane 10. Compound **9** (5.447 g, 10.00 mmol) was dissolved in ethyl acetate (60 mL), and water (6 mL) was added. While the mixture was well stirred, $NaBH_4$ (1.895 g, 50.09 mmol) was added in portions for 15 min at room temperature. After the addition was finished, the mixture was further stirred for 1 h. Ethyl acetate (60 mL) and water (50 mL) were added, and the biphasic mixture was vigorously stirred for 5 min. Two phases were separated, and the aqueous phase was extracted again with ethyl acetate (60 mL). Organic extracts were combined and dried over anhydrous $MgSO_4$. The organic solution was concentrated under vacuum to give the crude product, which was then purified by flash chromatography (eluent, EtOAc/hexane = 1:2) to afford compound **10** (4.705 g, 9.107 mmol) as white crystals in 91% yield; mp 174−176 °C. $[\alpha]_D^{25}$ = −14.7 (*c* 1.0, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.01 (s, 9H, *t*-Bu), 1.40 (dd, J_1 = 13.8 Hz, J_2 = 9.2 Hz, 1H, H-6), 1.72 (dd, J_1 = 13.8 Hz, J_2 = 5.0 Hz, 1H, another H-6), 1.77 (s, 3H, CH_3 in Ac), 1.99 (s, 3H, CH_3 in another Ac), 2.90 (br. s, 1H, OH), 3.04 (br. s, 1H, OH), 3.30 (dd, J_1 = 11.2 Hz, J_1 = 6.0 Hz, 1H, C*H*HOH), 3.43 (dd, J_1 = 11.2 Hz, J_2 = 3.5 Hz, 1H, CH*H*OH), 3.52 (d, J = 6.0 Hz, 1H, OH), 3.62 (dd, J_1 = 9.3 Hz, J_2 = 5.7 Hz, 1H, H-2), 4.18−4.26 (m, 1H, H-5), 4.96 (dd, J_1 = 8.8 Hz, J_2 = 8.5 Hz, 1H, H-4), 5.04 (dd, J_1 = 9.3 Hz, J_2 = 8.5 Hz, 1H, H-3), 7.32−7.44 (m, 6H, Ph-H), 7.59−7.68 (m, 4H, Ph-H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.89, 170.44, 135.91 (2C), 135.74 (2C), 133.53, 133.48, 129.89, 129.74, 127.72 (2C), 127.63 (2C), 75.86, 74.47, 74.36, 72.19, 72.18, 68.48, 37.91, 26.79 (3C), 20.93, 20.82, 19.19. HRMS (ESI) calcd for $C_{27}H_{36}O_8SiNa$ $[M + Na]^+$: 527.2077, found: 527.2071. IR (KBr film) ν 3572, 3493, 3072, 2952, 2932, 2860, 1734, 1709, 1428, 1379, 1234, 1112, 1049, 823, 706, 608, 512 cm^{-1}.

4.9. (1*S*,2*S*,3*R*,4*R*,5*R*)-2-Benzoyloxy-1-benzoyloxymethyl-5-(*tert*-butyldiphenylsilyloxy)-3,4-diacetoxy-1-hydroxy-cyclohexane 11. Compound **10** (4.000 g, 7.742

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mmol) was dissolved in dichloromethane (50 mL), and the solution was cooled to 0 °C by an ice bath. Et_3N (3.134 g, 30.97 mmol), DMAP (95.0 mg, 0.778 mmol), and BzCl (3.265 g, 23.23 mmol) were added in turn. After the addition was finished, the ice bath was removed, and the mixture was further stirred at room temperature for 5 h. When the reaction was complete (checked by TLC; eluent, EtOAc/hexane = 1:3), dichloromethane was removed by vacuum distillation. Ethyl acetate (120 mL) and an aqueous solution of potassium carbonate (15% w/w, 50 mL) were added, and the biphasic mixture was vigorously stirred for 2 h. Two phases were separated, and aqueous phase was extracted again with ethyl acetate (60 mL). Organic extracts were combined and successively washed with an aqueous solution of HCl (2 N, 30 mL) and brine (15 mL). The organic solution was dried over anhydrous $MgSO_4$ and then concentrated under vacuum to give the crude product, which was purified by flash chromatography (eluent, EtOAc/hexane = 1:4) to afford compound **11** (5.276 g, 7.278 mmol) as white crystals in 94% yield; mp 127−128 °C. $[\alpha]_D^{25}$ = −20.2 (*c* 1.0, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$) δ 1.04 (s, 9H, *t*-Bu), 1.70−1.80 (m, 1H, H-6), 1.81 (s, 3H, CH_3 in Ac), 1.85 (s, 3H, CH_3 in another Ac), 2.00 (dd, J_1 = 13.9 Hz, J_2 = 5.0 Hz, 1H, another H-6), 2.45 (br. s, 1H, OH), 3.99 (d, *J* = 11.6 Hz, 1H, C*H*HOBz), 4.16 (d, *J* = 11.6 Hz, 1H, CH*H*OBz), 4.38 (ddd, J_1 = 10.0 Hz, J_2 = 5.2 Hz, J_3 = 5.0 Hz, 1H, H-5), 5.29 (dd, J_1 = 10.0 Hz, J_2 = 10.1 Hz, 1H, H-4), 5.43 (d, *J* = 9.9 Hz, 1H, H-2), 5.51 (dd, J_1 = 10.1 Hz, J_2 = 9.9 Hz, 1H, H-3), 7.28−7.46 (m, 10H, Ph-H), 7.52 (t, *J* = 7.8 Hz, 2H, *para*-H in Bz), 7.66 (t, *J* = 7.8 Hz, 4H), 7.81 (d, *J* = 7.8 Hz, 2H, *meta*-H in Bz), 7.89 (d, *J* = 7.8 Hz, 2H, *ortho*-H in Bz). ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.16, 170.15, 166.18, 165.25, 135.88 (2C), 135.76 (2C), 133.59 (2C), 133.44, 133.26, 129.93 (2C), 129.81 (2C), 129.66, 129.10, 128.73 (2C), 128.58 (2C), 128.35 (2C), 127.71 (2C), 127.66 (2C), 75.86, 73.97, 72.37, 71.21, 68.24, 68.08, 38.53, 26.78 (3C), 20.83, 20.54, 19.20. HRMS (ESI) calcd for $C_{41}H_{44}O_{10}SiNa$ $[M + Na]^+$: 747.2601, found: 747.2598. IR (KBr film) ν 3474, 3071, 2960, 2932, 2857, 1724, 1601, 1428, 1365, 1269, 1111, 1050, 825, 708, 612, 514 cm^{-1}.

4.10. (1*R*,2*R*,3*S*,4*R*)-4-Benzoyloxy-5-benzoyloxymethyl-1-(*tert*-butyldiphenylsilyloxy)-2,3-diacetoxy-cyclohex-5-ene 12. Compound **11** (5.019 g, 6.924 mmol) was dissolved in dichloromethane (50 mL), and the solution was cooled to 0 °C by an ice bath. $SOCl_2$ (4.120 g, 34.63 mmol) and pyridine (1.643 g, 20.77 mmol) were slowly added. After the addition was finished, the ice bath was removed, and the mixture was heated to reflux (41 °C). The mixture was further stirred under reflux for 6 h. When the reaction was complete (checked by TLC; eluent, EtOAc/hexane = 1:4), dichloromethane was removed by vacuum distillation. Ethyl acetate (100 mL) and water (50 mL) were added, and the biphasic mixture was vigorously stirred for 10 min. Two phases were separated, and the aqueous phase was extracted again with ethyl acetate (60 mL). Organic extracts were combined and successively washed with an aqueous solution of potassium carbonate (15% w/w, 25 mL) and brine (15 mL). The organic solution was dried over anhydrous $MgSO_4$ and then concentrated under vacuum to give the crude product, which was purified by flash chromatography (eluent, EtOAc/hexane = 1:5) to afford compound **12** (4.258 g, 6.024 mmol) as colorless oil in 87% yield. $[\alpha]_D^{25}$ = −94.5 (c 1.0, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$) δ 1.06 (s, 9H, *t*-Bu), 1.87 (s, 3H, CH_3 in Ac), 1.92 (s, 3H, CH_3 in another Ac), 4.64 (dd, J_1 = 7.9 Hz, J_2 = 2.4 Hz, 1H, H-1), 4.70 (s, 2H, CH_2OBz), 5.35 (dd, J_1 = 11.0 Hz, J_2 = 7.9 Hz, 1H, H-2), 5.51 (dd, J_1 = 11.0 Hz, J_2 = 8.0 Hz, 1H, H-3), 5.77 (d, *J* = 1.9 Hz, 1H, H-6), 6.18 (d, *J* = 1.9 Hz, 1H, H-4), 7.34−7.45 (m, 10H, Ph-H), 7.49−7.58 (m, 2H, Ph-H), 7.61−7.66 (m, 2H, Ph-H), 7.66−7.72 (m, 2H, Ph-H), 7.87−7.93 (m, 4H, Ph-H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.11, 169.80, 165.67, 165.66, 135.93 (2C), 135.79 (2C), 133.43, 133.10, 132.94, 132.87, 130.88, 130.34, 130.11, 130.00, 129.78, 129.69 (2C), 129.51 (2C), 129.02, 128.49 (2C), 128.35 (2C), 127.88 (2C), 127.82 (2C), 73.88, 72.12, 71.67, 70.98, 63.24, 26.76 (3C), 20.73, 20.59, 19.22. HRMS (ESI) calcd for $C_{41}H_{42}O_9SiNa$ $[M + Na]^+$: 729.2496, found: 729.2490. IR (neat) ν 3071, 2955, 2933, 2858, 1757, 1727, 1602, 1452, 1428, 1368, 1234, 1109, 823, 707, 610, 503 cm^{-1}.

4.11. (1*R*,2*S*,3*S*,4*R*)-4-Benzoyloxy-5-benzoyloxymethyl-2,3-diacetoxy-1-hydroxy-cyclohex-5-ene 13. Compound **12** (4.109 g, 5.813 mmol) was dissolved in tetrahydrofuran (35 mL). Bu_4NF (6.840 g, 26.16 mmol) and AcOH (1.571 g, 26.16 mmol) were added. The mixture was then stirred at room temperature for 8 h. When the reaction was complete (checked by TLC; eluent, EtOAc/hexane = 1:4), tetrahydrofuran was removed by vacuum distillation. Ethyl acetate (50 mL) and an aqueous solution of potassium carbonate (10% w/w, 30 mL) were added, and the biphasic mixture was vigorously stirred for 10 min. The two phases were separated, and the aqueous phase was extracted again with ethyl acetate (50 mL). Organic extracts were combined and dried over anhydrous $MgSO_4$ and then concentrated under vacuum to give the crude product that was purified by flash chromatography (eluent, EtOAc/hexane = 1:4) to afford compound **13** (2.505 g, 5.347 mmol) as white crystals in 92% yield; mp 131−132 °C. $[\alpha]_D^{25}$ = −75.6 (*c* 1.0, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$) δ 1.96 (s, 3H, CH_3 in Ac), 2.11 (s, 3H, CH_3 in another Ac), 3.04 (br. s, 1H, OH), 4.54 (dd, J_1 = 7.9 Hz, J_2 = 2.1 Hz, 1H, H-1), 4.83 (s, 2H, CH_2OBz), 5.22 (dd, J_1 = 10.2 Hz, J_2 = 7.9 Hz, 1H, H-2), 5.53 (dd, J_1 = 10.2 Hz, J_2 = 7.7 Hz, 1H, H-3), 6.03 (d, *J* = 2.1 Hz, 1H, H-6), 6.18 (d, J_1 = 7.7 Hz, 1H, H-4), 7.35−7.44 (m, 4H, Ph-H), 7.50−7.59 (m, 2H, Ph-H), 7.92-8.00 (m, 4H, Ph-H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.20, 170.04, 165.94, 165.75, 133.52, 133.21, 131.69, 130.30, 129.82 (2C), 129.70 (2C), 129.41, 128.97, 128.54 (2C), 128.37 (2C), 74.98, 71.64, 71.51, 70.12, 63.47, 20.83, 20.59. HRMS (ESI) calcd for $C_{25}H_{24}O_9Na$ $[M + Na]^+$: 491.1318, found: 491.1315. IR (KBr film) ν 3424, 3071, 2951, 2926, 2873, 1752, 1724, 1601, 1451, 1377, 1261, 1120, 1068, 959, 712 cm^{-1}.

4.12. (1*S*,2*S*,3*S*,4*R*)-4-Benzoyloxy-5-benzoyloxymethyl-1,2,3-triacetoxy-cyclohex-5-ene 14. Compound **13** (1.450 g, 3.095 mmol) was dissolved in anhydrous ethyl acetate (15 mL), and the solution was cooled to 0 °C in an ice bath. Methanesulfonyl chloride (709.0 mg, 6.190 mmol) and Et_3N (470.0 mg, 4.645 mmol) were added, and the mixture was stirred at 0 °C for 1 h. When the reaction was complete (checked by TLC; eluent, EtOAc/hexane = 1:4), ethyl acetate (30 mL) and an aqueous solution of HCl (1 N, 20 mL) were added. After the biphasic mixture was vigorously stirred for 10 min, two phases were separated, and the aqueous phase was extracted again with ethyl acetate (30 mL). Organic extracts were combined, washed with an aqueous solution of potassium carbonate (10% w/w, 15 mL), and then dried over anhydrous $MgSO_4$. Removal of ethyl acetate under vacuum gave the crude unstable intermediate compound **I-A**, which was dissolved in

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toluene (5 mL). AcOH (1.115 g, 18.57 mmol) and DBU (1.414 g, 9.288 mmol) were added. The mixture was then heated to 85 °C and was stirred at this temperature for 5 h. When the reaction was complete (checked by TLC; eluent, EtOAc/hexane = 1:4), toluene was removed by vacuum distillation. Ethyl acetate (30 mL) and an aqueous solution of HCl (1 N, 15 mL) were added. After the biphasic mixture was vigorously stirred for 5 min, two phases were separated, and the aqueous phase was extracted twice with ethyl acetate (2 × 30 mL). Organic extracts were combined, washed with an aqueous solution of potassium carbonate (10% w/w, 15 mL), and then dried over anhydrous $MgSO_4$. Evaporation of ethyl acetate under vacuum gave the crude product that was then purified by flash chromatography (eluent, EtOAc/hexane = 1:5) to furnish compound **14** (1.264 g, 2.476 mmol) as colorless viscous oil in 80% yield. $[\alpha]_D^{25}$ = +10.7 (*c* 1.0, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.99 (s, 3H, CH_3 in Ac), 2.04 (s, 3H, CH_3 in Ac), 2.15 (s, 3H, CH_3 in Ac), 4.86 (s, 2H, C*H*$_2$OBz), 5.26 (dd, J_1 = 7.8 Hz, J_2 = 4.2 Hz, H-2), 5.68−5.78 (m, 2H, H-6 and H-3), 6.03−6.13 (m, 2H, H-1 and H-4), 7.38−7.48 (m, 4H, Ph-H), 7.52−7.62 (m, 2H, Ph-H), 7.94-8.06 (m, 4H, Ph-H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.23, 169.94, 169.77, 165.73, 165.68, 137.62, 133.58, 133.28, 129.89 (2C), 129.71 (2C), 129.34, 128.91, 128.85, 128.55, 128.42 (2C), 123.61, 71.14, 69.51, 68.12, 65.40, 63.29, 20.93, 20.68, 20.62. HRMS (ESI) calcd for $C_{27}H_{26}O_{10}Na$ $[M + Na]^+$: 533.1424, found: 533.1420. IR (neat) ν 3066, 2928, 2853, 1751, 1727, 1602, 1452, 1371, 1242, 1112, 1068, 940, 712 cm^{-1}.

4.13. (1*S*,2*S*,3*S*,4*R*)-5-Hydroxymethyl-1,2,3,4-tetrahydr-oxy-cyclohex-5-ene [(+)-Streptol] 1. Compound **14** (1.020 g, 1.998 mmol) was dissolved in methanol (25 mL). Aqueous ammonia (25% w/w, 5 mL) was added, and the mixture was then stirred at room temperature for 24 h. The reaction solution was concentrated to dryness under vacumm. Ether (20 mL) and pure water (20 mL) were added, the biphasic mixture was vigorously stirred for 5 min, two phases were separated, and the organic phase was extracted again with pure water (20 mL). Aqueous extracts were combined and concentrated under vacumm to give the crude product that was then purified by chromatography on a column of Duolite-C20 resin (eluent, methanol/water =1:2) to afford pure (+)-streptol **1** (317.0 mg, 1.799 mmol) as colorless viscous oil in 90% yield. $[\alpha]_D^{25}$ = +95.2 (*c* 0.5, CH_3OH) {lit.[6c] $[\alpha]_D^{25}$ = +95.6 (*c* 0.45, CH_3OH)} ^{1}H NMR (400 MHz, D_2O) δ 3.58 (dd, J_1 = 10.7 Hz, J_2 = 4.2 Hz, 1H, H-2), 3.71 (dd, J_1 = 10.7 Hz, J_2 = 7.8 Hz, 1H, H-3), 4.09 (dd, J_1 = 7.8 Hz, J_1 = 1.8 Hz, 1H, H-4), 4.15 (d, *J* = 14.2 Hz, 1H, C*H*HO), 4.24 (d, *J* = 14.2 Hz, 1H, CH*H*O), 4.30 (dd, J_1 = 4.3 Hz, J_2 = 4.2 Hz, 1H, H-1), 5.85 (dd, 1H, J_1 = 4.3 Hz, J_2 = 1.8 Hz, H-6). ^{13}C NMR (100 MHz, D_2O) δ 144.34, 124.31, 74.73, 74.43, 72.88, 68.31, 63.46. HRMS (ESI) calcd for $C_7H_{12}O_5Na$ $[M + Na]^+$: 199.0582, found: 199.0580. IR (neat) ν 3420, 2923, 1640, 1564, 1411, 1102, 1060, 998, 621 cm^{-1}.

4.14. (1*R*,2*S*,3*S*,4*R*)-5-Hydroxymethyl-1,2,3,4-tetrahydr-oxy-cyclohex-5-ene [(−)-1-*epi*-Streptol] 2. Compound **13** (1.005 g, 2.145 mmol) was dissolved in methanol (25 mL). Aqueous ammonia (25% w/w, 5 mL) was added, and the mixture was then stirred at room temperature for 24 h. The reaction solution was concentrated to dryness under vacumm. Ether (20 mL) and pure water (20 mL) were added, the biphasic mixture was vigorously stirred for 5 min, two phases were separated, and the organic phase was extracted again with pure water (20 mL). Aqueous extracts were combined and concentrated under vacumm to give the crude product that was then purified by chromatography on a column of Duolite-C20 resin (eluent, methanol/water =1:2) to afford pure (−)-1-*epi*-streptol **2** (340.5 mg, 1.933 mmol) as a colorless viscous oil in 90% yield. $[\alpha]_D^{25}$ = −33.2 (*c* 1.0, CH_3OH) {lit.[6i] $[\alpha]_D^{22}$ = −32.5 (*c* 0.22, CH_3OH)}. ^{1}H NMR (400 MHz, D_2O) δ 3.36 (dd, J_1 = 9.5 Hz, J_2 = 4.6 Hz, 1H, H-2), 3.42 (dd, J_1 = 9.5 Hz, J_2 = 7.8 Hz, 1H, H-3), 3.99 (d, *J* = 13.5 Hz, 1H, C*H*HO), 4.10 (m, 3H, H-1, H-4 and CH*H*O), 5.51 (dd, J_1 = 1.8 Hz, J_2 = 1.6 Hz, 1H, H-6). ^{13}C NMR (100 MHz, D_2O) δ 138.30, 124.91, 75.49, 75.10, 71.85, 71.33, 60.96. HRMS (ESI) calcd for $C_7H_{12}O_5Na$ $[M + Na]^+$: 199.0582, found: 199.0582. IR (neat) ν 3360, 2975, 2897, 1658, 1564, 1422, 1091, 1049, 882, 651 cm^{-1}.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acsomega.1c02502.

^{1}H and ^{13}C NMR spectra of compounds **1**, **2**, and **4**−**14** (PDF)

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Notes

The authors declare no competing financial interest.

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