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Asymmetric syntheses of (−)-methyl shikimate and (−)-5a-carba-β-D-gulopyranose from D-arabinose via Mukaiyama-type intramolecular aldolization

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ABSTRACT

New asymmetric syntheses of (−)-methyl shikimate **1** and (−)-5a-carba-β-D-gulopyranose **11** from D-arabinose through a common route which employed Mukaiyama-type intramolecular aldolization as a key step were described.

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1. Introduction

(−)-Shikimic acid has currently been used as a chiral starting material for the manufacture of a potent antiinfluenza drug, oseltamivir phosphate (Tamiflu),[1] which would protect humans from a possible influenza pandemic. (−)-Shikimic acid can be isolated from plant sources, for example, it was first isolated from the fruit of *Illicium religiosum* in 1885 by Eykman.[2] However, the isolation of (−)-shikimic acid from natural materials is limited in quantity, so it may retard the use of (−)-shikimic acid in a large-scale synthesis of oseltamivir phosphate. Accordingly, endeavor should be made by synthetic chemists to develop a practical approach to (−)-shikimic acid.

The two original syntheses of racemic shikimic acid were reported almost simultaneously by the groups of Raphael[3] and Smissman.[4] A series of methods over the last decades have been found to synthesize racemic or enantiomerically pure shikimic acid, and an excellent review has summarized these methods.[5] They can be briefly classified into four categories: (a) syntheses based on the Diels–Alder reaction;[3,4,6] (b) syntheses from benzene and its derivatives;[7] (c) syntheses from (−)-quinic acid;[8] and (d) syntheses from carbohydrates.[9]

Carbohydrates that are naturally abundant and inherently rich in chiral centers have played an important role in the syntheses of natural products.[10] The resemblance of configuration of the three adjacent hydroxyl groups in D-arabinose to that of (−)-shikimic acid prompted us to investigate a novel synthesis of (−)-shikimic acid from D-arabinose. Though Bestmann and Heid have reported a synthesis of (−)-shikimic acid from D-arabinose,[9a] herein, we would like to disclose a different concise synthesis of (−)-methyl shikimate **1** also from D-arabinose, in which the key step was a Mukaiyama-type intramolecular aldolization.[11]

2. Results and discussion

As outlined in Scheme 1, the Wittig olefination of D-arabinose with (ethoxycarbonylmethylene)triphenylphosphorane in dioxane affords an unsaturated ester **2** in 74% yield according to the modified version of a known procedure.[12] Then, Pd/C-catalyzed hydrogenation of **2** in methanol at room temperature produced saturated ester **3** in an almost quantitative yield. Protection of the primary hydroxyl group of compound **3** by reacting with 1.2 equiv of triphenylmethyl chloride in the presence of 2 equiv of pyridine and 0.2 equiv of 4-dimethylaminopyridine (DMAP) in DMF afforded compound **4** in 90% yield. The reaction of compound **4** with 12 equiv of allyl bromide in the presence of 3.5 equiv of sodium hydride in dry DMF produced the lactone **5** in 76% yield; meanwhile, both secondary hydroxyl groups were masked by two allyl groups. In order to efficiently reduce the formation of the by-product in which all three secondary hydroxyl groups were allylated, we allowed the reaction to continue for 2 h after the addition of the first batch of sodium hydride (1.5 equiv) to allow the lactonization to be matured, and then added the second batch of sodium hydride (2.0 equiv) and allyl bromide to protect the remaining two hydroxyl groups. Removal of the triphenylmethyl group of compound **5** with a catalytic amount of concentrated HCl in a mixed solvent of acetonitrile–water (40:1) at 0 °C produced compound **6** in 98% yield. Swern oxidation of the alcohol **6** affords an aldehyde **7** in 91% yield. Other attempts to prepare aldehyde **7** from alcohol **6** by using pyridinium chlorochromate (PCC)[13] or Dess–Martin reagent[14] as an oxidant failed. We found that aldehyde **7** is not stable and should be used for the next step as soon as possible.

The key step for constructing the skeleton of the title compounds is the annulation of the aldehyde **7**. We first tried the intramolecular aldolization of **7** under strongly basic conditions using LDA or LHDMS in THF at low temperature. The reaction was complicated, and none of the desired product was isolated, although Rassu and his colleagues obtained moderate yields in a similar intramolecular aldolization.[15] Fortunately, when we employed a

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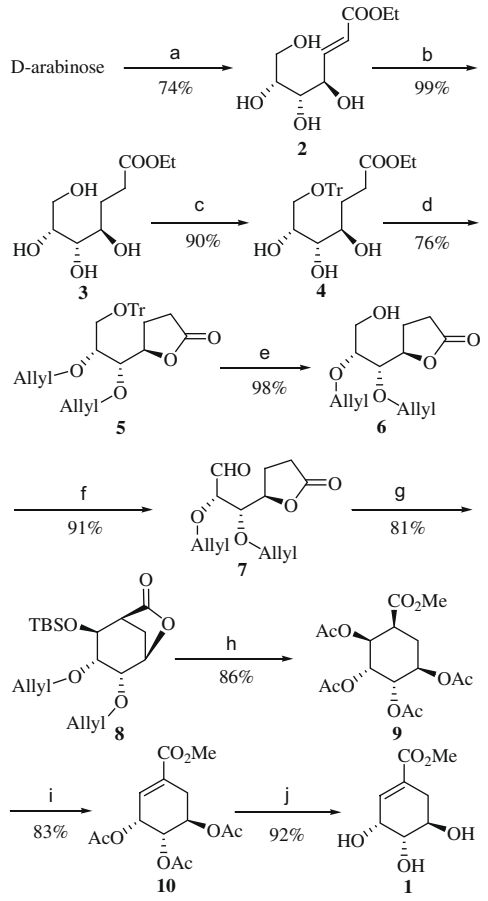


Scheme 1. Synthesis of (−)-methyl shikimate **1**. Reaction conditions: (a) 1.3 equiv of $Ph_3PCH{=}CHCOOEt$, rt for 8 h, then 60 °C for 4 h in dioxane under N_2; (b) 10% of Pd/C, rt for 50 h in methanol under H_2; (c) 1.2 equiv of triphenylmethyl chloride, 0.2 equiv of DMAP and 2 equiv of pyridine, rt overnight in DMF; (d) 1.5 equiv of NaH, rt for 2 h in dry DMF; then 12 equiv of allyl bromide, 2.0 equiv of NaH, rt for 7 h; (e) cat. HCl, 0 °C for 4 h in a mixed solvent of acetonitrile and water (40:1); (f) 2.5 equiv of oxalyl chloride, 5.0 equiv of DMSO and 6 equiv of Et_3N, in CH_2Cl_2, −78 to −60 °C for 3 h, then 0 °C for 2 h; (g) 3 equiv of DIPEA, 3 equiv of TBSOTf, in CH_2Cl_2, 0 °C for 0.5 h, then rt for 2 h. (h) 1.5 equiv of HF, 0.25 equiv of $PdCl_2$, refluxing for 2 h in methanol; then 20 equiv of pyridine, 0.2 equiv of DMAP, 10 equiv of Ac_2O, 0 °C to rt overnight in CH_2Cl_2; (i) 5 equiv of DBU, rt for 6 h in CH_2Cl_2; (j) cat. NH_4OH, refluxing in methanol for 5 h.

Mukaiyama-type aldolization protocol, the desired cyclization via an intramolecular aldolization occurred.[16] The aldehyde **7** was treated with 3.0 equiv of *tert*-butyldimethylsilyl trifluoromethanesulfonate (TBSOTf) and with 3.0 equiv of diisopropylethylamine (DIPEA) in dichloromethane at 0 °C to room temperature to produce a bicyclic lactone **8** in 81% yield. The structure and stereochemistry of compound **8** were unequivocally identified by ^1H NMR, ^{13}C NMR, ^1H–^1H COSY, and ^1H–^1H NOESY spectra. It was noteworthy that use of an excess of TBSOTf and DIPEA was necessary, when 3 equiv of both the reagents were used, the diastereoselectivity of the intramolecular aldolization was very high, and almost no other stereoisomer could be detected by TLC. When less than 2 equiv of TBSOTf and DIPEA were used, the reaction rate was decreased and the yield was lowered; moreover, the product **8** was contaminated with around 2% of 2-*epi*-**8**. A plausible pathway for the intramolecular aldolization is drawn in Figure 1, during the nucleophilic cycloaddition of the silyl enol ether intermediate **A**, a *re*/*si* face attack (conformation **B**) was favored and should be followed to form a thermodynamically more stable product **8** where the *tert*-butyldimethylsilyloxy group at the C-2 position was equatorial. While a *re*/*re* face attack (conformation **C**) was disfavored

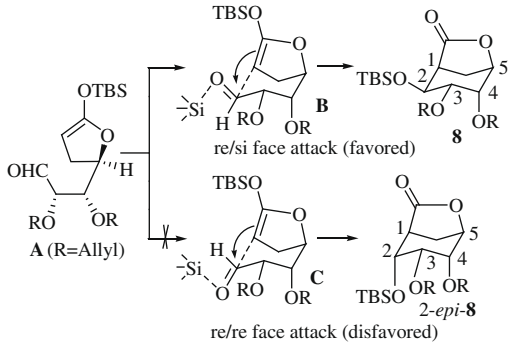
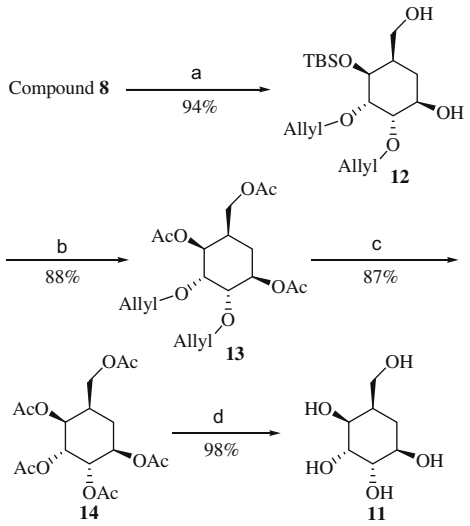


Figure 1. Pathway for the intramolecular aldolization.

and would form a thermodynamically less stable product 2-*epi*-**8** where the *tert*-butyldimethylsilyloxy group at the C-2 position was axial. Coordination of the silyl reagent with the aldehyde group may play an important role, it could accelerate the reaction rate, and the bulkiness of the coordinated silyl group should also promote the diastereoselectivity.

The compound **8** was then treated with 0.25 equiv of $PdCl_2$ and with 1.5 equiv of HF in methanol at reflux. The silyl group and both allyl groups of compound **8** were removed simultaneously, along with the alcoholysis of the lactone. Exposure of the crude product to 10 equiv of Ac_2O and 20 equiv of pyridine in the presence of 0.2 equiv of DMAP in dichloromethane at room temperature furnished compound **9** in 86% yield. The compound **9** was treated with 5.0 equiv of DBU at room temperature in dichloromethane to afford (−)-methyl 3,4,5-triacetylshikimate **10** in 83% yield. Compound **10** was finally transformed into the title compound (−)-methyl shikimate **1** in 92% yield after methanolysis of **10** in absolute methanol at reflux in the presence of catalytic ammonia.

Pseudo-sugars, also referred to as carbasugars, are a subclass of the largely represented family of cyclitols.[17] Carbasugars display a wide range of biological properties owing to their close resemblance to carbohydrates.[17,18] Some of carbasugars have been proven to be potent inhibitors of a variety of glycosidase enzymes.[19] In this work, we found that bicyclic compound **8** could be a very useful intermediate for the synthesis of carbasugar 5a-carba-β-D-gulopyranose **11** (Scheme 2). The bicyclic lactone **8** was first treated with 10 equiv of diisobutylaluminum hydride (DIBAL-H) in dichloromethane at −78 to −20 °C to produce a crude product, which was then treated with sodium borohydride in methanol at 0 °C to give pure alcohol **12** in 94% yield. Here, it should be pointed out that treatment of the crude product with sodium borohydride was necessary, otherwise it would have been contaminated by a lactol (15–20%). Alcohol **12** was allowed to react with 2.0 equiv of tetrabutylammonium fluoride (TBAF) in THF at 0 °C to remove the silyl group, and the crude product was subjected to acylation with 10 equiv of Ac_2O, 20 equiv of pyridine, and 0.2 equiv of DMAP in dichloromethane at 0 °C to room temperature to furnish compound **13** in 88% yield. The structure and stereochemistry of the compound **13** were also confirmed by ^1H NMR, ^{13}C NMR, ^1H–^1H COSY, and ^1H–^1H NOESY spectra. After the deprotection of both allyl groups of compound **13** with 0.25 equiv of $PdCl_2$ in methanol at reflux, the crude product was further treated with 20 equiv of Ac_2O, 20 equiv of pyridine, and 0.2 equiv of DMAP in dichloromethane, and thus compound **14** could be obtained in 87% yield. We have also tried the direct transformation of compound **12** into compound **14** in one step, in which the silyl group and both allyl groups were supposed to be removed simultaneously, but the yield was quite low, so the two-step transformation of **12** into **14** should be followed. Finally, the five acetyl groups of compound **14** were removed in a one-pot reaction by methanolysis in the presence



Scheme 2. Synthesis of (−)-5a-carba-β-D-gulopyranose **11**. Reaction conditions: (a) 10 equiv of DIBAL-H, −78 to −20 °C for 2 h in CH_2Cl_2; then 3 equiv of $NaBH_4$, 0 °C for 0.5 h in methanol; (b) 2 equiv of TBAF·$3H_2O$, 0 °C for 3 h in THF; then 20 equiv of pyridine, 0.2 equiv of DMAP, 10 equiv of Ac_2O, 0 °C to rt overnight in CH_2Cl_2; (c) 0.25 equiv of $PdCl_2$, refluxing for 2 h in methanol; then 20 equiv of pyridine, 0.2 equiv of DMAP, 10 equiv of Ac_2O, 0 °C to rt overnight in CH_2Cl_2; (d) cat. NH_4OH, rt for 12 h, and then refluxing for 16 h in methanol.

of a catalytic amount of ammonia, and thus another title compound 5a-carba-β-D-gulopyranose **11** was obtained in almost quantitative yield.

It is worthy to point out that 2D ^1H NMR analyses support the stereochemistry of compound **8** and compound **13** as drawn in Figure 2. In ^1H–^1H NOESY spectra of **8**, H-2 correlates with axial H_α-5a, which suggests that H-2 is at axial position in the chair conformation of the hexanoid ring, thus the stereogenic center C-2 should possess an (*S*)-configuration. H-1 correlates with vicinal H-2, but it does not correlate with H-3; moreover, the correlation spot between H-1 and H_α-5a is obviously greater than the correlation spot between H-1 and H_β-5a, which suggests that H-1 is at an equatorial position, and the stereogenic center C-1 should also possess an (*S*)-configuration. In ^1H–^1H NOESY spectra of **13**, H-5 correlates with vicinal H-4, H_α-5a and axial H-1, which suggests that H-5 is at axial position of the chair conformation, and C-5 has a (*R*)-configuration. H-4 correlates with H-3 and H-5, but it does not correlate with H-2, which suggests that H-4 is at an equatorial position, and C-4 has an (*S*)-configuration.

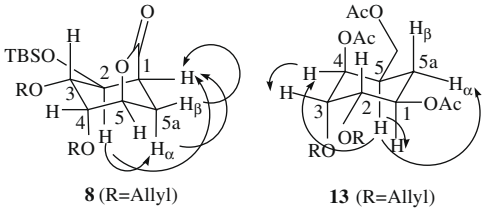


Figure 2. Stereochemistry and NOE of compounds **8** and **13**.

3. Conclusion

In conclusion, the work described herein provides an efficient common approach to (−)-methyl shikimate **1** and (−)-5a-carba-β-D-gulopyranose **11**. The compound **1** could be obtained via a 10-step synthesis in around 23.8% overall yield from D-arabinose, and compound **11** could be obtained via an 11-step synthesis in around 25.5% overall yield from D-arabinose.

4. Experimental

4.1. General methods

Melting points are uncorrected. ^1H NMR and ^{13}C NMR spectra were acquired on Bruker AM-500. Chemical shifts were given on the delta scale as parts per million (ppm) with tetramethylsilane (TMS) as the internal standard. IR spectra were recorded on Nicolet Magna IR-550. Mass spectra were recorded on HP5989A. Optical rotations of chiral compounds were measured on WZZ-1S automatic polarimeter at room temperature. Column chromatography was performed on silica gel. All chemicals were analytically pure.

4.2. (*E*)-(4*R*,5*S*,6*R*)-Ethyl 4,5,6,7-tetrahydroxy-hept-2-enoate 2

To a solution of (ethoxycarbonylmethylene)triphenylphosphorane (30.00 g, 86.11 mmol) in dry dioxane (150 mL), was added D-arabinose (10.00 g, 66.61 mmol). The mixture was stirred under an atmosphere of N_2 at room temperature for 8 h, then warmed to 60 °C and stirred for 4 h. The resulting clear solution was concentrated in vacuum to give a semisolid residue, water (250 mL) was added, and the suspension was vigorously stirred for 3 h and then filtered. After that the filtrate was extracted with CH_2Cl_2 (3 × 50 mL). The aqueous solution was evaporated under reduced pressure to dryness to give a residue, which was recrystallized from ethanol to afford a white solid **2** (10.86 g, 49.29 mmol) in 74% yield, mp 138–139 °C, $[\alpha]_D^{25} = +15.1$ (*c* 0.4, MeOH). ^1H NMR (D_2O) δ 1.24 (t, *J* = 7.0 Hz, 3H), 3.55–3.67 (m, 2H), 3.68–3.82 (m, 2H), 4.18 (q, *J* = 7.0 Hz, 2H), 4.56–4.64 (m, 1H), 6.10 (d, *J* = 15.8 Hz, 1H), 7.01 (dd, J_1 = 15.7 Hz, J_2 = 4.2 Hz, 1H). MS *m/z* (relative intensity) 221 (M^++1, 0.3), 203 (0.1), 189 (1), 171 (3), 157 (2), 147 (3), 143 (6), 130 (22), 101 (30), 84 (53), 73 (100), 57 (71), 43 (39). IR (KBr) 3318, 2954, 1721, 1666, 1449, 1386, 1270, 1165, 1087, 730, 650 cm^{-1}.

4.3. (4*R*,5*S*,6*R*)-Ethyl 4,5,6,7-tetrahydroxy-heptanoate 3

To a solution of **2** (5.00 g, 22.70 mmol) in methanol (150 mL), was added Pd/C (500 mg). The suspension was purged with hydrogen gas several times, and then was well stirred under an atmosphere of H_2 at room temperature for 50 h. After the catalyst Pd/C was filtered off, the clear solution was evaporated under a vacuum to give a neat white solid **3** (4.99 g, 22.45 mmol) in 99% yield, $[\alpha]_D^{25} = +9.2$ (*c* 0.5, H_2O). ^1H NMR (D_2O) δ 1.15 (t, *J* = 7.2 Hz, 3H), 1.65–1.76 (m, 2H), 2.35–2.47 (m, 2H), 3.32 (dd, J_1 = 1.7 Hz, J_2 = 8.3 Hz, 1H), 3.53 (dd, J_1 = 11.8 Hz, J_2 = 6.5 Hz, 1H), 3.59–3.65 (m, 1H), 3.69–3.78 (m, 2H), 4.06 (q, *J* = 7.1 Hz, 2H). MS *m/z* (relative intensity) 223 (M^++1, 0.05), 177 (0.2), 159 (1), 145 (2), 127 (4), 115 (21), 98 (57), 85 (100), 73 (18), 57 (35), 43 (37). IR (KBr) 3548, 3301, 2981, 2909, 1712, 1459, 1443, 1375, 1229, 1087, 1012, 872, 664 cm^{-1}.

4.4. (4*R*,5*S*,6*R*)-Ethyl 4,5,6-trihydroxy-7-triphenylmethoxy-heptanoate 4

To a cold (ice bath) solution of **3** (2.00 g, 9.00 mmol) in DMF (15 mL), were added DMAP (0.22 g, 1.80 mmol), pyridine (1.45 mL, 18 mmol), and triphenylmethyl chloride (3.02 g, 10.83 mmol). After the addition was finished, the mixture was allowed to warm to room temperature and stirred overnight. Distilled water (100 mL) and benzene (100 mL) were added and vigorously stirred for 0.5 h. After the mixture was transferred into a separatory funnel, the aqueous phase was separated, and the organic phase was successively washed with dilute aqueous solution of acetic acid, water, and brine. The organic solution was dried over

anhydrous $MgSO_4$, and then concentrated to give a syrup, which was purified by chromatography to furnish compound **4** (3.77 g, 8.12 mmol) in 90% yield, $[\alpha]_D^{25} = +6.8$ (*c* 2.6, ethyl acetate). ^{1}H NMR ($CDCl_3$) δ 1.15 (t, J = 7.1 Hz, 3H), 1.63–1.72 (m, 1H), 1.76–1.88 (m, 1H), 2.29–2.42 (m, 2H), 2.69 (d, J = 7.0 Hz, 1H), 2.79 (s, 1H), 2.97 (d, J = 3.6 Hz, 1H), 3.21–3.28 (m, 2H), 3.37 (dd, J_1 = 5.6 Hz, J_2 = 5.7 Hz, 1H), 3.63–3.3.69 (m, 1H), 3.77 (dd, J_1 = 5.3 Hz, J_2 = 5.4 Hz, 1H), 4.03 (q, J = 7.2 Hz, 2H), 7.14–7.28 (m, 9H), 7.32–7.39 (m, 6H). MS *m/z* (relative intensity) 465 (M^++1, 0.02), 418 (0.7), 341 (2), 259 (6), 243 (100), 228 (5), 183 (10), 165 (36), 105 (11), 85 (4), 77 (4), 44 (5). HRMS (FAB) calcd for ($C_{28}H_{32}O_6 + Na^+$): 487.2097, found: 487.2097. IR (KBr) 3442, 2931, 1731, 1490, 1447, 1070, 706 cm^{-1}.

4.5. (4*R*,5*S*,6*R*)-5,6-Diallyloxy-7-triphenylmethoxy-heptano-1,4-lactone 5

Compound **4** (2.79 g, 6.00 mmol) was dissolved in dry DMF (20 ml), which was freshly distilled over calcium hydride. The first batch of NaH (393 mg, 55%, 9.01 mmol) was added, and the suspension was stirred at room temperature for 2 h. Allyl bromide (8.60 g, 71.08 mmol) and a second batch of NaH (524 mg, 55%, 12.01 mmol) were added, and then stirring was continued at room temperature for 7 h. The mixture was filtered through a thin layer of Celite to remove the suspended solid, the filtrate was then partitioned between benzene (100 mL) and water (100 mL). Aqueous layer was separated, organic layer was dried over anhydrous $MgSO_4$, and concentrated under a reduced pressure to give a crude oil, which was purified by flash chromatography to produce **5** (2.28 g, 4.57 mmol) in 76% yield, mp 137–138 °C. $[\alpha]_D^{25} = -5.7$ (*c* 3, ethyl acetate). ^{1}H NMR ($CDCl_3$) δ 2.10–2.21 (m, 1H), 2.28–2.38 (m, 1H), 2.41–2.49 (m, 1H), 2.55–2.65 (m, 1H), 3.01 (dd, J_1 = 10.1 Hz, J_2 = 2.6 Hz, 1H), 3.53–3.61 (m, 2H), 3.72 (dd, J_1 = 8.6 Hz, J_2 = 2.0 Hz, 1H), 3.86–3.98 (m, 2H), 4.04 (dd, J_1 = 12.2 Hz, J_2 = 5.6 Hz, 1H), 4.18 (dd, J_1 = 12.2 Hz, J_2 = 5.7 Hz, 1H), 4.95–5.08 (m, 3H), 5.23 (dd, J_1 = 10.3 Hz, J_2 = 1.3 Hz, 1H), 5.35 (dd, J = 17.2 Hz, J = 1.6 Hz, 1H), 5.53–5.65 (m, 1H), 5.95–6.06 (m, 1H), 7.18–7.35 (m, 9H), 7.45–7.58 (m, 6H). MS *m/z* (relative intensity) 498 (M^+, 0.03), 421 (0.2), 283 (0.3), 259 (1), 243 (100), 228 (3), 199 (1), 165 (24), 105 (3), 85 (3), 77 (2), 41 (7). HRMS (FAB) calcd for ($C_{32}H_{34}O_5 + Na^+$): 521.2304, found: 521.2313. IR (KBr) 3385, 2983, 1764, 1449, 1184, 1100, 1039, 702 cm^{-1}.

4.6. (4*R*,5*S*,6*R*)-5,6-Diallyloxy-7-hydroxy-heptano-1,4-lactone 6

Compound **5** (2.00 g, 4.01 mmol) was dissolved in a mixed solvent of acetonitrile (20 mL) and water (0.5 mL). After the solution was cooled to 0 °C by an ice bath, concentrated hydrochloric acid (0.1 mL) was added, the mixture was stirred at 0 °C for 4 h, and the reaction was traced by TLC. After the reaction was complete, sodium carbonate (2.00 g, 18.86 mmol) powder was added, and stirring was continued for 0.5 h. The solid was filtered and rinsed with acetonitrile, the filtrate was evaporated in a vacuum to yield a crude product, which was purified by flash chromatography to give **6** (1.00 g, 3.92 mmol) in 98% yield, $[\alpha]_D^{25} = -37.5$ (*c* 1.4, ethyl acetate). ^{1}H NMR ($CDCl_3$) δ 2.04–2.13 (m, 1H), 2.21–2.31 (m, 1H), 2.36–2.44 (m, 1H), 2.53–2.62 (m, 1H), 3.44 (dd, J_1 = 8.5 Hz, J_2 = 2.0 Hz, 1H), 3.48–3.54 (m, 1H), 3.61 (dd, J_1 = 12.2 Hz, J_2 = 2.2 Hz, 1H), 3.84 (dd, J_1 = 12.2 Hz, J_2 = 3.0 Hz, 1H), 3.96–4.10 (m, 3H), 4.24 (dd, J_1 = 12.6 Hz, J_2 = 5.1 Hz, 1H), 4.72–4.79 (m 1H,), 5.12 (dd, J_1 = 10.6 Hz, J_2 = 10.9 Hz, 2H), 5.17–5.28 (m, 2H), 5.77–5.91 (m, 2H). HRMS (EI) calcd for $C_{13}H_{20}O_5$: 256.1311, found: 256.1343. IR (KBr) 3474, 2922, 1774, 1645, 1460, 1423, 1361, 1186, 1097, 1038, 926, 655, 530 cm^{-1}.

4.7. (4*R*,5*S*,6*R*)-5,6-Diallyloxy-7-oxy-heptano-1,4-lactone 7

A solution of oxalyl chloride (1.054 g, 8.30 mmol) in dichloromethane (20 mL) was cooled to −78 °C by a dry ice-acetone bath, a solution of DMSO (1.30 g, 16.64 mmol) in dichloromethane (40 mL) was then dropwise added within a period of 30 min. After the addition was finished, the mixture was stirred at −78 °C for one more hour, then a solution of **6** (0.85 g, 3.32 mmol) in dichloromethane (10 mL) was added. After triethylamine (2.11 g, 20.85 mmol) was added, the stirring was continued at −78 to −60 °C for 2 h. The mixture was then allowed to warm to 0 °C, and stirring was continued at 0 °C for 2 h. The reaction was quenched by adding water (50 mL) and the mixture was well stirred for 15 min. The aqueous phase was separated and extracted once more with dichloromethane (20 mL). Extracts were combined and dried over anhydrous Na_2SO_4. The organic solution was concentrated under a vacuum to produce a crude oil, which was purified by flash chromatography to afford aldehyde **7** (0.77 g, 3.03 mmol) in 91% yield. ^{1}H NMR ($CDCl_3$) δ 2.00–2.10 (m, 1H), 2.21–2.32 (m, 1H), 2.37–2.49 (m, 1H), 2.50–2.61 (m, 1H), 3.60–3.69 (m, 1H), 3.95–4.07 (m, 3H), 4.07–4.17 (m, 2H), 4.67–4.74 (m, 1H), 5.08–5.29 (m, 4H), 5.72–5.88 (m, 2H), 9.71 (d, J = 1.6 Hz, 1H). HRMS (EI) calcd for $C_{13}H_{18}O_5$: 254.1311, found: 254.1315.

4.8. (1*S*,2*S*,3*S*,4*S*,5*R*)-2-(*tert*-Butyldimethylsilyloxy)-3,4-diallyloxy-6-oxa-bicyclo[3,2,1]octan-7-one 8

To a solution of diisopropylethyl amine (DIPEA, 0.504 g, 3.90 mmol) in anhydrous dichloromethane (10 mL) at 0 °C (ice bath) under argon, was added TBSOTf (1.03 g, 3.90 mmol), and the resulting mixture was stirred at 0 °C for 15 min. A solution of aldehyde **7** (0.33 g, 1.30 mmol) in dichloromethane (5 mL) was then added. The mixture was stirred at 0 °C for 30 min, then was allowed to warm to room temperature and stirred at room temperature for 2 h. The reaction was quenched with water (20 mL) and saturated NH_4Cl aqueous solution until pH 5, organic layer was separated and the aqueous layer was extracted twice with dichloromethane (20 mL × 2). The combined extracts were dried over anhydrous $MgSO_4$ and concentrated under a vacuum. The crude oil was purified by flash chromatography to give 8 (0.388 g, 1.05 mmol) in 81% yield, $[\alpha]_D^{25} = +56.0$ (*c* 1.05, EtOH). ^{1}H NMR ($CDCl_3$) δ 0.09 (s, 3H), 0.12 (s, 3H), 0.92 (s, 9H), 2.15–2.21 (m, 1H), 2.31 (d, J = 12.3 Hz, 1H), 2.55 (dd, J_1 = 3.5 Hz, J_2 = 4.8 Hz, 1H), 3.41 (dd, J_1 = 4.8 Hz, J_2 = 8.6 Hz, 1H), 3.91 (dd, J_1 = 8.6 Hz, J_2 = 3.2 Hz, 1H), 4.01 (t, J = 4.5 Hz, 1H), 4.05–4.11 (m, 2H), 4.16 (dd, J_1 = 12.9 Hz, J_2 = 5.3 Hz, 1H), 4.27 (dd, J_1 = 12.9 Hz, J_2 = 5.5 Hz, 1H), 4.65 (t, J = 5.0 Hz, 1H), 5.14–5.22 (m, 2H), 5.23–5.30 (m, 2H), 5.83–5.95 (m, 2H). ^{13}C NMR ($CDCl_3$) δ 179.46, 139.29, 139.20, 122.19, 121.64, 85.87, 77.58, 77.43, 77.02, 76.52, 48.92, 34.16, 30.21, 22.50, −0.09, −0.30. HRMS (EI) calcd for $C_{19}H_{32}O_5Si$: 368.2019, found: 368.2031. IR (KBr) 3081, 2930, 2857, 1795, 1645, 1462, 1362, 1255, 1117, 987, 836, 778 cm^{-1}.

4.9. (1*S*,2*S*,3*R*,4*S*,5*R*)-Methyl 2,3,4,5-tetraacetoxy-cyclohexanecarboxylate 9

To a solution of **8** (0.299 g, 0.81 mmol) in methanol (15 mL), was added hydrofluoric acid (48% in water, 51 mg, 1.22 mmol) and palladium chloride (36 mg, 0.20 mmol), and the reaction mixture was heated at reflux and stirred for 2 h. The solvent was removed off by evaporation under a reduced pressure to give a residue. Dichloromethane (30 mL), pyridine (1.28 g, 16.2 mmol), and DMAP (20 mg, 0.164 mmol) were added. The resulting mixture was stirred and cooled to 0 °C, and acetic anhydrous (0.835 g, 8.2 mmol) was then added. After addition, stirring was continued at room temperature overnight. The reaction was quenched with

aqueous solution of sodium carbonate (10%, 20 mL). The organic layer was separated, and aqueous layer was extracted twice with dichloromethane (30 mL × 2), combined extracts were wished with dilute aqueous HCl solution (2 M, 30 mL), and then dried over anhydrous $MgSO_4$. Evaporation of the solvent gave crude product, which was purified by flash chromatography to furnish **9** (0.262 g, 0.70 mmol) in 86% yield, $[\alpha]_D^{20} = -3.3$ (*c* 1.5, $CHCl_3$). ^1H NMR ($CDCl_3$) δ 1.94–2.05 (m, 1H), 1.99 (s, 3H), 2.05 (s, 3H), 2.09 (s, 3H), 2.13 (s, 3H), 2.32 (ddd, J_1 = 13.5 Hz, J_2 = 3.2 Hz, J_3 = 4.0 Hz, 1H), 3.03 (ddd, J_1 = 13.4 Hz, J_2 =3.4 Hz, J_3 = 4.1 Hz, 1H), 3.67 (s, 3H), 5.08–5.19 (m, 2H), 5.34–5.42 (m, 2H). ^{13}C NMR ($CDCl_3$) δ 170.77, 170.25, 169.98, 168.93, 168.91, 69.96, 68.84, 68.60, 68.34, 52.28, 39.89, 26.51, 20.93, 20.73, 20.67, 20.64. HRMS (EI) calcd for $C_{16}H_{22}O_{10}$: 374.1213, found: 374.1207.

4.10. (−)-Methyl 3,4,5-*O*-triacetyl shikimate 10

To a solution of **9** (0.260 g, 0.69 mmol) in dichloromethane (10 mL), was added 1,8-diazabicyclo[5,4,0]undec-7-ene (DBU, 0.530 g, 3.48 mmol). The reaction mixture was then stirred at room temperature for 6 h. After the reaction was complete, dichloromethane (20 mL) and dilute aqueous HCl solution (2 N, 25 mL) were added, and stirring was continued for 15 min. The organic layer was separated, and the aqueous layer was extracted once more with dichloromethane (20 mL). The extracts were combined and dried over anhydrous $MgSO_4$. Evaporation of the solvent produced a crude product, which was purified by flash chromatography to give **10** (0.180 g, 0.57 mmol) in 83% yield, $[\alpha]_D^{25} = -172.4$ (*c* 0.47, $CHCl_3$) [lit.[9c] $[\alpha]_D^{26} = -173$ (*c* 0.47, $CHCl_3$)]. ^1H NMR ($CDCl_3$) δ 2.04 (s, 3H), 2.06 (s, 3H), 2.07 (s, 3H), 2.43 (dd, J_1 = 18.5 Hz, J_2 = 5.2 Hz, 1H), 2.92 (dd, J_1 = 18.4 Hz, J_2 = 4.8 Hz, 1H), 3.77 (s, 3H), 5.22–5.32 (m, 2H), 5.71–5.79 (m, 1H), 6.75 (d, J = 4.0 Hz, 1H). ^{13}C NMR ($CDCl_3$) δ 169.92, 169.81, 169.82, 165.86, 132.69, 131.18, 67.70, 66.75, 66.00, 52.18, 28.50, 20.94, 20.71, 20.68. HRMS (EI) calcd for $C_{14}H_{18}O_8$: 314.1002, found: 314.1003.

4.11. (−)-Methyl shikimate 1

To a solution of **10** (0.302 g, 0.96 mmol) in absolute methanol (6 mL), was added two drops of concentrated ammonium hydroxide. The solution was heated at reflux and stirred at this temperature for 5 h. The solution was then concentrated to dryness to give crude pale yellow solid, which was crystallized in ethyl acetate to afford compound **1** (0.166 g, 0.88 mmol) in 92% yield, mp 115–116 °C (lit.[9c] 115–116.5 °C), $[\alpha]_D^{25} = -131.5$ (*c* 0.75, EtOH) [lit.[9c] $[\alpha]_D^{25} = -132$ (*c* 0.75, EtOH)]. ^1H NMR (D_2O) δ 2.16 (dd, J_1 = 18.4 Hz, J_2 = 4.8 Hz, 1H), 2.68 (dd, J_1 = 18.4 Hz, J_2 = 5.2 Hz, 1H), 3.69 (s, 3H), 3.64–3.73 (m, 1H), 3.93–3.99 (m, 1H), 4.37 (t, J = 4.0 Hz, 1H), 6.74 (d, J = 4.0 Hz, 1H). ^{13}C NMR (D_2O) δ 168.92, 137.03, 129.50, 70.99, 66.52, 65.71, 52.49, 30.25. HRMS (EI) calcd for $C_8H_{12}O_5$: 188.0685; found: 188.0688.

4.12. (1*R*,2*S*,3*S*,4*S*,5*R*)-4-(*tert*-Butyldimethylsilyloxy)-2,3-diallyloxy-5-hydroxy-methyl cyclohexanol 12

A solution of compound **8** (0.40 g, 1.08 mmol) in dichloromethane (20 mL) was stirred and cooled to −78 °C by a dry-ice bath. A solution of DIBAL-H (1 M, 10.8 mL, 10.80 mmol) in toluene was added within 5 min. After addition, the mixture was stirred at −78 to −20 °C for 2 h. The reaction was quenched with aqueous HCl solution (1 M, 13 mL). The mixture was allowed to warm to room temperature, then aqueous layer was separated and extracted twice with dichloromethane (2 × 20 mL). The extracts were combined and dried over anhydrous $MgSO_4$. Removal of the solvent under reduced pressure produced a residue that was allowed to dissolve in methanol (10 mL). The solution was cooled to 0 °C, and $NaBH_4$ (125 mg, 3.30 mmol) was added. After stirring at 0 °C for 30 min, water (20 mL) was added, and the aqueous solution was extracted twice with dichloromethane (2 × 20 mL). The extracts were combined and dried over anhydrous $MgSO_4$. Evaporation of the solvent gave a crude product, which was purified by chromatography to furnish **12** (0.38 g, 1.02 mmol) in 94% yield, $[\alpha]_D^{25} = -38.3$ (*c* 1.2, EtOH). ^1H NMR ($CDCl_3$) δ 0.06 (s, 3H), 0.07 (s, 3H), 0.87 (s, 9H), 1.22 (dd, J_1 = 2.3 Hz, J_2 = 12.0 Hz, 1H), 1.42 (dd, J_1 = 12.1 Hz, J_2 = 24.2 Hz, 1H), 1.72 (ddd, J_1 = 12.2 Hz, J_2 = 5.6 Hz, J_3 = 5.5 Hz, 1H), 3.45 (dd, J_1 = 9.5 Hz, J_2 = 2.8 Hz, 1H), 3.49–3.58 (m, 2H), 3.67 (dd, J_1 = 3.5 Hz, J_2 = 3.4 Hz, 1H), 3.84–3.93 (m, 1H), 3.97 (dd, J_1 = 12.6 Hz, J_2 = 5.9 Hz, 1H), 4.01–4.18 (m, 4H), 5.17 (d, J = 10.3 Hz, 2H), 5.21–5.32 (m, 2H), 5.81–5.97 (m, 2H). ^{13}C NMR ($CDCl_3$) δ 135.23, 134.78, 117.41, 117.25, 81.65, 75.93, 72.01, 70.65, 69.08, 68.49, 63.79, 37.94, 26.61, 25.73, 17.90, −4.44, −5.19. HRMS (EI) calcd for $C_{19}H_{36}O_5Si$: 372.2332, found: 372.2340.

4.13. (1*R*,2*S*,3*R*,4*S*,5*R*)-5-Acetoxymethyl-1,4-diacetoxy-2,3-diallyloxy-cyclo-hexane 13

A solution of **12** (0.12 g, 0.32 mmol) in THF (6 mL) was cooled to 0 °C, TBAF·$3H_2O$ (205 mg, 0.65 mmol) was added, and stirring was then continued for 3 h. After the solvent was removed, the residue was allowed to dissolve in dichloromethane (6 mL). Pyridine (0.515 g, 6.51 mmol), DMAP (7.9 mg, 0.065 mmol), and Ac_2O (0.34 g, 3.33 mmol) were added at 0 °C, the mixture was then stirred at room temperature overnight. Dichloromethane (25 mL) and aqueous solution of dilute HCl (1 M, 15 mL) were added, and after that the mixture was well stirred for 15 min; the organic phase was separated and washed with saturated aqueous $NaHCO_3$ solution (10 mL). The organic phase was dried and concentrated to give a crude product, which was purified by chromatography to produce **13** (109 mg, 0.28 mmol) in 88% yield, $[\alpha]_D^{25} = -43.7$ (*c* 1.1, MeOH). ^1H NMR ($CDCl_3$) δ 1.38 (dd, J_1 = 12.4 Hz, J_2 = 24.3 Hz, 1H), 1.95–2.05 (m, 1H), 2.03 (s, 3H), 2.05 (s, 3H), 2.06 (s, 3H), 2.42–2.53 (m, 1H), 3.49 (dd, J_1 = 2.9 Hz, J_2 = 10.0 Hz, 1H), 3.80–3.87 (m, 2H), 4.01 (dd, J_1 = 10.9 Hz, J_2 = 8.2 Hz, 1H), 4.08 (d, J = 5.5 Hz, 2H), 4.13 (dd, J_1 = 12.9 Hz, J_2 = 5.7 Hz, 1H), 4.22 (dd, J_1 = 12.9 Hz, J_2 = 5.6 Hz, 1H), 5.06–5.20 (m, 4H), 5.21–5.32 (m, 2H), 5.82–5.93 (m, 2H). ^{13}C NMR ($CDCl_3$) δ 170.85, 170.28, 169.85, 134.90, 134.67, 117.33, 116.83, 77.92, 74.52, 72.54, 71.70, 71.34, 69.65, 63.76, 32.88, 27.91, 21.21, 20.86, 20.78. HRMS (EI) calcd for $C_{19}H_{28}O_8$: 384.1784, found: 384.1784.

4.14. (1*R*,2*S*,3*R*,4*S*,5*R*)-1,2,3,4-*O*-Tetraacetyl-5-acetoxymethyl-cyclohexane-1,2,3,4-tetrol 14

Compound **13** (160 g, 0.416 mmol) was dissolved in methanol (8 mL), $PdCl_2$ (18.5 mg, 0.104 mmol) was added, and the mixture was heated at reflux. After stirring was continued at reflux for 2 h, methanol was removed under a reduced pressure. Dichloromethane (15 mL), pyridine (0.66 g, 8.32 mmol), and DMAP (10.2 mg, 0.084 mmol) were added, the mixture was cooled to 0 °C, and Ac_2O (0.85 g, 8.32 mmol) was added. The mixture was then allowed to warm to room temperature and stirred overnight. Dichloromethane (25 mL) and aqueous solution of dilute HCl (1 M, 25 mL) were added, and after that the mixture was well stirred for 15 min, the organic phase was separated and washed with saturated aqueous $NaHCO_3$ solution (20 mL). The organic phase was dried and concentrated to give a crude product, which was purified by chromatography to produce compound **14** (141 mg, 0.362 mmol) in 87% yield, $[\alpha]_D^{25} = -22.3$ (*c* 1, $CHCl_3$). ^1H NMR ($CDCl_3$) δ 1.46–1.56 (m, 1H), 1.93 (s, 3H), 1.95–2.05 (m, 1H), 1.98 (s, 6H), 2.06 (s, 6H), 2.33–2.43 (m, 1H), 3.80 (dd, J_1 = 6.5 Hz, J_2 = 11.0 Hz, 1H), 3.98 (dd, J_1 = 8.3 Hz, J_2 = 11.1 Hz, 1H), 5.02–5.05

(m, 1H), 5.05–5.16 (m, 2H), 5.26–5.35 (m, 1H). ^{13}C NMR ($CDCl_3$) δ 170.70, 170.31, 170.03, 169.26, 169.10, 70.40, 68.96, 68.36, 68.17, 63.20, 33.60, 27.56, 20.97, 20.78, 20.74, 20.71, 20.68. HRMS (EI) calcd for $C_{17}H_{24}O_{10}$: 388.1369, found: 388.1341.

4.15. 5a-Carba-β-D-gulopyranose [(1*R*,2*S*,3*R*,4*S*,5*R*)-5-hydroxymethyl-cyclo-hexane-1,2,3,4-tetrol] 11

To a solution of compound **14** (92 mg, 0.237 mmol) in methanol (10 mL), was added concentrated ammonia (0.20 mL). The mixture was stirred at room temperature for 12 h, and then was heated at reflux. After stirring was continued at reflux for 16 h, methanol was removed under a reduced pressure to produce a glassy solid that was dried in vacuum for 5 h to afford the title compound **11** (41.4 mg, 0.232 mmol) in 98% yield,[15,20] $[\alpha]_D^{25} = -58.3$ (*c* 0.4, MeOH). ^{1}H NMR (D_2O) δ 1.23–1.33 (m, 1H), 1.71–1.79 (m, 1H), 1.95–2.03 (m, 1H), 3.45–3.53 (m, 1H), 3.56–3.63 (m, 2H), 3.68–3.77 (m, 1H), 3.91–3.96 (m, 2H). ^{13}C NMR (D_2O) δ 72.95, 72.61, 69.71, 69.05, 62.39, 36.47, 29.20. HRMS (EI) calcd for $C_7H_{14}O_5$: 178.0841, found: 178.0853.

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