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Homochiral 4-hydroxy-5-hexenoic acids and their derivatives and homologues from carbohydrates

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Abstract—Efficient routes to chiral 4-hydroxy-5-hexenoic acids and lactones from D-gluconic acid-δ-lactone and L-mannonic acid-γ-lactone are described. In this approach, the starting lactones are converted to 2,6-dibromo compounds that readily undergo zinc mediated elimination to generate the terminal alkene group in concert with 2-deoxygenation. The integrity of the remaining stereocenters is preserved during the reaction. The related important pharmaceutical intermediates (*S*)-3-hydroxy-4-pentenoic acid and (*S*)-1,3-dihydroxy-4-pentene were also prepared from 2-deoxyribose via the corresponding aldonolactone.

1. Introduction

3-Hydroxy-4-pentenoic and 4-hydroxy-5-hexenoic acids are important synthetic building blocks in many natural product syntheses. These include Mevinic acids,[1] some polyether antibiotics[2] and a number of natural hormones.[3–6] They are also intermediates of important metabolic processes such as the pentalene synthase biosynthetic pathway, and are logical precursors for the preparation of β- or γ-amino acids and *N*-heterocycles, which are key elements in the preparation of unnatural amino acids, enzyme inhibitors and β-peptides. The vinyl group in these molecules also affords a range of possibilities for further transformation, including halogenation, epoxidation, reduction, ozonolysis and cyclopropanation, which can provide additional functionality for integrating these chiral building blocks into other molecular architectures.

Because of their biological importance and synthetic value, much effort has been expended on the synthesis of these compounds.[7–19] However, cost effective methods for the preparation of homochiral 3-hydroxy-4-pentenoic and 4-hydroxy-5-hexenoic acids are still lacking. Current methods involve either asymmetric synthesis using chiral auxiliaries,[7,8] chiral transition metal catalysts[9–11] or synthesis from natural α-amino acids;[12–16] traditional resolution procedures are also commonly used.[17–19] Despite their utility, all of these methods have drawbacks from a commercial standpoint. They may involve the use of toxic metal catalysts,[9–11] costly materials[7,8] or employ laborious synthetic schemes.[13–16] In the case of chiral allylic hydroxy acids, introduction of the vinyl group is often effected by a Wittig reaction,[10,11,14,16] which is undesirable in industrial scale processes. There is still, therefore, a need for more direct, high yielding and cost efficient routes to these compounds. In the approach we describe herein, we take advantage of the low cost and structural richness of carbohydrates to give an economic and environmentally favorable entry to homochiral 3-hydroxy-4-pentenoic and 4-hydroxy-5-hexenoic acids.

2. Results and discussion

A simple three-step reaction sequence using mild conditions to transform 2-deoxyribose **3** into (*S*)-3-hydroxy-4-pentenoic acid **1a** and eventually to (*S*)-1,3-dihydroxy-4-pentene **2** was first developed. The known elimination of vicinal acyloxy halo compounds with elemental zinc was utilized. The preparation of (*S*)-3-hydroxy-4-pentenoic acid is summarized in Scheme 1. The key steps are conversion of the deoxypentose to the lactone **4**,[20] bromination of the 5-position with simultaneous acetylation of the other two hydroxyl groups followed by zinc mediated elimination,[21] which upon basic hydrolysis gave the 4,5-unsaturated product **1a**. Alcoholic acid work-up then afforded ester **1b**. Lithium aluminum hydride reduction

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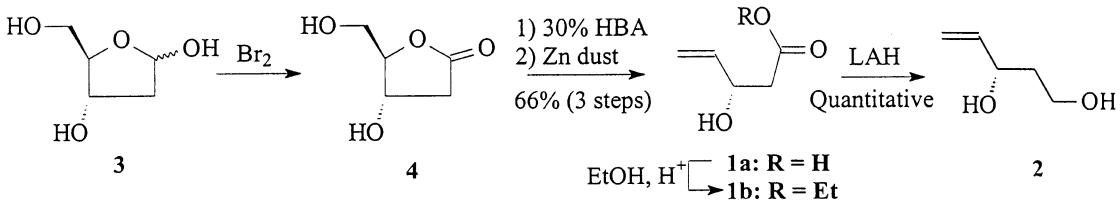
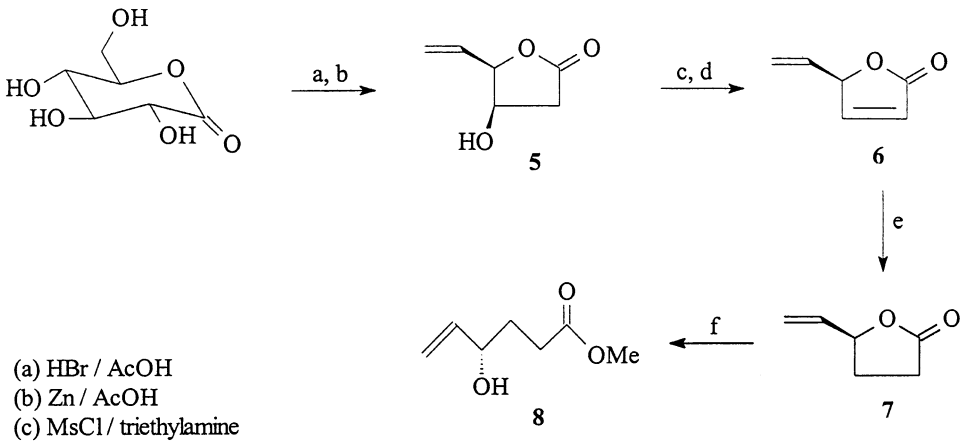


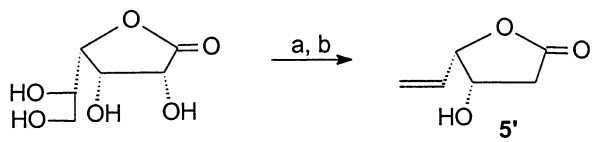
Scheme 1. Synthesis of (*S*)-3-hydroxy-4-pentenoic acid and (*S*)-dihydroxy-4-pentene.



Scheme 2. Synthesis of (*S*)-4-hydroxy-5-hexenoic acid lactone and (*S*)-4-hydroxy-5-hexenoic acid methyl ester. *Reagents, conditions and yields*: (a) 30% HBr in HOAc, 60°C for 1 h and rt overnight; (b) Zn dust, 50% HOAc in water, rt for 2 h, reflux 1 h, 58% (two steps); (c) 1.2 equiv. MsCl, 1.1 equiv. Et_3N, CH_2Cl_2, −40°C, 2 h; (d) 0.8 equiv. Et_3N, CH_2Cl_2, −78°C, 30 min, 70% (two steps, based on converted 3-mesylated intermediate); (e) 2 equiv. CuI, 5 equiv. LiCl, 4 equiv. TMSCl, 3.6 equiv. *n*-Bu_3SnH, anhydrous THF, −70°C, 30–45 min, 80%; (f) 1.1 equiv. NaOMe, MeOH, 0°C, 3 h, quantitative. MsCl = methanesulfonyl chloride; TMSCl = chlorotrimethylsilane.

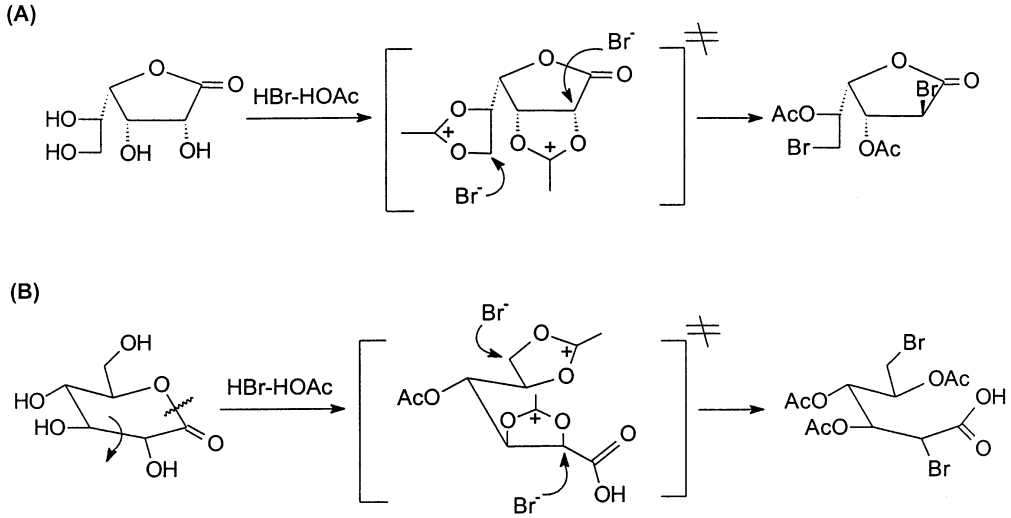
of this ester at room temperature gave diol **2** quantitatively (66% overall yield). Chiral GC analysis of diol **2** indicated a >99% enantiomeric excess of the (*S*)-enantiomer.

The method described above was used as a basis for the transformations of hexonic acid lactones to the key intermediates in the preparation of 4-hydroxy-5-hexenoic acids. Unlike the homologous 4-pentenoic acid compounds, 2-deoxygenation was effected from a 2-bromo-2-deoxy function accompanying the elimination reaction. The relatively inexpensive D-glucono-δ-lactone was used as the starting material for the synthesis of (*S*)-4-hydroxy-5-hexenoic acid and the corresponding lactone. The (*R*)-acid and its corresponding lactone were obtained using L-mannonic-γ-lactone, which has the opposite C-(4) stereochemistry to glucose. The synthesis is summarized in Scheme 2. D-Glucono-δ-lactone was treated with 30% hydrogen bromide in acetic acid (HBA) followed by zinc dust to open the lactone ring and introduce the 5,6-vinyl function via zinc facilitated elimination.[21] During this process, an effective simultaneous 2-debromination by zinc occurred. This one-pot process quickly led to the first key intermediate (3*R*,4*R*)-3,4-dihydroxy-4-hexenoic acid-γ-lactone **5** in 58% yield. When L-mannonic-γ-lactone was used instead of D-glucono-δ-lactone, the (3*S*,4*S*)-enantiomer **5′** was obtained in comparable yield (Scheme 3). ^1H NMR spectroscopy indicated that there was no scrambling of the stereocenters during this process.



(a) HBr / AcOH
(b) Zn / AcOH

Scheme 3. Synthesis of compound **5′** from L-mannonic-γ-lactone. *Reagents, conditions and yields*: (a) 30% HBr in HOAc, 60°C for 1 h and rt overnight; (b) Zn dust, 50% HOAc in water, rt for 2 h and reflux for 1 h, 50% (two steps).



Scheme 4. Proposed mechanism for dibromination of L-mannonic-γ-lactone (A) and δ-gluconolactone (B).

The formation of the 2-bromo-2-deoxy function deserves some discussion. Despite the similar reaction outcome, the dibromination of D-glucono-δ-lactone and L-mannonic-γ-lactone may involve slightly different reaction mechanisms. It is known[26] that, in strongly acidic medium, bromination of aldonolactones occurs at either (or both) the 2- or primary positions. Lactones having hydroxyl groups *cis* on the lactone ring tend to form an acetoxonium ion, while *trans*-oriented hydroxy groups do not.[26] Opening of a 2,3-acetoxonium ion has been found to take place exclusively at C-(2) with inversion of the stereochemistry. This is probably the case for the 2-bromination of L-mannonic-γ-lactone (Scheme 4A). In the case of D-glucono-δ-lactone, despite the *trans*-relationship of the 2,3-hydroxy groups, dibromination was still observed although prolonged reaction times were required.[21] A possible rationalization of this, involving opening of the six-membered lactone ring, is illustrated in Scheme 4B.

Deoxygenation at the 3-position was accomplished by mesylation followed by elimination. A 1,4-reduction[27] of the resulting α,β-unsaturated lactone **6** with LiCl/CuI/iodotrimethylsilane/tributylzinc hydride reagent followed by ring opening of saturated lactone **7** gave (*S*)-4-hydroxy-5-hexenoic acid methyl ester **8** in a satisfactory yield. Because of the acidity of the doubly allylic C-(4) proton of lactone **6**, a rearrangement tended to occur under basic conditions to give an achiral conjugated side product (Scheme 5), and if the amount of base used was not controlled carefully, straightforward elimination of the 3-mesylate was not observed.

3. Conclusion

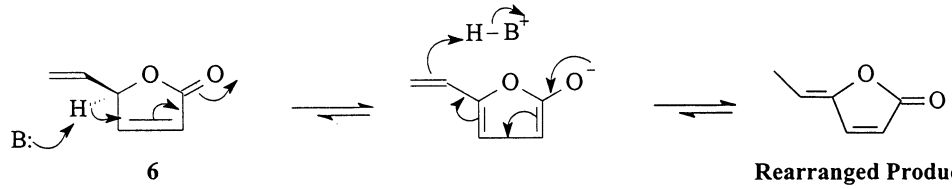
General and efficient routes to chiral unsaturated β-hydroxy pentanoic acids and γ-hydroxy hexanoic acids from naturally occurring carbohydrates have been developed in which aldonic acid lactones with the D-ribo, D-gluco and L-manno stereochemistries were utilized and zinc mediated elimination and deoxygenation were key processes. The products are important intermediates in a wide spectrum of pharmacologically important compounds.

This approach takes advantage of the variety of chiral functionalities in carbohydrates in a way that does not require the tedious protection and deprotection manipulations commonly associated with the chemistry of these substrates. It provides an efficient, economical and environmentally benign alternative to existing approaches to these important chiral intermediates.

4. Experimental

4.1. 2-Deoxy-D-ribonolactone 4

2-Deoxy-D-ribose **1** (25 g) was stirred with bromine (29 mL) in water (1.5 L) at 0°C in the dark for 16 h. The product was concentrated under vacuum with mild heating to give a yellow syrup. NMR analysis indicated clean conversion to 2-deoxyribonolactone. ^{1}H NMR (300 MHz, D_2O): δ 4.34 (2H, m), 3.66 (1H, dd, J= 12.9, 3 Hz), 3.55 (1H, dd, J=12.9, 4.2 Hz), 2.84 (1H, dd, J=18.6, 6.9 Hz), 2.36 (1H, dd, J=18.6, 3.0 Hz);



Scheme 5. Rearrangement and loss of chirality of compound **6** under basic conditions.

^{13}C NMR (75 MHz, D_2O): δ 174.72, 84.14, 63.49, 56.19, 32.94; FAB-HRMS (Gly): calcd $C_5H_9O_4$ $[M+H]^+$: 133.0457; found: 133.0501.

4.2. (*S*)-3-Hydroxy-4-pentenoic acid 1a and the ethyl ester 1b

Lactone **3** (1 g) was stirred with 30% HBr in acetic acid (HBA, 5 mL) at room temperature overnight. Excess HBA was evaporated and the resulting syrup was dissolved in 50% acetic acid in water (10 mL). Zinc dust (3 g) was added in portions and stirred at room temperature for 3 h. The mixture was filtered and the filtrate concentrated. To remove zinc salt and deacetylate the 3-OH position, the residue was dissolved in water and the pH adjusted to 10 using KOH. A white precipitate of zinc hydroxide formed and was removed by filtration. The filtrate was concentrated and the syrup was dissolved in cold ethanol and acidified with concentrated HCl. The KCl salt formed was removed by filtration. Removal of ethanol gave crude compound **1a** (0.7 g). ^{1}H NMR (300 MHz, D_2O): δ 5.72 (1H, m), 5.09 (1H, m), 4.98 (1H, m), 4.31 (1H, m), 2.33 (2H, m); ^{13}C NMR (75 MHz, D_2O): δ 175.20, 134.16, 110.90, 65.05, 38.51; FAB-HRMS (Gly): calcd $C_5H_9O_3$ $[M+H]^+$: 117.0508; found: 117.0552. Ethyl ester **1b** was prepared by a similar method to lactone **3** (20 g) except that warm acidic ethanol was used for extended time in the final step. The product was isolated by flash chromatography (chloroform as eluent) with an overall yield of 66% for three steps. $[\alpha]_D$ −5 (*c* 0.98, $CHCl_3$); ^{1}H NMR (300 MHz, D_2O): δ 5.85 (1H, m), 5.27 (1H, m), 5.11 (1H, m), 4.50 (1H, m), 4.14 (2H, q, J=7.2 Hz), 2.52 (2H, m), 1.23 (3H, t, J=7.2 Hz); ^{13}C NMR (75 MHz, D_2O): δ 172.22, 138.76, 115.33, 68.89, 60.74, 41.11, 14.11 (both ^{1}H and ^{13}C NMR data agree with literature data[22,23]); FAB-HRMS (NBA): calcd $C_7H_{13}O_3$ $[M+H]^+$: 145.0865; found: 145.0849.

4.3. (*S*)-1,3-Dihydroxy-4-pentene 2

Ester **1b** (0.5 g) was dissolved in THF (15 mL) and stirred with LAH (0.17 g) at room temperature for 3 h. The reaction mixture was then quenched by slow addition of methanol and poured into cold acidified water then extracted with ethyl acetate. Removal of solvent yielded the 1,3-diol **2** quantitatively as a colorless liquid. $[\alpha]_D$ +11 (*c* 1, MeOH) [lit.[24] $[\alpha]_D$ +11 (*c* 1, MeOH)]; ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.87 (1H, m), 5.24 (1H, m), 5.09 (1H, m), 4.34 (1H, m), 3.80 (2H, m), 3.04 (2H, b), 1.74 (2H, m) (^{1}H NMR data agree with literature data[25]); ^{13}C NMR (75 MHz, $CDCl_3$): δ 140.54, 114.60, 72.47, 60.84, 38.05; e.e. >99% by chiral GC; FAB-HRMS (Gly): calcd $C_5H_{11}O_2$ $[M+H]^+$: 103.0759; found: 103.0741.

4.4. (3*R*,4*R*)-3,4-Dihydroxy-4-hexenoic acid-γ-lactone 5

D-Glucono-δ-lactone (25 g) was stirred at 60°C with 30% hydrogen bromide in acetic acid (HBA, 80 mL) for 1 h and then overnight at room temperature. Excess HBA was removed under reduced pressure. The resultant oil was dissolved in 50% acetic acid in water (200 mL). Zinc dust (50 g) was added in portions and the mixture stirred at room temperature for 2 h and then refluxed for an additional 1 h. The mixture was filtered and the filtrate concentrated under reduced pressure. The resultant syrup was dissolved in water (100 mL) and potassium hydroxide was added to precipitate the remaining zinc as the insoluble hydroxide and effect C-(3) deacetylation. After filtration, the basic filtrate was acidified to pH 5 using concentrated hydrochloric acid. Water was removed under reduced pressure and the residue dissolved in cold ethanol. Precipitated potassium chloride was removed by filtration, and the filtrate evaporated. The evaporation residue was purified by flash column chromatography using ethyl acetate/hexanes (1:1 v:v) as eluent to yield pure **5** (10.5 g, 58% overall yield for two steps). $[\alpha]_D$ +43 (*c* 1.15); ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.93 (1H, m), 5.49 (2H, m), 4.87 (1H, m), 4.51 (1H, m), 2.77 (1H, dd, J=17.7, 5.4 Hz), 2.58 (1H, dd, J=17.7, 1.5 Hz); ^{13}C NMR (75 MHz, $CDCl_3$): δ 175.74, 130.12, 120.77, 84.65, 69.42, 38.60; FAB-HRMS (NBA): $[M+H]^+$ $C_6H_9O_3$ calcd: 129.0552; found: 129.0553.

4.5. (3*S*,4*S*)-3,4-Dihydroxy-4-hexenoic acid-γ-lactone 5′

L-Mannonic-γ-lactone (25 g) was subjected to the one-pot reaction sequence described above for the D-glucono-δ-lactone. After flash column chromatographic purification, pure **5′** was obtained (9.1 g, 50% overall yield). $[\alpha]_D$ −44 (*c* 1.56, $CHCl_3$); ^{1}H and ^{13}C NMR (300 MHz, $CDCl_3$): identical with those of compound **5**; FAB-HRMS (NBA): $[M+H]^+$ $C_6H_9O_3$ calcd: 129.0552; found: 129.0551.

4.6. (*R*)-4-Hydroxyhexane-2,5-(*Z*)-dienoic acid lactone 6

Compound **5** (1.5 g) was dissolved in dichloromethane (25 mL) and the solution was cooled to −40°C. Methanesulfonyl chloride (1.1 mL) was added followed by addition of a solution of triethylamine (1.8 mL) in dichloromethane (10 mL) over 30 min. After stirring for 2 h at −40°C, TLC analysis indicated that compound **5** was completely converted to the 3-mesylated compound. The reaction temperature was then reduced to −78°C and a solution of triethylamine (1.3 mL) in dichloromethane (5 mL) was slowly introduced over 30 min. The reaction was monitored by TLC and stopped when a less polar, UV-active product (from unwanted rearrangement) started to form. N.B. At this point some 3-mesylated compound was not completely converted to the elimination product. The reaction mixture was poured into ice cold dilute hydrochloric acid solution (40 mL) and extracted with dichloromethane. The organic layer was dried over anhydrous sodium sulfate and then concentrated and flash column chromatography of the evaporation residue (chloroform as eluent) afforded **6** (0.64 g, 50% yield) as a pale yellow liquid. Unconverted 3-methylated product (0.7 g, 29%) was also recovered. *(3*R*,4*R*)-3-Mesyloxy-5-hexenoic acid lactone*: ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.88 (1H, m), 5.49 (2H, m), 5.36 (1H, m), 5.00 (1H, m), 3.01 (3H, s), 2.96 (1H, dd, J=18.3, 5.7 Hz), 2.82 (1H, dd, J=18.3,

1.5 Hz); ^{13}C NMR (75 MHz, $CDCl_3$): δ 172.75, 129.01, 121.49, 82.49, 76.80, 38.52, 36.68. *Rearrangement product*: ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.32 (1H, d, $J=5.1$ Hz), 6.09 (1H, d, $J=5.1$ Hz), 5.32 (1H, q, $J=7.5$ Hz), 1.92 (3H, d, $J=7.5$ Hz); ^{13}C NMR (75 MHz, $CDCl_3$): δ 170.04, 150.30, 143.51, 118.70, 112.28, 11.88. *Compound* **6**: ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.39 (1H, dd, $J=5.7$, 1.5 Hz), 6.12 (1H, dd, $J=5.7$, 2.1 Hz), 5.70 (1H, m), 5.46 (1H, m), 5.41 (1H, m), 5.34 (1H, m); ^{13}C NMR (75 MHz, $CDCl_3$): δ 172.67, 154.69, 131.62, 121.45, 119.82, 83.63; HRMS-EI(+): M^+ $C_6H_6O_2$ calcd: 110.0368; found: 110.0352.

4.7. (*S*)-4-Hydroxy-5-hexenoic acid lactone 7

Lithium chloride (0.21 g) and copper(I) iodide (0.38 g) were dissolved in anhydrous THF (10 mL) under nitrogen flow. After stirring for 20 min at room temperature, the mixture was cooled to −70°C. Neat **6** (0.11 g) was added followed by chlorotrimethylsilane (0.54 mL) and the mixture stirred for 15 min. Tributyltin hydride (1 mL) was slowly added over 5 min. The reaction mixture was then allowed to warm to 0°C over 1 h. The reaction was quenched with 10% potassium fluoride solution (5 mL) and stirred for 30 min. The mixture was filtered through a Celite pad and the filtrate was extracted with THF. The organic layer was concentrated and the residue was stirred with 10% potassium fluoride solution (10 mL) for 15 min. Ether (10 mL) was then added and the stirring was continued for another 15 min. The mixture was passed through a Celite pad and the filtrate was extracted with ether. The ether solution was washed with brine, dried over anhydrous sodium sulfate and then concentrated. Flash column chromatography afforded pure **7** as a colorless liquid (90 mg, 80% yield). $[\alpha]_D$ +28 (*c* 1.48, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.85 (1H, m), 5.34 (1H, m), 5.23 (1H, m), 4.92 (1H, m), 2.51 (1H, m), 2.39 (1H, m), 1.98 (1H, m) [Lit. ^{1}H NMR (60 MHz):[28] δ 4.78–6.20 (4H, m), 1.78–3.15 (4H, m); ^{1}H NMR (60 MHz, CD_3CN):[29–31] δ 4.7–6.3 (4H, m), 1.6–2.7 (4H, m)]; ^{13}C NMR (75 MHz, $CDCl_3$): δ 176.94, 135.49, 117.44, 80.48, 31.54, 28.24 [Lit. ^{13}C NMR (d_5-pyridine):[29–31] δ 178.4, 137.8, 118.1, 81.9, 29.3 (2)]; HRMS-EI(+): M^+ $C_6H_8O_2$ calcd: 112.0524; found: 112.0541.

4.8. (*S*)-4-Hydroxy-5-hexenoic acid methyl ester 8

Compound **5** (50 mg) was stirred with sodium methoxide (26 mg) in absolute methanol (5 mL) at 0°C for 3 h. The solution was then neutralized with concentrated hydrochloric acid. The reaction mixture was concentrated and the product was extracted with chloroform. Compound **8** was obtained quantitatively. $[\alpha]_D$ +1.6 (*c* 1.33, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.84 (1H, m), 5.24 (1H, m), 5.12 (1H, m), 4.16 (1H, m), 3.68 (3H, s), 2.43 (2H, t, $J=7.2$ Hz), 1.85 (2H, m); ^{13}C NMR (75 MHz, $CDCl_3$): δ 174.35, 140.33, 115.13, 72.13, 51.68, 31.58, 29.93; FAB-HRMS (NBA): $[M+H]^+$ $C_7H_{13}O_3$ calcd: 145.0865; found: 145.0866.

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