Enantiodivergent Syntheses of Pantolactone and Pantothenic Acid from D-Mannitol

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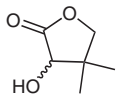
Abstract: Efficient synthetic routes to both the enantiomers of pantolactone and pantothenic acid have been developed starting from D-mannitol-based D-glyceraldehyde acetonide through its conversion into a protected pantoic acid intermediate followed by either cyclization or amide bond formation with a β-amino ester, and subsequent appropriate deprotection.

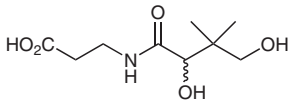
Key words: syntheses, enantiomers, pantolactone, pantothenic acid, D-mannitol

A significant amount of research interest has been focused on the synthesis of pantolactone (**1**),[1] pantothenic acid (**2**) (Figure 1) and analogues[2] due to their biological activity and utility as chiral building blocks and/or chiral auxiliaries for a number of natural products syntheses.[3–5] The biologically active dextrorotatory enantiomer of pantothenic acid (**2b**), known as vitamin B5, a member of vitamin B complex, plays a key role in the biosynthesis of coenzyme A, releasing energy from carbohydrates,[6] synthesizing steroids, hormones, and the neurotransmitter acetylcholine,[6] and affecting cell division and DNA replication.[7] Pantothenic acid and its supplements have a wide therapeutic role. They are effective in the treatment of acne vulgaris by decreasing sebum secretion[8] and help to lower total cholesterol, low-density lipoprotein cholesterol, and triglyceride levels in blood.[9] Pantothenic acid deficiency results in many abnormalities in health and can be supplied as dietary supplement through natural food sources, benefiting patients suffering from diabetes. The cosmetic industry also routinely use pantothenic acid as an additive in many cosmetic products because of its ability to optimize hydration and wound healing.[10]

Considering the importance of these compounds, many reports of the chiral synthesis of pantolactone have been documented that involve, among others, (i) chemical[11] and enzymatic[12] resolution of its racemates, (ii) asymmetric hydrogenation of ketopantolactone with rhodium complexes,[13] (iii) Sharpless asymmetric epoxidation of an allylic alcohol[14a] and Sharpless asymmetric dihydroxylation of a cyclic silyl enol ether,[14b] (iv) α,α-dialkylation of an ephedrine-derived chiral morpholin-3-one ester,[15] (v) enantioselective aldol reaction between a thiosilyl ketene acetal and ethyl glyoxylate,[16] and (vi) asymmetric hydrocyanation with oxynitrilase.[17] On the other hand, pantothenic acid (mostly isolated as its calcium salt) has been chemically synthesized by condensation of pantolactone and the calcium salt of β-alanine.[18]



1a α-OH: (*S*)-pantolactone
1b β-OH: (*R*)-pantolactone



2a α-OH: (*S*)-pantothenic acid
2b β-OH: (*R*)-pantothenic acid

Figure 1 Structure of pantolactone and pantothenic acid

A recent report describes the synthesis of pantothenic acid starting from pantolactone through an *N*-formyl imide intermediate.[19] In spite of these methods available in the literature, the development of expedient and flexible synthetic routes to these molecules in both the enantiomerically pure forms still continues due to the fact that the desired biological activity of a molecule often resides in one enantiomer; the other enantiomer may either be inactive or shows different activity. It is, therefore, conceivable that the biological profiles of both the enantiomers need to be known, and for this reason both the enantiomers should be available for investigation. The importance of a synthetic strategy that provides both the enantiomers by using a common precursor cannot be over-emphasized. Towards the realization of such a strategy, we embarked upon the enantiodivergent synthesis of both the enantiomers of pantolactone (**1**) and pantothenic acid (**2**) from inexpensive and commercially available D-mannitol, which to the best of our knowledge has not been previously reported; the results are presented herein.

To realize our goals, we set about as follows. Aldol condensation reaction between D-glyceraldehyde acetonide (**3**)[20] and ethyl isobutyrate in the presence of lithium diisopropylamide at –78 °C furnished the hydroxy esters **4a** and **4b** as a diastereomeric mixture (9:1) by GC analysis (Scheme 1). The components of the original mixture were separated by chromatography and characterized. Interestingly, the minor isomer **4b** was exclusively obtained by oxidation of the diastereomeric mixture of **4a** and **4b** with Dess–Martin periodinane to the keto ester **5** followed by

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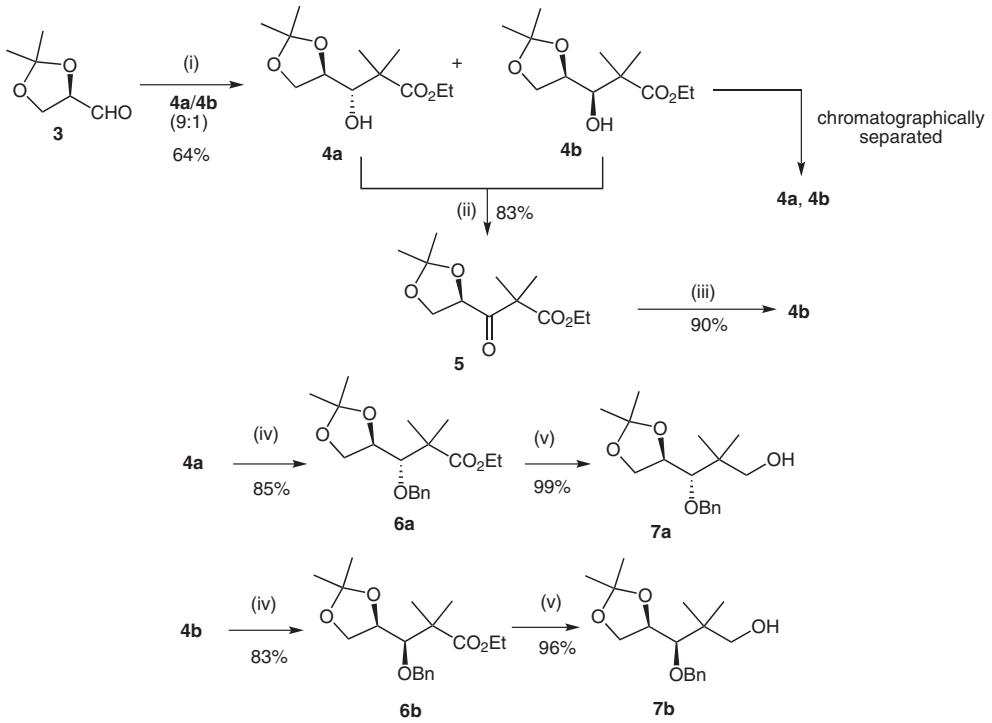
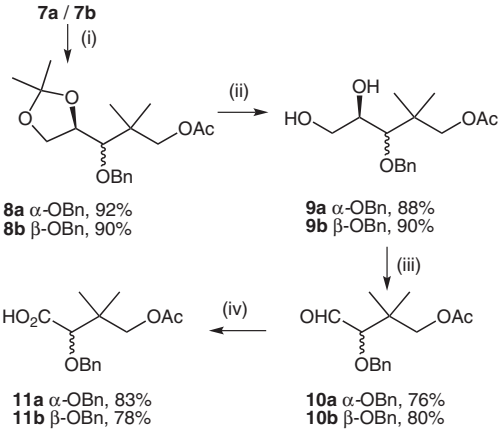


Scheme 1 *Reagents and conditions*: (i) ethyl isobutyrate, LDA, THF, –78 °C, 45 min; (ii) Dess–Martin periodinane, CH_2Cl_2, r.t., 4 h; (iii) $NaBH_4$, MeOH, –40 °C, 1 h; (iv) BnBr, NaH, DMF, 0 °C to r.t., 16 h; (v) $LiAlH_4$, Et_2O, 0 °C, 4 h.

reduction with sodium borohydride at –40 °C. The hydroxy esters **4a** and **4b** were then separately subjected to the following sequence of reactions as depicted in Scheme 1. The hydroxy group in **4a** and **4b** was benzylated with benzyl bromide in the presence of sodium hydride to produce **6a** and **6b** respectively, and subsequent reduction of the ester groups with lithium aluminum hydride provided quantitatively the corresponding alcohols **7a** and **7b**. The absolute stereochemistry, spectroscopic data, and specific rotation values of the alcohols **7a** and **7b** obtained were in agreement with those reported by Paquette et al.[21]

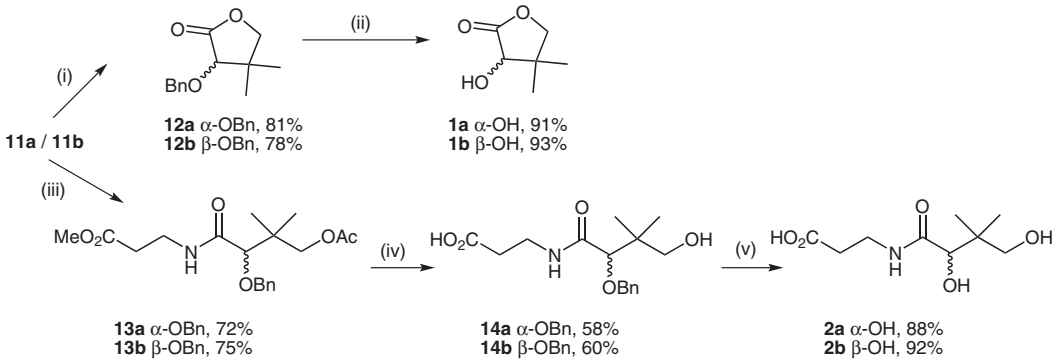
Subsequent acetylation of the alcohols **7a** and **7b** followed by acetonide deprotection of the acetyl derivatives **8a** and **8b** under acidic condition yielded the diols **9a** and **9b** (Scheme 2). Oxidative cleavage of these diols with sodium periodate furnished the aldehydes **10a** and **10b**, which were further oxidized to the protected pantoic acids **11a** (*S* form) and **11b** (*R* form). These protected pantoic acids **11a** and **11b** were used as the prime intermediates to synthesize pantolactone and pantothenic acid by two different approaches.



Scheme 2 *Reagents and conditions*: (i) Ac_2O, Et_3N, DMAP, CH_2Cl_2, 0 °C to r.t., 12 h; (ii) AcOH, H_2O (4:1), 24 h; (iii) $NaIO_4$, MeOH, H_2O, r.t., 2 h; (iv) $NaClO_2$, NaH_2PO_4, MeOH–CH_2Cl_2–H_2O (6:3:2), r.t., 4 h.

In one approach, the protected (*R*)-pantoic acid **11b** upon deacetylation with potassium carbonate followed by treatment of dilute hydrochloric acid produced the lactone **12b** in 78% yield (Scheme 3). Debenzylation of the lactone with hydrogen and palladium-on-carbon furnished (*R*)-pantolactone (**1b**) with 95% ee. In the alternative approach **11b** was condensed with the methyl ester of β-alanine[22] in the presence of *N*-(3-dimethylaminopropyl)-*N*′-ethylcarbodiimide hydrochloride (EDC·HCl) and 1-hydroxybenzotriazole hydrate (HOBt·H_2O) to generate the pantamide derivative **13b**, which was then hydrolyzed with lithium hydroxide in methanol–tetrahydrofuran–water to **14b** and finally debenzylated to afford (*R*)-pantothenic acid (**2b**).

With the success of synthesizing *R*-enantiomers of both pantolactone and pantothenic acid in hand, the syntheses of (*S*)-pantolactone (**1a**) and (*S*)-pantothenic acid (**2a**) were subsequently completed using the same sequences (Scheme 3).



Scheme 3 *Reagents and conditions*: (i) (a) K_2CO_3, MeOH, r.t., 6 h; (b) 6 M HCl, 1 h; (ii) H_2, 10% Pd/C, EtOH, r.t., 24 h; (iii) $NH_2CH_2CH_2CO_2Me$, EDC·HCl, HOBt, DIPEA, CH_2Cl_2, r.t., 16 h; (iv) LiOH·H_2O, MeOH–THF–H_2O, (2:2:1), r.t., 3 h; (v) H_2, 10% Pd/C, MeOH, r.t., 24 h.

In conclusion, syntheses of both enantiomers of pantolactone and pantothenic acid from D-mannitol through the intermediacy of the protected pantoic acid by employing a simple and effective strategy have been demonstrated. The scope and limitation of the method for the synthesis of other analogues is under study.

Melting points were taken in open capillaries and are uncorrected. IR spectra were recorded in neat or $CHCl_3$. Gas chromatographic analyses were carried out using ZB-5 column (30 m × 0.25 mm, film thickness 0.25 μm) with He as a carrier gas. ^{1}H and ^{13}C NMR spectra were recorded in deuterated solvent using TMS as internal standard. Mass spectra were recorded in FAB mode. Specific rotations were measured at 589 nm. Pre-coated plates (0.25 mm, silica gel 60 F_{254}) were used for TLC; PE = petroleum ether. All reactions were performed under N_2 atmosphere using anhyd solvents unless otherwise mentioned.

Ethyl (*S*)-3-[(*R*)-2,2-Dimethyl-1,3-dioxolan-4-yl]-3-hydroxy-2,2-dimethylpropanoate (4a) and Ethyl (*R*)-3-[(*R*)-2,2-Dimethyl-1,3-dioxolan-4-yl]-3-hydroxy-2,2-dimethylpropanoate (4b)

To a stirred soln of 1.6 M LDA in cyclohexane (56.4 mL, 84.4 mmol) in THF (50 mL) at –78 °C was added dropwise ethyl isobutyrate (11.34 mL, 84.4 mmol) in THF (40 mL). The mixture was stirred for 1 h and then aldehyde **3** (10 g, 76.8 mmol) in THF (30 mL) was added dropwise and the mixture was stirred for 45 min at the same temperature. The mixture was quenched with sat. NH_4Cl soln (100 mL) and allowed to warm up to r.t. The organic layer was separated, concentrated under reduced pressure, and the residue was taken up in EtOAc (100 mL). The aqueous soln was extracted with EtOAc (3 × 100 mL). The combined organic extracts were washed with brine (2 × 80 mL), dried (Na_2SO_4), and concentrated in vacuo to give **4a** and **4b** as a diastereomeric mixture (ratio 9:1) as an oil [GC (temperature program: 50 °C increasing 20 °C/min up to 310 °C, 4 min): t_R = 5.787 (**4a**), 5.405 min (**4b**)]. The crude material was chromatographed (silica gel, 100–200 mesh), elution with 5% EtOAc–PE gave minor product **4b**, and 10% EtOAc–PE gave and major product **4a** both as colorless oils.

Enantiomer 4a

Yield: 10.97 g (58%).

$[\alpha]_D^{27}$ +7.7 (*c* 0.5, $CHCl_3$).

IR (neat): 3482, 1719, 1468, 1377, 1261, 1060, 857 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.24 (s, 6 H), 1.27 (t, *J* = 6.9 Hz, 3 H), 1.34 (s, 3 H), 1.39 (s, 3 H), 2.66 (d, *J* = 5.7 Hz, 1 H), 3.84 (t, *J* = 5.4 Hz, 1 H), 3.95–4.20 (m, 5 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.0, 21.2, 21.5, 25.3, 26.3, 45.9, 60.7, 66.8, 76.0, 76.5, 108.8, 177.1.

HRMS (FAB): *m*/*z* $[M + H]^+$ calcd for $C_{12}H_{23}O_5$: 247.1546; found: 247.1539.

Enantiomer 4b

Yield: 1.04 g (5.5%).

$[\alpha]_D^{27}$ +1.4 (*c* 0.4, $CHCl_3$).

IR (neat): 3529, 1727, 1468, 1377, 1252, 1063, 862 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.24 (s, 3 H), 1.25 (s, 3 H), 1.27 (t, *J* = 7.2 Hz, 3 H), 1.35 (s, 3 H), 1.40 (s, 3 H), 3.05 (d, *J* = 9.6 Hz, 1 H), 3.53 (dd, *J* = 9.6, 1.8 Hz, 1 H), 3.87 (t, *J* = 7.5 Hz, 1 H), 4.02 (t, *J* = 8.1 Hz, 1 H), 4.10–4.22 (m, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.0, 21.8, 22.3, 25.6, 26.1, 46.0, 60.7, 67.1, 74.6, 74.9, 109.5, 176.6.

HRMS (FAB): *m*/*z* $[M + H]^+$ calcd for $C_{12}H_{23}O_5$: 247.1546; found: 247.1536.

Ethyl (*R*)-3-(2,2-Dimethyl-1,3-dioxolan-4-yl)-2,2-dimethyl-3-oxopropanoate (5)

To a stirred soln of **4a** and **4b** (9:1, 5.08 g, 20.64 mmol) in CH_2Cl_2 (180 mL), Dess–Martin periodinane (11.43 g, 26.95 mmol) was added and the mixture was stirred at r.t. for 4 h. Sat. $Na_2S_2O_3$ soln (80 mL) was added and the aqueous layer was extracted with CH_2Cl_2 (2 × 50 mL). The combined CH_2Cl_2 layers were washed with 10% $NaHCO_3$ soln (50 mL) and brine (2 × 50 mL), dried (Na_2SO_4), and concentrated in vacuo. The crude material was chromatographed (silica gel, 100–200 mesh, 5% EtOAc–PE) to yield **5** as a colorless oil; yield: 4.18 g (83%).

$[\alpha]_D^{27}$ +41.3 (*c* 1.9, $CHCl_3$).

IR (neat): 1749, 1716, 1465, 1380, 1263, 1073, 855 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.25 (t, *J* = 7.2 Hz, 3 H), 1.34 (s, 3 H), 1.37 (s, 3 H), 1.41 (s, 3 H), 1.46 (s, 3 H), 3.91 (dd, *J* = 8.1, 6.6 Hz, 1 H), 4.09–4.29 (m, 3 H), 4.66 (dd, *J* = 8.1, 6.6 Hz, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 13.8, 21.4, 21.6, 24.4, 25.4, 53.4, 61.1, 67.6, 78.7, 110.7, 172.8, 207.4.

HRMS (FAB): *m*/*z* $[M + H]^+$ calcd for $C_{12}H_{21}O_5$: 245.1390; found: 245.1398.

Alternative Preparation of 4b

To a stirred soln of **5** (3.2 g, 13.1 mmol) in MeOH (60 mL) at –40 °C, $NaBH_4$ (580 mg, 15.26 mmol) was added in portions and stirring was continued for 1 h. Acetone (20 mL) was added to quench the reaction and the mixture was stirred for 30 min at r.t. The organic layer was concentrated; the residue was taken in EtOAc (100 mL), washed with brine (2 × 30 mL), dried (Na_2SO_4), and concen-

trated under reduced pressure. Crude material was found to be a single diastereomer **4b** [GC (temperature program: 50 °C, increasing 20 °C/min up to 310 °C): t_R = 5.405 min] and was chromatographed (silica gel, 100–200 mesh, 5% EtOAc–PE) to yield **4b** as a colorless oil; yield: 2.90 g (90%).

Ethyl (*S*)-3-(Benzyloxy)-3-[(*R*)-2,2-dimethyl-1,3-dioxolan-4-yl]-2,2-dimethylpropanoate (6a); Typical Procedure

To a stirred soln of **4a** (5 g, 20.32 mmol) in DMF (80 mL) at 0 °C was added NaH (1.46 g, 50% oil dispersion, 30.48 mmol) in several portions over 1 h. After stirring for a further 1 h at 0 °C, BnBr (4.17 g, 2.9 mL, 24.38 mmol) in DMF (20 mL) was added dropwise. When the addition was complete, the mixture was stirred overnight at r.t. The mixture was cooled to 0 °C and quenched with sat. NH_4Cl soln (100 mL). The aqueous layer was extracted with Et_2O (3 × 100 mL) and the combined organic extracts were washed with brine (2 × 50 mL), dried (Na_2SO_4), and concentrated under reduced pressure. The crude material was chromatographed (silica gel, 100–200 mesh, 5% EtOAc–PE) to yield **6a** as a colorless oil; yield: 5.80 g (85%).

$[\alpha]_D^{27}$ +2.5 (*c* 1.15, $CHCl_3$).

IR (neat): 1729, 1462, 1377, 1258, 1067, 861 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 1.18 (s, 3 H), 1.22 (s, 3 H), 1.23 (t, *J* = 7.1 Hz, 3 H), 1.33 (s, 3 H), 1.41 (s, 3 H), 3.98–4.18 (m, 6 H), 4.63 (d, *J* = 11.3 Hz, 1 H), 4.83 (d, *J* = 11.3 Hz, 1 H), 7.29–7.33 (m, 5 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.0, 20.6, 22.2, 24.8, 26.2, 46.4, 60.5, 65.6, 75.3, 76.5, 83.6, 108.0, 127.3 (2 C), 127.4, 128.2 (2 C), 138.5, 176.0.

HRMS (FAB): *m*/*z* $[M + H]^+$ calcd for $C_{19}H_{29}O_5$: 337.2015; found: 337.1994.

Ethyl (*R*)-3-Benzyloxy-3-[(*R*)-2,2-dimethyl-1,3-dioxolan-4-yl]-2,2-dimethylpropanoate (6b)

Following the typical procedure for **6a** using **4b** (2.83 g, 11.5 mmol), NaH (0.83 g, 50% oil dispersion, 17.29 mmol), BnBr (2.36 g, 1.64 mL, 13.79 mmol) in DMF (60 mL) with column chromatography (silica gel, 100–200 mesh, 3% EtOAc–PE) afforded **6b** as a colorless oil; yield: 3.20 g (83%).

$[\alpha]_D^{27}$ +26.8 (*c* 0.72, $CHCl_3$).

IR (neat): 1729, 1461, 1375, 1256, 1067, 862 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 1.16 (s, 3 H), 1.24 (t, *J* = 7.2 Hz, 3 H), 1.28 (s, 3 H), 1.36 (s, 3 H), 1.43 (s, 3 H), 3.62 (t, *J* = 8.1 Hz, 1 H), 3.78 (d, *J* = 6.9 Hz, 1 H), 3.74 (dd, *J* = 8.1, 6.3 Hz, 1 H), 4.09 (q, *J* = 6.9 Hz, 2 H), 4.24 (q, *J* = 7.2 Hz, 1 H), 4.58 (d, *J* = 11.1 Hz, 1 H), 4.92 (d, *J* = 11.3 Hz, 1 H), 7.27–7.34 (m, 5 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.1, 20.6, 22.2, 25.7, 26.5, 46.8, 60.7, 66.6, 75.3, 77.4, 84.2, 108.5, 127.3, 127.5 (2 C), 128.2 (2 C), 138.8, 176.4.

HRMS (FAB): *m*/*z* $[M + H]^+$ calcd for $C_{19}H_{29}O_5$: 337.2015; found: 337.2004.

(*S*)-3-(Benzyloxy)-3-[(*R*)-2,2-dimethyl-1,3-dioxolan-4-yl]-2,2-dimethylpropan-1-ol (7a); Typical Procedure

Compound **6a** (6.5 g, 19.34 mmol) in Et_2O (40 mL) at 0 °C was added dropwise to a stirred suspension of $LiAlH_4$ (3.25 g, 85.63 mmol) in Et_2O (30 mL) and the mixture was stirred for 4 h at 0 °C. The reaction was quenched with sat. Na_2SO_4 soln (50 mL). Excess H_2O was absorbed with solid Na_2SO_4, which was then filtered through a Büchner funnel and the filtercake was washed with $CHCl_3$ (3 × 120 mL). The solvent was evaporated under reduced pressure to yield sufficiently pure **7a** as a colorless; yield: 5.63 g (99%).

$[\alpha]_D^{27}$ +10.3 (*c* 1.33, $CHCl_3$) {Lit.[21] $[\alpha]_D^{20}$ +12.2 (*c* 2.8, $CHCl_3$)}.

IR (neat): 3467, 1460, 1375, 1214, 1057, 859 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 0.91 (s, 3 H), 0.98 (s, 3 H), 1.37 (s, 3 H), 1.47 (s, 3 H), 2.04–2.08 (br s, 1 H), 3.39 (s, 2 H), 3.67 (d, *J* = 3.3 Hz, 1 H), 4.05 (dd, *J* = 6.9, 1.2 Hz, 2 H), 4.33 (td, *J* = 7.2, 3.6 Hz, 1 H), 4.64 (d, *J* = 11.1 Hz, 1 H), 4.87 (d, *J* = 11.1 Hz, 1 H), 7.28–7.36 (m, 5 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 21.2, 22.0, 24.9, 26.4, 39.1, 65.3, 70.6, 75.5, 76.5, 84.6, 108.0, 126.9, 127.7 (2 C), 128.4 (2 C), 138.2.

HRMS (FAB): *m*/*z* $[M + H]^+$ calcd for $C_{17}H_{27}O_4$: 295.1909; found: 295.1905.

(*R*)-3-(Benzyloxy)-3-[(*R*)-2,2-dimethyl-1,3-dioxolan-4-yl]-2,2-dimethylpropan-1-ol (7b)

Following the typical procedure for **7a** using **6b** (3.105 g, 9.23 mmol) and $LiAlH_4$ (1.55 g, 40.84 mmol) in Et_2O (30 mL) afforded **7b** as pure colorless oil; yield: 2.61 g (96%).

$[\alpha]_D^{27}$ +24.7 (*c* 0.53, $CHCl_3$) {Lit.[21] $[\alpha]_D^{20}$ +25.8 (*c* 1.21, $CHCl_3$)}.

IR (neat): 3443, 1460, 1375, 1218, 1063, 860 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 0.95 (s, 3 H), 1.02 (s, 3 H), 1.39 (s, 3 H), 1.43 (s, 3 H), 2.97 (t, *J* = 6.3 Hz, 1 H), 3.22 (d, *J* = 3.9 Hz, 1 H), 3.47 (t, *J* = 6.0 Hz, 2 H), 3.78 (t, *J* = 7.8 Hz, 1 H), 4.06 (dd, *J* = 7.8, 6.9 Hz, 1 H), 4.33–4.39 (m, 1 H), 4.65 (d, *J* = 11.1 Hz, 1 H), 4.78 (d, *J* = 11.1 Hz, 1 H), 7.29–7.37 (m, 5 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 21.5, 24.2, 25.8, 26.2, 40.1, 67.2, 69.0, 76.0, 76.2, 85.4, 109.0, 127.6, 127.7 (2 C), 128.3 (2 C), 138.3.

HRMS (FAB): *m*/*z* $[M + H]^+$ calcd for $C_{17}H_{27}O_4$: 295.1909; found: 295.1902.

(*S*)-3-(Benzyloxy)-3-[(*R*)-2,2-dimethyl-1,3-dioxolan-4-yl]-2,2-dimethylpropyl Acetate (8a); Typical Procedure

To a stirred soln of **7a** (5.53 g, 18.84 mmol) in anhyd CH_2Cl_2 (150 mL) at 0 °C were added Et_3N (13.14 mL, 94.2 mmol) and DMAP (460 mg, 3.77 mmol). After 15 min, Ac_2O (4.45 mL, 47.1 mmol) was added dropwise and the mixture was stirred for 12 h at r.t. The reaction was quenched with H_2O (50 mL) and the CH_2Cl_2 layer was separated. The aqueous layer was extracted with CH_2Cl_2 (2 × 50 mL). The combined organic layers were washed with H_2O (1 × 50 mL) and brine (2 × 50 mL), dried (Na_2SO_4), and concentrated under reduced pressure to yield a crude material which was chromatographed (silica gel, 100–200 mesh, 5% EtOAc–PE) to yield **8a** as a colorless oil; yield: 5.82 g (92%).

$[\alpha]_D^{27}$ –7.9 (*c* 1.15, $CHCl_3$).

IR (neat): 1740, 1465, 1375, 1241, 1056, 861 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 0.89 (s, 3 H), 0.99 (s, 3 H), 1.37 (s, 3 H), 1.45 (s, 3 H), 2.04 (s, 3 H), 3.73 (d, *J* = 2.4 Hz, 1 H), 3.85 (d, *J* = 10.5 Hz, 1 H), 3.96–4.00 (m, 2 H), 4.06 (t, *J* = 7.7 Hz, 1 H), 4.34 (td, *J* = 7.5, 2.4 Hz, 1 H), 4.56 (d, *J* = 11.1 Hz, 1 H), 4.90 (d, *J* = 11.1 Hz, 1 H), 7.26–7.34 (m, 5 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 20.6, 20.8, 22.2, 24.9, 26.4, 38.0, 64.9, 70.3, 75.3, 76.7, 81.6, 107.6, 127.4, 127.5 (2 C), 128.2 (2 C), 138.5, 170.8.

HRMS (FAB): *m*/*z* $[M + H]^+$ calcd for $C_{19}H_{29}O_5$: 337.2015; found: 337.2003.

(*R*)-3-(Benzyloxy)-3-[(*R*)-2,2-dimethyl-1,3-dioxolan-4-yl]-2,2-dimethylpropyl Acetate (8b)

Following the typical procedure for **8a** using **7b** (2.4 g, 8.18 mmol), Et_3N (5.70 mL, 40.86 mmol), Ac_2O (1.93 mL, 20.43 mmol), and DMAP (200 mg, 1.64 mmol) in CH_2Cl_2 (65 mL) with column chromatography (silica gel, 100–200 mesh, 5% EtOAc–PE) furnished **8b** as a colorless oil; yield: 2.47 g (90%).

$[\alpha]_D^{27}$ +26.6 (*c* 2.10, $CHCl_3$).

IR (neat): 1738, 1461, 1375, 1243, 1058, 861 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 0.95 (s, 3 H), 0.99 (s, 3 H), 1.38 (s, 3 H), 1.45 (s, 3 H), 2.04 (s, 3 H), 3.30 (d, *J* = 6.3 Hz, 1 H), 3.69

(t, J = 7.8 Hz, 1 H), 3.87 (d, J = 10.8 Hz, 1 H), 3.99–4.06 (m, 2 H), 4.28–4.35 (m, 1 H), 4.53 (d, J = 11.1 Hz, 1 H), 4.88 (d, J = 11.1 Hz, 1 H), 7.28–7.37 (m, 5 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 20.6, 20.9, 22.1, 25.6, 26.5, 38.5, 67.4, 70.5, 75.7, 76.9, 83.4, 108.4, 127.5, 127.8 (2 C), 128.2 (2 C), 138.6, 170.8.

HRMS (FAB): m/z $[M + H]^+$ calcd for $C_{19}H_{29}O_5$: 337.2015; found: 337.2009.

(3*S*,4*R*)-3-(Benzyloxy)-4,5-dihydroxy-2,2-dimethylpentyl Acetate (9a); Typical Procedure

AcOH (80%, 130 mL) was added to **8a** (5.74 g, 17 mmol) and the mixture was stirred at r.t. for 24 h. AcOH was removed in vacuo and the last trace was azeotropically removed with toluene to give a crude material that was chromatographed (silica gel, 100–200 mesh, 30% EtOAc–PE) to yield the diol **9a** as a colorless oil; yield: 4.45 g (88%).

$[\alpha]_D^{27}$ –15.6 (*c* 1.89, $CHCl_3$).

IR (neat): 3433, 1732, 1462, 1380, 1250, 1037 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.02 (s, 3 H), 1.04 (s, 3 H), 2.07 (s, 3 H), 2.07–2.14 (m, 2 H), 3.54 (d, J = 4.4 Hz, 1 H), 3.80–3.82 (m, 2 H), 3.88–3.93 (m, 1 H), 3.99 (s, 2 H), 4.60 (d, J = 11.2 Hz, 1 H), 4.73 (d, J = 11.2 Hz, 1 H), 7.28–7.38 (m, 5 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 20.9, 21.0, 21.6, 38.6, 64.4, 70.6, 72.3, 75.5, 85.0, 127.6 (2 C), 127.7, 128.4 (2 C), 138.1, 171.3.

HRMS (FAB): m/z $[M + H]^+$ calcd for $C_{16}H_{25}O_5$: 297.1702; found: 297.1704.

(3*R*,4*R*)-3-(Benzyloxy)-4,5-dihydroxy-2,2-dimethylpentyl Acetate (9b)

Following the typical procedure for **9a** using **8b** (2.25 g, 6.66 mmol) and AcOH (80%, 52 mL) with column chromatography (silica gel, 100–200 mesh, 35% EtOAc–PE) yielded **9b** as a colorless oil; yield: 1.78 g (90%).

$[\alpha]_D^{27}$ +13.4 (*c* 1.11, $CHCl_3$).

IR (neat): 3447, 1734, 1463, 1377, 1247, 1040 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.01 (s, 3 H), 1.02 (s, 3 H), 2.07 (s, 3 H), 2.10 (br m, 1 H), 2.82 (d, J = 7.5 Hz, 1 H), 3.36 (d, J = 1.5 Hz, 1 H), 3.55 (d, J = 5.7 Hz, 2 H), 3.82–3.84 (m, 1 H), 3.95 (d, J = 10.8 Hz, 1 H), 4.03 (d, J = 10.8 Hz, 1 H), 4.62 (s, 2 H), 7.30–7.39 (m, 5 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 20.3, 20.9, 21.7, 38.9, 66.1, 69.4, 70.0, 75.6, 80.9, 127.8 (2 C), 128.0, 128.5 (2 C), 137.5, 171.0.

HRMS (FAB): m/z $[M + H]^+$ calcd for $C_{16}H_{25}O_5$: 297.1702; found: 297.1709.

(*S*)-3-(Benzyloxy)-2,2-dimethyl-4-oxobutyl Acetate (10a); Typical Procedure

To a stirred soln of **9a** (500 mg, 1.69 mmol) in MeOH (16 mL) was added $NaIO_4$ (903 mg, 4.22 mmol) in H_2O (4 mL) in portions and the soln was stirred for 2 h. The mixture was filtered, washed with MeOH and the filtrate was concentrated in vacuo. The residue was taken up in EtOAc (50 mL), washed with brine (50 mL), and dried (Na_2SO_4), and concentrated under reduced pressure. The crude material was purified by flash chromatography (silica gel, 230–400 mesh, 2% EtOAc–PE) to give aldehyde **10a** as a colorless oil; yield: 340 mg (76%).

$[\alpha]_D^{27}$ –47.2 (*c* 1.28, $CHCl_3$).

IR (neat): 1735, 1464, 1374, 1238, 1087, 1039, 914 cm^{-1}.

^{1}H NMR (300 MHz, CDCl3): δ = 1.02 (s, 6 H), 1.98 (s, 3 H), 3.49 (d, J = 3.0 Hz, 1 H), 3.9 (d, J = 10.8 Hz, 1 H), 4.0 (d, J = 10.8 Hz, 1 H), 4.43 (d, J = 12.0 Hz, 1 H), 4.68 (d, J = 11.7 Hz, 1 H), 7.33–7.34 (m, 5 H), 9.75 (d, J = 3.0 Hz, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 20.3, 20.7, 21.9, 38.7, 68.8, 73.0, 86.8, 128.1 (3 C), 128.5 (2 C), 137.1, 170.6, 204.1.

HRMS (FAB): m/z $[M + H]^+$ calcd for $C_{15}H_{21}O_4$: 265.1440; found: 265.1449.

(*R*)-3-(Benzyloxy)-2,2-dimethyl-4-oxobutyl Acetate (10b)

Following the typical procedure for **10a** using diol **9b** (2.1 g, 7.1 mmol) in MeOH (64 mL) and $NaIO_4$ (3.79 g, 17.71 mmol) in H_2O (16 mL) with flash column chromatography (silica gel, 230–400 mesh, 2% EtOAc–PE) gave aldehyde **10b** as a colorless oil; yield: 1.50 g (80%).

$[\alpha]_D^{27}$ +47.7 (*c* 1.04, $CHCl_3$).

HRMS (FAB): m/z $[M + H]^+$ calcd for $C_{15}H_{21}O_4$: 265.1440; found 265.1452.

All other spectral data were identical to those of **10a**.

(2*S*)-4-Acetoxy-2-(benzyloxy)-3,3-dimethylbutanoic Acid (11a); Typical Procedure

To a stirred soln of **10a** (330 mg, 1.25 mmol) in MeOH–CH_2Cl_2–H_2O (6:3:2, 41 mL) were added NaH_2PO_4 (1.03 g, 7.5 mmol) and $NaClO_2$ (339 mg, 3.75 mmol). The soln turned yellowish green within 5 min. After stirring for 4 h at r.t., the reaction was quenched with 1 M HCl, stirred for 15 min, and concentrated under reduced pressure. The residual aqueous layer was extracted with CH_2Cl_2 (3 × 30 mL). The combined organic layers were washed with brine (2 × 20 mL), dried (Na_2SO_4), and concentrated to a crude material that was chromatographed (silica gel, 100–200 mesh, 20% EtOAc–PE) to yield **11a** as a colorless oil; yield: 291 mg (83%).

$[\alpha]_D^{27}$ –57.3 (*c* 1.89, $CHCl_3$).

IR (neat): 3451, 1733, 1464, 1379, 1246, 1109, 1040 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.04 (s, 3 H), 1.06 (s, 3 H), 1.95 (s, 3 H), 3.87 (d, J = 10.7 Hz, 1 H), 3.88 (s, 1 H), 4.06 (d, J = 10.9 Hz, 1 H), 4.41 (d, J = 11.3 Hz, 1 H), 4.68 (d, J = 11.3 Hz, 1 H), 7.34–7.37 (m, 5 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 20.2, 20.7, 21.7, 38.0, 69.4, 73.0, 81.5, 128.1, 128.3 (2 C), 128.4 (2 C), 136.7, 171.1, 175.6.

HRMS (FAB): m/z $[M + H]^+$ calcd for $C_{15}H_{21}O_5$: 281.1389; found: 281.1396.

(2*R*)-4-Acetoxy-2-(benzyloxy)-3,3-dimethylbutanoic Acid (11b)

Following the typical procedure for **11a** using **10b** (1.33 g, 5.03 mmol) in MeOH–CH_2Cl_2–H_2O (6:3:2, 160 mL) and NaH_2PO_4 (4.15 g, 5.04 mmol) and $NaClO_2$ (1.35 g, 14.93 mmol) with by column chromatography (silica gel, 100–200 mesh, 20% EtOAc–PE) afforded **11b** as a colorless oil; yield: 1.103 g (78%).

$[\alpha]_D^{27}$ +57.5 (*c* 1.06, $CHCl_3$).

HRMS (FAB): m/z $[M + H]^+$ calcd for $C_{15}H_{21}O_5$: 281.1389; found: 281.1394.

All other spectral data were identical to those of **11a**.

(*R*)-3-(Benzyloxy)-4,4-dimethyldihydrofuran-2(3*H*)-one (12b);[23] Typical Procedure

To a stirred soln of **11b** (80 mg, 0.28 mmol) in anhyd MeOH (2 mL) was added K_2CO_3 (99 mg, 0.85 mmol) and the mixture was stirred for 6 h at r.t. 6 M HCl (1.5 mL) was added and the mixture was stirred for a further 1 h. The mixture was concentrated under reduced pressure to a residue that was taken up in EtOAc (40 mL). The organic solvent was washed with brine (2 × 20 mL), dried (Na_2SO_4), and concentrated under reduced pressure to give a crude material that was chromatographed (silica gel, 100–200 mesh, 10% EtOAc–PE) to yield **12b** as a colorless oil; yield: 49 mg (78%).

$[\alpha]_D^{27}$ +112.5 (*c* 0.86, $CHCl_3$) {Lit.[23a] $[\alpha]_D$ +112.5 (*c* 0.22, $CHCl_3$)}.

IR (neat): 1775, 1463, 1203, 1121, 994 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.10 (s, 3 H), 1.14 (s, 3 H), 3.74 (s, 1 H), 3.87 (d, *J* = 8.8 Hz, 1 H), 4.00 (d, *J* = 8.7 Hz, 1 H), 4.75 (d, *J* = 12.1 Hz, 1 H), 5.04 (d, *J* = 12.1 Hz, 1 H), 7.32–7.38 (m, 5 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 19.3, 23.2, 40.3, 72.3, 76.3, 80.4, 127.93 (2 C), 127.95, 128.4 (2 C), 137.2, 175.3.

HRMS (FAB): *m*/*z* $[M + H]^+$ calcd for $C_{13}H_{17}O_3$: 221.1178; found: 221.1166.

(*S*)-3-(Benzyloxy)-4,4-dimethyldihydrofuran-2(3*H*)-one (12a)
Following the typical procedure for **12b** using **11a** (600 mg, 2.1 mmol) in MeOH (15 mL) and K_2CO_3 (742 mg, 6.37 mmol) with 6 M HCl (11.5 mL) and column chromatography (silica gel, 100–200 mesh, 10% EtOAc–PE) yielded **12a** as a colorless oil; yield: 380 mg (81%).

$[\alpha]_D^{27}$ –112.4 (*c* 0.98, $CHCl_3$) {Lit.[24] $[\alpha]_D$ –114.0 (*c* 1.90, $CHCl_3$)}.

HRMS (FAB): *m*/*z* $[M + H]^+$ calcd for $C_{13}H_{17}O_3$: 221.1178; found: 221.1170.

All other spectral data were identical to those of **12b**.

(*R*)-3-Hydroxy-4,4-dimethyldihydrofuran-2(3*H*)-one (1b); Typical Procedure
To a soln of **12b** (52 mg, 0.4 mmol) in MeOH (5 mL) was added 10% Pd/C (100 mg, 0.1 mmol). The mixture was degassed and hydrogenated under a H_2 atmosphere for 24 h. The catalyst was filtered off and the solvent was concentrated in vacuo to a crude material, which was column chromatographed (silica gel, 100–200 mesh, 40% EtOAc–PE) to yield **1b** as a white solid; yield: 28 mg (93%); mp 88–90 °C.

$[\alpha]_D^{27}$ –48.3 (*c* 2.0, H_2O) {Lit.[1] $[\alpha]_D^{25}$ –50.7 (*c* 2.07, H_2O)}.

IR ($CHCl_3$): 3445, 1782, 1480, 1410, 1390, 1180, 1007 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.08 (s, 3 H), 1.23 (s, 3 H), 3.33 (br s, 1 H), 3.95 (d, *J* = 8.7 Hz, 1 H), 4.03 (d, *J* = 8.7 Hz, 1 H), 4.2 (s, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 18.8, 22.8, 40.8, 75.7, 76.4, 177.9.

HRMS (FAB): *m*/*z* $[M + H]^+$ calcd for $C_6H_{11}O_3$: 131.0708; found: 131.0696.

(*S*)-3-Hydroxy-4,4-dimethyldihydrofuran-2(3*H*)-one (1a)
Following the typical procedure for **1b** using **12a** (220 mg, 1.69 mmol) in MeOH (20 mL) with 10% Pd/C (420 mg, 0.1 mmol) under a H_2 atmosphere gave **1a** as a pure white solid; yield: 116 mg (91%); mp 89–91 °C.

$[\alpha]_D^{27}$ +51.2 (*c* 2.05, H_2O) {Lit.[15] $[\alpha]_D^{25}$ +51.8 (*c* 2.07, H_2O)}.

HRMS (FAB): *m*/*z* $[M + H]^+$ calcd for $C_6H_{11}O_3$: 131.0708; found: 131.0699.

All other spectral data were identical to those of **1b**.

Methyl 3-[(*R*)-4-Acetoxy-2-(benzyloxy)-3,3-dimethylbutylamino]propanoate (13b); Typical Procedure
To a stirred soln of **11b** (200 mg, 0.72 mmol) in anhyd CH_2Cl_2 (5 mL) at 0 °C, EDC·HCl (137 mg, 0.72 mmol) and HOBt·H_2O (97 mg, 0.72 mmol) were added. After stirring for 30 min, β-alanine methyl ester (100 mg, 0.72 mmol) was added followed by DIPEA (0.13 mL, 0.72 mmol) and the mixture was stirred for 16 h at r.t. CH_2Cl_2 (50 mL) was added, the CH_2Cl_2 layer was washed with brine (2 × 20 mL), dried (Na_2SO_4), and concentrated in vacuo to a crude material that was column chromatographed (silica gel, 100–200 mesh, 30% EtOAc–PE) to afford **13b** as a colorless oil; yield: 194 mg (75%).

$[\alpha]_D^{27}$ +60.4 (*c* 1.09, $CHCl_3$).

IR (neat): 1736, 1671, 1579, 1372, 1243, 1087, 1038 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.93 (s, 3 H), 1.01 (s, 3 H), 1.97 (s, 3 H), 2.56 (t, *J* = 6.0 Hz, 2 H), 3.53–3.60 (m, 2 H), 3.66 (s, 3 H), 3.75 (s, 1 H), 3.83 (d, *J* = 10.8 Hz, 1 H), 4.04 (d, *J* = 10.8 Hz, 1 H), 4.35 (d, *J* = 11.4 Hz, 1 H), 4.54 (d, *J* = 11.4 Hz, 1 H), 7.02 (br s, 1 H), 7.32–7.34 (m, 5 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 20.1, 20.8, 21.6, 33.9, 34.4, 37.9, 51.7, 69.7, 73.4, 83.3, 128.11 (2 C), 128.14, 128.5 (2 C), 136.8, 170.6, 170.9, 172.5.

HRMS (FAB): *m*/*z* $[M + H]^+$ calcd for $C_{19}H_{28}NO_6$: 366.1917; found: 366.1926.

Methyl 3-[(*S*)-4-Acetoxy-2-(benzyloxy)-3,3-dimethylbutylamino]propanoate (13a)
Following the typical procedure for **13b** using **11a** (220 mg, 0.79 mmol) in CH_2Cl_2 (6 mL) and EDC·HCl (151 mg, 0.79 mmol), HOBt·H_2O (107 mg, 0.79 mmol), β-alanine methyl ester (110 mg, 0.79 mmol), and DIPEA (0.14 mL, 0.79 mmol) with column chromatography (silica gel, 100–200 mesh, 30% EtOAc–PE) produced **13a** as a colorless oil; yield: 206 mg (72%).

$[\alpha]_D^{27}$ –61.6 (*c* 1.22, $CHCl_3$).

HRMS (FAB): *m*/*z* $[M + H]^+$ calcd for $C_{19}H_{28}NO_6$: 366.1917; found: 366.1930.

All other spectral data were identical to those of **13b.**

3-[(*R*)-2-(Benzyloxy)-4-hydroxy-3,3-dimethylbutylamino]propanoic Acid (14b); Typical Procedure
To a stirred soln of **13b** (150 mg, 0.51 mmol) in MeOH–THF–H_2O (2:2:1, 3.25 mL) at 0 °C, LiOH·H_2O (69 mg, 1.64 mmol) was added, and the mixture was stirred for 3 h at r.t. The solvent was evaporated in vacuo, the residue taken in EtOAc (50 mL), cooled with ice, and acidified with 10% aq HCl to pH 3. The EtOAc solvent was separated and the aqueous layer was extracted with EtOAc (3 × 25 mL). The combined organic extracts were washed with brine (2 × 30 mL), dried (Na_2SO_4), and concentrated under reduced pressure. The crude material was purified by column chromatography (silica gel, 100–200 mesh, 3% MeOH–$CHCl_3$) to provide **14b** as a light-yellow oil; yield: 72 mg (60%).

$[\alpha]_D^{27}$ +46.3 (*c* 0.85, $CHCl_3$).

IR (neat): 3410, 1724, 1650, 1530, 1461, 1398, 1112 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.84 (s, 3 H), 1.02 (s, 3 H), 2.57 (t, *J* = 5.7 Hz, 2 H), 3.40 (s, 2 H), 3.55 (br s, 2 H), 3.76 (s, 1 H), 4.41 (d, *J* = 11.1 Hz, 1 H), 4.55 (d, *J* = 11.1 Hz, 1 H), 7.16 (br s, 1 H), 7.33–7.38 (m, 5 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 19.6, 22.7, 33.9, 34.5, 40.1, 70.2, 74.1, 85.3, 128.1 (2 C), 128.3, 128.6 (2 C), 136.8, 172.5, 175.7.

HRMS (FAB): *m*/*z* $[M + H]^+$ calcd for $C_{16}H_{24}NO_5$: 310.1654; found: 310.1682.

3-[(*S*)-2-(Benzyloxy)-4-hydroxy-3,3-dimethylbutylamino]propanoic Acid (14a)
Following the typical procedure for **14b** using **13a** (180 mg, 0.61 mmol) in MeOH–THF–H_2O (2:2:1, 4.0 mL) and LiOH·H_2O (83 mg, 1.97 mmol) with column chromatography (silica gel, 100–200 mesh, 3% MeOH–$CHCl_3$) furnished **14a** as a light-yellow oil; yield: 84 mg (58%).

$[\alpha]_D^{27}$ –47.8 (*c* 1.15, $CHCl_3$).

HRMS (FAB): *m*/*z* $[M + H]^+$ calcd for $C_{16}H_{24}NO_5$: 310.1654; found: 310.1678.

^{1}H and ^{13}C NMR spectral data were identical to those of **14b**.

3-[(*R*)-2,4-Dihydroxy-3,3-dimethylbutylamino]propanoic Acid (2b); Typical Procedure
Compound **14b** (60 mg, 0.2 mmol) in MeOH (5 mL) was treated with 10% Pd/C (50 mg, 0.05 mmol). The heterogeneous mixture was degassed and hydrogenated under H_2 atmosphere for 24 h. The catalyst was filtered off and the solvent was concentrated in vacuo and dried. The product was found by NMR to be the desired panto-

thenic acid **2b** obtained as light-yellow oil, which required no further purification; yield: 39 mg (92%).

$[\alpha]_D^{27}$ +81.2 (*c* 1.28, MeOH) {Lit.[19] $[\alpha]_D^{25}$ +82.4 (*c* 1.3, MeOH)}.

IR (neat): 3400, 2948, 1722, 1650 cm^{-1}.

^1H NMR (300 MHz, CD_3OD): δ = 0.93 (s, 6 H), 2.51 (t, *J* = 6.6 Hz, 2 H), 3.37–3.50 (m, 4 H), 3.91 (s, 1 H).

^{13}C NMR (75 MHz, CD_3OD): δ = 21.2, 21.6, 35.8, 36.4, 40.6, 70.7, 77.6, 176.2, 176.8.

HRMS (FAB): *m*/*z* $[M + H]^+$ calcd for $C_9H_{18}NO_5$: 220.1185; found: 220.1209.

3-[(*S*)-2,4-Dihydroxy-3,3-dimethylbutylamino]propanoic Acid (2a)

Following the typical procedure for **2b** using **14a** (60 mg, 0.2 mmol) and Pd/C (50 mg, 0.05 mmol) under a H_2 atmosphere gave **2a** as a pure light-yellow oil; yield: 37 mg (88%).

$[\alpha]_D^{27}$ –80.1 (*c* 1.12, MeOH).

HRMS (FAB): *m*/*z* $[M + H]^+$ calcd for $C_9H_{18}NO_5$: 220.1185; found: 220.1204.

^1H and ^{13}C NMR spectral data were identical to those of **2b**.

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