Biomimetic Synthesis of Hyperolactones

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Biomimetic Synthesis of Hyperolactones

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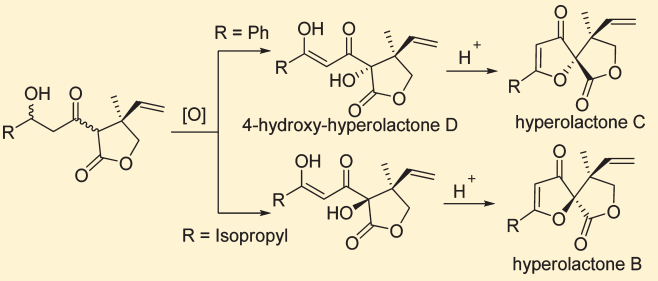
Supporting Information

ABSTRACT: Through a biomimetic pathway, hyperolactone D, 4-hydroxyhyperolactone D, and hyperolactone C were synthesized from methyl acetoacetate via Weiler's dianion method, asymmetric allylic alkylation, biomimetic lactonization, oxidation, and cyclization. The stereochemistry of the quaternary carbon was controlled efficiently by Palladium-catalyzed asymmetric allylic alkylation. This strategy was also used for the synthesis of hyperolactone B.



The plant of *Hypericum chinense L*, which belongs to the *Guttiferae* family, has been used as a folk medicine in Asian countries for a long time. The pharmacological activity inspired Tada and co-workers to investigate the secondary metabolites from this plant. Their work resulted in the isolation of three unique spiro-lactones, hyperolactones A−C, and related compound hyperolactone D (Figure 1).[1] Recently, two new spiro-lactone-related derivatives, 4-hydroxyhyperolactone D (**5**) and 5,6-dihydrohyperolactone D (**6**), were discovered by Kashiwada from the same species.[2] On the basis of spectroscopic and mass spectrometric analysis, the structure of 4-hydroxyhyperolactone D was deduced. However, the structural ambiguity remained at the tertiary-hydroxy-attached carbon (Figure 1).

These spiro-lactone compounds have become synthetic targets due to their unique structure and biological activity. The total synthesis of (±)-hyperolactone A was accomplished from 3-furoic acid and 2-methylbutanal by Kinoshita,[3] and the (+)-hyperolactone B has been synthesized by the same group.[4] Hyperolactone C has been synthesized by several groups.[5] In the course of our research for total synthesis of anti-HIV natural products, we previously reported on the synthesis of hyperolactone C and biyouyanagin A.[6] We have now expanded this work to related molecules, and in this paper we want to report the biomimetic syntheses of 4-hydroxyhyperolactone D and hyperolactones B−D. Through our studies the absolute configuration of 4-hydroxyhyperolactone D was determined.

Biomimetic synthesis of natural products can provide numerous advantages,[7] such as oxidative diversification of low-oxidation-state precursors[8] and exclusion of protecting groups.[9] On the basis of a common skeleton found in hyperolactones A−D, Tada[1b] suggested that the common skeleton may be biosynthesized from polyketide (**7**) and isopentenyl pyrophosphate (**8**). The oxidation and cyclization of an intermediate polyketone (**10**) may give hyperolactone D (R = benzene) and its acyl analogues (**12**), which will be oxidized and cyclized to give hyperolactones as indicated in Scheme 1 (path a).

Since the 1-hydroxy-2-methyl-2-(*E*)-butenyl 4-diphosphate was discovered as a key intermediate for the second isoprenoid biosynthetic pathway starting from 1-deoxy-D-xylulose 5-phosphate,[10] we proposed that the hyperolactones's biogenetic synthesis might preferably start from polyketide (**7**) and 1-hydroxy-2-methyl-2-(*E*)-butenyl 4-diphosphate (**9**). We envisioned that if nucleophilic β-ketoester **7** and electrophilic 1-hydroxy-2-methyl-2-(*E*)-butenyl 4-diphosphate (**9**) could be merged together by an enzyme, a short and efficient synthesis of hyperolactones could be realized after lactonization, selective oxidation, and cyclization of the key intermediate polyketone **11**. (Scheme 1, path b)

With this view in mind, our synthesis of hyperolactone D commenced with benzaldehyde. The δ-hydroxy-β-oxo-pentanoate **13a** was prepared in 92% yield from methyl acetoacetate and benzaldehyde as starting material.[6] With β-ketoester **13a** in hand, the key palladium-catalyzed asymmetric allylic alkylation reaction was investigated. When β-ketoester **13a** was treated with 3 mol % of ligand (*R*,*R*)-**L1** and 1 mol % of $Pd_2(dba)_3 \cdot CHCl_3$ in the presence of isoprene monoepoxide in CH_2Cl_2, the desired branched product **14** and its linear isomer **15** were obtained in 40% and 44% yield, respectively (see Scheme 2). To increase the desired branched product **14**, β-ketoester **13b**, which was prepared from **13a** in 79% yield, was used as the starting material. However, the Pd-AAA reaction did not occur. The effectiveness of the palladium-catalyzed AAA reaction was determined after converting **14** to **16**, and it was found that the enantioselectivity was 89% ee. To improve the selectivity, ligand (*R*,*R*)-**L2** was also used. The desired product **14** was obtained with both better

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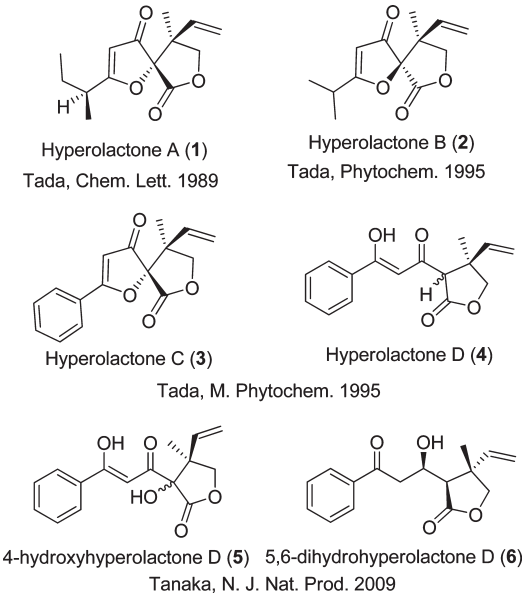
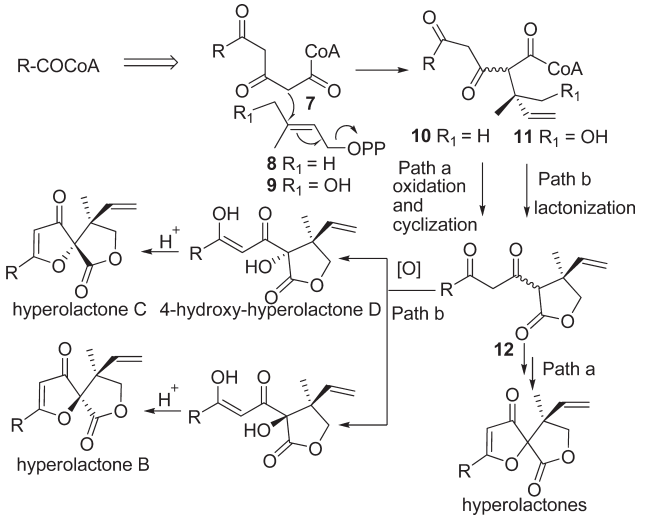


Figure 1. Structures of spiro-lactone hyperolactone A−C and its related derivatives.

Scheme 1. Biosynthesis of Hyperolactones



enantioselectivity (99% ee) and regioselectivity [**14** (48%) and **15** (37%)]. Trost has shown that using tetra-*n*-butylammonium triphenyldifluorosilicate (TBAT) as an additive would increase the regioselectivity without sacrificing the ee in similar reactions.[11] However, in our case TBAT was not effective, and with it the branched and linear product ratio was only 1:1.5. With the desired product **14** in hand, the hyperolactone D was obtained uneventfully after subsequent lactonization and oxidation. Exposure of compound **14** to DBU in methylene chloride at room temperature led to the formation of the corresponding lactone **17** in 71% yield. The lactone **17** was smoothly transformed into hyperolactone D as both diastereomers in the presence of Dess−Martin periodinane. The spectral data of our fully synthetic hyperolactone D (**4**) (^{1}H, ^{13}C NMR, IR, and HRMS) were consistent with those of the natural product.[1b]

The key intermediate **17** was then employed for the synthesis and determination of the absolute configuration of 4-hydroxyhyperolactone D (Scheme 3). The key biomimetic oxidation was first tried by using $CeCl_3 \cdot 7H_2O$ in *i*-PrOH.[12] The oxidation of lactone **17** generated **18a** and **18b** in the ratio of 3:1. We then attempted the method reported by Jens's[13] using $Mn(OAc)_2$ in CH_2Cl_2. Unfortunately, the ratio of **18a** and **18b** was not improved under this condition. Finally, we found that treatment of the lactone **17** with *m*-CPBA in CH_2Cl_2 led to the formation of **18a** and **18b** in a ratio of 4.5:1 with overall yield of 84%, and the use of $FeCl_3 \cdot 6H_2O$ and H_2O_2 in *tert*-amyl alcohol[14] reversed the ratio of **18a** to **18b** 1:2 in 65% yield. The alcohol **18a** was oxidized by DMP to compound **19**, which was treated with HCl to give 4-*epi*-hyperolactone C (**20**). Compound **18b** was oxidized in the same procedure to give the 4-hydroxyhyperolactone D (**5**), which by treatment of HCl was transformed to hyperolactone C (**3**). The spectral data of our synthesized 4-hydroxyhyperolactone D (**5**) (^{1}H, ^{13}C NMR, IR, and HRMS) were consistent with those of natural product,[2] and thus the absolute stereochemistry of 4-hydroxyhyperolactone D was assigned as 3*S*,4*S*-4-hydroxyhyperolactone D.

The method for biomimetic synthesis of hyperolactone C and 4-*epi*-hyperolactone C could be used for synthesizing hyperolactone B (**2**). As shown in Scheme 4, the synthesis of hyperolactone B commenced with isobutyraldehyde and methyl acetoacetate, which were converted to δ-hydroxy-β-oxo-pentanoate **21** via Weiler's dianion method.[15] After the palladium-catalyzed asymmetric allylic alkylation reaction of **21**, the desired branched product **23** and its linear isomer **22** were obtained in the yields of 37% and 33%, respectively. The ee value of the desired branched product **23** could be increased from 92% to 99% when (*R*,*R*)-**L2** was used instead of (*R*,*R*)-**L1** (determined after conversion to the corresponding dihydrofuran **24**). Exposure of compound **23** to DBU and the oxidation of the corresponding lactone **25** by *m*-CPBA provide **26a** and **26b** as a 1:1.1 mixture. After separation by silica gel column chromatography, the hydroxy **26a** was smoothly transformed to hyperolactone B (**2**) in two steps. The spectral data of our fully synthetic hyperolactone B (**2**) (^{1}H, ^{13}C NMR, IR, and HRMS) were consistent with those of the natural product.[1b]

In summary, we have developed a new biomimetic pathway toward hyperolactone D, 4-hydroxyhyperolactone D, and hyperolactone C from methyl acetoacetate. Through our studies the absolute configuration of 4-hydroxyhyperolactone D was determined. The stereochemistry of the quaternary carbon was controlled efficiently by palladium-catalyzed asymmetric allylic alkylation. This strategy was also successfully applied to the total syntheses of hyperolactone B and the stereoisomers of hyperolactone C.

EXPERIMENTAL SECTION

5-Hydroxy-5-aryl-3-oxo-pentanoates 13a. To a suspension of sodium hydride (60%, 0.40 g, 10 mmol) in dry THF (5 mL) was added acetoacetate (0.89 mL, 8.33 mmol) under nitrogen, then after 30 min at rt, butyllithium (in hexane 2.4 M, 4.16 mL, 10 mmol) was added at −15 to −10 °C (ice-salt bath). The mixture was kept at this temperature for 30 min, and then aldehydes (1.06 g, 10 mmol) were added at this temperature. After the mixture was stirred for 1−2 h at low temperature, saturated NH_4Cl (30 mL) was added and the aqueous was extracted with ethyl acetate (3 × 30 mL). The combined extracts was dried and evaporated under vacuum. The residues were subjected to flash chromatography and afforded **13a** (1.70 g, 92%). R_f = 0.33 (silica gel, petroleum ether:ethyl acetate 2:1); IR (thin film) 3494, 2955, 1746, 1713, 1494, 1439, 1405, 1326,

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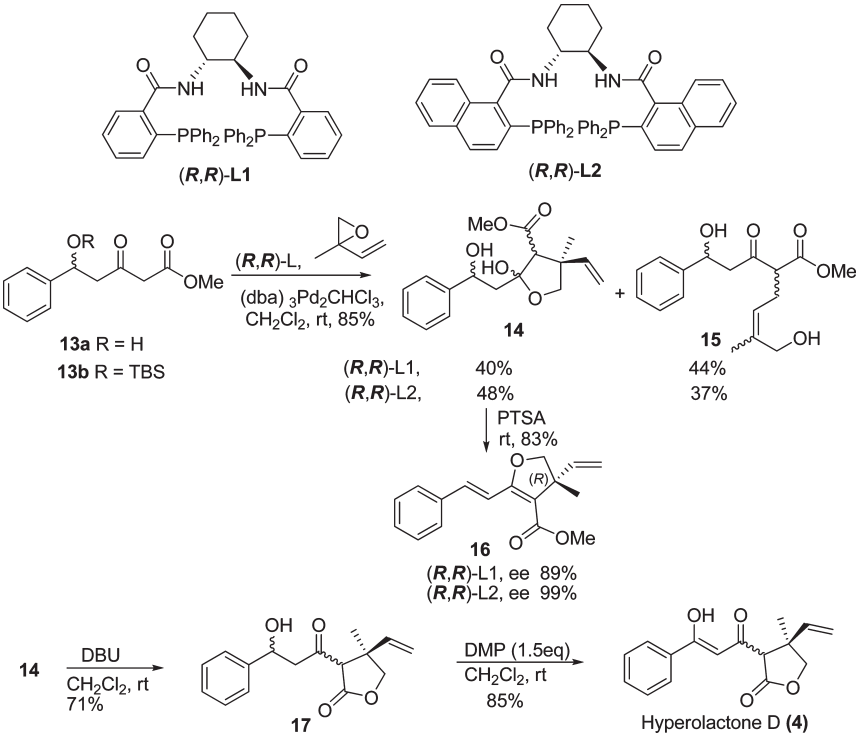
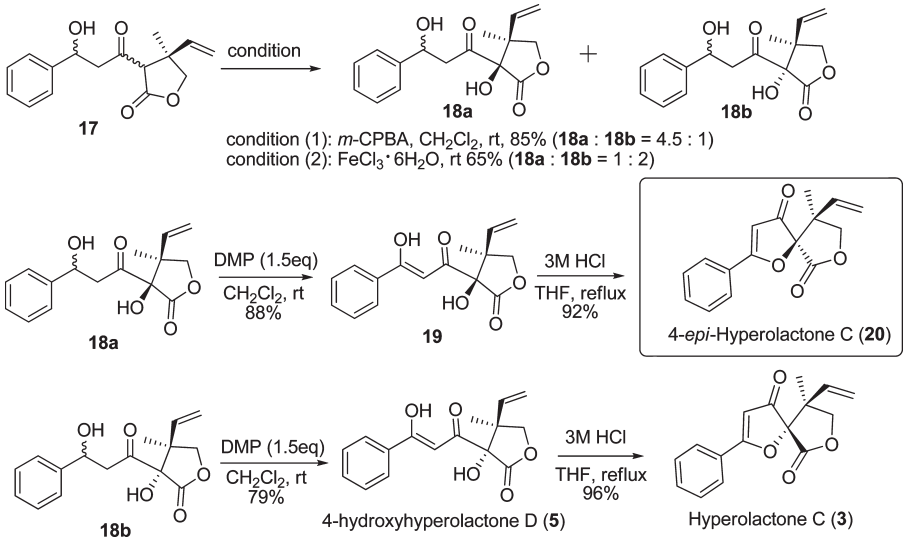
Scheme 2. Synthesis of Hyperolactone D



Scheme 3. Biomimetic Synthesis of 4-Hydroxyhyperolactone D (5), Hyperolactone C (3), and 4-*epi*-Hyperolactone C (20)



754, 702 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.32−7.34 (m, 4H), 7.25−7.28 (m, 1H), 5.14 (dd, J = 9.2, 3.2 Hz, 1H), 3.69 (s, 3H), 3.47 (s, 2H), 2.96 (dd, J = 17.2, 9.2 Hz, 1H), 2.84 (dd, J = 17.2, 3.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 202.7, 167.5, 142.8, 128.6, 128.6, 127.9, 125.7, 69.9, 52.5, 51.7, 49.7; MS (EI) m/z 222 (M^+, 6), 204 (9), 162 (5), 149 (9), 145 (10), 131 (28), 116 (63), 107 (84), 84 (34), 77 (100).

(3*R*)-Methyl Tetrahydro-5-hydroxy-2-(2-hydroxy-2-phenylethyl)-3-methyl-3-vinylfuran-4-carboxylate, 14, and Compound 15. To an oven-dried round-bottomed flask were added $Pd_2dba_3 \cdot CHCl_3$ (4.6 mg, 0.0045 mmol), (*R*,*R*)-**L1** (10.6 mg, 0.0135 mmol) and a stirring bar. The flask was then placed under reduced pressure (vacuum pump) for 10 s and refilled with Ar; this purging procedure was repeated five times to ensure no oxygen remained in the reaction vessel. After being placed under an Ar atmosphere, freshly distilled CH_2Cl_2 (4 mL) was added and the resulting dark purple solution was stirred at room temperature until it turned a deep orange color. During this time, **13a** (100 mg, 0.45 mmol) was added. Finally, 2-methyl-2-vinyloxirane (53 μL, 0.54 mmol) was added to the reaction mixture and the solution turned bright yellow. After 30 min, the solvent was removed in vacuo. The crude product was purified by flash column chromatography (silica gel, petroleum ether:ethyl acetate 6:1) to afford compound **14** (67 mg, 49%) as a colorless oil and **15** (50 mg, 36%) with a total yield of 85%.

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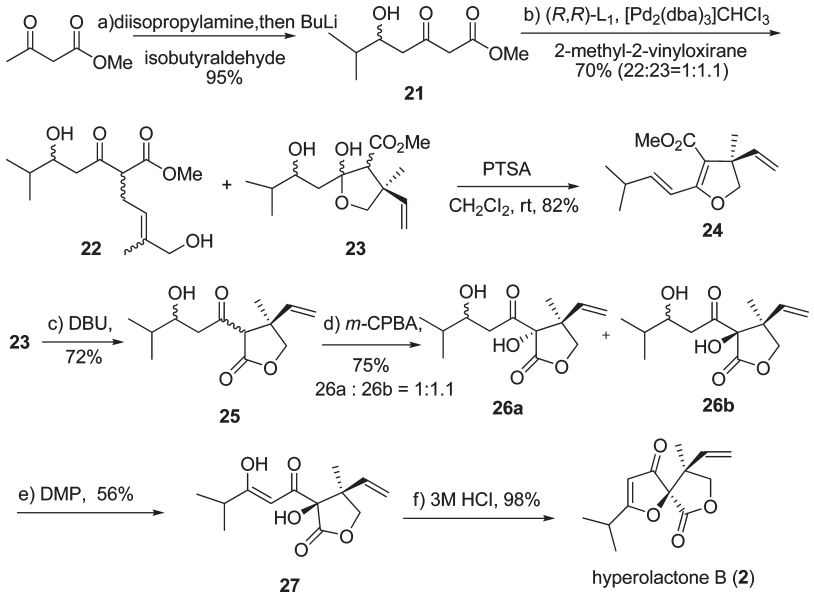
Scheme 4. Total Synthesis of Hyperolactone B (2)



14: R_f = 0.5 (silica gel, petroleum ether:ethyl acetate 2:1); ^{1}H NMR (400 MHz,$CDCl_3$) δ 7.32−7.4 (m, 4H), 7.27−7.28 (m, 1H), 6.14 (dd, J = 10.8, 17.6 Hz, 1H), 5.98 (s, 1H), 5.17 (br s, 1H), 5.16 (d, J = 4.8 Hz, 1H), 5.12 (d, J = 11.2 Hz, 1H), 4.15 (d, J = 8.4 Hz, 1H), 3.74 (d, J = 8.8 Hz, 1H), 3.71 (s, 3 H), 3.49 (br s, 1H), 2.81 (s, 1H), 2.20 (dd, J = 10.4, 14.4 Hz, 1H), 5.14 (dd, J = 1.6, 14.4 Hz, 1H), 1.41 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.0, 144.2, 141.2, 128.4, 127.4, 125.7, 114.3, 105.7, 77.7, 70.9, 62.2, 52.2, 48.5, 47.6, 24.8. MS m/z 306, 288, 270, 256, 241, 226, 221, 189, 182, 167, 150, 135, 127, 125, 106, 105, 104, 95, 81, 79, 77, 67, 55, 43; HRMS (ESI) calcd for $C_{17}H_{22}O_5Na^+$ $[M + Na]^+$ 329.1359, found 329.1353.

15: R_f = 0.2 (silica gel, petroleum ether:ethyl acetate 2:1) ^{1}H NMR (400 MHz,$CDCl_3$) δ 7.35 (m, 4H), 7.27 (m, 1H), 5.19 (m, 1H), 4.06 (m, 1H), 3.98 (s,1H), 3.69 (s, 1H), 3.40 (br s, 1H), 2.82−3.04 (m, 2H), 2.62 (m, 2H), 1.77 (s, 2H), 1.65 (s,1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 206.5, 204.9, 204.7, 171.9, 169.6, 169.4, 142.6, 138.9, 138.2, 138.1, 128.5, 127.8, 125.6, 122.7, 120.4, 120.2, 120.0, 69.8, 69.7, 69.6, 68.1, 68.0, 63.4, 61.1, 60.8, 60.7, 59.1, 58.8, 58.7, 52.7, 52.6, 52.5, 51.6, 51.4, 50.8, 48.2, 29.5, 29.3, 26.2, 21.6, 21.3, 13.7. HRMS (ESI) calcd for $C_{17}H_{22}O_5Na^+$ $[M + Na]^+$ 329.1359, found 329.1362.

(*R*,*E*)-Methyl 4-Methyl-2-styryl-4-vinyl-4,5-dihydrofuran-3-carboxylate, 16. To a solution of compound **14** (36 mg) in CH_2Cl_2 (2 mL) was added catalyzed PTSA, and the resulting mixture was allowed to stir overnight at rt and then the solvent was removed in vacuo. The crude product was purified by flash column chromatography (silica gel, petroleum ether:ethyl acetate 10:1) to afford the product **16** (26 mg) with a yield of 83%. The ee value was 89% when (*R R*)-**L1** was used and it could be improved to more than 99% with use of (*R*,*R*)-**L2** (Chiralcel OD-H, λ = 325.1 nm, hexane:isopropanol 99:1, flow rate = 0.5 mL/min). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.60 (d, J = 16.0 Hz, 1H), 7.53 (d, J = 7.2 Hz, 2H), 7.31−7.38 (m, 3H), 7.25 (d, J = 16.0 Hz, 1H), 6.06 (dd, J = 10.4, 17.6 Hz, 1H), 5.09 (dd, J = 10.8, 17.2 Hz, 2H), 4.35 (d, J = 8.8 Hz, 1H), 4.15 (d, J = 8.8 Hz, 1H), 3.76 (s, 3H), 1.46 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$,) δ 165.7, 164.1, 142.8, 137.1, 136.0, 129.1, 128.7, 127.6, 116.6, 112.8, 111.6, 81.6, 50.8, 49.3, 23.3; HRMS (ESI) calcd for $C_{17}H_{18}O_3Na^+$ $[M + Na]^+$ 293.0784, found 293.0776.

(3*R*)-3-(3-Hydroxy-3-phenylpropanoyl)-3-methyl-3-vinyldihydrofuran-5(3*H*)-one, 17. To a round-bottomed flask was added **14** (215 mg, 0.70 mmol) in 18 mL of CH_2Cl_2, then DBU (6 equiv) in 2 mL of CH_2Cl_2 was added to the above mixture and the solution was stirred overnight at room temperature. The mixture was diluted with saturated NH_4Cl, then dried over anhydrous Na_2SO_4. The solvent was removed. The residue was purified by flash column chromatography (silica gel, petroleum ether:ethyl acetate 6:1) to afford **16** (134 mg, 71%) as a red oil. R_f = 0.42 (silica gel, petroleum ether:ethyl acetate 2:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.79−11.81, 3.44−3.64 and 4.38−4.44 (m, 1H), 7.28−7.36 (m, 5H), 5.11−5.28 (m, 1H), 5.66−5.94 (m, 3H), 3.94−4.12 (m, 2H), 2.95−3.08 (m, 2H), 2.56−2.76 (m, 1H), 1.20 and 1.38 and 1.39 and 1.27 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 204.2, 203.9, 203.3, 203.2, 176.4, 176.4, 172.4, 172.3, 171.9, 171.9, 170.2, 170.0, 143.2, 142.4, 142.4, 142.3, 142.2, 141.8, 139.9, 136.6, 128.6, 128.5, 127.9, 127.8, 127.8, 125.7, 125.6, 125.6, 125.6, 117.2,117.1, 116.0, 114.7, 105.0, 104.8, 78.9, 78.8, 77.3, 77.2, 77.0, 76.7, 76.6, 76.5, 76.4, 76.3, 71.2, 71.1, 69.8, 69.6, 69.4, 69.3, 64.2, 64.1, 61.2, 61.1, 53.5, 53.4, 53.3, 46.6, 43.4, 43.3, 41.2, 23.8, 23.7, 23.6, 23.5, 18.5, 18.4; MS m/z 256, 241, 225, 206, 188, 168, 153, 150, 137, 125, 111, 107, 105, 104, 95, 84, 81, 79, 77, 68, 67, 55, 44, 43; HRMS (ESI) calcd for $C_{16}H_{18}O_4Na^+$ $[M + Na]^+$ 297.1097, found 297.1091.

Hyperolactone D. To a solution of alcohol **17** (76 mg, 0.26 mmol) in CH_2Cl_2 (4 mL) was added DMP (1.5 equiv). The heterogeneous mixture was stirred at rt until the complete consumption of the starting material was observed by TLC (1−3 h). The reaction mixture was diluted with a 1:1 mixture of $NaHCO_3$ (aq) and $Na_2S_2O_3$ (aq). The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2. The combined organic layers were dried with Na_2SO_4 and the solvent was removed in vacuo. The resulting crude residue was purified by flash column chromatography on silica gel, using a mixture of ethyl acetate and hexanes to afford hyperolactone D (66 mg, 88%). R_f = 0.63 (silica gel, petroleum ether:ethyl acetate 2:1); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.86−7.92 (m, 2H), 7.54−7.59 (m, 1H), 7.45−7.49 (m, 2H), 6.36 and 6.29 (s, 1H), 6.01 and 5.91 (dd, J = 11.4, 17.6 Hz, 1H), 5.22 and 5.24 (d, J = 17.6 Hz, 1H), 5.23 and 5.28 (d, J = 11.4 Hz, 1H), 4.52 and 4.23 (d, J = 9.0 Hz, 1H), 4.05 and 4.09 (d, J = 9.0 Hz, 1H), 3.29 and 3.46 (s, 1H), 1.28 and 1.46 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 187.8, 187.2, 184.8, 184.6, 173.1, 172.7, 140.7, 136.9, 134.2 × 2, 133.0 × 2, 128.7 × 2, 127.4, 116.5, 115.2, 98.0, 97.8, 60.9, 58.6, 46.9, 46.8, 23.9, 18.8; MS m/z 272, 267, 257, 249, 241, 225, 209, 193, 183, 181, 167, 147,125, 111, 105, 97, 95, 85, 83, 81, 77, 71, 69, 67, 57, 55, 51, 43, 41;

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HRMS (ESI) calcd for $C_{16}H_{16}O_4Na^+$ $[M + Na]^+$ 295.0941, found 295.0937.

(4*R*,3*S*)-4-Hydroxyl-4-(3-hydroxyl-3-phenylpropanoyl)-3-methyl-3-vinyldihydrofuran-5-(3*H*)-one, 18a, and (4*S*,3*S*)-4-Hydroxyl-4-(3-hydroxyl-3-phenylpropanoyl)-3-methyl-3-vinyldihydrofuran-5(3*H*)-one, 18b. To a solution of **17** (274 mg, 1.0 mmol) in CH_2Cl_2 (25 mL) was added *m*-CPBA (245 mg, 85%, 1.2 equiv) and the resulting mixture was stirred overnight at room temperature. The reaction mixture was quenched with a mixture of saturated $Na_2S_2O_3$ and saturated $NaHCO_3$ and extracted with EtOAc. Combined extracts were dried (Na_2SO_4), filtered, and concentrated in vacuo. Flash chromatography (petroleum ether:EtOAc 6:1) afforded **18b** (44 mg) and **18a** (199 mg) with a total yield of 84%.

18b: R_f = 0.70 (silica gel, petroleum ether:ethyl acetate 2:1); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.29−7.38 (m, 5H), 5.66 (dd, *J* = 11.1, 17.4 Hz, 1H), 5.21 (d, *J* = 10.8 Hz, 1H), 5.17 (d, *J* = 17.6 Hz, 1H), 5.05 (dd, *J* = 10.5, 3.0 Hz, 1H), 4.43 (d, *J* = 8.7 Hz, 1H), 4.02 (d, *J* = 8.7 Hz, 1H), 3.52 (br s, 1H, OH), 3.39 (dd, *J* = 14.1, 11.1 Hz, 1H), 2.48 (dd, *J* = 13.5, 3.0 Hz, 1H), 1.31 (s, 3H); ^{13}C (NMR 75 MHz, $CDCl_3$) δ 209.3, 175.3, 142.3, 135.1, 128.7, 128.2, 125.5, 118.3, 87.1, 73.8, 72.3, 49.4, 48.2, 19.4; HRMS (ESI) calcd for $C_{16}H_{18}O_5Na^+$ $[M + Na]^+$ 313.1046, found 313.1051.

18a: R_f = 0.60 (silica gel, petroleum ether:ethyl acetate 2:1); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.31−7.42 (m, 5 H), 5.99 (dd, *J* = 11.4, 17.4 Hz, 1H), 5.60 (b, 1 H), 5.30 (d, *J* = 11.2 Hz, 1H), 5.22 (d, *J* = 17.6 Hz, 1H), 5.12 (dd, *J* = 10.5, 3.0 Hz, 1H), 4.28 (d, *J* = 9.3 Hz, 1H), 4.17 (d, *J* = 9.3 Hz, 1H), 3.65 (b, 1H), 3.52 (dd, *J* = 13.5, 10.5 Hz, 1H), 2.59 (dd, *J* = 13.5, 3.0 Hz, 1H), 1.12 (s, 3H); ^{13}C (NMR 75 MHz, $CDCl_3$) δ 209.1, 175.1, 142.2, 136.6, 128.7, 128.2, 125.6, 116.0, 86.0, 73.7, 72.3, 49.0, 48.3, 16.0; MS *m*/*z* 290, 272, 257, 238, 205, 149, 142, 131, 127, 125, 107, 106, 105, 97, 96, 91, 85, 81, 77, 71, 69, 68, 67, 51, 50, 43, 40; HRMS (ESI) calcd for $C_{16}H_{18}O_5Na^+$ $[M + Na]^+$ 313.1046, found 313.1059.

4-Hyproxyhyperolactone D. Following the procedure for hyperolactone D with **18b** (76 mg, 0.26 mmol) gave a residue that was purified by flash column chromatography (silica gel, petroleum ether:ethyl acetate 6:1) to afford compound 4-hyproxyhyperolactone D (66 mg, 88%). $[\alpha]^{20}_D$ −166 (*c* 1.0, $CHCl_3$) [lit. $[\alpha]^{20}_D$ −118 (*c* 0.3, $CHCl_3$)]; ^{1}H NMR (300 MHz, $CDCl_3$) δ 15.59 (b, 1H), 7.88−7.90 (m, 2H), 7.54−7.58 (m, 1H), 7.45−7.48 (m, 2H), 6.63 (s, 1H), 5.80 (dd, *J* = 11.2, 17.6 Hz, 1H), 5.19 (dd, *J* = 10.8, 17.2 Hz, 2H), 4.68 (d, *J* = 8.8 Hz, 1H), 4.12 (d, *J* = 8.8 Hz, 1H), 3.60 (b, 1H), 1.34 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 195.6, 181.6, 175.6, 135.6, 133.3, 133.1, 128.8, 127.2, 117.6, 93.3, 84.0, 75.2, 49.8, 19.8; MS *m*/*z* 288, 272, 257, 238, 205, 149, 142, 131, 127, 125, 107, 106, 105, 97, 96, 91, 85, 81, 77, 71, 69, 68, 67, 51, 50, 43, 41; HRMS (ESI) calcd for $C_{16}H_{16}O_5Na^+$ $[M + Na]^+$ 311.0890, found 311.0888.

(3*R*,4*S*,*Z*)-3-Hydroxy-3-(3-hydroxy-3-phenylacryloyl)-4-methyl-4-vinyldihydrofuran-2(3*H*)-one, 19. To a solution of alcohol **18a** (92 mg, 0.32 mmol) in CH_2Cl_2 (4 mL) was added DMP (1.5 equiv). The heterogeneous mixture was stirred at rt until the complete consumption of the starting material was observed by TLC (1−3 h). The reaction mixture was diluted with a 1:1 mixture of $NaHCO_3$ (aq) and $Na_2S_2O_3$ (aq). The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2. The combined organic layers were dried with Na_2SO_4 and the solvent was removed in vacuo. The resulting crude residue was purified by flash column chromatography on silica gel with use of a mixture of ethyl acetate and hexanes to afford compound **19** (72 mg, 79%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 15.73 (br s, 1H), 7.89−7.92 (m, 2H), 7.54−7.59 (m, 1H), 7.36−7.48 (m, 2H), 6.74 (s, 1H), 5.98 (dd, *J* = 10.5, 17.7 Hz, 1H), 5.31 (dd, *J* = 10.8, 17.1 Hz, 2H), 4.44 (d, *J* = 8.7 Hz, 1H), 4.36 (d, *J* = 8.7 Hz, 1H), 3.57 (br s, 1H), 1.21 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 194.9, 182.1, 175.4, 137.1, 133.3, 133.1, 128.8, 127.3, 116.4, 93.6, 83.3, 74.5, 49.4, 16.6; HRMS (ESI) calcd for $C_{16}H_{16}O_5Na^+$ $[M + Na]^+$ 311.0890, found 311.0898.

4-*epi*-Hyperolactone C. To a solution of **19** (72 mg, 0.25 mmol) in THF (10 mL) was added several drops of 3 M HCl, and then the solution was heated under reflux for 4 h. After cooling, the solution was diluted with saturated $NaHCO_3$ (aq) and extracted with ethyl acetate. The combined organic layers were dried with Na_2SO_4 and the solvent was removed in vacuo. The resulting crude residue was purified by flash column chromatography on silica gel with use of a mixture of ethyl acetate and hexanes to afford 4-*epi*-hperolactone C (**20**) (64 mg, 96%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.84−7.86 (m, 2H), 7.60−7.63 (m, 1H), 7.50−7.54 (m, 2H), 6.06 (dd, *J* = 11.2, 17.6 Hz, 1H), 6.06 (s, 1 H), 5.35 (dd, *J* = 10.8, 17.6 Hz, 2H), 4.79 (d, *J* = 8.8 Hz, 1H), 4.39 (d, *J* = 8.8 Hz, 1H), 1.30 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 196.6, 187.4, 168.1, 136.7, 133.6, 129.0, 127.6, 127.4, 127.4, 116.2, 100.3, 92.3, 73.3, 48.8, 15.4; HRMS (ESI) calcd for $C_{16}H_{14}O_4Na^+$ $[M + Na]^+$ 293.0784, found 293.0789.

Methyl 5-Hydroxy-6-methyl-3-oxoheptanoate, 21. *n*-Butyllithium (3.8 mL, 2.5M, 2.2 equiv) was added to a solution of diisopropylamine (1.4 mL, 2.4 equiv) in THF under Ar at −60 °C. The solution was stirred at this temperature for 8 min and 3 min at room temperature. Then acetoacetate (464 μL, 4.31 mmol, 1 equiv) was added to the above solution at −60 °C. The solution was stirred at this temperature for 20 min and 5 min at room temperature, and then isobutyraldehyde was added to the solution at −60 °C. With naturally elevating the temperature, the mixture was stirred for 4 h and then diluted with saturated NH_4Cl. The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2. The combined organic layers were dried with Na_2SO_4 and the solvent was removed in vacuo. The resulting mixture was purified by flash column chromatography (silica gel, petroleum ether:ethyl acetate 6:1) to afford compound **21** (769 mg, 95%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.68 (m, 1H), 3.57 (s, 3H), 3.40 (s, 2H), 3.09 (br s, 1H), 2.50 (m, 2H), 1.52 (dd, *J* = 6.4, 12.8 Hz, 1H), 0.78 (d, *J* = 6.4 Hz, 3H), 0.75 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 203.5, 167.4, 71.8, 51.9, 49.3, 46.6, 33.0, 18.0, 17.2; MS *m*/*z* 89, 171, 157, 155, 153, 145, 116, 113, 101, 97, 85, 71, 49, 43.

(4*R*)-Methyl 2-Hydroxy-2-(2-hydroxy-3-methylbutyl)-4-methyl-4-vinyltetrahydrofuran-3-carboxylate, 22. Following the procedure for **14** with **21** (370 mg, 1.97 mmol) as the starting material gave a residue that was purified by flash column chromatography (silica gel, petroleum ether:ethyl acetate 6:1) to afford compound **22** (177 mg, 33%) and **23** (198 mg, 37%) with a total yield of 70%.

23: ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.76−6.13 (m, 1H), 5.03−5.11 (m, 2H), 3.84 (m, 2H), 3.65−3.74 (m, 3H), 2.76−2.92 (m, 1H), 1.60−1.87 (m, 3H), 1.22−1.37 (m, 3H), 0.87−0.89 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.9, 144.0 × 2, 141.0 × 2, 114.5, 114.1, 112.8, 112.5, 106.1 × 3, 72.9, 72.8, 72.9, 72.8, 72.0 × 2, 62.7, 62.1, 60.1, 59.8, 52.3, 52.1, 52.0, 47.5, 47.4, 43.5, 43.3, 43.0, 42.7, 33.9 × 2, 33.5 × 2, 24.8, 24.7, 20.4, 20.3, 18.2 × 2, 17.5 × 2, 17.3 × 2; MS *m*/*z* 255, 137, 211, 183, 179, 165, 152, 141, 127, 109, 95, 81, 73, 67, 55, 43; HRMS (ESI) calcd for $C_{14}H_{24}O_5Na$ $[M + Na]$ 295.1516, found 295.1519.

22: ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.20 (m, 1H), 4.12 (dd, *J* = 13.4, 20 Hz, 2H), 3.89 (br s, 1H), 3.74 (s, 3H), 3.60 (dd, *J* = 7.6, 15.6 Hz, 1H), 2.70 (m, 4H), 2.24 (br s, 1H), 1.79 (s, 3H), 1.70 (m, 1H), 0.93 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 206.4, 206.1, 169.7, 138.4, 122.8, 72.1, 71.0, 61.2, 59.2, 59.0, 52.6, 46.8, 45.9, 33.0, 26.5, 21.7, 18.4, 18.3, 17.7, 17.6; HRMS (ESI) calcd for $C_{14}H_{24}O_5Na^+$ $[M + Na]^+$ 295.1516, found 295.1508.

(4*R*)-3-(3-Hydroxy-4-methylpentanoyl)-4-methyl-4-vinyldihydrofuran-2(3*H*)-one, 25. Following the procedure for **17** with **23** (323 mg, 1.19 mmol) as the starting material gave a residue that was purified by flash column chromatography (silica gel, petroleum ether:ethyl acetate 6:1) to afford compound **25** (205 mg, 72%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.83−5.98 (m, 1H), 5.17−5.30 (m, 2H), 4.08−4.15(m, 1H), 3.99−4.03 (m, 1H), 3.75−3.88 (br s, 1H), 3.48−3.69 (dd, *J* = 15.2 Hz, 1H), 2.65−2.79 (m, 2H), 2.28−2.41 (m, 1H), 1.67−1.74 (br s, 1H), 1.28−1.44 (m, 3H), 0.90−0.95 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 205.6, 205.1, 204.8, 204.4, 176.4, 176.3,

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172.6, 172.1, 172.0, 171.9, 141.9, 140.1, 136.7 × 2, 117.1, 115.8 × 2, 114.6, 104.5, 104.3, 78.9, 78.7, 73.7, 73.3, 72.3, 72.1, 71.8, 71.7, 64.4, 64.2, 61.4, 61.2, 48.9 × 2, 48.7, 48.5, 46.5, 46.4, 43.4, 36.1, 35.8, 33.7 × 2, 33.1 × 2, 33.0 × 2, 23.9, 23.8, 23.7, 23.6, 18.5, 18.3 × 3, 17.6, 17.5 × 2, 17.4; MS *m*/*z* 241, 223, 207, 197, 179, 168, 153, 150, 135, 125, 111, 109, 95, 81, 79, 77, 73, 67, 55, 43, 39; HRMS (ESI) calcd for $C_{13}H_{24}O_4N^+$ $[M + NH_4]^+$ 258.1700, found 258.1707.

(3*S*,4*S*)-3-Hydroxy-3-(3-hydroxy-4-methylpentanoyl)-4-methyl-4-vinyldihydrofuran-2(3*H*)-one, 26a, and (3*S*,4*S*)-3-Hydroxy-3-(3-hydroxy-4-methylpentanoyl)-4-methyl-4-vinyldihydrofuran-2(3*H*)-one 26b. Following the procedure for **18a** and **18b** with **27** (111 mg) as the starting material gave a residue that was purified by flash column chromatography (silica gel, petroleum ether:ethyl acetate 6:1) to afford compound **26a** (41 mg) and **26b** (47 mg) with a total yield of 75%.

26a: ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.71 (dd, J = 10.8, 17.6 Hz, 1H), 5.28 (d, J = 11.2 Hz, 1H), 5.18 (d, J = 17.6 Hz, 1H), 4.43 (d, J = 8.8 Hz, 1H), 4.00 (d, J = 8.8 Hz, 1H), 3.75−3.80 (br s, 1H), 3.09 (dd, J = 11.2, 12.8 Hz, 1H), 3.21 (d, J = 13.2 Hz, 1H), 1.70−1.78 (m, 1H), 1.31 (s, 3H), 0.92−0.98 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 211.2, 175.7, 135.3, 118.2, 87.1, 77.3, 77.0, 76.7, 75.3, 73.8, 49.4, 42.8, 34.2, 19.4, 17.9, 17.3; MS *m*/*z* 257, 239, 210, 195, 185, 171, 159, 155, 142, 127, 97, 81, 73, 69, 55, 43, 39; HRMS (ESI) calcd for $C_{13}H_{24}O_5N^+$ $[M + NH_4]^+$ 274.1649, found 274.1647.

26b: ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.01 (dd, J = 10.8, 17.2 Hz, 1H), 5.30 (d, J = 10.8 Hz, 1H), 5.23 (d, J = 17.6 Hz, 1H), 4.26 (d, J = 8.8 Hz, 1H), 4.14 (d, J = 8.8 Hz, 1H), 3.79−3.84 (br s, 1H), 3.20 (dd, J = 11.2, 12.8 Hz, 1H), 2.30 (d, J = 12.8 Hz, 1H), 1.73−1.78 (m, 1H), 1.14 (s, 3H), 0.92−0.94 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 211.0, 175.5, 136.8, 115.6, 86.1, 77.3, 77.0, 76.7, 75.2, 73.7, 48.9, 42.9, 34.1, 17.9, 17.3, 16.2; MS *m*/*z* 257, 239, 210, 195, 185, 171, 159, 155, 142, 127, 97, 81, 73, 69, 55, 43, 39; HRMS (ESI) calcd for $C_{13}H_{20}O_5Na^+$ $[M + Na]^+$ 279.1203, found 279.1209.

(3*R*,4*S*)-3-Hydroxy-3-((*Z*)-3-hydroxy-4-methylpent-2-enoyl)-4-methyl-4-vinyldihydrofuran-2(3*H*)-one, 27. Following the procedure for hyperolactone D (**4**) with **26b** (47 mg, 0.18 mmol) as the starting material gave a residue that was purified by flash column chromatography (silica gel, petroleum ether:ethyl acetate 6:1) to afford compound **27** (26 mg, 55.8%) and it could also be directly used in the next step without purification (there was only one product in this step, but the yield was not very satisfiying after purification and the reason was unclear). ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.93 (dd, J = 10.8, 17.6 Hz, 1H), 5.43 (s, 1H), 5.30 (d, J = 9.2 Hz, 1H), 5.27 (d, J = 16.0 Hz, 1H), 4.70 (d, J = 8.8 Hz 1H), 4.31 (d, J = 8.4 Hz, 1H), 2.83 (dd, J = 6.8, 14.0 Hz, 1H), 1.58 (br s, 1H), 1.31 (d, J = 12 Hz, 3H), 1.29 (d, J = 2.4 Hz, 3H), 1.27 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 201.2, 197.5, 168.1, 136.7, 116.0, 101.2, 73.2, 48.4, 37.0, 30.4, 19.7, 19.4, 15.4; MS *m*/*z* 254, 237, 211, 193, 153, 142, 125, 113, 97, 86, 71, 68, 53, 43, 41, 39; $C_{13}H_{18}O_5$ Na^+ $[M + Na]^+$ 277.1046, found 277.1051.

Hyperolactone B. To a solution of **27** (8 mg) in THF was added three drops of 3 M HCl, and the mixture was heated under reflux for 4 h. The resulting solution was diluted with saturated $NaHCO_3$ (aq) and extrated with ethyl acetate. The combined organic layers were dried with Na_2SO_4 and the solvent was removed in vacuo. The resulting crude residue was purified by flash column chromatography on silica gel with a mixture of ethyl acetate and hexanes to afford hyperolactone B (7.3 mg, 98%). HRMS (ESI) calcd for $C_{13}H_{20}O_4N^+$ $[M + NH_4]^+$ 254.1387, found 254.1383. $[\alpha]^{20}_D$ +262.5(*c* 0.16, ethanol) [lit. $[\alpha]^{20}_D$ +411 (*c* 0.018, ethanol)], mp 51 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.93 (dd, J = 11.5, 18.0 Hz, 1H), 5.42 (s, 1H), 5.28 (dd, J = 1.2, 10.4 Hz, 2H), 4.69 (d, J = 9.0 Hz, 1H), 4.30 (d, J = 9.0 Hz, 1H), 2.83 (m, 1H), 1.26−1.28 (m, 6H), 1.22 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 201.2, 197.4, 168.1, 136.7, 116.0, 101.2, 91.8, 73.2, 48.4, 30.4, 19.7, 19.4, 15.4; MS *m*/*z* 136, 193, 177, 165, 153, 95, 81, 67, 53, 43, 39.

(*R*,*E*)-Methyl 4-Methyl-2-(3-methylbut-1-en-1-yl)-4-vinyl-4,5-dihydrofuran-3-carboxylate, 24. Following the procedure for preparing compound **16**, compound **23** (100 mg) was used as starting material to give a residue that was purified by flash column chromatography (silica gel, petroleum ether:ethyl acetate (10:1) to afford product **24** (71 mg, 82%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.83 (dd, J = 1.6, 16 Hz, 1H), 6.42 (dd, J = 6.8, 16 Hz, 1H), 6.00 (dd, J = 10, 17.6 Hz, 1H), 5.04 (s, 1H), 5.00 (dd, J = 0.8, 6 Hz, 1H), 4.24 (d, J = 8.8 Hz, 1H), 4.03 (d, J = 8.8 Hz, 1H), 3.68 (s, 3H), 2.45 (m, 1H), 1.37 (d, J = 10 Hz, 3H), 1.03 (d, J = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.7, 164.4, 148.0, 142.9, 116.4, 112.5, 109.7, 81.4, 50.5, 49.1, 31.6, 23.2, 21.7; $C_{14}H_{20}O_3Na^+$ $[M + Na]^+$ 259.1305, found 259.1299. The ee value was 92% when (*R*,*R*)-**L1** was used and it could be improved to abpout 99% with (*R*,*R*)-**L2** (Chiralcel OD-H, λ = 290.6 nm, hexane:isopropanol 99:1, flow rate = 0.5 mL/min).

■ ASSOCIATED CONTENT

Supporting Information. ^{1}H and ^{13}C spectra, and HPLC for all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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