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Construction of Chiral Tertiary Alcohol Stereocenters via the [2,3]-Meisenheimer Rearrangement: Enantioselective Synthesis of the Side-Chain Acids of Homoharringtonine and Harringtonine

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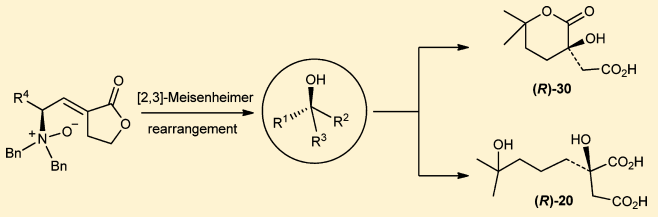
Supporting Information

ABSTRACT: For the first time, the [2,3]-Meisenheimer rearrangement has been developed into a general strategy for the construction of chiral tertiary alcohols. The effectiveness and practicality of this methodology are illustrated by the successful synthesis of (*R*)-**20** and (*R*)-**30**, the side chain acids of homoharringtonine and harringtonine, respectively.



INTRODUCTION

The construction of chiral tertiary alcohol functionalities is a continuing challenge in the synthesis of complex bioactive molecules.[1] Although successful strategies for the construction of chiral tertiary alcohols have been developed over the past three decades, there is still a strong demand for new strategies due to the complexity and diversity of bioactive molecules. Successful strategies include the following: (a) the Sharpless asymmetric dihydroxylation, Sharpless asymmetric epoxidation, Jacobsen asymmetric epoxidation, Shi asymmetric epoxidation of trisubstituted olefins,[1] (b) a most exciting discovery in 2008 of the 1,2-metalate rearrangement of boronate complexes,[2] (c) the kinetic resolution of tertiary alcohols derived from aldol reactions of ketones, which is efficient and suitable for large-scale preparation,[3] (d) the catalytic asymmetric additions of organometallic reagents to ketones,[1] (e) a variety of aldol-type reactions catalyzed by chiral Lewis acid, Lewis base or chiral copper reagents,[1] and (f) a variety of other types of reactions.[1] In connection with our interest in the enantioselective synthesis of the side chain acids of homoharringtonine and harringtonine, we intended to create a new strategy based on the [2,3]-Meisenheimer rearrangement (Figure 1), which we hypothesized would be able to satisfy the requirements of the complexity and diversity of bioactive molecules.

While the Meisenheimer rearrangement is a 90-year-old reaction, it was not efficiently utilized for the construction of chiral secondary alcohol stereocenters until 1991 when Reetz et al.[4] used it with a self-immolative method. In the ensuing 10 years, Enders, Coldham, Micouin, and Guarna each studied the chiral auxiliary method for carrying out this transformation.[5] Unfortunately, only moderate diastereoselectivities were achieved (de < 73%). However, Davies and Micouin reached excellent diastereoselectivities (de >95%) using a combination of the self-immolative and chiral auxiliary methods.[5] After another decade, Tambar and co-workers[6] achieved a milestone for developing the first catalyzed enantioselective [2,3]-Meisenheimer rearrangement with high ee values (>87%). To the best of our knowledge, in spite of the significant progress made in the synthesis of chiral secondary alcohol via the [2,3]-Meisenheimer rearrangement,[7] no substantial efforts were made to construct the chiral tertiary alcohols via the [2, 3]-Meisenheimer rearrangement. Despite the unfavorable factors (Scheme 1, eq 1, −50 °C, 2 days) encountered during the synthesis of chiral secondary alcohols, we decided to modify Reetz's system, which uses a disubstituted alkene, to use a trisubstituted alkene for the construction of chiral tertiary alcohol.

RESULTS AND DISCUSSION

Trisubstituted alkene **3**[8] (Scheme 1) was chosen as a substrate for model studies. We hoped to observe 100% transfer of chirality in the transformation of **3**→**4** as observed by Reetz and Lauterbach[4] in the transformation of **1** → **2**. To our great delight, after oxidation with *m*-CPBA, **3** immediately took a spontaneous [2,3]-Meisenheimer rearrangement to form an unstable compound, **4**, which slowly underwent a [1,3]-transfer to yield compound **5** when allowed to stand at room temperature or during purification using silica gel column chromatography.[9] As such, the reaction mixture was washed with 10% NaOH aqueous solution to yield crude compound **4**, which was immediately hydrogenated at 10 °C to afford **6** in which the N−O bond could be cleaved at 60 °C to afford the chiral tertiary alcohol **7**. The transformation of **3** → **4** → **5** was difficult to monitor by TLC because compounds **3**−**5** had identical R_f values. The 100% transfer of chirality of **3** → **4** was confirmed by comparing the ee values of **3** and **6** (75% ee vs 75% ee). We propose that transition state **3a** leads to the observed *S*-configured products **4**, as opposed to the sterically less favorable transition state, **3b**, which would provide the *R*-configured analogues of **4** (not observed).[10] Next, the

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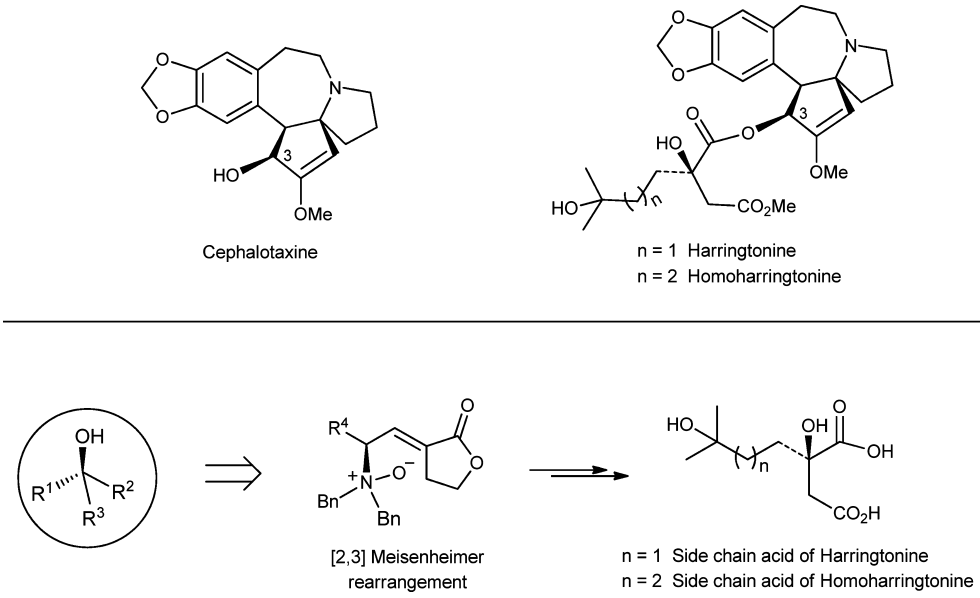

Figure 1. [2,3]-Meisenheimer rearrangement has the potential to be a general strategy for the construction of chiral tertiary alcohol stereocenters.

trisubstituted alkene **8** (E/Z = 1:0.52) was prepared.[11] It rearranged with the same ease as **3** to afford compound **9**, which was more unstable than compound **4** and necessitated hydrogenation at −10 °C.[12] The configuration of chiral carbon atom in product **9** was expected to be both *S* and *R* because compound **8** was a mixture of *cis*- and *trans*-olefins. With the success of these model studies, we decided to undertake the enantioselective synthesis of side chain acids of homoharringtonine and harringtonine.

Homoharringtonine (HHT) and its homologue harringtonine (HT) have potent antileukemic activities. In particular, HHT has reached phase III clinical trials in the United States against chronic myelogenous leukemia, while in China, it is used as a front-line therapy for acute myeloid leukemia and shows activity against the chloroquinine-resistant *Plasmodium falciparum* malaria parasite in vitro.[13c] Because the inactive cephalotaxine (Figure 1) can compose as much as ca. 50% of total alkaloid extracts, the most practical path for obtaining large quantities of HHT and HT at the present time is through semisynthesis by coupling the carboxyl group of the respective ester side chain to the C-3 hydroxyl group of cephalotaxine. Several groups have reported enantioselective syntheses of the side chains of HHT and HT.[13] In this paper, we present a new route for synthesizing these side chains and elucidate the important role that the [2,3]-Meisenheimer rearrangement plays in the construction of chiral tertiary alcohol motif (vide infra).

As shown in Scheme 2, side chain acid **20** of HHT was synthesized from methyl 3(*S*)-[(*tert*-butoxycarbonyl)amino]-4-hydroxybutanoate **11**, which was commercially available and also easily prepared from L-aspartic acid according to the literature procedure.[14] Treatment of ester **11** with MeMgI afforded 1,4-diol **12** in 85% yield.[15] Attempted oxidation of **12** using PCC or PDC led to the undesired lactone. Swern oxidation of **12** resulted in decomposition of the starting material. However, to our delight, the employment of IBX as an oxidizing reagent furnished lactol **13** as a 1:1 diastereomeric mixture in almost quantitative yield.[16] Next, Witting coupling between lactol **13** and 1-butyrolactonylidene triphenylphosphorane **14** provided exclusively the desired (*E*)-olefin **15** in 85% yield.[17,18] Deprotection of olefin **15** and subsequent benzyl bromide alkylation of the resulting TFA salt in the presence of K_2CO_3 provided allylamine **16**, the precursor for the [2,3]-Meisenheimer rearrangement, in 80% yield. Allylamine **16** was treated with *m*-CPBA, while the reaction was cooled in an ice bath to provide **17** as an unstable [2,3]-Meisenheimer product. After the reaction mixtures were washed with 10% NaOH aqueous solution, the concentrated residues were hydrogenated without further purification first at 5−20 °C to saturate the double bonds and then at 60 °C to cleave the N−O bond to furnish **18** and **19** in a 7:3 ratio (column chromatographic separation).[19] After surveying a large number of oxidation methods, including Jones oxidation,[19] PDC−DMF oxidation,[20] CrO_3−H_5IO_6 oxidation,[21] $KMnO_4$ oxidation,[19] etc., we found that oxidation with the TEMPO−NaClO−$NaClO_2$ system gave diacid **20** cleanly and in excellent yield.[22] The overall yield for **11** → **20** was 36.2% over eight linear steps. However, the NMR spectra, optical rotation, and solubility in $CHCl_3$ for diacid **20** were not identical to those reported by Tietze et al.[13d,23] To confirm the structure, we further converted **20** to its diester **21** with 2,2-dimethoxypropane in the presence of TMSCl.[24] The NMR data, optical rotations, EIMS, IR, and melting point of diester **21** are completely identical with the data reported by d'Angelo et al.[13f] and Powell et al.[25] Therefore, the structure assigned to **20** by Tietze et al. is most likely mis-assigned. In addition, the very small difference between the $[\alpha]^{20}_{D}$ −17.5 (c = 0.7, $CHCl_3$) of our own material and the $[\alpha]^{20}_{D}$ −18.0 (c = 0.7, $CHCl_3$) for the methanolysis of natural HHT[25] indicated a perfect chirality transfer of **16** → **17** at 5 °C (using an ice bath) during the [2,3]-Meisenheimer rearrangement.

To the best of our knowledge, the construction of a chiral quaternary carbon through a [2,3]-Meisenheimer rearrangement has never been developed as a general and viable strategy.[1] Our enantioselective synthesis of the side chain acid of homoharringtonine serves as the first illustrative example of this strategy.[4−7] To improve the practicality and effectiveness of this strategy, the double bond must be left intact during the N−O bond cleavage, which would allow for further elaboration of the rearranged side chain of chiral quaternary carbon. This is

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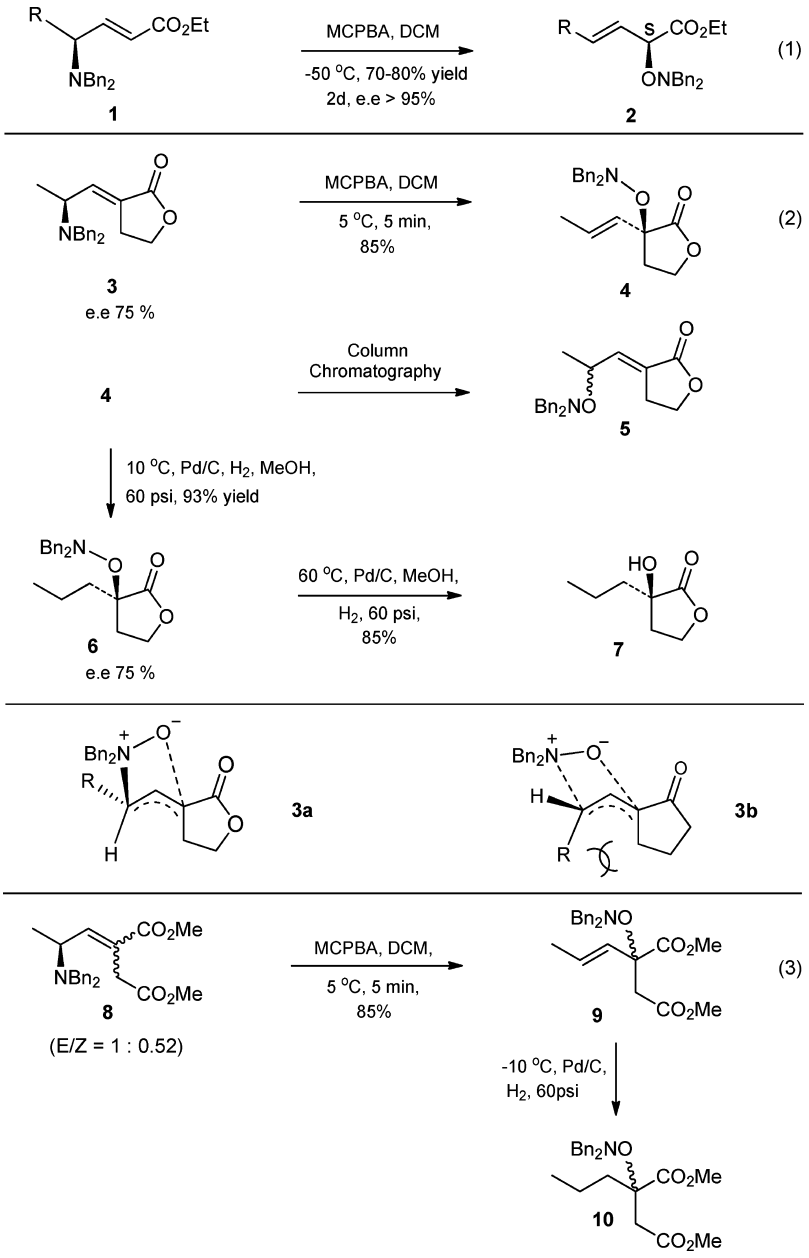
Scheme 1. Model Studies of the [2,3]-Meisenheimer Rearrangement



illustrated in the synthesis of side chain acid HT, **30** (Scheme 3).

The synthesis of **30** began from *N*-Boc-aldehyde **22**, which was conveniently prepared from L-threonine according to the literature procedure.[26] Protected aldehyde **22** was transformed into *E*-substituted alkene **24** by successive manipulation involving the Wittig reaction, deprotection, and *N*-bisbenzylation. Upon treating **24** with *m*-CPBA in CH_2C1_2 at 5 °C, hydroxylamine **25** was formed as the sole product. After the reaction system was washed with 10% NaOH aqueous solution, the concentrated residues were dissolved in concentrated HCl–MeOH solution without further purification, and zinc powder was added under vigorous stirring. TLC indicated a complete reaction after 20 min, and the reaction was quenched with a cold saturated ammonium hydroxide solution. Extraction and column chromatographic separation afforded **26** in 75% total yield.[27] Attempts to improve the reduction yield by using other reductants, including Al (Hg),[28] Na (liq NH_3),[29] $CuSO_4$,[30] and TMSI[31] proved fruitless. Compound **26** is a versatile chiral building block because any of the carbon chains from the chiral stereocenter are suitable for further elaboration to achieve desired functionalities. Compound **26** was easily transformed into the side chain acid of HT, **30**, by successive manipulation involving a MnO_2 oxidation,[32] a selective Grignard reaction with the enone,[33] double-bond hydrogenation, a TEMPO-mediated oxidation of the lactone, and the formation of a new 6-membered lactone.[34] The total yield was 34.7% over nine linear steps.

■ CONCLUSIONS

In conclusion, we have developed a highly enantioselective process for the synthesis of the side-chain acids of homoharringtonine and harringtonine. This study expands the usefulness of the [2,3]-Meisenheimer rearrangement to include the efficient synthesis of chiral tertiary alcohols for the

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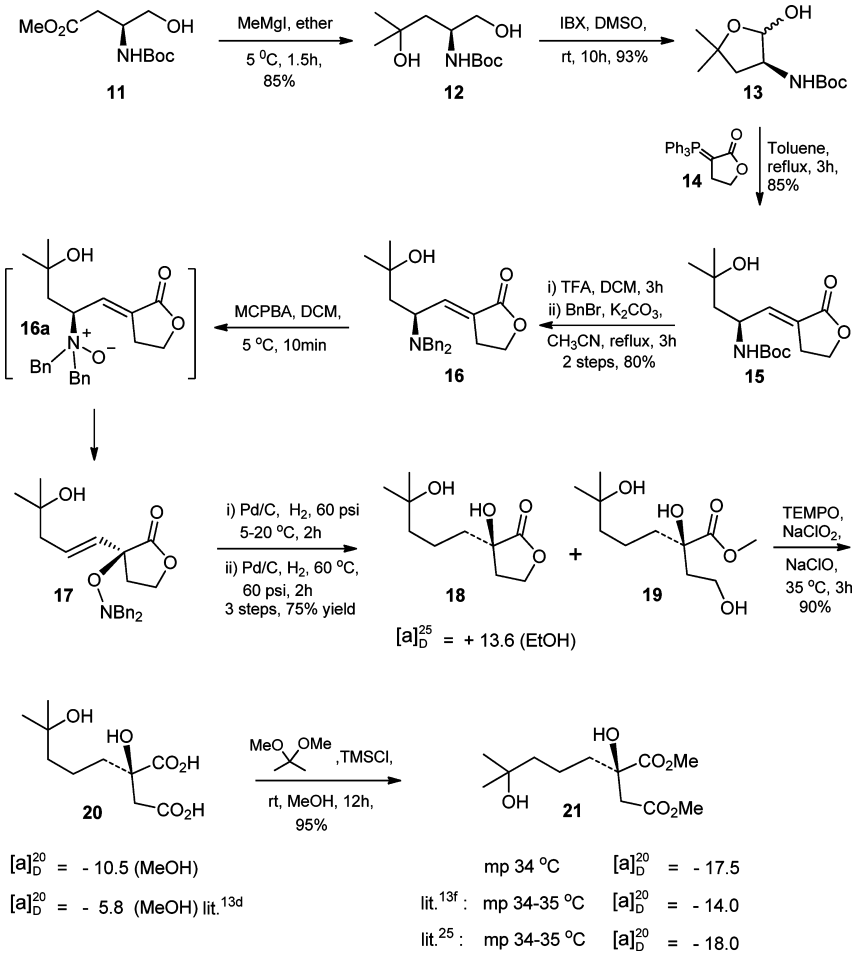
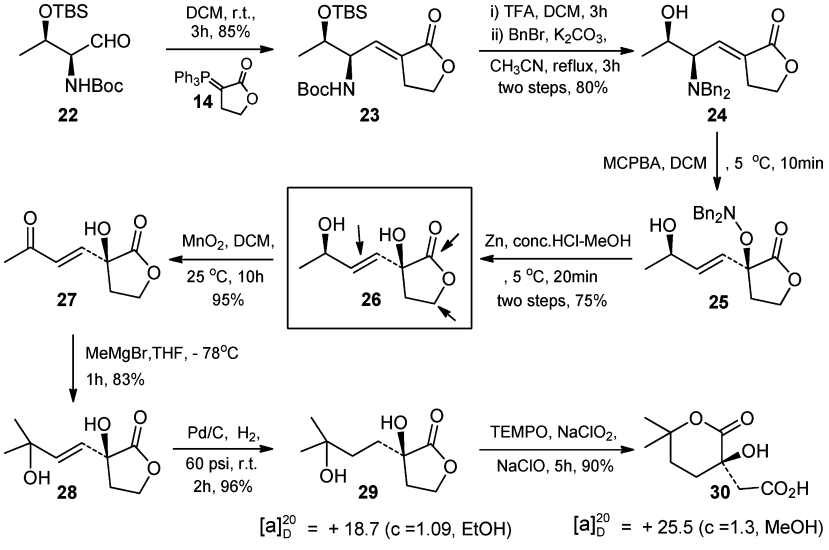
Scheme 2. Synthesis of the Side-Chain Acid of HHT, 20



Scheme 3. Synthesis of the Side Chain Acid HT, 30



first time. This strategy has the potential for enabling the brief syntheses of a large number of complex bioactive molecules bearing chiral tertiary alcohol functionalities. Further investigations into the substrate scopes and Wittig reagents used and the application of this strategy to the synthesis of fostriecin, erythronolide A, and integerrimine are underway, and the results will be reported in due course.

EXPERIMENTAL SECTION

General Methods. For product purification by flash column chromatography, silica gel (200−300 mesh) and petroleum ether (bp 60−90 °C)are used. All solvents were purified and dried by standard techniques and distilled prior to use. All organic extracts were dried over $MgSO_4$, unless otherwise noted. IR spectra were recorded using KBr disks in the 400−4000 cm^{-1} region. Optical rotations were

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measured using a polarimeter. HR-MS was obtained by ESI (positive ion mode) on TOF mass analyzer. Melting points were determined without correction. ^{1}H and ^{13}C NMR spectra were recorded with TMS as an internal standard and $CDCl_3$ or CD_3COCD_3 as solvent.

General Procedure for *N*-Boc Deprotection with TFA and *N*-Bisbenzylation with BnBr To Yield Products 16 and 24. To a solution of *N*-Boc olefin (8.53 mmol) in dry dichloromethane (20 mL) was added TFA (42.65 mmol). The mixture was stirred at reflux for 3 h, after which time it was evaporated to give a white solid. To a solution of the white solid in dry acetonitrile (100 mL) was added K_2CO_3 (42.65 mmol), followed by BnBr (12 mmol). The reaction mixture was stirred at reflux for 3 h, at which point most of the solvent was evaporated under reduced pressure. The residue was diluted with water, and the mixture was extracted with EtOAc (3 × 80 mL). The combined extracts were washed with brine, dried over $MgSO_4$, and concentrated under reduced pressure. The product was purified by chromatography on silica gel to afford the *N*-bisbenzylated olefin. Greater than 80% yield could be stably achieved using the strictly dry TFA, DCM, BnBr, and CH_3CN.

General Procedure for the Oxidation of Allyl Tertiary Amines 3, 8, 16, and 24 To Yield the Crude [2,3]-Meisenheimer Rearrangement Products 4, 9, 17, and 25, Respectively. To a solution of allylic tertiary amine (14.40 mmol) in CH_2Cl_2 (50 mL) was added *m*-CPBA (75%, 3.66 g, 15.91 mmol) at 5 °C. The reaction mixture was stirred at this temperature for 10 min. Then, the suspension was filtered, and the filtrate was washed with 10% NaOH (3 × 10 mL), saturated $NaHCO_3$ (2 × 10 mL), and saturated NaCl (2 × 10 mL), dried over $MgSO_4$, filtered, and concentrated at 30 °C under reduced pressure to give an oily residue (crude **4**, **9**, **17**, and **25**, respectively), which was used in the next step without further purification.

(*E*)-3-(2-((Dibenzylamino)oxy)propylidene)dihydrofuran-2(3*H*)-one (5). Crude **4** (289 mg, 0.86 mmol) decomposed into the compound **5** and other impurities during purification by chromatography on silica gel. Pure **5** (183 mg, 63% yield) was obtained as a colorless oil via purification using a second silica gel column (petroleum ether−EtOAc, 8:1): IR (KBr) 1769 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37−7.23 (m, 10H), 6.27 (d, J = 9.0 Hz, 1H), 4.27 (m, 2H), 3.87 (d, J = 12.84 Hz, 2H), 3.83−3.79 (m, 1H), 3.80 (d, J = 12.84 Hz, 2H), 2.70−2.50 (m, 2H), 0.94 (d, J = 6.52 Hz, 3H); ^{13}C NMR (DEPT) (100 MHz, $CDCl_3$) δ 170.9 (C), 140.7 (CH), 137.5 (C), 129.8 (CH), 128.2 (CH), 127.5 (CH), 125.2 (C), 75.9 (CH), 65.4 (CH_2), 63.4 (CH_2), 25.0 (CH_2), 18.4 (CH_3); HRMS (ESI-TOF) m/z [M + Na]$^+$, calcd for $C_{21}H_{23}NNaO_3$ 360.1576, found 360.1573.

(*R*)-3-((Dibenzylamino)oxy)-3-propyldihydrofuran-2(3*H*)-one (6). To a solution of crude **4** (500 mg, 1.48 mmol) in MeOH (30 mL) was added 10% Pd/C (25 mg) at 0 °C. The mixture was stirred under a hydrogen atmosphere (60 psi) at 10 °C for 3 h. After the reaction was complete, the catalyst was removed by filtration over Celite and washed with MeOH (3 × 6 mL). The filtrate was concentrated under reduced pressure. The residue was purified by chromatography on silica gel (petroleum ether−EtOAc, 5:1) to yield **6** (465 mg, 93%) as a colorless oil: IR (KBr) 1756 cm^{-1}; ^{1}H NMR (400 MHz,$CDCl_3$) δ 7.36−7.15 (m, 10H), 4.41 (d, J = 12.72 Hz, 1H), 4.22−4.16 (m, 1H), 4.06−4.00 (m, 1H), 3.90−3.52 (m, 2H), 3.57 (d, J = 13.36 Hz, 1H), 1.80−1.60 (m, 3H), 1.58−1.38 (m, 2H), 1.22−1.18 (m, 1H), 0.90 (t, J = 7.20 Hz, 3H); ^{13}C NMR (DEPT) (100 MHz, $CDCl_3$) δ 176.1 (C), 137.1 (C), 136.7 (C), 130.5 (CH_2), 129.9 (CH_2), 128.3 (CH_2), 128.2 (CH_2), 127.7 (CH_2), 127.5 (CH_2), 83.0 (C), 66.0 (CH_2), 63.4 (CH_2), 61.9 (CH_2), 37.9 (CH_2), 30.6 (CH_2), 16.8 (CH_2),16.4 (CH_3); HRMS (ESI-TOF) m/z [M + Na]$^+$ calcd for $C_{21}H_{25}NO_3Na$ 362.1732, found 362.1730.

(*R*)-3-Hydroxy-3-propyldihydrofuran-2(3*H*)-one (7). To a solution of crude **6** (300 mg, 0.89 mmol) in MeOH (30 mL) was added 10% Pd/C (15 mg). The mixture was stirred under a hydrogen atmosphere (60 psi) at 60 °C for 3 h. After the reaction was complete, the catalyst was removed by filtration over Celite and washed with MeOH (3 × 5 mL). The filtrate was concentrated under reduced pressure. The residue was purified by chromatography on silica gel (petroleum ether−EtOAc, 3:1) to yield **6** (108 mg, 85%) as a colorless oil: IR (KBr) 1756 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.43−4.37 (m, 1H), 4.26−4.20 (m, 1H), 3.30−3.10 (brs, 1H), 2.40−2.28 (m, 2H), 1.81−1.72 (m, 1H), 1.72−1.60 (m,1H), 1.60−1.48 (m, 1H), 1.48−1.38 (m, 1H), 0.98 (t, J = 7.32 Hz, 3H); ^{13}C NMR (DEPT) (100 MHz, $CDCl_3$) δ 179.3 (C), 74.8 (C), 65.4 (CH_2), 38.7 (CH_2), 34.4 (CH_2), 16.6 (CH_2), 14.2 (CH_3); HRMS (ESI-TOF) m/z [M + Na]$^+$ calcd for $C_7H_{12}O_3Na$ 167.0684, found 167.0685.

(*S*)-Dimethyl 2-(2-(Dibenzylamino)propylidene)succinate (8). To a solution of diethyl phosphite (967 mg, 7.00 mmol) in EtOH (35 mL) was added NaH (168 mg, 7.00 mmol) at 0 °C. The mixture was allowed to reach room temperature and stirred for 30 min. After the addition of diethyl maleate (1.21 g, 7.00 mmol), stirring was continued for 1 h. (*S*)-2-(Dibenzylamino)propanal (1.77 g, 7.00 mmol) was added, and the mixture was stirred for 4 h. After the addition of aq NH_4Cl (25 mL), the mixture was extracted with EtOAc (4 × 30 mL). The combined extracts were washed with brine, dried over $MgSO_4$, and concentrated under reduced pressure. The residue was purified by chromatography on silica gel (petroleum ether−EtOAc, 8:1) to afford **8** (E/Z = 1:0.52) (2.24 g, 83%) as a colorless oil.

Dimethyl 2-((Dibenzylamino)oxy)-2-propylsuccinate (10). To a solution of **9** (397 mg, 1 mmol) in MeOH (30 mL) was added 10% Pd/C (20 mg). The mixture was stirred under a hydrogen atmosphere (60 psi) at −10 °C for 3 h. After the reaction was complete, the catalyst was removed by filtration over Celite and washed with MeOH (3 × 6 mL). The filtrate was concentrated under reduced pressure. Because pure **10** was difficult to obtain via column chromatography, crude **10** was reduced with $LiAlH_4$ in THF. The obtained product proved to be 2-((dibenzylamino)oxy)-2-propylbutane-1,4-diol (216 mg, 65% from **8**) after purification by column chromatography: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40−7.25 (m, 10H), 4.01 (d, J = 13.0 Hz, 1H), 3.95−3.80 (m, 3H), 3.75−3.65 (m, 1H), 3.65−3.55 (m, 1H), 3.29 (d, 1H, J = 12.4 Hz, 1H), 3.20 (d, J = 12.4 Hz, 1H), 2.60−2.40 (brs, 1H), 1.80−1.60 (m, 4H), 1.50−1.40 (m, 1H), 1.40−1.20 (m, 2H), 0.87 (t, J = 7.2 Hz, 3H); ^{13}C NMR (DEPT) (100 MHz, $CDCl_3$) δ 136.3 (C), 130.1 (CH), 129.9 (CH), 128.5 (CH), 127.9 (CH), 85.1 (C), 67.6 (CH_2), 63.8 (CH_2), 63.2 (CH_2), 58.7 (CH_2), 36.3 (CH_2), 36.2 (CH_2), 17.2 (CH_2), 14.7 (CH_3); HRMS (ESI-TOF) m/z [M + Na]$^+$ calcd for $C_{21}H_{29}NO_3Na$ 366.2045, found 366.2046.

(*S*)-*tert*-Butyl (1,4-Dihydroxy-4-methylpentan-2-yl)-carbamate (12). A three-necked, round-bottomed flask equipped with a reflux condenser and a dropping funnel was charged with magnesium turnings (1.44 g, 58.4 mmol) and anhydrous ethyl ether (20 mL). A solution of iodomethane (3.35 mL, 40.7 mmol) in anhydrous ethyl ether (40 mL) was added dropwise to this suspension, maintaining slight boiling, and the suspension was stirred for an additional 90 min at ca. 20 °C. A solution of **11** (2.1 g, 9.05 mmol) in anhydrous ethyl ether (20 mL) was added dropwise at 5 °C to the Grignard reagent. The dropping funnel was rinsed with THF (10 mL), and the white suspension was stirred at ca. 20 °C for a further 90 min. The reaction mixture was cooled to 0 °C, cautiously quenched by addition of ether (40 mL) and 1 N HCl (20 mL), and poured into a separating funnel. The aqueous phase was extracted with ethyl ether (3 × 70 mL). The combined extracts were washed with brine, dried over $MgSO_4$, and concentrated under reduced pressure. The residue was purified by chromatography on silica gel (petroleum ether−EtOAc, 3:2) to afford **12** (1.78 g 85%) as a colorless oil: IR (KBr) 3430, 1717, 1682 cm^{-1}; $[\alpha]^{25}_D$ = −15.1 (c 1.45, EtOH); ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.82−3.73 (m, 1H), 3.70−3.61 (m, 1H), 3.61−3.55 (m, 1H), 2.78 (brs, OH, 2H), 1.69−1.66 (m, 2H), 1.44 (s, 9H), 1.29(s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.6, 79.8, 70.3, 66.6, 50.1, 44.2, 30.0, 28.4; HRMS (ESI-TOF) m/z [M + Na]$^+$ calcd for $C_{11}H_{23}NO_4Na$ 256.1525, found 256.1526.

***tert*-Butyl ((3*S*)-2-Hydroxy-5,5-dimethyltetrahydrofuran-3-yl)carbamate (13).** To a solution of **12** (3.00 g, 12.9 mmol) in dimethyl sulfoxide (30 mL) was added *o*-iodoxybenzoic acid (4.33 g, 15.5 mmol). The mixture was stirred at room temperature for 10 h. Then, the reaction mixture was quenched with water (5 mL). The suspension was filtered over Celite and washed with EtOAc. The filtrate was extracted with methylene chloride (3 × 50 mL). The

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combined extracts were washed with brine, dried over $MgSO_4$, and concentrated under reduced pressure. The residue was purified by chromatography on silica gel (petroleum ether−EtOAc, 2:1) to afford **13** (2.76g, 93%) as a white solid: R_f 0.21 (1:1 EtOAc−petroleum ether); mp 129.0−129.8 °C (EtOAc); IR (KBr) 3442, 1717, 1691 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.27−5.24 (m, 1H), 5.16−5.08 (m, 1H), 4.39−4.20 (m, 1H), 4.20−3.90 (m, 1H), 2.35−2.30 (m, 0.6H), 2.20−2.10 (m, 1H), 1.71 (t, 1H, J = 11.7 Hz), 1.50−1.40 (m, 2H), 1.43 (s, 9H), 1.39 (s, 3H), 1.21 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.5, 102.4, 95.4, 82.5, 81.2, 79.9, 79.5, 58.8, 53.4, 43.0, 41.4, 31.0, 30.4, 29.2, 28.4, 28.3; HRMS (ESI-TOF) m/z $[M + Na]^+$ calcd for $C_{11}H_{21}NO_4Na$ 254.1368, found 254.1364.

***tert*-Butyl (4-Hydroxy-4-methyl-1-(2-oxodihydrofuran-3-ylidene)pentan-2-yl)carbamate (15).** To a solution of lactol **13** (2.76 g, 11.9 mmol) in dry toluene (50 mL) was added 1-butyrolactonylidene triphenylphosphorane **14** (4.53 g, 13.1 mmol). The mixture was heated at reflux for 3 h. After completing the reaction, the solvent was removed under reduced pressure. The residue was purified by chromatography on silica gel (petroleum ether−EtOAc, 2:1) to yield olefin **15** (3.03 g, 85%) as a white solid: mp 102.3−103.1 °C (EtOAc); $[\alpha]^{25}_D$ = −22.5 (c 8.7, $CHCl_3$); IR (KBr) 3401, 3322, 1725, 1682 cm^{-1}; ^1H NMR(400 MHz, $CDCl_3$) δ 6.50 (d, J = 7.92 Hz, 1H), 5.66 (brs, 1H), 4.33 (brs, 1H), 4.33−4.29 (m, 2H), 3.18−3.08 (brs, 1H), 2.96−2.84 (m, 1H), 1.75−1.69 (m, 1H), 1.58−1.50 (m, 1H), 1.34 (s, 9H), 1.20 (s, 6 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.7, 155.6, 140.9, 125.0, 79.6, 70.3, 65.8, 48.1, 45.9, 30.7, 29.1, 28.4, 24.9; HRMS (ESI-TOF) m/z $[M + Na]^+$ calcd for $C_{15}H_{25}N\ O_5Na$ 322.1630, found 322.1631.

3-(2-(Dibenzylamino)-4-hydroxy-4-methylpentylidene)-dihydrofuran-2(3*H*)-one (16). See the general procedure for preparation: white solid; mp 141.6−142.5 °C; IR (KBr) 3596, 3481, 3298, 1751, 1675 cm^{-1}; $[\alpha]^{25}_D$ = −32.6 (c 1.0, EtOH); ^1H NMR (400 MHz, $CDCl_3$) δ 7.38−7.22 (m, 10H), 7.09−6.97 (dt, 1H, J = 9.84 Hz), 5.90 (s, 1H), 4.49−4.33(m, 2H), 4.11(d, 2H, J = 12.92 Hz), 3.82 (t, J = 12.04 Hz, 1H), 3.28 (d, J = 12.92 Hz, 2H), 2.81−2.62 (m, 2H), 2.27−2.16 (m, 1H), 1.19 (s, 3H), 1.22−1.11 (m, 1H), 0.81 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.7, 137.7, 136.2, 129.4, 128.7, 128.0, 127.7, 70.7, 65.4, 55.8, 54.2, 41.5, 31.5, 27.8, 25.2; HRMS (ESI-TOF) m/z $[M + Na]^+$ calcd for $C_{24}H_{29}NO_3Na$ 402.2045, found 402.2047.

(*R*)-3-Hydroxy-3-(4-hydroxy-4-methylpentyl)dihydrofuran-2(3*H*)-one (18), (*R*)-Methyl 2,6-Dihydroxy-2-(2-hydroxyethyl)-6-methylheptanoate (19). To a solution of **16** (5.46g, 14.40 mmol) in CH_2Cl_2 (50 mL) was added *m*-CPBA (75%, 3.66 g, 15.91 mmol) at 5 °C. The reaction mixture was stirred at this temperature for 10 min. Then the suspension was filtered, and the filtrate was washed with 10% NaOH (3 × 10 mL), saturated $NaHCO_3$ (2 × 10 mL), and saturated NaCl (2 × 10 mL), dried over $MgSO_4$, filtered, and concentrated at 40 °C under reduced pressure to give an oily residue (crude **17**), which was used in next step without further purification. To a solution of the crude **17** (14.40 mol) in MeOH (50 mL) was added 10% Pd/C (250 mg) at 0 °C. The mixture was stirred under a hydrogen atmosphere (60 psi) at 10 °C for 2 h. Then the temperature was raised to 60 °C. The solution was kept under stirring for another 2 h. After completing the reaction, the catalyst was removed by filtration over Celite and washed with MeOH (3 × 15 mL). The filtrate was concentrated under reduced pressure. The residue was purified by chromatography on silica gel (petroleum ether−EtOAc, 2:1) to afford **18** (1.91 g, 66%) and **19** (0.30 g, 9%), respectively, as a white solid. Compound **18**: mp 98.0−98.8 °C (EtOAc); IR (KBr) 3500, 3280, 1769 cm^{-1}; $[\alpha]^{25}_D$ = +13.6 (c 1.728, EtOH); ^1H NMR (400 MHz, $CDCl_3$) δ 4.43−4.37 (m, 1H), 4.26−4.20 (m, 1H), 4.10−3.90 (brs, 1H), 2.59−2.20 (brs, 1H), 2.40−2.24 (m, 2H), 1.83−1.73 (m, 1H), 1.73−1.58 (m, 2H), 1.58−1.40 (m, 3H), 1.22 (s, 3H), 1.21 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 179.2, 74.7, 71.1, 65.5, 43.4, 36.7, 34.7, 29.3, 29.2, 17.9; HRMS (ESI-TOF) m/z $[M + Na]^+$ calcd for $C_{10}H_{18}O_4Na$ 225.1103, found 225.1103. Compound **19**: ^1H NMR (400 MHz, $CDCl_3$) δ 3.91 (s, 1H), 3.79 (s, 3H), 3.88−3.75 (m, 1H), 3.75−3.65 (m, 1H), 2.75 (brs, 1H), 2.21−2.01 (m, 1H), 2.01−1.88 (m, 1H), 1.82−1.63 (m, 3H), 1.62−1.40 (m, 3H), 1.26−1.06 (m, 7H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.0, 77.5, 70.8, 59.1, 52.8, 43.62, 40.4, 40.1, 29.3, 29.1, 18.1; HRMS (ESI-TOF) m/z $[M + Na]^+$ calcd for $C_{11}H_{22}O_5Na$ 257.1365, found 257.1364.

(*R*)-2-Hydroxy-2-(4-hydroxy-4-methylpentyl)succinic Acid (20). Compounds **18** (1.23 g, 6.09 mmol) and **19** (0.30 g, 1.28 mmol) were stirred for 20 min with 2.8 mL of 5 M NaOH. Sodium phosphate buffer (30 mL, 0.67 M) was added, and the pH was adjusted to 6.8 (5 M HCl). Acetonitrile (37.0 mL) and TEMPO (452 mg, 2.90 mmol) were added, and the mixture was heated to 35 °C. Over a period of 5 h, sodium hypochlorite solution (9.24 mL in 51 mL of H_2O, 0.24 M) and $NaClO_2$ (1.68 g, 18.7 mmol in 7.28 mL H_2O) were added dropwise from separate syringes at 35 °C with stirring. (Caution: Do not mix sodium hypochlorite solution and $NaClO_2$ before adding to the reaction!) At room temperature, the pH was adjusted to 8.5 with 5 M NaOH. The mixture was quenched with Na_2SO_3 (37.7 mL, 6.72 g in 112 mL water) at 0 °C, and the resulting solution was stirred at room temperature for 0.5 h (pH 8.5−9.0). After acidification to pH 1, most of the water was removed under reduced pressure. The mixture was extracted with EtOAc (5 × 60 mL). The combined extracts were washed with brine, dried over $MgSO_4$, and concentrated under reduced pressure. The residue was purified by chromatography on silica gel (petroleum ether−EtOAc, 1:5) to afford **20** (1.55 g, 90%) as a white crystalline solid: mp 112.1−112.9 °C (EtOAc); IR (KBr) 3569, 3456, 1709 cm^{-1}; $[\alpha]^{25}_D$ = −10.5 (c 1.14, MeOH); ^1H NMR (400 MHz, acetone-d_6) δ 1.17 (s, 6H), 1.30−1.40 (m, 1H), 1.40−1.50 (m, 2H), 1.55−1.78 (m, 3H), 2.67 (d, J = 16.0 Hz, 1H), 2.95 (d, J = 16.0 Hz, 1H); ^{13}C NMR (100 MHz, acetone-d_6) δ 18.0 (CH_2), 28.7 (CH_3), 28.8 (CH_3), 39.5 (CH_2), 42.8 (CH_2), 43.8 (CH_2), 69.4 (C), 74.5 (C), 171.7 (C), 175.5 (C); HRMS (ESI-TOF) m/z $[M + Na - 2H]^+$ calcd for $C_{10}H_{16}O_6Na$ 255.0845, found 255.0847.

(*R*)-Dimethyl 2-Hydroxy-2-(4-hydroxy-4-methylpentyl)-succinate (21). To a solution of **20** (0.5 g, 2.14 mmol) in dry MeOH (1.2 mL) were added 2, 2-dimethoxypropane (4.8 mL) and TMSCl (0.076 mL, 0.6 mmol). The mixture was stirred at the room temperature for 12 h. After the reaction was complete, the solvent was removed under reduced pressure. The residue was purified by chromatography on silica gel (petroleum ether−EtOAc, 5:1) to afford **21** (532 mg, 95%) as a white solid: mp 33.8−34.2 °C (EtOAc); IR (KBr) 3499, 1740 cm^{-1}; $[\alpha]^{20}_D$ = −17.5 (c 0.74, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 3.80 (s, 3H), 3.77 (s, 1H), 3.67 (s, 3H), 2.93 (d, J = 16.3 Hz, 1H), 2.70 (d, J = 16.3 Hz, 1H), 1.72−1.61 (m, 2H), 1.59−1.45 (m, 2H), 1.45−1.40 (m, 2H), 1.28−1.15 (m, 1H), 1.19 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.6, 171.4, 75.2, 70.8, 53.0, 51.9, 43.5, 43.4, 39.6, 29.3, 29.1, 18.1; HRMS (ESI-TOF) m/z $[M + Na]^+$ calcd for $C_{12}H_{22}O_6Na$ 285.1314, found 285. 1314.

***tert*-Butyl ((2*R*,3*R*,*E*)-3-((*tert*-Butyldimethylsilyl)oxy)-1-(2-oxodihydrofuran-3(2*H*)-ylidene)butan-2-yl)carbamate (23).** To a solution of **22** (8.88 g, 28.01 mmol) in dry CH_2Cl_2 (100 mL) was added 1-butyrolactonylidene triphenylphosphorane **14** (10.7 g, 30.83 mmol). The mixture was heated at reflux for 3 h. After the reaction was complete, the solvent was removed under reduced pressure. The residue was purified by chromatography on silica gel (petroleum ether−EtOAc, 4:1) to yield **23** (9.17 g, 85%) as an oil: IR (KBr) 3448, 1760, 1714 cm^{-1}; $[\alpha]^{20}_D$ = 14.8 (c 1.348, EtOH); ^1HNMR (400 MHz, $CDCl_3$) δ 6.65−6.54 (m, 1H), 4.98 (d, J = 8.0 Hz, 1H), 4.37 (t, J = 7.6 Hz, 2H), 4.18−4.14 (m, 1H), 3.96−3.87 (m, 1H), 3.19−3.05 (m, 1H), 2.95−2.87 (m, 1H), 1.44 (s, 9H), 1.20 (d, J = 6.0 Hz, 3H), 0.90 (s, 1H), 0.89 (s, 9H), 0.06 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.1, 155.8, 138.3, 126.8, 79.8, 69.7, 65.6, 55.9, 28.4, 25.8, 25.7, 25.2, 20.7, 18.0, 3.58, 4.45, 4.91; HRMS (ESI-TOF) m/z $[M + Na]^+$ calcd for $C_{19}H_{35}NO_5SiNa$ 408.2182, found 408.2185.

(*E*)-3-((2*R*,3*R*)-2-(Dibenzylamino)-3-hydroxybutylidene)-dihydrofuran-2(3*H*)-one (24). See the general procedure for preparation. The compound **24** was obtained as a white solid: mp 175.9−176.5 °C (EtOAc); IR (KBr) 3429, 1755, 1677 cm^{-1}; $[\alpha]^{20}_D$ = −34.9 (c 1.60, EtOH); ^1H NMR (400 MHz, $CDCl_3$) δ 7.38−7.29 (m, 10H), 6.86 (dt, J = 11.2, 2.8 Hz, 1H), 4.46−4.39 (m, 2H), 4.13 (s, 1H), 4.06 (d, J = 13.6 Hz, 2H), 4.00−3.90 (m, 1H), 3.40 (d, J = 13.6 Hz, 2H), 3.09 (dd, J = 10.0, 11.2 Hz, 1H), 2.84−2.67 (m, 2H), 1.04 (d,

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J = 6.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.1, 138.3, 134.0, 131.7, 128.8, 128.7, 127.6, 65.6, 65.5, 65.1, 54.2, 26.0, 19.3; HRMS (ESI-TOF) m/z [M + Na]$^+$ calcd for $C_{22}H_{25}NO_3Na$ 374.1732, found 374.1733.

(*S*)-3-Hydroxy-3-((*R*,*E*)-3-hydroxybut-1-en-1-yl)-dihydrofuran-2(3*H*)-one (26). To a solution of **24** (5.05 g, 14.38 mmol) in CH_2Cl_2 (50 mL) was added *m*-CPBA (75%, 3.66 g, 15.91 mmol) at 5 °C. The reaction mixture was stirred at this temperature for 20 min. Then the suspension was filtered, and the filtrate was washed with 10% NaOH (3 × 10 mL), saturated $NaHCO_3$ (2 × 10 mL), and saturated NaCl (2 × 10 mL), dried over $MgSO_4$, filtered, and concentrated at 30 °C under reduced pressure to give an oily residue (crude **25**) that was used in the next step without further purification. To a solution of crude **25** (14.38 mol) in MeOH (24 mL) were added concd HCl (1.2 mL) and Zn powder (9 g, 140 mmol) at 5 °C. The reaction mixture was stirred at this temperature for 20 min. Then the suspension was filtered and washed with MeOH, and the filtrate was neutralized with a 25% ammonium hydroxide solution to pH = 8. The mixture was extracted with EtOAc (5 × 60 mL).The combined extracts were washed with brine, dried over $MgSO_4$, and concentrated under reduced pressure. The residue was purified by chromatography on silica gel (petroleum ether−EtOAc, 1:1) to afford **26** (1.86 g, 75%) as a colorless oil: IR (KBr) 3405, 1767 cm^{-1}; $[\alpha]^{20}_D$ = +22.0 (c, 0.55, MeOH); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.94 (dd, J = 5.48, 15.84 Hz, 1H), 5.82 (d, J = 15.84 Hz, 1H), 4.65 (brs, 1H), 4.50−4.32 (m, 2H), 4.23 (q, J = 7.88 Hz, 1H), 3.53 (brs, 1H), 2.50−2.38 (m, 2H), 1.27 (d, J = 6.48 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 178.0, 136.8, 126.8, 74.8, 67.5, 65.5, 36.2, 22.8; HRMS (ESI-TOF) m/z [M + Na]$^+$ calcd for $C_8H_{12}O_4Na$ 195.0633, found 195.0635.

3-Hydroxy-3-(3-oxobut-1-en-1-yl)dihydrofuran-2(3*H*)-one (27). To a solution of **26** (850 mg, 5 mmol) in 30 mL of CH_2Cl_2 was added activated MnO_2 (85 wt.%, 4.35g, 50 mmol) at 0 °C. The reaction mixture was stirred at this temperature for 20 min. Then the reaction mixture was allowed to reach room temperature. The reaction mixture was further stirred at room temperature overnight. The mixture was filtered over Celite and washed with CH_2Cl_2. The filtrate was concentrated under reduced pressure. The residue was purified by chromatography on silica gel (petroleum ether−EtOAc, 1:1) to afford enone **27** (798 mg, 95%) as a colorless oil: IR (KBr) 3475, 1775, 1715, 1677, 1629 cm^{-1}; $[\alpha]^{20}_D$ = −4.1 (*c* 1.50, MeOH); ^{1}HNMR (400 MHz, $CDCl_3$) δ 6.79 (d, J = 15.9 Hz, 1H), 6.45 (d, J = 15.9 Hz, 1H), 4.54−4.48 (m, 1H), 4.36−4.30 (m, 1H), 4.15−4.08 (brm, 1H), 2.59−2.46 (m, 2H), 2.31 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 198.0, 176.1, 141.2, 130.3, 74.9, 65.4, 36.2, 28.2; HRMS (ESI-TOF) m/z [M + Na]$^+$ calcd for $C_8H_{10}O_4Na$ 193.0477, found 193.0478.

3-Hydroxy-3-(3-hydroxy-3-methylbut-1-en-1-yl)-dihydrofuran-2(3*H*)-one (28). A solution of methylmagnesium bromide in ether (4 mL, 4 mmol) was added to a solution of **27** (340 mg, 2 mmol) in THF (15 mL) at −78 °C. The reaction mixture allowed to reach room temperature after methylmagnesium bromide was added. The reaction mixture was further stirred at room temperature for 60 min, and water (10 mL) was added. The mixture was extracted with EtOAc (3 × 40 mL). The combined extracts were washed with brine, dried over $MgSO_4$, and concentrated under reduced pressure. The residue was purified by chromatography on silica gel (petroleum ether−EtOAc, 1:3) to afford **28** (308 mg, 83%) as a colorless oil: IR (KBr) 3421, 1764, 1708 cm^{-1}; $[\alpha]^{20}_D$ = +18.2 (*c* 0.85, MeOH); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.99 (d, J = 15.82 Hz, 1H), 5.85 (d, J = 15.88 Hz, 1H), 4.46−4.41 (m, 1H), 4.24−4.18 (m, 1H), 2.54−2.46 (m, 1H), 2.43−2.38 (m, 1H), 1.34 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.5, 140.7, 124.3, 74.8, 70.6, 65.0, 36.3, 29.8, 29.7; HRMS (ESI-TOF) m/z [M + Na]$^+$ calcd for $C_9H_{14}O_4Na$ 209.0790, found 209.0792.

(*R*)-3-Hydroxy-3-(3-hydroxy-3-methylbutyl)dihydrofuran-2(3*H*)-one (29). To a solution of **28** (250 mg, 1.34 mmol) in MeOH (10 mL) was added 10% Pd/C (25 mg). The mixture was stirred under a hydrogen atmosphere (60 psi) at room temperature for 2 h. After the reaction was complete, the catalyst was removed by filtration over Celite and washed with MeOH (3 × 5 mL). The filtrate was concentrated under reduced pressure. The residue was purified by chromatography on silica gel (petroleum ether−EtOAc, 1:3) to afford **29** (242 mg, 96%) as a white solid: mp 98.0−98.6 °C (EtOAc); IR (KBr) 3416, 3258, 1752 cm^{-1}; $[\alpha]^{20}_D$ = 18.7 (*c* 1.09, EtOH); ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.93 (brs, 1H), 4.43−4.37 (m, 1H), 4.25−4.18 (m, 1H), 2.55 (brs, 1H), 2.44−2.35 (m, 1H), 2.28−2.20 (m, 1H), 1.98−1.83 (m, 2H), 1.70 (t, J = 6.8 Hz, 2H), 1.28 (s, 3H), 1.27 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 179.2, 74.2, 70.7, 65.4, 36.9, 35.8, 31.2, 30.2, 28.3; HRMS (ESI-TOF) m/z [M + Na]$^+$ calcd for $C_9H_{16}O_4Na$ 211.0946, found 211.0947.

(*R*)-2-(3-Hydroxy-6,6-dimethyl-2-oxotetrahydro-2*H*-pyran-3-yl)acetic Acid (30). The experimental procedure was the same as that described for the preparation of compound **20**. The compound **30** was obtained as a white solid: mp 133.1−133.7 °C (EtOAc); IR (KBr) 3350−3000 (broad peak), 1715, 1693 cm^{-1}; $[\alpha]^{20}_D$ = +25.5 (*c* 1.30, MeOH); ^{1}H NMR (400 MHz, acetone-d_6) δ 1.41 (s, 3H), 1.45 (s, 3H), 1.78 (dt, J = 14.0, 4.28, 4.00 Hz, 1H), 1.87 (dt, J = 14.0, 3.64, 4.44 Hz, 1H), 2.20 (td, J = 13.44, 3.32 Hz, 1H), 2.44 (td, J = 13.5, 3.64 Hz, 1H), 2.65 (d, J = 16.56 Hz, 1H), 3.10 (d, J = 16.56 Hz, 1H); ^{13}CNMR (100 MHz, acetone-d_6) δ 26.3, 29.6, 29.7, 30.2, 69.2, 82.8, 171.6, 171.8; HRMS (ESI-TOF) m/z [M + Na]$^+$ calcd for $C_9H_{14}O_5Na$ 225.0739, found 225.0736.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Copies of ^{1}H NMR and ^{13}C NMR spectra for compounds **5**−**8**, **12**−**16**, **18**−**21**, **23**, **24**, and **26**−**30**. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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