Enantioselective synthesis of the side-chain acid of homoharringtonine and harringtonine from the same γ-butyrolactone intermediate

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Abstract

A versatile intermediate γ-butyrolactone **7** was prepared from L-alanine with 96% ee value, which could be used as a common intermediate for the preparation of the side-chain acid of homoharringtonine and harringtonine in 26.6% and 27% overall yield respectively. The key steps involved [2, 3]-Meisenheimer rearrangement, allylic bromination, and Barbier reaction. Some interesting experimental phenomena and effective solutions to these issues are reported herein.

Keywords: homoharringtonine, harringtonine, [2,3]-Meisenheimer rearrangement, allylic bromination, γ-butyrolactone

Introduction

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*.[1] 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 semi-synthesis by coupling the carboxyl group of the respective ester side chain to the C-3 hydroxyl group of cephalotaxine. Several groups have reported enantioselective synthesis of the side-chains of HHT and HT.[1-8] We have also developed an efficient strategy to construct chiral tertiary alcohol via [2,3]-Meisenheimer rearrangement. Through this strategy, the **(*R*)-20,** side-chain acid of homoharringtonine, and **(*R*)-30,** side-chain acid of harringtonine, were enantioselectively prepared from *L*-aspartic acid and *L*-threonine respectively.[9] Obviously, the linear and parallel synthesis of **(*R*)-20** and **(*R*)-30** require two different α-amino acids as starting materials and two sets of different reagents

(Figure **1**). Considering the economic cost and manpower cost in future laboratory preparation and possible industrial-scale production, we explore a divergent synthesis for **(*R*)-20** and **(*R*)-30** from the same intermediate γ-butyrolactone **7**.

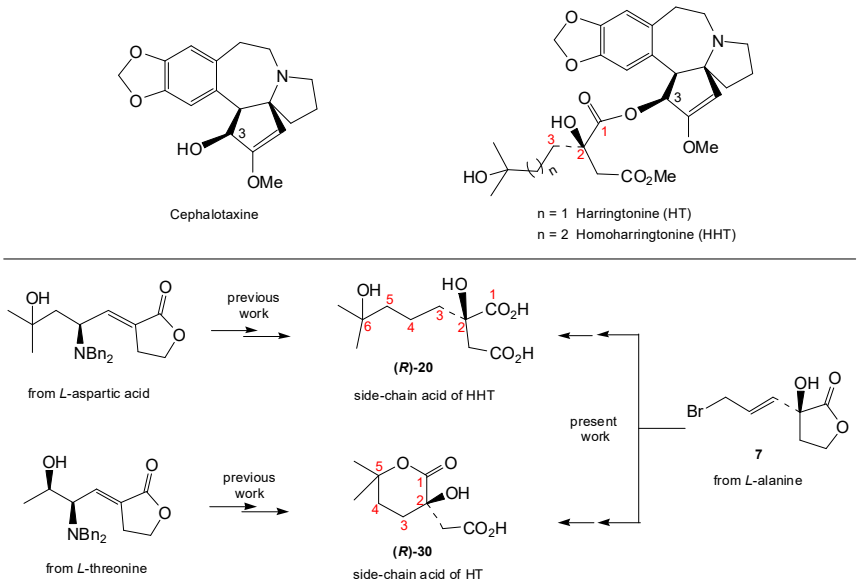


Figure **1**. Synthesis of (R)-**20** and (R)-**30**: parallel synthesis vs divergent synthesis

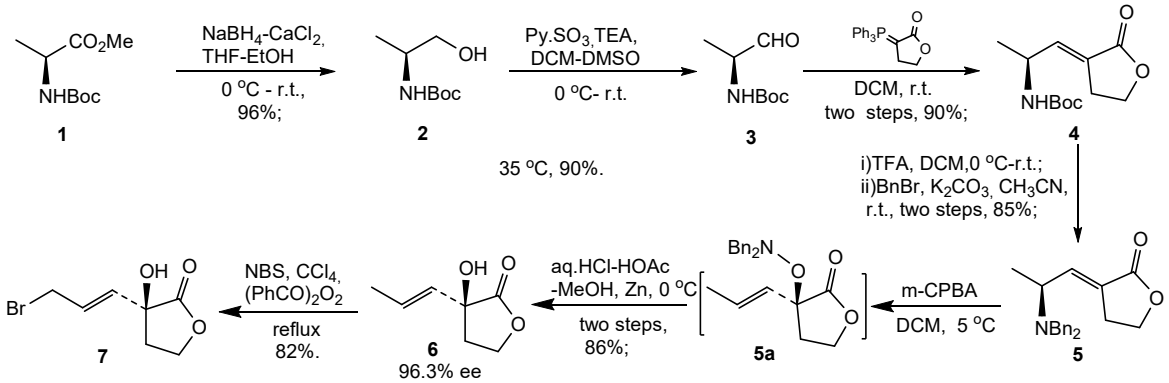
Results and Discussion

The first step towards key intermediate **7** (Scheme **1**) commenced with the reduction of *N*-Boc-*L*-alanine methyl ester **1**, which was derived from *L*-alanine.[10] *N*-Boc-*L*-ala-OH **2** was delivered under $NaBH_4$-$CaCl_2$-THF-EtOH condition[11] in excellent yield and optical purity (96%, $[\alpha]^{20}_D$ − 11.4 (c 0.99, $CHCl_3$); lit.[12] $[\alpha]^{20}_D$ − 11.6 (c 0.6, $CHCl_3$)). **2** were originally subjected to Swern condition [13] and *N*-Boc-alaninal **3** was readily obtained as white solid. For the obtained aldehyde **3** an $[\alpha]^{20}_D$ =-4.3 (c 0.8, MeOH) was measured, which is lower than that record of literature $[\alpha]^{20}_D$ =35.2 (c 1, MeOH) [14]. This result revealed that serious racemization had occurred during Swern oxidation or subsequent flash column chromatography. To avoid the undesired decomposition and racemization of aldehyde **3**, the obtained crude product were used immediately to couple with 1-butyrolactonylidene triphenylphosphorane in dry dichloromethane, delivering (*E*)-olefin **4** as the only isolated product (95% yield for the two-step sequence). Unexpectedly, (*E*)-olefin **4** had only 34% *ee*. After several trials, we observed that careful manipulation under rigorous conditions had a crucial influence on the *ee* value, which fluctuate between 30% and 80%.[15] Furthermore, it was verified by us that the corresponding aldehyde of Boc-*L*-Leu-OH and Boc-*L*-Val-OH don't racemize under the same Swern conditions. Accordingly, we have to sough to Parikh-Doering oxidization, which was reported to oxidize *N*-Boc-*L*-ala-OH **2** to **3** with no racemization[16]. Eventually, aldehyde **3** was acquired with 99% *ee*

and applied into Wittig reaction without purification by column chromatography. It is worth of note that (*E*)-olefin **4** was obtained as white solid under Parikh-Doering conditions while under Swern conditions as colorless liquid.

Removal of the Boc protecting group followed by doubly benzylated [9] in CH_3CN afforded (*E*)-olefin **5**[17] (99% *ee*) in 85% yield over two steps. Treatment of **5** with *m*-CPBA at 5 °C immediately provide unstable [2, 3]-Meisenheimer rearrangement product **5a**.[9] Cleavage of N-O bond appear to be a challenge due to the instability of **5a**. Common used methods such as Al (Hg),[18] Na (liq. NH_3),[19] $CuSO_4$[20], TMSI[21] and Zn (HOAc)[22] proved fruitlessness at room temperature, and Zn (aq.HCl-MeOH)[23] provided 3%−5% racemized **6**. The troublesome racemization was finally circumvented by addition of HOAc to Zn (aq. HCl-MeOH) reduction system, which reduced the acidity of reductive system and so the risk of racemization was depressed. **6** could be obtained in 86% yield with 96.3% *ee* and only about 1.5% level of racemization occurred.

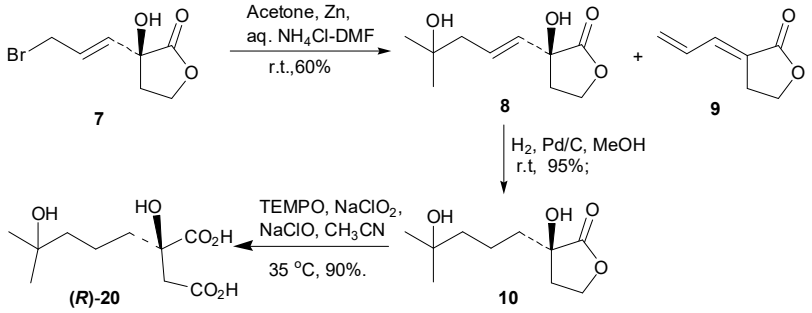
During Wohl-Ziegler bromination[24] of compound **6**, routine monitoring technique did not work because that **6** and **7** had identical R_f values, and moreover, product **7** was visualized under 254 nm violet lamp while **6** were not. One simple technique has been developed to monitor such reactions. While the reaction proceed, just take a small quantity of solution, concentrate under reduced pressure, add CH_3CN (0.5 mL) and aqueous $AgNO_3$ (10%) sucessively, shake violently for a few minutes, then monitor the produced solution by TLC. Since bromide **7** can be completely transformed into other compounds by $AgNO_3$ and these compounds have different R_f values with **6** and **7**, we can determine whether starting material **6** was present after spraying phosphomolybdic acid solution (5% in EtOH) on TLC plate. By this simple technique, Wohl-Ziegler bromination can been quenched appropriately and intermediate **7** was obtained in 82% yields. The total yield from *L*-alanine to **7** was 51.8%.



Scheme 1. Synthesis of key intermediate **7**.

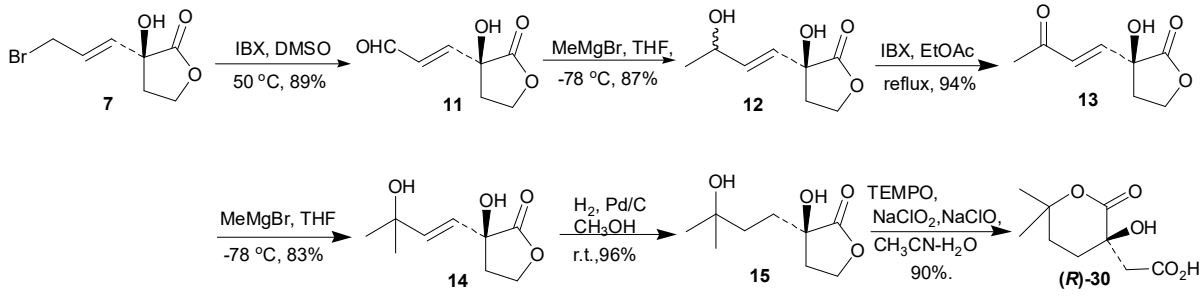
With bromide **7** in hand, Barbier-type coupling with acetone was investigated (Scheme 2). A variety of coupling reagents (Zn, Mg, Sn, Al[25] with additives such as saturated NH_4Cl, [26]saturated NH_4OAc,[27] DMF[28] and formamide[29]) were examined and none lead to satisfactory

result. With THF, THF-H_2O or saturated NH_4Cl-H_2O as solvents, Barbier-type coupling was very sluggish, giving only a trace of **8** after 12 h and the main byproduct was allyl-metal protonolysis product **6**. With DMF as solvents and solid NH_4Cl as additives, [30] compound **7** was transformed into **8** in 60% yield, together with dehydroxylation material **9** in 20% yield. Generally, excessive bromide ought to be employed for increasing the yield, in our present work, however, acetone was used in two-fold excess. Further increasing loading of acetone will decrease the isolated yield. Next, **(*R*)-20** was smoothly obtained from **8** via the sequential step of catalytic hydrogenation and lactone oxidation. The total yield from **7** to **(*R*)-20** was 51.3%.



Scheme 2. Synthesis of said-chain acid of HHT, **(*R*)-20**

Direct oxidation of **6** using SeO_2[31] to obtain enal **11** was proved to lead to decomposed products, the easily available intermediate **7** was inevitably employed to prepare unstable **11** by IBX oxidation[32], which is the first step for the elaboration of side-chain acid of HT, **(*R*)-30** (Scheme **3**). The addition of MeMgBr to enal **11** produced **12**,[33] further oxidation of **15** with IBX furnished enone **13**.[34] Subsequent MeMgBr addition to enone **13**,[33] double bond hydrogenation and TEMPO-mediated lactone oxidation furnished **(*R*)-30** in 71.8% yield over three steps. [9] The total yield from **7** to **(*R*)-30** was 52.2%.



Scheme 3. Synthesis of said-chain acid of HT, **(*R*)-30**.

Conclusions

The common used intermediate **7** for the synthesis of side-chain acids of HHT and HT was conveniently prepared from *L*-alanine in 51.8% yield over eight steps with more than 96% *ee*.

Meanwhile, Parikh-Doering oxidization was confirmed to be suitable for the oxidation of *N*-Boc-*L*-Ala-OH into *N*-Boc-*L*-Alaninal with no racemization. The introduced technique for monitoring Wohl-Ziegler bromination by TLC could be widely used. In the respect of conciseness and yield, this second-generation route is superior to the reported one (overall yield: 26.6% vs 25% for **(*R*)-20**, 27.0% vs 18% for **(*R*)-30**). In addition, the key intermediate **7** was a versatile synthon, which can couple with isopropyl bromide to produce deoxyhomoharringtonine skeleton or couple with 2,2-dimethyloxirane to produce bishomoharringtonine skeleton[35].

Experimental Section

General. For product purification by flash column chromatography, silica gel (200~300 mesh) and petroleum ether (b.p. 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 400-4000cm^{-1} region. Optical rotations were measured using a polarimeter. HR-MS was obtained by ESI (positive ion mode) on TOF mass analyzer. Melting points were determined without correction. ^1H and ^{13}C NMR spectra were recorded with TMS as an internal standard and $CDCl_3$ or CD_3COCD_3 as solvent. The enantiomeric excess (e.e.) of the products were determined by HPLC using a Chiralpak IC (250 mm×4. 6 mm, 5μm) and UV detector at 25 °C and detected at 205 nm. The mobile phase used was n-hexane – isopropanol (70: 30) at a flow rate of 0. 8 mL·min^{-1}.

((*S*)-2-Hydroxy-1-methylethyl)carbamic acid tert-butyl ester (2). To a solution of **1** (5 g, 24.606 mmol) in THF/ethanol (12 mL/22 mL) was added $CaCl_2$ (5.462 g, 49.212 mmol) and $NaBH_4$ (3.724 g, 98.425 mmol) successively at 0 °C. The mixture was allowed to reach room temperature and stirred for 6 h. Then the solution was poured into citric acid/ice (80 mL) and extracted with EtOAc (3 × 100 mL). The combined extracts were washed with brine, dried and concentrated under reduced pressure. The residue was purified by column chromatography (petroleum ether/EtOAc, 2.5:1) to afford **2** (4.311 g, 96%) as a colourless crystalline solid. mp 59.5−60.5 °C (petroleum ether − EtOAc); $[\alpha]^{20}_D$ −11.4 (c 0.99, $CHCl_3$).

(*S, E*)-tert-Butyl(1-(2-oxodihydrofuran-3(2H)-ylidene)propan-2-yl)carbamate (4). To a solution of **2** (1.500 g, 8.560 mmol) and TEA (3.58 mL, 25.680 mmol) in dry CH_2Cl_2 (12 mL) was added a solution of $Py.SO_3$ (4.087 g, 25.680 mmol) in dry DMSO (12 mL) at 0 °C. Then the reaction mixture was allowed to reach room temperature and stirred for 35 min, quenched with water/ice (30 mL). The solution was extracted with CH_2Cl_2 (3 × 60 mL) and washed successively with 10% citric acid (2 × 20 mL), H_2O (2 × 20 mL), saturated $NaHCO_3$ (20 mL), brine (20 mL), dried over $MgSO_4$, and concentrated under reduced pressure to afford crude **3** as a white solid, which was used immediately for the next step without further purification. $[\alpha]^{20}_D$ −28.0 (c 0.72, $CHCl_3$); IR (KBr) 1526 , 1696, 2814, 2938, 2981, 3331 cm^{-1}.

To a solution of crude aldehyde **3** in dry CH_2Cl_2 (10 mL) was added 1-butyrolactonylidene triphenylphosphorane (3.344 g, 9.654 mmol). The mixture was stirred at room temperature for 1 h. Then solvent was removed under reduced pressure and the residue was purified by chromatography (petroleum ether/ EtOAc, 3:1) to yield olefin **4** (1.859 g, 90%, 99% *ee*) as a white crystal: mp 101.5−103.0 °C (petroleum ether−EtOAc); IR (KBr) 3397, 1752 cm^{-1}; $[\alpha]^{20}_D$ −28.0 (c 0.72, $CHCl_3$); 1H NMR (400MHz, $CDCl_3$) δ 6.43 (d, *J* 8.4Hz, 1H), 4.69 (d, *J* 5.6Hz, 1H), 4.34−4.30 (m, 3H), 3.10 (m, 1H), 2.88−2.80 (m, 1H), 1.34 (s, 9H), 1.21 (d, *J* 7.2, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.5 (C), 155.0 (C), 140.62 (CH), 125.7 (C), 79.8 (C), 65.7 (CH_2), 46.0 (CH), 28.4 ($3CH_3$), 24.9 (CH_2), 20.0 (CH_3); HRMS (ESI-TOF) *m/z*: $[M + Na]^+$ calcd for $C_{12}H_{19}NO_4Na$, 264.1212; found 264.1213;

(*S, E*)-3-(2-(Dibenzylamino)propylidene)dihydrofuran-2(3*H*)-one (5). To a solution of *N*-Boc olefin **4** (3.2 g, 13.263 mmol) in dry CH_2Cl_2 (20 mL) was added trifluoroacetic acid (7.561 g, 66.313 mmol), and the reaction was refluxed for 3 h. Then, it was evaporated to give a white solid. To a solution of the white solid in dry acetonitrile (40 mL) was added K_2CO_3 (5.499 g, 39.795 mmol), followed by BnBr (4.991 g, 29.183 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 extracted with EtOAc (3 × 60 mL). The combined extracts were washed with brine, dried, and concentrated under reduced pressure. The residue was recrystallized from petroleum ether and EtOAc to give *N, N*-dibenzyl olefin **5** (3.624 g, 85%, 99% *ee*) as white crystals: mp 101.5−103.0 °C; IR(KBr) 3056, 3028, 1751 cm^{-1}; $[\alpha]^{20}_D$ + 3.6 (c 1.0, $CHCl_3$); ^1H NMR (400MHz, $CDCl_3$) δ 7.39−7.33 (m, 8H), 7.29−7.24 (m, 2H), 6.91 (dt, *J* 6.0, 9.6, 1H), 4.36−4.31 (m, 2H), 3.82 (d, *J* 13.6Hz, 2H), 3.56−3.52 (m, 3H), 2.63−2.59 (m, 2H), 1.63 (s, 1H), 1.30 (d, *J* 6.8Hz, 3H); ^{13}C NMR (100MHz, $CDCl_3$) δ 171.1 (C), 140.7 (C), 139.8 (CH), 128.5 (CH), 128.3 (CH), 127.0 (CH), 126.7 (C), 65.5 (CH_2), 54.0 (CH_2), 53.0 (CH), 25.1 CH_2), 16.3 (CH_3); HRMS (ESI-TOF) *m/z*: $[M + Na]^+$ calcd for $C_{21}H_{23}NO_2Na$, 344.1626; found 344.1628.

(*S*, *E*)-3-Hydroxy-3-(prop-1-en-1-yl) dihydrofuran-2(3*H*)-one (6). To a solution of **5** (500 mg, 1.556 mmol) in CH_2Cl_2 (6 mL) was added *m*-CPBA (80% pure, 369 mg, 1.711 mmol) at 5 °C. The reaction mixture was stirred at this temperature for 10 min. After the suspension was filtered, the filtrate was washed with 10% NaOH (3 × 5 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 **5a**), which was used in the next step without further purification. To a solution of crude **5a** (1.556 mmol) in MeOH (5 mL) was added glacial acetic acid (0.6 mL, 10.892 mmol), hydrochloric acid (0.9 mL, 10.892 mmol, 37% HCl) and zinc powder (1.017 g, 15.56 mmol) at 0 °C. The reaction mixture was stirred at this temperature for 10 min. Then the suspension was filtered and washed with EtOAc, and the filtrate was neutralized with 25% ammonium hydroxide solution to pH 8. The mixture was extracted with EtOAc (3 × 30 mL). The combined extracts were washed with brine, dried, concentrated. The residue was purified by chromatography (petroleum ether/EtOAc, 2:1) to afford **6** (190 mg, 86%, 96.3% *ee*) as a colorless oil: IR (KBr) 3445, 1770 cm^{-1}, 1667 cm^{-1}; $[\alpha]^{20}_D$ + 74.5 (c 1.2, $CHCl_3$);

^{1}H NMR (400MHz, $CDCl_3$) δ 5.86 (dq, *J* 15.7, 6.5 Hz, 1H), 5.63 (d, *J* 15.7, 1.2 Hz, 1H), 4.39 (td, *J* 8.8, 3.0 Hz, 1H), 4.19−4.13 (m, 1H), 3.35(brs, 1H), 2.51−2.42 (m, 1H), 2.40−2.34 (m, 1H), 1.76(dd, *J* 6.5, 1.0 Hz, 3H); ^{13}C NMR (100MHz, $CDCl_3$) δ 177.9 (C), 129.0 (CH), 128.8 (CH), 75.0 (C), 65.0 (CH_2), 36.2 (CH_2), 17.8 (CH_3); HRMS (ESI-TOF) *m/z*: $[M + Na]^+$ calcd for $C_7H_{10}O_3Na$, 165.0528; found 165.0526.

(*S*, *E*)-3-(3-Bromoprop-1-en-1-yl)-3-hydroxydihydrofuran-2(3*H*)-one (7). To a solution of **6** (1.2 g, 8.442 mmol) in dry CCl_4 (12 mL) was added *N*-bromosuccinimide (1.803 g, 10.110 mmol) and benzoyl peroxide (102 mg, 0.442 mmol). The reaction was stirred under reflux and monitored by TLC using the method described in the text. After the reaction was complete, the suspension was filtered and the filtrate was concentrated under reduced pressure. The residue was purified by chromatography (petroleum ether/EtOAc, 3：1) to give **7** (1.530 mg, 82%) as pale-yellow sticky oil. $[\alpha]^{20}_D$ + 46.0 (c 1.06, $CHCl_3$); IR (KBr) 3426, 1770 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.12–6.05 (m, 1H), 5.90 (d, *J* 15.5 Hz, 1H), 4.47–4.42(m, 1H), 4.23 (td, *J* 9.0, 6.6 Hz, 1H), 3.96 (dd, *J* 7.2, 0.9 Hz, 2H), 3.07 (s, 1H), 2.55 − 2.48 (m, 1H), 2.42 (ddd, *J* 13.1, 6.5, 3.7 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.9 (C), 131.9 (CH), 129.1 (CH), 74.6 (C), 65.1 (CH_2), 36.1 (CH_2), 30.5 (CH_2); HRMS (ESI-TOF) *m/z*: $[M + Na]^+$ calcd for $C_7H_9BrO_3Na$, 242.9633; found 242.9634.

(*S*, *E*)-3-Hydroxy-3-(4-hydroxy-4-methylpent-1-en-1-yl) dihydrofuran-2(3*H*)-one (8). To a solution of bromide **7** (685 mg, 3.099 mmol) and acetone (540 mg, 9.297 mmol) in DMF (5 mL) was added zinc dust (304 mg, 4.649 mmol) and NH_4Cl (166 mg, 3.099 mmol) in one portion at room temperature. The reaction mixture was stirred at this temperature for 1.5 h, then extracted with EtOAc (3 × 40 mL), washed with saturated brine (2 × 10 mL), dried and concentrated. The residue was purified by chromatography (petroleum ether/EtOAc, 1:3) to afford diol **8** (373 mg, 60%) as a colorless oil and conjugated olefin **9** (77 mg, 20%) as a colorless oil. Diol **8**: $[\alpha]^{25}_D$ + 30.1 (c 0.98, EtOH); IR (KBr) :3419, 1770 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.97−5.89 (m, 1H), 5.69 (d, *J* 15.7 Hz, 1H), 4.59 (brs, 1H), 4.41 (td, *J* 8.3, 3.5 Hz, 1H), 4.22−4.16 (m, 1H), 2.85 (brs, 1H), 2.51−2.43 (m, 1H), 2.40−2.35 (m, 1H), 2.24 (d, *J* 7.5 Hz, 2H), 1.23 (d, *J* 5.2 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 178.1 (C), 131.4 (CH), 129.5 (CH), 75.1 (C), 70.9 (C), 65.2 (CH_2), 46.1 (CH_2), 36.4 (CH_2), 29.3 (CH_3), 29.0 (CH_3); HRMS (ESI-TOF) *m/z*: $[M + Na]^+$ calcd for $C_{10}H_{16}O_4Na$, 223.0946; found 223.0948; conjugated olefin **9**: IR (KBr): 3446, 1748, 1656 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.10 (d, *J* 11.4 Hz, 1H), 6.46 (dt, *J* 16.9, 10.8 Hz, 1H), 5.66 (dd, *J* 16.9, 10.0 Hz, 2H), 4.42 (t, *J* 7.4 Hz, 2H), 3.01 (td, *J* 7.3, 2.2 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.6 (C), 135.8(CH), 132.2 (CH), 126.7 (CH_2), 125.3 (C), 65.4 (CH_2), 25.3 (CH_2); HRMS (ESI-TOF) *m/z*: $[M + Na]^+$ calcd for $C_7H_8O_2Na$, 147.0422; found 147.0420.

(*R*)-3-Hydroxy-3-(4-hydroxy-4-methylpentyl) dihydrofuran-2(3*H*)-one (10). To a solution of **8** (516 mg, 2.577 mmol) in MeOH (6 mL) was added 10% Pd/C (52 mg). The mixture was stirred under hydrogen atmosphere (60 psi) at room temperature for 2 h. Then catalyst was removed by filtration over Celite and washed with MeOH (3 × 5 mL). The filtrate was concentrated under reduced pressure and the residue was purified by chromatography (petroleum ether/EtOAc, 1:2.5) to afford **10** (495 mg, 95%) as a white solid. $[\alpha]^{25}_D$ + 14.4 (c 0.8, EtOH); mp

97.8−98.9 °C (EtOAc); IR (KBr): 3500, 3280, 1769 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.42−4.37 (m, 1H), 4.26−4.20 (m, 1H), 3.72−3.67 (m, 1H), 2.54 (brs, 1H), 2.38−2.25 (m, 2H), 1.83−1.78 (m, 1H), 1.67−1.60 (m, 2H), 1.52−1.40 (m, 3H), 1.21 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 179.2 (C), 74.7 (C), 71.1 (C), 65.5 (CH_2), 43.4 (CH_2), 36.7 (CH_2), 34.7 (CH_2), 29.3 (CH_3), 29.2 (CH_3), 17.9 (CH_2); HRMS (ESI-TOF) *m/z*: $[M + Na]^+$ calcd for $C_{10}H_{18}O_4Na$ 225.1103, found 225.1103.

(*R*)-2-Hydroxy-2-(4-hydroxy-4-methylpentyl)succinic acid (20). Saturated diol **10** (857 mg, 4.237 mmol) was stirred for 20 min with 5 M NaOH(1.6 mL). Sodium phosphate buffer (18ml, 0.67 M) was added and the pH was adjusted to 6.8 (5M HCl). Then, acetonitrile (16.5 ml) and TEMPO (232 mg, 1.483 mmol) were added and the mixture was heated to 35 °C. Over a period of 3 h sodium hypochlorite solution (5.38 mL in 29.82 mL H_2O, 0.24 M) and $NaClO_2$ (978 mg, 80%, 8.65 mmol in 4.24 mL H_2O) were added dropwise from separate syringes at 35 °C while 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 (9.92 mL, 1.923 g in 15mL water) at 0 °C and the resulting solution was stirred at room temperature for 1 h (pH 8.5−9.0). After acidification to pH 1, most of the water was removed using rotary evaporator. Then the mixture was extracted with EtOAc (6 × 30 mL), washed with saturated brine (2 × 10 mL), dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by chromatography (petroleum ether /EtOAc, 1:6) to afford **20** (893 mg, 90%) as a white crystalline solid. $[\alpha]^{25}_D$ − 10.2 (c 1.08, MeOH); mp 112.1−112.9 ºC (EtOAc); IR (KBr) 3569, 3456, 1709 cm^{-1}; ^1H NMR (400 MHz, d_6-acetone) δ 2.95 (d, *J* 16.3 Hz, 1H), 2.67 (d, *J* 16.3 Hz, 1H),1.76 − 1.55 (m, 3H), 1.45 (dd, *J* 9.3, 6.4 Hz, 2H), 1.39 − 1.29 (m, 1H), 1.17 (s, 6H); ^{13}C NMR (100MHz, d_6-acetone) δ 175.8 (C), 171.7 (C), 74.7 (C), 69.5 (C), 43.8 (CH_2), 42.9 (CH_2), 39.9 (CH_2), 29.0 (CH_3), 28.8(CH_3), 18.0 (CH_2); HRMS (ESI -TOF) *m/z*: calcd for $[M + Na - 2H]^+$, 255.0845, found 255.0847.

(*S*, *E*)-3-(3-Hydroxy-2-oxotetrahydrofuran-3-yl)acrylaldehyde (11). A solution of bromide **7** (609 mg, 2.755 mmol) in DMSO (8 mL) was added IBX (1.543g, 5.510 mmol). The reaction mixture was stirred at 50 ºC for 1.5 h. Then the mixture was diluted with EtOAc (100 mL), washed with saturated aqueous $NaHCO_3$ (2 × 10 mL), brine (10 mL), dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by chromatography (petroleum ether /EtOAc, 1:1) to afford **11** (383 mg, 89%) as a colorless oil. IR (KBr) 3420, 2923, 2850, 1771, 1690 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 9.63 (d, *J* 7.5 Hz, 1H), 6.85 (d, *J* 15.8 Hz, 1H), 6.46 (dd, *J* 15.8, 7.5 Hz, 1H), 4.56−4.52 (m, 1H), 4.40− 4.35 (m, 1H), 4.09 (s, 1H), 2.63−2.50 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 192.8 (CH), 175.9 (C), 151.3 (CH), 132.3 (CH), 75.2 (C), 65.8 (CH_2), 36.2 (CH_2); HRMS (ESI-TOF) *m/z*: $[M + Na]^+$ calcd for $C_7H_8O_4Na$, 179.0320, found 179.0322.

(*3S*)-3-Hydroxy-3-((*E*)-3-hydroxybut-1-en-1-yl) dihydrofuran-2(3H)-one (12). A solution of methylmagnesium bromide in ether (4 mL, 4.6 mmol) was added to a solution of **11** (653 mg, 4.182mmol) in THF (10 ml) at -78 ºC. The reaction mixture was allowed to reach room temperature. After further stirred at room temperature for 30 min, water (10 ml) was added. The

mixture was extracted with EtOAc (3 × 30 mL). The combined extracts were washed with brine, dried, and concentrated under reduced pressure. The residue was purified by chromatography (petroleum ether/ EtOAc, 1:3) to afford **12** as colorless oil (628 mg, 87%, dr 2:1). IR (KBr) 3405, 1767 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.99−5.92 (m, 1H) , 5.88−5.83 (m, 1H) , 4.45− 4.39 (m, 2H) , 4.25−4.21 (m, 1H), 3.63 (brs, 1H), 3.01(s, 1H) , 2.52−2.41 (m, 2H), 2.40 (brs, 1H), 1.31 (d, *J* 6.4 Hz, 3H); ^{13}C NMR (100MHz, $CDCl_3$) 177.6 (1C), 137.0 (1C), 136.9 (1C), 126.8 (1C), 74.8 (2C), 67.6 (2C), 65.2 (1C), 65.1 (1C), 36.2 (2C), 23.1(2C); HRMS (ESI-TOF) *m/z*: $[M + Na]^+$ calcd for $C_8H_{12}O_4Na$, 195.0633; found 195.0634.

(*3S*)-3-Hydroxy-3-(3-oxobut-1-en-1-yl) dihydrofuran-2(3*H*)-one(13). To a solution of diol **12** (520 mg, 3.020 mmol) in EtOAc (15 mL) was added IBX (2.537 g, 9.060 mmol) at room temperature. The reaction mixture was stirred at reflux for 3 h. After cooling to room temperature, the insoluble material was filtered and the filtrate was concentrated under reduced pressure. The residue was purified by chromatography (petroleum ether/EtOAc, 1:1) to afford **13** (484 mg, 94 %) as a colorless oil. IR(KBr): 3475 , 1775, 1715, 1677, 1629 cm^{-1}; $[\alpha]^{20}_D$= − 4.1(c 1.50, MeOH); ^1H NMR (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 (14). The procedure is similar to the preparation of compound **12**. IR (KBr): 3421, 1764, 1708 cm^{-1}; $[\alpha]^{20}_D$ + 18.2 (c, 0.85, MeOH); ^1H 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 (15). The procedure is similar to the preparation of compound **10**. mp 98.0−98.6 °C (EtOAc); IR (KBr) 3416, 3258, 1752 cm^{-1}; $[\alpha]^{20}_D$ +18.7(c, 1.09, EtOH); ^1H 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 compound **30** was obtained as a white solid, by the same procedure used for the preparation of diacid 20. 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); ^1H NMR (400 MHz, d_6-acetone) 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* 16.6 Hz, 1H), 3.10 (d, *J* 16.56 Hz, 1H); ^{13}CNMR (100 MHz, d_6-acetone) δ 171.8, 171.6, 82.8, 69.2, 42.6, 30.2, 29.7, 29.6, 26.3; HRMS (ESI-TOF) *m/z*: $[M+Na]^+$ Calcd for $C_9H_{14}O_5Na$ 225.0739, Found 225.0736.

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