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An Enantioselective Total Synthesis of (+)-Altholactone from Diethyl L-Tartrate

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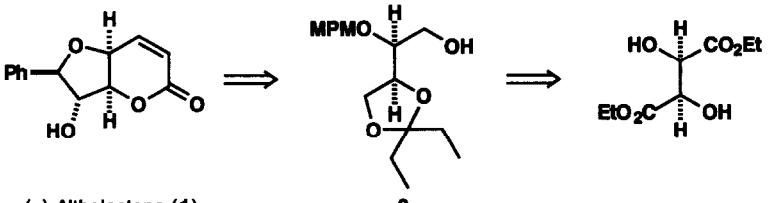
Abstract: An enantioselective total synthesis of the *cis*-fused tetrahydrofurano-2-pyrone (+)-altholactone (**1**) from diethyl L-tartrate *via* the L-threitol derivative **2** is described. The remaining two stereogenic centers of **1** are introduced by a highly stereoselective hydroboration-oxidation sequence.

(+)-Altholactone (**1**) is an unusual *cis*-fused tetrahydrofurano-2-pyrone that has been independently isolated from an unnamed *Polyalthia* species [1a] and from *Goniothalamus giganteus* [1b], and which has been shown to be active against P 388 leukemia (*in vivo*) as well as possessing some cytotoxic activity (*in vitro*) [1b]. The structural elucidation of (+)-altholactone was originally based on degradation studies in combination with ^{1}H NMR experiments [1a] and later confirmed by an X-ray crystallographic analysis [1b], although the absolute stereochemical assignment had to await the first enantioselective total synthesis of **1**, starting from D-glucose [2]. Subsequent syntheses of lactone **1** have been based on carbohydrate precursors [3a-c] or on optically active glyceraldehyde derivatives [3d,e]. Herein we describe a total synthesis of (+)-altholactone (**1**) from the protected L-threitol derivative **2**, itself available in large quantities from natural diethyl L-tartrate [4], as shown retrosynthetically below.

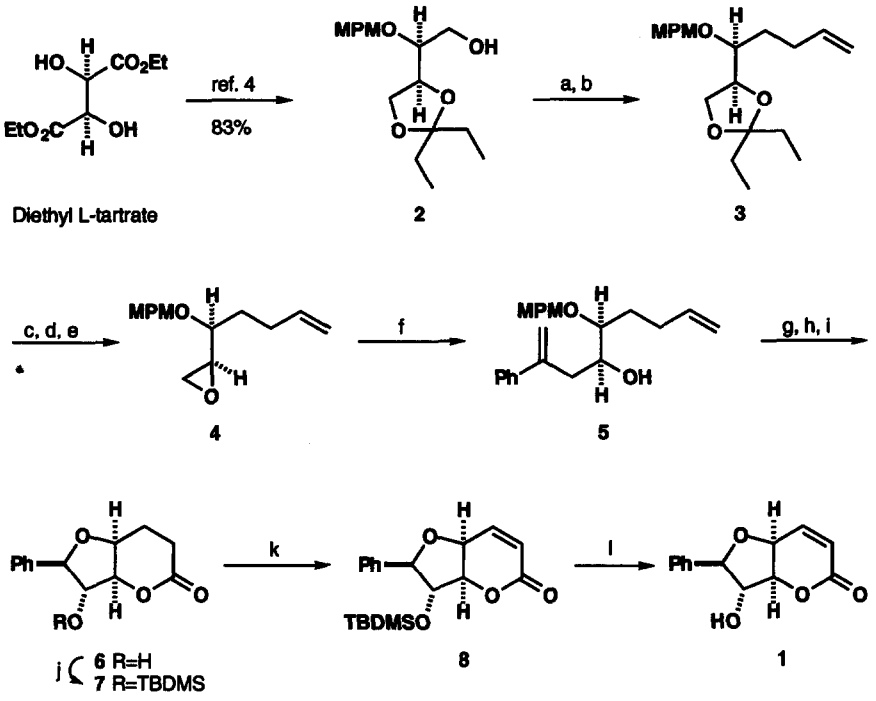


(+)-Altholactone (**1**) **2**

The synthesis starts with a tosylation of alcohol **2** followed by a copper catalysed [5] addition of allylmagnesium chloride affording alkene **3** in 78% yield over two steps (Scheme). Conversion of **3** into epoxide **4** was effected by removal of the acetal moiety in compound **3** by mild acidic hydrolysis [6], selective tosylation of the resultant 1,2-diol at the primary hydroxyl and then treatment with potassium carbonate in methanol. Addition of compound **4** to a solution of the higher-order cuprate formed by

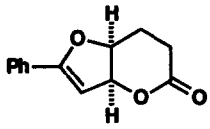
reacting copper cyanide with two equivalents of 1-lithio-1-phenylethylene[7] then gave diene **5** in good yield.

Conversion of diene **5** into dihydroaltholactone **6** proved to be more difficult than anticipated, but was eventually carried out as follows. Thus, ozonolysis of compound **5** in acetone (-78°C→-50°C), involving oxidation of both alkenes and concomitant removal of the MPM-protecting group[8], afforded the corresponding bis-lactol as a complicated mixture of isomers[9]. Treating this mixture with PCC, without using sodium acetate as a buffer, resulted in oxidation of the aldehyde hemi-acetal to the corresponding δ-lactone and simultaneous acid catalysed elimination of the ketone hemi-acetal to yield the unstable dihydrofuran **9** which consistently resisted all attempts at purification. However, the formation of alkene **9** was evident from the ^{1}H NMR spectra of the crude reaction product, showing a characteristic resonance for the vinylic proton at δ 5.54 as a doublet (J=2.4 Hz). Gratifyingly, when subjecting the reaction product from above to hydroboration (BH_3·THF, THF, 0°C) followed by



Scheme. TBDMS=*tert*-$BuMe_2Si$, MPM=*p*-$MeOC_6H_4CH_2$; (a) p-TsCl, pyridine, 93% (b) allylmagnesium chloride, CuI (10 mol-%), -30°C, THF, 84% (c) 2% aq. H_2SO_4, MeOH, 96% (d) p-TsCl, pyridine (e) K_2CO_3, MeOH 84% (two steps) (f) 1-lithio-1-phenylethylene, CuCN, THF, -78°C→ -20°C, 87% (g) O_3, acetone, -78°C→ -50°C, then Me_2S (h) PCC, CH_2Cl_2 (i) BH_3·THF, THF, 0°C, then NaOH, H_2O_2; H_2SO_4, 57-65% from **5** (j) TBDMSOTf, pyridine, CH_2Cl_2, 87% (k) LDA, PhSeBr, THF, -78°C; H_2O_2, CH_2ClCH_2Cl, 60°C, 79% from **7** (l) Bu_4NF, THF, 91%.

oxidation and acidic work up, alcohol **6** could be obtained reproducibly in good yield (57-65% from diene **5**) and as a single isomer, the hydroboration taking place from the sterically less hindered α-face of alkene **9**[10].



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Completion of the synthesis was then straightforward. Silylation of the secondary hydroxyl group in **6** yielded ether **7** that was converted into the corresponding diastereomeric mixture of α-phenyl selenides (LDA, PhSeBr, -78°C, THF)[11] followed by oxidation and elimination to afford the unsaturated lactone **8** in 79% yield. Standard removal of the silyl group then gave (+)-altholactone, its spectroscopic data being in agreement with published values[1].

In conclusion, we have developed an enantioselective total synthesis of (+)-altholactone (**1**) in twelve steps and 20% overall yield starting from the protected L-threitol derivative **2**, itself readily available from diethyl L-tartrate. Two of the stereogenic centers embedded in the title compound are derived from diethyl L-tartrate while the remaining two are introduced by a highly selective hydroboration-oxidation sequence.

EXPERIMENTAL

^1H and ^{13}C NMR spectra were obtained on a Varian XL-300 spectrometer using $CDCl_3$ ($CHCl_3$, δ 7.26) as solvent. IR spectra were run on a Perkin-Elmer 298 spectrophotometer and only the strongest/structurally most important peaks (ν, cm^{-1}) are listed. Optical rotations, $[\alpha]_D$, were measured on a Perkin Elmer 141 polarimeter at the sodium D line and at ambient temperatures. Flash chromatography employed Grace Amicon silica gel 60 (0.035-0.070 mm). Methylene chloride and pyridine were distilled from calcium hydride immediately before use; tetrahydrofuran (THF) and diethyl ether were distilled from sodium-benzophenone ketyl. All reactions were run in septum-capped, oven-dried flasks under atmospheric pressure of nitrogen, solvents, reactant solutions and liquid reagents being transferred *via* oven dried syringes.

Alkene 3. To a solution of **2**[4] (1.326 g, 4.277 mmol) in pyridine (10 ml) at 0°C was added *p*-toluenesulfonyl chloride (0.856 g, 4.491 mmol). The resultant mixture was stirred at 0°C for 9 h and then poured into Et_2O/ aq. $CuSO_4$. The layers were separated and the aqueous phase extracted once with Et_2O. The combined organic phases were washed once with water and once with brine, dried ($MgSO_4$) and evaporated. Flash chromatography (EtOAc/heptane: 1/9→1/3) of the residue gave the corresponding tosylate (1.850 g, 93%) as an oil. ^1H NMR ($CDCl_3$, 300 MHz) δ 7.79 (2H, m), 7.33 (2H, m), 7.21 (2H, m), 6.87 (2H, m), 4.55 (2H, m), 4.19-4.03 (3H, m), 3.92 (1H, m), 3.79 (3H, s), 3.71-3.57 (2H, m), 3.42 (3H, s), 1.64-1.49 (4H, m), 0.91-0.81 (6H, m).

To a stirred suspension of CuI (0.528 g, 2.78 mmol) in THF (40 ml) at -30°C was added allylmagnesium chloride (13.6 ml, 27.8 mmol, 2 M in THF). After stirring the resultant mixture for 10 min the tosylate from above (1.839 g, 3.963 mmol) in THF (3 ml) was added dropwise. The mixture was kept at -30°C for

2 h and then poured into Et_2O and aq. NH_4Cl/NH_4OH with rapid stirring. The organic layer was separated, dried ($MgSO_4$) and evaporated. Flash chromatography (EtOAc/heptane: 1/19→1/9) of the residue gave alkene **3** (1.111 g, 84%) as an oil. ^1H NMR ($CDCl_3$, 300 MHz) δ 7.31 (2H, d, J=8.9 Hz), 6.87 (2H, d, J=8.9 Hz), 5.76 (1H, m), 5.04-4.95 (2H, m), 4.78 (1H, d, J=11.0 Hz), 4.66 (1H, d, J=11.0 Hz), 4.19 (1H, m), 4.01 (1H, bt, J= 8.1 Hz), 3.81 (3H, s), 3.58, (1H, bt, J=8.1 Hz), 3.42 (1H, m), 2.26 (1H, m), 2.11 (1H, m), 1.74-1.59 (4H, m), 1.53 (1H, m), 1.44 (1H, m), 0.99-0.87 (6H, m); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 159.2, 138.3, 131.0, 129.6, 114.9, 113.7, 113.3, 79.3, 78.9, 72.6, 66.7, 55.3, 30.3, 29.7, 29.3, 8.1, 8.1; IR (film) 3080, 2920, 1535 cm^{-1}; $[\alpha]_D$=-42.6 (*c* 1.72, $CHCl_3$); HRMS [M^+] calcd for $C_{20}H_{30}O_4$: 334.2144, found: 334.2147.

Epoxide 4. To a solution of **3** (0.729 g, 2.183 mmol) in MeOH (10 ml) was added 2% aq. H_2SO_4 (10 drops) and the resultant solution was stirred at ambient temperature until TLC indicated that all the starting material was consumed. Then solid K_2CO_3 (0.5 g) was added, the mixture was filtered and the solvents were removed. Flash chromatography (EtOAc/heptane: 1/1→EtOAc) gave the corresponding diol (0.577 g, 96%) as an oil. ^1H NMR ($CDCl_3$, 300 MHz) δ 7.27 (2H, d, J=8.9 Hz), 6.89 (2H, d, J=8.9 Hz), 5.81 (1H, m), 5.09-4.97 (2H, m), 4.59 (1H, d, J=10.9 Hz), 4.41 (1H, d, J=10.9 Hz), 3.81 (3H, s), 3.72-3.54 (5H, m), 3.48 (1H, m), 2.65 (1H, bs, -OH), 2.31 (1H, bs, -OH), 2.21-2.10 (2H, m), 1.85-1.59 (2H, m); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 159.5, 138.1, 130.1, 129.6, 115.1, 114.0, 78.8, 72.7, 72.0, 64.1, 55.3, 29.4, 29.3; IR (film) 3400, 3060, 2930, 1640 cm^{-1}; $[\alpha]_D$=+22.8 (*c* 1.85, $CHCl_3$); HRMS [M^+] calcd for $C_{15}H_{22}O_4$: 266.1518, found: 266.1523.

To a solution of the diol from above (0.819 g, 3.079 mmol) in pyridine (5 ml) at 0°C was added *p*-toluenesulfonyl chloride (0.646 g, 3.387 mmol). After stirring at 0°C for 2 days the reaction mixture was poured into Et_2O/ aq. $CuSO_4$ and worked-up as described above.

The crude tosylate from above was dissolved in MeOH (10 ml) and K_2CO_3 (0.851 g, 6.158 mmol) was added. After stirring at room temperature for 30 min the solvent was removed and the residue diluted with Et_2O/H_2O. The phases were separated and the aqueous layer was extracted once with Et_2O. The combined organic phases were then washed with brine, dried (MgSO4), and evaporated. Flash chromatography (EtOAc/heptane: 1/9→1/4) then gave **4** (0.643 g, 84%) as an oil. ^1H NMR ($CDCl_3$, 300 MHz) δ 7.31 (2H, d, J=8.9 Hz), 6.88 (2H, d, J=8.9 Hz), 5.77 (1H, m), 5.04-4-93 (2H, m), 4.77 (1H, d, J=11.1 Hz), 4.51 (1H, d, J=11.1 Hz), 3.82 (3H, s), 3.04 (2H, m), 2.78 (1H, dd, J=5.0, 4.2 Hz), 2.49 (1H, dd, J=5.0, 2.4 Hz), 2.29-2.04 (2H, m), 1.76 (1H, m), 1.61 (1H, m); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 159.2, 138.0, 130.7, 129.5, 115.0, 113.7, 79.4, 71.5, 55.2, 43.1, 31.5, 29.6; IR (film) 3040, 2910, 1640 cm^{-1}; $[\alpha]_D$=-34.5 (*c* 1.40, $CHCl_3$); HRMS [M^+] calcd for $C_{15}H_{20}O_3$: 248.1412, found: 248.1416.

Alkene 5. To a solution of freshly distilled α-bromostyrene (4.82 ml, 37.18 mmol) in Et_2O (25 ml) at -78° C was added butyllithium (23.2 ml, 37.18 mmol, 1.6 M in hexanes) and the resultant mixture was warmed to -40°C[7]. After stirring for 30 min the mixture was recooled to -78°C and then cannulated into a slurry of CuCN (1.665 g, 18.59 mmol) in Et_2O (25 ml) at -78°C. The heterogeneous mixture was warmed briefly to -40°C until a clear solution was obtained and then recooled to -78°C. A solution of **4** (0.922 g, 3.718 mmol) in Et_2O (3 ml) was added dropwise and the resultant mixture was allowed to warm to -20°C. After 2 h TLC indicated complete consumption of the starting material and the reaction mixture was poured into Et_2O/ aq. NH_4Cl. The organic phase was separated, washed once with water and once with brine, dried ($MgSO_4$), and evaporated. Flash chromatography (EtOAc/heptane: 1/9→1/4) of the residue gave **5** (1.145 g, 87%). ^1H NMR ($CDCl_3$, 300 MHz) δ 7.49-7.18 (7H, m), 6.90 (2H, m), 5.78 (1H, m, C<u>H</u>=CH_2), 5.38 (1H, m, PhC=C<u>H</u>H), 5.16 (1H, m, PhC=CH<u>H</u>), 5.02-4.92 (2H, m, CH=C<u>H</u>2), 4.54 (1H, d, J=11.0 Hz, benzylic), 4.42 (1H, d, J=11.0 Hz, benzylic), 3.84 (3H, s, -O<u>Me</u>), 3.69 (1H, m), 3.38 (1H, m), 2.84 (1H, dd, J=14.1, 4.8 Hz), 2.65 (1H, dd, J=14.1, 8.2 Hz), 2.09 (2H, m), 1.82-1.59 (2H, m); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 159.3, 145.5, 140.6, 138.3, 130.5, 129.5, 128.4, 127.6, 126.3, 115.0,

114.8, 113.8, 80.0, 72.1, 70.3, 55.3, 39.6, 29.7, 29.3; IR (film) 3480, 2935, 1610 cm^{-1}; $[\alpha]_D$=+12.7 (*c* 3.79, $CHCl_3$); HRMS [M^+] calcd for $C_{23}H_{28}O_3$: 352.2038, found: 352.2045.

Alcohol 6. Alkene **5** (1.211 g, 3.440 mmol) in acetone (30 ml) was ozonized at -78°C→-50°C for 90 min. Dimethyl sulfide (2.53 ml, 34.4 mmol) was added and the resultant mixture warmed to room temperature and stirred over night. Removal of the solvents gave a crude product that was processed in the next step without further purification.
To a stirred solution of pyridinium chlorochromate (1.112 g, 5.160 mmol) in CH_2Cl_2 (20 ml) was added the crude product from above. After 3 h dry Et_2O (100 ml) was added and the resultant heterogeneous mixture was filtered through a short pad of Florosil. Removal of the solvents then gave the sensitive alkene **9** which was immediately taken on to the next step. IR (film) 3040, 2960, 1750, 1640 cm^{-1}.
To a stirred solution of the crude alkene from above in THF (20 ml) at 0°C was added BH_3·THF (5.0 ml, 5.0 mmol, 1.0 M in THF). After 2 h water (5 ml) and 2 M NaOH (5 ml) were added and the mixture was warmed to room temperature followed by addition of H_2O_2 (5 ml, 30 wt-%). The resultant mixture was stirred vigorously for 1.5 h and then acidified to pH 3 by careful addition of 2 M H_2SO_4. The phases were separated, the aqueous phase was extracted twice with Et_2O and the combined organic phases were washed with brine. Drying ($MgSO_4$), removal of the solvents and flash chromatography (EtOAc/heptane: 1/1→7/3) then gave **6** (0.493 g, 61%) as an oil. ^1H NMR ($CDCl_3$, 300 MHz) δ 7.42-7.24 (5H, m, Ar), 4.80 (1H, dd, J=5.2, 2.3 Hz, -$CO_2C\underline{H}$-), 4.64 (1H, d, J=6.5 Hz, Ph$C\underline{H}$-), 4.47 (1H, m, -OC$\underline{H}CH_2$-), 4.23 (1H, dd, J=6.5, 2.3 Hz, -C$\underline{H}$OH), 2.71 (1H, ddd, J=16.9, 10.7, 5.9 Hz, one of -$C\underline{H}_2CO_2$-), 2.49 (1H d tr, J=16.9, 5.3 Hz, one of -$C\underline{H}_2CO_2$-), 2.31-2.10 (2H, m, -OCHC$\underline{H}_2$-); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 171.2, 138.3, 128.6, 128.3, 126.0, 88.4, 85.2, 84.5, 72.2, 26.1, 23.0; IR (KBr) 3400, 1745 cm^{-1}; $[\alpha]_D$=-23.3 (*c* 2.45, $CHCl_3$); HRMS [M^+] calcd for $C_{13}H_{14}O_4$: 234.0892, found: 234.0889.

Silyl ether 7. To a solution of **6** (0.540 g, 2.477 mmol) in CH_2Cl_2 (10 ml) at 0°C was added *tert*-butyldimethylsilyl trifluoromethanesulfonate (0.683 ml, 2.972 mmol) and 2,6-lutidine (0.577 ml, 4.954 mmol) and the resultant mixture was slowly warmed to room temperature. After 2 h the mixture was poured into Et_2O/H_2O. The organic layer was separated, washed once with brine, dried ($MgSO_4$) and the solvents were evaporated. Flash chromatography (EtOAc/heptane: 1/4→1/3) of the residue gave **7** (0.749 g, 87%) as an oil. ^1H NMR ($CDCl_3$, 300 MHz) δ 7.42-7.29 (5H, m), 4.69 (1H, dd, J=5.2, 2.4 Hz), 4.57 (1H, d, J=6.3 Hz), 4.48 (1H, m), 4.12 (1H, dd, J=6.3, 2.4 Hz, 2.74 (1H, ddd, J=16.9, 10.7, 5.9 Hz), 2.50 (1H, dt, J=16.9, 5.4 Hz), 2.31-2.10 (2H, m), 0.85 (9H, s), 0.01 (3H, s), -0.12 (3H, s); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 170.5, 138.2, 128.6, 128.4, 126.4, 88.2, 86.4, 85.8, 72.4, 26.3, 25.6, 23.2, 17.9, -4.9, -5.1; IR (film) 3020, 2910, 1750 cm^{-1}; $[\alpha]_D$=-0.62 (*c* 2.76, $CHCl_3$); HRMS [M+H^+] calcd for $C_{19}H_{29}O_4Si$: 349.1835, found: 349.1839.

Alkene 8. To a solution of diisopropylamine (0.109 ml, 0.781 mmol) in THF (5 ml) at 0°C was added butyllithium (0.488 ml, 0.781 mmol, 1.6 M in hexanes). After stirring for 15 min the mixture was cooled to -78°C and **7** (0.247 g, 0.710 mmol) in THF (2 ml) was added dropwise. The resultant mixture was stirred at -78°C for 40 min and then phenylselenyl bromide (0.176 g, 0.745 mmol) in THF (2 ml) was added. After 40 min the reaction mixture was poured into Et_2O/H_2O and the layers were separated. The organic phase was washed once with water and once with brine, dried ($MgSO_4$) and evaporated to yield the crude selenides which were taken on to the next step without further purification.
To a solution of the crude selenides from above in 1,2-dichloroethane (10 ml) was added pyridine (0.574 ml, 7.81 mmol) and H_2O_2 (2 ml, 35 wt-%) and the resultant mixture was refluxed for 3 h. After cooling to room temperature the phases were separated, the organic phase was extracted once with water, dried ($MgSO_4$) and evaporated. Flash chromatography (EtOAc/heptane: 1/9→1/3) of the residue then gave **8** (0.195 g, 79%) as an oil. ^1H NMR ($CDCl_3$, 300 MHz) δ 7.39-7.27 (5H, m), 7.00 (1H, dd, J=9.9, 5.1 Hz),

6.23 (1H, d, J=9.9 Hz), 4.81 (1H, dd, J=5.1, 2.2 Hz), 4.68 (1H, d, J=5.1 Hz), 4.62 (1H, t, J=5.1 Hz), 4.34 (1H, dd, J=5.1, 2.2 Hz), 0.89 (9H, s), 0.01 (3H, s), -0.11 (3H, s); ^{13}C NMR ($CDCl_3$, 75 MHz) δ ; IR (film) 3040, 2950, 1730 cm-1; $[\alpha]_D$=+102.2 (*c* 0.753, $CHCl_3$).

(+)-Altholactone (1). To a solution of **8** (0.107 g, 0.309 mmol) in THF (5 ml) was added tetrabutylammonium fluoride trihydrate (0.107 g, 0.340 mmol). After stirring at room temperature for 40 min the mixture was poured into Et_2O/H_2O. The organic layer was separated, washed with brine, dried ($MgSO_4$) and evaporated. Flash chromatography (EtOAc/heptane: 1/1→EtOAc) of the residue gave **1** (0.066 g, 91%) as a crystalline solid (mp 111°C [lit.[1b] mp 110°C, lit.[3c] mp 113-114°C]). ^1H NMR ($CDCl_3$, 300 MHz) δ 7.39-7.29 (5H, m), 7.01 (1H, dd, J=9.9, 5.1 Hz), 6.24 (1H, d, J=9.9 Hz), 4.94 (1H, dd, J=5.1, 2.4 Hz), 4.75 (1H, d, J=5.7 Hz), 4.63 (1H, t, J=5.1 Hz), 4.46 (1H, b s), 2.91 (1H, b s, -OH); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 161.2, 140.3, 138.0, 128.7, 128.4, 126.1, 123.6, 86.3, 86.0, 83.7, 68.1; IR (KBr) 33410, 2940, 1710 cm-1; $[\alpha]_D$=+186.1 (*c* 0.4, EtOH) [lit.[1a] $[\alpha]_D$=+188 (*c* 0.5, EtOH), lit.[1b] $[\alpha]_D$=+184.7 (EtOH)]; HRMS [M^+] calcd for $C_{13}H_{12}O_4$: 232.0736, found: 232.0737.

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