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An efficient Amano PS-catalyzed chemo-, regio- and enantioselective hydrolysis of (±)-2,3-di-*O*-acetyl-2-*C*-methyl-D-erythrono-1,4-lactone: a facile preparation of bioactive natural products (−)-saccharinic acid lactone and potassium (2*R*,3*R*)-2,3,4-trihydroxy-2-methylbutanoate☆

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Abstract—Saccharinic acid lactone (−)-**1a** is a suitable building block for the synthesis of many bioactive natural products. Amano PS-induced chemo-, regio- and enantioselective hydrolysis of diacetyl lactone (±)-**3** has been carried out to obtain (−)-**1a** in 46% yield with 99% ee and diacetyl lactone (+)-**3** in 49% yield with 99% ee. The Amano PS-catalyzed enantioselective acylation of (±)-**1a** with vinyl acetate as an acyl donor was relatively less efficient and furnished (−)-**7** in 31% yield with 99% ee and (+)-**1a** in 63% yield. The conversion of (−)-**1a** to leaf-closing substance **2a** and an attempted approach to naturally occurring compounds **1b** and **2b** have been also described.

1. Introduction

In recent years, a number of natural products have been isolated, which contain the saccharinic acid lactone [(2*R*,3*R*)-2,3-dihydroxy-2-methyl-γ-butyrolactone, (−)-**1a**] unit (Fig. 1). Very recently, Ogawa et al. have isolated a new sugar lactone derivative, 3-*O*-caffeoyl-2-*C*-methyl-D-erythrono-1,4-lactone (−)-**1b** from the leaves of *Bidens pilosa*.[1] The natural products such as potassium 2,3,4-trihydroxy-2-methylbutanoate **2a** and potassium aeshynomate **2b** have been isolated as the leaf-closing and leaf-opening substances from *Leucaena leucocephalam*[2] and *Aeshynomene indica* L.,[3] respectively. The saccharinic acid lactone (−)-**1a** is itself a bioactive natural product isolated from *Astragalus lusitanicus* L.[4] and *Cicer arietinum* L.[5] Natural lactone (−)-**1a** was thought to be a plant growth regulator involved in feedback inhibition in the biosynthesis of valine.[6] To date, three syntheses of enantiomerically pure erythro-saccaharinic acid lactone (−)-**1a** are known from D-mannitol,[6] D-erythrose[7] and using the chiral tin(II) Lewis acid mediated asymmetric aldol reaction.[8] Biotransformations are often more efficient[9] and in continuation of our earlier studies[10] on the enzymatic resolution of important chiral intermediates, we herein report an efficient enzyme-catalyzed hydrolysis of lactone (±)-**3** and our studies on the synthesis of natural products (−)-**1b** and (−)-**2b** (Schemes 1–3).

2. Results and discussion

In our focused efforts to convert cyclic anhydrides to bioactive natural and unnatural products,[11] starting from citraconic anhydride, we synthesized lactone (±)-**1a** in five steps with 29% overall yield.[12] In our hands, the asymmetric dihydroxylation of 3-methyl-2(5*H*)-furanone was unsuccessful and we prepared a systematic plan to study the enzyme-catalyzed enantioselective hydrolysis of diacetyl lactone (±)-**3** and the enzyme-catalyzed enantioselective acylation of dihydroxy lactone (±)-**1a**. Lactone (±)-**1a**, on treatment with Ac_2O in the presence of pyridine, gave diacetyl lactone (±)-**3** in 90% yield (Scheme 1). The enzyme Amano PS did not recognize substrate (±)-**3** at 25 °C, while we observed 26%, 30% and 33% hydrolysis of (±)-**3** to (−)-**1a** at 30, 35 and 40 °C, respectively, in 36 h time. The Amano PS-catalyzed biphasic chemo-, regio- and enantioselective

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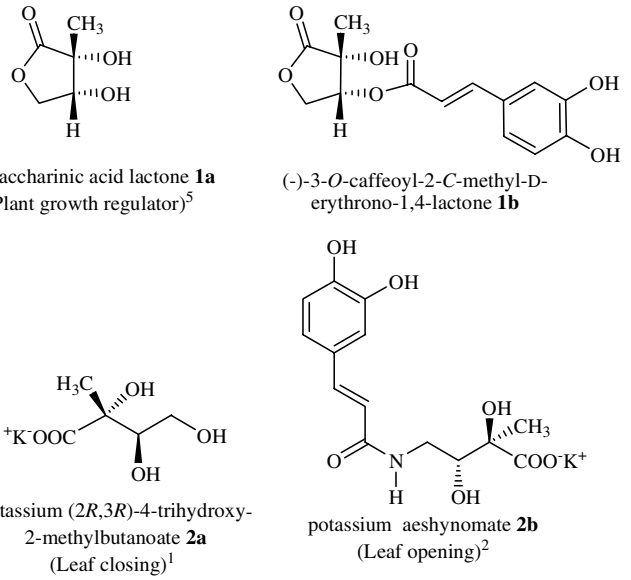
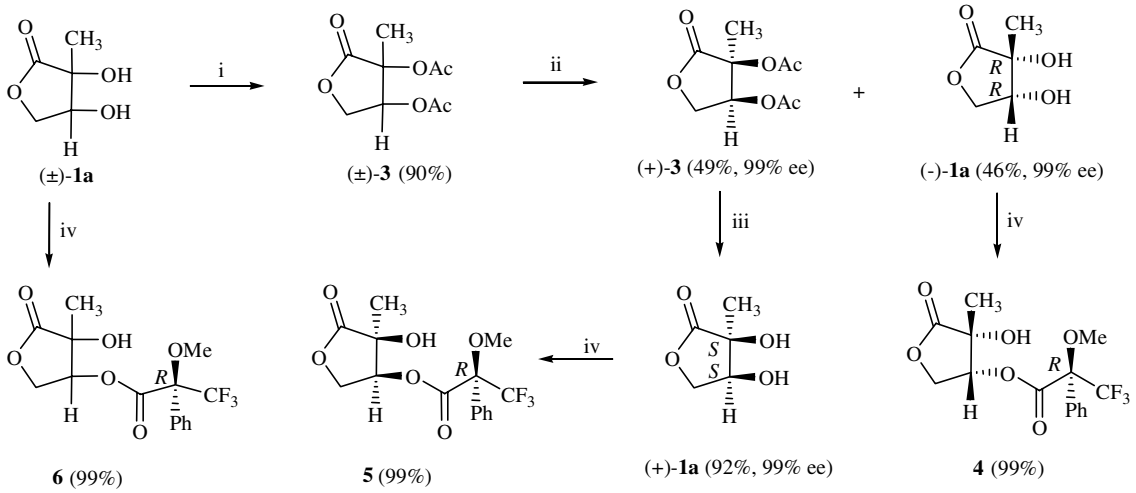


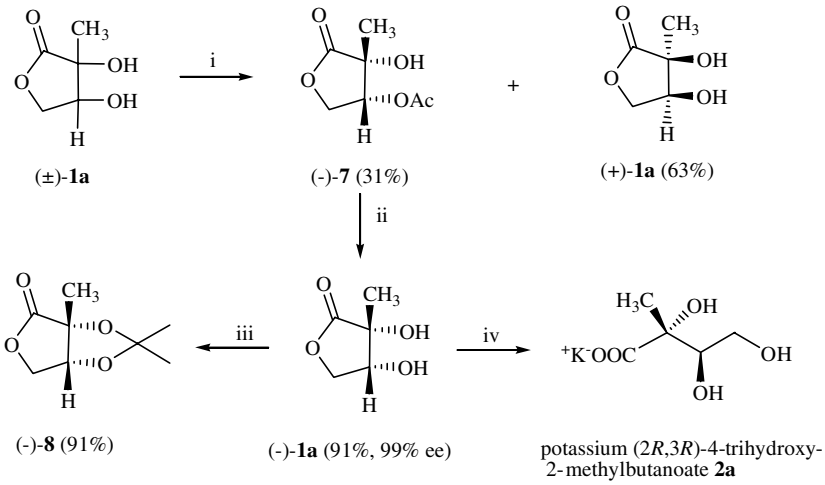
Figure 1. Naturally occurring bioactive α,β-dihydroxylactones/carboxylic acids.

hydrolysis of the diacetyl lactone (±)-**3** at 45 °C directly furnished nearly a 1:1 mixture (by ^{1}H NMR) of the dihydroxy lactone (−)-**1a** with the recognition of secondary (*R*)-acetate in the presence of γ-lactone and tertiary acetate and the unrecognized diacetyl lactone (+)-**3** in 36 h reaction time. The above formed mixture of (−)-**1a** and (+)-**3** was easily separated using silica gel column chromatography to obtain (−)-**1a** in 46% yield and (+)-**3** in 49% yield. Herein, we propose[10b] that the enzyme first recognizes the secondary acetate group to form the unisolable intermediate vicinal hydroxyacetate, which on in situ intramolecular hydroxy catalyzed further hydrolysis, furnished (−)-**1a**. Diacetyl lactone (+)-**3** in base catalyzed methanolysis gave (+)-**1a** in 92% yield. The stereochemical assignments of lactones (+)-**1a** and (−)-**1a** were done on the basis of comparison with literature data.[6,7] The ^{1}H NMR spectrum of a diastereomeric mixture of Mosher's esters[13] obtained from dihydroxy lactone (±)-**1a** and (*R*)-Mosher's acid showed a very clean resolution of the signals for the methoxy and methylene group protons on the lactone moiety. The ^{1}H NMR spectrum of Mosher's esters of lactones (+)-**1a** and (−)-**1a** revealed that both of them possess >99% ee. Next, we performed the Amano PS-catalyzed acylation of dihydroxy lactone (±)-**1a** using vinyl acetate as an acyl donor at 45 °C and obtained the monoacetyl lactone (−)-**7** in 31% yield and dihydroxy lactone (+)-**1a** in 63% yield (Scheme 2). The present enzyme-catalyzed acylation was also highly regio- and enantioselective and, as expected, exclusively furnished the secondary alcohol, acylated product, (−)-**7**. This monoacetyl lactone (−)-**7** on methanolysis in the presence of K_2CO_3 as a catalyst furnished the dihydroxy lactone (−)-**1a** in 91% yield with 99% ee. The dihydroxy lactone (−)-**1a** on treatment with aqueous KOH at room temperature gave the enantiomerically pure naturally occurring leaf-closing compound, potassium (2*R*,3*R*)-2,3,4-trihydroxy-2-methylbutanoate **2a** in quantitative yield.[12,14] This plant-specific leaf-movement factor **2a** could be useful as a herbicide.[15]

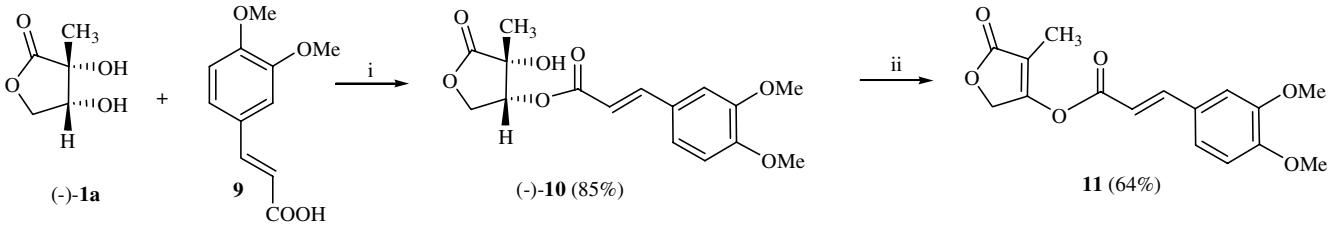
We then planned to synthesize natural products (−)-**1b** and (−)-**2b** from enantiomerically pure lactone (−)-**1a**. Lactone (−)-**1a**, on treatment with 3,4-dimethoxycinnamic acid **9** in the presence of DCC and a catalytic amount of DMAP at room temperature, exclusively furnished the desired ester (−)-**10** in 85% yield (Scheme 3). Unfortunately, BBr_3-induced demethylation at −78 °C furnished the dehydrated product **11**. Herein the tertiary hydroxyl group was eliminated, forming the α,β-unsaturated lactone **11** in preference to the deprotection of the two methyl ether units. However, the synthesis of unnatural (+)-**1b** using TBDMS protection of phenolic hydroxy groups is well known in the literature.[16] Lactone (−)-**1a** on reaction with 2,2-dimethoxypropane gave the protected lactone (−)-**8** in 91% yield. In our hands, all our attempts to ring open the lactone (−)-**8** with



Scheme 1. Reagents, conditions and yields: (i) Ac_2O, pyridine, rt, 12 h (90%); (ii) Amano PS, petroleum ether/benzene (2:1), sodium phosphate buffer (0.1 M, pH 7.0), 45 °C, 36 h, (+)-**3** (49%) and (−)-**1a** (46%); (iii) K_2CO_3, CH_3OH, 0 °C to rt, 3 h (92%); (iv) (*R*)-Mosher's acid, DCC, DMAP, CH_2Cl_2, 0 °C to rt, 8 h (99%).



Scheme 2. Reagents, conditions and yields: (i) Amano PS, vinyl acetate, *n*-hexane/benzene (2:1), 45 °C, 96 h, (+)-**1a** (63%) and (−)-**7** (31%); (ii) K_2CO_3, CH_3OH, 0 °C to rt, 3 h (91%); (iii) $(CH_3)_2C(OCH_3)_2$, *p*-TSA, rt, 10 h (91%); (iv) aq KOH (1 equiv), rt, 10 min (~100%).



Scheme 3. Reagents, conditions and yields: (i) DCC, DMAP, CH_2Cl_2, rt, 10 h (85%); (ii) BBr_3, CH_2Cl_2, −78 °C, 0.5 h (64%).

sodium azide[17] via the nucleophilic attack of the azide anion on a methylene carbon met with failure and hence we were unable to design naturally occurring **2b**.

3. Conclusion

In summary, we have demonstrated an efficient practical chemo-, regio- and enantioselective Amano PS-catalyzed hydrolysis of diacetyl lactone (±)-**3** to obtain the enantiomerically pure lactones (+)-**1a** and (−)-**1a** in 45% yield (99% ee) (two steps) and 46% yield (99% ee), respectively. We feel that the present highly efficient and selective enzymatic resolution of saccharinic acid lactone is noteworthy and these enantiomerically pure lactones will serve as potential building blocks for the synthesis of several natural and unnatural bioactive products.

4. Experimental

4.1. General

Stereochemical assignments are based on the optical rotation of known compounds. Melting points are uncorrected. Amano PS-1400 U from Amano Pharmaceuticals, Japan was used. The activity of the lipase powder used is expressed in terms of units, 1 unit corresponding to micromoles of butyric acid liberated (estimation by GC) from glyceryl tributyrate per minute per milligram of enzyme powder.[18] Column chromatographic separations were done on ACME silica gel (60–120 mesh). Commercially available acetic anhydride, DCC, DMAP, vinyl acetate, 3,4-dimethoxycinnamic acid, boron tribromide, 2,2-dimethoxypropane and (*R*)-Mosher's acid were used.

4.2. (±)-2,3-Di-*O*-acetyl-2-*C*-methyl-D-erythrono-1,4-lactone, 3

To a stirred solution of dihydroxy lactone (±)-**1a** (400 mg, 3.03 mmol) in pyridine (5 mL) were added acetic anhydride (0.9 mL, 9.09 mmol) and a catalytic amount of DMAP (10 mg). The reaction mixture was stirred at room temperature for 5 h and then concentrated in vacuo and diluted with water (15 mL). The aqueous layer was extracted with ethyl acetate (15 mL × 5) and the combined organic layer washed with 5% $CuSO_4$ solution, water, brine and dried over Na_2SO_4. Concentration of the organic layer in vacuo followed by silica gel column chromatographic purification of the residue using a mixture of ethyl acetate and petroleum ether (1:9) as an eluant gave diacetyl lactone (±)-**3**: 589 mg (90% yield); colourless solid; mp 86–87 °C; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.65 (s, 3H), 2.06 (s, 3H), 2.11 (s, 3H), 4.29 (dd, $J = 10$ and 4 Hz, 1H), 4.57 (dd, $J = 10$ and 6 Hz, 1H), 5.33 (dd, $J = 6$ and 4 Hz, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 20.0, 20.1, 21.3, 69.8, 71.5,

74.7, 169.2, 169.3, 172.9; IR ($CHCl_3$) ν_{max} 1794, 1760, 1751, 1219, 1109 cm^{-1}. Anal. Calcd for $C_9H_{12}O_6$: C, 50.00; H, 5.59. Found: C, 50.08; H, 5.65.

4.3. Amano PS-catalyzed hydrolysis of diacetyl lactone (±)-3

A solution of diacetyl lactone (±)-**3** (400 mg, 1.85 mmol) in petroleum ether/benzene (2:1) mixture (12 mL) was added to a suspension of Amano PS lipase (40 mg) in aqueous sodium phosphate (0.01 M, 4 mL) at pH 7.0. The reaction mixture was stirred at 45 °C for 36 h. The reaction mixture was filtered through Celite and the aqueous layer extracted with ethyl acetate (15 mL × 5). The combined organic layer was washed with water, brine and dried over Na_2SO_4. Concentration of the organic layer in vacuo followed by silica gel column chromatographic separation using a mixture of ethyl acetate and petroleum ether (2:8) mixture as an eluant gave diacetyl lactone (+)-**3** (196 mg, 49%) and dihydroxy lactone (−)-**1a** (112 mg, 46%).

4.3.1. (−)-(3*R*,4*R*)-3,4-Dihydroxy-3-methyldihydrofuran-2-one, 1a. Colourless thick oil; $[\alpha]_D^{20} = -58.6$ (*c* 0.50, H_2O). Analytical and spectral data obtained were identical with (±)-**1a**.[12]

4.3.2. (+)-(2*S*,3*S*)-2,3-Di-*O*-acetyl-2-*C*-methyl-D-erythrono-1,4-lactone, 3. Colourless solid; $[\alpha]_D^{20} = +8.96$ (*c* 1.6, $CHCl_3$). Analytical and spectral data obtained were identical with (±)-**3**.

4.4. (+)-(3*S*,4*S*)-3,4-Dihydroxy-3-methyldihydrofuran-2-one, 1a

To a stirred solution of diacetyl lactone (+)-**3** (60 mg, 0.28 mmol) in dry methanol (3 mL) was added anhydrous K_2CO_3 (10 mg, 0.07 mmol) at 0 °C. The reaction mixture was allowed to warm to room temperature and stirred for 3 h. Methanol was removed in vacuo at room temperature and water (10 mL) was added to the reaction mixture, then acidified to pH 2 using 2 M HCl and extracted with ethyl acetate (15 mL × 4). The combined organic layer was washed with water, brine and dried over Na_2SO_4. Concentration of the organic layer in vacuo, followed by silica gel column chromatographic purification of the residue using a mixture of ethyl acetate and petroleum ether (2:8) as an eluant gave (+)-**1a**: 34 mg (92% yield); colourless thick oil; $[\alpha]_D^{20} = +58.5$ (*c* 0.50, H_2O). Analytical and spectral data obtained were identical with (±)-**1a**.[12]

4.5. Amano PS-catalyzed acylation of (±)-1a

A solution of dihydroxy lactone (±)-**1a** (200 mg, 1.52 mmol) in *n*-hexane/benzene (2:1) (12 mL) was added to Amano PS lipase (40 mg) and vinyl acetate (0.8 mL, 7.6 mmol). The reaction mixture was stirred at 45 °C for 96 h and then allowed to cool to room temperature. The enzyme was filtered off, washed with ethyl acetate and the organic layer concentrated in vacuo. The residue was chromatographed over silica gel using a mixture of ethyl acetate and petroleum ether (2.5:7.5) as an eluant to give acetyl lactone (−)-**7** (82 mg, 31%) and dihydroxy lactone (+)-**1a** (126 mg, 63%), respectively.

4.5.1. (−)-(3*R*,4*R*)-Acetic acid 4-hydroxy-4-methyl-5-oxotetrahydrofuran-3-yl ester, 7. Colourless oil; $[\alpha]_D^{20} = -44.0$ (*c* 0.2, $CHCl_3$); ^1H NMR ($CDCl_3$, 200 MHz) δ 1.52 (s, 3H), 2.13 (s, 3H), 3.41 (br s, 1H), 4.29 (dd, $J = 10$ and 2 Hz, 1H), 4.47 (dd, $J = 12$ and 4 Hz, 1H), 5.16 (dd, $J = 4$ and 2 Hz, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 20.6, 21.7, 69.6, 72.3, 74.4, 170.1, 177.0; IR ($CHCl_3$) ν_{max} 3460, 1788, 1744, 1232, 1215 cm^{-1}. Anal. Calcd for $C_7H_{10}O_5$: C, 48.28; H, 5.79. Found: C, 48.35; H, 5.69.

4.5.2. (+)-(3*S*,4*S*)-3,4-Dihydroxy-3-methyldihydrofuran-2-one, 1a. Colourless thick oil; $[\alpha]_D^{20} = +35.0$ (*c* 0.40, H_2O). Analytical and spectral data obtained were identical with (±)-**1a**.[12]

4.6. (−)-(3*R*,4*R*)-3,4-Dihydroxy-3-methyldihydrofuran-2-one, 1a

To a stirred solution of acetyl lactone (−)-**7** (80 mg, 0.45 mmol) in dry methanol (6 mL) was added anhydrous K_2CO_3 (5 mg) at 0 °C. The reaction mixture was allowed to warm to room temperature and stirred for 3 h. Methanol was removed in vacuo at room temperature and water (7 mL) was added to the reaction mixture, then acidified to pH 2 using 2 M HCl and extracted with ethyl acetate (10 mL × 4). The combined organic layer was washed with water, brine and dried over Na_2SO_4. Concentration of the organic layer in vacuo followed by silica gel column chromatographic purification of the residue using a mixture of ethyl acetate and petroleum ether (2.5:7.5) as an eluant gave (−)-**1a**: 55 mg (91% yield); colourless thick oil; $[\alpha]_D^{20} = -58.5$ (*c* 0.50, H_2O). Analytical and spectral data obtained were identical with (±)-**1a**.[12]

4.7. (−)-(2*R*,3*R*)-2,3-*O*-Isopropylidene-2-*C*-methyl-D-erythrono-1,4-lactone, 8

To a stirred solution of lactone (−)-**1a** (50 mg, 0.38 mmol) in 2,2-dimethoxypropane (5 mL) was added *p*-toluenesulfonic acid monohydrate (4 mg, 0.02 mmol). The reaction mixture was stirred at room temperature for 10 h and then concentrated in vacuo. The residue was chromatographed over silica gel using a mixture of ethyl acetate and petroleum ether (0.5:9.5) as an eluant to give lactone (−)-**8**: 59 mg (91% yield); colourless thick oil; $[\alpha]_D^{20} = -82.2$ (*c* 2.0, acetone); ^1H NMR ($CDCl_3$, 200 MHz) δ 1.42 (s, 3H), 1.47 (s, 3H), 1.57 (s, 3H), 4.32 (dd, $J = 10$ and 4 Hz, 1H), 4.44 (d, $J = 10$ Hz, 1H), 4.49 (d, $J = 4$ Hz, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 18.4, 26.6, 26.9, 68.9, 80.3, 81.4, 113.0, 176.7; IR ($CHCl_3$) ν_{max} 1788, 1379, 1105 cm^{-1}. Anal. Calcd for $C_8H_{12}O_4$: C, 55.81; H, 7.02. Found: C, 55.72; H, 6.97.

4.8. (−)-(3*R*,4*R*)-β-(3,4-Dimethoxyphenyl)acrylic acid 4-hydroxy-4-methyl-5-oxotetrahydrofuran-3-yl ester, 10

To a stirred solution of acid **9** (158 mg, 0.76 mmol), dihydroxy lactone (−)-**1a** (100 mg, 0.76 mmol) and DMAP (cat.) in dry CH_2Cl_2 (7 mL) was added a solution of DCC (156 mg, 0.76 mmol) in dry CH_2Cl_2 (5 mL) at 0 °C. The reaction mixture was allowed to warm to room temperature and stirred for 10 h. The formed urea was filtered

off and the organic layer concentrated in vacuo. Silica gel column chromatographic purification of the residue using ethyl acetate and petroleum ether (2:8) as an eluant yielded ester (−)-**10**: 208 mg (85% yield); yellow crystalline solid; mp 123–124 °C; $[\alpha]_D^{20} = -70.0$ (*c* 0.4, $CHCl_3$); ^1H NMR ($CDCl_3$, 200 MHz) δ 1.58 (s, 3H), 3.32 (br s, 1H), 3.90 (s, 6H), 4.38 (dd, $J = 12$ and 2 Hz, 1H), 4.54 (dd, $J = 10$ and 4 Hz, 1H), 5.30 (d, $J = 4$ Hz, 1H), 6.33 (d, $J = 16$ Hz, 1H), 6.85 (d, $J = 8$ Hz, 1H), 7.04–7.13 (m, 2H), 7.69 (d, $J = 16$ Hz, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 21.9, 55.8, 55.9, 69.9, 72.6, 74.5, 109.6, 111.0, 113.7, 123.1, 126.8, 147.0, 149.2, 151.6, 166.1, 177.0; IR ($CHCl_3$) ν_{max} 3477, 1786, 1719, 1632, 1599, 1512, 1263, 1215, 1140 cm^{-1}. Anal. Calcd for $C_{16}H_{18}O_7$: C, 59.62; H, 5.63. Found: C, 59.58; H, 5.68.

4.9. 3-(3,4-Dimethoxyphenyl)acrylic acid 4-methyl-5-oxo-2,5-dihydrofuran-3-yl ester, 11

To a stirred solution of lactone **10** (100 mg, 0.31 mmol) in CH_2Cl_2 (5 mL) was added a 1.0 M solution of boron tribromide (2.20 mL, 2.18 mmol) in CH_2Cl_2 at −78 °C in a drop wise fashion under an argon atmosphere. The reaction mixture was stirred at −78 °C temperature for 30 min. The reaction was then slowly quenched with water and extracted with ethyl acetate (15 mL × 3) and the combined organic layer washed with brine and dried over Na_2SO_4. Concentration of the organic layer in vacuo followed by silica gel column chromatographic purification of the residue using ethyl acetate and petroleum ether (0.5:9.5) as an eluant gave **11**: 60 mg (64% yield); yellow crystalline solid; mp 115–116 °C; ^1H NMR ($CDCl_3$, 200 MHz) δ 2.22 (s, 3H), 3.89 (s, 3H), 3.92 (s, 3H), 5.30 (s, 2H), 6.60 (d, $J = 16$ Hz, 1H), 6.87 (d, $J = 8$ Hz, 1H), 7.00–7.11 (m, 2H), 7.62 (d, $J = 16$ Hz, 1H); IR ($CHCl_3$) ν_{max} 1779, 1733, 1640, 1602, 1260 cm^{-1}. Anal. Calcd for $C_{16}H_{16}O_6$: C, 63.15; H, 5.30. Found: C, 63.04; H, 5.36.

4.10. General procedure for MTPA-ester preparation

To a solution of (*R*)-Mosher's acid (27 mg, 0.11 mmol), dihydroxy alcohol (±)-**1a** or (+)-**1a** or (−)-**1a** (15 mg, 0.11 mmol) and DMAP (cat.) in dry CH_2Cl_2 (3 mL) was added a solution of DCC (24 mg, 0.11 mmol) in dry CH_2Cl_2 (2 mL) at 0 °C. The reaction mixture was allowed to warm to room temperature and stirred for 8 h. The formed urea was filtered off and the organic layer concentrated in vacuo. Silica gel column chromatographic purification of the residue using ethyl acetate and petroleum ether mixture (1:9) gave the MTPA-ester in quantitative yield.

4.10.1. MTPA-ester of (±)-3,4-dihydroxy-3-methyldihydrofuran-2-one, 6. Colourless thick oil; ^1H NMR ($CDCl_3$, 200 MHz) δ 1.57 (s, 3H), 1.59 (s, 3H), 2.70 (br s, 1H), 2.96 (br s, 1H), 3.53 (s, 3H), 3.57 (s, 3H), 4.27 (dd, $J = 12$ and 2 Hz, 1H), 4.40 (dd, $J = 12$ and 2 Hz, 1H), 4.50 (dd, $J = 12$ and 4 Hz, 1H), 4.56 (dd, $J = 12$ and 4 Hz, 1H), 5.41 (d, $J = 4$ Hz, 2H), 7.38–7.56 (m, 10H).

4.10.2. MTPA-ester of (−)-(3*R*,4*R*)-3,4-dihydroxy-3-methyldihydrofuran-2-one, 4. Colourless thick oil; ^1H NMR ($CDCl_3$, 200 MHz) δ 1.60 (s, 3H), 2.82 (br s, 1H), 3.57 (s, 3H), 4.27 (dd, $J = 12$ and 2 Hz, 1H), 4.51 (dd, $J = 12$ and 4 Hz, 1H), 5.41 (d, $J = 4$ Hz, 1H), 7.41–7.57 (m, 5H).

4.10.3. MTPA-ester of (+)-(3*S*,4*S*)-3,4-dihydroxy-3-methyldihydrofuran-2-one, 5. Colourless thick oil; ^1H NMR ($CDCl_3$, 200 MHz) δ 1.57 (s, 3H), 2.57 (br s, 1H), 3.53 (s, 3H), 4.40 (dd, $J = 12$ and 2 Hz, 1H), 4.56 (dd, $J = 12$ and 4 Hz, 1H), 5.41 (d, $J = 4$ Hz, 1H), 7.41–7.57 (m, 5H).

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