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A facile chemoenzymatic approach to natural cytotoxic ellipsoidone A and natural ellipsoidone B☆

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Abstract—Starting from citraconic anhydride (**3**) a facile four-step synthesis of deoxyellipsoidone **8** has been reported with 37% overall yield. An elegant six-step access to naturally occurring cytotoxic ellipsoidone A (**1**) and ellipsoidone B (**2**) has been reported with good overall yields, via the conversion of itaconic anhydride (**9**) to the acetoxymethylmaleic anhydride (**11**), regioselective sodium borohydride reduction of anhydride **11** to acetoxymethylbutyrolactone **12**, Knoevenagel condensation of lactone **12** with 5-methylfurfural, selenium dioxide induced oxidation of the formed butenolide **13** and an Amano PS catalyzed deacylation of the formed diacetoxybutenolide **14** as a pathway.

1. Introduction

Plants of the genus *Hemsleya* are distributed throughout the southwest region of China and the tubers of these plants have been used in Chinese folk medicine system.[1] As a part of survey of Chinese medicinal resources, Nomura et al. in collaboration with group of researchers from China isolated the new compounds ellipsoidones A (**1**) and B (**2**) along with the known glucosidyl butenolide, siphonoside from the tubers of *Hemsleya ellipsoidea*[2] (Fig. 1). One can easily make out that siphonoside[3] is a biological precursor of **1** and **2**. Siphonoside on loss of three water molecules would generate **1** and **2** via an intramolecular condensation and dehydrative ring contraction pathway. The structural assignment of **1** and **2** was done on the basis of UV, ^{1}H NMR, ^{13}C NMR, 2D NMR, NOE and HRFABMS data. The two new acetogenins **1** and **2** are geometric stereoisomers of each other and ellipsoidone A (**1**) possesses cytotoxic activity against P-388 cells [IC_{50} 47 mg/mL].[2] A large number of structurally interesting butenolides have been isolated previously as bioactive natural products and several elegant methods for synthesis of this class of compounds are known in the literature.[4] Synthesis of these two geometric isomers **1** and **2** with two hydroxymethyl moieties is a challenging task as Nature derives them from the sugar, siphonodin 6-*O*-β-D-glycopyranoside.[3] In continuation of our studies on cyclic anhydrides to structurally interesting

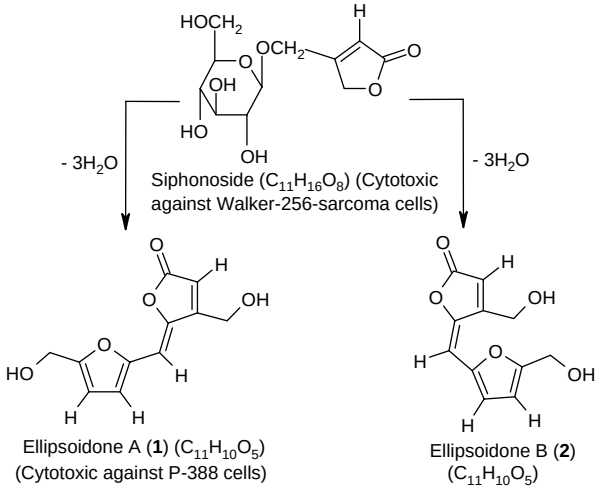

Figure 1. Bioactive natural products from *Hemsleya ellipsoidea*.

bioactive natural and unnatural products, now herein, we report a facile chemoenzymatic route to **1** and **2** using acetoxymethylmaleic anhydride (**11**) as a precursor[4,5] (Schemes 1 and 2).

2. Results and discussion

Selenium dioxide oxidation of the β-methyl group of α,β-unsaturated esters and several types of allylic/benzylic methyl groups are known in the literature.[6–8] We felt that the butenolide **5** would be a potential starting material for the synthesis of ellipsoidones A (**1**) and B (**2**) and selenium dioxide oxidation of both the allylic methyl groups in **5** would

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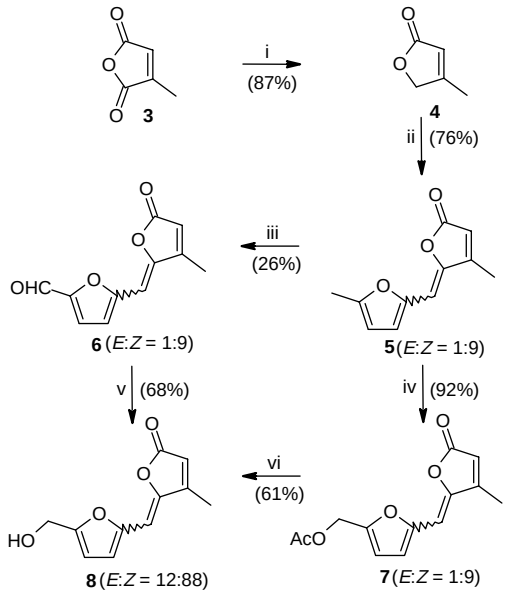
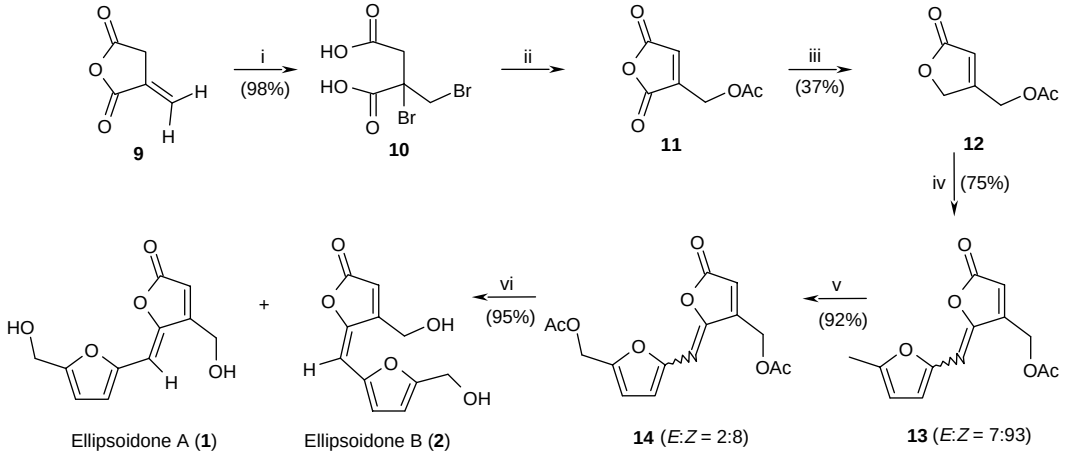


Scheme 1. Reagents, conditions and yields: (i) (a) $NaBH_4$, THF, 0 °C, 2 h, (b) H^+/HCl (87%); (ii) 5-methylfurfural, piperidine, CH_3OH, rt, 15 h (76%); (iii) SeO_2, CH_3COOH, reflux, 2 h (26%); (iv) SeO_2, CH_3COOH (anhydrous), reflux, 1.5 h (92%); (v) (a) $NaBH_4$, C_2H_5OH, rt, 1 h, (b) H^+/HCl (68%); (vi) K_2CO_3, CH_3OH, 0 °C to rt, 2 h (61%).

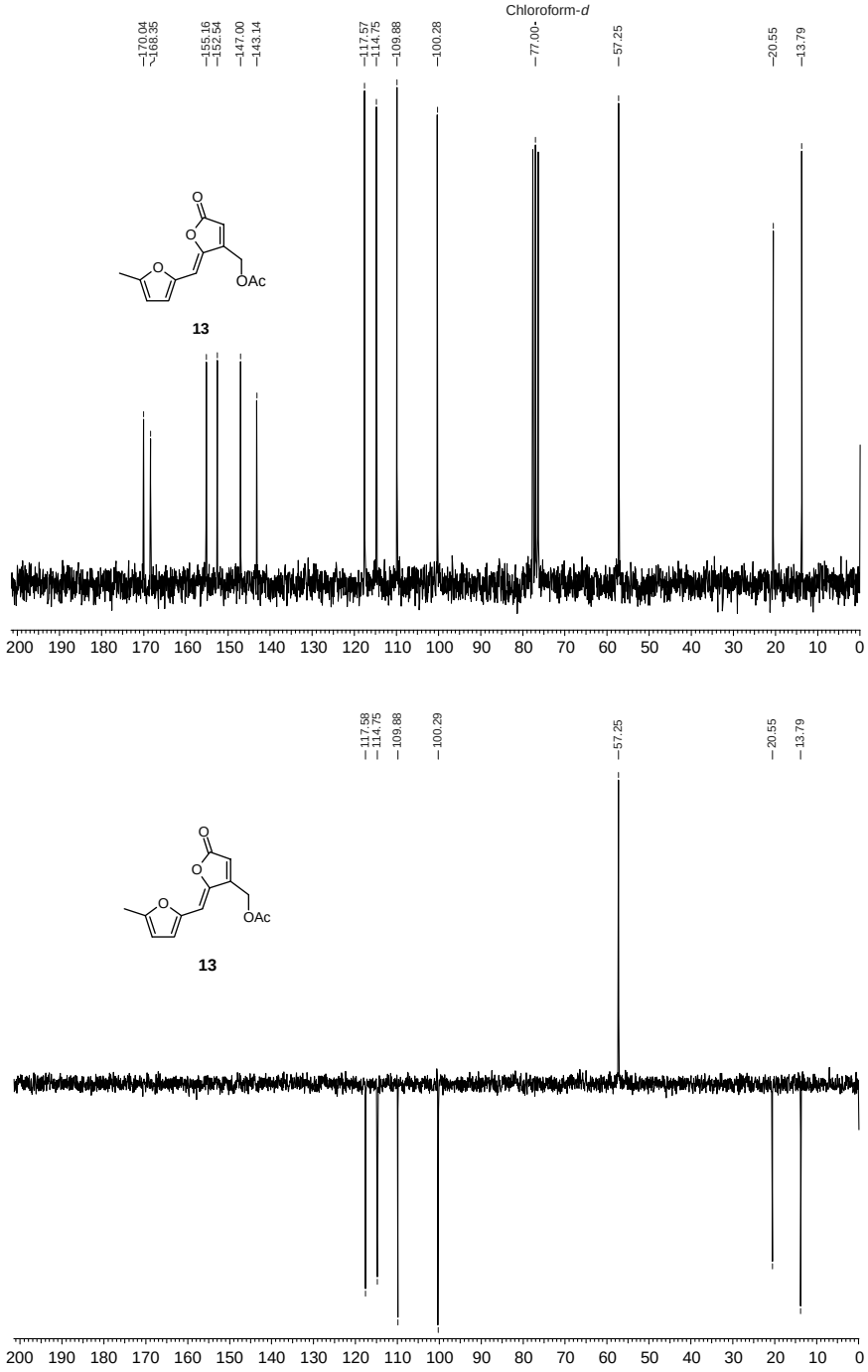
provide a simple and efficient access to these natural products. In this context, for the preparation of **5**, we performed the sodium borohydride reduction of citraconic anhydride (**3**) and obtained the known[9] butyrolactone **4** in 87% yield (Scheme 1). Piperidine catalyzed Knoevenagel condensation of lactone **4** with 5-methylfurfural gave the desired butenolide **5** in 76% yield (*E*:*Z*=1:9, by ^{1}H NMR). The butenolide **5** was strongly resistant to selenium dioxide oxidation in refluxing ethanol and 1,4-dioxane solutions and the starting material was recovered after 12 h reflux time. The SeO_2 oxidation of **5** in 98% acetic acid directly furnished the aldehyde **6**, but only in 26% yield, wherein both the hydroxylation and further oxidation of the alcohol to the aldehyde took place in one pot. To arrest the SeO_2 oxidation of **5** at the alcohol stage, we performed the reaction in a freshly dried anhydrous acetic acid and exclusively obtained the monoacetoxymethylbutenolide **7** in 92% yield. The aldehyde **6** on $NaBH_4$ reduction as well as the monoacetate **7** on base catalyzed deacylation gave the deoxyellipsoidone **8** (*E*:*Z*=12:88, by ^{1}H NMR) in 68 and 61% yields, respectively. Most of the naturally occurring butenolides of such type exist as the thermodynamically more stable *Z*-isomer[4] and herein, we could assign the *Z*-geometry to the exocyclic carbon–carbon double bonds in compounds **5** to **8** on the basis of ^{1}H NMR data. As expected, in compounds **5** to **8** the lactone methyl group signals for the minor *E*-isomers in ^{1}H NMR spectra were more deshielded (ca. δ 2.51) than the corresponding major *Z*-isomer signals (ca. δ 2.22), due to the anisotropic effect of the furan ring. All our attempts to oxidize the allylic methyl group of the lactone moiety in **5** met with failure. We feel that, on the formation of new exocyclic carbon–carbon double bond in **5**, the allylic methyl group hydrogens lose the sacrificial hyperconjugation with the lactone carbonyl group and hence it becomes inactive to the SeO_2-oxidation. Therefore, we altered our strategy and decided to start the synthesis of **1** and **2** from acetoxymethylbutenolide **12**.

We envisaged the preparation of acetoxymethyllactone **12** from itaconic anhydride (**9**). The bromination of itaconic anhydride (**9**) furnished the dibromodiacid **10**[10] in 98% yield (Scheme 2). The diacid **10** on treatment with Ac_2O/NaOAc mixture at room temperature for 6 h followed by removal of acetic anhydride in vacuo gave the crude acetoxymethylmaleic anhydride (**11**). Herein all the three-steps, the ring closure of acid **10** to the intermediate succinic anhydride derivative, dehydrobromination to form the second intermediate bromomethylmaleic anhydride and the allylic substitution of the bromide with the acetoxy group took place in one pot. The acetoxymethylmaleic anhydride (**11**) was very unstable and we were unable to purify it. The structure of the anhydride **11** was established on the basis of IR, ^{1}H NMR data of crude **11**. The direct regioselective $NaBH_4$ reduction of the crude anhydride **11** in THF furnished the desired lactone **12** in 37% yield (two-steps), without deacylation of the acetate moiety in **11/12**. Alternately, the desired lactone **12** can also be obtained from dihydroxy acetone in four-steps with 38% overall yield.[11] The Knoevenagel condensation of lactone **12** with 5-methylfurfural gave the required monoacetoxymethylbutenolide **13** (*E*:*Z*=7:93, by ^{1}H NMR) in 75% yield. Herein, the regioselective carbanion formation on an internal butyrolactone methylene group, rather than the external



Scheme 2. Reagents, conditions and yields: (i) Br_2, CCl_4, rt, 24 h (98%); (ii) Ac_2O, AcONa, rt, 6 h; (iii) (a) $NaBH_4$, THF, 0 °C, 2 h, (b) H^+/HCl (two steps, 37%); (iv) 5-methylfurfural, piperidine, rt, 15 h (75%); (v) SeO_2, AcOH (anhydrous), reflux, 6 h (92%); (vi) Amano PS, hexane–benzene (2/1), phosphate buffer pH 7.0, rt, 40 h (95%, **1**:**2**=86:14).

acetoxymethyl moiety is noteworthy and could be due to the generation of the stable oxyfurananion in the former case. As expected, here too the methylene proton signals from the $-CH_2OAc$ groups on lactone moieties for the minor *E*-isomers in compounds **13** and **14** appeared more downfield than the corresponding signals for their major *Z*-isomers. The SeO_2 oxidation of **13** in anhydrous acetic acid gave the desired diacetoxymethylbutenolide **14** in 92% yield. To obtain the natural products **1** and **2**, we systematically studied the deacylation of **14**, both under acidic and basic conditions and observed that the starting material **14** and formed products **1** and **2** are not very stable under these conditions. In our hands, we always got a complex mixture of products and this could be due to the intermolecular reactions of the two hydroxymethyl groups with the reactive enol-lactone. Finally, we carried out the Amano PS catalyzed double deacylation of **14** at pH 7 and obtained the mixture of desired products **1** and **2** (**1**:**2**=86:14, by ^{1}H NMR) in 95% yield. All our attempts to obtain the pure major isomer **1** from the **1** plus **2** mixture by recrystallization were unsuccessful. Finally, we did the HPLC separation of **1** plus **2** mixture using the known procedure[2] and obtained pure **1** and **2** with quantitative recovery. The analytical and spectral data obtained for **1** and **2** were in complete agreement with the reported data.[2] In the present six-step synthesis, starting from itaconic anhydride (**9**), the overall yield of ellipsoidone A (**1**) and ellipsoidone B (**2**) were 20.4 and 3.3%, respectively. The photochemical conversion of ellipsoidone B to ellipsoidone A is known.[2]



3. Conclusion

In summary, we have demonstrated the first total synthesis of isomeric natural cytotoxic ellipsoidone A (**1**) and natural ellipsoidone B (**2**) using regioselective reduction of acetoxymethylmaleic anhydride (**11**), selenium dioxide hydroxylation of butenolide **13** and an enzymetic deacylation of diacetoxybutenolide **14** as key reactions. In the present stepwise approaches, we could design the acetyl derivatives of both the unnatural deoxyellipsoidone regioisomers. In the present synthesis, the enzymatic hydrolysis of diacetate **14** to obtain the labile multifunctional ellipsoidones A and B in 95% yield is noteworthy. We feel that the present approach to **1** and **2** is general in nature and it would be useful to design the analogs and congeners of these bioactive natural products for the structure–activity relationship studies.

4. Experimental

4.1. General

Melting points are uncorrected. Column chromatographic separations were carried out on ACME silica gel (60–120 mesh). Commercially available citraconic anhydride, sodium borohydride, 5-methylfurfural, piperidine, selenium dioxide, bromine, sodium acetate, and Amano PS-1310 U from Amano Pharmaceuticals, Japan were used. The activity of the lipase powder[12] 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. Dry acetic acid was obtained by refluxing it over active $CuSO_4$ for 12 h, followed by distillation.

4.1.1. 4-Methyl-5*H*-furan-2-one (4). To a stirred solution of citraconic anhydride **3** (800 mg, 7.14 mmol) in THF (15 mL), was added $NaBH_4$ (675 mg, 17.85 mmol) at 0 °C and the reaction mixture was further stirred at 0 °C for 2 h. The reaction was quenched with water, acidified with dilute HCl and extracted with ethyl acetate (50 mL×3). The 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 (3:7) furnished pure **4**.[9]

Compound **4**: 609 mg (87% yield); thick oil; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 2.16 (s, 3H), 4.76 (s, 2H), 5.83 (q, J= 2 Hz, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 13.5, 73.5, 115.5, 166.4, 173.8; IR ($CHCl_3$) ν_{max} 1782, 1751, 1647, 1215 cm^{-1}. Anal. Calcd for $C_5H_6O_2$: C, 61.22; H, 6.17. Found: C, 61.37; H, 6.21.

4.1.2. 4-Methyl-5-(5-methyl-furan-2-ylmethylene)-5*H*-furan-2-one (5). To a stirred solution of lactone **4** (300 mg, 3.06 mmol) in methanol were added piperidine (0.21 mL, 2.14 mmol) and 5-methylfurfural (0.30 mL, 3.06 mmol) at room temperature and the reaction mixture was stirred for 15 h. Removal of solvent in vacuo followed by column chromatographic purification of the residue using a mixture of ethyl acetate and petroleum ether (0.5:9.5) furnished **5** as a yellow crystalline solid.

Compound **5**: 442 mg (76% yield); mp 103–105 °C; ^{1}H NMR ($CDCl_3$, 200 MHz), major *Z*-isomer: δ 2.19 (d, J= 1 Hz, 3H), 2.35 (s, 2.7H), 5.91 (br s, 1H), 6.04 (s, 0.9H), 6.15 (d, J=4 Hz, 0.9H), 6.94 (d, J=4 Hz, 0.9H), [the following four signals for the minor *E*-isomer showed splitting and appeared at δ 2.49 (d, J=1 Hz, 0.3H), 6.10 (d, J=4 Hz, 0.1H), 6.44 (s, 0.1H), 6.49 (d, J=4 Hz, 0.1H)]; ^{13}C NMR ($CDCl_3$, 50 MHz), major *Z*-isomer: δ 11.5, 13.7, 98.9, 109.6, 114.8, 116.6, 146.7, 147.5, 154.5, 154.7, 169.2; IR ($CHCl_3$) ν_{max} 1773, 1751, 1651, 1520, 1215 cm^{-1}. Anal. Calcd for $C_{11}H_{10}O_3$: C, 69.46; H, 5.30. Found: C, 69.22; H, 5.51.

4.1.3. 5-(3-Methyl-5-oxo-5*H*-furan-2-ylidenemethyl)-furan-2-carbaldehyde (6). To a stirred solution of lactone **5** (100 mg, 0.53 mmol) in acetic acid (5 mL) was added SeO_2 (117 mg, 1.05 mmol) and the reaction mixture was refluxed for 2 h. The reaction mixture was filtered through Celite and acetic acid was removed in vacuo. The residue was purified by silica gel column chromatography using a mixture of ethyl acetate and petroleum ether (1:4) to furnish **6** as a yellow crystalline solid.

Compound **6**: 28 mg (26% yield); mp 187–190 °C; ^{1}H NMR ($CDCl_3$, 200 MHz), major *Z*-isomer: δ 2.26 (s, 2.7H), 6.10 (s, 1H), 6.19 (s, 0.9H), 7.23 (d, J=4 Hz, 1H), 7.34 (d, J= 4 Hz, 0.9H), 9.65 (s, 1H), [the following three signals for the minor *E*-isomer showed splitting and appeared at δ 2.58 (s, 0.3H), 6.53 (s, 0.1H), 6.71 (d, J=4 Hz, 0.1H)]; ^{13}C NMR ($CDCl_3$, 50 MHz), major *Z*-isomer: δ 11.6, 97.2, 116.1, 117.3, 123.5, 151.7, 152.0, 153.8, 154.9, 168.0, 177.3; IR ($CHCl_3$) ν_{max} 1782, 1676, 1215 cm^{-1}. Anal. Calcd for $C_{11}H_8O_4$: C, 64.71; H, 3.95. Found: C, 64.67; H, 4.04.

4.1.4. Acetic acid 5-(3-methyl-5-oxo-5*H*-furan-2-ylidene methyl)-furan-2-ylmethyl ester (7). To a stirred solution of lactone **5** (100 mg, 0.53 mmol) in dry acetic acid (5 mL) was added SeO_2 (117 mg, 1.05 mmol) and the reaction mixture was refluxed for 1.5 h. The reaction mixture was filtered through Celite and acetic acid was removed in vacuo. The residue was purified by silica gel column chromatography using a mixture of ethyl acetate and petroleum ether (1:9) to furnish **7** as a yellow crystalline solid.

Compound **7**: 120 mg (92% yield); mp 84–86 °C; ^{1}H NMR ($CDCl_3$, 200 MHz), major *Z*-isomer: δ 2.10 (s, 2.7H), 2.22 (d, J=2 Hz, 3H), 5.08 (s, 2H), 5.97 (s, 1H), 6.09 (s, 1H), 6.55 (d, J=4 Hz, 0.9H), 7.02 (d, J=4 Hz, 1H), [the following two signals for the minor *E*-isomer showed splitting and appeared at δ 2.48 (s, 0.3H), 6.50 (d, J=4 Hz, 0.1H)]; ^{13}C NMR ($CDCl_3$, 50 MHz), major *Z*-isomer: δ 11.6, 20.8, 57.9, 98.4, 113.7, 115.6, 115.7, 148.1, 149.4, 150.6, 154.8, 168.9, 170.5; IR ($CHCl_3$) ν_{max} 1774, 1751, 1651, 1601, 1234 cm^{-1}. Anal. Calcd for $C_{13}H_{12}O_5$: C, 62.90; H, 4.87. Found: C, 63.03; H, 4.62.

4.1.5. 5-(5-Hydroxymethyl-furan-2-ylmethylene)-4-methyl-5*H*-furan-2-one (8). To a stirred solution of lactone **7** (70 mg, 0.28 mmol) in methanol (5 mL) was added K_2CO_3 (5 mg, 0.04 mmol) and the reaction mixture was

stirred at room temperature for 1 h. Methanol was removed in vacuo at room temperature and water (10 mL) was added to the reaction mixture. The reaction mixture was acidified to pH 4 using 2 N HCl and immediately 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 eluent gave **8**.

Butenolide **6** (25 mg, 0.12 mmol) on $NaBH_4$ (5 mg, 0.14 mmol) reduction in EtOH (3 mL) at room temperature for 1 h followed by acidification with 2 N HCl gave **8** in 68% yield as a yellow crystalline solid.

Compound **8**: 35 mg (61% yield); mp 95–96 °C; ^{1}H NMR ($CDCl_3$, 200 MHz), major *Z*-isomer: δ 2.20 (s, 2.64H), 4.64 (s, 3H), 5.94 (s, 1H), 6.07 (s, 1H), 6.43 (d, J=4 Hz, 0.88H), 6.95 (d, J=4 Hz, 1H), [the following two signals for the minor *E*-isomer showed splitting and appeared at δ 2.49 (s, 0.36H), 6.53 (d, J=4 Hz, 0.12H)]; ^{13}C NMR ($CDCl_3$, 50 MHz), major *Z*-isomer: δ 11.6, 57.5, 98.6, 111.0, 115.4, 115.8, 147.7, 148.8, 154.9, 155.6, 169.1; IR ($CHCl_3$) ν_{max} 3449, 1780, 1755, 1649, 1599, 1217 cm^{-1}. Anal. Calcd for $C_{11}H_{10}O_4$: C, 64.07; H, 4.89. Found: C, 63.91; H, 4.99.

4.1.6. 2-Bromo-2-(bromomethyl)succinic acid (10). To a stirred solution of itaconic anhydride **9** (4.0 g, 35.70 mmol) in carbon tetrachloride (30 mL) was added a solution of bromine (3.60 mL, 71.40 mmol) in carbon tetrachloride (20 mL) at room temperature over a period of 20 min. The reaction mixture was further stirred for 24 h and then it was concentrated in vacuo. The obtained crude residue was recrystallized from petroleum ether plus ethyl acetate (1:1) mixture to obtain pure **10**[10] as a white crystalline solid.

Compound **10**: 10.13 g (98% yield); mp 163–165 °C (lit.[10] mp 167–168 °C); ^{1}H NMR (D_2O, 200 MHz) δ 3.27 (dd, J=18, 4 Hz, 2H), 4.03 (s, 2H); ^{13}C NMR (D_2O, 50 MHz) δ 40.0, 44.7, 59.5, 173.5, 174.8; IR (Nujol) ν_{max} 2700–2500, 1720, 1713, 1462 cm^{-1}.

4.1.7. Acetic acid 5-oxo-2,5-dihydro-furan-3-ylmethyl ester (12). To a stirred solution of acid **10** (2.0 g, 6.90 mmol) in Ac_2O (15 mL) was added NaOAc (1.70 g, 20.70 mmol) and the reaction mixture was stirred at room temperature for 6 h. Acetic anhydride was removed in vacuo to obtain crude **11**. To the stirred solution of this residue in THF (20 mL) was added $NaBH_4$ (522 mg, 13.80 mmol) at 0 °C. The reaction mixture was further stirred at 0 °C for 2 h and then quenched with water and acidified with dilute HCl and extracted with ethyl acetate (50 mL×3). The organic layer was washed with water, brine and dried over Na_2SO_4. Concentration of the organic layer in vacuo followed by the silica gel column chromatographic purification of the residue using a mixture of ethyl acetate and petroleum ether (3:7) furnished **12**.[11]

Compound **11** (crude): ^{1}H NMR ($CDCl_3$, 200 MHz) δ 2.19 (s, 3H), 5.05 (d, J=2 Hz, 2H), 6.83 (t, J=2 Hz, 1H); IR (neat) ν_{max} 1771, 1738, 1730 cm^{-1}.

Compound **12**: 400 mg (37% yield); thick oil; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 2.11 (s, 3H), 4.81 (d, J=2 Hz, 2H), 4.93 (d, J=2 Hz, 2H), 6.01 (quintet, J=2 Hz, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 20.3, 59.2, 71.0, 116.6, 163.6, 170.0, 172.7; IR (neat) ν_{max} 1782, 1747, 1651, 1229 cm^{-1}. Anal. Calcd for $C_7H_8O_4$: C, 53.85; H, 5.16. Found: C, 53.77; H, 5.04.

4.1.8. Acetic acid 2-(5-methyl-furan-2-ylmethylene)-5-oxo-2,5-dihydro-furan-3-ylmethyl ester (13). To a stirred solution of lactone **12** (300 mg, 1.92 mmol) in methanol was added piperidine (0.13 mL, 1.35 mmol) and 5-methyl-furfural (0.19 mL, 1.92 mmol) at room temperature and the reaction mixture was stirred for 15 h. Removal of solvent in vacuo followed by column chromatographic purification of the residue using a mixture of ethyl acetate and petroleum ether (1:9) furnished **13** as a faint yellow solid.

Compound **13**: 358 mg (75% yield); mp 83–85 °C; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 2.16 (s, 2.79H), 2.23 (s, 0.21H), 2.35 (s, 2.79H), 2.43 (s, 0.21H), 5.06 (d, J=2 Hz, 1.86H), 5.43 (d, J=2 Hz, 0.14H), 6.08 (s, 0.93H), 6.11 (s, 0.93H), 6.17 (d, J=4 Hz, 0.93H), 6.23 (s, 0.07H), 6.26–6.31 (m, 0.07H), 6.50 (br s, 0.07H), 6.53 (d, J=4 Hz, 0.07H), 6.97 (d, J=4 Hz, 0.93H); ^{13}C NMR ($CDCl_3$, 50 MHz), major *Z*-isomer: δ 13.8, 20.6, 57.3, 100.3, 109.9, 114.8, 117.6, 143.1, 147.0, 152.5, 155.2, 168.4, 170.0; IR ($CHCl_3$) ν_{max} 1773, 1751, 1653, 1597, 1215 cm^{-1}. Anal. Calcd for $C_{13}H_{12}O_5$: C, 62.90; H, 4.87. Found: C, 63.02; H, 4.95.

4.1.9. Acetic acid 2-(5-acetoxymethyl-furan-2-ylmethylene)-5-oxo-2,5-dihydro-furan-3-ylmethyl ester (14). To a stirred solution of lactone **13** (300 mg, 1.21 mmol) in dry acetic acid (10 mL) was added SeO_2 (268 mg, 2.42 mmol) and the reaction mixture was refluxed for 6 h. The reaction mixture was filtered through Celite and acetic acid was removed in vacuo. The residue was purified by silica gel column chromatography using a mixture of ethyl acetate and petroleum ether (0.5:9.5) to furnish **14** as a faint yellow solid.

Compound **14**: 341 mg (92% yield); mp 93–96 °C; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 2.10 (s, 3H), 2.18 (s, 3H), 5.07 (d, J=1 Hz, 1.6H), 5.08 (s, 1.6H), 5.11 (s, 0.4H), 5.42 (d, J=1 Hz, 0.4H), 6.13 (s, 0.8H), 6.19 (d, J=2 Hz, 0.8H), 6.30–6.35 (m, 0.2H), 6.50–6.60 (m, 0.6H), 6.56 (d, J=4 Hz, 0.8H), 7.05 (d, J=4 Hz, 0.8H); very clean two sets of ^{13}C carbon signals were obtained for the major and minor isomers, ^{13}C NMR ($CDCl_3$, 125 MHz), major isomer: δ 20.6, 20.8, 57.2, 57.9, 99.8, 113.8, 116.1, 116.6, 144.9, 149.0, 151.3, 152.7, 167.9, 170.0, 170.4, minor isomer: δ 20.6, 20.7, 57.7, 60.8, 103.5, 113.3, 117.2, 118.4, 145.4, 147.6, 152.0, 152.1, 167.6, 169.9, 170.5; IR ($CHCl_3$) ν_{max} 1776, 1746, 1676, 1653, 1605, 1219 cm^{-1}. Anal. Calcd for $C_{15}H_{14}O_7$: C, 58.83; H, 4.61. Found: C, 58.72; H, 4.80.

4.1.10. 4-Hydroxymethyl-5-(5-hydroxymethyl-furan-2-ylmethylene)-5*H*-furan-2-one (ellipsoidone A, 1 and ellipsoidone B, 2). A solution of diacetate **14** (100 mg, 0.33 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. The reaction mixture was stirred at room temperature for 40 h. The reaction mixture was filtered through Celite

and the aqueous layer was extracted with ethyl acetate (20 mL×4). The combined organic layer was washed with water, brine and dried over Na_2SO_4. The organic layer was concentrated in vacuo and the residue was purified by silica gel column chromatography using a mixture of ethyl acetate and petroleum ether (1:1) as an eluent to furnish ellipsoidone A (**1**) plus ellipsoidone B (**2**) in 95% yield. HPLC separation of **1** plus **2** mixture was done using the known literature procedure.[2]

Compound **1**: 59 mg (81.4% yield); yellow crystalline solid; mp 141–143 °C; ^{1}H NMR (acetone-d_6, 500 MHz) δ 4.57 (s, 2H), 4.73 (s, 2H), 6.20 (s, 1H), 6.31 (s, 1H), 6.49 (d, J= 5 Hz, 1H), 6.90 (d, J=5 Hz, 1H); ^{13}C NMR (acetone-d_6, 125 MHz) δ 57.1, 57.3, 99.8, 111.0, 114.2, 116.4, 145.7, 149.3, 158.5, 161.5, 169.2; IR (Nujol) ν_{max} 3329, 3211, 1749, 1638, 1462 cm^{-1}. Anal. Calcd for $C_{11}H_{10}O_5$: C, 59.46; H, 4.54. Found: C, 59.52; H, 4.63.

Compound **2**: 9.6 mg (13.2% yield); yellow crystalline solid; mp 159–161 °C; ^{1}H NMR (acetone-d_6, 500 MHz) δ 4.63 (s, 2H), 4.97 (d, J=2 Hz, 2H), 6.41 (m, 1H), 6.46 (d, J=1 Hz, 1H), 6.62 (s, 1H), 6.74 (d, J=2 Hz, 1H); ^{13}C NMR (acetone-d_6, 125 MHz) δ 57.3, 60.0, 103.6, 110.5, 117.8, 117.9, 146.1, 147.8, 159.0, 160.5, 168.4; IR (Nujol) ν_{max} 3331, 3302, 1736, 1638, 1460 cm^{-1}. Anal. Calcd for $C_{11}H_{10}O_5$: C, 59.46; H, 4.54. Found: C, 59.31; H, 4.60.

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