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A facile two-step chemoenzymatic access to natural germination inhibitor (+)-erigeronic acid A☆

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Abstract—A facile two-step synthesis of natural germination inhibitor 5-butyl-3-oxo-2,3-dihydrofuran-2-yl-acetic acid [(+)-erigeronic acid A, **1**] has been described via highly regioselective ring opening of (*R*)-acetoxysuccinic anhydride with the primary enolate of butyl methyl ketone, followed by an enzymatic hydrolysis and an in situ dehydrative cyclization pathway with 77% overall yield. On the basis of the present chemoenzymatic approach, (*R*)-configuration has been assigned to the C-2 chiral centre of the natural erigeronic acid.

1. Introduction

Plants are known to produce secondary metabolites, which affect the germination and growth of other plants and allelopathy is the term used to describe such interactions.[1] 5-Butyl-3-oxo-2,3-dihydrofuran-2-yl-acetic acid [erigeronic acid A, **1** (Fig. 1)] was isolated by Kwon et al.[2] from the flowers of *Erigeron annuus* and it possesses strong lettuce seed germination inhibitory activity [IC_{50} (mM) 2.13]. The structure of acid **1** was unambiguously deduced by analysis of 2D NMR spectroscopic data (COSY, HMQC and HMBC) but the configuration at the C-2 centre was not determined.[2] The structure of compound **1** represents a unique natural alkyl furanone possessing carboxylic acid and *n*-butyl substituents and it can be a agriculturally useful product. During the past several years, we have been using cyclic anhydrides as potential precursors for the synthesis of structurally interesting bioactive natural and unnatural products[3] and we could reason and foresee (*S*)/(*R*)-acetoxysuccinic anhydride as a suitable building block for the synthesis and stereochemical assignment of acid **1**. Acetoxysuccinic anhydride is known to react regioselectively at the hindered, more electron deficient carbonyl with oxygen and nitrogen nucleophiles[3f,4] and the stable carbanion from ethyl acetoacetate.[5] Now we herein report a highly regioselective ring opening of (*S*)- and (*R*)-acetoxysuccinic anhydrides with the kinetic enolate from alkyl methyl ketones, to design natural/unnatural **1** and its congeners (Schemes 1 and 2).

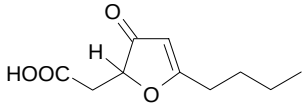

Figure 1. 5-Butyl-3-oxo-2,3-dihydrofuran-2-yl-acetic acid (erigeronic acid A, **1**).

2. Results and discussion

(*S*)/(*R*)-Malic acids on treatment with acetyl chloride furnished the corresponding (*S*)/(*R*)-acetoxysuccinic anhydrides (**2**) in 98% yield.[6] As desired, the (*S*)-acetoxysuccinic anhydride underwent a highly regioselective ring opening at the more reactive hindered carbonyl at −78 °C with the kinetic enolate generated from butyl methyl ketone using LDA as a base to exclusively provide the intermediate diketo compound in 93% yield, which was transformed in situ to a mixture of enantiomerically pure enols **3** and **4** in the ratio 80:20 (by ^{1}H NMR) (Scheme 1). The structural assignment of **3** and **4** was done on the basis of the presence of vinylic and enolic protons in the ^{1}H NMR spectrum. As expected the allylic methine proton in **3** was more deshielded than the corresponding methine proton in **4**, whereas the allylic methylene protons in **4** were more deshielded in comparison with the corresponding methylene protons in **3**. We feel that, due to the electron withdrawing influence of the acetoxy group, the enolization of an adjacent carbonyl occurs to a larger extent, forming **3** as

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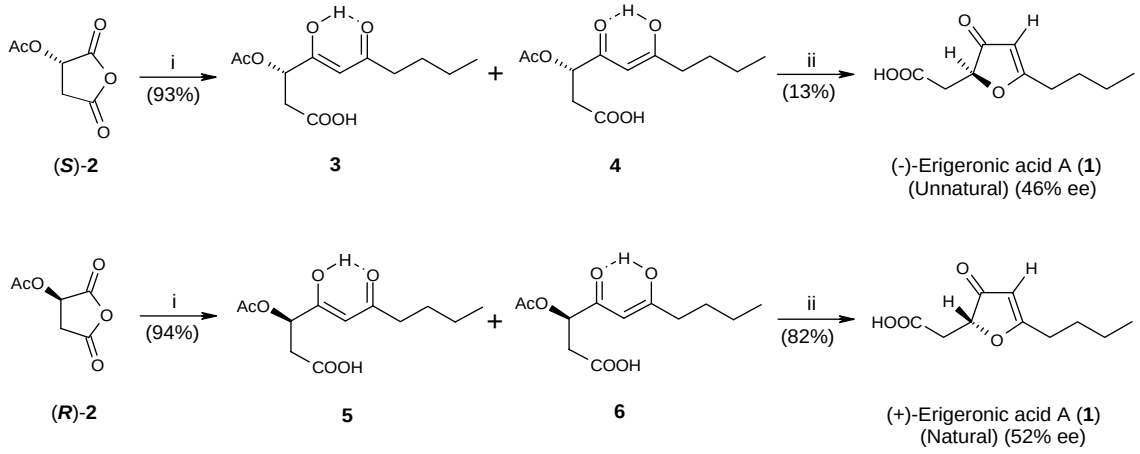
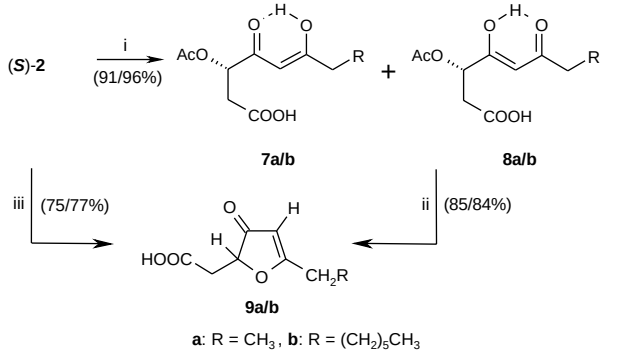


Scheme 1. Reagents, conditions and yields: (i) (a) $CH_3COCH_2(CH_2)_2CH_3$, LDA, THF, −78 °C, 90 min, (b) H^+/HCl (**3**:**4**/**5**:**6**=8:2); (ii) Amano PS, petroleum ether–benzene (2/1), rt, 40 h, phosphate buffer pH 7.0.



Scheme 2. Reagents, conditions and yields: (i) (a) $CH_3COCH_2CH_3$/$CH_3COCH_2(CH_2)_5CH_3$, LDA, THF, −78 °C, 90 min, (b) H^+/HCl (a: 91%, b: 96%; **7a/b**:**8a/b**=8:2); (ii) (a) K_2CO_3, MeOH, 6 h, (b) H^+/HCl (a: 85%, b: 84%); (iii) (a) $CH_3COCH_2CH_3$/$CH_3COCH_2(CH_2)_5CH_3$, LDA, THF, −78 °C, 90 min, (b) 10% aq LiOH, rt, 8 h, (c) H^+/HCl (a: 75%, b: 77%).

a major isomer. The potassium carbonate catalyzed alcoholysis of the acetoxy group in **3** plus **4** mixture directly furnished the desired erigeronic acid in 89% yield via the intramolecular dehydrative cyclization pathway, but in a racemic form. The triethylamine/(−)-quinine catalyzed alcoholysis of the acetoxy group in **3** plus **4** mixture also directly furnished the erigeronic acid in 62–65% yield but with only 10–15% ee (by rotation). The acid catalyzed alcoholysis of the acetoxy group in **3** plus **4** mixture in methanol directly furnished the methyl ester of desired natural product in 95% yield, following the same pathway but again in racemic form. Under both acidic and basic conditions, we could isolate the erigeronic acid/ester in racemic form only and hence we planned for an enzymatic hydrolysis of **3** plus **4** mixture under neutral conditions at pH 7. The Amano PS catalyzed hydrolysis of **3** plus **4** mixture was very slow and gave the unnatural (−)-erigeronic acid only in 13% yield (46% ee, from the comparison with reported rotation value of the natural product). With the hope that the enzyme Amano PS will better recognize opposite isomer, we similarly obtained the mixture of **5** plus **6** from the corresponding (*R*)-acetoxysuccinic anhydride with 94% yield. The Amano PS catalyzed hydrolysis of **5** plus **6** mixture directly furnished the desired natural (+)-erigeronic acid A in 82% yield (52% ee, from the comparison with reported rotation value of the natural product). The analytical and spectral data obtained for (+)-erigeronic acid A was in agreement with the reported data[2] (Table 1) and thus we could assign the (*R*)-configuration to C-2 chiral centre in the natural acid using the present chiral pool strategy and chemoenzymetic pathway. During these studies we noticed that the (+)-erigeronic acid A in its neat form at room temperature undergoes a continuous racemization process and becomes completely racemic in 96 h time. The present racemization of (+)-**1** could be attributed to the high acidity of the C-2 proton and the higher propensity for keto-enol tautomerism. We feel that alike the preparation of enantiomerically pure α-hydroxycyclopentanone,[7] herein too, after the enzymatic hydrolysis of **5** plus **6** mixture, the formed product (+)-**1** undergoes a partial racemization process during the course of reaction and isolation procedures and hence, we could get only the 52% ee for (+)-**1**.

The present approach to 5-alkyl-3-oxo-dihydrofuranyl-2-acetic acids is general in nature and starting from **2** and ethyl methyl ketone/heptyl methyl ketone, we could synthesize **9a/b** in very good yields both in one pot and a stepwise fashion, with or without isolation of the intermediates **7a/b**+**8a/b** (Scheme 2). In the one pot synthesis, we quenched the anhydride **2** and ketone condensation reactions with 10% aqueous lithium hydroxide and then acidified the reaction mixture with 2 M hydrochloric acid to obtain **9a/b** in 75–77% yield.

3. Conclusions

In summary, starting from (*R*)-acetoxysuccinic anhydride, an elegant first synthesis of natural germination inhibitor (+)-erigeronic acid has been demonstrated using chiral pool strategy and an enzymatic hydrolysis pathway, which helped us to assign (*R*)-configuration to the C-2 chiral centre in acid (+)-**1**. In the present synthesis of (+)-**1**, the highly regioselective ring opening of anhydride (+)-**2** with the primary enolate of butyl methyl ketone and an enzymatic hydrolysis of **5** plus **6** mixture and subsequent in situ dehydrative cyclization to form (+)-**1** are noteworthy.

Table 1. ^{1}H and ^{13}C NMR data of natural and synthetic erigeronic acid (**1**)

Position[2]	^{1}H NMR data of erigeronic acid (**1**)		^{13}C NMR data of erigeronic acid (**1**)	
	Natural (Ref. 2)[a]	Synthetic[b]	Natural (Ref. 2)[c]	Synthetic[d]
1	2.90 (dd, J=16.9, 3.2 Hz, 1H) and 2.61 (dd, J=16.9, 8.3 Hz, 1H)	2.91 (d, J=18 Hz, 1H) and 2.61 (d, J=18 Hz, 1H)	36.9	36.4
2	4.83 (m, 1H)	4.83 (m, 1H)	82.4	83.3
3	—	—	206.4	206.4
4	5.54 (s, 1H)	5.54 (s, 1H)	102.7	104.1
5	—	—	195.8	197.3
6	2.56 (t, J=8.3 Hz, 2H)	2.57 (t, J=8 Hz, 2H)	31.3	31.4
7	1.65 (quintet, J=7.4 Hz, 2H)	1.65 (quintet, J=8 Hz, 2H)	29.2	29.3
8	1.42 (sextet, J=7.4 Hz, 2H)	1.41 (sextet, J=8 Hz, 2H)	23.2	23.3
9	0.95 (t, J=7.4 Hz, 3H)	0.95 (t, J=8 Hz, 3H)	14.0	14.1
10	—	—	171.6	172.8

[a] CD_3OD, 500 MHz.
[b] CD_3OD, 200 MHz.
[c] CD_3OD, 125 MHz.
[d] CD_3OD, 50 MHz.

The present approach is general in nature and can be used to design the analogs of **1**.

4. Experimental

4.1. General

Column chromatographic separations were carried out on ACME silica gel (60–120 mesh). Commercially available (*S*)-malic acid (97% ee), (*R*)-malic acid (98% ee), ethyl methyl ketone, butyl methyl ketone, heptyl methyl ketone, acetyl chloride and *n*-butyllithium were used. Amano PS-1360 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.[8]

4.1.1. (*R*)-3-Acetoxy-4-hydroxy-6-oxo-dec-4-enoic acid (5) plus (*R*)-3-acetoxy-6-hydroxy-4-oxo-dec-5-enoic acid (6). To a stirred solution of butyl methyl ketone (253 mg, 2.53 mmol) in THF (8 mL) at −78 °C was added freshly prepared LDA (271 mg, 2.53 mmol) in THF (5 mL) in a drop wise fashion under argon atmosphere. The reaction mixture was stirred at −78 °C temperature for 30 min and the above reaction mixture was added to a stirred solution of the anhydride (*R*)-**2** (400 mg, 2.53 mmol) in THF (10 mL) at −78 °C under argon atmosphere in a drop wise fashion. Further stirring was continued for 90 min at the same temperature. The reaction was then quenched with water and acidified with 2 M HCl. The reaction mixture was then immediately extracted with ethyl acetate (30 mL×4) and the combined organic layer was 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 a mixture of ethyl acetate–petroleum ether (2/8) as an eluent gave **5** plus **6** as a thick oil.

Compound **5**+**6** (8:2): 614 mg (94% yield); $[\alpha]_D^{20}$ +40 (*c* 1.0, CH_3OH); ^{1}H NMR ($CDCl_3$, 200 MHz) δ 0.90 (t, J=8 Hz, 0.6H), 0.91 (t, J=8 Hz, 2.4H), 1.15–1.45 (m, 2H), 1.45–1.70 (m, 2H), 2.13 (s, 0.6H), 2.15 (s, 2.4H), 2.30 (t, J=8 Hz, 1.6H), 2.51 (t, J=8 Hz, 0.4H), 2.75–3.00 (m, 2H), 5.25–5.40 (m, 0.2H), 5.53 (dd, J=8, 6 Hz, 0.8H), 5.63 (s, 1H), 9.00 (br s, 1H), 15.02 (br s, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz) (major enol isomer **5**) δ 13.7, 20.7, 22.2, 27.8, 36.2, 37.2, 71.1, 96.1, 169.8, 174.9, 191.7, 192.8; MS (*m*/*e*) 297, 281, 276, 259, 199, 144; IR ($CHCl_3$) ν_{max} 3207, 2700–2500, 1747, 1733, 1719, 1603 cm^{-1}. Anal. Calcd for $C_{12}H_{18}O_6$: C, 55.81; H, 7.02. Found: C, 55.73; H, 6.99.

The compounds **3**+**4**, **7a**+**8a** and **7b**+**8b** were similarly prepared using the above procedure.

4.1.2. (*S*)-3-Acetoxy-4-hydroxy-6-oxo-dec-4-enoic acid (3) plus (*S*)-3-acetoxy-6-hydroxy-4-oxo-dec-5-enoic acid (4). Starting from (*S*)-**2** (400 mg, 2.53 mmol), the title compounds mixture was obtained as a thick oil.

Compound **3**+**4** (8:2): 607 mg (93% yield); $[\alpha]_D^{20}$ −41 (*c* 1.4, CH_3OH); IR and ^{1}H NMR spectral data was identical with **5**+**6**.

4.1.3. (*S*)-3-Acetoxy-6-hydroxy-4-oxo-oct-5-enoic acid (7a) plus (*S*)-3-acetoxy-4-hydroxy-6-oxo-oct-4-enoic acid (8a). Starting from (*S*)-**2** (400 mg, 2.53 mmol) and ethyl methyl ketone (183 mg, 2.53 mmol) the title compounds mixture was obtained as a thick oil.

Compound **7a**+**8a** (8:2): 530 mg (91% yield); $[\alpha]_D^{20}$ −42 (*c* 1.7, CH_3OH); ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.07 (t, J=8 Hz, 0.6H), 1.15 (t, J=8 Hz, 2.4H), 2.14 (s, 0.6H), 2.15 (s, 2.4H), 2.36 (q, J=8 Hz, 1.6H), 2.55 (q, J=8 Hz, 0.4H), 2.75–3.02 (m, 2H), 5.25–5.40 (m, 0.2H), 5.54 (dd, J=8, 6 Hz, 0.8H), 5.64 (s, 1H), 7.80 (br s, 1H), 15.04 (br s, 1H); MS (*m*/*e*) 269, 253, 248, 231, 193, 171, 153; IR (neat) ν_{max} 3225, 2700–2500, 1744, 1735, 1720, 1605 cm^{-1}. Anal. Calcd for $C_{10}H_{14}O_6$: C, 52.17; H, 6.13. Found: C, 52.31; H, 6.22.

4.1.4. (*S*)-3-Acetoxy-6-hydroxy-4-oxo-tridec-5-enoic acid (7b) plus (*S*)-3-acetoxy-4-hydroxy-6-oxo-tridec-4-enoic acid (8b). Starting from (*S*)-**2** (400 mg, 2.53 mmol) and heptyl methyl ketone (360 mg, 2.53 mmol) the title compounds mixture was obtained as a thick oil.

Compound **7b**+**8b** (8:2): 729 mg (96% yield); $[\alpha]_D^{20}$ −35 (*c* 1.4, CH_3OH); ^1H NMR ($CDCl_3$, 200 MHz) δ 0.88 (t, J= 6 Hz, 3H), 1.28 (br s, 8H), 1.50–1.70 (m, 2H), 2.14 (s, 0.6H), 2.16 (s, 2.4H), 2.31 (t, J=6 Hz, 1.6H), 2.51 (t, J=6 Hz, 0.4H), 2.75–3.05 (m, 2H), 5.30–5.45 (m, 0.2H), 5.54 (dd, J= 8, 4 Hz, 0.8H), 5.63 (s, 1H), 9.00 (br s, 1H), 15.03 (br s, 1H); MS (*m*/*e*) 339, 323, 318, 301, 255, 241; IR (neat) ν_{max} 3220, 2700–2500, 1751, 1730, 1720, 1597 cm^{-1}. Anal. Calcd for $C_{15}H_{24}O_6$: C, 59.98; H, 8.05. Found: C, 60.11; H, 7.86.

4.1.5. (±)-Erigeronic acid A [(±)-1]. To a stirred solution of enols **5** and **6** (60 mg, 0.23 mmol) in methanol (3 mL) was added K_2CO_3 (42 mg, 0.30 mmol) and the reaction mixture was stirred at room temperature for 4 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 N 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–petroleum ether (2/8) as an eluent gave (±)-**1** as a thick oil.

Compound (±)-**1**: 41 mg (89% yield); ^1H NMR (CD_3OD, 200 MHz) δ 0.95 (t, J=8 Hz, 3H), 1.41 (sextet, J=8 Hz, 2H), 1.65 (quintet, J=8 Hz, 2H), 2.57 (t, J=8 Hz, 2H), 2.61 (d, J=18 Hz, 1H), 2.91 (d, J=18 Hz, 1H), 4.83 (m, 1H), 5.54 (s, 1H); ^{13}C NMR (CD_3OD, 50 MHz) δ 14.1, 23.3, 29.3, 31.4, 36.4, 83.3, 104.1, 172.8, 197.3, 206.4; ^1H NMR ($CDCl_3$, 200 MHz) δ 0.94 (t, J=8 Hz, 3H), 1.40 (sextet, J=8 Hz, 2H), 1.65 (quintet, J=8 Hz, 2H), 2.52 (t, J=8 Hz, 2H), 2.65 (dd, J=17, 8 Hz, 1H), 3.04 (dd, J=17, 4 Hz, 1H), 4.84 (dd, J=9, 4 Hz, 1H), 5.51 (s, 1H), 7.50 (br s, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 13.6, 22.2, 28.0, 30.5, 35.7, 81.5, 103.2, 174.5, 195.3, 203.6; IR (neat) ν_{max} 2700–2500, 1732, 1713, 1585 cm^{-1}. Anal. Calcd for $C_{10}H_{14}O_4$: C, 60.59; H, 7.12. Found: C, 60.60; H, 7.19.

The compounds **9a** and **9b** were similarly prepared using the above procedure.

4.1.6. (5-Ethyl-3-oxo-2,3-dihydro-furan-2-yl)-acetic acid (9a). Starting from acids **7a** and **8a** (60 mg, 0.26 mmol), and K_2CO_3 (42 mg, 0.30 mmol) the title compound was obtained as a thick oil.

Compound **9a**: 38 mg (85% yield); ^1H NMR ($CDCl_3$, 200 MHz) δ 1.24 (t, J=8 Hz, 3H), 2.55 (q, J=6 Hz, 2H), 2.65 (dd, J=18, 8 Hz, 1H), 3.04 (dd, J=18, 4 Hz, 1H), 4.85 (dd, J=10, 4 Hz, 1H), 5.53 (s, 1H), 8.77 (br s, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 10.1, 24.2, 35.7, 81.5, 102.6, 174.6, 196.2, 203.5; IR (neat) ν_{max} 2700–2500, 1722, 1684, 1585 cm^{-1}. Anal. Calcd for $C_8H_{10}O_4$: C, 56.47; H, 5.92. Found: C, 56.33; H, 6.06.

4.1.7. (5-Heptyl-3-oxo-2,3-dihydro-furan-2-yl)-acetic acid (9b). Starting from acids **7b** and **8b** (60 mg, 0.20 mmol), and K_2CO_3 (42 mg, 0.30 mmol) the title compound was obtained as a thick oil.

Compound **9b**: 40 mg (84% yield); ^1H NMR ($CDCl_3$, 200 MHz) δ 0.88 (t, J=8 Hz, 3H), 1.15–1.45 (br m, 8H), 1.64 (quintet, J=8 Hz, 2H), 2.51 (t, J=8 Hz, 2H), 2.63 (dd, J=16, 8 Hz, 1H), 3.04 (dd, J=17, 4 Hz, 1H), 4.85 (dd, J=9, 4 Hz, 1H), 5.52 (s, 1H), 9.78 (br s, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 14.0, 22.5, 25.9, 28.8, 29.0, 30.8, 31.5, 35.7, 81.5, 103.2, 174.5, 195.3, 203.7; IR (neat) ν_{max} 2700–2500, 1734, 1707, 1584 cm^{-1}. Anal. Calcd for $C_{13}H_{20}O_4$: C, 64.98; H, 8.39. Found: C, 65.11; H, 8.23.

4.1.8. Methyl (5-butyl-3-oxo-2,3-dihydro-furan-2-yl)acetate. To a stirred solution of **5** plus **6** (60 mg, 0.23 mmol) in methanol was added concd HCl (0.1 mL) and the reaction mixture was stirred for 8 h at room temperature. The reaction mixture was concentrated in vacuo and diluted with water (10 mL). The aqueous layer was extracted with ethyl actetate (15 mL×4) and the combined organic layer was washed with water, brine and dried over Na_2SO_4. Concentration of the organic layer in vacuo gave the corresponding methyl ester as a thick oil.

Methyl ester of (±)-**1**: 47 mg (95% yield); ^1H NMR ($CDCl_3$, 200 MHz) δ 0.93 (t, J=8 Hz, 3H), 1.39 (sextet, J=8 Hz, 2H), 1.63 (quintet, J=8 Hz, 2H), 2.50 (t, J=8 Hz, 2H), 2.59 (dd, J=17, 8 Hz, 1H), 2.97 (dd, J=16, 4 Hz, 1H), 3.74 (s, 3H), 4.81 (dd, J=10, 4 Hz, 1H), 5.47 (s, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 13.6, 22.2, 28.0, 30.4, 35.7, 52.2, 81.6, 103.2, 170.0, 194.5, 203.1; IR (neat) ν_{max} 1744, 1703, 1593 cm^{-1}. Anal. Calcd for $C_{11}H_{16}O_4$: C, 62.25; H, 7.60. Found: C, 62.37; H, 7.49.

4.1.9. (+)-Erigeronic acid A (1). A solution of acids **5** and **6** (74 mg, 0.29 mmol) in petroleum ether–benzene (2/1) mixture (6 mL) was added to a suspension of Amano PS lipase (20 mg) in aqueous sodium phosphate (0.01 M, 2 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 (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 separation using a mixture of ethyl acetate–petroleum ether (2/8) as an eluent gave (+)-**1** as a thick oil.

Compound (+)-**1**: 47 mg (82% yield); $[\alpha]_D^{20}$ +15.1 (*c* 1.0, CH_3OH), [lit.[2] +29 (*c* 0.07, CH_3OH)]; IR and ^1H NMR spectral data was identical with (±)-**1**.

Similarly starting from **3** and **4** (100 mg, 0.39 mmol) the title compound (−)-**1** was obtained as a thick oil.

Compound (−)-**1**: 10 mg (13% yield); $[\alpha]_D^{20}$ − 13.3 (*c* 0.3, CH_3OH); IR and ^1H NMR spectral data was identical with (±)-**1**.

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