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The combination of domino process and kinetic resolution: organocatalytic synthesis of functionalised cyclopentenes by sequential S_N2'-Michael reaction

Lun Fu Yeh, Shaik Anwar, Kwunmin Chen *

Department of Chemistry, National Taiwan Normal University, Taipei 116, Taiwan, ROC

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ABSTRACT

An interesting combination of organocatalytic cascade reaction and kinetic resolution was developed for the synthesis of functionalised cyclopentenes by sequential S_N2'-Michael process. Treatment of the racemic nitroallylic acetates with glutaraldehyde in the presence of diphenylprolinol silyl ether to give tetrasubstituted cyclopentenes with high to excellent stereoselectivities (up to 96% ee and 12:1 dr). The less reactive enantiomeric substrates were generally recovered with good to excellent optical purities (up to 99% ee).

1. Introduction

The use of small molecule organocatalysts for kinetic resolution (KR) has now become an important method for the preparation of enantiomerically-enriched substances from its racemic starting materials.[1] Generally, the KR process generates an excess of the less reactive substrate. In this regard, metal-mediated KR variants have also been developed.[2] On the other hand, various alcohols and amines have been efficiently resolved via organic molecule-mediated O/N-acylation[3] and O-silylation.[4] The construction of new stereogenic carbon centers on the more reactive enantiomer of a racemate in a KR process is potentially advantageous, but only rare examples were reported.[5]

Substituted five-membered carbocycles are important structural elements of many biologically active natural and pharmaceutical products. Though there are numerous reports on the synthesis of cyclopentane derivatives,[6] much less attention has been directed toward the preparation of substituted cyclopentene derivatives. Organocatalysed [3+2] cycloaddition routes to cyclopentene derivatives have been accomplished recently via Michael–aldol,[7] homoenolate Michael–aldol,[8] benzoin–oxy–Cope,[9] iminium–enamine metal-catalysed enyne cycloisomerisation,[10] and sequential Stetter–Michael–Aldol reactions.[11] However, efficient methods for the preparation of diverse multi-substituted cyclopentenes are still in demand. In continuation of our research efforts in the organocatalytic KR,[12] we present here an interesting organocatalytic cascade reaction that involves the kinetic resolution of racemic nitroallylic acetates for the synthesis of functionalized cyclopentenes with high to excellent stereoselectivities (up to 96% ee and 12:1 dr). The less reactive enantiomeric substrates were recovered with good to excellent optical purities (up to 99% ee).

2. Results and discussion

We envisioned that the cyclopentene derivatives **3** could be obtained from the reaction of functionalised nitroallylic acetates with inexpensive glutaraldehyde,[13] mediated by organocatalyst (Scheme 1). Toward this, we initially investigated the test reaction of *rac*-**1a** and glutaraldehyde in the presence of various organocatalysts (Table 1). Treatment of nitroallylic acetate **1a** with glutaraldehyde in the presence of 20 mol % diphenylprolinol silyl ether catalyst (**Cat. I**) took 6 days to reach completion. Due to the instability of the dicarbonyl functionality, the isolated product was reduced to the corresponding cyclopentene diol **3a** (86% ee) directly using $NaCNBH_3$ (Table 1, entry 1). The less reactive enantiomeric substrate was determined as having an ee of 77%. The use of diaryl substituted silyl ether catalyst **II** gave rise to poor stereoselectivity and yield (Table 1, entry 2). The reactivity was improved slightly when the camphor-derived organocatalyst **III** was employed. However, it gave rise to only moderate enantioselectivity (57% ee) (Table 1, entry 3). The use of naphthyl-derived amide (**Cat. IV**) and sulfonamide (**Cat. V**) catalysts failed to improve the level of enantioselectivity (Table 1, entries 4 and 5). A

* Corresponding author. Tel.: +886 2 7734 6124; fax: +886 2 2932 4249; e-mail address: kchen@ntnu.edu.tw (K. Chen).

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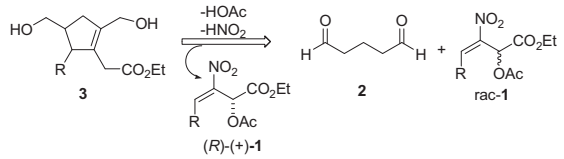
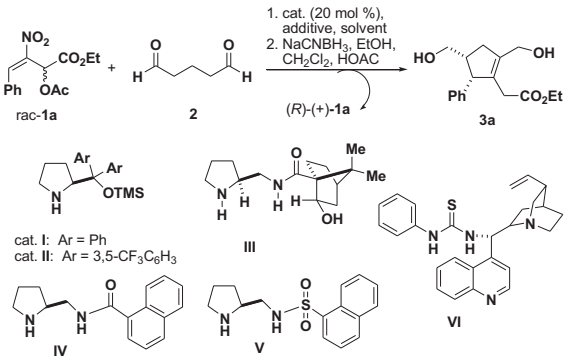
cinchonidine-derived organocatalyst (**Cat**. **VI**) also proved rather ineffective at producing the product **3a** (Table 1, entry 6).



Scheme 1. Organocatalysed cascade reaction for functionalized cyclopentene derivatives.

Table 1
Optimisation of the S_N2'/Michael addition–elimination reaction[a]



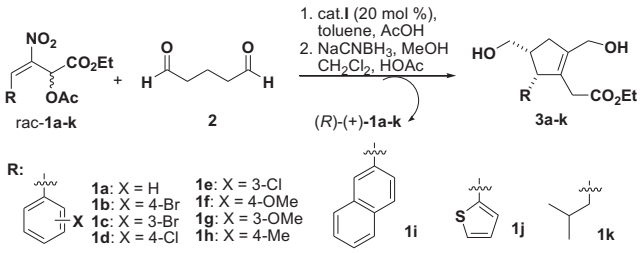
Entry	**Cat**.	Solvent	Time/h	Conv[b]/dr[b]	Yield **3a**(%)[c]	Yield **1a**(%)[c]	% ee **3a**[d]/**1a**[d]
1	**I**	CH_2Cl_2	6 d	76/5:1	15	10	86/77
2	**II**	CH_2Cl_2	4 d	75/1:3	12	11	19/78
3	**III**	CH_2Cl_2	3 d	84/9:1	28	13	57/67
4	**IV**	CH_2Cl_2	4 d	68/35:1	16	18	42/28
5	**V**	CH_2Cl_2	6 d	91/21:1	10	5	49/11
6	**VI**	CH_2Cl_2	3 d	100/15:1	14	0	37/nd
7	**I**	MTBE	6	83/1:1	42	10	69/70
8	**I**	Toluene	24	52/5:1	24	22	91/90
9[e]	**I**	Toluene	6	48/5:1	27	25	87/86
10[f]	**I**	**Toluene**	**6**	**48/9:1**	**45**	**33**	**96/88**
11[f, g]	**I**	Toluene	2 d	47/2:1	24	37	92/82
12[f,h]	**I**	Toluene	18	49/2:1	34	38	94/89

[a] Unless otherwise noted, all reactions were carried out with **1a** (0.1 mmol) and glutaraldehyde **2** (0.4 mmol) with **Cat**. (20 mol %) in the indicated solvent (0.5 mL) at 35 °C.
[b] Conversion and dr were determined by ^{1}H NMR analysis of the crude reaction mixture.
[c] Isolated yield.
[d] Determined by chiral HPLC analyses.
[e] The reaction was carried out using 1.0 equiv of acetic acid.
[f] The reaction was carried out using 1.5 equiv of acetic acid.
[g] The reaction was carried out using 10 mol % **Cat**. **I**.
[h] The reaction was carried out at 5 °C.

Next, we varied the solvents, the reaction concentration, the reaction temperature and incorporated various additives (Table 1, entries 7–12). Unsatisfactory results were observed when the reaction was carried out in methyl *tert*-butyl ether (MTBE) (Table 1 entry 7). However, the level of enantioselectivity could be considerably improved to 91% ee, when the reaction was conducted in toluene, which led to a 52% conversion, following an overnight run (Table 1, entry 8). We next investigated whether an acidic additive might enhance reactivity, and initially observed that when 1.0 equiv of acetic acid was added to the reaction mixture, it gave rise to a comparable stereochemical outcome (Table 1, entry 9). However, when 1.5 equiv of HOAc was included, the chemical yield and overall stereoselectivity of the products markedly improved (Table 1, entry 10). Thus the product **3a** could now be isolated in 45% yield with an enantioselectivity of 96% ee, while the unreacted substrate **1a** could be recovered in 33% yield (88% ee at 48% conversion). However, this level of reactivity diminished significantly when only 10 mol % of the catalyst was employed (Table 1, entry 11). Decreasing the reaction temperature also failed to improve the enantioselectivity of cyclopentene formation or the optical purity of the resolved starting nitroallylic acetate (Table 1, entry 12). The structure of the product **3a** was fully characterised by IR, HRMS and ^{1}H-, ^{13}C spectroscopic data.[14]

With the optimised reaction conditions now identified, we next examined substrate scope to establish the general utility of our new domino kinetic resolution process (Table 2). It was observed that the reaction tolerated various aryl and heteroaromatic in the starting nitroallylic acetates (**1b**–**k**). The reactivity and enantioselectivity was also found to be dependent on the substituents present in the phenyl ring of **1**. The diastereoselectivity ratios varied from 12/1 to 3/1.

Table 2
Substrate scope for the S_N2'/Michael addition–elimination[a]



	1	*t*/h	Conv[b] /dr[b]	Yield **3** (%)[c]	**3**[d,e] (%ee)	Yield **1** (%)[c]	**1**[d]% ee	S[f]
1	**1a**	6	48/9:1	45	**3a** 96	33	88	143
2	**1b**	5	48/6:1	45	**3b** 91	43	84	56
3	**1c**	2	47/3:1	43	**3c** 95	46	85	106
4	**1d**	6	48/6:1	37	**3d** 91	37	85	58
5	**1e**	2	46/4:1	34	**3e** 94	46	81	81
6	**1f**	7	45/6:1	34	**3f** 95	46	76	93
7	**1g**	6	49/6:1	32	**3g** 91	31	88	62
8	**1h**	6	48/4:1	42	**3h** 94	45	88	94
9	**1i**	6	49/6:1	32	**3i** 90	37	85	53
10	**1j**	18	52/12:1	35	**3j** 91	46	99	111

[a] Unless otherwise noted, all reactions were carried out with **1** (0.1 mmol) and glutaraldehyde (0.4 mmol) with **Cat**. **I** (20 mol %) using toluene (0.5 mL) at 35 °C.
[b] Conversion and dr were determined by ^{1}H NMR analysis of the crude reaction mixture.
[c] Isolated yield.
[d] Determined by chiral HPLC analyses.
[e] Ee of the corresponding diol minor isomer was found to be >99% ee in most of the entries.
[f] $S=\ln[(1-C)(1-ee_s)]/\ln[(1-C)(1+ee_s)]$.

In general, a *meta*-substituent outperformed a *para*-substituent for generating both the products and the resolved nitroallylic acetates stereoselectively. For example, product **3c** was obtained in 95% ee alongside an 85% ee of recovered **1c,** which compared with a product of only 91% ee for **3b** and 84% ee for **1b** (Table 2, entry 2 vs 3). Comparable results were found in the case of the chloro-substituted derivatives **1d** and **1e** (Table 2, entry 4 vs 5). The electron-donating/withdrawing nature of the substituents on the phenyl ring only affected the reactivity slightly (Table 2, entries 6–8). It was found that a 2-naphthyl substrate **1i** caused a decrease in overall reaction yield, and only moderate enantioselectivity was seen for the product **3i** (Table 2, entry 9). Heteroaromatic substrates, such as **1j** also took a longer time to afford the product **3j**, but they did so with very high levels of diastereoselectivity and optical purity (99% ee) for the recovered acetate (Table 2, entry 10). Aliphatic substrates, such as **1k** reacted sluggishly with glutaraldehyde, with the latter requiring 2 days to furnish the product **3k** in

a rather low chemical yield of 27% (data not shown). The range of S factors for these unusual reactions ranged from 53–143.[15]

Domino reactions that involve a kinetic reaction are interesting and might have many applications in organic reaction.[16] Formation of the functionalised cyclopentenes **3** can potentially be rationalised by the mechanistic sequence shown in Fig. 1. It is presumed that the enamine **A**, formed from glutaraldehyde **2** and **Cat**. **I**, attacks the more reactive nitroallylic acetate (*S*)-**1** in an S_N2' fashion leading to intermediate **B**. The less reactive (*R*)-enantiomer then sits in the reaction mixture undisturbed. Subsequently, intermediate **B** re-enters the catalytic cycle to generate second enamine species **C**, which reacts preferentially via a 5-*exo*-trig addition[17] to give **D** with the release of the organocatalyst. Cyclisation might readily arise from the spatial proximity of the trisubstituted alkene in **C**, which looks energetically conducive to the formation of cyclopentene ring system. Deprotonation and elimination of nitrous acid in **D** then finally affords the desired cyclopentene products **E**.[18]

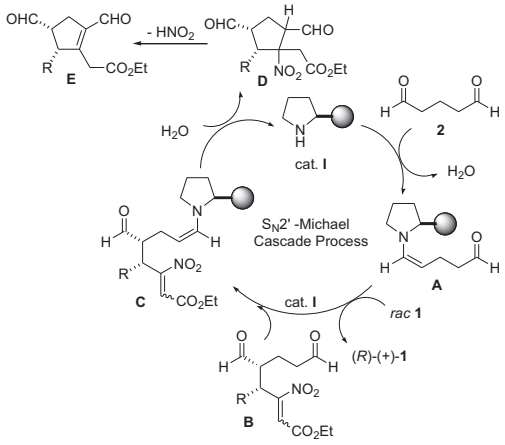


Fig. 1. Proposed catalytic cycle.

3. Conclusions

In conclusion, we have successfully developed an interesting organocatalytic reaction for the synthesis of functionalised cyclopentene derivatives. The protocol exploits the reaction of racemic nitroallylic acetates and glutaraldehyde and is accompanied by a kinetic resolution. The more reactive enantiomeric nitroallylic acetates are typically converted into multi-substituted cyclopentene derivatives **3** with high enantiomeric excess (up to 96% ee). The less reactive enantiomeric starting nitroallylic acetates are recovered with good to excellent optical purity (up to 99% ee). To the best of our knowledge, this is the first organocatalytic process for preparing cyclopentenes via an S_N2'/Michael conjugate addition–elimination process catalysed by the popular diphenylprolinol silyl ether catalyst. More studies are under investigation.

4. Experimental

4.1. General remarks

All reagents were used as purchased from commercial suppliers without further purification. IR spectra were recorded on a Perkin Elmer 500 spectrometer. NMR spectra were recorded on a Bruker Avance 500 NMR spectrometer (500 MHz for ^{1}H and 125 MHz for ^{13}C). Chemical shifts are reported in δ parts per million referenced to an internal TMS standard for ^{1}H NMR and chloroform-*d* (77.0 ppm) for ^{13}C NMR. Optical rotations were measured on a JASCO P-1010 polarimeter. HRMS spectra were recorded on JEOL SX-102A. Routine monitoring of reactions was performed using silica gel, glass-backed TLC plates (Merck Kieselgel 60 F254) and visualized by UV light (254 nm). Solutions were evaporated to dryness under reduced pressure on a rotary evaporator and the residues purified by flash column chromatography on silica gel (230–400 mesh) with the indicated eluents. Air and/or moisture sensitive reactions were performed under the usual inert atmosphere conditions.

4.2. Typical reaction procedure

To a solution of racemic nitroallylic acetate **1a**–**j** (0.1 mmol), glutaraldehyde (0.4 mmol) and HOAc (0.15 mmol) in toluene (0.5 mL) was added organocatalyst I (20 mol %) in one portion at 35 °C. The reaction mixture was allowed to stir for a needful time (monitored by TLC and crude 1H NMR analysis). The reaction mixture was stopped at ~50% conversion and subject directly to flash column chromatography (silica gel with ethyl acetate/hexanes=1:4) to give cyclopentendialdehyde and the less reactive enantiomeric substrates **1a**–**j**. The isolated cyclopentendialdehyde was dissolved in CH_2Cl_2 (1.0 mL), EtOH (1.0 mL), HOAc (0.5 equiv) and sodium cyanoborohydride (4.0 equiv) was added portionwise. The mixture was stirred for 3 h and subject directly to flash column chromatography (silica gel with ethyl acetate/hexanes=3:1) to afford cyclopentenediols **3a**–**j**.

*4.2.1. Ethyl 2-(2,4-bis(hydroxymethyl)-5-phenylcyclopent-1-en-1-yl) acetate (**3a**).* Purification: EA/hexanes=3:1 (R_f=0.28) to give **3a** as a colorless oil. $[\alpha]_D^{24}$+79.2 (*c*=0.5, CH_2Cl_2); IR (CH_2Cl_2): ν 3300, 2915, 2847, 1731, 1552, 1450, 1368, 1258, 1193, 1028 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ=7.29 (dd, *J*=7.5 and 7.5 Hz, 2H), 7.24–7.19 (m, 1H), 7.14 (m, 2H), 4.24 (s, 2H), 4.05–3.93 (m, 2H), 3.69 (d, *J*=5.8 Hz, 2H), 3.65 (s, 1H), 3.10 (d, *J*=15.6, 1H), 2.88–2.81 (m, 2H), 2.43–2.39 (m, 2H), 1.15 (t, *J*=7.2 Hz, 3H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ=172.2, 143.6, 140.8, 133.3, 128.7, 127.9, 126.7, 66.4, 61.1, 59.5, 58.7, 48.5, 36.9, 32.7, 14.0 ppm; HRMS (ESI) *m*/*z* calcd for $C_{17}H_{22}O_4$ (M^++Na) 313.1418, found 313.1416. The enantiomeric excess (96% ee) of **3a** was determined by HPLC with AD-H column (*i*-PrOH/hexanes: 5/95; flow rate: 1.0 mL/min; λ=220 nm); t_R (major)=51.23 min; t_R (minor)=57.96 min.

For recovery acetate (**1a**): Spectroscopic data are in agreement with racemic substrate **1a**. isolated yield: 33% (10 mg). The enantiomeric excess (88% ee) was determined by HPLC with AD-H column (*i*-PrOH/hexanes: 5/95; flow rate: 0.5 mL/min; λ=254 nm); t_R (major)=25.92 min; t_R (minor)=22.54 min.

*4.2.2. Ethyl 2-(5-(4-bromophenyl)-2,4-bis(hydroxymethyl)cyclopent-1-en-1-yl)acetate (**3b**).* purification: CH_2Cl_2/MeOH=20:1 (R_f=0.19) to give **3b** as a colorless oil. $[\alpha]_D^{25}$+71.0 (*c*=0.6, CH_2Cl_2); IR (CH_2Cl_2): ν 3290, 2920, 2847, 1728, 1552, 1462, 1371, 1172, 1075, 1045 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ=7.41 (d, *J*=8.4 Hz, 2H), 7.02 (d, *J*=8.3 Hz, 2H), 4.23 (s, 2H), 4.05–3.94 (m, 2H), 3.67–3.64 (m, 3H), 3.08 (d, *J*=15.5 Hz, 1H), 2.86–2.79 (m, 2H), 2.42–2.32 (m, 2H), 1.16 (t, *J*=7.2 Hz, 3H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ=172.0, 142.7, 141.3, 132.6, 131.7, 129.7, 120.4, 66.1, 61.2, 59.4, 58.1, 48.5, 36.8, 32.6, 14.0 ppm; HRMS (ESI) *m*/*z* calcd for $C_{17}H_{21}BrO_4$ (M^++Na) 391.0527, found 391.0521. The enantiomeric excess (91% ee) of **3b** was determined by HPLC with AD-H column (*i*-PrOH/hexanes: 8/92; flow rate: 1.0 mL/min; λ=220 nm); t_R (major)=19.40 min; t_R (minor)=32.12 min.

For recovery acetate (**1b**): Spectroscopic data are in agreement with recemic substrate **1b**. Yield: 43% (16 mg). The enantiomeric excess (84% ee) was determined by HPLC with OD-H column (*i*-PrOH/hexanes: 5/95; flow rate: 0.5 mL/min; λ=220 nm); t_R (major)=20.27 min; t_R (minor)=24.51 min.

*4.2.3. Ethyl 2-(5-(3-bromophenyl)-2,4-bis(hydroxymethyl)cyclopent-1-en-1-yl)acetate (**3c**).* Purification: EA/hexane=3:1 (R_f=0.33) to give **3c** as a colorless oil. $[\alpha]_D^{20}$+80.4 (c=1.3, CH_2Cl_2); IR (CH_2Cl_2): ν 3307, 2920, 2847, 1643, 1470, 1261, 1065 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ=7.34 (d, J=8.2 Hz, 1H), 7.28 (s, 1H), 7.16 (dd, J=7.8 and 7.8 Hz, 1H), 7.07 (d, J=7.7 Hz, 1H), 4.24 (dd, J=19.7 and 13.0 Hz, 2H), 4.07–3.96 (m, 2H), 3.67–3.65 (m, 3H), 3.10 (d, J=15.7 Hz, 1H), 2.86–2.79 (m, 2H), 2.44–2.34 (m, 2H), 1.17 (t, J=7.2 Hz, 3H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ=172.0, 146.2, 141.6, 132.3, 130.9, 130.2, 129.8, 126.7, 122.8, 65.9, 61.2, 59.3, 58.2, 48.4, 36.7, 32.6, 14.0 ppm; HRMS (ESI) m/z calcd for $C_{17}H_{21}BrO_4$ (M^++Na) 391.0518, found 391.0521. The enantiomeric excess (95% ee) was determined by HPLC with AD-H column (*i*-PrOH/hexanes: 5/95; flow rate: 1.0 mL/min; λ=220 nm); t_R (major)=42.98 min; t_R (minor)=47.78 min.

For recovery acetate (**1c**): spectroscopic data are in agreement with racemic substrate **1c**. Yield: 46% (17 mg). The enantiomeric excess (85% ee) was determined by HPLC with OD-H column (*i*-PrOH/hexanes: 5/95; flow rate: 0.5 mL/min; λ=220 nm); t_R (major)=23.75 min; t_R (minor)=27.89 min.

*4.2.4. Ethyl 2-(5-(4-chlorophenyl)-2,4-bis(hydroxymethyl)cyclopent-1-en-1-yl)acetate (**3d**).* Purification: EA/hexane=3:1 (R_f=0.35) to **3d** give as a colorless oil. $[\alpha]_D^{25}$+96.4 (c=0.5, CH_2Cl_2); IR (CH_2Cl_2): ν 3432, 2955, 2920, 2852, 1710, 1649, 1555, 1490, 1365, 1255, 1193, 1088, 1028 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ=7.26 (d, J=8.3 Hz, 2H), 7.08 (d, J=8.4 Hz, 2H), 4.24 (s, 2H), 4.05–3.94 (m, 2H), 3.67–3.66 (m, 3H), 3.08 (d, J=15.6 Hz, 1H), 2.86–2.79 (m, 2H), 2.42–2.33 (m, 2H), 1.16 (t, J=7.2 Hz, 3H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ=172.0, 142.2, 141.3, 132.7, 132.4, 129.3, 128.8, 66.1, 61.2, 59.4, 58.0, 48.6, 36.8, 32.6, 14.0 ppm; HRMS (ESI) m/z calcd for $C_{17}H_{21}ClO_4$ (M^++Na) 347.1030, found 347.1026. The enantiomeric excess (91% ee) was determined by HPLC with IA column (*i*-PrOH/hexanes: 5/95; flow rate: 1.0 mL/min; λ=220 nm); t_R (major)=35.08 min; t_R (minor)=41.41 min.

For recovery acetate (**1d**): spectroscopic data are in agreement with racemic substrate **1d**. Yield: 37% (12 mg). The enantiomeric excess (85% ee) was determined by HPLC with OD-H column (*i*-PrOH/hexanes: 10/90; flow rate: 1.0 mL/min; λ=254 nm); t_R (major)=6.76 min; t_R (minor)=7.62 min.

*4.2.5. Ethyl 2-(5-(3-chlorophenyl)-2,4-bis(hydroxymethyl)cyclopent-1-en-1-yl)acetate (**3e**).* Purification: EA/hexane=3:1 (R_f=0.35) to give **3e** as a colorless oil. $[\alpha]_D^{21}$+82.7 (c=0.5, CH_2Cl_2); IR (CH_2Cl_2): ν 3460, 2920, 2858, 1640, 1473, 1365, 1076, 1023 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ=7.24–7.18 (m, 2H), 7.12 (s, 1H), 7.03 (d, J=7.2 Hz, 1H), 4.27–4.22 (m, 2H), 4.07–3.96 (m, 2H), 3.68–3.66 (m, 3H), 3.10 (d, J=15.7 Hz, 1H), 2.87–2.80 (m, 2H), 2.42–2.35 (m, 2H), 1.17 (t, J=7.2 Hz, 3H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ=172.0, 145.9, 141.5, 134.5, 132.4, 129.9, 128.0, 126.9, 126.2, 66.1, 61.2, 59.4, 58.3, 48.5, 36.7, 32.7, 14.0 ppm; HRMS (ESI) m/z calculated for $C_{17}H_{21}ClO_4$ (M^++Na) 347.1024, found 347.1026. The enantiomeric excess (94% ee) was determined by HPLC with AD-H column (*i*-PrOH/hexanes: 5/95; flow rate: 0.5 mL/min; λ=220 nm); t_R (major)=81.56 min; t_R (minor)=92.78 min.

For recovery acetate (**1e**): spectroscopic data are in agreement with racemic substrate **1e**. Yield: 46% (15 mg). The enantiomeric excess (81% ee) was determined by HPLC with AD-H column (*i*-PrOH/hexanes: 5/95; flow rate: 0.5 mL/min; λ=254 nm); t_R (major)=23.82 min; t_R (minor)=18.85 min.

*4.2.6. Ethyl 2-(2,4-bis(hydroxymethyl)-5-(4-methoxyphenyl)cyclopent-1-en-1-yl)acetate (**3f**).* Purification: EA/hexane=3:1 (R_f=0.32) to give **3f** as a colorless oil. $[\alpha]_D^{24}$+62.4 (c=0.7, CH_2Cl_2); IR (CH_2Cl_2): ν 3210, 2915, 2847, 1728, 1552, 1510, 1246, 1176, 1028 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ=7.05 (d, J=8.7 Hz, 2H), 6.8 (d, J=8.7 Hz, 2H), 4.23 (s, 2H), 4.05–3.96 (m, 2H), 3.79 (s, 3H), 3.69 (d, J=5.6 Hz, 2H), 3.60 (d, J=4.1 Hz, 1H), 3.09 (d, J=15.8 Hz, 1H), 2.86–2.80 (m, 2H), 2.43–2.35 (m, 2H), 1.17 (t, J=7.2 Hz, 3H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ=172.4, 158.4, 140.4, 135.6, 133.8, 128.9, 114.1, 66.4, 61.2, 59.4, 57.9, 55.3, 48.5, 36.8, 32.6, 14.0 ppm; HRMS (ESI) m/z calcd for $C_{18}H_{24}O_5$ (M^++Na) 343.1516, found 343.1521. The enantiomeric excess (95% ee) was determined by HPLC with AD-H column (*i*-PrOH/hexanes: 5/95; flow rate: 1.0 mL/min; λ=220 nm); t_R (major)=60.99 min; t_R (minor)=82.05 min.

For recovery acetate (**1f**): spectroscopic data are in agreement with racemic substrate **1f**. Yield: 46% (15 mg). The enantiomeric excess (76% ee) was determined by HPLC with AD-H column (*i*-PrOH/hexanes: 10/90; flow rate: 1.0 mL/min; λ=254 nm); t_R (major)=12.43 min; t_R (minor)=10.82 min.

*4.2.7. Ethyl 2-(2,4-bis(hydroxymethyl)-5-(3-methoxyphenyl)cyclopent-1-en-1-yl)acetate (**3g**).* Purification: EA/hexane=3:1 (R_f=0.32) to give **3g** as a colorless oil. $[\alpha]_D^{21}$+90.2 (c=0.3, CH_2Cl_2); IR (CH_2Cl_2): ν 3380, 2920, 2847, 1725, 1601, 1584, 1552, 1487, 1261, 1181, 1034 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ=7.21 (dd, J=7.9 Hz, 1H), 6.76–6.73 (m, 2H), 6.68 (s, 1H), 4.23 (s, 2H), 4.05–3.96 (m, 2H), 3.79 (s, 3H), 3.68 (d, J=5.7 Hz, 2H), 3.62 (s, 1H), 3.09 (d, J=15.6 Hz, 1H), 2.89–2.80 (m, 2H), 2.43–2.39 (m, 2H), 1.16 (t, J=7.2 Hz, 3H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ=172.3, 159.9, 145.3, 141.0, 133.1, 129.6, 120.4, 113.7, 111.8, 66.4, 61.1, 59.4, 58.7, 55.2, 48.5, 36.9, 32.6, 14.0 ppm; HRMS (ESI) m/z calcd for $C_{18}H_{24}O_5$ (M^++Na) 343.1529, found 343.1521. The enantiomeric excess (91% ee) was determined by HPLC with AD-H column (*i*-PrOH/hexanes: 5/95; flow rate: 1.0 mL/min; λ=220 nm); t_R (major)=66.82 min; t_R (minor)=76.62 min.

For recovery acetate (**1g**): spectroscopic data are in agreement with racemic substrate **1g**. Yield: 31% (10 mg). The enantiomeric excess (88% ee) was determined by HPLC with AD-H column (*i*-PrOH/hexanes: 5/95; flow rate: 0.3 mL/min; λ=254 nm); t_R (major)=43.26 min; t_R (minor)=39.36 min.

*4.2.8. Ethyl 2-(2,4-bis(hydroxymethyl)-5-(p-tolyl)cyclopent-1-en-1-yl)acetate (**3h**).* Purification: EA/hexane=3:1 (R_f=0.41) to give **3h** as a colorless oil. $[\alpha]_D^{24}$+81.5 (c=0.5, CH_2Cl_2); IR (CH_2Cl_2): ν 3210, 2920, 2852, 1731, 1552, 1510, 1258, 1178, 1025 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ=7.10 (d, J=8.0 Hz, 2H), 7.02 (d, J=8.0 Hz, 2H), 4.26–4.20 (m, 2H), 4.05–3.94 (m, 2H), 3.67 (d, J=5.8 Hz, 2H), 3.61 (d, J=4.2 Hz, 1H), 3.10 (d, J=15.6 Hz, 1H), 2.86–2.80 (m, 2H), 2.41–2.35 (m, 2H), 2.32 (s, 3H), 1.15 (t, J=7.2 Hz, 3H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ=172.6, 140.8, 140.7, 136.4, 133.7, 129.6, 128.0, 66.6, 61.4, 59.6, 58.4, 48.7, 37.0, 32.8, 21.2, 14.1 ppm; HRMS (ESI) m/z calcd for $C_{18}H_{24}O_4$ (M^++Na) 327.1570, found 327.1572. The enantiomeric excess (94% ee) was determined by HPLC with AD-H column (*i*-PrOH/hexanes: 10/90; flow rate: 1.0 mL/min; λ=220 nm); t_R (major)=13.77 min; t_R (minor)=17.71 min.

For recovery acetate (**1h**): spectroscopic data are in agreement with racemic substrate **1h**. Yield: 45% (14 mg). The enantiomeric excess (79% ee) was determined by HPLC with AD-H column (*i*-PrOH/hexanes: 5/95; flow rate: 0.5 mL/min; λ=254 nm); t_R (major)=21.46 min; t_R (minor)=18.44 min.

*4.2.9. Ethyl 2-(2,4-bis(hydroxymethyl)-5-(naphthalen-2-yl)cyclopent-1-en-1-yl)acetate (**3i**).* Purification: EA/hexanes=3:1 (R_f=0.38) to give as a colorless oil. $[\alpha]_D^{25}$+98.6 (c=0.6, CH_2Cl_2); IR (CH_2Cl_2): ν 3205, 2920, 2847, 1728, 1711, 1598, 1550, 1368, 1176, 1025 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ=7.81–7.75 (m, 3H), 7.59 (s, 1H), 7.48–7.42 (m, 2H), 7.27 (dd, J=6.8 and 1.6 Hz, 1H), 4.28 (s, 2H), 3.99–3.84 (m, 3H), 3.73 (d, J=6.0 Hz, 2H), 3.11 (d, J=15.6 Hz, 1H), 2.92–2.87 (m, 2H), 2.53–2.44 (m, 2H), 1.02 (t, J=7.2 Hz, 3H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ=172.2, 141.1, 141.0, 133.5, 133.1, 132.5, 128.5, 127.6, 127.6, 126.6, 126.1, 126.1, 125.5, 66.3, 61.1, 59.5, 58.8, 48.5, 37.0, 32.7, 13.8 ppm; HRMS (ESI) m/z calcd for $C_{21}H_{24}O_4$ (M^++Na) 363.1574, found 363.1572. The enantiomeric excess (90% ee) was

determined by HPLC with AD-H column (*i*-PrOH/hexanes: 10/90; flow rate: 1.0 mL/min; λ=220 nm); t_R (major)=19.47 min; t_R (minor)=23.39 min.

For recovery acetate (**1i**): spectroscopic data are in agreement with racemic substrate **1i**. Yield: 37% (13 mg). The enantiomeric excess (85% ee) was determined by HPLC with OD-H column (*i*-PrOH/hexanes: 5/95; flow rate: 1.0 mL/min; λ=254 nm); t_R (major)=14.26 min; t_R (minor)=17.48 min.

*4.2.10. Ethyl 2-(2,4-bis(hydroxymethyl)-5-(thiophen-3-yl)cyclopent-1-en-1-yl)acetate (**3j**).* Purification: EA/hexanes=3:1 (R_f=0.43) to give as a colorless oil. $[\alpha]_D^{24}$+59.5 (c=0.5, CH_2Cl_2); IR (CH_2Cl_2): ν 3443, 2920, 2847, 1640, 1442, 1365, 1190, 1020 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ=7.16 (d, J=5 Hz, 1H), 6.92 (dd, J=5 and 3.4 Hz, 1H), 6.83 (d, J=3.4 Hz, 1H), 4.22 (dd, J=21.3 and 13.6 Hz, 2H), 4.09–4.00 (m, 2H), 3.70 (d, J=5.9 Hz, 2H), 3.70 (d, J=5.9 Hz, 2H), 3.18 (d, J=15.9 Hz, 1H), 2.95 (d, J=15.9 Hz, 1H), 2.83 (dd, J=16.3 and 8.4 Hz, 1H), 2.39 (dd, J=16.3 and 5.2 Hz, 2H), 1.20 (t, J=7.2 Hz, 3H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ=172.1, 147.4, 140.5, 133.0, 126.9, 124.7, 124.0, 66.0, 61.2, 59.5, 53.1, 49.3, 36.2, 32.4, 14.1 ppm; HRMS (ESI) m/z calcd for $C_{15}H_{20}O_4S$ (M^++Na) 319.0986, found 319.0980. The enantiomeric excess (91% ee) was determined by HPLC with AD-H column (*i*-PrOH/hexanes: 10/90; flow rate: 1.0 mL/min; λ=220 nm); t_R (major)=15.98 min; t_R (minor)=18.12 min.

For recovery acetate (**1j**): spectroscopic data are in agreement with racemic substrate **1j**. Yield: 46% (14 mg). The enantiomeric excess (99% ee) was determined by HPLC with AD-H column (*i*-PrOH/hexanes: 10/90; flow rate: 0.5 mL/min; λ=254 nm); t_R (major)=24.04 min; t_R (minor)=26.47 min.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tet.2012.06.085.

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