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Asymmetric Alkylation Using Chiral Cyclic Diols to Prepare a Quaternary Carbon

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Keywords: asymmetric alkylation; diastereoselective alkylation; quaternary carbon, C_2-symmetry; (*R,R*)-cyclohexane-1,2-diol; (*S,S*)-cycloheptane-1,2-diol; β-keto ester; acetal

Abstract: *Asymmetric alkylation of cyclic and acyclic β-keto ester acetals (4, 5, 13, 14, and 18) with C_2-symmetric cycloalkane-1,2-dioxy moiety proceeded in a highly diastereoselective manner to afford enol ethers (9-12, 15-17, 19a-c) with a chiral quaternary carbon.*

Preparation of an asymmetric quaternary carbon, which plays an important role in organic syntheses, has been studied by several groups.[1] Koga *et al.* reported a method using chiral enamine,[1b] Schultz *et al.* also reported a method using chiral enolate produced under Birch reduction conditions.[1d] In the course of our study of asymmetric reactions using C_2-symmetric cyclic diols,[2] we have found a new method for asymmetric alkylation of α-substituted β-keto esters to prepare a quaternary carbon.[3]

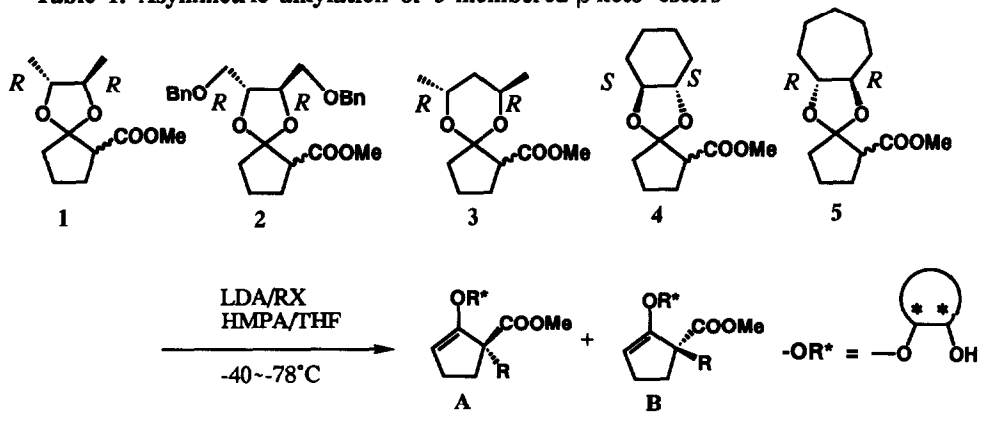
Substrates (**1-5**, **13**, **14**, **18** and **21**) for alkylation were prepared in 58-98% yields by the usual acetalization of the corresponding β-keto esters with optically active diols such as (*R,R*)-butane-2,3-diol, (*R,R*)-1,4-dibenzyloxybutane-2,3-diol, (*R,R*)-pentane-2,4-diol, (*S,S*)-cyclohexane-1,2-diol,[4] and (*R,R*)-cycloheptane-1,2-diol[4] under azeotropic conditions using *p*-TsOH (0.1 eq.) in refluxing benzene for 3-10 h. From ^{1}H-NMR spectra, these compounds were found to be a diastereomeric mixture (2:3 - 1:1) at C1.

As shown in Table 1, alkylation of substrates **1-5** derived from 2-methoxycarbonylcyclopentanone using LDA (5 eq.)[5]/RX(5 eq.)/HMPA (5 eq.)/THF at -78°C afforded the enol ethers **6-12** in reasonable yields. In this reaction, the alkylated product retaining the original acetal structure was not detected. In regard to diastereoselectivity on methylation (entries 1-4 and 6), substrates **4** and **5** (entries 4 and 6) gave better results (92% and >99% d.e., respectively) relative to substrates **1-3** which derived from acyclic diols. Nonylation of **4** and **5** (entries 5 and 7) also proceeded in a highly diastereoselective manner to afford **10** and **12** of >99% d.e., respectively.

These successful results prompted us to study the generalities of the reaction and diastereoselectivity caused by C_2 symmetric cycloalkane-1,2-dioxy moiety. Accordingly, asymmetric alkylation of substrates **13** and **14** prepared from acyclic β-keto ester was studied (Table 2). Benzylation of **13** under similar conditions to

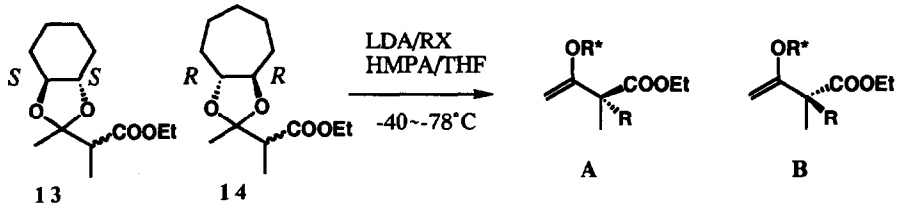
those aforementioned afforded **15B** (57% yield, 94% d.e.), and that of **14** proceeded in a completely diastereoselective manner to give **16A** (78% yield, >99% d.e.) as well as its allylation affording **17A** (70% yield, >99% d.e.). Thus, optically active cyclohexane- and cycloheptane-1,2-diols have been found to be an excellent chiral auxiliary for asymmetric alkylation of acyclic and five-membered β-keto esters.

Table 1. Asymmetric alkylation of 5-membered β-keto esters



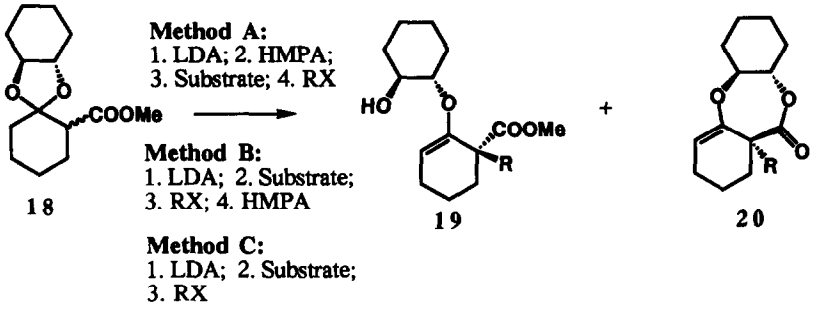
Entry	Substrate	RX	Product	Yield (%)	A : B	D.e.(%)	Abs. congfig.
1	1	MeI	6	91	65 : 35	30	*S*
2	2	MeI	7	55	66 : 34	32	*S*
3	3	MeI	8	57	87 : 13	74	*S*
4	4	MeI	9	57	4 : 96	92	*R*
5	4	$C_9H_{19}Br$	10	66	>99	>99	*R*
6	5	MeI	11	73	>99	>99	*S*
7	5	$C_9H_{19}Br$	12	74	>99	>99	*S*

Table 2. Asymmetric alkylation of acyclic β-keto esters



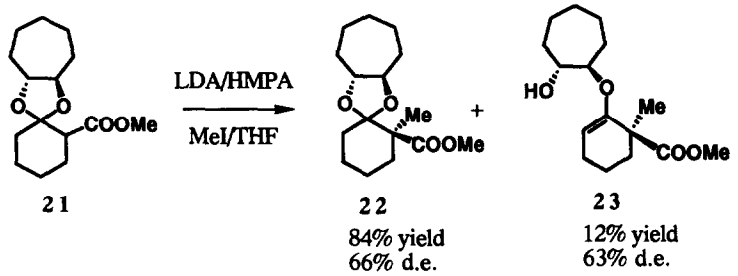
Entry	Substrate	RX	Product	Yield (%)	A : B	D.e.(%)	Abs. congfig.
1	13	BnBr	15	57	3 : 97	94	*S*
2	14	BnBr	16	78	>99	>99	*R*
3	14	CH_2=$CHCH_2Br$	17	70	>99	>99	*R*

Table 3. Asymmetric alkylation of 6-membered β-keto ester



Entry	Conditions	RX		Yield (%)	D.e.(%)		Yield (%)	D.e.(%)
1	A	MeI	**19a**	37	77	**20a**	59	95
2	A	BnBr	**19b**	43	>99	**20b**	51	>99
3	A	CH_2=$CHCH_2I$	**19c**	27	92	**20c**	53	>99
4	B	MeI	**19a**	96	85			
5	B	BnBr	**19b**	90	97			
6	B	CH_2=$CHCH_2I$	**19c**	84	96			
7	C	MeI	**19a**	95	69			
8	C	BnBr	**19b**	complex mixture				
9	C	CH_2=$CHCH_2I$	**19c**	43	96			

Scheme 1



The pattern of the reaction was not the same with alkylation of substrates **18** and **21** prepared from six-membered β-keto ester. Aklylation of **18** gave quite different results according to the order of reagents added. In the cases of method A [1. LDA; 2. HMPA; 3. **18**; 4. electrophile] (entries 1-3 in Table 3), the usual alkylated products **19a-c** (27-43% yields, 77-99% d.e.) and alkylated tricyclic lactones **20a-c** (51-59% yields, 95-99% d.e.) were obtained. Interestingly, the absolute configuration of the newly generated stereogenic center of **20** was found to be contrary to that of **19**. On the other hand, products **19a-c** (84-96% yields, 85-97% d.e.) were obtained as the sole products in the cases of method B [1. LDA; 2. **18**; 3. electrophile; 4. HMPA] (entries 4-6 in Table 3). In the cases of method C (entries 7-9, reaction without HMPA), yields of alkylated products were decreased because of formation of a complex mixture except for methylation (entry 7).

Furthermore, methylation of **21** under conditions of method A showed an unsatisfactory diastereoselectivity to afford a methylated acetal **22** (84% yield, 65% d.e.) as a major product accompanied with **23** (12% yield, 63% d.e.) as a minor product (Scheme 1).

Diastereomeric excess (d.e.) of alkylated products **6-12**, **15-17**, **19**, **22** and **23** was determined by 270 MHz ^{1}H NMR spectra in the presence of a chiral shift reagent (+)-Eu(hfc)$_3$ after conversion into the corresponding ketones **24-26** (Fig. 1) by treatment with $BF_3/THF/H_2O$. Absolute configuration of these ketones could be determined by comparison of the specific rotations reported.[6] That of **20** was also determined by the same manner. That is to say, compound **20** was converted into **26** *via* enol ether **27** by treatment with NaOMe in MeOH and subsequent acidic hydrolysis of enol ether (Scheme 2).

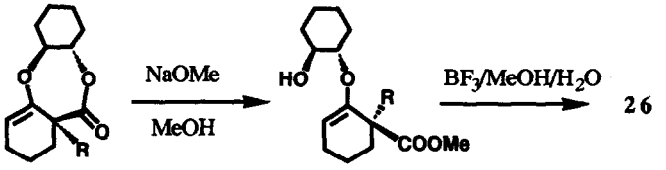
Fig. 1

24a : R= Me
24b: R= C_9H_{19}

25a: R= Bn
25b: R= $CH_2CH{=}CH_2$

26a: R= Me
26b: R= Bn
26c: R= $CH_2CH{=}CH_2$

Scheme 2



20 **27**

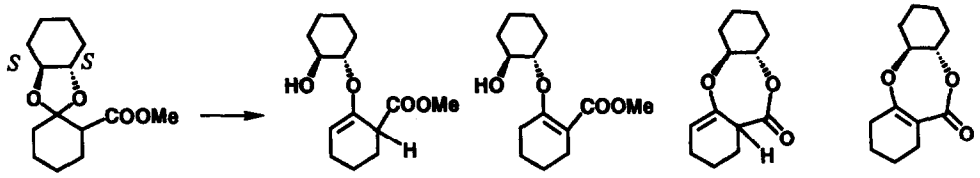
Discussion

To clarify the reaction pathway especially from **18** to **19** and **20**, several experiments were performed and following results were obtained.

1. Treatment of **18** with LDA/HMPA in THF at -78°C and the usual work-up gave a mixture of enol ethers **28** (30 % yield, 33 % d.e.) and **29** (21% yield), and that of tricyclic lactones **30** (20% yield, 14 % d.e.) and **31** (9% yield). On the other hand, the same reaction without HMPA exclusively afforded enol ethers **28** (59 % yield, 33 % d.e.) and **29** (32 % yield), and no lactone formation could be detected (Scheme 3).
2. Lactonization of **27a** (R=Me), which was derived from **20a**, did not take place under the employed reaction conditions (LDA/HMPA/THF/-78°C).
3. Alkylation of optically active tricyclic **31** proceeded in a highly diastereoselective manner to afford **20** (52-86%, 94-99% d.e.).[7]

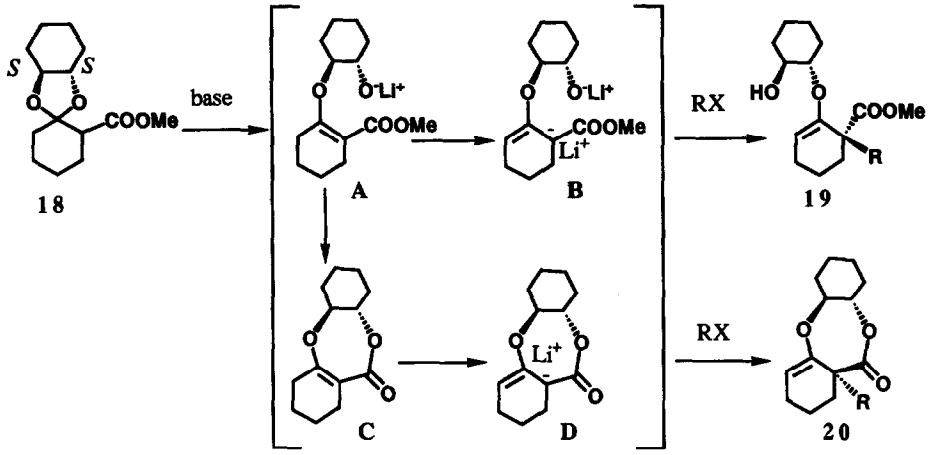
The above findings suggest the reaction pathway of entries 1-3 in Table 3 to be as shown in Scheme 4. Firstly, enol ether **A** might be formed by acetal-ring opening of the substrate **18** under basic conditions and the usual alkylated product **19** might be produced *via* dianion **B**. On the other hand, a lactone **C** produced from **A** might give α-alkylated **20** *via* an anion **D**. The effect of HMPA (5 eq.) in entries 1-3 (Table 3) was considered to be an enhancement of nucleophilicity of alkoxide anion **A** to form a lactone **C**, while that of HMPA (1.5 eq.)

Scheme 3



18	Conditions:	28	29	30	31
	LDA/HMPA/THF	30%	21%	20%	9%
	LDA/THF	59%	32%	0%	0%

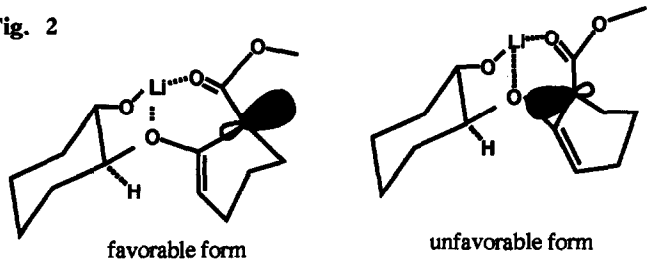
Scheme 4



in entries 4-6 (Table 3) was rationalized to accelerate the alkylation of dianion **B** prior to lactonization of **A** into **C** by taking into account the results in entries 8 and 9 (Table 3). Actually, reactions in entries 1-7 almost completed within 0.5 h. Another possible reaction pathway of lower diastereoselective alkylation as a first step and subsequent kinetic resolution on lactonization might be ignored by the results 2 and 3. On methylation of **21**, it was confirmed that the substrate was firstly converted into enol ether (A-type in Scheme 4) by TLC detection before addition of MeI. Reconstruction of the acetal ring in **22** might take place after alkylation. These different behaviors such as the formation of lactone **20** and acetal **22** might be attributed to thermodynamic stabilities of individual ring systems.

The stereochemical course of asymmetric alkylation was tentatively proposed by considering intermediate **B** in Scheme 4 as shown in Fig.2 **A**, which might be preferable to Fig. 2 **B** because of the stereoelectronic factor.

Fig. 2



favorable form
A

unfavorable form
B

EXPERIMENTAL

IR spectra were measured with a JASCO A-202 spectrometer, and ^{1}H- and ^{13}C-NMR spectra were recorded on a JEOL JNM-GX-270 or JEOL JNM-FX-100 spectrometer. Mass spectra (Ms) were taken on a JEOL JMS-D 300 spectrometer. Optical rotations were measured on a JASCO DIP-360 polarimeter at the sodium line. For column chromatography, silica gel (Merck, Kieselgel 60, 70-230 mesh) was used. Thin layer chromatography (TLC) was performed on Silica gel 60F-254 plates (Merck).

General procedure for preparation of acetals (1-5, 13, 14, 18 and 21).

To a solution of β-keto esters (3 mmol) and chiral diols (2 mmol) in benzene (30 ml) was added *p*-TsOH-H_2O (38 mg, 0.2 mmol), and the resultig mixture was refluxed with azeotropic removal of water for 3-10 h. Reaction was quenched with $NaHCO_3$ (504 mg, 6 mmol) and aqueous saturated $NaHCO_3$ (20 ml) at 0°C. The whole was extracted with ethyl acetate. The combined extracts were dried over $MgSO_4$ and concentrated *in vacuo* to afford an oily residue, which was purified by silica gel column chromatography. The fraction eluted with hexane/ethyl acetate (40:1-30:1) afforded **1-5, 13, 14, 18** and **21** as a colorless oil.

Methyl (1*RS*)-2,2-[(*R,R*)-Butane-2,3-dioxy]cyclopentanecarboxylate (1)

Compound **1** was obtained as a 2 to 3 diastereomeric mixture at C1 in 85% yield. ^{1}H-NMR ($CDCl_3$) δ 3.71 (1H, m), 3.70, 3.69 (total 3H, s each, ratio=2:3) 3.57 (1H, m), 2.91 (1H, d-d, *J*=11, 7 Hz), 2.37-2.07 (2H, m), 1.98-1.58 (4H, m), 1.27, 1.24 (total 3H, d each, *J*=6, 6 Hz, ratio=2:3), 1.21, 1.19 (total 3H, d each, *J*=6, 6 Hz, ratio=2:3); MS *m/z* (EI) 214 (M^+), 185, 127; IR (neat, cm^{-1}) 2980, 1740, 1100.

Methyl (1*RS*)-2,2-[(*R,R*)-1,4-Dibenzyloxybutane-2,3-dioxy]cyclopentanecarboxylate (2)

Compound **2** was obtained as a 1 to 1 diastereomeric mixture at C1 in 70% yield. ^{1}H-NMR ($CDCl_3$) δ 7.35-7.26 (10H, m), 4.54 (4H, d, *J*=11 Hz), 4.09-3.96 (2H, m), 3.67-3.56 (4H, m), 3.64, 3.57 (total 3H, s each, ratio=1:1), 2.98 (1H, m), 2.12-1.64 (6H, m); MS *m/z* (EI) 426 (M^+), 339, 249, 159, 105, 91; IR (neat, cm^{-1}) 2970, 1730, 1455, 1220, 740, 700.

Methyl (1*RS*)-2,2-[(*R,R*)-Pentane-2,4-dioxy]cyclopentanecarboxylate (3)

Compound **3** was obtained as a 1 to 1 diastereomeric mixture at C1 in 80% yield. ^{1}H-NMR ($CDCl_3$) δ 4.16, 4.05 (total 1H, m each, ratio=1:1), 3.91 (1H, m), 3.69 (3H, s), 2.99 (1H, d-d, *J*=14, 9 Hz), 2.09-1.53 (8H, m), 1.21 (3H, d, *J*=6 Hz), 1.21 (3H, d, *J*=6 Hz); MS *m/z* (EI) 228 (M^+), 199, 69; IR (neat, cm^{-1}) 2970, 1740, 1435.

Methyl (1*RS*)-2,2-[(*S,S*)-Cyclohexane-1,2-dioxy]cyclopentanecarboxylate (4)

To a solution of NaOMe prepared from Na (460 mg, 20 mmol) in MeOH (5 ml) was added (3*S*,8*S*)-2,9-dioxa-10-oxotricyclo[9,3,0,$0^{3,8}$]tetradeca-1(11)-ene[7] (104 mg, 0.5 mmol) under an Ar atmosphere. The mixture was stirred at room temperature for 48 h, then diluted with saturated aqueous NH_4Cl (20 ml), and extracted with ethyl acetate. The extracts were dried over $MgSO_4$, then concentrated *in vacuo* to afford an oily residue, which was purified by silica gel column chromatography. The fraction eluted with hexane/ethyl acetate (30:1) afforded **4** (99.5 mg, 83%) as a 1 to 1 diastereomeric mixture at C(1). ^{1}H-NMR ($CDCl_3$) δ 3.70, 3.69 (total 3H, s each, ratio=1:1), 3.44-3.15 (2H, m), 2.98 (1H, dd, *J*=17, 7 Hz), 2.15-1.78 (9H, m), 1.46-1.26 (5H, m). Ms *m/z* (EI) 240 (M^+) 153, 114. IR (neat, cm^{-1}) 1740, 1435, 1100.

Methyl (1*RS*)-2,2-[(*R,R*)-Cycloheptane-1,2-dioxy]cyclopentanecarboxylate (5)

Compound **5** was obtained as a 3 to 4 diastereomeric mixture at C1 in 98% yield. ^{1}H-NMR ($CDCl_3$) δ 3.81-3.68 (2H, m), 3.71, 3.70 (total 3H, s each, ratio=3:4), 2.92 (1H, dd, *J*=16, 8 Hz), 2.19-1.82 (7H, m), 1.68-1.43 (9H, m). Ms *m/z* (EI) 254 (M^+) 167. IR (neat, cm^{-1}) 1730, 1440, 1100.

Ethyl (2*RS*)-3,3-[(*S,S*)-Cyclohexane-1,2-dioxy]-2-methylbutanoate (13)

Compound **13** was obtained as a 1 to 1 diastereomeric mixture at C1 in 58% yield. ^{1}H-NMR ($CDCl_3$) δ 4.19-4.21 (2H, m), 3.36-3.22 (2H,m), 2.82, 2.74 (total 1H, d-d each, *J*=14, 7 Hz, ratio=1:1), 2.15-2.10 (2H, m), 1.85-1.78 (2H, m), 1.47 (3H, d, *J*=5 Hz), 1.44-1.21 (10H, m); MS *m/z* (FD) 242 (M^+), 198, 141; IR (neat, cm^{-1}) 2930, 1725, 1440, 1100.

Ethyl (2*RS*)-3,3-[(*R,R*)-Cycloheptane-1,2-dioxy]-2-methylbutanoate (14)

Compound **14** was obtained as a 1 to 1 diastereomeric mixture at C1 in 98% yield. ^{1}H-NMR ($CDCl_3$) δ 4.23-4.10 (2H, m), 3.81-3.73 (2H,m), 2.77, 2.73 (total 1H, d-d each, *J*= 14, 7 Hz, ratio=1:1), 2.24-2.12 (2H, m), 1.63-1.45 (8H, m), 1.43 (3H, d, *J*=4 Hz), 1.29-1.19 (6H, m); MS *m/z* (EI) 241 (M^+-15), 155, 95, 43; IR (neat, cm^{-1}) 2920, 1720, 1440, 1100.

Methyl (1*RS*)-2,2-[(*S,S*)-Cyclohexane-1,2-dioxy]cyclohexanecarboxylate (18)

Compound **18** was obtained as a 1 to 1 diastereomeric mixture at C1 in 80% yield.^{1}H-NMR ($CDCl_3$) δ 3.70, 3.69 (total 3H, s each, ratio=1:1), 3.32-3.05 (2H, m), 2.72 (1H, m), 2.17-1.45 (11H, m), 1.43-1.24 (5H, m). Ms *m/z* (EI) 254 (M^+) 153. IR (neat, cm^{-1}) 2930, 1725, 1430, 1100.

Methyl (1*RS*)-2,2-[(*R,R*)-Cycloheptane-1,2-dioxy]cyclohexanecarboxylate (21)

Compound **21** was obtained as a 2 to 1 diastereomeric mixture at C1 in 99% yield.^{1}H-NMR ($CDCl_3$) δ 3.83-3.69 (2H, m), 3.69, 3.68 (total 3H, s each, ratio=2:1), 2.69 (1H, m), 2.23-2.14 (2H, m), 1.93-1.42 (16H, m). Ms *m/z* (EI) 268 (M^+) 167. IR (neat, cm^{-1}) 2940, 1740, 1440.

General procedure for asymmetric alkylation of acetals (Method A).

A solution of *n*-BuLi (15% hexane solution, 1.4 ml, 2.25 mmol) was added dropwise to a stirred solution of diisopropylamine (223 mg, 2.25 mol) in THF (8 ml) at -78°C under an Ar atmosphere. After 10 min, HMPA (403 mg, 2.25 mmol) in THF (0.5 ml) and substrate (0.45 mmol) in THF (2 ml) were added. The whole was stirred for 10 min, then alkyl halide (2.25 mmol) in THF (1 ml) was added. After being stirred for 3-5 h at -78°C and for additional 12-24 h at -40°C, the reaction was quenched with aqueous saturated NH_4Cl, and extracted with ethyl acetate. The extracts were washed with brine, dried over $MgSO_4$, and concentrated *in vacuo*. The crude product was purified by flash column chromatography on silica gel (50:1-5:1 hexane/ethyl acetate).

Methyl (1*S*)-2-[(2*R*,3*R*)-3-Hydroxybutan-2-yl]oxy-1-methyl-2-cyclopenten-1-carboxylate(6A) Colorless oil, 11-59% yield. ^{1}H-NMR ($CDCl_3$) δ 4.56 (1H, br. s), 3.82 (1H, m), 3.70 (3H, s), 3.67 (1H, m) 3.34 (1H, br. s), 2.40-2.26 (3H, m),1.79 (1H, m), 1.35 (3H, s), 1.18 (3H, d, *J*=10 Hz), 1.16 (3H, d, *J*=10 Hz); ^{13}C-NMR ($CDCl_3$) δ 176.7 (s), 158.4 (s), 95.7 (d), 81.0 (d), 71.2 (d), 53.9 (s), 52.2 (q), 35.6 (t), 26.2 (t), 21.9 (q), 18.1 (q), 15.5 (q); MS *m/z* (EI) 228 (M^+), 156, 127; IR (neat, cm^{-1}) 3500, 2990, 1730, 1647, 1440, 1105; $[\alpha]_D^{24}$ -79.8° (c=0.61, $CHCl_3$).

Methyl (1*R*)-2-[(2*R*,3*R*)-3-Hydroxybutan-2-yl]oxy-1-methyl-2-cyclopenten-1-carboxylate(6B) Colorless oil , 7-32% yield. ^{1}H-NMR ($CDCl_3$) δ 4.58 (1H, br. s), 3.80 (1H, m), 3.69 (1H, m), 3.68 (3H, s), 2.43-2.26 (4H, m),1.80 (1H, m), 1.37 (3H, s), 1.18 (3H, d, *J*=6Hz), 1.17 (3H, d, *J*=6Hz); ^{13}C-NMR ($CDCl_3$) δ 176.2 (s), 158.4 (s), 96.2 (d), 79.5 (d), 70.3 (d), 54.1 (s), 51.9 (q), 35.7 (t), 26.4 (t), 21.6 (q), 18.3 (q), 14.5 (q); MS *m/z* (EI) 228 (M^+), 156, 127; IR (neat, cm^{-1}) 3500, 3000, 1740, 1650, 1440, 1105; $[\alpha]_D^{24}$ +9.9° (c=0.92, $CHCl_3$).

Methyl (1*S*)-2-[(2*R*,3*R*)-1,4-Dibenzyloxy-3-Hydroxybutan-2-yl]oxy-1-methyl-2-cyclopenten-1-carboxylate (7) Compound **7** was obtained as a 1 to 2 diastereomeric mixture at C1 in 55% yield. Colorless oil. ^{1}H-NMR ($CDCl_3$) δ 7.34-7.26 (10H, m), 4.65 (1H, br. s), 4.65-4.45 (4H, m), 4.29-4.05 (2H, m), 3.81-3.54 (4H, m), 3.65, 3.61 (total 3H, each-s, ratio=1:2), 2.38-2.26 (3H, m), 1.85-1.72 (1H, m), 1.37, 1.38 (total 3H, each-s, ratio=1:2); MS *m/z* (EI) 426(M^+), 339, 249, 159; IR (neat, cm^{-1}) 3460, 2850, 1725, 1645, 1445, 1235, 740, 700; $[\alpha]_D^{26}$ +1.41° (c=0.85, $CHCl_3$).

Methyl (1*R*)-2-[(2*R*,4*R*)-4-Hydroxypentan-2-yl]oxy-1-methyl-2-cyclopenten-1-carboxylate

(8A) Colorless oil, 49% yield. ^{1}H-NMR ($CDCl_3$) δ 4.57 (1H, br. s), 4.30 (1H, m), 4.09 (1H, m), 3.68 (3H, s), 2.75 (1H, br. s), 2.43-2.25 (3H, m),1.77-1.66 (3H, m), 1.34 (3H, s), 1.24 (3H, d, *J*=6 Hz), 1.20 (3H, d, *J*=6 Hz); ^{13}C-NMR ($CDCl_3$) δ 176.3 , 158.6 (s), 95.7 (d), 72.7, 64.6 (d), 54.0 (s), 52.0 (q), 45.0, 35.5, 26.5 (t), 23.8, 21.7, 18.7 (q); MS *m/z* (EI) 242 (M^+), 97, 69; IR (neat, cm^{-1}) 3430, 2950, 1735, 1645, 1440, 1110; $[\alpha]_D^{24}$ -83.8° (c=0.75, $CHCl_3$).

Methyl (1*S*)-2-[(2*R*,4*R*)-4-Hydroxypentan-2-yl]oxy-1-methyl-2-cyclopenten-1-carboxylate (8B) Colorless oil, 7.6% yield. ^{1}H-NMR ($CDCl_3$) δ 4.57 (1H, br. s), 4.34 (1H, m), 3.99 (1H, m), 3.69 (3H, s), 2.50 (1H, br. s), 2.37-2.29 (3H, m), 1.77-1.67 (3H, m), 1.33 (3H, s), 1.24 (3H, d, *J*=6Hz), 1.18 (3H, d, *J*=6Hz); ^{13}C-NMR ($CDCl_3$) δ 176.6 (s), 158.6 (s), 95.5 (d), 72.7 (d), 64.2 (d), 54.0 (s), 52.1 (q), 44.8 (t), 35.6 (t), 26.4 (t), 23.2 (q), 21.7 (q), 19.1 (q); MS *m/z* (EI) 242 (M^+), 97, 69; IR (neat, cm^{-1}) 3430, 2950, 1735, 1645, 1440, 1110; $[\alpha]_D^{24}$ +3.9° (c=0.93, $CHCl_3$).

Methyl (1*R*)-2-[(1*S*,2*S*)-2-Hydroxycyclohexan-1-yl]oxy-1-methyl-2-cyclopenten-1-carboxylate (9) Colorless oil, 57% yield, 92% d.e. at C1. ^{1}H-NMR ($CDCl_3$) δ 4.62 (1H, br. s), 3.70, 3.68 (3H, each-s, ratio=96:4), 3.72 (1H, m), 3.52 (1H, m), 3.50 (1H, br. s), 2.36-2.01 (4H, m), 1.83-1.65 (4H, m), 1.36 (3H, s) 1.32-1.27 (4H, m),; ^{13}C-NMR ($CDCl_3$) δ 176.9 (s), 159.0 (s), 96.0 (d), 84.1 (d), 73.8 (d), 54.1 (s), 52.2 (q), 35.7 (t), 31.9 (t), 29.4 (t), 26.2 (t), 24.2 (t), 23.9 (t), 21.9 (q); MS *m/z* (FD) 254(M^+); IR (neat, cm^{-1}) 3500, 2950, 1730, 1650, 1450, 1150; $[\alpha]_D^{21}$ +71.5°(c=1.02, $CHCl_3$).

Methyl (1*R*)-2-[(1*S*,2*S*)-2-Hydroxycyclohexan-1-yl]oxy-1-nonyl-2-cyclopenten-1-carboxylate (10) Colorless oil, 66% yield, >99% d.e. at C1. ^{1}H-NMR ($CDCl_3$) δ 4.64 (1H, br. s), 3.69 (3H, s), 3.63 (1H, br. s), 3.70-3.48 (2H, m), 2.33-2.05 (6H, m), 1.88-1.59 (6H, m),1.26 (16H, br. s), 0.88 (3H, t, *J*=7Hz); ^{13}C-NMR ($CDCl_3$) δ 176.6 (s), 157.3 (s), 96.9 (d), 84.4 (d), 73.7 (d), 58.1 (s), 52.1 (q), 35.2 (t), 32.9 (t), 32.5 (t), 31.9 (t), 31.8 (t), 30.0 (t), 29.5 (t), 29.4 (t), 26.4 (t), 25.8 (t), 24.4 (t), 24.3 (t), 23.9 (t), 22.7 (t), 14.1 (q); MS *m/z* (EI) 366 (M^+), 191, 142, 110, 69, 55; IR (neat, cm^{-1}) 3550, 3030, 1740, 1665, 1250; $[\alpha]_D^{25}$ +55.6° (c=1.0, $CHCl_3$).

Methyl (1*S*)-2-[(1*R*,2*R*)-2-Hydroxycycloheptan-1-yl]oxy-1-methyl-2-cyclopenten-1-carboxylate (11) Colorless oil , 73% yield, >99% d.e. at C1. ^{1}H-NMR ($CDCl_3$) δ 4.52 (1H, br. s), 3.81-3.64 (2H, m), 3.70 (3H, s), 3.38 (1H, br. s), 2.41-2.27 (3H, m), 1.98-1.50 (11H, m), 1.35 (3H, s); ^{13}C-NMR ($CDCl_3$) δ 176.8 (s), 158.5 (s), 95.9 (d), 86.5 (d), 75.8 (d), 54.0 (s), 52.2 (q), 35.7 (t), 31.6 (t), 28.5 (t), 27.4 (t), 26.2 (t), 22.5 (t), 22.2 (t), 21.9 (q); MS *m/z* (EI) 268 (M^+), 156, 55; IR (neat, cm^{-1}) 3480, 2910, 1720, 1640, 1440, 1100; $[\alpha]_D^{25}$ -63.6° (c=0.33, $CHCl_3$). HRms *m/z* 268.1665 (M^+, calcd for $C_{15}H_{24}O_4$ 268.1674).

Methyl (1*S*)-2-[(1*R*,2*R*)-2-Hydroxycycloheptan-1-yl]oxy-1-nonyl-2-cyclopenten-1-carboxylate (12) Colorless oil, 74% yield, >99% d.e. at C1. ^{1}H-NMR ($CDCl_3$) δ 4.53 (1H, br. s), 3.78-3.63 (2H, m), 3.69 (3H, s), 3.55 (1H, br. s), 2.39-2.24 (3H, m), 1.98-1.48 (11H, m),1.26 (16H, br. s), 0.88 (3H, t, *J*=7Hz); ^{13}C-NMR ($CDCl_3$) δ 176.3 (s), 156.9 (s), 96.9 (d), 86.6 (d), 75.8 (d), 58.0 (s), 52.1 (q), 35.3 (t), 32.5 (t), 31.9 (t), 31.9 (t), 30.0 (t), 29.5 (t), 29.4 (t), 29.3 (t), 28.4 (t), 27.3 (t), 26.4 (t), 24.4 (t), 22.7 (t), 22.4 (t), 22.2 (t), 14.2 (q); MS *m/z* (EI) 380 (M^+), 254, 167, 142, 110, 55; IR (neat, cm^{-1}) 3500, 2930, 1720, 1640, 1455; $[\alpha]_D^{25}$ -24.1° (c=0.46, $CHCl_3$). HRms *m/z* 380.2935 (M^+, calcd for $C_{23}H_{40}O_4$ 380.2926).

Ethyl (2*S*)-2-Benzyl-3-[(1*S*,2*S*)-2-hydroxycyclohexan-1-yl]oxy-3-butenoate (15) Colorless oil, 70% yield, >94% d.e. at C2. ^{1}H-NMR ($CDCl_3$) δ 7.26-7.10 (5H, m), 4.27-4.15 (2H, m), 4.14 (1H, d, *J*=3Hz), 3.90 (1H, d, *J*=3Hz), 3.84 (1H, m), 3.59 (1H, m), 3.29 (1H, s), 3.27 (1H, d, *J*=14Hz), 3.00 (1H, d, *J*=14Hz), 2.24-2.04 (2H, m), 1.82-1.73 (2H, m), 1.41-1.29 (4H, m), 1.28 (3H, t, *J*=7Hz), 1.21 (3H, s); ^{13}C-NMR ($CDCl_3$) δ 175.6 (s), 161.0 (s), 137.0 (s), 130.6 (d), 127.6 (d), 126.4 (d), 84.0 (t), 81.5, 73.5 (d), 61.3 (t), 52.2 (s), 41.0 (t), 32.0 (t), 29.2 (t), 24.2 (t), 23.8 (t), 20.8 (q), 14.1 (q); MS *m/z* (EI) 332 (M^+), 234; IR (neat, cm^{-1}) 3450, 2900, 1710, 1640, 1620, 1440, 1100, 700; $[\alpha]_D^{25}$ -73.8° (c=0.68, $CHCl_3$).

Ethyl (2*R*)-2-Benzyl-3-[(1*R*,2*R*)-2-hydroxycycloheptan-1-yl]oxy-3-butenoate (16)

Colorless oil , 78% yield, >99% d.e. at C2. ^{1}H-NMR ($CDCl_3$) δ 7.26-7.10 (5H, m), 4.27-4.14 (2H, m), 3.99 (1H, d, *J*=3Hz), 3.93 (1H, d, *J*=3Hz), 3.89 (1H, m), 3.74 (1H, m), 3.25 (1H, d, *J*=13Hz), 3.20 (1H, s), 3.03 (1H, d, *J*=13Hz), 2.03-1.47 (10H, m), 1.27 (3H, t, *J*=7Hz), 1.21 (3H, s); ^{13}C-NMR ($CDCl_3$) δ 175.6 (s), 160.8 (s), 137.0 (s), 130.6 (d), 127.7 (d), 126.4 (d), 84.2 (t), 84.2 (d), 83.7 (d), 61.4 (t), 52.1 (s), 41.0 (t), 31.7 (t), 28.0 (t), 27.8 (t), 22.5 (t), 22.3 (t), 20.9 (q), 14.1 (q); MS *m/z* (EI) 331 (M^+-15), 241, 155; IR (neat, cm^{-1}) 3475, 2900, 1720, 1660, 1640, 1440, 1100; $[\alpha]_D^{25}$ -65.3° (c=1.4, $CHCl_3$). HRms *m/z* 346.2153 (M^+, calcd for $C_{21}H_{30}O_4$ 346.2144).

Ethyl (2*R*)-2-Allyl-3-[(1*R*,2*R*)-2-hydroxycycloheptan-1-yl]oxy-3-butenoate (17)

Colorless oil, 70% yield, >99% d.e. at C2 ^{1}H-NMR ($CDCl_3$) δ 5.68-5.58 (1H, m), 5.08 (1H, d, *J*=4Hz), 5.30 (1H, s), 4.22-4.10 (2H, m), 4.11 (1H, d, *J*=3Hz), 4.04 (1H, d, *J*=3Hz), 3.89-3.82 (1H, m), 3.72-3.64 (1H, m), 3.01 (1H, s), 2.65 (1H, d-d, *J*=14, 6Hz), 2.43 (1H, d-d, *J*=14, 8Hz), 1.97-1.46 (10H, m), 1.30 (3H, s), 1.25 (3H, t, *J*=7); ^{13}C-NMR ($CDCl_3$) δ 175.3 (s), 161.2 (s), 133.7 (d), 118.1 (t), 83.3 (d), 83.0 (t), 75.6(d), 61.2 (t), 50.8 (s), 40.3 (t), 31.8 (t), 27.8 (t), 27.8 (t), 22.5 (t), 22.3 (t), 20.9 (q), 14.2 (q); MS *m/z* (EI) 296 (M^+), 281, 142, 155, 114, 95, 43; IR (neat, cm^{-1}) 3450, 2900, 1720, 1660, 1640, 1440, 1100; $[\alpha]_D^{25}$ -69.6° (c=0.77, $CHCl_3$). HRms *m/z* 296.1979 (M^+, calcd for $C_{17}H_{28}O_4$ 296.1987).

Methyl (1*R*)-2-[(1*S*,2*S*)-2-Hydroxycyclohexan-1-yl]oxy-1-methyl-2-cyclohexen-1-carboxylate (19a) Colorless oil, 37% yield, 77% d.e. at C1.^{1}H-NMR ($CDCl_3$) δ 4.81 (1H, br. s), 3.82-3.73 (1H, m), 3.70 (3H, s), 3.63 (1H, br. s), 3.54-3.44 (1H, m), 2.15-1.50 (10H, m), 1.37 (3H, s), 1.32-1.25 (4H, m); ^{13}C-NMR ($CDCl_3$) δ 177.4 (s), 154.0 (s), 96.2(d), 80.5 (d), 73.7 (d), 52.2 (q), 47.2 (s), 35.8 (t), 32.1 (t), 29.6 (t), 24.3 (t), 24.1 (t), 23.9 (t), 15.6 (t), 23.0 (q); MS *m/z* (EI) 268 (M^+), 153, 41; IR (neat, cm^{-1}) 3450, 2900, 1710, 1660, 1430; $[\alpha]_D^{25}$ +61.9° (c=0.3, $CHCl_3$). HRms *m/z* 268.1665 (M^+, calcd for $C_{15}H_{24}O_4$ 268.1674).

(3*S*,8*S*,11*S*)-11-Methyl-2,9-dioxa-10-oxotricyclo[9,4,0,0^{3,8}]pentadec-1(15)-ene (20a)

Colorless needles, 59% yield, mp 95°C. 95% d.e. at C11. ^{1}H-NMR ($CDCl_3$) δ 5.31 (1H, br. s), 4.49 (1H, m), 3.92 (1H, m), 2.19-1.65 (9H, m), 1.52 (3H, s), 1.53-1.18 (5H, m). ^{13}C-NMR ($CDCl_3$) δ 175.9 (s), 150.2 (s), 115.1 (d), 81.6 (d), 76.9 (d), 47.7(s), 34.6 (t), 31.2 (t), 31.1 (t), 31.1 (t), 23.6 (t), 23.5 (t), 18.2 (t), 26.0 (q). Ms *m/z* (EI) 236 (M^+) 111. IR(Nujol, cm^{-1}) 1720, 1650, 1440. $[\alpha]_D^{24}$ -8.9° (c 0.56, $CHCl_3$). HRms *m/z* 236.1426 (M^+, calcd for $C_{14}H_{20}O_3$ 236.1412).

Methyl (1*R*)-1-Benzyl-2-[(1*S*,2*S*)-2-Hydroxycyclohexan-1-yl]oxy-2-cyclohexen-1-carboxylate (19b) Colorless oil, 43% yield, >99% d.e. at C1.^{1}H-NMR ($CDCl_3$) δ 7.27-7.18 (5H, m), 4.87 (1H, t, *J*=3 Hz), 4.20 (1H, s), 3.82 (1H, m), 3.72 (3H, s), 3.62 (1H, m), 3.32 (1H, d, *J*=13 Hz), 3.13(1H, d, *J*=13 Hz), 2.23-1.77 (7H, m), 1.54-1.27 (7H, m); ^{13}C-NMR ($CDCl_3$) δ 176.6 (s), 151.5 (s), 137.3 (s), 130.7 (d), 127.7 (d), 126.4 (d), 99.1 (d), 81.7 (d), 73.7 (d), 52.4 (q), 52.2 (s), 40.8 (t), 32.1 (t), 31.6 (t), 30.0 (t), 24.4 (t), 24.0 (t), 23.7 (t), 19.7 (t); MS *m/z* (EI) 344 (M^+), 186, 143, 123, 91; IR (neat, cm^{-1}) 3450, 2900, 1720, 1660, 1440, 1120, 700; $[\alpha]_D^{27}$ +64.0° (c=0.4, $CHCl_3$). HRms *m/z* 344.1978 (M^+, calcd for $C_{21}H_{28}O_4$ 344.1987).

(3*S*,8*S*,11*R*)-11-Benzyl-2,9-dioxa-10-oxotricyclo[9,4,0,0^{3,8}]pentadec-1(15)-ene (20b)

Colorless oil , 51% yield, >99% d.e. at C11. ^{1}H-NMR ($CDCl_3$) δ 7.29-7.21 (5H, m), 5.47 (1H, t, *J*=4 Hz), 4.57-4.48 (1H, m), 3.85 (1H, m), 3.39 (1H, d, *J*=13 Hz), 2.96 (1H, d, *J*=13 Hz), 2.24-1.86 (5H, m), 1.78-1.68 (2H, m), 1.57-1.18 (7H, m). ^{13}C-NMR ($CDCl_3$) δ 175.0 (s), 147.4 (s), 136.8 (s), 130.8 (d), 128.4 (d), 126.5 (d), 118.8 (d), 80.9 (d), 77.3 (d), 53.4 (s), 44.4 (t), 33.2 (t), 31.8 (t), 31.5 (t), 23.9 (t), 23.6 (t), 23.3 (t), 19.1 (t). Ms *m/z* (EI) 312 (M^+) 180, 107. IR (neat, cm^{-1}) 1750, 1690, 1460. $[\alpha]_D^{27}$ +17.6° (c=0.76, $CHCl_3$). HRms *m/z* 312.1711 (M^+, calcd for $C_{20}H_{24}O_3$ 312.1725).

Methyl (1*R*)-1-Allyl-2-[(1*S*,2*S*)-2-hydroxycyclohexan-1-yl]oxy-2-cyclohexen-1-carboxylate (19c) Colorless oil, 27% yield, 92% d.e. at C1.^{1}H-NMR ($CDCl_3$) δ 5.72 (1H, m), 5.08 (1H, d, *J*=6 Hz), 5.03 (1H, s), 4.88 (1H, t, *J*=4 Hz), 3.86 (1H, br. s), 3.83-3.70 (1H, m), 3.71, 3.68 (total 3H, s each, ratio=100:3.9), 3.51 (1H, m), 2.65 (1H, d-d, *J*=13, 6 Hz), 2.38 (1H, d-d, *J*=13, 8 Hz), 2.29-2.03 (6H, m), 1.85-1.27 (8H, m); ^{13}C-NMR ($CDCl_3$) δ 176.5 (s), 150.2 (s), 136.5 (d), 118.0 (t), 97.9 (d), 80.8 (d), 73.7 (d), 52.3 (q), 50.6 (s), 40.1 (t), 32.0 (t), 31.9 (t), 29.7 (t), 24.3 (t), 23.9 (t), 23.8 (t), 19.7 (t); MS *m/z* (EI) 294

(M+), 164, 137; IR (neat, cm^{-1}) 3500, 2950, 1720, 1660, 1620, 1450; $[\alpha]_D^{30}$ +52.3° (c=0.6, $CHCl_3$). HRms *m/z* 294.1841 (M+, calcd for $C_{17}H_{26}O_4$ 294.1831).

(3*S*,8*S*,11*R*)-11-Allyl-2,9-dioxa-10-oxotricyclo[9,4,0,0^{3,8}]pentadec-1(15)-ene (20c)

Colorless oil, 53% yield, >99% d.e. at C11. ^{1}H-NMR ($CDCl_3$) δ 5.87 (1H, m), 5.43 (1H, t,*J*=4 Hz), 5.11 (1H, d, *J*=8 Hz), 5.05 (1H, s), 4.46 (1H, m), 3.92 (1H, m), 2.73 (1H, dd, *J*=13, 6 Hz), 2.47 (1H, dd, *J*=13, 8 Hz), 2.20-2.07 (5H, m), 1.86-1.73 (4H, m), 1.61-1.17 (5H, m). ^{13}C-NMR ($CDCl_3$) δ 174.6 (s), 148.5 (s), 134.1 (d), 117.8 (t), 117.2 (d), 81.4 (d), 77.0 (d), 51.7 (s), 44.1 (t), 33.2 (t), 31.5 (t), 31.3 (t), 23.8 (t), 23.6 (t), 23.4 (t), 18.7 (t); Ms *m/z* (EI) 262 (M+), 163, 123. IR (neat, cm^{-1}) 1720, 1660, 1440. $[\alpha]_D^{30}$ -0.8° (c=0.50, $CHCl_3$). HRms *m/z* 262.1553 (M+, calcd for $C_{16}H_{22}O_3$ 262.1569).

Methyl (1*S*)-2,2-[(*R*,*R*)-Cycloheptane-1,2-dioxy]-1-methyl-cyclohexanecarboxylate (22)

Colorless oil, 84% yield, 66% d.e. at C1. ^{1}H-NMR($CDCl_3$) δ 3.78 (1H, m), 3.68 (3H, s) 3.59 (1H, m), 2.26-2.15 (2H, m), 2.12-1.38 (16H, m), 1.27, 1.25 (total 3H, s each, ratio=13.6:68); ^{13}C-NMR($CDCl_3$) δ 175.4 (s), 110.0 (s), 82.3 (d), 80.0 (d), 51.6 (q), 51.4 (s), 37.1 (t), 34.5 (t), 33.6 (t), 30.9 (t), 28.8 (t), 25.2 (t), 25.0 (t), 23.3 (t), 21.5 (t), 19.3 (q); Ms, *m/z* (EI) 282 (M+), 268, 181, 167, 154; IR (neat, cm^{-1}) 2900, 1720, 1440; $[\alpha]_D^{25}$ -8.2° (c=0.83, $CHCl_3$).

Methyl (1*S*)-2-[(1*R*,2*R*)-2-Hydroxycycloheptan-1-yl]oxy-1-methyl-2-cyclohexen-1-carboxylate (23) Colorless oil, 12% yield, 63% d.e. at C1. ^{1}H-NMR($CDCl_3$) δ 4.66 (1H, t, *J*=4 Hz), 4.20 (1H, m), 3.70 (3H, s), 3.83-3.58 (2H, m), 2.26-1.38 (16H, m), 1.36 (3H, s), ; ^{13}C-NMR($CDCl_3$) δ 177.2 (s), 153.6 (s), 96.2(d), 82.6 (d), 75.8 (d), 52.2 (q), 47.2 (s), 35.7 (t), 31.7 (t), 28.5 (t), 27.6 (t), 23.9 (t), 23.1 (q), 22.5 (t), 22.3 (t), 19.5 (t); Ms, *m/z* (FD) 282 (M+); IR (neat, cm^{-1}) 3480, 2910, 1718, 1660, 1440, 1250, 1150, 745; $[\alpha]_D^{27}$ +9.4° (c=0.42, $CHCl_3$) .

General procedure for asymmetric alkylation of 18 (Method B).

A solution of *n*-BuLi (15% hexane solution, 1.4 ml, 2.25 mmol) was added dropwise to a stirred solution of diisopropylamine (223 mg, 2.25 mol) in THF (8 ml) at -78°C under an Ar atmosphere. After 10 min, **18** (0.45 mmol) in THF (2 ml) and alkyl halide (2.25 mmol) in THF (1 ml) were added. The whole was stirred for 10 min, then HMPA (121 mg, 0.68 mmol) in THF (0.5 ml) was added. After being stirred for 1-3 h at -40°C, the reaction mixture was quenched with aqueous saturated NH_4Cl, and extracted with ethyl acetate. The extract was washed with brine, dried over $MgSO_4$, and concentrated *in vacuo*. The crude product was purified by flash column chromatography on silica gel .The fraction eluted with 20:1 hexane/ethyl acetate gave alkylated enol ether **(19a)** in 96% yield (85% d.e.), **(19b)** in 90% yield (97% d.e.) and **(19c)** in 84% yield (96% d.e.).

Enol ethers (27a-c)

Compounds **27a-c** were obtained as colorless oil by a similar manner to that described for the preparation of 4.

27a: 95% yield. ^{1}H-NMR ($CDCl_3$) δ 4.81 (1H, t, *J*=4 Hz), 3.78-3.68 (1H, m), 3.67 (3H, s), 3.51 (1H, m), 2.35 (1H, br.s), 2.23-2.01 (5H, m), 1.74-1.56 (5H, m), 1.40 (3H, s), 1.33-1.20 (4H, m). ^{13}C-NMR($CDCl_3$) δ 176.7 (s), 153.5 (s), 96.5 (d), 79.3 (d), 73.3 (d), 51.9 (q), 47.1 (s), 35.5 (t), 31.9 (t), 28.1 (t), 23.9 (t), 23.9 (t), 23.7 (t), 19.2 (t), 22.6 (q). Ms *m/z* (EI) 268 (M+), 170, 153, 138, 110. IR (neat, cm^{-1}) 3400, 1720, 1660, 1450. $[\alpha]_D^{24}$ +11.7° (c=0.29, $CHCl_3$).

27b: 93% yield.^{1}H-NMR ($CDCl_3$) δ 7.27-7.20 (5H, m), 4.91 (1H, t, *J*=4 Hz), 3.75 (1H, m), 3.70 (3H, s), 3.46 (1H, m), 3.36 (1H, d, *J*=13 Hz), 3.04 (1H, d, *J*=13 Hz), 2.23-1.85 (6H, m), 1.74-1.66 (3H, m), 1.55-1.20 (6H, m). ^{13}C-NMR ($CDCl_3$) δ 176.1 (s), 150.8 (s), 138.4 (s), 130.5 (d), 128.0 (d), 126.3 (d), 99.3 (d), 79.3 (d), 73.2 (d), 51.9 (q), 51.8 (s), 40.5 (t), 32.4 (t), 32.0 (t), 27.8 (t), 23.9 (t), 23.9 (t), 23.5 (t), 19.0 (t). Ms *m/z* (EI) 344 (M+), 228, 186, 107. IR (neat, cm^{-1}) 3450, 1720, 1660, 1440. $[\alpha]_D^{26}$ -4.7° (c=0.45, $CHCl_3$).

27c: 98% yield.^{1}H-NMR ($CDCl_3$) δ 5.88 (1H, m), 5.24-5.40 (2H, m), 4.88 (1H, t, *J*=4 Hz), 3.72 (1H, m), 3.68 (3H, s), 3.54 (1H, m), 2.70 (1H, dd, *J*=14, 6 Hz), 2.46 (1H, dd, *J*=14, 7 Hz), 2.51 (1H, br.s), 2.23-1.91 (5H, m), 1.82-1.55 (5H, m), 1.38-1.22 (4H, m). ^{13}C-NMR ($CDCl_3$) δ 175.9 (s), 151.3 (s), 135.8 (t), 116.8 (d), 97.9 (d), 80.6 (d), 79.7 (d), 51.8 (q), 50.2 (s), 39.8 (t), 32.6 (t), 31.9 (t), 28.1 (t), 27.9 (t), 23.9 (t), 23.6 (t), 19.1 (t). Ms *m/z* (EI) 294 (M+), 164, 136. IR (neat, cm^{-1}) 3500, 1720, 1660, 1640, 1230. $[\alpha]_D^{28}$ -10.1° (c= 0.73, $CHCl_3$).

General procedure for deprotection of enol ethers (27a-c).

To a mixture of BF_3-etherate (0.5 ml, 4 mmol) and H_2O (0.5 ml) was added a solution of **27** (0.2 mmol) in MeOH (4 ml) at room temperature, the reaction mixture was heated at 60-70°C for 3-5 h, then diluted with saturated aqueous NaCl (20 ml), and extracted with ethyl acetate. The extracts were washed with saturated aqueous $NaHCO_3$, and dried over $MgSO_4$, then concentrated *in vacuo* to afford an oily residue, which was purified by silica gel column chromatography. The fraction eluted with 40:1-30:1 hexane/ethyl acetate afforded **15a-c** as a colorless oil.

Methyl (*R*)- and (*S*)-1-Methyl-2-oxocyclopentanecarboxylate (24a)

70-85% yield. ^{1}H-NMR ($CDCl_3$) δ 3.71 (3H, s), 2.59-2.24 (3H, m), 2.12-1.78 (3H, m), 1.32 (3H, s); MS *m/z* (EI) 156(M^+), 128, 125, 113, 101, 69, 41; IR (neat, cm^{-1}) 2950, 1735(br), 1720, 1450, 1270, 1150, 1060, 940. (*R*)-**24a** (>99% e.e.) $[\alpha]_D^{22}$ -10.7° (c=1.1, $CHCl_3$), (*S*)-**24a** (>99% e.e.) $[\alpha]_D^{27}$ +10.5° (c= 0.41, $CHCl_3$). lit[6] for (*R*)-**24a** (>96% e.e.) $[\alpha]_D^{23}$ -10.6° (c=1.15, $CHCl_3$).

Methyl (*R*) and (*S*)-1-Nonyl-2-oxocyclopentanecarboxylate (24b)

80-95% yield. ^{1}H-NMR ($CDCl_3$) δ 3.71 (3H, s), 2.61-2.20 (3H, m), 2.01-1.87 (3H, m), 1.25 (16H, s), 0.88 (3H, t, *J*=7 Hz); MS *m/z* (EI) 268 (M^+), 237, 143, 142, 110, 98; IR (neat, cm^{-1}) 2950, 1755, 1720, 1460, 1230, 1160. (*R*)-**24b** (>99% e.e.) $[\alpha]_D^{26}$ +20.5° (c=0.65, $CHCl_3$), (*S*)-**24b** (>99% e.e.) $[\alpha]_D^{28}$ -21.0° (c=0.4, $CHCl_3$). lit[6] for (*R*)-**24b** (>96% e.e.) $[\alpha]_D^{23}$ +20.9° (c=1.13, $CHCl_3$).

Ethyl (*R*) and (*S*)-2-Benzyl-2-methylacetoacetate (25a)

85-90% yield. ^{1}H-NMR ($CDCl_3$) δ 7.28-7.03 (5H, m), 4.19 (2H, q, *J*=7 Hz), 3.29 (1H, d, *J*=14 Hz), 3.04 (1H, d, *J*=14 Hz), 2.17 (3H, s), 1.28 (3H, s), 1.25 (3H, t, *J*=7 Hz); MS *m/z* (EI) 234(M^+), 191, 145, 91, 78; IR (neat, cm^{-1}) 2980, 1720, 1710, 1605, 1500, 1450, 1360, 1270, 1100, 1020, 860, 745, 700. (*R*)-**25a** (>99% e.e.) $[\alpha]_D^{25}$ +62.5° (c=0.42, $CHCl_3$), (*S*)-**25a** (>99% e.e.) $[\alpha]_D^{24}$ -58.5° (c=0.75, $CHCl_3$). lit[6] for (*S*)-**25a** (92% e.e.) $[\alpha]_D^{22}$ -58.2° ($CHCl_3$).

Ethyl (*R*)-2-Allyl-2-methylacetoacetate (25b)

92% yield. ^{1}H-NMR ($CDCl_3$) δ 5.83-5.63 (1H, m), 5.17 (1H, m), 5.0 (1H, m), 4.20 (2H, q, *J*=7 Hz), 2.61 (1H, d, *J*=7 Hz), 2.55 (1H, d, *J*=7 Hz), 2.15 (3H, s), 1.33 (3H, s), 1.26 (3H, t, *J*=7 Hz); MS *m/z* (EI) 184 (M^+), 142, 114, 97, 69, 43; IR (neat, cm^{-1}) 2980, 1740, 1708, 1640, 1450, 1240, 1140, 1100. (*R*)-**15a** (>99% e.e.) $[\alpha]_D^{27}$ +29.3° (c=0.36, $CHCl_3$). lit[6] for (*R*)-**25b** (95% e.e.) $[\alpha]_D^{22}$ -28.2° ($CHCl_3$).

Methyl (*R*) and (*S*)-1-Methyl-2-oxocyclohexanecarboxylate (26a)

85-90% yield. ^{1}H-NMR ($CDCl_3$) δ 3.73 (3H, s), 2.60-2.39 (3H, m), 2.10-1.40 (5H, m), 1.30 (3H, s). Ms *m/z* (EI) 170 (M^+), 142, 127, 110. IR (neat, cm^{-1}) 1720 (br), 1450, 1375, 1300, 1250, 1150, 1180. (*R*)-**26a** (85% e.e.) $[\alpha]_D^{26}$ -91.0° (c=0.43, ethanol), (*S*)-**26a** (95% e.e.) $[\alpha]_D^{25}$ +103.9° (c=1.1, ethanol). lit[6] for (*R*)-**26a** (>99% e.e.) $[\alpha]_D^{25}$ -108° (ethanol).

Methyl (*R*) and (*S*)-1-Benzyl-2-oxocyclohexanecarboxylate (26b)

93% yield. ^{1}H-NMR ($CDCl_3$) δ 7.2-7.0 (5H, m), 3.64 (3H, s), 3.33 (1H, d, *J*=14 Hz), 3.86 (1H, d, *J*=14 Hz), 2.53-2.24 (3H, m), 2.17-1.37 (5H, m). Ms *m/z* (EI) 246 (M^+), 228, 187, 186, 117. IR (neat, cm^{-1}) 1708 (br), 1600, 1500, 1450, 1430. (*R*)-**26b** (>99% e.e.) $[\alpha]_D^{26}$ +110.7° (c=0.45, ethanol), (*S*)-**26b** (>99% e.e.) $[\alpha]_D^{26}$ -110.5° (c=0.42, ethanol). lit[6] for (*S*)-**26b** (>99% e.e.) $[\alpha]_D^{25}$ -111° (ethanol).

Methyl (*R*) and (*S*)-1-Allyl-2-oxocyclohexanecarboxylate (26c)

85-91% yield. ^{1}H-NMR ($CDCl_3$) δ 5.75 (1H, m), 5.06 (1H, br.s), 5.02 (1H, br.s), 3.71 (3H, s), 2.63 (1H, dd, *J*=14, 7 Hz), 2.53-2.43 (3H, m), 2.33 (1H, dd, *J*=14, 8 Hz), 2.14 (1H, m), 1.82-1.57 (3H, m), 1.47 (1H, m). Ms *m/z* (EI) 196 (M^+), 137, 136, 119. IR (neat, cm^{-1}) 1710 (br), 1640, 1435, 1270, 1150, 1000. (*R*)-**15b** (>99% e.e.) $[\alpha]_D^{25}$ +133.8° (c 1.12, ethanol), (*S*)-**26c** (96% e.e.) $[\alpha]_D^{27}$ -128.5° (c=1.1, ethanol). lit[6] for (*S*)-**26c** (76% e.e.) $[\alpha]_D^{25}$ -102° (ethanol).

Reaction of 18 under basic conditions.

(I) Treatment of **18** (102 mg, 0.4 mmol) with LDA in accordance with method A at -78°C without HMPA. After 1h, the reaction mixture was diluted with aqueous saturated NH_4Cl, and extracted with ethyl acetate. The extract was washed with brine, dried over $MgSO_4$, and concentrated *in vacuo*. The crude product was purified by flash column chromatography on silica gel.

Methyl (1*R,S*)-2-[(1*S,2S*)-2-Hydroxycyclohexan-1-yl]oxy-2-cyclohexen-1-carboxylate (28)

Compound **28** was obtained as a 1 to 2 diastereomeric mixture at C1 in 30-59% yield. Colorless oil. ^{1}H-NMR ($CDCl_3$) δ 4.91 (1H, t, *J*=4 Hz), 3.79 (1H, m), 3.78 (1H, br. s), 3.72 (3H, s), 3.50 (1H, m), 3.16 (1H, t, *J*=5 Hz), 2.13-1.70 (7H, m), 1.57-1.24 (7H, m); ^{13}C-NMR ($CDCl_3$) δ 175.1 (s), 150.2 (s), 97.8 (d), 81.1 (d), 73.8 (d), 52.2 (q), 44.6 (d), 32.0 (t), 29.9 (t), 26.9 (t), 24.3 (t), 23.9 (t), 23.2 (t), 20.4 (t); MS *m/z* (EI) 254 (M^+), 211, 156, 153, 124; IR (neat, cm^{-1}) 3500, 2900, 1720, 1660, 1440, 1170.

Methyl 2-[(1*S,2S*)-2-Hydroxycyclohexan-1-yl]oxy-1-cyclohexen-1-carboxylate (29)

Colorless oil, 21-32% yield. ^{1}H-NMR ($CDCl_3$) δ 5.37 (1H, br. s), 3.72 (3H, s), 3.64-3.57 (2H, m), 2.55-2.38 (2H, m), 2.32-1.97 (4H, m), 1.77-1.27 (10H, m); ^{13}C-NMR ($CDCl_3$) δ 169.7 (s), 164.2 (s), 109.4 (s), 84.5 (d), 73.9 (d), 52.0 (q), 32.3 (t), 32.1 (t), 27.5 (t), 25.2 (t), 24.5 (t), 24.0 (t), 22.4 (t), 22.0 (t); MS *m/z* (EI) 254 (M^+), 222, 156, 153, 124, 96; IR (neat, cm^{-1}) 3400, 2900, 1680, 1610, 1430, 1050; $[\alpha]_D^{26}$ +169.6° (c=0.57, $CHCl_3$).

(II) Treatment of **18** (102 mg, 0.4 mmol) with LDA in accordance with method A at -78°C. After 1h, the reaction mixture was diluted with aqueous saturated NH_4Cl, and extracted with ethyl acetate. The extract was washed with brine, dried over $MgSO_4$, and concentrated *in vacuo*. The crude product was purified by flash column chromatography on silica gel. Compounds **28** and **29** were obtained in 30 and 21% yields, respectively.

(3*S*,8*S*)-(11*R,S*)-2,9-Dioxa-10-oxotricyclo[9,4,0,0^{3,8}]pentadec-1(15)-ene (30)

Compound **28** was obtained as a 3 to 4 diastereomeric mixture at C11 in 20% yield.Colorless oil. ^{1}H-NMR ($CDCl_3$) δ 5.45 (1H, t, *J*=4 Hz), 4.37 (1H, m), 3.55 (1H, m), 3.35 (1H, d, *J*=5 Hz), 2.31 (1H, m), 2.21-2.02 (4H, m), 1.84-1.65 (4H, m), 1.59-1.20 (5H, m); ^{13}C-NMR ($CDCl_3$) δ 172.2 (s), 146.3 (s), 113.7 (d), 81.8 (d), 81.4 (d), 41.3 (d), 31.8 (t), 31.3 (t), 25.0 (t), 23.6 (t), 23.4 (t), 23.4 (t), 18.5 (t); MS *m/z* (EI) 222 (M^+), 141, 124, 123, 96, 79, 68; IR (neat, cm^{-1}) 2920, 1723, 1663, 1455, 1378, 1222, 1160, 1020.

(3*S*,8*S*)-2,9-Dioxa-10-oxotricyclo[9,4,0,0^{3,8}]pentadec-1(11)-ene (31)

Colorless needles, 9% yield. mp 96°C. ^{1}H-NMR ($CDCl_3$) δ 4.26 (1H, m), 4.12 (1H, m), 2.59 (1H, m), 2.33-2.18 (5H, m), 1.83-1.19 (10H, m). ^{13}C-NMR ($CDCl_3$) δ 169.1 (s), 161.3 (s), 101.9 (s), 82.1 (d), 76.8 (d), 32.1 (t), 31.2 (t), 31.0 (t), 29.7 (t), 27.0 (t), 23.1 (t), 23.1 (t), 22.4 (t). Ms *m/z* (EI) 222 (M^+) 141, 125, 123. IR (Nujol, cm^{-1}) 1690, 1630, 1300, 1220. $[\alpha]_D^{27}$ -199.2° (c=0.25, $CHCl_3$). HRms *m/z* 222.1268 (M^+, calcd for $C_{13}H_{18}O_3$ 222.1256).

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