

PREPARATION OF OPTICALLY ACTIVE TRICYCLIC 1,4-DIOXEPIN-5-ONE DERIVATIVES AND ITS APPLICATION TO ASYMMETRIC ALKYLATION

Keisuke Kato, Hiroshi Suemune, and Kiyoshi Sakai*

Faculty of Pharmaceutical Sciences, Kyushu University, Fukuoka 812, Japan

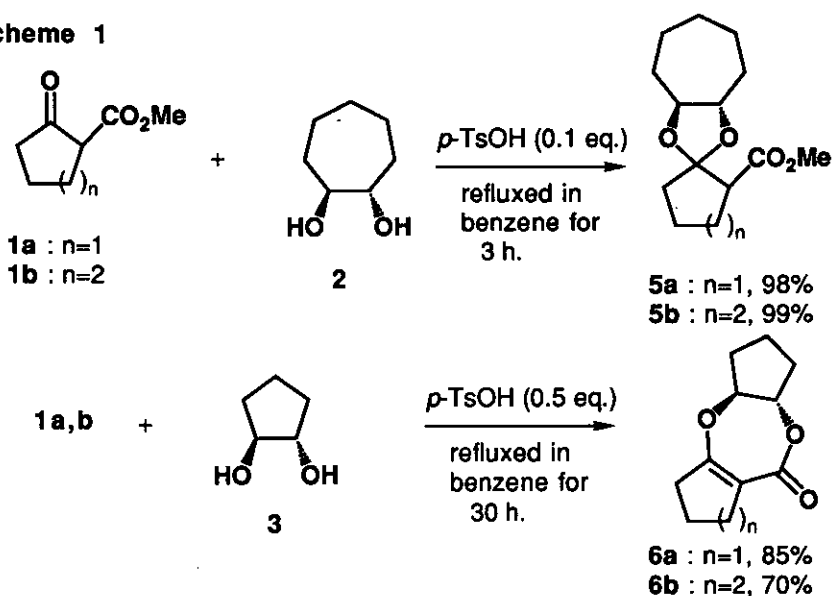
Abstract- Chiral tricyclic α,β -unsaturated lactones (**6a,b** and **8a,b**) were easily synthesized from chiral cyclic diols (**2-4**) and cyclic β -keto esters (**1a,b**). Alkylation of **8b** proceeded in a highly diastereoselective manner to afford a quaternary carbon.

Recently, we have found optically active cycloalkane-1,2-diols¹ with C_2 -symmetry to be effective as a chiral auxiliary for asymmetric synthesis, that is to say, these chiral diols have been utilized as a chiral ester and as an acetal for asymmetric conjugate addition^{2a,b} and alkylation.^{2c,d} In this report, we wish to describe a new aspect in the utilization of these diols as 7-membered γ -oxalactone (1,4-dioxepin-5-one) derivatives.

Preparation of chiral tricyclic γ -oxa- α,β -unsaturated lactones

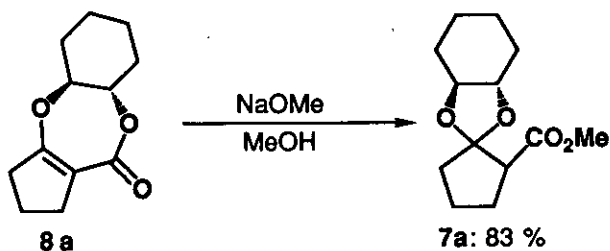
Reaction of 5- and 6-membered cyclic β -keto esters (**1a,b**) with (*S,S*)-cycloheptane-1,2-diol (**2**) in the presence of *p*-TsOH (0.1 eq.) under azeotropic condition for 3 h afforded the usual acetals (**5a,b**) in quantitative yields as a diastereomeric mixture at C(1). On the other hand, reaction of **1a,b** with (*S,S*)-cyclopentane-1,2-diol (**3**) in the presence of *p*-TsOH (0.5 eq.) under the same conditions for 30 h afforded exclusively tricyclic α,β -unsaturated lactones (**6a,b**) in 85 and 70% yields, respectively (Scheme 1).³ Reaction of **1a,b** with (*S,S*)-cyclohexane-1,2-diol (**4**) resulted in a similar product-selectivity, that is to say, reaction of **1a** and **4** under the same reaction conditions using 0.1 eq. of *p*-TsOH resulted in recovery of the substrate (75%). The same reaction using 0.5 eq. of *p*-TsOH afforded **8a** as the sole product in 84% yield (Entry 1 in Table 1). Furthermore, reaction of **1b** and **4** in the presence of *p*-TsOH (0.1 eq.) for 10 h afforded the acetal (**7b**) in 80% yield (Entry 2). This reaction mixture, refluxed for additional 60 h with occasional addition of *p*-TsOH (total

Scheme 1

Table 1 Reaction of (*S,S*)-cyclohexanediol (**4**) with cyclic β -keto esters (**1a, b**)

1a, b +		4		Products	
Entry	Substrate	Conditions (eq. of p -TsOH, room temp.)			
1	1a ($n=1$)	0.5 eq., 53 h	7a : ---	8a : 84%	
2	1b ($n=2$)	0.1 eq., 10 h	7b : 80%	8b : ---	
3	1b ($n=2$)	0.5 eq., 70 h	7b : 5%	8b : 51%	

Scheme 2

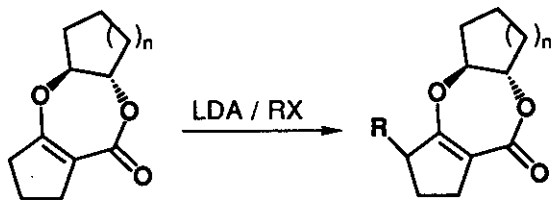


amount: 0.5 eq.), gave the tricyclic lactone (**8b**) in 51% yield with a small amount of **7b** (Entry 3). The structure of lactones (**6**, **8**) was determined by spectroscopic analyses. For example, the mass spectrum of **8a** showed a molecular ion peak at m/z 208. The ir absorption (1670 and 1615 cm^{-1}) suggested the existence of α,β -unsaturated carbonyl group. The ^{13}C -nmr spectrum indicated the presence of ester carbonyl (δ 166.4 (s)) and two olefinic carbons (δ 166.3 (s), 101.4 (s)). The ^1H -nmr spectrum showed C(3)-H at δ 4.13 and C(8)-H at δ 4.25. In addition, chemical conversion from **8a** to the acetal (**7a**, 83%) by treatment with NaOMe in MeOH at room temperature also supported the structure of **8a** (Scheme 2). The above results of product-selectivity in Scheme 1 and Table 1 might be rationalized based on thermodynamical stability of products.

Asymmetric alkylation of chiral tricyclic α,β -unsaturated lactones^{2d}

Alkylation of **6a** and **8a** with RX (5 eq.)/LDA (5 eq.) in THF at -78 to -40°C afforded γ -alkylated products (**9**) and (**10**), respectively (Table 2). Each reaction resulted in low diastereoselectivity (3:1 to 3:2), but it is noteworthy that the alkylation took place in a highly regioselective manner at γ -position of lactone carbonyl, and that no α -alkylated products could be detected. Methylation of **6b** under the same reaction conditions gave γ -alkylated product (**11**) and α -alkylated product (**12**) in 59% (diastereomeric ratio= 3:1) and 26% (1:1) yields, respectively (Scheme 3). Diastereomeric ratio of (**9**-**12**) was estimated by 270 MHz ^1H -nmr spectra.⁴

Table 2 Regioselective alkylation of **6a** and **8a**

				
6a ($n=1$), 8a ($n=2$)	9 ($n=1$), 10 ($n=2$)	Products	RX	Yield(%) D.s.
		9a	MeI	65 3:1
		9b	BnBr	67 3:2
		10a	MeI	70 3:1
		10b	BnBr	63 3:2

Scheme 3

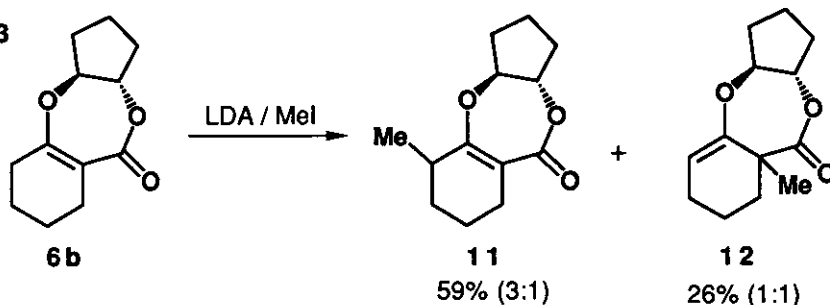
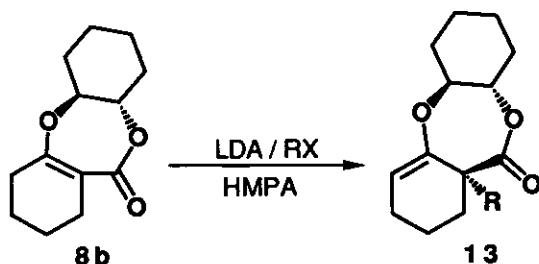
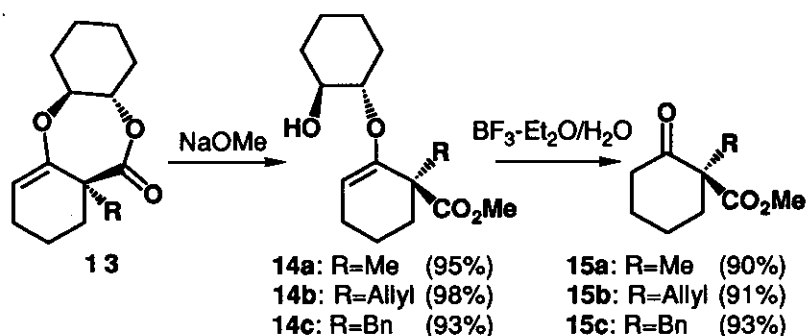
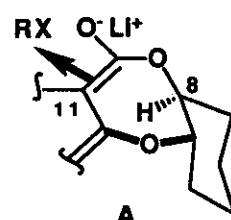


Table 3 Asymmetric alkylation of **8b**

Products	RX	Yield (%)	D.e. (%)
13a	MeI	86	94
13b	Allyl-I	51	94
13c	BnBr	52	>99

Scheme 4**Figure 1**

On the other hand, alkylation of **8b** showed quite different behavior from the cases of **6a,b** and **8a** to afford α -alkylated products (**13a-c**) in a highly regio- and diastereoselective manner (94->99% d.e.) as shown in Table 3. The absolute configuration of products (**13a-c**) was determined by conversion to the corresponding keto esters (**15a-c**)⁵ via a two-step sequence [i) NaOMe / MeOH; ii) BF₃·Et₂O/H₂O] (Scheme 4). Diastereomeric excess of **13a-c** was determined by the examination of 270 MHz ¹H-nmr spectroscopy of keto esters (**15a-c**) using a chiral shift reagent ((+)-Eu(hfc)₃).⁵ The reaction mechanism is tentatively proposed as follows. The reaction presumably starts with abstraction of allylic hydrogen to form a dienolate anion **A**. Dreiding stereomodels suggest that the conformation of a 7-membered ring as depicted in Figure 1 defined by (*S,S*)-cyclocyclohexane-1,2-diol moiety might be favorable because of little ring strain. The axial hydrogen atom at C(8) shielded *si*-face at C(11), so alkylation might occur predominantly from *re*-face.

EXPERIMENTAL

General methods. Ir spectra were measured with a JASCO A-202 spectrometer, and ¹H nmr and ¹³C 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) was used. Thin layer chromatography (tlc) was performed on Silica gel F₂₅₄ plates (Merck).

General procedure for preparation of acetals (5a,b and 7b).

To a solution of 2-methoxycarbonylcyclopentanone (or cyclohexanone) (1a or 1b) (3 mmol) and (*S,S*)-cycloheptane-1,2-diol (or cyclohexane-1,2-diol) (2 or 4) (2 mmol) in benzene (30 ml) was added *p*-TsOH·H₂O (38 mg, 0.2 mmol), and the resulting mixture was refluxed with azeotropic removal of water for 3-10 h, and then quenched with NaHCO₃ (504 mg, 6 mmol) and aqueous saturated NaHCO₃ (20 ml) at 0°C, and extracted with ethyl acetate. The extracts were dried over MgSO₄, 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 5a,b and 7b as a colorless oil.

Methyl 2,2-[(*S,S*)-Cycloheptane-1,2-dioxy]cyclopentanecarboxylate (5a)

Compound (5a) was obtained as a 3 to 4 diastereomeric mixture at C(1) in 98% yield. ¹H-Nmr (CDCl₃) 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.

Methyl 2,2-[(*S,S*)-Cycloheptane-1,2-dioxy]cyclohexanecarboxylate (5b)

Compound (5b) was obtained as a 2 to 1 diastereomeric mixture at C(1) in 99% yield. ¹H-Nmr (CDCl₃) 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) 1740, 1440.

Methyl 2,2-[(*S,S*)-Cyclohexane-1,2-dioxy]cyclohexanecarboxylate (7b)

Compound (7b) was obtained as a 1 to 1 diastereomeric mixture at C(1) in 80% yield. ¹H-Nmr (CDCl₃) 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) 1725, 1430, 1100.

Methyl 2,2-[(*S,S*)-Cyclohexane-1,2-dioxy]cyclopentanecarboxylate (7a)

To a solution of NaOMe prepared from Na (460 mg, 20 mmol) in MeOH (5 ml) was added lactone (8a) (104 mg, 0.5 mmol) under an Ar atmosphere. The mixture was stirred at room temperature for 48 h, then diluted with saturated aqueous NH₄Cl (20 ml), and extracted with ethyl acetate. The extracts were dried over MgSO₄, 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 7a (99.5 mg, 83%) as a 1 to 1 diastereomeric mixture at C(1). Colorless oil. ¹H-Nmr (CDCl₃) 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.

General procedure for preparation of lactones (6a,b and 8a,b).

To a solution of **1a** or **1b** (3 mmol) and **3** or **4** (2 mmol) in benzene (30 ml) was added *p*-TsOH H_2O (38 mg, 0.2 mmol), and the resulting mixture was refluxed with azeotropic removal of water for 6-18 h. After four times addition of *p*-TsOH H_2O (38 mg $\times$ 4) with an interval of 6-13 h under above conditions, the reaction was quenched with $NaHCO_3$ (504 mg, 6 mmol) and aqueous saturated $NaHCO_3$ (20 ml) at 0°C, 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(10:1) afforded lactones (6a,b and 8a,b).

(3S,7S)-2,8-Dioxa-9-oxotricyclo[8,3,0,0^{3,7}]tridec-1(10)-ene (6a)

Compound (**6a**) was obtained as a colorless oil in 85% yield. 1H -Nmr ($CDCl_3$) δ 4.62 (1H, m), 4.48 (1H, m), 2.83 (1H, m), 2.75-2.63 (3H, m), 2.38-2.26 (2H, m), 1.97-1.81 (6H, m). ^{13}C -Nmr ($CDCl_3$) δ 166.5 (s), 166.5 (s), 103.5 (s), 87.1 (d), 80.9 (d), 35.4 (t), 33.2 (t), 30.5 (t), 30.2 (t), 20.8 (t), 19.5 (t). Ms m/z (EI) 194 (M^+) 127, 111, 109. Ir (neat, cm^{-1}) 1680, 1600, 1400, 1360, 1120. $[\alpha]_D^{22}$ -289.7° (c 0.53, $CHCl_3$). HRms m/z 194.0932 (M^+ , calcd for $C_{11}H_{14}O_3$ 194.0943).

(3S,7S)-2,8-Dioxa-9-oxotricyclo[8,4,0,0^{3,7}]tetradec-1(10)-ene (6b)

Compound (**6b**) was obtained as a colorless oil in 70% yield. 1H -Nmr ($CDCl_3$) δ 4.57 (1H, m), 4.41 (1H, m), 2.68 (1H, m), 2.33-2.18 (5H, m), 1.94-1.78 (3H, m), 1.73-1.57 (5H, m). ^{13}C -Nmr ($CDCl_3$) δ 168.9 (s), 161.9 (s), 102.4 (s), 85.9 (d), 80.6 (d), 30.6 (t), 30.4 (t), 30.1 (t), 28.3 (t), 22.8 (t), 22.1 (t), 21.2 (t). Ms m/z (EI) 208 (M^+) 141, 125, 123. Ir (neat, cm^{-1}) 1680, 1600, 1360, 1280, 1140. $[\alpha]_D^{19}$ -200.7° (c 1.1, $CHCl_3$). HRms m/z 208.1113 (M^+ , calcd for $C_{12}H_{16}O_3$ 208.1099).

(3S,8S)-2,9-Dioxa-10-oxotricyclo[9,3,0,0^{3,8}]tetradeca-1(11)-ene (8a)

Compound (**8a**) was obtained as colorless needles in 84% yield. mp 87°C. 1H -Nmr ($CDCl_3$) δ 4.25 (1H, dt, $J=11, 7$ Hz), 4.13 (1H, dt, $J=11, 7$ Hz), 2.83-2.54 (4H, m), 2.37-2.22 (2H, m), 1.93-1.75 (4H, m), 1.58-1.24 (4H, m). ^{13}C -Nmr ($CDCl_3$) δ 166.4 (s), 166.3 (s), 101.4 (s), 82.1 (d), 76.8 (d), 35.9 (t), 32.1 (t), 31.6 (t), 31.2 (t), 23.0 (t), 22.9 (t), 19.2 (t). Ms m/z (EI) 208 (M^+), 111. Ir (Nujol, cm^{-1}) 1670, 1615, 1405, 1120. $[\alpha]_D^{25}$ -219.1° (c 0.59, $CHCl_3$). HRms m/z 208.1087 (M^+ , calcd for $C_{12}H_{16}O_3$ 208.1099).

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

Compound (**8b**) was obtained as colorless needles in 51% yield. mp 96°C. 1H -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. $[\alpha]_{\text{D}}^{27}$ -199.2° (c 0.25, CHCl_3). HRms m/z 222.1268 (M^+ , calcd for $\text{C}_{13}\text{H}_{18}\text{O}_3$ 222.1256).

General procedure for asymmetric alkylation of lactones (6a,b and 8a,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 mmol) in THF (8 ml) at -78°C under an Ar atmosphere. After 10 min, HMPA (403 mg, 2.25 mmol) in THF (2 ml) and 6 or 8 (0.45 mmol) in THF (1ml) was added. The whole was stirred for 10 min, then alkyl halide (2.25 mmol) in THF (0.5 ml) was added. After being stirred for 3-5 h at -78°C and for additional 12-24 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 (10:1 hexane/ethyl acetate).

(3*S*,7*S*,13*RS*)-13-Methyl-2,8-dioxa-9-oxotricyclo[8,3,0,0^{3,7}]tridec-1(10)-ene (9a)

Compound (9a) was obtained as a 3 to 1 diastereomeric mixture at C(13) in 65% yield. Colorless oil. ^1H -Nmr (CDCl_3) δ 4.58 (1H, m), 4.43 (1H, m), 2.93-2.78 (2H, m), 2.64 (1H, m), 2.40-2.25 (2H, m), 2.15-1.83 (5H, m), 1.48 (1H, m), 1.14, 1.12 (total 3H, d each, $J=7$ Hz, ratio=3:1). ^{13}C -Nmr (CDCl_3) δ 169.5 (s), 166.7 (s), 102.4 (s), 87.2 (d), 80.9 (d), 47.1 (d), 30.7 (t), 30.2 (t), 30.1 (t), 28.3 (t), 20.8 (t), 18.0 (q). Ms m/z (EI) 208 (M^+), 151, 141, 123. Ir (neat, cm^{-1}) 1680, 1600, 1400, 1350, 1117.

(3*S*,7*S*,13*RS*)-13-Benzyl-2,8-dioxa-9-oxotricyclo[8,3,0,0^{3,7}]tridec-1(10)-ene (9b)

Compound (9b) was obtained as a 3 to 2 diastereomeric mixture at C(13) in 67% yield. Colorless oil. ^1H -Nmr (CDCl_3) δ 7.33-7.15 (5H, m), 4.56 (1H, m), 4.44 (1H, m), 3.17-2.97 (2H, m), 2.82-2.48 (3H, m), 2.37-2.25 (2H, m), 1.97-1.83 (5H, m), 1.68 (1H, m). ^{13}C -Nmr (CDCl_3) δ 167.8 (s), 166.5 (s), 139.4 (s), 129.0 (d), 128.4 (d), 126.3 (d), 103.7 (s), 87.1 (d), 80.8 (d), 48.6 (d), 38.3 (t), 30.7 (t), 30.2 (t), 25.9 (t), 25.1 (t), 20.8 (t). Ms m/z (EI) 284 (M^+), 201, 111, 109. Ir (neat, cm^{-1}) 1690, 1618, 1410, 1375, 1140.

(3*S*,8*S*,14*RS*)-14-Methyl-2,9-dioxa-10-oxotricyclo[9,3,0,0^{3,8}]tetradec-1(11)-ene (10a)

Compound (10a) was obtained as a 3 to 1 diastereomeric mixture at C(14) in 70% yield by the similar manner to that described for the general procedure without HMPA. ^1H -Nmr (CDCl_3) δ 4.24 (1H, m), 4.14 (1H, m), 2.87-2.72 (2H, m), 2.55 (1H, m), 2.37-2.25 (2H, m), 2.06 (1H, m), 1.83-1.75 (2H, m), 1.57-1.19 (5H, m), 1.12, 1.10 (total 3H, d each, $J=7$ Hz, ratio=3:1). ^{13}C -Nmr (CDCl_3) δ 169.2 (s), 166.5 (s), 100.5 (s),

82.3 (d), 76.7 (d), 42.1 (d), 31.5 (t), 31.2 (t), 29.5 (t), 28.1 (t), 23.1 (t), 22.8 (t), 18.0 (q). Ms m/z (EI) 222 (M^+) 141, 125. Ir (neat, cm^{-1}) 1670, 1620, 1410, 1130.

(3S,8S,14RS)-14-Benzyl-2,9-dioxa-10-oxotricyclo[9,3,0,0^{3,8}]tetradec-1(11)-ene (10b)

Compound (10b) was obtained as a 3 to 2 diastereomeric mixture at C(14) in 63% yield by the similar manner to that described for the general procedure without HMPA. Colorless oil. $^1\text{H-Nmr}$ (CDCl_3) δ 7.33-7.14 (5H, m), 4.31-4.19 (2H, m), 3.12-2.94 (2H, m), 2.70-2.44 (3H, m), 2.38-2.21 (2H, m), 1.98-1.75 (3H, m), 1.64-1.24 (5H, m). $^{13}\text{C-Nmr}$ (CDCl_3) δ 167.2 (s), 166.2 (s), 139.5 (s), 129.0 (d), 128.3 (d), 126.2 (d), 101.6 (s), 82.3 (d), 76.8 (d), 48.6 (d), 38.4 (t), 31.5 (t), 31.2 (t), 29.4 (t), 25.8 (t), 23.1 (t), 22.8 (t). Ms m/z (EI) 298 (M^+), 201, 109. Ir (neat, cm^{-1}) 1680, 1620, 1415, 1315, 1120.

(3S,7S,14RS)-14-Methyl-2,8-dioxa-9-oxotricyclo[8,4,0,0^{3,7}]tetradec-1(10)-ene (11)

Compound (11) was obtained as a 3 to 1 diastereomeric mixture at C(14) in 59% yield. Colorless oil. $^1\text{H-Nmr}$ (CDCl_3) δ 4.55 (1H, m), 4.41 (1H, m), 2.70 (1H, m), 2.52-2.19 (4H, m), 1.94-1.73 (5H, m), 1.69-1.39 (3H, m), 1.20, 1.13 (total 3H, d each, $J=7$ Hz, ratio=3:1). $^{13}\text{C-Nmr}$ (CDCl_3) δ 169.4 (s), 165.6 (s), 102.1 (s), 85.8 (d), 80.7 (d), 34.7 (d), 30.4 (t), 30.1 (t), 29.3 (t), 29.0 (t), 21.2 (t), 19.9 (t), 20.1 (q). Ms m/z (EI) 222 (M^+), 139, 137. Ir (neat, cm^{-1}) 1680, 1600, 1250, 1140.

(3S,7S,10RS)-10-Methyl-2,8-dioxa-9-oxotricyclo[8,4,0,0^{3,7}]tetradec-1(14)-ene (12)

Compound (12) was obtained as a 1 to 1 diastereomeric mixture at C(10) in 26% yield. Colorless oil. $^1\text{H-Nmr}$ (CDCl_3) δ 5.55, 5.42 (total 1H, t each, $J=4$ Hz, ratio=1:1), 4.90 (1H, m), 4.51, 3.83 (total 1H, m each, ratio=1:1), 2.58 (1H, m), 2.24-2.04 (5H, m), 1.84-1.55 (6H, m), 1.52, 1.48 (total 3H, s each, ratio=1:1). Ms m/z (EI) 222 (M^+), 135, 111. Ir (neat, cm^{-1}) 1725, 1665, 1250, 1220, 1190.

(3S,8S,11S)-11-Methyl-2,9-dioxa-10-oxotricyclo[9,4,0,0^{3,8}]pentadec-1(15)-ene (13a)

Colorless needles (86% yield). mp 95°C. 94% d.e. at C(11). $^1\text{H-Nmr}$ (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). $^{13}\text{C-Nmr}$ (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 $\text{C}_{14}\text{H}_{20}\text{O}_3$ 236.1412).

(3S,8S,11R)-11-Allyl-2,9-dioxa-10-oxotricyclo[9,4,0,0^{3,8}]pentadec-1(15)-ene (13b)

Colorless oil (51% yield). 94% d.e. at C(11). $^1\text{H-Nmr}$ (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. $[\alpha]_{\text{D}}^{30}$ -0.8° (c 0.50, CHCl_3). HRms m/z 262.1553 (M^+ , calcd for $\text{C}_{16}\text{H}_{22}\text{O}_3$ 262.1569).

(3S,8S,11R)-11-Benzyl-2,9-dioxo-10-oxotricyclo[9,4,0,0^{3,8}]pentadec-1(15)-ene (13c)

Colorless oil (52% yield). >99% d.e. at C(11). ^1H -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. $[\alpha]_{\text{D}}^{27}$ $+17.6^\circ$ (c 0.76, CHCl_3). HRms m/z 312.1711 (M^+ , calcd for $\text{C}_{20}\text{H}_{24}\text{O}_3$ 312.1725).

Enol ethers (14a-c)

Compounds (14a-c) were obtained as a colorless oil by a similar manner to that described for the preparation of 6a.

14a: 95% yield. ^1H -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. $[\alpha]_{\text{D}}^{24}$ $+11.7^\circ$ (c 0.29, CHCl_3).

14b: 98% yield. ^1H -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. $[\alpha]_{\text{D}}^{28}$ -10.1° (c 0.73, CHCl_3).

14c: 93% yield. ^1H -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. $[\alpha]_D^{26} -4.7^\circ$ (c 0.45, CHCl_3).

General Procedure for deprotection of enol ethers (14a-c).

To a mixture of BF_3 -etherate (0.5 ml, 4 mmol) and H_2O (0.5 ml) was added a solution of **14** (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 hexane/ethyl acetate (40:1) afforded **15a-c** as a colorless oil.

Methyl (S)-1-Methyl-2-oxocyclohexanecarboxylate (15a)

90% yield. 94% e.e. $^1\text{H-Nmr}$ (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. $[\alpha]_D^{25} +104.0^\circ$ (c 1.19, ethanol). lit.,⁵ for (**R**)-**15a** (>99% e.e.) $[\alpha]_D^{25} -108^\circ$ (ethanol).

Methyl (R)-1-Allyl-2-oxocyclohexanecarboxylate (15b)

91% yield. 94% e.e. $^1\text{H-Nmr}$ (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), 2.07-1.97 (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. $[\alpha]_D^{25} +127.3^\circ$ (c 1.12, ethanol). lit.,⁵ for (**S**)-**15b** (76% e.e.) $[\alpha]_D^{25} -102^\circ$ (ethanol).

Methyl (R)-1-Benzyl-2-oxocyclohexanecarboxylate (15c)

93% yield. >99% e.e. $^1\text{H-Nmr}$ (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. $[\alpha]_D^{26} +109.3^\circ$ (c 0.45, ethanol). lit.,⁵ for (**S**)-**15c** (>99% e.e.) $[\alpha]_D^{25} -111^\circ$ (ethanol).

This paper is dedicated to Prof. Alan R. Katritzky on the occasion of his 65th birthday.

REFERENCES AND NOTES

- (a) Chiral diols were prepared by enzymatic procedure. See Z.-F. Xie, H. Suemune, and K. Sakai, *J. Chem. Soc., Chem. Commun.*, **1987**, 838. (b) Z.-F. Xie, H. Suemune, I. Nakamura, and K. Sakai,

- Chem. Pharm. Bull., **1987**, 35, 4454. (c) Z.-F. Xie, H. Suemune, and K. Sakai, J. Chem. Soc., Chem. Commun., **1988**, 966.
2. (a) C.-L. Fang, T. Ogawa, H. Suemune, and K. Sakai, Tetrahedron: Asymmetry, **1991**, 2, 389.
(b) C.-L. Fang, H. Suemune, and K. Sakai, J. Org. Chem., **1992**, 57, 4300. (c) K. Kato, H. Suemune, and K. Sakai, Tetrahedron Lett., **1992**, 33, 247. (d) K. Kato, H. Suemune, and K. Sakai, Tetrahedron Lett., **1992**, 33, 3482.
3. Reaction of **1a,b** with **2** in the presence of 0.5 eq. of *p*-TsOH for 30 h afforded **5a,b** in 40-45% yields, but corresponding lactones were not obtained. That of **1a,b** with **3** in the presence of 0.1 eq. of *p*-TsOH for 10 h afforded a small amount of **6a,b** in 10-15% yields.
4. Absolute configuration of products (**9-12**) was not determined.
5. K. Tomioka, K. Ando, Y. Takemasa, and K. Koga, J. Am. Chem. Soc., **1984**, 106, 2718.

Received, 23rd July, 1993