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

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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-diols[1] 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

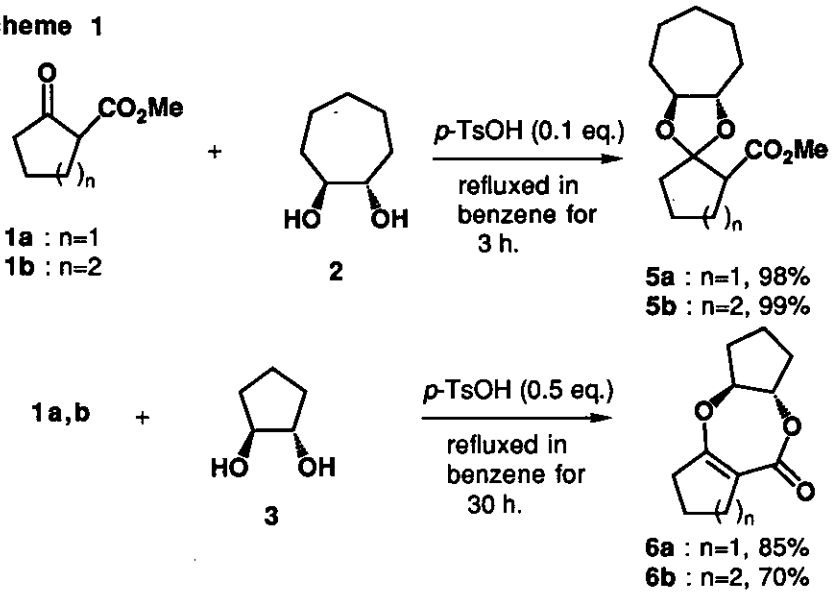
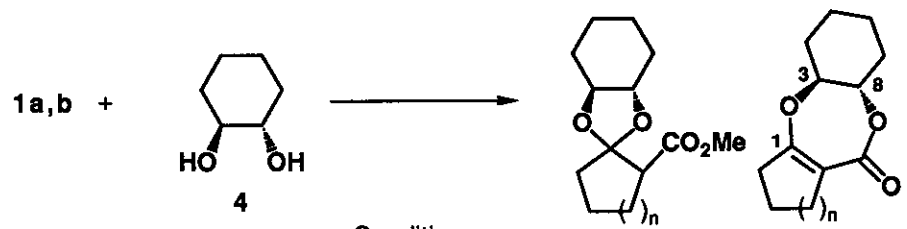
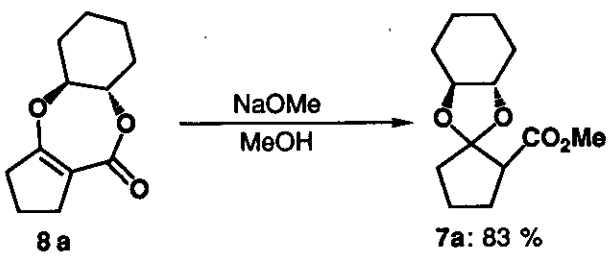


Table 1 Reaction of (S,S)-cyclohexanediol (**4**) with cyclic β-keto esters (**1a,b**)



Entry	Substrate	Conditions (eq. of *p*-TsOH, room temp.)	Products	
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

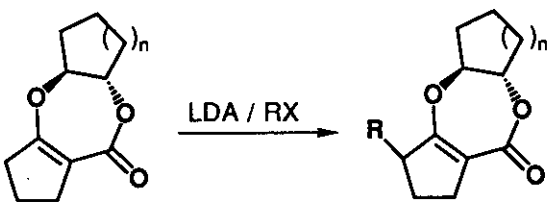


amount: 0.5 eq.), gave the tricyclic lactone (**8b**) in 51% yield with a small amount of **7b** (Entry 3). The structure of lactones (**6, 8**) was determined by spectroscopic analyses. For example, the mass spectrum of **8a** showed a molecular ion peak at m/z 208. The ir absorption (1670 and 1615 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 ^{1}H-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 ^{1}H-nmr spectra.[4]

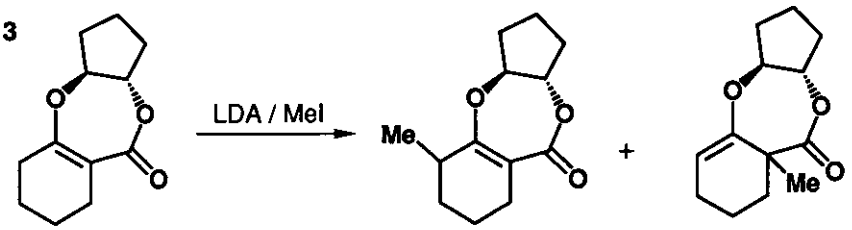
Table 2 Regioselective alkylation of **6a** and **8a**



6a (n=1), **8a** (n=2) **9** (n=1), **10** (n=2)

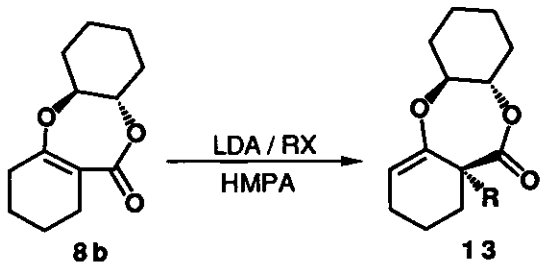
Products	RX	Yield(%)	D.s.
9a	MeI	65	3:1
9b	BnBr	67	3:2
10a	MeI	70	3:1
10b	BnBr	63	3:2

Scheme 3



6b **11** 59% (3:1) **12** 26% (1:1)

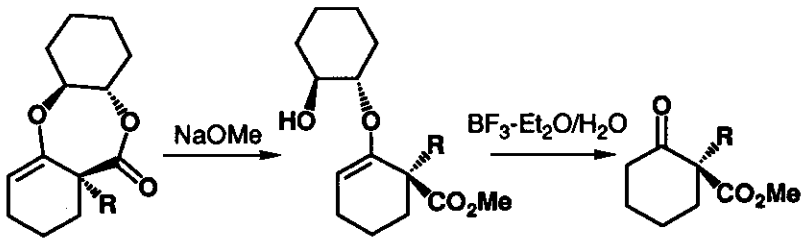
Table 3 Asymmetric alkylation of **8b**



8b **13**

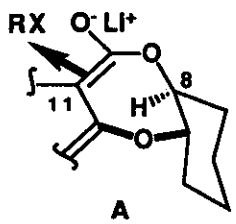
Products	RX	Yield (%)	D.e. (%)
13a	MeI	86	94
13b	Allyl-I	51	94
13c	BnBr	52	>99

Scheme 4



13 **14a**: R=Me (95%) **15a**: R=Me (90%)
14b: R=Allyl (98%) **15b**: R=Allyl (91%)
14c: R=Bn (93%) **15c**: R=Bn (93%)

Figure 1



A

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) BF_3-Et_2O/H_2O] (Scheme 4). Diastereomeric excess of **13a-c** was determined by the examination of 270 MHz ^{1}H-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 ^{1}H nmr 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) was used. Thin layer chromatography (tlc) was performed on Silica gel F_{254} 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-H_2O (38 mg, 0.2 mmol), and the resultig mixture was refluxed with azeotropic removal of water for 3-10 h, and then 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 (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. ^{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.

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.^{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}) 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.^{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}) 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 dilluted 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 **7a** (99.5 mg, 83%) as a 1 to 1 diastereomeric mixture at C(1). Colorless oil. ^{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.

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 resultig mixture was refluxed with azeotropic removal of water for 6-18 h. After four times addition of p-TsOH H_2O (38 mg x 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. ^{1}H-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. ^{1}H-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. ^{1}H-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. ^{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).

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 mol) 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).*

(3S,7S,13RS)-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. ^{1}H-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.

(3S,7S,13RS)-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. ^{1}H-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.

(3S,8S,14RS)-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. ^{1}H-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}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}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}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}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}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}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).

(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}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).

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

Colorless oil (52% yield). >99% d.e. at C(11). ^{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).

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. ^{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, $CHCl_3$).

14b: 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, $CHCl_3$).

14c: 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, $CHCl_3$).

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}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° (c 1.19, ethanol). lit.,[5] for (R)-**15a** (>99% e.e.) $[\alpha]_D^{25}$ -108° (ethanol).

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

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

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

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

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

REFERENCES AND NOTES

1. (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.

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