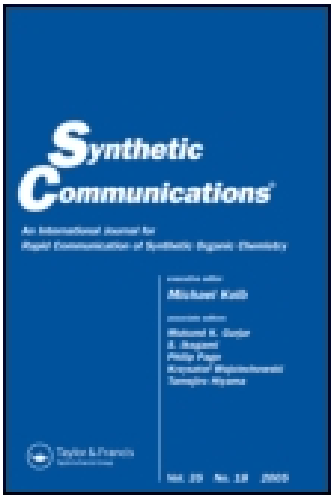

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Diastereoselective Synthesis of Cyclic Ethers by Radical Cyclization at β-Position of β-Alkoxyacrylates

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DIASTEREOSELECTIVE SYNTHESIS OF CYCLIC ETHERS BY RADICAL CYCLIZATION AT β-POSITION OF β-ALKOXYACRYLATES

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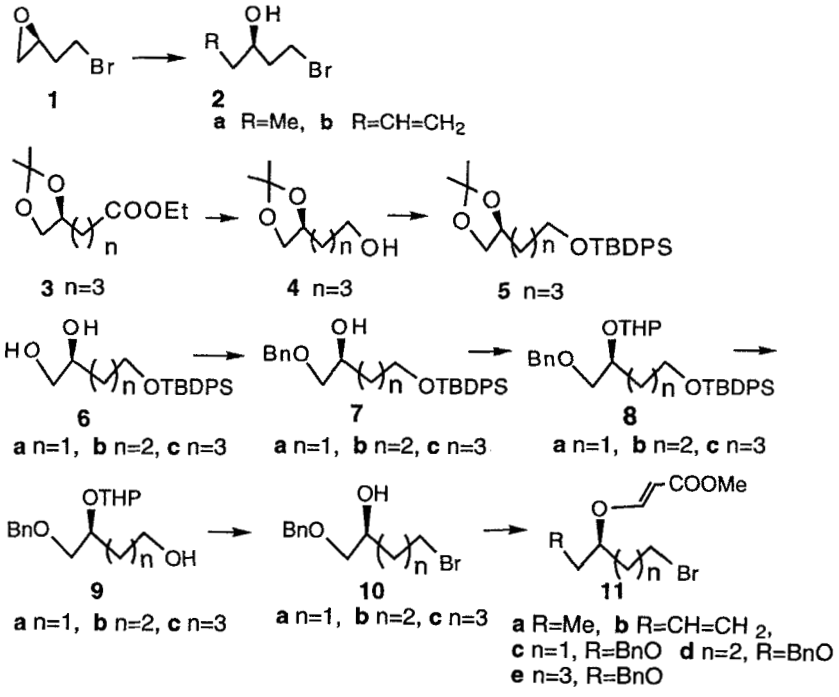
ABSTRACT: Regioselective carbon-carbon bond formation by radical reaction at the β-position of β-alkoxyacrylate was applied to a synthesis of 2,5-disubstituted tetrahydrofuran, 2,6-disubstituted tetrahydropyran, 2,7-disubstituted oxepane derivatives.

Radical cyclization is well established methodology for the carbon-carbon bond formation.[1] Stereocontrolled construction of 5-, 6- and 7-membered cyclic ether derivatives has been remarkably developed because of their interesting biological activity.[2] In this paper, we wish to report the efficient elaboration of such oxacyclic compounds through a regioselective formation of carbon-carbon bond at the β-position of β-oxygenated α,β-unsaturated esters by radical reaction.

At the first stage of this study, methyl β-alkoxyacrylates **11a-e** which contain a latent radical center were prepared as outlined in the Scheme 1. Ring opening of (*S*)-3,4-epoxybutyl bromide **1**[3] with methylmagnesium bromide and vinylmag-

nesium bromide in the presence of CuI afforded the corresponding alcohols **2a,b** in 82.7, 86.4 % yield, respectively. Reduction of **3**[4] with $LiAlH_4$, followed by protection of the hydroxy group of the resulting alcohol **4** with the *tert*-butyldiphenylsilyl (81%), and subsequent ring cleavage (*p*-TsOH in MeOH) of the acetonide **5** afforded the diol **6c**. Regioselective benzylation of the primary hydroxyl group of the diols **6a**,[5] **6b**[6] and **6c**, was successfully achieved by treatment with *n*-Bu_2SnO[7] and subsequent benzylation (benzyl bromide, tetrabutylammonium bromide) to give **7a**[5],**b**,**c** in around 90 % yield. THP protection of hydroxyl group of **7a**,**b**,**c**, followed by removal of silyl group by treatment of **8a**,**b**,**c** with tetrabutylammonium fluoride afforded **9a**,**b**,**c**, which were led to **10a**,**b**,**c** (i. CH_3SO_2Cl, Et_3N, ii. LiBr, in acetone, iii. *p*-TsOH in MeOH), respectvely. Treatment of **2a,b**, **10a-c** with methyl propiolate in the

Scheme 1



presence of tributylphosphine afforded the corresponding β-alkoxyacrylate **11a-e**, respectively.

The β-carbon of β-alkoxyacrylates can be considered as an efficient radical acceptor[8] because of the presence of electron withdrawing substitutents at the β-position and enol oxygen function at the α-position of the double bond.

A benzene solution (2mM solution) of **11a** was heated in the presence of tributyltin hydride at reflux, afforded 2,5-*cis* methyl 5-ethyltetrahydrofurano-acetate **12a** in 76% yield accompanying with a formation of small quantity of the 2,5-*trans*-isomer **13a** in a ratio of 24:1, which was clearly determined by capillary GC analyses. The stereochemistry of **12a** was ascertained by NOE observed between the two methine hydrogenes at C-2 and C-5 (Figure 1).

Scheme 2

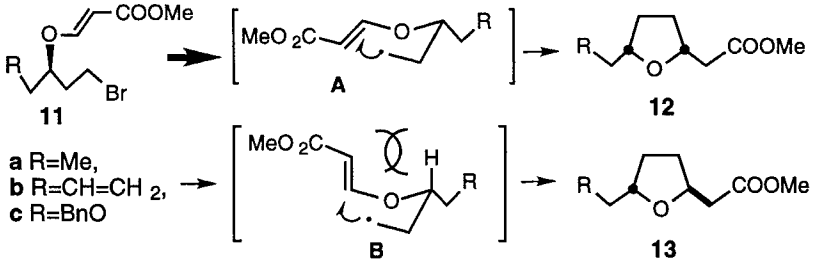


Table 1 Radical cyclization of **11a-c**

R	Reaction condition	Ratio of **12** : **13**	Yield (%)
Me	Bu_3SnH / AIBN / benzene / 80°C	24 : 1	76
Me	Bu_3SnH / Et_3B / toluene / 0°C	**12** single isomer	98
vinyl	Bu_3SnH / Et_3B / toluene / 0°C	**12** single isomer	84
BnO	Bu_3SnH / Et_3B / toluene / 0°C	**12** single isomer	93

2mM of **11a-c** was used for this reaction

The *cis*-selective exo-trig-cyclization can be explained by taking the thermodynamically more stable transition state **A** rather than **B** which contain 1,3-steric interaction as shown in Scheme 2. The rotamer popurations of component in radical reaction are known to be controlled by factors such as temperatures,[9]

Lewis acids,[9] dipole-dipole interactions,[9] and steric repulsions.[9] It can be expected that yields and diastereoselectivity of products can be improved by conduction of the reaction at lower temeperature. When the reaction of **11a** was carried out in toluene solution (2mM) at 0°C by using Et_3B as a radical initiator instead of AIBN, **12a** was obtained as a single isomer in 98% yield. In a similar way, **11b**,**c** were subjected to the radical cyclization at 0°C to yield **12b** and **12c** in 82%, 93 % yield, respectively.

Scheme 3

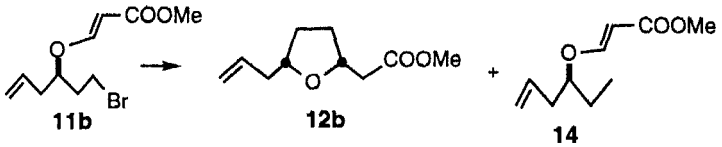


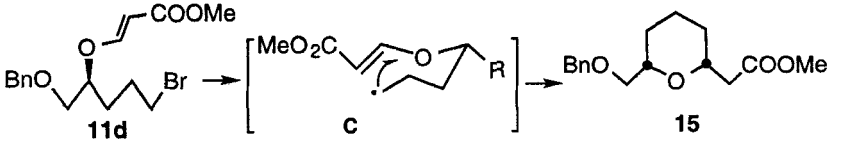
Table 2 Radical cyclization of **11b**

Reaction condition	**11b** conc(M)	ratio **12b** : **14**	Combined Yield (%)
Bu_3SnH / Et_3B / toluene / 0°C	0.1	12.1 : 1	86
Bu_3SnH / Et_3B / toluene / 0°C	0.5	4.5 : 1	81
Bu_3SnH / Et_3B / Et_2AlCl / toluene / 0°C	0.1	14.5 : 1	84
Bu_3SnH / Et_3B / Et_2AlCl / toluene / 0°C	0.5	9.1 : 1	86

Next, we examined the reaction of **11b** by using the higher concentration solution in the presence and absence of the Lewis acid (Scheme 3, Table 2). The use of 0.1M solution of **11b** gives rise to a formation of small quantity of reduction product **14**, **12b/14**= (12.1:1). When 0.5M solution was used, considerable amount of **14** was accompanied, in a ratio of **12b/14**=4.5:1 without formation of 2,5-*trans*-isomer. Since Lewis acid lowers the LUMO energy, the addition rate of radical species to the unsaturated component can be accelerated because of reduction of the SOMO-LUMO energy difference.[1a] Upon addition of Et_2AlCl, the ratio for **12b/14** could be raised to 14.5:1 in the case of 0.1 M solution, and in the case of 0.5 M solution, the ratio was considerably improved to 9:1. In these reactions, the formation of the *trans*-isomer was not observed.

The current method was found to be particularly useful for a synthesis of 2,6-disubstituted tetrahydropyrane derivatives. The radical reaction of **11d** was carried out in toluene at 0 °C in the presence of Et_3B afforded **15** in 98% yield without formation of any amounts of the *trans*-isomer (Scheme 4).

Scheme 4



The method was extensively applied to a synthesis of 2,7-disubstituted oxepane ring system. In view of the increasing number of biological active marine natural product containing medium- and large sized cyclic ether derivatives,[1] much attention has recently been focused on efficient approaches toward the stereoselective synthesis of oxepane ring system.[10] Radical cyclization of **11e** was carried out by using tributyltin hydride in the presence of Et_3B in toluene at 0 °C did not give any desired cyclization product. When the reaction was conducted in benzene at reflux resulted in a predominant formation of 2,7-*cis*-isomer **16** in 3.4:1 ratio for **16/17** (43 % yield) owing to taking the more thermodynamically stable transition state **D** than **E** (Scheme 5). When the reaction was carried out at 0 °C in the presence of Et_2ACl, yield of the cyclization product raised to 61% yield, though the ratio for **16/17** (=3.6:1) was not improved. Thus, the presence of Lewis

Scheme 5

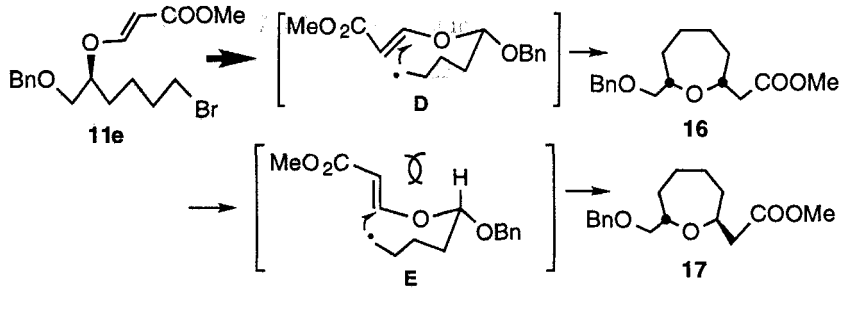


Table 3 Radical cyclization of **11e**

Reaction Condition	Ratio **16** : **17**	Yield (%)
Bu_3SnH / AIBN / benzene / 80°C	3.4 : 1	43
Bu_3SnH / Et_3B / toluene / 0°C	—	—
Bu_3SnH / Et_3B / Et_2AlCl / toluene / 0°C	3.6 : 1	61

2mM of **11e** was used for this reaction

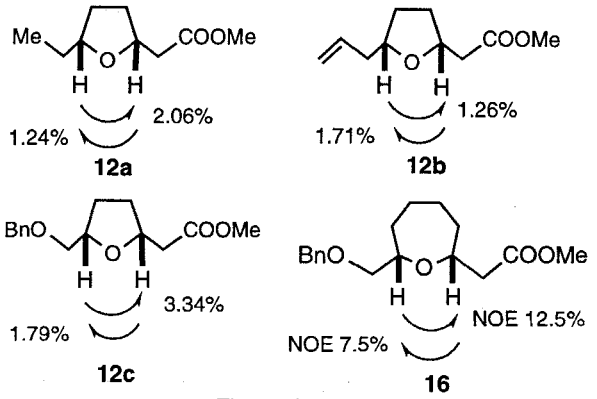


Figure 1

acid (Et_2AlCl) was found to considerably accelerate the cyclization reaction. Stereochemistry of **16** was ascertained by NOE experiments (Figure 1).

In Conclusion, the radical cyclization at β-alkoxyacryalate was found to be useful tool for a diastereoselective synthesis of five and six-membered cyclic ethers and oxepane ring system was also formed in favor of *cis*-isomer.

Experimental

General. All reactions were conducted under nitrogen. Tetrahydrofuran (THF) and ether were distilled from sodium benzophenone ketyl, methylene chloride (CH_2Cl_2) was distilled from CaH_2. All reactions were monitored by TLC using commercially available glass-backed plates. For column chromatography, silica gel 60 (0.043-0.063 mm) was used and the columns were eluted in the flash mode. ^1H NMR spectra were recorded on the Bruker AM 400 or Varian Gemini 300 operating at 400MHz and 300MHz in $CDCl_3$. ^{13}C NMR spectra were recorded in

$CDCl_3$ on the Bruker AM-400 (100MHz). Chemical shifts are reported relative to $CDCl_3$ (central line of triplet, δc 77.0). Optical rotations were determined with a JASCO DIP-4 polarimeter and IR spectra were recorded with Perkin-Elmer 1710 spectrometer and only characteristic bands were given. Mass spectra (MS) were measured on a TSQ 700 and VG Auto Spec instrument.

(*R*)-1-Bromopentan-3-ol 2a

To a stirred mixture of CuI (0.94 g) and THF (150 ml) was added methylmagnesium bromide (49.7 ml of 1M solution) at -30°C. After 15 min, **1** (5 g, 33.1 mmol) was slowly added to the mixure. After stirring at 0°C for 2 hr, the mixture was poured onto water and extracted with ether. The extract was washed with 10 % NH_4Cl, dried (Na_2SO_4) and evaporated. The resulting residue was chromatographed. Elution with hexane-ethyl acetate (8:1) gave **2a** (4.9 g, 82.7 %) as a colorless oil. $[\alpha]_D$ -1.90 (*c* 0.8, $CHCl_3$). IR (neat) 3359. ^1H NMR 0.98 (3H, t, J 7.4), 1.45-1.59 (2H, m), 1.90-2.03 (2H, m), 3.51-3.62 (2H, m), 3.70-3.81 (1H, m). EIMS (m/z): 153 and 151 (M^+-CH_3).

(*R*)-1-Bromohex-5-en-3-ol 2b

The compound **2b** (5.1g, 86.4%) was obtained as an oil by the reaction of **1** (5.0g, 33.1 mmol) with vinylmagnesium bromide (49.7 ml of 1M solution) according to the same conditions as **2a**. $[\alpha]_D$ -44.4 (*c* 2.1, $CHCl_3$). IR (neat) 3392, 1641. ^1H NMR 1.95-2.04 (2H, m), 2.13-2.38 (2H, m), 3.50-3.63 (2H, m), 3.83-3.93 (1H, m), 5.12-5.22 (2H, m), 5.74-5.90 (1H, m). EIMS (m/z) 137 (M^+-CH_2=$CHCH_2$-).

(*S*)-1,2-Isopropylidenedioxyhexan-6-ol 4

To a suspension of $LiAlH_4$ (1.76g, 46.3mmol) in THF (80 ml) was slowly added a solution of **3** (9.10g, 42.1mmol) in THF (30 ml) at 0°C under stirring. The mixture was stirred at 0°C for 30 min and at room temperature for 2 hr and then quenched with 10% NaOH (10 ml), extracted with benzene. The organic layer was washed with brine, dried ($MgSO_4$) and evaporated. The residue was chromatographed. Elution with hexane-ethyl acetate (2:1) gave **4** (6.2 g, 88.0%) as a colorless oil. $[\alpha]_D$ +17.4 (*c* 2.0, $CHCl_3$). IR (neat) 3413. ^1H NMR 1.35 (3H, s), 1.41 (3H, s), 1.41-1.74 (6H, m), 3.48-3.53 (1H, m), 3.62-3.70 (2H, m), 4.02-4.12 (2H, m). EIMS (m/z) 175 (M^++1).

(*S*)-5,6-Isopropylidenedioxyhexy-*tert*-butyldiphenylsilyl ether 5

To a mixture of **4** (6.2g, 35.6 mmol), TBDPSCl (9.78g, 35.6 mmol), 4-DMAP (0.43g, 3.5 mmol) and CH_2Cl_2 (100 ml) was slowly added Et_3N (5.4 g, 53.4 mmol) under ice-cooling. After the stirring at room temperature for 10 hr, the mixture was poured onto water and extracted with $CHCl_3$. The solvent was evaporated and the remaining residue was chromatographed. Elution with hexane-ethyl acetate (10:1) afforded **5** (10.7 g, 81.0 %) as a colourless oil. $[\alpha]_D$ +8.6 (*c* 1.4, $CHCl_3$). ^1H NMR 1.04 (9H, s), 1.35 (3H, s), 1.40 (3H, s), 1.42-1.65 (6H, m), 3.44-3.53 (1H, m), 3.60-3.63 (2H, m), 3.98-4.09 (2H, m), 7.34-7.42 (6H, m), 7.64-7.68 (4H, m). EIMS (m/z) 392 (M^+-CH_3).

(*S*)-6-*tert*-Butyldiphenylsilyloxyhexane-1,2-diol 6c

To a solution of **5** (10.7 g, 25.9 mmol) in MeOH (100 ml) was added *p*-TsOH·H_2O (50 mg) under stirring at room temperature. After 30 min, the mixture was made basic with 5% $NaHCO_3$. The solvent was evaporated and the residue was diluted with water, extracted with $CHCl_3$. The solvent was evaporated and the residue was chromatographed. Elution with hexane-ethyl acetate (2:1) gave **6c** (9.31 g, 96.5%) as a colorless oil. $[\alpha]_D$ +1.26 (*c* 0.6, $CHCl_3$). IR (neat) 3354. ^1H NMR 1.05 (9H, s), 1.37-1.64 (6H, m), 3.37-3.45 (1H, m), 3.60-3.73 (4H, m), 7.34-7.45 (6H, m), 7.64-7.68 (4H, m). EIMS (m/z) 373 (M^++1).

(*S*)-1-Benzyloxy-5-*tert*-butyldiphenylsilyloxypentan-2-ol 7b

A mixture of **6b** (5.0 g, 13.9 mmol), Bu_2SnO (5.20 g, 20.9 mmol) and toluene (500 ml) was stirred under reflux in a Dean-Stark apparatus with removal of water for 4 hr. After the solvent was evaporated to 250 ml, the mixture was treated with benzyl bromide (7.13 g, 41.7 mmol) and tetrabutylammonium bromide (2.24 g, 6.95 mmol) at 80°C. After the stirring at the same temperature for 24 h, the mixture was poured onto water and extracted with $CHCl_3$. The extract was evaporated and the residue was chromatographed. Elution with hexane-ethyl acetate gave **7b** (5.52 g, 88.5 %) as a colorless oil. $[\alpha]_D$ +1.60 (*c* 2.0, $CHCl_3$). IR (neat) 3436. ^1H NMR 1.04 (9H, s), 1.47-1.80 (4H, m), 3.35 (1H, dd, J 7.6, 9.6), 3.49 (1H, dd, J 3.4, 9.4), 3.68(2H, t, J 6.1), 4.56 (2H, s), 7.28-7.46 (11H, m), 7.64-7.68 (4H, m). EIMS (m/z) 449 (M^++1).

(*S*)-1-Benzyloxy-6-*tert*-butyldiphenylsilyloxyhexan-2-ol 7c

Compound **7c** (10.7 g, 92.5 %) was obtained from **6c** (9.31g, 25.0 mmol) as a

colorless oil as in a preparation of **7b**. $[\alpha]_D$ +1.9 (*c* 1.4, $CHCl_3$). IR (neat) 3460. ^1H NMR 1.03 (9H, s), 1.35-1.63, (6H, m), 3.30 (1H, dd, J 7.9, 9.4), 3.49 (1H, dd, J 3.0, 9.4), 3.65(2H, t, 6.3), 3.74-3.84 (1H, m), 7.29-7.45 (11H, m), 7.64-7.67 (4H, m). EIMS (m/z) 463 (M^++1).

(*S*)-1-Benzyloxy-2-tetrahydropyranyloxybutan-4-ol 9a

A mixture of **7a** (8.7 g, 20 mmol), 3,4-dihydropyrane (2.0 g, 24.0 mmol), ether (100 ml) and *p*-TsOH·H_2O (0.4 g, 2.0 mmol) was stirred at room temperature for 10 h and then the mixture was made basic with 5% $NaHCO_3$. Evaporation of the solvent gave **8a** (9.4 g, 91.0 %), to a solution of which (9.4 g, 18.1 mmol) in THF (40 ml) was added portionwisely tetrabutylammonium fluoride (7.1 g, 27.2 mmol) at room temperature. After stirring for 1.5 hr, the solvent was evaporated and the resulting residue was chromatographed. Elution with hexane-etyl acetate (8:1) gave **9a** (4.60 g, 90.7%) as a colorless oil. $[\alpha]_D$ -5.5 (*c* 1.3, $CHCl_3$). IR (neat) 3436. ^1H NMR 1.45-2.00 (8H, m), 3.44-3.53 (2H, m), 3.56 (1H, dd, J 6.5, 9.6), 3.70 (1H, dd, J 4.3, 9.6), 3.72-3.78 (2H, m), 4.57 (2H, m), 7.28-7.38 (5H, m). EIMS (m/z) 280 (M^+), 195.1174 found (Calcd. for $C_{11}H_{15}O_3$: 197.1178), M^+-C_5H_9O.

(*S*)-1-Benzyloxy-2-tetrahydropyranyloxypentan-5-ol 9b

Compound **9b** (2.89 g, 85.3 %) was obtained as a colorless oil from **7b** (5.52 g, 11.9 mmol) via **8b** (6.13 g, 11.2 mmol) as in a preparation of **9a**. $[\alpha]_D$ -11.5 (*c* 2.7, $CHCl_3$). IR (neat) 3418. ^1H NMR 1.48-1.87 (10H, m), 3.42-3.53 (3H, m), 3.60-3.71 (2H, m), 3.79-4.00 (2H, m), 4.55 (2H, d, J 7.2), 4.68-4.71 (0.5H, m), 4.77-4.80 (0.5H, m), 7.27-7.37 (5H, m). EIMS (m/z) 209 (M^+-C_5H_9O).

(*S*)-1-Benzyloxy-2-tetrahydropyranyloxyhexan-6-ol 9c

Compound **9c** (6.45 g, 89.8%) was obtained as a colorless oil from **7c** (9.31 g, 20.1mmol) via **8c** (10.8g, 23.3mmol) as in a preparation of **9a**. $[\alpha]_D$-15.1 (*c* 2.0, $CHCl_3$). IR (neat) 3436. ^1H NMR 1.30-1.86(12H, m), 3.42-3.66 (5H, m), 3.73-3.96 (2H, m), 4.48-4.59 (2H, m), 4.65-4.68 (0.5H, m), 4.77-4.79 (0.5H, m), 7.27-7.40 (5H, m). EIMS (m/z) 309 (M^++1).

(*S*)-4-Bromo-1-benzyloxybutan-2-ol 10a

To a mixture of **9a** (4.60 g, 16.4 mmol), Et_3N (2.49 g, 24.6 mmol) and CH_2Cl_2 (40

ml) was slowly added CH_3SO_2Cl (2.26g, 19.7 mmol) at 0°C. After stirring at room temperature for 12 hr. the mixture was washed with 10 % HCl, 5 % $NaHCO_3$, brine, dried (Na_2SO_4), and evaporated. The residue was heated to reflux with LiBr (2.85 g, 32.8 mmol) in acetone (15 ml) for 2 h. The solvent was evaporated and the residue was extracted with $CHCl_3$. The extract was washed with 5 % $NaHCO_3$, brine, dried (Na_2SO_4) and evaporated. A mixture of the residue, MeOH (50 ml) and *p*-TsOH·H_2O (50 mg) was allowed at room temperature under stirring for 0.5 h. The mixture was made basic with 5% $NaHCO_3$ and the solvent was evaporated. The residue was diluted with water and extracted with $CHCl_3$. The solvent was evaporated and the residue was chromatographed. Elution with hexane-etyl acetate (5:1) gave **10a** (3.22 g, 76.0%) as a colorless oil. $[\alpha]_D$ -16.4 (*c* 2.85, $CHCl_3$). IR (neat) 3435. ^{1}H NMR 1.86-2.10 (2H, m), 3.38 (1H, dd, J 7.2,9.4), 3.48-3.62 (3H, m), 3.98-4.08 (1H, m), 4.56 (2H, s), 7.27-7.41 (5H, m). EIMS (m/z) 260 and 258 (M^+), 258.0245 found (Calcd. for $C_{11}H_{15}O_2Br$: 258.0255), M^+

(*S*)-1-Benzyloxy-5-bromopentan-2-ol 10b

Compound **10b** (1.66g, 65.3%) was obtained as a colorless oil from **9b** (2.89 g, 9.36 mmol) as in a preparation of **10a**. $[\alpha]_D$ -0.90 (*c* 0.9, $CHCl_3$). IR (neat) 3435. ^{1}H NMR 1.47-1.70 (2H, m), 1.86-2.16 (2H, m), 3.34 (1H, dd, J 3.1, 9.4), 3.78-3.88 (1H, m), 4.56 (2H, s), 7.27-7.42 (5H, m). EIMS (m/z) 274 and 272 (M^+), 272.0388 found (Calcd. for $C_{12}H_{17}O_2Br$: 272.0412), M^+.

(*S*)-1-Benzyloxy-6-bromohexan-2-ol 10c

Compound **10c** (4.14g, 69.3 %) was obtained from **9c** (6.45g, 20.9 mmol) as a colorless oil as in a preparation of **10a**. $[\alpha]_D$ +1.90 (*c* 1.26, $CHCl_3$). IR (neat) 3436. ^{1}H NMR 1.40-1.69 (4H, m), 1.81-1.96 (2H, m), 3.33 (1H, dd, J 7.8, 9.4), 3.41 (2H, t, J 6.8), 3.51 (1H, dd, J 3.1, 9.4), 3.76-3.87 (1H, m), 4.60 (2H, s), 7.26-7.41 (5H, m). EIMS (m/z) 288 and 286 (M^+), 286.0552 found (Calcd. for $C_{13}H_{19}O_2Br$: 286.0568, (M^+).

β-Alkoxyacrylate 11a-e

To a stirred mixture of **2a** (or **2b**, **10a-c**) (20.0 mmol), methyl propiolate (2.35g, 28.0 mmol) and CH_2Cl_2 (10ml) was added Bu_3P (1.2g, 6.0 mmol) at room temperature. After 10 min, the solvent was evaporated and the residue was chromatographed. Elution with hexane-ethyl acetate (7:1) gave **11a-e**

11a (3.43 g, 68.6%), colorless oil. $[\alpha]_D$ -3.1 (*c* 0.1, $CHCl_3$). IR (neat) 1713, 1641. ^1H NMR 0.94 (3H, t, 7.6), 1.57-1.71 (2H, m), 1.98-2.24 (2H, m), 3.35-3.54 (2H, m), 3.69 (3H, s), 4.05-4.13 (1H, m), 5.30 (1H, d, J 12.3), 7.54 (1H, d, J 12.3). EIMS (m/z) 253 and 251 (M^++1), 250.0219 found (Calcd. for $C_9H_{15}O_3Br$: 250.0205), M^+

11b (2.65g, 50.6 %), colorless oil. $[\alpha]_D$-65.5 (*c* 2.0, $CHCl_3$). IR (neat) 1713, 1641. ^1H NMR 2.00-2.25 (2H, m), 2.36-2.44 (2H, m), 3.36-3.53 (2H, m), 3.69 (3H, s), 4.16-4.27 (1H, m), 5.09-5.20 (2H, m), 5.31 (1H, d, J 12.4), 5.66-5.82 (1H, m), 7.53 (1H, d, J 12.4). EIMS (m/z) 265 and 263 (M^++1), 263.0283 found (Calcd. for $C_9H_{15}O_3Br$: 263.0279), M^++1.

11c (2.79g, 44.8 %), colorless oil. $[\alpha]_D$ -54.2 (*c* 2.3, $CHCl_3$); IR (neat) 1708, 1640. ^1H NMR 2.03-2.30 (2H, m), 3.38-3.64 (4H, m), 3.70 (3H, s), 4.28-4.38 (1H, m), 4.52 (1H, d, J 12.2), 4.57 (1H, d, J 12.2), 5.34 (1H, d,J 12.3), 7.27-7.36 (5H, m), 7.60 (1H, d, J 12.3). EIMS (m/z) 345 and 343 (M^++1), 311.0271 found (Calcd. for $C_{14}H_{16}O_3Br$: 311.0283), (M^+-OCH_3).

11d (5.65g, 79.3 %), colorless oil.$[\alpha]_D$-8.7 (*c* 0.7, $CHCl_3$). IR (neat) 1740, 1640. ^1H NMR 1.72-2.04 (4H, m), 3.40 (2H, t, *J* 6.4), 3.45-3.60 (2H, m), 3.70 (3H, s), 4.04-4.14 (1H, m), 4.54 (2H, s), 5.31 (1H, d, J 12.3), 7.27-7.40 (5H, m), 7.58 (1H, d, J 12.3). EIMS (m/z) 358 and 356 (M^+), 356.0622 found (Calcd. for $C_{16}H_{21}O_4Br$: 356.0623), M^+.

11e (4.42g, 59.7 %), colorless oil. $[\alpha]_D$-12.5 (*c* 2.1, $CHCl_3$). IR (neat) 1713, 1642. ^1H NMR 1.40-1.70 (4H, m), 1.80-1.93 (2H, m), 3.39 (2H, t, J 6.7), 3.46-3.60 (2H, m), 3.70 (3H, s), 4.01-4.11 (1H, m), 4.54 (2H, s), 5.30 (1H, d, J 12.3), 7.25-7.39 (5H, m), 7.59 (1H, d, J 12.3). EIMS (m/z) 372 and 370 (M^+), 370.0774 found (Calcd. for $C_{17}H_{23}O_4Br$: 370.0780), M^+.

Radical cyclization of 11a,e in the presence of AIBN

To a stirred solution of **11a,e** (2.0 mmol) in benzene (250 ml) was slowly added a benzene solution of Bu_3SnH (0.88g, 3.0 mmol) and AIBN (10 mg) under reflux. During the addition of Bu_3SnH, AIBN was added in each 30 min. After 5 hr, the solvent was evaporated. The residue was chromatographed on silica gel. After removal of non-polar material by elution with hexane, successive elution with hexane-etyl acetate (4:1) afforded **12a,16** in yields shown in the Table 1, 3.

Radical cyclization of 11a-e in the presence of Et_3B

To a stirred mixture of **11a-e** (2.0 mmol), Et_3B (2.2 ml, 1M hexane solution) and

toluene (250 ml) was slowly added a toluene solution of Bu_3SnH (0.88 g, 3.0 mmol) at 0°C. After 12 hr, the mixture was quenched with MeOH (1ml) and worked up as above to give **12a-c**, **15**, **16** in yields shown in the Table 1-3.

Radical cyclization of 11b,e in the presence of Et_3B and Et_2AlCl

A mixture of **11b**, **e** (2.0 mmol) was reacted with Bu_3SnH (0.88g, 3.0 mmol)) in toluene (250 ml) containing Et_2AlCl (6.0 ml, 1M hexane solution) and Et_3B (2.2 ml, 1M hexane) at 0°C and worked up as above to give **12b**, **16** in yields shown in the Table 2, 3.

12a, colorless oil. $[\alpha]_D$ -2.0 (*c* 0.8, $CHCl_3$). IR (neat) 1742. ^1H NMR 0.8 7 (3H, t, *J* 7.6), 1.35-1.67(4H, m), 1.87-2.09 (2H, m), 2.43 (1H, dd, J 6.5, 15.2), 2.60(1H, dd, J 6.8,15.2), 3.65(3H, s), 3.71-3.81(1H, m), 4.16-4.26 (1H, m). ^{13}C NMR 10.12. 28.74, 30.23, 30.95, 40.93, 51.52, 75.06, 81.00, 171.71. CIMS (m/z) 173 (M^++1), 172.1105 found (Calcd. for $C_9H_{16}O_3$: 172.1099), M^+.

12b, colorless oil. $[\alpha]_D$ -12.2 (*c* 3.2, $CHCl_3$). IR (neat) 1741, 1643. ^1H NMR 1.52-1.67 (2H, m), 1.88-2.12 (2H, m), 2.16-2.41 (2H, m), 2.46 (1H, dd, J 6, 15.2), 2.64 (1H, dd, J 6.7, 15.2), 3.68 (3H, s), 3.87-3.97 (1H, m), 4.20-4.30 (1H, m), 5.00-5.12 (2H, m), 5.72-5.87 (1H, m). ^{13}C NMR 30.14, 30.93, 40.24, 40.87, 51.57, 75.33, 78.92, 116.90, 134.73, 171.70. CIMS (m/z) 185 (M^++1), 183.1014. found (Calcd. for $C_{10}H_{15}O_3$: 183.1021), M^+-1.

12c, colorless oil. $[\alpha]_D$ -6.2(*c* 1.5., $CHCl_3$). IR (neat) 1740. ^1H NMR 1.55-1.80 (2H, m), 1.90-2.13 (2H, m), 2.48 (1H, dd, J 6.6, 15.4), 2.68 (1H, dd, J 6.7, 15.4), 3.45 (1H, dd, J 4.9, 10.0), 3.49 (1H, dd, J 5.3, 10.0), 3.68 (3H, s), 4.06-4.16 (1H, m), 4.24-4.34 (1H, m), 4.54 (1H, d, J 12.1), 4.59 (1H, d, J 12.1), 7.23-7.38 (5H,m). ^{13}C NMR : 28.0, 30.9, 40.7, 51.6, 72.8, 73.3, 75.9, 78.4, 127.5, 127.6 (2 lines), 128.3 (2 lines), 138.3, 171.7. EIMS (m/z) 264, (M^+), 264.1373 found (Calcd. for $C_{15}H_{20}O_4$: 264.1362), M^+.

15, colorless oil. $[\alpha]_D$ -8.7 (*c* 0.7, $CHCl_3$). IR (neat) 1740. ^1H NMR 1.50-1.70 (5H, m), 1.80-1.91 (1H, m), 2.42 (1H, dd, J 6.2, 15.1), 2.62 (1H, dd, J 7.1,15.1), 3.41 (1H, dd, J 4.6, 10.2), 3.48 (1H, dd, J 5.8, 10.2), 3.56-3.66 (1H, m), 3.66 (3H, s), 3.76-3.86 (1H, m), 4.53 (1H, d, J 12.1), 4.59 (1H, d, J 12.1), 7.25-7.38 (5H, m); ^{13}C NMR: 22.98, 27.77, 31.07, 41.45, 51.51, 73.22, 73.45, 74.40, 77.30, 127.44, 127.62, 128.26 (2 lines), 128.41, 138.48, 171.70. EIMS (m/z) 279 (M^++1), 278.1516 found (Calcd. for $C_{16}H_{22}O_4$: 278.1518), M^+.

16, colorless oil. $[\alpha]_D$ -15.1 (*c* 0.6, $CHCl_3$). IR (neat) 1741. ^1H NMR 1.48-1.85 (8H, m), 2.40 (1H, dd, *J* 5.0, 15.1), 2.58 (1H, dd, J 8.8, 15.1), 3.34 (1H, dd, J 5.3,

10.0), 3.44 (1H, dd, J 6.1, 10.0), 3.62 (3H, s), 3.72-3.82 (1H, m), 3.95-4.05 (1H, m), 4.53 (2H, s), 7.23-7.38 (5H, m). ^{13}C NMR 24.50, 25.50, 32.68, 35.83, 42.01, 51.43, 73.09, 73.52, 76.76, 78.91, 127.38, 127.45, 127.53, 128.23, 128.36, 138.54, 171.97. EIMS (m/z) 292 (M^+), 292.1657 found (Calcd. for $C_{17}H_{24}O_4$: 292.1675), M^+.

References

1. a) Gies, B. " Radical in Organic Synthesis. Formation of Carbobn-Carbon Bonds, " Oxford, **1986**. b) Jasperse, C. P. Curran, D.P. and Fevig, T. L. *Chem.Rev.* **1991**, *91*, 1237. c) Porter, N, A. Giese, B. and Curran, D. P. *Acc. Chem. Res.* **1991**, *24*, 296.
2. a) Scheuer, P. J., Ed. Academic. "Marine Natural Product " **1978**, *1*, Chap 1. Erckson, K.K. ibid. **1983**, *5*, Chap 4, 131. b) Faulker, D.J. "Nat. Prod, Rep." **1984**, *1*, 251.**1986**, *3*, 1. **1988**, *5*, 613.
3. a) Seuring, B. and Seebach, D. *Helv. Chim. Acta.* **1977**, *60*, 1175. b) Hungerbuhler, E. Naef, R. Wasmuth, D. and Seebach, D. Helv. Chim. Acta. **1980**, *63*, 1960.
4. Gerth, D.B. Giese, B.*J, Org, Chem.* **1986**, *51*, 3726..
5. Yuasa, Y. Ando, J. and Shibuya, S. *J. Chem. Soc. perkin Trans.1* **1996**, 465.
6. Yuasa, Y. Ando, J. and Shibuya, S. *J. Chem. Soc. perkin Trans.1* **1996**, 793.
7. a) Veyrieres, A. *J. Chem. Soc. perkin Trans.1* **1981**, 1626. b) Nashed, M, A. and Anderon, L. *Tetrahedron Lett*, **1976**, *39*, 3503.
8. a) Landlow, M. Pattenden, G. *J. Chem. Soc. perkin Trans.1* **1988**, 1107. b) Lee, E. Tae, J.S. Lee, C. and Park, C, M.*Tetrahedron Lett*. **1993**, *34*, 4831.
9. Mukund, P.S. and Jianguo, J. *J. Am. Chem. Soc.* **1996**, *118*, 3063, and recent publications cited therein.
10. Kotuki, H. Ushio, Y. Kadota, I. and Ochi, M. *J. Org. Chem.* **1989**, *54*, 5153.

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