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Novel Ring Cleavage Based on Intermolecular Aldol Condensation

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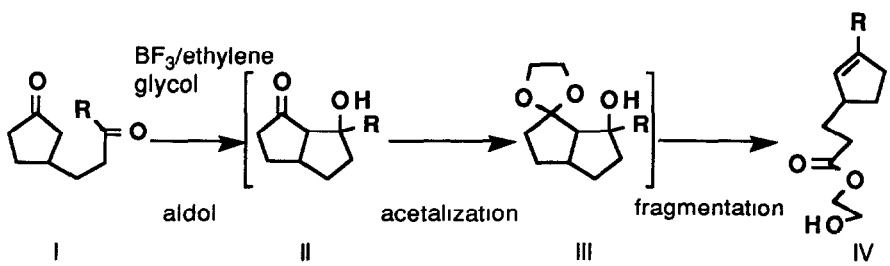
Abstract Ring cleavage and reconstruction via intramolecular aldol condensation followed by Grob fragmentation under acetalization conditions (BF3/ethylene glycol) was developed into a novel ring cleavage based on intermolecular aldol condensation On the basis of this reaction, (R,R)-3,5-dimethylcyclohexanone was converted into the chiral straight-chain compound with syndiotactic methyl function The ring cleavage reaction based on a crossed intermolecular aldol condensation was also examined, and the reaction pathway was discussed

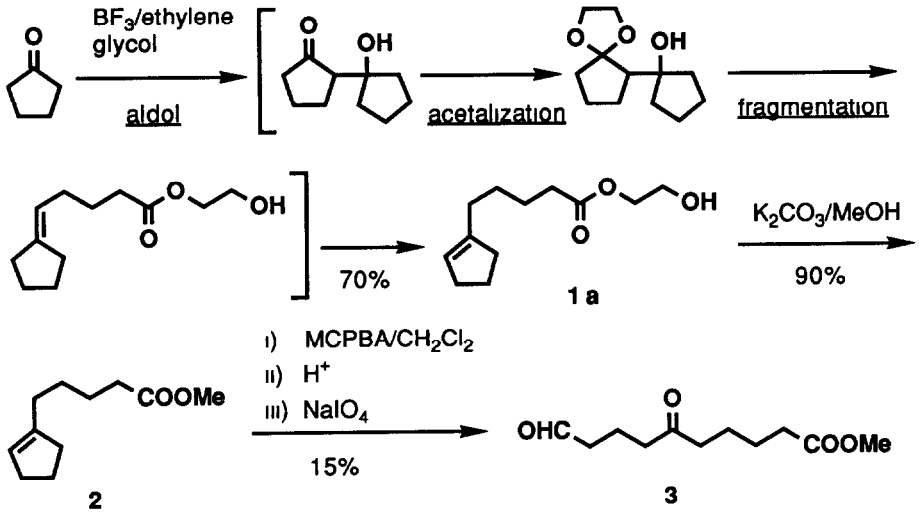
We previously reported a new ring transformation of cyclic ketones with the carbonyl function at the C3 or C4 position of β-side chain under acetalization conditions (BF_3-etherate and ethylene glycol) as shown in Scheme 1 [3] This reaction seems to involve three steps a) intramolecular aldol condensation, b) acetalization, c) fragmentation [4]



Scheme 1

This finding suggested the feasibility of a novel ring cleavage based on intermolecular aldol condensation (Scheme 2) Treatment of cyclopentanone with BF_3-etherate and ethylene glycol in CH_2Cl_2 gave the hydroxyethyl ester (**1a**) in 70% yield The structure of **1a** was established on the basis of spectroscopic data Mass spectrum showed a molecular ion peak at *m/z* 212, and a prominent ion peak resulting from elimination of ethylene glycol from the parent ion at *m/z* 150 IR absorption (3430 cm^{-1} and 1730 cm^{-1}) suggested the existence

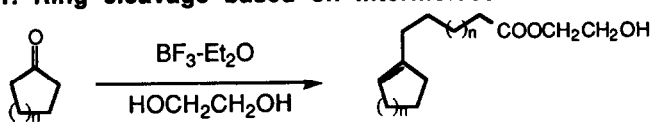
of hydroxy and carbonyl functions, respectively The ^{1}H-NMR spectrum exhibited signals attributable to hydroxyethyl ester moiety at δ 4 22 (2H, m, CO_2CH_2) and δ 3 82 (2H, m, CH_2O) and characteristic olefinic proton at δ 5 33 (1H, m) The ^{13}C-NMR spectrum (δ 174 (s), 144 (s), 124 (d)) also supported this structure



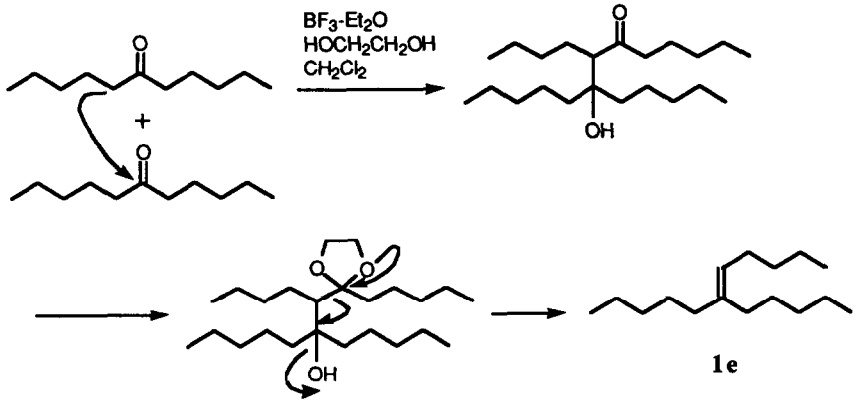
Scheme 2

To confirm the position of the double bond in **1a**, the following chemical conversion was examined (Scheme 2) Transesterification of **1a** with MeOH/K_2CO_3 gave the methyl ester (**2**) in 90% yield Epoxidation of **2** with MCPBA followed by hydrolysis and subsequent oxidative C-C bond cleavage with sodium periodate afforded the aldehyde (**3**) in 15% yield The ^{1}H-NMR spectrum of **3** exhibited the signals assignable to the aldehyde [δ 9 76 (1H, t, J = 1 4 Hz)] and the methyl ester [δ 3 67 (3H, s)] The FD mass spectrum showed [M^++1] peak at *m/z* 215 Thus, the position of the double bond in **1a** was definitely determined to be *endo*

Table 1. Ring cleavage based on intermolecular aldol condensation



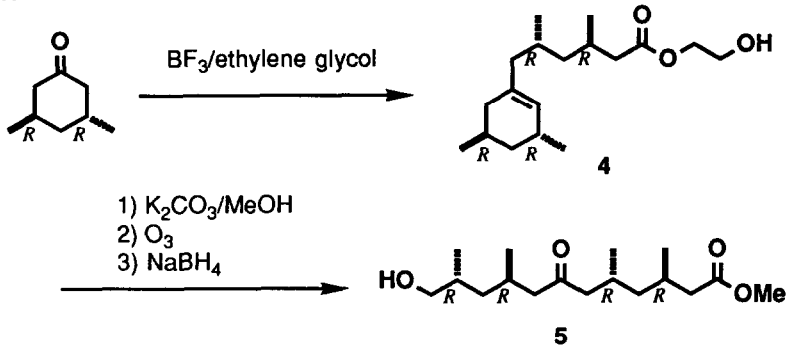
Entry	Substrates	Products
1	n = 1	**1a** 70%
2	n = 2	**1b** 75%
3	n = 3	**1c** 45%
4	n = 8	**1d** 30%



Scheme 3

As shown in Table 1, the other cycloalkanones also underwent ring cleavage to give the corresponding hydroxyethyl esters (**1b-d**) In addition, an acyclic 6-undecanone gave the hydrocarbon (**1e**) in 35% yield (Scheme 3) In the case of over 7-membered cycloalkanones (entries 3 and 4) as well as 6-undecanone, the yields of products were reduced and the starting substrates were recovered in 40-60% yields, which may be ascribed to the difficulty of first aldol condensation

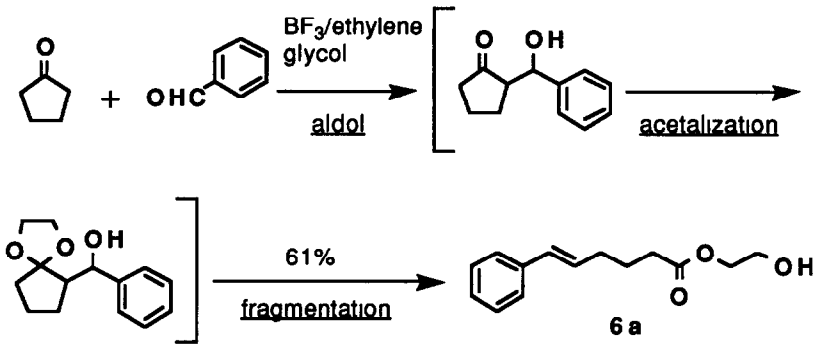
As a further application of this reaction, we investigated the synthesis of chiral straight-chain compounds with syndiotactic methyl function, in which successive methyl groups appear alternately on one side and then on the other side Macrolide antibiotics feature[5] a 12- to 16-membered lactone, in which the basic skeleton possesses in part the isotactic or syndiotactic hydroxy and/or methyl functions, as exemplified by lardolure[6] of insect pheromones



Scheme 4

Reaction of C_2-symmetric (*R*,*R*)-3,5-dimethylcyclohexanone[7] with BF_3/ethylene glycol proceeded smoothly to give the ester (**4**) in 72% yield as an inseparable mixture with an *exo*-olefinic isomer (8% content, determined from the ^{13}C-NMR spectrum)(Scheme 4) Transesterification of **4** with MeOH followed by ozonolysis and reduction using sodium borohydride afforded the ester (**5**)($[\alpha]_D$+29 3) with syndiotactic methyl function as a single isomer (68% yield from **4**) Thus, the ring cleavage and subsequent oxidative cleavage of the resulted double bond provided the novel procedure for the synthesis of chiral straight-chain compounds with

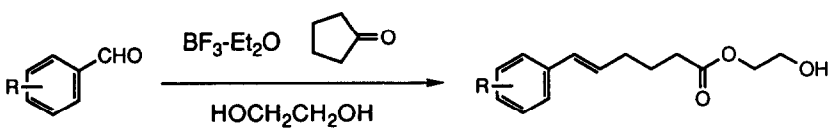
syndiotactic or isotactic configuration, starting from the monocyclic substrate with a configurationally desired substituent



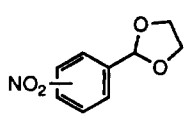
Scheme 5

Next, our attention was directed to the ring cleavage reaction based on a crossed aldol condensation The reaction of cyclopentanone and benzaldehyde under the same reaction conditions was carried out, and the hydroxyethyl ester (**6a**) was obtained in 61% yield (Scheme 5) The ^{1}H-NMR spectrum exhibited typical signals assignable to the hydroxyethyl ester [δ 4 21 (2H, m, CO_2CH_2), 3 81 (2H, m, CH_2O)], two olefinic protons [δ 6 40, 6 17], and aromatic protons [δ 7 36-7 22 (5H)] The coupling constant between two olefinic protons was 15 9 Hz, suggesting *trans* geometry of the double bond Next, the reaction of cyclopentanone with aryl aldehydes was examined to study the effect of substituents on the benzene ring, and the results are summarized in Table 2 Anisaldehydes having an electron-releasing substituent (OMe) afforded the corresponding esters (**6b-d**) similarly as in the case of using benzaldehyde However, similar treatment of nitrobenzaldehydes with an electron-withdrawing substituent gave only the acetals (**7g-i**) and no hydroxyethyl esters were detected.

Table 2. Ring cleavage based on crossed aldol condensation



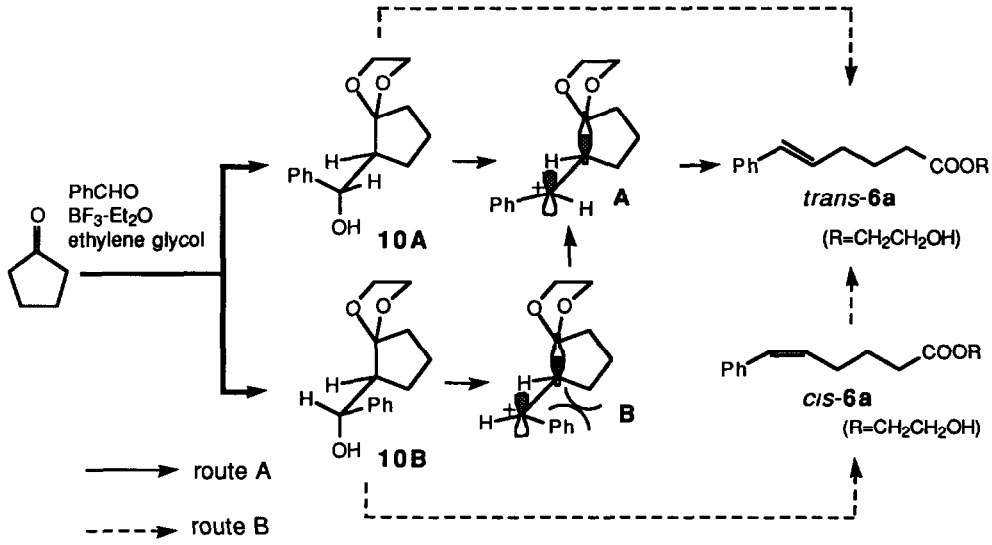
Entry	Substrates	Products	
1	R = H	**6a**	61%
2	R = *o*-MeO	**6b**	59%
3	R = *m*-MeO	**6c**	30%
4	R = *p*-MeO	**6d**	58%
5	R = *o*-Me	**6e**	32%
6	R = *p*-Cl	**6f**	24%
7	R = (*o*,*m* or *p*)-NO_2		0%



7g-i

Discussion

It is noteworthy that the cleavage of cyclopentanone based on the crossed aldol condensation with benzaldehyde proceeded stereoselectively to give only the *trans* isomer This finding allows us to consider the following two reaction mechanisms (route A and B) as shown in Scheme 6 Aldol condensation of cyclopentanone with benzaldehyde followed by acetalization gives a mixture of **10A** and **10B** Route A Subsequent elimination of the hydroxy function might provide the corresponding cationic intermediates (**A** and **B**) Intermediate **A** should be favorable to **B** because of the steric repulsion between the benzene ring and the cyclopentane skeleton to afford *trans* product Route B Isomerization of the *cis*-**6a** to the *trans*-**6a** might be catalyzed by BF_3-etherate



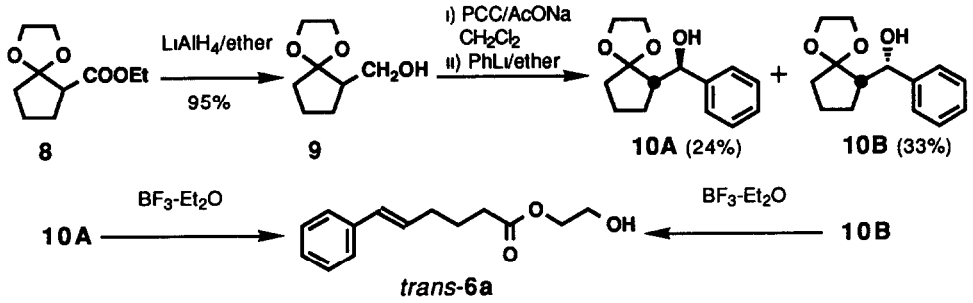
Scheme 6

To clarify the reaction pathway, the following two experiments were examined (Scheme 7 and 8)

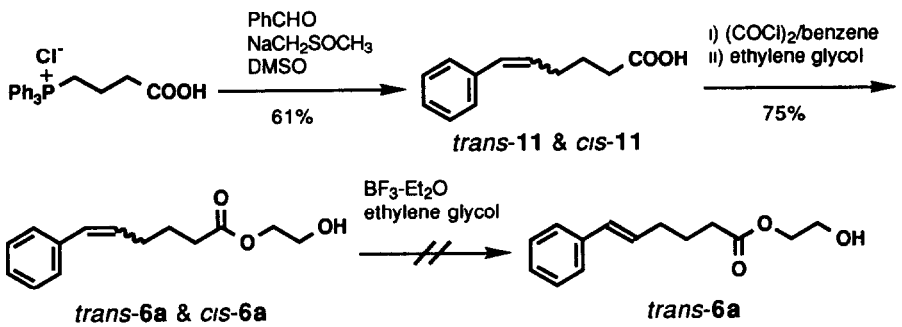
1) Reduction of the ester (**8**) with $LiAlH_4$, and subsequent oxidation of **9** with PCC followed by alkylation with PhLi afforded a mixture of **10A** and **10B**, which could be separated by column chromatography on silica gel Independent fragmentation of **10A** and **10B** with BF_3-etherate gave the same *trans*-**6a** in fairly good yields, but no *cis*-**6a** could be detected (Scheme 7)

2) Wittig reaction of benzaldehyde with phosphonium salt[8] derived from 5-bromovaleric acid afforded a mixture of *trans*- and *cis*-**11**, which was converted to an inseparable mixture (1 to 1) of *cis*- and *trans*-**6a** *via* conventional methods The ratio of two geometrical isomers was easily determined by ^{1}H-NMR spectroscopy, because two olefinic protons in *cis*-**6a** were observed at δ 6 46 (d, J = 11 6 Hz) and 5 60 (dt, J = 11 6, 7 3 Hz), and those of *trans*-**6a** at δ 6 40 (d, J = 15 9 Hz) and 6 17 (d, J = 15 9 Hz) After treatment of the 1 to 1 mixture of *cis*- and *trans*-**6a** with BF_3-etherate in CH_2Cl_2 for 1 day, the conversion of *cis*-**6a** to *trans*-**6a** was not observed (Scheme 8)

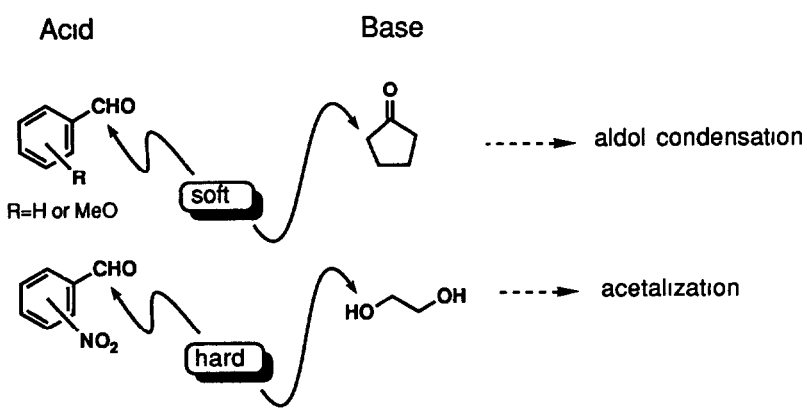
These results suggest the route A in Scheme 6 may be conceivable for the stereoselective formation of the *trans*-**6a**



Scheme 7



Scheme 8



Scheme 9

Scheme 9 explains a difference between nitrobenzaldehyde and anisaldehyde for the reaction using BF_3-etherate/ethylene glycol Based on the hard-soft acid-base concepts, ethylene glycol is a hard base and enol carbon is a soft one The carbonyl carbon of benzaldehyde is considered to be softer than that of aliphatic aldehydes because of the resonance effect of the benzene nucleus Thus, the crossed aldol condensation of cyclopentanone with anisaldehyde or benzaldehyde proceeds to induce the fragmentation *via* acetalization In contrast, the carbonyl carbon of nitrobenzaldehyde is a hard acid as is also that of aliphatic aldehydes because the nitro function, considered as a strong electron-withdrawing substituent, circumvents the resonance effect of the benzene nucleus on the carbonyl function Consequently, nitrobenzaldehydes underwent acetalization with ethylene glycol prior to aldol condensation

Experimental

IR spectra were measured with a JASCO A-202 spectrometer ^{1}H-NMR and ^{13}C-NMR spectra were measured in $CDCl_3$ on JNM-FX 100 and JEOL JNM-GX 270 spectrometers with tetramethylsilane as an internal standard Mass spectra were taken on a JEOL-D 300 or DX 300 spectrometers Optical rotations were measured on JASCO DIP-360 polarimeter Each reaction was monitored by TLC (silica gel 60F-254 plates) Column chromatography was performed using Merck Kieselgel 60 (70-230 mesh)

Ring cleavage of cycloalkanone based on the intermolecular aldol condensation

General procedure (Table 1): To a solution of cycloalkanone (6 mmol, 1eq) in CH_2Cl_2 (10-15 ml), was added BF_3-etherate (5 3 ml, 42 mmol, 7 eq) at 0°C After 1 h, ethylene glycol (1 84 g, 30 mmol, 5 eq) was added to the solution The mixture was stirred at room temperature for 24 h (150 h for entry 4), then diluted with saturated aqueous $NaHCO_3$, and extracted with ether The ether extract was washed with brine, then dried over $MgSO_4$, and concentrated to dryness The crude product was purified by column chromatography on silica gel (25% AcOEt in hexane) to give the hydroxyethyl ester as a colorless oil The reaction of 6-undecanone was also carried out in a similar manner **1a** IR (neat, cm^{-1}) 3430, 3050, 1730, 1650, ^{1}H-NMR ($CDCl_3$) δ 5 33 (1H, m), 4 22 (2H,m), 3 82 (2H, m), 2 43-1 46 (15H, m), MS *m/z* (EI) 212 (M^+), 151, 150,108, 93, HRMS *m/z* calcd for $C_{12}H_{20}O_3$ 212 1412, found 212 1425 **1b** IR (neat, cm^{-1}) 3450, 3050, 1740, 1650, ^{1}H-NMR ($CDCl_3$) δ 5 37 (1H, m), 4 22 (2H, m), 3 75 (2H, m), 2 43-1 24 (19H, m), MS *m/z* (EI) 240 (M^+), 179, 178, 149, 107, HRMS *m/z* calcd for $C_{14}H_{24}O_4$ 240 1725, found 240 1711 **1c** IR (neat, cm^{-1}) 3450, 3050, 1740, 1650, ^{1}H-NMR ($CDCl_3$) δ 5 51 (1H, m), 4 22 (2H, m), 3 84 (2H, m), 2 43-1 19 (23H, m), MS *m/z* (EI) 268 (M^+), 207, 206, 163, HRMS *m/z* calcd for $C_{16}H_{28}O_3$ 268 2038, found 268 2051 **1d** IR (neat, cm^{-1}) 3400, 3050,1730, 1650, ^{1}H-NMR ($CDCl_3$) δ 5 09 (1H, m), 4 22 (2H, m), 3 85 (2H, m), 2 43-1 27 (43H, m), MS *m/z* (EI) 408 (M^+), 347, 346, 180, HRMS *m/z* calcd for $C_{26}H_{48}O_3$ 408 3603, found 408 3609 **1e** IR (neat, cm^{-1}) 1660, ^{1}H-NMR ($CDCl_3$) δ 5 09 (1H, m), 1 95-0 83 (31H, m), MS *m/z* (EI) 224 (M^+), 168, 112, 97, HRMS *m/z* calcd for $C_{16}H_{32}$ 224 2504, found 224 2519

Transesterification of 1a

To a solution of **1a** (200 mg, 0 943 mmol) in MeOH (5 ml) was added K_2CO_3 (55 mg) at room temperature After 5 h, the MeOH was evaporated under reduced pressure The residual oil was neutralized with aqueous 5% HCl, and extracted with ether The ether extract was washed with brine, then dried over $MgSO_4$, and evaporated The crude product was purified by column chromatography on silica gel (5% AcOEt in hexane)

to give 154 mg (0 849 mmol, 90% yield) of the methyl ester (**2**) as a colorless oil ^{1}H-NMR ($CDCl_3$) δ 5 30 (1H, brs), 3 60 (3H, s), 2 40-1 10 (14H, m)

Methyl 9-Formyl-6-oxononanoate (3)

To a solution of **2** (126 mg, 0 693 mmol) in CH_2Cl_2 (2ml) was added a solution of MCPBA (80% purity) (150 mg, 0 693 mmol) in CH_2Cl_2 (2 ml) at 0°C After being stirred at room temperature for 6 h, the reaction mixture was diluted with aqueous 10% $NaHSO_3$ and aqueous 10% Na_2CO_3, and extracted with ether The extract was washed with brine, dried over $MgSO_4$, and evaporated to give the crude epoxide compound To a solution of the crude epoxide in acetone (5 ml) was added 1% H_2SO_4 (5 ml) at room temperature After being stirred at room temperature for 12 h, the reaction mixture was saturated with NaCl, and extracted with $CHCl_3$ The extract was dried over $MgSO_4$, and evaporated under reduced pressure to give the crude diol To a solution of the crude diol in ether (1 ml) was added a solution of $NaIO_4$ (148 mg, 0 693 mmol) in H_2O (1 ml) at 0°C After being vigorously stirred at room temperature for 12 h, the reaction mixture was extracted with ether The extract was washed with brine, then dried over $MgSO_4$, and concentrated to dryness The crude product was purified by column chromatography on silica gel eluted with hexane followed by ethylacetate to give 22 2 mg (0 104 mmol, 15%) of the aldehyde (**3**) as a colorless oil IR (neat, cm^{-1}) 2950, 2875, 2720, 1740, 1725, 1710, 1440, 1410, 1370, 1200, ^{1}H-NMR ($CDCl_3$) δ 9 76 (1H, m), 3 67 (3H, s), 2 56-1 57 (14H, m), ^{13}C-NMR ($CDCl_3$) δ 209 6 (s), 201 8 (d), 173 8 (d), 51 5 (q), 43 0 (t), 42 4 (t), 41 4 (t), 33 8 (t), 24 5 (t), 23.2 (t), 16 1 (t), MS *m/z* (FD) 214 (M^+)

Hydroxyethyl 6-[(3*R*,5*R*)-3,5-Dimethylcyclohexenyl]-(3*R*,5*R*)-3,5-dimethylhexanoate (4)

Colorless oil $[\alpha]_D^{22}$ +77 3 (c=4 54, $CHCl_3$), IR (neat, cm^{-1}) 3450, 1740, 1660, 1450, 1380, 1170, 1080, 880, ^{1}H-NMR ($CDCl_3$) δ 5 25 (1H, brs), 4 22 (2H, m), 3 83 (2H, m), 2 08 (8H, m), 1 80-1 00 (7H, m), 0 96 (3H, d, *J*=7 3Hz, CH_3), 0 93 (3H, d, *J*=6 6Hz, CH_3), 0 91 (3H, d, *J*=6 6Hz, CH_3), 0 81 (3H, d, *J*=6 6Hz, CH_3), ^{13}C-NMR (67 8 MHz, $CDCl_3$) δ 173 6 (CO), 134 5 (=C=), 128 4 (=CH-), 65 9, 61 4 (-OCH_2), 46 6, 43 9, 42 7, 37 9, 36 6 (CH_2), 28 5, 27 9, 27 9, 24 9 (-CH(CH_3)-), 21 9, 21 3, 19 3, 19 3 (CH_3), HRMS *m/z* calcd for $C_{18}H_{32}O_3$ 296 2351, found 296 2355

Methyl (3*R*,5*R*,9*R*,11*R*)-12-Hydroxy-3,5,9,11-tetramethyl-7-oxododecanoate (5)

Conversion of **4** to **5** was accomplished *via* the following three steps Compound **4** (411 mg) was converted to the corresponding methyl ester (329 mg) by stirring in MeOH (5 ml) in the presence of K_2CO_3 at room temperature, and subsequent ozonolysis of the methyl ester in CH_2Cl_2 followed by reduction with $NaBH_4$ in MeOH afforded **5** Colorless oil $[\alpha]_D^{24}$ +29 3 (c=2 88, $CHCl_3$), IR (neat, cm^{-1}) 3400, 1730, 1710, 1430, 1360, 1170, 1030, ^{1}H-NMR ($CDCl_3$) δ 3 66 (3H, d), 3 44 (2H, m), 2 17 (2H,m), 1 71 (3H,m), 1 52 (1H, br), 1 14 (4H, m), 0 91 (12H, m), ^{13}C-NMR (67 8 MHz, $CDCl_3$) δ 210 5 (CO), 173 6 (C=O), 68 7 (CH_2OH), 51 7 (CH_2), 51 4 (OCH_3), 51 3, 44 0, 42 2, 40 4 (CH_2), 33 2, 27 7, 26 4, 26 3 (-CH(CH_3)-), 19 6, 19 5, 19 3, 16 2 (CH_3), HRMS *m/z* calcd for $C_{17}H_{32}O_4$ 300 2300, found 300 2305

Cleavage of cyclopentanone based on the crossed aldol condensation

General procedure (Table 2): To a mixture of benzaldehyde (630 mg, 5 94 mmol), BF_3-etherate (5 3 ml, 42 2 mmol), and CH_2Cl_2 (4 ml), was added dropwise a solution of cyclopentanone (500 mg, 5 94 mmol) in CH_2Cl_2 (2 ml) at 0°C After 1 h, ethylene glycol (1 84 g, 29 7 mmol) was added to the solution The mixture was stirred at room temperature for 24 h, then diluted with aqueous saturated $NaHCO_3$, and extracted with ether Ether extract was washed with brine, then dried over $MgSO_4$, and evaporated The crude product was purified by column chromatography on silica gel to give the hydroxyethyl ester compound (*trans*-**6a**) (848 mg, 3 62 mmol,

61%) as a colorless oil The reaction using *o*-, *m*-, *p*-anisaldehydes, *o*-tolualdehyde and *p*-chlorobenzaldehyde were carried out in a similar manner to give **6b-f** Treatment of *o*-, *m*-, *p*-nitrobenzaldehydes with BF_3-etherate/ ethylene glycol in a similar manner gave the acetals (**7g-i**) *trans*-**6a** IR (neat, cm^{-1}) 3430, 3025, 1730, 1640, ^{1}H-NMR ($CDCl_3$) δ 7 36-7 22 (5H, m), 6 40 (1H, d, *J*=15.9 Hz), 6 17 (1H, dt, *J*=15 9, 6 0 Hz), 4 21 (2H, m), 3 80 (2H, m), 2 50-1.76 (7H, m); ^{13}C-NMR ($CDCl_3$) δ 173 9 (s), 137 5 (s), 130 9 (d), 129 4 (d), 128 5 (2 C, d), 127 0 (d), 126.0 (2 C, d), 65 9 (t), 61 1 (t), 33 8 (t), 32 3 (t), 24 5 (t), MS *m/z* (EI) 234 (M^+), 173, 130, 117, HRMS *m/z* calcd for $C_{14}H_{18}O_3$ 234 1256, found 234 1244 **6b** IR (neat, cm^{-1}) 3450, 3040, 1730, 1600, ^{1}H-NMR ($CDCl_3$) δ 7 43-6 89 (4H, m), 6 73 (1H, d, *J*=15 9 Hz), 6 15 (1H, dt, *J*=15 9, 6 7 Hz), 4 20 (2H, m), 3 84-3 76 (5H, m), 2 50-1 76 (7H, m), ^{13}C-NMR ($CDCl_3$) δ 174 0 (s), 156 4 (2 C, s), 130 1 (d), 128 1 (d), 126 5 (d), 125 6 (d), 120 7 (d), 110 9 (d), 66 0 (t), 61 25 (t), 55 5 (q), 33 5 (t), 32 8 (t), 24 6 (t), MS *m/z* (EI) 264 (M^+), 203, 160, 147, HRMS *m/z* calcd for $C_{15}H_{20}O_4$ 264 1361, found 264 1368 **6c** IR (neat, cm^{-1}) 3450, 3000, 1730, 1590, ^{1}H-NMR ($CDCl_3$) δ 7 29-6 69 (4H, m), 6.40 (1H, d, *J*=15 9 Hz), 6 14 (1H, dt, *J*=15 9, 5.9 Hz), 4 20 (2H, m), 3 89-3 75 (5H, m), 2 49-1 73 (7H, m), MS *m/z* (EI) 264 (M^+), 203, 160, 147, HRMS *m/z* calcd for $C_{15}H_{20}O_4$ 264 1361, found 264 1375 **6d** IR (neat, cm^{-1}) 3400, 3040, 1730, 1600, ^{1}H-NMR ($CDCl_3$) δ 7 25 (2H, m), 6 84 (2H, m), 6 35 (1H, d, *J*=15 9 Hz), 6 00 (1H, dt, *J*=15 9, 6 5 Hz), 4 20 (2H, m), 3 76 (5H, m), MS *m/z* (EI) 264 (M^+), 203, 160, 147, HRMS *m/z* calcd for $C_{15}H_{20}O_4$ 264 1361, found 264 1381 **6e** IR (neat, cm^{-1}) 3450, 3050, 1730, 1600, ^{1}H-NMR ($CDCl_3$) δ 7 30-7 20 (4H, m), 6 38 (1H, d, *J*=15 9 Hz), 6 13 (1H, dt, *J*=15 6, 5 8 Hz), 4 21 (2H, m), 3 81 (2H, m), 2 33 (3H, s), MS *m/z* (EI) 248 (M^+), 187, 144, HRMS *m/z* calcd for $C_{15}H_{20}O_3$ 248 1412, found 248 1400 **6f** IR (neat, cm^{-1}) 3450, 3100, 1730, 1600, ^{1}H-NMR ($CDCl_3$) δ 7 34-7 22 (4H, m), 6 61 (1H, d, *J*=15 6 Hz), 6 07 (1H, dt, *J*=15 6, 6 8 Hz), 4 21 (2H, m), 3 82 (2H, m), MS *m/z* (EI) 270 (M^+), 268, 207, 166 **7g** ^{1}H-NMR ($CDCl_3$) δ 7 60 (4H, m), 6 40 (1H, s), 4 00 (4H, m) **7h** IR (neat, cm^{-1}) 3100,1610, 1530, 1480, ^{1}H-NMR ($CDCl_3$) δ 7 81 (4H, m), 5 89 (1H, s), 4 11 (4H, m) **7i** ^{1}H-NMR ($CDCl_3$) δ 8 10 (2H, m), 7 60 (2H, m), 5 80 (1H, s), 4 00 (4H, m)

1,1-Ethylenedioxy-2-hydroxymethylcyclopentane (9)

To a suspended solution of lithium alminium hydride (500 mg, 13 2 mmol) in ether (50 ml) was added dropwise a solution of **8** (3g, 15 0 mmol) in ether (50 ml) at 0°C After 1 h, AcOEt and aqueous 10% NaOH were added to the suspended solution The mixture was filtered, and the filtrate was evaporated The crude product was purified by column chromatography on silica gel with hexane/ethylacetate (6 4) to give the alcohol (**9**) (2 25 g, 14 2 mmol, 95%) as a colorless oil IR (neat, cm^{-1}) 3430, 1020, ^{1}H-NMR ($CDCl_3$) δ 3 94 (4H, m), 3 65 (2H, t, *J*= 5 1 Hz), 2 63 (1H, brs), 2 21-1 51 (7H, m), MS *m/z* (EI) 158 (M^+), 129, 99, 55

1,1-Ethylenedioxy-2-(1-hydroxy-1-phenylmethyl)cyclopentane (10A), (10B)

To a mixture of PCC (546 mg, 1 45 mmol), AcONa (52 mg, 0 64 mmol) in CH_2Cl_2 (5 ml) was added 200 mg of **9** (1 27 mmol) at 0°C After being stirred at room temperature for 3 h, the reaction mixture was quenched with isopropanol, diluted with ether, and filtered through a short pad of Florisil The filtrate was evaporated under reduced pressure to give the crude aldehyde compound (150 mg) To a solution of the crude product in ether (10 ml), was added dropwise 1 4M-PhLi/ether (0 9 ml, 1 26 mmol) at 0°C under an Ar atmosphere After being stirred at 0°C for 30 min, the reaction mixture was diluted with aqueous saturated NH_4Cl, and extracted with ethylacetate The extract was dried over $MgSO_4$, and evaporated under reduced pressure The residue was purified by column chromatography on silica gel with hexane/AcOEt to give **10B** (98 1 mg, 0 419 mmol, 33%) (Hexane AcOEt = 8 2) and **10A** (71 3 mg, 0 305 mmol, 24%) (Hexane AcOEt = 7 3) **10A** IR (neat, cm^{-1})

3500, 3060, 3030, 1600, 1500, ^{1}H-NMR ($CDCl_3$) δ 7 39-7 26 (5H, m), 4 73 (1H, d, *J*=9 3 Hz), 3 97 (4H, m), 2 49-1 23 (8H, m); MS *m/z* (EI) 234 (M^+), 216, 99 **10B** IR (neat, cm^{-1}) 3500, 3060, 3030, 1600, 1500, ^{1}H-NMR ($CDCl_3$) δ 7 38-7 24 (5H, m), 5 06 (1H, d, *J*=2 2 Hz), 3 99 (4H, m), 2 42-1 46 (8H, m); MS *m/z* (EI) 234 (M^+), 216, 99. To a solution of **10A,B** (60 mg, 0 256 mmol) in CH_2Cl_2 (1 ml) was added BF_3-etherate (0 22 ml, 1 79 mmol) at 0°C The reaction mixture was stirred at room temperature for 14 h to afford *trans*-**6a** (45 mg, 75 % yield from **10A**, 47 mg, 78% yield from **10B**)

6-Phenyl-5-hexenoic acid (*trans*-11 & *cis*-11)

To a solution of 4-carboxybutyltriphenylphosphonium bromide (4 15 g, 9 37 mmol) in DMSO (4 ml) was added $NaCH_2COCH_3$ (2M in DMSO, 9 4 ml, 18 8 mmol) under Ar atmosphere After 30 min, a solution of benzaldehyde (140 mg, 1 32 mmol) in DMSO (1 ml) was added to the solution The mixture was warmed at 50°C for 19 h, then cooled to 0°C, diluted with H_2O (20 ml), and extracted with ethyl acetate After being acidified with 6N aqueous HCl, the aqueous layer was further extracted with ethyl acetate The organic extract was dried over $MgSO_4$, and evaporated under reduced pressure. The residue was purified by column chromatography on silica gel (40% hexane in AcOEt) to give the carboxylic acid (*trans*- & *cis*-**11**) (153 mg, 0 805 mmol, 61%) IR (neat, cm^{-1}) 3200, 3025, 1700, 1600, 1580, 1500, ^{1}H-NMR ($CDCl_3$) δ 9 50 (1H, brs), 7 20 (5H, m), 6 30 (1H, m), 5 70 (1H, m), 2 70-1 70 (6H, m)

Esterification of *trans*-11 & *cis*-11

A solution of *trans*- and *cis*-**11** (145 mg, 0 763 mmol) in benzene (2 ml) was treated with oxalic chloride (145 mg, 1 14 mmol) at room temperature After being stirred at room temperature for 30 min, the reaction mixture was evaporated under reduced pressure To the residue was added ethylene glycol (1 ml) After being stirred at room temperature for 3 h, the reaction mixture was diluted with H_2O, and extracted with ether The extract was washed with aqueous saturated $NaHCO_3$ and brine, dried over $MgSO_4$, and concentrated to dryness The residue was purified by column chromatography on silica gel (20% AcOEt in hexane) to give a 1 1 mixture of the *cis*- and *trans*-**6a** (134 mg, 0 572 mmol, 75%) IR (neat, cm^{-1}) 3400, 1720, 1600, 1500, ^{1}H-NMR ($CDCl_3$) δ 7 25 (5H, m), 6 46 (0 5H, d, *J*=11 6 Hz), 6 40 (0 5H, d, *J*=15 9 Hz), 6 17 (0 5H, dt, *J*=15 9 Hz, 6 0 Hz), 5 60 (0 5H, dt, *J*=11 6, 7 3 Hz), 4 18 (2H, m), 3 79 (2H, m), 2 47-1 74 (6H, m), ^{13}C-NMR ($CDCl_3$) δ 174 0 (s), 173 9 (s), 137 5 (s), 137 4 (s), 133 2 (d), 130 9 (d), 129 7 (d), 129 4 (d), 128 7 (t), 128 5 (d), 128 4 (d), 128 2 (d), 127 0 (d), 126 0 (d), 66 0 (t), 61 2 (t), 33 6 (t), 33 5 (t), 32 3 (t), 27 8 (t), 25 0 (t), 24 4 (t), MS *m/z* (FD) 234 (M^+)

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