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ASYMMETRIC SIMMONS-SMITH REACTIONS USING HOMOCHIRAL PROTECTING GROUPS[1]

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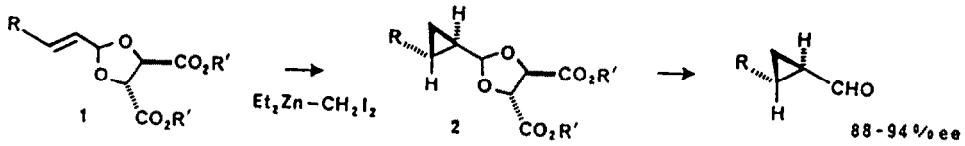
ABSTRACT Asymmetric Simmons-Smith reactions of α,β-unsaturated acetals derived from chiral dialkyl tartrate or (2R,4R)-2,4-pentanediol are described. Treatment of the acetal with diethylzinc and methylene iodide gives a cyclopropane with high diastereoselectivity. The acetal group is readily transformed to the aldehyde or the ester group. In addition, the method is successfully applied to the enantioselective synthesis of 5,6-methanoleukotriene A_4, a stable and selective inhibitor of leukotriene biosynthesis.

Introduction of the cyclopropane ring to organic molecule in enantiomerically pure manner is one of the most important problem in organic synthesis. Although Simmons-Smith reaction is the powerful method for cyclopropanation of the olefin and its scope and mechanism have been widely studied,[2] there have been little studied on its application to the asymmetric reactions. Recent studies of asymmetric syntheses using homochiral protecting groups[3] encouraged us to explore possibility of the asymmetric Simmons-Smith reactions using homochiral acetals. In this paper, we describe a new method for asymmetric cyclopropanation and its application to the synthesis of chiral 5,6-methanoleukotriene A_4, a stable and selective inhibitor of leukotriene biosynthesis.[4]

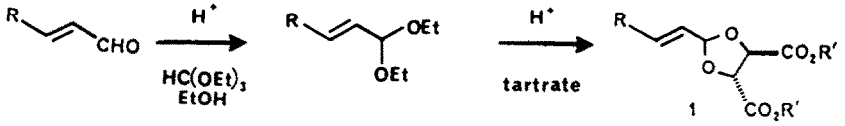
Asymmetric Simmons-Smith Reactions: When an α,β-unsaturated acetal dissolved in hydrocarbon was treated with excess methylene iodide and diethylzinc,[5] the corresponding cyclopropane was obtained in a reasonable yield with high diastereoselectivity. The acetal group was readily transformed to the aldehyde (hydrolysis) or to the ester (ozonolysis).[6] The process is illustrated in Scheme 1.

Scheme 1.



The starting acetal was readily synthesized from the corresponding aldehyde as shown in Scheme 2. The direct preparation of **1** from their aldehyde gave rise to rather low yield. It should be noted that a single isomer of the starting acetal was formed from dialkyl tartrate which has C_2 axis symmetry, thus avoiding troublesome separation of diastereoisomer.

Scheme 2.



Results are given in Table 1. Since both (R,R)- and (S,S)- tartaric acid esters are readily available in optically pure form,[7] this method allows the synthesis of both enantiomers of cyclopropanes from α,β-unsaturated aldehyde in a predictable manner. Generally the acetal derived from diisopropyl tartrate (DIPT) gave a slightly higher diasteromeric excess than that of diethyl tartrate (DET) (**2b**, **2c** and **2d**, **2e**). The reactions of **1h** and **1i** indicated that the asymmetric inductions are totally controlled by the auxiliary tartrate ligand and are independent of the chirality of isopropenyl group. The diastereomeric ratio was determined by ^{1}H NMR analysis of the acetal of (2R,4R)-2,4-pentanediol obtained by transacetalization of **2**. Thus, a base-line separation of the two doublets of C<u>H</u>(OR)$_2$ was obtained in the presence of the shift reagent, Eu(fod)$_3$ (90 or 60 MHz) or in the absence of the shift reagent (500 MHz). The absolute configuration has proven by the measurement of $[\alpha]_D$ value after transformation to the corresponding aldehyde or carboxylic acid.

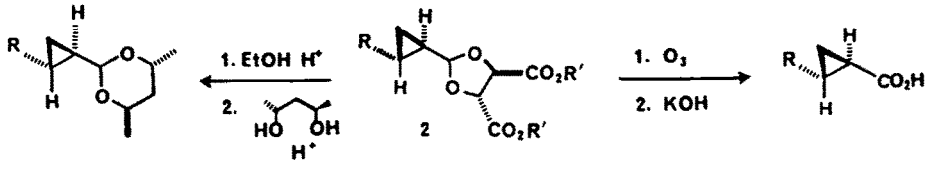
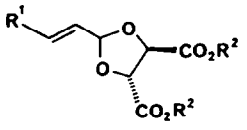
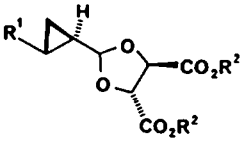
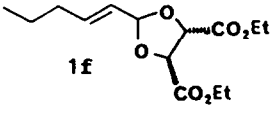
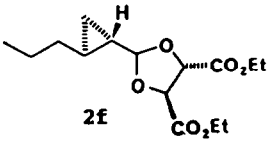
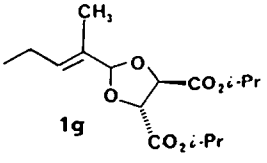
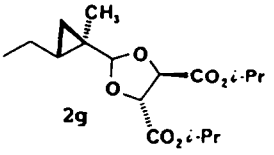
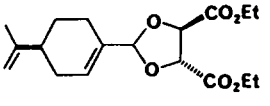
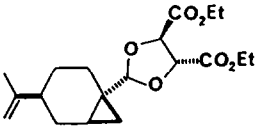
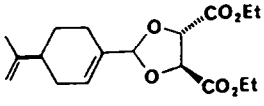
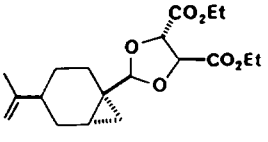


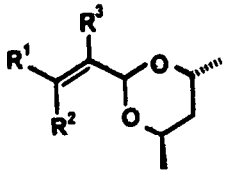
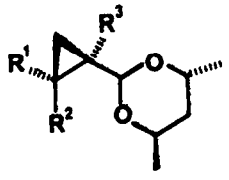
Table 1. Asymmetric Simmons-Smith Reaction of 1

Acetal			Conditions (°C, h)	Product	Yield of 2[a] (%)	%de[b]
						
R^1	R^2					
Me	i-Pr	(1a)	-20, 1; 0, 4	2a	90	94
n-Pr	Et	(1b)	-20, 3	2b	95	88
n-Pr	i-Pr	(1c)	-20, 1; 0, 5	2c	80	91
Ph	Et	(1d)	-20, 6; 0, 6	2d	82	87
Ph	i-Pr	(1e)	-20, 1; 0, 3	2e	92	91
 1f			-20, 5	 2f	94	89
 1g			-20, 1; 0, 4	 2g	81	89
 1h			-20, 7; 20, 10	 2h	61	88[c]
 1i			-20, 7; 20, 10	 2i	50	85[c]

[a] Isolated yield. [b] Diastereomeric excess (de). Unless otherwise specified, the diastereoselectivity was determined as described in text. [c] The diastereomeric ratio and absolute configuration were tentatively assigned by ^1H NMR spectra ($CDCl_3$) of the corresponding aldehyde after the mild hydrolysis.

Chiral acetals derived from (2R,4R)-2,4-pentanediol was also studied and results are shown in Table 2. The (R,R)-stereochemistry of the produced cyclopropane was established by the conversion to the corresponding acid.

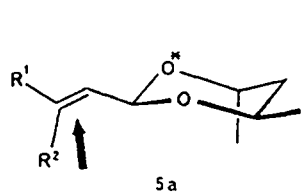
Table 2. Asymmetric Simmons-Smith Reaction of 3

Acetal				Product		
	R^1	R^2	R^3		Yield of 4[a] (%)	%de[b]
						
3a	Me	H	H	**4a**	74	69
3b	n-Pr	H	H	**4b**	95	71
3c	Ph	H	H	**4c**	85	68
3d	Me	Me	H	**4d**	81	-29[c]
3e	Et	H	Me	**4e**	69	75

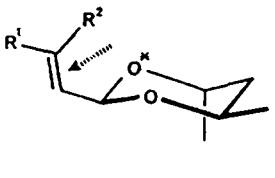
[a] Isolated yield. [b] Diastereomeric excess determined by ^{1}H NMR analysis of the product in the presence of shift reagent, Eu(fod)$_3$. [c] The absolute configuration was confirmed by the transformation to the corresponding carboxylic acid.

Apparently the observed selectivity is ascribed to the eminent affinity of zinc reagent for ethereal oxygen. Complex formation between the oxygen atom and the organozinc reagent, followed by methylene transfer to the nearest face of the neighboring double bond, has been proposed to account for the stereoselectivity and the large rate enhancement found for methylene addition to allylic alcohols and ethers relative to simple olefins.[2,8] The stereochemical outcome of Table 2 was surprising because it is in contrast to the regioselectivity reported for the previous reaction of acetal with (2R,4R)-2,4-pentanediol[3] in which one of the ether oxygen, O* in 5, should be coordinated preferentially by Lewis acid of the system. The same oxygen therefore should function as a syn director for the transfer of methylene: However, the observed stereochemical course is the opposite and this might be the result, inter alia, of different geometry relating olefinic linkage during cyclopropanation process (5b rather than 5a).[9] Indeed, the trisubstituted olefin 3d, $R^1 = R^2 = Me$, $R^3 = H$, for which the corresponding 5b may be rather unlikely from the steric interaction of R^2 and the ring, gave the corresponding cyclopropane with the opposite stereochemistry. Thus, the substitution pattern of the starting trisubstituted double bond can have a pronounced effect on diastereoselectivities of the reaction: R^2 should be H for the selective reaction. In the reaction of the acetal 1, the similar structure is also a responsible conformer. Although the exact mechanism of

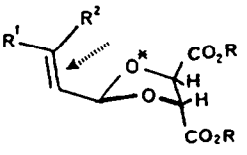
the cyclopropanation is not clear, at least O* in **5c** should be a preferable coordination site of the Lewis acid.



5a

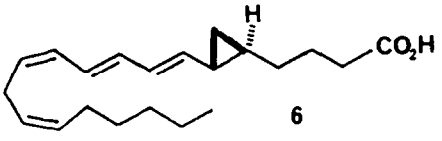


5b

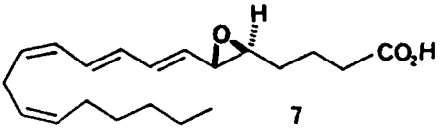


5c

Synthesis of (5R,6R)-5,6-methanoleukotriene A_4: It seems clear that the present method can encompass an availability of chiral cyclopropanes, increasingly important class of biologically active functionalities. One attractive target was (5R,6R)-5,6-methanoleukotriene A_4 (**6**), a stable and selective inhibitor of leukotriene A_4 (**7**) biosynthesis.[10]



6



7

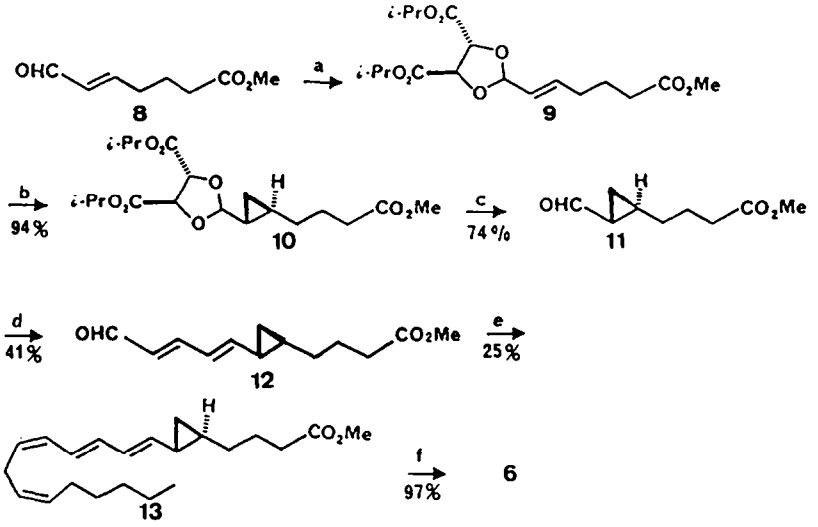
An enantioselective route of **6** is shown in Scheme 3. Acetalization of the α,β-unsaturated aldehyde **8** afforded the corresponding chiral acetal **9**, which was treated with methylene iodide and diethylzinc to give the cyclopropane **10**. Mild hydrolysis of **10** by p-toluenesulfonic acid in methanol-water gave **11**. The enantiomeric ratio of **11** was determined by conversion to the corresponding acetal of (-)-(2R,4R)-2,4-pentanediol whose 500 MHz ^{1}H NMR spectrum showed the purity of 90% ee. Reaction of aldehyde **11** with 1-lithio-4-ethoxybutadiene gave a dienal ester **12**. Selective Wittig reaction of **12** followed by mild hydrolysis of the methyl ester **13** afforded the desired inhibitor **6**. Some biological results of **6** compared with its racemate were shown in Table 3.

Table 3 % Inhibition for 5-lipoxygenase

	100μM	50μM	5μM	IC_{50} (μM)
(-)-**6**	100	100	31.0	9.3
(±)-**6**	100	100	21.0	10.3

In conclusion the asymmetric Simmons-Smith reaction described herein appeares to offer special advantages including high efficiency, procedural simplicity, predictable chirality of the product, and mildness of the conditions. Further application of the process to the synthesis of biologically active compounds and its derivatives is in progress.

Scheme 3.



a) 1) $HC(OEt)_3$-EtOH, NH_4NO_3, 78% 2) L-(+)-DIPT, TsOH-Py. 50%;
b) CH_2I_2-Et_2Zn; c) TsOH, MeOH-H_2O; d) 1) n-Bu_3Sn OEt, n-BuLi;
2) TsOH, THF-H_2O; e) $Ph_3\overset{\oplus}{P}$ $I^{\ominus}$, n-BuLi- HMPA
f) NaOH, MeOH-THF-H_2O

Experimental Section

General. Infrared (IR) spectra were recorded on a Hitachi 260-10 spectrometer. ^1H NMR spectra were measured on a JNM-PMX 60 (60 MHz), JNM-FX 90 QE (90 MHz) or JNM-GX 500 (500 MHz) spectrometer. The chemical shifts are expressed in parts per million downfield from internal tetramethylsilane (δ= 0). Splitting patterns are indicated as s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broad peak. Optical rotations were measured on a JASCO DIP-140 digital polarimeter. All experiments were carried out under an atmosphere of dry argon. For thin layer chromatography (TLC) analyses throughout this work, Merck precoated TLC plates (silica gel 60 GF_{254}, 0.25 mm) were used. The products were purified by preparative column chromatography on silica gel Fuji Davison BW-200 MH. Microanalyses were accomplished at the Institute of Applied Chemistry, Faculty of Engineering, Nagoya University. In experiments requiring dry solvents, ether and THF were distilled from sodium-benzophenone. Hexane and benzene were dried over sodium metal. Dichloromethane, chloroform, and carbon tetrachloride was dried over 4A molecular sieves. (-)-(2R,4R)-2,4-pentanediol was purchased and used after recrystallization from ether; $[\alpha]^{24}_D$ -41.2° (c 9.99, $CHCl_3$). Diethylzinc available as a 3.1 M hexane solution was used as such or after dilution to 2 M solution.[11] Other chemicals were purchased and used as such.

General procedure for the preparation of α,β-unsaturated acetal 1a-i and 3a-e. The mixture of the aldehyde, triethyl orthoformate (1.2 equiv) and a catalytic amount of ammonium nitrate in ethanol was stirred at room temperature until the consumption of the most of the starting aldehyde was confirmed by tlc. The product was washed with aqueous sodium bicarbonate and the organic layers were dried over anhydrous sodium sulfate. Removal of the dried solvent left the corresponding diethylacetal which was used for the next reaction without further purification. The mixture of the aldehyde diethylacetal (3.0 mmol), pyridinium tosylate (30 mg), and dialkyl tartrate (3.3 mmol) or (-)-(2R,4R)-2,4-pentanediol (344 mg, 3.3 mmol) in 30 mL of benzene was heated for 1 h to distill off the solvent and the producing ethanol. After cooling to room temperature, the residue was purified by column chromatography on silica gel (hexane-ether, 3-5:1) to give the corresponding acetal. The physical properties and analytical data of the acetal thus obtained were listed in Table 4a and 4b.

Table 4a. Spectral Data of α,β-Unsaturated Acetals 1 and 3

acetal[a]	IR (cm^{-1})[a]	^1H NMR (δ; ppm)[b]
1a	2970, 2920, 1735, 1365, 935	5.30-6.17 (m, 3 H), 5.03 (m, 2 H), 4.37-4.57 (m, 2 H), 1.78 (d, J = 6.0 Hz, 3 H), 1.28 (d, J = 6.0 Hz, 12 H)
1b	2970, 1750, 1210, 1095	5.30-6.33 (m, 3 H), 4.51 (m, 2 H), 4.29 (q, J = 7.5 Hz, 4 H), 1.32 (t, J = 7.5 Hz, 6 H)
1c	2970, 1740, 1215, 1100	5.30-6.23 (m, 3 H), 5.03 (m, 2 H), 4.47 (m, 2 H), 1.30 (d, J = 7.5 Hz, 4 H)
1d	2990, 1760, 1205, 1150, 1115, 795	7.30 (m, 5 H, ArH), 6.80 (d, J = 16.0 Hz, 1 H), 6.13 (dd, J = 16.0, 6.0 Hz, 1 H), 5.68 (d, J = 6.0 Hz, 1 H), 4.61 (m, 2 H) 4,29 (q, J = 7.6 Hz, 4 H), 1.33 (t, J = 7.6 Hz, 6 H)
1e	2980, 2930, 1745, 1680, 970, 750	7.13-7.63 (m, 5 H), 6.82 (d, J = 16.0 Hz, 1 H), 6.14 (dd, J = 16.0 Hz, 6.0 Hz, 1 H), 5.68 (d, J = 6.0 Hz, 1 H), 1.30 (d, J = 6.0 Hz, 12 H)
1g	2960, 2920, 1730, 1450, 950	5.43-5.63 (m, 1 H), 5.27 (s, 1 H), 5.03 (m, 2 H), 4.47 (m, 2 H), 1.30 (d, J = 6.5 Hz, 12 H)
1h	2970, 2900, 1735, 1640, 945	5.93 (br, 1 H), 5.33 (s, 1 H), 4.67 (br, 2 H), 4.20 (q, J = 6.4 Hz, 4 H), 1.73 (s, 3 H), 1.30 (t, J = 6.4 Hz, 6 H)
3a	2970, 2920, 2850, 1680, 1375	5.43-6.20 (m, 2 H), 5.17-5.33 (m, 1 H), 3.70-4.53 (m, 2 H), 1.72 (d, J = 6.0 Hz, 3 H)
3b	2970, 2920, 1455, 995,	5.33-6.00 (m, 2 H), 5.10 (d, J = 5.0 Hz, 1 H), 3.64-4.50 (m, 2 H)
3c	2985, 2935, 1370, 1130	7.30 (m, 5 H), 6.64 (d, J = 16.0 Hz, 1 H), 6.00 (dd, J = 16.0 Hz, 4.0 Hz, 1 H), 5.31 (d, J = 4.0 Hz, 1 H), 3.67-4.57 (m, 2 H)
3d	2980, 2950, 1690, 1380, 980	5.27 (d, J = 6.0 Hz, 1 H), 1.63 and 1.70 (s, 3 H each), 1.14 and 1.34 (d, J = 7.4 Hz, 3 H each)
3e	2970, 2920, 2860, 1680, 1370, 980	5.20-5.57 (m, 1 H), 4.87 (s, 1 H), 3.60-4.27 (m, 2 H), 1.53 (s, 3 H)

[a] Film. [b] ^1H NMR spectra were taken in CCl_4 solution.

Table 4b. Elemental Analyses of the acetals 1 and 3

acetal	Yield (%)	formula	Calcd C	Calcd H	Found C	Found H
1a	79	$C_{14}H_{22}O_6$	58.73	7.75	58.76	7.72
1b	53	$C_{14}H_{22}O_6$	58.73	7.75	58.69	7.79
1c	48	$C_{16}H_{26}O_6$	61.13	8.34	61.13	8.28
1d[a]	63	$C_{17}H_{20}O_6$	63.74	6.29	63.56	6.36
1e[b]	93	$C_{19}H_{24}O_6$	65.50	6.94	65.66	7.00
1g	61	$C_{16}H_{26}O_6$	61.13	8.34	61.14	8.33
1h	70	$C_{18}H_{26}O_6$	63.87	7.76	63.93	7.72
3a	77	$C_9H_{16}O_2$	69.19	10.32	68.89	10.62
3b	91	$C_{11}H_{20}O_2$	71,70	10.94	71.59	11.05
3c	99	$C_{14}H_{18}O_2$	77.03	8.31	76.95	8.28
3d	78	$C_{10}H_{18}O_2$	70.55	10.66	70.36	10.85
3e	78	$C_{11}H_{20}O_2$	71.70	10.94	71.51	11.13

[a] Mp 55.5-56.0°C. [b] Mp 56.0-57.5°C

General procedure for the cyclopropanation of 1a-i. Small scale: To a solution of the acetal (1.0 mmol) in 10 mL of dry hexane was added diethylzinc (5.0 mmol, 2.5 mL of a 2 M hexane solution) at -20°C. Methylene iodide (0.86 mL, 10 mmol) was added dropwise to the resulting vigorously stirred solution and the mixture was stirred under the condition as shown in Table 1. The reaction mixture was poured into cold aqueous ammonium chloride and the product was extracted with ether repeatedly. The organic layers were washed with sodium thiosulfate, dried over sodium sulfate and concentrated in vacuo. Chromatography of the residual oil on silica gel (hexane-ether, 3-5:1) afforded the corresponding cyclopropane **2a-i**.

For larger scale (20 mmol): To a solution of the acetal **1d**, R^1 = Ph, R^2 = Et (6.4 g, 20 mmol), in dry hexane (220 mL) was added diethylzinc (100 mmol, 32.3 mL of a 3.1 M hexane solution) at -20°C. Methylene iodide (16.2 mL, 0.20 mol) was added dropwise to the resulting mechanically stirred solution and the mixture was mechanically stirred vigorously at -20°C for 6 h and 0°C for 6 h.[12] Treatment of the reaction mixture with aqueous ammonium chloride, sodium thiosulfate and water followed by the purification of the concentrated residue by column chromatography on silica gel (hexane-ether, 5:1) afforded the pure cyclopropane **2d**, R^1 = Ph, R^2 = Et, as a colorless oil (6.08 g, 91%).

The physical properties and analytical data of the cyclopropanes obtained are shown in Table 5a and 5b.

Table 5a. Spectral data of the acetal **2**.

Acetal	IR (cm^{-1})[a]	^1H NMR (δ; ppm)[b]
2a	2930, 1740, 1215, 1200	4.34-4.50 (m, 5 H), 1.30 (d, J = 6.0 Hz, 12 H)
2b	2930, 1750, 1205, 1115	3.93-4.83 (m, 7 H)
2c	2975, 2920, 1730, 1275, 1100	4.17-5.17 (m, 5 H), 1.17 (d, J = 6.0 Hz, 12 H)
2d	3000, 2960, 1755, 1620, 1380, 1160, 870, 760	7.07 (br s, 5 H, ArH), 5.03 (d, J = 5.6 Hz, 1 H), 4.47-4.67 (m, 2 H), 4.20 (q, J = 8 Hz, 4 H), 1.87-2.37 (m, 1 H), 1.27, 1.30 (2t, J = 8 Hz, 3 H each), 0.67-1.87 (m, 3 H)
2e	2970, 1735, 1215, 1100	7.03 (s, 5 H), 4.73-5.27 (m, 3 H), 4.50 (m, 2 H), 1.27 (d, J = 6.5 Hz, 6 H), 1.22 (d, J = 6.5 Hz, 2 H)
2g	2975, 2930, 2870, 1735, 1370, 1215, 1100	5.00 (m, 2 H), 4.27-4.60 (m, 3 H), 1.28 (d, J = 6.0 Hz, 12 H), 1.07 (s, 3 H)
2h	3070, 2990, 2920, 2860, 1740, 1210, 1115	4.63 (s, 1 H), 4.48 (m, 2 H), 4.21 (q, J = 7.5 Hz, 4 H), 1.30 (t, J = 7.5 Hz, 6 H), 0.83 (s, 3 H)

[a] Film. [b] Taken in CCl_4 solution.

Table 5b $[\alpha]_D$ and elemental analyses of the acetal **2**.

acetal	$[\alpha]_D$[a] degree (c, °C)	formula	Calcd C	Calcd H	Found C	Found H
2a	-56.1 (1.10, 24)	$C_{15}H_{24}O_6$	59.98	8.05	60.01	8.12
2b	-45.8 (1.26, 24)	$C_{15}H_{24}O_6$	59.98	8.05	60.12	8.04
2c	-49.3 (1.05, 25)	$C_{17}H_{28}O_6$	62.17	8.59	62.31	8.65
2d	-94.2 (1.03, 25)	$C_{18}H_{22}O_6$	64.66	6.63	64.66	6.63
2e	-84.5 (0.98, 23)	$C_{20}H_{26}O_6$	66.28	7.23	66.05	7.34
2f	+47.8 (1.02, 28)					
2g	-43.6 (0.97, 24)	$C_{17}H_{28}O_6$	62.17	8.59	62.13	8.63
2h	-44.8 (1.13, 26)	$C_{20}H_{30}O_6$	65.55	8.25	65.56	8.24
2i	+15.6 (1.00, 25)					

[a] Measured in ethanol solution

General procedure for the cyclopropanation of 3a-e. To a solution of the acetal 3 (1.0 mmol) in dry hexane (10 mL) was added diethylzinc (5.0 mmol, 2.5 mL of a 2 N hexane solution) at -20°C. Methylene iodide was added dropwise to the vigorously stirred solution[12] and the stirring was continued for 2 h at -20°C. The reaction mixture was poured into 1 N NaOH and extracted with ether repeatedly. The organic layers were dried over sodium sulfate and concentrated in vacuo. Purification of the residual oil by column chromatography on silica gel (hexane-ether, 3-4:1) afforded the cyclopropane **4**.

The physical properties and analytical data of the cyclopropanes thus obtained are listed in Table 6a and 6b.

Table 6a Spectral data of the acetal **4**

acetal	IR (cm^{-1})[a]	^1H NMR (δ; ppm)[b]
4a	2910, 2850, 1370, 1140, 995	4.53 (d, J = 3.5 Hz, 1 H), 3.53-4.43 (m, 2 H)
4b	2960, 2920, 1155, 1140, 1000	4.40 (d, J = 4.0 Hz, 1 H), 3.47-4.30 (m, 2 H)
4c	3030, 2970, 2920, 2850, 1600, 1495, 1370, 995	7.00 (m, 5 H, ArH), 4.57 (d, J = 4.5 Hz, 1 H), 3.50-4.40 (m, 2 H)
4d	2970, 2930, 1450, 1380, 1000	3.43-4.47 (m, 3 H), 1.03 (s, 6 H)
4e	2950, 2920, 2850, 1370, 1150, 1130, 1100	3.67-4.67 (m, 3 H), 1.17 (s, 3 H)

[a] Film. [b] Taken in CCl_4 solution.

Table 6b. $[\alpha]_D$ and elemental analyses of the acetal **4**.

Acetal	$[\alpha]_D$[a] degree (c, °C)	Formula	Calcd C	Calcd H	Found C	Found H
4a	-4.5 (1.06, 25)	$C_{10}H_{18}O_2$	70.55	10.66	70.30	10.91
4b	-13.5 (1.08, 32)	$C_{12}H_{22}O_2$	72.68	11.18	72.65	11.21
4c	-76.5 (0.98, 29)	$C_{15}H_{20}O_2$	77.55	8.68	77.52	8.71
4d		$C_{11}H_{20}O_2$	71.70	10.94	71.58	11.06
4e	-12.8 (1.00, 26)	$C_{12}H_{22}O_2$	72.58	11.18	72.44	11.42

[a] Measured in ethanol solution

The transacetalization of the acetal 2: The mixture of the acetal **2** (0.5 mmol) and p-toluenesulfonic acid (30 mg) in methanol (15 mL) was stirred at 25°C for 24 h. The reaction mixture was poured into saturated sodium bicarbonate and the product was extracted with hexane twice. The organic layers were dried over sodium sulfate and concentrated in vacuo. The residue was dissolved in 10 mL of benzene. To the mixture was added (2R,4R)-2,4-pentanediol (52 mg, 0.5 mmol) and pyridinium tosylate (10 mg). The resulting reaction mixture was heated for 1 h to distill off the solvent. The resulting mixture was poured into saturated sodium bicaronate and the product was extracted with hexane twice. The combined organic layers were dried over sodium sulfate and concentrated in vacuo. Purification by column chromatography on silica gel (hexane-ether, 3-5:1) afforded the corresponding acetal in ca. 60-70% yield. IR and ^1H NMR spectra of the acetal obtained were identical with those of the acetal **4**.

Hydrolysis of the acetal 2d: A mixture of the acetal **2d** (1.67 g) and p-toluenesulfonic acid (1.0 g) in THF-water (50 mL- 10 mL) was heated with reflux for 7 h. The reaction mixture was poured into saturated sodium bicarbonate and the product was extracted with hexane twice. The organic layers were dried over sodium sulfate and concentrated in vacuo. Bulb to bulb distillation of the residue afforded a colorless oil (450 mg, 62% yield): bp (bath temp) 120°C (1 torr); IR (neat) 3040, 2850, 2730, 1695, 760, 700 cm^{-1}; ^1H NMR (CCl_4) δ 9.33 (d, J = 3.8 Hz, 1 H, CHO), 7.10 (m, 5 H, ArH); $[\alpha]^{25}_D$ -378° (c 0.378, $CHCl_3$); lit. $[\alpha]^{25}_D$ -340° (c 0.363, $CHCl_3$).[4c]

Hydrolysis of the acetal 2h: A mixture of the acetal **2h** (100 mg, 0.27 mmol) and p-toluenesulfonic acid (50 mg) in ethanol (3 mL)-water (3 mL) was

stirred at 25°C for 36 h. The product was washed with saturated sodium bicarbonate. Concentration of the dried solvent left a crude oil, which was purified by column chromatography on silica gel (hexane-ether, 5:1) to give the corresponding aldehyde as a colorless oil in 75% yield: IR (neat) 3070, 2980, 2920, 2850, 2700, 1700, 1440, 1005, 925 cm^{-1}; ^1H NMR (CCl_4) δ 8.66 (s, CHO of the axial aldehyde), 8.59 (s, equatorial isomer), 0.75 (s, 3 H).[13] Hydrolysis of **2i** was also carried out in the similar manner (79% yield).

(1R,2R)-2-Phenylcyclopropanecarboxylic acid: A solution of the acetal **2d** (1.67 g, 5.0 mmol) in 50 mL of carbon tetrachloride was treated with the excess ozone at 0°C for 5 h.[6] The solvent and the remaining ozone was removed in vacuo and the residue was dissolved in ethyl acetate and washed with brine. The separated organic layers were dried over sodium sulfate and concentrated in vacuo to give the crude oil. The ester thus obtained was dissolved in ethanol (25 mL) - 10 N KOH (5 mL) and stirred at 0°C for 2 h to complete the hydrolysis of the ester. The mixture was poured into cold 2 N hydrochloric acid (50 mL) and the product was extracted with ethyl acetate repeatedly. The concentration of the dried organic layers followed by the purification by column chromatography on silica gel (hexane-ethyl acetate, 1:2) afforded (1R,2R)-2-Phenylcyclopropanecarboxylic acid as a colorless oil (0.44 g, 43%): $[\alpha]^{26}_D$ -287.6° (c 1.21, ethanol); lit. 1S,2S isomer: $[\alpha]^{25}_D$ +311.7° (c 1.776, 1 dm, ethanol).[14] The $[\alpha]_D$ of other carboxylic acid thus obtained are listed below.

(1R,2R)-2-Methylcyclopropanecarboxylic acid: $[\alpha]^{24}_D$-71.9° (c 1.00, ethanol); lit. 1R,2R isomer (51% ee): $[\alpha]^{24}_D$-39.7 (ethanol)[15]

1-(S)-2,2-dimethylcyclopropanecarboxylic acid: 4d was transformed to the carboxylic acid in the manner as described above in 85% yield: $[\alpha]^{27}_D$ +38.89° (c 1.01, $CHCl_3$); lit. 1S isomer: $[\alpha]^{25}_D$ +146° (c 1.06, $CHCl_3$).[16]

L-Diisopropyl-2,3-O-trans-6'-carbomethoxy-1'-pentenylidene-tartrate (9): The mixture of methyl trans-7-oxo-5-heptenoate **8** (1.56 g, 10 mmol),[17] triethyl orthoformate (1.80 g, 12 mmol) and 10 mL of ethanol was stirred at room temperature for 12 h. The reaction mixture was poured into saturated sodium bicarbonate and the product was extracted with hexane twice. The organic layers were dried over anhydrous sodium sulfate and concentrated in vacuo. The product was purified by column chromatography on silica gel (hexane-ether, 5:1) to give the diethylacetal (1.80 g, 78%). The mixture of the diethylacetal (1.80 g, 7.8 mmol), L-(+)-diisopropyl tartrate (1.76 g, 7.5 mmol) and pyridinium tosylate (10 mg) in 50 mL of benzene was heated for 30 min to distill off the solvent and resultant ethanol. The residue was purified by column chromatography on silica gel (hexane-ethyl acetate, 10:1-5:1, gradient elution) to give the acetal **9** as a colorless oil (1.44 g, 50% yield): IR (neat) 2980, 2950, 1750, 1735, 1220, 965 cm^{-1}; ^1H NMR (CCl_4) δ 3.60 (s, 3 H), 1.18 (d, J = 6.2 Hz, 12 H); Anal. Calcd for $C_{18}H_{28}O_8$: C, 58.05; H, 7.58. Found: C, 58.27; H, 7.70.

Asymmetric Simmons-Smith reaction of the acetal 9 : To a solution of the acetal **9** (0.744 g, 2 mmol) in 20 mL of dry hexane was added diethylzinc (10 mmol, 5 mL of 2.0 M hexane solution) at -20°C. Methylene iodide (1.62 mL, 20 mmol) was added dropwise to the resulting stirred solution and the mixture was vigorously stirred at -20°C for 4 h and at 0°C for 4 h. The reaction mixture was poured into cold aqueous ammonium chloride and the product was extracted with ether repeatedly. The ether layers were washed with sodium thiosulfate and water. The combined ether layers were dried over sodium sulfate and concentrated in vacuo. Purification by chromatography on silica gel (hexane-ethyl acetate, 3:1) afforded the pure cyclopropane **10** as a colorless oil (0.726 g, 94% yield): IR (neat) 3000, 2950, 1750, 1735, 1375, 1220, 1105, 905 cm^{-1}; ^1H NMR (CCl_4) δ 4.75 (d, J = 5.8 Hz, 1 H), 3.57 (s, 3 H), 1.28 (d, J = 6.2 Hz, 12 H), 0.17-1.17 (m, 4 H); Anal. Calcd for $C_{19}H_{30}O_8$: C, 59.05; H, 7.83. Found: C, 59.07; H, 7.81.

(2R,3R)-6-Carbomethoxy-2,3-methanohexanal (11): A mixture of the acetal **10** (292 mg, 0.76 mmol) and p-toluenesulfonic acid (100 mg) in methanol-water (8 mL - 3 mL) was stirred at room temperature for 72 h. The reaction mixture was poured into saturated sodium bicarbonate and the product was extracted with ether repeatedly. The organic layers were dried over sodium sulfate and concentrated in vacuo. Purification by chromatography on silica gel (hexane-ethyl acetate, 5:1) afforded the aldehyde **11** (95.5 mg, 74%), spectral data of which was identical with the reported racemic aldehyde: $[\alpha]^{27}_D$ -51.2° (c 1.05, $CHCl_3$); Stereochemical purity (90% ee) of the product was determined after the following: Treatment of **11** (94 mg, 0.56 mmol) and (2R,4R)-2,4-pentanediol

(104 mg, 1.0 mmol) in the presence of pyridinium tosylate (5 mg) in benzene at reflux for 1 h gave the corresponding acetal (125 mg, 87% yield): ^{1}H NMR ($CDCl_3$) (500 MHz) δ 4.31 (d, J = 5.65 Hz); the S isomer 4.35 (d, J = 5.65 Hz).

(5R,6R)-Methyl-5,6-methano-11-oxo-undeca-7,9-dienoate (12): To a solution of tributylstannyl-4-ethoxy-1,3-butadiene (542 mg, 1.40 mmol)[17] in 5 mL of THF was added n-butyllithium (0.9 mL of 1.45 N hexane solution, 1.31 mmol) at -78°C under argon. The temperature was raised to -40°C in 15 min. The reaction mixture was cooled to -78°C, and the aldehyde **11** (188 mg, 1.10 mmol) dissolved in 5 mL of THF was added. After being stirred at -78°C for 1 h, the resulting mixtrure was poured into aq. sodium bicarbonate and the product was extracted with ether repeatedly. The combined organic layers were dried over anhydrous sodium sulfate and concentrated in vacuo to give a crude oil, which was dissolved in THF-water (4.5 mL-0.5 mL) and exposed with catalytic amount of p-toluenesulfonic acid at room temperature for 15 min. The mixture was poured into aq. sodium bicarbonate and the product was extracted with ether. Removal of the dried solvent left a crude oil, which was purified by column chromatography on silica gel (ether-hexane, 1:2) to give unstable **12** (100 mg, 41%): ^{1}H NMR ($CDCl_3$) δ 9.47 (1 H, d, J = 8 Hz), 7.01 (1 H, dd, J = 16 and 12 Hz), 6.34 (1 H, dd, J = 16 and 10 Hz), 6.03 (1 H, dd, J = 16 and 8 Hz), 5.77 (1 H, dd, J = 16 and 10 Hz), 3.33 (3 H, s), 2.34 (2 H, t, J = 7 Hz), 1.00-0.74 (4 H, m)

(5R,6R)-5,6-Methanoleukotriene A_4 (6): To a solution of cis-3-nonenyltriphenylphosphonium iodide (450 mg, 0.88 mmol)[17] in 5 mL of THF was added n-butyllithium (0.58 mL of 1.5 N hexane solution, 0.87 mmol) followed by addition of HMPA (1.5 mL) at -78°C under argon. After being stirred for 5 min, the freshly prepared aldehyde **12** (162 mg, 0.73 mmol) dissolved in 5 mL of THF was added and stirring was continued for 15 min. The resulting mixture was poured into aq. sodium bicarbonate and the product was extracted with ether. The dried organic layer was concentrated in vacuo and the residue was purified by column chromatography on silica gel (ether-hexane, 1:40) to give **13** (60 mg, 25%)[18]. To a solution of **13** (60 mg, 0.18 mmol) in methanol-THF (5 mL- 5 mL) was added 1 mL of 2 N NaOH and the mixture was stirred at 40°C for 5 h under argon. After being recooled to 0°C, the mixture was acidified by 1 N hydrochloric acid and the product was extracted with ether. The organic layer was dried over anhydrous sodium sulfate and concentrated in vacuo to give **6** (55 mg, 97%): $[\alpha]^{22}_D$ -19.3° (c 2.55, $CHCl_3$); IR(neat) 3700-2200, 1710, 1630, 995 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 6.44-6.26 (1 H, m), 6.24-6.05 (2 H, m), 6.05-5.90 (1 H, m), 5.50-5.20 (4 H, m), 2.98 (2 H, t, J = 7 Hz), 2.39 (2 H, t, J = 7 Hz), 0.70-0.50 (2 H, m); MS m/e 316 (M^+: $C_{21}H_{32}O_2$).

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