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ASYMMETRIZATION OF MESO-CYCLIC KETONES USING HOMOCHIRAL ACETAL TEMPLATES

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Abstract: Employing the homochiral acetal template, asymmetrization of meso-substituted cyclohexanones is explored. By the use of optically-active 2,4-pentanediol as a chiral protecting group, highly diastereoselective acetal cleavage is achieved when treated with organoaluminum reagent. Dialkylaluminum amides are also effective reagents for this reaction.

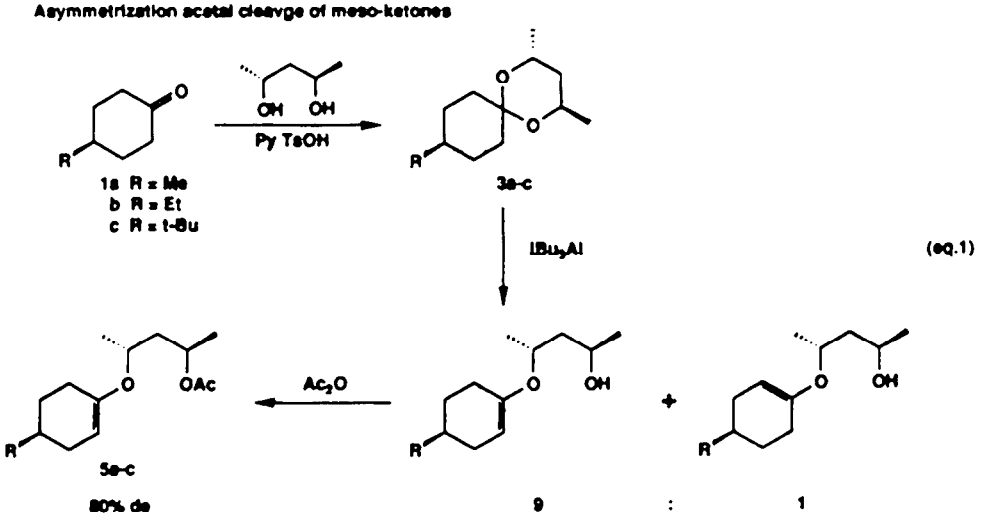
Enantiotopic-group selective reactions (asymmetrization processes) promise to be an exciting transformation in asymmetric synthesis. They can offer a method to introduce a number of chiral centers of remote positions at one time. Enzymes have a remarkable ability to recognize the stereochemical properties of chiral or prochiral substrate. One of the most spectacular application of these unique properties is demonstrated in monohydrolysis of meso-diesters using pig liver esterase (PLE), and its unique application for the synthesis of antibiotics.[1]

Due the success of homochiral acetal methodology in asymmetric synthesis, developed by us[2] and others,[3] we have occasion to study application of the method in asymmetrization process: asymmetric enolization of meso cyclic ketones.[4]

Reaction of homochiral acetals with trialkylaluminum reagent.

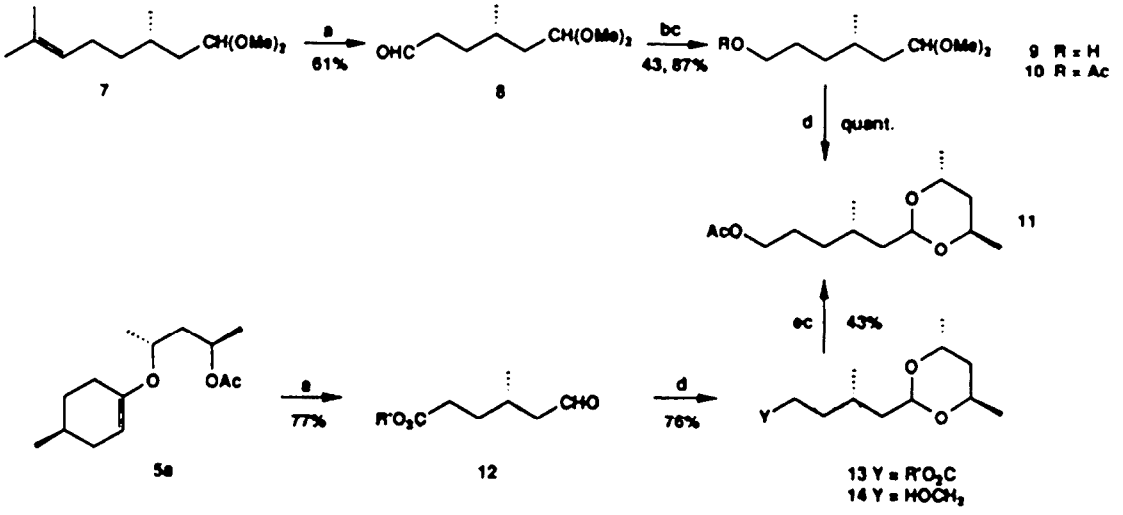
The homochiral acetal **3a**, which was prepared from the ketone **1a** and (2R, 4R)-2,4-pentanediol in the usual manner, was treated with triisobutylaluminum in dichloromethane at 0°C. Quenching with aqueous sodium hydroxide after 4 h gave the vinyl ether almost in quantitative yield. The resulting alcohol was converted to the corresponding acetate **5a** by exposure with acetic anhydride. Glc analysis of the product revealed the diastereoratio of 9 : 1.

Asymmetrization acetal cleavge of meso-ketones



The absolute configuration was determined as S by the method as shown in Scheme 1. Thus, ozonolysis of the vinyl ether **5a** followed by conversion to the corresponding acetal with (2R, 4R)-

Scheme 1. Determination of absolute configuration of 3a

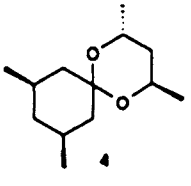


a: O_3, MeOH; then Me_2S; b: $NaBH_4$; c: Ac_2O; d: (2R, 4R)-2,4-pentanediol, H^+; e: $LiAlH_4$

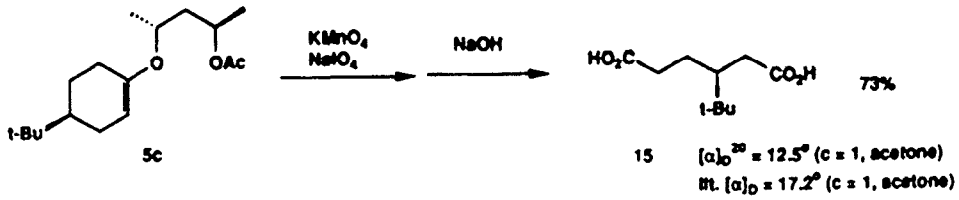
2,4-pentanediol produced **13** and, after reduction by lithium aluminum hydride, **14**. Acetylation of hydroxyl group of **14** afforded **11**. It was compared with the authentic sample, which was prepared from (S)-citronellal dimethylacetal by the following sequential transformation: (1) ozonolysis, (2)

Table 1. Asymmetrizing acetal cleavage by triisobutylaluminum

subst.	iBu_3Al (eq.)	solvent	cond.	yield(%)	ratio
3a	1.5	CH_2Cl_2	0°C, 5 h	49	78 : 22
	4	CH_2Cl_2	0°C, 4 h	99	87 : 13
	10	CH_2Cl_2	0°C, 12h	76	88 : 12
	20	CH_2Cl_2	0°C, 9 h	89	88 : 12
	20	CH_2Cl_2	-40°C, 4.5 h	72	88 : 12
	20	CH_2Cl_2	-78°C, 23 h	43	72 : 28
	4	CH_2Cl_2	-78°C, 0.5 h; 0°C, 4 h	99	90 : 10
	4	$ClCH_2CH_2Cl$	0°C, 6 h	90	77 : 23
	4	toluene	0°C, 6 h	53	76 : 24
	4	hexane	0°C, 6 h	37	84 : 16
	10	$CHCl_3$	0°C, 5 h	58	84 : 16
3b	4	CH_2Cl_2	-78°C, 0.5 h; 0°C, 4 h	99	86 : 14
3c	4	CH_2Cl_2	-78°C, 0.5 h; 0°C, 4 h	99	89 : 11
4	4	CH_2Cl_2	-78°C, 0.5 h; 0°C, 4 h	99	91 : 9



Scheme 2. Determination of absolute configration of 5c



5c

15 $[\alpha]_D^{20} = 12.5°$ (c = 1, acetone)
lit. $[\alpha]_D = 17.2°$ (c = 1, acetone)

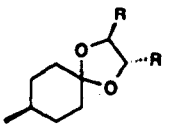
reduction with sodium borohydride, (3) acetylation, (4) acetal exchange with (2R, 4R)-2,4-pentanediol. The absolute configuration for t-butyl derivative 5c was determined by transformation to dicarboxylic acid 15 by oxidative double bond cleavage and hydrolysis, illustrated as Scheme 2.[5]

For further improvement of the stereoselectivity of triisobitylaluminum reaction, we attempted various reaction conditions. The results were summerized in Table 1. The ratio of the product was not significantly affected by the reaction conditions. We also realized that no significant effect were observed by the changes of the alkyl group at C-4 position.

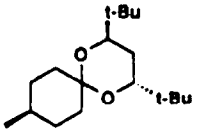
Attempted reaction using other diols.

We turned our attention to modify the structure of the diols. A variety of chiral C_2 -symmetrical diols were tested. Unfortunately, after addition of acetic anhydride for in situ trapping of the hydroxyl group, we could not isolate any vinyl ether acetate from the dioxolane acetals 16-19. The other bulky 1,3-diols, e.g. t-butyl derivative 20[6], failed to proceed the desired reaction.

Modification of diol component



16 R = Me
17 R = CH_2OH
18 R = CH_2OEt
19 R = $CONMe_2$



20 (racemic)

Reaction of homochiral acetals treated by dialkylaluminum amides.

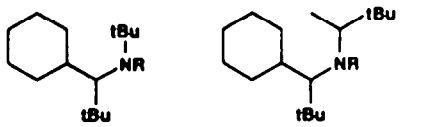
While triisobutylaluminum is excellent reagent for the reaction, further studies are required for the better stereoselectivity. Among various possible aluminum reagents, dialkylaluminum amides[7] proceeded the reaction smoothly at 0°C. Table 2 summerized the results. Although most of them gave less satisfactory results than triisobutylaluminum, it was found that the amide 22b[8] performed the desired transformation with the superior reactivity and selectivity to the triisobutylaluminum method.

Discussion.

The observed results may come from the specific conformation of 3a. Thus the conformation of 3a should be either A, or B, and the conformer A should be the more stable isomer. The equatorial ether group of A may be attacked by Lewis acid to generate the oxonium ion. The steric repulsion existing between the cyclohexane ring and the dioxane substituent at axial position would control the course of the reaction. The remaining axial C-O bond therefore rotates down to equatorial, and deprotonation undergoes at more strained site by one of the ligands of the reagent. No enhancement of selectivity regardless of the substituents of cyclohexanones (Table 1) may be explained by the favorable chair conformation of six-membered ring.

Table 2. Asymmetrizating acetal cleavage by dialkylaluminum amides

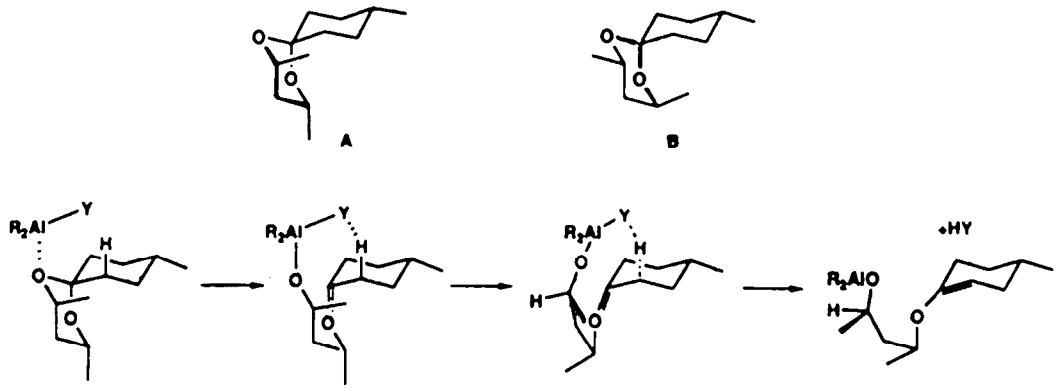
subst.	$R_2AlNR'_2$	equiv.	cond.	yield(%)	ratio
3a	Me_2AlTMP	4	0°C, 2 h	16	82 : 18
	Et_2AlTMP	4	0°C, 6 h	90	84 : 16
	IBu_2AlTMP	4	0°C, 10 h	70	81 : 19
	22a	4	0°C, 4 h	99	89 : 11
	22a	10	-78°C, 1 h, 0°C, 6 h	48	90 : 10
	24a	4	0°C, 8 h	-	-
3b	22a	10	-78°C, 1 h; 0°C, 6 h	91	92 : 8
3c	22a	10	-78°C, 1 h; 0°C, 6 h	95	88 : 12
4	22a	10	-78°C, 1 h; 0°C, 6 h	69	94 : 6



22a R = H
b R = IBu_2Al

24a R = H
b R = IBu_2Al

Figure 1. Mechanism for asymmetrizating acetal cleavage



Experimental section

General: Infrared (IR) spectra were recorded on a Hitachi 260-10 spectrometer. Relative intensities were expressed as s, strong; m, medium; w, weak; br., broad signals. ^1H NMR spectra were measured on a JNM-PMX 60 spectrometer or a Varian Gemini 200 spectrometer. The chemical shifts were expressed in parts per million downfield from internal standard tetramethylsilane (TMS, δ = 0). Splitting patterns were indicated as s, singlet; d, doublet, t, triplet; q, quartet; m, multiplet; br, broad peaks. Gas liquid-phase chromatographic (glc) analyses were performed on Gasukuro Kogyo Model 370 or Shimadzu GC-8A. Instruments equipped with PEG 25 meter column detected by flame ionization detector, using nitrogen as the career gas. High performance liquid chromatography (hplc) analyses were made by Shimadzu LC-6A equipped with Wako Wakopak (Finesil) detected by UV detector Shimadzu SPD-6A. All experiments were carried out under inert atmosphere. For thin layer chromatographic (tlc) analyses were used Merck precoated tlc plates (silica gel 60 GF_{254}, 0.25 mm thickness) otherwise noted. Elemental analyses were made at the Institute of Applied Organic Chemistry, Faculty of Engineering, Nagoya University. In experiments requiring dry solvents, ether and tetrahydrofuran (THF) were distilled from sodium-benzophenone ketyl. Dichloromethane was distilled over phosphorous pentoxide under argon. Chloroform was freshly passed through a column of neutral alumina before use. Hexane and benzene were dried over sodium metal. For flash column

chromatography was used silica gel Merck Kieselgel 60 (Art. 9385).

Preparation of 4-ethylcyclohexanone 1b: To a solution of 4-ethylcyclohexanol (cis-trans mixture, commercially available from Aldrich Co., 6.1 g, 50 mmol) in ether (20 mL) was added chromic acid solution[11] (prepared from sodium dichromate (5.0 g, 17 mmol) and sulfuric acid (96%, 3.8 mL) in water (25 mL)) at 0°C dropwise. The two-phase solution was stirred at ambient temperature for 2 h. Organic layer was seperated and the water layer was extracted with ether. The combined organic layers were dried over sodium sulfate. Concentration in vacuo and purification by chromatography on silica gel (eluant: hexane-ethyl acetate, 4:1) afforded a colorless oil (4.5 g, 36 mmol, 72%): tlc Rf=0.42 (hexane-ethyl acetate, 4:1); IR: 3000-2750 s, 1710 s, 1185 m, 935 m; ^{1}H NMR (CCl_4): δ 2.40- 2.10 (br. m, 4H), 2.07-1.10 (br. m, 7H), 0.93 (d, J = 7.3 Hz, 3H); Elemental analysis calcd for $C_8H_{14}O$: C, 76.18; H, 11.18%. Found: C, 76.37; H, 10.95%.

Preparation of cis-3,5-dimethylcyclohexanone 2: A cis-trans mixture of 3,5-dimethylcyclohexanone (3.8 g, 30 mmol) was reduced with sodium borohydride (1.2 g, 30 mmol) in ethanol (30 mL) at 0°C. After stirring for 2 h, the resulting solution was poured into brine and extracted with ether. The combined ether extracts were dried over sodium sulfate. Three spots were observed on tlc analysis, and the highest Rf product (Rf=0.24, hexane-ethyl acetate, 4:1) was characterized as cis-cis-cis isomer from ^{1}H NMR investigation (430 mg, 3.3 mmol, 11%): mp. 36.0-36.3°C uncorr. (lit.: 38-39°C);[12] ^{1}H NMR; δ 4.00 (m, 1H), 2.10-1.40 (m, 9H), 0.85 (d, J = 6 Hz, 6H). Oxidation with chromic acid solution as mentioned above gave cis-2 as a colorless oil (320 mg, 2.5 mmol, 79%): tlc Rf = 0.40 (hexane-ethyl acetate, 4:1); ^{1}H NMR (CCl_4): δ 2.40-2.10 (m, 4H), 2.10-1.50 (m, 4H), 1.07 (d, J = 6.4 Hz, 6H). Its glc analysis in comparison with cis-trans mixture revealed that sole pure cis-isomer was obtained; cis-isomer: tr = 16.8 min; trans-isomer: tr = 19.7 min.

Preparation of acetals, general procedure (3b, R = Et): A solution of **1b**, (2R, 4R)-2,4-pentanediol (540 mg, 5.2 mmol), and pyridinium p-toluenesulfonate (35 mg) in benzene (10 mL) was refluxed azeotropically for 7 h. The resulting mixture was poured into saturated aqueous solution of sodium hydrogencarbonate and extracted with ether. The combined ether extracts were dried over sodium sulfate and concentrated in vacuo. Purification by column chromatography on silica gel (hexane-ethyl acetate, 4:1) gave a colorless oil **3b** (906 mg, 4.3 mmol, 84%): tlc Rf=0.62 (hexane-ethyl acetate, 4:1); IR (neat film): 3000-2800 s, 1435 m, 1340 m, 1140 s; ^{1}H NMR (CCl_4): δ 3.87 (m, 2H), 2.20-1.30 (m, 13H), 1.13 (d, J = 6 Hz, 3H), 1.08 (d, J = 6 Hz, 3H), 0.90 (d, J = 5.4 Hz, 3H); $[\alpha]_D^{20}$ = -22.24° (c = 1 .7, $CHCl_3$); Elemental analysis calcd for $C_{13}H_{24}O_2$: C, 73.54; H, 11.39. Found: C, 73.49, H, 11.44%.

Preparation of acetal 3a (R = Me): Refluxing a solution of the ketone **1a** (1.13 g, 9.9 mmol) and (2R, 4R)-2,4-pentanediol (1.13 g, 11 mmol) in the presence of pyridinium p-toluenesulfonate (35 mg) in benzene afforded the acetal **3a** (1.74 g, 8.8 mmol, 89%)): tlc Rf = 0.59 (hexane-ethyl acetate, 4:1); IR (neat film): 3000-2800 s, 1450 s, 1380 s, 1165 s, 995 s; ^{1}H NMR (CCl_4): ¥ 3.86 (m, 2H), 2.20-1.20 (m, 11H), 1.13 (d, J = 6 Hz, 3H), 1.10 (d, J = 6 Hz, 3H), 0.93 (d, J = 5.4 Hz, 3H); $[\alpha]_D^{20}$ = -25.58° (c = 1.02, $CHCl_3$); Elemental analysis calcd for $C_{12}H_{22}O_2$: C, 72.68; H, 11.18. Found: C, 72.68; H, 11.33%.

Preparation of acetal 3c (R = t-Bu): Refluxing a solution of the ketone **3c** (797 mg, 5.2 mmol) and (2R, 4R)-2,4-pentanediol (560 mg, 5.3 mmol) in the presence of pyridinium p-toluenesulfonate (23 mg) in benzene (10 mL) afforded the acetal **3c** (1.26 g, 5.2 mmol, 99%): tlc Rf = 0.59 (hexane-ethyl acetate, 4:1); IR (neat film): 3000-2800 br. s, 1370 s, 1150 s, 1100 s, 990 m; ^{1}H NMR ($CDCl_3$): δ 4.03 (m, 1H), 3.92 (m, 1H), 2.13-2.02 (m, 2H), 1.67-1.54 (m, 2H), 1.37-1.24 (m, 5H), 1.20 (d, J = 6.5 Hz, 3H), 1.08 (d, J = 6.3 Hz, 3H), 0.85 (s, 9H); $[\alpha]_D^{20}$ = -16.26° (c = 1.09, $CHCl_3$); Elemental analysis calcd for $C_{15}H_{28}O_2$: C, 74.95; H, 11.74%. Found: C, 74.77; H, 11.84%.

Preparation of acetal 4 (3,5-dimethyl): Refluxing a solution fo the ketone cis-2 (134 mg, 1.1 mmol) and (2R, 4R)-2,4-pentanediol (178 mg, 1.1 mmol) in the presence of pyridinium p-toluenesulfonate (10 mg) in benzene (10 mL) afforded the acetal **4** (183 mg, 0.86 mmol, 78%): tlc Rf = 0.56 (hexane-ethyl acetate, 4:1); IR (neat film): 3000-2800 br. s, 1445 s, 1255 s, 795 s; ^{1}H NMR (CCl_4): δ 3.87 (m, 2H), 2.20-1.30 (m, 9H), 1.13 (d, J = 6.6 Hz, 6H), 0.87 (d, J = 6.0 Hz, 6H); $[\alpha]_D^{20}$ = -24.44 (c = 0.53, $CHCl_3$); Elemental analysis calcd for $C_{13}H_{24}O_2$: C, 73.54; H, 11.39%. Found: C, 73.49; H, 11.44%.

Reaction of acetal 3a with triisobutylaluminum. General procedure: To a solution of acetal **3a** (100 mg, 0.5 mmol) in the solvent (10 mL) was added triisobutylaluminum (2 M in hexane). On disappearance of most of the acetal **3a** by tlc analysis the reaction solution was poured into ice-cooled 2 N aqueous solution of sodium hydroxide, and extracted with ether. The combined ether extracts were dried over magnesium sulfate. Concentration in vacuo gave a crude oil, which was acetylated in acetic anhydride (1 mL) and triethylamine (1 mL) in the presence of 4-(dimethylamino)pyridine (10 mg) to afford a colorless oil of **5a**. Its diastereomeric ratio was determined by glc; tr = 43.3 and 44.1 min. (100°C). Physical data were described in the following.

Reaction of acetals with triisobutylaluminum. General procedure (R = Et): To a solution of the acetal **3b** (57 mg, 0.28 mmol) in dichloromethane (5 mL) was added triisobutylaluminum (2 M in hexane, 0.5 mL, 1 mmol) at -78°C. Stirring was continued at that temperature for 30 min., and at 0°C for 4 h. The reaction solution was poured into ice-cooled 2 N aqueous solution of sodium hydroxide and extracted with ether. The combined ether extracts were dried over sodium sulfate and concentrated in vacuo. The residual oil was acetylated in acetic anhydride (1 mL) and

triethylamine (3 mL) in the presence of 4-(dimethylamino)pyridine (5 mg). On disappearance of most of the vinyl ether alcohol by tlc analysis (ca. 6 h later), the reaction solution was poured into saturated aqueous solution of sodium hydrogencarbonate and extracted with ether. The combined ether extracts were dried over sodium sulfate. Concentration in vacuo and purification by column chromatography on silica gel (eluant: hexane-ethyl acetate, 4:1) gave a colorless oil **5b** (68 mg, 0.28 mmol, 99%): tlc Rf = 0.49 (hexane-ethyl acetate, 4:1); IR (neat film): 3000-2800 br. s, 1730 s, 1665 s, 1440 s, 1365 s, 1230 s, 1110 m, 810 m, 790 m; ^{1}H NMR (CCl_4): δ 4.90 (m, 1H), 4.60-4.30 (br. m, 1H), 4.05 (m, 1H), 1.90 (s, 3H), 1.85-1.30 (m, 11H), 1.18 (d, J = 6.6 Hz, 3H), 1.15 (d, J = 6.6 Hz, 3H), 0.83 (d, J = 5.4 Hz, 3H); $[\alpha]_D^{20}$ = -77.49° (c = 0.234, $CHCl_3$); Elemental analysis calcd for $C_{15}H_{26}O_3$: C, 73.54; H, 11.39%. Found: C, 73.28; H, 11.65%. Its glc analysis showed the the diastereoratio of 86:14 (tr = 106.4 and 107.6 min. (100°C))

Reaction of acetal 3a (R = Me): Treatment of the acetal **3a** (110 mg, 0.50 mmol) in dichloromethane (10 mL) with triisobutylaluminum (2 M in hexane, 1.0 mL, 2.0 mmol) followed by acetylation gave a colorless oil **5a** (120 mg, 0.50 mmol, 99%): tlc Rf = 0.37 (hexane-ethyl acetate, 4:1); IR (neat film): 3000-2800 br. s, 1730 s, 1660 s, 1435 m, 1360 s, 1180 s, 1100m, 790 m; ^{1}H NMR (CCl_4): δ 4.88 (m, 1H), 4.50-4.30 (br. m, 1H), 4.03 (m, 1H), 1.89 (s, 3H), 1.86-1.20 (m, 9H), 1.18 (d, J = 6.6 Hz, 3H), 1.14 (d, J = 6.6 Hz, 3H), 0.93 (d, J = 5.4 Hz, 3H); $[\alpha]_D^{20}$ = -81.69° (c = 0.225, $CHCl_3$); Elemental analysis calcd for $C_{14}H_{24}O_3$: C, 72.68; H, 11.18%. Found: C, 72.53; H, 11.33%. Its diastereoratio was determined by glc analysis to be 91:9 (tr = 122.0 and 123.6 min. (75°C)).

Reaction of acetal 3c (R = t-Bu): Treatment of the acetal **3c** (55 mg, 0.23 mmol) in dichloromethane (5 mL) with triisobutylaluminum (2 M in hexane, 0.50 mL, 1.0 mmol) followed by acetylation gave a colorless oil **5a** (63 mg, 0.23 mmol, 99%): tlc Rf = 0.73 (hexane-ether, 1:1); IR (neat film): 3000-1800 br. s, 1740 s, 1675 m, 1370 m, 1235 m, 1030 m, 790 m; ^{1}H NMR (CCl_4) δ 4.88 (m, 1H), 4.50-4.30 (br. m, 1H), 4.03 (m, 1H), 1.90 (s, 3H), 1.85-1.40 (m, 9H), 1.18 (d, J = 6.6 Hz, 3H), 1.15 (d, J = 6.6 Hz, 3H), 0.87 (s, 9H); $[\alpha]_D^{20}$ = -76.12° (c = 0.244, $CHCl_3$); Elemental analysis calcd for $C_{17}H_{30}O_3$: C, 72.54; H, 11.39%. Found: C, 73.49; H, 11.44%. Its diastereoratio was determined by glc analysis to be 89:11 (tr = 87.2 and 92.0 min. (130°C)).

Reaction of acetal 4 (3,5-dimethyl): Treatment of the acetal **4** (57 mg, 0.27 mmol) in dichloromethane (5 mL) with triisobutylaluminum (2 M in hexane, 0.50 mL, 1.0 mmol) followed by acetylation gave a colorless oil (64 mg, 0.27 mmol, 99%): tlc Rf = 0.44 (hexane-ethyl acetate, 10:1); IR (neat film): 3000-2800 br. s, 1740 s, 1370 m, 1235 m, 1030 m, 790 m; ^{1}H NMR (CCl_4): δ 4.88 (m, 1H), 4.50-4.30 (br. m, 1H), 4.03 (m, 1H), 1.92 (s, 3H), 1.85-1.35 (m, 8H), 1.18 (d, J = 6.6 Hz, 3H), 1.15 (d, J = 6.6 Hz, 3H), 0.90 (d, J = 5.4 Hz, 6H); $[\alpha]_D^{20}$ = -46.74° (c = 0.196, $CHCl_3$); Elemental analysis calcd for $C_{15}H_{26}O_3$: C, 72.54; H, 11.39%. Found: C, 73.49; H, 11.44%. Its diastereoratio was determined by glc analysis to be 91:9 (tr = 122.0 and 123.6 min. (75°C)).

Preparation of the authentic sample. (S)-citronellal dimethyl acetal 7: A solution of (S)-citronellal (3.1 g, 20 mmol) and trimethyl orthoformate (5.0 mL, 46 mmol) in methanol(10 mL) with ammonium nitrate (53 mg) and pyridinium 4-methylbenzenesulfonate (29 mg) was stirred at ambient temperature for 2 days. The resulting mixture was poured into saturated aqueous solution of sodium hydrogen carbonate and the combined ether extracts were dried over magnesium sulfate. Concentration in vacuo gave a crude product **7** which was used for the next reaction without any further purification: tlc Rf = 0.46 (hexane-ethyl acetate, 4:1); ^{1}H NMR ($CDCl_3$): δ 5.10 (m, 1H), 4.23 (t, J = 5.4 Hz), 3.30 (s, 6H), 2.20-1.80 (m, 2H), 1.70 (d, J = 4.8 Hz), 1.65-1.10 (m, 5H), 0.92 (d, J = 5.4 Hz, 3H).

Cleavage of double bond with ozonolysis: A solution of (S)-citronellal dimethyl acetal **7** in methanol (15 mL) was ozonized at -78°C until it was turnd to dark blue (ca. 2 h). The resulting solution was released to ambient temperature, and to this was added dimethyl sulfide (10 mL) dropwise. After removal of solvents in vacuo the residue was poured into saturated aqueous solution of sodium hydrogen sulfite and extracted with ether. The combined ether extracts were dried over sodium sulfate. Concentration in vacuo and purification by column chromatography on silica gel (eluant: hexane-ethyl acetate, 4:1) afforded a colorless oil **8** (2.1 g, 12 mmol, 61%): tlc Rf = 0.20 (hexane-ethyl acetate, 4:1); IR (neat film): 3000-2800 s, 1710 s, 1440 s, 1370 s, 1190 s, 1110 s, 1050 s, 960 m; ^{1}H NMR (CCl_4): δ 9.02 (t, J = 1.2 Hz, 1H), 4.32 (t, J = 5.4 Hz, 1H), 3.13 (s, 6H), 2.32 (m, 2H), 1.90-1.10 (m, 5H), 0.92 (d, J = 5.4 Hz, 3H); $[\alpha]_D^{17}$ = -4.39 (c = 1.08, $CHCl_3$); Elemental analysis calcd for $C_9H_{18}O_3$: C, 62.04; H. 10.41%. Found: C, 62.03; H, 10.42%.

Acetal alcohol 9: To a solution of acetal aldehyde **8** (1.6 g, 9.0 mmol) in ethanol (10 mL) was added sodium borohydride (400 mg, 10 mmol) at 0°C. Stirring was continued for 2 h. The resulting solution was poured into ice-cooled water, and extracted with ethyl acetate. The combined extracts were dried over magnesium sulfate, and concentrated in vacuo. Purification by column chromatography on silica gel (eluant:hexane-ethyl acetate, 1:1) afforded a colorless oil **9** (680 mg, 3.9 mmol, 43%): tlc Rf = 0.31 (hexane-ethyl acetate, 1:1); IR (neat film): 3600-3100 br. s, 3000-2800 s, 1455 m, 1370 m, 1190 m, 1130 s, 1155 s, 960 m; ^{1}H NMR (CCl_4): δ 4.36 (t, J = 4.8 Hz, 1H), 3.53 (t, J = 6.0 Hz, 2H), 3.20 (s, 6 H), 1.90-1.06 (m, 8H), 0.90 (d, J = 5.4 Hz, 3H); $[\alpha]_D^{20}$ = -2.57° (c = 1.026, methanol); Elemental analysis calcd for $C_9H_{20}O_3$: C, 61.33; H, 11.44%. Found: C, 61.44; H, 11.33%.

Acetal ester 10: The resulting acetal alcohol **9** was acetylated in acetic anhydride (1 mL) and triethylamine (3 mL) in the presence of 4-(dimethylamino)pyridine (8 mg). The reaction mixture was

stirred at ambient temperature overnight, poured into aqueous solution of sodium hydrogen carbonate, and extracted with ether. The combined ether extracts were dried over magnesium sulfate. Concentration in vacuo and purification by column chromatography on silica gel (eluant: hexane-ethyl acetate, 4:1) gave a colorless oil **10** (55 mg, 2.5 mmol, 87%): tlc Rf = 0.21 (hexane-ethyl acetate, 0.21); IR (neat film): 3000-2800 s, 1740 s, 1450 m, 1370 m, 1240 s, 1130 s, 1050 m; ^{1}H NMR (CCl_4): δ 4.33 (t, J = 5.4 Hz, 1H), 3.96 (t, J = 6.0 Hz, 2H), 3.18 (s, 6H), 1.97 (s, 3H), 1.90-1.06 (m, 7H), 0.92 (d, J = 5.4 Hz, 3H); $[\alpha]_D^{20}$ = -3.88 (c = 1.042, methanol); Elemental analysis calcd for $C_{11}H_{22}O_4$: C, 60.52; H, 10.16%. Found: C, 60.39; H, 10.29%.

Acetal exchange with (2R, 4R)-2,4-pentanediol: A solution of acetal ester **10** (45 mg, 0.21 mmol) and (2R, 4R)-2,4-pentanediol (53 mg, 0.50 mmol) in the presence of pyridinium p-toluenesulfonate (8 mg) in benzene (10 mL) was refluxed for 4 h. After addtion of a few drops of triethylamine, concentration in vacuo and purification by column chromatography on silica gel (eluant: hexane-ethyl acetate, 4:1) gave a colorless oil **11** (53 mg, 0.21 mmol, 99%): tlc Rf = 0.24 (hexane-ethyl acetate, 4:1); IR (neat film): 3000-2800 s, 1765 s, 1385 m, 1245 s, 1150 m; ^{1}H NMR ($CDCl_3$): δ 4.89 (dd, 6.2, 4.4 Hz, 1H), 4.27 (m, 1H), 4.00 (t, J = 6.7 Hz, 2H), 3.91 (m, 1H), 2.01 (s, 3H), 1.88-1.20 (m, 9H), 1.33 (d, J = 7.0 Hz, 3H), 1.18 (d, J = 6.2 Hz, 3H), 0.88 (d, J = 6.6 Hz, 3H); $[\alpha]_D^{23}$ = 19.36 (c = 1.388, ether). Elemental analysis calcd for $C_{14}H_{26}O_4$: C, 71.76; H, 11.18%. Found: C, 71.85; H, 11.09%.

Determination of absolute configuration of vinyl ether acetate 5a (R = Me). Preparation of ester aldehyde 12: Ozone was introduced to a solution of **5a** (250 mg, 1.1 mmol, diastereoratio of 81:19) in methanol (20 mL) at -78°C. The solution was turned to dark blue. On consuming of most of the substrate (ca. 1 h later), introduction of ozone was stopped, and the reaction solution was allowed to warm to room temperature. To this was added dimethylsulfide (0.8 mL, 11 mmol), and stirring was continued for 2 h. Removal of solvents in vacuo gave a crude oil, which was purified by column chromatography on silica gel (eluant hexane-ethyl acetate, 3:1) to afford a colorless oil **12** (240 mg, 0.85 mmol, 77%); tlc (hexane-ethyl acetate, 4:1) Rf = 0.15; IR (neat film): 3000-2800 s, 1730 s, 1240 s, 1175 m, 1140 m, 960 m; ^{1}H NMR (CCl_4): δ 9.67 (t, J = 1.8 Hz, 1H), 4.88 (m, 2H), 2,50-2.00 (br. m, 2H), 1.93 (s, 3H), 1.90-1.40 (m, 5H), 1.18 (d, J = 6.0 Hz, 6H), 0.95 (d, J = 6.0 Hz, 3H). Elemental analysis calcd for $C_{19}H_{36}O_6$: C, 63.31; H. 10.02%. Found: C, 63.31; H, 9.78%.

Acetal ester 13: A solution of ester aldehyde **12** (180 mg, 0.63 mmol) and (2R, 4R)-2,4-pentanediol (110 mg, 1.1 mmol) in the presence of pyridinium p-toluenesulfonate (9 mg) in bezene (10 mL) was refluxed azeotropically for 5 h. The solution was poured into saturated aqueous solution of sodium hydrogen carbonate, and extracted with ether. The combined ether extracts were dried over sodium sulfate. Concentration in vacuo and purification by column chromatography on silica gel (eluant: hexane-ethyl acetate, 3:1) gave a colorless oil **13** (130 mg, 0.48 mmol, 76%): tlc Rf = 0.47 (hexane-ethyl acetate, 4:1); IR (neat film): 3000-2800 s, 1750 s, 1385 s, 1250 s, 1155 s; ^{1}H NMR ($CDCl_3$): δ 4.99-4.86 (m, 3H), 4.29-4.22 (m, 1H), 3.98-3.87 (m, 1H), 2.29-2.20 (m, 2H), 1.98 (s, 3H), 1.87-1.38 (m, 9H), 1.32 (d, J = 7.0 Hz, 3H), 1.20-1.15 (complex of doublets, 9H), 0.88 (d, J = 6.6 Hz, 3H); $[\alpha]_D^{23}$ = -21.54° (c = 1.344, ether).

Acetal alcohol 14: To a solution of lithium aluminum hydride (46 mg, 1.2 mmol) in ether (5 mL) was added a solution of acetal ester **13** (120 mg, 0.42 mmol) in ether (1 mL), and the mixture was stirred at room temperature for 4 h. The excess of lithium aluminum hydride was consumed with ethyl acetate, followed by addition of sodium fluoride (100 mg) and water (0.1 mL). The resulting mixture was poured into 1 N hydrochloric acidand extracted with ether. The combined ether extracts were dried over sodium sulfate. Concentration in vacuo and purification by column chromatography on silica gel (eluant: hexane-ethyl acetate, 1:1) afforded a colorless volatile syrup **14** (49 mg, 0.21 mmol, 51%); tlc Rf = 0.29 (hexane-ethyl acetate, 1:1); ^{1}H NMR ($CDCl_3$): δ 4.90 (dd, J = 6.4, 4.4 Hz, 1H), 4.27 (m, 1H), 3.94 (m, 1H), 3.61 (dd, 12.0, 6.5 Hz, 2H), 1.88-1.23 (m, 10H), 1.33 (d, J = 6.9 Hz, 3H), 1.17 (d, J = 6.1 Hz, 3H), 0.86 (d, J = 6.5 Hz, 3H).

Acetal acetate 11: The acetal alcohol was acetylated in acetic anhydride (1 mL) and pyridine (3 mL) in the presence of 4-(dimethylamino)pyridine (7 mg). Th reaction mixture was stirred overnight and concentrated in vacuo. The residual oil was subjected to column chromatography on silica gel (eluant: hexane-ethyl acetate, 4:1) to give acetal acetate (47 mg, 0.18 mmol, 87%). Glc analysis showed the diastereoratio of 14:86. The major peak was identical with the authentic sample prepared from (S)-citronellal.

Determination of the absolute configuration of 5c (R = t-Bu). Oxidative cleavage of double bond: The vinyl ether acetate **5c** (250 mg, 1.0 mmol), potassium permanganate (210 mg, 1.3 mmol), sodium periodate (1.7 g, 8.0 mmol), and potassium carbonate (430 mg, 3.0 mmol) were suspended in t-butanol (8 mL) and water (10 mL) at 0°C. After 12 h with stirring at ambinet temperature, the reaction mixture was acidified with conc. hydrochloric acid, and extracted with ether. The combined ether extracts were dried over magnesium sulfate and concentrated in vacuo. The crude product of monoester was diluted in 2 N aqueous solution of sodium hydroxide (3 mL) and tetrahydrofuran (3 mL). After 12 h, the reaction mixture was poured into water, and the alkaline solution was washed with ether, the acidified with conc. hydrochloric acid. The acidic water layer was extracted with ether repeatedly. The combined organic layers were dried over magnesium sulfate. Concentration in vacuo and purification by column chromatography on silica gel (eluant: ethyl acetate-methanol, 30:1) afforded the diacid **15** (120 mg, 0.57 mmol, 56%); tlc Rf = 0.22 (ethyl acetate-methanol, 30:1). The value of optical rotation ($[\alpha]_D^{20}$ = 12.54° (c = 1.012, acetone)) showed

73% e.e. of (S)-isomer (lit. $[\alpha]_D$ = 17.2° (c = 1, acetone) for (S)-isomer).[5]

Reaction of acetals with aluminum amides. Preparation of the imine 21[8]: To a mixture of t-butylamine (14 mL, 110 mmol) and cyclohexanecarboxaldehyde (8.3 g, 110 mmol) was added pulverized potassium hydroxide (1.0 g, 16 mmol). After 26 h with stirring at ambient temperature, the resulting mixture was poured into 2 N aqueous solution of sodium hydroxide and extracted with ether. The combined ether extracts were dried over magnesium sulfate. Concentration in vacuo and distillation under reduced pressure gave the imine **21** (9.5 g, 57 mmol, 50%); b.p. 100-105°C (23 Torr); tlc Rf = 0.62 (hexane-ethyl acetate, 1:1); IR (neat film): 3000-2800 s, 1680 s, 1460 m; ^{1}H NMR (CCl_4): δ 7.30 (d, J = 4.2 Hz, 1H), 2.30-0.80 (m, 11H), 1.10 (s, 9H).

Treatment of imine 21 with t-butyllithium: To a solution of the imine **21** (8.1 g, 48 mmol) in ether (30 mL) was introduced t-butyllithium (2.35 M in heptane, 21 mL, 49 mmol) at -78°C. After 2 h, the reaction solution was diluted with hexane and poured into ice-cooled 2 N aqueous solution of sodium hydroxide. The combined ether extracts were dried over magnesium sulfate. Concentration in vacuo and distillation under reduced pressure afforded the amine **22a** (8.7 g, 34 mmol, 72%); b.p. 86-93°C (7 Torr); tlc Rf = 0.65 (hexane-ethyl acetate, 1:1); IR (neat film): 3000-2800 s, 1470 m, 1445 m, 1365 m; ^{1}H NMR (CCl_4): δ 2.20-1.13 (m, 13H), 1.04 (s, 9H), 0.82 (s, 9H); Elemental analysis calcd for $C_{15}H_{31}N$: C, 79.93; H, 13.86; N, 6.21%. Found: C, 79.68; H, 13.85; N, 6.47%.

Preparation of imine 23: To a mixture of 3,3-dimethyl-2-butylamine (3,0 g, 30 mmol) and cyclohexanecarboxaldehyde (3.6 mL, 30 mmol) was added pulverlized potassium hydroxide (1,0 g, 16 mmol). After 10 h with stirring at ambient temperature, the resulting mixture was poured into 2 N aqueous solution of sodium hydroxide and extracted with ether. The combined ether extracts were dried over magnesium sulfate. Concentration in vacuo and distillation under reduced pressure gave a colorless oil **23** (4.5 g, 24 mmol, 81%); b.p. 116-118°C (28 Torr); tlc Rf = 0.63 (hexane-ethyl acetate, 1:1); IR (neat film): 3000-2800 s, 1680 s, 1465 m; ^{1}H NMR (CCl_4): δ 7.26 (d, J = 4.2 Hz, 1H), 2.60 (q, J = 6.0 Hz, 1H), 2.20-1.10 (m, 11H), 0.93 (d, J = 6.6 Hz, 3H), 0.80 (s, 9H).

Treatment of imine 23 with t-butyllithium: To a solution of the imine **23** (4.0 g, 20 mmol) in ether (20 mL) was added t-butyllithium (2.35 M in heptane, 10 mL, 24 mmol) at -78°C. After 2 h, the resulting solution was diluted with hexane and poured into ace-cooled 2 N aqueous solution of sodium hydroxide. The combined ether extracts were dried over magnesium sulfate and concentrated in vacuo. Distillation under reduced pressure afforded the amine **24a** (4.3 g, 19 mmol, 85%); b.p. 81-100°C (8 Torr); tlc Rf = 0.65 (hexane-ethyl acetate, 1:1); IR (neat film): 3000-2800 s, 1650 w, 1445 m, 1360 m, 1125 m; ^{1}H NMR (CCl_4): δ 2.60 (q, J = 6.0 Hz, 1H), 2.20-1.10 (m, 11H), 1.00-0.90 (m, 21H); Elemental analysis calcd: C, 80.56; H, 13.92; N, 5.53%; Found: C, 80.61; H, 13.82; N, 5.56%.

Reaction of acetal with dialkylaluminum 2,2,6,6-tetramethylpiperidide: LTMP (lithium 2,2,6,6-tetramethylpiperidide) was prepared from 2,2,6,6-tetramethylpiperidine (250 mg, 2.0 mmol) and butyllithium (1.76 M in hexane, 1,2 mL, 2.0 mmol) in toluene (5 mL) at 0°C. After addition of dialkylaluminum chloride (1 M in hexane, 2.0 mL, 2.0 mmol), the solutiomn was stirred at 0°C for 30 min., and then cooled to -78°C. To this solution was added acetal **3a** (99 mg, 0.50 mmol) in toluene (2 mL). Stirring was continued at that temperature for 1 h, and at 0°C untill almost all the acetal had consumed. The resulting solution was poured into ice-cooled 2 N aqueous solution of sodium hydroxide and extracted with ether. The combined ether extracts were dried over magnesium sulfate. Concentration in vacuo and purification by column chromatography on silica gel (eluant: hexane-ethyl acetate, 4:1) gave a colorless oil, which was acetylated in acetic anhydride (1 mL) and triethylamine (3 mL) in the presence of 4-(dimethylamino)pyridine (5 mg) to afford the vinyl ether acetate **5a**; Yield: dimethylalunimum amide (18 mg, 0.080 mmol, 16%, ratio 82:18); diethylaluminum amide (110 mg, 0.47 mmol, 90%, ratio 84:16); diisobutylaluminum amide (84 mg, 0.37 mmol, 70 %, ratio 81:19).

General procedure for treatment with 22b (3b, R = Et): To a solution of amine **22a** (638 mg, 2.5 mmol) in toluene (5 mL) was added butyllithium (1.56 M in hexane, 1.6 mL, 2.5 mmol) at 0°C. The resulting mixture was stirred at that temperature for 1 h, and at ambient temperature overnight. After cooling to 0°C, diisobutylaluminum chloride (1 M in hexane, 2.5 mL, 2.5 mmol) was added. After 1 h, the resulting mixture was cooled to -78°C, and to this was introduced acetal **3b** (56 mg) in toluene (2 mL). Stirring was continued at that temperature for 1 h, and at 0°C for 6 h. The reaction solution was poured into 2 N aqueous solution of sodium hydroxide and extracted with ether. Concentration in vacuo and purification by column chromatography on silica gel (eluant: hexane-ethyl acetate, 4:1) gave a colorless oil, which was acetylated in acetic anhydride (1 mL) and triethylamine (3 mL) in the presence of 4-(dimethylamino)pyridine (5 mg) to afford the vinyl ether acetate **5b** (58 mg, 0.24 mmol, 91%). Its diasteroratio determined by glc analysis was found to be 92:8.

Reaction with acetal 3a (R = Me): The acetal **3a** (55 mg, 0.28 mmol) reacted with the amide **22b** followed by acetylation produced the vinyl ether acetate **5a** (30 mg, 0.13 mmol, 48%). Its diastereoratio determined by glc analysis was found to be 90:10.

Reaction with acetal 3c (R = t-Bu): The acetal **3c** (60 mg, 0.23 mmol) reacted with the amide **22b** followed by acetylation produced the vinyl ether acetate **5c** (62 mg, 0.23 mmol, 95%). Its diastereoratio determined by glc analysis was found to be 88:12.

Reaction with acetal 4 (3,5-dimethyl): The acetal **4** (56 mg, 0.27 mmol) reacted with the amide **22b** followed by acetylation produced the vunyl ether acetate **6** (44 mg, 0.18 mmol, 69%). Its diastereoratio determined by glc analysis was found to be 94:6.

Treatment of acetal 3a with diisobutylaluminum amide 24b: To a solution of amine **24a** (260 mg, 1.0 mmol) in toluene (2.5 mL) was added butyllithium (1.56 M in hexane, 0.56 mL, 1.0 mmol) at 0°C. The resulting solution was refluxed for 2 h. Diisobutylaluminum chloride (1 M in hexane, 1.0 mL, 1.0 mmol) was introduced at 0°C. After 1 h, at ambient temperature, the solution was cooled to 0°C, and to this was added acetal **3a** (57 mg, 0.25 mmol). Stirring was continued for 4 h. The reaction solution was poured into aqueous solution of sodium hydroxide and extracted with ether. The combined ether extracts were dried over magnesium sulfate. Concentration in vacuo and purification by column chromatography on silica gel (eluant: hexane-ethyl acetate, 4:1) gave trace of the product with recovery of acetal.

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