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KINETIC RESOLUTION OF EPOXIDES BY CHIRAL ORGANOALUMINUM CATALYST SHORT SYNTHESIS OF (-)-C_{16} JUVENILE HORMONE

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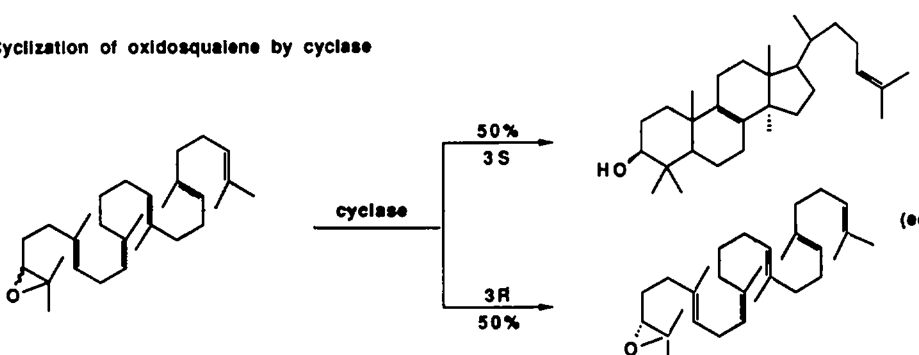
Abstruct: The use of chiral organoaluminum reagent as a catalyst to resolve simple ketoepoxides is explored. The optically pure ketoepoxide **10** was recovered after 80% conversion. The recovered pure epoxide is a useful chiral building block in the synthesis of chirel terpenes. The method applies for the short asymmetric synthesis of the juvenile hormone by the synthetic route which depends on the palladium-catalyzed coupling process.

The sterol biosynthetic pathway from 2,3-oxidosqualene is truly unique in the number of asymmetric centers it produces in a single operation. It was shown that racemic 2,3-oxidosqualene **1** was converted to lanosterol and the recovered oxidosqualene both in optically pure form when treated with the cyclase (eq. 1).[1] This process is an impressive example of a complete kinetic resolution. In connection with studies on the asymmetric induction in oxrane ring opening,[2] we have occasion to study the possible approach which models such an enzymatic transformation. Thus we have been studying a variety of chiral Lewis acids which promote kinetic resolution of epoxides, and exploring the synthetic efficiency of such approaches. Here we report the first realization of this enterprise.

Cyclization of oxidosqualene by cyclase



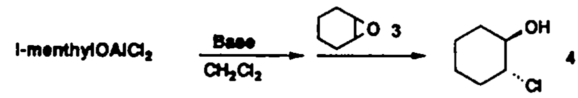
(eq. 1)

R-1

Transformation of cyclohexene oxides

Initial study was focused on the ring opening of oxiranes into α-chlorohydrins.[3] We have examined a variety of chiral Lewis acid catalyst, i.e. $R^*{}_3Al$, $R^*{}_2AlCl$, R^*BX_2, and so on, without any significant success. However, we have observed substantial increase of induction of these reaction when these catalysts were pretreated with base. For example, the reagent produced by addition of l-menthoxyaluminum dichloride **2**[4] and s-butyllithium in dichloromethane transforms cyclohexene oxide **3** into chlorohydrin **4** in 44% yield, and the resulting chlorohydrin **4** was found to be 34% e.e.[5] by hplc analysis of its MTPA ester.[6] Some of the results are shown below (Table 1).

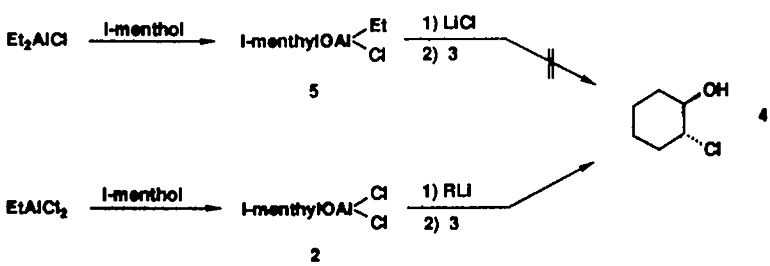
Table 1. Formation of chlorohydrin 3 by menthoxyaluminum reagent



Base	Temp.(°C)	Time(h)	Yield(%)	ee(%)	config.
none	-78	0.1	37	10	(1R, 2S)
BuLi	0	0.5	40	23	(1R, 2S)
s-BuLi	-20	2.0	40	34	(1R, 2S)
t-BuLi	-40	2.0	40	17	(1R, 2S)
l-menthylOLi	-20	1.0	59	26	(1R, 2S)
t-BuMgCl	-40	2.0	40	17	(1R, 2S)

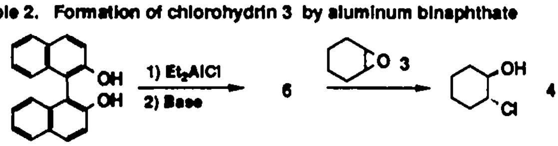
l-Menthoxyethylaluminum chloride 5, prepared in situ from diethylaluminum chloride and l-menthol, was treated first with lithium chloride, and then with epoxides. None of the desired chlorohydrin was produced even at room temperature for two days. On the other hand, treatment of l-menthoxyaluminum dichloride 2 with alkyllithium gave an active reagent for the above transformation (Scheme 2). These experimental evidences clearly showed that the true catalyst should be an 'ate' complex, rather than trivalent aluminum reagent.

Scheme 1.



The chiral induction observed in this reaction using the 'ate' complex as the catalyst prompted us to explore further modification of the reagent, and we turned our attention to test binaphthol as a chiral ligand. Table 2 summerized the results. The reagent 6, prepared from (R)-binaphthol, diethylaluminum chloride, and lithium butoxide, was treated with the epoxide 3 at -78°C.

Table 2. Formation of chlorohydrin 3 by aluminum binaphthate



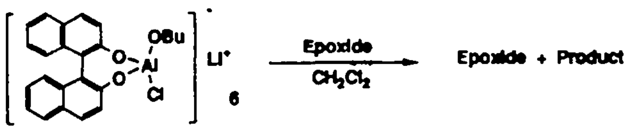
R	Temp. (°C)	Time (h)	Yield (%)	ee (%)	config.
Et_2NLi	-20	2	43	24	(1S, 2R)
LDA	0	48	52	26	(1S, 2R)
LTMP	-20	12	56	26	(1S, 2R)
EtOLi	40	24	22	26	(1S, 2R)
i-PrOLi	r.t.	48	26	18	(1S, 2R)
BuOLi	40	36	26	40	(1S, 2R)
BuOLi[1]	0	2	15	0	-
t-BuOLi	r.t.	2	24	16	(1S, 2R)

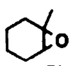
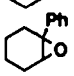
Solvent: CH_2Cl_2 1. Reaction was performed in THF.

After gradually warming to ambient temperature, the reaction mixture was refluxed for 1.5 days. The chlorohydrin 4 was thus obtained in 40% e.e.

We employed the same catalyst to the reaction with racemic epoxides. Treatment of 1-phenylcyclohexene oxide 8 with 0.2 equivalent of the aluminum reagent 6 gave the rearranged aldehyde 9. The optical purity of the recovered epoxide 8 was determined by proton NMR in the presence of the chiral shift reagent, which was shown to be 52% e.e.

Table 3. Kinetic resolution of epoxides by 6



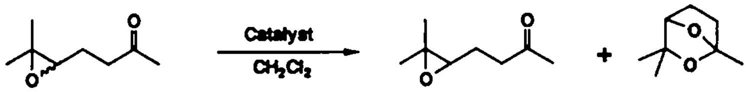
eq. of cat.	Epoxide	Temp (°C)	Time (h)	Recovered Epoxide Recov. (%)	Recovered Epoxide %ee	Aldehyde (% yield)
1.0	 7	r.t.	3	15	27	——
0.75	 8	-20 0	2 0.5	11	36	 9 (44)
0.20	8	0 r.t.	18 10	21	52	9 (50)

Kinetic resolution

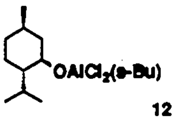
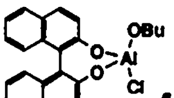
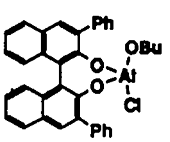
Modelling of the enzymatic reactions remains an important contemporary problem for the highly selective reactions. Undoubtedly polyene cyclization is believed to be one of these goals worthy to challenge. Since the existence of π-epoxide interaction is established in this olefin cyclization process,[2] we tested the ring opening of epoxide which has an appropriate functional group at a suitable position. We, thus, elected the ketoepoxide 10 as a test substrate. It has the carbonyl group at the γ-position which may play the role of an appropriate cation stabilizer. Treatment with a variety of chiral Lewis acids led only to give the cyclized acetal 11 in a racemic form. However, due to the significant difference in the reactivity of the reagent, the mild 'ate' reagent was found to be an ideal catalyst in the acetal formation and have an ability to recognize the chirality of the epoxide. Addition of the menthoxyaluminum reagent 12 to one equivalent of ketoepoxide 10 proceeded the cyclization rather slowly at -20°C. When the conversion was completed in 94%, the recovered ketoepoxide 10 was shown to be 71% e.e. The optical purity of the recovered material was determined using the chiral shift reagent (+)-Eu(hfc)$_3$ which showed two different triplet peaks of oxirane proton whereas the racemate showed two of equal intensity at δ5.20 (for R-isomer) and 4.90 (for S-isomer) with 16 mole% of the shift reagent. The absolute configuration was determined by the comparison with the authentic product prepared from geranyl acetate.[7] Having established the utility of the 'ate' complex in this kinetic resolution, we examined many of the reagent of this type to give higher selectivity.

The ketoepoxide 10 in dichloromethane was treated with the aluminum reagent 6 at -78°C. After stirring at that temperature for 30 minutes, the resulting mixture was allowed to warm gradually to -30°C to proceed the slow cyclization. On most of the material was consumed judging from tlc analysis (ca. 5 h), the reaction was stopped by addition of triethylamine. The recovered ketoepoxide 10 was perfectly resolved by the proton NMR analysis (>95% e.e.). Use of this 6 to cyclize the polyene terminal epoxide 1 did not proceed smoothly at low temperature, and at the higher temperature the effective kinetic resolution could not be achieved.[8] Although we failed the attempt to realize the real model of cyclase and yet the nature of the reagent might be open un-

Table 4. Kinetic resolution of ketoepoxide 10 by aluminum reagent



10 → 10 + 11

catalyst	Temp (°C)	Time (h)	Recov. (%)	ee(%)
 12	-20	0.2	6	71 (S)
 6	-30	5	20	>95 (R)
	-40	4.5	<10	43 (R)

til now, we believe that we have demonstrated the first successful artificial system realized by the chiral aluminum reagent.

Application for the juvenile hormone synthesis

This process is convenient and amenable to scale-up, and can provide a powerful route to the useful building block of chiral terpenes. The method was now applied on the synthesis of juvenile hormone.

Optically active juvenile hormone III (C_{16}-JH) **20** has been synthesized previously,[9] the approaches which have been used are, however, of relatively lengthy.

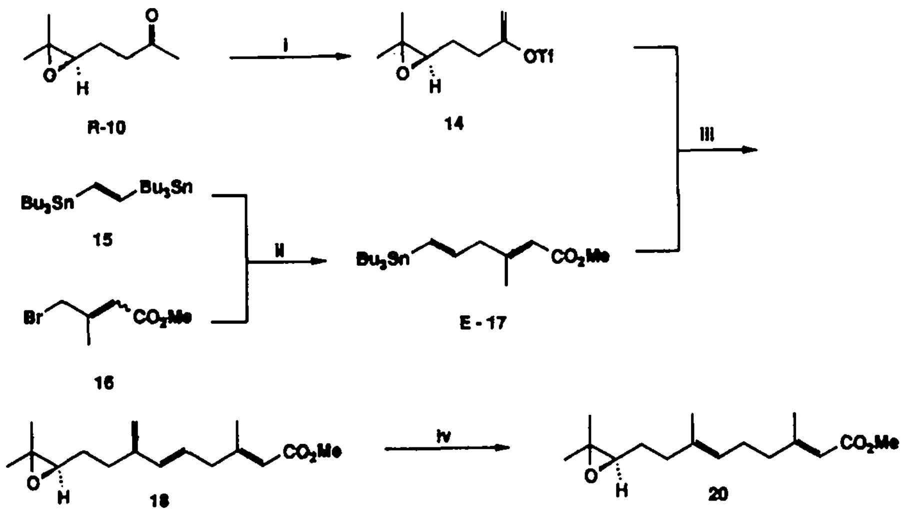
The starting point for the synthetic plan was the observation that the vinyl phosphate or vinyl triflate **14**, which were derived from the ketoepoxide **10**, can undergo smooth coupling with organometallic reagents. For example, treatment of epoxyvinyl phosphate with vinyl Grignard reagent in the presence of the nickel catalyst gave the coupled diene smoothly at ambient temperature.[10] Employing the method developed by Stille, however, the reaction proceeded under even milder conditions. The coupling of **14** and E-**17** proceeded smoothly and the ester group of E-**17** was intact under the coupling condition.[11,12]

The synthesis was summerized in Scheme 2. The optically pure ketoepoxide R-**10** was converted to the enol triflate **14** with the triflic imide **13** and lithium diisopropylamide in tetrahydrofuran and hexamethylphosphoric triamide (HMPA) at -78°C.[13] tert-Butyl **13** was used as the triflating reagent due to difficulties in chromatographic separation of the product from amide residues of non-substituted derivatives.

The other component **17** required for the assembly of juvenile hormone was prepared in a straight forward manner. Radical bromination of methyl 3-methyl-2-butenoate with N-bromosuccilmide in carbon tetrachloride gave the bromoester **16**[14]. Since isomerization of the double bond occurred under the coupling conditions, this cis-trans mixture of **16** (E/Z = ca. 1:1) was used without any further separation. Tinester **17** was produced in 72% yield from ditin **15**[15] and the bromoester **16** with palladium catalyzed coupling.[11] After careful chromatographic separation of the stereoisomer, the pure E-**17** was used for the subsequent coupling reaction. The juvenile hormone skeleton was now connected with the C_8-unit of the enol triflate **14** and C_7-unit of the tinester E-**17** as follows.[12] A mixture of tetrakis(triphenylphosphine)palladium (2 mol%), cesium fluoride (3.0 equiv.),[16] 14, and E-17 in dry degassed tetrahydrofuran was heated at reflux for 5 h, after column chromatography on silica gel, to yield the desired triene ester 18 in 58%.

Partial and selective hydrogenation of the resulting ester 18 was accomplished in the presence of tricarbonyl(1,2,3,4,4a,8a,-η)naphthalenechromium catalyst 19 under 80 atm of hydrogen in dry tetrahydrofuran at 45°C for 5 h to afford the juvenile hormone 20 in 62% yield without contamination of any of the corresponding Z-isomer.[17] The above mentioned synthesis of juvenile hormone contains a number of noteworthy methods, which may be used for the other synthesis.

Scheme 2. Total synthesis of juvenile hormone III 20



i $4\text{-}t\text{-}BuC_6H_4NTf_2$, LDA / THF - HMPA, -78 - -20°C, 80%

ii $PdCl_2(CH_3CN)_2$, PPh_3 / $CHCl_3$ 80°C, 76%

iii $Pd(PPh_3)_4$, CsF / THF reflux, 58%

iv $Cr(CO)_3Np$, H_2 (80 atm.)/ THF, 45°C, 66%

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 GMX-500 spectrometer. The chemical shifts are expressed in parts par million downfield from internal tetramethylsilane (TMS, δ = 0). Splitting patterns are indicated as s, singlet; d, doublet; t, triplet; q, quartet; dt, doubletting triplet; m, multiplet; br, broad peak. Gas liquid-phase chromatographic (glc) analyses were performed on Hitachi Model 163, 164, or Gasukuro Kogyo Model 370, or Shimadzu GC-8A instruments equipped with PEG 25 meter column detected by a flame ionization detector, using nitrogen as the carrier 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) analysis throughout this work, Merck precoated tlc plates (silica gel 60 GF_{254}, 0.25 mm thickness) were used. Elemental analysis 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 described by Stille[11]. Hexane and benzene were dried over sodium metal. The chemicals other than described in the literatures were purchased and used as such. For flash column chromatography used was silica gel Merck Kieselgel 60 (Art. 9385).

(1RS, 2SR)-2-chlorocyclohexanol: A two-phase mixture of cyclohexene oxide (7.0 mL, 69 mmol) in dichloromethane (60 mL) and conc. hydrochloric acid (ca. 12 N, 6 mL, 72 mmol) was stirred at ambient temperature for 20 min. The organic layer was separated, and the water layer was extracted with ether. The combined organic layers were dried over magnesium sulfate. Concentration in vacuo and distillation under reduced pressure afforded a colorless oil (6.34 g, 48 mmol, 69%): b.p. 38-39°C (6 Torr); tlc Rf = 0.30 (hexane-ether = 1:1); IR (neat film) 3800-3000 br. s, 3000-2800 s, 1445 s, 1075 s, 960 s, 740 m; ^1H NMR ($CDCl_3$) δ 3.75 (m, 1H), 2.58 (m, 1H), 2.28-2.07 (m, 2H), 1.78-1.23 (m, 6H)

This chlorohydrin was exposed to optical resolution according the procedure by Zeelen et al[5]. Its optical purity was determined by hplc analysis of its MTPA ester[6]. Two peaks were identified; the former peak (tr = 10.6 min.) was corresponded to its (1S, 2R)-isomer and the latter (tr = 12.3 min.) to (1R, 2S)-isomer (eluant: hexane-ether = 30:1 detected by UV absorption (254 nm)).

Reaction of menthoxyaluminum dichloride 2: To a solution of l-menthoxyaluminum dichloride (202 mg, 0.80 mmol)[4] in dichloromethane (4 mL) was introduced cyclohexene oxide 3 (79 mg, 0.80 mmol) in dichloromethane (1.5 mL) dropwise at -78°C. The resulting solution was stirred at that temperature for 90 min., at -40°C for 2 h, and at -20°C for 2 h. It was poured into 1 N hydrochloric acid and extracted with ether. The combined ether extracts were washed with brine, and dried over sodium sulfate. Concentration in vacuo and purification by column chromatography on silica gel (eluant: hexane-ethyl acetate = 6:1) gave a colorless oil 4 (40 mg, 0.30 mmol, 37%).

Reaction of 2 treated with butyllithium: To a solution of 2 (380 mg, 1.5 mmol) in dichloromethane (6 mL) was introduced butyllithium (1.59 M in hexane, 1 mL, 1.6 mmol) at -78°C. The resulting mixture was stirred at 0°C for 30 min. After cooling to -78°C, to this was introduced cyclohexene oxide 3 (118 mg, 1.2 mmol) in dichloromethane (1.2 mL) dropwise. The reaction solution was stirred at that temperature for 50 min., at -40°C for 90 min., and at 0°C for 1 h. It was poured into 1 N hydrochloric acid and extracted with ether. The combined ether extracts were washed with brine, and dried over sodium sulfate. Concentration in vacuo and purification by column chromatography on silica gel (eluant: hexane-ethyl acetate = 6:1) gave a colorless oil 4 (74 mg, 0.55mmol, 46%).

Reaction of 2 treated with s-butyllithium: To a solution of 2 (378 mg, 1.1 mmol) in dichloromethane (5 mL) was introduced s-butyllithium (1.11 M in cyclohexane, 1.04 mL, 1.2 mmol) at -78°C. The resulting mixture was stirred at 0°C for 40 min. After being chilled to -78°C, cyclohexene oxide 3 (98 mg, 1.0 mmol) in dichloromethane (1.5 mL) was introduced dropwise. The reaction solution was stirred at that temperature for 1 h, at -40°C for 2 h, at -20°C for 2 h, and at 0°C for 1 h. It was poured into 1 N hydrochloric acid and extracted with ether. The combined ether extracts were washed with brine and dried over sodium sulfate. Concentration in vacuo and purification by column chromatography on silica gel (eluant: hexane-ethyl acetate = 6:1) gave a colorless oil 4 (59 mg, 0.44 mmol, 44%).

Reaction of 2 treated with lithium l-menthoxide: To a solution of l-menthol (172 mg, 1.1 mmol) in hexane (1.3 mL) was added butyllithium (1.52 M in hexane, 0.72 mL, 1.1 mmol) at 0°C. The resulting gel was cooled to -78°C, and introduced was 2 (278 mg, 1.1 mmol) in dichloromethane (3 mL). The resulting mixture was stirred at 0°C for 1 h. After being cooled to -78°C, cyclohexene oxide 3 (98 mg, 1.0 mmol) in dichloromethane (1.5 mL) dropwise. Stirring was continued at that temperature for 30 min., at -40°C for 30 min., at -20°C for 1 h, and at 0°C for 2 h. The resulting white suspension was poured into 1 N hydrochloric acid and extracted with ether. The combined ether extracts were washed with brine, dried over sodium sulfate. Concentration in vacuo and purification by column chromatography on silica gel (eluant: hexane-ethyl acetate = 6:1) gave a colorless oil 4 (79 mg, 0.59 mmol, 59%).

Reaction of 2 treated with t-butylmagnesium chloride: To a solution of 2 (278 mg, 1.1 mmol) in dichloromethane (5 mL) was introduced t-butylmagnesium chloride (TCI reagent, 0.82 M in ether, 1.46 mL, 1.2 mmol) at -78°C. The mixure was strirred at 0°C for 1 h. After being cooled to -78°C, cyclohexene oxide 3 (98 mg, 1.0 mmol) in dichloromethane (1.5 mL) was added dropwise. Stirring was continued at that temperature for 1 h, at -40°C for 45 min., at -20°C for 70 min., and at 0°C for 2 h. The reaction mixture was poured into 1 N hydrochloric acid and extracted with ether. The combined ether extracts were washed with brine, and dried over sodium sulfate. Concentration in vacuo and purification by column chromatogarphy on silica gel gave a colorless oil 4 (86 mg, 0.63 mmol, 63%).

Reaction of ethylmenthoxyaluminum chloride treated with lithium chloride: To a solution of l-menthol (172 mg, 1.1 mmol) in dichloromethane (5 mL) was introduced diethylaluminum chloride (1 M in hexane, 1 mL, 1.0 mmol) at ambient temperature. After 1.5 h, dry lithium chloride was added, and the resulting suspension was refluxed for 2.5 h. After being cooled to -78°C, cyclohexene oxide 3 (98 mg, 1.0 mmol) in dichloromethane (1.5 mL) was introduced dropwise. Stirring was continued at that temperature for 20 min., at -40°C for 70 min., and gradually warmed to room temperature. No chlorohydrin, however, was produced after 2 days.

Reaction of aluminum binaphthate treated with lithium ethoxide: To a solution of (R)-1,1'-bi-2-naphthol (172 mg, 0.60 mmol) in dichloromethahe (2 mL) was introduced diethylaluminum chloride (1 M in hexane, 0.60 mL, 0.60 mmol) at -78°C. The resulting white suspension was transferred to lithium ethoxide, prepared from ethanol (38 uL, 0.65 mmol) and butyllithium (1.52 M in hexane, 0.43 mL, 0.65 mmol), in hexane (0.5 mL). After stirring at 0°C for 45 min., cyclohexene oxide 3 (39 mg, 0.40 mmol) in dichloromethane (1.5 mL) was added. The reaction solution was refluxed for 1 day, and poured into 1 N hydrochloric acid, and extracted with ether. The combined ether extracts were washed with brine, and dried over sodium sulfate. Concentration in vacuo and purification by column chromatography on silica gel (eluant: hexane-ethyl acetate = 6:1) gave a colorless oil 4 (12 mg, 0.089 mmol, 22%).

Reaction of aluminum binaphthate treated with lithium isopropoxide: To a solution of (R)-1,1'-bi-2-naphthol (172 mg, 0.60 mmol) in dichloromethane (5 mL) was introduced diethylaluminum chloride (1 M in hexane, 0.60 mL, 0.60 mmol) at -78°C. After stirring at 0°C for 20 min., the resulting white suspension was transferred to lithium isopropoxide, prepared from isopropanol (39 mg, 0.65 mmol) and butyllithium (1.52 M in hexane, 0.43 mL, 0.65 mmol), in hexane (0.5 mL) at -78°C. After stirring at 0°C for 20 min., cyclohexene oxide 3 (39 mg, 0.40 mmol) in dichloromethane (1.5 mL) was introduced. Stirring was continued at room temperature for 2 days. The reaction mixture was poured into 1 N hydrochloric acid, and extracted with ether. The combined ether extracts were washed with brine, and dried over sodium sulfate. Concentration in vacuo and purification by column chromatography on silica gel (eluant: heane-ethyl acetate = 6:1) gave a colorless oil of 4 (14 mg, 0.10 mmol, 26%).

Reaction of aluminum binaphthate treated with lithium butoxide: To a solution of (R)-1,1'-bi-2-naphthol (172 mg, 0.60 mmol) in dichloromethane (4 mL) was introduced diethylaluminum chloride (1 M in hexane, 0.60 mL, 0.60 mmol) at -78°C. After stirring at 0°C for 20 min., cyclohexene oxide 3 in dichloromethane was added dropwise. Stirring was continued at room temperature for 1.5 days. The mixture was poured into 1 N hydrochloric acid, and extracted with ether. The combined ether extracts were washed with brine, and dried over sodium sulfate. Concentration in vacuo and purification by column chromatography on silica gel (eluant: hexane-ethyl acetate = 6:1) gave a colorless oil of 4 (14 mg, 0.10 mmol, 26%).

Reaction of aluminum binaphthate treated with lithium butoxide in tetrahydrofuran: To a solution of (R)-1,1'-bi-2-naphthol (172 mg, 0.60 mmol) in tetrahydrofuran (2 mL) was introduced diethylaluminum chloride (1 M in hexane, 0.60 mL, 0.60 mmol) at -78°C. After stirring at 0°C for 10 min., introduced was lithium butoxide, prepared from 1-butanol (48 mg, 0.65 mmol) and butyllithium (1.52 M in hexane, 0.43 mL, 0.65 mmol), in tetrahydrofuran (1.5 mL), followed by cyclohexene oxide 3 (39 mmol, 0.40 mmol) in tetrahydrofuran (1 mL). The reaction solution was gradually warmed to 0°C, but only trace of chlorohydrin was produced.

Reaction of aluminum binaphthate treated with lithium t-butoxide: To a solution of (R)-1,1'-bi-2-naphthol (172 mg, 0.60 mmol) in dichloromethane (4 mL) was introduced diethylaluminum chloride (1 M in hexane, 0.60 mL, 0.60 mmol) -78°C. After stirring at 0°C for 30 min., the resulting white suspension was transferred to lithium t-butoxide, prepared from t-butanol (48 mg, 0.65 mmol) and butyllithium (1.52 M in hexane, 0.43 mL, 0.65 mmol), in hexane (0.5 mL). After stirring at 0°C for 30 min., cyclohexene oxide 3 (39 mg, 0.40 mmol) in dichloromethane (1.5 mL) was introduced. The reaction mixture was stirred at that temperature for 30 min., and allowed to warm to ambient temperature. After 2.5 h, it was poured into 1 N hydrochloric acid and extracted with ether. The combined ether extracts were washed with brine, and dried over sodium sulfate. Concentration in vacuo and purification by column chromatography on silica gel (eluant: hexane-ethyl acetate = 6:1) gave an slight yellow oil of 4 (13 mg, 0.096 mmol, 24%).

Reaction of aluminum binaphthate treated with lithium amide: To a solution of (R)-1,1'-bi-2-naphthol (172 mg, 0.60 mmol) in dichloromethane (5 mL) was added diethylaluminum chloride (1 M in hexane, 0.60 mL, 0.60 mmol) at -78°C. After stirring at 0°C for 30 min., the resulting white suspension was transferred to a suspension to lithium amide, prepared from amine (0.60 mmol) and butyllithium (1.52 M in hexane, 0.40 mL, 0.60 mmol), in hexane (0.5 mL). After 15 min, the resulting mixture was cooled to -78°C, and to this was introduced cyclohexene oxide 3 (39 mg, 0.40 mmol) in dichloromethane (1.5 mL) dropwise. After most of epoxide 3 was consumed, the reaction solution was poured into 1 N hydrochloric acid and extracted with ether. The combined ether extracts were washed with brine, and dried over sodium sulfate. Concentration in vacuo and purification by column chromatography on silica gel (eluant hexane-ethyl acetate = 6:1) gave a colorless oil of 4: lithium diethylamide (23 mg, 0.17 mmol, 43%); lithium diisopropylamide (LDA, 28 mg, 0.19 mmol, 52%); lithium 2,2,6,6-tetramethylpiperidide (LTMP, 30 mg, 0.22 mmol, 56%).

Kinetic resolution of 1-methylcyclohexene oxide 7 by aluminum binaphthate 6: To a solution of (R)-1,1'-bi-2-naphthol (172 mg, 0.60 mmol)in dichloromethane (7 mL) was added dimethylaluminum chloride (1 M in hexane, 0.60 mL, 0.60 mmol) at -78°C. After stirring at 0°C for 10 min., the resulting white suspension was transferred to a suspension of lithium butoxide, prepared from 1-butanol (60 uL, 0.65 mmol) and butyllithium (1.59 M in hexane, 0.41 mL, 0.65 mmol) in hexane (0.5 mL). After 20 min. at 0°C, 1-methylcyclohexene oxide (prepared by the similar manner as 3, 67 mg, 0.60 mmol) in dichloromethane (1.5 mL) was added. Stirring was continued at ambient temperature for 3 h. The resulting mixture was diluted with ether and washed with 1 N aqueous solution of sodium hydroxide and brine. Dryness over magnesium sulfate, concentration in vacuo, and purification by column chromatography on silica gel (eluant: pentane-ether = 20:1) gave a colorless oil (10 mg, 15%). Its optical purity was determined by ^{1}H NMR in the presence of (+)-Eu(hfc)$_3$ (δ = 12.52 and 12.35) to be 27% e.e.; tlc Rf = 0.35 (hexane-ether = 9:1); ^{1}H NMR (CCl_4): δ 2.75 (t, J = 2.0 Hz, 1H), 1.21 (s, 3H), 2.04-1.10 (m, 8H).

Kinetic resolution of 1-phenylcyclohexene oxide 8 by aluminum binaphthate 6: To a solution of (R)-1,1'-bi-2-naphthol (172 mg, 0.60 mmol) in dichloromethane (7 mL) was added dimethylaluminum chloride (1 M in hexane, 0.60 mL, 0.60 mmol) at -78C°C. After 10 min. at 0°C, the resulting white suspension was transferred to a suspension of lithium butoxide, prepared from 1-butanol (60 uL, 0.65 mmol) and butyllithium (1.59 M in hexane, 0.41 mL, 0.65 mmol) in hexane (0.5 mL) at -78°C. After 30 min. at 0°C, a portion of the resulting mixture was transferred (6.75 mL, 0.45 mmol). To this was added 1-phenylcyclohexene oxide 8 (prepared by the similar manner as 3, 105 mg, 0.60 mmol). Stirring was continued at that temperature for 30 min., at -40°C for 30 min., at -20 °C for 2 h, and at 0°C for 30 min. After addition of triethylamine (1 mL), the reaction solution was diluted with ether. The mixture was washed with 1 N aqueous solution of sodium hydroxide and brine. Dryness over magnesium sulfate, concentration in vacuo, and purification by column chromatography on silica gel (eluant: hexane-ether = 25:1) afforded the recovered epoxide **8** (11 mg, 11%) and the rearranged aldehyde (46 mg, 44%): physical data of **8**: tlc Rf = 0.41 (benzene); ^{1}H NMR (CCl_4): δ 7.63-6.92 (m, 5H), 3.87 (t, J = 2.1 Hz, 1H), 2.34-0.75 (m, 8H); its optical yield was determined by ^{1}H NMR in the presence of (+)-Eu(hfc)$_3$ (δ = 5.42 and 4.87) to be 36% e.e.; **9**: tlc Rf = 0.47 (benzene); IR (neat film): 3000-2850 s, 1715 s, 1440 s; ^{1}H NMR (CCl_4): δ 9.37 (s, 1H), 7.26 (br. s, 5H), 2.75-1.43 (m, 8H).

Kinetic resolution of 8 by aluminum binaphthate 6. Catalytic system: To a suspension of thus prepared **6** in dichloromethane (1.8 mL, 0.12 mmol) was added the epoxide **8** (105 mg, 0.60 mmol) in dichloroemethane (4 mL) at -20°C. Stirring was continued at that temperature for 2 h, at 0°C for 20 h, and at room temperature for 10 h. After addition of triethylamine (1 mL), the resulting solution was diluted with ether. It was washed with 1 N aqueous solution fo sodium hydroxide and brine. Dryness over magnesium sulfate, concentration in vacuo, and purification by column chromatography on slica gel (eluant: hexane-ether = 25:1) gave the recovered epoxide **8** (22 mg, 21%) and the aldehyde **9** (53 mg, 50%). The optical purity of recovered **8** was found to be 52% e.e.

Ketoepoxide 10: To a suspension of the ketone (18,9 g, 150 mmol) and sodium hydrogencarbonate (18.1 g, 220 mmol) in dichloromethane (250 mL) was added m-chloroperbenzoic acid (70% assay, 37.1 g, 150 mmol) at 0°C in small portions. The resulting suspension was stirred at that temperature for 1 h, and filtrated. The filtrate was washed with saturated aqueous solution of sodium sulfite and saturated aqueous solution of sodium hydrogencarbonate. The organic layer was separated, and dried over magnesium sulfate and concentrated in vacuo. The residual oil was distilled under reduced pressure gave a colorless oil (17.2 g, 120 mmol, 81%): b.p. 48-56°C (1 Torr); tlc Rf = 0.26 (hexane-ethyl acetate, 2:1); IR (neat film) 3050-2800 br. s, 1720 s, 1380 m, 1165 m; ^{1}H NMR (CCl_4) δ 2.52 (t, J = 7 Hz, 2H), 2.50 (d, J = 7.6 Hz, 1H), 2.10 (s, 3H), 2.00-1.35 (m, 2H), 1,23 (s, 6H).

Resolution of ketoepoxide 10 by l-menthoxyaluminum reagent 12: A solution of aluminum l-menthoxydichloride (prepared from l-menthol (79.6 mg, 0.50 mmol) and ethylaluminum dichloride (0.50 mL of 1.0 M solution in hexane, 0.50 mmol) in hexane (1 mL))[4] was introduced s-butyllithium (1.03 M in hexanes, 0.50 mL, 0.50 mmol) at -78°C and the resulting mixture was stirred at that temperature for 30 min. To this white suspension was introduced was the ketoepoxide **10** (714 mg, 5.0 mmol) in dichloromethane (3 mL) dropwise. Stirring was continued for 30 min. at that temperature, at -40°C for 30 min., and at -20°C for 10 min. Triethylamine (1 mL) was added into the reaction mixture to stop the reaction, and the resulting mixture was poured into 1 N aqueous solution of sodium hydroxide, 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: pentane-ether = 2:1 - 1:2) afforded the cyclized acetal and recovered ketoepoxide **10** (46.7 mg, 6.5% recovery). Its optical purity determined by ^{1}H NMR in the presence of the chiral shift reagent Eu(hfc)$_3$ was shown to be 71% e.e. of the (S)-isomer.

Kinetic resolution of ketoepoxide 10 by aluminum binaphthate reagent 6: To a solution of (R)-1,1'-bi-2-naphthol (174 mg, 0.60 mmol) in dichloromethane (7 mL) was introduced dimethylaluminum chloride (1 M in hexane, 0.60 mL, 0.60 mmol) at -78°C. After being stirred at 0 °C for 10 min., the resulting white suspension was cooled to -78°C, and transferred to a suspension of lithium butoxide, prepared from butyllithium (1.59 M in hexane, 0.41 mL, 0.65 mmol) and 1-butanol (60 uL, 0.65 mmol), in hexane (0.5 mL). The faint white suspension was stirred at 0°C for 10 min., and chilled to -78°C. To this was added ketoepoxide **10** (106 mg, 0.80 mmol) in dichloromethane (2 mL). The reaction mixture was stirred at -40°C for 3 h. After introduction of triethylamine (0.5 mL), it was poured into 2 N aqueous solution of sodium hydroxide, and extracted with ether. The combined ether extracts were washed with 2 N aqueous solution of sodium hydroxide and brine. Dryness over magnesium sulfate, concentration in vacuo, and purification by column chromatography on silica gel (eluant: pentane-ether = 3:1 - 1:1) afforded the recovered material (17 mg, 10%). Its optical purity, determined by ^{1}H NMR in the presence of Eu(hfc)$_3$, was found to be >95% e.e. of (R)-isomer.

Kinetic resolution of ketoepoxide 10 by aluminum diphenylbinaphthate reagent: To a solution of 3,3'-diphenyl-(R)-1,1'-bi-2-naphthol (90% pure, 351 mg, 0.80 mmol) in dichloromethane (10 mL) was introduced dimethylaluminum chloride (1 M in hexane, 0.80 mL, 0.80 mmol) at -78°C. After being stirred at ambient temperature for 30 min., the resulting solution was cooled to -78°C, the resulting solution was transferred to a suspension of lithium butoxide, prepared from butyllithium (1.61 M in hexane, 0.55 mL, 0.88 mmol) and 1-butanol (81 uL, 0.88 mmol), in hexane (0.7 mL). The yellow suspension was stirred at 0°C for 30 min. (ca. 0.67 M of aluminum reagent solution).

A portion of thus prepared aluminum reagent (9.0 mL, 0.60 mmol) was transferred, and to this was introduced ketoepoxide **10** (85 mg, 0.60 mmol) in dichloromethane (1.5 mL) at -78°C. The reaction mixture was stirred at -40°C for 30 min. After introduction of triethylamine (0.5 mL), it was poured into 2 N aqueous solution of sodium hydroxide, and extracted with ether. The combined ether extracts were dried washed with 2 N aqueous solution of sodium hydroxide and brine, and dried over sodium sulfate. Concentration in vacuo and purification by column chromatography on silica gel (eluant: pentane-ether = 2:1 - 2:3) gave the recovered material (38 mg, ca. 50% pure, ca. 10%). Its optical purity, determined by ^{1}H NMR in the presence of Eu(hfc)$_3$, was found to be 43% e.e. of (R)-isomer.

Juvenile hormone III synthesis. Kinetic resolution of ketoepoxide 10 by aluminum binaphthate reagent 6 in large scale: To a solution of (R)-1,1'-bi-2-naphthol (8.61 g, 30 mmol) in dichloromethane (410 mL) was introduced dimethylaluminum chloride (2.8 mL, 30 mmol) at -78°C. The white suspension was stirred at that temperature for 15 min. and at 0°C for 15 min. In another flask was placed 1-butanol (3.1 mL, 33 mmol) in hexane (29 mL), and to this was introduced butyllithium (1.59 M in hexanes, 21 mL, 33 mmol) at -78°C. The aluminum reagent thus prepared was transfered to the alcoholate suspension at that temperature. The resulting mixture was stirred for 30 min. and at 0°C for 30 minutes. The resulting mixture, turned to faintly clear, was cooled to -78°C. To this was introduced the ketoepoxide 10 (4.98 g, 35 mmol) dropwise. Stirring was continued for 30 min. at that temperature and at -40°C for 2.5 h (gradually warmed to -27°C). The reaction was stopped by introduction of triethylamine (30 mL). The resulting mixture was poured into 2 N aqueous solution of sodium hydroxide and extracted with ether. The combined ether extracts were washed with 2 N aqueous solution of sodium hydroxide and brine, dried over magnesium sulfate, and concentrated in vacuo and purification by column chromatography on silica gel (eluant: pentane-ether = 2:1 - 1:2) gave a clear oil. After removal of solvents, the residual oil was diluted in hexane, and to this was added anhydrous calsium chloride (1.5 g) to remove remaining 1-butanol[19]. The white suspension was filtrated and the filtrate was concentrated in vacuo to afford the pure ketoepoxide 10 (420 mg, 8.4% recovery). Its optical purity determined by the ^1H NMR analysis in the presence of the chiral shift reagent $Eu(hfc)_3$ was shown to be >95% e.e. Its optical rotation $[\alpha]_D^{22}$ = 28.29 (c = 0.94, chloroform) revealed this to be (R)-isomer (lit. for (S)-isomer $[\alpha]_D^{24}$ = -23.07 (c =1.07, chloroform)

N-(4-t-butylphenyl)-trifluoromethanesulfonamide 13: To a solution of 4-tert-butylaniline (7.2 mL, 45 mmol) and triethylamine (12.6 mL, 90 mmol) in dichloromethane (60 mL) was introduced trific anhydride (15 mL, 90 mmol) at -78°C dropwise. Stirring was continued for 4 h at that temperature. The resulting white suspension was poured into saturated aqueous solution of sodium hydrogencarbonate 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: benzene) gave a white solid 13 (15.8 g, 38.2 mmol, 85%). This product can be recrystalized from hexane. m.p. 109-110°C; tlc Rf = 0.76 (benzene-ethyl acetate = 30:1); IR (nujol mull) 1210 s, 1110 s, 900 s; ^1H NMR (CCl_4) δ 7.60-7.20 (m, 4H), 1.36 (s, 9H).

Enol triflate 14[13]: To a solution of lithium diisopropylamide (10 mmol, prepared by addition of butyllithium (1.59 M in hexane, 6.3 mL, 10 mmol) and diisopropylamine (1.55 mL, 11 mmol)) in tetrahydrofuran (9 mL) was introduced the optically pure ketoepoxide at -78°C. After 30 minutes imide 13 (4.43 g, 11 mmol. This hydroscopic reagent should be dried over benzene/tetrahydrofuran azeotropically before use.) in tetrahydrofuran (6 mL) and HMPA (2.9 mL, 18 mmol) dropwise. Stirring was continued for 1 h at that temperature and at -20°C for 2 h. The resulting solution was poured into saturated aqueous solution of sodium hydrogencarbonate, 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: benzene) afforded a clear oil 14 (1.98 g, 7.2 mmol, 80%). This oil can be distilled under reduced pressure. b.p. (bulb-to-bulb) 100-120°C (2 Torr); tlc Rf = 0.27 (benzene: ethyl acetate = 30/1); IR (neat film) 3100-2800 s, 1680 s, 1420 s, 1255 s, 1220 s, 1150 s, 955 s, 905 s; ^1H NMR($CDCl_3$) δ 5.20 (d, J = 3 Hz, 1H), 3.05 (d, J = 3 Hz, 1H), 2.80 (t, J = 7.0 Hz, 1H), 2.60 (dd, J = 7.0 Hz, 2H), 2,06 (br. d, 1H), 2.00-1.60 (m, 2H), 1.23 (s, 6H).

Coupling of bromoester 16[14] and ditin 15[11]: To a suspension of bis(acetonitrile)palladiumdichloride (59 mg, 0.20 mmol), triphenylphosphine (26 mg, 0.10 mmol) in chloroform (10 mL) was introduced ditin 15[15] (5.90 g, 9.7 mmol), followed by bromoester 16 (1.80 g, 9.5 mmol). The resulting yellow solution was degassed, and heated at 80°C for 8 h. Concentration in vacuo left the residual oil which was purified by column chromatography on silica gel (eluant: hexane then followed by ether) to give a clear oil of 17 (3.10 g, 7.3 mmol, 76% yield). tlc Rf = 0.77 (for Z-isomer) and 0.70 (for E-isomer) (eluant: benzene-ethyl acetate = 30:1); Two isomers were separated by column chromatography on silica gel (eluant: hexane-benzene = 1:1) to give pure E-isomer. IR (neat film) 3050-2800 br. s, 1720 s, 1650 s, 1215 s, 1135 s; ^1H NMR ($CDCl_3$) δ 5.90 (m, 2H), 5.62 (m, 1H), 3.63 (s, 3H), 2.94 (m, 2H), 3.13 (m, 3H), 2.90-0.70 (m, 27H).

Coupling of enol triflate 14 and tinester 17[12]: To a suspension of tetrakis(triphenylphosphine)palladium (11.2 mg, 0.010 mmol) and cesium fluoride[16] (370 mg, 2.4 mmol) in tetrahydrofuran (2 mL) was introduced enol triflate 14 (220 mg, 0.80 mmol) in tetrahydrofuran (1 mL), followed by tinester 17 (340 mg, 0.80 mmol) in tetrahydrofuran (1 mL). The resulting mixture was degassed, and refluxed for 6 h. The reaction mixture was poured into brine, and extracted with ether. The combined ether extracts were washed with ammoniac water, water, and brine. Dryness over magnesium sulfate, concentration in vacuo, and purification by column chromatography on silica gel (eluant: benzene-ethyl acetate = 40:1) gave a colorless oil of 18 (120 mg, 0.46 mmol, 58% yield). tlc Rf = 0.30 (benzene-ethyl acetate = 30:1); IR (neat film) 3200-2800 s, 1735 s, 1660 s, 1445 m, 1230 w; ^1H NMR ($CDCl_3$) δ 6.14 (d, J = 14 Hz, 1H), 5.70 (s, 1H), 5.66 (dd, J = 14 and 8.5 Hz, 1H), 5.00 (d, J = 2 Hz, 1H), 4.98 (d, J = 2 Hz, 1H), 3.70 (s, 3H), 2.93 (d, J = 8.5 Hz, 2H), 2.76 (t, J = 6 Hz, 1H), 2.42 (m, 1H), 2.31 (m, 1H), 2.16 (s, 3H), 1.73 (m, 2H), 1.31 (s, 3H), 1.26 (s, 3H); Elemental analysis calcd for $C_{16}H_{24}O_3$: C, 72.7; H, 9.2. Found C, 72.4; H, 9.1. $[\alpha]_D^{21}$ = 7.6° (c = 0.94, diethylether).

Hydrogenation of 18 with chromium catalyst[17]: The degassed solution of ester 18 (83 mg, 0.31 mmol), chromium catalyst 19[17] (73 mg, 0.27 mmol) in tetrahydrofuran (8 mL) was heated at 45°C under hydrogen atmosphere (80 atm.) for 37 h. The orange solution was exposed to the air to be a green suspension, which was concentrated in vacuo and purified by column chromatography on silica gel (eluant: benzene-ethyl acetate = 40:1 - 30:1) to afford a slight yellow oil of juvenile hormone **20** (55.0 mg, 0.21 mmol, 66%). tlc Rf = 0.24 (benzene-ethyl acetate = 30:1); IR (neat film) 3000-2800 s, 1735 s, 1660 s, 1445 m, 1235 w, 1160 s; ^1H NMR ($CDCl_3$) δ 5.68 (br. s, 1H), 5.15 (br. s, 1H), 3.69 (s, 3H), 2.71 (t, J = 6.8 Hz, 1H), 2.19 (s, 3H), 2.18 (s, 3H), 2.11 (m, 2H), 1.70-1.50 (m, 6H), 1.31 (s, 3H), 1.26 (s, 3H); Elemental analysis Calcd for $C_{16}H_{26}O_3$: C, 72.1, H, 9.8; Found: C, 71.9, H, 9.6; $[\alpha]_D^{21}$ = 5.4° (c = 0.4, methanol), lit. $[\alpha]_D^{23}$ = 5.75° (c = 0.4, methanol);[9a] 6.71° (methanol)[9b] for (R)-isomer, and $[\alpha]_D^{23}$ = -5.44° (c = 0.7, methanol);[9a] -6.55° (methanol) for (S)-isomer.[9b,20]

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