Highly Diastereoselective Reaction of Chiral *o*-[2-(1,3-Oxazolidinyl)]benzaldehydes with Alkylmetallic Reagents: Synthesis of Chiral 3-Substituted Phthalides

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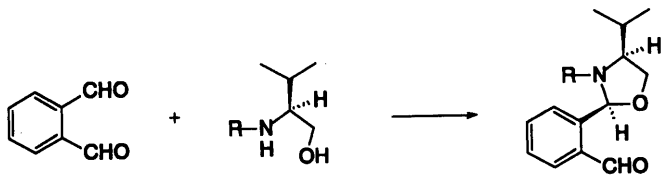
Highly diastereoselective reaction of chiral *o*-[2-(1,3-oxazolidinyl)]benzaldehydes (4—6) with alkylmetallic reagents provides a new synthetic method for chiral 3-alkylphthalides.

Keywords asymmetric synthesis; butylmagnesium chloride; (*S*)-3-butylphthalide; diethylzinc; (*S*)-3-ethylphthalide; (*S*)-*N*-isopropylvalinol; highly diastereoselective reaction; *o*-[2-(1,3-oxazolidinyl)]benzaldehyde; pyridinium chlorochromate

Many papers[1-3] and reviews[4-6] have been published on the synthesis of phthalides. In particular, asymmetric synthesis of chiral phthalides has recently been achieved by diastereoselective reaction of *ortho*-substituted benzaldehydes and lithiobenzenes bearing a chiral heterocyclic group, *e.g.*, 2,6a-diazaperhydropentalenyl,[7] 1,3-oxazolinyl,[8] imidazolidinyl,[9] and 1,3-dioxolanyl[9,10] groups. We have also reported highly diastereoselective reactions of chiral 1,3-oxazolidines,[11] 5-oxa-7,8a-diazaperhydroazulen-8-ones,[12] and 4-oxa-7,7a-diazaperhydroindans,[13] prepared from easily available enantiomerically pure (*S*)- and (*R*)-ethanolamines. In this paper, we wish to report a diastereoselective reaction of *o*-[2-(1,3-oxazolidinyl)]-benzaldehydes with alkylmetallic reagents, resulting the asymmetric synthesis of 3-alkylphthalides having a chiral center at the 3-position of the ring.

Chiral *o*-[2-(1,3-oxazolidinyl)]benzaldehydes (**4—6**) were synthesized by condensation of phthalaldehyde with (*S*)-*N*-methyl,[14,15] (*S*)-*N*-ethyl, and (*S*)-*N*-isopropyl[11,16] valinols (**1—3**) in 56—65% yields. These products were obtained as mixtures of two isomers, and the ratio of the major to the minor components was estimated as 93:7, 93:7, and 92:8, respectively, by proton nuclear magnetic resonance (^{1}H-NMR) spectral analysis. Diastereomerically pure compounds could not be isolated from the mixtures by column chromatography. The diastereomers may have equilibrated during column chromatography. The aryl group linked to the newly created asymmetric carbon atom at the 2-position of 1,3-oxazolidine ring is assumed to be in a *cis* relationship to the isopropyl group at the 4-position.[11,14]



	R
1, 4	CH_3
2, 5	C_2H_5
3, 6	iso-C_3H_7

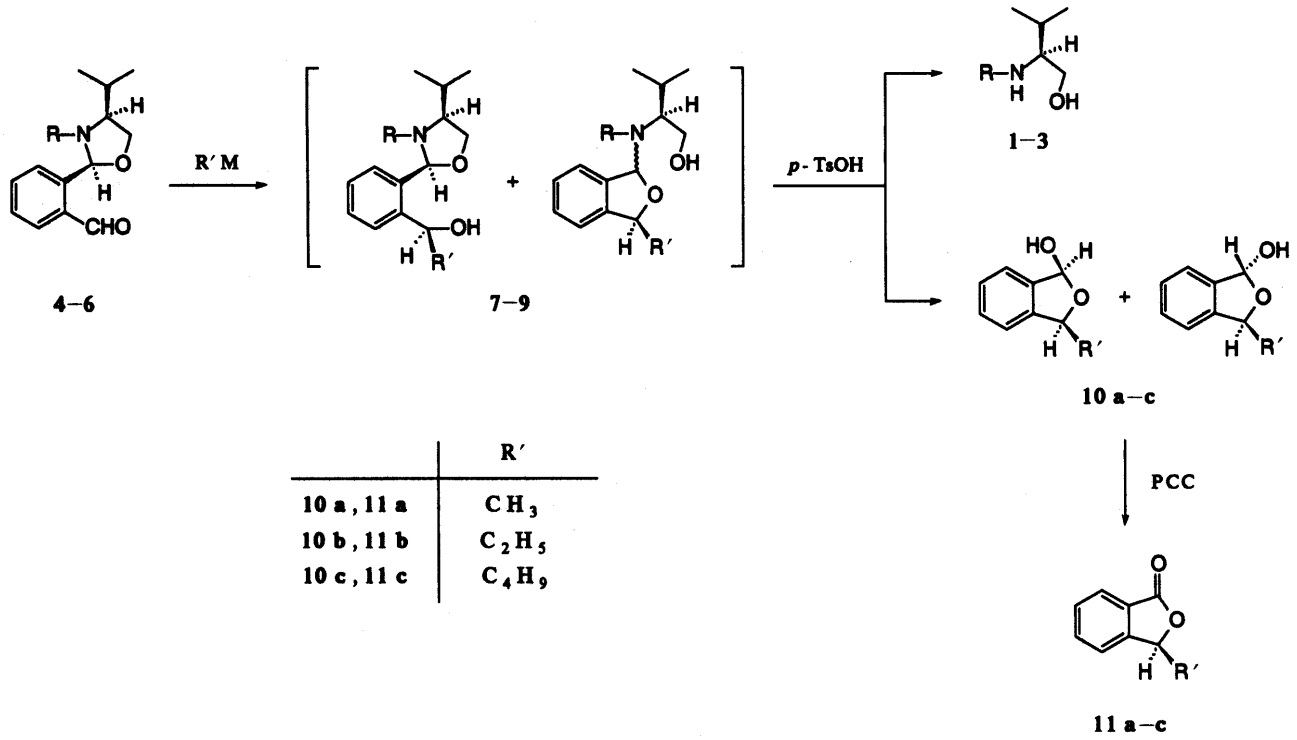
Chart 1

The reaction of chiral *o*-[2-(1,3-oxazolidinyl)]benzaldehydes (**4—6**) with dibutylcupriolithium, diethylzinc, and alkylmagnesium halides gave oily products (**7—9**). These products were considered to be *o*-[2-(1,3-oxazolidinyl)]-benzylalcohols and/or 1-(2-hydroxyethyl)amino-2-oxaindans, but the structures were difficult to elucidate. The carbon–nitrogen bond of these products was easily cleaved by hydrolysis using *p*-toluenesulfonic acid monohydrate to give the corresponding 3-alkyl-1-hydroxy-2-oxaindans (**10a—c**). The chiral auxiliary reagents, *i.e.*, (*S*)-*N*-alkylvalinols (**1—3**), were recovered in good yields with no loss of optical purity. The products (**10a—c**) were confirmed to consist of two sets of diastereomers, *i.e.*, [(1*R*,3*R*)- and (1*S*,3*R*)-compounds] and [(1*S*,3*S*)- and (1*R*,3*S*)-compounds], by ^{1}H-NMR spectral analysis. The specific rotation of 3-ethyl-1-hydroxy-2-oxaindan (**10b**) thus obtained was consistent with that reported by Asami and Mukaiyama.[7]

The diastereomeric mixtures of 3-alkyl-1-hydroxy-2-oxaindans (**10a—c**) were oxidized with pyridinium chlorochromate (PCC) to give chiral 3-alkylphthalides (**11a—c**). The enantiomeric excesses (ee) of **11a—c** were estimated from the peak areas in a high performance liquid chromatography (HPLC) using a chiral packed column. Further, the absolute configurations were determined by comparison of the specific rotations with those of known 3-alkylphthalides [**11a**[8] and **11c**[17]] and 3-ethyl-1-hydroxy-2-oxaindan (**10b**).[7] These experimental data are summarized in Table I together with the total yields based on the originally used **4—6**.

The reactions of *o*-[2-(1,3-oxazolidinyl)]benzaldehydes (**4** and **6**) with diethylzinc in dichloromethane were highly diastereoselective (entries 4 and 6). The reaction of **6** with alkylmagnesium halides in dioxane (entry 10) and in a mixed solvent of tetrahydrofuran (THF)–dioxane (5:1) (entries 18 and 20) gave the corresponding chiral 3-alkylphthalides (**11a** and **11c**) of 85—90% ee However, the absolute configurations of the products depended on the solvents used and the bulkiness of the substituents, as shown in Table I.

In conclusion, this reaction proceeds with high diastereoselectivity, and the stereoselectivity is influenced by the bulkiness of substituents and the solvent used. Similar results have been reported in the diastereoselective reaction of *ortho*-substituted benzaldehydes with chiral heterocyclic groups, *e.g.*, 1,3-oxazolinyl,[8] imidazolidinyl,[9] and 1,3-dioxolanyl[9,10] groups. We propose a mechanism in which the oxygen atom of the 1,3-oxazolidine ring is nearly in the



	R′
10 a, 11 a	CH_3
10 b, 11 b	C_2H_5
10 c, 11 c	C_4H_9

Chart 2

TABLE I. Diastereoselective Reaction of Chiral *o*-[2-(1,3-Oxazolidinyl)]benzaldehydes (4—6) with Alkylmetallic Reagents

Entry	Reactant	Reagent	Solvent	Temp (°C)	Time (h)	Product	Yield[a] (%)	ee[b] (%)	Configuration[c]
1	6	$(C_4H_9)_2CuLi$	Et_2O	−50	16	11c	82	28	*R*
2	6	$(C_4H_9)_2CuLi$	THF	−50	16	11c	80	58	*S*
3	4	$(C_2H_5)_2Zn$	THF	rt[d]	44	11b	56	7	*R*
4	4	$(C_2H_5)_2Zn$	CH_2Cl_2	rt[d]	16	11b	63	87	*R*
5	5	$(C_2H_5)_2Zn$	CH_2Cl_2	rt[d]	42	11b	82	76	*S*
6	6	$(C_2H_5)_2Zn$	CH_2Cl_2	rt[d]	18	11b	70	96	*S*
7	6	CH_3MgBr	Toluene	−50	16	11a	62	12	*R*
8	6	CH_3MgBr	Et_2O	−50	16	11a	65	33	*R*
9	6	CH_3MgBr	THF	−50	16	11a	72	73	*S*
10	6	CH_3MgBr	Dioxane	rt[d]	16	11a	53	85	*S*
11	6	CH_3MgBr	Mixed[e]	0	16	11a	62	80	*S*
12	4	CH_3MgBr	Mixed[f]	−50	16	11a	57	46	*S*
13	4	C_2H_5MgBr	Mixed[f]	−50	16	11b	43	47	*S*
14	4	C_4H_9MgCl	Mixed[f]	−50	16	11c	41	58	*S*
15	5	CH_3MgBr	Mixed[f]	−50	20	11a	52	66	*S*
16	5	C_2H_5MgBr	Mixed[f]	−50	19	11b	42	57	*S*
17	5	C_4H_9MgCl	Mixed[f]	−50	42	11c	65	70	*S*
18	6	CH_3MgBr	Mixed[f]	−50	16	11a	69	86	*S*
19	6	C_2H_5MgBr	Mixed[f]	−50	16	11b	63	77	*S*
20	6	C_4H_9MgCl	Mixed[f]	−50	20	11c	73	90	*S*

a) The yield was the isolated yield from *o*-[2-(1,3-oxazolidinyl)]benzaldehyde (4—6). *b*) The enantiomeric excess was estimated by HPLC using a chiral packed column. *c*) The absolute configuration was determined by comparison of the specific rotation with that of the known compound. *d*) Room temperature. *e*) Mixed solvent of ether–dioxane (5:1). *f*) Mixed solvent of THF–dioxane (5:1).

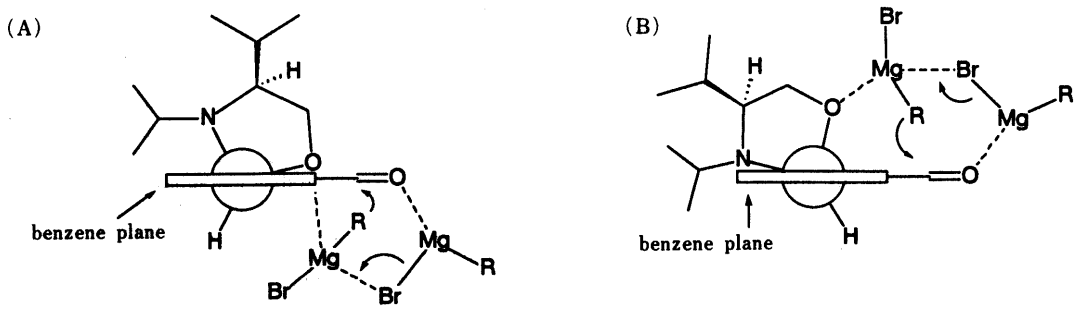


Fig. 1

plane of the benzene ring, forming a favorable intermediate (A) which is attacked by the alkylmetallic reagent from the *si*-face of the carbonyl carbon atom. If the nitrogen atom at the 1,3-oxazolidine ring is nearly in the plane of the benzene ring (B), attack of the reagent occurs from the *re*-face, as shown in Fig. 1.

Experimental

The ^{1}H-NMR spectra were obtained with a JEOL JNM-GSX270 spectrometer and the mass spectra (MS) were recorded with a JEOL JMS-D300 spectrometer by using the electron impact (EI) method. The melting points were measured with a Yanagimoto micromelting point apparatus and are uncorrected. The optical rotations were measured with a JASCO DIP-370 digital polarimeter.

(*S*)-*N*-Ethylvalinol (2) Acetyl chloride (9.42 g, 120 mmol) was added dropwise to a stirred solution of (*S*)-valinol (10.3 g, 100 mmol) and triethylamine (13.2 g, 130 mmol) in CH_2Cl_2 (150 ml) at 0 °C. After being stirred at room temperature for 3 h, the reaction mixture was concentrated under reduced pressure. The residue was dissolved in THF (70 ml) and the solution was added dropwise to a stirred suspension of $LiAlH_4$ (7.7 g, 203 mmol) in THF (120 ml). After refluxing for 3 h, the reaction mixture was made alkaline. The resultant precipitate was filtered off and the filtrate was evaporated. The oily residue was distilled *in vacuo* to give a colorless oil (11.2 g, 85%), bp 83 °C (22 mmHg). $[\alpha]_D^{24}$ +17.1° (c=8.25, ethanol). MS *m/z*: 132 (M^++1, 100%). ^{1}H-NMR ($CDCl_3$) δ: 0.89 (3H, d, J=6.71 Hz, $CHCH_3$), 0.96 (3H, d, J=6.71 Hz, $CHCH_3$), 1.11 (3H, t, J=7.32 Hz, CH_2CH_3), 1.79 (1H, octet, J=6.71 Hz, $CH(CH_3)_2$), 2.14 (2H, br, NH and OH), 2.38 (1H, dt, J=4.27, 6.71 Hz, $NCHCH_2O$), 2.60 (1H, dq, J=11.59, 7.32 Hz, CH_2CH_3), 2.71 (1H, dq, J=11.59, 7.32 Hz, CH_2CH_3), 3.30 (1H, dd, J=6.71, 10.38 Hz, $NCHCH_2O$), 3.59 (1H, dd, J=4.27, 10.38 Hz, $NCHCH_2O$).

(2*S*,4*S*)-*o*-[2-(4-Isopropyl-*N*-methyl-1,3-oxazolidinyl)]benzaldehyde (4) (*S*)-*N*-Methylvalinol (4.69 g, 40 mmol) was added dropwise to a solution of phthalaldehyde (5.37 g, 40 mmol) in CH_2Cl_2 (100 ml) in the presence of anhydrous Na_2SO_4 (10 g), and the reaction mixture was stirred at room temperature for 16 h. The precipitate was filtered off and the filtrate was evaporated under reduced pressure. The residue was distilled *in vacuo* to give **4** as a colorless oil (5.00 g, 56%), bp 143—145 °C (3.5 mmHg) (93 : 7 mixture). $[\alpha]_D^{24}$ −65.6° (c=2.89, hexane). *Anal.* Calcd for $C_{14}H_{19}NO_2$: C, 72.07; H, 8.21; N, 6.00. Found: C, 71.98; H, 8.34; N, 6.03. IR ($CHCl_3$): 1682 (C=O) cm^{-1}. MS *m/z*: 233 (M^+, 48%), 218 (M^+-CH_3, 23%), 190 ($M^+-C_3H_7$, 87%), 133 (86%). ^{1}H-NMR ($CDCl_3$) δ: major component; 0.97 (6H, d, J=7.02 Hz, $CH(CH_3)_2$), 1.96 (1H, d and septet, J=5.19, 7.02 Hz, $CH(CH_3)_2$), 2.16 (3H, s, NCH_3), 2.67 (1H, dt, J=5.19, 7.94 Hz, $NCHCH_2O$), 3.91 (1H, t, J=7.94 Hz, $NCHCH_2O$), 4.04 (1H, t, J=7.94 Hz, $NCHCH_2O$), 5.06 (1H, s, NCHO), 7.45—7.62 (3H, m, aromatic H), 7.90—7.94 (1H, m, aromatic H), 10.69 (1H, s, CHO).

(2*S*,4*S*)-*o*-[2-(*N*-Ethyl-4-isopropyl-1,3-oxazolidinyl)]benzaldehyde (5) Condensation of (*S*)-*N*-ethylvalinol (5.25 g, 40 mmol) with phthalaldehyde (5.37 g, 40 mmol) in CH_2Cl_2 (100 ml) was achieved in a similar manner to that described for the preparation of **4** to give **5** (6.13 g, 62%) as a colorless oil, bp 149—151 °C (3 mmHg) (93 : 7 mixture). $[\alpha]_D^{24}$ −93.5° (c=3.09, hexane). *Anal.* Calcd for $C_{15}H_{21}NO_2$: C, 72.84; H, 8.56; N, 5.66. Found: C, 72.61; H, 8.70; N, 5.66. IR ($CHCl_3$): 1680 (C=O) cm^{-1}. MS *m/z*: 247 (M^+, 20%), 218 ($M^+-C_2H_5$, 69%), 204 ($M^+-C_3H_7$, 71%), 133 (100%). ^{1}H-NMR ($CDCl_3$) δ: major component; 0.90 (3H, d, J=6.72 Hz, $CH(CH_3)_2$), 0.91 (3H, t, J=7.32 Hz, NCH_2CH_3), 0.97 (3H, d, J=6.72 Hz, $CH(CH_3)_2$), 1.72 (1H, octet, J=6.72 Hz, $CH(CH_3)_2$), 2.65—2.76 (2H, m, NCH_2CH_3), 2.83 (1H, q, J=6.72 Hz, $NCHCH_2O$), 3.77 (1H, dd, J=6.72, 8.54 Hz, $NCHCH_2O$), 4.00 (1H, dd, J=6.72, 8.54 Hz, $NCHCH_2O$), 5.58 (1H, s, NCHO), 7.43—7.91 (4H, m, aromatic H), 10.64 (1H, s, CHO).

(2*S*,4*S*)-*o*-[2-(4,*N*-Diisopropyl-1,3-oxazolidinyl)]benzaldehyde (6) A mixture of (*S*)-*N*-isopropylvalinol (5.81 g, 40 mmol) and phthalaldehyde (5.37 g, 40 mmol) in toluene (20 ml) was refluxed for 40 h using a Dean–Stark trap. The mixture was concentrated under reduced pressure and the residue was distilled *in vacuo* to give **6** as a colorless oil (6.8 g, 65%), bp 134—136 °C (0.45 mmHg) (92 : 8 mixture). $[\alpha]_D^{27}$ −93.7° (c=2.39, hexane). *Anal.* Calcd for $C_{16}H_{23}NO_2$: C, 73.53; H, 8.87; N, 5.36. Found: C, 73.74; H, 8.97; N, 5.39. IR ($CHCl_3$): 1680 (C=O) cm^{-1}. MS *m/z*: 261 (M^+, 2.5%), 246 (M^+-CH_3, 1.3%), 218 ($M^+-C_3H_7$, 100%), 133 (66%). ^{1}H-NMR ($CDCl_3$) δ: major component; 0.79 (3H, d, J=6.71 Hz, $CH(CH_3)_2$), 0.99 (3H, d, J=6.71 Hz, $CH(CH_3)_2$), 1.05 (3H, d, J=6.71 Hz, $CH(CH_3)_2$), 1.11 (3H, d, J=6.71 Hz, $CH(CH_3)_2$), 1.42 (1H, d and septet, J=8.39, 6.71 Hz, $CH(CH_3)_2$), 2.88 (1H, ddd, J=5.34, 7.32, 8.39 Hz, $NCHCH_2O$), 3.13 (1H, septet, J=6.71 Hz, $NCH(CH_3)_2$), 3.56 (1H, dd, J=5.34, 8.39 Hz, $NCHCH_2O$), 3.94 (1H, dd, J=7.32, 8.39 Hz, $NCHCH_2O$), 6.05 (1H, s, NCHO), 7.39—7.90 (4H, m, aromatic H), 10.58 (1H, s, CHO).

General Procedure for the Reaction of 4—6 with Alkylmetallic Reagent An alkylmetallic reagent [6 mmol; $(C_4H_9)_2CuLi$ (prepared from C_4H_9Li and CuI), $(C_2H_5)_2Zn$ (6 ml of a 1 M solution in hexane), CH_3MgBr (2 ml of a 3 M solution in ether), C_2H_5MgBr (2 ml of a 3 M solution in ether), or C_4H_9MgCl (3 ml of a 2 M solution in THF)] was added dropwise to a stirred solution of **4—6** (3 mmol) in the appropriate solvent (15 ml) under a nitrogen atmosphere. After being stirred at −50 °C or at room temperature for 16—42 h, the reaction mixture was treated with a saturated NH_4Cl aqueous solution (1 ml). The resulting precipitate was filtered off, and the filtrate was concentrated under reduced pressure to give a colorless oil (**7a—c**, **8a—c**, and **9a—c**). The product was used for the following reaction without purification.

General Procedure for the Cleavage of 7—9 with *p*-Toluenesulfonic Acid: Preparation of 3-Alkyl-1-hydroxy-2-oxaindanes (10a—c) and (*S*)-*N*-Alkylvalinols (1—3) *p*-Toluenesulfonic acid monohydrate (628 mg, 3.3 mmol) was added to a solution of an above product (**7a—c**, **8a—c**, or **9a—c**) in THF (10 ml) and H_2O (2 ml), and the refluxing was continued for 30 min. The reaction mixture was extracted with ether, and the organic layer was washed with water and dried over Na_2SO_4. Removal of the solvent gave a 3-alkyl-1-hydroxy-2-oxaindane (**10a—c**). On the other hand, the aqueous layer was saturated with K_2CO_3 and extracted with ether. The solution was washed with a saline solution and dried over Na_2SO_4. Removal of the solvent gave the corresponding (*S*)-*N*-alkylvalinol (**1—3**) in almost quantitative yield.

1-Hydroxy-3-methyl-2-oxaindan (**10a**): This product was confirmed to consist of an equimolar mixture of two diastereomers by ^{1}H-NMR spectral analysis. ^{1}H-NMR ($CDCl_3$) δ: 1.50 (3H, d, J=6.71 Hz, $CHCH_3$) and 1.58 (3H, d, J=6.71 Hz, $CHCH_3$), 2.88 (1H, d, J=8.51 Hz, OH) and 2.89 (1H, d, J=8.54 Hz, OH), 5.27 (1H, q, J=6.71 Hz, $CHCH_3$) and 5.51 (1H, dq, J=1.83, 6.71 Hz, $CHCH_3$), 6.41 (1H, d, J=8.54 Hz, CHOH) and 6.49 (1H, dd, J=1.83, 8.54 Hz, CHOH), 7.19—7.45 (4H, m, aromatic H).

2-Ethyl-1-hydroxy-2-oxaindan (**10b**): This product was confirmed to consist of an equimolar mixture of two diastereomers by ^{1}H-NMR spectral analysis. Specific rotation of the product was $[\alpha]_D^{27}$ −46.5° (c=2.01, benzene); lit.,[7] $[\alpha]_D$ −42.6° (c=5.35, benzene), 88% ee ^{1}H-NMR ($CDCl_3$) δ: 0.92 (3H, t, J=7.32 Hz, CH_2CH_3) and 1.00 (3H, t, J=7.32 Hz, CH_2CH_3), 1.60—2.03 (2H, m, CH_2CH_3), 3.52 (1H, d, J=7.93 Hz, OH) and 3.62 (1H, d, J=7.93 Hz, OH), 5.13 (1H, dd, J=4.27, 6.71 Hz, $CHCH_2$) and 5.39 (1H, ddd, J=2.44, 4.27, 6.71 Hz, $CHCH_2$), 6.42 (1H, d, J=7.93 Hz, CHOH) and 6.48 (1H, dd, J=2.44, 7.93 Hz, CHOH), 7.18—7.43 (4H, m, aromatic H).

3-Butyl-1-hydroxy-2-oxaindan (**10c**): This product was confirmed to consist of an equimolar mixture of two diastereomers by ^{1}H-NMR spectral analysis. ^{1}H-NMR ($CDCl_3$) δ: 0.90 (3H, t, J=7.32 Hz, $(CH_2)_3CH_3$) and 0.91 (3H, t, J=7.32 Hz, $(CH_2)_3CH_3$), 1.20—2.00 (6H, m, $(CH_2)_3CH_3$), 3.62 (1H, d, J=7.32 Hz, OH) and 3.75 (1H, d, J=7.32 Hz, OH), 5.14 (1H, dd, J=4.27, 7.32 Hz, $CH(CH_2)_3$) and 5.40 (1H, ddd, J=2.44, 4.27, 7.32 Hz, $CH(CH_2)_3$), 6.40 (1H, d, J=7.32 Hz, CHOH) and 6.46 (1H, dd, J=2.44, 7.32 Hz, CHOH), 7.18—7.43 (4H, m, aromatic H).

General Procedure for the Oxidation of 10a—c with Pyridinium Chlorochromate: Preparation of 3-Alkylphthalides (11a—c) PCC[18] (1.29 g, 6 mmol) was added to a stirred solution of **10a—c** in CH_2Cl_2 (5 ml). The mixture was stirred at room temperature for 30 min, then ether (10 ml) was added and the supernatant liquid was decanted from a black gum. The insoluble residue was washed with ether (3 ml × 5), leaving a black granular solid. The combined organic solution was passed through a short column of silica gel, and removal of the solvent gave **11a—c**. The ee of **11a—c** was estimated by HPLC using a chiral packed column "Chiralcel OB" (Daisel Chemical Industries, Ltd.), and the absolute configuration of **11a—c** was determined by comparison with known compounds. The crude product was subjected to column chromatography on silica gel. The values of ee and the absolute configuration are summarized in Table I together with the total isolated yields.

(*S*)-3-Methylphthalide (**11a**) Eluent: HPLC, hexane–isopropanol (80 : 20); column chromatography, hexane–ether (2 : 1). Optically pure **11a** was isolated from the isomeric mixture by recrystallization. Colorless needles, mp 41.5—42.5 °C (pentane–ether). The specific rotation of

100% ee compound, $[\alpha]_D^{24}$ −43.2° (c=5.11, $CHCl_3$) and $[\alpha]_D^{25}$ −43.5° (c=0.51, methanol); lit.,[8] (*S*)-3-methylphthalide $[\alpha]_D$ −13.2° (c=4.8, methanol), 44% ee ^{1}H-NMR ($CDCl_3$) δ: 1.65 (3H, d, J=6.72 Hz, $CHC\underline{H}_3$), 5.57 (1H, q, J=6.72 Hz, $C\underline{H}CH_3$), 7.46 (1H, d, J=7.33 Hz, aromatic H), 7.53 (1H, t, J=7.33 Hz, aromatic H), 7.69 (1H, t, J=7.33 Hz, aromatic H), 7.88 (1H, d, J=7.33 Hz, aromatic H).

(*S*)-3-Ethylphthalide (**11b**) Eluent: HPLC, hexane–isopropanol (95:5); column chromatography, hexane–THF (8:1). Colorless oil, bp 160°C (3 mmHg) (bulb-to-bulb distillation); Racemate, lit.,[19] bp 94°C (0.028 mmHg). The specific rotation of 96% ee compound, $[\alpha]_D^{25}$ −73.5° (c=3.60, $CHCl_3$). ^{1}H-NMR ($CDCl_3$) δ: 1.01 (3H, t, J=7.32 Hz, $CH_2C\underline{H}_3$), 1.83 (1H, d and quintet, J=14.64, 7.32 Hz, $CHC\underline{H}_2CH_3$), 2.13 (1H, ddq, J=4.27, 14.64, 7.32 Hz, $CHC\underline{H}_2CH_3$), 5.46 (1H, dd, J=4.27, 7.32 Hz, $C\underline{H}CH_2CH_3$), 7.45 (1H, d, J=7.93 Hz, aromatic H), 7.52 (1H, t, J=7.93 Hz, aromatic H), 7.68 (1H, t, J=7.93 Hz, aromatic H), 7.90 (1H, d, J=7.93 Hz, aromatic H).

(*S*)-3-Butylphthalide (**11c**) Eluent: HPLC, hexane–isopropanol (95:5); column chromatography, hexane–ether (3:1). Colorless oil, bp 160—165°C (2 mmHg) (bulb-to-bulb distillation). The specific rotation of 73% ee compound $[\alpha]_D^{24}$ −51.7° (c=6.71, $CHCl_3$); lit.,[17] $[\alpha]_D$ −57° ($CHCl_3$). ^{1}H-NMR ($CDCl_3$) δ: 0.91 (3H, t, J=7.32 Hz, $CH_2C\underline{H}_3$), 1.31—1.53 (4H, m, $CHCH_2C\underline{H}_2C\underline{H}_2CH_3$), 1.70—1.83 (1H, m, $CHC\underline{H}_2$-$CH_2CH_2CH_3$), 1.99—2.12 (1H, m, $CHC\underline{H}_2CH_2CH_2CH_3$), 5.48 (1H, dd, J=4.27, 7.93 Hz, $C\underline{H}C_4H_9$), 7.44 (1H, d, J=7.32 Hz, aromatic H), 7.52 (1H, t, J=7.32 Hz, aromatic H), 7.67 (1H, t, J=7.32 Hz, aromatic H), 7.89 (1H, d, J=7.32 Hz, aromatic H).

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