A New and Highly Effective Aldol Synthesis[1)]

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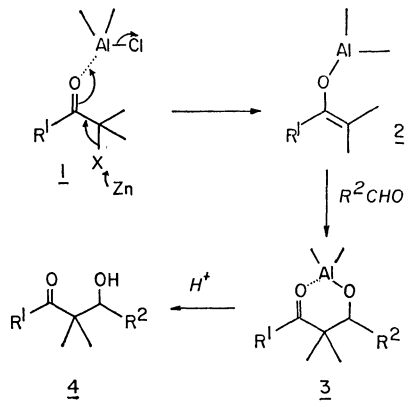
A new approach has been demonstrated for the regiospecific aldol synthesis by the simultaneous addition of α-halo carbonyl derivatives and aldehydes or ketones to a suspension of diethylaluminum chloride and zinc in tetrahydrofuran at low temperature. This technique is also employable under mild conditions for the Reformatsky reaction to give β-hydroxy esters in excellent yield. One of the unique synthetic applications of this process is illustrated by the intramolecular cyclization of α-bromo esters of ω-hydroxy aldehyde, which produces macrolides, an important class of compounds in the antibiotic field.

Carbon-carbon σ-bond formation, one of the most fundamental operations in organic chemistry, is often accomplished by the aldol synthesis.[2)] During the past decade numerous directed intermolecular aldol condensations have been explored with generation of the regiospecific metal enolates and interception of the initially formed aldol products as stable metal chelates.[3)] Certain regiospecifically generated, kinetic lithium enolates can retain their integrity in the aldol reaction at low temperature. The use of magnesium and zinc enolates prevents the unfavorable dissociation of the metal chelate, and boron enolates have recently been employed in stereoselective aldol syntheses.[4)]

Compared to the metals described above, aluminum shows an exceptionally high affinity for oxygen atom (138 kcal/mol for Al–O bond),[5)] and, therefore, its enolate would be one of the most attractive candidates to enhance the stability of the metal chelates in the aldol condensation. In principle, organoaluminum compounds have a vast potential as an agent of aldol reaction. However, this concept has not been generally accepted for synthesis owing to the lack of an effective procedure for converting a carbonyl compound into a reactive aluminum enolate.[6)]

Herein, we describe a new process for regioselective generation of aluminum enolate by the coupled attack of dialkylaluminum chloride and zinc on the α-halo ketone.[7)] The enolate **2**, thus obtained, is sufficiently reactive to carbonyl compound activated by trivalent aluminum producing the stable tetradentate chelate of the ketolate **3**. Aqueous work-up yields the aldol **4** in excellent yield.



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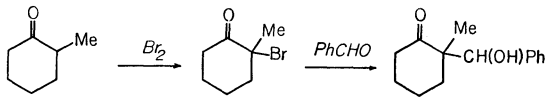
Although a comparable path can be followed by two molecules of an α-halo ketone condensing each other, this would be subject to experimental control using the simultaneous addition of α-halo ketones and carbonyl compounds at low temperature provided that the reduction is sufficiently faster under acceptable conditions.[8)] This new approach has now been realized: Gradual addition (40 min) of a mixture of carbonyl compound and α-halo ketone in dry tetrahydrofuran (THF) to a suspension of zinc dust and diethylaluminum chloride (Et_2AlCl) in THF–hexane in the presence of a catalytic amount of copper(I) bromide with stirring at −20 °C under argon resulted in clean generation of the ketolate. Addition of pyridine, removal of cooling bath, and aqueous work-up afforded the desired β-hydroxy ketone in high yield (Table 1).

The regioselectivity of this reaction was demonstrated by the treatment of 2-bromo-2-methylcyclohexanone (**5**) and benzaldehyde with Et_2AlCl–Zn in THF at −20 °C to furnish the expected β-hydroxy ketone **6** in quantitative yield, without any contamination of the regioisomer (Entry 3). Since the starting bromide **5** may be prepared with high regioselectivity,[9)] the present method must be the simplest route to the β-hydroxy ketone **6**.



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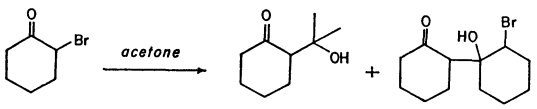
Additional examples are also summarized in Table 1. It should be noted that the use of diethylaluminum chloride and the choice of solvents and temperatures are crucial to the success of these reactions. In the absence of diethylaluminum chloride, only unchanged carbonyl compounds were recovered under these mild conditions. The relative effect of solvents and temperatures was indicated by the reaction of 2-bromocyclohexanone with isobutyraldehyde. In diethyl ether at −40 °C, only a trace amount of the desired 2-(1-hydroxy-2-methylpropyl)cyclohexanone (**7**) was produced, whereas at high temperature (25 °C) many side products were detected by TLC. The use of THF as solvent with reaction temperatures of −78 and −40 °C afforded **7** in yields of 0 and 85%, respectively. At 0 °C, the reaction proceeds as expected (86%), but with some contamination of undesired dehydrated and retro-aldol products of **7**.

Table 1. Synthesis of β-hydroxy carbonyl compounds[a)]

Entry	Bromo ketone or bromo ester	Aldehyde or ketone	Temp °C	Additive[b)]	Products	Isolated yield(%) (*erythro*/*threo*)
1	α-Bromoacetophenone	Isobutyraldehyde	−20	CuBr	$PhCOCH_2CH(OH)CH(CH_3)_2$	92
		Cinnamaldehyde	−20	CuBr	$PhCOCH_2CH(OH)CH{=}CHPh$	92
		Cyclohexanone	−20	CuBr	$PhCOCH_2C(OH)(CH_2)_5$	83
2	2-Bromocyclohexanone	Benzaldehyde	−20	CuBr	2-(α-Hydroxybenzyl)-cyclohexanone	97(1/1)[f)]
		Isobutyraldehyde	−20	CuBr	2-(1-Hydroxy-2-methylpropyl)-cyclohexanone	93[g)]
		Acetone[c)]	−20	d)	2-(1-Hydroxy-1-methylethyl)-cyclohexanone	75
3	2-Bromo-2-methyl-cyclohexanone	Benzaldehyde	−20	CuBr	2-(α-Hydroxybenzyl)-2-methylcyclohexanone	100(4/3)[f)]
4	2-Bromocamphor	Acetone	r.t.	d)	3-(1-Hydroxy-1-methylethyl)-camphor	79
5	Ethyl bromoacetate	Benzaldehyde	0	CuBr	$PhCH(OH)CH_2COOEt$	94
		Cyclohexanone	r.t.	CuBr	$(CH_2)_5C(OH)CH_2COOEt$	93
6	Methyl γ-bromo-crotonate	Benzaldehyde	−20	CuBr	$PhCH(OH)CH(CH{=}CH_2)COOMe$[e)]	100(50/44)[h)]

a) Unless specified, the reactions were carried out according to the general procedure in the experimental section. b) A catalytic amount of copper(I) bromide (0.05 equiv) was added. c) Excess acetone (5 equiv) was used for this reaction. d) Zn–Ag couple was employed without any additive. e) None of the γ-alkylation product ("normal Reformatsky ester") was detected in the reaction mixture. See Ref. 7. f) The ratio of the stereoisomers (*threo* and *erythro*) was determined by an absorption due to the benzylic proton ($CDCl_3$) as shown in the experimental section. See also Refs. 3-a and 3-b. g) *Erythro*/*threo* ratio could not be determined by NMR and TLC analyses. h) Determined by the isolated yield: See the experimental section for this compound.

Treatment of 2-bromocyclohexanone (1 equiv) and acetone (1.1 equiv) with Et_2AlCl–Zn gave the cross aldol product **8** (42%) along with the self-condensation product. Thus, with less reactive carbonyl compounds, the relative amount of self-condensation product increases. Such difficulty might be circumvented by using excess carbonyl compounds with more reactive zinc. Accordingly, the zinc–silver couple[10] was chosen with excess acetone (5 equiv) to furnish **8** in 79% yield (Entry 2).



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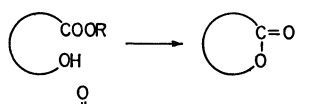
This new technique for the regiospecific aldol synthesis can be employed equally well under mild conditions for the Reformatsky reaction.[11] In a similar manner described above, Reformatsky products were produced from the corresponding α-halo esters and carbonyl compounds in excellent yield as were indicated in Table 1 (Entry 5, 6). In contrast with the normal Reformatsky reaction,[12] the reaction of methyl γ-bromocrotonate with benzaldehyde in the presence of Et_2AlCl–Zn afforded only the α-adduct in quantitative yield. This result suggests that the addition of aluminum enolate to the carbonyl component (initially activated by trivalent aluminum) proceeds *via* a six-membered transition state to furnish the stable aluminum chelate **3**.

Although simplicity and convenience of this aldol synthesis are appealing, the fact that the reaction proceeds in high yield with simultaneous addition of a halo ketone and an aldehyde is even more important. The highly successful application of the new method is the synthesis of macrocyclic lactones which forms the next subject of this paper.

Although the macrolide has been the attractive synthetic target in a number of laboratories, most synthetic methodologies for the macrolide are based on the internal esterification in the cyclization step (Eq. 1) and there exist a few basically different approaches.[13]

Indeed at the outset of this work there were no known synthetic methods capable of generating efficiently 3-hydroxy lactones from acyclic structures (Eq. 2). Gradual addition of the bromoacetate of



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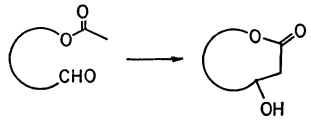
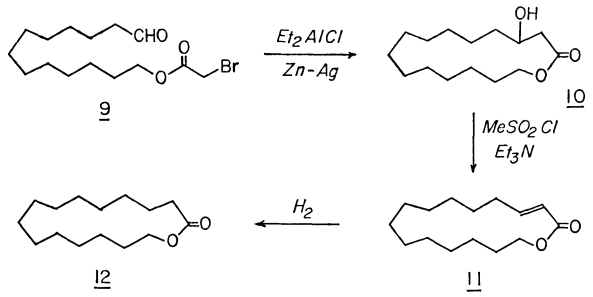


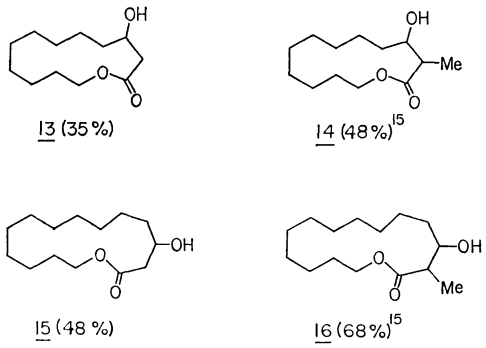
(2)

13-hydroxytridecanal **9**[14] in THF from a mechanically driven syringe over 4 h to a stirred suspension of zinc–silver couple and diethylaluminum chloride in THF at 35 °C under argon effected cyclization to 3-hydroxypentadecanolide (**10**) as the major product. Termination of the reaction with pyridine, followed by acidic

work-up gave the crude product, which was purified by column chromatography on silica gel (ether–hexane, 1:1) to afford pure lactone **10** in 48% yield. Dehydration of **10** in CH_2Cl_2 with methanesulfonyl chloride and excess triethylamine at room temperature for 11 h gave 2-pentadecenolide (**11**). Hydrogenation of **11** in ethanol–ethyl acetate over palladium on charcoal produced exaltolide (**12**).



Similarly, several 3-hydroxymacrolides **13**—**16** were prepared starting from α-bromo esters of ω-hydroxy aldehyde, $BrCHRCOO(CH_2)_nCHO$ with $n=9$ or 11, and R=H or CH_3. The following list of macrolides shows the effectiveness of the new method with good yields as indicated in the parenthesis. Of crucial importance to this macrolide synthesis was the observation that the more substituted aluminum enolates derived from $BrCHRCOO(CH_2)_nCHO$ with $R=CH_3$ are substantially more reactive toward the carbonyl component to give **14** or **16** in higher yield relative to that of the unsubstituted homologs. Since the α-methyl-β-hydroxy unit in macrolides **14** or **16** is a common functionality in a variety of macrolide antibiotics including erythromycin and methymycin,[16] this method may provide a useful entry to the antibiotic field, starting with simple α,ω-diols.[17]



Experimental

Instrumentation. The infrared spectra were taken with a Shimadzu IR-27-G spectrometer; the mass spectra with a Hitachi RMU-6L mass machine; the GLPC analyses with a Yanagimoto GCG-550F; and NMR spectra with a JNM-PMX 60 or Varian EM-360 spectrometer. The chemical shifts are expressed in parts per million downfield from internal tetramethylsilane ($\delta=0$). Splitting patterns are indicated as s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet. The microanalyses were performed at the Elemental Analyses Center of Kyoto University. All experiments were carried out under an atmosphere of dry argon. The products were purified by preparative thin layer chromatography on silica gel PF-254 plates (Merck), or by preparative column chromatography on silica gel E. Merck Art. 7734.

Purification or Preparation of Solvents, Metals, and Reagents. The following solvents were used: tetrahydrofuran—freshly distilled from sodium benzophenone ketyl; dichloromethane—dried over 4 Å molecular sieves. Zinc dust was washed with 5% hydrochloric acid.[17] Zinc-silver couple was obtained from zinc dust and silver acetate by a literature procedure.[10] A 1 M solution of diethylaluminum chloride was prepared by the dilution of neat diethylaluminum chloride (Ethyl Co.) with hexane under argon. Commercially available α-bromoacetophenone, 3-bromocamphor, ethyl bromoacetate, and methyl γ-bromocrotonate were used without purification. 2-Bromocyclohexanone was prepared according to the procedure in the literature.[18] 2-Bromo-2-methylcyclohexanone was obtained by the bromination of 2-methylcyclohexanone with bromine in ether at −40——50 °C.[9] 1,10-Decanediol and 1,12-dodecanediol were the commercial products of the highest purity. 1,13-Tridecanediol was prepared as follows: Reaction of cyclododecanone with diethyl carbonate and metallic sodium under reflux gave diethyl tridecanedionate, which was reduced with lithium aluminum hydride in THF to afford 1,13-tridecanediol.[19]

Preparation of β-Hydroxy Ketones. The β-hydroxy ketones were prepared by reaction of α-bromo ketones with either ketones or aldehydes according to the following general procedure: A solution of diethylaluminum chloride (1.1 mmol) in hexane was added to a slurry of zinc dust (1.5 mmol) and a catalytic amount of copper(I) bromide (0.05 mmol) in anhydrous THF (3 ml) with stirring under argon at 20 °C. The resulting mixture was cooled to −20 °C, and a solution of an α-bromo ketone (1 mmol) and an aldehyde (or a ketone) (1.1 mmol) in anhydrous THF (5 ml) was added slowly over 40 min at −20 °C. After 15 min at −20 °C, the cooling bath was removed. The reaction mixture was quenched by the addition of pyridine (0.3 ml)[20] and then poured into 2 mol dm^{-3} hydrochloric acid (10 ml). The ether extracts were washed with brine, dried over magnesium sulfate, and concentrated *in vacuo* to afford a β-hydroxy ketone after purification by preparative TLC (ether–benzene, 1:5).

3-Hydroxy-4-methyl-1-phenyl-1-pentanone. Reaction of α-bromoacetophenone with isobutyraldehyde gave the title compound as a colorless oil:[21] IR (neat) 3450 cm^{-1} (OH), 1673 cm^{-1} (C=O); NMR ($CDCl_3$) δ 7.10—8.13 (5H, m, aryl CH), 3.79—4.20 (1H, m, CH–O), 3.69 (1H, s, OH), 3.00 (2H, m, CH_2C=O), 1.78 (1H, m, CH), 0.99 (6H, d, $J=6.6$ Hz, CH_3); mass *m/e*(%) 105 (100), 174 (4, M^+-18); mp 50.5—52.0 °C (recrystallized from pentane as white crystals).

1,5-Diphenyl-3-hydroxy-4-penten-1-one. The title compound was prepared by the reaction of α-bromoacetophenone with cinnamaldehyde as a yellow oil: IR (neat) 3470 cm^{-1} (OH), 1675 cm^{-1} (C=O); NMR ($CDCl_3$) δ 6.94—8.31 (10H, m, aryl CH), 6.70 (1H, d, $J=16$ Hz, PhCH=C), 6.24 (1H, dd, $J=16$, 5.6 Hz, PhC=CH), 4.91 (1H, q, $J=5.6$ Hz, CH–O), 3.22 (2H, d, $J=6$ Hz, CH_2C=O), 2.84—3.61 (1H, s, OH); exact mass spectrum *m/e* 252.301 (Calcd for $C_{17}H_{16}O_2$ 252.313); mp 51—53 °C (recrystallized from pentane–ether as white crystals).

α-(1-Hydroxycyclohexyl)acetophenone. Reaction of α-bromoacetophenone with cyclohexanone afforded the title compound as a colorless oil;[22] IR (neat) 3513 cm^{-1} (OH), 1672 cm^{-1} (C=O); NMR ($CDCl_3$) δ 7.05—8.18 (10H, m, aryl CH), 3.88—4.01 (1H, s, OH), 3.10 (2H, s, CH_2C=O), 1.05—2.17 (10H, broad s, aliphatic CH); mass *m/e*(%) 105 (100),

200 (3, M^+-18); mp 79—80 °C (recrystallized from pentane as white crystals).

*2-(α-Hydroxybenzyl)-2-methylcyclohexanone (**6**).* Reaction of 2-bromo-2-methylcyclohexanone (191 mg, 1 mmol) with benzaldehyde (117 mg, 1.1 mmol) afforded *erythro* and *threo* mixtures of **6** (218 mg) as a pale yellow oil[21] in quantitative yield after purification by preparative TLC (ether–hexane, 1:1): NMR ($CDCl_3$) δ 7.23 (5H, s, aryl CH), 4.92, 5.00 (1H, s, CH–O), 3.53 (1H, s, OH), 2.26—266. (2H, m, $CH_2C{=}O$), 1.35—2.09 (6H, broad s, aliphatic CH), 1.00, 1.09 (3H, s, CH_3). The ratio of the *erythro* and *threo* isomers was determined by the relative intensities of the benzylic proton absorptions (NMR ($CDCl_3$) δ 4.92 (*erythro*) and 5.00 (*threo*)) to be nearly 4:3. Column chromatography of the pure **6** on silica gel (ether–hexane, 3:1) gave the fraction of pure *threo* isomer and a mixture of *erythro* and *threo* isomers (34 mg). The pure *threo* isomer has the following physical properties: IR (neat) 3503 cm^{-1}, (OH), 1690 cm^{-1} (C=O): NMR ($CDCl_3$) δ 7.15 (5H, s, aryl CH), 4.97 (1H, s, CH–O), 2.87 (1H, s, OH), 2.27—2.59 (2H, m, $CH_2C{=}O$), 1.35—2.05 (6H, broad s, aliphatic CH), 1.01 (3H, s, CH_3); mass *m/e*(%) 77 (100) 200 (0.1, M^+-18).

2-(α-Hydroxybenzyl)cyclohexanone. Condensation of 2-bromocyclohexanone with benzaldehyde yielded *erythro* and *threo* mixtures of the title compound (198 mg, 97% yield) as white solids after purification by preparative TLC (ether–hexane, 1:1). The NMR spectrum ($CDCl_3$) of the product showed the ratio of the *threo* and *erythro* isomers to be 1:1. This analysis was determined by an absorption due to the benzylic proton peak at δ 4.73 and 5.30. Column chromatography of the product on silica gel (benzene–ether, 10:1) separated two isomers. The first fraction was the *erythro* isomer: IR (neat) 3496 cm^{-1} (OH), 1697 cm^{-1} (C=O); NMR ($CDCl_3$) δ 7.27 (5H, s, aryl CH), 5.35 (1H, d, J= 2.3 Hz, CH–O), 2.90 (1H, s, OH), 1.08—2.73 (9H, broad s, aliphatic CH and CHC=O); mass *m/e*(%) 77 (100), 186 (2.5, M^+-18); mp 103—105 °C (recrystallized from hexane–ethyl acetate; lit,[21] mp 103.5—104.5 °C). From the second fraction the *threo* isomer was obtained: IR (neat) 3483 cm^{-1} (OH), 1698 cm^{-1} (C=O); NMR ($CDCl_3$) δ 7.30 (5H, s, aryl CH), 4.77 (1H, d, J=9 Hz, CH–O), 3.72 (1H, s, OH), 1.03—2.86 (9H, broad s, aliphatic CH and CHC–O); mass *m/e*(%) 77 (100), 186 (3.5, M^+-18); mp 75.5—77.5 °C (recrystallized from hexane; lit,[21] mp 75 °C).

*2-(1-Hydroxy-2-methylpropyl)cyclohexanone (**7**).* Reaction of 2-bromocyclohexanone with isobutyraldehyde produced **7** as a pale yellow oil[21]: bp 74—78 °C (bath temp, 1 mmHg); IR (neat) 3510 cm^{-1} (OH), 1688 cm^{-1} (C=O); NMR ($CDCl_3$) δ 3.47 (1H, m, CH–O), 3.03 (1H, s, OH), 1.32—2.74 (9H, broad s, aliphatic CH and CHC=O), 0.89 (6H, m, CH_3); mass *m/e*(%) 55 (100), 152 (15, M^+-18). The *erythro*/*threo* ratio of **7** could not be determined by TLC and NMR analyses.

2-(1-Hydroxy-1-methylethyl)cyclohexanone. The title compound was obtained from 2-bromocyclohexanone (1 equiv) and excess acetone (5 equiv) in the presence of diethylaluminum chloride and zinc-silver couple at −20 °C: bp 68—71 °C (bath temp, 1 mmHg (lit,[23] bp 78—80 °C/4 mmHg)); IR (neat) 3488 cm^{-1} (OH), 1690 cm^{-1} (C=O); NMR ($CDCl_3$) δ 3.95 (1H, s, CH–O), 1.42—2.62 (10H, aliphatic CH, CHC=O, and OH), 1.22 (6H, m, CH_3): mass *m/e*(%) 43 (100), 141 (5, M^+-15).

3-(1-Hydroxy-1-methylethyl)camphor. Reaction of 3-bromocamphor with acetone was performed at 20 °C using zinc-silver couple. Stirring was further continued for 1 h at 20 °C. The mixture was then quenched in a usual manner and purified by preparative TLC (ether–hexane, 1:1) to give the title compound as white crystals: mp 80—90.5 °C (recrystallized from hexane); IR (Nujol) 3473 cm^{-1} (OH), 1728 cm^{-1} (C=O); NMR ($CDCl_3$) δ 1.27, 1.46 (6H, two s, CH_3C–O); exact mass spectrum *m/e* 210.330 (Calcd for $C_{13}H_{22}O_2$ 210.317).

Preparation of β-Hydroxy Esters. The β-hydroxy esters were prepared in the same way as the β-hydroxy ketones.

Ethyl 3-Hydroxy-3-phenylpropionate. The title compound was produced from ethyl bromoacetate and benzaldehyde as a colorless oil: bp 120—123 °C (bath temp, 1 mmHg (lit,[24] bp 154 °C/12 mmHg)); IR (neat) 3435 cm^{-1} (OH), 1728 cm^{-1} (C=O); NMR ($CDCl_3$) δ 7.28 (5H, s, aryl CH), 5.06 (1H, t, J=7 Hz, CH–O), 4.08 (2H, q, J=7 Hz, CH_2–O), 3.40 (1H, s, OH), 2.65 (2H, d, J=7 Hz, $CH_2C{=}O$), 1.18 (3H, t, J=7 Hz, CH_3); mass *m/e*(%) 107 (100), 165 (5, M^+-29), 176 (4, M^+-18), 194 (22, M^+).

Ethyl 1-Hydroxycyclohexylacetate. Reaction of ethyl bromoacetate with cyclohexanone at 20 °C yielded the title compound as a colorless oil: bp 85—88 °C/2 mmHg (lit,[25] bp 89—93 °C/4 mmHg); IR (neat) 3499 cm^{-1} (OH), 1710 cm^{-1} (C=O); NMR ($CDCl_3$) δ 4.32 (2H, q, J=7 Hz, CH_2–O), 3.37 (1H, s, OH), 2.43 (2H, s, $CH_2C{=}O$), 1.52 (10H, broad s, aliphatic CH), 1.26 (3H, t, J=7 Hz, CH_3); mass *m/e* (%) 55 (100), 168 (6.8, M^+-18), 186 (6.5, M^+).

Methyl 2-(α-Hydroxybenzyl)-3-butenoate. Reaction of methyl γ-bromocrotonate (179 mg, 1 mmol) with benzaldehyde (117 mg, 1.1 mmol) at −20 °C gave the *erythro* and *threo* isomers of the title compound in quantitative yield as a colorless oil[12] after purification by preparative TLC (ether–hexane, 1:1). None of the γ-alkylation product was detected in the crude product. Column chromatography of the product on the silica gel (ether–hexane, 1:3) separated the pure *erythro* isomer (92 mg), a mixture of two isomers (16 mg), and the pure *threo* isomer (80 mg). These isomers have the following physical properties. *Erythro* isomer: IR (neat) 3549 cm^{-1} (OH), 1726 cm^{-1} (C=O); NMR ($CDCl_3$) δ 7.24 (5H, s, aryl CH), 5.96 (1H, ddd, J=8.0, 11.4, 18.8 Hz, =CH–C), 5.36—4.98 (3H, m, CH_2=C and CH–O), 3.63 (3H, s, CH_3), 3.39 (1H, dd, J=6.4, 8.0 Hz, C=C–CH), 2.92 (1H, s, OH); mass *m/e*(%) 77 (100), 188 (18.8, M^+-18): *Threo* isomer: IR (neat) 3437 cm^{-1} (OH), 1707 cm^{-1} (C=O); NMR ($CDCl_3$) δ 7.31 (5H, s, aryl CH), 5.72 (1H, ddd, J=7.8, 10.8, 17.2 Hz, =CH–C), 4.79—5.40 (3H, m, CH_2=C and CH–O), 3.77 (3H, s, CH_3), 3.50 (1H, dd, J= 8.8, 17.2 Hz, C=C–CH), 2.84 (1H, s, OH).

Preparation of Macrolides. Five hydroxy macrolides were prepared by the intramolecular aldol condensation of α-bromo esters of ω-hydroxy aldehydes. The synthesis of 3-hydroxypentadecanolide (**10**), starting from 1,13-tridecanediol is representative.

*13-Hydroxytridecyl Bromoacetate (**17**).* A solution of bromoacetyl bromide (5.18 g, 24 mmol) in anhydrous THF (20 ml) was added dropwise to a solution of 1,13-tridecanediol (4.32 g, 20 mmol) in THF (100 ml) containing *N,N*-dimethylaniline (2.79 ml, 22 mmol) under argon at 20 °C. Stirring was continued for 15 min at 20 °C. Then the solution was diluted with ether, washed with 2 mol dm^{-3} hydrochloric acid. The ether extracts were washed with brine, dried over sodium sulfate, and concentrated *in vacuo* to afford **17** (3.57 g, 53%) as white crystals after purification by column chromatography on silica gel (ethyl acetate–hexane, 2:5): IR (Nujol) 3375 cm^{-1} (OH), 1731 cm^{-1} (C=O); NMR ($CDCl_3$) δ 4.10 (2H, t, J=6 Hz, $CH_2OC{=}C$), 3.76 (2H, s, CH_2Br), 3.57 (2H, t, J=6 Hz, CH_2–O), 1.00—1.98 (23H, broad s, aliphatic CH and OH).

Found: C, 53.32; H, 8.98%. Calcd for $C_{15}H_{28}BrO_3$: C, 53.41; H, 8.67%.

TABLE 2. PHYSICAL PROPERTIES AND ANALYTICAL DATA OF MACROLIDES AND THEIR PRECURSORS

Products	Boiling point (°C)[a] (Melting point)	IR (cm^{-1})[b]	NMR (δ)	Found, % (Calcd)
$BrCH_2COO(CH_2)_{10}OH$		3345 (OH) 1735 (C=O)	4.08 (2H, t, J=6, CH_2OC=O), 3.75 (2H, s, CH_2Br), 3.54 (2H, t, J=6, CH_2O), 1.90 (1H, s, OH), 1.30 (16H, br s, aliphatic CH)	C, 48.57(48.82) H, 7.90(7.85)
$BrCH_2COO(CH_2)_9CHO$		2733 (CHO) 1720 1735 (C=O)	9.75 (1H, t, J=1.8, CHO), 4.08 (2H, t, J=6, CH_2O), 3.75 (2H, s, CH_2Br), 2.38 (2H, td, J=1.8, 6.4, CH_2C=O), 1.30 (14H, br s, aliphatic CH)	C, 48.90(49.16) H, 7.03(7.22)
13	165/2 mm Hg	3430 (OH) 1724 (C=O)	4.02 (3H, m, CH_2O, CH-O), 2.60 (1H, s, OH), 2.07—2.57 (2H, m, CH_2C=O), 1.32 (14H, br s, aliphatic CH)	C, 67.05(67.25) H, 10.11(10.35)
$CH_3CHBrCOO(CH_2)_{10}OH$	170/1 mm Hg	3360 (OH) 1731 (C=O)	4.31 (1H, q, J=6.6, CHBr), 4.10 (2H, t, J=6.2, CH_2OC=O), 3.57 (2H, t, J=5.6, CH_2O), 1.79 (3H, d, J=6.6, CH_3), 1.66 (1H, s, OH), 1.30 (16H, br s, aliphatic CH)	C, 50.23(50.49) H, 8.32(8.15)
$CH_3CHBrCOO(CH_2)_9CHO$	(72—75)	2710 (CHO) 1731 (C=O)	9.54 (1H, t, J=1.6, CHO), 4.31 (1H, q, J=6.6, CHBr), 4.02 (2H, t, J=6.6, CH_2O), 2.33 (2H, td, J=1.6, 6, CH_2C=O), 1.76 (3H, d, J=6.6, CH_3), 1.32 (14H, br s, aliphatic CH)	C, 46.59(46.82) H, 5.35(5.59)
14		3432 (OH) 1710 1726 (C=O)	3.37—4.25 (3H, m, CH_2O, CH-O), 2.10—2.97 (2H, m, CHC=O, OH), 1.32 (16H, br s, aliphatic CH)	C, 68.43(68.38) H, 10.47(10.60)
$BrCH_2COO(CH_2)_{12}OH$	170—173/1 mm Hg	3279 (OH) 1737 (C=O)	4.15 (2H, t, J=6.2, CH_2OC=O), 3.80 (2H, s, CH_2Br), 3.60 (2H, t, J=6, CH_2O), 2.22 (1H, s, OH), 1.29 (20H, br s, aliphatic CH)	C, 52.05(52.01) H, 8.57(8.42)
$BrCH_2COO(CH_2)_{11}CHO$		2730 (CHO) 1723 1736 (COO)	9.68 (1H, t, J=2, CHO), 4.13 (2H, t, J=6.2, CH_2O), 3.79 (2H, s, CH_2Br), 2.40 (2H, td, J=6.2, CH_2C=O), 1.29 (18H, br s, aliphatic CH)	C, 52.30(52.34) H, 7.55(7.84)
15	168/2 mm Hg	3398 (OH)	3.53—4.13 (3H, m, CH_2O, CH-O) 2.47 (2H, d, J=4.8, CH_2C=O), 1.30 (21H, br s, aliphatic CH, OH)	C, 69.41(69.38) H, 10.89(10.81)
$CH_3CHBrCOO(CH_2)_{12}OH$	174—177/1 mm Hg	3352 3405 (OH)[c] 1723 (C=O)	4.28 (1H, q, J=6.6, CHBr), 4.08 (2H, t, J=6, CH_2OCO), 3.55 (2H, t, J=6, CH_2O), 1.89 (1H, s, OH), 1.76 (3H, d J=6.6, CH_3), 1.27 (20H, s, aliphatic CH)	C, 53.67(53.41) H, 8.87(8.67)
$CH_3CHBrCOO(CH_2)_{11}CHO$	(51—53)	2737 (CHO) 1733 (C=O)	9.57 (1H, t, J=1.6, CHO), 4.29 (1H, q, J=7, CHBr), 4.09 (2H, t, J=6.4, CH_2O), 2.39 (2H, td,	C, 48.58(48.93) H, 6.40(6.06)

Table 2. Continued

Products	Boiling point (°C)[a] (Melting point)	IR (cm^{-1})[b]	NMR (δ)	Found, % (Calcd)
			J=1.6, 6.8, CH_2C=O), 1.78 (3H, d, J=7, CH_3), 1.28 (18H, s, aliphatic CH_2)	
16	180/2 mm Hg	3425 (OH) 1725 (C=O)	3.40—4.53 (3H, m, CH_2O, CH-O), 2.80 (1H, s, OH), 2.52 (1H, q, J=6.8, CHC=O), 1.33 (23H, br s, aliphatic CH, CH_3)	C, 70.31(70.27) H, 11.21(11.01)

a) Bath temperature. b) Liquid film. c) Nujol mull.

*Bromoacetate of 13-Hydroxytridecanal (**9**).* Collins oxidation of **17** was slightly modified as follows: Chromium trioxide (5 g, 50 mmol) was added portionwise to a solution of pyridine (8.09 ml, 100 mmol) in dry dichloromethane (125 ml) at 0 °C, and the resulting brown suspension was stirred for 5 min at 0 °C followed by 1 h at 20 °C. Celite-545 (dried *in vacuo* for 1 h at 150 °C before use) and then **17** (1.685 g, 5 mmol) dissolved in dry dichloromethane (25 ml) were added at 0 °C. After further stirring for 10 min, the suspension was treated with powdered $NaHSO_4 \cdot H_2O$ (6.25 g). The complete removal of pyridine was checked by TLC. The suspension was diluted with hexane (200 ml), filtered through Celite-545, and washed with hexane. The filtrate was concentrated *in vacuo* to afford **9** (1.495 g, 89% yield) as a colorless oil after purification by column chromatography on silica gel (ether–hexane, 1:2): IR (neat) 2723 cm^{-1} (CHO), 1721, 1731 cm^{-1} (C=O); NMR ($CDCl_3$) δ 9.65 (1H, m, CHO), 4.06 (2H, t, J=6 Hz, CH_2O), 3.67 (2H, s, CH_2Br), 2.33 (2H, t, J=6 Hz, CCH_2C=O), 1.28 (20H, broad s, aliphatic CH).

Found: C, 53.51; H, 8.33%. Calcd for $C_{15}H_{27}BrO_3$: C, 53.74; H, 8.12%.

*3-Hydroxypentadecanolide (**10**).* A solution of diethylaluminum chloride (1.5 mmol, 1.5 ml of a 1 M solution) in hexane was added to a slurry of zinc-silver couple (3.27 g, 50 mmol) in anhydrous THF (50 ml) under argon at 20 °C. After 10 min, the suspension was warmed to 35 °C and a solution of **9** (335 mg, 1 mmol) in THF (10 ml) was added slowly over a period of 4 h. Stirring was continued for an additional 20 min, and the reaction was terminated by the addition of pyridine (0.9 ml). Then the suspension was diluted with ether, washed with iced 2 mol dm^{-3} hydrochloric acid, and brine. The organic layer and ether extracts of the aqueous washings were dried and concentrated to afford **10** (175 mg, 48% yield) as a colorless oil after purification by column chromatography on silica gel (ether–hexane, 1:1): IR (neat) 3427 cm^{-1} (OH), 1729 cm^{-1} (C=O); NMR ($CDCl_3$) δ 3.58—4.25 (1H, m, CH-O), 4.13 (2H, t, J=5 Hz, CH_2O), 2.82 (1H, s, OH), 2.53 (2H, d, J=5.5 Hz, CH_2C=O), 1.35 (22H, broad s, aliphatic CH); mass m/e(%) 238 (M^+-H_2O).

Found: C, 70.30; H, 10.88%. Calcd for $C_{15}H_{28}O_3$: C, 70.27; H, 11.01%.

*2-Pentadecenolide (**11**).* A solution of **10** (85 mg, 0.33 mmol) in dichloromethane (1.5 ml) was treated with methanesulfonyl chloride (51 μl, 0.66 mmol) in the presence of triethylamine (0.37 ml, 2.66 mmol) at −20 °C. The resulting white suspension was allowed to warm to room temperature. Further stirring was continued for one day at room temperature. The mixture was poured onto iced water and extracted with ether. Purification of the crude product by column chromatography on silica gel (ether–hexane, 1:15) gave **11** in 79% yield as a colorless oil: IR (neat) 1716 cm^{-1} (C=O), 983, 1460 cm^{-1} (C=C); NMR (CCl_4) δ 6.75 (1H, dt, J=7.2, 15.4 Hz, CH=C-C=O), 5.63 (1H, d, J=15.4 Hz, CH-C=O), 4.10 (2H, t, J=5.2 Hz, CH_2O), 2.19 (2H, m, CH_2C=C), 1.31 (20H, broad s, aliphatic CH); mass m/e(%) 238 (M^+).

Found: C, 75.31; H, 10.92%. Calcd for $C_{15}H_{26}O_2$: C, 75.58; H, 10.99%.

*Synthesis of Exaltolide (**12**).* 2-Pentadecenolide (**11**) (65 mg) was hydrogenated in ethanol–ethyl acetate over 10% palladium on charcoal at room temperature for two days to give **12** (48 mg) as colorless semi-solids: IR (neat) 1730 cm^{-1} (C=O); NMR (CCl_4) δ 4.02 (2H, t, J=5.2 Hz, CH_2O), 2.22 (2H, t, J=6.2 Hz, CH_2C=O), 1.32 (24H, broad s, aliphatic CH); mass m/e(%) 240 (M^+).

The syntheses of other hydroxy macrolides such as 3-hydroxydodecanolide (**13**), 3-hydroxy-2-methyldodecanolide (**14**), 3-hydroxytetradecanolide (**15**), and 3-hydroxy-2-methyltetradecanolide (**16**), starting from the corresponding α,ω-diols, $HO(CH_2)_nOH$ with n=10, 12 were carried out exactly as described above. The physical properties and analytical data of these four macrolides and their precursors are shown in Table 2.

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15) Although **14** and **16** were found to be mixtures of *erythro* and *threo* isomers ($\approx 1:1$ by TLC assay (ether–hexane, 1:2, two developments) and trimethylsilylations; attempted separation of these isomers by GLC or column chromatography was unsuccessful), the better selectivities would be expected in the naturally occurring macrolide synthesis by this methodology since such compounds were known to be conformationally rather rigid molecules. A study on the synthesis of macrolides along this possibility is under way.

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