To the extent that this may be a general phenomenon, it will need to be considered in schemes (e.g., those of ref 17) where the composition of products formed upon chlorination of chloroalkanes is predicted.

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Registry No. *meso*-$H_3C(CHCl)_2CH_3$, 4028-56-2; (±)-*dl*-$H_3C(CHCl)_2CH_3$, 2211-67-8; $H_3CCHClCH_2CH_3$, 78-86-4.

Asymmetric Reduction of Aliphatic δ-Keto Acids with Sodium Borohydride in the Presence of Bovine Serum Albumin

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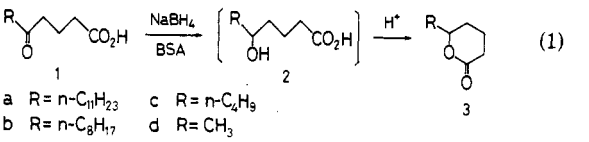
The asymmetric reduction of the prochiral carbonyl group of δ-keto acids attracts interest because it is a key step for the facile synthesis of optically active δ-lactones. The asymmetric reduction of prochiral ketones has been studied extensively,[1] and considerable success has been attained especially for aromatic or α,β-unsaturated ketones with high optical yields of more than 90% ee.[2] In contrast, aliphatic ketones have generally been reduced with rather low optical yields.[3] Recently we have reported that the δ-keto groups of 5-oxohexadecanoic acid (**1a**) and its homologues **1b,c** were reduced to secondary hydroxyl groups with a high enantioselectivity of more than 98% ee by using fermenting bakers' yeast.[4] This constitutes the most effective preparation of optically pure (*R*)-(+)-5-hexadecanolide, pheromone of Oriental hornet.[5] We now report a nonmicrobial approach to the asymmetric reduction of δ-keto acid **1** by using sodium borohydride with bovine serum albumin (BSA) as chiral auxiliary in aqueous media (eq 1).



BSA in blood plasma serves as a transport protein for various endogeneous and exogeneous materials, among which long-chain fatty acids show high binding tendencies to BSA.[6] Then, the chiral binding domain of BSA is expected to differentiate the enantioface of the prochiral carbonyl group of δ-keto acids. In fact, BSA has been used successfully to induce asymmetric reduction of aromatic ketones.[7] It is also of interest to compare the result for δ-keto acids with that for the aromatic ketones reported.

Results and Discussion

The asymmetric reduction was carried out under various conditions as shown in Table I. Several features for the maximum optical yield can be pointed out. The optimum pH value was found to be in the range of 9–10 (entries 1–5), which is almost identical with the value (9–11) that Sugimoto et al.[7] found for trifluoroacetophenone as substrate. Lowering of the reaction temperature improved the optical yield remarkably from 16 to 44% for a change from 25 to 0 °C but only slightly from 44 to 49% for that from 0 to −10 °C (entries 6–10). The latter may be due to a reversed effect of the electrolyte (NaCl) added for prevention of freezing. Quite interesting is the fact that the maximum optical yield was obtained when 0.076 molar equiv of BSA was used to the δ-keto acid **1a** (entries 11–16). Namely, 13 molecules of δ-keto acid/molecule of BSA gave the best result. A higher or lower ratio of the acid to BSA resulted in decrease of the optical yield. This is in sharp contrast to the result for aromatic ketones reported by Sugimoto et al.,[7] where 3 or less molecules of aromatic ketone/molecule of BSA brought about the best result. They rationalized the observation in terms of the presence of three analogous main binding domains on BSA.

The binding of long-chain fatty acids to BSA has been investigated rather extensively, suggesting that BSA possesses 6–7,[8] 8,[9] or 27[10] binding sites with different affinities for the ligand. Although the number of the sites is liable to a wide variation, the binding of 13 molecules of the δ-keto acid/molecule of BSA seems to be probable. The fact that the maximum optical yield is not realized with 6–7 molecules of the δ-keto acid/molecule of BSA (entry 15) may be explained by the assumption that high-affinity bindings are unfavorable to the asymmetric induction.

Since the binding is expected to be highly dependent on the length of hydrophobic carbon chain, we have examined 5-oxotridecanoic, 5-oxononanoic, and 5-oxohexanoic acids (**1b,c,d**) as substrates. The results shown in Table II indicate that a long chain is essential for the induction of asymmetry.

We propose the binding of long-chain 5-oxoalkanoic acids **1** to BSA at its chiral hydrophobic pockets or crevices in the following way. The nonpolar chain of the acid could be inserted into the hydrophobic domain, and the hydrophilic carboxylate group would be projecting toward bulk

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Table I. Asymmetric Reduction of 5-Oxohexadecanoic Acid (1a) with Sodium Borohydride in the Presence of Bovine Serum Albumin Leading to (*R*)-(+)-5-Hexadecanolide (3a)

			BSA		(*R*)-(+)-5-hexadecanolide (3a)			
entry	pH[a]	temp,[b] °C	equiv	concn, mM	yield, %	opt yield,[c] %	ee,[d] %	$[\alpha]_D$, deg (*c*, THF)
1	6.5	0	0.125	3.8	50	21		+8.3 (6.3)
2	7.5	0	0.076	1.9	53	26		+10.2 (4.8)
3	9	0	0.076	1.9	56	44		+17.5 (1.4)
4	10	0	0.076	1.9	61	44	46	+17.2 (2.6)
5	11.5	0	0.076	1.9	55	19		+7.5 (4.6)
6	7.5	25	0.076	1.9	73	13		+5.2 (5.0)
7	7.5	0	0.076	1.9	53	26		+10.2 (4.8)
8	10	25	0.076	1.9	50	16		+6.3 (2.1)
9	10	0	0.076	1.9	61	44	46	+17.2 (2.6)
10	10	−10[e]	0.076	1.9	52[f]	49	48	+19.5 (2.4)
11	10	0	0.019	0.48	44	31	34	+12.4 (2.6)
12	10	0	0.038	0.95	70	37		+14.8 (5.2)
13	10	0	0.076	1.9	61	44	46	+17.2 (2.6)
14	10	0	0.12	3.0	51	35		+13.7 (3.8)
15	10	0	0.15	1.9	65	27		+10.6 (5.3)
16	10	0	0.076	0.95	55	39		+15.6 (3.1)

[a] Accuracy ±0.2. [b] The reaction time was 3 h except for entry 10. [c] Estimated by using $[\alpha]_D$ +39.5° (*c* 1.74, THF) for 100%. See ref 4. [d] The percent ee was determined by ^1H NMR using Eu(hfc)$_3$ after conversion to the diol with MeLi. [e] To prevent freezing of the solution (20 mL), 4.6 g of NaCl was added. The reaction time was 12 h. [f] The yield is based on the acid consumed. The recovery of the acid was 20%.

Table II. Asymmetric Reduction of Various 5-Oxoalkanoic Acids (1b–d) with Sodium Borohydride in the Presence of Bovine Serum Albumin[a] Leading to 5-Alkanolide (3b–d)

acid	5-alkanolide	yield, %	opt yield, %	$[\alpha]_D$ (*c*, THF)
5-oxotridecanoic (**1b**)	**3b**	52	26	+11.8 (2.02)[b]
5-oxononanoic (**1c**)	**3c**	74	0	0
5-oxohexanoic (**1d**)	**3d**	22[c]	0	0

[a] At pH 10 and 0 °C; BSA 0.076 mol equiv, 1.9 mM. [b] $[\alpha]_D$ +45.2° (*c* 1.58, THF) for the optically pure **3b**. See ref 4. [c] The low yield is attributable to losses due to volatility.

water.[11] The oxygen of the δ-keto group would be fixed by a hydrogen-bonding or an electrostatic force so as to expose the *si* face to the attack by a hydride anion.

In conclusion, although further work is needed to improve the optical yield, the present result indicates the potential use of proteins as chiral auxiliary for the asymmetric reduction of prochiral ketones that are not reduced enantioselectively by conventional chiral reagents.

Experimental Section

All boiling and melting points are uncorrected. IR spectra were recorded with a Jasco A-102 spectrometer. ^1H NMR spectra (60 MHz) and ^{13}C NMR spectra (25 MHz) were obtained on JEOL PMX 60 SI and JEOL FX-100 spectrometers, respectively. Tetramethylsilane was used as internal standard. Optical rotations were measured on a JASCO DIP-4 polarimeter, and pH values were determined by using a Toa HM-5A pH meter equipped with a combined-glass electrode. Elemental analyses were performed by Ei-ichiro Amano of our laboratory.

Materials. BSA of fraction V grade from Armour was used as received. Extrapure-grade $NaBH_4$ was from Nakarai Chemicals. 5-Oxohexadecanoic acid (**1a**) was prepared by using glutaric anhydride and *n*-undecylmagnesium bromide according to the method reported.[12] 5-Oxotridecanoic, 5-oxononanoic, and 5-oxohexanoic acids (**1b–d**) were prepared from 2-*n*-octyl-, 2-*n*-butyl-, and 2-methyl-substituted cyclohexanones via the corresponding 3-alkyl-1,2-cyclohexanediones as described earlier.[13]

Asymmetric Reduction of 5-Oxoalkanoic Acid 1 with Sodium Borohydride in the Presence of BSA and Conversion of the Hydroxy Acid 2 to 5-Alkanolide 3. The procedure is exemplified as follows: BSA (2.5 g, 0.038 mmol) was dissolved in a buffer solution ($Na_2B_4O_7$; pH 9.2, 17.0 mL), and the solution was cooled slowly to −10 °C with addition of NaCl (4.6 g) and stirring. Then, 5-oxohexadecanoic acid (**1**; 135 mg, 0.50 mmol) dissolved in 0.5 N NaOH was added, and the solution was adjusted to pH 10.0 with 0.5 N NaOH (total 3.0 mL). After the mixture was stirred for 1 h, $NaBH_4$ (38 mg, 1.0 mmol) was added and the stirring was continued further for 12 h. The solution was adjusted to pH 2–3 with 10% HCl and saturated with NaCl. The BSA was filtered after centrifugation (3000 rpm, 1 h). The aqueous solution was extracted five times with ether, and the BSA was washed five times with hexane–ether (9:1). The combined extracts, after drying ($MgSO_4$) and evaporation, gave a crude solid that was refluxed in benzene for 1 h with *p*-TsOH as catalyst. The crude product thus obtained was passed through a silica gel column (Wako gel C 200, 10 g; hexane–acetone, 20:1) to give colorless crystals of 5-hexadecanolide (**3a**):[4,14] 52 mg (52% based on the acid **1a** consumed; mp 32.0–33.0 °C; $[\alpha]^{18}_D$ +19.5° (*c* 2.40, THF) [lit. mp 37.5–38.0 °C, $[\alpha]_D$ +39.5° (*c* 1.74, THF)[4] and $[\alpha]_D$ +40.2° (*c* 1.76, THF)[14h]]. Then, the starting acid **1a** [29 mg (21%)] was eluted with a 5:1 mixture of hexane–acetone. The optical yield was estimated to be 49% by using $[\alpha]_D$ +39.5° for 100%. The percent ee was also determined to be 48% by measuring ^1H NMR spectra in the presence of Eu(hfc)$_3$ after conversion to the diol with MeLi,[4,15] which is in good agreement with the value obtained from the optical rotation.

5-Oxohexadecanoic Acid (1a): yield 40% from glutaric anhydride; mp 78.0–79.0 °C; colorless crystals purified by LC (silica gel, hexane–acetone, 1:1); IR (KBr) 3600–2200, 1715, 1700 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.88 (t, 3 H), 1.02–2.20 (m, 20 H), 2.20–2.70 (m, 6 H), 8.70 (s, 1 H); ^{13}C NMR ($CDCl_3$) δ 14.1 (q), 18.6 (t), 22.7 (t), 23.8 (t), 29.26 (t), 29.36 (t), 29.44 (t), 29.50 (t), 29.63 (2 C, t), 31.9 (t), 33.1 (t), 41.4 (t), 42.9 (t), 179.3 (s), 210.6 (s). Anal. Calcd for $C_{16}H_{30}O_3$: C, 71.06; H, 11.18. Found: C, 71.04; H, 10.97.

5-Oxotridecanoic Acid (1b): yield 75% from 3-*n*-octyl-1,2-cyclohexanedione; mp 69.5–70.2 °C; colorless crystals purified by

(11) Recovery of the methyl ester of **1a** was 90% when it was subjected to the reduction. This result indicates the key role of the carboxyl group to solubilize the substrate.

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LC (silica gel, hexane–AcOEt, 10:1, 5:1); IR (KBr) 3600–2200, 1725, 1700 cm^{-1}; ^1H NMR (CCl_4) δ 0.85 (t, 3 H), 1.0–2.2 (m, 14 H), 2.2–2.7 (m, 6 H), 10.8 (br s); ^{13}C NMR ($CDCl_3$) δ 14.1 (q), 18.5 (t), 22.6 (t), 23.9 (t), 29.1 (t), 29.3 (t), 29.4 (t), 31.8 (t), 33.1 (t), 41.3 (t), 42.9 (t), 179.4 (s), 210.5 (s). Anal. Calcd for $C_{13}H_{24}O_3$: C, 68.19; H, 10.44. Found: C, 68.33; H, 10.59.

5-Oxononanoic Acid (1c): yield 75% from 3-*n*-butyl-1,2-cyclohexanedione; mp 42.0–43.0 °C; colorless crystals purified by LC (silica gel, hexane–AcOEt, 10:1, 2:1); IR (KBr) 3600–2400, 1720, 1700 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.90 (t, 3 H), 1.1–2.2 (m, 6 H), 2.2–2.7 (m, 6 H), 6.7 (br s); ^{13}C NMR ($CDCl_3$) δ 13.9 (q), 18.6 (t), 22.3 (t), 26.0 (t), 33.0 (t), 41.3 (t), 42.6 (t), 179.3 (s), 210.5 (s). Anal. Calcd for $C_9H_{16}O_3$: C, 62.77; H, 9.36. Found: C, 62.83; H, 9.37.

5-Hexadecanolide (3a):[4,14] identified by using the IR and NMR spectra in comparison with those reported;[14h] ^{13}C NMR ($CDCl_3$) δ 14.2 (q), 18.5 (t), 22.7 (t), 24.9 (t), 27.8 (t), 29.36 (t), 29.44 (t), 29.48 (t), 29.52 (t), 29.58 (t), 29.63 (t), 29.65 (t), 31.9 (t), 35.9 (t), 80.7 (d), 172.1 (s).

5-Tridecanolide (3b): bp 120–130 °C (0.4 mm); IR (neat) 1735 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.86 (t, 3 H), 1.12–2.30 (m, 18 H), 2.30–2.75 (m, 2 H), 4.00–4.60 (m, 1 H); ^{13}C NMR ($CDCl_3$) δ 14.1 (q), 18.5 (t), 22.6 (t), 24.9 (t), 27.8 (t), 29.4 (4 C, t), 31.8 (t), 35.7 (t), 80.6 (d), 172.1 (s); $[\alpha]^{26}_D$ +11.8° (*c* 2.02, THF) [lit.[4] $[\alpha]^{27}_D$ +45.2° (*c* 1.58, THF)]. Anal. Calcd for $C_{13}H_{24}O_2$: C, 73.54; H, 11.39. Found: C, 73.38; H, 11.27.

5-Nonanolide (3c):[16] bp 70–80 °C (2 mm); IR (neat) 1740 cm^{-1}; ^1H NMR (CCl_4) δ 0.92 (t, 3 H), 1.12–2.10 (m, 10 H), 2.10–2.52 (m, 2 H), 3.90–4.40 (m, 1 H). Anal. Calcd for $C_9H_{16}O_2$: C, 69.19; H, 10.32. Found: C, 69.25; H, 10.35.

5-Hexanolide (3d):[17] bp 80 °C (3 mm); identified by using IR and ^1H NMR spectra in comparison with those reported.[17a]

Acknowledgment. We thank Dr. Toyonari Sugimoto of Kyoto University for valuable discussions.

Registry No. **1a**, 70444-63-2; **16**, 869-99-8; **1c**, 3637-15-5; **1d**, 3128-06-1; **3a**, 59812-96-3; (+)-**3b**, 99461-66-2; (±)-**3c**, 105140-26-9; (±)-**3d**, 26991-67-3; BSA, 9048-46-8.

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2-Chloro-1-(chloromethyl)ethyl Methoxymethyl Ether as a Reagent for Acetonylation of Alcohols and Phenol

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Since the acetonyl group is a useful functional unit due to its high reactivity and versatility, introduction of this unit is one of the important operations in organic synthesis. By acetonylation, not only many kinds of elaborations are possible by successive reactions but also the property of chemicals itself can be controlled and adjusted, so it offers an effective methodology for us in designing the organic synthesis.[1] Among the many kinds of acetonylation reagents reported, alkoxyallyl bromide developed by Horning[2] and Jacobson[3] has attracted attention as the most useful acetonylation reagent at present. Although the electrophilic reactivity is high and effective for acetonylation, this reagent requires some care in its preparation and preservation, for example, high pyrolytic temperature, inevitable side reactions, difficult isolation, and unstableness to undesirable polymerization etc.[2-4]

Very recently, in the course of study on the reactivity of epichlorohydrin under phase-transfer (PT) catalytic conditions,[5] we synthesized a series of 2-substituted 1-(chloromethyl)ethyl ethers from epoxides and chlorides in high yield in the presence of dodecyltrimethylammonium chloride under mild conditions.[6] Among them, we found 2-chloro-1-(chloromethyl)ethyl methoxymethyl ether (**1**), which can be prepared by a simple process and isolated easily by distillation, and is also stable in the air, is a superior reagent for converting various hydroxyl compounds to the corresponding acetonyl ethers.

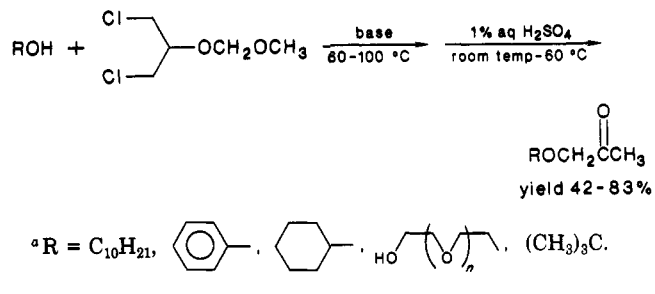
The acetonylation of hydroxyl compounds was carried out under basic conditions, generally in the presence of PT catalyst, and the successive acidic hydrolysis completed the reaction path to acetonyl ethers is shown in Scheme I.

The reaction pathway may be considered as follows (Scheme II); 2-(chloromethyl)-3,5-dioxahex-1-ene (**2**) formed through elimination of hydrogen chloride is attacked by alkoxide anion to afford **3**, which is then converted to acetonyl ether by hydrolysis in acidic medium. Compounds **2**, **3**, and acetonyl ethers **4** were isolated by distillation at reduced pressure and identified by the spectral and elemental analyses.

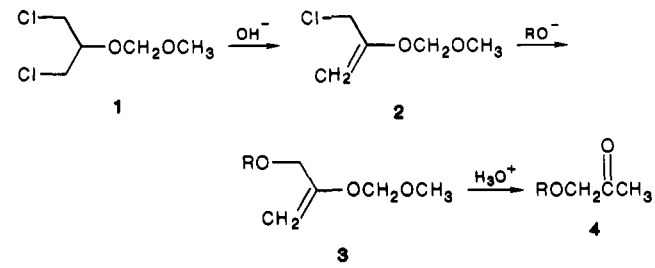
When solid sodium hydroxide (pellet form) in dioxane is employed, this reaction proceeds only in the presence of PT catalyst except for the case of oligoethylene glycol. In the latter case, the reaction proceeds smoothly even without PT catalyst. Since alkali hydroxide can be dissolved into the reaction system by solvation of metal cation with oligooxyethylene moieties of the substrate, promoted are the formation of **2**, the alkoxide anion, and then inevitably the objective compound **3**.

The hydrolysis of compounds **3** bearing hydrophobic decyl or phenyl group required relatively intensive conditions, namely at 60 °C in aqueous dioxane. In the other

Scheme I[a]



Scheme II



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