Table I. Percentage of Undesired Isomer in the Final Product ($100P_D/P$) for Various Values of $m = k_r/k_c$ and $r = E_o/A_o$, Assuming Complete Reaction of the Limiting Reactant, A

values of $r = E_o/A_o$	values of $m = k_r/k_c$				
	1	0.5	0.1	0.05	0.01
1	25.0	16.7	4.5	2.38	0.495
2	12.5	6.9	1.5	0.76	0.153
4	6.3	3.3	0.68	0.34	0.068
6	4.2	2.2	0.44	0.22	0.044
10	2.5	1.3	0.26	0.13	0.026

automatically limits the maximum value of x.

In this case of excess E, that is, for $r < 1$, x equals r when the reaction is completed. Since x never reaches 1, the impurity fraction does not reach $(m/2)/(m + 1)$. Table I shows the advantage in product purity to be gained by using various ratios of E_0 to A_0 for several selected small values of $m = k_r/k_c$, assuming the reaction goes until the limiting reagent, A, is depleted.

It is interesting to note that eq 10 does not show any explicit dependence of purity on the initial concentration ratio, r. But when r is less than one (excess E), it affects the product purity by limiting the maximum value of x to r. An excess of ester has the effect of terminating the reaction before the worst stage. An excess of the amine reactant has no effect at all on the product purity. This is because it has no effect on the extent of reaction of E at completion (100%); that is, the maximum value of x remains at 1 for all values of r greater than 1.

In actual practice, the reaction does not go all the way to completion because that would require, theoretically, an infinite time. But, as we have shown previously,[7] the time required for reaction of, say, 99% of the limiting reagent (A in our case) is considerably reduced by using an excess of the other reagent (E). From the usual second-order kinetics equations, the time required to reach a given x is, for $r = 1$, $t = x/(kA_0(1 - x))$, and, for $r < 1$, $t = (r \ln ((1 - rx)/(1 - x)))/(kA_0(1 - r))$. Applied to our case, these expressions show that the time required to react 99% of A is about *25 times* shorter when $E_0 = 2A_0$ ($r = {}^1/_2$), than when $E_0 = A_0$, ($r = 1$). An excess of E thus has the double effect of considerably shortening the reaction time and significantly improving the optical purity of the product. It is hoped that this strategem will prove useful in practical peptide synthesis.

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Stereochemical Effects in Free Radical Hydrogen Abstraction from 2,3-Dichlorobutane

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The stereochemical features of free radical hydrogen abstraction from a saturated carbon are almost unexplored. One relevant study is that of Dneprovskii et al.[1] who found that hydrogen abstraction from norbornane by a series of

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Table I. Chlorination of 2,3-Dichlorobutane Isomers

	isomer ratio[a] $1,2,3\text{-}Cl_3/2,2,3\text{-}Cl_3$	rel reactivity[b] $k(meso)/k(dl)$
Cl_2	*meso* 0.43 ± 0.01 (6)[c] *dl* 1.10 ± 0.04 (6)	1.10 ± 0.05 (6)
t-BuOCl	*meso* 0.16 ± 0.01 (3) *dl* 1.06 ± 0.02 (3)	0.64 ± 0.02 (3)

Relative Rate Constants

	k_1 (*meso*)	k_2 (*meso*)	k_1 (*dl*)	k_2 (*dl*)
$Cl^\bullet$	1.0[d]	7.0	1.6	4.3
t-$BuO^\bullet$	1.0[d]	18.8	5.8	16.5

[a] Isomer ratio = $3k_1/k_2$. Subscripts 1 and 2 refer to the numbering of the carbon chain in 2,3-dichlorobutane. [b] $k(meso)/k(dl) = [3k_1(meso) + k_2(meso)]/[3k_1(dl) + k_2(dl)]$. [c] Numbers in parentheses are the numbers of of independent experiments, each analyzed in triplicate. [d] Assumed.

radicals $ArICl^\bullet$ had values $k(exo)/k(endo)$ in the range 1.8-3.8. Abstraction by $Cl^\bullet$ from the same substrate was almost unselective, $k(exo)/k(endo) = 1.1 \pm 0.3$. Our interest in this stereochemical problem was sparked by the report of Lukas et al.,[2] who found that when a mixture of 2,4-dichloropentane isomers was photochlorinated, the *dl* isomer reacted slightly faster than the *meso*. Quantitative treatment[3] of the original data gave $k(dl)/k(meso) = 1.03$ for the overall hydrogen abstraction by $Cl^\bullet$ from these molecules. In this paper we examine the effect of neighboring chiral centres in the chlorination of 2,3-dichlorobutane by elemental chlorine and by *tert*-butyl hypochlorite. This substrate is easier to study than 2,4-dichloropentane because each dichlorobutane isomer has only two products of further monochlorination.

Experimental Section

All chlorinations were done in CCl_4 solvent at substrate concentrations <0.5 M using photoinitiation at room temperature (ca. 22 °C). Samples (2.0 mL) were sealed in vacuo into 8 mm o.d. Pyrex ampules by using the freeze-pump-thaw technique. In the experiments done in the presence of $CaCO_3$, the end of the ampule was blown out to give a round bulb, so that a micro magnetic stirring bar could be used to stir the mixture. All reaction mixtures were made up by mixing appropriate volumes of stock solutions of the reactants. For experiments where products were to be analyzed the ratio of substrate to chlorinating agent was always >10. Reaction mixtures were analyzed by VPC using gas chromatographs equipped with FID and electronic integration (Carle model 211 GC and Hewlett-Packard Model 3390 integrator or Carle Model 9500 GC and Spectraphysics "Minigrator"). VPC columns were 10% SE 30 on 60/80 mesh acid-washed Chromosorb W. Experiments were done at least in duplicate and were normally analyzed in triplicate. The response of the FID was assumed to be equal toward isomers.

tert-Butyl hypochlorite[4] and the separate isomers of 2,3-dichlorobutane[5] were obtained by the literature methods. Their purities by VPC were *dl* 96% and *meso* 97%. The mixed 2,3-dichlorobutane isomers were obtained commercially (Aldrich). The trichlorobutanes were obtained by chlorination, isolated by preparative VPC (elution order 2,2,3-trichlorobutane and then 1,2,3-trichlorobutane; the erythro and threo isomers of 1,2,3-trichlorobutane were not separable under our conditions), and analyzed by proton NMR at 400 MHz, using $CDCl_3$ as the solvent.[6]

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$$k_A/k_B = \ln ([A_o]/[A])/\ln ([B_o]/[B]) \quad (1)$$

$[A_o]$ and $[B_o]$ are the starting concentrations, and [A] and [B] are the concentrations after reaction.

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Table II. Chlorination of 2-Chlorobutane[a]

chlorinating agent	rel selectivity per hydrogen			
	CH_3–	–CHCl–	$-CH_2$[d]	$-CH_3$
Cl_2,[b] 25 °C	0.29	2.3	2.5	1.0
Cl_2,[c] 22 °C	0.20	1.5	2.3	1.0
t-BuOCl,[c] 22 °C	0.26	33.4	5.4	1.0

[a] In CCl_4. [b] Reference 8. [c] This work; average of four runs each. We note that even at a 20:1 ratio of 2-chlorobutane to the chlorinating agent, about 3–4% of the product consisted of trichlorobutanes. This is presumably a cage effect; cf.: Skell, P. S.; Baxter, H. W. *J. Am. Chem. Soc.* **1985**, *107*, 2823. [d] Sum of *meso* and *dl* isomers.

2,2,3-Trichlorobutane: δ 1.80 (d, 3 H, J = 6 Hz), 2.25 (s, 3 H), 4.26 (q, 1 H, J = 6 Hz). *erythro*-1,2,3-Trichlorobutane ($CH_3^aCH^bClCH^cClCH_2^{d,e}Cl$): δ 1.67 (d, 3 H, J = 6.5 Hz, H(a)), 3.82 (dd, 1 H, J_1 = 5 Hz, J_2 = 12 Hz, H(d) or H(e)), 4.00 (dd, 1 H, J_1 = 4.5 Hz, J_2 = 12 Hz, H(d) or H(e)), 4.10 (ddd, appears as dt, 1 H, $J_1 = J_2$ = 5 Hz, J_3 = 7 Hz, H(c)); 4.30 (dq, appears as quintet, 1 H, $J_1 = J_2$ = 7 Hz, H(b)). *threo*-1,2,3-Trichlorobutane: δ 1.64 (d, 3 H, J = 7 Hz, H(a)), 3.73 (dd, 1 H, J_1 = 5 Hz, J_2 = 11 Hz, H(d) or H(e)), 3.88 (approximately t, 1 H, J = 9–11 Hz, H(d) or H(e)), 4.04 (ddd, 1 H, J_1 = 2 Hz, J_2 = 5 Hz, J_3 = 9 Hz, H(c)), 4.58 (dq, J_1 = 2 Hz, J_2 = 7 Hz, H(b)).

Results and Discussion

Table I shows (a) the isomer ratios obtained by chlorinating the separate stereoisomers of 2,3-dichlorobutane, (b) the relative rates of disappearance of *meso*- and *dl*-2,3-dichlorobutanes obtained by chlorinating the mixture competitively,[3] and (c) the relative rate constants for attack on the different hydrogens of each isomer, obtained from a and b. The latter are normalized to the reactivity of a single methyl hydrogen of the *meso* isomer taken as unity. The chlorinations involving *tert*-butyl hypochlorite were done in the presence of 0.1 M trichloroethylene.[7] It is clear that a significant stereochemical effect is operating in these chlorinations; both chlorinating agents afford a much greater proportion of 2,2,3-trichlorobutane when the substrate to be chlorinated is the meso isomer.[9]

The selectivity of an abstracting radical for methyl and CHCl hydrogens in 2,3-dichlorobutane is a complicated affair. Polar effects deactivate positions close to the chloro substituent, while resonance effects promote abstraction specifically of the CHCl hydrogen.[10] Thus in 2,3-dichlorobutane, the CH_3 hydrogens are deactivated, while the CHCl hydrogens are activated by resonance with the geminal chlorine and deactivated by the polar effects of both the geminal and vicinal chlorines. To try to assess a "normal" behavior for the CH_3CHCl group, we examined 2-chlorobutane (Table II). As expected, the CHCl group of 2-chlorobutane (which lacks the deactivating chlorine at C(3)) is more readily attacked relative to the methyl hydrogens at C(1) in comparison with 2,3-dichlorobutane.

We had hoped to ascribe the stereochemical differences for hydrogen abstraction from *meso*- and *dl*-2,3-dichlorobutanes to the conformational preferences of these molecules. This was not possible. Many papers have been written on the conformational analysis of 2,3-dichlorobutane, but there is much disagreement on the subject.[11-16] For the *meso* isomer it is accepted that the anti conformer is most stable, with the gauche pair of conformers <10 kJ mol^{-1} higher in energy. For the *dl* isomer it is not even clear which conformation is preferred and the three conformers are separated by perhaps as little as 5 kJ mol^{-1}.[16] Since Bell, Perkins, and Perkins[17] have calculated the activation energies (in the gas phase) for abstraction of CH_3CHCl and CH_3CHCl hydrogens by Cl· to be ≥20 kJ mol^{-1}, we see that no simple rationalization of our data in terms of ground-state conformational preference is possible.

We attempted to normalize our relative rate constants (Table I) against 2,2,3,3-tetramethylbutane, for which the rate of hydrogen abstraction by Cl· is known absolutely.[18] When the competitive loss technique was used, the relative reactivities $k(C_8H_{18})/k(C_4H_8Cl_2)$ but not those $k(meso)/k(dl)$ varied with percent conversion. This effect was shown not to be due to the HX reversal reaction[19] (eq 1).

$$R\cdot + HX \rightarrow RH + X\cdot \quad (1)$$

Thus in the reactions with Cl_2, the reactivities were unchanged either by adding HCl deliberately to the reaction or by removing the HCl chemically with powdered $CaCO_3$. Likewise when *tert*-butyl hypochlorite was the chlorinating agent the relative reactivities were unaffected by adding *tert*-butyl alcohol to the reaction mixtures. When the appearance of products in competitive chlorination was studied in order to extrapolate to zero conversion, an unexpected result was obtained: only the chlorination products of tetramethylbutane could be detected, even at conversions high enough to cause a noticeable loss of 2,3-dichlorobutane.

At this stage in our work, the mechanism of chlorination of 2,3-dichlorobutane is not completely defined. Hydrogen abstraction from 2,3-dichlorobutane affords the alkyl radicals **1** and **2**, and in the simplest view, the distributions of trichlorobutanes from the diastereomeric 2,3-dichlorobutanes reflects the relative rates of formation of radicals **1** and **2**. Besides direct reaction with Cl_2, radicals **1** and

$$\underset{\mathbf{1}}{\cdot CH_2CHClCHClCH_3} \qquad \underset{\mathbf{2}}{CH_3\dot{C}ClCHClCH_3}$$

2 can also afford trichlorides by elimination/addition or by chlorine atom migration followed by direct reaction with Cl_2. However, the intervention of these reactions still leads to 1,2,3-trichlorobutane from **1** and 2,2,3-trichlorobutane from **2**.[20]

In conclusion, we have observed for the first time that the abstraction of hydrogen from 2,3-dichlorobutane is affected by the stereochemistry of adjacent chiral centres.

(6) Formation of *erythro*-1,2,3-trichlorobutane from *meso*-2,3-dichlorobutane was stereospecific, but the *threo*-1,2,3-trichlorobutane obtained from *dl*-2,3-dichlorobutane contained ca. 15% of the erythro isomer. This loss of stereospecificity seems to suggest that Cl· migration or elimination/addition reactions are occurring (see Results and Discussion).

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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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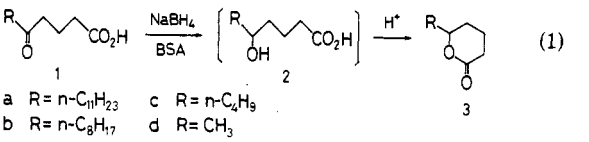
The asymmetric reduction of the prochiral carbonyl group of δ-keto acids attracts interest because it is a key step for the facile synthesis of optically active δ-lactones. The asymmetric reduction of prochiral ketones has been studied extensively,[1] and considerable success has been attained especially 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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