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Enzyme Catalyzed Asymmetric Hydrolysis of Chloral Acetyl Methyl Acetal

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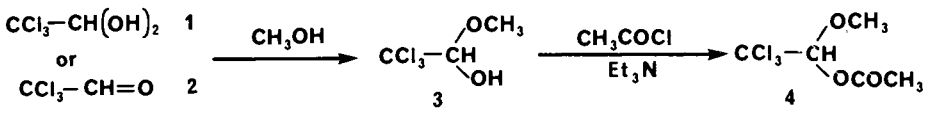
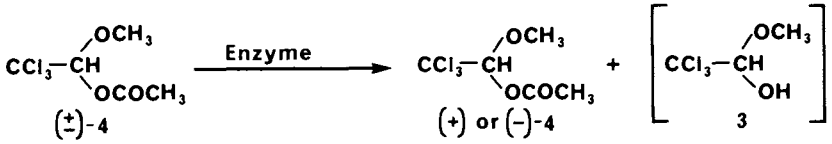
Hydrolysis of racemic chloral acetyl methyl acetal using lipase from Candida cylindraceae, porcine pancreatic lipase or cholesterol esterase gives the optically pure (-)-enantiomer whereas hydrolysis using subtilisin gives the pure (+)-enantiomer.

The presence of two functional groups, carbonyl and trichloromethyl, and their mutual activating influences, gives to chloral a distinctive and diversified reactivity.[1] Unlike most aldehydes, it reacts with water to give a stable hydrate. Chloral has also several industrial applications.[1,2] For instance, chloral is used in the synthesis of several pesticides and polymers. Chloral hydrate is a hypnotic-sedative and chloral derivatives, mostly hemiacetals, are used as prodrugs.[3] We report here the enzyme catalyzed asymmetric hydrolysis of chloral acetyl methyl acetal 4 (2,2,2-trichloro-1-methoxy-ethyl acetate).

Compound 4 was prepared from chloral hydrate 1 or chloral 2 according to a known procedure (Eq. 1).[4] The general procedure for enzymatic hydrolyses is the following: acetal 4 (333 mg, 1.5 mmol) was suspended in a buffered aqueous solution (50 ml, 0.05 M phosphate, pH 7) at 25 °C, in a closed flask. The enzyme[5] was added and the reaction was indicated by the decrease of pH, which was maintained at its initial value by the addition of NaOH (0.1 M) from a burette. The reaction was monitored by the consumption of the base and terminated when 50% of the ester was hydrolysed. The mixture was extracted at pH 7 with ether (3 x 50 ml) to remove the unchanged ester. Ether extracts were washed with aqueous $NaHCO_3$, dried and evaporated. The ester was purified by distillation. Details pertaining to each enzyme are the following: lipase from Candida cylindraceae (CCL, 99 mg), time (61 min); cholesterol esterase (CE, 23 mg), time (50 min); lipase from porcine pancreas (PPL, 202 mg), time (17 h); lipase from wheat germ (WGL, 77 mg), time (4.2 h); subtilisin (70 mg), time (17 h); acetylesterase



(1)



(2)

Table 1. Enzyme catalyzed hydrolysis of chloral acetyl methyl acetal 4

Enzyme	Conversion/%	Recovered ester (4)		
		Yield/%	e.e./%	Sign of $[\alpha]_D$
Lipase (CCL)	50	77	>97	(-)
Cholesterol esterase (CE)	50	80	>97	(-)
Lipase (PPL)	50	63	>97	(-)
Acetylesterase	50	72	68	(-)
Esterase (PLE)	50	73	92	(-)
Lipase (WGL)	50	51	70	(-)
Subtilisin	50	60	>97	(+)
Chymotrypsin	50	70	41	(+)

(500 µl), time (4.25 h), a phosphate buffer solution pH 6 was used in this case; chymotrypsin (100 mg), time (50 h), pH 7.7; pig liver esterase (PLE, 300 µl), time (40 h). Enantiomeric excess (e.e.) values were determined by ^{1}H nmr (200 MHz) analysis using Eu(hfc)$_3$ as a chiral shift reagent. Well resolved signals of both enantiomers were obtained for the acetyl methyl protons; the accuracy of this method is ±3%. The hemiacetal 3 (Eq. 2) is unstable in the medium and is in equilibrium with chloral hydrate 1 and chloral 2. Recovery yields of 4 ranged from 50-80% of the amount estimated to be present based on acid released. The results are summarized in Table 1. CCL, PPL and CE were enantiospecific and gave (-)-4 in high optical yield (ee > 97%). Hydrolyses in the presence of WGL, PLE or acetylesterase gave the same enantiomer with a lower selectivity (ee= 68-92%). Subtilisin, a serine protease, was also enantiospecific but gave the other enantiomer ((+)-4, ee > 97%). Chymotrypsin, another serine protease, gave the same enantiomer ((+)-4) but the reaction was slow and the ee value was low (ee=41%). By exploiting the different specificities of subtilisin and esterases, both enantiomers can be obtained in high optical yield. The specific rotation $[\alpha]_D^{23}$ of compound 4 is 6.4 ± 0.2° (c 1, $CHCl_3$).

This reaction is a good illustration of the potential of hydrolases for resolution of compounds very different from their natural substrates. As far as we know this is the first resolution of compound 4 and the first resolution of an acyclic acyl alkyl acetal. Mention has been made of the preparation of (-)-4 by acetalyzation-acetylation of chloral with methanol-acetic anhydride in the presence of (S)-(-)-PhCHMeNMe$_2$ in low optical purity (ee=11%).[6)]

References

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5) CCL (EC 3.1.1.3, type VII), CE (EC 3.1.1.13, from bovine pancreas), PPL (EC 3.1.1.3, type II), WGL (EC 3.1.1.3, type I), subtilisin (EC 3.4.21.14, type VIII), acetylesterase (EC 3.1.1.6, from orange peel), chymotrypsin (EC 3.4.21.1, type II) and PLE (EC 3.1.1.1, type 1) were purchased from Sigma.
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