Pergamon

Tetrahedron Letters 39 (1998) 635–638

TETRAHEDRON LETTERS

Lipase-Mediated Diastereoselective and Enantioselective Acetylations of 3-Substituted Cyclohexanols

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Received 16 September 1997; revised 17 November 1997; accepted 21 November 1997

Abstract: Lipase-mediated acetylation of four diastereomeric and enatiomeric isomers of 3-substituted cyclohexanols **2** has led to an efficient resolution to provide a single stereoisomer, (1*R*,3*S*)-cyclohexyl acetate (1*R*,3*S*)-**3** in a high enantiomeric excess.

Kinetic resolutions of alcohols utilizing a lipase have been widely used to obtain chiral building blocks, because it is cheap, versatile, and easy to perform.[1] Since enantiomerically pure cycloalkane ring system is a common feature in a wide variety of natural products, lipase-mediated acylations are frequently used in resolutions of cycloalkanediols. In addition, enantioselective hydrolysis of *trans*-2-phenylcyclohexyl acetate[2] and *trans*-2-*t*-butylcyclohexyl chloroacetate[3] using porcine liver esterase have been reported. Recently lipase PS is employed in the kinetic separation of a diastereomeric mixture of the acetates derived from 4-*t*-butylcyclohexylmethanols.[4] Although enantioselective hydrolysis of 3-methyl-1-cyclohexenyl acetate with porcine liver esterase has been described,[5] there is no report on the kinetic resolution of 3-substituted cyclohexanols. Here we report that a lipase is applicable to the ready separation of a mixture of diastereomeric and enantiomeric cyclohexanols **2** containing a subsutituent at C-3.

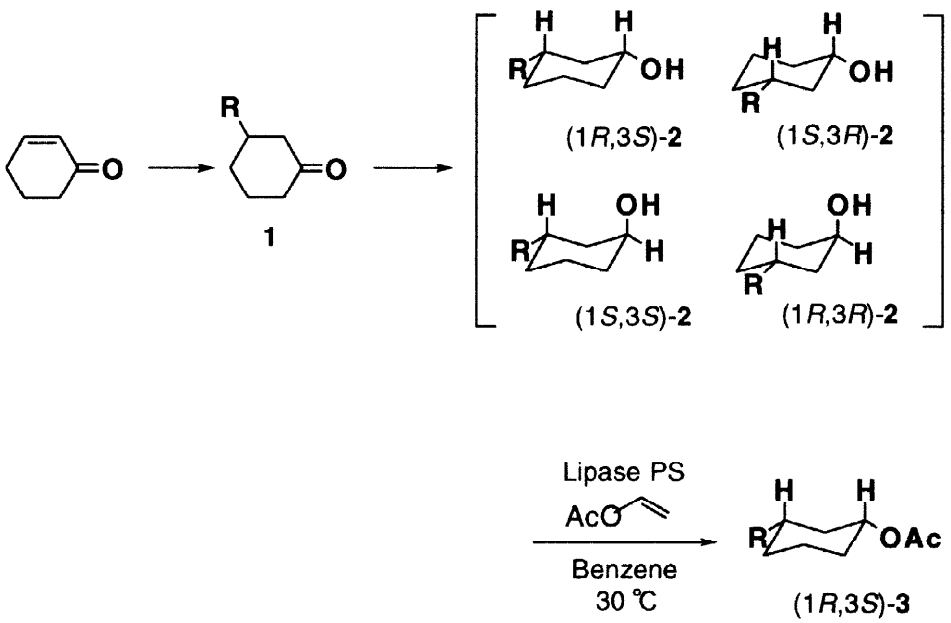
The base-catalyzed 1,4-addition of nitromethane, 2-nitro-2-propane, and benzenethiol to 2-cyclohexenone readily gave cyclohexanones **1a-1c**, respectively, and subsequent oxidation of **1c** quantitatively afforded **1d**. Treatment of 2-cyclohexenone with Grignard reagents in the presence of CuI generated cyclohexanones **1e-1g** in high yields.

At first we prepared cyclohexanols (1*R**,3*S**)-**2** and (1*R**,3*R**)-**2** by reduction of **1** with $NaBH_4$, followed by separation of the diastereoisomeric products using column chromatography. Treatment of equatorial alcohols (1*R**,3*S**)-**2** with lipase PS (Amano) and vinyl acetate led to enantioselective acetylation to provide acetates (1*R*,3*S*)-**3** in high e.e., whereas the similar acetylation of axial alcohols (1*R**,3*R**)-**2** did not result in efficient resolution. For example, when (1*R**,3*S**)-3-benzylcyclohexanol (1*R**,3*S**)-**2g** in benzene was treated with vinyl acetate and lipase PS at 30 ℃ for 6.5 h, (1*R*,3*S*)-3-benzylcyclohexyl acetate (1*R*,3*S*)-**3g** was obtained in 48% yield (>97% e.e.). On the other hand, in the similar acetylation of (1*R**,3*R**)-3-

0040-4039/98/$19.00
PII: S0040-4039(97)10705-5

benzylcyclohexanol (1*R**,3*R**)-**2g** the time taken to reach 50% conversion was 130 h, and after that time (1*R*,3*R*)- 3-benzylcyclohexyl acetate (1*R*,3*R*)-**3 g** was isolated in 43% yield (75% e.e.).

Therefore, (1*R*,3*S*)-**3** may be prepared readily by a combination of two procedures, the reduction of **1** with a small hydride reagent and the subsequent acetylation using lipase and vinyl acetate.



Typical procedure: To a stirred solution of 3-benzylcylohexanone **1g** (2 mmol) in methanol (10 ml) was added $NaBH_4$ (1 mmol) at 0 ℃ and the resulting mixture was stirred for 1 h at room temperature before being quenched with water. The aqueous phase extracted with ethyl acetate, and the organic phase was washed with brine and dried. Evaporation of solvents left a viscous residue containing (1*R**,3*S**)-**2 g** and (1*R**,3*R**)-**2 g** [(1*R**,3*S**)/(1*R**,3*R**)=78/22]. Without further purification the crude mixture of **2g** was dissolved in benzene (10 ml), and to the resulting solution was added lipase PS (Amano, 0.3 g), vinyl acetate (1.0 mmol) and molecular sieves 4A (1.0 g). The mixture was then stirred at 30 ℃ for 6.5 h, and the reaction was terminated by filtration of the enzyme. The filtrate was washed with brine, dried, and freed of the solvent. Purification by column chromatography [silica gel, eluent hexane-ethyl acetate (4:1)] afforded (1*R*,3*S*)-**3g** (35 % yield, >97% e.e.), (1*S*,3*R*)-**2g** (31% yield, 88% e.e.[6]), and (1*R**,3*R**)-**2g** (19% yield).

In a similar manner described above, the acetates (1*R*,3*S*)-**3** were isolated as a major product, while the enantiomer remained as the alcohols (1*S*,3*R*)-**2** (26-34% yield), and the axial alcohols (1*R**,3*R**)-**2** were almost recovered unchanged (15-20% yield). Acetylation was terminated after 45-55% conversion of (1*R**,3*S**)-**2**, and e.e. of (1*R*,3*S*)-**3** was determined by HPLC analysis using chiral column (CHIRALPAK OB-H or OD-H). These results are shown in **Table 1**.

Table 1. Preparation of (1*R*,3*S*)-**3**

	R	ax/eq[a]	time (h)[b]	yield (%)[c]	e.e. (%)[d]	$[\alpha]_D^{23}$ (MeOH)
a	CH_2NO_2	20/80	4.5	37	86	-4.8
b	CMe_2NO_2	22/78	25.0	31	>97	-3.7
c	SPh	12/88	5.0	42	>97	-1.5
d	SO_2Ph	12/88	48.0	32	>97	-2.5
e	*n*-Bu	22/78	4.5	38	65	-3.4
f	Ph	21/79	7.5	36	>97	-4.5
g	Bn	22/78	6.5	35	>97	-3.6

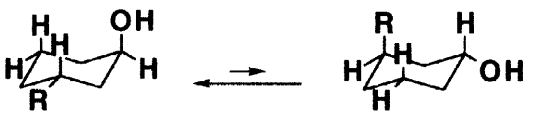
a, Axial (1*R**,3*R**) / equatorial (1*R**,3*S**) ratio of the alcohol **2** obtained by reduction of **1**.
b, Reaction time for lipase-mediated acylation. *c*, Isolated total yield based on **1**.
d, Determined by HPLC using chiral column.

The relative configurations of (1*R*,3*S*)-**3** were determined by observation of NOE between *H*-C(OAc) and *H*-CR in the NMR spectra. The absolute configurations possessing the (*R*)-configuration at the alcoholic center (C-1) were estimated on the basis of the "Kazlauslas-rule",[1e,7] and moreover, those of (1*R*,3*S*)-**3a,c,d,e** were confirmed by comparison of their enantiomers (1*S*,3*R*)-**3a,c,d,e** prepared according to the literature procedures. Asymmetric 1,4-addition of nitromethane to 2-cyclohexenone catalyzed by the rubidium salt of L-proline[8] yielded (3*R*)-3-(nitromethyl)cyclohexanone, and the subsequent reduction with $NaBH_4$ gave a mixture of diastereoisomeric (1*S*,3*R*)-3-(nitromethyl)cyclohexanol (1*S*,3*R*)-**2a** (71% e.e.) and (1*R*,3*R*)-3-(nitromethyl)cyclohexanol (1*R*,3*R*)-**2a** (71% e.e.). In a similar fashion to that described above treatment of 2-cyclohexenone with benzenethiol gave (3*R*)-3-(phenylthio)cyclohexanone,[9] followed by reduction generating (1*S*,3*R*)-**2c** (6% e.e.). Oxidation of this sulfide (1*S*,3*R*)-**2c** led to formation of the corresponding sulfone (1*S*,3*R*)-**2d**. Authentic acetates (1*S*,3*R*)-**3a,c,d** were obtained by acetylation of the corresponding alcohols (1*S*,3*R*)-**2a,c,d**. In the presence of optically active aminoalcohol and CuI[10] treatment of 2-cyclohexenone with *n*-butyllithium gave (3*R*)-3-butylcyclohexanone, which was then transformed to (1*S*,3*R*)-**3e** (85% e.e.) by a combination of the reduction and the acetylation as described above.

The present findings suggest that the resolution arises from differentiation at the C-1 position, and is not influenced by the polarity of a substituent at the C-3 position. If the yield of (1*R**,3*S**)-**2** in the reduction stage is increased, the overall yield of (1*R*,3*S*)-**3** will approach 50%.

Calculation (MM-2) suggests that a group R is located dominantly at the equatorial position, for example, the

the CH_2NO_2-equatorial conformation of (1*R**,3*R**)-**2a** is favored by 9:1. In the lipase-mediated acetylation of the major conformer (1*R*,3*R*)-**2** binding of the axial OH group to Amano-PS might be prevented by the 1,3-diaxial interaction, and hence the minor conformer (1*R*,3*R*)-$\mathbf{2}_{\text{eq-OH}}$ plays an important role. The acetylation of (1*R**,3*R**)-**2** is assumed to be affected by the rate of conformational inversion in two conformers. However, at present we cannot exclude the mechanism that an axial OH group of (1*R*,3*R*)-**2** or an axial R group in (1*R*,3*R*)-$\mathbf{2}_{\text{eq-OH}}$ takes part in binding to the lipase.



(1*R*,3*R*)-**2** (1*R*,3*R*)-$\mathbf{2}_{\text{eq-OH}}$

Details on the lipase-mediated acetylations of axial and equatorial alcohols under various conditions will be reported in the near future.

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