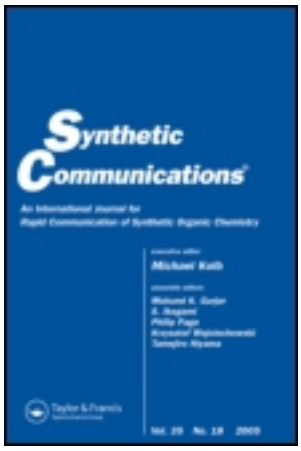

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Chemo-enzymatic Preparations of (*R*)- and (*S*)-3-Iodocyclohex-2-en-1-yl Acetate

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ABSTRACT

Kinetic resolutions by lipase-catalyzed transesterification with 3-iodocyclohex-2-en-1-ol or 3-iodocyclohex-2-en-1-yl acetate followed by inversion of the chirality of the optically active alcohol without separation from the acetate have allowed the preparation of (*R*)- and (*S*)-3-iodocyclohex-2-en-1-yl acetate with more than 70% yield and more than 85% ee.

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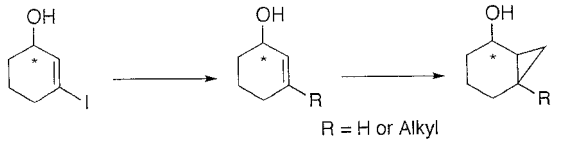
INTRODUCTION

Optically active 3-iodocyclohex-2-en-1-ols may be regarded as chirons in the sense proposed by E. J. Corey. They were used to prepare enantiomerically enriched unsubstituted and 3-substituted cyclohex-2-en-1-ols[1–3] and also optically active *endo*-bicyclo[4.1.0]hexan-2-ol derivatives[3] (Sch. 1).

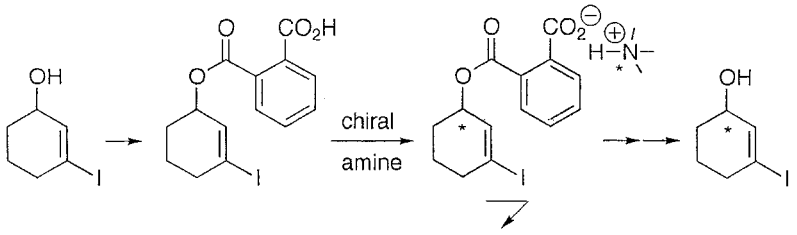
Optically active (*R*)- and (*S*)-3-iodocyclohex-2-en-1-ol have been prepared[1] after resolution of the corresponding racemic phthalic half ester, by preferential crystallization of the salt obtained from (*S*)-phthalate and cinchonine (3–4 days) or that obtained from (*R*)-phthalate and cinchonidine (2–3 days). In both cases a diastereomerically pure salt was obtained after four recrystallizations. Treatment of these salts with acidic medium and reaction with $LiAlH_4$ of the phthalic half esters delivers the enantiopure (*R*)- and (*S*)-3-iodocyclohex-2-en-1-ol[4] (Sch. 2).

This article concerns a faster enzymatic method to prepare optically active 3-iodocyclohex-2-en-1-ols.

To our knowledge the preparation of optically active 3-iodocyclohex-2-en-1-ol by lipase-catalyzed resolution or by treatment of 3-iodocyclohex-2-en-1-one with a chiral reducing agent has not been reported. A close analogue to this iodocyclohexenol is probably 3-bromocyclohex-2-en-1-ol. Reduction of 3-bromocyclohex-2-en-1-one with complexes of $LiAlH_4$ with DARVON or NOVRAD alcohols allows the preparation of



Scheme 1.



Scheme 2.

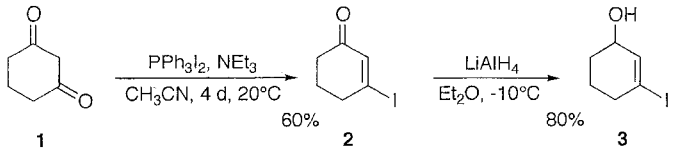
optically active 3-bromocyclohex-2-en-1-ol with, at best, 60% enantiomeric excess.[5] The (*R*)- and (*S*)-3-bromocyclohex-2-en-1-ol were prepared with higher enantiomeric excesses ($ee \leq 79\%$) when the corresponding racemic chloroacetate was subjected to hydrolysis in the presence of lipase P-30.[4] The enantiomeric ratio (E) of this reaction, calculated from the reported enantiomeric excess of the product (ee_p) and that of the remaining chloroacetate (ee_s), was about 21.[6] A higher enantiomeric ratio ($E = 44$) was reported for the transesterification of vinyl acetate with this 3-bromocyclohexenol in the presence of lipase from *Pseudomonas cepacia* immobilized on Hyflo Supercel.[7]

The transesterification of isopropenyl acetate with 2-iodocyclohex-2-en-1-ol afforded a lower enantioselectivity ($E = 50$) when using the lipase from *Pseudomonas cepacia* as compared to the immobilized recombinant *Candida antarctica* lipase B ($E \geq 450$).[8] Therefore we decided to try the resolution of 3-iodocyclohex-2-en-1-ol by enzymatic reaction using the lipase B from *Candida antarctica*.

RESULTS AND DISCUSSION

Racemic 3-iodocyclohex-2-en-1-ol **3** was prepared by $LiAlH_4$-mediated reduction of 3-iodocyclohex-2-en-1-one **2**,[1] itself obtained by treatment of commercial cyclohexan-1,3-dione **1** with triphenylphosphine diiodide and triethylamine in acetonitrile[9] (Sch. 3)

Transesterification of isopropenyl acetate with 3-iodocyclohexenol **3** was performed at 37°C in *tert*-butyl methyl ether in the presence of Novozym®[10] (62% weight based on alcohol) and the conversion (c) was monitored by ^{1}H-NMR. After 55 min ($c \sim 50\%$) the reaction was stopped by removal of the enzyme by filtration, and the unreacted iodocyclohexenol **3-(*S*)** and the iodocyclohexenyl acetate **4-(*R*)** were separated by silica gel column chromatography. The absolute configuration of the major enantiomers of these optically active compounds was attributed by comparison of the chiroptical properties of **3-(*S*)** with those described in the literature.[2] The enantiomeric excess (ee_s) of alcohol **3-(*S*)** was



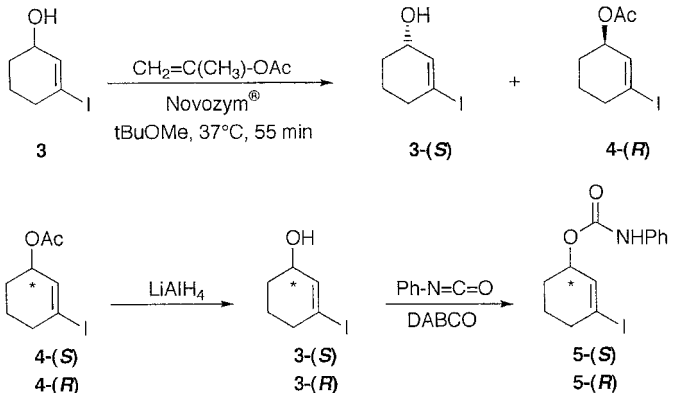
Scheme 3.

determined by HPLC using a chiral column (Pharmachir 4C) of the phenylcarbamate **5-(*S*)** obtained by reaction of this alcohol with phenyl isocyanate in the presence of DABCO. Enantiomeric excess (ee_p) of acetate **4-(*R*)** was measured by the same method as above after treatment with $LiAlH_4$ to deliver the corresponding alcohol **3-(*R*)** and formation of the phenylcarbamate **5-(*R*)**[11] (Sch. 4).

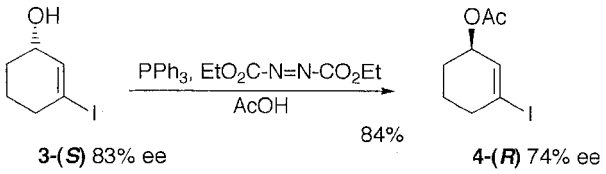
Enantiomeric excess of the isolated 3-iodocyclohexenol **3-(*S*)** (46% yield) and that of the iodocyclohexenyl acetate **4-(*R*)** (42.5% yield) were respectively 83% and 94%. Using the usual formulas[6] it was calculated that the transformation was stopped when c was equal to 47% and *E* of the reaction was approximatively 84.

When the objective is the preparation of one enantiomer of this class of secondary alcohol by resolution, the major drawback is the loss of half of the starting racemic mixture. One way to overcome this limitation is to perform an inversion at the chiral centre of one of the optically active compounds.[12] Inversion of chirality of the alcohol **3-(*S*)** (83% ee) by the Mitsunobu method[13] using acetic acid allowed the isolation of the iodocyclohexenyl acetate **4-(*R*)** with 74% ee (Sch. 5).

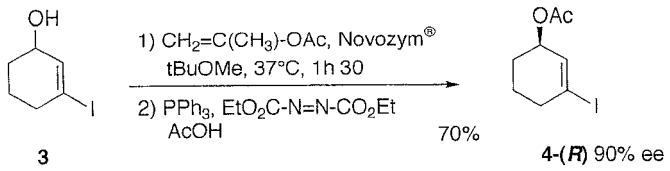
Although this inversion occured with some loss of the enantiomeric excess, a more convenient sequence to prepare the optically active ester **4-(*R*)** was envisaged owing to the high enantioselectivity of the enzymatic reaction. By performing the lipase-catalyzed transesterification with a conversion slightly greater than 50%, an optically active alcohol with a higher enantiomeric excess could be obtained, followed by an inversion of alcohol chirality without separation from the optically active acetate.



Scheme 4.



Scheme 5.

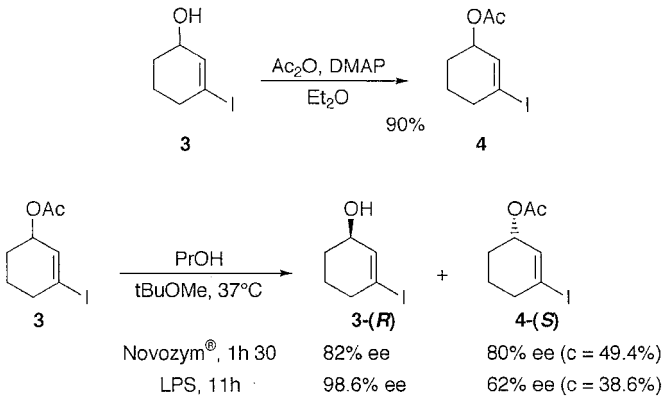


Scheme 6.

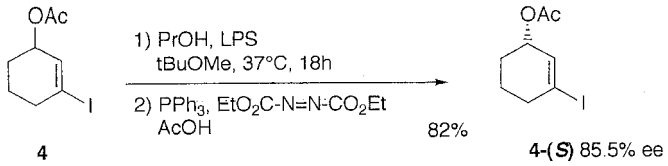
Transesterification of isopropenyl acetate with iodocyclohexenol **3** in the presence of Novozym® was performed for 90 min. The crude mixture of optically active alcohol **3-(*S*)** and ester **4-(*R*)** was treated as above by the Mitsunobu method with acetic acid. The iodocyclohexenyl acetate **4-(*R*)** was isolated in 70% yield and high enantiomeric excess (90%) after only one chromatographic purification for this two steps sequence (Sch. 6).

In order to prepare selectively the iodocyclohexenyl acetate **4-(*S*)** by a lipase-catalyzed reaction/inversion of alcohol chirality sequence, we decided to attempt the transesterification of the racemic acetate **4** with propan-1-ol in the presence of a lipase. The racemic ester **4** was easily prepared by treatment of alcohol **3** with acetic anhydride in the presence of 4-dimethylaminopyridine (DMAP). The calculated enantiomeric ratio ($E = 25$) of the Novozym®-catalyzed reaction seemed too low to obtain the desired ester with a good enantiomeric excess after the Mitsunobu reaction. With the lipase from *Pseudomonas cepacia* (LPS) (170% weight based on ester) the reaction was much slower and the enantioselectivity was higher ($E = 267$) (Sch. 7).

Transesterification of iodocyclohexenyl acetate **4** with propan-1-ol in the presence of LPS was performed for 18 h. After treatment of the crude reaction mixture with acetic acid using the Mitsunobu method and silica gel chromatography, the iodocyclohexenyl acetate **4-(*S*)** was isolated in 82% yield and 85.5% enantiomeric excess (Sch. 8).



Scheme 7.



Scheme 8.

It is notable that a single recrystallization of the phenylcarbamate **5-(*S*)** prepared from the acetate **4-(*S*)** afforded an increase in the enantiomeric excess from 85.5% to 99.7%.

EXPERIMENTAL PART

3-iodocyclohex-2-en-1-one **2**[8] and 3-iodocyclohex-2-en-1-ol **3**[2] were prepared as reported in the literature. Dry solvents were obtained as follows: diethyl ether was distilled over $LiAlH_4$ and THF over sodium-benzophenone radical-anion, *tert*-butyl methyl ether was filtered through a pad of basic alumina (activity I).

Preparation of Racemic 3-Iodocyclohex-3-en-1-yl Acetate 4

To a solution of 168 mg of iodocylohexenol **3** (0.75 mmol) in 2 mL of ether maintained under argon atmosphere were added 80 μL of acetic

anhydride (0.80 mmol) and 12 mg of DMAP (0.1 mmol). After stirring for 1 h the solvent was evaporated under reduced pressure and a silica gel column chromatography (pentane/ether: 95/5) provided 180 mg of 3-iodocyclohex-3-en-1-yl acetate **4** (90%). IR (film) (cm^{-1}): 1735 ($\nu_{C=O}$), 1634 ($\nu_{C=C}$). ^1H NMR (200 MHz, $CDCl_3$) δ: 6.49–6.00 (m, 1H, –CH=), 5.72–5.62 (m, 1H, CH-OAc), 2.70–2.48 (m, 2H), 2.07 (s, 3H), 2.00–1.59 (m, 4H). ^{13}C NMR (63 MHz, $CDCl_3$) δ: 170.27 (–C=O), 135.50 (–CH=), 103.74 (–CI=), 69.25 (CH-O), 39.17, 26.66, 21.33, 21.11. Anal. calcd. for $C_8H_{11}IO_2$: C, 36.10; H, 4.13; O, 12.03. Found: C, 36.35; H, 4.23; O, 11.81.

Preparation of (*R*)-3-Iodocyclohex-3-en-1-yl Acetate 4-(*R*)

Thirty milligrams of Novozym® were added to a solution of 115 mg of alcohol **3** (0.50 mmol) and 0.1 mL of isopropenyl acetate (0.91 mmol) in 1.5 mL of tBuOMe and the mixture was shaken for 90 min at 37°C. The immobilized enzyme was removed by filtration and washed with tBuOMe. The filtrate was concentrated under reduced pressure, the remaining mixture of optically active alcohol **3-(*S*)** and acetate **4-(*R*)** was diluted with 1 mL of ether and a solution of 68 mg of triphenylphosphine (0.26 mmol) in 1 mL of ether was added. A solution of 45 mg of DEAD (0.26 mmol) and 16 mg of acetic acid (0.26 mmol) in 1 mL of ether was subsequently added dropwise at 20°C and allowed to react for 1 h. The solvent was removed under reduced pressure and 4 mL of a mixture ether/pentane (1/1) were added. The suspension was filtered and the solvent was removed under reduced pressure. Silica gel column chromatography (pentane/ether: 95/5) of the crude product provided 94 mg of the purified acetate **4-(*R*)** (70%), $[\alpha]_D^{20} +$ 132 ($c = 1.90$, THF).

Preparation of (*S*)-3-Iodocyclohex-3-en-1-yl Acetate 4-(*S*)

Zero point four four millimolar of acetate **4** was treated with 200 mg (2.66 mmol) of dry propan-1-ol and 200 mg of LPS in 2 mL of dry tBuOMe at 37°C. After 18 h stirring, the crude enzyme was removed by filtration, washed with tBuOMe and the solvent was evaporated under reduced pressure. The remaining product was diluted in 1 mL of ether and 64 mg of triphenylphosphine (0.24 mmol) were added followed

by a solution of 43 mg of DEAD (0.24 mmol) and 15 mg of acetic acid (0.24 mmol) in 1 mL of ether. This was allowed to react for 1 h at 20°C. After evaporation of the solvent, precipitation and separation of triphenylphosphine oxide as above, the crude product was purified by silica gel column chromatography (pentane/ether: 95/5) to provide 95.5 mg of the acetate **4-(*S*)** (82%), $[\alpha]_D^{20}$ −130.5 ($c = 1.04$, THF).

Synthesis of 3-Iodocyclohex-3-en-1-ol 3-(*R*) or 3-(*S*) from Acetates 4-(*R*) and 4-(*S*)

A solution of 80 mg of acetate (0.3 mmol) in 1 mL of ether was added dropwise with a syringe at 20°C to a solution of 10 mg of $LiAlH_4$ (0.26 mmol) in 2 mL of ether and the mixture was stirred for 1 h. Hydrolysis was performed with wet Na_2SO_4 and, after filtration and evaporation of the solvent, silica gel column chromatography (pentane/ether: 80/20) of the crude product gave 64 mg of the corresponding alcohol (95%). **3-(*R*)** $[\alpha]_D^{20}$ +11.1 ($c = 0.68$, $CHCl_3$) from acetate **4-(*R*)** ($[\alpha]_D^{20}$ +132). Litt. $[\alpha]_D^{20}$ +12.8 ($c = 0.416$, $CHCl_3$) for pure (*R*) alcohol.[2] **3-(*S*)** $[\alpha]_D^{20}$ −11 ($c = 1.96$, $CHCl_3$) from acetate **4-(*S*)** ($[\alpha]_D^{20}$ +132).

Synthesis of *O*-3-Iodocyclohex-3-en-1-yl-*N*-phenyl Carbamate 5-(*S*) or 5-(*R*) from Alcohols 3-(*S*) and 3-(*R*)

To a solution of 27 mg of alcohol (0.12 mmol) in 2 mL of THF under argon atmosphere were added 13 μL of phenyl isocyanate (0.12 mmol) and 3 mg of DABCO (27 μmol). The reaction mixture was stirred for 1 h at 20°C, and the solvent was removed under reduced pressure. Silica gel column chromatography of the crude product (pentane/ether: 97/3) afforded 34 mg of pure phenylcarbamate (81%). Enantiomeric excesses were determined by HPLC on a Pharmachir 4C column (250 × 4.6 mm), eluent hexane/ethanol: 94/6, flow rate: 1.5 mL/min, retention times: $t_{\mathbf{5\text{-}(R)}} = 11.8$ min, $t_{\mathbf{5\text{-}(S)}} = 14.3$ min. **5-(*R*)** ee = 90% from alcohol **3-(*R*)** ($[\alpha]_D^{20}$+11.1). **5-(*S*)** ee = 85.5% from alcohol **3-(*S*)** ($[\alpha]_D^{20}$ −11). This solid carbamate was recrystallized in pentane at −10°C: ee = 99.7%, m.p. = 80°C. ^{1}H NMR (250 MHz, $CDCl_3$) δ: 7.42–7.24 (m, 4H), 7.12–7.02 (m, 1H), 6.62 (broad s, 1H), 6.57–6.49 (m, 1H), 5.25–5.12 (m, 1H), 2.70–2.40 (m, 1H), 2.04–1.60 (m, 4H). ^{13}C NMR (63 MHz, $CDCl_3$) δ: 152.75 (C=O), 137.65 (C-NH), 135.74 (CH=), 129.03, 123.48, 118.62,

103.92 (–CI=), 70.07, 39.28, 26.98, 21.36. Anal. calcd. for $C_{13}H_{14}INO_2$: C, 45.48; H, 4.08. Found: C, 45.66; H, 4.15.

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