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Diastereoselective and enantioselective lipase-catalyzed hydrolysis of stereoisomeric 2-methylene, 5-*t*-butylcyclohexyl acetates

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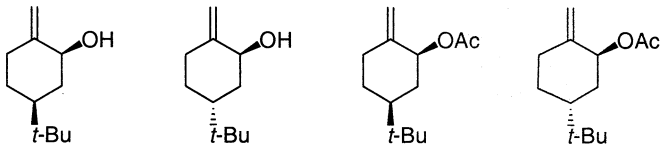
Abstract—*cis*- and *trans*-2-Methylene-5-*t*-butylcyclohexanols are obtained in high (>90%) e.e. through Rabbit Gastric Lipase (RGL)-catalyzed acylation or hydrolysis of the stereoisomeric racemic alcohols or their corresponding acetates. Since these reactions were diastereomer-selective, enantiomerically enriched *cis*- and *trans*-5-*t*-butyl-2-methylenecyclohexanols could also be prepared from *cis*/*trans* isomeric mixtures. © 2002 Elsevier Science Ltd. All rights reserved.

The stereoisomeric *cis*- and *trans*-2-methylene, 5-*t*-butylcyclohexanols **1** and their corresponding acetates **2** are useful models to investigate the stereochemistry of transition metal-catalyzed transformations operating with allylic compounds.



(±)-*cis*-**1** (±)-*trans*-**1** (±)-*cis*-**2** (±)-*trans*-**2**

We have demonstrated with these models the strong stereoelectronic control exerted in palladium-catalyzed alkylations of allylic acetates and molybdenum-catalyzed isomerization of allylic alcohols.[1] These compounds have also been used in stereochemical investigations of hydroformylation,[2] epoxidation[3,4] and osmylation[4] reactions. Enantiomerically enriched (−)-*cis*-**1** has been prepared in 70% e.e., and (+)-*trans*-**1** in 25% e.e. (^{1}H NMR spectroscopy in the presence of a chiral shift reagent).[5] However, to the best of our knowledge, these compounds are unknown in enantiomerically pure form. It would thus be desirable to get them in high e.e., as references for evaluating kinetic resolution processes in the above-described reactions.

We looked for ways of preparing **1** or **2** in enantioenriched forms by kinetic resolution through lipase-catalyzed acylation of racemic **1** or hydrolysis of the corresponding acetates **2**. Lipase-catalyzed acylation[6] of (±)-*trans*-**1**[7] with isopropenyl acetate in diethyl ether at room temperature was performed with pig pancreatic lipase (PPL),[8a] rabbit gastric lipase (RGL),[8b] *Candida cylindracea* lipase (CCL),[8c] immobilized *Candida antarctica* (SP 435).[8d] Only RGL showed a low-rate conversion of (±)-*trans*-**1** with 11% conversion into a single enantiomer of (+)-*trans*-**2** (non-isolated and of unknown configuration) over 8 days, corresponding to a high enantioselectivity (E>200) (Scheme 1). Under the same conditions, (±)-*cis*-**1**[7] underwent a faster acylation, albeit less enantioselective. After 2 days, at 41% extent of conversion of the starting alcohol, (−)-*cis*-**2** was produced in 45% e.e. (E=4). SP 435 was less efficient as a catalyst (27% conversion after 5 days of reaction) but more enantioselective (E>200), since the (+)-*cis*-**2** acetate was produced enantiomerically pure, as determined by chiral GLC.[9] RGL and SP 435 thus showed opposite enantiopreference.

These results indicate that with RGL, the acylation should be diastereoselective. Since the mixture of *cis*-**1** and *trans*-**1** (25:75) is more readily prepared than each separate stereoisomer, we looked whether (−)-*cis*-**1** and (+)-*trans*-**2** could be produced in high enantiomeric purity. Indeed, an 8 day RGL-catalyzed acylation of a stereomeric mixture of (±)-*cis*-**1** and (±)-*trans*-**1** gave 7.5% of enantioenriched (>99% e.e., by chiral GLC) (+)-*trans*-**2**, readily separated from the unreacted alcohols and *cis*-**2** (Scheme 2).

Keywords: kinetic resolution; enzyme; catalysis; enantioselective; acylation; hydrolysis.

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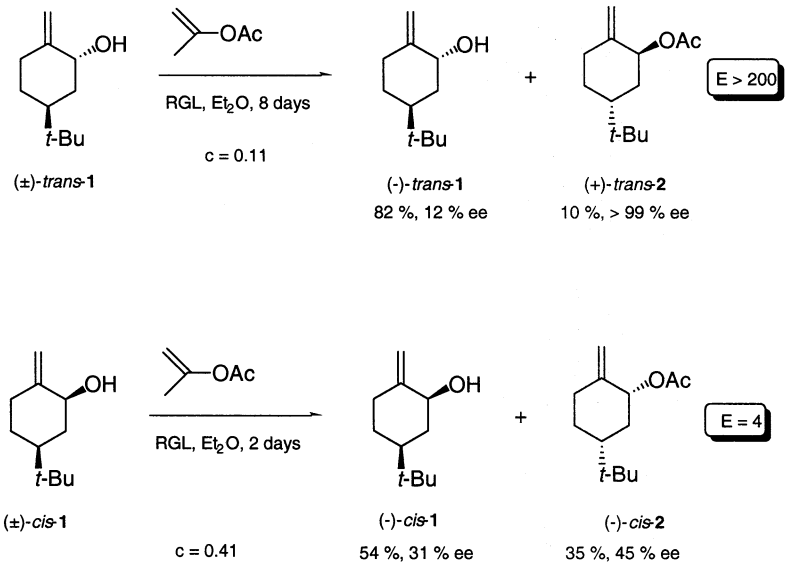
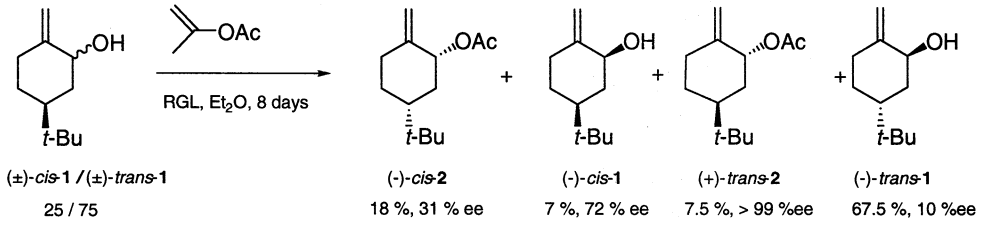
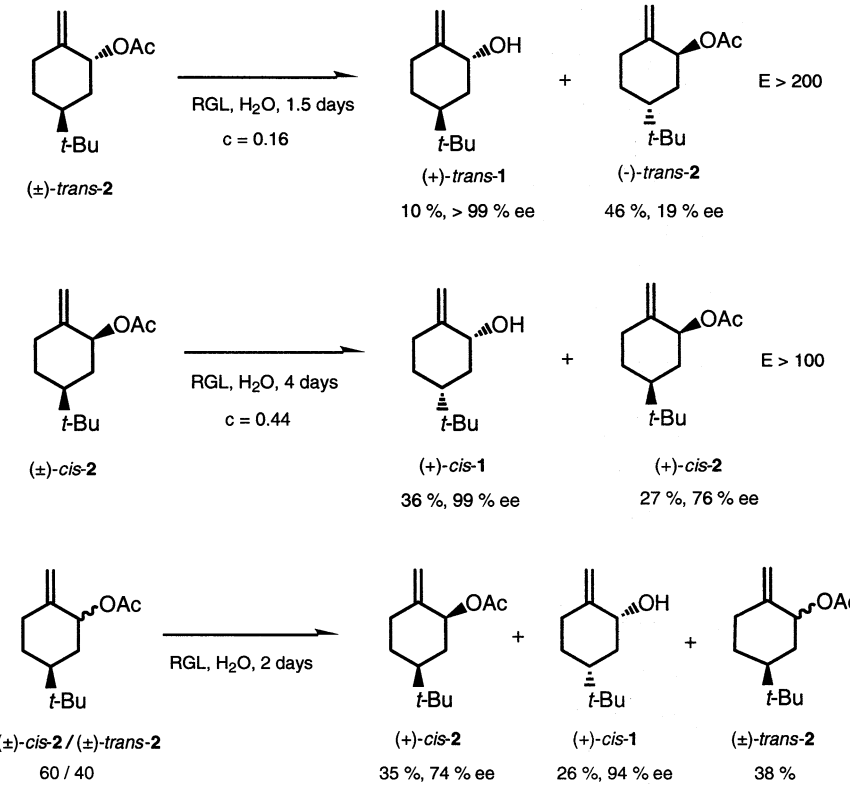


Scheme 1. RGL-catalyzed acylation of (±)-*trans*-**1** and (±)-*cis*-**1**.



Scheme 2. RGL-catalyzed acylation of a diastereomeric mixture of (±)-*trans*-**1** and (±)-*cis*-**1**.



Scheme 3. RGL-catalyzed hydrolysis of (±)-*trans*-**2** and (±)-*cis*-**2**.

Enzymatic hydrolysis by the same lipases in phosphate buffer[10] showed the same trends. PFL PPL, SP 435 were inefficient as catalysts for hydrolysis of both (±)-*cis*-**2** and (±)-*trans*-**2**. Once again RGL was the most performing (Scheme 3). At 16% conversion, hydrolysis of (±)-*trans*-**2** produced 10% of (+)-*trans*-**1** (corresponding to an enantioselectivity factor over 200). RGL performed well on kinetic resolution of (±)-*cis*-**2**, producing (+)-*cis*-**1** of 90% e.e. at 27% conversion and 99% e.e. at 44% conversion. This corresponds to a satisfactory $E>100$. Interestingly, a 60:40 mixture of racemic *cis*-**2** and *trans*-**2** afforded through RGL-catalyzed hydrolysis 26% of (+)-*cis*-**1** (94% e.e.). Only traces of *trans*-**1** were formed, facilitating the isolation of the *cis*-alcohol.

It is worth noting that hydrolysis of (±)-*cis*-**2** with CCL as catalyst afforded 12% ($c=0.13$) of enantiomerically pure (>99% e.e., GLC) (+)-*cis*-**1** (corresponding to $E>200$).[11]

In summary, both the RGL-catalyzed acylation and hydrolysis of 2-methylene 5-*t*-butylcyclohexanols **1** and their acetates **2**, respectively, were diastereoselective. The *cis*-compounds were more reactive than the *trans* stereoisomers. This allowed us to carry out the reactions onto the more readily available *cis–trans* mixtures of racemic **1** or **2** and to isolate either *cis* or *trans* material (alcohol or acetate) in high (>95%) enantiomeric purities.

Acknowledgements

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6. To a solution of alcohol-**1** (2 mmol) and isopropenyl acetate (6 mmol) in diethyl ether (12 mL) was added the enzyme (100 mg RGL, or 300 mg CCL, or 300 mg SP435) and the reaction mixture was stirred at room (18–22°C) temperature for the required time. After filtration (Celite), yields and e.e.s were measured by chiral GLC (Chiraldex β-PM, 50 m.). The relative retention times were, at 120°C (in min): (−)-*cis*-**1**: 73.5; (+)-*cis*-**1**: 77.5; (−)-*cis*-**2**: 69.0; (+)-*cis*-**2**: 66.0; *trans*-**1**: 47.3 and 48.8; *trans*-**2**: 52.5. The compounds were isolated through silicagel column chromatography (heptane/ethyle acetate: 80/20).
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9. (+)-*cis*-(1*S*,5*S*)-**2**: $[\alpha]_D^{20}=+15.4$ ($c=1$, ethanol).
10. To 12 mL of a phosphate buffer (pH 7) was added the racemic acetate (2 mmol) dissolved in 2 mL diethyl ether, followed by the enzyme. After being stirred at room temperature for the required time, the mixture was extracted with diethyl ether. The extracts were treated and analyzed as above.
11. (+)-*cis*-(1*R*,5*R*)-**1**: $[\alpha]_D^{20}=+8.0$ ($c=1$, ethanol).