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Synthesis of (1-*S*) and (1-*R*) *cis* 2-methylcyclopentanols Through Lipase Mediated Resolution

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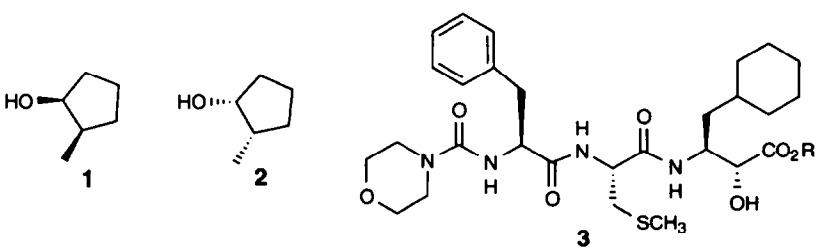
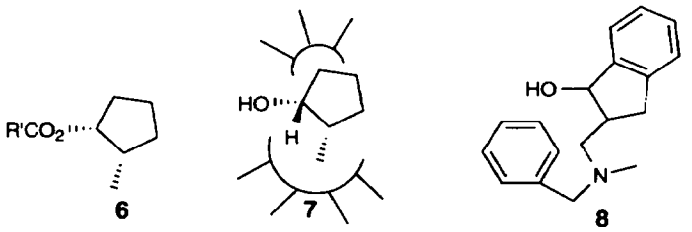
Abstract: The lipase catalyzed enantioselective transacylation of (±) *cis*-2-methylcyclopentanol is described.

Enantiomerically pure (1-*S*) and (1-*R*) *cis* 2-methylcyclopentanols **1** and **2**, respectively, were required for the synthesis of renin inhibitors **3** possessing hindered ester functionality at the C-terminus (R).[1] While **2** was unknown, **1** is described in a publication[2] concerned in part with the determination of the absolute configuration of the microbial stereospecific reduction of keto ester **4**. The resulting cyclopentanol **5** was converted to **1** by a three step route, but there was no proof offered for the absolute configurational assignments. *Aspergillus niger* reduction[3] of racemic 2-methylcyclopentanone affords a poor yield of a mixture of presumably optically active *cis* and *trans* methylcyclopentanols, which were not isolated and characterized with respect to optical purity and absolute configuration. In order to prepare synthetically useful quantities of **1** and **2** of confirmed absolute configuration, we undertook a study to resolve (±) *cis* 2-methyl-cyclopentanol through a lipase catalyzed process. The porcine pancreatic lipase catalyzed trans-esterification of racemic *cis* 2-methylcyclopentanol has been studied; however, no information was reported as to the stereochemical outcome.[4]



Stereospecific reduction of 2-methylcyclopentanone by L-Selectride®[5] affords the corresponding racemic *cis* alcohol, which on lipase catalyzed resolution should by literature[6] analogy afford (1-*S*) **1** and (1-*R*) ester **6**. The model **7**, employed to predict this stereochemical outcome, which was recently advanced by Kazlauskas[6], states that the *R* enantiomer (shown docked to the esterase) reacts faster under lipase catalysis than the corresponding *S* enantiomer. The initial conditions chosen for the enzymatic resolution are modifications of those described for the resolution[7] under irreversible conditions for a complex 2-alkyl cyclopentanol derivative **8.**



6 **7** **8**

Thus, subjection of racemic *cis* 2-methylcyclopentanol to Amano lipase P-30 (*Pseudomonas cepacea*, formerly[6] *Pseudomonas fluorescens*) with vinyl acetate as the acyl donor and *t*-butylmethylether as the solvent afforded rapid reaction at room temperature (250 MHz NMR monitoring) which was stopped at 50% conversion (4 hours of rapid stirring). However, on subsequent filtration and distillation, two significant problems became apparent. First, because of the similar boiling points of **1** and **6** (R'=CH_3), complete separation by distillation proved quite difficult. Second, NMR analysis (250 MHz) of the *R* Mosher ester[8] of **1** indicated an ee of only 60%.

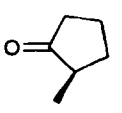
It occurred to us that both of these difficulties could be addressed by modifying the acyl donor (i.e., employing a larger acyl moiety such as lauroyl). In addition to the expected large difference in boiling points between the alcohol and its corresponding laurate, there would also be potential for increased enantioselectivity induced by the larger acyl segment.[9] Since anhydrides have also been employed in irreversible lipase-catalyzed transacylations,[10] we chose commercially available lauric anhydride as the acyl donor. There was no esterification of the racemic alcohol even after 48 hours in the absence of lipase. On the other hand, the lauric anhydride/P-30 lipase variation proceeded quickly taking about 8 hours to achieve 50% completion. Subsequent distillation of the crude reaction mixture after filtration afforded (1-*S*) *cis* methylcyclopentanol (**1**) of 92% ee (NMR analysis of Mosher ester) $[\alpha]_D^{25}$ +24.4 (c = 0.05, CH_2Cl_2).[11] We are especially pleased with the large increase in enantioselectivity achieved through substitution of acetyl by lauroyl, since a previous investigation[12] found no significant increase in stereoselectivity with increasing acyl size in lipase catalyzed transacylations employing anhydrides. However, it should be noted

that this study employed benzene as solvent, a medium which appears to be suboptimal for conducting such reactions (*vide infra*).

In order to prepare the corresponding (1-*R*) alcohol (**2**), the laurate ester **6** [R'=$(CH_2)_{10}CH_3$] must be isolated and chemically modified. After all **1** had been removed by distillation *in vacuo* from the reaction mixture, a lithium aluminum hydride reduction in ether was performed. Subsequent quenching with sodium sulfate dodecahydrate, followed by filtration and distillation, afforded **2** of 90% ee (NMR analysis of Mosher ester[8]) $[\alpha]_D^{25}$ −15.8 (c = 0.05,CH_2Cl_2).[11]

An investigation into various reaction parameters (i.e., solvent polarity, reaction stoichiometry) was conducted to further improve lipase stereoselectivity. Benzene as solvent was inferior, while toluene was equivalent to t-butylmethylether. Addition of the weak base collidine, reported to improve lipase enantioselectivity, was ineffective.[13] In addition, changing the lauric anhydride equivalents from 1.0 to 0.5 did not change stereoselectively. The effect of replacing the *Pseudomonas* lipase by *Candida cylindacea* lipase was detrimental to ee.

It was critical for our purposes to know with certainty the absolute configuration of our target cyclopentanols **1** and **2**. As was mentioned previously, the lipase method of resolution predicts[6] the isolation of the *S*-alcohol and the acylation of the *R*-enantiomer. An NMR comparison of the chemical shifts for the well resolved 2-CH_3 resonances of the *R* Mosher esters of **1** and **2**, followed by application of the Mosher correlation model,[8] was consistent with the structures as written. In addition, chromic acid oxidation[14] of **1** afforded levorotatory 2-methylcyclopentanone **9** $[\alpha]_D^{25}$ −106 (Lit[15] $[\alpha]_D^{25}$ −110.5) which possesses the (2-*R*) configuration and through inference confirmed the (1-*S*) configuration of **1**. To unequivocally confirm the absolute configuration of **1**, an X-ray approach was pursued; suitable crystals of the corresponding 3,5-dibromobenzoate[16] **10** were obtained which yielded X-ray data[17] that confirmed **1** as written.[18]



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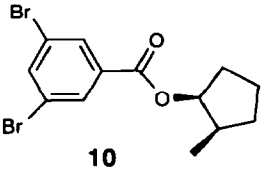

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In conclusion, a resolution method has been developed that allows the synthesis of *R* and *S cis* 2-methyl-cyclopentanols in excellent enantiomeric purity. The absolute configuration of these alcohols was confirmed by X-ray diffraction studies. Moreover, the stereospecificity of the lipase catalyzed resolution is consistent with, and further validates, the Kazlauskas model.[6]

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11. Procedure: To 5.0 g (0.05 mol) of racemic alcohol in 100 ml of *t*-butylmethylether was added 5.0 g of P-30 lipase followed by 19.1 g (0.05 mol) of lauric anhydride. After 8 hrs. of rapid stirring at 25°, the reaction mixture was filtered and the filtrate subjected to fraction distillation to afford 1.4 g of **1** (28% yield) : BP 70-72°/60 mm; corresponding racemic cyclopentanol; BP 76°/54 mm (Hückel, W.; Mögle, E. *Ann. Chem.* **1961**, *649*, 13).
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17. The X-ray data (forwarded to Cambridge Structural Database) was acquired and solved by Dr. J. Bordner of Pfizer Central Research; space group P1; cell dimensions, a = 7.081 (3) Å, b = 8.729 (3) Å, c = 11.144 (5) Å, a = 97.33 (4)°, b = 94.10 (3)°, g = 94.25 (3)°.
18. Our results confirm the absolute configuration claimed in the previously cited report[2] of the synthesis of **1** (Lit. $[\alpha]_D^{25}$ +19.8 [c = 0.76, MeOH]).

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