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Resolution of a chiral alcohol through lipase-catalyzed transesterification of its mixed carbonate by poly(ethylene glycol) in organic media

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Abstract

A simple approach to the resolution of chiral alcohols through a lipase-catalyzed transesterification of one enantiomer of the corresponding trifluoroethyl carbonate by a low molecular weight poly(ethylene glycol), PEG, is described. The method was demonstrated through resolution of (*RS*)-*sec*-phenethyl alcohol. The alcohol was converted to its 2,2,2-trifluoroethyl carbonate, **2**, and the (*R*)-enantiomer was selectively transesterified with PEG in warm diisopropyl ether using porcine pancreas lipase, PPL, as the catalyst. The two carbonate enantiomers were easily separated by cooling and filtering off the solid PEG having the (*R*)-alcohol covalently attached. Hydrolysis of the unchanged (*S*)-carbonate was achieved in dilute aqueous base, and the enantiomeric excess of the (*S*)-alcohol was found to be 80% by NMR in the presence of the chiral shift reagent Eu(hfc)$_3$. Methanolysis of the modified (*R*)-PEG carbonate yielded (*R*)-*sec*-phenethyl alcohol having enantiomeric excess = 96% by NMR with Eu(hfc)$_3$.

1. Introduction

The resolution of enantiomers by enantioselective hydrolysis with an enzyme has been exploited extensively for many years.[1–5] However, the discovery that many enzymes work well in low polarity organic solvents[6–10] has allowed enzymatic resolution to be extended to reactions such as esterification and transesterification. These approaches have been reviewed by Koskinen and Klibanov[4] and by Drauz and Waldmann.[5] Resolution by enzymatic transesterification in an organic solvent solves some of the problems associated with the enzymatic hydrolyses such as the low solubility of many organic compounds in water, the difficulty of recovering the enzyme for reuse,

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and the requirement for adjusting the pH as the reaction progresses.[11] Also, an increase in enzyme stability has been reported when it is used in an organic solvent, so higher reaction temperatures are tolerated.[7] Resolution of a racemic ester may be carried out by having one enantiomer of the ester transesterified with an achiral alcohol so that a difference in chemical properties between the two ester enantiomers is established.[4,5] More commonly, a racemic alcohol has been resolved by having one enantiomer of the alcohol transesterify an achiral ester, so that the enantiomer is converted to an ester and its enantiomer is left unchanged as an alcohol.[4,5] The difference in the chemical and physical properties that is established enables separation of the two enantiomers by chromatography.

Nearly a decade ago, we showed that, if a high molecular weight polymeric alcohol such as poly(ethylene glycol) is used as the achiral transesterifying alcohol, one enantiomer of a chiral ester can be converted to an ester of poly(ethylene glycol) (PEG),[12] while its mirror image is left as the original ester.[13] A significant difference in chemical properties is established between the enantiomeric pair and separation is readily achieved without the need for chromatography. If the enzymatic transesterification takes place in an appropriate solvent, such as diisopropyl ether, separation of the enantiomers can be achieved by methodology as simple as cooling the mixture to 0°C and filtering off the solid PEG carrying the modified enantiomer. The unchanged ester enantiomer remains dissolved in the filtrate.[13] We have now shown that this approach, which is termed a 'phase switch' by Curran,[14] can be easily extended to the resolution of chiral alcohols if the racemic alcohol is converted to a mixed carbonate functional group.

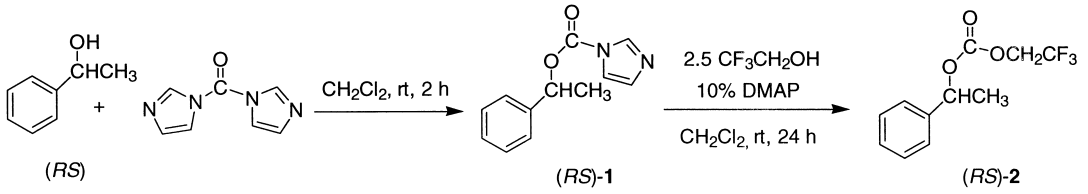
Limited work has been reported on enzyme-catalyzed reactions of carbonates. In 1989, Abramowicz and Keese reported lipase-catalyzed transesterification of diphenyl carbonate with a variety of alcohols.[15] Gotor and co-workers subsequently demonstrated the use of enzyme-catalyzed transformations utilizing carbonates leading to progress on the kinetic resolution of chiral aminoalcohols[16] and chiral vinyl carbonates,[17] and in the enzymatic synthesis of chiral carbonates[18–20] and chiral carbamates.[18,21] Similarly, the use of enzyme-catalyzed enantioselective hydrolysis of carbonates[22–24] in the synthesis of optically active diols[25] and diol derivatives[26] has been reported by various groups.

For the demonstration study reported here, an extensively studied chiral alcohol, (*RS*)-*sec*-phenethyl alcohol, was chosen. This alcohol has been previously resolved using enzyme-catalyzed enantioselective transesterification involving a variety of acyl sources.[27] However, each of these methods required a tedious separation such as chromatography to achieve the actual resolution.

2. Results and discussion

In developing the current strategy for resolution of (*RS*)-*sec*-phenethyl alcohol, incorporation of two features was sought: (1) modification of the chiral alcohol into a functional group that could be transesterified enantioselectively by porcine pancreas lipase (PPL); (2) use of a low molecular weight PEG as the transesterifying alcohol so that a strong difference in solubility properties could be imparted to one of the enantiomers.

The (*RS*)-*sec*-phenethyl alcohol was initially converted to urethane **1** by treating it with 1,1′-carbonyldiimidazole as shown in the first reaction of Eq. (1). It was hoped that PPL would replace the imidazole moiety of this urethane with PEG enantioselectively. However, control experiments run without the enzyme showed that displacement of the remaining imidazole in **1** by PEG occurred non-catalytically, and this avenue was abandoned.

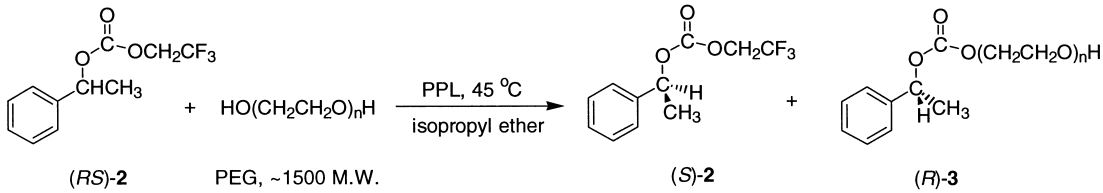


(1)

Enzyme-catalyzed resolutions of chiral esters in which the stereogenic center is located on the carbonyl moiety of the ester at a site to the carbonyl functional group are relatively rare but often very successful, especially when PPL or porcine liver esterase (PLE) is used as the catalyst.[11,28–41] Our previous success using a 2,2,2-trihaloethyl ester of a β-chiral carboxylic acid in an enantioselective PPL-catalyzed transesterification reaction[13] suggested conversion of **1** to the mixed carbonate (*RS*)-**2** in which one side of the carbonate is the chiral alcohol to be resolved and the other side is the 2,2,2-trihaloethyl leaving group. This structure places the stereogenic center of the alcohol β to the carbonyl of the carbonate and takes advantage of PPL's ability to catalyze the transesterification of such substrates enantioselectively. Carbonate (*RS*)-**2** was synthesized directly from (*RS*)-**1** by treating it with 2,2,2-trifluoroethanol in the presence of DMAP as shown in the second step of Eq. (1). The presence of chirality in **2** and its impact on a site at some distance from the center of chirality was readily observed by the appearance of two doublets of quartets for the diastereotopic methylene protons in the trifluoroethyl group.

The resolution was achieved by stirring a mixture of (*RS*)-**2** dissolved in diisopropyl ether with PEG having a molecular weight of about 1500 and dried PPL at 45°C as shown in Eq. (2). Under these conditions, the PEG is molten, but only partially dissolved, while the PPL is a separate solid phase. To allow the reaction to be monitored by VPC, *o*-dichlorobenzene (*o*-DCB) was added as an internal standard. Aliquots were drawn for analysis at the beginning of the reaction and periodically afterwards. The reaction was allowed to continue until the ratio of the VPC peaks for **2** and for *o*-DCB ceased changing at about half of its original value, approximately nine days being required. A control experiment run in parallel, but lacking the PPL, confirmed that the catalyst was required for transesterification to take place. A mixture containing (*R*)-**3**, the PPL, and any unchanged PEG was separated from the unchanged (*S*)-**2** by cooling the mixture to 0°C to freeze the PEG and acylated PEG then filtering. Dissolving the PEG and (*R*)-**3** from the solid phase in CH_2Cl_2 and again filtering removed the enzyme.

Repetition of the experiment without *o*-DCB had an interesting result. The reaction described by Eq. (2) was stopped at nine days, assuming that the previous analysis conducted with *o*-DCB was valid. However, the yield of the unchanged carbonate phase was higher than expected, indicating that the reaction had not reached completion. It is suspected that *o*-DCB may be acting as a cosolvent with isopropyl ether, possibly facilitating import of PEG to the active site of the enzyme.



(2)

The ^{1}H NMR spectrum of the fraction containing the (*R*)-**3** and unchanged PEG displayed two significant peaks: (1) a complex multiplet at 4.26 ppm, downfield of the PEG methylene envelope,

showed the presence of acylated PEG in the insoluble fraction. At 500 MHz this signal is resolved into two doublets of triplets due to the diastereotopic methylene Hs that result from bonding the chiral carbonate group to the PEG; (2) a pair of doublets of quartets at 4.5 ppm which was known to arise from the diastereotopic methylene hydrogens of the trifluoroethyl group in **2**, and which was expected to be absent from the spectrum of this fraction. Two possibilities were suggested: either the separation had not been complete or the transesterification had replaced the *sec*-phenethyl group rather than the trifluoroethyl group. The separation step using isopropyl ether was repeated, and ^{1}H NMR confirmed that the source of the quartets was unreacted carbonate, presumably (*S*)-**2**, that had become entrained in the PEG/enzyme fraction.

The ^{1}H NMR spectrum of product in the combined filtrates from the separations confirmed that this fraction contained unreacted carbonate **2**. A very tiny peak at 3.6 ppm, corresponding to the envelope of signals from the many PEG methylene groups, was the only evidence of PEG in the filtrate fraction. Thus, the separation of the PEG having bound (*R*)-**3** from the filtrate containing unchanged carbonate (*S*)-**2** was excellent.

Signals indicative of a small amount of *sec*-phenethyl alcohol were also present in the spectrum of the product from the filtrate fraction expected to contain (*S*)-**2**. Hydrolysis rather than transesterification can occur if the water content of the enzyme is too high.[15,42] If enzymatic hydrolysis is the source of the *sec*-phenethyl alcohol, it is expected that the enantiomeric excess of the alcohol should be high and consistent with the selectivity of PPL. Thus, it should have the (*R*) configuration rather than the (*S*) configuration expected for the unchanged carbonate presumed to comprise the rest of this fraction, and separating the two was essential to evaluating the enzyme's selectivity in transesterifying (*R*)-**2**. Using column chromatography, the alcohol was separated from (*S*)-**2** but the presence of another minor side product, suspected to be the *sec*-phenethyl carbonate of ethylene glycol, interfered with the analysis of the alcohol's configuration and enantiomeric excess. Efforts to prevent the hydrolysis side reaction have not yet been successful.

Conversion of both products (*R*)-**3** and (*S*)-**2** back to the corresponding *sec*-phenethyl alcohol enantiomers was carried out to determine the enantiomeric excess, the selectivity of the enzyme, and the overall success of the method for effecting an alcohol resolution. Hydrolysis of the unchanged carbonate (*S*)-**2** was easily achieved with aqueous alkali and ^{1}H NMR analysis of the product proved that, as expected, (*S*)-*sec*-phenethyl alcohol was the product formed. Methanolysis of (*R*)-**3** was also successful as demonstrated by TLC analysis and confirmed by ^{1}H NMR analysis of the isolated product. The methanolysis did not yield the methyl carbonate of *sec*-phenethyl alcohol, as was expected, but instead gave back (*R*)-*sec*-phenethyl alcohol directly. Surprisingly, there was no evidence of the methyl carbonate of PEG having formed. Rather, VPC analysis of the crude reaction mixture prior to evaporating the methanol showed that methanolysis on both sides of the carbonate had occurred, and that dimethyl carbonate was a product of the reaction along with the (*R*)-*sec*-phenethyl alcohol and unacylated PEG.

The enantiomeric excess of the two alcohols was determined by their ^{1}H NMR analysis in the presence of the chiral lanthanide shift reagent (tris-3-heptafluorobutyryl-D-camphorato)europium(III) [Eu(hfc)$_3$].[43] The enantiomeric composition of non-racemic *sec*-phenethyl alcohol has been determined previously with this shift reagent.[43] In the present work, control experiments were carried out with racemic and partially resolved *sec*-phenethyl alcohol to verify the technique. Resolution of the methine proton of (*R*)- and (*S*)-*sec*-phenethyl alcohol was achieved with a $\Delta\Delta\delta$ of 0.3 ppm at approximately 13 ppm by using a molar ratio of Eu(hfc)$_3$ to alcohol of 0.4. Approximately 2% of the minor enantiomer could be detected. The recovered (*R*)-alcohol from methanolysis of (*R*)-**3** showed no detectable amount of the (*S*)-enantiomer, so its enantiomeric

excess is at least 96%. To prove that the (*S*)-enantiomer was missing, alcohol known to be enriched in (*S*)-enantiomer was added to the NMR sample and the NMR experiment repeated. The appearance of a small absorption in the region where the signal from the (*S*)-enantiomer was expected confirmed that PPL had selected the (*R*)-enantiomer of the racemic carbonate for reaction with the PEG to give **3** and left behind the (*S*)-enantiomer as carbonate **2**. This result is consistent with configurational selectivities reported in the literature for PPL-catalyzed transesterification of a β chiral ester.[13,36,37,40] The *E* value of the reaction was found to be 35 with a 54.5% conversion of (*RS*)-**2** to (*R*)-**3**.[†]

The enantiomeric excess of (*S*)-*sec*-phenethyl alcohol was determined to be 80%. The alcohol sample used was prepared from carbonate that was hydrolyzed only after removing the presumed (*R*)-*sec*-phenethyl alcohol side product by column chromatography. Similar analysis of a sample from which the (*R*)-*sec*-phenethyl alcohol had not been removed prior to hydrolysis showed an enantiomeric excess of 54%. This result provides evidence that the observed *sec*-phenethyl alcohol side product arises from PPL-catalyzed hydrolysis of (*R*)-**2** to (*R*)-*sec*-phenethyl alcohol.

3. Conclusion

This study has demonstrated the viability of enantioselective, enzyme-catalyzed transesterification of a mixed carbonate with poly(ethylene glycol) as a method of resolving a racemic chiral alcohol. The separation when isopropyl ether is used as the solvent is excellent, but there is some tendency for unchanged carbonate enantiomer to be entrained in the PEG-containing fraction requiring that the simple separation protocol be repeated with fresh diisopropyl ether. The source of the water that leads to some hydrolysis rather than transesterification is almost certainly the matrix in which the enzyme is supplied. PPL is an attractive enzyme for the method because of its high selectivity in transesterifying β chiral esters as well as its stability and very low cost. However, attempts to reduce the available water content have not yet been fully successful.

4. Experimental

4.1. General

Anhydrous diisopropyl ether, $i\mathrm{Pr_2O}$, was purchased from Aldrich Chemical Co. in a Sure-Seal™ bottle (stabilized with BHT, packaged under N_2) and used as received (caution: unstabilized $i\mathrm{Pr_2O}$ can form explosive peroxides upon exposure to air,[44] but this has not been a problem in the inert atmosphere reactions we have been carrying out). As a further precaution, a sample of the $i\mathrm{Pr_2O}$ being used was periodically tested for peroxide formation with moist KI/starch paper (available from Aldrich). All tests were negative. Poly(ethylene glycol), PEG, of average molecular weight 1500 (Aldrich cat. no. 20,243-6) and porcine pancreas lipase, PPL (25% protein, activity = 50 units/mg using triacetin at pH 7.4, 179 units/mg using olive oil at pH 7.7, Sigma cat. no. L-3126), were treated as described below. All reactions were stirred magnetically under a dry N_2 atmosphere. Other chemicals were the best available grade, and were used as received.

[†] The *E* value reported is based on the e.e.s for *sec*-phenethyl alcohol and requires the assumption that there is no change in e.e. in steps subsequent to the enzymatic step.

Organic extracts were dried with a 1:1 mixture of Na_2SO_4 and $MgSO_4$. NMR spectra were recorded at 250 MHz except where otherwise noted. VPC analyses were carried out on a fused silica column having a bonded liquid phase of cross-linked methyl silicone. TLC analyses were carried out on silica gel coated plastic plates using 4:1 (v/v) hexanes:ethyl acetate as eluent.

4.2. (RS)-sec-*Phenethyl 1*H-*imidazole-1-carboxylate [(RS)-**1**]*

In a modification of the method of Ohta et al.[45] 25 mL methylene chloride was added to a dry 250 mL flask followed, with stirring, by 17.8 g (110 mmol) 1,1′-carbonyldiimidazole, then an additional 10 mL methylene chloride, and, finally, 12.2 g (100 mmol) (*RS*)-*sec*-phenethyl alcohol dissolved in 10 mL methylene chloride. Upon addition of the alcohol the solution became light yellow and boiled for a few minutes. A yellow precipitate of imidazole could be seen in the reaction flask after 10 min. After 4 h stirring at room temperature, VPC analysis showed that the alcohol had been consumed. The mixture was extracted with three 20 mL portions of distilled water to remove the imidazole and dried (note: if the imidazole is not removed by the aqueous extraction, it interferes with the next reaction). Evaporation of the methylene chloride yielded 21.12 g (98% yield) of a light yellow oil that solidified into a brittle white solid while stored in the freezer. ^{1}H NMR ($CDCl_3$): δ 1.73 (d, J = 6.6 Hz, 3H), 6.07 (q, J = 6.6 Hz, 1H), 7.04 (s, 1H), 7.37 (m, 6H), 8.15 (s, 1H); ^{13}C NMR ($CDCl_3$): δ_C 147.8, 139.5, 136.9, 130.4, 128.6, 128.5, 125.9, 116.9, 76.9, 21.7.

4.3. (RS)-sec-*Phenethyl 2,2,2-trifluoroethyl carbonate [(RS)-**2**]*

Following the procedure given above, 8.9 g (55 mmol) 1,1′-carbonyldiimidazole and 6.1 g (50 mmol) (*RS*)-*sec*-phenethyl alcohol were used to prepare (*RS*)-**1**. After extracting with three 15 mL portions of distilled water and drying, the solution was transferred to a new 250 mL flask, and 12.31 g (123 mmol) 2,2,2-trifluoroethanol dissolved in 10 mL methylene chloride was added followed by 0.61 g (5 mmol) DMAP. After 20 h at rt VPC analysis showed that the mixture was >95% carbonate (*RS*)-**2**. The mixture was then stirred with 20 mL of 0.05 M HCl and 2.9 M HCl was added dropwise with stirring until pH = 2, 17 mL being required. The phases were separated and the organic phase was extracted successively with 20 mL each of 0.05 M HCl, distilled water, saturated aqueous sodium bicarbonate, and two 20 mL portions of saturated sodium chloride solution. After drying, the methylene chloride was evaporated to give 10.52 g (84.8% yield) of a clear liquid that could be further purified by vacuum distillation, bp 44°C/0.001 mm Hg. ^{1}H NMR ($CDCl_3$): δ 1.62 (d, J = 6.6 Hz, 3H), 4.36 (dq, $J_{H,H}$ = 12.6 Hz, $J_{H,F}$ = 8.3 Hz, 1H), 4.55 (dq, $J_{H,H}$ = 12.6 Hz, $J_{H,F}$ = 8.3 Hz, 1H), 5.75 (q, J = 6.6 Hz, 1H), 7.34 (m, 5H); ^{13}C NMR ($CDCl_3$): δ_C 153.3, 140.2, 128.6, 128,4, 125.9, 122.6 (q, $J_{C,F}$ = 277 Hz), 77.9, 63.15 (q, $J_{C,F}$ = 37 Hz), 21.9. Mass spectrum: m/z 248 (12.7), 105 (60.0), 104 (100), 83 (20.9), 77 (22.0), 51 (13.1). Anal. calcd for $C_{11}H_{11}F_3O_3$: C, 53.23; H, 4.47; Found: C, 53.03; H, 4.48.

4.4. *Preparation of the poly(ethylene glycol) (PEG) substrate*

To a dried 500 mL round-bottomed boiling flask was added 82.4 g PEG having an average molecular weight of 1500. Approximately 250 mL toluene was added and the mixture distilled at an atmospheric pressure of 630 mm Hg. Toluene and water co-distilled at 103°C, with the distillate appearing cloudy until approximately 1 h later, when a few drops collected in a separate

flask were clear. Upon cooling overnight, the PEG precipitated from the toluene. The toluene was decanted and was replaced with 150 mL of iPr$_2$O. To remove low molecular weight oligomers, the mixture was heated at 45°C with stirring in a water bath for 30 min. The flask was then placed in the freezer for 30 min and the iPr$_2$O was decanted. The process was repeated with 150 mL of fresh iPr$_2$O except that the flask allowed to return to room temperature slowly with rapid stirring to fracture the PEG into a fine white powder. The powder was filtered off and dried in vacuo for 2 h, yielding 79.8 g (97%) of PEG. ^{1}H NMR ($CDCl_3$): δ 1.7 (s), 3.6 (br s).

4.5. *Resolution of (*RS*)-*sec*-phenethyl 2,2,2-trifluoroethyl carbonate [(*RS*)-**2**]*

To a dry 250 mL flask was added 20 mL iPr$_2$O followed by 1.25 g (5.0 mmol) (*RS*)-**2** dissolved in 5 mL iPr$_2$O and 0.046 g (0.31 mmol) *ortho*-dichlorobenzene (*o*-DCB). A sample of the mixture was withdrawn and the ratio of the area below the (*RS*)-**2** peak in the VPC to the area under the *o*-DCB peak was measured at time zero. To the flask were then added 4.87 g (3.25 mmol) of the PEG prepared above and 2.51 g PPL that had been dried in vacuo for three days over P_2O_5. The mixture was heated to 45°C with stirring in an oil bath. The PEG and PPL formed a separate phase which collected at the bottom of the flask once the polymer had melted. Periodically, the flask was cooled to 0°C in an ice/water bath and an aliquot withdrawn for VPC analysis of the (*RS*)-**2**:*o*-DCB peak ratio. After nine days the analysis showed that the ratio had decreased by half. The reaction mixture was placed in a freezer for 30 min, then the solid phase comprising the PPL, PEG, and acylated PEG was separated from the filtrate containing unchanged carbonate and iPr$_2$O by suction filtration.

4.6. *Recovery of (*R*)-**3***

The solid collected in the filtration was washed with cold iPr$_2$O then was stirred with 20 mL CH_2Cl_2 and the insoluble material, presumed to be PPL, was removed by centrifugation followed by suction filtration of the supernatant with a fritted glass funnel. The CH_2Cl_2 filtrate had a yellowish–orange color that remained in the waxy solid isolated after evaporation of the solvent. In the ^{1}H NMR spectrum of the solid, the characteristic pair of doublets of quartets at 4.5 ppm from the trifluoroethyl group of **2** showed that further purification was needed. The waxy solid was dissolved in 12.5 mL iPr$_2$O, and the solution was heated to 45°C for 10 min with stirring so that the PEG could melt and unchanged **2** could dissolve. The flask was then placed in a freezer for 1 h and the solid phase separated from the ether phase by suction filtration. This process of heating, stirring, cooling, and filtering was repeated three times. The combined filtrates were concentrated by evaporation and confirmed by ^{1}H NMR to consist of unreacted **2**. The purified solid PEG fraction was dissolved in methylene chloride and filtered through a fritted glass funnel, then the solvent removed to obtain 4.75 g of (*R*)-**3** and unchanged PEG. ^{1}H NMR analysis indicated that the trifluoroethyl group was absent but showed a strong signal from the PEG at 3.6 ppm. Signals for the *sec*-phenethyl group appeared at 1.6 (d), 5.7 (q), and 7.3 (m). At 4.2 was a multiplet arising from the diastereotopic methylene Hs in the esterified PEG.

4.7. *Recovery of (*S*)-**2***

The ^{1}H NMR spectrum of the product recovered by evaporating the original iPr$_2$O filtrate was identical with that of the original, racemic carbonate but VPC analysis showed that the carbonate

contained 7% *sec*-phenethyl alcohol. However, only a small peak at 3.6 ppm was seen as evidence of PEG in this fraction. After column chromatography on 200 mesh silica gel using methylene chloride as the solvent to remove the *sec*-phenethyl alcohol from the mixture, 0.75 g carbonate (*S*)-**2** having ^{1}H NMR data identical with those of (*RS*)-**2** was isolated.

4.8. *Hydrolysis of (*S*)-sec-phenethyl 2,2,2-trifluoroethyl carbonate [(*S*)-**2**]*

In a 100 mL flask were placed 0.75 g (3.0 mmol) of the (*S*)-**2** isolated above and 5 mL THF. Dry N_2 was bubbled through the solution with a Pasteur pipette while 9.0 mL of 1 M NaOH was added. The flask was then flushed with N_2 and the mixture allowed to stir at rt. After 18 h, TLC showed the disappearance of (*S*)-**2**, so 1.5 mL of 2.9 M HCl was added to neutralize the alkali. Evaporation of the THF and trifluoroethanol gave a bright yellow mixture which was dissolved in 20 mL CH_2Cl_2. The solution was extracted with three 5 mL portions of half-saturated NaCl solution, then dried. Evaporation of the CH_2Cl_2 yielded 0.204 g (66% yield) of a bright yellow oil. ^{1}H NMR analysis showed peaks from *sec*-phenethyl alcohol: 1.4 (d, J = 5.7 Hz), 4.9 (q, J = 6.4 Hz), 7.3 (m). For ^{1}H NMR experiments with Eu(hfc)$_3$, a 0.40 M solution of the isolated (*S*)-*sec*-phenethyl alcohol in $CDCl_3$ was prepared and 0.5 mL of the solution was added to an NMR tube followed by 0.1 mL of a 0.194 M solution of Eu(hfc)$_3$ in $CDCl_3$. After allowing 15 min for equilibration, a ^{1}H NMR spectrum was obtained at 250 MHz and examined for evidence of signal resolution. Additional 0.1 mL increments of the Eu(hfc)$_3$ solution were added, allowed to reach equilibrium, and ^{1}H NMR spectra obtained after each addition until baseline resolution of the signal for the methine proton of *sec*-phenethyl alcohol was achieved at ~13 ppm with a $\Delta\Delta\delta$ of 0.3 ppm.

4.9. *Methanolysis of PEG-carbonate [(*R*)-**3**]*

To a 100 mL flask containing 4.75 g (*R*)-**3** was added 15 mL CH_3OH. The contents were stirred magnetically to dissolve the solid then 0.304 g (5.6 mmol) $NaOCH_3$ was added with stirring. Immediately the mixture turned light yellow and cloudy, but after 15 min, the cloudiness disappeared. Dry N_2 was bubbled through the solution for 2 min using a Pasteur pipette, then the flask was flushed with dry N_2 and the mixture allowed to stir at rt for two days. The reaction was stopped by neutralizing the mixture with 1 M H_2SO_4 in CH_3OH, 0.9 mL being required. The CH_3OH was evaporated and the residual CH_3OH removed in vacuo. ^{1}H NMR analysis of the residue showed peaks indicative of non-acylated PEG and *sec*-phenethyl alcohol. The absence of two doublets of triplets at 4.26 shows removal of PEG from the carbonate. The solid was dissolved in 10 mL CH_2Cl_2 then gravity filtered to remove the Na_2SO_4 from the neutralization step. The CH_2Cl_2 was evaporated and replaced with 10 mL iPr$_2$O. The mixture was heated at 45°C with stirring, during which time most of the PEG melted and formed a separate phase at the bottom of the flask. After 10 min of heating and stirring, the flask was placed in the freezer for 20 min. The solidified PEG was filtered off and the procedure repeated with 10 mL of fresh iPr$_2$O. The filtrates were combined in a tared 100 mL flask and the iPr$_2$O was evaporated with the last traces being removed on the vacuum manifold to yield 0.193 g (63%) of a clear, yellowish oil. ^{1}H NMR analysis of the product showed peaks from *sec*-phenethyl alcohol but no singlets indicative of a methyl carbonate. For ^{1}H NMR experiments with Eu(hfc)$_3$, the same procedure as described above was followed. When the methine proton signal had been shifted to ~13 ppm and no resolution had been observed, 46 μL of a 1.3 M solution of (*R*)-*sec*-phenethyl alcohol having

e.e. = 54% was added to the NMR tube containing the recovered (*R*)-alcohol and shift reagent, and allowed to stand for 3 h. The ^{1}H NMR experiment was repeated and a new quartet 0.25 ppm upfield of the original quartet appeared.

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