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PEG_{600}-Carboxylates as Efficient Reusable Reaction Media and Acylating Agents for the Resolution of *sec*-Alcohols

Carlos M. Monteiro,[a] Nuno M. T. Lourenço,*[b] Frederico C. Ferreira,[b] and Carlos A. M. Afonso*[a]

Herein is presented a simple, attractive, and reusable methodology for one-pot resolution/separation of free *sec*-alcohols with enantiomeric excess (*ee*) values over 90% by the combination of sustainable acylating agents/solvents (polyethylene glycol derivatives) and an easily available and common biocatalyst (*Candida antarctica* lipase B, or CAL B) under irreversible conditions, along with a separation process by extraction or distillation. A scale-up reaction was carried out with the Fluoxetine precursor with *ee* values close to 90% for the *R* enantiomer.

Enantiomerically pure *sec*-alcohols are an important class of biologically relevant compounds amenable to facile and selective functional-group transformation. Stereoselective synthesis of a desired enantiomer can be achieved through asymmetric reduction of ketones, stereoselective nucleophilic addition to aldehydes, dynamic kinetic resolution of racemic *sec*-alcohols, and modification of enantiomeric natural products available from the chiral pool.

Resolution of racemic alcohols is an appealing strategy, particularly when both enantiomers are valuable. Standard chromatographic methods such as chiral high-performance liquid chromatography (HPLC) and gas–liquid chromatography (GLC) excel for analytical purposes and small-scale preparative purposes but are not viable for any meaningful scale-up. Simulated moving-bed chromatography has allowed for continuous operation but the high cost of chiral stationary phases and need for careful optimization for each substrate has reserved this method for more intensive resolutions.[1] Membrane technology using chiral selectors is another continuous resolution method.[2] Crystallization has been the standard for racemic resolution, particularly for substrates that can form organic salts, such as amines and carboxylic acids. By contrast, the formation of inclusion complexes is the only described method for resolution of *sec*-alcohols by crystallization.[3]

The preferred method for *sec*-alcohol resolution has been kinetic resolution (KR). There are a few instances of chemical KR methods,[4] but the majority of applications focus on the enzymatic kinetic resolution (EKR), either by acylation of an alcohol or by hydrolysis of the acylated product. EKR is a well-established method given that the biocatalysts employed accept a broad range of substrates and afford very high enantioselectivity. The success of an EKR is dependent on three factors: 1) high efficiency of the enzyme, the stability of which can be increased in selected organic solvents, ionic liquids (ILs),[5] and eutectic solvents;[6] 2) the occurrence of EKR under irreversible conditions achieved by either using vinyl esters or anhydrides as acylating agents,[7] or drying agents for water removal or product removal (water or volatile alcohol) by evaporation under vacuum;[8] and 3) effective separation of the two enantiomers as free alcohol and ester.[9] The separation step is an important factor for upscaling a process. Separation methods are based on the type of acylating agent. Simple nonfunctionalized acyl groups are commonly separated by flash chromatography on silica and more rarely by distillation.[8, 9d, 10] Separation by extraction is a very common method applied to a variety of acylating agents and esters including succinic esters,[9a, 10e, 11] amine-based acylating agents,[10e] carbonate esters that contain a pendant polyethylene glycol (PEG) unit,[12] and a fluorinated pendant acylating agent in combination with a fluorinated extraction phase.[9c, 13] Extraction techniques have also used ILs as membranes,[14] extraction with supercritical CO_2 (sc-CO_2), and sc-CO_2 in combination with ILs.[15] Other separation methods have also been reported such as distillation,[8] precipitation,[9d, 12b, 16] and sublimation.[17]

The extraction methods listed above do possess certain limitations such as the need for expensive and poorly reusable reaction media (e.g., ILs or fluorinated solvents), quite technical complex procedures (e.g., sc-CO_2) and non-reusable enzymes or acylating reagents. Also, the isolation of the other enantiomer can require even further chemical modification (e.g., hydrolysis, transesterification of the ester or deprotection of the *tert*-butyloxycarbonyl (Boc) group).[9a, 11a]

To overcome these limitations, we have developed a methodology with the following features: 1) The use of low-volatile reaction media such as ILs[9b, 18] or fatty esters to avoid the use of vinyl esters[10b, 19] and to enable continuous removal of the volatile alcohol (transesterification) or water (esterification) under vacuum. These conditions should drastically minimize EKR reversibility and afford high yields. 2) The use of the same

[a] *Dr. C. M. Monteiro, Prof. Dr. C. A. M. Afonso*
Instituto de Investigação do Medicamento(iMed.ULisboa)Faculdade de Farmácia da Universidade de Lisboa
Av. Prof. Gama Pinto, 1649-003 Lisboa(Portugal)
E-mail: carlosafonso@ff.ul.pt

[b] *Dr. N. M. T. Lourenço, Dr. F. C. Ferreira*
Department of Bioengineering
IBB (Institute for Biotechnology and Bioengineering)
Centre for Biological and Chemical Engineering
Instituto Superior Técnico, 1049-001 Lisboa(Portugal)
E-mail: nmtl@tecnico.ulisboa.pt

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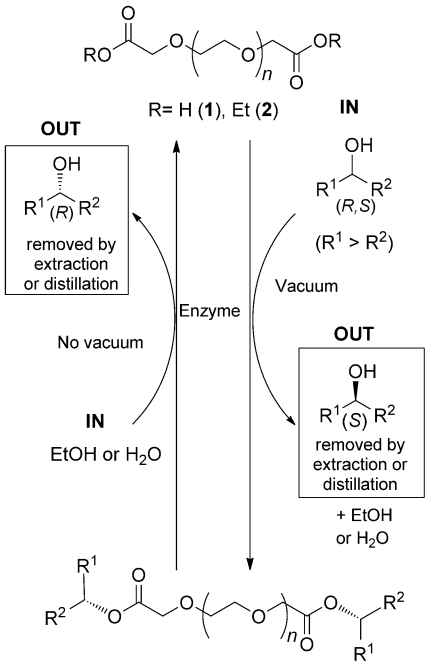
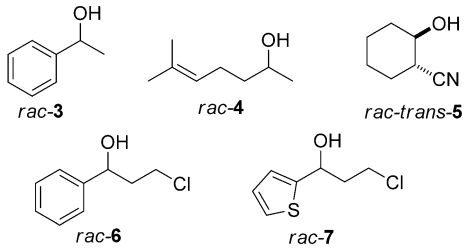
enzyme for both enzymatic reactions (kinetic resolution and reverse transesterification) to afford both enantiomers as free alcohols and regeneration of the acylating agent for the next cycle. 3) Simple separation of each enantiomer by sequential extraction or distillation. 4) Reuse of the acylating agent, reaction media, and enzyme.

Compounds PEG_{600}-diacid **1** and the corresponding PEG_{600}-diester **2** are efficient, biocompatible, and commercially available enzymatic acylating agents, which we have explored as reaction media for the EKR (Scheme 1). Their low melting point and moderate viscosity do not require any additional solvent. In addition, the high molecular weight, low volatility, water miscibility, and low miscibility in apolar organic solvents facilitate product isolation by nanofiltration, extraction, and distillation.[12b,c,16,20]



Scheme 1. Overview of the methodology for enzymatic kinetic resolution and separation of secondary alcohols based on the use of PEG_{600} carboxylates as acylating agents and reaction media.

We began our studies by using 1-phenylethanol (**3**) as a model substrate and other valuable *sec*-alcohols **4**–**7** in which both enantiomers are important compounds (Scheme 2). Sulcatol (6-methylhept-5-en-2-ol; **4**) is a pheromone used for pest control of *Gnathotrichus retusus* and *Gnathotrichus sulcatus* as the pure *S* enantiomer and as a controlled mixture of both enantiomers in an *S*/*R* ratio of 65:35, respectively.[21] 2-Hydroxycyclohexanecarbonitrile (**5**) is a key precursor to an androgen receptor antagonist that is being developed for the treatment of alopecia and excess amounts of sebum.[22] 3-Chloro-1-phenylpropan-1-ol (**6**) is a precursor of Fluoxetine (Prozac, Lilly), in which the *R* enantiomer is used to treat depression, whereas the *S* enantiomer is active in migraine treatment.[23] 3-Chloro-1-(2-thienyl)-1-propanol (**7**) is



Scheme 2. Substrates used on the EKR using PEG carboxylates as acylating agents.

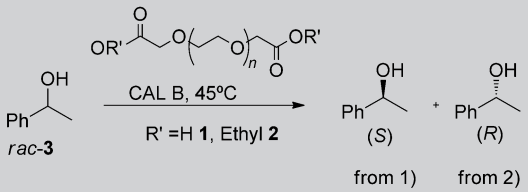
a precursor of (*S*)-duloxetine and (*R*)-norduloxetine, which are also used to treat depression.[24]

We carried out the EKR for substrates **3**–**7** using PEG_{600}-diacid **1** and PEG_{600}-diester **2** as acylating agents. The EKR was followed by chiral GLC to determine the conversion and enantiomeric excess (*ee*) of the remaining alcohol (see the Supporting Information). 1-Phenylethanol (**3**) was resolved using *Candida antarctica* lipase B (CAL B) and PEG_{600}-diester **2** was found to be more efficient than the corresponding diacid **1**. A temperature of 45 °C was also found to be beneficial relative to 35 °C on account of the higher EKR conversion rate (55% conversion versus 43% conversion after 72 h; see the Supporting Information) and lower viscosity of the acylating agent PEG_{600}-diester **2**. These optimized conditions were applied to substrates **3**–**7**. Sulcatol **4** afforded good enantioselectivity (76% *ee*) after 48 h, whereas substrates **5**, **6**, and **7** yielded moderate enantioselectivities of 24, 35, and 37% *ee*, respectively. They also showed a slower reactivity, likely on account of a lower recognition at the enzyme active site.

We sought to separate the free alcohol enantiomer from the esterified enantiomer by means of nanofiltration. We chose membranes with a molecular-weight cutoff (MWCO) between 200 and 250 Da, and ethyl acetate and methyl ethyl ketone as organic solvents. We observed desirable high rejection of PEG_{600}-diester (up to 98%) and undesirable high rejection of model alcohol **3** of 74 to 90% (see the Supporting Information). The low permeability of **3** is probably due to high affinity of the PEG_{600} for the pores of the membrane, thus blocking transport across them.

We decided to take advantage of the low solubility of PEG_{600} derivatives in *n*-hexane and attempted to use it to extract the free alcohol. Unfortunately, extraction of (*S*)-**3** from the reaction mixture was incomplete, thus causing the erosion of recovered (*R*)-**3** enantiomeric excess after the second enzymatic transesterification step (Table 1, entries 1 and 3). In another direction, the high affinity of PEG_{600}-diester **2** for the aqueous phase allowed an efficient extraction of the free alcohol with a *n*-hexane/diethyl ether/water system (see the Supporting Information). The minor contamination of **2** in the organic phase was removed simply by filtration of the organic solution through silica gel, thus providing pure alcohol **3** (see SI Table 3, entry 3, in the Supporting Information). In this way, the addition of water during the extraction step allowed an improvement on the *ee* of (*R*)-**3** for the second step (Table 1, entries 2 and 4 versus entries 1 and 3).

Table 1. EKR and separation of **3** using PEG_{600}-carboxylates **1** and **2** as acylating agents.



1) Enzymatic transesterification: 48h;
S enantiomer removal by extraction
2) Enzymatic transesterification: EtOH (2.5 equiv), 24h;
R enantiomer removal by extraction

Entry	AA	*t* [h] first/second steps	(*S*)-Alcohol yield/*ee* [%][f]	(*R*)-Alcohol yield/*ee* [%][f]
1[a,b]	**1**	72/24	40/92	36/90
2[a,c]	**1**	72/24	49/90	36/96
3[a,b]	**2**	48/24	43/90	40/90
4[a,c]	**2**	48/24	46/90	31/94
5[b,d]	**1**	72/24	53/50	30/65
6[b,d]	**2**	48/24	55/60	44/36
7[c,d,e]	**2**	48/24	51/86	32/90

[a] All reactions were carried out with 0.414 mmol of alcohol, 0.414 mmol of acylating agent (AA), and 20 mg of CAL B, 45 °C, 150 mm Hg. To perform the second step, 2.5 equivalents of ethanol were added (based on acylated alcohol). [b] The extraction step was carried out by adding *n*-hexane to the reaction mixture. [c] The extraction step was carried out by dissolving the reaction mixture in water and extraction with *n*-hexane/diethyl ether (4:1). [d] Transformation carried out using 8.28 mmol of alcohol and acylating agent, and 400 mg of CAL B. To perform the second step, 2.5 equivalents of absolute ethanol were added. [e] Reaction performed in a Kugelrohr oven. [f] Yield of isolated product obtained after solvent evaporation and filtration through silica; enantiomeric excess determined by GLC analysis.

To test the viability of this process, the reaction scale was increased 20 times (from 0.414 to 8.28 mmol of compound **3**) using PEG_{600}-diester **2** as acylating agent. However, the viscosity of the PEG derivatives led to inefficient stirring and therefore a very low enantiomeric excess for both enantiomers (Table 1, entries 5 and 6). To circumvent this, the reaction was performed in a Kugelrohr oven under horizontal rotation. This allowed the reaction mixture to form a thin film in the flask resulting in a more efficient interaction with the enzyme and at the same time, an ethanol removal improvement (Table 1, entry 7). Under these conditions, (*S*)-**3** was isolated in 51% yield and 86% *ee*, and (*R*)-**3** was isolated in 32% yield and 90% *ee*.

We applied this method to substrates **4**–**7** (Table 2). We assessed sulcatol **4** with both acylating agents **1** and **2** and found PEG_{600}-diester **2** to afford the best results once again. Compound (*S*)-**4** was isolated from the first step after 48 hours in 45% yield and 75% *ee*, and (*R*)-**4** was isolated from the second step after 24 hours in 33% yield and 93% *ee* (Table 2, entry 1). We scaled up the reaction (8.3 versus 0.41 mmol) and found, as before, the film formation leads to an enantioselectivity increase (Table 2, entry 3). Some loss of sulcatol **4** alcohol was unavoidable even when the reaction was performed at low temperature owing to its volatility. Under these conditions, (*S*)-**4** was isolated in 33% yield and 99% *ee*, and (*R*)-**4** was isolated in 30% yield and 90% *ee*. Substrates **5**, **6**, and **7** presented a slower reactivity (Table 2, entries 4–7) in the first step with these acylating agents but showed overall comparable yields and *ee* values to substrates **3** and **4**, thus indicating that the second enzymatic transesterification is more efficient. The experiments with acylating agents **1** and **2** provided comparable results and yielded (*S*)-**5** in 62% yield and 48–52% *ee* and (*R*)-**5** in 32–35% yield and 86–88% *ee*. Similar results were obtained for the duloxetine and norduloxetine precursor **7** by using PEG carboxylate **2** as the acyl donor. We were able to isolate (*S*)-**7** in 64% yield and 50% *ee* and (*R*)-**7** in 30% yield and 94% *ee* (Table 2, entry 7).

Owing to the low solubility of **6** in *n*-hexane/diethyl ether, we were unable to extract it from the aqueous phase. To overcome this, we took advantage of the high boiling point of PEG_{600}-diester **2**, which allowed the distillation of the free alcohol, thereby providing the precursor of fluoxetine (*S*)-**6** in 58% yield and 40% *ee* and (*R*)-**6** in 33% yield and 88% *ee* (Table 2, entry 6).

Furthermore, we decided to perform the resolution of the secondary alcohol **6** on a five-gram scale (Table 3). At this scale, the reactions were performed in a rotary evaporator under horizontal rotation. Under these conditions, parameters such as temperature, substrate concentration, and enzyme loadings were evaluated (Table 3).

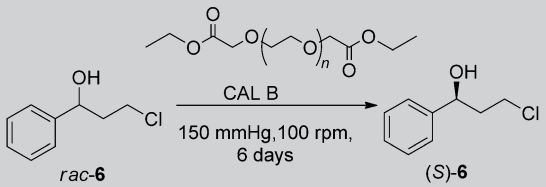
With regard to the effect of temperature on EKR, we observed that a higher temperature of 55 °C led to an improve-

Table 2. EKR and separation of target substrates **4**–**7** using PEG_{600}-carboxylates **1** and **2** as acylating agents.

Entry	AA/alcohol	*T* [°C]/vacuum [mm Hg]	*t* [h] first/second steps	(*S*)-Alcohol yield/*ee* [%][g]	(*R*)-Alcohol yield/*ee* [%][g]
1[a,b]	**2/4**	45/350	48/24	45/75	33/93
2[a,b]	**1/4**	45/350	48/24	56/42	26/93
3[b,c,d]	**2/4**	35/450	96/24	33/99	30/90
4[a,b]	**1/5**	45/150	120/24	62/48	35/88
5[a,b]	**2/5**	45/150	120/24	62/52	32/86
6[a,e]	**2/6**	45/150	144/24	58/40	33/88
7[a,f]	**2/7**	45/150	144/24	64/50	30/94

[a] All reactions were carried out with 0.414 mmol of alcohol, 0.414 mmol of acylating agent, and 20 mg of CAL B. To perform the second step, 2.5 equivalents of ethanol were added. [b] The extraction step was carried out by dissolving the reaction mixture in water and extraction with *n*-hexane/diethyl ether (4:1). [c] Reaction was carried out with 8.28 mmol of alcohol and acylating agent, and 400 mg of CAL B. To perform the second step, 2.5 equivalents of absolute ethanol were added. [d] Reaction performed in a Kugelrohr oven. [e] The separation was carried out by low-pressure distillation. [f] The extraction step was carried out by dissolving the reaction mixture in water and extraction with *n*-hexane/diethyl ether (2:1). [g] Yield of isolated product obtained after distillation (entry 6) or by solvent evaporation and filtration through silica; enantiomeric excess determined by GLC analysis.

Table 3. EKR and separation of **6** on the five-gram scale using PEG_{600}-carboxylates **1** and **2** as acylating agents.



Entry	AA/*rac*-**6** ratio	*T* [°C]	CAL B [g]	*ee* [%][c]	(*S*)-**6** conv. [%][c]
1[a]	**1:1**	45	2.0	13	10
2[a]	**1:1**	55	2.0	20	15
3[b]	**2:1**	55	2.0	14	10
4[a]	**1:1**	55	4.0	75	47

[a] All reactions were carried out with 29.4 mmol of alcohol, 29.4 mmol of acylating agent (AA), and under vacuum (150 mm Hg) in a rotary evaporator at 100 rpm. [b] The reaction was performed with 29.4 mmol of alcohol, 58.8 mmol of acylating agent. [c] Enantiomeric excess and conversion to the PEG ester were determined by GLC analysis.

Table 4. Reuse process for one-pot EKR.

Entry[a]	*t* [h] first/second steps	(*S*)-Alcohol yeld/*ee* [%][b]	(*R*)-Alcohol yield/*ee* [%][b]
1	48/24	46/85	31/94
2	48/24	44/90	40/90
3	48/24	43/88	32/90

[a] All reactions were carried out with 0.414 mmol of 1-phenylethanol **3**, 0.414 mmol of PEG_{600}-diester **2**, and 20 mg of CAL B. To perform the second step, 2.5 equivalents of ethanol was added. The extraction step was carried out by dissolving the reaction mixture in water and extraction with *n*-hexane/diethyl ether (4:1). [b] Enantiomeric excess determined by GLC analysis.

ment in conversion rate (Table 3, entries 1 and 2). Furthermore, increasing the amount of the acylating agent did not improve resolution (Table 3, entry 2 versus 3). Satisfactorily, an increase in enzyme loading significantly improved resolution and provided good conversion and enantioselectivity of 47% and 75% *ee*, respectively (Table 3, entry 4). The best results were obtained in an optimized procedure that used vacuum (150 mm Hg) at 55 °C with of CAL B (5.0 g) for six days. Compound (*S*)-**6** was isolated from the first step in 54% yield and 71% *ee*, and (*R*)-**6** from the second step after one day in 37% yield and 89% *ee*.

Finally, we have explored the ability to reuse both the enzyme CAL B and PEG_{600}-diester **2**, the latter of which doubles as the acylating agent and reaction media. We chose 1-phenylethanol **3** as substrate in a 1:1 ratio in the presence of CAL B at 45 °C. As displayed in Table 4, the enzyme efficiency was retained over at least three cycles (>30% yield, >85% *ee*), which corresponds to six sequential enzymatic reactions using the same batch of enzyme and acylating agent. These results demonstrate the simplicity, feasibility, and robustness of this enzymatic resolution process.

In conclusion, a facile, efficient, and practical method is described for enzymatic kinetic resolution and enantiomer separation of secondary alcohols with the following key advantages: 1) readily available and biocompatible acylating agents PEG_{600}-diacid **1** and PEG_{600}-diethyl ester **2** that double as reaction media; 2) efficient EKR achieved under irreversible conditions by the removal of formed volatile ethanol or water under vacuum, coupled with subsequent hydrolysis of the esterified enantiomer using the same enzyme to afford both enantiomers as free alcohols; and 3) the low volatility and high affinity of the PEG_{600}-diester for the aqueous phase, which allows for the simple removal of the free alcohol by distillation or organic solvent extraction.

The simplicity of this method, which combines single enzyme use with the ability to separate pure volatile and nonvolatile products by a simple extraction or distillation while affording both enantiomers as free alcohols, grants great benefits over other kinetic resolution protocols. Furthermore, we have shown the ease of scale-up for important enantiomerically pure products such as fluoxetine precursor **6**.

Experimental Section

General procedure for enzymatic kinetic resolution and separation of *sec*-alcohol enantiomers

CAL B (Novozym 435; 20 mg) and a secondary alcohol (0.414 mmol) were added to a plastic test tube (10 mL) inside a glass trap attached to a controlled vacuum pump system, in which PEG_{600}-carboxylates (0.414 mmol) were being stirred. The reaction mixture was stirred for 48–144 h under reduced pressure (150–350 mm Hg) in a thermostatic water bath. Afterwards, the reaction mixture was filtered and the enzyme was washed with dichloromethane, followed by concentration of the filtrate under reduced pressure. The isolation step was carried out by distillation or by adding water to the reaction mixture and extraction with a solution of *n*-hexane/diethyl ether (three times), then passed through silica to obtain the *S* enantiomer in the organic phase. The enzyme was dried under reduced pressure (20 mm Hg) for 2 h. After extraction, the water was evaporated under reduced pressure. The recovered enzyme and the collected reaction medium that contained the other enantiomer as an ester and the PEG_{600}-derivative were transferred to a plastic test tube (10 mL). Alcohol (absolute ethanol, 2.5 equiv based on acylated alcohol) was added, and the mixture was stirred for 24 h in a thermostatic water bath. Afterwards, the above reaction mixture was filtered and the enzyme was washed with dichloromethane, followed by concentration of the filtrate under reduced pressure. The isolation step was carried out by distillation or by adding water to the reaction mixture, extraction with a solution of *n*-hexane/diethyl ether (three times), and then passed through silica to obtain the *R* enantiomer in the organic phase. The enzyme was dried under reduced pressure (20 mm Hg) for 2 h. After extraction, the water was evaporated under reduced pressure. Both obtained enriched enantiomers were analyzed by chiral GLC for the determination of *ee* values.

Acknowledgements

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Keywords: acylation · alcohols · enzyme catalysis · kinetic resolution · polyethers

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