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An efficient process for the resolution of *cis*-4-O-protected-2-cyclopenten-1,4-diol using pancreatin lipase in [C_8mim][PF_6] as a reusable system

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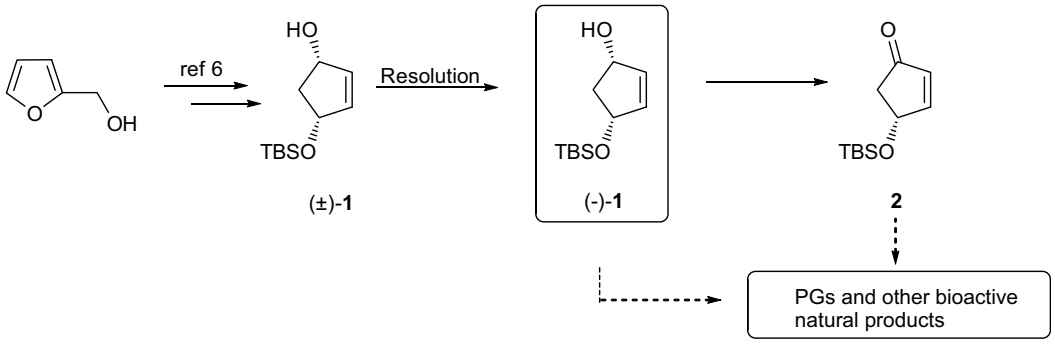
ABSTRACT

An efficient porcine pancreatin lipase-catalyzed transesterification of *cis*-4-*O*-TBS-2-cyclopenten-1,4-diol has been demonstrated in 1-octyl-3-methylimidazolium hexafluorophosphate, [C_8mim][PF_6] ionic liquid, furnishing both the alcohol and the corresponding acetate in excellent enantiomeric purity and yields. This typical reaction system containing the suspension of enzymes in ionic liquid medium could be reused up to five times to prepare the required products in consistent yields and ee's. The corresponding optically active derivatives are very useful intermediates towards the synthesis of various types of compounds, including prostanoids.

1. Introduction

Room temperature ionic liquids (RTILs) belong to a significant class of solvents, which has attracted growing interest over the last decade because of their unique physical, chemical and fine tuneable properties.[1] Since they can dissolve a large number of organic compounds as well as transition metal derivatives, as well as possess no effective vapour pressure and can be often recycled, RTILs offer an attractive alternative to conventional organic solvents.[1,2] In recent years, they have also been demonstrated as very useful reaction media for bio-catalytic transformations and enzymatic resolutions.[3] In particular, it has been established that enzymes are stabilized in some RTILs, allowing the use of increased temperatures in specific reaction conditions and moreover, in combination with *sc*CO_2 leading to novel and very efficient processes.[4] In addition, specially designed Task Specific Ionic Liquids (TSILs) have recently been used for the enzymatic kinetic resolution of *sec*-alcohols.[5]

Optically active *cis*-2-cyclopenten-1,4-diol derivatives, and more specifically, the *O*-TBS compound **1**,[6] are known to be very important intermediates towards the preparation of prostaglandins (PGs),[7] carbocyclic nucleosides[8] and other natural products.[9] Furthermore, they have been used to prepare the corresponding enone **2**, which is another key intermediate in the synthesis of



Scheme 1. Access to (−)-*cis*-4-*O*-TBS-2-cyclopentene-1-ol, (−) **1**.

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various prostanoids and important biologically active molecules (Scheme 1).[10] Therefore, improvements towards the synthesis and resolution of (±)-**1** and its analogues are always a subject of interest to fulfil with regard to the ongoing requirement towards the corresponding syntheses.

As part of our research programme on new developments towards the total synthesis of prostaglandins[7b] (PGs), and based on our previous interest and results obtained in the use of RTILs,[11] we became involved in the development of new and efficient methods for the resolution of compound (±)-**1**. Herein, we report that the ionic liquid, [C_8mim][PF_6], can be used as a solvent medium to perform a very efficient resolution of (±)-**1** using Pancreatin Lipase, with significant advantages concerning the reaction conditions used, the purification procedure, and the reutilizations of the suspended enzyme in ionic liquid reaction mixture.[12]

2. Results and discussion

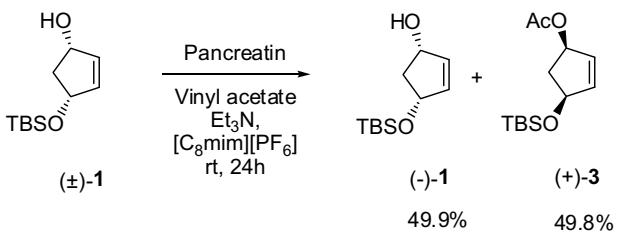
We have selected the ionic liquid, [C_8mim][PF_6], as the solvent medium, based on its physical properties:[13] due to the long aliphatic C_8 chain, it has a low viscosity, density and melting point and should allow its use in a wide range of temperatures for certain reactions. Moreover, it also has low miscibility with water, which should minimize its loss during the extraction and washing procedures. Furthermore, it is also known that enzymes are usually active in RTILs containing the PF_6 anion, contrary to certain other counter anions.[14]

The resolution of *cis*-(±)-4-*O*-TBS-2-cyclopentene-1-ol (±)-**1** was performed using porcine pancreatin lipase in the ionic liquid [C_8mim][PF_6] under the required reaction parameters, based on the literature data,[6] as indicated in Scheme 2. After optimization of the reaction conditions, (−)-*cis*-4-*O*-TBS-2-cyclopentene-1-ol (−)-**1** was obtained along with its corresponding acetate derivative (+)-*cis*-4-*O*-TBS-2-cyclopentenyl acetate (+)-**3** in 49.9% and 49.8% isolated yields, respectively, after ether extraction followed by chromatography on SiO_2.

The HPLC analysis was performed using Chiralcel OD column (*i*PrOH/hex = 1:99, 1 ml/min) indicating that the mono-protected diol (−)-**1** (detected at 199.9 nm) was obtained in >99% ee. On the other hand, the acetate derivative (+)-**3** (detected at 201.1 nm) was obtained in >96% ee.[15]

The above-mentioned resolution process using the porcine pancreatin lipase in the ionic liquid [C_8mim][PF_6] worked out to be a very efficient system for our purpose. It was observed that, after the extraction of the desired products, the enzyme was retained back in the ionic liquid medium as a uniform suspension. Therefore, it became of interest to check the possibility of reusing this particular homogeneous system for further runs. After drying this suspension under high vacuum (0.1 mmHg) for 5 h at 30 °C, it was subjected again to the resolution process on the same scale as for the first run by the addition of (±)-**1** and the other required reagents.

As indicated in Table 1, five runs could be successfully performed using the same reaction mixture containing porcine pancreatin lipase in [C_8mim][PF_6]. It was observed that each run gave excellent to good yields and ee's for the desired products. This result demonstrates that the enzyme porcine pancreatin lipase remains stable in ionic liquid [C_8mim][PF_6] even after 5 runs, showing no major loss in its activity and adding worth to our process for resolution. Extension of this methodology to other *sec*-alcohols is currently under active study in our groups.



Scheme 2. Resolution of (±)-**1** using pancreatin lipase in [C_8mim][PF_6)].

Table 1
Recycling and reuse of the porcine pancreatin lipase in [C_8mim][PF_6]

Runs	Enantiomerically pure alcohol (−)-**1**		Acetate derivative (+)-**3**	
	ee's[a] (%)	Yield[b] (%)	ee's[a] (%)	Yield[b] (%)
1	>99	49.9	>96	49.8
2	>99	46.2	>96	48.8
3	>99	43.2	>96	47.6
4	>98	42.4	>96	47.6
5	>98	42.0	>96	46.8

[a] Obtained using HPLC analysis using Chiral OD column.
[b] Isolated yield after chromatography on SiO_2.

3. Conclusion

In conclusion, we have demonstrated the first lipase-catalyzed enantioselective transesterification of *cis*-4-*O*-TBS-2-cyclopenten-1,4-diol in an ionic liquid as solvent medium to obtain enantiomerically pure compound in excellent ee's. Furthermore, the porcine pancreatin lipase was found to be stable and active in ionic liquid [C_8mim][PF_6]; the system containing enzyme and ionic liquid could be recycled and reused efficiently for further runs.

Acknowledgements

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Data for compound (−)-**1**; ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.85 (dt, 1H, J = 5.6, 1.2 Hz), 5.74 (dt, 1H, J = 5.5, 1.3 Hz), 4.57 (t, 1H, 6.0 Hz), 4.50 (t, 1H, J = 6.0 Hz), 2.59 (dt, 1H, J = 13.8, 7.0 Hz), 1.78 (br s, 1H, OH), 1.52 (dt, 1H, J = 13.7, 4.4 Hz), 0.81 (s, 9H), 0.00 (s, 6H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 136.9, 135.6, 75.2, 75.1, 44.6, 25.8, 18.1, −4.6. HPLC analysis: Column Chiralcel OD column, *i*PrOH/hex = 1:99, 1 ml/min, UV detection at 199.9 nm, R_t = 6.3 min for (−)-**1**. $[\alpha]_D^{21} = -21.7$ (c 1.6, $CHCl_3$). {Literature value; $[\alpha]_D^{20} = -21.2$ (c 0.89, $CHCl_3$); Cpd (−) 10 of Ref. 6}.
Data for compound (+)-**3**; ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.89 (dt, 1H, J = 5.6, 1.5 Hz), 5.80 (dt, 1H, J = 5.5, 1.5 Hz), 5.37 (t, 1H, 6.0 Hz), 4.63 (t, 1H, J = 6.0 Hz), 2.72 (dt, 1H, J = 13.8, 7.3 Hz), 1.96 (s, 3H), 1.52 (dt, 1H, J = 13.8, 5.1), 0.81 (s, 9H), 0.00 (d, 6H, J = 1.7 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ 170.8, 138.8, 131.1, 76.9, 74.8, 41.1, 25.8, 21.1, 18.1, −4.6 (d, J = 3.7 Hz). HPLC analysis: Column Chiralcel OD column, iPrOH/hex = 1:99, 0.8 ml/min, UV detection at 201.1 nm, R_t = 5.9 min for (+)-**3**. $[\alpha]_D^{21} = +0.3$ (c 1.4, $CHCl_3$). {Literature value; $[\alpha]_D^{20} = +0.4$ (c 1, $CHCl_3$)); Cpd (+)-**27** within Ref. 6}.