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Preparation of 2-oxazolidinones by enzymatic desymmetrisation

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Abstract—Desymmetrisation of achiral *N*-Boc-serinol was achieved through enzymatic acetylation. Further transformation provided oxazolidinones with >98% enantiomeric excess.

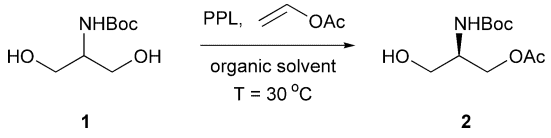
Previous work within this research group has investigated enzymatic routes for the resolution of chiral auxiliaries.[1] In addition, we have also developed an unusual approach to the use of racemic chiral auxiliaries in Evans'-type aldol reactions with subsequent enzymatic resolution leading to enantiomerically enriched recovered auxiliaries and aldol adducts.[2]

Herein, we wish to report an enzymatic desymmetrisation strategy, which has been successfully applied to the preparation of enantiomerically enriched oxazolidinones.

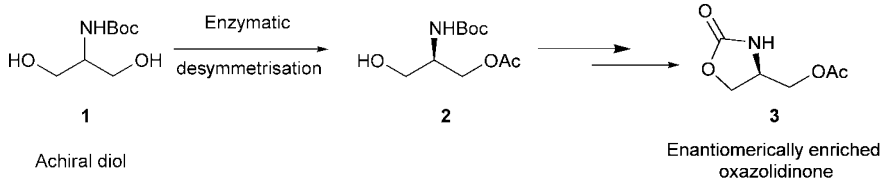
Desymmetrisation of achiral diols using enzymes is a well known process for the formation of enantiomerically enriched mono-esters.[3] The advantage of desymmetrisation over conventional kinetic resolution reactions being the potential ability to achieve high enantiomeric excess even at 100% conversion.[4] Serinol derivatives have received only limited attention in desymmetrisation reactions.[5] A derivative of serinol possessing an enantiomerically pure α-methyl benzyl group on the nitrogen has been used in a chemical/auxiliary based diastereoselective synthesis of oxazolidinones on treatment with chloroformate with up to 92% d.e. (62% yield).[6] Racemisation, during oxazolidinone formation of a mono-silyl ether of *N*-Boc-serinol, has been reported previously and a 1,3-silyl shift was suggested in this case as a likely cause of racemisation.[7]

Our overall desymmetrisation strategy involves the use of *N*-Boc-protected serinol **1** to give a monoacetate **2**, followed by appropriate chemical transformation to afford enantiomerically enriched oxazolidinones (e.g. compound **3**) (Scheme 1).

Boc-protection of achiral serinol (1,3-dihydroxy-2-aminopropane) was achieved in 90% yield by treatment of serinol with Boc anhydride in ethanol at 20°C for 1 h.[8] The desymmetrisation of *N*-Boc-serinol was achieved by selective monoacetylation using PPL (Porcine pancreatic lipase) and vinyl acetate as acylating agent, in organic solvent at 25°C (Scheme 2).[9] A small amount of diacetylated material was also observed, providing a self-correcting process[10] for the removal of the unwanted enantiomer of monoacetyl-



Scheme 2. Desymmetrisation of *N*-Boc-serinol by PPL.



Scheme 1. General approach to preparation of oxazolidinones by enzymatic desymmetrisation.

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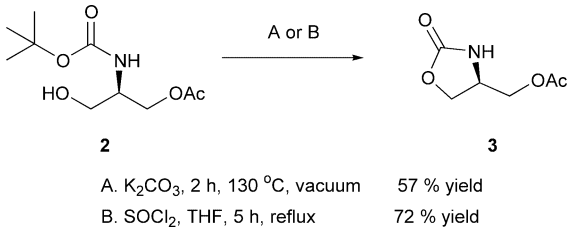
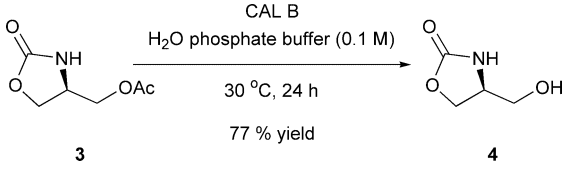
Table 1. Influence of solvent on conversion, e.e. and mono-/diacetylated product ratio[a,b]

Entry	Solvent	Time (h)	Conversion (%)	E.e. (%)	Mono-/diacetylated
1	THF/hexane 1:1	2	96	>99	87
2	iPr$_2$O	22	87	>99	93
3	Vinyl acetate	2	>99	>99	>99

[a] 140 $mg_{enzyme}/mmol_{substrate}$ in solvent (5 mL) using *N*-Boc-serinol (1 mmol) and vinyl acetate (3 mmol); PPL was Porcine pancreas lipase (EC 3.1.1.3.) Type II, from Sigma®; CAL B was Chirazyme® L-2, carrier-fixed, Carrier 3, lyophilizate from Boehringer Mannheim.
[b] Conversion, enantiomeric excess and mono-/diacetylated ratio were determined by HPLC analysis (see text).



Scheme 3. Synthesis of enantiomerically enriched 4-acetoxymethyl-2-oxazolidinone.



Scheme 4. Hydrolysis of 4-acetoxymethyl-2-oxazolidinone.

ated product. Only one enantiomer of the monoacetylated product was detected by chiral HPLC (Chiralcel® OD column, hexane/*iso*-propanol 95:5, 1 mL min^{-1}, $\lambda = 210$ nm).

The choice of solvent was found to influence the enzymatic reaction, and solvent effects are illustrated in Table 1.

The reaction rate of the lipase-catalysed transesterification was faster when vinyl acetate or a mixture THF/hexane was used as solvent, whilst the reaction took 22 h to reach completion in iPr$_2$O.

The use of CAL B (*Candida antarctica* lipase B) as catalyst afforded the monoacetylated product only, in both vinyl acetate and a THF/hexane mixture.

Treatment of enantiomerically enriched acetate **2** with potassium carbonate at 130°C under vacuum afforded the oxazolidinone **3** although this product was obtained as a racemic mixture.[11] We assume that intramolecular acetyl transfer occurs prior to the cyclisation, thereby affording the racemic product. Nevertheless, oxazolidinone **3**[12] was obtained with >98% e.e. on cyclisation with thionyl chloride (Scheme 3).[13]

The absolute stereochemistry of oxazolidinone **3** was confirmed by enzymatic hydrolysis of the acetate group and comparison of the specific rotation with the literature value.[14] The 4-hydroxymethyl-2-oxazolidonone **4** has previously been converted into a range of 4-substituted oxazolidinones including the 4-benzyl and 4-ethyl derivatives (Scheme 4).[14]

6 alternative approach, the enantiomerically enriched mono-acetate **2** was benzylated using benzyl trichloroacetimidate in reasonable yield,[15] followed by cyclisation to provide the oxazolidinone **6** (Scheme 5).[16]

In summary, we have developed an efficient enzymatic desymmetrisation of *N*-Boc-serinol and exploited this to prepare enantiomerically enriched 4-substituted 2-oxazolidinones.

Acknowledgements

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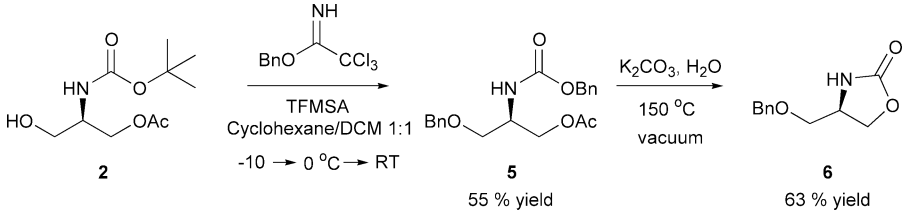
References

1. Haughton, L.; Williams, J. M. J.; Zimmerman, J. A. *Tetrahedron: Asymmetry* **2000**, *11*, 1697.
2. Neri, C.; Williams, J. M. J. *Tetrahedron Lett*. **2002**, *43*, 4257.
3. (a) Takabe, K.; Iida, Y.; Hiyoshi, H.; Ono, M.; Hirose, Y.; Fukui, Y.; Yoda, H.; Mase, N. *Tetrahedron: Asymmetry* **2000**, *11*, 4825; (b) Bódai, V.; Novák, L.; Poppe, L. *Synlett* **1999**, *6*, 759; (c) Goswami, A.; Mirfakhrae, K. D.;



Scheme 5. Synthesis of enantiomerically enriched 4-benzyloxymethyl-2-oxazolidinone.

Patel, R. N. *Tetrahedron: Asymmetry* **1999**, *10*, 4239; (d) Levayer, F.; Rabillier, C.; Tellier, C. *Tetrahedron: Asymmetry* **1995**, *7*, 1675.
4. Willis, M. C. *J. Chem. Soc., Perkin Trans. 1* **1999**, *13*, 1765.
5. Wang, Y.-F.; Lalonde, J. J.; Momongan, M.; Bergbreiter, D. E.; Wong, C.-H. *J. Am. Chem. Soc.* **1988**, *110*, 7200.
6. Sugiyama, S.; Watanabe, S.; Ishii, K. *Tetrahedron Lett.* **1999**, *40*, 7489.
7. Hanessian, S.; Ninkovic, S. *J. Org. Chem.* **1996**, *61*, 5418.
8. Benoist, E.; Loussoruarn, A.; Remaud, P.; Chatal, J. F.; Gestin, J. F. *Synthesis* **1998**, 1113.
9. **(*R*)-(+)-3-*O*-Acetyl-2-*N*-(*tert*-butoxycarbonyl)serinol**: colourless oil; $R_f=0.31$ (SiO_2, EtOAc/hexane 1:1); HPLC 10.8 min (Chiralcel OD® column, hexane/isopropanol 95:5, 1 mL min^{-1}, $\lambda=210$ nm; $[\alpha]_D^{30}=+3.5$ (*c* 0.56, $CHCl_3$); ν_{max} (neat)/cm^{-1} 3370, 2975, 2965, 1710, 1690, 1525, 1370, 1240, 1170; ^1H NMR (300 MHz; $CDCl_3$) δ 5.10 (1H, br d, $J=8.4$, N*H*), 4.19 (2H, d, $J=5.7$, CH_2OAc), 3.98–3.88 (1H, m, C*H*N), 3.65 (2H, dq, $J=4.7$ and 11.4, CH_2OH), 3.02 (1H, s br, O*H*), 2.09 (3H, s, COCH_3) 1.45 (9H, s, 3×CCH_3); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 171.8 (O*C*O), 155.2 (N*C*O), 80.3 (*C*$(CH_3)_3$), 63.4 (*C*H_2OAc), 62.2 (*C*H_2OH), 51.4 (*C*HN), 28.7 (3× C*C*H_3), 21.2 (CO*C*H_3); MS (70 eV): *m*/*z* (%): 234 Da ($M^{\bullet+}$+1, 45%), 178 (100), 160 (53), 134 (62), 118 (60), 102 (72). Anal. calcd for $C_{10}H_{19}NO_5$: C, 51.49; H, 8.21; N 6.00. Found: C, 51.1; H, 8.2; N, 5.9.
10. *Enzyme Catalysis in Organic Synthesis*; Drauz, K.; Waldman, H., Eds.; VCH: Weinheim, 2002; Vol. II, p. 417.
11. Wu, Y.; Shen, X. *Tetrahedron: Asymmetry* **2000**, *11*, 4353.
12. **(*S*)-(−)-4-Acetoxymethyl-2-oxazolidinone**: white solid, mp 77–79°C; $R_f=0.31$ (SiO_2, EtOAc/hexane 9:1); HPLC 18.8 min (Chiralcel AD® column, hexane/isopropanol 90:10, 1 mL min^{-1}, $\lambda=210$ nm); $[\alpha]_D^{30}=-40.7$ (*c* 1.35, $CHCl_3$); ν_{max} (CH_2Cl_2)/cm^{-1} 3435, 2950, 1720, 1660, 1450, 1370, 995; ^1H NMR (300 MHz; $CDCl_3$) δ 5.71 (1H, br s, N*H*), 4.51 (1H, dd with the appearance of a t, $J=8.5$, CH*H*OCON), 4.24–4.01 (4H, m, CH_2OAc, C*H*HOCON, C*H*N), 2.11 (3H, s, COCH_3); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 170.8 (O*C*O), 159.8 (N*C*O), 66.9 (*C*H_2OAc), 64.9 (*C*H_2O), 51.1 (*C*HN), 20.7 (CO*C*H_3); MS (70 eV): *m*/*z* (%): 160 Da ($M^{\bullet+}$+1, 100%), 118 (23), 99 (20), 86 (30). Anal. calcd for $C_6H_9NO_4$: C, 45.28; H, 5.70; N 8.80. Found: C, 45.3; H, 5.7; N, 8.6%.
13. (a) Matsunaga, H.; Ishizuka, T.; Marubayashi, N.; Kuneida, T. *Chem. Pharm. Bull.* **1992**, *40*, 1077; (b) Miyata, O.; Ozawa, Y.; Ninomiya, I.; Naito, T. *Tetrahedron* **2000**, *56*, 6199.
14. Sibi, M. P.; Rutherford, D.; Sharma, R. *J. Chem. Soc., Perkin Trans. 1* **1994**, *13*, 1675.
15. (a) Iversen, T.; Bundle, D. R. *J. Chem. Soc., Chem. Commun.* **1981**, 1240; (b) Suhara, Y.; Achiwa, K. *Chem. Pharm. Bull.* **1995**, *43*, 414; (c) Barrett, A. G. M.; Pilipauskas, D. *J. Org. Chem.* **1990**, *55*, 5170.
16. **(*R*)-(+)-4-Benzyloxymethyl-2-oxazolidinone**: cream solid, mp 49–51°C; $R_f=0.34$ (SiO_2, EtOAc/hexane 2:1); HPLC 22.0 min (Chiralcel OD® column, hexane/isopropanol 75:25, 1 mL min^{-1}, $\lambda=254$ nm); $[\alpha]_D^{30}=+25.0$ (*c* 0.08, $CHCl_3$); ν_{max} (CH_2Cl_2)/cm^{-1} 3450, 2865, 1760, 1400, 1225, 1098; ^1H NMR (300 MHz; $CDCl_3$) δ 5.28 (1H, br s, N*H*), 4.54 (2H, s, $CH_2OCH_2C_6H_5$) 4.47 (1H, dd with the appearance of a t, $J=8.4$, CH*H*OCO), 4.13–4.02 (2H, m, C*H*HOCO, C*H*N), 3.50–3.46 (2H, m, $CH_2OCH_2C_6H_5$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.0 (N*C*O), 137.3, 128.8 (2C), 128.3, 128.0 (2C) (aromatic C), 73.9 ($CH_2OCH_2C_6H_5$), 72.1 (*C*$H_2OCH_2C_6H_5$), 67.3 (*C*H_2OCO), 52.2 (*C*HN); MS (70eV): *m*/*z* (%): 208 Da ($M^{\bullet+}$+1, 100%), 174 (21), 91 (36). Anal. calcd for $C_{11}H_{13}NO_3$: C, 63.76; H, 6.32; N 6.76. Found: C, 64.1; H, 6.3; N, 6.4%.