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Lipase Mediated Optical Resolution of Bicyclic Secondary Carbinols

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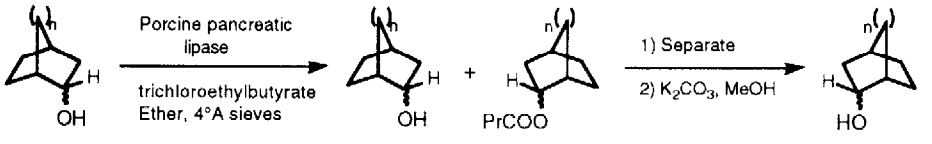
***Abstract**: The optical resolution of (±) -endo-bicyclo[2.2.1.] heptan-2-ol and (±) bicyclo [2.2.2.] octan-2-ol proceeds by porcine lipase catalyzed transesterification under anhydrous conditions.*

Bicyclic hydrocarbon derivatives and, in particular, the 2-norbornyl system occupy an important position in synthetic and physical organic chemistry.[1] Methods for the preparation[2] of optically active endo and exo-[2.2.1]-bicycloheptan-2-ol (**1** and **2**) and [2.2.2.]-bicyclooctan-2-ol (**3**) include asymmetric hydroboration[2a] and microbe mediated reduction of the corresponding ketones.[2b] Notably, Griengl, Faber and coworkers[3] have described lipase catalyzed hydrolyses of esters of bicyclic alcohols. The use of readily available lipases (triacylglycerol hydrolases EC 3.1.1.3) to catalyze the optically discriminating transesterification of racemic alcohols under anhydrous conditions has emerged as a useful synthetic method.[4] Herein is reported our results on the lipase catalyzed resolution of alcohols (±)-**1**, (±)-**2** and (±)-**3**.

Initial results showed that the reaction of alcohols (±)-**1**, (±)-**2** or (±)-**3** with trichloroethyl butyrate was catalyzed efficiently by porcine pancreatic lipase.[5] The progression of the transesterification could be accurately monitored by ^{1}H NMR. While the rate of reaction of (±)-**1** and (±)-**3** slowed dramatically near 50% completion, reaction of the exo isomer (±)-**2** proceeded at a constant and comparable rate to ~ 100 % transformation.



n=1 endo (±)-**1**
n=1 exo (±)-**2**
n=2 (±)-**3**

n=1 endo (-)-**1**,
n=1 exo (±)-**2**,
n=2 (+)-**3**,

n=1 endo (+)-**1**
n=1 exo (±)-**2**
n=2 (-)-**3**

In accord with this observation was the high optical yields obtained for alcohols **1** [(-)-**1**; 87.2%e.e./ (+)-**1**; 87.6%e.e. at 50% conversion][6] and **3** [(+)-**3**; 69%e.e./ (-)-**3**; 87.2% e.e. @ 45 % conversion].[7] Moreover, the level of optical resolution obtained could be optimized by adjusting the % conversion: [(+)-**1**; > 95% e.e./ (-)-**1**; 71.4% e.e. @ 44% conversion].[8] A much higher degree of enantioselection is seen than was reported for the hydrolytic resolution employing *Candida cylindracea*.[3,5a] In sharp contrast, exo-norborneol (±)-**2** provided optically inactive products (< 2 %e.e.) regardless of % conversion.[9] It was believed, based on the following results that the lack of enantioselectivity seen for the transesterification of exo-norborneol was caused by the enzyme's inability to distinguish the enantiomeric alcohols (+) and (-)-**2**. The butyrate esters obtained were shown not to be products of uncatalyzed transesterifications as the reaction does not proceed in the absence of enzyme. Pathways that employ product ester as substrate were not operative since no transesterification occurred using the (±)-**2** butyrate as the butyryl donor and benzyl alcohol as

the butyryl acceptor. Processes utilizing norbornyl cation intermediates, which would be expected to produce optically inactive products, were ruled out on the basis of deuterium labelling experiments.[10] The results describe a useful process for obtaining optically active bicyclic carbinols, **1** and **3** and the exquisite substrate specificity of porcine pancreatic lipase for **1** and **3** vs. **2**.

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Experimental: (Enzyme Catalyzed Transesterification) Endo-norborneol (±)-**1** (5.0 g, 44.6 mmol) and trichloroethyl butyrate, (5.1 g, 23.2 mmol) are dissolved in 40 ml of diethyl ether , 4 g of 4°A molecular sieves is added and the mixture is stirred vigorously at room temperature. Porcine pancreatic lipase (Sigma, Type II, crude) was added portion wise in 0.5-1.0g lots at times 0, 24, 48 and 72 h. The reaction is monitored by ^{1}H NMR in which % conversion is determined by integration of the C_2 - H resonance. At 50% completion (92 h) the reaction suspension is filtered through celite and the filtrate is concentrated in vacuo at ambient bath temperature to avoid sublimation of the endo-norborneol. The remaining alcohol and product ester are recovered by flash chromatography (2->25% ether/hexane) which afforded 2.9 g (15.9 mmol) endo-norborneol butyrate as a clear oil and 1.8 g (16.0 mmol) of endo-norborneol as a white solid (Mp = 147-148.5 °C). Enantiomeric excesses for each substrate transesterification studied, (±)-**1**,**2** and **3**, is determined as outlined in ref 7-9. Absolute configuration of product butyrates and alcohols are determined by optical rotation and correlation with previously published data.[2,3]

References and Notes

1. (a) W. Kirmse *Acc. Chem.Res.* 1986, **19**, 36 and references therein.
2. (a) Chiral hydroboration: H.C. Brown, J.V.N. Prasad and M. Zaidlewicz *J. Org. Chem.* 1988, **53**, 2911.; H.C. Brown and B. Singaram *Acc. Chem. Res.* 1988, **21**, 287. ; H.C. Brown, M.C. Desai and P.K. Jadhav *J. Org. Chem.* 1982, **47**, 5065.(b) Microbial reductions: A. J. Irwin and J.B. Jones *J. Am. Chem. Soc.* 1976, **98**, 8476. ; M. Nakazaki, H. Chikamatsu, K. Naemura and M. Asao *J.Org. Chem.* 1980, **45**, 4432.
3. (a) G. Eichberger, G. Penn, K. Faber and H. Griengl *Tetrahedron Lett.* 1986, **27**, 2843 ; (b) Th. Oberhauser, M. Bodenteich, K. Faber, G. Penn and H. Griengl *Tetrahedron* 1987, **43**, 3931; (c) K.Konigsberger, K. Faber, Ch. Marschner, G. Penn, P. Baumgartner and H. Griengl *Tetrahedron* 1989, **45**, 673; (d) Th. Oberhauser, K. Faber and H. Griengl *Tetrahedron* 1989, **45**, 1679: (e) Optical yields of (+) and (-)-**1** of 75 % e.e. (@ 40 % conversion.) and 72 % e.e. (@ 60 % conversion.) respectively were obtained by *Candida c.* lipase hydrolysis of endo-norborneol esters (ref 3b); (f) Optical yields of (+) and (-)-**2** of 22 % e.e. (@ 60 % conversion.) and 17 % e.e.(@ 40 % conversion) respectively were obtained by *Candida c.* lipase hydrolysis of exo-norborneol esters (ref 3b).
4. (a) G. Kirchner, M. P. Scollar and A.M. Klibanov *J. Am. Chem. Soc.* 1985, **107**, 7072. (b) C. Chen and C.J. Sih *Angew. Chem. Int. Ed. Engl.* 1989, **28**, 695. (c) B. Cambou and A. Klibanov *J.Am.Chem. Soc.* 1984, **106**, 2687.
5. (a) All enzymes were obtained from Sigma Chemical company and used as provided (b)The lipase from Candida cyclindricea did not catalyze the transesterification of (±)-**1** (c) all compounds were characterized by ^{1}H and ^{13}C NMR, IR, low resolution MS.
6. Ratios were determined by integration of the baseline resolved diastereomeric methoxy resonances of the (S)-(-)-α-methoxy-α-(trifluoro methyl)phenylacetates in the ^{1}H NMR (500 MHz, $CDCl_3$). Absolute configuration was determined by optical rotation. The predominant enantiomer obtained as the butyrate ester has the absolute configuration 1S,2R,4R ($[\alpha]_D$ = +2.70°, c=12.75/$CHCl_3$). The predominant enantiomer obtained as unreacted alcohol has the absolute configuration 1R,2S,4S ($[\alpha]_D$ = -2.03°, c=11.15/$CHCl_3$)
7. Ratios were determined by integration of the baseline resolved diastereomeric methoxy resonances of the (S)-(-)-α-methoxy-α-(trifluoro methyl)phenylacetates in the ^{1}H NMR (500 MHz, $CDCl_3$). Absolute configuration was determined by optical rotation. The predominant enantiomer obtained as the butyrate ester has the absolute configuration 2R ($[\alpha]_D$ = -28.09°, c=10.2/$CHCl_3$). The predominant enantiomer obtained as unreacted alcohol has the absolute configuration 2S ($[\alpha]_D$ = +23.29°, c=10.45/$CHCl_3$).
8. Ratios were determined by integration of the baseline resolved diastereomeric C-3 endo hydrogen resonances in the ^{1}H NMR (300 MHz, $CDCl_3$) produced by admixture of $Pr(tfc)_3$. The assignment of > 95 % e.e. denotes the limits of detection of the spectrometer. Absolute configuration was determined by optical rotation. The predominant enantiomer obtained as the butyrate ester has the absolute configuration 1S,2R,4R.($[\alpha]_D$ = +1.28°, c=1.32/$CHCl_3$). The predominant enantiomer obtained as unreacted alcohol has the absolute configuration 1R,2S,4S ($[\alpha]_D$ = -0.89°, c=1.7/$CHCl_3$).
9. Ratios were determined by integration of the baseline resolved diastereomeric C_1-H resonances of the (S)-(-)-α-methoxy-α-(trifluoro methyl)phenylacetates in the ^{1}H NMR (500 MHz, $CDCl_3$). No optical rotation could be detected for the exo-norborneols (**2**), produced by porcine lipase catalyzed transesterification. Optically active standards for analytical comparison were produced by reaction of (+) and (-)-**1** with (S)-(-)-α-methoxy-α-(trifluoromethyl) phenylacetic acid (DIAD/Ph_3P).
10. A deuterium label in (±)-endo-2-d-exo-2-norborneol was shown not to move to C-1 during the transesterification reaction.

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