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Resolution of *anti*-3-Oxotricyclo[2.2.1.0]heptane-7-Carboxylic Acid by *Candidia antartica* Lipase A

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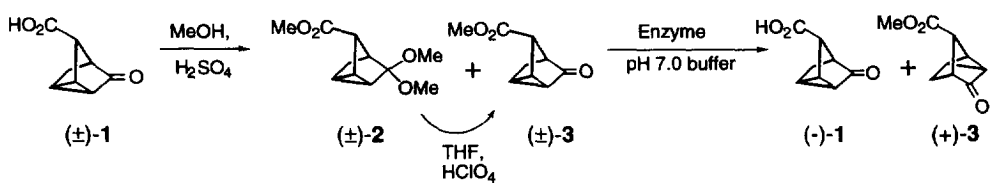
Abstract: An enzyme-based resolution for *anti*-3-oxotricyclo [2.2.1.0]heptane-7-carboxylic acid (**1**) that gives a higher yield of recovery and is more expedient than previously reported procedures. Copyright © 1996 Elsevier Science Ltd

Anti-3-oxotricyclo[2.2.1.0]heptane-7-carboxylic acid (**1**) is a synthetically versatile chiral intermediate and has been reported in the literature primarily with respect to prostaglandin syntheses.[1] The literature procedures rely on crystallization with a chiral amine, *l*-(-)-α-methylbenzylamine to obtain the (+)-enantiomer of the acid. Unfortunately, 3 or 4 recrystallizations are needed to obtain material of >98% ee and the recovery is 12% (24% of the theoretical value of the single enantiomer).[1d] We were interested in synthesizing multi-gram quantities of (-)-**1** by a more efficient procedure.

Several resolution methods were investigated: crystallizations with chiral amines other than α-methylbenzylamine, esterification with a chiral alcohol, and enzymatic hydrolysis of the butyl or methyl ester (Scheme 1). The first two procedures proved ineffective, however, we discovered several enzymes accepted the ester as a substrate. We first examined a few common lipases and esterases, *Candidia cylindracea*, porcine pancreatic lipase, *Pseudomonas fluorescens*, pig liver esterase (PLE), Subtilisin Carlsberg (SC), PS30 Lipase, cholesterol esterase, and acetyl cholinesterase.[2] Of these, only PLE and SC hydrolyzed the butyl or methyl ester at an appreciable rate.[3] We screened several more enzymes[4] to find the optimum enzyme for the resolution of methyl ester **3**.[1c,5] Approximately 1 mg of **3** was dissolved in pH 7.0 buffer and subjected to treatment with each enzyme at rt. The reactions were monitored for completeness by TLC and after 90 h, each reaction was worked-up for analysis by chiral HPLC.[6] *Mucor miehei* lipase and ChiroCLEC-BL[7] produced (+)-**1** with moderate selectivity. *Pseudomonas cepacia*, PLE, *Candidia rugosa* lipase, α-chymotrypsin, *Candidia antartica* B lipase and *Bacillus* sp. proteases showed little or no stereoselectivity, producing nearly racemic **1**. ChiroCLEC-CR and *Candidia antartica* A (CA-A) lipase gave good selectivity for the production of (-)-**1**.

Scheme 1.[5,8]



Since both the ChiroCLEC-CR and CA-A lipase showed potential for large scale use in the production of (-)-**1**, they were investigated further. Reactions with the two enzymes were run with 100 mg of methyl ester **3** in pH 7 phosphate buffer at rt. The ChiroCLEC-CR was much slower (2 weeks) than the CA-A reaction (14 - 17 h) under these conditions. Optimization of conditions for the ChiroCLEC-CR, such as organic co-solvents to increase the conversion rate, was not pursued. With minimal optimization in reaction conditions (i.e., temperature, concentration) for CA-A lipase,[8] we were able to resolve multigram quantities of (-)-**1**[1d] efficiently. The average recovery on a 9 g scale of (±)-**3** was 2.50 g (30%) of (-)-**1** (>99 % ee) and 5.0 g (56%) of (+)-**3** (60% ee). The enzyme was not recovered.

Our goal to establish a viable large-scale resolution of *anti*-3-oxotricyclo[2.2.1.0]heptane-7-carboxylic acid (**1**) has been met through enzymatic hydrolysis of the corresponding methyl ester. Overall the CA-A lipase method is more efficient than the chiral amine crystallization method; the yield from the enzyme method is higher (30% vs. 12%) and faster (2 days vs. 4 days). To resolve a gram of (-)-**1**, the cost of the enzyme is less than one third that of the α-methylbenzylamine. Finally, the number of manipulations has been reduced significantly which, in turn greatly reduces the amount of organic solvent and processing time needed.

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References and Notes:

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2. Enzymes were purchased from the following sources: Sigma: *Candidia cylindracea* (L-1754); porcine pancreatic lipase (L-3126); *Pseudomonas fluorescens* (P-6380); PLE (E-3128); SC (P-5380); cholesterol esterase (C-3766); Acetyl cholinesterase (C-2629); Amano: PS30 Lipase; Altus Biologics, Inc: CA-A lipase and ChiroCLEC-CR.
3. No difference in selectivity between the two esters was seen, only the methyl ester was pursued.
4. A ChiroScreen-EH kit from Altus Biologics Inc., 40 Allston Street, Cambridge, MA, 02139-4211. All of the enzymes in the kit are available individually from Altus Biologics Inc.
5. To avoid using diazomethane on large scale, the methyl ester was prepared as follows: *anti*-3-Oxotricyclo[2.2.1.0]heptane-7-carboxylic acid **1** (10.1 g, 66.4 mmol) was dissolved in methanol (221 mL) and conc. H_2SO_4 (1.0 mL) and heated to reflux for 18 h. The reaction was allowed to cool to rt and the methanol removed *in vacuo*. The residue was diluted in EtOAc (150 mL) and washed with a sat. $NaHCO_3$ solution (150 mL). The aqueous layer was extracted with EtOAc (3 x 150 mL) then the combined organic portions were washed with sat. NaCl solution and dried over Na_2SO_4. The solution was concentrated *in vacuo* to give a mixture of **2** and **3**. This oil was dissolved in THF (265 mL) and $HClO_4$ (70%, 3.9 mL) at 0 °C for 45 min. The THF was removed *in vacuo* and the residue dissolved in EtOAc (150 mL) and washed with a sat. $NaHCO_3$ solution (150 mL). The aqueous layer was extracted with EtOAc (2 x 150 mL) then the combined organic portions were washed with sat. NaCl solution and dried over Na_2SO_4. The solution was filtered and concentrated *in vacuo* to give **3** (11.0 g, 99%) as a pale yellow oil: ^1H NMR (300 MHz, $CDCl_3$) δ 1.49 (t, J = 5.2 Hz, 1 H), 1.86 (d, J = 11.4 Hz, 1 H); 1.98 (d, J = 11.0 Hz, 1 H); 2.25 (m, 2 H), 2.41 (t, J = 5.2 Hz, 1 H); 3.02 (s, 1 H); 3.71 (s, 3 H).
6. Chiral HPLC analysis was conducted using a Rainin Dynamax SD-1 system equipped with a Chiralpak AS column (25 cm x 0.46 cm). Solvent system, 7% - 1%AcOH/EtOH, 93% - Hexane; flow rate, 1 mL/min; detection at λ = 280 nm. Approximate t_R for (-)-**3**, 13.1 min, (+)-**3**, 15.0 min, (-)-**1**, 20.5 min, (+)-**1**, 25.6 min.
7. CLEC = Cross-Linked Enzyme Crystals: a) Lalonde, J. J.; Govardhan, C.; Khalaf, N.; Martinez, A. G.; Visuri, K.; Margolin, A. L. *J. Am. Chem. Soc.* **1995**, *117*, 6845-6852. b) St. Clair, N. L.; Navia, M. A. *J. Am. Chem. Soc.* **1992**, *114*, 7314-7316.
8. Racemic **3** (9.0 g, 54.2 mmol) was dissolved in TRIS buffer (7.25 g TRIZMA•HCl + 0.55 g TRIZMA base in 500 mL H_2O; pH 7.0, 450 mL) at rt. CA-A lipase (350 mg) was added and the mixture was stirred rapidly at 40 °C. After 16 h, the reaction was acidified to pH 2 with 1 M HCl and extracted with EtOAc (4 x 400 mL). The EtOAc layer was then washed with saturated sodium bicarbonate solution (2 x 400 mL) followed by sat. NaCl solution (1 x 50 mL). The ethyl acetate solution was dried over Na_2SO_4 then filtered and concentrated *in vacuo* to give 5.25 g (58%) of (+)-**3**. The sat. $NaHCO_3$ and sat. NaCl solution layers were combined and cooled in an ice bath, then acidified to pH 2 with conc. HCl (approx. 40 mL), and extracted with EtOAc (4 x 450 mL). The EtOAc solution was dried over Na_2SO_4 then filtered and concentrated *in vacuo* to give 2.82 g (34%) of the desired (-)-**1**.

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