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Evaluation of animal liver acetone powders for the resolution of 1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid

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Abstract—Butyl, ethyl and methyl esters of 1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid were hydrolyzed stereoselectively under very mild conditions to give the corresponding (*S*)-acid and the unreacted (*R*)-ester using readily available animal liver (chicken, mouse, rat and rabbit) acetone powders.

1. Introduction

1,2,3,4-Tetrahydroisoquinoline-3-carboxylic acid **2**, is a non-natural α-amino acid, that has attracted the attention since the 1930s as a synthon for biologically active compounds. It is used in the synthesis of semi-synthetic peptides and peptide analogs, like bradykinines antagonists,[1–3] ACE inhibitors[2–8] and hypotensive drugs.[9,10] Furthermore, it is also a valuable starting material for the synthesis of several tetrahydroisoquinolines[11] used recently as pseudomimetic HIV-protease inhibitors,[12–14] a novel class of antifungal agents,[15] and α-, γ-, and κ-opioid analgesics.[16–23] The synthesis of (*S*)-**2**,[24] from L-phenylalanine, under Pictet–Spengler conditions, occurs with 32% racemization.[12,13,18–23]

In recent years the use of lipases, esterases and proteases for the resolution of esters has been continuously growing,[25,26] because this methodology provides an easy access to optically active esters, carboxylic acids, amines and alcohols. Because an enzymatic procedure for the resolution of **2** is not available, we decided to study this type of resolution. Taking into consideration the scarcity of enzymatic transformations using the readily available liver acetone powders (LAPs),[27] we report the biocatalyzed resolution of butyl, ethyl and methyl esters of **2** using the crude liver enzymes.[†]

The (±)-1,2,3,4-tetrahydroisoquiniline-3-carboxylic acid **2** and the corresponding esters **3a**–**c** were prepared by a Pictet–Spengler reaction[5,10] from DL-phenylalanine **1** and formaldehyde (in 87% yield), followed by esterification using thionyl chloride and methanol,[10] ethanol or butanol. The esters were isolated in 90, 80 and 90% yields respectively, Scheme 1).

Our investigation began with a biocatalyst screening using the racemic methyl ester (±)-**3a** as a model substrate. The sources of enzymes tested were porcine pancreas lipase (PPL), *Candida cylindracea* lipase (CCL), chicken liver acetone powder (CLAP), and in-lab prepared chicken, rat, mouse, pig, and rabbit liver acetone powders (LAPs).[14] These experiments showed that, with the exception of rat and mouse LAPs, all were able to hydrolyze the ester **3a** with (*S*)-configuration with different degrees of enantioselectivity. The best results were obtained using chicken LAP.

Due to the fact that we were using crude enzyme preparations with uknown amounts of lipase, it was necessary to determine the minimum amount of biocatalyst needed for the resolution reaction. It was found that for PPL 100% (w/w) was needed; 30% was required when CCL or rabbit-LAP were the biocatalysts and 10% for the commercial CLAP and the in-lab LAPs.

The enzymatic resolution via ester hydrolysis of (±)-**3a** was also studied at different pHs (6.0, 7.0, 7.5, 8.0, 10.0) with all LAPs, it was found that pH 7.5 was the optimum. It was also observed that the addition of methanol, to help dissolve the ester, led to a decrease in enantioselectivity at ratios higher than 10% (v/v).

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† Chicken, pig and rabbit livers were purchased from a local grocery store; rat and mouse livers were provided by the university animal facility. The acetone powders were prepared as reported (Ref. 27) and stored at 4°C in tightly closed bottles.

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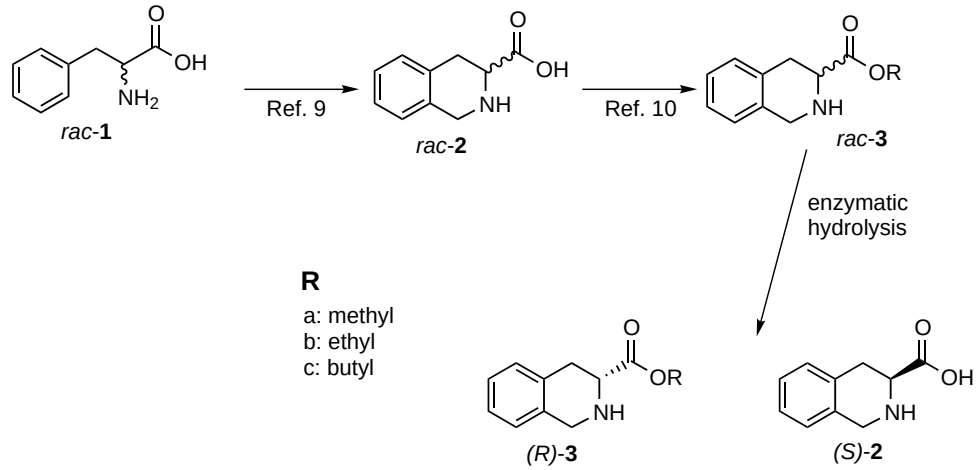

Scheme 1.

Our result demonstrated that mouse and rat LAPs showed no enantioselectivity, even at shorter reaction times. On the other hand either commercial lipase or animal LAPs were equally efficient to resolve the ester **3** with excellent enantioselectivity, toward the (*S*)-enantiomer. The chicken LAP and commercial CLAP showed the best enantioselectivity, after only 2 h of reaction. It is worth mentioning that even after longer reaction times the enantioselectivity remained unchanged. Moreover, when purified (*R*)-**3a** was subjected to biotransformation with fresh biocatalyst there was no reaction, even after stirring the mixture for 144 h, clearly demonstrating that the enzymes in the crude biocatalyst were unable to react with this enantiomer.

We also observed no significant differences related to the type of ester, methyl, ethyl or butyl and all three were well resolved in excellent yield with chicken LAP.

In conclusion, the three esters of 1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid tested were successfully resolved via enzymatic hydrolysis using chicken liver acetone powder. These bioresolutions showed enantioselectivity towards the (*S*)-isomer. Additionally, this procedure is remarkable in its simplicity and low cost, because the biocatalyst is both readily available and easy to prepare.

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References

1. Hock, F. J.; Wirth, K.; Albus, U.; Linz, W.; Gerhards, J. M.; Wiemer, G.; Henke, St.; Breipohl, G.; Köning, W. *J. Pharmacol*. **1991**, *102*, 769–773 (*Chem. Abstr*. **1991**, *114*, 200391).
2. Lembeck, F.; Greisbacher, T.; Henke, S.; Breipohl, G.; Knolle, J. *Br J. Pharmacol*. **1991**, *102*, 297–304 (*Chem. Abstr*. **1991**, *114*, 157636).
3. Henke, S.; Anagnostopoulos, H.; Breipohl, G.; Gerhards, H.; Knolle, J.; Schölkens, B.; Lembeck, F. Ger. Offen. DE 4,013,270 (1992) Heocht AG (*Chem. Abstr*. **1992**, *116*, 106824a).
4. Klutchko, S.; Blankey, C. J.; Fleming, R. W.; Hinkley, J. M.; Werner, A. E.; Nordin, I.; Hoefle, M. L.; Cohen, D. M. *J. Med Chem*. **1986**, *29*, 1953–1961.
5. Suh, J. T.; Williams, B. E.; Skiles, J. W. Eur. Patent-A 34804 (1981) USV Pharmaceuticals (*Chem. Abstr*. **1982**, *96*, 122647).
6. Arzeno, H. B.; Morgans, D. J. Eur. Patent-A 260118 (1988) Syntex, Inc. (*Chem. Abstr*. **1989**, *110*, 8697).
7. Remond, G.; Lambie, M.; Vincent, M. Eur. Patent-A 49658 (1982) Science Union et Cie.-Societe Francaise de Reserche Medicale (*Chem. Abstr*. **1982**, *97*, 216716).
8. Nestor, J. J. Eur. Patent-A 196841 (1986) Syntex Inc. (*Chem. Abstr*. **1987**, *106*, 214389)
9. Portlock, D. E. DOS 3018545 (1980) Morton-Norwich Prod. Inc. (*Chem. Abstr*. **1981**, *94*, 208725).
10. Geiger, R.; Teetz, V.; Urbach, H.; Schölkens, B.; Henning, R.; Eur. Patent-A 46956 (1982) Hoechst A.G. (*Chem. Abstr*. **1982**, *87*, 92759)
11. Huber, I. M. P.; Seebach, D. *Helv. Chim. Acta* **1987**, *70*, 1944–1954.
12. Yu, K.-L.; Harte, W. E.; Spinazze, P.; Martin, J. C.; Mansuri, M. M. *Bioorg. Med. Chem. Lett*. **1996**, *6*, 535–538.
13. Houpis, I. N.; Molina, A.; Reamer, R. A.; Lynch, J. E.; Volante, R. P.; Reider, P. J. *Tetrahedron Lett*. **1993**, *34*, 2593–2596.
14. Roberts, N. A.; Martin, J. A.; Kinchington, D.; Broadhurst, A. V.; Craig, J. C.; Duncan, I. B.; Gaplin, S. A.; Handa, B. K.; Kay; Kroehn, A.; Lambert, R. W.; Merret, J. H.; Mills, J. S.; Parkes, K. E. B.; Redshaw, S.; Ritchie, A. J.; Taylor, D. L.; Thomas, G. J.; Manchin, P. J. *Science* **1990**, *248*, 358–361.
15. Liu, L. T.; Lin, Y.-C.; Wang, C.-L.; Lin, M.-S.; Yen, S.-C.; Chen, H.-J. *Bioorg. Med. Chem. Lett*. **1996**, *6*, 1335–1338.

16. Vecchietti, V.; Clarke, G. D.; Colle, R.; Giardina, G.; Petrone, G.; Sbacchi, M. *J. Med. Chem.* **1991**, *34*, 2624–2633.
17. Schultz, A. G.; Guzi, T. J.; Larsson, E.; Rahm, R.; Thakkar, K.; Bidlack, J. M. *J. Org. Chem.* **1998**, *63*, 7795–7804.
18. Hayashi, K.; Ozaki, Y.; Numani, K.-I.; Yoneda, N. *Chem. Pharm. Bull.* **1983**, *31*, 312–314 and references cited therein.
19. Jualian, P. L.; Karpel, W. J.; Magnani, A.; Meyer, E. W. *J. Am. Chem. Soc.* **1948**, *70*, 180–183.
20. Tachibana, S.; Matsua, H.; Yamada, S. S. *Chem. Pharm. Bull.* **1968**, *16*, 414–420.
21. Kato, H.; Kashinaka, E.; Nishikawa, T.; Arata, Y. *Yakugaku Zasshi* **1974**, *94*, 934 (*Chem. Abstr.* **1975**, *82*, 57654p).
22. Archer, J. *J. Org. Chem.* **1951**, *16*, 430–432.
23. Kammermeier, B. O. T.; Leerch, U.; Sommer, C. *Synthesis* **1992**, 1157–1160.
24. (*S*)-1,2,3,4-Tetrahydroisoquinoline-3-carboxylic acid (*S*)-**2** is available from the NutraSweet Company and Aldrich Chemical Co.
25. De Zoete, M. C.; Van Rantwijk, F.; Sheldon, R. A. *Catal. Today* **1994**, *22*, 563–690.
26. Davies, H. G.; Green, R. M. *Biotransformations in Preparative Organic Chemistry*; Academic Press: London, 1989; pp. 25–62.
27. Basavaian, D.; Dharma Rao, P. *Synth. Commun.* **1994**, *24*, 925.