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ScienceDirect
Mendeleev Commun., 2010, **20**, 314–315

Mendeleev Communications

Enzymatic resolution of (±)-venlafaxine

Konstantin A. Kochetkov,* Maria A. Galkina and Oleg M. Galkin

A. N. Nesmeyanov Institute of Organoelement Compounds, Russian Academy of Sciences, 119991 Moscow, Russian Federation. Fax: +7 499 135 5085; e-mail: const@ineos.ac.ru

DOI: 10.1016/j.mencom.2010.11.003

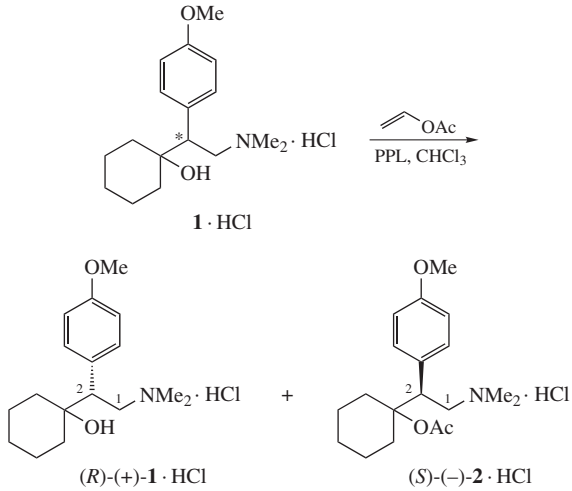
Lipase-catalyzed acylation of the racemic venlafaxine with vinyl acetate in chloroform at 20 °C gives its (*R*)-enantiomer and (*S*)-acetate, the *ee* value of the latter being > 99%.

Racemic venlafaxine, (±)-*N*,*N*-dimethyl-2-(1-hydroxycyclohexyl)-2-(4-methoxyphenyl)ethylamine, **1** is one of the most important representatives of a new generation of antidepressants.[1] Its hydrochloride is known to be a strong inhibitor of reverse neutral capture of serotonin and noradrenaline, as well as a weak inhibitor of dopamine reuptake. The methods for its preparation,[2–4] crystalline structure,[5–7] polymorphism,[6] biological activity,[8] enantiomeric analysis,[9,10] and pharmaceutical properties,[11–13] its metabolites and analogues[2–14] are comprehensively studied. However, a very limited number of publications[2,3] are devoted to the obtaining of pure venlafaxine enantiomers. This was probably due to the fact that both enantiomers show close biological activity[10] and therefore venlafaxine **1** is normally used as a racemate. Nevertheless, the recent data[14] indicate that the main active metabolite of **1** – *O*-demethylvenlafaxine – has a substantially different biological activity for two enantiomers, just as the analogue of **1** having the silicon atom in the 1-position of the cyclohexane ring.[15] The only known way for enantiomeric resolution of **1** is the formation of diastereomeric salts of the free base **1** (or its *O*-demethyl analogue) with di-*p*-tolyl-L-tartaric acid[2,15] (or L-camphorsulfonic acid,[16] respectively). Therefore, the search for new accessible ways to the both enantiomeric forms of **1** and its physiologically active functional derivatives is highly relevant.

Biocatalytic resolution of racemic molecules has been intensively studied recently.[17,18] However, enzyme-catalyzed enantioselective resolution of venlafaxine has not been investigated so far. Lipases are often used in organic synthesis for enantioselective separation of racemic amines and alcohols.[18] Earlier we used Porcine pancreatic lipase (PPL) for the hydrolytic cleavage of some amino acid esters.[19,20] Here we report the possibility of lipases application for enantioselective acylation of venlafaxine with vinyl acetate.

For enzymatic cleavage, the crude racemic venlafaxine hydrochloride (**1**·HCl) was obtained by the known method.[3] It was purified and recrystallized using the substantially altered procedure† (for details, see ref. 21). The products purity was confirmed by elemental analysis, differential scanning calorimetry, NMR and IR spectroscopy.[21]

† Starting racemic **1**·HCl (1 g)[3] was preliminarily purified by washing with 30 ml of light petroleum (40–70 °C), 30 ml of diethyl ether, a 5:3 mixture of CCl_4 and diethyl ether (30 ml) and 30 ml of CCl_4, followed by the recrystallization of residue from a mixture of ethyl acetate and methanol (4:1). Thus, (±)-**1**·HCl with over 99.5 wt% purity was obtained, according to HPLC data. The ^{1}H NMR spectra were recorded with a Bruker Avance 300 (300 MHz) spectrometer in $CDCl_3$ at 30 °C. IR spectra were recorded in KBr with an UR-20 instrument. Lipases PPL (EC 3.1.1.3) and CCL were purchased from Fluka, vinyl acetate and SiO_2 from Aldrich.



Scheme 1

Earlier it was shown that vinyl acetate is a convenient acylation agent for the enzymatic resolution of poorly nucleophilic alcohols which remain unchanged in the absence of enzyme.[17] We also tried ethyl acetate as the acyl donor and a solvent for **1** under similar reaction conditions; however, the enantioselectivity was low at a small conversion. To improve the enantioselectivity of acylation, different solvents were tested, and the best results were obtained in chloroform. PPL-catalyzed acylation‡ of racemic **1** with vinyl acetate leads to scalemic alcohol (*R*)-(+)-**1** and its acetate (*S*)-(–)-**2**§ (Scheme 1, Table 1). Note that the application of *Candida cilindraceae* lipase (CCL) was unsuccessful.

Table 1 PPL-catalyzed acylation of racemic (±)-**1** in $CHCl_3$ at 20 °C.

Entry	Time/h	Conversion (%)	*ee* of remaining alcohol (+)-**1**	ee of formed acetate[a] (–)-**2**
1	20	5	—[b]	—[b]
2	120	17	20	>99
3	240	25	31	>99

[a]Determined by chiral HPLC analysis with Daicel Chiracel OD-H column; eluent: hexane–propan-2-ol (95:15) + 0.2% diethylaniline; 0.75 ml min^{-1}, UV detector 225 nm. [b]Not determined.

‡ Enzymatic acylation of (±)-**1**·HCl (300 mg) was carried out in $CHCl_3$ (3 ml) with 6 ml of vinyl acetate and 300 mg of PPL at 20 °C with stirring for several hours (Table 1), monitoring by TLC (CH_2Cl_2:Pr^{i}OH: $NH_{3(aq)}$ ratio of 100:10:3 or light petroleum:Et_2O ratio of 10:1) and ^{1}H NMR. The reaction mixture was filtered, evaporated and (+)-**1**·HCl and (–)-**2**·HCl were separated by preparative TLC on a plate with SiO_2 (10% $CaSO_4$, Merck) in the light petroleum–diethyl ether (10:1) system.

To determine the configuration, the acetate (–)-**2** was converted into the corresponding alcohol, which turned to be levorotatory and according to the literature[2,15] thus prossessed (*S*)-configuration. The absolute configuration of (–)-enantiomer of **1** has already been established[2] as (*S*)-configuration. The enantiomeric purity of the obtained acetate (–)-**2** was measured using chiral HPLC which showed the enantiomeric purity > 99% ee (the other enantiomer was not detected). Venlafaxine racemic acetate (±)-**2**, obtained in high yield from (±)-**1** by acylation with acetic anhydride under DMAP catalysis was used as a standard. The (*R*)-(+)-**1** alcohol accumulating during enantioselective acylation after double recrystallization exhibits > 98% *ee*.

The high enantioselectivity of PPL-catalyzed acylation, as well as the simplicity of the procedure, make this method a possible alternative to the well-known way of obtaining non-racemic derivatives of venlafaxine **1** through diastereomeric salt.[2,14,15]

This work was supported by the Programme no. 09-OHNM of the Russian Academy of Sciences (RAS) 'Bioorganic Medical Chemistry' and the Presidium of the RAS (no. P-5 'Basic Sciences for Medicine'). The authors are grateful to M. M. Il'in (Institute of Organoelement Compounds, RAS) for performing the enantiomeric HPLC analysis.

§ (+)-N,N-*Dimethyl-2-(1-hydroxycyclohexyl)-2-(4-methoxyphenyl)ethylamine hydrochloride* (+)-**1**·HCl. Yield 29% (from theory), mp 240–241 °C, $[\alpha]_D^{25}$ +4.7 (*c* 1, EtOH) {lit.,[2] mp 240–241 °C, $[\alpha]_D^{25}$ +4.6 (*c* 1, EtOH)}. ^{1}H NMR ($CDCl_3$) δ: 0.93–1.74 (m, 10H, C_6H_{10}), 2.73 (s, 6H, NMe_2), 3.18 (dd, 1H, C^2H, H_a, $J_{H_aH_b}$ 12.4 Hz, $J_{H_aH_c}$ 6.3 Hz), 3.41 (dd, 1H, C^1H, H_c, $J_{H_aH_c}$ 6.3 Hz, $J_{H_bH_c}$ 3.9 Hz), 3.85 (s, 3H, OMe), 4.08 (dd, 1H, C^2H, H_b, $J_{H_aH_b}$12.4 Hz, $J_{H_bH_c}$ 3.9 Hz), 6.91, 7.18 (AA′BB′, 4H, C_6H_4). IR (Nujol, ν/cm^{-1}): 1179 (OMe), 1247 (N–C), 1514 [C=C(Ar)], 2582 (H–Cl), 2936 [C–H(Ar)], 3349 (OH). Found (%): C, 65.01; H, 9.04; N, 4.39; Cl, 11.26. Calc. for $C_{17}H_{27}NO_2$·HCl (%): C, 65.05; H, 8.99; N, 4.44; Cl, 11.30.

(–)-N,N-*Dimethyl-2-(1-acetoxycyclohexyl)-2-(4-methoxyphenyl)ethylamine hydrochloride* (–)-**2**·HCl. Yield 48% (from theory), mp 203–206 °C, $[\alpha]_D^{25}$ –5.15 (*c* 1, EtOH). ^{1}H NMR ($CDCl_3$) δ: 1.12–1.59 (m, 10H, C_6H_{10}), 2.14 (s, 3H, OAc), 2.15 (s, 3H, NMe), 2.21 (s, 3H, NMe), 3.62 (dd, 1H, C^2H, H_a, $J_{H_aH_b}$ 8.9 Hz, $J_{H_aH_c}$ 4.9 Hz), 3.66 (dd, 1H, CH, H_c, $J_{H_aH_c}$ 4.9 Hz, $J_{H_bH_c}$ 3.4 Hz), 3.86 (s, 3H, OMe), 4.24 (dd, 1H, CH_2, H_b, $J_{H_aH_b}$ 8.9 Hz, $J_{H_bH_c}$ 3.4 Hz), 6.92, 7.19 (AA′BB′, 4H, C_6H_4). IR (Nujol, ν/cm^{-1}): 1179 (OMe), 1247 (N–C), 1514 [C=C(Ar)], 2582 (H–Cl), 2936 [C–H(Ar)], 1650 (OAc). Found (%): C, 61.28; H, 8.66; N, 3.78; Cl, 9.52. Calc. for $C_{19}H_{29}NO_3$·HCl·H_2O (%): C, 61.03; H, 8.63; N, 3.75; Cl, 9.48.

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Received: 27th April 2010; Com. 10/3514