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Lipase-catalysed Resolution of 3,3'-Bi-indolizines: The First Preparative Access to Enantiomerically Pure Samples

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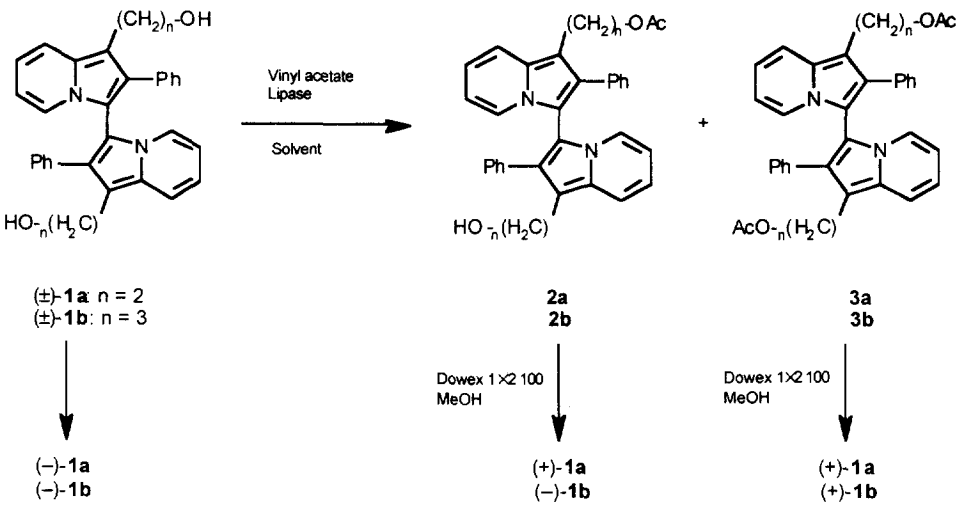
Abstract: The lipase-catalysed kinetic resolution of the axially chiral 3,3'-bis[1-(2-hydroxyethyl)-2-phenylindolizine] [(±)-**1a**] and the corresponding 3-hydroxypropyl derivative (±)-**1b** by acylation with vinyl acetate in the presence of lipases from different origins has been investigated. For the first time, enantiomerically pure 3,3'-biindolizine derivatives were obtained on a preparative scale by careful monitoring of the conversion.

Bi-indolizines possess a stereogenic axis if the rotation around the bond which connects both indolizine moieties is sufficiently hindered. Very recently, the existence and thermal stability of enantiomers of 3,3'-bi-indolizines was discovered[1] by separation on chiral HPLC columns. Due to this observation, we looked for a way to separate both enantiomers of 3,3'-bi-indolizines in order to obtain a sufficient quantity of enantiomerically pure or enriched compounds. Enantiomerically pure 3,3'-bi-indolizines with appropriate functional groups could be of interest as chiral auxiliaries like the well known 1,1'-binaphthols.[2] It is known that stereogenic and prostereogenic diols of different structures are substrates in enantioselective lipase-catalysed acylations.[3,4] Therefore, we have prepared bi-indolizines substituted with hydroxyalkyl groups. The 1,1'-bis(hydroxyethyl)bi-indolizine (±)-**1a** was synthesised by a Chichibabin reaction,[5] starting from the commercial available 2-pyridinepropanol. The diol (±)-**1b** was obtained by cleavage of the cyclic ether groups of 1,1'-bis[2-(1,3-dioxolane-2-yl)-ethyl]-2,2'-diphenyl-3,3'-bi-indolizine[6] and subsequent reduction of the resulting aldehyde functions.[7]

The obtained diols (±)-**1a** and (±)-**1b** were subjected to enantiomer selective transesterifications with vinyl acetate in organic solvents in the presence of lipases of different origin (Scheme 1).

In order to resolve the axially chiral diols (±)-**1a** and (±)-**1b** in a first series, kinetic resolution was carried out with vinyl acetate in THF by variation of the lipase. In the case of diol (±)-**1a**, amongst twelve commercial lipases tested only lipase from *Candida antarctica* B (Novozym 435) was able to catalyse the sequential acetylation furnishing in the first step the monoacetate **2a**, which subsequently reacts to the diacetate **3a**. Other lipases such as Porcine Pancreatic lipase, the lipases PS, AK, CE and M from Amano, SP 433 and SP 526 from Novo or *Rhizopus sp.* from Serva were not useful because the degree of conversion of the diol (±)-**1a** into the monoacetate **2a** was less than 5 % within 24 h.



Scheme 1

In the next series solvent engineering revealed that a mixture of THF/NEt_3 was the best one regarding rate of conversion and enantiomer selectivity. In other solvents the diol (±)-**1a** was almost insoluble. The optimal conditions were evaluated by terminating the reaction at different degrees of conversion, separation of the products by flash chromatography, deacetylation of **2a** and **3a** to afford (+)-**1a** and determination of the enantiomeric excess of the unchanged diol (–)-**1a**; (–)-**1a** from the monoacetate **2a**, and (+)-**1a** from the diacetate **3a**. The results are depicted in Table 1.

Table 1: Kinetic resolution of (±)-**1a** – Dependence of the enantiomeric excess (ee) on the degree of conversion and solvent

Entry	Solvent	Time (h)	Diol (–)-**1a**		Monoacetate **2a**		Diacetate **3a**	
			Yield (%)	ee (%)	Yield (%)	ee (%)[a]	Yield (%)	ee (%)[a]
1	THF[b]	8	82	19.2	17	94.6	< 1	–
2	THF[b]	24	62	49.0	29	71.6	9	98.6
3	THF[b]	72	58	60.2	30	70.6	12	97.6
4	THF/NEt_3[b]	30	55	62.4	31	61.4	14	99.9
5	THF/NEt_3[b]	43	43.4	92.8	25.3	38.6	31.3	99.0
6	THF/NEt_3[c]	40[d]	41	90.0	27	34.8	31.7	99.0

[a]Determined after deacetylation into (+)-**1a**. [b]25 mg of diol, 65 µL of vinyl acetate, 1.5 mL of solvent (for Entries 4 and 5 10 µL of NEt_3), and 10 mg of Novozym 435. [c]Corresponds to the preparative procedure described in the Experimental Part. [d]Conversion on the preparative scale was faster than on the analytical scale (Figure 1).

As observed in former cases,[8] the addition of triethylamine to lipase-catalysed transesterifications caused an increasing reaction rate and enantioselectivity (entries 4–6). The reason for this effect is still unclear. Ter-

mination of the transesterification when about 60 % of the diol **1a** were converted, yielded the slow reacting diol (–)-**1a** with an ee of ≥ 90 %, the monoacetate **2a** which was deacetylated to furnish (–)-**1a** with an ee of 34–40 % and diacetate **3a** which was deacetylated to afford (+)-**1a** with an ee ≥ 99 %.

Figure 1 demonstrates the time course of the conversion of the diol (±)-**1a** into **2a** and **3a** on treatment with vinyl acetate in THF/NEt_3 in the presence of the immobilised enzyme preparation from *Candida antarctica* B lipase (Novozym 435). On the contrary, the non-immobilised lipase from the same yeast, SP 525 from Novo, is a much worse catalyst for this reaction. In comparison to the above described experiments (Table 1, Entries 4–6) the conversion of (±)-**1a** into **2a** was only 10 % besides 1 % of the diacetate **3a** within 46 h.

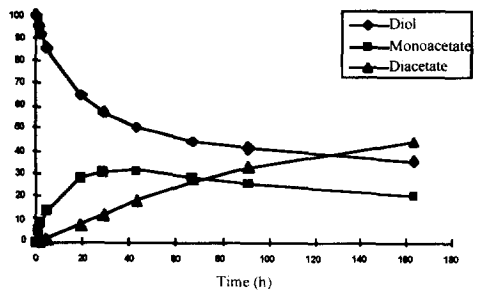


Figure 1: Time Course for the Transesterification of the Diol (±)-**1a** in THF/NEt_3 in the Presence of Novozym 435

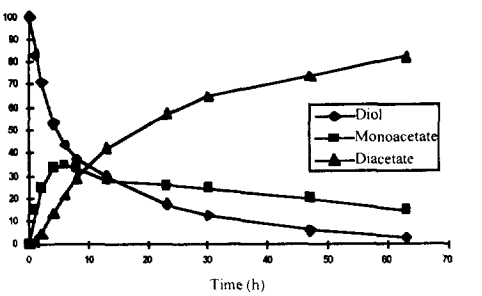


Figure 2: Time Course for the Transesterification of the Diol (±)-**1b** in 1,4-Dioxane in the Presence of Lipase Amano AK

The Diol (±)-**1b** was accepted as substrate from some lipases (Table 2). However, in most cases (Entries 1–5) there was no or an extremely poor enantiomer selectivity. Only lipase Amano AK showed an enantiomer selectivity sufficient for the preparation of the slow reacting diol (–)-**1b** in enantiomerically pure form (Entries 7 and 9) as unchanged (–)-**1b** and from the monoacetate **2b** after deacetylation. Solvent engineering showed that 1,4-dioxane was the solvent of choice. Solvents such as THF, *tert*-butyl methyl ether, vinyl acetate, toluene, diethylether, 3-methyl-3-pentanol or addition of NEt_3 caused a lower selectivity.

Figure 2 shows the time course for the transesterification of the diol (±)-**1b** with vinyl acetate in 1,4-dioxane in the presence of lipase Amano AK. The time course clearly demonstrates that enantiomer selectivity for the lipase-catalysed transesterification (±)-**1b** must be lower than for the corresponding hydroxyethyl derivative (±)-**1a**. Due to a sufficient difference of the reaction rate both enantiomers of the diol (±)-**1a** could be obtained with high enantiomeric excess. Compared with (±)-**1a**, due to a lower rate difference between the enantiomers of (±)-**1b**, only (–)-**1b** could be obtained with high ee at a high degree of conversion at the expense of its chemical yield.

The absolute configurations of the enantiomers (–)-and (+)-**1a** or (–)-**1b** could not be determined.

Table 2: Lipase-catalysed Kinetic Resolution of the Diol (±)-**1b**

Entry	Lipase	Solvent	Time (h)	Diol (–)-**1b**		Monoacetate **2b**		Diacetate **3b**	
				Yield (%)	ee (%)	Yield (%)	ee (%)[a]	Yield (%)	ee (%)[b]
1	Novozym-435[c]	THF	43	0	–	0	–	100	0
2	Amano PS[c]	THF	72	2.6	n. d.[d]	23.3	26.0	72	10.8
3	Amano CE[c]	THF	100	72	3.6	25	7.2	2.7	n. d.
4	Lipozyme[c]	THF	44	0	–	16	n. d.	84	n. d.
5	SP 525[c]	THF	24	0	–	0	–	100	0
6	Amano AK[c]	THF	21	31	75.4	38.5	1.4	30.5	71.4
7	Amano AK[c]	1,4-Dioxane	22	18	> 99	27	83.6	55	66.4
8	Amano AK[c]	1,4-Dioxane	5	47	66.6	34	38.2	18.6	88.4
9	Amano AK[e]	1,4-Dioxane	27[f]	9	> 99	18	> 98	73	29.9

[a]Determined after deacetylation into (–)-**1b**, [b]determined after deacetylation into (+)-**1b**. [c]25 mg of diol, 65 µL of vinyl acetate, 1.5 mL of solvent, and 10 mg of Lipase Amano AK. [d]Not determined. [e]Corresponds to the preparative procedure described in the Experimental Part. [f]Conversion on the preparative scale was faster than on the analytical scale (Figure 2).

In conclusion we could demonstrate that the axially chiral 3,3'-bis[1-(2-hydroxyethyl)-2-phenylindolizine] (±)-**1a** and the corresponding 3-hydroxypropyl compound (±)-**1b** were substrates in lipase-catalysed transesterifications. By means of this biocatalytical process, enantiomerically pure 3,3'-bi-indolizinediols could be prepared for the first time.

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Experimental Part

All reactions were monitored by HPLC on a Merck-Hitachi system consisting of L-6200A Pump, L-4000 UV Detector, and Chromato-Integrator D-2500. Flash chromatography was performed with silica gel 60 (0.040–0.063 mm). ^{1}H NMR and ^{13}C NMR spectra were recorded on the Varian instrument Gemini 300 at 300 and 75 MHz, respectively. Coupling constants (J in Hz) were taken directly from the obtained spectra. Mass spectra were recorded on the Autospec VG. Optical rotations were measured on a Perkin-Elmer 241 polarimeter, and are given in units of 10^{-1} deg cm^2 g^{-1}. The enantiomeric excess of the products was determined by HPLC on Chiralpak AD (250×4.6 mm) with *n*-heptane–2-propanol (4:1) with a flow rate of 1 mL/min and UV detection at 254 nm.

Kinetic Resolution of 3,3'-Bis[1-(2-hydroxyethyl)-2-phenylindolizine] (±)-1a

A solution of the diol (±)-**1a** (1.12 g, 2.37 mmol) in THF (35 mL) was treated with vinyl acetate (2.92 mL, 31.7 mmol), NEt_3 (0.45 mL) and Novozym 435 (0.45 g). The reaction mixture was stirred at room temperature for 40 h. The concentration of the products formed is given in Table 1 (Entry 6). The mixture

was filtrated through a pad of Celite and the filter cake was washed with THF (3×10 mL). To the combined filtrates silica gel 60 (0.2–0.5 mm, 3 g) was added. The solvent was removed under reduced pressure and the silica-adsorbed mixture of substances was separated by flash chromatography (120 g, 22×3.6 cm) with *n*-hexane/THF (2:1) as eluent to furnish the diacetate **3a** (0.408 g, 31 %) , monoacetate **2a** (0.329 g, 27 %), and diol (–)-**1a** (0.448 g, 41 %) with an ee of 90 %. The diacetate **3a** and the monoacetate **2a** were deacetylated by treatment with the strong basic ion-exchange resin Dowex 1×2 100 (OH^-, 3 g) in MeOH (20 mL) and stirring at room temperature for 6 h. The ion-exchange resin was filtered off, washed with MeOH (3×10 mL) and the solvent was evaporated under reduced pressure to yield from **3a** the diol (+)-**1a** with an ee of > 99 % and from **2a** the diol (+)-**1a** with an ee of 34.8 %.

(–)-**1a**: ^{1}H NMR (DMSO-d_6): 2.89 (m, 4 H), 3.53 (br t, 4 H, J = 5.3), 4.67 (t, 2 H, J = 5.3), 6.41 (t, 2 H, J = 6.4), 6.72 (dd, 2 H, J = 8.8 and 6.4), 7.01 (m, 4 H), 7.16–7.26 (m, 8 H), 7.53 (d, 2 H, J = 9.2); ^{13}C NMR (DMSO-d_6), 27.92, 62.01, 108.12, 110.52, 110.84, 117.18, 117.82, 122.65, 126.55, 128.13, 129.04, 130.87, 131.35, 135.20; MS (CI), 473 [(M + H)$^+$, 100 %], 455, 441. Found C 80.36, H 5.80, N 5.69; calcd. C 81.33, H 5.97, N 5.93; $[\alpha]_D^{20}$ –20.5, (*c* 1.0, MeOH), ee 90 %

(+)-**1a**: $[\alpha]_D^{20}$ +22.0, (*c* 1.0, MeOH), ee > 99 %. The NMR and MS spectra are identical with those of (–)-**1a**.

Kinetic Resolution of 3,3'-Bis[1-(3-hydroxypropyl)-2-phenylindolizine] (±)-1b

In analogy to the above described procedure a solution of the diol (±)-**1b** (1.07 g, 2.14 mmol) in 1,4-dioxane (30 mL) was treated with vinyl acetate (2.60 mL, 28.2 mmol), and lipase Amano AK (0.40 g). The ratio of the products formed after 27 h is given in Table 2 (Entry 9). Flash chromatography with *n*-hexane/THF (2:1) afforded the diacetate **3b** (0.912 g, 73 %), monoacetate **2b** (0.185 g, 16 %), and diol (–)-**1b** (0.08 g, 8 %) with an ee > 99 %. Deacetylation of **3b** and **2b** as described above furnished the diols (+)-**1b** with an ee of 29.9 % and (–)-**1b** with an ee of > 98 %, respectively.

The diol (+)-**1b** (ee 29.9 %, 780 mg, 1.56 mmol) in 1,4-dioxane was subjected to a second lipase AK-catalysed transesterification with vinyl acetate (2.0 mL, 28.8 mmol) with lipase AK (0.20 g). After 25 h the reaction mixture consists of 70 % of the diacetate **3b**, 20 % of the monoacetate **2b**, and 10 % of the diol (–)-**1b**. Flash chromatography yielded **3b** (0.620 g, 69 %), **2b** (0.160 g, 18 %), and (–)-**1b** (0.070 g, 9 %) with an ee of > 98 % ee. Deacetylation of **3b** and **2b** furnished the diols (+)-**1b** with an ee of 69 % and (–)-**1b** with an ee of 64.4 %, respectively.

(–)-**1b**: ^{1}H NMR (DMSO-d_6): 1.62 (t, 4 H, J =7.0), 2.78 (dd, 4 H, J = 8.8 and 6.2), 3.34 (m, 4 H, after D_2O t, J = 6.6), 4.39 (t, 2 H, J = 5.2, exchanges with D_2O), 6.41 (dt, 2 H, J = 6.8 and 1,1), 6.70 (ddd, 2H, J = 9.0, 6.5 and 0.9), 6.94 (m, 4 H), 7.17 (m, 8 H), 7.51 (td, 2 H, J = 9.0 and 1.1), ^{13}C NMR (DMSO-d_6): 20.39, 34.70, 60.73, 110.83, 111.14, 111.52, 117.28, 117.93, 122.83, 126.77, 128.40, 129.16, 130.61, 131.14, 135.62; MS (FAB): 500 (M$^+$, 100 %). Found C 80.89, H 6.55, N 5.37, calcd. C 81.54, H 6.94, N 5.59. $[\alpha]_D^{20}$ –41.8, (*c* 1.0, MeOH), ee >99 %

(+)-**1b**: $[\alpha]_D^{20}$ +28.4, (*c* 0.85, MeOH), ee 69 %. The NMR and MS spectra are identical with those of (−)-**1b**.

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