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Kinetic Resolution of Chiral Auxiliaries with C_2-Symmetry by Lipase-Catalyzed Alcoholysis and Aminolysis

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Three cyclic diols, 1,2-cyclohexanediol (**1**), 1,3-cyclohexanediol (**2**), and 1,3-cyclopentanediol (**3**), two acyclic unsaturated diols, 1,5-hexadiene-3,4-diol (**4**) and 1,7-octadiyne-3,6-diol (**5**), and a cyclic diamine, 1,2-cyclohexanediamine (**6**), have been kinetically resolved in alcoholysis and aminolysis reactions, catalyzed by *Candida antarctica* component B lipase, using *S*-ethyl thiooctanoate or ethyl octanoate as acyl donors. Acceptable stereoselectivity was achieved in most cases.

Compounds with C_2-symmetry have gained considerable attention[1] since Kagan *et al.*,[2] more than twenty years ago reported the first asymmetric synthesis using an optically pure chiral auxiliary with C_2-symmetry. The facile preparation of such compounds is thus of great interest. We have previously shown that some acyclic aliphatic diols with C_2-symmetry can easily be resolved by lipase-catalyzed alcoholysis.[3] This concept is hereby extended to both cyclic and unsaturated acyclic diols as well as a diamine.

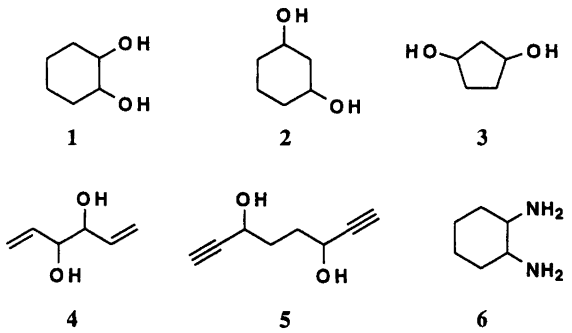

Fig. 1. Chiral compounds with C_2-symmetry that were subjected to kinetic resolution.

Results and discussion

Five of the substrates investigated, compounds **1**–**4** and **6** (Fig. 1), were commercially available as diastereomeric mixtures and were used as such without any attempts at further purification. A mixture of the diastereomers of the diyne **5** was synthesized. The enantiomerically enriched C_2-symmetrical products of lipase-catalyzed kinetic resolutions of these substrates could be used in different ways in asymmetric synthesis, as chiral auxiliaries, as ligands, or as chiral starting materials. The diols **4** and **5** were of particular interest as chiral starting materials because of their additional functionalities.

S-Ethyl thiooctanoate was used as the acyl donor in the resolution of all of the diols.[4] The reactions were performed at 39 °C in order to effectively displace the equilibrium towards product formation by evaporation of ethanethiol.[5] However, the diamine reacted spontaneously with the *S*-ethyl thiooctanoate. Hence, ethyl octanoate was used as acyl donor in the lipase-catalyzed aminolysis. Since ethanol is less volatile than ethanethiol, the reaction had to be run under reduced pressure to ensure an adequate equilibrium displacement (Scheme 1).[6] No solvent was used in the resolutions of the diols and the diamine. The substrates were simply mixed with the acyl donor.

In order to determine the absolute configurations of the products, the optical rotations of the remaining substrates (Table 1) were examined and compared with data reported in the literature. The absolute configurations of the diols **3** and **5** had not been established previously but are now predicted to be 1*S*,3*S*- for

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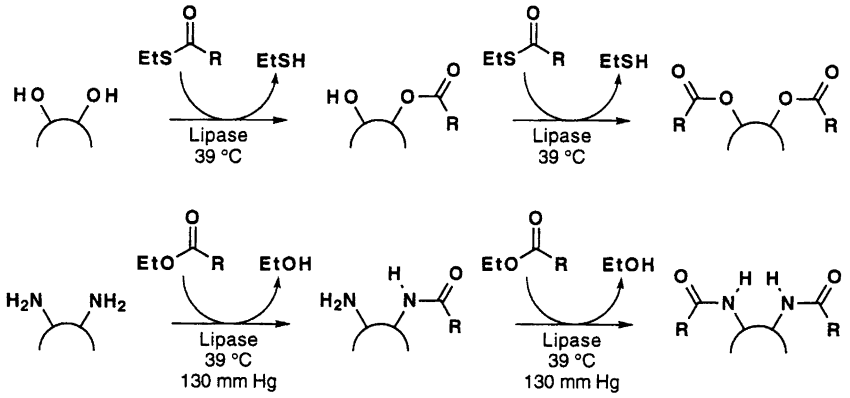

Scheme 1. Reaction scheme.

Table 1. Absolute configurations of remaining substrates.

	Substrate	Optical rotation of remaining substrate	Absolute configuration
1	1,2-cyclohexanediol	+	1*S*, 2*S*[7]
2	1,3-cyclohexanediol	+	1*S*, 3*S*[8]
3	1,3-cyclopentanediol	+	1*S*, 3*S* (predicted)
4	1,5-hexadiene-3,4-diol	−	3*S*, 4*S*[9]
5	1,7-octadiyne-3,6-diol	+	3*R*, 6*R* (predicted)
6	1,2-cyclohexanediamine	+	1*S*, 2*S*[10]

(+)-1,3-cyclopentanediol (**3**) and the 3*R*,6*R*† for (+)-1,7-octadiyne-3,6-diol (**5**) by comparison with the configuration determined for the other substrates, and in analogy with earlier investigations.[3]

The fastest reacting isomer of each substrate was the *R*,*R*-isomer (an exception was the diyne **5**, where the fastest reacting isomer was the *S*,*S*-isomer, not due to a different fit into the catalytic cleft of the lipase but due to the Cahn–Ingold–Prelog nomenclature rules), which was predominantly isolated as the diacylated product. The corresponding *S*,*S*-isomer might be expected to be the slowest reacting one and thus be isolated mainly as the remaining substrate, whereas the *meso*-isomer would be found as the monoadduct. However, for the vicinal substrates **1**, **4** and **6**, the *meso*-isomer was the slowest reacting isomer in the formation of the mono adduct. This is illustrated by the diastereomeric excess of the *meso*-isomer in the remaining substrate (Table 2).

The large proportions of the *R*,*S*-isomers in the di-adducts of the 1,3-disubstituted substrates, **2** and **3**, might be explained by intramolecular acyl migration in the monoadducts.‡

The hypothesis regarding compounds **1**, **2**, **4** and **6** is that the reaction order was $R,R > S,S \geqslant R,S$ for the formation of the monoadduct, and $R,R > R,S > S,S$ for the formation of the diadduct. The change in selectivity between the first and the second step can be explained by steric differences between the original substrate and the monoadduct, mainly affecting the diastereoselectivity (Fig. 2).

The 2,5-hexanediol previously investigated§ gave a diester showing a high diastereomeric excess, 97%. Analogously, a high diastereomeric excess was expected for the diadduct of compound **5**. However, the diastereomeric excess was only 35%. The result obtained with compound **5** is perhaps also attributable to acyl migration at the monoadduct stage.

In the resolutions in which the *R*,*S*-isomers reacted significantly faster than the slow-reacting enantiomers in the formation of the corresponding monoadducts (substrates **3** and **5**), the fast-reacting enantiomers (*R*,*R*-**3** and *S*,*S*-**5**) were in excess of the slow-reacting ones in the monoadduct fractions. In all of the other resolutions, the opposite was true. Still, concerning the ratio of the enantiomers, the purest *S*,*S*-enantiomers were found in the remaining substrate fractions and the purest *R*,*R*-isomers in the diadduct fractions in the resolutions of **1**–**4** and **6**, and *vice versa* for the diyne **5**.

In summary, it is possible to obtain acceptable enantiomeric excesses with some cyclic as well as some unsaturated acyclic alcohols with C_2-symmetry in kinetic resolutions through alcoholysis catalyzed by the component B lipase of *Candida antarctica*. Furthermore, the resolution of a diamine was achieved, and in the process, a simple procedure for the preparation of enantiomerically enriched primary amines useful in organic synthesis was illustrated.

† According to the Cahn–Ingold–Prelog sequence rules, the absolute configuration of the remaining substrate of 1,7-octadiyne-3,6-diol should be denoted *R*,*R* instead of *S*,*S* as in the other substrates.

‡ For a more detailed discussion of the effect of acyl migration in related resolutions, see Ref. 3.

§ In an analogous resolution 2,5-hexanediol formed a diester of 97% de and 99% ee. See Ref. 3.

Table 2. Compositions (%) of hydrolyzed products.

	Substrate composition			Remaining substrate					Products: Monoadduct					Products: Diadduct				
	SS	*RS*	*RR*	*SS*	*RS*	*RR*	ee	de	*SS*	*RS*	*RR*	ee	de	*SS*	*RS*	*RR*	ee	de
1	26	48	26	3	96	1	46	93	34	46	20	27	8	5	16	79	88	68
2	18	64	18	31	66	3	83	33	65	12	22	49	75	1	60	39	94	20
3	25	50	25	89	9	2	96	82	4	88	8	25	76	1	53	46	95	5
4	18	64	18	12	88	1	86	75	43	23	34	12	77	1	31	68	98	38
5	*a*	*a*	*a*	2	5	93	96	90	25	71	4	72	43	67	32	1	97	35
6	27	46	27	35	61	4	82	23	41	46	13	51	8	12	6	81	73	88

[a] Not determined.

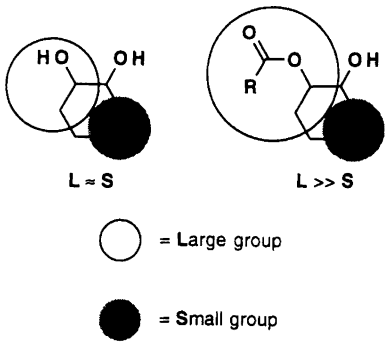

Fig. 2. Explanation of the change in selectivity between the first and the second step (steric effects).

Experimental

Enzyme. The lipase (component B) derived from *Candida antarctica* was a product from Novo-Nordisk A/S (Novozym® 435). The enzyme was used as an immobilized preparation on a macroporous resin, containing approximately 1% enzyme w/w. The catalytic activity was approximately 42 600 LU per gram of enzyme preparation.

Gas chromatography. Capillary GC was performed on Carlo Erba Fractovap 2150, Perkin Elmer 8500, Varian 3300, and Varian 3500 instruments. The conversions of the acyl donor and the substrate were measured either with a Chrompak CP-SIL® 19CB or a J&W Scientific DB1-30W column. Diastereomeric and enantiomeric excess values were determined either with an Astec Chiraldex® G-TA or a Chrompak CP-cyclodextrin-β-2,3,6-M-19 column.

Absolute configurations. The absolute configurations were determined by comparison of the optical rotations of the diols and the diamine with data from the literature. No data were found for the cyclopentanediol **3** and for the diyne **5**.

Column chromatography. Liquid chromatography was performed on silica gel (Merck 60, 0.040–0.063 mm) and the compounds were eluted with a hexane–ethyl acetate gradient, directly followed by an ethyl acetate–ethanol gradient, as described by Baeckström *et al.*[11]

S-Ethyl thiooctanoate. Ethanethiol (59.2 ml, 0.80 mol) and pyridine (77.6 ml, 0.96 mol) were dissolved in dry diethyl ether (300 ml) and the solution was cooled to 0 °C. Octanoyl chloride (68.5 ml, 0.40 mol), dissolved in dry diethyl ether (100 ml), was added dropwise to the ethanethiol solution. The temperature was allowed to rise to room temperature. The reaction was complete within 24 h. The reaction mixture was filtered, washed twice with water and dried over $MgSO_4$. Distillation yielded the crude thioester product, b.p. 65 °C (2 mmHg). After column chromatography on silica gel (Merck 60; hexane–EtOAc, 90 : 10 v/v) 74.4 g (99%) of pure product were isolated. ^{1}H NMR ($CDCl_3$): 0.88 (t, 3 H), 1.21–1.4 (m, 8 H), 1.25 (t, 3 H), 1.59–1.68 (m, 2 H), 2.49–2.55 (t, 2 H), 2.72–2.91 (m, 2 H).

Lipase-catalyzed alcoholysis, general procedure. The diol substrate (4.0 mmol) was mixed with *S*-ethyl thiooctanoate (8.0 mmol, 1.51 g) and the enzyme preparation (50 mg) was added. The reaction was monitored by GC. After approximately 75% conversion of the substrate, the enzyme was removed by filtration. The products were separated by liquid column chromatography and hydrolyzed separately.

Hydrolysis of product esters, general procedure. Each ester was dissolved in MeOH (20 ml) and after addition of KOH (0.5 g) the reaction mixture was stirred overnight. Formic acid (1 ml) was then added and the solvent was evaporated off. EtOAc (50 ml) was added and the solid material was collected on a filter and washed with EtOAc. The product was purified by liquid column chromatography.

Lipase-catalyzed aminolysis with 1,2-cyclohexanediamine. 4.0 mmol (457 mg) of 1,2-cyclohexanediamine was mixed with 8.0 mmol (1380 mg) of ethyl octanoate and 50 mg of the enzyme preparation was added. The pressure was adjusted to 130 mmHg. The reaction was monitored by GC and after 75% conversion of the substrate, the reaction was stopped by removal of the enzyme. The products were separated by column chromatography and hydrolyzed separately.

Hydrolysis of product amides. Each amide was mixed with 70% H_2SO_4 (4 ml). After 30 min of refluxing, the

mixture was cooled and diluted with water (20 ml) and the pH was adjusted to ≈14 by KOH addition. Any solid material was removed by filtration and the filtrate was saturated with NaCl. Extraction with CH_2Cl_2 yielded the diamine.

1,7-Octadiyne-3,6-diol (5). 1,7-Octadiyne-3,6-diol (**5**) was synthesized in two steps according to the procedure of Chiarino and Fantucci.[12] The first step was the liberation of succinaldehyde from the commercial precursor 2,5-dimethoxytetrahydrofuran.[13] The second step was a double Grignard reaction of succinaldehyde with ethynylmagnesium bromide in THF.[14] ^{1}H NMR (DMSO-d_6) δ: 1.66 (m, 4 H, CH_2), 3.27 (dt, J=2.0 Hz, 2 H, ≡CH), 4.21 (brs, 2 H, CHO), 5.36 (d, J=5.6 Hz, 2 H, OH). ^{13}C NMR ($CDCl_3$) δ: 32.8 (CH_2, *meso* or ±), 32.9 (CH_2, *meso* or ±), 61.3 (CHO), 73.3 (≡CH), 84.4 (≡C–).

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