Stereoselective Synthesis of 1,2,3-Triazolooxazine and Fused 1,2,3-Triazolo-δ-Lactone Derivatives

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The stereoselective synthesis of 1,2,3-triazolooxazine and fused 1,2,3-triazolo-δ-lactone by applying chemoenzymatic methods is described. *trans*-2-Azidocyclohexanol was successfully resolved by *Novozyme 435* with an ee value of 99%. Installation of the alkyne moiety on the enantiomerically enriched azidoalcohol by *O*-alkylation, followed by intramolecular azide–alkyne [3+2] cycloaddition resulted in the desired 1,2,3-triazolooxazine derivative. Enantiomerically pure azidocyclohexanol was also subjected to the *Huisgen* 1,3-dipolar cycloaddition reaction with dimethylacetylene dicarboxylate, followed by intramolecular cyclization of the corresponding cycloadduct, to furnish a fused 1,2,3-triazolo-δ-lactone.

1. Introduction. – In recent years, the chemistry of 1,2,3-triazoles has gained new significance due to their wide range of applications in chemical, biological, medicinal, and materials science. Initially studied by *Huisgen* in the 1960s, the 1,3-dipolar cycloaddition of azides and alkynes is the most efficient method for the synthesis of substituted 1,2,3-triazoles [1]. These compounds are variously used as chemotherapeutic agents, synthetic intermediates for bioactive compounds, agrochemicals, optical brighteners, photostabilizers, anticorrosive agents, and metal chelators (for some recent reviews on the synthesis of 1,2,3-triazoles, see [2]). The extraordinary stability towards metabolic transformations and the aromatic nature of the triazole ring, along with its high dipole moment and H-bonding capability, make it a paramount functional group of great potential utility as a connecting group [3]. The asymmetric synthesis of fused 1,2,3-triazolo-δ-lactone and lactam derivatives has gained further importance, since they can easily be converted to biologically active precursors [4].

Optically pure 2-azido alcohols are very important intermediates for the synthesis of chiral 1,2-aminoalkanols, which have received wide attention in recent years due to their diverse applications as starting materials for the construction of bioactive compounds such as antibiotics [5], alkaloids [6], and enzyme inhibitors [7], and also as chiral resolving agents [8] and chiral auxiliaries for asymmetric synthesis [9]. Moreover, optically pure 2-azido alcohols can efficiently be obtained by lipase-catalyzed resolution of their racemic forms [10].

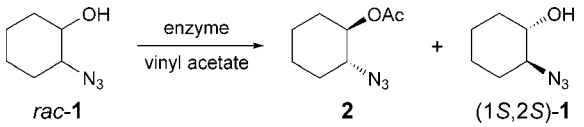
We report here the enzymatic resolution of *trans*-2-azidocyclohexanol and the asymmetric synthesis of fused 1,2,3-triazolo-δ-lactone and 1,2,3-triazolooxazine by intramolecular azide–alkyne 1,3-dipolar cycloaddition. To the best of our knowledge, this is the first stereoselective synthesis of fused 1,2,3-triazolo-δ-lactone and 1,2,3-triazolooxazine derivatives.

2. Results and Discussion. – 2.1. *Enzymatic Resolution of* rac-**1**. The key substrate *rac*-**1** was prepared from cyclohexene by oxidation with *m*-chloroperbenzoic acid (*m*CPBA) and then by ring opening of 7-oxabicyclo[4.1.0]heptane, with azide as the nucleophile (NaN_3) to give (±)-*trans*-2-azidocyclohexanol.

Initially, the enantiomeric resolution of *rac*-**1** was performed by using *Novozyme 435*, and vinyl acetate as both the acyl donor and as solvent at 40° (*Scheme 1*). The reaction was carried out by using a substrate/enzyme ratio of 1:1 (*w*/*w*). The conversion was monitored by TLC and 30% yield (for alcohol) was achieved after 7 d. The products were separated by flash column chromatography, and relatively low ee values of 45% for the ester (1*R*,2*R*)-**2** and 77% for the alcohol (1*S*,2*S*)-**1** were obtained (*Table*, *Entry 1*). We also carried out the enzyme-mediated resolution of the same substrate with *Lipozyme*, PS-C *Amano*, CRL (*Candida rugosa lipase*), and PPL (*porcine pancreative lipase*) under the same conditions. Lipozyme gave the best enantioselectivity (87% ee for (1*S*,2*S*)-**1** and 60% ee for **2**, *Entry 2*). To improve the ee values, experimental conditions were screened in detail using a co-solvent and by changing the reaction temperature. Resolution with *Novozyme 435* using $(^iPr)_2O$ as co-solvent at 30° gave excellent enantioselectivity for alcohol (1*S*,2*S*)-**1** (99% ee, *Entry 6*), which is comparable with the literature values [10], and a better ee value for **2** (68% ee, *Entry 6*). Also the enantioselectivity increased in PS-C *Amano*-catalyzed resolution performed at 30° in $(^iPr)_2O$ ((1*S*,2*S*)-**1**, 90% ee; and **2**, 65% ee, *Entry 7*).

The absolute configurations of (+)-**1** and (+)-**2** were determined as (1*S*,2*S*) and (1*R*,2*R*), respectively, by comparing the specific rotation signs determined at equal concentrations in the same solvents, which have been reported in [10]. The

Scheme 1



rac-**1** **2** (1*S*,2*S*)-**1**

Table. *Results of the Enzyme Catalyzed Kinetic Resolution of* rac-**1**

Entry	Enzyme	Temp. [°]	Time [h]	(1*R*,2*R*)-**2**		(1*S*,2*S*)-**1**		*c*	*E*[e])
				Yield [%]	ee_p[c]) [%]	Yield [%]	ee_s[c]) [%]	[%][d])	
1	*Novozyme 435*[a])	40	168	62	45	30	77	63	6
2	*Lipozyme*[a])	40	168	48	60	44	87	59	11
3	PS-C *Amano*[a])	40	168	50	56	45	71	56	10
4	CRL[a])	40	168	51	42	36	81	66	6
5	PPL[a])	40	168	–	–	–	–	–	–
6	*Novozyme 435*[b])	30	48	49	68	45	99	59	27
7	PS-C *Amano*[b])	30	48	52	65	43	90	58	14

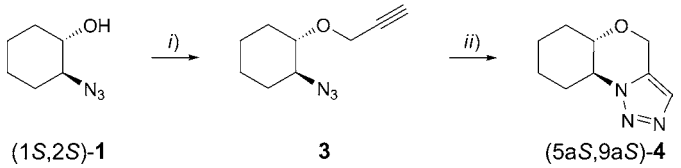
[a]) The reactions were carried out in vinyl acetate at 40°. [b]) The reactions were carried out in vinyl acetate and $(^iPr)_2O$ as co-solvent at 30°. [c]) Enantiomeric excess (ee) values were determined by HPLC using *Chiralcel AD-H* chiral column. [d]) $c = ee_s/(ee_s + ee_p)$. [e]) Calculated by the method of *Sih* and co-workers: $E = \ln[(1-c)(1-ee_s)]/\ln[(1-c)(1+ee_s)]$ [11].

spectroscopic and analytical data of **1** and **2** are in accordance with the reported values [10], confirming the assigned structures and stereochemical integrity.

2.2. *Stereoselective Synthesis of 1,2,3-Triazolooxazine.* After successful enzymatic resolution and determination of absolute configuration of the key compound (1*S*,2*S*)-(+)-**1**, we turned our attention to the transformation of the vicinal azidocyclohexanol into a triazolooxazine derivative. Installation of the alkyne group on (+)-(1*S*,2*S*)-**1** was achieved by base-mediated *O*-alkylation with $CH{\equiv}CCH_2Br$, leading to the desired 'azide–alkyne' **3** in excellent yield (*Scheme 2*). Having obtained the appropriate substrates for intramolecular azide–alkyne cycloaddition ('click chemistry'), thermally induced cycloaddition was performed (for racemic synthesis, see [12])[1]). Unlike in the intermolecular azide–alkyne 1,3-dipolar cycloadditions, the appropriate positioning of the two reacting moieties eliminated the need of any metal catalyst, and the desired cycloaddition could be efficiently achieved at a moderate temperature. Cycloaddition in refluxing toluene resulted in the formation of enantiomerically pure tricyclic 1,2,3-triazolooxazine, (5a*S*,9a*S*)-(+)-**4**, in 80% yield.

2.3. *Stereoselective Synthesis of Fused 1,2,3-Triazolo-δ-Lactone.* The azido alcohol (1*S*,2*S*)-(+)-**1** can also serve as a potential precursor for the synthesis of enantiomerically enriched triazole lactone derivatives, since the N_3 moiety can be easily transformed to many functional groups by intermolecular cyclization. The vicinal azido alcohol (+)-**1** was exposed to 'click' 1,3-dipolar cycloaddition reaction with dimethyl acetylenedicarboxylate (DMAD) by refluxing in toluene to afford the corresponding triazol cycloadduct **5** (*Scheme 3*). The next step was planned to be the construction of the lactone ring to yield the tricyclic product **6**. However, the desired **6**

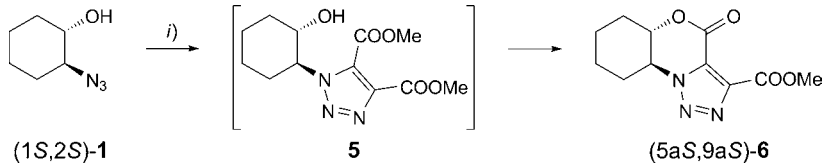
Scheme 2



(1*S*,2*S*)-**1** **3** (5a*S*,9a*S*)-**4**

i) $CH{\equiv}CCH_2Br$, NaH, Bu_4NI, THF. *ii*) Toluene, reflux.

Scheme 3



(1*S*,2*S*)-**1** **5** (5a*S*,9a*S*)-**6**

i) Dimethyl acetylenedicarboxylate (DMAD), toluene, reflux.

[1]) The spectroscopic data of 1,2,3-triazolooxazine **4** are in accordance with those of the corresponding racemic form reported in [12].

was obtained without lactonization step. Enantiomerically pure methyl (5a*S*,9a*S*)-5a,6,7,8,9,9a-hexahydro-4-oxo-4*H*-[1,2,3]triazolo[5,1-*c*][1,4]benzoxazine-3-carboxylate ((+)-**6**)was obtained as yellow solid in good yield.

3. Conclusions. – In conclusion, *trans*-2-azidocyclohexanol was successfully resolved by *Novozyme 435* with high enantioselectivity (99% ee). The enantiomerically pure (1*S*,2*S*)-azido alcohol is a key compound for asymmetric synthesis of both intermolecular and intramolecular cyclization products. We have demonstrated that the *Huisgen* 1,3-dipolar cycloaddition of this enantiomerically pure azide with an alkyne moiety introduced to the OH group yields the enantiomerically pure tricyclic 1,2,3-triazolooxazine. Also, we have described the stereoselective synthesis of the optically active fused 1,2,3-triazolo-δ-lactone by 'click reaction' of the chiral azide with DMAD as an activated alkyne, followed by intramolecular lactonization.

Experimental Part

General. Lipozyme, PS-C *Amano* lipase, CRL (*Candida rugosa* Lipase), PPL (lipase type II, from porcine pancreas) were purchased from *Aldrich. Novozyme 435* was donated by *Novo Nordisk AS*, DK Bagsverd. TLC: *Merck* silica gel *60 F_{254}* anal. aluminium plates (SiO_2; 0.2 mm thickness). Flash column chromatography (FC): SiO_2 (60 mesh; *Merck*). HPLC: *Thermo Separation Products, Inc., P1500-SN-4000-UV2000* instrument, *Chiralcel AD-H* anal. column (250 × 4.60 mm). Optical rotations: *Rudolph Research Analytical Autopol III* automatic polarimeter (1-dm cell). ^{1}H- and ^{13}C-NMR spectra: *Bruker Spectrospin Advance DPX 400* spectrometer; in $CDCl_3$; δ in ppm rel. to Me_4Si as internal standard, *J* in Hz. HR-ESI-MS: *Agilent 6224* LC/TOF-MS; in *m*/*z*.

Synthesis of (±)-trans-*2-Azidocyclohexanol* (*rac*-**1**). To a soln. of cyclohexene epoxide (0.97 g, 1 mmol) in MeCN/H_2O 1:1 (20 ml) was added NaN_3 (1.92 g, 3 mmol). The mixture was stirred under reflux for 4.5 h and then extracted with Et_2O (3 × 50 ml). The org. phase was washed with brine and dried ($MgSO_4$), concentrated *in vacuo*, and the crude product was purified by FC (AcOEt/hexane 1:5) to afford *rac*-**1** (0.95 g, 0.98 mmol, 98%). Colorless oil (see [11]). ^{1}H-NMR: 3.32 (*td*, *J* = 8.8, 4.4, 1 H); 3.24–3.04 (*m*, 1 H); 2.74 (*s*, 1 H); 2.10–1.87 (*m*, 2 H); 1.78–1.62 (*m*, 2 H); 1.34–1.08 (*m*, 4 H). ^{13}C-NMR: 73.5; 67.1; 33.1; 29.8; 24.2; 23.8.

General Procedure of the Enzymatic Resolution of rac-**1**. To a stirred soln. of *rac*-**1** (155 mg, 1 mmol) in vinyl acetate (5 ml), enzyme (155 mg; *cf.* the *Table*) was added in one portion, and the mixture was stirred at 40°. The conversion was monitored by TLC. The mixture was filtered, and vinyl acetate was evaporated under reduced pressure. The products were purified by FC (AcOEt/hexane 1:5).

(+)-(1S,2S)-2-Azidocyclohexanol ((+)-(1*S*,2*S*)-**1**). Yield: 70 mg (45%). Colorless oil. $[\alpha]_D^{20} = +68.5$ ($c = 1$, CH_2Cl_2); 99% ee [10]. The enantiomeric purity of the product was determined by HPLC (*Daicel Chiralcel AD-H*; hexane/^{i}PrOH 90:10; flow rate, 1 ml min^{-1}; λ, 210 nm; t_R 7.1 min (minor); t_R 78.1 min (major); in comparison with the racemic sample).

(+)-(1R,2R)-2-Azidocyclohexyl Acetate (**2**). Yield: 90 mg (49%). Colorless oil. $[\alpha]_D^{20} = +8.0$ ($c = 1$, CH_2Cl_2); 68% ee [10]. ^{1}H-NMR: 4.61 (*td*, *J* = 9.7, 4.6, 1 H); 3.31 (*td*, *J* = 10.3, 4.4, 1 H); 2.02 (*s*, 3 H); 2.01–1.92 (*m*, 2 H); 1.78–1.60 (*m*, 2 H); 1.34–1.14 (*m*, 4 H). ^{13}C-NMR: 169.2; 74.5; 62.2; 29.6; 29.3; 22.1; 22.5; 20.1.

(+)-(1S,2S)-1-Azido-2-(prop-2-yn-1-yloxy)cyclohexane (**3**). A mixture of NaH (0.21 g, 60%, 1.5 mmol) and 2-azidocyclohexanol (500 mg, 1 mmol) dissolved in dry THF (10 ml) was stirred in an ice-bath for 30 min. Then, $CH{\equiv}CCH_2Br$ (0.72 ml, 1.3 mmol) was added slowly, followed by Bu_4NI (0.5 mmol), and the mixture was stirred overnight at r.t. After the reaction was completed, sat. NH_4Cl soln. was added, and the mixture was extracted with AcOEt (3 × 15 ml). The org. phase was washed with brine, dried ($MgSO_4$), and concentrated *in vacuo*. Since the product easily decomposes, the crude one was used in the next step without further purification (see [11] for racemic synthesis).

*(+)-(5a*S*,9a*S*)-5a,6,7,8,9,9a-Hexahydro-4*H*-[1,2,3]triazolo[5,1-*c*][1,4]benzoxazine* (**4**). Compound **3** (500 mg, 2.8 mmol) was dissolved in toluene (15 ml), and the soln. was heated at reflux for 6 h. After the reaction was complete, the solvent was evaporated, and product **4** was obtained as white crystals. The spectroscopic data were in accordance with those reported in [11]. Yield: 400 mg (80%). M.p. 102–104°. $[\alpha]_D^{20} = +93.9$ ($c = 1$, CH_2Cl_2). ^{1}H-NMR: 7.35 (*s*, 1 H); 5.01–4.96 (*m*, 1 H); 4.83–4.78 (*m*, 1 H); 3.86–3.80 (*m*, 1 H); 3.38–3.32 (*m*, 1 H); 2.89–2.86 (*m*, 1 H); 2.07–2.04 (*m*, 1 H); 1.90–1.74 (*m*, 2 H); 1.52–1.33 (*m*, 4 H). ^{13}C-NMR: 130.8; 128.1; 78.3; 62.0; 60.9; 30.1; 27.9; 23.7; 23.6.

*(+)-Methyl (5a*S*,9a*S*)-5a,6,7,8,9,9a-Hexahydro-4-oxo-4*H*-[1,2,3]triazolo[5,1-*c*][1,4]benzoxazine-3-carboxylate* (**6**). To a stirred soln. of (1*S*,2*S*)-**1** (80 mg, 0.57 mmol) in toluene (11 ml), DMAD (0.456 g, 10 mmol) was added. The mixture was stirred for 4 h under reflux. The solvent was evaporated, and the crude product was purified by FC (AcOEt/hexane 2:3) to furnish **6**. Yield: 93 mg (65%). $[\alpha]_D^{20} = +78.1$ ($c = 1$, CH_2Cl_2). ^{1}H-NMR: 4.35–4.20 (*m*, 2 H); 3.94 (*s*, 3 H); 3.07–3.03 (*m*, 1 H); 2.33–2.29 (*m*, 1 H); 2.01–1.94 (*m*, 2 H); 1.81–1.65 (*m*, 2 H); 1.56–1.37 (*m*, 2 H). ^{13}C-NMR: 158.7; 152.5; 140.3; 124.8; 80.0; 59.0; 51.9; 28.2; 25.9; 22.3; 22.1. HR-ESI-MS: 252.1032 ($[M+H]^+$, $C_{11}H_{14}N_3O_4^+$; calc. 252.0984).

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