Pergamon

Tetrahedron Letters, Vol. 38, No. 31, pp. 5485-5488, 1997

0040-4039/97 $17.00 + 0.00

PII: S0040-4039(97)01227-6

Biocatalysis in the Chiral Recognition of *meso*-Diamides - An Efficient Route from Cyclic Olefinic Hydrocarbons to Optically Pure Diamino-Polyols

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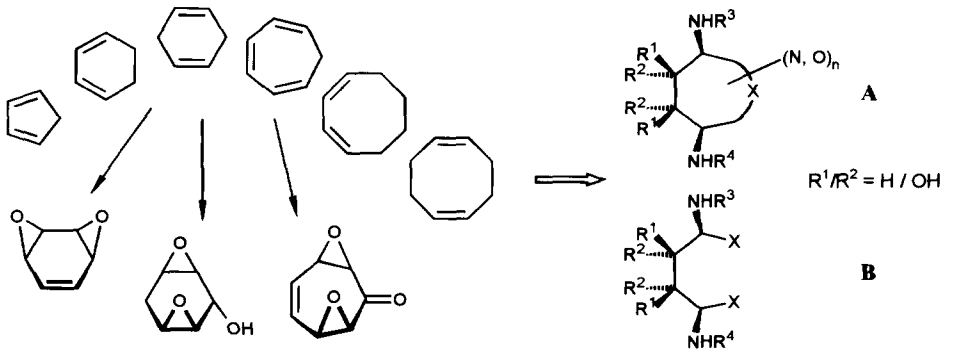
Summary: *meso*-Diamino-di(tri,tetr)ols **1** - **8** were synthesized starting from cheap carbocyclic olefins and *cis*-diepoxy derivatives. Enantioselective hydrolysis of the corresponding bis(phenylacet)amides with penicillin amidase from *E. coli* (EC 3.5.1.11) was effected in good yields (73 - 90%) and with high optical purities (ee 91 - >97). © 1997 Elsevier Science Ltd.

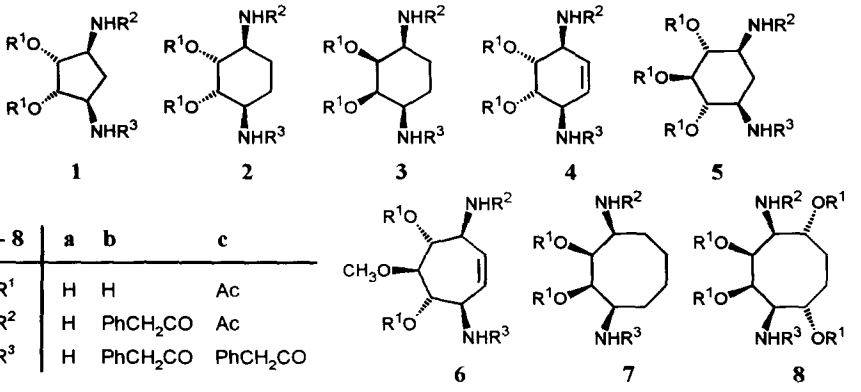
The β-amino alcohol motifs generalized with formula **A** and **B** (Scheme 1) are core units in various bioactive compounds, e.g. aminoglycoside antibiotics[1] and antiviral nucleosides.[2] Effective methods have been developed to cope with the direct stereo- and enantioselective conversion of a C=C double bond into a N,O-functionalized unit (cf. the asymmetric aminohydroxylation by Sharpless[3]). A still rarely applied alternative, desymmetrization of *meso*-diamino-polyols by biocatalysis,[4] makes up the central aspect of this letter.



Scheme 1

As substrates for this explorative study the diamine-di(tri,tetr)ols **1** - **8** (Scheme 2) were efficiently prepared starting from carbocyclic 1,3(1,4)-dienes and *cis*-diepoxy derivatives. After unsatisfactory results with enzyme catalyzed acylation methods,[5] hydrolysis of the respective bis(phenylacet)amides catalyzed by penicillin amidase lived up to expectation - the latter was known to be highly (*S*)-selective on the phenylacetamides of amino acid related compounds.[6] The known drawbacks - low solubility of phenylacetamides in the aqueous reaction medium and activity

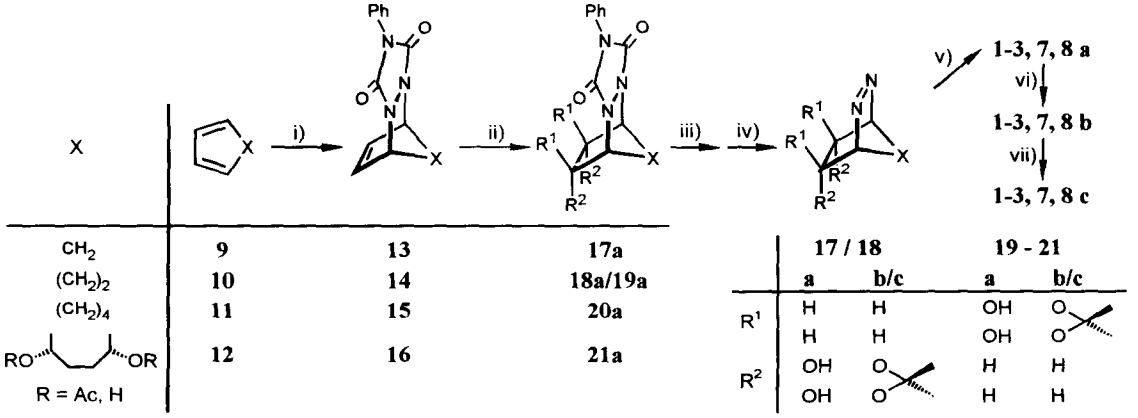
loss of the enzyme due to organic cosolvents[7] - could adequately be managed.



1 - 8	a	b	c
R^1	H	H	Ac
R^2	H	$PhCH_2CO$	Ac
R^3	H	$PhCH_2CO$	$PhCH_2CO$

Scheme 2

The known adducts **13** - **16**[8] of cyclopentadiene **9**, cyclohexa-1,3-diene **10**, cycloocta-1,3-diene **11** and *cis*-cycloocta-2,4-diene-1,6-diol diacetate **12**[9] with 4-phenyl-1,2,4-triazoline-3,5-dione (PTAD) were dihydroxylated along standard procedures (OsO_4, N-methyl-morpholine oxide (NMO)) to give **17a** - **21a** (Scheme 3).[10] The stereoselectivity of these reactions was confirmed by NOE and was in line with expectation ([2.2.1]: > 97% *exo*-**17a**; [2.2.2]: *exo*-**18a**/*endo*-**19a** = 30:70; [2.2.4]: > 97% *endo*-**20a**, **21a**). After conversion to the acetonides **17b** - **21b** the urazole ring was transformed into the azo-bridge (**17c** - **21c**).[11] For N-N cleavage hydrogenation either over Pt in acidic medium (**17** - **19**) or over Raney-Ni in aqueous KOH (**20**, **21**)[12] proved favorable and afforded the free diamino-di(tetr)ols **1a**[13] - **3a** and **7a/8a** in good to high yields (isolated as bishydrochlorides). The diamino-di(tri)ols **4a**,[14a] **5a** (2-*deoxystreptamine*)[14b] and **6a**[14c] were prepared according to literature *via* the respective diepoxides.



X			
CH_2	**9**	**13**	**17a**
$(CH_2)_2$	**10**	**14**	**18a/19a**
$(CH_2)_4$	**11**	**15**	**20a**
RO, OR	**12**	**16**	**21a**
R = Ac, H			

	17 / 18		**19 - 21**	
	a	**b/c**	**a**	**b/c**
R^1	H	H	OH	O
	H	H	OH	O
R^2	OH	O	H	H
	OH	O	H	H

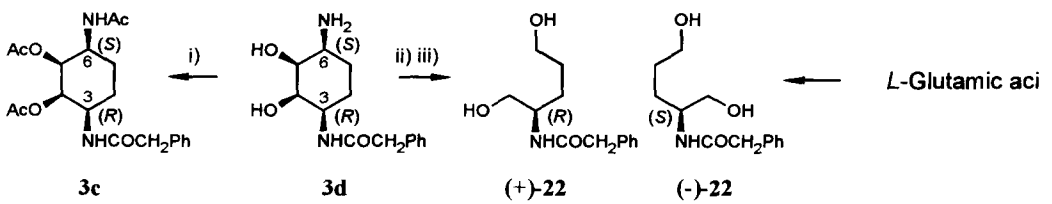
Scheme 3. i) PTAD, CH_2Cl_2, r.t., 30 min, 94%. - ii) cat. OsO_4, 1.2 equiv. NMO, acetone/H_2O 2:1, r.t., 24 h, 80 - 88%. - iii) 2,2-dimethoxypropane/CH_2Cl_2 1:1, cat. camphorsulfonic acid, r.t., 12 h, 95%. - iv) 2 N KOH in 2-propanol, reflux, 2 h, then HCl, 3 equiv. $CuCl_2$, then NH_3 (aq.), 85%. - v) [H_2, Pt, glacial acetic acid, r.t., 12 h, then HCl (aq.)]; or [Ni/Al alloy, MeOH/1 N KOH (aq.) 1:1, r.t., 24 h], 83 - 96%. - vi) $PhCH_2COCl$, $NaHCO_3$, *tert*-BuOH/H_2O 1:1, r.t., 30 min, 75 - 85%. - vii) penicillin amidase, 0.2 M phosphate buffer (pH 7.6) (see Table 1), then Ac_2O, pyridine, DMAP, N_2, 12 h, r.t.

As expected the bis(phenylacet)amides **1b** - **8b** proved only slightly soluble in aqueous media; hydrolysis with penicillin amidase remained slow and incomplete. To avoid enzyme-inactivating cosolvents[7] and to further the rate-determining dissolution, suspensions of powdered bisamides in aqueous phosphate buffer (pH 7.6, 0.2 N) were prepared by sonification (15 min), for the non-crystalline compounds **4b** and **6b** adsorbates on silicagel were sonificated in the buffer. The suspensions were incubated with penicillin amidase on Eupergit (shaking at 25 - 35°C). After a clear solution had developed (ca. 24 h) TLC showed total conversion to the monoamide (occasionally traces of diamine). A Cosolvent (DMF) was only necessary in case of the practically insoluble substrate **5b**. The enzyme was filtered off, the filtrate was evaporated, and the residue acetylated under standard conditions (pyridine, Ac_2O, DMAP, N_2 atm., 12 h, r.t.). After concentration and chromatography the peracetylated monophenylacetamides **1c** - **8c** were isolated in 73 - 90% yields and high optical purity (determined by HPLC on a Daicel CHIRALPAK AD or CHIRALCEL OD-H column, Table 1). For reference racemic samples of **1c** - **8c** were prepared "chemically".

Table 1. Penicillin amidase catalyzed hydrolysis of diamides **1b** - **8b**

substrate	substrate conditioning	time	product	$[\alpha]_D^{25}$ (MeOH)	yield (%)	ee
1b	powdered	24 h	**(-)-1c**	-3.7 (*c* = 0.4)	82	91
2b	powdered	24 h	**(-)-2c**	-9.3 (*c* = 0.6)	90	> 97
3b	powdered	72 h	**(-)-3c**	-25.3 (*c* = 1.0)	73	95
4b	adsorption on SiO_2	24 h	**(-)-4c**	-22.3 (*c* = 0.7)	83	> 97
5b	powdered, 20% DMF	18 d	**(-)-5c**	-8.3 (*c* = 0.7)	76	> 97
6b	adsorption on SiO_2	5 d	**(-)-6c**	-12.4 (*c* = 1.2)	65	93
7b	powdered	24 h	**(-)-7c**	-11.1 (*c* = 1.9)	73	95
8b	powdered	48 h	**(-)-8c**	-13.2 (*c* = 1.7)	86	> 97

For **3c** (**3d**) the absolute configuration at C-3 (*R*) was determined by correlation with *L*-glutamic acid ((+)-**22**: $[\alpha]_D^{25}$ = + 13.2 (*c* = 1.0, MeOH) from **3d** vs. (-)-**22**: $[\alpha]_D^{25}$ = -16.1 (*c* = 1.3, MeOH) from *L*-glutamic acid)[15] (Scheme 4). This is in line with the known (*S*)-selectivity of penicillin amidase. The generally negative sign of the measured optical rotations for **1c** - **8c** supports the assumption that in all cases the enzyme had attacked the phenylacetyl group on the (*S*) site.



Scheme 4. i) Ac_2O, pyridine, DMAP.- ii) $NaIO_4$, EtOH. - iii) $LiEt_3BH$, THF

Acknowledgement: This work has been supported by the *Fonds der Chemischen Industrie* and the *BASF AG*. - *S.G.* and *J.A.* thank the *Landesgraduiertenförderung* of Baden-Württemberg for a fellowship. We thank *Dr. D. Hunkler* for NMR-spectroscopy, *Dr. J. Wörth* for MS-, and *G. Fehrenbach* for HPLC-analyses.

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10. All new compounds have been fully characterized (^{1}H, ^{13}C NMR, MS, IR, elemental analysis). E.g. (1α,2α,3β,6β)-3-phenylacetylamino-6-acetylamino-cyclohex-4-ene-1,2-diol diacetate (-)-**4c**: HPLC (Daicel CHIRALPAK AD, *n*-hexane/2-propanol 70:30, 0.8 ml/min): ee > 97 ($R_{t\ (-)\text{-}4c}$ = 9.54, $R_{t\ (+)\text{-}4c}$ = 6.73 min); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.39 - 7.22 (m, phenyl-H), 5.71 (d, br, NH), 5.68 (m, 4-H, 5-H), 5.65 (d, br, NH), 5.19 - 5.13 (m, 1-H, 2-H), 4.61 - 4.51 (m, 3-H, 6-H), 3.56 (s, CH_2), 2.06 (s, CH_3), 1.99 (s, CH_3), 1.96 (s, CH_3), $J_{NH,3}$ = 7.8, $J_{NH,6}$ = 7.8, $J_{1,2}$ = 2.4 Hz; ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 171.0, 170.4, 170.1, 169.6 (4 C=O), 134.5, 129.4, 129.1, 128.9, 127.5, 127.2 (phenyl, C-4, C-5), 70.0, 69.4 (C-1, C-2), 48.4, 48.2 (C-3, C-6), 43.8 (CH_2), 23.2, 20.9, 20.8 (3 CH_3); MS (70eV; EI): m/z (%) = 388(M^+, 10), 297(M^+-$PhCH_2$, 18), 269(M^+-$PhCH_2CO$, 53), 255(18), 237(36), 227(89), 193(58), 151(100), 136(31), 110(83), 109(89), 91($PhCH_2^+$, 93), 44(76).
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(*Received in Germany* 21 *May* 1997; *accepted* 18 *June* 1997)