Tetrahedron Letters, Vol. 34, No. 30, pp. 4761-4764, 1993
Printed in Great Britain

0040-4039/93 $6.00 + .00
Pergamon Press Ltd

BIOCATALYSIS EN ROUTE TO DIAMINO-DI(TRI)DEOXYCYCLOHEXITOLS AND DIAMINO-TETRADEOXYCYCLOHEPTITOLS

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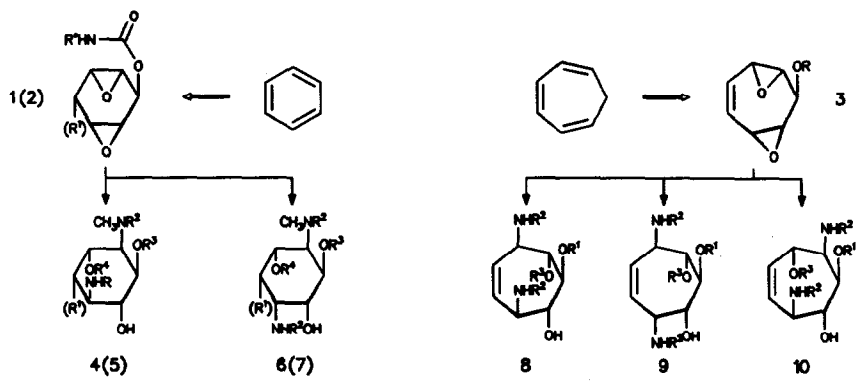
Summary. Efficient enzymatic resolutions at two stages of our route from benzene to amino(deoxy)inositols (*rac*-**11a,b**; **12a,b**; **13a,b**) and highly selective enzymatic asymmetrizations of *meso*-precursors (**16d**; **18a,b**; **21b**) on the way from tropilidene to diaminotetradeoxyheptitols provide enantiomerically pure (highly enriched) aminoglycoside building blocks.

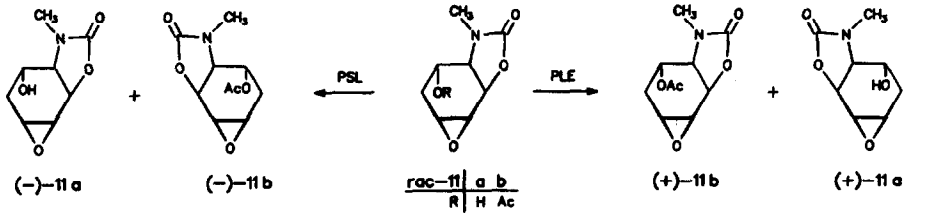
For total syntheses of chemically modified, binuclear aminoglycoside antibiotics - in every possible combination of the respective enantiomerically pure sugar and non-sugar components[1] - we have worked out efficient preparative routes to appropriately protected, racemic diaminodi(tri)deoxyhexitols (**4-7**)[2-5] and diaminotetradeoxyheptitols (**8-10**)[6] starting out ultimately from benzene[7] and tropilidene**, respectively.[8] A few aglyca of type **4-6** had been secured as pure enantiomers through epoxide opening with (R)-/(S)-1-phenylethylamine or through resolution of esters with (R)-/(S)-camphanic acid,[2,4] a few of type **8** through enzymatic asymmetrization of *meso*-precursors.[6] Our continuing efforts to further the synthetic enterprises by biocatalytic methodologies have resulted in some preparatively valuable preparations on the way to enantiomerically pure aglyca **4-7** and **8-9**.[9,10]



The epoxycarbamates *rac*-**11a,b** - the first chiral intermediates on the way from **1** to aglyca of type **4**[2] and **6**[4] - are through their OR-functionalities amenable to enzymatic resolution (irreversible acyl-transfer, ester hydrolysis).[11] For acyl-transfer to *rac*-**11a**, from an extensive study with a number of lipases[12] and various solvents, the combination of PS lipase[12] and *tert*-butylmethyl ether emerged as the combination of choice: Under the actually practiced

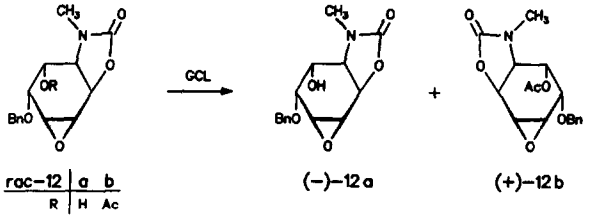
** !! **Warning** !! The bisepoxidation of tropone as detailed in Chem. Ber. 1984, 117, 1834 (cf. A. McKillop et al. J. Chem. Soc. Chem. Comm. 1992, 1589), has been performed in our laboratory many times. Before work-up, excess of reagent and peroxides were reduced, the reaction solution (after monitoring for peroxides) was not totally concentrated. For not understood reasons, during work-up of our last preparation a detonation caused severe personal damage.

conditions (10.0 mmol *rac*-**11a**, 20 ml vinyl acetate, 500 mg PS lipase, r.t., 6d, chromatographic work-up on silica gel, not optimized) the acetate (-)-**11b** was isolated in slightly more than 50% (52-54%) and therefore a somewhat reduced ee value of 91%; yet, for the recovered alcohol (-)-**11a** (46-48% isolated) the ee value was up to 96%. It is remarkable, that in diethyl ether as the next best solvent, the selectivity was significantly lower (ee of 74% and 85% at 42% conversion). For the hydrolysis of acetate *rac*-**11b** (*n*-hexane, pH 7 phosphate buffer, r.t.) the same collection of enzymes[12] was tested with only two of them being found to be active: With AY lipase[12] the reaction



proved very slow and only weakly selective; PLE[12], however, provided preparatively useful results: From a typical run (5.0 mmol *rac*-**11b**, 260 U PLE, r.t.,100 ml H_2O/5 ml *n*-hexane, 0.5 equiv. of NaOH, 1.5 d, chromatography on silica gel) 53% of (+)-**11a** with moderate 80-84% ee and 44-46% of (+)-**11b** with at least 94% ee were obtained.[13] Optical purities could be reliably determined with R(-)-1-(9)-anthryl-2,2,2-trifluoroethanol (δ_{NCH3} = 2.70, $\Delta\delta$ = 0.03 ppm). For confirmation of the given configurational assignments, (-)-**11a** and (+)-**11a** were transformed into natural and unnatural sporamine, respectively ((+)-**6**; (-)-**6**; $R^1 = R^2 = R^3 = H$; $R^4 = CH_3$).[4]

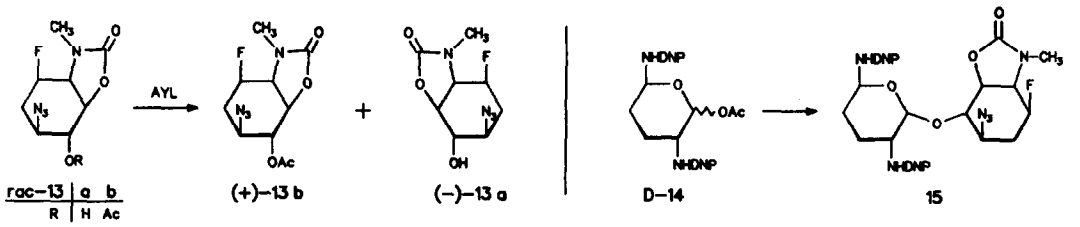
The epoxycarbamates *rac*-**12a,b** are proven intermediates in the fortamine (**5**) and *epi*-fortamine series (**7**) and offered themselves for analogous enzymatic resolutions. In contrast to *rac*-**11a**, esterification experiments carried out with *rac*-**12a** analogously to *rac*-**11a** were not successful. On the other hand, hydrolysis of acetate *rac*-**12b** with GC lipase[12] in the two-phase system (*n*-hexane, pH 7 buffer) was found to be efficient and highly selective: After a very slow reaction (1 mmol scale, 7 d, r.t., ca.50% conversion), optically pure alcohol (-)-**12a** ($[\alpha]^{20}_D$ = -14.1°, c = 0.16, CH_2Cl_2) and acetate (+)-**12b** ((+)-**12a**: $[\alpha]^{20}_D$ = +15.2°, c = 0.07, CH_2Cl_2) were obtained in nearly quantitative yields after chromatography (silica gel), with practically total optical purity (ee ≥ 97%) in both cases; determined



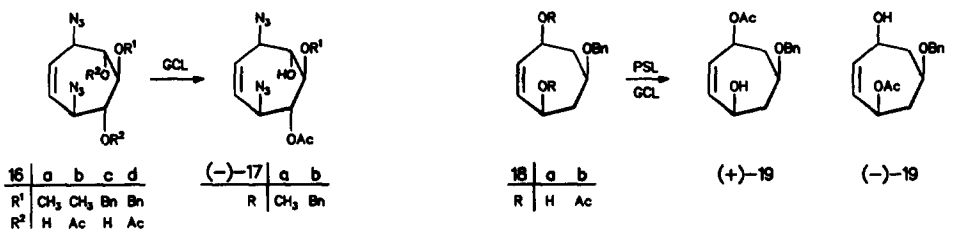
through Mosher esters [14]; the 1-H and 6-H signals for the diastereomers formed with (+)-and (-)-MTPA are diamagnetically shifted by 0.15 ppm. The reaction time can be vastly reduced (to ca. 4 h) by sonification, with yields and ee values being not measurably affected. Additionally *rac*-**12a** was resolved (if only incompletely) via its esters with (+)-/(-)-camphanic acid which are easily separable by crystallization from methanol. The structure of the latter diastereomer has been analyzed by X-ray crystallography.[5] In line with the configurational assignments, natural ((-)-**5**; R^1 = OH, $R^2 = R^3$ = H; $R^4 = CH_3$) and non-natural fortamine ((+)-**5**) were generated from (-)-**12a** and (+)-**12b**, respectively, in the described fashion.[3]

Searching for enzymatic resolutions in the next stage of the general route to the aglyca, several bicyclic carbamates have been exposed to various lipases and hydrolases, respectively. In case of the hydrolysis of acetate

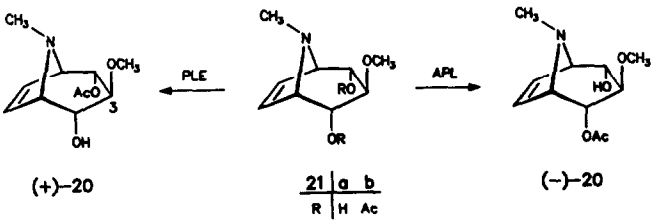
rac-**13b** (1.2 mmol) with the AY lipase[12] (100 mg) in the *n*-hexane/pH 7 phosphate buffer system, as applied to *rac*-**11b**, a preparatively useful result was achieved: alcohol (-)-**13a** was isolated in 46% yield and with ee of 89%. From the reaction of such an alcohol fraction with the glycosyl donor D-**14**,[1] the α-glycoside **15** was obtained in ca. 85% yield (admixed with ca. 5% of the α-glycoside from (+)-**13a** and less than 10% of the two β-glycosides). Crystallization was sufficient to provide pure diastereomer **15**, which then was transformed into the novel non-natural fluorinated sannamycin.[1]



An interesting discrepancy in their response to PLE (in water) and GC lipase (in water/*n*-hexane) has been noted for the two *meso*-diacetates **16b** and **16d** (the benzyl "protecting" group has the advantage of making **16d** less prone to hampering Cope rearrangement).[6] From the reaction of methoxydiacetate **16b** in water/acetone (PLE) after uptake of one equivalent of base monoacetate (-)-**17a** had been obtained in high yield (88%) with moderate 86% ee. Under the same conditions benzyloxydiacetate **16d** yielded a practically 50 to 50 mixture of **16c** and **16d** with only traces of **17b** being observable. Most of the lipases[12] tested for hydrolysis showed no activity, except GC lipase which catalyzed the selective formation of **17b** (2 mmol, 5d, r. t., ee ≥ 97%, $[\alpha]^{20}_D$ = - 23.7° (c = 0.59, CH_2Cl_2)).[15] Both diols **16a** and **16c** proved resistant to vinyl acetate in the presence of all the tested enzymes.[12] For the asymmetrization of benzyloxydiol **18a** the PS lipase[12] successfully applied by Johnson et al.[16] to the corresponding TBS diol proved similarly selective (6 mmol **18a**, vinyl acetate, 3d, 50°C, 89% (+)-**19**, ee ≥ 97%, $[\alpha]^{20}_D$ = + 32.5°, c = 0.97, CH_2Cl_2). In addition, diacetate **18b** under standard conditions (*n*-hexane, pH 7, phosphate buffer, r. t.) was selectively hydrolyzed (pro - S) to give (-)-**19** (60%, not optimized, ee ≥ 97%, $[\alpha]^{20}_D$ = - 32.8°, c = 0.96, CH_2Cl_2).



The *meso*-azabicyclo[3.2.1]diacetate **21b** and other 3-derivatives are the established precursors for the diamines **9**/**10**. Diacetate **21b** was now found to be another case[17] - though outstanding with regard to chemical and optical yield - where esterases and lipases exert opposite enantioselectivity. Whilst PLE[12] had exclusively catalyzed the hydrolysis of the pro-(R)-acyl group, ((+)-**20**; 100%, ee > 99%; $[\alpha]^{20}_D$ = +55.5°, c = 0.70, $CHCl_3$),[6] the AP



lipase[12] (*n*-hexane/ pH 7 phosphate buffer, 1 mmol scale) showed comparably high selectivity for the pro-(S)-acyl group (100% (-)-**20**; ee ≥ 97%; $[\alpha]^{20}_D$ = - 54.0°, c = 0.72, $CHCl_3$).

Acknowledgment Financial support by the *Deutsche Forschungsgemeinschaft*, the *Fonds der Chemischen Industrie* the *BASF AG* and the *Ministerium für Wissenschaft und Kunst des Landes Baden-Württemberg (Forschungsschwerpunkt "Synthese - Enzyme")* is gratefully acknowledged. We thank *Dr. M. Keller* for the X-ray structural analysis, Fa. Amano Co. for a generous gift of enzymes.

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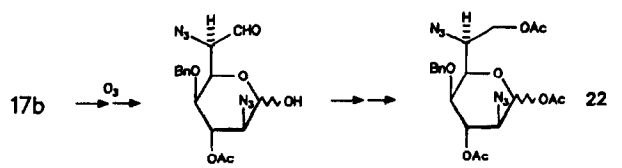

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(Received in Germany 17 May 1993)