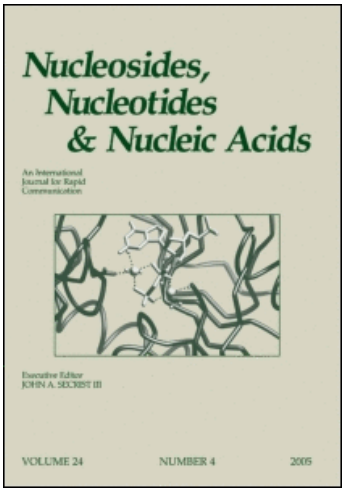

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BIOPHYSICS/BIOCHEMISTRY

RESOLUTION OF (±)-CYTALLENE — A HIGHLY ACTIVE ANTI-HIV AGENT WITH AXIAL DISSYMMETRY

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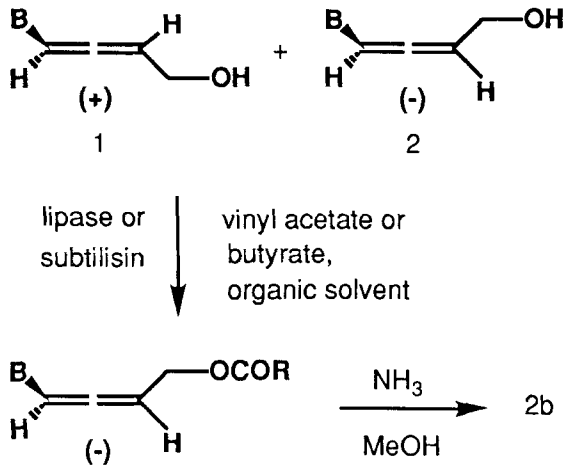
Abstract. Anti-HIV agent (±)-cytallene (1b + 2b) was resolved by enantioselective acylation of (±)-N^4-benzoylcytallene (1d + 2d) with vinyl butyrate in tetrahydrofuran catalyzed by lipase AK from *Pseudomonas sp.* and subsequent deacylation of 4d and 1d with ammonia in methanol. Optically pure enantiomers 1b and 2b were obtained.

Effective anti-HIV agents (±)-adenallene (1a + 2a) and (±)-cytallene (1b + 2b) belong to a unique class of acyclic nucleoside analogues with axial dissymmetry[1-3]. (±)-Adenallene (1a + 2a) was resolved by enantioselective deamination with adenosine deaminase giving directly the more active R-(-)-enantiomer whereas S-(+)-enantiomer was obtained from the deamination product, S-(+)-hypoxallene, by chemical synthesis[4]. This approach could not be applied to resolution of (±)-cytallene (1b + 2b), an anti-HIV agent more effective[2] than (±)-adenallene (1a + 2a), because the former analogue is not a substrate for cytidine deaminase[3]. In addition, a non-destructive method for obtaining enantiomers 1b and 2b in high optical purity was deemed preferable to a procedure yielding only a single enantiomer with unaltered heterocyclic base.

The initial model experiments were carried out with racemic adenallene (1a + 2a), cytallene (1b + 2b) and N^4-acetylcytallene (1c + 2c) using vinyl acet-



Scheme 1

ate or butyrate as acylating agents. Thus, acetylation of 1a + 2a with vinyl acetate and lipase PS30 in tetrahydrofuran (THF) - acetone (1 : 2) for 24 h at room temperature gave (-)-4'-O-acetyladenallene (3b, 25 %), $[\alpha]_D$ -58°, 30.5 % ee[5] (based on $[\alpha]_D$ of the corresponding S-(+)-enantiomer[4]) and (+)-adenallene (1a, 74 %), $[\alpha]_D$ 23° (c 0.15), 12 % ee (Scheme 1). Under similar conditions (with lipase AK and vinyl butyrate), (±)-N^4-acetylcytallene (1c + 2c) gave (-)-butyrate (4c, 30 %), $[\alpha]_D$ -58° and (+)-N^4-acetylcytallene (1c, 57 %), $[\alpha]_D$ 54°. It was not possible to investigate (±)-cytallene (1b + 2b) as a substrate for lipases in ordinary organic solvents because of poor solubility. Nevertheless, with subtilisin in pyridine and vinyl butyrate (-)-4'-O-butyrylcytallene (4b, 39.5 %, $[\alpha]_D$ -14°, 6 % ee) and (+)-cytallene (1b, 37 %, $[\alpha]_D$ 42°, 18 % ee) were obtained.

Although enantioselectivity of these acylations was poor, the results indicated that the prevailing acylated products derived from both adenallene and cytallene are levorotatory and probably of the same absolute configuration. It is likely that the " allene " (Lowe's) rule[3] is followed and that the dextrorotatory compounds have an S configuration. It was also possible that introduction of a more lipophilic substituent at the N-4 of (±)-cytallene (1b + 2b) would increase both the solubility and binding efficiency of the substrate. Also, following the

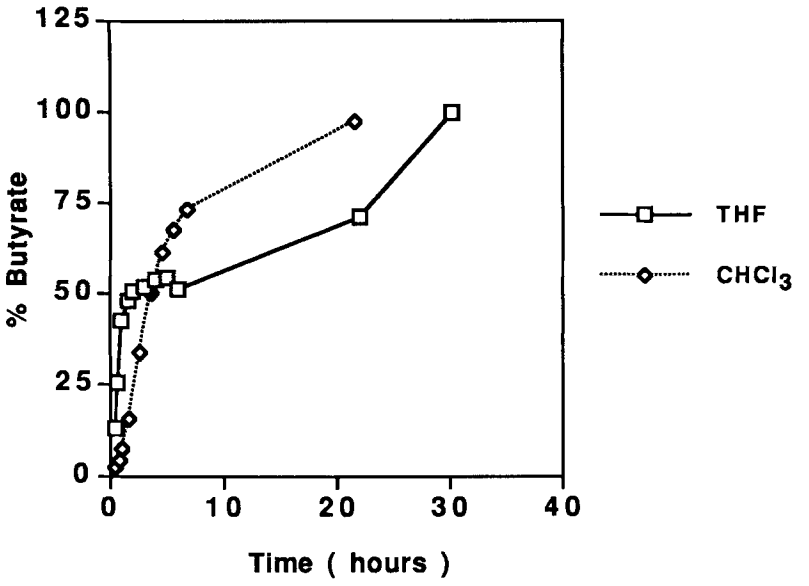


Fig. 1. Time-course of the reaction of (±)-N^4-benzoylcytallene (1d + 2d, 23 μmol) with vinyl butyrate (1.4 mmol) and lipase AK (99 units) in THF or $CHCl_3$ (1 mL) at room temperature. Aliquots were removed from a magnetically stirred mixture, they were subjected to TLC (CH_2Cl_2 - methanol, 95 : 5), the appropriate spots were eluted with ethanol and examined by UV spectrophotometry at 330 nm.

time-course of the reaction could provide additional information on enantioselectivity of acylation.

Such studies conducted with (±)-N^4-benzoylcytallene (1d + 2d), vinyl butyrate and lipases PS30 or AK in $CHCl_3$, THF and dioxane showed that acylations catalyzed by the former enzyme were very slow. Thus, in $CHCl_3$ little enantioselectivity was seen from the time-course of the reaction (96 % conversion after 172 h) whereas in THF some deceleration was noted at ca. 50 % conversion. The reaction in dioxane was very slow (35 % conversion after 93 h). The acylations catalyzed by lipase AK were significantly faster. Again, in $CHCl_3$ no apparent enantioselectivity was seen (97 % conversion after 22 h, Fig. 1). In THF, a plateau was reached at ca. 50 % conversion and the reaction continued at a significantly slower rate (100 % conversion after 30 h). The rate of acylation of (-)-enantiomer 2d in THF is approximately 20 - 40 times higher than that of

(+)-enantiomer 1d. The acylation of 1d + 2d in dioxane albeit much slower also indicated a deceleration at ca. 50 % conversion.

Based on these results, the acylation of (±)-cytallene (1b) with vinyl butyrate (3.3 equivalents) in THF (160 mL) catalyzed by lipase AK (22,220 units) was performed on a preparative (3.6 mmol) scale. The 4A molecular sieves were also included to scavenge acetaldehyde released during acylation[6]. The mixture was stirred for 2 h at room temperature. Compounds 1d and 4d were separated by chromatography. Deacylation with methanolic ammonia furnished (-)-cytallene 2b (100 %, 94 % ee) and (+)-cytallene 1b (82 %, >95 % ee). A single recrystallization from methanol furnished optically pure 2b, $[\alpha]_D$ -232.4° and 1b, $[\alpha]_D$ 229.5° (c 0.2)[5]. Both enantiomers gave single peaks on HPLC chiral column Chiralcel OB (silica gel coated with cellulose tribenzoate), 10 μm, 250 x 4.6 mm, elution with 80 % 1-hexane (0.3 % diethylamine) - 20 % 2-propanol at 40°C, flow-rate 1mL/min., detection at 290 nm.

Biological activity and absolute configuration of (-)- and (+)-cytallene 2b and 1b are under investigation.

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