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AN INTERESTING EXAMPLE OF COMPLEMENTARY REGIOSELECTIVE ACYLATION OF SECONDARY HYDROXYL GROUPS BY DIFFERENT LIPASES

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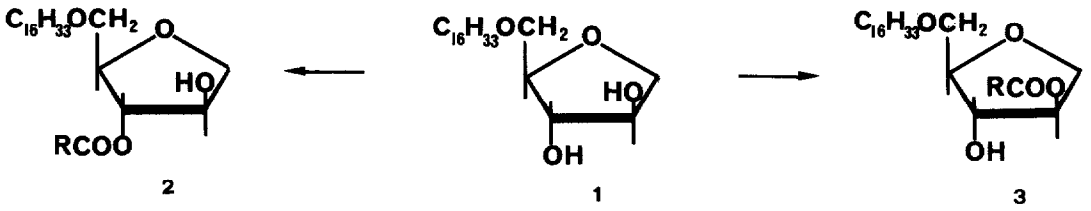
Abstract: acylation of 1,4-anhydro-5-O-hexadecyl-D-arabinitol (1) by different lipases afforded alternatively the monoacylated products (2) or (3).

In our studies directed towards the synthesis of analogs of glycolipids, we were looking for an efficient way to acylate selectively the two hydroxyl groups in (1). As classical chemical methods gave unsatisfactory results, we turned our attention to the enzymatic approach recently developed by Klibanov and coworkers[1-4].

Following the general methodology[1], 100 mg of commercially available lipase were added to a solution of 1,4-anhydro-5-O-hexadecyl-D-arabinitol (1) (10 mg) and trichloroethylbutyrate (5 molar equivalent) in dry benzene (1 ml). The suspension[5] was shaken at 250 rpm at 45°C, and the progress of the reaction was monitored via gaschromatography and TLC. Out of twenty different lipases tested, the eight enzymes reported in Table 1 showed an appreciable degree of conversion within 24 hours. In all cases except two a good degree of regioselectivity was observed. More interestingly, the monoacylated products (2) and (3) were alternatively obtained using different enzymes. Rhizopus japonicus and Humicula lanuginosa gave the best complementary results.



2 1 3

R = *n*-Pr

Table 1

Lipase	% Conversion[a]	(2):(3)
Humicula lanuginosa[b]	71	3:97
Pseudomonas fluorescens[b]	70	15:85
Candida cylindracea[c]	91	84:16
Porcine pancreatic[c]	62	9:91
Chromobacterium viscosum[d]	54	26:74
Mucor meheii[e]	73	4:96
Rhizopus japonicus[e]	96	86:14
Penicillium cyclopium[e]	91	56:44

a, the degree of conversion and the ratio of (2) and (3) was gaschromatographically monitored (Supelco SPB-1 30m x 0.75mm, 1.0μm film capillary column, Tc 280°C; retention times: (1), 8.0 min.; (2), 11.8 min; (3), 12.5 min.
b, Amano Pharmaceutical LTD; c, Sigma Chemical Co; d, Finnsugar Biochemicals, INC.; e, Biocatalysts LTD.

Using these two enzymes as catalysts, the reactions were scaled up to 400 mg of (1) and the products were purified by flash chromatography (eluent ethyl acetate/hexane = 2:8). Compounds (2) and (3) were obtained in 79% and 66% yield respectively[6].

As polyhydroxylated furanosidic rings are useful synthons for biologically important compounds, any achievement for the regioselective protection of their hydroxyl groups is noteworthy.

References and notes

1. A.M. Klibanov, Chemtech, 1986, 16, 354.
2. M. Therisod and A. M. Klibanov, J. Am. Chem. Soc., 1987, 109, 3977.
3. S. Riva, J. Chopineau, A.P.G. Kieboom, A.M. Klibanov, J. Am. Chem. Soc., 1988, 110, 584.
4. S. Riva, A.M. Klibanov, J. Am. Chem. Soc., 1988, 110, 3291.
5. Lipases are insoluble in benzene.
6. Selected analytical data. (2), m.p. 44-45°C (from EtOH), $|\alpha|_D$ +8.1 (c 1, $CHCl_3$). ^1H n.m.r. (200 MHz, $CDCl_3$) δ 3.88 (dd, J 10 and 3 Hz, H-1a); 3.96 (d, J 4 Hz, H-1b); 4.09 (broad dd, J 11 and 3 Hz, H-2); 4.31 (d, J 11 Hz, OH); 4.97 (broad s, H-3). Found: C, 70.22; H, 11.41%. $C_{25}H_{48}O_5$ requires: C, 70.05; H, 11.29%.
(3), m.p. 54-55°C (from EtOH-Hexane), $|\alpha|_D$ +17.6° (c 1, $CHCl_3$). ^1H n.m.r. (200 MHz, $CDCl_3$) δ 3.84 (dt, J 6 and 4.5 Hz, H-4); 3.95 (dd, J 11 and 2.5 Hz, H-1a); 4.01 (dd, J 6 and 2.5 Hz, H-3); 4.09 (dd, J 11 and 5.5 Hz, H-1b); 4.93 (dt, J 5.5 and 2.5 Hz, H-2). Found: C, 69.66; H, 11.18%.

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