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FACILE CHEMO-ENZYMATIC SYNTHESES OF SELECTIVELY PROTECTED DERIVATIVES OF DEOXY-INOSITOLS

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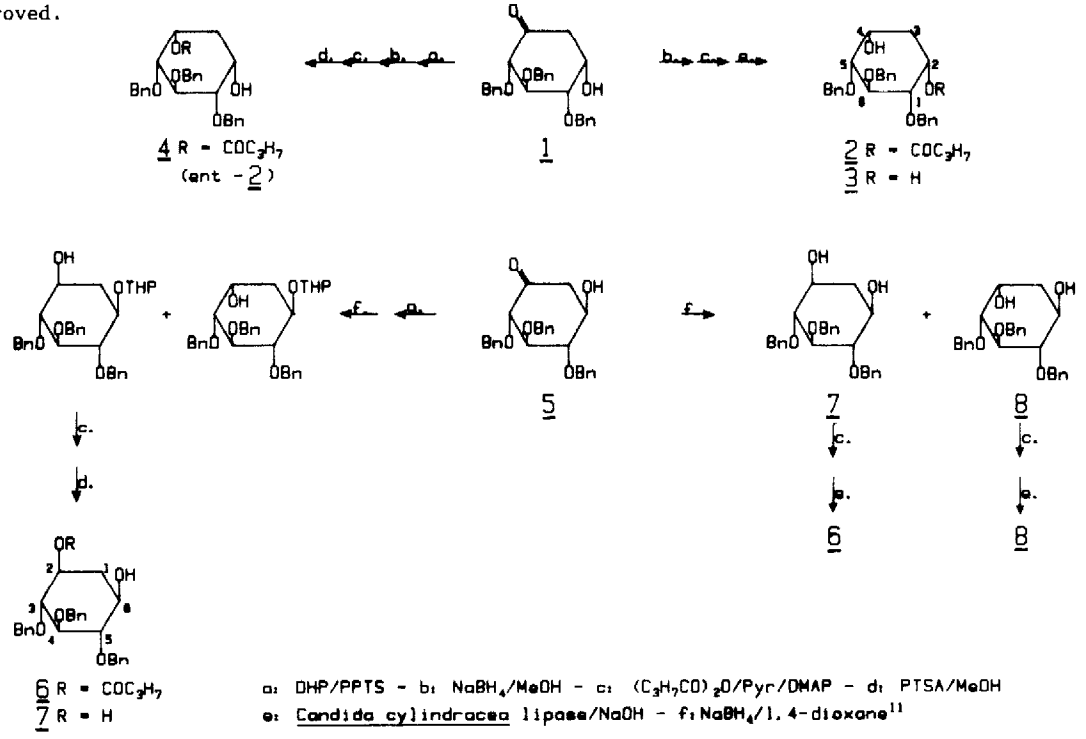
Abstract: Selectively substituted symmetrical polyhydroxycyclohexanols like 3-deoxy-*epi*-(e.g. 2,4) and 1-deoxy-*scyllo*-inositol derivatives (e.g. 6) conveniently can be prepared by chemo-enzymatic methods.

Deoxy cyclitols constitute interesting synthons for possible enzyme inhibitors in many fundamental cellular processes[1]. Of the ten possible deoxy cyclitols (cyclohexanepentols) known[2], four are meso forms, which at regioselective substitution simultaneously create enantiomers. Up to now, mostly racemates have been prepared[1].

We have shown, that enzymatic hydrolysis of some 2-substituted cyclohexanoates is an excellent method for preparing enantiomerically pure derivatives[3]. In this case again the preference of *Candida cylindracea* lipase for selectively hydrolyzing *R*-esters[4] has been proved.



Enzymatic hydrolysis of 1,2- and 1,3-diacyloxycycloalkanols with pig liver esterase is known from the literature[5a,b].

Based on these facts, we wish to present a facile approach to some enantiomerically pure substituted derivatives of 3-deoxy-*epi*-inositol [*muco*-quercitol (3), derivatives 2 and 4] and 1-deoxy-*scyllo*-inositol [*scyllo*-quercitol (7), derivative 6].

Selectively substituted cyclohexanone derivatives 1 and 5 are easily prepared as a 4:1 mixture from methyl-α-D-glucopyranoside in 42% yield[6a,b]. After separation, 1 can be chemically converted to (2*R*)-2-O-acyl-1,5,6-tri-O-benzyl-3-deoxy-*epi*-inositol 4 in four steps, whereas the enantiomer thereof, 2, can be prepared in a chemo-enzymatic approach in three steps. Thus 1 is converted to the THP derivative (mixture of isomers, 92% yield), reduced stereoselectively by $NaBH_4$/MeOH (86%), acylated[6], and deprotected to give 4 in 66% overall yield (sirup, $[\alpha]_D^{20}$ -16.1(*c* = 5, CH_2Cl_2)). To prepare the enantiomer 2, 1 is first reduced to 3[6a] by $NaBH_4$/MeOH and after diacylation[7] and enzymatic hydrolysis (75% by conversion) 2 is obtained in 60% yield (sirup, $[\alpha]_D^{20}$ +15.7(*c* = 5, CH_2Cl_2)); e.e. = 97.5%)[8].

Likewise 5, after hydroxyl function blocking with DHP, can be reduced to a 1:1 mixture of regiospecifically THP-protected derivatives of 7 and 8. After acylation, deblocking, and separation, the respective derivative 6 can be obtained in 32% overall yield ($[\alpha]_D^{20}$ -10.2(*c* = 4, CH_2Cl_2)). In this case, the enzymatic pathway (due to the preference of *Candida cylindracea* lipase for *R*-configurated esters), after reduction of 5 with $NaBH_4$/1,4-dioxane[6a], separation, acylation and enzymatic hydrolysis (80% by conversion) results in compounds 6 (32%, $[\alpha]_D^{20}$ -9.7(*c* = 2, CH_2Cl_2)); e.e. = 95%) and 8[6a]. Thus the sequence to 6 can be facilitated by the chemoenzymatic approach, reducing the number of necessary steps from 4 to 3.

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References and Notes

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8. e.e. and absolute configurations were determined by comparison with optical rotations of the product obtained by the chemical approach and independently checked by ^1H- and ^{19}F-nmr of the respective MTPA esters[9]. All new compounds were identified by their ^{13}C-(75 MHz) nmr spectra[10].
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10. ^{13}C-nmr ($CDCl_3$, δ): 2: C_1 79.5; C_2 68.9; C_3 30.8; C_4 67.2; C_5 81.5; C_6 77.9
6: C_1 34.1; C_2 68.5*; C_3 83.9; C_4 83.3; C_5 86.0; C_6 68.1*;(*: could be reversed).
11. Bn = $C_6H_5CH_2$-, THP = tetrahydropyranyl-, DHP = 3,4-dihydro-2H-pyran, PPTS = pyridinium-toluene-4-sulfonate, DMAP = 4-dimethylaminopyridine, PTSA = 4-toluenesulfonic acid.

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