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ENZYMATIC RESOLUTION OF RACEMIC GLYCALS: AN APPLICATION OF THE WONG ACYLATION METHOD

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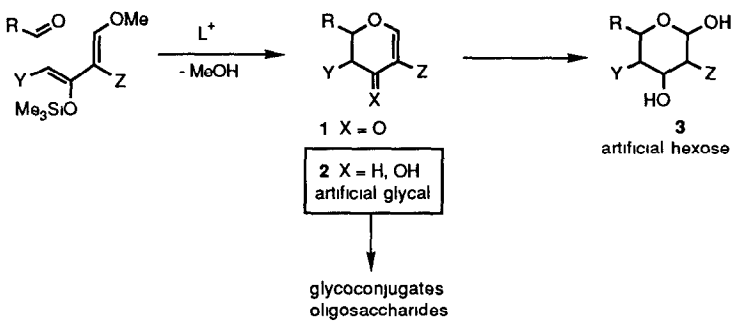
Abstract. Kinetic resolution of racemic, fully synthetic, artificial glycals bearing a free hydroxyl group at C_3 was accomplished through the more rapid acylation of the "D"-antipode with vinyl acetate as acyl donor and Lipase PS-30 from *Pseudomonas cepacia* as catalyst.

The Lewis Acid Catalyzed Diene-Aldehyde Cyclocondensation (LACDAC) reaction,[1] though mechanistically diverse,[1d] provides a general route to dihydropyrones such as **1**. High stereoselectivity can be attained in transforming **1** to hexose-like systems **3**. A useful intermediate in this regard is the glycal-like system **2**.



Glycals are also valuable participants in the synthesis of glycoconjugates and oligosaccharides. Pioneering efforts by Lemieux and Thiem were followed by the implementation of a broad range of "E"-glycosylation reactions ("E" halonium, mercurinium, sulfenium etc).[2] The convertability of glycals in one step to stable 1,2-anhydrohexoses,[3] and, in two steps, to labile 1,2-sulfonylaziridine equivalents[4] adds to their applicability. Furthermore, the recently demonstrated feasibility of using glycals as glycosyl acceptors[5] has multiplied their usefulness. The total synthesis of ciclamycin O[6] and the complete oligosaccharide domains of the enediyne antibiotics[7] is suggestive of the power of glycal based methodology.

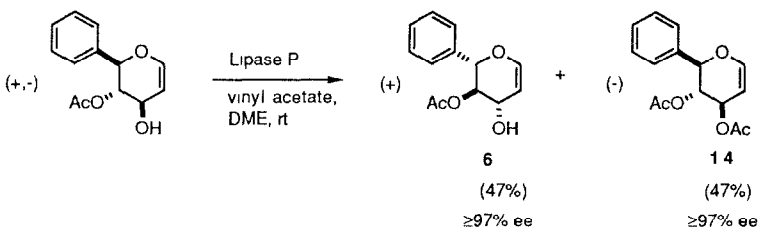
For the novel, fully synthetic glycals to be valuable in the synthesis of "artificial" oligosaccharides and glycoconjugates, they must be available in enantiomerically pure form. While success has been attained in some cases through the use of chiral L^+ agents alone,[8] or in concert with chiral diene auxiliaries,[9] a need existed for

broadly applicable, operationally simple, and inexpensive access to "artificial" glycals of high enantiomeric enrichment.

The remarkable discovery of Wong and co-workers wherein a vinyl ester is used as an irreversible acyl donor in enzymatically modulated transesterification reactions[10] was central to our solution. Also suggestive was Holla's report that Lipase PS-30 from *Pseudomonas cepacia* catalyzed the regiospecific deacylation of the 3-position of 3,4,6-triacetyl-D-glucal [11] We therefore posed the question as to whether racemic artificial glycals bearing a free hydroxyl at C_3 could be resolved through enzymatic acylation. The substrate glycals were all available through the previously described protocols of the LACDAC reaction [1]

In the event, Lipase PS-30 displayed remarkably broad substrate specificity. For instance, both the fucal (**4**) and rhamnal (**5**) skeletons are efficiently acetylated by the lipase. Even introduction of a bulky phenyl group in place of the usual methyl or hydroxymethyl substituent at the 5-position yields excellent substrates for the lipase. As is seen in Table I, those possessing either a benzoyloxy group at C-4 or a methyl group at C-2 are acylated more slowly by the enzyme.

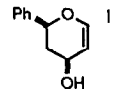
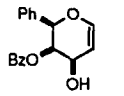
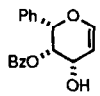
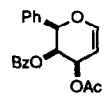
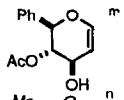
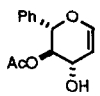
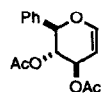
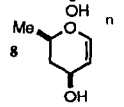
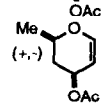
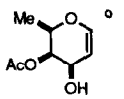
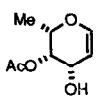
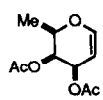
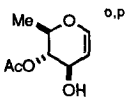
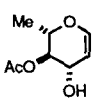
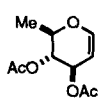
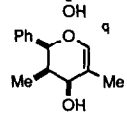
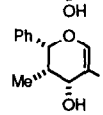
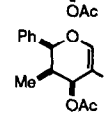
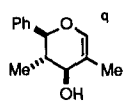
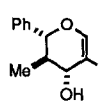
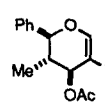
In several cases, enantiodiscrimination is essentially perfect (see **5** and **6**) or very nearly so (see **7**). In only one case (see **8**) was no selectivity observed. Furthermore, a stereoregular pattern emerges in that, in all cases where selectivity was realized, the "D"-enantiomer was preferentially acylated by Lipase PS-30. The ideal glycal substrate would appear to be one in which C-1 and C-2 bear hydrogens and substituents are disposed in a 3,4,5-*tris*-pseudoequatorial fashion (as in **5** and **6**)



Typical Kinetic Resolution Procedure:

To a solution of racemic **6** (1 00 g, 4 27 mmol) in vinyl acetate (58 mL, 629 mmol)/dimethoxyethane (29 mL) was added Lipase PS-30 (2 0 g), and the resulting suspension stirred vigorously in a stoppered round bottom flask for 11 h The reaction was stopped by addition of Et_2O (100 mL) and filtration through a medium (ASTM 10-15) fritted funnel. The filter cake was washed with Et_2O (5 x 100 mL) and the combined filtrates concentrated in vacuo. Flash chromatography (20-80% Et_2O/hexane) gave, in order of elution, (-)-**14** (561 mg, 47 5%, ≥97% ee) and (+)-**6** (474 mg, 47 4 %, ≥97% ee)

Table I. Enzymatically Mediated Resolutions of Glycals

glycal[12]	wgt eq enz, time (h)	recovered alcohol[12]	yield (%), ee(%)		product acetate[12]	yield (%), ee(%)
 l (2.0 g)	2, 26	9		37, ≥97[a,d]	12		63; 60[b]
 (1.0 g)	6, 7 days	7		48, ≥97[a,e]	13		50, 91[b]
 m (1.0 g)	2, 11	6		47, ≥97[a,d]	14		47; ≥97[b]
 n 8	2, 11				15	 (+,-)	f
 o (1.4 g)	1, 33	4		51, 64[c]	16		37; ≥97[b,g]
 o,p	0.5, 37	5		44, ≥97[c,h]	17		48; ≥97[b,i]
 q	(a) 6, 4.5 days (b) 2, 3 days	10		41, ≥97[a] 54, 72[a,j]	18		59; 70[b] 44; 86[b]
 q	(a) 6, 10 days (b) 2, 4 days	11		44; ≥97[k] 74	19		50, 74[b] 26, ≥96[b]

[a]Enantiomeric excess determined by integration of the ^{1}H-NMR spectrum of the corresponding Mosher ester(s) (ref. 13). [b]Enantiomeric excess determined from chiral shift experiments using (+)-Eu(hfc)$_3$ (ref. 14). [c]Enantiomeric excess determined by conversion to the corresponding diacetate (Ac_2O, NEt_3, CH_2Cl_2, DMAP) and then incubation with (+)-Eu(hfc)$_3$ (ref. 14). [d]Absolute configuration determined from the optical rotation of the corresponding dihydropyrone (ref. 9) obtained by oxidation (PDC, CH_2Cl_2, HOAC, 4Å MS). [e]Absolute configuration determined from the crystal structure of a glycoconjugate derived from this glycal and daunomycinone. [f]Starting glycal was completely consumed (TLC) and the product acetate displayed no optical rotation. [g]Absolute configuration determined from the measured optical rotation (ref. 15). [h]Absolute configuration determined from the measured optical rotation (ref. 16). [i]Absolute configuration determined from the measured optical rotation (ref. 17). [j]Absolute configuration determined from the optical rotation of the corresponding dihydropyrone (ref. 8c) obtained by oxidation (PDC, CH_2Cl_2, HOAC, 4Å MS). [k]Enantiomeric excess determined by conversion to (2*S*,3*R*)-methyl 3-hydroxy-2-methyl-3-phenylpropanoate [(a) Dess-Martin periodinane (ref. 18), CH_2Cl_2 (b) O_3, MeOH, -78°C (c) H_2O_2, KOH (d) H_3O^+ (e) CH_2N_2] (ref. 19); and incubation with (+)-Eu(hfc)$_3$ (ref. 14). Absolute configuration determined from the optical rotation of this degradation product (ref. 20). [l]ref. 21. [m]ref. 9. [n]ref. 22. [o]ref. 23. [p]ref. 16. [q]ref. 24.

Since Lipase PS-30 currently sells for about $2/g, the methodology described herein is not unreasonably expensive. The sequence hetero-Diels-Alder reaction/Luche reduction/enzymatic acylation is perhaps the most operationally convenient route to unnatural optically pure D- and L-glycals yet described. The extension of the capability described in this Letter to the synthesis of artificial oligosaccharides and novel glycoconjugates has been achieved and will be described shortly.[25]

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