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HOMOCHIRAL ACETALS IN ORGANIC SYNTHESIS. A GENERAL ENANTIOSELECTIVE ENTRY TO CARBOHYDRATE DERIVATIVES FROM NON-CARBOHYDRATE PRECURSORS

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Abstract A general chromatographic separation of furanosides and pyranosides derived from esters of lactic acid is disclosed. Application of this separation methodology to rapid syntheses of the diastereomers of (S)-methyl lactyl 4-deoxyribopyranose is described.

The tetrahydropyranyl (THP) ether has frequently been employed in organic synthesis as a protecting group for alcohols.[1] One problem associated with use of the THP ether for protection of chiral alcohols is the creation of a new and stereorandom chiral center at the anomeric carbon, thereby producing a mixture of product diastereoisomers. Since diastereoisomers are occasionally separable[2], and since a considerable body of literature describing racemic syntheses of carbohydrates from non-carbohydrate precursors currently exists[3], we decided to examine the chromatographic separability of the diasteromeric THP ethers of several commercially available homochiral alcohols. Results of our survey are presented herein.

Diastereomeric THP ethers[4] of the following homochiral alcohols proved to be inseparable on analytical tlc plates[5] using mixtures of ethyl acetate and hexanes as the eluant: (-)-menthol, (+)-isomenthol, (-)-borneol, (-)-isopinocampheol, (-)-nopol, and (-)-myrtenol. However, the diastereomeric THP ethers of (S)-(-)-methyl lactate 1a and 1b (Table 1)[6] were readily separable on analytical thin layer plates[5] and also by preparative column chromatography.[7] The diastereomeric THP ethers of (S)-(-)-ethyl lactate (2a and 2b) and of (S)-(-)-isopropyl lactate (3a and 3b) were similarly separable. The diastereomeric THP ethers of (S)-(+)-methyl mandelate (4a and 4b) were also separable. Interestingly, the diastereomeric THP ethers of 3-methyl-2-butanol, 1-methoxy-2-propanol, *sec*-phenethyl alcohol, and 2-pentanol were not chromatographically separable.

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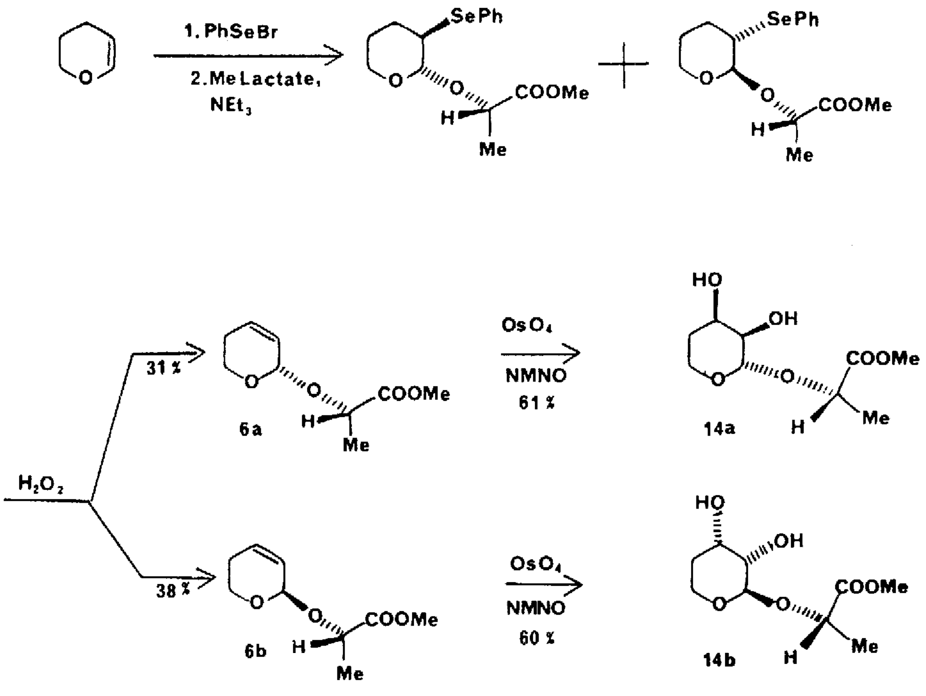
Most important was the generality of the separability of diastereomeric (S)-methyl lactyl pyranosides (entries 1,5-9, Table 1) and furanosides (entries 10-12). Note that in entries 5,9,11, and 12, a second stereogenic center in the ring bearing a substituent is stereochemically "linked" to the chirality at the anomeric center and can thus be resolved by this separation methodology.[8] However, diastereomeric ketofuranosides 13a and 13b were not chromatographically separable.

As a preliminary demonstration of the utility of this methodology, an economical synthesis of the (S)-methyl lactyl pyranosides of (+) and (-)-4-deoxyribose is outlined in Scheme 1. Diastereomers 6a and 6b were obtained in 31% and 38% yields, respectively, from dihydropyran. The identity of 14a was confirmed by conversion to (2S,3R)-tetra-O-benzoyl-1,2,3,5-pentanetetrol (15a).[9] Further applications of this methodology to enantioselective syntheses of carbohydrates, and in particular, of deoxysugars and heteroatom-containing sugars, are underway in our laboratories.[10]

SCHEME 1.



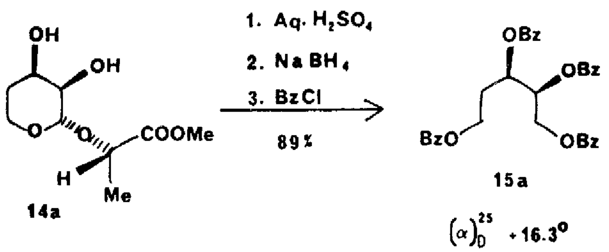
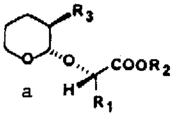
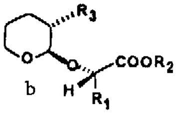


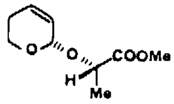
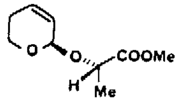
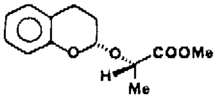
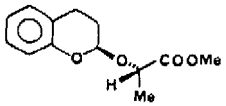
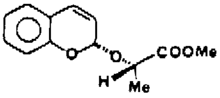
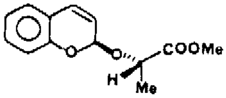
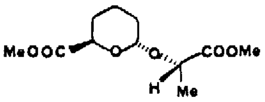
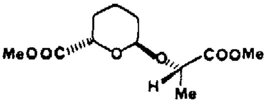
Table 1. Chromatographic Separations of Lactate Pyranosides and Furanosides.

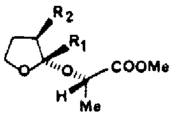
DIASTEREOMERIC ACETALS

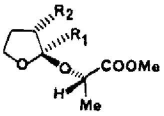




ENTRY	R_1	R_2	R_3	YIELDS,%[a]	α[b] (SOLVENT)[c]	LOADING[d] (SOLVENT)[c]
1	Me	Me	H	49,49	1.19(20)	10(15)
2	Me	Et	H	45,38	1.18(20)	4.5(10)
3	Me	*i*-Pr	H	49,45	1.13(20)	3.8(5)
4	Ph	Me	H	42,49	1.10(20)	1.9(10)
5	Me	Me	Br	42,42	1.30(20)	14(15)

6			31,38	1.34(20)	7(15)
7			48,23	1.22(10)	8(10)
8			41,17	1.58(5)[e]	5(5)[e]
9			42,40	1.09(50)	1(20)[f]





	R_1	R_2			
10	H	H	45,48	1.25(20)	9(15)
11	H	OSiMe$_2$*t*-Bu	36,36	1.19(20)	14(5)[f]
12	H	Br	43,44	1.10(20)	7(10)
13	Me	H	---	1.00(20)[g]	----

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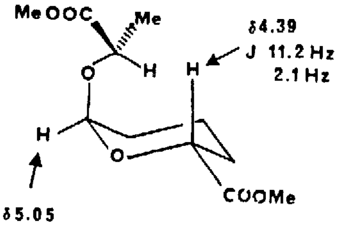
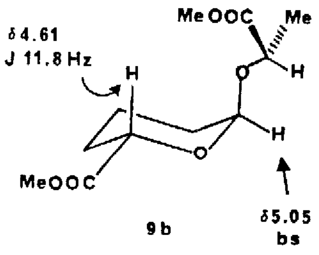
[a] Isolated yields of the less and more polar diastereomers, respectively. [b] The separation factor, α, is the ratio of R_f values for diastereomers a and b on 0.25 mm silica gel 60 plates (Merck, 70-230 mesh). [c] Solvent is given as the percent ethyl acetate used in hexanes. [d] Column loading is given as mg sample loaded per gram of silica gel 60 used (Merck, 70-230 mesh). [e] Silica pretreated with triethylamine. [f] Flash chromatography employed. [g] Inseparable in several different solvent systems.

References and Footnotes

1. Greene, T.W. "Protecting Groups in Organic Synthesis," Wiley, New York, 1981, pp. 21-26.
2. (a) Feringa, B.L.; deJong, J.C. J. Org. Chem. 1988, 53. 1125-1127. (b) White, J.D.; Theramongkol, P.; Kuroda, C.; Engebrecht, J.R.; J. Org. Chem., 1988. 53. 5909-5921. (c) David, S.; Eustache, J. J.C.S. Perkin I 1979, 2230-2234.
3. Zamojski, A.; Grynkeiwicz, G., in "The Total Synthesis of Natural Products," J. ApSimon, Ed.; Wiley Interscience, New York; Vol 6, 141-235, and references cited therein.
4. All tetrahydropyranyl and tetrahydrofuranyl ethers were prepared via acid-catalyzed addition of the alcohol to 3,4-dihydro-2H-pyran or 2,3-dihydrofuran, or by exchange with the corresponding methyl or ethyl pyranoside or furanoside.
5. Analytical thin-layer chromatography was performed on Merck silica gel 60 plates (0.25mm, 70-230 mesh ASTM).
6. All yields refer to isolated and purified compounds. Satisfactory NMR, IR, and HRMS data were obtained for all compounds.
7. Chromatographic separations were performed using gravity-driven column chromatography on 70-230 mesh silica gel 60 (Merck) and commercially available solvents. Column loading and solvent system information is given in Table 1. All separations required two chromatographies to complete the indicated separations.
8. For example for both diastereomers of 9 the carbomethoxy substituent adopts a pseudoequatorial orientation and the lactate adopts a psueudoaxial orientation; this follows from the observed ^{1}H-NMR coupling constants:



9a



9b

9. Verheyden, J.P.H.; Moffatt, J.G. J. Org. Chem.1969, 34 2643-2645.

10. Acknowledgement is made to the donors of the Petroleum Research Fund, administered by the American Chemical Society, for support of this research. Partial support of this research by the American Heart Association, Arizona Affiliate, by the American Cancer Society, and by the University of Arizona Foundation and the Office of the Vice President for Research, is gratefully acknowledged.

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