Pergamon

Tetrahedron Letters, Vol. 36, No. 15, pp. 2591-2594, 1995
Elsevier Science Ltd
Printed in Great Britain
0040-4039/95 $9.50+0.00

0040-4039(95)00347-9

Synthesis of Pseudosugars From Microbial Metabolites

David A. Entwistle and Tomas Hudlicky*‡
Department of Chemistry, Virginia Polytechnic Institute and State University,
Blacksburg, VA 24061-0212, USA.

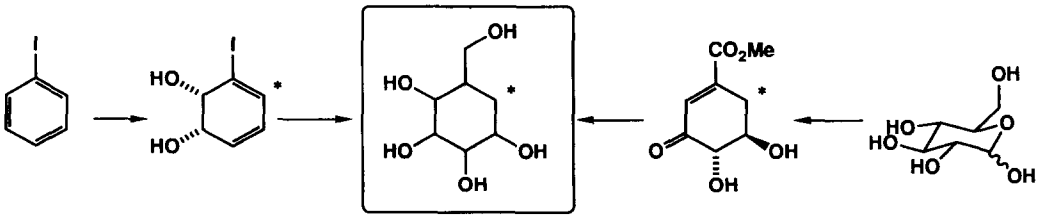
Abstract: The short syntheses of three pseudosugars, pseudo-β-D-altropyranose, pseudo-α-L-mannopyranose and pseudo-β-D-glucopyranose starting from homochiral microbial metabolites obtained from complimentary sources are described.

Since their initial synthesis and subsequent isolation from natural sources in 1966 and 1973 respectively, pseudo sugars have been of considerable synthetic and medicinal interest.[1,2] Pseudo sugars differ from the parent carbohydrates in that they possess an endocyclic methylene unit instead of oxygen atom and many have interesting properties such as acting as inhibitors of glucose stimulated insulin release,[3] as glycosidase and other specific enzyme inhibitors,[4] and being useful as non-nutritive artificial sweeteners.[5] With these and other important pharmaceutical properties interest in these compounds is high and to date all of the basic sixteen racemic and ten optically active pseudo hexopyranoses have been synthesized.[1b]

Previous work in these laboratories has expanded the use of highly functionalized arene mutant microbial metabolites as homochiral starting materials for organic synthesis. Using these versatile metabolites as homochiral starting materials has allowed the rational and in some cases stereodivergent synthesis of cyclitols, carbohydrates, aza sugars and aminosugars.[6]

We now wish to report the synthesis of the pseudosugar, pseudo-β-D-altropyranose pentaacetate from the iodobenzene metabolite **1** (scheme 1), and also to describe the syntheses of pseudo-β-D-glucopyranose and pseudo-α-L-mannopyranose derivatives from dehydroshikimic acid **2** obtained from natural saccharides using a recombinant aromatic aminoacid pathway (scheme 1).[7]

Scheme 1. Asterisk denotes related carbon atoms



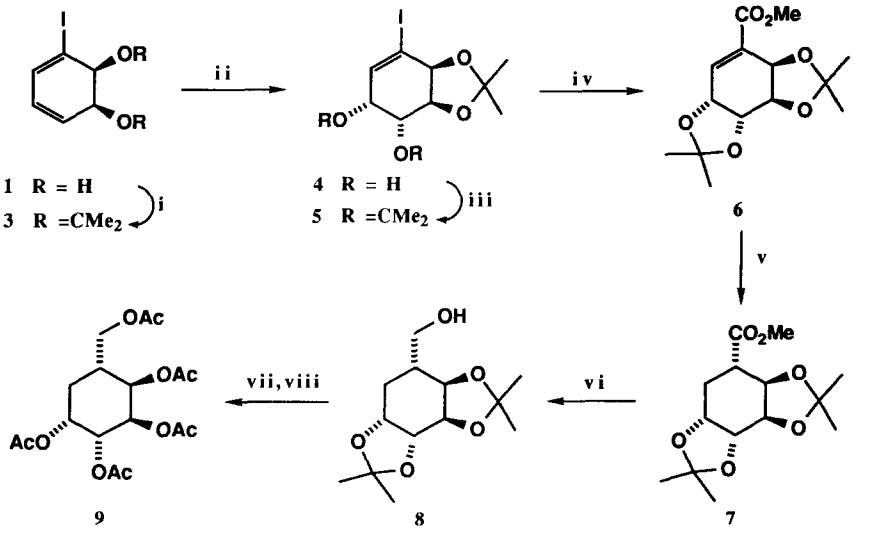
1 **Pseudo hexopyranose** **2**

Use of just one of these microbial starting materials, such as **1** for example, would, after oxidation and hydroxymethylation, give access to several pseudo sugars. To reach other sugars would involve inversion chemistry at, at least, one of the centers generated by the dioxygenase which, for efficiency's sake, we prefer to

avoid. This situation can be circumvented by utilizing the stereochemically complimentary dehydroshikimic acid **2** as a pool material. As shown in scheme 1 iodobenzene metabolite **1** has a *cis* diol moiety and in the analogous positions on metabolite **2**, after elaboration (*vide infra*), a *trans* diol unit is readily installed. Using both microbial metabolites **1** and **2** as stereochemically complimentary starting materials will allow, by judicious design, access to a wide range of pseudosugar targets of both the L and D series, three of which are outlined below.

Iodocyclohexadienediol **1** is made by whole cell fermentation of iodobenzene with *Pseudamonas Putida* 39D and is available from Eastman Fine Chemicals. The diol **1** was converted to the acetonide **3**, which on treatment with catalytic osmium tetroxide and *N*-methylmorpholine-*N*-oxide (NMO) cooxidant stereoselectively gave the diol **4** (scheme 2). Treatment with dimethoxypropane (DMP) and tosic acid monohydrate (TsOH.H_2O) in acetone furnished the bis acetonide **5** in 75% yield from dienediol **1** with only one final chromatographic purification. Deiodomethoxycarbonylation of the vinyliodide **5** was achieved by halogen lithium exchange with tertiary butyllithium, quenching with carbon dioxide and esterification with potassium carbonate and methyl iodide to give the α,β-unsaturated ester **6** in 90% yield. Stereoselective hydrogenolysis over palladium on charcoal gave the saturated ester **7** in 92% yield. DIBAL-H reduction of the ester **7** yielded the alcohol **8** in 74% yield. The acetonide protecting groups were cleaved with wet Amberlyst 15 resin in methanol and the resultant crude pentol peracetylated. The single pentaacetate **9**, obtained in 41% overall yield from the dienediol **1**, was assigned the pseudo-β-D-altropyranose structure on the basis of extensive 1D ^1H nmr spectroscopic analysis.[8]

Scheme 2



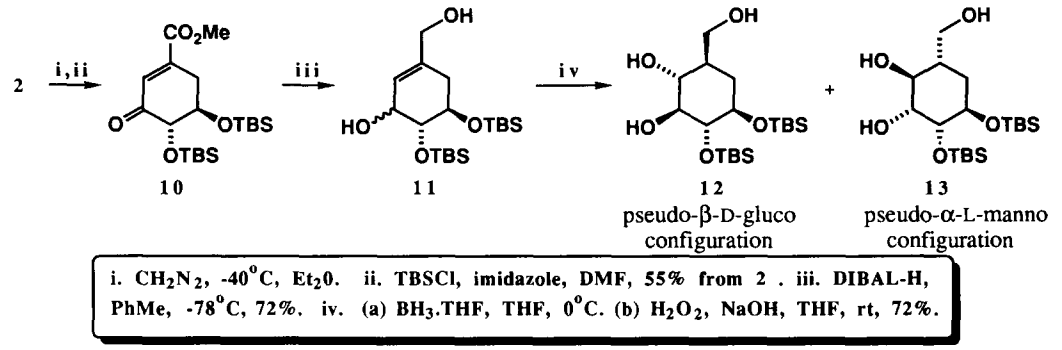
i. DMP, TsOH; ii. OsO_4, NMO, ^tBuOH, H_2O; iii. DMP, TsOH, 75% from 1; iv. (a) ^tBuLi, Et_2O, -78°C, CO_2, (b) MeI, K_2CO_3, Me_2CO, 90%; v. Pd/C, H_2 50 psi, EtOAc, EtOH, 92%; vi. DIBAL-H, PhMe, -78°C, 74%; vii. Amberlyst 15 resin, wet MeOH; viii. Ac_2O, Py, DMAP, 89% from 8.

Although aromatic derived dienediols have previously been used in other pseudosugar syntheses[9] this represents the first synthesis of an optically active pseudo-β-D-altropyranose ($[\alpha]_D^{31}$ -8.1 (c = 1.16, $CHCl_3$)),

although the β-L version ($[\alpha]_D^{24}$ +7 (c = 0.75, $CHCl_3$)) was synthesized by Suami in 1984 using a much lengthier route.[10] Other methods used routinely in these laboratories to obtain all the diastereoisomers of diol **4** from diene **3** (scheme 2) are presently underway. Elaboration of these products will give entry to other pseudosugars motifs. Syntheses of the remaining pseudosugars will require one or more of the asymmetric centers created by the dioxygenase to be inverted. In practical terms this approach tends to add at least two steps to a synthesis sometimes making them unattractive for scale up. With this in mind we undertook to synthesize pseudo glucopyranose from a different microbial metabolite, dehydroshikimic acid **2**, as the gluco-configuration is one that is not readily available from the dienediol **1** by the methods outlined above.

The bis silylether **10** was made by the known route of Ganem in 55% overall yield from dehydroshikimic acid **2** (Scheme 3).[11] Total reduction of ester and ketone moieties with DIBAL-H proceeded in 72% yield giving an inseparable 2:1 mixture of diastereoisomeric alcohols **11**. Hydroboration of the diastereomeric mix of alcohols occurred stereoselectively *anti* to the *pro* C-3 hydroxyl group[12] to give the readily separable 1,2-disilylprotected pseudo-β-D-glucopyranose **12** and pseudo-α-L-mannopyranose **13** in 28% and 44% respectively (here again ^1H nmr analysis was greatly simplified by the peracetylation of the individual triols). This represents a highly concise synthesis of both sugars in 11% and 17% overall yield respectively.

Scheme 3



i. CH_2N_2, -40°C, Et_2O. ii. TBSCl, imidazole, DMF, 55% from 2 . iii. DIBAL-H, PhMe, -78°C, 72%. iv. (a) BH_3.THF, THF, 0°C. (b) H_2O_2, NaOH, THF, rt, 72%.

Unlike the dienediol **1** which requires further carbon-carbon bond formation, dehydroshikimic acid **2** is well suited as a starting material for the synthesis of pseudosugars as it has the requisite number of carbon atoms. With **2** all the reactions performed are either protections or adjustments of oxidation state, which gives rise to the very short pseudosugar syntheses shown. The use of more selective reducing agents[13] in the reduction of the ketone moiety of **10** will in future bring about even easier access to molecules of this kind.

Another shikimate metabolite, quinic acid, has recently been used as the starting material in the synthesis of carbocyclic sugar analogs.[14] These syntheses tended to be long (over 12 steps) as several manipulations of the ring oxygenation are required to attain the basic oxygenation pattern of the simple hexose sugars. Utilization of dehydroshikimic acid also now commercially available as a starting material reduces the number of steps required as only reduction of the two carbonyl systems and selective oxidation of the alkene is required.

In summary, we hope to have highlighted the potential of the microbial metabolites **1** and **2** as pool materials for pseudosugar synthesis. The syntheses reported are both simple, short and compare favorably with present literature routes. The limitations to the type of pseudosugar obtainable from either dienediol **1** or

dehydroshkimic acid **2** due to their inherent hydroxyl group stereochemistry can be overcome not by lengthy inversion sequences but by the judicial choice of the other stereochemically complimentary starting material. Other applications of these compounds to sugar synthesis will reported in the future. Also, in line with this groups interest in the general synthesis of novel glycoconjugate carba analogs with potential antidiabetic activities,[15] the intermediates **8** and **11** are currently being converted to organometallic reagents that will be coupled to dienediol derived epoxides.

Acknowledgments

The authors are grateful to NSF (CHE-9315684) and TDC Research Inc. for the support of this work and Dr. Gregg Whited of Genencor International, Inc. for the generous gift of dehydroshikimic acid. We also wish to thank TDC Research Foundation for a Fellowship (DAE).

References and footnotes

‡ Address correspondence to this author at the Department of Chemistry, University of Florida, P.O. Box 117200, Gainesville, Fl 32611-7200.

1. (a) McCasland G.E., Furuta S., Durham L.J., *J. Org. Chem.*, **1966**, *31*, 1516. (b) For a review of pseudosugars see, Suami T., *Top.Curr.Chem.*, **1990**, *154*, 257.
2. Miller T.W., Arison B.H., Albers-Schonberg G., *Biotech. and Bioeng.*, **1973**, *15*, 1075
3. Miwa I., Hara H., Okuda J., Suami T., Ogawa S., *Biochem. Intern.*, **1985**, *11*, 809.
4. Wilcox C.S., Gaudino J.J., *J.Am.Chem.Soc.*, **1986**, *108*, 3102.
5. Ogawa S., Uematsa Y., Yoshida S., Sasaki N., Suami T., *J.Carbohydrate Chem..*, **1987**, *6*, 471.
6. (a) Mandel, M.; Hudlicky, T., *J. Chem. Soc. Perkin Trans. 1*, **1993**, 741.; (b) Mandel, M.; Hudlicky, T.; Kwart, L.D.; Whited, G.M., *J. Org. Chem.*, **1993**, *58*, 2331.; (c) Hudlicky, T.; Rulin, F.; Tsunoda, T.; Luna, H.; Andersen, C.; Price, J.D., *Isr. J. Chem.*, **1991**, *31*, 229. (d) Hudlicky, T.; Price, J.D.; Rulin, F.; Tsunoda, T., *J. Am. Chem. Soc.*, **1991**, *112*, 9439. (e) Hudlicky, T., U.S. Patent 5 306 846, 1994. (f) Hudlicky, T.; Olivo, H.F., *Tetrahedron Lett.*, **1991**, *32*, 6077. (g) Hudlicky, T.; Olivo, H.F., *J. Am. Chem. Soc.*, **1992**, *114*, 9694. (h) Mandel, M.; Hudlicky, T.; Kwart, L.D.; Whited, G.M., *Collect. Czech. Chem. Commun.*, **1993**, *58*, 2517.; (i) Hudlicky, T.; Luna, H.; Price, J.D.; Rulin, F., *Tetrahedron Lett.*, **1989**, *30*, 4053.; (j) Hudlicky, T.; Price, J.D., *Synlett*, **1990**, *3*, 159.; (k) Hudlicky, T.; Mandel, M.; Rouden, J.; Lee, R.S.; Bachmann, B.; Dudding, T.; Yost, K.; Merola, J.S., *Perkin Transactions 1*, **1994**, 1553. (l) Hudlicky, T.; Rouden, J.; Luna, H., *J. Org. Chem.*, **1993**, *58*, 985.; (m) Hudlicky, T.; Rouden, J., *J. Chem. Soc. Perkin Trans. 1*, **1993**, 1095. (n) Mandel, M.; Hudlicky, T., *Synlett*, **1993**, 418.; (o) Hudlicky, T.; Luna, H.; Olivo, H.F.; Andersen, C.; Nugent, T.; Price, J.D. *J. Chem. Soc. Perkin Trans. 1*, **1991**, 2907.
7. Dell K.A., Frost J.W., *J.Am.Chem.Soc.*, **1993**, *115*, 11581.
8. Data for pseudo-β-D-altropyranose pentaacetate **9**. $[\alpha]_D^{31}$ -8.1 (*c* = 1.16, $CHCl_3$); IR (thin film) 2966, 1747, 1435, 1371, 1230, 1165, 1116, 1075, 1047, 956, 920, 666 cm^{-1}; MS (CI) *m/z* (relative intensity) 389 (7), 330 (16), 329 (100), 287 (287), 269 (15), 227 (18), 149 (20), 107 (29), 61 (86); ^1H NMR ($CDCl_3$, 270 MHz) δ 1.82 (1 H, m, H-7_{ax}), 2.00 (7 H, br.s, H-7_{eq}, Ac x 2), 2.06 (3 H, s, Ac), 2.10 (3 H, s, Ac), 2.13 (3 H, s, Ac), 2.34 (1 H, m, H-5), 4.07 (2 H, d, *J*= 5.4, H-6), 5.07 (1 H, dd, *J*= 10.6, 3.0, H-4), 5.19 (1 H, m, H-1), 5.26 (1 H, m, H-2), 5.33 (1 H, dd, *J*= 4.8, 3.0, H-3);^{13}C NMR ($CDCl_3$, 67 MHz) 170.42, 169.70, 169.05, 169.00, 68.71, 68.64, 68.28, 67.87, 63.80, 34.37, 26.96, 20.62, 20.48. Found C, 52.71%. H, 6.16%. $C_{17}H_{24}O_{10}$ requires C, 52.58%. H, 6.23%.
9. (a) Pingli, L.; Vandewalle, M., *Synlett*, **1994**, 228. (b) Ley, S.V.; Yeung, L.L., *Synlett*, **1992**, 291.
10. Suami T., Tadano K., Kameda Y., Timura Y., *Chem.Lett.*, **1984**, 1919.
11. Wood H.B., Ganem B., *Tetrahedron Lett.*, **1993**, *34*, 1403.
12. The numbering system used is analogous to that of normal saccharides in all respects except that the exocyclic methylene carbon is numbered 7.
13. J.R. Falck, private communication.
14. (a) McComsey D.F., Maryanoff B.E., *J. Org. Chem.*, **1994**, *59*, 2652. (b) Maycock C., Barros T.M., Santos A.G., Godinho L.S., *Tetrahedron Lett.*, **1993**, *34*, 7985. (c) Shing T.K.M., Cui Y.-X., Tang Y., *Tetrahedron* , **1992**, *48*, 2349.
15. Hudlicky T., Thorpe A.J., *Synlett*, **1994**, 899.

(*Received in USA* 13 *January* 1995; *revised* 13 *February* 1995; *accepted* 17 *February* 1995)