Pergamon

Tetrahedron Letters, Vol. 35, No. 36, pp. 6755-6758, 1994
Elsevier Science Ltd
Printed in Great Britain
0040-4039/94 $7.00+0.00

0040-4039(94)01415-9

Asymmetric Synthesis of Carbohydrates: Synthesis of 2-Deoxy-D- and 2-Deoxy-L-xylofuranosides from a Simple Achiral Precursor.

Michael E. Jung[a]* and John M. Gardiner[b]*

[a]Department of Chemistry & Biochemistry, University of California at Los Angeles, Los Angeles, California 90024-1569, USA

[b]Department of Chemistry, University of Manchester Institute of Science and Technology (UMIST), PO Box 88, Manchester M60 1QD, United Kingdom

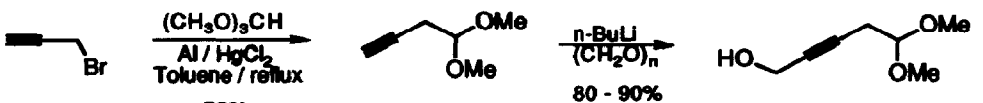
Abstract: The acetylenic alcohol, **3**, readily prepared in two steps from propargyl bromide, **1**, is converted to methyl 2-deoxy-D-xylofuranoside, **13**, and to the unnatural L-enantiomer, **12**, in 5 steps and 50% overall yield, utilizing asymmetric dihydroxylation (AD) of alkene **7** for introduction of chirality. A similar strategy from the isomeric *Z*-allylic alcohol, **4**, afforded the 2-deoxy-L-ribofuranoside, but in modest enantiomeric excess.

The stereoselective synthesis of carbohydrates from acyclic non-carbohydrate precursors continues to be an important focus for a number of research groups.[1,2] Asymmetric synthesis of carbohydrates from readily available *achiral* intermediates is an attractive goal, offering several advantages over, and complimentary to, chiron strategies. In particular, if an asymmetric methodology can be employed for which both enantiomeric variants are readily available, then both natural and unnatural carbohydrate stereochemistries can be obtained from a common substrate.[2c,3] A *de novo* approach could also offer the potential of introducing isotopic labels or other substituent patterns (deoxy, alkyl substituted) which would be problematic to introduce via a chiron approach.

We have previously reported the conversion of a simple five-carbon *E*-allylic alcohol to a number of furanosides of both D- and L-enantiomeric series, and to derived modified nucleosides, for example AZT,[3a] ddC[3b] and d4T,[3c] utilizing the Sharpless-Katsuki asymmetric epoxidation for introduction of chirality.

We envisaged that asymmetric dihydroxylation (AD)[4,5] offers a potentially complimentary approach to the synthesis of the parent 2-deoxycarbohydrates from the same *E*-allylic alcohol and/or from the isomeric *Z*-allylic alcohol. We report here an improved route to the *E*-allylic alcohol, **5**, and its conversion in only 4 steps, in high yield and good enantioselectivity, to both the 2-deoxy-L- and D-xylofuranoside enantiomers, utilizing asymmetric dihydroxylation[6].

We considered that the *E*-allylic alcohol, **5**, could be prepared from the acetylene **3** (by lithium aluminium hydride reduction) and that synthesis of **5** via an acetylene precursor would also be attractive for two other reasons. Firstly the *Z*-allylic alcohol should also then be available from this intermediate, and secondly an acetylenic intermediate would allow for introduction of deuterium via reduction (to either *Z*- or *E*-dideuterated alkenes) and thus to specifically dideuterated furanoside carbohydrates,[7] which are precursors, for example, to deuterated nucleosides. Therefore, acetylene **3** would serve as a potentially highly versatile common achiral intermediate.

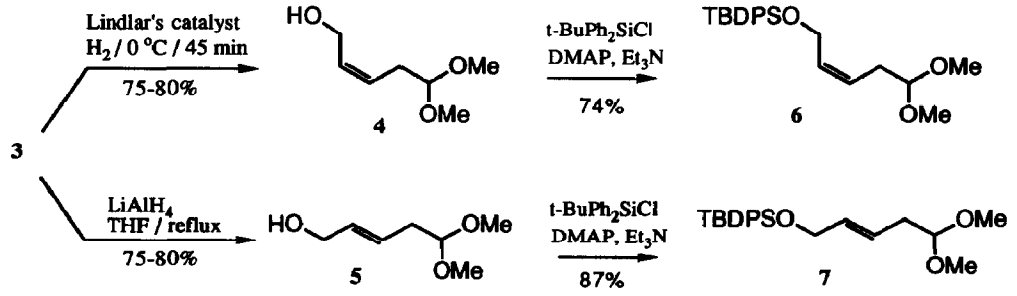


1 50% **2** 80 - 90% **3**

Scheme 1

The acetylenic alcohol, **3**, was prepared on multigram scale in two steps from propargyl bromide (Scheme 1). The aluminium organometallic[8] derived from propargyl bromide was reacted with trimethyl orthoformate to yield, in 50% yield after distillation, the acetylene **2** which was hydroxymethylated to give the alcohol, **3**, in high yield[9].

The crude propargylic alcohol, **3**, 90-95% pure by ^{1}H NMR spectroscopy, was taken on without the need for further purification. The *Z*-alkene was obtained in 75-80% yield by hydrogenation in the presence of Lindlar's catalyst. The optimum conditions for selective reduction were reaction at 0 °C for 45 minutes in the *absence* of quinoline. Longer reaction times or higher temperatures led to contamination by the fully reduced product. Reduction with lithium aluminium hydride in THF provided the *E*-allylic alcohol **5** in 75-80% pure yield after column chromatography (Scheme 2). This route to **5** offers several advantages over our previously employed route from crotonaldehyde,[3] in that chromatography is only required for the final step, and the allylic alcohol is also significantly purer prior to chromatography, thus making synthesis much more practicable on multigram scale.



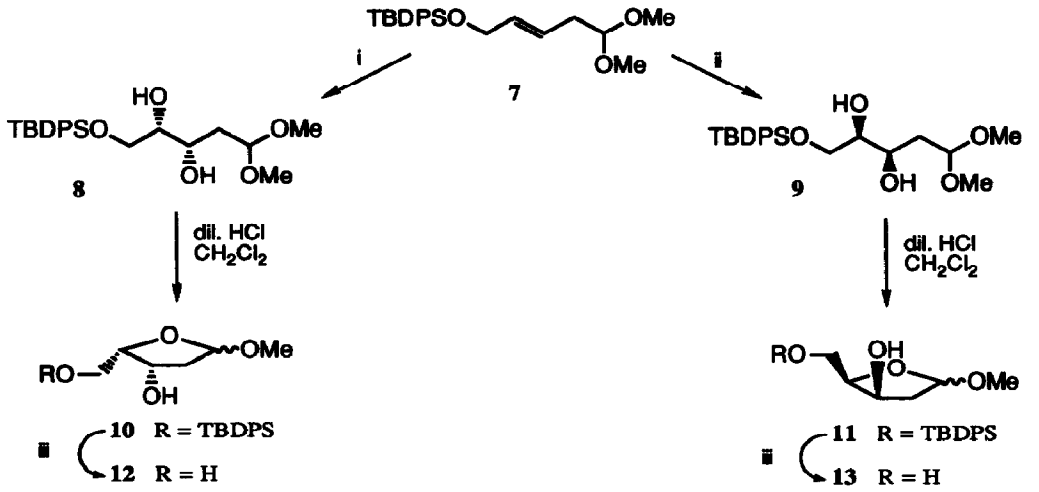
Scheme 2

The C_2 phthalazine ligands, $(DHQD)_2PHAL$ and $(DHQ)_2PHAL$ are the current optimum catalysts for AD of several alkene classes,[5,10] including *E*-disubstituted alkenes, which are generally excellent substrates[11]. The *E*-alkene silyl ether, **7**, was asymmetrically dihydroxylated using $(DHQD)_2PHAL$ to afford diol, **9**, in 81% yield, and using $(DHQ)_2PHAL$ to give the enantiomeric diol, **8**, in similarly good yield (Scheme 3)[12]. Treatment of these diols with dilute hydrochloric acid in dichloromethane,[3] led to very rapid,[13] near quantitative conversion to the known corresponding glycoside derivatives[14]. Very little anomeric selectivity was observed at either 25 °C or at -10 °C,[15] but the anomers were easily separated by chromatography. Treatment with tetrabutylammonium fluoride (TBAF) provided the glycosides, **12** and **13**[16], in ≥95% yield after chromatographic purification.

The enantiomeric excess of the D-xylofuranoside, **11**, was determined by ^{1}H NMR analysis of the derived Mosher's ester derivative[17]. Only the sterically less hindered α-anomer reacted with Mosher's acid, affording the ester in >95% yield, with no remaining alcohol detected by tlc or NMR spectroscopy of the crude reaction product. The spectroscopic[17] enantiomeric excess (ee) of the D-xylo carbohydrate, **11**, was determined to be 91%,[18a] and the ee for the L-series was determined to be 84-86%.[18b] The absolute enantiofacial selectivity in the AD reactions was predicted using Sharpless' mnemonic[5a] or modified mnemonic[5c(iii)] for AD with these ligands, assuming the silyl ether-bearing alkene substitutent to be the larger. Proof of the absolute stereochemistry was established by preparing the chiral pool derived[19] (stereochemically unambiguous) Mosher's ester derivative of the α-anomer of **11**, and comparing the ^{1}H NMR shifts with those of the major and minor diastereomers of the *AD derived* carbohydrate Mosher's ester derivatives of **10** and **11**[17]. This confirmed that use of the $(DHQD)_2PHAL$ ligand afforded the D-xylo configuration consistent with the mnemonic.

The AD of *Z*-disubstituted alkenes with sterically similar groups, such as substituted methylene groups, is problematic, since it is known to give generally lower ee's than the *E*-isomers.[20] However, we examined the AD of the *Z*-alkene silyl ether, **6**, using the ligand DHQD-IND.[20,21] This led to good chemical yields but, as anticipated, relatively poor enantioselectivity, affording ultimately the unnatural, methyl 2-deoxy-L-ribofuranoside in 30-35% ee[22]. Proof of the absolute stereochemistry was established by comparison of the diastereomeric shifts of the Mosher's ester with those for the

Mosher's ester derivative of methyl 5-tert-butyldiphenylsilyloxy-2-deoxy-D-ribofuranoside[23]. Interestingly, in this case, acid catalysed cyclization of the diol to the glycoside carried out at -20 °C afforded a *single* anomer (identified as the β-anomer), isolated in 85% purified yield.



Scheme 3. i. $(DHQ)_2PHAL$, $K_2OsO_2(OH)_2$, K_2CO_3, $MeSONH_2$, t-BuOH-H_2O;
ii. $(DHQD)_2PHAL$, $K_2OsO_2(OH)_2$, K_2CO_3, $MeSONH_2$, t-BuOH-H_2O; iii. Bu_4NF, THF

In summary, we have developed a short, asymmetric synthesis of the D- and L-2-deoxyxylofuranosides from a common, simple achiral intermediate, preparable in multigram quantities in two steps from propargyl bromide and trimethyl orthoformate. This methodology should be applicable to the synthesis of specifically deuterated 2-deoxyxylofuranosides, and potentially to 2-deoxyribofuranosides and thence to deuterated nucleosides, the subject of a future report[24].

Acknowledgements: We would like to thank the National Institutes of Health (GM47228) for financial support, the SERC (GR/H21746) for travel assistance (JMG), and Claire Castro (UCLA) for provision of samples of the D-xylose and D-ribose derived anomers for proof of the absolute stereochemistries.

References and notes

1. "Trends in Carbohydrate Chemistry," Horton, D.; Hawkins, L. D.; McGarvey, G. J.; eds.; ACS Symposium Series 386, Washington, **1989**; (a) Roush, W. R.: Ch. 14: "*Allylboronates in Carbohydrate Synthesis.*" (b) Schmidt, R. R.: Ch. 12: "*Stereoselective Synthesis of Carbohydrates from Acyclic Precursors.*" (c) Mukaiyama, T.: Ch. 15: "*A Fresh Approach to the Synthesis of Carbohydrates.*"
2. (a) Danishefsky, S. J.; DeNinno, M. P. *Angew. Chem. Int. Ed.* **1987**,*26*, 15. (b) Schmidt, R. R. *Pure Appl. Chem.* **1987**, *59*, 415 and refs. therein. (c) Ko, S. Y.; Lee, A. W. M.; Masamune, S.; Reed, L. A., III; Sharpless, K. B.; Walker, F. J. *Science* **1983**, *220*, 949. (d) Kobayashi, S.; Kawasuji, T. *Synlett* **1993**, 911.
3. (a) Jung, M. E.; Gardiner, J. M. *J. Org. Chem.* **1991**, *56*, 2614. (b) Jung, M. E.; Castro, C.; Gardiner, J. M. *Tetrahedron Lett.* **1991**, *32*, 5717. (c) Jung, M. E.; Gardiner, J. M. *Tetrahedron Lett.* **1992**, *33*, 3841.
4. For a recent review: Lohray, B.B. *Tetrahedron Asym.* **1992**, *3*, 1317.
5. (a) Sharpless, K. B.; Amberg, W.; Bennani, Y.; Crispino, G. A.; Hartung, J.; Jeong, K.-S.; Kwong, H.-L.; Morikawa, K.; Wang, Z.-M.; Xu, D.; Zhang, X.-L. *J. Org. Chem.* **1992**, *57*, 2768. (b) Latest paper giving structures of $(DHQD)_2PHAL$ and $(DHQ)_2PHAL$: Sharpless, K. B.; Amberg, W.; Bennani, Y.; Chadha, R. K.; Crispino, G. A.; Davis, W. D.; Hartung, J.; Jeong, K.-S.; Ogino, Y.; Shibata, T.; Sharpless, K. B. *J. Org. Chem.* **1993**, *58*, 844. (c) Recent reports on origins of the enantioselectivity of these catalysts: (i) Corey, E. J.; Noe, M. C. *J. Am. Chem. Soc.* **1993**, *115*, 12579 and refs therein. (ii) Corey, E. J.; Noe, M. C.; Sarshar, S. *Tetrahedron Lett.* **1994**, *35*, 2861. (iii) Kolb, H. C.; Andersson, P. G.; Sharpless, K. B. *J. Am. Chem. Soc.* **1994**, *116*, 1278
6. Whilst preparing this manuscript, an AD/aldolase strategy for asymmetric synthesis of C_6 and C_7 carbohydrates was reported: Henderson, I.; Sharpless, K. B.; Wong, C.-H. *J. Am. Chem. Soc.* **1994**, *116*, 2495.
7. A synthesis of perdeuterated ribofuranoses using an AE strategy similar to our own has recently been reported: Goering, B. K.; Lee, K.; An, B.; Cha, J. K. *J. Org. Chem.* **1993**, *58*, 1100.

8. The acetal **2** could also be obtained from the Grignard of **1** catalysed by $AlCl_3$, but the yields were poor (<50%).
9. Yields quoted are for purified chromatographically homogeneous products, unless indicated. All compounds **2-7** gave satisfactory spectral and analytical data. Selected data[24]:
3: ^1H NMR (200MHz, $CDCl_3$) δ 4.49 (t, *J*=5.5Hz, 1H), 4.19 (t, *J*=1.9Hz, 2H), 3.33 (s, 6H), 2.83 (br s, 1H, OH), 2.5 (dt, *J*= 2.1, 5.5Hz, 2H). ^{13}C NMR (50MHz, $CDCl_3$) δ 102.3, 80.5, 80.4, 53.4, 51.0, 23.9. IR ν_{max} cm^{-1}: 3422, 2939, 2835, 1448, 1364, 1193, 1122, 1067, 1014. HR MS: $C_7H_{12}O_3$ M+NH_4^+ requires 162.1126, found 162.1130
4: ^1H NMR (200MHz, $CDCl_3$) δ 5.62-5.74 (m, 1H), 5.38-5.51 (m, 1H), 4.28 (t, *J*=5.6Hz, 1H), 4.05 (d, *J*=6.6Hz, 2H), 3.25 (s, 6H), 2.9 (br s, 1H, OH), 2.33 (t, *J*=6.8Hz, 2H). ^{13}C NMR (50MHz, $CDCl_3$) δ 131.6, 126.1, 103.8, 57.9, 53.3, 31.2. IR ν_{max} cm^{-1}: 3415, 2937, 2835, 1656, 1191, 1125, 1060.
5: We have reported this compound previously[3], and all spectral data also matched that reported by others: Hughes, P.; Clardy, J. *J. Org. Chem.* **1989** *54* 3260.
6: ^1H NMR (360MHz, $CDCl_3$) δ 7.73-7.67 (m, 4H), 7.47-7.36 (m, 6H), 5.80-5.65 (m, 1H), 5.50-5.38 (m, 1H), 4.27 (m, 3H), 3.32 (s, 6H), 2.22 (t, *J*=6.2Hz, 2H), 1.06 (s, 9H).
7: ^1H NMR (250MHz, $CDCl_3$) δ 7.63 (m, 4H), 7.38 (m, 6H), 5.58 (m, 2H), 4.30 (t, *J*=5.8Hz, 1H), 4.1 (s, 2H), 3.26 (s, 6H), 2.29 (m, 2H), 0.98 (s, 9H). ^{13}C NMR (50MHz, $CDCl_3$) δ 135.5, 133.7, 131.7, 129.5, 127.5, 125.1, 104.0, 64.3, 52.8, 35.5, 26.7, 19.1. IR ν_{max} cm^{-1}: 3070, 3048, 2931, 2856, 1472, 1427, 1362, 1113, 1056. HR MS: $C_{23}H_{32}O_3Si$ M+NH_4^+ requires 402.2455, found 402.2464.
10. Several other effective AD catalysts have been reported by other groups, e.g. 1,2-diaminocyclohexane derivatives: Hanessian, S.; Meffre, P.; Girard, M.; Beaudoin, S.; Sancéau, J.-Y.; Benanni, Y. *J. Org. Chem.* **1993**, *58*, 1991.
11. Unprotected *E*-allylic alcohols give poor ees: Xu, D.: Park, C. Y.; Sharpless, K. B. *Tetrahedron Lett.* **1994**, *35*, 2495
12. Spectral data for **8** and **9** [enantiomeric diols] : ^1H NMR (250MHz, $CDCl_3$) δ 7.68 (m, 4H), 7.41 (m, 6H), 4.61 (t, *J*=5.3Hz, 1H), 3.89 (m, dt, *J*=3.3, 9.2Hz), 3.75 (dd, *J*=1.9, 5.3Hz, 2H), 3.55 (m, 1H), 3.34 (s, 6H), 3.15 (br s, 1H, OH), 2.86 (br s, 1H, OH), 1.95-1.73 (m, 2H), 1.07 (s, 9H). ^{13}C NMR (50MHz, $CDCl_3$) δ 135.5, 132.9, 129.8, 127.7, 103.1, 73.8, 68.3, 65.5, 53.4, 53.2, 36.4, 26.8, 19.1. IR ν_{max} cm^{-1}: 3450, 3070, 3049, 2932, 2857, 1427, 1114, 1054.
13. At 20 °C, the reaction was complete in ≤1 minute, but a period of 15 to 20 minutes was more typical at -10 °C.
14. The L- and D-series glycosides **10** and **11** were characterised spectroscopically by comparison with authentic sample of **11** prepared by Fleet's route, and comparison with reported literature values[19]. Selected spectral data for the [minor] β-anomer of **11**: ^1H NMR (360MHz, $CDCl_3$) δ 7.70 (m, 4H), 7.40 (m, 6H), 5.05 (dd, *J*=1.6, 3.7Hz, 1H), 4.34 (m, 1H), 4.08 (m, 2H), 3.86 (dd, *J*=5.8, 10.3Hz, 1H), 3.35 (s, 3H), 2.95 (d, *J*=9.6Hz, 1H, OH), 2.12 (m, 2H), 1.05 (s, 9H). ^{13}C NMR (62.5MHz, $CDCl_3$) δ 136.0, 133.8, 130.0, 128.0, 105.4, 84.9, 71.8, 64.0, 55.3, 41.7, 27.1, 19.5. IR ν_{max} cm^{-1}: 3521, 3070, 3049, 2931, 2857, 1486, 1428, 1112, 1046. Selected data for the [major] α-anomer: ^1H NMR (360MHz, $CDCl_3$) δ 7.69 (m, 4H), 7.42 (m, 6H), 5.16 (t, *J*=4.1Hz, 1H), 4.60 (m, 1H), 4.08-3.94 (m, 3H), 3.34 (s, 3H), 2.98 (d, *J*=5.1Hz, 1H, OH), 2.17 (m, 2H, apparent triplet), 1.06 (s, 9H). ^{13}C NMR (62.5MHz, $CDCl_3$) δ 135.9, 133.1, 130.3, 128.2, 104.9, 79.5, 73.0, 63.3, 55.6, 42.9, 27.1, 19.5. [Spectra for enantiomeric **10** were identical]
NMR data for Mosher's ester derivative of [major] α-anomer of **11**: 7.64 (m, 4H), 7.24-7.45 (m, 11H), 5.58 (m, 1H), 5.12 (minor diastereomer, dd, *J*=3.5, 5.2Hz), 5.00 (major diastereomer, dd, *J*=3.4, 5.4Hz) [total=1H], 4.17 (dt, *J*=3.1, 9.9Hz, 1H), 3.81 (d, *J*=6.0Hz, 2H), 3.36 (s, 3H) [minor diastereomer 3.40], 3.30 (s, 3H) [minor diastereomer 3.34], 2.27 (ddd, *J*=3.3, 5.8, 15.1Hz, 1H), 2.11 (ddd, *J*=1.7, 5.6, 15.1Hz, 1H), 1.03 (s, 9H).
15. This is in contrast to the xylo- case here, and also in contrast to the lack of such selectivity observed in cyclizations to give 2,3-dideoxy,[3b] or 3-azido-ribofuranosides.[3a]
16. Spectral data matched literature for **13**: Dyatkina, N. B.; Azhayev, A. V. *Synthesis* **1984** 961.
17. The *major* diastereomeric peaks for **11** were coincident with those for the authentic D-glycoside Mosher's ester derivative, while those of our synthetic **10** had *minor* diastereomer peaks coincident with the authentic glycoside, and *major* diastereomer peaks coincident with those of the *minor* diastereomer from the synthetic samples of **11**, thus *confirming unambiguously* both the structures of **10** and **11** and absolute stereochemical assignments.
18. (a) NMR ee value from the Mosher's ester derivative of **11** agreed with chiral gas chromatography (gc) [Chrompak β-cyclodextrin column] of the α-anomer of **13**. (b) Chiral gc of the triacetate derivative of desilylated **8**.
19. Fleet, G. W. J.; Son, J. C.; Derome, A. E. *Tetrahedron* **1988**, *44*, 625.
20. Wang, L.; Sharpless, K.B. *J. Org. Chem.* **1992**, *114*, 7568.
21. While preparing this manuscript a comparison of DHQD-IND[20] and $(DHQD)_2PHAL$ for AD of *unprotected* Z-allylic alcohol substrates has appeared, indicating that the latter may be superior to DHQD-IND for some of these substrates. Van Nieuwenhze, M. S.; Sharpless, K. B. *Tetrahedron Lett.* **1994**, *35*, 843.
22. Two options for an indirect route to ribo furanosides from the higher ee *threo* diols, **8** and **9**, are a Mitsunobu inversion on the glycosides, **10** and **11**, or conversion of the diol to the cyclic sulfate and subsequent Payne rearrangement-thiophenyl opening-Pummerer rearrangement. see: Ko, S. Y.; Malik, M. *J. Org. Chem.* **1994**, *116*, 2570.
23. Methyl 5-O-t-butyldiphenylsilyl-2-deoxy-α-D-ribofuranoside Mosher ester derivative - key ^1H NMR signals: 5.64 (m, 1H), 5.11 (dd, *J*=3.3, 5.4Hz, 1H), 4.11 (m, 1H), 3.29 (s, 3H). Enantiomeric mixture from AD route: 5.64 (m, 1H), 5.11 (dd, *J*=3.3, 5.4Hz) and 5.05 (dd, *J*=3.3, 5.4Hz) [total 1H], 4.20 (m) and 4.11 (m) [total 1H], 3.29 (s) and 3.28 (s) [total 3H]
24. Full experimental data for all new compounds described here will be reported in a forthcoming full paper.

(*Received in UK* 23 *May* 1994; *revised* 7 *July* 1994; *accepted* 22 *July* 1994)