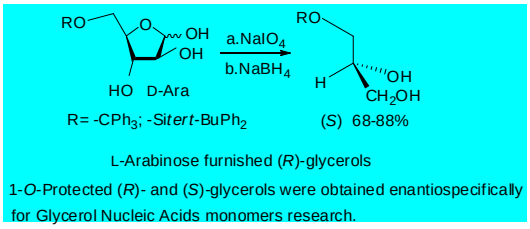
Simple approach to 1-*O*-protected (*R*)- and (*S*)-glycerols from L- and D-arabinose for Glycerol Nucleic Acids (GNA) monomers research

Bogdan Doboszewski and Piet Herdewijn



L-Arabinose furnished (*R*)-glycerols

1-*O*-Protected (*R*)- and (*S*)-glycerols were obtained enantiospecifically for Glycerol Nucleic Acids monomers research.

Simple approach to 1-*O*-protected *(R)*- and *(S)*-glycerols from L- and D-arabinose for Glycerol Nucleic Acids (GNA) monomers research.

Bogdan Doboszewski[a,b] and Piet Herdewijn[a*]

[a] *Rega Institute for Medical Research, Laboratory of Medicinal Chemistry, Katholieke Universiteit Leuven, Minderbroedersstraat 10, B-3000 Leuven, Belgium*
[b] *On leave from the Departamento de Química, Universidade Federal Rural de Pernambuco, 52171-900, Recife, PE, Brasil*

Article history:
Received
Received in revised form
Accepted
Available online

Keywords:
Chiral pool
Enantiomer
Glycerol Nucleic Acid
GNA
Stereospecific

ABSTRACT

5-*O*-protected (-Tr, -Si*tert*-BuPh$_2$) D- and L-arabinofuranoses easily available in multigram quantities were converted to (*S*)- and (*R*)-1-*O*-protected glycerols, respectively, *via* oxidation ($NaIO_4$) and reduction ($NaBH_4$). Sources of chirality in the targets are the C4 atoms in the substrates. This stereospecific procedure permits a very simple access to both enantiomeric 1-*O*-protected glycerols for GNA monomers work.

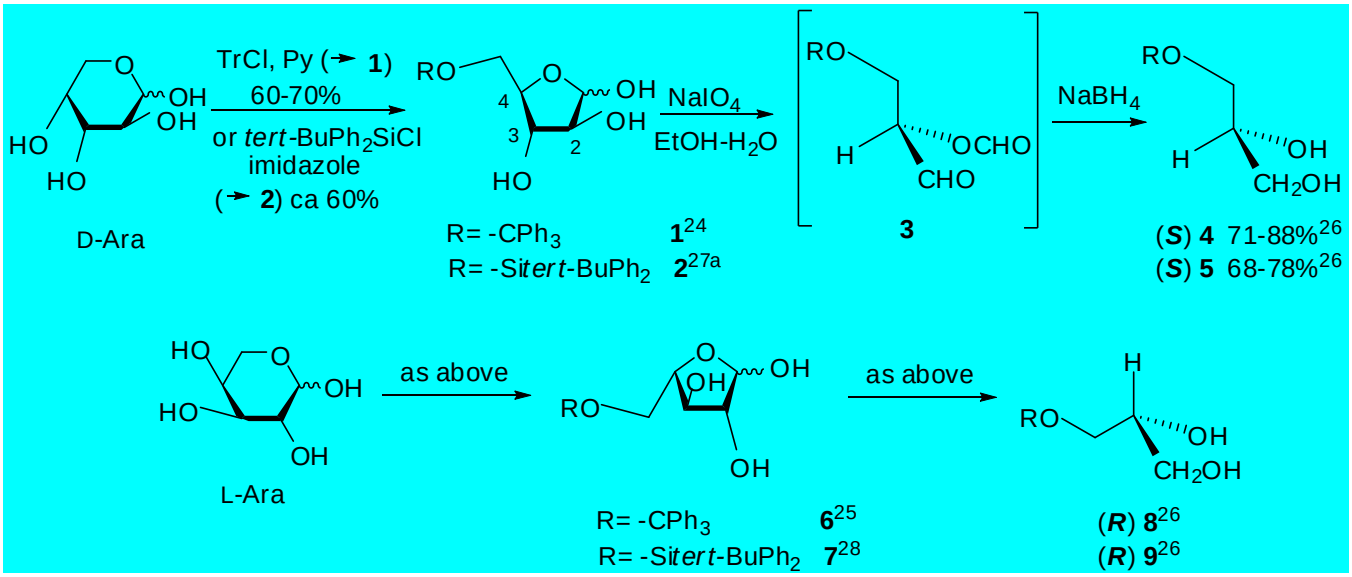
Chiral glyceraldehydes and glycerols are frequently used as building blocks in lipid-related and Glycerol Nucleic Acids (also known as Glycol Nucleic Acids, GNA) research, just like in stereoselective synthesis.[1a-l] Both enantiomers are sometimes required and they can be obtained mainly using a chiral pool approach starting from D-mannitol,[2] L-mannitol,[3] L-ascorbic and D-isoascorbic acids,[4] dimethyl (*R*,*R*)-tartarate,[5] methyl (*S*)-glycerate,[6a,b] D- and L-serine,[7a,b] D-glucitol,[8] L-erythrulose,[9] dithioacetals of L-arabinose,[10a,b] L-galactono-1,4-lactone,[11] D-ribofuranosyl-lactone,[12] L-gulono-1,4-lactone,[13a,b] or by conversion of D-isopropylidene-glycerol into its enantiomer.[14]

Other procedures include desymmetrization of 1,2-isopropylideneglycerol phthalate using (*R*)- and (*S*)-1-phenylethylamines,[15] enzymic resolution with variable enantiomeric excess,[11d, 16a,b] enantioselective acylation of 2-substituted glycerol,[17] asymmetric cis-hydroxylation of allyl alcohol derivatives,[18] stereoselective synthesis using glycolic acid derivative and chiral sulfoxides,[19] or use of chiral glycidol.[1a]

In most of the chiral pool methods, the (*R*)- or (*S*)-1,2-isopropylidene-glyceraldehydes are the intermediates, which are subsequently elaborated into the desired building blocks. D-Mannitol is the most frequently used source of (*S*)-1,2-isopropylidene-glyceraldehyde since it is very cheap. The (*R*) enantiomer can be elaborated from L-mannitol, but prohibitively high price limited its application, even though it can be prepared from L-arabinose, but the whole procedure is lengthy and time-consuming.[3] Some care should be exercised during the preparation of chiral isopropylidene-glycerols since racemization may take place *via* ketal function migration even in the presence of traces of acids.[20]

Considering the popularity of triphenylmethyl (trityl, -Tr) group to protect primary –OH functions, and the ease of its removal, some research was performed to obtain chiral (*R*)- and (*S*)-1-*O*-triphenylmethyl-glycerol **8** and **4**, respectively. Thus, Molotkovskii *et al*. tried to hydrolyze selectively the ketal function in (*R*)-1-*O*-triphenylmethyl-2,3-isopropylidene- glycerol using diluted trichloroacetic acid. This resulted in partial removal of the *O*-triphenylmethyl group, so the procedure was low-yielding.[21a,b] To overcome the selective hydrolysis problems, an extensive protecting groups manipulation was performed.[22a-c] An alternative to get (*R*) **8** or its (*S*) enantiomer **4** is to use highly toxic (*S*)-glycidol[1a] or 1,6-di-*O*-triphenylmethyl-D-mannitol[23]. Considering all these factors we felt that there is a need to devise an easy and enantispecific procedure which would permit to obtain both (*R*)-**8** and (*S*)-**4** in a uniform manner for synthesis of chiral GNA monomers and for other purposes. Objective of this communication is to show that 5-*O*-triphenylmethyl-D- and L-arabinofuranose **1**[24] and **6**,[25] easily available in multigram quantities in one step reaction, can be converted to (*S*)- and (*R*)-1-*O*-triphenylmethyl-glycerol **4** and **8**, respectively, in yields up to 88% *via* $NaIO_4$ and $NaBH_4$ sequential treatment without isolation of the intermediates (Scheme 1).[26] The two vicinal diol systems present in **1**/**6** are amenable to periodate attack, and consequently both stereogenic centers at the C2 and C3 atoms are destroyed. A source of chirality in the targets **4** and **8** are the atoms C4 in the starting furanoses **1** and **6**. No effort has been made to isolate and characterize the transiently formed **3**.

* Tel.: +32 16 337387; fax: +32 16 337340; E-mail address: piet.herdewijn@rega.kuleuven.be



Scheme 1. Synthesis of chiral glycerols from D- and L-arabinose

The same procedure was applied to D- and L-5-*O*-*tert*-butyldiphenylsilyl-arabinofuranose **2**[27a] and **7**[28] and allowed to obtain (*S*)- and (*R*)-1-*O*- *tert*-butyldiphenylsilyl-glycerol **5** and **9**, respectively.[26]

In the present chiral pool approach we concentrated our attention on both arabinoses, due to our former interest in these two sugars, which we used in the stereoselective synthesis of degradation product of the promising antibiotic Batumin/Kalimantacin,[27a,b] as well as in the synthesis of the branched-chain pyranosyl nucleosides.[30a,b] Additionally both arabinoses are reasonably priced, making them convenient starting materials for the present application. Another pentose which could be used for the same purpose is D- and L-xylose, also available in both enantiomeric forms.

In conclusion, a very simple method was devised to obtain (*R*)- and (*S*)-1-*O*-triphenylmethyl- glycerol, and (*R*)- and (*S*)-1-*O*-*tert*-butyldiphenylsilyl-glycerol in good yields starting from L- and D-arabinose.

Acknowledgements

The authors thank the K.U. Leuven for financial support (GOA/10/13 and IDO IDO/09/006).

References and notes

1. (a) Miyachi, A.; Miyazaki, A.; Shingu, Y.; Matsuda, K.; Dohi, H.; Nishida Y. *Carbohydr.Res.* **2009**, *344*, 36-43; (b) Iwashita, M.; Makide, K.; Nonomura, T.; Misumi, Y.; Otani, Y.; Ishida M.; Taguchi, R.; Tsujimoto, M.; Aoki, J.; Arai, H.; Ohwada, T. *J.Med.Chem.* **2009**, *52*, 5837-5863; (c) Greimel, P.; Ito, Y. *Tetrahedron Lett.* **2008**, *49*, 3562-3566; (d) Hachiya, I.; Sugiura, Y.; Araki, H.; Inaoka, O.; Shimizu, M.; Akita, M.; Hamaguchi, T. *Tetrahedron*: *Asymmetry* **2007**, *18*, 915-918; (e) Toshima, K.; Okuno, Y.; Matsumura, S. *Bioorg.Med.Chem.Lett.* **2003**, *13*, 3281-3283; (f) Zhang, S.; Switzer, C.; Chaput, J.C. *Chem.Biodivers.* **2010**, *7*, 245-258; (g) Schlegel, M.K.; Essen, L.-O.; Meggers, E. *J.Am.Chem.Soc.* **2008**, *130*, 8158-8159; (h) Schlegel, M.K.; Peritz, A.E.; Kittigowittana, K.; Zhang, L.; Meggers, E. *Chem.BioChem.* **2007**, *8*, 927-935; (i) Nielsen, P.; Dreiøe, L.H.; Wengel, J. *Bioorg.Med.Chem.* **1995**, *3*, 19-28; (j) Nagaiah, K.; Sreenu, D.; Rao, R.S.; Yadav, J.S. *Tetrahedron Lett.* **2007**, 48, 7173-7176; (k) Jurczak, J.; Pikul, S.; Bauer, T. *Tetrahedron* **1986**, *42*, 447-488; (l) Inch, T.D. *Tetrahedron* **1984**, *40*, 3161-3213.
2. Schmid, C. R.; Bryant, J. D. *Org. Synth.* **1998**, *Coll. Vol. 9*, 450-453.
3. Baer, E.; Fischer, H. O. L. *J. Am. Chem. Soc.* **1939**, *61*, 761-765.
4. Mikkilineni, A. B.; Kumar, P.; Abushanab, E. *J.Org. Chem.* **1988**, *53*, 6005-6009.
5. Al-Hakim, A. H.; Haines, A. H.; Morley, C. *Synthesis* **1985**, 207-208.
6. (a) Roodsari, F. S.; Wu, D.; Pum, G. S.; Hajdu, J. *J. Org .Chem.* **1999**, *64*, 7727-7737; (b) Srivastava, R.P.; Hajdu, J. *Tetrahedron Lett.* **1991**, *32*, 6525-6528.
7. (a) Lok, C. M.; Ward, J. P.; van Dorp, D. A. *Chem. Phys. Lipids* **1976**, *16*, 115-122; (b) De Witt, P.; Misiti, D.; Zappia, G. *Tetrahedron Lett.* **1989**, *30*, 5505-5506.
8. Pressman, B. C.; Anderson, L.; Lardy, H.A. *J. Am. Chem. Soc.* **1950**, *72*, 2404-2406.
9. De Wilde, H.; De Clercq, P.; Vandewalle, M. *Tetrahedron Lett.* **1987**, *28*, 4757-4758.
10. (a) Kanda, P.; Wells, M.A. *J. Lipid Res.* **1980**, *21*, 257-258; (b) Kodali, D. R. *J. Lipid Res.* **1987**, *28*, 464-469.
11. Morgenlie, S. *Carbohydr. Res.* **1982**, *107*, 137-141.
12. Pfaendler, H. R.; Maier, F. K. *Liebigs Ann. Chem.* **1989**, 691-693.
13. (a) Schmid, C. R.; Bradley, D. A. *Synthesis* **1992**, 587-590; (b) Hubschwerlen, C.; Specklin, J.-L., Higelin, J. *Org. Synth.* **1998**, *Coll. Vol. 9*, 454-456.
14. Baer, E.; Fischer, H. O. L. *J. Am. Chem. Soc.* **1945**, *67*, 944-646.
15. Pallavicini, M.; Valoti, E.; Villa, L.; Piccolo, O. *Tetrahedron: Asymmetry* **1994**, *5*, 5-8.
16. (a) Cesarotti, E.; Antognazza, P.; Pallavicini, M. Villa, L. *Helv. Chim. Acta* **1993**, *76*, 2344-2349; (b) Liljeblad, A.; Vänttinen, E.; Kanerva, L. T. *Chirality* **1999**, *11*, 432-439.
17. Ichikawa, J.; Asami, M.; Mukaiyama, T. *Chem. Lett.* **1984**, 949-952.
18. Noe, M. C.; Letavic, M. A.; Snow, S. L. *Org. React.* **2005**, *66*, 109-625.
19. Ekhato, I.V.; Palazzolo, M. *Synth. Commun.* **1998**, 28, 3727-3741.
20. Baldwin, J. J.; Raab, A. W.; Mensler, K.; Arison, B. H.; McClure D. E. *J. Org. Chem.* **1978**, *43*, 4876-4878.
21. (a) Molotkovskii, Yu. G.; Bergelson, L. D. *Izv. Acad. Nauk SSSR, Ser. Khim.* **1967**, 925-926; (b) Molotkovskii, Yu. G.; Nikulina, L. F.; Bergelson, L. D. *Izv. Acad. Nauk SSSR, Ser. Khim.* **1967**, 927-929.
22. (a) Pfeiffer, F. R.; Miao, C. K.; Weisbach, J. A. *J. Org. Chem.* **1970**, *35*, 221-224; (b) Gent, P. A.; Gigg, R. *Chem. Phys. Lipids* **1976**, *17*, 111-119; (c) Pfeiffer, F. R.; Miao, K. C.; Weisbach, J. A. *Prep. Biochem.* **1971**, *1*, 221-232.
23. Virtanen, J. A.; Brotherus, J. R.; Renkonen, O.; Kates, M. *Chem. Phys. Lipids* **1980**, *27*, 185-190.
24. Kam, B. L.; Oppenheimer, N. J. *Carbohydr. Res.* **1979**, *69*, 308-310.
25. Cabaret, D.; Wakselman, M. *Can. J. Chem.* **1990**, *68*, 2253-2257.
26. To a magnetically stirred ice-cold solution of 5-O-*tert*-butyldiphenylsilyl-D-arabinofuranose [27a] **2,** 1.7 g, 4.4 mmol in technical EtOH, 50 ml, was added portionwise a solution of $NaIO_4$ 2.3 g, 10.0 mmol in water 21 ml. Cooling bath was removed after completion of addition. After 45 min more $NaIO_4$ 0.14 g in H_2O 2 ml was added. 5 min. later 12 drops of ethylene glycol were added. After additional 5 min. the solid material was filtered on a sintered glass and washed with EtOH. The so obtained slightly opaque filtrate was chilled in ice bath and $NaBH_4$, 0.38 g, 10 mmol was

added. 25 min. later the whole mixture was transferred to a separatory funnel and extraction was performed using CH_2Cl_2- aq. dil. $(NH_4)_2SO_4$. Organic phase was dried ($MgSO_4$) and evaporated. In some preparations the product crystallized already at this stage. Chromatography using hexane- EtOAc, gradient 6:4→ 6:5 furnished 1.14 g, 78.5% of (*S*)-**5**, mp. 58-60°, from hexane-diethyl ether, α_D -5.3°, c 6.2 dioxane. ^{1}H NMR (600MHz, $CDCl_3$): 7.660-7.646, 4H; 7.456-7.432, 2H; 7.396-7.385, 4H, H aromatic; 3.805(m of 12 lines, J=4.1Hz, 4.2Hz, 5.5Hz, 10.9Hz, 1H, H2); 3.734(dd, J=4.4Hz, 10.4Hz); 3.704(dd, J=5.9Hz, 10.5Hz); 3.702(dd, J=3.8Hz, 6.4Hz); 3.683(dd, J=4.0Hz, 7.0Hz), 3.634(m of five lines, J=5.3Hz, 1H,); 2.626(d, J=5.2Hz, 1H, -OH); 2.068(dd, J=5.3Hz, 7.0Hz 1H, -OH); 1.069(s, 9H). ^{13}C(125MHz, $CDCl_3$): 135.51, 132.85, 132.80, 129.93, 127.84, 71.79, 65.22, 63.83, 26.82, 19.19. Exact mass (electrospray): calc. for $[C_{19}H_{26}O_3Si + Na]^+$=353.1549, found: 353.1540. Following the same procedure L-**7**[28] furnished the (*R*) enantiomer **9**, mp. 58-60° hexane-diethyl ether, α_D +5.2° c 6.0 dioxane; lit.[29] mp.54°, α_D +6.5° *c* 2, MeOH; exact mass: found: 353.1532.

The same procedure was used to obtain 1-*O*-triphenylmethyl-(*S*)-**4** starting from D-arabinose **1**[24] and to obtain 1-O-triphenylmethyl-(*R*)-**8** from L-arabinose **6**[25] in 71-88% yield after chromatography in hexane-EtOAc 1:1. **4** mp. 98-100°C (hexane-Et_2O), α_D -9.1°, c 5.1 dioxane, or -5.3° c 1.1 $CHCl_3$-MeOH 4:1. ^{1}H NMR (600 MHz, $CDCl_3$): 7.42-7.41; 7.30-7.29; 7.24-7.21, 15H, aromatic; 3.842 (m of five lines, J=4.9 Hz, 1H); 3.657(dd, J=3.2Hz, 11.3Hz, 1H); 3.571(dd, J=5.8Hz, 11.4Hz, 1H); 3.240(dd, J=4.6Hz, 9.7Hz, 1H); 3.199(dd, J=6.0Hz, 9.9Hz, 1H); 2.72(bs, 1H); 2.28(bs, 1H). ^{13}C (125MHz, $CDCl_3$): 143.83; 128.80; 128.12; 127.39; 87.14; 71.32; 65.21; 64.47. Exact mass (electrospray): calc. for $[C_{22}H_{22}O_3 + Na]^+$ = 357.1467, found: 357.1472. (*R*)-**8** mp. 98-100°C, α_D +9.2°, c 5.2 dioxane, α_D +5.2° c 2.3 $CHCl_3$-MeOH 4:1, lit.[21a] mp. 95-96°C, α_D +9.55°, dioxane; lit.[1a] α_D +5.2°, c 0.91 $CHCl_3$-MeOH 4:1. Exact mass (electrospray): calc. for $[M+Na]^+$, found: 357.1467.

27. (a) Doboszewski, B.; Herdewijn, P. *Tetrahedron* **2008**, *64*, 5551-5562; (b) Mattheus, W.; Gao, L.-J.; Herdewijn, P.; Landuyt, B.; Verhaegen, J.; Masschelein, J.; Volckaert, G.; Lavigne, R. *Chem. Biol*. **2010**, *17*, 149-159.
28. Dahlman, O.; Garegg, P. J.; Mayer, H.; Schramek, S. *Acta Chem. Scand. B* **1986**, *40*, 15-20.
29. Leftheris, K.; Goodman, M. *J. Med. Chem*. **1990**, *33*, 216-223.
30. (a) Herdewijn, P.; De Winter, H.; Doboszewski, B.; Verheggen, I.; Augustyns, K.; Hendrix, C.; Saison-Behmoaras, T.; De Ranter, C.; Van Aerschot, A. in: Carbohydrate Modifications in Antisense Research. *ACS Symp. Ser*. Sanghvi Y.S.; Dan Cook, P. *eds*. **1994**, *580*, 80-99; (b) Doboszewski, B.; Herdewijn, P. *Tetrahedron* **1996**, *52*, 1651-1668.