Tetrahedron Letters,Vol.30,No.44,pp 6015-6018,1989 0040-4039/89 $3.00 + .00
Printed in Great Britain Pergamon Press plc

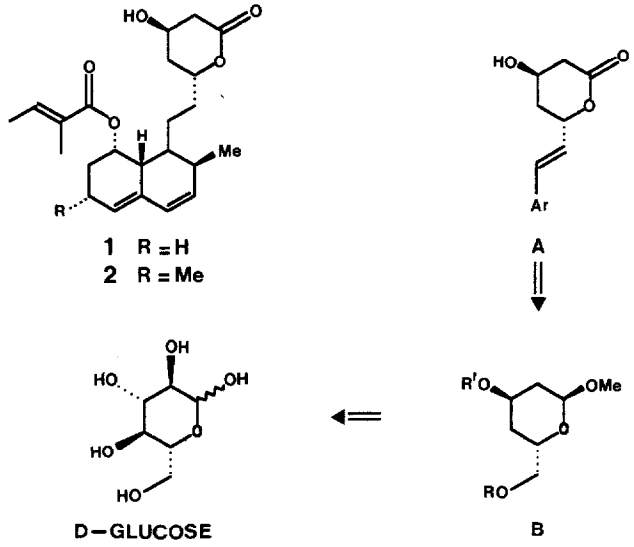
# MEVINIC ACIDS AND ANALOGS : A NOVEL EFFICIENT ROUTE TO CHIRAL SYNTHONS FROM 1,6-ANHYDRO-D-GLUCOSE

C.DAVID[1], J.P. GESSON AND J.C. JACQUESY

Laboratoire de Chimie XII, associé au CNRS - Faculté des Sciences
40, Avenue du Recteur Pineau - 86022 POITIERS (France)

**ABSTRACT** : *1,6-anhydro-D-glucose is efficiently and regioselectively deoxygenated at C-2 and C-4 by displacement of the corresponding ditosylate with thiophenol followed by Raney Ni hydrogenolysis. This route provides a short access to chirons of the key lactonic moiety of mevinic acids.*

Mevinic acids (i.e. Compactin 1 and Mevinolin 2) are potent inhibitors of HMG-CoA reductase, an enzyme involved in one of the early steps of cholesterol biosynthesis.[2]



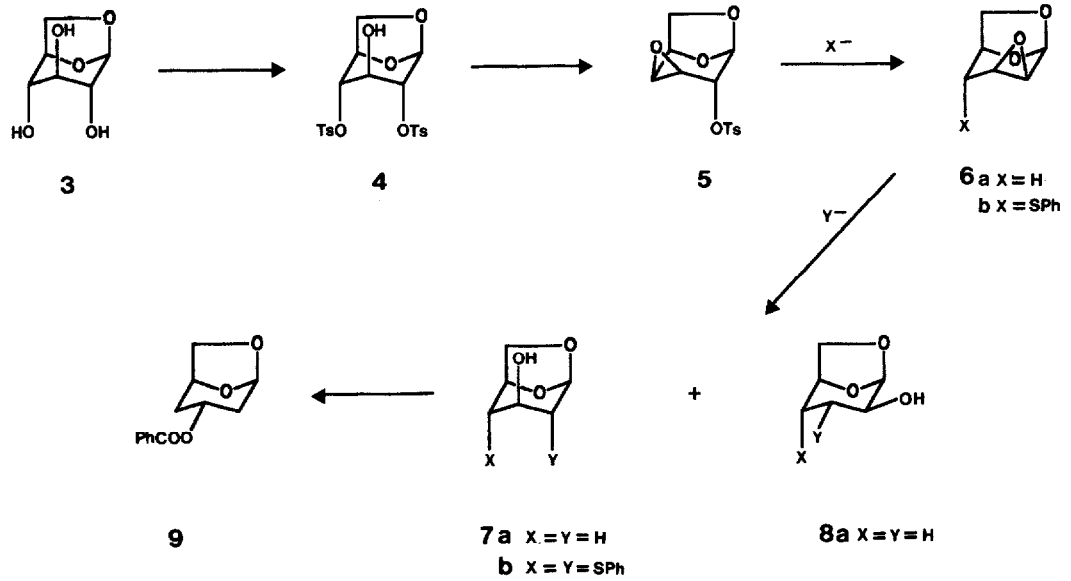

The potential importance of this new class of hypocholesterolemic agents[3] has spurred many recent synthetic studies,[4] and the discovery of active analogs such as **A** which retain the lactonic moiety of mevinic acids has emphasized the need for suitable chirons such as **B**.

Among the published routes to B[5] the conversion of a readily available carbohydrate such as D-Glucose has been the most studied : it implies two deoxygenation reactions at C-2 and C-4 and an inversion of configuration at C-3.

However their length and the use of complex reagents or protecting groups appear unsatisfactory for a large scale process.

Our approach which intends to circumvent these drawbacks starts from 1,6-anhydro-D-glucose (levoglucosan) **3** which is readily obtained by pyrolysis of starch[6] or alternatively by hydrolysis of ß-phenyl glucoside **7** or by base-treatment of 6-O-Tosyl glucose.[8] The rigid structure of **3** allows selective tosylation of the less hindered hydroxyl groups to yield the ditosylated **4** (61 %)[9] which has been previously reduced. However the use of $LiBHEt_3$ gives an unseparable mixture of **7a** and **8a** in a 5.25/1 ratio[10] which rules out any synthetic application. This reaction has been shown to proceed by successive opening of the intermediate epoxides **5** and **6a**, the lack of regioselectivity resulting from competitive attack of **6a** at C-2 and C-3 by the nucleophile.[11] However if the first nucleophile introduced at C-4 is not an hydride but a more bulky group (allyl[12], methyl[13], O-benzyl[14]) opening of epoxide **6** is then completly regioselective using different nucleophiles ($LiBHEt_3$, $PhSCH_2Li$ and $CH_2=CH-CH_2MgCl$ respectively).

*These observations lead us to propose a simple and selective deoxygenation of 3 by the introduction of a bulky and easily hydrogenolysable group such as -SR.*



As expected, reaction of **4** with 10 eq. of thiophenol (NaOH 10 eq., dioxane/water 1/1, 65°C, 24 h) results in clean formation of **7b**, mp 93-94°C $[\alpha]_D$ -51° (c = 1.6,$CHCl_3$), in 92% isolated yield.[15] A 2D COSY experiment allows assignement of all signals and particularly those of H-2 and H-4 which appear as singlets at 3.29 and 3.32 ppm respectively shielded by 2.03 and 1.91 ppm compared to starting material **4**.
Interestingly reaction of **4** with 2 eq. of thiophenol gives epoxide **6b** as an oil (78%),[15] thereby confirming the initial formation of epoxide **5**.
Hydrogenolysis of **7b**[16] is then carried out using W-2 Raney Ni (14 eq.) in ethanol ($H_2$ : 10 atm, room temperature) to give **7a** as a colorless oil, bp 50°C (0.01 torr), $[\alpha]_D$ -81° (c = 1, $H_2O$), Litt. $[\alpha]_D$ -80° (c = 1, $H_2O$) in 85% yield.[17]
It has been reported that inversion at C-3 on the mixture **7a** + **8a** leads to benzoate **9** (57%) overall yield based on **7a**) after treatment of the intermediate tosylate with sodium benzoate.[11] Although other methodologies may be explored to achieve both epimerization and protection, the application of the above methodology already affords in c.a. 27% overall yield from 1,6-anhydro-D-glucose **3**, the key intermediate **9** in only five steps which appear well suited for a large scale process.
Further studies on the chemistry of these sulfur intermediates are underway.

C. DAVID acknowledges financial support from CNRS and Laboratoires HOECHST (BDI grant). We thank Prof. Dr. Bartmann (Hoechst AG, Frankfurt, FRG) for his interest and for allowing one of us (CD) to run larger scale experiments at Hoechst.

**REFERENCES AND NOTES:**

1. This work is part of the Thesis of C.D. (Doctorat, Poitiers, Sept. 28, 1988).
2.(a) Endo, A.; Kuroda, M.; Tsujita, Y. *J.Antibiot.* **1976**, *29*, 1346.
(b) Kaneko, I.; Hazama-Shimada, Y.; Endo, A. *Eur. J. Biochem.* **1978**, *87*, 313.
3.(a) The Lovastatin Study Group II, *J. Amer. Med. Assoc.* **1986**, *256*, 2829.
(b) Endo, A. *Pharmac. Ther.* **1985**, *31*, 257.
(c) Roger Hillingworth, D. *Drugs*, **1987**, *31*, 259.
4. Clive, D.L.J.; Keshava Murthy, K.S.; Wee, A.G.H.; Siva Prasad, J.; Da Silva, G.V.J.; Majewski, M.; Anderson, P.C.; Haugen, R.D.; Heerze, L.D. *J. Am. Chem. Soc.* **1988**, *110*, 6914. and references cited therein.
5. Chiral syntheses are listed below (starting material, *number of steps* and overall yield are given in brackets) :
(a) Prugh, J.D.; Deana, A.A. *Tetrahedron Lett.* **1982**, *23*, 281 (Methyl α-D-Glucopyranoside, *12*, 17%).
(b) Yank, Y.L.; Falck, J.R. *Tetrahedron Lett.* **1982**, *23*, 4305. (Triacetyl D-Glucal, *8*,48%).
(c) Danishefsky, S.; Kobayashi, S.; Kerwin Jr., J.F. *J. Org. Chem.* **1982**, *47*, 1983 ((R)-isopropylidene glyceraldehyde, *7*,25%).

(d) Majewski, M.; Clive, D.L.J.; Anderson, P.C. *Tetrahedron Lett.* **1984**, *25*, 2101 ((S)-Malic diethyl ester, *10*,5%).

(e) Rosen, T.; Taschner, M.J.; Heathcock, C.M. *J. Org. Chem.* **1984**, *49*, 3994 (D-Gulono--lactone, *9*,3% and (S)-Malic acid, *11*, 15%).

(f) Guindon, Y.; Yoakim, C.; Berstein, M.A. *Tetrahedron Lett.* **1985**, *29*, 1185 ((S)-Malic acid, *12*, 10%).

(g) Lee, T.J. *Tetrahedron Lett.* **1985**, *29*, 1255 (D-Glucose, *8*, 15%).

(h) Roark, W.M.; Roth, B.D. *Tetrahedron Lett.* **1988**, *29*, 1255 (Triacetyl D-Glucal, *8*, 22%).

(i) Baader, E.; Bartmann, W.; Beck, G.; Bergmann, A.; Fehlhaber, H.W.; Jendralla, H.; Kessler, K.; Saric, R.; Schüssler, H.; Teetz, V.; Weber, M.; Wess, G. *Tetrahedron Lett.* **1988**, *29*, 2563 (3-oxo glutaric acid, *9*, 37%).

6. Shafizadeh, F.; Fu, Y.L. *Carbohydr. Res.* **1973**, *23*, 113.

7. McCloskey, C.M.; Coleman, G.H. *J. Org.Chem.* **1945**, *10*, 184.

8. Lafont, D.; Boullanger, P.; Cadas, O.; Descotes, G. *Synthesis*, **1988**, 191.

9. Cerny, M.; Gut, V.; Pacak, J. *Collect. Czech. Chem. Comm.*, **1961**, *26*, 2542.

10. Kelly A.G.; Roberts, J.S. *Carbohydr. Res.* **1979**, *77*, 231.

11. Reduction of epoxide **6** with $LiAlH_4$ gives a 1.7/1 ration of **7a** and **8a**.
(Pecka, J.; Stanek Jr, J.; Cerny, M. *Collect. Czech. Comm.* **1974**, *39*, 1192).

12. Kelly, A.G.; Roberts, J.S. *J. Chem.Soc. Chem. Comm.*, **1980**, 228.

13. Hodges, P.J.; Procter, G. *Tetrahedron Lett.* **1985**, *26*, 4111.

14. Challenger, S. Procter, G. *Tetrahedron Lett.* **1986**, *27*, 391.

15. New compounds have been characterized by elemental analysis, MS, IR. Chemical shifts relative to TMS as internal standard are given below (BRUKER WP 200 SY) :
**6b** : NRM $^1H$ ($CDCl_3$) : 3.25 (d, J = 3 Hz, H-2), 3.47-3.55 (m, H-4 and H-6 exo), 4.57 (m, H-5), 5.76 (d, J = 3Hz, H-1), 7.3-7.6 (m, 5H, H arom.).
**7a** : NMR $^1H$ ($CDCl_3$) : 1.85-2.3 (m, H-2ax., H-2eq., H-4ax., H-4 eq.), 2.67 (s, OH), 3.73 (dd, J = 2 and 5 Hz, H-6 exo), 4.03 (m, H-3), 4.33 (d, J = 5 Hz, H-6 endo), 4.54 (m, H-5), 5.64 (s, H-1).
**7b** : NMR $^1H$ ($CDCl_3$) : 3.29 (s, H-2), 3.32 (s, H-4), 3.72 (m, H-6 exo and OH), 4.15 (s, H-3), 4.16 (d, J = 7 Hz, H-6 endo), 4.68 (d, J = 5 Hz, H-5), 5.69 (s, H-1) and 7.2-7.7 (m, 10 H, H arom.).

16. Only complex mixtures were obtained using $Li/NH_3$ and $Zn/NH_4Cl$.

17. When the reaction is carried out on mmolar scale a single compound is still detected by TLC. However the isolated yield of **7a** is probably due to loss of material on excess Raney Ni (1.3 mmole : 70%, 0.56 mmole : 30%). Extensive washing of the catalyst does not allow complete recovery of **7a**. Therefore the reaction should be carried out in presence of a limited amount of Raney Ni.

(Received in France 28 May 1989)