Tetrahedron Letters, Vol.27, No.3, pp 391-394, 1986 0040-4039/86 $3.00 + .00
Printed in Great Britain

ANHYDRO-D-GLUCOPYRANOSE IN ORGANIC SYNTHESIS; PREPARATION OF A FRAGMENT FOR A SYNTHESIS OF ROSARAMYCIN

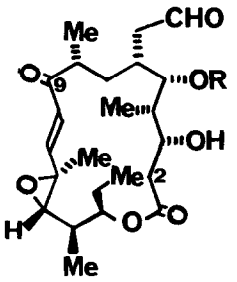
S. Challenger [a] and G. Procter*[b]

[a]Department of Chemistry, University College, Cardiff CF1 1XL

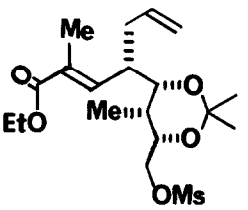
[b]Department of Chemistry and Applied Chemistry, University of Salford, Salford M5 4WT

SUMMARY *Intermediate (3) has been prepared by an enantiospecific and stereospecific route from 1,6-anhydro-D-glucopyranose (2).*

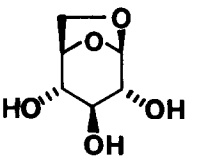
Rosaramycin (1) is a macrolide antibiotic with an unusual spectrum of antibiotic action,[1] whose relative and absolute stereochemistry have been determined by X-ray crystallography.[2] We are interested in the use of 1,6-anhydro-D-glucopyranose (2) for the synthesis of natural products and have initiated a project aimed at the total synthesis of rosaramycin using this readily available optically active starting material. In this communication we disclose a short, stereocontrolled synthesis of intermediate (3), which represents the C-2 to C-9 sequence of rosaramycin, and certain other macrolide antibiotics.[3]



(1)



(3)

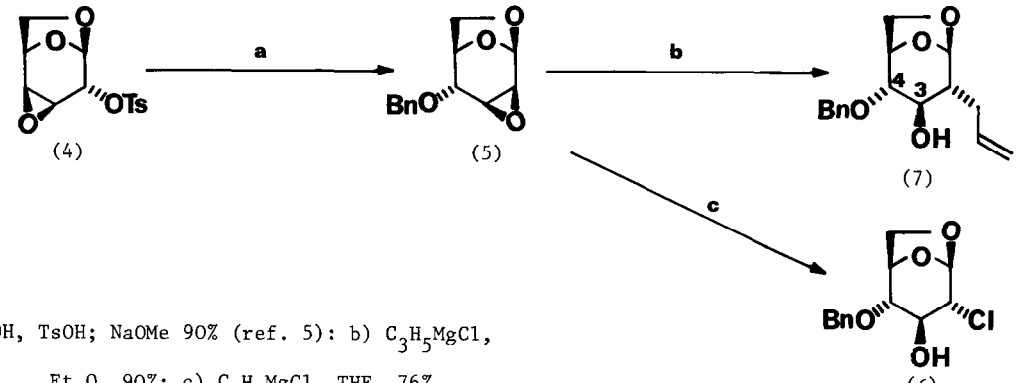


(2)

The epoxy-tosylate (4) is easily prepared from 1,6-anhydro-D-glucopyranose[4] and is converted into the benzyloxy-epoxide (5) in 90% yield using the published procedure.[5] Introduction of the allyl group, (Scheme 1) which will eventually provide the "aldehyde" side chain of rosaramycin, was achieved by trans-diaxial opening of the epoxide (5) with

allylmagnesium chloride in ether.[6] The choice of solvent is critical for this reaction, the use of THF produces only the chlorohydrin (6).

Scheme 1

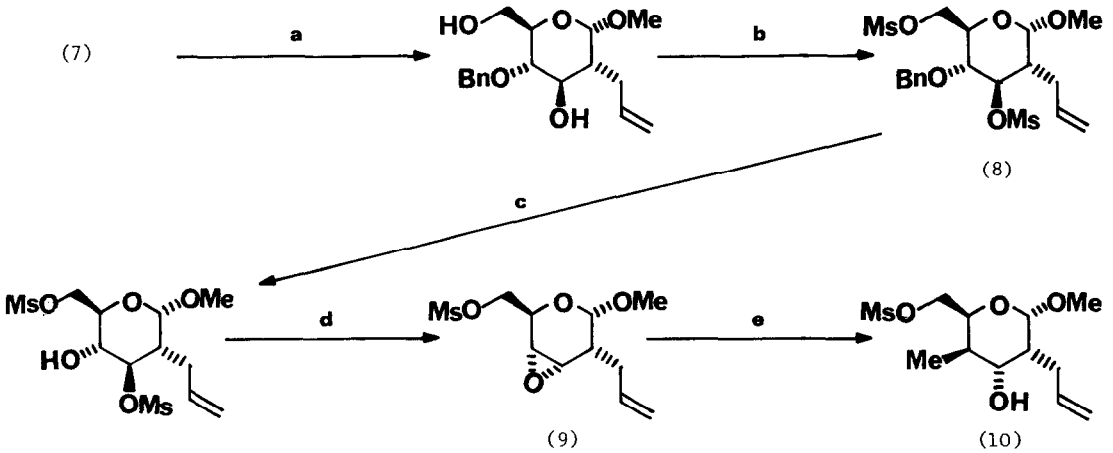


(4) (5) (7) (6)

a) BnOH, TsOH; NaOMe 90% (ref. 5): b) C_3H_5MgCl, Et_2O, 90%: c) C_3H_5MgCl, THF, 76%

The preparation of a suitable intermediate for the synthesis of rosaramycin (1) requires the inversion of the hydroxyl function at C-3 and introduction of a methyl group at C-4 with inversion in compound (7). After investigation of a number of alternative routes we have developed an efficient solution to these problems. Methanolysis of (7) followed by mesylation of both hydroxyl groups gave the bis-mesylate (8) in high yield. Selective removal of the benzyl group followed by treatment with base gave the epoxide (9) (Scheme 2).

Scheme 2

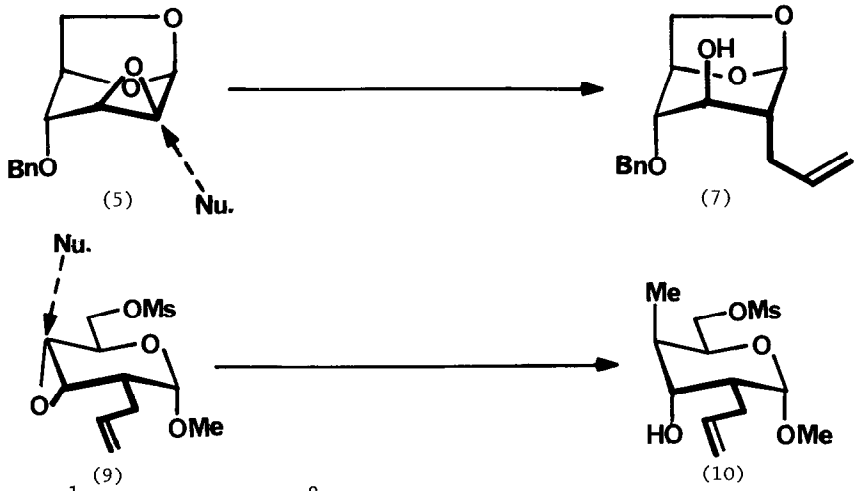


(8) (9) (10)

a) MeOH, HCl, 96%: b) MsCl, Et_3N, 92%: c) Na, NH_3, 97%: d) NaOMe, 83%: e) MeMgCl, CuBr, 92% or Me_2CuLi, 81%

The remaining problem in the preparation of (3) is the introduction of the C-4 methyl group, via opening the epoxide function in (9) in a trans-diaxial manner.[7] Treatment of (9) with either methylmagnesium chloride in the presence of Cu(I), or lithium dimethylcuprate gave the desired product (10) in good yield. We could detect none of the product corresponding to opening at C-3 (by 360 MHz ^{1}H n.m.r. spectrometry). The structure and stereochemistry of (10) were supported by n.O.e. difference and decoupling measurements at 360 MHz.

The stereochemical control in the preparation of (10) derives from the trans-diaxial opening of the appropriate epoxide. The sense of epoxide opening is determined by the conformation of the ring which contains the epoxide group. In establishing the stereocentre at C-2 we have used 1,6-anhydro-D-glucopyranose derivative (5) in which the pyranose ring is

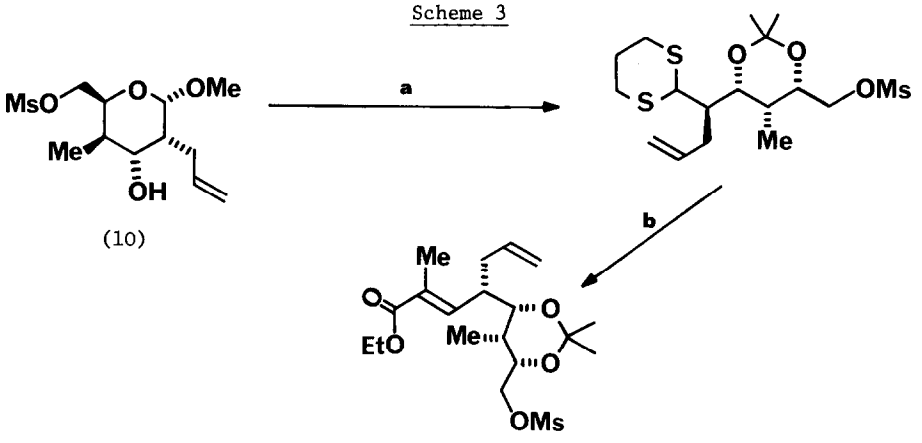


locked into the $^{1}C_{4}$(D) conformation,[8] resulting in trans-diaxial attack as shown. Trans-diaxial opening of the epoxide (9), in which the pyranose ring adopts the more usual $^{4}C_{1}$(D) conformation, then provides the remaining stereocentres.

The conversion of (10) into (3) requires addition of a stabilised Wittig reagent to the masked aldehyde group at C-1. All attempts to react the lactol corresponding to (10) with stabilised phosphoranes failed, and we adopted the stepwise procedure outlined in Scheme 3.

In conclusion, we have prepared fragment (3) for the total synthesis of rosaramycin in an efficient, regio- and stereospecific manner, starting from 1,6-anhydro-D-glucopyranose. It is worthy of note that all the asymmetric centres of D-glucose have been used efficiently and that none of these centres become trigonal during the synthesis. Further applications of 1,6-anhydro-D-glucopyranose in organic synthesis will be reported in due course.

Scheme 3



(10)

(3)

a) $HS(CH_2)_3SH$, $BF_3.OEt_2$; $(MeO)_2CMe_2$, TsOH, 56%: b) MeI, $CaCO_3$,MeCN,H_2O; $EtO_2C(Me)C{=}PPh_3$, 53%.

Acknowledgements We thank Drs. A.H. Davidson and S.M. Roberts for discussions relating to this work, and Glaxo Group Research (Greenford) and the S.E.R.C. for a CASE studentship (to S.C.).

References

1. R.E. Baughn, D.M. Musher, C.B. Adams and J.M. Knox, Antimicrob. Agents Chemother., 19, 117, (1981), and references therein.
2. A.K. Ganguly, Y.-T. Liu, O. Sarre, R.S. Jaret, A.T. McPhail and K.K. Onan, Tetrahedron Letters, 21, 4699, (1980).
3. For example the Tylosin family, see R.F.C. Jones, Natural Products Reports, 1, 87, (1984).
4. L.J. Carlson, J. Org. Chem., 30, 3953, (1965).
5. M. Cerný and T. Trinka, Collect. Czech. Chem. Comm., 36, 2,216, (1971).
6. Trans-diaxial opening in this series is well documented, see M. Cerný and J. Stanek, Adv. Carbohydr. Chem. Biochem., 34, 23, (1971), and P.J. Hodges and G. Procter, Tetrahedron Letters, 34, 4111, (1985) and references therein.
7. E.J. Corey, L.O. Weigel, A.R. Chamberlin and B. Lipschutz, J. Amer. Chem. Soc., 102, 1439, (1980).
8. S.J. Angyal and K. Dawes, Aust. J. Chem., 21, 2747, (1968).

(Received in UK 20 November 1985)