Tetrahedron Letters,Vol.24,No.6,pp 587-588,1983 0040-4039/83/060587-02$03.00/0
Printed in Great Britain

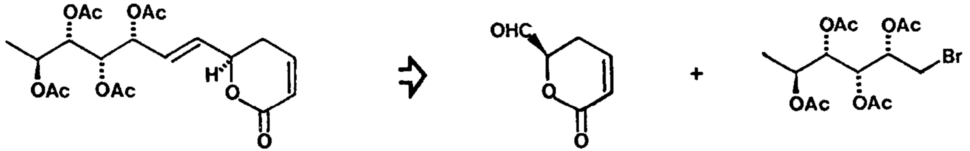
A SYNTHETIC APPROACH TO (+)-ANAMARIN
SYNTHESIS OF A PRECURSOR OF THE SIDE-CHAIN

Frédéric GILLARD and Jean-Jacques RIEHL
Institut de Chimie, Université Louis Pasteur
BP 296/R8 67008 STRASBOURG (FRANCE)

Abstract : *The synthesis of the enantiomerically pure bromide* 3, *precursor of the (+)-anamarin side-chain is described from D-gulonolactone.*

The synthesis of enantiomerically pure compounds has received increasing attention over the past years, especially to produce physiologically active compounds. One of the most direct approaches to their synthesis is the use of carbohydrates or other enantiomerically pure building blocks of natural origin (1).

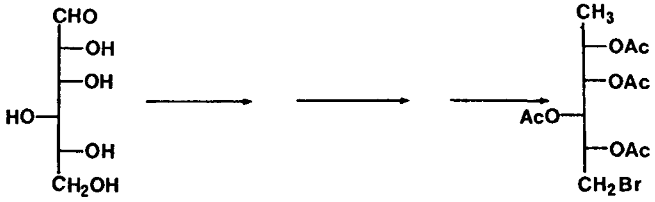
We report here the first part of our synthetic approach to (+)-anamarin 1, an unsaturated δ-lactone with a tetraacetoxylated side-chain, isolated from an unclassified Hyptis species by S. VALVERDE et al. (2). A retrosynthetic analysis of its structure, determined by X-ray studies (3), shows that (+)- anamarin 1 may be obtained by a Wittig reaction between aldehyde 2 and the Wittig reagent derived from bromide 3. The synthesis of the latter compounds, which can be planned from D-gulose 4, is described in this letter.



1, anamarin

2

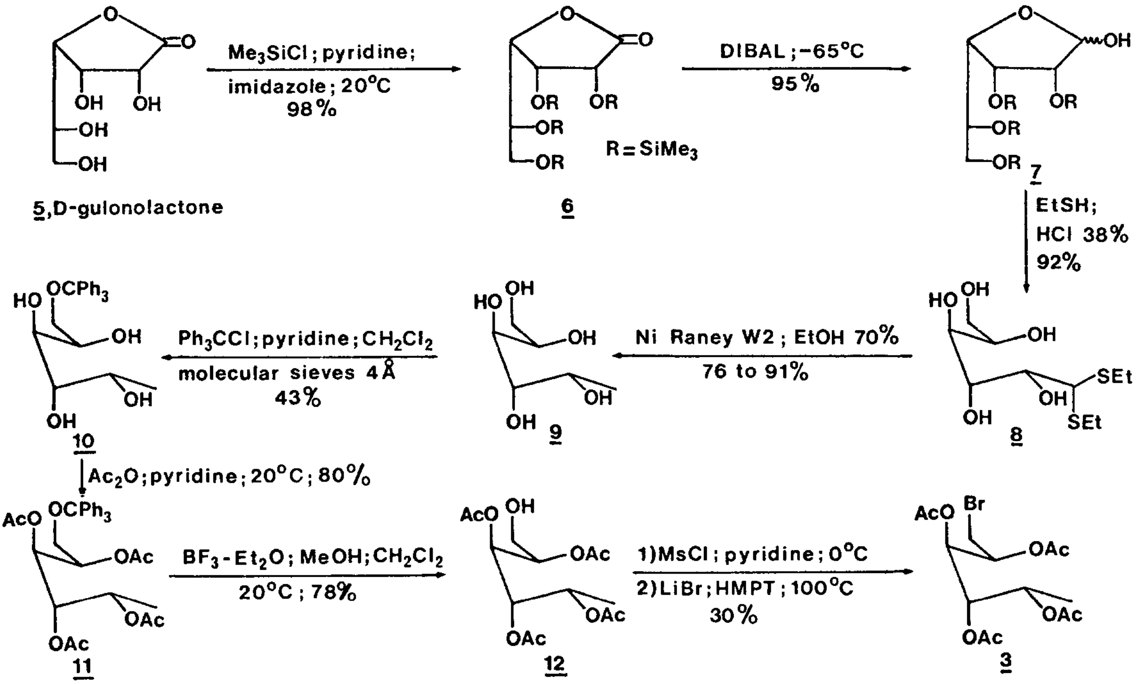
3



4, D-gulose

3

Since D-gulose 4 is very expensive, we used the cheaper D-gulonolactone 5 as starting material. D-gulonolactone 5 was silylated (5.0 eq. Me_3SiCl ; pyridine ; imidazole ; 20°C ; yield : 98 %) to give compound 6 ($[\alpha]_D^{29} = +19.3°$, c = 3.28, CCl_4), which was reduced without purification (2.0 eq. $i\text{-}Bu_2AlH$; toluene ; -65°C ; yield : 95 %) into the unstable hemiacetal 7. Treatment of 7 with ethanethiol by Cooper's method (4) (excess HSEt ; HCl 38 % ; 0°C ;



yield : 90-92 %) afforded thioacetal 8 (m.p. = 84.5-85.5°C ; $[\alpha]_D^{27}$ = -12.1°, c = 1.443, EtOH). Reduction of 8 with Raney Nickel W2 (5) (15 eq. (w/w) Raney Ni W2 ; EtOH 70 % ; reflux ; yield : 76 to 91 %) yields 1-deoxy-D-gulitol 9 ($[\alpha]_D^{27}$ = +1.45°, c = 3.105, EtOH). Tritylation of the primary hydroxy group of 9 by Kohli's method (6) (1.5 eq. ϕ_3CCl ; pyridine ; 4 Å molecular sieves ; CH_2Cl_2, 20°C ; yield 43 %) gives 10 ($[\alpha]_D^{26}$ = + 9.2°, c = 2.44, $CHCl_3$), which was peracetylated with an excess of acetic anhydride in pyridine to furnish compound 11 ($[\alpha]_D^{27}$ = -23.7°, c = 3.45, $CHCl_3$) in 80 % yield. Detritylation with BF_3 in methanol-methylene chloride (7) gives alcohol 12 ($[\alpha]_D^{24}$ = -10.3°, c = 3.71, $CHCl_3$) in 78 % yield. Sequential treatment of 12 with excess mesyl chloride in pyridine at 0°C and LiBr (10 eq ; HMPA ; 100°C) gives bromide 3 ($[\alpha]_D^{24}$ = -4.5°, C = 0.53, $CHCl_3$) in 30 % yield. Further synthetic work directed toward the total synthesis of (+)-anamarin is underway.

REFERENCES

1)a) D. SEEBACH and E. HUNGERBUHLER in "Modern Synthetic Methods" 1980, p. 91, R. Scheffold Editor, Salle + Sauerländer, Frankfurt am Main, 1980
b) A. VASELLA ibid, p. 173
2) A. ALEMANY, C. MARQUEZ, C. PASCUAL, S. VALVERDE, A. PERALES, J. FAYOS, M. MARTINEZ-RIPOLL Tetrahedron Lett. 3579 (1979)
3) A. ALEMANY, C. MARQUEZ, C. PASCUAL S. VALVERDE, M. MARTINEZ-RIPOLL, J. FAYOS, A. PERALES Tetrahedron Lett. 3583 (1979)
4) D.J. COOPER, M.D. YUDIS, H.M. MARIGLIANO and T. TRAUBEL - J. Chem. Soc. (C) 2876 (1971)
5) R. MOZINGO - Org. Synth. Coll. Vol. III, 181 ; John Wiley & Sons, Inc., 1955
6) V. KOHLI, H. BLOCKER and H. KOSTER - Tetrahedron Lett. 2863 (1980)
7) K. DAX, W.WOLFLEHNER and H. WEIDMANN - Carbohydr. Res. 65, 132 (1978)

(Received in France 1 October 1982)