Tetrahedron Letters, Vol.31, No.34, pp 4931-4932, 1990
Printed in Great Britain

0040-4039/90 $3.00 + .00
Pergamon Press plc

A SIMPLE AND STEREOSELECTIVE SYNTHESIS OF AVENACIOLIDE FROM D-GLUCOSE

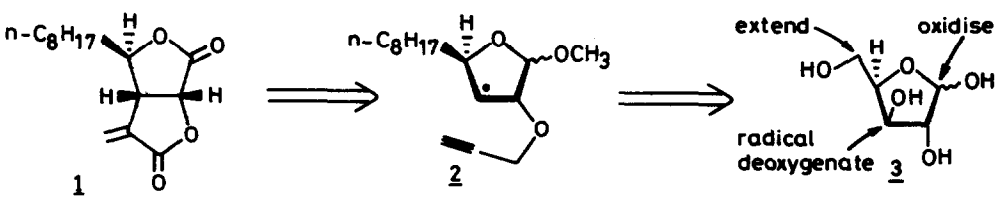
G V M Sharma* and Sreenivasa Rao Vepachedu
Indian Institute of Chemical Technology, Hyderabad 500 007, India

Abstract A stereoselective synthesis of avenaciolide starting from D-glucose, involving intramolecular radical cyclisation, has been described.

Avenaciolide (**1**), a naturally occurring antifungal agent, having an unusual α-methylene bis (butyrolactone) system, has been isolated by Brookes et al[1] from Aspergillus avenaceaus. The unique structural features have earlier resulted in four racemic[2] and three chiral syntheses[3] of **1**. We now wish to describe a stereoselective synthesis of **1**, employing radical mediated cyclisation as the key step.

Retrosynthetic analysis (Scheme 1) of **1** indicated that the radical intermediate **2** would stereoselectively form the C_2-C_3 bond by intramolecular cyclisation and simultaneously incorporate the exo-methylene group at C-2. **2** could be obtained by transformations such as extension of side chain at C-5 and radical generation at C-3 on xylo-sugar **3**, as shown in Scheme 1.

Scheme 1

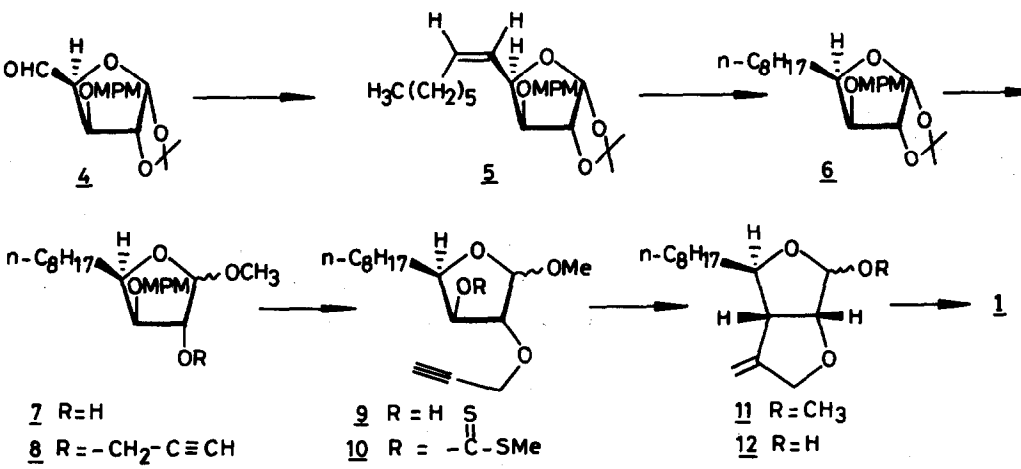


Thus, the first objective of side chain extension was achieved by Wittig olefination reaction ($C_7H_{15}P^+Ph_3Br^-$,nBuLi, THF, RT) on the known aldehyde **4**[4] followed by catalytic hydrogenation of the resultant olefin **5** (10% Pd-C, EtOH, RT, 6 h, 1 atm) to obtain **6** in 60% yield (Scheme 2). Methanolysis (MeOH, Amberlite IR 120 H^+, 80°, 12 h) of **6** afforded **7**, which on reaction with propargyl bromide (NaH, THF, RT, 2 h) gave the propargyl ether **8** (80%). This propargyl ether **8** would be taken to our advantage to perform two different functions, viz., as a protecting group during the transformations at C-3 OH and to provide the needed carbon framework of **1** through intramolecular radical cyclisation. After the deprotection of MPM group (DDQ, aq.CH_2Cl_2 19:1, RT, 1 h) the produced alcohol **9** was converted to the xanthate ester **10** (NaH, CS_2, THF, MeI) which underwent the desired radical cyclisation[5] with n-Bu_3SnH and catalytic amount of AIBN in refluxing benzene for 6 h, to afford a single stereoisomer **11** in 80% yield.

IICT Communication No. 2633

Having obtained the required carbon skeleton of **1**, with all the stereocentres appropriately placed, the remaining two simple transformations were carried out in stepwise manner as shown in Scheme 2. Thus, hydrolysis (AcOH-H_2O-HCl 1:1:0.1, 80°, 1 h) of **11** followed by simultaneous

Scheme 2



oxidation of the allylic methylene and hemiacetal functionalities in **12** with CrO_3-pyridine (CH_2Cl_2, 45°, 1 h) gave avenaciolide (**1**) $[\alpha]_D$ -42.4° (c 0.25, EtOH), lit.[3a] $[\alpha]_D$ -41.6° (c 0.27, EtOH), whose spectral data are in full agreement with the reported[1b] values.

Thus, we have achieved a stereoselective synthesis of **1**, a functionally complex molecule, starting from cheaply available carbohydrate precursor, D-glucose, by demonstrating the power of radical cyclisation for the formation of chiral α-methylene γ-butyrolactone system. This methodology therefore may find wide spread application in the synthesis of natural products with α-methylene γ-butyrolactone moieties.[6]

Acknowledgement The authors thank Drs A V Rama Rao and J S Yadav for the helpful discussions.

References

1. a) D Brookes, B K Tidd and W B Turner, J Chem Soc., 5385 (1965); b) J J Ellis, F H Stodola, R F Vesonder and C A Glass, Nature (London), **203**, 1982 (1964).
2. a) W L Parker and F Johnson, J Org Chem., **38**, 2489 (1973); b) J L Herrmann, M H Berger and R H Schlessinger, J Am Chem Soc., **95**, 7923 (1973); **101**, 1544 (1979); c) H Takai, Y Fukuda, T Taguchi, T Kawara, H Mizutani and T Mukuta, Chemistry Lett., 1311 (1980).
3. a) H Ohuri and S Emoto, Tetrahedron Lett., **16**, 3657 (1975); b) R C Anderson and B Fraser-Reid, J Am Chem Soc., **97**, 3870 (1975); c) S Tsuboi, J Sakamoto, T Sakai and M Utaka, Chemistry Lett., 1427 (1980).
4. K Horita, S Nagato, Y Oikawa and O Yonemitsu, Tetrahedron Lett., **28**, 3253 (1987).
5. A Srikrishna, J C S Chem Comm., 587 (1987) and references cited therein.
6. J C Sharma and R P Sharma, Heterocycles, **24**, 441 (1986).

(Received in UK 19 June 1990)