Tetrahedron Letters,Vol.30,No.46,pp 6271-6274,1989
Printed in Great Britain

0040-4039/89 $3.00 + .00
Pergamon Press plc

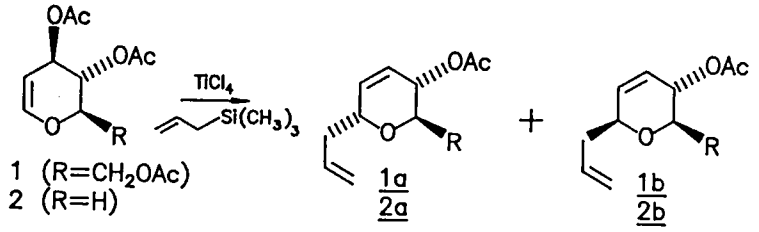
CONFORMATIONALLY RESTRICTED LEUKOTRIENE ANTAGONISTS. SYNTHESIS OF SOME LEUKOTRIENE D_4 ANALOGS FROM D-XYLOSE.

Jeffrey S. Sabol*
Merrell Dow Research Institute
2110 East Galbraith Road, Cincinnati, Ohio 45215, U.S.A.

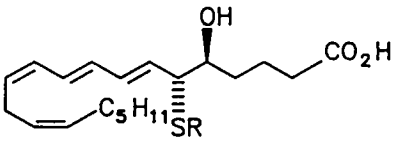
Robert J. Cregge
Merrell Dow Research Institute
9550 North Zionsville Road, Indianapolis, Indiana 46268, U.S.A.

Summary: Lewis acid catalyzed allylation of diacetyl-D-xylal 2 is stereoselective for β-C-glycoside 2b, a result used in the syntheses of pyrans 8a, b, from D-xylose.

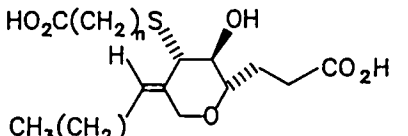
While pursuing approaches to the stereocontrolled syntheses of conformationally-restricted LTD_4 receptor antagonists, we became aware of a highly stereoselective route to C_1-allylated



glycosides bearing C_2-C_3 unsaturation[1] in which reaction of D-glucal triacetate 1 with allyltrimethylsilane (ATMS) under Lewis acid activation led to 1a and 1b in a ratio of 16:1. We felt that this approach could be used as an entry into the synthesis of novel, conformationally-restricted LTD_4 antagonists. Although reaction of diacetyl-D-xylal 2 with ATMS was expected to lead to the C_1-allylated glycosides 2a and/or 2b, we could not predict with certainty the stereochemical outcome of the reaction.



LTD_4 SR=cysteinylglycine



8a n=2
8b n=3

In this letter, we report that the Lewis acid catalyzed allylation of xylal 2, in contrast to 1, is highly stereoselective for the β-C-glycoside 2b, and that this reaction plays a pivotal role in the syntheses of the pyrans 8a, b (Scheme I).

Thus, reaction of diacetyl-D-xylal 2[2], with ATMS and 1 equivalent of $TiCl_4$ following the reported conditions gave rise in 73% yield to a 14:1 (by GC) mixture of C_1-allylated glycosides, with 2b ($[\alpha]_D^{20}$ + 175° (c 1.79, $CHCl_3$)) being the major epimer[1,3] and only regioisomer. Replacement of the acetate group of 2b with a t-butyldiphenylsilyl-ether (TBDPS) in 95% yield for the 2 steps, followed by chemoselective hydroboration-oxidation of the terminal olefin, afforded mono-protected diol 3 ($[\alpha]_D^{20}$ + 54°(c 1.34, $CHCl_3$)) in 74% yield.

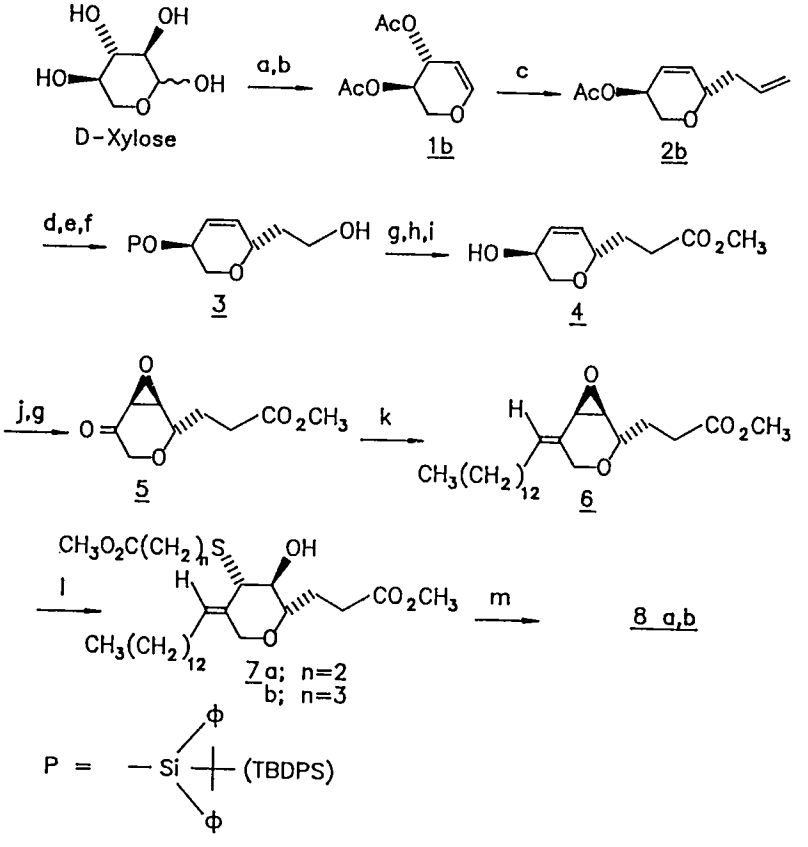
The next phase of the synthesis involved adjusting the oxidation state of alcohol 3 prior to removal of the TBDPS protecting group. This was achieved with a two-step oxidation procedure followed by an acid catalyzed esterification in which the TBDPS group was concomitantly removed; the allylic alcohol 4 ($[\alpha]_D^{20}$ + 95.3°(c 1.16, $CHCl_3$)) was obtained in 52% overall yield for the three steps.[4] Hydroxyl-assisted epoxidation[5] followed by Swern[6] oxidation completed the synthesis of 5[7] ($[\alpha]_D^{20}$ - 12°(c 1.16, $CHCl_3$)).

The completion of the synthesis utilized our previously published procedure.[8] Wittig reaction of 5 under lithium-free conditions[9] was highly stereoselective[10] and afforded E olefin 6 ($[\alpha]_D^{20}$ + 47.2°(c 0.66, $CHCl_3$)) in 72% yield. The double bond geometry was determined using Nuclear Overhauser Enhancement (NOE) difference spectroscopy.[11] Irradiation of the olefinic signal at δ 5.74 (t, 1H, 7.6 Hz) resulted in enhancement (17%) of the epoxy-methine resonance at δ 3.50 (d, 1H, J=4.4 Hz) in addition to a slight NOE (3.5%) with the allylic methylene resonance at δ 1.94-2.09 (m, 2H). Regiospecific opening of the oxirane 6 with either methyl 3-mercaptoproprionate or methyl 4-mercaptobutyrate produced the di-esters 7a and 7b respectively in 85-90% yield. In both cases only S_N2 products were detected, the olefinic resonance at δ 5.86 (t, 1H) clearly excluding any S_N2'-derived product. Saponification of 7a and 7b respectively in 85-90% yield afforded the di-acids 8a[12] ($[\alpha]_D^{20}$ + 26.6° (c 1.02, $CHCl_3$)) and 8b[12] ($[\alpha]_D^{20}$ + 26.2°(c 1.03, $CHCl_3$)). In the 300 mHz ^1H NMR, the -CH-OH coupling constants for 8a (J = 8.9 Hz, 9.4 Hz) and 8b (J = 8.9 Hz, 9.8 Hz) both showed two axial-axial couplings to adjacent ring protons, thereby confirming the trans-equatorial relative stereochemistry of the three contiguous stereogenic centers.

In conclusion, an approach to rigid LTD_4 analogs 8a, b from D-xylose is outlined. These conformationally-restricted analogs effectively antagonized LTD_4 induced contractions of guinea pig ileum in vitro.[13]

Acknowledgements: We thank Dr. Michael Whalon (MDRI-Indianapolis) and Robert J. Barbuch (MDRI-Cincinnati) for their assistance in obtaining analytical data, and Dr. Tim Burkholder (MDRI-Cincinnati) for helpful discussions.

Scheme I



CONDITIONS: a) Ac_2O,HBr,0°; b) Zn,50%HOAc; c) $CH_2{=}CHCH_2Si(CH_3)_3$, $TiCl_4$,CH_2Cl_2,-20°; d) NaOMe,MeOH,rt; e) TBDPS-Cl, imidazole,DMF,rt; f) 9-BBN,THF,Δ(1.5h),then30%H_2O_2,NaOH, EtOH,50°(1h); g) $(COCl)_2$,DMSO,CH_2Cl_2,Et_3N,-70°→rt; h) Ag_2O,NaOH,EtOH,rt(1h); i) $CH_3O\!\!\times\!\!OCH_3$,p-TsOH(cat.), CH_3OH,45°(5h); j) MCPBA,$NaHCO_3$,CH_2Cl_2,rt(20h); k) $KN(TMS)_2$, THF,HMPA,$CH_3(CH_2)_{12}CH_2\overset{\oplus}{P}\phi_3Br^{\ominus}$,-70°→rt; l) $HS(CH_2)_nCO_2CH_3$, Et_3N,MeOH,rt(18h); m) KOH,EtOH,H_2O,rt(6h).

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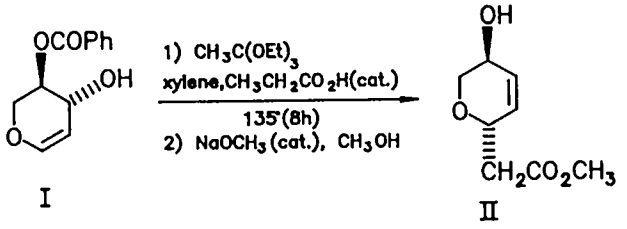
2) Weygand, F. "Methods in Carbohydrate Chemistry," Vol. 1, Academic Press, New York, (1962), 182.

3) Dawe, R.D.; Fraser-Reid, B. J. Chem. Soc., Chem Commun. 1981, 1180. This paper uses triacetylglucal as an alkylating agent with respect to the trimethylsilyl enol ether of acetophenone.

4) This alcohol had identical olefinic couplings in the 300 MHz ^{1}H NMR as alcohol II ($[\alpha]_D^{20}$ + 93.4°(c 1.19, $CHCl_3$)), which was prepared by stereoselective C-glycoside formation via Claisen rearrangement of I, thus confirming the assignment of stereochemistry of 4 and 2b.



I II

5) Henbest, H.B., Proc. Chem. Soc. 1963. 159.

6) Omura, K.; Swern, D. Tetrahedron, 1978, 34, 1651.

7) ^{1}H NMR (300 MHz, $CDCl_3$) δ2.01 (m, 2H), 2.52 (m, 2H), 3.41 (d, 1H, J = 4.2 Hz), 3.57 (dd, 1H, J = 1.1 Hz, 4.2 Hz), 3.70 (s, 3H), 3.91 (d, 1H, J = 16.7 Hz), 4.15 (brdd, 1H, J = 1.1 Hz, 4.5 Hz, 9.5 Hz), 4.17 (d, 1H, J = 16.7 Hz).

8) Sabol, J.S., and Cregge, R. J. Tetrahedron Lett., in press.

9) (a) Sreekumar, C.; Darst, K.P.,; Still, W.C. J. Org. Chem. 1980, 45, 4260 (b) Koreeda, M.; Patel, P.D.; Brown, L., J. Org. Chem. 1985, 50, 5910.

10) A ratio of 7/1 was determined on the crude product by TLC and 60-MHz ^{1}H NMR.

11) The NOE difference spectroscopy experiment was done on a Varian 300 MHz spectrometer by Dr. Edward Huber of MDRI, Cincinnati.

12) These compounds gave satisfactory spectral (IR, MS, NMR) and elemental analyses.

13) Dr. T.H. Gieske (MDRI-Cincinnati), unpublished results.

(Received in USA 25 July 1989)