Tetrahedron Letters, Vol.31, No.16, pp 2229-2232, 1990
Printed in Great Britain

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

NEW SYNTHESES OF THE NOVEL IMMUNOACTIVATOR FR900483

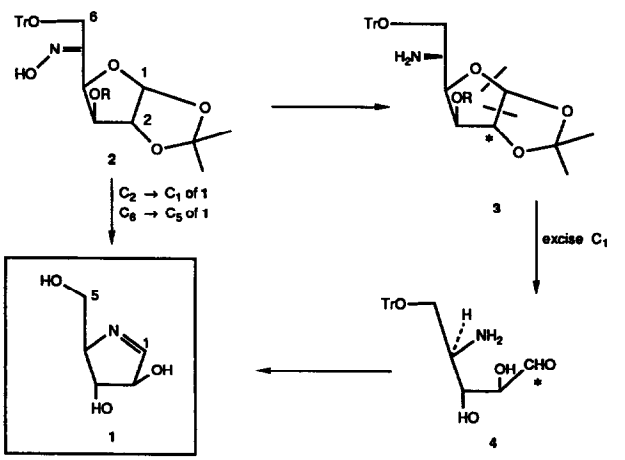
Sui-Hui Chen and Samuel J. Danishefsky
Department of Chemistry, Yale University, New Haven, CT 06511-8118

Summary: Syntheses of the title compound from D-glucal or D-arabinose are reported.

Recently Shibata et. al. described the isolation of metabalite, FR-900483 from the fungus Necritia lucidia 4490.[1,2] The compound was shown to have the structure **1**. A novel kind of biological activity was reported for this substance. A factor isolated from the sera of sarcoma 180 bearing mice has the capacity to inhibit concanavalin A induced lymphocyte production. FR-900483 suppresses this inhibition. It also suppresses similar inhibition occasioned by mitomycin C.

As part of the studies leading to the determination of its structure, FR-900483 was synthesized from a glucose derivative, **2**.[2] Raney Nickel reduction of oxime **2** provided the 5-amino system, **3**. Excision of C_1 was used in generating a synthetic equivalent of the formal aminoaldehyde **4** en route to **1**.

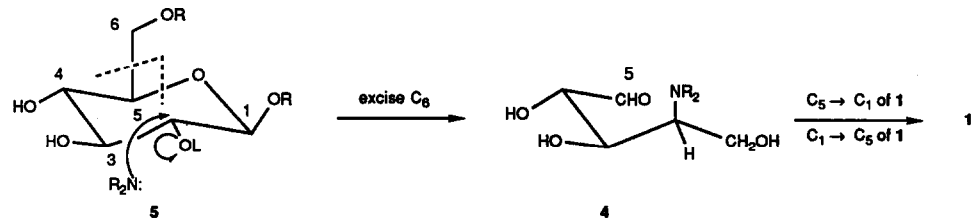
Scheme I



Our interest in applications of the Vasella reaction[3,4] prompted a different proposal for synthesizing **1**. In this alternative view, C_5 of the glucose precursor would emerge as C_1 of compound **1** and C_2 would become C_4. The stereochemistry of C_4 would be controlled by displacement of a leaving group at C_2 of the pyranose by a nitrogen based nucleophile. A

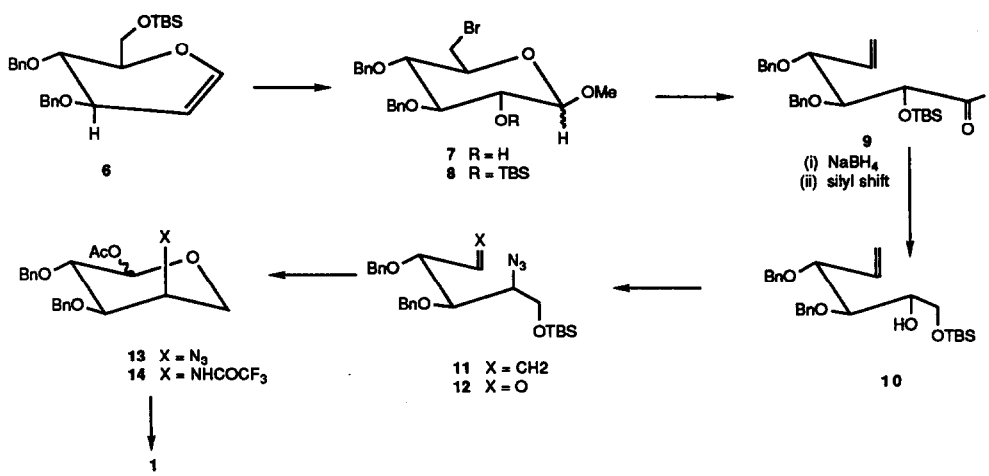
Vasella reaction would be used to pave the way for excising C_6 of the glucose and converting C_5 to the aldehyde level of oxidation. This approach is summarized in Scheme II.

SCHEME II



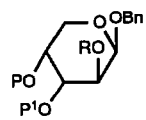
Glycal **6** was prepared from D-glucal (40% overall) by mono silylation (TBS Cl/imidazole) and di-benzylation (NaH; BnBr). Reaction of **6** with MCPBA in methanol[6] followed by disylylation (TBAF-THF) and thence by selective bromination (Ph_3P/CBr_4),[7] afforded compound **7**. Protection of the hydroxyl function with TBSCl-imidazole gave the ether **8** (50-60% from **6**). Treatment of the latter with zinc in aqueous ethanol[3] afforded **9** in 75% yield. Reduction of **1** with sodium borohydride gave rise to **10** *the product of silyl transfer,* in 76% yield. Inversion at C_2 was accomplished (40-45% overall) by triflyation followed by azidolysis (sodium azide, DMF rt.). Ozonolysis (O_3-CH_2Cl_2 -78°) of **11** gave **12** which, upon de-silylation and acetylation gave the pyranosyl acetate **13** in 80% yield. Reduction of the latter ($H_2/Pd/Al_2O_3$) followed by acylation with triflouroacetic anhydride afforded a quantitative yield of **14**. Finally, debenzylation (Pearlman's catalyst)[8] followed by sequential treatment with 1N sodium hydroxide and Dowex acidic resin afforded FR900483[9] in high yield.

SCHEME III

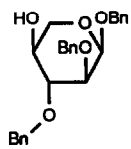


Although this route did demonstrate some of the potentialities of the Vasella reaction,[3] the importance of the goal system prompted us to evaluate an alternate route which turned out to be shorter and more efficient. This route started with **15**[10] derived from D-arabinose. Benzylation (BnBr; Ag_2O) afforded **16**. After cleavage of the acetonide (H_2SO; acetone - water) diol **17** was obtained (65% overall). Preferential (4:1) benzylation at the C_3, rather than the C_4 alcohol via the stannylidene method[11] ((i) nBu_2SnO; (ii)CsF/BnBr DMF) afforded **18** (70%). Inversion of configuration at the C_4 hydroxyl ((i) EtO_2 C N = N CO_2 Et Ph_3P; benzoic acid;[12] (ii) NaOMe/MeOH) gave rise to **19** (55% overall). Triflylation (Tf_2O; Py) and azidolysis (NaN_3/DMF) led to **20** which upon acetolysis[13] at C_1 (conc H_2SO_4; Ac_2O) afforded **14** (65% overall) and thence, as above, FR 900483.

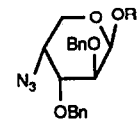
SCHEME IV



15 P, P' = C(Me); R = H
16 P, P = C(Me); R = Bn
17 P, P' = H; = R = Bn
18 P = H, P' = R = Bn



19



20 R = Bn
14 R = Ac

In summary, new routes to **1** via D-glucal and D-arabinose have been developed. These pathways produce various synthetic intermediates which may be helpful in evaluating structure activity relationships of this novel immunomodulator.

Acknowledgments. This work was supported by PHS Grant AI16943. A Department of Education Fellowship from the People's Republic of China to S.-H. C. is gratefully acknowledged. NMR spectra were obtained through the auspices of the Northeast Regional NSF/NMR Facility at Yale University, which is supported by NSF Chemistry Division Grant CHE 7916210.

References and Notes

1. Shibata, T.; Nakayama, O.; Tsurimi, Y.; Okuhara, M.; Terano, H.; Kohsaka, M. *J. of Antibiot.* **1988**, *41*, 296.

2. Kayakiri, H.; Takare, H.; Shighiro, T.; Setor, H.; Uchida, I.; Terano, H.; Hashimoto, M. *Tetrahedron Lett.* **1988**, *29*, 1725.

3. For some striking examples of the Vasella reaction, see: (**a**) Bernet, B.; Vasella, A. *Helvetica Chimica Acta* **1979**, *62*, 2400. (**b**) Bernet, B.; Vasella, A. *Helvetica Chimica Acta* **1984**, *67*, 1328.

4. The Vasella reaction was used at two stages in a recent synthesis of FK506 accomplished in our laboratory. (a) Villalobos, A.; Danishefsky, S. J. *J. Org. Chem.* In Press. (b) Jones, A. B.; R. G. Linde II; Coleman, R. S.; Danishefsky, S. J. *J. Org. Chem.* In Press.

5. Blackburne, I. D.; Fredericks, P. M.; Guthrie, R. D. *Aust. J. Chem.* **1976**, *29*, 381.

6. cf. Sweet, F.; Brown, R. K. *Can. J. Chem.* **1966**, *44*, 1571.

7. Castro, B. C. R.; *Organic Reactions* **1983**, 29.

8. Pearlman, W. M. *Tetrahedron Lett.* **1967**, *10*, 1663.

9. The proton (250 MHz) and ^{13}C spectra NMR of synthetic FR900483 as well as the chromatographic mobilities in two solvent systems agree very closely with reported values. A sample of the compound was not available from Fujisawa.

10. Fletcher, H. G., Jr. *Methods in Carb. Chem. Vol II*, 386.

11. For related cases, see: (a) Ogawa, T.; Matsui, M. *Tetrahedron* **1981**, *37*, 2363. (b) David, S.; Hanessian, S. *Tetrahedron* **1985**, *41*, 643.

12. cf. Mitsonobu, O. *Synthesis* **1981**, *1*.

13. Biermann, C. J. *Advances in Carbohydr. Chem. and Biochem.* **1988**, *46*, 251.

(Received in USA 31 January 1990)