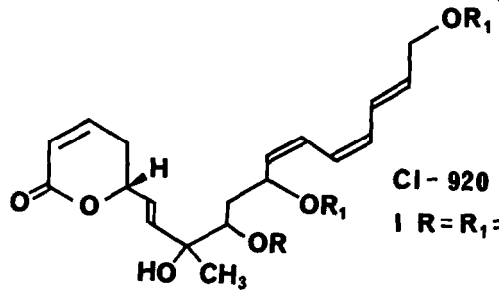
Tetrahedron Letters,Vol.29,No.7,pp 753-756,1988 0040-4039/88 $3.00 + .00
Printed in Great Britain Pergamon Journals Ltd.

# SYNTHESIS OF THE 5R, 8R, 9S, 11R DEPHOSPHORYLATED DERIVATIVE OF CI-920, A NOVEL ANTITUMOR AGENT.

George Just* and Brian O'Connor
Department of Chemistry, McGill University
Montreal, Canada H3A 2K6

**Abstract:** A synthesis of the 5R, 8R, 9S, 11R dephosphorylated derivative of CI-920 is described. It is shown to be different from the naturally occurring dephosphorylated CI-920 where only the 5R stereochemistry has been demonstrated.

In 1984, several articles[1] were published describing CI-920, a structurally novel antibiotic isolated from a fermentation broth of a new actinomycete (*Streptomyces pulveraceus*) that exhibited antileukemic activity against a wide spectrum of tumor cells *in vitro* and *in vivo*. The chemical structure, determined by Hokanson and French[2], was found to possess a 5R configuration. We set out to prepare a diastereomer of the dephosphorylated derivative **I** in an effort to determine the configurations at C(8), C(9) and C(11).

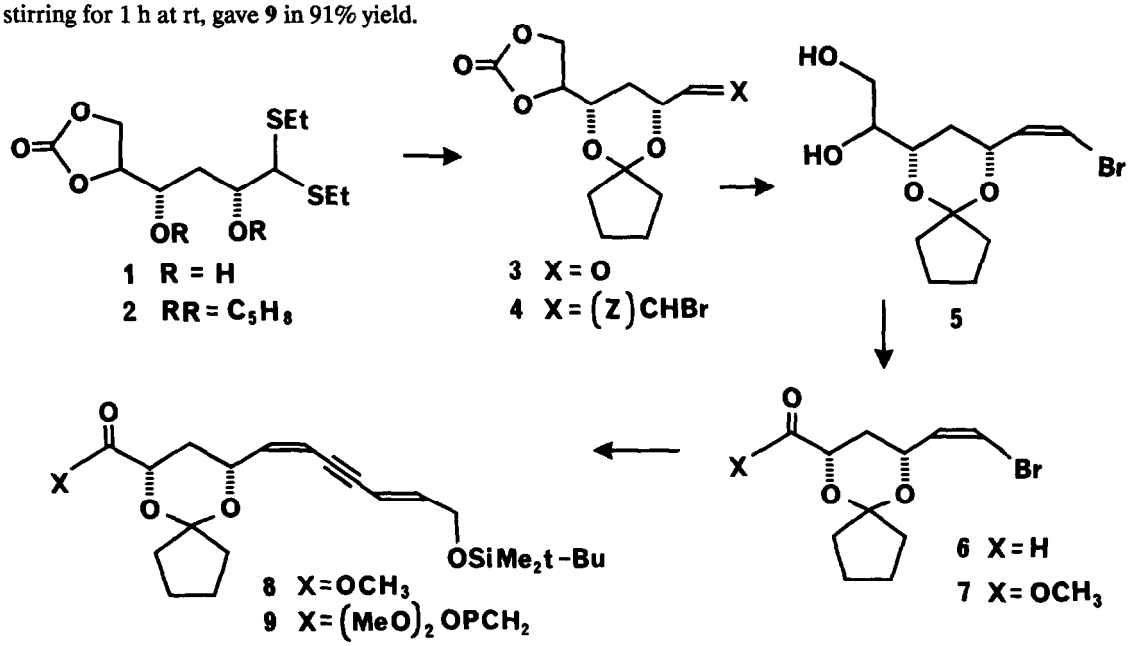



CI - 920 R= $PO_3HNa$ $R_1$= H

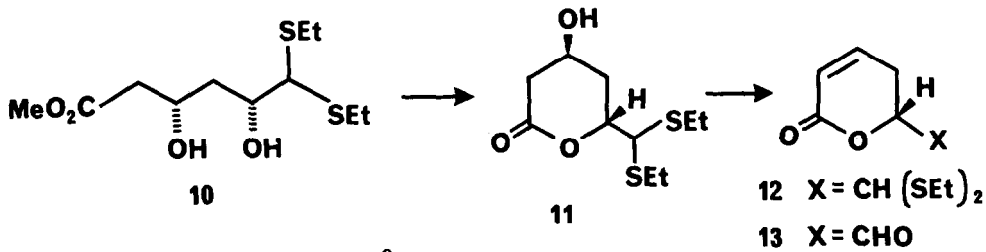
I R= $R_1$= H

The known dihydroxy diethyldithioacetal **1**[3], obtained in four steps from 1,2-*O*-isopropylidene-D-glucofuranose, was protected as the cyclopentanone derivative **2**. Removal of the thioacetal protecting group with mercuric chloride and mercuric oxide provided crude aldehyde **3**, which upon treatment with bromomethylene triphenylphosphorane[4] gave the cis bromo derivative **4** (61% from **2**). Diol **5**, prepared in quantitative yield by treating **4** with a 0.5N NaOH solution in dioxane/water[5], was cleaved with sodium periodate to give aldehyde **6**. Methyl ester **7** was prepared, in one step, by treating **6** with methanol (5 equiv) and pyridinium dichromate (6 equiv) in dry DMF (rt/ 20 h/ 60%)[6]. The dimethyl-t-butylsilyl derivative of the commercially available 2E-penten-4-yne-1-ol, was then coupled with **7** according to the procedure of Sonogashira[7] and Linstrumelle[8] ($(PPh_3)_4Pd$/ CuI/ tert-butylamine/ benzene, rt/ 88%) providing **8**. Treating **8** at -78°C with the anion of dimethyl methylphosphonate (n-Buli/ THF/ -78°C, 30 min) and

stirring for 1 h at rt, gave **9** in 91% yield.




After several unsuccessful attempts, we succeeded in preparing aldehyde **13** from the previously described dithioacetal **10**[9]. Cyclization, affected by treating **10** with p-toluenesulfonic acid in dry methylene chloride at room temperature provided hydroxy lactone **11** in low yield only (35% based on recovered **10**), due to competing side reactions[10]. Treatment of **11** with methanesulfonyl chloride

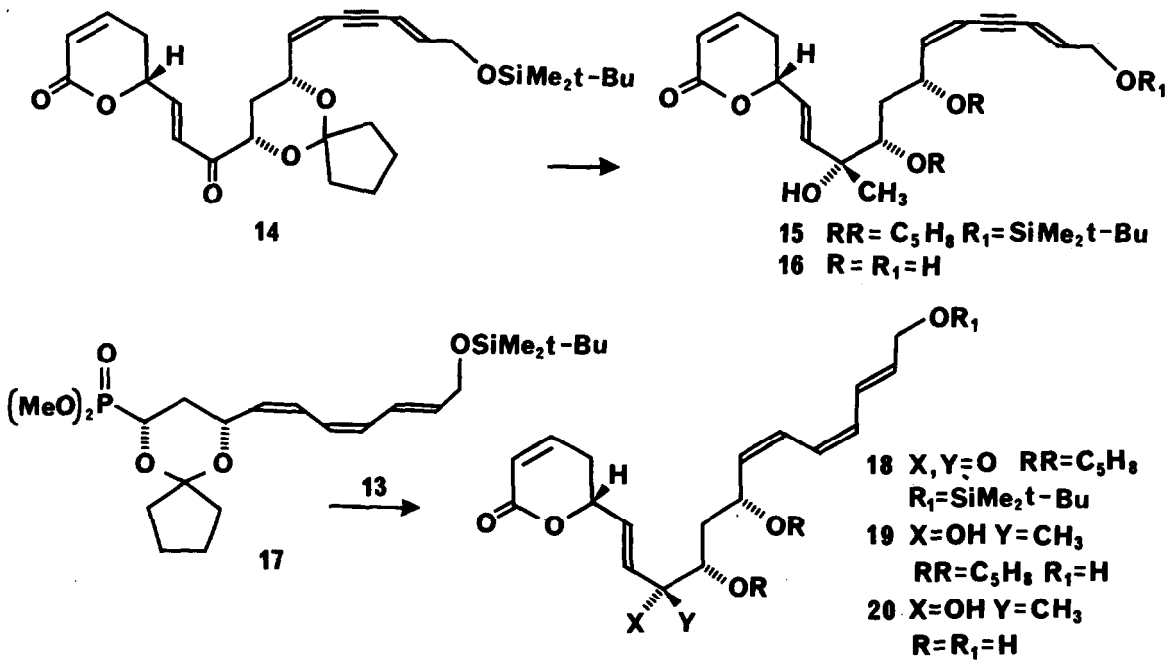



(2 equiv) and triethylamine (4 equiv) at -50$^0$C in dry $CH_2Cl_2$ provided unsaturated lactone **12** in 95% yield.

Attempts to remove the thioacetal protecting group of **12** using $HgCl_2$ and HgO proved unsuccessful. However, the use of N-chlorosuccinimide and silver nitrate[11], provided aldehyde **13** instantaneously. Unfortunately succinimide, which is formed as a by product of the reaction, exhibited an identical $R_F$ value on tlc, making a separation by chromatography impossible. When **12** was treated with bromine in an ether/water solution[12], aldehyde **13** was formed in good yield with diethyldisulfide being the only contaminant. The simple workup (diluting with ethyl acetate and drying over $MgSO_4$) facilitated recovery of

13, although the aldehyde had to be used in its crude form since purification by flash chromatography led to partial decomposition.

Coupling of crude aldehyde **13** with the anion of phosphonate **9** (NaH/ THF/ rt, 30 min) provided trans $\alpha,\beta$-unsaturated ketone **14** in 55% yield ($[\ ]^{22}$ +130.0$^0$ (c 4.0, $CH_2Cl_2$) ). Treatment of **14** with trimethylaluminum (4 equiv) in dry $CH_2Cl_2$ at -15$^0$C for 1 hour gave a 60% yield of tertiary alcohol **15** as a 98:2 mixture of diastereomers. We assume that the major diastereomer would have the 8R configuration, using Crams cyclic model[13]. However, it is not certain whether Cram's model applies with trimethylaluminum as reagent. Removal of the cyclopentanone and silyl protecting groups was effected by treating a solution of **15** in THF with 0.1N HCl and stirring the reaction mixture




overnight. Purification by flash chromatography provided **16** in 60% yield. Hydrogenation of **16** using the Lindlar catalyst, however, resulted in a mixture of overreduced products. We suspected that this overreduction was due to the small amount of material we were working with (6 mg of **16** requires 0.4 mL of hydrogen).

Hydrogenation was then attempted on methyl ester **8** since this was available in near gram quantities. The use of Brown's NiB catalyst[14] on 200 mg of **8** provided, after 1 equiv. of $H_2$ was absorbed, a mixture of

unreacted **8**, the desired triene and several products of overreduction. Preparation of the phosphonate, as described previously, allowed for the separation of **17** from the other products obtained in the hydrogenation reaction. The following sequence of reactions were run using the conditions described for the acetylenic derivatives **14-16**. Coupling of phosphonate **17** with crude aldehyde **13** provided trans unsaturated ketone **18** in 50% yield. Treatment of **18** with trimethylaluminuma gave a 65% yield of the 8R tertiary alcohol **19**. Removal of the protecting groups then provided the 5R, 8R, 9S, 11R dephosphorylated derivative **20**[15]. The $^{13}C$ NMR spectra (400 MHz, $D_2O$) of **20** was found to be different from that reported for the natural dephosphorylated derivative.

Efforts are currently underway to prepare the remaining diastereomers.

**Acknowledgements**

We thank the Natural Sciences and Engineering Research Council of Canada, the Ministry of Education, Province of Quebec and Lederle Laboratories for financial support, and Drs. Orval Mamer, Medical Mass Spectrometry Unit, McGill University, and John Finkenbine for mass spectra.

**References and Notes**

1) a) Tunac, J.B.; Graham, B.D.; Dobson, W.E. *J. Antibiotics,* **1983**, *36*, 1595. b) Stampwala, S.S.; Bunge, R.H.; Hurley, T.R.; Willmer, N.E.; Brankiewicz, A.J.; Steinman, C.E.; Smitka, T.A.; French, J.C. *J. Antibiotics*, **1983**, *36*, 1601. c) Leopold, W.R.; Shillis, J.L; Mertus, A.E.; Nelson, J.M.; Roberts, B.J.; Jackson, R.C. *Cancer Research*, **1984**, *44*, 1928.
2) Hokanson, G.C.; French, J.C. *J. Org. Chem.*, **1985**, *50*, 462.
3) Unpublished results in the Ph.D. thesis of P. Potvin, McGill Univ. **1981**.
4) Matsumoto, M.; Kurodo, K. *Tetrahedron Lett.*, **1980**, *21*, 4021.
5) Letsinger, R.L.; Ogilvie, K.K. *J. Org. Chem.*, **1967**, *32*, 296.
6) O'Connor, B.; Just, G. *Tetrahedron Lett.*, **1987**, *28*, 3235.
7) Sonogashira, K.; Tohda, Y.; Hagihara, N. *Tetrahedron Lett.*, **1975**, *50*, 4467.
8) Ratevelomana,V.; Linstrumelle, G. *Synthetic Comm.*, **1981**, *11*, 917.
9) O'Connor, B.; Just, G. *Tetrahedron Lett.*, **1986**, *27*, 5201.
10) The results of the unsuccessful attempts and the competing side reactions will be discussed in a full paper.
11) Corey, E.J.; Erickson, B.W. *J. Org. Chem.*, **1971**, *36*, 3553.
12) Defaye, J. *Bull. Soc. Chim. Fr.*, **1964**, 2686.
13) Cram, D.J.; Wilson, R.J. *J. Am. Chem. Soc.*, **1963**, *85*, 1245.
14) Brown, H.C.; Brown, C.A. *J. Am. Chem. Soc.*, **1963**, *85*, 1005.
15) $^1H$ (400 MHz,$D_2O$) of **20**: 1.24-1.33 (m, 1H, C(10)H), 1.27 (s, 3H, $CH_3$), 1.70-1.79 (m, 1H, C(10)H), 2.52-2.70 (m, 2H, C(4)H), 3.37 (dd, 1H, J=9.8 Hz, J=2.4 Hz, C(9)H), 4.20 (d, 2H, J=5.7 Hz, C(18)H), 4.80-4.90 (m, 1H, C(11)H), 5.08-5.17 (m, 1H, C(5)H), 5.40-5.48 (m, 1H, C(12)H), 5.84-6.07 (m, 4H, C(2)H, C(6)H, C(7)H, C(17)H), 6.20 (t, 1H, J=11.2 Hz, C(15)H), 6.36 (t, 1H, J=11.5 Hz, C(14)H), 6.73 (t, 1H, J=11.4 Hz, C(13)H), 6.82 (dd, 1H, J=14.9 Hz, J=12.0 Hz, C(16)H), 7.12-7.17 (m, 1H, C(3)H); $^{13}C$ (400 MHz, $D_2O$) of **20**: 24.341, 30.514, 39.642, 63.530, 66.808, 75.753, 76.697, 80.232, 120.925, 125.403, 127.518, 127.914, 132.448, 134.354, 135.833, 139.232, 139.356, 150.532, 175.407; ms ($NH_3$-desorption CI); 333($M^+$ + 1-$H_2O$), 315 ($M^+$ + 1 - 2$H_2O$), 297($M^+$ + 1-3$H_2O$), 281 ($M^+$ + 1 - 4$H_2O$).

(Received in USA 17 August 1987)