Carbohydrate Research, 130 (1984) C1–C3
Elsevier Science Publishers B.V., Amsterdam – Printed in The Netherlands

Preliminary communication

Synthesis of antitumor-active (7*S*,9*S*)-4-demethoxy-7-*O*-(2,6-dideoxy-2-iodo-α-L-mannopyranosyl)adriamycinone: preparative resolution of a racemic anthracyclinone by alkoxyhalogenation of a glycal*

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(Received April 19th, 1984; accepted for publication, May 1st, 1984)

Various 2′-halo-3′-hydroxy analogs[1] of daunorubicin[2], doxorubicin[2], and 4-demethoxydaunorubicin[2] have demonstrated high antitumor activity *in vivo*, and low cardiotoxicity[1]. We demonstrate here how L-rhamnal diacetate may be used in oxyiodination of a derivative of racemic 4-demethoxydaunomycinone[3–5] to resolve the aglycon and furnish the optically pure, crystalline, title compound **6**; its 7*R*,9*R* isomer (**8**) was biologically inactive.

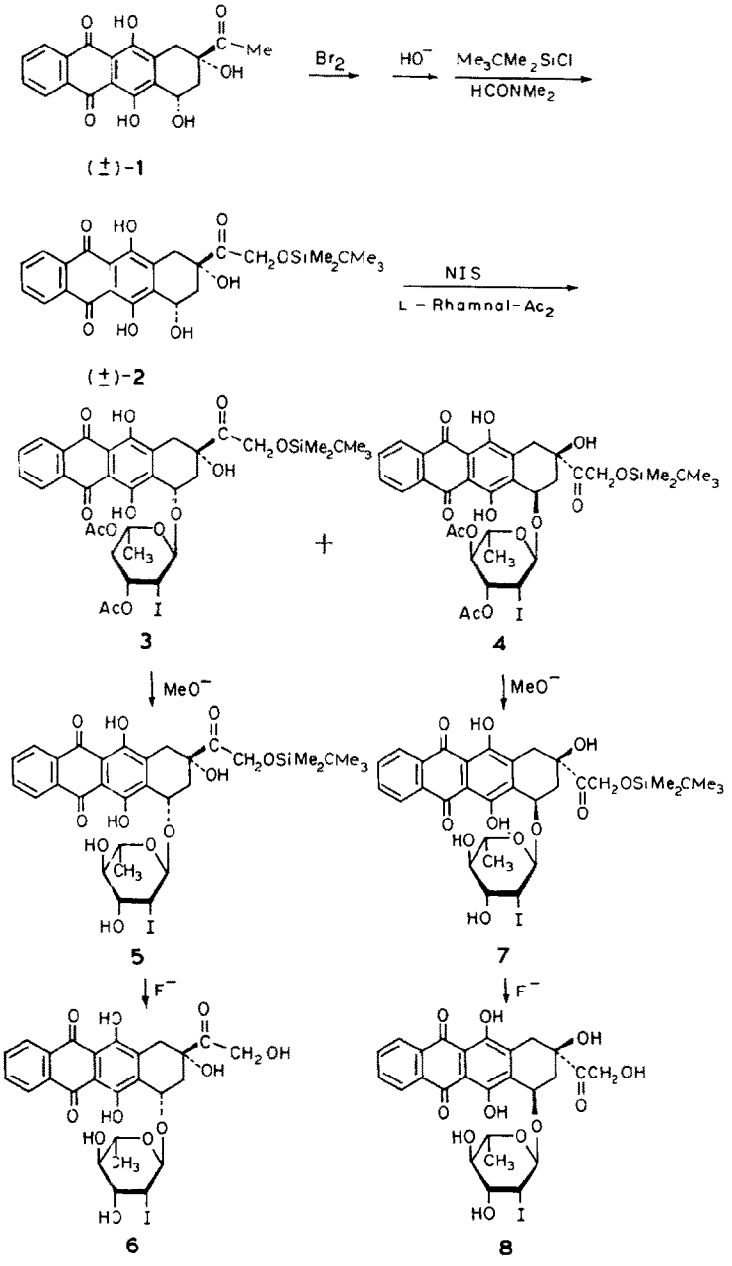
Racemic 4-demethoxydaunomycinone[3–5] (**1**) was converted by the general procedure of Smith *et al.*[6] into its 14-bromo derivative, which was then readily hydrolyzed by aqueous potassium carbonate[7], or by heating for 0.5–1 h at ~80° in dimethyl sulfoxide–water solution, to afford racemic 4-demethoxyadriamycinone. The latter was then silylated with *tert*-butylchlorodimethylsilane in *N*,*N*-dimethylformamide in the presence of imidazole to give racemic 14-*O*-(*tert*-butyldimethylsilyl)-4-demethoxyadriamycinone (**2**) in 54% yield as red crystals** having m.p. 193–195°.

Solutions of compound **2** (1.26 mmol) in oxolane and of 3,4-di-*O*-acetyl-L-rhamnal (1.95 mmol) in acetonitrile were mixed under dry argon, and *N*-iodosuccinimide (NIS; 2.68 mmol) was added with stirring[8]. After 3 h, further portions of 3,4-di-*O*-acetyl-L-rhamnal (1.91 mmol) and *N*-iodosuccinimide (2.64 mmol) were added. The reaction was terminated after a further 3 h. Chromatography of the product-mixture on a column of silica gel, with 50:1 toluene–acetone as the eluant, and crystallization, afforded 27% of (7R,9R)-*14*-O-(tert-*butyldimethylsilyl*)-*4-demethoxy-7*-O-(*3,4-di*-O-*acetyl-2,6-dideoxy-2-iodo*-α-L-*mannopyranosyl*)*adriamycinone* (**4**) as the less-polar component; m.p. 153°; $[\alpha]_D^{25}$ −209° ($CHCl_3$); ^{1}H-n.m.r.: δ 5.53 (d, 1 H, H-1′), 5.50 (m, 1 H, H-7), and 4.53 (dd, 1 H, $J_{1',2'}$ 1.6, $J_{2',3'}$ 4.3 Hz, H-2′).

The more-polar diastereoisomer, namely, (7S,9S)-*14*-O-(tert-*butyldimethylsilyl*)-*4*-

*Dedicated to Professor Raymond U. Lemieux.
**All products described were chromatographically homogeneous, and gave satisfactory elemental analyses, and their ^{1}H-n.m.r. spectra (200 MHz, $CDCl_3$) substantiated their homogeneity and were assigned in detail.

0008-6215/84/$03.00



demethoxy-7-O-(3,4-di-O-acetyl-2,6-dideoxy-2-iodo-α-L-mannopyranosyl)adriamycinone (**3**), was isolated in 29% yield as a red solid having m.p. 128–130°, $[\alpha]_D^{22}$ +44° ($CHCl_3$); ^{1}H-n.m.r.: δ 5.75 (bs, 1 H, H-1′), 5.26 (dd, 1 H, H-7), and 4.63 (dd, 1 H, $J_{1',2'}$ 1.4, $J_{2',3'}$ 4.4 Hz, H-2′).

Saponification of compound **3** with methanolic sodium methoxide gave 51% of (7S,9S)-*14*-O-(tert-*butyldimethylsilyl*)-*4-demethoxy-7*-O-(*2,6-dideoxy-2-iodo*-α-L-*manno-pyranosyl*)*adriamycinone* (**5**) as red crystals having m.p. 179–181°, $[\alpha]_D^{22}$ +15° ($CHCl_3$); ^{1}H-n.m.r.: δ 5.77 (s, 1 H, H-1′), 5.24 (dd, 1 H, $J_{7,8e}$ 1.9 Hz, H-7), and 4.54 (dd, 1 H, $J_{1',2'}$ <1.0, $J_{2',3'}$ 4.1 Hz, H-2′); ^{13}C-n.m.r. (50 MHz, $CDCl_3$): δ 104.8 (C-1′), 76.9 (C-9), 75.5 (C-4′), 70.5 (C-7,5′), 69.3 (C-3′), and 36.9 (C-2′).

Compound **5** was desilylated in dichloromethane–oxolane with tetrabutylammonium fluoride in oxolane. Crystallization from dichloromethane–acetone–hexane gave 41% of (7S,9S)-*4-demethoxy-7*-O-(*2,6-dideoxy-2-iodo*-α-L-*mannopyranosyl*)*adriamycinone* (**6**) as a red solid, m.p. 173–175° (dec.); ^{1}H-n.m.r. (acetone-d_6): δ 5.73 (s, 1 H, H-1′), 5.26 (dd, 1 H, $J_{7,8a}$ 5.0, $J_{7,8e}$ 3.0 Hz, H-7), and 4.52 (dd, 1 H, $J_{1',2'}$ 1.0, $J_{2',3'}$ 4.0 Hz, H-2′).

By similar conversions, the protected 7*R*,9*R* derivative **4** was saponified to give **7**, m.p. 200–201°, $[\alpha]_D^{25}$ −237° ($CHCl_3$), which was desilylated to the product **8**, m.p. 180–181° (dec.).

In the *in vivo*, murine P-388 lymphocytic leukemia assay (single i.p. injection on day 1), compound **6** showed T/C 218 at a dose of 3.12 mg/kg, whereas compound **8**, in which the aglycon has the unnatural enantiomeric configuration, was essentially inactive at doses up to 20 mg/kg.

The procedure described herein constitutes a facile, synthetic route to optically pure 4-demethoxydoxorubicin analogs from racemic 4-demethoxydaunomycinone, and demonstrates the general feasibility of using a chiral sugar for the resolution of racemic aglycons of the adriamycinone type.

ACKNOWLEDGMENTS

The authors thank Drs. D. Lednicer and R. Wolgemuth of Adria Laboratories, Dublin, Ohio, for a supply of compound **1** and for arranging the biological screening.

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