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THE FIRST TOTAL SYNTHESIS OF A POTENT ß-RHODOMYCIN, OXAUNOMYCIN: REGIOSELECTIVE GLYCOSIDATION OF THE C-7 HYDROXYL GROUP OF ß-RHODOMYCINONE

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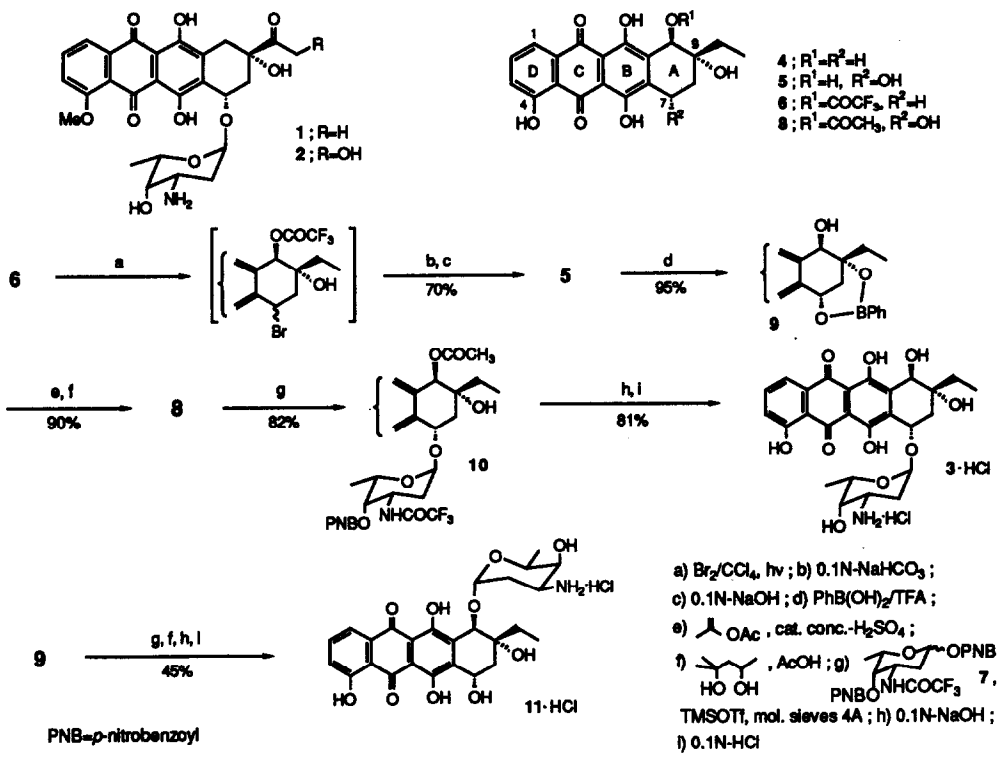
Summary: The first total synthesis of oxaunomycin (3) was achieved through a regioselective glycosidation of the C-7 hydroxyl group of ß-rhodomycinone (5).

Anthracycline antibiotics, daunomycin (1) and adriamycin (2) are powerful antitumor agents in the treatment of a broad spectrum of human cancers.[1] A new potent rhodomycin, oxaunomycin (3) has now been assumed to have a considerable clinical importance since it was found to be about 100-fold more active than 2 against leukemic L1210 culture.[2] Very recently, we communicated an asymmetric synthesis of (-)-γ-rhodomycinone (4) using regioselective coupling reaction of the new chiral AB and CD building blocks[3] and now succeeded in a total synthesis of 3 from 4 involving a novel regioselective glycosidation of ß-rhodomycinone (5).

ß-Rhodomycinone (5) was obtained from O-trifluoroacetate (6) of 4 by a similar method to Krohn's[4]: The C-7 bromide obtained from 6 was treated with 0.1N-$NaHCO_3$ to give the 7,9-cis-diol, which was detrifluoroacetylated with 0.1N-NaOH to give 5 [mp 227-230°C, $[\alpha]_D^{25}$ = +111° (c=0.047, $CHCl_3$)] . This was identical with natural ß-rhodomycinone.

For the total synthesis of 3, the regiochemistry of glycosidation has to be controlled. Thus, glycosidation of 5 with the 1,4-bis(O-p-nitobenzoyl)-L-daunosamine derivative (7) using trimethylsilyl triflate (TMSOTf)[6] resulted in an inseparable mixture (2:1) of the C-7 and C-10 O-glycosides in 50% yield. Regioselective C-7-O-glycosidation of 5 was accomplished by the use of the C-10-O-acetylated compound (8): The phenylboronate (9), readily obtained from 5 and $PhB(OH)_2$ in trifluoroacetic acid (TFA),[7] was acetylated with isopropenyl acetate, which was deboronated with 2-methylpentane-2,4-diol and acetic acid to give 8 in 85% overall yield from 5. Glycosidation of 8 with 7 in the presence of TMSOTf gave the C-7-O-glycoside (10) in 82% yield, which was deprotected with 0.1N-NaOH to give 3. The hydrochloride (3·HCl) was identical[8] with natural oxaunomycin·HCl. The regioisomer (11·HCl) was obtained by direct glycosidation of 9 with 7 followed by deprotection as described above.

The present method is useful for the synthesis of other oxaunomycin analogues.



References and Notes

1 Reviews on biological activities: S. T. Crooke and S. D. Reich (eds.), "Anthracyclines: Current Status and New Developments," Academic Press, New York, 1980; T. Oki and T. Takeuchi, Yuki Gosei Kagaku Kyokai Shi, 40, 2 (1982); F. Arcamone, Med. Res. Rev., 4, 153 (1984). Reviews on synthetic studies: S. Terashima, Yuki Gosei Kagaku Kyokai Shi, 40, 20 (1982); M. J. Broadhurst, C. H. Hassall, and G. J. Thomas, Chem. Ind. (London), 1985, 106; K. Krohn, Ang. Chem. Int. Ed. Engl., 25, 790 (1986); Y. Tamura and Y. Kita, Yuki Gosei Kagaku Kyokai Shi, 46, 205 (1988); K. Krohn, Tetrahedron, 46, 291 (1990).

2 A. Yoshimoto, S. Fujii, O. Johdo, K. Kubo, T. Ishikura, H. Naganawa, T. Sawa, T. Takeuchi, and H. Umezawa, J. Antibiot., 39, 902 (1986).

3 H. Fujioka, H. Yamamoto, H. Kondo, H. Annoura, and Y. Kita, J. Chem. Soc., Chem. Commun., 1989, 1509.

4 K. Krohn and I. Hamann, Liebigs Ann. Chem., 1988, 949. Although Krohn obtained 5 from 6 by bromination followed by solvolysis of both bromo and trifluoroacetyl groups at the same time with 0.1N-$NaHCO_3$, the melting point (195°C) is different from the reported value (lit.[5] mp 224-225°C). Therefore, a stepwise hydrolysis was done.

5 H. Brockmann, P. Boldt, and J. Niemeyer, Chem. Ber., 96, 1356 (1963).

6 Y. Kimura, M. Suzuki, M. Matsumoto, R. Abe, and S. Terashima, Bull. Chem. Soc. Jpn., 59, 423 (1986).

7 cf. M. J. Broadhurst, C. H. Hassall, and G. J. Thomas, J. Chem. Soc., Perkin Trans. 1, 1982, 2239; Y. Tamura, M. Kirihara, J. Sekihachi, R. Okunaka, S. Mohri, T. Tsugoshi, S. Akai, M. Sasho, and Y. Kita, Tetrahedron Lett., 28, 3971 (1987).

8 3 HCl [mp 208-210°C, $[\alpha]_D^{25}$ = +98° (c=0.012, EtOH) : natural oxaunomycin·HCl [mp 209-211°C $[\alpha]_D^{25}$ = +100° (c=0.013, EtOH)] generously provided by Dr. Akihiro Yoshimoto (Sanraku Inc.)

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