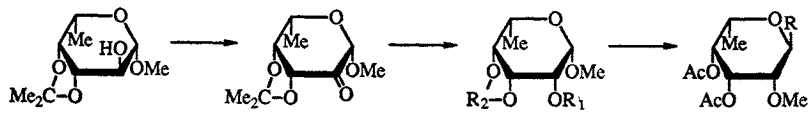
SYNTHESES AND ANTITUMOR ACTIVITIES OF 7-*O*-(6-DEOXY-2-*O*-METHYL-α-L-TALOPYRANOSYL)-DAUNOMYCINONE AND -ADRIAMYCINONE

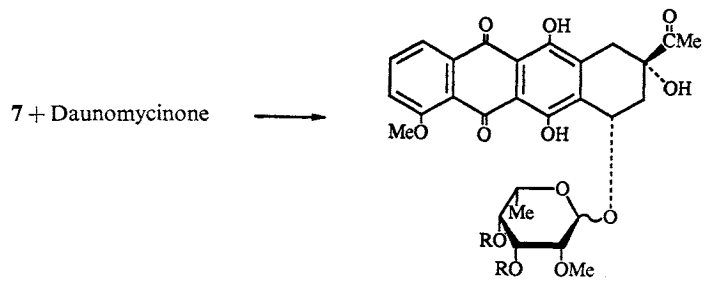
Sir:

As described in preceding papers[1~4], we prepared several fluorine-containing daunorubicin and doxorubicin analogs and showed that a combination of α-side 2′-fluoro and α-side 3′-hydroxyl substituents in the sugar moiety gave the most promising compounds in terms of anticancer activity. In this paper we describe the synthesis and activities of analogs **10** and **14** having an α-side 2′-methoxyl group with α-L-talopyranoside structure instead of the 2′-fluorine. The methoxyl group is electron-attractive similar to the fluorine atom although the action is weaker than the fluorine atom, therefore, **10** and **14** should show similar activities to those of the corresponding fluorine analogs. Interestingly steffimycins[5] and nogalamycin[6], the anthracycline antibiotics of natural origin, have an α-side 2-methoxyl group at C-2 of the sugar moieties.

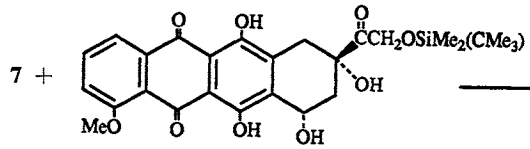
3,4-Di-*O*-acetyl-6-deoxy-2-*O*-methyl-α-L-talopyranosyl bromide (**7**) has been prepared



1 **2** **3** R_1=H R_2=CMe_2 **6** R=OAc
4 R_1=Me R_2=CMe_2 **7** R=Br
5 R_1=Me R_2=H, H



8 α-L-Anomer R=Ac
9 β-L-Anomer R=Ac
10 α-L-Anomer R=H



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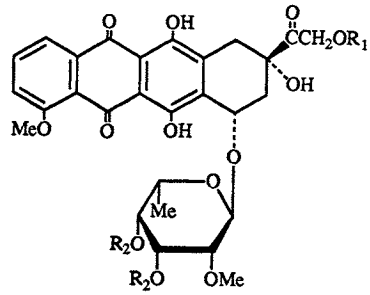

12 R_1=$SiMe_2(CMe_3)$ R_2=Ac
13 R_1=$SiMe_2(CMe_3)$ R_2=H
14 R_1=R_2=H
15 R_1=H R_2=Ac
16 R_1=SO_3Na R_2=Ac
17 R_1=SO_3Na R_2=H

from methyl 3,4-*O*-isopropylidene-β-L-fucopyranoside (**1**)[2] *via* 6 steps. Oxidation of **1** with pyridinium chlorochromate (in CH_2Cl_2 in the presence of powdered Molecular Sieves 3A) gave the 2-oxo derivative (**2**, 73%), mp 64~65.5°C, which, on reduction with $LiAlH_4$ (in THF, 0°C to room temperature), gave the β-L-talopyranoside (**3**, 83%): MP 91~92°C; $[\alpha]_D^{21}$ +17° ($CHCl_3$); ^1H NMR ($CDCl_3$) δ 4.36 (1H, d, 1-H), 3.76 (1H, ddd, 2-H); $J_{1,2}$=1.5 Hz, $J_{2,3}$=5 Hz, $J_{2,OH}$=8.5 Hz. Methylation of **3** with MeI (in MeCN in the presence of Ag_2O, 80°C) gave the 2-*O*-methyl derivative (**4**, 89%): MP 116~118°C; ^1H NMR ($CDCl_3$) δ 3.58 and 3.53 (each 3H, s, OCH_3). Deacetonation (aq 80% AcOH, 80°C) gave **5** (98%): MP 102.5~104°C (needles); $[\alpha]_D^{23}$ +91° ($CHCl_3$). Acetylation of **5** (Ac_2O - H_2SO_4, 1:0.03 in $MeNO_2$, 0°C) gave the 1,3,4-tri-*O*-acetyl-6-deoxy-2-*O*-methyl-α-L-talopyranose (**6**, 64%): MP 128.5~130.5°C; $[\alpha]_D^{23}$ −75° ($CHCl_3$); ^1H NMR ($CDCl_3$) δ 6.27 (1H, d, 1-H), 3.53 (3H, s, OCH_3), 2.19, 2.13 and 2.10 (each 3H, s, Ac). Bromination of **6** ($TiBr_4$ in CH_2Cl_2 - EtOAc, 10:1, 27°C) gave the 1-bromide (**7**, syrup, 90%).

Coupling of **7** with daunomycinone was carried out by a Koenigs-Knorr type of reaction (HgO(yellow) - $HgBr_2$ - powdered Molecular Sieves 3A, in CH_2Cl_2) to give the desired α-L-glycoside (**8**, 69%), a red solid: $[\alpha]_D^{20}$ +202° (*c*, 0.1, $CHCl_3$), along with its β-L-anomer (**9**, 9%): $[\alpha]_D^{23}$ +368° (*c* 0.02, $CHCl_3$). Deprotection of **8** (0.2 N aq NaOH, 0°C to room temperature) gave 7-*O*-(6-deoxy-2-*O*-methyl-α-L-talopyranosyl)daunomycinone (**10**, 73%), a red solid: $[\alpha]_D^{22}$ +132° (*c* 0.05, $CHCl_3$ - MeOH, 1:1); ^1H NMR ($CDCl_3$) δ 5.59 (1H, br s, 1′-H), 3.52 (3H, s, 2′-OCH_3), 3.41 (1H, dt, 2′-H), 2.41 (3H, s, 14-CH_3): $J_{1',2'}=J_{2',4'}=\sim 1.5$ Hz, $J_{2',3'}=3.5$ Hz. The α-L-configuration of **10** was confirmed by the observation of nuclear Overhauser effect (NOE) between 1′-H and 2′-OCH_3 in its ^1H-^1H NOE difference spectrum. The corresponding 14-hydroxy compound (**14**) was obtained by coupling of **7** with 14-*O*-*tert*-butyldimethylsilyladriamycinone (**11**)[7] in a similar manner as described for **8**. The coupled compound **12** (52%), a red solid; $[\alpha]_D^{24}$ +166° (*c* 0.05, $CHCl_3$) was deacetylated (with MeONa - MeOH, to give **13** (98%)) and desilylated (aq 80% AcOH, 80°C) to give **14** (72%), a red powder: $[\alpha]_D^{21}$ +129° (*c* 0.02, $CHCl_3$ - MeOH, 1:1); ^1H NMR ($CDCl_3$) δ 5.60 (1H, d, 1′-H), 4.75 (2H, d, CH_2OH), 3.52 (3H, s, 2′-OCH_3).

In order to obtain a water-soluble derivative of **14**, which is sparingly soluble in water, sodium salt of 14-hemisulfate (**17**) was prepared. A reaction intermediate (**12**) was desilylated (aq 80% AcOH, 80°C) to give the 14-hydroxy derivative (**15**, 90%), $[\alpha]_D^{20}$ +190° (*c* 0.02, $CHCl_3$). Sulfation of **15** ($C_5H_5N \cdot SO_3$ in DMF, 80°C, then neutralized with aq NaOH to give **16** (66%)) followed by deacetylation (MeONa - MeOH) gave the water - soluble **17** (81%): $[\alpha]_D^{21}$ +208° (*c* 0.01, $CHCl_3$ - MeOH, 1:1); $[\alpha]_D^{19}$ −82° (*c* 0.02, H_2O); ^{13}C NMR (DMSO-d_6) δ 208.7 (C-13), 67.2 (C-14) (*cf.* **14**: δ 213.7 (C-13), 63.7 (C-14); *Anal* Calcd for $C_{28}H_{29}NaO_{16}S \cdot 2H_2O$: C 47.19, H 4.67, S 4.50. Found: C 47.47, H 4.86, S 4.60.

Table 1. Antitumor activities (T/C, %; 60 days survivor numbers/treated numbers of mice) of **10** and **14** in comparison with daunorubicin (DNR) and doxorubicin (DOX) on L1210.

Compound		Dose (μg/mouse/day)										
		400	200	100	50	25	12.5	6.25	3.13	1.56	0.78	0.39
10	T/C (%)	106*	>463*	>389	137	109	94					
	Survivor	0/4	2/4	1/4	0/4	0/4	0/4					
14	T/C (%)		101*	153*	>477	>494	172	230	141	107	95	103
	Survivor		0/4	0/4	2/4	2/4	0/4	0/4	0/4	0/4	0/4	0/4
DNR·HCl	T/C (%)			117*	151*	193	166	133	130			
	Survivor			0/4	0/4	0/4	0/4	0/4	0/4			
DOX·HCl	T/C (%)			177*	273*	330	208	132	140			
	Survivor			0/4	0/4	0/4	0/4	0/4	0/4			

Leukemia L1210 cells (10^5) were inoculated into CDF_1 mice (20±1 g) intraperitoneally. Drugs were administered daily, starting 24 hours after inoculation, from day-1 to -9, intraperitoneally.

* Toxic.

As shown in Table 1, **10** and **14** showed much improved antitumor activities in comparison with daunorubicin and doxorubicin. The sodium salt of 14-hemisulfate (**17**) was, however, inactive at doses up to 200 μg/mouse/day. These results indicate that introduction of a methoxyl group at C-2′, which strengthens a glycosyl bond as the fluorine atom does, is also expected to give compounds with similarly promising biological activities as those of the corresponding 2′-fluorine compounds.

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YASUSHI TAKAGI
NAOKI KOBAYASHI
TSUTOMU TSUCHIYA*
SUMIO UMEZAWA

Institute of Bioorganic Chemistry, 1614 Ida, Nakahara-ku, Kawasaki, Kanagawa 211, Japan

TOMIO TAKEUCHI
KEIKO KOMURO
CHISATO NOSAKA

Institute of Microbial Chemistry, 3-14-23 Kamiosaki, Shinagawa-ku, Tokyo 141, Japan

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