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# SYNTHESIS AND ANTITUMOR ACTIVITY OF 7-*O*-(3,4-DI-*O*-ACETYL-2,6-DIDEOXY-α-L-*lyxo*-HEXOPYRANOSYL)ADRIAMYCINONE*

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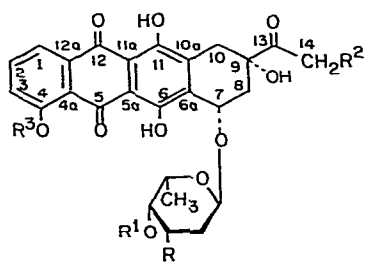
ABSTRACT

The title compound (7), the 3′-acetoxy-4′-*O*-acetyl analog of adriamycin (doxorubicin), was synthesized in ~50% net yield from daunomycinone by bromination at C-14, glycosylation of the product at O-7 with 3,4-di-*O*-acetyl-2,6-dideoxy-α-L-*lyxo*-hexopyranosyl chloride, and replacement of the 14-bromo substituent by a hydroxyl group; other possible routes to 7 gave lower yields. The product 7, a non-aminated analog of the anthracycline antibiotics, showed high antitumor activity coupled with low acute toxicity in a broad range of tests in mice.



| | R | $R^1$ | $R^2$ | $R^3$ |
|---|---|---|---|---|
| 1 | $NH_2$ | H | H | Me |
| 2 | $NH_2$ | H | H | H |
| 3 | $NH_2$ | H | OH | Me |
| 4 | OH | H | H | Me |
| 5 | OAc | Ac | H | Me |
| 6 | OH | H | OH | Me |
| 7 | OAc | Ac | OH | Me |

*For preliminary reports, see refs. 1 and 2.

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## INTRODUCTION

In a quest for semisynthetic, anthracycline antibiotics effective as antitumor agents, but less toxic than such potent, clinically useful[3], microbial products as daunorubicin (**1**), adriamycin (**3**), and carminomycin (**2**), this synthetic program has focused on analogs of **1** modified stereochemically, or functionally, or both, in the sugar residue[4-7]. In many instances, minor modifications of the sugar have been shown[4-7] to bring about severe attenuation or total abolition of antitumor activity. However, the 3′-hydroxy analog (**4**) of daunorubicin (**1**), and its 3′,4′-diacetate **5**, were found[5] to display high antitumor activity in a range of murine assays, and they are markedly less toxic than **1**–**3**. This result discredits a previous notion[8] that the 3′-amino group is essential for biological activity.

As adriamycin (doxorubicin, **3**) has demonstrably higher antitumor efficacy[3,9] than daunorubicin (**1**), persuasive justification was evident for the synthesis and biological evaluation of 3′-oxygenated analogs of **3**, and this is the subject of the present article. It is shown that the 3′,4′-diacetate (**7**) of "3′-hydroxyadriamycin" (**6**) has high antitumor activity in a wide range of tests on mice, and is much less toxic than **3**.

## RESULTS AND DISCUSSION

*Chemical synthesis.* — Of the various approaches possible for synthesis of the 3′-hydroxy analog **6** of adriamycin (**3**) from an available anthracycline precursor, three alternatives appeared the most feasible. In the first, adriamycinone, the aglycon obtained by acid hydrolysis of adriamycin (**3**), would be protected at the primary alcohol group (HO-14), glycosylated at the benzylic (HO-7) position, and the product deprotected. A second possibility, modeled after the demonstrated[10] chemical conversion of daunorubicin (**1**) into adriamycin (**3**), would involve monobromination of 7-*O*-(2,6-dideoxy-α-L-*lyxo*-hexopyranosyl)daunomycinone[4,5] (**4**, the 3′-hydroxy analog of daunorubicin **1**) or its 3′,4′-diacetate (**5**), at C-14, followed by replacement of the bromo group by hydroxyl. The third route would start from daunomycinone (obtained by acid hydrolysis of daunorubicin) with initial bromination at C-14 followed by glycosylation at O-7, subsequent replacement of Br-14 by a hydroxyl group, and final deprotection of the product. The elevated cost of the starting antibiotics **1** and **3** mandated an efficient synthesis giving the final product in high, net yield.

The second of these routes initially appeared the most promising, inasmuch as "3′-hydroxydaunorubicin" (**4**) and its 3′,4′-diacetate (**5**) had been obtained in 25-g amounts in this laboratory, in reactions giving 80–90% net yields from daunomycinone[5]. However, even though the literature[10] conversion of **1** into **3** by this route gave acceptable (~60%) yields in our hands, the reaction of either **4** or **5** under comparable conditions did not give the 14-bromo analogs in satisfactory yield. Numerous variations of the procedure were conducted, but, in all instances, the

reaction gave complex mixtures (t.l.c.), with the major conversion appearing to involve glycosyl–aglycon bond-scission. Detailed speculation on the reason for this behavior is not warranted without further studies, but it is noteworthy that exceptional lability of the sugar–aglycon bond appears to be associated with presence of a 14-substituent and a non-aminated sugar group at O-7, as manifested in the exceptional difficulty encountered in *O*-deacylation of compound **7** (see later), in contrast to the uneventful deprotection of the daunorubicin analog **5** to give **4**, and of various adriamycin derivatives to the parent antibiotic.

In exploring the first route, adriamycinone was protected at HO-14 as the *p*-anisyldiphenylmethyl ether (**8**), as advocated by Henry *et al.*[11], in order to introduce a substituent subsequently removable under very mild, acid conditions. This product was then glycosylated with 2.5 molar equiv. of 3,4-di-*O*-acetyl-2,6-dideoxy-α-L-*lyxo*-hexopyranosyl chloride[12,13] (**9**) in the presence of yellow mercuric oxide, mercuric bromide, and molecular sieve 3A in dichloromethane for 24 h at 25° (the modification of the Koenigs–Knorr conditions found useful for preparative synthesis[5] of compounds **4** and **5**). Glycosidic coupling was accomplished in 87% yield, but t.l.c. indicated that a mixture of two coupled products had been formed. These were readily resolved by column chromatography on silica gel. The major, faster-migrating product was the anticipated 7-*O*-glycosylated derivative **10**, obtained in 70% net yield as a pure, sharp-melting solid whose X-ray powder diffraction pattern showed it to be amorphous. Its homogeneity was further affirmed by its 200-MHz, $^1$H-n.m.r. spectrum (see Experimental section), which was largely first-order. The α-L configuration was readily apparent from the H-1′ signal ($\delta$ 5.52), which showed couplings of 2.9 and $<1$ Hz with the protons at C-2′; the stereospecificity of this coupling is anticipated as the aglycon enters *trans* to all substituents on the pyranoid ring, and by comparison with experience in similar coupling-reactions[5].

The second coupling-product, eluted later from the column and isolated pure as a sharp-melting solid (which, nevertheless, gave a diffuse X-ray powder pattern) in 17% net yield, was identified as the 7,14-bis(glycosylated) derivative **11**, initially from its elemental analysis. The $^1$H-n.m.r. spectrum of **11** confirmed that the 14-aryl substituent had been lost, and that a second glycosyl group had been introduced, presumably at the 14-position. An additional, anomeric-proton signal was present, consistent with α-L substitution at O-14. The 20.115-MHz, $^{13}$C-n.m.r. spectrum of **11** further indicated the product to be a homogeneous, single compound, and no $^{13}$C signals for β-L-linked glycosyl groups were detected at either point of glycosylation.

The reason for partial removal of the 14-protecting group from **8** during this reaction is not clear. Trial experiments with only 1 equiv. of **9**, at either ~25 or 0°, still led to production of some **11**. No comparable 14-deprotection was reported[11] in a synthesis of adriamycin (**3**) employing 2,3,6-trideoxy-4-*O*-(*p*-nitrobenzoyl)-3-(trifluoroacetamido)-α,β-L-*lyxo*-hexopyranosyl chloride for glycosylation.

Removal of the *O*-acetyl groups from **10** by the action of sodium hydroxide in aqueous oxolane afforded the glycoside **12** in moderate yield as a sharp-melting, albeit amorphous (X-ray) solid whose 200-MHz, $^1$H-n.m.r. spectrum could be

assigned in detail (see Experimental section). Removal of the *p*-anisyldiphenylmethyl group from **12** was effected by aqueous acetic acid at 28°, and the amorphous, deprotected product **6** was obtained in moderate yield. The chemical-ionization spectrum (isobutane) of **6** showed the major peaks anticipated[14], at *m/z* 337 from the anthracycline nucleus and at *m/z* 131 for the glycosyl cation. This reaction step did, however, lead to some glycosidic scission, and the yield of "3′-hydroxyadriamycin" (**6**) was not readily improved.

The fact that the sequence **8** → **10** → **12** → **6** gave poor, net yields of **6**, and difficulties of purification at certain steps, led to a major and successful effort to exploit the third possible approach. Daunomycinone was converted[11] into its 14-bromo derivative **13**, and the latter was glycosylated with ~3 molar equiv. of 3,4-di-*O*-acetyl-2,6-dideoxy-α-L-*lyxo*-hexopyranosyl chloride[12,13] (**9**) by the general method[5] already described for **8**. The coupled product (**14**) was obtained pure, as a single anomer, in 70–94% yield. The $^1$H- and $^{13}$C-n.m.r. spectra of **14** (see Experimental section) affirmed the homogeneity of the product and the α-L configuration, although the apparently crystalline product was indicated to be amorphous by its

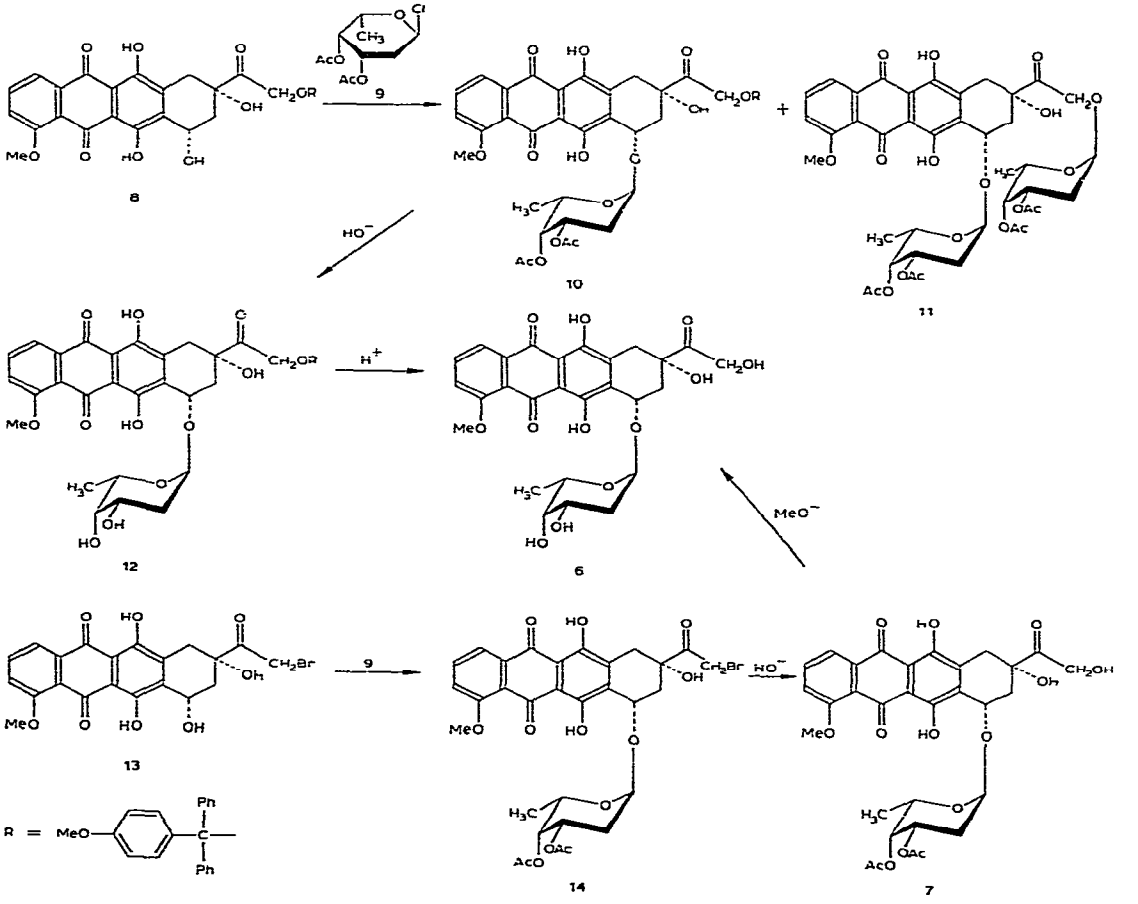

TABLE I

ANTITUMOR EVALUATION[a], IN MICE, OF COMPOUND 7 (NSC 307,990) AND COMPOUND 4 (NSC 284,682)

| *Test system* | | | | | *Dose* | *T/C* | *Toxic* | *T/C* | *Toxic* |
|---|---|---|---|---|---|---|---|---|---|
| *Mouse strain* | *Tumor* | *Route*[b] | *Schedule*[c] | *Parameter*[d] | *(mg/kg)* | *(%)* | *deaths* | *(%)* | *deaths* |
| **7-*O*-(3,4-Di-*O*-acetyl-2,6-dideoxy-α-L-*lyxo*-hexopyranosyl)adriamycinone (7, NSC 307,990)** | | | | | | | | | |
| $CD_2F_1$ | P388 | I.p. | 5,9,13 | M.s.t. | 100 | | | 125 | 0/6 |
| | lymphocytic | | | | 50 | 211 | 0/6 | 269 | 0/6 |
| ($CDF_1$) | leukemia | | | | 25 | 185 | 0/6 | 192 | 1/6 |
| | (PS) | | | | 12.5 | 163 | 0/6 | 137 | 0/6 |
| | | | | | 6.25 | 123 | 0/6 | 123 | 1/6 |
| | | | | | 3.13 | 99 | 1/6 | 123 | 1/6 |
| $CD_2F_1$ | L-1210 | I.p. | 1–9 | M.s.t. | 100 | | 0/6 | | 0/6 |
| ($CDF_1$) | lymphoid | | | | 50 | | 0/6 | | 0/6 |
| | leukemia | | | | 25 | 93 | 0/6 | 100 | 0/6 |
| | (LE) | | | | 12.5 | 203 | 0/6 | 153 | 0/6 |
| | | | | | 6.25 | 167 | 0/6 | 147 | 0/6 |
| | | | | | 3.13 | 131 | 0/6 | 129 | 0/6 |
| | | | | | 1.56 | | | 115 | 0/6 |
| $B_6C_3F_1$ | B-16 | I.p. | 1 | M.s.t. | 200 | | 0/10 | | 6/10 |
| | melanocarcinoma | | | | 100 | | 0/10 | | 5/10 |
| | (B1) | | | | 50 | 202 | 0/10 | 176 | 0/10 |
| | | | | | 25 | 195 | 0/10 | 159 | 0/10 |
| | | | | | 12.5 | 126 | 0/10 | 150 | 0/10 |
| | | | 1–9 | | 100 | | | | 1/10 |
| | | | | | 50 | | 2/10 | | 0/10 |
| | | | | | 25 | | 1/10 | | 1/10 |
| | | | | | 12.5 | | 0/10 | | 0/10 |
| | | | | | 6.25 | 131 | 0/10 | 178 | 0/10 |
| | | | | | 3.12 | 115 | 0/10 | 149 | 0/10 |

TABLE I *(continued)*

| *Test system* | | | | | *Dose* | *T/C* | *Toxic* | *T/C* | *Toxic* |
|---|---|---|---|---|---|---|---|---|---|
| *Mouse strain* | *Tumor* | *Route*[b] | *Schedule*[c] | *Parameter*[d] | *(mg/kg)* | *(%)* | *deaths* | *(%)* | *deaths* |
| $B_6D_2F_1$ (BDF1) | | | 1–7 | | 100 | | 1/10 | | |
| | | | | | 50 | | 0/10 | | |
| | | | | | 25 | | 1/10 | | |
| | | | | | 12.5 | | 0/10 | | |
| | | | | | 6.25 | 154 | 1/10 | | |
| | | | | | 3.12 | 144 | 0/10 | | |
| $CD_2F_1$ (CDF1) | Colon 26 (C6) | I.p. | 1,8(so) | M.s.t. | 300 | 150 | 0/10 | | |
| | | | | | 174 | 142 | 0/10 | | |
| | | | | | 101 | 120 | 0/9 | | |
| | | | | | 58 | 109 | 0/10 | | |
| | | | 1,8,15(su) | | 130 | 123 | 0/10 | | |
| | | | | | 81 | 103 | 0/10 | | |
| | | | | | 50 | 104 | 0/10 | | |
| | | | | | 31 | 100 | 0/10 | | |
| Nu/Nu-BALB/C (nude mouse) | LX-1 lung xenograft (LK) | I.r.i. | 1–10 | Delta | 200 | | 3/3 | | |
| | | | | | 100 | | 3/3 | | |
| | | | | | 50 | | 2/3 | | |
| | | | | | 25 | 53 | 0/3 | | |
| CD8F1 | CD8F1 mammary tumor (CD) | S.c. | 1,8,15,22,29 | M.t.w. | 100 | | 4/10 | | 10/10 |
| | | | | | 50 | 7 | 0/10 | | 5/10 |
| | | | | | 25 | 41 | 0/10 | 13 | 0/10 |
| | | | | | 12.5 | 48 | 0/10 | 6 | 0/10 |
| | | | | | 6.25 | 78 | 0/10 | 58 | 0/10 |
| | | | | | 3.12 | | | 65 | 2/10 |
| | | | | | 100 | | 10/10 | | |
| | | | | | 50 | | 7/10 | | |
| | | | | | 25 | 1 | 1/10 | | |
| | | | | | 12.5 | 11 | 0/10 | | |
| | | | | | 6.25 | 46 | 1/10 | | |
| | | | | | 3.12 | 35 | 2/10 | | |

| | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| Nu/Nu Swiss (nude mouse) | CX-1 colon xenograft (C-2) | I.r.i. | 1–10 | Delta | 200 | | 3/3 | | | |
| | | | | | 100 | | 3/3 | | | |
| | | | | | 50 | | 3/3 | | | |
| | | | | | 25 | 35 | 0/3 | | | |
| $B_6D_6F_1$ (BDF$_1$) | Colon 38 (C8) | S.c. | 1,8,15 | M.s.t. | 250 | 124 | 1/10 | 111 (at 300 mg/kg) | | |
| | | | | | 155 | 104 | 1/10 | 115 (at 174 mg/kg) | | |
| | | | | | 96 | 130 | 0/10 | 88 (at 101 mg/kg) | | |
| | | | | | 59 | 93 | 0/10 | (schedule 1,8) | | |
| | | | 1,8 | M.t.w. | 100 | | 5/10 | | | |
| | | | | | 50 | 62 | 0/10 | | | |
| | | | | | 25 | 90 | 0/10 | | | |
| | | | | | 12.5 | 65 | 0/10 | | | |
| | | | | | 6.25 | 88 | 0/10 | | | |
| | | | | | 3.12 | 89 | 0/10 | | | |
| $B_6C_3F_1$ | Lewis lung carcinoma (LL) | I.v. | 1–9 | M.s.t. | 100 | | 0/10 | | | |
| | | | | | 50 | | 0/10 | | | |
| | | | | | 25 | | 0/10 | | 0/10 | |
| | | | | | 12.5 | 280 | 0/10 | | 1/10 | |
| | | | | | 6.25 | 144 | 0/10 | 145 | 0/10 | |
| | | | | | 3.12 | 104 | 0/10 | 111 | 0/10 | |
| | | | | | 1.56 | | | 103 | 0/10 | |
| | | | | | 0.76 | | | 91 | 0/8 | |
| | | | | | 100 | | 0/10 | | | at mg/kg |
| | | | | | 50 | | 0/10 | | 0/10 | 24 |
| | | | | | 25 | | 0/10 | 266 | 0/10 | 12 |
| | | | | | 12.5 | | 0/10 | 133 | 0/10 | 6 |
| | | | | | 6.25 | 120 | 0/10 | 111 | 0/10 | 3 |
| | | | | | 3.12 | 111 | 0/10 | 119 | 0/10 | 1.5 |
| | | | | | | | | | | at mg/kg |
| $B_6D_2F_1$ (BDF$_1$) | | | | | 24 | | 0/10 | | 0/10 | 25 |
| | | | | | 12 | 338 | 0/10 | 285 | 1/10 | 12.5 in |
| | | | | | 6 | 128 | 0/10 | 133 | 1/10 | 6.25 $B_6C_3F_1$ |
| | | | | | 3 | 120 | 0/10 | 113 | 1/10 | 3.12 mice |
| | | | | | 1.5 | 111 | 0/10 | 106 | 0/10 | 1.56 |
| Nu/Nu Swiss (nude mouse) | MX-1 breast xenograft (MB) | I.r.i. | 1–10 | Delta | 50 | | 3/3 | | | |
| | | | | | 25 | | 2/3 | | | |
| | | | | | 12.5 | 96 | 0/3 | | | |
| | | | | | 6.25 | 82 | 0/3 | | | |

TABLE I *(continued)*

| *Test system* | | | | | *Dose* | *T/C* | *Toxic* | *T/C* | *Toxic* |
|---|---|---|---|---|---|---|---|---|---|
| *Mouse strain* | *Tumor* | *Route*[b] | *Schedule*[c] | *Parameter*[d] | *(mg/kg)* | *(%)* | *deaths* | *(%)* | *deaths* |
| **7-*O*-(2,6-Dideoxy-α-L-*lyxo*-hexopyranosyl)daunomycinone (4, NSC 284,682)** | | | | | | | | | |
| $CD_2F_1$ | P-388 | I.p. | 5,9,13 | M.s.t. | 400 | 89 | 2/5 | | |
| ($CDF_1$) | lymphocytic | | | | 200 | | 0/5 | 192 | 1/6 |
| | leukemia | | | | 100 | 156 | 0/5 | 161 | 1/6 |
| | (PS) | | | | 50 | 183 | 0/5 | 147 | 1/6 |
| | | | | | 25 | 125 | 0/5 | 127 | 0/6 |
| | | | | | 12.5 | | | 123 | 0/6 |
| $B_6D_2F_1$ | | | | | 50 | 150 | 0/6 | | |
| ($BDF_1$) | | | | | 25 | 124 | 0/6 | | |
| | | | | | 12.5 | 113 | 0/6 | | |
| | | | | | 6.25 | 115 | 1/6 | | |
| | | | | | 3.13 | 106 | 0/6 | | |
| $CD8F_1$ | $CD8F_1$ | I.p. | 1,8,15,22,29 | M.t.w. | 400 | | 10/10 | | |
| | mammary | | | | 200 | | 10/10 | | |
| | tumor | | | | 100 | 1 | 0/10 | | |
| | (CD) | | | | 50 | 14 | 0/10 | | |
| | | | | | 25 | 24 | 0/10 | | |
| | | | | | 12.5 | 57 | 0/10 | | |
| $B_6D_2F_1$ | B-16 | I.p. | 1 | M.s.t. | 200 | | 6/10 | | 5/10 |
| ($BDF_1$) | melanocarcinoma | | | | 100 | 179 | 2/10 | 152 | 1/10 |
| | (B1) | | | | 50 | 140 | 0/10 | 153 | 0/10 |
| | | | | | 25 | 139 | 0/10 | 147 | 0/10 |
| | | | | | 12.5 | 132 | 1/10 | 127 | 1/10 |
| | | | 5 | | 200 | | 8/10 | 119 | 0/10 |
| | | | | | 100 | | 4/10 | 137 | 0/10 |
| | | | | | 50 | 146 | 0/10 | 143 | 0/10 |
| | | | | | 25 | 126 | 0/10 | 140 | 0/10 |
| | | | | | 12.5 | 113 | 0/10 | 113 | 0/10 |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| $B_6C_3F_1$ | C3H mammary adenocarcinoma 16/C (16) | S.c. | 2,9 | M.t.w. | 400 | | 10/10 |
| | | | | | 200 | | 9/10 |
| | | | | | 100 | 38 | 0/10 |
| | | | | | 50 | 91 | 0/10 |
| | | | | | 25 | 142 | 0/10 |
| | | | | | 12.5 | 67 | 0/10 |
| $B_6D_2F_1$ (BDF1) | Colon 38 (C8) | S.c. | 3 | M.s.t. | 530 | | 6/6 |
| | | | | | 390 | | 6/6 |
| | | | | | 240 | | 6/6 |
| | | | | | 150 | | 4/6 |
| | | | 3,10,17 | | 120 | 123 | 3/10 |
| | | | | | 75 | 135 | 0/10 |
| | | | | | 46 | 101 | 1/10 |
| | | | | | 29 | 102 | 0/10 |
| | | | | | 130 | | 5/6 |
| | | | | | 80 | 111 | 1/5 |
| | | | | | 50 | 127 | 0/6 |
| | | | | | 31 | 119 | 0/6 |
| $CD_2F_2$ (CDF1) | Colon 26 (C6) | I.p. | 1,8 | M.s.t. | 130 | | 1/10 |
| | | | | | 80 | 131 | 0/10 |
| | | | | | 50 | 131 | 0/10 |
| | | | | | 31 | 108 | 0/10 |

[a]Data obtained under the auspices of the National Cancer Institute, Division of Cancer Treatment, Drug Research and Development Branch. Detailed protocols are given in ref. 15. [b]I.p., intraperitoneal; i.r.i., intrarenal inoculation or subrenal capsule; s.c., subcutaneous; i.v., intravenous. [c]P, q, r.: injections on day p, q, and r; 1–*n*; injections on each day of days 1–*n*; 1 : 1 injection; 1,8 (so): injections on days 1 and 8 (*solution*); 1, 8, 15 (su): injections on days 1, 8, and 15 (suspension). [d]M.s.t., median survival time; Delta, change in average tumor diameter between day 0 and day of final evaluation; M.t.w., median tumor weight estimated from tumor diameter.

X-ray powder diffraction pattern. Optimal yields of **14** were obtained when at least a 3-molar excess of the chloride **9** was used; multi-gram preparations gave lower percentage yields than small-scale reactions.

The 14-bromo group of **14** was readily replaced by a hydroxyl group upon treatment with aqueous potassium carbonate, to afford the target compound, 7-*O*-(3,4-di-*O*-acetyl-2,6-dideoxy-α-L-*lyxo*-hexopyranosyl)adriamycinone (7), in 78–90% yield. The red, powdery product was amorphous (X-ray), but was quite pure from the evidence of t.l.c., elemental analysis, and $^{1}H$- and $^{13}C$-n.m.r. spectra. The net yield of 7, calculated on all steps from daunorubicin, was >50% in preparations performed on amounts of up to 25 g, if intermediates were not processed to analytical purity. The product 7, as used in detailed, antitumor evaluations, gave a compact, single spot in t.l.c., melted at 154–157°, and showed no extraneous signals in its 200-MHz, $^{1}H$-n.m.r. spectrum.

*O*-Deacetylation of 7 by the Zemplén procedure led to extensive glycosidic cleavage, and yields of the deacetylated product **6** were low. No significant improvement was realized in a range of alternative procedures attempted with the objective of removing the *O*-acetyl groups from 7.

*Antitumor evaluation.* — The results of *in vivo*, antitumor assays in mice on 7-*O*-(3,4-di-*O*-acetyl-2,6-dideoxy-α-L-*lyxo*-hexopyranosyl)adriamycinone (7; NSC 307,990) are presented in Table I. The compound shows significant activity against a range of tumors, including P-388 lymphocytic leukemia, L-1210 lymphoid leukemia, B-16 melanocarcinoma, $CD8F_1$ mammary tumor, Lewis lung carcinoma, and colon 26 tumor. In two instances (CX-1 colon xenograft and LX-1 lung xenograft), further tests are needed, in order to confirm or reject activity. In only one of the tests performed, against colon 38 tumor, was compound 7 apparently inactive.

For comparative purposes, Table I also records antitumor assay-data for 7-*O*-(2,6-dideoxy-α-L-*lyxo*-hexopyranosyl)daunomycinone[5] (**4**; NSC 284,682). Compound **4** shows significant activity, but the comparison does confirm the earlier expectation that the adriamycin analog (7) would be more active than the daunorubicin derivative (**4**). Thus, in the P-388 lymphocytic leukemia screen at a dose level of 50 mg/kg, the daunorubicin analog **4** showed T/C 183, whereas the adriamycin analog exhibited T/C 269. At lower dose-levels, compound 7 still showed significant activity. In the same assay at 8 mg/kg, daunorubicin (**1**) displayed T/C 151 and adriamycin (3) T/C 150; higher dose-levels of the latter two agents elicited a toxic response, and lower T/C values.

The tolerance of the test animals to much higher dose-levels of the agents **7** and **4** than of the clinical drugs **1** and **3** is noteworthy. Even though higher doses of the 3-deamino derivatives 7 and **4** are needed in order to elicit initial manifestation of antitumor activity, the much higher doses of these that can be administered before the onset of toxic symptoms may permit a useful improvement in therapeutic margin by use of these agents.

Cardiotoxicity screening *in vivo* in the rat by the Zbinden assay[16] was performed on the daunorubicin analog **4** and no cardiotoxicity was observed at 6 ×

16 mg/kg (namely, a total dose of 96 mg/kg); higher doses were not tested, and the minimum, cumulative cardiotoxic dose for **4** is not yet established. The adriamycin analog (**7**) has not been screened for cardiotoxicity, but the similarities in overall behavior of **4** and **7** suggest that the cardiotoxicity of **7** will also prove to be low.

"3′-Hydroxydaunorubicin" (**4**) and its diacetate (**5**) show comparable tumor-inhibitory responses[5], indicating that *O*-acetylation is no impediment to activity. Indeed, the greater lipophilicity of the acetylated derivatives may facilitate transport of the agents, and esterases of broad specificity can be expected to effect deacetylation *in vivo*. Because of difficulties in securing the *O*-deacetylated adriamycin analog **6**, all detailed biological tests were performed on the diacetate **7**. However, if the similarity in biological behavior of **4** and **5** is any guide, the activity of **6** may be expected to differ little from that of **7**.

The results presented here for the 3′-deaminoadriamycin analog **7**, and earlier[5] for the 3′-deaminodaunorubicin analog **4**, suggest that these two compounds may have significant potential for development as antitumor agents. The corresponding carminomycinone derivative has also recently been found[17] to be active.

A widely held hypothesis on the mode of action of the anthracycline antitumor agents is that the fused-ring system intercalates in the base-pair stacks of nuclear DNA, and that the pendant 3′-amino group, supposed to be essential for activity, is then involved in a key inhibitory step[8,18]. This interpretation is manifestly untenable for the active 3-deamino analogs **4** and **7**, and the general validity of this proposed biochemical mechanism is in need of re-evaluation in the light of the present results.

## EXPERIMENTAL

*General methods.* — T.l.c. was performed on precoated, plastic sheets (0.2 mm) and glass plates (0.25 mm) of Silica Gel 60F-254 (E. Merck, Darmstadt, G.F.R.); zones of colorless compounds were detected by u.v. light, and by spraying the plates with 0.1M ceric sulfate in 2M sulfuric acid, with subsequent heating. Melting points were determined with a Thomas–Hoover apparatus and are uncorrected. Optical rotations were measured with a Perkin–Elmer 141 polarimeter. I.r. spectra were recorded with a Perkin–Elmer 457 grating spectrophotometer. $^1$H-N.m.r. spectra at 200 MHz were recorded by Dr. O. Mols, for solutions in chloroform-*d*, with a Bruker WP-200 spectrometer; $^{13}$C spectra were recorded by Dr. C. Cottrell at 20.115 MHz with a Bruker WP-80 instrument. Chemical shifts refer to an internal standard of tetramethylsilane ($\delta = 0.00$). Microanalyses were performed by W. N. Rond.

*14*-O-(p-*Anisyldiphenylmethyl*)*adriamycinone* (**8**). — Adriamycinone (700 mg, 1.69 mmol), obtained from adriamycin (**3**) by acid hydrolysis, was dissolved in pyridine (30 mL) and treated with *p*-anisylchlorodiphenylmethane (5.6 g, 18.12 mmol) for 7 days at 0° according to the general procedure of Henry *et al.*[11], to afford **8**, obtained crystalline from chloroform–petroleum ether (b.p. 30–60°); yield 1.66 g (84%), m.p. 197–200° (lit.[11] m.p. 198–203°).

*Glycosylation of* **8** *with 3,4-di*-O-*acetyl-2,6-dideoxy-α*-L-lyxo-*hexopyranosyl*

*chloride* (**9**) *to give 14-*O*-(p-anisyldiphenylmethyl)-7-*O*-(3,4-di-*O*-acetyl-2,6-dideoxy-α-*L*-lyxo-hexopyranosyl)adriamycinone* (**10**, *NSC 314,330*) *and 7,14-di-*O*-(3,4-di-*O*-acetyl-2,6-dideoxy-α-*L*-lyxo-hexopyranosyl)adriamycinone* (**11**, *NSC 311,156*). — A mixture of compound **8** (600 mg, 0.88 mmol), yellow mercuric oxide (1.14 g), mercuric bromide (330 mg), and molecular sieve 3A (5 g) in dichloromethane (50 mL) was stirred for 1 h at 25°. A solution of the chloride[12,13] **9** (570 mg, 2.27 mmol; prepared by the procedure of El Khadem *et al.*[13], except that the time of reaction was extended to 15–25 min at ~25°) in dichloromethane (10 mL) was then added in one portion, and the mixture was stirred for an additional 12 h. Inorganic material was filtered off, and the filtrate was washed successively with 30% potassium iodide (100 mL), saturated aqueous sodium hydrogencarbonate (100 mL), and water (100 mL), dried (magnesium sulfate), and evaporated. Sugar side-products were removed by chromatography on silica gel G (Merck) with 3:1 ether–petroleum ether as the eluant. The resultant mixture of **10** and **11** was then recovered with acetone, and resolved on a second column with 4:1 benzene–acetone as the eluant. The first fraction afforded the desired monoglycosyl derivative **10**, which was recrystallized from chloroform–hexane; yield 557 mg (70%), m.p. 147–148°, $[\alpha]_D^{22}$ +115° (*c* 0.01, chloroform); $\nu_{max}^{KBr}$ 3500 (OH), 1748 (C=O), 1620 and 1575 $cm^{-1}$ (chelated quinone); $^1$H-n.m.r.: $\delta$ 13.93, 13.18 (s, 1 H, HO-6, 11), 8.00 (d, 1 H, $J_{1,2}$ 7.7 Hz, H-1), 7.75 (apparent t, 1 H, H-2), 7.54–7.20 (m, aryl), 6.87 (d, aryl), 5.52 (d, 1 H, $J_{1',2e}$ ~0, $J_{1',2ax}$ 2.9 Hz, H-1'), 5.18 (bs, 1 H, H-7), 5.12 (apparent narrow d, 1 H, $J_{4',5'}$ <1 Hz, H-4'), 4.93 (ddd, 1 H, $J_{2'ax,3'}$ 12.8, $J_{2'e,3'}$ 5.0, $J_{3',4'}$ 2.9 Hz, H-3'), 4.49 (d, 1 H, $J_{14A,14B}$ 18.7 Hz, H-14A), 4.42 (d, 1 H, H-14B), 4.11 (s, 1 H, HO-9), 4.07 (s, 3 H, OMe), 3.97 (m, 1 H, H-5'), 3.80 (s, 3 H, OMe), 3.04 (d, 1 H, $J_{10ax,10e}$ 18.8 Hz, H-10*e*), 2.87 (d, 1 H, H-10*ax*), 2.24–1.88 (m, 3 H, H-2'*ax*, $CH_2$-8), 2.16, 1.92 (s, 3 H, OAc), 1.81 (dd, 1 H, $J_{2'ax,2'e}$ 12.1 Hz, H-2'*e*), and 0.98 (d, 3 H, $J_{5',6'}$ 6.6 Hz, H-6'). The 100-MHz, n.m.r. spectrum of **10** in acetone-$d_6$ was recorded in ref. 1.

*Anal.* Calc. for $C_{51}H_{48}O_{15} \cdot 1.5\ H_2O$: C, 66.01; H, 5.54. Found: C, 65.83; H, 5.77.

Evaporation of the second fraction afforded the bisglycosylated derivative **11** which was recrystallized from acetone–hexane; yield 128 mg (17%), m.p. 148–149°, $[\alpha]_D^{22}$ +54° (*c* 0.07, chloroform); $\nu_{max}^{KBr}$ 3490 (OH), 1750 (C=O), 1630 and 1580 $cm^{-1}$ (chelated quinone); $^{13}$C-n.m.r. (20.115 MHz): $\delta$ 209.9 (C=O), 187.2, 186.7 (C-5, 12), 170.8, 170.6, 170.0 (4 C=O), 161.1 (C-4), 156.3, 155.8 (C-6, 11), 135.8 (C-2), 135.6, 134.0, 133.5 (C-6a, 10a, 12a), 121.0 (C-4a), 119.9 (C-1), 118.5 (C-3), 111.6, 111.5 (C-5a, 11a), 101.2 (C-1'), 97.8 (C-1''), 77.1 (C-9), 70.0, 69.8, 69.4, 68.7, 66.7, 66.4, 66.0, 65.4 (C-7, 5', 5'', 4', 4'', 3', 3'', 14), 56.7 (OMe), 35.6 (C-8), 33.9 (C-10), 29.7 (C-2', 2''), 20.8 (4 OAc), and 16.6 (C-6', 6'').

*Anal.* Calc. for $C_{41}H_{45}O_{19} \cdot H_2O$: C, 56.60; H, 5.70. Found: C, 56.77; H, 5.74.

The 100-MHz, $^1$H-n.m.r. spectrum of **11** in chloroform-*d* showed only signals for H-1,2,3 in the aryl-proton region, the methoxyl signal of the *p*-anisyl group was absent, and signals attributable to a second glycosyl group were present. In addition to a poorly resolved, narrow doublet at $\delta$ ~5.55 (H-1' of the 7-substituent), a second,

similar signal at $\delta \sim 5.35$ was observed, not clearly separated from signals for H-3′,4′, and 7, attributable to H-1′ of the 14-substituent. The $^1$H- and $^{13}$C-n.m.r. data provide clear indication of the α-L configuration for the substituents at C-7 and C-14.

*14*-O-(p-*Anisyldiphenylmethyl*)-7-O-(*2,6-dideoxy*-α-L-lyxo-*hexopyranosyl*)*adriamycinone* (**12**, *NSC 314,331*). — Aqueous sodium hydroxide (200 μM, 22 mL) was added to a cold (0°) solution of the protected glycoside **10** (100 mg, 0.11 mmol) in oxolane (25 mL). After 6 h at 0°, the solution was made neutral by careful addition of 200 μM acetic acid, and extracted with dichloromethane (five 50-mL portions). The extracts were combined, successively washed with saturated aqueous potassium hydrogencarbonate (50 mL) and water (50 mL), dried (sodium sulfate), and evaporated. The solid residue was recrystallized from acetone–ether–petroleum ether, to give pure **12**; yield 50 mg (35%), m.p. 152–153° (dec.), $[\alpha]_D^{22}$ +80° (*c* 0.01, chloroform); $\nu_{max}^{KBr}$ 3480 (OH), 1740 (C=O), 1620, and 1580 cm$^{-1}$ (chelated quinone); $^1$H-n.m.r.: $\delta$ 14.40, 14.25 (s, 1 H, HO-6, 11), 8.03 (d, 1 H, $J_{1,2}$ 7.0 Hz, H-1) 7.76 (apparent t, 1 H, $J_{2,3}$ 8.1 Hz, H-2), 7.62–7.12 (m, aryl), 6.86 (d, 2 H, *J* 8.8 Hz, aryl), 5.45 (bs, 1 H, H-1′), 5.21 (bs, 1 H, H-7), 4.48 (d, 1 H, $J_{14A,14B}$ 19.1 Hz, H-14A), 4.39 (d, 1 H, H-14B), 4.34 (s, 1 H, HO-9), 4.07 (s, 3 H, OMe-3), 3.80 (s, 3 H, OMe), 3.87–3.64 (m, 2 H, H-3′, 5′), 3.56 (bs, 1 H, H-4′), 3.08 (d, 1 H, $J_{10ax,10e}$ 19.1 Hz, H-10*e*), 2.95 (d, 1 H, H-10*ax*), 2.11 (m, 2 H, 2 H-8), 1.8 (m, 2 H, 2 H-2′), and 1.12 (d, 3 H, $J_{5',6'}$ 6.6 Hz, H-6′).

*Anal.* Calc. for $C_{47}H_{34}O_{12} \cdot H_2O$: C, 67.62; H, 5.54. Found: C, 67.38; H, 5.74.

*7*-O-(*2,6-Dideoxy*-α-L-lyxo-*hexopyranosyl*)*adriamycinone* (**6**). — The ether **12** (10 mg, 12.6 mmol) was treated with 80% acetic acid (5 mL) for 4 h at 28°. Lyophilization afforded a solid residue that was dissolved in 2:1 chloroform–methanol (3 mL). The suspension was filtered, and the filtrate treated with hexane. The precipitate formed was collected and dried, to give the title compound **6** as an amorphous powder; yield 5 mg; *m/z* (chemical ionization, isobutane): 337 ($MH^+$ — glycon — C-13,14 fragment) and 131 (glycosyl cation).

This product was also obtained by *O*-deacetylation of the diacetate **7**. Compound **7** (53 mg) was dissolved in dry methanol (50 mL), the solution was blanketed with nitrogen, and M sodium methoxide (50 μL) was added at 0°. After 24 h, Amberlite IRC-50 ($H^+$) ion-exchange resin (5 mL) was added at 0°, and the mixture was stirred for 12 h at 0°, during which time the color of the solution changed from blue to red. The mixture was filtered, and the filtrate evaporated, to give **6** as a red solid, identical with the product obtained from **12**. The yield of **6** in this reaction was low, and t.l.c. indicated that the major product of the reaction was formed with cleavage of the glycosyl group from the anthracycline. Numerous repetitions and variations of standard *O*-deacylation procedures failed to give a preparatively acceptable yield of **6** from **7**.

*14-Bromodaunomycinone* (**13**). — Daunorubicin (**1**; 17.62 g) was hydrolyzed with 0.2M hydrochloric acid (950 mL), and the resultant daunomycinone (10.92 g, 88% after crystallization from methanol) was converted into **13** by the procedure of Henry *et al.*[11] in 85% net yield.

*14-Bromo-7-*O*-(3,4-di-*O*-acetyl-2,6-dideoxy-α-*L*-lyxo-hexopyranosyl)daunomycinone* (**14**, *NSC 307,989*). — A mixture of **13** (7.05 g, 14.77 mmol), yellow mercuric oxide (18 g), mercuric bromide (5.57 g), and powdered molecular sieve 4A (4.30 g) in dichloromethane (700 mL) was stirred for 1 h at 25°, and then a solution of the chloride **9** [obtained[13] from 8.6 g (40.15 mmol) of 3,4-di-*O*-acetyl-1,5-anhydro-3,6-dideoxy-L-*lyxo*-hex-1-enitol] in dichloromethane (200 mL) was added in one portion. The mixture was stirred for 12 h at 27°, and then processed as described for the synthesis of compounds **10** and **11**, to afford crude **14**, which was recrystallized from acetone–hexane or, in other preparations, from a small volume of chloroform plus ethyl ether and an excess of hexane; yield 7.31 g (71%), m.p. 152–156°, $[\alpha]_D^{25}$ +119° (*c* 0.01, chloroform); $\nu_{max}^{KBr}$ 3480 (OH), 1745 (C=O), 1620, and 1584 $cm^{-1}$ (H-bonded quinone): $^1$H-n.m.r.: δ 13.98, 13.22 (s, 1 H, HO-6, 11), 8.04 (d, 1 H, $J_{1,2}$ 6.9 Hz, H-1), 7.78 (apparent t, 1 H, H-2), 7.40 (d, 1 H, $J_{2,3}$ 7.7 Hz, H-3), 5.63 (d, 1 H, $J_{1',2'e}$ <1.5, $J_{1',2'ax}$ 3.4 Hz, H-1'), 5.30 (m, 1 H, H-7), 5.21 (broadened, narrow d, 1 H, $J_{4',5'}$ <1 Hz, H-4'), 5.05 (ddd, 1 H, $J_{2'ax,3'}$ 12.2, $J_{2'e,3'}$ 5.2, $J_{3',4'}$ 2.6 Hz, H-3'), 4.57 (s, 1 H, OH-9), 4.62 (d, 1 H, $J_{14A,14B}$ 13.8 Hz, H-14A), 4.39 (d, 1 H, H-14B), 4.25 (q, 1 H, H-5'), 4.09 (s, 3 H, OMe), 3.29 (dd, 1 H, $J_{8e,10e}$ 1.5, $J_{10ax,10e}$ 18.9 Hz, H-10*e*), 2.98 (d, 1 H, H-10*ax*), 2.45 (bd, 1 H, $J_{8ax,8e}$ 15.0 Hz, H-8*e*), 2.27 (dd, 1 H, $J_{7,8ax}$ 3.9 Hz, H-8*ax*), 1.80–2.14 (m, 2 H, H-2'), 2.21, 1.94 (s, 3 H, 2 OAc), and 1.21 (d, 3 H, $J_{5',6'}$ 6.5 Hz, H-6'); $^{13}$C-n.m.r.: δ 205.2 (C-13), 187.0, 186.6 (C-5, 12), 170.5, 169.9 (2 C=O), 161.2 (C-4), 156.2, 155.6 (C-6, 11), 135.8 (C-2), 135.6, 133.8, 133.6 (C-6a, 10a, 12a), 120.9 (C-4a), 119.9 (C-1), 118.6 (C-3), 111.7, 111.5 (C-5a, 11a), 101.2 (C-1'), 77.4 (C-9), 69.9, 69.5 (C-7, 4'), 66.4, 66.1 (C-3', 5'), 56.7 (OMe), 36.4, 34.5, 31.7 (C-8, 10, 14), 29.7 (C-2'), 20.8, 20.7 (2 OAc), and 16.7 (C-6').

*Anal.* Calc. for $C_{31}H_{21}BrO_{13} \cdot 0.5\ H_2O$: C, 53.15; H, 4.60; Br, 11.41. Found: C, 53.37; H, 5.07; Br, 11.84.

*7-*O*-(3,4-Di-*O*-acetyl-2,6-dideoxy-α-*L*-lyxo-hexopyranosyl)adriamycinone* (**7**, *NSC 307,990*). — To a solution of the 14-bromo derivative **14** (3.95 g, 5.64 mmol) in oxolane (350 mL), blanketed with nitrogen, was added a solution of aqueous potassium carbonate (5%, 175 mL). After 0.5 h at 25°, the mixture was monitored by t.l.c. (4:1 benzene–acetone). Water (750 mL) was added and the solution was extracted with chloroform (four 800-mL portions). The extracts were combined, washed with water, dried (magnesium sulfate), and evaporated, to afford crude **7**, which was recrystallized from acetone–petroleum ether (b.p. 30–60°); yield 2.84 g (78%). A repetition of the experiment at 0°, with 0.5094 g of **14**, afforded 0.4175 (90%) of **7**; m.p. 154–157°, $[\alpha]_D^{25}$ +138° (*c* 0.007, chloroform); $\nu_{max}^{KBr}$ 3480 (OH), 1745 (C=O), 1621, and 1582 $cm^{-1}$ (H-bonded quinone); $^1$H-n.m.r.: δ 13.99, 13.23 (s, 1 H, HO-6, 11), 8.05 (d, 1 H, $J_{1,2}$ 7.7 Hz, H-1), 7.79 (apparent t, 1 H, H-2), 7.40 (d, 1 H, $J_{2,3}$ 8.1 Hz, H-3), 5.61 (d, 1 H, $J_{1',2'e}$ <1.0, $J_{1',2'ax}$ 3.5 Hz, H-1'), 5.30 (dd, 1 H, $J_{7,8ax}$ 4.0, $J_{7,8e}$ 2.0 Hz, H-7), 5.25 (broadened, narrow d, 1 H, H-4'), 5.04 (ddd, 1 H, $J_{2'ax,3'}$ 12.4, $J_{2'e,3'}$ 5.2, $J_{3',4'}$ 3.0 Hz, H-3'), 4.77 (AB system, 2 H, 2 H-14), 4.42 (s, 1 H, HO-9), 4.20 (q, 1 H, H-5'), 4.08 (s, 3 H, OMe), 3.28 (d, 1 H, $J_{10ax,10e}$ 19.0 Hz, H-10*e*), 3.03 (d, 1 H, H-10*ax*), 2.34 (bd, 1 H, $J_{8ax,8e}$ 15.1 Hz, H-8*e*), 2.22

(dd, 1 H, H-8*ax*), 2.09–1.80 (m, 2 H, 2 H-2'), 2.18, 1.94 (s, 3 H, 2 OAc), and 1.21 (d, 3 H, $J_{5',6'}$, 6.3 Hz, H-6'); $^{13}$C-n.m.r.: $\delta$ 213.7 (C-13), 187.1, 186.7 (C-5, 12), 170.5, 169.9 (2 C=O), 161.2 (C-4), 156.2, 155.7 (C-6, 11), 135.8 (C-2), 135.6, 133.7, 133.5 (C-6a, 10a, 12a), 121.0 (C-4a), 119.9 (C-1), 118.6 (C-3), 111.7, 111.5 (C-5a, 11a), 101.2 (C-1'), 76.6 (C-9), 69.9, 69.4 (C-4', 7), 66.4, 66.1 (C-3', 5'), 65.5 (C-14), 56.7 (OMe), 35.7, 34.1 (C-8, 10), 29.8 (C-2'), 20.8, 20.7 (2 OAc), and 16.7 (C-6').

*Anal.* Calc. for $C_{31}H_{32}O_{14} \cdot H_2O$: C, 57.58; H, 5.30. Found: C, 57.42; H, 5.69.

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