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Note

A new approach to 2-deoxyglycosides permitting access to anthracycline glycosides specifically labeled at the 2′-position*

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Alkoxyhalogenation of L-rhamnal diacetate (**1**) with daunomycinone and *N*-iodosuccinimide (NIS), and subsequent dehalogenation with tributylstannane, afforded 7-*O*-(3,4-di-*O*-acetyl-2,6-dideoxy-α-L-*arabino*-hexopyranosyl)-daunomycinone (**4**) in 36% net yield. When the dehalogenation was conducted with $DSnBu_3$, the 2′-axial deuterio analog (**5**) was obtained with ~100% stereospecificity. A similar procedure with L-fucal diacetate (**6**) gave a 40% net yield of 7-*O*-(3,4-di-*O*-acetyl-2,6-dideoxy-α-L-*lyxo*-hexopyranosyl)-daunomycinone (**8**). With $DSnBu_3$ as the reductant, the 2-axial deuterio analog (**9**) was obtained with ~90% stereoselectivity.

The acetylated 3′-deamino-3′-hydroxy (**8**) and 3′-deamino-4′-epi-3′-hydroxy (**4**) analogs of daunorubicin were earlier synthesized in our laboratory[2,3] by a Koenigs–Knorr coupling-reaction between daunomycinone and appropriate glycosyl chlorides. Based on daunomycinone, compound **8** was obtained in 78% yield by this method[2]. However, compound **4** was obtained as an inseparable mixture of α and β anomers when mercuric salts were employed. The use of silver triflate gave the pure α anomer, but only in 14% yield. In order to improve the yields of compounds **4** and **8** and eliminate the use of mercury salts in the synthesis, an alternative approach is used here. The first step involves *trans* alkoxyhalogenation of the corresponding glycals with *N*-iodosuccinimide (NIS) and daunomycinone. This glycosidation method has proved useful with sugar derivatives, as demonstrated by Thiem *et al.*[4], and with daunomycinone in earlier work from our group[5]. The second step employs dehalogenation with tributylstannane. This general sequence was used by Umezawa *et al.*[6] to obtain simple 2-deoxy-α-glycosides, and the steric course of dehalogenation of methyl 2-haloglycosides by $DSnBu_3$ has been studied in detail in our laboratory[7].

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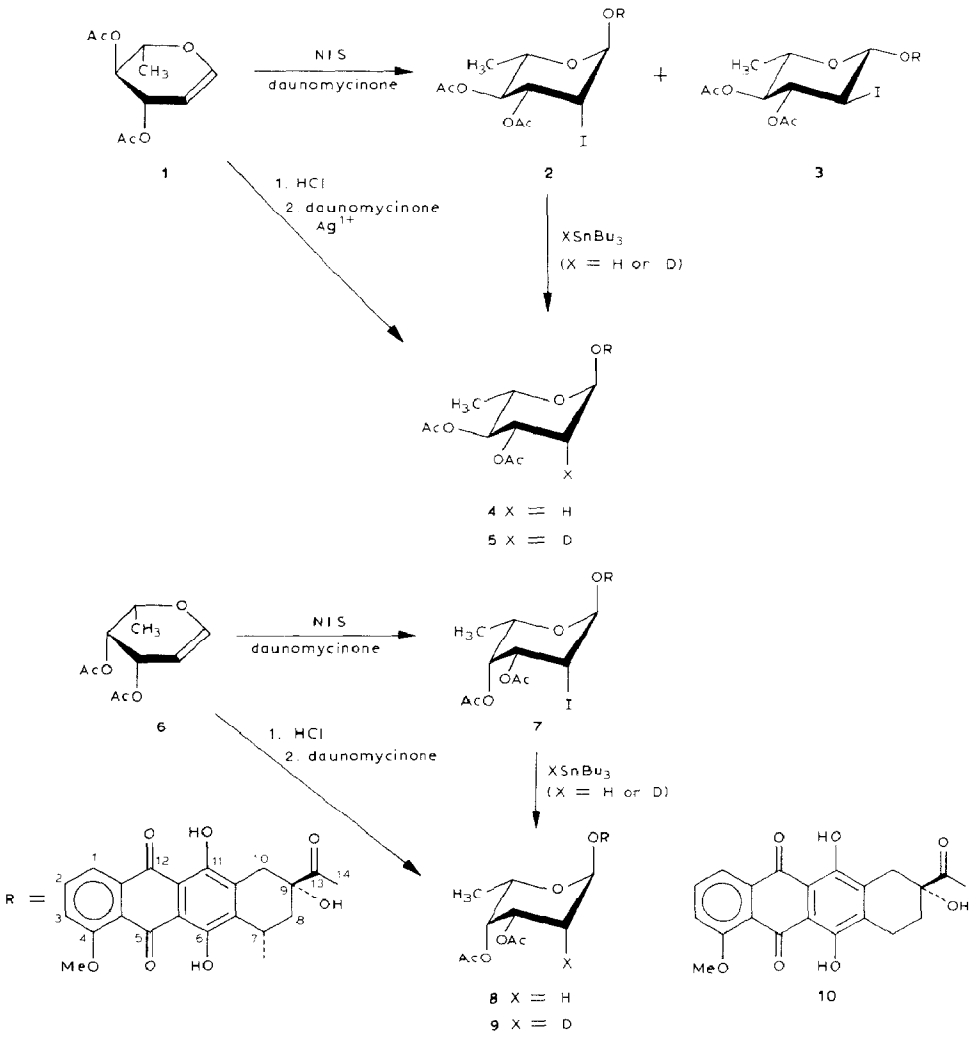

The 2′-iodo α-L-*manno* and α-L-*talo* glycosides (**2** and **7**, respectively) were obtained as already described[5] by treating L-rhamnal diacetate (**1**) and L-fucal diacetate (**6**), respectively, with NIS and daunomycinone. The yield of **2** was improved from 37 to 55% by adding more glycal after 12 h and allowing the reaction to continue for a further 6 h.

Compound **2** was subjected to dehalogenation with $HSnBu_3$. When the reaction was performed at room temperature, ~6–7 days were required for completion; poor yields were encountered, even when AIBN was used as a radical initiator. When the reaction was performed at 80° or higher, a large proportion of 7-deoxydaunomycinone (**10**) was produced and very little of the desired product was obtained. The best results were obtained at 55° with AIBN as a catalyst. Under these conditions, the α-L-*arabino* glycoside **4** was obtained in 65% yield.

All of the physical data for **4** were in agreement with those already published for this compound[3]. However, the present ^{1}H-n.m.r. spectra were recorded at 500 MHz so that better resolution was secured, especially in the range 1.8–2.5 p.p.m. where the signals of H-8*e*, H-8*ax*, H-2′*e*, and H-2′*a* overlapped in the previously recorded 200-MHz spectra[3].

When the deiodination reaction of **2** was effected with $DSnBu_3$, no signal at 1.81 p.p.m. corresponding to H-2′*a* was detected, and the H-2′*e* signal (2.22 p.p.m.) appeared as a doublet of doublets ($J_{2'e,3'}$ 5.3 Hz; $J_{1',2'e}$ 0.9 Hz) instead of a doubled doublet of doublets (because of the absence of the large $J_{2'e,2'a}$ coupling). This result shows that introduction of deuterium at C-2′ occurred with essentially complete stereospecificity in the axial disposition. Formation of only one epimer was somewhat surprising, as dehalogenation with $HSnBu_3$ presumably occurs by a radical mechanism[8], and so a mixture of C-2′ epimers might have been expected.

When compound **7** was treated with $HSnBu_3$, the α-L-*lyxo* glycoside **8** was obtained in 55% yield. Again, the physical constants were in agreement with those already published[2], but now 500-MHz ^{1}H-n.m.r. spectroscopy afforded completely resolved spectra (in the previous work, H-2′*e* and H-2′*a* had been wrongly assigned). When $DSnBu_3$ was used as the reagent, the signal at 1.88 p.p.m. corresponding to H-2′*e* in the product became a doublet instead of a doublet of doublets because of the absence of the large coupling between H-2′*a* and H-2′*e*. The integrated intensity of this signal was 0.9 proton. The signal corresponding to H-2′*a* appeared as a doublet of doublets (instead of a triplet of doublets) at δ 2.07 p.p.m., but its integrated intensity was only 0.1 proton. The ratios of these two signals shows the product to be **9** with ~90% deuterium in axial disposition, thus indicating again a high, but in this instance not complete, stereoselectivity.

The sequence of iodoalkoxylation of a glycal and subsequent dehalogenation with $HSnBu_3$ provides a valuable route of access to 2-deoxyglycosides of complex or sensitive aglycons, as demonstrated with the daunorubicin analogs described here, where the route proved especially valuable for compound **4**, whereas poor yields or inseparable anomeric mixtures were encountered in previous syntheses by traditional coupling methods[3].

The present sequence also provides convenient access to anthracycline analogs labeled in the sugar portion by a stable isotope, deuterium. An equivalent sequence employing $^3HSnBu_3$ would furnish the radiolabeled analogs incorporating tritium. Such analogs are of potential value for drug-metabolism studies with monitoring by mass spectrometry or radiolabel tracing.

A combination of stereoelectronic effects exerted by the bulky aglycon may be responsible for the high stereoselectivity leading mainly or exclusively to the axially labeled compounds. Further studies on the stereochemistry and mechanism of this reaction in model systems will be reported separately[7].

EXPERIMENTAL

General methods. — T.l.c. was performed on Silica Gel 60 F_{254} (Merck), and column chromatography with Silica Gel 60 (230–400 mesh, Merck). Melting points were determined with a Thomas–Hoover apparatus and are uncorrected. Optical rotations were measured with a Perkin–Elmer 141 polarimeter. N.m.r. spectra were recorded by Dr. C. Cottrell for solutions in chloroform-*d* (internal Me_4Si) with a Bruker AM-500 instrument.

*7-O-(3,4-Di-O-acetyl-2,6-dideoxy-2-iodo-α-*L*-mannopyranosyl)daunomycinone* (**2**) *and 7-O-(3,4-di-O-acetyl-2,6-dideoxy-2-iodo-β-*L*-glucopyranosyl)-daunomycinone* (**3**). — The procedure used was as already described[5] except that, after allowing the reaction to proceed overnight, an additional 0.5 equiv. of L-rhamnal diacetate (**1**) was added, and the mixture was kept for an additional 6 h. After column chromatography (10:1 toluene–acetone), compounds **2** and **3** were obtained in 55 and 10% yields, respectively.

*7-O-(3,4-Di-O-acetyl-2,6-dideoxy-α-*L*-*arabino*-hexopyranosyl)-daunomycinone* (**4**). — To a solution of compound **2** (105 mg, 0.142 mmol) in dry benzene (1 mL) was added AIBN (~5 mg) followed by $HSnBu_3$ (48 μL, 0.18 mmol). The mixture was kept at 55° in an oil bath and the reaction was monitored by t.l.c. (6:1 toluene–acetone) and was found to be complete after 48 h. To stop the reaction, the procedure of Berge and Roberts[9] was used: acetonitrile (5 mL) was added and the mixture was washed three times with hexane to remove tin residues. The acetonitrile solution was evaporated to give a red solid that was crystallized from CH_2Cl_2–hexane to afford 57 mg (65%) of a product that was identical to an original sample[2,3] of **4**.

^{1}H-N.m.r. data: δ 13.97 and 13.23 (2 s, each 1 H, O*H*-6, O*H*-11), 8.03 (dd, 1 H, $J_{1,2}$ 7.7, $J_{1,3}$ 1.0 Hz, H-1), 7.76 (t, 1 H, H-2), 7.38 (dd, 1 H, $J_{2,3}$ 8.2 Hz, H-3), 5.51 (d, 1 H, $J_{1',2'a}$ 4.2, $J_{1',2'e}$ 0.9 Hz, H-1'), 5.25 (dd, 1 H, $J_{7,8e}$ 1.9, $J_{7,8ax}$ 3.8 Hz, H-7), 5.05 (ddd, 1 H, $J_{2'e,3'}$ 5.3, $J_{2'a,3'}$ 11.6, $J_{3',4'}$ 9.3 Hz, H-3'), 4.78 (t, 1 H, $J_{4',5'}$ 9.5 Hz, H-4'), 4.38 (bs, 1 H, O*H*-9), 4.07 (s, 3 H, CH_3), 4.05 (dq, 1 H, $J_{5',6'}$ 6.2 Hz, H-5'), 3.22 (dd, 1 H, $J_{8e,10e}$, 1.6, $J_{10e,10ax}$ 18.8 Hz, H-10*e*), 2.91 (d, 1 H, H-10*ax*), 2.43 (s, 3 H, H-14), 2.32 (dt, 1 H, $J_{8e,8a}$ 14.8 Hz, H-8*e*), 2.22 (dd, $J_{2'e,2'a}$ 13.6 Hz, H-2'*e*), 2.13 (dd, 1 H, H-8*ax*), 2.06 (s, 3 H, $COCH_3$), 1.96 (s, 3 H, $COCH_3$), 1.81 (ddd, 1 H, H-2'*a*), and 1.24 (d, 3 H, H-6').

The experiment was repeated under the same conditions, but with $DSnBu_3$ as the reagent. The ^{1}H-n.m.r. spectrum of the product (**5**) was essentially the same as that of **4**, except that no signal was present at δ 1.81 (H-2'*a*), the signal at δ 2.22 (H-2'*e*) was now a doublet ($J_{2'e,3'}$ 5.3 Hz), the signal at δ 5.05 (H-3') was now a doublet of doublets ($J_{3',4'}$ 9.3 Hz), and the signal at δ 5.51 (H-1') became a broad singlet ($J_{1',2'e}$ 0.9 Hz).

*7-O-(3,4-Di-O-acetyl-2,6-dideoxy-α-*L*-*lyxo*-hexopyranosyl)daunomycinone* (**8**). — A sample (105 mg, 0.142 mmol) of compound **7** was dehalogenated under the conditions just described for compound **2**. After precipitation from EtOH, 48

mg (55%) of a product was obtained that was identical to an original sample[2,3] of **8**.

^{1}H-N.m.r. data: δ 13.99 and 13.26 (2 s, each 1 H, O*H*-6, O*H*-11), 8.03 (dd, 1 H, $J_{1,2}$ 7.6, $J_{1,3}$ 0.8 Hz, H-1), 7.78 (t, 1 H, $J_{2,3}$ 8.1 Hz, H-2), 7.38 (dd, 1 H, H-3), 5.60 (d, 1 H, $J_{1',2'a}$ 4.1 Hz, H-1'), 5.28 (dd, 1 H, $J_{7,8e}$ 1.9, $J_{7,8ax}$ 4.0 Hz, H-7), 5.22 (d, 1 H, $J_{3',4'}$ 3.0 Hz, H-4'), 5.07 (ddd, 1 H, $J_{2'a,3'}$ 12.6, $J_{2'e,3'}$ 5.0 Hz, H-3'), 4.34 (bs, 1 H, O*H*-9), 4.28 (q, 1 H, $J_{5',6'}$ 6.2 Hz, H-5'), 4.08 (s, 3 H, OCH_3), 3.22 (dd, 1 H, $J_{8e,10e}$ 1.8, $J_{10ax,10e}$ 18.8 Hz, H-10*e*), 2.94 (d, 1 H, H-10*ax*), 2.42 (s, 3 H, H-14), 2.31 (dt, 1 H, $J_{8e,8ax}$ 14.9 Hz, H-8*e*), 2.16 (s, 3 H, COCH_3), 2.13 (dd, 1 H, H-8*ax*), 2.07 (td, 1 H, $J_{2'e,2'a}$ 13.0 Hz, H-2'*a*), 1.94 (s, 3 H, COCH_3), 1.88 (dd, 1 H, H-2'*e*), and 1.20 (d, 3 H, H-6').

The experiment was repeated but with use of $DSnBu_3$ as the reagent. The ^{1}H-n.m.r. spectrum of the product (**9**) was essentially identical with that just recorded, except that the signal at δ 2.07 (H-2'*a*) had an integrated intensity of only 0.1 proton and appeared as a doublet of doublets ($J_{1',2'a}$ 4.1, $J_{2'a,3}$ 12.6 Hz), the signal at δ 1.88 (H-2'*e*) had an integrated intensity of 0.9 proton and appeared as a doublet ($J_{2'e,3'}$ 5.0 Hz), the signal at δ 5.07 (H-3') appeared as a doublet of doublets ($J_{2'e,3'}$ 5.0, $J_{3',4'}$ 3.0 Hz), and finally, the signal at δ 5.60 (H-1') appeared as a broad singlet.

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