COMMUNICATION

New anthracycline disaccharides. Synthesis of L-daunosaminyl-α(1→4)-2-deoxy-L-rhamnosyl and of L-daunosaminyl-α(1→4)-2-deoxy-L-fucosyl daunorubicin analogues

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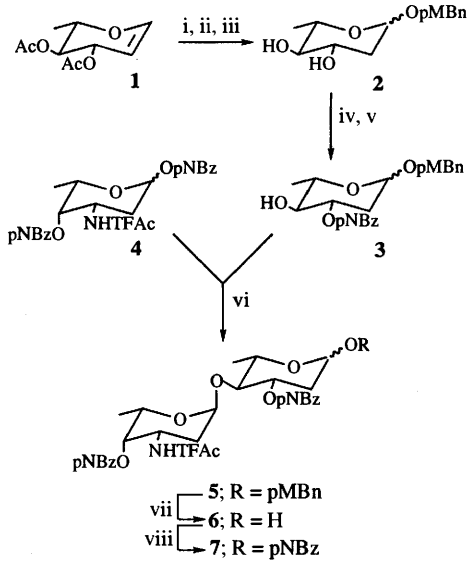
The synthesis of the new disaccharide anthracyclines 20, 21, 24 and 25, where the daunosamine moiety is separated from the aglycone by either a rhamnose or a fucose residue, performed following a convergent procedure, gives insight into the configurational requirement of the first sugar residue and opens the way to a new class of antitumour anthracyclines.

Anthracycline glycosides containing a disaccharide or trisaccharide chain reported in the literature[1] bear the aminosugar directly attached to the anthracyclinone. According to X-ray analysis of drug–DNA complexes[2] and to theoretical calculations,[3] the amino group in the first residue dictates the presence of an AT base pair in the position adjacent to the intercalation site, contributing to the DNA sequence specificity of the anthracyclines. In the course of our programme aimed at new antitumour anthracyclines, we became interested in the evaluation of the antitumour properties of anthracycline disaccharides *not* containing the amino group in the aglycone bound sugar residue.

We report here the synthesis of disaccharide daunorubicin analogues **20**, **21**, **24** and **25** having either a 2-deoxy-L-rhamnose or a 2-deoxy-L-fucose moiety directly linked to the aglycone, where the second sugar residue, daunosamine, is bound to the first one *via* an α(1→4) linkage. Anthracycline glycosides bearing such sugar sequences have not yet been synthesized, although recently the preparation of a (1–3) linked α-L-daunosaminyl 2-deoxy-L-rhamnosyl daunorubicin analogue has been disclosed.[4]

A convergent synthetic strategy, implying the separate construction of the two disaccharide moieties **7** (Scheme 1) and **15** (Scheme 2) and their successive coupling with both the aglycones **16** and **17**, was adopted (Scheme 3) in order to avoid transglycosidation products[5] which may arise during the glycosylation of the anthracycline monosaccharide intermediate with the terminal sugar unit in the alternative stepwise strategy.

Starting materials for the synthesis of the *p*-nitrobenzoyl 3-*O*-*p*-nitrobenzoyl-4-*O*-(3-*N*-trifluoroacetyl-4-*O*-*p*-nitrobenzoyl-α-L-daunosaminyl)-2-deoxy-L-rhamnoside **7** (Scheme 1) were 1,4-*O*-bis-*p*-nitrobenzoyl-3-*N*-trifluoroacetyldaunosamine **4**, obtained by *p*-nitrobenzoylation of 3-*N*-trifluoroacetyldaunosamine,[6] and *p*-methoxybenzyl 3-*O*-*p*-nitrobenzoyl-2-deoxy-L-rhamnoside **3**. This was synthesized from 3,4-di-*O*-acetyl-L-rhamnal **1**[7] by reaction with *p*-methoxybenzyl alcohol (pMBnOH) and *N*-iodosuccinimide, followed by reduction with tributyltin hydride and de-*O*-acetylation to give **2**. Selective protection in position C-3 was performed *via* formation of a stannylene cyclic acetal that exists in a dimeric form preferentially cleaved at the apical position,[8] therefore affording **3** (72%) when treated with *p*-nitrobenzoyl chloride (pNBzCl) in pyridine. The reaction between **3** and **4**, carried out in the presence of trimethylsilyltriflate (TMSOTf)[6] gave the disaccharide **5** in high yield (79%) and with the desired α

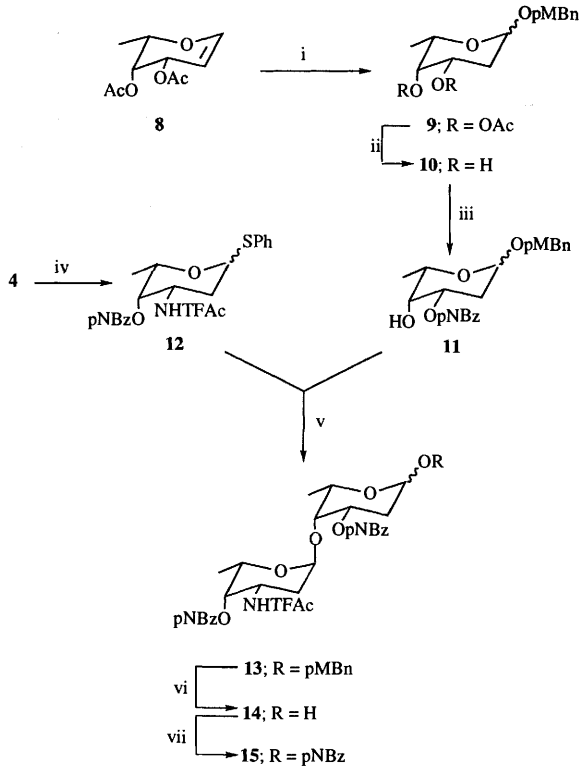


Scheme 1 *Reagents and conditions:* i, (*p*-MeO)$C_6H_4CH_2OH$ (*p*-MBnOH), *N*-iodosuccinimide (NIS), MeCN, −50 °C, 1 h; ii, Bu_3SnH, AIBN, reflux, 30 min; iii, MeONa, MeOH, room temp., 1 h; iv, Bu_2SnO, toluene, reflux, 6 h; v, (*p*-NO_2)C_6H_4COCl (*p*-NBzCl), Et_3N, toluene, −40 °C, 2 h; vi, TMSOTf, CH_2Cl_2, −15 °C, 40 min; vii, $Ce(NH_4)_2(NO_3)_6$, MeCN–H_2O, room temp., 1 h; viii, *p*-NBzCl, pyridine, CH_2Cl_2, 0 °C, 2 h

configuration. The same disaccharide had been previously obtained as the methyl glycoside *via* Koenigs–Knorr glycosidation and subsequent alkoxyhalogenation and reduction of the disaccharide glycal intermediate.[4] Our approach has the advantage that **4**, more stable and easier to handle than the L-daunosamine glycal derivative, allows a faster entry to the disaccharide **5**. Quantitative removal of the anomeric *p*-methoxybenzyl group in **5** with ceric ammonium nitrate[9] gave **6**, that was activated (90% yield) at the anomeric position as the *p*-nitrobenzoyl ester **7**. This was coupled with the aglycones **16**[10] and **17**[11] according to a known procedure[6] to give the corresponding α glycosides **18** and **19** in 60 and 57% yield, respectively (Scheme 3). Deprotection with 0.2 mol dm^{-3} $Ba(OH)_2$ afforded the final aminoglycosides **20** {δ_H[$(CD_3)_2SO$] 5.2, d, 1 H, $J_{1',2'ax}$ = 4 Hz} and **21** {δ_H[$(CD_3)_2SO$] 5.13, br s, 1 H, width$_{\frac{1}{2}}$ = 9 Hz},† isolated as hydrochlorides, in approximately 70% yield.

Starting materials for the synthesis of the activated protected disaccharide unit *p*-nitrobenzoyl 3-*O*-*p*-nitrobenzoyl-4-*O*-(3-*N*-trifluoroacetyl-4-*O*-*p*-nitrobenzoyl-α-L-daunosaminyl)-2-

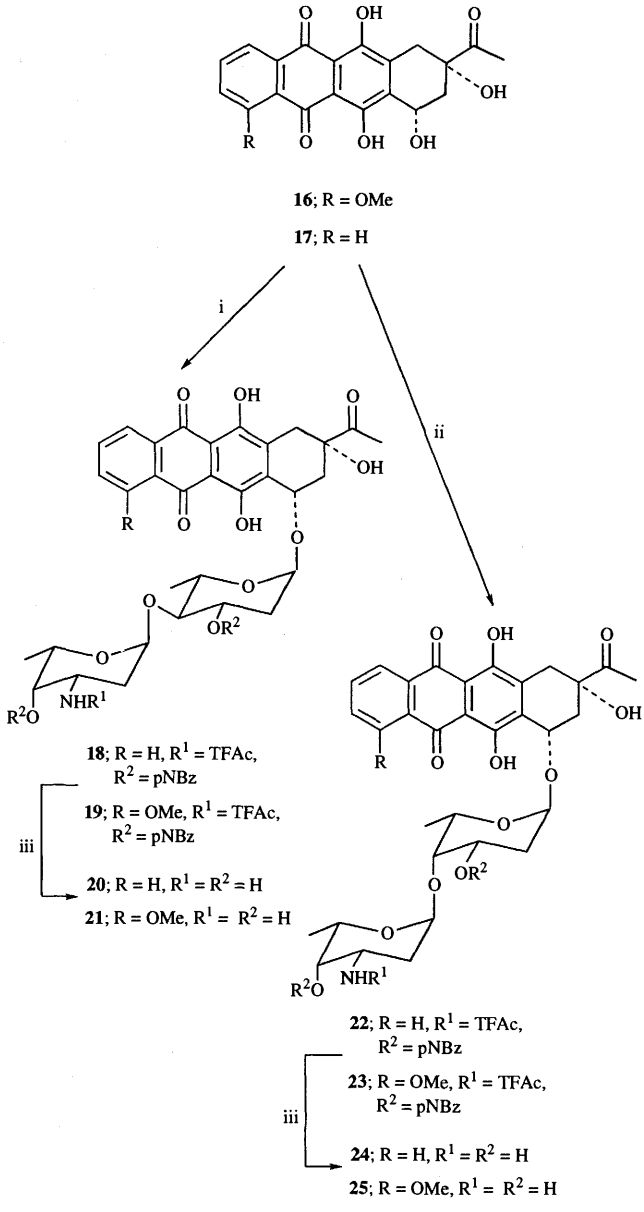
† NMR spectra were recorded on a Varian Gemini 300 MHz spectrometer. Supplementary data: see Instructions for Authors in the January issue.



Scheme 2 *Reagents and conditions:* i, *p*-MBnOH, Ph_3PHBr, CH_2Cl_2, room temp., 1 h; ii, MeONa 1 mol dm^{-3}, MeOH, room temp.; iii, *p*-NBzCl, pyridine, CH_2Cl_2, −15 °C, 1 h; iv, $PhSSiMe_3$, $CF_3SO_3SiMe_3$, CH_2Cl_2, room temp., 12 h; v, Iodonium dicollidine perchlorate (IDCP), $(CH_2Cl)_2$–Et_2O, 4 Å molecular sieves, 5–10 °C, 2 h; vi, $Ce(NH_4)_2(NO_3)_6$, MeCN–H_2O, room temp., vii, *p*-NBzCl, pyridine, CH_2Cl_2, 0 °C, 2 h

deoxy-L-fucoside **15** (Scheme 2) were phenyl 4-*O*-*p*-nitrobenzoyl-3-*N*-trifluoroacetyl-1-thiodaunosaminide **12**, obtained from **4** upon treatment with (phenylsulfanyl)trimethylsilane and TMSOTf,[12] and *p*-methoxybenzyl 3-*O*-*p*-nitrobenzoyl-2-deoxyfucoside **11**. This derivative was prepared by the addition of *p*-methoxybenzyl alcohol to 3,4-di-*O*-acetyl-L-fucal **8**[13] in the presence of a Lewis acid catalyst to give **9**, followed by de-*O*-acetylation and selective *p*-nitrobenzoylation of the resulting **10**. Various glycosylation reactions using different methods[1d,14] for the activation of the glycosylating daunosamine derivative failed or gave poor yields of the desired disaccharide derivative **13**. This known difficulty in the glycosylation of the C-4 axial hydroxy group[15] of the sugar acceptor was overcome in the reaction of **11** with **12**, carried out in the presence of iodonium dicollidine perchlorate[16] to afford **13** in moderate yield. Conversion of **13** to the glycosylating disaccharide intermediate **15** was performed as above *via* oxidative cleavage of the *p*-methoxybenzyl group, followed by activation of **14** by *p*-nitrobenzoylation in practically quantitative overall yield. Finally, glycosylation of aglycones **16** and **17** to **22** and **23** followed by the deprotection step as above afforded the desired 4′-epimeric anthracycline disaccharides **24** and **25** in similar yield (40%) after purification as hydrochlorides by preparative reversed-phase HPLC (Scheme 3).

Biological evaluation of the four aminoglycosides showed that **20**, **21** and **25** were less potent than clinically useful idarubicin and daunorubicin, whereas **24**, possessing the 'natural' configuration at C-4′ and lacking the 4-methoxy group at C-4, was endowed with a particularly high activity in inhibiting the growth of human tumour cells in culture.[17] Therefore, our results open the way to an interesting new series of synthetic analogues of the antitumour anthracyclines that can be obtained in reasonable yields for further developments within this class of important pharmacological agents. We have



Scheme 3 *Reagents and conditions:* i, disaccharide **7**, $CF_3SO_3SiMe_3$, CH_2Cl_2–Et_2O, −20 °C, 1 h; ii, disaccharide **15**, $CF_3SO_3SiMe_3$, CH_2Cl_2–Et_2O, −20 °C, 1 h; iii, 0.2 mol dm^{-3} $Ba(OH)_2$, MeOH, 0 °C, 4 h

now found that the 14-hydroxy derivative of **24**, *i.e.* 3′-deamino-3′-hydroxy-4′-*O*-α-L-daunosaminyl-4-demethoxydoxorubicin, shows, according to our experience, unprecedented activity when compared with doxorubicin in different human cancers implanted in immunodepressed mice.[18] The synthesis and the biological properties of the first doxorubicin disaccharide analogue will be reported in due course.

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