Anthracyclinones.† Enantioselective Synthesis of 9-Alkylanthracyclinone *via* Highly Diastereocontrolled Alkylation of 4-Cyanofuranosugars

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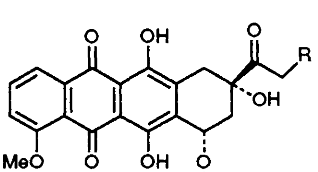
An efficient method for the enantio- and diastereo-controlled construction of potentially tertiary alcohol by alkylation of an α-cyano-carbanion derived from 1,2-*O*-isopropylidene-3-deoxy-β-L-threo-pentofuranuronitrile **6** as chiral template has been developed; the method has been applied to the stereocontrolled synthesis of optically active 4-demethoxy feudomycinone C **4**.

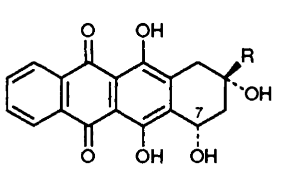
The clinical utility of the anthracycline antitumour antibiotics such as doxorubicin **1** and daunomycin **2** is well established, but toxic side-effects and intrinsic or acquired anthracycline resistance in tumours hampers their clinical effectiveness.[2] Much work still has to be done to improve the therapeutic effect and reduce the toxicity of these compounds. For these reasons, extensive efforts have been made, devoted to the synthesis of new analogues.[3] As part of a programme towards the synthesis of new 9-alkylanthracyclines potentially active against tumour-resistant cell lines,[4] we needed to develop a general and convenient method to have access to various 9-alkylanthracyclinones of general formula **3** homologues of 4-demethoxy feudomycinone C **4**. Since the biological activity of anthracyclines is critically dependent on the chirality at C-9 and a *cis*-relationship at C-7, C-9, as in natural aglycone, it is necessary to have a stereocontrolled construction of this C-9 stereogenic centre in the desired absolute configuration. This problem has been solved before by incorporating chiral building blocks derived from natural templates[3] or by asymmetric construction.[5]

In the course of our studies on the effective utilization of carbohydrates as optically pure starting materials for chiral synthesis of anthracyclinones,[6] it occurred to us that the alkylation of the 4-cyanosugar **6**, which can be obtained in five steps from commercial 1,2-*O*-isopropylidene glucose **5**,[7] would allow a stereoselective incorporation of various alkyl groups at the C-4 position of the furanose ring (Scheme 1), which still remains a problem.[8]

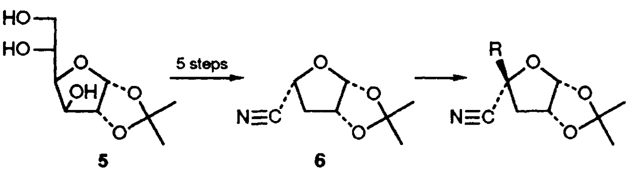
Indeed, if we consider the cyanosugar template **6** as a chiral protected cyanohydrin, an α-metallation on the cyano group would give reactions typical of active methylene carbanion, such as alkylation and acylation. When compound **6** was added in dry tetrahydrofuran (THF) to 2.1 equiv. of lithium diisopropylamide (LDA) at −78 °C, and the resulting α-cyano-carbanion subsequently alkylated with MeI as electrophile (Table 1, entry a), the alkylation adduct **7** [50%, m.p. 89 °C, $[\alpha]_D^{20}$: −53.5 (*c* 0.5 $CHCl_3$)] was obtained. As we postulated, alkylation took place very diastereoselectively (>95%) from the β-face, opposite to the bulky 1,2-*O*-isopropylidene group. This was determined by an X-ray analysis‡ realized on this crystalline compound (Fig. 1). The same facial metallation was observed with some other electrophiles- EtBr



1; R = OH
2; R = H

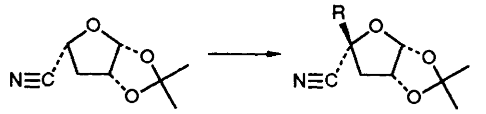


3; R = alkyl
4; R = Me



5 **6**

Scheme 1



6

7; = Me
8; = Et
9; = Me(CHOH)
10; = $CH_2(OMOM){=}CH_2$

Table 1 Enolate alkylation of **6**

Entry	RX or RCHO	Method[a]	Product	Yield (%)
a	MeI	A	**7**	50
b	MeI	B	**7**	84
c	EtBr	A	**8**	60
d	EtBr	B	**8**	80
e	$ICH_2(OMOM){=}CH_2$	A	**10**	30
f	$ICH_2(OMOM){=}CH_2$	B	**10**	67
g	MeCHO	A	**9**[b]	55

[a] Method A involves: addition of the nitrile (1 equiv.) to a solution of LDA (2.1 equiv.) in THF at −78 °C followed by addition after 0.5 h of the electrophile (1.5 equiv.). Method B involves: addition of KHMDS (1.2 equiv.) to a preformed mixture of nitrile (1 equiv.) and electrophile (1.5 equiv.) in THF at −78 °C. The experiments were run on a 20 mmol scale. [b] As a mixture of C-5 OH diastereoisomers in a 3:1 ratio from NMR data.

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† Part IX in the series.[1]

‡ *Crystal data:* $C_9H_{13}O_3N$, M = 183.207, monoclinic, a = 10.070(6), b = 12.940(7), c = 7.449(5) Å, β = 92.74(5)°, U = 970(4) Å^3, space group $P2_1$, Z = 4, D_c = 1.255 g cm^{-3}, $F(000)$ = 392, colourless, air stable prisms. Crystal dimensions 0.3 × 0.2 × 0.05 mm, μ(Cu-Kα) = 0.75 mm^{-1}. Intensity data were collected at room temperature with graphite-monochromated Cu-Kα radiation (λ = 1.5418 Å) on a Philips PW100 diffractometer. Of 1924 measured reflections (θ 1.5–68°, three standard reflections, decomposition less than 0.03), 1692 independent reflections with $I \leq 3\sigma(I)$ were used in the structure analysis ($-12 \geq h \geq 12$, $0 \geq k \geq 15$, $0 \geq l \geq 8$). An absorption correction was made using DIFABS (N. Walker and D. Stuart *Acta Crystallogr.*, 1983, **139**, 158–166). The structure was solved by direct methods (SHELXS86, Program for the solution of crystal structures, G. M. Sheldrick, 1986, University of Göttingen, Germany) and refined through full-matrix least-squares calculations (CRYSTALS Software, D. J. Watkin, J. R. Carruthers and P. W. Betteridge, 1985, Chemical Crystallography Laboratory, University of Oxford, England), anisotropically for non-hydrogen atoms and isotropically for hydrogen atoms, hydrogen atom positions calculated and refined to final R = 4.6% and R_w = 4.5% (unit weights). On the last Fourier-difference, ρ_{max} = 0.12 and ρ_{min} = −0.12. Atomic coordinates, bond lengths and angles, and thermal parameters have been deposited at the Cambridge Crystallographic Data Centre. See Notice to Authors, Issue No. 1.

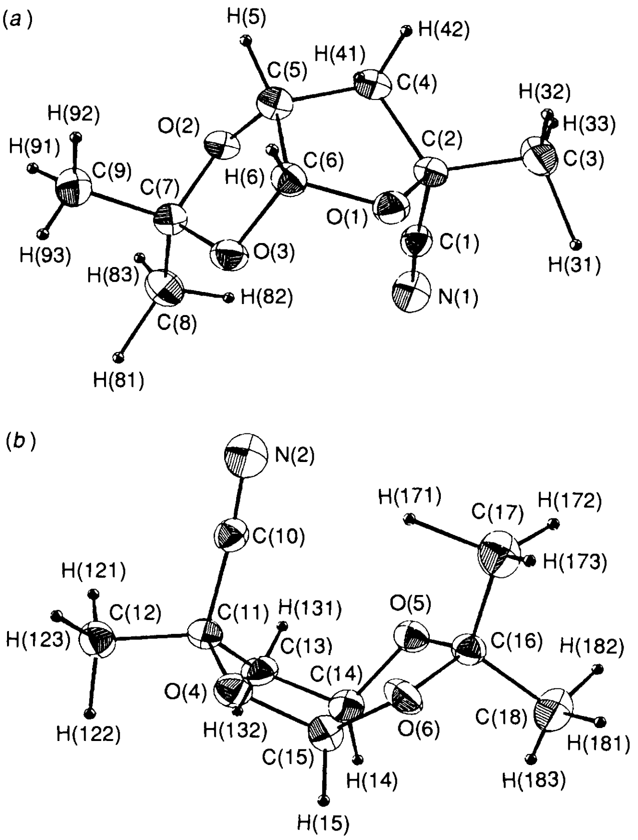
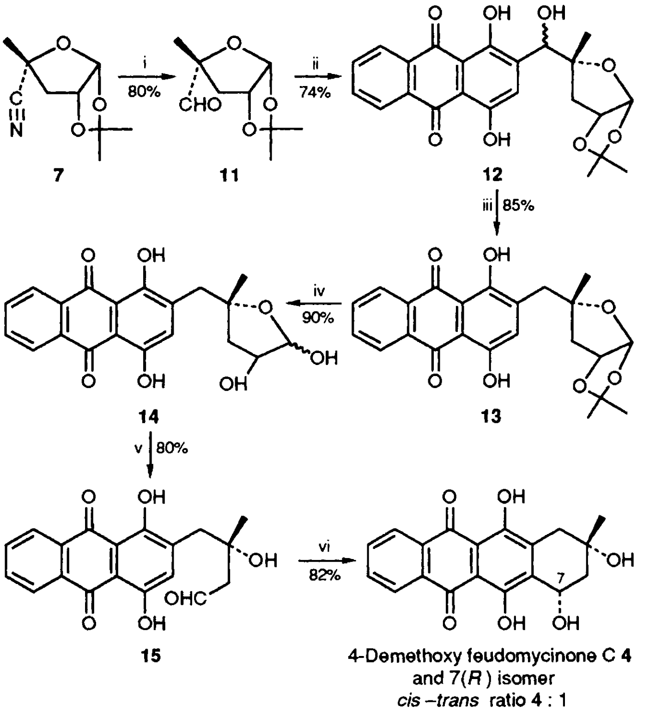


Fig. 1 ORTEP view of the two independent molecules showing the atom numbering, thermal ellipsoids (50%) for non-H atoms

(entry c), MeCHO (entry g) and 2-(iodomethyl)-3,5-dioxahex-1-ene[9] (entry e). The compounds **8** [60%, m.p. 64 °C; $[\alpha]_D^{20}$ −42 (*c* 0,7 $CHCl_3$)], **9** [55%, as a mixture of C-5(OH) diastereoisomers in a 3 : 1 ratio], and **10** [30%. $[\alpha]_D^{20}$ −36 (*c* 1, $CHCl_3$)] were respectively obtained, along with dimers, unconverted starting material and substantial by-products. In order to provide more reactive enolate and to avoid such problems, stoichiometric amounts of metal chelating tertiary diamine [*N,N,N′,N′*-tetramethylethylenediamine (TMEDA) or 1,4-dimethyl piperazine] or of strongly dissociating agents [hexamethylphosphoramide (HMPA) or dimethyltetrahydropyrimidinone (DMPU)] were added. Nevertheless, comparable results were obtained. On the other hand, the inverse addition of LDA (2 equiv. at −78 °C) to a preformed mixture of cyano compound and electrophile (MeI) was also disappointing. However, using this method of inverse addition, but with potassium bis(trimethylsilylamide) (KHMDS) as strong base, we observed a dramatic improvement in the yields for **7** (84%) (entry b), for **8** (80%) (entry d) and for **10** (67%) (entry f). This reveals that the reactivity of the enolate was sensitive to the counterion effect and these results are best understood in terms of the intimacy of the metal counterion and the enolate association.[10]

The synthetic utility of these C-4 branched cyano sugars was next demonstrated by the synthesis of 4-demethoxy feudomycinone C **4** (Scheme 2). The cyano adduct **7** was converted to the aldehyde **11** {$[\alpha]_D^{20}$ −38 (*c* 1, $CHCl_3$)} by reductive hydrolysis with Raney nickel, following a slight modification of the Moffat procedure.[11] Condensation of leucoquinizarin with **11** in dimethylformamide (DMF) at room temp. gave, after air oxidation, **12** (74%) as a mixture of diastereoisomers directly treated with $Na_2S_2O_4$ in DMF–H_2O (5 : 1) to give **13** (85%) (m.p. 115–120 °C, {$[\alpha]_D^{20}$ −167 (*c* 0,04 THF)}. The isopropylidene group was removed by heating with 75% aqueous AcOH to produce **14** (90%). Cleavage of the glycol moiety by $NaIO_4$ in AcOH–H_2O (1 : 1) gave the aldehyde **15** (80%) {$[\alpha]_D^{20}$ +1 (*c* 0,04 THF)}]. Treatment of the latter with 7% aqueous NaOH for 0.5 h under argon followed by addition of aq. $Na_2S_2O_4$ (1.1 equiv.) in THF–MeOH (1 : 1) and subsequent reoxidation furnished the 4-demethoxy feudomycinone C **4** (82%) with a good stereocontrol as a mixture of 7(*S*)- and 7(*R*)-diastereoisomers in a 4 : 1 ratio. Both compounds were easily separated by flash chromatography and identified with authentical samples yet correlated resulted from precedent synthesis.[12]§



7 11 12 13 14 15

4-Demethoxy feudomycinone C 4 and 7(*R*) isomer *cis–trans* ratio 4 : 1

Scheme 2 i, Ni Raney, H_2O–Pyr–AcOH 1 : 1 : 1; ii, leucoquinizarin 1 equiv., DBU in DMF at room temp.; iii, $Na_2S_2O_4$, DMF–H_2O; iv, AcOH–H_2O 4 : 1 reflux; v, $NaIO_4$ in AcOH–H_2O; vi, 7% aq.NaOH, $Na_2S_2O_4$, MeOH–THF 0 °C, 0.5 h.

We have thus demonstrated that compound **6** could be a useful chiral synthon for the synthesis of anthracyclinones with natural C-7 and C-9 configurations. Further studies on the scope and limitations as well as applications of this method of alkylation of cyano sugars to the synthesis of others biologic-

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§ All new substances exhibited spectroscopic data in agreement with the assigned structure and provided acceptable microanalytical data. *Selected ¹H NMR data* (90 MHz, $CDCl_3$) for **7**: δ 5.87 (d, 1H, *J* 4.2 Hz, 1-H), 4.83 (1H, *J* 13.5, *J′* 4.5 Hz, 2-H), 2.66 (d, 1H, *J* 13.5 Hz, 3a-H), 1.92 (dd, 1H, *J* 13.5, *J′* 4.5 Hz, 3b-H), 1.66 [s, 6H, C(Me)₂)] and 1.26 (s, 3H, Me). For compound **8** (90 MHz, $CDCl_3$): δ 5.80 (d, 1H, *J* 3.5 Hz, 1-H), 4.78 (dd, 1H, *J J′* 3.5 Hz, 2-H), 2.60 (d, 1H, *J* 13.5 Hz, 3a-H), 2.17–1.68 (m, 3H, CH_2-Me and 3b-H), 1.70 and 1.34 [2s, 2 × 3H, C(Me)₂], 1.14 (t, 3H, CH_3-CH_2).

For compound **9** (mixt. of C-5 isomers, 90 MHz, $CDCl_3$): 5.97 (d, 0.3H, *J* 3.5 Hz, 1-H), 5.77 (d, 0.7H, *J* 3.5 Hz, 1-H), 4.76 (m, 1H, 2-H), 3.99 (q, 0.3H, *J* 6Hz, CH_3-CH), 3.00–2.00 (m, 2H, 3-H), 1.65 and 1.29 [2s, 2 × 3H, C(Me)₂], 1.41 (2d, CH_3–CH]. For **4** [7(*S*)-isomer, 270 MHz, $CDCl_3$]: δ 13.62 (s, 1H) and 13.34 (s, 1H)(phenol), 8.37–8.34 (m, 2H) and 7.90–7.87 (m, 2H)(AA′BB′ syst. H arom.), 5.22 (m, 1H, 7H), 3.20 (dd, 1H, *J* 19, *J′* 1 Hz) and 2.53 (d, *J* 19 Hz, 10-H), 2.32 (d, 1H, *J* 15 Hz) and 1.90 (dd, 1H, *J* 15, *J′* 5Hz, 8-H), 1.56 (s, 3H, Me). For **4** [7(*R*)-isomer, 270 MHz, $CDCl_3$]: δ 13.96 (s, 1H) and 13.37 (s, 1H)(phenol), 8.40–8.36 (m, 2H) and 7.92–7.87 (m, 2H)(AA′BB′ syst. H arom.), 5.31 (dd, 1H, *J* 7, *J′* 6 Hz, 7-H), 2.97 (dd, 1H, *J* 15, *J′* < 1 Hz) and 2.70 (d, 1H, *J* 15 Hz, 10-H), 2.34 (m, 1H) and 1.80 (m, 1H, 8-H), 1.44 (s, 3H, Me).

For **4**: 7-α isomer: m.p. 190 °C, $[\alpha]_D^{20}$ +133 (*c* 0,1, dioxane); lit.:[13] m.p. 185 °C, $[\alpha]_D^{20}$ +125.4 (*c* 0,4, $CHCl_3$–MeOH, 6 : 1). 7-β-Isomer: m.p. 202 °C, $[\alpha]_D^{20}$ −120 (*c* 0,1, dioxane); lit.:[13] m.p. 194 °C, $[\alpha]_D^{20}$ −131.5 (*c* 0,4, $CHCl_3$–MeOH, 6 : 1).

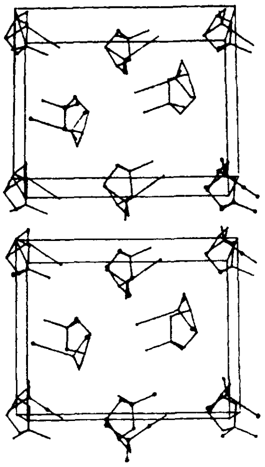

Fig. 2 Stereoscopic view of the packing

ally active compounds bearing a chiral tertiary alcohol are now under investigation.

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