Regiospecific Total Synthesis of 6-Deoxyanthracyclines: 6-Deoxycarminomycin

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The regiospecific synthesis of the novel anthracycline 6-deoxycarminomycin (**14b**) is reported: the construction of the aglycone is based on the coupling of 1,4,5-trimethoxy-3-lithionaphthalene (**3**) to lactone (**9**) in a regioselective fashion, a new synthetic approach which provides a general route to 6-deoxyanthracyclinones.

In our continuing search for new antitumour anthracyclines related to doxorubicin, we have investigated new synthetic approaches to the 6-deoxyanthracyclines, hitherto little studied. Recently we reported the first regioselective synthesis of 4-demethoxy-6-deoxydaunorubicin (**1**).[1] We herein report a new improved regioselective route which allows the preparation of 6-deoxyanthracyclinones bearing substituents in ring D as illustrated by (**5**).

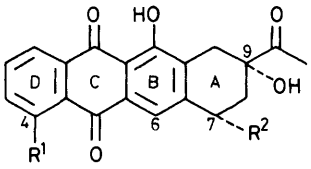
Our synthesis utilizes the new lactone (**9**), as a key intermediate for the construction of the tetracycle, instead of (**4**).† The crystalline AB ring precursor (**9**) (m.p. 67—69 °C)‡ is easily obtainable from the inexpensive *trans* dimethyl 1,2,3,6-tetrahydrophthalate (**6**),[3] following the reaction sequence reported in Scheme 1. Compound (**9**) is particularly interesting because it has already the functionalization at the future C–9 of (**5**); it condenses with (**3**) in a completely regioselective fashion, and could allow a control of the chirality at an early stage of the synthetic process through classical optical resolution. The addition [−78 °C, tetrahydrofuran (THF)] of (**3**), obtained from 1,4,5-trimethoxy-3-bromonaphthalene[4] (Bu^{n}Li, THF, −78 °C), to (**9**) followed by treatment with MeOH–HCl afforded only (**10**), as a yellow oil, in 60% yield after chromatographic purification.§

The further synthetic elaboration of (**10**) involved two critical steps: the reduction of the benzylic carbonyl group to methylene and the suppression of the easy formation of the five-membered lactone under the Friedel–Crafts cyclization reaction conditions. After extensive experimental trials we found that treatment of (**10**) with the BH_3–pyridine(py) complex[5] allowed reduction of the benzylic ketone function to methylene although the undesirable reduction of the other ketone function to alcohol could not be avoided. The benzylic ester (**11**), obtained from (**10**) in 70% overall yield (i, BH_3–py, CF_3CO_2H, room temp., 2 h; ii, aqueous 10% NaOH, room temp.; iii, H^+; iv, $PhCHN_2$, room temp., 3 h) after acetylation of the hydroxy groups (Ac_2O, py, 4-*N*,*N*-dimethylaminopyridine, room temp., 24 h) was converted to the corresponding acid (cyclohexane, 10% Pd/C, reflux, 1 h) and cyclized [$(CF_3CO)_2O$, CF_3CO_2H, 0 °C, 1 h] to give, after methanolysis of the acetates, (**12**) in 60% overall yield.

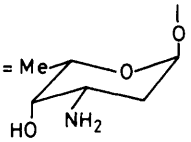
† An attempt to perform the synthesis of (**5**) using the coupling reaction between (**3**) and the aldehyde (**4**), following the procedure described for (**2**),[1] showed lack of regioselectivity affording 6-deoxydaunomycinone together with 6-deoxyisodaunomycinone, whose u.v. spectra are in agreement with those reported for (**15a,b**).[2]

‡ All new compounds were fully characterized by spectroscopic means (i.r., u.v., ^{1}H n.m.r., and mass) and gave satisfactory elemental analysis (crystalline compounds). The yields are not optimized.

§ The same regioselectivity was observed using (**3**) and carrying out the coupling reaction at −78 °C or −20 °C in THF as well as in dimethoxyethane (DME). On the other hand the reaction between (**3**) and (**16**) at −78 °C in THF afforded a 1 : 1 mixture of products derived from the nucleophilic attack on both of the carbonyl groups, whereas if the reaction was carried out at −20 °C in THF or DME, the attack was preferentially on the lactonic group in the ratio 3 : 2 and 4 : 1 respectively. These results seem to indicate that the preferential attack on the lactonic carbonyl in (**16**) depends on the degree of dissociation of the lithium salt.



(1) R^1 = H, R^2 = Me

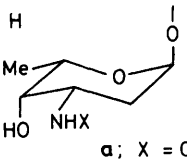


(2) R^1 = H, R^2 = OH

(5) R^1 = R^2 = OH

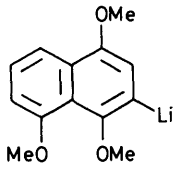
(13) R^1 = OH, R^2 = H

(14) R^1 = OH, R^2 = Me

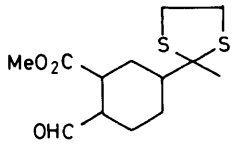


a; X = $COCF_3$

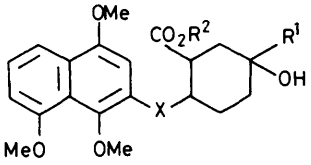
b; X = H



(3)

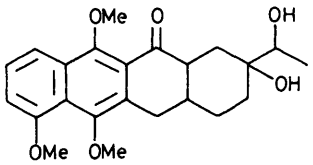


(4)

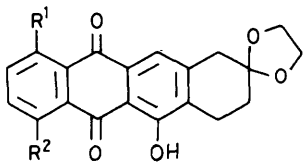


(10) X = C=O, R^1 = COMe, R^2 = Me

(11) X = CH_2, R^1 = CH(OH)Me, R^2 = CH_2Ph



(12)



(15)

a; R^1 = OMe, R^2 = H

b; R^1 = H, R^2 = OMe

(16)

Oxidation of the secondary alcohol (**12**) (dimethyl sulphoxide, triethylamine, SO_3, 90% yield) followed by oxidative dealkylation in nitrobenzene with $AlCl_3$ in the presence of air, gave 6,7-dideoxycarminomycinone (**13**) (m.p. 188—190 °C) in 40% yield. After the protection of the ketone function ($HOCH_2$-CH_2OH, H^+), the introduction of the hydroxy group at C-7 to give (**5**) was carried out following a procedure already described[6] (i, *N*-bromosuccinimide, azoisobutyronitrile, *hν*; ii, $MeCO_2Ag$; iii, H^+; iv, NaOMe, MeOH). The racemic (**5**) [m.p. 211—213 °C; u.v. (MeOH) λ_{max} 248, 256, 330, 406 nm; ^1H n.m.r. (200 MHz, $CDCl_3$) at δ: 2.2—2.14 (m, 8-H), 2.40 (s, COMe), 2.8—3.2 (2 d, *J* 18 Hz, 10-H), 4.12 (d, *J* 11 Hz 7-OH), 4.45 (s, 9-OH), 4.92 (m, 7-H), 7.33 (d, 3-H), 7.68 (t, 2-H), 7.84 (d, 1-H), 8.01 (s, 6-H), 12.70 (s, 4-OH), and 13.13 (s, 11-OH)] was glycosylated with 1-chloro-*N*,*O*-di(trifluoroacetyl)daunosamine in the presence of silver trifluoromethanesulphonate.[1] The diastereoisomeric α-glycosides 7(*S*), 9(*S*) and 7(*R*), 9(*R*) were separated by chromatography and the absolute configurations were assigned on the basis of circular dichroism (c.d.) curves.[7] The mild alkaline hydrolysis of the 7(*S*), 9(*S*) diastereoisomer (**14a**) [m.p. 210—212 °C; *m/z* 593 (M^+); ^1H n.m.r. (200 MHz, $CDCl_3$) *inter alia* at δ: 1.44 (d, *J* 6.5 Hz, 5′-Me), 2.42 (s, COMe), 2.90—3.40 (2 d, *J* 19 Hz, 10-H), 5.07 (t, *J* 3.3 Hz, 7-H), 5.27 (t, *J* 1.8 Hz, 1′-H)] afforded (**14b**) isolated as the hydrochloride.

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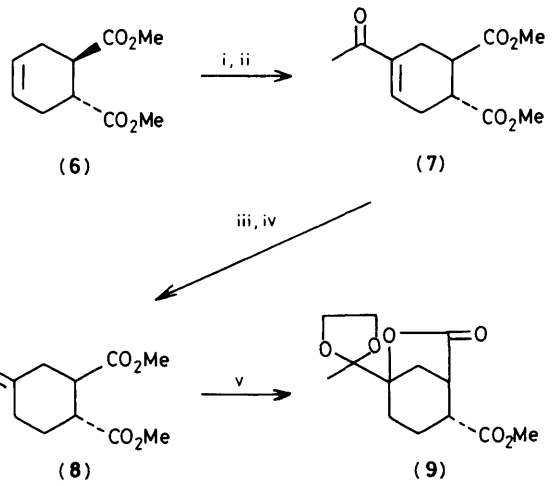

Scheme 1. *Reagents and conditions:* i, Ac_2O, $SnCl_4$, −10 °C, 3 h, 45%; ii, MeOH–HCl 1 M, reflux, 2 h, 75%; iii, *p*-$MeC_6H_4SO_2NHNH_2$ EtOH, reflux, 4 h, 90%; iv, catecholborane, CH_2Cl_2, 5 °C; AcONa, H_2O, toluene, reflux, 3 h, 75% over two steps; v, $KMnO_4$, H_2O–$(CH_3)_2CO$, AcOH, room temp., 3 h; toluene-*p*-sulphonic acid, benzene, reflux, 1 h; $HO[CH_2]_2OH$, toluene, toluene-*p*-sulphonic acid, reflux, 2 h, 30% over three steps.

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