

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-bromonaphthalene⁴

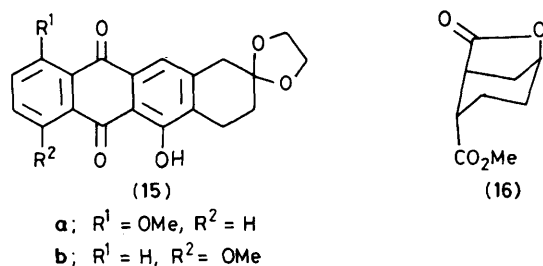
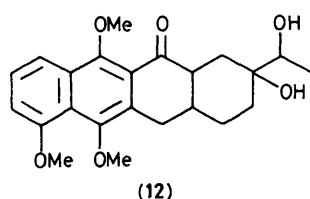
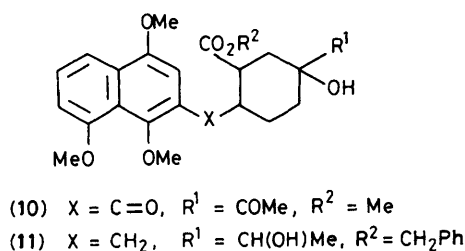
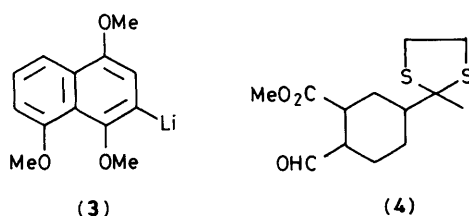
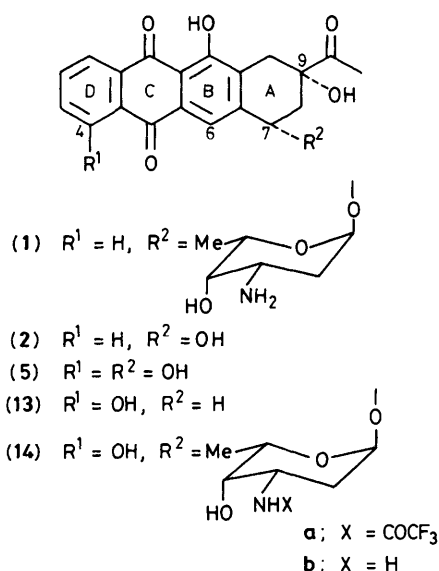
(BuⁿLi, THF, –78 °C), to (**9**) followed by treatment with MeOH–HCl afforded only (**10**), as a yellow oil, in 60% yield after chromatographic purification.[§]

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 BH₃–pyridine(py) complex⁵ 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, BH₃–py, CF₃CO₂H, room temp., 2 h; ii, aqueous 10% NaOH, room temp.; iii, H⁺; iv, PhCHN₂, room temp., 3 h) after acetylation of the hydroxy groups (Ac₂O, py, 4-*N,N*-dimethylaminopyridine, room temp., 24 h) was converted to the corresponding acid (cyclohexane, 10% Pd/C, reflux, 1 h) and cyclized [(CF₃CO)₂O, CF₃CO₂H, 0 °C, 1 h] to give, after methanolysis of the acetates, (**12**) in 60% overall yield.

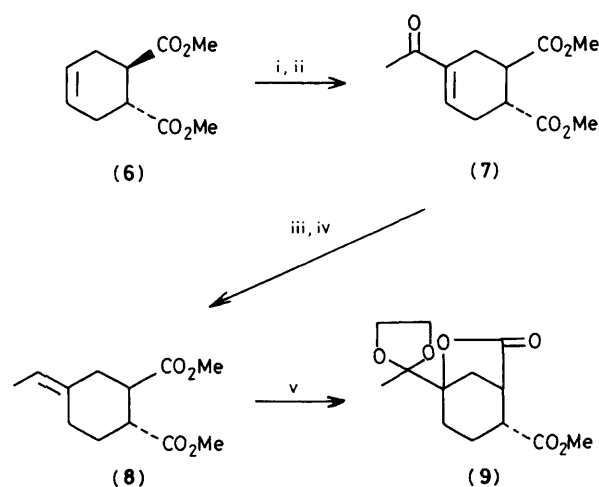
† An attempt to perform the synthesis of (**5**) using the coupling reaction between (**3**) and the aldehyde (**4**), following the procedure described for (**2**),¹ showed lack of regioselectivity affording 6-deoxydaunomycinone together with 6-deoxyisodaunomycinone, whose u.v. spectra are in agreement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

‡ All new compounds were fully characterized by spectroscopic means (i.r., u.v., ¹H 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.



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%



Scheme 1. Reagents and conditions: i, Ac_2O , $SnCl_4$, $-10^\circ C$, 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 , $5^\circ C$; $AcONa$, 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.

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 described⁶ (i, *N*-bromosuccinimide, azoisobutyronitrile, $h\nu$; 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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References

- S. Penco, F. Angelucci, F. Arcamone, M. Ballabio, G. Barchielli, G. Franceschi, G. Franchi, A. Suarato, and E. Vanotti, *J. Org. Chem.*, 1983, **48**, 405.
- J. G. Bauman, R. B. Barber, R. D. Gless, and H. Rapoport, *Tetrahedron Lett.*, 1980, **21**, 4777.
- E. Casadevall, C. Largeau, and P. Moreau, *Bull. Soc. Chim. Fr.*, 1968, 1514.
- R. L. Hannan, R. B. Barber, and H. Rapoport, *J. Org. Chem.*, 1979, **44**, 2153.
- Y. Kikugawa and Y. Ogawa, *Chem. Pharm. Bull.*, 1979, **10**, 2405.
- D. Dominguez, R. J. Ardec, and M. P. Cava, *J. Am. Chem. Soc.*, 1983, **105**, 1608.
- J. P. Marsh, R. H. Iwamoto, and L. Goodman, *Chem. Commun.*, 1968, 589.