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REGIOSPECIFIC SYNTHESIS OF 11-DESOXYANTHRACYCLINE ANTIBIOTICS STARTING WITH ALOE-EMODIN

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ABSTRACT: The regiospecific synthesis of an established 11-desoxyanthracycline synthon (8b) from aloe-emodin (3a) is described.

The contemporary search for analogues of the anthracycline antitumor antibiotics daunomycin[1] and doxorubicin[2] is intense. Particularly desired is the development of analogues retaining antitumor activity but with reduced cardiotoxicity.[3] Toward this end, we consider the 11-desoxyanthracyclines as an attractive area for synthetic exploration. Recently, the isolation and antitumor activities of aclacinomycin A (1a),[4] and 11-desoxydaunomycin (2a),[5] as well as 11-desoxydoxorubicin (2b)[5] have been reported. Although much synthetic effort has been directed toward daunomycinone, none of these procedures appear applicable to the regiospecific synthesis of 11-desoxyanthracyclinones 1b, 2c, or 2d.[6,7]

Recent communications describing the synthesis of the 11-desoxydaunomycinone synthon 8b[8,9] have prompted us to report our quite different approach. Our work is based upon the convenient availability of the naturally-occurring anthraquinone, aloe-emodin (3a).[10] O-Allylation (3c) and Claisen rearrangement (4a) proceed from known ether 3b[10] in 66 and 96% yields.[11] Peracetylation (4b, pyridine/Ac_2O; 98%) followed by hydroboration (BH_3/THF; H_2O_2/NaOAc; 42%) gave the desired primary alcohol (5a). Oxidation ($CrO_3/H_2SO_4/Me_2CO$) and esterification/ethanolysis (EtOH/cat. H_2SO_4) completed elaboration of the lower side chain in the form of ester 5b (64% from 5a): mp 155-158°C; IR (KBr): 1730 cm^{-1}, 1668, 1626, 1584; PMR ($CDCl_3$): 1.14δ (3H, t, J=7 Hz, $-OCH_2\underline{CH_3}$), 1.62 (1H, s, -OH), 2.66-3.30 (4H, m, $ArCH_2CH_2CO_2Et$), 4.10 (3H, s, $ArOCH_3$), 4.12 (2H, q, J=7 Hz, $-OCH_2CH_3$), 4.86 (2H, d (broad), J=6 Hz, $-CH_2OH$), 7.40-8.04 (4H, m, ArH-4,5-7), 13.16 (1H, s, ArOH); e.i.m.s. 384 (M^+); λ^{max}_{MeOH} 228 nm (ε 37450), 258 (24575), 418 (10650). Attempts at direct introduction of this side chain via a Marschalk-type sequence were considerably less successful.

After numerous failures with various sequences, homologation/elaboration of the original benzylic alcohol moiety was achieved by oxidation of 5b (pcc/CH_2Cl_2; 89%) to aldehyde 6a followed by olefination (6b; 83%) with methoxymethyltriphenylphosphorane (n-BuLi/DMSO).

Hydrolysis to homologated aldehyde 7a proceeded cleanly but isolation was complicated by dimerization/polymerization. Thus, 6b was more conveniently hydrolyzed ($Me_2CO/H_2O/H_2SO_4$) to 7a and this was oxidized in situ (CrO_3/H_2SO_4) to 7b. Without further purification, 7b was esterified ($MeOH/H_2SO_4$) to give diester 7c in 83% overall yield from 6b: mp 167.5-169°C; IR (KBr): 1732 cm^{-1}, 1670, 1628, 1588; PMR ($CDCl_3$): 2.44-2.72δ (2H, m, $ArCH_2CH_2CO_2Me$), 2.84-3.12 (2H, m, $ArCH_2CH_2CO_2Me$), 3.55 (3H, s, CO_2CH_3), 3.60 (3H, s, CO_2CH_3), 3.74 (2H, s, $ArCH_2CO_2Me$), 3.94 (3H, s, $ArOCH_3$), 7.12-7.90 (4H, m, ArH-4,5-7), 13.06 (1H, s, ArOH); e.i.m.s. 412 (M^+); λ^{max}_{MeOH} 228 nm (ε 38450), 259 (23950), 417 (10400).

Dieckmann cyclization of 7c (t-BuOK/DMSO) afforded keto ester 8a in 88% yield. Hydrolysis/decarboxylation ($AcOH/H_2O/H_2SO_4$) afforded the desired 11-desoxydaunomycinone precursor (8b) in 76% isolated yield: dp 241-243°C; IR (KBr): 1702 cm^{-1}, 1668, 1624, 1580; PMR ($CDCl_3$): 2.62δ (2H, t, J=7 Hz, $ArCH_2CH_2CO$-), 3.27 (2H, t, J=7 Hz, $ArCH_2CH_2CO$-), 3.71 (2H, s, $ArCH_2CO$-), 4.11 (3H, s, OCH_3), 7.40 (1H, d, d, J=8.0, 1.5 Hz, ArH-3), 7.58 (1H, s, ArH-11), 7.77 (1H, t, J=8.0 Hz, ArH-2), 8.00 (1H, d, d, J=8.0, 1.5 Hz, ArH-1) and 14.27 (1H, s, ArOH); e.i.m.s. 322 (M^+); λ^{max}_{MeOH} 225 nm (ε 29425), 259 (22950) and 416 (9550).

Since methods exist for the elaboration of the requisite side chain at C-9 and hydroxylation at C-7 of 8c,[12a-d] it has been suggested that similar transformation of 8b into the aglycones 2c or 2d should be straightforward.[8] Coupling of these aglycones with L-daunosamine by known methodology [12d,e, 13] would complete the synthetic preparation of 11-desoxydaunomycin (2a) and 11-desoxydoxorubicin (2b).

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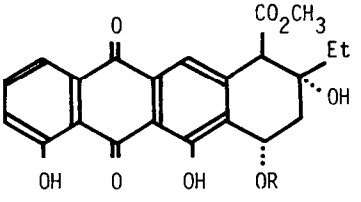
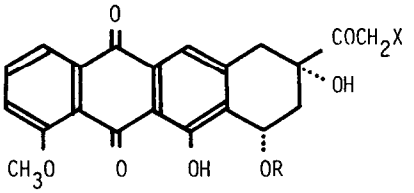
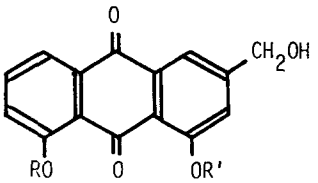


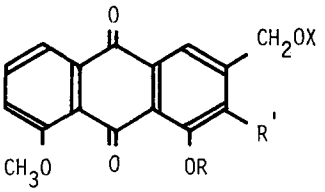
1a, R=L-Daunosamine
1b, R=H



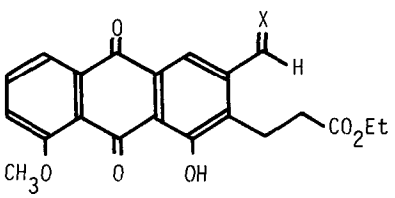
2a, R=L-Daunosamine, X=H
2b, R=L-Duanosamine, X=OH
2c, R=X=H
2d, R=H, X=OH



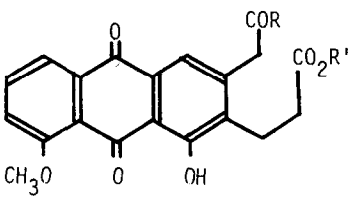
3a, R=R'=H
3b, R=CH_3, R'=H
3c, R=CH_3, R'=$CH_2CH{=}CH_2$



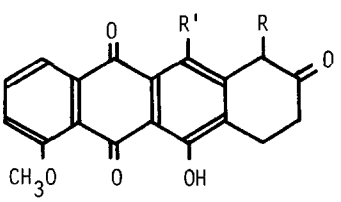
4a, R=X=H, R'=$CH_2CH{=}CH_2$
4b, R=X=Ac, R'=$CH_2CH{=}CH_2$
5a, R=X=Ac, R'=$(CH_2)_3OH$
5b, R=X=H, R'=$(CH_2)_2CO_2Et$



6a, X=O
6b, X=$CHOCH_3$



7a, R=H, R'=Et
7b, R=OH, R'=H
7c, R=OCH_3, R'=CH_3



8a, R=CO_2CH_3, R'=H
8b, R=R'=H
8c, R=H, R'=OH

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