A Short Asymmetric Synthesis of Anthracycline Antibiotics

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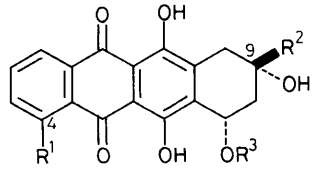
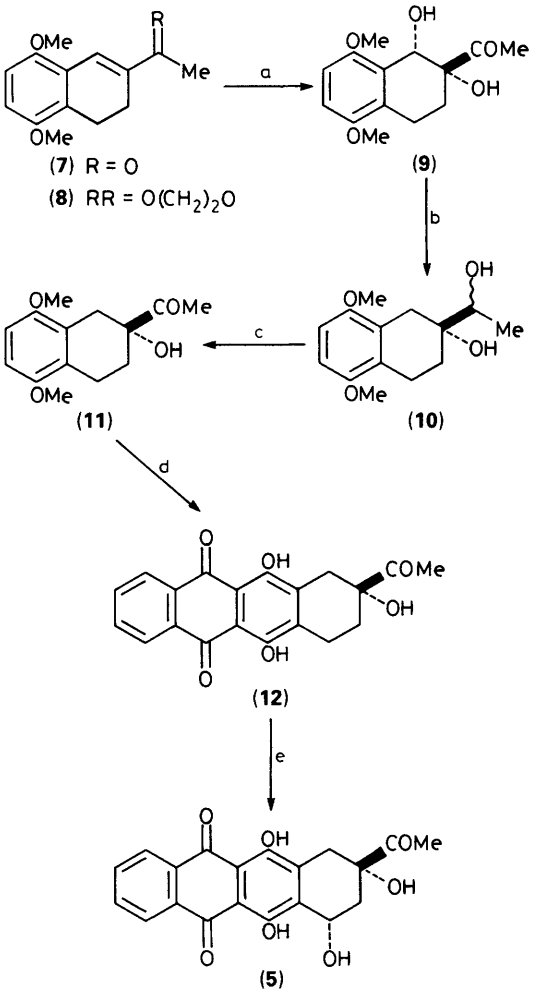
Enantioselective dihydroxylation of (**7**) with osmium tetroxide with mediation by the chiral diamine (−)-(**6**) afforded (**9**) of 82% enantiomeric excess which was then successfully converted to (+)-4-demethoxydaunomycinone (**5**).

Anthracycline antibiotics such as daunorubicin (**1**) and doxorubicin (**2**) are antineoplastic agents of established clinical utility.[1] The 4-demethoxy series of compounds (**3**) and (**4**) have been developed as artificial anthracyclines of improved pharmacological profile.[1,2] Since the anticancer activity of these compounds is strictly dependent on the chirality at C-9, much effort has been devoted to the asymmetric construction of this chiral centre in the desired absolute configuration.[3] We describe herein a short asymmetric construction of the key intermediate (+)-4-demethoxydaunomycinone (**5**) for the synthesis of (**3**).

Dihydroxylation of the alkenes (**7**) and (**8**) was studied with regard to the effect of vinylic substituents on efficiency in



	R^1	R^2	R^3
(**1**)	OMe	COMe	Daunosaminyl
(**2**)	OMe	$COCH_2OH$	Daunosaminyl
(**3**)	H	COMe	Daunosaminyl
(**4**)	H	CH_2OH	Daunosaminyl
(**5**)	H	COMe	H

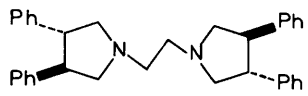


Scheme 1. *Reagents and conditions*: (a) OsO_4-(−)-(**6**)/THF 96%; (b) Et_3SiH/CF_3CO_2H 78%, (c) pyridine–SO_3–NEt_3/Me_2SO, 87%; (d) *o*-$C_6H_4(COCl)_2$–$AlCl_3$/$PhNO_2$, 76% (53% after recrystallization); (e) see ref. 7.

asymmetric induction. Treatment of (**7**) with osmium tetroxide (1.1 equiv.) in the presence of (−)-(**6**)[4] (1.2 equiv.) in tetrahydrofuran (THF) (0.01 M) at −110 °C for 6 h and reductive hydrolysis of the resultant osmate ester with sodium hydrogen sulphite in refluxing aqueous THF, provided the diol (**9**) {$[\alpha]_D^{25}$ −17.6° (*c* 1.10, $CHCl_3$)} with the predicted absolute configuration in 96% yield and in 82% enantiomeric excess (e.e.).† The optical purity and absolute configuration were determined by its conversion to (**11**) (*vide infra*). However, the alkene (**8**), with an ethylene acetal group, provided the corresponding diol in 36% e.e.‡ The steric size of the substituents apparently affects the enantioselectivity.

† Satisfactory analytical and spectroscopic data were obtained for all compounds described.

‡ The absolute configuration and enantiomeric excess of the oxidation product of (**8**) were determined by conversion of the corresponding diol to (**11**).



(−)-(**6**)

The total synthesis of (**5**) was performed as shown in Scheme 1. The diol (**9**) was treated with Et_3SiH in CF_3CO_2H to provide (**10**) as a 3 : 4 diastereoisomeric mixture which was then oxidized with pyridine (Py)–SO_3, Et_3N in Me_2SO to afford (**11**) {82% e.e.; $[\alpha]_D^{20}$ −39.3° ($CHCl_3$); lit.[5] $[\alpha]_D^{20}$ −48.2° ($CHCl_3$)} in 68% overall yield. Friedel–Crafts cyclization of (**11**) was carried out with phthaloyl chloride–$AlCl_3$ in nitrobenzene[6] to provide the core skeleton; recrystallization from benzene afforded (**12**) {$[\alpha]_D^{20}$ −86.0° ($CHCl_3$); lit.[7] $[\alpha]_D^{20}$ −90.3° ($CHCl_3$)} in 53% yield. According to the reported procedure,[7] (**12**) was readily converted to (**5**) {$[\alpha]_D^{20}$ +150° (dioxane); lit.[7] $[\alpha]_D^{20}$ +157° (dioxane)}. The present four-step asymmetric synthesis of the optically active (**12**) constitutes the shortest route to (**5**).[3] Elaboration of (**5**) to (**3**) and its sugar analogues is established technology.[1—3]

The synthesis proves that enantioselective dihydroxylation mediated by the chiral diamine (−)-(**6**) is effective in constructing the requisite chiral centres of the target molecules.

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