

A Short Asymmetric Synthesis of Anthracycline Antibiotics

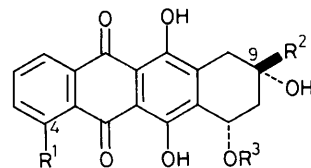
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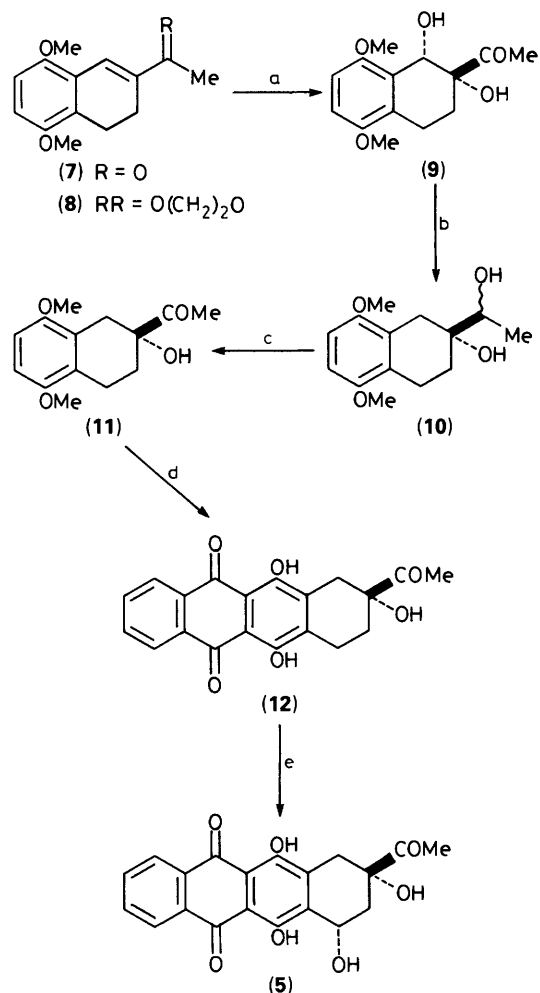
Enantioselective dihydroxylation of (7) with osmium tetroxide with mediation by the chiral diamine (–)-(6) afforded (9) of 82% enantiomeric excess which was then successfully converted to (+)-4-demethoxydaunomycinone (5).

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 ₂ OH	Daunosaminyl
(3)	H	COMe	Daunosaminyl
(4)	H	CH ₂ OH	Daunosaminyl
(5)	H	COMe	H

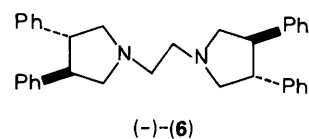


Scheme 1. Reagents and conditions: (a) OsO₄-(-)-(6)/THF 96%; (b) Et₃SiH/CF₃CO₂H 78%, (c) pyridine-SO₃-NEt₃/Me₂SO, 87%; (d) *o*-C₆H₄(COCl)₂-AlCl₃/PhNO₂, 76% (53% after recrystallization); (e) see ref. 7.

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) {[α]_D²⁵ -17.6° (c 1.10, CHCl₃)} 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).



The total synthesis of (5) was performed as shown in Scheme 1. The diol (9) was treated with Et₃SiH in CF₃CO₂H to provide (10) as a 3 : 4 diastereoisomeric mixture which was then oxidized with pyridine (Py)-SO₃, Et₃N in Me₂SO to afford (11) {82% e.e.; [α]_D²⁰ -39.3° (CHCl₃); lit.⁵ [α]_D²⁰ -48.2° (CHCl₃)} in 68% overall yield. Friedel-Crafts cyclization of (11) was carried out with phthaloyl chloride-AlCl₃ in nitrobenzene⁶ to provide the core skeleton; recrystallization from benzene afforded (12) {[α]_D²⁰ -86.0° (CHCl₃); lit.⁷ [α]_D²⁰ -90.3° (CHCl₃)} in 53% yield. According to the reported procedure,⁷ (12) was readily converted to (5) {[α]_D²⁰ +150° (dioxane); lit.⁷ [α]_D²⁰ +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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