Preparation of (−)-(7*R*)-7-Acetyl-7-hydroxy-4,4-dimethoxy-5,6,7,8-tetrahydronaphthalen-1(4*H*)-one, a Chiral AB-Synthon for Anthracycline Synthesis

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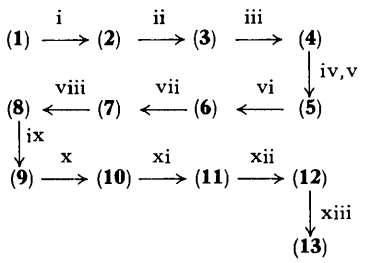
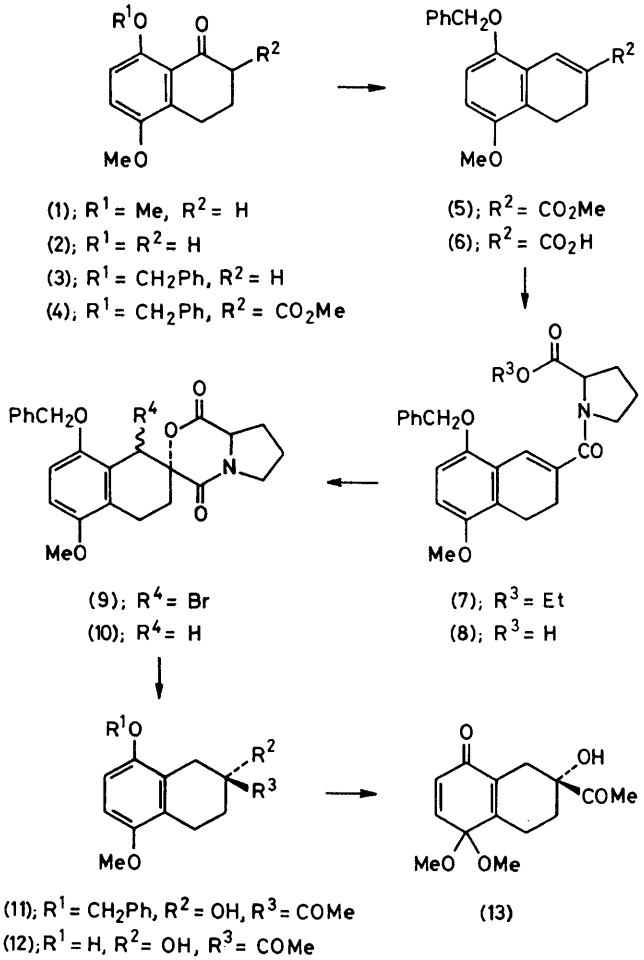
Summary The (−)-(*R*)-dienone (**13**) was prepared in 10 steps from the known 8-hydroxy-5-methoxy-2,3-dihydronaphthalen-1(4*H*)-one (**2**), and the chirality at C(7) in (**13**) corresponds to that found at C(9) in the naturally occurring anthracyclines related to daunomycin.

QUINONE ACETALS have recently emerged as valuable reagents in organic synthesis. We[1] and others[2] have demonstrated that such acetals can function as key reagents in the regiocontrolled synthesis of model anthracyclines. The common feature of these syntheses has been the use of a Michael addition to a dienone to control the regiochemistry of the convergent linking step. In this respect the use of quinone acetals has provided an alternative to other regiospecific methods of anthracycline synthesis.[3] However, like the majority of methods in this area, these quinone-acetal routes have previously lacked the ability to introduce chirality at C(7) and C(9) of the naphthalene ring. This communication reports the synthesis of the first chiral quinone acetal potentially valuable in anthracycline synthesis.



SCHEME. *Reagents and conditions:* i, KI, HCO_2H, 105 °C; ii, NaOMe, $PhCH_2Br$, dimethylformamide (DMF); iii, NaH, $(MeO)_2CO$, tetrahydrofuran (THF), reflux; iv, $NaBH_4$, MeOH, 0—5 °C; v, *p*-$MeC_6H_4SO_3H$ (cat.), C_6H_6, reflux; vi, KOH, MeOH, reflux; vii, (−)-(2*S*)-ethyl prolinate, dicyclohexylcarbodi-imide, MeCN, CH_2Cl_2; viii, 1 M, NaOH in aqueous EtOH; ix, dry Na salt, 2 equiv. *N*-bromosuccinimide (NBS), DMF; x, Bu_3SnH, PhBr, 70 °C; xi, MeLi, Et_2O; xii, H_2, Pd–C, HOAc; xiii, $Tl(NO_3)_3.3H_2O$, MeOH, THF, 0 °C.

Our approach sets up the site-specific location of the potential chiral centre by selective demethylation (Scheme) of 5,8-dimethoxy-2,3-dihydronaphthalen-1(4*H*)-one[4] (**1**). Protection of the resultant phenolic group as the benzyl ether allows selectivity later in the synthesis. Conversion into the dihydronaphthoic acid (**6**) follows standard procedures and is achieved in high yield (Table). Introduction of chirality into the A-ring is achieved by the method of Terashima.[5] Thus, condensation of acid (**6**) with (−)-(2*S*)-ethyl prolinate afforded the amido-ester (**7**) which was converted into the amido-acid (**8**) by selective alkaline hydrolysis. Spirolactonisation of the dried sodium salt of



(**8**) yielded the bromo-lactone (**9**) which was debrominated to yield, after recrystallisation, a single diasteromeric lactone (**10**), m.p. 226—227 °C. *Direct* treatment of (**10**) with excess of methyl-lithium gave the chiral (−)-(*R*)-hydroxy-ketone (**11**) in good yield,† the chiral integrity of

† This process is more efficient than those previously described (ref. 6) and eliminates the need to hydrolyse the amido-lactone to the corresponding hydroxy-acid prior to reaction with methyl-lithium.

TABLE

Compound[a]	M.p./°C	$[\alpha]_D$/°; (*c*)[b]	% Yield[c]
(**2**)	93·5 (lit.[4] 93·5)		97
(**3**)	88—89		84
(**4**)	Oil		95
(**5**)	75—76		80
(**6**)	198—198·5		79
(**7**)	Foam	−16·6 (1·06)	*ca.* 100
(**8**)	142—142·5	−98·6 (1·04)	83
(**9**)	Gum	−9·0 (1·07)	75
(**10**)	226—227	−174 (1·24)	94
(**11**)	84·5—85	−22·9 (1·03)	69
(**12**)	175		85
(**13**)	Oil	−46·5 (1·09)	93

[a] With the exception of the bromo-lactone (**9**), which was characterised by high-resolution mass spectrometry, all new compounds gave satisfactory combustion analyses and spectral data. [b] All specific rotations were measured for $CHCl_3$ solutions. [c] All yields are quoted for a single-step transformation from the immediate precursor, except for products from (**4**). Reduction of (**4**) followed by dehydration of the alcohol (m.p. 113 °C) afforded the ester (**5**) in overall yields ranging from 80—90% (crude yields).

which was evaluated with the aid of chiral shift reagents, using the ketonic methyl resonance as probe.‡ These results indicate an optical purity of > 92% enantiomeric excess. Debenzylation of (**11**) by hydrogenolysis was sluggish even in acidic solution, but the phenol (**12**) was obtained in excellent yield. Efficient conversion of (**12**) into the dienone (**13**) was achieved by oxidation with thallium(III) nitrate.[6] The dienone (**13**) represents the first chiral reagent capable of being regiochemically converted into a daunomycinone derivative.[1] Application of (**13**) and related quinone acetals to the total synthesis of anthracyclines will be reported in due course.

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‡ A signal separation of 0·025 p.p.m. is observed at 270 MHz for a $CDCl_3$ solution (0·16 M in ketone) containing 8·5 mol% of Eu(tfc)$_3$ (tfc = trifluorocamphorato).

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