Optically Active Pentadienyltin Reagent and its Application to Asymmetric Synthesis of (*R*)-7,11-Dideoxydaunomycinone

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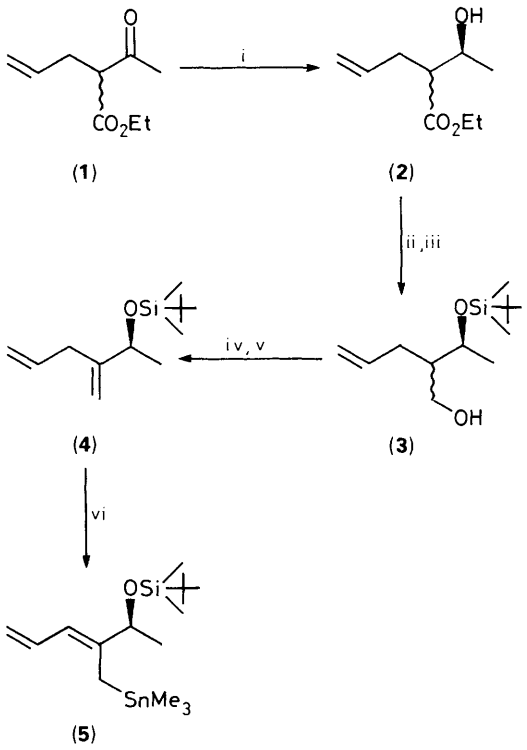
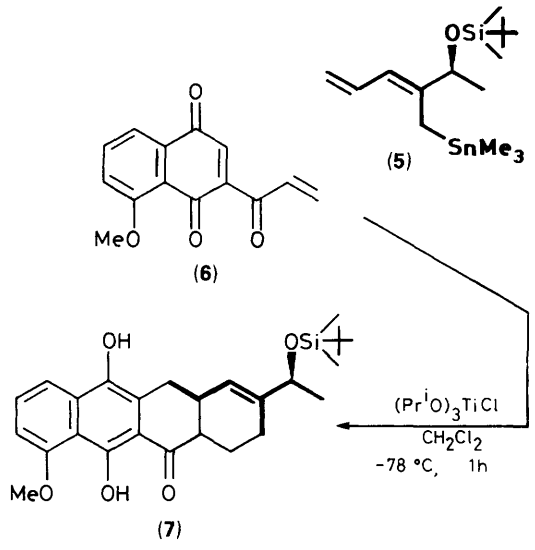
Highly optically active 2-substituted 2,4-pentadienyltin reagent was synthesised and applied to an efficient asymmetric synthesis of (*R*)-7,11-dideoxydaunomycinone by means of tandem Michael/Diels–Alder reaction in a key step.

In spite of the synthetic and pharmaceutical importance,[1] asymmetric synthesis of 11-deoxyanthracyclinones is limited.[2] We have, therefore, pursued it by applying our methodology, tandem Michael/Diels–Alder reaction,[3] where an optically active 2-substituted 2,4-pentadienyltin (PDT) is essential as the key reagent. Here we describe an effective preparation of the chiral tin reagent (**5**) with high regioisomeric and enantiomeric purity and its application to an efficient asymmetric synthesis of 11-deoxydaunomycinone.

The chirality of (**5**) was originally introduced by yeast reduction of the β-ketoester (**1**)[4] as shown in Scheme 1. The enantiomeric purity at the carbinolic carbon of (**2**) was extremely high as noted later. After protection of the resultant hydroxy group by Bu^tMe_2Si group, the ester moiety was



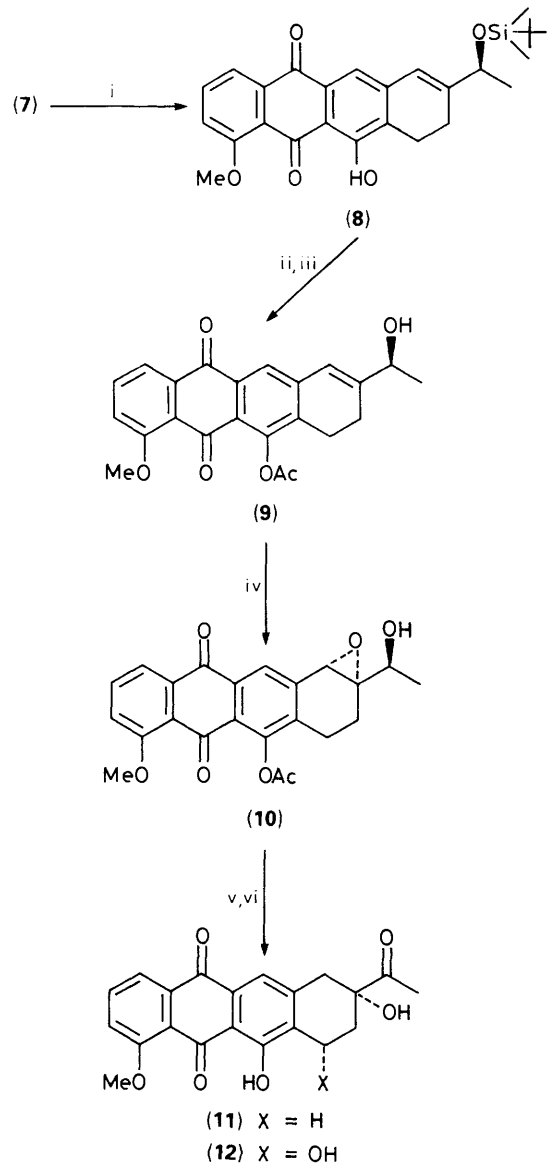
Scheme 1. *Reagents*: i, Baker's yeast; ii, Bu^tMe_2SiCl, imidazole; iii, Bu^i_2AlH; iv, TsCl, pyridine; v, NaI, diazabicyclo [5.4.0]undec-7-ene (DBU); vi, Bu^tOK, Bu^nLi, Me_3SnCl.



Scheme 2. Tandem Michael/Diels–Alder reaction.

reduced to the alcohol (**3**) with Bu^i_2AlH preventing the cleavage of the silyl ether. Then a series of reactions, tosylation, iodination, and dehydroiodination, were applied to give the optically active 1,4-diene (**4**)† in 54% overall yield from (**2**). The optical purity of (**4**) was determined to be as high as 97% by means of ^1H n.m.r. spectroscopy of the corresponding methoxytrifluoromethylphenylacetic acid (MTPA) ester.

† B.p. 113—117 °C/17 mmHg (Kugelrohr); $[\alpha]_D$ +21.2° (*c* 1.0 in CCl_4).



Scheme 3. *Reagents*: i, O_2; ii, Ac_2O, Et_3N, *N*,*N*-dimethylaminopyridine; iii, HF; iv, Bu^tOOH, $VO(acac)_2$; v, pyridinium dichromate; vi, $Na_2S_2O_4$, NaOH.

The optically active tin reagent (**5**) can be prepared from the corresponding alkaline metal complex of the pentadiene moiety followed by its electrophilic trapping with Me_3SnCl. An initial trial to prepare the complex with Bu^nLi in tetrahydrofuran (THF)–hexane was unsuccessful, presumably owing to steric hindrance of the 1,4-diene. Treatment with a stronger base, Bu^tOK/Bu^nLi mixture,[5] which is kinetically more favourable, afforded an orange precipitate in hexane indicating formation of the corresponding pentadienyl metal salt. Reaction of the resultant salt with Me_3SnCl in THF afforded (*Z*)-2-substituted 2,4-pentadienyltin (**5**)‡ in a highly

‡ $[\alpha]_D$ +79° (*c* 2.0 in CCl_4); ^1H n.m.r. ($CDCl_3$), δ 0.03 (3 H, s), 0.05 (3 H, s), 0.12 [9 H, s, *J* (Sn–H) 51, 53 Hz], 0.90 (9 H, s), 1.22 (3 H, d, *J* 6.4 Hz), 1.83 (1 H, d, *J* 11.9 Hz), 1.91 (1 H, d, *J* 11.9 Hz), 4.14 (1 H, q, *J* 6.4 Hz), 4.96 (1 H, dd, *J* 10.4, 2.1 Hz), 5.07 (1 H, dd, *J* 16.8, 2.1 Hz), 5.90 (1 H, d, *J* 11.0 Hz), 6.41 (1 H, ddd, *J* 16.8, 11.0, 10.4 Hz).

regio- and stereo-selective manner[6] in *ca.* 80% yield. Its enantiomeric purity was unharmed even with such an alkaline metal complex. Potentially, this tin reagent has versatile utility in asymmetric synthesis.

The tandem Michael/Diels–Alder reaction (Scheme 2) between the optically active PDT [(**5**); 1.2 mmol] and the acryloylquinone [(**6**); 1.0 mmol] at −78 °C proceeded giving a good yield [62% in 2 steps as the tetracyclic quinone (**8**) after oxidation] with use of $(Pr^iO)_3TiCl$ (3.0 mmol), which was found to be the best Lewis acid from previous experiments with more simple PDTs.[3c] After acetyl protection of the phenolic hydroxy group of (**8**), the silyl protecting group was removed under acidic conditions to give the alcohol (**9**) in 89% overall yield from (**8**) (Scheme 3). It was ascertained that there was almost no loss of the enantiomeric purity in (**9**) [95% enantiomeric excess (e.e.) as its MTPA ester] at this stage.

Diastereoselective epoxidation by $Bu^tOOH/VO(acac)_2$[7] was applied to the chiral allylic alcohol in the tetracyclic quinonoid system to afford the only diastereoisomer of the corresponding epoxide [(**10**); 76%] detected. In a similar asymmetric epoxidation, reverse combination of reagent–substrate, *i.e.* chiral reagent and racemic alcohol, was reported to give the optically active epoxide in a moderate e.e. (56%).[8]

The epoxide (**10**) was converted to (*R*)-7,11-dideoxydaunomycinone (**11**)§ by oxidation to the ketone and reductive oxirane-ring opening under alkaline conditions. Since stereoselective introduction of 7-OH has already been established,[9] the formal total synthesis of 11-deoxydaunomycinone (**12**) of the natural enantiomer was completed. Owing to the high enantiomeric purity and efficiency of the reactions, the present procedure appears to be one of the most promising routes to optically active 11-deoxydaunomycinone.

§ M.p. 217.5—219 °C; $[\alpha]_D$ −28° (*c* 0.26 in $CHCl_3$).

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