Concise Enantioselective Synthesis of a Key Synthetic Intermediate for Anticancer Anthracyclines Based on the Chemistry of 1-Trimethylsilylbuta-2,3-diene

Susumi Hatakeyama, Kazutoshi Sugawara and Seiichi Takano*

Pharmaceutical Institute, Tohoku University, Aobayama, Sendai 980, Japan

(*R*)-(−)-2-Acetyl-5,8-dimethoxy-1,2,3,4-tetrahydro-2-naphthol **6**, a key intermediate for the synthesis of anticancer anthracyclines, has been synthesized enantioselectively in 39% overall yield (8 steps) starting from highly diastereoselective reaction of 1-trimethylsilylbuta-2,3-diene with the chiral acetal **7**.

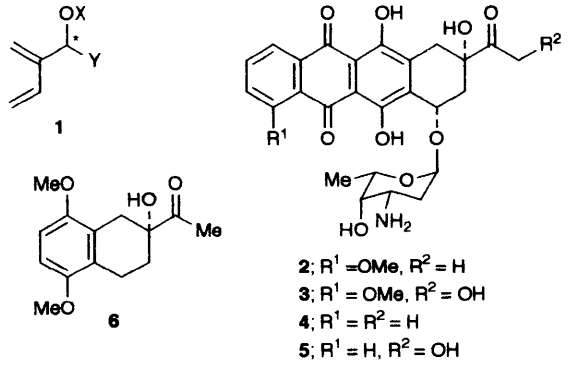
We have recently developed[1] an efficient method for the preparation of the chiral alkyl(buta-1,3-dien-2-yl)methanol derivative **1**. In an effort to explore the synthetic utility of **1** as a chiral building block, we have been engaged in studies directed towards the enantioselective synthesis of anticancer anthracyclines. Naturally occurring anthracycline antibiotics, daunorubicin **2** and adriamycin **3**, have attracted considerable attention[2,3] because of their therapeutic efficacy in the treatment of a broad range of human cancers. These compounds, however, have serious dose-dependent cardiotoxicity[2] and so, in recent years, much effort has been focused on a search for analogues with reduced toxicity as well as improved neoplastic activity. Of the analogues discovered to date, 4-demethoxydaunorubicin **4** and 4-demethoxyadriamycin **5** are the most clinically promising anticancer drugs.[4] We now report a new enantioselective route to the key synthetic intermediate **6**[5] for the preparation of **4** and **5** utilizing a diene of type **1** as a chiral building block.

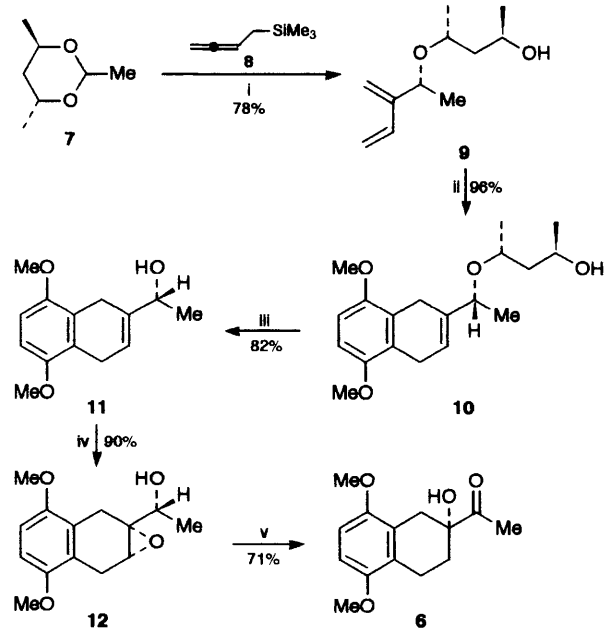
Our synthesis started from Lewis acid-mediated addition[1] of 1-trimethylsilylbuta-2,3-diene **8**[6] to the chiral acetal **7**,† easily prepared by the reaction of acetaldehyde with (*R,R*)-2,4-bis(trimethylsilyloxy)pentane in the presence of a catalytic amount of trimethylsilyl trifluoromethanesulphonate.[7] Thus, the chiral acetal **7**, b.p. 70–80 °C (40 mmHg), $[\alpha]_D^{30}$ +45.2° (*c* 1.150, $CHCl_3$), was allowed to react with **8** at −78 °C by slow addition of a mixed titanium catalyst [$5Ti(OPr^i)_4 \cdot 6TiCl_4$][1,8] using a motorized syringe to give the diene **9**, $[\alpha]_D^{31}$ +35.5° (*c* 1.106, $CHCl_3$). Diels–Alder reaction of **9** with 1,4-benzoquinone‡ followed by methylation afforded the ether **10**, $[\alpha]_D^{26}$ +42.0° (*c* 1.000, $CHCl_3$), almost quantitatively. Removal of the chiral auxiliary *via* a two-step sequence according to the established method[9] caused conversion of **10** to the allylic alcohol **11**. The alcohol **11** was determined to be formed in ≥95% enantiomeric excess (e.e.) by 500 MHz ^1H NMR spectroscopic analysis of the corresponding (*R*)- and (*S*)-α-methoxy-α-trifluoromethylphenylacetic acid (MTPA) esters. Recrystallization of this material from ether gave enantiometrically pure **11**, m.p. 108–109 °C, $[\alpha]_D^{31}$ +25.2° (*c* 0.975, $CHCl_3$). The allylic alcohol **11** was then converted to the epoxy alcohol **12** in a highly diastereoselective manner§ by vanadium-catalysed epoxidation.[10,11] It turned out that, in this particular case, the diastereoselectivity was somewhat temperature dependent as shown in Table 1. $LiAlH_4$ reduction of **12** followed by Fetizon oxidation[11–13] furnished the required ketone **6**. After purification by column chromatography, the

Table 1 Vanadium-catalysed epoxidation of **11**

Conditions[a]		Epoxy alcohol **12**	
T/°C	*t*/h	Yield[b] (%)	D.e.[c] (%)
0	4	80	86
−30	8	81	89
−45	20	90	92

[a] The reaction was carried out in CH_2Cl_2 using $VO(acac)_2$ (10 mol%) and Bu^tOOH (1.2 equiv.) (acac = pentane-2,4-dione). [b] Isolated yield. [c] Diastereoisomeric excess, determined by ^1H NMR spectroscopy (500 MHz).





Scheme 1 *Reagents and conditions*: i, 4 equiv. **8**, $5Ti(O_2Pr^i)_4 \cdot 6TiCl_4$, CH_2Cl_2, −78 °C; ii, 4 equiv. 1,4-benzoquinone, toluene, 90 °C, then Me_2SO_4, K_2CO_3, acetone, reflux; iii, $(COCl)_2$, Me_2SO, CH_2Cl_2, −60 °C then Et_3N, then KOH (7.5 mol dm^{-3})–MeOH–tetrahydrofuran (THF) (1:2:4); iv, see Table 1; v, $LiAlH_4$, THF, then Ag_2CO_3–Celite, benzene, reflux

† All new compounds exhibited satisfactory spectral (^1H NMR, IR, MS) and analytical data.

‡ A tautomeric mixture of the corresponding hydroquinone and diketone was obtained at this stage.

§ Epoxidation of **11** with *m*-chloroperbenzoic acid gave a 1:1 diastereoisomeric mixture of epoxy alcohols.

enantiomeric excess of **6** was determined to be 91% by HPLC analysis using a chiral column.¶ Recrystallization of this material from ether–n-hexane gave enantiomerically pure **6**, m.p. 130–131 °C, $[\alpha]_D^{28}$ −47.2° (*c* 1.120, $CHCl_3$) [lit.[5] m.p. 128–129 °C, $[\alpha]_D^{20}$ −48.7° (*c* 0.825, $CHCl_3$)]. The ketone **6** thus obtained exhibited spectral properties (^1H NMR, IR) in accord with those reported.[5]

The present work shows the synthetic utility of dienes of type **1** as chiral building blocks.

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¶ CHIRAL OD, DAICEL Chemical Industries, Ltd. (Japan), was used employing 15% Pr^iOH–n-hexane as eluent.