A Novel Synthetic Route to 11-Deoxyanthracycline AB Synthons

Hee-doo Kim¹, Sang-ae Park¹ and Sang-sup Jew²

¹College of Pharmacy, Sookmyung Women's University, Seoul 140-742 and ²College of Pharmacy, Seoul National University, Seoul 139-742, Korea

(Received April 28, 1994)

An efficient synthetic method for 11-deoxyanthracycline AB synthons is described. A versatile key intermediate vinyl bromide 3 was prepared from 5-methoxy-1-tetralone in three steps, and then was converted to the allylic alcohols 4 and 8 which, in turn, furnished highly functionalized AB synthons 7 and 12, respectively, via sequential epoxidation-reduction-protection processes.

Key words: 11-Deoxyanthracyline, AB synthon, Vinyl bromide, Allylic alcohol, Epoxidation, 5-Methoxy-1-tetralone

INTRODUCTION

The clinical utility (Arcamone, 1981) of anthracyclines such as adriamycin and daunomycin in the chemotherapy of acute leukemia and solid tumors of the breast, lung, bladder, and ovary, as well as their interesting structures, has brought intense interest in the area of anthracycline synthesis (Thomas, 1990). However, these drugs were exposed to undesirable side effects such as a dose-related and irreversible cardiotoxicity. Consequently, current anthracycline research is focused on the development of new analogues with reduced toxicity as well as a broader spectrum of antitumor activity. From the structure-activity relationship study on the anthracyclines derivatives, it has been suggested that the hydroquinone type B ring in anthracyclines (Fig. 1) might participate in redox reactions leading to radical species responsible for the cardiotoxic side effect (Kleyer and Koch, 1983). Support for this supposition has come from the pharmacological properties of the naturally derived second generation anthracycline 11-deoxydaunomycin: this drug has anticancer properties comparable to daunomycin but shows reduced dose-limiting side effects (Arcamone et al., 1980). Therefore, we have selected 11-deoxyanthracycline as a lead compound for further molecular modification to develop a more potent and less toxic anticancer agent. Many new anthracyclines have been obtained through chemical modification of fermentation derived products. However, the degree of modification which can be achieved in this way is limited by the lability of the functionality in the A ring, and this has stimulated considerable interest in the total synthesis of anthracyclines (Abdallah et al., 1986; Bauman et al., 1980; Gessen et al., 1983; Hauser et al., 1989; Jung et al., 1984; Kimball et al., 1981; Kraus and Woo, 1987; Naruta et al., 1988; Rachandran et al., 1986; Tamura et al., 1984, 1985). The principle synthetic challenge posed by the anthracyclines AB ring system involves construction of the AB ring skeleton, introduction and retention of the labile functionality of ring A and B, and achievement of the correct stereochemistry of ring A substituents. We now report an efficient synthetic route to 11-deoxyanthracycline AB synthons.

Fig. 1.

MATERIALS AND METHODS

Melting points were taken on a hot-stage microscope and are uncorrected. 1H NMR spectra were obtained on a Brucker WP 80 SY spectrometer and che-
chemical shifts are reported as values in parts per million relative to tetramethylsilane (TMS) as an internal standard. Infrared spectra were recorded on a Shimadzu IR-435 IR spectrophotometer and are recorded as $\lambda_{max}$ in cm$^{-1}$. Thin layer chromatography (TLC) was carried out on 0.25-mm E. Merck precoated silical gel glass plates (60F-254) by using 5% phosphomolybdic acid in ethanol-heat/ or UV light as developing agent. Flash chromatography was performed by using E. Merck silica gel 60 (230-400 mesh). Unless otherwise noted, materials were obtained from commercially available sources and used without further purification. Tetrahydrofuran (THF) was freshly distilled from sodium benzenophenone ketyl under an argon atmosphere. Dichloromethane, benzene, and dimethylformamide were freshly distilled under a nitrogen atmosphere from calcium hydride. Anhydrous tert-butyl hydroperoxide was prepared from 70% tert-butyl hydroperoxide according to the literature (Hill et al., 1990). Activated zinc was also prepared by the usual purification method (Pemlin and Armarego, 1988).

2,2-Dibromo-5-methoxy-1-tetralone (1)

To a stirred solution of 5-methoxy-1-tetralone (1 g, 5.68 mmol, purchased from Aldrich Chem. Co.) in acetic acid (30 ml) at 40°C was added dropwise a solution of bromine (0.34 ml, 6.53 mmol) in acetic acid (10 ml) over 60 min. After the solution was stirred at 40°C for 20 min., another solution of bromine (0.34 ml, 6.53 mmol) in acetic acid (10 ml) was added dropwise to the mixture at 40°C over 60 min. The solution was stirred at 40°C for 20 min., cooled to room temperature, and diluted with benzene. The organic phase was washed with water, sat. sodium bicarbonate solution and brine, dried over anhydrous sodium sulfate, filtered and concentrated. The crude product was purified by column chromatography (eluted with 1% ethyl acetate in hexane) to afford 0.91 g (80%) of 2 as a syrup: IR(neat) 3400; $^1$H-NMR (80 MHz, CDCl$_3$) 2.55-2.38 (m, 4H), 3.82 (s, 3H), 4.8 (br s, 1H, D$_2$O exchangeable), 6.81 (d, $J$=7.25 Hz, 1H), 7.26-7.71 (m, 2H).

2-Bromo-5-methoxy-3,4-dihydronaphthalene (3)

To a stirred solution of 2 (9.51 g, 28.3 mmol) in acetic acid (100 ml) at 40°C was added activated zinc (3.7 g×5, 0.28 mol) by 5 portions at an interval of a day during 4 days. After stirring for 24 hours more, the solution was cooled to room temperature, and diluted with benzene. The mixture was filtered, and the organic phase was washed with water, sat. sodium bicarbonate solution and brine, dried over anhydrous sodium sulfate, filtered and concentrated. The crude product was purified by column chromatography (eluted with 1% ethyl acetate in hexane) to afford 6.88 g (68%) of 3 as a pale yellow oil: IR (neat) 3010-3000, 1625; $^1$H-NMR (80 MHz, CDCl$_3$) 2.4-2.2 (m, 2H), 2.9-2.7 (m, 2H), 3.85 (s, 3H), 6.1-5.9 (m, 1H), 6.6-6.8 (m, 2H), 7.15 (dd, $J$=7.9, 7.7 Hz, 1H).

2-(1'-Hydroxyethyl)-5-methoxy-3,4-dihydronaphthalene (4)

To a stirred solution of 3 (3.35 g, 13.8 mmol) and N,N,N',N'-tetramethylethylenediamine (2.29 ml, 15.2 mmol) in tetrahydrofuran (20 ml) at -78°C under a nitrogen atmosphere was added n-butyllithium in hexane (9.4 ml, 15.2 mmol). The solution was stirred at -78°C for 20 min, and then acetaldehyde (3.08 ml, 55.1 mmol) was added. The mixture was stirred for 20 min, and the reaction was quenched by addition of 3 ml of a saturated ammonium chloride solution. The mixture was warmed to room temperature, and diluted with ethyl acetate, washed with water, and brine, dried over anhydrous sodium sulfate, filtered and concentrated. The crude product was purified by column chromatography (eluted with 12% ethyl acetate in hexane) to afford 1.44 g (51%) of 4 as a pale yellow liquid: IR(neat) 3400, 1645; $^1$H-NMR (80 MHz, CDCl$_3$) 1.35 (dd, $J$=6.82 Hz, 1H), 1.93 (br s, 1H, D$_2$O exchangeable), 2.38-2.17 (m, 2H), 2.94-2.74 (m, 2H), 3.83 (s, 3H), 4.42 (q, $J$=6.82 Hz, 1H), 6.41 (br s, 1H), 6.70 (d, $J$=7.7 Hz, 1H), 6.74 (d, $J$=7.8 Hz, 1H), 7.13 (dd, $J$=7.8, 7.7 Hz, 1H).

1,2-Epoxy-2-(1'-hydroxyethyl)-5-methoxy-1,2,3,4-tetrahydronaphthalene (5)

To the allylic alcohol 4 (578 mg, 2.78 mmol) and vanadium oxyacetylacetonate (112 mg, 0.42 mmol) in dry CH$_2$Cl$_2$-benzene (1:1, 10 ml) was added anhydrous tert-butyl hydroperoxide in toluene (3.3 ml, 1.01 mol, 3.33 mmol). The solution was stirred at 0°C for